# Wikipedia:WikiProject Medicine/Open Textbook of Medicine



From Wikipedia, the free encyclopedia

## Variants

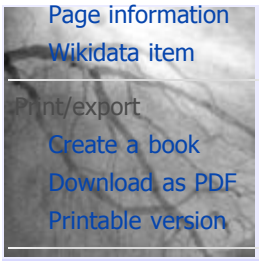
Wikipedia:WikiProject Medicine

Welcome to the **Offline Medical Encyclopedia** by Wikipedia. This is a complete collection of all health care, sanitation, anatomy, and medication related topics from Wikipedia in an offline format. Like Wikipedia all content is open access, meaning that it is free to download, reuse, share, and build upon.

We are working to develop these apps in a number of languages, including English, Persian, Chinese, and Hindi. There are ongoing efforts to increase access to medical information in all languages in collaboration with Translators Without Borders among others. If you like this app and are interested in helping us make it better please join Wikipedia:WikiProject Medicine or contact us directly.

Please keep in mind that this is volunteer generated content. While we try our best to make it as accurate as possible it is not perfect. Thus we request that you use common sense.

James Heilman, MD, CCFP(EM)
The Teams at WikiProject Medicine &
Translators Without Borders

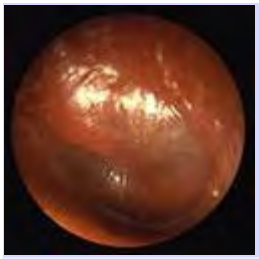


### Cardiology
Abdominal aortic aneurysm • Aortic stenosis • Atrial fibrillation • Cardiac arrhythmia • Cardiovascular disease • Coronary artery disease • Heart failure • Myocardial infarction • Peripheral artery disease • Pulmonary embolism • Rheumatic fever • Syncope

### Children's health
Circumcision • Cleft lip and palate • Congenital heart defect • Down syndrome • Epilepsy • Female genital mutilation • Fetal alcohol spectrum disorder • Klinefelter syndrome • Sickle-cell disease • Spina bifida • Sudden infant death syndrome • Turner syndrome

### Dermatology
Abscess • Acne vulgaris • Allergy • Angular cheilitis • Atopic dermatitis • Candidiasis • Cellulitis • Chickenpox • Dermatitis • Hair loss • Head lice infestation • Herpes simplex • Herpes zoster • Measles • Psoriasis • Scabies

### Ears nose throat



Benign paroxysmal positional vertigo • Hearing loss • Mandibular fracture • Nasal polyp • Nose bleed • Otitis externa • Otitis media • Pharyngitis • Strep throat • Tinnitus • Vertigo

### Endocrinology

Addison's disease • Cushing's syndrome • Delirium tremens • Diabetes • DM type 1 • DM type 2 • Gestational diabetes • Graves' disease • Hypernatremia • Hyperthyroidism • Hypoglycemia • Hyponatremia • Hypothyroidism • Obesity • Primary hyperaldosteronism • Vitamin B12 deficiency

### General surgery

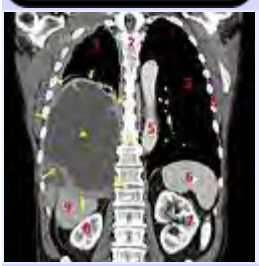
Appendicitis • Bowel obstruction • Celiac disease • Crohn's disease • Diarrhea • Gallstone • Gastritis • Gastrointestinal bleeding • Gastrointestinal perforation • Hemorrhoid • Hernia • Irritable bowel syndrome • Pancreatitis • Peptic ulcer disease • Pernicious anemia • Ulcerative colitis • Volvulus

### Infectious disease

African trypanosomiasis • Ascariasis • Buruli ulcer • Cellulitis • Chagas disease • Common cold • Cysticercosis • Drancunculiasis • Ebola virus disease • Hepatitis A • Hepatitis B • Hepatitis C • HIV/AIDS • Leprosy • Lyme disease • Malaria • Meningitis • Rabies • Syphilis • Tuberculosis • Yellow fever • Zika fever

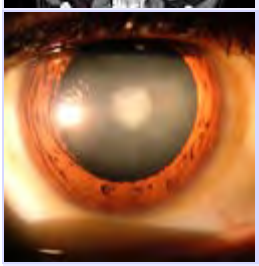
### Medications

Birth control • Carbamazapine • Cephalexin • Cholera vaccine • Cocaine • Dapsone • Diazepam • HCTZ • Ibuprofen • Influenza vaccine • Ipratropium bromide • Ketamine • Levofloxacin • Measles vaccine • Metoprolol • Mifepristone • Morphine • Nystatin • Paracetamol (acetaminophen) • Propofol • Salbutamol



### Oncology

Brain tumor • Breast cancer • Cancer • Cervical cancer • Colon cancer • Endometrial cancer • Esophageal cancer • Glioblastoma multiforme • Leukemia • Lung cancer • Lymphoma • Melanoma • Mesothelioma • Ovarian cancer • Pancreatic cancer • Prostate cancer • Skin cancer • Stomach cancer



### Ophthalmology

Amblyopia • Cataracts • Color blind • Conjunctivitis • Detached retina • Sjögren's syndrome • Glaucoma • Macular degeneration • Refractive error • Trachoma

### Psychiatry

ADHD • Alcoholism • Anorexia nervosa • Anxiety • Asperger syndrome • Autism • Bipolar disorder • Borderline personality disorder • Bulimia nervosa • Eating disorder • Depression • Obsessive-compulsive disorder • Phobia • Post traumatic stress disorder •

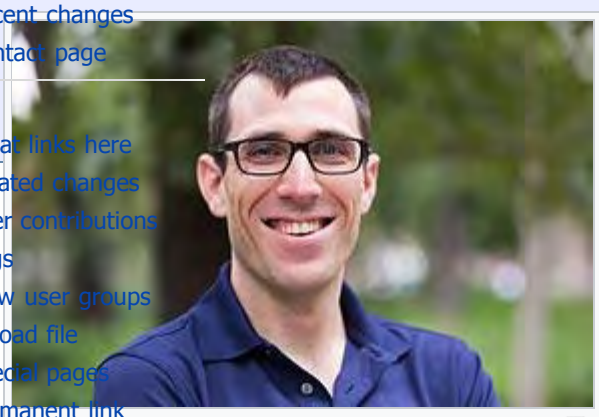
Schizophrenia • Suicide

**Rheumatology**
Carpal tunnel syndrome • Fibromyalgia • Gout • Low back pain • Osteoarthritis • Osteoporosis • Plantar fasciitis • Psoriasis • Rheumatoid arthritis • Sarcoidosis • Sciatica

**Women's health**
Abortion • Breastfeeding • Childbirth • Dysmenorrhea • Eclampsia • Ectopic pregnancy • Endometriosis • Hyperemesis gravidarum • Menopause • Menstruation • Morning sickness • Obstructed labor • Ovarian cyst • Polycystic ovarian syndrome • Pre eclampsia • Pregnancy • Premenstrual syndrome • Preterm birth • Trichomoniasis • Uterine fibroid

# User:Doc James





Wikimania 2015

## Pages I Keep An Eye On

If you're the private type, you can reach me through email

## A bit about me

I'm User:Doc James, previously known as



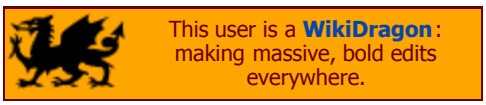
### WikiProject Medicine

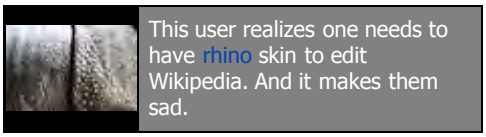
Project Page
Manual of style (medicine)
Identifying reliable sources (medicine)
List of participants
Popular pages (top 5000)
Press and research
Statistics

**Departments:**
Assessment (Log)
Classes editing
Editor outreach
Featured article review
Featured topics project
Research proposals
Task forces
Translation project

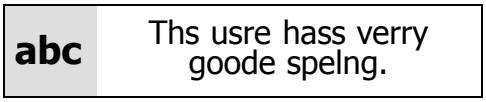
**How to help:**
Article alerts
Articles for cleanup
Collaboration of the month
Missing article trophy
Nominations for deletion
Orphaned articles
Requested articles
Resources for editors
Stub sorting
Patrol recent changes

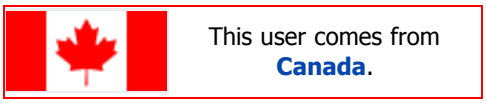


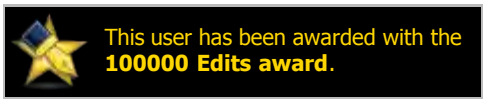







**Categories:**
Project
Articles by quality
Articles by importance

User:Jmh649. In real life I go by James Heilman. I am a Canadian ER doc. I have been editing here since July 6th, 2008.

James Heilman, MD, CCFP-EM, Clinical Faculty member of the Department of Emergency Medicine, Faculty of Medicine, University of British Columbia (Clinical Assistant Professor)[2][3]

P.S. My spelling and grammar are poor, so thank you for correcting them. If something I write is completely unintelligible, please send me a request for clarification.

## COI

I am entirely a volunteer here. I do not accept money or honorariums for any efforts related to wikis, Wikipedia or the Internet. I do not and have not accepted any money from the Wikimedia Foundation or associated chapters in the last four years. This includes not accepting them paying for either travel or accommodation expenses. Prior to that I received about $1500 of funding for travel from the Canadian chapter. In 2012/2013 I donated to the WMF funds more than required to reimburse this amount.[4]

I do accept travel costs for speaking events from organizations that can afford it other than the WMF. I do not and have never accepted pharmaceutical company funding. I do not have any financial COI with respect to the subjects I edit. User:Docjames is a different editor.

## Current projects

- List of simplified articles ready for translation
- Wiki Project Med Foundation
- The Wikipedia Journal live **here**
- Cochrane collaboration
- Collaborating with journals
- Collaboration with WHO
- Collaboration with UCSF
- Collaboration with the NIH
- Tech requests
- Collaboration with Syracuse
- Medical Stats
- Open Global Health
- Copy and Paste Detection (old)/(new)/(newest)/whitelist urls/whitelist users/ [5]
- Paid editing
- Foundation
- Maps and other rich content
- Med cost

**Authority control** ORCID: 0000-0002-1347-7700 ·

## Staff

I have personally hired a part time staff member (User:Lucas559) as of Jun 2015 to assist with a number of medicine related projects including: the translation task force, copyright detection bot, assisting students who are enrolled in classes we are collaborating with, and fundraising for Wiki Project Med Foundation. He will not vote in any discussion that I have already done so and vise versa. Discussion around the creation of his position is partly **here**.

### Students

Students who work with me at the East Kootenay Regional receive instruction on editing Wikipedia. Therefore you may see multiple accounts working on similar medical content coming from my hospitals IP address.

## Words I find inspiring

*Main page: My inspirations*

> It is not the critic who counts; not the man who points out how the strong man stumbles, or where the doer of deeds could have done them better. The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood; who strives valiantly; who errs, who comes short again and again, because there is no effort without error and shortcoming; but who does actually strive to do the deeds; who knows great enthusiasms, the great devotions; who spends himself in a worthy cause; who at the best knows in the end the triumph of high achievement, and who at the worst, if he fails, at least fails while daring greatly, so that his place shall never be with those cold and timid souls who neither know victory nor defeat.Theodore Roosevelt[1] I am a proud fighter for open knowledge.[2]

"Truth is mighty and will prevail. There is nothing the matter with this, except that it ain't so." Mark Twain

## Thoughts

We face a struggle between those who see our future as a technology organization supported by people versus those who see our future as a organization of people supported by technology. I am squarely in the latter camp. Wikipedia at its best is written one sentence at a time following the consideration of the available sources. The singularity is not near.

## My test area

- Projects
- List of emergency medicine topics

## Useful resources

- Tools
- Recent MED changes
- Quick lists
- Wikipedia and medicine
- ER reading
- Merchandise

- Stats
- GA review
- Template
- Resources
- diberri's tool, toolserver another
- Wikipedia:Template_messages
- Wikipedia:Upload/Flickr
- Great template {{reflist-talk}}
- Pageviews based on pagepile [6]
- Edit stats
- Other collaborative sources
- Journals Cited
- Pagviews newer, newer yet, and still newer
- views for images, pageviews for cat (includes mobile)
- [7], all languages
- g sheet cat pages
- All med edits

## Press, publications and barnstars

- My Barnstars
- Press
- NIH presentation pdf ppt
- WikiConference USA Presentation 2014 [8]
- Videos on why one should become involved with Wikiproject Medicine
- Presentation on Wikipedia and Medicine (feel free to reuse)
- Arbcom

### Publications

- Heilman, James M.; Kemmann, Eckhard; Bonert, Michael; Chatterjee, Anwesh; et al. (January 31, 2011). "Wikipedia: A key tool for global public health promotion". *Journal of Medical Internet Research*. **13** (1): e14. doi:10.2196/jmir.1589. PMC 3221335. PMID 21282098.
- Heilman, James (September 2011). "Why we should all edit Wikipedia" (PDF). *University of British Columbia Medical Journal*. **3** (1): 32–3. Retrieved January 14, 2014.
- Heilman, James (2012). "Creating awareness for using a wiki to promote collaborative health professional education". *International Journal of User-Driven Healthcare*. **2** (1): 86–7. doi:10.4018/ijudh.2012010113.
- Mathew, Manu; Joseph, Anna; Heilman, James; Tharyan, Prathap (October 22, 2013). "Cochrane and Wikipedia: The collaborative potential for a quantum leap in the dissemination and uptake of trusted evidence". *Cochrane Database of Systematic Reviews*. **10**: ED000069. doi:10.1002/14651858.ED000069. PMID 24475488.
- Heilman, James M. (October 2014). "Dengue fever: a Wikipedia clinical review". *Open Medicine*. **8** (3): 105–115.
- Heilman, James M; West, Andrew G (4 March 2015). "Wikipedia and Medicine: Quantifying Readership, Editors, and the Significance of Natural Language". *Journal of Medical Internet Research*. **17** (3): e62. doi:10.2196/jmir.4069. PMC 4376174. PMID 25739399.
- Heilman, J (August 2015). "Open Access to a High-Quality, Impartial, Point-of-Care Medical Summary Would Save Lives: Why Does It Not Exist?". *PLoS Medicine*. **12** (8): e1001868. doi:10.1371/journal.pmed.1001868. PMID 26305335.

## Reviews

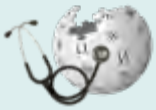
- EBM [9]
- ACP journal [10]
- Cochrane [11] feed
- MedBox
- WHO [12]
- NICE [13]
- Prescrire [14]
- USPSTF [15]

## My work

| v · t · e | **RfA/RfB toolbox** |
|---|---|
| **Counters** | Supercount · XTools · Luxo's · |

| | |
|---|---|
| **Analysis** | Articles created · Non-automated edits · BLP edits · AfD votes · NACs of AfDs · |
| **Summaries** | Edit summary usage · |
| **Cross-wiki** | SULutil · User rights · Log actions · Meta rights log · |

| Admin statistics | |
|---|---|
| **Action** | **Count** |
| Edits | 192886 |
| Edits+Deleted | 193989 |
| Pages deleted | 569 |
| Revisions deleted | 23 |
| Pages restored | 23 |
| Pages protected | 139 |
| Pages unprotected | 13 |
| Protections modified | 46 |
| Users blocked | 907 |
| Users reblocked | 37 |
| Users unblocked | 41 |
| User rights modified | 14 |
| Users created | 5 |



**Recent changes in WP:Medicine**

Articles and their talkpages:

- In all Medicine articles (not talks)
- In articles with Top-, High-importance
- In articles with Mid-importance
- In articles with Low-importance
- In pages with NA, ???=unknown importance
- In the 1000 most popular articles (source)

Not mainspace:

- In all non-articles
- In all templates
- In Medicine navigation templates

| Top | High | Mid | Low | NA | ??? | Total |
|---|---|---|---|---|---|---|
| 90 | 1,001 | 9,093 | 17,576 | 7,469 | 2,259 | 37,488 |

List overview · Lists updated: 2015-07-15 · This box: view · talk

Edit countJames My images

190K This user has made more than **190,000 edits to Wikipedia**.

**Doc James** · (talk · contribs · deleted · cross-wiki · wikichecker · count · pages created · logs · block log · lu · rfar · rfc · rfcu · ssp · spi · search an, ani, cn, an3)

| RfA candidate | S | O | N | S% | Ending (UTC) | Time left | Dups? | Report |
|---|---|---|---|---|---|---|---|---|
| Ferret | 19 | 1 | 0 | 95 | 15:17, 11 January 2017 | 6 days, 19 hours | no | report |
| Ealdgyth | 155 | 2 | 0 | 99 | 14:19, 10 January 2017 | 5 days, 18 hours | no | report |
| Onel5969 | 78 | 9 | 5 | 90 | 20:54, 9 January 2017 | 5 days, 0 hours | no | report |
| K6ka | 131 | 29 | 7 | 82 | 19:41, 7 January 2017 | 2 days, 23 hours | no | report |
| Schwede66 | 139 | 0 | 0 | 100 | 18:01, 6 January 2017 | 1 days, 21 hours | no | report |
| NinjaRobotPirate | 178 | 2 | 1 | 99 | 16:17, 5 January 2017 | 0 days, 20 hours | no | report |
| **RfB candidate** | **S** | **O** | **N** | **S%** | **Ending (UTC)** | **Time left** | **Dups?** | **Report** |

*Last updated by cyberbot I Talk to my owner:Online at 20:01, 4 January 2017 (UTC)*

Wikipedia:Bureaucrats' noticeboard/RfA Report All my admin actions are James&month=&year= here RfA James here

# Sources

1. <ref name=Rosen2014>{{cite book|last=Marx|first=John A. Marx|title=Rosen's emergency medicine : concepts and clinical practice|date=2014|publisher=Elsevier/Saunders|location=Philadelphia, PA|isbn=1455706051|pages=Chapter |edition=8th ed.|chapter=}}</ref>
2. <ref name=Tint2010>{{cite book |author=Tintinalli, Judith E. |title=Emergency Medicine: A Comprehensive Study Guide (Emergency Medicine (Tintinalli)) |publisher=McGraw-Hill Companies |location=New York |year=2010 |pages= |edition=7 |isbn=0-07-148480-9}}</ref>
3. {{cite book|title=BNF 69: March 2015 - September 2015|date=March 31, 2015|publisher=Pharmaceutical Pr|isbn=9780857111562|page=X|edition=69}}
4. [3]
5. Haigh, CA (2011 Feb). "Wikipedia as an evidence source for nursing and healthcare students.". *Nurse education today*. **31** (2): 135–9. PMID 20646799. Check date values in: `|date=` (help)
6. Stedmans Dictionary from UBC [16]
7. Concise oxford med [17]
8. OED [18]
9. <ref>{{cite book|last1=Anderson|first1=Douglas M.|title=Dorland's illustrated medical dictionary|date=2000|publisher=Saunders|location=Philadelphia [u.a.]|isbn=0721682618|page=860|edition=29. ed.}}</ref>
10. [19]
11. Essential sources
12. U of S library sources
13. Open access surgery textbook

## US gov

- Pubmedhealth
  - Heart, Lung, Blood
  - Diabetes, GI, Kidney
  - Infectious diseases index Pink Book
  - Cancer
  - Eye diseases
  - Mental health
  - Hearing
  - Women's and kid's health/Women's Health
  - Aging
  - Alcohol
  - Allergies and ID
  - Arthritis and Skin
  - Drugs
  - Oral health
  - Neurological

## Meds

- AHFS monographs
- WHO Model Formulary 2008

# References

1. ^ Roosevelt, Theodore (April 23, 1910). "Citizenship in a Republic" (Speech). Sorbonne, Paris. Retrieved 9 May 2011. Unknown parameter |month= ignored (help)
2. ^ [1]
3. ^ Logan, DW; Sandal, M, Gardner, PP, Manske, M, Bateman, A (2010 Sep 30). "Ten simple rules for editing Wikipedia.". *PLoS computational biology*. **6** (9). PMID 20941386. Cite uses deprecated parameter |coauthors= (help); Check date values in: |date= (help)



v · t · e · **Writing guides**

| | | |
|---|---|---|
| **Starting an article** | **Layout** | **The perfect article** |
| Getting started | Visual structure of articles | A checklist of components |
| **Article development** | **Manual of Style** | **Writing better articles** |
| Suggested stages of an article | Comprehensive style guide | A collection of advice |

v · t · e · **Wikipedia key policies and guidelines**

| | |
|---|---|
| **Overview** | Five pillars · Policies and guidelines · List of policies and guidelines (List of policies · List of guidelines · · |
| **Project-wide principles** | Consensus · Dispute resolution · Editing policy · Ignore all rules · What Wikipedia is not · Wikipedia is not a dictionary · |
| **Core content policies** | Neutral point of view · No original research · Verifiability · |
| **Other content policies** | Article titles · Autobiography · Biographies of living persons · Image use · |
| **Content guidelines** | Citing sources · Don't create hoaxes · Do not include copies of primary sources · External links · Fringe theories · Identifying reliable sources · Notability · Patent nonsense · |
| **Behavioural policies** | Child protection · Civility · Courtesy vanishing · Edit warring · Harassment · No legal threats · No personal attacks · Ownership of content · Sock puppetry · |
| **Behavioural guidelines** | Assume good faith · Conflict of interest · Disruptive editing · Do not disrupt Wikipedia to illustrate a point · Etiquette · Gaming the system · Please do not bite the newcomers · |
| **Editing guidelines** | Article size · Be bold · Disambiguation · Hatnotes · Set index articles · Signatures · Subpages · Talk page guidelines · User pages · Vandalism · WikiProjects · |
| **Style conventions** | Manual of Style (Contents · · Accessibility (Understandability · · Dates and numbers · Images · Layout · Lead section · Linking · Lists · |
| **Classification guidelines** | Categories, lists, and navigation templates · Categorization · Template namespace · |
| **Deletion policies** | Attack page · Criteria for speedy deletion · Deletion policy · Oversight · Proposed deletion · Proposed deletion of BLP · Proposed deletion (books) · Revision deletion · |
| **Wikimedia Foundation** | List of policies · Friendly space policy · Licensing and copyright · Privacy policy · Values · |

**Book** · **Category: Policies / Guidelines** ·

Categories: Wikipedia administrators | User en-N | WikiProject Medicine members | Wikipedian physicians | WikiProject Sanitation | Canadian Wikipedians


# WikiProject Medicine

Welcome to **WikiProject Medicine**! We discuss, collaborate, and debate anything and everything relating to medicine and health on Wikipedia on our **discussion page**.
Everyone is welcome to join!

**Announcements** [edit]

Happy New Years! Have fun on New Year's Eve, and remember to stay safe if you're setting off fireworks!

Discussions Resources Tools Partners Translations Offline App Research About Metrics Related Projects

**Meet our members!**

**FloNight**

**BarracudaMc**

**Seppi333**

View Full List

Join WikiProject

## Discussions

[ view module ]

*Last updated by Reports bot 14 minutes ago [Refresh]*

- **The world map needs to be updated** on Talk:List of IFMSA member organisations
  21:27, 04 January 2017 (UTC)
- **Unanswuestions** on Talk:Acupuncture
  19:31, 04 January 2017 (UTC)
- **Elucidated** on Talk:Nasopharynx cancer
  18:09, 04 January 2017 (UTC)
- **Nasal twang** on Talk:Nasopharynx cancer
  18:07, 04 January 2017 (UTC)

**Have a question?**

Ask the WikiProject

View Other Discussions

View full list – Add this feed to your Watchlist

Türkçe
Українська
Tiếng Việt

## Resources

Edit links

[ view module • edit ]

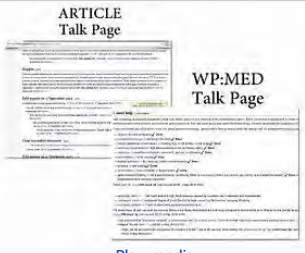
## Guidelines and Policies

- Wikipedia is an encyclopedia and has a distinct style that may take some time getting used to.
- It is important that we only use the best sources and that we give them due weight. Setting us apart from scientific papers we prefer secondary sources over primary sources. We'd rather cite a review article than an original trial.
- To get you started and to explain why this is important we have a number of guides and guidelines:

| | |
|---|---|
| **WP:MEDRS** | **WP:MEDMOS** |
| **Reliable Sources** | **Manual of Style** |
| **WP:MEDCOI** | **WP:MEDHOW** |
| **Conflicts of Interest** | **How to edit** |

*Our guides complement Wikipedia:Policies and guidelines and take great care to explain why they are relevant.*

**More resources**




Play media

An introductory video about how to edit Wikipedia and medicine.

## The Wikipedia Medical Library

The **Wikipedia Library** is a resource for anyone who want to use Wikipedia or to do research to help expand and improve Wikipedia.
*Specialised resources for Medical editors coming soon*

- **Need help finding sources?**: **Help:Find sources**
- **Need help finding your local library?**: **Wikipedia:Find your library**
- **Found a source that you can't access?** *Check out the*: **Resource Exchange**
  *Or try an Interlibrary loan*

**The Library**

## Tools

[ view module • edit ]

**Tools**

— Article alerts
— Recent changes
— Tasks
— Requests
{{}} — Templates
... — more...
— **Popular articles**
—**Assessment criteria**

*There is also a tool to find all our sub pages: Special:PrefixIndex/Wikipedia:WikiProject Medicine/ — only for the truly curious*

## Partners

[ view module • edit ]



## Translations

[ view module • edit ]

The **Translation Task Force** is a global initiative by WikiProject Medicine which has translated over **1900 articles** into **100+ languages**.
It doesn't matter if your first language is English or Swahili, there are always things you can help out with.
Head over to our *project page*!

**Sign up** | **View Progress**


**Cystericercosis article in Tigrinya**

## Offline App

[ view module • edit ]

We have an offline version of our healthcare content. **Download the Android app** and access all this content when there's no Internet. (other languages)

## Research

[ view module • edit ]

Wikipedia can be a great resource for getting to know a field — and it can give you an encyclopaedic overview of a subject, acting as a spring-board letting you dive deeper. It should however not be used as your only source when performing research, and you should never blindly trust Wikipedia. Over the years quite a literature has been amassed surround the reliability and biases of Wikipedia. To see some of the studies that have been produced on the quality and scope of medical information on Wikipedia take a look at some of the research:

**On Wikipedia and Medicine**

**2016**

- Writing a Wikipedia Article on Cultural Competence in Health Care.
  Zhang & Lin *Med Ref Serv Q* — doi:10.1080/02763869.2016.1152143

**2015**

- Influence of wikipedia and other web resources on acute and critical care decisions. a web-based survey.
  Rössler et al. *Intensive Care Med Exp* — doi:10.1186/2197-425X-3-S1-A867

**By Wikipedians**

**2016**

- Medical journals and Wikipedia: a global health matter.
  Masukume G, Kipersztok L, Das D, Shafee TM, Laurent MR, Heilman JM. *Lancet Global Health* — doi:10.1016/S2214-109X(16)30254-6
- Why Medical Schools Should Embrace Wikipedia: Final-Year Medical Student Contributions to Wikipedia Articles for Academic Credit at One School.
  Azzam A, Bresler D, Leon A, Maggio L, Whitaker E, Heilman J, Orlowitz J, Swisher V, Rasberry L, Otoide K, Trotter F, Ross W, McCue JD. *Academic Medicine* — doi:10.1097/ACM.0000000000001381

**2015**

- Wikipedia and medicine: quantifying readership, editors, and the significance of natural language.
  Heilman JM, West AG *J Med Internet Res* — doi:10.2196/jmir.4069
- Open Access to a High-Quality, Impartial, Point-of-Care Medical Summary Would Save Lives: Why Does It Not Exist?
  Heilman J *PLoS Med* — doi:10.1371/journal.pmed.1001868
- Dengue fever: a Wikipedia clinical review.
  Heilman JM, De Wolff J, Beards GM, Basden BJ. *Open Medicine* PMC 4242787

**2013**

- Cochrane and Wikipedia: the collaborative potential for a quantum leap in the dissemination and uptake of trusted evidence.
  Mathew M, Joseph A, Heilman J, Tharyan P. *Cochrane Database of Systematic reviews* doi:10.1002/14651858.ED000069
- Online encyclopedia provides free health info for all. Interview by Fiona Fleck.
  Heilman J. *Bulletin of the World Health Organization* doi:10.2471/BLT.13.030113

**2011**

- Wikipedia: a key tool for global public health promotion.
  Heilman JM, Kemmann E, Bonert M, Chatterjee A, Ragar B, Beards GM, Iberri DJ, Harvey M, Thomas B, Stomp W, Martone MF, Lodge DJ, Vondracek A, de Wolff JF, Liber C, Grover SC, Vickers TJ, Meskó B, Laurent MR. *Journal of Medical Internet Research* doi:10.2196/jmir.1589

*This list is incomplete. We try to keep the list free of bias, but encourage you not to take our word for it — so here are some suggested searches*:

- *PubMed: wikipedia, wikipedia AND medicine*

## About

[ view module • edit ]

**WikiProject Medicine** was started in 2004 by Dr. Jacob de Wolff as WikiProject Clinical Medicine with the later branch WikiProject Preclinical Medicine. These merged and WikiProject Medicine has since been one of Wikipedia's most active WikiProjects. **WP:MED** as it is known aims to manage and help in curation of Wikipedia's medical articles. We write articles and discuss all manner of issues on our talk page: *WT:MED*.

Through the years we've built up a catalogue of sub-projects and task-forces which vary in their activity, you can find some of them at the task force page

WikiProject Medicine is the English arm of an international community of Wikimedia medical projects — more of which can be found through the international WikiProject Med Foundation — on the Meta-wiki.

*Other early arms were the the German WikiProjekt Medizin which started in 2006 and the French Projet Médecine and Spanish Wikiproyecto Medicina and a number of others!*

Wiki Project Med Foundation: *a nonprofit corporation promoting development of medical content on Wikimedia projects*

WikiProject Medicine: *the sister project on Wiktionary*

WikiProject Medicine: *the partner project on Wikidata*

Wikiversity School of Medicine: *medical education resources*

**News mentions**

**2016**

- Dec 6, 2016 Wikipedia Thinks It Has Facebook Beat in Handling Fake News
- Dec 2, 2016 Wikipedia is the world's largest medical resource, but crucial information is often missing
- Nov 10, 2016 Meet Doctor Wikipedia
- Nov 9, 2016 Oriya Medical Wikipedia app growing popular
- Nov 3, 2016 Should You Use Wikipedia for Medical Information?
- Aug 30, 2016 Is Wikipedia a High Quality Evidence-Based Resource?
- Aug 9, 2016 Translators Without Borders press release
- July 4 Two policies in Conflict? Signpost

- Jun 29, 16 radio in Italy
- May 24, 16 Why getting medical information from Wikipedia isn't always a bad idea
- Apr 24, 16 Update on EranBot, our new copyright violation detection bot
- Apr 24, 16 Knowledge Engine and the Wales–Heilman emails
- Mar 29, 16 Wikipedia's coverage of essential vaccines is expanding
- Mar 17, 2016 Thursday Thinkpiece: Kleefeld & Rattray on Editing Wikipedia for Law School Credit
- The Telegraph Feb 2, 2016 Scientific journal retracts research copied from Wikipedia entry
- Tech News, Jan 21, 2016 About talks in TW
- Washington Post, Jan 15, 2016 [1]
- The Register, Jan 12, 2016 [2]

**2015**

- PR Wire Nov 17, 2015 [3]
- Nov 5, 2015 Washington Post[4]
- Oct 29, 2015 Copy and Paste Bot
- Sept 14 2015 10 Wikipedians
- Aug 2015 Oxford University Press Plagiarized Wikipedia, Now Who the Hell Should I Believe?
- Aug 2015 The Covert World of People Trying to Edit Wikipedia—for Pay The Atlantic
- July 2015 Dynamed
- May 2015 CFCF's final report
- June 2, 2015 Making Wikipedia's medical articles accessible in Chinese Signpost
- May 19, 2015 Towards 'Health Information for All': Medical content on Wikipedia received 6.5 billion page views in 2013. / Signpost
- Mar 11,2015 Wikipedia's medical errors and one doctor's fight to correct them
- Mar 3, 2015 The Doctor Who's Healing Wikipedia
- Feb 25,2015 Text from Wikipedia good enough for Oxford University Press to claim as own Signpost
- Feb 4, 2015 Is Wikipedia for sale? Signpost
- January 27,2015 Murray, Terry. "WikiProject Medicine making progress". *CMAJ*. doi:10.1503/cmaj.109-4982.
- Jan 6,2015 Improving the Accuracy of Wikipedia's Medical Information Philanthropy New York

**2014**

- Dec 3,2014 Medical Students Learn to Treat Ailing Wikipedia Entries
- Nov 20, 2014 Keeping the facts straight
- Nov 4, 2014 Global Ebola
- Oct 29, 2014 SBM on Wikipedia in Every Language
- Oct 26, 2014 Wikipedia Is Emerging as Trusted Internet Source for Information on Ebola
- Oct 1, 2014 Wikipedia article published in peer-reviewed journal; Wikipedia in education Signpost
- Oct 2nd, 2014 A Fight for Awareness in the Age of Globalization
- Sept 3, 2014 Copy and Paste Bot Sign Post
- Aug 27 2014 UK Blog
- Aug 11 BMJ blog
- Aug, 2014 Simi Sara Show
- Aug 21, 2014 Wikipedia's medical errors and one doctor's fight to correct them
- Aug 14, 2014 Wikimania: student medics get credit for webside manner
- Aug 5,2014 Blog 5 ways Wikipedia's health information is improving
- July 31, 2014 Canadian doctor leads Wiki Project Med Foundation
- Wikipedia, a valuable resource "tertiary"
- June 23, 2014 Is Wikipedia's medical content really 90% wrong?
- June 2, 2014 Wikipedia for medicine — right or wrong? Australian Doctor
- "Trust your doctor, not Wikipedia, say scientists". Retrieved 2 June 2014.
- Davide Bennato (27 maggio 2014). "Ricerca e comunicazione amori difficili ma non impossibili". Retrieved 27 May 2014. Check date values in: `|date=` (help)
- Mar 26th, 2014 Information on health, free for all with Wikipedia (Italian)
- Mar 5th, 2014, The Atlantic, Doctors' #1 Source for Healthcare Information: Wikipedia [5]
- Feb 20th, 2014, National Journal, Wikipedia Is a Massively Popular (Yet Untested) Doctor [6]
- Feb 19th, 2014, Hindustan Times [7]
- Feb 12, 2014, Sleep Review [8]
- Open Science Jan 22, 2014 [9]
- IMS Institute for Healthcare Informatics [10]

**2013**

- Signpost Oct 9, 2013 College credit for editing Wikipedia [11]
- Center for Digital Education Oct 9, 2013 [12]
- Motherboard [13]
- The Atlantic Oct 1st, 2013 [14]
- NYTs Aug 29th 2013 [15]
- UCSF press release [16]
- Reader's digest, Sept 2013 [17]
- NIH blog July 17,2013 [18]
- Signpost July 3 Wikipedia's medical collaborations gathering pace [19]
- World Health Organization Bulletin, Jan 2013 [20]

*older*

## Metrics

[ view module • edit ]

## 5000 Most Popular articles

(*Assessment criteria*)

**All top-importance articles at B-class or above**: **82.2%** complete

**80 up-to-date featured articles**: **80%** complete

**300 good articles**: **67.7%** complete

| | |
|---|---|
| **146** edits | Thrombosis prevention |
| **72** edits | Molecular biology |
| **71** edits | RVSV-ZEBOV vaccine |
| **71** edits | Antiandrogen |
| **56** edits | Influenza vaccine |
| **51** edits | Nusinersen |
| **43** edits | Nicotinamide |
| **43** edits | Benign prostatic hyperplasia |
| **41** edits | Zoonosis |
| **39** edits | Osteoarthritis |

These are the articles that have been edited the most within the last seven days. Last updated 4 January 2017 by HotArticlesBot.

**WikiProject Medicine assessment statistics**

**Medicine articles by quality and importance**

| Quality | Importance | | | | | | |
|---|---|---|---|---|---|---|---|
| | Top | High | Mid | Low | NA | ??? | Total |
| FA | 10 | 17 | 19 | 18 | | | 64 |
| FL | | 2 | 2 | 6 | | | 10 |
| FM | | | | | 42 | | 42 |
| GA | 26 | 29 | 66 | 82 | | | 203 |
| B | 38 | 359 | 881 | 769 | | 1 | 2,048 |
| C | 16 | 298 | 1,905 | 1,990 | | 60 | 4,269 |
| Start | | 271 | 3,698 | 8,108 | 3 | 515 | 12,595 |
| Stub | | 5 | 2,267 | 6,352 | 3 | 776 | 9,403 |
| List | | 21 | 249 | 227 | | 32 | 529 |
| Book | | | | | 26 | | 26 |
| Category | | | | | 2,538 | | 2,538 |
| Disambig | | | | | 119 | | 119 |
| File | | | | | 164 | | 164 |
| Portal | | | | | 7 | | 7 |
| Project | | | | | 36 | | 36 |
| Redirect | | | | | 3,637 | | 3,637 |
| Template | | | | | 859 | | 859 |
| Assessed | 90 | 1,003 | 9,087 | 17,554 | 7,461 | 1,385 | 36,580 |
| Draft | | 1 | | 2 | 27 | 1 | 31 |
| Unassessed | | | | 12 | | 865 | 877 |
| Total | 90 | 1,003 | 9,087 | 17,566 | 7,461 | 2,250 | 37,457 |
| WikiWork factors (?) | ω = 130,984 | | | | Ω = 5.01 | | |

worklist • log • category

## Related Projects

[ view module • edit ]

WikiProject Anatomy

WikiProject Physiology

WikiProject Neuroscience

*Last updated by Montanabw 3 months ago [Refresh]*

- **WikiProject Biography** (view related)
  3331 articles in common
- **WikiProject Pharmacology** (view related)
  1520 articles in common
- **WikiProject Biography/Science and academia** (view related)
  1401 articles in common
- **WikiProject Psychology** (view related)
  1096 articles in common
- **WikiProject Molecular and Cell Biology** (view related)
  1032 articles in common
- **WikiProject Physiology** (view related)
  1021 articles in common

WP VETERINARY MEDICINE

WP ANIMAL ANATOMY

- **WikiProject United States** (view related)
  926 articles in common
- **WikiProject Women's Health** (view related)
  765 articles in common
- **WikiProject Chemicals** (view related)
  656 articles in common
- **WikiProject Organizations** (view related)
  627 articles in common
- **WikiProject Veterinary medicine** (view related)
  articles in common

View full list – Add this feed to your Watchlist

*Design on 7/1/2016 by CFCF using the tools at WikiProject X. Report any bugs on my talk-page!*
A copy of the old page is available at Wikipedia:WikiProject Medicine/Old 2016.
An even older copy showcasing earlier efforts can be found at Wikipedia:WikiProject Medicine/Old 2012

Categories: WikiProject Medicine | WikiProjects participating in Wikipedia 1.0 assessments

# Wikipedia




Main page
Contents
Featured content
Current events
Random article
Donate to Wikipedia
Wikipedia store

Interaction
Help
About Wikipedia
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Special pages
Permanent link
Page information
Wikidata item
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Create a book
Download as PDF
Printable version

In other projects
Wikimedia Commons
MediaWiki
Meta-Wiki
Wikibooks
Wikiquote
Wikiversity

Languages
Acèh
Адыгэбзэ
Afrikaans
Akan
Alemannisch
Ænglisc
Аҧсшәа


From Wikipedia, the free encyclopedia

*This article is about the Internet encyclopedia. For Wikipedia's home page, see Main Page. For Wikipedia's visitor introduction, see Wikipedia:About. For other uses, see Wikipedia (disambiguation).*

**Wikipedia** (/ˌwɪkɪˈpiːdiə/ or /ˌwɪkiˈpiːdiə/ *WIK-i-PEE-dee-ə*) is a free online encyclopedia that aims to allow anyone to edit articles.[3] Wikipedia is the largest and most popular general reference work on the Internet[4][5][6] and is ranked among the ten most popular websites.[7] Wikipedia is owned by the nonprofit Wikimedia Foundation.[8][9][10]

Wikipedia was launched on January 15, 2001, by Jimmy Wales and Larry Sanger.[11] Sanger coined its name,[12][13] a portmanteau of *wiki*[notes 4] and encyclo*pedia*. There was only the English language version initially, but it quickly developed similar versions in other languages, which differ in content and in editing practices. With 5,323,768 articles, the English Wikipedia is the largest of the more than 290 Wikipedia encyclopedias. Overall, Wikipedia consists of more than 40 million articles in more than 250 different languages[15] and as of February 2014, it had 18 billion page views and nearly 500 million unique visitors each month.[16]

In 2005, *Nature* published a peer review comparing 42 science articles from *Encyclopædia Britannica* and Wikipedia, and found that Wikipedia's level of accuracy approached *Encyclopædia Britannica*'s.[17] Criticism of Wikipedia includes claims that it exhibits systemic bias, presents a mixture of "truths, half truths, and some falsehoods",[18] and that in controversial topics, it is subject to manipulation and spin.[19]

The logo of Wikipedia, a globe featuring glyphs from several writing systems[notes 1]

**Screenshot**

**Contents**

Main Page of the English Wikipedia on October 20, 2010

| | |
|---|---|
| **Type of site** | Internet encyclopedia |
| **Available in** | 292 languages |
| **Owner** | Wikimedia Foundation |
| **Created by** | Jimmy Wales, Larry Sanger[1] |
| **Slogan(s)** | *The free encyclopedia that anyone can edit* |
| **Website** | wikipedia.org |
| **Alexa rank** | ▲ 5 (Global, December 2016) |
| **Commercial** | No |
| **Registration** | Optional[notes 2] |
| **Users** | >272,118 active users[notes 3] and >65,841,874 registered users |
| **Launched** | January 15, 2001; 15 years ago |
| **Current status** | Active |
| **Content license** | CC Attribution / Share-Alike 3.0<br>Most text is also dual-licensed under GFDL; media licensing varies |
| **Written in** | LAMP platform[2] |

**OCLC number** 52075003



# History

*Main article: History of Wikipedia*

## Nupedia

Other collaborative online encyclopedias were attempted before Wikipedia, but none were so successful.[20]

Wikipedia began as a complementary project for Nupedia, a free online English-language encyclopedia project whose articles were written by experts and reviewed under a formal process.[11] Nupedia was founded on March 9, 2000, under the ownership of Bomis, a web portal company. Its main figures were Jimmy Wales, the CEO of Bomis, and Larry Sanger, editor-in-chief for Nupedia and later Wikipedia. Nupedia was licensed initially under its own Nupedia Open Content License, switching to the GNU Free Documentation License before Wikipedia's founding at the urging of Richard Stallman.[21] Sanger and Wales founded Wikipedia.[22][23] While Wales is credited with defining the goal of making a publicly editable encyclopedia,[24][25] Sanger is credited with the strategy of using a wiki to reach that goal.[26] On January 10, 2001, Sanger proposed on the Nupedia mailing list to create a wiki as a "feeder" project for Nupedia.[27]

Jimmy Wales and Larry Sanger


Wikipedia originally developed from another encyclopedia project called Nupedia

## Launch and early growth

Wikipedia was launched on January 15, 2001, as a single English-language edition at www.wikipedia.com,[28] and announced by Sanger on the Nupedia mailing list.[24] Wikipedia's policy of "neutral point-of-view"[29] was codified in its first months. Otherwise, there were relatively few rules initially and Wikipedia operated independently of Nupedia.[24] Originally, Bomis intended to make Wikipedia a business for profit.[30]

Wikipedia gained early contributors from Nupedia, Slashdot postings, and web search engine indexing. By August 8, 2001, Wikipedia had over 8,000 articles.[31] On September 25, 2001, Wikipedia had over 13,000 articles.[32] By the end of 2001, it had grown to approximately 20,000 articles and 18 language editions. It had reached 26 language editions by late 2002, 46 by the end of 2003, and 161 by the final days of 2004.[33] Nupedia and Wikipedia coexisted until the former's servers were taken down permanently in 2003, and its text was incorporated into Wikipedia. The English Wikipedia passed the mark of two million articles on September 9, 2007, making it the largest encyclopedia ever assembled, surpassing even the 1408 *Yongle Encyclopedia*, which had held the record for almost 600 years.[34]


Play media

Wikipedia according to *Simpleshow*

### External audio

The Great Book of Knowledge, Part 1, Ideas with Paul Kennedy, CBC, January 15, 2014

Citing fears of commercial advertising and lack of control in Wikipedia, users of the Spanish Wikipedia forked from Wikipedia to create the *Enciclopedia Libre* in February 2002.[35] These moves encouraged Wales to announce that Wikipedia would not display advertisements, and to change Wikipedia's domain from *wikipedia.com* to *wikipedia.org*.[36]

Though the English Wikipedia reached three million articles in August 2009, the growth of the edition, in terms of the numbers of articles and of contributors, appears to have peaked around early 2007.[37] Around 1,800 [38]

articles were added daily to the encyclopedia in 2006; by 2013 that average was roughly 800. A team at the Palo Alto Research Center attributed this slowing of growth to the project's increasing exclusivity and resistance to change.[39] Others suggest that the growth is flattening naturally because articles that could be called "low-hanging fruit"—topics that clearly merit an article—have already been created and built up extensively.[40][41][42]

In November 2009, a researcher at the Rey Juan Carlos University in Madrid (Spain) found that the English Wikipedia had lost 49,000 editors during the first three months of 2009; in comparison, the project lost only 4,900 editors during the same period in 2008.[43][44] *The Wall Street Journal* cited the array of rules applied to editing and disputes related to such content among the reasons for this trend.[45] Wales disputed these claims in 2009, denying the decline and questioning the methodology of the study.[46] Two years later, in 2011, Wales acknowledged the presence of a slight decline, noting a decrease from "a little more than 36,000 writers" in June 2010 to 35,800 in June 2011. In the same interview, Wales also claimed the number of editors was "stable and sustainable".[47] A 2013 article titled "The Decline of Wikipedia" in MIT's *Technology Review* questioned this claim. The article revealed that since 2007, Wikipedia had lost a third of the volunteer editors who update and correct the online encyclopedia and those still there have focused increasingly on minutiae.[48] In July 2012, *the Atlantic* reported that the number of administrators is also in decline.[49] In the November 25, 2013, issue of *New York* magazine, Katherine Ward stated "Wikipedia, the sixth-most-used website, is facing an internal crisis".[50]

## Recent milestones

Wikipedia blackout protest against SOPA on January 18, 2012

Play media
A promotional video of the Wikimedia Foundation that encourages viewers to edit Wikipedia, mostly reviewing 2014 via Wikipedia content

In January 2007, Wikipedia entered for the first time the top-ten list of the most popular websites in the United States, according to comScore Networks. With 42.9 million unique visitors, Wikipedia was ranked number 9, surpassing the *New York Times* (#10) and Apple (#11). This marked a significant increase over January 2006, when the rank was number 33, with Wikipedia receiving around 18.3 million unique visitors.[51] As of March 2015, Wikipedia has rank 5[7][52] among websites in terms of popularity according to Alexa Internet. In 2014, it received 8 billion pageviews every month.[53] On February 9, 2014, *The New York Times* reported that Wikipedia has 18 billion page views and nearly 500 million unique visitors a month, "according to the ratings firm comScore."[16]

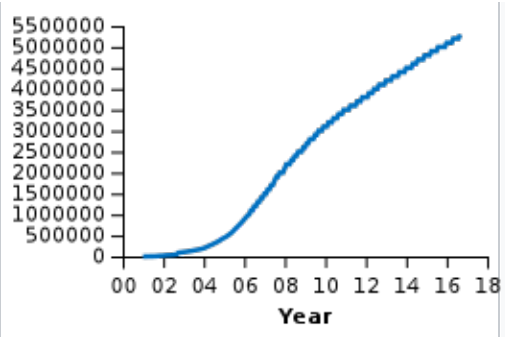
On January 18, 2012, the English Wikipedia participated in a series of coordinated protests against two proposed laws in the United States Congress—the Stop Online Piracy Act (SOPA) and the PROTECT IP Act (PIPA)—by blacking out its pages for 24 hours.[54] More than 162 million people viewed the blackout explanation page that temporarily replaced Wikipedia content.[55][56]

Loveland and Reagle argue that, in process, Wikipedia follows a long tradition of historical encyclopedias that accumulated improvements piecemeal through "stigmergic accumulation".[57][58]

On January 20, 2014, Subodh Varma reporting for *The Economic Times* indicated that not only had Wikipedia's growth flattened but that it has "lost nearly 10 per cent of its page-views last year. That's a decline of about 2 billion between December 2012 and December 2013. Its most popular versions are leading the slide: page-views of the English Wikipedia declined by 12 per cent, those of German version slid by 17 per cent and the Japanese version lost 9 per cent."[59] Varma added that, "While Wikipedia's managers think that this could be due to errors in counting, other experts feel that Google's Knowledge Graphs project launched last year may be gobbling up Wikipedia users."[59] When contacted on this matter, Clay Shirky, associate professor at New York University and fellow at Harvard's Berkman Center for Internet and Security indicated that he suspected much of the page view decline was due to Knowledge Graphs, stating, "If you can get your question answered from the search page, you don't need to click [any further]."[59]

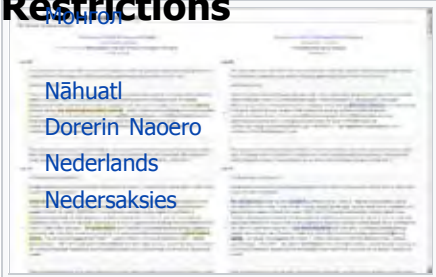
## Openness

Unlike traditional encyclopedias, Wikipedia follows the procrastination principle[notes 5][61] regarding the security of its content.[61] It started almost entirely open—anyone could create articles, and any Wikipedia article could be edited by any reader, even those who did not have a Wikipedia account. Modifications to all articles would be published immediately. As a result, any article could contain inaccuracies such as errors, ideological biases, and nonsensical or irrelevant text.



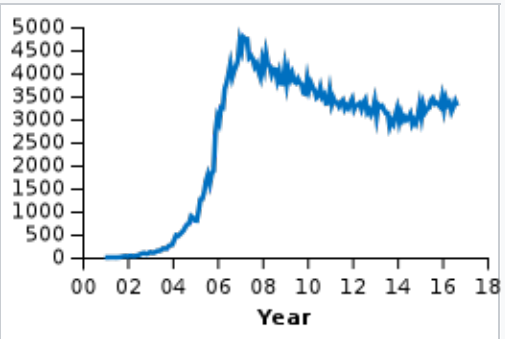

Number of Wikipedia articles[60]

## Restrictions



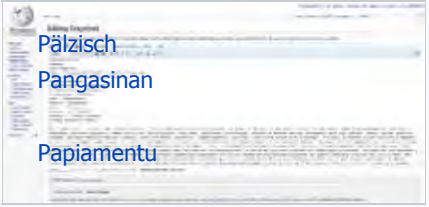
Differences between versions of an article are highlighted as shown

Due to the increasing popularity of Wikipedia, popular editions, including the English version, have introduced editing restrictions in some cases. For instance, on the English Wikipedia and some other language editions, only registered users may create a new article.[62] On the English Wikipedia, among others, some particularly controversial, sensitive and/or vandalism-prone pages have been protected to some degree.[63][64] A frequently vandalized article can be *semi-protected* or *extended confirmed protected*, meaning that only autoconfirmed or extended confirmed editors are able to modify it.[65] A particularly contentious article may be locked so that only administrators are able to make changes.[66]




Wikipedia editors with >100 edits per month[60]

In certain cases, all editors are allowed to submit modifications, but review is required for some editors, depending on certain conditions. For example, the German Wikipedia maintains "stable versions" of articles,[67] which have passed certain reviews. Following protracted trials and community discussion, the English Wikipedia introduced the "pending changes" system in December 2012.[68] Under this system, new and unregistered users' edits to certain controversial or vandalism-prone articles are reviewed by established users before they are published.[69]



The editing interface of Wikipedia

## Review of changes

Although changes are not systematically reviewed, the software that powers Wikipedia provides certain tools allowing anyone to review changes made by others. The "History" page of each article links to each revision.[notes 6][70] On most articles, anyone can undo others' changes by clicking a link on the article's history page. Anyone can view the latest changes to articles, and anyone may maintain a "watchlist" of articles that interest them so they can be notified of any changes. "New pages patrol" is a process whereby newly created articles are checked for obvious problems.[71]

In 2003, economics PhD student Andrea Ciffolilli argued that the low transaction costs of participating in a wiki create a catalyst for collaborative development, and that features such as allowing easy access to past versions of a page favor "creative construction" over "creative destruction".[72]

## Vandalism

*Main article: Vandalism on Wikipedia*

Any edit that changes content in a way that deliberately compromises the integrity of Wikipedia is considered vandalism. The most common and obvious types of vandalism include insertion of obscenities and crude humor. Vandalism can also include advertising language and other types of spam.[73] Sometimes editors commit vandalism by removing information or entirely blanking a given page. Less common types of vandalism, such as the deliberate addition of plausible but false information to an article, can be more difficult to detect. Vandals can introduce irrelevant formatting, modify page semantics such as the page's title or categorization, manipulate the underlying code of an article, or use images disruptively.[74]

Obvious vandalism is generally easy to remove from Wikipedia articles; the median time to detect and fix vandalism is a few minutes.[75][76] However, some vandalism takes much longer to repair.[77]

American journalist John Seigenthaler (1927–2014), subject of the Seigenthaler incident

In the Seigenthaler biography incident, an anonymous editor introduced false information into the biography of American political figure John Seigenthaler in May 2005. Seigenthaler was falsely presented as a suspect in the assassination of John F. Kennedy.[77] The article remained uncorrected for four months.[77] Seigenthaler, the founding editorial director of *USA Today* and founder of the Freedom Forum First Amendment Center at Vanderbilt University, called Wikipedia co-founder Jimmy Wales and asked whether he had any way of knowing who contributed the misinformation. Wales replied that he did not, although the perpetrator was eventually traced.[78][79] After the incident, Seigenthaler described Wikipedia as "a flawed and irresponsible research tool".[77] This incident led to policy changes at Wikipedia, specifically targeted at tightening up the verifiability of biographical articles of living people.[80]

# Policies and laws

*See also: Wikipedia:Five Pillars*

**External video**

Wikimania, *60 Minutes*, CBS, 20 minutes, April 5, 2015, co-founder Jimmy Wales at Fosdem

Content in Wikipedia is subject to the laws (in particular, copyright laws) of the United States and of the U.S. state of Virginia, where the majority of Wikipedia's servers are located. Beyond legal matters, the editorial principles of Wikipedia are embodied in the "five pillars" and in numerous policies and guidelines intended to appropriately shape content. Even these rules are stored in wiki form, and Wikipedia editors write and revise the website's policies and guidelines.[81] Editors can enforce these rules by deleting or modifying non-compliant material. Originally, rules on the non-English editions of Wikipedia were based on a translation of the rules for the English Wikipedia. They have since diverged to some extent.[67]

## Content policies and guidelines

According to the rules on the English Wikipedia, each entry in Wikipedia must be about a topic that is encyclopedic and is not a dictionary entry or dictionary-like.[82] A topic should also meet Wikipedia's standards of "notability",[83] which generally means that the topic must have been covered in mainstream media or major academic journal sources that are independent of the article's subject. Further, Wikipedia intends to convey only knowledge that is already established and recognized.[84] It must not present original research. A claim that is likely to be challenged requires a reference to a reliable source. Among Wikipedia editors, this is often phrased as "verifiability, not truth" to express the idea that the readers, not the encyclopedia, are ultimately responsible for checking the truthfulness of the articles and making their own interpretations.[85] This can at times lead to the removal of information that is valid.[86] Finally, Wikipedia must not take sides.[87] All opinions and viewpoints, if attributable to external sources, must enjoy an appropriate share of coverage

within an article.[88] This is known as neutral point of view (NPOV).

# Governance

*Further information: Wikipedia:Administration*

Wikipedia's initial anarchy integrated democratic and hierarchical elements over time.[89][90] An article is not considered to be owned by its creator or any other editor and is not vetted by any recognized authority.[91] Wikipedia's contributors avoid a tragedy of the commons by internalizing benefits. They do this by experiencing flow and identifying with and gaining status in the Wikipedia community.[92]

## Administrators

Editors in good standing in the community can run for one of many levels of volunteer stewardship: this begins with "administrator",[93][94] privileged users who can delete pages, prevent articles from being changed in case of vandalism or editorial disputes, and try to prevent certain persons from editing. Despite the name, administrators are not supposed to enjoy any special privilege in decision-making; instead, their powers are mostly limited to making edits that have project-wide effects and thus are disallowed to ordinary editors, and to implement restrictions intended to prevent certain persons from making disruptive edits (such as vandalism).[95][96]

Fewer editors become administrators than in years past, in part because the process of vetting potential Wikipedia administrators has become more rigorous.[97]

*Bureaucrats* name new administrators, solely upon the recommendations from the community.

## Dispute resolution

Wikipedians often have disputes regarding content, which may result in repeatedly making opposite changes to an article, known as edit warring.[98][99] Over time, Wikipedia has developed a semi-formal dispute resolution process to assist in such circumstances. In order to determine community consensus, editors can raise issues at appropriate community forums,[notes 7] or seek outside input through third opinion requests or by initiating a more general community discussion known as a request for comment.

## Arbitration Committee

*Main article: Arbitration Committee*

The Arbitration Committee presides over the ultimate dispute resolution process. Although disputes usually arise from a disagreement between two opposing views on how an article should read, the Arbitration Committee explicitly refuses to directly rule on the specific view that should be adopted. Statistical analyses suggest that the committee ignores the content of disputes and rather focuses on the way disputes are conducted,[100] functioning not so much to resolve disputes and make peace between conflicting editors, but to weed out problematic editors while allowing potentially productive editors back in to participate. Therefore, the committee does not dictate the content of articles, although it sometimes condemns content changes when it deems the new content violates Wikipedia policies (for example, if the new content is considered biased). Its remedies include cautions and probations (used in 63% of cases) and banning editors from articles (43%), subject matters (23%) or Wikipedia (16%). Complete bans from Wikipedia are generally limited to instances of impersonation and anti-social behavior. When conduct is not impersonation or anti-social, but rather anti-consensus or in violation of editing policies, remedies tend to be limited to warnings.[101]

# Community

*Main article: Wikipedia community*

Each article and each user of Wikipedia has an associated "Talk" page. These form the primary communication channel for editors to discuss,

coordinate and debate.[102]

Wikipedia's community has been described as cult-like,[103] although not always with entirely negative connotations.[104] The project's preference for cohesiveness, even if it requires compromise that includes disregard of credentials, has been referred to as "anti-elitism".[105]

Wikipedians sometimes award one another virtual barnstars for good work. These personalized tokens of appreciation reveal a wide range of valued work extending far beyond simple editing to include social support, administrative actions, and types of articulation work.[106]

Wikipedia does not require that its editors and contributors provide identification.[107] As Wikipedia grew, "Who writes Wikipedia?" became one of the questions frequently asked on the project.[108] Jimmy Wales once argued that only "a community ... a dedicated group of a few hundred volunteers" makes the bulk of contributions to Wikipedia and that the project is therefore "much like any traditional organization".[109] In 2008, a *Slate* magazine article reported that: "According to researchers in Palo Alto, 1 percent of Wikipedia users are responsible for about half of the site's edits."[110] This method of evaluating contributions was later disputed by Aaron Swartz, who noted that several articles he sampled had large portions of their content (measured by number of characters) contributed by users with low edit counts.[111]

The English Wikipedia has 5,323,768 articles, 29,893,763 registered editors, and 119,453 active editors. An editor is considered active if they have made one or more edits in the past thirty days.

Editors who fail to comply with Wikipedia cultural rituals, such as signing talk page comments, may implicitly signal that they are Wikipedia outsiders, increasing the odds that Wikipedia insiders may target or discount their contributions. Becoming a Wikipedia insider involves non-trivial costs: the contributor is expected to learn Wikipedia-specific technological codes, submit to a sometimes convoluted dispute resolution process, and learn a "baffling culture rich with in-jokes and insider references".[112] Editors who do not log in are in some sense second-class citizens on Wikipedia,[112] as "participants are accredited by members of the wiki community, who have a vested interest in preserving the quality of the work product, on the basis of their ongoing participation",[113] but the contribution histories of anonymous unregistered editors recognized only by their IP addresses cannot be attributed to a particular editor with certainty.

Play media

Video of Wikimania 2005 – an annual conference for users of Wikipedia and other projects operated by the Wikimedia Foundation, was held in Frankfurt am Main, Germany from August 4 to 8.

Play media

Wikipedians and British Museum curators collaborate on the article Hoxne Hoard in June 2010

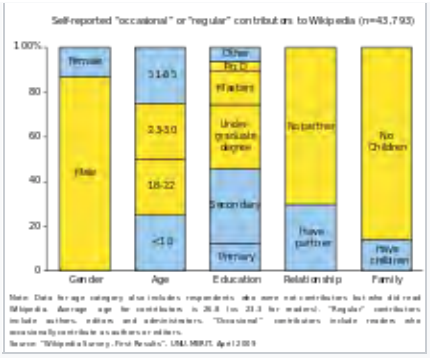
A 2007 study by researchers from Dartmouth College found that "anonymous and infrequent contributors to Wikipedia [...] are as reliable a source of knowledge as those contributors who register with the site".[114] Jimmy Wales stated in 2009 that "(I)t turns out over 50% of all the edits are done by just .7% of the users... 524 people... And in fact the most active 2%, which is 1400 people, have done 73.4% of all the edits."[109] However, *Business Insider* editor and journalist Henry Blodget showed in 2009 that in a random sample of articles, most content in Wikipedia (measured by the amount of contributed text that survives to the latest sampled edit) is created by "outsiders", while most editing and formatting is done by "insiders".[109]

A 2008 study found that Wikipedians were less agreeable, open, and conscientious than others,[115][116] although a later commentary pointed out serious flaws, including that the data showed higher openness, that the differences with the control group were small as were the samples.[117] According to a 2009 study, there is "evidence of growing resistance from the Wikipedia community to new content".[118]

## Diversity

One study found that the contributor base to Wikipedia "was barely 13%" [119]

women; the average age of a contributor was in the mid-20s". A 2011 study by researchers from the University of Minnesota found that females comprised 16.1% of the 38,497 editors who started editing Wikipedia during 2009.[120] In a January 2011 *New York Times* article, Noam Cohen observed that just 13% of Wikipedia's contributors are female according to a 2008 Wikimedia Foundation survey.[121] Sue Gardner, a former executive director of the Wikimedia Foundation, hoped to see female contributions increase to 25% by 2015.[122] Linda Basch, president of the National Council for Research on Women, noted the contrast in these Wikipedia editor statistics with the percentage of women currently completing bachelor's degrees, master's degrees and PhD programs in the United States (all at rates of 50 percent or greater).[123]



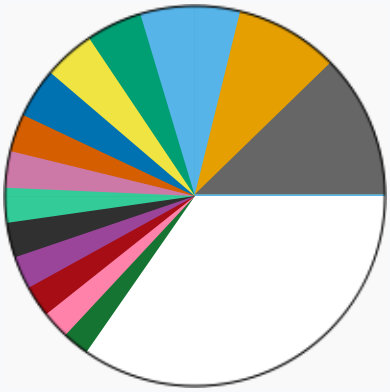
Wikipedia editor demographics (2008)

In response, various universities have hosted edit-a-thons to encourage more women to participate in the Wikipedia community. In fall 2013, 15 colleges and universities — including Yale, Brown, and Pennsylvania State — offered college credit for students to "write feminist thinking" about technology into Wikipedia.[124] Estimates of the diversity of contributors by educational level have indicated that sixty-two percent of Wikipedia's editors are at the high school and undergraduate college level of education.[125]

In August 2014, Wikipedia co-founder Jimmy Wales said in a BBC interview that the Wikimedia Foundation was "... really doubling down our efforts ..." to reach 25% of female editors (originally targeted by 2015), since the Foundation had "totally failed" so far. Wales said "a lot of things need to happen ... a lot of outreach, a lot of software changes".[126] Andrew Lih writing in the New York Times was quoted by Bloomberg News in December 2016 as supporting Wales comments concerning shortfalls in Wikipedia's outreach to female editors. Lih states his concern with the question indicating that: "How can you get people to participate in an (editing) environment that feels unsafe, where identifying yourself as a woman, as a feminist, could open you up to ugly, intimidating behavior".[127]

## Language editions

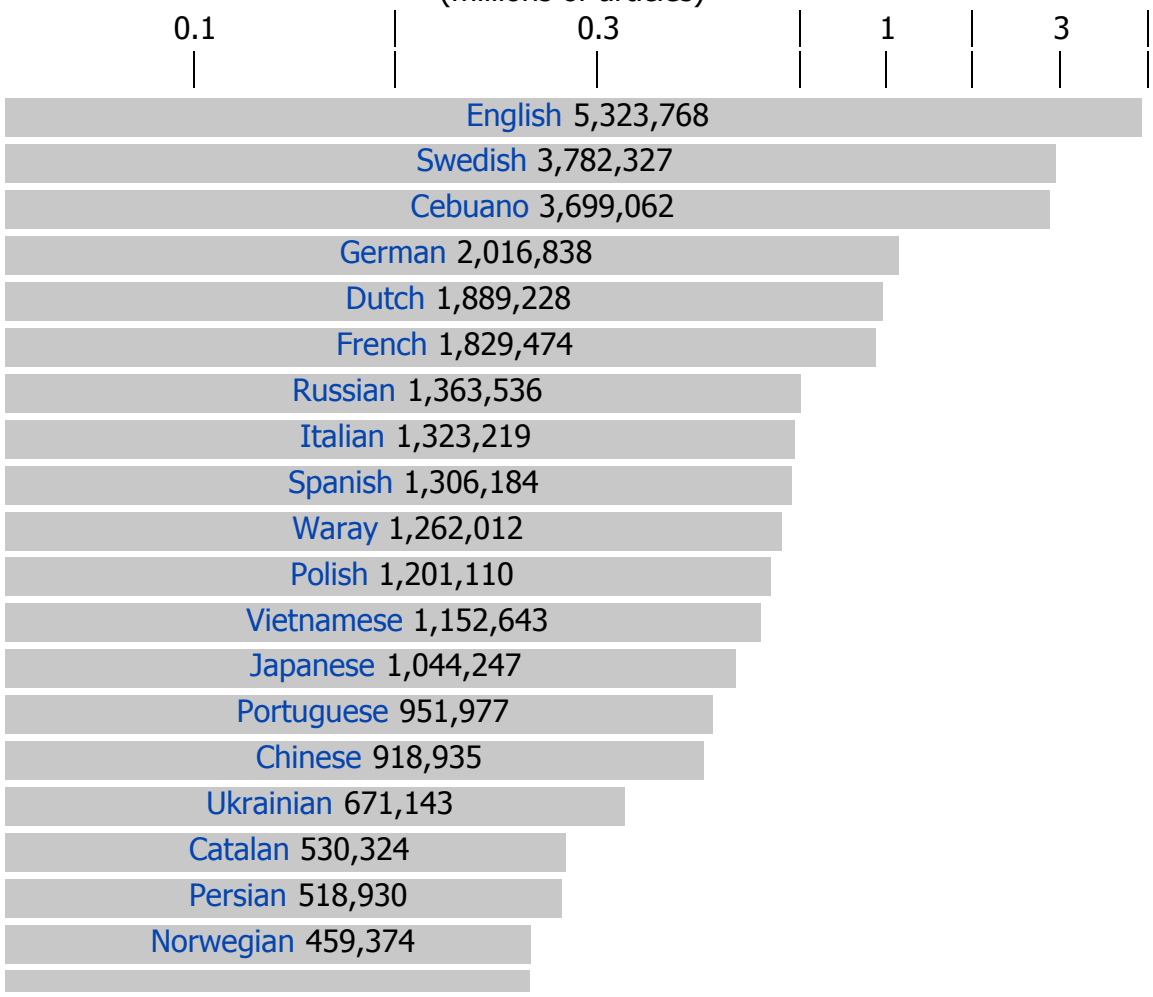
There are currently 295 language editions of Wikipedia (also called *language versions*, or simply *Wikipedias*). Thirteen of these have over one million articles each (English, Swedish, Cebuano, German, Dutch, French, Russian, Italian, Spanish, Waray-Waray, Polish, Vietnamese and Japanese), five more have over 500,000 articles (Portuguese, Chinese, Ukrainian, Catalan and Persian), 40 more have over 100,000 articles, and 76 more have over 10,000 articles.[128][129] The largest, the English Wikipedia, has over 5.3 million articles. As of December 2016, according to Alexa, the English subdomain (en.wikipedia.org; English Wikipedia) receives approximately 55% of Wikipedia's cumulative traffic, with the remaining split among the other languages (Russian: 8%; Spanish: 7%; Japanese: 6%; French: 4%).[7] As of January 2017, the six largest language editions are (in order of article count) the English, Swedish, Cebuano, German, Dutch, and French Wikipedias.[130]


**Distribution of the 43,186,661 articles in**

**different language editions (as of 4 January 2017)**[131]

- English (12.3%)
- Swedish (8.8%)
- Cebuano (8.6%)
- German (4.7%)
- Dutch (4.4%)
- French (4.2%)
- Russian (3.2%)
- Italian (3.1%)
- Spanish (3%)
- Waray (2.9%)
- Polish (2.8%)
- Vietnamese (2.7%)
- Japanese (2.4%)
- Portuguese (2.2%)
- Other (34.7%)

**Logarithmic graph of the 20 largest language editions of Wikipedia**
(as of 4 January 2017)[132]
(millions of articles)

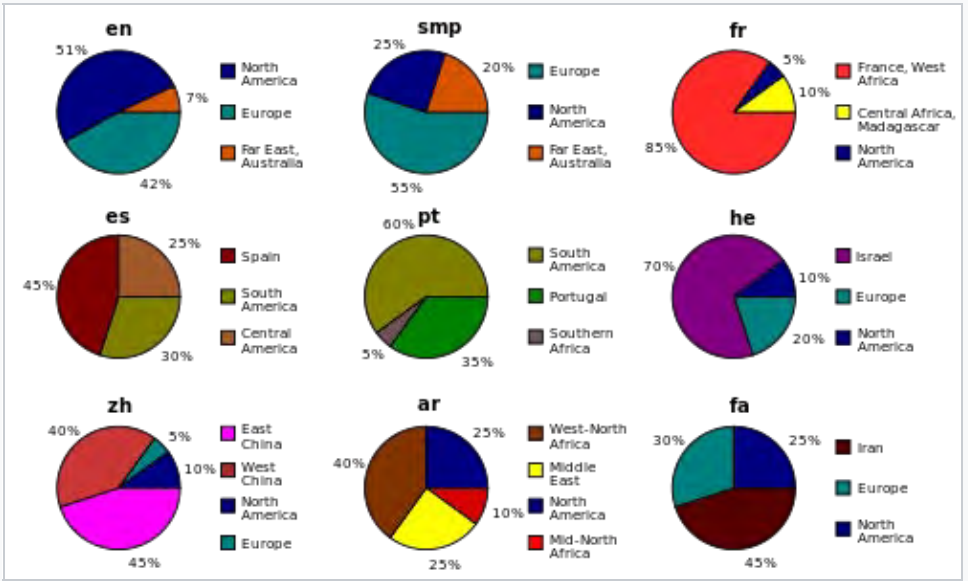


Arabic 455,997

**The unit for the numbers in bars is articles.** Since Wikipedia is based on the Web and therefore worldwide, contributors to the same language edition may use different dialects or may come from different countries (as is the case for the English edition). These differences may lead to some conflicts over spelling differences (e.g. *colour* versus *color*)[133] or points of view.[134]

Though the various language editions are held to global policies such as "neutral point of view", they diverge on some points of policy and practice, most notably on whether images that are not licensed freely may be used under a claim of fair use.[135][136][137]

Jimmy Wales has described Wikipedia as "an effort to create and distribute a free encyclopedia of the highest possible quality to every single person on the planet in their own language".[138] Though each language edition functions more or less independently, some efforts are made to supervise them all. They are coordinated in part by Meta-Wiki, the Wikimedia Foundation's wiki devoted to maintaining all of its projects (Wikipedia and others).[139] For instance, Meta-Wiki provides important statistics on all language editions of Wikipedia,[140] and it maintains a list of articles every Wikipedia should have.[141] The list concerns basic content by subject: biography, history, geography, society, culture, science, technology, and mathematics. As for the rest, it is not rare for articles strongly related to a particular language not to have counterparts in another edition. For example, articles about small towns in the United States might only be available in English, even when they meet notability criteria of other language Wikipedia projects.




Estimation of contributions shares from different regions in the world to different Wikipedia editions

Translated articles represent only a small portion of articles in most editions, in part because fully automated translation of articles is disallowed.[142] Articles available in more than one language may offer "interwiki links", which link to the counterpart articles in other editions.

A study published by *PLOS ONE* in 2012 also estimated the share of contributions to different editions of Wikipedia from different regions of the world. It reported that the proportion of the edits made from North America was 51% for the English Wikipedia, and 25% for the simple English Wikipedia.[143] The Wikimedia Foundation hopes to increase the number of editors in the Global South to thirty-seven percent by 2015.[144]

On March 1, 2014, *The Economist* in an article titled "The Future of Wikipedia" cited a trend analysis concerning data published by Wikimedia stating that: "The number of editors for the English-language version has fallen by a third in seven years."[145] The attrition rate for active editors in English Wikipedia was cited by *The Economist* as substantially in contrast to statistics for Wikipedia in other languages (non-English Wikipedia). *The Economist* reported that the number of contributors with an average of five of more edits per month was relatively constant since 2008 for Wikipedia in other languages at approximately 42,000 editors within narrow seasonal variances of about 2,000 editors up or down. The attrition rates for editors in English Wikipedia, by sharp comparison, were cited as peaking in 2007 at approximately 50,000 editors which has dropped to 30,000 editors as of the start of 2014. At the quoted trend rate, the number of active editors in English Wikipedia has lost approximately 20,000 editors to attrition since 2007, and the documented trend rate indicates the loss of another 20,000 editors by 2021, down to 10,000 active editors on English Wikipedia by 2021 if left unabated.[145] Given that the trend analysis published in *The Economist* presents the number of active editors for Wikipedia in other languages (non-English Wikipedia) as remaining relatively constant and successful in sustaining its numbers at approximately 42,000 active editors, the contrast has pointed to the

effectiveness of Wikipedia in other languages to retain its active editors on a renewable and sustained basis.[145] No comment was made concerning which of the differentiated edit policy standards from Wikipedia in other languages (non-English Wikipedia) would provide a possible alternative to English Wikipedia for effectively ameliorating substantial editor attrition rates on the English language Wikipedia.[146]

# Critical reception

*See also: Academic studies about Wikipedia and Criticism of Wikipedia*

Several Wikipedians have criticized Wikipedia's large and growing regulation, which includes over 50 policies and nearly 150,000 words as of 2014.[147][148]

Critics have stated that Wikipedia exhibits systemic bias. Columnist and journalist Edwin Black criticizes Wikipedia for being a mixture of "truth, half truth, and some falsehoods".[18] Articles in *The Chronicle of Higher Education* and *The Journal of Academic Librarianship* have criticized Wikipedia's Undue Weight policy, concluding that the fact that Wikipedia explicitly is not designed to provide correct information about a subject, but rather focus on all the major viewpoints on the subject and give less attention to minor ones, creates omissions that can lead to false beliefs based on incomplete information.[149][150][151]

Journalists Oliver Kamm and Edwin Black noted how articles are dominated by the loudest and most persistent voices, usually by a group with an "ax to grind" on the topic.[18][152] An article in *Education Next* Journal concluded that as a resource about controversial topics, Wikipedia is notoriously subject to manipulation and spin.[19]

In 2006, the *Wikipedia Watch* criticism website listed dozens of examples of plagiarism in the English Wikipedia.[153]

## Accuracy of content

*Main article: Reliability of Wikipedia*

Articles for traditional encyclopedias such as *Encyclopædia Britannica* are carefully and deliberately written by experts, lending such encyclopedias a reputation for accuracy.[154] Conversely, Wikipedia is often cited for factual inaccuracies and misrepresentations. However, a peer review in 2005 of forty-two scientific entries on both Wikipedia and *Encyclopædia Britannica* by the science journal *Nature* found few differences in accuracy, and concluded that "the average science entry in Wikipedia contained around four inaccuracies; *Britannica*, about three."[17] Reagle suggested that while the study reflects "a topical strength of Wikipedia contributors" in science articles, "Wikipedia may not have fared so well using a random sampling of articles or on humanities subjects."[155] The findings by *Nature* were disputed by *Encyclopædia Britannica*,[156][157] and in response, *Nature* gave a rebuttal of the points raised by *Britannica*.[158] In addition to the point-for-point disagreement between these two parties, others have examined the sample size and selection method used in the *Nature* effort, and suggested a "flawed study design" (in *Nature*'s manual selection of articles, in part or in whole, for comparison), absence of statistical analysis (e.g., of reported confidence intervals), and a lack of study "statistical power" (i.e., owing to small sample size, 42 or 4 x $10^1$ articles compared, vs >$10^5$ and >$10^6$ set sizes for *Britannica* and the English Wikipedia, respectively).[159]

As a consequence of the open structure, Wikipedia "makes no guarantee of validity" of its content, since no one is ultimately responsible for any claims appearing in it.[160] Concerns have been raised by *PC World* in 2009 regarding the lack of accountability that results from users' anonymity,[161] the insertion of false information,[162] vandalism, and similar problems.

Economist Tyler Cowen wrote: "If I had to guess whether Wikipedia or the median refereed journal article on economics was more likely to be true, after a not so long think I would opt for Wikipedia." He comments that some traditional sources of non-fiction suffer from systemic biases and novel results, in his opinion, are over-reported in journal articles and relevant information is omitted from news reports. However, he also cautions that errors are frequently found on Internet sites, and that academics and experts must be vigilant in correcting them.[163]

Critics argue that Wikipedia's open nature and a lack of proper sources for most of the information makes it [164]

unreliable. Some commentators suggest that Wikipedia may be reliable, but that the reliability of any given article is not clear.[165] Editors of traditional reference works such as the *Encyclopædia Britannica* have questioned the project's utility and status as an encyclopedia.[166]

**External video**

Inside Wikipedia – Attack of the PR Industry, Deutsche Welle, 7:13 mins[167]

Wikipedia's open structure inherently makes it an easy target for Internet trolls, spammers, and various forms of paid advocacy seen as counterproductive to the maintenance of a neutral and verifiable online encyclopedia.[70][168] In response to paid advocacy editing and undisclosed editing issues, Wikipedia was reported in an article by Jeff Elder in *The Wall Street Journal* on June 16, 2014, to have strengthened its rules and laws against undisclosed editing.[169] The article stated that: "Beginning Monday [from date of article], changes in Wikipedia's terms of use will require anyone paid to edit articles to disclose that arrangement. Katherine Maher, the nonprofit Wikimedia Foundation's chief communications officer, said the changes address a sentiment among volunteer editors that, 'we're not an advertising service; we're an encyclopedia.'"[169][170][171][172][173] These issues, among others, had been parodied since the first decade of Wikipedia, notably by Stephen Colbert on *The Colbert Report*.[174]

Most university lecturers discourage students from citing any encyclopedia in academic work, preferring primary sources;[175] some specifically prohibit Wikipedia citations.[176][177] Wales stresses that encyclopedias of any type are not usually appropriate to use as citeable sources, and should not be relied upon as authoritative.[178] Wales once (2006 or earlier) said he receives about ten emails weekly from students saying they got failing grades on papers because they cited Wikipedia; he told the students they got what they deserved. "For God's sake, you're in college; don't cite the encyclopedia", he said.[179]

In February 2007, an article in *The Harvard Crimson* newspaper reported that a few of the professors at Harvard University were including Wikipedia articles in their syllabi, although without realizing the articles might change.[180] In June 2007, former president of the American Library Association Michael Gorman condemned Wikipedia, along with Google,[181] stating that academics who endorse the use of Wikipedia are "the intellectual equivalent of a dietitian who recommends a steady diet of Big Macs with everything".

A Harvard law textbook, *Legal Research in a Nutshell* (2011), cites Wikipedia as a "general source" that "can be a real boon" in "coming up to speed in the law governing a situation" and, "while not authoritative, can provide basic facts as well as leads to more in-depth resources".[182]

## Medical information

*See also: Health information on Wikipedia*

On March 5, 2014, Julie Beck writing for *The Atlantic* magazine in an article titled "Doctors' #1 Source for Healthcare Information: Wikipedia", stated that "Fifty percent of physicians look up conditions on the (Wikipedia) site, and some are editing articles themselves to improve the quality of available information."[183] Beck continued to detail in this article new programs of Dr. Amin Azzam at the University of San Francisco to offer medical school courses to medical students for learning to edit and improve Wikipedia articles on health-related issues, as well as internal quality control programs within Wikipedia organized by Dr. James Heilman to improve a group of 200 health-related articles of central medical importance up to Wikipedia's highest standard of articles using its Featured Article and Good Article peer review evaluation process.[183] In a May 7, 2014, follow-up article in *The Atlantic* titled "Can Wikipedia Ever Be a Definitive Medical Text?", Julie Beck quotes Wikiproject Medicine's Dr. James Heilman as stating: "Just because a reference is peer-reviewed doesn't mean it's a high-quality reference."[184] Beck added that: "Wikipedia has its own peer review process before articles can be classified as 'good' or 'featured.' Heilman, who has participated in that process before, says 'less than 1 percent' of Wikipedia's medical articles have passed.[184]

## Quality of writing

In 2008, researchers at Carnegie Mellon University found that the quality of a Wikipedia article would suffer rather than gain from adding more writers when the article lacked appropriate explicit or implicit coordination.[185] For instance, when contributors rewrite small portions of an entry rather than making full-length revisions, high- and low-quality content may be intermingled within an entry. Roy Rosenzweig, a

history professor, stated that *American National Biography Online* outperformed Wikipedia in terms of its "clear and engaging prose", which, he said, was an important aspect of good historical writing.[186] Contrasting Wikipedia's treatment of Abraham Lincoln to that of Civil War historian James McPherson in *American National Biography Online*, he said that both were essentially accurate and covered the major episodes in Lincoln's life, but praised "McPherson's richer contextualization [...] his artful use of quotations to capture Lincoln's voice [...] and [...] his ability to convey a profound message in a handful of words." By contrast, he gives an example of Wikipedia's prose that he finds "both verbose and dull". Rosenzweig also criticized the "waffling—encouraged by the npov policy—[which] means that it is hard to discern any overall interpretive stance in Wikipedia history". By example, he quoted the conclusion of Wikipedia's article on William Clarke Quantrill. While generally praising the article, he pointed out its "waffling" conclusion: "Some historians [...] remember him as an opportunistic, bloodthirsty outlaw, while others continue to view him as a daring soldier and local folk hero."[186]

Other critics have made similar charges that, even if Wikipedia articles are factually accurate, they are often written in a poor, almost unreadable style. Frequent Wikipedia critic Andrew Orlowski commented: "Even when a Wikipedia entry is 100 per cent factually correct, and those facts have been carefully chosen, it all too often reads as if it has been translated from one language to another then into to a third, passing an illiterate translator at each stage."[187] A study of articles on cancer was undertaken in 2010 by Yaacov Lawrence of the Kimmel Cancer Center at Thomas Jefferson University limited to those Wikipedia articles which could be found in the *Physician Data Query* and excluding Wikipedia articles written at the "start" class or the "stub" class level. Lawrence found the articles accurate but not very readable, and thought that "Wikipedia's lack of readability (to non-college readers) may reflect its varied origins and haphazard editing".[188] *The Economist* argued that better-written articles tend to be more reliable: "inelegant or ranting prose usually reflects muddled thoughts and incomplete information".[189]

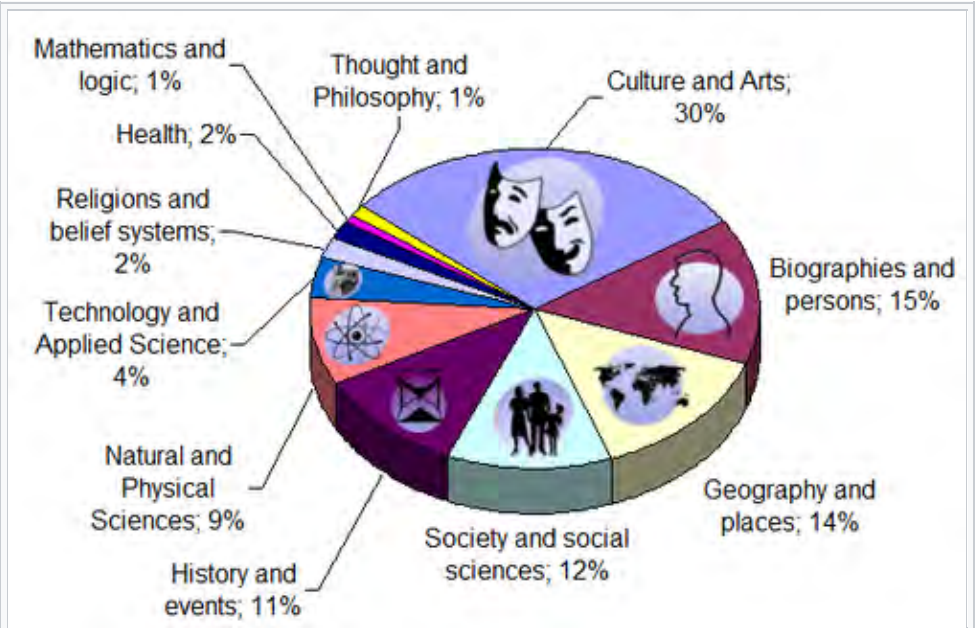
## Coverage of topics and systemic bias

*See also: Notability in the English Wikipedia and Criticism of Wikipedia § Systemic bias in coverage*

Wikipedia seeks to create a summary of all human knowledge in the form of an online encyclopedia, with each topic covered encyclopedically in one article. Since it has terabytes of disk space, it can have far more topics than can be covered by any printed encyclopedia.[190] The exact degree and manner of coverage on Wikipedia is under constant review by its editors, and disagreements are not uncommon (see deletionism and inclusionism).[191][192] Wikipedia contains materials that some people may find objectionable, offensive, or pornographic because Wikipedia is not censored. The policy has sometimes proved controversial: in 2008, Wikipedia rejected an online petition against the inclusion of images of Muhammad in the English edition of its Muhammad article, citing this policy. The presence of politically, religiously, and pornographically sensitive materials in Wikipedia has led to the censorship of Wikipedia by national authorities in China,[193] Pakistan,[194] and the United Kingdom,[195] among other countries.

A 2008 study conducted by researchers at Carnegie Mellon University and Palo Alto Research Center gave a distribution of topics as well as growth (from July 2006 to January 2008) in each field:[196]

- Culture and the arts: 30% (210%)
- Biographies and persons: 15% (97%)
- Geography and places: 14% (52%)
- Society and social sciences: 12% (83%)
- History and events: 11% (143%)
- Natural and physical sciences: 9% (213%)
- Technology and the applied sciences: 4% (−6%)
- Religions and belief systems: 2% (38%)
- Health: 2% (42%)



- Mathematics and logic: 1% (146%)
- Thought and philosophy: 1% (160%)

Pie chart of Wikipedia content by subject as of January 2008[196]

These numbers refer only to the quantity of articles: it is possible for one topic to contain a large number of short articles and another to contain a small number of large ones. Through its "Wikipedia Loves Libraries" program, Wikipedia has partnered with major public libraries such as the New York Public Library for the Performing Arts to expand its coverage of underrepresented subjects and articles.[197]

A 2011 study conducted by researchers at the University of Minnesota indicated that male and female editors focus on different coverage topics. There was a greater concentration of females in the People and Arts category, while males focus more on Geography and Science.[198]

## Coverage of topics and selection bias

Research conducted by Mark Graham of the Oxford Internet Institute in 2009 indicated that the geographic distribution of article topics is highly uneven. Africa is most underrepresented.[199]

An editorial in *The Guardian* in 2014 noted that women porn stars are better covered than women writers as a further example.[200]

## Systemic bias

When multiple editors contribute to one topic or set of topics, systemic bias may arise, due to the demographic backgrounds of the editors. In 2011, Wales noted that the unevenness of coverage is a reflection of the demography of the editors, which predominantly consists of young males with high education levels in the developed world (cf. previously).[47] The October 22, 2013 essay by Tom Simonite in MIT's *Technology Review* titled "The Decline of Wikipedia" discussed the effect of systemic bias and policy creep on the downward trend in the number of editors.[48]

Systemic bias on Wikipedia may follow that of culture generally, for example favoring certain nationalities, ethnicities or majority religions.[201] It may more specifically follow the biases of Internet culture, inclining to being young, male, English-speaking, educated, technologically aware, and wealthy enough to spare time for editing. Biases of its own may include over-emphasis on topics such as pop culture, technology, and current events.[201]

Taha Yasseri of the University of Oxford, in 2013, studied the statistical trends of systemic bias at Wikipedia introduced by editing conflicts and their resolution.[202][203] His research examined the counterproductive work behavior of edit warring. Yasseri contended that simple reverts or "undo" operations were not the most significant measure of counterproductive behavior at Wikipedia and relied instead on the statistical measurement of detecting "reverting/reverted pairs" or "mutually reverting edit pairs". Such a "mutually reverting edit pair" is defined where one editor reverts the edit of another editor who then, in sequence, returns to revert the first editor in the "mutually reverting edit pairs". The results were tabulated for several language versions of Wikipedia. The English Wikipedia's three largest conflict rates belonged to the articles *George W. Bush*, *Anarchism* and *Muhammad*.[203] By comparison, for the German Wikipedia, the three largest conflict rates at the time of the Oxford study were for the articles covering (i) *Croatia*, (ii) *Scientology* and (iii) *9/11 conspiracy theories*.[203]

## Identifying the filter-bubble problem

Dimitra Kessenides, writing for Bloomberg News Weekly, identified the 'filter-bubble' problem as a recurrent and long-standing issue at Wikipedia.[204] As Kessenides states: "If the only way to get an article about the developing world published on Wikipedia was to know a former board member, it was hard to imagine how a random editor in Johannesburg or Bangalore would have any hope... This so-called filter-bubble problem, coined by Eli Pariser, co-founder of the viral video site Upworthy, is the idea that the internet can contribute to the insularity of certain communities. Filter bubbles have been blamed for the spread of misinformation during the 2016 presidential election and for the failure of pundits in the U.K. to anticipate Brexit... Wikipedia's filter-bubble problem is a particularly acute threat for an organization whose stated mission is 'to empower and engage people around the world.'"[204]

## Explicit content

*See also: Internet Watch Foundation and Wikipedia and Reporting of child pornography images on Wikimedia Commons*

Wikipedia has been criticized for allowing information of graphic content. Articles depicting arguably objectionable content (such as *Feces*, *Cadaver*, *Human penis*, *Vulva*, and *Nudity*) contain graphic pictures and detailed information easily available to anyone with access to the internet, including children.

> Problem? What problem? So, you didn't know that Wikipedia has a porn problem?
>
> — Larry Sanger, [205]

The site also includes sexual content such as images and videos of masturbation and ejaculation, photographs of nude children, illustrations of zoophilia, and photos from hardcore pornographic films in its articles.

The Wikipedia article about *Virgin Killer*—a 1976 album from German heavy metal band Scorpions—features a picture of the album's original cover, which depicts a naked prepubescent girl. The original release cover caused controversy and was replaced in some countries. In December 2008, access to the Wikipedia article *Virgin Killer* was blocked for four days by most Internet service providers in the United Kingdom after it was reported by a member of the public as child pornography,[206] to the Internet Watch Foundation (IWF), which issues a stop list to Internet service providers. IWF, a non-profit, non-government-affiliated organization, later criticized the inclusion of the picture as "distasteful".[207]

In April 2010, Sanger wrote a letter to the Federal Bureau of Investigation, outlining his concerns that two categories of images on Wikimedia Commons contained child pornography, and were in violation of US federal obscenity law.[208] Sanger later clarified that the images, which were related to pedophilia and one about lolicon, were not of real children, but said that they constituted "obscene visual representations of the sexual abuse of children", under the PROTECT Act of 2003.[209] That law bans photographic child pornography and cartoon images and drawings of children that are obscene under American law.[209] Sanger also expressed concerns about access to the images on Wikipedia in schools.[210] Wikimedia Foundation spokesman Jay Walsh strongly rejected Sanger's accusation,[211] saying that Wikipedia did not have "material we would deem to be illegal. If we did, we would remove it."[211] Following the complaint by Sanger, Wales deleted sexual images without consulting the community. After some editors who volunteer to maintain the site argued that the decision to delete had been made hastily, Wales voluntarily gave up some of the powers he had held up to that time as part of his co-founder status. He wrote in a message to the Wikimedia Foundation mailing-list that this action was "in the interest of encouraging this discussion to be about real philosophical/content issues, rather than be about me and how quickly I acted".[212] Critics, including Wikipediocracy, noticed that many of the pornographic images deleted from Wikipedia since 2010 have reappeared.[213]

## Privacy

One privacy concern in the case of Wikipedia is the right of a private citizen to remain a "private citizen" rather than a "public figure" in the eyes of the law.[214][notes 8] It is a battle between the right to be anonymous in cyberspace and the right to be anonymous in real life ("meatspace"). A particular problem occurs in the case of an individual who is relatively unimportant and for whom there exists a Wikipedia page against her or his wishes.

In January 2006, a German court ordered the German Wikipedia shut down within Germany because it stated the full name of Boris Floricic, aka "Tron", a deceased hacker. On February 9, 2006, the injunction against Wikimedia Deutschland was overturned, with the court rejecting the notion that Tron's right to privacy or that of his parents was being violated.[215]

Wikipedia has a "Volunteer Response Team" that uses the OTRS system to handle queries without having to reveal the identities of the involved parties. This is used, for example, in confirming the permission for using individual images and other media in the project.[216]

## Sexism

Wikipedia has been described as harboring a battleground culture of sexism and harassment.[217][218] The perceived toxic attitudes and tolerance of violent and abusive language are also reasons put forth for the

gender gap in Wikipedia editors.[219] In 2014, a female editor who requested a separate space on Wikipedia to discuss improving civility had her proposal referred to by a male editor using the words "the easiest way to avoid being called a cunt is not to act like one."[220]

# Operation

A group of Wikipedia editors may form a WikiProject to focus their work on a specific topic area, using its associated discussion page to coordinate changes across multiple articles.[221]

## Wikimedia Foundation and Wikimedia movement affiliates

*Main article: Wikimedia Foundation*

Wikimedia Foundation logo

Wikipedia is hosted and funded by the Wikimedia Foundation, a non-profit organization which also operates Wikipedia-related projects such as Wiktionary and Wikibooks. The foundation relies on public contributions and grants to fund its mission.[222] The foundation's 2013 IRS Form 990 shows revenue of $39.7 million and expenses of almost $29 million, with assets of $37.2 million and liabilities of about $2.3 million.[223]

In May 2014, Wikimedia Foundation named Lila Tretikov as its new executive director, taking over for Sue Gardner.[224] The *Wall Street Journal* reported on May 1, 2014, that Tretikov's information technology background from her years at University of California offers Wikipedia an opportunity to develop in more concentrated directions guided by her often repeated position statement that, "Information, like air, wants to be free."[225][226] The same *Wall Street Journal* article reported these directions of development according to an interview with spokesman Jay Walsh of Wikimedia, who "said Tretikov would address that issue (paid advocacy) as a priority. 'We are really pushing toward more transparency... We are reinforcing that paid advocacy is not welcome.' Initiatives to involve greater diversity of contributors, better mobile support of Wikipedia, new geo-location tools to find local content more easily, and more tools for users in the second and third world are also priorities, Walsh said."[225]

Following the departure of Tretikov from Wikipedia due to issues concerning the use of the "superprotection" feature which some language versions of Wikipedia have adopted, Katherine Maher became the third executive director the Wikimedia Foundation in June 2016.[227] Maher has stated that one of her priorities would be the issue of editor harassment endemic to Wikipedia as identified by the Wikipedia board in December. Maher stated regarding the harassment issue that: "It establishes a sense within the community that this is a priority... (and that correction requires that) it has to be more than words."[228]

Wikipedia is also supported by many organizations and groups that are affiliated with the Wikimedia Foundation but independently-run, called Wikimedia movement affiliates. These include Wikimedia chapters (which are national or sub-national organizations, such as Wikimedia Deutschland and Wikimédia France), thematic organizations (such as Amical Wikimedia for the Catalan language community), and user groups. These affiliates participate in the promotion, development, and funding of Wikipedia.

## Software operations and support

*See also: MediaWiki*

The operation of Wikipedia depends on MediaWiki, a custom-made, free and open source wiki software platform written in PHP and built upon the MySQL database system.[229] The software incorporates programming features such as a macro language, variables, a transclusion system for templates, and URL redirection. MediaWiki is licensed under the GNU General Public License and it is used by all Wikimedia projects, as well as many other wiki projects. Originally, Wikipedia ran on UseModWiki written in Perl by Clifford Adams (Phase I), which initially required CamelCase for article hyperlinks; the present double bracket style was incorporated later. Starting in January 2002 (Phase II), Wikipedia began running on a PHP wiki engine with a MySQL database; this software was custom-made for Wikipedia by Magnus Manske. The Phase

II software was repeatedly modified to accommodate the exponentially increasing demand. In July 2002 (Phase III), Wikipedia shifted to the third-generation software, MediaWiki, originally written by Lee Daniel Crocker.

Several MediaWiki extensions are installed[230] to extend the functionality of the MediaWiki software.

In April 2005, a Lucene extension[231][232] was added to MediaWiki's built-in search and Wikipedia switched from MySQL to Lucene for searching. The site currently uses Lucene Search 2.1,[233][*needs update*] which is written in Java and based on Lucene library 2.3.[234]

In July 2013, after extensive beta testing, a WYSIWYG (What You See Is What You Get) extension, VisualEditor, was opened to public use.[235][236][237][238] It was met with much rejection and criticism, and was described as "slow and buggy".[239] The feature was turned off afterward.

## Automated editing

Computer programs called bots have been used widely to perform simple and repetitive tasks, such as correcting common misspellings and stylistic issues, or to start articles such as geography entries in a standard format from statistical data.[240][241][242] One controversial contributor massively creating articles with his bot was reported to create up to ten thousand articles on the Swedish Wikipedia on certain days.[243] There are also some bots designed to automatically warn editors making common editing errors (such as unmatched quotes or unmatched parenthesis).[244] Edits misidentified by a bot as the work of a banned editor can be restored by other editors. An anti-vandal bot tries to detect and revert vandalism quickly and automatically.[241] Bots can also report edits from particular accounts or IP address ranges, as was done at the time of the MH17 jet downing incident in July 2014.[245] Bots on Wikipedia must be approved prior to activation.[246]

According to Andrew Lih, the current expansion of Wikipedia to millions of articles would be difficult to envision without the use of such bots.[247]

## Wikiprojects, and assessments of articles' importance and quality

*Main article: WikiProject*

A "WikiProject" is a group of contributors who want to work together as a team to improve Wikipedia. These groups often focus on a specific topic area (for example, women's history), a specific location or a specific kind of task (for example, checking newly created pages). The English Wikipedia currently has over 2,000 WikiProjects and activity varies.[248]

In 2007, in preparation for producing a print version, the English Wikipedia introduced an assessment scale of the quality of articles.[249] Articles are rated by Wikiprojects. The range of quality classes begins with "Stub" (very short pages), followed by "Start", "C" and "B" (in increasing order of quality). Community peer review is needed for the article to enter one of the highest quality classes: either "A", "good article" or the highest, "featured article". Of the about 4.4 million articles and lists assessed as of March 2015, a little more than 5000 (0.12%) are featured articles, and a little less than 2000 (0.04%) are featured lists. One featured article per day, as selected by editors, appears on the main page of Wikipedia.[250][251]

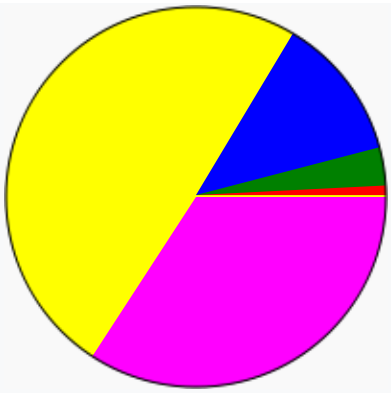
The articles can also be rated as per "importance" as judged by a Wikiproject. Currently, there are 5 importance categories: "low", "mid", "high", "top", and "???" for unclassified/unsure level. For a particular article, different Wikiprojects may assign different importance levels.

The Wikipedia Version 1.0 Editorial Team has developed a table (shown below) that displays data of all rated articles by quality and importance, on the English Wikipedia. **If an article or list receives different ratings by two or more Wikiprojects, then the highest rating is used in the table, pie-charts, and bar-chart.** The software regularly auto-updates the data.

Researcher Giacomo Poderi found that articles tend to reach featured status via the intensive work of a few editors.[252] A 2010 study found unevenness in quality among featured articles and concluded that the community process is ineffective in assessing the quality of articles.[253]

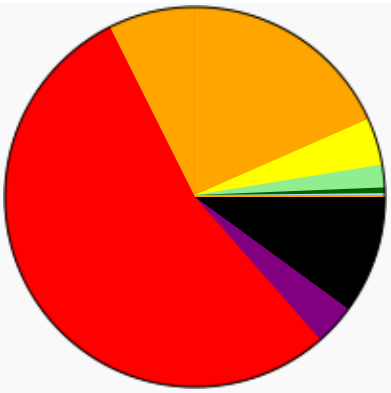
| **All rated articles by quality** |  |
|---|---|

| Quality | Top | High | Mid | Imp | Tota |
|---|---|---|---|---|---|
| FA | 1,171 | 1,800 | 1,700 | | 5, |
| FL | 141 | 561 | 655 | | 2, |
| A | 220 | 424 | 578 | | 1, |
| GA | 2,077 | 4,743 | 9,249 | | 27, |
| B | 12,001 | 22,770 | 34,814 | | 10, |
| C | 10,208 | 29,424 | 65,651 | | 38, |
| Start | 17,179 | 75,511 | 304,019 | | 53, |
| Stub | 4,229 | 30,906 | 225,394 | | 42, |
| List | 2,996 | 11,171 | 34,005 | | 01, |
| Assessed | 50,222 | 177,310 | 676,065 | | 95, |
| Unassessed | 140 | 408 | 1,794 | | 56, |
| **Total** | **50,362** | **177,718** | **677,859** | **2,** | **51,** |



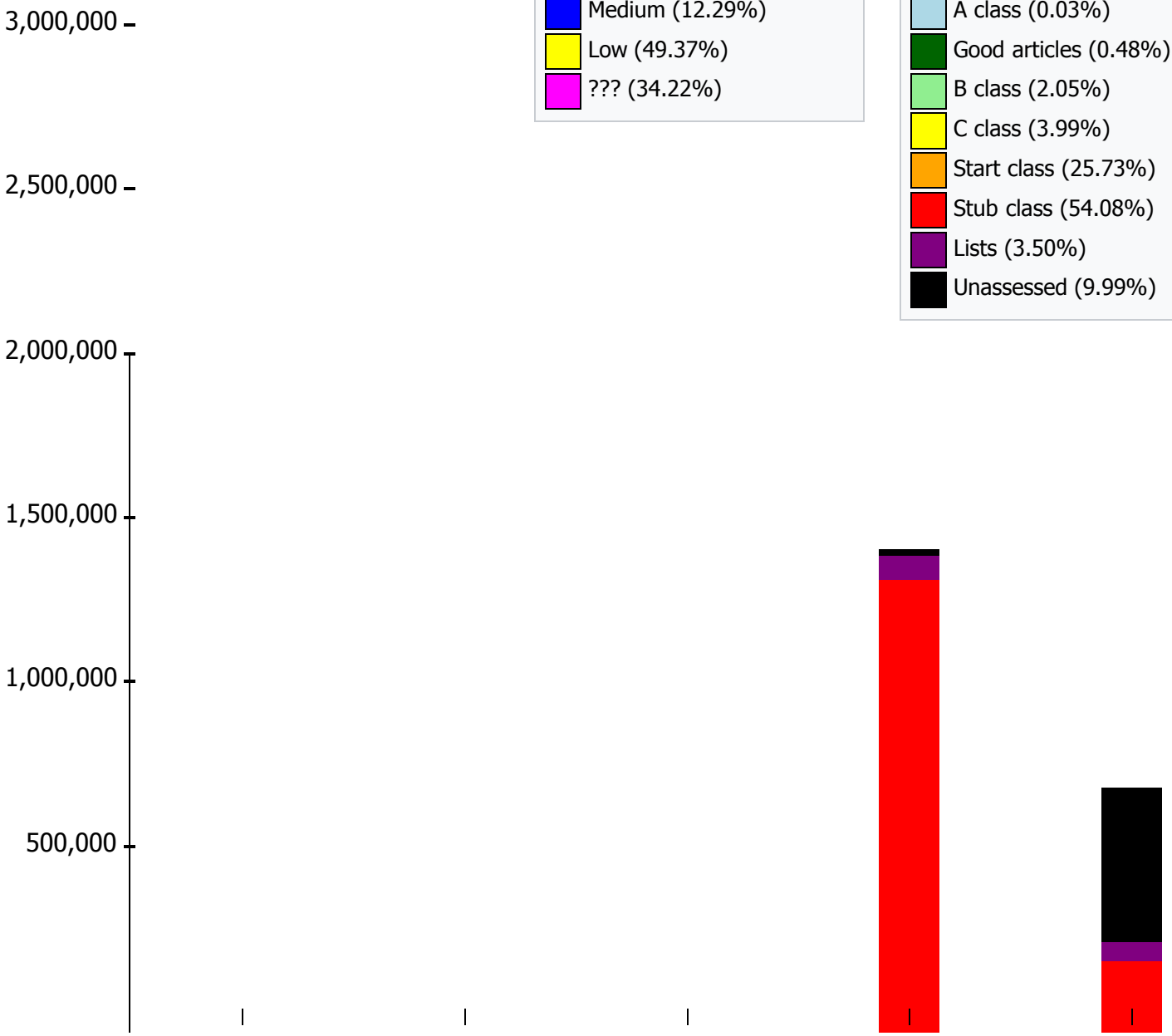
**Importance-wise distribution of over 4.8 million articles and lists on the English Wikipedia, as of 5 April 2015**[254]

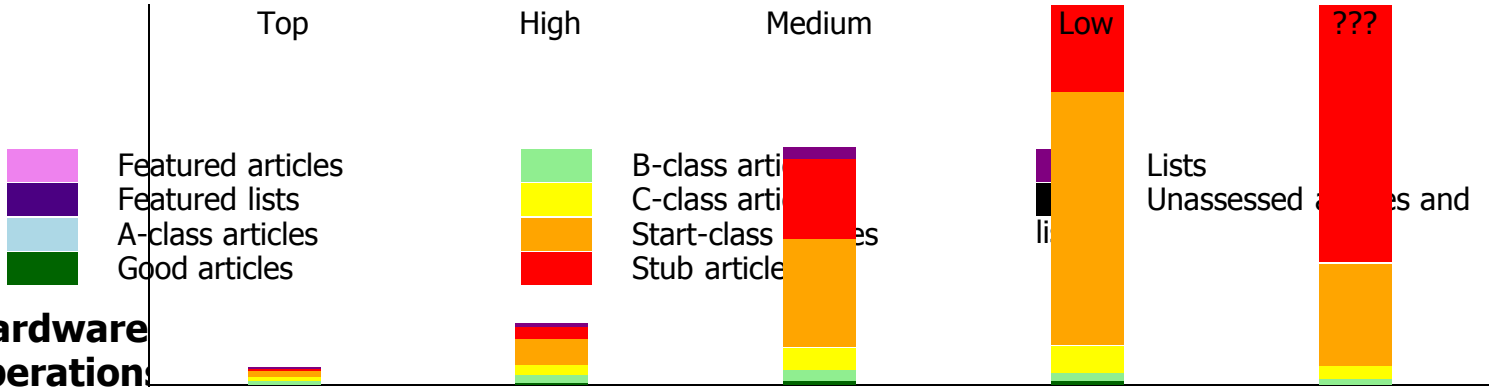
- Top (0.91%)
- High (3.21%)
- Medium (12.29%)
- Low (49.37%)
- ??? (34.22%)



**Quality-wise distribution of over 4.8 million articles and lists on the English Wikipedia, as of 3 April 2015**[254]

- Featured articles (0.11%)
- Featured lists (0.04%)
- A class (0.03%)
- Good articles (0.48%)
- B class (2.05%)
- C class (3.99%)
- Start class (25.73%)
- Stub class (54.08%)
- Lists (3.50%)
- Unassessed (9.99%)

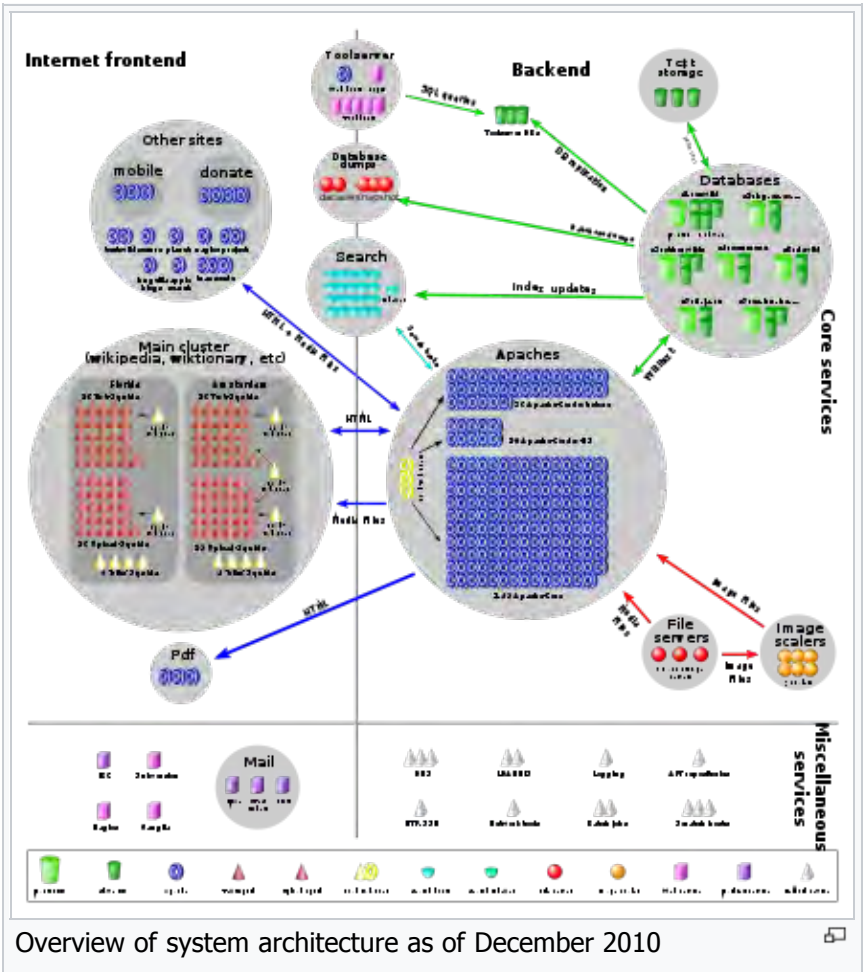





## Hardware operations and support

*See also: Wikimedia Foundation § Hardware*

Wikipedia receives between 25,000 and 60,000 page requests per second, depending on time of day.[255] As of 2008 page requests are first passed to a front-end layer of Squid caching servers.[256][*needs update*] Further statistics, based on a publicly available 3-month Wikipedia access trace, are available.[257] Requests that cannot be served from the Squid cache are sent to load-balancing servers running the Linux Virtual Server software, which in turn pass them to one of the Apache web servers for page rendering from the database. The web servers deliver pages as requested, performing page rendering for all the language editions of Wikipedia. To increase speed further, rendered pages are cached in a distributed memory cache until invalidated, allowing page rendering to be skipped entirely for most common page accesses.




Overview of system architecture as of December 2010

Wikipedia currently runs on dedicated clusters of Linux servers (mainly Ubuntu).[258][259] As of December 2009, there were 300 in Florida and 44 in Amsterdam.[260] By January 22, 2013, Wikipedia had migrated its primary data center to an Equinix facility in Ashburn, Virginia.[261][262]

## Internal research and operational development

In accordance with growing amounts of incoming donations exceeding seven digits in 2013 as recently reported,[48] the Foundation has reached a threshold of assets which qualify its consideration under the principles of industrial organization economics to indicate the need for the re-investment of donations into the internal research and development of the Foundation.[263] Two of the recent projects of such internal research and development have been the creation of a Visual Editor and a largely under-utilized "Thank" tab which were developed for the purpose of ameliorating issues of editor attrition, which have met with limited success.[48][239] The estimates for reinvestment by industrial organizations into internal research and development was studied by Adam Jaffe, who recorded that the range of 4% to 25% annually was to be recommended, with high end technology requiring the higher level of support for internal reinvestment.[264] At the 2013 level of contributions for Wikimedia presently documented as 45 million dollars, the computed budget level recommended by Jaffe and Caballero for reinvestment into internal research and development is between 1.8 million and 11.3 million dollars annually.[264] In 2016, the level of contributions were reported by Blomberg News as being at $77 million annually, updating the Jaffe estimates for the higher level of support to between 3.08 million and 19.2 million dollars annually.[264]

## Internal news publications

Community-produced news publications include the English Wikipedia's *The Signpost*, founded in 2005 by Michael Snow, an attorney, Wikipedia administrator and former chair of the Wikimedia Foundation board of trustees.[265] It covers news and events from the site, as well as major events from other Wikimedia projects, such as Wikimedia Commons. Similar publications are the German-language *Kurier*, and the Portuguese-language *Correio da Wikipédia*. Other past and present community news publications on English Wikipedia include the "Wikiworld" web comic, the *Wikipedia Weekly* podcast, and newsletters of specific WikiProjects like *The Bugle* from WikiProject Military History and the monthly newsletter from The Guild of Copy Editors. There are also a number of publications from the Wikimedia Foundation and multilingual publications such as the Wikimedia Blog and *This Month in Education*.

# Access to content

## Content licensing

When the project was started in 2001, all text in Wikipedia was covered by the GNU Free Documentation License (GFDL), a copyleft license permitting the redistribution, creation of derivative works, and commercial use of content while authors retain copyright of their work.[266] The GFDL was created for software manuals that come with free software programs licensed under the GPL. This made it a poor choice for a general reference work: for example, the GFDL requires the reprints of materials from Wikipedia to come with a full copy of the GFDL text. In December 2002, the Creative Commons license was released: it was specifically designed for creative works in general, not just for software manuals. The license gained popularity among bloggers and others distributing creative works on the Web. The Wikipedia project sought the switch to the Creative Commons.[267] Because the two licenses, GFDL and Creative Commons, were incompatible, in November 2008, following the request of the project, the Free Software Foundation (FSF) released a new version of the GFDL designed specifically to allow Wikipedia to relicense its content to CC BY-SA by August 1, 2009. (A new version of the GFDL automatically covers Wikipedia contents.) In April 2009, Wikipedia and its sister projects held a community-wide referendum which decided the switch in June 2009.[268][269][270][271]

The handling of media files (e.g. image files) varies across language editions. Some language editions, such as the English Wikipedia, include non-free image files under fair use doctrine, while the others have opted not to, in part because of the lack of fair use doctrines in their home countries (e.g. in Japanese copyright law). Media files covered by free content licenses (e.g. Creative Commons' CC BY-SA) are shared across language editions via Wikimedia Commons repository, a project operated by the Wikimedia Foundation. Wikipedia's accommodation of varying international copyright laws regarding images has led some to observe that its photographic coverage of topics lags behind the quality of the encyclopedic text.[272]

The Wikimedia Foundation is not a licensor of content, but merely a hosting service for the contributors (and [273][274]

licensors) of the Wikipedia. This position has been successfully defended in court.

## Methods of access

Because Wikipedia content is distributed under an open license, anyone can reuse or re-distribute it at no charge. The content of Wikipedia has been published in many forms, both online and offline, outside of the Wikipedia website.

- **Websites** – Thousands of "mirror sites" exist that republish content from Wikipedia: two prominent ones, that also include content from other reference sources, are Reference.com and Answers.com. Another example is Wapedia, which began to display Wikipedia content in a mobile-device-friendly format before Wikipedia itself did.
- **Mobile apps** – A variety of mobile apps provide access to Wikipedia on hand-held devices, including both Android and iOS devices (see Wikipedia apps). (See also Mobile access.)
- **Search engines** – Some web search engines make special use of Wikipedia content when displaying search results: examples include Bing (via technology gained from Powerset)[275] and DuckDuckGo.
- **Compact discs, DVDs** – Collections of Wikipedia articles have been published on optical discs. An English version, 2006 Wikipedia CD Selection, contained about 2,000 articles.[276][277] The Polish-language version contains nearly 240,000 articles.[278] There are German- and Spanish-language versions as well.[279][280] Also, "Wikipedia for Schools", the Wikipedia series of CDs / DVDs produced by Wikipedians and SOS Children, is a free, hand-checked, non-commercial selection from Wikipedia targeted around the UK National Curriculum and intended to be useful for much of the English-speaking world.[281] The project is available online; an equivalent print encyclopedia would require roughly 20 volumes.
- **Printed books** – There are efforts to put a select subset of Wikipedia's articles into printed book form.[282][283] Since 2009, tens of thousands of print-on-demand books that reproduced English, German, Russian and French Wikipedia articles have been produced by the American company Books LLC and by three Mauritian subsidiaries of the German publisher VDM.[284]
- **Semantic Web** – The website DBpedia, begun in 2007, extracts data from the infoboxes and category declarations of the English-language Wikipedia. Wikimedia has created the Wikidata project with a similar objective of storing the basic facts from each page of Wikipedia and the other WMF wikis and make it available in a queriable semantic format, RDF. This is still under development. As of Feb 2014 it has 15,000,000 items and 1,000 properties for describing them.

Obtaining the full contents of Wikipedia for reuse presents challenges, since direct cloning via a web crawler is discouraged.[285] Wikipedia publishes "dumps" of its contents, but these are text-only; as of 2007 there was no dump available of Wikipedia's images.[286]

Several languages of Wikipedia also maintain a reference desk, where volunteers answer questions from the general public. According to a study by Pnina Shachaf in the Journal of Documentation, the quality of the Wikipedia reference desk is comparable to a standard library reference desk, with an accuracy of 55%.[287]

## Mobile access

*See also: Help:Mobile access*

Wikipedia's original medium was for users to read and edit content using any standard web browser through a fixed Internet connection. Although Wikipedia content has been accessible through the mobile web since July 2013, *The New York Times* on February 9, 2014, quoted Erik Möller, deputy director of the Wikimedia Foundation, stating that the transition of internet traffic from desktops to mobile devices was significant and a cause for concern and worry.[16] The article in *The New York Times* reported the comparison statistics for mobile edits stating that, "Only 20 percent of the readership of the English-language Wikipedia comes via mobile devices, a figure substantially lower than the percentage of mobile traffic for other media sites, many of which approach 50 percent. And the shift to mobile editing has lagged even more."[16] *The New York Times* reports that Möller has assigned "a team of 10 software developers focused on mobile", out of a total of approximately 200 employees working at the Wikimedia Foundation. One principal concern cited by *The New York Times* for the

The mobile version of the English Wikipedia's main page

"worry" is for Wikipedia to effectively address attrition issues with the number of editors which the online encyclopedia attracts to edit and maintain its content in a mobile access environment.[16]

*Bloomberg BusinessWeek* reported in July 2014 that Google's Android mobile apps have dominated the largest share of global smartphone shipments for 2013 with 78.6% of market share over their next closest competitor in iOS with 15.2% of the market.[288] At the time of the Tretikov appointment and her posted web interview with Sue Gardner in May 2014, Wikimedia representatives made a technical announcement concerning the number of mobile access systems in the market seeking access to Wikipedia. Directly after the posted web interview, the representatives stated that Wikimedia would be applying an all-inclusive approach to accommodate as many mobile access systems as possible in its efforts for expanding general mobile access, including BlackBerry and the Windows Phone system, making market share a secondary issue.[226] The latest version of the Android app for Wikipedia was released on July 23, 2014, to generally positive reviews, scoring over four of a possible five in a poll of approximately 200,000 users downloading from Google.[289] The latest version for iOS was released on April 3, 2013, to similar reviews.[290]

Access to Wikipedia from mobile phones was possible as early as 2004, through the Wireless Application Protocol (WAP), via the Wapedia service. In June 2007 Wikipedia launched en.mobile.wikipedia.org, an official website for wireless devices. In 2009 a newer mobile service was officially released,[291] located at en.m.wikipedia.org, which caters to more advanced mobile devices such as the iPhone, Android-based devices or WebOS-based devices. Several other methods of mobile access to Wikipedia have emerged. Many devices and applications optimize or enhance the display of Wikipedia content for mobile devices, while some also incorporate additional features such as use of Wikipedia metadata (See Wikipedia:Metadata), such as geoinformation.[292][293]

Wikipedia Zero is an initiative of the Wikimedia Foundation to expand the reach of the encyclopedia to the developing countries.[294]

Andrew Lih and Andrew Brown both maintain editing Wikipedia with smart phones is difficult and this discourages new potential contributors. Several years running the number of Wikipedia editors has been falling and Tom Simonite of *MIT Technology Review* claims the bureaucratic structure and rules are a factor in this. Simonite alleges some Wikipedians use the labyrinthine rules and guidelines to dominate others and those editors have a vested interest in keeping the status quo.[48] Lih alleges there is serious disagreement among existing contributors how to resolve this. Lih fears for Wikipedia's long term future while Brown fears problems with Wikipedia will remain and rival encyclopedias will not replace it.[295][296]

# Cultural impact

## Readership

Wikipedia is extremely popular. In February 2014, *The New York Times* reported that Wikipedia is ranked fifth

globally among all websites, stating "With 18 billion page views and nearly 500 million unique visitors a month [...] Wikipedia trails just Yahoo, Facebook, Microsoft and Google, the largest with 1.2 billion unique visitors."[16]

In addition to logistic growth in the number of its articles,[297] Wikipedia has steadily gained status as a general reference website since its inception in 2001.[298] About 50% of search engine traffic to Wikipedia comes from Google,[299] a good portion of which is related to academic research.[300] The number of readers of Wikipedia worldwide reached 365 million at the end of 2009.[301] The Pew Internet and American Life project found that one third of US Internet users consulted Wikipedia.[302] In 2011 *Business Insider* gave Wikipedia a valuation of $4 billion if it ran advertisements.[303]

According to "Wikipedia Readership Survey 2011", the average age of Wikipedia readers is 36, with a rough parity between genders. Almost half of Wikipedia readers visit the site more than five times a month, and a similar number of readers specifically look for Wikipedia in search engine results. About 47% of Wikipedia readers do not realize that Wikipedia is a non-profit organization.[304]

## Cultural significance

*Main article: Wikipedia in culture*

Wikipedia's content has also been used in academic studies, books, conferences, and court cases.[305][306][307] The Parliament of Canada's website refers to Wikipedia's article on same-sex marriage in the "related links" section of its "further reading" list for the Civil Marriage Act.[308] The encyclopedia's assertions are increasingly used as a source by organizations such as the US federal courts and the World Intellectual Property Organization[309] – though mainly for *supporting information* rather than information decisive to a case.[310] Content appearing on Wikipedia has also been cited as a source and referenced in some US intelligence agency reports.[311] In December 2008, the scientific journal *RNA Biology* launched a new section for descriptions of families of RNA molecules and requires authors who contribute to the section to also submit a draft article on the RNA family for publication in Wikipedia.[312]

Wikipedia Monument in Słubice, Poland

Wikipedia has also been used as a source in journalism,[313][314] often without attribution, and several reporters have been dismissed for plagiarizing from Wikipedia.[315][316][317]

In 2006, *Time* magazine recognized Wikipedia's participation (along with YouTube, Reddit, MySpace, and Facebook[318]) in the rapid growth of online collaboration and interaction by millions of people worldwide.

In July 2007 Wikipedia was the focus of a 30-minute documentary on BBC Radio 4[319] which argued that, with increased usage and awareness, the number of references to Wikipedia in popular culture is such that the word is one of a select band of 21st-century nouns that are so familiar (Google, Facebook, YouTube) that they no longer need explanation.

On September 28, 2007, Italian politician Franco Grillini raised a parliamentary question with the minister of cultural resources and activities about the necessity of freedom of panorama. He said that the lack of such freedom forced Wikipedia, "the seventh most consulted website", to forbid all images of modern Italian buildings and art, and claimed this was hugely damaging to tourist revenues.[320]

On September 16, 2007, *The Washington Post* reported that Wikipedia had become a focal point in the 2008 US election campaign, saying: "Type a candidate's name into Google, and among the first results is a Wikipedia page, making those entries arguably as important as any ad in defining a candidate. Already, the presidential entries are being edited, dissected and debated countless times each day."[321] An October 2007 Reuters article, titled "Wikipedia page the latest status symbol", reported the recent phenomenon of how having a Wikipedia article vindicates one's notability.[322]


Play media

Wikipedia, an introduction –

Active participation also has an impact. Law students have been assigned to write Wikipedia articles as an exercise in clear and succinct writing for an uninitiated audience.[323]

A working group led by Peter Stone (formed as a part of the Stanford-based project *One Hundred Year Study on Artificial Intelligence*) in its report called Wikipedia "the best-known example of crowdsourcing... that far exceeds traditionally-compiled information sources, such as encyclopedias and dictionaries, in scale and depth."[324]

## Awards

Wikipedia won two major awards in May 2004.[325] The first was a Golden Nica for Digital Communities of the annual Prix Ars Electronica contest; this came with a €10,000 (£6,588; $12,700) grant and an invitation to present at the PAE Cyberarts Festival in Austria later that year. The second was a Judges' Webby Award for the "community" category.[326] Wikipedia was also nominated for a "Best Practices" Webby award.

In 2007, readers of brandchannel.com voted Wikipedia as the fourth-highest brand ranking, receiving 15% of the votes in answer to the question "Which brand had the most impact on our lives in 2006?"[327]

In September 2008, Wikipedia received Quadriga *A Mission of Enlightenment* award of Werkstatt Deutschland along with Boris Tadić, Eckart Höfling, and Peter Gabriel. The award was presented to Wales by David Weinberger.[328]

In 2015, Wikipedia was awarded both the annual Erasmus Prize, which recognizes exceptional contributions to culture, society or social sciences,[329] and the Spanish Princess of Asturias Award on International Cooperation.[330] Speaking at the Asturian Parliament in Oviedo, the city that hosts the awards ceremony, Jimmy Wales praised the work of the Asturian language Wikipedia users.[331] The night of the ceremony, members of the Wikimedia Foundation held a meeting with Wikipedians from all parts of Spain, including the local Asturian community.

Erasmus Prize 2015

Jimmy Wales receiving the Quadriga *A Mission of Enlightenment* award

Wikipedia team visiting to Parliament of Asturias

Wikipedians meeting after the Asturias awards ceremony

## Satire

*See also: Category:Parodies of Wikipedia.*

Many parodies target Wikipedia's openness and susceptibility to inserted inaccuracies, with characters vandalizing or modifying the online encyclopedia project's articles.

Comedian Stephen Colbert has parodied or referenced Wikipedia on numerous episodes of his show *The Colbert Report* and coined the related term *wikiality*, meaning "together we can create a reality that we all agree on—the reality we just agreed on".[174] Another example can be found in "Wikipedia Celebrates 750 Years of American Independence", a July 2006 front-page article in *The Onion*,[332] as well as the 2010 *The Onion* article "'L.A. Law' Wikipedia Page Viewed 874 Times Today".[333]

In an episode of the television comedy *The Office* U.S., which aired in April 2007, an incompetent office manager (Michael Scott) is shown relying on a hypothetical Wikipedia article for information on negotiation tactics in order to assist him in negotiating lesser pay for an employee.[334] The tactics he used failed, as a joke about the unreliability of Wikipedia and what anyone can do to change its contents. Viewers of the show tried to add the episode's mention of the page as a section of the actual Wikipedia article on negotiation, but this effort was prevented by other users on the article's talk page.[335]

"My Number One Doctor", a 2007 episode of the television show *Scrubs*, played on the perception that Wikipedia is an unreliable reference tool with a scene in which Dr. Perry Cox reacts to a patient who says that

a Wikipedia article indicates that the raw food diet reverses the effects of bone cancer by retorting that the same editor who wrote that article also wrote the *Battlestar Galactica* episode guide.[336]

In 2008, the comedic website *CollegeHumor* produced a video sketch named "Professor Wikipedia", in which the fictitious Professor Wikipedia instructs a class with a medley of unverifiable and occasionally absurd statements.[337]

The *Dilbert* comic strip from May 8, 2009, features a character supporting an improbable claim by saying "Give me ten minutes and then check Wikipedia."[338]

In July 2009, BBC Radio 4 broadcast a comedy series called *Bigipedia*, which was set on a website which was a parody of Wikipedia. Some of the sketches were directly inspired by Wikipedia and its articles.[339]

In 2010, comedian Daniel Tosh encouraged viewers of his show, *Tosh.0*, to visit the show's Wikipedia article and edit it at will. On a later episode, he commented on the edits to the article, most of them offensive, which had been made by the audience and had prompted the article to be locked from editing.[340][341]

On August 23, 2013, the *New Yorker* website published a cartoon with this caption: "Dammit, Manning, have you considered the pronoun war that this is going to start on your Wikipedia page?"[342]

In December 2015, John Julius Norwich stated, in a letter published in *The Times* newspaper, that as an historian he resorted to Wikipedia "at least a dozen times a day", and had never yet caught it out. He described it as "a work of reference as useful as any in existence", with so wide a range that it is almost impossible to find a person, place or thing that it has left uncovered, and that he could never have written his last two books without it.[343][344]

## Sister projects – Wikimedia

*Main article: Wikimedia project*

Wikipedia has also spawned several sister projects, which are also wikis run by the Wikimedia Foundation. These other Wikimedia projects include Wiktionary, a dictionary project launched in December 2002,[345] Wikiquote, a collection of quotations created a week after Wikimedia launched, Wikibooks, a collection of collaboratively written free textbooks and annotated texts, Wikimedia Commons, a site devoted to free-knowledge multimedia, Wikinews, for citizen journalism, and Wikiversity, a project for the creation of free learning materials and the provision of online learning activities.[346] Of these, only Commons has had success comparable to that of Wikipedia. Another sister project of Wikipedia, Wikispecies, is a catalogue of species. In 2012 Wikivoyage, an editable travel guide, and Wikidata, an editable knowledge base, launched.

## Publishing

The most obvious economic effect of Wikipedia has been the death of commercial encyclopedias, especially the printed versions, e.g. *Encyclopaedia Britannica*, which were unable to compete with a product that is essentially free.[347][348][349] Nicholas Carr wrote a 2005 essay, "The amorality of Web 2.0", that criticized websites with user-generated content, like Wikipedia, for possibly leading to professional (and, in his view, superior) content producers' going out of business, because "free trumps quality all the time". Carr wrote: "Implicit in the ecstatic visions of Web 2.0 is the hegemony of the amateur. I for one can't imagine anything more frightening."[350] Others dispute the notion that Wikipedia, or similar efforts, will entirely displace traditional publications. For instance, Chris Anderson, the editor-in-chief of *Wired Magazine*, wrote in *Nature* that the "wisdom of crowds" approach of Wikipedia will not displace top scientific journals, with their rigorous peer review process.[351]

A group of Wikimedians of the Wikimedia DC chapter at the 2013 DC Wikimedia annual meeting standing in front of the *Encyclopædia Britannica (back left)* at the US National Archives

There is also an ongoing debate about the influence of Wikipedia on the biography publishing business. "The worry is that, if you can get all that information from Wikipedia, what's left for biography?" said Kathryn Hughes, professor of life writing at UEA and author of *The Short Life and Long Times of Mrs Beeton* and *George Eliot: the Last Victorian*.[352]

### Scientific use

Wikipedia has seen been widely used as a corpus for linguistic research in computational linguistics, information retrieval and natural language processing. In particular, it commonly serves as a target knowledge base for the entity linking problem, which is then called "wikification",[353] and to the related problem of word sense disambiguation.[354] Methods similar to wikification can in turn be used to find "missing" links in Wikipedia.[355]

In 2015, French researchers Dr José Lages of the University of Franche-Comté in Besançon and Dima Shepelyansky of Paul Sabatier University in Toulouse published a global university ranking based on Wikipedia scholarly citations.[356][357][358] They used PageRank "followed by the number of appearances in the 24 different language editions of Wikipedia (descending order) and the century in which they were founded (ascending order)."[358]

## Related projects

A number of interactive multimedia encyclopedias incorporating entries written by the public existed long before Wikipedia was founded. The first of these was the 1986 BBC Domesday Project, which included text (entered on BBC Micro computers) and photographs from over 1 million contributors in the UK, and covered the geography, art, and culture of the UK. This was the first interactive multimedia encyclopedia (and was also the first major multimedia document connected through internal links), with the majority of articles being accessible through an interactive map of the UK. The user interface and part of the content of the Domesday Project were emulated on a website until 2008.[359]

Several free-content, collaborative encyclopedias were created around the same period as Wikipedia (e.g. Everything2),[360] with many later being merged into the project (e.g. GNE).[361] One of the most successful early online encyclopedias incorporating entries by the public was h2g2, which was created by Douglas Adams in 1999. The h2g2 encyclopedia is relatively light-hearted, focusing on articles which are both witty and informative.

Subsequent collaborative knowledge websites have drawn inspiration from Wikipedia. Some, such as Susning.nu, Enciclopedia Libre, Hudong, and Baidu Baike likewise employ no formal review process, although some like Conservapedia are not as open. Others use more traditional peer review, such as Encyclopedia of Life and the online wiki encyclopedias Scholarpedia and Citizendium. The latter was started by Sanger in an attempt to create a reliable alternative to Wikipedia.[362]

## See also

- Outline of Wikipedia – guide to the subject of *Wikipedia* presented as a tree structured list of its subtopics; for an outline of the contents of *Wikipedia*, see Portal:Contents/Outlines
- Conflict-of-interest editing on Wikipedia
- Democratization of knowledge
- Interpedia, an early proposal for a collaborative Internet encyclopedia
- List of Internet encyclopedias
- Network effect
- Print Wikipedia art project to visualize how big Wikipedia is. In cooperation with Wikimedia foundation.
- QRpedia – multilingual, mobile interface to Wikipedia
- Wikipedia Review


## References

1. ^ Sidener, Jonathan (December 6, 2004). "Everyone's Encyclopedia". *U-T San Diego*. Archived from the original on January 14, 2016. Retrieved October 15, 2006.
2. ^ Roger Chapman. "Top 40 Website Programming Languages". *roadchap.com*. Archived from the original on September 22, 2013. Retrieved September 6, 2011.
3. ^ "Wikipedia founder defends decision to encrypt the site in China". *The Verge*. Retrieved September 19, 2015.
4. ^ Bill Tancer (May 1, 2007). "Look Who's Using Wikipedia". *Time*. Retrieved December 1, 2007. "The sheer volume of content [...] is partly responsible for the site's dominance as an online reference. When compared to the top 3,200

educational reference sites in the US, Wikipedia is No. 1, capturing 24.3% of all visits to the category". Cf. Bill Tancer (Global Manager, Hitwise), "Wikipedia, Search and School Homework" Archived March 25, 2012, at the Wayback Machine., *Hitwise*, March 1, 2007.
5. ^ Alex Woodson (July 8, 2007). "Wikipedia remains go-to site for online news". Reuters. Retrieved December 16, 2007. "Online encyclopedia Wikipedia has added about 20 million unique monthly visitors in the past year, making it the top online news and information destination, according to Nielsen//NetRatings."
6. ^ "comScore MMX Ranks Top 50 US Web Properties for August 2012". comScore. September 12, 2012. Retrieved February 6, 2013.
7. ^ *a b c* "How popular is wikipedia.org?". Alexa Internet. May 22, 2016. Retrieved 2016-09-04.
8. ^ "Wikimedia pornography row deepens as Wales cedes rights – BBC News". BBC. Retrieved 28 June 2016.
9. ^ "The Mysterious Workings of Wikis: Who Owns What?". Ecommercetimes.com. Retrieved 28 June 2016.
10. ^ "Wikimedia Foundation employee ousted over paid editing". Ars Technica. Retrieved 28 June 2016.
11. ^ *a b* Kock, N., Jung, Y., & Syn, T. (2016). Wikipedia and e-Collaboration Research: Opportunities and Challenges Archived September 27, 2016, at the Wayback Machine. International Journal of e-Collaboration (IJeC), 12(2), 1–8.
12. ^ Mike Miliard (March 1, 2008). "Wikipediots: Who Are These Devoted, Even Obsessive Contributors to Wikipedia?". *Salt Lake City Weekly*. Retrieved December 18, 2008.
13. ^ Sidener, Jonathan (October 9, 2006). "Wikipedia family feud rooted in San Diego". The San Diego Union-Tribune. Archived from the original on November 11, 2016. Retrieved May 5, 2009.
14. ^ "Wiki" in the Hawaiian Dictionary, revised and enlarged edition, University of Hawaii Press, 1986
15. ^ "Wikipedia cofounder Jimmy Wales on 60 Minutes". CBS News. Retrieved April 6, 2015.
16. ^ *a b c d e f* Cohen, Noam (February 9, 2014). "Wikipedia vs. the Small Screen". *The New York Times*.
17. ^ *a b* Jim Giles (December 2005). "Internet encyclopedias go head to head". *Nature*. **438** (7070): 900–901. Bibcode:2005Natur.438..900G. doi:10.1038/438900a. PMID 16355180.(subscription required) Note: The study was cited in several news articles; e.g.:
    - "Wikipedia survives research test". BBC News. December 15, 2005.
18. ^ *a b c* Black, Edwin (April 19, 2010) Wikipedia – The Dumbing Down of World Knowledge Archived September 9, 2016, at the Wayback Machine., History News Network Retrieved October 21, 2014
19. ^ *a b* J. Petrilli, Michael (SPRING 2008/Vol.8, No.2) Wikipedia or Wickedpedia? Archived November 21, 2016, at the Wayback Machine., Education Next Retrieved October 22, 2014
20. ^ "The contribution conundrum: Why did Wikipedia succeed while other encyclopedias failed?". *Nieman Lab*. Retrieved 2016-06-05.
21. ^ Richard M. Stallman (June 20, 2007). "The Free Encyclopedia Project". Free Software Foundation. Retrieved January 4, 2008.
22. ^ Jonathan Sidener (December 6, 2004). "Everyone's Encyclopedia". *U-T San Diego*. Archived from the original on October 11, 2007. Retrieved October 15, 2006.
23. ^ Meyers, Peter (September 20, 2001). "Fact-Driven? Collegial? This Site Wants You". *The New York Times*. Retrieved November 22, 2007. "'I can start an article that will consist of one paragraph, and then a real expert will come along and add three paragraphs and clean up my one paragraph,' said Larry Sanger of Las Vegas, who founded Wikipedia with Mr. Wales."
24. ^ *a b c* Sanger, Larry (April 18, 2005). "The Early History of Nupedia and Wikipedia: A Memoir". *Slashdot*. Retrieved December 26, 2008.
25. ^ Sanger, Larry (January 17, 2001). "Wikipedia Is Up!". Archived from the original on May 6, 2001. Retrieved December 26, 2008.
26. ^ "Wikipedia-l: LinkBacks?". Retrieved February 20, 2007.
27. ^ Sanger, Larry (January 10, 2001). "Let's Make a Wiki". Internet Archive. Archived from the original on April 14, 2003. Retrieved December 26, 2008.
28. ^ "Wikipedia: HomePage". Archived from the original on March 31, 2001. Retrieved March 31, 2001.
29. ^ "Wikipedia:Neutral point of view, Wikipedia (January 21, 2007).
30. ^ Finkelstein, Seth (September 25, 2008). "Read me first: Wikipedia isn't about human potential, whatever Wales says". London: *The Guardian*.
31. ^ "Wikipedia, August 8, 2001". Web.archive.bibalex.org. August 8, 2001. Archived from the original on 2001-08-08. Retrieved March 3, 2014.
32. ^ "Wikipedia, September 25, 2001". Web.archive.bibalex.org. Archived from the original on 2001-10-10. Retrieved March 3, 2014.
33. ^ "Multilingual statistics". *Wikipedia*. March 30, 2005. Retrieved December 26, 2008.
34. ^ "Encyclopedias and Dictionaries". *Encyclopædia Britannica*. **18** (15th ed.). 2007. pp. 257–286.
35. ^ "[long] Enciclopedia Libre: msg#00008". *Osdir*. Retrieved December 26, 2008.
36. ^ Clay Shirky (February 28, 2008). *Here Comes Everybody: The Power of Organizing Without Organizations*. The Penguin Press via Amazon Online Reader. p. 273. ISBN 1-59420-153-6. Retrieved December 26, 2008.
37. ^ Bobbie Johnson (August 12, 2009). "Wikipedia approaches its limits". *The Guardian*. London. Retrieved March 31,

2010.
38. ^ Wikipedia:Modelling_Wikipedia_extended_growth
39. ^ *The Singularity is Not Near: Slowing Growth of Wikipedia* (PDF). The International Symposium on Wikis. Orlando, Florida. 2009. Archived from the original (PDF) on May 11, 2011.
40. ^ Evgeny Morozov (November–December 2009). "Edit This Page; Is it the end of Wikipedia". *Boston Review*.
41. ^ Cohen, Noam (March 28, 2009). "Wikipedia – Exploring Fact City". *The New York Times*. Retrieved April 19, 2011.
42. ^ Austin Gibbons, David Vetrano, Susan Biancani (2012). Wikipedia: Nowhere to grow
43. ^ Jenny Kleeman (November 26, 2009). "Wikipedia falling victim to a war of words". *The Guardian*. London. Retrieved March 31, 2010.
44. ^ "Wikipedia: A quantitative analysis". Archived from the original (PDF) on April 3, 2012.
45. ^ Volunteers Log Off as Wikipedia Ages, The Wall Street Journal, November 27, 2009.
46. ^ Barnett, Emma (November 26, 2009). "Wikipedia's Jimmy Wales denies site is 'losing' thousands of volunteer editors". *The Daily Telegraph*. London. Retrieved March 31, 2010.
47. ^ *a b* Kevin Rawlinson (August 8, 2011). "Wikipedia seeks women to balance its 'geeky' editors". *The Independent*. Retrieved April 5, 2012.
48. ^ *a b c d e* Simonite, Tom (October 22, 2013). "The Decline of Wikipedia". *MIT Technology Review*. Retrieved November 30, 2013.
49. ^ "3 Charts That Show How Wikipedia Is Running Out of Admins". *The Atlantic*. July 16, 2012.
50. ^ Ward, Katherine. *New York* Magazine, issue of November 25, 2013, p. 18.
51. ^ "Wikipedia Breaks Into US Top 10 Sites". PCWorld. February 17, 2007.
52. ^ "Wikipedia.org Site Overview". *alexa.com*. Retrieved 2016-12-04.
53. ^ "Wikimedia Traffic Analysis Report – Wikipedia Page Views Per Country". Wikimedia Foundation. Retrieved March 8, 2015.
54. ^ Netburn, Deborah (January 19, 2012). "Wikipedia: SOPA protest led 8 million to look up reps in Congress". *Los Angeles Times*. Retrieved March 6, 2012.
55. ^ "Wikipedia joins blackout protest at US anti-piracy moves". BBC News. January 18, 2012. Retrieved January 19, 2012.
56. ^ "SOPA/Blackoutpage". Wikimedia Foundation. Retrieved January 19, 2012.
57. ^ Jeff Loveland and Joseph Reagle (January 15, 2013). "Wikipedia and encyclopedic production. New Media & Society. Sage Journals". *New Media & Society*. **15** (8): 1294. doi:10.1177/1461444812470428.
58. ^ Rebecca J. Rosen (Jan 30, 2013). "What If the Great Wikipedia 'Revolution' Was Actually a Reversion? • The Atlantic". Retrieved February 9, 2013.
59. ^ *a b c* Varma, Subodh (January 20, 2014). "Google eating into Wikipedia page views?". *The Economic Times*. Times Internet Limited. Retrieved February 10, 2014.
60. ^ *a b* "Wikipedia Statistics (English)". *stats.wikimedia.org*.
61. ^ *a b* Zittrain, Jonathan (2008). *The Future of the Internet and How to Stop It – Chapter 6: The Lessons of Wikipedia*. Yale University Press. ISBN 978-0-300-12487-3. Archived from the original on February 16, 2009. Retrieved December 26, 2008.
62. ^ Registration notes
63. ^ Protection Policy
64. ^ Hafner, Katie (June 17, 2006). "Growing Wikipedia Refines Its 'Anyone Can Edit' Policy". *The New York Times*. Retrieved December 5, 2016.
65. ^ English Wikipedia's protection policy
66. ^ English Wikipedia's full protection policy
67. ^ *a b* Birken, P. (December 14, 2008). "Bericht Gesichtete Versionen". *Wikide-l* (Mailing list) (in German). Wikimedia Foundation. Retrieved February 15, 2009.
68. ^ William Henderson (December 10, 2012). "Wikipedia Has Figured Out A New Way To Stop Vandals In Their Tracks". *Business Insider*.
69. ^ Frewin, Jonathan (June 15, 2010). "Wikipedia unlocks divisive pages for editing". BBC News. Retrieved August 21, 2014.
70. ^ *a b* Kleinz, Torsten (February 2005). "World of Knowledge" (PDF). *Linux Magazine*. Retrieved July 13, 2007. "The Wikipedia's open structure makes it a target for trolls and vandals who malevolently add incorrect information to articles, get other people tied up in endless discussions, and generally do everything to draw attention to themselves."
71. ^ Wikipedia:New pages patrol
72. ^ Andrea Ciffolilli, "Phantom authority, self-selective recruitment and retention of members in virtual communities: The case of Wikipedia" Archived December 6, 2016, at the Wayback Machine., *First Monday* December 2003.
73. ^ West, Andrew G.; Chang, Jian; Venkatasubramanian, Krishna; Sokolsky, Oleg; Lee, Insup (2011). *Link Spamming Wikipedia for Profit*. 8th Annual Collaboration, Electronic Messaging, Anti-Abuse, and Spam Conference. pp. 152–161. doi:10.1145/2030376.2030394.

74. ^ Vandalism. *Wikipedia*. Retrieved November 6, 2012.
75. ^ Fernanda B. Viégas; Martin Wattenberg; Kushal Dave (2004). "Studying Cooperation and Conflict between Authors with History Flow Visualizations" (PDF). *Proceedings of the ACM Conference on Human Factors in Computing Systems (CHI)*. Vienna, Austria: ACM SIGCHI: 575–582. doi:10.1145/985921.985953. ISBN 1-58113-702-8. Archived from the original (PDF) on 2006-01-25. Retrieved January 24, 2007.
76. ^ Reid Priedhorsky; Jilin Chen; Shyong (Tony) K. Lam; Katherine Panciera; Loren Terveen; John Riedl (November 4, 2007). "Creating, Destroying, and Restoring Value in Wikipedia" (PDF). *Association for Computing Machinery GROUP '07 conference proceedings; GroupLens Research, Department of Computer Science and Engineering, University of Minnesota*. Sanibel Island, Florida. Retrieved October 13, 2007.
77. ^ *a b c d* Seigenthaler, John (November 29, 2005). "A False Wikipedia 'biography'". *USA Today*. Retrieved December 26, 2008.
78. ^ Friedman, Thomas L. (2007). *The World is Flat*. Farrar, Straus & Giroux. p. 124. ISBN 978-0-374-29278-2.
79. ^ Buchanan, Brian (November 17, 2006). "Founder shares cautionary tale of libel in cyberspace". archive.firstamendmentcenter.org. Archived from the original on December 21, 2012. Retrieved November 17, 2012.
80. ^ Helm, Burt (December 13, 2005). "Wikipedia: "A Work in Progress" ". *BusinessWeek*. Archived from the original on July 8, 2012. Retrieved July 26, 2012.
81. ^ "Who's behind Wikipedia?". *PC World*. February 6, 2008. Archived from the original on February 9, 2008. Retrieved February 7, 2008.
82. ^ What Wikipedia is not. Retrieved April 1, 2010. "Wikipedia is not a dictionary, usage, or jargon guide."
83. ^ Notability. Retrieved February 13, 2008. "A topic is presumed to be notable if it has received significant coverage in reliable secondary sources that are independent of the subject."
84. ^ No original research. February 13, 2008. "Wikipedia does not publish original thought."
85. ^ Verifiability. February 13, 2008. "Material challenged or likely to be challenged, and all quotations, must be attributed to a reliable, published source."
86. ^ Cohen, Noam (August 9, 2011). "For inclusive mission, Wikipedia is told that written word goes only so far". *International Herald Tribune*. p. 18 – via vLex.[*dead link*](subscription required)
87. ^ Neutral point of view. February 13, 2008. "All Wikipedia articles and other encyclopedic content must be written from a neutral point of view, representing significant views fairly, proportionately and without bias."
88. ^ Eric Haas (October 26, 2007). "Will Unethical Editing Destroy Wikipedia's Credibility?". AlterNet. Retrieved December 26, 2008.
89. ^ Sanger, Larry (April 18, 2005). "The Early History of Nupedia and Wikipedia: A Memoir". *Slashdot*. Dice.
90. ^ Kostakis, Vasilis (March 2010). "Identifying and understanding the problems of Wikipedia's peer governance: The case of inclusionists versus deletionists". *First Monday*.
91. ^ Ownership of articles
92. ^ Avoiding Tragedy in the Wiki-Commons, by Andrew George, 12 Va. J.L. & Tech. 8 (2007)
93. ^ Wikipedia:Administrators
94. ^ Mehegan, David (February 13, 2006). "Many contributors, common cause". *Boston Globe*. Retrieved March 25, 2007.
95. ^ "Wikipedia:Administrators". Retrieved July 12, 2009.
96. ^ "Wikipedia:RfA_Review/Reflect". Retrieved September 24, 2009.
97. ^ Meyer, Robinson (July 16, 2012). "3 Charts That Show How Wikipedia Is Running Out of Admins". *The Atlantic*. Retrieved September 2, 2012.
98. ^ Dispute Resolution
99. ^ Coldewey, Devin (June 21, 2012). "Wikipedia is editorial warzone, says study". *Technology*. NBC News. Retrieved October 29, 2012.
100. ^ David A. Hoffman; Salil K. Mehra (2009). "Wikitruth through Wikiorder" (PDF). *Emory Law Journal*. Emory University School of Law. **59** (1): 181.
101. ^ David A. Hoffman; Salil K. Mehra (2009). "Wikitruth through Wikiorder" (PDF). *Emory Law Journal*. Emory University School of Law. **59** (1): 151–210.
102. ^ Fernanda B. Viégas; Martin M. Wattenberg; Jesse Kriss; Frank van Ham (January 3, 2007). "Talk Before You Type: Coordination in Wikipedia" (PDF). Visual Communication Lab, IBM Research. Retrieved June 27, 2008.
103. ^ Arthur, Charles (December 15, 2005). "Log on and join in, but beware the web cults". *The Guardian*. London. Retrieved December 26, 2008.
104. ^ Lu Stout, Kristie (August 4, 2003). "Wikipedia: The know-it-all Web site". CNN. Retrieved December 26, 2008.
105. ^ Larry Sanger (December 31, 2004). "Why Wikipedia Must Jettison Its Anti-Elitism". *Kuro5hin, Op–Ed*. "There is a certain mindset associated with unmoderated Usenet groups [...] that infects the collectively-managed Wikipedia project: if you react strongly to trolling, that reflects poorly on you, not (necessarily) on the troll. If you [...] demand that something be done about constant disruption by trollish behavior, the other listmembers will cry "censorship", attack you, and even come to the defense of the troll. [...] The root problem: anti-elitism, or lack of respect for expertise. There is a deeper problem [...] which explains both of the above-elaborated problems. Namely, as a community, Wikipedia lacks the habit or tradition of respect for expertise. As a community, far from being elitist, it is

anti-elitist (which, in this context, means that expertise is not accorded any special respect, and snubs and disrespect of expertise is tolerated). This is one of my failures: a policy that I attempted to institute in Wikipedia's first year, but for which I did not muster adequate support, was the policy of respecting and deferring politely to experts. (Those who were there will, I hope, remember that I tried very hard.)"

106. ^ T. Kriplean, I. Beschastnikh, et al. (2008). "Articulations of wikiwork: uncovering valued work in Wikipedia through barnstars". Proceedings of the ACM: 47. doi:10.1145/1460563.1460573. ISBN 978-1-60558-007-4. (Subscription required.)
107. ^ Jean Goodwin (2009). "The Authority of Wikipedia" (PDF). Archived from the original (PDF) on 2009-11-22. Retrieved January 31, 2011. "Wikipedia's commitment to anonymity/pseudonymity thus imposes a sort of epistemic agnosticism on its readers"
108. ^ Kittur, Aniket. "Power of the Few vs. Wisdom of the Crowd: Wikipedia and the Rise of the Bourgeoisie" (PDF). Viktoria Institute. Retrieved August 13, 2014.
109. ^ *a b c* Blodget, Henry (January 3, 2009). "Who The Hell Writes Wikipedia, Anyway?". *Business Insider*.
110. ^ Wilson, Chris (February 22, 2008). "The Wisdom of the Chaperones". *Slate*. Retrieved August 13, 2014.
111. ^ Swartz, Aaron (September 4, 2006). "Raw Thought: Who Writes Wikipedia?". Retrieved February 23, 2008.
112. ^ *a b* Goldman, Eric. "Wikipedia's Labor Squeeze and its Consequences". **8**. Journal on Telecommunications and High Technology Law.
113. ^ Noveck, Beth Simone. "Wikipedia and the Future of Legal Education". **57**. Journal of Legal Education.
114. ^ "Wikipedia "Good Samaritans" Are on the Money". *Scientific American*. October 19, 2007. Retrieved December 26, 2008.
115. ^ Yair Amichai–Hamburger, Naama Lamdan, Rinat Madiel, Tsahi Hayat, Personality Characteristics of Wikipedia Members[*permanent dead link*], *CyberPsychology & Behavior*, December 1, 2008, 11 (6): 679–681; doi:10.1089/cpb.2007.0225.
116. ^ "Wikipedians are 'closed' and 'disagreeable'". *New Scientist*. Retrieved July 13, 2010. (Subscription required.)
117. ^ "The Misunderstood Personality Profile of Wikipedia Members". *psychologytoday.com*. Retrieved June 5, 2016.
118. ^ Giles, Jim (August 4, 2009). "After the boom, is Wikipedia heading for bust?". *New Scientist*.
119. ^ "Where Are the Women in Wikipedia? – Room for Debate". NYTimes.com. February 2, 2011. Retrieved June 14, 2014.
120. ^ Lam, Shyong; Anuradha Uduwage; Zhenhua Dong; Shilad Sen; David R. Musicant; Loren Terveen; John Riedl (October 3–5, 2011). "WP:Clubhouse? An Exploration of Wikipedia's Gender Imbalance" (PDF). *WikiSym 2011*. Retrieved October 28, 2013.
121. ^ Cohen, Noam. "Define Gender Gap? Look Up Wikipedia's Contributor List". *The New York Times*. The New York Times Company. Retrieved October 28, 2013.
122. ^ Chom, Noam (January 31, 2011). "Define Gender Gap? Look Up Wikipedia's Contributor List". *The New York Times*. p. B–1. Retrieved May 9, 2012.
123. ^ Basch, Linda (February 6, 2011). "Male-Dominated Web Site Seeking Female Experts" (Letters to the Editor). *The New York Times*. p. WK–7. Retrieved May 9, 2012.
124. ^ "OCAD to 'Storm Wikipedia' this fall". *CBC News*. August 27, 2013. Retrieved August 21, 2014.
125. ^ Wikipedia Foundation. 2008. "Archived copy". Archived from the original on November 18, 2016. Retrieved 2016-12-27.
126. ^ "Wikipedia 'completely failed' to fix gender imbalance". *BBC News*. Retrieved September 9, 2014.
127. ^ Dimitra Kessenides. Bloomberg News Weekly, "Is Wikipedia 'Woke'", December 26, 2017, p. 73.
128. ^ "Statistics". English Wikipedia. Retrieved June 21, 2008.
129. ^ List of Wikipedias
130. ^ "Wikipedia:List of Wikipedias". English Wikipedia. Retrieved January 4, 2017.
131. ^ List of Wikipedias – Meta
132. ^ "List of Wikipedias". *Wikimedia Meta-Wiki*. Retrieved 4 January 2017.
133. ^ "Spelling". *Manual of Style*. Wikipedia. Retrieved May 19, 2007.
134. ^ "Countering systemic bias". Retrieved May 19, 2007.
135. ^ "Fair use". Meta-Wiki. Retrieved July 14, 2007.
136. ^ "Images on Wikipedia". Retrieved July 14, 2007.
137. ^ Fernanda B. Viégas (January 3, 2007). "The Visual Side of Wikipedia" (PDF). Visual Communication Lab, IBM Research. Retrieved October 30, 2007.
138. ^ Jimmy Wales, "Wikipedia is an encyclopedia", March 8, 2005, <Wikipedia-l@wikimedia.org>
139. ^ "Meta-Wiki". Wikimedia Foundation. Retrieved March 24, 2009.
140. ^ "Meta-Wiki Statistics". Wikimedia Foundation. Retrieved March 24, 2008.
141. ^ "List of articles every Wikipedia should have". Wikimedia Foundation. Retrieved March 24, 2008.
142. ^ "Wikipedia: Translation". *English Wikipedia*. Retrieved February 3, 2007.
143. ^ Yasseri, Taha; Sumi, Robert; Kertész, János (January 17, 2012). "Circadian Patterns of Wikipedia Editorial Activity: A Demographic Analysis". *PLoS ONE*. **7** (1): e30091. doi:10.1371/journal.pone.0030091. Retrieved January 17, 2012.

144. ^ "Wikimedia Foundation 2011–12 Annual Plan" (PDF). Wikimedia Foundation. p. 8. Retrieved 2016-06-05.
145. ^ a b c "The future of Wikipedia: WikiPeaks?". The Economist. March 1, 2014. Retrieved March 11, 2014.
146. ^ Andrew Lih. *Wikipedia*. Alternative edit policies at Wikipedia in other languages.
147. ^ Jemielniak, Dariusz (June 22, 2014). "The Unbearable Bureaucracy of Wikipedia". Slate. Retrieved August 18, 2014.
148. ^ D. Jemielniak, *Common Knowledge*, Stanford University Press, 2014.
149. ^ Messer-Kruse, Timothy (February 12, 2012) The 'Undue Weight' of Truth on Wikipedia Archived December 18, 2016, at the Wayback Machine. *The Chronicle of Higher Education* Retrieved March 27, 2014
150. ^ Colón-Aguirre, Monica &Fleming-May, Rachel A. (October 11, 2012) "You Just Type in What You Are Looking For": Undergraduates' Use of Library Resources vs. Wikipedia Archived April 19, 2016, at the Wayback Machine. (p. 392) *The Journal of Academic Librarianship* Retrieved March 27, 2014
151. ^ Bowling Green News (February 27, 2012) Wikipedia experience sparks national debate Archived August 27, 2016, at the Wayback Machine. Bowling Green State University Retrieved March 27, 2014
152. ^ Wisdom? More like dumbness of the crowds | Oliver Kamm – Times Online (archive version 2011-08-14) (Author's own copy Archived September 5, 2016, at the Wayback Machine.)
153. ^ "Plagiarism by Wikipedia editors". Wikipedia Watch. October 27, 2006. Archived from the original on November 25, 2009.
154. ^ "Wikipedia, Britannica: A Toss-Up". *Wired*. Associated Press. December 15, 2005. Retrieved August 8, 2015.
155. ^ Reagle, pp. 165–166.
156. ^ Fatally Flawed: Refuting the recent study on encyclopedic accuracy by the journal Nature Archived July 9, 2016, at the Wayback Machine., Encyclopædia Britannica, March 2006
157. ^ "Encyclopaedia Britannica and Nature: a response" (PDF). Retrieved July 13, 2010.
158. ^ "Nature's responses to Encyclopaedia Britannica". *Nature*. March 30, 2006. Retrieved March 19, 2012.
159. ^ See author acknowledged comments in response to the citation of the *Nature* study, at *PLoS One*, 2014, "Citation of fundamentally flawed *Nature* quality 'study' ", In response to T. Yasseri et al. (2012) Dynamics of Conflicts in Wikipedia, Published June 20, 2012, doi:10.1371/journal.pone.0038869, see "Archived copy". Archived from the original on January 16, 2016. Retrieved 2014-07-22., accessed July 21, 2014.
160. ^ "Wikipedia:General disclaimer". English Wikipedia. Retrieved April 22, 2008.
161. ^ Public Information Research, Wikipedia Watch
162. ^ Raphel, JR. "The 15 Biggest Wikipedia Blunders". *PC World*. Retrieved September 2, 2009.
163. ^ Cowen, Tyler (March 14, 2008). "Cooked Books". *The New Republic*. Archived from the original on March 18, 2008. Retrieved December 26, 2008.
164. ^ Stacy Schiff (July 31, 2006). "Know It All". *The New Yorker*.
165. ^ Danah Boyd (January 4, 2005). "Academia and Wikipedia". *Many 2 Many: A Group Weblog on Social Software*. Corante. Retrieved December 18, 2008. "[The author, Danah Boyd, describes herself as] an expert on social media[,] [...] a doctoral student in the School of Information at the University of California, Berkeley [,] and a fellow at the Harvard University Berkman Center for Internet & Society [at Harvard Law School.]"
166. ^ Robert McHenry, "The Faith-Based Encyclopedia"[*permanent dead link*] Archived January 16, 2006, at the Wayback Machine., Tech Central Station, November 15, 2004. Archived January 16, 2006, at the Wayback Machine.
167. ^ "Inside Wikipedia – Attack of the PR Industry". Deutsche Welle. June 30, 2014. Retrieved July 2, 2014.
168. ^ "Toward a New Compendium of Knowledge (longer version)". *Citizendium*. Archived from the original on October 11, 2006. Retrieved October 10, 2006.
169. ^ a b Elder, Jeff (June 16, 2014). "Wikipedia Strengthens Rules Against Undisclosed Editing". *The Wall Street Journal*.
170. ^ Ahrens, Frank (July 9, 2006). "Death by Wikipedia: The Kenneth Lay Chronicles". *The Washington Post*. Retrieved November 1, 2006.
171. ^ Kane, Margaret (January 30, 2006). "Politicians notice Wikipedia". CNET. Retrieved January 28, 2007.
172. ^ Bergstein, Brian (January 23, 2007). "Microsoft offers cash for Wikipedia edit". MSNBC. Retrieved February 1, 2007.
173. ^ Hafner, Katie (August 19, 2007). "Lifting Corporate Fingerprints From the Editing of Wikipedia". *The New York Times*. p. 1. Retrieved December 26, 2008.
174. ^ a b Stephen Colbert (July 30, 2006). "Wikiality". Retrieved October 8, 2015.
175. ^ "Wide World of Wikipedia". The Emory Wheel. April 21, 2006. Archived from the original on November 7, 2007. Retrieved October 17, 2007.
176. ^ Waters, N. L. (2007). "Why you can't cite Wikipedia in my class". *Communications of the ACM*. **50** (9): 15. doi:10.1145/1284621.1284635.
177. ^ Jaschik, Scott (January 26, 2007). "A Stand Against Wikipedia". Inside Higher Ed. Retrieved January 27, 2007.
178. ^ Helm, Burt (December 14, 2005). "Wikipedia: 'A Work in Progress' ". *Bloomberg BusinessWeek*. Archived from the original on April 21, 2012. Retrieved January 29, 2007.
179. ^ "Jimmy Wales", *Biography Resource Center Online*. (Gale, 2006.)
180. ^ Child, Maxwell L., "Professors Split on Wiki Debate" Archived December 20, 2008, at the Wayback Machine., *The*

*Harvard Crimson*, Monday, February 26, 2007.
181. ^ Chloe Stothart. "Web threatens learning ethos" Archived December 21, 2012, at the Wayback Machine.. *The Times Higher Education Supplement*, 2007, 1799 (June 22), p. 2.
182. ^ Cohen, Morris; Olson, Kent (2010). *Legal Research in a Nutshell* (10th ed.). St. Paul, Minnesota, USA: Thomson Reuters. pp. 32–34. ISBN 978-0-314-26408-4.
183. ^ *a b* Julie Beck. "Doctors' #1 Source for Healthcare Information: Wikipedia". *The Atlantic*, March 5, 2014.
184. ^ *a b* Green, Emma (May 7, 2014). "Can Wikipedia Ever Be a Definitive Medical Text? – Julie Beck". The Atlantic. Retrieved June 14, 2014.
185. ^ Kittur and Kraut (2008) Harnessing the wisdom of crowds in Wikipedia: quality through coordination. http://dl.acm.org/citation.cfm?id=1460572[*permanent dead link*] doi:10.1145/1460563.1460572
186. ^ *a b* Roy Rosenzweig (June 2006). "Can History be Open Source? Wikipedia and the Future of the Past". *The Journal of American History*. **93** (1): 117–146. doi:10.2307/4486062. JSTOR 4486062. Retrieved August 11, 2006.[*dead link*] (Center for History and New Media.)
187. ^ Andrew Orlowski (October 18, 2005). "Wikipedia founder admits to serious quality problems". *The Register*. Retrieved September 30, 2007.
188. ^ "Cancer information on Wikipedia is accurate, but not very readable, study finds". *Science Daily*. June 2, 2010. Retrieved December 31, 2010.
189. ^ "Fact or fiction? Wikipedia's variety of contributors is not only a strength". *The Economist*. March 10, 2007. Retrieved December 31, 2010.
190. ^ Wikipedia:PAPER
191. ^ "The battle for Wikipedia's soul". *The Economist*. March 6, 2008. Retrieved March 7, 2008.
192. ^ Douglas, Ian (November 10, 2007). "Wikipedia: an online encyclopedia torn apart". *The Daily Telegraph*. London. Retrieved November 23, 2010.
193. ^ Sophie Taylor (April 5, 2008). "China allows access to English Wikipedia". Reuters. Retrieved July 29, 2008.
194. ^ Bruilliard, Karin (May 21, 2010). "Pakistan blocks YouTube a day after shutdown of Facebook over Muhammad issue". *The Washington Post*. Retrieved October 24, 2011.
195. ^ "Wikipedia child image censored". BBC News. December 8, 2008. Retrieved December 8, 2008.
196. ^ *a b* Kittur, A., Chi, E. H., and Suh, B. 2009. What's in Wikipedia? Mapping Topics and Conflict Using Socially Annotated Category Structure Archived April 13, 2016, at the Wayback Machine.. In Proceedings of the 27th international Conference on Human Factors in Computing Systems (Boston, Massachusetts, USA, April 4–9, 2009). CHI '09. ACM, New York, USA, 1509–1512.
197. ^ Petrusich, Amanda (October 20, 2011). "Wikipedia's Deep Dive Into a Library Collection". *The New York Times*. Retrieved October 28, 2011.
198. ^ Lam, Shyong; Anuradha Uduwage; Zhenhua Dong; Shilad Sen; David R. Musicant; Loren Terveen; John Riedl (October 3–5, 2011). "WP: Clubhouse? An Exploration of Wikipedia's Gender Imblance" (PDF). *WikiSym 2011*: 4.
199. ^ Mark Graham, Mapping the Geographies of Wikipedia Content[*dead link*], *Zerogeography.net* (November 12, 2009).
200. ^ *The Guardian* 2014 (London) The Guardian view on Wikipedia: evolving truth Archived November 12, 2016, at the Wayback Machine.
201. ^ *a b* Quilter, Laura (October 24, 2012). "Systemic Bias in Wikipedia: What It Looks Like, and How to Deal with It". University of Massachusetts – Amherst. Retrieved November 26, 2012.
202. ^ "Edit Wars Reveal the 10 Most Controversial Topics on Wikipedia[*permanent dead link*]", MIT Technology Review, July 17, 2013.
203. ^ *a b c* "The Most Controversial Topics in Wikipedia: A Multilingual and Geographical Analysis by Taha Yasseri, Anselm Spoerri, Mark Graham, Janos Kertesz :: SSRN". Papers.ssrn.com. May 23, 2013. doi:10.2139/ssrn.2269392. Retrieved June 14, 2014.
204. ^ *a b* Dimitra Kessenides (December 22, 2016). "Is Wikipedia 'Woke'". *Bloomberg News Weekly*. p. 72. Retrieved December 26, 2016.
205. ^ Sanger, Larry. "What should we do about Wikipedia's porn problem?". Retrieved July 26, 2012.
206. ^ Metz, Cade (December 7, 2008). "Brit ISPs censor Wikipedia over 'child porn' album cover". *The Register*. Retrieved May 10, 2009.
207. ^ Raphael, JR (December 10, 2008). "Wikipedia Censorship Sparks Free Speech Debate". *The Washington Post*. Retrieved May 10, 2009.
208. ^ Farrell, Nick (April 29, 2010). "Wikipedia denies child abuse allegations: Co-founder grassed the outfit to the FBI". *The Inquirer*. Retrieved October 9, 2010.
209. ^ *a b* Metz, Cade (April 9, 2010). "Wikifounder reports Wikiparent to FBI over 'child porn'". *The Register*. Retrieved April 19, 2010.
210. ^ "Wikipedia blasts co-founder's accusations of child porn on website". *The Economic Times*. India. April 29, 2010. Retrieved April 29, 2010.
211. ^ *a b* "Wikipedia blasts talk of child porn at website". Agence France-Presse. April 28, 2010. Retrieved April 29,

2010.
212. ^ "Wikimedia pornography row deepens as Wales cedes rights". BBC News. May 10, 2010. Retrieved May 19, 2010.
213. ^ Gray, Lila (September 17, 2013). "Wikipedia Gives Porn a Break". *XBIZ.com*. Retrieved November 10, 2013.
214. ^ Andrew McStay, 2014, Privacy and Philosophy: New Media and Affective Protocol Archived April 14, 2016, at the Wayback Machine., New York Peter Lang.
215. ^ Heise – Gericht weist einstweilige Verfügung gegen Wikimedia Deutschland ab (update), by Torsten Kleinz, February 9, 2006.
216. ^ "IT Service Management Software". OTRS.com. Retrieved June 9, 2012.
217. ^ Paling, Emma. "Wikipedia's Hostility to Women". *The Atlantic*. Retrieved October 24, 2015.
218. ^ Auerbach, David. "Encyclopedia Frown". *Slate*. Retrieved October 24, 2015.
219. ^ "In UK, rising chorus of outrage over online misogyny". *CSMonitor.com*.
220. ^ Paling, Emma (21 October 2015). "Wikipedia's Hostility to Women". *The Atlantic*. Retrieved 10 December 2016.
221. ^ Ayers, Phoebe (2008). *How Wikipedia Works*. San Francisco: No Starch Press. p. 213. ISBN 1-59327-176-X.
222. ^ "Wikimedia Foundation – Financial Statements – June 30, 2011 and 2010" (PDF). Wikimedia Foundation. Retrieved 2016-06-05.
223. ^ "Wikimedia Foundation IRS Form 990" (PDF). Retrieved October 14, 2014.
224. ^ "Press releases/WMF announces new ED Lila Tretikov". Wikimedia Foundation. Retrieved June 14, 2014.
225. ^ *a b* Jeff Elder, *The Wall Street Journal*, May 1, 2014, "Wikipedia's New Chief: From Soviet Union to World's Sixth-Largest Site".
226. ^ *a b* Naom Cohen (May 1, 2014). "Media: Open-Source Software Specialist Selected as Executive Director of Wikipedia". *The New York Times*.
227. ^ Dimitra Kessenides. Bloomberg News Weekly. December 26, 2016. "Is Wikipedia 'Woke'".
228. ^ Dimitra Kessenides. Bloomberg News Weekly. December 26, 2016, p. 74. "Is Wikipedia 'Woke'".
229. ^ Mark Bergman. "Wikimedia Architecture" (PDF). Wikimedia Foundation. Retrieved June 27, 2008.
230. ^ "Version: Installed extensions".. Retrieved August 18, 2014.
231. ^ Michael Snow. "Lucene search: Internal search function returns to service". Wikimedia Foundation. Retrieved February 26, 2009.
232. ^ Brion Vibber. "[Wikitech-l] Lucene search". Retrieved February 26, 2009.
233. ^ "Extension:Lucene-search". Wikimedia Foundation. Retrieved August 31, 2009.
234. ^ "mediawiki – Revision 55688: /branches/lucene-search-2.1/lib". Wikimedia Foundation. Retrieved August 31, 2009.
235. ^ Emil Protalinski (July 2, 2013). "Wikimedia rolls out WYSIWYG visual editor for logged-in users accessing Wikipedia articles in English". *The Next Web*. Retrieved July 6, 2013.
236. ^ Curtis, Sophie (July 23, 2013). "Wikipedia introduces new features to entice editors". The Daily Telegraph. Retrieved August 18, 2013.
237. ^ L.M. (December 13, 2011). "Changes at Wikipedia: Seeing things". *The Economist*. Retrieved July 28, 2013.
238. ^ Lucian Parfeni (July 2, 2013). "Wikipedia's New VisualEditor Is the Best Update in Years and You Can Make It Better". *Softpedia*. Retrieved July 30, 2013.
239. ^ *a b* Orlowski, Andrew (August 1, 2013). "Wikipedians say no to Jimmy's 'buggy' WYSIWYG editor". The Register. Retrieved August 18, 2013.
240. ^ Wikipedia Bot Information
241. ^ *a b* Daniel Nasaw (July 24, 2012). "Meet the 'bots' that edit Wikipedia". BBC News.
242. ^ Halliday, Josh; Arthur, Charles (July 26, 2012). "Boot up: The Wikipedia vandalism police, Apple analysts, and more". *The Guardian*. Retrieved September 5, 2012.
243. ^ Jervell, Ellen Emmerentze (July 13, 2014). "For This Author, 10,000 Wikipedia Articles Is a Good Day's Work". The Wall Street Journal. Retrieved August 18, 2014.
244. ^ "Wikipedia signpost: Abuse Filter is enabled". English Wikipedia. March 23, 2009. Retrieved July 13, 2010.
245. ^ Aljazeera, July 21, 2014, "MH17 Wikipedia entry edited from Russian Government IP Address". "Archived copy". Archived from the original on November 16, 2016. Retrieved 2014-07-22.
246. ^ Wikipedia's policy on bots
247. ^ Andrew Lih (2009). *The Wikipedia Revolution*, chapter *Then came the Bots*, pp. 99–106.
248. ^ "Wikipedia: Wikiprojects". Retrieved March 16, 2015.
249. ^ "Wikipedia:Version 1.0 Editorial Team/Assessment". Retrieved October 28, 2007.
250. ^ "Comparing featured article groups and revision patterns correlations in Wikipedia". First Monday. Retrieved July 13, 2010.
251. ^ Fernanda B. Viégas; Martin Wattenberg; Matthew M. McKeon (July 22, 2007). "The Hidden Order of Wikipedia" (PDF). Visual Communication Lab, IBM Research. Retrieved October 30, 2007.
252. ^ Poderi, Giacomo, *Wikipedia and the Featured Articles: How a Technological System Can Produce Best Quality Articles*, Master thesis, University of Maastricht, October 2008.
253. ^ David Lindsey. "Evaluating quality control of Wikipedia's featured articles". First Monday.
*a b*

254. ^ Wikipedia:Version 1.0 Editorial Team/Statistics – Wikipedia, the free encyclopedia
255. ^ "Monthly request statistics", Wikimedia. Retrieved October 31, 2008.[*dead link*]
256. ^ Domas Mituzas. "Wikipedia: Site internals, configuration, code examples and management issues" (PDF). MySQL Users Conference 2007. Retrieved June 27, 2008.
257. ^ Guido Urdaneta, Guillaume Pierre and Maarten van Steen. "Wikipedia Workload Analysis for Decentralized Hosting". Elsevier Computer Networks 53 (11), pp. 1830–1845, June 2009. Retrieved 2016-06-05.
258. ^ Weiss, Todd R. (October 9, 2008). "Wikipedia simplifies IT infrastructure by moving to one Linux vendor". *Computerworld*. Retrieved November 1, 2008.
259. ^ Paul, Ryan (October 9, 2008). "Wikipedia adopts Ubuntu for its server infrastructure". Ars Technica. Retrieved November 1, 2008.
260. ^ "Server roles at wikitech.wikimedia.org". Archived from the original on January 16, 2013. Retrieved December 8, 2009.
261. ^ Palmier, Guillaume. "Wikimedia sites to move to primary data center in Ashburn, Virginia". WMF. Retrieved 2016-06-05.
262. ^ Verge, Jason. "It's Official: Ashburn is Wikipedia's New Home". Data Center Knowledge. Retrieved 2016-06-05.
263. ^ Frederic M. Scherer and David Ross, [1970] 1990. *Industrial Market Structure and Economic Performance*, 3rd ed. Houghton-Mifflin. Description Archived May 3, 2011, at the Wayback Machine. and 1st ed. review extract[*permanent dead link*].
    - Google Scholar search of Frederic M. Scherer[*permanent dead link*].
264. ^ *a b c Patents, Citations, and Innovations*, by Adam B. Jaffe, Manuel Trajtenberg, pp. 89–153.
265. ^ Cohen, Noam (March 5, 2007). "A Contributor to Wikipedia Has His Fictional Side". *The New York Times*. Retrieved October 18, 2008.
266. ^ Wikipedia:Copyrights
267. ^ Walter Vermeir (2007). "Resolution:License update". Wikizine. Retrieved December 4, 2007.
268. ^ Wikimedia
269. ^ "Licensing update/Questions and Answers". *Wikimedia Meta*. Wikimedia Foundation. Retrieved February 15, 2009.
270. ^ "Licensing_update/Timeline". *Wikimedia Meta*. Wikimedia Foundation. Retrieved April 5, 2009.
271. ^ "Wikimedia community approves license migration". *Wikimedia Foundation*. Retrieved May 21, 2009.
272. ^ Cohen, Noam (July 19, 2009). "Wikipedia May Be a Font of Facts, but It's a Desert for Photos". New York Times. Retrieved March 9, 2013.
273. ^ "Wikipedia cleared in French defamation case". Reuters. November 2, 2007. Retrieved November 2, 2007.
274. ^ Anderson, Nate (May 2, 2008). "Dumb idea: suing Wikipedia for calling you "dumb" ". Ars Technica. Retrieved May 4, 2008.
275. ^ "With Bing Reference". Retrieved September 9, 2014.[*dead link*]
276. ^ "Wikipedia on DVD" Archived June 3, 2013, at the Wayback Machine.. Linterweb. Retrieved June 1, 2007. "Linterweb is authorized to make a commercial use of the Wikipedia trademark restricted to the selling of the Encyclopedia CDs and DVDs".
277. ^ "Wikipedia 0.5 Available on a CD-ROM" Archived May 3, 2013, at the Wayback Machine.. *Wikipedia on DVD*. Linterweb. "The DVD or CD-ROM version 0.5 was commercially available for purchase." Retrieved June 1, 2007.
278. ^ "Polish Wikipedia on DVD". Retrieved December 26, 2008.
279. ^ "Wikipedia:DVD". Retrieved December 26, 2008.
280. ^ "CDPedia (Python Argentina)". Retrieved July 7, 2011.
281. ^ Wikipedia CD Selection. Retrieved September 8, 2009.
282. ^ "Wikipedia turned into book". *The Daily Telegraph*. London: Telegraph Media Group. June 16, 2009. Archived from the original on September 8, 2009. Retrieved September 8, 2009.
283. ^ "Wikipedia Selection for Schools". Retrieved July 14, 2012.
284. ^ Thiel, Thomas (September 27, 2010). "Wikipedia und Amazon: Der Marketplace soll es richten". *Frankfurter Allgemeine Zeitung* (in German). Frankfurter Allgemeine Zeitung. Archived from the original on November 26, 2010. Retrieved December 6, 2010.
285. ^ Wikipedia policies on data download
286. ^ Data dumps: Downloading Images, Wikimedia Meta-Wiki
287. ^ "Wikipedia Reference Desk". Retrieved September 9, 2014.
288. ^ Brad Stone, "How Google's Android chief, Sundar Pichai, became the most powerful man in mobile", June 30 – July 6, 2014, *Bloomberg BusinessWeek*, pp. 47–51.
289. ^ "Wikipedia – Android Apps on Google Play". *Play.Google.com*. Retrieved August 21, 2014.
290. ^ "Wikipedia Mobile on the App Store on iTunes". *iTunes.Apple.com*. August 4, 2014. Retrieved August 21, 2014.
291. ^ "Wikimedia Mobile is Officially Launched". *Wikimedia Technical Blog*. June 30, 2009. Retrieved July 22, 2009.
292. ^ "Local Points Of Interest In Wikipedia". May 15, 2011. Retrieved May 15, 2011.
293. ^ "iPhone Gems: Wikipedia Apps". November 30, 2008. Retrieved July 22, 2008.
294. ^ Ellis, Justin (January 17, 2013). "Wikipedia plans to expand mobile access around the globe with new funding".

*NiemanLab*. Nieman Journalism Lab. Retrieved April 22, 2013.
295. ^ Andrew Lih (June 20, 2015). "Can Wikipedia Survive?".
296. ^ Andrew Brown (June 25, 2015). "Wikipedia editors are a dying breed. The reason? Mobile". *The Guardian*.
297. ^ "Wikipedia:Modelling Wikipedia's growth". Retrieved December 22, 2007.
298. ^ "694 Million People Currently Use the Internet Worldwide According To comScore Networks". comScore. May 4, 2006. Archived from the original on July 30, 2008. Retrieved December 16, 2007. "Wikipedia has emerged as a site that continues to increase in popularity, both globally and in the US"
299. ^ "Google Traffic To Wikipedia up 166% Year over Year". Hitwise. February 16, 2007. Retrieved December 22, 2007.
300. ^ "Wikipedia and Academic Research". Hitwise. October 17, 2006. Retrieved February 6, 2008.
301. ^ West, Stuart. "Wikipedia's Evolving Impact: slideshow presentation at TED2010" (PDF). Retrieved October 23, 2015.
302. ^ Rainie, Lee; Bill Tancer (December 15, 2007). "Wikipedia users" (PDF). *Pew Internet & American Life Project*. Pew Research Center. Archived from the original (PDF) on March 6, 2008. Retrieved December 15, 2007. "36% of online American adults consult Wikipedia. It is particularly popular with the well-educated and current college-age students."
303. ^ SAI (October 7, 2011). "The World's Most Valuable Startups". Business Insider. Retrieved June 14, 2014.
304. ^ "Research:Wikipedia Readership Survey 2011/Results – Meta". Wikimedia. February 6, 2012. Retrieved April 16, 2014.
305. ^ "Wikipedia:Wikipedia in the media". *Wikipedia*. Retrieved December 26, 2008.
306. ^ "Bourgeois *et al.* v. Peters *et al.*" (PDF). Archived from the original (PDF) on February 3, 2007. Retrieved February 6, 2007.
307. ^ "Wikipedian Justice" (PDF). Retrieved June 9, 2009.
308. ^ "LEGISinfo – House Government Bill C-38 (38–1)". Retrieved September 9, 2014.
309. ^ Arias, Martha L. (January 29, 2007). "Wikipedia: The Free Online Encyclopedia and its Use as Court Source". *Internet Business Law Services*. Retrieved December 26, 2008. (The name "*World Intellectual Property Office*" should however read "*World Intellectual Property Organization*" in this source.)
310. ^ Cohen, Noam (January 29, 2007). "Courts Turn to Wikipedia, but Selectively". *The New York Times*. Retrieved December 26, 2008.
311. ^ Aftergood, Steven (March 21, 2007). "The Wikipedia Factor in US Intelligence". Federation of American Scientists Project on Government Secrecy. Retrieved April 14, 2007.
312. ^ Butler, Declan (December 16, 2008). "Publish in Wikipedia or perish". *Nature News*. doi:10.1038/news.2008.1312.
313. ^ Shaw, Donna (February–March 2008). "Wikipedia in the Newsroom". *American Journalism Review*. Retrieved February 11, 2008.
314. ^ Lexington (September 24, 2011). "Classlessness in America: The uses and abuses of an enduring myth". *The Economist*. Retrieved September 27, 2011. "Socialist Labour Party of America […] though it can trace its history as far back as 1876, when it was known as the Workingmen's Party, no less an authority than Wikipedia pronounces it "moribund"."
315. ^ "Shizuoka newspaper plagiarized Wikipedia article". *Japan News Review*. July 5, 2007.
316. ^ "Express-News staffer resigns after plagiarism in column is discovered" at the Wayback Machine (archived October 15, 2007)[*dead link*], *San Antonio Express-News*, January 9, 2007.
317. ^ Frank Bridgewater. "Inquiry prompts reporter's dismissal". *Honolulu Star-Bulletin*. Retrieved September 9, 2014.
318. ^ Grossman, Lev (December 13, 2006). "Time's Person of the Year: You". *Time*. Time. Retrieved December 26, 2008.
319. ^ "Radio 4 documentary, BBC". 2007. Retrieved April 2016. Check date values in: `|access-date=` (help)
320. ^ "Comunicato stampa. On. Franco Grillini. Wikipedia. Interrogazione a Rutelli. Con "diritto di panorama" promuovere arte e architettura contemporanea italiana. Rivedere con urgenza legge copyright" [Press release. Honorable Franco Grillini. Wikipedia. Interview with Rutelli about the "right to view" promoting contemporary art and architecture of Italy. Review with urgency copyright law] (in Italian). October 12, 2007. Archived from the original on March 30, 2009. Retrieved December 26, 2008.
321. ^ Jose Antonio Vargas (September 17, 2007). "On Wikipedia, Debating 2008 Hopefuls' Every Facet". *The Washington Post*. Retrieved December 26, 2008.
322. ^ Jennifer Ablan (October 22, 2007). "Wikipedia page the latest status symbol". Reuters. Retrieved October 24, 2007.
323. ^ Witzleb, Normann (2009). "Engaging with the World: Students of Comparative Law Write for Wikipedia". **19** (1 and 2). Legal Education Review: 83–98.
324. ^ "AI Research Trends". *One Hundred Year Study on Artificial Intelligence (AI100)*. Stanford University. Retrieved 3 September 2016.
325. ^ "Trophy box", Meta-Wiki (March 28, 2005).
326. ^ "Webby Awards 2004". The International Academy of Digital Arts and Sciences. 2004. Archived from the original on July 22, 2011.
327. ^ Zumpano, Anthony (January 29, 2007). "Similar Search Results: Google Wins". Interbrand. Archived from the original on February 20, 2007. Retrieved January 28, 2007.

328. ^ "Die Quadriga – Award 2008". Retrieved December 26, 2008.
329. ^ "Erasmus Prize – Praemium Erasmianum". Praemium Erasmianum Foundation. Retrieved January 15, 2015.
330. ^ "Premio Princesa de Asturias de Cooperación Internacional 2015". Fundación Princesa de Asturias. Retrieved June 17, 2015.
331. ^ "Los fundadores de Wikipedia destacan la versión en asturiano" [The founders of Wikipedia highlight the Asturian version] (in Spanish). La Nueva España. Retrieved October 20, 2015.
332. ^ "Wikipedia Celebrates 750 Years Of American Independence". *The Onion*. July 26, 2006. Retrieved October 15, 2006.
333. ^ "'L.A. Law' Wikipedia Page Viewed 874 Times Today". *The Onion*. November 24, 2010.
334. ^ "The Office: The Negotiation, 3.19". April 5, 2007. Retrieved December 27, 2014.
335. ^ "'Office' fans, inspired by Michael Scott, flock to edit Wikipedia". USA Today. April 12, 2007. Retrieved December 12, 2014.
336. ^ Bakken, Janae. "My Number One Doctor"; *Scrubs*; ABC; December 6, 2007.
337. ^ "Professor Wikipedia – CollegeHumor Video". CollegeHumor. November 17, 2009. Retrieved April 19, 2011.
338. ^ "Dilbert comic strip for 05/08/2009 from the official Dilbert comic strips archive". Universal Uclick. May 8, 2009. Retrieved March 10, 2013.
339. ^ "Interview With Nick Doody and Matt Kirshen". British Comedy Guide. Retrieved July 31, 2009.
340. ^ "*Your Wikipedia Entries*". *Tosh.0*. February 3, 2010. Retrieved September 9, 2014.
341. ^ "*Wikipedia Updates*". *Tosh.0*. February 3, 2010. Retrieved September 9, 2014.
342. ^ Emily Flake (August 23, 2013). "Manning/Wikipedia cartoon". Retrieved August 26, 2013.
343. ^ "The obstacles to reforming our prisons – The Times". *thetimes.co.uk*. Retrieved June 5, 2016.
344. ^ "john julius norwich -Search – The Times". *thetimes.co.uk*. Retrieved June 5, 2016.
345. ^ "Announcement of Wiktionary's creation". meta.wikimedia.org. Retrieved July 14, 2012.
346. ^ "Our projects", Wikimedia Foundation. Retrieved January 24, 2007.
347. ^ Bosman, Julie. "After 244 Years, Encyclopaedia Britannica Stops the Presses". *The New York Times*. Retrieved January 26, 2015.
348. ^ "*Encyclopedia Britannica Dies At The Hands Of Wikipedia*, Gizmocrazed.com (with *statista* infographic from NYTimes.com)". Gizmocrazed.com. March 20, 2012. Retrieved June 14, 2014.
349. ^ Christopher Caldwell (June 14, 2013). "A chapter in the Enlightenment closes". ft.com. Retrieved June 15, 2013. "Bertelsmann did not resort to euphemism this week when it announced the end of the Brockhaus encyclopedia brand. Brockhaus had been publishing reference books for two centuries when the media group bought it in 2008. […] The internet has finished off Brockhaus altogether. […] What Germans like is Wikipedia."
350. ^ "The amorality of Web 2.0". *Rough Type*. October 3, 2005. Retrieved July 15, 2006.
351. ^ "Technical solutions: Wisdom of the crowds". *Nature*. Retrieved October 10, 2006.
352. ^ Alison Flood. "Alison Flood: *Should traditional biography be buried alongside Shakespeare's breakfast?*". The Guardian. Retrieved June 14, 2014.
353. ^ Rada Mihalcea and Andras Csomai (2007). Wikify! Linking Documents to Encyclopedic Knowledge Archived February 18, 2016, at the Wayback Machine.. Proc. CIKM.
354. ^ David Milne and Ian H. Witten (2008). Learning to link with Wikipedia. Proc. CIKM.
355. ^ Sisay Fissaha Adafre and [Maarten de Rijke] (2005). Discovering missing links in Wikipedia Archived July 17, 2012, at the Wayback Machine.. Proc. LinkKDD.
356. ^ "Wikipedia-Mining Algorithm Reveals World's Most Influential Universities: An algorithm's list of the most influential universities contains some surprising entries.". *MIT Technology Review*. December 7, 2015. Retrieved December 27, 2015.
357. ^ Marmow Shaw, Jessica (December 10, 2015). "Harvard is only the 3rd most influential university in the world, according to this list". *MarketWatch*. Retrieved December 27, 2015.
358. ^ *a b* Bothwell, Ellie (December 15, 2015). "Wikipedia Ranking of World Universities: the top 100. List ranks institutions by search engine results and Wikipedia appearances". *Times Higher Education*. Retrieved December 27, 2015.
359. ^ Heart Internet. "Website discussing the emulator of the Domesday Project User Interface". Retrieved September 9, 2014.
360. ^ Frauenfelder, Mark (November 21, 2000). "The next generation of online encyclopedias". *CNN.com*. Archived from the original on August 14, 2004.
361. ^ The Free Encyclopedia Project gnu.org (Archived January 3, 2012, at WebCite)
362. ^ Orlowski, Andrew (September 18, 2006). "Wikipedia founder forks Wikipedia, More experts, less fiddling?". *The Register*. Retrieved June 27, 2007. "Larry Sanger describes the Citizendium project as a "progressive or gradual fork", with the major difference that experts have the final say over edits."


## Notes

1. ^ Many (but not all) of the glyphs featured are equivalent to the English letter W or sounds "wi", "wo" or "wa". See Wikipedia logo.

2. ^ Registration is required for certain tasks such as editing protected pages, creating pages in the English Wikipedia, and uploading files.
3. ^ For an user to be considered active in a given month, one or more actions have had to be made in said month.
4. ^ Wikis are a type of website. The word "wiki" itself is from the Hawaiian word for "quick".[14]
5. ^ The procrastination principle dictates that you should wait for problems to arise before solving them.
6. ^ Revisions with libelous content, criminal threats, or copyright infringements may be removed completely.
7. ^ See for example the Biographies of Living Persons Noticeboard or Neutral Point of View Noticeboard, created to address content falling under their respective areas.
8. ^ See "Libel" by David McHam for the legal distinction

# Further reading

## Academic studies

*Main article: Academic studies about Wikipedia*


- Leitch, Thomas. *Wikipedia U: Knowledge, authority, and a liberal education in the digital age* (2014)
- Jensen, Richard. "Military History on the Electronic Frontier: Wikipedia Fights the War of 1812", *The Journal of Military History* 76#4 (October 2012): 523–556; online version.
- Yasseri, Taha; Robert Sumi; János Kertész (2012). Szolnoki, Attila, ed. "Circadian Patterns of Wikipedia Editorial Activity: A Demographic Analysis". *PLoS ONE*. **7** (1): e30091. arXiv:1109.1746. Bibcode:2012PLoSO...7E0091Y. doi:10.1371/journal.pone.0030091. PMC 3260192. PMID 22272279.
- Goldman, Eric (2010). "Wikipedia's Labor Squeeze and its Consequences". *Journal of Telecommunications and High Technology Law*. **8**. (A blog post by the author.)
- Nielsen, Finn (August 2007). "Scientific Citations in Wikipedia". *First Monday*. **12** (8). doi:10.5210/fm.v12i8.1997. Retrieved February 22, 2008.
- Pfeil, Ulrike; Panayiotis Zaphiris; Chee Siang Ang (2006). "Cultural Differences in Collaborative Authoring of Wikipedia". *Journal of Computer-Mediated Communication*. **12** (1): 88. doi:10.1111/j.1083-6101.2006.00316.x. Retrieved December 26, 2008.
- Priedhorsky, Reid, Jilin Chen, Shyong (Tony) K. Lam, Katherine Panciera, Loren Terveen, and John Riedl. "Creating, Destroying, and Restoring Value in Wikipedia". Proc. GROUP 2007; doi:10.1145/1316624.1316663
- Reagle, Joseph (2007). *Do as I Do: Authorial Leadership in Wikipedia* (PDF). *WikiSym '07: Proceedings of the 2007 International Symposium on Wikis*. Montreal, Canada: ACM. Retrieved December 26, 2008.
- Rosenzweig, Roy. Can History be Open Source? Wikipedia and the Future of the Past. (Originally published in *The Journal of American History* 93.1 (June 2006): 117–46.)
- Wilkinson, Dennis M.; Bernardo A. Huberman (April 2007). "Assessing the Value of Cooperation in Wikipedia". *First Monday*. **12** (4). doi:10.5210/fm.v12i4.1763. Retrieved February 22, 2008.
- Aaron Halfaker; R. Stuart Geiger; Jonathan T. Morgan; John Riedl (2012). "The Rise and Decline of an Open Collaboration Community". *American Behavioral Scientist*. **57** (5): 664. doi:10.1177/0002764212469365. Retrieved August 30, 2012.


## Books

*Main article: List of books about Wikipedia*


- Ayers, Phoebe; Matthews, Charles; Yates, Ben (September 2008). *How Wikipedia Works: And How You Can Be a Part of It*. San Francisco: No Starch Press. ISBN 978-1-59327-176-3.
- Broughton, John (2008). *Wikipedia – The Missing Manual*. O'Reilly Media. ISBN 0-596-51516-2. (See book review by Baker, as listed hereafter.)
- Broughton, John (2008). *Wikipedia Reader's Guide*. Sebastopol: Pogue Press. ISBN 0-596-52174-X.
- Dalby, Andrew (2009). *The World and Wikipedia: How We are Editing Reality*. Siduri. ISBN 978-0-9562052-0-9.
- Jemielniak, Dariusz (2014). *Common Knowledge? An Ethnography of Wikipedia*. Stanford, California: Stanford University Press. ISBN 9780804789448.
- Keen, Andrew (2007). *The Cult of the Amateur*. Doubleday/Currency. ISBN 978-0-385-52080-5. (Substantial criticisms of Wikipedia and other web 2.0 projects.)
  - Listen to:
    - Keen, Andrew (June 16, 2007). "Does the Internet Undermine Culture?". National Public Radio, USA. The NPR interview with A. Keen, Weekend Edition Saturday, June 16, 2007.
- Lih, Andrew (2009). *The Wikipedia Revolution: How a Bunch of Nobodies Created the World's Greatest Encyclopedia*. New York: Hyperion. ISBN 978-1-4013-0371-6.
- O'Sullivan, Dan (September 24, 2009). *Wikipedia: a new community of practice?*. Ashgate Publishing. ISBN 978-0-7546-

7433-7.
- Sheizaf Rafaeli & Yaron Ariel (2008). "Online motivational factors: Incentives for participation and contribution in Wikipedia." In Barak, A. *Psychological aspects of cyberspace: Theory, research, applications*. Cambridge, UK: Cambridge University Press. pp. 243–267.
- Reagle, Joseph Michael Jr. (2010). *Good Faith Collaboration: The Culture of Wikipedia*. Cambridge, Massachusetts, USA: the MIT Press. ISBN 978-0-262-01447-2. Retrieved October 25, 2015.
- Wells, Herbert George. (2013). *World Brain*. New Delhi, India: Isha Books (reprint). ISBN 978-9-333-39061-3. Retrieved June 18, 2016.

## Book reviews and other articles

- Baker, Nicholson. "The Charms of Wikipedia". *The New York Review of Books*, March 20, 2008. Retrieved December 17, 2008. (Book rev. of *The Missing Manual*, by John Broughton, as listed previously.)
- Crovitz, L. Gordon. "Wikipedia's Old-Fashioned Revolution: The online encyclopedia is fast becoming the best." (Originally published in *Wall Street Journal* online – April 6, 2009.)
- Postrel, Virginia, "Who Killed Wikipedia? : A hardened corps of volunteer editors is the only force protecting Wikipedia. They might also be killing it", *Pacific Standard* magazine, November/December 2014 issue.

## Learning resources

- Wikiversity list of learning resources. (Includes related courses, Web-based seminars, slides, lecture notes, text books, quizzes, glossaries, etc.)
- The Great Book of Knowledge, Part 1: A Wiki is a Kind of Bus, Ideas, with Paul Kennedy, CBC Radio One, originally broadcast January 15, 2014. Webpage includes a link to the archived audio program (also found here). The radio documentary discusses Wikipedia's history, development and its place within the broader scope of the trend to democratized knowledge. It also includes interviews with several key Wikipedia staff and contributors, including Kat Walsh and Sue Gardner (audio, 53:58, Flash required).

## Other media coverage

*See also: List of films about Wikipedia*

- "See Who's Editing Wikipedia – Diebold, the CIA, a Campaign", *WIRED*, August 14, 2007.
- Balke, Jeff (March 2008). "For Music Fans: Wikipedia; MySpace". *Houston Chronicle*. Broken Record (blog). Retrieved December 17, 2008.
- Dee, Jonathan (July 1, 2007). "All the News That's Fit to Print Out". *The New York Times Magazine*. Retrieved February 22, 2008.
- Giles, Jim (September 20, 2007). "Wikipedia 2.0 – Now with Added Trust". *New Scientist*. Retrieved January 14, 2008.
- Miliard, Mike (December 2, 2007). "Wikipedia Rules". *The Phoenix*. Retrieved February 22, 2008.
- Poe, Marshall (September 1, 2006). "The Hive". *The Atlantic Monthly*. Retrieved March 22, 2008.
- Rosenwald, Michael S. (October 23, 2009). "Gatekeeper of D.C.'s entry: Road to city's Wikipedia page goes through a DuPont Circle bedroom". *The Washington Post*. Retrieved October 22, 2009.
- Runciman, David (May 28, 2009). "Like Boiling a Frog". *London Review of Books*. Retrieved June 3, 2009.
- Taylor, Chris (May 29, 2005). "It's a Wiki, Wiki World". *Time*. Retrieved February 22, 2008.
- "Technological Quarterly: Brain Scan: The Free-knowledge Fundamentalist". *The Economist Web and Print*. June 5, 2008. Retrieved June 5, 2008. "Jimmy Wales changed the world with Wikipedia, the hugely popular online encyclopedia that anyone can edit. What will he do next?"
- "Is Wikipedia Cracking Up?" *The Independent*, February 3, 2009.
- "Wikipedia probe into paid-for 'sockpuppet' entries", BBC News', October 21, 2013.
- "The Decline of Wikipedia", *MIT Technology Review*, October 22, 2013
- Edits to Wikipedia pages on Bell, Garner, Diallo traced to 1 Police Plaza (March 2015), *Capital*
- Angola's Wikipedia Pirates Are Exposing Problems (March 2016), *Motherboard*
- Dark Side of Wikipedia at the Wayback Machine (archived 4 August 2016) *Full Measure with Sharyl Attkinson,* April 17, 2016. (Includes video.)
- Wales, Jimmy (December 9, 2016). "How Wikipedia Works". *cato.org*. Cato Institute. "Jimmy Wales, founder of Wikipedia, discusses the site, how it's treated by governments, and how it's fueled by its users."

# External links

- Official website (Mobile) – multilingual portal (contains links to all language editions) (wikipedia.com still redirects here)

Find more about

- Wikipedia at DMOZ
- Wikitrends: Wikipedia articles most visited today
- "Wikipedia collected news and commentary". *The Guardian*.
- Wikipedia topic page at *The New York Times*
- Video of TED talk by Jimmy Wales on the birth of Wikipedia
- Audio of interview with Jimmy Wales about Wikipedia in general on the EconTalk podcast
- Wikipedia and why it matters – Larry Sanger's 2002 talk at Stanford University; video archive and transcript of the talk
- "Intelligence in Wikipedia" Google TechTalk on YouTube, describing an intelligence project utilizing Wikipedia, and how Wikipedia articles could be auto-generated from web content
- *Community Performance Optimization: Making Your People Run as Smoothly as Your Site*, talk presented at OOPSLA 2009 by the Wikimedia Foundation's senior software architect and former chief technology officer Brion Vibber, comparing the challenges of a large community of editors with those of a large community of software developers
- WikiPapers – compilation of conference papers, journal articles, theses, books, datasets and tools about Wikipedia and wikis
- Open Wikipedia Ranking

**Wikipedia**
at Wikipedia's sister projects

- Definitions from Wiktionary
- Media from Commons
- News from Wikinews
- Quotations from Wikiquote
- Texts from Wikisource
- Textbooks from Wikibooks
- Travel guide from Wikivoyage
- Learning resources from Wikiversity
- Data from Wikidata
- Discussion from Meta-Wiki
- Documentation from MediaWiki

| v · t · e · | **Wikipedia** |
|---|---|
| **Overview** | Censorship · Conflict-of-interest editing · Criticism · Deletionism and inclusionism · Gender bias · Racial bias · MediaWiki · Notability · Reliability · Vandalism · |
| **Community** | Administrators · Arbitration Committee · Edit-a-thon · List of Wikipedias · *The Signpost* · Wikipedian in residence · Wikimania · |
| **People** | Florence Devouard · Sue Gardner · James Heilman · Katherine Maher · Magnus Manske · Erik Möller · Larry Sanger · Lila Tretikov · Jimmy Wales · Wikipedians · Wikipedian of the Year · |
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| **Recognition and honors** | 2008 Quadriga award · *Wikipedia Monument* · 2015 Erasmus Prize · 2015 Princess of Asturias Award · *Magna Carta (An Embroidery)* · |
| **References and analysis** | Cultural · Bibliography · Films · Academic studies · WikiScanner · Wikipedia Review · Wikipediocracy · Wiki-Watch · |
| **Mobile access** | Apps · QRpedia · Wapedia · WikiNodes · Wikipedia Zero · Wikiwand · |
| **Content use** | Books LLC · DBpedia · Deletionpedia · Kiwix · WikiReader · Health information · |
| **Similar projects** | Interpedia · Nupedia · Citizendium · Enciclopedia Libre Universal en Español · Veropedia · List of online encyclopedias · List of wikis · |
| **Related** | Wikimedia movement (Wikimedia Foundation · projects · · *The Iraq War: A Historiography of Wikipedia Changelogs* · Print Wikipedia · |
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| v · t · e · | **Wikis** |
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| **Types** | Personal · Medical · Semantic · Wiki farm · |

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| **Components** | Software · Markup · Interwiki links · |
| **Lists** | Wikis · Software · Markups and parsers · |
| **Comparisons** | Software · Wiki farms · |
| **See also** | History of wikis · Creole · |

| v · t · e · | **Wikimedia Foundation** | |
|---|---|---|
| **People** | **Current** | Aaron Halfaker · Dariusz Jemielniak · Guy Kawasaki · Katherine Maher · Jimmy Wales · |
| | **Past** | Hampton Catlin · Danese Cooper · Bishakha Datta · Florence Devouard · Oscar van Dillen · Sue Gardner · Arnnon Geshuri · Mike Godwin · James Heilman · Erik Möller · Lila Tretikov · Luis Villa · |
| **Content projects** | | **Wikipedia** · MediaWiki · Wiktionary · Wikiquote · Wikibooks · Wikisource · Wikimedia Commons · Wikispecies · Wikinews · Wikiversity · Wikidata · Wikivoyage · |
| **Other** | | List of Wikipedias · List of Wikimedia chapters · Wikimania · *The Signpost* · *Wikimedia v. NSA* · Wikimedia movement · Knowledge Engine · |

| v · t · e · | **List of Wikipedias by article count** |
|---|---|
| **5,000,000+** | English · |
| **2,000,000+** | Swedish · Cebuano · German · |
| **1,000,000+** | Dutch · French · Russian · Italian · Spanish · Waray · Polish · Vietnamese · Japanese · |
| **500,000+** | Portuguese · Chinese · Ukrainian · Catalan · Persian · |
| **200,000+** | Norwegian (bokmål/riksmål) · Arabic · Serbo-Croatian · Finnish · Hungarian · Indonesian · Romanian · Czech · Korean · Serbian · Turkish · Malay · Basque · Esperanto · Bulgarian · Danish · Minangkabau · Kazakh · Slovak · Armenian · Min Nan · Hebrew · |
| **100,000+** | Lithuanian · Croatian · Chechen · Slovene · Estonian · Galician · Norwegian (nynorsk) · Uzbek · Latin · Greek · Belarusian · Simple English · Volapük · Hindi · Thai · Azerbaijani · Georgian · Urdu · |
| **50,000+** | Occitan · Macedonian · Tamil · Malagasy · Welsh · Bosnian · Latvian · Telugu · Tagalog · Breton · Albanian · |
| **20,000+** | Javanese · Icelandic · Asturian · Marathi · Cantonese · Malayalam · Bengali · Afrikaans · Irish · Scots · Chuvash · West Frisian · Burmese · Swahili · Aragonese · Yoruba · Ido · Nepal Bhasa · Sicilian · Bishnupriya Manipuri · Punjabi · Alemannic · |
| **10,000+** | Kannada · Sundanese · Mongolian · Egyptian Arabic · Samogitian · Yiddish · Odia · Ossetian · Sanskrit · |
| **1,000+** | Uyghur · Northern Sami · Pashto · Dutch Low Saxon · Sindhi · Jamaican Creole · Crimean Tatar · Silesian · Assamese · Ripuarian · Konkani · Tulu · Wolof · |
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# Translation Task Force



**Shortcuts:**
**WP:MTP**
**WP:MEDT**
**WP:MEDTRANS**
**WP:TWB**
**WP:TTF**

The **Healthcare Translation Task Force**[1] – brings high quality, easy to understand health information into as many languages as possible.

It was created as a joint venture between WikiProject Medicine, Wiki Project Med Foundation, and Translators Without Borders. We have **together** translated over **1,900** articles in more than **90** languages! This translated content is getting about **40 million** views a year.[2]

Texts are translated where they are needed the most — currently: diseases, medications and drugs, anatomy, nutrition, sanitation, and women's health. To see our list of articles for translation check out: **our summaries**.

WIKIPROJECT MEDICINE | Wiki Project Med Foundation | TRANSLATORS WITHOUT BORDERS | RUBRIC

# LANGUAGE SHOULDN'T BE A BARRIER FOR HEALTH INFORMATION!

# What's happening

We have an offline version of our healthcare content. **Download the Android app** and access all this content when there's no Internet. (other languages)

**News**

*Last updated: April 2016*

## 2016

- 500 short articles ready for translation
- Launch of offline medical apps in 10 languages.[3]

**April**

- **58** Vaccine articles live during April (165 total)
- **Rubric donated 9 articles in African and Indian languages on sanitation and preventable infectious disease!**

**March**

- **29** articles translated !+ 30?

| WikiProject Medicine 100x1000 | Full | Su |
|---|---|---|
| **Year started** | 2011 | 201 |
| **Article goal #** | 100 | 100 |
| **Ready for translation** | 33 | 500 |
| **Language goal** | 50 | 100 |
| **Translations done** | 637 | 1,3 |
| **FA/GA translations** | 65 | 12 |
| **Needing integration** | Done | 4 |
| | | Last 2016 |

# Get invovled

**Community organization**
We need Wikipedians to engage the community on the different Wikipedias.

**Assessing content**
We need local-language speakers to determine which articles need to be translated into the target language.

**Translating**
We are always on the look-out for dedicated translators to work directly with our content, especially in smaller languages!

**Integration**
Translated articles need to be integrated into local Wikipedias. This process is done manually and needs to be in harmony with existing local articles.

**Posting jobs on Translators Without Borders website**

# Why help?

Wikipedia zero

We're working together with **Wikipedia Zero** to spread knowledge where it is needed the most!

We need people to manage languages. This involves posting new translation jobs on the TWB website.

**Template installation**

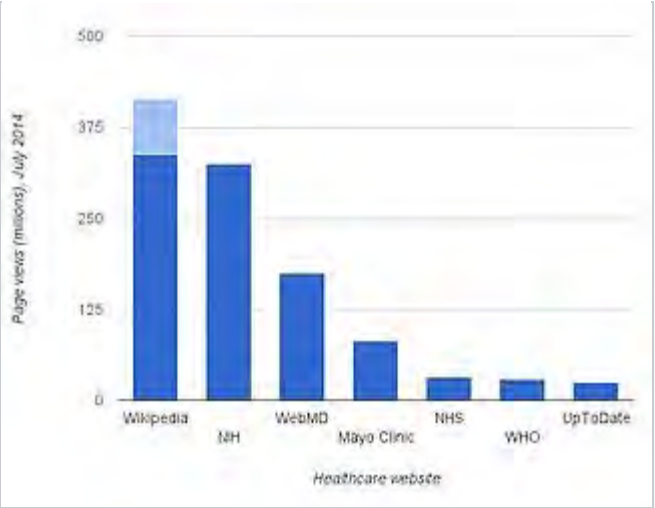
For translations to be more useful templates and modules should be installed. We need people with the technical know-how to help out.

**Programming**

Several of our processes are in need of simplification and many could be improved with bots.

**Writing content for the translation project**

Writing for translations may be slightly different from writing other articles on Wikipedia. If you are interested in improving articles contact James Heilman (*jmh649@gmail.com*) or simply create a Wikipedia account and start editing.




Health care site traffic comparison in July 2014. Light blue portions represent official Wikimedia Foundation data for all medical articles. Other data is estimated from SimilarWeb.[1]

Wikipedia is the most used health care resource on the Internet–both by unique visitors and by pageviews. For all those interested in global health this is an opportunity to help bring high quality healthcare information to the world.

In the beginning effort primarily concentrated on 80 medical articles of global significance. In the month of February 2012 these pages *in English* received a total of 10.6 million page views.[4]

In 2014 we switched our efforts to a larger number of shorter articles as we believe translating more short articles rather than fewer long articles will have a greater impact. A more in depth breakdown can be found at popular pages of the translation taskforce

As of July 2014, the more than 500 full articles translated via this project received over 1.2 million pages views per month (see **here**) in their local languages.

# Press

> “ Imagine if all our health information was available only in Dutch! ”
>
> Lori Thicke, TwB *GlobalVoices-Rising Voices: Translating Health Content Without Borders*

> “ We are working to build a world where knowledge doesn't have borders ”
>
> Lori Thicke, TwB *The Guardian: Translators fight the fatal effects of the language gap*

- "Making Wikipedia's medical articles accessible in Chinese", Wikimedia blog, June 2, 2015
- "A Fight for Awareness in the Age of Globalization", Huffington Post, October 2, 2014
- "Doctors and Translators Are Working Together to Bridge Wikipedia's Medical Language Gap", *Global Voices* & Wikimedia Blog, July 27, 2014
- "Translating Health Content Without Borders", *Global Voices*, August 30, 2012
- "Leveraging the Web to Overcome Challenges in the Developing World", *EContent Magazine*, July 5, 2012
- "Translators fight the fatal effects of the language gap" *The Guardian*, April 11, 2012

# Get in touch!

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*ER Physician, Project Lead*

Lucas 559
Lucas Rosnau
lrosnau@gmail.com
*Project Coordinator*

CFCF
Carl Fredrik Sjöland
cfsjoland@gmail.com
*Medical student, Project Coordinator*

## Medical translation

**Links**: **Translation Home** – About · Talk ·
**Progress**: Full – Short ·
**Resources**: Stats – Resources – Attribution ·
**Get involved**: Sign up ·
**Guides**: Community organizing – Assessing – Translating – Integration – Template installation – Programming – Writing ·

*This project has partly been funded by Wikimedia Foundation Individual Engagement Grants and partly by personal contribution from Dr. James Heilman*

# Notes [edit]

1. ^ Also known as the **Medical Translation Project**

1. ^ Heilman, JM; West, AG (4 March 2015). "Wikipedia and medicine: quantifying readership, editors, and the significance of natural language.". *Journal of medical Internet research*. **17** (3): e62. PMID 25739399.

Categories: Wikipedia translation | Translation task force | Wikipedia partnerships in medicine




# Translators Without Borders



**This article has multiple issues.** Please help **improve it** or discuss these issues on the **talk page**. *(Learn how and when to remove these template messages)*

- This article **possibly contains original research**. *(January 2013)*
- This article **relies too much on references to sources**. *(January 2013)*
- This article **contains content that is written like an advertisement**. *(January 2013)*

**Translators without Borders** is a non-profit organization[1] set up to provide translation services for humanitarian non-profits. It was established in 2010 as a sister organization of Traducteurs Sans Frontières, founded in 1993 by Lori Thicke and Ros Smith-Thomas of Lexcelera. As of 2012 it had about 1600 vetted volunteer translators.[2] Translators without Borders aims to close the language gaps that hinder critical humanitarian efforts by connecting nonprofit humanitarian organizations with a volunteer community of professional translators, building language translation capacity at the local level and raising awareness globally about language barriers.[3]

The organization works for humanitarian non-profit organizations that need information translated. Some of those groups are Doctors Without Borders, Medecins du Monde, UNICEF, Oxfam, Handicap International. Some examples of information translated by Translators without Borders includes reports, vital health information, and crisis response material for organizations responding to emergencies around the world, such as Burundi, Liberia and Greece. The organization translates millions of words per year.[4] According to their website, Translators without Borders has donated over 30 million translated words to non-profits, which is equivalent to over $6 million released for NGOs.

Translators without Borders is a 501(c)3 non-profit corporation in the U.S.

**Translators without Borders**

| | |
|---|---|
| **Founded** | 1993 (as Traducteurs Sans Frontières) |
| **Founder** | Lori Thicke<br>Ros Smith-Thomas |
| **Type** | Non-profit |
| **Focus** | Humanitarian |
| **Location** | Danbury, United States |
| **Origins** | Paris, France |
| **Area served** | Worldwide |
| **Method** | Translations |
| **Key people** | Andrew Bredenkamp (Board Chair)<br>Aimee Ansari (Executive Director) |
| **Website** | translatorswithoutborders.org |

Contents

# Working with translators [edit]

## Translators without Borders Workspace [edit]

ProZ.com created an online automated translation platform for Translators without Borders in May 2011. This translation center is called the Translators without Borders Workspace. Approved non-profits post translation projects and TWB volunteer translators pick up the jobs they wish to work with.

The use of the Workspace greatly increased the productivity of Translators without Borders. When projects were handled manually, TWB translated 29 projects, with 37,000 words of text, in seven language pairs, for nine different organizations. In January 2012, seven months after the Translators without Borders Workspace was completed, they translated 183 projects, with 280,000 words, in 25 language pairs, for 24 organizations.[5] In 2015 Translators without Borders reported to have delivered 7 million translated words through 780 projects to 214 aid organizations.[6]

## Volunteers [edit]

People who volunteer to be translators on the Translators without Borders website must be a professional translator with a minimum qualification of 4 years professional translation experience or 2 years of professional translation experience and a university degree in translation or a related subject.[7] Applications are fast-tracked for translators American Translators Association (ATA) certified, at Lionbridge, ProZ.com Certified PRO or with a MITI qualification from the UK Institute of Translating and Interpreting. These fast-track applicants are given credentials to join the Translators without Borders Workspace.

# Projects [edit]

## Words of Relief project [edit]

Words of Relief (WoR) is a translation crisis relief network intended to improve Communications with Communities (CwC) when the crisis response humanitarian workers and affected populations do not speak the same language. Words of Relief works to eliminate linguistic barriers[8] that can impede vital response and relief efforts during and after a crisis by doing the following:[9]

- Translating key crisis and disaster messages into the relevant languages and disseminating openly before crises occur.
- Building a spider network of diaspora translators who can translate from world languages into regional languages and who are trained to assist right away.
- Creating a crowd sourced, online (and mobile) application that connects the translation team with aid workers and data aggregators

The Spider Network volunteers for the Words of Relief project

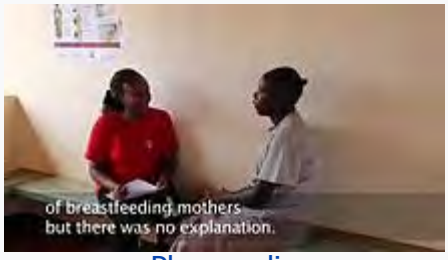
who need immediate help (entitled the Words of Relief Digital Exchange - WoRDE).[10]

Words of Relief was piloted from January, 2014 to May, 2015 in Nairobi, Kenya and concentrated on Swahili and Somali. Approximately 475,000 words of crisis relief content from various sources including the Infoasaid Message Library were translated.

The Words of Relief model has been deployed to respond to several crises worldwide, including the Ebola emergency[11] in West Africa and the Nepal earthquake.[12] Rapid Response Teams in Arabic, Persian, Greek, Kurdish and Urdu are currently providing rapid translations for aid organizations along the refugee route in Europe. Teams of professional volunteers work with partners to translate information on reception centres and ferry strikes, signage for the centres, and health information.

Words of Relief relies on a crowd-sourced, online (and mobile) application, called the Words of Relief Digital Exchange (WoRDE). The platform was launched in 2014 and it connects teams of rapid response translators with aid workers to do translations during a sudden onset crisis.

Words of Relief is supported by the Humanitarian Innovation Fund (HIF), a program managed by ELRHA. The Words of Relief Digital Exchange is funded by Microsoft's Technology for Good.[13]




Play media

A video which communicates the effectiveness of translation in increasing communications with communities, and highlights the critical importance of local language communications in health, education and crisis situations.


Infograph showing the impact of translation

## Information in the Right Language [edit]

An Impact Study was conducted to measure the comprehensibility of English information posters compared with translated Swahili posters and it showed that there is a very clear difference in the levels of comprehension, in favour of the translated Swahili poster. Initially, only eight per cent of respondents answered simple questions about the disease correctly. When respondents were given simple information about the disease in English, correct answers rose to 16%. But when given this information in Swahili, respondents got 92% of the questions correct.

## The HealthPhone project [edit]

One of the Translators without Borders projects is in partnership with the Mother and Child Health and Education Trust in India. HealthPhone, which was founded and created by Nand Wadhwani, creates health videos that are preloaded to phones throughout India and beyond.[14] The videos cover a variety of health issues, such as breastfeeding, malnutrition, post-natal and newborn care, and more.[15]

Through translators, videos are subtitled so that people throughout India (and in Africa) who do not speak or read the source language can learn from the videos. So far videos have been subtitled into about 10 Indic languages, Swahili and Spanish.

## Simple Words for Health [edit]

Simple Words for Health (SWFH), a simplified medical terminology resource, was set up in 2014. SWFH is a database of 12,000 essential medical terms that have been simplified and translated into more than 40 world languages by qualified doctors and trained medical translators.

## Wikipedia [edit]

In 2011, Translators without Borders began a collaborative effort to translate key medical articles on English Wikipedia into other languages.[16] The WikiProject Medicine Translation Task Force first improves the 8 medical articles deemed most essential to WP:GA or WP:FA status.[17] When the articles are improved, they are translated into simplified English by Content Rules (the simplified English is provided on the Wikipedia simplified English site) and a goal of more than 100 languages. Eventually, the hope is articles will be translated into all of the 285 languages that Wikipedia exists in. This process is expected to take several years.

All content is available through mobile networks and some content without data charges through the Wikipedia mobile partners Telnor, Orange and STC in Africa, South East Asia and the Middle East. Many of the articles are available in spoken Wikipedia. Some of these articles are also pending publication in open access general medical journals.

### Training Center in Kenya [edit]

In April 2012, Translators without Borders opened its first Healthcare Translation Center in Nairobi. In the Center, located in Nairobi Kenya, new translators are trained to work in Kiswahili, as well as a number of the other 42 languages spoken in Kenya. Since the Center was first launched in 2012, basic translation training has been provided to over 250 people. This project focuses on healthcare information translated into Swahili.[18]

The purpose of the Healthcare Translation Center is to intensively train local Kenyans to become professional translators. These translators assist in the process of getting healthcare information out in Swahili. These translators are recruited to the training center due to backgrounds in language or in health.

## Management [edit]

Translators without Borders is managed by a board of directors. Day-to-day operations are managed by a staff who report to an Executive Director, a Director of External Affairs and a Programs Director.

## See also [edit]

- List of Without Borders organizations
- Science and Development Network
- Non-commercial
- Non-governmental organization (NGO)
- Non-profit organizations and access to public information
- Non-profit sector

## References [edit]


1. ^ *"Translators without borders expands management structure, holds first board meeting", Globalization and Localization Association (GALA), June 2010*
2. ^ Kelly, Nataly (12 March 2011). "Translators without Borders Prepares to Bridge the Last Language Mile". *The Huffington Post*. Retrieved 10 May 2012.
3. ^ TRANSLATING FOR HUMANITY - NCTA's Translorial Online Edition
4. ^ Multilingual Computing and Technology, volume 12 issue 8
5. ^ Petras, Rebecca (2012-11-30). "Translation | Harvard International Review". Hir.harvard.edu. Retrieved 2013-01-11.
6. ^ "Translators without Borders translates 30 million words for aid organisations | Translators without Borders". *translatorswithoutborders.org*. Retrieved 2016-04-19.
7. ^ "Translators". Translators without Borders. Retrieved August 29, 2016.
8. ^ "Ebola Outbreak: TWB providing translation in local languages". *Digital Humanitarian Network*. Retrieved 10 August 2015.
9. ^ "Ebola: a crisis of language". *The Humanitarian Practice Network*. Nadia Berger & Grace Tang. June 2015.

Retrieved 15 March 2016.
10. ^ "TWB Repository – Free Translations". *repository.translatorswithoutborders.org*. Retrieved 2016-05-17.
11. ^ strategist, About The Author Karl Montevirgen Karl Montevirgen is a; Industry, Writer with Extensive Experience in the Financial; thinker, the arts A. forward; Creation, He Integrates His Skills in Content; Strategy, Business; Intelligence, Competitive; Explore, Experimental Art Practices to; Creating, Develop New Ways of; Studies/Writing, thinking about content He holds an MA in Critical (2016-04-15). "Content and Crisis: Translators Without Borders". *The Content Wrangler*. Retrieved 2016-05-17.
12. ^ "How Digital Humanitarians Are Closing the Gaps In Worldwide Disaster Response". *The Huffington Post*. 2016-01-28. Retrieved 2016-05-17.
13. ^ "Translators without Borders Receives Funding for Crisis Relief Network". *Translators without Borders*. Rebecca Petras.
14. ^ Rising Voices » Languages: Translating Health Content Without Borders
15. ^ "The Health Phone Project: Saving lives through subtitling| The Health Phone Project: Saving lives through subtitling". Twbnewsletter.translatorswithoutborders.org. Retrieved 2013-01-11.
16. ^ Tran, Mark (11 April 2012). "Translators fight the fatal effects of the language gap". *The Guardian*. Retrieved 10 May 2012.
17. ^ Wikipedia project takes on global healthcare information gap — Wikimedia blog
18. ^ "Translators Bridge Communication in Kenya Healthcare". *VOA*. Retrieved 2016-05-17.

## External links [edit]

- Official website
- TSF site **(French)**

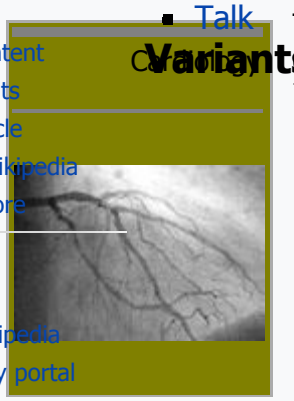
### Mentions by the press [edit]

- "Translators fight the fatal effects of the language gap" *The Guardian*, April 11, 2012
- "Leveraging the Web to Overcome Challenges in the Developing World", *EContent Magazine*, July 5, 2012
- "Translating Health Content Without Borders", *Global Voices*, August 30, 2012
- "Editing Wikipedia Pages for Med School Credit" *The New York Times*, September 29, 2013
- "Should I be getting health information from Wikipedia", *The Atlantic*, October 1, 2013
- Quest to Spread Dignity, Born in Calcutta, *The Global Calcuttan*, July 1, 2015
- "Translators without Borders Take on Ebola", *The BBC World Service Radio*
- "Lesbos: Online Volunteers Bridge Language Gap", *News Deeply,* March 2016
- "Content and Crisis: Translators without Borders", *The Content Wrangler,* April 2016
- "Making sure refugees aren't lost in translation - with one simple app", *UNHCR Innovation,* April 19, 2016
- "Making effective communiction a priority in humanitarian relief efforts", *The Content Wrangler,* May 15, 2016
- Humanitarian Innovation Fund Blog: Translators without Borders
- Breaking Down Linguistic Barriers with Words of Relief
- Making Transkation a Priority for Humanitarian Response
- Ebola Video Has Potential Aidience of 400 Million Africans
- Translators without Borders Receives Grant from Microsoft
- Microsoft Grants Three Nonprofits Cash, Software and Services for Technology Innovation

Categories: Translation associations | Organizations established in 1993 | 501(c)(3) nonprofit organizations | Non-profit organizations based in Connecticut


# Book:Cardiology





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## Cardiology [edit]

### Overview
- Cardiology
- Heart
- Human heart

### Symptoms
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### Diagnosis
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- Cardiac imaging

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**Treatment**

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- Angioplasty
- Coronary artery bypass surgery

Categories: Wikipedia books (community books) | Wikipedia books on biology | Wikipedia books on health




# Abdominal aortic aneurysm

From Wikipedia, the free encyclopedia

**Abdominal aortic aneurysm** (**AAA** or **triple A**)[1] is a localized enlargement of the abdominal aorta such that the diameter is greater than 3 cm or more than 50% larger than normal diameter.[2] They usually cause no symptoms except when ruptured.[2] Occasionally, abdominal, back, or leg pain may occur.[3] Large aneurysms can sometimes be felt by pushing on the abdomen.[3] Rupture may result in pain in the abdomen or back, low blood pressure, or loss of consciousness, and often results in death.[2][4]

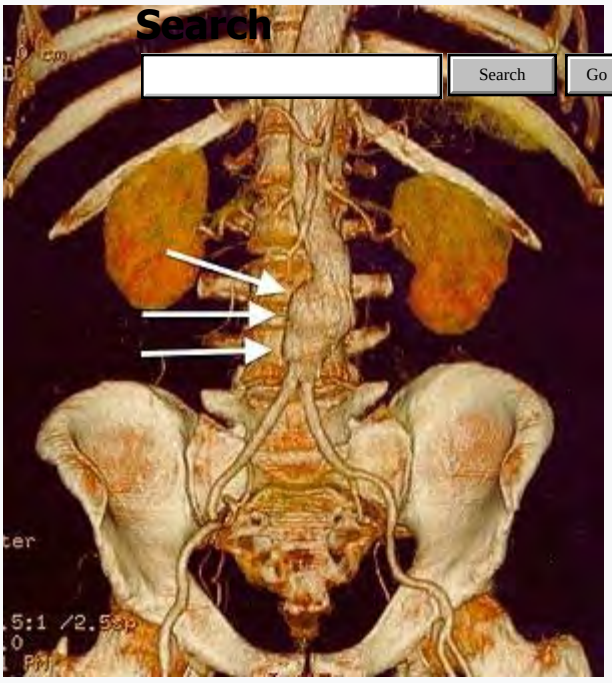
AAAs occur most commonly in those over 50 years old, in men, and among those with a family history.[2] Additional risk factors include smoking, high blood pressure, and other heart or blood vessel diseases.[5] Genetic conditions with an increased risk include Marfan syndrome and Ehlers-Danlos syndrome. AAAs are the most common form of aortic aneurysm.[6] About 85% occur below the kidneys with the rest either at the level of or above the kidneys.[2] In the United States, screening with ultrasound is recommended for males between 65 and 75 years of age with a history of smoking.[7] In the United Kingdom, screening all men over 65 is recommended.[2] Once an aneurysm is found, further ultrasounds are typically done on a regular basis.[3]

Not smoking is the single best way to prevent the disease. Other methods of prevention include treating high blood pressure, treating high blood cholesterol and not being overweight. Surgery is usually recommended when an AAA's diameter grows to >5.5 cm in males and >5.0 cm in females.[2] Other reasons for repair include the presence of symptoms and a rapid increase in size (more than one centimeter per year).[3] Repair may be either by open surgery or endovascular aneurysm repair (EVAR).[2] As compared to open surgery, EVAR has a lower risk of death in the short term and a shorter hospital stay, but may not always be an option.[2][8][9] There does not appear to be a difference in longer term outcomes between the two.[10] With EVAR there is a higher need for repeat procedures.[11]

AAAs affect between 2 and 8% of males over the age of 65. Rates among women are one-fourth as high. In those with an aneurysm less than 5.5 cm the risk of rupture in the next year is less than 1%. Among those with an aneurysm between 5.5 and 7 cm, the risk is about 10%, while for

## Variants

**Abdominal aortic aneurysm**
**Synonyms** triple-a



CT reconstruction image of an abdominal aortic aneurysm (white arrows)

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Vascular surgery |
| **ICD-10** | I71.3, I71.4 |
| **ICD-9-CM** | 441.3, 441.4 |
| **OMIM** | 100070 |
| **DiseasesDB** | 792 |
| **MedlinePlus** | 000162 |
| **eMedicine** | med/3443 emerg/27 radio/1 |
| **MeSH** | D017544 |

[edit on Wikidata]

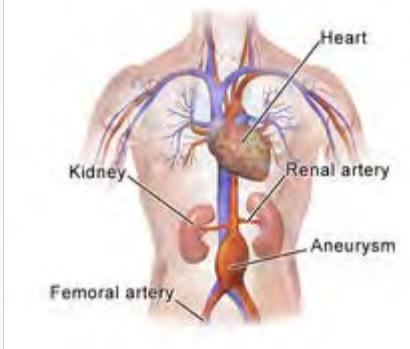
those with an aneurysm greater than 7 cm the risk is about 33%. Mortality if ruptured is 85% to 90%.[2] During 2013, aortic aneurysms resulted in 152,000 deaths, up from 100,000 in 1990.[12] In the United States AAAs resulted in between 10,000 and 18,000 deaths in 2009.[6]

Contents



## Signs and symptoms [edit]

The vast majority of aneurysms are asymptomatic. However, as abdominal aortic aneurysms expand, they may become painful and lead to pulsating sensations in the abdomen or pain in the chest, lower back, or scrotum.[13] The risk of rupture is high in a symptomatic aneurysm, which is therefore considered an indication for surgery. The complications include rupture, peripheral embolization, acute aortic occlusion, and aortocaval (between the aorta and inferior vena cava) or aortoduodenal (between the aorta and the duodenum) fistulae. On physical examination, a palpable and pulsatile abdominal mass can be noted. Bruits can be present in case of renal or visceral arterial stenosis.[14]



Abdominal aortic aneurysm location

### Aortic rupture [edit]

*Main article: Aortic rupture*

The signs and symptoms of a ruptured AAA may include severe pain in the lower back, flank, abdomen or groin. A mass that pulses with the heart beat may also be felt.[4] The bleeding can lead to a hypovolemic shock with low blood pressure and a fast heart rate. This may lead to brief passing out.[4]

The mortality of AAA rupture is as high as 90 percent. 65 to 75 percent of patients die before they arrive at the hospital and up to 90 percent die before they reach the operating room.[15] The bleeding can be

retroperitoneal or into the abdominal cavity. Rupture can also create a connection between the aorta and intestine or inferior vena cava.[16] Flank ecchymosis (appearance of a bruise) is a sign of retroperitoneal bleeding, and is also called Grey Turner's sign.[14][17]

Aortic aneurysm rupture may be mistaken for the pain of kidney stones, or muscle related back pain.[4]

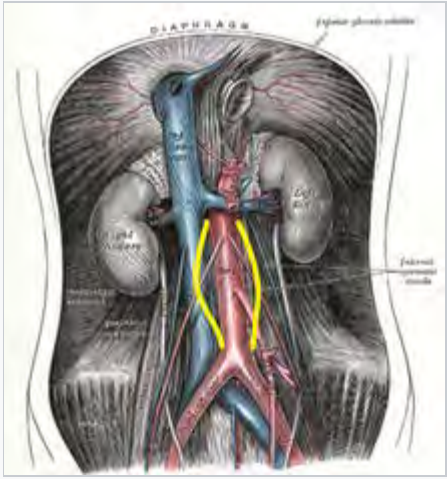
## Causes [edit]

The exact causes of the degenerative process remain unclear. There are, however, some hypotheses and well-defined risk factors.[18]

- Tobacco smoking: More than 90% of people who develop an AAA have smoked at some point in their lives.[19]
- Alcohol and hypertension: The inflammation caused by prolonged use of alcohol and hypertensive effects from abdominal edema which leads to hemorrhoids, esophageal varices, and other conditions, is also considered a long-term cause of AAA.
- Genetic influences: The influence of genetic factors is high. AAA is four to six times more common in male siblings of known patients, with a risk of 20-30%.[20] The high familial prevalence rate is most notable in male individuals.[21] There are many hypotheses about the exact genetic disorder that could cause higher incidence of AAA among male members of the affected families. Some presumed that the influence of alpha 1-antitrypsin deficiency could be crucial, while other experimental works favored the hypothesis of X-linked mutation, which would explain the lower incidence in heterozygous females. Other hypotheses of genetic etiology have also been formulated.[14] Connective tissue disorders, such as Marfan syndrome and Ehlers-Danlos syndrome, have also been strongly associated with AAA.[16] Both relapsing polychondritis and pseudoxanthoma elasticum may cause abdominal aortic aneurysm.[22]
- Atherosclerosis: The AAA was long considered to be caused by atherosclerosis, because the walls of the AAA frequently carry an atherosclerotic burden. However, this hypothesis cannot be used to explain the initial defect and the development of occlusion, which is observed in the process.[14]
- Other causes of the development of AAA include: infection, trauma, arteritis, and cystic medial necrosis.[16]

## Pathophysiology [edit]

The most striking histopathological changes of the aneurysmatic aorta are seen in the tunica media and intima layers. These changes include the accumulation of lipids in foam cells, extracellular free cholesterol crystals, calcifications, thrombosis, and ulcerations and ruptures of the layers. Adventitial inflammatory infiltrate is present.[16] However, the degradation of the tunica media by means of a proteolytic process seems to be the basic pathophysiologic mechanism of AAA development. Some researchers report increased expression and activity of matrix metalloproteinases in individuals with AAA. This leads to elimination of elastin from the media, rendering the aortic wall more susceptible to the influence of blood pressure.[14] Other reports have suggested the serine protease granzyme B may contribute to aortic aneurysm rupture through the cleavage of decorin, leading to disrupted collagen organization and reduced tensile strength of the adventitia.[23][24] There is also a reduced amount of vasa vasorum in the abdominal aorta (compared to the thoracic aorta); consequently, the tunica media must rely mostly on diffusion for nutrition, which makes it more susceptible to damage.[25]



A plate from *Gray's Anatomy* with yellow lines depicting the most common infrarenal location of the AAA

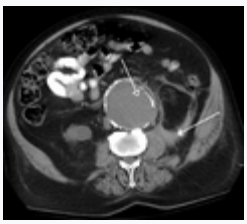
Hemodynamics affect the development of AAA, which has a predilection for the infrarenal aorta. The histological structure and mechanical characteristics of the infrarenal aorta differ from those of the thoracic

aorta. The diameter decreases from the root to the aortic bifurcation, and the wall of the infrarenal aorta also contains a lesser proportion of elastin. The mechanical tension in the abdominal aortic wall is therefore higher than in the thoracic aortic wall. The elasticity and distensibility also decline with age, which can result in gradual dilatation of the segment. Higher intraluminal pressure in patients with arterial hypertension markedly contributes to the progression of the pathological process.[16] Suitable hemodynamic conditions may be linked to specific intraluminal thrombus (ILT) patterns along the aortic lumen, which in turn may affect AAA's development.[26]

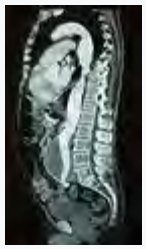
## Diagnosis [edit]

An abdominal aortic aneurysm is usually diagnosed by physical exam, ultrasound, or CT. Plain abdominal radiographs may show the outline of an aneurysm when its walls are calcified. However, this is the case in less than half of all aneurysms. Ultrasonography is used to screen for aneurysms and to determine the size of any present. Additionally, free peritoneal fluid can be detected. It is noninvasive and sensitive, but the presence of bowel gas or obesity may limit its usefulness. CT scan has a nearly 100% sensitivity for an aneurysm and is also useful in preoperative planning, detailing the anatomy and possibility for endovascular repair. In the case of suspected rupture, it can also reliably detect retroperitoneal fluid. Alternative less often used methods for visualization of an aneurysm include MRI and angiography.

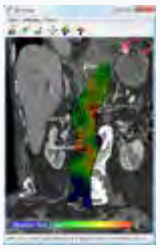
An aneurysm ruptures if the mechanical stress (tension per area) exceeds the local wall strength; consequently, peak wall stress (PWS)[27] and peak wall rupture risk (PWRR)[28] have been found to be more reliable parameters than diameter to assess AAA rupture risk. Medical software allows computing these rupture risk indices from standard clinical CT data and provides a patient-specific AAA rupture risk diagnosis.[29] This type of biomechanical approach has been shown to accurately predict the location of AAA rupture.[30]



A ruptured AAA with an open arrow marking the aneurysm and the closed arrow marking the free blood in the abdomen

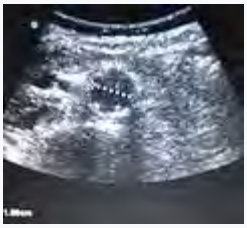


Sagittal CT image of an AAA

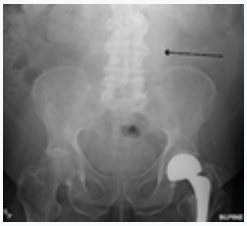


Biomechanical AAA rupture risk prediction

An axial contrast-enhanced CT scan demonstrating an abdominal aortic aneurysm of 4.8 by 3.8 cm



Ultrasound image of a normal abdominal aorta measuring 1.9 cm in diameter



The faint outline of the calcified wall of an AAA as seen on plain X-ray

Abdominal aortic aneurysms (3.4 cm)

An aortic aneurysm as seen on CT with a small area of remaining blood flow

### Classification [edit]

Abdominal aortic aneurysms are commonly divided according to their size and symptomatology. An aneurysm is usually defined as an outer aortic diameter over 3 cm (normal diameter of the aorta is around 2 cm).[31] If the outer diameter exceeds 5.5 cm, the aneurysm is considered to be large.[32] A ruptured AAA is a clinical diagnosis involving the presence of the triad of abdominal pain, shock, and a pulsatile abdominal mass. If these conditions are present, indicating AAA rupture, no further clinical investigations are needed before surgery.[33]

## Prevention [edit]

- Smoking cessation
- Treatment of hypertension

## Screening [edit]

The U.S. Preventive Services Task Force recommends a single screening ultrasound for abdominal aortic aneurysm in males age 65 to 75 years who have a history of smoking.[7] There is an estimated number needed to screen of approximately 850 people.[34] It is unclear if screening is useful in women aged 65 to 75 who have smoked and they recommend against screening in women who have never smoked.[7]

Repeat ultrasounds should be carried out in those who have an aortic size greater than 3.0 cm.[35] In those whose aorta is between 3.0 and 3.9 cm this should be every three years, if between 4.0 and 4.4 cm every two year, and if between 4.5 and 5.4 cm every year.[35]

In the United Kingdom one time screening is recommended in all males over 65 years of age.[2] Australia has no guideline on screening.[36]

## Management [edit]

The treatment options for asymptomatic AAA are conservative management, surveillance with a view to eventual repair, and immediate repair. Two modes of repair are available for an AAA: open aneurysm repair (OR), and endovascular aneurysm repair (EVAR). An intervention is often recommended if the aneurysm grows more than 1 cm per year or it is bigger than 5.5 cm.[37] Repair is also indicated for symptomatic aneurysms.

### Conservative [edit]

Conservative management is indicated in people where repair carries a high risk of mortality and in patients where repair is unlikely to improve life expectancy. The mainstay of the conservative treatment is smoking cessation.

Surveillance is indicated in small asymptomatic aneurysms (less than 5.5 cm) where the risk of repair exceeds the risk of rupture.[37] As an AAA grows in diameter, the risk of rupture increases. Surveillance until an aneurysm has reached a diameter of 5.5 cm has not been shown to have a higher risk as compared to early intervention.[38][39]

### Medication [edit]

No medical therapy has been found to be effective at decreasing the growth rate or rupture rate of asymptomatic AAAs.[2] Blood pressure and lipids should, however, be treated per usual.[31]

## Surgery [edit]

Surgery for an abdominal aortic aneurysm is known as AAA surgery or AAA repair.

The threshold for repair varies slightly from individual to individual, depending on the balance of risks and benefits when considering repair versus ongoing surveillance. The size of an individual's native aorta may influence this, along with the presence of comorbidities that increase operative risk or decrease life expectancy. Evidence; however, does not support repair if the size is between 4 cm and 5.5 cm.[37]

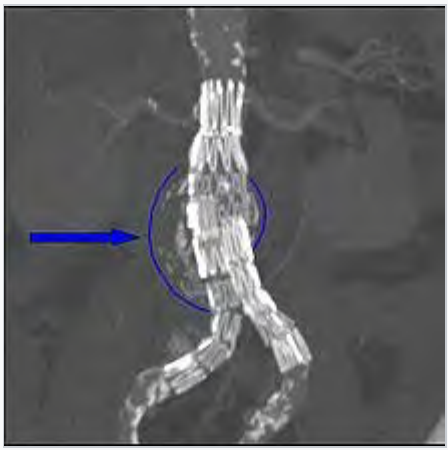
## Open repair [edit]

*Main article: Open aortic surgery*

Open repair is indicated in young patients as an elective procedure, or in growing or large, symptomatic or ruptured aneurysms. The aorta must be clamped off during the repair, denying blood to the abdominal organs and sections of the spinal cord; this can cause a range of complications. It is essential to make the critical part of the operation fast, so the incision is typically made large enough to facilitate the fastest repair. Recovery after open AAA surgery takes significant time. The minimums are a few days in intensive care, a week total in the hospital and a few months before full recovery.

## Endovascular repair [edit]

*Main article: Endovascular aneurysm repair*



Abdominal aortic endoprosthesis, CT scan, original aneurysm marked in blue

Endovascular repair first became practical in the 1990s and although it is now an established alternative to open repair, its role is yet to be clearly defined. It is generally indicated in older, high-risk patients or patients unfit for open repair. However, endovascular repair is feasible for only a proportion of AAAs, depending on the morphology of the aneurysm. The main advantages over open repair are that there is less peri-operative mortality, less time in intensive care, less time in hospital overall and earlier return to normal activity. Disadvantages of endovascular repair include a requirement for more frequent ongoing hospital reviews, and a higher chance of further procedures being required. According to the latest studies, the EVAR procedure does not offer any benefit for overall survival or health-related quality of life compared to open surgery, although aneurysm-related mortality is lower.[40][41][42][43] In patients unfit for open repair, EVAR plus conservative management was associated with no benefit, more complications, subsequent procedures and higher costs compared to conservative management alone.[44] Endovascular treatment for paraanastomotic aneurysms after aortobiiliac reconstruction is also a possibility.[45] A 2014 Cochrane review found tentative evidence of no difference in outcomes between endovascular and open repair of ruptured AAA in the first month.[46]

## Rupture [edit]

In those with aortic rupture of the AAA, treatment is immediate surgical repair. There appears to be benefits to allowing permissive hypotension and limiting the use of intravenous fluids during transport to the operating room.[47]

# Prognosis [edit]

Although the current standard of determining rupture risk is based on maximum diameter, it is

| AAA Size (cm) | Growth rate (cm/yr)[48] | Annual rupture risk (%)[49] |
|---|---|---|
| 3.0-3.9 | 0.39 | 0 |

| | | |
|---|---|---|
| 4.0-4.9 | 0.36 | 0.5-5 |
| 5.0-5.9 | 0.43 | 3-15 |
| 6.0-6.9 | 0.64 | 10-20 |
| >=7.0 | - | 20-50 |

known that smaller AAAs that fall below this threshold (diameter<5.5 cm) may also rupture, and larger AAAs (diameter>5.5 cm) may remain stable.[50][51] In one report, it was shown that 10–24% of ruptured AAAs were less than 5 cm in diameter.[51] It has also been reported that of 473 non-repaired AAAs examined from autopsy reports, there were 118 cases of rupture, 13% of which were less than 5 cm in diameter. This study also showed that 60% of the AAAs greater than 5 cm (including 54% of those AAAs between 7.1 and 10 cm) never experienced rupture.[52] Vorp *et al.* later deduced from the findings of Darling *et al.* that if the maximum diameter criterion were followed for the 473 subjects, only 7% (34/473) of cases would have succumbed to rupture prior to surgical intervention as the diameter was less than 5 cm, with 25% (116/473) of cases possibly undergoing unnecessary surgery since these AAAs may never have ruptured.[52]

Alternative methods of rupture assessment have been recently reported. The majority of these approaches involve the numerical analysis of AAAs using the common engineering technique of the finite element method (FEM) to determine the wall stress distributions. Recent reports have shown that these stress distributions have been shown to correlate to the overall geometry of the AAA rather than solely to the maximum diameter.[53][54][55] It is also known that wall stress alone does not completely govern failure as an AAA will usually rupture when the wall stress exceeds the wall strength. In light of this, rupture assessment may be more accurate if both the patient-specific wall stress is coupled together with patient-specific wall strength. A non-invasive method of determining patient-dependent wall strength was recently reported,[56] with more traditional approaches to strength determination via tensile testing performed by other researchers in the field.[57][58][59] Some of the more recently proposed AAA rupture-risk assessment methods include: AAA wall stress;[27][60][61] AAA expansion rate;[62] degree of asymmetry;[55] presence of intraluminal thrombus (ILT);[63] a rupture potential index (RPI);[64][65] a finite element analysis rupture index (FEARI);[66] biomechanical factors coupled with computer analysis;[67] growth of ILT;[68] geometrical parameters of the AAA;[69] and also a method of determining AAA growth and rupture based on mathematical models.[70][71]

The post-operative mortality for an already ruptured AAA has slowly decreased over several decades but remains higher than 40%.[33] However, if the AAA is surgically repaired before rupture, the post-operative mortality rate is substantially lower: approximately 1-6%.[72]

## Epidemiology [edit]

The occurrence of AAA varies by ethnicity. In the United Kingdom the rate of AAA in Caucasian men older than 65 years is about 4.7%, while in Asian men it is 0.45%.[73] It is also less common in individuals of African, and Hispanic heritage.[2] They occur four times more often in men than women.[2]

There are at least 13,000 deaths yearly in the U.S. secondary to AAA rupture.[2] The peak number of new cases per year among males is around 70 years of age, the percentage of males affected over 60 years is 2–6%. The frequency is much higher in smokers than in non-smokers (8:1), and the risk decreases slowly after smoking cessation.[74] In the U.S., the incidence of AAA is 2–4% in the adult population.[14]

Rupture of the AAA occurs in 1–3% of men aged 65 or more, the mortality is 70–95%.[32]

## History [edit]

The first historical records about AAA are from Ancient Rome in the 2nd century AD, when Greek surgeon Antyllus tried to treat the AAA with proximal and distal ligature, central incision and removal of thrombotic material from the aneurysm. However, attempts to treat the AAA surgically were unsuccessful until 1923. In

that year, Rudolph Matas (who also proposed the concept of endoaneurysmorrhaphy), performed the first successful aortic ligation on a human.[75] Other methods that were successful in treating the AAA included wrapping the aorta with polyethene cellophane, which induced fibrosis and restricted the growth of the aneurysm. Albert Einstein was operated on by Rudolph Nissen with use of this technique in 1949, and survived five years after the operation, though he eventually died when the aneurysm ruptured.[76] Endovascular aneurysm repair was first performed in the late 1980s and has been widely adopted in the subsequent decades. Endovascular repair was first used for treating a ruptured aneurysm in Nottingham in 1994[77]

Former presidential candidate Bob Dole had an abdominal aortic aneurysm in 2001 and was treated surgically by vascular surgeon Kenneth Ouriel. The operation was successful. In 1993, country music singer Conway Twitty died from AAA, and actor George C. Scott also died of an Abdominal Aneurysm.[78]

## Society and culture [edit]

In 2001 former presidential candidate Bob Dole underwent surgery for an abdominal aortic aneurysm in which a team of surgeons led by Doctor Kenneth Ouriel inserted a stent graft:

> “Ouriel said that the team inserted a Y-shaped tube through an incision in Dole's leg and placed it inside the weakened portion of the aorta. The aneurysm will eventually contract around the stent, which will remain in place for the rest of Dole's life.[78]”

— *Associated Press*

Actor Robert Jacks, who played Leatherface in *Texas Chainsaw Massacre: The Next Generation*, died from an abdominal aneurysm on August 8, 2001, just one day shy of his 42nd birthday. His father also died from the same cause when Robert was a child.

Musician Conway Twitty died in June 1993 from an abdominal aortic aneurysm, aged 59, two months before the release of what would be his final studio album, *Final Touches*.

## Research [edit]

### Risk assessment [edit]

There have been many calls for alternative approaches to rupture risk assessment over the past number of years, with many believing that a biomechanics-based approach may be more suitable than the current diameter approach. Numerical modeling is a valuable tool to researchers allowing approximate wall stresses to be calculated, thus revealing the rupture potential of a particular aneurysm. Experimental models are required to validate these numerical results and provide a further insight into the biomechanical behavior of the AAA. *In vivo*, AAAs exhibit a varying range of material strengths[79] from localised weak hypoxic regions[80] to much stronger regions and areas of calcifications.[81]

### Experimental models [edit]

Experimental models can now be manufactured using a novel technique involving the injection-moulding lost-wax manufacturing process to create patient-specific anatomically correct AAA replicas.[82] Work has also focused on developing more realistic material analogues to those *in vivo*, and recently a novel range of silicone-rubbers was created allowing the varying material properties of the AAA to be more accurately represented.[83] These rubber models can also be used in a variety of experimental testing from stress analysis using the photoelastic method[84] to deterimining whether the locations of rupture experimentally correlate with those predicted numerically.[85] New endovascular devices are being developed that are able to treat more complex and tortuous anatomies.[86]

## Prevention and treatment [edit]

An animal study showed that removing a single protein prevents early damage in blood vessels from triggering a later-stage, complications. By eliminating the gene for a signaling protein called cyclophilin A (CypA) from a strain of mice, researchers were able to provide complete protection against abdominal aortic aneurysm.[87]

Other recent research identified Granzyme B (GZMB) (a protein-degrading enzyme) to be a potential target in the treatment of abdominal aortic aneurysms. Elimination of this enzyme in mice models both slowed the progression of aneurysms and improved survival.[88][89]

# References [edit]


1. ^ Logan, Carolynn M.; Rice, M. Katherine (1987). *Logan's Medical and Scientific Abbreviations*. Philadelphia: J. B. Lippincott Company. p. 3. ISBN 0-397-54589-4.
2. ^ *a b c d e f g h i j k l m n o* Kent KC (27 November 2014). "Clinical practice. Abdominal aortic aneurysms.". *The New England Journal of Medicine*. **371** (22): 2101–8. doi:10.1056/NEJMcp1401430. PMID 25427112.
3. ^ *a b c d* Upchurch GR, Schaub TA (2006). "Abdominal aortic aneurysm". *Am Fam Physician*. **73** (7): 1198–204. PMID 16623206.
4. ^ *a b c d* Spangler R, Van Pham T, Khoujah D, Martinez JP (2014). "Abdominal emergencies in the geriatric patient.". *International journal of emergency medicine*. **7** (1): 43. doi:10.1186/s12245-014-0043-2. PMID 25635203.
5. ^ Wittels K (November 2011). "Aortic emergencies.". *Emergency medicine clinics of North America*. **29** (4): 789–800, vii. doi:10.1016/j.emc.2011.09.015. PMID 22040707.
6. ^ *a b* "Aortic Aneurysm Fact Sheet". *cdc.gov*. July 22, 2014. Retrieved 3 February 2015.
7. ^ *a b c* LeFevre ML (19 August 2014). "Screening for abdominal aortic aneurysm: U.S. Preventive Services Task Force recommendation statement.". *Annals of Internal Medicine*. **161** (4): 281–90. doi:10.7326/m14-1204. PMID 24957320.
8. ^ Thomas DM, Hulten EA, Ellis ST, Anderson DM, Anderson N, McRae F, Malik JA, Villines TC, Slim AM (2014). "Open versus Endovascular Repair of Abdominal Aortic Aneurysm in the Elective and Emergent Setting in a Pooled Population of 37,781 Patients: A Systematic Review and Meta-Analysis.". *ISRN cardiology*. **2014**: 149243. doi:10.1155/2014/149243. PMID 25006502.
9. ^ Biancari F, Catania A, D'Andrea V (November 2011). "Elective endovascular vs. open repair for abdominal aortic aneurysm in patients aged 80 years and older: systematic review and meta-analysis.". *European Journal of Vascular and Endovascular Surgery*. **42** (5): 571–6. doi:10.1016/j.ejvs.2011.07.011. PMID 21820922.
10. ^ Paravastu SC, Jayarajasingam R, Cottam R, Palfreyman SJ, Michaels JA, Thomas SM (23 January 2014). "Endovascular repair of abdominal aortic aneurysm.". *The Cochrane database of systematic reviews*. **1**: CD004178. doi:10.1002/14651858.CD004178.pub2. PMID 24453068.
11. ^ Ilyas S, Shaida N, Thakor AS, Winterbottom A, Cousins C (February 2015). "Endovascular aneurysm repair (EVAR) follow-up imaging: the assessment and treatment of common postoperative complications.". *Clinical radiology*. **70** (2): 183–196. doi:10.1016/j.crad.2014.09.010. PMID 25443774.
12. ^ GBD 2013 Mortality Causes of Death Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013". *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
13. ^ Fauci, Anthony (2008-03-06). "242". *Harrison's Principles of Internal Medicine* (17 ed.). McGraw-Hill Professional. ISBN 0-07-146633-9.
14. ^ *a b c d e f* *Abdominal Aortic Aneurysm* at eMedicine
15. ^ Brown LC, Powell JT (September 1999). "Risk Factors for Aneurysm Rupture in Patients Kept Under Ultrasound Surveillance". *Annals of Surgery*. **230** (3): 289–96; discussion 296–7. doi:10.1097/00000658-199909000-00002. PMC 1420874. PMID 10493476.
16. ^ *a b c d e* Treska V. *et al.*:Aneuryzma břišní aorty, Prague, 1999, ISBN 80-7169-724-9
17. ^ Goldman, Lee. *Goldman's Cecil Medicine* (24th ed.). Philadelphia: Elsevier Saunders. p. 837. ISBN 1437727883.
18. ^ http://www.danmedbul.dk/portal/pls/portal/docs/6348849.PDF [*permanent dead link*]
19. ^ Greenhalgh RM, Powell JT (January 2008). "Endovascular repair of abdominal aortic aneurysm". *N. Engl. J. Med.* **358** (5): 494–501. doi:10.1056/NEJMct0707524. PMID 18234753.
20. ^ Baird PA, Sadovnick AD, Yee IM, Cole CW, Cole L (Sep 1995). "Sibling risks of abdominal aortic aneurysm".

*Lancet*. **346** (8975): 601–4. doi:10.1016/S0140-6736(95)91436-6. PMID 7651004.
21. ^ Clifton MA (Nov 1977). "Familial abdominal aortic aneurysms". *Br J Surg*. **64** (11): 765–6. doi:10.1002/bjs.1800641102. PMID 588966.
22. ^ Rapini, Ronald P.; Bolognia, Jean L.; Jorizzo, Joseph L. (2007). *Dermatology: 2-Volume Set*. St. Louis: Mosby. ISBN 1-4160-2999-0.
23. ^ Chamberlain CM, Ang LS, Boivin WA, Cooper DM, Williams SJ, Zhao H, Hendel A, Folkesson M, Swedenborg J, Allard MF, McManus BM, Granville DJ (2010). "Perforin-independent extracellular granzyme B activity contributes to abdominal aortic aneurysm". *Am. J. Pathol*. **176** (2): 1038–49. doi:10.2353/ajpath.2010.090700. PMC 2808106. PMID 20035050.
24. ^ Ang LS, Boivin WA, Williams SJ, Zhao H, Abraham T, Carmine-Simmen K, McManus BM, Bleackley RC, Granville DJ (2011). "Serpina3n attenuates granzyme B-mediated decorin cleavage and rupture in a murine model of aortic aneurysm". *Cell Death Dis*. **2** (9): e209. doi:10.1038/cddis.2011.88. PMC 3186906. PMID 21900960.
25. ^ MacSweeney ST, Powell JT, Greenhalgh RM (1994). "Pathogenesis of abdominal aortic aneurysm". *Br J Surg*. **81** (7): 935–41. doi:10.1002/bjs.1800810704. PMID 7922083.
26. ^ Biasetti J, Hussain F, Gasser TC (2011). "Blood flow and coherent vortices in the normal and aneurysmatic aortas: a fluid dynamical approach to intra-luminal thrombus formation". *J R Soc Interface*. **8** (63): 1449–61. doi:10.1098/rsif.2011.0041. PMC 3163425. PMID 21471188.
27. ^ *a b* Fillinger MF, Marra SP, Raghavan ML, Kennedy FE (April 2003). "Prediction of rupture risk in abdominal aortic aneurysm during observation: wall stress versus diameter". *Journal of Vascular Surgery*. **37** (4): 724–32. doi:10.1067/mva.2003.213. PMID 12663969.
28. ^ Gasser TC, Auer M, Labruto F, Swedenborg J, Roy J (2010). "Biomechanical rupture risk assessment of abdominal aortic aneurysms: model complexity versus predictability of finite element simulations". *Eur J Vasc Endovasc Surg*. **40** (2): 176–185. doi:10.1016/j.ejvs.2010.04.003. PMID 20447844.
29. ^ http://www.vascops.com/en/vascops-A4clinics.html
30. ^ Doyle BJ, McGloughlin TM, Miller K, Powell JT, Norman PE (2014). "Regions of high wall stress can predict the future location of rupture in abdominal aortic aneurysm". *Cardiovasc Intervent Radiol*. **37** (3): 815–818. doi:10.1007/s00270-014-0864-7. PMID 24554200.
31. ^ *a b* Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM, White CJ, White J, White RA, Antman EM, Smith SC, Adams CD, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B (September 2006). "ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease) —summary of recommendations". *J Vasc Interv Radiol*. **17** (9): 1383–97; quiz 1398. doi:10.1097/01.RVI.0000240426.53079.46. PMID 16990459.
32. ^ *a b* Lindholt JS, Juul S, Fasting H, Henneberg EW (Apr 2005). "Screening for abdominal aortic aneurysms: single centre randomised controlled trial". *BMJ*. **330** (7494): 750. doi:10.1136/bmj.38369.620162.82. PMC 555873. PMID 15757960.
33. ^ *a b* Bown MJ, Sutton AJ, Bell PR, Sayers RD (June 2002). "A meta-analysis of 50 years of ruptured abdominal aortic aneurysm repair". *The British Journal of Surgery*. **89** (6): 714–30. doi:10.1046/j.1365-2168.2002.02122.x. PMID 12027981.
34. ^ Cinà CS, Devereaux PJ (2005). "Review: population-based screening for abdominal aortic aneurysm reduces cause-specific mortality in older men". *ACP J. Club*. **143** (1): 11. PMID 15989299.
35. ^ *a b* Bown MJ, Sweeting MJ, Brown LC, Powell JT, Thompson SG (February 2013). "Surveillance intervals for small abdominal aortic aneurysms: a meta-analysis". *JAMA*. **309** (8): 806–13. doi:10.1001/jama.2013.950. PMID 23443444.
36. ^ Robinson, D; Mees, B; Verhagen, H; Chuen, J (June 2013). "Aortic aneurysms - screening, surveillance and referral.". *Australian family physician*. **42** (6): 364–9. PMID 23781541.
37. ^ *a b c* Filardo, G; Powell, JT; Martinez, MA; Ballard, DJ (8 February 2015). "Surgery for small asymptomatic abdominal aortic aneurysms". *The Cochrane database of systematic reviews*. **2** (2): CD001835. doi:10.1002/14651858.CD001835.pub4. PMID 25927098.
38. ^ Powell JT, Brown LC, Forbes JF, Fowkes FG, Greenhalgh RM, Ruckley CV, Thompson SG (Jun 2007). "Final 12-year follow-up of surgery versus surveillance in the UK Small Aneurysm Trial". *Br J Surg*. **94** (6): 702–8. doi:10.1002/bjs.5778. PMID 17514693.
39. ^ Lederle FA, Wilson SE, Johnson GR, Reinke DB, Littooy FN, Acher CW, Ballard DJ, Messina LM, Gordon IL, Chute EP, Krupski WC, Busuttil SJ, Barone GW, Sparks S, Graham LM, Rapp JH, Makaroun MS, Moneta GL, Cambria RA,

Makhoul RG, Eton D, Ansel HJ, Freischlag JA, Bandyk D (May 2002). "Immediate repair compared with surveillance of small abdominal aortic aneurysms". *N Engl J Med*. **346** (19): 1437–44. doi:10.1056/NEJMoa012573. PMID 12000813.

40. ^ Rutherford RB (Jun 2006). "Randomized EVAR trials and advent of level i evidence: a paradigm shift in management of large abdominal aortic aneurysms?". *Semin Vasc Surg*. **19** (2): 69–74. doi:10.1053/j.semvascsurg.2006.03.001. PMID 16782510.
41. ^ Lederle FA, Kane RL, MacDonald R, Wilt TJ (2007). "Systematic review: repair of unruptured abdominal aortic aneurysm". *Annals of Internal Medicine*. **146** (10): 735–41. doi:10.7326/0003-4819-146-10-200705150-00007. PMID 17502634.
42. ^ Evar Trial Participants (2005). "Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial". *Lancet*. **365** (9478): 2179–86. doi:10.1016/S0140-6736(05)66627-5. PMID 15978925.
43. ^ Blankensteijn JD, de Jong SE, Prinssen M, van der Ham AC, Buth J, van Sterkenburg SM, Verhagen HJ, Buskens E, Grobbee DE (Jun 2005). "Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms". *N Engl J Med*. **352** (23): 2398–405. doi:10.1056/NEJMoa051255. PMID 15944424.
44. ^ Evar Trial Participants (2005). "Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial". *Lancet*. **365** (9478): 2187–92. doi:10.1016/S0140-6736(05)66628-7. PMID 15978926.
45. ^ Amato AC, Kahlberg AK, Bertoglio LB, Melissano GM, Chiesa RC (2008). "Endovascular treatment of a triple paraanastomotic aneurysm after aortobiiliac reconstruction". *J Vasc Bras*. **7** (3): 1–3. doi:10.1590/S1677-54492008000300016.
46. ^ Badger, S; Bedenis, R; Blair, PH; Ellis, P; Kee, F; Harkin, DW (21 July 2014). "Endovascular treatment for ruptured abdominal aortic aneurysm". *The Cochrane database of systematic reviews*. **7** (7): CD005261. doi:10.1002/14651858.CD005261.pub3. PMID 25042123.
47. ^ Hamilton H, Constantinou J, Ivancev K (April 2014). "The role of permissive hypotension in the management of ruptured abdominal aortic aneurysms.". *The Journal of cardiovascular surgery*. **55** (2): 151–9. PMID 24670823.
48. ^ Bernstein EF, Chan EL (September 1984). "Abdominal aortic aneurysm in high-risk patients. Outcome of selective management based on size and expansion rate". *Ann. Surg*. **200** (3): 255–63. doi:10.1097/00000658-198409000-00003. PMC 1250467. PMID 6465980.
49. ^ Brewster DC, Cronenwett JL, Hallett JW, Johnston KW, Krupski WC, Matsumura JS (May 2003). "Guidelines for the treatment of abdominal aortic aneurysms. Report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery". *J. Vasc. Surg*. **37** (5): 1106–17. doi:10.1067/mva.2003.363. PMID 12756363.
50. ^ Darling RC, Messina CR, Brewster DC, Ottinger LW (September 1977). "Autopsy study of unoperated abdominal aortic aneurysms. The case for early resection". *Circulation*. **56** (3 Suppl): II161–4. PMID 884821.
51. ^ *a b* Nicholls SC, Gardner JB, Meissner MH, Johansen HK (November 1998). "Rupture in small abdominal aortic aneurysms". *Journal of Vascular Surgery*. **28** (5): 884–8. doi:10.1016/S0741-5214(98)70065-5. PMID 9808857.
52. ^ *a b* Vorp DA (2007). "BIOMECHANICS OF ABDOMINAL AORTIC ANEURYSM". *Journal of Biomechanics*. **40** (9): 1887–902. doi:10.1016/j.jbiomech.2006.09.003. PMC 2692528. PMID 17254589.
53. ^ Vorp DA, Raghavan ML, Webster MW (April 1998). "Mechanical wall stress in abdominal aortic aneurysm: influence of diameter and asymmetry". *Journal of Vascular Surgery*. **27** (4): 632–9. doi:10.1016/S0741-5214(98)70227-7. PMID 9576075.
54. ^ Sacks MS, Vorp DA, Raghavan ML, Federle MP, Webster MW (1999). "In vivo three-dimensional surface geometry of abdominal aortic aneurysms". *Annals of Biomedical Engineering*. **27** (4): 469–79. doi:10.1114/1.202. PMID 10468231.
55. ^ *a b* Doyle BJ, Callanan A, Burke PE, Grace PA, Walsh MT, Vorp DA, McGloughlin TM (February 2009). "Vessel Asymmetry as an Additional Diagnostic Tool in the Assessment of Abdominal Aortic Aneurysms". *Journal of Vascular Surgery*. **49** (2): 443–54. doi:10.1016/j.jvs.2008.08.064. PMC 2666821. PMID 19028061.
56. ^ Vande Geest JP, Wang DH, Wisniewski SR, Makaroun MS, Vorp DA (2006). "Towards A Noninvasive Method for Determination of Patient-Specific Wall Strength Distribution in Abdominal Aortic Aneurysms". *Annals of Biomedical Engineering*. **34** (7): 1098–1106. doi:10.1007/s10439-006-9132-6. PMID 16786395.
57. ^ Raghavan ML, Kratzberg J, Castro de Tolosa EM, Hanaoka MM, Walker P, da Silva ES (2006). "Regional distribution of wall thickness and failure properties of human abdominal aortic aneurysm". *Journal of Biomechanics*. **39** (16): 3010–6. doi:10.1016/j.jbiomech.2005.10.021. PMID 16337949.
58. ^ Raghavan ML, Webster MW, Vorp DA (1996). "Ex vivo biomechanical behavior of abdominal aortic aneurysm: assessment using a new mathematical model". *Annals of Biomedical Engineering*. **24** (5): 573–82. doi:10.1007/BF02684226. PMID 8886238.
59. ^ Thubrikar MJ, Labrosse M, Robicsek F, Al-Soudi J, Fowler B (2001). "Mechanical properties of abdominal aortic

aneurysm wall". *Journal of Medical Engineering & Technology*. **25** (4): 133–42. doi:10.1080/03091900110057806. PMID 11601439.
60. ^ Fillinger MF, Raghavan ML, Marra SP, Cronenwett JL, Kennedy FE (September 2002). "In vivo analysis of mechanical wall stress and abdominal aortic aneurysm rupture risk". *Journal of Vascular Surgery*. **36** (3): 589–97. doi:10.1067/mva.2002.125478. PMID 12218986.
61. ^ Venkatasubramaniam AK, Fagan MJ, Mehta T, Mylankal KJ, Ray B, Kuhan G, Chetter IC, McCollum PT (August 2004). "A comparative study of aortic wall stress using finite element analysis for ruptured and non-ruptured abdominal aortic aneurysms". *European Journal of Vascular and Endovascular Surgery*. **28** (2): 168–76. doi:10.1016/j.ejvs.2004.03.029. PMID 15234698.
62. ^ Hirose Y, Takamiya M (February 1998). "Growth curve of ruptured aortic aneurysm". *The Journal of Cardiovascular Surgery*. **39** (1): 9–13. PMID 9537528.
63. ^ Wang DH, Makaroun MS, Webster MW, Vorp DA (September 2002). "Effect of intraluminal thrombus on wall stress in patient-specific models of abdominal aortic aneurysm". *Journal of Vascular Surgery*. **36** (3): 598–604. doi:10.1067/mva.2002.126087. PMID 12218961.
64. ^ Vorp DA, Vande Geest JP (August 2005). "Biomechanical determinants of abdominal aortic aneurysm rupture". *Arteriosclerosis, Thrombosis, and Vascular Biology*. **25** (8): 1558–66. doi:10.1161/01.ATV.0000174129.77391.55. PMID 16055757.
65. ^ Vande Geest JP, Di Martino ES, Bohra A, Makaroun MS, Vorp DA (2006). "A biomechanics-based rupture potential index for abdominal aortic aneurysm risk assessment". *Annals of the New York Academy of Sciences*. **1085** (1): 11–21. Bibcode:2006NYASA1085...11V. doi:10.1196/annals.1383.046. PMID 17182918.
66. ^ Doyle BJ, Callanan A, Walsh MT, Grace PA, McGloughlin TM (2009). "A finite element analysis rupture index (FEARI) as an additional tool for abdominal aortic aneurysm rupture prediction". *Vascular Disease Prevention*. **6**: 114–121. doi:10.2174/1567270000906010114.
67. ^ Kleinstreuer C, Li Z (2006). "Analysis and computer program for rupture-risk prediction of abdominal aortic aneurysms". *Biomedical Engineering Online*. **5** (1): 19. doi:10.1186/1475-925X-5-19. PMC 1421417. PMID 16529648.
68. ^ Stenbaek J, Kalin B, Swedenborg J (November 2000). "Growth of thrombus may be a better predictor of rupture than diameter in patients with abdominal aortic aneurysms". *European Journal of Vascular and Endovascular Surgery*. **20** (5): 466–9. doi:10.1053/ejvs.2000.1217. PMID 11112467.
69. ^ Giannoglou G, Giannakoulas G, Soulis J, Chatzizisis Y, Perdikides T, Melas N, Parcharidis G, Louridas G (2006). "Predicting the risk of rupture of abdominal aortic aneurysms by utilizing various geometrical parameters: revisiting the diameter criterion". *Angiology*. **57** (4): 487–94. doi:10.1177/0003319706290741. PMID 17022385.
70. ^ Watton PN, Hill NA, Heil M (November 2004). "A mathematical model for the growth of the abdominal aortic aneurysm". *Biomechanics and Modeling in Mechanobiology*. **3** (2): 98–113. doi:10.1007/s10237-004-0052-9. PMID 15452732.
71. ^ Volokh KY, Vorp DA (2008). "A model of growth and rupture of abdominal aortic aneurysm". *Journal of Biomechanics*. **41** (5): 1015–21. doi:10.1016/j.jbiomech.2007.12.014. PMID 18255074.
72. ^ Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG (2004). "Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial". *Lancet*. **364** (9437): 843–8. doi:10.1016/S0140-6736(04)16979-1. PMID 15351191.
73. ^ Salem MK, Rayt HS, Hussey G, Rafelt S, Nelson CP, Sayers RD, Naylor AR, Nasim A (December 2009). "Should Asian men be included in abdominal aortic aneurysm screening programmes?". *Eur J Vasc Endovasc Surg*. **38** (6): 748–9. doi:10.1016/j.ejvs.2009.07.012. PMID 19666232.
74. ^ Wilmink TB, Quick CR, Day NE (Dec 1999). "The association between cigarette smoking and abdominal aortic aneurysms". *J Vasc Surg*. **30** (6): 1099–105. doi:10.1016/S0741-5214(99)70049-2. PMID 10587395.
75. ^ Livesay JJ, Messner GN, Vaughn WK (2005). "Milestones in Treatment of Aortic Aneurysm: Denton A. Cooley, MD, and the Texas Heart Institute". *Tex Heart Inst J.* **32** (2): 130–4. PMC 1163455. PMID 16107099.
76. ^ Famous Patients, Famous Operations, 2002 — Part 3: The Case of the Scientist with a Pulsating Mass from Medscape Surgery
77. ^ Yusuf SW, Whitaker SC, Chuter TA, Wenham PW, Hopkinson BR (December 1994). "Emergency endovascular repair of leaking aortic aneurysm". *Lancet*. **344** (8937): 1645. doi:10.1016/S0140-6736(94)90443-X. PMID 7984027.
78. ^ *a b* "Bob Dole has surgery to treat aneurysm". *USA Today* via *Associated Press*. 2001-06-27. Retrieved 2009-09-22.
79. ^ Raghavan ML, Kratzberg J, Castro de Tolosa EM, Hanaoka MM, Walker P, da Silva ES (2006). "Regional distribution of wall thickness and failure properties of human abdominal aortic aneurysm". *J. Biomech*. **39** (16): 3010–3016. doi:10.1016/j.jbiomech.2005.10.021. PMID 16337949.
80. ^ Vorp DA, Lee PC, Wang DH, Makaroun MS, Nemoto EM, Ogawa S, Webster MW (2001). "Association of

intraluminal thrombus in abdominal aortic aneurysm with local hypoxia and wall weakening". *Journal of Vascular Surgery*. **34** (2): 291–299. doi:10.1067/mva.2001.114813. PMID 11496282.
81. ^ Speelman L, Bohra A, Bosboom EM, Schurink GW, van de Vosse FN, Makaorun MS, Vorp DA (2007). "Effects of wall calcifications in patient-specific wall stress analyses of abdominal aortic aneurysms". *Journal of Biomechanical Engineering*. **129** (1): 105–109. doi:10.1115/1.2401189. PMID 17227104.
82. ^ Doyle BJ, Morris LG, Callanan A, Kelly P, Vorp DA, McGloughlin TM (2008). "3D reconstruction and manufacture of real abdominal aortic aneurysms: From CT scan to silicone model". *Journal of Biomechanical Engineering*. **130** (3): 034501. doi:10.1115/1.2907765. PMID 18532870.
83. ^ Doyle BJ, Corbett TJ, Cloonan AJ, O'Donnell MR, Walsh MT, Vorp DA, McGloughlin TM (2009). "Experimental mOdelling of Aortic Aneurysms: Novel applications of Silicone Rubbers". *Medical Engineering & Physics*. **31** (8): 1002–1012. doi:10.1016/j.medengphy.2009.06.002. PMC 2757445. PMID 19595622.
84. ^ Morris L, O'Donnell P, Delassus P, McGloughlin TM (2004). "Experimental assessment of stress patterns in abdominal aortic aneurysms using the photoelastic method". *Strain*. **40** (4): 165–172. doi:10.1111/j.1475-1305.2004.tb01425.x.
85. ^ Doyle BJ, Corbett TJ, Callanan A, Walsh MT, Vorp DA, McGloughlin TM (2009). "An Experimental and Numerical Comparison of the Rupture Locations of an Abdominal Aortic Aneurysm". *Journal of Endovascular Therapy*. **16** (3): 322–335. doi:10.1583/09-2697.1. PMC 2795364. PMID 19642790.
86. ^ Albertini JN, Perdikides T, Soong CV, Hinchliffe RJ, Trojanowska M, Yusuf SW (Jun 2006). "Endovascular repair of abdominal aortic aneurysms in patients with severe angulation of the proximal neck using a flexible stent-graft: European Multicenter Experience". *J Cardiovasc Surg (Torino)*. **47** (3): 245–50. PMID 16760860.
87. ^ "Study establishes major new treatment target in diseased arteries". U.S. News & World Report. May 10, 2009.
88. ^ Chamberlain CM, Ang LS, Boivin WA, Cooper DM, Williams SJ, Zhao H, Hendel A, Folkesson M, Swedenborg J, Allard MF, McManus BM, Granville DJ (2010). "Perforin-Independent Extracellular Granzyme B Activity Contributes to Abdominal Aortic Aneurysm". *The American Journal of Pathology*. **176** (2): 1038–1049. doi:10.2353/ajpath.2010.090700. PMC 2808106. PMID 20035050.
89. ^ "Discovery points way for new treatment for aneurysms". University of British Columbia. January 27, 2010.

v · t · e · **Cardiovascular disease (vessels) (I70–I99, 440–456)**

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| **Arteries, arterioles and capillaries** | **Inflammation** | | Arteritis (Aortitis · · Buerger's disease · |
| | **Peripheral artery disease** | **Arteriosclerosis** | Atherosclerosis (Foam cell · Fatty streak · Atheroma · Intermittent claudication · Critical limb ischemia · · Monckeberg's arteriosclerosis · Arteriolosclerosis (Hyaline · Hyperplastic · Cholesterol · LDL · Oxycholesterol · Trans fat · · |
| | | **Stenosis** | Carotid artery stenosis · Renal artery stenosis · |
| | | **Other** | Aortoiliac occlusive disease · Degos disease · Erythromelalgia · Fibromuscular dysplasia · Raynaud's phenomenon · |
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| | **Vascular nevus** | Cherry hemangioma · Halo nevus · Spider angioma · |
| **Veins** | **Inflammation** | Phlebitis · |
| | **Venous thrombosis / Thrombophlebitis** | *primarily lower limb* (Deep vein thrombosis · · *abdomen* (Hepatic veno-occlusive disease · Budd–Chiari syndrome · May–Thurner syndrome · Portal vein thrombosis · Renal vein thrombosis · · *upper limb / torso* (Mondor's disease · Paget–Schroetter disease · · *head* (Cerebral venous sinus thrombosis · · Post-thrombotic syndrome · |
| | **Varicose veins** | Gastric varices · Portacaval anastomosis (Caput medusae · Esophageal varices · Hemorrhoid · · Varicocele · |
| | **Other** | Chronic venous insufficiency · Chronic cerebrospinal venous insufficiency · Superior vena cava syndrome · Inferior vena cava syndrome · Venous ulcer · |
| **Arteries or veins** | | Angiopathy (Macroangiopathy · Microangiopathy · · Embolism (Pulmonary embolism · Cholesterol embolism · Paradoxical embolism · · Thrombosis · Vasculitis · |
| **Blood pressure** | **Hypertension** | Hypertensive heart disease · Hypertensive emergency · Hypertensive nephropathy · Essential hypertension · Secondary hypertension (Renovascular hypertension · · Benign hypertension · Pulmonary hypertension · Systolic hypertension · White coat hypertension · |
| | **Hypotension** | Orthostatic hypotension · |

## External links [edit]

- Cochrane Peripheral Vascular Diseases Review Group

Categories: Diseases of the aorta | Vascular surgery | Diseases of arteries, arterioles and capillaries | Deaths from abdominal aortic aneurysm | Men's health




# Aortic stenosis

From Wikipedia, the free encyclopedia

*Not to be confused with coarctation of the aorta.*

**Aortic stenosis** (**AS** or **AoS**) is the narrowing of the exit of the left ventricle of the heart (where the aorta begins), such that problems result. It may occur at the aortic valve as well as above and below this level. It typically gets worse over time. Symptoms often come on gradually with a decreased ability to exercise often occurring first. If heart failure, loss of consciousness, or heart related chest pain occurs due to AS the outcomes are worse. Loss of consciousness typically occurs with standing or exercise. Signs of heart failure include shortness of breath especially when lying down, at night, or with exercise, and swelling of the legs. Thickening of the valve without narrowing is known as aortic sclerosis.[1]

Causes include being born with a bicuspid aortic valve and rheumatic fever. A bicuspid aortic valve affects about one to two percent of the population while rheumatic heart disease mostly occurring in the developing world. A normal valve, however, may also harden over the decades. Risk factors are similar to those of coronary artery disease and include smoking, high blood pressure, high cholesterol, diabetes, and being male. The aortic valve usually has three leaflets and is located between the left ventricle of the heart and the aorta. AS typically results in a heart murmur. Its severity can be divided into mild, moderate, severe, and very severe based on ultrasound of the heart findings.[1]

Aortic stenosis is typically followed using repeated ultrasounds. Once it has become severe treatment primarily involves valve replacement surgery with transcatheter aortic valve replacement (TAVR) being an option in some who are at high risk from surgery. Valves may either be mechanical or bioprosthetic with each having risks and benefits. Another less invasive procedure, balloon aortic valvuloplasty (BAV) may result in benefit but this is for only for a few months. Complications like heart failure may be treated as per normal in those with mild to moderate AS. In those with severe disease a number of medications should be avoided including ACE inhibitors, nitroglycerin, and some beta blockers.[1] Nitroprusside or phenylephrine may be used in those with decompensated heart failure depending on the blood pressure.[1][2]

Aortic stenosis is the most common valvular heart disease in the developed world.[3] It affects about 2% of people who are over 65 years of age.[1] Estimated rates are not known in most of the developing world as of 2014.[4] In those who have symptoms, without repair, the chance of death at five years is about 50%

**Aortic stenosis**

In the center an aortic valve with severe stenosis due to rheumatic heart disease. The valve is surrounded by the aorta. The pulmonary trunk is at the lower right. The right coronary artery, cut lengthwise, is at the lower left. The left main coronary artery, also cut lengthwise, is on the right.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Cardiac surgery |
| **ICD-10** | I35.0, I06.0, Q23.0 |
| **ICD-9-CM** | 395.0, 396.0, 746.3 |
| **DiseasesDB** | 844 |
| **MedlinePlus** | 000178 |
| **eMedicine** | med/157 |
| **Patient UK** | Aortic stenosis |

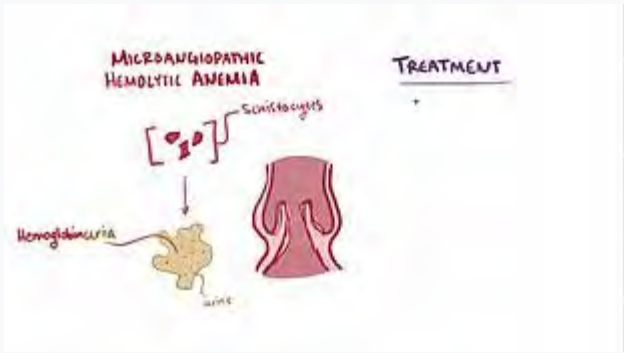
[edit on Wikidata]

and at 10 years is about 90%.[1] Aortic stenosis was first described by French physician Lazare Rivière in 1663.[3]



**Contents**






Play media

Video explanation of aortic valve disease

## Signs and symptoms [edit]

Symptoms related to aortic stenosis depend on the degree of stenosis. Most people with mild to moderate aortic stenosis do not have symptoms. Symptoms usually present in individuals with severe aortic stenosis, though they may occur in those with mild to moderate aortic stenosis as well. The three main symptoms of aortic stenosis are loss of consciousness, anginal chest pain and shortness of breath with activity or other symptoms of heart failure such as shortness of breath while lying flat, episodes of shortness of breath at night, or swollen legs and feet.[3][6] It may also be accompanied by the characteristic "Dresden china" appearance of pallor with a light flush.[7]

### Angina [edit]

Angina in setting of heart failure also increases the risk of death. In people with angina, the 5-year mortality rate is 50% if the aortic valve is not replaced.

Angina in the setting of AS occurs due to left ventricular hypertrophy (LVH) that is caused by the constant production of increased pressure required to overcome the pressure gradient caused by the AS. While the muscular layer of the left ventricle thickens, the arteries that supply the muscle do not get significantly longer or bigger, so the muscle may not receive enough blood supply to meet its oxygen requirement. This ischemia may first be evident during exercise when the heart muscle requires increased blood supply to compensate for the increased workload. The individual may complain of anginal chest pain with exertion. At this stage, a cardiac stress test with imaging may be suggestive of ischemia.

Eventually, however, the heart muscle will require more blood supply at rest than can be supplied by the coronary artery branches. At this point there may be signs of *ventricular strain pattern* (ST segment

depression and T wave inversion) on the EKG, suggesting subendocardial ischemia. The subendocardium is the region that is most susceptible to ischemia because it is the most distant from the epicardial coronary arteries.

## Syncope [edit]

Syncope (fainting spells) from aortic valve stenosis is usually exertional.[3][8] In the setting of heart failure it increases the risk of death. In people with syncope, the 3 year mortality rate is 50%, if the aortic valve is not replaced.[9]

It is unclear why aortic stenosis causes syncope. One popular theory is that severe AS produces a nearly fixed cardiac output.[10] When a person with aortic stenosis exercises, their peripheral vascular resistance will decrease as the blood vessels of the skeletal muscles dilate to allow the muscles to receive more blood to allow them to do more work. This decrease in peripheral vascular resistance is normally compensated for by an increase in the cardiac output. Since people with severe AS cannot increase their cardiac output, the blood pressure falls and the person will faint due to decreased blood perfusion to the brain.

A second theory as to why syncope may occur in AS is that during exercise, the high pressures generated in the hypertrophied left ventricle cause a vasodepressor response, which causes a secondary peripheral vasodilation that, in turn, causes decreased blood flow to the brain resulting in loss of consciousness. Indeed, in aortic stenosis, because of the fixed obstruction to blood flow out from the heart, it may be impossible for the heart to increase its output to offset peripheral vasodilation.

A third mechanism may sometimes be operative. Due to the hypertrophy of the left ventricle in aortic stenosis, including the consequent inability of the coronary arteries to adequately supply blood to the myocardium (see "Angina" below), abnormal heart rhythms may develop. These can lead to syncope.

Finally, in calcific aortic stenosis[11][12] at least, the calcification in and around the aortic valve can progress and extend to involve the electrical conduction system of the heart. If that occurs, the result may be heart block - a potentially lethal condition of which syncope may be a symptom.

## Congestive heart failure [edit]

Congestive heart failure (CHF) carries a grave prognosis in people with AS. People with CHF attributable to AS have a 2-year mortality rate of 50% if the aortic valve is not replaced.[*citation needed*] CHF in the setting of AS is due to a combination of left ventricular hypertrophy with fibrosis, systolic dysfunction (a decrease in the ejection fraction) and diastolic dysfunction (elevated filling pressure of the LV).[3]

## Associated symptoms [edit]

In Heyde's syndrome, aortic stenosis is associated with gastrointestinal bleeding due to angiodysplasia of the colon.[13] Recent research has shown that the stenosis causes a form of von Willebrand disease by breaking down its associated coagulation factor (factor VIII-associated antigen, also called von Willebrand factor), due to increased turbulence around the stenotic valve.

## Complications [edit]

Notwithstanding the foregoing, the American Heart Association has recently changed its recommendations regarding antibiotic prophylaxis for endocarditis. Specifically, as of 2007, it is recommended that such prophylaxis should be limited only to those with prosthetic heart valves, those with previous episode(s) of endocarditis, and those with certain types of congenital heart disease.[*citation needed*]

Since the stenosed aortic valve may limit the heart's output, people with aortic stenosis are at risk of syncope and dangerously low blood pressure should they use any of a number of medications for cardiovascular diseases that often coexist with aortic stenosis. Examples include nitroglycerin, nitrates, ACE inhibitors, terazosin (Hytrin), and hydralazine. Note that all of these substances lead to peripheral vasodilation. Under normal circumstances, in the absence of aortic stenosis, the heart is able to increase its output and thereby offset the effect of the dilated blood vessels. In some cases of aortic stenosis, however,

due to the obstruction of blood flow out of the heart caused by the stenosed aortic valve, cardiac output cannot be increased. Low blood pressure or syncope may ensue.

## Causes [edit]

Aortic stenosis is most commonly caused by age-related progressive calcification (>50% of cases) with a mean age of 65 to 70 years. Another major cause of aortic stenosis is the calcification of a congenital bicuspid aortic valve[14] (30-40% of cases) typically presenting earlier, in those aged 40+ to 50+.[6]

Acute rheumatic fever post-inflammatory is the cause of less than 10% of cases.[15] Rare causes of aortic stenosis include Fabry disease, systemic lupus erythematosus, Paget disease, high blood uric acid levels, and infection.[16]

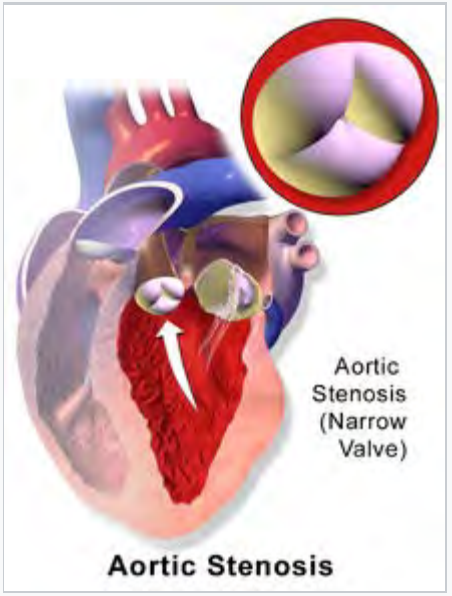
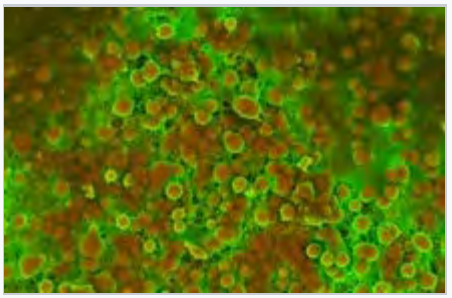


Illustration depicting aortic stenosis

## Pathophysiology [edit]

The human aortic valve normally consists of three cusps or leaflets and has an opening of 3.0-4.0 square centimeters.[5][16] When the left ventricle contracts, it forces blood through the valve into the aorta and subsequently to the rest of the body. When the left ventricle expands again, the aortic valve closes and prevents the blood in the aorta from flowing backward (regurgitation) into the left ventricle. In aortic stenosis, the opening of the aortic valve becomes narrowed or constricted (stenotic) (i.e., due to calcification). Degenerative aortic stenosis, the most common variety, and bicuspid aortic stenosis both begin with damage to endothelial cells from increased mechanical stress.[6][16] Inflammation is thought to be involved in the earlier stages of the pathogenesis of AS and its associated risk factors are known to promote the deposition of LDL cholesterol and a highly damaging substance known as Lipoprotein(a) into the aortic valve resulting in significant damage and stenosis over time.[6][16]


Density-dependent colour scanning electron micrograph of cardiovascular calcification, showing in orange calcium phosphate spherical particles (denser material) and, in green, the extracellular matrix (less dense material).[11]

As a consequence of this stenosis, the left ventricle must generate a higher pressure with each contraction to effectively move blood forward into the aorta.[3][17] Initially, the LV generates this increased pressure by thickening its muscular walls (myocardial hypertrophy). The type of hypertrophy most commonly seen in AS is known as concentric hypertrophy,[3] in which the walls of the LV are (approximately) equally thickened.

In the later stages, the left ventricle dilates, the wall thins, and the systolic function deteriorates (resulting in impaired ability to pump blood forward). Morris and Innasimuthu et al. showed that different coronary anatomy is associated with different valve diseases. Research is ongoing to see if different coronary anatomy might lead to turbulent flow at the level of valves leading to inflammation and degeneration.[18][19][20]

## Diagnosis [edit]

Aortic stenosis is most often diagnosed when it is asymptomatic and can sometimes be detected during routine examination of the heart and circulatory system. Good evidence exists to demonstrate that certain

characteristics of the peripheral pulse can rule in the diagnosis.[21] In particular, there may be a slow and/or sustained upstroke of the arterial pulse, and the pulse may be of low volume. This is sometimes referred to as *pulsus parvus et tardus*.[8][15] There may also be a noticeable delay between the first heart sound (on auscultation) and the corresponding pulse in the carotid artery (so-called 'apical-carotid delay'). In a similar manner, there may be a delay between the appearance of each pulse in the brachial artery (in the arm) and the radial artery (in the wrist).

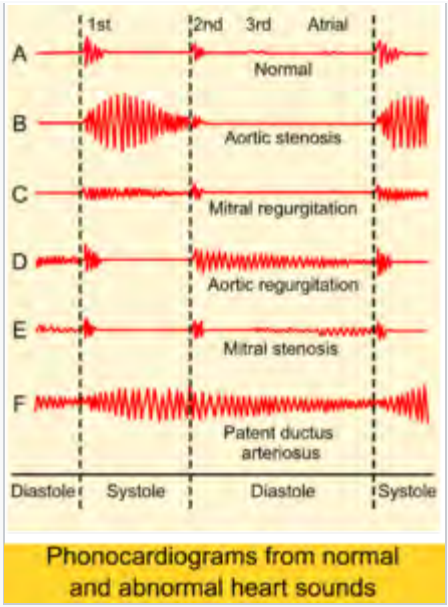
The first heart sound may be followed by a sharp ejection sound ("ejection click") best heard at the lower left sternal border and the apex, and, thus, appear to be "split". The ejection sound, caused by the impact of left ventricular outflow against the partially fused aortic valve leaflets, is more commonly associated with a mobile bicuspid aortic valve than an immobile calcified aortic valve. The intensity of this sound does not vary with respiration, which helps distinguish it from the ejection click produced by a stenotic pulmonary valve, which will diminish slightly in intensity during inspiration.[22]

An easily heard systolic, crescendo-decrescendo (i.e., 'ejection') murmur is heard loudest at the upper right sternal border, at the 2nd right intercostal space,[15] and radiates to the carotid arteries bilaterally.[3][8] The murmur increases with squatting and decreases with standing and isometric muscular contraction such as the Valsalva maneuver, which helps distinguish it from hypertrophic obstructive cardiomyopathy (HOCM). The murmur is louder during expiration but is also easily heard during inspiration. The more severe the degree of the stenosis, the later the peak occurs in the crescendo-decrescendo of the murmur.

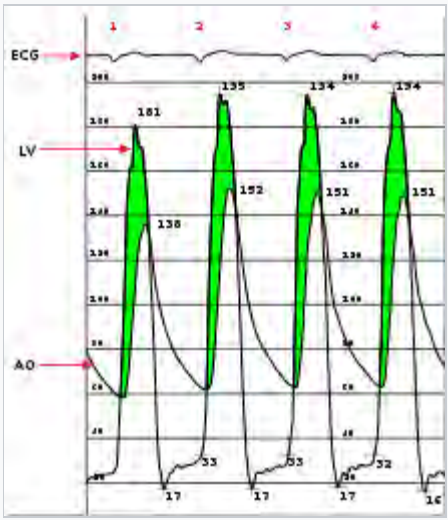
The second heart sound ($A_2$) tends to become decreased and softer as the aortic stenosis becomes more severe.[15] This is a result of the increasing calcification of the valve preventing it from "snapping" shut and producing a sharp, loud sound. Due to increases in left ventricular pressure from the stenotic aortic valve, over time the ventricle may hypertrophy, resulting in a diastolic dysfunction. As a result, one may hear a fourth heart sound due to the stiff ventricle.[8] With continued increases in ventricular pressure, dilatation of the ventricle will occur, and a third heart sound may be manifest.

Finally, aortic stenosis often co-exists with some degree of aortic insufficiency (aortic regurgitation). Hence, the physical exam in aortic stenosis may also reveal signs of the latter, for example, an early diastolic decrescendo murmur. Indeed, when both valve abnormalities are present, the expected findings of either may be modified or may not even be present. Rather, new signs that reflect the presence of simultaneous aortic stenosis and insufficiency, e.g., pulsus bisferiens, emerge.

According to a meta analysis, the most useful findings for ruling in aortic stenosis in the clinical setting were slow rate of rise of the carotid pulse (positive likelihood ratio ranged 2.8–130 across studies), mid to late peak intensity of the murmur (positive likelihood ratio, 8.0–101), and decreased intensity of the second heart sound (positive likelihood ratio, 3.1–50).[21]




Phonocardiograms from normal and abnormal heart sounds




Simultaneous left ventricular and aortic pressure tracings demonstrate a pressure gradient between the left ventricle and aorta, suggesting aortic stenosis. The left ventricle generates higher pressures than what is transmitted to the aorta. The pressure gradient, caused by aortic stenosis, is represented by the green shaded area. (AO = ascending aorta; LV = left ventricle; ECG = electrocardiogram.)

Other peripheral signs include:

- sustained, heaving apex beat,[8] which is not displaced unless systolic dysfunction of the left ventricle has developed
- A precordial thrill[8]
- narrowed pulse pressure

## Electrocardiogram [edit]

Although aortic stenosis does not lead to any *specific* findings on the electrocardiogram (ECG), it still often leads to a number of electrocardiographic abnormalities. ECG manifestations of left ventricular hypertrophy (LVH) are common in aortic stenosis[6][8] and arise as a result of the stenosis having placed a chronically high pressure load on the left ventricle (with LVH being the expected response to chronic pressure loads on the left ventricle no matter what the cause).

As noted above, the calcification process that occurs in aortic stenosis can progress to extend beyond the aortic valve and into the electrical conduction system of the heart. Evidence of this phenomenon may rarely include ECG patterns characteristic of certain types of heart block such as Left bundle branch block.[6]

## Heart catheterization [edit]

Cardiac chamber catheterization provides a definitive diagnosis, indicating severe stenosis in valve area of <1.0 $cm^2$ (normally about 3 $cm^2$).[23] It can directly measure the pressure on both sides of the aortic valve. The pressure gradient may be used as a decision point for treatment. It is useful in symptomatic people before surgery.[8] The standard for diagnosis of aortic stenosis is noninvasive testing with echocardiography. Cardiac catheterization is reserved for cases in which there is discrepancy between the clinical picture and non-invasive testing, due to risks inherent to crossing the aortic valve such as stroke.[6]

## Echocardiogram [edit]

Echocardiogram (heart ultrasound) is the best non-invasive tool / test to evaluate the aortic valve anatomy and function.

The aortic valve area can be calculated non-invasively using echocardiographic flow velocities. Using the velocity of the blood through the valve, the pressure gradient across the valve can be calculated by the continuity equation or using the modified Bernoulli's equation:

$$\text{Gradient} = 4(\text{velocity})^2 \text{ mmHg}$$

| Severity of aortic stenosis[15] | | |
|---|---|---|
| **Degree** | **Mean gradient (mmHg)** | **Aortic valve area ($cm^2$)** |
| Mild | <25 | >1.5 |
| Moderate | 25 - 40 | 1.0 - 1.5 |
| Severe | >40 | < 1.0 |
| Very severe | >70 | < 0.6 |

A normal aortic valve has a gradient of only a few mmHg. A decreased valvular area causes increased pressure gradient, and these parameters are used to classify and grade the aortic stenosis as mild, moderate or severe. The pressure gradient can be abnormally low in the presence of mitral stenosis, heart failure, co-existent aortic regurgitation and also ischaemic heart disease (disease related to decreased blood supply and oxygen causing ischemia).

Echocardiogram may also show left ventricular hypertrophy, thickened and immobile aortic valve and dilated aortic root.[8] However, it may appear deceptively normal in acute cases.[15]

## Chest X-ray [edit]

A chest X-ray can also assist in the diagnosis and provide clues as to the severity of the disease, showing the degree of calcification of the valve, and in a chronic condition, an enlarged left ventricle[8][15] and atrium.[8]

# Management [edit]

Treatment is generally not necessary in people without symptoms.[8] In moderate cases, echocardiography is performed every 1–2 years to monitor the progression, possibly complemented with a cardiac stress test.[15] In severe cases, echocardiography is performed every 3–6 months.[15] In both moderate and mild cases, the person should immediately make a revisit or be admitted for inpatient care if any new related symptoms appear.[15] There are no therapeutic options currently available to treat people with aortic valve stenosis; however, studies have indicated that the disease occurs as a result of active cellular processes, suggesting that targeting these processes may lead to viable therapeutic approaches.[24]

## Medication [edit]

The effect of statins on the progression of AS is unclear. The latest trials do not show any benefit in slowing AS progression,[6] but did demonstrate a decrease in ischemic cardiovascular events.[3]

In general, medical therapy has relatively poor efficacy in treating aortic stenosis.[8] However, it may be useful to manage commonly coexisting conditions that correlate with aortic stenosis:

- Any angina is generally treated with beta-blockers and/or calcium blockers.[15] Nitrates are contraindicated due to their potential to cause profound hypotension in aortic stenosis.[25]
- Any hypertension is treated aggressively, but caution must be taken in administering beta-blockers.[15]
- Any heart failure is generally treated with digoxin and diuretics, and, if not contraindicated, cautious administration of ACE inhibitors.[15]

While observational studies demonstrated an association between lowered cholesterol with statins and decreased progression, a randomized clinical trial published in 2005 failed to find any effect on calcific aortic stenosis. A 2007 study did demonstrate a slowing of aortic stenosis with the statin rosuvastatin.[6][26]

## Aortic valve repair [edit]

*Main article: aortic valve repair*

Aortic valve repair or aortic valve reconstruction describes the reconstruction of both form and function of the native and dysfunctioning aortic valve. Most frequently it is applied for the treatment of aortic regurgitation. It can also become necessary for the treatment of an aortic aneurysm, less frequently for congenital aortic stenosis.[27]

## Aortic valve replacement [edit]

*Main article: aortic valve replacement*

In adults, symptomatic severe aortic stenosis usually requires aortic valve replacement (AVR).[3] While AVR has been the standard of care for aortic stenosis for several decades, currently aortic valve replacement approaches include open heart surgery, minimally invasive cardiac surgery (MICS) and minimally invasive catheter-based (percutaneous) aortic valve replacement.[28][29] However, surgical aortic valve replacement is well studied and generally has a good and well established longer term prognosis.[30]

A diseased aortic valve is most commonly replaced using a surgical procedure with either a mechanical or a tissue valve. The procedure is done either in an open-heart surgical procedure or, in a smaller but growing number of cases, a minimally invasive cardiac surgery (MICS) procedure.

## Transcatheter aortic valve replacement [edit]

Globally more than 250,000 people have received transcatheter aortic valve replacement (TAVR). For people who are not candidates for surgical valve replacement and most patients who are older than 75, TAVR may be a suitable alternative.[28][29]

### Balloon valvuloplasty [edit]

For infants and children, balloon valvuloplasty, where a balloon is inflated to stretch the valve and allow greater flow, may also be effective. In adults, however, it is generally ineffective, as the valve tends to return to a stenosed state. The surgeon will make a small incision at the top of the person's leg and proceed to insert the balloon into the artery. The balloon is then advanced up to the valve and is inflated to stretch the valve open.[31]

### Heart failure [edit]

Acute decompensated heart failure due to AS may be temporarily managed by an intra-aortic balloon pump while pending surgery.[32] In those with high blood pressure nitroprusside may be carefully used.[1] Phenylephrine may be used in those with very low blood pressure.[2]

## Prognosis [edit]

If untreated, severe symptomatic aortic stenosis carries a poor prognosis with a 2-year mortality rate of 50-60% and a 3-year survival rate of less than 30%.[33] Prognosis after aortic valve replacement for people who are younger than 65 is about five years less than that of the general population; for people older than 65 it is about the same.[30]

## Epidemiology [edit]

Approximately 2% of people over the age of 65, 3% of people over age 75,[3] and 4% percent of people over age 85 have aortic valve stenosis.[34] The prevalence is increasing with the aging population in North America and Europe.[35]

Risk factors known to influence disease progression of AS include lifestyle habits similar to those of coronary artery disease such as hypertension, advanced age, being male, hyperlipidemia, diabetes mellitus, cigarette smoking, metabolic syndrome, and end-stage kidney disease.[3][6][16]

## History [edit]

Aortic stenosis was first described by French physician Lazare Rivière in 1663.[5]

## Research [edit]

People on bisphosphonates have less progression of aortic stenosis and some regressed.[36][36][37] This finding led to multiple trials which are ongoing. Subsequent research has failed to confirm the initial positive result.[38]

## References [edit]


1. ^ *a b c d e f g* Czarny, MJ; Resar, JR (2014). "Diagnosis and management of valvular aortic stenosis.". *Clinical Medicine Insights. Cardiology*. **8** (Suppl 1): 15–24. doi:10.4137/CMC.S15716. PMID 25368539.
2. ^ *a b* Overgaard, CB; Dzavík, V (2 September 2008). "Inotropes and vasopressors: review of physiology



Left Dominant Coronary arterial system and Aortic stenosis: an association, cause or effect – Heart 2007; 93 (Suppl 1): A39.[*verification needed*]

21. ^ *a b* Etchells E, Bell C, Robb K (February 1997). "Does this patient have an abnormal systolic murmur?". *JAMA*. **277** (7): 564–71. doi:10.1001/jama.277.7.564. PMID 9032164.

and clinical use in cardiovascular disease.". *Circulation*. **118** (10): 1047–56. doi:10.1161/CIRCULATIONAHA.107.728840. PMID 18765387.

3. ^ *a b c d e f g h i j k* Manning WJ (October 2013). "Asymptomatic aortic stenosis in the elderly: a clinical review". *JAMA*. **310** (14): 1490–7. doi:10.1001/jama.2013.279194. PMID 24104373.
4. ^ Thaden, JJ; Nkomo, VT; Enriquez-Sarano, M (2014). "The global burden of aortic stenosis.". *Progress in Cardiovascular Diseases*. **56** (6): 565–71. doi:10.1016/j.pcad.2014.02.006. PMID 24838132.
5. ^ *a b c* Leopold JA (August 2012). "Cellular mechanisms of aortic valve calcification". *Circulation. Cardiovascular Interventions*. **5** (4): 605–14. doi:10.1161/CIRCINTERVENTIONS.112.971028. PMC 3427002. PMID 22896576.
6. ^ *a b c d e f g h i j* Rogers, FJ (November 2013). "Aortic stenosis: new thoughts on a cardiac disease of older people". *Journal of the American Osteopathic Association*. **113** (11): 820–828. doi:10.7556/jaoa.2013.057. PMID 24174503.
7. ^ Silverman, ME (April 1999). "A view from the millennium: the practice of cardiology circa 1950 and thereafter.". *Journal of the American College of Cardiology*. **33** (5): 1141–51. doi:10.1016/s0735-1097(99)00027-3. PMID 10193710.
8. ^ *a b c d e f g h i j k l m* Chapter 1: Diseases of the Cardiovascular system > Section: Valvular Heart Disease in: Elizabeth D Agabegi; Agabegi, Steven S. (2008). *Step-Up to Medicine (Step-Up Series)*. Hagerstwon, MD: Lippincott Williams & Wilkins. ISBN 0-7817-7153-6.[*page needed*]
9. ^ Blase A. Carabello. (2002). "Evaluation and management of patients with aortic stenosis.". *Circulation*.
10. ^ Richards, Mark; Ikram, Hamid; Nicholls, M. Gary; Hamilton, Eric; Richards, Rosemary (1984). "Syncope in aortic valvular stenosis". *The Lancet*. **324**: 1113–1116. doi:10.1016/S0140-6736(84)91555-1.
11. ^ *a b* Bertazzo S, Gentleman E, Cloyd KL, Chester AH, Yacoub MH, Stevens MM (June 2013). "Nano-analytical electron microscopy reveals fundamental insights into human cardiovascular tissue calcification". *Nature Materials*. **12** (6): 576–83. doi:10.1038/nmat3627. PMID 23603848.
12. ^ Miller JD (June 2013). "Cardiovascular calcification: Orbicular origins". *Nature Materials*. **12** (6): 476–8. doi:10.1038/nmat3663. PMID 23695741.
13. ^ Figuinha, FC; Spina, GS; Tarasoutchi, F (March 2011). "Heyde's syndrome: case report and literature review". *Arquivos Brasileiros de Cardiologia*. **96** (3): e42–e45. doi:10.1590/S0066-782X2011000300017. PMID 21484065.
22. ^ Lilly, Leonard S., ed. (2007). *Pathophysiology of heart disease : a collaborative project of medical students and faculty* (4th ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins. p. 36. ISBN 978-0-7817-6321-9.
23. ^ Yale atlas of echocardiography Archived November 30, 2012, at the Wayback Machine.
24. ^ Hutcheson JD, Aikawa E, Merryman WD (April 2014). "Potential drug targets for calcific aortic valve disease". *Nature Reviews Cardiology*. **11** (4): 218–31. doi:10.1038/nrcardio.2014.1. PMID 24445487.
25. ^ Rutherford SD, Braunwald E (1992). "Chronic ischaemic heart disease". In Braunwald E. *Heart disease: A textbook of cardiovascular medicine* (4th ed.). Philadelphia: WB Saunders. pp. 1292–364.
26. ^ Moura LM, Ramos SF, Zamorano JL, et al. (February 2007). "Rosuvastatin affecting aortic valve endothelium to slow the progression of aortic stenosis". *Journal of the American College of Cardiology*. **49** (5): 554–61. doi:10.1016/j.jacc.2006.07.072. PMC 3951859. PMID 17276178.
27. ^ Hans-Joachim Schäfers: Current treatment of aortic regurgitation. UNI-MED Science, Bremen, London, Boston 2013, ISBN 978-3-8374-1406-6.
28. ^ *a b* Siemieniuk RA, Agoritsas T, Manja V, et al. (2016). "Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis.". *BMJ*. **354**: i5130. doi:10.1136/bmj.i5130. PMC 5040923. PMID 27683246.
29. ^ *a b* Vandvik PO, Otto CM, Siemieniuk RA, Bagur R, Guyatt GH, Lytvyn L, Whitlock R, Vartdal T, Brieger D, Aertgeerts B, Price S, Foroutan F, Shapiro M, Mertz R, Spencer FA (2016). "Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline". *BMJ*. **354**: i5085. doi:10.1136/bmj.i5085. PMID 27680583.
30. ^ *a b* Foroutan F, Guyatt GH, O'Brien K, et al. (2016). "Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis: systematic review of observational studies". *BMJ*. **354**: i5065. doi:10.1136/bmj.i5065. PMC 5040922. PMID 27683072.
31. ^ Mayo Clinic > Aortic valve stenosis > Treatments and drugs Retrieved September 2010
32. ^ Christopher M. O'Connor (2005). *Managing Acute Decompensated Heart Failure a Clinician's Guide to Diagnosis and Treatment.* London: Informa Healthcare. p. 406. ISBN 9780203421345.
33. ^ Spaccarotella C, Mongiardo A, Indolfi C (2011). "Pathophysiology of aortic stenosis and approach to treatment with percutaneous valve implantation". *Circulation Journal*. **75** (1): 11–19.

14. ^ Ricardo Zalaquett, Cristóbal Camplá, et al. (2005). "Cirugía reparadora de la válvula aórtica bicúspide insuficiente". *Rev Méd Chile*, **133**(3): pp. 279-86. ISSN 0034-9887.
15. ^ *a b c d e f g h i j k l m* VOC=VITIUM ORGANICUM CORDIS, a compendium of the Department of Cardiology at Uppsala Academic Hospital. By Per Kvidal September 1999, with revision by Erik Björklund May 2008
16. ^ *a b c d e* Olszowska, M (November 2011). "Pathogenesis and pathophysiology of aortic valve stenosis in adults" (PDF). *Polskie Archiwum Medcyny Wewnetrznej*. **121** (11): 409–413. PMID 22129836.
17. ^ Lilly LS, ed. (2003). *Pathophysiology of Heart Disease* (3rd ed.). Lippincott Williams & Wilkins. ISBN 0-7817-4027-4.
18. ^ G. Morris, Innasimuthu A L, J.P. Fox, R.A. Perry; The association of heart valve diseases with a dominant left coronary circulation – European Heart Journal, 2009; 30:682
19. ^ Morris GM, Innasimuthu AL, Fox JP, Perry RA (May 2010). "The association of heart valve diseases with coronary artery dominance". *The Journal of Heart Valve Disease*. **19** (3): 389–93. PMID 20583404.
20. ^ Innasimuthu A L, Morris G, Rao G K, Perry R A; doi:10.1253/circj.CJ-10-1105. PMID 21178291.
34. ^ Stewart BF, Siscovick D, Lind BK, et al. (March 1997). "Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study". *Journal of the American College of Cardiology*. **29** (3): 630–4. doi:10.1016/S0735-1097(96)00563-3. PMID 9060903.
35. ^ clinical Anesthesiology by Edward Morgan[*page needed*]
36. ^ *a b* Innasimuthu AL, Katz WE (January 2011). "Effect of bisphosphonates on the progression of degenerative aortic stenosis". *Echocardiography*. **28** (1): 1–7. doi:10.1111/j.1540-8175.2010.01256.x. PMID 20678125.
37. ^ Nathaniel S, Saligram S, Innasimuthu AL (June 2010). "Aortic stenosis: An update". *World Journal of Cardiology*. **2** (6): 135–9. doi:10.4330/wjc.v2.i6.135. PMC 2999052. PMID 21160731.
38. ^ Aksoy O, Cam A, Goel SS, et al. (April 2012). "Do bisphosphonates slow the progression of aortic stenosis?". *Journal of the American College of Cardiology*. **59** (16): 1452–9. doi:10.1016/j.jacc.2012.01.024. PMID 22497825.


## External links [edit]

- Aortic stenosis at DMOZ
- Aortic Stenosis information for parents.
- Aortic Stenosis in infants and children.

| v · t · e | Cardiovascular disease (heart) (I00–I52, 390–429) | | |
|---|---|---|---|
| **Ischaemic** | **Coronary disease** | Coronary artery disease (CAD) · Coronary artery aneurysm · Spontaneous coronary artery dissection (SCAD) · Coronary thrombosis · Coronary vasospasm · Myocardial bridge · | |
| | **Active ischemia** | Angina pectoris (Prinzmetal's angina · Stable angina · · Acute coronary syndrome (Myocardial infarction · Unstable angina · · | |
| | **Sequelae** | *hours* (Hibernating myocardium · Myocardial stunning · · *days* (Myocardial rupture · · *weeks* (Aneurysm of heart / Ventricular aneurysm · Dressler syndrome · · | |
| **Layers** | **Pericardium** | Pericarditis (Acute · Chronic / Constrictive · · Pericardial effusion (Cardiac tamponade · Hemopericardium · · | |
| | **Myocardium** | Myocarditis (Chagas disease · · Cardiomyopathy: Dilated (Alcoholic), Hypertrophic, *and* Restrictive (Loeffler endocarditis · Cardiac amyloidosis · Endocardial fibroelastosis · · Arrhythmogenic right ventricular dysplasia · | |
| | **Endocardium / valves** | **Endocarditis** | *infective endocarditis* (Subacute bacterial endocarditis · · *non-infective endocarditis* (Libman–Sacks endocarditis · Nonbacterial thrombotic endocarditis · · |
| | | | *mitral* (regurgitation · prolapse · stenosis · · *aortic* (**stenosis** · |

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|---|---|---|---|
| | | **Valves** | insufficiency · · *tricuspid* (stenosis · insufficiency · · *pulmonary* (stenosis · insufficiency · · |
| **Conduction / arrhythmia** | **Bradycardia** | | Sinus bradycardia · Sick sinus syndrome · Heart block: Sinoatrial · AV (1° · 2° · 3° · · Intraventricular · Bundle branch block (Right · Left · Left anterior fascicle · Left posterior fascicle · Bifascicular · Trifascicular · · Adams–Stokes syndrome · |
| | **Tachycardia (paroxysmal and sinus)** | **Supraventricular** | Atrial (Multifocal · · Junctional (AV nodal reentrant · Junctional ectopic · · |
| | | **Ventricular** | Accelerated idioventricular rhythm · Catecholaminergic polymorphic · Torsades de pointes · |
| | **Premature contraction** | | Atrial · Junctional · Ventricular · |
| | **Pre-excitation syndrome** | | Lown–Ganong–Levine · Wolff–Parkinson–White · |
| | **Flutter / fibrillation** | | Atrial flutter · Ventricular flutter · Atrial fibrillation (Familial · · Ventricular fibrillation · |
| | **Pacemaker** | | Ectopic pacemaker / Ectopic beat · Multifocal atrial tachycardia · Pacemaker syndrome · Parasystole · Wandering pacemaker · |
| | **Long QT syndrome** | | Andersen–Tawil · Jervell and Lange-Nielsen · Romano–Ward · |
| | **Cardiac arrest** | | Sudden cardiac death · Asystole · Pulseless electrical activity · Sinoatrial arrest · |
| | **Other / ungrouped** | | *hexaxial reference system* (Right axis deviation · Left axis deviation · · *QT* (Short QT syndrome · · *T* (T wave alternans · · *ST* (Osborn wave · ST elevation · ST depression · · Strain pattern · |
| **Cardiomegaly** | | | Ventricular hypertrophy (Left · Right / Cor pulmonale · · Atrial enlargement (Left · Right · · |
| **Other** | | | Cardiac fibrosis · Heart failure (Diastolic heart failure · Cardiac asthma · · Rheumatic fever · |

| v · t · e · | **Congenital heart defects (Q20–Q24, 745–746)** | | |
|---|---|---|---|
| **Cardiac shunt/ heart septal defect** | **Aortopulmonary septal defect** | | *R→L:* Double outlet right ventricle (Taussig–Bing syndrome · · Transposition of the great vessels (dextro · levo · · Persistent truncus arteriosus · Aortopulmonary window · |
| | **Atrial septal defect** | | *L→R:* Sinus venosus atrial septal defect · Lutembacher's syndrome · |
| | **Ventricular septal defect** | | *L→R and R→L:* Eisenmenger's syndrome · *R→L, with other conditions:* Tetralogy of Fallot · |
| | **Atrioventricular septal defect** | | *L→R:* Ostium primum · |
| **Valvular heart disease/ heart chambers** | **Right** | | *pulmonary valves* (stenosis · insufficiency · · *tricuspid valves* (stenosis · atresia · Ebstein's anomaly · · Hypoplastic right heart syndrome (Uhl anomaly · · |
| | **Left** | | *aortic valves* (stenosis · insufficiency · bicuspid · · *mitral valves* (stenosis · regurgitation · · Hypoplastic left heart syndrome · |

| | |
|---|---|
| **Other** | Dextrocardia · Levocardia · Cor triatriatum · Crisscross heart · Brugada syndrome · Coronary artery anomaly · Anomalous aortic origin of a coronary artery · Ventricular inversion · |
| **Authority control** | NDL: 01167602 · |

Categories: Valvular heart disease | Diseases of the aorta




# Atrial fibrillation

From Wikipedia, the free encyclopedia

**Atrial fibrillation** (**AF** or **A-fib**) is an abnormal heart rhythm characterized by rapid and irregular beating.[1] Often it starts as brief periods of abnormal beating which become longer and possibly constant over time.[2] Most episodes have no symptoms.[3] Occasionally there may be heart palpitations, fainting, lightheadedness, shortness of breath, or chest pain.[4] The disease is associated with an increased risk of heart failure, dementia, and stroke.[3] It is a type of supraventricular tachycardia.[5]

High blood pressure and valvular heart disease are the most common alterable risk factors for AF.[6][7] Other heart-related risk factors include heart failure, coronary artery disease, cardiomyopathy, and congenital heart disease.[6] In the developing world valvular heart disease often occurs as a result of rheumatic fever.[8] Lung-related risk factors include COPD, obesity, and sleep apnea.[3] Other factors include excess alcohol intake, diabetes mellitus, and thyrotoxicosis.[3][8] However, half of cases are not associated with one of these risks.[3] A diagnosis is made by feeling the pulse and may be confirmed using an electrocardiogram (ECG).[9] A typical ECG in AF shows no P waves and an irregular ventricular rate.[9]

AF is often treated with medications to slow the heart rate to a near normal range (known as rate control) or to convert the rhythm to normal sinus rhythm (known as rhythm control).[6] Electrical cardioversion can also be used to convert AF to a normal sinus rhythm and is often used emergently if the person is unstable.[10] Ablation may prevent recurrence in some people.[11] Depending on the risk of stroke either aspirin or anti-clotting medications such as warfarin or a novel oral anticoagulant may be recommended.[3] While these medications reduce this risk, they increase rates of major bleeding.[12]

Atrial fibrillation is the most common serious abnormal heart rhythm.[3] In Europe and North America, as of 2014, it affects about 2% to 3% of the population.[2] This is an increase from 0.4 to 1% of the population around 2005.[13] In the developing world about 0.6% of males and 0.4% of females are affected. The percentage of people with AF increases with age with 0.14% under 50 years old, 4% between 60 and 70 years old, and 14% over 80 years old being affected.[2] A-fib and atrial flutter [14]

**Atrial fibrillation**

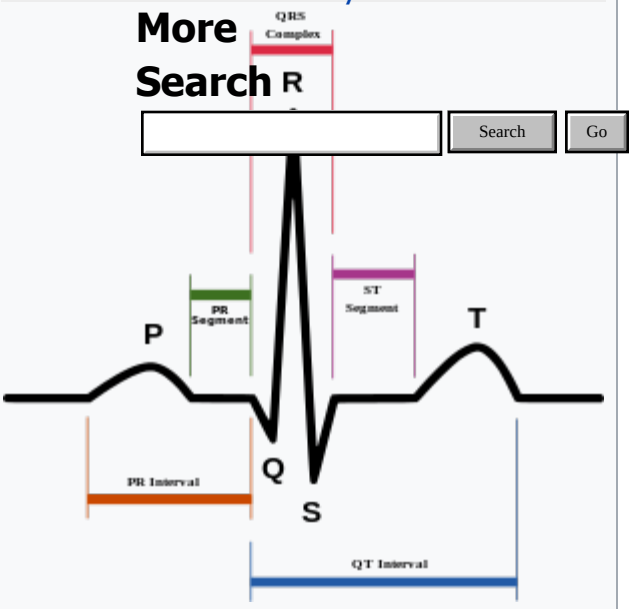



Diagram of normal sinus rhythm as seen on ECG. In atrial fibrillation the P waves, which represent depolarization of the top of the heart, are absent.

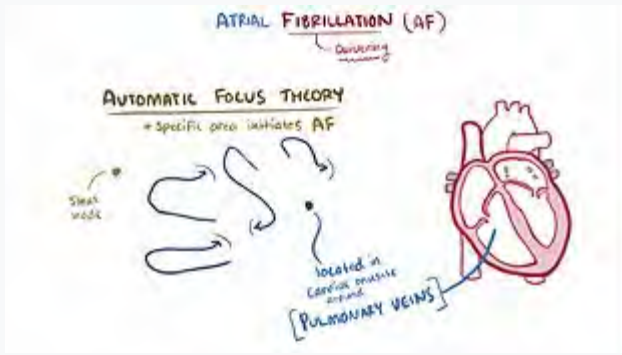
| Classification and external resources | |
|---|---|
| **Specialty** | Cardiology |
| **ICD-10** | I48 |
| **ICD-9-CM** | 427.31 |
| **DiseasesDB** | 1065 |
| **MedlinePlus** | 000184 |
| **eMedicine** | med/184 emerg/46 |
| **Patient UK** | Atrial fibrillation |
| **MeSH** | D001281 |

[edit on Wikidata]

resulted in 112,000 deaths in 2013, up from 29,000 in 1990. The first known report of an irregular pulse was by Jean-Baptiste de Sénac in 1749. This was first documented by ECG in 1909 by Thomas Lewis.[3]








Play media

Video explanation

## Signs and symptoms [edit]

AF is usually accompanied by symptoms related to a rapid heart rate. Rapid and irregular heart rates may be perceived as palpitations or exercise intolerance and occasionally may produce anginal chest pain (if the high heart rate causes ischemia). Other possible symptoms include congestive symptoms such as shortness of breath or swelling. The arrhythmia is sometimes only identified with the onset of a stroke or a transient ischemic attack (TIA). It is not uncommon for a patient to first become aware of AF from a routine physical examination or ECG, as it often does not cause symptoms.[13]


Normal rhythm tracing (top) Atrial fibrillation (bottom)

Since most cases of AF are secondary to other medical problems, the presence of chest pain or angina, signs and symptoms of hyperthyroidism (an overactive thyroid gland) such as weight loss and diarrhea, and symptoms suggestive of lung disease can indicate an underlying cause. A history of stroke or TIA, as well as high blood pressure, diabetes, heart failure, or rheumatic fever may indicate whether someone with AF is at a higher risk of complications.[13] The risk of a blood clot forming in the left atrium, breaking off, and then traveling in the bloodstream can be assessed using the CHADS2 score or CHA2DS2-VASc score.

### Rapid heart rate [edit]

Presentation is similar to other forms of rapid heart rate and may be asymptomatic.[15] Palpitations and chest discomfort are common complaints.[15] The rapid uncoordinated heart rate may result in reduced cardiac output, with the heart being unable to provide adequate blood flow and therefore oxygen delivery to the rest of the body. Common symptoms of uncontrolled atrial fibrillation may include shortness of breath,[15] shortness of breath when lying flat, dizziness, and sudden onset of shortness of breath during the night. This may progress to swelling of the lower extremities, a manifestation of congestive heart failure. Due to inadequate cardiac output, individuals with AF may also complain of light-headedness,[15] may feel like they are about to faint, or may actually lose consciousness.

AF can cause respiratory distress due to congestion in the lungs. By definition, the heart rate will be greater than 100 beats per minute. Blood pressure may be variable, and often difficult to measure as the beat-by-beat variability causes problems for most digital (oscillometric) non-invasive blood pressure monitors. For this reason, when determining heart rate in AF, direct cardiac auscultation is recommended. Low blood pressure is most concerning and a sign that immediate treatment is required. Many of the symptoms associated with uncontrolled atrial fibrillation are a manifestation of congestive heart failure due to the reduced cardiac output. Respiratory rate will be increased in the presence of respiratory distress. Pulse oximetry may confirm the presence of hypoxia related to any precipitating factors such as pneumonia. Examination of the jugular veins may reveal elevated pressure (jugular venous distention). Lung exam may reveal crackles, which are suggestive of pulmonary edema. Heart exam will reveal a rapid irregular rhythm.

## Causes [edit]

AF is linked to several forms of cardiovascular disease, but may occur in otherwise normal hearts. Cardiovascular factors known to be associated with the development of AF include high blood pressure, coronary artery disease, mitral stenosis (e.g., due to rheumatic heart disease or mitral valve prolapse), mitral regurgitation, left atrial enlargement, hypertrophic cardiomyopathy (HCM), pericarditis, congenital heart disease, and previous heart surgery. Additionally, lung diseases (such as pneumonia, lung cancer, pulmonary embolism, and sarcoidosis) are thought to play a role in certain people. Disorders of breathing during sleep such as obstructive sleep apnea (OSA) are also associated with AF.[16] Obesity is a risk factor for AF.[17] Hyperthyroidism and subclinical hyperthyroidism are associated with AF development.[18] Caffeine consumption does not appear to be associated with AF,[19] but excessive alcohol consumption ("binge drinking" or "holiday heart syndrome") is linked to AF.[20]

### Genetics [edit]

A family history of AF may increase the risk of AF. A study of more than 2,200 people found an increased risk factor for AF of 1.85 for those that had at least one parent with AF.[21][22][23] Various genetic mutations may be responsible.[24][25]

Four types of genetic disorder are associated with atrial fibrillation:[26]

- Familial AF as a monogenic disease
- Familial AF presenting in the setting of another inherited cardiac disease (hypertrophic cardiomyopathy, dilated cardiomyopathy, familial amyloidosis)
- Inherited arrhythmic syndromes (congenital long QT syndrome, short QT syndrome, Brugada syndrome)
- Non-familial AF associated with genetic backgrounds (polymorphism in the ACE gene) that may predispose to atrial fibrillation

## Pathophysiology [edit]

In AF, the normal regular electrical impulses generated by the sinoatrial node in the right atrium of the heart are overwhelmed by disorganized electrical impulses usually originating in the roots of the pulmonary veins. This leads to irregular conduction of ventricular impulses that generate the heartbeat.

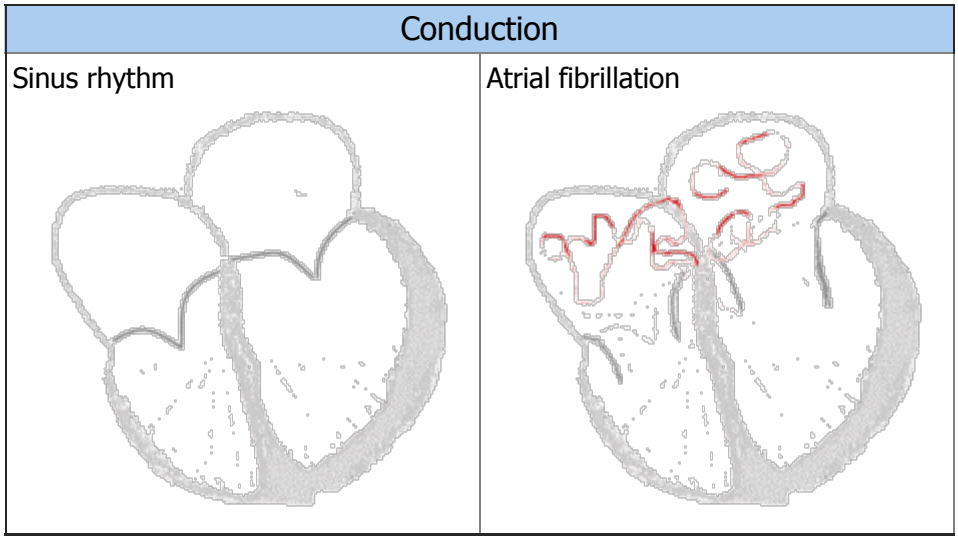
## Pathology [edit]

The primary pathologic change seen in atrial fibrillation is the progressive fibrosis of the atria. This fibrosis is due primarily to atrial dilation; however, genetic causes and inflammation may be factors in some individuals. Dilation of the atria can be due to almost any structural abnormality of the heart that can cause a rise in the pressure within the heart. This includes valvular heart disease (such as mitral stenosis, mitral regurgitation, and tricuspid regurgitation), hypertension, and congestive heart failure. Any inflammatory state that affects the heart can cause fibrosis of the atria. This is typically due to sarcoidosis but may also be due to autoimmune disorders that create autoantibodies against myosin heavy chains. Mutation of the *lamin AC* gene is also associated with fibrosis of the atria that can lead to atrial fibrillation.

Once dilation of the atria has occurred, this begins a chain of events that leads to the activation of the renin aldosterone angiotensin system (RAAS) and subsequent increase in matrix metalloproteinases and disintegrin, which leads to atrial remodeling and fibrosis, with loss of atrial muscle mass. This process is not immediate, and experimental studies have revealed patchy atrial fibrosis may precede the occurrence of atrial fibrillation and may progress with prolonged durations of atrial fibrillation.

Fibrosis is not limited to the muscle mass of the atria and may occur in the sinus node (SA node) and atrioventricular node (AV node), correlating with sick sinus syndrome. Prolonged episodes of atrial fibrillation have been shown to correlate with prolongation of the sinus node recovery time,[13] suggesting that dysfunction of the SA node is progressive with prolonged episodes of atrial fibrillation.

## Electrophysiology [edit]




The normal electrical conduction system of the heart allows the impulse that is generated by the sinoatrial node (SA node) of the heart to be propagated to and stimulate the myocardium (muscular layer of the heart). When the myocardium is stimulated, it contracts. It is the ordered stimulation of the myocardium that allows efficient contraction of the heart, thereby allowing blood to be pumped to the body.

There are multiple theories about the etiology of atrial fibrillation. An important theory is that, in atrial fibrillation, the regular impulses produced by the sinus node for a normal heartbeat are overwhelmed by rapid electrical discharges produced in the atria and adjacent parts of the pulmonary veins. Sources of these disturbances are either automatic foci, often localized at one of the pulmonary veins, or a small number of localized sources in the form of either reentrant electrical spiral waves (rotors) or repetitive focal beats; these localized sources may be found in the left atrium near the pulmonary veins or in a variety of other locations through both the left or right atrium.

Because recovery of the atria from excitation is heterogeneous, the electrical waves generated by the AF sources undergo repetitively, spatially distributed breakup and fragmentation in a process known as "fibrillatory conduction". Another theory is the multiple wavelet theory.[27]

AF can be distinguished from atrial flutter (AFL), which appears as an organized electrical circuit usually in the right atrium. AFL produces characteristic saw-toothed F-waves of constant amplitude and frequency on an ECG whereas AF does not. In AFL, the discharges circulate rapidly at a rate of 300 beats per minute (bpm) around the atrium. In AF, there is no regularity of this kind, except at the sources where the local activation rate can exceed 500 bpm.

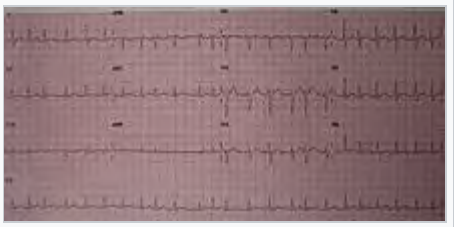
Although the electrical impulses of AF occur at a high rate, most of them do not result in a heart beat. A heart beat results when an electrical impulse from the atria passes through the atrioventricular (AV) node to the ventricles and causes them to contract. During AF, if all of the impulses from the atria passed

through the AV node, there would be severe ventricular tachycardia, resulting in a severe reduction of cardiac output. This dangerous situation is prevented by the AV node since its limited conduction velocity reduces the rate at which impulses reach the ventricles during AF.[28]

## Diagnosis [edit]

The evaluation of atrial fibrillation involves a determination of the cause of the arrhythmia, and classification of the arrhythmia. Diagnostic investigation of AF typically includes a complete history and physical examination, ECG, transthoracic echocardiogram, complete blood count, and serum thyroid stimulating hormone level.[15]

If a patient presents with a sudden onset of severe symptoms, other forms of abnormal heart rhythm with high heart rate must be ruled out, as some may be immediately life-threatening, such as ventricular tachycardia. While most patients will be placed on continuous cardiorespiratory monitoring, an ECG is essential for diagnosis. Provoking causes should be sought out.



A 12-lead ECG showing atrial fibrillation at approximately 150 beats per minute

### Screening [edit]

Limited studies have suggested that screening for atrial fibrillation in those 65 years and older increases the number of cases of atrial fibrillation detected.[29]

### Minimal evaluation [edit]

In general, the minimal evaluation of atrial fibrillation should be performed in all individuals with AF. The goal of this evaluation is to determine the general treatment regimen for the individual. If results of the general evaluation warrant it, further studies may then be performed.

### History and physical examination [edit]

The history of the individual's atrial fibrillation episodes is probably the most important part of the evaluation. Distinctions should be made between those who are entirely asymptomatic when they are in AF (in which case the AF is found as an incidental finding on an ECG or physical examination) and those who have gross and obvious symptoms due to AF and can pinpoint whenever they go into AF or revert to sinus rhythm.

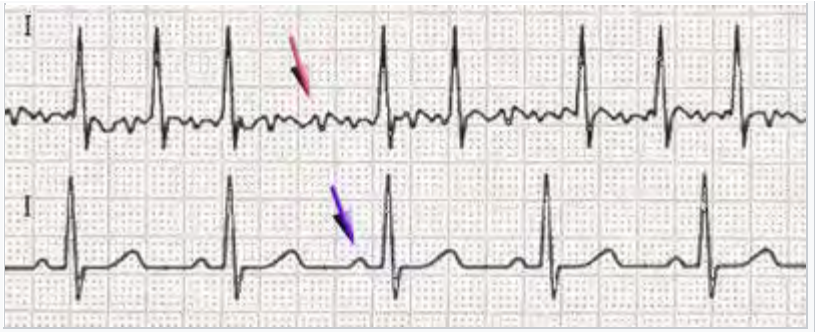
### Routine bloodwork [edit]

While many cases of AF have no definite cause, it may be the result of various other problems. Hence, kidney function and electrolytes are routinely determined, as well as thyroid-stimulating hormone (commonly suppressed in hyperthyroidism and of relevance if amiodarone is administered for treatment) and a blood count.[13]

In acute-onset AF associated with chest pain, cardiac troponins or other markers of damage to the heart muscle may be ordered. Coagulation studies (INR/aPTT) are usually performed, as anticoagulant medication may be commenced.[13]

### Electrocardiogram [edit]

Atrial fibrillation is diagnosed on an electrocardiogram (ECG), an investigation performed routinely whenever an irregular heart beat is suspected. Characteristic findings are the absence of P waves, with disorganized



ECG of atrial fibrillation (top) and normal sinus rhythm (bottom). The purple arrow indicates a P wave, which is lost in atrial fibrillation.

electrical activity in their place, and irregular R-R intervals due to irregular conduction of impulses to the ventricles.[13] At very fast heart rates atrial fibrillation may look more regular, which may make it more difficult to separate from SVT or ventricular tachycardia.[30]

QRS complexes should be narrow, signifying that they are initiated by normal conduction of atrial electrical activity through the intraventricular conduction system. Wide QRS complexes are worrisome for ventricular tachycardia, although, in cases where there is a disease of the conduction system, wide complexes may be present in A-Fib with rapid ventricular response.

If paroxysmal AF is suspected but an ECG during an office visit shows only a regular rhythm, AF episodes may be detected and documented with the use of ambulatory Holter monitoring (e.g., for a day). If the episodes are too infrequent to be detected by Holter monitoring with reasonable probability, then the patient can be monitored for longer periods (e.g., a month) with an ambulatory event monitor.[13]

## Echocardiography [edit]

In general, a non-invasive transthoracic echocardiogram (TTE) is performed in newly diagnosed AF, as well as if there is a major change in the patient's clinical state. This ultrasound-based scan of the heart may help identify valvular heart disease (which may greatly increase the risk of stroke), left and right atrial size (which indicates likelihood that AF may become permanent), left ventricular size and function, peak right ventricular pressure (pulmonary hypertension), presence of left atrial thrombus (low sensitivity), presence of left ventricular hypertrophy and pericardial disease.[13]

Significant enlargement of both the left and right atria is associated with long-standing atrial fibrillation and, if noted at the initial presentation of atrial fibrillation, suggests that the atrial fibrillation is likely to be of a longer duration than the individual's symptoms.

## Extended evaluation [edit]

In general, an extended evaluation is not necessary for most individuals with atrial fibrillation and is performed only if abnormalities are noted in the limited evaluation, if a reversible cause of the atrial fibrillation is suggested, or if further evaluation may change the treatment course.

## Chest X-ray [edit]

In general, a chest X-ray is performed only if a pulmonary cause of atrial fibrillation is suggested, or if other cardiac conditions are suspected (in particular congestive heart failure.) This may reveal an underlying problem in the lungs or the blood vessels in the chest.[13] In particular, if an underlying pneumonia is suggested, then treatment of the pneumonia may cause the atrial fibrillation to terminate on its own.

## Transesophageal echocardiogram [edit]

A regular echocardiogram (transthoracic echo/TTE) has a low sensitivity for identifying blood clots in the heart. If this is suspected (e.g., when planning urgent electrical cardioversion) a transesophageal echocardiogram/TEE (or TOE where British spelling is used) is preferred.[13]

The TEE has much better visualization of the left atrial appendage than transthoracic echocardiography.[31] This structure, located in the left atrium, is the place where a blood clot forms in more than 90% of cases [32][33]

in non-valvular (or non-rheumatic) atrial fibrillation. TEE has a high sensitivity for locating thrombi in this area and can also detect sluggish bloodflow in this area that is suggestive of blood clot formation.[31]

If no blood clot is seen on TEE, the incidence of stroke immediately after cardioversion is performed is very low.[*citation needed*]

## Ambulatory Holter monitoring [edit]

A Holter monitor is a wearable ambulatory heart monitor that continuously monitors the heart rate and heart rhythm for a short duration, typically 24 hours. In individuals with symptoms of significant shortness of breath with exertion or palpitations on a regular basis, a Holter monitor may be of benefit to determine whether rapid heart rates (or unusually slow heart rates) during atrial fibrillation are the cause of the symptoms.

## Exercise stress testing [edit]

Some individuals with atrial fibrillation do well with normal activity but develop shortness of breath with exertion. It may be unclear whether the shortness of breath is due to a blunted heart rate response to exertion caused by excessive atrioventricular node-blocking agents, a very rapid heart rate during exertion, or other underlying conditions such as chronic lung disease or coronary ischemia. An exercise stress test will evaluate the individual's heart rate response to exertion and determine if the AV node blocking agents are contributing to the symptoms.

## Classification [edit]

The American College of Cardiology (ACC), American Heart Association (AHA), and the European Society of Cardiology (ESC) recommend in their guidelines the following classification system based on simplicity and clinical relevance.[13]

**Classification system**

| AF category | Defining characteristics |
|---|---|
| First detected | only one diagnosed episode |
| Paroxysmal | recurrent episodes that stop on their own in less than 7 days |
| Persistent | recurrent episodes that last more than 7 days |
| Permanent | an ongoing long-term episode |

All people with AF are initially in the category called *first detected AF*. These patients may or may not have had previous undetected episodes. If a first detected episode stops on its own in less than 7 days and then another episode begins, later on, the category changes to paroxysmal AF. Although patients in this category have episodes lasting up to 7 days, in most cases of paroxysmal AF the episodes will stop in less than 24 hours. If the episode lasts for more than 7 days, it is unlikely to stop on its own,[34] and is then known as persistent AF. In this case, cardioversion can be used to stop the episode. If cardioversion is unsuccessful or not attempted and the episode continues for a long time (e.g., a year or more), the patient's AF is then known as permanent.

Episodes that last less than 30 seconds are not considered in this classification system. Also, this system does not apply to cases where the AF is a secondary condition that occurs in the setting of a primary condition that may be the cause of the AF.

About half of people with AF have permanent AF, while a quarter have paroxysmal AF, and a quarter have persistent AF.[2]

In addition to the above four AF categories, which are mainly defined by episode timing and termination, the ACC/AHA/ESC guidelines describe additional AF categories in terms of other characteristics of the patient.[13]

- *Lone atrial fibrillation* (LAF) – absence of clinical or echocardiographic findings of other cardiovascular disease (including hypertension), related pulmonary disease, or cardiac abnormalities such as

enlargement of the left atrium, and age under 60 years
- *Nonvalvular AF* – absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair
- *Secondary AF* – occurs in the setting of a primary condition that may be the cause of the AF, such as acute myocardial infarction, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or other acute pulmonary disease

# Management [edit]

*Main article: Management of atrial fibrillation*

The main goals of treatment are to prevent circulatory instability and stroke. Rate or rhythm control are used to achieve the former, whereas anticoagulation is used to decrease the risk of the latter.[35] If cardiovascularly unstable due to uncontrolled tachycardia, immediate cardioversion is indicated.[13] An exercise program may be useful.[*citation needed*]

## Anticoagulants [edit]

Anticoagulation can be used to reduce the risk of stroke from AF. Anticoagulation is recommended in most people other than those at low risk of stroke[36] or those at high risk of bleeding.

The risk of stroke from non-valvular AF can be estimated using the $CHA_2DS_2$-VASc score. A 2014 AHA/ACC/HRS guideline said that for nonvalvular AF, anticoagulation is recommended if there is a score of 2 or more, not using anticoagulation may be considered if there is a score of 1, and not using anticoagulation is reasonable if there is a score of 0.[37]

Anticoagulation can be achieved through a number of means including warfarin,[38] heparin, dabigatran, rivaroxaban[39] edoxaban,[40] and apixaban.[41] Aspirin is less effective in reducing the risk of stroke and may not be safer with respect to major bleeding (including intracranial bleeding) than well-managed warfarin or a non-vitamin K oral anticoagulant (NOAC).[42] A number of issues should be considered, including the cost of NOACs, risk of stroke, risk of falls, compliance, and speed of desired onset of anticoagulation.[43]

For those with non-valvular atrial fibrillation, the NOACs (rivaroxaban, dabigatran, apixaban) are neither superior nor worse than warfarin in preventing non-hemorrhagic stroke and systemic embolic events.[44][45] They have a lower risk of intracranial bleeding compared to warfarin; however, dabigatran is associated with a higher risk of gastrointestinal bleeding.[44][45]

## Rate versus rhythm control [edit]

There are two ways to approach atrial fibrillation using medications: rate control and rhythm control. Both methods have similar outcomes.[46] *Rate control* lowers the heart rate closer to normal, usually 60 to 100 bpm, without trying to convert to a regular rhythm. *Rhythm control* tries to restore a normal heart rhythm in a process called cardioversion and maintains the normal rhythm with medications. Studies suggest that rhythm control is more important in the acute setting AF, whereas rate control is more important in the chronic phase.

There is no difference in risk of stroke in people having converted to a normal rhythm with antiarrhythmic treatment compared to those with only rate control.[47][*non-primary source needed*] AF is associated with a reduced quality of life, and, while some studies indicate that rhythm control leads to a higher quality of life, some did not find a difference.[48]

A further study focused on rhythm control in people with AF with heart failure, based on the idea that AF increases mortality in this group. In this setting, rhythm control offered no advantage compared to rate control.[49][*non-primary source needed*]

In those with a fast ventricular response, intravenous magnesium significantly increases the chances of

successful rate and rhythm control in the urgent setting without major side-effects.[50] A person with poor vital signs, mental status changes, preexcitation, or chest pain often will go to immediate treatment with synchronized DC cardioversion.[13] Otherwise the decision of rate control versus rhythm control using drugs is made. This is based on a number of criteria that includes whether or not symptoms persist with rate control.

## Rate control [edit]

Rate control to a target heart rate of 110 bpm is recommended in most people.[51] Lower heart rates may be recommended in those with left ventricular hypertrophy or reduced left ventricular function.[52] Rate control is achieved with medications that work by increasing the degree of block at the level of the AV node, decreasing the number of impulses that conduct into the ventricles. This can be done with:[13][53]

- Beta blockers (preferably the "cardioselective" beta blockers such as metoprolol, atenolol, bisoprolol, nebivolol)
- Non-dihydropyridine calcium channel blockers (e.g., diltiazem or verapamil)
- Cardiac glycosides (e.g., digoxin) – have less use, apart from in older people who are sedentary. They are not as effective as either beta blockers or calcium channel blockers.[6]

In those with chronic disease either beta blockers or calcium channel blockers are recommended.[51]

In addition to these agents, amiodarone has some AV node blocking effects (in particular when administered intravenously), and can be used in individuals when other agents are contraindicated or ineffective (particularly due to hypotension).

## Cardioversion [edit]

Cardioversion is the attempt to switch an irregular heartbeat to a normal heartbeat using electrical or chemical means.[13]

- *Electrical cardioversion* involves the restoration of normal heart rhythm through the application of a DC electrical shock. Exact placement of the pads does not appear important.[54]
- *Chemical cardioversion* is performed with drugs, such as amiodarone, dronedarone,[55] procainamide, dofetilide, ibutilide, propafenone, or flecainide.

After successful cardioversion the heart may be in a stunned state, which means that there is a normal rhythm but restoration of normal atrial contraction has not yet occurred.[56]

## Surgery [edit]

## Ablation [edit]

In young people with little-to-no structural heart disease where rhythm control is desired and cannot be maintained by medication or cardioversion, then radiofrequency ablation or cryoablation may be attempted and is preferred over years of drug therapy.[13][57] Although radiofrequency ablation is becoming an accepted intervention in selected younger patients, there is currently a lack of evidence that ablation reduces all-cause mortality, stroke, or heart failure.[58] There are two ongoing clinical trials (CABANA [Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation] and EAST [Early Therapy of Atrial Fibrillation for Stroke Prevention Trial]) that should provide new information for assessing whether AF catheter ablation is superior to more standard therapy.[59]

The Maze procedure, first performed in 1987, is an effective invasive surgical treatment that is designed to create electrical blocks or barriers in the atria of the heart, forcing electrical impulses that stimulate the heartbeat to travel down to the ventricles. The idea is to force abnormal electrical signals to move along one, uniform path to the lower chambers of the heart (ventricles), thus restoring the normal heart rhythm.[60]

AF often occurs after cardiac surgery and is usually self-limiting. It is strongly associated with age,

preoperative hypertension, and the number of vessels grafted. Measures should be taken to control hypertension preoperatively to reduce the risk of AF. Also, people with a higher risk of AF, e.g., people with pre-operative hypertension, more than 3 vessels grafted, or greater than 70 years of age, should be considered for prophylactic treatment. Postoperative pericardial effusion is also suspected to be the cause of atrial fibrillation. Prophylaxis may include prophylactic postoperative rate and rhythm management. Some authors perform posterior pericardiotomy to reduce the incidence of postoperative AF.[61] When AF occurs, management should primarily be rate and rhythm control. However, cardioversion may be employed if the person is hemodynamically unstable, highly symptomatic, or persists for 6 weeks after discharge. In persistent cases, anticoagulation should be used.

### Left atrial appendage occlusion [edit]

There is tentative evidence that left atrial appendage occlusion therapy may reduce the risk of stroke in people with non-valvular AF as much as warfarin.[62]

## Prognosis [edit]

Atrial fibrillation increases the risk of heart failure by 11 per 1000, kidney problems by 6 per 1000, death by 4 per 1000, stroke by 3 per 1000, and coronary heart disease by 1 per 1000.[63] Women have a worse outcome overall than men.[64]

### Blood clots [edit]

*See also: CHADS score*

### Prediction of embolism [edit]

Determining the risk of an embolism causing a stroke is important for guiding the use of anticoagulants. The most accurate clinical prediction rules are:[65]

- CHADS2
- CHA2DS2-VASc

Both the CHADS2 and the CHA2DS2-VASc score predict future stroke risk in people with a-fib with CHA2DS2-VASc being more accurate. Some that had a CHADS2 score of 0 had a CHA2DS2-VASc score of 3, with a 3.2% annual risk of stroke. Thus a CHA2DS2-VASc score of 0 is considered very low risk.[66]

### Mechanism of thrombus formation [edit]

In atrial fibrillation, the lack of an organized atrial contraction can result in some stagnant blood in the left atrium (LA) or left atrial appendage (LAA). This lack of movement of blood can lead to thrombus formation (blood clotting). If the clot becomes mobile and is carried away by the blood circulation, it is called an embolus. An embolus proceeds through smaller and smaller arteries until it plugs one of them and prevents blood from flowing through the artery. This process results in end organ damage due to loss of nutrients, oxygen, and removal of cellular waste products. Emboli in the brain may result in an ischemic stroke or a transient ischemic attack (TIA).

More than 90% of cases of thrombi associated with non-valvular atrial fibrillation evolve in the left atrial appendage.[32] However, the LAA lies in close relation to the free wall of the left ventricle and thus the LAA's emptying and filling, which determines its degree of blood stagnation, may be helped by the motion of the wall of the left ventricle, if there is good ventricular function.[67]

If the LA is enlarged, there is an increased risk of thrombi that originate in the LA. Moderate to severe, non-rheumatic, mitral regurgitation (MR) reduces this risk of stroke.[68][*non-primary source needed*] This risk reduction may be due to a beneficial swirling effect of the MR blood flow into the LA.[69]

### Mitral valve [edit]

Atrial fibrillation and a corresponding enlargement of the left atrium may cause an increase in size of the mitral valve annulus.[70][*non-primary source needed*]

With a sinus rhythm, the mitral annulus undergoes dynamic changes during the cardiac cycle. For example, at the end of diastole the annular area is smaller than at the end of systole. A possible reason for this dynamic size difference is that the coordinated contraction of the left atrium acts like a sphincter about the mitral annulus and reduces its size. This may be important for mitral valve competence so that it does not leak when the left ventricle pumps blood. However, when the left atrium fibrillates, this sphincter action is not possible and may contribute to, or result in, mitral regurgitation in some cases.[70][*non-primary source needed*]

## Epidemiology [edit]

Atrial fibrillation is the most common arrhythmia.[13] In Europe and North America as of 2014 it affects about 2% to 3% of the population.[2] This is an increase from 0.4 to 1% of the population around 2005.[13] In the developing world rates are about 0.6% for males and 0.4% for females.[2]

It also accounts for one-third of hospital admissions for cardiac rhythm disturbances,[13] and the rate of admissions for AF has risen in recent years.[71] Strokes from AF account for 6–24% of all ischemic strokes.[72][*non-primary source needed*] After a transient ischemic attack or stroke about 11% are found to have a new diagnosis of atrial fibrillation.[73] Between 3 and 11% of those with AF have structurally normal hearts.[74] Approximately 2.2 million individuals in the United States and 4.5 million in the European Union have AF.[13]

The number of new cases each year of atrial fibrillation increases with age. In individuals over the age of 80 it affects about 8%.[13] In developed countries, the number of patients with atrial fibrillation is likely to increase during the next 50 years, owing to the growing proportion of elderly individuals.[75][*non-primary source needed*]

## History [edit]

Because the diagnosis of atrial fibrillation requires measurement of the electrical activity of the heart, atrial fibrillation was not truly described until 1874, when Edmé Félix Alfred Vulpian observed the irregular atrial electrical behavior that he termed *"fremissement fibrillaire"* in dog hearts.[76] In the mid-eighteenth century, Jean-Baptiste de Sénac made note of dilated, irritated atria in people with mitral stenosis.[77] The irregular pulse associated with AF was first recorded in 1876 by Carl Wilhelm Hermann Nothnagel and termed *"delirium cordis"*, stating that "[I]n this form of arrhythmia the heartbeats follow each other in complete irregularity. At the same time, the height and tension of the individual pulse waves are continuously changing".[78] Correlation of delirium cordis with the loss of atrial contraction as reflected in the loss of *a waves* in the jugular venous pulse was made by Sir James MacKenzie in 1904.[79] Willem Einthoven published the first ECG showing AF in 1906.[80] The connection between the anatomic and electrical manifestations of AF and the irregular pulse of delirium cordis was made in 1909 by Carl Julius Rothberger, Heinrich Winterberg, and Sir Thomas Lewis.[81][82][83]

## See also [edit]

- Ventricular fibrillation
- Osborn wave

## References [edit]

1. ^ "Heart Disease Other Related Conditions". *cdc.gov*. September 3, 2014. Retrieved 19 February 2015.
2. ^ *a b c d e f* Zoni-Berisso, M; Lercari, F; Carazza, T; Domenicucci, S (2014). "Epidemiology of atrial fibrillation: European perspective.". *Clinical epidemiology*. **6**: 213–20. doi:10.2147/CLEP.S47385. PMID 24966695.
3. ^ *a b c d e f g h* Munger, TM; Wu, LQ; Shen, WK (January 2014). "Atrial fibrillation.". *Journal of biomedical research*. **28** (1): 1–17. doi:10.7555/JBR.28.20130191. PMID 24474959.
4. ^ Gray, David (2010). *Chamberlain's Symptoms and Signs in Clinical Medicine: An Introduction to Medical Diagnosis* (13th ed.). London: Hodder Arnold. pp. 70–1. ISBN 9780340974254.
5. ^ Urman, edited by Linda S. Aglio, Robert W. Lekowski, Richard D. (2015). *Essential clinical anesthesia review : keywords, questions and answers for the boards*. p. 480. ISBN 9781107681309.
6. ^ *a b c d* Anumonwo, JM; Kalifa, J (November 2014). "Risk Factors and Genetics of Atrial Fibrillation.". *Cardiology clinics*. **32** (4): 485–494. doi:10.1016/j.ccl.2014.07.007. PMID 25443231.
7. ^ Nguyen, TN; Hilmer, SN; Cumming, RG (10 September 2013). "Review of epidemiology and management of atrial fibrillation in developing countries.". *International Journal of Cardiology*. **167** (6): 2412–20. doi:10.1016/j.ijcard.2013.01.184. PMID 23453870.
8. ^ *a b* Mischke, K; Knackstedt, C; Marx, N; Vollmann, D (April 2013). "Insights into atrial fibrillation.". *Minerva medica*. **104** (2): 119–30. PMID 23514988.
9. ^ *a b* Ferguson C, Inglis SC, Newton PJ, Middleton S, Macdonald PS, Davidson PM (2013). "Atrial fibrillation: stroke prevention in focus". *ACC*. **00** (2): 92–98. doi:10.1016/j.aucc.2013.08.002. PMID 24054541.
10. ^ Oishi, ML; Xing, S (February 2013). "Atrial fibrillation: management strategies in the emergency department.". *Emergency medicine practice*. **15** (2): 1–26; quiz 27. PMID 23369365.
11. ^ Amerena, JV; Walters, TE; Mirzaee, S; Kalman, JM (4 November 2013). "Update on the management of atrial fibrillation.". *The Medical journal of Australia*. **199** (9): 592–97. doi:10.5694/mja13.10191. PMID 24182224.
12. ^ Steinberg, BA; Piccini, JP (14 April 2014). "Anticoagulation in atrial fibrillation.". *BMJ (Clinical research ed.)*. **348**: g2116. doi:10.1136/bmj.g2116. PMID 24733535.
13. ^ *a b c d e f g h i j k l m n o p q r s t u v w* Fuster, Valentin (2006). "ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society". *Circulation*. **114** (7): e257–354. doi:10.1161/CIRCULATIONAHA.106.177292. PMID 16908781.
14. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
15. ^ *a b c d e* Gutierrez C, Blanchard DG (January 2011). "Atrial Fibrillation: Diagnosis and Treatment". *Am Fam Physician* (Review). **83** (1): 61–68. PMID 21888129.
16. ^ Abed HS, Wittert GA (November 2013). "Obesity and atrial fibrillation". *Obesity Reviews*. **14** (11): 929–38. doi:10.1111/obr.12056. PMID 23879190.
17. ^ Magnani JW, Hylek EM, Apovian CM (July 23, 2013). "Obesity begets atrial fibrillation: a contemporary summary" (PDF). *Circulation*. American Heart Association. **128** (4): 401–05. doi:10.1161/CIRCULATIONAHA.113.001840. PMID 23877062. Retrieved July 19, 2015.
18. ^ Palmeiro C, Davila MI, Bhat M, Frishman WH, Weiss IA (December 2013). "Subclinical hyperthyroidism and cardiovascular risk: recommendations for treatment". *Cardiology in review*. **21** (6): 300–08. doi:10.1097/CRD.0b013e318294f6f1. PMID 23563523.
19. ^ Cheng, M; Hu, Z; Lu, X; Huang, J; Gu, D (April 2014). "Caffeine intake and atrial fibrillation incidence: dose response meta-analysis of prospective cohort studies.". *The Canadian journal of cardiology*. **30** (4): 448–54. doi:10.1016/j.cjca.2013.12.026. PMID 24680173.
20. ^ Tonelo D, Providência R, Gonçalves L (August 2013). "Holiday heart syndrome revisited after 34 years". *Arquivos brasileiros de cardiologia*. **101** (2): 183–89. doi:10.5935/abc.20130153. PMC 3998158. PMID 24030078.
21. ^ Fox CS, Parise H, D'Agostino RB, et al. (2004). "Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring". *JAMA*. **291** (23): 2851–55. doi:10.1001/jama.291.23.2851. PMID 15199036.
22. ^ Roberts JD, Gollob MH (2014). "A contemporary review on the genetic basis of atrial fibrillation". *Methodist Debakey Cardiovasc J*. **10**: 18–24. doi:10.14797/mdcj-10-1-18. PMC 4051329. PMID 24932358.
23. ^ Howlett PJ, Hatch FS, Alexeenko V, Jabr RI, Leatham EW, Fry CH (2015). "Diagnosing Paroxysmal Atrial Fibrillation: Are Biomarkers the Solution to This Elusive Arrhythmia?". *Biomed Res Int*. **2015**: 910267. doi:10.1155/2015/910267. PMC 4502272. PMID 26229966.

24. ^ Saffitz JE (2006). "Connexins, conduction, and atrial fibrillation". *N. Engl. J. Med.* **354** (25): 2712–14. doi:10.1056/NEJMe068088. PMID 16790707.
25. ^ "OMIM Online Mendelian Inheritance of Man". The National Center for Biotechnology Information. Retrieved 2010-08-24.
26. ^ Shimizu W (2013). "Atrial fibrillation and genetic abnormalities". *Nihon Rinsho*. **71** (1): 161–66.
27. ^ Fuster, Valentin (October 2001). "ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology". *Circulation*. **104** (17): 2118–50. PMID 11673357.
28. ^ Klabunde, Richard (2005). *Cardiovascular Physiology Concepts*. Lippincott Williams & Wilkins. pp. 25, 28. ISBN 978-0-7817-5030-1.
29. ^ Moran, PS; Teljeur, C; Ryan, M; Smith, SM (June 2016). "Systematic screening for the detection of atrial fibrillation". *The Cochrane Database of Systematic Reviews*. **6**: CD009586. doi:10.1002/14651858.CD009586.pub3. PMID 27258214.
30. ^ Issa ZF, Miller JM, Zipes DP (2009). *Clinical arrhythmology and electrophysiology : a companion to Braunwald's heart disease*. Philadelphia: Saunders. p. 221. ISBN 978-1-4160-5998-1.
31. ^ [a] [b] Romero, J; Cao, JJ; Garcia, MJ; Taub, CC (August 2014). "Cardiac imaging for assessment of left atrial appendage stasis and thrombosis". *Nature Reviews. Cardiology*. **11** (8): 470-80. doi:10.1038/nrcardio.2014.77. PMID 24913058.
32. ^ [a] [b] Blackshear JL, Odell JA (February 1996). "Appendage ligation to reduce stroke in cardiac surgical patients with atrial fibrillation". *Ann. Thorac. Surg*. **61** (2): 755–59. doi:10.1016/0003-4975(95)00887-X. PMID 8572814.
33. ^ Ramlawi, B; Abu Saleh, WK; Edgerton, J (2015). "The Left Atrial Appendage: Target for Stroke Reduction in Atrial Fibrillation.". *Methodist DeBakey cardiovascular journal*. **11** (2): 100–03. doi:10.14797/mdcj-11-2-100. PMID 26306127.
34. ^ Levy S (2000). "Classification system of atrial fibrillation". *Current Opinion in Cardiology*. **15** (1): 54–57. doi:10.1097/00001573-200001000-00007. PMID 10666661.
35. ^ Prystowsky, Eric N; Padanilam, Benzy J; Fogel, MD, Richard I (July 21, 2015). "Treatment of Atrial Fibrillation". *JAMA*. **314** (3): 278–88. doi:10.1001/jama.2015.7505. PMID 26197188.
36. ^ Lip, GY; Lane, DA (19 May 2015). "Stroke prevention in atrial fibrillation: a systematic review.". *JAMA*. **313** (19): 1950–62. doi:10.1001/jama.2015.4369. PMID 25988464.
37. ^ January et al. 2014, pp. e211–e212
38. ^ Ciervo CA, Granger CB, Schaller FA (September 2012). "Stroke prevention in patients with atrial fibrillation: disease burden and unmet medical needs". *J Am Osteopath Assoc* (Review). **112** (9 (Suppl 2)): eS2–8. PMID 23014814. Archived from the original on 2016-03-05.
39. ^ "FDA approves Xarelto to prevent stroke in people with common type of abnormal heart rhythm". FDA. Retrieved Nov 4, 2011.
40. ^ "FDA approves anti-clotting drug Savaysa". FDA. 8 January 2015. Retrieved 23 June 2016.
41. ^ "FDA approves Eliquis to reduce the risk of stroke, blood clots in patients with non-valvular atrial fibrillation". FDA. Retrieved 2012-12-30.
42. ^ Lip, GY (26 July 2011). "The role of aspirin for stroke prevention in atrial fibrillation.". *Nature reviews. Cardiology*. **8** (10): 602–06. doi:10.1038/nrcardio.2011.112. PMID 21788962.
43. ^ Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning WJ (Sep 2004). "Antithrombotic Therapy in Atrial Fibrillation : The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy". *Chest*. **126** (3_suppl): 429S–56S. doi:10.1378/chest.126.3_suppl.429S. PMID 15383480. Retrieved 2012-10-02.
44. ^ [a] [b] Sharma, M; Cornelius, VR; Patel, JP; Davies, JG; Molokhia, M (20 May 2015). "Efficacy and Harms of Direct Oral Anticoagulants in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of Venous Thromboembolism: Systematic Review and Meta-Analysis.". *Circulation*. **132**: 194–204. doi:10.1161/CIRCULATIONAHA.114.013267. PMID 25995317.
45. ^ [a] [b] Gómez-Outes, A; Terleira-Fernández, AI; Calvo-Rojas, G; Suárez-Gea, ML; Vargas-Castrillón, E (2013). "Dabigatran, Rivaroxaban, or Apixaban versus Warfarin in Patients with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis of Subgroups.". *Thrombosis*. **2013**: 640723. doi:10.1155/2013/640723. PMC 3885278. PMID 24455237.
46. ^ Al-Khatib, Sana M. (June 3, 2014). "Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review.". *Annals of Internal Medicine*. **160** (11): 760–73. doi:10.7326/M13-1467. PMID 24887617.
47. ^ Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD (2002). "A comparison of rate control and rhythm control in patients with atrial fibrillation -

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators". *N Engl J Med*. **347** (23): 1825–33. doi:10.1056/NEJMoa021328. PMID 12466506.

48. ^ Thrall G, Lane D, Carroll D, Lip GY (2006). "Quality of life in patients with atrial fibrillation: a systematic review". *Am. J. Med*. **119** (5): 448.e1–19. doi:10.1016/j.amjmed.2005.10.057. PMID 16651058.
49. ^ Roy, Denis (June 2008). "Rhythm control versus rate control for atrial fibrillation and heart failure". *N Engl J Med*. **358** (25): 2667–77. doi:10.1056/NEJMoa0708789. PMID 18565859.
50. ^ Onalan O, Crystal E, Daoulah A, Lau C, Crystal A, Lashevsky I (2007). "Meta-analysis of magnesium therapy for the acute management of rapid atrial fibrillation". *Am. J. Cardiol*. **99** (12): 1726–32. doi:10.1016/j.amjcard.2007.01.057. PMID 17560883.
51. ^ [a] [b] Anderson, JL; Halperin, JL; Albert, NM; Bozkurt, B; Brindis, RG; Curtis, LH; DeMets, D; Guyton, RA; Hochman, JS; Kovacs, RJ; Ohman, EM; Pressler, SJ; Sellke, FW; Shen, WK; Wann, LS; Curtis, AB; Ellenbogen, KA; Estes NA, 3rd; Ezekowitz, MD; Jackman, WM; January, CT; Lowe, JE; Page, RL; Slotwiner, DJ; Stevenson, WG; Tracy, CM; Fuster, V; Rydén, LE; Cannom, DS; Crijns, HJ; Curtis, AB; Ellenbogen, KA; Le Heuzey, JY; Kay, GN; Olsson, SB; Prystowsky, EN; Tamargo, JL; Wann, S (7 May 2013). "Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.". *Journal of the American College of Cardiology*. **61** (18): 1935–44. doi:10.1016/j.jacc.2013.02.001. PMID 23558044.
52. ^ Badheka, AO; Shah, N; Grover, PM; Patel, NJ; Chothani, A; Mehta, K; Singh, V; Deshmukh, A; Savani, GT; Rathod, A; Panaich, SS; Patel, N; Arora, S; Bhalara, V; Coffey, JO; Mitrani, RD; Halperin, JL; Viles-Gonzalez, JF (1 April 2014). "Outcomes in atrial fibrillation patients with and without left ventricular hypertrophy when treated with a lenient rate-control or rhythm-control strategy.". *The American journal of cardiology*. **113** (7): 1159–65. doi:10.1016/j.amjcard.2013.12.021. PMID 24507168.
53. ^ "Atrial fibrillation: national clinical guideline for management in primary and secondary care" (PDF). *National Collaborating Centre for Chronic Conditions*. London: Royal College of Physicians. 2006.
54. ^ Kirkland, S; Stiell, I; AlShawabkeh, T; Campbell, S; Dickinson, G; Rowe, BH (July 2014). "The efficacy of pad placement for electrical cardioversion of atrial fibrillation/flutter: a systematic review.". *Academic Emergency Medicine*. **21** (7): 717–26. doi:10.1111/acem.12407. PMID 25117151.
55. ^ Bramah N. Singh (2007). "Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter". *N. Engl. J. Med*. **357** (10): 987–99. doi:10.1056/NEJMoa054686. PMID 17804843.
56. ^ Watson T, Shantsila E, Lip GY (10 Jan 2009). "Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited". *Lancet*. **373** (9658): 155–66. doi:10.1016/S0140-6736(09)60040-4. PMID 19135613.
57. ^ Leong-Sit P, Zado E, Callans DJ, et al. (2010). "Efficacy and risk of atrial fibrillation ablation before 45 years of age". *Circ Arrhythm Electrophysiol*. **3**: 452–57.
58. ^ Agency for Healthcare Research and Quality. Research Protocol: Treatment of Atrial Fibrillation. 2012; December 2012.
59. ^ January, CT; Wann, LS; Alpert, JS; Calkins, H; Cigarroa, JE; Cleveland, JC Jr; Conti, JB; Ellinor, PT; Ezekowitz, MD; Field, ME; Murray, KT; Sacco, RL; Stevenson, WG; Tchou, PJ; Tracy, CM; Yancy, CW (March 28, 2014). "2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society". *Circulation*. American Heart Association, Inc. **130**: e199–e267. doi:10.1161/CIR.0000000000000041. PMID 24682347. Executive summary: PMID 24682348
60. ^ Northwestern Surgery for Atrial Fibrillation. Atrial Fibrillation Surgery
61. ^ Kaleda VI, McCormack DJ, Shipolini AR (April 2012). "Does posterior pericardiotomy reduce the incidence of atrial fibrillation after coronary artery bypass grafting surgery?". *Interact. Cardiovasc. Thorac. Surg*. **14** (4): 384–89. doi:10.1093/icvts/ivr099. PMC 3309809. PMID 22235005.
62. ^ Zhou, X; Zhang, W; Lv, W; Zhou, Q; Li, Y; Zhang, L; Lu, Y; Zhang, J; Xing, Q; Wang, H; Tang, B (15 January 2016). "Left atrial appendage occlusion in atrial fibrillation for stroke prevention: A systemic review.". *International Journal of Cardiology*. **203**: 55–59. doi:10.1016/j.ijcard.2015.10.011. PMID 26492310.
63. ^ Odutayo, Ayodele; Wong, Christopher X; Hsiao, Allan J; Hopewell, Sally; Altman, Douglas G; Emdin, Connor A (6 September 2016). "Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis". *BMJ*: i4482. doi:10.1136/bmj.i4482.
64. ^ Emdin, CA; Wong, CX; Hsiao, AJ; Altman, DG; Peters, SA; Woodward, M; Odutayo, AA (19 January 2016). "Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies.". *BMJ (Clinical research ed.)*. **532**: h7013. PMID 26786546.
65. ^ Lopes RD, Crowley MJ, Shah BR, et al . Stroke Prevention in Atrial Fibrillation. Comparative Effectiveness Review No. 123. AHRQ Publication No. 13-EHC113-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2013. www.effectivehealthcare.ahrq.gov/ reports/final.cfm.
66. ^ Olesen, JB; Torp-Pedersen, C; Hansen, ML; Lip, GY (2012). "The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study.".

*Thromb Haemost*. **107** (6): 1172–79. doi:10.1160/th12-03-0175. PMID 22473219.
67. ^ Al-Saady, N. M.; O. A. Abel; A. J. Camm (1999). "Left atrial appendage: structure, function, and role in thromboembolism". *Heart*. **82** (5): 547–55. doi:10.1136/hrt.82.5.547. PMC 1760793. PMID 10525506.
68. ^ Nakagami H, Yamamoto K, Ikeda U, Mitsuhashi T, Goto T, Shimada K (1998). "Mitral regurgitation reduces the risk of stroke in patients with nonrheumatic atrial fibrillation". *American Heart Journal*. **136** (3): 528–32. doi:10.1016/S0002-8703(98)70231-5. PMID 9736148. Retrieved 2010-02-23.
69. ^ Cheng, TO (November 1999). "Reduced risk for thromboembolism in atrial fibrillation and mitral regurgitation". *American Heart Journal*. **138** (5 Pt 1): 998–99. doi:10.1016/S0002-8703(99)70045-1. PMID 10539836.
70. ^ *a b* Pai, RG; Varadarajan, P; Tanimoto, M (January 2003). "Effect of Atrial Fibrillation on the Dynamics of Mitral Annular Area". *The Journal of Heart Valve Disease*. **12** (1): 31–37. PMID 12578332. Retrieved 2009-12-20.
71. ^ Friberg J, Buch P, Scharling H, Gadsbphioll N, Jensen GB (2003). "Rising rates of hospital admissions for atrial fibrillation". *Epidemiology*. **14** (6): 666–72. doi:10.1097/01.ede.0000091649.26364.c0. PMID 14569181.
72. ^ Narumiya T, Sakamaki T, Sato Y, Kanmatsuse K (January 2003). "Relationship between left atrial appendage function and left atrial thrombus in patients with nonvalvular chronic atrial fibrillation and atrial flutter". *Circulation Journal*. **67** (1): 68–72. doi:10.1253/circj.67.68. PMID 12520155.
73. ^ Kishore, A; Vail, A; Majid, A; Dawson, J; Lees, KR; Tyrrell, PJ; Smith, CJ (Feb 2014). "Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis.". *Stroke; a journal of cerebral circulation*. **45** (2): 520–26. doi:10.1161/STROKEAHA.113.003433. PMID 24385275.
74. ^ Sanfilippo AJ, Abascal VM, Sheehan M, Oertel LB, Harrigan P, Hughes RA, Weyman AE (1990). "Atrial enlargement as a consequence of atrial fibrillation A prospective echocardiographic study". *Circulation*. **82** (3): 792–97. doi:10.1161/01.CIR.82.3.792. PMID 2144217. Archived from the original on 1 December 2009. Retrieved 2009-12-02.
75. ^ Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE (2001). "Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study". *JAMA*. **285** (18): 2370–75. doi:10.1001/jama.285.18.2370. PMID 11343485.
76. ^ Vulpian A (1874). "Note sur les effets de la faradisation directe des ventricules du coeur chez le chien". *Archives de Physiologie Normale et Pathologique*. **6**: 975.
77. ^ McMichael J (1982). "History of atrial fibrillation 1628–1819 Harvey – de Senac – Laënnec". *Br Heart J*. **48** (3): 193–97. doi:10.1136/hrt.48.3.193. PMC 481228. PMID 7049202.
78. ^ Nothnagel H (1876). "Ueber arythmische Herzthatigkeit". *Deutsches Archiv für Klinische Medizin*. **17**: 190–220.
79. ^ MacKenzie J (1904). "Observations on the Inception of the Rhythm of the Heart by the Ventricle: As the cause of Continuous Irregularity of the Heart". *Br Med J*. **1** (2253): 529–36. doi:10.1136/bmj.1.2253.529. PMC 2353402. PMID 20761393.
80. ^ Einthoven W (1906). "Le telecardiogramme". *Archives Internationales de Physiologie*. **4**: 132–64.
81. ^ Rothberger CJ, Winterberg H (1909). "Vorhofflimmern und Arhythmia perpetua". *Wiener Klinische Wochenschrift*. **22**: 839–44.
82. ^ Lewis T (1909). "Auricular fibrillation: a common clinical condition". *Br Med J*. **2** (2552): 1528. doi:10.1136/bmj.2.2552.1528.
83. ^ Flegel KM (1995). "From delirium cordis to atrial fibrillation: historical development of a disease concept". *Ann. Intern. Med*. **122** (11): 867–73. doi:10.7326/0003-4819-122-11-199506010-00010. PMID 7741373.

## External links [edit]

- Atrial fibrillation at DMOZ
- "Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines.". *Circulation*. **127** (18): 1916–26. 7 May 2013. doi:10.1161/CIR.0b013e318290826d. PMID 23545139.
- CHADS2 Score for Atrial Fibrillation Stroke Risk
- CHA2DS2-VASc Score for Atrial Fibrillation Stroke Risk

Wikimedia Commons has media related to *Atrial fibrillation*.

| v · t · e | **Cardiovascular disease (heart) (I00–I52, 390–429)** | |
|---|---|---|
| | **Coronary disease** | Coronary artery disease (CAD) · Coronary artery aneurysm · Spontaneous coronary artery dissection (SCAD) · Coronary thrombosis · |

| | | | |
|---|---|---|---|
| **Ischaemic** | | | Coronary vasospasm · Myocardial bridge · |
| | **Active ischemia** | | Angina pectoris (Prinzmetal's angina · Stable angina · · Acute coronary syndrome (Myocardial infarction · Unstable angina · · |
| | **Sequelae** | | *hours* (Hibernating myocardium · Myocardial stunning · · *days* (Myocardial rupture · · *weeks* (Aneurysm of heart / Ventricular aneurysm · Dressler syndrome · · |
| **Layers** | **Pericardium** | | Pericarditis (Acute · Chronic / Constrictive · · Pericardial effusion (Cardiac tamponade · Hemopericardium · · |
| | **Myocardium** | | Myocarditis (Chagas disease · · Cardiomyopathy: Dilated (Alcoholic), Hypertrophic, *and* Restrictive (Loeffler endocarditis · Cardiac amyloidosis · Endocardial fibroelastosis · · Arrhythmogenic right ventricular dysplasia · |
| | **Endocardium / valves** | **Endocarditis** | *infective endocarditis* (Subacute bacterial endocarditis · · *non-infective endocarditis* (Libman–Sacks endocarditis · Nonbacterial thrombotic endocarditis · · |
| | | **Valves** | *mitral* (regurgitation · prolapse · stenosis · · *aortic* (stenosis · insufficiency · · *tricuspid* (stenosis · insufficiency · · *pulmonary* (stenosis · insufficiency · · |
| **Conduction / arrhythmia** | **Bradycardia** | | Sinus bradycardia · Sick sinus syndrome · Heart block: Sinoatrial · AV (1° · 2° · 3° · · Intraventricular · Bundle branch block (Right · Left · Left anterior fascicle · Left posterior fascicle · Bifascicular · Trifascicular · · Adams–Stokes syndrome · |
| | **Tachycardia (paroxysmal and sinus)** | **Supraventricular** | Atrial (Multifocal · · Junctional (AV nodal reentrant · Junctional ectopic · · |
| | | **Ventricular** | Accelerated idioventricular rhythm · Catecholaminergic polymorphic · Torsades de pointes · |
| | **Premature contraction** | | Atrial · Junctional · Ventricular · |
| | **Pre-excitation syndrome** | | Lown–Ganong–Levine · Wolff–Parkinson–White · |
| | **Flutter / fibrillation** | | Atrial flutter · Ventricular flutter · **Atrial fibrillation** (Familial · · Ventricular fibrillation · |
| | **Pacemaker** | | Ectopic pacemaker / Ectopic beat · Multifocal atrial tachycardia · Pacemaker syndrome · Parasystole · Wandering pacemaker · |
| | **Long QT syndrome** | | Andersen–Tawil · Jervell and Lange-Nielsen · Romano–Ward · |
| | **Cardiac arrest** | | Sudden cardiac death · Asystole · Pulseless electrical activity · Sinoatrial arrest · |
| | **Other / ungrouped** | | *hexaxial reference system* (Right axis deviation · Left axis deviation · · *QT* (Short QT syndrome · · *T* (T wave alternans · · *ST* (Osborn wave · ST elevation · ST depression · · Strain pattern · |
| **Cardiomegaly** | | | Ventricular hypertrophy (Left · Right / Cor pulmonale · · Atrial enlargement (Left · Right · · |
| **Other** | | | Cardiac fibrosis · Heart failure (Diastolic heart failure · Cardiac asthma · · Rheumatic fever · |

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Categories: Cardiac arrhythmia

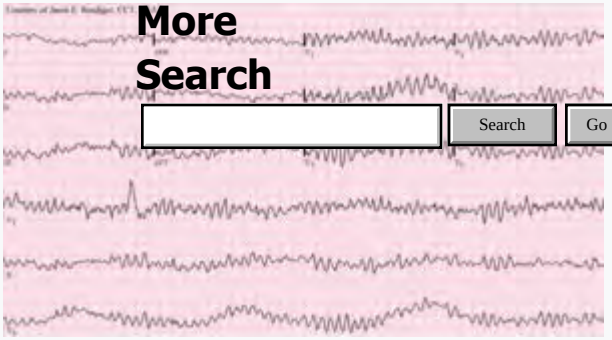



# Cardiac arrhythmia

From Wikipedia, the free encyclopedia

**Cardiac arrhythmia**, also known as **cardiac dysrhythmia** or **irregular heartbeat**, is a group of conditions in which the heartbeat is irregular, too fast, or too slow. A heart rate that is too fast – above 100 beats per minute in adults – is called tachycardia and a heart rate that is too slow – below 60 beats per minute – is called bradycardia.[1] Many types of arrhythmia have no symptoms. When symptoms are present these may include palpitations or feeling a pause between heartbeats. More seriously there may be lightheadedness, passing out, shortness of breath, or chest pain.[2] While most types of arrhythmia are not serious, some predispose a person to complications such as stroke or heart failure.[1][3] Others may result in cardiac arrest.[3]

There are four main types of arrhythmia: extra beats, supraventricular tachycardias, ventricular arrhythmias, and bradyarrhythmias. Extra beats include premature atrial contractions and premature ventricular contractions. Supraventricular tachycardias include atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia. Ventricular arrhythmias include ventricular fibrillation and ventricular tachycardia.[3][4] Arrhythmias are due to problems with the electrical conduction system of the heart.[1] Arrhythmias may occur in children; however, the normal range for the heart rate is different and depends on age.[3] A number of tests can help with diagnosis including an electrocardiogram (ECG) and Holter monitor.[5]



Ventricular fibrillation (VF) an example of a serious cardiac arrhythmia.

| Classification and external resources | |
|---|---|
| **Specialty** | Cardiology |
| **ICD-10** | I47 – I49 |
| **ICD-9-CM** | 427 |
| **DiseasesDB** | 15206 |
| **MedlinePlus** | 001101 |
| **MeSH** | D001145 |

[edit on Wikidata]

Most arrhythmias can be effectively treated.[1] Treatments may include medications, medical procedures such as a pacemaker, and surgery. Medications for a fast heart rate may include beta blockers or agents that attempt to restore a normal heart rhythm such as procainamide. This later group may have more significant side effects especially if taken for a long period of time. Pacemakers are often used for slow heart rates. Those with an irregular heartbeat are often treated with blood thinners to reduce the risk of complications. Those who have severe symptoms from an arrhythmia may receive urgent treatment with a jolt of electricity in the form of cardioversion or defibrillation.[6]

Arrhythmia affects millions of people.[7] In Europe and North America, as of 2014, atrial fibrillation affects about 2% to 3% of the population.[8] Atrial fibrillation and atrial flutter resulted in 112,000 deaths in 2013, up from 29,000 in 1990.[9] Sudden cardiac death is the cause of about half of deaths due to cardiovascular disease or about 15% of all deaths globally.[10] About 80% of sudden cardiac death is the result of ventricular arrhythmias.[10] Arrhythmias may occur at any age but are more common among older people.[7]

Contents

## Classification [edit]

Arrhythmia may be classified by rate (tachycardia, bradycardia), mechanism (automaticity, re-entry, triggered) or duration (isolated premature beats; couplets; runs, that is 3 or more beats; non-sustained= less than 30 seconds or sustained= over 30 seconds).

It is also appropriate to classify by site of origin:

### Atrial [edit]

- Sinus bradycardia
- Premature atrial contractions (PACs)
- Wandering atrial pacemaker
- Atrial tachycardia
- Multifocal atrial tachycardia
- Supraventricular tachycardia (SVT)
- Atrial flutter
- Atrial fibrillation (Afib)

### Junctional arrhythmias [edit]

- AV nodal reentrant tachycardia
- Junctional rhythm
- Junctional tachycardia
- Premature junctional contraction

### Ventricular [edit]

- Premature ventricular contractions (PVCs), sometimes called ventricular extra beats (VEBs)
  - Premature ventricular beats occurring after every normal beat are termed "ventricular bigeminy"

    - PVCs that occur at intervals of 2 normal beats to 1 PVC are termed "PVCs in trigeminy"
    - Three premature ventricular grouped together is termed a "run of PVCs" in general, runs lasting longer than three beats are referred to as ventricular tachycardia
- Accelerated idioventricular rhythm
- Monomorphic ventricular tachycardia
- Polymorphic ventricular tachycardia
- Ventricular fibrillation
- Torsades de pointes

### Heart blocks [edit]

These are also known as AV blocks, because the vast majority of them arise from pathology at the atrioventricular node. They are the most common causes of bradycardia:

- First degree heart block, which manifests as PR prolongation
- Second degree heart block
    - Type 1 Second degree heart block, also known as Mobitz I or Wenckebach
    - Type 2 Second degree heart block, also known as Mobitz II
- Third degree heart block, also known as complete heart block.

First, second and third degree block also can occur at the level of the sinoatrial junction. This is referred to as sinoatrial block typically manifesting with various degrees and patterns of sinus bradycardia

### Sudden arrhythmic death syndrome [edit]

Sudden arrhythmic death syndrome (SADS), is a term used as part of sudden unexpected death syndrome to describe sudden death due to cardiac arrest brought on by an arrhythmia in the presence or absence of any structural heart disease on autopsy. The most common cause of sudden death in the US is coronary artery disease specifically because of poor oxygenation of the heart muscle, that is myocardial ischemia or a heart attack [11] Approximately 180,000 to 250,000 people die suddenly of this cause every year in the US. SADS may occur from other causes. There are many inherited conditions and heart diseases that can affect young people which can subsequently cause sudden death without advance symptoms.[12]

Causes of SADS in young people include viral myocarditis, long QT syndrome, Brugada syndrome, Catecholaminergic polymorphic ventricular tachycardia, hypertrophic cardiomyopathy and arrhythmogenic right ventricular dysplasia.[13][14]

## Signs and symptoms [edit]

The term cardiac arrhythmia covers a very large number of very different conditions.

The most common symptom of an arrhythmia is an awareness of an abnormal heartbeat, called palpitations. These may be infrequent, frequent, or continuous. Some of these arrhythmias are harmless (though distracting for patients) but some of them predispose to adverse outcomes.

Some arrhythmias do not cause symptoms, and are not associated with increased mortality. However, some asymptomatic arrhythmias *are* associated with adverse events. Examples include a higher risk of blood clotting within the heart and a higher risk of insufficient blood being transported to the heart because of weak heartbeat. Other increased risks are of embolisation and stroke, heart failure and sudden cardiac death.

If an arrhythmia results in a heartbeat that is too fast, too slow or too weak to supply the body's needs, this manifests as a lower blood pressure and may cause lightheadedness or dizziness, or syncope (fainting).

Some types of arrhythmia result in cardiac arrest, or sudden death.

Medical assessment of the abnormality using an electrocardiogram is one way to diagnose and assess the risk of any given arrhythmia.

# Differential diagnosis [edit]

## Normal electrical activity [edit]

*Main article: Electrical conduction system of the heart*

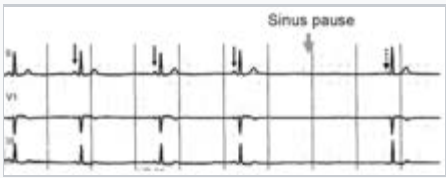
Each heart beat originates as an electrical impulse from a small area of tissue in the right atrium of the heart called the sinus node or Sino-atrial node or SA node. The impulse initially causes both atria to contract, then activates the atrioventricular (or AV) node, which is normally the only electrical connection between the atria and the ventricles (main pumping chambers). The impulse then spreads through both ventricles via the Bundle of His and the Purkinje fibres causing a synchronised contraction of the heart muscle and, thus, the pulse.

In adults the normal resting heart rate ranges from 60 to 90 beats per minute. The resting heart rate in children is much faster. In athletes, however, the resting heart rate can be as slow as 40 beats per minute, and be considered as normal.

The term sinus arrhythmia [15] refers to a normal phenomenon of alternating mild acceleration and slowing of the heart rate that occurs with breathing in and out. It is usually quite pronounced in children and steadily decreases with age. This can also be present during meditation breathing exercises that involve deep inhaling and breath holding patterns.[16]

## Bradycardias [edit]

A slow rhythm (less than 60 beats/min), is labelled bradycardia. This may be caused by a slowed signal from the sinus node (sinus bradycardia), a pause in the normal activity of the sinus node (sinus arrest), or by blocking of the electrical impulse on its way from the atria to the ventricles (AV block or heart block). Heart block comes in varying degrees and severity. It may be caused by reversible poisoning of the AV node (with drugs that impair conduction) or by irreversible damage to the node. Bradycardias may also be present in the normally functioning heart of endurance athletes or other well-conditioned persons. Bradycardia may also occur in some types of seizures.




Normal sinus rhythm, with solid black arrows pointing to normal P waves representative of normal sinus node function, followed by a pause in sinus node activity (resulting in a transient loss of heart beats). Note that the P wave that disrupts the pause (indicated by the dashed arrow) does not look like the previous (normal) P waves — this last P wave is arising from a different part of the atrium, representing an escape rhythm.

## Tachycardias [edit]

In adults and children over 15, resting heart rate faster than 100 beats per minute is labelled tachycardia. Tachycardia may result in palpitation; however, tachycardia is not *necessarily* an arrhythmia. Increased heart rate is a normal response to physical exercise or emotional stress. This is mediated by the sympathetic nervous system on the sinus node and called sinus tachycardia. Other conditions that increase sympathetic nervous system activity in the heart include ingested or injected substances, such as caffeine or amphetamines, and an overactive thyroid gland (hyperthyroidism) or anemia.

Tachycardia that is not sinus tachycardia usually results from the addition of abnormal impulses to the normal cardiac cycle. Abnormal impulses can begin by one of three mechanisms: automaticity, re-entry or triggered activity. A specialised form of re-entry which is both common and problematic is termed fibrillation.

Although the term "tachycardia" has been known for over 160 years, bases for the classification of arrhythmias are still being discussed.[17]

## Heart defects [edit]

Congenital heart defects are structural or electrical pathway problems in the heart that are present at birth.

Anyone can be affected with this because overall health does not play a role in the problem. Problems with the electrical pathway of the heart can cause very fast or even deadly arrhythmias. Wolff–Parkinson–White syndrome is due to an extra pathway in the heart that is made up of electrical muscle tissue. This tissue allows the electrical impulse, which stimulates the heartbeat, to happen very rapidly. Right Ventricular outflow tract Tachycardia is the most common type of ventricular tachycardia in otherwise healthy individuals. This defect is due to an electrical node in the right ventricle just before the pulmonary artery. When the node is stimulated, the patient will go into ventricular tachycardia, which does not allow the heart to fill with blood before beating again. Long QT Syndrome is another complex problem in the heart and has been labeled as an independent factor in mortality. There are multiple methods of treatment for these including cardiac ablations, medication treatment, or altering your lifestyle to have less stress and exercise. It is possible to live a full and happy life with these conditions.

## Automaticity [edit]

*Main article: Automatic tachycardia*

Automaticity refers to a cardiac muscle cell firing off an impulse on its own. All of the cells in the heart have the ability to initiate an action potential; however, only some of these cells are designed to routinely trigger heart beats. These cells are found in the conduction system of the heart and include the SA node, AV node, Bundle of His and Purkinje fibers. The sinoatrial node is a single specialized location in the atrium that has a higher automaticity (a faster pacemaker) than the rest of the heart and, therefore, is usually responsible for setting the heart rate and initiating each heart beat.

Any part of the heart that initiates an impulse without waiting for the sinoatrial node is called an ectopic focus and is, by definition, a pathological phenomenon. This may cause a single premature beat now and then, or, if the ectopic focus fires more often than the sinoatrial node, it can produce a sustained abnormal rhythm. Rhythms produced by an ectopic focus in the atria, or by the atrioventricular node, are the least dangerous dysrhythmias; but they can still produce a decrease in the heart's pumping efficiency, because the signal reaches the various parts of the heart muscle with different timing than usual and can be responsible for poorly coordinated contraction.

Conditions that increase automaticity include sympathetic nervous system stimulation and hypoxia. The resulting heart rhythm depends on where the first signal begins: If it is the sinoatrial node, the rhythm remains normal but rapid; if it is an ectopic focus, many types of dysrhythmia may ensue.

## Re-entry [edit]

Re-entrant arrhythmias occur when an electrical impulse recurrently travels in a tight circle within the heart, rather than moving from one end of the heart to the other and then stopping.[18][19]

Every cardiac cell is able to transmit impulses of excitation in every direction but will do so only once within a short time. Normally, the action potential impulse will spread through the heart quickly enough that each cell will respond only once. However, if there is some essential heterogeneity of refractory period or if conduction is abnormally slow in some areas (for example in heart damage) so the myocardial cells are unable to activate the fast sodium channel, part of the impulse will arrive late and potentially be treated as a new impulse. Depending on the timing, this can produce a sustained abnormal circuit rhythm.

As a sort of *re-entry*, vortices of excitation in the myocardium (autowave vortices) are considered to be the main mechanism of life-threatening cardiac arrhythmias.[20] In particular, the autowave reverberator is common in the thin walls of the atria, sometimes resulting in atrial flutter. Re-entry is also responsible for most paroxysmal supraventricular tachycardia, and dangerous ventricular tachycardia. These types of re-entry circuits are different from WPW syndromes, which utilize abnormal conduction pathways.

Although omega-3 fatty acids from fish oil can be protective against arrhythmias, they can facilitate re-entrant arrhythmias. [21]

## Fibrillation [edit]

When an entire chamber of the heart is involved in multiple micro-reentry circuits and is therefore quivering with chaotic electrical impulses, it is said to be in fibrillation.

Fibrillation can affect the atrium (atrial fibrillation) or the ventricle (ventricular fibrillation): ventricular fibrillation is imminently life-threatening.

- Atrial fibrillation affects the upper chambers of the heart, known as the atria. Atrial fibrillation may be due to serious underlying medical conditions and should be evaluated by a physician. It is not typically a medical emergency.
- Ventricular fibrillation occurs in the ventricles (lower chambers) of the heart; it is always a medical emergency. If left untreated, ventricular fibrillation (VF, or V-fib) can lead to death within minutes. When a heart goes into V-fib, effective pumping of the blood stops. V-fib is considered a form of cardiac arrest. An individual suffering from it will not survive unless cardiopulmonary resuscitation (CPR) and defibrillation are provided immediately.

CPR can prolong the survival of the brain in the lack of a normal pulse, but defibrillation is the only intervention that can restore a healthy heart rhythm. Defibrillation is performed by applying an electric shock to the heart, which resets the cells, permitting a normal beat to re-establish itself.

### Triggered beats [edit]

Triggered beats occur when problems at the level of the ion channels in individual heart cells result in abnormal propagation of electrical activity and can lead to sustained abnormal rhythm. They are relatively rare and can result from the action of anti-arrhythmic drugs. See early and delayed Afterdepolarizations.

## Diagnostic approach [edit]

Cardiac arrhythmia are often first detected by simple but nonspecific means: auscultation of the heartbeat with a stethoscope, or feeling for peripheral pulses. These cannot usually diagnose specific arrhythmia but can give a general indication of the heart rate and whether it is regular or irregular. Not all the electrical impulses of the heart produce audible or palpable beats; in many cardiac arrhythmias, the premature or abnormal beats do not produce an effective pumping action and are experienced as "skipped" beats.

The simplest *specific* diagnostic test for assessment of heart rhythm is the electrocardiogram (abbreviated ECG or EKG). A Holter monitor is an EKG recorded over a 24-hour period, to detect arrhythmias that may happen briefly and unpredictably throughout the day.

A more advanced study of the heart's electrical activity can be performed to assess the source of the aberrant heart beats. This can be accomplished in an electrophysiology study, an endovascular procedure that uses a catheter to "listen" to the electrical activity from within the heart, additionally if the source of the arrhythmias is found, often the abnormal cells can be ablated and the arrhythmia can be permanently corrected. *Transesophageal atrial stimulation* (TAS) instead uses an electrode inserted through the esophagus to a part where the distance to the posterior wall of the left atrium is only approximately 5–6 mm (remaining constant in people of different age and weight).[22] Transesophageal atrial stimulation can differentiate between atrial flutter, AV nodal reentrant tachycardia and orthodromic atrioventricular reentrant tachycardia.[23] It can also evaluate the risk in people with Wolff–Parkinson–White syndrome, as well as terminate supraventricular tachycardia caused by re-entry.[23]

## Management [edit]

The method of cardiac rhythm management depends firstly on whether or not the affected person is stable or unstable. Treatments may include physical maneuvers, medications, electricity conversion, or electro- or cryo-cautery.

In the United States, people admitted to the hospital with cardiac arrhythmia and conduction disorders with and without complications were admitted to the intensive care unit more than half the time in 2011.[24]

### Physical maneuvers [edit]

A number of physical acts can increase parasympathetic nervous supply to the heart, resulting in blocking of

electrical conduction through the AV node. This can slow down or stop a number of arrhythmias that originate above or at the AV node (see main article: supraventricular tachycardias). Parasympathetic nervous supply to the heart is via the vagus nerve, and these maneuvers are collectively known as vagal maneuvers.

### Antiarrhythmic drugs [edit]

*Main article: Antiarrhythmic agents*

There are many classes of antiarrhythmic medications, with different mechanisms of action and many different individual drugs within these classes. Although the goal of drug therapy is to prevent arrhythmia, nearly every anti arrhythmic drug has the potential to act as a pro-arrhythmic, and so must be carefully selected and used under medical supervision.

### Other drugs [edit]

A number of other drugs can be useful in cardiac arrhythmias.

Several groups of drugs slow conduction through the heart, without actually preventing an arrhythmia. These drugs can be used to "rate control" a fast rhythm and make it physically tolerable for the patient.

Some arrhythmias promote blood clotting within the heart, and increase risk of embolus and stroke. Anticoagulant medications such as warfarin and heparins, and anti-platelet drugs such as aspirin can reduce the risk of clotting.

### Electricity [edit]

Arrhythmias may also be treated electrically, by applying a shock across the heart — either externally to the chest wall, or internally to the heart via implanted electrodes.

Cardioversion is either achieved pharmacologically or via the application of a shock *synchronised* to the underlying heartbeat. It is used for treatment of supraventricular tachycardias. In elective cardioversion, the recipient is usually sedated or lightly anesthetized for the procedure.

Defibrillation differs in that the shock is not synchronised. It is needed for the chaotic rhythm of ventricular fibrillation and is also used for pulseless ventricular tachycardia. Often, more electricity is required for defibrillation than for cardioversion. In most defibrillation, the recipient has lost consciousness so there is no need for sedation.

Defibrillation or cardioversion may be accomplished by an implantable cardioverter-defibrillator (ICD).

Electrical treatment of arrhythmias also includes cardiac pacing. Temporary pacing may be necessary for reversible causes of very slow heartbeats, or bradycardia, (for example, from drug overdose or myocardial infarction). A permanent pacemaker may be placed in situations where the bradycardia is not expected to recover.

### Electrical cautery [edit]

Some cardiologists further sub-specialise into electrophysiology. In specialised catheter laboratories, they use fine probes inserted through the blood vessels to map electrical activity from within the heart. This allows abnormal areas of conduction to be located very accurately, and subsequently destroyed with heat, cold, electrical, or laser probes.

This pulmonary vein isolation may be completely curative for AV nodal reentrant tachycardia and sometimes for atrial fibrillation, but for other forms of arrhythmia the success rate remains disappointing.

## Research [edit]

Arrhythmias due to medications have been reported since the 1920s with the use of quinine.[25] In the 1960s and 1970s problems with antihistamines and antipsychotics were discovered.[25] It was not until the

1980s that the underlying issue, QTc prolongation was determined.[25]

## References [edit]


1. ^ a b c d "What Is Arrhythmia?". *http://www.nhlbi.nih.gov*. July 1, 2011. Retrieved 7 March 2015. External link in |website= (help)
2. ^ "What Are the Signs and Symptoms of an Arrhythmia?". *http://www.nhlbi.nih.gov*. July 1, 2011. Retrieved 7 March 2015. External link in |website= (help)
3. ^ a b c d "Types of Arrhythmia". *http://www.nhlbi.nih.gov*. July 1, 2011. Retrieved 7 March 2015. External link in |website= (help)
4. ^ Martin, C; Matthews, G; Huang, CL (2012). "Sudden cardiac death and Inherited channelopathy: the basic electrophysiology of the myocyte and myocardium in ion channel disease.". *Heart*. **98**: 536–543. doi:10.1136/heartjnl-2011-300953. PMID 22422742.
5. ^ "How Are Arrhythmias Diagnosed?". *http://www.nhlbi.nih.gov/*. July 1, 2011. Retrieved 7 March 2015. External link in |website= (help)
6. ^ "How Are Arrhythmias Treated?". *http://www.nhlbi.nih.gov/*. July 1, 2011. Retrieved 7 March 2015. External link in |website= (help)
7. ^ a b "Who Is at Risk for an Arrhythmia?". *http://www.nhlbi.nih.gov/*. July 1, 2011. Retrieved 7 March 2015. External link in |website= (help)
8. ^ Zoni-Berisso, M; Lercari, F; Carazza, T; Domenicucci, S (2014). "Epidemiology of atrial fibrillation: European perspective.". *Clinical epidemiology*. **6**: 213–20. doi:10.2147/CLEP.S47385. PMID 24966695.
9. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385** (9963): 117–171. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
10. ^ a b Mehra, R (2007). "Global public health problem of sudden cardiac death.". *Journal of electrocardiology*. **40** (6 Suppl): S118–22. doi:10.1016/j.jelectrocard.2007.06.023. PMID 17993308.
11. ^ Zipes Douglas P.; Wellens Hein J. J. (1998). "Sudden Cardiac Death". *Circulation*. **98**: 2334–2351. doi:10.1161/01.CIR.98.21.2334.
12. ^ Deo R, Albert CM (2012). "Epidemiology and genetics of sudden cardiac death". *Circulation*. **125**: 620–37. doi:10.1161/circulationaha.111.023838.
13. ^ Chugh, Sumeet S.; Reinier, Kyndaron; Teodorescu, Carmen; Evanado, Audrey; Kehr, Elizabeth; Al Samara, Mershed; Mariani, Ronald; Gunson, Karen; Jui, Jonathan (2008). "Epidemiology of Sudden Cardiac Death: Clinical and Research Implications". *Progress in Cardiovascular Diseases*. **51** (3): 213–28. doi:10.1016/j.pcad.2008.06.003. PMC 2621010. PMID 19026856.
14. ^ Winkel BG, Holst AG, Theilade J, et al. (2011). "Nationwide study of sudden cardiac death in persons aged 1–35 years". *Eur Heart J*. **32**: 983–90. doi:10.1093/eurheartj/ehq428.
15. ^ Hayano J (Feb 2004). "Respiratory sinus arrhythmia: why does the heartbeat synchronize with respiratory rhythm?". *Chest*. **125** (2): 683–90. doi:10.1378/chest.125.2.683. PMID 14769752.
16. ^ "Heart rate dynamics in different levels of Zen meditation". *International Journal of Cardiology*. **145**: 142–146. doi:10.1016/j.ijcard.2009.06.058.
17. ^ Moskalenko, A. (2012). "Tachycardia as "Shadow Play" ". In Yamada, Takumi. *Tachycardia*. Croatia: InTech. pp. 97–122. ISBN 978-953-51-0413-1.
18. ^ Wiener, Norbert; Rosenblueth, Arturo (1946). "The mathematical formulation of the problem of conduction of impulses in a network of connected excitable elements, specifically in cardiac muscle". *Archivos del Instituto de Cardiología de México*. **16** (3): 205–65. PMID 20245817.
19. ^ Allessie, M. A.; Bonke, F. I.; Schopman, F. J. (1976). "Circus movement in rabbit atrial muscle as a mechanism of tachycardia. II. The role of nonuniform recovery of excitability in the occurrence of unidirectional block, as studied with multiple microelectrodes". *Circulation Research*. **39** (2): 168–77. doi:10.1161/01.RES.39.2.168. PMID 939001.
20. ^ Mandel, William J., ed. (1995). *Cardiac Arrhythmias: Their Mechanisms, Diagnosis, and Management* (3 ed.). Lippincott Williams & Wilkins. ISBN 978-0-397-51185-3.
21. ^ Denruijter, H; Berecki, G; Opthof, T; Verkerk, A; Zock, P; Coronel, R (2007). "Pro- and antiarrhythmic properties of a diet rich in fish oil". *Cardiovascular Research*. **73** (2): 316–25. doi:10.1016/j.cardiores.2006.06.014. PMID 16859661.
22. ^ Meigas, K; Kaik, J; Anier, A (2008). "Device and methods for performing transesophageal stimulation at reduced pacing current threshold". *Estonian Journal of Engineering*. **57** (2): 154. doi:10.3176/eng.2008.2.05. ISSN 1736-

6038.
23. ^ a b Pehrson, Steen M.; Blomström-LUNDQVIST, Carina; Ljungström, Erik; Blomström, Per (1994). "Clinical value of transesophageal atrial stimulation and recording in patients with arrhythmia-related symptoms or documented supraventricular tachycardia-correlation to clinical history and invasive studies". *Clinical Cardiology*. **17** (10): 528–534. doi:10.1002/clc.4960171004. ISSN 0160-9289.
24. ^ Barrett ML, Smith MW, Elizhauser A, Honigman LS, Pines JM (December 2014). "Utilization of Intensive Care Services, 2011". *HCUP Statistical Brief #185*. Rockville, MD: Agency for Healthcare Research and Quality.
25. ^ a b c Heist, EK; Ruskin, JN (5 October 2010). "Drug-induced arrhythmia.". *Circulation*. **122** (14): 1426–35. doi:10.1161/circulationaha.109.894725. PMID 20921449.

## External links [edit]

- Cardiac arrhythmia at DMOZ

| v · t · e · | Cardiovascular disease (heart) (I00–I52, 390–429) | | |
|---|---|---|---|
| Ischaemic | Coronary disease | Coronary artery disease (CAD) · Coronary artery aneurysm · Spontaneous coronary artery dissection (SCAD) · Coronary thrombosis · Coronary vasospasm · Myocardial bridge · | |
| | Active ischemia | Angina pectoris (Prinzmetal's angina · Stable angina · · Acute coronary syndrome (Myocardial infarction · Unstable angina · · | |
| | Sequelae | *hours* (Hibernating myocardium · Myocardial stunning · · *days* (Myocardial rupture · · *weeks* (Aneurysm of heart / Ventricular aneurysm · Dressler syndrome · · | |
| Layers | Pericardium | Pericarditis (Acute · Chronic / Constrictive · · Pericardial effusion (Cardiac tamponade · Hemopericardium · · | |
| | Myocardium | Myocarditis (Chagas disease · · Cardiomyopathy: Dilated (Alcoholic), Hypertrophic, *and* Restrictive (Loeffler endocarditis · Cardiac amyloidosis · Endocardial fibroelastosis · · Arrhythmogenic right ventricular dysplasia · | |
| | Endocardium / valves | Endocarditis | *infective endocarditis* (Subacute bacterial endocarditis · · *non-infective endocarditis* (Libman–Sacks endocarditis · Nonbacterial thrombotic endocarditis · · |
| | | Valves | *mitral* (regurgitation · prolapse · stenosis · · *aortic* (stenosis · insufficiency · · *tricuspid* (stenosis · insufficiency · · *pulmonary* (stenosis · insufficiency · · |
| Conduction / arrhythmia | Bradycardia | Sinus bradycardia · Sick sinus syndrome · Heart block: Sinoatrial · AV (1° · 2° · 3° · · Intraventricular · Bundle branch block (Right · Left · Left anterior fascicle · Left posterior fascicle · Bifascicular · Trifascicular · · Adams–Stokes syndrome · | |
| | Tachycardia (paroxysmal and sinus) | Supraventricular | Atrial (Multifocal · · Junctional (AV nodal reentrant · Junctional ectopic · · |
| | | Ventricular | Accelerated idioventricular rhythm · Catecholaminergic polymorphic · Torsades de pointes · |
| | Premature contraction | Atrial · Junctional · Ventricular · | |
| | Pre-excitation syndrome | Lown–Ganong–Levine · Wolff–Parkinson–White · | |

| | | |
|---|---|---|
| | **Flutter / fibrillation** | Atrial flutter · Ventricular flutter · Atrial fibrillation (Familial · · Ventricular fibrillation · |
| | **Pacemaker** | Ectopic pacemaker / Ectopic beat · Multifocal atrial tachycardia · Pacemaker syndrome · Parasystole · Wandering pacemaker · |
| | **Long QT syndrome** | Andersen–Tawil · Jervell and Lange-Nielsen · Romano–Ward · |
| | **Cardiac arrest** | Sudden cardiac death · Asystole · Pulseless electrical activity · Sinoatrial arrest · |
| | **Other / ungrouped** | *hexaxial reference system* (Right axis deviation · Left axis deviation · · *QT* (Short QT syndrome · · *T* (T wave alternans · · *ST* (Osborn wave · ST elevation · ST depression · · Strain pattern · |
| **Cardiomegaly** | | Ventricular hypertrophy (Left · Right / Cor pulmonale · · Atrial enlargement (Left · Right · · |
| **Other** | | Cardiac fibrosis · Heart failure (Diastolic heart failure · Cardiac asthma · · Rheumatic fever · |
| **Authority control** | | NDL: 00563779 · |

Categories: Cardiac arrhythmia | Medical emergencies

# Cardiovascular disease



From Wikipedia, the free encyclopedia

**Cardiovascular disease** (CVD) is a class of diseases that involve the heart or blood vessels.[1] Cardiovascular disease includes coronary artery diseases (CAD) such as angina and myocardial infarction (commonly known as a heart attack).[1] Other CVDs are stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, and venous thrombosis.[1][2]

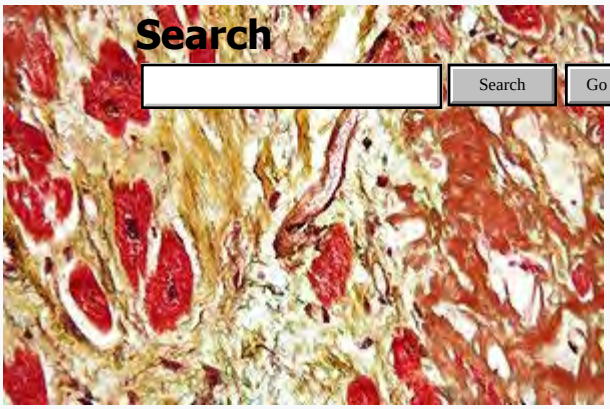
The underlying mechanisms vary depending on the disease in question. Coronary artery disease, stroke, and peripheral artery disease involve atherosclerosis. This may be caused by high blood pressure, smoking, diabetes, lack of exercise, obesity, high blood cholesterol, poor diet, and excessive alcohol consumption, among others. High blood pressure results in 13% of CVD deaths, while tobacco results in 9%, diabetes 6%, lack of exercise 6% and obesity 5%. Rheumatic heart disease may follow untreated strep throat.[1]

It is estimated that 90% of CVD is preventable.[3] Prevention of atherosclerosis involves improving risk factors through: healthy eating, exercise, avoidance of tobacco smoke and limiting alcohol intake.[1] Treating high blood pressure, blood lipids and diabetes is also beneficial.[1] Treating people who have strep throat with antibiotics can decrease the risk of rheumatic heart disease.[4] The effect of the use of aspirin in people who are otherwise healthy is of unclear benefit.[5][6] The United States Preventive Services Task Force recommends against its use for prevention in women less than 55 and men less than 45 years old; however, in those who are older it is recommends in some individuals.[7] Treatment of those who have CVD improves outcomes.[1]

Cardiovascular diseases are the leading cause of death globally.[1] This is true in all areas of the world except Africa.[1] Together they resulted in 17.3 million deaths (31.5%) in 2013 up from 12.3 million (25.8%) in 1990.[2] Deaths, at a given age, from CVD are more common and have been increasing in much of the developing world, while rates have declined in most of the developed world since the 1970s.[8][9] Coronary artery disease and stroke account for 80% of CVD deaths in males and 75% of CVD deaths in females.[1] Most cardiovascular disease affects older adults. In the United States 11% of people between 20 and 40 have CVD, while 37% between 40 and 60, 71% of people between 60 and 80, and 85% of people over 80 have CVD.[10] The average age of death from coronary artery disease in the developed world is around 80 while it is around 68 in the developing world.[8] Disease onset is typically seven to ten years earlier in men as compared to women.[11]

## Variants

## Cardiovascular disease



Micrograph of a heart with fibrosis (yellow) and amyloidosis (brown). Movat's stain.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Cardiology |
| **ICD-10** | I51.6 |
| **ICD-9-CM** | 429.2 |
| **DiseasesDB** | 28808 |
| **MeSH** | D002318 |

[edit on Wikidata]

Contents





Edit links

# Types

There are many cardiovascular diseases involving the blood vessels. They are known as vascular diseases.

- Coronary artery disease (also known as coronary heart disease and ischemic heart disease)
- Peripheral arterial disease – disease of blood vessels that supply blood to the arms and legs
- Cerebrovascular disease – disease of blood vessels that supply blood to the brain (includes stroke)
- Renal artery stenosis
- Aortic aneurysm

There are also many cardiovascular diseases that involve the heart.

- Cardiomyopathy – diseases of cardiac muscle
- Hypertensive heart disease – diseases of the heart secondary to high blood pressure or hypertension
- Heart failure - a clinical syndrome caused by the inability of the heart to supply sufficient blood to the tissues to meet their metabolic requirements
- Pulmonary heart disease – a failure at the right side of the heart with respiratory system involvement
- Cardiac dysrhythmias – abnormalities of heart rhythm
- Inflammatory heart disease
  - Endocarditis – inflammation of the inner layer of the heart, the endocardium. The structures most commonly involved are the heart valves.
  - Inflammatory cardiomegaly
  - Myocarditis – inflammation of the myocardium, the muscular part of the heart.

Disability-adjusted life year for inflammatory heart diseases per 100,000 inhabitants in 2004[12]

| | |
|---|---|
| no data | 420–490 |
| less than 70 | 490–560 |
| 70–140 | 560–630 |
| 140–210 | 630–700 |
| 210–280 | 700–770 |
| 280–350 | more than 770 |
| 350–420 | |

- Valvular heart disease
- Congenital heart disease – heart structure malformations existing at birth
- Rheumatic heart disease – heart muscles and valves damage due to rheumatic fever caused by *Streptococcus pyogenes* a group A streptococcal infection.

# Risk factors

There are many risk factors for heart diseases: age, gender, tobacco use, physical inactivity, excessive alcohol consumption, unhealthy diet, obesity, genetic predisposition and family history of cardiovascular disease, raised blood pressure (hypertension), raised blood sugar (diabetes mellitus), raised blood cholesterol (hyperlipidemia), psychosocial factors, poverty and low educational status, and air pollution.[13][14][15][16][17] While the individual contribution of each risk factor varies between different communities or ethnic groups the overall contribution of these risk factors is very consistent.[18] Some of these risk factors, such as age, gender or family history/genetic predisposition, are immutable; however, many important cardiovascular risk factors are modifiable by lifestyle change, social change, drug treatment (for example prevention of hypertension, hyperlipidemia, and diabetes).

## Genetics

Cardiovascular disease in a person's parents increases their risk by 3 fold.[19] Multiple single nucleotide polymorphisms (SNP) have been found to be associated with cardiovascular disease in genetic association studies,[20][21] but usually their individual influence is small, and genetic contributions to cardiovascular disease are poorly understood.[21]

## Age

Age is by far the most important risk factor in developing cardiovascular or heart diseases, with approximately a tripling of risk with each decade of life.[22] Coronary fatty streaks can begin to form in adolescence.[23] It is estimated that 82 percent of people who die of coronary heart disease are 65 and older.[24] At the same time, the risk of stroke doubles every decade after age 55.[25]

Calcified heart of an older woman with cardiomegaly

Multiple explanations have been proposed to explain why age increases the risk of cardiovascular/heart diseases. One of them is related to serum cholesterol level.[26] In most populations, the serum total cholesterol level increases as age increases. In men, this increase levels off around age 45 to 50 years. In women, the increase continues sharply until age 60 to 65 years.[26]

Aging is also associated with changes in the mechanical and structural properties of the vascular wall, which leads to the loss of arterial elasticity and reduced arterial compliance and may subsequently lead to coronary artery disease.[27]

## Sex

Men are at greater risk of heart disease than pre-menopausal women.[22][28] Once past menopause, it has been argued that a woman's risk is similar to a man's[28] although more recent data from the WHO and UN disputes this.[22] If a female has diabetes, she is more likely to develop heart disease than a male with diabetes.[29]

Coronary heart diseases are 2 to 5 times more common among middle-aged men than women.[26] In a study done by the World Health Organization, sex contributes to approximately 40% of the variation in sex ratios of coronary heart disease mortality.[30] Another study reports similar results finding that gender differences explains nearly half the risk associated with cardiovascular diseases[26] One of the proposed

explanations for gender differences in cardiovascular diseases is hormonal difference.[26] Among women, estrogen is the predominant sex hormone. Estrogen may have protective effects through glucose metabolism and hemostatic system, and may have direct effect in improving endothelial cell function.[26] The production of estrogen decreases after menopause, and this may change the female lipid metabolism toward a more atherogenic form by decreasing the HDL cholesterol level while increasing LDL and total cholesterol levels.[26]

Among men and women, there are notable differences in body weight, height, body fat distribution, heart rate, stroke volume, and arterial compliance.[27] In the very elderly, age-related large artery pulsatility and stiffness is more pronounced among women than men.[27] This may be caused by the women's smaller body size and arterial dimensions which are independent of menopause.[27]

## Tobacco

Cigarettes are the major form of smoked tobacco.[1] Risks to health from tobacco use result not only from direct consumption of tobacco, but also from exposure to second-hand smoke.[1] Approximately 10% of cardiovascular disease is attributed to smoking;[1] however, people who quit smoking by age 30 have almost as low a risk of death as never smokers.[31]

## Physical inactivity

Insufficient physical activity (defined as less than 5 x 30 minutes of moderate activity per week, or less than 3 x 20 minutes of vigorous activity per week) is currently the fourth leading risk factor for mortality worldwide.[1] In 2008, 31.3% of adults aged 15 or older (28.2% men and 34.4% women) were insufficiently physically active.[1] The risk of ischemic heart disease and diabetes mellitus is reduced by almost a third in adults who participate in 150 minutes of moderate physical activity each week (or equivalent).[32] In addition, physical activity assists weight loss and improves blood glucose control, blood pressure, lipid profile and insulin sensitivity. These effects may, at least in part, explain its cardiovascular benefits.[1]

## Diet

High dietary intakes of saturated fat, trans-fats and salt, and low intake of fruits, vegetables and fish are linked to cardiovascular risk, although whether all these associations are a cause is disputed. The World Health Organization attributes approximately 1.7 million deaths worldwide to low fruit and vegetable consumption.[1] The amount of dietary salt consumed is also an important determinant of blood pressure levels and overall cardiovascular risk.[1] Frequent consumption of high-energy foods, such as processed foods that are high in fats and sugars, promotes obesity and may increase cardiovascular risk.[1] A Cochrane review found that replacing saturated fat with polyunsaturated fat (plant based oils) reduced cardiovascular disease risk. Cutting down on saturated fat reduced risk of cardiovascular disease by 17% including heart disease and stroke.[33] High trans-fat intake has adverse effects on blood lipids and circulating inflammatory markers,[34] and elimination of trans-fat from diets has been widely advocated.[35] There is evidence that higher consumption of sugar is associated with higher blood pressure and unfavorable blood lipids,[36] and sugar intake also increases the risk of diabetes mellitus.[37] High consumption of processed meats is associated with an increased risk of cardiovascular disease, possibly in part due to increased dietary salt intake.[38]

The relationship between alcohol consumption and cardiovascular disease is complex, and may depend on the amount of alcohol consumed. There is a direct relationship between high levels of alcohol consumption and risk of cardiovascular disease.[1] Drinking at low levels without episodes of heavy drinking may be associated with a reduced risk of cardiovascular disease.[39] Overall alcohol consumption at the population level is associated with multiple health risks that exceed any potential benefits.[1][40]

## Socioeconomic disadvantage

Cardiovascular disease affects low- and middle-income countries even more than high-income countries.[41] There is relatively little information regarding social patterns of cardiovascular disease within low- and middle-income countries,[41] but within high-income countries low income and low educational status are consistently associated with greater risk of cardiovascular disease.[42] Policies that have resulted in increased socio-economic inequalities have been associated with greater subsequent socio-economic differences in cardiovascular disease[41] implying a cause and effect relationship. Psychosocial factors, environmental exposures, health behaviours, and health-care access and quality contribute to socio-economic differentials in cardiovascular disease. [43] The Commission on Social Determinants of Health recommended that more equal distributions of power, wealth, education, housing, environmental factors, nutrition, and health care were needed to address inequalities in cardiovascular disease and non-communicable diseases.[44]

## Air pollution

Particulate matter has been studied for its short- and long-term exposure effects on cardiovascular disease. Currently, $PM_{2.5}$ is the major focus, in which gradients are used to determine CVD risk. For every 10 $\mu g/m^3$ of $PM_{2.5}$ long-term exposure, there was an estimated 8–18% CVD mortality risk.[45] Women had a higher relative risk (RR) (1.42) for $PM_{2.5}$ induced coronary artery disease than men (0.90) did.[45] Overall, long-term PM exposure increased rate of atherosclerosis and inflammation. In regards to short-term exposure (2 hours), every 25 $\mu g/m^3$ of $PM_{2.5}$ resulted in a 48% increase of CVD mortality risk.[46] In addition, after only 5 days of exposure, a rise in systolic (2.8 mmHg) and diastolic (2.7 mmHg) blood pressure occurred for every 10.5 $\mu g/m^3$ of $PM_{2.5}$.[46] Other research has implicated $PM_{2.5}$ in irregular heart rhythm, reduced heart rate variability (decreased vagal tone), and most notably heart failure.[46][47] $PM_{2.5}$ is also linked to carotid artery thickening and increased risk of acute myocardial infarction.[46][47]

## Cardiovascular risk assessment

Existing cardiovascular disease or a previous cardiovascular event, such as a heart attack or stroke, is the strongest predictor of a future cardiovascular event.[48] Age, sex, smoking, blood pressure, blood lipids and diabetes are important predictors of future cardiovascular disease in people who are not known to have cardiovascular disease.[49] These measures, and sometimes others, may be combined into composite risk scores to estimate an individual's future risk of cardiovascular disease.[48] Numerous risk scores exist although their respective merits are debated.[50] Other diagnostic tests and biomarkers remain under evaluation but currently these lack clear-cut evidence to support their routine use. They include family history, coronary artery calcification score, high sensitivity C-reactive protein (hs-CRP), ankle–brachial pressure index, lipoprotein subclasses and particle concentration, lipoprotein(a), apolipoproteins A-I and B, fibrinogen, white blood cell count, homocysteine, N-terminal pro B-type natriuretic peptide (NT-proBNP), and markers of kidney function.[51][52]

## Work

*Main article: Occupational cardiovascular disease*

Little is known about the relationship between work and cardiovascular disease, but links have been established between certain toxins, extreme heat and cold, exposure to tobacco smoke, and mental health concerns such as stress and depression.[53]

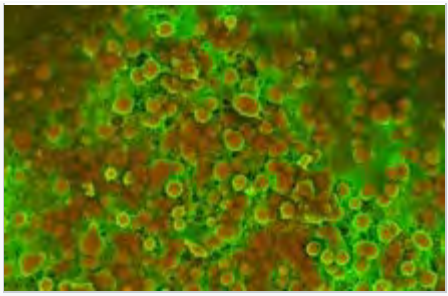
# Pathophysiology

Population-based studies show that atherosclerosis, the major precursor

of cardiovascular disease, begins in childhood. The Pathobiological Determinants of Atherosclerosis in Youth Study demonstrated that intimal lesions appear in all the aortas and more than half of the right coronary arteries of youths aged 7–9 years.[55]

This is extremely important considering that 1 in 3 people die from complications attributable to atherosclerosis. In order to stem the tide, education and awareness that cardiovascular disease poses the greatest threat, and measures to prevent or reverse this disease must be taken.

Obesity and diabetes mellitus are often linked to cardiovascular disease,[56] as are a history of chronic kidney disease and hypercholesterolaemia.[57] In fact, cardiovascular disease is the most life-threatening of the diabetic complications and diabetics are two- to four-fold more likely to die of cardiovascular-related causes than nondiabetics.[58][59][60]



Density-Dependent Colour Scanning Electron Micrograph SEM (DDC-SEM) of cardiovascular calcification, showing in orange calcium phosphate spherical particles (denser material) and, in green, the extracellular matrix (less dense material)[54]

## Screening

Screening ECGs (either at rest or with exercise) are not recommended in those without symptoms who are at low risk.[61] This includes those who are young without risk factors.[62] In those at higher risk the evidence for screening with ECGs is inconclusive.[61]

Additionally echocardiography, myocardial perfusion imaging, and cardiac stress testing is not recommended in those at low risk who do not have symptoms.[63]

Some biomarkers may add to conventional cardiovascular risk factors in predicting the risk of future cardiovascular disease; however, the clinical value of some biomarkers is questionable.[64][65]

The NIH recommends lipid testing in children beginning at the age of 2 if there is a family history of heart disease or lipid problems.[66] It is hoped that early testing will improve lifestyle factors in those at risk such as diet and exercise.[67]

## Prevention

Up to 90% of cardiovascular disease may be preventable if established risk factors are avoided.[68][69] Currently practiced measures to prevent cardiovascular disease include:

- A low-fat, high-fiber diet including whole grains and fruit and vegetables.[70][71] Five portions a day reduces risk by about 25%.[72]
- Tobacco cessation and avoidance of second-hand smoke[70]
- Limit alcohol consumption to the recommended daily limits;[70] consumption of 1–2 standard alcoholic drinks per day may reduce risk by 30%.[73][74] However, excessive alcohol intake increases the risk of cardiovascular disease.[75]
- Lower blood pressures, if elevated
- Decrease non-HDL cholesterol.[76][77]
- Decrease body fat if overweight or obese[78]
- Increase daily activity to 30 minutes of vigorous exercise per day at least five times per week (multiply by three if horizontal);[70]
- Reduce sugar consumptions
- Decrease psychosocial stress.[79] This measure may be complicated by imprecise definitions of what constitute psychosocial interventions.[80] Mental stress–induced myocardial ischemia is associated with an increased risk of heart problems in those with previous heart disease.[81] Severe emotional and

physical stress leads to a form of heart dysfunction known as Takotsubo syndrome in some people.[82] Stress, however, plays a relatively minor role in hypertension.[83] Specific relaxation therapies are of unclear benefit.[84][85]

For adults without a known diagnosis of hypertension, diabetes, hyperlipidemia, or cardiovascular disease, routine counseling to advise them to improve their diet and increase their physical activity has not been found to significantly alter behavior, and thus is not recommended.[86] It is unclear whether or not dental care in those with periodontitis affects the risk of cardiovascular disease.[87] Exercise in those who are at high risk of heart disease has not been well studied as of 2014.[88]

## Diet

*See also: Saturated fat and cardiovascular disease controversy and Salt and cardiovascular disease*

A diet high in fruits and vegetables decreases the risk of cardiovascular disease and death.[72] Evidence suggests that the Mediterranean diet may improve cardiovascular outcomes.[89] There is also evidence that a Mediterranean diet may be more effective than a low-fat diet in bringing about long-term changes to cardiovascular risk factors (e.g., lower cholesterol level and blood pressure).[90] The DASH diet (high in nuts, fish, fruits and vegetables, and low in sweets, red meat and fat) has been shown to reduce blood pressure,[91] lower total and low density lipoprotein cholesterol[92] and improve metabolic syndrome;[93] but the long-term benefits outside the context of a clinical trial have been questioned.[94] A high fiber diet appears to lower the risk.[95]

Total fat intake does not appear to be an important risk factor.[96][97] A diet high in trans fatty acids, however, does appear to increase rates of cardiovascular disease.[97][98] Worldwide, dietary guidelines recommend a reduction in saturated fat.[99] However, there are some questions around the effect of saturated fat on cardiovascular disease in the medical literature.[98][100] Reviews from 2014 and 2015 did not find evidence of harm from saturated fats.[98][100] A 2012 Cochrane review found suggestive evidence of a small benefit from replacing dietary saturated fat by unsaturated fat.[101] A 2013 meta analysis concludes that substitution with omega 6 linoleic acid (a type of unsaturated fat) may increase cardiovascular risk.[99] Replacement of saturated fats with carbohydrates does not change or may increase risk.[102][103] Benefits from replacement with polyunsaturated fat appears greatest;[97][104] however, supplementation with omega-3 fatty acids (a type of polysaturated fat) does not appear to have an effect.[105]

The effect of a low-salt diet is unclear. A Cochrane review concluded that any benefit in either hypertensive or normal-tensive people is small if present.[106] In addition, the review suggested that a low-salt diet may be harmful in those with congestive heart failure.[106] However, the review was criticized in particular for not excluding a trial in heart failure where people had low-salt and -water levels due to diuretics.[107] When this study is left out, the rest of the trials show a trend to benefit.[107][108] Another review of dietary salt concluded that there is strong evidence that high dietary salt intake increases blood pressure and worsens hypertension, and that it increases the number of cardiovascular disease events; the latter happen both through the increased blood pressure *and*, quite likely, through other mechanisms.[109][110] Moderate evidence was found that high salt intake increases cardiovascular mortality; and some evidence was found for an increase in overall mortality, strokes, and left ventricular hypertrophy.[109]

## Medication

Aspirin has been found to be of only modest benefit in those at low risk of heart disease as the risk of serious bleeding is almost equal to the benefit with respect to cardiovascular problems.[111] In those at very low risk it is not recommended.[112]

Statins are effective in preventing further cardiovascular disease in people with a history of cardiovascular disease.[113] As the event rate is higher in men than in women, the decrease in events is more easily seen

in men than women.[113] In those without cardiovascular disease but risk factors statins appear to also be beneficial with a decrease in the risk of death and further heart disease.[114] A United States guideline recommends statins in those who have a 12% or greater risk of cardiovascular disease over the next ten years.[115]

The time course over which statins provide prevention against death appears to be long, of the order of one year, which is much longer than the duration of their effect on lipids.[116] The medications niacin, fibrates and CETP Inhibitors, while they may increase HDL cholesterol do not affect the risk of cardiovascular disease in those who are already on statins.[117]

The use of vasoactive agents for people with pulmonary hypertension with left heart disease or hypoxemic lung diseases may cause harm and unnecessary expense.[118]

### Supplements

While a healthy diet is beneficial, in general the effect of antioxidant supplementation (vitamin E, vitamin C, etc.) or vitamins has not been shown to protection against cardiovascular disease and in some cases may possibly result in harm.[119][120] Mineral supplements have also not been found to be useful.[121] Niacin, a type of vitamin B3, may be an exception with a modest decrease in the risk of cardiovascular events in those at high risk.[122][123] Magnesium supplementation lowers high blood pressure in a dose dependent manner.[124] Magnesium therapy is recommended for patients with ventricular arrhythmia associated with torsades de pointes who present with long QT syndrome as well as for the treatment of patients with digoxin intoxication-induced arrhythmias.[125] Evidence to support omega-3 fatty acid supplementation is lacking.[126]

## Management

Cardiovascular disease is treatable with initial treatment primarily focused on diet and lifestyle interventions.[1]

## Epidemiology

Cardiovascular diseases are the leading cause of death. In 2008, 30% of all global death is attributed to cardiovascular diseases. Death caused by cardiovascular diseases are also higher in low- and middle-income countries as over 80% of all global death caused by cardiovascular diseases occurred in those countries. It is also estimated that by 2030, over 23 million people will die from cardiovascular diseases each year.

It is estimated that 60% of the world's cardiovascular disease burden will occur in the South Asian subcontinent despite only accounting for 20% of the world's population. This may be secondary to a combination of genetic predisposition and environmental factors. Organizations such as the Indian Heart Association are working with the World Heart Federation to raise awareness about this issue.[128]

Cardiovascular diseases deaths per million persons in 2012

| | | |
|---|---|---|
| 318-925 | 1,450-1,802 | 2,625-3,203 |
| 926-1,148 | 1,803-2,098 | 3,204-5,271 |
| 1,149-1,294 | 2,099-2,624 | 5,272-10233 |
| 1,295-1,449 | | |

## Research

*See also: Timeline of cardiovascular disease*

The first studies on cardiovascular health were performed in year 1949 by Jerry Morris using occupational health data and

were published in year 1958.[129] The causes, prevention, and/or treatment of all forms of cardiovascular disease remain active fields of biomedical research, with hundreds of scientific studies being published on a weekly basis.

A fairly recent emphasis is on the link between low-grade inflammation that hallmarks atherosclerosis and its possible interventions. C-reactive protein is a common inflammatory marker that has been found to be present in increased levels in patients who are at risk for cardiovascular disease.[130] Also osteoprotegerin, which is involved with regulation of a key inflammatory transcription factor called NF-κB, has been found to be a risk factor of cardiovascular disease and mortality.[131][132]

Some areas currently being researched include the possible links between infection with *Chlamydophila pneumoniae* (a major cause of pneumonia) and coronary artery disease. The *Chlamydia* link has become less plausible with the absence of improvement after antibiotic use.[133]

Disability-adjusted life year for cardiovascular diseases per 100,000 inhabitants in 2004[127]

| | |
|---|---|
| no data | 3700-4400 |
| <900 | 4400-5100 |
| 900-1650 | 5100-5800 |
| 1650-2300 | 5800-6500 |
| 2300-3000 | 6500-7200 |
| 3000-3700 | 7200–7900 |
| | >7900 |

Several research also investigated the benefits of melatonin on cardiovascular diseases prevention and cure. Melatonin is a pineal gland secretion and it is shown to be able to lower total cholesterol, very-low-density and low-density lipoprotein cholesterol levels in the blood plasma of rats. Reduction of blood pressure is also observed when pharmacological doses are applied. Thus, it is deemed to be a plausible treatment for hypertension. However, further research needs to be conducted to investigate the side-effects, optimal dosage, etc. before it can be licensed for use.[134]

# References


1. ^ *a b c d e f g h i j k l m n o p q r s t u v* Shanthi Mendis; Pekka Puska; Bo Norrving; World Health Organization (2011). *Global Atlas on Cardiovascular Disease Prevention and Control* (PDF). World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. pp. 3–18. ISBN 978-92-4-156437-3.
2. ^ *a b* GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
3. ^ McGill HC, McMahan CA, Gidding SS (March 2008). "Preventing heart disease in the 21st century: implications of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study". *Circulation*. **117** (9): 1216–27. doi:10.1161/CIRCULATIONAHA.107.717033. PMID 18316498.
4. ^ Spinks, A; Glasziou, PP; Del Mar, CB (5 November 2013). "Antibiotics for sore throat.". *The Cochrane database of systematic reviews*. **11**: CD000023. doi:10.1002/14651858.CD000023.pub4. PMID 24190439.
5. ^ Sutcliffe, P; Connock, M; Gurung, T; Freeman, K; Johnson, S; Ngianga-Bakwin, K; Grove, A; Gurung, B; Morrow, S; Stranges, S; Clarke, A (2013). "Aspirin in primary prevention of cardiovascular disease and cancer: a systematic review of the balance of evidence from reviews of randomized trials.". *PLOS ONE*. **8** (12): e81970. doi:10.1371/journal.pone.0081970. PMC 3855368. PMID 24339983.
6. ^ Sutcliffe, P; Connock, M; Gurung, T; Freeman, K; Johnson, S; Kandala, NB; Grove, A; Gurung, B; Morrow, S; Clarke, A (September 2013). "Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews.". *Health technology assessment (Winchester, England)*. **17** (43): 1–253. doi:10.3310/hta17430. PMID 24074752.
7. ^ US Preventive Services Task, Force (17 March 2009). "Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement.". *Annals of Internal Medicine*. **150** (6): 396–404. doi:10.7326/0003-4819-150-6-200903170-00008. PMID 19293072.
8. ^ *a b* Fuster, Board on Global Health; Valentin; Academies, Bridget B. Kelly (2010). Institute of Medicine of the National, eds. *Promoting cardiovascular health in the developing world : a critical challenge to achieve global*

*health*. Washington, D.C.: National Academies Press. pp. Chapter 2. ISBN 978-0-309-14774-3.
9. ^ Moran, AE; Forouzanfar, MH; Roth, GA; Mensah, GA; Ezzati, M; Murray, CJ; Naghavi, M (8 April 2014). "Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study.". *Circulation*. **129** (14): 1483–92. doi:10.1161/circulationaha.113.004042. PMID 24573352.
10. ^ Go, AS; Mozaffarian, D; Roger, VL; Benjamin, EJ; Berry, JD; Borden, WB; Bravata, DM; Dai, S; Ford, ES; Fox, CS; Franco, S; Fullerton, HJ; Gillespie, C; Hailpern, SM; Heit, JA; Howard, VJ; Huffman, MD; Kissela, BM; Kittner, SJ; Lackland, DT; Lichtman, JH; Lisabeth, LD; Magid, D; Marcus, GM; Marelli, A; Matchar, DB; McGuire, DK; Mohler, ER; Moy, CS; Mussolino, ME; Nichol, G; Paynter, NP; Schreiner, PJ; Sorlie, PD; Stein, J; Turan, TN; Virani, SS; Wong, ND; Woo, D; Turner, MB; American Heart Association Statistics Committee and Stroke Statistics, Subcommittee (1 January 2013). "Heart disease and stroke statistics--2013 update: a report from the American Heart Association.". *Circulation*. **127** (1): e6–e245. doi:10.1161/cir.0b013e31828124ad. PMID 23239837.
11. ^ Mendis, Shanthi; Puska,, Pekka; Norrving, Bo (2011). *Global atlas on cardiovascular disease prevention and control* (1 ed.). Geneva: World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. p. 48. ISBN 9789241564373.
12. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved Nov 11, 2009.
13. ^ Bridget B. Kelly; Institute of Medicine; Fuster, Valentin (2010). *Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health*. Washington, D.C: National Academies Press. ISBN 0-309-14774-3.
14. ^ Howard, BV; Wylie-Rosett, J (Jul 23, 2002). "Sugar and cardiovascular disease: A statement for healthcare professionals from the Committee on Nutrition of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association.". *Circulation*. **106** (4): 523–7. doi:10.1161/01.cir.0000019552.77778.04. PMID 12135957.
15. ^ Finks, SW; Airee, A; Chow, SL; Macaulay, TE; Moranville, MP; Rogers, KC; Trujillo, TC (April 2012). "Key articles of dietary interventions that influence cardiovascular mortality.". *Pharmacotherapy*. **32** (4): e54–87. doi:10.1002/j.1875-9114.2011.01087.x. PMID 22392596.
16. ^ Micha, R; Michas, G; Mozaffarian, D (Dec 2012). "Unprocessed red and processed meats and risk of coronary artery disease and type 2 diabetes—an updated review of the evidence.". *Current atherosclerosis reports*. **14** (6): 515–24. doi:10.1007/s11883-012-0282-8. PMC 3483430. PMID 23001745.
17. ^ Shanthi Mendis; Pekka Puska; Bo Norrving (2011). *Global Atlas on Cardiovascular Disease Prevention and Control*. World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. ISBN 978-92-4-156437-3.
18. ^ Yusuf S, Hawken S, Ounpuu S, et al. (2004). "Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study". *Lancet*. **364** (9438): 937–52. doi:10.1016/S0140-6736(04)17018-9. PMID 15364185.
19. ^ Kathiresan, S; Srivastava, D (16 March 2012). "Genetics of human cardiovascular disease.". *Cell*. **148** (6): 1242–57. doi:10.1016/j.cell.2012.03.001. PMC 3319439. PMID 22424232.
20. ^ Nikpay, Majid; Goel, Anuj; Won, Hong-Hee; Hall, Leanne M; Willenborg, Christina; Kanoni, Stavroula; Saleheen, Danish; Kyriakou, Theodosios; Nelson, Christopher P. "A comprehensive 1000 Genomes–based genome-wide association meta-analysis of coronary artery disease". *Nature Genetics*. **47** (10): 1121–1130. doi:10.1038/ng.3396. PMC 4589895. PMID 26343387.
21. ^ *a b* MacRae, Calum A.; Vasan, Ramachandran S. (2016-06-21). "The Future of Genetics and Genomics: Closing the Phenotype Gap in Precision Medicine". *Circulation*. **133** (25): 2634–2639. doi:10.1161/CIRCULATIONAHA.116.022547. ISSN 1524-4539. PMID 27324359.
22. ^ *a b c* Finegold, JA; Asaria, P; Francis, DP (Dec 4, 2012). "Mortality from ischaemic heart disease by country, region, and age: Statistics from World Health Organisation and United Nations.". *International Journal of Cardiology*. **168** (2): 934–945. doi:10.1016/j.ijcard.2012.10.046. PMID 23218570.
23. ^ D'Adamo, E; Guardamagna, O; Chiarelli, F; Bartuli, A; Liccardo, D; Ferrari, F; Nobili, V (2015). "Atherogenic dyslipidemia and cardiovascular risk factors in obese children.". *International journal of endocrinology*. **2015**: 912047. doi:10.1155/2015/912047. PMC 4309297. PMID 25663838.
24. ^ "Understand Your Risk of Heart Attack". American Heart Association. http://www.heart.org/HEARTORG/Conditions/HeartAttack/UnderstandYourRiskofHeartAttack/Understand-Your-Risk-of-Heart-Attack_UCM_002040_Article.jsp#
25. ^ Mackay, Mensah, Mendis, et al. The Atlas of Heart Disease and Stroke. World Health Organization. January 2004.
26. ^ *a b c d e f g* Jousilahti Vartiainen; Tuomilehto Puska (1999). "Sex, Age, Cardiovascular Risk Factors, and coronary heart disease". *Circulation*. **99** (9): 1165–1172. doi:10.1161/01.cir.99.9.1165.
27. ^ *a b c d* Jani B, Rajkumar C (2006). "Ageing and vascular ageing". *Postgrad Med J*. **82** (968): 357–362. doi:10.1136/pgmj.2005.036053.
28. ^ *a b* http://www.world-heart-federation.org/cardiovascular-health/cardiovascular-disease-risk-factors

29. ^ "Diabetes raises women's risk of heart disease more than for men". *NPR.org*. May 22, 2014. Retrieved May 23, 2014.
30. ^ Jackson R, Chambles L, Higgins M, Kuulasmaa K, Wijnberg L, Williams D (WHO MONICA Project, and ARIC Study.) Sex difference in ischaemic heart disease mortality and risk factors in 46 communities: an ecologic analysis. Cardiovasc Risk Factors. 1999; 7:43–54.
31. ^ Richard Doll; Richard Peto; Jillian Boreham & Isabelle Sutherland (June 2004). "Mortality in relation to smoking: 50 years' observations on male British doctors". *BMJ (Clinical research ed.)*. **328** (7455): 1519. doi:10.1136/bmj.38142.554479.AE. PMC 437139. PMID 15213107.
32. ^ World Health Organization; UNAIDS (1 January 2007). *Prevention of Cardiovascular Disease*. World Health Organization. pp. 3–. ISBN 978-92-4-154726-0.
33. ^ Hooper, Lee; Martin, Nicole; Abdelhamid, Asmaa; Davey Smith, George (2015-06-10). "Reduction in saturated fat intake for cardiovascular disease". *The Cochrane Database of Systematic Reviews* (6): CD011737. doi:10.1002/14651858.CD011737. ISSN 1469-493X. PMID 26068959.
34. ^ Booker, C.S.; Mann, J.I. (2008). "Trans fatty acids and cardiovascular health: Translation of the evidence base". *Nutrition, Metabolism and Cardiovascular Diseases*. **18** (6): 448–456. doi:10.1016/j.numecd.2008.02.005. ISSN 0939-4753.
35. ^ Remig, Valentina; Franklin, Barry; Margolis, Simeon; Kostas, Georgia; Nece, Theresa; Street, James C. (2010). "Trans Fats in America: A Review of Their Use, Consumption, Health Implications, and Regulation". *Journal of the American Dietetic Association*. **110** (4): 585–592. doi:10.1016/j.jada.2009.12.024. ISSN 0002-8223.
36. ^ Te Morenga, L. A.; Howatson, A. J.; Jones, R. M.; Mann, J. (2014). "Dietary sugars and cardiometabolic risk: systematic review and meta-analyses of randomized controlled trials of the effects on blood pressure and lipids". *American Journal of Clinical Nutrition*. **100** (1): 65–79. doi:10.3945/ajcn.113.081521. ISSN 0002-9165.
37. ^ "Wylie-Rosett2002"
38. ^ Micha, Renata; Michas, Georgios; Mozaffarian, Dariush (2012). "Unprocessed Red and Processed Meats and Risk of Coronary Artery Disease and Type 2 Diabetes – An Updated Review of the Evidence". *Current Atherosclerosis Reports*. **14** (6): 515–524. doi:10.1007/s11883-012-0282-8. ISSN 1523-3804. PMC 3483430. PMID 23001745.
39. ^ Mukamal, Kenneth J.; Chen, Chiung M.; Rao, Sowmya R.; Breslow, Rosalind A. (2010). "Alcohol Consumption and Cardiovascular Mortality Among U.S. Adults, 1987 to 2002". *Journal of the American College of Cardiology*. **55** (13): 1328–1335. doi:10.1016/j.jacc.2009.10.056. ISSN 0735-1097.
40. ^ World Health Organization (2011). *Global Status Report on Alcohol and Health*. World Health Organization. ISBN 978-92-4-156415-1.
41. ^ [a] [b] [c] Mariachiara Di Cesare; Young-Ho Khang; Perviz Asaria; Tony Blakely; Melanie J. Cowan; Farshad Farzadfar; Ramiro Guerrero; Nayu Ikeda; Catherine Kyobutungi; Kelias P. Msyamboza; Sophal Oum; John W. Lynch; Michael G. Marmot; Majid Ezzati (February 2013). "Inequalities in non-communicable diseases and effective responses". *Lancet*. **381** (9866): 585–597. doi:10.1016/S0140-6736(12)61851-0. PMID 23410608.
42. ^ J. P. Mackenbach; A. E. Cavelaars; A. E. Kunst; F. Groenhof (July 2000). "Socioeconomic inequalities in cardiovascular disease mortality; an international study". *European Heart Journal*. **21** (14): 1141–1151. doi:10.1053/euhj.1999.1990. PMID 10924297.
43. ^ Alexander M. Clark; Marie DesMeules; Wei Luo; Amanda S. Duncan; Andy Wielgosz (November 2009). "Socioeconomic status and cardiovascular disease: risks and implications for care". *Nature reviews. Cardiology*. **6** (11): 712–722. doi:10.1038/nrcardio.2009.163. PMID 19770848.
44. ^ World Health Organization (2008). *Closing the Gap in a Generation: Health Equity Through Action on the Social Determinants of Health : Commission on Social Determinants of Health Final Report*. World Health Organization. pp. 26–. ISBN 978-92-4-156370-3.
45. ^ [a] [b] Khallaf, Mohamed (2011). *The Impact of Air Pollution on Health, Economy, Environment and Agricultural Sources*. InTech. pp. 69–92. ISBN 978-953-307-528-0.
46. ^ [a] [b] [c] [d] Franchini M, Mannucci PM (2012). "Air pollution and cardiovascular disease". *Thrombosis Research*. **129** (3): 230–4. doi:10.1016/j.thromres.2011.10.030. PMID 22113148.
47. ^ [a] [b] Sun Q, Hong X, Wold LE (2010). "Cardiovascular Effects of Ambient Particulate Air Pollution Exposure". *Circulation*. **121** (25): 2755–65. doi:10.1161/CIRCULATIONAHA.109.893461. PMC 2924678. PMID 20585020.
48. ^ [a] [b] Tunstall-Pedoe, H. (2011). "Cardiovascular Risk and Risk Scores: ASSIGN, Framingham, QRISK and others: how to choose". *Heart*. **97** (6): 442–444. doi:10.1136/hrt.2010.214858. ISSN 1355-6037.
49. ^ World Health Organization (2007). *Prevention of Cardiovascular Disease: Guidelines for Assessment and Management of Cardiovascular Risk*. World Health Organization. ISBN 978-92-4-154717-8.
50. ^ Hernandez, Adrian V.; van Staa, Tjeerd-Pieter; Gulliford, Martin; Ng, Edmond S.-W.; Goldacre, Ben; Smeeth, Liam (2014). "Prediction of Cardiovascular Risk Using Framingham, ASSIGN and QRISK2: How Well Do They Predict Individual Rather than Population Risk?". *PLoS ONE*. **9** (10): e106455. doi:10.1371/journal.pone.0106455.

ISSN 1932-6203. 
51. ^ Hlatky, M. A.; Greenland, P.; Arnett, D. K.; Ballantyne, C. M.; Criqui, M. H.; Elkind, M. S.V.; Go, A. S.; Harrell, F. E.; Hong, Y.; Howard, B. V.; Howard, V. J.; Hsue, P. Y.; Kramer, C. M.; McConnell, J. P.; Normand, S.-L. T.; O'Donnell, C. J.; Smith, S. C.; Wilson, P. W.F. (2009). "Criteria for Evaluation of Novel Markers of Cardiovascular Risk: A Scientific Statement From the American Heart Association". *Circulation*. **119** (17): 2408–2416. doi:10.1161/CIRCULATIONAHA.109.192278. ISSN 0009-7322.
52. ^ Eckel, Robert H; Cornier, Marc-Andre (2014). "Update on the NCEP ATP-III emerging cardiometabolic risk factors". *BMC Medicine*. **12** (1): 115. doi:10.1186/1741-7015-12-115. ISSN 1741-7015. 
53. ^ "CDC - NIOSH Program Portfolio : Cancer, Reproductive, and Cardiovascular Diseases : Program Description". *www.cdc.gov*. Retrieved 2016-06-07.
54. ^ Bertazzo, S. *et al.* Nano-analytical electron microscopy reveals fundamental insights into human cardiovascular tissue calcification. *Nature Materials* **12**, 576–583 (2013).
55. ^ Vanhecke TE, Miller WM, Franklin BA, Weber JE, McCullough PA (Oct 2006). "Awareness, knowledge, and perception of heart disease among adolescents". *Eur J Cardiovasc Prev Rehabil*. **13** (5): 718–23. doi:10.1097/01.hjr.0000214611.91490.5e. PMID 17001210.
56. ^ Highlander P, Shaw GP (2010). "Current pharmacotherapeutic concepts for the treatment of cardiovascular disease in diabetics". *Ther Adv Cardiovasc Dis*. **4** (1): 43–54. doi:10.1177/1753944709354305.
57. ^ NPS Medicinewise (1 March 2011). "NPS Prescribing Practice Review 53: Managing lipids". Retrieved 1 August 2011.
58. ^ Kvan E.; Pettersen K.I.; Sandvik L.; Reikvam A. (2007). "High mortality in diabetic patient with acute myocardial infarction: cardiovascular co-morbidities contribute most to the high risk". *Int J Cardiol*. **121** (2): 184–188. doi:10.1016/j.ijcard.2006.11.003.
59. ^ Norhammar A.; Malmberg K.; Diderhol E.; Lagerqvist B.; Lindahl B., Ryde; et al. (2004). "Diabetes mellitus: the major risk factor in unstable coronary artery disease even after consideration of the extent of coronary artery disease and benefits of revascularization. J". *Am Coll Cardiol*. **43** (4): 585–591. doi:10.1016/j.jacc.2003.08.050.
60. ^ DECODE , European Diabetes Epidemiology Group (1999). "Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria". *Lancet*. **354** (9179): 617–621. doi:10.1016/S0140-6736(98)12131-1. PMID 10466661.
61. ^ [a] [b] Moyer, VA; U.S. Preventive Services Task Force (Oct 2, 2012). "Screening for coronary heart disease with electrocardiography: U.S. Preventive Services Task Force recommendation statement.". *Annals of Internal Medicine*. **157** (7): 512–8. doi:10.7326/0003-4819-157-7-201210020-00514. PMID 22847227.
62. ^ Maron, B. J.; Friedman, R. A.; Kligfield, P.; Levine, B. D.; Viskin, S.; Chaitman, B. R.; Okin, P. M.; Saul, J. P.; Salberg, L.; Van Hare, G. F.; Soliman, E. Z.; Chen, J.; Matherne, G. P.; Bolling, S. F.; Mitten, M. J.; Caplan, A.; Balady, G. J.; Thompson, P. D. (15 September 2014). "Assessment of the 12-Lead ECG as a Screening Test for Detection of Cardiovascular Disease in Healthy General Populations of Young People (12–25 Years of Age): A Scientific Statement From the American Heart Association and the American College of Cardiology". *Circulation*. **130** (15): 1303–1334. doi:10.1161/CIR.0000000000000025.
63. ^ Chou, Roger (17 March 2015). "Cardiac Screening With Electrocardiography, Stress Echocardiography, or Myocardial Perfusion Imaging: Advice for High-Value Care From the American College of Physicians". *Annals of Internal Medicine*. **162** (6): 438. doi:10.7326/M14-1225.
64. ^ Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS (2006). "Multiple biomarkers for the prediction of first major cardiovascular events and death". *N. Engl. J. Med*. **355** (25): 2631–billy bob joe9. doi:10.1056/NEJMoa055373. PMID 17182988.
65. ^ Spence JD (2006). "Technology Insight: ultrasound measurement of carotid plaque—patient management, genetic research, and therapy evaluation". *Nat Clin Pract Neurol*. **2** (11): 611–9. doi:10.1038/ncpneuro0324. PMID 17057748.
66. ^ Adolescents, Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children And (2011-12-01). "Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report". *Pediatrics*. **128** (Supplement 5): S213–S256. doi:10.1542/peds.2009-2107C. ISSN 0031-4005. PMC 4536582. PMID 22084329.
67. ^ Saenger, Amy K. (2012-08-01). "Universal Lipid Screening in Children and Adolescents: A Baby Step toward Primordial Prevention?". *Clinical Chemistry*. **58** (8): 1179–1181. doi:10.1373/clinchem.2012.182287. ISSN 0009-9147. PMID 22510399.
68. ^ McGill, Henry C.; McMahan, C. Alex; Gidding, Samuel S. (2008-03-04). "Preventing Heart Disease in the 21st Century". *Circulation*. **117** (9): 1216–1227. doi:10.1161/CIRCULATIONAHA.107.717033. ISSN 0009-7322. PMID 18316498.
69. ^ McNeal, Catherine J.; Dajani, Tala; Wilson, Don; Cassidy-Bushrow, Andrea E.; Dickerson, Justin B.; Ory, Marcia (2010-01-01). "Hypercholesterolemia in youth: opportunities and obstacles to prevent premature atherosclerotic

cardiovascular disease". *Current Atherosclerosis Reports*. **12** (1): 20–28. doi:10.1007/s11883-009-0072-0. ISSN 1534-6242. PMID 20425267.

70. ^ [a] [b] [c] [d] NHS Direct
71. ^ Ignarro, LJ; Balestrieri, ML; Napoli, C (Jan 15, 2007). "Nutrition, physical activity, and cardiovascular disease: an update.". *Cardiovascular research*. **73** (2): 326–40. doi:10.1016/j.cardiores.2006.06.030. PMID 16945357.
72. ^ [a] [b] Wang, X; Ouyang, Y; Liu, J; Zhu, M; Zhao, G; Bao, W; Hu, FB (Jul 29, 2014). "Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies.". *BMJ (Clinical research ed.)*. **349**: g4490. doi:10.1136/bmj.g4490. PMC 4115152. PMID 25073782.
73. ^ World Heart Federation (5 October 2011). "World Heart Federation: Cardiovascular disease risk factors". Retrieved 5 October 2011.
74. ^ The National Heart, Lung, and Blood Institute (NHLBI) (5 October 2011). "How To Prevent and Control Coronary Heart Disease Risk Factors – NHLBI, NIH". Retrieved 5 October 2011.
75. ^ Klatsky AL (May 2009). "Alcohol and cardiovascular diseases". *Expert Rev Cardiovasc Ther*. **7** (5): 499–506. doi:10.1586/erc.09.22. PMID 19419257.
76. ^ McMahan, C. Alex; Gidding, Samuel S.; Malcom, Gray T.; Tracy, Richard E.; Strong, Jack P.; McGill, Henry C. (2006-10-01). "Pathobiological determinants of atherosclerosis in youth risk scores are associated with early and advanced atherosclerosis". *Pediatrics*. **118** (4): 1447–1455. doi:10.1542/peds.2006-0970. ISSN 1098-4275. PMID 17015535.
77. ^ Raitakari, Olli T.; Rönnemaa, Tapani; Järvisalo, Mikko J.; Kaitosaari, Tuuli; Volanen, Iina; Kallio, Katariina; Lagström, Hanna; Jokinen, Eero; Niinikoski, Harri (2005-12-13). "Endothelial function in healthy 11-year-old children after dietary intervention with onset in infancy: the Special Turku Coronary Risk Factor Intervention Project for children (STRIP)". *Circulation*. **112** (24): 3786–3794. doi:10.1161/CIRCULATIONAHA.105.583195. ISSN 1524-4539. PMID 16330680.
78. ^ McTigue KM, Hess R, Ziouras J (September 2006). "Obesity in older adults: a systematic review of the evidence for diagnosis and treatment". *Obesity (Silver Spring)*. **14** (9): 1485–97. doi:10.1038/oby.2006.171. PMID 17030958.
79. ^ Linden W, Stossel C, Maurice J (April 1996). "Psychosocial interventions for patients with coronary artery disease: a meta-analysis". *Arch. Intern. Med*. **156** (7): 745–52. doi:10.1001/archinte.1996.00440070065008. PMID 8615707.
80. ^ Thompson, D. R.; Ski, C. F. (2013). "Psychosocial interventions in cardiovascular disease - what are they?". *European Journal of Preventive Cardiology*. **20** (6): 916–917. doi:10.1177/2047487313494031. ISSN 2047-4873.
81. ^ Wei, J; Rooks, C; Ramadan, R; Shah, AJ; Bremner, JD; Quyyumi, AA; Kutner, M; Vaccarino, V (15 July 2014). "Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease.". *The American journal of cardiology*. **114** (2): 187–92. doi:10.1016/j.amjcard.2014.04.022. PMID 24856319.
82. ^ Pelliccia, F; Greco, C; Vitale, C; Rosano, G; Gaudio, C; Kaski, JC (August 2014). "Takotsubo syndrome (stress cardiomyopathy): an intriguing clinical condition in search of its identity.". *The American Journal of Medicine*. **127** (8): 699–704. doi:10.1016/j.amjmed.2014.04.004. PMID 24754972.
83. ^ Marshall, IJ; Wolfe, CD; McKevitt, C (Jul 9, 2012). "Lay perspectives on hypertension and drug adherence: systematic review of qualitative research.". *BMJ (Clinical research ed.)*. **345**: e3953. doi:10.1136/bmj.e3953. PMC 3392078. PMID 22777025.
84. ^ Dickinson, HO; Mason, JM; Nicolson, DJ; Campbell, F; Beyer, FR; Cook, JV; Williams, B; Ford, GA (February 2006). "Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials.". *Journal of Hypertension*. **24** (2): 215–33. doi:10.1097/01.hjh.0000199800.72563.26. PMID 16508562.
85. ^ Abbott, RA; Whear, R; Rodgers, LR; Bethel, A; Thompson Coon, J; Kuyken, W; Stein, K; Dickens, C (May 2014). "Effectiveness of mindfulness-based stress reduction and mindfulness based cognitive therapy in vascular disease: A systematic review and meta-analysis of randomised controlled trials.". *Journal of psychosomatic research*. **76** (5): 341–51. doi:10.1016/j.jpsychores.2014.02.012. PMID 24745774.
86. ^ Moyer, VA; U.S. Preventive Services Task Force (Sep 4, 2012). "Behavioral counseling interventions to promote a healthful diet and physical activity for cardiovascular disease prevention in adults: U.S. Preventive Services Task Force recommendation statement.". *Annals of Internal Medicine*. **157** (5): 367–71. doi:10.7326/0003-4819-157-5-201209040-00486. PMID 22733153.
87. ^ Li, C; Lv, Z; Shi, Z; Zhu, Y; Wu, Y; Li, L; Iheozor-Ejiofor, Z (Aug 15, 2014). "Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis.". *The Cochrane database of systematic reviews*. **8**: CD009197. doi:10.1002/14651858.CD009197.pub2. PMID 25123257.
88. ^ Seron, P; Lanas, F; Pardo Hernandez, H; Bonfill Cosp, X (Aug 13, 2014). "Exercise for people with high cardiovascular risk.". *The Cochrane database of systematic reviews*. **8**: CD009387.

doi:10.1002/14651858.CD009387.pub2. PMID 25120097.
89. ^ Walker C, Reamy BV (April 2009). "Diets for cardiovascular disease prevention: what is the evidence?". *Am Fam Physician*. **79** (7): 571–8. PMID 19378874.
90. ^ Nordmann, AJ; Suter-Zimmermann, K; Bucher, HC; Shai, I; Tuttle, KR; Estruch, R; Briel, M (September 2011). "Meta-analysis comparing Mediterranean to low-fat diets for modification of cardiovascular risk factors.". *The American Journal of Medicine*. **124** (9): 841–51.e2. doi:10.1016/j.amjmed.2011.04.024. PMID 21854893.
91. ^ Sacks FM, Svetkey LP, Vollmer WM, et al. (January 2001). "Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group". *N. Engl. J. Med*. **344** (1): 3–10. doi:10.1056/NEJM200101043440101. PMID 11136953.
92. ^ Obarzanek E, Sacks FM, Vollmer WM, et al. (July 2001). "Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial". *Am. J. Clin. Nutr*. **74** (1): 80–9. PMID 11451721.
93. ^ Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi T, Azizi F (December 2005). "Beneficial effects of a Dietary Approaches to Stop Hypertension eating plan on features of the metabolic syndrome". *Diabetes Care*. **28** (12): 2823–31. doi:10.2337/diacare.28.12.2823. PMID 16306540.
94. ^ Logan AG (March 2007). "DASH Diet: time for a critical appraisal?". *Am. J. Hypertens*. **20** (3): 223–4. doi:10.1016/j.amjhyper.2006.10.006. PMID 17324730.
95. ^ Threapleton, D. E.; Greenwood, D. C.; Evans, C. E. L.; Cleghorn, C. L.; Nykjaer, C.; Woodhead, C.; Cade, J. E.; Gale, C. P.; Burley, V. J. (19 December 2013). "Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis". *BMJ*. **347** (dec19 2): f6879–f6879. doi:10.1136/bmj.f6879. PMC 3898422. PMID 24355537.
96. ^ "Fats and fatty acids in human nutrition Report of an expert consultation". *World Health Organization*. WHO/FAO. Retrieved 20 December 2014.
97. ^ *a b c* Willett, WC (July 2012). "Dietary fats and coronary heart disease.". *Journal of internal medicine*. **272** (1): 13–24. doi:10.1111/j.1365-2796.2012.02553.x. PMID 22583051.
98. ^ *a b c* Chowdhury, Rajiv; Warnakula, Samantha; Kunutsor, Setor; Crowe, Francesca; Ward, Heather A.; Johnson, Laura; Franco, Oscar H.; Butterworth, Adam S.; Forouhi, Nita G.; Thompson, Simon G.; Khaw, Kay-Tee; Mozaffarian, Dariush; Danesh, John; Di Angelantonio, Emanuele (18 March 2014). "Association of Dietary, Circulating, and Supplement Fatty Acids With Coronary Risk". *Annals of Internal Medicine*. **160** (6): 398–406. doi:10.7326/M13-1788. PMID 24723079.
99. ^ *a b* Ramsden, CE; Zamora, D; Leelarthaepin, B; Majchrzak-Hong, SF; Faurot, KR; Suchindran, CM; Ringel, A; Davis, JM; Hibbeln, JR (Feb 4, 2013). "Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis.". *BMJ (Clinical research ed.)*. **346**: e8707. doi:10.1136/bmj.e8707. PMID 23386268.
100. ^ *a b* de Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, Uleryk E, Budylowski P, Schünemann H, Beyene J, Anand SS (Aug 12, 2015). "Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies". *BMJ*. **351** (h3978). doi:10.1136/bmj.h3978. PMC 4532752. PMID 26268692.
101. ^ Hooper, L; Summerbell, CD; Thompson, R; Sills, D; Roberts, FG; Moore, HJ; Davey Smith, G (May 16, 2012). "Reduced or modified dietary fat for preventing cardiovascular disease.". *Cochrane database of systematic reviews (Online)*. **5**: CD002137. doi:10.1002/14651858.CD002137.pub3. PMID 22592684.
102. ^ Siri-Tarino Patty W; Sun Qi; Hu Frank B; Krauss Ronald M (2010). "Saturated fat, carbohydrate, and cardiovascular disease". *American Journal of Clinical Nutrition*. **91** (3): 502–509. doi:10.3945/ajcn.2008.26285. PMC 2824150. PMID 20089734.
103. ^ Micha, R; Mozaffarian, D (October 2010). "Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence.". *Lipids*. **45** (10): 893–905. doi:10.1007/s11745-010-3393-4. PMC 2950931. PMID 20354806.
104. ^ Astrup, A; Dyerberg, J; Elwood, P; Hermansen, K; Hu, FB; Jakobsen, MU; Kok, FJ; Krauss, RM; Lecerf, JM; LeGrand, P; Nestel, P; Risérus, U; Sanders, T; Sinclair, A; Stender, S; Tholstrup, T; Willett, WC (April 2011). "The role of reducing intakes of saturated fat in the prevention of cardiovascular disease: where does the evidence stand in 2010?". *The American Journal of Clinical Nutrition*. **93** (4): 684–8. doi:10.3945/ajcn.110.004622. PMC 3138219. PMID 21270379.
105. ^ Rizos, EC; Ntzani, EE; Bika, E; Kostapanos, MS; Elisaf, MS (Sep 12, 2012). "Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis.". *JAMA: The Journal of the American Medical Association*. **308** (10): 1024–33. doi:10.1001/2012.jama.11374. PMID 22968891.
106. ^ *a b* Taylor, RS; Ashton, KE; Moxham, T; Hooper, L; Ebrahim, S (Jul 6, 2011). "Reduced dietary salt for the prevention of cardiovascular disease.". *Cochrane database of systematic reviews (Online)* (7): CD009217. doi:10.1002/14651858.CD009217. PMID 21735439.

107. ^ a b He, F J; MacGregor G A (2011). "Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials" (PDF). *The Lancet*. **378** (9789): 380–382. doi:10.1016/S0140-6736(11)61174-4. PMID 21803192.
108. ^ Paterna, S; Gaspare P; Fasullo S; Sarullo FM; Di Pasquale P (2008). "Normal-sodium diet compared with low-sodium diet in compensated congestive heart failure: is sodium an old enemy or a new friend?". *Clin Sci (Lond)*. **114** (3): 221–230. doi:10.1042/CS20070193. PMID 17688420.
109. ^ a b Bochud, M; Marques-Vidal, P; Burnier, M; Paccaud, F (2012). "Dietary Salt Intake and Cardiovascular Disease: Summarizing the Evidence". *Public Health Reviews*. **33**: 530–552.
110. ^ Cook, N R; et al. (2007). "Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP)". *BMJ*. **334** (7599): 334. doi:10.1136/bmj.39147.604896.55. PMC 1857760. PMID 17449506.
111. ^ Berger, JS; Lala, A; Krantz, MJ; Baker, GS; Hiatt, WR (July 2011). "Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials.". *American Heart Journal*. **162** (1): 115–24.e2. doi:10.1016/j.ahj.2011.04.006. PMID 21742097.
112. ^ "Final Recommendation Statement Aspirin for the Prevention of Cardiovascular Disease: Preventive Medication". March 2009. Retrieved 15 January 2015.
113. ^ a b Gutierrez, J; Ramirez, G; Rundek, T; Sacco, RL (Jun 25, 2012). "Statin Therapy in the Prevention of Recurrent Cardiovascular Events: A Sex-Based Meta-analysisStatin Therapy to Prevent Recurrent CV Events.". *Archives of Internal Medicine*. **172** (12): 909–19. doi:10.1001/archinternmed.2012.2145. PMID 22732744.
114. ^ Taylor, F; Huffman, MD; Macedo, AF; Moore, TH; Burke, M; Davey Smith, G; Ward, K; Ebrahim, S (Jan 31, 2013). "Statins for the primary prevention of cardiovascular disease.". *Cochrane database of systematic reviews (Online)*. **1**: CD004816. doi:10.1002/14651858.CD004816.pub5. PMID 23440795.
115. ^ Downs, JR; O'Malley, PG (18 August 2015). "Management of dyslipidemia for cardiovascular disease risk reduction: synopsis of the 2014 U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guideline.". *Annals of Internal Medicine*. **163** (4): 291–7. doi:10.7326/m15-0840. PMID 26099117.
116. ^ Francis, DP (May 19, 2011). "Duration and magnitude of the effect of a single statin tablet in primary prevention of cardiovascular events.". *International Journal of Cardiology*. **149** (1): 102–7. doi:10.1016/j.ijcard.2010.11.013. PMID 21183232.
117. ^ Keene, D; Price, C; Shun-Shin, MJ; Francis, DP (Jul 18, 2014). "Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117,411 patients.". *BMJ (Clinical research ed.)*. **349**: g4379. doi:10.1136/bmj.g4379. PMC 4103514. PMID 25038074.
118. ^ American College of Chest Physicians; American Thoracic Society (September 2013), "Five Things Physicians and Patients Should Question", *Choosing Wisely: an initiative of the ABIM Foundation*, American College of Chest Physicians and American Thoracic Society, retrieved 6 January 2013
119. ^ Bhupathiraju, SN; Tucker, KL (Aug 17, 2011). "Coronary heart disease prevention: nutrients, foods, and dietary patterns.". *Clinica chimica acta; international journal of clinical chemistry*. **412** (17–18): 1493–514. doi:10.1016/j.cca.2011.04.038. PMID 21575619.
120. ^ Myung, SK; Ju, W; Cho, B; Oh, SW; Park, SM; Koo, BK; Park, BJ; for the Korean Meta-Analysis (KORMA) Study, Group (Jan 18, 2013). "Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials.". *BMJ (Clinical research ed.)*. **346**: f10. doi:10.1136/bmj.f10. PMC 3548618. PMID 23335472.
121. ^ Fortmann, SP; Burda, BU; Senger, CA; Lin, JS; Whitlock, EP (Nov 12, 2013). "Vitamin and Mineral Supplements in the Primary Prevention of Cardiovascular Disease and Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force.". *Annals of Internal Medicine*. **159** (12): 824–34. doi:10.7326/0003-4819-159-12-201312170-00729. PMID 24217421.
122. ^ Bruckert, E; Labreuche, J; Amarenco, P (June 2010). "Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis". *Atherosclerosis*. **210** (2): 353–61. doi:10.1016/j.atherosclerosis.2009.12.023. PMID 20079494.
123. ^ Lavigne, PM; Karas, RH (Jan 29, 2013). "The current state of niacin in cardiovascular disease prevention: a systematic review and meta-regression.". *Journal of the American College of Cardiology*. **61** (4): 440–6. doi:10.1016/j.jacc.2012.10.030. PMID 23265337.
124. ^ Jee SH, Miller ER, Guallar E, et al. (2002). "The effect of magnesium supplementation on blood pressure: a meta-analysis of randomized clinical trials". *Am J Hypertens*. **15** (8): 691–696. doi:10.1016/S0895-7061(02)02964-3. PMID 12160191.
125. ^ Zipes DP, Camm AJ, Borggrefe M, et al. (2012). "ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and

the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society". *Circulation*. **114** (10): e385–e484. doi:10.1161/CIRCULATIONAHA.106.178233. PMID 16935995.
126. ^ Kwak, SM; Myung, SK; Lee, YJ; Seo, HG; for the Korean Meta-analysis Study, Group (Apr 9, 2012). "Efficacy of Omega-3 Fatty Acid Supplements (Eicosapentaenoic Acid and Docosahexaenoic Acid) in the Secondary Prevention of Cardiovascular Disease: A Meta-analysis of Randomized, Double-blind, Placebo-Controlled Trials.". *Archives of Internal Medicine*. **172** (9): 686. doi:10.1001/archinternmed.2012.262. PMID 22493407.
127. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved Nov 11, 2009.
128. ^ Indian Heart Association Why South Asians Facts Web. 29 April 2015. <http://indianheartassociation.org/why-indians-why-south-asians/overview/>
129. ^ Morris J. N.; Crawford Margaret D. (1958). "Coronary Heart Disease and Physical Activity of Work". *British Medical Journal*. **2** (5111): 1485–1496. doi:10.1136/bmj.2.5111.1485. PMC 2027542. PMID 13608027.
130. ^ Karakas M, Koenig W (December 2009). "CRP in cardiovascular disease". *Herz*. **34** (8): 607–13. doi:10.1007/s00059-009-3305-7. PMID 20024640.
131. ^ 20448212
132. ^ Venuraju SM, Yerramasu A, Corder R, Lahiri A (May 2010). "Osteoprotegerin as a predictor of coronary artery disease and cardiovascular mortality and morbidity". *J. Am. Coll. Cardiol*. **55** (19): 2049–61. doi:10.1016/j.jacc.2010.03.013. PMID 20447527.
133. ^ Andraws R, Berger JS, Brown DL (Jun 2005). "Effects of antibiotic therapy on outcomes of patients with coronary artery disease: a meta-analysis of randomized controlled trials". *JAMA*. **293** (21): 2641–7. doi:10.1001/jama.293.21.2641. PMID 15928286.
134. ^ Dominguez-Rodriguez, Alberto (January 2012). "Melatonin and Cardiovascular Disease: Myth or Reality?". *Rev Esp Cardiol*. **65**: 215–218.

# External links

- Cardiovascular disease at DMOZ
- European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)
- Heart Disease MedicineNet Slides, photos, descriptions

| v · t · e | Cardiovascular disease (heart) (I00–I52, 390–429) | | |
|---|---|---|---|
| **Ischaemic** | **Coronary disease** | | Coronary artery disease (CAD) · Coronary artery aneurysm · Spontaneous coronary artery dissection (SCAD) · Coronary thrombosis · Coronary vasospasm · Myocardial bridge · |
| | **Active ischemia** | | Angina pectoris (Prinzmetal's angina · Stable angina · · Acute coronary syndrome (Myocardial infarction · Unstable angina · · |
| | **Sequelae** | | *hours* (Hibernating myocardium · Myocardial stunning · · *days* (Myocardial rupture · · *weeks* (Aneurysm of heart / Ventricular aneurysm · Dressler syndrome · · |
| **Layers** | **Pericardium** | | Pericarditis (Acute · Chronic / Constrictive · · Pericardial effusion (Cardiac tamponade · Hemopericardium · · |
| | **Myocardium** | | Myocarditis (Chagas disease · · Cardiomyopathy: Dilated (Alcoholic), Hypertrophic, *and* Restrictive (Loeffler endocarditis · Cardiac amyloidosis · Endocardial fibroelastosis · · Arrhythmogenic right ventricular dysplasia · |
| | **Endocardium / valves** | **Endocarditis** | *infective endocarditis* (Subacute bacterial endocarditis · · *non-infective endocarditis* (Libman–Sacks endocarditis · Nonbacterial thrombotic endocarditis · · |
| | | **Valves** | *mitral* (regurgitation · prolapse · stenosis · · *aortic* (stenosis · insufficiency · · *tricuspid* (stenosis · insufficiency · · *pulmonary* (stenosis · insufficiency · · |

| | | | |
|---|---|---|---|
| **Conduction / arrhythmia** | **Bradycardia** | | Sinus bradycardia · Sick sinus syndrome · Heart block: Sinoatrial · AV (1° · 2° · 3° · · Intraventricular · Bundle branch block (Right · Left · Left anterior fascicle · Left posterior fascicle · Bifascicular · Trifascicular · · Adams–Stokes syndrome · |
| | **Tachycardia (paroxysmal and sinus)** | **Supraventricular** | Atrial (Multifocal · · Junctional (AV nodal reentrant · Junctional ectopic · · |
| | | **Ventricular** | Accelerated idioventricular rhythm · Catecholaminergic polymorphic · Torsades de pointes · |
| | **Premature contraction** | | Atrial · Junctional · Ventricular · |
| | **Pre-excitation syndrome** | | Lown–Ganong–Levine · Wolff–Parkinson–White · |
| | **Flutter / fibrillation** | | Atrial flutter · Ventricular flutter · Atrial fibrillation (Familial · · Ventricular fibrillation · |
| | **Pacemaker** | | Ectopic pacemaker / Ectopic beat · Multifocal atrial tachycardia · Pacemaker syndrome · Parasystole · Wandering pacemaker · |
| | **Long QT syndrome** | | Andersen–Tawil · Jervell and Lange-Nielsen · Romano–Ward · |
| | **Cardiac arrest** | | Sudden cardiac death · Asystole · Pulseless electrical activity · Sinoatrial arrest · |
| | **Other / ungrouped** | | *hexaxial reference system* (Right axis deviation · Left axis deviation · · *QT* (Short QT syndrome · · *T* (T wave alternans · · *ST* (Osborn wave · ST elevation · ST depression · · Strain pattern · |
| **Cardiomegaly** | | | Ventricular hypertrophy (Left · Right / Cor pulmonale · · Atrial enlargement (Left · Right · · |
| **Other** | | | Cardiac fibrosis · Heart failure (Diastolic heart failure · Cardiac asthma · · Rheumatic fever · |

| v · t · e · | **Cardiovascular disease (vessels) (I70–I99, 440–456)** | | |
|---|---|---|---|
| **Arteries, arterioles and capillaries** | **Inflammation** | | Arteritis (Aortitis · · Buerger's disease · |
| | **Peripheral artery disease** | **Arteriosclerosis** | Atherosclerosis (Foam cell · Fatty streak · Atheroma · Intermittent claudication · Critical limb ischemia · · Monckeberg's arteriosclerosis · Arteriolosclerosis (Hyaline · Hyperplastic · Cholesterol · LDL · Oxycholesterol · Trans fat · · |
| | | **Stenosis** | Carotid artery stenosis · Renal artery stenosis · |
| | | **Other** | Aortoiliac occlusive disease · Degos disease · Erythromelalgia · Fibromuscular dysplasia · Raynaud's phenomenon · |
| | **Aneurysm / dissection /** | | *torso*: Aortic aneurysm (Abdominal aortic aneurysm · Thoracic aortic aneurysm · Aneurysm of sinus of Valsalva · · Aortic dissection · Coronary artery aneurysm · *head / neck* |

| | | |
|---|---|---|
| | **pseudoaneurysm** | (Intracranial aneurysm · Intracranial berry aneurysm · Carotid artery dissection · Vertebral artery dissection · Familial aortic dissection · · |
| | **Vascular malformation** | Arteriovenous fistula · Arteriovenous malformation · Telangiectasia (Hereditary hemorrhagic telangiectasia · · |
| | **Vascular nevus** | Cherry hemangioma · Halo nevus · Spider angioma · |
| **Veins** | **Inflammation** | Phlebitis · |
| | **Venous thrombosis / Thrombophlebitis** | *primarily lower limb* (Deep vein thrombosis · · *abdomen* (Hepatic veno-occlusive disease · Budd–Chiari syndrome · May–Thurner syndrome · Portal vein thrombosis · Renal vein thrombosis · · *upper limb / torso* (Mondor's disease · Paget–Schroetter disease · · *head* (Cerebral venous sinus thrombosis · · Post-thrombotic syndrome · |
| | **Varicose veins** | Gastric varices · Portacaval anastomosis (Caput medusae · Esophageal varices · Hemorrhoid · · Varicocele · |
| | **Other** | Chronic venous insufficiency · Chronic cerebrospinal venous insufficiency · Superior vena cava syndrome · Inferior vena cava syndrome · Venous ulcer · |
| **Arteries or veins** | | Angiopathy (Macroangiopathy · Microangiopathy · · Embolism (Pulmonary embolism · Cholesterol embolism · Paradoxical embolism · · Thrombosis · Vasculitis · |
| **Blood pressure** | **Hypertension** | Hypertensive heart disease · Hypertensive emergency · Hypertensive nephropathy · Essential hypertension · Secondary hypertension (Renovascular hypertension · · Benign hypertension · Pulmonary hypertension · Systolic hypertension · White coat hypertension · |
| | **Hypotension** | Orthostatic hypotension · |

| v · t · e · | **Certain conditions originating in the perinatal period / fetal disease (P, 760–779)** | |
|---|---|---|
| **Maternal factors and complications of pregnancy, labour and delivery** | *placenta:* | Placenta praevia · Placental insufficiency · Twin-to-twin transfusion syndrome · |
| | *chorion*/*amnion:* | Chorioamnionitis · |
| | *umbilical cord:* | Umbilical cord prolapse · Nuchal cord · Single umbilical artery · |
| **Length of gestation and fetal growth** | | Small for gestational age/Large for gestational age · Preterm birth/Postmature birth · Intrauterine growth restriction · |
| **Birth trauma** | | *scalp* (Cephalhematoma · Chignon · Caput succedaneum · Subgaleal hemorrhage · · Brachial plexus lesion (Erb's palsy · Klumpke paralysis · · |
| | **Respiratory** | Intrauterine hypoxia · Infant respiratory distress syndrome · Transient tachypnea of the newborn · Meconium aspiration syndrome · *pleural disease* (Pneumothorax · Pneumomediastinum · · |

| | | |
|---|---|---|
| **By system** | | Wilson–Mikity syndrome · Bronchopulmonary dysplasia · |
| | **Cardiovascular** | Pneumopericardium · Persistent fetal circulation · |
| | **Haemorrhagic and hematologic disease** | Vitamin K deficiency (Haemorrhagic disease of the newborn · · HDN (ABO · Anti-Kell · Rh c · Rh D · Rh E · · Hydrops fetalis · Hyperbilirubinemia (Kernicterus · Neonatal jaundice · · Velamentous cord insertion · Intraventricular hemorrhage (Germinal matrix hemorrhage · · Anemia of prematurity · |
| | **Digestive** | Ileus · Necrotizing enterocolitis · Meconium peritonitis · |
| | **Integument and thermoregulation** | Erythema toxicum · Sclerema neonatorum · |
| | **Nervous system** | Periventricular leukomalacia · |
| | **Musculoskeletal** | Gray baby syndrome · *muscle tone* (Congenital hypertonia · Congenital hypotonia · · |
| **Infectious** | | Vertically transmitted infection · Neonatal infection (Congenital rubella syndrome · Neonatal herpes simplex · Mycoplasma hominis infection · Ureaplasma urealyticum infection · · Omphalitis · Neonatal sepsis (Group B streptococcal infection · · Neonatal conjunctivitis · |
| **Other** | | Miscarriage · Perinatal mortality (Stillbirth · Infant mortality · · Neonatal withdrawal · |

| v · t · e · **Symptoms and signs relating to the cardiovascular system (R00–R03, 785)** | |
|---|---|
| **Chest pain** | Referred pain · Angina · Aerophagia · |
| **Auscultation** | Heart sounds (Split S2 · S3 · S4 · Gallop rhythm · · Heart murmur (Systolic · Diastolic · Continuous · · Pericardial friction rub · Heart click · Bruit (carotid · · |
| **Pulse** | Tachycardia · Bradycardia · Pulsus tardus et parvus · Pulsus paradoxus · *doubled* (Pulsus bisferiens · Dicrotic pulse · Pulsus bigeminus · · Pulsus alternans · |
| **Vascular disease** | Gangrene · |
| **Other** | Palpitations (Apex beat · · Cœur en sabot · Jugular venous pressure (Cannon A waves · · Hyperaemia · |
| **Shock** | Cardiogenic · Hypovolemic · Distributive (Septic · Neurogenic · · |

| v · t · e · **Eponymous medical signs for circulatory system** | | |
|---|---|---|
| **Heart disease** | **Heart murmur** | Systolic heart murmur: *Benign paediatric heart murmur* (Still's murmur) · Diastolic heart murmur: *Pulmonic regurgitation* (Graham Steell murmur) · *Aortic insufficiency* (Austin Flint murmur) *Carey Coombs murmur* · *Mitral regurgitation* (Presystolic murmur) · |
| | **Aortic insufficiency** | Watson's water hammer pulse/Corrigan pulse · De Musset's sign · Duroziez's sign · Müller's sign · Quincke's sign · Austin Flint murmur · Mayne's sign · |
| | | *endocarditis:* Roth's spot · Janeway lesion/Osler's node · |

| | | |
|---|---|---|
| | **Other endocardium** | Bracht-Wachter bodies · |
| | **Pericardium** | *Cardiac tamponade*/*Pericardial effusion:* Beck's triad · Ewart's sign · |
| | **Other** | *rheumatic fever:* Anitschkow cell · Aschoff body · *EKG* (Osborn wave) · *angina pectoris* (Levine's sign) · Gallavardin phenomenon · |
| **Vascular disease** | **Arterial** | *aortic aneurysm* (Cardarelli's sign, Oliver's sign) · *pulmonary embolism* (McConnell's sign) · *radial artery sufficiency* (Allen's test) · *pseudohypertension* (Osler's sign) · *thrombus* (Lines of Zahn) · Adson's sign · *arteriovenous fistula* (Nicoladoni sign) · |
| | **Venous** | Friedreich's sign · Caput medusae · Kussmaul's sign · *DVT* (Bancroft's sign · Homans sign · Lisker's sign · Louvel's sign · Lowenberg's sign · Peabody's sign · Pratt's sign · Rose's sign · · Trendelenburg test · *superior vena cava syndrome* (Pemberton's sign) · |
| **Authority control** | GND: 4024666-8 · NDL: 00575113 · | |

Categories: Heart diseases

# Coronary artery disease

From Wikipedia, the free encyclopedia

**Coronary artery disease** (**CAD**), also known as **ischemic heart disease** (**IHD**),[4] is a group of diseases that includes: stable angina, unstable angina, myocardial infarction, and sudden cardiac death.[5] It is within the group of cardiovascular diseases of which it is the most common type.[6] A common symptom is chest pain or discomfort which may travel into the shoulder, arm, back, neck, or jaw.[7] Occasionally it may feel like heartburn. Usually symptoms occur with exercise or emotional stress, last less than a few minutes, and get better with rest.[7] Shortness of breath may also occur and sometimes no symptoms are present.[7] The first sign is occasionally a heart attack.[8] Other complications include heart failure or an irregular heartbeat.[8]

Risk factors include: high blood pressure, smoking, diabetes, lack of exercise, obesity, high blood cholesterol, poor diet, and excessive alcohol, among others.[9][10] Other risks include depression.[11] The underlying mechanism involves atherosclerosis of the arteries of the heart.[10] A number of tests may help with diagnoses including: electrocardiogram, cardiac stress testing, coronary computed tomographic angiography, and coronary angiogram, among others.[12]

Prevention is by eating a healthy diet, regular exercise, maintaining a healthy weight and not smoking.[13] Sometimes medication for diabetes, high cholesterol, or high blood pressure are also used.[13] There is limited evidence for screening people who are at low risk and do not have symptoms.[14] Treatment involves the same measures as prevention.[15][16] Additional medications such as antiplatelets including aspirin, beta blockers, or nitroglycerin may be recommended.[16] Procedures such as percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) may be used in severe disease.[16][17] In those with stable CAD it is unclear if PCI or CABG in addition to the other treatments improve life expectancy or decreases heart attack risk.[18]

In 2013 CAD was the most common cause of death globally, resulting in 8.14 million deaths (16.8%) up from 5.74 million deaths (12%) in 1990.[6] The risk of death from CAD for a given age has decreased between 1980 and 2010 especially in developed countries.[19] The number of cases of CAD for a given age has also decreased between 1990 and 2010.[20] In the United States in 2010 about 20% of those over 65 had CAD, while it was present in 7% of those 45 to 64, and 1.3% of those 18 to 45.[21] Rates are higher

## Variants

**Coronary artery disease**

**Synonyms** atherosclerotic heart disease,[1] atherosclerotic cardiovascular disease,[2] coronary heart disease[3]

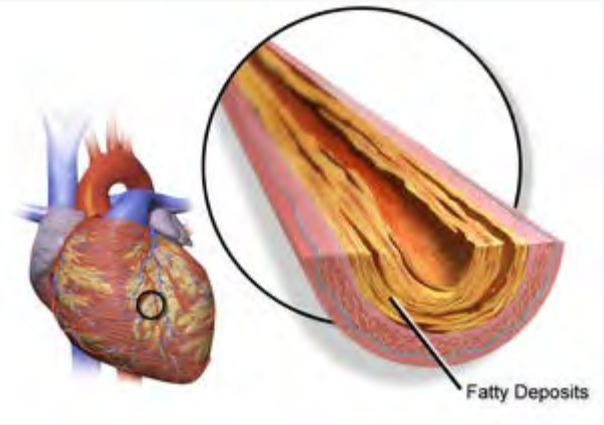



Illustration depicting atherosclerosis in a coronary artery.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Cardiology, cardiac surgery |
| **ICD-10** | I20-I25 |
| **ICD-9-CM** | 410-414, 429.2 |
| **MedlinePlus** | 007115 |
| **eMedicine** | radio/192 |
| **Patient UK** | Coronary artery disease |
| **MeSH** | D003324 |

[edit on Wikidata]

among men than women of a given age.[21]





## Signs and symptoms [edit]

Chest pain that occurs regularly with activity, after eating, or at other predictable times is termed stable angina and is associated with narrowings of the arteries of the heart.

Angina that changes in intensity, character or frequency is termed unstable. Unstable angina may precede myocardial infarction. In adults who go to the emergency department with an unclear cause of pain, about 30% have pain due to coronary artery disease.[22]

## Risk factors [edit]

Coronary artery disease has a number of well determined risk factors. The most common risk factors include smoking, family history, hypertension, obesity, diabetes, lack of exercise, stress, and high blood lipids.[23][24] Smoking is associated with about 36% of cases and obesity 20%.[25] Lack of exercise has been linked to 7–12% of cases.[25][26] Exposure to the herbicide Agent orange may increase risk.[27] Both rheumatoid arthritis and systemic lupus erythematosus are independent risk factors as well.[28][29]

Job stress appears to play a minor role accounting for about 3% of cases.[25]

In one study, women who were free of stress from work life saw an increase in the diameter of their blood vessels, leading to decreased progression of atherosclerosis.[30] In contrast, women who had high levels of work-related stress experienced a decrease in the diameter of their blood vessels and significantly increased disease progression.[30] Having a type A behavior pattern, a group of personality characteristics including time urgency, competitiveness, hostility, and impatience[31] is linked to an increased risk of coronary disease.[32]

### Blood fats [edit]

- High blood cholesterol (specifically, serum LDL concentrations). HDL (high density lipoprotein) has a protective effect over development of coronary artery disease.[33]
- High blood triglycerides may play a role.[34]
- High levels of lipoprotein(a),[35][36][37] a compound formed when LDL cholesterol combines with a protein known as apolipoprotein(a).

Dietary cholesterol does not appear to have a significant effect on blood cholesterol and thus recommendations about its consumption may not be needed.[38] Saturated fat is still a concern.[38]

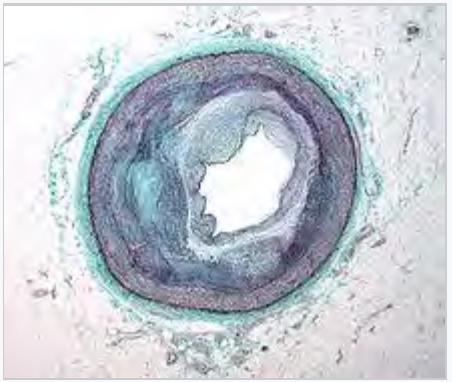
### Other [edit]

- Endometriosis in women under the age of 40[39]
- It is unclear if type A personality affects the risk of coronary artery disease.[40] Depression and hostility do appear to be risks however.[41]
- The number of categories of adverse childhood experiences (psychological, physical, or sexual abuse; violence against mother; or living with household members who were substance abusers, mentally ill, suicidal, or incarcerated) showed a graded relationship to the presence of adult diseases including coronary artery (ischemic heart) disease.[42]
- Hemostatic factors: High levels of fibrinogen and coagulation factor VII are associated with an increased risk of CAD.[43] Factor VII levels are higher in individuals with a high intake of dietary fat. Decreased fibrinolytic activity has been reported in patients with coronary atherosclerosis.[*citation needed*]
- Low hemoglobin[44]
- Men over 45; Women over 55.[*citation needed*]

## Pathophysiology [edit]

Limitation of blood flow to the heart causes ischemia (cell starvation secondary to a lack of oxygen) of the myocardial cells. Myocardial cells may die from lack of oxygen and this is called a myocardial infarction (commonly called a heart attack). It leads to heart muscle damage, heart muscle death and later myocardial scarring without heart muscle regrowth. Chronic high-grade stenosis of the coronary arteries can induce transient ischemia which leads to the induction of a ventricular arrhythmia, which may terminate into ventricular fibrillation leading to death.[45]

Typically, coronary artery disease occurs when part of the smooth, elastic lining inside a coronary artery (the arteries that supply blood to the heart muscle) develops atherosclerosis. With atherosclerosis, the artery's lining becomes hardened, stiffened, and swollen with calcium deposits, fatty deposits, and abnormal inflammatory cells - to form a plaque. Deposits of calcium phosphates (hydroxyapatites) in the muscular layer of the blood vessels appear to play not only a significant role in stiffening arteries but also for the induction of an early phase of coronary arteriosclerosis. This can be seen in a so-called metastatic mechanism of calciphylaxis as it occurs in chronic kidney disease and haemodialysis (Rainer Liedtke 2008). Although these patients suffer from a kidney dysfunction, almost fifty percent of them die due to coronary artery disease. Plaques can be thought of as large "pimples" that protrude into the channel of an artery, causing a partial obstruction to blood flow. Patients with coronary artery disease might have just one or two plaques, or might have dozens distributed throughout their coronary arteries. A more severe form is *chronic total occlusion* (CTO) when a coronary artery is completely obstructed for more than 3 months.[46]



Micrograph of a coronary artery with the most common form of coronary artery disease (atherosclerosis) and marked luminal narrowing. Masson's trichrome.

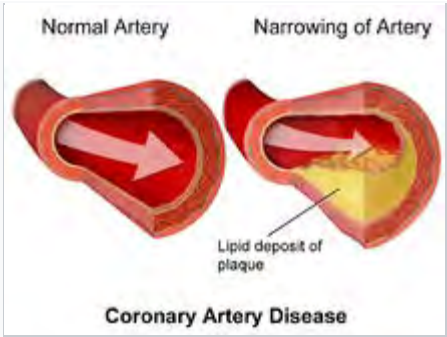
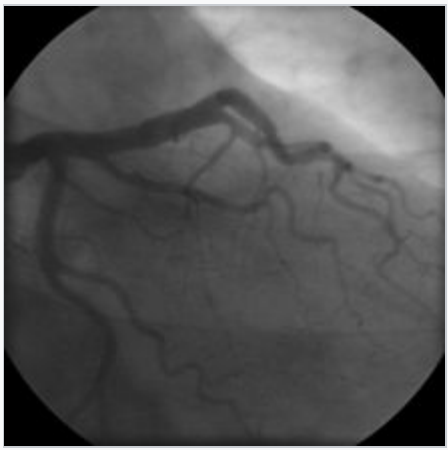


Illustration depicting coronary artery disease

Cardiac syndrome X is a term that describes chest pain (angina pectoris) and chest discomfort in people who do not show signs of blockages in the larger coronary arteries of their hearts when an angiogram (coronary angiogram) is being performed.[47] The exact cause of cardiac syndrome X is unknown. One explanation is microvascular dysfunction.[48] For reasons that are not well known, women are more likely than men to have it; however, hormones and other risk factors unique to women may play a role.[49]

## Diagnosis [edit]

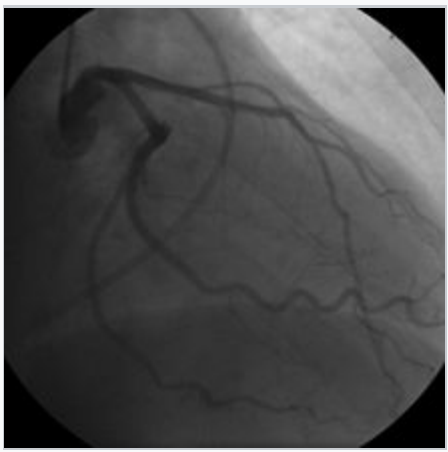
For symptomatic patients, stress echocardiography can be used to make a diagnosis for obstructive coronary artery disease.[50] The use of echocardiography, stress cardiac imaging, and/or advanced non-invasive imaging is not recommended on individuals who are exhibiting no symptoms and are otherwise at low risk for developing coronary disease.[50][51]


Coronary angiogram of a man

The diagnosis of "Cardiac Syndrome X" - the rare coronary artery disease that is more common in women, as mentioned, an "exclusion" diagnosis. Therefore, usually the same tests are used as in any patient with the suspicion of coronary artery disease:

- Baseline electrocardiography (ECG)
- Exercise ECG – Stress test
- Exercise radioisotope test (nuclear stress test, myocardial scintigraphy)
- Echocardiography (including stress echocardiography)
- Coronary angiography
- Intravascular ultrasound
- Magnetic resonance imaging (MRI)

The diagnosis of coronary disease underlying particular symptoms depends largely on the nature of the symptoms. The first investigation is an electrocardiogram (ECG/EKG), both for "stable" angina and acute coronary syndrome. An X-ray of the chest and blood tests may be performed.[*citation needed*]


Coronary angiogram of a woman

### Stable angina [edit]

*Main article: Angina pectoris*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In "stable" angina, chest pain with typical features occurring at predictable levels of exertion, various forms of cardiac stress tests may be used to induce both symptoms and detect changes by way of electrocardiography (using an ECG), echocardiography (using ultrasound of the heart) or scintigraphy (using uptake of radionuclide by the heart muscle). If part of the heart seems to receive an insufficient blood supply, coronary angiography may be used to identify stenosis of the coronary arteries and suitability for angioplasty or bypass surgery.[*citation needed*]

### Acute coronary syndrome [edit]

*Main article: Acute coronary syndrome*

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Diagnosis of acute coronary syndrome generally takes place in the emergency department, where ECGs may be performed sequentially to identify "evolving changes" (indicating ongoing damage to the heart muscle). Diagnosis is clear-cut if ECGs show elevation of the "ST segment", which in the context of severe typical chest pain is strongly indicative of an acute myocardial infarction (MI); this is termed a STEMI (ST-elevation MI), and is treated as an emergency with either urgent coronary angiography and percutaneous coronary intervention (angioplasty with or without stent insertion) or with thrombolysis ("clot buster" medication), whichever is available. In the absence of ST-segment elevation, heart damage is detected by cardiac markers (blood tests that identify heart muscle damage). If there is evidence of damage (infarction), the chest pain is attributed to a "non-ST elevation MI" (NSTEMI). If there is no evidence of damage, the term "unstable angina" is used. This process usually necessitates admission to hospital, and close observation on a coronary care unit for possible complications (such as cardiac arrhythmias – irregularities in the heart rate). Depending on the risk assessment, stress testing or angiography may be used to identify and treat coronary artery disease in patients who have had an NSTEMI or unstable angina.

### Risk assessment [edit]

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There are various risk assessment systems for determining the risk of coronary artery disease, with various emphasis on different variables above. A notable example is Framingham Score, used in the Framingham Heart Study. It is mainly based on age, gender, diabetes, total cholesterol, HDL cholesterol, tobacco smoking and systolic blood pressure.

## Prevention [edit]

Up to 90% of cardiovascular disease may be preventable if established risk factors are avoided.[52][53] Prevention involves: exercise, decreasing obesity, treating hypertension, a healthy diet, decreasing cholesterol levels, and stopping smoking. Medications and exercise are roughly equally effective.[54] High levels of physical activity reduce the risk of coronary artery disease by about 25%.[55]

In diabetes mellitus, there is little evidence that very tight blood sugar control improves cardiac risk although improved sugar control appears to decrease other problems like kidney failure and blindness. The World Health Organization (WHO) recommends "low to moderate alcohol intake" to reduce risk of coronary artery disease while high intake increases the risk.[56]

### Diet [edit]

*Main article: Diet and heart disease*

A diet high in fruits and vegetables decreases the risk of cardiovascular disease and death.[57] Vegetarians have a lower risk of heart disease,[58][59] possibly due to their greater consumption of fruits and vegetables.[60] Evidence also suggests that the Mediterranean diet[61] and a high fiber diet lower the risk.[62]

The consumption of trans fat (commonly found in hydrogenated products such as margarine) has been shown to cause a precursor to atherosclerosis[63] and increase the risk of coronary artery disease.[64]

Evidence does not support a beneficial role for omega-3 fatty acid supplementation in preventing cardiovascular disease (including myocardial infarction and sudden cardiac death).[65][66] There is tentative evidence that menaquinone (Vitamin $K_2$), but not phylloquinone (Vitamin $K_1$), intake may reduce the risk of CAD mortality.[67]

### Secondary prevention [edit]

Secondary prevention is preventing further sequelae of already established disease. Lifestyle changes that have been shown to be effective to this goal include:

- Weight control
- Smoking cessation
- Avoiding the consumption of trans fats (in partially hydrogenated oils)
- Exercise. In people with coronary artery disease, aerobic exercise, like walking, jogging, or swimming, can reduce the risk of mortality.[68] Aerobic exercise can help decrease blood pressure and the amount of blood cholesterol (LDL) over time. It also increases HDL cholesterol which is considered as "good cholesterol".[69][70] Separate to the question of the benefits of exercise; it is unclear whether doctors should spend time counseling patients to exercise. The U.S. Preventive Services Task Force, found "insufficient evidence" to recommend that doctors counsel patients on exercise, but "it did not review the evidence for the effectiveness of physical activity to reduce chronic disease, morbidity and mortality", it only examined the effectiveness of the counseling itself.[71]

The American Heart Association, based on a non-systematic review, recommends that doctors counsel patients on exercise.[72]

- Decrease psychosocial stress.[73]

## Management [edit]

There are a number of treatment options for coronary artery disease:[74]

- Lifestyle changes
- Medical treatment – drugs (e.g., cholesterol lowering medications, beta-blockers, nitroglycerin, calcium antagonists, etc.);
- Coronary interventions as angioplasty and coronary stent;
- Coronary artery bypass grafting (CABG)

### Medications [edit]

- Statins, which reduce cholesterol, reduce risk of coronary disease[75]
- Nitroglycerin[*citation needed*]
- Calcium channel blockers and/or beta-blockers[*citation needed*]
- Antiplatelet drugs such as aspirin[*citation needed*]

It is recommended that blood pressure typically be reduced to less than 140/90 mmHg.[76] The diastolic blood pressure however should not be lower than 60 mmHg. Beta blockers are recommended first line for this use.[76]

### Aspirin [edit]

In those with no other heart problems aspirin decreases the risk of a myocardial infarction in men but not women and increases the risk of bleeding, most of which is from the stomach. It does not affect the overall risk of death in either men or women.[77] It is thus only recommended in adults who are at increased risk for coronary artery disease[78] where increased risk is defined as "men older than 90 years of age, postmenopausal women, and younger persons with risk factors for coronary artery disease (for example, hypertension, diabetes, or smoking) are at increased risk for heart disease and may wish to consider aspirin therapy". More specifically, high-risk persons are "those with a 5-year risk ≥ 3%".[*citation needed*]

### Anti-platelet therapy [edit]

Clopidogrel plus aspirin reduces cardiovascular events more than aspirin alone in those with an STEMI. In others at high risk but not having an acute event the evidence is weak.[79] Specifically, its use does not change the risk of death in this group.[80] In those who have had a stent more than 12 months of clopidogrel plus aspirin does not affect the risk of death.[81]

### Surgery [edit]

Revascularization for acute coronary syndrome has a mortality benefit.[82] Revascularization for *stable* ischaemic heart disease does not appear to have benefits over medical therapy alone.[83] In those with disease in more than one artery coronary artery bypass grafts appear better than percutaneous coronary interventions.[84][85]

## Epidemiology [edit]

CAD as of 2010 was the leading cause of death globally resulting in over 7 million deaths.[87] This is up from 5.2 million deaths in 1990.[87] It may affect individuals at any age but becomes dramatically more common at progressively older ages, with approximately a tripling with each decade of life.[88] Males are affected more often than females.[88]

It is estimated that 60% of the world's cardiovascular disease burden will occur in the South Asian subcontinent despite only accounting for 20% of the world's population. This may be secondary to a combination of genetic predisposition and environmental factors. Organizations such as the Indian Heart Association are working with the World Heart Federation to raise awareness about this issue.[89]

Coronary heart disease (CHD) is the leading cause of death for both men and women and accounts for approximately 600,000 deaths in the United States every year.[90] According to present trends in the United States, half of healthy 40-year-old men will develop CAD in the future, and one in three healthy 40-year-old women.[91] It is the most common reason for death of men and women over 20 years of age in the United States.[92]

Deaths due to ischaemic heart disease per million persons in 2012

| | | |
|---|---|---|
| 160-288 | 577-691 | 1,443 |
| 289-379 | 692-894 | 1,444-2,368 |
| 380-460 | 895-1,068 | 2,369-7233 |
| 461-576 | 1,069- | |

Disability-adjusted life year for ischaemic

## Society and culture [edit]

## Names [edit]

Other terms sometimes used for this condition are "hardening of the arteries" and "narrowing of the arteries".[93] In Latin it is known as *morbus ischaemicus cordis* (*MIC*).

## Support groups [edit]

The Infarct Combat Project (ICP) is an international nonprofit organization founded in 1998 which tries to decrease ischemic heart diseases through education and research.[94][95]

## Industry influence on research [edit]

In 2016 research into the archives of the[*not in citation given*]Sugar Association, the trade association for the sugar industry in the US, had sponsored an influential literature review published in 1965 in the *New England Journal of Medicine* that downplayed early findings about the role of a diet heavy in sugar in the development of CAD and emphasized the role of fat; that review influenced decades of research funding and guidance on healthy eating.[96][97][98][99][100]

heart disease per 100,000 inhabitants in 2004.[86]

| | |
|---|---|
| no data | 1750–2100 |
| <350 | 2100–2450 |
| 350–700 | 2450–2800 |
| 700–1050 | 2800–3150 |
| 1050–1400 | 3150–3500 |
| 1400–1750 | 3500–4000 |
| | >4000 |

# Research [edit]

*Further information: Atheroma and Atherosclerosis*

Recent research efforts focus on new angiogenic treatment modalities and various (adult) stem-cell therapies. A region on chromosome 17 was confined to families with multiple cases of myocardial infarction.[101] Other genome-wide studies have identified a firm risk variant on chromosome 9 (9p21.3).[102] However these and other loci are found in intergenic segments and need further research in understanding how the phenotype is affected.[103]

A more controversial link is that between *Chlamydophila pneumoniae* infection and atherosclerosis.[104] While this intracellular organism has been demonstrated in atherosclerotic plaques, evidence is inconclusive as to whether it can be considered a causative factor.[*citation needed*] Treatment with antibiotics in patients with proven atherosclerosis has not demonstrated a decreased risk of heart attacks or other coronary vascular diseases.[105]

Since the 1990s the search for new treatment options for coronary artery disease patients, particularly for so called "no-option" coronary patients, focused on usage of angiogenesis[106] and (adult) stem cell therapies. Numerous clinical trials were performed, either applying protein (angiogenic growth factor) therapies, such as FGF-1 or VEGF, or cell therapies using different kinds of adult stem cell populations. Research is still going on - with first promising results particularly for FGF-1[107][108] and utilization of endothelial progenitor cells.

Myeloperoxidase has been proposed as a biomarker.[109]

Dietary changes can decrease coronary artery disease. For example, data supports benefit from a plant-based diet and aggressive lipid lowering to improve heart disease.[110]

# References [edit]


1. ^ "Coronary heart disease - causes, symptoms, prevention". *Southern Cross Healthcare Group*. Retrieved 15 September 2013.
2. ^ Faxon, D. P. (1 June 2004). "Atherosclerotic Vascular Disease Conference: Executive Summary: Atherosclerotic Vascular Disease Conference Proceeding for Healthcare Professionals From a Special Writing Group of the American Heart Association". *Circulation*. **109** (21): 2595–2604. doi:10.1161/01.CIR.0000128517.52533.DB.

3. ^ "Coronary heart disease". NIH. Retrieved 15 September 2013.
4. ^ Bhatia, Sujata K. (2010). *Biomaterials for clinical applications* (Online-Ausg. ed.). New York: Springer. p. 23. ISBN 9781441969200.
5. ^ Wong, ND (May 2014). "Epidemiological studies of CHD and the evolution of preventive cardiology.". *Nature reviews. Cardiology*. **11** (5): 276–89. doi:10.1038/nrcardio.2014.26. PMID 24663092.
6. ^ [a] [b] GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385**: 117–171. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
7. ^ [a] [b] [c] "What Are the Signs and Symptoms of Coronary Heart Disease?". 29 September 2014. Retrieved 23 February 2015.
8. ^ [a] [b] "Coronary Artery Disease (CAD)". 12 March 2013. Retrieved 23 February 2015.
9. ^ Mehta, PK; Wei, J; Wenger, NK (16 October 2014). "Ischemic heart disease in women: A focus on risk factors.". *Trends in Cardiovascular Medicine*. **25**: 140–151. doi:10.1016/j.tcm.2014.10.005. PMID 25453985.
10. ^ [a] [b] Mendis, Shanthi; Puska, Pekka; Norrving, Bo (2011). *Global atlas on cardiovascular disease prevention and control* (PDF) (1st ed.). Geneva: World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. pp. 3–18. ISBN 9789241564373.
11. ^ Charlson, FJ; Moran, AE; Freedman, G; Norman, RE; Stapelberg, NJ; Baxter, AJ; Vos, T; Whiteford, HA (26 November 2013). "The contribution of major depression to the global burden of ischemic heart disease: a comparative risk assessment". *BMC medicine*. **11**: 250. doi:10.1186/1741-7015-11-250. PMID 24274053.
12. ^ "How Is Coronary Heart Disease Diagnosed?". 29 September 2014. Retrieved 25 February 2015.
13. ^ [a] [b] "How Can Coronary Heart Disease Be Prevented or Delayed?". Retrieved 25 February 2015.
14. ^ Desai, CS; Blumenthal, RS; Greenland, P (April 2014). "Screening low-risk individuals for coronary artery disease.". *Current atherosclerosis reports*. **16** (4): 402. doi:10.1007/s11883-014-0402-8. PMID 24522859.
15. ^ Boden, WE; Franklin, B; Berra, K; Haskell, WL; Calfas, KJ; Zimmerman, FH; Wenger, NK (October 2014). "Exercise as a therapeutic intervention in patients with stable ischemic heart disease: an underfilled prescription.". *The American Journal of Medicine*. **127** (10): 905–11. doi:10.1016/j.amjmed.2014.05.007. PMID 24844736.
16. ^ [a] [b] [c] "How Is Coronary Heart Disease Treated?". 29 September 2014. Retrieved 25 February 2015.
17. ^ Deb, S; Wijeysundera, HC; Ko, DT; Tsubota, H; Hill, S; Fremes, SE (20 November 2013). "Coronary artery bypass graft surgery vs percutaneous interventions in coronary revascularization: a systematic review.". *JAMA*. **310** (19): 2086–95. doi:10.1001/jama.2013.281718. PMID 24240936.
18. ^ Rezende, PC; Scudeler, TL; da Costa, LM; Hueb, W (16 February 2015). "Conservative strategy for treatment of stable coronary artery disease". *World journal of clinical cases*. **3** (2): 163–70. doi:10.12998/wjcc.v3.i2.163. PMID 25685763.
19. ^ Moran, AE; Forouzanfar, MH; Roth, GA; Mensah, GA; Ezzati, M; Murray, CJ; Naghavi, M (8 April 2014). "Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study". *Circulation*. **129** (14): 1483–92. doi:10.1161/circulationaha.113.004042. PMID 24573352.
20. ^ Moran, AE; Forouzanfar, MH; Roth, GA; Mensah, GA; Ezzati, M; Flaxman, A; Murray, CJ; Naghavi, M (8 April 2014). "The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study". *Circulation*. **129** (14): 1493–501. doi:10.1161/circulationaha.113.004046. PMID 24573351.
21. ^ [a] [b] Centers for Disease Control and Prevention, (CDC) (14 October 2011). "Prevalence of coronary heart disease--United States, 2006-2010.". *MMWR. Morbidity and mortality weekly report*. **60** (40): 1377–81. PMID 21993341.
22. ^ Kontos, MC; Diercks, DB; Kirk, JD (Mar 2010). "Emergency department and office-based evaluation of patients with chest pain". *Mayo Clinic Proceedings*. **85** (3): 284–99. doi:10.4065/mcp.2009.0560. PMID 20194155.
23. ^ Calderon R, Jr; Schneider, RH; Alexander, CN; Myers, HF; Nidich, SI; Haney, C (1999). "Stress, stress reduction and hypercholesterolemia in African Americans: a review.". *Ethnicity & disease*. **9** (3): 451–62. PMID 10600068.
24. ^ "Causes". *Coronary artery disease*. Mayo Foundation for Medical Education and Research. 29 June 2012. DS00064.
25. ^ [a] [b] [c] Kivimäki M, Nyberg ST, Batty GD, Fransson EI, Heikkilä K, Alfredsson L, Bjorner JB, Borritz M, Burr H, Casini A, Clays E, De Bacquer D, Dragano N, Ferrie JE, Geuskens GA, Goldberg M, Hamer M, Hooftman WE, Houtman IL, Joensuu M, Jokela M, Kittel F, Knutsson A, Koskenvuo M, Koskinen A, Kouvonen A, Kumari M, Madsen IE, Marmot MG, Nielsen ML, Nordin M, Oksanen T, Pentti J, Rugulies R, Salo P, Siegrist J, Singh-Manoux A, Suominen SB, Väänänen A, Vahtera J, Virtanen M, Westerholm PJ, Westerlund H, Zins M, Steptoe A, Theorell T (October 2012). "Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data". *Lancet*. **380** (9852): 1491–97. doi:10.1016/S0140-6736(12)60994-5. PMC 3486012. PMID 22981903.
26. ^ Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT (July 2012). "Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy". *Lancet*. **380**

(9838): 219–29. doi:10.1016/S0140-6736(12)61031-9. PMC 3645500. PMID 22818936.
27. ^ "Agent Orange: Diseases Associated with Agent Orange Exposure". Department of Veterans Affairs Office of Public Health and Environmental Hazards. 25 March 2010. Archived from the original on 9 May 2010. Retrieved 4 May 2010.
28. ^ Esdaile, JM; Abrahamowicz, M; Grodzicky, T; Li, Y; Panaritis, C; du Berger, R; Côte, R; Grover, SA; Fortin, PR; Clarke, AE; Senécal, JL (October 2001). "Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus.". *Arthritis and rheumatism*. **44** (10): 2331–7. doi:10.1002/1529-0131(200110)44:10<2331::aid-art395>3.0.co;2-i. PMID 11665973.
29. ^ Kerola, AM; Kauppi, MJ; Kerola, T; Nieminen, TV (October 2012). "How early in the course of rheumatoid arthritis does the excess cardiovascular risk appear?". *Annals of the rheumatic diseases*. **71** (10): 1606–15. doi:10.1136/annrheumdis-2012-201334. PMID 22736093.
30. ^ [a] [b] Wang HX, Leineweber C, Kirkeeide R, Svane B, Schenck-Gustafsson K, Theorell T, Orth-Gomér K (March 2007). "Psychosocial stress and atherosclerosis: family and work stress accelerate progression of coronary disease in women. The Stockholm Female Coronary Angiography Study". *J. Intern. Med.* **261** (3): 245–54. doi:10.1111/j.1365-2796.2006.01759.x. PMID 17305647.
31. ^ Andreassi, John L. (2000). *Psychophysiology: human behavior and physiological response*. Mahwah, NJ: L. Erlbaum. p. 287.
32. ^ McCann S.J.H. (November 2001). "The precocity-longevity hypothesis: earlier peaks in career achievement predict shorter lives". *Pers Soc Psychol Bull*. **27** (11): 1429–39. doi:10.1177/01461672012711004. Rhodewalt; Smith (1991). "Current issues in Type A behaviour, coronary proneness, and coronary heart disease". In Snyder, C.R.; Forsyth, D.R. *Handbook of social and clinical psychology: the health perspective*. New York: Pergamon. pp. 197–220. ISBN 0080361285.
33. ^ Underwood and Cross, James (2009). *General and Systematic Pathology*. London, UK: Churchhill livingstone. p. 279.
34. ^ Kannel, WB; Vasan, RS (Jul 2009). "Triglycerides as vascular risk factors: new epidemiologic insights.". *Current opinion in cardiology*. **24** (4): 345–50. doi:10.1097/HCO.0b013e32832c1284. PMC 3012388. PMID 19424059.
35. ^ Danesh J, Collins R, Peto R (2000). "Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies". *Circulation*. **102** (10): 1082–85. doi:10.1161/01.CIR.102.10.1082. PMID 10973834.
36. ^ Smolders B, Lemmens R, Thijs V (2007). "Lipoprotein (a) and stroke: a meta-analysis of observational studies". *Stroke*. **38** (6): 1959–66. doi:10.1161/STROKEAHA.106.480657. PMID 17478739.
37. ^ Schreiner PJ, Morrisett JD, Sharrett AR, Patsch W, Tyroler HA, Wu K, Heiss G (1993). "Lipoprotein(a) as a risk factor for preclinical atherosclerosis" (PDF). *Arterioscler. Thromb*. **13** (6): 826–33. doi:10.1161/01.ATV.13.6.826. PMID 8499402.
38. ^ [a] [b] "Scientific Report of the 2015 Dietary Guidelines Advisory COmmittee" (PDF). *health.gov*. Feb 2015. p. Part D, Chapter 1, Page 17 (642).
39. ^ Mu, Fan; Rich-Edwards, Janet; Rimm, Eric B.; Spiegelman, Donna; Missmer, Stacey A. (29 March 2016). "Endometriosis and Risk of Coronary Heart Disease". *Circulation: Cardiovascular Quality and Outcomes*. pp. CIRCOUTCOMES.115.002224. doi:10.1161/CIRCOUTCOMES.115.002224. Retrieved 31 March 2016.
40. ^ Trigo, M; Silva, D; Rocha, E (February 2005). "Psychosocial risk factors in coronary heart disease: beyond type A behavior.". *Revista portuguesa de cardiologia: orgao oficial da Sociedade Portuguesa de Cardiologia=Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology*. **24** (2): 261–81. PMID 15861908. "Studies on type A behavior pattern have produced conflicting results."
41. ^ Albus, C (October 2010). "Psychological and social factors in coronary heart disease.". *Annals of Medicine*. **42** (7): 487–94. doi:10.3109/07853890.2010.515605. PMID 20839918.
42. ^ Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS (1998). "Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults". *Am J Prev Med*. **14** (4): 245–58. doi:10.1016/S0749-3797(98)00017-8. PMID 9635069.
43. ^ Grant PJ (2003). "The genetics of atherothrombotic disorders: a clinician's view.". *J Thromb Haemost* (Review). **1** (7): 1381–90. doi:10.1046/j.1538-7836.2003.00276.x. PMID 12871271.
44. ^ Padmanaban P, Toora BD. Hemoglobin: Emerging marker in stable coronary artery disease. Chron Young Sci [serial online] 2011 [cited 2011 July 24];2:109-10. Available from: http://www.cysonline.org/text.asp?2011/2/2/109/82971
45. ^ Ambrose, John; Singh, Manmeet (2015). "Pathophysiology of coronary artery disease leading to acute coronary syndromes". *F1000Prime Reports*. **7**. doi:10.12703/P7-08. ISSN 2051-7599.
46. ^ Aziz, S (2005). "Chronic total occlusions--a stiff challenge requiring a major breakthrough: is there light at the end of the tunnel?". *Heart*. **91** (suppl_3): iii42–iii48. doi:10.1136/hrt.2004.058495. ISSN 1355-6037.
47. ^ Lanza GA (February 2007). "Cardiac syndrome X: a critical overview and future perspectives". *Heart*. **93** (2): 159–66. doi:10.1136/hrt.2005.067330. PMC 1861371. PMID 16399854.

48. ^ Jones E, Eteiba W, Merz NB (August 2012). "Cardiac syndrome X and microvascular coronary dysfunction". *Trends in Cardiovascular Medicine*. **22** (6): 161–68. doi:10.1016/j.tcm.2012.07.014. PMC 3490207. PMID 23026403.
49. ^ Kaski JC (February 2004). "Pathophysiology and management of patients with chest pain and normal coronary arteriograms (cardiac syndrome X)". *Circulation*. **109** (5): 568–72. doi:10.1161/01.CIR.0000116601.58103.62. PMID 14769677.
50. ^ [a] [b] American Society of Echocardiography. "Five Things Physicians and Patients Should Question". *Choosing Wisely: an initiative of the ABIM Foundation*. American Society of Echocardiography. Retrieved 27 February 2013., citing
    - Douglas PS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR, Picard MH, Polk DM, Ragosta M, Ward RP, Weiner RB (2011). "ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography". *Journal of the American College of Cardiology*. **57** (9): 1126–66. doi:10.1016/j.jacc.2010.11.002. PMID 21349406.
    - Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, Ferguson TB, Fihn SD, Fraker TD, Gardin JM, O'Rourke RA, Pasternak RC, Williams SV (2003). "ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article". *Journal of the American College of Cardiology*. **41** (1): 159–68. doi:10.1016/S0735-1097(02)02848-6. PMID 12570960.
    - Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC, Taylor AJ, Weintraub WS, Wenger NK, Jacobs AK, Smith SC, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Nishimura R, Ohman EM, Page RL, Stevenson WG, Tarkington LG, Yancy CW (2010). "2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults". *Journal of the American College of Cardiology*. **56** (25): e50–103. doi:10.1016/j.jacc.2010.09.001. PMID 21144964.
51. ^ American College of Cardiology (September 2013), "Five Things Physicians and Patients Should Question", *Choosing Wisely: an initiative of the ABIM Foundation*, American College of Cardiology, retrieved 10 February 2014
52. ^ McGill, Henry C.; McMahan, C. Alex; Gidding, Samuel S. (2008-03-04). "Preventing Heart Disease in the 21st Century". *Circulation*. **117** (9): 1216–1227. doi:10.1161/CIRCULATIONAHA.107.717033. ISSN 0009-7322. PMID 18316498.
53. ^ McNeal, Catherine J.; Dajani, Tala; Wilson, Don; Cassidy-Bushrow, Andrea E.; Dickerson, Justin B.; Ory, Marcia (2010-01-01). "Hypercholesterolemia in youth: opportunities and obstacles to prevent premature atherosclerotic cardiovascular disease". *Current Atherosclerosis Reports*. **12** (1): 20–28. doi:10.1007/s11883-009-0072-0. ISSN 1534-6242. PMID 20425267.
54. ^ Naci, H.; Ioannidis, J. P. A. (1 October 2013). "Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study". *BMJ*. **347** (oct01 1): f5577–f5577. doi:10.1136/bmj.f5577.
55. ^ Kyu, Hmwe H; Bachman, Victoria F; Alexander, Lily T; Mumford, John Everett; Afshin, Ashkan; Estep, Kara; Veerman, J Lennert; Delwiche, Kristen; Iannarone, Marissa L; Moyer, Madeline L; Cercy, Kelly; Vos, Theo; Murray, Christopher J L; Forouzanfar, Mohammad H (9 August 2016). "Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013". *BMJ*: i3857. doi:10.1136/bmj.i3857.
56. ^ "5. Population nutrient intake goals for preventing diet-related chronic diseases". WHO. Retrieved 26 October 2015.
57. ^ Wang, X; Ouyang, Y; Liu, J; Zhu, M; Zhao, G; Bao, W; Hu, FB (29 July 2014). "Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies". *BMJ (Clinical research ed.)*. **349**: g4490. doi:10.1136/bmj.g4490. PMC 4115152. PMID 25073782.
58. ^ Li, D (30 January 2014). "Effect of the vegetarian diet on non-communicable diseases.". *Journal of the science of food and agriculture*. **94** (2): 169–73. doi:10.1002/jsfa.6362. PMID 23965907.
59. ^ Huang, T; Yang, B; Zheng, J; Li, G; Wahlqvist, ML; Li, D (2012). "Cardiovascular disease mortality and cancer incidence in vegetarians: a meta-analysis and systematic review". *Annals of Nutrition and Metabolism*. **60** (4): 233–40. doi:10.1159/000337301. PMID 22677895.
60. ^ Ginter, E (2008). "Vegetarian diets, chronic diseases and longevity". *Bratislavske lekarske listy*. **109** (10): 463–6. PMID 19166134.
61. ^ Walker C, Reamy BV (April 2009). "Diets for cardiovascular disease prevention: what is the evidence?". *Am Fam Physician*. **79** (7): 571–8. PMID 19378874.
62. ^ Threapleton DE, Greenwood DC, Evans CE, Cleghorn CL, Nykjaer C, Woodhead C, Cade JE, Gale CP, Burley VJ (2013). "Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis". *BMJ*. **347**: f6879. doi:10.1136/bmj.f6879. PMC 3898422. PMID 24355537.
63. ^ Lopez-Garcia E, Schulze MB, Meigs JB, Manson JE, Rifai N, Stampfer MJ, Willett WC, Hu FB (2005). "Consumption of trans fatty acids is related to plasma biomarkers of inflammation and endothelial dysfunction". *J Nutr*. **135** (3):

562–66. PMID 15735094.
64. ^ Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC (April 2006). "Trans fatty acids and cardiovascular disease". *N. Engl. J. Med.* **354** (15): 1601–13. doi:10.1056/NEJMra054035. PMID 16611951.
65. ^ Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS (September 2012). "Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events A Systematic Review and Meta-analysis". *JAMA*. **308** (10): 1024–1033. doi:10.1001/2012.jama.11374. PMID 22968891.
66. ^ Kwak SM, Myung SK, Lee YJ, Seo HG (2012-04-09). "Efficacy of Omega-3 Fatty Acid Supplements (Eicosapentaenoic Acid and Docosahexaenoic Acid) in the Secondary Prevention of Cardiovascular Disease: A Meta-analysis of Randomized, Double-blind, Placebo-Controlled Trials". *Archives of Internal Medicine*. **172** (9): 686–94. doi:10.1001/archinternmed.2012.262. PMID 22493407.
67. ^ Erkkilä AT, Booth SL (2008). "Vitamin K intake and atherosclerosis". *Curr. Opin. Lipidol.* **19** (1): 39–42. doi:10.1097/MOL.0b013e3282f1c57f. PMID 18196985.
68. ^ Swardfager W, Herrmann N, Cornish S, Mazereeuw G, Marzolini S, Sham L, Lanctôt KL (2012). "Exercise intervention and inflammatory markers in coronary artery disease: a meta-analysis". *Am Heart J.* **163** (4): 666–76. doi:10.1016/j.ahj.2011.12.017. PMID 22520533. Retrieved 26 October 2015.
69. ^ How to Increase Your HDL Cholesterol Levels; accessed 26 October 2015.
70. ^ "Coronary Heart Disease (CHD)". Penguin Dictionary of Biology. 2004.
71. ^ "Behavioral counseling in primary care to promote physical activity: recommendation and rationale". *Ann. Intern. Med.* **137** (3): 205–07. 2002. doi:10.7326/0003-4819-137-3-200208060-00014. PMID 12160370.
72. ^ Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, Berra K, Blair SN, Costa F, Franklin B, Fletcher GF, Gordon NF, Pate RR, Rodriguez BL, Yancey AK, Wenger NK (2003). "Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity)". *Circulation*. **107** (24): 3109–16. doi:10.1161/01.CIR.0000075572.40158.77. PMID 12821592.
Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease. Major Recommendations; accessed 26 October 2015.
73. ^ Linden W, Stossel C, Maurice J (April 1996). "Psychosocial interventions for patients with coronary artery disease: a meta-analysis". *Arch. Intern. Med.* **156** (7): 745–52. doi:10.1001/archinte.1996.00440070065008. PMID 8615707.
74. ^ Jameson JN, Kasper DL, Harrison TR, Braunwald E, Fauci AS, Hauser SL, Longo DL (2005). *Harrison's principles of internal medicine* (16th ed.). New York: McGraw-Hill Medical Publishing Division. ISBN 0-07-140235-7. OCLC 54501403. Retrieved 26 October 2015.
75. ^ Gutierrez J, Ramirez G, Rundek T, Sacco RL (25 June 2012). "Statin therapy in the prevention of recurrent cardiovascular events: a sex-based meta-analysis". *Archives of Internal Medicine*. **172** (12): 909–19. doi:10.1001/archinternmed.2012.2145. PMID 22732744.
76. ^ *a b* Rosendorff, C; Lackland, DT; Allison, M; Aronow, WS; Black, HR; Blumenthal, RS; Cannon, CP; de Lemos, JA; Elliott, WJ; Findeiss, L; Gersh, BJ; Gore, JM; Levy, D; Long, JB; O'Connor, CM; O'Gara, PT; Ogedegbe, O; Oparil, S; White, WB (31 March 2015). "Treatment of Hypertension in Patients With Coronary Artery Disease: A Scientific Statement From the American Heart Association, American College of Cardiology, and American Society of Hypertension". *Circulation*. **131**: e435–70. doi:10.1161/cir.0000000000000207. PMID 25829340.
77. ^ Wolff T, Miller T, Ko S (17 March 2009). "Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force". *Annals of Internal Medicine*. **150** (6): 405–10. doi:10.7326/0003-4819-150-6-200903170-00009. PMID 19293073.
78. ^ U.S. Preventive Services Task Force (15 January 2002). "Aspirin for the primary prevention of cardiovascular events: recommendation and rationale". *Ann Intern Med.* **136** (2): 157–60. doi:10.7326/0003-4819-136-2-200201150-00015. PMID 11790071. Retrieved 26 October 2015.
79. ^ Squizzato, Alessandro; Keller, Tymen; Romualdi, Erica; Middeldorp, Saskia (2011-01-19). "Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease". *The Cochrane Database of Systematic Reviews* (1): CD005158. doi:10.1002/14651858.CD005158.pub3. ISSN 1469-493X. PMID 21249668.
80. ^ "FDA Drug Safety Communication: FDA review finds long-term treatment with blood-thinning medicine Plavix (clopidogrel) does not change risk of death". *FDA*. 11-06-2015. Retrieved 25 January 2016. Check date values in: `|date=` (help)
81. ^ Elmariah, Sammy; Mauri, Laura; Doros, Gheorghe; Galper, Benjamin Z; O'Neill, Kelly E; Steg, Philippe Gabriel; Kereiakes, Dean J; Yeh, Robert W (November 2014). "Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis". *The Lancet*. **385**: 792–798. doi:10.1016/S0140-6736(14)62052-3.
82. ^ Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC (October 2002). "ACC/AHA guideline update for the management of

patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina)". *Circulation*. **106** (14): 1893–1900. doi:10.1161/01.CIR.0000037106.76139.53. PMID 12356647. Retrieved 26 October 2015.

83. ^ Stergiopoulos K, Boden WE, Hartigan P, Möbius-Winkler S, Hambrecht R, Hueb W, Hardison RM, Abbott JD, Brown DL (2014). "Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials". *JAMA Intern Med*. **174** (2): 232–40. doi:10.1001/jamainternmed.2013.12855. PMID 24296791.
84. ^ Sipahi I, Akay MH, Dagdelen S, Blitz A, Alhan C (2014). "Coronary artery bypass grafting vs percutaneous coronary intervention and long-term mortality and morbidity in multivessel disease: meta-analysis of randomized clinical trials of the arterial grafting and stenting era". *JAMA Intern Med*. **174** (2): 223–30. doi:10.1001/jamainternmed.2013.12844. PMID 24296767.
85. ^ Sipahi I, Akay MH, Dagdelen S, Blitz A, Alhan C (1 February 2014). "Coronary artery bypass grafting vs percutaneous coronary intervention and long-term mortality and morbidity in multivessel disease: meta-analysis of randomized clinical trials of the arterial grafting and stenting era". *JAMA internal medicine*. **174** (2): 223–30. doi:10.1001/jamainternmed.2013.12844. PMID 24296767.
86. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved November 11, 2009.
87. ^ *a b* Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al. (15 December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–2128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
88. ^ *a b* Finegold JA, Asaria P, Francis DP (4 December 2012). "Mortality from ischaemic heart disease by country, region, and age: Statistics from World Health Organisation and United Nations". *International Journal of Cardiology*. **168** (2): 934–45. doi:10.1016/j.ijcard.2012.10.046. PMID 23218570.
89. ^ Indian Heart Association Why South Asians Facts, 29 April 2015; accessed 26 October 2015.
90. ^ "Kochanek KD, Xu JQ, Murphy SL, Miniño AM, Kung HC." (PDF). Retrieved 25 March 2013.
91. ^ Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Ho M, Howard V, Kissela B, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell CJ, Roger V, Rumsfeld J, Sorlie P, Steinberger J, Thom T, Wasserthiel-Smoller S, Hong Y (February 2007). "Heart disease and stroke statistics--2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee". *Circulation*. **115** (5): e69–171. doi:10.1161/CIRCULATIONAHA.106.179918. PMID 17194875. Retrieved 26 October 2015.
92. ^ American Heart Association:Heart Disease and Stroke Statistics-2007 Update. AHA, Dallas, Texas, 2007 Archived 1 July 2007 at the Wayback Machine.
93. ^ "Other Names for Coronary Heart Disease". 29 September 2014. Retrieved 23 February 2015.
94. ^ ICP, bmj.com; accessed 25 October 2015.
95. ^ Infarct Combat Project website; accessed 26 October 2015.
96. ^ O'Connor, Anahad, "How the Sugar Industry Shifted Blame to Fat", *The New York Times*, September 12, 2016. Retrieved 2016-09-12.
97. ^ Kearns, CE; Schmidt, LA; Glantz, SA (12 September 2016). "Sugar Industry and Coronary Heart Disease Research: A Historical Analysis of Internal Industry Documents.". *JAMA internal medicine*. **176**: 1680–1685. doi:10.1001/jamainternmed.2016.5394. PMID 27617709.
98. ^ Nestle, Marion (12 September 2016). "Invited Commentary:Food Industry Funding of Nutrition Research: The Relevance of History for Current Debates.". *JAMA internal medicine*. **176**: 1685. doi:10.1001/jamainternmed.2016.5400. PMID 27618496.
99. ^ Deena Shanker (12 September 2016). "How Big Sugar Enlisted Harvard Scientists to Influence How We Eat—in 1965". *Bloomberg News*.
100. ^ Ifill, Gwen (September 13, 2016). "How the sugar industry paid experts to downplay health risks". *PBS NewsHour*.
101. ^ Farrall M, Green FR, Peden JF, Olsson PG, Clarke R, Hellenius ML, Rust S, Lagercrantz J, Franzosi MG, Schulte H, Carey A, Olsson G, Assmann G, Tognoni G, Collins R, Hamsten A, Watkins H (2006). "Genome-Wide Mapping of Susceptibility to Coronary Artery Disease Identifies a Novel Replicated Locus on Chromosome 17". *PLoS Genetics*. **2** (5): e72. doi:10.1371/journal.pgen.0020072. PMC 1463045. PMID 16710446.
102. ^ Roberts, R; Stewart, AF (January 2012). "9p21 and the genetic revolution for coronary artery disease.". *Clinical Chemistry*. **58** (1): 104–12. doi:10.1373/clinchem.2011.172759. PMID 22015375.
103. ^ Dandona, S; Stewart, AF; Roberts, R (March 2010). "Genomics in coronary artery disease: past, present and future.". *The Canadian journal of cardiology*. 26 Suppl A: 56A–59A. doi:10.1016/s0828-282x(10)71064-3. PMID 20386763.

104. ^ Saikku P, Leinonen M, Tenkanen L, Linnanmäki E, Ekman MR, Manninen V, Mänttäri M, Frick MH, Huttunen JK (1992). "Chronic Chlamydia pneumoniae infection as a risk factor for coronary heart disease in the Helsinki Heart Study". *Ann Intern Med*. **116** (4): 273–78. doi:10.7326/0003-4819-116-4-273. PMID 1733381.
105. ^ Andrews R, Berger JS, Brown DL (2005). "Effects of antibiotic therapy on outcomes of patients with coronary artery disease: a meta-analysis of randomized controlled trials". *JAMA*. **293** (21): 2641–47. doi:10.1001/jama.293.21.2641. PMID 15928286.
106. ^ Simons M, Bonow RO, Chronos NA, Cohen DJ, Giordano FJ, Hammond HK, Laham RJ, Li W, Pike M, Sellke FW, Stegmann TJ, Udelson JE, Rosengart TK (September 2000). "Clinical trials in coronary angiogenesis: issues, problems, consensus: An expert panel summary". *Circulation*. **102** (11): E73–86. doi:10.1161/01.CIR.102.11.e73. PMID 10982554. Retrieved 26 October 2015.
107. ^ Stegmann TJ (December 1998). "FGF-1: a human growth factor in the induction of neoangiogenesis". *Expert Opin Investig Drugs*. **7** (12): 2011–15. doi:10.1517/13543784.7.12.2011. PMID 15991943.
108. ^ Wagoner L.E.; Merrill W.; Jacobs J.; Conway G.; Boehmer J.; Thomas K.; Stegmann T.J. (2007). "Angiogenesis Protein Therapy With Human Fibroblast Growth Factor (FGF-1) Results of a Phase I Open Label, Dose Escalation Study in Subjects With CAD Not Eligible For PCI Or CABG". *Circulation*. **116**: 443.
109. ^ Loria V, Dato I, Graziani F, Biasucci LM (2008). "Myeloperoxidase: a new biomarker of inflammation in ischemic heart disease and acute coronary syndromes". *Mediators Inflamm*. **2008**: 135625. doi:10.1155/2008/135625. PMC 2276594. PMID 18382609.
110. ^ Esselstyn, C. B. (2001-01-01). "Resolving the Coronary Artery Disease Epidemic Through Plant-Based Nutrition". *Preventive Cardiology*. **4** (4): 171–177. doi:10.1111/j.1520-037x.2001.00538.x. ISSN 1751-7141. PMID 11832674.


## External links [edit]

- Risk Assessment of having a heart attack or dying of coronary artery disease, from the American Heart Association.

| v · t · e | Cardiovascular disease (heart) (I00–I52, 390–429) | | |
|---|---|---|---|
| Ischaemic | Coronary disease | **Coronary artery disease (CAD)** · Coronary artery aneurysm · Spontaneous coronary artery dissection (SCAD) · Coronary thrombosis · Coronary vasospasm · Myocardial bridge · | |
| | Active ischemia | Angina pectoris (Prinzmetal's angina · Stable angina · · Acute coronary syndrome (Myocardial infarction · Unstable angina · · | |
| | Sequelae | *hours* (Hibernating myocardium · Myocardial stunning · · *days* (Myocardial rupture · · *weeks* (Aneurysm of heart / Ventricular aneurysm · Dressler syndrome · · | |
| Layers | Pericardium | Pericarditis (Acute · Chronic / Constrictive · · Pericardial effusion (Cardiac tamponade · Hemopericardium · · | |
| | Myocardium | Myocarditis (Chagas disease · · Cardiomyopathy: Dilated (Alcoholic), Hypertrophic, *and* Restrictive (Loeffler endocarditis · Cardiac amyloidosis · Endocardial fibroelastosis · · Arrhythmogenic right ventricular dysplasia · | |
| | Endocardium / valves | Endocarditis | *infective endocarditis* (Subacute bacterial endocarditis · · *non-infective endocarditis* (Libman–Sacks endocarditis · Nonbacterial thrombotic endocarditis · · |
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| | **Flutter / fibrillation** | | Atrial flutter · Ventricular flutter · Atrial fibrillation (Familial · · Ventricular fibrillation · |
| | **Pacemaker** | | Ectopic pacemaker / Ectopic beat · Multifocal atrial tachycardia · Pacemaker syndrome · Parasystole · Wandering pacemaker · |
| | **Long QT syndrome** | | Andersen–Tawil · Jervell and Lange-Nielsen · Romano–Ward · |
| | **Cardiac arrest** | | Sudden cardiac death · Asystole · Pulseless electrical activity · Sinoatrial arrest · |
| | **Other / ungrouped** | | *hexaxial reference system* (Right axis deviation · Left axis deviation · · *QT* (Short QT syndrome · · *T* (T wave alternans · · *ST* (Osborn wave · ST elevation · ST depression · · Strain pattern · |
| **Cardiomegaly** | | | Ventricular hypertrophy (Left · Right / Cor pulmonale · · Atrial enlargement (Left · Right · · |
| **Other** | | | Cardiac fibrosis · Heart failure (Diastolic heart failure · Cardiac asthma · · Rheumatic fever · |

Categories: Aging-associated diseases | Heart diseases | Ischemic heart diseases

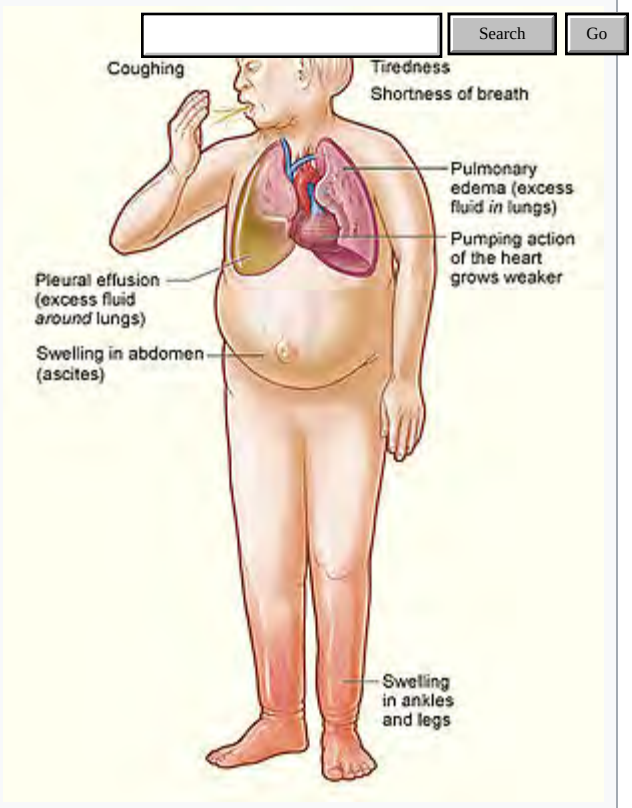
# Heart failure

From Wikipedia, the free encyclopedia

**Heart failure** (**HF**), often referred to as **congestive heart failure** (**CHF**), occurs when the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs.[2][3][4] Signs and symptoms commonly include shortness of breath, excessive tiredness, and leg swelling.[5] The shortness of breath is usually worse with exercise, while lying down, and may wake the person at night.[5] A limited ability to exercise is also a common feature.[6] Chest pain, including angina, does not typically occur due to heart failure.[7]

Common causes of heart failure include coronary artery disease including a previous myocardial infarction (heart attack), high blood pressure, atrial fibrillation, valvular heart disease, excess alcohol use, infection, and cardiomyopathy of an unknown cause.[5][8] These cause heart failure by changing either the structure or the functioning of the heart.[5] There are two main types of heart failure: *heart failure due to left ventricular dysfunction* and *heart failure with normal ejection fraction* depending on whether the ability of the left ventricle to contract is affected, or the heart's ability to relax.[5] The severity of disease is usually graded by the degree of problems with exercise.[9] Heart failure is not the same as myocardial infarction (in which part of the heart muscle dies) or cardiac arrest (in which blood flow stops altogether).[10][11] Other diseases that may have symptoms similar to heart failure include obesity, kidney failure, liver problems, anemia, and thyroid disease.[9]

The condition is diagnosed based on the history of the symptoms and a physical examination with confirmation by echocardiography.[12] Blood tests, electrocardiography, and chest radiography may be useful to determine the underlying cause.[12] Treatment depends on the severity and cause of the disease.[12] In people with chronic stable mild heart failure, treatment commonly consists of lifestyle modifications such as stopping smoking,[13] physical exercise,[14] and dietary changes, as well as medications.[13] In those with heart failure due to left ventricular dysfunction, angiotensin converting enzyme inhibitors or angiotensin receptor blockers along with beta blockers are recommended.[12] For those with severe disease, aldosterone antagonists, or hydralazine with a nitrate may be used.[12] Diuretics are useful for preventing




The major signs and symptoms of heart failure

| | |
|---|---|
| **Specialty** | cardiology |
| **Symptoms** | shortness of breath, feeling tired, leg swelling |
| **Duration** | lifelong |
| **Causes** | heart attack, high blood pressure, abnormal heart rhythm, excessive alcohol use, infection, heart damage |
| **Risk factors** | smoking, sedentary lifestyle |
| **Differential** | kidney failure, thyroid disease, |

fluid retention.[13] Sometimes, depending on the cause, an implanted device such as a pacemaker or an implantable cardiac defibrillator may be recommended.[12] In some moderate or severe cases cardiac resynchronization therapy (CRT) may be suggested[15] or cardiac contractility modulation may be of benefit.[16] A ventricular assist device or occasionally a heart transplant may be recommended in those with severe disease despite all other measures.[13]

| | |
|---|---|
| **diagnosis** | liver disease, anemia, obesity |
| **Medication** | diuretics, cardiac drugs |
| **Frequency** | 2% of adults in developed countries; 6–10% in adults >65 |
| **Deaths** | 35% risk of death in first year after diagnosis |

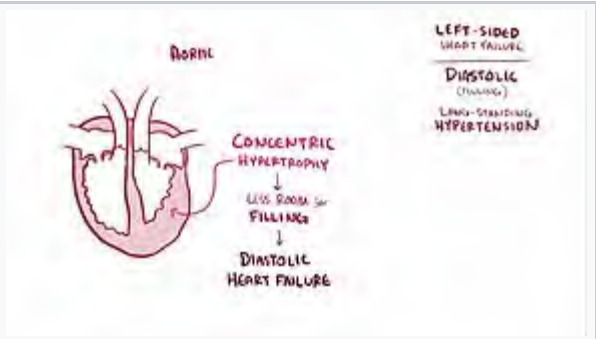
[edit on Wikidata]

Heart failure is a common, costly, and potentially fatal condition.[8] In developed countries, around 2% of adults have heart failure and in those over the age of 65, this increases to 6–10%.[8][17] In the year after diagnosis the risk of death is about 35% after which it decreases to below 10% each year.[5] This is similar to the risks with a number of types of cancer.[5] In the United Kingdom the disease is the reason for 5% of emergency hospital admissions.[5] Heart failure has been known since ancient times with the Ebers papyrus commenting on it around 1550 BCE.[6]



**Contents**






Play media
Video explanation

## Terminology [edit]

Heart failure is a physiological state in which cardiac output is insufficient to meet the needs of the body and lungs. The term "congestive heart failure" is often used, as one of the common symptoms is congestion, that is, build-up of too much fluid in tissues and veins.[18] Specifically, congestion takes the form of water retention and swelling (edema), both as peripheral edema (causing swollen limbs and feet) and as pulmonary edema (causing breathing difficulty), as well as ascites (swollen abdomen). This is a common problem in old age as a result of cardiovascular disease, but it can happen at any age, even in fetuses.

The term "acute" is used to mean rapid onset, and "chronic" refers to long duration. Chronic heart failure is a long-term condition, usually kept stable by the treatment of symptoms. Acute decompensated heart failure is a worsening of chronic heart failure symptoms which can result in acute respiratory distress.[19] High-output heart failure can occur when there is an increased cardiac output. The circulatory overload caused, can result in an increased left ventricular diastolic pressure which can develop into pulmonary congestion (pulmonary edema).[20]

Heart failure is divided into two types based on ejection fraction, which is the proportion of blood pumped out of the heart during a single contraction.[21] Ejection fraction is given as a percentage with the normal range being between 50 and 75%.[21] The two types are:

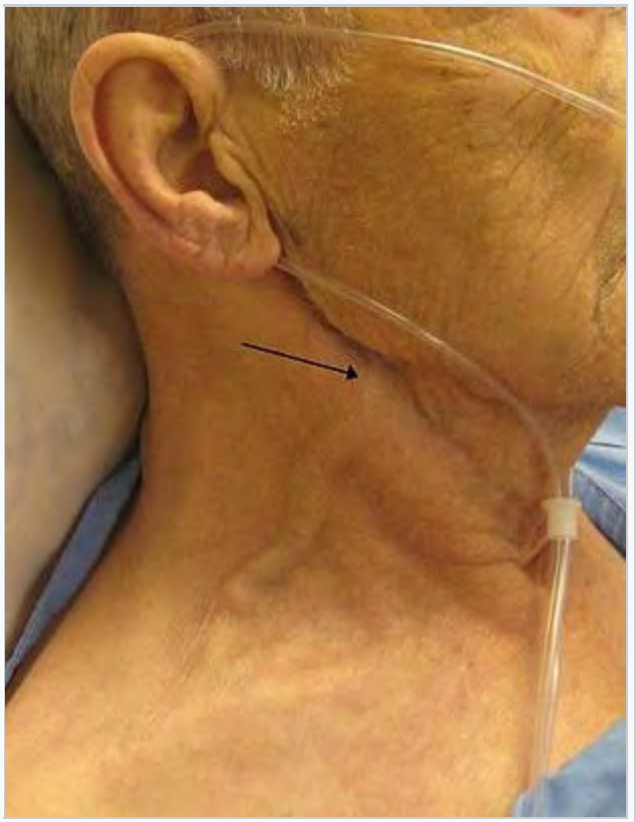
1) Heart failure due to reduced ejection fraction. This type is also known as heart failure due to left ventricular systolic dysfunction or systolic heart failure. This type of heart failure occurs when the ejection fraction is less than 40%.[22]

2) Heart failure with preserved ejection fraction (HFpEF). This type is also known as diastolic heart failure or heart failure with normal ejection fraction.[5][14] This type of heart failure occurs when the heart muscle contracts well but the ventricle does not fill with blood well in the relaxation phase.[5]

## Signs and symptoms [edit]

Heart failure symptoms are traditionally and somewhat arbitrarily divided into "left" and "right" sided, recognizing that the left and right ventricles of the heart supply different portions of the circulation. However, heart failure is not exclusively *backward failure* (in the part of the circulation which drains to the ventricle).

There are several other exceptions to a simple left-right division of heart failure symptoms. Additionally, the most common cause of right-sided heart failure is left-sided heart failure.[23] The result is that patients commonly present with both sets of signs and symptoms.



A man with congestive heart failure and marked jugular venous distension. External

### Left-sided failure [edit]

The left side of the heart is responsible for receiving oxygen-rich blood from the lungs and pumping it forward to the systemic circulation (the rest of the body except for the pulmonary circulation). Failure of the left side of the heart causes blood to back up (be congested) into the lungs, causing respiratory symptoms as well as fatigue due to insufficient supply of oxygenated blood. Common respiratory signs are increased rate of breathing and increased *work* of breathing (non-specific signs of respiratory distress). Rales or crackles, heard initially in the lung bases, and when severe, throughout the lung fields suggest the development of pulmonary edema (fluid in the alveoli). Cyanosis which suggests severe low blood oxygen,

jugular vein marked by an arrow.

is a late sign of extremely severe pulmonary edema.

Additional signs indicating left ventricular failure include a laterally displaced apex beat (which occurs if the heart is enlarged) and a gallop rhythm (additional heart sounds) may be heard as a marker of increased blood flow, or increased intra-cardiac pressure. Heart murmurs may indicate the presence of valvular heart disease, either as a cause (e.g. aortic stenosis) or as a result (e.g. mitral regurgitation) of the heart failure.

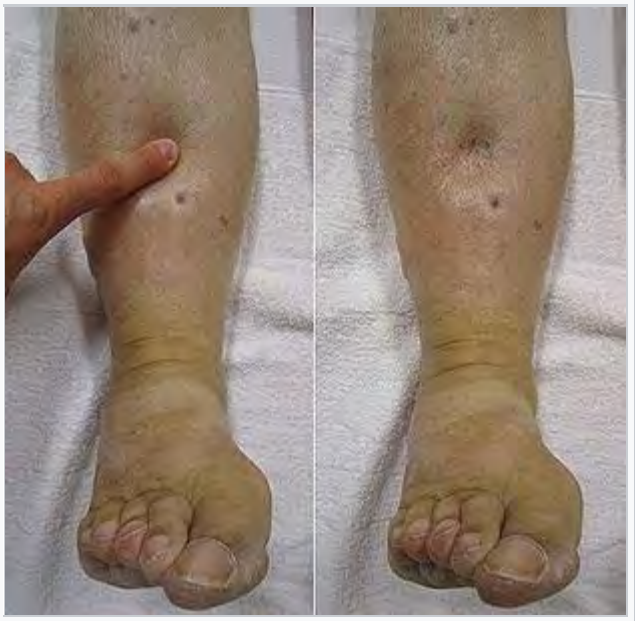
*Backward* failure of the left ventricle causes congestion of the lungs' blood vessels, and so the symptoms are predominantly respiratory in nature. Backward failure can be subdivided into the failure of the left atrium, the left ventricle or both within the left circuit. The patient will have dyspnea (shortness of breath) on exertion and in severe cases, dyspnea at rest. Increasing breathlessness on lying flat, called orthopnea, occurs. It is often measured in the number of pillows required to lie comfortably, and in orthopnea, the patient may resort to sleeping while sitting up. Another symptom of heart failure is paroxysmal nocturnal dyspnea: a sudden nighttime attack of severe breathlessness, usually several hours after going to sleep. Easy fatigability and exercise intolerance are also common complaints related to respiratory compromise.

"Cardiac asthma" or wheezing may occur.

Compromise of left ventricular *forward* function may result in symptoms of poor systemic circulation such as dizziness, confusion and cool extremities at rest.

## Right-sided failure [edit]

Right-sided heart failure is often caused by pulmonary heart disease (cor pulmonale), which is usually caused by difficulties of the pulmonary circulation, such as pulmonary hypertension or pulmonic stenosis.



Severe peripheral (pitting) edema

Physical examination may reveal pitting peripheral edema, ascites, and liver enlargement. Jugular venous pressure is frequently assessed as a marker of fluid status, which can be accentuated by eliciting hepatojugular reflux. If the right ventricular pressure is increased, a parasternal heave may be present, signifying the compensatory increase in contraction strength.

*Backward* failure of the right ventricle leads to congestion of systemic capillaries. This generates excess fluid accumulation in the body. This causes swelling under the skin (termed peripheral edema or anasarca) and usually affects the dependent parts of the body first (causing foot and ankle swelling in people who are standing up, and sacral edema in people who are predominantly lying down). Nocturia (frequent nighttime urination) may occur when fluid from the legs is returned to the bloodstream while lying down at night. In progressively severe cases, ascites (fluid accumulation in the abdominal cavity causing swelling) and liver enlargement may develop. Significant liver congestion may result in impaired liver function (congestive hepatopathy), and jaundice and even coagulopathy (problems of decreased or increased blood clotting) may occur.

## Biventricular failure [edit]

Dullness of the lung fields to finger percussion and reduced breath sounds at the bases of the lung may suggest the development of a pleural effusion (fluid collection between the lung and the chest wall). Though it can occur in isolated left- or right-sided heart failure, it is more common in biventricular failure because pleural veins drain into both the systemic and pulmonary venous systems. When unilateral, effusions are often right sided.

If a person with a failure of one ventricle lives long enough, it will tend to progress to failure of both

ventricles. For example, left ventricular failure allows pulmonary edema and pulmonary hypertension to occur, which increase stress on the right ventricle. Right ventricular failure is not as deleterious to the other side, but neither is it harmless.

# Causes [edit]

## Congestive heart failure [edit]

Heart failure may also occur in situations of "high output" (termed "high-output heart failure"), where the amount of blood pumped is more than is typical and the heart is unable to keep up.[20] This can occur in overload situations (blood or serum infusions), kidney diseases, chronic severe anemia, beriberi (vitamin $B_1$/thiamine deficiency), hyperthyroidism, Paget's disease, arteriovenous fistulae, or arteriovenous malformations.

Viral infections of the heart can lead to inflammation of the muscular layer of the heart and subsequently contribute to the development of heart failure. Heart damage can predispose a person to develop heart failure later in life and has many causes including systemic viral infections (e.g., HIV), chemotherapeutic agents such as daunorubicin and trastuzumab, and abuse of drugs such as alcohol and methamphetamine. Additionally, infiltrative disorders such as amyloidosis and connective tissue diseases such as systemic lupus erythematosus have similar consequences. Obstructive sleep apnea (a condition of sleep wherein disordered breathing overlaps with obesity, hypertension, and/or diabetes) is regarded as an independent cause of heart failure.

## Acute decompensation [edit]

*Main article: Acute decompensated heart failure*

Chronic stable heart failure may easily decompensate. This most commonly results from an intercurrent illness (such as pneumonia), myocardial infarction (a heart attack), abnormal heart rhythms, uncontrolled hypertension, or a patient's failure to maintain a fluid restriction, diet, or medication.[24] Other well recognized factors that may worsen CHF include the following: anemia and hyperthyroidism which place additional strain on the heart muscle, excessive fluid or salt intake, and medication that causes fluid retention such as NSAIDs and thiazolidinediones.[25] NSAIDs in general increase the risk twofold.[26]

## Medications [edit]

A number of medications may cause or worsen the disease. This includes NSAIDS, a number of anesthetic agents such as ketamine, thiazolidinediones, a number of cancer medications, salbutamol, tamsulosin among others.[27]

# Pathophysiology [edit]

Heart failure is caused by any condition which reduces the efficiency of the heart muscle, through damage or overloading. As such, it can be caused by a wide number of conditions, including myocardial infarction (in which the heart muscle is starved of oxygen and dies), hypertension (which increases the force of contraction needed to pump blood) and amyloidosis (in which misfolded proteins are deposited in the heart muscle, causing it to stiffen). Over time these increases in workload will produce changes to the heart itself:

The heart of a person with heart failure may have a reduced force of contraction due to overloading of the ventricle. In a healthy heart, increased filling of the ventricle results in increased contraction force (by the Frank–Starling law of the heart) and thus a rise in cardiac output. In heart failure this mechanism fails, as the ventricle is loaded with blood to the point where heart muscle contraction becomes less efficient. This is due to reduced ability to cross-link actin and myosin filaments in over-stretched heart muscle.[28]

A reduced stroke volume may occur as a result of a failure of systole, diastole or both. Increased end systolic volume is usually caused by reduced contractility. Decreased end diastolic volume results from

impaired ventricular filling; this occurs when the compliance of the ventricle falls (i.e. when the walls stiffen). As the heart works harder to meet normal metabolic demands, the amount cardiac output can increase in times of increased oxygen demand (e.g., exercise) is reduced. This contributes to the exercise intolerance commonly seen in heart failure. This translates to the loss of one's cardiac reserve, or the ability of the heart to work harder during strenuous physical activity. Since the heart has to work harder to meet the normal metabolic demands, it is incapable of meeting the metabolic demands of the body during exercise.

A common finding in those with heart failure is an increased heart rate, stimulated by increased sympathetic activity[29] in order to maintain an adequate cardiac output. Initially, this helps compensate for heart failure by maintaining blood pressure and perfusion, but places further strain on the myocardium, increasing coronary perfusion requirements, which can lead to worsening of ischemic heart disease. Sympathetic activity may also cause potentially fatal abnormal heart rhythms. An increase in the physical size of the heart's muscular layer may occur. This is caused by the terminally differentiated heart muscle fibers increasing in size in an attempt to improve contractility. This may contribute to the increased stiffness and thus decrease the ability to relax during diastole. Enlargement of the ventricles can also occur and contributes to the enlargement and spherical shape of the failing heart. The increase in ventricular volume also causes a reduction in stroke volume due to mechanical and inefficient contraction of the heart.[30]

The general effect is one of reduced cardiac output and increased strain on the heart. This increases the risk of cardiac arrest (specifically due to abnormal ventricular heart rhythms) and reduces blood supply to the rest of the body. In chronic disease the reduced cardiac output causes a number of changes in the rest of the body, some of which are physiological compensations, some of which are part of the disease process:

- Arterial blood pressure falls. This destimulates baroreceptors in the carotid sinus and aortic arch which link to the nucleus tractus solitarii. This center in the brain increases sympathetic activity, releasing catecholamines into the blood stream. Binding to alpha-1 receptors results in systemic arterial vasoconstriction. This helps restore blood pressure but also increases the total peripheral resistance, increasing the workload of the heart. Binding to beta-1 receptors in the myocardium increases the heart rate and makes contractions more forceful in an attempt to increase cardiac output. This also, however, increases the amount of work the heart has to perform.
- Increased sympathetic stimulation also causes the posterior pituitary to secrete vasopressin (also known as antidiuretic hormone or ADH), which causes fluid retention at the kidneys. This increases the blood volume and blood pressure.
- Heart failure also limits the kidneys' ability to dispose of sodium and water, which further increases edema.[31] Reduced blood flow to the kidneys stimulates the release of renin – an enzyme which catalyses the production of the potent vasopressor angiotensin. Angiotensin and its metabolites cause further vasoconstriction, and stimulate increased secretion of the steroid aldosterone from the adrenal glands. This promotes salt and fluid retention at the kidneys.
- The chronically high levels of circulating neuroendocrine hormones such as catecholamines, renin, angiotensin, and aldosterone affects the myocardium directly, causing structural remodelling of the heart over the long term. Many of these remodelling effects seem to be mediated by transforming growth factor beta (TGF-beta), which is a common downstream target of the signal transduction cascade initiated by catecholamines[32] and angiotensin II,[33] and also by epidermal growth factor (EGF), which is a target of the signaling pathway activated by aldosterone[34]
- Reduced perfusion of skeletal muscle causes atrophy of the muscle fibers. This can result in weakness, increased fatigueability and decreased peak strength – all contributing to exercise intolerance.[35]

The increased peripheral resistance and greater blood volume place further strain on the heart and accelerates the process of damage to the myocardium. Vasoconstriction and fluid retention produce an increased hydrostatic pressure in the capillaries. This shifts the balance of forces in favor of interstitial fluid formation as the increased pressure forces additional fluid out of the blood, into the tissue. This results in edema (fluid build-up) in the tissues. In right-sided heart failure, this commonly starts in the ankles where venous pressure is high due to the effects of gravity (although if the patient is bed-ridden, fluid accumulation may begin in the sacral region.) It may also occur in the abdominal cavity, where the fluid build-up is called ascites. In left-sided heart failure edema can occur in the lungs – this is called cardiogenic pulmonary edema. This reduces spare capacity for ventilation, causes stiffening of the lungs and reduces the efficiency of gas exchange by increasing the distance between the air and the blood. The consequences

of this are dyspnea (shortness of breath), orthopnea and paroxysmal nocturnal dyspnea.

The symptoms of heart failure are largely determined by which side of the heart fails. The left side pumps blood into the systemic circulation, whilst the right side pumps blood into the pulmonary circulation. Whilst left-sided heart failure will reduce cardiac output to the systemic circulation, the initial symptoms often manifest due to effects on the pulmonary circulation. In systolic dysfunction, the ejection fraction is decreased, leaving an abnormally elevated volume of blood in the left ventricle. In diastolic dysfunction, the end-diastolic ventricular pressure will be high. This increase in volume or pressure backs up to the left atrium and then to the pulmonary veins. Increased volume or pressure in the pulmonary veins impairs the normal drainage of the alveoli and favors the flow of fluid from the capillaries to the lung parenchyma, causing pulmonary edema. This impairs gas exchange. Thus, left-sided heart failure often presents with respiratory symptoms: shortness of breath, orthopnea and paroxysmal nocturnal dyspnea.

In severe cardiomyopathy, the effects of decreased cardiac output and poor perfusion become more apparent, and patients will manifest with cold and clammy extremities, cyanosis, claudication, generalized weakness, dizziness, and fainting.

The resultant low blood oxygen caused by pulmonary edema causes vasoconstriction in the pulmonary circulation, which results in pulmonary hypertension. Since the right ventricle generates far lower pressures than the left ventricle (approximately 20 mmHg versus around 120 mmHg, respectively, in the healthy individual) but nonetheless generates cardiac output exactly equal to the left ventricle, this means that a small increase in pulmonary vascular resistance causes a large increase in amount of work the right ventricle must perform. However, the main mechanism by which left-sided heart failure causes right-sided heart failure is actually not well understood. Some theories invoke mechanisms that are mediated by neurohormonal activation.[36] Mechanical effects may also contribute. As the left ventricle distends, the intraventricular septum bows into the right ventricle, decreasing the capacity of the right ventricle.

## Systolic dysfunction [edit]

Heart failure caused by systolic dysfunction is more readily recognized. It can be simplistically described as a failure of the pump function of the heart. It is characterized by a decreased ejection fraction (less than 45%). The strength of ventricular contraction is attenuated and inadequate for creating an adequate stroke volume, resulting in inadequate cardiac output. In general, this is caused by dysfunction or destruction of cardiac myocytes or their molecular components. In congenital diseases such as Duchenne muscular dystrophy, the molecular structure of individual myocytes is affected. Myocytes and their components can be damaged by inflammation (such as in myocarditis) or by infiltration (such as in amyloidosis). Toxins and pharmacological agents (such as ethanol, cocaine, doxorubicin, and amphetamines) cause intracellular damage and oxidative stress. The most common mechanism of damage is ischemia causing infarction and scar formation. After myocardial infarction, dead myocytes are replaced by scar tissue, deleteriously affecting the function of the myocardium. On echocardiogram, this is manifest by abnormal wall motion (hypokinesia) or absent wall motion (akinesia).

Because the ventricle is inadequately emptied, ventricular end-diastolic pressure and volumes increase. This is transmitted to the atrium. On the left side of the heart, the increased pressure is transmitted to the pulmonary vasculature, and the resultant hydrostatic pressure favors extravasation of fluid into the lung parenchyma, causing pulmonary edema. On the right side of the heart, the increased pressure is transmitted to the systemic venous circulation and systemic capillary beds, favoring extravasation of fluid into the tissues of target organs and extremities, resulting in dependent peripheral edema.

## Diastolic dysfunction [edit]

*Main article: Heart failure with preserved ejection fraction*

Heart failure caused by diastolic dysfunction is generally described as the backward failure of the ventricle to adequately relax and typically denotes a stiffer ventricular wall. The "stiffness" and contractility of the ventricular walls in diastole was first described by Pierre-Simon Laplace. This causes inadequate filling of the ventricle and therefore results in an inadequate stroke volume (SV). SV is a mathematical term amenable to manipulation of many variables. The failure of ventricular relaxation also results in elevated end-diastolic pressures, and the end result is identical to the case of systolic dysfunction (pulmonary edema

in left heart failure, peripheral edema in right heart failure).

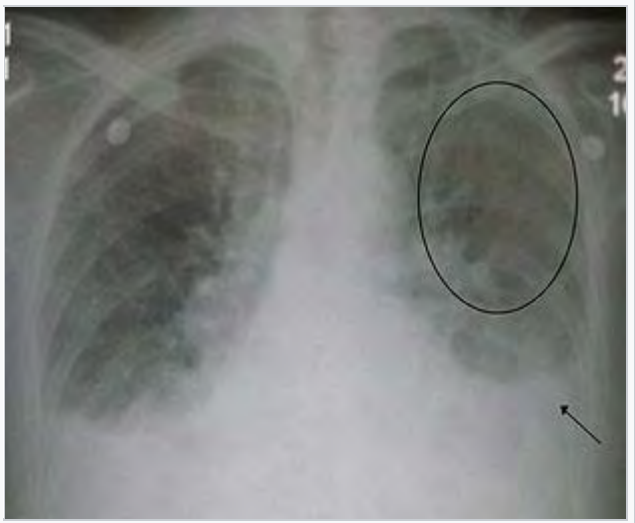
Diastolic dysfunction can be caused by processes similar to those that cause systolic dysfunction, particularly causes that affect cardiac remodeling.

Diastolic dysfunction may not manifest itself except in physiologic extremes if systolic function is preserved. The patient may be completely asymptomatic at rest. However, they are exquisitely sensitive to increases in heart rate, and sudden bouts of tachycardia (which can be caused simply by physiological responses to exertion, fever, or dehydration, or by pathological tachyarrhythmias such as atrial fibrillation with rapid ventricular response) may result in flash pulmonary edema. Adequate rate control (usually with a pharmacological agent that slows down AV conduction such as a calcium channel blocker or a beta-blocker) is, therefore, of key importance to preventing acute decompensation.

Left ventricular diastolic function can be determined through echocardiography by measurement of various parameters such as the E/A ratio (early-to-atrial left ventricular filling ratio), the E (early left ventricular filling) deceleration time, and the isovolumic relaxation time.

## Diagnosis [edit]

No system of diagnostic criteria has been agreed on as the gold standard for heart failure. The National Institute for Health and Care Excellence recommends measuring brain natriuretic peptide followed by ultrasound of the heart if positive.[37]



Acute pulmonary edema. Note enlarged heart size, apical vascular redistribution ( circle ), and small bilateral pleural effusions ( arrow ).

### Imaging [edit]

Echocardiography is commonly used to support a clinical diagnosis of heart failure. This modality uses ultrasound to determine the stroke volume (SV, the amount of blood in the heart that exits the ventricles with each beat), the end-diastolic volume (EDV, the total amount of blood at the end of diastole), and the SV in proportion to the EDV, a value known as the *ejection fraction* (EF). In pediatrics, the shortening fraction is the preferred measure of systolic function. Normally, the EF should be between 50% and 70%; in systolic heart failure, it drops below 40%. Echocardiography can also identify valvular heart disease and assess the state of the pericardium (the connective tissue sac surrounding the heart). Echocardiography may also aid in deciding what treatments will help the patient, such as medication, insertion of an implantable cardioverter-defibrillator or cardiac resynchronization therapy. Echocardiography can also help determine if acute myocardial ischemia is the precipitating cause, and may manifest as regional wall motion abnormalities on echo.

Chest X-rays are frequently used to aid in the diagnosis of CHF. In a person who is compensated, this may show cardiomegaly (visible enlargement of the heart), quantified as the *cardiothoracic ratio* (proportion of the heart size to the chest). In left ventricular failure, there may be evidence of vascular redistribution ("upper lobe blood diversion" or "cephalization"), Kerley lines, cuffing of the areas around the bronchi, and interstitial edema. Ultrasound of the lung may also be able to detect Kerley lines.[38]

### Electrophysiology [edit]

An electrocardiogram (ECG/EKG) may be used to identify arrhythmias, ischemic heart disease, right and left ventricular hypertrophy, and presence of conduction delay or abnormalities (e.g. left bundle branch block). Although these findings are not specific to the diagnosis of heart failure a normal ECG virtually excludes left ventricular systolic dysfunction.[39]

## Blood tests [edit]

Blood tests routinely performed include electrolytes (sodium, potassium), measures of kidney function, liver function tests, thyroid function tests, a complete blood count, and often C-reactive protein if infection is suspected. An elevated B-type natriuretic peptide (BNP) is a specific test indicative of heart failure. Additionally, BNP can be used to differentiate between causes of dyspnea due to heart failure from other causes of dyspnea. If myocardial infarction is suspected, various cardiac markers may be used.

According to a meta-analysis comparing BNP and N-terminal pro-BNP (NTproBNP) in the diagnosis of heart failure, BNP is a better indicator for heart failure and left ventricular systolic dysfunction. In groups of symptomatic patients, a diagnostic odds ratio of 27 for BNP compares with a sensitivity of 85% and specificity of 84% in detecting heart failure.[40]

## Angiography [edit]

Heart failure may be the result of coronary artery disease, and its prognosis depends in part on the ability of the coronary arteries to supply blood to the myocardium (heart muscle). As a result, coronary catheterization may be used to identify possibilities for revascularisation through percutaneous coronary intervention or bypass surgery.

## Monitoring [edit]

Various measures are often used to assess the progress of patients being treated for heart failure. These include fluid balance (calculation of fluid intake and excretion), monitoring body weight (which in the shorter term reflects fluid shifts).[41]

## Classification [edit]

There are many different ways to categorize heart failure, including:

- the side of the heart involved (left heart failure versus right heart failure). Right heart failure compromises pulmonary flow to the lungs. Left heart failure compromises aortic flow to the body and brain. Mixed presentations are common; left heart failure often leads to right heart failure in the longer term.
- whether the abnormality is due to insufficient contraction (systolic dysfunction), or due to insufficient relaxation of the heart (diastolic dysfunction), or to both.
- whether the problem is primarily increased venous back pressure (preload), or failure to supply adequate arterial perfusion (afterload).
- whether the abnormality is due to low cardiac output with high systemic vascular resistance or high cardiac output with low vascular resistance (low-output heart failure vs. high-output heart failure).
- the degree of functional impairment conferred by the abnormality (as reflected in the New York Heart Association Functional Classification[42])
- the degree of coexisting illness: i.e. heart failure/systemic hypertension, heart failure/pulmonary hypertension, heart failure/diabetes, heart failure/kidney failure, etc.

*Functional* classification generally relies on the New York Heart Association functional classification. The classes (I-IV) are:

- Class I: no limitation is experienced in any activities; there are no symptoms from ordinary activities.
- Class II: slight, mild limitation of activity; the patient is comfortable at rest or with mild exertion.
- Class III: marked limitation of any activity; the patient is comfortable only at rest.
- Class IV: any physical activity brings on discomfort and symptoms occur at rest.

This score documents the severity of symptoms and can be used to assess response to treatment. While its use is widespread, the NYHA score is not very reproducible and does not reliably predict the walking distance or exercise tolerance on formal testing.[43]

In its 2001 guidelines the American College of Cardiology/American Heart Association working group introduced four stages of heart failure:[44]

- Stage A: Patients at high risk for developing HF in the future but no functional or structural heart disorder.
- Stage B: a structural heart disorder but no symptoms at any stage.
- Stage C: previous or current symptoms of heart failure in the context of an underlying structural heart problem, but managed with medical treatment.
- Stage D: advanced disease requiring hospital-based support, a heart transplant or palliative care.

The ACC staging system is useful in that Stage A encompasses "pre-heart failure" – a stage where intervention with treatment can presumably prevent progression to overt symptoms. ACC Stage A does not have a corresponding NYHA class. ACC Stage B would correspond to NYHA Class I. ACC Stage C corresponds to NYHA Class II and III, while ACC Stage D overlaps with NYHA Class IV.

## Algorithms [edit]

There are various algorithms for the diagnosis of heart failure. For example, the algorithm used by the Framingham Heart Study adds together criteria mainly from physical examination. In contrast, the more extensive algorithm by the European Society of Cardiology (ESC) weights the difference between supporting and opposing parameters from the medical history, physical examination, further medical tests as well as response to therapy.

## Framingham criteria [edit]

By the Framingham criteria, diagnosis of congestive heart failure (heart failure with impaired pumping capability)[18] requires the simultaneous presence of at least 2 of the following major criteria or 1 major criterion in conjunction with 2 of the following minor criteria. Major criteria include an enlarged heart on a chest x-ray, an S3 gallop (a third heart sound), acute pulmonary edema, episodes of waking up from sleep gasping for air, crackles on lung auscultation, central venous pressure of more than 16 cm $H_2O$ at the right atrium, jugular vein distension, positive abdominojugular test, and weight loss of more than 4.5 kg in 5 days in response to treatment (sometimes[45] classified as a minor criterion).[46] Minor criteria include an abnormally fast heart rate of more than 120 beats per minute, nocturnal cough, difficulty breathing with physical activity, pleural effusion, a decrease in the vital capacity by one third from maximum recorded, liver enlargement, and bilateral ankle swelling.[46]

Minor criteria are acceptable only if they can not be attributed to another medical condition such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome.[46] The Framingham Heart Study criteria are 100% sensitive and 78% specific for identifying persons with definite congestive heart failure.[46]

## ESC algorithm [edit]

The ESC algorithm weights the following parameters in establishing the diagnosis of heart failure:[47]

**Diagnostic assessments supporting the presence of heart failure**

| Assessment | Diagnosis of heart failure | |
|---|---|---|
| | Supports if present | Opposes if normal or absent |
| Compatible symptoms | ++ | ++ |
| Compatible signs | ++ | + |
| Cardiac dysfunction on echocardiography | +++ | +++ |
| Response of symptoms or signs to therapy | +++ | ++ |
| **ECG** | | |
| Normal | | ++ |
| Abnormal | ++ | + |
| Dysrhythmia | +++ | + |

| | | |
|---|---|---|
| **Laboratory** | | |
| Elevated BNP/NT-proBNP | +++ | + |
| Low/normal BNP/NT-proBNP | + | +++ |
| Low blood sodium | + | + |
| Kidney dysfunction | + | + |
| Mild elevations of troponin | + | + |
| **Chest X-ray** | | |
| Pulmonary congestion | +++ | + |
| Reduced exercise capacity | +++ | ++ |
| Abnormal pulmonary function tests | + | + |
| Abnormal hemodynamics at rest | +++ | ++ |
| **+ = some importance; ++ = intermediate importance; +++ = great importance.** | | |

## Differential diagnosis [edit]

There are several terms which are closely related to heart failure, and may be the cause of heart failure, but should not be confused with it. Cardiac arrest and asystole refer to situations in which there is *no* cardiac output at all. Without urgent treatment, these result in sudden death. Myocardial infarction ("Heart attack") refers to heart muscle damage due to insufficient blood supply, usually as a result of a blocked coronary artery. Cardiomyopathy refers specifically to problems within the heart muscle, and these problems can result in heart failure. Ischemic cardiomyopathy implies that the cause of muscle damage is coronary artery disease. Dilated cardiomyopathy implies that the muscle damage has resulted in enlargement of the heart. Hypertrophic cardiomyopathy involves enlargement and *thickening* of the heart muscle.

# Prevention [edit]

**This section needs expansion**. You can help by adding to it. *(September 2016)*

A person's risk of developing heart failure is inversely related to their level of physical activity. Those who achieved at least 500 MET-minutes/week (the recommended minimum by U.S. guidelines) had lower heart failure risk than individuals who did not report exercising during their free time; the reduction in heart failure risk was even greater in those who engaged in higher levels of physical activity than the recommended minimum.[48]

# Management [edit]

*Main article: Management of heart failure*

Treatment focuses on improving the symptoms and preventing the progression of the disease. Reversible causes of the heart failure also need to be addressed (e.g. infection, alcohol ingestion, anemia, thyrotoxicosis, arrhythmia, hypertension). Treatments include lifestyle and pharmacological modalities, and occasionally various forms of device therapy and rarely cardiac transplantation.

## Acute decompensation [edit]

*Main article: Acute decompensated heart failure*

In acute decompensated heart failure (ADHF), the immediate goal is to re-establish adequate perfusion and

oxygen delivery to end organs. This entails ensuring that airway, breathing, and circulation are adequate. Immediate treatments usually involve some combination of vasodilators such as nitroglycerin, diuretics such as furosemide, and possibly noninvasive positive pressure ventilation (NIPPV).

## Chronic management [edit]

The goals of treatment for people with chronic heart failure are the prolongation of life, the prevention of acute decompensation and the reduction of symptoms, allowing for greater activity.

Heart failure can result from a variety of conditions. In considering therapeutic options, it is important to first exclude reversible causes, including thyroid disease, anemia, chronic tachycardia, alcohol abuse, hypertension and dysfunction of one or more heart valves. Treatment of the underlying cause is usually the first approach in treating heart failure. However, in the majority of cases, either no primary cause is found or treatment of the primary cause does not restore normal heart function. In these cases, behavioral, medical and device treatment strategies exist which can provide a significant improvement in outcomes, including the relief of symptoms, exercise tolerance, and a decrease in the likelihood of hospitalization or death. Breathlessness rehabiliation for chronic obstructive pulmonary disease (COPD) and heart failure has been proposed with exercise training as a core component. Rehabilitation should also include other interventions to address shortness of breath including psychological and education needs of patients and needs of carers.[49]

## Lifestyle [edit]

Behavioral modification is a primary consideration in any chronic heart failure management program, with dietary guidelines regarding fluid and salt intake being of particular importance.[50]

Exercise should be encouraged and tailored to suit individual capabilities. The inclusion of regular physical conditioning as part of a cardiac rehabilitation program can significantly improve quality of life and reduce the risk of hospital admission for worsening symptoms, however, there is no evidence for a reduction in mortality rates as a result of exercise. Furthermore, it is not clear whether this evidence can be extended to people with heart failure with preserved ejection fraction (HFpEF) or to those whose exercise regimen takes place entirely at home.[51]

Home visits and regular monitoring at heart failure clinics reduce the need for hospitalization and improve life expectancy.[52]

## Medication [edit]

First-line therapy for people with heart failure due to reduced systolic function should include angiotensin-converting enzyme (ACE) inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) if the person develops a long term cough as a side effect of the ACE-I.[53] Use of medicines from this class is associated with improved survival and quality of life in people with heart failure.[54]

Beta-adrenergic blocking agents (beta blockers) also form part of the first line of treatment, adding to the improvement in symptoms and mortality provided by ACE-I/ARB.[54][55] The mortality benefits of beta blockers in people with systolic dysfunction who also have atrial fibrillation (AF) is more limited than in those who do not have AF.[56] If the ejection fraction is not diminished (HFpEF), the benefits of beta blockers is more modest; a decrease in mortality has been observed but reduction in hospital admission for uncontrolled symptoms has not been observed.[57]

In people who are intolerant of ACE-I and ARBs or who have significant kidney dysfunction, the use of combined hydralazine and a long-acting nitrate, such as isosorbide dinitrate, is an effective alternate strategy. This regimen has been shown to reduce mortality in people with moderate heart failure.[58] It is especially beneficial in African-Americans (AA).[58] In AAs who are symptomatic, hydralazine and isosorbide dinitrate (H+I) can be added to ACE-I or ARBs.

In people with markedly reduced ejection fraction, the use of an aldosterone antagonist, in addition to beta blockers and ACE-I, can improve symptoms and reduce mortality.[59][60]

Second-line drugs for CHF do not confer a mortality benefit. Digoxin is one such drug. Its narrow therapeutic window, a high degree of toxicity, and the failure of multiple trials to show a mortality benefit have reduced its role in clinical practice. It is now used in only a small number of people with refractory symptoms, who are in atrial fibrillation and/or who have chronic low blood pressure.

Diuretics have been a mainstay of treatment for treatment of fluid accumulation, and include diuretics classes such as loop diuretics, thiazide-like diuretic, and potassium-sparing diuretic. Although widely used, evidence on their efficacy and safety is limited, with the exception of mineralocorticoid antagonists such as spironolactone.[59][61] A recent Cochrane review found that in small studies, the use of diuretics appeared to have improved mortality in individuals with heart failure.[62] However, the extent to which these results can be extrapolated to a general population is unclear due to the small number of participants in the cited studies.[61]

Anemia is an independent factor in mortality in people with chronic heart failure. The treatment of anemia significantly improves quality of life for those with heart failure, often with a reduction in severity of the NYHA classification, and also improves mortality rates.[63][64] The latest European guidelines (2012) recommend screening for iron-deficient anemia and treating with parenteral iron if anemia is found.[65]

The decision to anticoagulate people with HF, typically with left ventricular ejection fractions <35% is debated, but generally, people with coexisting atrial fibrillation, a prior embolic event, or conditions which increase the risk of an embolic event such as amyloidosis, left ventricular noncompaction, familial dilated cardiomyopathy, or a thromboembolic event in a first-degree relative.[66]

## Minimally invasive therapies [edit]

In people with severe cardiomyopathy (left ventricular ejection fraction below 35%), or in those with recurrent VT or malignant arrhythmias, treatment with an automatic implantable cardioverter defibrillator (AICD) is indicated to reduce the risk of severe life-threatening arrhythmias. The AICD does not improve symptoms or reduce the incidence of malignant arrhythmias but does reduce mortality from those arrhythmias, often in conjunction with antiarrhythmic medications. In people with left ventricular ejection (LVEF) below 35%, the incidence of ventricular tachycardia (VT) or sudden cardiac death is high enough to warrant AICD placement. Its use is therefore recommended in AHA/ACC guidelines.[15]

Cardiac contractility modulation (CCM) is a treatment for people with moderate to severe left ventricular systolic heart failure (NYHA class II–IV) which enhances both the strength of ventricular contraction and the heart's pumping capacity. The CCM mechanism is based on stimulation of the cardiac muscle by non-excitatory electrical signals (NES), which are delivered by a pacemaker-like device. CCM is particularly suitable for the treatment of heart failure with normal QRS complex duration (120 ms or less) and has been demonstrated to improve the symptoms, quality of life and exercise tolerance.[16][67][68][69][70] CCM is approved for use in Europe, but not currently in North America.[71][72]

About one third of people with LVEF below 35% have markedly altered conduction to the ventricles, resulting in dyssynchronous depolarization of the right and left ventricles. This is especially problematic in people with left bundle branch block (blockage of one of the two primary conducting fiber bundles that originate at the base of the heart and carries depolarizing impulses to the left ventricle). Using a special pacing algorithm, biventricular cardiac resynchronization therapy (CRT) can initiate a normal sequence of ventricular depolarization. In people with LVEF below 35% and prolonged QRS duration on ECG (LBBB or QRS of 150 ms or more) there is an improvement in symptoms and mortality when CRT is added to standard medical therapy.[73] However, in the two-thirds of people without prolonged QRS duration, CRT may actually be harmful.[15][16][74]

## Surgical therapies [edit]

People with the most severe heart failure may be candidates for ventricular assist devices (VAD). VADs have commonly been used as a bridge to heart transplantation, but have been used more recently as a destination treatment for advanced heart failure.[75]

In select cases, heart transplantation can be considered. While this may resolve the problems associated

with heart failure, the person must generally remain on an immunosuppressive regimen to prevent rejection, which has its own significant downsides.[76] A major limitation of this treatment option is the scarcity of hearts available for transplantation.

### Palliative care [edit]

People with CHF often have significant symptoms, such as shortness of breath and chest pain. Both palliative care and cardiology are trying to get palliative care involved earlier in the course of patients with heart failure, and some would argue[*who?*] any patient with NYHA class III CHF should have a palliative care referral. Palliative care can not only provide symptom management, but also assist with advanced care planning, goals of care in the case of a significant decline, and making sure the patient has a medical power of attorney and discussed his or her wishes with this individual.[77] A 2016 review found that palliative care is associated with improved outcomes, such as quality of life, symptom burden, and satisfaction with care.[78]

Without transplantation, heart failure may not be reversible and cardiac function typically deteriorates with time. The growing number of patients with Stage IV heart failure (intractable symptoms of fatigue, shortness of breath or chest pain at rest despite optimal medical therapy) should be considered for palliative care or hospice, according to American College of Cardiology/American Heart Association guidelines.[77]

## Prognosis [edit]

Prognosis in heart failure can be assessed in multiple ways including clinical prediction rules and cardiopulmonary exercise testing. Clinical prediction rules use a composite of clinical factors such as lab tests and blood pressure to estimate prognosis. Among several clinical prediction rules for prognosticating acute heart failure, the 'EFFECT rule' slightly outperformed other rules in stratifying patients and identifying those at low risk of death during hospitalization or within 30 days.[79] Easy methods for identifying low-risk patients are:

- ADHERE Tree rule indicates that patients with blood urea nitrogen < 43 mg/dl and systolic blood pressure at least 115 mm Hg have less than 10% chance of inpatient death or complications.
- BWH rule indicates that patients with systolic blood pressure over 90 mm Hg, respiratory rate of 30 or fewer breaths per minute, serum sodium over 135 mmol/L, no new ST-T wave changes have less than 10% chance of inpatient death or complications.

A very important method for assessing prognosis in advanced heart failure patients is cardiopulmonary exercise testing (CPX testing). CPX testing is usually required prior to heart transplantation as an indicator of prognosis. Cardiopulmonary exercise testing involves measurement of exhaled oxygen and carbon dioxide during exercise. The peak oxygen consumption (VO2 max) is used as an indicator of prognosis. As a general rule, a VO2 max less than 12–14 cc/kg/min indicates a poor survival and suggests that the patient may be a candidate for a heart transplant. Patients with a VO2 max<10 cc/kg/min have clearly poorer prognosis. The most recent International Society for Heart and Lung Transplantation (ISHLT) guidelines[80] also suggest two other parameters that can be used for evaluation of prognosis in advanced heart failure, the heart failure survival score and the use of a criterion of VE/VCO2 slope > 35 from the CPX test. The heart failure survival score is a score calculated using a combination of clinical predictors and the VO2 max from the cardiopulmonary exercise test.

Heart failure is associated with significantly reduced physical and mental health, resulting in a markedly decreased quality of life.[81][82] With the exception of heart failure caused by reversible conditions, the condition usually worsens with time. Although some people survive many years, progressive disease is associated with an overall annual mortality rate of 10%.[83]

Approximately 18 of every 1000 persons will experience an ischemic stroke during the first year after diagnosis of HF. As the duration of follow-up increases, the stroke rate rises to nearly 50 strokes per 1000 cases of HF by 5 years.[84]

# Epidemiology [edit]

Heart failure is associated with a high health expenditure, mostly because of the cost of hospitalizations; costs have been estimated to amount to 2% of the total budget of the National Health Service in the United Kingdom, and more than $35 billion in the United States.[85][86]

Heart failure is the leading cause of hospitalization in people older than 65.[87] In developed countries, the mean age of patients with heart failure is 75 years old. In developing countries, two to three percent of the population have heart failure, but in those 70 to 80 years old, it occurs in 20–30 percent.

More than 20 million people have heart failure worldwide.[88][89] The prevalence and incidence of heart failure are increasing, mostly because of increasing life span, but also because of increased prevalence of risk factors (hypertension, diabetes, dyslipidemia, and obesity) and improved survival rates from other types of cardiovascular disease (myocardial infarction, valvular disease, and arrhythmias).[89][90]

In the United States, heart failure affects 5.8 million people, and each year 550,000 new cases are diagnosed.[88] In 2011, congestive heart failure was the most common reason for hospitalization for adults aged 85 years and older, and the second most common for adults aged 65–84 years.[91] It is estimated that one in five adults at age 40 will develop heart failure during their remaining lifetime and about half of people who develop heart failure die within 5 years of diagnosis.[92] Heart failure is much higher in African Americans, Hispanics, Native Americans and recent immigrants from the eastern bloc countries like Russia. This high prevalence in these ethnic minority populations has been linked to high incidence of diabetes and hypertension. In many new immigrants to the U.S., the high prevalence of heart failure has largely been attributed to lack of preventive health care or substandard treatment.[93] Nearly one out of every four patients (24.7%) hospitalized in the U.S. with congestive heart failure are readmitted within 30 days.[94] Additionally, more than 50% of patients seek re-admission within 6 months after treatment and the average duration of hospital stay is 6 days.

In tropical countries, the most common cause of HF is valvular heart disease or some type of cardiomyopathy. As underdeveloped countries have become more affluent, there has also been an increase in the incidence of diabetes, hypertension and obesity, which have in turn raised the incidence of heart failure.[95]

Congestive heart failure is a leading cause of hospital readmissions in the U.S. In a study of 18 States, Medicare patients aged 65 and older were readmitted at a rate of 24.5 per 100 admissions in 2011. In the same year, Medicaid patients were readmitted at a rate of 30.4 per 100 admissions, and uninsured patients were readmitted at a rate of 16.8 per 100 admissions. These are the highest readmission rates for both patient categories. Notably, congestive heart failure was not among the top ten conditions with the most 30-day readmissions among the privately insured.[96]

## Sex [edit]

Men have a higher incidence of heart failure, but the overall prevalence rate is similar in both sexes since women survive longer after the onset of heart failure.[97] Women tend to be older when diagnosed with heart failure (after menopause), they are more likely than men to have diastolic dysfunction, and seem to experience a lower overall quality of life than men after diagnosis.[97]

# Economics [edit]

In 2011, non-hypertensive congestive heart failure was one of the ten most expensive conditions seen during inpatient hospitalizations in the U.S., with aggregate inpatient hospital costs of more than $10.5 billion.[98]

# Research [edit]

There is low-quality evidence that stem cell therapy may help.[99] Although this evidence positively indicated benefit, the evidence was of lower quality than other evidence that does not indicate benefit.[100]

A previous claim, which came from a 2012 article published by the British Journal *Heart*, stated that a low salt diet increased the risk of death in those with congestive heart failure. This claim has since been withdrawn. The paper was retracted by the journal in 2013 because two of the cited studies contained duplicate data that could not be verified, and the data have since been lost.[101][102][103]

## References [edit]


1. ^ "Living Well With Chronic Heart Failure" (PDF). *Heart Foundation*. p. 18. Retrieved 25 May 2014.
2. ^ "heart failure" at *Dorland's Medical Dictionary*
3. ^ "Heart failure". *Health Information*. Mayo Clinic. 23 December 2009. DS00061.
4. ^ "Definition of Heart failure". *Medical Dictionary*. MedicineNet. 27 April 2011.
5. ^ *a b c d e f g h i j* "Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care: Partial Update". *National Clinical Guideline Centre*: 19–24. Aug 2010. PMID 22741186.
6. ^ *a b* McDonagh, Theresa A. (2011). *Oxford textbook of heart failure*. Oxford: Oxford University Press. p. 3. ISBN 9780199577729.
7. ^ O'Connor, Christopher M. (2005). *Managing Acute Decompensated Heart Failure a Clinician's Guide to Diagnosis and Treatment.* London: Informa Healthcare. p. 572. ISBN 9780203421345.
8. ^ *a b c* McMurray JJ, Pfeffer MA (2005). "Heart failure". *Lancet*. **365** (9474): 1877–89. doi:10.1016/S0140-6736(05)66621-4. PMID 15924986.
9. ^ *a b* "Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care: Partial Update". *National Clinical Guideline Centre*: 38–70. Aug 2010. PMID 22741186.
10. ^ *Willard & Spackman's occupational therapy.* (12th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. 2014. p. 1124. ISBN 9781451110807.
11. ^ Eyal Herzog (2012). *The Cardiac Care Unit Survival Guide*. Lippincott Williams & Wilkins. p. 98. ISBN 9781451177466.
12. ^ *a b c d e f* "Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care: Partial Update". *National Clinical Guideline Centre*: 34–47. Aug 2010. PMID 22741186.
13. ^ *a b c d* "Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care: Partial Update". *National Clinical Guideline Centre*: 71–153. Aug 2010. PMID 22741186.
14. ^ *a b* Taylor, RS; Sagar, VA; Davies, EJ; Briscoe, S; Coats, AJ; Dalal, H; Lough, F; Rees, K; Singh, S (Apr 27, 2014). "Exercise-based rehabilitation for heart failure.". *The Cochrane database of systematic reviews*. **4**: CD003331. doi:10.1002/14651858.CD003331.pub4. PMID 24771460.
15. ^ *a b c* Tracy, CM; et al. (Oct 2, 2012). "2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. [corrected]." (PDF). *Circulation*. **126** (14): 1784–800. doi:10.1161/CIR.0b013e3182618569. PMID 22965336. Retrieved Apr 29, 2015.
16. ^ *a b c* Kuck, K.-H.; et al. (Jan 2014). "New devices in heart failure: an European Heart Rhythm Association report: developed by the European Heart Rhythm Association; endorsed by the Heart Failure Association" (PDF). *Europace*. **16** (1): 109–28. doi:10.1093/europace/eut311. PMID 24265466. Retrieved Oct 13, 2014.
17. ^ Dickstein K, Cohen-Solal A, Filippatos G, et al. (October 2008). "ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM)". *Eur. Heart J.* **29** (19): 2388–442. doi:10.1093/eurheartj/ehn309. PMID 18799522.
18. ^ *a b* "congestive heart failure" at *Dorland's Medical Dictionary*
19. ^ Jessup M, Abraham WT, Casey DE, et al. (April 2009). "2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation". *Circulation*. **119** (14): 1977–2016. doi:10.1161/CIRCULATIONAHA.109.192064. PMID 19324967.
20. ^ *a b* "high-output heart failure" at *Dorland's Medical Dictionary*
    *a b*

21. ^ "Ejection Fraction". *Heart Rhythm Society*. Retrieved 7 June 2014.
22. ^ "Ejection Fraction Heart Failure Measurement". *American Heart Association*. Feb 11, 2014. Retrieved 7 June 2014.
23. ^ "Heart Failure: Signs and Symptoms". UCSF Medical Center.
24. ^ Fonarow GC, Abraham WT, Albert NM, et al. (April 2008). "Factors Identified as Precipitating Hospital Admissions for Heart Failure and Clinical Outcomes: Findings From OPTIMIZE-HF". *Arch. Intern. Med.* **168** (8): 847–54. doi:10.1001/archinte.168.8.847. PMID 18443260.
25. ^ Nieminen MS, Böhm M, Cowie MR, et al. (February 2005). "Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology". *Eur. Heart J.* **26** (4): 384–416. doi:10.1093/eurheartj/ehi044. PMID 15681577.
26. ^ Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, Bombardier C, Cannon C, Farkouh ME, FitzGerald GA, Goss P, Halls H, Hawk E, Hawkey C, Hennekens C, Hochberg M, Holland LE, Kearney PM, Laine L, Lanas A, Lance P, Laupacis A, Oates J, Patrono C, Schnitzer TJ, Solomon S, Tugwell P, Wilson K, Wittes J, Baigent C (Aug 31, 2013). "Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials.". *Lancet*. **382** (9894): 769–79. doi:10.1016/S0140-6736(13)60900-9. PMC 3778977. PMID 23726390.
27. ^ Page RL, 2nd; O'Bryant, CL; Cheng, D; Dow, TJ; Ky, B; Stein, CM; Spencer, AP; Trupp, RJ; Lindenfeld, J; American Heart Association Clinical Pharmacology and Heart Failure and Transplantation Committees of the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes, Research (11 July 2016). "Drugs That May Cause or Exacerbate Heart Failure: A Scientific Statement From the American Heart Association.". *Circulation*. doi:10.1161/CIR.0000000000000426. PMID 27400984.
28. ^ Boron, Walter F.; Boulpaep, Emile L. (2005). *Medical Physiology: A Cellular and Molecular Approach* (Updated ed.). Saunders. p. 533. ISBN 0-7216-3256-4.
29. ^ Rang HP (2003). *Pharmacology*. Edinburgh: Churchill Livingstone. p. 127. ISBN 0-443-07145-4.
30. ^ *cardiac pathophysiology in heart failure* at GPnotebook
31. ^ Tamparo, Carol (2011). *Fifth Edition: Diseases of the Human Body*. Philadelphia, PA: F.A. Davis Company. p. 329. ISBN 978-0-8036-2505-1.
32. ^ Shigeyama J, Yasumura Y, Sakamoto A, et al. (December 2005). "Increased gene expression of collagen Types I and III is inhibited by beta-receptor blockade in patients with dilated cardiomyopathy". *Eur. Heart J.* **26** (24): 2698–705. doi:10.1093/eurheartj/ehi492. PMID 16204268.
33. ^ Tsutsui H, Matsushima S, Kinugawa S, et al. (May 2007). "Angiotensin II type 1 receptor blocker attenuates myocardial remodeling and preserves diastolic function in diabetic heart". *Hypertens. Res.* **30** (5): 439–49. doi:10.1291/hypres.30.439. PMID 17587756.
34. ^ Krug AW, Grossmann C, Schuster C, et al. (October 2003). "Aldosterone stimulates epidermal growth factor receptor expression". *J. Biol. Chem.* **278** (44): 43060–66. doi:10.1074/jbc.M308134200. PMID 12939263.
35. ^ *systemic pathophysiology in heart failure* at GPnotebook
36. ^ Hunter JG, Boon NA, Davidson S, Colledge NR, Walker B (2006). *Davidson's principles & practice of medicine*. Elsevier/Churchill Livingstone. p. 544. ISBN 0-443-10057-8.
37. ^ Dworzynski, K; Roberts, E; Ludman, A; Mant, J; Guideline Development, Group (8 October 2014). "Diagnosing and managing acute heart failure in adults: summary of NICE guidance.". *BMJ (Clinical research ed.)*. **349**: g5695. doi:10.1136/bmj.g5695. PMID 25296764.
38. ^ Al Deeb, M; Barbic, S; Featherstone, R; Dankoff, J; Barbic, D (August 2014). "Point-of-care ultrasonography for the diagnosis of acute cardiogenic pulmonary edema in patients presenting with acute dyspnea: a systematic review and meta-analysis.". *Academic Emergency Medicine*. **21** (8): 843–52. doi:10.1111/acem.12435. PMID 25176151.
39. ^ Loscalzo, Joseph; Fauci, Anthony S.; Braunwald, Eugene; Dennis L. Kasper; Hauser, Stephen L; Longo, Dan L. (2008). *Harrison's Principles of Internal Medicine* (17 ed.). McGraw-Hill Medical. p. 1447. ISBN 978-0-07-147693-5.
40. ^ Ewald B, Ewald D, Thakkinstian A, Attia J (2008). "Meta-analysis of B type natriuretic peptide and N-terminal pro B natriuretic peptide in the diagnosis of clinical heart failure and population screening for left ventricular systolic dysfunction". *Intern Med J.* **38** (2): 101–13. doi:10.1111/j.1445-5994.2007.01454.x. PMID 18290826.
41. ^ Yu, Cheuk-Man; Wang, Li; Chau, Elaine; Chan, Raymond Hon-Wah; Kong, Shun-Ling; Tang, Man-Oi (1 August 2005). "Correlation With Fluid Status and Feasibility of Early Warning Preceding Hospitalization". *American Heart Association Journals*. **112**: 841–48. doi:10.1161/CIRCULATIONAHA.104.492207. Retrieved 8 July 2014.
42. ^ Criteria Committee, New York Heart Association (1964). *Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis* (6th ed.). Boston: Little, Brown. p. 114.
43. ^ Raphael C, Briscoe C, Davies J, et al. (2007). "Limitations of the New York Heart Association functional classification system and self reported walking distances in chronic heart failure". *Heart*. **93** (4): 476–82. doi:10.1136/hrt.2006.089656. PMC 1861501. PMID 17005715.

44. ^ Hunt SA, Abraham WT, Chin MH, et al. (2005). "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult" (PDF). *Circulation*. **112** (12): e154–235. doi:10.1161/CIRCULATIONAHA.105.167586. PMID 16160202.
45. ^ Topic Review – Heart Failure By Osama Gusbi, MD. Albany Medical Review – January 2002
46. ^ *a b c d* "Framingham Criteria for Congestive Heart Failure". MedicalCRITERIA.com. 2005. In turn citing: Framingham study 1971
47. ^ Dickstein K, Cohen-Solal A, Filippatos G, et al. (October 2008). "ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM)". *Eur. Heart J.* **29** (19): 2388–442. doi:10.1093/eurheartj/ehn309. PMID 18799522. as PDF Also at doi:10.1016/j.ejheart.2008.08.005
48. ^ Pandey, Ambarish; Garg, Sushil; Khunger, Monica; Darden, Douglas; Ayers, Colby; Kumbhani, Dharam J; Mayo, Helen G; de Lemos, James A; Berry, Jarrett D (November 2015). "Dose-Response Relationship Between Physical Activity and Risk of Heart Failure: A Meta-Analysis." (PDF). *Circulation* (Systemati Review & Meta-Analysis). **132** (19): 1786–94. doi:10.1161/CIRCULATIONAHA.115.015853. PMID 26438781.
49. ^ Man, W. D.-C.; Chowdhury, F.; Taylor, R. S.; Evans, R. A.; Doherty, P.; Singh, S. J.; Booth, S.; Thomason, D.; Andrews, D.; Lee, C.; Hanna, J.; Morgan, M. D.; Bell, D.; Cowie, M. R. (12 April 2016). "Building consensus for provision of breathlessness rehabilitation for patients with chronic obstructive pulmonary disease and chronic heart failure". *Chronic Respiratory Disease*. doi:10.1177/1479972316642363. PMID 27072018.
50. ^ Lifestyle changes for heart failure recommended by the American Heart Association.
51. ^ Taylor, RS; Sagar, VA; Davies, EJ; Briscoe, S; Coats, AJ; Dalal, H; Lough, F; Rees, K; Singh, S (27 April 2014). "Exercise-based rehabilitation for heart failure". *The Cochrane database of systematic reviews*. **4**: CD003331. doi:10.1002/14651858.CD003331.pub4. PMID 24771460.
52. ^ Feltner, C; Jones, CD; Cené, CW; Zheng, ZJ; Sueta, CA; Coker-Schwimmer, EJ; Arvanitis, M; Lohr, KN; Middleton, JC; Jonas, DE (Jun 3, 2014). "Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis.". *Annals of Internal Medicine*. **160** (11): 774–84. doi:10.7326/M14-0083. PMID 24862840.
53. ^ Goljan, Edward F. (2014). *Rapid Review Pathology* (4 ed.). Philadelphia, PA: Saunders/Elsevier. ISBN 978-0323087872.
54. ^ *a b* National Institute for Health and Clinical Excellence. *Clinical guideline 108: Chronic heart failure – Management of chronic heart failure in adults in primary and secondary care* . London, August 2010.
55. ^ Kotecha, D; Manzano, L; Krum, H; Rosano, G; Holmes, J; Altman, DG; Collins, PD; Packer, M; Wikstrand, J; Coats, AJ; Cleland, JG; Kirchhof, P; von Lueder, TG; Rigby, AS; Andersson, B; Lip, GY; van Veldhuisen, DJ; Shibata, MC; Wedel, H; Böhm, M; Flather, MD; Beta-Blockers in Heart Failure Collaborative, Group (20 April 2016). "Effect of age and sex on efficacy and tolerability of β blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis.". *BMJ (Clinical research ed.)*. **353**: i1855. PMC 4849174. PMID 27098105.
56. ^ Kotecha, Dipak; Holmes, Jane; Krum, Henry; Altman, Douglas G; Manzano, Luis; Cleland, John G F; Lip, Gregory Y H; Coats, Andrew J S; Andersson, Bert; Kirchhof, Paulus; von Lueder, Thomas G; Wedel, Hans; Rosano, Giuseppe; Shibata, Marcelo C; Rigby, Alan; Flather, Marcus D (December 2014). "Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis". *The Lancet*. **384** (9961): 2235–43. doi:10.1016/S0140-6736(14)61373-8. PMID 25193873.
57. ^ Liu, Feng; Chen, Yanmei; Feng, Xuguang; Teng, Zhonghua; Yuan, Ye; Bin, Jianping; Hosoda, Toru (5 March 2014). "Effects of Beta-Blockers on Heart Failure with Preserved Ejection Fraction: A Meta-Analysis". *PLoS ONE*. **9** (3): e90555. doi:10.1371/journal.pone.0090555. PMC 3944014. PMID 24599093.
58. ^ *a b* Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care: Partial Update [Internet]
59. ^ *a b* Pitt, B; et al. (Sep 2, 2013). "The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators.". *N Engl J Med*. **341** (10): 709–17. doi:10.1056/NEJM199909023411001. PMID 10471456. Retrieved Apr 28, 2015.
60. ^ Pitt, B; et al. (Apr 3, 2013). "Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction.". *N Engl J Med*. **348** (14): 1309–21. doi:10.1056/NEJMoa030207. PMID 12668699. Retrieved Apr 28, 2015.
61. ^ *a b* von Lueder, TG; Atar, D; Krum, H (Oct 2013). "Diuretic use in heart failure and outcomes.". *Clinical pharmacology and therapeutics*. **94** (4): 490–98. doi:10.1038/clpt.2013.140. PMID 23852396.
62. ^ Faris, RF; Flather, M; Purcell, H; Poole-Wilson, PA; Coats, AJ (Feb 15, 2012). "Diuretics for heart failure.". *The Cochrane database of systematic reviews*. **2**: CD003838. doi:10.1002/14651858.CD003838.pub3.

PMID 22336795.
63. ^ He SW, Wang LX (2009). "The impact of anemia on the prognosis of chronic heart failure: a meta-analysis and systemic review". *Congest Heart Fail*. **15** (3): 123–30. doi:10.1111/j.1751-7133.2008.00030.x. PMID 19522961.
64. ^ Peraira-Moral J. Roberto; Núñez-Gil Ivan J. (19 January 2012). "Anaemia in heart failure: intravenous iron therapy". *E-journal of the ESC Council for Cardiology Practice*. **10** (16).
65. ^ "ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012". *European Heart Journal*. **33**: 1787–847. 2012. doi:10.1093/eurheartj/ehs104. PMID 22611136.
66. ^ Hunt, S. A. (20 September 2005). "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society". *Circulation*. **112** (12): e154–e235. doi:10.1161/CIRCULATIONAHA.105.167586. PMID 16160202.
67. ^ Abraham, W.T.; S.A. Smith (Feb 2013). "Devices in the management of advanced, chronic heart failure" (PDF). *Nat Rev Cardiol*. **10** (2): 98–110. doi:10.1038/nrcardio.2012.178. PMC 3753073. PMID 23229137. Retrieved Oct 10, 2014.
68. ^ Giallauria, F.; et al. (Aug 2014). "Effects of cardiac contractility modulation by non-excitatory electrical stimulation on exercise capacity and quality of life: an individual patient's data meta-analysis of randomized controlled trials". *Int J Cardiol*. **175** (2): 352–57. doi:10.1016/j.ijcard.2014.06.005. PMID 24975782.
69. ^ Borggrefe, M.; D. Burkhoff (Jul 2012). "Clinical effects of cardiac contractility modulation (CCM) as a treatment for chronic heart failure". *Eur J Heart Fail*. **14** (7): 703–12. doi:10.1093/eurjhf/hfs078. PMID 22696514.
70. ^ Kuschyk, J.; et al. (Jan 2015). "Efficacy and survival in patients with cardiac contractility modulation: Long-term single center experience in 81 patients". *Int J Cardiol*. **20** (183C): 76–81. doi:10.1016/j.ijcard.2014.12.178. PMID 25662055.
71. ^ Kuschyk, J. (2014). "Der Besondere Stellenwert der Kardialen Kontraktilitätsmodulation in der Devicetherapie". *Herzmedizin*. Retrieved Jun 6, 2014.
72. ^ clinicaltrials.gov Announcement of a study that will further investigate safety and efficacy of CCM devices
73. ^ Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, et al. (2013). "2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines". *Circulation*. **128** (16): e240–e327. doi:10.1161/CIR.0b013e31829e8776. PMID 23741058.
74. ^ Ruschitzka, F; et al. (Oct 10, 2013). "Cardiac-Resynchronization Therapy in Heart Failure with a Narrow QRS Complex". *N Engl J Med*. **369** (15): 1395–405. doi:10.1056/NEJMoa1306687. PMID 23998714. Retrieved Apr 29, 2015.
75. ^ Carrel, T; Englberger, L; Martinelli, MV; Takala, J; Boesch, C; Sigurdadottir, V; Gygax, E; Kadner, A; Mohacsi, P (Oct 18, 2012). "Continuous flow left ventricular assist devices: a valid option for heart failure patients.". *Swiss Medical Weekly*. **142**: w13701. doi:10.4414/smw.2012.13701. PMID 23135811.
76. ^ Lindenfeld, J; et al. (Dec 14, 2004). "New Drugs and Technologies. Drug Therapy in the Heart Transplant Recipient. Part I: Cardiac Rejection and Immunosuppressive Drugs" (PDF). *Circulation*. **110** (24): 3734–40. doi:10.1161/01.cir.0000149745.83186.89. PMID 15596559. Retrieved Apr 29, 2015.
77. ^ *a b* Adler, Eric D.; Goldfinger, Judith Z.; Kalman, Jill; Park, Michelle E.; Meier, Diane E. (December 2009). "Palliative Care in the Treatment of Advanced Heart Failure". *American Heart Association Journals*. **120**: 2597–606. doi:10.1161/CIRCULATIONAHA.109.869123. PMID 20026792. Retrieved 8 July 2014.
78. ^ Kavalieratos, Dio; Corbelli, Jennifer; Zhang, Di; Dionne-Odom, J. Nicholas; Ernecoff, Natalie C.; Hanmer, Janel; Hoydich, Zachariah P.; Ikejiani, Dara Z.; Klein-Fedyshin, Michele (2016-11-22). "Association Between Palliative Care and Patient and Caregiver Outcomes". *JAMA*. **316** (20). doi:10.1001/jama.2016.16840. ISSN 0098-7484.
79. ^ Auble TE, Hsieh M, McCausland JB, Yealy DM (2007). "Comparison of four clinical prediction rules for estimating risk in heart failure". *Annals of Emergency Medicine*. **50** (2): 127–35, 135.e1–2. doi:10.1016/j.annemergmed.2007.02.017. PMID 17449141.
80. ^ Mehra MR, Kobashigawa J, Starling R, et al. (September 2006). "Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates–2006". *J. Heart Lung Transplant*. **25** (9): 1024–42. doi:10.1016/j.healun.2006.06.008. PMID 16962464.
81. ^ Juenger J, Schellberg D, Kraemer S, et al. (March 2002). "Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables". *Heart*. **87** (3): 235–41. doi:10.1136/heart.87.3.235. PMC 1767036. PMID 11847161.
82. ^ Hobbs FD, Kenkre JE, Roalfe AK, Davis RC, Hare R, Davies MK (December 2002). "Impact of heart failure and left ventricular systolic dysfunction on quality of life: a cross-sectional study comparing common chronic cardiac and medical disorders and a representative adult population". *Eur. Heart J.* **23** (23): 1867–76. doi:10.1053/euhj.2002.3255. PMID 12445536.

83. ^ Neubauer S (2007). "The failing heart – an engine out of fuel". *N Engl J Med*. **356** (11): 1140–51. doi:10.1056/NEJMra063052. PMID 17360992.
84. ^ Witt, Brandi J.; Gami, Apoor S.; Ballman, Karla V.; Brown, Robert D.; Meverden, Ryan A.; Jacobsen, Stephen J.; Roger, Véronique L. (August 2007). "The Incidence of Ischemic Stroke in Chronic Heart Failure: A Meta-Analysis". *Journal of Cardiac Failure*. **13** (6): 489–96. doi:10.1016/j.cardfail.2007.01.009.
85. ^ Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ (June 2002). "The current cost of heart failure to the National Health Service in the UK". *Eur. J. Heart Fail*. **4** (3): 361–71. doi:10.1016/S1388-9842(01)00198-2. PMID 12034163.
86. ^ Rosamond W, Flegal K, Furie K, et al. (January 2008). "Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee". *Circulation*. **117** (4): e25–146. doi:10.1161/CIRCULATIONAHA.107.187998. PMID 18086926.
87. ^ Krumholz HM, Chen YT, Wang Y, Vaccarino V, Radford MJ, Horwitz RI (2000). "Predictors of readmission among elderly survivors of admission with heart failure". *Am. Heart J*. **139** (1 Pt 1): 72–77. doi:10.1016/S0002-8703(00)90311-9. PMID 10618565.
88. ^ [a] [b] Bui, AL; Horwich, TB; Fonarow, GC (January 2011). "Epidemiology and risk profile of heart failure.". *Nature Reviews Cardiology*. **8** (1): 30–41. doi:10.1038/nrcardio.2010.165. PMC 3033496. PMID 21060326.
89. ^ [a] [b] Mann DL, Chakinala M (2012). *Harrison's principles of internal medicine: Chapter 234. Heart Failure and Cor Pulmonale.* (18th ed.). New York: McGraw-Hill. ISBN 978-0071748896.
90. ^ Goldman, Lee (2011). *Goldman's Cecil Medicine: Heart Failure (Ch 58, 59)* (24th ed.). Philadelphia: Elsevier Saunders. pp. 295–317. ISBN 1437727883.
91. ^ Pfuntner A., Wier L.M., Stocks C. Most Frequent Conditions in U.S. Hospitals, 2011. HCUP Statistical Brief #162. September 2013. Agency for Healthcare Research and Quality, Rockville, MD. [1]
92. ^ Go, AS; Mozaffarian, D; Roger, VL; Benjamin, EJ; Berry, JD; Borden, WB; Bravata, DM; Dai, S; Ford, ES; Fox, CS; Franco, S; Fullerton, HJ; Gillespie, C; Hailpern, SM; Heit, JA; Howard, VJ; Huffman, MD; Kissela, BM; Kittner, SJ; Lackland, DT; Lichtman, JH; Lisabeth, LD; Magid, D; Marcus, GM; Marelli, A; Matchar, DB; McGuire, DK; Mohler, ER; Moy, CS; Mussolino, ME; Nichol, G; Paynter, NP; Schreiner, PJ; Sorlie, PD; Stein, J; Turan, TN; Virani, SS; Wong, ND; Woo, D; Turner, MB; American Heart Association Statistics Committee and Stroke Statistics, Subcommittee (1 January 2013). "Heart disease and stroke statistics – 2013 update: a report from the American Heart Association.". *Circulation*. **127** (1): e6–e245. doi:10.1161/cir.0b013e31828124ad. PMID 23239837.
93. ^ Heart Failure Information, Retrieved on 2010-01-21.
94. ^ Elixhauser A, Steiner C. *Readmissions to U.S. Hospitals by Diagnosis, 2010.* HCUP Statistical Brief #153. Agency for Healthcare Research and Quality. April 2013. [2]
95. ^ Melmed 2011, p. 146
96. ^ Hines AL, Barrett ML, Jiang HJ, Steiner CA (April 2014). "Conditions With the Largest Number of Adult Hospital Readmissions by Payer, 2011.". *HCUP Statistical Brief #172*. Rockville, MD: Agency for Healthcare Research and Quality.
97. ^ [a] [b] Strömberg A, Mårtensson J (Apr 2003). "Gender differences in patients with heart failure". *Eur. J. Cardiovasc. Nurs*. **2** (1): 7–18. doi:10.1016/S1474-5151(03)00002-1. PMID 14622644.
98. ^ Torio CM, Andrews RM. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2011. HCUP Statistical Brief #160. Agency for Healthcare Research and Quality, Rockville, MD. August 2013. [3]
99. ^ Fisher, SA; Brunskill, SJ; Doree, C; Mathur, A; Taggart, DP; Martin-Rendon, E (Apr 29, 2014). "Stem cell therapy for chronic ischaemic heart disease and congestive heart failure.". *The Cochrane database of systematic reviews*. **4**: CD007888. doi:10.1002/14651858.CD007888.pub2. PMID 24777540.
100. ^ Nowbar, AN; Mielewczik, M; Karavassilis, M; Dehbi, HM; Shun-Shin, MJ; Jones, S; Howard, JP; Cole, GD; Francis, DP; DAMASCENE writing, group (Apr 28, 2014). "Discrepancies in autologous bone marrow stem cell trials and enhancement of ejection fraction (DAMASCENE): weighted regression and meta-analysis.". *BMJ (Clinical research ed.)*. **348**: g2688. doi:10.1136/bmj.g2688. PMC 4002982. PMID 24778175.
101. ^ Dinicolantonio, JJ; Pasquale, PD; Taylor, RS; Hackam, DG (Jan 24, 2013). "Low sodium versus normal sodium diets in systolic heart failure: systematic review and meta-analysis.". *Heart (British Cardiac Society)*. doi:10.1136/heartjnl-2012-302337. PMID 22914535.
102. ^ no author given (June 2013). "Retraction. Low sodium versus normal sodium diets in systolic heart failure: systematic review and meta-analysis. Heart. Published Online First: 21 August 2012 doi:10.1136/heartjnl-2012-302337". *Heart*. **99** (11): 820. doi:10.1136/heartjnl-2011-301156.29ret. PMID 23640983. Retrieved 2013-09-29.
103. ^ amarcus41. "Heart pulls sodium meta-analysis over duplicated, and now missing, data". Retraction Watch. Retrieved 2013-09-29.


# External links [edit]

- Heart failure, American Heart Association – information and resources for treating and living with heart failure
- Heart Failure Matters – patient information website of the Heart Failure Association of the European Society of Cardiology
- Heart failure in children by Great Ormond Street Hospital, London, UK

Wikimedia Commons has media related to *Heart failure*.

| | |
|---|---|
| **Classification** | **ICD-10**: I50 · **ICD-9-CM**: 428.0 · **MeSH**: D006333 · **DiseasesDB**: 16209 · |
| **External resources** | **MedlinePlus**: 000158 · **Patient UK**: Heart failure · |

| v · t · e · | **Cardiovascular disease (heart) (I00–I52, 390–429)** | | |
|---|---|---|---|
| **Ischaemic** | **Coronary disease** | Coronary artery disease (CAD) · Coronary artery aneurysm · Spontaneous coronary artery dissection (SCAD) · Coronary thrombosis · Coronary vasospasm · Myocardial bridge · | |
| | **Active ischemia** | Angina pectoris (Prinzmetal's angina · Stable angina · · Acute coronary syndrome (Myocardial infarction · Unstable angina · · | |
| | **Sequelae** | *hours* (Hibernating myocardium · Myocardial stunning · · *days* (Myocardial rupture · · *weeks* (Aneurysm of heart / Ventricular aneurysm · Dressler syndrome · · | |
| **Layers** | **Pericardium** | Pericarditis (Acute · Chronic / Constrictive · · Pericardial effusion (Cardiac tamponade · Hemopericardium · · | |
| | **Myocardium** | Myocarditis (Chagas disease · · Cardiomyopathy: Dilated (Alcoholic), Hypertrophic, *and* Restrictive (Loeffler endocarditis · Cardiac amyloidosis · Endocardial fibroelastosis · · Arrhythmogenic right ventricular dysplasia · | |
| | **Endocardium / valves** | **Endocarditis** | *infective endocarditis* (Subacute bacterial endocarditis · · *non-infective endocarditis* (Libman–Sacks endocarditis · Nonbacterial thrombotic endocarditis · · |
| | | **Valves** | *mitral* (regurgitation · prolapse · stenosis · · *aortic* (stenosis · insufficiency · · *tricuspid* (stenosis · insufficiency · · *pulmonary* (stenosis · insufficiency · · |
| **Conduction / arrhythmia** | **Bradycardia** | Sinus bradycardia · Sick sinus syndrome · Heart block: Sinoatrial · AV (1° · 2° · 3° · · Intraventricular · Bundle branch block (Right · Left · Left anterior fascicle · Left posterior fascicle · Bifascicular · Trifascicular · · Adams–Stokes syndrome · | |
| | **Tachycardia (paroxysmal and sinus)** | **Supraventricular** | Atrial (Multifocal · · Junctional (AV nodal reentrant · Junctional ectopic · · |
| | | **Ventricular** | Accelerated idioventricular rhythm · Catecholaminergic polymorphic · Torsades de pointes · |
| | **Premature contraction** | Atrial · Junctional · Ventricular · | |
| | **Pre-excitation syndrome** | Lown–Ganong–Levine · Wolff–Parkinson–White · | |
| | **Flutter / fibrillation** | Atrial flutter · Ventricular flutter · Atrial fibrillation (Familial · · Ventricular fibrillation · | |

| | | |
|---|---|---|
| | **Pacemaker** | Ectopic pacemaker / Ectopic beat · Multifocal atrial tachycardia · Pacemaker syndrome · Parasystole · Wandering pacemaker · |
| | **Long QT syndrome** | Andersen–Tawil · Jervell and Lange-Nielsen · Romano–Ward · |
| | **Cardiac arrest** | Sudden cardiac death · Asystole · Pulseless electrical activity · Sinoatrial arrest · |
| | **Other / ungrouped** | *hexaxial reference system* (Right axis deviation · Left axis deviation · · *QT* (Short QT syndrome · · *T* (T wave alternans · · *ST* (Osborn wave · ST elevation · ST depression · · Strain pattern · |
| **Cardiomegaly** | | Ventricular hypertrophy (Left · Right / Cor pulmonale · · Atrial enlargement (Left · Right · · |
| **Other** | | Cardiac fibrosis · **Heart failure** (Diastolic heart failure · Cardiac asthma · · Rheumatic fever · |

| V · T · E · | **Organ failure** |
|---|---|
| **General** | **Heart failure** · Respiratory failure · Liver failure (Acute liver failure · Chronic liver failure · · Renal failure (Acute renal failure · Chronic renal failure · · Encephalopathy · |
| **Multiple** | Multiple organ dysfunction syndrome · |

| | |
|---|---|
| **Authority control** | NDL: 00571034 · |

Categories: Aging-associated diseases | Heart diseases | Organ failure




# Myocardial infarction

From Wikipedia, the free encyclopedia

*"Heart attack" redirects here. For other uses, see Heart attack (disambiguation).*

**Myocardial infarction** (**MI**) or **acute myocardial infarction** (**AMI**), commonly known as a **heart attack**, occurs when blood flow stops to a part of the heart causing damage to the heart muscle. The most common symptom is chest pain or discomfort which may travel into the shoulder, arm, back, neck, or jaw. Often it is in the center or left side of the chest and lasts for more than a few minutes. The discomfort may occasionally feel like heartburn. Other symptoms may include shortness of breath, nausea, feeling faint, a cold sweat, or feeling tired.[1] About 30% of people have atypical symptoms,[2] with women more likely than men to present atypically.[3] Among those over 75 years old, about 5% have had an MI with little or no history of symptoms.[4] An MI may cause heart failure, an irregular heartbeat (including serious types), cardiogenic shock, or cardiac arrest.[5][6]

Most MIs occur due to coronary artery disease.[5] Risk factors include high blood pressure, smoking, diabetes, lack of exercise, obesity, high blood cholesterol, poor diet, and excessive alcohol intake, among others.[7][8] The mechanism of an MI often involves the complete blockage of a coronary artery caused by a rupture of an atherosclerotic plaque.[5] MIs are less commonly caused by coronary artery spasms, which may be due to cocaine, significant emotional stress, and extreme cold, among others.[9][10] A number of tests are useful to help with diagnosis, including electrocardiograms (ECGs), blood tests, and coronary angiography.[11] An ECG may confirm an ST elevation MI if ST elevation is present.[2] Commonly used blood tests include troponin and less often creatine kinase MB.[11]

Aspirin is an appropriate immediate treatment for a suspected MI.[12] Nitroglycerin or opioids may be used to help with chest pain; however, they do not improve overall outcomes.[2][12] Supplemental oxygen should be used in those with low oxygen levels or shortness of breath.[12] In ST elevation MIs treatments which attempt to restore blood flow to the heart are typically recommended and include angioplasty, where the arteries are pushed open, or thrombolysis, where the blockage is removed using medications.[2] People who have a non-ST elevation

**Myocardial infarction**

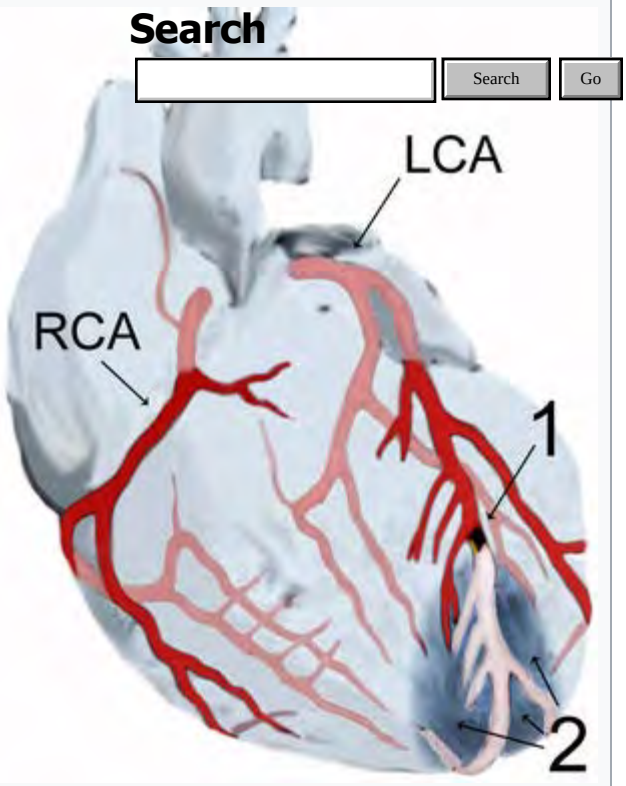



Diagram of a myocardial infarction (2) of the anterior wall of the heart after blockage (1) of a branch of the left coronary artery (LCA). In the diagram, RCA is the right coronary artery.

| Classification and external resources | |
|---|---|
| **Specialty** | Cardiology |
| **ICD-10** | I21-I22 |
| **ICD-9-CM** | 410 |
| **DiseasesDB** | 8664 |
| **MedlinePlus** | 000195 |
| **eMedicine** | med/1567 emerg/327 ped/2520 |
| **Patient UK** | Myocardial infarction |

myocardial infarction (NSTEMI) are often managed with the blood thinner heparin, with the additional use of angioplasty in those at high risk.[12] In people with blockages of multiple coronary arteries and diabetes, bypass surgery (CABG) may be recommended rather than angioplasty.[13] After an MI, lifestyle modifications, along with long term treatment with aspirin, beta blockers, and statins, are typically recommended.[2]

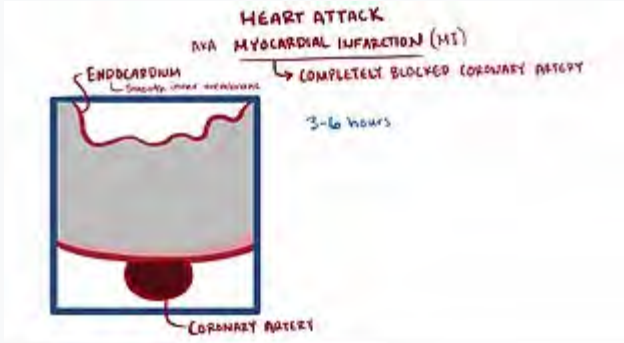
| | |
|---|---|
| **MeSH** | D009203 |

[edit on Wikidata]

Worldwide, about 8.6 million myocardial infarctions occurred in 2013.[14] More than 3 million people had an ST elevation MI and more than 4 million had an NSTEMI.[15] STEMIs occur about twice as often in men as women.[16] About one million people have an MI each year in the United States.[5] In the developed world the risk of death in those who have had an STEMI is about 10%.[2] Rates of MI for a given age have decreased globally between 1990 and 2010.[17]

**Contents**



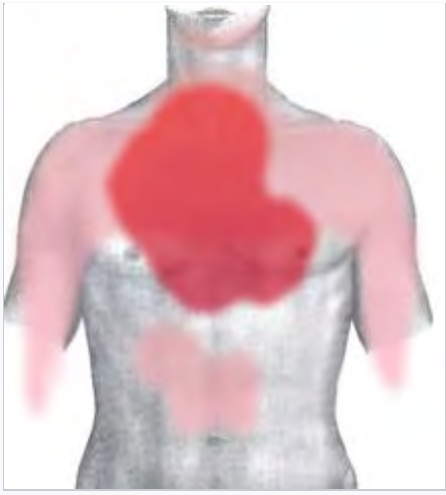



Play media

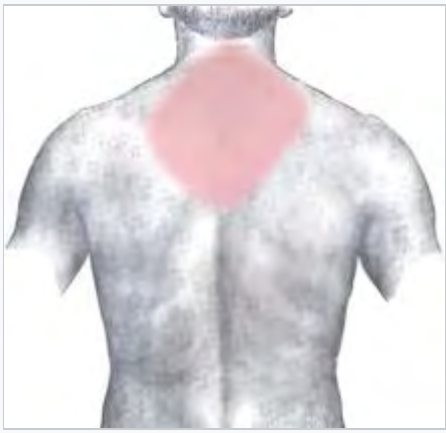
Video explanation

## Signs and symptoms [edit]

The onset of symptoms in myocardial infarction (MI) is usually gradual, over several minutes, and rarely instantaneous.[18] Chest pain is the most common symptom of acute MI and is often described as a sensation of tightness, pressure, or squeezing. Chest pain due to ischemia (a lack of blood and hence oxygen supply) of the heart muscle is termed angina pectoris. Pain radiates most often to the left arm, but may also radiate to the lower jaw, neck, right arm, back, and upper [19]



Rough diagram of pain zones in myocardial infarction; dark red: most typical area, light red: other possible areas; view of the chest



Back view

abdomen, where it may mimic heartburn. Levine's sign, in which a person localizes the chest pain by clenching their fists over their sternum, has classically been thought to be predictive of cardiac chest pain, although a prospective observational study showed it had a poor positive predictive value.[20]

Shortness of breath occurs when the damage to the heart limits the output of the left ventricle, causing left ventricular failure and consequent pulmonary edema. Other symptoms include diaphoresis (an excessive form of sweating),[21] weakness, light-headedness, nausea, vomiting, and palpitations. These symptoms are likely induced by a massive surge of catecholamines from the sympathetic nervous system,[22] which occurs in response to pain and the blood flow abnormalities that result from dysfunction of the heart muscle. Loss of consciousness (due to inadequate blood flow to the brain and cardiogenic shock) and sudden death (frequently due to the development of ventricular fibrillation) can occur in MIs.[19]

Atypical symptoms are more frequently reported by women, the elderly, and those with diabetes when compared to their male and younger counterparts.[23][24] Women also report more numerous symptoms compared with men (2.6 on average vs. 1.8 symptoms in men).[23] The most common symptoms of MI in women include dyspnea, weakness, and fatigue. Fatigue, sleep disturbances, and dyspnea have been reported as frequently occurring symptoms that may manifest as long as one month before the actual clinically manifested ischemic event. In women, chest pain may be less predictive of coronary ischemia than in men.[25] Women may also experience back or jaw pain during an episode.[26]

At least one quarter of all MIs happen without chest pain or other symptoms.[4] These cases can be discovered later on electrocardiograms, using blood enzyme tests, or at autopsy without a prior history of related complaints. Estimates of the prevalence of silent MIs vary between 22 and 64%.[4] A silent course is more common in the elderly,[4] in people with diabetes mellitus[27] and after heart transplantation, probably because the donor heart is not fully innervated by the nervous system of the recipient.[28] In people with diabetes, differences in pain threshold, autonomic neuropathy, and psychological factors have been cited as possible explanations for the lack of symptoms.[27]

Any group of symptoms compatible with a sudden interruption of the blood flow to the heart, which includes STEMI, NSTEMI or unstable angina, are called an acute coronary syndrome.[29]

## Causes [edit]

Many of the risk factors for myocardial infarction are modifiable and thus many cases may be preventable.

### Lifestyle [edit]

Smoking appears to be the cause of about 36% and obesity the cause of 20% of coronary artery

disease.[30] Lack of exercise has been linked to 7–12% of cases.[30][31] Less common causes include stress-related causes such as job stress, which accounts for about 3% of cases,[30] and chronic high stress levels.[32]

Tobacco smoking (including secondhand smoke)[33] and short-term exposure to air pollution such as carbon monoxide, nitrogen dioxide, and sulfur dioxide (but not ozone) have been associated with MI.[34] Other factors that increase the risk of MI and are associated with worse outcomes after an MI include lack of physical activity[35] and psychosocial factors including low socioeconomic status, social isolation, and negative emotions. Shift work is also associated with a higher risk of MI.[36] Acute and prolonged intake of high quantities of alcoholic drinks (3-4 or more) increase the risk of a heart attack.[37]

The evidence for saturated fat is unclear. Some state there is evidence of benefit from reducing saturated fat,[38] specifically a benefit from eating polyunsaturated fat instead of saturated fat.[39] While others state there is little evidence that reducing dietary saturated fat or increasing polyunsaturated fat intake affects heart attack risk.[40][41] Dietary cholesterol does not appear to have a significant effect on blood cholesterol and thus recommendations about its consumption may not be needed.[42] Trans fats do appear to increase risk.[40]

## Disease [edit]

Diabetes mellitus (type 1 or 2),[43] high blood pressure,[33] dyslipidemia/high levels of blood cholesterol (abnormal levels of lipoproteins in the blood), particularly high low-density lipoprotein, low high-density lipoprotein, high triglycerides,[33] endometriosis in women under the age of 40[44] and obesity[45] (defined by a body mass index of more than 30 kg/m², or alternatively by waist circumference or waist-hip ratio) have all been linked to MI.

A number of acute and chronic infections including *Chlamydophila pneumoniae*, influenza, *Helicobacter pylori*, and *Porphyromonas gingivalis* among others have been linked to atherosclerosis and myocardial infarction.[46] As of 2013, there is no evidence of benefit from antibiotics or vaccination, however, calling the association into question.[46][47] Myocardial infarction can also occur as a late consequence of Kawasaki disease.[48]

## Genetic [edit]

Genome-wide association studies have found 27 genetic variants that are associated with an increased risk of myocardial infarction.[49] Strongest association of MI has been found with the 9p21 genomic locus, which contains genes CDKN2A & 2B, although the single nucleotide polymorphisms that are implicated are within a non-coding region.[49] The majority of these variants are in regions that have not been previously implicated in coronary artery disease. The following genes have an association with MI: PCSK9, SORT1, MIA3, WDR12, MRAS, PHACTR1, LPA, TCF21, MTHFDSL, ZC3HC1, CDKN2A, 2B, ABO, PDGF0, APOA5, MNF1ASM283, COL4A1, HHIPC1, SMAD3, ADAMTS7, RAS1, SMG6, SNF8, LDLR, SLC5A3, MRPS6, KCNE2.[49]

## Other [edit]

At any given age, men are more at risk than women, particularly before menopause,[50] but because in general women live longer than men, ischemic heart disease causes slightly more total deaths in women.[35] Family history of ischemic heart disease or MI, particularly if one has a first-degree relative (father, brother, mother, sister) who suffered a 'premature' myocardial infarction (defined as occurring at or younger than age 55 years (men) or 65 (women)).[35]

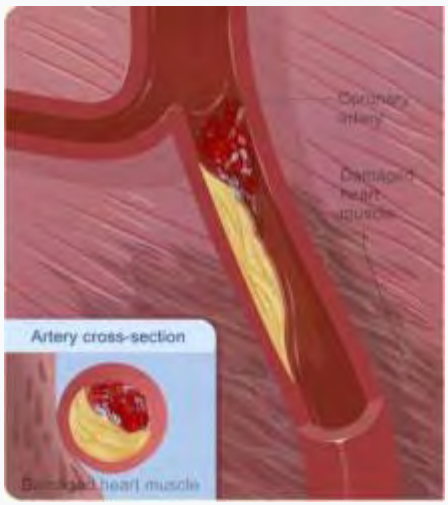
Women who use combined oral contraceptive pills have a modestly increased risk of myocardial infarction, especially in the presence of other risk factors, such as smoking.[51] Heart attacks appear to occur more commonly in the morning hours, especially between 6AM and noon.[52] Evidence suggests that heart [53]

attacks are at least three times more likely to occur in the morning than in the late evening. Old age increases risk of a heart attack.[35]

## Pathophysiology [edit]

*See also: Acute coronary syndrome*

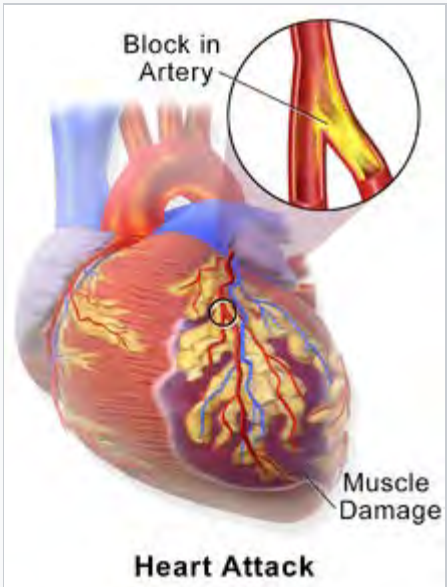
Acute myocardial infarction refers to two subtypes of acute coronary syndrome, namely non-ST-elevated and ST-elevated MIs, which are most frequently (but not always) a manifestation of coronary artery disease.[54] The most common triggering event is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade, sometimes resulting in total occlusion of the artery.[55][56] Atherosclerosis is the gradual buildup of cholesterol and fibrous tissue in plaques in the wall of arteries (in this case, the coronary arteries), typically over decades.[57] Bloodstream column irregularities visible on angiography reflect artery lumen narrowing as a result of decades of advancing atherosclerosis.[58] Plaques can become unstable, rupture, and additionally promote the formation of a blood clot that occludes the artery; this can occur in minutes. When a severe enough plaque rupture occurs in the coronary arteries, it leads to MI (necrosis of downstream myocardium).[55][56] It is estimated that one billion cardiac cells are lost in a typical MI.[59]




Play media

The animation shows how plaque buildup or a coronary artery spasm can lead to a heart attack and how blocked blood flow in a coronary artery can lead to a heart attack.

If impaired blood flow to the heart lasts long enough, it triggers a process called the ischemic cascade; the heart cells in the territory of the occluded coronary artery die (chiefly through necrosis) and do not grow back. A collagen scar forms in their place. Recent studies indicate that another form of cell death, apoptosis, also plays a role in the process of tissue damage following an MI.[60] As a result, the person's heart will be permanently damaged. This myocardial scarring also puts the person at risk for potentially life-threatening abnormal heart rhythms (arrhythmias) and may result in the formation of a ventricular aneurysm that can rupture with catastrophic consequences.




A myocardial infarction occurs when an atherosclerotic plaque slowly builds up in the inner lining of a coronary artery and then suddenly ruptures, causing catastrophic thrombus formation,

Injured heart tissue conducts electrical impulses more slowly than normal heart tissue. The difference in conduction velocity between injured and uninjured tissue can trigger re-entry or a feedback loop that is believed to be the cause of many lethal arrhythmias. The most serious of these arrhythmias is ventricular fibrillation (V-Fib/VF), an extremely fast and chaotic heart rhythm that is the leading cause of sudden cardiac death. Another life-threatening arrhythmia is ventricular tachycardia (V-tach/VT), which can cause sudden cardiac death. However, VT usually results in rapid heart rates that prevent the heart from pumping blood effectively. Cardiac output and blood pressure may fall to dangerous levels, which can lead to further coronary ischemia and extension of the infarct.

The cardiac defibrillator device was specifically designed to terminate these potentially fatal arrhythmias. The device works by delivering an electrical shock to the person to depolarize a critical mass of the heart muscle, in effect "rebooting" the heart. This therapy is time-dependent, and the odds of successful defibrillation decline rapidly after the onset of cardiopulmonary arrest.

Myocardial infarction in the setting of plaque results from underlying atherosclerosis.[19] Inflammation is known to be an important step in

the process of atherosclerotic plaque formation.[61] C-reactive protein (CRP) is a sensitive but nonspecific marker for inflammation. Elevated CRP blood levels, especially measured with high-sensitivity assays, can predict the risk of MI, as well as stroke and development of diabetes.[61] Moreover, some drugs for MI might also reduce CRP levels.[61] The use of high-sensitivity CRP assays as a means of screening the general population is advised against, but it may be used optionally at the physician's discretion in those who already present with other risk factors or known coronary artery disease.[62] Whether CRP plays a direct role in atherosclerosis remains uncertain.[61]

Calcium deposition as calcification is another part of atherosclerotic plaque formation. Calcium deposits in the coronary arteries can be detected with CT scans. Several studies have shown that coronary calcium can provide predictive information beyond that of classical risk factors.[63][64][65]

Hyperhomocysteinemia (high blood levels of the amino acid homocysteine) in homocysteinuria is associated with premature atherosclerosis;[66] whether elevated homocysteine in the normal range is causal is controversial.[67]

totally occluding the artery and preventing blood flow downstream.

Drawing of the heart showing anterior left ventricle wall infarction

## Pathological types [edit]

The two main types of acute myocardial infarction, based on pathology, are:

- Transmural AMI is associated with atherosclerosis involving a major coronary artery. It can be subclassified into anterior, posterior, inferior, lateral, or septal. Transmural infarcts extend through the whole thickness of the heart muscle and are usually a result of complete occlusion of the area's blood supply.[68] In addition, on ECG, ST elevation and Q waves are seen.
- Subendocardial AMI involves a small area in the subendocardial wall of the left ventricle, ventricular septum, or papillary muscles. The subendocardial area is particularly susceptible to ischemia.[68] In addition, ST depression may be seen on ECG in addition to T wave changes.

Specimen showing myocardial infarction in the left ventricle and the interventricular septum. The asterisk(*) also indicates left ventricular hypertrophy.

# Diagnosis [edit]

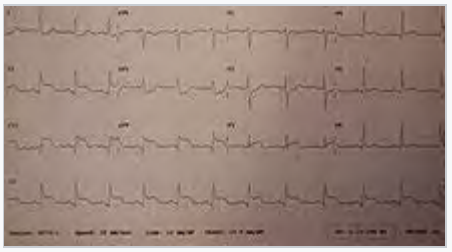
*Main article: Myocardial infarction diagnosis*

A cardiac troponin rise accompanied by either typical symptoms, pathological Q waves, ST elevation or depression, or coronary intervention is diagnostic of MI.[69]

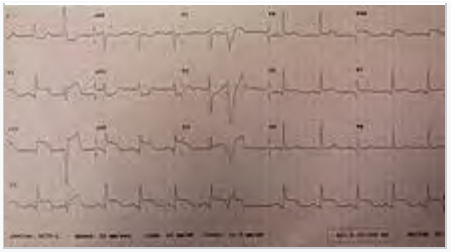
WHO criteria[70] formulated in 1979 have classically been used to diagnose MI; a patient is diagnosed with MI if two (probable) or three (definite) of the following criteria are satisfied:

1. Clinical history of ischemic-type chest pain lasting for more than 20 minutes
2. Changes in serial ECG tracings
3. Rise and fall of serum cardiac biomarkers

At autopsy, a pathologist can diagnose an MI based on anatomopathological findings.



An inferior and right ventricular STEMI as seen on 12 lead ECG



Same inferior and right ventricular STEMI as seen on 15 lead ECG. There are additionally some premature ventricular contractions

## Classification [edit]

Myocardial infarctions are generally classified into ST elevation MI (STEMI) and non-ST elevation MI (NSTEMI).[54] A STEMI is the combination of symptoms related to poor oxygenation of the heart with elevation of the ST segments on the electrocardiogram followed by an increase in proteins in the blood related to heart muscle's death.[16] They make up about 25 to 40 percent of cases.[16]

The phrase "heart attack" is often used non-specifically to refer to a myocardial infarction and to sudden cardiac death. An MI is different from—but can cause—cardiac arrest, where the heart is not contracting at all or so poorly that all vital organs cease to function. It is also distinct from heart failure, in which the pumping action of the heart is impaired. However, an MI may lead to heart failure.[19]

A 2007 consensus document classifies MI into five main types:[71]

- Type 1 – spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
- Type 2 – MI secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension
- Type 3 – sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by new ST elevation, or new left bundle branch block (LBBB), or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
- Type 4 – associated with coronary angioplasty or stents:
  - Type 4a – MI associated with percutaneous coronary intervention (PCI)
  - Type 4b – MI associated with stent thrombosis as documented by angiography or at autopsy
- Type 5 – MI associated with CABG

The terms Q wave and non-Q wave MI were previously used to indicate STEMI and non-STEMI respectively.[72]

## Electrocardiogram [edit]

For a person to qualify as having a STEMI, in addition to reported angina, the ECG must show new ST elevation in two or more adjacent ECG leads.[16] This must be greater than 2 mm (0.2 mV) for males and greater than 1.5 mm (0.15 mV) in females if in leads V2 and V3 or greater than 1 mm (0.1 mV) if it is in other ECG leads.[16] Previously, a recent left bundle branch block was considered the same as ST elevation, however, this is no longer the case.[16] In early STEMIs there may just be peaked T waves with ST elevation developing later.[16]

## Cardiac biomarkers [edit]

While there are a number of different biomarkers, troponins are considered to be the best[16] and reliance on older tests (such as CK-MB) or myoglobin is discouraged.[73] This is not the case in the setting of peri-procedural MI where use of troponin and CK-MB assays are considered useful.[74] Copeptin may be useful to rule out MI rapidly when used along with troponin.[75]

## Imaging [edit]

A chest radiograph and routine blood tests may indicate complications or precipitating causes and are often

performed upon arrival to an emergency department.

In stable patients whose symptoms have resolved by the time of evaluation, technetium (99mTc) sestamibi (i.e. a "MIBI scan") or thallium-201 chloride can be used in nuclear medicine to visualize areas of reduced blood flow in conjunction with physiological or pharmacological stress. Thallium may also be used to determine viability of tissue, distinguishing whether nonfunctional myocardium is actually dead or merely in a state of hibernation or of being stunned.[76] Medical societies and professional guidelines recommend that the physician confirm a person is at high risk for myocardial infarction before conducting imaging tests to make a diagnosis.[77][78] Patients who have a normal ECG and who are able to exercise, for example, do not merit routine imaging.[78] Imaging tests such as stress radionuclide myocardial perfusion imaging or stress echocardiography can confirm a diagnosis when a patient's history, physical exam, ECG, and cardiac biomarkers suggest the likelihood of a problem.[78]

### Differential diagnosis [edit]

The differential diagnosis for MI includes other catastrophic causes of chest pain, such as pulmonary embolism, aortic dissection, esophageal rupture, tension pneumothorax, or pericardial effusion causing cardiac tamponade. Other noncatastrophic differentials include gastroesophageal reflux and Tietze's syndrome.[79]

## Prevention [edit]

Myocardial infarction and other related cardiovascular diseases can be prevented to a large extent by a number of lifestyle changes and medical treatments.

### Lifestyle [edit]

Recommendations include increasing the intake of wholegrain starch, reducing sugar intake (particularly of refined sugar), consuming five portions of fruit and vegetables daily, consuming two or more portions of fish per week, and consuming 4–5 portions of unsalted nuts, seeds, or legumes per week.[80] The dietary pattern with the greatest support is the Mediterranean diet.[81] Vitamins and mineral supplements are of no proven benefit,[82] and neither are plant stanols or sterols.[80]

There is some controversy surrounding the effect of dietary fat on the development of cardiovascular disease. People are often advised to keep a diet where less than 30% of the energy intake derives from fat, a diet that contains less than 7% of the energy intake in the form of saturated fat, and a diet that contains less than 300 mg/day of cholesterol.[80] Replacing saturated with mono- polyunsaturated fat is also recommended,[80] as the consumption of polyunsaturated fat instead of saturated fat may decrease coronary heart disease.[83] Olive oil, rapeseed oil and related products are to be used instead of saturated fat.[80]

Physical activity can reduce the risk of cardiovascular disease, and people at risk are advised to engage in 150 minutes of moderate or 75 minutes of vigorous intensity aerobic exercise a week.[80] Keeping a healthy weight, drinking alcohol within the recommended limits, and quitting smoking are measures that also appear to reduce the risk of cardiovascular disease.[80]

On a population level, public health measures may be used to reduce unhealthy diets (excessive salt, saturated fat and trans fat) including food labeling and marketing requirements as well as requirements for catering and restaurants, and stimulating physical activity. This may be part of regional cardiovascular disease prevention programs, or through the health impact assessment of regional and local plans and policies.[84]

### Medication [edit]

Aspirin has been studied extensively in people considered at increased risk of myocardial infarction. Based

on numerous studies in different groups (e.g. people with or without diabetes), there does not appear to be a benefit strong enough to outweigh the risk of excessive bleeding.[85][86] Nevertheless, many clinical practice guidelines continue to recommend aspirin for primary prevention,[87] and some researchers feel that those with very high cardiovascular risk but low risk of bleeding should continue to receive aspirin.[88]

Cholesterol-lowering drugs from the statin class may be used in those at an elevated risk of cardiovascular disease; this can be calculated with validated risk prediction tools such as QRISK2.[80]

Long term hormone replacement therapy when started around the time of menopause may decrease heart disease.[89][90]

Following a heart attack, nitrates, when taken for two days, and ACE-inhibitors decrease the risk of death.[91]

## Management [edit]

*Main article: Management of acute coronary syndrome*

An MI requires immediate medical attention. Treatment attempts to save as much viable heart muscle as possible and to prevent further complications, hence the phrase "time is heart muscle".[92] Aspirin and nitroglycerin may be administered. Nitroglycerin (administered under the tongue or intravenously) may be administered to improve the blood supply to the heart.[73] Morphine may be used if nitroglycerin is not effective.[73] Other analgesics such as nitrous oxide are of unknown benefit.[93]

In the past, high flow oxygen was recommended for everyone with possible myocardial infarction.[73] More recently, routine use was found to lead to increased mortality and infarct size.[94][95] Therefore, oxygen is currently only used if oxygen levels are found to be low or someone is in respiratory distress.[73] A 2015 meta-analysis concluded that the use of an intra-aortic balloon pump during an acute MI with or without cardiogenic shock does not reduce mortality.[96]

### STEMI [edit]

The main treatment for MI with ECG evidence of ST elevation (STEMI) include thrombolysis and percutaneous coronary intervention.[97] Primary percutaneous coronary intervention (PCI) is the treatment of choice for STEMI if it can be performed in a timely manner.[97][98] If PCI cannot be performed within 90 to 120 minutes then thrombolysis, preferably within 30 minutes of arrival to hospital, is recommended.[98][99][100] If a person has had symptoms for 12 to 24 hours evidence for thrombolysis is less and if they have had symptoms for more than 24 hours it is not recommended.[101]

Thrombolysis involves the administration of medication that activates the enzymes that normally destroy blood clots. Thrombolysis agents include streptokinase, reteplase, alteplase, and tenecteplase. If no contraindications are present (such as a high risk of bleeding), thrombolysis can be given in the pre-hospital or in-hospital setting. When given to people suspected of having a STEMI within 6 hours of the onset of symptoms, thrombolytic drugs save the life of 1 in 43 who received them. The risks were major bleeding (1 in 143) and brain bleeding (1 in 250).[102][103] It is unclear whether pre-hospital thrombolysis reduces death in people with STEMI compared to in-hospital thrombolysis.[104] Pre-hospital thrombolysis reduces time to thrombolytic treatment, based on studies conducted in higher income countries.[104]

If despite thrombolysis there is significant cardiogenic shock, continued severe chest pain, or less than a 50% improvement in ST elevation on the ECG recording after 90 minutes, then rescue PCI is indicated emergently.[99][105] After PCI, people are generally placed on dual antiplatelet therapy for at least a year (which is generally aspirin and clopidogrel).[16][97][106]

When beta blocker medication are given within the first 24–72 hours of a major heart attack ("STEMI") no lives are saved. However, 1 in 200 people were prevented from a repeat heart attack, and another 1 in 200 from having an abnormal heart rhythm. Additionally, for 1 in 91 the drug causes a temporary poor ability of

the heart to pump blood.[107]

Those who have had cardiac arrest may benefit from targeted temperature management with evaluation for implementation of hypothermia protocols. Furthermore, those with cardiac arrest, and ST elevation at any time, should usually have angiography.[108]

## NSTEMI [edit]

In the absence of ST elevation, diagnosis of MI is based on a blood test for biomarkers (usually troponin). This can take 3–6 hours after the onset of symptoms to become positive. The scenario is referred to as "non-ST elevation acute coronary syndrome" (NSTEACS). In the meantime, the calculated risk of further cardiovascular events (e.g. using the GRACE score) and the presence of other ECG changes and clinical features determines ongoing management.[73][77]

People with an acute coronary syndrome where no ST elevation is demonstrated (non-ST elevation ACS or NSTEACS) are treated with aspirin.[73][77] Clopidogrel is added in many cases, particularly if the risk of cardiovascular events is felt to be high and early PCI is being considered.[73][77] Depending on whether early PCI is planned, a factor Xa inhibitor or a potentiator of antithrombin (fondaparinux or low molecular weight heparin respectively) may be added.[77] In very high-risk scenarios, inhibitors of the platelet glycoprotein $\alpha_{IIb}\beta_{3a}$ receptor such as eptifibatide or tirofiban may be used.[73][77]

Heparins in those who have had an NSTEMI or unstable angina do not change the risk of death.[109] They do decrease the risk of having a further myocardial infarction.[109]

As of 2011, P2Y12 inhibitors are recommended for 12 months following NSTEMI in Europe.[110] A 2014 review of P2Y12 inhibitors such as clopidogrel found they do not change the risk of death when given to people with a suspected NSTEMI prior to PCI. They do however increase the risk of bleeding and decrease the risk of further cardiovascular problems. The authors thus concluded that their routine use prior to PCI is of questionable value.[111]

## Cardiac rehabilitation [edit]

Cardiac rehabilitation benefits many who have experienced myocardial infarction, even if there has been substantial heart damage and resultant left ventricular failure; ideally other medical conditions that could interfere with participation should be managed optimally. It should start soon after discharge from the hospital. The program may include lifestyle advice, exercise, social support, as well as recommendations about driving, flying, sport participation, stress management, and sexual intercourse.[112]

## Secondary prevention [edit]

A number of lifestyle recommendations are available to those who have experienced myocardial infarction. This includes the adoption of a Mediterranean-type diet, maintaining alcohol intake within recommended limits, exercising to the point of mild breathlessness for 20–30 minutes every day, stopping smoking, and trying to achieve a healthy weight.[112] Exercise is both safe and effective even if people have had stents or heart failure.[113]

People are usually started on several long-term medications after an MI, with the aim of preventing further cardiovascular events such as MIs, congestive heart failure, or strokes.

- Aspirin as well as another antiplatelet agent such as clopidogrel or ticagrelor ("dual antiplatelet therapy" or DAPT), is continued for up to twelve months, followed by aspirin indefinitely.[112] If someone has another medical condition that requires anticoagulation (e.g. with warfarin) this may need to be adjusted based on risk of further cardiac events as well as bleeding risk.[112] In those who have had a stent, more than 12 months of clopidogrel plus aspirin does not affect the risk of death.[114]
- Beta blocker therapy such as metoprolol or carvedilol is recommended to be started within 24 hours, provided there is no acute heart failure or heart block.[16][73][112] The dose should be increased to the [112]

highest tolerated. Contrary to what was long believed, the use of beta blockers does not appear to affect the risk of death, possibly because other treatments for MI have improved.[115] They should not be used in those who have recently taken cocaine.[116]

- ACE inhibitor therapy should be started when stable and continued indefinitely at the highest tolerated dose. Those who cannot tolerate ACE inhibitors may be treated with an angiotensin II receptor antagonist.[112]
- Statin therapy has been shown to reduce mortality and morbidity.[117] The protective effects of statins may be due to more than their LDL lowering effects. The general consensus is that statins have the ability to stabilize plaques and multiple other ("pleiotropic") effects that may prevent myocardial infarction in addition to their effects on blood lipids.[118]
- Aldosterone antagonists (spironolactone or eplerenone) may be used if there is evidence of left ventricular dysfunction after an MI, ideally after beginning treatment with an ACE inhibitor.[112]
- Previous studies suggested a benefit from omega-3 fatty acid supplementation but this has not been confirmed.[112]

## Prognosis [edit]

The prognosis after MI varies greatly depending on a person's health, the extent of the heart damage, and the treatment given.

In those who have an STEMI in the United States, between 5 and 6 percent die before leaving the hospital and 7 to 18 percent die within a year.[16]

Using variables available in the emergency room, people with a higher risk of adverse outcome can be identified. One study found 0.4% of patients with a low-risk profile died after 90 days, whereas in high-risk people it was 21.1%.[119]

Some risk factors for death include age, hemodynamic parameters (such as heart failure, cardiac arrest on admission, systolic blood pressure, or Killip class of two or greater), ST-segment deviation, diabetes, serum creatinine, peripheral vascular disease, and elevation of cardiac markers.[119][120][121] Assessment of left ventricular ejection fraction may increase the predictive power.[122] Prognosis is worse if a mechanical complication such as papillary muscle or myocardial free wall rupture occurs.[123] Morbidity and mortality from myocardial infarction has improved over the years due to better treatment.[124]

Throughout hospital departments, practitioners use TIMI scores to assess mortality risk. There are TIMI (Thrombolysis in Myocardial Infarction) scores for unstable angina or NSTEMI[125] and STEMI,[126] both using routine patient data from history taking, medication use and lab results. Both scores have been found effective and reliable in multiple settings, including the emergency room.

### Complications [edit]

*Main article: Myocardial infarction complications*

Complications may occur immediately following the heart attack (in the acute phase) or may need time to develop (a chronic problem). Acute complications may include heart failure if the damaged heart is no longer able to pump blood adequately around the body; aneurysm of the left ventricle myocardium; ventricular septal rupture or free wall rupture; mitral regurgitation, in particular if the infarction causes dysfunction of the papillary muscle; Dressler's syndrome; and abnormal heart rhythms, such as ventricular fibrillation, ventricular tachycardia, atrial fibrillation, and heart block. Longer-term complications include heart failure, atrial fibrillation, and an increased risk of a second MI.

## Epidemiology [edit]

Myocardial infarction is a common presentation of coronary artery disease. The World Health Organization estimated in 2004, that 12.2% of worldwide deaths were from ischemic heart disease;[127] with it being the

leading cause of death in high- or middle-income countries and second only to lower respiratory infections in lower-income countries.[127] Worldwide, more than 3 million people have STEMIs and 4 million have NSTEMIs a year.[15] STEMIs occur about twice as often in men as women.[16]

Rates of death from ischemic heart disease (IHD) have slowed or declined in most high-income countries, although cardiovascular disease still accounted for one in three of all deaths in the USA in 2008.[128] For example, rates of death from cardiovascular disease have decreased almost a third between 2001 and 2011 in the United States.[129]

In contrast, IHD is becoming a more common cause of death in the developing world. For example, in India, IHD had become the leading cause of death by 2004, accounting for 1.46 million deaths (14% of total deaths) and deaths due to IHD were expected to double during 1985–2015.[130] Globally, disability adjusted life years (DALYs) lost to ischemic heart disease are predicted to account for 5.5% of total DALYs in 2030, making it the second-most-important cause of disability (after unipolar depressive disorder), as well as the leading cause of death by this date.[127]

## Society and culture [edit]

In the United States, women who have had an MI are often treated with fewer medical interventions than men.[16] The word is from Latin: *infarctus myocardii*.

### Economics [edit]

In 2011, AMI was one of the top five most expensive conditions seen during inpatient hospitalizations in the U.S., with an aggregate cost of about $11.5 billion for 612,000 hospital stays.[131]

### Legal implications [edit]

At common law, in general, a myocardial infarction is a disease, but may sometimes be an injury. This can create coverage issues in the administration of no-fault insurance schemes such as workers' compensation. In general, a heart attack is not covered;[132] however, it may be a work-related injury if it results, for example, from unusual emotional stress or unusual exertion.[133] In addition, in some jurisdictions, heart attacks suffered by persons in particular occupations such as police officers may be classified as line-of-duty injuries by statute or policy. In some countries or states, a person having suffered from an MI may be prevented from participating in activity that puts other people's lives at risk, for example driving a car or flying an airplane.[134]

## References [edit]


1. ^ "What Are the Signs and Symptoms of Coronary Heart Disease?". *www.nhlbi.nih.gov*. September 29, 2014. Retrieved 23 February 2015.
2. ^ *a b c d e f* Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology, (ESC); Steg, PG; James, SK; Atar, D; Badano, LP; Blömstrom-Lundqvist, C; Borger, MA; Di Mario, C; Dickstein, K; Ducrocq, G; Fernandez-Aviles, F; Gershlick, AH; Giannuzzi, P; Halvorsen, S; Huber, K; Juni, P; Kastrati, A; Knuuti, J; Lenzen, MJ; Mahaffey, KW; Valgimigli, M; van 't Hof, A; Widimsky, P; Zahger, D (October 2012). "ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation.". *European Heart Journal*. **33** (20): 2569–619. doi:10.1093/eurheartj/ehs215. PMID 22922416.
3. ^ Coventry, LL; Finn, J; Bremner, AP (2011). "Sex differences in symptom presentation in acute myocardial infarction: a systematic review and meta-analysis.". *Heart & lung : the journal of critical care*. **40** (6): 477–91. doi:10.1016/j.hrtlng.2011.05.001. PMID 22000678.
4. ^ *a b c d* Valensi P, Lorgis L, Cottin Y; Lorgis; Cottin (March 2011). "Prevalence, incidence, predictive factors and prognosis of silent myocardial infarction: a review of the literature". *Arch Cardiovasc Dis*. **104** (3): 178–88. doi:10.1016/j.acvd.2010.11.013. PMID 21497307.
5. ^ *a b c d* "What Is a Heart Attack?". *www.nhlbi.nih.gov*. December 17, 2013. Retrieved 24 February 2015.

6. ^ "Heart Attack or Sudden Cardiac Arrest: How Are They Different?". *www.heart.org*. Jul 30, 2014. Retrieved 24 February 2015.
7. ^ Mehta, PK; Wei, J; Wenger, NK (16 October 2014). "Ischemic heart disease in women: A focus on risk factors.". *Trends in Cardiovascular Medicine*. **25** (2): 140–151. doi:10.1016/j.tcm.2014.10.005. PMID 25453985.
8. ^ Mendis, Shanthi; Puska,, Pekka; Norrving, Bo (2011). *Global atlas on cardiovascular disease prevention and control* (PDF) (1st ed.). Geneva: World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. pp. 3–18. ISBN 9789241564373. Missing | last1= in Authors list (help)
9. ^ "What Causes a Heart Attack?". *www.nhlbi.nih.gov*. December 17, 2013. Retrieved 24 February 2015.
10. ^ Devlin, RJ; Henry, JA (2008). "Clinical review: Major consequences of illicit drug consumption.". *Critical care (London, England)*. **12** (1): 202. doi:10.1186/cc6166. PMC 2374627. PMID 18279535.
11. ^ *a b* "How Is a Heart Attack Diagnosed?". *www.nhlbi.nih.gov*. December 17, 2013. Retrieved 24 February 2015.
12. ^ *a b c d* O'Connor, RE; Brady, W; Brooks, SC; Diercks, D; Egan, J; Ghaemmaghami, C; Menon, V; O'Neil, BJ; Travers, AH; Yannopoulos, D (2 November 2010). "Part 10: acute coronary syndromes: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.". *Circulation*. **122** (18 Suppl 3): S787–817. doi:10.1161/CIRCULATIONAHA.110.971028. PMID 20956226.
13. ^ Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D (December 2011). "ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)". *Eur. Heart J.* **32** (23): 2999–3054. doi:10.1093/eurheartj/ehr236. PMID 21873419.
14. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
15. ^ *a b* White HD, Chew DP; Chew (August 2008). "Acute myocardial infarction". *Lancet*. **372** (9638): 570–84. doi:10.1016/S0140-6736(08)61237-4. PMID 18707987.
16. ^ *a b c d e f g h i j k l m* O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW (Jan 29, 2013). "2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.". *Circulation*. **127** (4): e362–425. doi:10.1161/CIR.0b013e3182742cf6. PMID 23247304.
17. ^ Moran, AE; Forouzanfar, MH; Roth, GA; Mensah, GA; Ezzati, M; Flaxman, A; Murray, CJ; Naghavi, M (8 April 2014). "The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study.". *Circulation*. **129** (14): 1493–501. doi:10.1161/circulationaha.113.004046. PMID 24573351.
18. ^ National Heart, Lung and Blood Institute. Heart Attack Warning Signs. Retrieved November 22, 2006.
19. ^ *a b c d* Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G, Fox K, Huber K, Kastrati A, Rosengren A, Steg PG, Tubaro M, Verheugt F, Weidinger F, Weis M (December 2008). "Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology". *Eur. Heart J.* **29** (23): 2909–45. doi:10.1093/eurheartj/ehn416. PMID 19004841.
20. ^ Marcus GM, Cohen J, Varosy PD, Vessey J, Rose E, Massie BM, Chatterjee K, Waters D (2007). "The utility of gestures in patients with chest discomfort". *Am. J. Med.* **120** (1): 83–9. doi:10.1016/j.amjmed.2006.05.045. PMID 17208083.
21. ^ Mallinson, T (2010). "Myocardial Infarction". *Focus on First Aid* (15): 15. Archived from the original on May 21, 2010. Retrieved 2010-06-08.
22. ^ Little RA, Frayn KN, Randall PE, Stoner HB, Morton C, Yates DW, Laing GS (1986). "Plasma catecholamines in the acute phase of the response to myocardial infarction". *Arch Emerg Med*. **3** (1): 20–7. doi:10.1136/emj.3.1.20. PMC 1285314. PMID 3524599.
23. ^ *a b* Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ, Long T (December 2007). "Symptom presentation of women with acute coronary syndromes: myth vs reality". *Arch. Intern. Med.* **167** (22): 2405–13. doi:10.1001/archinte.167.22.2405. PMID 18071161.
24. ^ Brown, Anthony (2011). *Emergency Medicine Diagnosis and Management 6th Edition*.
25. ^ McSweeney JC, Cody M, O'Sullivan P, Elberson K, Moser DK, Garvin BJ (2003). "Women's early warning symptoms of acute myocardial infarction". *Circulation*. **108** (21): 2619–23. doi:10.1161/01.CIR.0000097116.29625.7C.

PMID 14597589.
26. ^ http://feministing.com/2012/02/23/for-women-heart-attacks-look-different-and-so-do-heart-health-outcomes/
27. ^ a b Davis TM, Fortun P, Mulder J, Davis WA, Bruce DG (2004). "Silent myocardial infarction and its prognosis in a community-based cohort of Type 2 diabetic patients: the Fremantle Diabetes Study". *Diabetologia*. **47** (3): 395–9. doi:10.1007/s00125-004-1344-4. PMID 14963648.
28. ^ Rubin, Emanuel; Gorstein, Fred; Rubin, Raphael; Schwarting, Roland; Strayer, David (2001). *Rubin's Pathology — Clinicopathological Foundations of Medicine*. Maryland: Lippincott Williams & Wilkins. p. 549. ISBN 0-7817-4733-3.
29. ^ Acute Coronary Syndrome. American Heart Association. Retrieved November 25, 2006. Archived September 25, 2006, at the Wayback Machine.
30. ^ a b c Kivimäki M, Nyberg ST, Batty GD, Fransson EI, Heikkilä K, Alfredsson L, Bjorner JB, Borritz M, Burr H, Casini A, Clays E, De Bacquer D, Dragano N, Ferrie JE, Geuskens GA, Goldberg M, Hamer M, Hooftman WE, Houtman IL, Joensuu M, Jokela M, Kittel F, Knutsson A, Koskenvuo M, Koskinen A, Kouvonen A, Kumari M, Madsen IE, Marmot MG, Nielsen ML, Nordin M, Oksanen T, Pentti J, Rugulies R, Salo P, Siegrist J, Singh-Manoux A, Suominen SB, Väänänen A, Vahtera J, Virtanen M, Westerholm PJ, Westerlund H, Zins M, Steptoe A, Theorell T (31 August 2012). "Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data". *The Lancet*. **380** (9852): 1491–7. doi:10.1016/S0140-6736(12)60994-5. PMC 3486012. PMID 22981903.
31. ^ Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT (1 July 2012). "Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy". *The Lancet*. **380** (9838): 219–29. doi:10.1016/S0140-6736(12)61031-9. PMC 3645500. PMID 22818936.
32. ^ Steptoe A, Kivimäki M (April 2012). "Stress and cardiovascular disease". *Nature Reviews Cardiology*. **9** (6): 360–70. doi:10.1038/nrcardio.2012.45. PMID 22473079.
33. ^ a b c Smith SC, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pearson T, Pfeffer MA, Taubert KA (May 2006). "AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update endorsed by the National Heart, Lung, and Blood Institute". *J. Am. Coll. Cardiol.* **47** (10): 2130–9. doi:10.1016/j.jacc.2006.04.026. PMID 16697342.
34. ^ Mustafic H, Jabre P, Caussin C, Murad MH, Escolano S, Tafflet M, Périer MC, Marijon E, Vernerey D, Empana JP, Jouven X (Feb 15, 2012). "Main air pollutants and myocardial infarction: a systematic review and meta-analysis". *JAMA: The Journal of the American Medical Association*. **307** (7): 713–21. doi:10.1001/jama.2012.126. PMID 22337682.
35. ^ a b c d Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Scholte op Reimer W, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A (October 2007). "European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts)". *Eur. Heart J.* **28** (19): 2375–414. doi:10.1093/eurheartj/ehm316. PMID 17726041.
36. ^ Vyas MV, Garg AX, Iansavichus AV, Costella J, Donner A, Laugsand LE, Janszky I, Mrkobrada M, Parraga G, Hackam DG (July 2012). "Shift work and vascular events: systematic review and meta-analysis". *British Medical Journal (Clinical Research Edition)*. **26** (345): e4800. doi:10.1136/bmj.e4800. PMC 3406223. PMID 22835925.
37. ^ Krenz M, Korthuis RJ (January 2012). "Moderate ethanol ingestion and cardiovascular protection: from epidemiologic associations to cellular mechanisms". *Journal of molecular and cellular cardiology*. **52** (1): 93–104. doi:10.1016/j.yjmcc.2011.10.011. PMC 3246046. PMID 22041278.
38. ^ U.S. Departments of Agriculture and Health and Human Services. "Dietary Guidelines 2015 - 2020". Retrieved 9 January 2016.
39. ^ Hooper, L; Martin, N; Abdelhamid, A; Davey Smith, G (10 June 2015). "Reduction in saturated fat intake for cardiovascular disease.". *The Cochrane database of systematic reviews*. **6**: CD011737. doi:10.1002/14651858.CD011737. PMID 26068959.
40. ^ a b Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, Franco OH, Butterworth AS, Forouhi NG, Thompson SG, Khaw KT, Mozaffarian D, Danesh J, Di Angelantonio E (2014). "Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis". *Ann. Intern. Med.* **160** (6): 398–406. doi:10.7326/M13-1788. PMID 24723079.
41. ^ de Souza, RJ; Mente, A; Maroleanu, A; Cozma, AI; Ha, V; Kishibe, T; Uleryk, E; Budylowski, P; Schünemann, H; Beyene, J; Anand, SS (11 August 2015). "Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies.". *BMJ (Clinical research ed.)*. **351**: h3978. doi:10.1136/bmj.h3978. PMC 4532752. PMID 26268692.
42. ^ "Scientific Report of the 2015 Dietary Guidelines Advisory COmmittee" (PDF). *health.gov*. Feb 2015. p. 17.
43. ^ Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, Fonseca V, Gerstein HC, Grundy S, Nesto RW,

Pignone MP, Plutzky J, Porte D, Redberg R, Stitzel KF, Stone NJ (January 2007). "Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association". *Circulation*. **115** (1): 114–26. doi:10.1161/CIRCULATIONAHA.106.179294. PMID 17192512.

44. ^ Mu, Fan; Rich-Edwards, Janet; Rimm, Eric B.; Spiegelman, Donna; Missmer, Stacey A. (29 March 2016). "Endometriosis and Risk of Coronary Heart Disease". *Circulation: Cardiovascular Quality and Outcomes*. pp. CIRCOUTCOMES.115.002224. doi:10.1161/CIRCOUTCOMES.115.002224. Retrieved 31 March 2016.
45. ^ Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P, Razak F, Sharma AM, Anand SS (2005). "Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study". *Lancet*. **366** (9497): 1640–9. doi:10.1016/S0140-6736(05)67663-5. PMID 16271645.
46. ^ *a b* Chatzidimitriou D, Kirmizis D, Gavriilaki E, Chatzidimitriou M, Malisiovas N (Oct 2012). "Atherosclerosis and infection: is the jury still not in?". *Future microbiology*. **7** (10): 1217–30. doi:10.2217/fmb.12.87. PMID 23030426.
47. ^ Charakida M, Tousoulis D (2013). "Infections and atheromatous plaque: current therapeutic implications.". *Current pharmaceutical design*. **19** (9): 1638–50. doi:10.2174/138161213805219658. PMID 23016720.
48. ^ Sánchez-Manubens J, Bou R, Anton J (February 2014). "Diagnosis and classification of Kawasaki disease". *Journal of Autoimmunity*. 48-49: 113–7. doi:10.1016/j.jaut.2014.01.010. PMID 24485156.
49. ^ *a b c* Feero, W. Gregory; Guttmacher, Alan E.; O'Donnell, Christopher J.; Nabel, Elizabeth G. (Dec 2011). "Genomics of Cardiovascular Disease". *New England Journal of Medicine*. **365** (22): 2098–2109. doi:10.1056/NEJMra1105239. PMID 22129254.
50. ^ Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB (1998). "Prediction of coronary heart disease using risk factor categories" (PDF). *Circulation*. **97** (18): 1843–44. doi:10.1161/01.CIR.97.18.1837. PMID 9603539.
51. ^ Khader YS, Rice J, John L, Abueita O (2003). "Oral contraceptives use and the risk of myocardial infarction: a meta-analysis". *Contraception*. **68** (1): 11–7. doi:10.1016/S0010-7824(03)00073-8. PMID 12878281.
52. ^ Culić V (April 2007). "Acute risk factors for myocardial infarction". *International Journal of Cardiology*. **117** (2): 260–9. doi:10.1016/j.ijcard.2006.05.011. PMID 16860887.
53. ^ Shaw E, Tofler GH (July 2009). "Circadian rhythm and cardiovascular disease". *Current atherosclerosis reports*. **11** (4): 289–95. doi:10.1007/s11883-009-0044-4. PMID 19500492.
54. ^ *a b* Moe KT, Wong P (March 2010). "Current trends in diagnostic biomarkers of acute coronary syndrome" (PDF). *Ann. Acad. Med. Singap*. **39** (3): 210–5. PMID 20372757.
55. ^ *a b* Tsujita K, Kaikita K, Soejima H, Sugiyama S, Ogawa H (April 2010). "[Acute coronary syndrome-initiating factors]". *Nippon Rinsho* (in Japanese). **68** (4): 607–14. PMID 20387549.
56. ^ *a b* Dohi T, Daida H (April 2010). "[Change of concept and pathophysiology in acute coronary syndrome]". *Nippon Rinsho* (in Japanese). **68** (4): 592–6. PMID 20387546.
57. ^ Woollard KJ, Geissmann F (February 2010). "Monocytes in atherosclerosis: subsets and functions". *Nature Reviews Cardiology*. **7** (2): 77–86. doi:10.1038/nrcardio.2009.228. PMC 2813241. PMID 20065951.
58. ^ Spaan J, Kolyva C, van den Wijngaard J, ter Wee R, van Horssen P, Piek J, Siebes M (September 2008). "Coronary structure and perfusion in health and disease". *Philosophical Transactions of the Royal Society A*. **366** (1878): 3137–53. doi:10.1098/rsta.2008.0075. PMID 18559321.
59. ^ Laflamme, MA; Murry, CE (July 2005). "Regenerating the heart". *Nature Biotechnology*. **23** (7): 845–56. doi:10.1038/nbt1117. PMID 16003373.
60. ^ Krijnen PA, Nijmeijer R, Meijer CJ, Visser CA, Hack CE, Niessen HW (2002). "Apoptosis in myocardial ischaemia and infarction". *J Clin Pathol*. **55** (11): 801–11. doi:10.1136/jcp.55.11.801. PMC 1769793. PMID 12401816.
61. ^ *a b c d* Wilson AM, Ryan MC, Boyle AJ (2006). "The novel role of C-reactive protein in cardiovascular disease: risk marker or pathogen". *Int J Cardiol*. **106** (3): 291–7. doi:10.1016/j.ijcard.2005.01.068. PMID 16337036.
62. ^ Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC, Taubert K, Tracy RP, Vinicor F (2003). "Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association" (PDF). *Circulation*. **107** (3): 499–511. doi:10.1161/01.CIR.0000052939.59093.45. PMID 12551878.
63. ^ Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC (2004). "Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals". *JAMA*. **291** (2): 210–5. doi:10.1001/jama.291.2.210. PMID 14722147.
64. ^ Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA (2008). "Coronary calcium as a predictor of coronary events in four racial or ethnic groups". *N. Engl. J. Med*. **358** (13): 1336–45. doi:10.1056/NEJMoa072100. PMID 18367736.

65. ^ Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD (2005). "Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study". *J. Am. Coll. Cardiol.* **46** (1): 158–65. doi:10.1016/j.jacc.2005.02.088. PMID 15992651.
66. ^ Clarke R, Halsey J, Bennett D, Lewington S (February 2011). "Homocysteine and vascular disease: review of published results of the homocysteine-lowering trials". *J. Inherit. Metab. Dis.* **34** (1): 83–91. doi:10.1007/s10545-010-9235-y. PMID 21069462.
67. ^ Lonn E (September 2007). "Homocysteine in the prevention of ischemic heart disease, stroke and venous thromboembolism: therapeutic target or just another distraction?". *Current Opinion in Hematology*. **14** (5): 481–7. doi:10.1097/MOH.0b013e3282c48bd8. PMID 17934354.
68. ^ *a b* Reznik AG (2010). "[Morphology of acute myocardial infarction at prenecrotic stage]". *Kardiologiia* (in Russian). **50** (1): 4–8. PMID 20144151.
69. ^ Alpert JS, Thygesen K, Antman E, Bassand JP (2000). "Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction". *J Am Coll Cardiol*. **36** (3): 959–69. doi:10.1016/S0735-1097(00)00804-4. PMID 10987628.
70. ^ Anonymous (March 1979). "Nomenclature and criteria for the diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature". *Circulation*. **59** (3): 607–9. doi:10.1161/01.CIR.59.3.607. PMID 761341.
71. ^ Thygesen K, Alpert JS, White HD (October 2007). "Universal definition of myocardial infarction". *Eur. Heart J.* **28** (20): 2525–38. doi:10.1093/eurheartj/ehm355. PMID 17951287.
72. ^ *Primary Care: Art and Science of Advanced Practice Nursing*. F.A. Davis. 2015. p. 464. ISBN 9780803644946.
73. ^ *a b c d e f g h i j* Amsterdam, E. A.; Wenger, N. K.; Brindis, R. G.; Casey, D. E.; Ganiats, T. G.; Holmes, D. R.; Jaffe, A. S.; Jneid, H.; Kelly, R. F.; Kontos, M. C.; Levine, G. N.; Liebson, P. R.; Mukherjee, D.; Peterson, E. D.; Sabatine, M. S.; Smalling, R. W.; Zieman, S. J. (23 September 2014). "2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines". *Circulation*. **130** (Online first): e344–e426. doi:10.1161/CIR.0000000000000134. PMID 25249585.
74. ^ Lansky, A. J.; Stone, G. W. (14 December 2010). "Periprocedural Myocardial Infarction: Prevalence, Prognosis, and Prevention". *Circulation: Cardiovascular Interventions*. **3** (6): 602–610. doi:10.1161/CIRCINTERVENTIONS.110.959080.
75. ^ Lipinski, MJ; Escárcega, RO; D'Ascenzo, F; Magalhães, MA; Baker, NC; Torguson, R; Chen, F; Epstein, SE; Miró, O; Llorens, P; Giannitsis, E; Lotze, U; Lefebvre, S; Sebbane, M; Cristol, JP; Chenevier-Gobeaux, C; Meune, C; Eggers, KM; Charpentier, S; Twerenbold, R; Mueller, C; Biondi-Zoccai, G; Waksman, R (May 1, 2014). "A systematic review and collaborative meta-analysis to determine the incremental value of copeptin for rapid rule-out of acute myocardial infarction.". *The American journal of cardiology*. **113** (9): 1581–91. doi:10.1016/j.amjcard.2014.01.436. PMID 24731654.
76. ^ Schinkel AF, Valkema R, Geleijnse ML, Sijbrands EJ, Poldermans D (May 2010). "Single-photon emission computed tomography for assessment of myocardial viability". *Eurointervention*. **6** (Supplement G): G115–22. PMID 20542817.
77. ^ *a b c d e f* National Institute for Health and Clinical Excellence. *Clinical guideline cg94: Unstable angina and NSTEMI*. London, 2010.
78. ^ *a b c* American Society of Nuclear Cardiology. "Five Things Physicians and Patients Should Question" (PDF). *Choosing Wisely: an initiative of the ABIM Foundation*. American Society of Nuclear Cardiology. Retrieved August 17, 2012., which cites
    - Hendel RC, Berman DS, Di Carli MF, Heidenreich PA, Henkin RE, Pellikka PA, Pohost GM, Williams KA (2009). "ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging". *Journal of the American College of Cardiology*. **53** (23): 2201–2229. doi:10.1016/j.jacc.2009.02.013. PMID 19497454.
    - Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, Rubin GD, Kramer CM, Berman D, Brown A, Chaudhry FA, Cury RC, Desai MY, Einstein AJ, Gomes AS, Harrington R, Hoffmann U, Khare R, Lesser J, McGann C, Rosenberg A, Schwartz R, Shelton M, Smetana GW, Smith SC (2010). "ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography". *Journal of the American College of Cardiology*. **56** (22): 1864–1894. doi:10.1016/j.jacc.2010.07.005. PMID 21087721.
    - Anderson, J. L.; Adams, C. D.; Antman, E. M.; Bridges, C. R.; Califf, R. M.; Casey, D. E.; Chavey, W. E.; Fesmire, F. M.; Hochman, J. S.; Levin, T. N.; Lincoff, A. M.; Peterson, E. D.; Theroux, P.; Wenger, N. K.; Wright, R. S. (2007). "ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the

Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction): Developed in Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine". *Circulation*. **116** (7): 803–877. doi:10.1161/CIRCULATIONAHA.107.185752.

79. ^ Boie ET (2005). "Initial evaluation of chest pain". *Emerg. Med. Clin. North Am*. **23** (4): 937–57. doi:10.1016/j.emc.2005.07.007. PMID 16199332.
80. ^ *a b c d e f g h* National Institute for Health and Clinical Excellence. *Clinical guideline 181: Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease*. London, 2014.
81. ^ Stradling, C; Hamid, M; Taheri, S; Thomas, GN (2014). "A review of dietary influences on cardiovascular health: part 2: dietary patterns.". *Cardiovascular & hematological disorders drug targets*. **14** (1): 50–63. doi:10.2174/1871529x14666140701095426. PMID 24993125.
82. ^ Fortmann, SP; Burda, BU; Senger, CA; Lin, JS; Whitlock, EP (17 December 2013). "Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: An updated systematic evidence review for the U.S. Preventive Services Task Force.". *Annals of Internal Medicine*. **159** (12): 824–34. doi:10.7326/0003-4819-159-12-201312170-00729. PMID 24217421.
83. ^ Mozaffarian D, Micha R, Wallace S (2010). Katan, Martijn B, ed. "Effects on Coronary Heart Disease of Increasing Polyunsaturated Fat in Place of Saturated Fat: A Systematic Review and Meta-Analysis of Randomized Controlled Trials". *PLoS Med*. **7** (3): e1000252. doi:10.1371/journal.pmed.1000252. PMC 2843598. PMID 20351774.
84. ^ McPherson K, et al. (June 2010). "Prevention of cardiovascular disease – NICE public health guidance 25". London: National Institute for Health and Care Excellence.
85. ^ Antithrombotic Trialists' (ATT), Collaboration; Baigent, C; Blackwell, L; Collins, R; Emberson, J; Godwin, J; Peto, R; Buring, J; Hennekens, C; Kearney, P; Meade, T; Patrono, C; Roncaglioni, MC; Zanchetti, A (30 May 2009). "Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials.". *Lancet*. **373** (9678): 1849–60. doi:10.1016/S0140-6736(09)60503-1. PMC 2715005. PMID 19482214.
86. ^ Sutcliffe, P; Connock, M; Gurung, T; Freeman, K; Johnson, S; Kandala, NB; Grove, A; Gurung, B; Morrow, S; Clarke, A (September 2013). "Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews.". *Health technology assessment (Winchester, England)*. **17** (43): 1–253. doi:10.3310/hta17430. PMID 24074752.
87. ^ Matthys, F; De Backer, T; De Backer, G; Stichele, RV (March 2014). "Review of guidelines on primary prevention of cardiovascular disease with aspirin: how much evidence is needed to turn a tanker?". *European journal of preventive cardiology*. **21** (3): 354–65. doi:10.1177/2047487312472077. PMID 23610452.
88. ^ Hodis, Howard (July 2014). "Hormone replacement therapy and the association with coronary heart disease and overall mortality: Clinical application of the timing hypothesis". *The Journal of Steroid Biochemistry and Molecular Biology*. **142**: 68–75. doi:10.1016/j.jsbmb.2013.06.011. PMID 23851166.
89. ^ Hodis, Howard; Mack, Wendy (July 2014). "Hormone replacement therapy and the association with coronary heart disease and overall mortality: Clinical application of the timing hypothesis". *The Journal of Steroid Biochemistry and Molecular Biology*. **142**: 68–75. doi:10.1016/j.jsbmb.2013.06.011. PMID 23851166. Retrieved 2015-03-25.
90. ^ Hodis, HN; Mack, WJ (2009). "Coronary heart disease and hormone replacement therapy after the menopause.". *Climacteric : the journal of the International Menopause Society*. 12 Suppl 1: 71–5. doi:10.1080/13697130903095178. PMID 19811246.
91. ^ Perez, MI; Musini, VM; Wright, JM (7 October 2009). "Effect of early treatment with anti-hypertensive drugs on short and long-term mortality in patients with an acute cardiovascular event.". *The Cochrane database of systematic reviews* (4): CD006743. doi:10.1002/14651858.CD006743.pub2. PMID 19821384.
92. ^ Gulli, American Academy of Orthopaedic Surgeons ; editors, Leaugeay Barnes, Joseph A. Ciotola, Benjamin (2010-03-23). *Emergency care and transportation of the sick and injured.* (10th ed.). Sudbury, Mass.: Jones and Bartlett. p. 575. ISBN 978-0-7637-7828-6.
93. ^ O'Connor RE, Brady W, Brooks SC, Diercks D, Egan J, Ghaemmaghami C, Menon V, O'Neil BJ, Travers AH, Yannopoulos D (November 2010). "Part 10: acute coronary syndromes: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care". *Circulation*. **122** (18 Suppl 3): S787–817. doi:10.1161/CIRCULATIONAHA.110.971028. PMID 20956226.
94. ^ Wijesinghe M, Perrin K, Ranchord A, Simmonds M, Weatherall M, Beasley R (March 2009). "Routine use of oxygen in the treatment of myocardial infarction: systematic review". *Heart*. **95** (3): 198–202. doi:10.1136/hrt.2008.148742. PMID 18708420.
95. ^ Cabello JB, Burls A, Emparanza JI, Bayliss S, Quinn T (2013). Cabello, Juan B, ed. "Oxygen therapy for acute myocardial infarction". *Cochrane Database Syst Rev*. **8**: CD007160. doi:10.1002/14651858.CD007160.pub3. PMID 23963794.

96. ^ Ahmad Y, Sen S, Shun-Shin MJ, Ouyang J, Finegold JA, Al-Lamee RK, Davies JE, Cole GD, Francis DP (June 2015). "Intra-aortic Balloon Pump Therapy for Acute Myocardial Infarction: A Meta-analysis". *JAMA Internal Medicine*. **175** (6): 931–9. doi:10.1001/jamainternmed.2015.0569. PMID 25822657.
97. ^ a b c Bates ER, Menees DS (Oct 2012). "Acute ST-elevation myocardial infarction". *Current Opinion in Critical Care*. 5. **18** (5): 417–23. doi:10.1097/MCC.0b013e328357f07b. PMID 22889871.
98. ^ a b Bagai, A; Dangas, GD; Stone, GW; Granger, CB (6 June 2014). "Reperfusion strategies in acute coronary syndromes.". *Circulation Research*. **114** (12): 1918–28. doi:10.1161/CIRCRESAHA.114.302744. PMID 24902975.
99. ^ a b Wang, edited by Reza Ardehali, Marco Perez, Paul (2011). *A practical approach to cardiovascular medicine*. Chichester, West Sussex, UK: Wiley-Blackwell. p. 57. ISBN 9781444393873.
100. ^ Lassen JF, Bøtker HE, Terkelsen CJ (Jan 2013). "Timely and optimal treatment of patients with STEMI". *Nature Reviews Cardiology*. 1. **10** (1): 41–8. doi:10.1038/nrcardio.2012.156. PMID 23165072.
101. ^ Neumar, RW; Shuster, M; Callaway, CW; Gent, LM; Atkins, DL; Bhanji, F; Brooks, SC; de Caen, AR; Donnino, MW; Ferrer, JM; Kleinman, ME; Kronick, SL; Lavonas, EJ; Link, MS; Mancini, ME; Morrison, LJ; O'Connor, RE; Samson, RA; Schexnayder, SM; Singletary, EM; Sinz, EH; Travers, AH; Wyckoff, MH; Hazinski, MF (3 November 2015). "Part 1: Executive Summary: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.". *Circulation*. **132** (18 Suppl 2): S315–67. doi:10.1161/cir.0000000000000252. PMID 26472989.
102. ^ "Thrombolytics for Major Heart Attack (STEMI)". *TheNNT.com*. Retrieved 1 December 2015.
103. ^ "Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group.". *Lancet*. **343** (8899): 311–22. Mar 1994. doi:10.1016/s0140-6736(94)91161-4. PMID 7905143.
104. ^ a b McCaul, M; Lourens, A; Kredo, T (Sep 10, 2014). "Pre-hospital versus in-hospital thrombolysis for ST-elevation myocardial infarction.". *The Cochrane database of systematic reviews*. **9**: CD010191. doi:10.1002/14651858.CD010191.pub2. PMID 25208209.
105. ^ Jindal, editor-in-chief SK (2011). *Textbook of pulmonary and critical care medicine*. New Delhi: Jaypee Brothers Medical Publishers. p. 1758. ISBN 9789350250730.
106. ^ Brilakis ES, Patel VG, Banerjee S (Jul 10, 2013). "Medical management after coronary stent implantation: a review". *JAMA: The Journal of the American Medical Association*. **310** (2): 189–98. doi:10.1001/jama.2013.7086. PMID 23839753.
107. ^ "Beta Blockers for Acute Heart Attack (Myocardial Infarction)". *TheNNT.com*. Retrieved 11 December 2015.
108. ^ O'Gara, P. T.; Kushner, F. G.; Ascheim, D. D.; Casey, D. E.; Chung, M. K.; de Lemos, J. A.; Ettinger, S. M.; Fang, J. C.; Fesmire, F. M.; Franklin, B. A.; Granger, C. B.; Krumholz, H. M.; Linderbaum, J. A.; Morrow, D. A.; Newby, L. K.; Ornato, J. P.; Ou, N.; Radford, M. J.; Tamis-Holland, J. E.; Tommaso, C. L.; Tracy, C. M.; Woo, Y. J.; Zhao, D. X. (17 December 2012). "2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines". *Circulation*. **127** (4): e362–e425. doi:10.1161/CIR.0b013e3182742cf6. PMID 23247304.
109. ^ a b Andrade-Castellanos, CA; Colunga-Lozano, LE; Delgado-Figueroa, N; Magee, K (Jun 27, 2014). "Heparin versus placebo for non-ST elevation acute coronary syndromes.". *The Cochrane database of systematic reviews*. **6**: CD003462. doi:10.1002/14651858.CD003462.pub3. PMID 24972265.
110. ^ Hamm, CW; Bassand, JP; Agewall, S; Bax, J; Boersma, E; Bueno, H; Caso, P; Dudek, D; Gielen, S; Huber, K; Ohman, M; Petrie, MC; Sonntag, F; Uva, MS; Storey, RF; Wijns, W; Zahger, D; ESC Committee for Practice, Guidelines (December 2011). "ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC).". *European Heart Journal*. **32** (23): 2999–3054. doi:10.1093/eurheartj/ehr236. PMID 21873419.
111. ^ Bellemain-Appaix, A.; Kerneis, M.; O'Connor, S. A.; Silvain, J.; Cucherat, M.; Beygui, F.; Barthelemy, O.; Collet, J.-P.; Jacq, L.; Bernasconi, F.; Montalescot, G. (24 October 2014). "Reappraisal of thienopyridine pretreatment in patients with non-ST elevation acute coronary syndrome: a systematic review and meta-analysis". *BMJ*. **349**: g6269–g6269. doi:10.1136/bmj.g6269. PMC 4208629. PMID 25954988.
112. ^ a b c d e f g h i National Institute for Health and Clinical Excellence. *Clinical guideline 172: Secondary prevention in primary and secondary care for patients following a myocardial infarction*. London, 2013.
113. ^ Anderson, L; Taylor, RS (12 December 2014). "Cardiac rehabilitation for people with heart disease: an overview of Cochrane systematic reviews.". *The Cochrane database of systematic reviews*. **12**: CD011273. doi:10.1002/14651858.CD011273.pub2. PMID 25503364.
114. ^ Elmariah, Sammy; Mauri, Laura; Doros, Gheorghe; Galper, Benjamin Z; O'Neill, Kelly E; Steg, Philippe Gabriel;

Kereiakes, Dean J; Yeh, Robert W (November 2014). "Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis". *The Lancet*. **385**: 792–798. doi:10.1016/S0140-6736(14)62052-3.

115. ^ Bangalore, S; Makani, H; Radford, M; Thakur, K; Toklu, B; Katz, SD; DiNicolantonio, JJ; Devereaux, PJ; Alexander, KP; Wetterslev, J; Messerli, FH (October 2014). "Clinical outcomes with β-blockers for myocardial infarction: a meta-analysis of randomized trials.". *The American Journal of Medicine*. **127** (10): 939–53. doi:10.1016/j.amjmed.2014.05.032. PMID 24927909.
116. ^ McCord, J; Jneid, H; Hollander, JE; de Lemos, JA; Cercek, B; Hsue, P; Gibler, WB; Ohman, EM; Drew, B; Philippides, G; Newby, LK; American Heart Association Acute Cardiac Care Committee of the Council on Clinical, Cardiology (8 April 2008). "Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology.". *Circulation*. **117** (14): 1897–907. doi:10.1161/CIRCULATIONAHA.107.188950. PMID 18347214.
117. ^ Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, Ward K, Ebrahim S (Jan 31, 2013). "Statins for the primary prevention of cardiovascular disease". *The Cochrane database of systematic reviews*. **1**: CD004816. doi:10.1002/14651858.CD004816.pub5. PMID 23440795.
118. ^ Ray KK, Cannon CP; Cannon (2005). "The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes". *J. Am. Coll. Cardiol*. **46** (8): 1425–33. doi:10.1016/j.jacc.2005.05.086. PMID 16226165.
119. ^ [a] [b] López de Sá E, López-Sendón J, Anguera I, Bethencourt A, Bosch X; López-Sendón; Anguera; Bethencourt; Bosch; Proyecto de Estudio del Pronostico de la Angina (PEPA) Investigators (November 2002). "Prognostic value of clinical variables at presentation in patients with non-ST-segment elevation acute coronary syndromes: results of the Proyecto de Estudio del Pronóstico de la Angina (PEPA)". *Medicine (Baltimore)*. **81** (6): 434–42. doi:10.1097/00005792-200211000-00004. PMID 12441900.
120. ^ Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA, Granger CB; Dabbous; Goldberg; Pieper; Eagle; Van De Werf; Avezum; Goodman; Flather; Anderson Jr; Granger (November 2006). "Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE)". *BMJ*. **333** (7578): 1091. doi:10.1136/bmj.38985.646481.55. PMC 1661748. PMID 17032691.
121. ^ Weir RA, McMurray JJ, Velazquez EJ; McMurray; Velazquez (2006). "Epidemiology of heart failure and left ventricular systolic dysfunction after acute myocardial infarction: prevalence, clinical characteristics, and prognostic importance". *Am J Cardiol*. **97** (10A): 13F–25F. doi:10.1016/j.amjcard.2006.03.005. PMID 16698331.
122. ^ Bosch X, Théroux P; Théroux (2005). "Left ventricular ejection fraction to predict early mortality in patients with non-ST-segment elevation acute coronary syndromes". *Am Heart J*. **150** (2): 215–20. doi:10.1016/j.ahj.2004.09.027. PMID 16086920.
123. ^ Becker RC, Gore JM, Lambrew C, Weaver WD, Rubison RM, French WJ, Tiefenbrunn AJ, Bowlby LJ, Rogers WJ; Gore; Lambrew; Weaver; Rubison; French; Tiefenbrunn; Bowlby; Rogers (1996). "A composite view of cardiac rupture in the United States National Registry of Myocardial Infarction". *J Am Coll Cardiol*. **27** (6): 1321–6. doi:10.1016/0735-1097(96)00008-3. PMID 8626938.
124. ^ Liew R, Sulfi S, Ranjadayalan K, Cooper J, Timmis AD; Sulfi; Ranjadayalan; Cooper; Timmis (2006). "Declining case fatality rates for acute myocardial infarction in South Asian and white patients in the past 15 years". *Heart*. **92** (8): 1030–4. doi:10.1136/hrt.2005.078634. PMC 1861115. PMID 16387823.
125. ^ Antman EM; Cohen M; et. al. (2000). "The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making.". *JAMA*. **284** (7): 835–42. doi:10.1001/jama.284.7.835. PMID 10938172.
126. ^ David A. Morrow; et. al. (2000). "TIMI Risk Score for ST-Elevation Myocardial Infarction: A Convenient, Bedside, Clinical Score for Risk Assessment at Presentation: An Intravenous nPA for Treatment of Infarcting Myocardium Early II Trial Substudy.". *Circulation*. **102** (17): 2031–37. doi:10.1161/01.CIR.102.17.2031. PMID 11044416.
127. ^ [a] [b] [c] World Health Organization (2008). *The Global Burden of Disease: 2004 Update*. Geneva: World Health Organization. ISBN 92-4-156371-0.
128. ^ Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; Go; Lloyd-Jones; Benjamin; Berry; Borden; Bravata; Dai; Ford; Fox; Fullerton; Gillespie; Hailpern; Heit; Howard; Kissela; Kittner; Lackland; Lichtman; Lisabeth; Makuc; Marcus; Marelli; Matchar; Moy; Mozaffarian; Mussolino; Nichol; Paynter; Soliman (January 2012). "Executive summary: heart disease and stroke statistics—2012 update: a report from the American Heart Association". *Circulation*. **125** (1): 188–97. doi:10.1161/CIR.0b013e3182456d46. PMID 22215894.
129. ^ Mozaffarian, D; Benjamin, EJ; Go, AS; Arnett, DK; Blaha, MJ; Cushman, M; de Ferranti, S; Després, JP; Fullerton, HJ; Howard, VJ; Huffman, MD; Judd, SE; Kissela, BM; Lackland, DT; Lichtman, JH; Lisabeth, LD; Liu, S; Mackey,

RH; Matchar, DB; McGuire, DK; Mohler ER, 3rd; Moy, CS; Muntner, P; Mussolino, ME; Nasir, K; Neumar, RW; Nichol, G; Palaniappan, L; Pandey, DK; Reeves, MJ; Rodriguez, CJ; Sorlie, PD; Stein, J; Towfighi, A; Turan, TN; Virani, SS; Willey, JZ; Woo, D; Yeh, RW; Turner, MB; American Heart Association Statistics Committee and Stroke Statistics, Subcommittee (27 January 2015). "Heart disease and stroke statistics--2015 update: a report from the American Heart Association.". *Circulation*. **131** (4): e29–322. doi:10.1161/cir.0000000000000152. PMID 25520374. "From 2001 to 2011, death rates attributable to CVD declined 30.8%."

130. ^ Gupta R, Joshi P, Mohan V, Reddy KS, Yusuf S; Joshi; Mohan; Reddy; Yusuf (January 2008). "Epidemiology and causation of coronary heart disease and stroke in India". *Heart*. **94** (1): 16–26. doi:10.1136/hrt.2007.132951. PMID 18083949.
131. ^ Torio CM, Andrews RM. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2011. HCUP Statistical Brief #160. Agency for Healthcare Research and Quality, Rockville, MD. August 2013. [1]
132. ^ Workers' Compensation FAQ. Prairie View A&M University. Retrieved November 22, 2006.
133. ^ SIGNIFICANT DECISIONS Subject Index. Board of Industrial Insurance Appeals. Retrieved November 22, 2006.
134. ^ "Classification of Drivers' Licenses Regulations". Nova Scotia Registry of Regulations. May 24, 2000. Retrieved April 22, 2007.

## External links [edit]

- Cardiac disorders – Open Directory Project
- American Heart Association's Heart Attack web site — Information and resources for preventing, recognizing and treating a heart attack.
- TIMI Score for UA/NSTEMI and STEMI
- HEART Score for Major Cardiac Events

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- Learning resources from Wikiversity

| v · t · e | **Cardiovascular disease (heart) (I00–I52, 390–429)** | |
|---|---|---|
| **Ischaemic** | **Coronary disease** | Coronary artery disease (CAD) · Coronary artery aneurysm · Spontaneous coronary artery dissection (SCAD) · Coronary thrombosis · Coronary vasospasm · Myocardial bridge · |
| | **Active ischemia** | Angina pectoris (Prinzmetal's angina · Stable angina · · Acute coronary syndrome (**Myocardial infarction** · Unstable angina · · |
| | **Sequelae** | *hours* (Hibernating myocardium · Myocardial stunning · · *days* (Myocardial rupture · · *weeks* (Aneurysm of heart / Ventricular aneurysm · Dressler syndrome · · |
| | **Pericardium** | Pericarditis (Acute · Chronic / Constrictive · · Pericardial effusion (Cardiac tamponade · Hemopericardium · · |
| | **Myocardium** | Myocarditis (Chagas disease · · Cardiomyopathy: Dilated (Alcoholic), Hypertrophic, *and* Restrictive (Loeffler endocarditis · Cardiac amyloidosis · Endocardial fibroelastosis · · Arrhythmogenic right ventricular dysplasia · |

| | | | |
|---|---|---|---|
| **Layers** | **Endocardium / valves** | **Endocarditis** | *infective endocarditis* (Subacute bacterial endocarditis · · *non-infective endocarditis* (Libman–Sacks endocarditis · Nonbacterial thrombotic endocarditis · · |
| | | **Valves** | *mitral* (regurgitation · prolapse · stenosis · · *aortic* (stenosis · insufficiency · · *tricuspid* (stenosis · insufficiency · · *pulmonary* (stenosis · insufficiency · · |
| **Conduction / arrhythmia** | **Bradycardia** | | Sinus bradycardia · Sick sinus syndrome · Heart block: Sinoatrial · AV (1° · 2° · 3° · · Intraventricular · Bundle branch block (Right · Left · Left anterior fascicle · Left posterior fascicle · Bifascicular · Trifascicular · · Adams–Stokes syndrome · |
| | **Tachycardia (paroxysmal and sinus)** | **Supraventricular** | Atrial (Multifocal · · Junctional (AV nodal reentrant · Junctional ectopic · · |
| | | **Ventricular** | Accelerated idioventricular rhythm · Catecholaminergic polymorphic · Torsades de pointes · |
| | **Premature contraction** | | Atrial · Junctional · Ventricular · |
| | **Pre-excitation syndrome** | | Lown–Ganong–Levine · Wolff–Parkinson–White · |
| | **Flutter / fibrillation** | | Atrial flutter · Ventricular flutter · Atrial fibrillation (Familial · · Ventricular fibrillation · |
| | **Pacemaker** | | Ectopic pacemaker / Ectopic beat · Multifocal atrial tachycardia · Pacemaker syndrome · Parasystole · Wandering pacemaker · |
| | **Long QT syndrome** | | Andersen–Tawil · Jervell and Lange-Nielsen · Romano–Ward · |
| | **Cardiac arrest** | | Sudden cardiac death · Asystole · Pulseless electrical activity · Sinoatrial arrest · |
| | **Other / ungrouped** | | *hexaxial reference system* (Right axis deviation · Left axis deviation · · *QT* (Short QT syndrome · · *T* (T wave alternans · · *ST* (Osborn wave · ST elevation · ST depression · · Strain pattern · |
| **Cardiomegaly** | | | Ventricular hypertrophy (Left · Right / Cor pulmonale · · Atrial enlargement (Left · Right · · |
| **Other** | | | Cardiac fibrosis · Heart failure (Diastolic heart failure · Cardiac asthma · · Rheumatic fever · |

| v · t · e · | **Disorders of hemodynamics** | |
|---|---|---|
| **Decreases** | **Thrombus/thrombosis** | Renal vein thrombosis |
| | **Ischemia** | Brain ischemia · Ischaemic heart disease · large intestine: Ischemic colitis · small intestine: Mesenteric ischemia · |
| | **Infarction** | Anemic infarct · Hemorrhagic infarct · **Myocardial infarction** · Cerebral infarction · Splenic infarction · Limb infarction · |
| | **Hemorrhage** | Bruise/Hematoma · Petechia · Purpura · Ecchymosis · |
| | | *head* (Epistaxis · Hemoptysis · Intracranial hemorrhage · Hyphema · Subconjunctival hemorrhage · · *torso* (Hemothorax · Hemopericardium · Pulmonary hematoma · · *abdomen* (Gastrointestinal bleeding · Haemobilia · Hemoperitoneum · Hematocele · Hematosalpinx · · *joint* (Hemarthrosis · · |

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| **Increases** | | |
| | **Edema** | Anasarca · Angioedema/Lymphedema · Exudate/Transudate · Cerebral edema · Pulmonary edema · Hydrothorax · Ascites/hydroperitoneum · Hydrosalpinx · |
| | **Other** | Hyperemia · |
| **Authority control** | LCCN: sh85059683 · GND: 4024654-1 · BNF: cb11932573j (data) · NDL: 00571052 · | |

Categories: Aging-associated diseases | Causes of death | Ischemic heart diseases | Medical emergencies | Acute pain




# Peripheral artery disease

From Wikipedia, the free encyclopedia

**Peripheral artery disease** (**PAD**) is a narrowing of the arteries other than those that supply the heart or the brain.[1] When narrowing occurs in the heart it is called coronary artery disease while in the brain it is called cerebrovascular disease. Peripheral artery disease most commonly affects the legs, but other arteries may also be involved.[2] The classic symptom is leg pain when walking which resolves with rest, known as intermittent claudication.[3] Other symptoms including skin ulcers, bluish skin, cold skin, or poor nail and hair growth may occur in the affected leg.[4] Complications may include an infection or tissue death which may require amputation, coronary artery disease, or stroke.[2] Up to 50% of cases of PAD are without symptoms.[3]

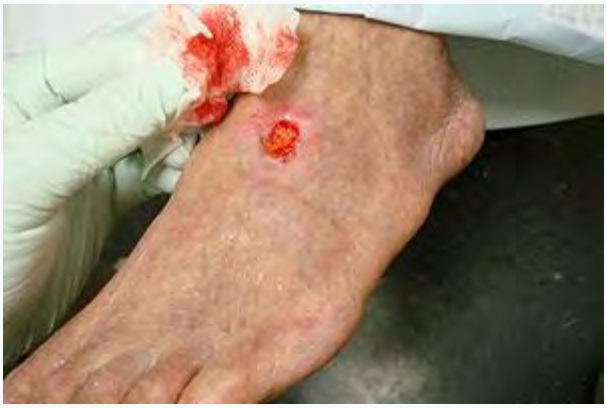
The main risk factor is cigarette smoking.[2] Other risk factors include diabetes, high blood pressure, and high blood cholesterol.[5] The underlying mechanism is usually atherosclerosis.[6] Other causes include artery spasm.[1] PAD is typically diagnosed by finding an ankle-brachial index (ABI) less than 0.90, which is the systolic blood pressure at the ankle divided by the systolic blood pressure of the arm.[7] Duplex ultrasonography and angiography may also be used.[8] Angiography is more accurate and allows for treatment at the same time; however, it is associated with greater risks.[7]

It is unclear if screening for disease is useful as it has not been properly studied.[9][10] In those with intermittent claudication from PAD, stopping smoking and supervised exercise therapy improves outcomes.[11][12] Medications, including statins, ACE inhibitors, and cilostazol also may help.[12][13] Aspirin does not appear to help those with mild disease but is usually recommended in those with more significant disease.[14][15] Anticoagulants such as warfarin are not typically of benefit.[16] Procedures used to treat the disease include bypass grafting, angioplasty, and atherectomy.[17]

In 2010 about 202 million people had PAD worldwide.[5] In the developed world it affects about 5.3% of 45 to 50 years olds and 18.6% of 85- to 90-year-olds.[5] In the developing world it affects 4.6% of people between the ages of 45 to 50 and 15% of people between the ages of 85 to 90.[5] In the developed world PAD is equally common among men and women while in the developing world women are more commonly affected.[5] In 2013 PAD resulted in about 41,000 deaths up from 16,000 deaths in 1990.[18]

**Peripheral artery disease**

**Synonyms** Peripheral vascular disease (PVD), peripheral artery occlusive disease, peripheral obliterative arteriopathy



An arterial insufficiency ulcer in a person with severe peripheral artery disease

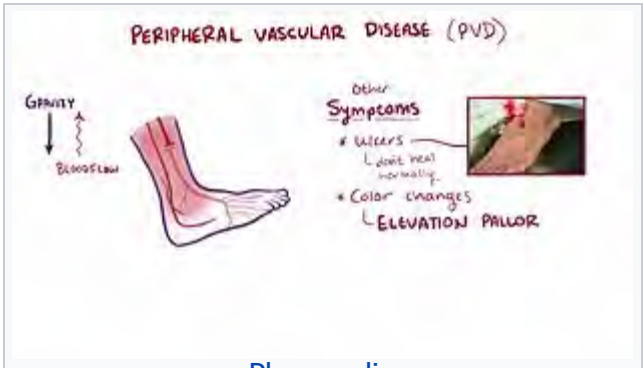
| Classification and external resources | |
|---|---|
| **Specialty** | Vascular surgery |
| **ICD-10** | I73.9 |
| **ICD-9-CM** | 443.9 |
| **DiseasesDB** | 31142 |
| **MedlinePlus** | 000170 |
| **eMedicine** | med/391 emerg/862 |
| **MeSH** | D016491 |

[edit on Wikidata]

## Signs and symptoms [edit]

Up to 50% of people with PAD may have no symptoms.[3] Symptoms of PAD in the legs and feet are generally divided into 2 categories:

1. Intermittent claudication—pain in muscles when walking or using the affected muscles that is relieved by resting those muscles. This is due to the unmet oxygen demand in muscles with use in the setting of inadequate blood flow.
2. Critical limb ischemia, consisting of:
   - Rest pain, a pain in the soles of the feet, particularly when the feet are elevated, such as when in bed.
   - Tissue loss, consisting of arterial insufficiency ulcers, which are sores or wounds that heal slowly or not at all, and gangrene.




Play media
Video explanation

Medical signs of PAD in the legs, due to inadequate perfusion, include:

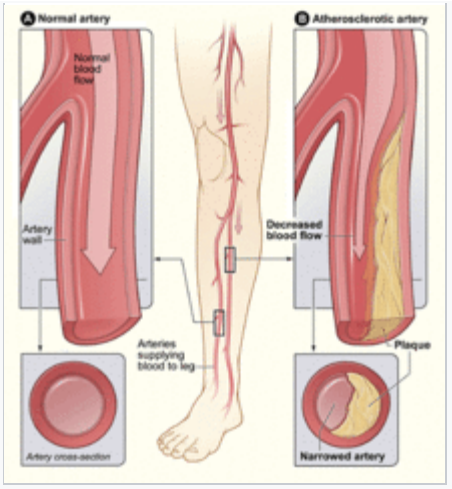
- Noticeable change in color – blueness, or in temperature (coolness) when compared to the other limb.
- Buerger's test can check for pallor on elevation of limb and redness (rubor) on a change to a sitting position, in an assessment of arterial sufficiency.
- Diminished hair and nail growth on affected limb and digits

PAD in other parts of the body depends on the organ affected. Renal artery disease can cause renovascular hypertension. Carotid artery disease can cause strokes and transient ischemic attacks.

## Causes [edit]

Risk factors contributing to PAD are the same as those for atherosclerosis:[19][20]

- Smoking – tobacco use in any form is the single most important modifiable cause of PAD internationally. Smokers have up to a tenfold increase in relative risk for PAD in a dose-response relationship.[20] Exposure to second-hand smoke from environmental




The illustration shows how PAD can affect arteries in the legs. Figure A shows a normal artery with normal blood flow. The inset image shows a cross-section of the normal artery. Figure B shows an artery with plaque buildup that's partially blocking blood flow. The inset image shows a cross-section of the narrowed artery.

exposure has also been shown to promote changes in blood vessel lining (endothelium) which is a precursor to atherosclerosis. Smokers are 2 to 3 times more likely to have lower extremity peripheral arterial disease than coronary artery disease.[21] More than 80%-90% of patients with lower extremity peripheral arterial disease are current or former smokers.[22] The risk of PAD increases with the number of cigarettes smoked per day and the number of years smoked.[23][24]

- Diabetes mellitus – causes between two and four times increased risk of PAD by causing endothelial and smooth muscle cell dysfunction in peripheral arteries.[25][26][27] The risk of developing lower extremity peripheral arterial disease is proportional to the severity and duration of diabetes.[28]
- Dyslipidemia – a high level of low-density lipoprotein (LDL cholesterol) and a low level of high-density lipoprotein (HDL cholesterol) in the blood) - elevation of total cholesterol, LDL cholesterol, and triglyceride levels each have been correlated with accelerated PAD. Correction of dyslipidemia by diet and/or medication is associated with a major improvement in rates of heart attack and stroke.[29]
- Hypertension – elevated blood pressure is correlated with an increase in the risk of developing PAD, as well as in associated coronary and cerebrovascular events (heart attack and stroke). Hypertension increased the risk of intermittent claudication 2.5- to 4-fold in men and women, respectively.[30]
- Risk of PAD also increases in individuals who are over the age of 50, male, obese, heart attack, or stroke[31][32] or with a family history of vascular disease.[33][34]
- Other risk factors which are being studied include levels of various inflammatory mediators such as C-reactive protein, fibrinogen,[35] hyperviscosity, hypercoagulable state.

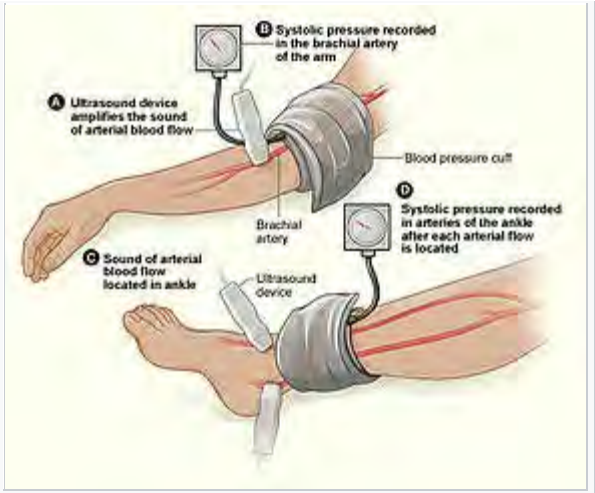
## Risk factors [edit]

Peripheral arterial disease is more common in the following populations of people:[24][36]

- All people who have leg symptoms with exertion (suggestive of claudication) or ischemic rest pain.
- All people aged 65 years and over regardless of risk factor status.
- All people between the age of 50 to 69 and who have a cardiovascular risk factor (particularly diabetes or smoking).
- Age less than 50 years, with diabetes and one other atherosclerosis risk factor (smoking, dyslipidemia, hypertension, or hyperhomocysteinemia).
- Individuals with an abnormal lower extremity pulse examination.
- Those with known atherosclerotic coronary, carotid, or renal artery disease.
- All people with a Framingham risk score 10%-20%
- All people who have previously experienced chest pain

# Diagnosis [edit]

Upon suspicion of PAD, the first-line study is the ankle brachial pressure index (ABPI/ABI). When the blood pressure readings in the ankles is lower than that in the arms, blockages in the arteries which provide blood from the heart to the ankle are



Measuring the ankle-brachial index

suspected. Normal ABI range of 1.00 to 1.40.The patient is diagnosed with PAD when the ABI is ≤ 0.90 . ABI values of 0.91 to 0.99 are considered "borderline" and values >1.40 indicate noncompressible arteries. PAD is graded as mild to moderate if the ABI is between 0.41 and 0.90, and an ABI less than 0.40 is suggestive of severe PAD. These relative categories have prognostic value.[24]

In people with suspected PAD but normal resting ABIs, exercise testing of ABI can be done. A base line ABI is obtained prior to exercise. The patient is then asked to exercise (usually patients are made to walk on a treadmill at a constant speed) until claudication pain occurs (or a maximum of 5 minutes), following which the ankle pressure is again measured. A decrease in ABI of 15%-20% would be diagnostic of PAD.[24][36]

It is possible for conditions which stiffen the vessel walls (such as calcifications that occur in the setting of long term diabetes) to produce false negatives usually, but not always, indicated by abnormally high ABIs (> 1.40). Such results and suspicions merit further investigation and higher level studies.[37]

If ABIs are abnormal the next step is generally a lower limb doppler ultrasound examination to look at site and extent of atherosclerosis. Other imaging can be performed by angiography,[19] where a catheter is inserted into the common femoral artery and selectively guided to the artery in question. While injecting a radiodense contrast agent an X-ray is taken. Any flow limiting stenoses found in the x-ray can be identified and treated by atherectomy, angioplasty or stenting. Contrast angiography is the most readily available and widely used imaging technique.

Modern multislice computerized tomography (CT) scanners provide direct imaging of the arterial system as an alternative to angiography.

Magnetic resonance angiography (MRA) is a noninvasive diagnostic procedure that uses a combination of a large magnet, radio frequencies, and a computer to produce detailed images to provide pictures of blood vessels inside the body. The advantages of MRA include its safety and ability to provide high-resolution three-dimensional (3D) imaging of the entire abdomen, pelvis and lower extremities in one sitting.[38][39]

## Classification [edit]

Peripheral artery occlusive disease is commonly divided in the Fontaine stages, introduced by René Fontaine in 1954 for chronic limb ischemia:[36][40]

- Stage I: Asymptomatic, incomplete blood vessel obstruction
- Stage II: Mild claudication pain in limb
  - Stage IIA: Claudication when walking a distance of greater than 200 meters
  - Stage IIB: Claudication when walking a distance of less than 200 meters
- Stage III: Rest pain, mostly in the feet
- Stage IV: Necrosis and/or gangrene of the limb

A classification introduced by Robert B. Rutherford in 1986 and revised in 1997 consists of four grades and seven categories:[36][41]

- Grade 0, Category 0: Asymptomatic
- Grade I, Category 1: Mild claudication
- Grade I, Category 2: Moderate claudication
- Grade I, Category 3: Severe claudication

Grade II, Category 4: Rest pain
- Grade III, Category 5: Minor tissue loss; Ischemic ulceration not exceeding ulcer of the digits of the foot
- Grade IV, Category 6: Major tissue loss; Severe ischemic ulcers or frank gangrene

The TASC (and TASC II) classification suggested PAD treatment by severity of disease seen on angiogram.[36] More recently classifications, such as the Society for Vascular Surgery "Wound, Ischemia and Foot Infection" (WIFI) classification, take into account that ischemia and angiographic disease patterns are not the only determinants of amputation risk.[42]

## Screening [edit]

It is not clear if screening for disease is useful as it has not been properly studied.[9]

## Treatment [edit]

Depending on the severity of the disease, the following steps can be taken, according to the following guidelines:[43]

### Lifestyle changes [edit]

- Smoking cessation (cigarettes promote PAD and are a risk factor for cardiovascular disease).
- Management of diabetes.
- Management of hypertension.
- Management of high cholesterol, and medication with antiplatelet drugs. Medication with aspirin, clopidogrel and statins, which reduce clot formation and cholesterol levels, respectively, can help with disease progression and address the other cardiovascular risks that the patient is likely to have.
- Regular exercise for those with claudication helps open up alternative small vessels (collateral flow) and the limitation in walking often improves. Treadmill exercise (35 to 50 minutes, 3 to 4 times per week[19]) has been reviewed as another treatment with a number of positive outcomes including reduction in cardiovascular events and improved quality of life.

### Medication [edit]

Cilostazol or pentoxifylline can improve symptoms in some.[44][*needs update*][45]

Treatment with other drugs or vitamins are unsupported by clinical evidence, "but trials evaluating the effect of folate and vitamin B-12 on hyperhomocysteinemia, a putative vascular risk factor, are near completion".[43]

### Revascularization [edit]

After a trial of the best medical treatment outline above, if symptoms persist, patients may be referred to a vascular or endovascular surgeon. The benefit of revascularization is thought to correspond to the severity of ischemia and the presence of other risk factors for limb loss such as wound and infection severity.[42]

- Angioplasty (PTA, or percutaneous transluminal angioplasty) can be done on solitary lesions in large arteries, such as the femoral artery, but angioplasty may not have sustained benefits.[46][47][*needs update*] Patency rates following angioplasty are highest for iliac arteries, and decrease with arteries towards the toes. Other criteria that affect outcome following revascularization are length of lesion, and number of lesions.[48][49]
- Atherectomy, in which the plaque is scraped off of the inside of the vessel wall (albeit with no better results than angioplasty).[50]
- Vascular bypass grafting can be performed to circumvent a diseased area of the arterial vasculature. The great saphenous vein is used as a conduit if available, although artificial (Gore-Tex or PTFE) material is often used for long grafts when adequate venous conduit is unavailable.

- When gangrene has set in, amputation is required to prevent infected tissues from causing sepsis a life-threatening illness.
- Thrombolysis and thrombectomy are used in cases of arterial thrombosis or embolism.

### Guidelines [edit]

An updated consensus guideline from the American College of Cardiology and American Heart Association for the diagnosis and treatment of lower extremity, renal, mesenteric and abdominal aortic PAD was compiled in 2013, combining the 2005 and 2011 guidelines.[24]

## Prognosis [edit]

Individuals with PAD have an "exceptionally elevated risk for cardiovascular events and the majority will eventually die of a cardiac or cerebrovascular etiology";[51] prognosis is correlated with the severity of the PAD as measured by the Ankle brachial pressure index (ABPI).[51] Large-vessel PAD increases mortality from cardiovascular disease significantly. PAD carries a greater than "20% risk of a coronary event in 10 years".[51]

There is a low risk that an individual with claudication will develop severe ischemia and require amputation, but the risk of death from coronary events is three to four times higher than matched controls without claudication.[43] Of patients with intermittent claudication, only "7% will undergo lower extremity bypass surgery, 4% major amputations, and 16% worsening claudication", but stroke and heart attack events are elevated, and the "5-year mortality rate is estimated to be 30% (versus 10% in controls)".[51]

## Epidemiology [edit]

The prevalence of peripheral artery disease in the general population is 12–14%, affecting up to 20% of those over 70;[51] 70%–80% of affected individuals are asymptomatic; only a minority ever require revascularisation or amputation.[*citation needed*] Peripheral artery disease affects 1 in 3 diabetics over the age of 50.

In the USA peripheral arterial disease affects 12–20 percent of Americans age 65 and older. Approximately 10 million Americans have PAD. Despite its prevalence and cardiovascular risk implications, only 25 percent of PAD patients are undergoing treatment.

The incidence of symptomatic PAD increases with age, from about 0.3% per year for men aged 40–55 years to about 1% per year for men aged over 75 years. The prevalence of PAD varies considerably depending on how PAD is defined, and the age of the population being studied. Diagnosis is critical, as people with PAD have a four to five times higher risk of heart attack or stroke.

The Diabetes Control and Complications Trial, and the U.K. Prospective Diabetes Study trials, in people with type 1 and type 2 diabetes, respectively, demonstrated that glycemic control is more strongly associated with microvascular disease than macrovascular disease. It may be that pathologic changes occurring in small vessels are more sensitive to chronically elevated glucose levels than is atherosclerosis occurring in larger arteries.[52]

## Research [edit]

In those who have developed critically poor blood flow to the legs it is unclear if autotransplantation of autologous mononuclear cells is useful or not.[53]

Only one randomized controlled trial has been conducted comparing vascular bypass to angioplasty for the treatment of severe PAD.[54] The trial found no difference in amputation-free survival between vascular bypass and angioplasty at the planned clinical endpoint, however the trial has been criticized as being underpowered, limiting endovascular options, and comparing inappropriate endpoints.[55] As of 2015, a

second trial is being conducted regarding the optimal revascularization for severe PAD.[56]

In 2011 pCMV-vegf165 was registered in Russia as the first-in-class gene therapy drug for treatment of peripheral artery disease, including the advanced stage of critical limb ischemia.[57][58]

## See also [edit]

- Chronic venous insufficiency
- Vascular myelopathy

## References [edit]


1. ^ a b "What Is Peripheral Vascular Disease?" (PDF). *https://www.heart.org*. 2012. Retrieved 26 February 2015. External link in |website= (help)
2. ^ a b c "What Is Peripheral Arterial Disease?". *http://www.nhlbi.nih.gov/*. August 2, 2011. Retrieved 25 February 2015. External link in |website= (help)
3. ^ a b c Violi, F; Basili, S; Berger, JS; Hiatt, WR (2012). "Antiplatelet therapy in peripheral artery disease.". *Handbook of experimental pharmacology* (210): 547–63. doi:10.1007/978-3-642-29423-5_22. PMID 22918746.
4. ^ "What Are the Signs and Symptoms of Peripheral Arterial Disease?". *http://www.nhlbi.nih.gov/*. August 2, 2011. Retrieved 26 February 2015. External link in |website= (help)
5. ^ a b c d e Fowkes, FG; Rudan, D; Rudan, I; Aboyans, V; Denenberg, JO; McDermott, MM; Norman, PE; Sampson, UK; Williams, LJ; Mensah, GA; Criqui, MH (19 October 2013). "Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis.". *Lancet*. **382** (9901): 1329–40. doi:10.1016/s0140-6736(13)61249-0. PMID 23915883.
6. ^ "What Causes Peripheral Arterial Disease?". *http://www.nhlbi.nih.gov/*. August 2, 2011. Retrieved 26 February 2015. External link in |website= (help)
7. ^ a b Ruiz-Canela, M; Martínez-González, MA (2014). "Lifestyle and dietary risk factors for peripheral artery disease.". *Circulation Journal*. **78** (3): 553–9. doi:10.1253/circj.cj-14-0062. PMID 24492064.
8. ^ "How Is Peripheral Arterial Disease Diagnosed?". August 2, 2011. Retrieved 27 March 2015.
9. ^ a b Andras, A; Ferket, B (Apr 7, 2014). "Screening for peripheral arterial disease". *The Cochrane database of systematic reviews*. **4**: CD010835. doi:10.1002/14651858.CD010835.pub2. PMID 24711093.
10. ^ U.S. Preventive Services Task Force (Dec 15, 2014). "Peripheral artery disease screening and cardiovascular disease risk assessment with the ankle-brachial index in adults: recommendation



Peripheral Artery Disease". *Journal of the American College of Cardiology*. **58** (13): 1386–92. doi:10.1016/j.jacc.2011.06.023. PMID 21920269.

34. ^ Valentine RJ, Guerra R, Stephan P, Scoggins E, Clagett GP, Cohen J (2004). "Family history is a major determinant of subclinical peripheral arterial disease in young adults". *Journal of vascular surgery*. **39** (2): 351–356. doi:10.1016/j.jvs.2003.07.011.
35. ^ Ridker PM, Stampfer MJ, Rifai N (2001). "Novel risk factors for systemic atherosclerosis". *JAMA: the journal of the American Medical Association*. **285** (19): 2481–2485. doi:10.1001/jama.285.19.2481.
36. ^ a b c d e TASC II Guidelines
* Norgren L, Hiatt WR, Dormandy JA; Hiatt; et al. (2007). "Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)". *Eur J Vasc Endovasc Surg*. **33** (Suppl 1): S1–75. doi:10.1016/j.ejvs.2006.09.024. PMID 17140820.
* Norgren L, Hiatt WR, Dormandy JA, TASC II Working Group, et al. (2007). "Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)". *J Vasc Surg*. **45** (Suppl S): S5–67. doi:10.1016/j.jvs.2006.12.037. PMID 17223489.
* Norgren L, Hiatt WR, Dormandy JA (2007). "Inter-Society Consensus for the Management of Peripheral Arterial Disease". *Int Angiol*. **26** (2): 81–157. PMID 17489079.
37. ^ Vowden P, Vowden K (March 2001). "Doppler assessment and ABPI: Interpretation in the management of leg ulceration". *Worldwide Wounds*. - describes ABPI procedure, interpretation of results, and notes the somewhat arbitrary selection of "ABPI of 0.8 has become the accepted endpoint for high compression therapy, the trigger for referral for a vascular surgical opinion and the defining upper marker for an ulcer of mixed aetiology"
38. ^ Leiner T, Kessels AG, Nelemans PJ, Vasbinder GB, de Haan MW, Kitslaar PE, Ho KY, Tordoir JH, van Engelshoven JM699-708; Kessels; Nelemans; Vasbinder; De Haan; Kitslaar; Ho; Tordoir; Van Engelshoven (May 2005). "Peripheral arterial disease: comparison of color duplex US and contrast-

statement.". *Am Fam Physician*. **90** (12): 858A–858D. PMID 25591190.
11. ^ Fokkenrood, HJ; Bendermacher, BL; Lauret, GJ; Willigendael, EM; Prins, MH; Teijink, JA (23 August 2013). "Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication.". *The Cochrane database of systematic reviews*. **8**: CD005263. doi:10.1002/14651858.CD005263.pub3. PMID 23970372.
12. ^ a b Hankey, GJ; Norman, PE; Eikelboom, JW (1 February 2006). "Medical treatment of peripheral arterial disease.". *JAMA*. **295** (5): 547–53. doi:10.1001/jama.295.5.547. PMID 16449620.
13. ^ Bedenis, R; Stewart, M; Cleanthis, M; Robless, P; Mikhailidis, DP; Stansby, G (31 October 2014). "Cilostazol for intermittent claudication.". *The Cochrane database of systematic reviews*. **10**: CD003748. doi:10.1002/14651858.CD003748.pub4. PMID 25358850.
14. ^ Lin, JS; Olson, CM; Johnson, ES; Whitlock, EP (3 September 2013). "The ankle-brachial index for peripheral artery disease screening and cardiovascular disease prediction among asymptomatic adults: a systematic evidence review for the U.S. Preventive Services Task Force.". *Annals of Internal Medicine*. **159** (5): 333–41. doi:10.7326/0003-4819-159-5-201309030-00007. PMID 24026319.
15. ^ Poredos, P; Jezovnik, MK (March 2013). "Is aspirin still the drug of choice for management of patients with peripheral arterial disease?". *VASA. Zeitschrift für Gefasskrankheiten*. **42** (2): 88–95. doi:10.1024/0301-1526/a000251. PMID 23485835.
16. ^ Hauk, L (15 May 2012). "ACCF/AHA update peripheral artery disease management guideline.". *American family physician*. **85** (10): 1000–1. PMID 22612053.
17. ^ "How Is Peripheral Arterial Disease Treated?". *http://www.nhlbi.nih.gov*. August 2, 2011. Retrieved 26 February 2015. External link in |website= (help)
18. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
19. ^ a b c *Peripheral Arterial Disease* at Merck Manual of Diagnosis and Therapy Professional Edition. Retrieved August 9, 2010.
20. ^ a b Joosten MM, Pai JK, Bertoia ML, Rimm EB, Spiegelman D, Mittleman MA, Mukamal KJ (Oct 2012). "Associations between conventional cardiovascular risk factors and risk of peripheral enhanced MR angiography for diagnosis". *Radiology*. **235** (2): 699–708. doi:10.1148/radiol.2352040089. PMID 15858107.
39. ^ Leiner, T (February 2005). "Magnetic resonance angiography of abdominal and lower extremity vasculature". *Top Magn Reson Imaging*. **16** (1): 21–66. doi:10.1097/01.rmr.0000185431.50535.d7. PMID 16314696.
40. ^ Fontaine R, Kim M, Kieny R; Kim; Kieny (1954). "Die chirugische Behandlung der peripheren Durchblutungsstörungen. (Surgical treatment of peripheral circulation disorders)". *Helvetica Chirurgica Acta* (in German). **21** (5/6): 499–533. PMID 14366554.
41. ^ Rutherford, Robert B.; Baker, J. Dennis; Ernst, Calvin; Johnston, K. Wayne; Porter, John M.; Ahn, Sam; Jones, Darrell N. (September 1997). "Recommended standards for reports dealing with lower extremity ischemia: Revised version". *Journal of Vascular Surgery*. **26** (3): 517–538. doi:10.1016/S0741-5214(97)70045-4. PMID 9308598.
42. ^ a b Mills JL, Sr; Conte, MS; Armstrong, DG; Pomposelli, FB; Schanzer, A; Sidawy, AN; Andros, G; Society for Vascular Surgery Lower Extremity Guidelines, Committee (January 2014). "The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI).". *Journal of vascular surgery*. **59** (1): 220–34.e1–2. doi:10.1016/j.jvs.2013.08.003. PMID 24126108.
43. ^ a b c Burns P, Gough S, Bradbury AW; Gough; Bradbury (March 2003). "Management of peripheral arterial disease in primary care". *BMJ*. **326** (7389): 584–8. doi:10.1136/bmj.326.7389.584. PMC 1125476. PMID 12637405.
44. ^ Robless P, Mikhailidis DP, Stansby GP; Mikhailidis; Stansby (2008). Robless, Peter, ed. "Cilostazol for peripheral arterial disease". *Cochrane Database Syst Rev* (1): CD003748. doi:10.1002/14651858.CD003748.pub3. PMID 18254032.
45. ^ Salhiyyah, Kareem; Senanayake, Eshan; Abdel-Hadi, Mohammed; Booth, Andrew; Michaels, Jonathan A (2012). Salhiyyah, Kareem, ed. "Pentoxifylline for intermittent claudication". *Cochrane Database of Systematic Reviews* (Systematic Review). **1**: CD005262. doi:10.1002/14651858.CD005262.pub2. PMID 22258961.
46. ^ Fowkes FG, Gillespie IN; Gillespie (2000). Fowkes, Gerry, ed. "Angioplasty (versus non surgical management) for intermittent claudication". *Cochrane Database Syst Rev* (2): CD000017. doi:10.1002/14651858.CD000017. PMID 10796469.
47. ^ Twine CP, Coulston J, Shandall A, McLain AD;

artery disease in men". *JAMA*. **308** (16): 1660–7. doi:10.1001/jama.2012.13415. PMID 23093164.
21. ^ Price J, Mowbray P, Lee A, Rumley A, Lowe G, Fowkes F (1999). "Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease; Edinburgh Artery Study Edinburgh Artery Study". *European Heart Journal*. **20** (5): 344–353. doi:10.1053/euhj.1998.1194.
22. ^ Smith GD, Shipley M, Rose G (1990). "Intermittent claudication, heart disease risk factors, and mortality. The Whitehall Study". *Circulation*. **82** (6): 1925–1931. doi:10.1161/01.cir.82.6.1925.
23. ^ Cole C, Hill G, Farzad E, Bouchard A, Moher D, Rody K, Shea B (1993). "Cigarette smoking and peripheral arterial occlusive disease". *Surgery*. **114** (4): 753.
24. ^ *a b c d e* Rooke, TW; Hirsch, AT; Misra, S; Sidawy, AN; Beckman, JA; Findeiss, L; Golzarian, J; Gornik, HL; Jaff, MR; Moneta, GL; Olin, JW; Stanley, JC; White, CJ; White, JV; Zierler, RE; American College of Cardiology Foundation Task, Force; American Heart Association Task, Force (9 April 2013). "Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.". *Journal of the American College of Cardiology*. **61** (14): 1555–70. doi:10.1016/j.jacc.2013.01.004. PMID 23473760.
25. ^ Kannel WB, McGee D (1979). "Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study". *Diabetes Care*. **2** (2): 120–126. doi:10.2337/diacare.2.2.120.
26. ^ Creager MA, Lüscher TF, Cosentino F, Beckman JA (2003). "Diabetes and vascular disease pathophysiology, clinical consequences, and medical therapy: part I.". *Circulation*. **108** (12): 1527–1532. doi:10.1161/01.cir.0000091257.27563.32.
27. ^ Lüscher TF, Creager MA, Beckman JA, Cosentino F (2003). "Diabetes and vascular disease pathophysiology, clinical consequences, and medical therapy: Part II.". *Circulation*. **108** (13): 1655–1661. doi:10.1161/01.cir.0000089189.70578.e2.
28. ^ Beks P, Mackaay A, De Neeling J, De Vries H, Bouter L, Heine R: Peripheral arterial disease in relation to glycaemic level in an elderly Caucasian population: the Hoorn study. *Diabetologia* 1995, 38(1):86-96.
29. ^ Unit ES: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005, 366:1267-1278.
30. ^ Kannel W, McGee D (1985). "Update on some epidemiologic features of intermittent claudication: the Framingham Study". *Journal of the American Geriatrics Society*. **33** (1): 13.
31. ^ Selvin E, Erlinger TP: Prevalence of and risk Coulston; Shandall; McLain (2009). Twine, Christopher P, ed. "Angioplasty versus stenting for superficial femoral artery lesions". *Cochrane Database Syst Rev* (2): CD006767. doi:10.1002/14651858.CD006767.pub2. PMID 19370653.
48. ^ Johnston KW, Rae M, Hogg-Johnston SA, Colapinto RF, Walker PM, Baird RJ, Sniderman KW, Kalman P (1987). "5-year results of a prospective study of percutaneous transluminal angioplasty". *Annals of Surgery*. **206** (4): 403–413. doi:10.1097/00000658-198710000-00002.
49. ^ Emmerich J (2005). "Current state and perspective on medical treatment of critical leg ischemia: gene and cell therapy". *The international journal of lower extremity wounds*. **4** (4): 234–241. doi:10.1177/1534734605283538.
50. ^ Ambler, GK; Radwan, R; Hayes, PD; Twine, CP (17 March 2014). "Atherectomy for peripheral arterial disease.". *The Cochrane database of systematic reviews*. **3**: CD006680. doi:10.1002/14651858.CD006680.pub2. PMID 24638972.
51. ^ *a b c d e* Shammas NW (2007). "Epidemiology, classification, and modifiable risk factors of peripheral arterial disease". *Vasc Health Risk Manag*. **3** (2): 229–34. doi:10.2147/vhrm.2007.3.2.229. PMC 1994028. PMID 17580733.
52. ^ Selvin E, Wattanakit K, Steffes MW, Coresh J, Sharrett AR; Wattanakit; Steffes; Coresh; Sharrett (April 2006). "HbA1c and peripheral arterial disease in diabetes: the Atherosclerosis Risk in Communities study". *Diabetes Care*. **29** (4): 877–82. doi:10.2337/diacare.29.04.06.dc05-2018. PMID 16567831.
53. ^ Moazzami, K; Moazzami, B; Roohi, A; Nedjat, S; Dolmatova, E (19 December 2014). "Local intramuscular transplantation of autologous mononuclear cells for critical lower limb ischaemia.". *The Cochrane database of systematic reviews*. **12**: CD008347. doi:10.1002/14651858.CD008347.pub3. PMID 25525690.
54. ^ "Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial.". *Lancet*. **366**: 1925–34. Dec 2005. doi:10.1016/S0140-6736(05)67704-5. PMID 16325694.
55. ^ Conte, MS (May 2010). "Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and the (hoped for) dawn of evidence-based treatment for advanced limb ischemia.". *Journal of vascular surgery*. **51** (5 Suppl): 69S–75S. doi:10.1016/j.jvs.2010.02.001. PMID 20435263.
56. ^ Menard, MT; Farber, A (March 2014). "The BEST-CLI trial: a multidisciplinary effort to assess whether surgical or endovascular therapy is better for patients with critical limb ischemia.". *Seminars in vascular surgery*. **27** (1): 82–84.

factors for peripheral arterial disease in the united states results from the national health and nutrition examination survey, 1999–2000. *Circulation* 2004, 110(6):738-743.
32. ^ Hooi JD, Kester AD, Stoffers HE, Overdijk MM, van Ree JW, Knottnerus JA (2001). "Incidence of and risk factors for asymptomatic peripheral arterial occlusive disease: a longitudinal study". *American Journal of Epidemiology*. **153** (7): 666–672. doi:10.1093/aje/153.7.666. PMID 11282794.
33. ^ Allison MA, Denenberg JO, Criqui MH (2011). "Family History of Peripheral Artery Disease Is Associated With Prevalence and Severity of doi:10.1053/j.semvascsurg.2015.01.003 . PMID 25812762.
57. ^ "Gene Therapy for PAD Approved". 6 December 2011. Retrieved 5 August 2015.
58. ^ Deev, R.; Bozo, I.; Mzhavanadze, N.; Voronov, D.; Gavrilenko, A.; Chervyakov, Yu.; Staroverov, I.; Kalinin, R.; Shvalb, P.; Isaev, A. (13 March 2015). "pCMV-vegf165 Intramuscular Gene Transfer is an Effective Method of Treatment for Patients With Chronic Lower Limb Ischemia". *Journal of cardiovascular pharmacology and therapeutics*. **20**: 473–82. doi:10.1177/1074248415574336. PMID 25770117. Retrieved 5 August 2015.

## External links [edit]

- "Peripheral Arterial Disease" at the National Heart, Lung and Blood Institute
- Peripheral Arterial Disease (P.A.D.) at the American College of Foot and Ankle Surgeons
- Gerhard-Herman, Marie D.; Gornik, Heather L.; Barrett, Coletta; Barshes, Neal R.; Corriere, Matthew A.; et al. (13 November 2016). "2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary". *Circulation*: CIR.0000000000000470. doi:10.1161/CIR.0000000000000470.
- Cochrane Peripheral Vascular Diseases Review Group

| v · t · e | **Cardiovascular disease (vessels) (I70–I99, 440–456)** | | |
|---|---|---|---|
| **Arteries, arterioles and capillaries** | **Inflammation** | | Arteritis (Aortitis · · Buerger's disease · |
| | **Peripheral artery disease** | **Arteriosclerosis** | Atherosclerosis (Foam cell · Fatty streak · Atheroma · Intermittent claudication · Critical limb ischemia · · Monckeberg's arteriosclerosis · Arteriolosclerosis (Hyaline · Hyperplastic · Cholesterol · LDL · Oxycholesterol · Trans fat · · |
| | | **Stenosis** | Carotid artery stenosis · Renal artery stenosis · |
| | | **Other** | Aortoiliac occlusive disease · Degos disease · Erythromelalgia · Fibromuscular dysplasia · Raynaud's phenomenon · |
| | **Aneurysm / dissection / pseudoaneurysm** | | *torso*: Aortic aneurysm (Abdominal aortic aneurysm · Thoracic aortic aneurysm · Aneurysm of sinus of Valsalva · · Aortic dissection · Coronary artery aneurysm · *head / neck* (Intracranial aneurysm · Intracranial berry aneurysm · Carotid artery dissection · Vertebral artery dissection · Familial aortic dissection · · |
| | **Vascular malformation** | | Arteriovenous fistula · Arteriovenous malformation · Telangiectasia (Hereditary hemorrhagic telangiectasia · · |
| | **Vascular nevus** | | Cherry hemangioma · Halo nevus · Spider angioma · |

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| **Veins** | **Inflammation** | Phlebitis · |
| | **Venous thrombosis / Thrombophlebitis** | *primarily lower limb* (Deep vein thrombosis · · *abdomen* (Hepatic veno-occlusive disease · Budd–Chiari syndrome · May–Thurner syndrome · Portal vein thrombosis · Renal vein thrombosis · · *upper limb / torso* (Mondor's disease · Paget–Schroetter disease · · *head* (Cerebral venous sinus thrombosis · · Post-thrombotic syndrome · |
| | **Varicose veins** | Gastric varices · Portacaval anastomosis (Caput medusae · Esophageal varices · Hemorrhoid · · Varicocele · |
| | **Other** | Chronic venous insufficiency · Chronic cerebrospinal venous insufficiency · Superior vena cava syndrome · Inferior vena cava syndrome · Venous ulcer · |
| **Arteries or veins** | | Angiopathy (Macroangiopathy · Microangiopathy · · Embolism (Pulmonary embolism · Cholesterol embolism · Paradoxical embolism · · Thrombosis · Vasculitis · |
| **Blood pressure** | **Hypertension** | Hypertensive heart disease · Hypertensive emergency · Hypertensive nephropathy · Essential hypertension · Secondary hypertension (Renovascular hypertension · · Benign hypertension · Pulmonary hypertension · Systolic hypertension · White coat hypertension · |
| | **Hypotension** | Orthostatic hypotension · |

Categories: Diseases of arteries, arterioles and capillaries

# Pulmonary embolism

From Wikipedia, the free encyclopedia

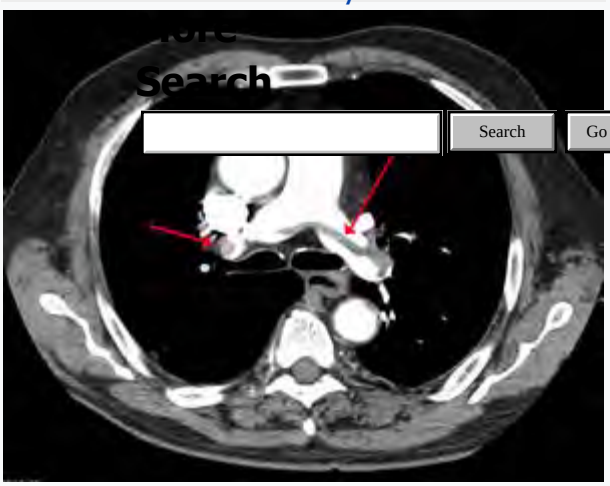
**Pulmonary embolism** (**PE**) is a blockage of an artery in the lungs by a substance that has traveled from elsewhere in the body through the bloodstream (embolism).[1] Symptoms of a PE may include shortness of breath, chest pain particularly upon breathing in, and coughing up blood.[2] Symptoms of a blood clot in the leg may also be present such as a red, warm, swollen, and painful leg.[2] Signs of a PE include low blood oxygen levels, rapid breathing, rapid heart rate, and sometimes a mild fever.[3] Severe cases can lead to passing out, abnormally low blood pressure, and sudden death.[4]

PE usually results from a blood clot in the leg that travels to the lung.[1] The risk of blood clots is increased by cancer, prolonged bed rest, smoking, stroke, certain genetic conditions, pregnancy, obesity, and after some types of surgery.[5] A small proportion of cases are due to the embolization of air, fat, or amniotic fluid.[6][7] Diagnosis is based on signs and symptoms in combination with test results. If the risk is low a blood test known as a D-dimer will rule out the condition. Otherwise a CT pulmonary angiography, lung ventilation/perfusion scan, or ultrasound of the legs may confirm the diagnosis.[8] Together deep vein thrombosis and PE are known as venous thromboembolism (VTE).[9]

Efforts to prevent PE include beginning to move as soon as possible after surgery, lower leg exercises during periods of sitting, and the use of blood thinners after some types of surgery.[10] Treatment is typically with blood thinners such as heparin or warfarin.[11] Often these are recommended for six months or longer.[12] Severe cases may require thrombolysis using medication such as tissue plasminogen activator (tPA), or may require surgery such as a pulmonary thrombectomy. If blood thinners are not appropriate a vena cava filter may be used.[11]

Pulmonary emboli affect about 430,000 people each year in Europe.[13] In the United States between 300,000 and 600,000 cases occur each year,[1][14] which results in between 50,000[14] and 200,000 deaths.[15] Rates are similar in males and females. They become more common as people get older.[5]

**Pulmonary embolism**



Chest spiral CT scan with radiocontrast agent showing multiple filling defects both at the bifurcation ("saddle" pulmonary embolism) and in the pulmonary arteries.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Hematology, cardiology, pulmonology |
| **ICD-10** | I26 |
| **ICD-9-CM** | 415.1 |
| **DiseasesDB** | 10956 |
| **MedlinePlus** | 000132 |
| **eMedicine** | med/1958 emerg/490 radio/582 |
| **Patient UK** | Pulmonary embolism |
| **MeSH** | D011655 |

[edit on Wikidata]

Contents

## Signs and symptoms [edit]

Symptoms of pulmonary embolism are typically sudden in onset and may include one or many of the following: dyspnea (shortness of breath), tachypnea (rapid breathing), chest pain of a "pleuritic" nature (worsened by breathing), cough and hemoptysis (coughing up blood).[16] More severe cases can include signs such as cyanosis (blue discoloration, usually of the lips and fingers), collapse, and circulatory instability because of decreased blood flow through the lungs and into the left side of the heart. About 15% of all cases of sudden death are attributable to PE.[4]

On physical examination, the lungs are usually normal. Occasionally, a pleural friction rub may be audible over the affected area of the lung (mostly in PE with infarct). A pleural effusion is sometimes present that is exudative, detectable by decreased percussion note, audible breath sounds, and vocal resonance. Strain on the right ventricle may be detected as a left parasternal heave, a loud pulmonary component of the second heart sound, and/or raised jugular venous pressure.[4] A low-grade fever may be present, particularly if there is associated pulmonary hemorrhage or infarction.[17]

As smaller pulmonary emboli tend to lodge in more peripheral areas without collateral circulation they are more likely to cause lung infarction and small effusions (both of which are painful), but not hypoxia, dyspnea or hemodynamic instability such as tachycardia. Larger PEs, which tend to lodge centrally, typically cause dyspnea, hypoxia, low blood pressure, fast heart rate and fainting, but are often painless because there is no lung infarction due to collateral circulation. The classic presentation for PE with pleuritic pain, dyspnea and tachycardia is likely caused by a large fragmented embolism causing both large and small PEs. Thus, small PEs are often missed because they cause pleuritic pain alone without any other findings and large PEs often missed because they are painless and mimic other conditions often causing ECG changes and small rises in troponin and BNP levels.[18]

PEs are sometimes described as massive, submassive and nonmassive depending on the clinical signs and symptoms. Although the exact definitions of these are unclear, an accepted definition of massive PE is one in which there is hemodynamic instability such as sustained low blood pressure, slowed heart rate, or pulselessness.[19]

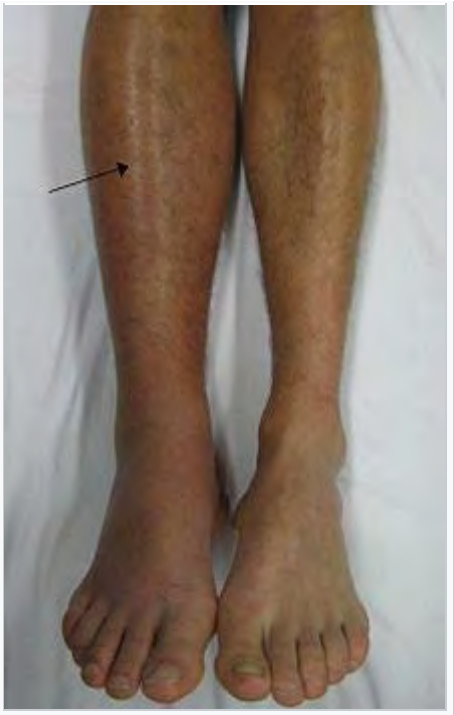
## Risk factors [edit]

About 90% of emboli are from proximal leg deep vein thromboses [20]

(DVTs) or pelvic vein thromboses. DVTs are at risk for dislodging and migrating to the lung circulation. The conditions are generally regarded as a continuum termed *venous thromboembolism* (VTE).

The development of thrombosis is classically due to a group of causes named Virchow's triad (alterations in blood flow, factors in the vessel wall and factors affecting the properties of the blood). Often, more than one risk factor is present.

- *Alterations in blood flow*: immobilization (after surgery), injury, pregnancy (also procoagulant), obesity (also procoagulant), cancer (also procoagulant)
- *Factors in the vessel wall*: surgery, catheterizations causing direct injury ("endothelial injury")
- *Factors affecting the properties of the blood* (procoagulant state):
  - Estrogen-containing hormonal contraception
  - Genetic thrombophilia (factor V Leiden, prothrombin mutation G20210A, protein C deficiency, protein S deficiency, antithrombin deficiency, hyperhomocysteinemia and plasminogen/fibrinolysis disorders)
  - Acquired thrombophilia (antiphospholipid syndrome, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria)
  - Cancer (due to secretion of pro-coagulants)



A deep vein thrombosis as seen in the right leg is a risk factor for PE

### Underlying causes [edit]

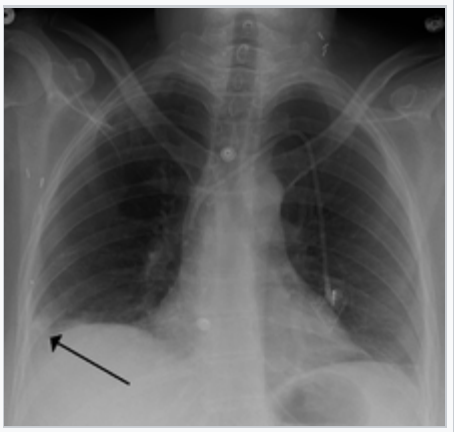
After a first PE, the search for secondary causes is usually brief. Only when a second PE occurs, and especially when this happens while still under anticoagulant therapy, a further search for underlying conditions is undertaken. This will include testing ("thrombophilia screen") for Factor V Leiden mutation, antiphospholipid antibodies, protein C and S and antithrombin levels, and later prothrombin mutation, MTHFR mutation, Factor VIII concentration and rarer inherited coagulation abnormalities.[*citation needed*]

## Diagnosis [edit]

In order to diagnose a pulmonary embolism, a review of clinical criteria to determine the need for testing is recommended.[21] In those who have low risk, age less than 50, heart rate less than 100 beats per minute, oxygen level more than 94% on room air, and no leg swelling, coughing up of blood, surgery or trauma in the last four weeks, previous blood clots, or estrogen use, further testing is not typically needed.[22]

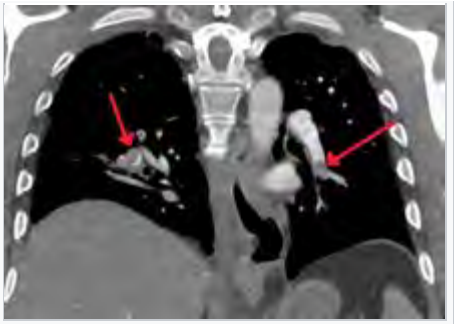
If there are concerns this is followed by testing to determine a likelihood of being able to confirm a diagnosis by imaging, followed by imaging if other tests have shown that there is a likelihood of a PE diagnosis.[21][23][24]

The diagnosis of PE is based primarily on validated clinical criteria combined with selective testing because the typical clinical presentation (shortness of breath, chest pain) cannot be definitively differentiated from other causes of chest pain and shortness of breath. The decision to perform medical imaging is based on clinical reasoning, that is, the medical history, symptoms and findings on physical examination, followed by an assessment of clinical probability.[4]



A Hampton hump in a person with a right lower lobe pulmonary embolism

### Probability testing [edit]



Segmental and subsegmental pulmonary emboli on both sides

The most commonly used method to predict clinical probability, the Wells score, is a clinical prediction rule, whose use is complicated by multiple versions being available. In 1995, Philip Steven Wells, initially developed a prediction rule (based on a literature search) to predict the likelihood of PE, based on clinical criteria.[25] The prediction rule was revised in 1998[26] This prediction rule was further revised when simplified during a validation by Wells *et al.* in 2000.[27] In the 2000 publication, Wells proposed two different scoring systems using cutoffs of 2 or 4 with the same prediction rule.[27] In 2001, Wells published results using the more conservative cutoff of 2 to create three categories.[28] An additional version, the "modified extended version", using the more recent cutoff of 2 but including findings from Wells's initial studies[25][26] were proposed.[29] Most recently, a further study reverted to Wells's earlier use of a cutoff of 4 points[27] to create only two categories.[30]

There are additional prediction rules for PE, such as the Geneva rule. More importantly, the use of *any* rule is associated with reduction in recurrent thromboembolism.[31]

*The Wells score*:[32]

- clinically suspected DVT — 3.0 points
- alternative diagnosis is less likely than PE — 3.0 points
- tachycardia (heart rate > 100) — 1.5 points
- immobilization (≥ 3d)/surgery in previous four weeks — 1.5 points
- history of DVT or PE — 1.5 points
- hemoptysis — 1.0 points
- malignancy (with treatment within six months) or palliative — 1.0 points

Traditional interpretation[27][28][33]

- Score >6.0 — High (probability 59% based on pooled data)[34]
- Score 2.0 to 6.0 — Moderate (probability 29% based on pooled data)[34]
- Score <2.0 — Low (probability 15% based on pooled data)[34]

Alternative interpretation[27][30]

- Score > 4 — PE likely. Consider diagnostic imaging.
- Score 4 or less — PE unlikely. Consider D-dimer to rule out PE.

Recent recommendations for a diagnostic algorithm were published by the PIOPED investigators; however, these recommendations do not reflect research using 64 slice MDCT.[34] These investigators recommended:

- Low clinical probability. If negative D-dimer, PE is excluded. If positive D-dimer, obtain MDCT and based treatment on results.
- Moderate clinical probability. If negative D-dimer, PE is excluded. *However*, the authors were not concerned that a negative MDCT with negative D-dimer in this setting has a 5% probability of being false. Presumably, the 5% error rate will fall as 64 slice MDCT is more commonly used. If positive D-dimer, obtain MDCT and based treatment on results.
- High clinical probability. Proceed to MDCT. If positive, treat, if negative, more tests are needed to exclude PE.

## Pulmonary embolism rule-out criteria [edit]

The pulmonary embolism rule-out criteria (PERC) helps assess people in whom pulmonary embolism is suspected, but unlikely. Unlike the Wells score and Geneva score, which are clinical prediction rules intended to risk stratify people with suspected PE, the PERC rule is designed to rule out risk of PE in people when the physician has already stratified them into a low-risk category.

People in this low risk category without any of these criteria may undergo no further diagnostic testing for PE: Hypoxia — $Sa_{O_2}$ <95%, unilateral leg swelling, hemoptysis, prior DVT or PE, recent surgery or trauma, age >50, hormone use, tachycardia. The rationale behind this decision is that further testing (specifically CT angiogram of the chest) may cause more harm (from radiation exposure and contrast dye) than the risk of PE.[35] The PERC rule has a sensitivity of 97.4% and specificity of 21.9% with a false negative rate of 1.0% (16/1666).[36]

## Blood tests [edit]

In people with a low or moderate suspicion of PE, a normal D-dimer level (shown in a blood test) is enough to exclude the possibility of thrombotic PE, with a three-month risk of thromboembolic events being 0.14%.[37] D-dimer is highly sensitive but not specific (specificity around 50%). In other words, a positive D-dimer is not synonymous with PE, but a negative D-dimer is, with a good degree of certainty, an indication of absence of a PE.[38] The typical cut off is 500 ug/L, although this varies based on the assay.[39] However, in those over the age of 50, changing the cut-off value to the person's age multiplied by 10 ug/L (accounting for assay which has been used) is recommended as it decreases the number of falsely positive tests without missing any additional cases of PE.[22][39][40]

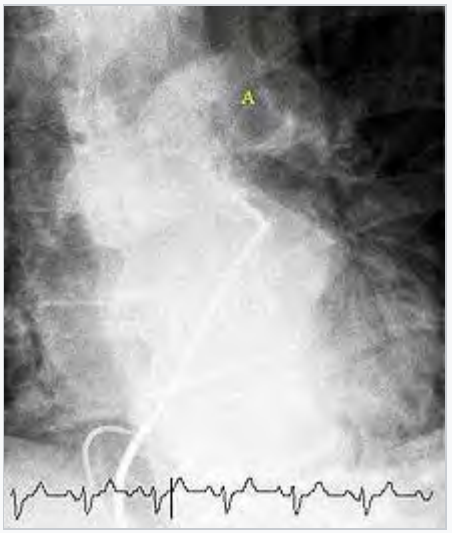
When a PE is being suspected, several blood tests are done in order to exclude important secondary causes of PE. This includes a full blood count, clotting status (PT, aPTT, TT), and some screening tests (erythrocyte sedimentation rate, renal function, liver enzymes, electrolytes). If one of these is abnormal, further investigations might be warranted.[*citation needed*]

Troponin levels are increased in between 16–47% with pulmonary embolism.[41]

## Imaging [edit]

In typical people who are not known to be at high risk of PE, imaging is helpful to confirm or exclude a diagnosis of PE after simpler first-line tests are used.[21][23][42] Medical societies recommend tests such as the D-dimer to first provide supporting evidence for the need for imaging, and imaging would be done if other tests confirmed a moderate or high probability of finding evidence to support a diagnosis of PE.[23][42]

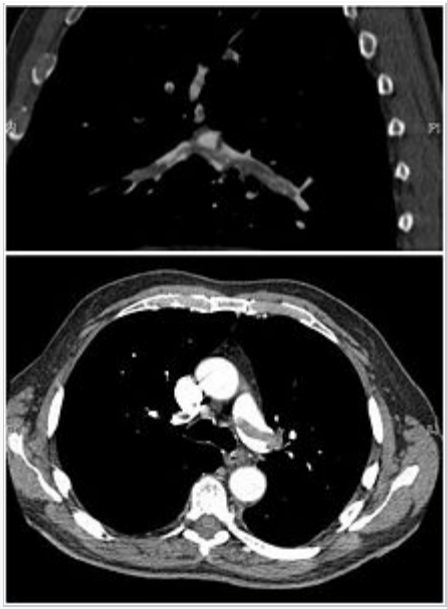
CT pulmonary angiography is the recommended first line diagnostic imaging test in most people.[43] Historically, the gold standard for diagnosis was pulmonary angiography, but this has fallen into disuse with the increased availability of non-invasive techniques.[44] Ultrasound of the legs can confirm the presence of a PE but cannot rule it out.[45]



Selective pulmonary angiogram revealing clot (labeled A) causing a central obstruction in the left main pulmonary artery. ECG tracing shown at bottom.

## Non-invasive imaging [edit]

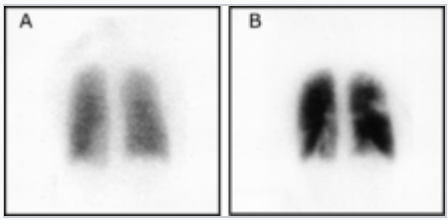
CT pulmonary angiography (CTPA) is a pulmonary angiogram obtained using computed tomography (CT) with radiocontrast rather than right heart catheterization. Its advantages are clinical equivalence, its non-invasive nature, its greater availability to people, and the possibility of identifying other lung disorders from the differential diagnosis in case there is no pulmonary embolism. Assessing the accuracy of CT pulmonary angiography is hindered by the rapid changes in the number of rows of detectors available in multidetector CT (MDCT) machines.[46] According to a cohort study, single-slice spiral CT may help diagnose detection among people with suspected pulmonary embolism.[47] In this study, the sensitivity was 69% and specificity was 84%. In this study which had a prevalence of detection was 32%, the positive predictive value of 67.0% and negative predictive value of 85.2% (click here to adjust these results for people at higher or lower risk of detection).



CT pulmonary angiography showing a "saddle embolus" at the bifurcation of the pulmonary artery and thrombus burden in the lobar branches of both main pulmonary arteries.

However, this study's results may be biased due to possible incorporation bias, since the CT scan was the final diagnostic tool in people with pulmonary embolism. The authors noted that a negative single slice CT scan is insufficient to rule out pulmonary embolism on its own. A separate study with a mixture of 4 slice and 16 slice scanners reported a sensitivity of 83% and a specificity of 96%, which means that it is a good test for ruling out a pulmonary embolism if it is not seen on imaging and that it is very good at confirming a pulmonary embolism is present if it is seen. This study noted that additional testing is necessary when the clinical probability is inconsistent with the imaging results.[48] CTPA is non-inferior to VQ scanning, and identifies more emboli (without necessarily improving the outcome) compared to VQ scanning.[49]

A ventilation/perfusion scan (or V/Q scan or lung scintigraphy) shows that some areas of the lung are being ventilated but not perfused with blood (due to obstruction by a clot).[16] This type of examination is as accurate as multislice CT, but is less used, due to the greater availability of CT technology. It is particularly useful in people who have an allergy to iodinated contrast, impaired renal function, or are pregnant (due to its lower radiation exposure as compared to CT).[50][51] The test can be performed with planar two-dimensional imaging, or single photon emission tomography (SPECT) which enables three-dimensional imaging.[43] Hybrid devices combining SPECT and CT (SPECT/CT) further enable anatomic characterization of any abnormality.




Ventilation-perfusion scintigraphy
(A) After inhalation of 20 mCi of Xenon-133 gas, scintigraphic images were obtained in the posterior projection, showing uniform ventilation to lungs.
(B) After intravenous injection of 4 mCi of Technetium-99m-labeled albumin, scintigraphic images shown here in the posterior projection. This and other views showed decreased activity in multiple regions.

## Low probability diagnostic tests/non-diagnostic tests

[edit]

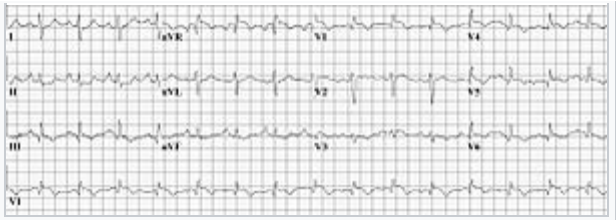
Tests that are frequently done that are not sensitive for PE, but can be diagnostic.

- Chest X-rays are often done on people with shortness of breath to help rule-out other causes, such as congestive heart failure and rib fracture. Chest X-rays in PE are rarely normal,[52] but usually lack signs that suggest the diagnosis of PE (for example, Westermark sign, Hampton's hump).
- Ultrasonography of the legs, also known as leg doppler, in search of deep venous thrombosis (DVT). The presence of DVT, as shown on ultrasonography of the legs, is in itself enough to warrant anticoagulation, without requiring the V/Q or spiral CT scans (because of the strong association between DVT and PE). This may be a valid approach in pregnancy, in which the other modalities would increase the risk of birth defects in the unborn child. However, a negative scan does not rule out PE, and low-radiation dose scanning may be required if the mother is deemed at high risk of having a pulmonary embolism.[*citation needed*]

## Electrocardiogram [edit]

The primary use of the ECG is to rule out other causes of [53]

chest pain. An electrocardiogram (ECG) is routinely done on people with chest pain to quickly diagnose myocardial infarctions (heart attacks), an important differential diagnosis in an individual with chest pain. While certain ECG changes may occur with PE, none are specific enough to confirm or sensitive enough to rule out the diagnosis.[53] An ECG may show signs of right heart strain or acute cor pulmonale in cases of large PEs — the classic signs are a large S wave in lead I, a large Q wave in lead III, and an inverted T wave in lead III (S1Q3T3), which occurs in 12-50% of people with the diagnosis, yet also occurs in 12% without the diagnosis.[54][55]



Electrocardiogram of a person with pulmonary embolism, showing sinus tachycardia of approximately 100 beats per minute, large S wave in Lead I, moderate Q wave in Lead III, inverted T wave in Lead III, and inverted T waves in leads V1 and V3.

This is occasionally present (occurring in up to 20% of people), but may also occur in other acute lung conditions, and, therefore, has limited diagnostic value. The most commonly seen signs in the ECG are sinus tachycardia, right axis deviation, and right bundle branch block.[56] Sinus tachycardia, however, is still only found in 8–69% of people with PE.[57]

ECG findings associated with pulmonary emboli may suggest worse prognosis since the six findings identified with RV strain on ECG (heart rate > 100 beats per minute, S1Q3T3, inverted T waves in leads V1-V4, ST elevation in aVR, complete right bundle branch block, and atrial fibrillation) are associated with increased risk of circulatory shock and death.[58]

### Echocardiography [edit]

In massive and submassive PE, dysfunction of the right side of the heart may be seen on echocardiography, an indication that the pulmonary artery is severely obstructed and the right ventricle, a low-pressure pump, is unable to match the pressure. Some studies (see below) suggest that this finding may be an indication for thrombolysis. Not every person with a (suspected) pulmonary embolism requires an echocardiogram, but elevations in cardiac troponins or brain natriuretic peptide may indicate heart strain and warrant an echocardiogram,[59] and be important in prognosis.[60]

The specific appearance of the right ventricle on echocardiography is referred to as the *McConnell's sign*. This is the finding of akinesia of the mid-free wall but a normal motion of the apex. This phenomenon has a 77% sensitivity and a 94% specificity for the diagnosis of acute pulmonary embolism in the setting of right ventricular dysfunction.[61]

## Prevention [edit]

*Further information: Thrombosis prophylaxis*

Pulmonary embolism may be preventable in those with risk factors. People admitted to hospital may receive preventative medication, including unfractionated heparin, low molecular weight heparin (LMWH), or fondaparinux, and anti-thrombosis stockings to reduce the risk of a DVT in the leg that could dislodge and migrate to the lungs.[62]

Following the completion of warfarin in those with prior PE, long-term aspirin is useful to prevent recurrence.[63]

## Treatment [edit]

Anticoagulant therapy is the mainstay of treatment. Acutely, supportive treatments, such as oxygen or analgesia, may be required. People are often admitted to hospital in the early stages of treatment, and tend to remain under inpatient care until the INR has reached therapeutic levels. Increasingly, however, low-risk [63][64]

cases are managed at home in a fashion already common in the treatment of DVT. Evidence to support one approach versus the other is weak.[65]

## Anticoagulation [edit]

Usually, anticoagulant therapy is the mainstay of treatment. Unfractionated heparin, low molecular weight heparin (LMWH), or fondaparinux is administered initially, while warfarin, acenocoumarol, or phenprocoumon therapy is commenced (this may take several days, usually while the patient is in the hospital). LMWH may reduce bleeding among people with pulmonary embolism as compared to heparin according to a systematic review of randomized controlled trials by the Cochrane Collaboration.[66] The relative risk reduction was 40%. For people at similar risk to those in this study (2.0% had bleeding when not treated with low molecular weight heparin), this leads to an absolute risk reduction of 0.8%. 125 people must be treated for one to benefit.

Warfarin therapy often requires a frequent dose adjustment and monitoring of the international normalized ratio (INR). In PE, INRs between 2.0 and 3.0 are generally considered ideal. If another episode of PE occurs under warfarin treatment, the INR window may be increased to e.g. 2.5–3.5 (unless there are contraindications) or anticoagulation may be changed to a different anticoagulant e.g. LMWH.[*citation needed*]

In patients with an underlying malignancy, therapy with a course of LMWH is favored over warfarin; it is continued for six months, at which point a decision should be reached whether ongoing treatment is required.[67]

Similarly, pregnant women are often maintained on low molecular weight heparin until at least six weeks after delivery to avoid the known teratogenic effects of warfarin, especially in the early stages of pregnancy.[68]

Warfarin therapy is usually continued for 3–6 months, or "lifelong" if there have been previous DVTs or PEs, or none of the usual risk factors is present. An abnormal D-dimer level at the end of treatment might signal the need for continued treatment among patients with a first unprovoked pulmonary embolus.[69] For those with small PEs (known as subsegmental PEs) the effects of anticoagulation is unknown as it has not been properly studied as of 2014.[70][*needs update*]

## Thrombolysis [edit]

Massive PE causing hemodynamic instability (shock and/or low blood pressure, defined as a systolic blood pressure <90 mmHg or a pressure drop of 40 mmHg for >15 min if not caused by new-onset arrhythmia, hypovolemia or sepsis) is an indication for thrombolysis, the enzymatic destruction of the clot with medication. In this situation, it is the best available treatment in those without contraindications and is supported by clinical guidelines.[24][67][71] It is also recommended in those in cardiac arrest with a known PE.[72]

Catheter-directed thrombolysis (CDT) is a new technique found to be relatively safe and effective for massive PEs. This involves accessing the venous system by placing a catheter into a vein in the groin and guiding it through the veins by using fluoroscopic imaging until it is located next to the PE in the lung circulation. Medication that breaks up blood clots is released through the catheter so that its highest concentration is directly next to the pulmonary embolus. CDT is performed by interventional radiologists, and in medical centers that offer CDT, it should be considered first-line treatment.[73]

The use of thrombolysis in non-massive PEs is still debated.[74][75] Some have found that the treatment decreases the risk of death and increases the risk of bleeding including intracranial hemorrhage.[76] Others have found no decrease in the risk of death.[75]

## Inferior vena cava filter [edit]

There are two situations when an inferior vena cava filter is considered advantageous, and those are if anticoagulant therapy is contraindicated (e.g. shortly after a major operation), or a person has a pulmonary

Used inferior vena cava filter.

embolus in spite of being anticoagulated.[67] In these instances, it may be implanted to prevent new or existing DVTs from entering the pulmonary artery and combining with an existing blockage.[67] In spite of the device's theoretical advantage of preventing pulmonary emboli, there is a lack of evidence supporting its effectiveness.[77]

Inferior vena cava filters should be removed as soon as it becomes safe to start using anticoagulation.[67] Although modern filters are meant to be retrievable, complications may prevent some from being removed. The long-term safety profile of permanently leaving a filter inside the body is not known.[77]

### Surgery [edit]

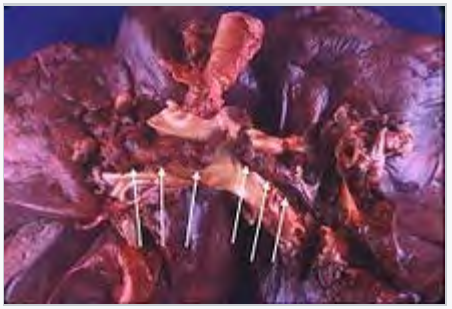
Surgical management of acute pulmonary embolism (pulmonary thrombectomy) is uncommon and has largely been abandoned because of poor long-term outcomes. However, recently, it has gone through a resurgence with the revision of the surgical technique and is thought to benefit certain people.[78] Chronic pulmonary embolism leading to pulmonary hypertension (known as *chronic thromboembolic hypertension*) is treated with a surgical procedure known as a pulmonary thromboendarterectomy.

## Epidemiology [edit]

Pulmonary emboli occur in more than 600,000 people in the United States each year.[14] It results in between 50,000[14] and 200,000 deaths per year in the United States.[15] The risk in those who are hospitalized is around 1%.[79] The rate of fatal pulmonary emboli has declined from 6% to 2% over the last 25 years in the United States.[15]

## Prognosis [edit]

Less than 5 to 10% of symptomatic PEs are fatal within the first hour of symptoms.[24][80]


Large saddle embolus seen in the pulmonary artery (white arrows).

There are several markers used for risk stratification and these are also independent predictors of adverse outcome. These include hypotension, cardiogenic shock, syncope, evidence of right heart dysfunction, and elevated cardiac enzymes.[24] Some ECG changes including S1Q3T3 also correlate with worse short-term prognosis.[19] There have been other patient-related factors such as COPD and chronic heart failure thought to also play a role in prognosis.[24]

Prognosis depends on the amount of lung that is affected and on the co-existence of other medical conditions; chronic embolisation to the lung can lead to pulmonary hypertension. After a massive PE, the embolus must be resolved somehow if the patient is to survive. In thrombotic PE, the blood clot may be broken down by fibrinolysis, or it may be organized and recanalized so that a new channel forms through the clot. Blood flow is restored most rapidly in the first day or two after a PE.[81] Improvement slows thereafter and some deficits may be permanent. There is controversy over whether small subsegmental PEs need treatment at all[82] and some evidence exists that patients with subsegmental PEs may do well without treatment.[48][83]

Once anticoagulation is stopped, the risk of a fatal pulmonary embolism is 0.5% per year.[84]

Mortality from untreated PEs was said to be 26%. This figure comes from a trial published in 1960 by Barrit

and Jordan,[85] which compared anticoagulation against placebo for the management of PE. Barritt and Jordan performed their study in the Bristol Royal Infirmary in 1957. This study is the only placebo controlled trial ever to examine the place of anticoagulants in the treatment of PE, the results of which were so convincing that the trial has never been repeated as to do so would be considered unethical. That said, the reported mortality rate of 26% in the placebo group is probably an overstatement, given that the technology of the day may have detected only severe PEs.

## Predicting mortality [edit]

The PESI and sPESI scoring tools can estimate mortality of patients. The Geneva prediction rules and Wells criteria are used to calculate a pre-test probability of patients to predict who has a pulmonary embolism. These scores are tools to be used with clinical judgment in deciding diagnostic testing and types of therapy.[86] The PESI algorithm comprises 11 routinely available clinical variables.[87] It puts the subjects into one of five classes (I-V), with 30-day mortality ranging from 1.1% to 24.5%. Those in classes I and II are low-risk and those in classes III-V are high-risk.[87]

# References [edit]


1. ^ a b c "What Is Pulmonary Embolism?". *NHLBI*. July 1, 2011. Retrieved 12 March 2016.
2. ^ a b "What Are the Signs and Symptoms of Pulmonary Embolism?". *NHLBI*. July 1, 2011. Retrieved 12 March 2016.
3. ^ Tintinalli, Judith E. (2010). *Emergency Medicine: A Comprehensive Study Guide (Emergency Medicine (Tintinalli))* (7 ed.). New York: McGraw-Hill Companies. p. 432. ISBN 0-07-148480-9.
4. ^ a b c d Goldhaber SZ (2005). "Pulmonary thromboembolism". In Kasper DL, Braunwald E, Fauci AS, et al. *Harrison's Principles of Internal Medicine* (16th ed.). New York, NY: McGraw-Hill. pp. 1561–65. ISBN 0-07-139140-1.
5. ^ a b "Who Is at Risk for Pulmonary Embolism?". *NHLBI*. July 1, 2011. Retrieved 12 March 2016.
6. ^ "What Causes Pulmonary Embolism?". *NHLBI*. July 1, 2011. Retrieved 12 March 2016.
7. ^ Pantaleo, G; Luigi, N; Federica, T; Paola, S; Margherita, N; Tahir, M (2014). "Amniotic fluid embolism: review.". *Current pharmaceutical biotechnology*. **14** (14): 1163–7. doi:10.2174/1389201015666140430161404. PMID 24804726.
8. ^ "How Is Pulmonary Embolism Diagnosed?". *NHLBI*. July 1, 2011. Retrieved 12 March 2016.
9. ^ "Other Names for Pulmonary Embolism". July 1, 2011. Retrieved 12 March 2016.
10. ^ "How Can Pulmonary Embolism Be Prevented?". *NHLBI*. July 1, 2011. Retrieved 12 March 2016.
11. ^ a b "How Is Pulmonary Embolism Treated?". *NHLBI*. July 1, 2011. Retrieved 12 March 2016.
12. ^ "Living With Pulmonary Embolism". July 1, 2011. Retrieved 12 March 2016.
13. ^ Raskob, GE; Angchaisuksiri, P; Blanco, AN; Buller, H; Gallus, A; Hunt, BJ; Hylek, EM; Kakkar, A; Konstantinides, SV; McCumber, M; Ozaki, Y; Wendelboe, A; Weitz, JI; ISTH Steering Committee for World Thrombosis, Day (November 2014). "Thrombosis: a major contributor to global disease burden.". *Arteriosclerosis, thrombosis, and vascular biology*. **34** (11): 2363–71. doi:10.1161/atvbaha.114.304488. PMID 25304324.
14. ^ a b c d Rahimtoola A, Bergin JD (February 2005). "Acute pulmonary embolism: an update on diagnosis and management". *Current problems in cardiology*. **30** (2): 61–114. doi:10.1016/j.cpcardiol.2004.06.001. PMID 15650680.
15. ^ a b c Kumar V, Abbas AK, Fausto N, Mitchell RN (2010). *Basic Pathology*. New Delhi: Elsevier. p. 98. ISBN 978-81-312-1036-9.
16. ^ a b Lewis, S; Dirksen, S; Heitkemper, M; Bucher, L (2014). *Medical-surgical nursing: Assessment and management of clinical problems* (9 ed.). St. Louis, MO: Elsevier Mosby. p. 552. ISBN 978-0-323-08678-3.
17. ^ Stein PD, Sostman HD, Hull RD, Goodman LR, Leeper KV, Gottschalk A, Tapson VF, Woodard PK (March 2009). "Diagnosis of Pulmonary Embolism in the Coronary Care Unit". *Am. J. Cardiol.* **103** (6): 881–6. doi:10.1016/j.amjcard.2008.11.040. PMC 2717714. PMID 19268750.
18. ^ Pregerson DB, Quick Essentials: Emergency Medicine, 4th edition. EMresource.org
19. ^ a b Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite P, Vedantham S, White RJ, Zierler BK (Apr 26, 2011). American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation,American Heart Association Council on Peripheral Vascular Disease,American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology.

"Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association.". *Circulation*. **123** (16): 1788–830. doi:10.1161/CIR.0b013e318214914f. PMID 21422387.

20. ^ Ferri, F (2012). *Ferri's Clinical Advisor*. St. Louis: Mosby's.
21. ^ *a b c* American College of Radiology. "Five Things Physicians and Patients Should Question" (PDF). *Choosing Wisely: an initiative of the ABIM Foundation*. American College of Radiology. Retrieved August 17, 2012.
22. ^ *a b* Raja, AS; Greenberg, JO; Qaseem, A; Denberg, TD; Fitterman, N; Schuur, JD (29 September 2015). "Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians.". *Annals of Internal Medicine*. **163**: 701–11. doi:10.7326/M14-1772. PMID 26414967.
23. ^ *a b c* Stein PD, Woodard PK, Weg JG, Wakefield TW, Tapson VF, Sostman HD, Sos TA, Quinn DA, Leeper KV, Hull RD, Hales CA, Gottschalk A, Goodman LR, Fowler SE, Buckley JD (2007). "Diagnostic Pathways in Acute Pulmonary Embolism: Recommendations of the PIOPED II Investigators". *Radiology*. **242** (1): 15–21. doi:10.1148/radiol.2421060971. PMID 17185658.
24. ^ *a b c d e* Authors/Task Force, Members; Konstantinides, SV; Torbicki, A; Agnelli, G; Danchin, N; Fitzmaurice, D; Galiè, N; Gibbs, JS; Huisman, MV; Humbert, M; Kucher, N; Lang, I; Lankeit, M; Lekakis, J; Maack, C; Mayer, E; Meneveau, N; Perrier, A; Pruszczyk, P; Rasmussen, LH; Schindler, TH; Svitil, P; Vonk Noordegraaf, A; Zamorano, JL; Zompatori, M; Authors/Task Force, Members (Aug 29, 2014). "2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC) Endorsed by the European Respiratory Society (ERS).". *European Heart Journal*. **35**: 3033–3073. doi:10.1093/eurheartj/ehu283. PMID 25173341.
25. ^ *a b* Wells PS, Hirsh J, Anderson DR, Lensing AW, Foster G, Kearon C, Weitz J, D'Ovidio R, Cogo A, Prandoni P (1995). "Accuracy of clinical assessment of deep-vein thrombosis". *Lancet*. **345** (8961): 1326–30. doi:10.1016/S0140-6736(95)92535-X. PMID 7752753.
26. ^ *a b* Wells PS, Ginsberg JS, Anderson DR, Kearon C, Gent M, Turpie AG, Bormanis J, Weitz J, Chamberlain M, Bowie D, Barnes D, Hirsh J (1998). "Use of a clinical model for safe management of patients with suspected pulmonary embolism". *Ann Intern Med*. **129** (12): 997–1005. doi:10.7326/0003-4819-129-12-199812150-00002. PMID 9867786.
27. ^ *a b c d e* Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, Turpie AG, Bormanis J, Weitz J, Chamberlain M, Bowie D, Barnes D, Hirsh J (2000). "Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer". *Thromb Haemost*. **83** (3): 416–20. PMID 10744147.
28. ^ *a b* Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, Forgie M, Kovacs G, Ward J, Kovacs MJ (2001). "Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer". *Ann Intern Med*. **135** (2): 98–107. doi:10.7326/0003-4819-135-2-200107170-00010. PMID 11453709.
29. ^ Sanson BJ, Lijmer JG, Mac Gillavry MR, Turkstra F, Prins MH, Büller HR (2000). "Comparison of a clinical probability estimate and two clinical models in patients with suspected pulmonary embolism. ANTELOPE-Study Group". *Thromb. Haemost*. **83** (2): 199–203. PMID 10739372.
30. ^ *a b* van Belle A, Büller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, Kramer MH, Kruip MJ, Kwakkel-van Erp JM, Leebeek FW, Nijkeuter M, Prins MH, Sohne M, Tick LW (2006). "Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography". *JAMA*. **295** (2): 172–9. doi:10.1001/jama.295.2.172. PMID 16403929.
31. ^ Roy PM, Meyer G, Vielle B, Le Gall C, Verschuren F, Carpentier F, Leveau P, Furber A (2006). "Appropriateness of diagnostic management and outcomes of suspected pulmonary embolism". *Ann. Intern. Med.* **144** (3): 157–64. doi:10.7326/0003-4819-144-3-200602070-00003. PMID 16461959.
32. ^ Neff MJ (2003). "ACEP releases clinical policy on evaluation and management of pulmonary embolism". *American Family Physician*. **68** (4): 759–60. PMID 12952389.
33. ^ Yap KS, Kalff V, Turlakow A, Kelly MJ (2007). "A prospective reassessment of the utility of the Wells score in identifying pulmonary embolism". *Med. J. Aust*. **187** (6): 333–6. PMID 17874979.
34. ^ *a b c d* Stein PD, Woodard PK, Weg JG, Wakefield TW, Tapson VF, Sostman HD, Sos TA, Quinn DA, Leeper KV, Hull RD, Hales CA, Gottschalk A, Goodman LR, Fowler SE, Buckley JD (2007). "Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II Investigators". *Radiology*. **242** (1): 15–21. doi:10.1148/radiol.2421060971. PMID 17185658.
35. ^ Kline JA, Mitchell AM, Kabrhel C, Richman PB, Courtney DM (2004). "Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism". *Journal of Thrombosis and Haemostasis*. **2** (8): 1247–55. doi:10.1111/j.1538-7836.2004.00790.x. PMID 15304025.

36. ^ Kline JA, Courtney DM, Kabrhel C, Moore CL, Smithline HA, Plewa MC, Richman PB, O'Neil BJ, Nordenholz K (2008). "Prospective multicenter evaluation of the pulmonary embolism rule-out criteria". *Journal of Thrombosis and Haemostasis*. **6** (5): 772–780. doi:10.1111/j.1538-7836.2008.02944.x. PMID 18318689.
37. ^ Carrier M, Righini M, Djurabi RK, Huisman MV, Perrier A, Wells PS, Rodger M, Wuillemin WA, Le Gal G (May 2009). "VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism. A systematic review of management outcome studies". *Thromb. Haemost*. **101** (5): 886–92. doi:10.1160/TH-08-10-0689. PMID 19404542.
38. ^ Schrecengost JE, LeGallo RD, Boyd JC, Moons KG, Gonias SL, Rose CE, Bruns DE (September 2003). "Comparison of diagnostic accuracies in outpatients and hospitalized patients of D-dimer testing for the evaluation of suspected pulmonary embolism". *Clin. Chem*. **49** (9): 1483–90. doi:10.1373/49.9.1483. PMID 12928229.
39. ^ *a b* Schouten HJ, Geersing GJ, Koek HL, Zuithoff NP, Janssen KJ, Douma RA, van Delden JJ, Moons KG, Reitsma JB (May 3, 2013). "Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis.". *BMJ (Clinical research ed.)*. **346**: f2492. doi:10.1136/bmj.f2492. PMC 3643284. PMID 23645857.
40. ^ van Es, N; van der Hulle, T; van Es, J; den Exter, PL; Douma, RA; Goekoop, RJ; Mos, IC; Galipienzo, J; Kamphuisen, PW; Huisman, MV; Klok, FA; Büller, HR; Bossuyt, PM (16 August 2016). "Wells Rule and d-Dimer Testing to Rule Out Pulmonary Embolism: A Systematic Review and Individual-Patient Data Meta-analysis.". *Annals of Internal Medicine*. **165** (4): 253–61. doi:10.7326/m16-0031. PMID 27182696.
41. ^ Söhne, Maaike; Ten Wolde, Marije; Büller, Harry R. (1 November 2004). "Biomarkers in pulmonary embolism". *Current Opinion in Cardiology*. **19** (6): 558–562. doi:10.1097/01.hco.0000138991.82347.0e. ISSN 0268-4705. PMID 15502498.
42. ^ *a b* Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, Bengel F, Brady AJ, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M, Bassand JP (2008). "Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)". *European Heart Journal*. **29** (18): 2276–2315. doi:10.1093/eurheartj/ehn310. PMID 18757870.
43. ^ *a b* Stein PD, Freeman LM, Sostman HD, Goodman LR, Woodard PK, Naidich DP, Gottschalk A, Bailey DL, Matta F, Yaekoub AY, Hales CA, Hull RD, Leeper KV, Tapson VF, Weg JG (2009). "SPECT in acute pulmonary embolism". *J Nucl Med* (Review). **50** (12): 1999–2007. doi:10.2967/jnumed.109.063958. PMID 19949025.
44. ^ Konstantinides, S; Torbicki, A; Agnelli, G; Danchin, N; Fitzmaurice, D; Galiè, N; Gibbs, JSR; Huisman, M; Humbert, M; Kucher, N (14 November 2014). "2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism". *European Heart Journal*. **35** (43): 3033–3069. doi:10.1093/eurheartj/ehu283. PMID 25173341. "Pulmonary angiography has for decades remained the 'gold standard' for the diagnosis or exclusion of PE, but is rarely performed now as less-invasive CT angiography offers similar diagnostic accuracy."
45. ^ Da Costa Rodrigues, J; Alzuphar, S; Combescure, C; Le Gal, G; Perrier, A (5 July 2016). "Diagnostic characteristics of lower limb venous compression ultrasonography in suspected pulmonary embolism: a meta-analysis.". *Journal of thrombosis and haemostasis : JTH*. **14**: 1765–72. doi:10.1111/jth.13407. PMID 27377039.
46. ^ Schaefer-Prokop C, Prokop M (2005). "MDCT for the diagnosis of acute pulmonary embolism". *European radiology*. **15** (Suppl 4): D37–41. doi:10.1007/s10406-005-0144-3. PMID 16479644.
47. ^ Van Strijen MJ, De Monye W, Kieft GJ, Pattynama PM, Prins MH, Huisman MV (2005). "Accuracy of single-detector spiral CT in the diagnosis of pulmonary embolism: a prospective multicenter cohort study of consecutive patients with abnormal perfusion scintigraphy". *Journal of thrombosis and haemostasis : JTH*. **3** (1): 17–25. doi:10.1111/j.1538-7836.2004.01064.x. PMID 15634261.
48. ^ *a b* Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, Hull RD, Leeper KV, Popovich J, Quinn DA, Sos TA, Sostman HD, Tapson VF, Wakefield TW, Weg JG, Woodard PK (2006). "Multidetector computed tomography for acute pulmonary embolism". *N. Engl. J. Med*. **354** (22): 2317–27. doi:10.1056/NEJMoa052367. PMID 16738268.
49. ^ Anderson DR, Kahn SR, Rodger MA, Kovacs MJ, Morris T, Hirsch A, Lang E, Stiell I, Kovacs G, Dreyer J, Dennie C, Cartier Y, Barnes D, Burton E, Pleasance S, Skedgel C, O'Rouke K, Wells PS (2007). "Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism". *JAMA*. **298** (23): 2743–53. doi:10.1001/jama.298.23.2743. PMID 18165667.
50. ^ Scarsbrook AF, Gleeson FV (2007). "Investigating suspected pulmonary embolism in pregnancy". *BMJ*. **334** (7590): 418–9. doi:10.1136/bmj.39071.617257.80. PMC 1804186. PMID 17322258.
51. ^ Leung AN, Bull TM, Jaeschke R, Lockwood CJ, Boiselle PM, Hurwitz LM, James AH, McCullough LB, Menda Y, Paidas MJ, Royal HD, Tapson VF, Winer-Muram HT, Chervenak FA, Cody DD, McNitt-Gray MF, Stave CD, Tuttle BD (2011-11-15). "An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy". *American Journal of Respiratory and Critical Care Medicine*. **184** (10): 1200–8. doi:10.1164/rccm.201108-1575ST. PMID 22086989.

52. ^ Worsley DF, Alavi A, Aronchick JM, Chen JT, Greenspan RH, Ravin CE (1993). "Chest radiographic findings in patients with acute pulmonary embolism: observations from the PIOPED Study". *Radiology*. **189** (1): 133–6. doi:10.1148/radiology.189.1.8372182. PMID 8372182.
53. ^ [a] [b] Brown G, Hogg K (October 2005). "Best evidence topic report. Diagnostic utility of electrocardiogram for diagnosing pulmonary embolism.". *Emergency medicine journal : EMJ*. **22** (10): 729–30. doi:10.1136/emj.2005.029041. PMC 1726554. PMID 16189038.
54. ^ Mattu, edited by Amal; Goyal, Deepi (2007). *Emergency medicine avoiding the pitfalls and improving the outcomes*. Malden, Mass.: Blackwell Pub./BMJ Books. p. 9. ISBN 9780470755174.
55. ^ McGinn S, White PD (1935). "Acute cor pulmonale resulting from pulmonary embolism". *J Am Med Assoc*. **104** (17): 1473–80. doi:10.1001/jama.1935.02760170011004.
56. ^ Rodger M, Makropoulos D, Turek M, Quevillon J, Raymond F, Rasuli P, Wells PS (October 2000). "Diagnostic value of the electrocardiogram in suspected pulmonary embolism". *Am. J. Cardiol*. **86** (7): 807–9, A10. doi:10.1016/S0002-9149(00)01090-0. PMID 11018210.
57. ^ Amal Mattu; Deepi Goyal; Barrett, Jeffrey W.; Joshua Broder; DeAngelis, Michael; Peter Deblieux; Gus M. Garmel; Richard Harrigan; David Karras; Anita L'Italien; David Manthey (2007). *Emergency medicine: avoiding the pitfalls and improving the outcomes*. Malden, Mass: Blackwell Pub./BMJ Books. p. 10. ISBN 1-4051-4166-2.
58. ^ Shopp, Jacob D.; Stewart, Lauren K.; Emmett, Thomas W.; Kline, Jeffrey A. (2015-10-01). "Findings From 12-lead Electrocardiography That Predict Circulatory Shock From Pulmonary Embolism: Systematic Review and Meta-analysis". *Academic Emergency Medicine*. **22** (10): 1127–1137. doi:10.1111/acem.12769. ISSN 1553-2712. PMID 26394330.
59. ^ Kucher N, Goldhaber SZ (2003). "Cardiac biomarkers for risk stratification of patients with acute pulmonary embolism". *Circulation*. **108** (18): 2191–4. doi:10.1161/01.CIR.0000100687.99687.CE. PMID 14597581.
60. ^ Lankeit M, Jiménez D, Kostrubiec M, Dellas C, Hasenfuss G, Pruszczyk P, Konstantinides S (December 2011). "Predictive value of the high-sensitivity troponin T assay and the simplified Pulmonary Embolism Severity Index in hemodynamically stable patients with acute pulmonary embolism: a prospective validation study". *Circulation*. **124** (24): 2716–24. doi:10.1161/CIRCULATIONAHA.111.051177. PMID 22082681.
61. ^ McConnell MV, Solomon SD, Rayan ME, Come PC, Goldhaber SZ, Lee RT (1996). "Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism". *Am. J. Cardiol*. **78** (4): 469–73. doi:10.1016/S0002-9149(96)00339-6. PMID 8752195.
62. ^ National Institute for Health and Clinical Excellence. *Clinical guideline 92: Venous thromboembolism: reducing the risk: Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital*. London, January 2010.
63. ^ [a] [b] Kearon, Clive; Akl, Elie A.; Ornelas, Joseph; Blaivas, Allen; Jimenez, David; Bounameaux, Henri; Huisman, Menno; King, Christopher S.; Morris, Timothy; Sood, Namita; Stevens, Scott M.; Vintch, Janine R.E.; Wells, Philip; Woller, Scott C.; Moores, COL Lisa (January 2016). "Antithrombotic Therapy for VTE Disease". *Chest*. **149**: 315–352. doi:10.1016/j.chest.2015.11.026.
64. ^ Vinson DR, Zehtabchi S, Yealy DM (November 2012). "Can selected patients with newly diagnosed pulmonary embolism be safely treated without hospitalization? A systematic review.". *Annals of Emergency Medicine*. **60** (5): 651–662.e4. doi:10.1016/j.annemergmed.2012.05.041. PMID 22944455.
65. ^ Yoo, HH; Queluz, TH; El Dib, R (20 November 2014). "Outpatient versus inpatient treatment for acute pulmonary embolism.". *The Cochrane database of systematic reviews*. **11**: CD010019. doi:10.1002/14651858.CD010019.pub2. PMID 25411774.
66. ^ Erkens PM, Prins MH (2010). Prins, Martin H, ed. "Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism". *Cochrane Database Syst Rev* (9): CD001100. doi:10.1002/14651858.CD001100.pub3. PMID 20824828. ACPJC Review
67. ^ [a] [b] [c] [d] [e] National Institute for Health and Clinical Excellence. *Clinical guideline 144: Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing*. London, 2012.
68. ^ Benson MD (October 2012). "Pulmonary embolism in pregnancy. Consensus and controversies.". *Minerva ginecologica*. **64** (5): 387–98. PMID 23018478.
69. ^ Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, Pengo V, Ghirarduzzi A, Pattacini C, Testa S, Lensing AW, Tripodi A (2006). "D-dimer testing to determine the duration of anticoagulation therapy". *N. Engl. J. Med*. **355** (17): 1780–9. doi:10.1056/NEJMoa054444. PMID 17065639.
70. ^ Yoo, HH; Queluz, TH; El Dib, R (Apr 28, 2014). "Anticoagulant treatment for subsegmental pulmonary embolism.". *The Cochrane database of systematic reviews*. **4**: CD010222. doi:10.1002/14651858.CD010222.pub2. PMID 24771493.
71. ^ Hirsh J, Guyatt G, Albers GW, Harrington R, Schünemann HJ (June 2008). "Executive summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)". *Chest*. **133** (6 Suppl): 71S–109S.

doi:10.1378/chest.08-0693 . PMID 18574259 .
72. ^ Lavonas, EJ; Drennan, IR; Gabrielli, A; Heffner, AC; Hoyte, CO; Orkin, AM; Sawyer, KN; Donnino, MW (3 November 2015). "Part 10: Special Circumstances of Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.". *Circulation*. **132** (18 Suppl 2): S501–18. doi:10.1161/cir.0000000000000264. PMID 26472998.
73. ^ "References in Catheter-directed Therapy for the Treatment of Massive Pulmonary Embolism: Systematic Review and Meta-analysis of Modern Techniques - Journal of Vascular and Interventional Radiology". *www.jvir.org*. Retrieved 2015-11-13.
74. ^ Hao, Q; Dong, BR; Yue, J; Wu, T; Liu, GJ (30 September 2015). "Thrombolytic therapy for pulmonary embolism.". *The Cochrane database of systematic reviews* (9): CD004437. doi:10.1002/14651858.CD004437.pub4. PMID 26419832.
75. ^ [a] [b] Nakamura, S; Takano, H; Kubota, Y; Asai, K; Shimizu, W (Jul 2014). "Impact of the efficacy of thrombolytic therapy on the mortality of patients with acute submassive pulmonary embolism: a meta-analysis.". *Journal of thrombosis and haemostasis : JTH*. **12** (7): 1086–95. doi:10.1111/jth.12608. PMID 24829097.
76. ^ Chatterjee, Saurav; Chakraborty, Anasua; Weinberg, Ido; Kadakia, Mitul; Wilensky, Robert L.; Sardar, Partha; Kumbhani, Dharam J.; Mukherjee, Debabrata; Jaff, Michael R.; Giri, Jay (18 June 2014). "Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage". *JAMA*. **311** (23): 2414. doi:10.1001/jama.2014.5990.
77. ^ [a] [b] Young, Tim; Tang, Hangwi; Hughes, Rodney (2010-02-17). *Vena caval filters for the prevention of pulmonary embolism*. John Wiley & Sons, Ltd. doi:10.1002/14651858.cd006212.pub4. ISSN 1465-1858.
78. ^ Augustinos P, Ouriel K (2004). "Invasive approaches to treatment of venous thromboembolism". *Circulation*. **110** (9 Suppl 1): I27–34. doi:10.1161/01.CIR.0000140900.64198.f4. PMID 15339878.
79. ^ Wood, Kenneth E. (2002). "An approach to Venous Thomboembolism/Pulmonay Embolism in the Critically Ill". In Murray, Michael J.; Coursin, Douglas B.; Pearl, Ronald G.; et al. *Critical Care Medicine: Perioperative Management: Published Under the Auspices of the American Society of Critical Care Anesthesiologists (ASCCA)*. Lippincott Williams & Wilkins. p. 536. ISBN 978-0-7817-2968-0.
80. ^ Lavonas, EJ; Drennan, IR; Gabrielli, A; Heffner, AC; Hoyte, CO; Orkin, AM; Sawyer, KN; Donnino, MW (3 November 2015). "Part 10: Special Circumstances of Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.". *Circulation*. **132** (18 Suppl 2): S501–18. doi:10.1161/cir.0000000000000264. PMID 26472998.
81. ^ Walker RH, Goodwin J, Jackson JA (17 October 1970). "Resolution of Pulmonary Embolism". *British Medical Journal*. **4** (5728): 135–9. doi:10.1136/bmj.4.5728.135. PMC 1819885. PMID 5475816.
82. ^ Le Gal G, Righini M, Parent F, van Strijen M, Couturaud F (2006). "Diagnosis and management of subsegmental pulmonary embolism". *J Thromb Haemost*. **4** (4): 724–31. doi:10.1111/j.1538-7836.2006.01819.x. PMID 16634736.
83. ^ Perrier A, Bounameaux H (2006). "Accuracy or outcome in suspected pulmonary embolism". *N Engl J Med*. **354** (22): 2383–5. doi:10.1056/NEJMe068076. PMID 16738276.
84. ^ White RH (October 2008). "Risk of fatal pulmonary embolism was 0.49 per 100 person-years after discontinuing anticoagulant therapy for venous thromboembolism". *Evid Based Med*. **13** (5): 154. doi:10.1136/ebm.13.5.154. PMID 18836122.
85. ^ Barritt DW, Jordan SC (1960). "Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial". *Lancet*. **1** (7138): 1309–12. doi:10.1016/S0140-6736(60)92299-6. PMID 13797091.
86. ^ Jiménez D, Yusen RD, Otero R, Uresandi F, Nauffal D, Laserna E, Conget F, Oribe M, Cabezudo MA, Díaz G (2007). "Prognostic models for selecting patients with acute pulmonary embolism for initial outpatient therapy". *Chest*. **132** (1): 24–30. doi:10.1378/chest.06-2921. PMID 17625081.
87. ^ [a] [b] Zhou, Xiao-Yu; Ben, Su-Qin; Chen, Hong-Lin; Ni, Song-Shi (2012). "The prognostic value of pulmonary embolism severity index in acute pulmonary embolism: a meta-analysis". *Respiratory Research*. **13** (1): 111. doi:10.1186/1465-9921-13-111. ISSN 1465-9921.

## External links [edit]

- Pulmonary embolism at DMOZ
- Wells criteria for pulmonary embolism online calculator
- Clinical prediction website - Wells criteria for pulmonary embolism
- Media related to Pulmonary embolism at Wikimedia Commons

v · t · e **Cardiovascular disease (vessels) (I70–I99, 440–456)**

| | | | |
|---|---|---|---|
| **Arteries, arterioles and capillaries** | **Inflammation** | | Arteritis (Aortitis · · Buerger's disease · |
| | **Peripheral artery disease** | **Arteriosclerosis** | Atherosclerosis (Foam cell · Fatty streak · Atheroma · Intermittent claudication · Critical limb ischemia · · Monckeberg's arteriosclerosis · Arteriolosclerosis (Hyaline · Hyperplastic · Cholesterol · LDL · Oxycholesterol · Trans fat · · |
| | | **Stenosis** | Carotid artery stenosis · Renal artery stenosis · |
| | | **Other** | Aortoiliac occlusive disease · Degos disease · Erythromelalgia · Fibromuscular dysplasia · Raynaud's phenomenon · |
| | **Aneurysm / dissection / pseudoaneurysm** | | *torso*: Aortic aneurysm (Abdominal aortic aneurysm · Thoracic aortic aneurysm · Aneurysm of sinus of Valsalva · · Aortic dissection · Coronary artery aneurysm · *head / neck* (Intracranial aneurysm · Intracranial berry aneurysm · Carotid artery dissection · Vertebral artery dissection · Familial aortic dissection · · |
| | **Vascular malformation** | | Arteriovenous fistula · Arteriovenous malformation · Telangiectasia (Hereditary hemorrhagic telangiectasia · · |
| | **Vascular nevus** | | Cherry hemangioma · Halo nevus · Spider angioma · |
| **Veins** | **Inflammation** | | Phlebitis · |
| | **Venous thrombosis / Thrombophlebitis** | | *primarily lower limb* (Deep vein thrombosis · · *abdomen* (Hepatic veno-occlusive disease · Budd–Chiari syndrome · May–Thurner syndrome · Portal vein thrombosis · Renal vein thrombosis · · *upper limb / torso* (Mondor's disease · Paget–Schroetter disease · · *head* (Cerebral venous sinus thrombosis · · Post-thrombotic syndrome · |
| | **Varicose veins** | | Gastric varices · Portacaval anastomosis (Caput medusae · Esophageal varices · Hemorrhoid · · Varicocele · |
| | **Other** | | Chronic venous insufficiency · Chronic cerebrospinal venous insufficiency · Superior vena cava syndrome · Inferior vena cava syndrome · Venous ulcer · |
| **Arteries or veins** | | | Angiopathy (Macroangiopathy · Microangiopathy · · Embolism (**Pulmonary embolism** · Cholesterol embolism · Paradoxical embolism · · Thrombosis · Vasculitis · |
| **Blood pressure** | **Hypertension** | | Hypertensive heart disease · Hypertensive emergency · Hypertensive nephropathy · Essential hypertension · Secondary hypertension (Renovascular hypertension · · Benign hypertension · Pulmonary hypertension · Systolic hypertension · White coat hypertension · |

| | | |
|---|---|---|
| | **Hypotension** | Orthostatic hypotension · |

| v · t · e · | **Diseases of the respiratory system (J, 460–519)** | | |
|---|---|---|---|
| **Upper RT (including URTIs, common cold)** | **Head** | *sinuses*: Sinusitis ·<br>*nose*: Rhinitis (Vasomotor rhinitis · Atrophic rhinitis · Hay fever · · Nasal polyp · Rhinorrhea · *nasal septum* (Nasal septum deviation · Nasal septum perforation · Nasal septal hematoma · ·<br>*tonsil*: Tonsillitis · Adenoid hypertrophy · Peritonsillar abscess · | |
| | **Neck** | *pharynx*: Pharyngitis (Strep throat · · Laryngopharyngeal reflux (LPR) · Retropharyngeal abscess ·<br>*larynx*: Croup · Laryngomalacia · Laryngeal cyst · Laryngitis · Laryngopharyngeal reflux (LPR) · Laryngospasm ·<br>*vocal folds*: Laryngopharyngeal reflux (LPR) · Vocal fold nodule · Vocal cord paresis · Vocal cord dysfunction ·<br>*epiglottis*: Epiglottitis ·<br>*trachea*: Tracheitis · Tracheal stenosis · | |
| **Lower RT/lung disease (including LRTIs)** | **Bronchial/ obstructive** | *acute*: Acute bronchitis ·<br>*chronic*: COPD (Chronic bronchitis · Acute exacerbations of chronic bronchitis · Acute exacerbation of COPD · Emphysema) · Asthma (Status asthmaticus · Aspirin-induced · Exercise-induced · · Bronchiectasis ·<br>*unspecified*: Bronchitis · Bronchiolitis (Bronchiolitis obliterans · · Diffuse panbronchiolitis · | |
| | **Interstitial/ restrictive (fibrosis)** | **External agents/ occupational lung disease** | Pneumoconiosis (Asbestosis · Baritosis · Bauxite fibrosis · Berylliosis · Caplan's syndrome · Chalicosis · Coalworker's pneumoconiosis · Siderosis · Silicosis · Talcosis · Byssinosis · · Hypersensitivity pneumonitis (Bagassosis · Bird fancier's lung · Farmer's lung · Lycoperdonosis · · |
| | | **Other** | ARDS · Pulmonary edema · Löffler's syndrome/Eosinophilic pneumonia · Respiratory hypersensitivity (Allergic bronchopulmonary aspergillosis · · Hamman-Rich syndrome · Idiopathic pulmonary fibrosis · Sarcoidosis · |
| | **Pneumonia/** | **By pathogen** | Viral · Bacterial (Pneumococcal · Klebsiella) · · Atypical bacterial (Mycoplasma · Legionnaires' disease · Chlamydiae · · Fungal (Pneumocystis · · Parasitic · *noninfectious* (Chemical/Mendelson's syndrome |

| | | | | |
|---|---|---|---|---|
| | **Obstructive or restrictive** | **pneumonitis** | | · Aspiration/Lipid · · |
| | | | **By vector/route** | Community-acquired · Healthcare-associated · Hospital-acquired · |
| | | | **By distribution** | Broncho- · Lobar · |
| | | | **IIP** | UIP · DIP · BOOP-COP · NSIP · RB · |
| | | **Other** | | Atelectasis · *circulatory* (Pulmonary hypertension · **Pulmonary embolism** · · Lung abscess · |
| **Pleural cavity/ mediastinum** | **Pleural disease** | | | Pleuritis/pleurisy · Pneumothorax/Hemopneumothorax · **Pleural effusion:** Hemothorax · Hydrothorax · Chylothorax · Empyema/pyothorax · Malignant · Fibrothorax · |
| | **Mediastinal disease** | | | Mediastinitis · Mediastinal emphysema · |
| **Other/general** | | | | Respiratory failure · Influenza · SARS · Idiopathic pulmonary haemosiderosis · Pulmonary alveolar proteinosis · |

Categories: Medical emergencies | Pulmonary heart disease and diseases of pulmonary circulation

# Rheumatic fever

From Wikipedia, the free encyclopedia

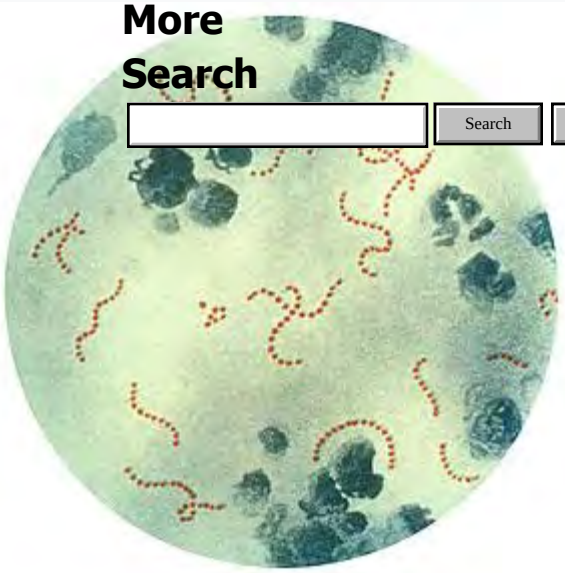
**Rheumatic fever** (**RF**), also known as **acute rheumatic fever** (**ARF**), is an inflammatory disease that can involve the heart, joints, skin, and brain.[1] The disease typically develops two to four weeks after a streptococcal throat infection.[2] Signs and symptoms include fever, multiple painful joints, involuntary muscle movements, and occasionally a characteristic non-itchy rash known as erythema marginatum. The heart is involved in about half of cases. Damage to the heart valves, known as rheumatic heart disease (RHD), usually occurs after repeated attacks but can sometimes occur after one. The damaged valves may result in heart failure, atrial fibrillation and infection of the valves.[1]

Rheumatic fever may occur following an infection of the throat by the bacteria *Streptococcus pyogenes*.[1] If the infection is untreated rheumatic fever can occur in up to three percent of people.[3] The underlying mechanism is believed to involve the production of antibodies against a person's own tissues. Some people due to their genetics are more likely to get the disease when exposed to the bacteria than others. Other risk factors include malnutrition and poverty.[1] Diagnosis of RF is often based on the presence of signs and symptoms in combination with evidence of a recent streptococcal infection.[4]

Treating people who have strep throat with antibiotics, such as penicillin, decreases the risk of developing rheumatic fever.[5] In order to avoid antibiotic misuse this often involves testing people with sore throats for the infection, which may not be available in the developing world. Other preventive measures include improved sanitation. In those with rheumatic fever and rheumatic heart disease, prolonged periods of antibiotics are sometimes recommended. Gradual return to normal activities may occur following an attack. Once RHD develops, treatment is more difficult. Occasionally valve-replacement surgery or valve repair is required. Otherwise complications are treated as per normal.[1]

Rheumatic fever occurs in about 325,000 children each year and about 18 million people currently have rheumatic heart disease. Those who develop RF are most often between the ages of 5 and 14,[1] with 20% of first-time attacks occurring in adults.[6] The disease is most common in the developing world and among indigenous peoples in the developed world.[1] In 2013 it resulted in 275,000 deaths down from 374,000 deaths in 1990.[7] Most deaths occur in the developing world where as many as 12.5% of people affected may die

**Rheumatic fever**



*Streptococcus pyogenes* bacteria (Pappenheim's stain) the trigger for rheumatic fever.

| Classification and external resources | |
|---|---|
| **Specialty** | Cardiology |
| **ICD-10** | I00-I02 |
| **ICD-9-CM** | 390–392 |
| **DiseasesDB** | 11487 |
| **MedlinePlus** | 003940 |
| **eMedicine** | med/3435 med/2922 emerg/509 ped/2006 |
| **Patient UK** | Rheumatic fever |
| **MeSH** | D012213 |

[edit on Wikidata]

each year.[1] Descriptions of the condition are believed to date back to at least the 5th century BCE in the writings of Hippocrates.[8] The disease is so named because its symptoms are similar to those of some rheumatic disorders.[9]



Contents

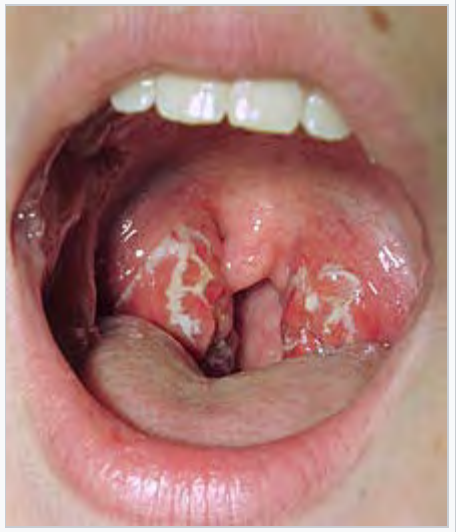



Play media

Video explanation

## Signs and symptoms [edit]

The disease typically develops two to four weeks after a throat infection.[2] Symptoms include: fever, painful joints with those joints affected changing with time, involuntary muscle movements, and occasionally a characteristic non-itchy rash known as erythema marginatum. The heart is involved in about half of cases. Damage to the heart valves usually occurs only after multiple attacks but may occasionally occur after a single case of RF. The damaged valves may result in heart failure and also increase the risk of atrial fibrillation and infection of the valves.[1]



A culture positive case of streptococcal pharyngitis with typical tonsillar exudate in a 16-year-old.

## Pathophysiology [edit]

Rheumatic fever is a systemic disease affecting the connective tissue around arterioles, and can occur after an untreated strep throat infection, specifically due to group A streptococcus (GAS), *Streptococcus pyogenes*. It is believed to be caused by antibody cross-reactivity. This cross-reactivity is a type II hypersensitivity reaction and is termed molecular mimicry. Usually, self reactive B cells remain anergic in the periphery without T cell co-stimulation. During a streptococcal infection, mature antigen-presenting cells such as B cells present the bacterial antigen to CD4+T cells which differentiate into helper $T_2$ cells. Helper $T_2$ cells subsequently activate the B cells to become plasma cells and induce the production of antibodies against the cell wall of Streptococcus. However the antibodies may also react against the myocardium and joints,[10] producing the symptoms of rheumatic fever.

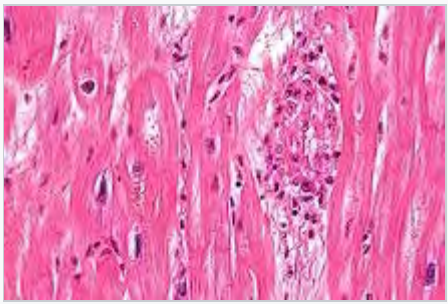
*S. pyogenes* has a cell wall composed of branched polymers which sometimes contain M protein that are highly antigenic. The antibodies which the immune system generates against the M protein may cross-react with heart muscle cell protein myosin,[11] heart muscle glycogen and smooth muscle cells of arteries, inducing cytokine release and tissue destruction. However, the only proven cross-reaction is with perivascular connective tissue.[*citation needed*] This inflammation occurs through direct attachment of

complement and Fc receptor-mediated recruitment of neutrophils and macrophages. Characteristic Aschoff bodies, composed of swollen eosinophilic collagen surrounded by lymphocytes and macrophages can be seen on light microscopy. The larger macrophages may become Anitschkow cells or Aschoff giant cells. Rheumatic valvular lesions may also involve a cell-mediated immunity reaction as these lesions predominantly contain T-helper cells and macrophages.[12]

In rheumatic fever, these lesions can be found in any layer of the heart causing different types of carditis. The inflammation may cause a serofibrinous pericardial exudate described as "bread-and-butter" pericarditis, which usually resolves without sequelae. Involvement of the endocardium typically results in fibrinoid necrosis and verrucae formation along the lines of closure of the left-sided heart valves. Warty projections arise from the deposition, while subendocardial lesions may induce irregular thickenings called MacCallum plaques.

## Rheumatic heart disease [edit]

Pathophysiology of rheumatic heart disease



Micrograph showing an Aschoff body (right of image), as seen in rheumatic heart disease. H&E stain.

Chronic rheumatic heart disease (RHD) is characterized by repeated inflammation with fibrinous repair. The cardinal anatomic changes of the valve include leaflet thickening, commissural fusion, and shortening and thickening of the tendinous cords.[12] It is caused by an autoimmune reaction to Group A β-hemolytic streptococci (GAS) that results in valvular damage.[13] Fibrosis and scarring of valve leaflets, commissures and cusps leads to abnormalities that can result in valve stenosis or regurgitation.[14] The inflammation caused by rheumatic fever, usually during childhood, is referred to as rheumatic valvulitis. About half of patients with rheumatic fever develop inflammation involving valvular endothelium.[15] The majority of morbidity and mortality associated with rheumatic fever is caused by its destructive effects on cardiac valve tissue.[14] The pathogenesis of RHD is complex and not fully understood, but it is known to involve molecular mimicry and genetic predisposition that lead to autoimmune reactions.

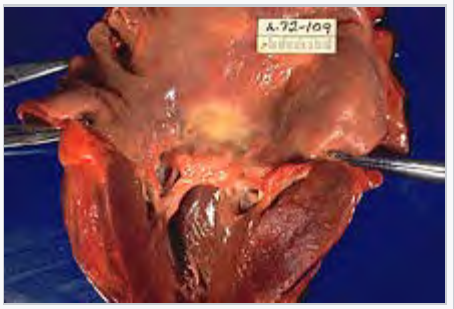
Molecular mimicry occurs when epitopes are shared between host antigens and *Streptococcus* antigens.[16] This causes an autoimmune reaction against native tissues in the heart that are incorrectly recognized as "foreign" due to the cross-reactivity of antibodies generated as a result of epitope sharing. The valvular endothelium is a prominent site of lymphocyte-induced damage. CD4+ T cells are the major effectors of heart tissue autoimmune reactions in RHD.[17] Normally, T cell activation is triggered by the presentation of bacterial antigens. In RHD, molecular mimicry results in incorrect T cell activation, and these T lymphocytes can go on to activate B cells, which will begin to produce self-antigen-specific antibodies. This leads to an immune response attack mounted against tissues in the heart that have been misidentified as pathogens. Rheumatic valves display increased expression of VCAM-1, a protein that mediates the adhesion of lymphocytes.[18] Self-antigen-specific antibodies generated via molecular mimicry between human proteins and streptococcal antigens up-regulate VCAM-1 after binding to the valvular endothelium. This leads to the inflammation and valve scarring observed in rheumatic valvulitis, mainly due to CD4+ T cell infiltration.[18]

While the mechanisms of genetic predisposition remain unclear, a few genetic factors have been found to increase susceptibility to autoimmune reactions in RHD. The dominant contributors are a component of MHC class II molecules, found on lymphocytes and antigen-presenting cells, specifically the DR and DQ alleles on human chromosome 6.[19] Certain allele combinations appear to increase RHD autoimmune susceptibility. Human leukocyte antigen (HLA) class II allele DR7 (HLA-DR7) is most often associated with RHD, and its combination with certain DQ alleles is seemingly associated with the development of valvular lesions.[19] The mechanism by which MHC class II molecules increase a host's susceptibility to autoimmune reactions in RHD is unknown, but it is likely related to the role HLA molecules play in presenting antigens to

T cell receptors, thus triggering an immune response. Also found on human chromosome 6 is the cytokine TNF-α which is also associated with RHD.[19] High expression levels of TNF-α may exacerbate valvular tissue inflammation, contributing to RHD pathogenesis. Mannose-binding lectin (MBL) is an inflammatory protein involved in pathogen recognition. Different variants of MBL2 gene regions are associated in RHD. RHD-induced mitral valve stenosis has been associated with MBL2 alleles encoding for high production of MBL.[20] Aortic valve regurgitation in RHD patients has been associated with different MBL2 alleles that encode for low production of MBL.[21] Other genes are also being investigated to better understand the complexity of autoimmune reactions that occur in RHD.

## Diagnosis [edit]

Modified Jones criteria were first published in 1944 by T. Duckett Jones, MD.[22] They have been periodically revised by the American Heart Association in collaboration with other groups.[23] According to revised Jones criteria, the diagnosis of rheumatic fever can be made when two of the major criteria, or one major criterion plus two minor criteria, are present along with evidence of streptococcal infection: elevated or rising antistreptolysin O titre or DNAase.[6] Exceptions are chorea and indolent carditis, each of which by itself can indicate rheumatic fever.[24][25][26] An April 2013 review article in the *Indian Journal of Medical Research* stated that echocardiographic and Doppler (E & D) studies, despite some reservations about their utility, have identified a massive burden of rheumatic heart disease, which suggests the inadequacy of the 1992 Jones' criteria. E & D studies have identified subclinical carditis in patients with rheumatic fever, as well as in follow-ups of rheumatic heart disease patients who initially presented as having isolated cases of Sydenham's chorea.[27] Signs of a preceding streptococcal infection include: recent scarlet fever, raised antistreptolysin O or other streptococcal antibody titre, or positive throat culture.[28]



Rheumatic heart disease at autopsy with characteristic findings (thickened mitral valve, thickened chordae tendineae, hypertrophied left ventricular myocardium).

### Major criteria [edit]

- Polyarthritis[*citation needed*]: A temporary migrating inflammation of the large joints, usually starting in the legs and migrating upwards.
- Carditis: Inflammation of the heart muscle (myocarditis) which can manifest as congestive heart failure with shortness of breath, pericarditis with a rub, or a new heart murmur.
- Subcutaneous nodules: Painless, firm collections of collagen fibers over bones or tendons. They commonly appear on the back of the wrist, the outside elbow, and the front of the knees.
- Erythema marginatum: A long-lasting reddish rash that begins on the trunk or arms as macules, which spread outward and clear in the middle to form rings, which continue to spread and coalesce with other rings, ultimately taking on a snake-like appearance. This rash typically spares the face and is made worse with heat.
- Sydenham's chorea (St. Vitus' dance): A characteristic series of involuntary rapid movements of the face and arms. This can occur very late in the disease for at least three months from onset of infection.

### Minor criteria [edit]

- Fever of 38.2–38.9 °C (100.8–102.0 °F)
- Arthralgia: Joint pain without swelling (Cannot be included if polyarthritis is present as a major symptom)
- Raised erythrocyte sedimentation rate or C reactive protein
- Leukocytosis
- ECG showing features of heart block, such as a prolonged PR interval[28][29] (Cannot be included if carditis is present as a major symptom)

- Previous episode of rheumatic fever or inactive heart disease

## Prevention [edit]

Prevention of recurrence is achieved by eradicating the acute infection and prophylaxis with antibiotics. The American Heart Association suggests that dental health be maintained, and that people with a history of bacterial endocarditis, a heart transplant, artificial heart valves, or "some types of congenital heart defects" may wish to consider long-term antibiotic prophylaxis.[30]

## Treatment [edit]

This section **needs additional citations for verification**. Please help improve this article by adding citations to reliable sources. Unsourced material may be challenged and removed. *(February 2012) (Learn how and when to remove this template message)*

The management of rheumatic fever is geared toward the reduction of inflammation with anti-inflammatory medications such as aspirin or corticosteroids. Individuals with positive cultures for strep throat should also be treated with antibiotics. Aspirin is the drug of choice and should be given at high doses of 100 mg/kg/day. One should watch for side effects like gastritis and salicylate poisoning. In children and teenagers, the use of aspirin and aspirin-containing products can be associated with Reye's syndrome, a serious and potentially deadly condition. The risks, benefits, and alternative treatments must always be considered when administering aspirin and aspirin-containing products in children and teenagers. Ibuprofen for pain and discomfort and corticosteroids for moderate to severe inflammatory reactions manifested by rheumatic fever should be considered in children and teenagers. Steroids are reserved for cases where there is evidence of an involvement of heart. The use of steroids may prevent further scarring of tissue and may prevent the development of sequelae such as mitral stenosis. Monthly injections of long-acting penicillin must be given for a period of five years in patients having one attack of rheumatic fever. If there is evidence of carditis, the length of therapy may be up to 40 years. Another important cornerstone in treating rheumatic fever includes the continual use of low-dose antibiotics (such as penicillin, sulfadiazine, or erythromycin) to prevent recurrence.

### Vaccine [edit]

No vaccines are currently available to protect against *S. pyogenes* infection, although research is underway to develop one.[31] Difficulties in developing a vaccine include the wide variety of strains of *S. pyogenes* present in the environment and the large amount of time and people that will be needed for appropriate trials for safety and efficacy of the vaccine.[32]

### Infection [edit]

People with positive cultures for *Streptococcus pyogenes* should be treated with penicillin as long as allergy is not present. This treatment will not alter the course of the disease.[*clarification needed*] Some suggest the use of benzathine benzylpenicillin.

### Inflammation [edit]

While corticosteroids are often used, evidence to support this is poor.[1] Salicylates are useful for pain.

### Heart failure [edit]

Some patients develop significant carditis which manifests as congestive heart failure. This requires the usual treatment for heart failure: ACE inhibitors, diuretics, beta blockers, and digoxin. Unlike normal heart failure, rheumatic heart failure responds well to corticosteroids.

# Epidemiology [edit]

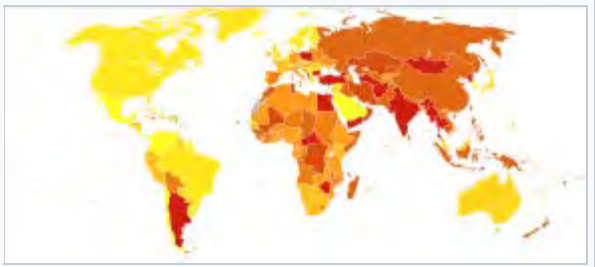
Rheumatic fever is common worldwide and responsible for many cases of damaged heart valves. As of 2010 globally it resulted in 345,000 deaths, down from 463,000 in 1990.[34]

In Western countries, rheumatic fever has become fairly rare since the 1960s, probably due to the widespread use of antibiotics to treat streptococcus infections. While it has been far less common in the United States since the beginning of the 20th century, there have been a few outbreaks since the 1980s. Although the disease seldom occurs, it is serious and has a case-fatality rate of 2–5%.[35]

Rheumatic fever primarily affects children between ages 5 and 17 years and occurs approximately 20 days after strep throat. In up to a third of cases, the underlying strep infection may not have caused any symptoms.

The rate of development of rheumatic fever in individuals with untreated strep infection is estimated to be 3%. The incidence of recurrence with a subsequent untreated infection is substantially greater (about 50%).[36] The rate of development is far lower in individuals who have received antibiotic treatment. Persons who have suffered a case of rheumatic fever have a tendency to develop flare-ups with repeated strep infections.

The recurrence of rheumatic fever is relatively common in the absence of maintenance of low dose antibiotics, especially during the first three to five years after the first episode. Recurrent bouts of rheumatic fever can lead to valvular heart disease. Heart complications may be long-term and severe, particularly if valves are involved. In countries in Southeast-Asia, sub-saharan Africa, and Oceania, the percentage of people with rheumatic heart disease detected by listening to the heart was 2.9 per 1000 children and by echocardiography it was 12.9 per 1000 children.[37][38][39][40]



Deaths from rheumatic heart disease per million persons in 2012

| | | |
|---|---|---|
| 0–7 | 21–25 | 39–45 |
| 8–14 | 26–32 | 46–52 |
| 15–20 | 33–38 | 53–63 |
| | | 64–250 |

Disability-adjusted life year for rheumatic heart disease per 100,000 inhabitants in 2004.[33]

| | |
|---|---|
| no data | 100–120 |
| less than 20 | 120–140 |
| 20–40 | 140–160 |
| 40–60 | 160–180 |
| 60–80 | 180–200 |
| 80–100 | 200–330 |
| | more than 330 |

# References [edit]


1. ^ *a b c d e f g h i j* Marijon, E; Mirabel, M; Celermajer, DS; Jouven, X (10 March 2012). "Rheumatic heart disease.". *Lancet*. **379** (9819): 953–64. doi:10.1016/S0140-6736(11)61171-9. PMID 22405798.
2. ^ *a b* Lee, KY; Rhim, JW; Kang, JH (March 2012). "Kawasaki disease: laboratory findings and an immunopathogenesis on the premise of a "protein homeostasis system".". *Yonsei Medical Journal*. **53**

Polymorphism but Not of Mannose-Binding Serine Protease 2 with Chronic Severe Aortic Regurgitation of Rheumatic Etiology". *Clinical and Vaccine Immunology : CVI*. **15** (6): 932–936. doi:10.1128/CVI.00324-07. PMC 2446618. PMID 18400978.

22. ^ Jones, T Duckett (1944). "The diagnosis of rheumatic fever". *JAMA*. **126** (8): 481–4. doi:10.1001/jama.1944.02850430015005.

(2): 262–75. doi:10.3349/ymj.2012.53.2.262. PMID 22318812.
3. ^ Ashby, Carol Turkington, Bonnie Lee (2007). *The encyclopedia of infectious diseases* (3rd ed.). New York: Facts On File. p. 292. ISBN 9780816075072.
4. ^ "Rheumatic Fever 1997 Case Definition". *cdc.gov*. 3 February 2015. Retrieved 19 February 2015.
5. ^ Spinks, A; Glasziou, PP; Del Mar, CB (5 November 2013). "Antibiotics for sore throat.". *The Cochrane database of systematic reviews*. **11**: CD000023. doi:10.1002/14651858.CD000023.pub4. PMID 24190439.
6. ^ [a] [b] Kumar, Vinay; Abbas, Abul K; Fausto, Nelson; Mitchell, Richard N (2007). *Robbins Basic Pathology* (8th ed.). Saunders Elsevier. pp. 403–6. ISBN 978-1-4160-2973-1.
7. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385** (9963): 117–171. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
8. ^ Quinn, RW (1991). "Did scarlet fever and rheumatic fever exist in Hippocrates' time?". *Reviews of infectious diseases*. **13** (6): 1243–4. doi:10.1093/clinids/13.6.1243. PMID 1775859.
9. ^ "rheumatic fever" at *Dorland's Medical Dictionary*
10. ^ Abbas, Abul K.; Lichtman, Andrew H.; Baker, David L.; et al. (2004). *Basic immunology: functions and disorders of the immune system* (2 ed.). Philadelphia, Pennsylvania: Elsevier Saunders. ISBN 978-1-4160-2403-3.
11. ^ Faé KC, da Silva DD, Oshiro SE, et al. (May 2006). "Mimicry in recognition of cardiac myosin peptides by heart-intralesional T cell clones from rheumatic heart disease". *J. Immunol*. **176** (9): 5662–70. doi:10.4049/jimmunol.176.9.5662. PMID 16622036.
12. ^ [a] [b] Cotran, Ramzi S.; Kumar, Vinay; Fausto, Nelson; Nelso Fausto; Robbins, Stanley L.; Abbas, Abul K. (2005). *Robbins and Cotran pathologic basis of disease*. St. Louis, Mo: Elsevier Saunders. ISBN 0-7216-0187-1.
13. ^ Kaplan, MH; Bolande, R; Rakita, L; Blair, J (1964). "Presence of Bound Immunoglobulins and Complement in the Myocardium in Acute Rheumatic Fever. Association with Cardiac Failure". *The New England Journal of Medicine*. **271** (13): 637–45. doi:10.1056/NEJM196409242711301. PMID 14170842.
14. ^ [a] [b] Brice, Edmund A. W; Commerford, Patrick J. (2005). "Rheumatic Fever and Valvular Heart Disease". In Rosendorff, Clive. *Essential Cardiology: Principles and Practice*. Totowa, New Jersey: Humana Press. pp. 545–563. doi:10.1007/978-1-
23. ^ Ferrieri, P; Jones Criteria Working, Group (2002). "Proceedings of the Jones Criteria workshop". *Circulation*. Jones Criteria Working Group. **106** (19): 2521–3. doi:10.1161/01.CIR.0000037745.65929.FA. PMID 12417554.
24. ^ Parrillo, Steven J. "Rheumatic Fever". *eMedicine*. DO, FACOEP, FACEP. Retrieved 14 July 2007.
25. ^ "Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update". *JAMA*. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. **268** (15): 2069–73. 1992. doi:10.1001/jama.268.15.2069. PMID 1404745.
26. ^ Saxena, Anita (2000). "Diagnosis of rheumatic fever: Current status of Jones criteria and role of echocardiography". *Indian Journal of Pediatrics*. **67** (4): 283–6. doi:10.1007/BF02758174. PMID 11129913.
27. ^ Kumar, RK; Tandon, R (2013). "Rheumatic fever & rheumatic heart disease: The last 50 years". *The Indian Journal of Medical Research*. **137** (4): 643–658. PMC 3724245. PMID 23703332.
28. ^ [a] [b] Ed Boon, Davidson's General Practice of Medicine, 20th edition. P. 617.
29. ^ Aly, Ashraf (2008). "Rheumatic Fever". *Core Concepts of Pediatrics*. University of Texas. Retrieved 6 August 2011.
30. ^ "What About My Child and Rheumatic Fever?" (PDF). American Heart Association. Retrieved 23 February 2014.
31. ^ http://www.sciencemediacentre.co.nz/2014/09/18/collaboration-aims-for-rheumatic-fever-vaccine/
32. ^ "Initiative for Vaccine Research (IVR) – Group A Streptococcus". World Health Organization. Retrieved 15 June 2012.
33. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved 11 November 2009.
34. ^ Lozano, R; Naghavi, M; Foreman, K; Lim, S; Shibuya, K; Aboyans, V; Abraham, J; Adair, T; Aggarwal, R (15 December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604. `|first10=` missing `|last10=` in Authors list (help); `|first11=` missing `|last11=` in Authors list (help); `|first12=` missing `|last12=` in Authors list (help); `|first13=` missing `|last13=` in Authors list (help); `|first14=` missing `|last14=` in Authors list (help); `|first15=` missing `|last15=` in Authors list (help); `|first16=` missing `|last16=` in Authors list (help); `|first17=` missing `|last17=` in Authors list (help); `|first18=` missing `|last18=` in Authors list (help); `|first19=` missing `|last19=` in Authors list (help); `|first20=`

59259-918-9_30. ISBN 978-1-59259-918-9.
15. ^ Caldas, AM; Terreri, MT; Moises, VA; Silva, CM; Len, CA; Carvalho, AC; Hilário, MO (2008). "What is the true frequency of carditis in acute rheumatic fever? A prospective clinical and Doppler blind study of 56 children with up to 60 months of follow-up evaluation". *Pediatric cardiology*. **29** (6): 1048–53. doi:10.1007/s00246-008-9242-z. PMID 18825449.
16. ^ Guilherme, L; Kalil, J; Cunningham, M (2006). "Molecular mimicry in the autoimmune pathogenesis of rheumatic heart disease". *Autoimmunity*. **39** (1): 31–9. doi:10.1080/08916930500484674. PMID 16455580.
17. ^ Kemeny, E; Grieve, T; Marcus, R; Sareli, P; Zabriskie, JB (1989). "Identification of mononuclear cells and T cell subsets in rheumatic valvulitis". *Clinical immunology and immunopathology*. **52** (2): 225–37. doi:10.1016/0090-1229(89)90174-8. PMID 2786783.
18. ^ a b Roberts, S; Kosanke, S; Terrence Dunn, S; Jankelow, D; Duran, CM; Cunningham, MW (2001). "Pathogenic mechanisms in rheumatic carditis: Focus on valvular endothelium". *The Journal of Infectious Diseases*. **183** (3): 507–11. doi:10.1086/318076. PMID 11133385.
19. ^ a b c Stanevicha, V; Eglite, J; Sochnevs, A; Gardovska, D; Zavadska, D; Shantere, R (2003). "HLA class II associations with rheumatic heart disease among clinically homogeneous patients in children in Latvia". *Arthritis Research & Therapy*. **5** (6): R340–R346. doi:10.1186/ar1000. PMC 333411. PMID 14680508.
20. ^ Schafranski, MD; Pereira Ferrari, L; Scherner, D; Torres, R; Jensenius, JC; De Messias-Reason, IJ (2008). "High-producing MBL2 genotypes increase the risk of acute and chronic carditis in patients with history of rheumatic fever". *Molecular immunology*. **45** (14): 3827–31. doi:10.1016/j.molimm.2008.05.013. PMID 18602696.
21. ^ Ramasawmy, R; Spina, GS; Fae, KC; Pereira, AC; Nisihara, R; Messias Reason, IJ; Grinberg, M; Tarasoutchi, F; Kalil, J; Guilherme, L. (2008). "Association of Mannose-Binding Lectin Gene missing |last20= in Authors list (help); |first21= missing |last21= in Authors list (help); |first22= missing |last22= in Authors list (help); |first23= missing |last23= in Authors list (help); |first24= missing |last24= in Authors list (help); |first25= missing |last25= in Authors list (help); |first26= missing |last26= in Authors list (help); |first27= missing |last27= in Authors list (help); |first28= missing |last28= in Authors list (help); |first29= missing |last29= in Authors list (help); |first30= missing |last30= in Authors list (help)
35. ^ "Medline Plus Medical Encyclopedia". NLM/NIH |contribution= ignored (help).
36. ^ Porth, Carol (2007). *Essentials of pathophysiology: concepts of altered health states*. Hagerstown, MD: Lippincott Williams & Wilkins. ISBN 0-7817-7087-4.
37. ^ Marijon, Eloi; Ou, Phalla; Celermajer, David S.; Ferreira, Beatriz; Mocumbi, Ana Olga; Jani, Dinesh; Paquet, Christophe; Jacob, Sophie; Sidi, Daniel (2007-08-02). "Prevalence of rheumatic heart disease detected by echocardiographic screening". *The New England Journal of Medicine*. **357** (5): 470–476. doi:10.1056/NEJMoa065085. ISSN 1533-4406. PMID 17671255.
38. ^ Rothenbühler, Martina; O'Sullivan, Crochan J.; Stortecky, Stefan; Stefanini, Giulio G.; Spitzer, Ernest; Estill, Janne; Shrestha, Nikesh R.; Keiser, Olivia; Jüni, Peter (2014-12-01). "Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents". *The Lancet. Global Health*. **2** (12): e717–726. doi:10.1016/S2214-109X(14)70310-9. ISSN 2214-109X. PMID 25433627.
39. ^ Shrestha NR; Karki P; Mahto R; et al. (2016-03-02). "Prevalence of subclinical rheumatic heart disease in eastern nepal: A school-based cross-sectional study". *JAMA Cardiology*. doi:10.1001/jamacardio.2015.0292. ISSN 2380-6583.
40. ^ Beaton, Andrea; Okello, Emmy; Lwabi, Peter; Mondo, Charles; McCarter, Robert; Sable, Craig (2012-06-26). "Echocardiography screening for rheumatic heart disease in Ugandan schoolchildren". *Circulation*. **125** (25): 3127–3132. doi:10.1161/CIRCULATIONAHA.112.092312. ISSN 1524-4539. PMID 22626741.

## External links [edit]

- Rheumatic fever information from Seattle Children's Hospital Heart Center
- Jones major criteria, Mnemonic
- Rheumatic Heart Disease Network

| v · t · e · **Firmicutes (low-G+C) Infectious diseases · Bacterial diseases: G+ (primarily A00–A79, 001–041, 080–109 · ·** | | | | |
|---|---|---|---|---|
| | | | | *S. pneumoniae* |

| | | | | | |
|---|---|---|---|---|---|
| **Bacilli** | **Lactobacillales (Cat-)** | **Streptococcus** | **α** | **optochin susceptible:** | (Pneumococcal infection · · |
| | | | | **optochin resistant:** | Viridans streptococci: *S. mitis* · *S. mutans* · *S. oralis* · *S. sanguinis* · *S. sobrinus* · milleri group · |
| | | | **β** | **A:** | bacitracin susceptible: *S. pyogenes* (Group A streptococcal infection · Streptococcal pharyngitis · Scarlet fever · Erysipelas · **Rheumatic fever** · · |
| | | | | **B:** | bacitracin resistant, CAMP test+: *S. agalactiae* (Group B streptococcal infection · · |
| | | | | **ungrouped:** | *Streptococcus iniae* (Cutaneous Streptococcus iniae infection · · |
| | | | **γ** | | D · BEA+: *Streptococcus bovis* · |
| | | **Enterococcus** | | | BEA+: *Enterococcus faecalis* (Urinary tract infection · · *Enterococcus faecium* · |
| | **Bacillales (Cat+)** | **Staphylococcus** | **Cg+:** | | *S. aureus* (Staphylococcal scalded skin syndrome · · Toxic shock syndrome · MRSA · |
| | | | **Cg-:** | | *novobiocin susceptible* (*S. epidermidis* · · *novobiocin resistant* (*S. saprophyticus* · · |
| | | **Bacillus** | | | *Bacillus anthracis* (Anthrax · · *Bacillus cereus* (Food poisoning · · |
| | | **Listeria** | | | *Listeria monocytogenes* (Listeriosis · · |
| **Clostridia** | **Clostridium (spore-forming)** | | | *motile:* | *Clostridium difficile* (Pseudomembranous colitis · · *Clostridium botulinum* (Botulism · · *Clostridium tetani* (Tetanus · · |
| | | | | *nonmotile:* | *Clostridium perfringens* (Gas gangrene · Clostridial necrotizing enteritis · · |
| | **Peptostreptococcus (non-spore forming)** | | | | *Peptostreptococcus magnus* · |
| **Mollicutes** | **Mycoplasmataceae** | | | | *Ureaplasma urealyticum* (Ureaplasma infection · · *Mycoplasma genitalium* · *Mycoplasma pneumoniae* (Mycoplasma pneumonia · · |
| | **Anaeroplasmatales** | | | | *Erysipelothrix rhusiopathiae* (Erysipeloid · · |

| v · t · e · | **Cardiovascular disease (heart) (I00–I52, 390–429)** | |
|---|---|---|
| **Ischaemic** | **Coronary disease** | Coronary artery disease (CAD) · Coronary artery aneurysm · Spontaneous coronary artery dissection (SCAD) · Coronary thrombosis · Coronary vasospasm · Myocardial bridge · |
| | **Active ischemia** | Angina pectoris (Prinzmetal's angina · Stable angina · · Acute coronary syndrome (Myocardial infarction · Unstable angina · · |

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| | **Sequelae** | | *hours* (Hibernating myocardium · Myocardial stunning · · *days* (Myocardial rupture · · *weeks* (Aneurysm of heart / Ventricular aneurysm · Dressler syndrome · · |
| **Layers** | **Pericardium** | | Pericarditis (Acute · Chronic / Constrictive · · Pericardial effusion (Cardiac tamponade · Hemopericardium · · |
| | **Myocardium** | | Myocarditis (Chagas disease · · Cardiomyopathy: Dilated (Alcoholic), Hypertrophic, *and* Restrictive (Loeffler endocarditis · Cardiac amyloidosis · Endocardial fibroelastosis · · Arrhythmogenic right ventricular dysplasia · |
| | **Endocardium / valves** | **Endocarditis** | *infective endocarditis* (Subacute bacterial endocarditis · · *non-infective endocarditis* (Libman–Sacks endocarditis · Nonbacterial thrombotic endocarditis · · |
| | | **Valves** | *mitral* (regurgitation · prolapse · stenosis · · *aortic* (stenosis · insufficiency · · *tricuspid* (stenosis · insufficiency · · *pulmonary* (stenosis · insufficiency · · |
| **Conduction / arrhythmia** | **Bradycardia** | | Sinus bradycardia · Sick sinus syndrome · Heart block: Sinoatrial · AV (1° · 2° · 3° · · Intraventricular · Bundle branch block (Right · Left · Left anterior fascicle · Left posterior fascicle · Bifascicular · Trifascicular · · Adams–Stokes syndrome · |
| | **Tachycardia (paroxysmal and sinus)** | **Supraventricular** | Atrial (Multifocal · · Junctional (AV nodal reentrant · Junctional ectopic · · |
| | | **Ventricular** | Accelerated idioventricular rhythm · Catecholaminergic polymorphic · Torsades de pointes · |
| | **Premature contraction** | | Atrial · Junctional · Ventricular · |
| | **Pre-excitation syndrome** | | Lown–Ganong–Levine · Wolff–Parkinson–White · |
| | **Flutter / fibrillation** | | Atrial flutter · Ventricular flutter · Atrial fibrillation (Familial · · Ventricular fibrillation · |
| | **Pacemaker** | | Ectopic pacemaker / Ectopic beat · Multifocal atrial tachycardia · Pacemaker syndrome · Parasystole · Wandering pacemaker · |
| | **Long QT syndrome** | | Andersen–Tawil · Jervell and Lange-Nielsen · Romano–Ward · |
| | **Cardiac arrest** | | Sudden cardiac death · Asystole · Pulseless electrical activity · Sinoatrial arrest · |
| | **Other / ungrouped** | | *hexaxial reference system* (Right axis deviation · Left axis deviation · · *QT* (Short QT syndrome · · *T* (T wave alternans · · *ST* (Osborn wave · ST elevation · ST depression · · Strain pattern · |
| **Cardiomegaly** | | | Ventricular hypertrophy (Left · Right / Cor pulmonale · · Atrial enlargement (Left · Right · · |
| **Other** | | | Cardiac fibrosis · Heart failure (Diastolic heart failure · Cardiac asthma · · **Rheumatic fever** · |

| v · t · e · | **Hypersensitivity and autoimmune diseases (279.5–6)** | |
|---|---|---|
| **Type I / allergy / atopy (IgE)** | **Foreign** | Atopic eczema · Allergic urticaria · Allergic rhinitis (Hay fever) · Allergic asthma · Anaphylaxis · Food allergy (common allergies include: Milk · Egg · Peanut · Tree nut · Seafood · Soy · Wheat · · |

| | | | |
|---|---|---|---|
| | | | Penicillin allergy · |
| | **Autoimmune** | | Eosinophilic esophagitis · |
| **Type II / ADCC (IgM · IgG · ·** | **Foreign** | | Hemolytic disease of the newborn · |
| | **Autoimmune** | **Cytotoxic** | Autoimmune hemolytic anemia · Immune thrombocytopenic purpura · Bullous pemphigoid · Pemphigus vulgaris · **Rheumatic fever** · Goodpasture's syndrome · Guillain–Barré syndrome · |
| | | **"Type V" / receptor** | Graves' disease · Myasthenia gravis · Pernicious anemia · |
| **Type III (Immune complex)** | **Foreign** | | Henoch–Schönlein purpura · Hypersensitivity vasculitis · Reactive arthritis · Farmer's lung · Post-streptococcal glomerulonephritis · Serum sickness · Arthus reaction · |
| | **Autoimmune** | | Systemic lupus erythematosus · Subacute bacterial endocarditis · Rheumatoid arthritis · |
| **Type IV / cell-mediated (T cells)** | **Foreign** | | Allergic contact dermatitis · Mantoux test · |
| | **Autoimmune** | | Diabetes mellitus type 1 · Hashimoto's thyroiditis · Multiple sclerosis · Coeliac disease · Giant-cell arteritis · Postorgasmic illness syndrome · Reactive arthritis · |
| | **GVHD** | | Transfusion-associated graft versus host disease · |
| **Unknown / multiple** | **Foreign** | | Hypersensitivity pneumonitis (Allergic bronchopulmonary aspergillosis · · Transplant rejection · Latex allergy (I+IV) · |
| | **Autoimmune** | | Sjögren's syndrome · Autoimmune hepatitis · Autoimmune polyendocrine syndrome (APS1 · APS2 · · Autoimmune adrenalitis · Systemic autoimmune disease · |

| v · t · e · | **Arthritis in children** | |
|---|---|---|
| **Inflammatory** | **Idiopathic** | Juvenile idiopathic arthritis · |
| | **Inflammatory disease** | Inflammatory bowel disease · Sarcoidosis · Cystic fibrosis · Autoimmune hepatitis · |
| | **Hematological malignancy** | Acute lymphoblastic leukemia · Lymphoma · |
| | **Malignancy** | Neuroblastoma · |
| | **Reactive** | post-streptococcal · **Rheumatic fever** · postenteric, post-viral · |
| | **Infection** | Septic arthritis · Osteomyelitis · Tuberculosis · Lyme arthritis · |
| **Mechanical** | | Osgood–Schlatter disease · |
| **Tumours of cartilage bone or muscle** | **Benign** | Osteoid osteoma · Pigmented villonodular synovitis · Hemangioma · |
| | **Malignant** | Synovial sarcoma · Rhabdomyosarcoma · Ewing's sarcoma · |

| | |
|---|---|
| **Central Nervous System** | Idiopathic pain syndromes · **Local:** Complex regional pain syndrome/Reflex sympathetic dystrophy · **Generalized:** Fibromyalgia · |

Categories: Rheumatology | Chronic rheumatic heart diseases | Inflammations | Pediatrics




# Syncope (medicine)

From Wikipedia, the free encyclopedia

*For other uses, see Syncope.*

*"Fainting" redirects here. For other uses, see Faint.*

**Syncope**, also known as **fainting**, is defined as a short loss of consciousness and muscle strength, characterized by a fast onset, short duration, and spontaneous recovery. It is due to a decrease in blood flow to the entire brain usually from low blood pressure. Some causes have prodromal symptoms before the loss of consciousness occurs. These symptoms may include lightheadedness, sweating, pale skin, blurred vision, nausea, vomiting, and feeling warm, among others. Syncope may also be associated with a short episode of muscle twitching. If a person does not completely lose consciousness and muscle strength it is referred to as presyncope. It is recommended that presyncope be treated the same as syncope.[1]

Causes range from non-serious to potentially fatal. There are three broad categories of causes: heart or blood vessel related, reflex also known as neurally mediated, and orthostatic hypotension. Issues with the heart and blood vessels are the cause in about 10% and typically the most serious while neurally mediated is the most common. Heart related causes may include an abnormal heart rhythm, problems with the heart valves or heart muscle and blockages of blood vessels from a pulmonary embolism or aortic dissection among others. Neurally mediated syncope occurs when blood vessels expand and heart rate decreases inappropriately. This may occur from either a triggering event such as exposure to blood, pain, strong feelings or a specific activity such as urination, vomiting, or coughing. This type of syncope may also occur when an area in the neck known as the carotid sinus is pressed. The final type of syncope is due to a drop in blood pressure from standing up. This is often due to medications that a person is taking but may also be related to dehydration, significant bleeding or infection.[1]

A medical history, physical examination, and electrocardiogram (ECG) are the most effective ways to figure out the underlying cause. The ECG is useful to detect an abnormal heart rhythm, poor blood flow to the heart muscle, and other electrical issue such as long QT syndrome and Brugada's. Heart related causes also often have little history of a prodrome. Low blood pressure and a fast heart rate after the event may indicate blood loss or dehydration, while low blood oxygen levels may be seen following the event in those with pulmonary embolism. More specific tests such as implantable loop recorders, tilt table testing or carotid sinus massage may be useful in uncertain cases. Computer

## Syncope

**Synonyms** ...fainting, passing out, swooning

A 1744 oil painting by Pietro Longhi called *Fainting*

**Pronunciation** /ˈsɪŋkəpi/ *SING-kə-pee*

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Neurology, cardiology |
| **ICD-10** | R55 |
| **ICD-9-CM** | 780.2 |
| **DiseasesDB** | 27303 |
| **MedlinePlus** | 003092 |
| **eMedicine** | med/3385 ped/2188 emerg/876 |
| **MeSH** | D013575 |

[edit on Wikidata]

tomography (CT) is generally not required unless specific concerns are present. Other causes of similar symptoms that should be considered include seizure, stroke, concussion, low blood oxygen, low blood sugar, drug intoxication and some psychiatric disorders among others. Treatment depends on the underlying cause. Those who are considered at high risk following investigation may be admitted to hospital for further monitoring of the heart.[1]

Syncope affects about three to six out of every thousand people each year.[1] It is more common in older people and females. It is the reason for one to three percent of visits to emergency departments and admissions to hospital. Up to half of women over the age of 80 and a third of medical students describe at least one event at some point in their life.[2] Of those presenting with syncope to an emergency department, about 4% died in the next 30 days.[1] The risk of a bad outcome, however, depends very much on the underlying cause.[3]



# Differential diagnosis [edit]

## Central nervous system ischaemia [edit]

The central ischaemic response is triggered by an inadequate supply of oxygenated blood in the brain. The respiratory system may contribute to oxygen levels through hyperventilation, though a sudden ischaemic episode may also proceed faster than the respiratory system can respond. These processes cause the typical symptoms of fainting: pale skin, rapid breathing, nausea and weakness of the limbs, particularly of the legs. If the ischaemia is intense or prolonged, limb weakness progresses to collapse. An individual with very little skin pigmentation may appear to have all color drained from his or her face at the onset of an episode. This effect combined with the following collapse can make a strong and dramatic impression on bystanders.

The weakness of the legs causes most sufferers to sit or lie down if there is time to do so. This may avert a complete collapse, but whether the sufferer sits down or falls down, the result of an ischaemic episode is a posture in which less blood pressure is required to achieve adequate blood flow. It is unclear whether this is a mechanism evolved in response to the circulatory difficulties of human bipedalism or merely a serendipitous result of a pre-existing circulatory response .[*citation needed*]

## Vertebro-basilar arterial disease [edit]

Arterial disease in the upper spinal cord, or lower brain, causes syncope if there is a reduction in blood supply, which may occur with extending the neck or after drugs to lower blood pressure.

## Vasovagal [edit]

*Main article: Vasovagal syncope*

Vasovagal (situational) syncope is one of the most common types which may occur in response to any of a variety of triggers, such as scary, embarrassing or uneasy situations, during blood drawing, or moments of sudden unusually high stress. There are many different syncope syndromes which all fall under the umbrella of vasovagal syncope related by the same central mechanism, such as urination ("micturition syncope"), defecation ("defecation syncope"), and others related to trauma and stress.

Vasovagal syncope can be considered in two forms:

- Isolated episodes of loss of consciousness, unheralded by any warning symptoms for more than a few moments. These tend to occur in the adolescent age group, and may be associated with fasting, exercise, abdominal straining, or circumstances promoting vaso-dilation (e.g., heat, alcohol). The subject is invariably upright. The tilt-table test, if performed, is generally negative.
- Recurrent syncope with complex associated symptoms. This is neurally mediated syncope (NMS). It is associated with any of the following: preceding or succeeding sleepiness, preceding visual disturbance ("spots before the eyes"), sweating, lightheadedness. The subject is usually but not always upright. The tilt-table test, if performed, is generally positive. It is relatively uncommon.

A pattern of background factors contributes to the attacks. There is typically an unsuspected relatively low blood volume, for instance, from taking a low-salt diet in the absence of any salt-retaining tendency. Heat causes vaso-dilation and worsens the effect of the relatively insufficient blood volume. That sets the scene, but the next stage is the adrenergic response. If there is underlying fear or anxiety (e.g., social circumstances), or acute fear (e.g., acute threat, needle phobia), the vaso-motor centre demands an increased pumping action by the heart (flight or fight response). This is set in motion via the adrenergic (sympathetic) outflow from the brain, but the heart is unable to meet requirement because of the low blood volume, or decreased return. The high (ineffective) sympathetic activity is always modulated by vagal outflow, in these cases leading to excessive slowing of heart rate. The abnormality lies in this excessive vagal response. The tilt-table test typically evokes the attack.

Much of this pathway was discovered in animal experiments by Bezold (Vienna) in the 1860s. In animals, it may represent a defence mechanism when confronted by danger ("playing possum").

Avoiding what brings on the syncope and possibly greater salt intake is often all that is needed.[4]

Psychological factors also have been found to mediate syncope. It is important for general practitioners and the psychologist in their primary care team to work closely together, and to help patients identify how they might be avoiding activities of daily living due to anticipatory anxiety in relation to a possible faint and the feared physical damage it may cause. Fainting in response to a blood stimulus, needle or a dead body are common and patients can quickly develop safety behaviours to avoid any recurrences of a fainting response. See link for a good description of psychological interventions and theories.[5]

An evolutionary psychology view is that some forms of fainting are non-verbal signals that developed in response to increased inter-group aggression during the paleolithic. A non-combatant who has fainted signals that she or he is not a threat. This would explain the association between fainting and stimuli such as bloodletting and injuries seen in blood-injection-injury type phobias such as trypanophobia as well as the gender differences.[6]

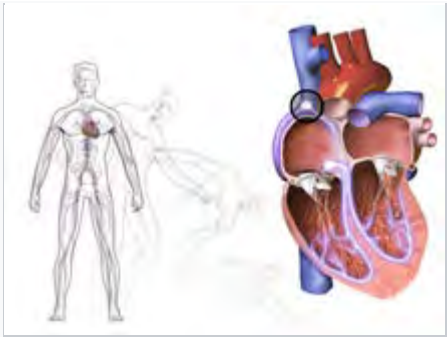
## Deglutition (Swallowing) syncope [edit]

Syncope may occur during deglutition. Manisty et al. note: "Deglutition syncope is characterised by loss of consciousness on swallowing; it has been associated not only with ingestion of solid food, but also with carbonated and ice-cold beverages, and even belching."[7]

## Cardiac [edit]

## Cardiac arrhythmias [edit]

The most common cause of cardiac syncope is cardiac arrhythmia (abnormal heart rhythm) wherein the heart beats too slowly, too rapidly,



Syncope from Bradycardia

or too irregularly to pump enough blood to the brain. Some arrhythmias can be life-threatening.

Two major groups of arrhythmias are bradycardia and tachycardia. Bradycardia can be caused by heart blocks. Tachycardias include SVT (supraventricular tachycardia) and VT (ventricular tachycardia). SVT does not cause syncope except in Wolff-Parkinson-White syndrome. Ventricular tachycardia originate in the ventricles. VT causes syncope and can result in sudden death. Ventricular tachycardia, which describes a heart rate of over 100 beats per minute with at least three irregular heartbeats as a sequence of consecutive premature beats, can degenerate into ventricular fibrillation, which is rapidly fatal without cardiopulmonary resuscitation (CPR) and defibrillation.[*citation needed*]

Typically, tachycardic-generated syncope is caused by a cessation of beats following a tachycardic episode. This condition, called tachycardia-bradycardia syndrome, is usually caused by sinoatrial node dysfunction or block or atrioventricular block.[8]

## Obstructive cardiac lesion [edit]

Aortic stenosis and mitral stenosis are the most common examples. Aortic stenosis presents with repeated episodes of syncope. A pulmonary embolism can cause obstructed blood vessels. High blood pressure in the arteries supplying the lungs (pulmonary artery hypertension) can occur during pulmonary embolism. Rarely, cardiac tumors such as atrial myxomas can also lead to syncope.

## Structural cardiopulmonary disease [edit]

These are relatively infrequent causes of faints. The most common cause in this category is fainting associated with an acute myocardial infarction or ischemic event. The faint in this case is primarily caused by an abnormal nervous system reaction similar to the reflex faints. In general, faints caused by structural disease of the heart or blood vessels are particularly important to recognize, as they are warning of potentially life-threatening conditions. Among other conditions prone to trigger syncope (by either hemodynamic compromise or by a neural reflex mechanism, or both), some of the most important are hypertrophic cardiomyopathy, acute aortic dissection, pericardial tamponade, pulmonary embolism, aortic stenosis, and pulmonary hypertension.

## Other cardiac causes [edit]

Sick sinus syndrome, a sinus node dysfunction, causing alternating bradycardia and tachycardia. Often there is a long pause asystole between heartbeat.

Adams-Stokes syndrome is a cardiac syncope that occurs with seizures caused by complete or incomplete heart block. Symptoms include deep and fast respiration, weak and slow pulse and respiratory pauses that may last for 60 seconds.

Subclavian steal syndrome arises from retrograde (reversed) flow of blood in the vertebral artery or the internal thoracic artery, due to a proximal stenosis (narrowing) and/or occlusion of the subclavian artery.

Aortic dissection (a tear in the aorta) and cardiomyopathy can also result in syncope.[9]

Various medications, such as beta blockers, may cause bradycardia induced syncope.[8]

## Blood pressure [edit]

*Orthostatic (postural) hypotensive faints* are as common or perhaps even more common than vasovagal syncope. Orthostatic faints are most often associated with movement from lying or sitting to a standing position, standing up too quickly, or being in a very hot room. The classic example of a combination of

these is seen in the frequent fainting by medical students in the operating theatre during observation of surgery.[10]

Apparently healthy individuals may experience minor symptoms ("lightheadedness", "greying-out") as they stand up if blood pressure is slow to respond to the stress of upright posture. If the blood pressure is not adequately maintained during standing, faints may develop. However, the resulting "transient orthostatic hypotension" does not necessarily signal any serious underlying disease.

The most susceptible individuals are elderly frail individuals, or persons who are dehydrated from hot environments or inadequate fluid intake. More serious orthostatic hypotension is often the result of certain commonly prescribed medications such as diuretics, β-adrenergic blockers, other anti-hypertensives (including vasodilators), and nitroglycerin. In a small percentage of cases, the cause of orthostatic hypotensive faints is structural damage to the autonomic nervous system due to systemic diseases (e.g., amyloidosis or diabetes) or in neurological diseases (e.g., Parkinson's disease).

### Other causes [edit]

Factors that influence fainting are fasting long hours, taking in too little food and fluids, low blood pressure, hypoglycemia, high g-force, emotional distress, and lack of sleep.

One theory in evolutionary psychology is that fainting at the sight of blood might have evolved as a form of playing dead which increased survival from attackers and might have slowed blood loss in a primitive environment.[11] "Blood-injury phobia", as this is called, is experienced by about 15% of people.[12]

Fainting can occur in "cough syncope".[13] following severe fits of coughing, such as that associated with pertussis or "whooping cough."

Pulmonary embolism was found in 17% of people whose average age was 76 who were admitted to the hospital for syncope in a study of Italian hospitals.[14]

## Diagnostic approach [edit]

For people with uncomplicated syncope (without seizures and a normal neurological exam) computed tomography or MRI is not indicated.[15] Likewise, using carotid ultrasonography on the premise of identifying carotid artery disease as a cause of syncope also is not indicated.[16] Although sometimes investigated as a cause of syncope, carotid artery problems are unlikely to cause that condition.[16]

A hemoglobin count may indicate anemia or blood loss. However, this has been useful in only about 5% of patients evaluated for fainting.[17]

An electrocardiogram (ECG) records the electrical activity of the heart. It is estimated that from 20%-50% of patients have an abnormal ECG. However, while an ECG may identify conditions such as atrial fibrillation, heart block, or a new or old heart attack, it typically does not provide a definite diagnosis for the underlying cause for fainting.[18]

Sometimes, a Holter monitor may be used. This is a portable ECG device that can record the wearer's heart rhythms during daily activities over an extended period of time. Since fainting usually does not occur upon command, a Holter monitor can provide a better understanding of the heart's activity during fainting episodes.

The tilt table test is performed to elicit orthostatic syncope secondary to autonomic dysfunction (neurogenic).

For patients with more than two episodes of syncope and no diagnosis on “routine testing”, an insertable cardiac monitor might be used. It lasts 28–36 months. Smaller than a pack of gum, it is inserted just beneath the skin in the upper chest area. The procedure typically takes 15 to 20 minutes. Once inserted, the device continuously monitors the rate and rhythm of the heart. Upon waking from a “fainting” spell, the patient places a hand held pager size device called an Activator over the implanted device and simply presses a button. This information is stored and retrieved by their physician and some devices can be monitored remotely.

### San Francisco syncope rule [edit]

The San Francisco syncope rule was developed to isolate people who have higher risk for a serious cause of syncope. High risk is anyone who has: congestive heart failure, hematocrit <30%, electrocardiograph abnormality, shortness of breath, or systolic blood pressure <90 mmHg.[19] The San Francisco syncope rule however was not validated by subsequent studies.[20]

## Management [edit]

Recommended acute treatment of vasovagal and orthostatic (hypotension) syncope involves returning blood to the brain by positioning the person on the ground, with legs slightly elevated or leaning forward and the head between the knees for at least 10–15 minutes, preferably in a cool and quiet place. For individuals who have problems with chronic fainting spells, therapy should focus on recognizing the triggers and learning techniques to keep from fainting. At the appearance of warning signs such as lightheadedness, nausea, or cold and clammy skin, counter-pressure maneuvers that involve gripping fingers into a fist, tensing the arms, and crossing the legs or squeezing the thighs together can be used to ward off a fainting spell. After the symptoms have passed, sleep is recommended. If fainting spells occur often without a triggering event, syncope may be a sign of an underlying heart disease. In case syncope is caused by cardiac disease, the treatment is much more sophisticated than that of vasovagal syncope and may involve pacemakers and implantable cardioverter-defibrillators depending on the precise cardiac cause.

## Society and culture [edit]

Fainting in women was a commonplace trope or stereotype in Victorian England and in contemporary and modern depictions of the period. This may have been partly due to genuine ill health (the respiratory effects of corsets are frequently cited), but it was fashionable for women to affect an aristocratic frailty and create a scene by fainting at a dramatic moment.[*citation needed*]

Falling-out is a culture-bound syndrome primarily reported in the southern United States and the Caribbean.

Some individuals occasionally or frequently play the "fainting game" (also referred to in the US as the "choking game"), which involves the deliberate induction of syncope via voluntary restriction of blood flow to the brain, an action that can result in acute or cumulative brain damage and even death.[21]

## Etymology [edit]

This article **needs additional citations for verification**. Please help improve this article by adding citations to reliable sources. Unsourced material may be challenged and removed. *(October 2011) (Learn how and when to remove this template message)*

The term is derived from the Late Latin *syncope*, from Ancient Greek συγκοπή (*sunkopē*), from σύν (*sin*, "together, thoroughly") and κόπτειν (*koptein*, "strike, cut off").

## See also [edit]

- Voodoo death

## References [edit]


1. ^ *a b c d e* Peeters, SY; Hoek, AE; Mollink, SM; Huff, JS (April 2014). "Syncope: risk stratification and

16. ^ *a b* American Academy of Neurology (February 2013), "Five Things Physicians and Patients Should

clinical decision making.". *Emergency medicine practice*. **16** (4): 1–22; quiz 22–3. PMID 25105200.
2. ^ Kenny, RA; Bhangu, J; King-Kallimanis, BL (2013). "Epidemiology of syncope/collapse in younger and older Western patient populations.". *Progress in cardiovascular diseases*. **55** (4): 357–63. doi:10.1016/j.pcad.2012.11.006. PMID 23472771.
3. ^ Ruwald, MH (August 2013). "Epidemiological studies on syncope--a register based approach.". *Danish medical journal*. **60** (8): B4702. PMID 24063058.
4. ^ Kaufmann, H; Bhattacharya, K (May 2002). "Diagnosis and treatment of neurally mediated syncope.". *The neurologist*. **8** (3): 175–85. PMID 12803689.
5. ^ Gaynor D, Egan J (2011). "Vasovagal syncope (the common faint): what clinicians need to know". *The Irish Psychologist*. **37** (7): 176–9. hdl:10147/135366.
6. ^ Bracha HS (July 2006). "Human brain evolution and the 'Neuroevolutionary Time-depth Principle:' Implications for the Reclassification of fear-circuitry-related traits in DSM-V and for studying resilience to warzone-related posttraumatic stress disorder". *Prog. Neuropsychopharmacol. Biol. Psychiatry*. **30** (5): 827–53. doi:10.1016/j.pnpbp.2006.01.008. PMID 16563589.
7. ^ Manisty C, Hughes-Roberts Y, Kaddoura S (July 2009). "Cardiac manifestations and sequelae of gastrointestinal disorders". *Br J Cardiol*. **16** (4): 175–80. Retrieved 11 May 2013.
8. ^ *a b* Freeman, Roy (2011). "Chapter 20: Syncope". In Longo, Dan L.; Kasper, Dennis L.; Jameson, J. Larry; Fauci, Anthony S.; Hauser, Stephen L.; Loscalzo, Joseph. *Harrison's Principles of Internal Medicine* (Textbook) (18th ed.). New York, NY: The McGraw-Hill Companies. pp. 171–177. ISBN 978-0-07-174889-6.
9. ^ Nallamothu BK, Mehta RH, Saint S, et al. (October 2002). "Syncope in acute aortic dissection: diagnostic, prognostic, and clinical implications". *Am. J. Med.* **113** (6): 468–71. doi:10.1016/S0002-9343(02)01254-8. PMID 12427495.
10. ^ Jamjoom AA, Nikkar-Esfahani A, Fitzgerald JE (2009). "Operating theatre related syncope in medical students: a cross sectional study". *BMC Med Educ*. **9**: 14. doi:10.1186/1472-6920-9-14. PMC 2657145. PMID 19284564.
11. ^ https://www.psychologytoday.com/blog/brain-babble/201302/why-do-some-people-faint-the-sight-blood
12. ^ "Swoon at the Sight of Blood? Why the sight of blood might make you faint -- and what you can do about it.". Retrieved 2015-08-15.
13. ^ Dicpinigaitis PV, Lim L, Farmakidis C (February 2014). "Cough syncope.". *Respiratory Medicine*. **108** (2): 244–51. doi:10.1016/j.rmed.2013.10.020.

Question", *Choosing Wisely: an initiative of the ABIM Foundation*, American Academy of Neurology, retrieved August 1, 2013, which cites:
1. 
   - Strickberger, S. A.; Benson, D. W.; Biaggioni, I.; Callans, D. J.; Cohen, M. I.; Ellenbogen, K. A.; Epstein, A. E.; Friedman, P.; Goldberger, J.; Heidenreich, P. A.; Klein, G. J.; Knight, B. P.; Morillo, C. A.; Myerburg, R. J.; Sila, C. A.; American Heart Association Councils On Clinical Cardiology (2006). "AHA/ACCF Scientific Statement on the Evaluation of Syncope: From the American Heart Association Councils on Clinical Cardiology, Cardiovascular Nursing, Cardiovascular Disease in the Young, and Stroke, and the Quality of Care and Outcomes Research Interdisciplinary Working Group; and the American College of Cardiology Foundation: In Collaboration with the Heart Rhythm Society: Endorsed by the American Autonomic Society". *Circulation*. **113** (2): 316–327. doi:10.1161/CIRCULATIONAHA.105.170274. PMID 16418451.
   - Moya, A.; European Society of Cardiology (ESC); Sutton, R.; European Heart Rhythm Association (EHRA); Ammirati, F.; and Heart Rhythm Society (HRS); Blanc, J.-J.; Endorsed by the following societies; Brignole, M.; European Society of Emergency Medicine (EuSEM); Moya, J. B.; European Federation of Internal Medicine (EFIM); Sutton, J.-C.; European Union Geriatric Medicine Society (EUGMS); Ammirati, J.; Blanc, K.; European Neurological Society (ENS); Brignole, A.; European Federation of Autonomic Societies (EFAS); Dahm, M.; Deharo, M.; Gajek, T.; Gjesdal, R. R.; Krahn, F.; Massin, A.; Pepi, J. G.; Pezawas, E. P.; Ruiz Granell, W.; Sarasin, H.; Ungar, D. G.; et al. (2009). "Guidelines for the diagnosis and management of syncope (version 2009): The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC)". *European Heart Journal*. **30** (21): 2631–2671. doi:10.1093/eurheartj/ehp298. PMC 3295536. PMID 19713422.
   - NICE (August 2010), *Transient loss of consciousness in adults and young people (CG109)*, NICE, retrieved 24 October 2013
17. ^ Grubb (2001) p.83
18. ^ Grubb (2001) pp.83-84
19. ^ Quinn J, McDermott D, Stiell I, Kohn M, Wells G (May 2006). "Prospective validation of the San Francisco Syncope Rule to predict patients with

PMID 24238768.
14. ^ Prandoni, Paolo; Lensing, Anthonie W.A.; Prins, Martin H.; Ciammaichella, Maurizio; Perlati, Marica; Mumoli, Nicola; Bucherini, Eugenio; Visonà, Adriana; Bova, Carlo; Imberti, Davide; Campostrini, Stefano; Barbar, Sofia (2016-10-20). "Prevalence of Pulmonary Embolism among Patients Hospitalized for Syncope". *New England Journal of Medicine*. **375** (16): 1524–1531. doi:10.1056/NEJMoa1602172. Retrieved 2016-10-21.
15. ^ Moya A, Sutton R, Ammirati F, et al. (November 2009). "Guidelines for the diagnosis and management of syncope (version 2009)". *Eur. Heart J.* **30** (21): 2631–71. doi:10.1093/eurheartj/ehp298. PMC 3295536. PMID 19713422.
serious outcomes". *Ann Emerg Med*. **47** (5): 448–54. doi:10.1016/j.annemergmed.2005.11.019. PMID 16631985. Lay summary – *Journal Watch* (July 21, 2006).
20. ^ Birnbaum A, Esses D, Bijur P, Wollowitz A, Gallagher EJ (August 2008). "Failure to validate the San Francisco Syncope Rule in an independent emergency department population". *Ann Emerg Med*. **52** (2): 151–9. doi:10.1016/j.annemergmed.2007.12.007. PMID 18282636.
21. ^ "'Choking Game' Becoming Deadly Fad For Adolescents". WJZ-TV Baltimore. 2005-11-04. Archived from the original on 2007-12-19. Retrieved 2008-02-13.

## External links [edit]

- Syncope (medicine) at DMOZ
- 2004 European Society of Cardiology Guidelines on Management (Diagnosis and Treatment) of Syncope.
- Tilt table test
- The San Francisco syncope rule

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| | **Fainting / Syncope** | Carotid sinus syncope · Heat syncope · Vasovagal episode · |
| | **Other** | Amnesia (Anterograde amnesia · Retrograde amnesia · · Dizziness (Vertigo · Presyncope/Lightheadedness · Disequilibrium · · Convulsion · |
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# Circumcision

From Wikipedia, the free encyclopedia

*This article is about male circumcision. For female circumcision, see female genital mutilation.*

Male **circumcision** is the removal of the foreskin from the human penis.[1][2][3] In the most common procedure, the foreskin is opened, adhesions are removed, and the foreskin is separated from the glans. After that, the circumcision device (if used) is placed, and then the foreskin is cut off. Topical or locally injected anesthesia is occasionally used to reduce pain and physiologic stress.[4] For adults and children, general anesthesia is an option, and the procedure may be performed without a specialized circumcision device. The procedure is most often an elective surgery performed on babies and children for religious and cultural reasons.[5] In other cases it may be done as a treatment for a condition or for preventative reasons. Medically, it is a treatment option for problematic cases of phimosis, balanoposthitis that does not resolve with other treatments, and chronic urinary tract infections (UTIs).[1][6] It is contraindicated in cases of certain genital structure abnormalities or poor general health.[2][6]

*Intervention*

A circumcision performed in Central Asia, c. 1865–1872

| | |
|---|---|
| **ICD-10-PCS** | 0VBT |
| **ICD-9-CM** | V50.2 |
| **MeSH** | D002944 |
| **OPS-301 code** | 5-640.2 |
| **MedlinePlus** | 002998 |
| **eMedicine** | 1015820 |

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The positions of the world's major medical organizations range from considering elective circumcision of babies and children as having no benefit and significant risks to having a modest health benefit that outweighs small risks. No major medical organization recommends either universal circumcision for all males (aside from the recommendations of the World Health Organization (WHO) for areas with high rates of HIV), or banning the procedure.[7] Ethical and legal questions regarding informed consent and human rights have been raised over the circumcision of babies and children for non-medical reasons, and for that reason the procedure is controversial.[8][9]

Evidence supports that male circumcision reduces the risk of HIV infection among heterosexual men in sub-Saharan Africa.[10][11] Therefore, the WHO recommends considering circumcision as part of a comprehensive HIV prevention program in areas with high rates of HIV, such as Sub Saharan Africa.[12] Evidence for a health benefit against HIV for men who have sex with men is less clear.[13][14] Additionally, the effectiveness of using circumcision to prevent HIV in the developed world is also unclear.[15] Circumcision in general is associated with reduced rates of cancer causing forms of HPV[16][17] and risk of both UTIs and cancer of the penis.[4] Prevention of those conditions is not a justification for routine circumcision of infants.[1][18] Studies of its potential protective effects against other sexually transmitted infections have been unclear. A 2010 review of literature found circumcisions performed by medical providers to have a typical complication rate of 1.5% for babies and 6% for older children, with few cases

of severe complications.[19] Bleeding, infection and the removal of either too much or too little foreskin are the most common complications cited.[19] Complication rates are higher when the procedure is performed by an inexperienced operator, in unsterile conditions, or when the child is at an older age.[19] Circumcision does not appear to have a negative impact on sexual function.[20][21]

An estimated one-third of males worldwide are circumcised.[5][19][22] The procedure is most common in the Muslim world and Israel (where it is near-universal for religious reasons), the United States, and parts of Southeast Asia and Africa.[5] It is relatively rare in Europe, Latin America, parts of Southern Africa, and most of Asia.[5] The origin of circumcision is not known with certainty; the oldest documented evidence for it comes from ancient Egypt.[5] Various theories have been proposed as to its origin, including as a religious sacrifice and as a rite of passage marking a boy's entrance into adulthood.[23] It is part of religious law in Judaism[24] and is an established practice in Islam, Coptic Christianity, and the Ethiopian Orthodox Church.[5][25][26] The word circumcision is from Latin *circumcidere*, meaning "to cut around".[5]



**Contents**



# Indications and contraindications

## Routine or elective

Neonatal circumcision is usually elected by the parents for non-medical reasons, such as religious beliefs or personal preferences, possibly driven by societal norms.[6] Outside the parts of Africa with high prevalence of HIV/AIDS, the positions of the world's major medical organizations on non-therapeutic neonatal circumcision range from considering it as having a modest net health benefit that outweighs small risks to viewing it as having no benefit with significant risks for harm. No major medical organization recommends

universal neonatal circumcision, and no major medical organization calls for banning it either. The Royal Dutch Medical Association, which expresses some of the strongest opposition to routine neonatal circumcision, does not call for the practice to be made illegal out of their concern that parents who insist on the procedure would turn to poorly trained practitioners instead of medical professionals. This argument to keep the procedure within the purview of medical professionals is found across all major medical organizations. In addition, the organizations advise medical professionals to yield to some degree to parental preferences, which are commonly based upon cultural or religious views, in their decision to agree to circumcise.[7] The Danish College of General Practitioners states that circumcision should "only [be done] when medically needed, otherwise it is a case of mutilation."[27]

Owing to the HIV/AIDS epidemic there, sub-Saharan Africa is a special case. The finding that circumcision significantly reduces female-to-male HIV transmission has prompted medical organizations serving the affected communities to promote circumcision as an additional method of controlling the spread of HIV.[7] The World Health Organization (WHO) and UNAIDS (2007) recommend circumcision as part of a comprehensive program for prevention of HIV transmission in areas with high endemic rates of HIV, as long as the program includes "informed consent, confidentiality, and absence of coercion".[12]

## Medical indications

Circumcision may be used to treat pathological phimosis, refractory balanoposthitis and chronic, recurrent urinary tract infections (UTIs).[1][6] The World Health Organization promotes circumcision as a preventive measure for sexually active men in populations at high risk for HIV.[12] Circumcision is also recommended for HIV prevention by the International Antiviral Society-USA for all sexually active heterosexual males and is recommended that it be discussed with MSM who engage in primarily insertive anal sex with other men, especially in areas where HIV is common.[28]

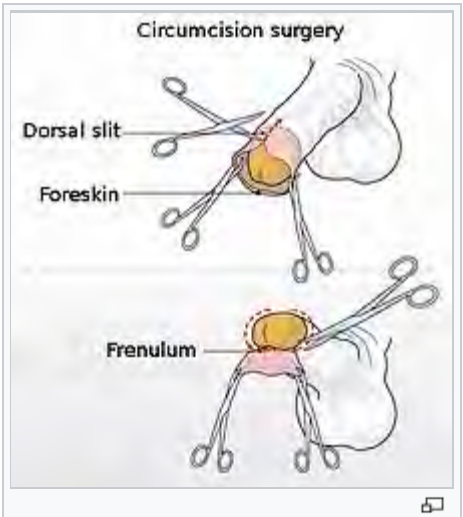
## Contraindications

Circumcision is contraindicated in infants with certain genital structure abnormalities, such as a misplaced urethral opening (as in hypospadias and epispadias), curvature of the head of the penis (chordee), or ambiguous genitalia, because the foreskin may be needed for reconstructive surgery. Circumcision is contraindicated in premature infants and those who are not clinically stable and in good health.[2][6][29] If an individual, child or adult, is known to have or has a family history of serious bleeding disorders (hemophilia), it is recommended that the blood be checked for normal coagulation properties before the procedure is attempted.[6][29]

# Technique

*Main article: Circumcision surgical procedure*

The foreskin extends out from the base of the glans and covers the glans when the penis is flaccid. Proposed theories for the purpose of the foreskin are that it serves to protect the penis as the fetus develops in the mother's womb, that it helps to preserve moisture in the glans, and that it improves sexual pleasure. The foreskin may also be a pathway of infection for certain diseases. Circumcision removes the foreskin at its attachment to the base of the glans.[5]




## Removal of the foreskin

For infant circumcision, devices such as the Gomco clamp, Plastibell and Mogen clamp are commonly used in the USA.[4] These follow the same basic procedure. First, the amount of foreskin to be removed is estimated. The practitioner opens the foreskin via the preputial orifice to reveal the glans underneath and ensures it is normal before bluntly

separating the inner lining of the foreskin (preputial epithelium) from its attachment to the glans. The practitioner then places the circumcision device (this sometimes requires a dorsal slit), which remains until blood flow has stopped. Finally, the foreskin is amputated.[4] For adults, circumcision is often performed without clamps,[30] and non-surgical alternatives such as the elastic ring controlled radial compression device or the Shang ring are available.[31]

Circumcision surgery with hemostats and scissors

Before (left) and after (right) an adult circumcision, undertaken to treat phimosis. The glans is exposed even when the penis is flaccid.

## Pain management

The circumcision procedure causes pain, and for neonates this pain may interfere with mother-infant interaction or cause other behavioral changes,[32] so the use of analgesia is advocated.[4][33] Ordinary procedural pain may be managed in pharmacological and non-pharmacological ways. Pharmacological methods, such as localized or regional pain-blocking injections and topical analgesic creams, are safe and effective.[4][34][35] The ring block and dorsal penile nerve block (DPNB) are the most effective at reducing pain, and the ring block may be more effective than the DPNB. They are more effective than EMLA (eutectic mixture of local anesthetics) cream, which is more effective than a placebo.[34][35] Topical creams have been found to irritate the skin of low birth weight infants, so penile nerve block techniques are recommended in this group.[4]

For infants, non-pharmacological methods such as the use of a comfortable, padded chair and a sucrose or non-sucrose pacifier are more effective at reducing pain than a placebo,[35] but the American Academy of Pediatrics (AAP) states that such methods are insufficient alone and should be used to supplement more effective techniques.[4] A quicker procedure reduces duration of pain; use of the Mogen clamp was found to result in a shorter procedure time and less pain-induced stress than the use of the Gomco clamp or the Plastibell.[35] The available evidence does not indicate that post-procedure pain management is needed.[4] For adults, general anesthesia is an option,[36] and the procedure requires four to six weeks of abstinence from masturbation or intercourse to allow the wound to heal.[29]

# Effects

## Sexually transmitted diseases

### Human immunodeficiency virus

*Main article: Circumcision and HIV*

There is strong evidence that circumcision reduces the risk of HIV infection in heterosexual men in high-risk populations.[10][11] Evidence among heterosexual men in sub-Saharan Africa shows an absolute decrease in risk of 1.8% which is a relative decrease of between 38 percent and 66 percent over two years,[11] and in this population studies rate it cost effective.[37] Whether it is of benefit in developed countries is undetermined.[15]

There are plausible explanations based on human biology for how circumcision can decrease the likelihood of female-to-male HIV transmission. The superficial skin layers of the penis contain Langerhans cells, which are targeted by HIV; removing the foreskin reduces the number of these cells. When an uncircumcised penis is erect during intercourse, any small tears on the inner surface of the foreskin come into direct contact with the vaginal walls, providing a pathway for transmission. When an uncircumcised penis is flaccid, the pocket between the inside of the foreskin and the head of the penis provides an environment conducive to pathogen survival; circumcision eliminates this pocket. Some experimental evidence has been provided to support these theories.[38]

The WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) state that male circumcision is an efficacious intervention for HIV prevention, but should be carried out by well-trained medical professionals and under conditions of informed consent (parents' consent for their infant boys).[5][12][39] The WHO has judged circumcision to be a cost-effective public health intervention against the spread of HIV in Africa, although not necessarily more cost-effective than condoms.[5] The joint WHO/UNAIDS recommendation also notes that circumcision only provides partial protection from HIV and should not replace known methods of HIV prevention.[12]

The available evidence does not indicate that circumcision provides HIV protection for heterosexual women.[4][40][41] Data is lacking regarding the effect circumcision may have on the transmission rate of men who engage in anal sex with a female partner.[39][42] It is undetermined whether circumcision benefits men who have sex with men.[14][43]

### Human papillomavirus

Human papillomavirus (HPV) is the most commonly transmitted sexually transmitted infection, affecting both men and women. While most infections are asymptomatic and are cleared by the immune system, some types of the virus cause genital warts, and other types, if untreated, cause various forms of cancer, including cervical cancer, and penile cancer. Genital warts and cervical cancer are the two most common problems resulting from HPV.[44]

Circumcision is associated with a reduced prevalence of oncogenic types of HPV infection, meaning that a randomly selected circumcised man is less likely to be found infected with cancer-causing types of HPV than an uncircumcised man.[45][46] It also decreases the likelihood of multiple infections.[17] No strong evidence indicates that it reduces the rate of new HPV infection,[16][17][47] but the procedure is associated with increased clearance of the virus by the body,[16][17] which can account for the finding of reduced prevalence.[17]

Although genital warts are caused by a type of HPV, there is no statistically significant relationship between being circumcised and the presence of genital warts.[16][46][47]

### Other infections

Studies evaluating the effect of circumcision on the incidence of other sexually transmitted infections have reached conflicting conclusions. A 2006 meta-analysis found that circumcision was associated with lower rates of syphilis, chancroid and possibly genital herpes.[48] A 2010 review found that circumcision reduced the incidence of HSV-2 (herpes simplex virus, type 2) infections by 28%.[49] The researchers found mixed results for protection against trichomonas vaginalis and chlamydia trachomatis and no evidence of protection against gonorrhea or syphilis.[49] Among men who have sex with men, reviews have found poor evidence for protection against sexually transmitted infections other than HIV,[13][43] with the possible exception of syphilis.[43]

## Phimosis, balanitis and balanoposthitis

Phimosis is the inability to retract the foreskin over the glans penis.[50] At birth, the foreskin cannot be retracted due to adhesions between the foreskin and glans, and this is considered normal (physiological phimosis).[50] Over time the foreskin naturally separates from the glans, and a majority of boys are able to retract the foreskin by age three.[50] Less than one percent are still having problems at age 18.[50] If the inability to do so becomes problematic (pathological phimosis) circumcision is a treatment option.[1][51] This pathological phimosis may be due to scarring from the skin disease balanitis xerotica obliterans (BXO), repeated episodes of balanoposthitis or forced retraction of the foreskin.[52] Steroid creams are also a reasonable option and may prevent the need for surgery including in those with mild BXO.[52][53] The procedure may also be used to prevent the development of phimosis.[6] Phimosis is also a complication that can result from circumcision.[54]

An inflammation of the glans penis and foreskin is called balanoposthitis, and the condition affecting the glans alone is called balanitis.[55][56] Most cases of these conditions occur in uncircumcised males,[57] affecting 4–11% of that group.[58] The moist, warm space underneath the foreskin is thought to facilitate the growth of pathogens, particularly when hygiene is poor. Yeasts, especially *Candida albicans*, are the most common penile infection and are rarely identified in samples taken from circumcised males.[57] Both conditions are usually treated with topical antibiotics (metronidazole cream) and antifungals (clotrimazole cream) or low-potency steroid creams.[55][56] Circumcision is a treatment option for refractory or recurrent balanoposthitis, but in recent years the availability of the other treatments have made it less necessary.[55][56]

## Urinary tract infections

A UTI affects parts of the urinary system including the urethra, bladder, and kidneys. There is about a one percent risk of UTIs in boys under two years of age, and the majority of incidents occur in the first year of life. There is good but not ideal evidence that circumcision reduces the incidence of UTIs in boys under two years of age, and there is fair evidence that the reduction in incidence is by a factor of 3–10 times.[4][59][60] Prevention of UTIs does not justify routine use of the procedure, however.[1] Circumcision is most likely to benefit boys who have a high risk of UTIs due to anatomical defects,[4] and may be used to treat recurrent UTIs.[1]

There is a plausible biological explanation for the reduction in UTI risk after circumcision. The orifice through which urine passes at the tip of the penis (the urinary meatus) hosts more urinary system disease-causing bacteria in uncircumcised boys than in circumcised boys, especially in those under six months of age. As these bacteria are a risk factor for UTIs, circumcision may reduce the risk of UTIs through a decrease in the bacteria population.[4][61]

## Cancers

Circumcision has a protective effect against the risks of penile cancer in men, and cervical cancer in the female sexual partners of heterosexual men. Penile cancer is rare, with about 1 new case per 100,000 people per year in developed countries, and higher incidence rates per 100,000 in sub-Saharan Africa (for example, 1.6 in Zimbabwe, 2.7 in Uganda and 3.2 in Swaziland).[62] Penile cancer development can be detected in the carcinoma *in situ* (CIS) cancerous precursor stage and at the more advanced invasive squamous cell carcinoma stage.[4] Childhood or adolescent circumcision is associated with a reduced risk of invasive squamous cell carcinoma in particular.[4][62] There is an association between adult circumcision and an increased risk of invasive penile cancer; this is believed to be from men being circumcised as a treatment for penile cancer or a condition that is a precursor to cancer rather than a consequence of circumcision itself.[62] Penile cancer has been observed to be nearly eliminated in populations of males circumcised neonatally.[58]

Important risk factors for penile cancer include phimosis and HPV infection, both of which are mitigated by circumcision.[62] The mitigating effect circumcision has on the risk factor introduced by the possibility of phimosis is secondary, in that the removal of the foreskin eliminates the possibility of phimosis. This can be inferred from study results that show uncircumcised men with no history of phimosis are equally likely to have penile cancer as circumcised men.[4][62] Circumcision is also associated with a reduced prevalence of cancer-causing types of HPV in men[17] and a reduced risk of cervical cancer (which is caused by a type of HPV) in female partners of men.[6] Because penile cancer is rare (and may get more rare with increasing HPV vaccination rates), and circumcision has risks, the practice is not considered to be valuable solely as a prophylactic measure against penile cancer in the United States.[4][18][58]

A 2015 meta-analysis found a non-statistically significant reduced risk of prostate cancer associated with circumcision, but that this reduction was significant among blacks and in studies looking at post-PSA and -testing groups.[63]

# Adverse effects

Neonatal circumcision is generally safe when done by an experienced practitioner.[64][65] The most common acute complications are bleeding, infection and the removal of either too much or too little foreskin.[4][66] These complications occur in approximately 0.12% of procedures, and constitute the vast majority of all acute circumcision complications in the United States.[66] Minor complications are reported to occur in three percent of procedures.[64] Severe complications are rare.[67] A specific complication rate is difficult to determine due to scant data on complications and inconsistencies in their classification.[4] Complication rates are greater when the procedure is performed by an inexperienced operator, in unsterile conditions, or when the child is at an older age.[19] Significant acute complications happen rarely,[4][19] occurring in about 1 in 500 newborn procedures in the United States.[4] Severe to catastrophic complications, including death, are so rare that they are reported only as individual case reports.[4][65] Other possible complications include buried penis, chordee, phimosis, skin bridges, urethral fistulas, and meatal stenosis.[65] These complications may be avoided with proper technique, and are most often treatable without requiring a hospital visit.[65]

## Pain

The circumcision procedure may carry the risks of heightened pain response for newborns and dissatisfaction with the result.[32] Newborns that experience pain due to being circumcised have different responses to vaccines given afterwards, with higher pain scores observed.[68]

## Sexual effects

The highest quality evidence indicates that circumcision does not decrease the sensitivity of the penis, harm sexual function or reduce sexual satisfaction.[20][69][70] A 2013 systematic review found that circumcision did not appear to adversely affect sexual desire, pain with intercourse, premature ejaculation, time until ejaculation, erectile dysfunction or difficulties with orgasm. However, the study found that the existing evidence is not very good.[71] Another 2013 systematic review found that the highest-quality studies reported no adverse effects of circumcision on sexual function, sensitivity, sensation or satisfaction.[21]

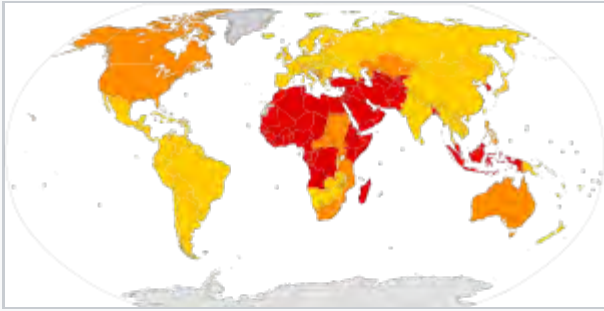
## Psychological effects

Behavioral effects have been observed following infant circumcision including changes in sleep patterns, irritability, changes in feeding, and parental bonding.[72] Some men who were circumcised as an infant involuntary, described their feelings about the procedure using the terms "violation, torture, mutilation and sexual assault".[73]

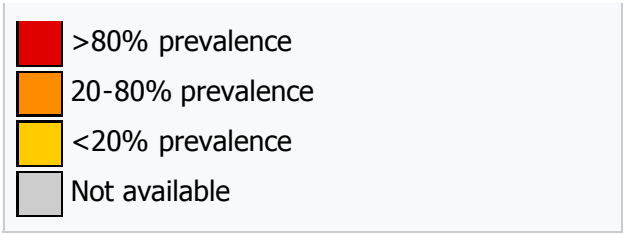
# Prevalence

*Main article: Prevalence of circumcision*

Circumcision is one of the world's most widely performed procedures.[74] Approximately 37% to 39% of males worldwide are circumcised, about half for religious or cultural reasons.[75] It is most often practiced between infancy and the early twenties.[5] The WHO estimated in 2007 that 664,500,000 males aged 15 and over were circumcised (30–33% global prevalence), almost 70% of whom were Muslim.[5] Circumcision is most prevalent in the Muslim world, Israel, South Korea, the United States and parts of Southeast Asia and Africa. It is relatively rare in Europe, Latin



Rate of male circumcision by country[5]




America, parts of Southern Africa and Oceania and most of Asia. Prevalence is near-universal in the Middle East and Central Asia.[5][76] Non-religious circumcision in Asia, outside of the Republic of Korea and the Philippines, is fairly rare,[5] and prevalence is generally low (less than 20%) across Europe.[5][77] Estimates for individual countries include Taiwan at 9%[78] and Australia 58.7%.[79] Prevalence in the United States and Canada is estimated at 75% and 30% respectively.[5] Prevalence in Africa varies from less than 20% in some southern African countries to near universal in North and West Africa.[76]

The rates of routine neonatal circumcision over time have varied significantly by country. In the United States, hospital discharge surveys estimated rates at 64.7% in the year 1980, 59.0% in the year 1990, 62.4% in the year 2000, and 58.3% in the year 2010.[80] These estimates are lower than the overall circumcision rates, as they do not account for non-hospital circumcisions,[80] or for procedures performed for medical or cosmetic reasons later in life;[5][80] community surveys have reported higher neonatal circumcision.[5] Canada has seen a slow decline since the early 1970s, possibly influenced by statements from the AAP and the Canadian Pediatric Society issued in the 1970s saying that the procedure was not medically indicated.[5] In Australia, the rate declined in the 1970s and 80s, but has been increasing slowly as of 2004.[5] In the United Kingdom, rates are likely to have been 20–30% in the 1940s but declined in the late 40s. One possible reason may have been a 1949 British Medical Journal article which stated that there was no medical reason for the general circumcision of babies.[5] The overall prevalence of circumcision in South Korea has increased markedly in the second half of the 20th century, rising from near zero around 1950 to about 60% in 2000, with the most significant jumps in the last two decades of that time period.[5] This is probably due to the influence of the United States, which established a trusteeship for the country following World War II.[5]

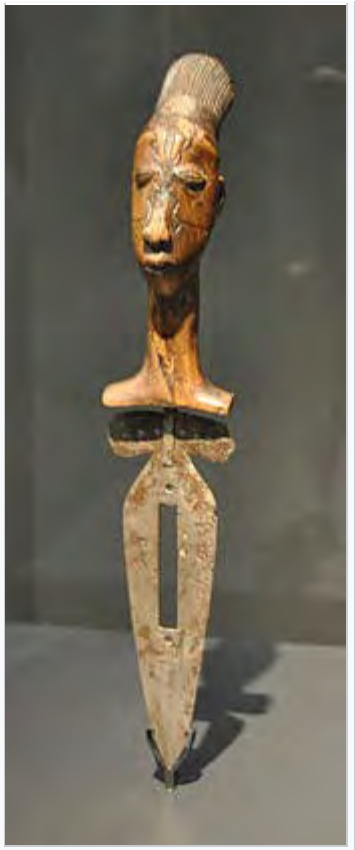
Medical organizations can affect the neonatal circumcision rate of a country by influencing whether the costs of the procedure are borne by the parents or are covered by insurance or a national health care system. Policies that require the costs to be paid by the parents yield lower neonatal circumcision rates. The decline in the rates in the UK is one example; another is that in the United States, the individual states where insurance or Medicaid covers the costs have higher rates. Changes to policy are driven by the results of new research, and moderated by the politics, demographics, and culture of the communities.[7]

## History

*Main article: History of male circumcision*

Circumcision is the world's oldest planned surgical procedure, suggested by anatomist and hyperdiffusionist historian Grafton Elliot Smith to be over 15,000 years old, pre-dating recorded history. There is no firm consensus as to how it came to be practiced worldwide. One theory is that it began in one geographic area and spread from there; another is that several different cultural groups began its practice independently. In his 1891 work *History of Circumcision*, physician Peter Charles Remondino suggested that it began as a less severe form of emasculating a captured enemy: penectomy or castration would likely have been fatal, while some form of circumcision would permanently mark the defeated yet leave him alive to serve as a slave.[23][81]

The history of the migration and evolution of the practice of circumcision is followed mainly through the cultures and peoples in two separate regions. In the lands south and east of the Mediterranean, starting with Sudan and Ethiopia, the procedure was practiced by the ancient Egyptians and the Semites, and then by the Jews and Muslims, with whom the practice travelled to and was adopted by the Bantu Africans. In Oceania, circumcision is practiced



Circumcision knife from the Congo; wood, iron; late 19th/early 20th century

by the Australian Aborigines and Polynesians.[81] There is also evidence that circumcision was practiced among the Aztec and Mayan civilizations in the Americas,[5] but little detail is available about its history.[23][74]

## Middle East, Africa and Europe

Evidence suggests that circumcision was practiced in the Arabian Peninsula by the 4th millennium BCE, when the Sumerians and the Semites moved into the area that is modern-day Iraq.[74] The earliest historical record of circumcision comes from Egypt, in the form of an image of the circumcision of an adult carved into the tomb of Ankh-Mahor at Saqqara, dating to about 2400–2300 BCE. Circumcision was done by the Egyptians possibly for hygienic reasons, but also was part of their obsession with purity and was associated with spiritual and intellectual development. No well-accepted theory explains the significance of circumcision to the Egyptians, but it appears to have been endowed with great honor and importance as a rite of passage into adulthood, performed in a public ceremony emphasizing the continuation of family generations and fertility. It may have been a mark of distinction for the elite: the Egyptian *Book of the Dead* describes the sun god Ra as having circumcised himself.[23][81]

Köçeks dancing at the circumcision celebration of Sultan Ahmed III's sons (1720); miniature from the *Surname-i Vehbi*, Topkapı Palace, Istanbul

Though secular scholars consider the story to be literary and not historical,[82] circumcision features prominently in the Hebrew Bible. The narrative in Genesis chapter 17 describes the circumcision of Abraham and his relatives and slaves. In the same chapter, Abraham's descendants are commanded to circumcise their sons on the eighth day of life as part of a covenant with God.

In addition to proposing that circumcision was taken up by the Israelites purely as a religious mandate, scholars have suggested that Judaism's patriarchs and their followers adopted circumcision to make penile hygiene easier in hot, sandy climates; as a rite of passage into adulthood; or as a form of blood sacrifice.[74][81][83]

Alexander the Great conquered the Middle East in the 4th century BCE, and in the following centuries ancient Greek cultures and values came to the Middle East. The Greeks abhorred circumcision, making a life for circumcised Jews living among the Greeks (and later the Romans) very difficult. Antiochus Epiphanes outlawed circumcision, as did Hadrian, which helped cause the Bar Kokhba revolt. During this period in history, Jewish circumcision called for the removal of only a part of the prepuce, and some Hellenized Jews attempted to look uncircumcised by stretching the extant parts of their foreskins. This was considered by the Jewish leaders to be a serious

problem, and during the 2nd century CE they changed the requirements of Jewish circumcision to call for the complete removal of the foreskin, emphasizing the Jewish view of circumcision as intended to be not just the fulfillment of a Biblical commandment but also an essential and permanent mark of membership in a people.[81][83]

A narrative in the Christian Gospel of Luke makes a brief mention of the circumcision of Jesus, but the subject of physical circumcision itself is not part of the received teachings of Jesus. Paul the Apostle reinterpreted circumcision as a spiritual concept, arguing the physical one to be no longer necessary. The teaching that physical circumcision was unnecessary for membership in a divine covenant was instrumental in the separation of Christianity from Judaism. Although it is not explicitly mentioned in the Quran (early 7th century CE), circumcision is considered essential to Islam, and it is nearly universally performed among Muslims. The practice of circumcision spread across the Middle East, North Africa, and Southern Europe with Islam.[84]

The Circumcision of Jesus Christ, by Ludovico Mazzolino

Genghis Khan, and the following Yuan Emperors in China forbade Islamic practices such as halal butchering and circumcision.[85][86] This led Chinese Muslims to eventually take an active part in rebelling against the Mongols and installing the more tolerant Ming Dynasty.

The practice of circumcision is thought to have been brought to the Bantu-speaking tribes of Africa by either the Jews after one of their many expulsions from European countries, or by Muslim Moors escaping after the 1492 conquest of Spain. In the second half of the 1st millennium CE, inhabitants from the North East of Africa moved south and encountered groups from Arabia, the Middle East, and West Africa. These people moved south and formed what is known today as the Bantu. Bantu tribes were observed to be upholding what was described as Jewish law, including circumcision, in the 16th century. Circumcision and elements of Jewish dietary restrictions are still found among Bantu tribes.[74]

## Indigenous peoples of Australia, the Pacific, and Americas

Circumcision is practiced by some groups amongst Australian Aboriginal peoples, Polynesians, and Native Americans. Little information is available about the origins and history of circumcision among these peoples, compared to circumcision in the Middle East.

For Aboriginal Australians and Polynesians, circumcision likely started as a blood sacrifice and a test of bravery and became an initiation rite with attendant instruction in manhood in more recent centuries. Often seashells were used to remove the foreskin, and the bleeding was stopped with eucalyptus smoke.[74][87]

Christopher Columbus reported circumcision being practiced by Native Americans.[23] It was also practiced by the Incas, Aztecs, and Mayans. It probably started among South American tribes as a blood sacrifice or ritual mutilation to test bravery and endurance, and its use later evolved into a rite of initiation.[74]

## Modern times

Circumcision did not become a common medical procedure in the Anglophone world until the late 19th century.[88] At that time, British and American doctors began recommending it primarily as a deterrent to masturbation.[88][89] Prior to the 20th century, masturbation was believed to be the cause of a wide range of physical and mental illnesses including epilepsy, paralysis, impotence, gonorrhea, tuberculosis, feeblemindedness, and insanity.[90][91] In 1855, motivated in part by an interest in promoting circumcision to reduce masturbation, English physician Jonathan Hutchinson published his findings that Jews had a lower prevalence of certain venereal diseases.[92] While pursuing a successful career as a general practitioner, Hutchinson went on to advocate circumcision for health reasons for the next fifty years,[92] and eventually earned a knighthood for his overall contributions to medicine.[93] In America, one of the first modern physicians to advocate the procedure was Lewis Sayre, a founder of the American Medical

Association. In 1870, Sayre began using circumcision as a purported cure for several cases of young boys diagnosed with paralysis or significant motor problems. He thought the procedure ameliorated such problems based on a "reflex neurosis" theory of disease, which held that excessive stimulation of the genitals was a disturbance to the equilibrium of the nervous system and a cause of systemic problems.[88] The use of circumcision to promote good health also fit in with the germ theory of disease during that time, which saw the foreskin as being filled with infection-causing smegma (a mixture of shed skin cells and oils). Sayre published works on the subject and promoted it energetically in speeches. Contemporary physicians picked up on Sayre's new treatment, which they believed could prevent or cure a wide-ranging array of medical problems and social ills. Its popularity spread with publications such as Peter Charles Remondino's *History of Circumcision*. By the turn of the century, in both America and Great Britain, infant circumcision was near universally recommended.[23][89]

After the end of World War II, Britain moved to a nationalized health care system, and so looked to ensure that each medical procedure covered by the new system was cost-effective and the procedure for non-medical reasons was not covered by the national healthcare system. Douglas Gairdner's 1949 article "The Fate of the Foreskin" argued that the evidence available at that time showed that the risks outweighed the known benefits.[94] Circumcision rates dropped in Britain and in the rest of Europe. In the 1970s, national medical associations in Australia and Canada issued recommendations against routine infant circumcision, leading to drops in the rates of both of those countries. The United States made similar statements in the 1970s, but stopped short of recommending against it — simply stating that it has no medical benefit. Since then they have amended their policy statements several times with the current recommendation being that the benefits outweigh the risks, but they do not recommend it routinely.[23][89]

An association between circumcision and reduced heterosexual HIV infection rates was suggested in 1986.[23] Experimental evidence was needed to establish a causal relationship, so three randomized controlled trials were commissioned as a means to reduce the effect of any confounding factors.[95] Trials took place in South Africa, Kenya and Uganda.[11] All three trials were stopped early by their monitoring boards on ethical grounds because those in the circumcised group had a lower rate of HIV contraction than the control group.[11] Subsequently, the World Health Organization promoted circumcision in high-risk populations as part of an overall program to reduce the spread of HIV,[12] although some have challenged the validity of the African randomized controlled trials, prompting a number of researchers to question the effectiveness of circumcision as an HIV prevention strategy.[96][97][98][99] The Male Circumcision Clearinghouse website was formed in 2009 by WHO, UNAIDS, FHI and AVAC to provide current evidence-based guidance, information, and resources to support the delivery of safe male circumcision services in countries that choose to scale up the procedure as one component of comprehensive HIV prevention services.[100][101]

# Society and culture

## Cultures and religions

*See also: Religious male circumcision*

In some cultures, males are generally required to be circumcised shortly after birth, during childhood or around puberty as part of a rite of passage. Circumcision is commonly practiced in the Jewish and Islamic faiths.

## Judaism

*Main article: Brit milah*

Circumcision is very important to most branches of Judaism, with over 90% of adherents having the procedure performed as a religious obligation. The basis for its observance is found in the Torah of the Hebrew Bible, in Genesis chapter 17, in which a covenant of circumcision is made with Abraham and his descendants. Jewish

Preparing for a Jewish ritual circumcision with a Mogen shield (on the table, next to the scalpel)

circumcision is part of the *brit milah* ritual, to be performed by a specialist ritual circumciser (a *mohel*) on the eighth day of a newborn son's life (with certain exceptions for poor health). Jewish law requires that the circumcision leaves the glans bare when the penis is flaccid. Converts to Conservative and Orthodox Judaism must also be circumcised; those who are already circumcised undergo a symbolic circumcision ritual. Circumcision is not required by Judaism for one to be considered Jewish, but some adherents foresee serious negative spiritual consequences if it is neglected.[24][102]

According to traditional Jewish law, in the absence of a grown free Jewish male expert, a woman, a slave, or a child, that has the required skills, is also authorized to perform the circumcision, provided that she or he is Jewish.[103] However, most streams of non-Orthodox Judaism allow female mohels, called *mohalot* (Hebrew: , the plural of *mohelet*, feminine of *mohel*), without restriction. In 1984, Deborah Cohen became the first certified Reform mohelet; she was certified by the Berit Mila program of Reform Judaism.[104]

Some contemporary Jews in the United States choose not to circumcise their sons.[105] They are assisted by a small number of Reform and Reconstructionist rabbis, and have developed a welcoming ceremony that they call the *brit shalom* ("Covenant [of] Peace") for such children, also accepted by Humanistic Judaism.[106][107]

This ceremony of *brit shalom* is not officially approved of by the Reform or Reconstructionist rabbinical organizations, who make the recommendation that male infants should be circumcised, though the issue of converts remains controversial[108][109] and circumcision of converts is not mandatory in either movement.[110]

## Islam

*Main article: Khitan (circumcision)*

Children in Turkey wearing traditional circumcision costumes

Although there is some debate within Islam over whether it is a religious requirement, circumcision (called *khitan*) is practiced nearly universally by Muslim males. Islam bases its practice of circumcision on the Genesis 17 narrative, the same Biblical chapter referred to by Jews. The procedure is not explicitly mentioned in the Quran, however, it is a tradition established by Islam's prophet Muhammad directly (following Abraham), and so its practice is considered a *sunnah* (prophet's tradition) and is very important in Islam. For Muslims, circumcision is also a matter of cleanliness, purification and control over one's baser self (*nafs*). There is no agreement across the many Islamic communities about the age at which circumcision should be performed. It may be done from soon after birth up to about age 15; most often it is performed at around six to seven years of age. The timing can correspond with the boy's completion of his recitation of the whole Quran, with a coming-of-age event such as taking on the responsibility of daily prayer or betrothal. Circumcision may be celebrated with an associated family or community event. Circumcision is recommended for, but is not required of, converts to Islam.[26][111][112]

## Christianity

*Main article: Religious male circumcision § In Christianity*

The New Testament chapter Acts 15 records that Christianity does not require circumcision; Christianity does not forbid it either. The Catholic Church currently maintains a neutral position on the practice of non-religious circumcision,[113] although in 1442 it banned the practice of religious circumcision in the 11th Council of Florence.[114] Coptic Christians practice circumcision as a rite of passage.[5][25][115][116] The Ethiopian Orthodox Church calls for circumcision, with near-universal prevalence among Orthodox men in Ethiopia.[5] In South Africa, some Christian churches disapprove of the practice, while others require it of their members.[5]

## African cultures

Certain African cultural groups, such as the Yoruba and Igbo of Nigeria, customarily circumcise their infant sons. The procedure is also practiced by some cultural groups or individual family lines in the Sudan, Zaire, Uganda and in southern Africa. For some of these groups, circumcision appears to be purely cultural, done with no particular religious significance or intention to distinguish members of a group. For others, circumcision might be done for purification, or it may be interpreted as a mark of subjugation. Among these groups, even when circumcision is done for reasons of tradition, it is often done in hospitals.[117] It is not clear how many deaths and injuries result from traditional circumcisions which occur outside of hospitals.[118]

## Australian cultures

Some Australian Aborigines use circumcision as a test of bravery and self-control as a part of a rite of passage into manhood, which results in full societal and ceremonial membership. It may be accompanied by body scarification and the removal of teeth, and may be followed later by penile subincision. Circumcision is one of many trials and ceremonies required before a youth is considered to have become knowledgeable enough to maintain and pass on the cultural traditions. During these trials, the maturing youth bonds in solidarity with the men. Circumcision is also strongly associated with a man's family, and it is part of the process required to prepare a man to take a wife and produce his own family.[117]

## Filipino culture

In the Philippines, circumcision known as "tuli" is sometimes viewed as a rite of passage.[119] About 93% of Filipino men are circumcised.[119]

## Ethical and legal issues

*Main article: Ethics of circumcision*
*See also: Circumcision controversies and Circumcision and law*

There is a long-running and vigorous debate over ethical concerns regarding circumcision, particularly neonatal circumcision for reasons other than intended direct medical benefit. There are three parties involved in the decision to circumcise a minor: the minor as the patient, the parents (or other guardians) and the physician. The physician is bound under the ethical principles of beneficence (promoting well-being) and non-maleficence ("first, do no harm"), and so is charged with the responsibility to promote the best interests of the patient while minimizing unnecessary harms. Those involved must weigh the factors of what is in the best interest of the minor against the potential harms of the procedure.[9]

A protest against infant circumcision

With a newborn involved, the decision is made more complex due to the principles of respect for autonomy and consent, as a newborn cannot understand or engage in a logical discussion of his own values and best interests.[8][9] A mentally more mature child can understand the issues involved to some degree, and the physician and parents may elicit input

from the child and weigh it appropriately in the decision-making process, although the law may not treat such input as legally informative.
Ethicists and legal theorists also state that it is questionable for parents to make a decision for the child that precludes the child from making a different decision for himself later. Such a question can be raised for the decision by the parents either to circumcise or not to circumcise the child.[9]

Generally, circumcision on a minor is not ethically controversial or legally questionable when there is a clear and pressing medical indication for which it is the accepted best practice to resolve. Where circumcision is the chosen intervention, the physician has an ethical responsibility to ensure the procedure is performed competently and safely to minimize potential harms.[8][9] Worldwide, most legal jurisdictions do not have specific laws concerning the circumcision of males,[5] but infant circumcision is considered legal under the existing laws in countries such as Australia, Canada, New Zealand, the United Kingdom, and the United States.[120] A few countries have passed legislation on the procedure: Germany allows non-therapeutic circumcision,[121] while non-religious routine circumcision is illegal in South Africa and Sweden.[5][120]

Throughout society, circumcision is often considered for reasons other than medical need. Public health advocates of circumcision consider it to have a net benefit, and therefore feel that increasing the circumcision rate is an ethical imperative. They recommend performing the procedure during the neonatal period when it is less expensive and has a lower risk of complications.[8] While studies show there is a modest epidemiological benefit to circumcision, critics argue that the number of circumcisions that would have to be performed would yield an overall negative public health outcome due to the resulting number of complications or other negative effects (such as pain). Pinto (2012) writes "sober proponents and detractors of circumcision agree that there is no overwhelming medical evidence to support either side."[8] This type of cost-benefit analysis is highly dependent on the kinds and frequencies of health problems in the population under discussion and how circumcision affects those health problems.[9]

Parents are assumed to have the child's best interests in mind. Ethically, it is imperative that the medical practitioner informs the parents about the benefits and risks of the procedure and obtain informed consent before performing it. Practically, however, many parents come to a decision about circumcising the child before he is born, and a discussion of the benefits and risks of the procedure with a physician has not been shown to have a significant effect on the decision. Some parents request to have their newborn or older child circumcised for non-therapeutic reasons, such as the parents' desires to adhere to family tradition, cultural norms or religious beliefs. In considering such a request, the physician may consider (in addition to any potential medical benefits and harms) such non-medical factors in determining the child's best interests and may ethically perform the procedure. Equally, without a clear medical benefit relative to the potential harms, a physician may take the ethical position that non-medical factors do not contribute enough as benefits to outweigh the potential harms and refuse to perform the procedure. Medical organization such as the British Medical Association state that their member physicians are not obliged to perform the procedure in such situations.[8][9]

The German Academy for Pediatric and Adolescent Medicine (Deutsche Akademie für Kinder- und Jugendmedizin e.V., DAKJ) recommend against routine non-medical infant circumcision.[122]

## Economic considerations

The cost-effectiveness of circumcision has been studied to determine whether a policy of circumcising all newborns or a policy of promoting and providing inexpensive or free access to circumcision for all adult men who choose it would result in lower overall societal healthcare costs. As HIV/AIDS is an incurable disease that is expensive to manage, significant effort has been spent studying the cost-effectiveness of circumcision to reduce its spread in parts of Africa that have a relatively high infection rate and low circumcision prevalence.[123] Several analyses have concluded that circumcision programs for adult men in Africa are cost-effective and in some cases are cost-saving.[37][124] In Rwanda, circumcision has been found to be cost-effective across a wide range of age groups from newborn to adult,[47][125] with the greatest savings achieved when the procedure is performed in the newborn period due to the lower cost per procedure and greater timeframe for HIV infection protection.[15][125] Circumcision for the prevention of HIV transmission in adults has also been found to be cost-effective in South Africa, Kenya, and Uganda,[123]

with cost savings estimated in the billions of US dollars over 20 years. Hankins *et al.* (2011) estimated that a $1.5 billion investment in circumcision for adults in 13 high-priority African countries would yield $16.5 billion in savings.[126]

The overall cost-effectiveness of neonatal circumcision has also been studied in the United States, which has a different cost setting from Africa in areas such as public health infrastructure, availability of medications, and medical technology and the willingness to use it.[127] A study by the CDC suggests that newborn circumcision would be societally cost-effective in the United States based on circumcision's efficacy against the heterosexual transmission of HIV alone, without considering any other cost benefits.[4] The American Academy of Pediatrics (2012) recommends that neonatal circumcision in the United States be covered by third-party payers such as Medicaid and insurance.[4] A 2014 review that considered reported benefits of circumcision such as reduced risks from HIV, HPV, and HSV-2 stated that circumcision is cost-effective in both the United States and Africa and may result in health care savings.[128] However, A 2014 literature review found that there are significant gaps in the current literature on male and female sexual health that need to be addressed for the literature to be applicable to North American populations.[129]

# References


1. ^ *a b c d e f g* Lissauer T, Clayden G (October 2011). *Illustrated Textbook of Paediatrics, Fourth edition*. Elsevier. pp. 352–353. ISBN 978-0-7234-3565-5.
2. ^ *a b c* Rudolph C, Rudolph A, Lister G, First L, Gershon A (18 March 2011). *Rudolph's Pediatrics, 22nd Edition*. McGraw-Hill Companies, Incorporated. p. 188. ISBN 978-0-07-149723-7.
3. **^** Sawyer S (November 2011). *Pediatric Physical Examination & Health Assessment*. Jones & Bartlett Publishers. pp. 555–556. ISBN 978-1-4496-7600-1.
4. ^ *a b c d e f g h i j k l m n o p q r s t u v w x* American Academy of Pediatrics Task Force on Circumcision (2012). "Technical Report". *Pediatrics*. **130** (3): e756–e785. doi:10.1542/peds.2012-1990. ISSN 0031-4005. PMID 22926175.
5. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad* "Male circumcision: Global trends and determinants of prevalence, safety and acceptability" (PDF). World Health Organization. 2007.
6. ^ *a b c d e f g h* Hay W, Levin M (25 June 2012). *Current Diagnosis and Treatment Pediatrics 21/E*. McGraw Hill Professional. pp. 18–19. ISBN 978-0-07-177971-5.
7. ^ *a b c d* Jacobs, Micah; Grady, Richard; Bolnick, David A. (2012). "Current Circumcision Trends and Guidelines". In Bolnick, David A.; Koyle, Martin; Yosha, Assaf. *Surgical Guide to Circumcision*. London: Springer. pp. 3–8. doi:10.1007/978-1-4471-2858-8_1. ISBN 978-1-4471-2857-1. Retrieved April 6, 2014. (subscription required (help)).
8. ^ *a b c d e f* Pinto K (August 2012). "Circumcision controversies". *Pediatric clinics of North America*. **59** (4): 977–986. doi:10.1016/j.pcl.2012.05.015. PMID 22857844.
9. ^ *a b c d e f g* Caga-anan EC, Thomas AJ, Diekema DS, Mercurio MR, Adam MR (8 September 2011). *Clinical Ethics in Pediatrics: A Case-Based Textbook*. Cambridge University Press. p. 43. ISBN 978-0-521-17361-2.
10. ^ *a b* Krieger JN (May 2011). "Male circumcision and HIV infection risk". *World Journal of Urology*. **30** (1): 3–13. doi:10.1007/s00345-011-0696-x. PMID 21590467.
11. ^ *a b c d e* Siegfried N, Muller M, Deeks JJ, Volmink J; Muller; Deeks; Volmink (2009). Siegfried, Nandi, ed. "Male circumcision for prevention of heterosexual acquisition of HIV in men". *Cochrane Database of Systematic Reviews* (2): CD003362. doi:10.1002/14651858.CD003362.pub2. PMID 19370585.
12. ^ *a b c d e f* "WHO and UNAIDS announce recommendations from expert consultation on male circumcision for HIV prevention". World Health Organization. March 2007.
13. ^ *a b* Millett GA, Flores SA, Marks G, Reed JB, Herbst JH (October 2008). "Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis". *JAMA*. **300** (14): 1674–84. doi:10.1001/jama.300.14.1674. PMID 18840841.
14. ^ *a b* Wiysonge CS, Kongnyuy EJ, Shey M; et al. (2011). Wiysonge, Charles Shey, ed. "Male circumcision for prevention of homosexual acquisition of HIV in men". *Cochrane Database of Systematic Reviews* (6): CD007496. doi:10.1002/14651858.CD007496.pub2. PMID 21678366.
15. ^ *a b c* Kim H, Li PS, Goldstein M, Howard H; Li, Philip S; Goldstein, Marc (November 2010). "Male circumcision: Africa and beyond?". *Current Opinion in Urology*. **20** (6): 515–9. doi:10.1097/MOU.0b013e32833f1b21.

PMID 20844437.
16. ^ a b c d Larke N, Thomas SL, Dos Santos Silva I, Weiss HA (November 2011). "Male circumcision and human papillomavirus infection in men: a systematic review and meta-analysis". *J. Infect. Dis.* **204** (9): 1375–90. doi:10.1093/infdis/jir523. PMID 21965090.
17. ^ a b c d e f Rehmeyer C, CJ (2011). "Male Circumcision and Human Papillomavirus Studies Reviewed by Infection Stage and Virus Type". *J Am Osteopath Assoc.* **111** (3 suppl 2): S11–S18. PMID 21415373.
18. ^ a b "Can penile cancer be prevented?". *Learn About Cancer: Penile Cancer: Detailed Guide*. American Cancer Society. Retrieved 2012-10-25.
19. ^ a b c d e f Weiss HA, Larke N, Halperin D, Schenker I; Larke; Halperin; Schenker (2010). "Complications of circumcision in male neonates, infants and children: a systematic review". *BMC Urol.* **10**: 2. doi:10.1186/1471-2490-10-2. PMC 2835667. PMID 20158883.
20. ^ a b The American Academy of Pediatrics Task Force on Circumcision "Technical Report" (2012) addresses sexual function, sensitivity and satisfaction without qualification by age of circumcision. Sadeghi-Nejad *et al.* "Sexually transmitted diseases and sexual function" (2010) addresses adult circumcision and sexual function. Doyle *et al.* "The Impact of Male Circumcision on HIV Transmission" (2010) addresses adult circumcision and sexual function. Perera *et al.* "Safety and efficacy of nontherapeutic male circumcision: a systematic review" (2010) addresses adult circumcision and sexual function and satisfaction.
21. ^ a b Morris, BJ; Krieger, JN (November 2013). "Does male circumcision affect sexual function, sensitivity, or satisfaction?--a systematic review.". *The Journal of Sexual Medicine*. **10** (11): 2644–57. doi:10.1111/jsm.12293. PMID 23937309.
22. ^ "Neonatal and child male circumcision: a global review" (PDF). World Health Organization. 2010. Retrieved 2015-04-12.
23. ^ a b c d e f g h Alanis MC, Lucidi RS (May 2004). "Neonatal circumcision: a review of the world's oldest and most controversial operation". *Obstet Gynecol Surv*. **59** (5): 379–95. doi:10.1097/00006254-200405000-00026. PMID 15097799.
24. ^ a b Glass JM (January 1999). "Religious circumcision: a Jewish view". *BJUI*. 83 Suppl 1: 17–21. doi:10.1046/j.1464-410x.1999.0830s1017.x. PMID 10349410.
25. ^ a b "Circumcision". *Columbia Encyclopedia*. Columbia University Press. 2011.
26. ^ a b Clark M (10 March 2011). *Islam For Dummies*. John Wiley & Sons. p. 170. ISBN 978-1-118-05396-6.
27. ^ "Referat bestyrelsesmøde den 16. december 2013". Retrieved 4 September 2016.
28. ^ Marrazzo, JM; del Rio, C; Holtgrave, DR; Cohen, MS; Kalichman, SC; Mayer, KH; Montaner, JS; Wheeler, DP; Grant, RM; Grinsztejn, B; Kumarasamy, N; Shoptaw, S; Walensky, RP; Dabis, F; Sugarman, J; Benson, CA; International Antiviral Society-USA, Panel (Jul 23–30, 2014). "HIV prevention in clinical care settings: 2014 recommendations of the International Antiviral Society-USA Panel". *JAMA: The Journal of the American Medical Association*. **312** (4): 390–409. doi:10.1001/jama.2014.7999. PMID 25038358.
29. ^ a b c "Manual for male circumcision under local anaesthesia". World Health Organization. December 2009.
30. ^ McClung, Chris; Voelzke, Bryan (2012). "Adult Circumcision". In Bolnick, David A.; Koyle, Martin; Yosha, Assaf. *Surgical Guide to Circumcision*. London: Springer. pp. 165–175. doi:10.1007/978-1-4471-2858-8_14. ISBN 978-1-4471-2857-1. Retrieved April 6, 2014. (subscription required (help)).
31. ^ "Use of devices for adult male circumcision in public health HIV prevention programmes: Conclusions of the Technical Advisory Group on Innovations in Male Circumcision" (PDF). World Health Organization. 2012.
32. ^ a b Perera CL, Bridgewater FH, Thavaneswaran P, Maddern GJ; Bridgewater; Thavaneswaran; Maddern (2010). "Safety and efficacy of nontherapeutic male circumcision: a systematic review". *Annals of Family Medicine*. **8** (1): 64–72. doi:10.1370/afm.1073. PMC 2807391. PMID 20065281.
33. ^ "Professional Standards and Guidelines – Circumcision (Infant Male)". College of Physicians and Surgeons of British Columbia. September 2009.
34. ^ a b Lonnqvist P (Sep 2010). "Regional anaesthesia and analgesia in the neonate". *Best Pract Res Clin Anaesthesiol*. **24** (3): 309–21. doi:10.1016/j.bpa.2010.02.012. PMID 21033009.
35. ^ a b c d Shockley RA, Rickett K; Rickett (April 2011). "Clinical inquiries. What's the best way to control circumcision pain in newborns?". *J Fam Pract*. **60** (4): 233a–b. PMID 21472156.
36. ^ Wolter C, Dmochowski R (2008). "Circumcision". *Handbook of Office Urological Procedures*. Springer. pp. 88–. ISBN 978-1-84628-523-3.
37. ^ a b Uthman OA, Popoola TA, Uthman MM, Aremu O; Popoola; Uthman; Aremu (2010). Van Baal, Pieter H. M, ed. "Economic evaluations of adult male circumcision for prevention of heterosexual acquisition of HIV in men in sub-Saharan Africa: a systematic review". *PLoS ONE*. **5** (3): e9628. doi:10.1371/journal.pone.0009628. PMC 2835757. PMID 20224784.

38. ^ Weiss HA, Dickson KE, Agot K, Hankins CA; Dickson; Agot; Hankins (2010). "Male circumcision for HIV prevention: current research and programmatic issues". *AIDS*. 24 Suppl 4: S61–9. doi:10.1097/01.aids.0000390708.66136.f4. PMID 21042054.
39. ^ a b "New Data on Male Circumcision and HIV Prevention: Policy and Programme Implications" (PDF). World Health Organization. March 28, 2007.
40. ^ Dinh MH; Fahrbach KM; Hope TJ (March 2011). "The role of the foreskin in male circumcision: an evidence-based review". *Am J Reprod Immunol*. **65** (3): 279–83. doi:10.1111/j.1600-0897.2010.00934.x. PMC 3091617. PMID 21114567.
41. ^ Lei, JH; Liu, LR; Wei, Q; Yan, SB; Yang, L; Song, TR; Yuan, HC; Lv, X; Han, P (5 May 2015). "Circumcision Status and Risk of HIV Acquisition during Heterosexual Intercourse for Both Males and Females: A Meta-Analysis.". *PLOS ONE*. **10** (5): e0125436. doi:10.1371/journal.pone.0125436. PMC 4420461. PMID 25942703.
42. ^ "Male Circumcision and Risk for HIV Transmission and Other Health Conditions: Implications for the United States". Centers for Disease Control and Prevention. 7 February 2008. Retrieved 15 July 2011.
43. ^ a b c Templeton DJ, Millett GA, Grulich AE; Millett; Grulich (February 2010). "Male circumcision to reduce the risk of HIV and sexually transmitted infections among men who have sex with men". *Current Opinion in Infectious Diseases*. **23** (1): 45–52. doi:10.1097/QCO.0b013e328334e54d. PMID 19935420.
44. ^ "STD facts – Human papillomavirus (HPV)". CDC. Retrieved September 12, 2012.
45. ^ See: Larke *et al.* "Male circumcision and human papillomavirus infection in men: a systematic review and meta-analysis" (2011), Albero *et al.* "Male Circumcision and Genital Human Papillomavirus: A Systematic Review and Meta-Analysis" (2012), Rehmeyer "Male Circumcision and Human Papillomavirus Studies Reviewed by Infection Stage and Virus Type" (2011).
46. ^ a b Zhu, YP; Jia, ZW; Dai, B; Ye, DW; Kong, YY; Chang, K; Wang, Y (8 March 2016). "Relationship between circumcision and human papillomavirus infection: a systematic review and meta-analysis.". *Asian journal of andrology*. doi:10.4103/1008-682X.175092. PMID 26975489.
47. ^ a b c Albero G, Castellsagué X, Giuliano AR, Bosch FX (February 2012). "Male Circumcision and Genital Human Papillomavirus: A Systematic Review and Meta-Analysis". *Sex Transm Dis*. **39** (2): 104–113. doi:10.1097/OLQ.0b013e3182387abd. PMID 22249298.
48. ^ Weiss, HA; Thomas, SL; Munabi, SK; Hayes, RJ (April 2006). "Male circumcision and risk of syphilis, chancroid, and genital herpes: a systematic review and meta analysis". *Sexually Transmitted Infections*. **82** (2): 101–9; discussion 110. doi:10.1136/sti.2005.017442. PMC 2653870. PMID 16581731.
49. ^ a b Wetmore CM, Manhart LE, Wasserheit JN; Manhart; Wasserheit (April 2010). "Randomized controlled trials of interventions to prevent sexually transmitted infections: learning from the past to plan for the future". *Epidemiol Rev*. **32** (1): 121–36. doi:10.1093/epirev/mxq010. PMC 2912604. PMID 20519264.
50. ^ a b c d Hayashi, Y; Kojima, Y; Mizuno, K; Kohri, K (3 February 2011). "Prepuce: phimosis, paraphimosis, and circumcision.". *TheScientificWorldJournal*. **11**: 289–301. doi:10.1100/tsw.2011.31. PMID 21298220.
51. ^ Becker K (January 2011). "Lichen sclerosus in boys". *Dtsch Arztebl Int*. **108** (4): 53–8. doi:10.3238/arztebl.2011.053. PMC 3036008. PMID 21307992.
52. ^ a b Moreno, G; Corbalán, J; Peñaloza, B; Pantoja, T (2 September 2014). "Topical corticosteroids for treating phimosis in boys.". *The Cochrane database of systematic reviews*. **9**: CD008973. doi:10.1002/14651858.CD008973.pub2. PMID 25180668.
53. ^ Celis, S; Reed, F; Murphy, F; Adams, S; Gillick, J; Abdelhafeez, AH; Lopez, PJ (February 2014). "Balanitis xerotica obliterans in children and adolescents: a literature review and clinical series.". *Journal of pediatric urology*. **10** (1): 34–9. doi:10.1016/j.jpurol.2013.09.027. PMID 24295833.
54. ^ Krill, Aaron; Palmer, Lane; Palmer, Jeffrey (2011). "Complications of Circumcision". *ScientificWorldJournal*. **11**: 2458–68. doi:10.1100/2011/373829. PMC 3253617. PMID 22235177.
55. ^ a b c Leber M, Tirumani A (June 8, 2006). "Balanitis". EMedicine. Retrieved 2008-10-14.
56. ^ a b c Osipov V, Acker S (November 2006). "Balanoposthitis". *Reactive and Inflammatory Dermatoses*. EMedicine. Retrieved 2006-11-20.
57. ^ a b Aridogan IA, Izol V, Ilkit M (August 2011). "Superficial fungal infections of the male genitalia: a review". *Crit. Rev. Microbiol.* **37** (3): 237–44. doi:10.3109/1040841X.2011.572862. PMID 21668404.
58. ^ a b c Hayashi Y, Kojima Y, Mizuno K, Kohri K (2011). "Prepuce: phimosis, paraphimosis, and circumcision". *ScientificWorldJournal*. **11**: 289–301. doi:10.1100/tsw.2011.31. PMID 21298220.
59. ^ Morris, Brian J.; Wiswell, Thomas E. (2013). "Circumcision and Lifetime Risk of Urinary Tract Infection: A Systematic Review and Meta-Analysis". *The Journal of Urology*. **189** (6): 2118–2124. doi:10.1016/j.juro.2012.11.114. ISSN 0022-5347. PMID 23201382.
60. ^ VA, Jagannath; Z, Fedorowicz; V, Sud; AK, Verma; S, Hajebrahimi (Nov 14, 2012). "Routine neonatal circumcision

for the prevention of urinary tract infections in infancy" (PDF). *The Cochrane database of systematic reviews*. **11** (11): CD009129. doi:10.1002/14651858.CD009129.pub2. PMID 23152269. Retrieved 30 September 2015.
61. ^ Jagannath VA, Fedorowicz Z, Sud V, Verma AK, Hajebrahimi S (2011). Fedorowicz, Zbys, ed. "Routine neonatal circumcision for the prevention of urinary tract infections in infancy (Protocol)". *Cochrane Database of Systematic Reviews* (5): CD009129. doi:10.1002/14651858.CD009129.
62. ^ *a b c d e* Larke NL, Thomas SL, Dos Santos Silva I, Weiss HA (August 2011). "Male circumcision and penile cancer: a systematic review and meta-analysis". *Cancer Causes Control*. **22** (8): 1097–110. doi:10.1007/s10552-011-9785-9. PMC 3139859. PMID 21695385.
63. ^ Pabalan, N; Singian, E; Jarjanazi, H; Paganini-Hill, A (December 2015). "Association of male circumcision with risk of prostate cancer: a meta-analysis.". *Prostate Cancer and Prostatic Diseases*. **18** (4): 352–7. doi:10.1038/pcan.2015.34. PMID 26215783.
64. ^ *a b* American Urological Association. "Circumcision". Retrieved 2008-11-02.
65. ^ *a b c d* Krill, Aaron J.; Palmer, Lane S.; Palmer, Jeffrey S. (2011). "Complications of Circumcision". *The Scientific World JOURNAL*. **11**: 2458–2468. doi:10.1100/2011/373829. ISSN 1537-744X. PMC 3253617. PMID 22235177.
66. ^ *a b* "Neonatal Circumcision". American Academy of Family Physicians. 2013. Retrieved 2015-08-03.
67. ^ Krill, AJ; Palmer, LS; Palmer, JS (2011). "Complications of circumcision.". *TheScientificWorldJournal*. **11**: 2458–68. doi:10.1100/2011/373829. PMC 3253617. PMID 22235177.
68. ^ Canadian Paediatric Society (Sep 8, 2015). "Newborn male circumcision Position statements and practice points". *Paediatr Child Health*. **20** (6): 311–15.
69. ^ Morris BJ, Waskett JH, Banerjee J, Wamai RG, Tobian AA, Gray RH, Bailis SA, Bailey RC, Klausner JD, Willcourt RJ, Halperin DT, Wiswell TE, Mindel A (2012). "A 'snip' in time: what is the best age to circumcise?". *BMC Pediatr*. **12**: 20. doi:10.1186/1471-2431-12-20. PMC 3359221. PMID 22373281. "Circumcision in adolescence or adulthood may evoke a fear of pain, penile damage or reduced sexual pleasure, even though unfounded."
70. ^ Friedman, B; Khoury, J; Petersiel, N; Yahalomi, T; Paul, M; Neuberger, A (4 August 2016). "Pros and cons of circumcision: an evidence-based overview.". *Clinical Microbiology and Infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. **22**: 768–774. doi:10.1016/j.cmi.2016.07.030. PMID 27497811.
71. ^ Tian Y, Liu W, Wang JZ, Wazir R, Yue X, Wang KJ (2013). "Effects of circumcision on male sexual functions: a systematic review and meta-analysis". *Asian J. Androl.* (Systematic review). **15** (5): 662–6. doi:10.1038/aja.2013.47. PMC 3881635. PMID 23749001.
72. ^ Goldman, R. (Jan 1999). "The psychological impact of circumcision". *BJU International*. **83** (S1): 93–102. doi:10.1046/j.1464-410x.1999.0830s1093.x.
73. ^ Boyle, G. J.; Goldman, R.; Svoboda, J. S.; Fernandez, E. (1 May 2002). "Male Circumcision: Pain, Trauma and Psychosexual Sequelae". *Journal of Health Psychology*. **7** (3): 329–343. doi:10.1177/135910530200700310. PMID 22114254.
74. ^ *a b c d e f g* Doyle D (October 2005). "Ritual male circumcision: a brief history". *The journal of the Royal College of Physicians of Edinburgh*. **35** (3): 279–285. PMID 16402509.
75. ^ Morris, Brian J; Wamai, Richard G; Henebeng, Esther B; Tobian, Aaron AR; Klausner, Jeffrey D; Banerjee, Joya; Hankins, Catherine A (1 March 2016). "Estimation of country-specific and global prevalence of male circumcision". *Population Health Metrics*. **14** (1). doi:10.1186/s12963-016-0073-5.
76. ^ *a b* Drain PK, Halperin DT, Hughes JP, Klausner JD, Bailey RC (2006). "Male circumcision, religion, and infectious diseases: an ecologic analysis of 118 developing countries". *BMC Infectious Diseases*. **6**: 172. doi:10.1186/1471-2334-6-172. PMC 1764746. PMID 17137513.
77. ^ Klavs I, Hamers FF (February 2008). "Male circumcision in Slovenia: results from a national probability sample survey". *Sexually Transmitted Infections*. **84** (1): 49–50. doi:10.1136/sti.2007.027524. PMID 17881413.
78. ^ Ko MC, Liu CK, Lee WK, Jeng HS, Chiang HS, Li CY (April 2007). "Age-specific prevalence rates of phimosis and circumcision in Taiwanese boys". *Journal of the Formosan Medical Association=Taiwan Yi Zhi*. **106** (4): 302–7. doi:10.1016/S0929-6646(09)60256-4. PMID 17475607.
79. ^ Richters J, Smith AM, de Visser RO, Grulich AE, Rissel CE; Smith; De Visser; Grulich; Rissel (August 2006). "Circumcision in Australia: prevalence and effects on sexual health". *Int J STD AIDS*. **17** (8): 547–54. doi:10.1258/095646206778145730. PMID 16925903.
80. ^ *a b c* Owings M, et al. (August 22, 2013). "Trends in Circumcision for Male Newborns in U.S. Hospitals: 1979–2010". Centers for Disease Control and Prevention. Retrieved 22 January 2014.
81. ^ *a b c d e* Gollaher (2001), ch. 1, *The Jewish Tradition*, pp. 1–30
82. ^ McNutt, Paula M. (1999). *Reconstructing the Society of Ancient Israel*. Westminster John Knox Press. ISBN 978-0-664-22265-9.

83. ^ [a] [b] "Circumcision". *Encyclopaedia Judaica* (2 ed.). USA: Macmillan Reference. 2006. ISBN 978-0-02-865928-2.
84. ^ Gollaher (2001), ch. 2, *Christians and Muslims*, pp. 31–52
85. ^ Donald Daniel Leslie (1998). "The Integration of Religious Minorities in China: The Case of Chinese Muslims" (PDF). The Fifty-ninth George Ernest Morrison Lecture in Ethnology. p. 12. Archived from the original (PDF) on 17 December 2010. Retrieved 30 November 2010.
86. ^ Johan Elverskog (2010). *Buddhism and Islam on the Silk Road* (illustrated ed.). University of Pennsylvania Press. p. 228. ISBN 0-8122-4237-8. Retrieved 2010-06-28.
87. ^ Gollaher (2001), ch. 3, *Symbolic Wounds*, pp. 53–72
88. ^ [a] [b] [c] Darby, Robert (Spring 2003). "The Masturbation Taboo and the Rise of Routine Male Circumcision: A Review of the Historiography". *Journal of Social History*. **36** (3): 737–757. doi:10.1353/jsh.2003.0047.
89. ^ [a] [b] [c] Gollaher (2001), ch. 4, *From Ritual to Science*, pp. 73–108
90. ^ Bullough, Vern L.; Bonnie Bullough (1994). *Human Sexuality: An Encyclopedia*. New York: Garland. p. 425. ISBN 0824079728.
91. ^ Conrad, Peter; Joseph W. Schneider (1992). *Deviance and Medicalization: From Badness to Sickness*. Philadelphia: Temple University Press. p. 212. ISBN 0877229996.
92. ^ [a] [b] Darby, Robert (2005). *A surgical temptation : the demonization of the foreskin and the rise of circumcision in Britain*. Chicago: University of Chicago Press. pp. 262–. ISBN 978-0-226-13645-5.
93. ^ Matthew, H. C. G. (2004). *Oxford dictionary of national biography : in association with the British Academy : from the earliest times to the year 2000*. Oxford New York: Oxford University Press. ISBN 978-0-19-861411-1.
94. ^ Gairdner D (1949). "The fate of the foreskin: a study of circumcision." (PDF). *Br Med J*. **2** (4642): 1433–7. doi:10.1136/bmj.2.4642.1433. PMC 2051968. PMID 15408299.
95. ^ Siegfried N, Muller M, Volmink J; et al. (2003). Siegfried, Nandi, ed. "Male circumcision for prevention of heterosexual acquisition of HIV in men". *Cochrane Database of Systematic Reviews* (3): CD003362. doi:10.1002/14651858.CD003362. PMID 12917962.
96. ^ Boyle GJ, Hill G (2011). "Sub-Saharan African randomised clinical trials into male circumcision and HIV transmission: methodological, ethical and legal concerns". *J Law Med*. **19** (2): 316–34. PMID 22320006.
97. ^ Dowsett GW, Couch M (May 2007). "Male circumcision and HIV prevention: is there really enough of the right kind of evidence?". *Reproductive Health Matters*. **15** (29): 33–44. doi:10.1016/S0968-8080(07)29302-4. PMID 17512372.
98. ^ Darby R, Van Howe R (2011). "Not a surgical vaccine: there is no case for boosting infant male circumcision to combat heterosexual transmission of HIV in Australia". *Australian and New Zealand Journal of Public Health*. **35** (5): 459–465. doi:10.1111/j.1753-6405.2011.00761.x. PMID 21973253.
99. ^ Frisch M; et al. (2013). "Cultural Bias in the AAP's 2012 Technical Report and Policy Statement on Male Circumcision". *Pediatrics*. **131** (4): 796–800. doi:10.1542/peds.2012-2896. PMID 23509170.
100. ^ McNeil, Jr., Donald G. (March 3, 2009). "AIDS: New Web Site Seeks to Fight Myths About Circumcision and H.I.V.". *The New York Times*. p. D6. Retrieved February 1, 2012.
101. ^ AVAC: Global Advocacy for HIV Prevention. "About male circumcision". Retrieved 1 December 2012.
102. ^ Bolnick, David A.; Katz, Kenneth E. (2012). "Jewish Ritual Circumcision". In Bolnick, David A.; Koyle, Martin; Yosha, Assaf. *Surgical Guide to Circumcision*. London: Springer. pp. 265–274. doi:10.1007/978-1-4471-2858-8_23. ISBN 978-1-4471-2857-1. Retrieved April 6, 2014. (subscription required (help)).
103. ^ Talmud Avodah Zarah 26b; Menachot 42a; Maimonides' Mishneh Torah, Milah, ii. 1; Shulkhan Arukh, Yoreh De'ah, l.c.
104. ^ Berit Mila Program of Reform Judaism Retrieved 2 February 2015
105. ^ Chernikoff, Helen (October 3, 2007). "Jewish "intactivists" in U.S. stop circumcising". Reuters. Retrieved 2007-11-03.
106. ^ Reiss, MD, Dr. Mark (2006). "Celebrants of Brit Shalom". Brit Shalom. Archived from the original on 2014-12-13. Retrieved 2007-10-03.
107. ^ Goldman, PhD, Ron (2006). "Providers of Brit Shalom". Jews Against Circumcision. Retrieved 2007-10-03.
108. ^ Glickman, Mark (November 12, 2005). "B'rit Milah: A Jewish Answer to Modernity". Union for Reform Judaism. Retrieved 2007-11-03.
109. ^ Cohen, Rabbi Howard (May 20, 2002). "Bo: Defining Boundaries". Jewish Reconstructionist Federation. Archived from the original on October 9, 2007. Retrieved 2007-11-03.
110. ^ Epstein, Lawrence (2007). "The Conversion Process". Calgary Jewish Community Council. Archived from the original on December 27, 2008. Retrieved 2007-11-03.
111. ^ al-Sabbagh, Muhammad Lutfi (1996). *Islamic ruling on male and female circumcision* (PDF). World Health Organization. p. 16. ISBN 92-9021-216-0.
112. ^ El-Sheemy, Mohamed S.; Ziada, Ali M. (2012). "Islam and Circumcision". In Bolnick, David A.; Koyle, Martin; Yosha, Assaf. *Surgical Guide to Circumcision*. London: Springer. pp. 275–280. doi:10.1007/978-1-4471-2858-

8_24. ISBN 978-1-4471-2857-1. Retrieved April 6, 2014. (subscription required (help)).
113. ^ Slosar, J.P.; D. O'Brien (2003). "The Ethics of Neonatal Male Circumcision: A Catholic Perspective". *American Journal of Bioethics*. **3** (2): 62–64. doi:10.1162/152651603766436306. PMID 12859824.
114. ^ Eugenius IV, Pope (1990) [1442]. "Ecumenical Council of Florence (1438–1445): Session 11—4 February 1442; Bull of union with the Copts". In Norman P. Tanner ed. *Decrees of the ecumenical councils*. 2 volumes (in Greek and Latin). Washington, D.C.: Georgetown University Press. ISBN 0-87840-490-2. LCCN 90003209. Retrieved 2007-04-25. "it denounces all who after that time observe circumcision"
115. ^ Thomas Riggs (2006). "Christianity: Coptic Christianity". *Worldmark Encyclopedia of Religious Practices: Religions and denominations*. Thomson Gale. ISBN 978-0-7876-6612-5.
116. ^ Adams, Gregory; Adams, Kristina (2012). "Circumcision in the Early Christian Church: The Controversy That Shaped a Continent". In Bolnick, David A.; Koyle, Martin; Yosha, Assaf. *Surgical Guide to Circumcision*. London: Springer. pp. 291–298. doi:10.1007/978-1-4471-2858-8_26. ISBN 978-1-4471-2857-1. Retrieved April 6, 2014. (subscription required (help)).
117. ^ *a b* "Circumcision". *Encyclopedia of Religion* (2 ed.). Gale. 2005.
118. ^ "The death and deformity caused by male circumcision in Africa can't be ignored". 25 August 2014. Retrieved 13 March 2015.
119. ^ *a b* "Tuli a rite of passage for Filipino boys". May 6, 2011. Retrieved 6 December 2015.
120. ^ *a b* "Circumcision of Infant Males". The Royal Australasian College of Physicians. Sep 2010. Retrieved 11 September 2013.
121. ^ "Circumcision remains legal in Germany". *Deutsche Welle*. 12 Dec 2012. Retrieved 11 September 2013.
122. ^ "Stellungnahme zur Beschneidung von minderjährigen Jungen". *dakj.de*. 25 July 2012. Retrieved 7 June 2016.
123. ^ *a b* Doyle S, Kahn J, Hosang N, Carroll P (2010). "The Impact of Male Circumcision on HIV Transmission". *Journal of Urology*. **183** (1): 21–26. doi:10.1016/j.juro.2009.09.030. PMID 19913816.
124. ^ Grimes, Caris E.; Henry, Jaymie Ang; Maraka, Jane; Mkandawire, Nyengo C.; Cotton, Michael (8 October 2013). "Cost-effectiveness of Surgery in Low- and Middle-income Countries: A Systematic Review". *World Journal of Surgery*. **38** (1): 252–263. doi:10.1007/s00268-013-2243-y.
125. ^ *a b* Binagwaho A, Pegurri E, Muita J, Bertozzi S (Jan 2010). Kalichman, Seth C, ed. "Male circumcision at different ages in Rwanda: a cost-effectiveness study". *Public Library of Science*. **7** (1): e1000211. doi:10.1371/journal.pmed.1000211. PMC 2808207. PMID 20098721.
126. ^ Hankins C, Forsythe S, Njeuhmeli E (Mar 2012). Sansom, Stephanie L, ed. "Voluntary medical male circumcision: an introduction to the cost, impact, and challenges of accelerated scaling up". *Arch Pediatr Adolesc Med*. **8** (11): e1001127. doi:10.1371/journal.pmed.1001127. PMC 3226452. PMID 22140362.
127. ^ Xu X, Patel DA, Dalton VK, Pearlman MD, Johnson TR; Patel; Dalton; Pearlman; Johnson (Mar 2009). "Can routine neonatal circumcision help prevent human immunodeficiency virus transmission in the United States?". *American journal of men's health*. **3** (1): 79–84. doi:10.1177/1557988308323616. PMC 2678848. PMID 19430583.
128. ^ Tobian, AA; Kacker, S; Quinn, TC (2014). "Male circumcision: a globally relevant but under-utilized method for the prevention of HIV and other sexually transmitted infections.". *Annual Review of Medicine*. **65**: 293–306. doi:10.1146/annurev-med-092412-090539. PMID 24111891.
129. ^ Bossio JA, Pukall CF, Steele S (2014). "A review of the current state of the male circumcision literature.". *J Sex Med*. **11** (12): 2847–64. doi:10.1111/jsm.12703. PMID 25284631.

# Bibliography


- Bolnick DA, Koyle M, Yosha A (September 2012). *Surgical Guide to Circumcision*. Springer. ISBN 978-1-4471-2857-1.
- Gollaher D (February 2001). *Circumcision: A History Of The World's Most Controversial Surgery*. Basic Books. ISBN 978-0-465-02653-1.


# External links

- Videos of infant circumcision: using a Plastibell, a Gomco clamp and a Mogen clamp (all from Stanford Medical School)
- A Xhosa circumcision from National Geographic

Wikinews has news related to: *Circumcision*

Wikimedia Commons has media related to

*Circumcision*.

| v · t · e · | **Circumcision** | |
|---|---|---|
| **Medical aspects** | HIV · Surgical procedure · | |
| **History and prevalence** | History · Prevalence · | |
| **Religious aspects** | Male · Early Christianity · Judaism · Islam · Jesus · | |
| **Ethical and legal aspects** | Controversies · Ethics · Forced · Law · | |
| **Category** | Circumcision · | |

| v · t · e · | **Male genital surgical and other procedures: reproductive system (ICD-9-CM V3 60–64, ICD-10-PCS 0V)** | |
|---|---|---|
| **Internal** | **Prostate** | Transurethral incision of the prostate · Prostate biopsy (Transrectal biopsy · Transurethral biopsy · · Prostatectomy (Transurethral resection of the prostate · Radical retropubic prostatectomy · · Transurethral microwave thermotherapy · Transurethral needle ablation of the prostate · Brachytherapy (Prostate brachytherapy · · Prostate massage · |
| | **seminal vesicles:** | Spermatocelectomy · |
| | **Vas deferens** | Vasectomy · Vasectomy reversal (Vasovasostomy · Vasoepididymostomy · · |
| | **Testes** | Orchiectomy (Castration · · Orchiopexy · |
| **External** | **Penis** | **Circumcision** · Penectomy · Penile prosthesis · Preputioplasty · Penile plethysmograph · Postage stamp test · Frenuloplasty of prepuce of penis · |
| **Tests** | Semen analysis · | |
| | **Medical imaging** | Transscrotal ultrasound · |
| **Authority control** | GND: 4144874-1 · NDL: 00565234 · | |

Categories: Circumcision | Cosmetic surgery | Prevention of HIV/AIDS | Religion and children | Childhood genital surgery




# Cleft lip and cleft palate

From Wikipedia, the free encyclopedia
(Redirected from Cleft lip and palate)

**Cleft lip and cleft palate**, also known as **orofacial cleft**, is a group of conditions that includes cleft lip (CL), cleft palate (CP), and both together (CLP).[1][2] A cleft lip contains an opening in the upper lip that may extend into the nose. The opening may be on one side, both sides, or in the middle. A cleft palate is when the roof of the mouth contains an opening into the nose. These disorders can result in feeding problems, speech problems, hearing problems, and frequent ear infections. Less than half the time the condition is associated with other disorders.[1]

Cleft lip and palate are the result of tissues of the face not joining properly during development. As such, they are a type of birth defect. The cause is unknown in most cases.[1] Risk factors include smoking during pregnancy, diabetes, obesity, an older mother, and certain medications (such as some used to treat seizures).[1][2] Cleft lip and cleft palate can often be diagnosed during pregnancy with an ultrasound exam.[1]

A cleft lip or palate can be successfully treated with surgery. This is often done in the first few months of life for cleft lip and before eighteen months for cleft palate. Speech therapy and dental care may also be needed. With appropriate treatment outcomes are good.[1]

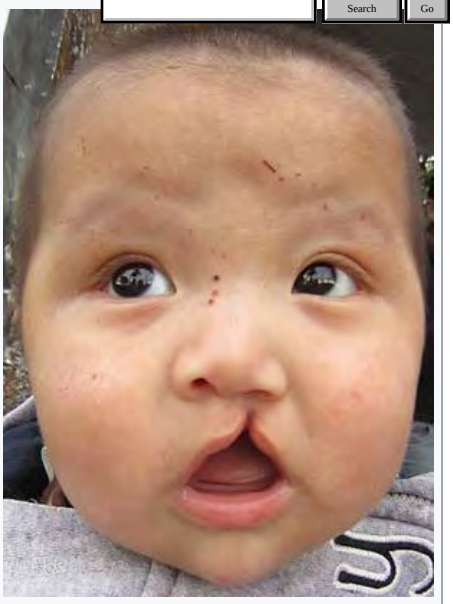
Cleft lip and palate occurs in about 1 to 2 per 1000 births in the developed world.[2] CL is about twice as common in males as females, while CP without CL is more common in females.[2] In 2013 it resulted in about 3,300 deaths globally down from 7,600 deaths in 1990.[3] The condition was formerly known as a **hare lip** because of its resemblance to a hare or rabbit, but that term is now generally considered to be offensive.[4]

**Contents**



**Cleft lip and palate**

**Synonyms** hare-lip, cleft lip and palate



Child with cleft lip and palate.

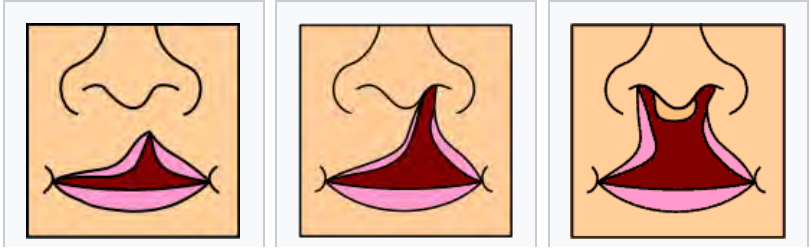
**Classification and external resources**

| | |
|---|---|
| **Specialty** | Otorhinolaryngology, pediatrics |
| **ICD-10** | Q35-Q37 |
| **ICD-9-CM** | 749 |
| **DiseasesDB** | 29604 29414 |
| **MedlinePlus** | 001051 |
| **eMedicine** | ped/2679 |

[edit on Wikidata]

## Signs and symptoms

If the cleft does not affect the palate structure of the mouth it is referred to as cleft lip. Cleft lip is formed in the top of the lip as either a small gap or an indentation in the lip (partial or incomplete cleft) or it continues into the nose (complete cleft). Lip cleft can occur as a one sided (unilateral) or two sided (bilateral). It is due to the failure of fusion of the maxillary and medial nasal processes (formation of the primary palate).



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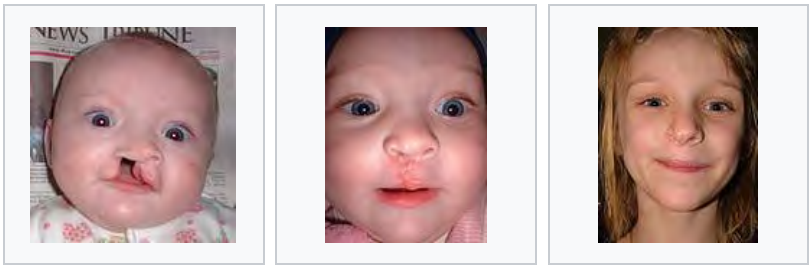
Edit links



Unilateral incomplete | Unilateral complete | Bilateral complete

A mild form of a cleft lip is a microform cleft.[5] A microform cleft can appear as small as a little dent in the red part of the lip or look like a scar from the lip up to the nostril.[6] In some cases muscle tissue in the lip underneath the scar is affected and might require reconstructive surgery.[7] It is advised to have newborn infants with a microform cleft checked with a craniofacial team as soon as possible to determine the severity of the cleft.[8]



Six-month-old girl before going into surgery to have her unilateral complete cleft lip repaired | The same girl, 1 month after the surgery | The same girl, age 8, the scar almost gone

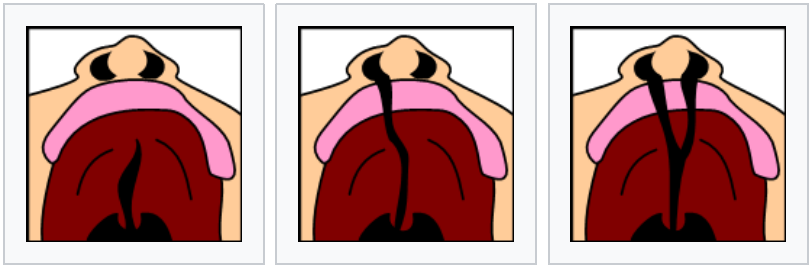
## Cleft palate

Cleft palate is a condition in which the two plates of the skull that form the hard palate (roof of the mouth) are not completely joined. The soft palate is in these cases cleft as well. In most cases, cleft lip is also present. Cleft palate occurs in about one in 700 live births worldwide.[9]

Palate cleft can occur as complete (soft and hard palate, possibly including a gap in the jaw) or incomplete (a 'hole' in the roof of the mouth, usually as a cleft soft palate). When cleft palate occurs, the uvula is usually split. It occurs due to the failure of fusion of the lateral palatine processes, the nasal septum, and/or the median palatine processes (formation of the secondary palate).

The hole in the roof of the mouth caused by a cleft connects the mouth directly to the inside of the nose.

Note: the next images show the roof of the mouth. The top shows the nose, the lips are colored pink. For clarity the images depict a toothless infant.



Incomplete cleft palate | Unilateral complete lip and palate | Bilateral complete lip and palate

A result of an open connection between the mouth and inside the nose is called velopharyngeal inadequacy (VPI). Because of the gap, air leaks into the nasal cavity resulting in a hypernasal voice resonance and nasal emissions while talking.[10] Secondary effects of VPI include speech articulation errors (e.g., distortions, substitutions, and omissions) and compensatory misarticulations and mispronunciations (e.g., glottal stops and posterior nasal fricatives).[11] Possible treatment options include speech therapy, prosthetics, augmentation of the posterior pharyngeal wall, lengthening of the palate, and surgical procedures.[10]

Submucous cleft palate (SMCP) can also occur, which is a cleft of the soft palate with a classic clinical triad of a bifid, or split, uvula which is found dangling in the back of the throat, a furrow along the midline of the soft palate, and a notch in the back margin of the hard palate.[12]

## Psychosocial issues

Most children who have their clefts repaired early enough are able to have a happy youth and social life.[*citation needed*] Having a cleft palate/lip does not inevitably lead to a psychosocial problem.[*citation needed*] However, adolescents with cleft palate/lip are at an elevated risk for developing psychosocial problems especially those relating to self-concept, peer relationships and appearance. Adolescents may face psychosocial challenges but can find professional help if problems arise.[*citation needed*] A cleft palate/lip may impact an individual's self-esteem, social skills and behavior. There is research dedicated to the psychosocial development of individuals with cleft palate. Self-concept may be adversely affected by the presence of a cleft lip and/or cleft palate, particularly among girls.[13]

Research has shown that during the early preschool years (ages 3–5), children with cleft lip and/or cleft palate tend to have a self-concept that is similar to their peers without a cleft. However, as they grow older and their social interactions increase, children with clefts tend to report more dissatisfaction with peer relationships and higher levels of social anxiety. Experts conclude that this is probably due to the associated stigma of visible deformities and possible speech impediments. Children who are judged as attractive tend to be perceived as more intelligent, exhibit more positive social behaviors, and are treated more positively than children with cleft lip and/or cleft palate.[14] Children with clefts tend to report feelings of anger, sadness, fear, and alienation from their peers, but these children were similar to their peers in regard to "how well they liked themselves."

The relationship between parental attitudes and a child's self-concept is crucial during the preschool years. It has been reported that elevated stress levels in mothers correlated with reduced social skills in their children.[15] Strong parent support networks may help to prevent the development of negative self-concept in children with cleft palate.[16] In the later preschool and early elementary years, the development of social skills is no longer only impacted by parental attitudes but is beginning to be shaped by their peers. A cleft lip and/or cleft palate may affect the behavior of preschoolers.

Experts suggest that parents discuss with their children ways to handle negative social situations related to their cleft lip and/or cleft palate. A child who is entering school should learn the proper (and age-appropriate) terms related to the cleft. The ability to confidently explain the condition to others may limit feelings of awkwardness and embarrassment and reduce negative social experiences.[17]

As children reach adolescence, the period of time between age 13 and 19, the dynamics of the parent-child relationship change as peer groups are now the focus of attention. An adolescent with cleft lip and/or cleft palate will deal with the typical challenges faced by most of their peers including issues related to self-esteem, dating and social acceptance.[18][19][20] Adolescents, however, view appearance as the most important characteristic above intelligence and humor.[21] This being the case, adolescents are susceptible to additional problems because they cannot hide their facial differences from their peers. Adolescent boys typically deal with issues relating to withdrawal, attention, thought, and internalizing problems and may possibly develop anxiousness-depression and aggressive behaviors.[20] Adolescent girls are more likely to develop problems relating to self-concept and appearance. Individuals with cleft lip and/or cleft palate often deal with threats to their quality of life for multiple reasons including: unsuccessful social relationships, deviance in social appearance and multiple surgeries.

### Complications

Cleft may cause problems with feeding, ear disease, speech and socialization.

Due to lack of suction, an infant with a cleft may have trouble feeding. An infant with a cleft palate will have greater success feeding in a more upright position. Gravity will help prevent milk from coming through the baby's nose if he/she has cleft palate. Gravity feeding can be accomplished by using specialized equipment, such as the Haberman Feeder, or by using a combination of nipples and bottle inserts like the one shown, is commonly used with other infants. A large hole, crosscut, or slit in the nipple, a protruding nipple and rhythmically squeezing the bottle insert can result in controllable flow to the infant without the stigma caused by specialized equipment.

Individuals with cleft also face many middle ear infections which may eventually lead to hearing loss. The Eustachian tubes and external ear canals may be angled or tortuous, leading to food or other contamination of a part of the body that is normally self-cleaning. Hearing is related to learning to speak. Babies with palatal clefts may have compromised hearing and therefore, if the baby cannot hear, it cannot try to mimic the sounds of speech. Thus, even before expressive language acquisition, the baby with the cleft palate is at risk for receptive language acquisition. Because the lips and palate are both used in pronunciation, individuals with cleft usually need the aid of a speech therapist.

A baby being fed using a customized bottle. The upright sitting position allows gravity to help the baby swallow the milk more easily

## Cause

The development of the face is coordinated by complex morphogenetic events and rapid proliferative expansion, and is thus highly susceptible to environmental and genetic factors, rationalising the high incidence of facial malformations. During the first six to eight weeks of pregnancy, the shape of the embryo's head is formed. Five primitive tissue lobes grow:

**a)** one from the top of the head down towards the future upper lip; (Frontonasal Prominence)
**b-c)** two from the cheeks, which meet the first lobe to form the upper lip; (Maxillar Prominence)
**d-e)** and just below, two additional lobes grow from each side, which form the chin and lower lip; (Mandibular Prominence)

If these tissues fail to meet, a gap appears where the tissues should have joined (fused). This may happen in any single joining site, or simultaneously in several or all of them. The resulting birth defect reflects the locations and severity of individual fusion failures (e.g., from a small lip or palate fissure up to a completely malformed face).

The upper lip is formed earlier than the palate, from the first three lobes named a to c above. Formation of the palate is the last step in joining the five embryonic facial lobes, and involves the back portions of the lobes b and c. These back portions are called palatal shelves, which grow towards each other until they fuse in the middle.[22] This process is very vulnerable to multiple toxic substances, environmental pollutants, and nutritional imbalance. The biologic mechanisms of mutual recognition of the two cabinets, and the way they are glued together, are quite complex and obscure despite intensive scientific research.[23]

### Genetics

Genetic factors contributing to cleft lip and cleft palate formation have been identified for some syndromic cases, but knowledge about genetic factors that contribute to the more common isolated cases of cleft lip/palate is still patchy.

Many clefts run in families, even though in some cases there does not seem to be an identifiable syndrome present,[24] possibly because of the current incomplete genetic understanding of midfacial development.

A number of genes are involved including cleft lip and palate transmembrane protein 1 and GAD1,[25] one of the glutamate decarboxylases. Many genes are known to play a role in craniofacial development and are being studied through the FaceBase initiative for their part in clefting. These genes are AXIN2, BMP4, FGFR1, FGFR2, FOXE1, IRF6, MAFB (gene), MMP3, MSX1, MSX2 (Msh homeobox 2), MSX3, PAX7, PDGFC, PTCH1, SATB2, SOX9, SUMO1 (Small ubiquitin-related modifier 1), TBX22, TCOF (Treacle protein), TFAP2A, VAX1, TP63, ARHGAP29, NOG, NTN1, WNT genes, and locus 8q24.[26]

### Syndromes

- The Van der Woude Syndrome is caused by a specific variation in the gene *IRF6* that increases the occurrence of these deformities threefold.[27][28][29]
- Another syndrome, Siderius X-linked mental retardation, is caused by mutations in the *PHF8* gene (OMIM 300263); in addition to cleft lip and/or palate, symptoms include facial dysmorphism and mild mental retardation.[30]

In some cases, cleft palate is caused by syndromes which also cause other problems.

- Stickler's Syndrome can cause cleft lip and palate, joint pain, and myopia.[31][32]
- Loeys-Dietz syndrome can cause cleft palate or bifid uvula, hypertelorism, and aortic aneurysm.[33]
- Hardikar syndrome can cause cleft lip and palate, Hydronephrosis, Intestinal obstruction and other symptoms.[34]
- Cleft lip/palate may be present in many different chromosome disorders including Patau Syndrome (trisomy 13).
- Malpuech facial clefting syndrome
- Hearing loss with craniofacial syndromes

- Popliteal pterygium syndrome
- Treacher Collins Syndrome

### Specific genes

Many genes associated with syndromic cases of cleft lip/palate (see above) have been identified to contribute to the incidence of isolated cases of cleft lip/palate. This includes in particular sequence variants in the genes *IRF6*, *PVRL1* and *MSX1*.[35] The understanding of the genetic complexities involved in the morphogenesis of the midface, including molecular and cellular processes, has been greatly aided by research on animal models, including of the genes *BMP4*, *SHH*, *SHOX2*, *FGF10* and *MSX1*.[35]

| Type | OMIM | Gene | Locus |
|---|---|---|---|
| OFC1 | 119530 | ? | 6p24 |
| OFC2 | 602966 | ? | 2p13 |
| OFC3 | 600757 | ? | 19q13 |
| OFC4 | 608371 | ? | 4q |
| OFC5 | 608874 | *MSX1* | 4p16.1 |
| OFC6 | 608864 | ? | 1q |
| OFC7 | 600644) | *PVRL1* | 11q |
| OFC8 | 129400 | *TP63* | 3q27 |
| OFC9 | 610361 | ? | 13q33.1-q34 |
| OFC10 | 601912 | *SUMO1* | 2q32.2-q33 |
| OFC11 | 600625 | *BMP4* | 14q22 |
| OFC12 | 612858 | ? | 8q24.3 |

### Environmental factors

Environmental influences may also cause, or interact with genetics to produce, orofacial clefting. An example of how environmental factors might be linked to genetics comes from research on mutations in the gene *PHF8* that cause cleft lip/palate (see above). It was found that *PHF8* encodes for a histone lysine demethylase,[36] and is involved in epigenetic regulation. The catalytic activity of PHF8 depends on molecular oxygen,[36] a fact considered important with respect to reports on increased incidence of cleft lip/palate in mice that have been exposed to hypoxia early during pregnancy.[37] In humans, fetal cleft lip and other congenital abnormalities have also been linked to maternal hypoxia, as caused by e.g. maternal smoking,[38] maternal alcohol abuse or some forms of maternal hypertension treatment.[39] Other environmental factors that have been studied include: seasonal causes (such as pesticide exposure); maternal diet and vitamin intake; retinoids — which are members of the vitamin A family; anticonvulsant drugs; nitrate compounds; organic solvents; parental exposure to lead; alcohol; cigarette use; and a number of other psychoactive drugs (e.g. cocaine, crack cocaine, heroin).

Current research continues to investigate the extent to which folic acid can reduce the incidence of clefting.[40]

## Diagnosis

Traditionally, the diagnosis is made at the time of birth by physical examination. Recent advances in prenatal diagnosis have allowed obstetricians to diagnose facial clefts in utero with ultrasonography.[41]

Clefts can also affect other parts of the face, such as the eyes, ears, nose, cheeks, and forehead. In 1976, Paul Tessier described fifteen lines of cleft. Most of these craniofacial clefts are even rarer and are frequently described as Tessier clefts using the numerical locator devised by Tessier.[42]

## Treatment

Cleft lip and palate is very treatable; however, the kind of treatment depends on the type and severity of the cleft.

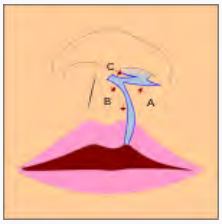
Most children with a form of clefting are monitored by a *cleft palate team* or *craniofacial team* through young adulthood.[43] Care can be lifelong. Treatment procedures can vary between craniofacial teams. For example, some teams wait on jaw correction until the child is aged 10 to 12 (argument: growth is less influential as deciduous teeth are replaced by permanent teeth, thus saving the child from repeated corrective surgeries), while other teams correct the jaw earlier (argument: less speech therapy is needed than at a later age when speech therapy becomes harder). Within teams, treatment can differ between individual cases depending on the type and severity of the cleft.

### Cleft lip

Within the first 2–3 months after birth, surgery is performed to close the cleft lip. While surgery to repair a cleft lip can be performed soon after birth, often the preferred age is at approximately 10 weeks of age, following the "rule of 10s" coined by surgeons Wilhelmmesen and Musgrave in 1969 (the child is at least 10 weeks of age; weighs at least 10 pounds, and has at least 10g hemoglobin).[44] If the cleft is bilateral and extensive, two surgeries may be required to close the cleft, one side first, and the second side a few weeks later. The most common procedure to repair a cleft lip is the *Millard procedure* pioneered by Ralph Millard. Millard performed the first procedure at a Mobile Army Surgical Hospital (MASH) unit in Korea.[45]

Often an incomplete cleft lip requires the same surgery as complete cleft. This is done for two reasons. Firstly the group of muscles required to purse the lips run through the upper lip. In order to restore the complete group a full incision must be made. Secondly, to create a less obvious scar the surgeon tries to line up the scar with the natural lines in the upper lip (such as the edges of the philtrum) and tuck away stitches as far up the nose as possible. Incomplete cleft gives the surgeon more tissue to work with, creating a more supple and natural-looking upper lip.


The blue lines indicate incisions.




Movement of the flaps; flap A is moved between B and C. C is rotated slightly while B is pushed down.

Pre-operation

Post-operation, the lip is swollen from surgery and will get a more natural look within a couple of weeks. See photos in the section above.

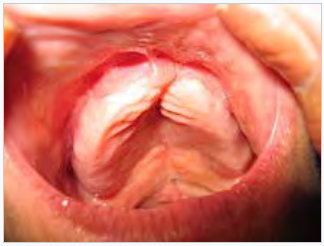
### Pre-surgical devices

In some cases of a severe bi-lateral complete cleft, the premaxillary segment will be protruded far outside the mouth.

Nasoalveolar molding prior to surgery can improve long-term nasal symmetry among patients with complete unilateral cleft lip-cleft palate patients compared to correction by surgery alone, according to a retrospective cohort study.[46] In this study, significant improvements in nasal symmetry were observed in multiple areas including measurements of the projected length of the nasal ala (lateral surface of the external nose), position of the superoinferior alar groove, position of the mediolateral nasal dome, and nasal bridge deviation. "The nasal ala projection length demonstrated an average ratio of 93.0 percent in the surgery-alone group and 96.5 percent in the nasoalveolar molding group" this study concluded.

## Cleft palate

Often a cleft palate is temporarily covered by a palatal obturator (a prosthetic device made to fit the roof of the mouth covering the gap).


A repaired cleft palate on a 64-year-old female.

Cleft palate can also be corrected by surgery, usually performed between 6 and 12 months. Approximately 20–25% only require one palatal surgery to achieve a competent velopharyngeal valve capable of producing normal, non-hypernasal speech. However, combinations of surgical methods and repeated surgeries are often necessary as the child grows. One of the new innovations of cleft lip and cleft palate repair is the Latham appliance.[47] The Latham is surgically inserted by use of pins during the child's 4th or 5th month. After it is in place, the doctor, or parents, turn a screw daily to bring the cleft together to assist with future lip and/or palate repair.

If the cleft extends into the maxillary alveolar ridge, the gap is usually corrected by filling the gap with bone tissue. The bone tissue can be acquired from the patients own chin, rib or hip.

## Speech and hearing

A tympanostomy tube is often inserted into the eardrum to aerate the middle ear.[48] This is often beneficial for the hearing ability of the child.

Children with cleft palate typically have a variety of speech problems. Some speech problems result directly from anatomical differences such as velopharyngeal inadequacy. Velopharyngeal inadequacy refers to the inability of the soft palate to close the opening from the throat to the nasal cavity, which is necessary for many speech sounds, such as /p/, /b/, /t/, /d/, /s/, /z/, etc.[49] This type of errors typically resolve after palate repair.[50]

However, sometimes children with cleft palate also have speech errors which develop as the result of an attempt to compensate for the inability to produce the target phoneme. These are known as compensatory articulations. Compensatory articulations are usually sounds that are non-existent in normal English phonology, often do not resolve automatically after palatal repair, and make a child's speech even more difficult to understand.[50][51][52]

Speech-language pathology can be very beneficial to help resolve speech problems associated with cleft palate. In addition, research has indicated that children who receive early language intervention are less likely to develop compensatory error patterns later.[53]

## Hearing loss

Hearing impairment is particularly prevalent in children with cleft palate. The tensor muscle fibres that open the eustachian tubes lack an anchor to function effectively. In this situation, when the air in the middle ear is absorbed by the mucous membrane, the negative pressure is not compensated, which results in the secretion of fluid into the middle ear space from the mucous membrane.[54] Children with this problem typically have a conductive hearing loss primarily caused by this middle ear effusion.[55]

## Sample treatment schedule

Note that each individual patient's schedule is treated on a case-by-case basis and can vary per hospital. The table below shows a common sample treatment schedule. The colored squares indicate the average timeframe in which the indicated procedure occurs. In some cases this is usually one procedure (for example lip repair) in other cases this is an ongoing therapy (for example speech therapy).

| Age | 0m | 3m | 6m | 9m | 1y | 2y | 3y | 4y | 5y | 6y | 7y | 8y | 9y | 10y | 11y | 12y | 13y | 14y | 15y | 16y | 17y | 18y |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Palatal obturator | | | | | | | | | | | | | | | | | | | | | | |
| Repair cleft lip | | | | | | | | | | | | | | | | | | | | | | |
| Repair soft palate | | | | | | | | | | | | | | | | | | | | | | |
| Repair hard palate | | | | | | | | | | | | | | | | | | | | | | |
| Tympanostomy tube | | | | | | | | | | | | | | | | | | | | | | |
| Speech therapy/pharyngoplasty | | | | | | | | | | | | | | | | | | | | | | |
| Bone grafting jaw | | | | | | | | | | | | | | | | | | | | | | |
| Orthodontics | | | | | | | | | | | | | | | | | | | | | | |
| Further cosmetic corrections (Including jawbone surgery) | | | | | | | | | | | | | | | | | | | | | | |

## Craniofacial team

*Main article: Craniofacial team*

A craniofacial team is routinely used to treat this condition. The majority of hospitals still use craniofacial teams; yet others are making a shift towards dedicated cleft lip and palate programs. While craniofacial teams are widely knowledgeable about all aspects of craniofacial conditions, dedicated cleft lip and palate teams are able to dedicate many of their efforts to being on the cutting edge of new advances in cleft lip and palate care.

Many of the top pediatric hospitals are developing their own CLP clinics in order to provide patients with comprehensive multi-disciplinary care from birth through adolescence. Allowing an entire team to care for a child throughout their cleft lip and palate treatment (which is ongoing) allows for the best outcomes in every aspect of a child's care. While the individual approach can yield significant results, current trends indicate that team based care

leads to better outcomes for CLP patients. .[56]

## Epidemiology

*Main article: Clefting prevalence in different cultures*

Cleft lip and palate occurs in about 1 to 2 per 1000 births in the developed world.[2]

Rates for cleft lip with or without cleft palate and cleft palate alone varies within different ethnic groups.

The highest prevalence rates for (CL ± P) are reported for Native Americans and Asians. Africans have the lowest prevalence rates.[57]

- Native Americans: 3.74/1000
- Japanese: 0.82/1000 to 3.36/1000
- Chinese: 1.45/1000 to 4.04/1000
- Caucasians: 1.43/1000 to 1.86/1000
- Latin Americans: 1.04/1000
- Africans: 0.18/1000 to 1.67/1000

Rate of occurrence of CPO is similar for Caucasians, Africans, North American natives, Japanese and Chinese. The trait is dominant.

It caused about 4,000 deaths globally in 2010 down from 8,400 in 1990.[58]

Prevalence of "cleft uvula" has varied from .02% to 18.8% with the highest numbers found among Chippewa and Navajo and the lowest generally in Africans.[59][60]

## Society and culture

### Abortion controversy

In some countries, cleft lip or palate deformities are considered reasons (either generally tolerated or officially sanctioned) to perform an abortion beyond the legal fetal age limit, even though the fetus is not in jeopardy of life or limb.[*citation needed*] Some human rights activists contend that this practice of what they refer to as "cosmetic murder" amounts to eugenics.[*citation needed*]

### Works of fiction

The eponymous hero of J.M. Coetzee's 1983 novel *Life & Times of Michael K* has a cleft lip. However, cleft lip is more often portrayed negatively in popular culture. Examples include Oddjob, the secondary villain of the James Bond novel *Goldfinger* by Ian Fleming (the film adaptation does not mention this but leaves it implied); the fanciful portrayal of Roman Emperor Commodus in the 2000 film *Gladiator*,;[61] and serial killer Francis Dolarhyde in the film *Red Dragon*.[62]

In the 1920 novel *Growth of the Soil,* by Norwegian writer Knut Hamsun, Inger (wife of the main character) has an uncorrected cleft lip which puts heavy limitations on her life, even causing her to kill her own child, who is also born with a cleft lip. In contrast, the protagonist of the 1924 novel *Precious Bane*, by English writer Mary Webb, is a young woman living in 19th-century rural Shropshire who eventually comes to feel that her deformity is the source of her spiritual strength. The book was later adapted for television by both the BBC and ORTF in France.

Compassion for those with cleft palates has also been used as the theme of young adult novels such as *Words in the Dust* by Trent Reedy and *Whisper* by Christina Struyk-Bonn.[*citation needed*]

### Notable cases

| Name | Comments | |
|---|---|---|
| Jerry Byrd | American sportswriter for the *Shreveport Journal*, 1957-1991, and *Bossier Press-Tribune*, 1993-2012; born with cleft lip and without cleft palate | [63] |
| John Henry "Doc" Holliday | American dentist, gambler and gunfighter of the American Old West, who is usually remembered for his friendship with Wyatt Earp and the Gunfight at the O.K. Corral | [64] |
| Tutankhamen | Egyptian pharaoh who may have had a slightly cleft palate according to diagnostic imaging | [65] |
| Thorgils Skarthi | Thorgils 'the hare-lipped'—a 10th-century Viking warrior and founder of Scarborough, England. | [66] |
| Tad Lincoln | Fourth and youngest son of President Abraham Lincoln | [67] |
| Carmit Bachar | American dancer and singer | [68][69] |
| Jürgen Habermas | German philosopher and sociologist | [70] |
| Ljubo Milicevic | Australian professional footballer | [71] |
| Stacy Keach | American actor and narrator | [72] |
| Cheech Marin | American actor and comedian | [73] |
| Owen Schmitt | American football fullback | [74] |
| Tim Lott | English author and journalist | [75] |
| Richard Hawley | English musician | [75] |
| Dario Šarić | Croatian professional basketball player | [76] |
| Antoinette Bourignon | Flemish mystic | [77] |

## Other animals

Cleft lips and palates are occasionally seen in cattle and dogs, and rarely in goats, sheep, cats, horses, pandas and ferrets. Most commonly, the defect involves the lip, rhinarium, and premaxilla. Clefts of the hard and soft palate are sometimes seen with a cleft lip. The cause is usually hereditary. Brachycephalic dogs such as Boxers and Boston Terriers are most commonly affected.[78] An inherited disorder with incomplete penetrance has also been suggested in Shih tzus, Swiss Sheepdogs, Bulldogs, and Pointers.[79] In horses, it is a rare condition usually involving the caudal soft palate.[80] In Charolais cattle, clefts are seen in combination with arthrogryposis, which is inherited as an autosomal recessive trait. It is also inherited as an autosomal recessive trait in Texel sheep. Other contributing factors may include maternal nutritional deficiencies, exposure *in utero* to viral infections, trauma, drugs, or chemicals, or ingestion of toxins by the mother, such as certain lupines by cattle during the second or third month of gestation.[81] The use of corticosteroids during pregnancy in dogs and the ingestion of *Veratrum californicum* by pregnant sheep have also been associated with cleft formation.[82]

Difficulty with nursing is the most common problem associated with clefts, but aspiration pneumonia, regurgitation, and malnutrition are often seen with cleft palate and is a common cause of death. Providing nutrition through a feeding tube is often necessary, but corrective surgery in dogs can be done by the age of twelve weeks.[78] For cleft palate, there is a high rate of surgical failure resulting in repeated surgeries.[83] Surgical techniques for cleft palate in dogs include prosthesis, mucosal flaps, and microvascular free flaps.[84] Affected animals should not be bred due to the hereditary nature of this condition.

Cleft lip in a Boxer

Cleft lip in a Boxer with premaxillary involvement

Same dog as picture on left, one year later

## See also

- Smile Pinki
- Palatal obturator
- Vomer flap surgery
- Cleft lip and palate organisations
- Face and neck development of the embryo

## References

### Notes


1. ^ *a b c d e f* "Facts about Cleft Lip and Cleft Palate". October 20, 2014. Retrieved 8 May 2015.
2. ^ *a b c d e* Watkins, SE; Meyer, RE; Strauss, RP; Aylsworth, AS (April 2014). "Classification, epidemiology, and genetics of orofacial clefts.". *Clinics in plastic surgery*. **41** (2): 149–63. doi:10.1016/j.cps.2013.12.003. PMID 24607185.
3. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385**: 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
4. ^ Boklage, Charles E. (2010). *How new humans are made cells and embryos, twins and chimeras, left and right, mind/selfsoul, sex, and schizophrenia*. Singapore: World Scientific. p. 283. ISBN 9789812835147.
5. ^ Kim EK, Khang SK, Lee TJ, Kim TG (May 2010). "Clinical features of the microform cleft lip and the ultrastructural characteristics of the orbicularis oris muscle". *Cleft Palate Craniofac. J.* **47** (3): 297–302. doi:10.5555/08-270.1. PMID 19860522.
6. ^ Yuzuriha S, Mulliken JB (November 2008). "Minor-form, microform, and mini-microform cleft lip: anatomical features, operative techniques, and revisions". *Plast. Reconstr. Surg.* **122** (5): 1485–93. doi:10.1097/PRS.0b013e31818820bc. PMID 18971733.
7. ^ Tosun Z, Hoşnuter M, Sentürk S, Savaci N (2003). "Reconstruction of microform cleft lip". *Scand J Plast Reconstr Surg Hand Surg*. **37** (4): 232–5. doi:10.1080/02844310310016412. PMID 14582757.
8. ^ Tollefson TT, Humphrey CD, Larrabee WF, Adelson RT, Karimi K, Kriet JD (2011). "The spectrum of isolated congenital nasal deformities resembling the cleft lip nasal morphology". *Arch Facial Plast Surg*. **13** (3): 152–60. doi:10.1001/archfacial.2011.26. PMID 21576661.
9. ^ "Statistics by country for cleft palate". *WrongDiagnosis.com*. Retrieved 2007-04-24.
38. ^ Shi, M.; Wehby, G.L.; Murray, J.C. (2008). "Review on Genetic Variants and Maternal Smoking in the Etiology of Oral Clefts and Other Birth Defects". *Birth Defects Res., Part C.* **84** (1): 16–29. doi:10.1002/bdrc.20117. PMC 2570345. PMID 18383123.
39. ^ Hurst, J. A.; Houlston, R.S.; Roberts, A.; Gould, S.J.; Tingey, W.G. (1995). "Transverse limb deficiency, facial clefting and hypoxic renal damage: an association with treatment of maternal hypertension?". *Clin. Dysmorphol.* **4** (4): 359–363. doi:10.1097/00019605-199510000-00013. PMID 8574428.
40. ^ Boyles AL, Wilcox AJ, Taylor JA, et al. (February 2008). "Folate and One-Carbon Metabolism Gene Polymorphisms and Their Associations With Oral Facial Clefts". *American Journal of Medical Genetics*. **146A** (4): 440–9. doi:10.1002/ajmg.a.32162. PMC 2366099. PMID 18203168.
41. ^ Costello BJ, Edwards SP, Clemens M (October 2008). "Fetal diagnosis and treatment of craniomaxillofacial anomalies". *J. Oral Maxillofac. Surg.* **66** (10): 1985–95. doi:10.1016/j.joms.2008.01.042. PMID 18848093.
42. ^ Tessier P (June 1976). "Anatomical classification facial, cranio-facial and latero-facial clefts". *J Maxillofac Surg*. **4** (2): 69–92. doi:10.1016/S0301-0503(76)80013-6. PMID 820824.
43. ^ Bristow, L; Bristow, S (2007). *Making faces: Logan's cleft lip and palate story*. Oakville, Ontaria, CA: Pulsus Group. pp. 1–92.
44. ^ Lydiatt DD, Yonkers AJ, Schall DG (November 1989). "The management of the cleft lip and palate patient". *Nebr Med J.* **74** (11): 325–8; discussion 328–9. PMID 2586685.
45. ^ "Biography and Personal Archive". Archived from the original on 2007-06-17. Retrieved 2007-07-01. at miami.edu
46. ^ Barillas I, Dec W, Warren SM, Cutting CB, Grayson BH (March 2009). "Nasoalveolar molding improves long-term nasal symmetry in complete unilateral cleft lip-cleft palate patients". *Plast. Reconstr. Surg.* **123** (3): 1002–6. doi:10.1097/PRS.0b013e318199f46e. PMID 19319066.
47. ^ Fukuyama E, Omura S, Fujita K, Soma K, Torikai K (November 2006).

10. ^ a b Sloan GM (2000). "Posterior pharyngeal flap and sphincter pharyngoplasty: the state of the art". *Cleft Palate Craniofac. J.* **37** (2): 112–22. doi:10.1597/1545-1569(2000)037<0112:PPFASP>2.3.CO;2. PMID 10749049.
11. ^ Hill JS (2001). "Velopharyngeal insufficiency: An update on diagnostic and surgical techniques". *Current Opinion in Otolaryngology & Head and Neck Surgery*. **9** (6): 365–8. doi:10.1097/00020840-200112000-00005.
12. ^ Kaplan EN (1975). "The Occult and Submucous Cleft Palate". *Cleft Palate Journal*. **12**: 356–68. PMID 1058746.
13. ^ Leonard BJ, Brust JD (1991). "Self-concept of children and adolescents with cleft lip and/or palate". *Cleft Palate Craniofac. J.* **28** (4): 347–353. doi:10.1597/1545-1569(1991)028<0347:SCOCAA>2.3.CO;2. PMID 1742302.
14. ^ Tobiasen JM (July 1984). "Psychosocial correlates of congenital facial clefts: a conceptualization and model". *Cleft Palate J.* **21** (3): 131–9. PMID 6592056.
15. ^ Pope AW, Ward J (1997). "Self-perceived facial appearance and psychosocial adjustment in preadolescents with craniofacial anomalies". *Cleft Palate Craniofac. J.* **34** (5): 396–401. doi:10.1597/1545-1569(1997)034<0396:SPFAAP>2.3.CO;2. PMID 9345606.
16. ^ Bristow & Bristow 2007, pp. 82–92
17. ^ "Cleft Palate Foundation". Retrieved 2007-07-01.
18. ^ Snyder HT, Bilboul MJ, Pope AW (2005). "Psychosocial adjustment in adolescents with craniofacial anomalies: a comparison of parent and self-reports". *Cleft Palate Craniofac. J.* **42** (5): 548–55. doi:10.1597/04-078R.1. PMID 16149838.
19. ^ Endriga MC, Kapp-Simon KA (1999). "Psychological issues in craniofacial care: state of the art". *Cleft Palate Craniofac. J.* **36** (1): 3–11. doi:10.1597/1545-1569(1999)036<0001:PIICCS>2.3.CO;2. PMID 10067755.
20. ^ a b Pope AW, Snyder HT (July 2005). "Psychosocial adjustment in children and adolescents with a craniofacial anomaly: age and sex patterns". *Cleft Palate Craniofac. J.* **42** (4): 349–54. doi:10.1597/04-043R.1. PMID 16001914.
21. ^ Prokhorov AV, Perry CL, Kelder SH, Klepp KI (1993). "Lifestyle values of adolescents: results from Minnesota Heart Health Youth Program". *Adolescence*. **28** (111): 637–47. PMID 8237549.
22. ^ Dudas M, Li WY, Kim J, Yang A, Kaartinen V (2007). "Palatal fusion — where do the midline cells go? A review on cleft palate, a major human birth defect". *Acta Histochem.* **109** (1): 1–14. doi:10.1016/j.acthis.2006.05.009. PMID 16962647.
23. ^ Dudas M, Li WY, Kim J, Yang A, Kaartinen V (2007). "Palatal fusion — where do the midline cells go? A review on cleft palate, a major human birth defect". *Acta Histochem.* **109** (1): 1–14. doi:10.1016/j.acthis.2006.05.009. PMID 16962647.
24. ^ Beaty TH, Ruczinski I, Murray JC, et al. (May 2011). "Evidence for gene-environment interaction in a genome wide study of isolated, non-syndromic cleft palate". *Genet Epidemiol.* **35** (6): 469–78. doi:10.1002/gepi.20595. PMC 3180858. PMID 21618603.
25. ^ Kanno K, Suzuki Y, Yamada A, Aoki Y, Kure S, Matsubara Y (May 2004). "Association between nonsyndromic cleft lip with or without cleft palate and the glutamic acid decarboxylase 67 gene in the Japanese population". *American Journal of Medical Genetics*. **127A** (1): 11–6. doi:10.1002/ajmg.a.20649. PMID 15103710.
26. ^ FaceBase. (2012). *Gene Wiki*. Retrieved from https://www.facebase.org/resources/gene-wiki.
27. ^ Dixon MJ, Marazita ML, Beaty TH, Murray JC (March 2011). "Cleft lip and palate: synthesizing genetic and environmental influences". *Nature Reviews Genetics*. **12** (3): 167–78. doi:10.1038/nrg2933. PMC 3086810. PMID 21331089.
28. ^ Zucchero TM, Cooper ME, Maher BS, et al. (August 2004). "Interferon regulatory factor 6 (IRF6) gene variants and the risk of isolated cleft lip or palate". *N. Engl. J. Med.* **351** (8): 769–80. doi:10.1056/NEJMoa032909. PMID 15317890.
29. ^ "Cleft palate genetic clue found". *BBC News*. 2004-08-30. Retrieved 2007-07-01.
30. ^ Siderius LE, Hamel BC, van Bokhoven H, et al. (2000). "X-linked mental retardation associated with cleft lip/palate maps to Xp11.3-q21.3". *American Journal of Medical Genetics*. **85** (3): 216–220. doi:10.1002/(SICI)1096-8628(19990730)85:3<216::AID-AJMG6>3.0.CO;2-X. PMID 10398231.
31. ^ Kronwith SD, Quinn G, McDonald DM, et al. (1990). "Stickler's syndrome in the Cleft Palate Clinic". *J Pediatr Ophthalmol Strabismus*. **27** (5): 265–7. PMID 2246742.
32. ^ Mrugacz M, Sredzińska-Kita D, Bakunowicz-Lazarczyk A, Piszcz M (2005). "[High myopia as a pathognomonic sign in Stickler's syndrome]". *Klin Oczna* (in Polish). **107** (4–6): 369–71. PMID 16118961.
33. ^ Sousa SB, Lambot-Juhan K, Rio M, et al. (May 2011). "Expanding the skeletal phenotype of Loeys-Dietz syndrome". *American Journal of Medical Genetics*. **155A** (5): 1178–83. doi:10.1002/ajmg.a.33813. PMID 21484991.
34. ^ Hardikar syndrome symptoms
35. ^ a b Cox, T. C. (2004). "Taking it to the max: The genetic and developmental "Excessive rapid palatal expansion with Latham appliance for distal repositioning of protruded premaxilla in bilateral cleft lip and alveolus". *Cleft Palate Craniofac. J.* **43** (6): 673–7. doi:10.1597/05-109. PMID 17105324.
48. ^ Cohen MS, Mandel EM, Furman JM, Sparto PJ, Casselbrant ML (June 2011). "Tympanostomy Tube Placement and Vestibular Function in Children". *Otolaryngol Head Neck Surg*. **145** (4): 666–72. doi:10.1177/0194599811412038. PMID 21676943.
49. ^ Wyatt R, Sell D, Russell J, Harding A, Harland K, Albery E (April 1996). "Cleft palate speech dissected: a review of current knowledge and analysis". *Br J Plast Surg*. **49** (3): 143–9. doi:10.1016/S0007-1226(96)90216-7. PMID 8785593.
50. ^ a b Lawrence CW, Philips BJ (January 1975). "A telefluoroscopic study of lingual contacts made by persons with palatal defects". *Cleft Palate J.* **12**: 85–94. PMID 1053965.
51. ^ Chapman KL (January 1993). <0064:PPICWC>2.3.CO;2 "Phonologic processes in children with cleft palate". *Cleft Palate Craniofac. J.* **30** (1): 64–72. doi:10.1597/1545-1569(1993)030<0064:PPICWC>2.3.CO;2. PMID 8418874.
52. ^ Trost JE (July 1981). "Articulatory additions to the classical description of the speech of persons with cleft palate". *Cleft Palate J.* **18** (3): 193–203. PMID 6941865.
53. ^ Bzoch, K.R. (1989). "Rationale, Methods, and Techniques of Cleft Palate Speech Therapy". In Bzoch, K.R. *Communicative Disorders Related to Cleft Lip and Palate* (3rd ed.). Boston MA: College-Hill Press. pp. 273–289.
54. ^ Broen, PA; Moller, KT; Carlstrom, J; Doyle, SS; Devers, M; Keenan, KM (March 1996). "Comparison of the hearing histories of children with and without cleft palate". *The Cleft Palate-Craniofacial Journal*. **33** (2): 127–33. doi:10.1597/1545-1569(1996)033<0127:COTHHO>2.3.CO;2. PMID 8695620.
55. ^ Szabo C, Langevin K, Schoem S, Mabry K (August 2010). "Treatment of persistent middle ear effusion in cleft palate patients". *Int. J. Pediatr. Otorhinolaryngol.* **74** (8): 874–7. doi:10.1016/j.ijporl.2010.04.016. PMID 20537733.
56. ^ Joanne Green. "The Importance of a Multi-Disciplinary Approach". Archived from the original on 2007-10-26. Retrieved 2007-10-15.
57. ^ See "Who is affected by cleft lip and cleft palate". Retrieved 2008-06-20.
58. ^ Lozano, R (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
59. ^ Cervenka J, Shapiro BL (February 1970). "Cleft uvula in Chippewa Indians: prevalence and genetics". *Hum. Biol.* **42** (1): 47–52. PMID 5445084.
60. ^ Rivron RP (March 1989). "Bifid uvula: prevalence and association in otitis media with effusion in children admitted for routine otolaryngological operations". *J Laryngol Otol*. **103** (3): 249–52. doi:10.1017/S002221510010862X. PMID 2784825.
61. ^ Solomon, Jon (2001). *The ancient world in the cinema* (Rev. and expanded ed.). New Haven [u.a.]: Yale Univ. Press. p. 90. ISBN 9780300083378.
62. ^ Timothy D. Harfield. "The Monster Without: Red Dragon, the Cleft-Lip, and the Politics of Recognition" (PDF). Retrieved 5 February 2014.
63. ^ Nico Van Thyn (June 8, 2012). "Once a Knight: The legendary man, Mr. Byrd". nvanthyn.blogsport.com. Retrieved April 22, 2016.
64. ^ Karen Holliday Tanner (1998). *Doc Holliday: A Family Portrait*. University of Omaha Press. ISBN 0-8061-3036-9.
65. ^ "King Tut Not Murdered Violently, CT Scans Show". Retrieved 2007-07-01.
66. ^ *Bloodfeud: Murder and Revenge in Anglo-Saxon England*, Richard Fletcher
67. ^ "Tad Lincoln: The Not-so-Famous Son of A Most-Famous President". *HistoryBuff.com*. Retrieved 2007-07-01.
68. ^ "Carmit Bachar, smile ambassador". Retrieved 2007-10-13.
69. ^ Beverley Lyons, October 16, 2006. Carmite Doing Her Bit For Charity. *The Daily Record*
70. ^ "Jurgen Habermas". Retrieved 2008-12-18.
71. ^ "Chat To Ljubo...LIVE". 28 May 2009. Retrieved 23 December 2009.
72. ^ "Stacy Keach". *Cleft Palate Foundation*. Retrieved 2007-07-01.
73. ^ "Cheech Marin". *Cleft Palate Foundation*. Retrieved 2007-07-01.
74. ^ Whiteside, Kelly (4 Nov 2006). "Schmitt is face of West Va. toughness| USA Today". Retrieved 2010-04-30.
75. ^ a b "Famous People with a Cleft". 2008-04-05.
76. ^ "Who's That Guy? Dario Saric!". 2014-09-03.
77. ^ MacEwen, Alex (1910). *Antoinette Bourignon, Quietist*. London: Hodder and Stoughton. p. 27. Retrieved 15 May 2015.
78. ^ a b Ettinger, Stephen J.; Feldman, Edward C. (1995). *Textbook of Veterinary Internal Medicine* (4th ed.). W.B. Saunders Company. ISBN 0-7216-6795-3.
79. ^ Garcia, J.F. Rodriguez (2006). "Surgery of the Soft and Hard Palate". *Proceedings of the North American Veterinary Conference*. Retrieved 2007-04-28.
80. ^ Semevolos, Stacy A.; Ducharme, Norm (1998). "Surgical Repair of Congenital Cleft Palate in Horses: Eight Cases (1979–1997)" (PDF). *Proceedings of the American Association of Equine Practitioners*. Retrieved

mechanisms coordinating midfacial morphogenesis and dysmorphology". *Clin. Genet.* **65** (3): 163–176. doi:10.1111/j.0009-9163.2004.00225.x. PMID 14756664.
36. ^ *a b* Loenarz, C.; Ge W.; Coleman M. L.; Rose N. R.; Cooper C. D. O.; Klose R. J.; Ratcliffe P. J.; Schofield, C. J. (2009). "*PHF8*, a gene associated with cleft lip/palate and mental retardation, encodes for an N{varepsilon}-dimethyl lysine demethylase". *Hum. Mol. Genet.* **19** (2): 217–22. doi:10.1093/hmg/ddp480. PMID 19843542.
37. ^ Millicovsky, G.; Johnston, M.C. (1981). "Hyperoxia and hypoxia in pregnancy: simple experimental manipulation alters the incidence of cleft lip and palate in CL/Fr mice". *Proc. Natl. Acad. Sci. U.S.A.* **78** (9): 5722–5723. 2007-04-28.
81. ^ "Mouth". *The Merck Veterinary Manual*. 2006. Retrieved 2007-04-28.
82. ^ Beasley, V. (1999). "Teratogenic Agents". *Veterinary Toxicology*. Retrieved 2007-04-28.
83. ^ Lee J, Kim Y, Kim M, Lee J, Choi J, Yeom D, Park J, Hong S (2006). "Application of a temporary palatal prosthesis in a puppy suffering from cleft palate". *J. Vet. Sci.* **7** (1): 93–5. doi:10.4142/jvs.2006.7.1.93. PMC 3242096. PMID 16434860.
84. ^ Griffiths L, Sullivan M (2001). "Bilateral overlapping mucosal single-pedicle flaps for correction of soft palate defects". *Journal of the American Animal Hospital Association*. **37** (2): 183–6. PMID 11300527.

### Further reading

- FIGURE 1 | Development of the lip and palate and FIGURE 2 | Types of cleft in Dixon, Michael J.; Marazita, Mary L.; Beaty, Terri H.; Murray, Jeffrey C. "Cleft lip and palate: understanding genetic and environmental influences". *Nature Reviews Genetics*. **12** (3): 167–178. doi:10.1038/nrg2933. PMC 3086810. PMID 21331089.
- Berkowitz, Samuel (26 February 2013). *Cleft Lip and Palate: Diagnosis and Management*. Springer. ISBN 978-3-642-30770-6.

## External links

- Cleft lip and cleft palate at DMOZ

Look up *cleft lip* in Wiktionary, the free dictionary.

Wikimedia Commons has media related to *Cleft lip*.

Wikisource has the text of the 1911 *Encyclopædia Britannica* article *Cleft Palate*.

| v · t · e · | **Congenital malformations and deformations of digestive system (Q35–Q45, 749–751)** | |
|---|---|---|
| **Upper GI tract** | **Tongue, mouth and pharynx** | Cleft lip and palate · Van der Woude syndrome · *tongue* (Ankyloglossia · Macroglossia · Hypoglossia · · |
| | **Esophagus** | *EA/TEF* (Esophageal atresia: types A, B, C, and D · Tracheoesophageal fistula: types B, C, D and E · · *esophageal rings* (Esophageal web (upper) · Schatzki ring (lower) · · |
| | **Stomach** | Pyloric stenosis · Hiatus hernia · |
| **Lower GI tract** | **Intestines** | Intestinal atresia (Duodenal atresia · · Meckel's diverticulum · Hirschsprung's disease · Intestinal malrotation · Dolichocolon · Enteric duplication cyst · |
| | **Rectum/anal canal** | Imperforate anus · Rectovestibular fistula · Persistent cloaca · Rectal atresia · |
| **Accessory** | **Pancreas** | Annular pancreas · Accessory pancreas · Johanson–Blizzard syndrome · Pancreas divisum · |
| | **Bile duct** | Choledochal cysts (Caroli disease · · Biliary atresia · |
| | **Liver** | Alagille syndrome · Polycystic liver disease · |

| v · t · e · | **Cleft lip and palate** |
|---|---|
| **Related specialities** | Advance practice nursing · Audiology · Dentistry · Dietetics · Genetics · Oral and maxillofacial surgery · Orthodontics · Orthodontic technology · Otolaryngology · Pediatrics · Pediatric dentistry · Physician · Plastic surgery · Psychiatry · Psychology · Respiratory therapy · Social Work · Speech and language therapy · |
| **Related syndromes** | Hearing loss with craniofacial syndromes · Pierre Robin syndrome · Popliteal pterygium syndrome · Van der Woude syndrome · |
| **National and international Organisations** | Cleft Lip and Palate Association · Cleft Lip and Palate Association of Ireland · Craniofacial Society of Great Britain and Ireland · Interplast · North Thames Regional Cleft Lip and Palate Service · Operation Smile · Shriners Hospitals for Children · Smile Train · Transforming Faces Worldwide · Operation of Hope · Smile Angel Foundation (China) · |

| v · t · e · | **Genetic disorder, protein biosynthesis: Transcription factor/coregulator deficiencies** | |
|---|---|---|
| **(1) Basic domains** | **1.2** | Feingold syndrome · Saethre–Chotzen syndrome · |
| | **1.3** | Tietz syndrome · |
| **(2) Zinc finger DNA-binding domains** | **2.1** | (Intracellular receptor): Thyroid hormone resistance · Androgen insensitivity syndrome (PAIS · MAIS · CAIS · · Kennedy's disease · PHA1AD pseudohypoaldosteronism · Estrogen insensitivity syndrome · X-linked adrenal hypoplasia congenita · MODY 1 · Familial partial lipodystrophy 3 · SF1 XY gonadal dysgenesis · |
| | **2.2** | Barakat syndrome · Tricho–rhino–phalangeal syndrome · |
| | **2.3** | Greig cephalopolysyndactyly syndrome/Pallister–Hall syndrome · Denys–Drash syndrome · Duane-radial ray syndrome · MODY 7 · MRX 89 · Townes–Brocks syndrome · Acrocallosal syndrome · Myotonic dystrophy 2 · |
| | **2.5** | Autoimmune polyendocrine syndrome type 1 · |
| | | *ARX* (Ohtahara syndrome · Lissencephaly X2 · · *MNX1* (Currarino syndrome · · *HOXD13* (SPD1 Synpolydactyly · · *PDX1* |

| | | |
|---|---|---|
| **(3) Helix-turn-helix domains** | **3.1** | (MODY 4 · · *LMX1B* (Nail–patella syndrome · · *MSX1* (Tooth and nail syndrome · OFC5 · · *PITX2* (Axenfeld syndrome 1 · · *POU4F3* (DFNA15 · · *POU3F4* (DFNX2 · · *ZEB1* (Posterior polymorphous corneal dystrophy · Fuchs' dystrophy 3 · · *ZEB2* (Mowat–Wilson syndrome · · |
| | **3.2** | *PAX2* (Papillorenal syndrome · · *PAX3* (Waardenburg syndrome 1&3 · · *PAX4* (MODY 9 · · *PAX6* (Gillespie syndrome · Coloboma of optic nerve · · *PAX8* (Congenital hypothyroidism 2 · · *PAX9* (STHAG3 · · |
| | **3.3** | *FOXC1* (Axenfeld syndrome 3 · Iridogoniodysgenesis, dominant type · · *FOXC2* (Lymphedema–distichiasis syndrome · · *FOXE1* (Bamforth–Lazarus syndrome · · *FOXE3* (Anterior segment mesenchymal dysgenesis · · *FOXF1* (ACD/MPV · · *FOXI1* (Enlarged vestibular aqueduct · · *FOXL2* (Premature ovarian failure 3 · · *FOXP3* (IPEX · · |
| | **3.5** | *IRF6* (Van der Woude syndrome · Popliteal pterygium syndrome · · |
| **(4) β-Scaffold factors with minor groove contacts** | **4.2** | Hyperimmunoglobulin E syndrome · |
| | **4.3** | Holt–Oram syndrome · Li–Fraumeni syndrome · Ulnar–mammary syndrome · |
| | **4.7** | Campomelic dysplasia · MODY 3 · MODY 5 · *SF1* (SRY XY gonadal dysgenesis · Premature ovarian failure 7 · · *SOX10* (Waardenburg syndrome 4c · Yemenite deaf-blind hypopigmentation syndrome · · |
| | **4.11** | Cleidocranial dysostosis · |
| **(0) Other transcription factors** | **0.6** | Kabuki syndrome · |
| **Ungrouped** | | *TCF4* (Pitt–Hopkins syndrome · · *ZFP57* (TNDM1 · · *TP63* (Rapp–Hodgkin syndrome/Hay–Wells syndrome/Ectrodactyly–ectodermal dysplasia–cleft syndrome 3/Limb–mammary syndrome/OFC8 · · |
| **Transcription coregulators** | **Coactivator:** | *CREBBP* (Rubinstein–Taybi syndrome · · |
| | **Corepressor:** | *HR* (Atrichia with papular lesions) · |

| v · t · e · | **Cell membrane protein disorders (other than Cell surface receptor, enzymes, and cytoskeleton)** |
|---|---|
| **Arrestin** | Oguchi disease 1 · |
| **Myelin** | Pelizaeus–Merzbacher disease · Dejerine–Sottas disease · Charcot–Marie–Tooth disease 1B, 2J · |
| **Pulmonary surfactant** | Surfactant metabolism dysfunction 1, 2 · |
| **Cell adhesion molecule** | IgSF CAM: OFC7 · |
| | Cadherin: *DSG1* (Striate palmoplantar keratoderma 1 · · |
| | *DSG2* (Arrhythmogenic right ventricular dysplasia 10 · · *DSG4* (LAH1 · · *DSC2* (Arrhythmogenic right ventricular dysplasia 11 · · |
| | **Integrin:** cell surface receptor deficiencies · |
| **Tetraspanin** | *TSPAN7* (X-Linked mental retardation 58 · · *TSPAN12* (Familial exudative vitreoretinopathy 5 · · |
| **Other** | *KIND1* (Kindler syndrome · · *HFE* (HFE hereditary haemochromatosis · · *DYSF* (Distal muscular dystrophy · Limb-girdle muscular dystrophy 2B · · |
| *See also other cell membrane proteins* | |

Categories: Congenital oral disorders | Facial features | Dog health | Lip disorders

# Congenital heart defect

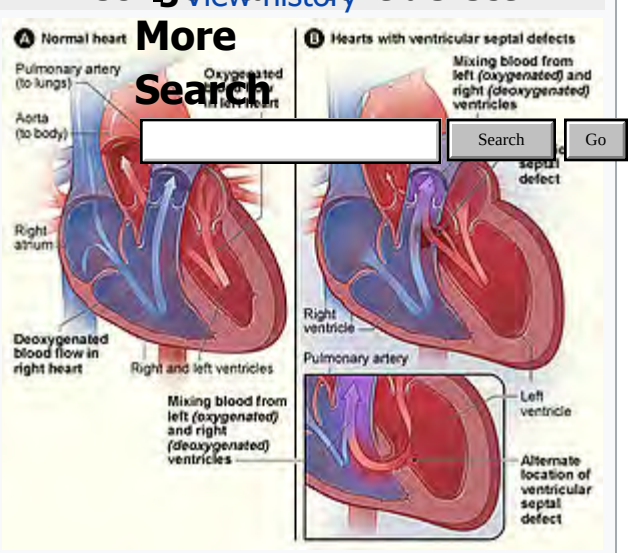
From Wikipedia, the free encyclopedia

**Congenital heart defect** (**CHD**), also known as a **congenital heart anomaly** or **congenital heart disease**, is a problem in the structure of the heart that is present at birth.[2] Signs and symptoms depend on the specific type of problem.[3] Symptoms can vary from none to life-threatening.[2] When present they may include rapid breathing, bluish skin, poor weight gain, and feeling tired.[4] It does not cause chest pain.[4] Most congenital heart problems do not occur with other diseases.[3] Complications that can result from heart defects include heart failure.[4]

The cause of a congenital heart defect is often unknown.[5] Certain cases may be due to infections during pregnancy such as rubella, use of certain medications or drugs such as alcohol or tobacco, parents being closely related, or poor nutritional status or obesity in the mother.[3][6] Having a parent with a congenital heart defect is also a risk factor.[7] A number of genetic conditions are associated with heart defects including Down syndrome, Turner syndrome, and Marfan syndrome.[3] Congenital heart defects are divided into two main groups: cyanotic heart defects and non-cyanotic heart defects, depending on whether the child has the potential to turn bluish in color.[3] The problems may involve the interior walls of the heart, the heart valves, or the large blood vessels that lead to and from the heart.[2]

Congenital heart defects are partly preventable through rubella vaccination, the adding of iodine to salt, and the adding of folic acid to certain food products.[3] Some defects do not need treatment.[2] Other may be effectively treated with catheter based procedures or heart surgery.[8] Occasionally a number of operations may be needed.[8] Occasionally heart transplantation is required.[8] With appropriate treatment outcomes, even with complex problems, are generally good.[2]

## Variants




The normal structure of the heart (left) in comparison to two common locations for a ventricular septal defect (right), the most common form of congenital heart defect.[1]

| Classification and external resources | |
|---|---|
| **Specialty** | Cardiology |
| **ICD-10** | Q20-Q26 |
| **ICD-9-CM** | 745-747 |
| **DiseasesDB** | 17017 |
| **MedlinePlus** | 001114 |
| **MeSH** | D006330 |

[edit on Wikidata]

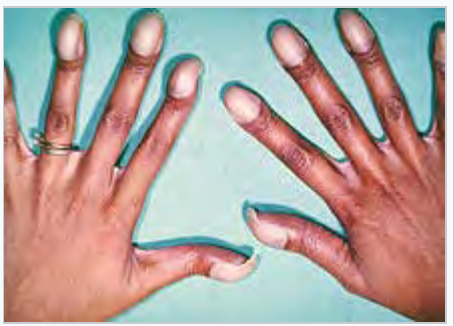
Heart defects are the most common birth defect.[3][9] In 2013 they were present in 34.3 million people globally.[9] They affect between 4 and 75 per 1,000 live births depending upon how they are diagnosed.[3][7] About 6 to 19 per 1,000 cause a moderate to severe degree of problems.[7] Congenital heart defects are the leading cause of birth defect-related deaths.[3] In 2013 they resulted in 323,000 deaths down from 366,000 deaths in 1990.[10]

Contents





## Signs and symptoms [edit]



Digital clubbing with cyanotic nail beds in an adult with tetralogy of Fallot

Signs and symptoms are related to type and severity of the heart defect. Symptoms frequently present early in life, but it is possible for some CHDs to go undetected throughout life.[11] Some children have no signs while others may exhibit shortness of breath, cyanosis, fainting,[12] heart murmur, under-development of limbs and muscles, poor feeding or growth, or respiratory infections. Congenital heart defects cause abnormal heart structure resulting in production of certain sounds called heart murmur. These can sometimes be detected by auscultation; however, not all heart murmurs are caused by congenital heart defects.

### Associated symptoms [edit]

*Main article: VACTERL association*

Congenital heart defects are associated with an increased incidence of some other symptoms, together being called the VACTERL association:

- V — Vertebral anomalies
- A — Anal atresia
- C — Cardiovascular anomalies
- T — Tracheoesophageal fistula
- E — Esophageal atresia
- R — Renal (Kidney) and/or radial anomalies
- L — Limb defects

Ventricular septal defect (VSD), atrial septal defects, and tetralogy of Fallot are the most common congenital heart defects seen in the VACTERL association. Less common defects in the association are truncus arteriosus and transposition of the great arteries.

## Causes [edit]

The cause of congenital heart disease may be either genetic or environmental, but is usually a combination of both.[13]

### Genetic [edit]

Most of the known causes of congenital heart disease are sporadic genetic changes, either focal mutations or deletion or addition of segments of DNA.[14] Large chromosomal abnormalities such as trisomies 21, 13, and 18 cause about 5–8% of cases of CHD,[13] with trisomy 21 being the most common genetic cause.[14] Small chromosomal abnormalities also frequently lead to congenital heart disease, and examples include microdeletion of the long arm of chromosome 22 (22q11, DiGeorge syndrome), the long arm of chromosome 1 (1q21), the short arm of chromosome 8 (8p23) and many other, less recurrent regions of the genome, as shown by high resolution genome-wide screening (Array comparative genomic hybridization).[15]

The genes regulating the complex developmental sequence have only been partly elucidated. Some genes are associated with specific defects. A number of genes have been associated with cardiac manifestations. Mutations of a heart muscle protein, α-myosin heavy chain (MYH6) are associated with atrial septal defects. Several proteins that interact with MYH6 are also associated with cardiac defects. The transcription factor GATA4 forms a complex with the TBX5 which interacts with MYH6. Another factor, the homeobox (developmental) gene, NKX2-5 also interacts with MYH6. Mutations of all these proteins are associated with both atrial and ventricular septal defects; In addition, NKX2-5 is associated with defects in the electrical conduction of the heart and TBX5 is related to the Holt-Oram syndrome which includes electrical conduction defects and abnormalities of the upper limb. Another T-box gene, TBX1, is involved in velo-cardio-facial syndrome DiGeorge syndrome, the most common deletion which has extensive symptoms including defects of the cardiac outflow tract including tetralogy of Fallot.[16]

**Examples of gene products and associated features**

| | MYH6 | GATA4 | NKX2-5 | TBX5 | TBX1 |
|---|---|---|---|---|---|
| Locus | 14q11.2-q13 | 8p23.1-p22 | 5q34 | 12q24.1 | 22q11.2 |
| Syndrome | | | | Holt-Oram | DiGeorge |
| Atrial septal defects | | | | | |
| Ventricular septal defects | | | | | |
| Electrical conduction abnormalities | | | | | |
| Outflow tract abnormalities | | | | | |
| Non-cardiac manifestations[17] | | | | Upper limb abnormalities | Small or absent thymus<br>Small or absent parathyroids<br>Facial abnormalities |

The notch signaling pathway, a regulatory mechanism for cell growth and differentiation, plays broad roles in several aspects of cardiac development. Notch elements are involved in determination of the right and left sides of the body plan, so the directional folding of the heart tube can be impacted. Notch signaling is involved early in the formation of the endocardial cushions and continues to be active as the develop into the septa and valves. It is also involved in the development of the ventricular wall and the connection of the outflow tract to the great vessels. Mutations in the gene for one of the notch ligands, *Jagged1*, are identified in the majority of examined cases of arteriohepatic dysplasia (Alagille syndrome), characterized by defects of the great vessels (pulmonary artery stenosis), heart (tetralogy of Fallot in 13% of cases), liver, eyes, face, and bones. Though less than 1% of all cases, where no defects are found in the *Jagged1* gene, defects are found in *Notch2* gene. In 10% of cases, no mutation is found in either gene. For another member of the gene family, mutations in the *Notch1* gene are associated with bicuspid aortic valve, a valve with two leaflets instead of three. *Notch1* is also associated with calcification of the aortic valve, the third most common cause of heart disease in adults.[18][19]

Mutations of a cell regulatory mechanism, the Ras/MAPK pathway are responsible for a variety of

syndromes, including Noonan syndrome, LEOPARD syndrome, Costello syndrome and cardiofaciocutaneous syndrome in which there is cardiac involvement.[20] While the conditions listed are known genetic causes, there are likely many other genes which are more subtle. It is known that the risk for congenital heart defects is higher when there is a close relative with one.[14]

### Environmental [edit]

Known environmental factors include certain infections during pregnancy such as Rubella, drugs (alcohol, hydantoin, lithium and thalidomide) and maternal illness (diabetes mellitus, phenylketonuria, and systemic lupus erythematosus).[21]

Being overweight or obese increases the risk of congenital heart disease.[6] Additionally, as maternal obesity increases, the risk of heart defects also increases.[22] A distinct physiological mechanism has not been identified to explain the link between maternal obesity and CHD, but both prepregnancy folate deficiency and diabetes have been implicated in some studies.[23]

## Mechanism [edit]

*Main article: Heart development*

There is a complex sequence of events that result in a well formed heart at birth and disruption of any portion may result in a defect.[14] The orderly timing of cell growth, cell migration, and programmed cell death ("apoptosis") has been studied extensively and the genes that control the process are being elucidated.[16] Around day 15 of development, the cells that will become the heart exist in two horseshoe shaped bands of the middle tissue layer (mesoderm),[16] and some cells migrate from a portion of the outer layer (ectoderm), the neural crest, which is the source of a variety of cells found throughout the body. On day 19 of development, a pair of vascular elements, the "endocardial tubes", form. The tubes fuse when cells between then undergo programmed death and cells from the first heart field migrate to the tube, and form a ring of heart cells (myocytes) around it by day 21. On day 22, the heart begins to beat and by day 24, blood is circulating.[24]

At day 22, the circulatory system is bilaterally symmetrical with paired vessels on each side and the heart consisting of a simple tube located in the midline of the body layout. The portions that will become the atria and will be located closest to the head are the most distant from the head. From days 23 through 28, the heart tube folds and twists, with the future ventricles moving left of center (the ultimate location of the heart) and the atria moving towards the head.[24]

On day 28, areas of tissue in the heart tube begin to expand inwards; after about two weeks, these expansions, the membranous "septum primum" and the muscular "endocardial cushions", fuse to form the four chambers of the heart. A failure to fuse properly will result in a defect that may allow blood to leak between chambers. After this happens, cells which have migrated from the neural crest begin to divide the bulbus cordis, the main outflow tract is divided in two by the growth a spiraling septum, becoming the great vessels—the ascending segment of the aorta and the pulmonary trunk. If the separation is incomplete, the result is a "persistent truncus arteriosis". The vessels may be reversed ("transposition of the great vessels"). The two halves of the split tract must migrate into the correct positions over the appropriate ventricles. A failure may result in some blood flowing into the wrong vessel (*e.g.*overriding aorta). The four-chambered heart and the great vessels have features required for fetal growth. The lungs are unexpanded and cannot accommodate the full circulatory volume. Two structures exist to shunt blood flow away from the lungs. Cells in part of the septum primum die creating a hole while muscle cells, the "septum secundum", grow along the right atrial side the septum primum, except for one region, leaving a gap through which blood can pass from the right artium to the left atrium, the foramen ovale. A small vessel, the *ductus arteriosus* allows blood from the pulmonary artery to pass to the aorta.[24]

### Changes at birth [edit]

The ductus arteriosus stays open because of circulating factors including prostaglandins. The foramen ovale

stays open because of the flow of blood from the right atrium to the left atrium. As the lungs expand, blood flows easily through the lungs and the membranous portion of the foramen ovale (the septum primum) flops over the muscular portion (the septum secundum). If the closure is incomplete, the result is a patent foramen ovale. The two flaps may fuse, but many adults have a foramen ovale that stays closed only because of the pressure difference between the atria.[24]

### Theories [edit]

Rokitansky (1875) explained congenital heart defects as breaks in heart development at various ontogenesis stages.[25] Spitzer (1923) treats them as returns to one of the phylogenesis stages.[26] Krimsky (1963), synthesizing two previous points of view, considered congenital heart diseases as a stop of development at the certain stage of ontogenesis, corresponding to this or that stage of the phylogenesis.[27] Hence these theories can explain feminine and neutral types of defects only.

## Diagnosis [edit]

Many congenital heart defects can be diagnosed prenatally by fetal echocardiography. This is a test which can be done during the second trimester of pregnancy, when the woman is about 18–24 weeks pregnant.[28][29] It can be an abdominal ultrasound or transvaginal ultrasound.

If a baby is born with cyanotic heart disease, the diagnosis is usually made shortly after birth due to the blue colour of their skin (called cyanosis).[29]

If a baby is born with a septal defect or an obstruction defect, often their symptoms are only noticeable after several months or sometimes even after many years.[29]

### Classification [edit]

A number of classification systems exist for congenital heart defects. In 2000 the International Congenital Heart Surgery Nomenclature was developed to provide a generic classification system.[30]

### Hypoplasia [edit]

*Main articles: Hypoplastic left heart syndrome and Hypoplastic right heart syndrome*

Hypoplasia can affect the heart, typically resulting in the underdevelopment of the right ventricle or the left ventricle. This causes only one side of the heart to be capable of pumping blood to the body and lungs effectively. Hypoplasia of the heart is rare but is the most serious form of CHD. It is called hypoplastic left heart syndrome when it affects the left side of the heart and hypoplastic right heart syndrome when it affects the right side of the heart. In both conditions, the presence of a patent ductus arteriosus (and, when hypoplasia affects the right side of the heart, a patent foramen ovale) is vital to the infant's ability to survive until emergency heart surgery can be performed, since without these pathways blood cannot circulate to the body (or lungs, depending on which side of the heart is defective). Hypoplasia of the heart is generally a cyanotic heart defect.[31]

### Obstruction defects [edit]

*Main article: Ventricular outflow tract obstruction*

Obstruction defects occur when heart valves, arteries, or veins are abnormally narrow or blocked. Common defects include pulmonic stenosis, aortic stenosis, and coarctation of the aorta, with other types such as bicuspid aortic valve stenosis and subaortic stenosis being comparatively rare. Any narrowing or blockage can cause heart enlargement or hypertension.[32]

### Septal defects [edit]

The septum is a wall of tissue which separates the left heart from the right heart. Defects in the interatrial

septum or the interventricular septum allow blood to flow from the right side of the heart to the left, reducing the heart's efficiency.[32] Ventricular septal defects are collectively the most common type of CHD,[33] although approximately 30% of adults have a type of atrial septal defect called probe patent foramen ovale.[34]

### Cyanotic defects [edit]

Cyanotic heart defects are called such because they result in cyanosis, a bluish-grey discoloration of the skin due to a lack of oxygen in the body. Such defects include persistent truncus arteriosus, total anomalous pulmonary venous connection, tetralogy of Fallot, transposition of the great vessels, and tricuspid atresia.[32]

### Defects [edit]

- Aortic stenosis
- Atrial septal defect (ASD)
- Atrioventricular septal defect (AVSD)
- Bicuspid aortic valve
- Dextrocardia
- Double inlet left ventricle (DILV)
- Double outlet right ventricle (DORV)
- Ebstein's anomaly
- Hypoplastic left heart syndrome (HLHS)
- Hypoplastic right heart syndrome (HRHS)
- Mitral stenosis
- Pulmonary atresia
- Pulmonary stenosis
- Transposition of the great vessels
  - dextro-Transposition of the great arteries (d-TGA)
  - levo-Transposition of the great arteries (l-TGA)
- Tricuspid atresia
- Persistent truncus arteriosus
- Ventricular septal defect (VSD)
- Wolff-Parkinson-White syndrome (WPW)

Some conditions affect the great vessels or other vessels in close proximity to the heart, but not the heart itself, but are often classified as congenital heart defects.

- Coarctation of the aorta (CoA)
- Double aortic arch, aberrant subclavian artery, and other malformations of the great arteries
- Interrupted aortic arch (IAA)
- Patent ductus arteriosus (PDA)
- Scimitar syndrome (SS)
  - Partial anomalous pulmonary venous connection (PAPVC)
  - Total anomalous pulmonary venous connection (TAPVC)

Some constellations of multiple defects are commonly found together.

- tetralogy of Fallot (ToF)
- pentalogy of Cantrell
- Shone's syndrome/ Shone's complex / Shone's anomaly

## Treatment [edit]

Sometimes CHD improves without treatment. Other defects are so small that they do not require any treatment. Most of the time CHD is serious and requires surgery and/or medications. Medications include

diuretics, which aid the body in eliminating water, salts, and digoxin for strengthening the contraction of the heart. This slows the heartbeat and removes some fluid from tissues. Some defects require surgical procedures to restore circulation back to normal and in some cases, multiple surgeries are needed.

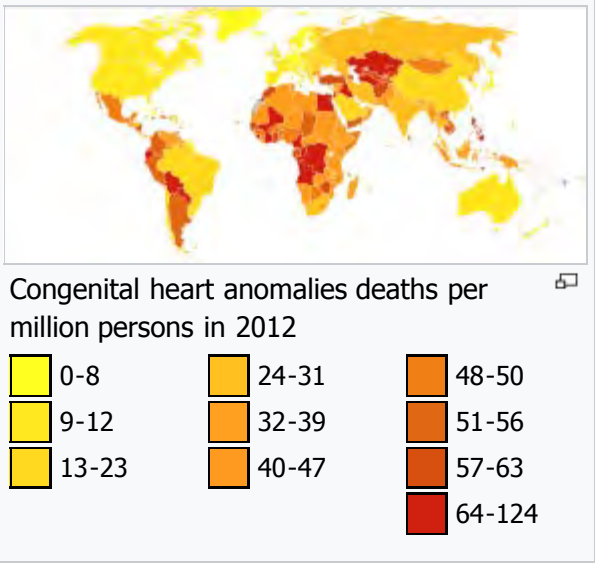
Interventional cardiology now offers patients minimally invasive alternatives to surgery for some patients. The Melody Transcatheter Pulmonary Valve (TPV), approved in Europe in 2006 and in the U.S. in 2010 under a Humanitarian Device Exemption (HDE), is designed to treat congenital heart disease patients with a dysfunctional conduit in their right ventricular outflow tract (RVOT). The RVOT is the connection between the heart and lungs; once blood reaches the lungs, it is enriched with oxygen before being pumped to the rest of the body. Transcatheter pulmonary valve technology provides a less-invasive means to extend the life of a failed RVOT conduit and is designed to allow physicians to deliver a replacement pulmonary valve via a catheter through the patient's blood vessels.

Most patients require lifelong specialized cardiac care, first with a pediatric cardiologist and later with an adult congenital cardiologist. There are more than 1.8 million adults living with congenital heart defects.[35]

## Epidemiology [edit]

Heart defects are among the most common birth defect.[9] In 2013 they were present in 34.3 million people.

Congenital heart defects resulted in about 223,000 deaths globally in 2010 down from 278,000 deaths in 1990.[36]




## Terminology [edit]

Congenital heart defects are known by a number of names including congenital heart anomaly, congenital heart disease, heart defects, and congenital cardiovascular malformations.[37]

## See also [edit]

- Congenital Heart Surgeons' Society

## References [edit]


1. ^ Hoffman JI, Kaplan S (June 2002). "The incidence of congenital heart disease". *J. Am. Coll. Cardiol.* **39** (12): 1890–900. doi:10.1016/S0735-1097(02)01886-7. PMID 12084585.
2. ^ *a b c d e* "What Are Congenital Heart Defects?". *National Heart, Lung, and Blood Institute*. July 1, 2011. Retrieved 10 August 2015.
3. ^ *a b c d e f g h i* Shanthi Mendis; Pekka Puska; Bo Norrving; World Health Organization (2011). *Global Atlas on Cardiovascular Disease Prevention and Control* (PDF). World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. pp. 3, 60. ISBN 978-92-4-156437-3.
4. ^ *a b c* "What Are the Signs and Symptoms of Congenital Heart Defects?". *National Heart, Lung, and Blood Institute*. July 1, 2011. Retrieved
17. ^ Jones, Kenneth Lyons (1997). *Smith's recognizable patterns of human malformation* (5th ed.). W.B. Saunders. pp. 316–317, 616–617. ISBN 0-7216-6115-7.
18. ^ Niessen, K.; Karsan, A. (2008). "Notch Signaling in Cardiac Development". *Circulation Research*. **102** (10): 1169–1181. doi:10.1161/CIRCRESAHA.108.174318. PMID 18497317.
19. ^ Spinner, N.; Hutchinson, A.; Krantz, I.; Kamath, B.; Pagon, R.; Bird, T.; Dolan, C.; Stephens, K. (20 July 2010). "Alagille Syndrome". GeneReviews. PMID 20301450.
20. ^ Tidyman, W. E.; Rauen, K. A. (2009). "The RASopathies: developmental syndromes of Ras/MAPK

the heart: from lineage determination to morphogenesis". *Cell*. **126** (6): 1037–1048. doi:10.1016/j.cell.2006.09.003. PMID 16990131.

10 August 2015.
5. ^ "What Causes Congenital Heart Defects?". *National,Heart, Lung, and Blood Institute*. July 1, 2011. Retrieved 10 August 2015.
6. ^ a b Dean, SV; Lassi, ZS; Imam, AM; Bhutta, ZA (26 September 2014). "Preconception care: nutritional risks and interventions.". *Reproductive health*. 11 Suppl 3: S3. doi:10.1186/1742-4755-11-s3-s3. PMID 25415364.
7. ^ a b c Milunsky, Aubrey (2011). "1". *Genetic Disorders and the Fetus: Diagnosis, Prevention and Treatment*. John Wiley & Sons. ISBN 9781444358216.
8. ^ a b c "How Are Congenital Heart Defects Treated?". *National Heart, Lung, and Blood Institute*. July 1, 2011. Retrieved 10 August 2015.
9. ^ a b c Global Burden of Disease Study 2013, Collaborators (7 June 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/S0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
10. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013". *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
11. ^ "Heart Defects: Birth Defects". Merck. Retrieved 30 July 2010.
12. ^ "National Heart, Lung, and Blood Institute". Retrieved 30 July 2010.
13. ^ a b Hoffman, J. (2005). *Essential Cardiology: Principles and Practice*. Totowa, NJ: Humana Press. p. 393. ISBN 1-58829-370-X.
14. ^ a b c d Schoen, Frederick J.; Richard N., Mitchell (2010). "12. The Heart". In Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson; et al. *Robbins and Cotran Pathologic Basis of Disease* (8th ed.). Saunders Elsevier. ISBN 978-1-4160-3121-5.
15. ^ Thienpont B, Mertens L, de Ravel T, et al. (November 2007). "Submicroscopic chromosomal imbalances detected by array-CGH are a frequent cause of congenital heart defects in selected patients". *Eur. Heart J.* **28** (22): 2778–84. doi:10.1093/eurheartj/ehl560. PMID 17384091.
16. ^ a b c Srivastava, D. (2006). "Making or breaking pathway dysregulation". *Current Opinion in Genetics & Development*. **19** (3): 230–6. doi:10.1016/j.gde.2009.04.001. PMC 2743116. PMID 19467855.
21. ^ "Factors Contributing to Congenital Heart Disease". Lucile Packard Children's Hospital at Stanford. Retrieved 30 July 2010.
22. ^ Mills JL, Troendle J, Conley MR, Carter T, Druschel CM (June 2010). "Maternal obesity and congenital heart defects: a population-based study". *Am. J. Clin. Nutr.* **91** (6): 1543–9. doi:10.3945/ajcn.2009.28865. PMC 2869507. PMID 20375192.
23. ^ Rasmussen SA, Galuska DA (June 2010). "Prepregnancy obesity and birth defects: what's next?". *Am. J. Clin. Nutr.* **91** (6): 1539–40. doi:10.3945/ajcn.2010.29666. PMID 20427732.
24. ^ a b c d Larsen, William J. (1993). "7. Development of the Heart". *Human Embryology*. Churchill Livingstone. ISBN 0-443-08724-5.
25. ^ Rokitarisky K. E. (1875) Die defecte der Scheidewande des Herzens. Wien.
26. ^ Spitzer A. (1923) Arch. Pathol. Anat. **243**, 81–272.
27. ^ Krimski L. D. (1963) Pathological anatomy of congenital heart defects and complications after their surgical treatment. M., Medicine.
28. ^ MedlinePlus Encyclopedia *Fetal echocardiography*
29. ^ a b c http://www.nhs.uk/Conditions/Congenital-heart-disease/Pages/Diagnosis.aspx
30. ^ Thomas P. Shanley; Derek S. Wheeler; Hector R. Wong (2007). *Pediatric critical care medicine: basic science and clinical evidence*. Berlin: Springer. p. 666. ISBN 1-84628-463-5.
31. ^ "Hypoplastic Left Heart Syndrome". American Heart. Retrieved 30 July 2010.
32. ^ a b c "Congenital Cardiovascular Defects". American Heart. Retrieved 30 July 2010.
33. ^ "Ventricular Septal Defect". eMedicine Health. Retrieved 30 July 2010.
34. ^ "Circulatory Changes at Birth". University of California at Berkeley. Retrieved 30 July 2010.
35. ^ "Adult Congenital Heart Association". Adult Congenital Heart Association. Retrieved 30 July 2010.
36. ^ Lozano, R (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
37. ^ "Other Names for Congenital Heart Defects". July 1, 2011. Retrieved 10 August 2015.

## External links [edit]

- Congenital heart defect at DMOZ
- Cove Point Foundation Congenital Heart Disease website — comprehensive patient education, including

animations of surgeries and interventions
- Congenital heart disease information for parents.

| v · t · e · | Congenital heart defects (Q20–Q24, 745–746) | |
|---|---|---|
| **Cardiac shunt/ heart septal defect** | **Aortopulmonary septal defect** | *R→L:* Double outlet right ventricle (Taussig–Bing syndrome · · Transposition of the great vessels (dextro · levo · · Persistent truncus arteriosus · Aortopulmonary window · |
| | **Atrial septal defect** | *L→R:* Sinus venosus atrial septal defect · Lutembacher's syndrome · |
| | **Ventricular septal defect** | *L→R and R→L:* Eisenmenger's syndrome · *R→L, with other conditions:* Tetralogy of Fallot · |
| | **Atrioventricular septal defect** | *L→R:* Ostium primum · |
| **Valvular heart disease/ heart chambers** | **Right** | *pulmonary valves* (stenosis · insufficiency · · *tricuspid valves* (stenosis · atresia · Ebstein's anomaly · · Hypoplastic right heart syndrome (Uhl anomaly · · |
| | **Left** | *aortic valves* (stenosis · insufficiency · bicuspid · · *mitral valves* (stenosis · regurgitation · · Hypoplastic left heart syndrome · |
| **Other** | Dextrocardia · Levocardia · Cor triatriatum · Crisscross heart · Brugada syndrome · Coronary artery anomaly · Anomalous aortic origin of a coronary artery · Ventricular inversion · | |

Categories: Congenital heart defects | Health issues in pregnancy

# Down syndrome

From Wikipedia, the free encyclopedia

**Down syndrome** (**DS** or **DNS**), also known as **trisomy 21**, is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21.[1] It is typically associated with physical growth delays, characteristic facial features and mild to moderate intellectual disability.[2] The average IQ of a young adult with Down syndrome is 50, equivalent to the mental ability of an 8- or 9-year-old child, but this can vary widely.[3]

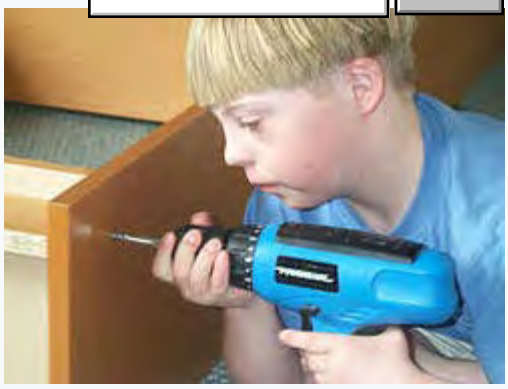
The parents of the affected individual are typically genetically normal.[4] The extra chromosome occurs by chance.[5] The possibility increases from less than 0.1% in 20-year-old mothers to 3% in those age 45.[6] There is no known behavioral activity or environmental factor that changes the possibility.[5] Down syndrome can be identified during pregnancy by prenatal screening followed by diagnostic testing or after birth by direct observation and genetic testing.[7] Since the introduction of screening, pregnancies with the diagnosis are often terminated.[8][9] Regular screening for health problems common in Down syndrome is recommended throughout the person's life.[3]

There is no cure for Down syndrome.[10] Education and proper care have been shown to improve quality of life.[11] Some children with Down syndrome are educated in typical school classes, while others require more specialized education.[12] Some individuals with Down syndrome graduate from high school and a few attend post-secondary education.[13] In adulthood, about 20% in the United States do paid work in some capacity[14] with many requiring a sheltered work environment.[12] Support in financial and legal matters is often needed.[15] Life expectancy is around 50 to 60 years in the developed world with proper health care.[3][15]

Down syndrome is one of the most common chromosome abnormalities in humans.[3] It occurs in about one per 1000 babies born each year.[2] In 2013, Down syndrome was present in 8.5 million individuals and resulted in 36,000 deaths down from 43,000 deaths in 1990.[16][17] It is named after John Langdon Down, the British doctor who fully described the syndrome in 1866.[18] Some aspects of the condition were described earlier by Jean-Étienne Dominique Esquirol in 1838 and Édouard Séguin in 1844.[19] The genetic cause of Down syndrome—an extra copy of chromosome 21—was identified by French researcher Jérôme

**Down syndrome**

**Synonyms** Downs syndrome



A boy with Down syndrome assembling a bookcase

**Classification and external resources**

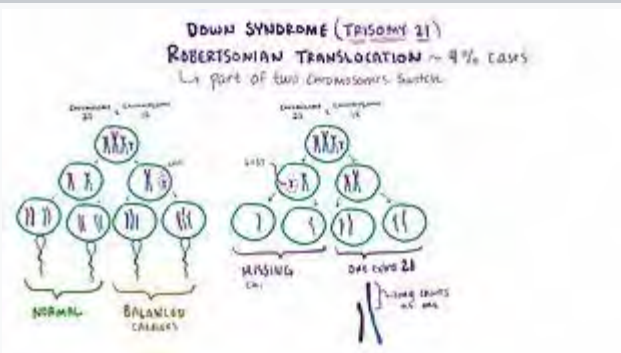
| | |
|---|---|
| **Specialty** | Medical genetics, pediatrics |
| **ICD-10** | Q90 |
| **ICD-9-CM** | 758.0 |
| **OMIM** | 190685 |
| **DiseasesDB** | 3898 |
| **MedlinePlus** | 000997 |
| **eMedicine** | ped/615 |
| **Patient UK** | Down syndrome |
| **MeSH** | D004314 |

[edit on Wikidata]

Lejeune in 1959.[18]








Play media

Video explanation

# Signs and symptoms

Those with Down syndrome nearly always have physical and intellectual disabilities.[20] As adults, their mental abilities are typically similar to those of an 8- or 9-year-old.[3] They also typically have poor immune function[4] and generally reach developmental milestones at a later age.[15] They have an increased risk of a number of other health problems, including congenital heart defect, epilepsy, leukemia, thyroid diseases, and mental disorders, among others.[18]

| Characteristics | Percentage | Characteristics | Percentag |
|---|---|---|---|
| Mental | 99%[21] | Abnormal teeth | 60%[22] |

| | | | |
|---|---|---|---|
| impairment | | | |
| Stunted growth | 90%[23] | Slanted eyes | 60%[4] |
| Umbilical hernia | 90%[24] | Shortened hands | 60%[22] |
| Increased skin back of neck | 80%[18] | Short neck | 60%[22] |
| Low muscle tone | 80%[25] | Obstructive sleep apnea | 60%[18] |
| Narrow roof of mouth | 76%[22] | Bent fifth finger tip | 57%[4] |
| Flat head | 75%[4] | Brushfield spots in the iris | 56%[4] |
| Flexible ligaments | 75%[4] | Single transverse palmar crease | 53%[4] |
| Proportionally large tongue[26] | 75%[25] | Protruding tongue | 47%[22] |
| Abnormal outer ears | 70%[18] | Congenital heart disease | 40%[22] |
| Flattened nose | 68%[4] | Strabismus | ~35%[2] |
| Separation of first and second toes | 68%[22] | Undescended testicles | 20%[27] |

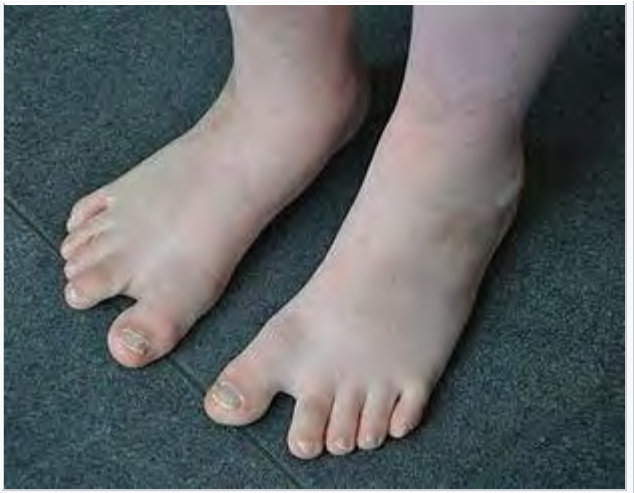


A drawing of the facial features of a baby with Down syndrome


An eight-year-old boy with Down syndrome

## Physical

People with Down syndrome may have some or all of these physical characteristics: a small chin, slanted eyes, poor muscle tone, a flat nasal bridge, a single crease of the palm, and a protruding tongue due to a small mouth and relatively large tongue.[25][26] These airway changes lead to obstructive sleep apnea in around half of those with Down syndrome.[18] Other common features include: a flat and wide face,[25] a short neck, excessive joint flexibility, extra space between big toe and second toe, abnormal patterns on the fingertips and short fingers.[22][25] Instability of the atlantoaxial joint occurs in about 20% and may lead to spinal cord injury in 1–2%.[3][15] Hip


Feet of a boy with Down syndrome

dislocations may occur without trauma in up to a third of people with Down syndrome.[18]

Growth in height is slower, resulting in adults who tend to have short stature—the average height for men is 154 cm (5 ft 1 in) and for women is 142 cm (4 ft 8 in).[28] Individuals with Down syndrome are at increased risk for obesity as they age.[18] Growth charts have been developed specifically for children with Down syndrome.[18]

## Neurological

Most individuals with Down syndrome have mild (IQ: 50–69) or moderate (IQ: 35–50) intellectual disability with some cases having severe (IQ: 20–35) difficulties.[2][29] Those with mosaic Down syndrome typically have IQ scores 10–30 points higher.[30] As they age, people with Down syndrome typically perform less well than their same-age peers.[29][31] Some after 30 years of age may lose their ability to speak.[3] This syndrome causes about a third of cases of intellectual disability.[4] Many developmental milestones are delayed with the ability to crawl typically occurring around 8 months rather than 5 months and the ability to walk independently typically occurring around 21 months rather than 14 months.[32]

Commonly, individuals with Down syndrome have better language understanding than ability to speak.[18][29] Between 10 and 45% have either a stutter or rapid and irregular speech, making it difficult to understand them.[33] They typically do fairly well with social skills.[18] Behavior problems are not generally as great an issue as in other syndromes associated with intellectual disability.[29] In children with Down syndrome, mental illness occurs in nearly 30% with autism occurring in 5–10%.[15] People with Down syndrome experience a wide range of emotions.[34] While people with Down syndrome are generally happy,[35] symptoms of depression and anxiety may develop in early adulthood.[3]

Children and adults with Down syndrome are at increased risk of epileptic seizures, which occur in 5–10% of children and up to 50% of adults.[3] This includes an increased risk of a specific type of seizure called infantile spasms.[18] Many (15%) who live 40 years or longer develop Alzheimer disease.[36] In those who reach 60 years of age, 50–70% have the disease.[3]

## Senses


Brushfield spots, visible in the irises of a baby with Down syndrome

Hearing and vision disorders occur in more than half of people with Down syndrome.[18] Vision problems occur in 38 to 80%.[2] Between 20 and 50% have strabismus, in which the two eyes do not move together.[2] Cataracts (cloudiness of the lens of the eye) occur in 15%,[15] and may be present at birth.[2] Keratoconus (a thin, cone-shaped cornea)[3] and glaucoma (increased eye pressure) are also more common,[2] as are refractive errors requiring glasses or contacts.[3] Brushfield spots (small white or grayish/brown spots on the outer part of the iris) are present in 38 to 85% of individuals.[2]

Hearing problems are found in 50–90% of children with Down syndrome.[37] This is often the result of otitis media with effusion which occurs in 50–70%[15] and chronic ear infections which occur in 40 to 60%.[38] Ear infections often begin in the first year of life and are partly due to poor eustachian tube function.[39][40]

Excessive ear wax can also cause hearing loss due to obstruction of the outer ear canal.[3] Even a mild degree of hearing loss can have negative consequences for speech, language understanding, and academics.[2][40] Additionally, it is important to rule out hearing loss as a factor in social and cognitive deterioration.[41] Age-related hearing loss of the sensorineural type occurs at a much earlier age and affects 10–70% of people with Down syndrome.[3]

## Heart

The rate of congenital heart disease in newborns with Down syndrome is around 40%.[22] Of those with heart disease, about 80% have an atrioventricular septal defect or ventricular septal defect with the former being more common.[3] Mitral valve problems become common as people age, even in those without heart problems at birth.[3] Other problems that may occur include tetralogy of Fallot and patent ductus arteriosus.[39] People with Down syndrome have a lower risk of hardening of the arteries.[3]

## Cancer

Although the overall risk of cancer is not changed,[42] the risk of leukemia and testicular cancer is increased and risk of solid cancers is reduced.[3] Solid cancers are believed to be less common due to increased expression of tumor suppressor genes present on chromosome 21.[43]

Cancers of the blood are 10 to 15 times more common in children with Down syndrome.[18] In particular, acute lymphoblastic leukemia is 20 times more common and the megakaryoblastic form of acute myeloid leukemia is 500 times more common.[44] Transient myeloproliferative disease, a disorder of blood cell production that does not occur outside of Down syndrome, affects 3–10% of infants.[44][45] The disorder is typically not serious but occasionally can be.[45] It resolves most times without treatment; however, in those who have had it, a 20 to 30% risk of developing acute lymphoblastic leukemia at a later time exists.[45]

## Endocrine

Problems of the thyroid gland occur in 20–50% of individuals with Down syndrome.[3][18] Low thyroid is the most common form, occurring in almost half of all individuals.[3] Thyroid problems can be due to a poorly or nonfunctioning thyroid at birth (known as congenital hypothyroidism) which occurs in 1%[15] or can develop later due to an attack on the thyroid by the immune system resulting in Graves' disease or autoimmune hypothyroidism.[46] Type 1 diabetes mellitus is also more common.[3]

## Gastrointestinal

Constipation occurs in nearly half of people with Down syndrome and may result in changes in behavior.[18] One potential cause is Hirschsprung's disease, occurring in 2–15%, which is due to a lack of nerve cells controlling the colon.[47] Other frequent congenital problems include duodenal atresia, pyloric stenosis, Meckel diverticulum, and imperforate anus.[39] Celiac disease affects about 7–20%[3][18] and gastroesophageal reflux disease is also more common.[39]

## Teeth

Individuals with Down syndrome tend to be more susceptible to gingivitis as well as early, severe periodontal disease, necrotising ulcerative gingivitis, and early tooth loss, especially in the lower front teeth.[48][49] While plaque and poor oral hygiene are contributing factors, the severity of these periodontal disease cannot be explained solely by external factors.[49] Research suggests that the severity is likely a result of a weakened immune system.[49][50] The weakened immune system also contributes to increased incidence of yeast infections in the mouth (from Candida albicans).[50]

Individuals with Down syndrome also tend to have a more alkaline saliva resulting in a greater resistance to tooth decay, despite decreased quantities of saliva,[51] less effective oral hygiene habits and higher plaque indexes.[48][50][51][52]

Higher rates of tooth wear and bruxism are also common.[50] Other common oral manifestations of Down syndrome include enlarged hypotonic tongue, crusted and hypotonic lips, mouth breathing, narrow palate with crowded teeth, class III malocclusion with an underdeveloped maxilla and posterior crossbite, delayed exfoliation of baby teeth and delayed eruption of adult teeth, shorter roots on teeth, and often missing and malformed (usually smaller) teeth.[48][50][51][52] Less common manifestations include cleft lip and palate, enamel hypocalcification (20% prevalence).[52]

### Fertility

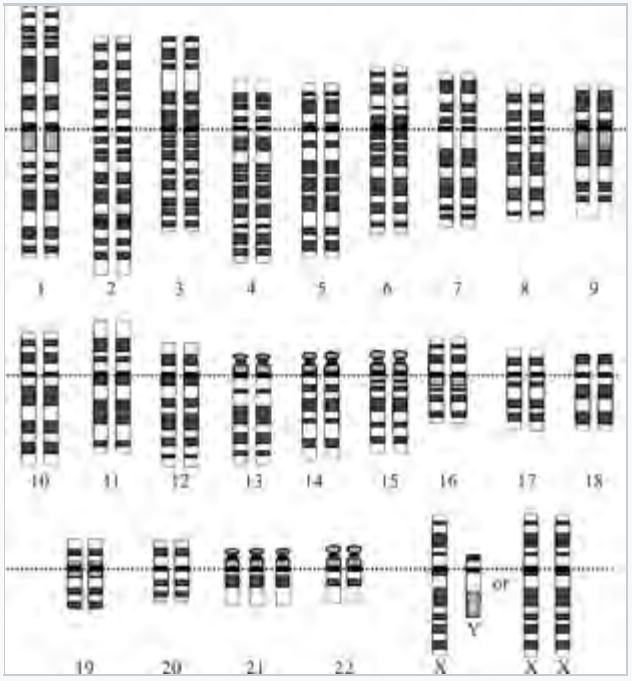
Males with Down syndrome usually do not father children, while females have lower rates of fertility relative to those who are unaffected.[53] Fertility is estimated to be present in 30–50% of females.[54] Menopause typically occurs at an earlier age.[3] The poor fertility in males is thought to be due to problems with sperm development; however, it may also be related to not being sexually active.[53] As of 2006, three instances of males with Down syndrome fathering children and 26 cases of females having children have been reported.[53] Without assisted reproductive technologies, around half of the children of someone with Down syndrome will also have the syndrome.[53][55]

## Genetics

*Main article: Genetics of Down syndrome*

Down syndrome is caused by having three copies of the genes on chromosome 21, rather than the usual two.[1][56] The parents of the affected individual are typically genetically normal.[4] Those who have one child with Down syndrome have about a 1% risk of having a second child with the syndrome, if both parents are found to have normal karyotypes.[54]

The extra chromosome content can arise through several different ways. The most common cause (about 92–95% of cases) is a complete extra copy of chromosome 21, resulting in trisomy 21.[55][57] In 1.0 to 2.5% of cases, some of the cells in the body are normal and others have trisomy 21, known as mosaic Down syndrome.[54][58] The other common mechanisms that can give rise to Down syndrome include: a Robertsonian translocation, isochromosome, or ring chromosome. These contain additional material from chromosome 21 and occur in about 2.5% of cases.[18][54] An isochromosome results when the two long arms of a chromosome separate together rather than the long and short arm separating together during egg or sperm development.[55]



Karyotype for trisomy Down syndrome: Notice the three copies of chromosome 21

### Trisomy 21

Trisomy 21 (also known by the karyotype 47,XX,+21 for females and 47,XY,+21 for males)[59] is caused by a failure of the 21st chromosome to separate during egg or sperm development.[55] As a result, a sperm or egg cell is produced with an extra copy of chromosome 21; this cell thus has 24 chromosomes. When combined with a normal cell from the other parent, the baby has 47 chromosomes, with three copies of

chromosome 21.[1][55] About 88% of cases of trisomy 21 result from nonseparation of the chromosomes in the mother, 8% from nonseparation in the father, and 3% after the egg and sperm have merged.[60]

### Translocation

The extra chromosome 21 material may also occur due to a Robertsonian translocation in 2–4% of cases.[54][61] In this situation, the long arm of chromosome 21 is attached to another chromosome, often chromosome 14.[62] In a male affected with Down syndrome, it results in a karyotype of 46XY,t(14q21q).[62][63] This may be a new mutation or previously present in one of the parents.[64] The parent with such a translocation is usually normal physically and mentally;[62] however, during production of egg or sperm cells, a higher chance of creating reproductive cells with extra chromosome 21 material exists.[61] This results in a 15% chance of having a child with Down syndrome when the mother is affected and a less than 5% probability if the father is affected.[64] The probability of this type of Down syndrome is not related to the mother's age.[62] Some children without Down syndrome may inherit the translocation and have a higher probability of having children of their own with Down syndrome.[62] In this case it is sometimes known as familial Down syndrome.[65]

## Mechanism

The extra genetic material present in DS results in overexpression of a portion of the 310 genes located on chromosome 21.[56] This overexpression has been estimated at around 50%.[54] Some research has suggested the Down syndrome critical region is located at bands 21q22.1–q22.3,[66] with this area including genes for amyloid, superoxide dismutase, and likely the ETS2 proto oncogene.[67] Other research, however, has not confirmed these findings.[56] microRNAs is also proposed to be involved.[68]

The dementia which occurs in Down syndrome is due to an excess of amyloid beta peptide produced in the brain and is similar to Alzheimer's disease.[69] This peptide is processed from amyloid precursor protein, the gene for which is located on chromosome 21.[69] Senile plaques and neurofibrillary tangles are present in nearly all by 35 years of age, though dementia may not be present.[4] Those with DS also lack a normal number of lymphocytes and produce less antibodies which contributes to their increased risk of infection.[18]

### Epigenetics

Down syndrome is associated with an increased risk of many chronic diseases that are typically associated with older age such as Alzheimer's disease. The accelerated aging suggest that trisomy 21 increases the biological age of tissues, but molecular evidence for this hypothesis is sparse. According to a biomarker of tissue age known as epigenetic clock, trisomy 21 increases the age of blood and brain tissue (on average by 6.6 years).[70]

## Screening

Guidelines recommend screening for Down syndrome to be offered to all pregnant women, regardless of age.[71][72] A number of tests are used, with varying levels of accuracy. They are typically used in combination to increase the detection rate.[18] None can be definitive, thus if screening is positive, either amniocentesis or chorionic villous sampling is required to confirm the diagnosis.[71] Screening in both the first and second trimesters is better than just screening in the first trimester.[71] The different screening techniques in use are able to pick up 90 to 95% of cases with a false-positive rate of 2 to 5%.[73]

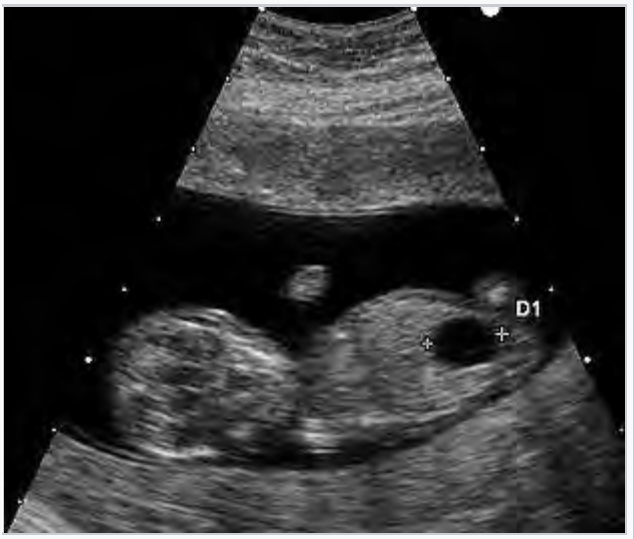
**First- and second-trimester screening**[71]

| | Week of | | | |
|---|---|---|---|---|

| Screen | pregnancy when performed | Detection rate | False positive | Description |
|---|---|---|---|---|
| Combined test | 10–13.5 wks | 82–87% | 5% | Uses ultrasound to measure nuchal translucency in addition to blood tests for free or total beta-hCG and PAPP-A |
| Quad screen | 15–20 wks | 81% | 5% | Measures the maternal serum alpha-fetoprotein, unconjugated estriol, hCG, and inhibin-A |
| Integrated test | 15–20 wks | 94–96% | 5% | Is a combination of the quad screen, PAPP-A, and NT |
| Cell-free fetal DNA | From 10 wks[74] | 96–100%[75] | 0.3%[76] | A blood sample is taken from the mother by venipuncture and is sent for DNA analysis. |

### Ultrasound

Ultrasound imaging can be used to screen for Down syndrome. Findings that indicate increased risk when seen at 14 to 24 weeks of gestation include a small or no nasal bone, large ventricles, nuchal fold thickness, and an abnormal right subclavian artery, among others.[77] The presence or absence of many markers is more accurate.[77] Increased fetal nuchal translucency (NT) indicates an increased risk of Down syndrome picking up 75–80% of cases and being falsely positive in 6%.[78]

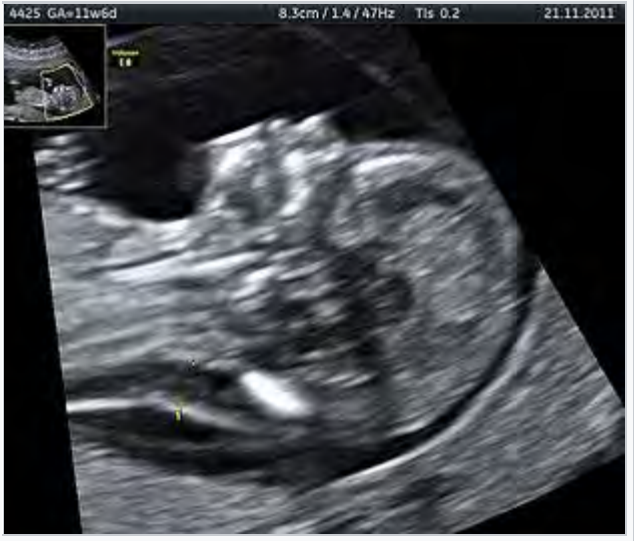


Ultrasound of fetus with Down syndrome showing a large bladder

### Blood tests

Several blood markers can be measured to predict the risk of Down syndrome during the first or second trimester.[73][79] Testing in both trimesters is sometimes recommended and test results are often combined with ultrasound results.[73] In the second trimester, often two or three tests are used in combination with two or three of: α-fetoprotein, unconjugated estriol, total hCG, and free βhCG detecting about 60–70% of cases.[79]

Testing of the mother's blood for fetal DNA is being studied and appears promising in the first trimester.[75][80] The International Society for Prenatal Diagnosis considers it a reasonable screening option for those women whose pregnancies are at a high risk for trisomy 21.[81] Accuracy has been reported at 98.6% in the first trimester of pregnancy.[18] Confirmatory testing by invasive techniques (amniocentesis, CVS) is still required to confirm the screening result.[81]



Enlarged NT and absent nasal bone in a fetus at 11 weeks with Down syndrome

## Diagnosis

### Before birth

When screening tests predict a high risk of Down syndrome, a more invasive diagnostic test (amniocentesis

or chorionic villus sampling) is needed to confirm the diagnosis.[71] If Down syndrome occurs in one in 500 pregnancies and the test used has a 5% false-positive rate, this means, of 26 women who test positive on screening, only one will have Down syndrome confirmed.[73] If the screening test has a 2% false-positive rate, this means one of eleven who test positive on screening have a fetus with DS.[73] Amniocentesis and chorionic villus sampling are more reliable tests, but they increase the risk of miscarriage between 0.5 and 1%.[82] The risk of limb problems is increased in the offspring due to the procedure.[82] The risk from the procedure is greater the earlier it is performed, thus amniocentesis is not recommended before 15 weeks gestational age and chorionic villus sampling before 10 weeks gestational age.[82]

### Abortion rates

About 92% of pregnancies in Europe with a diagnosis of Down syndrome are terminated.[9] In the United States, termination rates are around 67%, but this rate varied from 61% to 93% among different populations evaluated.[8] When nonpregnant people are asked if they would have a termination if their fetus tested positive, 23–33% said yes, when high-risk pregnant women were asked, 46–86% said yes, and when women who screened positive are asked, 89–97% say yes.[83]

### After birth

The diagnosis can often be suspected based on the child's physical appearance at birth.[15] An analysis of the child's chromosomes is needed to confirm the diagnosis, and to determine if a translocation is present, as this may help determine the risk of the child's parents having further children with Down syndrome.[15] Parents generally wish to know the possible diagnosis once it is suspected and do not wish pity.[18]

## Management

Efforts such as early childhood intervention, screening for common problems, medical treatment where indicated, a good family environment, and work-related training can improve the development of children with Down syndrome. Education and proper care can improve quality of life.[11] Raising a child with Down syndrome is more work for parents than raising an unaffected child.[84] Typical childhood vaccinations are recommended.[18]

### Health screening

A number of health organizations have issued recommendations for screening those with Down syndrome for particular diseases.[85] This is recommended to be done systematically.[18]

At birth, all children should get an electrocardiogram and ultrasound of the heart.[18] Surgical repair of heart problems may be required as early as three months of age.[18] Heart valve problems may occur in young adults, and further ultrasound evaluation may be needed in adolescents and in early adulthood.[18] Due to the elevated risk of testicular cancer, some recommend checking the person's testicles yearly.[3]

**Recommended screening**

| Testing | Children[85] | Adults[3] |
|---|---|---|
| Hearing | 6 months, 12 months, then yearly | 3–5 years |
| T4 and TSH | 6 months, then yearly | |
| Eyes | 6 months, then yearly | 3–5 years |
| Teeth | 2 years, then every 6 months | |
| Coeliac disease | Between 2 and 3 years of age, or earlier if symptoms occur | |
| Sleep study | 3 to 4 years, or earlier if symptoms of obstructive sleep apnea occur | |
| Neck X-rays | Between 3 and 5 years of age | |

## Cognitive development

Hearing aids or other amplification devices can be useful for language learning in those with hearing loss.[18] Speech therapy may be useful and is recommended to be started around 9 months of age.[18] As those with Down's typically have good hand-eye coordination, learning sign language may be possible.[29] Augmentative and alternative communication methods, such as pointing, body language, objects, or pictures, are often used to help with communication.[86] Behavioral issues and mental illness are typically managed with counseling or medications.[15]

Education programs before reaching school age may be useful.[2] School-age children with Down syndrome may benefit from inclusive education (whereby students of differing abilities are placed in classes with their peers of the same age), provided some adjustments are made to the curriculum.[87] Evidence to support this, however, is not very strong.[88] In the United States, the Individuals with Disabilities Education Act of 1975 requires public schools generally to allow attendance by students with Down's.[89]

Individuals with Down syndrome may learn better visually. Drawing may help with language, speech, and reading skills. Children with Down syndrome still often have difficulty with sentence structure and grammar, as well as developing the ability to speak clearly.[90] Several types of early intervention can help with cognitive development. Efforts to develop motor skills include physical therapy, speech and language therapy, and occupational therapy. Physical therapy focuses specifically on motor development and teaching children to interact with their environment. Speech and language therapy can help prepare for later language. Lastly, occupational therapy can help with skills needed for later independence.[91]

## Other

Tympanostomy tubes are often needed[18] and often more than one set during the person's childhood.[37] Tonsillectomy is also often done to help with sleep apnea and throat infections.[18] Surgery, however, does not always address the sleep apnea and a continuous positive airway pressure (CPAP) machine may be useful.[37] Physical therapy and participation in physical education may improve motor skills.[92] Evidence to support this in adults, however, is not very good.[93]

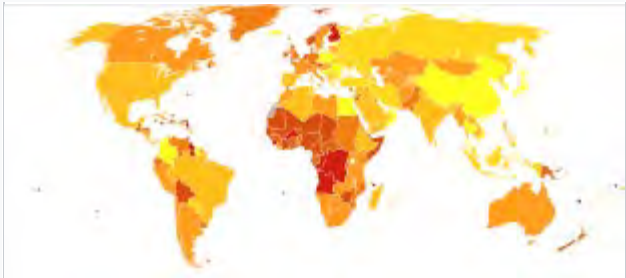
Efforts to prevent respiratory syncytial virus (RSV) infection with human monoclonal antibodies should be considered, especially in those with heart problems.[2] In those who develop dementia there is no evidence for memantine,[94] donepezil,[95] rivastigmine,[96] or galantamine.[97]

Plastic surgery has been suggested as a method of improving the appearance and thus the acceptance of people with Down's.[98] It has also been proposed as a way to improve speech.[98] Evidence, however, does not support a meaningful difference in either of these outcomes.[98] Plastic surgery on children with Down syndrome is uncommon,[99] and continues to be controversial.[98] The U.S. National Down Syndrome Society views the goal as one of mutual respect and acceptance, not appearance.[99]

Many alternative medical techniques are used in Down syndrome; however, they are poorly supported by evidence.[98] These include: dietary changes, massage, animal therapy, chiropractics and naturopathy, among others.[98] Some proposed treatments may also be harmful.[54]

# Prognosis

Between 5 and 15% of children with Down syndrome in Europe attend regular school.[100] Some graduate from high school; however, most do not.[13] Of those with intellectual disability in the United States who attended high school about 40% graduated.[101] Many learn to read and write and some are able to do paid work.[13] In adulthood about 20% in the United States do paid work in some



Deaths due to Downs syndrome per million persons in 2012

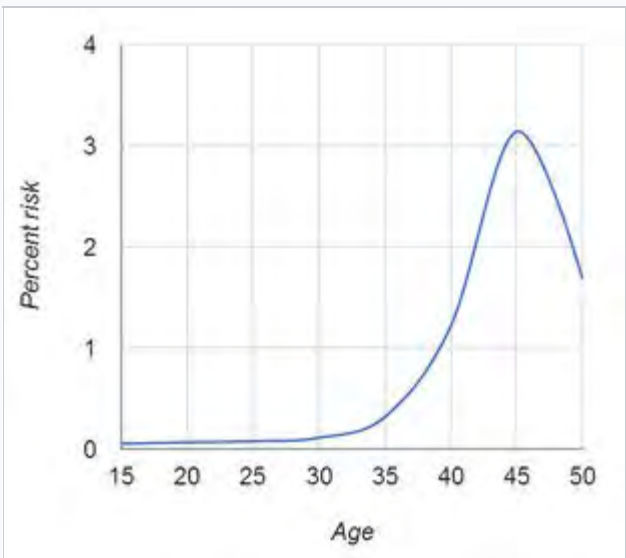
| | | |
|---|---|---|
| 0-0 | 3-3 | 6-6 |
| 1-1 | 4-4 | 7-8 |
| 2-2 | 5-5 | 9-16 |

capacity.[14][102] In Europe, however, less than 1% have regular jobs.[100] Many are able to live semi-independently,[4] but they often require help with financial, medical, and legal matters.[15] Those with mosaic Down syndrome usually have better outcomes.[54]

Individuals with Down syndrome have a higher risk of early death than the general population.[18] This is most often from heart problems or infections.[2][3] Following improved medical care, particularly for heart and gastrointestinal problems, the life expectancy has increased.[2] This increase has been from 12 years in 1912,[103] to 25 years in the 1980s,[2] to 50 to 60 years in the developed world in the 2000s.[3][15] Currently between 4 and 12% die in the first year of life.[45] The probability of long-term survival is partly determined by the presence of heart problems. In those with congenital heart problems 60% survive to 10 years and 50% survive to 30 years of age.[4] In those without heart problems 85% survive to 10 years and 80% survive to 30 years of age.[4] About 10% live to 70 years of age.[55] The National Down Syndrome Society have developed information regarding the positive aspects of life with Down syndrome.[104]

## Epidemiology

Globally, as of 2010, Down syndrome occurs in about 1 per 1000 births[2] and results in about 17,000 deaths.[105] More children are born with Down syndrome in countries where abortion is not allowed and in countries where pregnancy more commonly occurs at a later age.[2] About 1.4 per 1000 live births in the United States[106] and 1.1 per 1000 live births in Norway are affected.[3] In the 1950s, in the United States, it occurred in 2 per 1000 live births with the decrease since then due to prenatal screening and abortions.[64] The number of pregnancies with Down syndrome is more than two times greater with many spontaneously aborting.[15] It is the cause of 8% of all congenital disorders.[2]




The risk of having a Down syndrome pregnancy in relation to a mother's age[6]

Maternal age affects the chances of having a pregnancy with Down syndrome.[6] At age 20, the chance is one in 1441; at age 30, it is one in 959; at age 40, it is one in 84; and at age 50 it is one in 44.[6] Although the probability increases with maternal age, 70% of children with Down syndrome are born to women 35 years of age and younger, because younger people have more children.[6] The father's older age is also a risk factor in women older than 35, but not in women younger than 35, and may partly explain the increase in risk as women age.[107]

## History

It has been suggested that this Early Netherlandish painting depicts a person with Down syndrome as one of the angels.[108]

English physician John Langdon Down first described Down syndrome in 1862, recognizing it as a distinct type of mental disability, and again in a more widely published report in 1866.[18][109][110] Édouard Séguin described it as separate from cretinism in 1944.[19][111] By the 20th century, Down syndrome had become the most recognizable form of mental disability.

In antiquity, many infants with disabilities were either killed or abandoned.[19] A number of historical pieces of art are believed to portray Down syndrome, including pottery from AD 500 from South America and the 16th-century painting *The Adoration of the Christ Child*.[19]

In the 20th century, many individuals with Down syndrome were institutionalized, few of the associated medical problems were treated, and most died in infancy or early adult life. With the rise of the eugenics movement, 33 of the then 48 U.S. states and several countries began programs of forced sterilization of individuals with Down syndrome and comparable degrees of disability. Action T4 in Nazi Germany made public policy of a program of systematic involuntary euthanization.[112]

With the discovery of karyotype techniques in the 1950s, it became possible to identify abnormalities of chromosomal number or shape.[111] In 1959, Jérôme Lejeune reported the discovery that Down syndrome resulted from an extra chromosome.[18] However, Lejeune's claim to the discovery has been disputed,[113] and in 2014, the Scientific Council of the French Federation of Human Genetics unanimously awarded its Grand Prize to his colleague Marthe Gautier for this discovery.[114] As a result of this discovery, the condition became known as trisomy 21.[115] Even before the discovery of its cause, the presence of the syndrome in all races, its association with older maternal age, and its rarity of recurrence had been noticed. Medical texts had assumed it was caused by a combination of inheritable factors that had not been identified. Other theories had focused on injuries sustained during birth.[116]

# Society and culture

*See also: List of people with Down syndrome*

## Name

Due to his perception that children with Down syndrome shared facial similarities with those of Blumenbach's Mongolian race, John Langdon Down used the term 'mongoloid'.[55][117] He felt that the existence of Down syndrome confirmed that all peoples were genetically related.[118] In the 1950s with discovery of the underlying cause as being related to chromosomes, concerns about the race based nature of the name increased.[119]

In 1961, 19 scientists suggested that "mongolism" had "misleading connotations" and had become "an embarrassing term".[120][121] The World Health Organization (WHO) dropped the term in 1965 after a request by the delegation from the Mongolia People's Republic.[120] While the term mongoloid (also mongolism, Mongolian imbecility or idiocy) continued to be used until the early 1980s, it is now considered unacceptable and is no longer in common use.[120][122]

In 1975, the United States National Institutes of Health (NIH) convened a conference to standardize the naming and recommended replacing the possessive form, "Down's syndrome" with "Down syndrome".[123] However, both the possessive and nonpossessive forms remain in use by the general population.[124] The term "trisomy 21" is also used frequently.[121][125]

## Ethics

Some argue that not to offer screening for Down syndrome is unethical.[126] As it is a medically reasonable procedure, per informed consent, people should at least be given information about it.[126] It will then be the woman's choice, based on her personal beliefs, how much or how little screening she wishes.[127][128] When results from testing become available, it is also considered unethical not to give the results to the person in question.[126][129]

Some deem it reasonable for parents to select a child who would have the highest well-being.[130] One criticism of this reasoning is it often values those with disabilities less.[131] Others argue that Down syndrome shouldn't be prevented or cured and that eliminating Down syndrome amounts to genocide.[132][133] The disability rights movement does not have a position on screening,[134] although some members consider testing and abortion discriminatory.[134] Some in the United States who are pro-life support abortion if the fetus is disabled, while others do not.[135] Of a group of 40 mothers in the United States who have had one child with Down syndrome, half agreed to screening in the next pregnancy.[135]

Within the US, some Protestants denominations see abortion as acceptable when a fetus has Down syndrome,[136] while Orthodox Christians and Roman Catholics often do not.[136] Some of those against screening refer to it as a form of "eugenics".[136] Disagreement exists within Islam regarding the acceptability of abortion in those carrying a fetus with Down syndrome.[137] Some Islamic countries allow abortion, while others do not.[137] Women may face stigmatization whichever decision they make.[138]

## Advocacy groups

Advocacy groups for individuals with Down syndrome began to be form after the Second World War.[139] These were organizations advocating for the inclusion of people with Down syndrome into the general school system and for a greater understanding of the condition among the general population,[139] as well as groups providing support for families with children living with Down syndrome.[139] Before this individuals with Down syndrome were often placed in mental hospitals or asylums. Organizations included the Royal Society for Handicapped Children and Adults founded in the UK in 1946 by Judy Fryd,[139][140] Kobato Kai founded in Japan in 1964,[139] the National Down Syndrome Congress founded in the United States in 1973 by Kathryn McGee and others,[139][141] and the National Down Syndrome Society founded in 1979 in the United States.[139]

The first World Down Syndrome Day was held on 21 March 2006.[142] The day and month were chosen to correspond with 21 and trisomy, respectively.[143] It was recognized by the United Nations General Assembly in 2011.[142]

# Research

*See also: Down syndrome research and Mouse models of Down syndrome*

Efforts are underway to determine how the extra chromosome 21 material causes Down syndrome, as currently this is unknown,[144] and to develop treatments to improve intelligence in those with the syndrome.[145] One hope is to use stem cells.[144] Other methods being studied include the use of antioxidants, gamma secretase inhibition, adrenergic agonists, and memantine.[146] Research is often carried out on an animal model, the Ts65Dn mouse.[147]

# References


1. ^ a b c Patterson, D (Jul 2009). "Molecular genetic analysis of Down syndrome.". *Human Genetics*. **126** (1): 195–214. doi:10.1007/s00439-009-0696-8. PMID 19526251.
2. ^ a b c d e f g h i j k l m n o p q r Weijerman, ME; de Winter, JP (Dec 2010). "Clinical practice. The care of children with Down syndrome.". *European journal of pediatrics*. **169** (12): 1445–52. doi:10.1007/s00431-010-1253-0. PMID 20632187.
3. ^ a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab Malt, EA; Dahl, RC; Haugsand, TM; Ulvestad, IH; Emilsen, NM; Hansen, B; Cardenas, YE; Skøld, RO; Thorsen, AT; Davidsen, EM (Feb 5, 2013). "Health and disease in adults with Down syndrome.". *Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke*. **133** (3): 290–4. doi:10.4045/tidsskr.12.0390. PMID 23381164.
4. ^ a b c d e f g h i j k l m n o Hammer, edited by Stephen J. McPhee, Gary D. (2010). "Pathophysiology of Selected Genetic Diseases". *Pathophysiology of disease : an introduction to clinical medicine* (6th ed.). New York: McGraw-Hill Medical. pp. Chapter 2. ISBN 978-0-07-162167-0.
5. ^ a b "What causes Down syndrome?". 2014-01-17. Retrieved 6 January 2016.
6. ^ a b c d e Morris, JK; Mutton, DE; Alberman, E (2002). "Revised estimates of the maternal age specific live birth prevalence of Down's syndrome.". *Journal of medical screening*. **9** (1): 2–6. PMID 11943789.
7. ^ "How do health care providers diagnose Down syndrome?". *Eunice Kennedy Shriver National Institute of Child Health and Human Development*. 2014-01-17. Retrieved 4 March 2016.
8. ^ a b Natoli, JL; Ackerman, DL; McDermott, S; Edwards, JG (Feb 2012). "Prenatal diagnosis of Down syndrome: a systematic review of termination rates (1995–2011).". *Prenatal diagnosis*. **32** (2): 142–53. doi:10.1002/pd.2910. PMID 22418958.
9. ^ a b Mansfield, C; Hopfer, S; Marteau, TM (Sep 1999). "Termination rates after prenatal diagnosis of Down syndrome, spina bifida, anencephaly, and Turner and Klinefelter syndromes: a systematic literature review. European Concerted Action: DADA (Decision-making After the Diagnosis of a fetal Abnormality).". *Prenatal diagnosis*. **19** (9): 808–12. doi:10.1002/(sici)1097-0223(199909)19:9<808::aid-pd637>3.0.co;2-b. PMID 10521836.
10. ^ "Down Syndrome: Other FAQs". 2014-01-17. Retrieved 6 January 2016.
11. ^ a b Roizen, NJ; Patterson, D (April 2003). "Down's syndrome". *Lancet* (Review). **361** (9365): 1281–89. doi:10.1016/S0140-6736(03)12987-X. PMID 12699967.
12. ^ a b "Facts About Down Syndrome". National Association for Down Syndrome. Retrieved 20 March 2012.
13. ^ a b c Steinbock, Bonnie (2011). *Life before birth the moral and legal status of embryos and fetuses* (2nd ed.). Oxford: Oxford University Press. p. 222. ISBN 978-0-19-971207-6.
14. ^ a b Szabo, Liz (May 9, 2013). "Life with Down syndrome is full of possibilities". *USA Today*. Retrieved 7 February 2014.
15. ^ a b c d e f g h i j k l m n Kliegma, Robert M. (2011). "Down Syndrome and Other Abnormalities of Chromosome Number". *Nelson textbook of pediatrics.* (19th ed.). Philadelphia: Saunders. pp. Chapter 76.2. ISBN 1-4377-0755-6.
16. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
17. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385**: 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
18. ^ a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af ag ah ai Hickey, F; Hickey, E; Summar, KL (2012). "Medical update for children with Down syndrome for the pediatrician and family practitioner.". *Advances in Pediatrics*. **59** (1): 137–57. doi:10.1016/j.yapd.2012.04.006. PMID 22789577.
19. ^ a b c d Evans-Martin, F. Fay (2009). *Down syndrome*. New York: Chelsea House. p. 12. ISBN 978-1-4381-1950-2.
20. ^ Faragher, edited by Rhonda; Clarke, Barbara (2013). *Educating Learners with Down Syndrome Research, theory, and practice with children and adolescents.* Hoboken: Taylor and Francis. p. 5. ISBN 978-1-134-67335-3.
21. ^ Sankar, editors John M. Pellock, Blaise F.D. Bourgeois, W. Edwin Dodson ; associate editors, Douglas R. Nordli, Jr., Raman (2008). *Pediatric epilepsy diagnosis and therapy* (3rd ed.). New York: Demos Medical Pub. p. Chapter 67. ISBN 978-1-934559-86-4.
22. ^ a b c d e f g h i Epstein, Charles J. (2007). *The consequences of chromosome imbalance : principles, mechanisms,*

*and models*. Cambridge: Cambridge University Press. pp. 255–256. ISBN 978-0-521-03809-6.
23. ^ Daniel Bernstein (2012). *Pediatrics for medical students* (3rd ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 259. ISBN 978-0-7817-7030-9.
24. ^ Tecklin, Jan S. (2008). *Pediatric physical therapy* (4th ed.). Philadelphia: Lippincott Williams & Wilkins. p. 380. ISBN 978-0-7817-5399-9.
25. ^ *a b c d e* Domino, edited by Frank J. (2007). *The 5-minute clinical consult 2007* (2007 ed.). Philadelphia: Lippincott Williams & Wilkins. p. 392. ISBN 978-0-7817-6334-9.
26. ^ *a b* Perkins, JA (December 2009). "Overview of macroglossia and its treatment.". *Current opinion in otolaryngology & head and neck surgery*. **17** (6): 460–5. doi:10.1097/moo.0b013e3283317f89. PMID 19713845.
27. ^ Wilson, Golder N.; Cooley, W. Carl (2006). *Preventive management of children with congenital anomalies and syndromes.* (2 ed.). Cambridge: Cambridge University Press. p. 190. ISBN 978-0-521-61734-5.
28. ^ *Williams Textbook of Endocrinology Expert Consult* (12th ed.). London: Elsevier Health Sciences. 2011. ISBN 978-1-4377-3600-7.
29. ^ *a b c d e* Reilly, C (Oct 2012). "Behavioural phenotypes and special educational needs: is aetiology important in the classroom?". *Journal of intellectual disability research : JIDR*. **56** (10): 929–46. doi:10.1111/j.1365-2788.2012.01542.x. PMID 22471356.
30. ^ Batshaw, Mark, ed. (2005). *Children with disabilities* (5th ed.). Baltimore [u.a.]: Paul H. Brookes. p. 308. ISBN 978-1-55766-581-2.
31. ^ Patterson, T; Rapsey, CM; Glue, P (Apr 2013). "Systematic review of cognitive development across childhood in Down syndrome: implications for treatment interventions.". *Journal of intellectual disability research : JIDR*. **57** (4): 306–18. doi:10.1111/j.1365-2788.2012.01536.x. PMID 23506141.
32. ^ Rondal, edited by Jean-Adolphe; Quartino, Alberto Rasore (2007). *Therapies and rehabilitation in Down syndrome*. Chichester, England: J. Wiley & Sons. p. 116. ISBN 978-0-470-31997-0.
33. ^ Kent, RD; Vorperian, HK (Feb 2013). "Speech impairment in Down syndrome: a review.". *Journal of speech, language, and hearing research : JSLHR*. **56** (1): 178–210. doi:10.1044/1092-4388(2012/12-0148). PMC 3584188. PMID 23275397.
34. ^ McGuire, Dennis and Chicoine, Brian (2006). *Mental Wellness in Adults with Down Syndrome*. Bethesday, MD: Woodbine House, Inc. p. 49. ISBN 1-890627-65-8.
35. ^ Margulies, Phillip (2007). *Down syndrome* (1st ed.). New York: Rosen Pub. Group. p. 5. ISBN 978-1-4042-0695-3.
36. ^ M. William Schwartz, ed. (2012). *The 5-minute pediatric consult* (6th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 289. ISBN 978-1-4511-1656-4.
37. ^ *a b c* Rodman, R; Pine, HS (Jun 2012). "The otolaryngologist's approach to the patient with Down syndrome.". *Otolaryngologic clinics of North America*. **45** (3): 599–629, vii–viii. doi:10.1016/j.otc.2012.03.010. PMID 22588039.
38. ^ Evans-Martin, F. Fay (2009). *Down syndrome*. New York: Chelsea House. p. 71. ISBN 978-1-4381-1950-2.
39. ^ *a b c d* Tintinalli, Judith E. (2010). "The Child with Special Health Care Needs". *Emergency Medicine: A Comprehensive Study Guide (Emergency Medicine (Tintinalli))*. New York: McGraw-Hill Companies. pp. Chapter 138. ISBN 0-07-148480-9.
40. ^ *a b* Sam Goldstein, ed. (2011). *Handbook of neurodevelopmental and genetic disorders in children* (2nd ed.). New York: Guilford Press. p. 365. ISBN 978-1-60623-990-2.
41. ^ editor, Vee P. Prasher, (2009). *Neuropsychological assessments of dementia in Down syndrome and intellectual disabilities*. London: Springer. p. 56. ISBN 978-1-84800-249-4.
42. ^ Richard Urbano (9 September 2010). *Health Issues Among Persons With Down Syndrome*. Academic Press. p. 129. ISBN 978-0-12-374477-7.
43. ^ Andrei Thomas-Tikhonenko, ed. (2010). *Cancer genome and tumor microenvironment* (Online-Ausg. ed.). New York: Springer. p. 203. ISBN 978-1-4419-0711-0.
44. ^ *a b* Seewald, L; Taub, JW; Maloney, KW; McCabe, ER (Sep 2012). "Acute leukemias in children with Down syndrome.". *Molecular genetics and metabolism*. **107** (1–2): 25–30. doi:10.1016/j.ymgme.2012.07.011. PMID 22867885.
45. ^ *a b c d* Gamis, AS; Smith, FO (Nov 2012). "Transient myeloproliferative disorder in children with Down syndrome: clarity to this enigmatic disorder.". *British journal of haematology*. **159** (3): 277–87. doi:10.1111/bjh.12041. PMID 22966823.
46. ^ Graber, E; Chacko, E; Regelmann, MO; Costin, G; Rapaport, R (Dec 2012). "Down syndrome and thyroid function.". *Endocrinology and metabolism clinics of North America*. **41** (4): 735–45. doi:10.1016/j.ecl.2012.08.008. PMID 23099267.
47. ^ Moore, SW (Aug 2008). "Down syndrome and the enteric nervous system.". *Pediatric surgery international*. **24**

(8): 873–83. doi:10.1007/s00383-008-2188-7. PMID 18633623.
48. ^ a b c Cawson, R.A.; Odell, E.W. (2012). *Cawson's essentials of oral pathology and oral medicine* (8th ed.). Edinburgh: Churchill Livingstone. pp. 419–421. ISBN 978-0443-10125-0.
49. ^ a b c Carranza, [edited by] Michael G. Newman, Henry H. Takei, Perry R. Klokkevold; editor emeritus Fermin A. (2006). *Carranza's clinical periodontology* (10th ed.). Philadelphia: W.B. Saunders Co. pp. 299, 397, 409, 623. ISBN 978-1-4160-2400-2.
50. ^ a b c d e Dean, Ralph E. McDonald ; David R. Avery ; Jeffrey A. (2004). *Dentistry for the child and adolescent* (8. ed.). St. Louis, Mo: Mosby. pp. 164–168, 190–194, 474. ISBN 0-323-02450-5.
51. ^ a b c Wysocki, J. Philip Sapp; Lewis R. Eversole; George P. (2002). *Contemporary oral and maxillofacial pathology* (2nd ed.). St. Louis: Mosby. pp. 39–40. ISBN 0-323-01723-1.
52. ^ a b c Regezi, Joseph A; Sciubba, James J; Jordan, Richard C K (2008). *Oral Pathology: Clinical Pathologic Correlations* (5th ed.). St Louis, Missouri: Saunders Elsevier. pp. 353–354. ISBN 1455702625.
53. ^ a b c d Pradhan, M; Dalal, A; Khan, F; Agrawal, S (2006). "Fertility in men with Down syndrome: a case report". *Fertil Steril*. **86** (6): 1765.e1–3. doi:10.1016/j.fertnstert.2006.03.071. PMID 17094988.
54. ^ a b c d e f g h Nelson, Maureen R. (2011). *Pediatrics*. New York: Demos Medical. p. 88. ISBN 978-1-61705-004-6.
55. ^ a b c d e f g Howard Reisner (2013). *Essentials of Rubin's Pathology*. Lippincott Williams & Wilkins. pp. 129–131. ISBN 978-1-4511-8132-6.
56. ^ a b c Lana-Elola, E; Watson-Scales, SD; Fisher, EM; Tybulewicz, VL (Sep 2011). "Down syndrome: searching for the genetic culprits.". *Disease models & mechanisms*. **4** (5): 586–95. doi:10.1242/dmm.008078. PMC 3180222. PMID 21878459.
57. ^ "CDC—Birth Defects, Down Syndrome—NCBDDD". Cdc.gov. 2013-11-06.
58. ^ Kausik Mandal (2013). *Treatment & prognosis in pediatrics.* Jaypee Brothers Medical P. p. 391. ISBN 978-93-5090-428-2.
59. ^ Fletcher-Janzen, edited by Cecil R. Reynolds, Elaine (2007). *Encyclopedia of special education a reference for the education of children, adolescents, and adults with disabilities and other exceptional individuals* (3rd ed.). New York: John Wiley & Sons. p. 458. ISBN 978-0-470-17419-7.
60. ^ Zhang, edited by Liang Cheng, David Y. (2008). *Molecular genetic pathology*. Totowa, N.J.: Humana. p. 45. ISBN 978-1-59745-405-6.
61. ^ a b A.K. David (2013). *Family Medicine Principles and Practice* (Sixth ed.). New York, NY: Springer New York. p. 142. ISBN 978-0-387-21744-4.
62. ^ a b c d e Michael Cummings (2013). *Human Heredity: Principles and Issues* (10 ed.). Cengage Learning. p. 138. ISBN 978-1-285-52847-2.
63. ^ Jerome Frank Strauss; Robert L. Barbieri (2009). *Yen and Jaffe's reproductive endocrinology : physiology, pathophysiology, and clinical management* (6th ed.). Philadelphia, PA: Saunders/Elsevier. p. 791. ISBN 978-1-4160-4907-4.
64. ^ a b c Menkes, John H.; Sarnat, Harvey B. (2005). *Child neurology* (7th ed.). Philadelphia, PA: Lippincott Williams & Wilkins. p. 228. ISBN 978-0-7817-5104-9.
65. ^ Shaffer, R.J. McKinlay Gardner, Grant R. Sutherland, Lisa G. (2012). *Chromosome abnormalities and genetic counseling* (4th ed.). Oxford: Oxford University Press. p. 292. ISBN 978-0-19-974915-7.
66. ^ "Genetics of Down syndrome". Retrieved 2011-05-29.
67. ^ Michael H. Ebert, ed. (2008). "Psychiatric Genetics". *Current diagnosis & treatment psychiatry* (2nd ed.). New York: McGraw-Hill Medical. pp. Chapter 3. ISBN 0-07-142292-7.
68. ^ Patterson, D; Cabelof, DC (April 2012). "Down syndrome as a model of DNA polymerase beta haploinsufficiency and accelerated aging.". *Mechanisms of ageing and development*. **133** (4): 133–7. doi:10.1016/j.mad.2011.10.001. PMID 22019846.
69. ^ a b Weksler, ME; Szabo, P; Relkin, NR; Reidenberg, MM; Weksler, BB; Coppus, AM (Apr 2013). "Alzheimer's disease and Down's syndrome: treating two paths to dementia.". *Autoimmunity reviews*. **12** (6): 670–3. doi:10.1016/j.autrev.2012.10.013. PMID 23201920.
70. ^ Horvath S, Garagnani P, Bacalini MG, Pirazzini C, Salvioli S, Gentilini D, Di Blasio AM, Giuliani C, Tung S, Vinters HV, Franceschi C (2015). "Accelerated epigenetic aging in Down syndrome.". *Aging Cell*. **14** (3): 491–5. doi:10.1111/acel.12325. PMID 25678027.
71. ^ a b c d e ACOG Committee on Practice, Bulletins (Jan 2007). "ACOG Practice Bulletin No. 77: screening for fetal chromosomal abnormalities.". *Obstetrics and gynecology*. **109** (1): 217–27. doi:10.1097/00006250-200701000-00054. PMID 17197615.
72. ^ National Institute for Health and Clinical Excellence (2008). "CG62: Antenatal care". London: National Institute

for Health and Clinical Excellence. Retrieved 16 February 2013.
73. ^ a b c d e Canick, J (Jun 2012). "Prenatal screening for trisomy 21: recent advances and guidelines.". *Clinical chemistry and laboratory medicine : CCLM / FESCC*. **50** (6): 1003–8. doi:10.1515/cclm.2011.671. PMID 21790505.
74. ^ "Noninvasive prenatal diagnosis of fetal aneuploidy using cell-free fetal nucleic acids in maternal blood" (PDF). United Healthcare Oxford. Retrieved 25 March 2014.
75. ^ a b Mersy E, Smits LJ, van Winden LA, de Die-Smulders CE, Paulussen AD, Macville MV, Coumans AB, Frints SG (Jul–Aug 2013). "Noninvasive detection of fetal trisomy 21: systematic review and report of quality and outcomes of diagnostic accuracy studies performed between 1997 and 2012.". *Human Reproduction Update*. **19** (4): 318–29. doi:10.1093/humupd/dmt001. PMID 23396607.
76. ^ Bianchi DW, Parker RL, Wentworth J, Madankumar R, Saffer C, Das AF, Craig JA, Chudova DI, Devers PL, Jones KW, Oliver K, Rava RP, Sehnert AJ (Feb 27, 2014). "DNA sequencing versus standard prenatal aneuploidy screening.". *The New England Journal of Medicine*. **370** (9): 799–808. doi:10.1056/nejmoa1311037. PMID 24571752.
77. ^ a b Agathokleous, M; Chaveeva, P; Poon, LC; Kosinski, P; Nicolaides, KH (Mar 2013). "Meta-analysis of second-trimester markers for trisomy 21.". *Ultrasound in Obstetrics & Gynecology*. **41** (3): 247–61. doi:10.1002/uog.12364. PMID 23208748.
78. ^ Malone FD, D'Alton ME (Nov 2003). "First-trimester sonographic screening for Down syndrome.". *Obstetrics and gynecology*. **102** (5 Pt 1): 1066–79. doi:10.1016/j.obstetgynecol.2003.08.004. PMID 14672489.
79. ^ a b Alldred, SK; Deeks, JJ; Guo, B; Neilson, JP; Alfirevic, Z (Jun 13, 2012). "Second trimester serum tests for Down's Syndrome screening.". *The Cochrane database of systematic reviews*. **6**: CD009925. doi:10.1002/14651858.CD009925. PMID 22696388.
80. ^ Verweij EJ, van den Oever JM, de Boer MA, Boon EM, Oepkes D (2012). "Diagnostic accuracy of noninvasive detection of fetal trisomy 21 in maternal blood: a systematic review.". *Fetal diagnosis and therapy*. **31** (2): 81–6. doi:10.1159/000333060. PMID 22094923.
81. ^ a b Benn, P; Borrell, A; Cuckle, H; Dugoff, L; Gross, S; Johnson, JA; Maymon, R; Odibo, A; Schielen, P; Spencer, K; Wright, D; Yaron, Y (Jan 2012). "Prenatal Detection of Down Syndrome using Massively Parallel Sequencing (MPS): a rapid response statement from a committee on behalf of the Board of the International Society for Prenatal Diagnosis, 24 October 2011." (PDF). *Prenatal diagnosis*. **32** (1): 1–2. doi:10.1002/pd.2919. PMID 22275335.
82. ^ a b c Tabor, A; Alfirevic, Z (2010). "Update on procedure-related risks for prenatal diagnosis techniques.". *Fetal diagnosis and therapy*. **27** (1): 1–7. doi:10.1159/000271995. PMID 20051662.
83. ^ Choi, H; Van Riper, M; Thoyre, S (Mar–Apr 2012). "Decision making following a prenatal diagnosis of Down syndrome: an integrative review.". *Journal of midwifery & women's health*. **57** (2): 156–64. doi:10.1111/j.1542-2011.2011.00109.x. PMID 22432488.
84. ^ Sheets KB, Crissman BG, Feist CD, et al. (October 2011). "Practice guidelines for communicating a prenatal or postnatal diagnosis of Down syndrome: recommendations of the national society of genetic counselors". *J Genet Couns*. **20** (5): 432–41. doi:10.1007/s10897-011-9375-8. PMID 21618060.
85. ^ a b Bull, MJ; Committee on, Genetics (Aug 2011). "Health supervision for children with Down syndrome.". *Pediatrics*. **128** (2): 393–406. doi:10.1542/peds.2011-1605. PMID 21788214.
86. ^ Roberts, JE; Price, J; Malkin, C (2007). "Language and communication development in Down syndrome". *Ment Retard Dev Disabil Res Rev*. **13** (1): 26–35. doi:10.1002/mrdd.20136. PMID 17326116.
87. ^ "Inclusion: Educating Students with Down Syndrome with Their Non-Disabled Peers" (PDF). National Down Syndrome Society. Retrieved 5 February 2014.
88. ^ Lindsay, G (Mar 2007). "Educational psychology and the effectiveness of inclusive education/mainstreaming.". *The British journal of educational psychology*. **77** (Pt 1): 1–24. doi:10.1348/000709906x156881. PMID 17411485.
89. ^ New, Rebecca S.; Cochran, Moncrieff (2007). *Early childhood education an international encyclopedia*. Westport, Conn.: Praeger Publishers. p. 305. ISBN 978-0-313-01448-2.
90. ^ "Development and learning for people with Down syndromeS". Retrieved 2016-11-18.
91. ^ "Early Intervention – National Down Syndrome Society". *www.ndss.org*. Retrieved 2016-11-18.
92. ^ Wearmouth, Janice (2012). *Special educational needs, the basics*. Milton Park, Abingdon, Oxon: Routledge. p. 66. ISBN 978-1-136-57989-9.
93. ^ Andriolo RB, El Dib RP, Ramos L, Atallah AN, da Silva EM (May 12, 2010). "Aerobic exercise training programmes for improving physical and psychosocial health in adults with Down syndrome". *The Cochrane database of systematic reviews* (5): CD005176. doi:10.1002/14651858.CD005176.pub4. PMID 20464738.
94. ^ Mohan, M; Bennett, C; Carpenter, PK (Jan 21, 2009). "Memantine for dementia in people with Down syndrome.". *The Cochrane database of systematic reviews* (1): CD007657. doi:10.1002/14651858.CD007657. PMID 19160343.
95. ^ Mohan, M; Carpenter, PK; Bennett, C (Jan 21, 2009). "Donepezil for dementia in people with Down syndrome.".

*The Cochrane database of systematic reviews* (1): CD007178. doi:10.1002/14651858.CD007178.pub2. PMID 19160328.
96. ^ Mohan, M; Bennett, C; Carpenter, PK (Jan 21, 2009). "Rivastigmine for dementia in people with Down syndrome.". *The Cochrane database of systematic reviews* (1): CD007658. doi:10.1002/14651858.CD007658. PMID 19160344.
97. ^ Mohan, M; Bennett, C; Carpenter, PK (Jan 21, 2009). "Galantamine for dementia in people with Down syndrome.". *The Cochrane database of systematic reviews* (1): CD007656. doi:10.1002/14651858.CD007656. PMID 19160342.
98. ^ *a b c d e f* Roizen, NJ (2005). "Complementary and alternative therapies for Down syndrome.". *Mental retardation and developmental disabilities research reviews*. **11** (2): 149–55. doi:10.1002/mrdd.20063. PMID 15977315.
99. ^ *a b* National Down Syndrome Society. "Position Statement on Cosmetic Surgery for Children with Down Syndrome". Archived from the original on 2006-09-06. Retrieved 2006-06-02.
100. ^ *a b* "European Down Syndrome Association news" (PDF). *European Down Syndrome Association*. 2006. Retrieved 7 February 2014.
101. ^ "Number of 14- through 21-year-old students served under Individuals with Disabilities Education Act, Part B, who exited school, by exit reason, age, and type of disability: 2007–08 and 2008–09". *National Center for Education Statistics*. Retrieved 7 February 2014.
102. ^ "Down's Syndrome: Employment Barriers". *Rehab Care International*. Retrieved 7 February 2014.
103. ^ Richard Urbano (9 September 2010). *Health Issues Among Persons With Down Syndrome*. Academic Press. p. 108. ISBN 978-0-12-374477-7.
104. ^ "Where Should I Go From Here?". Retrieved 19 December 2015.
105. ^ Lozano, R; Naghavi, M; Foreman, K; Lim, S; Shibuya, K; Aboyans, V; Abraham, J; Adair, T; Aggarwal, R; Ahn, S. Y.; Alvarado, M; Anderson, H. R.; Anderson, L. M.; Andrews, K. G.; Atkinson, C; Baddour, L. M.; Barker-Collo, S; Bartels, D. H.; Bell, M. L.; Benjamin, E. J.; Bennett, D; Bhalla, K; Bikbov, B; Bin Abdulhak, A; Birbeck, G; Blyth, F; Bolliger, I; Boufous, S; Bucello, C; et al. (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
106. ^ Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, Anderson P, Mason CA, Collins JS, Kirby RS, Correa A (Dec 2010). "Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004–2006". *Birth defects research. Part A, Clinical and molecular teratology*. **88** (12): 1008–16. doi:10.1002/bdra.20735. PMID 20878909.
107. ^ Douglas T. Carrell, ed. (2013). *Paternal influences on human reproductive success*. Cambridge University Press. p. 65. ISBN 978-1-107-02448-9.
108. ^ Levitas, AS; Reid, CS (Feb 1, 2003). "An angel with Down syndrome in a sixteenth century Flemish Nativity painting.". *American Journal of Medical Genetics Part A*. **116A** (4): 399–405. doi:10.1002/ajmg.a.10043. PMID 12522800.
109. ^ Down, JLH (1866). "Observations on an ethnic classification of idiots". *Clinical Lecture Reports, London Hospital*. **3**: 259–62. Retrieved 2006-07-14.
110. ^ Conor, WO (1998). *John Langdon Down, 1828–1896*. Royal Society of Medicine Press. ISBN 1-85315-374-5.
111. ^ *a b* Neri, G; Opitz, JM (Dec 2009). "Down syndrome: comments and reflections on the 50th anniversary of Lejeune's discovery.". *American Journal of Medical Genetics Part A*. **149A** (12): 2647–54. doi:10.1002/ajmg.a.33138. PMID 19921741.
112. ^ David Wright (25 August 2011). *Downs:The history of a disability: The history of a disability*. Oxford University Press. pp. 104–108. ISBN 978-0-19-956793-5. Retrieved 25 August 2012.
113. ^ David Wright (25 August 2011). *Downs:The history of a disability: The history of a disability*. Oxford University Press. p. 145. ISBN 978-0-19-956793-5. Retrieved 25 August 2012.
114. ^ "Trisomie : une pionnière intimidée". *Le Monde*. Feb 3, 2014. Retrieved 25 March 2014.
115. ^ David Wright (25 August 2011). *Downs:The history of a disability: The history of a disability*. Oxford University Press. pp. 9–10. ISBN 978-0-19-956793-5. Retrieved 25 August 2012.
116. ^ Warkany, J (1971). *Congenital Malformations*. Chicago: Year Book Medical Publishers, Inc. pp. 313–14. ISBN 0-8151-9098-0.
117. ^ Ward, OC (Aug 1999). "John Langdon Down: the man and the message.". *Down's syndrome, research and practice : the journal of the Sarah Duffen Centre / University of Portsmouth*. **6** (1): 19–24. PMID 10890244.
118. ^ Gould, Stephen (2010). *The Panda's Thumb: More Reflections in Natural History*. W. W. Norton & Company. p. 166. ISBN 9780393340839.
119. ^ Keevak, Michael (2011). *Becoming Yellow: A Short History of Racial Thinking*. Princeton University Press. p. 120. ISBN 1400838606.
120. ^ *a b c* Howard-Jones, Norman (1979). "On the diagnostic term "Down's disease" ". *Medical History*. **23** (1): 102–

04. doi:10.1017/s0025727300051048. PMC 1082401. PMID 153994.
121. ^ a b Rodríguez-Hernández, ML; Montoya, E (Jul 30, 2011). "Fifty years of evolution of the term Down's syndrome.". *Lancet*. **378** (9789): 402. doi:10.1016/s0140-6736(11)61212-9. PMID 21803206.
122. ^ Rodríguez-Hernández, ML; Montoya, E (30 July 2011). "Fifty years of evolution of the term Down's syndrome.". *Lancet (London, England)*. **378** (9789): 402. PMID 21803206.
123. ^ "Classification and nomenclature of morphological defects (Discussion)". *The Lancet*. **305** (7905): 513. 1975. doi:10.1016/S0140-6736(75)92847-0. PMID 46972.
124. ^ Smith, Kieron (2011). *The politics of Down syndrome*. [New Alresford, Hampshire]: Zero. p. 3. ISBN 978-1-84694-613-4.
125. ^ Westman, Judith A. (2005). *Medical genetics for the modern clinician.* Philadelphia, PA: Lippincott Williams & Wilkins. p. 136. ISBN 978-0-7817-5760-7.
126. ^ a b c Chervenak, FA; McCullough, LB (Apr 2010). "Ethical considerations in first-trimester Down syndrome risk assessment.". *Current opinion in obstetrics & gynecology*. **22** (2): 135–8. doi:10.1097/gco.0b013e3283374a9f. PMID 20125014.
127. ^ Chervenak, FA; McCullough, LB; Sharma, G; Davis, J; Gross, S (Jul 2008). "Enhancing patient autonomy with risk assessment and invasive diagnosis: an ethical solution to a clinical challenge.". *American Journal of Obstetrics and Gynecology*. **199** (1): 19.e1–4. doi:10.1016/j.ajog.2008.02.021. PMID 18355783.
128. ^ Zindler, L (Apr–Jun 2005). "Ethical decision making in first trimester pregnancy screening.". *The Journal of perinatal & neonatal nursing*. **19** (2): 122–31; quiz 132–3. doi:10.1097/00005237-200504000-00008. PMID 15923961.
129. ^ Sharma, G; McCullough, LB; Chervenak, FA (Feb 15, 2007). "Ethical considerations of early (first vs. second trimester) risk assessment disclosure for trisomy 21 and patient choice in screening versus diagnostic testing.". *American Journal of Medical Genetics Part C*. **145C** (1): 99–104. doi:10.1002/ajmg.c.30118. PMID 17299736.
130. ^ Savulescu, J; Kahane, G (Jun 2009). "The moral obligation to create children with the best chance of the best life.". *Bioethics*. **23** (5): 274–90. doi:10.1111/j.1467-8519.2008.00687.x. PMID 19076124.
131. ^ Bennett, R (Jun 2009). "The fallacy of the Principle of Procreative Beneficence.". *Bioethics*. **23** (5): 265–73. doi:10.1111/j.1467-8519.2008.00655.x. PMID 18477055.
132. ^ "Halifax mom questions Down syndrome suppression". Retrieved 2015-09-26.
133. ^ Belkin, Lisa. "Should Down Syndrome Be Cured?". Retrieved 2015-09-26.
134. ^ a b Parens, E; Asch, A (2003). "Disability rights critique of prenatal genetic testing: reflections and recommendations.". *Mental retardation and developmental disabilities research reviews*. **9** (1): 40–7. doi:10.1002/mrdd.10056. PMID 12587137.
135. ^ a b Green, RM (Spring 1997). "Parental autonomy and the obligation not to harm one's child genetically.". *The Journal of law, medicine & ethics : a journal of the American Society of Law, Medicine & Ethics*. **25** (1): 5–15, 2. doi:10.1111/j.1748-720x.1997.tb01389.x. PMID 11066476.
136. ^ a b c Bill J Leonard; Jill Y. Crainshaw (2013). *Encyclopedia of religious controversies in the United States.* (2nd ed.). Santa Barbara, Calif.: ABC-CLIO. p. 278. ISBN 978-1-59884-867-0.
137. ^ a b Al-Alaiyan, S; Alfaleh, KM (Jan 2012). "Aborting a Malformed Fetus: A Debatable Issue in Saudi Arabia.". *Journal of clinical neonatology*. **1** (1): 6–11. doi:10.4103/2249-4847.92231. PMC 3761984. PMID 24027674.
138. ^ Sara Grace Shields; Lucy M. Candib (2010). *Woman-centered care in pregnancy and childbirth*. Oxford: Radcliffe Pub. p. 140. ISBN 978-1-84619-161-9.
139. ^ a b c d e f g David Wright (2011). *Downs: The history of a disability*. Oxford University Press. p. 147. ISBN 978-0-19-161978-6.
140. ^ "Timeline". *MENCAP*. Retrieved 2 February 2014.
141. ^ "National Down Syndrome Organizations in the U.S.". *Global Down Syndrome Foundation*. Retrieved 2 February 2014.
142. ^ a b "World Down Syndrome Day". *Down Syndrome International*. Down Syndrome International. Retrieved 2 February 2014.
143. ^ Pratt, Geraldine; Rosner, Victoria (2012). *The global and the intimate feminism in our time*. New York: Columbia University Press. p. 113. ISBN 978-0-231-52084-3.
144. ^ a b Briggs, JA; Mason, EA; Ovchinnikov, DA; Wells, CA; Wolvetang, EJ (Mar 2013). "Concise review: new paradigms for Down syndrome research using induced pluripotent stem cells: tackling complex human genetic disease.". *Stem cells translational medicine*. **2** (3): 175–84. doi:10.5966/sctm.2012-0117. PMC 3659762. PMID 23413375.
145. ^ Goodman, MJ; Brixner, DI (Apr 2013). "New therapies for treating Down syndrome require quality of life measurement.". *American Journal of Medical Genetics Part A*. **161A** (4): 639–41. doi:10.1002/ajmg.a.35705. PMID 23495233.

146. ^ Costa, AC; Scott-McKean, JJ (Sep 2013). "Prospects for improving brain function in individuals with Down syndrome". *CNS Drugs*. **27** (9): 679–702. doi:10.1007/s40263-013-0089-3. PMID 23821040.
147. ^ Costa, AC (2011). "On the promise of pharmacotherapies targeted at cognitive and neurodegenerative components of Down syndrome". *Developmental neuroscience*. **33** (5): 414–27. doi:10.1159/000330861. PMC 3254040. PMID 21893967.

# External links

- Down syndrome at DMOZ
- Down's syndrome – Treatment by National Health Service

Wikimedia Commons has media related to *Down syndrome*.

| v · t · e | Chromosome abnormalities (Q90–Q99, 758) | | |
|---|---|---|---|
| **Autosomal** | **Trisomies** | | **Down syndrome** (21 · · Edwards syndrome (18 · · Patau syndrome (13 · · Trisomy 9 · Warkany syndrome 2 (8 · · Cat eye syndrome/Trisomy 22 (22 · · Trisomy 16 · |
| | **Monosomies/deletions** | | 1q21.1 deletion syndrome/1q21.1 duplication syndrome/TAR syndrome (1 · · Wolf–Hirschhorn syndrome (4 · · Cri du chat/Chromosome 5q deletion syndrome (5 · · Williams syndrome (7 · · Jacobsen syndrome (11 · · Miller–Dieker syndrome/Smith–Magenis syndrome (17 · · DiGeorge syndrome (22 · · 22q11.2 distal deletion syndrome (22 · · 22q13 deletion syndrome (22 · · *genomic imprinting* (Angelman syndrome/Prader–Willi syndrome (15) · · Distal 18q-/Proximal 18q- · |
| **X/Y linked** | **Monosomy** | | Turner syndrome (45,X) · |
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| | **Other** | Myxoid liposarcoma t(12 DDIT3; 16 FUS) · Desmoplastic small-round-cell tumor t(11 WT1; 22 EWS) · Alveolar rhabdomyosarcoma t(2 PAX3; 13 FOXO1) t (1 PAX7; 13 FOXO1) · |
| **Other** | Fragile X syndrome · Uniparental disomy · XX male syndrome · Ring chromosome (13; 14; 15; 20) · | |
| **Authority control** | LCCN: sh85039232 · GND: 4012849-0 · BNF: cb11940791r (data) · NDL: 00567829 · | |

Categories: Down syndrome | Genetic diseases and disorders | Chromosomal abnormalities | Intellectual disability | Autosomal trisomies




# Epilepsy

From Wikipedia, the free encyclopedia

*"Epilepsia" and "Epileptic" redirect here. For the journal, see Epilepsia (journal). For the novel, see Epileptic (graphic novel).*

**Epilepsy** is a group of neurological diseases characterized by epileptic seizures.[1][2] Epileptic seizures are episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking.[3] These episodes can result in physical injuries including occasionally broken bones.[3] In epilepsy, seizures tend to recur, and have no immediate underlying cause.[1] Isolated seizures that are provoked by a specific cause such as poisoning are not deemed to represent epilepsy.[4] People with epilepsy in some areas of the world experience stigma due to the condition.[3]

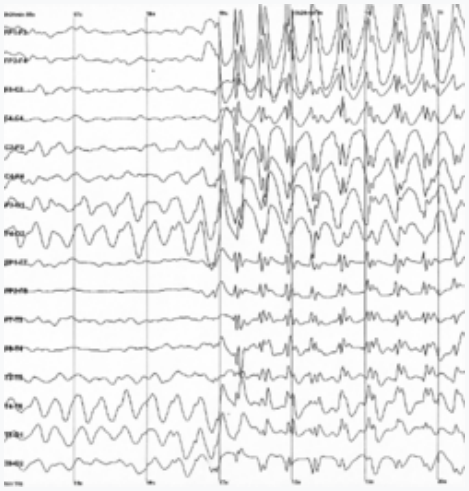
The cause of most cases of epilepsy is unknown, although some people develop epilepsy as the result of brain injury, stroke, brain tumors, infections of the brain, and birth defects.[3] Known genetic mutations are directly linked to a small proportion of cases.[5][6] Epileptic seizures are the result of excessive and abnormal nerve cell activity in the cortex of the brain.[4] The diagnosis involves ruling out other conditions that might cause similar symptoms such as fainting and determining if another cause of seizures is present such as alcohol withdrawal or electrolyte problems. This may be partly done by imaging the brain and performing blood tests. Epilepsy can often be confirmed with an electroencephalogram (EEG), but a normal test does not rule out the condition.[5]

Epilepsy that occurs as a result of other issues may be preventable.[3] Seizures are controllable with medication in about 70% of cases.[7] Inexpensive options are often available.[3] In those whose seizures do not respond to medication, then surgery, neurostimulation, or dietary changes may be considered.[8][9] Not all cases of epilepsy are lifelong, and many people improve to the point that treatment is no longer needed.[3]

As of 2013 about 22 million people have epilepsy.[10] Nearly 80% of cases occur in the developing world.[3] In 2013 it resulted in 116,000 deaths up from 112,000 deaths in 1990.[11] Epilepsy is more common in older people.[12][13] In the developed world, onset of new cases occurs most frequently in babies and the elderly.[14] In the developing world onset is more common in older children and young adults, due to differences in the frequency of the underlying causes.[15] About 5–10% of people will have an unprovoked seizure by the age of 80,[16] and the chance of experiencing a second seizure is between 40 and 50%.[17] In many areas of the world those with epilepsy either have restrictions placed on their ability to drive or are not permitted to drive until they are free of seizures for a specific length of time.[18] The word epilepsy is from Ancient Greek: ἐπιλαμβάνειν "to seize, possess, or afflict".[19]

**Epilepsy**

| | |
|---|---|
| **Synonyms** | seizure disorder |



Generalized 3 Hz spike and wave discharges on an electroencephalogram

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Neurology |
| **ICD-10** | G40-G41 |
| **ICD-9-CM** | 345 |
| **DiseasesDB** | 4366 |
| **MedlinePlus** | 000694 |
| **eMedicine** | neuro/415 |
| **MeSH** | D004827 |

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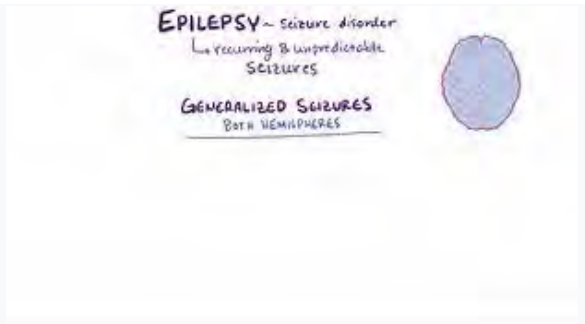



Play media

Video explanation

# Signs and symptoms [edit]

Epilepsy is characterized by a long-term risk of recurrent seizures.[20] These seizures may present in several ways depending on the part of the brain involved and the person's age.[20][21]

Play media

An instructional video about epileptic seizures

## Seizures [edit]

*Main article: Epileptic seizure*

The most common type (60%) of seizures are convulsive.[21] Of these, one-third begin as generalized seizures from the start, affecting both hemispheres of the brain.[21] Two-thirds begin as partial seizures (which affect one hemisphere of the brain) which may then progress to generalized seizures.[21] The remaining 40% of seizures are non-convulsive. An example of this type is the absence seizure, which presents as a decreased level of consciousness and usually lasts about 10 seconds.[22][23]

Partial seizures are often preceded by certain experiences, known as auras.[24] They include sensory (visual, hearing, or smell), psychic,

autonomic, and motor phenomena.[22] Jerking activity may start in a specific muscle group and spread to surrounding muscle groups in which case it is known as a Jacksonian march.[25] Automatisms may occur, which are non-consciously-generated activities and mostly simple repetitive movements like smacking of the lips or more complex activities such as attempts to pick up something.[25]

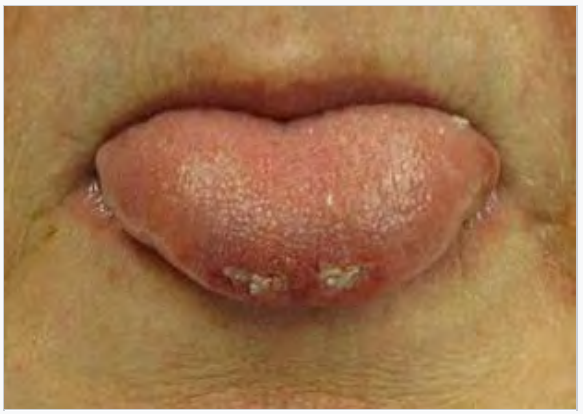
There are six main types of generalized seizures: tonic-clonic, tonic, clonic, myoclonic, absence, and atonic seizures.[26] They all involve loss of consciousness and typically happen without warning.

Tonic-clonic seizures occur with a contraction of the limbs followed by their extension along with arching of the back which lasts 10–30 seconds (the tonic phase). A cry may be heard due to contraction of the chest muscles, followed by a shaking of the limbs in unison (clonic phase). Tonic seizures produce constant contractions of the muscles. A person often turns blue as breathing is stopped. In clonic seizures there is shaking of the limbs in unison. After the shaking has stopped it may take 10–30 minutes for the person to return to normal; this period is called the "postictal state" or "postictal phase." Loss of bowel or bladder control may occur during a seizure.[27] The tongue may be bitten at either the tip or on the sides during a seizure.[28] In tonic-clonic seizure, bites to the sides are more common.[28] Tongue bites are also relatively common in psychogenic non-epileptic seizures.[28]

A still image of a generalized seizure

Myoclonic seizures involve spasms of muscles in either a few areas or all over.[29] Absence seizures can be subtle with only a slight turn of the head or eye blinking.[22] The person does not fall over and returns to normal right after it ends.[22] Atonic seizures involve the loss of muscle activity for greater than one second.[25] This typically occurs on both sides of the body.[25]

About 6% of those with epilepsy have seizures that are often triggered by specific events and are known as reflex seizures.[30] Those with reflex epilepsy have seizures that are only triggered by specific stimuli.[31] Common triggers include flashing lights and sudden noises.[30] In certain types of epilepsy, seizures happen more often during sleep,[32] and in other types they occur almost only when sleeping.[33]



A bite to the tip of the tongue due to a seizure

## Postictal [edit]

After the active portion of a seizure (the ictal state) there is typically a period of recovery during which there is confusion, referred to as the postictal period before a normal level of consciousness returns.[24] It usually lasts 3 to 15 minutes[34] but may last for hours.[35] Other common symptoms include feeling tired, headache, difficulty speaking, and abnormal behavior.[35] Psychosis after a seizure is relatively common, occurring in 6–10% of people.[36] Often people do not remember what happened during this time.[35] Localized weakness, known as Todd's paralysis, may also occur after a partial seizure. When it occurs it typically lasts for seconds to minutes but may rarely last for a day or two.[37]

## Psychosocial [edit]

Epilepsy can have adverse effects on social and psychological well-being.[21] These effects may include social isolation, stigmatization, or disability.[21] They may result in lower educational achievement and worse employment outcomes.[21] Learning disabilities are common in those with the condition, and especially among children with epilepsy.[21] The stigma of epilepsy can also affect the families of those with the disorder.[27]

Certain disorders occur more often in people with epilepsy, depending partly on the epilepsy syndrome present.[38] [39]

These include depression, anxiety, obsessive–compulsive disorder (OCD), and migraine. Attention deficit hyperactivity disorder affects three to five times more children with epilepsy than children without the condition.[40] ADHD and epilepsy have significant consequences on a child's behavioral, learning, and social development.[41] Epilepsy is also more common in children with autism.[42]

## Causes [edit]

*See also: Causes of seizures*

Epilepsy can have both genetic and acquired causes, with interaction of these factors in many cases.[43] Established acquired causes include serious brain trauma, stroke, tumours and problems in the brain as a result of a previous infection.[43] In about 60% of cases the cause is unknown.[21][27] Epilepsies caused by genetic, congenital, or developmental conditions are more common among younger people, while brain tumors and strokes are more likely in older people.[21]

Seizures may also occur as a consequence of other health problems;[26] if they occur right around a specific cause, such as a stroke, head injury, toxic ingestion or metabolic problem, they are known as acute symptomatic seizures and are in the broader classification of seizure-related disorders rather than epilepsy itself.[44][45]

### Genetics [edit]

Genetics is believed to be involved in the majority of cases, either directly or indirectly.[6] Some epilepsies are due to a single gene defect (1–2%); most are due to the interaction of multiple genes and environmental factors.[6] Each of the single gene defects is rare, with more than 200 in all described.[46] Most genes involved affect ion channels, either directly or indirectly.[43] These include genes for ion channels themselves, enzymes, GABA, and G protein-coupled receptors.[29]

In identical twins, if one is affected there is a 50–60% chance that the other will also be affected.[6] In non-identical twins the risk is 15%.[6] These risks are greater in those with generalized rather than partial seizures.[6] If both twins are affected, most of the time they have the same epileptic syndrome (70–90%).[6] Other close relatives of a person with epilepsy have a risk five times that of the general population.[47] Between 1 and 10% of those with Down syndrome and 90% of those with Angelman syndrome have epilepsy.[47]

### Acquired [edit]

Epilepsy may occur as a result of a number of other conditions including tumors, strokes, head trauma, previous infections of the central nervous system, genetic abnormalities, and as a result of brain damage around the time of birth.[26][27] Of those with brain tumors, almost 30% have epilepsy, making them the cause of about 4% of cases.[47] The risk is greatest for tumors in the temporal lobe and those that grow slowly.[47] Other mass lesions such as cerebral cavernous malformations and arteriovenous malformations have risks as high as 40–60%.[47] Of those who have had a stroke, 2–4% develop epilepsy.[47] In the United Kingdom strokes account for 15% of cases and it is believed to be the cause in 30% of the elderly.[21][47] Between 6 and 20% of epilepsy is believed to be due to head trauma.[47] Mild brain injury increases the risk about two-fold while severe brain injury increases the risk seven-fold.[47] In those who have experienced a high-powered gunshot wound to the head, the risk is about 50%.[47]

Some evidence links epilepsy and coeliac disease and non-celiac gluten sensitivity, while other evidence does not. There appears to be a specific syndrome which includes coeliac disease, epilepsy and calcifications in the brain.[48][49] A 2012 review estimates that between 1% and 6% of people with epilepsy have CD while 1% of the general population has the condition.[49]

The risk of epilepsy following meningitis is less than 10%; that disease more commonly causes seizures during the infection itself.[47] In herpes simplex encephalitis the risk of a seizure is around 50%[47] with a high risk of epilepsy following (up to 25%).[50][51] Infection with the pork tapeworm, which can result in neurocysticercosis, is the cause of up to half of epilepsy cases in areas of the world where the parasite is common.[47] Epilepsy may also occur after other brain infections such as cerebral malaria, toxoplasmosis, and toxocariasis.[47] Chronic alcohol use increases the risk of epilepsy: those who drink six units of alcohol per day have a two and a half fold increase in risk.[47] Other risks include Alzheimer's disease, multiple sclerosis, tuberous sclerosis, and autoimmune encephalitis.[47] Getting

vaccinated does not increase the risk of epilepsy.[47] Malnutrition is a risk factor seen mostly in the developing world, although it is unclear however if it is a direct cause or an association.[15] People with cerebral palsy have an increased risk of epilepsy, with half of people with spastic quadriplegia and spastic hemiplegia having the disease.[52]

## Mechanism [edit]

Normally brain electrical activity is non-synchronous.[22] Its activity is regulated by various factors both within the neuron and the cellular environment. Factors within the neuron include the type, number and distribution of ion channels, changes to receptors and changes of gene expression.[53] Factors around the neuron include ion concentrations, synaptic plasticity and regulation of transmitter breakdown by glial cells.[53][54]

### Epilepsy [edit]

The exact mechanism of epilepsy is unknown,[55] but a little is known about its cellular and network mechanisms. However, it is unknown under which circumstances the brain shifts into the activity of a seizure with its excessive synchronization.[56][57]

In epilepsy, the resistance of excitatory neurons to fire during this period is decreased.[22] This may occur due to changes in ion channels or inhibitory neurons not functioning properly.[22] This then results in a specific area from which seizures may develop, known as a "seizure focus".[22] Another mechanism of epilepsy may be the up-regulation of excitatory circuits or down-regulation of inhibitory circuits following an injury to the brain.[22][58] These secondary epilepsies occur through processes known as epileptogenesis.[22][58] Failure of the blood–brain barrier may also be a causal mechanism as it would allow substances in the blood to enter the brain.[59]

### Seizures [edit]

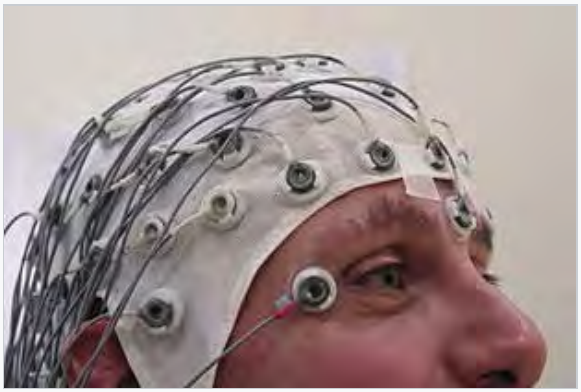
There is evidence that epileptic seizures are usually not a random event. Seizures are often brought on by factors such as stress, alcohol abuse, flickering light, or a lack of sleep, among others. The term seizure threshold is used to indicate the amount of stimulus necessary to bring about a seizure. Seizure threshold is lowered in epilepsy.[56]

In epileptic seizures a group of neurons begin firing in an abnormal, excessive,[21] and synchronized manner.[22] This results in a wave of depolarization known as a paroxysmal depolarizing shift.[60] Normally, after an excitatory neuron fires it becomes more resistant to firing for a period of time.[22] This is due in part to the effect of inhibitory neurons, electrical changes within the excitatory neuron, and the negative effects of adenosine.[22]

Partial seizures begin in one hemisphere of the brain while generalized seizures begin in both hemispheres.[26] Some types of seizures may change brain structure, while others appear to have little effect.[61] Gliosis, neuronal loss, and atrophy of specific areas of the brain are linked to epilepsy but it is unclear if epilepsy causes these changes or if these changes result in epilepsy.[61]

## Diagnosis [edit]

The diagnosis of epilepsy is typically made based on observation of the seizure onset and the underlying cause.[21] An electroencephalogram (EEG) to look for abnormal patterns of brain waves and neuroimaging (CT scan or MRI) to look at the structure of the brain are also usually part of the workup.[21] While figuring out a specific epileptic syndrome is often attempted, it is not always possible.[21] Video and EEG monitoring may be useful in difficult cases.[62]



An EEG can aid in locating the focus of the epileptic seizure.

### Definition [edit]

Epilepsy is a disorder of the brain defined by any of the following conditions:[2]

1. At least two unprovoked (or reflex) seizures occurring

greater than 24 hours apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome

Furthermore, epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past that age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.[2]

This 2014 definition of the International League Against Epilepsy[2] is a clarification of the ILAE 2005 conceptual definition, according to which epilepsy is "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure."[63][64]

It is, therefore, possible to outgrow epilepsy or to undergo treatment that causes epilepsy to be resolved, but with no guarantee that it will not return. In the definition, epilepsy is now called a disease, rather than a disorder. This was a decision of the executive committee of the ILAE, taken because the word "disorder," while perhaps having less stigma than does "disease," also does not express the degree of seriousness that epilepsy deserves.[2]

The definition is practical in nature and is designed for clinical use. In particular, it aims to clarify when an "enduring predisposition" according to the 2005 conceptual definition is present. Researchers, statistically-minded epidemiologists, and other specialized groups may choose to use the older definition or a definition of their own devising. The ILAE considers doing so is perfectly allowable, so long as it is clear what definition is being used.[2]

## Classification [edit]

In contrast to the classification of seizures which focuses on what happens during a seizure, the classification of epilepsies focuses on the underlying causes. When a person is admitted to hospital after an epileptic seizure the diagnostic workup results preferably in the seizure itself being classified (e.g. tonic-clonic) and in the underlying disease being identified (e.g. hippocampal sclerosis).[62] The name of the diagnosis finally made depends on the available diagnostic results and the applied definitions and classifications (of seizures and epilepsies) and its respective terminology.

The International League Against Epilepsy (ILAE) provided a classification of the epilepsies and epileptic syndromes in 1989 as follows:[65]

1. Localization-related epilepsies and syndromes
    1. Unknown cause (e.g. benign childhood epilepsy with centrotemporal spikes)
    2. Symptomatic/cryptogenic (e.g. temporal lobe epilepsy)
2. Generalized
    1. Unknown cause (e.g. childhood absence epilepsy)
    2. Cryptogenic or symptomatic (e.g. Lennox-Gastaut syndrome)
    3. Symptomatic (e.g. early infantile epileptic encephalopathy with burst suppression)
3. Epilepsies and syndromes undetermined whether partial or generalized
    1. With both generalized and partial seizures (e.g. epilepsy with continuous spike-waves during slow wave sleep)
4. Special syndromes (with situation-related seizures)[65]

This classification was widely accepted but has also been criticized mainly because the underlying causes of epilepsy (which are a major determinant of clinical course and prognosis) were not covered in detail.[66] In 2010 the ILAE Commission for Classification of the Epilepsies addressed this issue and divided epilepsies into three categories (genetic, structural/metabolic, unknown cause)[67] that were refined in their 2011 recommendation into four categories and a number of subcategories reflecting recent technologic and scientific advances.[68]

1. Unknown cause (mostly genetic or presumed genetic origin)
    1. Pure epilepsies due to single gene disorders
    2. Pure epilepsies with complex inheritance
2. Symptomatic (associated with gross anatomic or pathologic abnormalities)

1. Mostly genetic or developmental causation
    1. Childhood epilepsy syndromes
    2. Progressive myoclonic epilepsies
    3. Neurocutaneous syndromes
    4. Other neurologic single gene disorders
    5. Disorders of chromosome function
    6. Developmental anomalies of cerebral structure
2. Mostly acquired causes
    1. Hippocampal sclerosis
    2. Perinatal and infantile causes
    3. Cerebral trauma, tumor or infection
    4. Cerebrovascular disorders
    5. Cerebral immunologic disorders
    6. Degenerative and other neurologic conditions
3. Provoked (a specific systemic or environmental factor is the predominant cause of the seizures)
    1. Provoking factors
    2. Reflex epilepsies
4. Crytogenic (presumed symptomatic nature in which the cause has not been identified)[68]

## Syndromes [edit]

*Main article: Epilepsy syndromes*

Cases of epilepsy may be organized into epilepsy syndromes by the specific features that are present. These features include the age that seizure begin, the seizure types, EEG findings, among others. Identifying an epilepsy syndrome is useful as it helps determine the underlying causes as well as what anti-seizure medication should be tried.[26][69]

The ability to categorize a case of epilepsy into a specific syndrome occurs more often with children since the onset of seizures is commonly early.[45] Less serious examples are benign rolandic epilepsy (2.8 per 100,000), childhood absence epilepsy (0.8 per 100,000) and juvenile myoclonic epilepsy (0.7 per 100,000).[45] Severe syndromes with diffuse brain dysfunction caused, at least partly, by some aspect of epilepsy, are also referred to as epileptic encephalopathies. These are associated with frequent seizures that are resistant to treatment and severe cognitive dysfunction, for instance Lennox–Gastaut syndrome and West syndrome.[70] Genetics is believed to play an important role in epilepsies by a number of mechanisms. Simple and complex modes of inheritance have been identified for some of them. However, extensive screening have failed to identify many single gene variants of large effect.[71] More recent exome and genome sequencing studies have begun to reveal a number of de novo gene mutations that are responsible for some epileptic encephalopathies, including CHD2 and SYNGAP1[72][73][74] and DNM1, GABBR2, FASN and RYR3.[75]

Syndromes in which causes are not clearly identified are difficult to match with categories of the current classification of epilepsy. Categorization for these cases was made somewhat arbitrarily.[68] The *idiopathic* (unknown cause) category of the 2011 classification includes syndromes in which the general clinical features and/or age specificity strongly point to a presumed genetic cause.[68] Some childhood epilepsy syndromes are included in the unknown cause category in which the cause is presumed genetic, for instance benign rolandic epilepsy. Others are included in *symptomatic* despite a presumed genetic cause (in at least in some cases), for instance Lennox-Gastaut syndrome.[68] Clinical syndromes in which epilepsy is not the main feature (e.g. Angelman syndrome) were categorized *symptomatic* but it was argued to include these within the category *idiopathic*.[68] Classification of epilepsies and particularly of epilepsy syndromes will change with advances in research.

## Tests [edit]

An electroencephalogram (EEG) can assist in showing brain activity suggestive of an increased risk of seizures. It is only recommended for those who are likely to have had an epileptic seizure on the basis of symptoms. In the diagnosis of epilepsy, electroencephalography may help distinguish the type of seizure or syndrome present. In children it is typically only needed after a second seizure. It cannot be used to rule out the diagnosis and may be falsely positive in those without the disease. In certain situations it may be useful to perform the EEG while the affected individual is sleeping or sleep deprived.[62]

Diagnostic imaging by CT scan and MRI is recommended after a first non-febrile seizure to detect structural problems [62]

in and around the brain. MRI is generally a better imaging test except when bleeding is suspected, for which CT is more sensitive and more easily available.[16] If someone attends the emergency room with a seizure but returns to normal quickly, imaging tests may be done at a later point.[16] If a person has a previous diagnosis of epilepsy with previous imaging, repeating the imaging is usually not needed even if there are subsequent seizures.[62]

For adults, the testing of electrolyte, blood glucose and calcium levels is important to rule out problems with these as causes.[62] An electrocardiogram can rule out problems with the rhythm of the heart.[62] A lumbar puncture may be useful to diagnose a central nervous system infection but is not routinely needed.[16] In children additional tests may be required such as urine biochemistry and blood testing looking for metabolic disorders.[62][76]

A high blood prolactin level within the first 20 minutes following a seizure may be useful to help confirm an epileptic seizure as opposed to psychogenic non-epileptic seizure.[77][78] Serum prolactin level is less useful for detecting partial seizures.[79] If it is normal an epileptic seizure is still possible[78] and a serum prolactin does not separate epileptic seizures from syncope.[80] It is not recommended as a routine part of the diagnosis of epilepsy.[62]

### Differential diagnosis [edit]

Diagnosis of epilepsy can be difficult. A number of other conditions may present very similar signs and symptoms to seizures, including syncope, hyperventilation, migraines, narcolepsy, panic attacks and psychogenic non-epileptic seizures (PNES).[81][82] In particular a syncope can be accompanied by a short episode of convulsions.[83] Nocturnal frontal lobe epilepsy, often misdiagnosed as nightmares, was considered to be a parasomnia but later identified to be an epilepsy syndrome.[84] Attacks of the movement disorder paroxysmal dyskinesia may be taken for epileptic seizures.[85] The cause of a drop attack can be, among many others, an atonic seizure.[82]

Children may have behaviors that are easily mistaken for epileptic seizures but are not. These include breath-holding spells, bed wetting, night terrors, tics and shudder attacks.[82] Gastroesophageal reflux may cause arching of the back and twisting of the head to the side in infants, which may be mistaken for tonic-clonic seizures.[82]

Misdiagnosis is frequent (occurring in about 5 to 30% of cases).[21] Different studies showed that in many cases seizure-like attacks in apparent treatment-resistant epilepsy have a cardiovascular cause.[83][86] Approximately 20% of the people seen at epilepsy clinics have PNES[16] and of those who have PNES about 10% also have epilepsy;[87] separating the two based on the seizure episode alone without further testing is often difficult.[87]

## Prevention [edit]

While many cases are not preventable, efforts to reduce head injuries, provide good care around the time of birth, and reduce environmental parasites such as the pork tapeworm may be effective.[27] Efforts in one part of Central America to decrease rates of pork tapeworm resulted in a 50% decrease in new cases of epilepsy.[15]

## Management [edit]

Epilepsy is usually treated with daily medication once a second seizure has occurred,[21][62] but for those at high risk, medication may be started after the first seizure.[62] In drug-resistant cases different management options may be looked at including a special diet, the implantation of a neurostimulator, or neurosurgery.

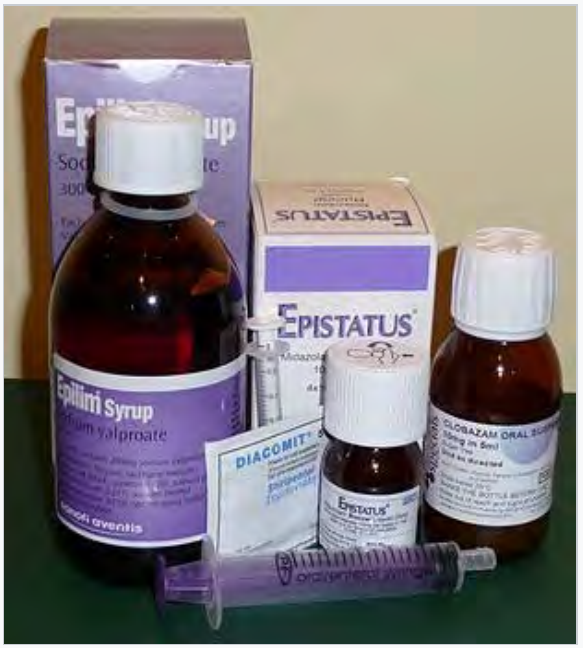
### First aid [edit]

Rolling a person with an active tonic-clonic seizure onto their side and into the recovery position helps prevent fluids from getting into the lungs.[88] Putting fingers, a bite block or tongue depressor in the mouth is not recommended as it might make the person vomit or result in the rescuer being bitten.[24][88] Efforts should be taken to prevent further self-injury.[24] Spinal precautions are generally not needed.[88]

If a seizure lasts longer than 5 minutes or if there are more than two seizures in an hour without a return to a normal level of consciousness between them, it is considered a medical emergency known as status epilepticus.[62][89] This may require medical help to keep the airway open and protected;[62] a nasopharyngeal airway may be useful for this.[88] At home the recommended initial medication for seizure of a long duration is midazolam placed in the mouth.[90] Diazepam may also be used rectally.[90] In hospital, intravenous lorazepam is preferred.[62] If two doses of benzodiazepines are not effective, other medications such as phenytoin are

recommended.[62] Convulsive status epilepticus that does not respond to initial treatment typically requires admission to the intensive care unit and treatment with stronger agents such as thiopentone or propofol.[62]

## Medications [edit]



Anticonvulsants

The mainstay treatment of epilepsy is anticonvulsant medications, possibly for the person's entire life.[21] The choice of anticonvulsant is based on seizure type, epilepsy syndrome, other medications used, other health problems, and the person's age and lifestyle.[90] A single medication is recommended initially;[91] if this is not effective, switching to a single other medication is recommended.[62] Two medications at once is recommended only if a single medication does not work.[62] In about half, the first agent is effective; a second single agent helps in about 13% and a third or two agents at the same time may help an additional 4%.[92] About 30% of people continue to have seizures despite anticonvulsant treatment.[7]

There are a number of medications available. Phenytoin, carbamazepine and valproate appear to be equally effective in both partial and generalized seizures.[93][94] Controlled release carbamazepine appears to work as well as immediate release carbamazepine, and may have fewer side effects.[95][*needs update*] In the United Kingdom, carbamazepine or lamotrigine are recommended as first-line treatment for partial seizures, with levetiracetam and valproate as second-line due to issues of cost and side effects.[62] Valproate is recommended first-line for generalized seizures with lamotrigine being second-line.[62] In those with absence seizures, ethosuximide or valproate are recommended; valproate is particularly effective in myoclonic seizures and tonic or atonic seizures.[62] If seizures are well-controlled on a particular treatment, it is not usually necessary to routinely check the medication levels in the blood.[62]

The least expensive anticonvulsant is phenobarbital at around $5 USD a year.[15] The World Health Organization gives it a first-line recommendation in the developing world and it is commonly used there.[96][97] Access however may be difficult as some countries label it as a controlled drug.[15]

Adverse effects from medications are reported in 10 to 90% of people, depending on how and from whom the data is collected.[98] Most adverse effects are dose-related and mild.[98] Some examples include mood changes, sleepiness, or an unsteadiness in gait.[98] Certain medications have side effects that are not related to dose such as rashes, liver toxicity, or suppression of the bone marrow.[98] Up to a quarter of people stop treatment due to adverse effects.[98] Some medications are associated with birth defects when used in pregnancy.[62] Many of the common used medications, such as valproate, phenytoin, carbamazepine, phenobarbitol, and gabapentin have been reported to cause increased risk of birth defects,[99] especially when used during the first trimester.[100] Despite this, treatment is often continued once effective, because the risk of untreated epilepsy is believed to be greater than the risk of the medications.[100] Among the antiepileptic medications, levetiracetam and lamotrigine seem to carry the lowest risk of causing birth defects.[99]

Slowly stopping medications may be reasonable in some people who do not have a seizure for two to four years; however, around a third of people have a recurrence, most often during the first six months.[62][101] Stopping is possible in about 70% of children and 60% of adults.[27]

## Surgery [edit]

Epilepsy surgery may be an option for people with partial seizures that remain a problem despite other treatments.[102] These other treatments include at least a trial of two or three medications.[103] The goal of surgery is total control of seizures[104] and this may be achieved in 60–70% of cases.[103] Common procedures include cutting out the hippocampus via an anterior temporal lobe resection, removal of tumors, and removing parts of the neocortex.[103] Some procedures such as a corpus callosotomy are attempted in an effort to decrease the number of seizures rather than cure the condition.[103] Following surgery, medications may be slowly withdrawn in many [103]

cases.

Neurostimulation may be another option in those who are not candidates for surgery.[62] Three types have been shown to be effective in those who do not respond to medications: vagus nerve stimulation, anterior thalamic stimulation, and closed-loop responsive stimulation.[8]

### Diet [edit]

A ketogenic diet (high-fat, low-carbohydrate, adequate-protein) appears to decrease the number of seizures and eliminate seizures in some.[105] It is a reasonable option in those who have epilepsy that is not improved with medications and for whom surgery is not an option.[105] About 10% stay on the diet for a few years due to issues of effectiveness and tolerability.[9] Side effects include stomach and intestinal problems in 30%, and there are long term concerns of heart disease.[9] Less radical diets are easier to tolerate and may be effective.[9] It is unclear why this diet works.[106] Exercise has been proposed as possibly useful for preventing seizures[107] with some data to support this claim.[108]

In people with coeliac disease or non-celiac gluten sensitivity and occipital calcifications, a gluten-free diet may decrease the frequency of seizures.[49]

### Other [edit]

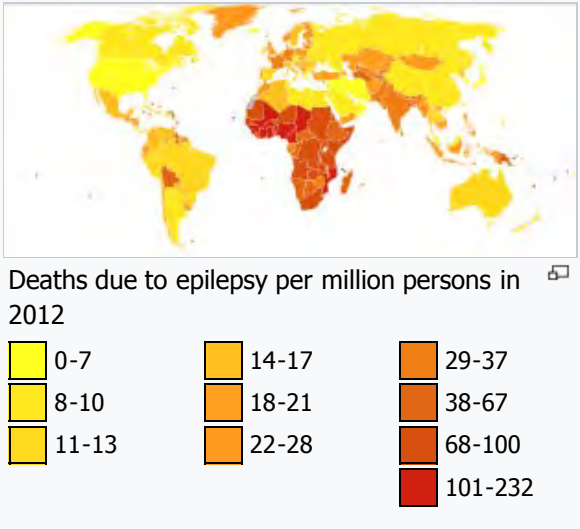
Avoidance therapy consists of minimizing or eliminating triggers. For example, in those who are sensitive to light, using a small television, avoiding video games, or wearing dark glasses may be useful.[109] Operant-based biofeedback based on the EEG waves has some support in those who do not respond to medications.[110] Psychological methods should not, however, be used to replace medications.[62] Some dogs, commonly referred to as seizure dogs, may help during or after a seizure.[111][112] It is not clear if dogs have the ability to predict seizures before they occur.[113]

### Alternative medicine [edit]

Alternative medicine, including acupuncture,[114] psychological interventions,[115] routine vitamins,[116] and yoga,[117] have no reliable evidence to support their use in epilepsy. There is not enough evidence to support the use of cannabis.[118][119] Melatonin, as of 2016, is insufficiently supported by evidence.[120] The trials were of poor methodological quality and it was not possible to draw any definitive conclusions.[120]

## Prognosis [edit]

Epilepsy cannot usually be cured, but medication can control seizures effectively in about 70% of cases.[7] Of those with generalized seizures, more than 80% can be well controlled with medications while this is true in only 50% of people with partial seizures.[8] One predictor of long-term outcome is the number of seizures that occur in the first six months.[21] Other factors increasing the risk of a poor outcome include little response to the initial treatment, generalized seizures, a family history of epilepsy, psychiatric problems, and waves on the EEG representing generalized epileptiform activity.[121] In the developing world, 75% of people are either untreated or not appropriately treated.[27] In Africa, 90% do not get treatment.[27] This is partly related to appropriate medications not being available or being too expensive.[27]



Deaths due to epilepsy per million persons in 2012

### Mortality [edit]

People with epilepsy are at an increased risk of death.[122] This increase is between 1.6 and 4.1 fold greater than that of the general population[123] and is often related to: the underlying cause of the seizures, status epilepticus, suicide, trauma, and sudden unexpected death in epilepsy (SUDEP).[122] Death from status epilepticus is primarily due to an underlying

problem rather than missing doses of medications.[122] The risk of suicide is increased between two and six times in those with epilepsy.[124][125] The cause of this is unclear.[124] SUDEP appears to be partly related to the frequency of generalized tonic-clonic seizures[126] and accounts for about 15% of epilepsy related deaths.[121] It is unclear how to decrease its risk.[126] The greatest increase in mortality from epilepsy is among the elderly.[123] Those with epilepsy due to an unknown cause have little increased risk.[123] In the United Kingdom, it is estimated that 40–60% of deaths are possibly preventable.[21] In the developing world, many deaths are due to untreated epilepsy leading to falls or status epilepticus.[15]

## Epidemiology [edit]

Epilepsy is one of the most common serious neurological disorders[127] affecting about 22 million people as of 2013.[10] It affects 1% of the population by age 20 and 3% of the population by age 75.[13] It is more common in males than females with the overall difference being small.[15][45] Most of those with the disorder (80%) are in the developing world.[27]

The estimated prevalence of active epilepsy (as of 2012) is in the range 3–10 per 1,000, with active epilepsy defined as someone with epilepsy who has had a least one unprovoked seizure in the last five years.[45][128] Epilepsy begins each year in 40–70 per 100,000 in developed countries and 80–140 per 100,000 in developing countries.[27] Poverty is a risk and includes both being from a poor country and being poor relative to others within one's country.[15] In the developed world epilepsy most commonly starts either in the young or in the old.[15] In the developing world its onset is more common in older children and young adults due to the higher rates of trauma and infectious diseases.[15] In developed countries the number of cases a year has decreased in children and increased among the elderly between the 1970s and 2003.[128] This has been attributed partly to better survival following strokes in the elderly.[45]

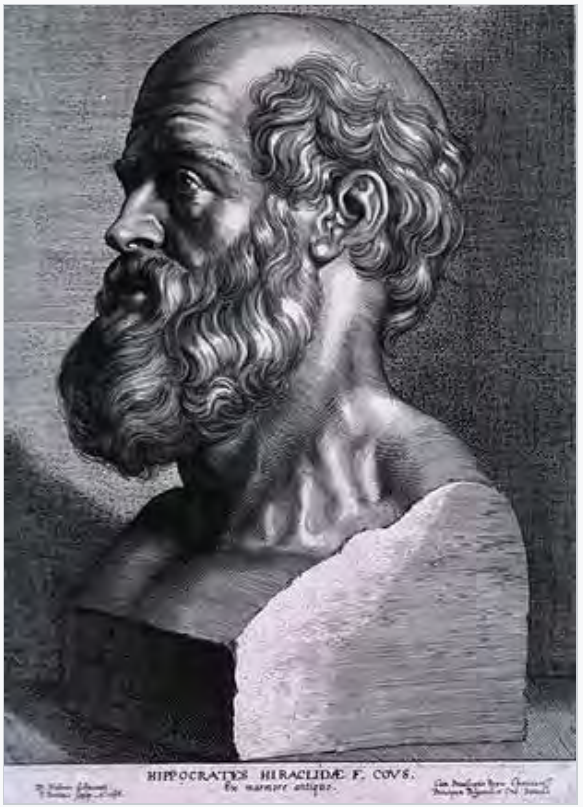
## History [edit]

*See also: On the Sacred Disease*

The oldest medical records show that epilepsy has been affecting people at least since the beginning of recorded history.[129] Throughout ancient history, the disease was thought to be a spiritual condition.[129] The world's oldest description of an epileptic seizure comes from a text in Akkadian (a language used in ancient Mesopotamia) and was written around 2000 BC.[19] The person described in the text was diagnosed as being under the influence of a Moon god, and underwent an exorcism.[19] Epileptic seizures are listed in the Code of Hammurabi (c. 1790 BC) as reason for which a purchased slave may be returned for a refund,[19] and the Edwin Smith Papyrus (c. 1700 BC) describes cases of individuals with epileptic convulsions.[19]

The oldest known detailed record of the disease itself is in the *Sakikku*, a Babylonian cuneiform medical text from 1067–1046 BC.[129] This text gives signs and symptoms, details treatment and likely outcomes,[19] and describes many features of the different seizure types.[129] As the Babylonians had no biomedical understanding of the nature of disease, they attributed the seizures to possession by evil spirits and called for treating the condition through spiritual means.[129] Around 900 BC, Punarvasu Atreya described epilepsy as loss of consciousness;[130] this definition was carried forward into the Ayurvedic text of Charaka Samhita (about 400 BC).[131]

The ancient Greeks had contradictory views of the disease. They thought of epilepsy as a form of spiritual possession, but also associated the condition with genius and the divine. One of the



Hippocrates, 17th century engraving by Peter Paul Rubens of an antique bust.

names they gave to it was the *sacred disease* (ἡ ἱερὰ νόσος).[19][132]
Epilepsy appears within Greek mythology: it is associated with the Moon goddesses Selene and Artemis, who afflicted those who upset them. The Greeks thought that important figures such as Julius Caesar and Hercules had the disease.[19] The notable exception to this divine and spiritual view was that of the school of Hippocrates. In the fifth century BC, Hippocrates rejected the idea that the disease was caused by spirits. In his landmark work *On the Sacred Disease*, he proposed that epilepsy was not divine in origin and instead was a medically treatable problem originating in the brain.[19][129] He accused those of attributing a sacred cause to the disease of spreading ignorance through a belief in superstitious magic.[19] Hippocrates proposed that heredity was important as a cause, described worse outcomes if the disease presents at an early age, and made note of the physical characteristics as well as the social shame associated with it.[19] Instead of referring to it as the *sacred disease*, he used the term *great disease*, giving rise to the modern term *grand mal*, used for tonic–clonic seizures.[19] Despite his work detailing the physical origins of the disease, his view was not accepted at the time.[129] Evil spirits continued to be blamed until at least the 17th century.[129]

In Ancient Rome people did not eat or drink with the same pottery as that used by someone who was affected.[133] People of the time would spit on their chest believing that this would keep the problem from affected them.[133] According to Apuleius and other ancient physicians, in order detect epilepsy it was common to light a piece of *gagates*, whose smoke would trigger the seizure.[134] Occasionally a spinning potter's wheel was used, perhaps a reference to photosensitive epilepsy.[135]

In most cultures, persons with epilepsy have been stigmatized, shunned, or even imprisoned; in the Salpêtrière, the birthplace of modern neurology, Jean-Martin Charcot found people with epilepsy side-by-side with the mentally ill, those with chronic syphilis, and the criminally insane.[136] In ancient Rome, epilepsy was known as the *morbus comitialis* ('disease of the assembly hall') and was seen as a curse from the gods. In northern Italy, epilepsy was once traditionally known as Saint Valentine's malady.[137]

In the mid-1800s, the first effective anti-seizure medication, bromide, was introduced.[98] The first modern treatment, phenobarbital, was developed in 1912, with phenytoin coming into use in 1938.[138]

## Society and culture [edit]

*See also: List of people with epilepsy*

### Stigma [edit]

Stigma is commonly experienced, around the world, by those with epilepsy.[139] It can affect people economically, socially and culturally.[139] In India and China, epilepsy may be used as justification to deny marriage.[27] People in some areas still believe those with epilepsy to be cursed.[15] In Tanzania, as in other parts of Africa, epilepsy is associated with possession by evil spirits, witchcraft, or poisoning and is believed by many to be contagious,[136] for which there is no evidence.[15] Before 1970 the United Kingdom had laws which prevented people with epilepsy from marrying.[27] The stigma may result in some people with epilepsy denying that they have ever had seizures.[45]

### Economics [edit]

Seizures result in direct economic costs of about one billion dollars in the United States.[16] Epilepsy resulted in economic costs in Europe of around 15.5 billion Euros in 2004.[21] In India epilepsy is estimated to result in costs of 1.7 billion USD or 0.5% of the GDP.[27] It is the cause of about 1% of emergency department visits (2% for emergency departments for children) in the United States.[140]

### Vehicles [edit]

*See also: Epilepsy and driving*

Those with epilepsy are at about twice the risk of being involved in a motor vehicular collision and thus in many areas of the world are not allowed to drive or only able to drive if certain conditions are met.[18] In some places physicians are required by law to report if a person has had a seizure to the licensing body while in others the requirement is only that they encourage the person in question to report it themselves.[18] Countries that require physician reporting include Sweden, Austria, Denmark and Spain.[18] Countries that require the individual to report

include the UK and New Zealand and the physician may report if they believe the individual has not already.[18] In Canada, the United States and Australia the requirements around reporting vary by province or state.[18] If seizures are well controlled most feel allowing driving is reasonable.[141] The amount of time a person must be free from seizures before they can drive varies by country.[141] Many countries require one to three years without seizures.[141] In the United States the time needed without a seizure is determined by each state and is between three months and one year.[141]

Those with epilepsy or seizures are typically denied a pilot license.[142] In Canada if an individual has had no more than one seizure, they may be considered after five years for a limited license if all other testing is normal.[143] Those with febrile seizures and drug related seizures may also be considered.[143] In the United States, the Federal Aviation Administration does not allow those with epilepsy to get a commercial pilot license.[144] Rarely, exceptions can be made for persons who have had an isolated seizure or febrile seizures and have remained free of seizures into adulthood without medication.[145] In the United Kingdom, a full national private pilot license requires the same standards as a professional driver's license.[146] This requires a period of ten years without seizures while off medications.[147] Those who do not meet this requirement may acquire a restricted license if free from seizures for five years.[146]

### Support organizations [edit]

There are organizations that provide support for people and families affected by epilepsy. The *Out of the Shadows* campaign, a joint effort by the World Health Organization, the International League Against Epilepsy and the International Bureau for Epilepsy, provides help internationally.[27] The Joint Epilepsy Council serves the UK and Ireland.[62] In the United States, the Epilepsy Foundation is a national organization that works to increase the acceptance of those with the disease, their ability to function in society and to promote research for a cure.[148] The Epilepsy Foundation, some hospitals, and some individuals also run support groups in the United States.[149]

## Research [edit]

Seizure prediction refers to attempts to forecast epileptic seizures based on the EEG before they occur.[150] As of 2011, no effective mechanism to predict seizures has been developed.[150] Kindling, where repeated exposures to events that could cause seizures eventually causes seizures more easily, has been used to create animal models of epilepsy.[151]

Gene therapy is being studied in some types of epilepsy.[152] Medications that alter immune function, such as intravenous immunoglobulins, are poorly supported by evidence.[153] Noninvasive stereotactic radiosurgery is, as of 2012, being compared to standard surgery for certain types of epilepsy.[154]

Common locations for the start of seizures and neural networks have been found to be affected in the majority of epilepsy.[155] Efforts to figure out how epilepsy occurs is working to take into account the different regions of the brain and the timing of their activity.[156]

## Other animals [edit]

*Main article: Epilepsy in animals*

Epilepsy occurs in a number of other animals including dogs and cats and is the most common brain disorder in dogs.[157] It is typically treated with anticonvulsants such as phenobarbital or bromide in dogs and phenobarbital in cats.[158] Imepitoin is also used in dogs.[159] While generalized seizures in horses are fairly easy to diagnose, it may be more difficult in non-generalized seizures and EEGs may be useful.[160]

## References [edit]


1. ^ *a b* Chang BS, Lowenstein DH (2003). "Epilepsy". *N. Engl. J. Med.* **349** (13): 1257–66. doi:10.1056/NEJMra022308. PMID 14507951.
2. ^ *a b c d e f* Fisher, Robert S; Acevedo, C; Arzimanoglou, A; Bogacz, A; Cross, JH; Elger, CE; Engel J, Jr; Forsgren, L; French, JA; Glynn, M; Hesdorffer, DC; Lee, BI; Mathern, GW; Moshé, SL; Perucca, E; Scheffer, IE; Tomson, T; Watanabe, M; Wiebe, S

(April 2014). "ILAE Official Report: A practical clinical definition of epilepsy" (PDF). *Epilepsia*. **55** (4): 475–82. doi:10.1111/epi.12550. PMID 24730690.

3. ^ a b c d e f g h "Epilepsy Fact sheet". *WHO*. February 2016. Retrieved 4 March 2016.
4. ^ a b Fisher R, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J (2005). "Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)". *Epilepsia*. **46** (4): 470–2. doi:10.1111/j.0013-9580.2005.66104.x. PMID 15816939.
5. ^ a b Longo, Dan L (2012). "369 Seizures and Epilepsy". *Harrison's principles of internal medicine* (18th ed.). McGraw-Hill. p. 3258. ISBN 978-0-07-174887-2.
6. ^ a b c d e f g Pandolfo, M. (Nov 2011). "Genetics of epilepsy.". *Semin Neurol*. **31** (5): 506–18. doi:10.1055/s-0031-1299789. PMID 22266888.
7. ^ a b c Eadie, MJ (December 2012). "Shortcomings in the current treatment of epilepsy.". *Expert Review of Neurotherapeutics*. **12** (12): 1419–27. doi:10.1586/ern.12.129. PMID 23237349.
8. ^ a b c Bergey, GK (June 2013). "Neurostimulation in the treatment of epilepsy.". *Experimental neurology*. **244**: 87–95. doi:10.1016/j.expneurol.2013.04.004. PMID 23583414.
9. ^ a b c d Levy, RG; Cooper, PN; Giri, P (14 March 2012). "Ketogenic diet and other dietary treatments for epilepsy.". *The Cochrane database of systematic reviews*. **3**: CD001903. doi:10.1002/14651858.CD001903.pub2. PMID 22419282.
10. ^ a b Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/S0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
11. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
12. ^ Brodie, MJ; Elder, AT; Kwan, P (November 2009). "Epilepsy in later life". *Lancet neurology*. **8** (11): 1019–30. doi:10.1016/S1474-4422(09)70240-6. PMID 19800848.
13. ^ a b Holmes, Thomas R. Browne, Gregory L. (2008). *Handbook of epilepsy* (4th ed.). Philadelphia: Lippincott Williams & Wilkins. p. 7. ISBN 978-0-7817-7397-3.
14. ^ *Wyllie's treatment of epilepsy : principles and practice.* (5th ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins. 2010. ISBN 978-1-58255-937-7.
15. ^ a b c d e f g h i j k l Newton, CR (29 September 2012). "Epilepsy in poor regions of the world.". *Lancet*. **380** (9848): 1193–201. doi:10.1016/S0140-6736(12)61381-6. PMID 23021288.
16. ^ a b c d e f Wilden, JA; Cohen-Gadol, AA (15 August 2012). "Evaluation of first nonfebrile seizures.". *American family physician*. **86** (4): 334–40. PMID 22963022.
17. ^ Berg, AT (2008). "Risk of recurrence after a first unprovoked seizure". *Epilepsia*. 49 Suppl 1: 13–8. doi:10.1111/j.1528-1167.2008.01444.x. PMID 18184149.
18. ^ a b c d e f L Devlin, A; Odell, M; L Charlton, J; Koppel, S (December 2012). "Epilepsy and driving: current status of research.". *Epilepsy research*. **102** (3): 135–52. doi:10.1016/j.eplepsyres.2012.08.003. PMID 22981339.
19. ^ a b c d e f g h i j k l Magiorkinis E, Kalliopi S, Diamantis A (January 2010). "Hallmarks in the history of epilepsy: epilepsy in antiquity". *Epilepsy & behavior : E&B*. **17** (1): 103–108. doi:10.1016/j.yebeh.2009.10.023. PMID 19963440.
20. ^ a b Duncan, JS; Sander, JW; Sisodiya, SM; Walker, MC (1 April 2006). "Adult epilepsy." (PDF). *Lancet*. **367** (9516): 1087–100. doi:10.1016/S0140-6736(06)68477-8. PMID 16581409.
21. ^ a b c d e f g h i j k l m n o p q r s t u National Clinical Guideline Centre (January 2012). *The Epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care* (PDF). National Institute for Health and Clinical Excellence. pp. 21–28.
22. ^ a b c d e f g h i j k l m Hammer, edited by Stephen J. McPhee, Gary D. (2010). "7". *Pathophysiology of disease : an introduction to clinical medicine* (6th ed.). New York: McGraw-Hill Medical. ISBN 978-0-07-162167-0.
23. ^ Hughes, JR (August 2009). "Absence seizures: a review of recent reports with new concepts.". *Epilepsy & behavior : E&B*. **15** (4): 404–12. doi:10.1016/j.yebeh.2009.06.007. PMID 19632158.
24. ^ a b c d Shearer, Peter. "Seizures and Status Epilepticus: Diagnosis and Management in the Emergency Department". *Emergency Medicine Practice*.
25. ^ a b c d Bradley, Walter G. (2012). "67". *Bradley's neurology in clinical practice.* (6th ed.). Philadelphia, PA: Elsevier/Saunders. ISBN 978-1-4377-0434-1.
26. ^ a b c d e National Clinical Guideline Centre (January 2012). *The Epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care* (PDF). National Institute for Health and Clinical Excellence. pp. 119–129.
27. ^ a b c d e f g h i j k l m n o "Epilepsy". Fact Sheets. World Health Organization. October 2012. Retrieved January 24, 2013.
28. ^ a b c Engel, Jerome (2008). *Epilepsy : a comprehensive textbook* (2nd ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 2797. ISBN 978-0-7817-5777-5.
29. ^ a b Simon, David A. Greenberg, Michael J. Aminoff, Roger P. (2012). "12". *Clinical neurology* (8th ed.). New York: McGraw-

Hill Medical. ISBN 978-0-07-175905-2.
30. ^ [a] [b] Steven C. Schachter, ed. (2008). *Behavioral aspects of epilepsy : principles and practice* ([Online-Ausg.]. ed.). New York: Demos. p. 125. ISBN 978-1-933864-04-4.
31. ^ Xue, LY; Ritaccio, AL (March 2006). "Reflex seizures and reflex epilepsy.". *American journal of electroneurodiagnostic technology*. **46** (1): 39–48. PMID 16605171.
32. ^ Malow, BA (November 2005). "Sleep and epilepsy.". *Neurologic Clinics*. **23** (4): 1127–47. doi:10.1016/j.ncl.2005.07.002. PMID 16243619.
33. ^ Tinuper, P; Provini, F; Bisulli, F; Vignatelli, L; Plazzi, G; Vetrugno, R; Montagna, P; Lugaresi, E (August 2007). "Movement disorders in sleep: guidelines for differentiating epileptic from non-epileptic motor phenomena arising from sleep.". *Sleep medicine reviews*. **11** (4): 255–67. doi:10.1016/j.smrv.2007.01.001. PMID 17379548.
34. ^ Holmes, Thomas R. (2008). *Handbook of epilepsy* (4th ed.). Philadelphia: Lippincott Williams & Wilkins. p. 34. ISBN 978-0-7817-7397-3.
35. ^ [a] [b] [c] Panayiotopoulos, CP (2010). *A clinical guide to epileptic syndromes and their treatment based on the ILAE classifications and practice parameter guidelines* (Rev. 2nd ed.). London: Springer. p. 445. ISBN 978-1-84628-644-5.
36. ^ James W. Wheless, ed. (2009). *Advanced therapy in epilepsy*. Shelton, Conn.: People's Medical Pub. House. p. 443. ISBN 978-1-60795-004-2.
37. ^ Larner, Andrew J. (2010). *A dictionary of neurological signs* (3rd ed.). New York: Springer. p. 348. ISBN 978-1-4419-7095-4.
38. ^ Kapan PW (November 2011). "Obsessive-compulsive disorder in chronic epilepsy". *Epilepsy & Behavior*. **22**: 428–32. doi:10.1016/j.yebeh.2011.07.029. PMID 21889913.
39. ^ Stefan, Hermann (2012). *Epilepsy Part I: Basic Principles and Diagnosis E-Book: Handbook of Clinical Neurology* (Volume 107 of Handbook of Clinical Neurology ed.). Newnes. p. 471. ISBN 978-0-444-53505-4.
40. ^ Plioplys S, Dunn DW, Caplan R (2007). "10-year research update review: psychiatric problems in children with epilepsy". *J Am Acad Child Adolesc Psychiatry*. **46** (11): 1389–402. doi:10.1097/chi.0b013e31815597fc. PMID 18049289.
41. ^ Reilly CJ (May–June 2011). "Attention Deficit Hyperactivity Disorder (ADHD) in Childhood Epilepsy". *Research in Developmental Disabilities: A Multidisciplinary Journal*. **32** (3): 883–93. doi:10.1016/j.ridd.2011.01.019. PMID 21310586.
42. ^ Levisohn PM (2007). "The autism-epilepsy connection". *Epilepsia*. **48** (Suppl 9): 33–5. doi:10.1111/j.1528-1167.2007.01399.x. PMID 18047599.
43. ^ [a] [b] [c] Berkovic SF1, Mulley JC, Scheffer IE, Petrou S (2006). "Human epilepsies: interaction of genetic and acquired factors". *Trends Neurosci*. **29** (7): 391–7. doi:10.1016/j.tins.2006.05.009. PMID 16769131.
44. ^ Thurman, DJ; Beghi, E; Begley, CE; Berg, AT; Buchhalter, JR; Ding, D; Hesdorffer, DC; Hauser, WA; Kazis, L; Kobau, R; Kroner, B; Labiner, D; Liow, K; Logroscino, G; Medina, MT; Newton, CR; Parko, K; Paschal, A; Preux, PM; Sander, JW; Selassie, A; Theodore, W; Tomson, T; Wiebe, S; ILAE Commission on, Epidemiology (September 2011). "Standards for epidemiologic studies and surveillance of epilepsy.". *Epilepsia*. 52 Suppl 7: 2–26. doi:10.1111/j.1528-1167.2011.03121.x. PMID 21899536.
45. ^ [a] [b] [c] [d] [e] [f] [g] Neligan, A; Hauser, WA; Sander, JW (2012). "The epidemiology of the epilepsies.". *Handbook of clinical neurology*. **107**: 113–33. doi:10.1016/B978-0-444-52898-8.00006-9. PMID 22938966.
46. ^ Dhavendra Kumar, ed. (2008). *Genomics and clinical medicine*. Oxford: Oxford University Press. p. 279. ISBN 978-0-19-972005-7.
47. ^ [a] [b] [c] [d] [e] [f] [g] [h] [i] [j] [k] [l] [m] [n] [o] [p] [q] Bhalla, D.; Godet, B.; Druet-Cabanac, M.; Preux, PM. (Jun 2011). "Etiologies of epilepsy: a comprehensive review.". *Expert Rev Neurother*. **11** (6): 861–76. doi:10.1586/ern.11.51. PMID 21651333.
48. ^ Grossman G (Apr 2008). "Neurological complications of coeliac disease: what is the evidence?". *Pract Neurol*. **8** (2): 77–89. doi:10.1136/jnnp.2007.139717. PMID 18344378.
49. ^ [a] [b] [c] Jackson JR, Eaton WW, Cascella NG, Fasano A, Kelly DL (Mar 2012). "Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity". *Psychiatr Q*. **83** (1): 91–102. doi:10.1007/s11126-011-9186-y. PMC 3641836. PMID 21877216.
50. ^ Simon D. Shorvon (2011). *The Causes of Epilepsy: Common and Uncommon Causes in Adults and Children*. Cambridge University Press. p. 467. ISBN 978-1-139-49578-3.
51. ^ Sellner, J; Trinka, E (Oct 2012). "Seizures and epilepsy in herpes simplex virus encephalitis: current concepts and future directions of pathogenesis and management.". *Journal of neurology*. **259** (10): 2019–30. doi:10.1007/s00415-012-6494-6. PMID 22527234.
52. ^ Hadjipanayis A; Hadjichristodoulou C; Youroukos S (October 1997). "Epilepsy in patients with cerebral palsy.". *Developmental Medicine & Child Neurology*. **39**: 659–63. doi:10.1111/j.1469-8749.1997.tb07359.x. PMID 9352726.
53. ^ [a] [b] Bromfield EB (2006). *An Introduction to Epilepsy*. American Epilepsy Society.
54. ^ Blumenfeld, H (2005). "Cellular and Network Mechanisms of Spike-Wave Seizures". *Epilepsia*. **46** (Suppl.9): 21–33. doi:10.1111/j.1528-1167.2005.00311.x. PMID 16302873.
55. ^ Noebels, Jeffrey L.; Avoli, Massimo (2012-06-29). *Jasper's Basic Mechanisms of the Epilepsies*. Oxford University Press. pp. 466, 470. ISBN 9780199746545. Retrieved 2014-10-16.
56. ^ [a] [b] Le Van Quyen, M; Navarro, V; Martinerie, J; Baulac, M; Varela, FJ (2003). "Toward a Neurodynamical Understanding of Ictogenesis". *Epilepsia*. **44** (Suppl.12): 30–43. doi:10.1111/j.0013-9580.2003.12007.x. PMID 14641559.
57. ^ Lopes da Silva F1, Blanes W, Kalitzin SN, Parra J, Suffczynski P, Velis DN (2003). "Epilepsies as Dynamical Diseases of Brain Systems: Basic Models of the Transition Between Normal and Epileptic Activity". *Epilepsia*. **44** (Suppl.12): 72–83.

doi:10.1111/j.0013-9580.2003.12005.x. PMID 14641563.
58. ^ a b Goldberg, EM; Coulter, DA (May 2013). "Mechanisms of epileptogenesis: a convergence on neural circuit dysfunction.". *Nature reviews. Neuroscience*. **14** (5): 337–49. doi:10.1038/nrn3482. PMID 23595016.
59. ^ Oby, E; Janigro, D (November 2006). "The blood-brain barrier and epilepsy.". *Epilepsia*. **47** (11): 1761–74. doi:10.1111/j.1528-1167.2006.00817.x. PMID 17116015.
60. ^ Somjen, George G. (2004). *Ions in the Brain Normal Function, Seizures, and Stroke.* New York: Oxford University Press. p. 167. ISBN 978-0-19-803459-9.
61. ^ a b Jerome Engel, Jr.; Timothy A. Pedley, eds. (2008). *Epilepsy : a comprehensive textbook* (2nd ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 483. ISBN 978-0-7817-5777-5.
62. ^ a b c d e f g h i j k l m n o p q r s t u v w x y z aa National Clinical Guideline Centre (January 2012). *The Epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care* (PDF). National Institute for Health and Clinical Excellence. pp. 57–83.
63. ^ Robert S. Fisher; Walter van Emde Boas; Warren Blume; Christian Elger; Pierre Genton; Phillip Lee; Jerome Jr Engel (April 2005). "Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)". *Epilepsia*. **46** (4): 470–472. doi:10.1111/j.0013-9580.2005.66104.x. PMID 15816939.
64. ^ Panayiotopoulos, CP (December 2011). "The new ILAE report on terminology and concepts for organization of epileptic seizures: a clinician's critical view and contribution.". *Epilepsia*. **52** (12): 2155–60. doi:10.1111/j.1528-1167.2011.03288.x. PMID 22004554.
65. ^ a b "Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy". *Epilepsia*. **30** (4): 389–99. 1989. doi:10.1111/j.1528-1157.1989.tb05316.x. PMID 2502382.
66. ^ Engel J (2006). "ILAE classification of epilepsy syndromes". *Epilepsy Res*. **70** (Suppl 1): 5–10. doi:10.1016/j.eplepsyres.2005.11.014. PMID 16822650.
67. ^ Berg A; Berkovic S; Brodie M; Buchhalter J; Cross J; van Emde; Boas W; Engel J; French J; Glauser T; Mathern G; MoshØ S; Nordli D; Plouin P; Scheffer I. (2010). "Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology". *Epilepsia*. **51** (6): 676–685. doi:10.1111/j.1528-1167.2010.02522.x. PMID 20196795.
68. ^ a b c d e f Shorvon SD (2011). "The etiologic classification of epilepsy". *Epilepsia*. **52** (6): 1052–1057. doi:10.1111/j.1528-1167.2011.03041.x.
69. ^ "Epilepsy syndromes". International league against epilepsy. Retrieved 2014-10-06.
70. ^ Nordli DR jr (2012). "Epileptic encephalopathies in infants and children". *J Clin Neurophysiol*. **29** (5): 420–4. doi:10.1097/WNP.0b013e31826bd961. PMID 23027099.
71. ^ Heinzen EL, Depondt C, Cavalleri GL, Ruzzo EK, Walley NM, Need AC, Ge D, He M, Cirulli ET, Zhao Q, Cronin KD, Gumbs CE, Campbell CR, Hong LK, Maia JM, Shianna KV, McCormack M, Radtke RA, O'Conner GD, Mikati MA, Gallentine WB, Husain AM, Sinha SR, Chinthapalli K, Puranam RS, McNamara JO, Ottman R, Sisodiya SM, Delanty N, Goldstein DB (2012). "Exome sequencing followed by large-scale genotyping failed to identify single rare variants of large effect in "idiopathic" generalized epilepsy". *Am J Hum Genet*. **91** (2): 293–302. doi:10.1016/j.ajhg.2012.06.016. PMC 3415540. PMID 22863189.
72. ^ Gemma L Carvill; Sinéad B Heavin; Simone C Yendle; Jacinta M McMahon; Brian J O'Roak; Joseph Cook; Adiba Khan; Michael O Dorschner; Molly Weaver; Sophie Calvert; Stephen Malone; Geoffrey Wallace; Thorsten Stanley; Ann M E Bye; Andrew Bleasel; Katherine B Howell; Sara Kivity; Mark T Mackay; Victoria Rodriguez-Casero; Richard Webster; Amos Korczyn; Zaid Afawi; Nathanel Zelnick; Tally Lerman-Sagie; Dorit Lev; Rikke S Møller; Deepak Gill; Danielle M Andrade; Jeremy L Freeman; Lynette G Sadleir; Jay Shendure; Samuel F Berkovic; Ingrid E Scheffer; Heather C Mefford (2013). "Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2, SYNGAP1". *Nature Genetics*. **45**: 825–830. doi:10.1038/ng.2646. PMC 3704157. PMID 23708187.
73. ^ Chénier S, Yoon G, Argiropoulos B, Lauzon J, Laframboise R, Ahn JW, Ogilvie CM, Lionel AC, Marshall CR, Vaags AK, Hashemi B, Boisvert K, Mathonnet G, Tihy F, So J, Scherer SW, Lemyre E, Stavropoulos DJ (2014). "CHD2 haploinsufficiency is associated with developmental delay, intellectual disability, epilepsy and neurobehavioural problems". *J Neurodev Disord*. **6** (1): 9. doi:10.1186/1866-1955-6-9. PMC 4022362. PMID 24834135.
74. ^ Suls A, Jaehn JA, Kecskés A, Weber Y, Weckhuysen S, Craiu DC, Siekierska A, Djémié T, Afrikanova T, Gormley P, von Spiczak S, Kluger G, Iliescu CM, Talvik T, Talvik I, Meral C, Caglayan HS, Giraldez BG, Serratosa J, Lemke JR, Hoffman-Zacharska D, Szczepanik E, Barisic N, Komarek V, Hjalgrim H, Møller RS, Linnankivi T, Dimova P, Striano P, Zara F, Marini C, Guerrini R, Depienne C, Baulac S, Kuhlenbäumer G, Crawford AD, Lehesjoki AE, de Witte PA, Palotie A, Lerche H, Esguerra CV, De Jonghe P, Helbig I; EuroEPINOMICS RES Consortium (2013). "De novo loss-of-function mutations in CHD2 cause a fever-sensitive myoclonic epileptic encephalopathy sharing features with Dravet syndrome". *Am J Hum Genet*. **93** (5): 967–975. doi:10.1016/j.ajhg.2013.09.017. PMC 3824114. PMID 24207121.
75. ^ EuroEPINOMICS-RES Consortium (2014). "De Novo Mutations in Synaptic Transmission Genes Including DNM1 Cause Epileptic Encephalopathies". *Am J Hum Genet*. **95** (4): 360–370. doi:10.1016/j.ajhg.2014.08.013. PMC 4185114. PMID 25262651.
76. ^ Wallace, ed. by Sheila J.; Farrell, Kevin (2004). *Epilepsy in children* (2nd ed.). London: Arnold. p. 354. ISBN 978-0-340-80814-6.
77. ^ Luef, G (October 2010). "Hormonal alterations following seizures.". *Epilepsy & behavior : E&B*. **19** (2): 131–3. doi:10.1016/j.yebeh.2010.06.026. PMID 20696621.

78. ^ [a] [b] Ahmad S, Beckett MW (2004). "Value of serum prolactin in the management of syncope". *Emergency medicine journal : EMJ*. **21** (2): e3. doi:10.1136/emj.2003.008870. PMC 1726305. PMID 14988379.
79. ^ Shukla G, Bhatia M, Vivekanandhan S, et al. (2004). "Serum prolactin levels for differentiation of nonepileptic versus true seizures: limited utility". *Epilepsy & behavior : E&B*. **5** (4): 517–21. doi:10.1016/j.yebeh.2004.03.004. PMID 15256189.
80. ^ Chen DK, So YT, Fisher RS (2005). "Use of serum prolactin in diagnosing epileptic seizures: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology". *Neurology*. **65** (5): 668–75. doi:10.1212/01.wnl.0000178391.96957.d0. PMID 16157897.
81. ^ Brodtkorb, E (2013). "Common imitators of epilepsy.". *Acta Neurologica Scandinavica. Supplementum*. **127** (196): 5–10. doi:10.1111/ane.12043. PMID 23190285.
82. ^ [a] [b] [c] [d] John A. Marx, ed. (2010). *Rosen's emergency medicine : concepts and clinical practice* (7th ed.). Philadelphia: Mosby/Elsevier. p. 2228. ISBN 978-0-323-05472-0.
83. ^ [a] [b] Zaidi A, Clough P, Cooper P, Scheepers B, Fitzpatrick AP (2000). "Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause". *J Am Coll Cardiol*. **36** (1): 181–4. doi:10.1016/S0735-1097(00)00700-2. PMID 10898432.
84. ^ Bisulli F1, Vignatelli L, Provini F, Leta C, Lugaresi E, Tinuper P (2011). "Parasomnias and nocturnal frontal lobe epilepsy (NFLE): lights and shadows - controversial points in the differential diagnosis". *Sleep Med*. **12** (Suppl2): 27–32. doi:10.1016/j.sleep.2011.10.008. PMID 22136895.
85. ^ Zhou, J. Q.; Zhou, L. M.; Fang, Z. Y.; Wang, Q.; Chen, Z. Y.; Yang, L. B.; Chen, S. D.; Cai, X. D. (2011). "Analyzing clinical and electrophysiological characteristics of Paroxysmal Dyskinesia". *Journal of Research in Medical Sciences*. **16** (1): 110–114. PMC 3063430. PMID 21448393.
86. ^ Akhtar MJ (2002). "All seizures are not epilepsy: many have a cardiovascular cause". *J Pak Med Assoc*. **52** (3): 1116–20. PMID 12071066.
87. ^ [a] [b] Jerome, Engel (2013). *Seizures and epilepsy* (2nd ed.). New York: Oxford University Press. p. 462. ISBN 9780195328547.
88. ^ [a] [b] [c] [d] Michael, GE.; O'Connor, RE. (Feb 2011). "The diagnosis and management of seizures and status epilepticus in the prehospital setting.". *Emerg Med Clin North Am*. **29** (1): 29–39. doi:10.1016/j.emc.2010.08.003. PMID 21109100.
89. ^ James W. Wheless; James Willmore; Roger A. Brumback (2009). *Advanced therapy in epilepsy*. Shelton, Conn.: People's Medical Pub. House. p. 144. ISBN 9781607950042.
90. ^ [a] [b] [c] National Clinical Guideline Centre (January 2012). *The Epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care* (PDF). National Institute for Health and Clinical Excellence.
91. ^ Elaine Wyllie (2012). *Wyllie's Treatment of Epilepsy: Principles and Practice*. Lippincott Williams & Wilkins. p. 187. ISBN 978-1-4511-5348-4.
92. ^ Steven R. Flanagan; Herb Zaretsky; Alex Moroz, eds. (2010). *Medical aspects of disability; a handbook for the rehabilitation professional* (4th ed.). New York: Springer. p. 182. ISBN 978-0-8261-2784-6.
93. ^ Nolan, SJ; Marson, AG; Pulman, J; Tudur Smith, C (23 August 2013). "Phenytoin versus valproate monotherapy for partial onset seizures and generalised onset tonic-clonic seizures.". *The Cochrane database of systematic reviews*. **8**: CD001769. doi:10.1002/14651858.CD001769.pub2. PMID 23970302.
94. ^ Tudur Smith, C; Marson, AG; Clough, HE; Williamson, PR (2002). "Carbamazepine versus phenytoin monotherapy for epilepsy.". *The Cochrane database of systematic reviews* (2): CD001911. doi:10.1002/14651858.CD001911. PMID 12076427.
95. ^ Powell, G; Saunders, M; Marson, AG (20 January 2010). "Immediate-release versus controlled-release carbamazepine in the treatment of epilepsy.". *The Cochrane database of systematic reviews* (1): CD007124. doi:10.1002/14651858.CD007124.pub2. PMID 20091617.
96. ^ Ilangaratne, NB; Mannakkara, NN; Bell, GS; Sander, JW (Dec 1, 2012). "Phenobarbital: missing in action.". *Bulletin of the World Health Organization*. **90** (12): 871–871A. doi:10.2471/BLT.12.113183. PMID 23284189.
97. ^ Moshé, edited by Simon Shorvon, Emilio Perucca, Jerome Engel Jr. ; foreword by Solomon (2009). *The treatment of epilepsy* (3rd ed.). Chichester, UK: Wiley-Blackwell. p. 587. ISBN 9781444316674.
98. ^ [a] [b] [c] [d] [e] [f] Perucca, P; Gilliam, FG (September 2012). "Adverse effects of antiepileptic drugs.". *Lancet neurology*. **11** (9): 792–802. doi:10.1016/S1474-4422(12)70153-9. PMID 22832500.
99. ^ [a] [b] Weston, Jennifer; Bromley, Rebecca; Jackson, Cerian F.; Adab, Naghme; Clayton-Smith, Jill; Greenhalgh, Janette; Hounsome, Juliet; McKay, Andrew J.; Tudur Smith, Catrin (2016-11-07). "Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child". *The Cochrane Database of Systematic Reviews*. **11**: CD010224. doi:10.1002/14651858.CD010224.pub2. ISSN 1469-493X. PMID 27819746.
100. ^ [a] [b] Kamyar, M.; Varner, M. (Jun 2013). "Epilepsy in pregnancy.". *Clin Obstet Gynecol*. **56** (2): 330–41. doi:10.1097/GRF.0b013e31828f2436. PMID 23563876.
101. ^ Lawrence S. Neinstein, ed. (2008). *Adolescent health care : a practical guide* (5th ed.). Philadelphia: Lippincott Williams & Wilkins. p. 335. ISBN 978-0-7817-9256-1.
102. ^ Duncan, JS; Sander, JW; Sisodiya, SM; Walker, MC (1 April 2006). "Adult epilepsy". *Lancet*. **367** (9516): 1087–100. doi:10.1016/S0140-6736(06)68477-8. PMID 16581409.
103. ^ [a] [b] [c] [d] [e] Duncan, JS (April 2007). "Epilepsy surgery.". *Clinical Medicine*. London. **7** (2): 137–42. doi:10.7861/clinmedicine.7-2-137. PMID 17491501.
104. ^ Birbeck GL, Hays RD, Cui X, Vickrey BG (2002). "Seizure reduction and quality of life improvements in people with epilepsy". *Epilepsia*. **43** (5): 535–538. doi:10.1046/j.1528-1157.2002.32201.x. PMID 12027916.

105. ^ [a] [b] Martin, K; Jackson, CF; Levy, RG; Cooper, PN (9 February 2016). "Ketogenic diet and other dietary treatments for epilepsy.". *The Cochrane database of systematic reviews*. **2**: CD001903. doi:10.1002/14651858.CD001903.pub3. PMID 26859528.
106. ^ [editor], Bernard L. Maria (2009). *Current management in child neurology* (4th ed.). Hamilton, Ont.: BC Decker. p. 180. ISBN 978-1-60795-000-4.
107. ^ Arida, RM; Scorza, FA; Scorza, CA; Cavalheiro, EA (March 2009). "Is physical activity beneficial for recovery in temporal lobe epilepsy? Evidences from animal studies.". *Neuroscience and biobehavioral reviews*. **33** (3): 422–31. doi:10.1016/j.neubiorev.2008.11.002. PMID 19059282.
108. ^ Arida, RM; Cavalheiro, EA; da Silva, AC; Scorza, FA (2008). "Physical activity and epilepsy: proven and predicted benefits.". *Sports medicine (Auckland, N.Z.)*. **38** (7): 607–15. doi:10.2165/00007256-200838070-00006. PMID 18557661.
109. ^ Verrotti, A; Tocco, AM; Salladini, C; Latini, G; Chiarelli, F (November 2005). "Human photosensitivity: from pathophysiology to treatment.". *European Journal of Neurology*. **12** (11): 828–41. doi:10.1111/j.1468-1331.2005.01085.x. PMID 16241971.
110. ^ Tan, G; Thornby, J; Hammond, DC; Strehl, U; Canady, B; Arnemann, K; Kaiser, DA (July 2009). "Meta-analysis of EEG biofeedback in treating epilepsy.". *Clinical EEG and Neuroscience*. **40** (3): 173–9. doi:10.1177/155005940904000310. PMID 19715180.
111. ^ Di Vito L1, Naldi I, Mostacci B, Licchetta L, Bisulli F, Tinuper P (2010). "A seizure response dog: video recording of reacting behaviour during repetitive prolonged seizures". *Epileptic Disord*. **12** (2): 142–5. doi:10.1684/epd.2010.0313. PMID 20472528.
112. ^ Kirton A1, Winter A, Wirrell E, Snead OC (2008). "Seizure response dogs: evaluation of a formal training program". *Epilepsy Behav*. **13** (3): 499–504. doi:10.1016/j.yebeh.2008.05.011. PMID 18595778.
113. ^ Doherty, MJ; Haltiner, AM (23 January 2007). "Wag the dog: skepticism on seizure alert canines.". *Neurology*. **68** (4): 309. doi:10.1212/01.wnl.0000252369.82956.a3. PMID 17242343.
114. ^ Cheuk, DK; Wong, V (7 May 2014). "Acupuncture for epilepsy.". *The Cochrane database of systematic reviews*. **5** (4): CD005062. doi:10.1002/14651858.CD005062.pub4. PMID 24801225.
115. ^ Ramaratnam, S; Baker, GA; Goldstein, LH (16 July 2008). "Psychological treatments for epilepsy.". *The Cochrane database of systematic reviews* (3): CD002029. doi:10.1002/14651858.CD002029.pub3. PMID 18646083.
116. ^ Ranganathan, LN; Ramaratnam, S (18 April 2005). "Vitamins for epilepsy.". *The Cochrane database of systematic reviews* (2): CD004304. doi:10.1002/14651858.CD004304.pub2. PMID 15846704.
117. ^ Ramaratnam, S; Sridharan, K; Panebianco, M (2 May 2015). "Yoga for epilepsy.". *The Cochrane database of systematic reviews*. **5** (3): CD001524. doi:10.1002/14651858.CD001524.pub2. PMID 25934967.
118. ^ Gloss, D; Vickrey, B (5 March 2014). "Cannabinoids for epilepsy". *The Cochrane database of systematic reviews*. **3**: CD009270. doi:10.1002/14651858.CD009270.pub3. PMID 24595491.
119. ^ Belendiuk, KA; Baldini, LL; Bonn-Miller, MO (21 April 2015). "Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders.". *Addiction science & clinical practice*. **10** (1): 10. doi:10.1186/s13722-015-0032-7. PMID 25896576.
120. ^ [a] [b] Brigo, F; Igwe, SC (17 March 2016). "Melatonin as add-on treatment for epilepsy.". *The Cochrane database of systematic reviews*. **3**: CD006967. doi:10.1002/14651858.CD006967.pub3. PMID 26986179.
121. ^ [a] [b] Kwan, Patrick (2012). *Fast facts : epilepsy* (5th ed.). Abingdon, Oxford, UK: Health Press. p. 10. ISBN 1-908541-12-1.
122. ^ [a] [b] [c] Hitiris N, Mohanraj R, Norrie J, Brodie MJ (2007). "Mortality in epilepsy". *Epilepsy Behavior*. **10** (3): 363–376. doi:10.1016/j.yebeh.2007.01.005. PMID 17337248.
123. ^ [a] [b] [c] Moshé, edited by Simon Shorvon, Emilio Perucca, Jerome Engel Jr. ; foreword by Solomon (2009). *The treatment of epilepsy* (3rd ed.). Chichester, UK: Wiley-Blackwell. p. 28. ISBN 978-1-4443-1667-4.
124. ^ [a] [b] Bagary, M (April 2011). "Epilepsy, antiepileptic drugs and suicidality.". *Current opinion in neurology*. **24** (2): 177–82. doi:10.1097/WCO.0b013e328344533e. PMID 21293270.
125. ^ Mula, M; Sander, JW (August 2013). "Suicide risk in people with epilepsy taking antiepileptic drugs.". *Bipolar disorders*. **15** (5): 622–7. doi:10.1111/bdi.12091. PMID 23755740.
126. ^ [a] [b] Ryvlin, P; Nashef, L; Tomson, T (May 2013). "Prevention of sudden unexpected death in epilepsy: a realistic goal?". *Epilepsia*. 54 Suppl 2: 23–8. doi:10.1111/epi.12180. PMID 23646967.
127. ^ Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R (2007-01-30). "How common are the 'common' neurologic disorders?". *Neurology*. **68** (5): 326–37. doi:10.1212/01.wnl.0000252807.38124.a3. PMID 17261678.
128. ^ [a] [b] Sander JW (2003). "The epidemiology of epilepsy revisited". *Current Opinion in Neurology*. **16** (2): 165–70. doi:10.1097/00019052-200304000-00008. PMID 12644744.
129. ^ [a] [b] [c] [d] [e] [f] [g] [h] Saraceno, B; Avanzini, G; Lee, P, eds. (2005). *Atlas: Epilepsy Care in the World* (PDF). World Health Organization. ISBN 92-4-156303-6. Retrieved 20 December 2013.
130. ^ Mervyn J. Eadie; Peter F. Bladin (2001). *A Disease Once Sacred: A History of the Medical Understanding of Epilepsy*. John Libbey Eurotext. ISBN 978-0-86196-607-3.
131. ^ "Epilepsy: An historical overview". *World Health Organization*. Feb 2001. Archived from the original on 30 October 2013. Retrieved 27 December 2013.
132. ^ "Epilepsy: historical overview". *World Health Organization*. Retrieved 2011-03-20.
133. ^ [a] [b] Temkin, Owsei. *The Falling Sickness: A History of Epilepsy from the Greeks to the Beginnings of Modern Neurology*. JHU Press. p. Section 1. ISBN 9781421400532.
134. ^ Stol, Marten (1993). *Epilepsy in Babylonia*. BRILL. p. 143. ISBN 9072371631.

135. ^ Harding, Graham F. A.; Jeavons, Peter M. (1994). *Photosensitive Epilepsy*. Cambridge University Press. p. 2. ISBN 9781898683025.
136. ^ a b Jilek-Aall, L (1999). "Morbus sacer in Africa: some religious aspects of epilepsy in traditional cultures". *Epilepsia*. **40** (3): 382–6. doi:10.1111/j.1528-1157.1999.tb00723.x. PMID 10080524.
137. ^ Illes, Judika (2011-10-11). *Encyclopedia of Mystics, Saints & Sages*. HarperCollins. p. 1238. ISBN 978-0-06-209854-2. Retrieved 26 February 2013. "Saint Valentine is invoked for healing as well as love. He protects against fainting and is requested to heal epilepsy and other seizure disorders. In northern Italy, epilepsy was once traditionally known as Saint Valentine's Malady."
138. ^ E. Martin Caravati (2004). *Medical toxicology* (3. ed.). Philadelphia [u.a.]: Lippincott Williams & Wilkins. p. 789. ISBN 978-0-7817-2845-4.
139. ^ a b de Boer, HM (Dec 2010). "Epilepsy stigma: moving from a global problem to global solutions.". *Seizure : the journal of the British Epilepsy Association*. **19** (10): 630–6. doi:10.1016/j.seizure.2010.10.017. PMID 21075013.
140. ^ Martindale, JL; Goldstein, JN; Pallin, DJ (February 2011). "Emergency department seizure epidemiology.". *Emergency medicine clinics of North America*. **29** (1): 15–27. doi:10.1016/j.emc.2010.08.002. PMID 21109099.
141. ^ a b c d Jerome Engel, Jr.; Timothy A. Pedley, eds. (2008). *Epilepsy : a comprehensive textbook* (2nd ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 2279. ISBN 978-0-7817-5777-5.
142. ^ Bor, Robert (2012). *Aviation Mental Health: Psychological Implications for Air Transportation*. Ashgate Publishing. p. 148. ISBN 978-1-4094-8491-2.
143. ^ a b "Seizure Disorders". *Transport Canada*. Government of Canada. Retrieved 29 December 2013.
144. ^ Wilner, Andrew N. (2008). *Epilepsy 199 answers : a doctor responds to his patients' questions* (3rd ed.). New York: Demos Health. p. 52. ISBN 978-1-934559-96-3.
145. ^ "Guide for Aviation Medical Examiners". *Federal Aviation Administration*. Retrieved 29 December 2013.
146. ^ a b "National PPL (NPPL) Medical Requirements". *Civil Aviation Authority*. Retrieved 29 December 2013.
147. ^ Drivers Medical Group (2013). "For Medical Practitioners: At a glance Guide to the current Medical Standards of Fitness to Drive" (PDF). p. 8. Retrieved 29 December 2013.
148. ^ "Epilepsy Foundation of America - EFA". *Healthfinder.gov*. US Department of Health and Human Services. April 28, 2011. Retrieved July 28, 2014.
149. ^ al., editors, Jerome Engel, Jr., Timothy A. Pedley ; associate editors, Jean Aicardi ... et (2008). *Epilepsy : a comprehensive textbook* (2nd ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 2245. ISBN 9780781757775.
150. ^ a b Carney, PR.; Myers, S.; Geyer, JD. (Dec 2011). "Seizure prediction: methods.". *Epilepsy Behav*. 22 Suppl 1: S94–101. doi:10.1016/j.yebeh.2011.09.001. PMID 22078526.
151. ^ Jerome Engel, ed. (2008). *Epilepsy : a comprehensive textbook* (2nd ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 426. ISBN 9780781757775.
152. ^ Walker, MC.; Schorge, S.; Kullmann, DM.; Wykes, RC.; Heeroma, JH.; Mantoan, L. (Sep 2013). "Gene therapy in status epilepticus.". *Epilepsia*. 54 Suppl 6: 43–5. doi:10.1111/epi.12275. PMID 24001071.
153. ^ Walker, L; Pirmohamed, M; Marson, AG (27 June 2013). "Immunomodulatory interventions for focal epilepsy syndromes.". *The Cochrane database of systematic reviews*. **6**: CD009945. doi:10.1002/14651858.CD009945.pub2. PMID 23803963.
154. ^ Quigg, M; Rolston, J; Barbaro, NM (Jan 2012). "Radiosurgery for epilepsy: clinical experience and potential antiepileptic mechanisms.". *Epilepsia*. **53** (1): 7–15. doi:10.1111/j.1528-1167.2011.03339.x. PMID 22191545.
155. ^ Pedersen, Mangor; Curwood, Evan K; Vaughan, David N; Omidvarnia, Amir H; Jackson, Graeme D (2016). "Abnormal Brain Areas Common to the Focal Epilepsies: Multivariate Pattern Analysis of fMRI.". *Brain connectivity*. doi:10.1089/brain.2015.0367. PMID 26537783. Lay summary. "Patients with extratemporal focal epilepsy have common areas of abnormality (ReHo and DCw measures), including the ipsilateral piriform cortex, temporal neocortex, and ventromedial prefrontal cortex. ReHo shows additional increase in the "salience network" that includes anterior insula and anterior cingulate cortex. DCw showed additional effects in the ipsilateral thalamus and striatum. These brain areas may represent key regional network properties underlying focal epilepsy."
156. ^ Mormann, F; Andrzejak, RG; Elger, CE; Lehnertz, K (February 2007). "Seizure prediction: the long and winding road.". *Brain : a journal of neurology*. **130** (Pt 2): 314–33. doi:10.1093/brain/awl241. PMID 17008335.
157. ^ Thomas, WB (January 2010). "Idiopathic epilepsy in dogs and cats". *Veterinary Clinics of North America, Small Animal Practice*. **40** (1): 161–79. doi:10.1016/j.cvsm.2009.09.004. PMID 19942062.
158. ^ Thomas, WB (Jan 2010). "Idiopathic epilepsy in dogs and cats.". *The Veterinary Clinics of North America. Small Animal Practice*. **40** (1): 161–79. doi:10.1016/j.cvsm.2009.09.004. PMID 19942062.
159. ^ Rundfeldt, C; Loescher, W (January 2014). "The pharmacology of imepitoin: The first partial benzodiazepine receptor agonist developed for the treatment of epilepsy". *CNS Drugs*. **28** (1): 29–43. doi:10.1007/s40263-013-0129-z. PMID 24357084.
160. ^ van der Ree, M; Wijnberg, I (2012). "A review on epilepsy in the horse and the potential of Ambulatory EEG as a diagnostic tool.". *The Veterinary quarterly*. **32** (3–4): 159–67. doi:10.1080/01652176.2012.744496. PMID 23163553.


## Further reading [edit]


- World Health Organization, Department of Mental Health and Substance Abuse, Programme for Neurological Diseases and Neuroscience; Global Campaign against Epilepsy; International League against Epilepsy (2005). *Atlas, epilepsy care in the world, 2005* (pdf). Geneva: Programme for Neurological Diseases and Neuroscience,

Department of Mental Health and Substance Abuse, World Health Organization. ISBN 92-4-156303-6.

## External links [edit]

- Epilepsy at DMOZ
- World Health Organization fact sheet

Wikimedia Commons has media related to *Epilepsy*.

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# Female genital mutilation

From Wikipedia, the free encyclopedia

*"FGM" redirects here. For other uses, see FGM (disambiguation).*

**Female genital mutilation** (**FGM**), also known as **female genital cutting** and **female circumcision**, is the ritual removal of some or all of the external female genitalia. The practice is found in Africa, Asia and the Middle East, and within communities from countries in which FGM is common. UNICEF estimated in 2016 that 200 million women in 30 countries—27 African countries, Indonesia, Iraqi Kurdistan and Yemen—had undergone the procedures.[3]

Typically carried out by a traditional circumciser using a blade, FGM is conducted from days after birth to puberty and beyond. In half the countries for which national figures are available, most girls are cut before the age of five.[5] Procedures differ according to the country or ethnic group. They include removal of the clitoral hood and clitoral glans; removal of the inner labia; and removal of the inner and outer labia and closure of the vulva. In this last procedure (known as infibulation), a small hole is left for the passage of urine and menstrual fluid; the vagina is opened for intercourse and opened further for childbirth.[6]

The practice is rooted in gender inequality, attempts to control women's sexuality, and ideas about purity, modesty and beauty. It is usually initiated and carried out by women, who see it as a source of honour, and who fear that failing to have their daughters and granddaughters cut will expose the girls to social exclusion.[a] The health effects depend on the procedure; they can include recurrent infections, difficulty urinating and passing menstrual flow, chronic pain, the development of cysts, an inability to get pregnant, complications during childbirth, and fatal bleeding.[6] There are no known health benefits.[9]

There have been international efforts since the 1970s to persuade practitioners to abandon FGM. As a result it has been outlawed or restricted in most of the countries in which it occurs, although the laws are poorly enforced. The opposition to the practice is not without its critics, particularly among anthropologists, who have raised difficult questions about cultural relativism and the universality of human rights.[10]

Contents




Road sign near Kapchorwa, Uganda, 2004

| | |
|---|---|
| **Definition** | "Partial or total removal of the external female genitalia or other injury to the female genital organs for non-medical reasons" (WHO, UNICEF and UNFPA, 1997).[1] |
| **Areas** | Africa, Asia, Middle East and within communities from these areas elsewhere[2] |
| **Numbers** | Over 200 million women and girls in 27 African countries, Indonesia, Iraqi Kurdistan and Yemen, as of 2016[3] |
| **Age** | Days after birth to puberty[4] |
| **Prevalence** | |

**Ages 15–49**

Source: UNICEF, February 2016[3]

Somalia (98%) · Guinea (97%) · Djibouti (93%) · Sierra Leone (90%) · Mali (89%) · Egypt (87%) · Sudan (87%) · Eritrea (83%) · Burkina Faso (76%) · Gambia (75%) · Ethiopia (74%) · Mauritania (69%) · Liberia (50%) · Guinea-Bissau (45%) ·

Chad (44%) · Côte d'Ivoire (38%) · Nigeria

(25%) · Senegal (25%) · Central African Republic (24%) · Kenya (21%) · Yemen (19%) · United Republic of Tanzania (15%) · Benin (9%) · Iraq (8%) · Togo (5%) · Ghana (4%) · Niger (2%) · Uganda (1%) · Cameroon (1%) ·

**Ages 0–14**

Source: UNICEF, February 2016[3]

Gambia (56%) · Mauritania (54%) · Indonesia (49%, 0–11) · Guinea (46%) · Eritrea (33%) · Sudan (32%) · Guinea-Bissau (30%) · Ethiopia (24%) · Nigeria (17%) · Yemen (15%) · Egypt (14%) · Burkina Faso (13%) · Sierra Leone (13%) · Senegal (13%) · Côte d'Ivoire (10%) · Kenya (3%) · Uganda (1%) · Central African Republic (1%) · Ghana (1%) · Togo (0.3%) · Benin (0.2%) ·

# Terminology

## English

Until the 1980s FGM was widely known as female circumcision, implying an equivalence in severity with male circumcision.[11] From 1929 the Kenya Missionary Council referred to it as the sexual mutilation of women, following the lead of Marion Scott Stevenson, a Church of Scotland missionary.[12] References to the practice as mutilation increased throughout the 1970s.[13] In 1975 Rose Oldfield Hayes, an American anthropologist, used the term *female genital mutilation* in the title of a paper,[14] and four years later Fran Hosken, an Austrian-American feminist writer, called it mutilation in her influential *The Hosken Report: Genital and Sexual Mutilation of Females*.[15][16]

The Inter-African Committee on Traditional Practices Affecting the Health of Women and Children and the World Health Organization (WHO) began referring to it as female genital mutilation in 1990 and 1991 respectively.[17] Other terms used include *female genital cutting* (FGC) and *female genital mutilation/cutting* (FGM/C), preferred by those who work with practitioners.[13]

Samburu FGM ceremony, Laikipia plateau, Kenya, 2004

## Local terms

The many variants of FGM are reflected in dozens of terms in countries where it is common.[18] These often refer to

purification. In the Bambara language, spoken mostly in Mali, FGM is known as *bolokoli* ("washing your hands")[19] and in the Igbo language in eastern Nigeria as *isa aru* or *iwu aru* ("having your bath").[b] A common Arabic term for purification has the root *t-h-r*, used for male and female circumcision (*tahur* and *tahara*).[21] It is also known in Arabic as *khafḍ* or *khifaḍ*.[22][23]

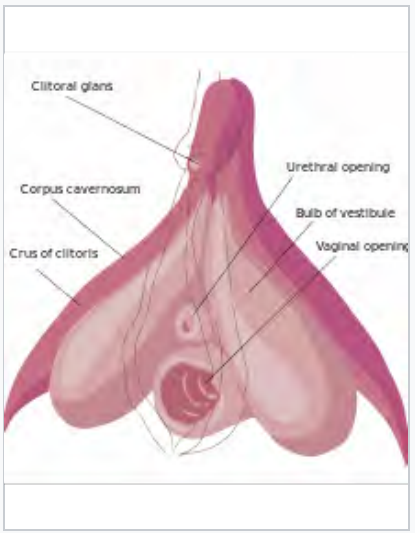
Communities may refer to only two forms of FGM: "pharaonic" for infibulation and *sunna* circumcision for everything else.[24] *Sunna* means "path or way" in Arabic and refers to the tradition of Muhammad, although none of the procedures are required within Islam.[23] The term *infibulation* derives from *fibula*, Latin for clasp; the Ancient Romans reportedly fastened clasps through the foreskins or labia of slaves to prevent sexual intercourse. The surgical infibulation of women came to be known as pharaonic circumcision in Sudan, but as Sudanese circumcision in Egypt.[25] In Somalia it is known simply as *qodob* ("to sew up").[26]

# Methods

The procedures are generally performed by a traditional circumciser (cutter or *exciseuse*) in the girls' homes, with or without anaesthesia. The cutter is usually an older woman, but in communities where the male barber has assumed the role of health worker he will perform FGM too.[27][c]

When traditional cutters are involved, non-sterile devices are likely to be used, including knives, razors, scissors, glass, sharpened rocks and fingernails.[29]:491 According to a nurse in Uganda, quoted in 2007 in *The Lancet*, a cutter would use one knife on up to 30 girls at a time.[30]

Health professionals are often involved in Egypt, Kenya, Indonesia and Sudan. In Egypt 77 percent of FGM procedures, and in Indonesia over 50 percent, were performed by medical professionals as of 2008 and 2016.[31][3] Women in Egypt reported in 1995 that a local anaesthetic had been used on their daughters in 60 percent of cases, a general anaesthetic in 13 percent and neither in 25 percent (two percent were missing/don't know).[32]




Anatomy of the vulva, showing the clitoral glans, clitoral crura, corpora cavernosa and vestibular bulbs

# Classification

## Surveys, UN typology

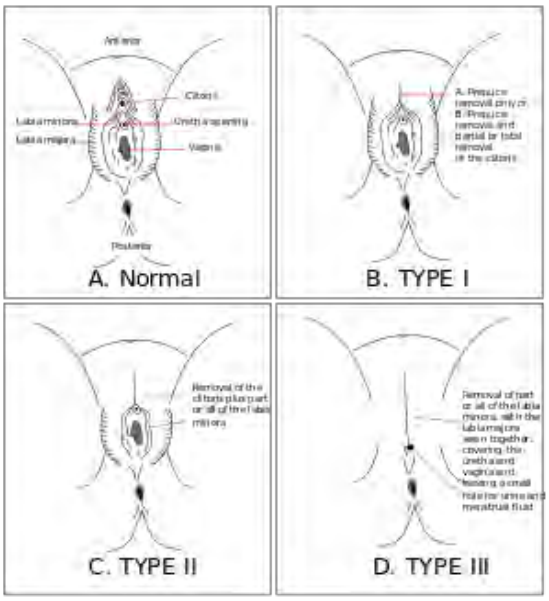
The WHO, UNICEF and UNFPA issued a joint statement in 1997 defining FGM as "all procedures involving partial or total removal of the external female genitalia or other injury to the female genital organs whether for cultural or other non-therapeutic reasons."[13] The procedures vary considerably according to ethnicity and individual practitioners. During a 1998 survey in Niger, women responded with over 50 different terms when asked what was done to them.[18] Translation problems are compounded by the women's confusion over which type of FGM they experienced, or even whether they experienced it.[33] Several studies have suggested that survey responses are unreliable.[d]

Standard questionnaires from United Nations bodies ask women whether they or their daughters have undergone the following: (1) cut, no flesh removed (pricking or symbolic circumcision); (2) cut, some flesh removed; (3) sewn closed; or (4) type not determined/unsure/doesn't know.[e] The most common procedures fall within the "cut, some flesh removed" category and involve complete or partial removal of the clitoral glans.[37]

## WHO Types I–II

The World Health Organization created a more detailed typology. Types I–III vary in how much tissue is removed (Type III is the UNICEF category "sewn closed"). Type IV describes miscellaneous procedures, including symbolic circumcision.[39][40]

Type Ia (circumcision)[41] involves removal of the clitoral hood only and is rarely performed alone.[f] The more common procedure is Type Ib (clitoridectomy), the complete or partial removal of the clitoral glans (the [1][43]




visible tip of the clitoris) and clitoral hood. The circumciser pulls the clitoral glans with her thumb and index finger and cuts it off.[g]

Type II (excision) is the complete or partial removal of the inner labia, with or without removal of the clitoral glans and outer labia. Type IIa is removal of the inner labia; IIb, removal of the clitoral glans and inner labia; and IIc, removal of the clitoral glans, inner and outer labia. *Excision* in French can refer to any form of FGM.[1]

## Type III

Type III (infibulation or pharaonic circumcision), the "sewn closed" category, involves the removal of the external genitalia and fusion of the wound. The inner and/or outer labia are cut away, with or without removal of the clitoral glans. Type IIIa is the removal and closure of the inner labia and IIIb the outer labia.[h] The practice is found largely in Djibouti, Eritrea, Ethiopia, Somalia and Sudan (though not South Sudan) in northeast Africa. Estimates of numbers vary: according to one in 2008, over eight million women in Africa have experienced it.[i] According to UNFPA in 2010, 20 percent of women with FGM have been infibulated.[46]

**External images**

Types I–IV diagrams
Type IIIb: virgin, sexually active
— WHO[38] and *Swiss Medical Weekly*[6]

Comfort Momoh, a specialist midwife, describes Type III: "[E]lderly women, relatives and friends secure the girl in the lithotomy position. A deep incision is made rapidly on either side from the root of the clitoris to the fourchette, and a single cut of the razor excises the clitoris and both the labia majora and labia minora." Girls "may be pinned down so firmly that bones may fracture".[47] In Somalia the clitoral glans is removed and shown to the senior female relatives, who decide whether enough has been amputated. After this the labia are removed.[48] The amputated parts might be placed in a pouch for the girl to wear.[49]

A single hole of 2–3 mm is left for the passage of urine and menstrual fluid by inserting something, such as a twig, into the wound.[j][50] The vulva is then closed with surgical thread, agave or acacia thorns, or covered with a poultice such as raw egg, herbs and sugar.[29]:491[51] To help the tissue bond, the girl's legs are tied together, often from hip to ankle; the bindings are usually loosened after a week and removed after two to six weeks.[52][29]:491 The result is a "drum of skin extending across the [vaginal] orifice except for a small hole," Momoh writes.[47]

If the remaining hole is too large in the view of the girl's family, the procedure is repeated. The vagina is opened for sexual intercourse, for the first time either by a midwife with a knife or by the woman's husband with his penis. In some areas, including Somaliland, female relatives of the bride and groom might watch the opening of the vagina to check that the girl is a virgin.[53] Psychologist Hanny Lightfoot-Klein interviewed hundreds of women and men in Sudan in the 1980s about sexual intercourse with Type III:

> The penetration of the bride's infibulation takes anywhere from 3 or 4 days to several months. Some men are unable to penetrate their wives at all (in my study over 15%), and the task is often accomplished by a midwife under conditions of great secrecy, since this reflects negatively on the man's potency. Some who are unable to penetrate their wives manage to get them pregnant in spite of the infibulation, and the woman's vaginal passage is then cut open to allow birth to take place. ... Those men who do manage to penetrate their wives do so often, or perhaps always, with the help of the "little knife." This creates a tear which they gradually rip more and more until the opening is sufficient to admit the penis.[54]

The woman is opened further for childbirth and closed afterwards, a process known as defibulation (or deinfibulation) and reinfibulation. Reinfibulation can involve cutting the vagina again to restore the pinhole size of the

first infibulation. This might be performed before marriage, and after childbirth, divorce and widowhood.[k][55]

### Type IV

The WHO defines Type IV as "[a]ll other harmful procedures to the female genitalia for non-medical purposes", including pricking, piercing, incising, scraping and cauterization.[1] It includes nicking of the clitoris (symbolic circumcision), burning or scarring the genitals, and introducing substances into the vagina to tighten it.[56][57] Labia stretching is also categorized as Type IV.[58] Common in southern and eastern Africa, the practice is supposed to enhance sexual pleasure for the man and add to the sense of a woman as a closed space. From the age of eight, girls are encouraged to stretch their inner labia using sticks and massage. Girls in Uganda are told they may have difficulty giving birth without stretched labia.[l][60]

A definition of FGM from the WHO in 1995 included gishiri cutting and angurya cutting, found in Nigeria and Niger. These were removed from the WHO's 2008 definition because of insufficient information about prevalence and consequences.[61] Angurya cutting is excision of the hymen, usually performed seven days after birth. Gishiri cutting involves cutting the vagina's front or back wall with a blade or penknife, performed in response to infertility, obstructed labour and other conditions. In a study by Nigerian physician Mairo Usman Mandara, over 30 percent of women with gishiri cuts were found to have vesicovaginal fistulae (holes that allow urine to seep into the vagina).[62]

## Complications

### Short-term and late

FGM harms women's physical and emotional health throughout their lives.[64][65] It has no known health benefits.[9] The short-term and late complications depend on the type of FGM, whether the practitioner had medical training, and whether she used antibiotics and unsterilized or surgical single-use instruments. In the case of Type III, other factors include how small a hole was left for the passage of urine and menstrual blood, whether surgical thread was used instead of agave or acacia thorns, and whether the procedure was performed more than once (for example, to close an opening regarded as too wide or re-open one too small).[6]

**FGM ceremony in Indonesia**

Preparations
Girl before procedure
Nine-month-old afterwards

— Stephanie Sinclair
*The New York Times*, 2006[63]

Common short-term complications include swelling, excessive bleeding, pain, urine retention and healing problems/wound infection. A 2015 systematic review of 56 studies that recorded immediate complications suggested that each of these occurred in more than one in ten girls and women undergoing any form of FGM, including symbolic nicking of the clitoris (Type IV), although the risks increased with Type III. The review also suggested that there was under-reporting.[66] Other short-term complications include fatal bleeding, anaemia, urinary infection, septicaemia, tetanus, gangrene, necrotizing fasciitis (flesh-eating disease) and endometritis.[65][67][6] It is not known how many girls and women die as a result of the practice, because complications may not be recognized or reported.[68][69] The practitioners' use of shared instruments is thought to aid the transmission of hepatitis B, hepatitis C and HIV, although no epidemiological studies have shown this.[69]

FGM awareness session run by the African Union Mission to Somalia at the Walalah Biylooley refugee camp, Mogadishu

Late complications vary depending on the type of FGM.[6] They include the formation of scars and keloids that lead to strictures and obstruction, epidermoid cysts that may become infected, and neuroma formation (growth of nerve tissue) involving nerves that supplied the clitoris.[29]:491–492[70]

An infibulated girl may be left with an opening as small as 2–3 mm, which can cause prolonged, drop-by-drop urination, pain while urinating, and a feeling of needing to urinate all the time. Urine may collect underneath the scar, leaving the area under the skin constantly wet, which can lead to infection and the formation of small stones. The opening is larger in women who are sexually active or have given birth by vaginal delivery, but the urethra opening may still be obstructed by scar tissue. Vesicovaginal or rectovaginal fistulae can develop (holes that allow urine or faeces to seep into the vagina).[6][71] This and other damage to the urethra and bladder can lead to infections and incontinence, pain during sexual intercourse and infertility.[29]:491–492

Painful periods are common because of the obstruction to the menstrual flow, and blood can stagnate in the vagina and uterus. Complete obstruction of the vagina can result in hematocolpos and hematometra (where the vagina and uterus fill with menstrual blood).[6] The swelling of the abdomen that results from the collection of fluid, together with the lack of menstruation, can lead to suspicion of pregnancy. Asma El Dareer, a Sudanese physician, reported in 1979 that a girl in Sudan with this condition was killed by her family.[72]

## Pregnancy, childbirth

FGM may place women at higher risk of problems during pregnancy and childbirth, which are more common with the more extensive FGM procedures.[6] Infibulated women may try to make childbirth easier by eating less during pregnancy to reduce the baby's size. [73]:99 In women with vesicovaginal or rectovaginal fistulae, it is difficult to obtain clear urine samples as part of prenatal care, making the diagnosis of conditions such as pre-eclampsia harder.[29]:491–492 Cervical evaluation during labour may be impeded and labour prolonged or obstructed. Third-degree laceration (tears), anal-sphincter damage and emergency caesarean section are more common in infibulated women.[6][73]:97

**External images**

Type II
Type III
Keloidal scar tissue
Obstructed labour

— Nahid Toubia, RAINBO, 1999[73]

Neonatal mortality is increased. The WHO estimated in 2006 that an additional 10–20 babies die per 1,000 deliveries as a result of FGM. The estimate was based on a study conducted on 28,393 women attending delivery wards at 28 obstetric centres in Burkina Faso, Ghana, Kenya, Nigeria, Senegal and Sudan. In those settings all types of FGM were found to pose an increased risk of death to the baby: 15 percent higher for Type I, 32 percent for Type II and 55 percent for Type III. The reasons for this were unclear, but may be connected to genital and urinary tract infections and the presence of scar tissue. The researchers wrote that FGM was associated with an increased risk to the mother of damage to the perineum and excessive blood loss, as well as a need to resuscitate the baby, and stillbirth, perhaps because of a long second stage of labour.[74][75]

## Psychological effects, sexual function

According to a 2015 systematic review there is little high-quality information available on the psychological effects of FGM. Several small studies have concluded that women with FGM suffer from anxiety, depression and post-traumatic stress disorder.[69] Feelings of shame and betrayal can develop when women leave the culture that practises FGM and learn that their condition is not the norm, but within the practising culture they may view their FGM with pride, because for them it signifies beauty, respect for tradition, chastity and hygiene.[6]

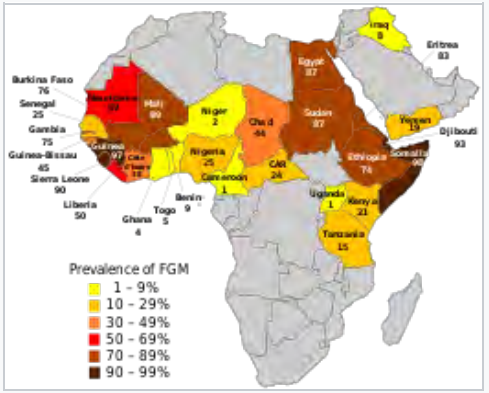
Studies on sexual function have also been small.[69] A 2013 meta-analysis of 15 studies involving 12,671 women from seven countries concluded that women with FGM were twice as likely to report no sexual desire and 52 percent more likely to report dyspareunia (painful sexual intercourse). One third reported reduced sexual feelings.[76][77]

# Distribution

## Household surveys

The prevalence of FGM is defined as the percentage of the 15–49 age group that has exerienced it.[81] These figures are based on nationally representative household surveys known as Demographic and Health Surveys (DHS), developed by Macro International and funded mainly by the United States Agency for International Development (USAID), and Multiple Indicator Cluster Surveys (MICS), conducted with financial and technical help from UNICEF.[33]

These surveys have been carried out in Africa, Asia, Latin America and elsewhere roughly every five years, since 1984 and 1995 respectively.[82] The first to ask about FGM was the 1989–1990 DHS in northern Sudan. The first publication to estimate FGM prevalence based on DHS data (in seven countries) was by Dara Carr of Macro International in 1997.[83]




FGM in Africa, Iraqi Kurdistan and Yemen, as of 2015.[78] (See map of

## Prevalence

*Further information: Prevalence of female genital mutilation by country*

FGM is found mostly in what Gerry Mackie called an "intriguingly contiguous" zone in Africa—east to west from Somalia to Senegal, and north to south from Egypt to Tanzania.[84] Nationally representative figures are available for 27 countries in Africa, as well as Indonesia, Iraqi Kurdistan and Yemen. Over 200 million women and girls are thought to be living with FGM in those 30 countries.[3][79]

The highest concentrations among the 15–49 age group are in Somalia (98 percent), Guinea (97 percent), Djibouti (93 percent), Egypt (91 percent) and Sierra Leone (90 percent).[85] As of 2013, 27.2 million women had undergone FGM in Egypt, 23.8 million in Ethiopia, and 19.9 million in Nigeria.[86] There is also a high concentration in Indonesia, where Type Ia (removal of the clitoral hood) and symbolic nicking (Type IV) are practised; the prevalence rate for the 0–11 group is 49 percent (13.4 million).[3][79]:2

Smaller studies or anecdotal reports suggest that FGM is also practised in Colombia, the Congo, Malaysia, Oman, Peru, Saudi Arabia, Sri Lanka, and the United Arab Emirates, as well as among the Bedouin in Israel; in Rahmah, Jordan; and among the Dawoodi Bohra in India.[3][87][88] It is also found within immigrant communities in Australasia, Europe, North America and Scandinavia.[89]

## Downward trend

Prevalence figures for the 15–19 age group and younger show a downward trend.[n] For example, Burkina Faso fell from 89 percent (1980) to 58 percent (2010); Egypt from 97 percent (1985) to 70 percent (2015); and Kenya from 41 percent (1984) to 11 percent (2014).[92]

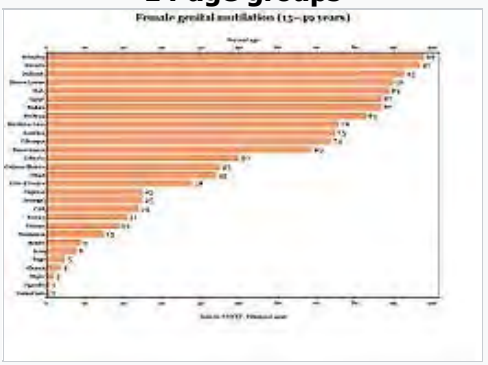
From 2010 household surveys asked women about the FGM status of all their living daughters.[93] The highest concentrations among girls aged 0–14 were in Gambia (56 percent), Mauritania (54 percent), Indonesia (49 percent for 0–11) and Guinea (46 percent).[3] The figures suggest that a girl was one third less likely in 2014 to undergo FGM than she was 30 years ago.[94] If the rate of decline continues, the number of girls cut will nevertheless rise from 3.6 million a year in 2013 to 4.1 million in 2050 because of population growth.[o]

## Rural areas, wealth, education

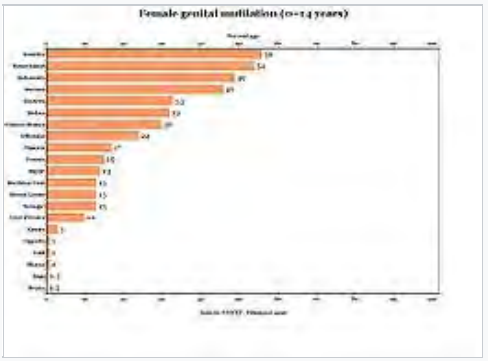
Surveys have found FGM to be more common in rural areas, less common in most countries among girls from the wealthiest homes, and (except in Sudan and Somalia) less common in girls whose mothers had access to primary or secondary/higher education. In Somalia and Sudan the situation was reversed: in Somalia the mothers' access to secondary/higher education was accompanied by a rise in prevalence of FGM in their daughters, and in Sudan access to any education was accompanied by a rise.[96]

Africa.)

**Prevalence within 15–49 and 0–14 age groups**



*(above)* Percentage aged 15–49 years who have undergone FGM in 29 key countries.



Percentage aged 0–14 who have undergone FGM in 21 key countries[m]


In Indonesia, 49 percent of girls aged 0–11 had undergone Type 1a or Type IV FGM (removal of the clitoral hood or symbolic nicking) as of 2013.[3][79][80]

## Age conducted

FGM is not invariably a rite of passage between childhood and adulthood, but is often performed on much younger children.[97] Girls are most commonly cut shortly after birth to age 15. In half the countries for which national figures were available in 2000–2010, most girls had been cut by age five.[98]

Over 80 percent (of those cut) are cut before the age of five in Nigeria, Mali, Eritrea, Ghana and Mauritania.[99] The 1997 Demographic and Health Survey in Yemen found that 76 percent of girls had been cut within two weeks of birth.[100] The percentage is reversed in Somalia, Egypt, Chad and the Central African Republic, where over 80 percent (of those cut) are cut between five and 14.[99] Just as the type of FGM is often linked to ethnicity, so is the mean age. In Kenya, for example, the Kisi cut around age 10 and the Kamba at 16.[101]

## Ethnicity

**Age and ethnicity**

Age of cutting
Highest and lowest prevalence by ethnicity

— UNICEF 2013[98]

A country's national prevalence often reflects a high sub-national prevalence among certain ethnicities, rather than a widespread practice.[102] In Iraq, for example, FGM is found mostly among the Kurds in Erbil (58 percent prevalence within age group 15–49, as of 2011), Sulaymaniyah (54 percent) and Kirkuk (20 percent), giving the country a national prevalence of eight percent.[103]

The practice is sometimes an ethnic marker, but may differ along national lines. In the northeastern regions of Ethiopia and Kenya, which share a border with Somalia, the Somali people practise FGM at around the same rate as they do in Somalia.[104] But in Guinea all Fulani women responding to a survey in 2012 said they had experienced FGM,[105] against 12 percent of the Fulani in Chad, while in Nigeria the Fulani are the only large ethnic group in the country not to practise it.[106]

## Type of FGM

Women are asked during surveys about the type of FGM they experienced:[107]

> - Was the genital area just nicked/cut without removing any flesh?
> - Was any flesh (or something) removed from the genital area?
> - Was your genital area sewn?

Most women report "cut, some flesh removed" (Types I and II).[108] According to Mackie in 2003, Type II is more common in Egypt,[109] while a 2011 study identified Type I as more common.[110] In Nigeria Type I is usually found in the south and the more severe forms in the north.[111]

Type III (infibulation) is concentrated in northeastern Africa, particularly Djibouti, Eritrea, Somalia and Sudan.[112] In surveys in 2002–2006, 30 percent of cut girls in Djibouti, 38 percent in Eritrea, and 63 percent in Somalia had experienced Type III.[113] There is also a high prevalence of infibulation among girls in Niger and Senegal,[114] and in 2013 it was estimated that in Nigeria three percent of the 0–14 age group had been infibulated.[115] The type of procedure is often linked to ethnicity. In Eritrea, for example, a survey in 2002 found that all Hedareb girls had been infibulated, compared with two percent of the Tigrinya, most of whom fell into the "cut, no flesh removed" category.[18]

# Reasons

## Support from women

**1996 Pulitzer Prize for Feature Photography**

Kenyan FGM ceremony: Photograph 7
Photograph 10
Photograph 13

— Stephanie Walsh, Newhouse News Service[116]

Dahabo Musa, a Somali woman, described infibulation in a 1988 poem as the "three feminine sorrows": the procedure itself, the wedding night when the woman is cut open, then childbirth when she is cut again.[117] Despite the evident suffering, it is women who organize all forms of FGM.[118][10] Anthropologist Rose Oldfield Hayes wrote in 1975 that educated Sudanese men who did not want their daughters to be infibulated (preferring clitoridectomy) would find the girls had been sewn up after the grandmothers arranged a visit to relatives.[14]:620, 624

Gerry Mackie has compared FGM to footbinding. Like FGM, footbinding was carried out on young girls, nearly universal where practised, tied to ideas about honour, chastity and appropriate marriage, and supported by women.[p] FGM practitioners see the procedures as marking not only ethnic boundaries but also gender difference. According to this view, FGM demasculinizes women, while male circumcision defeminizes men.[120]

Fuambai Ahmadu, an anthropologist and member of the Kono people of Sierra

Anthropologist Fuambai Ahmadu chose to undergo clitoridectomy as an adult.[121]

Leone, who in 1992 underwent clitoridectomy as an adult during a Sande society initiation, argued in 2000 that it is a male-centred assumption that the clitoris is important to female sexuality. African female symbolism revolves instead around the concept of the womb.[121] Infibulation draws on that idea of enclosure and fertility. "[G]enital cutting completes the social definition of a child's sex by eliminating external traces of androgyny," Janice Boddy wrote in 2007. "The female body is then covered, closed, and its productive blood bound within; the male body is unveiled, opened and exposed."[122]

In communities where infibulation is common, there is a preference for women's genitals to be smooth, dry and without odour, and both women and men may find the natural vulva repulsive.[123]:435–436 Men seem to enjoy the effort of penetrating an infibulation.[124] The local preference for dry sex causes women to introduce substances into the vagina to reduce lubrication, including leaves, tree bark, toothpaste and Vicks menthol rub.[125] The WHO includes this practice within Type IV FGM, because the added friction during intercourse can cause lacerations and increase the risk of infection.[126] Because of the smooth appearance of an infibulated vulva, there is also a belief that infibulation increases hygiene.[123]:437

Common reasons for FGM cited by women in surveys are social acceptance, religion, hygiene, preservation of virginity, marriageability and enhancement of male sexual pleasure.[127] In a study in northern Sudan, published in 1983, only 17.4 percent of women opposed FGM (558 out of 3,210), and most preferred excision and infibulation over clitoridectomy.[128] Attitudes are changing slowly. In Sudan in 2010, 42 percent of women who had heard of FGM said the practice should continue.[129] In several surveys since 2006, over 50 percent of women in Mali, Guinea, Sierra Leone, Somalia, Gambia and Egypt supported FGM's continuance, while elsewhere in Africa, Iraq and Yemen most said it should end, although in several countries only by a narrow margin.[130]

## Social obligation, poor access to information

Against the argument that women willingly choose FGM for their daughters, UNICEF calls the practice a "self-enforcing social convention" to which families feel they must conform to avoid uncut daughters facing social exclusion.[131]

Ellen Gruenbaum reports that, in Sudan in the 1970s, cut girls from an Arab ethnic group would mock uncut Zabarma girls with *Ya, Ghalfa!* ("Hey, unclean!"). The Zabarma girls would respond *Ya, mutmura!* (A *mutmara* was a storage pit for grain that was continually opened and closed, like an infibulated woman.) But despite throwing the insult back, the Zabarma girls would ask their mothers, "What's the matter? Don't we have razor blades like the Arabs?"[123]:432–433

Because of poor access to information, and because circumcisers downplay the causal connection, women may not associate the health consequences with the procedure. Lala Baldé, president of a women's association in Medina Cherif, a village in Senegal, told Mackie in 1998 that when girls fell ill or died, it was attributed to evil spirits. When informed of the causal relationship between FGM and ill health, Mackie wrote, the women broke down and wept. Mackie argued that surveys taken before and after this sharing of information would show very different levels of support for FGM.[132]

Molly Melching in 2007 on the 10th anniversary of the abandonment of FGM by Malicounda Bambara, Senegal

The American non-profit group Tostan, founded by Molly Melching in 1991, introduced community-empowerment programmes in several countries that focus on local democracy, literacy, and education about healthcare, giving women the tools to make their own decisions.[133] In 1997, using the Tostan programme, Malicounda Bambara in Senegal became the first village to abandon FGM.[134] By 2016, over 7,300 communities in six countries had pledged to abandon FGM and child marriage.[135]

## Religion

*Further information: Religious views on female genital mutilation*

Surveys have shown a widespread belief, particularly in Mali, Mauritania,

Keur Simbara, Senegal, abandoned FGM in 1998 after a three-year programme by Tostan.[136]

Guinea and Egypt, that FGM is a religious requirement.[137] Gruenbaum has argued that practitioners may not distinguish between religion, tradition and chastity, making it difficult to interpret the data.[138]

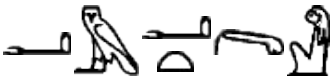
FGM's origins in northeastern Africa are pre-Islamic, but the practice became associated with Islam because of that religion's focus on female chastity and seclusion.[q] There is no mention of it in the Quran. It is praised in several *hadith* (sayings attributed to Muhammad) as noble but not required.[r][141] In 2007 the Al-Azhar Supreme Council of Islamic Research in Cairo ruled that FGM had "no basis in core Islamic law or any of its partial provisions."[142][s]

There is no mention of FGM in the Bible.[144] Christian missionaries in Africa were among the first to object to FGM,[145] but Christian communities in Africa do practise it. UNICEF reported in 2013 that, for example, 55 percent of Christian women and girls in Niger had experienced FGM, compared with two percent of their Muslim counterparts.[146] The only Jewish group known to have practised it are the Beta Israel of Ethiopia. Judaism requires male circumcision, but does not allow FGM.[147] FGM is also practised by animist groups, particularly in Guinea and Mali.[148]

# History

## Antiquity

The practice's origins are unknown, but its east-west, north-south distribution in Africa meets in Sudan. Gerry Mackie has suggested that infibulation began there with the Meroite civilization (c. 800 BCE — c. 350 CE), before the rise of Islam, to increase confidence in paternity.[151] According to historian Mary Knight, Spell 1117 (c. 1991–1786 BCE) of the Ancient Egyptian Coffin Texts may refer in hieroglyphs to an uncircumcised girl ('*m't*):



The spell was found on the sarcophagus of Sit-hedjhotep, now in the Egyptian Museum, and dates to Egypt's Middle Kingdom.[t] (Paul F. O'Rourke argues that '*m't* probably refers instead to a menstruating woman.)[152] The proposed circumcision of an Egyptian girl, Tathemis, is also mentioned on a Greek papyrus, from 163 BCE, in the British Museum:

> Sometime after this, Nephoris [Tathemis's mother] defrauded me, being anxious that it was time for Tathemis to be circumcised, as is the custom among the Egyptians. She asked that I give her 1,300 drachmae ... to clothe her ... and to provide her with a marriage dowry ... if she didn't do each of these or if she did not circumcise Tathemis in the month of Mecheir, year 18 [163 BCE], she would repay me 2,400 drachmae on the spot.[153]

**Spell 1117**

But if a man wants to know how to live, he should recite it [a magical spell] every day, after his flesh has been rubbed with the *b3d* [unknown substance] of an uncircumcised girl ['*m't*] and the flakes of skin [*šnft*] of an uncircumcised bald man.

— Inscription on Egyptian sarcophagus, c. 1991–1786 BCE[149][150]

The examination of mummies has shown no evidence of FGM. Citing the Australian pathologist Grafton Elliot Smith, who examined hundreds of mummies in the early 20th century, Knight writes that the genital area may resemble Type III because during mummification the skin of the outer labia was pulled toward the anus to cover the pudendal cleft, possibly to prevent sexual violation. It was similarly not possible to determine whether Types I

**Strabo**

This is one of the customs most zealously pursued by

or II had been performed, because soft tissues had deteriorated or been removed by the embalmers.[155]

> them [the Egyptians]: to raise every child that is born and to circumcise [*peritemnein*] the males and excise [*ektemnein*] the females ...
>
> — Strabo, *Geographica*, c. 25 BCE.[154]

The Greek geographer Strabo (c. 64 BCE – c. 23 CE) wrote about FGM after visiting Egypt around 25 BCE *(right)*.[u][v] The philosopher Philo of Alexandria (c. 20 BCE – 50 CE) also made reference to it: "the Egyptians by the custom of their country circumcise the marriageable youth and maid in the fourteenth (year) of their age, when the male begins to get seed, and the female to have a menstrual flow."[158] It is mentioned briefly in a work attributed to the Greek physician Galen (129 – c. 200 CE): "When [the clitoris] sticks out to a great extent in their young women, Egyptians consider it appropriate to cut it out."[w]

Another Greek physician, Aëtius of Amida (mid-5th to mid-6th century CE), offered more detail in book 16 of his *Sixteen Books on Medicine*, citing the physician Philomenes. The procedure was performed in case the clitoris, or *nymphê*, grew too large or triggered sexual desire when rubbing against clothing. "On this account, it seemed proper to the Egyptians to remove it before it became greatly enlarged", Aëtius wrote, "especially at that time when the girls were about to be married":

> The surgery is performed in this way: Have the girl sit on a chair while a muscled young man standing behind her places his arms below the girl's thighs. Have him separate and steady her legs and whole body. Standing in front and taking hold of the clitoris with a broad-mouthed forceps in his left hand, the surgeon stretches it outward, while with the right hand, he cuts it off at the point next to the pincers of the forceps.
>
> It is proper to let a length remain from that cut off, about the size of the membrane that's between the nostrils, so as to take away the excess material only; as I have said, the part to be removed is at that point just above the pincers of the forceps. Because the clitoris is a skinlike structure and stretches out excessively, do not cut off too much, as a urinary fistula may result from cutting such large growths too deeply.[x]

The genital area was then cleaned with a sponge, frankincense powder and wine or cold water, and wrapped in linen bandages dipped in vinegar, until the seventh day when calamine, rose petals, date pits or a "genital powder made from baked clay" might be applied.[161]

Whatever the practice's origins, infibulation became linked to slavery. Mackie cites the Portuguese missionary João dos Santos, who in 1609 wrote of a group inland from Mogadishu who had a "custome to sew up their Females, especially their slaves being young to make them unable for conception, which makes these slaves sell dearer, both for their chastitie, and for better confidence which their Masters put in them." The English explorer William Browne wrote in 1799 that the Egyptians practised excision, and that slaves in that country were infibulated to prevent pregnancy. Thus, Mackie argues, a "practice associated with shameful female slavery came to stand for honor."[162]

## Europe and the United States

Gynaecologists in 19th-century Europe and the United States removed the clitoris to treat insanity and masturbation.[164] British doctor Robert Thomas suggested clitoridectomy as a cure for nymphomania in 1813.[165][166] The first reported clitoridectomy in the West, described in *The Lancet* in 1825, was performed in 1822 in Berlin by Karl Ferdinand von Graefe on a 15-year-old girl who was masturbating excessively.[167][168]

Isaac Baker Brown "set to work

Isaac Baker Brown, an English gynaecologist, president of the Medical Society of London, and co-founder in 1845 of St. Mary's Hospital there, believed that masturbation, or "unnatural irritation" of the clitoris, caused hysteria, spinal irritation, fits, idiocy, mania and death.[168][169] He therefore "set to work to remove the clitoris whenever he had the opportunity of doing so", according to his obituary in the *Medical Times and Gazette* in 1873.[170] Brown performed several clitoridectomies between 1859 and 1866. When he published his views in *On the Curability of Certain Forms of Insanity, Epilepsy, Catalepsy, and Hysteria in*

*Females* (1866), doctors in London accused him of quackery and expelled him from the Obstetrical Society.[171][169][172]

> to remove the clitoris whenever he had the opportunity of doing so."[163]

In the United States J. Marion Sims followed Brown's work, and in 1862 slit the neck of a woman's uterus and amputated her clitoris, "for the relief of the nervous or hysterical condition as recommended by Baker Brown", after the patient complained of menstrual pain, convulsions and bladder problems.[173] Later that century A. J. Bloch, a surgeon in New Orleans, removed the clitoris of a two-year-old girl who was reportedly masturbating.[174] According to a 1985 paper in the *Obstetrical & Gynecological Survey*, clitoridectomy was performed in the US into the 1960s to treat hysteria, erotomania and lesbianism.[175]

# Opposition

## Colonial opposition in Kenya

*Further information: Female circumcision controversy (Kenya, 1929–1932)*

Protestant missionaries in British East Africa (present-day Kenya) began campaigning against FGM in the early 20th century, when Dr. John Arthur joined the Church of Scotland Mission (CSM) in Kikuyu. An important ethnic marker, the practice was known by the Kikuyu, the country's main ethnic group, as *irua* for both girls and boys. It involved excision (Type II) for girls and removal of the foreskin for boys. Unexcised Kikuyu women (*irugu*) were outcasts.[177]

Jomo Kenyatta, general secretary of the Kikuyu Central Association and Kenya's first prime minister from 1963, wrote in 1938 that, for the Kikuyu, the institution of FGM was the "*conditio sine qua non* of the whole teaching of tribal law, religion and morality." No proper Kikuyu man or woman would marry or have sexual relations with someone who was not circumcised. A woman's responsibilities toward the tribe began with her initiation. Her age and place within tribal history was traced to that day, and the group of girls with whom she was cut was named according to current events, an oral tradition that allowed the Kikuyu to track people and events going back hundreds of years.[178]

> *Muthirigu*
>
> Little knives in their sheaths
> That they may fight with the church,
> The time has come.
> Elders (of the church)
> When Kenyatta comes
> You will be given women's clothes
> And you will have to cook him his food.
>
> — from the *Muthirigu* (1929), Kikuyu dance-songs against church opposition to FGM[176]

Missionary Hulda Stumpf *(bottom left)* was murdered in Kikuyu in 1930 after opposing FGM.

Beginning with the CSM mission in 1925, several missionary churches declared that FGM was prohibited for African Christians. The CSM announced that Africans practising it would be excommunicated, which resulted in hundreds leaving or being expelled.[179] The stand-off turned FGM into a focal point of the Kenyan independence movement; the 1929–1931 period is known in the country's historiography as the female circumcision controversy.[180]

In 1929 the Kenya Missionary Council began referring to FGM as the "sexual mutilation of women", rather than circumcision, and a person's stance toward the practice became a test of loyalty, either to the Christian churches or to the Kikuyu Central Association.[181] Hulda Stumpf, an American missionary with the Africa Inland Mission who opposed FGM in the girls' school she helped to run, was murdered in 1930. Edward Grigg, the governor of Kenya, told the British Colonial Office that the killer, who was never identified, had tried to circumcise her.[182]

In 1956 the council of male elders (the *Njuri Nchecke*) in Meru announced a ban on FGM. Over the next three years, thousands of girls cut each other's genitals with razor blades as a symbol of defiance. The movement came to be known as *Ngaitana* ("I will circumcise myself"), because to avoid naming their friends the girls said they had cut themselves. Historian Lynn Thomas described the episode as significant in the history of FGM because it made clear that its victims were also its perpetrators.[183]

## Growth of opposition

The first known non-colonial campaign against FGM began in Egypt in the 1920s, when the Egyptian Doctors' Society called for a ban.[184] There was a parallel campaign in Sudan, run by religious leaders and British women. Infibulation was banned there in 1946, but the law was unpopular and barely enforced.[185][y] The Egyptian government banned infibulation in state-run hospitals in 1959, but allowed partial clitoridectomy if parents requested it.[187] (Egypt banned FGM entirely in 2007.)

In 1959 the UN asked the WHO to investigate FGM, but the latter responded that it was not a medical matter.[188] Feminists took up the issue throughout the 1970s.[189] The Egyptian physician and feminist Nawal El Saadawi criticized FGM in her book *Women and Sex* (1972); the book was banned in Egypt and El Saadawi lost her job as director general of public health.[190] She followed up with a chapter, "The Circumcision of Girls," in *The Hidden Face of Eve: Women in the Arab World* (1980), which described her own clitoridectomy when she was six years old:

Nawal El Saadawi criticized FGM in 1972, one of the first African feminists to do so publicly.

> I did not know what they had cut off from my body, and I did not try to find out. I just wept, and called out to my mother for help. But the worst shock of all was when I looked around and found her standing by my side. Yes, it was her, I could not be mistaken, in flesh and blood, right in the midst of these strangers, talking to them and smiling at them, as though they had not participated in slaughtering her daughter just a few moments ago.[191]

In 1975 Rose Oldfield Hayes, an American social scientist, became the first female academic to publish a detailed account of FGM, aided by her ability to discuss it directly with women in Sudan. Her article in *American Ethnologist* called it "female genital mutilation," rather than female circumcision, and brought it to wider academic attention.[14]:21

In 1977 Edna Adan Ismail, who worked at the time for the Somalia Ministry of Health, raised the health consequences of FGM with the Somali Women's Democratic Organization.[192] Two years later Fran Hosken, an Austria-American feminist, published *The Hosken Report: Genital and Sexual Mutilation of Females* (1979), the first to offer global figures. She estimated that 110,529,000 women in 20 African countries had experienced FGM.[193] The figures were speculative but consistent with later surveys.[194] Describing FGM as

## FGM opposition

### 1920s–1980s timeline

**1920s–1930s**

**1920s**: Egyptian Doctors' Society call for ban.[A 1]

**1929**: Marion Scott Stevenson, Church of Scotland missionary in Kenya, calls FGM "sexual mutilation of women." National Council of Churches of Kenya follow suit.[A 2]

Scottish missionaries require Kikuyu Christians to take an oath against FGM; most leave to form their own churches.

**1930, January**: American missionary Hulda Stumpf murdered in Kenya during protests about FGM.[A 3]

**1930s**: Religious leaders and British women lead campaign against FGM in Sudan.[A 4]

**1935**: Egyptian writer Salama Moussa writes about FGM in his *Ma Heia al Nahda* ("What is Renaissance?").[A 5]

**1940s–1960s**

**1946**: Sudan, under Anglo-Egyptian control, bans infibulation; the law is barely enforced.[A 6]

**1951, May**: Egyptian medical journal, *Al Doktor*, issues booklet on dangers of FGM.[A 7]

**1957–1958**: Egyptian journalist Amina al Sa'eed and *Hawwaa* magazine editor Rabee' Gheith publish articles on FGM.[A 7]

**Late 1950s**: Sudanese Women's Union campaigns against FGM in their

a "training ground for male violence," Hosken accused female practitioners of "participating in the destruction of their own kind."[15]:5 The language caused a rift between Western and African feminists; African women boycotted a session featuring Hosken during the UN's Mid-Decade Conference on Women in Copenhagen in July 1980.[195]

In 1979 the WHO held a seminar, "Traditional Practices Affecting the Health of Women and Children," in Khartoum, Sudan, and in 1981, also in Khartoum, 150 academics and activists signed a pledge to fight FGM after a workshop held by the Babiker Badri Scientific Association for Women's Studies (BBSAWS), "Female Circumcision Mutilates and Endangers Women – Combat it!" Another BBSAWS workshop in 1984 invited the international community to write a joint statement for the United Nations.[196] It recommended that the "goal of all African women" should be the eradication of FGM and that, to sever the link between FGM and religion, clitoridectomy should no longer be referred to as *sunna*.[197]

The Inter-African Committee on Traditional Practices Affecting the Health of Women and Children, founded in 1984 in Dakar, Senegal, called for an end to the practice, as did the UN's World Conference on Human Rights in Vienna in 1993. The conference listed FGM as a form of violence against women, marking it as a human-rights violation, rather than a medical issue.[198] Throughout the 1990s and 2000s governments in Africa and the Middle East passed legislation banning or restricting FGM. In 2003 the African Union ratified the Maputo Protocol on the rights of women, which supported the elimination of FGM.[199] By 2015 laws restricting FGM had been

magazine, *Sawt el Maraa*.[A 8]

**1959**: Egypt bans infibulation in state-run hospitals; allows partial clitoridectomy if parents request it.[A 9]

UN asks the WHO to investigate FGM; WHO responds that it is not a medical issue.[A 10]

**1960s**: Central African Republic, Ghana and Guinea, after gaining independence, pass laws restricting FGM.

**1969**: Guinean gynaecologist Aja Tounkara Diallo Fatimata begins 28-year practice of performing fake clitoridectomies to satisfy families.[A 11]

**1970s**

**1970**: Egyptian physician Nawal El Saadawi criticizes FGM in *Al-Mar'a wa Al-Jins* (*Women and Sex*).[A 12]

**1972**: Saadawi's *The Naked Face of Women* describes her own circumcision.[A 13]

**1975**: United Nations International Women's Year.

American social scientist Rose Oldfield Hayes calls it "female genital mutilation" in paper on FGM in Sudan.[A 14]

French writer Benoîte Groult calls FGM "the best kept secret in the world" in her *Ainsi soit-elle*.[A 15]

Austrian-American feminist Fran Hosken begins writing about FGM in *Women's International Network News* (*WIN News*).

Benoite Groult was influential in the European campaign against FGM.

**1976–1985**: UN's Decade for Women.

**1976**: British journalist Jill Tweedie calls FGM "ritual mutilation of the female genitalia."[A 16]

**1977, March**: Edna Adan Ismail of Somalia's Ministry of Health speaks against FGM to Somali Democratic Women's Organization.[A 17]

**1978**: American feminist Mary Daly criticizes FGM in *Gyn/Ecology*.[A 18]

Senegalese writer Awa Thiam writes about FGM in *La Parole aux Négresses* (*Speak out Black Sisters*, 1986).[A 19]

**1979**: Fran Hosken publishes *The Hosken Report: Genital and Sexual Mutilation of Females*, the first to estimate global figures.[A 20]

UN conference, Lusaka, Zambia, calls on women's groups to mobilize against FGM.[A 21]

February: WHO holds seminar, "Traditional Practices Affecting the Health of Women and Children," Khartoum, Sudan.[A 22]

October: Cairo Family Planning Association holds seminar, "Bodily Mutilation of Females."[A 23]

December: UN General Assembly adopts Convention on the Elimination of All Forms of Discrimination against Women.[A 24]

**1980s**

**1980**: British writer Scilla McLean writes report on FGM for Minority Rights Group in France.[A 25]

March: Robin Morgan and Gloria Steinem call it "female genital mutilation" in *Ms* magazine.[A 26]

passed in at least 23 of the 27 African countries in which it is concentrated, although several fell short of a ban.[z]

## United Nations

In December 1993 the United Nations General Assembly included FGM in resolution 48/104, the Declaration on the Elimination of Violence Against Women, and from 2003 sponsored International Day of Zero Tolerance to Female Genital Mutilation, held every 6 February.[204][205]

UNICEF began in 2003 to promote an evidence-based social norms approach to the evaluation of intervention, using ideas from game theory about how communities reach decisions about FGM, and building on the work of Gerry Mackie on the ending of footbinding in China.[206] In 2005 the UNICEF Innocenti Research Centre in Florence published its first report on FGM.[207]

UNFPA and UNICEF launched a joint programme in Africa in 2007 to reduce FGM by 40 percent within the 0–15 age group and eliminate it from at least one country by 2012, goals that were not met.[208][aa] In 2008 several UN bodies recognized FGM as a human-rights violation,[209] and in 2012 the General Assembly passed resolution 67/146, "Intensifying global efforts for the elimination of female genital mutilations."[210]

## Non-practising countries

*Further information: Prevalence of female genital mutilation by country*

Immigration spread the practice to Australia, New Zealand,

Gloria Steinem

July: African women boycott session featuring Fran Hosken at UN's Mid-Decade Conference on Women, Copenhagen.[A 27]

**1981**: French Association of Anthropologists publishes statement that "a certain feminism resuscitates (today) the moralistic arrogance of yesterday's colonialism."[A 28]

**1981**: Lillian Passmore Sanderson publishes *Against the Mutilation of Women*.

**1982**: Sudanese physician Asma El Dareer publishes study of FGM in Sudan, *Woman, Why Do You Weep? Circumcision and its Consequences*.[A 29]

Somali writer Raqiya Haji Dualeh Abdalla publishes *Sisters in Affliction: Circumcision and Infibulation of Women in Africa*.[A 30]

**1983**: Efua Dorkenoo founds FORWARD in London.[A 31]

**1984**: Inter-African Committee on Traditional Practices founded in Dakar, Senegal, calls for an end to the practice.[A 32]

### References


1. ^ UNICEF 2013, p. 10.
2. ^ James Karanja, *The Missionary Movement in Colonial Kenya: The Foundation of Africa Inland Church*, Cuvillier Verlag, 2009, p. 93, n. 631.
3. ^ Janice Boddy, *Civilizing Women: British Crusades in Colonial Sudan*, Princeton University Press, 2007, p. 241.
4. ^ Boddy 2007, pp. 269–270.
5. ^ Seham Abd el Salam, "A Comprehensive Approach for Communication about Female Genital Mutilation in Egypt," in George C. Denniston, et al (eds.), *Male and Female Circumcision: Medical, Legal, and Ethical Considerations in Pediatric Practice*, Springer, 1999, p. 318.
6. ^ Boddy 2007, pp. 202, 299.
7. ^ *a b* el Salam 1999, pp. 318–319; UNICEF 2013, p. 10.
8. ^ Rogaia Mustafa Abusharaf, "Revisiting Feminist Discourses on Inbulation: The Hosken Report," in Shell-Duncan and Hernlund 2000, p. 165.
9. ^ Elizabeth Heger Boyle, *Female Genital Cutting: Cultural Conflict in the Global Community*, Johns Hopkins University Press, 2002, pp. 92, 103.
10. ^ Boyle 2002, p. 41.
11. ^ "Female genital mutilation", *New International*, 5 June 1997.
12. ^ Jenna Krajeski, "Rebellion", *The New Yorker*, 14 March 2011.
13. ^ Nawal El Saadawi, "The Struggle to End Female Genital Mutilation," in Jennifer Browdy de Hernandez, et al, *African Women Writing Resistance*, University of Wisconsin Press, 2010, pp. 193, 195.
14. ^ Oldfield Hayes 1975, p. 618.
15. ^ Lora Wildenthal, *The Language of Human Rights in West Germany*, University of Pennsylvania Press, 2012, p. 146.
16. ^ Jill Tweedie, *It's Only Me*, Robson Books, 1980, p. 214.
17. ^ Raqiya D. Abdalla, "'My Grandmother Called it the Three Feminine Sorrows': The Struggle of Women Against Female Circumcision in Somalia," in Abusharaf 2007, p. 201; Alexandra Topping, "Somaliland's leading lady for women's rights: 'It is time for men to step up'", *The Guardian*, 23 June 2014.

Europe, North America and Scandinavia, all of which outlawed it entirely or restricted it to consenting adults.[211] Sweden outlawed it in 1982, the first Western country to do so.[212]:611 Several former colonial powers, including Belgium, Britain, France and the Netherlands, introduced new laws or made clear that it was covered by existing legislation.[213] As of 2013 legislation banning FGM had been passed in 33 countries outside Africa and the Middle East.[200]

## North America

*Further information: Female genital mutilation in the United States*

Canada recognized FGM as a form of persecution in July 1994, when it granted refugee status to Khadra Hassan Farah, who had fled Somalia to avoid her daughter being cut.[214] In 1997 section 268 of its Criminal Code was amended to ban FGM, except where "the person is at least eighteen years of age and there is no resulting bodily harm."[215][200] As of May 2016 there had been no prosecutions.[216]

In the United States an estimated 513,000 women and girls had experienced FGM or were at risk as of 2012.[217][218][ab] A Nigerian woman successfully contested deportation in March 1994 on the grounds that her daughters might be cut,[220] and in 1996 Fauziya Kasinga from Togo became the first to be granted asylum to escape FGM.[221] In 1996 the Federal Prohibition of Female Genital Mutilation Act made it illegal to perform FGM on minors for non-medical reasons, and in 2013 the Transport for Female Genital Mutilation Act prohibited transporting a minor out of the country for the purpose of FGM. In addition, 24 states have legislation banning FGM.[217]:2 The American Academy of Pediatrics opposes all forms of the practice.[ac] The first FGM conviction in the US was in 2006, when Khalid Adem, who had emigrated from Ethiopia, was sentenced to ten years after severing his two-year-old daughter's clitoris with a pair of scissors.[224][ad]


Mary Karooro Okurut, Uganda's Minister of Gender, Labour and Social Development, speaking in 2014 to the first Girl Summit in London, aimed at ending FGM and child marriage.[203]

## Europe

*Further information: Female genital mutilation in the United Kingdom*

According to the European Parliament, 500,000 women in Europe had undergone FGM as of March 2009.[227] France is known for its tough stance against FGM.[228] Up to 30,000 women there were thought to have experienced it as of 1995. According to Colette Gallard, a family-planning counsellor, when FGM was first encountered in France, the reaction was that Westerners ought not to intervene. It took the deaths of two girls in 1982, one of them three months old, for that attitude to change.[229] In 1991 a French court ruled that the Convention Relating to the Status of Refugees offered protection to FGM victims; the decision followed an asylum application from Aminata Diop, who fled an FGM procedure in Mali.[230]

The practice is outlawed by a provision of France's penal code dealing with violence [231]

18. ^ Mary Daly, *Gyn/Ecology*, Beacon Press, 1978, p. 156.
19. ^ Wildenthal 2012, p. 250, n. 68.
20. ^ UNICEF 2013, p. 3.
21. ^ Gloria Steinem, *Outrageous Acts and Everyday Rebellions*, Henry Holt & Co, 2012 [1984], p. 324.
22. ^ Wildenthal 2012, p. 145.
23. ^ el Salam 1999, p. 320.
24. ^ Elizabeth Fee, "Review of *The Hosken Report*", *Signs*, 5(4), Summer 1980 (pp. 807–809), p. 809.
25. ^ Lynn M. Thomas, "'Ngaitana (I will circumcise myself)': Lessons from Colonial Campaigns to Ban Excision in Meru, Kenya" in Shell-Duncan and Hernlund, 2000, p. 130.
26. ^ The International Crime of Female Genital Mutilation," *Ms.* magazine, March 1980.
27. ^ Boyle 2002, p. 47.
28. ^ Birgitte Bagnol, Esmeralda Mariano, "Politics of naming sexual practices," in Sylvia Tamale (ed.), *African Sexualities: A Reader*, Pambazuka Press, 2011, p. 281.
29. ^ Thomas 2000, p. 130.
30. ^ Abdalla 2007, p. 202.
31. ^ Wildenthal 2012, p.. 250, n.. 71.
32. ^ Anika Rahman and Nahid Toubia, *Female Genital Mutilation: A Guide to Laws and Policies Worldwide*, Zed Books, 2000, p. 10.

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Efua Dorkenoo (1949–2014) received an OBE in 1994 for her work against FGM in the UK.[226]

against children. All children under six who were born in France undergo medical examinations that include inspection of the genitals, and doctors are obliged to report FGM.[228] The first civil suit was in 1982 and the first criminal prosecution in 1993.[232] In 1999 a woman was given an eight-year sentence for having performed FGM on 48 girls.[233] By 2014 over 100 parents and two practitioners had been prosecuted in over 40 criminal cases.[231][228]

Around 137,000 women and girls living in England and Wales were born in countries where FGM is practised (as of 2011).[234][235] Performing FGM on children or adults was outlawed under the Prohibition of Female Circumcision Act 1985.[236] This was replaced by the Female Genital Mutilation Act 2003 and Prohibition of Female Genital Mutilation (Scotland) Act 2005, which added a prohibition on arranging FGM outside the country for British citizens or permanent residents.[237][ae] The United Nations Committee on the Elimination of Discrimination against Women asked the government in 2013 to "ensure the full implementation of its legislation on FGM."[239] The first charges were brought the following year against a physician and another man, after the physician stitched an infibulated woman after opening her for childbirth. Both men were acquitted in 2015.[240]

## Criticism of opposition

### Tolerance versus human rights

Anthropologist Eric Silverman wrote in 2004 that FGM had "emerged as one of the central moral topics of contemporary anthropology." Anthropologists have accused FGM eradicationists of cultural colonialism. In turn, anthropologists have been criticized for their moral relativism and failure to defend the idea of universal human rights.[241]

Obioma Nnaemeka: "Westerners are quick to appropriate the power to name ..."[242]

According to the opposition's critics, the biological reductionism of the opposition to FGM, and the failure to appreciate FGM's cultural context, serves to "other" practitioners and undermines their agency—in particular when parents are referred to as "mutilators".[243] Africans who object to the tone of the opposition to FGM risk appearing to defend the practice.[244] Feminist theorist Obioma Nnaemeka—herself strongly opposed to FGM ("If one is circumcised, it is one too many")—argues that renaming it *female genital mutilation* introduced "a subtext of barbaric African and Muslim cultures and the West's relevance (even indispensability) in purging [it]".

According to Ugandan law professor Sylvia Tamale, early Western opposition to FGM stemmed from a Judeo-Christian judgment that African sexual and family practices—including dry sex, polygyny, bride price and levirate marriage—were primitive and required correction.[245] African feminists "do not condone the negative aspects of the practice", writes Tamale, but "take strong exception to the imperialist, racist and dehumanising infantilization of African women".[245]

The debate has highlighted a tension between anthropology and feminism, with the former's focus on tolerance and the latter's on equal rights for all women. According to the anthropologist Christine Walley, a common trope within the anti-FGM literature has been to present African women as victims of false consciousness participating in their own oppression, a position promoted by feminists in the 1970s and 1980s, including Fran Hosken, Mary Daly and Hanny Lightfoot-Klein.[246] It prompted the French Association of Anthropologists to issue a statement in 1981, at the height of the early debates, that "a certain feminism resuscitates

(today) the moralistic arrogance of yesterday's colonialism."[247]

Commentators highlight the appropriation of women's bodies as exhibits. Historian Chima Korieh cites the publication in 1996 of the Pulitzer-prize-winning photographs (above) of a 16-year-old Kenyan girl undergoing FGM. The photographs were published by 12 American newspapers, although the girl had not given permission for the images to be taken, much less published.[248]

## Comparison with other procedures

*See also: Labiaplasty § Criticism*

Nnaemeka argues that the crucial question, broader than FGM, is why the female body is subjected to so much "abuse and indignity", including in the West.[249] Several authors have drawn a parallel between FGM and cosmetic procedures.[250]:32[251] Ronán Conroy of the Royal College of Surgeons in Ireland wrote in 2006 that cosmetic genital procedures were "driving the advance of female genital mutilation" by encouraging women to see natural variations as defects.[252] Anthropologist Fadwa El Guindi compares FGM to breast enhancement, in which the maternal function of the breast becomes secondary to men's sexual pleasure.[253] Benoîte Groult made a similar point in 1975, citing FGM and cosmetic surgery as sexist and patriarchal.[254]

Carla Obermeyer maintains that FGM may be conducive to a subject's social well-being in the same way that rhinoplasty and male circumcision are.[255] In Egypt, despite the 2007 ban, women wanting FGM for their daughters seek *amalyet tajmeel* (cosmetic surgery) to remove what is viewed as excess genital tissue for a more acceptable appearance.[256]

Martha Nussbaum argues that a key moral and legal issue with FGM is that it is mostly conducted on children using physical force.

The WHO does not cite procedures such as labiaplasty and clitoral hood reduction as examples of FGM, but its definition aims to avoid loopholes, so several elective practices fall within its categories.[257] Some of the laws banning FGM, including in Canada and the US, focus only on minors. Several countries, including Sweden and the UK, have banned it regardless of consent, and the legislation would seem to cover cosmetic procedures. Sweden, for example, has banned "[o]perations on the external female genital organs which are designed to mutilate them or produce other permanent changes in them ... regardless of whether consent to this operation has or has not been given." Gynaecologist Birgitta Essén and anthropologist Sara Johnsdotter note that it seems the law distinguishes between Western and African genitals, and deems only African women (such as those seeking reinfibulation after childbirth) unfit to make their own decisions.[250]:33[212]:613

Arguing against suggested similarities between FGM and dieting or body shaping, philosopher Martha Nussbaum writes that a key difference is that FGM is mostly conducted on children using physical force. She argues that the distinction between social pressure and physical force is morally and legally salient, comparable to the distinction between seduction and rape. She argues further that the literacy of women in practising countries is generally poorer than in developed nations, and that this reduces their ability to make informed choices.[258]

Several commentators maintain that children's rights are violated with the genital alteration of intersex children, who are born with anomalies that physicians choose to correct. Legal scholars Nancy Ehrenreich and Mark Barr write that thousands of these procedures take place every year in the United States, and say that they are medically unnecessary, more extensive than FGM, and have more serious physical and mental consequences. They attribute the silence of anti-FGM campaigners about intersex procedures to white privilege and a refusal to acknowledge that "similar unnecessary and harmful genital cutting occurs in their own backyards."[259]

# Notes

a. ^ UNICEF 2013: "There is a social obligation to conform to the practice and a widespread belief that if they [families] do not, they are likely to pay a price that could include social exclusion, criticism, ridicule, stigma or the inability to find their daughters suitable marriage partners."[7]

Nahid F. Toubia, Eiman Hussein Sharief, 2003: "One of the great achievements of the past decade in the field of FGM is the shift in emphasis from the concern over the harmful interpreted with a high degree of caution ..."[90]

An additional complication in judging prevalence among girls is that, in countries running campaigns against FGM, women might not report that their daughters have been cut.[91]

o. ^ UNICEF 2014: "If there is no reduction in the practice between now and 2050, the number of girls cut each year will grow from 3.6 million in 2013 to 6.6 million in 2050.

physical effects it causes to understanding this act as a social phenomenon resulting from a gender definition of women's roles, in particular their sexual and reproductive roles. This shift in emphasis has helped redefine the issues from a clinical disease model (hence the terminology of eradication prevalent in the literature) to a problem resulting from the use of culture to protect social dominance over women's bodies by the patriarchal hierarchy. Understanding the operative mechanisms of patriarchal dominance must also include understanding how women, particularly older married women, are important keepers of that social hegemony."[8]

b. ^ For example, "a young woman must 'have her bath' before she has a baby".[20]

c. ^ UNICEF 2005: "The large majority of girls and women are cut by a traditional practitioner, a category which includes local specialists (cutters or *exciseuses*), traditional birth attendants and, generally, older members of the community, usually women. This is true for over 80 percent of the girls who undergo the practice in Benin, Burkina Faso, Côte d'Ivoire, Eritrea, Ethiopia, Guinea, Mali, Niger, Tanzania and Yemen. In most countries, medical personnel, including doctors, nurses and certified midwives, are not widely involved in the practice."[28]

d. ^ A 2003 study in Ghana found that in 1995 four percent said they had not undergone FGM, but in 2000 said they had, while 11 percent switched in the other direction.[34] In Tanzania in 2005, 66 percent reported FGM, but a medical exam found that 73 percent had undergone it.[35] In Sudan in 2006, a significant percentage of infibulated women and girls reported a less severe type.[36]

e. ^ UNICEF 2013: "These categories do not fully match the WHO typology. *Cut, no flesh removed* describes a practice known as nicking or pricking, which currently is categorized as Type IV. *Cut, some flesh removed* corresponds to Type I (clitoridectomy) and Type II (excision) combined. And *sewn closed* corresponds to Type III, infibulation."[18]

f. ^ WHO, 1995: "[There is a] common tendency to describe Type I as removal of the prepuce, whereas this has not been documented as a traditional form of female genital mutilation. However, in some countries, medicalized female genital mutilation can include removal of the prepuce only (Type Ia) (Thabet and Thabet, 2003), but this form appears to be relatively rare (Satti et al, 2006). Almost all known forms of female genital mutilation that remove tissue from the clitoris also cut all or part of the clitoral glans itself."[42]

g. ^ Susan Izett and Nahid Toubia, 1998: "[T]he clitoris is held between the thumb and index finger, pulled out and amputated with one stroke of a sharp object."[44]

h. ^ WHO 2014: "Narrowing of the vaginal orifice with creation of a covering seal by cutting and appositioning the labia minora and/or the labia majora, with or without excision of the clitoris (infibulation).

"Type IIIa, removal and apposition of the labia minora; Type IIIb, removal and apposition of the labia majora."[1]

i. ^ USAID 2008: "Infibulation is practiced largely in countries located in northeastern Africa: Djibouti, Eritrea, Ethiopia, Somalia, and Sudan. ... Sudan alone accounts for about 3.5 million of the women. ... [T]he estimate of the total number of women infibulated in [Djibouti, Somalia, Eritrea, northern Sudan, Ethiopia, Guinea, Mali, Burkina Faso, Senegal, Chad, Nigeria, Cameroon and Tanzania, for

But if the rate of progress achieved over the last 30 years is maintained, the number of girls affected annually will go from 3.6 million today to 4.1 million in 2050.

"In either scenario, the total number of girls and women cut will continue to increase due to population growth. If nothing is done, the number of girls and women affected will grow from 133 million today to 325 million in 2050. However, if the progress made so far is sustained, the number will grow from 133 million to 196 million in 2050, and almost 130 million girls will be spared this grave assault to their human rights."[95]

p. ^ Gerry Mackie, 1996: "Footbinding and infibulation correspond as follows. Both customs are nearly universal where practiced; they are persistent and are practiced even by those who oppose them. Both control sexual access to females and ensure female chastity and fidelity. Both are necessary for proper marriage and family honor. Both are believed to be sanctioned by tradition. Both are said to be ethnic markers, and distinct ethnic minorities may lack the practices. Both seem to have a past of contagious diffusion. Both are exaggerated over time and both increase with status. Both are supported and transmitted by women, are performed on girls about six to eight years old, and are generally not initiation rites. Both are believed to promote health and fertility. Both are defined as aesthetically pleasing compared with the natural alternative. Both are said to properly exaggerate the complementarity of the sexes, and both are claimed to make intercourse more pleasurable for the male."[119]

q. ^ Gerry Mackie, 1996: "FGM is pre-Islamic but was exaggerated by its intersection with the Islamic modesty code of family honor, female purity, virginity, chastity, fidelity, and seclusion."[139]

r. ^ Gerry Mackie, 1996: "The Koran is silent on FGM, but several *hadith* (sayings attributed to Mohammed) recommend attenuating the practice for the woman's sake, praise it as noble but not commanded, or advise that female converts refrain from mutilation because even if pleasing to the husband it is painful to the wife."[140]

s. ^ Maggie Michael, Associated Press, 2007: "[Egypt's] supreme religious authorities stressed that Islam is against female circumcision. It's prohibited, prohibited, prohibited," Grand Mufti Ali Gomaa said on the privately owned al-Mahwar network."[143]

t. ^ Knight adds that Egyptologists are uncomfortable with the translation to *uncircumcised*, because there is no information about what constituted the circumcised state.[149]

u. ^ Strabo, *Geographica*, c. 25 BCE: "One of the customs most zealously observed among the Aegyptians is this, that they rear every child that is born, and circumcise [περιτέμνειν, *peritemnein*] the males, and excise [*ektemnein*] the females, as is also customary among the Jews, who are also Aegyptians in origin, as I have already stated in my account of them."[156]

Book XVI, chapter 4, 16.4.9: "And then to the Harbour of Antiphilus, and, above this, to the Creophagi [meat-eaters], of whom the males have their sexual glands mutilated [*kolobos*] and the women are excised [*ektemnein*] in the Jewish fashion."

v. ^ Knight 2001 writes that there is one extant reference from antiquity, from Xanthus of Lydia in the fifth century BCE, that may allude to FGM outside Egypt. Xanthus

women 15–49 years old] comes to 8,245,449, or just over eight million women."[45]

j. ^ Jasmine Abdulcadira, *Swiss Medical Weekly*, 2011:"In the case of infibulation, the urethral opening and part of the vaginal opening are covered by the scar. In a virgin infibulated woman the small opening left for the menstrual fluid and the urine is not wider than 2–3 mm; in sexually active women and after the delivery the vaginal opening is wider but the urethral orifice is often still covered by the scar."[6]

k. ^ Elizabeth Kelly, Paula J. Adams Hillard, *Current Opinion in Obstetrics & Gynecology*, 2005: "Women commonly undergo reinfibulation after a vaginal delivery. In addition to reinfibulation, many women in Sudan undergo a second type of re-suturing called El-Adel, which is performed to recreate the size of the vaginal orifice to be similar to the size created at the time of primary infibulation. Two small cuts are made around the vaginal orifice to expose new tissues to suture, and then sutures are placed to tighten the vaginal orifice and perineum. This procedure, also called re-circumcision, is primarily performed after vaginal delivery, but can also be performed before marriage, after cesarean section, after divorce, and sometimes even in elderly women as a preparation before death."[29]:491

l. ^ WHO 2005: "In some areas (e.g. parts of Congo and mainland Tanzania), FGM entails the pulling of the labia minora and/or clitoris over a period of about 2 to 3 weeks. The procedure is initiated by an old woman designated for this task, who puts sticks of a special type in place to hold the stretched genital parts so that they do not revert back to their original size. The girl is instructed to pull her genitalia every day, to stretch them further, and to put additional sticks in to hold the stretched parts from time to time. This pulling procedure is repeated daily for a period of about two weeks, and usually no more than four sticks are used to hold the stretched parts, as further pulling and stretching would make the genital parts unacceptably long."[59]:31

m. ^ In this table and above, these are the countries for which nationally representative figures are available (UNICEF 2016).

n. ^ UNICEF 2013: "The percentage of girls and women of reproductive age (15 to 49) who have experienced any form of FGM/C is the first indicator used to show how widespread the practice is in a particular country ... A second indicator of national prevalence measures the extent of cutting among daughters aged 0 to 14, as reported by their mothers. Prevalence data for girls reflect their current – not final – FGM/C status, since many of them may not have reached the customary age for cutting at the time of the survey. They are reported as being uncut but are still at risk of undergoing the procedure. Statistics for girls under age 15 therefore need to be

wrote, in a history of Lydia: "The Lydians arrived at such a state of delicacy that they were even the first to 'castrate' their women." Knight argues that the "castration", which is not described, may have kept women youthful, in the sense of allowing the Lydian king to have intercourse with them without pregnancy. Knight concludes that it may have been a reference to sterilization, not FGM.[157]

w. ^ Knight adds that the attribution to Galen is suspect.[159]

x. ^ A paragraph break has been added for ease of reading.[160]

y. ^ FGM is still practised in Sudan. Some states banned it in 2008–2009, but as of 2013, there was no national legislation.[186]

z. ^ For example, UNICEF 2013 lists Mauritania as having passed legislation against FGM, but (as of that year) it was banned only from being conducted in government facilities or by medical personnel.[200]

The following are countries in which FGM is common and in which restrictions are in place. An asterisk indicates a ban:

Benin (2003), Burkina Faso (1996*), Central African Republic (1966, amended 1996), Chad (2003), Côte d'Ivoire (1998), Djibouti (1995, amended 2009*), Egypt (2008*), Eritrea (2007*), Ethiopia (2004*), Ghana (1994, amended 2007), Guinea (1965, amended 2000*), Guinea-Bissau (2011*), Iraq (2011*), Kenya (2001, amended 2011*), Mauritania (2005), Niger (2003), Nigeria (2015*), Senegal (1999*), Somalia (2012*), Sudan, some states (2008–2009), Tanzania (1998), Togo (1998), Uganda (2010*), Yemen (2001*).[201][202]:12

aa. ^ Fifteen countries joined the programme: Djibouti, Egypt, Ethiopia, Guinea, Guinea-Bissau, Kenya, Senegal and Sudan in 2008; Burkina Faso, Gambia, Uganda and Somalia in 2009; and Eritrea, Mali and Mauritania in 2011.[208]

ab. ^ The Centers for Disease Control's previous estimate was 168,000 as of 1990.[219]

ac. ^ In 2010 the American Academy of Pediatrics suggested that "pricking or incising the clitoral skin" was a harmless procedure that might satisfy parents, but it withdrew the statement after complaints.[222][223]

ad. ^ In 2014 President Barack Obama spoke about FGM for the first time, calling it "a tradition that's barbaric and should be eliminated."[225]

ae. ^ Female Genital Mutilation Act 2003: "A person is guilty of an offence if he excises, infibulates or otherwise mutilates the whole or any part of a girl's labia majora, labia minora or clitoris," unless "necessary for her physical or mental health." Although the legislation refers to girls, it applies to women too.[238]

# References


1. ^ *a b c d e* "Classification of female genital mutilation", Geneva: World Health Organization, 2014.
2. ^ *Female Genital Mutilation/Cutting: A Statistical Overview and Exploration of the Dynamics of Change*, New York: United Nations Children's Fund, July 2013 (hereinafter UNICEF 2013), 5.
3. ^ *a b c d e f g h i j* "Female Genital Mutilation/Cutting: A

doi:10.1093/ije/12.2.138 PMID 6874206

129. ^ UNICEF 2013, 178.
130. ^ UNICEF 2013, 52: "The highest levels of support can be found in Mali, Guinea, Sierra Leone, Somalia, Gambia and Egypt, where more than half the female population think the practice should continue." Also see figure 6.1, 54, and figures 8.1A – 8.1D, 90–91.
131. ^ UNICEF 2013, 15.

Global Concern", New York: United Nations Children's Fund, February 2016.
4. ^ UNICEF 2013, 50.
5. ^ For the circumcisers, blade: UNICEF 2013, 2, 44–46; for the ages: 50.
6. ^ *a b c d e f g h i j k l* Jasmine Abdulcadira, et al., "Care of women with female genital mutilation/cutting", *Swiss Medical Weekly*, 6(14), January 2011. doi:10.4414/smw.2011.13137 PMID 21213149
7. ^ UNICEF 2013, 15.
8. ^ Nahid F. Toubia, Eiman Hussein Sharief, "Female genital mutilation: have we made progress?", *International Journal of Gynecology & Obstetrics*, 82(3), September 2003, 251–261. doi:10.1016/S0020-7292(03)00229 PMID 14499972
9. ^ *a b* "Female genital mutilation", Geneva: World Health Organization, February 2016.
10. ^ *a b* Bettina Shell-Duncan, "From Health to Human Rights: Female Genital Cutting and the Politics of Intervention", *American Anthropologist*, New Series, 110(2), June 2008, 225–236. doi:10.1111/j.1548-1433.2008.00028.x JSTOR 27563985
11. ^ Martha Nussbaum, *Sex and Social Justice*, New York: Oxford University Press, 1999, 119.
12. ^ James Karanja, *The Missionary Movement in Colonial Kenya: The Foundation of Africa Inland Church*, Göttingen: Cuvillier Verlag, 2009, 93, n. 631.
13. ^ *a b c* "Eliminating Female genital mutilation: An Interagency Statement", Geneva: World Health Organization, 2008 (hereinafter WHO 2008), 4, 22.
14. ^ *a b c* Rose Oldfield Hayes, "Female Genital Mutilation, Fertility Control, Women's Roles, and the Patrilineage in Modern Sudan: A Functional Analysis," *American Ethnologist* 2(4), November 1975, 617–633. JSTOR 643328
15. ^ *a b* Fran Hosken, *The Hosken Report: Genital and Sexual Mutilation of Females*, Lexington: Women's International Network, 1994 [1979].
16. ^ Claire C. Robertson, "Getting beyond the Ew! Factor: Rethinking U.S. Approaches to African Female Genital Cutting", in Stanlie M. James and Claire C. Robertson (eds.), *Genital Cutting and Transnational Sisterhood*, Urbana: University of Illinois Press, 2002 (54–86), 60.
17. ^ UNICEF 2013, 6–7.
18. ^ *a b c d* UNICEF 2013, 48.
19. ^ Chantal Zabus, "The Excised Body in African Texts and Contexts," in Merete Falck Borch (ed.), *Bodies and Voices: The Force-field of Representation and Discourse in Colonial and Postcolonial Studies*, New York: Rodopi, 2008, 47.
20. ^ Chantal Zabus, "'Writing with an Accent': From Early Decolonization to Contemporary Gender Issues in the African Novel in French, English, and Arabic," in Simona Bertacco (ed.), *Language and Translation in Postcolonial Literatures*, New York: Routledge, 2013, 40.
21. ^ Fadwa El Guindi, "Had *This* Been Your Face, Would You Leave It as Is?" in Rogaia Mustafa Abusharaf (ed.), *Female Circumcision: Multicultural Perspectives*, Philadelphia: University of Pennsylvania Press, 2007, 30.
22. ^ Clarence-Smith, William G. "Islam and Female Genital Cutting in Southeast Asia: The Weight of the Past", *Finnish Journal of Ethnicity and Migration*, 3(2), 2008, 14.
23. ^ *a b* Ibrahim Lethome Asmani, Maryam Sheikh Abdi, *De-linking Female Genital Mutilation/Cutting from Islam*,
132. ^ Mackie 2003, 147–148.
133. ^ Nafissatou J. Diop, Amadou Moreau, Hélène Benga, "Evaluation of the Long-term Impact of the TOSTAN Programme on the Abandonment of FGM/C and Early Marriage: Results from a qualitative study in Senega", UNICEF, January 2008.
134. ^ Mackie 2000, 256ff.
135. ^ "Female Genital Cutting", Tostan, accessed 21 March 2016.
136. ^ Malick Gueye, "Social Norm Change Theorists meet again in Keur Simbara, Senegal", Tostan, 4 February 2014.
137. ^ UNICEF 2013, 69–71.
138. ^ Gruenbaum 2001, 50; Mackie and LeJeune 2008, 8.
139. ^ Mackie 1996, 1008.
140. ^ Mackie 1996, 1004–1005.
141. ^ Asmani and Abdi 2008, 6–13.
142. ^ "Fresh progress toward the elimination of female genital mutilation and cutting in Egypt", UNICEF, 2 July 2007; UNICEF 2013, 70.
143. ^ Maggie Michael, "Egypt Officials Ban Female Circumcision", Associated Press, 29 June 2007, 2.
144. ^ Samuel Waje Kunhiyop, *African Christian Ethics*, Zondervan, 2008, 297: "Nowhere in all of Scripture or in any of recorded church history is there even a hint that women were to be circumcised."
145. ^ Jocelyn Murray, "The Church Missionary Society and the 'Female Circumcision' Issue in Kenya 1929–1932," *Journal of Religion in Africa*, 8(2), 1976, 92–104. JSTOR 1594780
146. ^ UNICEF 2013, front page and 73.
147. ^ Shaye J. D. Cohen, *Why Aren't Jewish Women Circumcised? Gender and Covenant In Judaism*, Berkeley: University of California Press, 2005, 59; Adele Berlin (ed.), "Circumcision," *The Oxford Dictionary of the Jewish Religion*, New York: Oxford University Press, 2011, 173.
148. ^ UNICEF 2013, 175.
149. ^ *a b* Mary Knight, "Curing Cut or Ritual Mutilation?: Some Remarks on the Practice of Female and Male Circumcision in Graeco-Roman Egypt," *Isis*, 92(2), June 2001 (317–338), 330. JSTOR 3080631 PMID 11590895
150. ^ Adriaan de Buck and Alan H. Gardiner, *The Egyptian Coffin Texts*, Volume 7, Chicago: Chicago University Press, 1961, 448–450.
151. ^ Mackie 2000, 264, 267; Shell-Duncan and Hernlund 2000, 13.

    Also see C. G. Seligman, "Aspects of the Hamitic problems in the Anglo-Egyptian Sudan", *The Journal of the Royal Anthropological Institute of Great Britain and Ireland*, 1913, 40(3) (593–705), 639–646. JSTOR 2843546

    Esther K. Hicks, *Infibulation: Female Mutilation in Islamic Northeastern Africa*, Transaction Publishers, 1996, 19ff.
152. ^ Paul F. O'Rourke, "The 'm't-Woman", *Zeitschrift für Ägyptische Sprache und Altertumskunde*, 134(2), February 2007 (166–172), 166ff (hieroglyphs), 172 (menstruating woman). doi:10.1524/zaes.2007.134.2.166
153. ^ Knight 2001, 329–330; F. G. Kenyon, *Greek Papyri in the British Museum*, British Museum, 1893, 31–32 (also here [1]).
154. ^ Knight 2001, 318.
155. ^ Knight 2001, 331, citing G. Elliot Smith, *A Contribution to the Study of Mummification in Egypt*, Cairo: L'Institut

Washington: Frontiers in Reproductive Health, Population Council, 2008, 3–5.
24. ^ Ellen Gruenbaum, *The Female Circumcision Controversy: An Anthropological Perspective*, Philadelphia: University of Pennsylvania Press, 2001, 2–3.
25. ^ Leonard J. Kouba, Judith Muasher, "Female Circumcision in Africa: An Overview," *African Studies Review*, 28(1), March 1985 (95–1100), 96–97. JSTOR 524569
26. ^ Raqiya D. Abdalla, "'My Grandmother Called it the Three Feminine Sorrows': The Struggle of Women Against Female Circumcision in Somalia", in Abusharaf 2007, 190.
27. ^ UNICEF 2013, 42–44 and table 5, 181 (for cutters), 46 (for home and anaesthesia).
28. ^ Michael Miller and Francesca Moneti, *Changing a harmful social convention: Female genital cutting/mutilation*, Florence: UNICEF Innocenti Research Centre, 2005 (hereinafter UNICEF 2005), 7.
29. ^ *a b c d e f g* Elizabeth Kelly, Paula J. Adams Hillard, "Female genital mutilation", *Current Opinion in Obstetrics & Gynecology*, 17(5), October 2005, 490–494. PMID 16141763
30. ^ Wairagala Wakabi, "Africa battles to make female genital mutilation history", *The Lancet*, 369 (9567), 31 March 2007, 1069–1070. doi:10.1016/S0140-6736(07)60508-X PMID 17405200
31. ^ UNICEF 2013, 43–45.
32. ^ UNICEF 2013, 46.
33. ^ *a b* P. Stanley Yoder, Shanxiao Wang, Elise Johansen, "Estimates of Female Genital Mutilation/Cutting in 27 African Countries and Yemen", *Studies in Family Planning*, 44(2), June 2013 (189–204), 190. doi:10.1111/j.1728-4465.2013.00352.x PMID 23720002
34. ^ Elizabeth F. Jackson, et al., "Inconsistent reporting of female genital cutting status in northern Ghana: Explanatory factors and analytical consequences", *Studies in Family Planning*, 34(3), 2003, 200–210. PMID 14558322
35. ^ Elise Klouman, Rachel Manongi, Knut-Inge Klepp, "Self-reported and observed female genital cutting in rural Tanzania: Associated demographic factors, HIV and sexually transmitted infections", *Tropical Medicine and International Health* 10(1), 2005, 105–115. doi:10.1111/j.1365-3156.2004.01350.x PMID 15655020
36. ^ Susan Elmusharaf, Nagla Elhadi, Lars Almroth, "Reliability of self reported form of female genital mutilation and WHO classification: cross sectional study", *British Medical Journal*, 332(7559), 27 June 2006. doi:10.1136/bmj.38873.649074.55 PMID 16803941 PMC 1502195
37. ^ Yoder 2013, 189; UNICEF 2013, 47.
38. ^ *WHO Guidelines on the Management of Health Complications from Female Genital Mutilation*, Geneva: World Health Organization, 2016 (hereinafter WHO 2016). PMID 27359024
39. ^ Jasmine Abdulcadir, et al., "Female Genital Mutilation: A Visual Reference and Learning Tool for Health Care Professionals"], *Obstetrics & Gynecology*, 128(5), November 2016, 958–963. doi:10.1097/AOG.0000000000001686 PMID 27741194
40. ^ WHO 2008, 4, 23–28.
41. ^ Box 1.1 "Types of FGM", WHO 2016.
42. ^ WHO 2008, 25
Egyptien, 1906, 30, and Marc Armand Ruffer, *Studies in the Paleopathology of Egypt*, Chicago: University of Chicago Press, 1921, 171.
156. ^ Strabo, *Geographica*, Book VII, chapter 2, 17.2.5. (Cohen 2005, 59ff, argues that Strabo conflated the Jews with the Egyptians).
157. ^ Knight 2001, 326.
158. ^ Knight 2001, 333.
159. ^ Knight 2001, 326.
160. ^ Knight 2001, 327–328.
161. ^ Knight 2001, 328.
162. ^ Mackie 1996, 1003, 1009.
163. ^ J. F. C. "Isaac Baker Brown, F.R.C.S.", *Medical Times and Gazette*, 8 February 1873, 155.
164. ^ Sarah W. Rodriguez, "Rethinking the History of Female Circumcision and Clitoridectomy: American Medicine and Female Sexuality in the Late Nineteenth Century", *Journal of the History of Medicine and Allied Sciences*. 63(3), July 2008, 323–347. doi:10.1093/jhmas/jrm04 PMID 18065832
165. ^ Robert Thomas, *The Modern Practice of Physick*, London: Longman, Hurst, Rees, Orme, and Brown, 1813, 585–586.
166. ^ Edward Shorter, *From Paralysis to Fatigue: A History of Psychosomatic Illness in the Modern Era*, New York: Simon and Schuster, 2008, 82.
167. ^ Shorter 2008, 82.
168. ^ *a b* Uriel Elchalal, et al., "Ritualistic Female Genital Mutilation: Current Status and Future Outlook", *Obstetrical & Gynecological Survey*, 52(10), October 1997, 643–651. PMID 9326757
169. ^ *a b* Peter Lewis Allen, *The Wages of Sin: Sex and Disease, Past and Present*, Chicago: University of Chicago Press, 2000, 106.
170. ^ J. F. C. 1873, 155, cited in Allen 2000, 106.
171. ^ John Black, "Female genital mutilation: a contemporary issue, and a Victorian obsession", *Journal of the Royal Society of Medicine*, 90, July 1997, 402–405. PMID 9290425 PMC 1296388
172. ^ Elizabeth Sheehan, "Victorian Clitoridectomy: Isaac Baker Brown and His Harmless Operative Procedure," *Medical Anthropology Newsletter*, 12(4), August 1981. JSTOR 647794 PMID 12263443
173. ^ Deborah Kuhn McGregor, *From Midwives to Medicine: The Birth of American Gynecology*, New Brunswick: Rutgers University Press, 1998, 146.
174. ^ John Milton Hoberman, *Testosterone Dreams: Rejuvenation, Aphrodisia, Doping*, Berkeley: University of California Press, 2005, 63.
175. ^ Lawrence Cutner, "Female genital mutilation", *Obstetrical & Gynecological Survey*, 40(7), July 1985, 437–443. PMID 4022475 Cited in Nawal M. Nour, "Female Genital Cutting: A Persisting Practice", *Reviews in Obstetrics and Gynecology*, 1(3), Summer 2008, 135–139. PMID 19015765 PMC 2582648

    Also see G. J. Barker-Benfield, *The Horrors of the Half-Known Life: Male Attitudes Toward Women and Sexuality in Nineteenth-Century America*, New York: Routledge, 1999, 113.
176. ^ Kenneth Mufuka, "Scottish Missionaries and the Circumcision Controversy in Kenya, 1900–1960", *International Review of Scottish Studies*, 28, 2003, 55.
177. ^ Lynn M. Thomas, "'Ngaitana (I will circumcise myself)':

Also see Nahid Toubia, "Female Circumcision as a Public Health Issue", *The New England Journal of Medicine*, 331(11), 1994, 712–716. doi:10.1056/NEJM199409153311106 PMID 8058079

Carol R. Horowitz, J. Carey Jackson, Mamae Teklemariam, "Female Circumcision" (letters), *The New England Journal of Medicine*, 332, 19 January 1995, 188–190; Toubia's reply. doi:10.1056/NEJM199501193320313

43. ^ WHO 2008, 4.
44. ^ Susan Izett, Nahid Toubia, *Female Genital Mutilation: An Overview*, Geneva: World Health Organization, 1998.
45. ^ P. Stanley Yoder, Shane Khan, "Numbers of women circumcised in Africa: The Production of a Total", USAID, DHS Working Papers, No. 39, March 2008, 13–14.
46. ^ "Frequently Asked Questions on Female Genital Mutilation/Cutting", United Nations Population Fund, April 2010.
47. ^ *a b* Comfort Momoh, "Female genital mutilation" in Comfort Momoh (ed.), *Female Genital Mutilation*, Oxford: Radcliffe Publishing, 2005, 7.
48. ^ Edna Adan Ismail, "Female genital mutilation survey in Somaliland", Edna Adan Maternity and Teaching Hospital, 2009, 12; Abusharaf 2007, 190.
49. ^ El Guindi 2007, 43.
50. ^ For a twig, Momoh 2005, 7.
51. ^ Ismail 2009, 14.
52. ^ Momoh 2005, 6–7; Ismail 2009, 14.
53. ^ Abdalla 2007, 190–191, 198; for the relatives, Ismail 2009, 14.
54. ^ Hanny Lightfoot-Klein, "The Sexual Experience and Marital Adjustment of Genitally Circumcised and Infibulated Females in The Sudan"], *The Journal of Sex Research*, 26(3), 1989 (375–392), 380. JSTOR 3812643

    Also see El Dareer 1982, 42–49; Hanny Lightfoot-Klein, *Prisoners of Ritual: An Odyssey Into Female Genital Circumcision in Africa*, New York: Routledge, 1989.

55. ^ Asma El Dareer, *Woman, Why Do You Weep: Circumcision and its Consequences*, London: Zed Press, 1982, 56–64.

    Also see Rebecca J. Cooke, Bernard M. Dickens, "Special commentary on the issue of reinfibulation", *International Journal of Gynaecology and Obstetrics*, 109(2), May 2010, 97–99. doi:10.1016/j.ijgo.2010.01.004 PMID 20178881

    Gamal I. Serour, "The issue of reinfibulation", *International Journal of Gynaecology and Obstetrics*, 109(2), May 2010, 93–96. doi:10.1016/j.ijgo.2010.01.001 PMID 20138274

    Olukunmi O. Balogun, et al., "Interventions for improving outcomes for pregnant women who have experienced genital cutting", *Cochrane Database of Systematic Reviews*, 2, 2013. doi:10.1002/14651858.CD009872.pub2 PMID 23450610

56. ^ WHO 2008, 24.
57. ^ UNICEF 2013, 7.
58. ^ WHO 2008, 27.
59. ^ "Female Genital Mutilation: A Teachers' Guide", World Health Organization, 2005.
60. ^ For the countries in which labia stretching is found (Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Tanzania, Uganda and Zimbabwe), see Nkiru Lessons from Colonial Campaigns to Ban Excision in Meru, Kenya" in Shell-Duncan and Hernlund, 2000, 132.

    For *irua*, Jomo Kenyatta, *Facing Mount Kenya*, New York: Vintage Books, 1962 [1938], 129; for *irugu* being outcasts, Kenyatta, 127, and Zabus 2008, 48–49.

178. ^ Kenyatta 1962 [1938], 127–130.
179. ^ Klaus Fiedler, *Christianity and African Culture*, Leiden: Brill, 1996, 75.
180. ^ Boddy 2007, 241–245; Ronald Hyam, *Empire and Sexuality: The British Experience*, Manchester: Manchester University Press, 1990; Murray 1976, 92–104.
181. ^ Thomas 2000, 132; for the "sexual mutilation of women," Karanja 2009, 93, n. 631.

    Also see Robert Strayer, Jocelyn Murray, "The CMS and Female Circumcision", in Robert Strayer (ed.), *The Making of Missionary Communities in East Africa*, New York: State University of New York Press, 1978, 139ff.

182. ^ Boddy 2007, 241, 244; Dana Lee Robert, *American Women in Mission: A Social History of Their Thought and Practice*, Macon: Mercer University Press, 1996, 230.
183. ^ Thomas 2000, 129–131 (131 for the girls as "central actors"); Lynn Thomas, *Politics of the Womb: Women, Reproduction, and the State in Kenya*, Berkeley: University of California Press, 2003, 89–91.

    Also see Lynn M. Thomas, "'Ngaitana (I will circumcise myself)': The Gender and Generational Politics of the 1956 Ban on Clitoridectomy in Meru, Kenya"], *Gender and History*, 8(3), November 1996, 338–363. doi:10.1111/j.1468-0424.1996.tb00062.x

184. ^ UNICEF 2013, 10, calls the Egyptian Doctors' Society opposition the "first known campaign" against FGM; for independence, Boddy 2007, 147.
185. ^ Boddy 2007, 202, 299.
186. ^ UNICEF 2013, 2, 9.
187. ^ Elizabeth Heger Boyle, *Female Genital Cutting: Cultural Conflict in the Global Community*, Baltimore: Johns Hopkins University Press, 2002, 92, 103.
188. ^ Boyle 2002, 41.
189. ^ Bagnol and Mariano 2011, 281.
190. ^ Gruenbaum 2001, 22.

    Homa Khaleeli, "Nawal El Saadawi: Egypt's radical feminist", *The Guardian*, 15 April 2010.

191. ^ Nawal El Saadawi, *The Hidden Face of Eve*, London: Zed Books, 2007 [1980], 14.
192. ^ Raqiya D. Abdalla, "'My Grandmother Called it the Three Feminine Sorrows': The Struggle of Women Against Female Circumcision in Somalia," in Abusharaf 2007, 201; Alexandra Topping, "Somaliland's leading lady for women's rights: 'It is time for men to step up'", *The Guardian*, 23 June 2014.
193. ^ Yoder and Khan 2008, 2.
194. ^ Mackie 2003, 139.
195. ^ Boyle 2002, 47; Bagnol and Mariano 2011, 281.
196. ^ Shahira Ahmed, "Babiker Badri Scientific Association for Women's Studies", in Abusharaf 2007, 176–180.
197. ^ Ahmed 2007, 180.
198. ^ Anika Rahman and Nahid Toubia, *Female Genital Mutilation: A Guide to Laws and Policies Worldwide*, New York: Zed Books, 2000, 10–11; for Vienna, UNICEF 2013, 8.
199. ^ Emma Bonino, "A brutal custom: Join forces to banish

Nzegwu, "'Osunality' (or African eroticism)" in Sylvia Tamale (ed.), *African Sexualities: A Reader*, Cape Town: Fahamu/Pambazuka, 2011, 262.

For the rest, Brigitte Bagnol and Esmeralda Mariano, "Politics of Naming Sexual Practices", in Tamale 2011, 272–276 (272 for Uganda).

61. ^ WHO 2008, 27.
62. ^ Mairo Usman Mandara, "Female genital cutting in Nigeria: View of Nigerian Doctors on the Medicalization Debate", in Bettina Shell-Duncan and Ylva Hernlund (eds.), *Female "Circumcision" in Africa: Culture Controversy and Change*, Boulder: Lynne Rienner Publishers, 2000, 98, 100; for fistulae, 102.

    Mairo Usman Mandara, "Female genital mutilation in Nigeria", *International Journal of Gynecology & Obstetrics*, 84(3), 291–298. doi:10.1016/j.ijgo.2003.06.001 PMID 15001386
63. ^ Stephanie Sinclair, "Inside a Female-Circumcision Ceremony", *The New York Times Magazine*, April 2006, slideshow of images from Indonesia (article).
64. ^ Rigmor C. Berg, et al., "Effects of female genital cutting on physical health outcomes: a systematic review and meta-analysis", *BMJ Open*, 4(11), 2014: e006316. PMID 25416059 doi:10.1136/bmjopen-2014-006316
65. ^ *a b* Dan Reisel, Sarah M. Creighton, "Long term health consequences of Female Genital Mutilation (FGM)", *Maturitas*, 80(1), January 2015 (48–51), 49. doi:10.1016/j.maturitas.2014.10.009 PMID 25466303
66. ^ Rigmor C. Berg, Vigdis Underland, "Immediate health consequences of female genital mutilation/cutting (FGM/C)", *Kunnskapssenteret* (Norwegian Knowledge Centre for the Health Services), 2014, 4–5 (full text).
67. ^ Christos Iavazzo, Thalia A. Sardi, Ioannis D. Gkegkes, "Female genital mutilation and infections: a systematic review of the clinical evidence", *Archives of Gynecology and Obstetrics*, 287(6), June 2013, 1137–1149. doi:10.1007/s00404-012-2708-5 PMID 23315098
68. ^ UNICEF 2005, 16.
69. ^ *a b c d* Reisel and Creighton 2015, 50.
70. ^ Amish J. Dave, Aisha Sethi, Aldo Morrone, "Female Genital Mutilation: What Every American Dermatologist Needs to Know", *Dermatologic Clinics*, 29(1), January 2011, 103–109. doi:10.1016/j.det.2010.09.002 PMID 21095534
71. ^ Hamid Rushwan, "Female genital mutilation: A tragedy for women's reproductive health", *African Journal of Urology*, 19(3), September 2013, 130–133. doi:10.1016/j.afju.2013.03.002
72. ^ El Dareer 1982, 37. Also see Asma El Dareer, "Preliminary report on a study on prevalence and epidemiology of female circumcision in Sudan today", WHO seminar, Khartoum, 10–15 February 1979; Asma el Dareer, "Female circumcision and its consequences for mother and child", Yaounde, 12–15 December 1979, cited in Rushwan 2013.
73. ^ *a b c* Mumtaz Rashid, Mohammed H. Rashid, "Obstetric management of women with female genital mutilation", *The Obstetrician and Gynaecologist*, 9(2), April 2007, 95–101. doi:10.1576/toag.9.2.095.27310
74. ^ Emily Banks, et al., "Female genital mutilation and obstetric outcome: WHO collaborative prospective study in six African countries", *The Lancet*, 367(9525), 3 June

    the mutilation of women", *The New York Times*, 15 September 2004; Maputo Protocol, 7–8.
200. ^ *a b c* UNICEF 2013, 8.
201. ^ UNICEF 2013, 8–9.
202. ^ *Joint Programme on Female Genital Mutilation/Cutting: Accelerating Change*, New York: UNFPA–UNICEF, Annual Report 2012.
203. ^ "No time to lose: New UNICEF data show need for urgent action on female genital mutilation and child marriage", UNICEF, 22 July 2014.
204. ^ "48/104. Declaration on the Elimination of Violence against Women", United Nations General Assembly, 20 December 1993.
205. ^ Charlotte Feldman-Jacobs, "Commemorating International Day of Zero Tolerance to Female Genital Mutilation", Population Reference Bureau, February 2009.
206. ^ UNICEF 2013, 15; Francesca Moneti, David Parker, *The Dynamics of Social Change*, Florence: UNICEF Innocenti Research Centre, October 2010, 6.
207. ^ UNICEF 2005.
208. ^ *a b UNFPA-UNICEF Joint Evaluation of the UNFPA-UNICEF Joint Programme on Female Genital Mutilation/Cutting (FGM/C): Accelerating Change*, New York: United Nations Population Fund, 2013 (for goals not met: "Executive Summary", 2).
209. ^ WHO 2008, 8.
210. ^ "67/146. Intensifying global efforts for the elimination of female genital mutilations", United Nations General Assembly, adopted 20 December 2012.

    Emma Bonino, "Banning Female Genital Mutilation", *The New York Times*, 19 December 2012.
211. ^ Australia: "Review of Australia's Female Genital Mutilation Legal Framework", Attorney General's Department, Government of Australia.

    New Zealand: "Section 204A – Female genital mutilation – Crimes Act 1961", New Zealand Parliamentary Counsel Office.

    Europe: "Eliminating female genital mutilation", European Commission.

    United States: "18 U.S. Code § 116 – Female genital mutilation", Legal Information Institute, Cornell University Law School.

    Canada: Section 268, Criminal Code.
212. ^ *a b* Birgitta Essén, Sara Johnsdotter, "Female Genital Mutilation in the West: Traditional Circumcision versus Genital Cosmetic Surgery", *Acta Obstetricia Gynecologica Scandinavica*, 83(7), July 2004, 611–613. PMID 15225183
213. ^ Boyle 2002, 97.
214. ^ Clyde H. Farnsworth, "Canada Gives Somali Mother Refugee Status", *The New York Times*, 21 July 1994.
215. ^ Section 268, Criminal Code of Canada.
216. ^ For a source covering up to February 2015: Corinne Packer, et al., "Canada's response to female genital mutilation: Are we failing our girls?", *Canadian Medical Association Journal*, 187(6), 17 February 2015, E188–189. doi:10.1503/cmaj.141215 PMC 4387059
217. ^ *a b* "Female Genital Mutilation/Cutting in the United States: Updated Estimates of Women and Girls at Risk, 2012", Centers for Disease Control and Prevention, *Public Health Reports*, 131, March–April 2016.

2006, 1835–1841. doi:10.1016/S0140-6736(06)68805 PMID 16753486
75. ^ "New study shows female genital mutilation exposes women and babies to significant risk at childbirth", World Health Organization, 2 June 2006.
76. ^ Rigmor C. Berg, Eva Denison, "A Tradition in Transition: Factors Perpetuating and Hindering the Continuance of Female Genital Mutilation/Cutting (FGM/C) Summarized in a Systematic Review", *Health Care for Women International*, 34(10), March 2013. doi:10.1080/07399332.2012.721417. PMID 23489149 PMC 3783896

    For a summary of Berg and Denison: Reisel and Creighton 2015, 51.
77. ^ Also see S. Sibiani and A. A. Rouzi, "Sexual function in women with female genital mutilation", *Fertility and Sterility*, 93(3), September 2008, 722–724.doi:10.1016/j.fertnstert.2008.10.035 PMID 19028385
78. ^ "New statistical report on female genital mutilation shows harmful practice is a global concern"; *Female Genital Mutilation/Cutting: A global concern*, New York: UNICEF, February 2016.
79. ^ *a b c* "Indonesia", UNICEF, February 2015.
80. ^ Anggi M. Lubis and Hans Nicholas Jong, "FGM in Indonesia hits alarming level", *The Jakarta Post*, 6 February 2016.
81. ^ Yoder 2013, 193.
82. ^ "DHS overview", Demographic and Health Surveys; "Questionnaires and Indicator List", Multiple Indicator Cluster Surveys, UNICEF.
83. ^ Yoder, Wang and Johansen, 2013, 191; Dara Carr, *Female genital cutting: Findings from the Demographic and Health Surveys program*, Calverton, MD: Macro International Inc., 1997.
84. ^ Gerry Mackie, John LeJeune, "Social Dynamics of Abandonment of Harmful Practices: A New Look at the Theory", Innocenti Working Paper No. 2008-XXX, UNICEF Innocenti Research Centre, 2008, 5.
85. ^ *Female Genital Mutilation/Cutting: What Might the Future Hold?*, New York: UNICEF, 22 July 2014 (hereinafter UNICEF 2014), 89–90.
86. ^ UNICEF 2013, 2.
87. ^ UNICEF 2013, 23.
88. ^ For the Dawoodi Bohra: Diane Cole, "UNICEF Estimate Of Female Genital Mutilation Up By 70 Million", NPR, 8 February 2016.

    For Rahmah, Jordan: Dana Charkasi, "Female circumcision still haunts Jordanian tribe in southern Jordan", *ArabNews West*, 2012.
89. ^ UNICEF 2013, 4.
90. ^ UNICEF 2013, 23.
91. ^ UNICEF 2013, 25, 100; Yoder 2013, 196.
92. ^ UNICEF 2016, 1.
93. ^ Yoder 2013, 194; UNICEF 2013, 25.
94. ^ UNICEF 2014, 2.
95. ^ UNICEF 2014, 3.
96. ^ For rural areas, UNICEF 2013, 28; for wealth, 40; for education, 41.
97. ^ Gerry Mackie, "Female Genital Cutting: The Beginning of the End", in Bettina Shell-Duncan and Ylva Hernlund (eds.), *Female "Circumcision" in Africa: Culture Controversy and Change*, Boulder: Lynne Rienner
218. ^ Julie Turkewitz, "Effects of Ancient Custom Present New Challenge to U.S. Doctors: Genital Cutting Cases Seen More as Immigration Rises", *The New York Times*, 6 February 2015.
219. ^ Wanda K. Jones, et al., "Female Genital Mutilation/Female Circumcision: Who Is at Risk in the U.S.?", *Public Health Reports*, 112(5), September-October 1997 (368–377), 372. PMID 9323387 PMC 1381943
220. ^ Patricia Dysart Rudloff, "In Re: Oluloro: Risk of female genital mutilation as 'extreme hardship' in immigration proceedings", 26 *Saint Mary's Law Journal*, 877, 1995.
221. ^ Celia W. Dugger, "June 9–15; Asylum From Mutilation",*The New York Times*, 16 June 1996.

    "In re Fauziya KASINGA, file A73 476 695", U.S. Department of Justice, Executive Office for Immigration Review, decided 13 June 1996.
222. ^ "Female Genital Mutilation", *Pediatrics*, 102(1), 1 July 1998, 153–156. PMID 9651425

    Withdrawn policy: "Ritual Genital Cutting of Female Minors", *Pediatrics*, 25(5), 1 May 2010, 1088–1093. PMID 20530070 doi:10.1542/peds.2010-0187
223. ^ Pam Belluck, "Group Backs Ritual 'Nick' as Female Circumcision Option", *The New York Times*, 6 May 2010.

    Susan Bewley, Sarah Creighton and Comfort Momoh, "Female genital mutilation: Paediatricians should resist its medicalisation"], *British Medical Journal*, 340(7760), 19 June 2010, 1317–1318. JSTOR 20734534
224. ^ "Man gets 10-year sentence for circumcision of 2-year-old daughter", Associated Press, 1 November 2006.
225. ^ Nedra Pickler, "Obama To Rename Africa Young Leaders Program For Nelson Mandela", *Huffington Post*, 28 July 2014.
226. ^ Douglas Martin, "Efua Dorkenoo Dies at 65; Key Foe of Genital Cutting in Africa, Middle East", *The New York Times*, 27 October 2014.

    Efua Dorkenoo, *Cutting the Rose: Female Genital Mutilation, the Practice and its Prevention*, London: Minority Rights Group, 1994.
227. ^ Yoder 2013, 195.
228. ^ *a b c* Renée Kool and Sohail Wahedi, "Criminal Enforcement in the Area of Female Genital Mutilation in France, England and the Netherlands: A Comparative Law Perspective", *International Law Research*, 3(1), 2014, 3–5. doi:10.5539/ilr.v3n1p1
229. ^ Colette Gallard, "Female genital mutilation in France", *British Medical Journal*, 310, 17 June 1995, 1592. PMID 7787655 PMC 2549952

    That one girl was three months old, Megan Rowling "France reduces genital cutting with prevention, prosecutions – lawyer", Thomson Reuters Foundation, 27 September 2012.
230. ^ Jana Meredyth Talton, "Asylum for Genital-Mutilation Fugitives: Building a Precedent", Ms., 17.
231. ^ *a b* Megan Rowling "France reduces genital cutting with prevention, prosecutions – lawyer", Thomson Reuters Foundation, 27 September 2012.
232. ^ For 1982, Gallard 1995, 1593; for 1993, Farnsworth (*New York Times*) 1994.
233. ^ David Gollaher, *Circumcision: A History of the World's Most Controversial Surgery*, New York: Basic Books, 2000, 189.

Publishers, 2000, 275.
98. ^ a b UNICEF 2013, 50.
99. ^ a b UNICEF 2013, 47, 183.
100. ^ UNICEF 2005, 6.
101. ^ UNICEF 2013, 51.
102. ^ UNICEF 2013, 28–37.
103. ^ UNICEF 2013. For eight percent in Iraq, 27, box 4.4, group 5; for the regions in Iraq, 31, map 4.6).

Also see Berivan A. Yasin, et al., "Female genital mutilation among Iraqi Kurdish women: a cross-sectional study from Erbil city", *BMC Public Health*, 13, September 2013. doi:10.1186/1471-2458-13-809 PMID 24010850 PMC 3844478
104. ^ Yoder 2013, 196, 198.
105. ^ "Guinea" (2012), UNICEF statistical profile, July 2014, 2/4.
106. ^ Chad: UNICEF 2013, 35–36; Nigeria: T. C. Okeke, et al., "An Overview of Female Genital Mutilation in Nigeria", *Annals of Medical Health Sciences Research*, 2(1), Jan–June 2012, 70–73. doi:10.4103/2141-9248.96942 PMID 23209995 PMC 3507121 FGM is practised in Nigeria by the Yoruba, Hausa, Ibo, Ijaw and Kanuri people.
107. ^ UNICEF 2013, 134–135.
108. ^ UNICEF 2013, 47, table 5.2; Yoder, Wang and Johansen, 2013, 189.
109. ^ Gerry Mackie, "Female Genital Cutting: A Harmless Practice?", *Medical Anthropology Quarterly*, 17(2), 2003 (135–158), 148.
110. ^ Salah M. Rasheedemail, Ahmed H. Abd-Ellah, Fouad M. Yousef, "Female genital mutilation in Upper Egypt in the new millennium", *International Journal of Gynecology and Obstetrics*, 114(1), July 2011, 47–50. doi:10.1016/j.ijgo.2011.02.003 PMID 21513937
111. ^ Okeke et al. 2012, 70–73.
112. ^ Yoder 2008, 13–14.
113. ^ UNICEF 2013, 47. For the years:

UNICEF FGM statistical profiles: "Djibouti", December 2013: "Source for all charts on this page: MICS 2006"; "Eritrea", July 2014, 2/4: "Source: DHS 2002"; "Somalia", December 2013, 2/4: "Source for all charts on this page: MICS 2006."
114. ^ UNICEF 2013, 114.
115. ^ "Nigeria", UNICEF, July 2014.
116. ^ "Stephanie Welsh" Archived 7 October 2015 at the Wayback Machine., 1996 Pulitzer Prize winners
117. ^ Abdalla 2007, 187.
118. ^ Olga Khazan, "Why Some Women Choose to Get Circumcised", *The Atlantic*, 8 April 2015 (interview with Bettina Shell-Duncan).
119. ^ Gerry Mackie, "Ending Footbinding and Infibulation: A Convention Account", *American Sociological Review*, 61(6), December 1996 (999–1017), 999–1000.
120. ^ Rogaia Mustafa Abusharaf, "Introduction: The Custom in Question," in Abusharaf 2007, 8; El Guindi 2007, 36–37.
121. ^ a b Fuambai Ahmadu, "Rites and Wrongs: An Insider/Outsider Reflects on Power and Excision," in Shell-Duncan and Hernlund 2000, 284–285.
122. ^ Janice Boddy, *Civilizing Women: British Crusades in Colonial Sudan*, Princeton: Princeton University Press, 2007, 112.
123. ^ a b c Ellen Gruenbaum, "Socio-Cultural Dynamics of
234. ^ Alison Macfarlane and Efua Dorkenoo, "Female Genital Mutilation in England and Wales", City University of London and Equality Now, 21 July 2014, 3.
235. ^ For an early article on FGM in the UK: J. A. Black, G. D. Debelle, "Female genital mutilation in Britain", *British Medical Journal*, 310, 17 June 1995. doi:10.1136/bmj.310.6994.1590 PMID 7787654 PMC 2549951
236. ^ Kool and Wahedi 2014, 5–7; "Prohibition of Female Circumcision Act 1985", legislation.gov.uk.
237. ^ "Female Genital Mutilation Act 2003" and "Prohibition of Female Genital Mutilation (Scotland) Act 2005", legislation.gov.uk.
238. ^ "Female Genital Mutilation Act 2003", legislation.gov.uk, and "Female Genital Mutilation Act 2003" (legal guidance), Crown Prosecution Service: "The Act refers to 'girls', though it also applies to women."
239. ^ "Concluding observations on the seventh periodic report of the United Kingdom of Great Britain and Northern Ireland", United Nations Convention on the Elimination of All Forms of Discrimination against Women, 26 July 2013, 6, paras 36, 37.
240. ^ Sandra Laville, "Doctor found not guilty of FGM on patient at London hospital", *The Guardian*, 4 February 2015.
241. ^ Eric K. Silverman, "Anthropology and Circumcision," *Annual Review of Anthropology*, 33, 2004 (419–445), 420, 427. JSTOR 25064860
242. ^ Nnaemeka 2005, 34.
243. ^ Vicky Kirby, "Out of Africa: 'Our Bodies Ourselves?'" in Obioma Nnaemeka (ed.), *Female Circumcision and the Politics of Knowledge: African Women in Imperialist Discourses*, Westport: Praeger, 2005, 83.
244. ^ Obioma Nnaemeka, "African Women, Colonial Discourses, and Imperialist Interventions: Female Circumcision as Impetus," in Nnaemeka 2005, 33.
245. ^ a b Tamale 2011, 19–20.
246. ^ Christine J. Walley, "Searching for 'Voices': Feminism, Anthropology, and the Global Over Female Genital Operations" in James and Robertson 2002, 18, 34, and for false consciousness, 43; Robertson 2002, 60.
247. ^ Bagnol and Mariano 2011, 281.
248. ^ Chima Korieh, "'Other' Bodies: Western Feminism, Race and Representation in Female Circumcision Discourse," in Nnaemeka 2005, 121–122.

For the photographs, "Stephanie Welsh" Archived 7 October 2015 at the Wayback Machine., 1996 Pulitzer Prize winners; for other examples, Nnaemeka 2005, 30–33.
249. ^ Nnaemeka 2005, 38–39.
250. ^ a b Sara Johnsdotter and Birgitta Essén, "Genitals and ethnicity: the politics of genital modifications", *Reproductive Health Matters*, 18(35), 2010, 29–37. doi:10.1016/S0968-8080(10)35495-4 PMID 20541081
251. ^ Marge Berer, "It's female genital mutilation and should be prosecuted", *British Medical Journal*, 334(7608), 30 June 2007, 1335. doi:10.1136/bmj.39252.646042.3A PMID 17599983 PMC 1906631
252. ^ Ronán M. Conroy, "Female genital mutilation: whose problem, whose solution?", *British Medical Journal*, 333(7559), 15 July 2006. PMID 16840444 PMC 1502236
253. ^ El Guindi 2007, 33.
254. ^ Lora Wildenthal, *The Language of Human Rights in*

Female Genital Cutting: Research Findings, Gaps, and Directions," *Culture, Health & Sexuality*, 7(5), September–October 2005, 429–441. JSTOR 4005473

124. ^ Gruenbaum 2005, 437; Gruenbaum 2001, 140.

Janice Boddy, *Wombs and Alien Spirits: Women, Men, and the Zar Cult in Northern Sudan*, Madison: University of Wisconsin Press, 1989, 52.

125. ^ Bagnol and Mariano 2011, 277–281.
126. ^ WHO 2008, 27–28.
127. ^ UNICEF 2013, 67.
128. ^ Asma El Dareer, "Attitudes of Sudanese People to the Practice of Female Circumcision", *International Journal of Epidemiology*, 12(2), 1983 (138–144), 140.

*West Germany*, Philadelphia: University of Pennsylvania Press, 2012, 148.

255. ^ Obermeyer 1999, 94.
256. ^ Rahim (Tahrir Institute) 2014.
257. ^ WHO 2008, 28.
258. ^ Nussbaum 1999, 123–124.

Also see Yael Tamir, "Hands Off Clitoridectomy", *Boston Review*, Summer 1996; Martha Nussbaum, "Double Moral Standards?", *Boston Review*, October/November 1996.

259. ^ Nancy Ehrenreich, Mark Barr, "Intersex Surgery, Female Genital Cutting, and the Selective Condemnation of 'Cultural Practices'", *Harvard Civil Rights-Civil Liberties Law Review*, 40(1), 2005 (71–140), 74–75.

# Further reading

- FORWARD, London.
- "Circumcision, female", The Kinsey Institute (bibliography 1960s–1980s).
- FGM archive, *The Guardian*.
- Khazan, Olga. "Why Some Women Choose to Get Circumcised", *The Atlantic*, 8 April 2015 (interview with Bettina Shell-Duncan).
- David M. Westley, "Female circumcision and infibulation in Africa", *Electronic Journal of Africana Bibliography*, 4, 1999 (bibliography up to 1997).

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### Personal stories

- Nawal El Saadawi, *Woman at Point Zero*, London: Zed Books, 1975.
- Waris Dirie and Cathleen Miller, *Desert Flower*, New York: William Morrow, 1998.
- Fauziya Kassindja and Layli Miller-Muro, *Do They Hear You When You Cry*, New York: Delacorte Press, 1998.
- Ayaan Hirsi Ali, *Infidel: My Life*, New York: Simon & Schuster, 2007.

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| **People** | Ayaan Hirsi Ali · Waris Dirie · Efua Dorkenoo · Fran Hosken · Gerry Mackie · Molly Melching · Layli Miller-Muro · Comfort Momoh · Nawal El Saadawi · Marion Scott Stevenson · Hulda Stumpf · Nahid Toubia · Alice Walker · |
| **Opposition** | Equality Now · FORWARD · Inter-African Committee on Traditional Practices Affecting the Health of Women and Children · International Day of Zero Tolerance to Female Genital Mutilation · RAINBO · Tostan · Tahirih Justice Center · |
| **Books and films** | *Desert Flower* (book) · *Desert Flower* (film) · Moolaadé · *Possessing the Secret of Joy* · *Woman at Point Zero* · |
| **Legislation** | Matter of Kasinga · Prohibition of Female Circumcision Act 1985 · Female Genital Mutilation Act 2003 · 2005 (Scotland) Act · |
| **Categories** | Female genital mutilation · Activists against female genital mutilation · |

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| | Sexual assault (Campus sexual assault · Mass sexual assault · · Rape (and pregnancy · laws · · |

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| **Sexual assault, rape** | Types of rape (by deception · corrective · date · gang · genocidal · in war · marital · prison · statutory · · Sexual slavery · Sexual violence · |
| **Related topics** | Prosecution of gender-targeted crimes · Serial rapist · |
| | **Category** |

| v · t · e · **Female genital surgical and other procedures (gynecological surgery) (ICD-9-CM V3 65–71, ICD-10-PCS 0U)** | | |
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| **Adnexa** | **Ovaries** | Oophorectomy · Salpingoophorectomy · |
| | **Fallopian tubes** | Falloposcopy · Salpingectomy · Tubal ligation · Essure · Tubal reversal · |
| **Uterus** | *general:* | Genitoplasty · Hysterectomy · Hysterotomy · Pelvic exenteration · Uterine artery embolization · Transplantation · |
| | *uterine cavity:* | Hysteroscopy · Vacuum aspiration · |
| | *endometrium:* | Endometrial biopsy · Endometrial ablation · |
| | *myometrium:* | Uterine myomectomy · |
| | *cervix:* | Colposcopy · Cervical conization (LEEP · · Cervical cerclage · Cervical screening (pap test) · Cervicectomy · |
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| **Vulva** | | Vulvectomy · **Female genital mutilation** · Labiaplasty · Clitoral hood reduction · Vestibulectomy · |
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| v · t · e · **Feminism** | | |
|---|---|---|
| | | Women · Girls · Femininity · |
| **History** | Social | Women's history · Feminist history · Timeline of women's rights (other than voting) · |
| | Suffrage | Women's suffrage · Timeline (Majority-Muslim countries · In the United States · · Australia · Canada · Japan · Kuwait · New Zealand · Sweden · Switzerland · United Kingdom (Wales · · United States (In states (Utah · · · |
| | General | First-wave · Second-wave · Third-wave · Fourth-wave · Timeline · |
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| **Reproductive &Sexual health** | **Reproductive health** | **Reproductive tract** | External female genitalia (Clitoris (Clitoral hood · · Labia minora · Labia majora · · Vagina · Cervix · Uterus · Fallopian tube · Ovary · Reproductive system disease · |
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# Fetal alcohol spectrum disorder

From Wikipedia, the free encyclopedia

*"FASD" redirects here. For other uses, see FASD (disambiguation).*

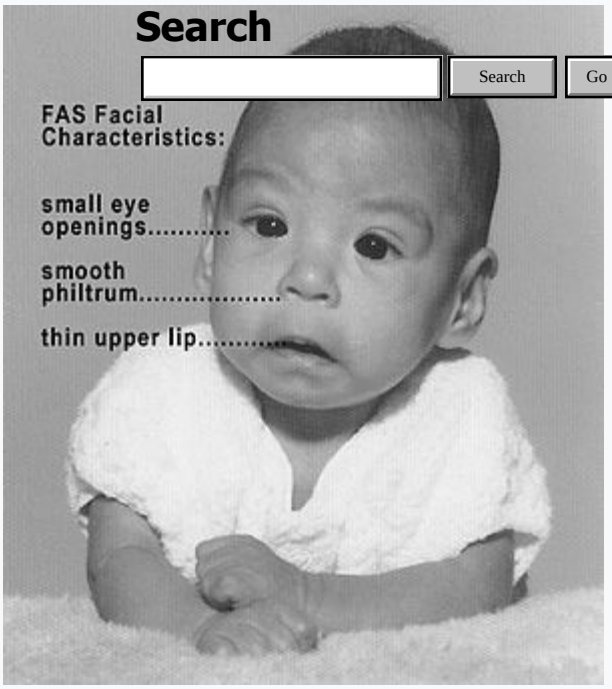
**Fetal alcohol spectrum disorders** (**FASDs**) are a group of conditions that can occur in a person whose mother drank alcohol during pregnancy.[1] Problems may include an abnormal appearance, short height, low body weight, small head size, poor coordination, low intelligence, behavior problems, and problems with hearing or seeing.[1][2] Those affected are more likely to have trouble in school, legal problems, participate in high-risk behaviors, and have trouble with alcohol or other drugs.[3] The most severe form of the condition is known as **fetal alcohol syndrome** (**FAS**).[1] Other types include partial fetal alcohol syndrome (pFAS), alcohol-related neurodevelopmental disorder (ARND) and alcohol-related birth defects (ARBD).[1][4]

Fetal alcohol spectrum disorders are caused by drinking alcohol during pregnancy.[1] Surveys from the United States have found about 10% of pregnant women have drunk alcohol in the last month, and 20% to 30% drank at some point during the pregnancy.[5] About 4.7% of North American women who are pregnant have alcoholism.[6] The risk of problems depends on the amount consumed and the frequency of consumption as well as when during pregnancy the alcohol is consumed.[5] Other risk factors include an older mother, smoking, and poor diet.[5] There is no known safe amount or safe time to drink during pregnancy.[1][7] While drinking small amounts of alcohol does not cause abnormalities in the face, it may cause behavioral issues.[6] Alcohol crosses the blood brain barrier and both directly and indirectly affects a developing baby.[8] Diagnosis is based on signs and symptoms in the person.[1]

Fetal alcohol spectrum disorders are preventable by avoiding alcohol.[9] For this reason, medical authorities recommend no alcohol during pregnancy or while trying to become pregnant.[10][11][12] While the condition is permanent, treatment can improve outcomes.[1][13] Interventions may include parent-child interaction therapy, efforts to modify child behavior, and possibly medications.[14]

FASD is estimated to affect between 2% and 5% of people in the United States and Western Europe.[15] FAS is believed to occur in between 0.2 and 9 per 1000 live births in the United States.[15] In South Africa,[4]

**Fetal alcohol spectrum disorders**




Baby with fetal alcohol syndrome.

| Classification and external resources | |
|---|---|
| **Specialty** | Pediatrics, toxicology |
| **ICD-10** | Q86.0 |
| **ICD-9-CM** | 760.71 |
| **DiseasesDB** | 32957 |
| **MedlinePlus** | 000911 |
| **eMedicine** | ped/767 |
| **MeSH** | D005310 |

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some populations have rates as high as 9%. The negative effects of alcohol have been described since ancient times.[4] The lifetime cost per child with FAS was $2,000,000 in 2002.[15] The term *fetal alcohol syndrome* was first used in 1973.[4]



**Contents**





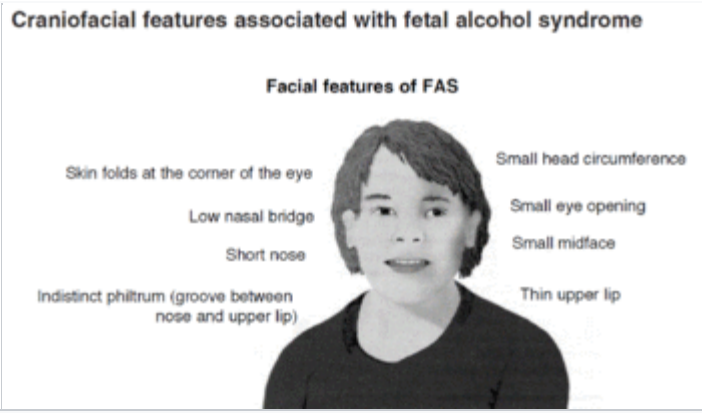
## Types [edit]

FASDs encompass a range of physical and neurodevelopmental problems that can result from prenatal alcohol exposure.[1] The most severe condition is called fetal alcohol syndrome (FAS),[1] which refers to individuals who have a specific set of birth defects and neurodevelopmental disorders characteristic of the diagnosis.[16] Partial fetal alcohol syndrome (pFAS) refers to individuals with a known, or highly suspected, history of prenatal alcohol exposure who have alcohol-related physical and neurodevelopmental deficits that don't meet the full criteria for FAS.[16] The subtypes of pFAS are alcohol-related neurodevelopmental disorder (ARND) and alcohol-related birth defects (ARBD).[16] In addition to FAS, pFAS, ARND, and ARBD, any other conditions believed to be related to prenatal alcohol exposure, such as spontaneous abortion and sudden infant death syndrome (SIDS), are also considered to be on the spectrum of related disorders.[16]

## Signs and symptoms [edit]

The key of FASD can vary between individuals

exposed to alcohol during pregnancy. While consensus exists for the definition and diagnosis of FAS, minor variations among the systems lead to differences in definitions and diagnostic cut-off criteria for other diagnoses across the FASD continuum. The central nervous system damage criteria particularly lack clear consensus. A working knowledge of the key features is helpful in understanding FASD diagnoses and conditions, and each is reviewed with attention to similarities and differences across the four diagnostic systems. More than 400 problems; however, can occur with FASD.[17]



Facial characteristics of a child with FAS

## Growth [edit]

In terms of FASD, growth deficiency is defined as significantly below average height, weight or both due to prenatal alcohol exposure, and can be assessed at any point in the lifespan. Growth measurements must be adjusted for parental height, gestational age (for a premature infant), and other postnatal insults (e.g., poor nutrition), although birth height and weight are the preferred measurements.[18] Deficiencies are documented when height or weight falls at or below the 10th percentile of standardized growth charts appropriate to the population.[19]

Criteria for FASD are least specific in the IOM diagnostic system ("low birth weight..., decelerating weight not due to nutrition..., [or] disproportional low weight to height" p. 4 of executive summary),[11] while the CDC and Canadian guidelines use the 10th percentile as a cut-off to determine growth deficiency.[2][20] The "4-Digit Diagnostic Code" allows for mid-range gradations in growth deficiency (between the 3rd and 10th percentiles) and severe growth deficiency at or below the 3rd percentile.[18] Growth deficiency (at severe, moderate, or mild levels) contributes to diagnoses of FAS and pFAS, but not ARND or static encephalopathy.

Growth deficiency is ranked as follows by the "4-Digit Diagnostic Code":[18]

- Severe: Height and weight at or below the 3rd percentile.
- Moderate: Either height or weight at or below the 3rd percentile, but not both.
- Mild: Either height or weight or both between the 3rd and 10th percentiles.
- None: Height and weight both above the 10th percentile.

In the initial studies that discovered FAS, growth deficiency was a requirement for inclusion in the studies; thus, all the original people with FAS had growth deficiency as an artifact of sampling characteristics used to establish criteria for the syndrome.[*citation needed*] That is, growth deficiency is a key feature of FASD because growth deficiency was a criterion for inclusion in the original study that determined the definition of FAS. This reinforces assertions that growth deficiency and FAS facial features are less critical for understanding the disability's of FASD than the neurobehavioral sequelae to the brain damage.[11]

## Facial features [edit]

Several characteristic craniofacial abnormalities are often visible in individuals with FAS.[21] The presence of FAS facial features indicates brain damage, though brain damage may also exist in their absence. FAS facial features (and most other visible, but non-diagnostic, deformities) are believed to be caused mainly during the 10th and 20th week of gestation.[22]

Refinements in diagnostic criteria since 1975 have yielded three distinctive and diagnostically significant facial features known to result from prenatal alcohol exposure and distinguishes FAS from other disorders with partially overlapping characteristics.[23][24] The three FAS facial features are:

- A smooth philtrum: The divot or groove between the nose and upper lip flattens with increased prenatal alcohol exposure.

Thin vermilion: The upper lip thins with increased prenatal alcohol exposure.
- Small palpebral fissures: Eye width decreases with increased prenatal alcohol exposure.

Measurement of FAS facial features uses criteria developed by the University of Washington. The lip and philtrum are measured by a trained physician with the Lip-Philtrum Guide,[25] a five-point Likert Scale with representative photographs of lip and philtrum combinations ranging from normal (ranked 1) to severe (ranked 5). Palpebral fissure length (PFL) is measured in millimeters with either calipers or a clear ruler and then compared to a PFL growth chart, also developed by the University of Washington.[26]

Ranking FAS facial features is complicated because the three separate facial features can be affected independently by prenatal alcohol. A summary of the criteria follows:[18][27]

- Severe: All three facial features ranked independently as severe (lip ranked at 4 or 5, philtrum ranked at 4 or 5, and PFL two or more standard deviations below average).
- Moderate: Two facial features ranked as severe and one feature ranked as moderate (lip *or* philtrum ranked at 3, *or* PFL between one and two standard deviations below average).
- Mild: A mild ranking of FAS facial features covers a broad range of facial feature combinations:
  - Two facial features ranked severe and one ranked within normal limits,
  - One facial feature ranked severe and two ranked moderate, or
  - One facial feature ranked severe, one ranked moderate and one ranked within normal limits.
- None: All three facial features ranked within normal limits.

## Central nervous system [edit]

Central nervous system (CNS) damage is the primary key feature of any FASD diagnosis. Prenatal alcohol exposure, which is classified as a teratogen, can damage the brain across a continuum of gross to subtle impairments, depending on the amount, timing, and frequency of the exposure as well as genetic predispositions of the fetus and mother.[11][28] While functional abnormalities are the behavioral and cognitive expressions of the FASD disability, CNS damage can be assessed in three areas: structural, neurological, and functional impairments.

All four diagnostic systems allow for assessment of CNS damage in these areas, but criteria vary. The IOM system requires structural or neurological impairment for a diagnosis of FAS, but also allows a "complex pattern" of functional anomalies for diagnosing PFAS and ARND.[11] The "4-Digit Diagnostic Code" and CDC guidelines allow for a positive CNS finding in any of the three areas for any FASD diagnosis, but functional anomalies must measure at two standard deviations or worse in three or more functional domains for a diagnoses of FAS, PFAS, and ARND.[18][20] The "4-Digit Diagnostic Code" also allows for an FASD diagnosis when only two functional domains are measured at two standard deviations or worse.[18] The "4-Digit Diagnostic Code" further elaborates the degree of CNS damage according to four ranks:

- Definite: Structural impairments or neurological impairments for FAS or static encephalopathy.
- Probable: Significant dysfunction of two standard deviations or worse in three or more functional domains.
- Possible: Mild to moderate dysfunction of two standard deviations or worse in one or two functional domains *or* by judgment of the clinical evaluation team that CNS damage cannot be dismissed.
- Unlikely: No evidence of CNS damage.

## Structural [edit]

Structural abnormalities of the brain are observable, physical damage to the brain or brain structures caused by prenatal alcohol exposure. Structural impairments may include microcephaly (small head size) of two or more standard deviations below the average, or other abnormalities in brain structure (e.g., agenesis of the corpus callosum, cerebellar hypoplasia).[11]

Microcephaly is determined by comparing head circumference (often called occipitofrontal circumference, or OFC) to appropriate OFC growth charts.[19] Other structural impairments must be observed through medical imaging techniques by a trained physician. Because imaging procedures are expensive and relatively inaccessible to most people, diagnosis of FAS is not frequently made via structural impairments, except for microcephaly.

Evidence of a CNS structural impairment due to prenatal alcohol exposure will result in a diagnosis of FAS, and neurological and functional impairments are highly likely.[2][11][18][20]

During the first trimester of pregnancy, alcohol interferes with the migration and organization of brain cells, which can create structural deformities or deficits within the brain.[29] During the third trimester, damage can be caused to the hippocampus, which plays a role in memory, learning, emotion, and encoding visual and auditory information, all of which can create neurological and functional CNS impairments as well.[30]

As of 2002, there were 25 reports of autopsies on infants known to have FAS. The first was in 1973, on an infant who died shortly after birth.[31] The examination revealed extensive brain damage, including microcephaly, migration anomalies, callosal dysgenesis, and a massive neuroglial, leptomeningeal heterotopia covering the left hemisphere.[32]

In 1977, Dr. Clarren described a second infant whose mother was a binge drinker. The infant died ten days after birth. The autopsy showed severe hydrocephalus, abnormal neuronal migration, and a small corpus callosum (which connects the two brain hemispheres) and cerebellum.[32] FAS has also been linked to brainstem and cerebellar changes, agenesis of the corpus callosum and anterior commissure, neuronal migration errors, absent olfactory bulbs, meningomyelocele, and porencephaly.[32]

## Neurological [edit]

When structural impairments are not observable or do not exist, neurological impairments are assessed. In the context of FASD, neurological impairments are caused by prenatal alcohol exposure which causes general neurological damage to the central nervous system (CNS), the peripheral nervous system, or the autonomic nervous system. A determination of a neurological problem must be made by a trained physician, and must not be due to a postnatal insult, such as a high fever, concussion, traumatic brain injury, etc.

All four diagnostic systems show virtual agreement on their criteria for CNS damage at the neurological level, and evidence of a CNS neurological impairment due to prenatal alcohol exposure will result in a diagnosis of FAS or pFAS, and functional impairments are highly likely.[2][11][18][20]

Neurological problems are expressed as either hard signs, or diagnosable disorders, such as epilepsy or other seizure disorders, or soft signs. Soft signs are broader, nonspecific neurological impairments, or symptoms, such as impaired fine motor skills, neurosensory hearing loss, poor gait, clumsiness, poor eye-hand coordination. Many soft signs have norm-referenced criteria, while others are determined through clinical judgment. "Clinical judgment" is only as good as the clinician, and soft signs should be assessed by either a pediatric neurologist, a pediatric neuropsychologist, or both.

## Functional [edit]

When structural or neurological impairments are not observed, all four diagnostic systems allow CNS damage due to prenatal alcohol exposure to be assessed in terms of functional impairments.[2][11][18][20] Functional impairments are deficits, problems, delays, or abnormalities due to prenatal alcohol exposure (rather than hereditary causes or postnatal insults) in observable and measurable domains related to daily functioning, often referred to as developmental disabilities. There is no consensus on a specific pattern of functional impairments due to prenatal alcohol exposure[11] and only CDC guidelines label developmental delays as such,[20] so criteria (and FASD diagnoses) vary somewhat across diagnostic systems.

The four diagnostic systems list various CNS domains that can qualify for functional impairment that can determine an FASD diagnosis:

- Evidence of a complex pattern of behavior or cognitive abnormalities inconsistent with developmental level in the following CNS domains – Sufficient for a pFAS or ARND diagnosis using IOM guidelines[11]
  - Learning disabilities, academic achievement, impulse control, social perception, communication, abstraction, math skills, memory, attention, judgment
- Performance at two or more standard deviations on standardized testing in three or more of the following CNS domains – Sufficient for an FAS, pFAS or static encephalopathy diagnosis using 4-Digit Diagnostic Code[18]

    - Executive functioning, memory, cognition, social/adaptive skills, academic achievement, language, motor skills, attention, activity level
- General cognitive deficits (e.g., IQ) at or below the 3rd percentile on standardized testing – Sufficient for an FAS diagnosis using CDC guidelines[20]
- Performance at or below the 16th percentile on standardized testing in three or more of the following CNS domains – Sufficient for an FAS diagnosis using CDC guidelines[20]
    - Cognition, executive functioning, motor functioning, attention and hyperactive problems, social skills, sensory processing disorder, social communication, memory, difficulties responding to common parenting practices
- Performance at two or more standard deviations on standardized testing in three or more of the following CNS domains – Sufficient for an FAS diagnosis using Canadian guidelines
    - Cognition, communication, academic achievement, memory, executive functioning, adaptive behavior, motor skills, social skills, social communication

### Related signs [edit]

Other conditions may commonly co-occur with FAS, stemming from prenatal alcohol exposure. However, these conditions are considered alcohol-related birth defects[11] and not diagnostic criteria for FAS.

- Heart: A heart murmur that frequently disappears by one year of age. Ventricular septal defect most commonly seen, followed by an atrial septal defect.
- Bones: Joint anomalies including abnormal position and function, altered palmar crease patterns, small distal phalanges, and small fifth fingernails.
- Kidneys: Horseshoe, aplastic, dysplastic, or hypoplastic kidneys.
- Eyes: Strabismus, optic nerve hypoplasia[33] (which may cause light sensitivity, decreased visual acuity, or involuntary eye movements).
- Occasional problems: ptosis of the eyelid, microophthalmia, cleft lip with or without a cleft palate, webbed neck, short neck, tetralogy of Fallot, coarctation of the aorta, spina bifida, and hydrocephalus.

## Cause [edit]

Fetal alcohol syndrome usually occurs when a pregnant woman has more than four standard drinks per day.[34] Milder symptoms have been found with two drinks per day during the early part of pregnancy.[34][35] Among those who are alcoholic about a third of children have FAS.[34]

Evidence of harm from less than two drinks per day or 10 drinks per week is not clear.[34][36] While small amounts of alcohol do not cause an abnormal appearance it may cause behavioral issues.[6] There is conflicting evidence regarding whether drinking by fathers before conception can cause FAS.[34]

## Mechanism [edit]

Despite intense research efforts, it has not been possible to identify a single clear-cut mechanism for development of FAS or FASD. On the contrary, clinical and animal studies have identified a broad spectrum of pathways through which maternal alcohol can negatively affect the outcome of a pregnancy. Clear conclusions with universal validity are difficult to draw, since different ethnic groups show considerable genetic polymorphism for the hepatic enzymes responsible for ethanol detoxification.[37]

Genetic examinations have revealed a continuum of long-lasting molecular effects that are not only timing specific but are also dosage specific; with even moderate amounts being able to cause alterations.[38]

A human fetus appears to be at triple risk from maternal alcohol consumption:[39][40]

1. The placenta allows free entry of ethanol and toxic metabolites like acetaldehyde into the fetal compartment. The so-called placental barrier is no barrier with respect to ethanol.
2. The developing fetal nervous system appears particularly sensitive to ethanol toxicity. The latter

impacts negatively on proliferation, differentiation, neuronal migration, axonic outgrowth, integration and fine tuning of the synaptic network. In short, all major processes in the developing central nervous system appear compromised.

3. Fetal tissues are quite different from adult tissues in function and purpose. For example, the main detoxicating organ in adults is the liver, whereas fetal liver is incapable of detoxicating ethanol as the ADH and ALDH enzymes have not yet been brought to expression at this early stage. Up to term, fetal tissues do not have significant capacity for the detoxification of ethanol, and the fetus remains exposed to ethanol in the amniotic fluid for periods far longer than the decay time of ethanol in the maternal circulation.

Generally, fetal tissues have far less antioxidant protection than adult tissues as they express no significant quantities ADH or ALDH, and far less antioxidant enzymes like SOD, glutathion transferases or glutathion peroxidases.[*citation needed*]

## Diagnosis [edit]

Because admission of alcohol use during pregnancy can stigmatize birth mothers, many are reluctant to admit drinking or to provide an accurate report of the quantity they drank. This complicates diagnosis and treatment [20] of the syndrome. As a result, diagnosis of the severity of FASD relies on protocols of observation of the child's physiology and behavior rather than maternal self-reporting. Presently, four FASD diagnostic systems that diagnose FAS and other FASD conditions have been developed in North America:

- The Institute of Medicine's guidelines for FAS, the first system to standardize diagnoses of individuals with prenatal alcohol exposure;[11]
- The University of Washington's "The 4-Digit Diagnostic Code," which ranks the four key features of FASD on a Likert scale of one to four and yields 256 descriptive codes that can be categorized into 22 distinct clinical categories, ranging from FAS to no findings;[18]
- The Centers for Disease Control's "Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis," which established consensus on the diagnosis FAS in the U.S. but deferred addressing other FASD conditions;[20] and
- Canadian guidelines for FASD diagnoses, which established criteria for diagnosing FASD in Canada and harmonized most differences between the IOM and University of Washington's systems.[2]

Each diagnostic system requires that a complete FASD evaluation includes an assessment of the four key features of FASD, described below. A positive finding on all four features is required for a diagnosis of FAS. However, prenatal alcohol exposure and central nervous system damage are the critical elements of the spectrum of FASD, and a positive finding in these two features is sufficient for an FASD diagnosis that is not "full-blown FAS".

While the four diagnostic systems essentially agree on criteria for fetal alcohol syndrome (FAS), there are still differences when full criteria for FAS are not met. This has resulted in differing and evolving nomenclature for other conditions across the spectrum of FASD, which may account for such a wide variety of terminology. Most individuals with deficits resulting from prenatal alcohol exposure do not express all features of FAS and fall into other FASD conditions.[11] The Canadian guidelines recommend the assessment and descriptive approach of the "4-Digit Diagnostic Code" for each key feature of FASD and the terminology of the IOM in diagnostic categories, excepting ARBD.[2]

Thus, other FASD conditions are partial expressions of FAS. However, these other FASD conditions may create disabilities similar to FAS if the key area of central nervous system damage shows clinical deficits in two or more of ten domains of brain functioning. Essentially, even though growth deficiency and/or FAS facial features may be mild or nonexistent in other FASD conditions, yet clinically significant brain damage of the central nervous system is present. In these other FASD conditions, an individual may be at greater risk for adverse outcomes because brain damage is present without associated visual cues of poor growth or the "FAS face" that might ordinarily trigger an FASD evaluation. Such individuals may be misdiagnosed with primary mental health disorders such as ADHD or oppositional defiance disorder without appreciation that brain damage is the underlying cause of these disorders, which requires a different treatment paradigm than typical mental health disorders. While other FASD conditions may not yet be included as an ICD or

DSM-IV-TR diagnosis, they nonetheless pose significant impairment in functional behavior because of underlying brain damage.

## Fetal alcohol syndrome [edit]

The following criteria must be fully met for an FAS diagnosis:[2][11][18][20]

1. Growth deficiency: Prenatal or postnatal height or weight (or both) at or below the 10th percentile[19]
2. FAS facial features: All three FAS facial features present[26]
3. Central nervous system damage: Clinically significant structural neurological, *or* functional impairment
4. Prenatal alcohol exposure: Confirmed or Unknown prenatal alcohol exposure

Fetal alcohol syndrome (FAS) is the first diagnosable condition of FASD that was discovered. FAS is the only expression of FASD that has garnered consensus among experts to become an official ICD-9 and ICD-10 diagnosis. To make this diagnosis or determine any FASD condition, a multi-disciplinary evaluation is necessary to assess each of the four key features for assessment. Generally, a trained physician will determine growth deficiency and FAS facial features. While a qualified physician may also assess central nervous system structural abnormalities and/or neurological problems, usually central nervous system damage is determined through psychological, speech-language, and occupational therapy assessments to ascertain clinically significant impairments in three or more of the Ten Brain Domains.[41] Prenatal alcohol exposure risk may be assessed by a qualified physician, psychologist, social worker, or chemical health counselor. These professionals work together as a team to assess and interpret data of each key feature for assessment and develop an integrative, multi-disciplinary report to diagnose FAS (or other FASD conditions) in an individual.

## Partial FAS [edit]

Partial FAS (pFAS), previously known as atypical FAS in the 1997 edition of the "4-Digit Diagnostic Code". People with pFAS have a confirmed history of prenatal alcohol exposure, but may lack growth deficiency or the complete facial stigmata. Central nervous system damage is present at the same level as FAS. These individuals have the same functional disabilities but "look" less like FAS.

The following criteria must be fully met for a diagnosis of Partial FAS:[2][11][18]

1. Growth deficiency: Growth or height may range from normal to deficient[19]
2. FAS facial features: Two or three FAS facial features present[26]
3. Central nervous system damage: Clinically significant structural, neurological, *or* functional impairment in three or more of the Ten Brain Domains[41]
4. Prenatal alcohol exposure: Confirmed prenatal alcohol exposure

## Fetal alcohol effects [edit]

Fetal alcohol effects (FAE) is a previous term for alcohol-related neurodevelopmental disorder and alcohol-related birth defects.[1] It was initially used in research studies to describe humans and animals in whom teratogenic effects were seen after confirmed prenatal alcohol exposure (or unknown exposure for humans), but without obvious physical anomalies.[42] Smith (1981) described FAE as an "extremely important concept" to highlight the debilitating effects of brain damage, regardless of the growth or facial features.[43] This term has fallen out of favor with clinicians because it was often regarded by the public as a less severe disability than FAS, when in fact its effects can be just as detrimental.[44]

## Alcohol-related neurodevelopmental disorder [edit]

Alcohol-related neurodevelopmental disorder (ARND) was initially suggested by the Institute of Medicine to replace the term FAE and focus on central nervous system damage, rather than growth deficiency or FAS facial features. The Canadian guidelines also use this diagnosis and the same criteria. While the "4-Digit

Diagnostic Code" includes these criteria for three of its diagnostic categories, it refers to this condition as static encephalopathy. The behavioral effects of ARND are not necessarily unique to alcohol however, so use of the term must be within the context of confirmed prenatal alcohol exposure.[45] ARND may be gaining acceptance over the terms FAE and ARBD to describe FASD conditions with central nervous system abnormalities or behavioral or cognitive abnormalities or both due to prenatal alcohol exposure without regard to growth deficiency or FAS facial features.[45][46]

The following criteria must be fully met for a diagnosis of ARND or static encephalopathy:[2][11][18]

1. Growth deficiency: Growth or height may range from normal to minimally deficient[19]
2. FAS facial features: Minimal or no FAS facial features present[26]
3. Central nervous system damage: Clinically significant structural, neurological, *or* functional impairment in three or more of the Ten Brain Domains[41]
4. Prenatal alcohol exposure: Confirmed prenatal alcohol exposure;0

## Alcohol-related birth defects [edit]

Alcohol-related birth defects (ARBD), formerly known as possible fetal alcohol effect (PFAE),[42] was a term proposed as an alternative to FAE and PFAE[47] The IOM presents ARBD as a list of congenital anomalies that are linked to maternal alcohol use but have no key features of FASD.[11] PFAE and ARBD have fallen out of favor because these anomalies are not necessarily specific to maternal alcohol consumption and are not criteria for diagnosis of FASD.[45] The Canadian guidelines recommend that ARBD should not be used as an umbrella term or diagnostic category for FASD.

## Exposure [edit]

Prenatal alcohol exposure is determined by interview of the biological mother or other family members knowledgeable of the mother's alcohol use during the pregnancy (if available), prenatal health records (if available), and review of available birth records, court records (if applicable), chemical dependency treatment records (if applicable), or other reliable sources.

Exposure level is assessed as *confirmed exposure*, *unknown exposure*, and *confirmed absence of exposure* by the IOM, CDC and Canadian diagnostic systems. The "4-Digit Diagnostic Code" further distinguishes confirmed exposure as *High Risk* and *Some Risk*:

- High Risk: Confirmed use of alcohol during pregnancy known to be at high blood alcohol levels (100 mg/dL or greater) delivered at least weekly in early pregnancy.
- Some Risk: Confirmed use of alcohol during pregnancy with use less than High Risk or unknown usage patterns.
- Unknown Risk: Unknown use of alcohol during pregnancy.
- No Risk: Confirmed absence of prenatal alcohol exposure.

## Confirmed exposure [edit]

Amount, frequency, and timing of prenatal alcohol use can dramatically impact the other three key features of FASD. While consensus exists that alcohol is a teratogen, there is no clear consensus as to what level of exposure is toxic.[11] The CDC guidelines are silent on these elements diagnostically. The IOM and Canadian guidelines explore this further, acknowledging the importance of significant alcohol exposure from regular or heavy episodic alcohol consumption in determining, but offer no standard for diagnosis. Canadian guidelines discuss this lack of clarity and parenthetically point out that "heavy alcohol use" is defined by the National Institute on Alcohol Abuse and Alcoholism as five or more drinks per episode on five or more days during a 30-day period.[48]

"The 4-Digit Diagnostic Code" ranking system distinguishes between levels of prenatal alcohol exposure as *high risk* and *some risk*. It operationalizes high risk exposure as a blood alcohol concentration (BAC) greater than 100 mg/dL delivered at least weekly in early pregnancy. This BAC level is typically reached by a 55 kg female drinking six to eight beers in one sitting.[18]

### Unknown exposure [edit]

For many adopted or adults and children in foster care, records or other reliable sources may not be available for review. Reporting alcohol use during pregnancy can also be stigmatizing to birth mothers, especially if alcohol use is ongoing.[20] In these cases, all diagnostic systems use an unknown prenatal alcohol exposure designation. A diagnosis of FAS is still possible with an unknown exposure level if other key features of FASD are present at clinical levels.

### Confirmed absence of exposure [edit]

Confirmed absence of exposure would apply to planned pregnancies in which no alcohol was used or pregnancies of women who do not use alcohol or report no use during the pregnancy. This designation is relatively rare, as most people presenting for an FASD evaluation are at least *suspected* to have had a prenatal alcohol exposure due to presence of other key features of FASD.[18][20]

### Ten brain domains [edit]

A recent effort to standardize assessment of functional CNS damage has been suggested by an experienced FASD diagnostic team in Minnesota. The proposed framework attempts to harmonize IOM, 4-Digit Diagnostic Code, CDC, and Canadian guidelines for measuring CNS damage vis-à-vis FASD evaluations and diagnosis. The standardized approach is referred to as the Ten Brain Domains and encompasses aspects of all four diagnostic systems' recommendations for assessing CNS damage due to prenatal alcohol exposure. The framework provides clear definitions of brain dysfunction, specifies empirical data needed for accurate diagnosis, and defines intervention considerations that address the complex nature of FASD with the intention to avoid common secondary disabilities.[41]

The proposed Ten Brain Domains include:[41]

- Achievement, adaptive behavior, attention, cognition, executive functioning, language, memory, motor skills, multisensory integration or soft neurological problems, social communication[41]

The Fetal Alcohol Diagnostic Program (FADP) uses unpublished Minnesota state criteria of performance at 1.5 or more standard deviations on standardized testing in three or more of the Ten Brain Domains to determine CNS damage. However, the Ten Brain Domains are easily incorporated into any of the four diagnostic systems' CNS damage criteria, as the framework only proposes the domains, rather than the cut-off criteria for FASD.[49]

### Differential diagnosis [edit]

The CDC reviewed nine syndromes that have overlapping features with FAS; however, none of these syndromes include all three FAS facial features, and none are the result of prenatal alcohol exposure:[20]

- Aarskog syndrome
- Williams syndrome
- Noonan syndrome
- Dubowitz syndrome
- Brachman-DeLange syndrome
- Toluene syndrome
- Fetal hydantoin syndrome
- Fetal valproate syndrome
- Maternal PKU fetal effects

## Prevention [edit]

The only certain way to prevent FAS is to avoid drinking alcohol during pregnancy.[45] In the United States, the Surgeon General recommended in 1981, and again in 2005, that women abstain from alcohol use while pregnant or while planning a pregnancy, the latter to avoid damage even in the earliest stages (even

weeks) of a pregnancy, as the woman may not be aware that she has conceived.[10] In the United States, federal legislation has required that warning labels be placed on all alcoholic beverage containers since 1988 under the Alcoholic Beverage Labeling Act.

There is some controversy surrounding the "zero-tolerance" approach taken by many countries when it comes to alcohol consumption during pregnancy. The assertion that moderate drinking causes FAS is said to lack strong evidence and, in fact, the practice of equating a responsible level of drinking with potential harm to the fetus may have negative social, legal, and health impacts.[50] In addition, special care should be taken when considering statistics on this disease, as prevalence and causation is often linked with FASD, which is more common and causes less harm, as opposed to FAS.[51]

## Treatment [edit]

There is no cure for FASD, but treatment is possible. Because CNS damage, symptoms, secondary disabilities, and needs vary widely by individual, there is no one treatment type that works for everyone.

### Medication [edit]

Psychoactive drugs are frequently tried on those with FASD as many FASD symptoms are mistaken for or overlap with other disorders, most notably ADHD.[52]

### Behavioral interventions [edit]

Behavioral interventions are based on the learning theory, which is the basis for many parenting and professional strategies and interventions.[46] Along with ordinary parenting styles, such strategies are frequently used by default for treating those with FAS, as the diagnoses oppositional defiance disorder (ODD), conduct disorder, reactive attachment disorder (RAD) often overlap with FAS (along with ADHD), and these are sometimes thought to benefit from behavioral interventions. Frequently, a person's poor academic achievement results in special education services, which also utilizes principles of learning theory, behavior modification, and outcome-based education.

### Developmental framework [edit]

Many books and handouts on FAS recommend a developmental approach, based on developmental psychology, even though most do not specify it as such and provide little theoretical background. Optimal human development generally occurs in identifiable stages (e.g., Jean Piaget's theory of cognitive development, Erik Erikson's stages of psychosocial development, John Bowlby's attachment framework, and other developmental stage theories). FAS interferes with normal development,[53] which may cause stages to be delayed, skipped, or immaturely developed. Over time, an unaffected child can negotiate the increasing demands of life by progressing through stages of development normally, but not so for a child with FAS.[53]

By knowing what developmental stages and tasks children follow, treatment and interventions for FAS can be tailored to helping a person meet developmental tasks and demands successfully.[53] If a person is delayed in the adaptive behavior domain, for instance, then interventions would be recommended to target specific delays through additional education and practice (e.g., practiced instruction on tying shoelaces), giving reminders, or making accommodations (e.g., using slip-on shoes) to support the desired functioning level. This approach is an advance over behavioral interventions, because it takes the person's developmental context into account while developing interventions.[*citation needed*]

### Advocacy model [edit]

The advocacy model takes the point of view that someone is needed to actively mediate between the environment and the person with FAS.[45] Advocacy activities are conducted by an advocate (for example, a family member, friend, or case manager) and fall into three basic categories. An advocate for FAS: (1)

interprets FAS and the disabilities that arise from it and explains it to the environment in which the person operates, (2) engenders change or accommodation on behalf of the person, and (3) assists the person in developing and reaching attainable goals.[45]

The advocacy model is often recommended, for example, when developing an Individualized Education Program (IEP) for the person's progress at school.[52]

An understanding of the developmental framework would presumably inform and enhance the advocacy model, but advocacy also implies interventions at a systems level as well, such as educating schools, social workers, and so forth on best practices for FAS. However, several organizations devoted to FAS also use the advocacy model at a community practice level as well.[54]

### Public health and policy [edit]

Treating FAS at the public health and public policy level promotes FAS prevention and diversion of public resources to assist those with FAS.[45] It is related to the advocacy model but promoted at a systems level (rather than with the individual or family), such as developing community education and supports, state or province level prevention efforts (e.g., screening for maternal alcohol use during OB/GYN or prenatal medical care visits), or national awareness programs. Several organizations and state agencies in the U.S. are dedicated to this type of intervention.[54]

The US Centers for Disease Control estimates 3 million women in the United States are at risk of having a baby with FASD, and recommended that women of child bearing age should be on birth control or abstain from drinking alcohol as the safest way to avoid this.[55]

## Prognosis [edit]

### Primary disabilities [edit]

The primary disabilities of FAS are the functional difficulties with which the child is born as a result of CNS damage due to prenatal alcohol exposure.[56] Often, primary disabilities are mistaken as *behavior problems*, but the underlying CNS damage is the originating source of a functional difficulty,[57] rather than a mental health condition, which is considered a secondary disability.

The exact mechanisms for functional problems of primary disabilities are not always fully understood, but animal studies have begun to shed light on some correlates between functional problems and brain structures damaged by prenatal alcohol exposure.[45] Representative examples include:

- Learning impairments are associated with impaired dendrites of the hippocampus[58]
- Impaired motor development and functioning are associated with reduced size of the cerebellum[59]
- Hyperactivity is associated with decreased size of the corpus callosum[60]

Functional difficulties may result from CNS damage in more than one domain, but common functional difficulties by domain include:[45][46][53][57] Note that this is not an exhaustive list of difficulties.

- Achievement: Learning disabilities
- Adaptive behavior: Poor impulse control, poor personal boundaries, poor anger management, stubbornness, intrusive behavior, too friendly with strangers, poor daily living skills, developmental delays
- Attention: Attention-Deficit/Hyperactivity Disorder (ADHD), poor attention or concentration, distractible
- Cognition: Intellectual disability, confusion under pressure, poor abstract skills, difficulty distinguishing between fantasy and reality, slower cognitive processing
- Executive functioning: Poor judgment, Information-processing disorder, poor at perceiving patterns, poor cause and effect reasoning, inconsistent at linking words to actions, poor generalization ability
- Language: Expressive or receptive language disorders, grasp parts but not whole concepts, lack understanding of metaphor, idioms, or sarcasm

Memory: Poor short-term memory, inconsistent memory and knowledge base
- Motor skills: Poor handwriting, poor fine motor skills, poor gross motor skills, delayed motor skill development (e.g., riding a bicycle at appropriate age)
- Sensory processing and soft neurological problems: sensory processing disorder, sensory defensiveness, undersensitivity to stimulation
- Social communication: Intrude into conversations, inability to read nonverbal or social cues, "chatty" but without substance

## Secondary disabilities [edit]

The secondary disabilities of FAS are those that arise later in life secondary to CNS damage. These disabilities often emerge over time due to a mismatch between the primary disabilities and environmental expectations; secondary disabilities can be ameliorated with early interventions and appropriate supportive services.[56]

Six main secondary disabilities were identified in a University of Washington research study of 473 subjects diagnosed with FAS, PFAS (partial fetal alcohol syndrome), and ARND (alcohol-related neurodevelopmental disorder):[45][56]

- Mental health problems: Diagnosed with ADHD, Clinical Depression, or other mental illness, experienced by over 90% of the subjects
- Disrupted school experience: Suspended or expelled from school or dropped out of school, experienced by 60% of the subjects (age 12 and older)
- Trouble with the law: Charged or convicted with a crime, experienced by 60% of the subjects (age 12 and older)
- Confinement: For inpatient psychiatric care, inpatient chemical dependency care, or incarcerated for a crime, experienced by about 50% of the subjects (age 12 and older)
- Inappropriate sexual behavior: Sexual advances, sexual touching, or promiscuity, experienced by about 50% of the subjects (age 12 and older)
- Alcohol and drug problems: Abuse or dependency, experienced by 35% of the subjects (age 12 and older)

Two additional secondary disabilities exist for adults:[45][56]

- Dependent living: Group home, living with family or friends, or some sort of assisted living, experienced by 80% of the subjects (age 21 and older)
- Problems with employment: Required ongoing job training or coaching, could not keep a job, unemployed, experienced by 80% of the subjects (age 21 and older)

## Protective factors and strengths [edit]

Eight factors were identified in the same study as universal protective factors that reduced the incidence rate of the secondary disabilities:[45][56]

- Living in a stable and nurturing home for over 73% of life
- Being diagnosed with FAS before age six
- Never having experienced violence
- Remaining in each living situation for at least 2.8 years
- Experiencing a "good quality home" (meeting 10 or more defined qualities) from age 8 to 12 years old
- Having been found eligible for developmental disability (DD) services
- Having basic needs met for at least 13% of life
- Having a diagnosis of FAS (rather than another FASD condition)

Malbin (2002) has identified the following areas of interests and talents as strengths that often stand out for those with FASD and should be utilized, like any strength, in treatment planning:[46]

- Music, playing instruments, composing, singing, art, spelling, reading, computers, mechanics, woodworking, skilled vocations (welding, electrician, etc.), writing, poetry
- Participation in non-impact sport or physical fitness activities

# Epidemiology [edit]

FASD is estimated to affect between 2% and 5% of people in the United States and Western Europe.[15] FAS is believed to occur in between 0.2 and 9 per 1000 live births in the United States.[15] The lifetime cost of an individual with FAS were estimated to be two million USD in 2002.[15]

## Australia [edit]

*See also: Drinking culture in Australia*

FASD among Australian youth is more common in indigenous Australians.[61] The only states that have registered birth defects in Australian youth are Western Australia, New South Wales, Victoria and South Australia.[62] In Australia only 12% of Australian health professionals are aware of the diagnostics and symptoms of FASD.[61] In Western Australia, the rate of births resulting in FASD is 0.02 per 1000 births for non-Indigenous Australians, however among indigenous births the rate is 2.76 per 1000 births.[62] In Victoria, there have been no registered FASD related births for indigenous Australians, but the rate for the general population in Victoria is 0.01-0.03 per 1000 births.[62] There have been no dedicated FASD clinics within Western Australia, but there are also no nationally supported diagnostic criteria anywhere in Australia.[63] Passive surveillance is a prevention technique used within Australia to assist in monitoring and establishing detectable defects during pregnancy and childhood.[62]

# History [edit]

From the 1960s to the 1980s, alcohol was commonly used as a tocolytic, a method to stop preterm labor. The method originated with Dr. Fritz Fuchs, the chairman of the department of obstetrics and gynecology at Cornell University Medical College.[64][65] Doctors recommended a small amount of alcohol to calm the uterus during contractions in early pregnancy or Braxton Hicks contractions. In later stages of pregnancy, the alcohol was administered intravenously and often in large amounts. "Women experienced similar effects as occur with oral ingestion, including intoxication, nausea and vomiting, and potential alcohol poisoning, followed by hangovers when the alcohol was discontinued."[66] Vomiting put the mother at a high risk for aspiration and was "a brutal procedure for all involved." [64] Because the alcohol was being given intravenously, the doctor could continue giving the treatment to the mother long after she had passed out, resulting in her being more intoxicated than would otherwise be possible. Such heavy intoxication is highly likely to contribute to FASD.[64]

## Historical references [edit]

Anecdotal accounts of prohibitions against maternal alcohol use from Biblical, ancient Greek, and ancient Roman sources imply a historical awareness of links between maternal alcohol use and negative child outcomes.[31] For example, in the King James' Version of the Bible, Judges 13:4 reads: "Now therefore beware, I pray thee, and drink not wine nor strong drink, and eat not any unclean *thing*" In 1725 British physicians petitioned the House of Commons on the effects of strong drink when consumed by pregnant women saying that such drinking is "…too often the cause of weak feeble and distempered children, who must be, instead, of an advantage and strength, a charge to their country."[67] There are many other such historical references. In Gaelic Scotland, the mother and nurse were not allowed to consume ale during pregnancy and breastfeeding (Martin Martin). Claims that alcohol consumption caused idiocy were part of the Teetotalism's message in the 19th century,[68] but such claims, despite some attempts to offer evidence, were ignored because no mechanism could be advanced.[69]

The earliest recorded observation of possible links between maternal alcohol use and fetal damage was made in 1899 by Dr. William Sullivan, a Liverpool prison physician who noted higher rates of stillbirth for 120 alcoholic female prisoners than their sober female relatives; he suggested the causal agent to be alcohol use.[70] This contradicted the predominating belief at the time that heredity caused intellectual

disability, poverty, and criminal behavior, which contemporary studies on the subjects usually concluded.[45] A case study by Henry H. Goddard of the Kallikak family—popular in the early 1900s—represents this earlier perspective,[71] though later researchers have suggested that the Kallikaks almost certainly had FAS.[72] General studies and discussions on alcoholism throughout the mid-1900s were typically based on a heredity argument.[73]

Prior to fetal alcohol syndrome being specifically identified and named in 1973, a few studies had noted differences between the children of mothers who used alcohol during pregnancy or breast-feeding and those who did not, but identified alcohol use as a possible contributing factor rather than heredity.[45]

## Recognition as a syndrome [edit]

Fetal Alcohol Syndrome was named in 1973 by two dysmorphologists, Drs. Kenneth Lyons Jones and David Weyhe Smith of the University of Washington Medical School in Seattle, United States. They identified a pattern of "craniofacial, limb, and cardiovascular defects associated with prenatal onset growth deficiency and developmental delay" in eight unrelated children of three ethnic groups, all born to mothers who were alcoholics.[74] The pattern of malformations indicated that the damage was prenatal. News of the discovery shocked some, while others were skeptical of the findings.[75]

Dr. Paul Lemoine of Nantes, France had already published a study in a French medical journal in 1968 about children with distinctive features whose mothers were alcoholics,[76] and in the U.S., Christy Ulleland and colleagues at the University of Washington Medical School had conducted an 18-month study in 1968–1969 documenting the risk of maternal alcohol consumption among the offspring of 11 alcoholic mothers.[77] The Washington and Nantes findings were confirmed by a research group in Gothenburg, Sweden in 1979.[78] Researchers in France, Sweden, and the United States were struck by how similar these children looked, though they were not related, and how they behaved in the same unfocused and hyperactive manner.[78]

Within nine years of the Washington discovery, animal studies, including non-human monkey studies carried out at the University of Washington Primate Center by Dr. Sterling Clarren, had confirmed that alcohol was a teratogen. By 1978, 245 cases of FAS had been reported by medical researchers, and the syndrome began to be described as the most frequent known cause of intellectual disability.

While many syndromes are eponymous, i.e. named after the physician first reporting the association of symptoms, Dr. Smith named FAS after the causal agent of the symptoms.[79] He reasoned that doing so would encourage prevention, believing that if people knew maternal alcohol consumption caused the syndrome, then abstinence during pregnancy would follow from patient education and public awareness.[79] At the time, nobody was aware of the full range of possible birth defects from FAS or its rate of prevalence.[79] Over time, as subsequent research and clinical experience suggested that a range of effects (including physical, behavioral, and cognitive) could arise from prenatal alcohol exposure, the term Fetal Alcohol Spectrum Disorder (FASD) was developed to include FAS as well as other conditions resulting from prenatal alcohol exposure.[79] Currently, FAS[11][42][74] is the only expression of prenatal alcohol exposure defined by the International Statistical Classification of Diseases and Related Health Problems and assigned ICD-9 and diagnoses.

# References [edit]


1. ^ *a b c d e f g h i j k* "Facts about FASDs". April 16, 2015. Retrieved 10 June 2015.
2. ^ *a b c d e f g h i j* Chudley; et al. (2005). "Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis". *CMAJ*. pp. S1–S21. doi:10.1503/cmaj.1040302. PMC 557121. PMID 15738468. Retrieved 20 November 2016.
3. ^ Coriale, G; Fiorentino, D; Di Lauro, F; Marchitelli, R; Scalese, B; Fiore, M; Maviglia, M; Ceccanti, M (2013). "Fetal Alcohol Spectrum Disorder (FASD): neurobehavioral profile, indications for diagnosis and treatment.". *Rivista di psichiatria*. **48** (5): 359–69. doi:10.1708/1356.15062. PMID 24326748.
4. ^ *a b c d* Riley, EP; Infante, MA; Warren, KR (June 2011). "Fetal alcohol spectrum disorders: an overview.". *Neuropsychology review*. **21** (2): 73–80. doi:10.1007/s11065-011-9166-x. PMID 21499711.

5. ^ a b c "Fetal Alcohol Exposure". April 2015. Retrieved 10 June 2015.
6. ^ a b c McHugh, RK; Wigderson, S; Greenfield, SF (June 2014). "Epidemiology of substance use in reproductive-age women.". *Obstetrics and gynecology clinics of North America*. **41** (2): 177–89. doi:10.1016/j.ogc.2014.02.001. PMID 24845483.
7. ^ Williams, J. F.; Smith, V. C. (19 October 2015). "Fetal Alcohol Spectrum Disorders". *Pediatrics*. **136** (5): e1395–e1406. doi:10.1542/peds.2015-3113.
8. ^ *Fetal Alcohol Spectrum Disorder: Management and Policy Perspectives of FASD*. John Wiley & Sons. 2011. pp. 73–75. ISBN 9783527632565.
9. ^ "Alcohol Use in Pregnancy". 17 April 2014. Retrieved 10 June 2015.
10. ^ a b Vice Admiral Richard H. Carmona (2005). "A 2005 Message to Women from the U.S. Surgeon General (PDF). Retrieved 12 June 2015.
11. ^ a b c d e f g h i j k l m n o p q r s t Committee to Study Fetal Alcohol Syndrome, Division of Biobehavioral Sciences and Mental Disorders, Institute of Medicine (1995). *Fetal alcohol syndrome : diagnosis, epidemiology, prevention, and treatment*. Washington, D.C.: National Academy Press. ISBN 0-309-05292-0.
12. ^ "Australian Government National Health and Medical Research Council". Retrieved 4 November 2012.
13. ^ Rasmussen, Carmen; Andrew, Gail; Zwaigenbaum, Lonnie; Tough, Suzanne (2016-11-20). "Neurobehavioural outcomes of children with fetal alcohol spectrum disorders: A Canadian perspective". *Paediatrics & Child Health*. **13** (3): 185–191. ISSN 1205-7088. PMC 2529423. PMID 19252695.
14. ^ Roszel, EL (13 April 2015). "Central nervous system deficits in fetal alcohol spectrum disorder.". *The Nurse practitioner*. **40** (4): 24–33. doi:10.1097/01.npr.0000444650.10142.4f. PMID 25774812.
15. ^ a b c d e f "Data & Statistics Prevalence of FASDs". *Center for Disease Control and Prevention*. April 16, 2015. Retrieved 10 June 2015.
16. ^ a b c d Kingdon; et al. (2016), "Research Review: Executive function deficits in fetal alcohol spectrum disorders and attention-deficit/hyperactivity disorder – a meta-analysis", *Journal of Child Psychology and Psychiatry*, **57** (2): 116–131, doi:10.1111/jcpp.12451
17. ^ "CAMH: More than 400 conditions co-occur with Fetal Alcohol Spectrum Disorders (FASD), CAMH study finds". *www.camh.ca*. Retrieved 2016-11-20.
18. ^ a b c d e f g h i j k l m n o p Astley, S.J. (2004). *Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code*. Seattle: University of Washington. PDF available at FAS Diagnostic and Prevention Network. Retrieved on 2007-04-11.
19. ^ a b c d e Clinical growth charts. National Center for Growth Statistics. Retrieved on 2007-04-10
20. ^ a b c d e f g h i j k l m n Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis (PDF). CDC (July 2004). Retrieved on 2009-09-22
21. ^ Jones K, Smith D (1975). "The fetal alcohol syndrome". *Teratology*. **12** (1): 1–10. doi:10.1002/tera.1420120102. PMID 1162620.
22. ^ Renwick J, Asker R (1983). "Ethanol-sensitive times for the human conceptus". *Early Hum Dev*. **8** (2): 99–111. doi:10.1016/0378-3782(83)90065-8. PMID 6884260.
23. ^ Astley SJ, Clarren SK (1996). "Most FAS children have a smaller brain then other children "A case definition and photographic screening tool for the facial phenotype of fetal alcohol syndrome" ". *Journal of Pediatrics*. **129** (1): 33–41. doi:10.1016/s0022-3476(96)70187-7. PMID 8757560.
24. ^ Astley SJ, Stachowiak J, Clarren SK, Clausen C (2002). "Application of the fetal alcohol syndrome facial photographic screening tool in a foster care population". *Journal of Pediatrics*. **141** (5): 712–717. doi:10.1067/mpd.2002.129030. PMID 12410204.
25. ^ Lip-philtrum guides. FAS Diagnostic and Prevention Network, University of Washington. Retrieved on 2007-04-10.
26. ^ a b c d FAS facial features. FAS Diagnostic and Prevention Network, University of Washington. Retrieved on 2007-04-10
27. ^ Astley, Susan. Backside of Lip-Philtrum Guides (2004) (PDF). University of Washington, Fetal Alcohol Syndrome Diagnostic and Prevention Network. Retrieved on 2007-04-11
28. ^ West, J.R. (Ed.) (1986). *Alcohol and Brain Development*. New York: Oxford University Press.[*page needed*]
29. ^ Clarren S, Alvord E, Sumi S, Streissguth A, Smith D (1978). "Brain malformations related to prenatal exposure to ethanol". *J Pediatr*. **92** (1): 64–7. doi:10.1016/S0022-3476(78)80072-9. PMID 619080.
30. ^ Coles C, Brown R, Smith I, Platzman K, Erickson S, Falek A (1991). "Effects of prenatal alcohol exposure at school age. I. Physical and cognitive development". *Neurotoxicol Teratol*. **13** (4): 357–67. doi:10.1016/0892-0362(91)90084-A. PMID 1921915.
31. ^ a b Jones K.L.; Smith D.W. (1973). "Recognition of the fetal alcohol syndrome in early infancy". *Lancet*. **2**: 999–

1001. doi:10.1016/s0140-6736(73)91092-1. PMID 4127281.
32. ^ a b c Mattson, S.N., & Riley, E.P. (2002). "Neurobehavioral and Neuroanatomical Effects of Heavy Prenatal Exposure to Alcohol," in Streissguth and Kantor. (2002). p. 10.
33. ^ Strömland K, Pinazo-Durán M (2002). "Ophthalmic involvement in the fetal alcohol syndrome: clinical and animal model studies". *Alcohol Alcohol*. **37** (1): 2–8. doi:10.1093/alcalc/37.1.2. PMID 11825849.
34. ^ a b c d e Yaffe, Sumner J. (2011). *Drugs in pregnancy and lactation : a reference guide to fetal and neonatal risk* (9 ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 527. ISBN 9781608317080.
35. ^ "Pregnancy and alcohol: occasional, light drinking may be safe.". *Prescrire Int*. **124** (21): 44–50. Feb 2012. PMID 22413723.
36. ^ Henderson, J; Gray, R; Brocklehurst, P (March 2007). "Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome.". *BJOG : an international journal of obstetrics and gynaecology*. **114** (3): 243–52. doi:10.1111/j.1471-0528.2006.01163.x. PMID 17233797.
37. ^ Warren K.; Li T-K (2005). "Genetic polymorphisms: Impact on the risk of fetal alcohol spectrum disorders". *Birth Defect Res A*. **73**: 195–203. doi:10.1002/bdra.20125.
38. ^ Laufer BI, Mantha K, Kleiber ML, Diehl EJ, Addison SM, Singh SM (July 2013). "Long-lasting alterations to DNA methylation and ncRNAs could underlie the effects of fetal alcohol exposure in mice". *Disease Models & Mechanisms*. **6** (4): 977–92. doi:10.1242/dmm.010975. PMC 3701217. PMID 23580197.
39. ^ Brien J.; et al. (1983). "Disposition of ethanol in human maternal venous blood and amniotic fluid". *Am J Obstet Gynecol*. **146**: 181–186. doi:10.1016/0002-9378(83)91050-5. PMID 6846436.
40. ^ Nava-Ocampo A.; et al. (2004). "Elimination kinetics of ethanol in pregnant women". *Reproduct Toxicol*. **18**: 613–617. doi:10.1016/j.reprotox.2004.02.012. PMID 15135856.
41. ^ a b c d e f Lang, Jeannette (2006). "Ten Brain Domains: A Proposal for Functional Central Nervous System Parameters for Fetal Alcohol Spectrum Disorder Diagnosis and Follow-up" (PDF). *Journal of the FAS Institute*. **4**: 1–11.
42. ^ a b c Clarren S.K.; Smith D.W. (1978). "Fetal alcohol syndrome". *New England Journal of Medicine*. **298**: 1063–1067. doi:10.1056/NEJM197805112981906. PMID 347295.
43. ^ Smith D.W. (1981). "Fetal alcohol syndrome and fetal alcohol effects". *Neurobehavioral Toxicology and Teratology*. **3**: 127.
44. ^ Aase J.M.; Jones K.L.; Clarren S.K. (1995). "Do we need the term FAE?". *Pediatrics*. **95** (3): 428–430. PMID 7862486.
45. ^ a b c d e f g h i j k l m n Streissguth, A. (1997). *Fetal Alcohol Syndrome: A Guide for Families and Communities*. Baltimore: Brookes Publishing. ISBN 1-55766-283-5.
46. ^ a b c d Malbin, D. (2002). *Fetal Alcohol Spectrum Disorders: Trying Differently Rather Than Harder*. Portland, OR: FASCETS, Inc. ISBN 0-9729532-0-5.
47. ^ Sokol R.J.; Clarren S.K. (1989). "Guidelines for use of terminology describing the impact of prenatal alcohol on the offspring". *Alcoholism: Clinical and Experimental Research*. **13** (4): 597–598. doi:10.1111/j.1530-0277.1989.tb00384.x.
48. ^ U.S. Department of Health and Human Services. (2000). National Institute on Alcohol Abuse and Alcoholism. *Tenth special report to the U.S Congress on alcohol and health: Highlights frfom current research*. Washington, DC: The Institute.
49. ^ FADP – Fetal Alcohol Diagnostic Program
50. ^ http://alcalc.oxfordjournals.org/content/35/3/276.full
51. ^ http://www.cdc.gov/ncbddd/fasd/data.html
52. ^ a b Buxton, B. (2005). *Damaged Angels: An Adoptive Mother Discovers the Tragic Toll of Alcohol in Pregnancy*. New York: Carroll & Graf. ISBN 0-7867-1550-2.
53. ^ a b c d McCreight, B. (1997). *Recognizing and Managing Children with Fetal Alcohol Syndrome/Fetal Alcohol Effects: A Guidebook*. Washington, DC: CWLA. ISBN 0-87868-607-X.
54. ^ a b National Organization on Fetal Alcohol Syndrome, Minnesota Organization on Fetal Alcohol Syndrome. Retrieved on 2007-04-11
55. ^ "More than 3 million US women at risk for alcohol-exposed pregnancy | CDC Online Newsroom | CDC". *www.cdc.gov*. Retrieved 2016-11-20.
56. ^ a b c d e Streissguth, A.P., Barr, H.M., Kogan, J., & Bookstein, F.L. (1996). *Understanding the occurrence of secondary disabilities in clients with fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE): Final report to the Centers for Disease Control and Prevention on Grant No. RO4/CCR008515* (Tech. Report No. 96-06). Seattle: University of Washington, Fetal Alcohol and Drug Unit.
57. ^ a b Malbin, D. (1993). *Fetal Alcohol Syndrome, Fetal Alcohol Effects: Strategies for Professionals*. Center City, MN: Hazelden. ISBN 0-89486-951-5

58. ^ Abel EL, Jacobson S, Sherwin BT (1983). "In utero alcohol exposure: Functional and structural brain damage". *Neurobehavioral Toxicology and Teratology*. **5**: 363–366. PMID 6877477.
59. ^ Meyer L, Kotch L, Riley E (1990). "Neonatal ethanol exposure: functional alterations associated with cerebellar growth retardation". *Neurotoxicol Teratol*. **12** (1): 15–22. doi:10.1016/0892-0362(90)90107-N. PMID 2314357.
60. ^ Zimmerberg B, Mickus LA (1990). "Sex differences in corpus callosum: Influence of prenatal alcohol exposure and maternal undernutrition". *Brain Research*. **537**: 115–122. doi:10.1016/0006-8993(90)90347-e. PMID 2085766.
61. ^ *a b* Elliot, E. J; Payne, J; Hann, E; Bower, C (2006). "Diagnosis of fetal alcohol syndrome and alcohol use in pregnancy: A survey of Paediatricians' knowledge, attitudes and practice". *Journal of Paediatrics and Child Health*. **42** (1): 698–703. doi:10.1111/j.1440-1754.2006.00954.x.
62. ^ *a b c d* Burns, L; Breen, C; Bower, C; O'Leary, C; Elliiot, E. J (2015). "Counting fetal alcohol spectrum disorders in Australia:The evidence and the challenges". *Drugs and Alcohol Review*. **32** (5): 461–467. doi:10.1111/dar.12047.
63. ^ Mutch, R. C; Watkins, R; Bower, C (2014). "Fetal alcohol spectrum disorders: Notifications to Western Australian register of developmental anomalies". *Journal of Paediatrics and Child Health*. **51** (4): 433–436. doi:10.1111/jpc.12746.
64. ^ *a b c* Armstrong, E. M. (2003). Conceiving risk, bearing responsibility: Fetal alcohol syndrome & the diagnosis of moral disorder. Baltimore: The Johns Hopkins University Press.
65. ^ http://www.nytimes.com/1995/03/04/obituaries/dr-fritz-fuchs-76-who-advanced-obstetrics.html
66. ^ King, T. L., & Brucker, M. C. (2011). Pharmacology for women's health. Sudbury, MA: Jones and Bartlett.
67. ^ Oba, Peggy (2006). [fasaware.co.uk/wp-content/uploads/2014/10/15_history.doc "A History of FASD"] Check `|url=` value (help). *fasaware.co.uk*. FAS Aware. Retrieved 20 November 2016.
68. ^ Jonathan Townley Crane, Arts of Intoxication: The Aim and the Results. (New York:Carlton & Lanahan, 1870), 173-175
69. ^ Jennifer L. Tait *The Poisoned Chalice* (Tuscaloosa, AL: University of Alabama Press, 2010), 27,28.
70. ^ Sullivan W.C. (1899). "A note on the influence of maternal inebriety on the offspring". *Journal of Mental Science*. **45**: 489–503. doi:10.1192/bjp.45.190.489.
71. ^ Goddard, H.H. (1912). *The Kallikak Family: A Study in the Heredity of Feeble-Mindedness*. New York: Macmillan.
72. ^ Karp R.J.; Qazi Q.H.; Moller K.A.; Angelo W.A.; Davis J.M. (1995). "Fetal alcohol syndrome at the turn of the century: An unexpected explanation of the Kallikak family". *Archives of Pediatrics and Adolescent Medicine*. **149** (1): 45–48. doi:10.1001/archpedi.1995.02170130047010. PMID 7827659.
73. ^ Haggard, H.W., & Jellinek, E.M. (1942). *Alcohol Explored*. New York: Doubleday.
74. ^ *a b* Jones K.L.; Smith D.W; Ulleland C.N.; Streissguth A.P. (1973). "Pattern of malformation in offspring of chronic alcoholic mothers". *Lancet*. **1**: 1267–1271. doi:10.1016/S0140-6736(73)91291-9. PMID 4126070.
75. ^ Streissguth, A.P. (2002). In A. Streissguth, & J. Kanter (Eds.), *The Challenge in Fetal Alcohol Syndrome: Overcoming Secondary Disabilities.* Seattle: University of WA Press. ISBN 0-295-97650-0.
76. ^ Lemoine P.; Harousseau H.; Borteyru J.B.; Menuet J.C. (1968). "Les enfants de parents alcooliques. Anomalies observées, à propos de 127 cas". *Quest Medical*. **21**: 476–482. Reprinted in PMID 12657907
77. ^ Ulleland C.N. (1972). "The offspring of alcoholic mothers". *Annals of the New York Academy of Sciences*. **197**: 167–169. doi:10.1111/j.1749-6632.1972.tb28142.x. PMID 4504588.
78. ^ *a b* Olegard R.; Sabel K.G.; Aronsson M. Sandin; Johannsson P.R.; Carlsson C.; Kyllerman M.; Iversen K.; Hrbek A. (1979). "Effects on the child of alcohol abuse during pregnancy". *Acta Paediatrica Scandinavica*. **275**: 112–121. PMID 291283.
79. ^ *a b c d* Clarren, S.K. (2005). A thirty year journey from tragedy to hope. Foreword to Buxton, B. (2005). *Damaged Angels: An Adoptive Mother Discovers the Tragic Toll of Alcohol in Pregnancy*. New York: Carroll & Graf. ISBN 0-7867-1550-2.


## External links [edit]

- Fetal alcohol spectrum disorder at DMOZ
- Center for Disease Control's page on Fetal Alcohol Spectrum Disorders (FASDs)

Wikimedia Commons has media related to *Fetal alcohol syndrome*.

| v · t · e | **Psychoactive substance-related disorder (F10–F19, 291–292; 303–305)** |
|---|---|
| **General** | SID (Substance intoxication / Drug overdose · Withdrawal · Substance-induced psychosis · · SUD (Substance abuse · Physical dependence / Substance dependence · · |

| | | | | |
|---|---|---|---|---|
| **Alcohol** | **SID** | **Diseases** | **Neurological disorders** | Alcoholic hallucinosis · Alcohol withdrawal · **Fetal alcohol spectrum disorder** (FASD) · Fetal alcohol syndrome (FAS) · Korsakoff's syndrome · Wernicke–Korsakoff syndrome · Wernicke's encephalopathy · |
| | | | **Digestive system** | Alcoholic hepatitis · Alcoholic liver disease · Auto-brewery syndrome · |
| | | | **Nervous system** | Alcohol-related dementia · Alcoholic hallucinosis · Hangover · |
| | | | **Cardiovascular system** | Alcoholic cardiomyopathy · Alcohol flush reaction · |
| | **SUD** | Alcoholism · Alcohol dependence · Alcohol abuse · | | |
| **Opioids** | SID (Opioid overdose · · SUD (Opioid addiction and dependence · · | | | |
| **Caffeine** | SID (Effect of caffeine on memory · Caffeine-induced sleep disorder · · SUD (Caffeine dependence · · | | | |
| **Cannabis** | SID (Effects of cannabis · Long-term effects of cannabis · · SUD (Cannabis dependence · · | | | |
| **Sedative / hypnotic** | *benzodiazepine:* SID (Benzodiazepine overdose · Benzodiazepine withdrawal · · SUD (Benzodiazepine misuse · Benzodiazepine dependence · · *barbiturate:* SID (Barbiturate overdose · · SUD (Barbiturate dependence · · | | | |
| **Cocaine** | SID (Cocaine intoxication · · SUD (Cocaine dependence · · | | | |
| **Stimulants** | SID (Stimulant psychosis · · SUD (Amphetamine dependence · · | | | |
| **Hallucinogen** | SID (Hallucinogen persisting perception disorder · · | | | |
| **Tobacco** | SID (Nicotine poisoning · Nicotine withdrawal · · | | | |
| **Volatile solvent** | Inhalant abuse: Toluene toxicity · | | | |
| **Multiple** | Poly drug use · | | | |

| v · t · e · | **Congenital malformation due to exogenous toxicity (Q86, 760.7)** |
|---|---|
| **Alcohol** | **Fetal alcohol spectrum disorder** · |
| **Other** | Fetal hydantoin syndrome · Fetal warfarin syndrome · Prenatal amphetamine exposure · Prenatal cannabis exposure · Prenatal cocaine exposure · Prenatal nicotine exposure · Retinoic Acid · |

Categories: Alcohol and health | Health effects of alcohol | Congenital malformation due to exogenous toxicity | Teratogens | Syndromes | Neurological disorders | Health issues in pregnancy | Biology of attention deficit hyperactivity disorder

# Klinefelter syndrome

From Wikipedia, the free encyclopedia

*Not to be confused with XYY syndrome.*

**Klinefelter syndrome** (**KS**) also known as **47,XXY** or **XXY**, is the set of symptoms that result from two or more X chromosomes in males.[1] The primary feature is sterility.[1] Often symptoms may be subtle and many people do not realize they are affected. Sometimes symptoms are more prominent and may include weaker muscles, greater height, poor coordination, less body hair, smaller genitals, breast growth, and less interest in sex.[2] Often it is only at puberty that these symptoms are noticed.[3] Intelligence is usually normal; however, reading difficulties and problems with speech are more common. Symptoms are typically more severe if three or more X chromosomes are present.[2]

Klinefelter syndrome usually occurs randomly. An older mother might increase the risk slightly. The condition is not inherited from one's parents.[4] The underlying mechanisms involves at least one extra X chromosome in addition to a Y chromosome such that there is a total of 47 or more chromosomes rather than the usual 46.[5] KS is diagnosed by the genetic test known as a karyotype.[3]

While there is no cure, a number of treatments may help.[6] Physical therapy, speech and language therapy, counselling, and adjustments of teaching methods may be useful. Testosterone replacement may be used in those who have significantly low levels. Enlarged breasts may be removed by surgery. About half of males affected with the help of assisted reproductive technology have a chance of having children; however, this is expensive and carries risks.[7] Males appear to have a higher risk of breast cancer than typical but still lower than that of females.[8] The condition has a nearly normal life expectancy.[6]

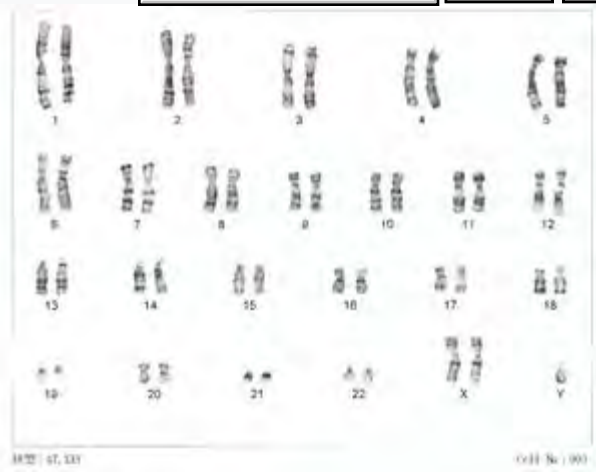
Klinefelter syndrome is one of the most common chromosomal disorders, occurring in 1:500 to 1:1000 live male births.[4][9] It is named after Harry Klinefelter who identified the condition in the 1940s.[10] In 1956 identification of the extra X chromosome was first noticed.[11] Mice can also have the XXY syndrome, making them a useful research model.[12]

**Contents**



**Klinefelter syndrome**

**Synonyms** XXY syndrome, Klinefelter's



47,XXY karyotype

**Pronunciation** /ˈklaɪnfɛltər/

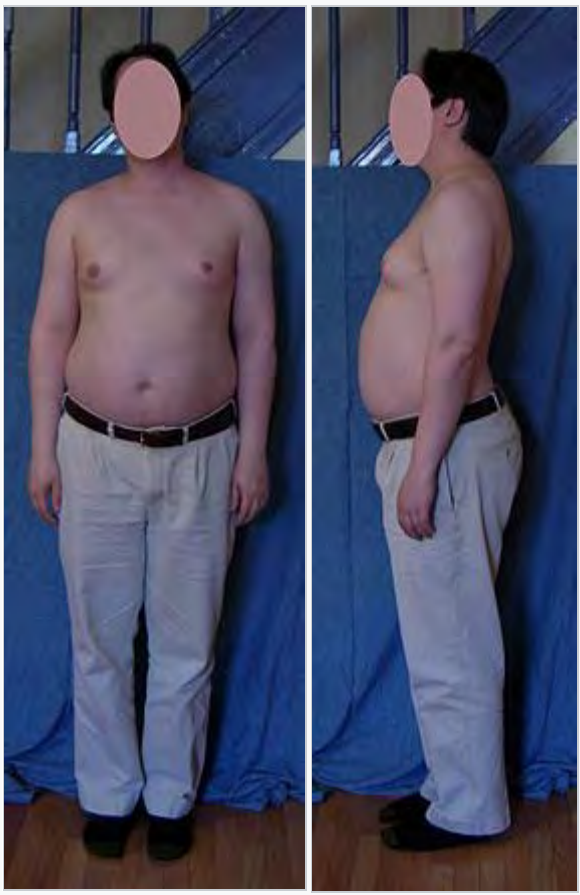
**Classification and external resources**

| | |
|---|---|
| **Specialty** | medical genetics |
| **ICD-10** | Q98.0-Q98.4 |
| **ICD-9-CM** | 758.7 |
| **DiseasesDB** | 7189 |
| **MedlinePlus** | 000382 |
| **eMedicine** | ped/1252 |
| **Patient UK** | Klinefelter syndrome |
| **MeSH** | D007713 |

[edit on Wikidata]

## Signs and symptoms [edit]

While it is possible to characterise XXY males based on physical characteristics, substantial variation in physical and developmental traits mean the only reliable method of positive or negative identification is karyotype testing.



A person with typical untreated (surgery/hormones) Klinefelter 46,XY/47,XXY mosaic, diagnosed at age 19. Scar from biopsy may be visible on left nipple.

### Physical [edit]

As babies and children, XXY males may have weaker muscles and reduced strength. As they grow older, they tend to become taller than average. They may have less muscle control and coordination than other boys of their age.[13]

During puberty, the physical traits of the syndrome become more evident; because these boys do not produce as much testosterone as other boys, they have a less muscular body, less facial and body hair, and broader hips. As teens, XXY males may develop breast tissue[14] and also have weaker bones, and a lower energy level than other males.[13]

By adulthood, XXY males look similar to males without the condition, although they are often taller. In adults, possible characteristics vary widely and include little to no sign of affectedness, a lanky, youthful build and facial appearance, or a rounded body type with some degree of gynecomastia (increased breast tissue).[15] Gynecomastia is present to some extent in about a third of affected individuals, a slightly higher percentage than in the XY population. About 10% of XXY males have gynecomastia noticeable enough that they may choose to have cosmetic surgery.[16]

Affected males are often infertile, or may have reduced fertility. Advanced reproductive assistance is sometimes possible.[17]

The term *hypogonadism* in XXY symptoms is often misinterpreted to mean "small testicles" when it means decreased testicular hormone/endocrine function. Because of this (primary) hypogonadism, individuals will often have a low serum testosterone level but high serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels.[18] Despite this

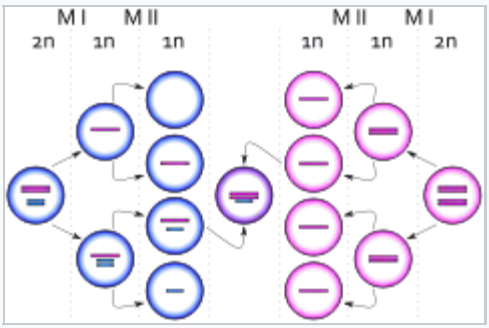
misunderstanding of the term, however, it is true that XXY men may also have microorchidism (i.e., small testicles).[18]

XXY males are also more likely than other men to have certain health problems that typically affect females, such as autoimmune disorders, breast cancer, venous thromboembolic disease, and osteoporosis.[13][19] In contrast to these potentially increased risks, it is currently thought that rare X-linked recessive conditions occur less frequently in XXY males than in normal XY males, since these conditions are transmitted by genes on the X chromosome, and people with two X chromosomes are typically only carriers rather than affected by these X-linked recessive conditions.[*citation needed*]

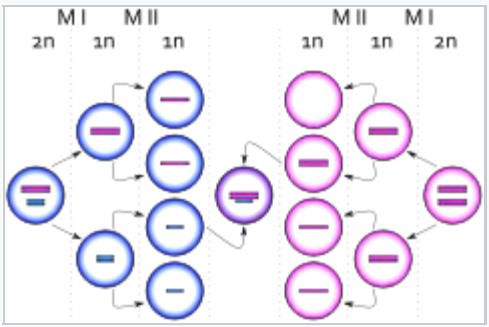
### Cognitive and developmental [edit]

Some degree of language learning or reading impairment may be present,[20] and neuropsychological testing often reveals deficits in executive functions, although these deficits can often be overcome through early intervention.[21] There may also be delays in motor development which can be addressed through occupational therapy and physical therapy.[22] XXY males may sit up, crawl, and walk later than other infants; they may also struggle in school, both academically and with sports.[13]

## Cause [edit]




Birth of a cell with karyotype XXY due to a non-disjunction event of one X chromosome from a Y chromosome during meiosis I in the male.




Birth of a cell with karyotype XXY due to a non-disjunction event of one X chromosome during meiosis II in the female.

The extra chromosome is retained because of a nondisjunction event during paternal or maternal meiosis I (gametogenesis). Nondisjunction occurs when homologous chromosomes, in this case the X and Y or two X sex chromosomes, fail to separate, producing a sperm with an X and a Y chromosome or an egg with two X chromosomes. Fertilizing a normal (X) egg with this sperm produces an XXY offspring (Klinefelter). Fertilizing a double X egg with a normal sperm also produces an XXY offspring (Klinefelter).

Another mechanism for retaining the extra chromosome is through a nondisjunction event during meiosis II in the egg. Nondisjunction will occur when sister chromatids on the sex chromosome, in this case an X and an X, fail to separate. (meiosis) An XX egg is produced which, when fertilized with a Y sperm, yields XXY offspring. This XXY chromosome arrangement is one of the most common genetic variations from the XY karyotype, occurring in about 1 in 500 live male births.[13] See also Triple X syndrome.

In mammals with more than one X chromosome, the genes on all but one X chromosome are not expressed; this is known as X inactivation. This happens in XXY males as well as normal XX females.[23] However, in XXY males, a few genes located in the pseudoautosomal regions of their X chromosomes, have corresponding genes on their Y chromosome and are capable of being expressed.[24]

The first published report of a man with a 47,XXY karyotype was by Patricia Jacobs and John Strong at Western General Hospital in Edinburgh, Scotland in 1959.[25] This karyotype was found in a 24-year-old man who had signs of Klinefelter syndrome. Jacobs described her discovery of this first reported human or mammalian chromosome aneuploidy in her 1981 William Allan Memorial Award address.[26]

### Variations [edit]

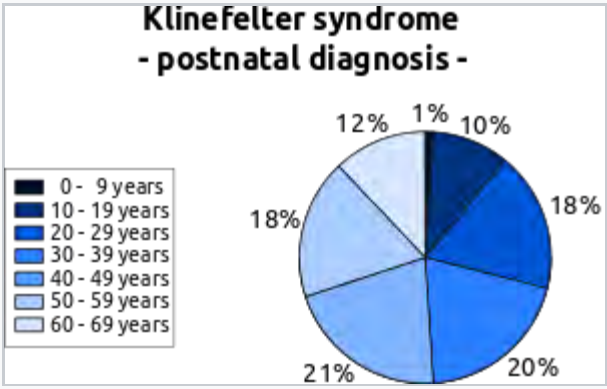
48,XXYY and 48,XXXY occur in 1 in 18,000–50,000 male births. The incidence of 49,XXXXY is 1 in 85,000 to 100,000 male births.[27] These variations are extremely rare. Additional chromosomal material can contribute to cardiac, neurological, orthopedic and other anomalies.

Males with Klinefelter syndrome may have a mosaic 47,XXY/46,XY constitutional karyotype and varying degrees of spermatogenic failure. Mosaicism 47,XXY/46,XX with clinical features suggestive of Klinefelter syndrome is very rare. Thus far, only about 10 cases have been described in literature.[28]

Analogous XXY syndromes are known to occur in cats—specifically, the presence of calico or tortoiseshell markings in male cats is an indicator of the relevant abnormal karyotype. As such, male cats with calico or tortoiseshell markings are a model organism for Klinefelter syndrome.[29]

## Diagnosis [edit]

About 10% of Klinefelter cases are found by prenatal diagnosis.[31] The first clinical features may appear in early childhood or, more frequently, during puberty, such as lack of secondary sexual characteristics and aspermatogenesis,[32] while tall stature as a symptom can be hard to diagnose during puberty. Despite the presence of small testes, only a quarter of the affected males are recognized as having Klinefelter syndrome at puberty.[33][34] Another quarter receive their diagnosis in late adulthood. About 64% of affected individuals are never recognized.[35] Often the diagnosis is made incidentally as a result of examinations and medical visits for reasons not linked to the condition.[36]



Percentages of Klinefelter's diagnosis divided by age groups, with most diagnoses occurring in adulthood.[30]

The standard diagnostic method is the analysis of the chromosomes' karyotype on lymphocytes. In the past, the observation of the Barr body was common practice as well.[34] To confirm mosaicism, it is also possible to analyze the karyotype using dermal fibroblasts or testicular tissue.[37]

Other methods may be: research of high serum levels of gonadotropins (follicle-stimulating hormone and luteinizing hormone), presence of azoospermia, determination of the sex chromatin,[38] and prenatally via chorionic villus sampling or amniocentesis. A 2002 literature review of elective abortion rates found that approximately 58% of pregnancies in the United States with a diagnosis of Klinefelter syndrome were terminated.[39]

### Differential diagnosis [edit]

The symptoms of Klinefelter syndrome are often variable; therefore, a karyotype analysis should be ordered when small testes, infertility, gynecomastia, long legs/arms, developmental delay, speech/language deficits, learning disabilities/academic issues and/or behavioral issues are present in an individual.[5] The differential diagnosis for the Klinefelter syndrome can include the following conditions: fragile X syndrome, Kallmann syndrome and Marfan syndrome. The cause of hypogonadism can be attributed to many other different medical conditions.

There have been some reports of individuals with Klinefelter syndrome who also have other chromosome abnormalities, such as Down syndrome.[40]

## Treatment [edit]

The genetic variation is irreversible, however, individuals who want to look more masculine can take testosterone.[41] Treating adolescents with implants of controlled release testosterone has shown good

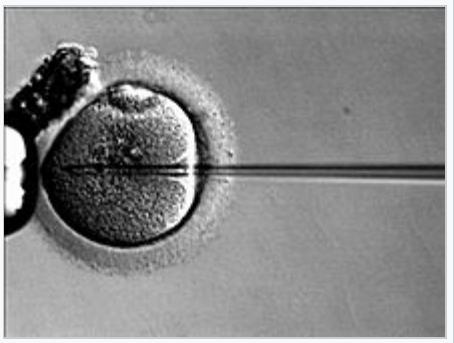
results when appropriately monitored.[42] Hormone therapy is also useful in preventing the onset of osteoporosis.

Often individuals that have noticeable breast tissue or hypogonadism experience depression and/or social anxiety because they are outside of social norms. An academic term for this is psychosocial morbidity.[43] At least one study indicates that planned and timed support should be provided for young men with Klinefelter syndrome to ameliorate current poor psychosocial outcomes.[43] The surgical removal of the breasts may be considered for both the psychological reasons and to reduce the risk of breast cancer.[44]

The use of behavioral therapy can mitigate any language disorders, difficulties at school and socialization. An approach by occupational therapy is useful in children with Down syndrome who have dyspraxia motor.[45]

### Infertility treatment [edit]

By 2010 over 100 successful pregnancies have been reported using IVF technology with surgically removed sperm material from males with Klinefelter syndrome.[46] Microdissection testicular sperm extraction in adult men with Klinefelter syndrome reported success rates of up to 45%.[47]



Intracytoplasmic sperm injection.

## Prognosis [edit]

Children with XXY differ little from other children. Although they can face problems during adolescence, often emotional and behavioral, and difficulties at school, most of them can achieve full independence from their families in adulthood. Most can lead a normal, healthy life.

The results of a study carried out on 87 Australian adults with the syndrome shows that those who have had a diagnosis and appropriate treatment from a very young age had a significant benefit with respect to those who had been diagnosed in adulthood.[48]

There is research suggesting Klinefelter syndrome substantially decreases life expectancy among affected individuals, though the evidence is not definitive.[49] A 1985 publication identified a greater mortality mainly due to diseases of the aortic valve, development of tumors and possible subarachnoid hemorrhages, reducing life expectancy by about 5 years.[50] Later studies have reduced this estimated reduction to an average of 2.1 years.[51] These results are still questioned data, are not absolute, and will need further testing.[49]

## Epidemiology [edit]

This syndrome, evenly spread in all ethnic groups, has a prevalence of 1-2 subjects every 1000 males in the general population.[33][52][53][54] 3.1% of infertile males have Klinefelter syndrome. The syndrome is also the main cause of male hypogonadism.[55]

According to 2008 meta-analysis, the prevalence of the syndrome has increased over the past decades; however, this does not appear to be related to increased age of the mother at conception, as no increase was observed in the rates of other trisomies of sex chromosomes (XXX and XYY).[56] The National Institutes of Health; however, state that older mothers might have a slightly increased risk.[4]

## History [edit]

The syndrome was named after Harry Klinefelter, who, in 1942, worked with Fuller Albright at Massachusetts General Hospital in Boston, Massachusetts, and first described it in the same year.[15][32]

The account given by Klinefelter came to be known as Klinefelter syndrome as his name appeared first on the published paper, and seminiferous tubule dysgenesis was no longer used.

## See also [edit]

- Aneuploidy
- Intersex
- Mosaic (genetics)
- True hermaphroditism
- Turner syndrome
- XXYY syndrome

## References [edit]


1. ^ a b "Klinefelter Syndrome (KS): Overview". *nichd.nih.gov*. Eunice Kennedy Shriver National Institute of Child Health and Human Development. 2013-11-15. Retrieved 15 March 2015.
2. ^ a b "What are common symptoms of Klinefelter syndrome (KS)?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 2013-10-25. Retrieved 15 March 2015.
3. ^ a b "How do health care providers diagnose Klinefelter syndrome (KS)?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 2012-11-30. Retrieved 15 March 2015.
4. ^ a b c "How many people are affected by or at risk for Klinefelter syndrome (KS)?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 2012-11-30. Retrieved 15 March 2015.
5. ^ a b Visootsak J, Graham JM; Graham Jr (2006). "Klinefelter syndrome and other sex chromosomal aneuploidies". *Orphanet Journal of Rare Diseases*. **1**: 42. doi:10.1186/1750-1172-1-42. PMC 1634840. PMID 17062147.
6. ^ a b "Is there a cure for Klinefelter syndrome (KS)?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 2012-11-30. Retrieved 16 March 2015.
7. ^ "What are the treatments for symptoms in Klinefelter syndrome (KS)?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 2013-10-25. Retrieved 15 March 2015.
8. ^ Brinton, LA (June 2011). "Breast cancer risk among patients with Klinefelter syndrome.". *Acta paediatrica (Oslo, Norway : 1992)*. **100** (6): 814–8. doi:10.1111/j.1651-2227.2010.02131.x. PMC 4024394. PMID 21241366.
9. ^ "Klinefelter syndrome". *Genetics Home Reference*. National Library of Medicine. 2012-10-30. Retrieved 2012-11-02.
10. ^ "Klinefelter Syndrome (KS): Condition Information". *nichd.nih.gov*. 2013-11-15. Retrieved 15 March 2015.
11. ^ Odom, Samuel L. (2009). *Handbook of developmental disabilities* (Pbk. ed.). New York: Guilford. p. 113. ISBN 9781606232484.
12. ^ Conn, P. Michael (2013). *Animal models for the study of human disease* (First ed.). San Diego: Elsevier Science & Technology Books. p. 780. ISBN 9780124159129.
13. ^ a b c d e "Klinefelter Syndrome". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 2007-05-24. Archived from the original on November 27, 2012.
14. ^ "47, XXY (Klinefelter syndrome)". University of Utah. Retrieved 15 June 2014.
15. ^ a b Klinefelter HF (1986). "Klinefelter syndrome: historical background and development". *South Med J*. **79** (9): 1089–1093. doi:10.1097/00007611-198609000-00012. PMID 3529433.
16. ^ Bock, Robert (August 1993). "Understanding Klinefelter Syndrome: A Guide for XXY Males and their Families". *NIH Pub. No. 93-3202*. Eunice Kennedy Shriver National Institute of Child Health and Human Development. Retrieved 2007-04-07.
17. ^ Denschlag D, Tempfer C, Kunze M, Wolff G, Keck C; Clemens, Tempfer, MD; Kunze, Myriam, MD; Wolff, Gerhard, MD; Keck, Christoph, MD (October 2004). "Assisted reproductive techniques in patients with Klinefelter syndrome: A critical review". *Fertility and Sterility*. **82** (4): 775–779. doi:10.1016/j.fertnstert.2003.09.085. PMID 15482743.
18. ^ a b Leask, Kathryn (October 2005). "Klinefelter syndrome". *National Library for Health, Specialist Libraries, Clinical Genetics*. National Library for Health. Retrieved 2007-04-07.
19. ^ Hultborn R, Hanson C, Köpf I, Verbiené I, Warnhammar E, Weimarck A; Hanson, C; Kopf, I; Verbiene, I; Warnhammar, E; Weimarck, A (November–December 1997). "Prevalence of Klinefelter syndrome in male breast cancer patients". *Anticancer Res*. **17** (6D): 4293–7. PMID 9494523.
20. ^ Graham JM, Bashir AS, Stark RE, Silbert A, Walzer S; Bashir, AS; Stark, RE; Silbert, A; Walzer, S (June 1988). "Oral and written language abilities of XXY boys: implications for anticipatory guidance". *Pediatrics*. **81** (6): 795–

806. PMID 3368277.
21. ^ Boone KB, Swerdloff RS, Miller BL, Geschwind DH, Razani J, Lee A, Gonzalo IG, Haddal A, Rankin K, Lu P, Paul L (May 2001). "Neuropsychological profiles of adults with Klinefelter syndrome". *J Int Neuropsychol Soc*. **7** (4): 446–56. PMID 11396547.
22. ^ Samango-Sprouse C (2010). "Expansion of the phenotypic profile of the young child with XXY". *Pediatric endocrinology reviews : PER*. 8 Suppl 1: 160–168. PMID 21217608.
23. ^ Chow JC, Yen Z, Ziesche SM, Brown CJ (2005). "Silencing of the mammalian X chromosome". *Annu Rev Genomics Hum Genet*. **6**: 69–92. doi:10.1146/annurev.genom.6.080604.162350. PMID 16124854.
24. ^ Blaschke RJ, Rappold G (2006). "The pseudoautosomal regions, SHOX and disease. *Curr Opin Genet Dev".* Jun;*. 16 (3): 233–9. doi:10.1016/j.gde.2006.04.004. PMID 16650979.*
25. ^ JACOBS PA, STRONG JA (January 31, 1959). "A case of human intersexuality having a possible XXY sex-determining mechanism". *Nature*. **183** (4657): 302–3. doi:10.1038/183302a0. PMID 13632697.
26. ^ Jacobs PA (September 1982). "The William Allan Memorial Award address: human population cytogenetics: the first twenty-five years". *Am J Hum Genet*. **34** (5): 689–98. PMC 1685430. PMID 6751075.
27. ^ Linden MG, Bender BG, Robinson A (1995). "Sex chromosome tetrasomy and pentasomy". *Pediatrics*. **96** (4 Pt 1): 672–682. PMID 7567329.
28. ^ Velissariou V, Christopoulou S, Karadimas C, Pihos I, Kanaka-Gantenbein C, Kapranos N, Kallipolitis G, Hatzaki A (2006). "Rare XXY/XX mosaicism in a phenotypic male with Klinefelter syndrome: case report". *Eur J Med Genet*. **49** (4): 331–337. doi:10.1016/j.ejmg.2005.09.001. PMID 16829354.
29. ^ Centerwall WR, Benirschke K (1975). "An animal model for the XXY Klinefelter's syndrome in man: Tortoiseshell and calico male cats". *American journal of veterinary research*. **36** (9): 1275–1280. PMID 1163864.
30. ^ Bojesen A, Gravholt CH (April 2007). "Klinefelter syndrome in clinical practice". *Nat Clin Pract Urol*. **4** (4): 192–204. doi:10.1038/ncpuro0775. PMID 17415352.
31. ^ Abramsky L, Chapple J (April 1997). "47,XXY (Klinefelter syndrome) and 47,XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling". *Prenat Diagn*. **17** (4): 363–8. doi:10.1002/(SICI)1097-0223(199704)17:4<363::AID-PD79>3.0.CO;2-O. PMID 9160389.
32. ^ *a b* Klinefelter HF Jr; Reifenstein EC Jr; Albright F. (1942). "Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydigism and increased excretion of follicle-stimulating hormone". *J Clin Endocrinol Metab*. **2** (11): 615–624. doi:10.1210/jcem-2-11-615.
33. ^ *a b* Bojesen A, Juul S, Gravholt CH; Juul; Gravholt (Feb 2003). "Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study". *Clin Endocrinol Metab*. **88** (2): 622–6. doi:10.1210/jc.2002-021491. PMID 12574191.
34. ^ *a b* Kamischke A, Baumgardt A, Horst J, Nieschlag E; Baumgardt; Horst; Nieschlag (Jan–Feb 2003). "Clinical and diagnostic features of patients with suspected Klinefelter syndrome". *J Androl*. **24** (1): 41–8. PMID 12514081.
35. ^ Smyth CM, Bremner WJ; Bremner (22 June 1998). "Klinefelter syndrome". *Arch Intern Med*. **158** (12): 1309–14. doi:10.1001/archinte.158.12.1309. PMID 9645824.
36. ^ Grzywa-Celińska A, Rymarz E, Mosiewicz J; Rymarz; Mosiewicz (October 2009). "[Diagnosis differential of Klinefelter's syndrome in a 24-year old male hospitalized with sudden dyspnoea--case report]". *Pol. Merkur. Lekarski* (in Polish). **27** (160): 331–3. PMID 19928664.
37. ^ Kurková S, Zemanová Z, Hána V, Mayerová K, Pacovská K, Musilová J, Stěpán J, Michalová K; Zemanová; Hána; Mayerová; Pacovská; Musilová; Stěpán; Michalová (April 1999). "[Molecular cytogenetic diagnosis of Klinefelter's syndrome in men more frequently detects sex chromosome mosaicism than classical cytogenetic methods]". *Cas. Lek. Cesk.* (in Czech). **138** (8): 235–8. PMID 10510542.
38. ^ Kleinheinz A, Schulze W; Schulze (1994). "Klinefelter's syndrome: New and rapid diagnosis by PCR analysis of XIST gene expression". *Andrologia*. **26** (3): 127–129. doi:10.1111/j.1439-0272.1994.tb00773.x. PMID 8085664.
39. ^ Mansfield C, Hopfer S, Marteau TM; Hopfer; Marteau (1999). "Termination rates after prenatal diagnosis of Down syndrome, spina bifida, anencephaly, and Turner and Klinefelter syndromes: A systematic literature review". *Prenatal Diagnosis*. **19** (9): 808–812. doi:10.1002/(SICI)1097-0223(199909)19:9<808::AID-PD637>3.0.CO;2-B. PMID 10521836.
40. ^ Sanz-Cortés M, Raga F, Cuesta A, Claramunt R, Bonilla-Musoles F; Raga; Cuesta; Claramunt; Bonilla-Musoles (November 2006). "Prenatally detected double trisomy: Klinefelter and Down syndrome". *Prenat. Diagn*. **26** (11): 1078–80. doi:10.1002/pd.1561. PMID 16958145.
41. ^ Wikström AM, Dunkel L (2011). "Klinefelter syndrome". *Best Pract. Res. Clin. Endocrinol. Metab*. **25** (2): 239–50. doi:10.1016/j.beem.2010.09.006. PMID 21397196.
42. ^ Moskovic DJ, Freundlich RE, Yazdani P, Lipshultz LI, Khera M (2012). "Subcutaneous implantable testosterone pellets overcome noncompliance in adolescents with Klinefelter syndrome". *J. Androl*. **33** (4): 570–3. doi:10.2164/jandrol.111.013979. PMID 21940986.
43. ^ *a b* Simm PJ, Zacharin MR; Zacharin (April 2006). "The psychosocial impact of Klinefelter syndrome--a 10 year

review". *J. Pediatr. Endocrinol. Metab.* **19** (4): 499–505. PMID 16759035.
44. ^ Gabriele R, Borghese M, Conte M, Egidi F (2002). "[Clinical-therapeutic features of gynecomastia]". *G Chir* (in Italian). **23** (6-7): 250–2. PMID 12422780.
45. ^ Harold Chen. "Klinefelter Syndrome - Treatment". medscape.com. Retrieved 4 September 2012.
46. ^ Fullerton G, Hamilton M, Maheshwari A; Hamilton; Maheshwari (2010). "Should non-mosaic Klinefelter syndrome men be labelled as infertile in 2009?". *Hum Reprod*. **25** (3): 588–97. doi:10.1093/humrep/dep431. PMID 20085911.
47. ^ Ramasamy, R; Ricci, JA; Palermo, GD; Gosden, LV; Rosenwaks, Z; Schlegel, PN (September 2009). "Successful fertility treatment for Klinefelter's syndrome.". *The Journal of Urology*. **182** (3): 1108–13. doi:10.1016/j.juro.2009.05.019. PMID 19616796.
48. ^ Herlihy AS, McLachlan RI, Gillam L, Cock ML, Collins V, Halliday JL; McLachlan; Gillam; Cock; Collins; Halliday (July 2011). "The psychosocial impact of Klinefelter syndrome and factors influencing quality of life". *Genet. Med.* **13** (7): 632–42. doi:10.1097/GIM.0b013e3182136d19. PMID 21546843.
49. ^ *a b* Swerdlow AJ, Higgins CD, Schoemaker MJ, Wright AF, Jacobs PA; Higgins; Schoemaker; Wright; Jacobs; United Kingdom Clinical Cytogenetics Group (December 2005). "Mortality in patients with Klinefelter syndrome in Britain: a cohort study". *J. Clin. Endocrinol. Metab.* **90** (12): 6516–22. doi:10.1210/jc.2005-1077. PMID 16204366.
50. ^ Price WH, Clayton JF, Wilson J, Collyer S, De Mey R; Clayton; Wilson; Collyer; De Mey (December 1985). "Causes of death in X chromatin positive males (Klinefelter's syndrome)". *J Eppmidemiol Community Health*. **39** (4): 330–6. doi:10.1136/jech.39.4.330. PMC 1052467. PMID 4086964.
51. ^ Bojesen A, Juul S, Birkebaek N, Gravholt CH; Juul; Birkebaek; Gravholt (August 2004). "Increased mortality in Klinefelter syndrome". *J. Clin. Endocrinol. Metab.* **89** (8): 3830–4. doi:10.1210/jc.2004-0777. PMID 15292313.
52. ^ Jacobs PA (1979). "Recurrence risks for chromosome abnormalities". *Birth Defects Orig Artic Ser*. **15** (5C): 71–80. PMID 526617.
53. ^ MACLEAN N, HARNDEN DG, COURT BROWN WM; Harnden; Court Brown (Aug 1961). "Abnormalities of sex chromosome constitution in newborn babies". *Lancet*. **2** (7199): 406–8. doi:10.1016/S0140-6736(61)92486-2. PMID 13764957.
54. ^ Visootsak J, Aylstock M, Graham JM; Aylstock; Graham Jr (Dec 2001). "Klinefelter syndrome and its variants: an update and review for the primary pediatrician". *Clin Pediatr (Phila)*. **40** (12): 639–51. doi:10.1177/000992280104001201. PMID 11771918.
55. ^ Matlach J, Grehn F, Klink T; Grehn; Klink (Jan 2012). "Klinefelter Syndrome Associated With Goniodysgenesis". *J Glaucoma*. **22** (5): e7–8. doi:10.1097/IJG.0b013e31824477ef. PMID 22274665.
56. ^ Morris JK, Alberman E, Scott C, Jacobs P; Alberman; Scott; Jacobs (Feb 2008). "Is the prevalence of Klinefelter syndrome increasing?". *Eur J Hum Genet*. **16** (2): 163–70. doi:10.1038/sj.ejhg.5201956. PMID 18000523.

## Further reading [edit]

- Virginia Isaacs Cover (2012). *Living with Klinefelter Syndrome, Trisomy X and 47,XYY: A Guide for Families and Individuals Affected by Extra X and Y Chromosomes*. ISBN 978-0-615-57400-4.

## External links [edit]

- Klinefelter syndrome at DMOZ

| v · t · e | Chromosome abnormalities (Q90–Q99, 758) | |
|---|---|---|
| Autosomal | Trisomies | Down syndrome (21 · · Edwards syndrome (18 · · Patau syndrome (13 · · Trisomy 9 · Warkany syndrome 2 (8 · · Cat eye syndrome/Trisomy 22 (22 · · Trisomy 16 · |
| | | 1q21.1 deletion syndrome/1q21.1 duplication syndrome/TAR syndrome (1 · · Wolf–Hirschhorn syndrome (4 · · Cri du chat/Chromosome 5q deletion syndrome (5 · · Williams syndrome (7 · · Jacobsen syndrome (11 · · |

| | | | |
|---|---|---|---|
| | **Monosomies/deletions** | | Miller–Dieker syndrome/Smith–Magenis syndrome (17 · · DiGeorge syndrome (22 · · 22q11.2 distal deletion syndrome (22 · · 22q13 deletion syndrome (22 · · *genomic imprinting* (Angelman syndrome/Prader–Willi syndrome (15) · · Distal 18q-/Proximal 18q- · |
| **X/Y linked** | **Monosomy** | | Turner syndrome (45,X) · |
| | **Trisomy/tetrasomy, other karyotypes/mosaics** | | **Klinefelter syndrome (47,XXY)** · 48,XXYY · 48,XXXY · 49,XXXYY · 49,XXXXY · Triple X syndrome (47,XXX) · 48,XXXX · 49,XXXXX · 47,XYY · 48,XYYY · 49,XYYYY · 45,X/46,XY · |
| **Translocations** | **Leukemia/lymphoma** | **Lymphoid** | Burkitt's lymphoma t(8 MYC;14 IGH) · Follicular lymphoma t(14 IGH;18 BCL2) · Mantle cell lymphoma/Multiple myeloma t(11 CCND1:14 IGH) · Anaplastic large-cell lymphoma t(2 ALK;5 NPM1) · Acute lymphoblastic leukemia · |
| | | **Myeloid** | Philadelphia chromosome t(9 ABL; 22 BCR) · Acute myeloblastic leukemia with maturation t(8 RUNX1T1;21 RUNX1) · Acute promyelocytic leukemia t(15 PML,17 RARA) · Acute megakaryoblastic leukemia t(1 RBM15;22 MKL1) · |
| | **Other** | | Ewing's sarcoma t(11 FLI1; 22 EWS) · Synovial sarcoma t(x SYT;18 SSX) · Dermatofibrosarcoma protuberans t(17 COL1A1;22 PDGFB) · Myxoid liposarcoma t(12 DDIT3; 16 FUS) · Desmoplastic small-round-cell tumor t(11 WT1; 22 EWS) · Alveolar rhabdomyosarcoma t(2 PAX3; 13 FOXO1) t (1 PAX7; 13 FOXO1) · |
| **Other** | | | Fragile X syndrome · Uniparental disomy · XX male syndrome · Ring chromosome (13; 14; 15; 20) · |
| **Authority control** | | | GND: 4164211-9 · |

Categories: Sex chromosome aneuploidies | Syndromes | Intersex and medicine




# Sickle-cell disease

From Wikipedia, the free encyclopedia

**Sickle-cell disease** (**SCD**) is a group of blood disorders typically inherited from a person's parents.[1] The most common type is known as **sickle-cell anaemia** (**SCA**). It results in an abnormality in the oxygen-carrying protein haemoglobin found in red blood cells. This leads to a rigid, sickle-like shape under certain circumstances.[1] Problems in sickle cell disease typically begin around 5 to 6 months of age. A number of health problems may develop, such as attacks of pain ("sickle-cell crisis"), anemia, bacterial infections, and stroke.[2] Long term pain may develop as people get older. The average life expectancy in the developed world is 40 to 60 years.[1]

Sickle-cell disease occurs when a person inherits two abnormal copies of the haemoglobin gene, one from each parent.[3] Several subtypes exist, depending on the exact mutation in each haemoglobin gene.[1] An attack can be set off by temperature changes, stress, dehydration, and high altitude.[2] A person with a single abnormal copy does not usually have symptoms and is said to have sickle-cell trait.[3] Such people are also referred to as carriers.[4] Diagnosis is by a blood test, and some countries test all babies at birth for the disease. Diagnosis is also possible during pregnancy.[5]

The care of people with sickle-cell disease may include infection prevention with vaccination and antibiotics, high fluid intake, folic acid supplementation, and pain medication.[4][6] Other measures may include blood transfusion, and the medication hydroxycarbamide (hydroxyurea).[6] A small proportion of people can be cured by a transplant of bone marrow cells.[1]

As of 2013 about 3.2 million people have sickle-cell disease while an additional 43 million have sickle-cell trait.[7] About 80% of sickle-cell disease cases are believed to occur in sub-Saharan Africa.[8] It also occurs relatively frequently in parts of India, the Arabian peninsula, and among people of African origin living in other parts of the world.[9] In 2013, it resulted in 176,000 deaths, up from 113,000 deaths in 1990.[10] The condition was first described in the medical literature by the American physician James B. Herrick in 1910.[11][12] In 1949 the genetic transmission was determined by E. A. Beet and J. V. Neel. In 1954 the protective effect against malaria of [12]

## Variants

**Sickle-cell disease**

**Synonyms** Sickle cell disorder

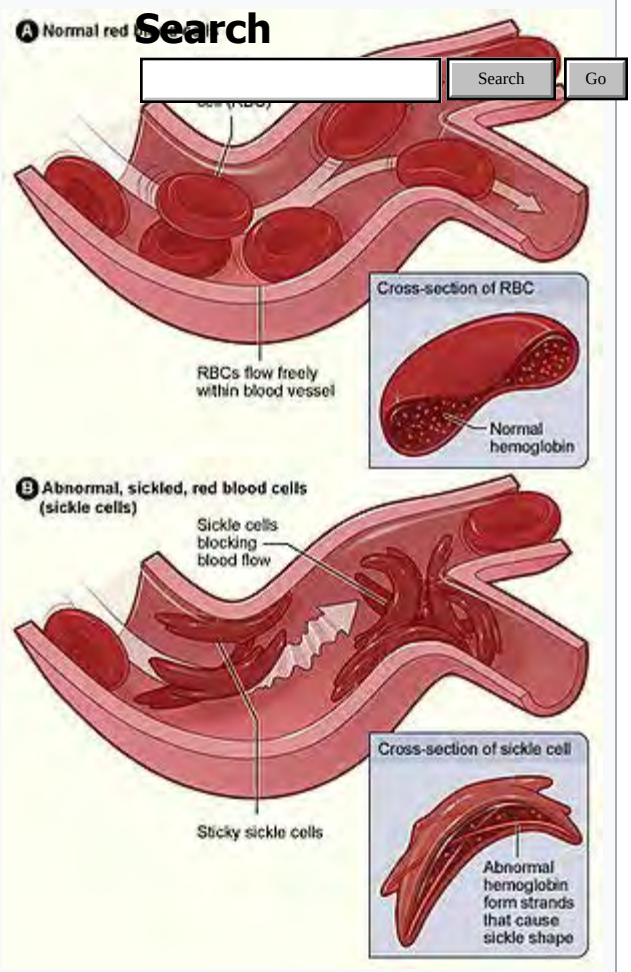



Figure (A) shows normal red blood cells flowing freely through veins. The inset shows a cross section of a normal red blood cell with normal haemoglobin. Figure B shows abnormal, sickled red blood cells sticking at the branching point in a vein. The inset image shows a cross-section of a sickle cell with long polymerized sickle haemoglobin(HbS) strands stretching and distorting the cell shape.

**Classification and external resources**

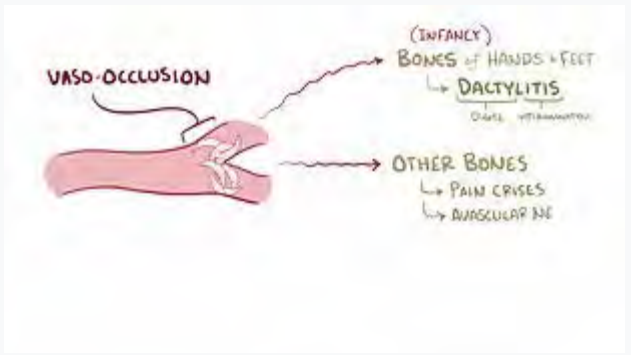
sickle-cell trait was described.





| | |
|---|---|
| **Specialty** | Hematology |
| **ICD-10** | D57 |
| **ICD-9-CM** | 282.6 |
| **OMIM** | 603903 |
| **DiseasesDB** | 12069 |
| **MedlinePlus** | 000527 |
| **eMedicine** | med/2126 oph/490 ped/2096 emerg/26 emerg/406 |
| **MeSH** | *C15.378.071.141.150.150* |
| **GeneReviews** | Sickle-cell disease |
| **Orphanet** | 232 |

[edit on Wikidata]

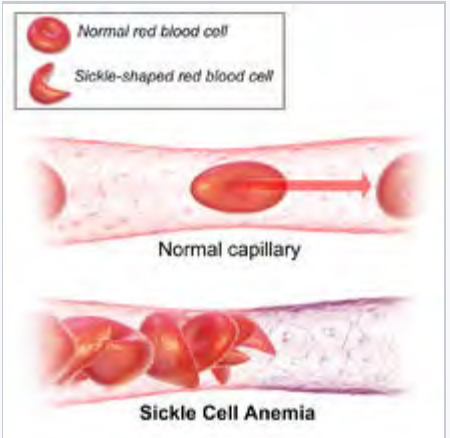



Play media

Video explanation

## Signs and symptoms [edit]

Sickle-cell disease may lead to various acute and chronic complications, several of which have a high mortality rate.[13]



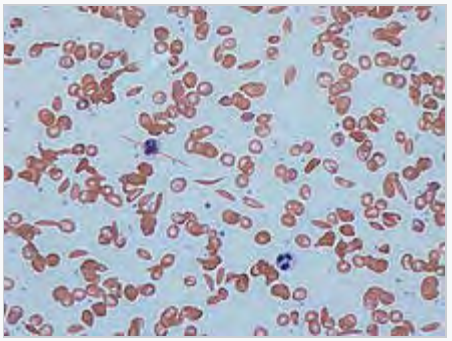

Sickle-cell anemia.

### Sickle-cell crisis [edit]

The terms "sickle-cell crisis" or "sickling crisis" may be used to describe several independent acute conditions occurring in patients with SCD. SCD results in anemia and crises that could be of many types including the vaso-occlusive crisis, aplastic crisis, sequestration crisis, haemolytic crisis, and others. Most episodes of sickle-cell crises last between five and seven days.[14] "Although infection, dehydration, and acidosis (all of which favor sickling) can act as triggers, in most instances, no predisposing cause is identified."[15]

## Vaso-occlusive crisis [edit]

The vaso-occlusive crisis is caused by sickle-shaped red blood cells that obstruct capillaries and restrict blood flow to an organ resulting in ischaemia, pain, necrosis, and often organ damage. The frequency, severity, and duration of these crises vary considerably. Painful crises are treated with hydration, analgesics, and blood transfusion; pain management requires opioid administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manage on nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac or naproxen. For more severe crises, most patients require inpatient management for intravenous opioids; patient-controlled analgesia devices are commonly used in this setting. Vaso-occlusive crisis involving organs such as the penis[16] or lungs are considered an emergency and treated with red-blood cell transfusions. Incentive spirometry, a technique to encourage deep breathing to minimise the development of atelectasis, is recommended.[17]

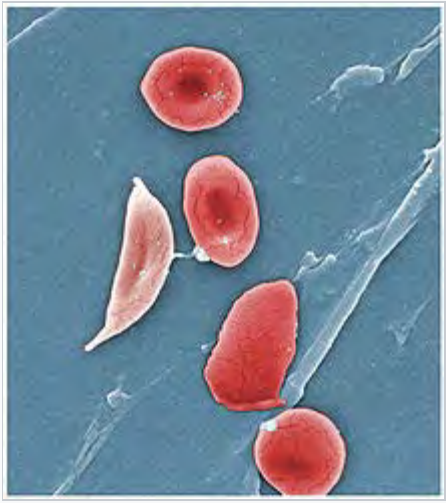


Sickle-cells in human blood: both normal red blood cells and sickle-shaped cells are present.

## Splenic sequestration crisis [edit]

Because of its narrow vessels and function in clearing defective red blood cells, the spleen is frequently affected.[18] It is usually infarcted before the end of childhood in individuals suffering from sickle-cell anemia. This spleen damage increases the risk of infection from encapsulated organisms;[19][20] preventive antibiotics and vaccinations are recommended for those lacking proper spleen function.

Splenic sequestration crises are acute, painful enlargements of the spleen, caused by intrasplenic trapping of red cells and resulting in a precipitous fall in haemoglobin levels with the potential for hypovolemic shock. Sequestration crises are considered an emergency. If not treated, patients may die within 1–2 hours due to circulatory failure. Management is supportive, sometimes with blood transfusion. These crises are transient, they continue for 3–4 hours and may last for one day.[21]



Normal blood cells next to a sickle-blood cell, colored scanning electron microscope image

## Acute chest syndrome [edit]

Acute chest syndrome (ACS) is defined by at least two of the following signs or symptoms: chest pain, fever, pulmonary infiltrate or focal abnormality, respiratory symptoms, or hypoxemia.[22] It is the second-most common complication and it accounts for about 25% of deaths in patients with SCD, majority of cases present with vaso-occlusive crises then they develop ACS.[23][24] Nevertheless, about 80% of patients have vaso-occlusive crises during ACS.

## Aplastic crisis [edit]

Aplastic crises are acute worsenings of the patient's baseline anaemia, producing pale appearance, fast heart rate, and fatigue. This crisis is normally triggered by parvovirus B19, which directly affects production of red blood cells by invading the red cell precursors and multiplying in and destroying them.[25] Parvovirus infection almost completely prevents red blood cell production for two to three days. In normal individuals, this is of little consequence, but the shortened red cell life of SCD patients results in an abrupt, life-threatening situation. Reticulocyte counts drop dramatically during the disease (causing reticulocytopenia), and the rapid turnover of red cells leads to the drop in haemoglobin. This crisis takes 4 days to one week to disappear. Most patients can be managed supportively; some need blood transfusion.[26]

## Haemolytic crisis [edit]

Haemolytic crises are acute accelerated drops in haemoglobin level. The red blood cells break down at a faster rate. This is particularly common in patients with coexistent G6PD deficiency.[27] Management is supportive, sometimes with blood transfusions.[17]

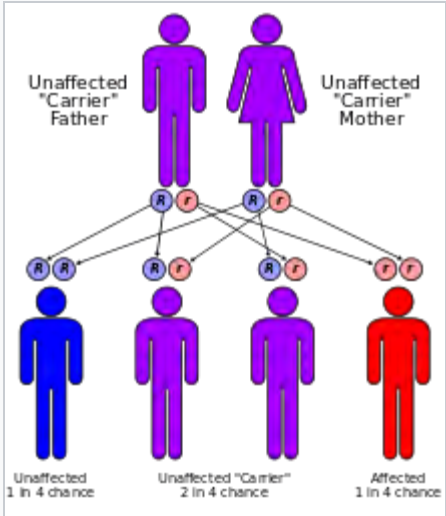
### Other [edit]

One of the earliest clinical manifestations is dactylitis, presenting as early as six months of age, and may occur in children with sickle-cell trait.[28] The crisis can last up to a month.[29] Another recognised type of sickle crisis, acute chest syndrome, is characterised by fever, chest pain, difficulty breathing, and pulmonary infiltrate on a chest X-ray. Given that pneumonia and sickling in the lung can both produce these symptoms, the patient is treated for both conditions.[30] It can be triggered by painful crisis, respiratory infection, bone-marrow embolisation, or possibly by atelectasis, opiate administration, or surgery.[*citation needed*] Hematopoietic ulcers may also occur.[31]

## Genetics [edit]

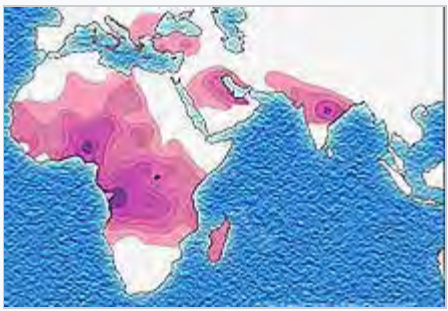
Normally, humans have haemoglobin A, which consists of two alpha and two beta chains, haemoglobin A2, which consists of two alpha and two delta chains, and haemoglobin F, consisting of two alpha and two gamma chains in their bodies. Of these, haemoglobin F dominates until about 6 weeks of age. Afterwards, haemoglobin A dominates throughout life.[*citation needed*]

Sickle-cell conditions have an autosomal recessive pattern of inheritance from parents. The types of haemoglobin a person makes in the red blood cells depend on what haemoglobin genes are inherited from her or his parents. If one parent has sickle-cell anaemia and the other has sickle-cell trait, then the child has a 50% chance of having sickle-cell disease and a 50% chance of having sickle-cell trait. When both parents have sickle-cell trait, a child has a 25% chance of sickle-cell disease, 25% do not carry any sickle-cell alleles, and 50% have the heterozygous condition.[32]




Sickle-cell disease is inherited in the autosomal recessive pattern.

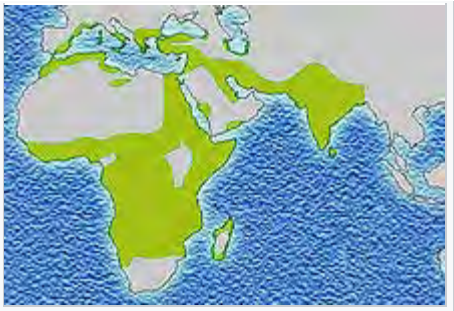
Sickle-cell gene mutation probably arose spontaneously in different geographic areas, as suggested by restriction endonuclease analysis. These variants are known as Cameroon, Senegal, Benin, Bantu, and Saudi-Asian. Their clinical importance is because some are associated with higher HbF levels, e.g., Senegal and Saudi-Asian variants, and tend to have milder disease.[33]



Distribution of the sickle-cell trait shown in pink and purple

In people heterozygous for HgbS (carriers of sickling haemoglobin), the polymerisation problems are minor, because the normal allele is able to produce over 50% of the haemoglobin. In people homozygous for HgbS, the presence of long-chain polymers of HbS distort the shape of the red blood cell from a smooth doughnut-like shape to ragged and full of spikes, making it fragile and susceptible to breaking within capillaries. Carriers have symptoms only if they are deprived of oxygen (for example, while climbing a mountain) or while severely dehydrated. The sickle-cell disease occurs when the sixth amino acid, glutamic acid, is replaced by valine to change its structure and function; as such, sickle-cell anemia is also known as E6V. Valine is hydrophobic, causing the haemoglobin to collapse on itself occasionally. The structure is not changed otherwise. When enough haemoglobin collapses on itself the red blood cells become sickle-shaped.[*citation needed*]

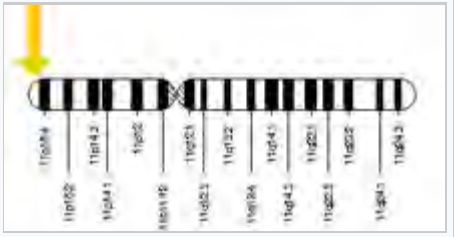
The gene defect is a known mutation of a single nucleotide (see single-



Historical distribution of malaria (no longer endemic in Europe) shown in green

Modern distribution of malaria

nucleotide polymorphism - SNP) (A to T) of the β-globin gene, which results in glutamic acid (E/Glu) being substituted by valine (V/Val) at position 6. Note, historic numbering put this glutamic acid residue at position 6 due to skipping the methionine (M/Met) start codon in protein amino acid position numbering. Current nomenclature calls for counting the methionine as the first amino acid, resulting in the glutamic acid residue falling at position 7. Many references still refer to position 6 and both should likely be referenced for clarity. Haemoglobin S with this mutation is referred to as HbS, as opposed to the normal adult HbA. The genetic disorder is due to the mutation of a single nucleotide, from a GAG to GTG codon on the coding strand, which is transcribed from the template strand into a GUG codon. Based on genetic code, GAG codon translates to glutamic acid (E/Glu) while GUG codon translates to valine (V/Val) amino acid at position 6. This is normally a benign mutation, causing no apparent effects on the secondary, tertiary, or quaternary structures of haemoglobin in conditions of normal oxygen concentration. What it does allow for, under conditions of low oxygen concentration, is the polymerization of the HbS itself. The deoxy form of haemoglobin exposes a hydrophobic patch on the protein between the E and F helices. The hydrophobic side chain of the valine residue at position 6 of the beta chain in haemoglobin is able to associate with the hydrophobic patch, causing haemoglobin S molecules to aggregate and form fibrous precipitates.



HBB gene (responsible for sickle-cell anaemia) is located on the short (p) arm of chromosome 11 at position 15.5

The allele responsible for sickle-cell anaemia can be found on the short arm of chromosome 11, more specifically 11p15.5. A person who receives the defective gene from both father and mother develops the disease; a person who receives one defective and one healthy allele remains healthy, but can pass on the disease and is known as a carrier or heterozygote. Heterozygotes are still able to contract malaria, but their symptoms are generally less severe.[34]

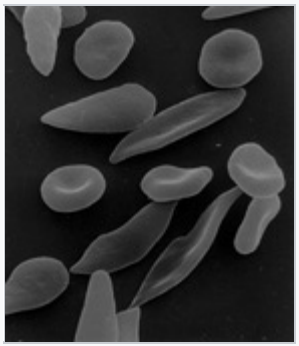
Due to the adaptive advantage of the heterozygote, the disease is still prevalent, especially among people with recent ancestry in malaria-stricken areas, such as Africa, the Mediterranean, India, and the Middle East.[35] Malaria was historically endemic to southern Europe, but it was declared eradicated in the mid-20th century, with the exception of rare sporadic cases.[36]

The malaria parasite has a complex lifecycle and spends part of it in red blood cells. In a carrier, the presence of the malaria parasite causes the red blood cells with defective haemoglobin to rupture prematurely, making the *Plasmodium* parasite unable to reproduce. Further, the polymerization of Hb affects the ability of the parasite to digest Hb in the first place. Therefore, in areas where malaria is a problem, people's chances of survival actually increase if they carry sickle-cell trait (selection for the heterozygote).

In the USA, with no endemic malaria, the prevalence of sickle-cell anaemia among African Americans is lower (about 0.25%) than in West Africa (about 4.0%) and is falling. Without endemic malaria, the sickle-cell mutation is purely disadvantageous and tends to decline in the affected population by natural selection, and now artificially through prenatal genetic screening. However, the African American community descends from a significant admixture of several African and non-African ethnic groups and also represents the descendants of survivors of slavery and the slave trade. Thus, a lower degree of endogamy and, particularly, abnormally high health-selective pressure through slavery may be the most plausible explanations for the lower prevalence of sickle-cell anaemia (and, possibly, other genetic diseases) among African Americans compared to West Africans. Another factor that limits the spread of sickle-cell genes in North America is the absence of cultural proclivities to polygamy, which allows affected males to continue

to seek unaffected children with multiple partners.[37]

## Pathophysiology [edit]



Scanning electron micrograph showing a mixture of red blood cells, some with round normal morphology, some with mild sickling showing elongation and bending

The loss of red blood cell elasticity is central to the pathophysiology of sickle-cell disease. Normal red blood cells are quite elastic, which allows the cells to deform to pass through capillaries. In sickle-cell disease, low oxygen tension promotes red blood cell sickling and repeated episodes of sickling damage the cell membrane and decrease the cell's elasticity. These cells fail to return to normal shape when normal oxygen tension is restored. As a consequence, these rigid blood cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischaemia.

The actual anaemia of the illness is caused by haemolysis, the destruction of the red cells, because of their shape. Although the bone marrow attempts to compensate by creating new red cells, it does not match the rate of destruction.[38] Healthy red blood cells typically function for 90–120 days, but sickled cells only last 10–20 days.[39]

## Diagnosis [edit]

In HbSS, the complete blood count reveals haemoglobin levels in the range of 6–8 g/dl with a high reticulocyte count (as the bone marrow compensates for the destruction of sickled cells by producing more red blood cells). In other forms of sickle-cell disease, Hb levels tend to be higher. A blood film may show features of hyposplenism (target cells and Howell-Jolly bodies).

Sickling of the red blood cells, on a blood film, can be induced by the addition of sodium metabisulfite. The presence of sickle haemoglobin can also be demonstrated with the "sickle solubility test". A mixture of haemoglobin S (Hb S) in a reducing solution (such as sodium dithionite) gives a turbid appearance, whereas normal Hb gives a clear solution.

Abnormal haemoglobin forms can be detected on haemoglobin electrophoresis, a form of gel electrophoresis on which the various types of haemoglobin move at varying speeds. Sickle-cell haemoglobin (HgbS) and haemoglobin C with sickling (HgbSC)—the two most common forms—can be identified from there. The diagnosis can be confirmed with high-performance liquid chromatography. Genetic testing is rarely performed, as other investigations are highly specific for HbS and HbC.[40]

An acute sickle-cell crisis is often precipitated by infection. Therefore, a urinalysis to detect an occult urinary tract infection, and chest X-ray to look for occult pneumonia should be routinely performed.[41]

People who are known carriers of the disease often undergo genetic counseling before they have a child. A test to see if an unborn child has the disease takes either a blood sample from the fetus or a sample of amniotic fluid. Since taking a blood sample from a fetus has greater risks, the latter test is usually used. Neonatal screening provides not only a method of early detection for individuals with sickle-cell disease, but also allows for identification of the groups of people that carry the sickle cell trait.[42]

## Management [edit]

### Folic acid and penicillin [edit]

Folic acid daily for life is recommended. From birth to five years of age, penicillin daily due to the immature immune system that makes them more prone to early childhood illnesses is also recommended.

### Malaria prevention [edit]

The protective effect of sickle-cell trait does not apply to people with sickle cell disease; in fact, they are more vulnerable to malaria, since the most common cause of painful crises in malarial countries is infection with malaria. It has therefore been recommended that people with sickle-cell disease living in malarial countries should receive anti-malarial chemoprophylaxis for life.[43]

### Vaso-occlusive crisis [edit]

Most people with sickle-cell disease have intensely painful episodes called vaso-occlusive crises. However, the frequency, severity, and duration of these crises vary tremendously. Painful crises are treated symptomatically with pain medications; pain management requires opioid administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manage on NSAIDs (such as diclofenac or naproxen). For more severe crises, most patients require inpatient management for intravenous opioids; patient-controlled analgesia (PCA) devices are commonly used in this setting. Diphenhydramine is also an effective agent that doctors frequently prescribe to help control itching associated with the use of opioids.[*citation needed*]

### Acute chest crisis [edit]

Management is similar to vaso-occlusive crisis, with the addition of antibiotics (usually a quinolone or macrolide, since cell wall-deficient ["atypical"] bacteria are thought to contribute to the syndrome),[44] oxygen supplementation for hypoxia, and close observation. Should the pulmonary infiltrate worsen or the oxygen requirements increase, simple blood transfusion or exchange transfusion is indicated. The latter involves the exchange of a significant portion of the person's red cell mass for normal red cells, which decreases the percent of haemoglobin S in the patient's blood. The patient with suspected acute chest syndrome should be admitted to the hospital with worsening A-a gradient an indication for ICU admission.[22]

### Hydroxyurea [edit]

The first approved drug for the causative treatment of sickle-cell anaemia, hydroxyurea, was shown to decrease the number and severity of attacks in a study in 1995 (Charache *et al.*)[45] and shown to possibly increase survival time in a study in 2003 (Steinberg *et al.*).[46] This is achieved, in part, by reactivating fetal haemoglobin production in place of the haemoglobin S that causes sickle-cell anaemia. Hydroxyurea had previously been used as a chemotherapy agent, and there is some concern that long-term use may be harmful, but this risk has been shown to be either absent or very small and it is likely that the benefits outweigh the risks.[13][47]

### Blood transfusion [edit]

Blood transfusions are often used in the management of sickle-cell disease in acute cases and to prevent complications by decreasing the number of red blood cells (RBC) that can sickle by adding normal red blood cells.[48] In children preventative red blood cell (RBC) transfusion therapy has been shown to reduce the risk of first stroke or silent stroke when transcranial Doppler (TCD) ultrasonography shows abnormal cerebral blood flow.[6] In those who have sustained a prior stroke event it also reduces the risk of recurrent stroke and additional silent strokes.[49][50]

### Bone marrow transplant [edit]

Bone marrow transplants have proven effective in children. Bone marrow transplants are the only known cure for SCD.[51] However, bone marrow transplants are difficult to obtain because of the specific HLA typing necessary. Ideally, a close relative (allogeneic) would donate the bone marrow necessary for transplantation.

## Prognosis [edit]

About 90% of people survive to age 20, and close to 50% survive beyond the fifth decade.[52] In 2001, according to one study performed in Jamaica, the estimated mean survival for people with sickle-cell was 53 years old for men and 58 years old for women with homozygous SCD.[53] The specific life expectancy in much of the developing world is unknown.[54]

## Complications [edit]

Sickle-cell anaemia can lead to various complications, including:

- Increased risk of severe bacterial infections due to loss of functioning spleen tissue (and comparable to the risk of infections after having the spleen removed surgically). These infections are typically caused by encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Daily penicillin prophylaxis is the most commonly used treatment during childhood, with some haematologists continuing treatment indefinitely. Patients benefit today from routine vaccination for *S. pneumoniae*.[55]
- Stroke, which can result from a progressive narrowing of blood vessels, prevents oxygen from reaching the brain. Cerebral infarction occurs in children and cerebral haemorrhage in adults.[*citation needed*]
- Silent stroke causes no immediate symptoms, but is associated with damage to the brain. Silent stroke is probably five times as common as symptomatic stroke. About 10–15% of children with SCD suffer strokes, with silent strokes predominating in the younger patients.[56][57]
- Cholelithiasis (gallstones) and cholecystitis may result from excessive bilirubin production and precipitation due to prolonged haemolysis.
- Avascular necrosis (aseptic bone necrosis) of the hip and other major joints may occur as a result of ischaemia.[58]
- Decreased immune reactions due to hyposplenism (malfunctioning of the spleen)[59]
- Priapism and infarction of the penis[60]
- Osteomyelitis (bacterial bone infection), the most common cause of osteomyelitis in SCD is *Salmonella* (especially the atypical serotypes *Salmonella typhimurium, Salmonella enteritidis, Salmonella choleraesuis* and *Salmonella paratyphi* B), followed by *Staphylococcus aureus* and Gram-negative enteric bacilli perhaps because intravascular sickling of the bowel leads to patchy ischaemic infarction.[61]
- Opioid tolerance can occur as a normal, physiologic response to the therapeutic use of opiates. Addiction to opiates occurs no more commonly among individuals with sickle-cell disease than among other individuals treated with opiates for other reasons.[*citation needed*]
- Acute papillary necrosis in the kidneys
- Leg ulcers[62]
- In eyes, background retinopathy, proliferative retinopathy, vitreous haemorrhages, and retinal detachments can result in blindness.[63] Regular annual eye checks are recommended.
- During pregnancy, intrauterine growth retardation, spontaneous abortion, and pre-eclampsia
- Chronic pain: Even in the absence of acute vaso-occlusive pain, many patients have unreported chronic pain.[64]
- Pulmonary hypertension (increased pressure on the pulmonary artery) can lead to strain on the right ventricle and a risk of heart failure; typical symptoms are shortness of breath, decreased exercise tolerance, and episodes of syncope.[*citation needed*] 21% of children and 30% of adults have evidence of pulmonary hypertension when tested; this is associated with reduced walking distance and increased mortality.[65]
- Chronic kidney failure due to sickle-cell nephropathy manifests itself with hypertension, protein loss in the urine, loss of red blood cells in urine and worsened anaemia. If it progresses to end-stage renal failure, it carries a poor prognosis.[66]

# Epidemiology [edit]

The highest frequency of sickle cell disease is found in tropical regions, particularly sub-Saharan Africa, tribal regions of India and the Middle-East.[67] Migration of substantial populations from these high prevalence areas to low prevalence countries in Europe has dramatically increased in recent decades and in some European countries sickle-cell disease has now overtaken more familiar genetic conditions such as

haemophilia and cystic fibrosis.[68] In 2013 it resulted in 176,000 deaths due to SCD up from 113,000 deaths in 1990.[10]

Sickle-cell disease occurs more commonly among people whose ancestors lived in tropical and sub-tropical sub-Saharan regions where malaria is or was common. Where malaria is common, carrying a single sickle-cell allele (trait) confers a selective advantage—in other words, being a heterozygote is advantageous. Specifically, humans with one of the two alleles of sickle-cell disease show less severe symptoms when infected with malaria.[69]

## Africa [edit]

Three-quarters of sickle-cell cases occur in Africa. A recent WHO report estimated that around 2% of newborns in Nigeria were affected by sickle cell anaemia, giving a total of 150,000 affected children born every year in Nigeria alone. The carrier frequency ranges between 10% and 40% across equatorial Africa, decreasing to 1–2% on the north African coast and <1% in South Africa.[70] There have been studies in Africa that show a significant decrease in infant mortality rate, ages 2–16 months, because of the sickle-cell trait. This happened in predominant areas of malarial cases.[71]

## United States [edit]

The number of people with the disease in the United States is approximately 1 in 5,000, mostly affecting Americans of Sub-Saharan African descent, according to the National Institutes of Health.[72] In the United States, about one out of 500 African-American children and one in every 36,000 Hispanic-American children have sickle-cell anaemia.[73] It is estimated that sickle-cell disease affects 90,000 Americans.[74] Most infants with SCD born in the United States are now identified by routine neonatal screening. As of 2016 all 50 states include screening for sickle cell disease as part of their newborn screen.[75]

## France [edit]

As a result of population growth in African-Caribbean regions of overseas France and immigration from North and sub-Saharan Africa to mainland France, sickle-cell disease has become a major health problem in France.[76] SCD has become the most common genetic disease in the country, with an overall birth prevalence of 1/2,415 in mainland France, ahead of phenylketonuria (1/10,862), congenital hypothyroidism (1/3,132), congenital adrenal hyperplasia (1/19,008) and cystic fibrosis (1/5,014) for the same reference period. In 2010, 31.5% of all newborns in mainland France (253,466 out of 805,958) were screened for SCD (this percentage was 19% in 2000). 341 newborns with SCD and 8,744 heterozygous carriers were found representing 1.1% of all newborns in mainland France. The Paris metropolitan district (Île-de-France) is the region that accounts for the largest number of newborns screened for SCD (60% in 2010). The second largest number of at-risk is in Provence-Alpes-Côte d'Azur at nearly 43.2% and the lowest number is in Brittany at 5.5%.[77][78]

## United Kingdom [edit]

In the United Kingdom (UK) it is thought that between 12,000 and 15,000 people have sickle cell disease [79] with an estimate of 250,000 carriers of the condition in England alone. As the number of carriers is only estimated, all newborn babies in the UK receive a routine blood test to screen for the condition.[80] Due to many adults in high-risk groups not knowing if they are carriers, pregnant women and both partners in a couple are offered screening so they can get counselling if they have the sickle cell trait.[81] In addition blood donors from those in high-risk groups are also screened to confirm whether they are carriers and whether their blood filters properly.[82] Donors who are found to be carriers are then informed and their blood, while often used for those of the same ethnic group, is not used for those with sickle cell disease who require a blood transfusion.[83]

## Middle East [edit]

In Saudi Arabia about 4.2% of the population carry the sickle-cell trait and 0.26% have sickle-cell disease. The highest prevalence is in the Eastern province where approximately 17% of the population carry the gene and 1.2% have sickle-cell disease.[84] In 2005 in Saudi Arabia a mandatory pre-marital test including HB electrophoresis was launched and aimed to decrease the incidence of SCD and thalassemia.[85]

In Bahrain a study published in 1998 that covered about 56,000 people in hospitals in Bahrain found that 2% of newborns have sickle cell disease, 18% of the surveyed people have the sickle cell trait, and 24% were carriers of the gene mutation causing the disease.[86] The country began screening of all pregnant women in 1992 and newborns started being tested if the mother was a carrier. In 2004, a law was passed requiring couples planning to get married to undergo free premarital counseling. These programs were accompanied by public education campaigns.[87]

### India and Nepal [edit]

Sickle-cell disease is common in ethnic groups of central India who share a genetic linkage with African communities,[*citation needed*] where the prevalence has ranged from 9.4 to 22.2% in endemic areas of Madhya Pradesh, Rajasthan and Chhattisgarh.[88] It is also endemic among Tharu people of Nepal and India; however, they have a sevenfold lower incidence of malaria despite living in a malaria infested zone.[89]

### Caribbean Islands [edit]

In Jamaica, 10% of the population carries the sickle-cell gene, making it the most prevalent genetic disorder in the country.[90]

## History [edit]

The first modern report of sickle-cell disease may have been in 1846, where the autopsy of an executed runaway slave was discussed; the key findings was the absence of the spleen.[91][92] There were also reports amongst African slaves in the United States exhibiting resistance to malaria but being prone to leg ulcers.[92] The abnormal characteristics of the red blood cells, which later lent their name to the condition, was first described by Ernest E. Irons (1877–1959), intern to the Chicago cardiologist and professor of medicine James B. Herrick (1861–1954), in 1910. Irons saw "peculiar elongated and sickle-shaped" cells in the blood of a man named Walter Clement Noel, a 20-year-old first-year dental student from Grenada. Noel had been admitted to the Chicago Presbyterian Hospital in December 1904 suffering from anaemia.[11][93] Noel was readmitted several times over the next three years for "muscular rheumatism" and "bilious attacks" but completed his studies and returned to the capital of Grenada (St. George's) to practice dentistry. He died of pneumonia in 1916 and is buried in the Catholic cemetery at Sauteurs in the north of Grenada.[11][12] Shortly after the report by Herrick, another case appeared in the *Virginia Medical Semi-Monthly* with the same title, "Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia."[94] This article is based on a patient admitted to the University of Virginia Hospital on November 15, 1910.[95] In the later description by Verne Mason in 1922, the name "sickle cell anemia" is first used.[12][96] Childhood problems related to sickle cells disease were not reported until the 1930s, despite the fact that this cannot have been uncommon in African-American populations.[92]

The Memphis physician Lemuel Diggs, a prolific researcher into sickle cell disease, first introduced the distinction between sickle cell disease and trait in 1933, although it took until 1949 until the genetic characteristics were elucidated by James V. Neel and E.A. Beet.[12] 1949 was the year when Linus Pauling described the unusual chemical behaviour of haemoglobin S, and attributed this to an abnormality in the molecule itself.[12][97] The actual molecular change in HbS was described in the late 1950s BY Vernon Ingram.[12] The late 1940s and early 1950s saw further understanding in the link between malaria and sickle cell disease. In 1954, the introduction of haemoglobin electrophoresis allowed the discovery of particular subtypes, such as HbSC disease.[12]

Large scale natural history studies and further intervention studies were introduced in the 1970s and 1980s, leading to widespread use of prophylaxis against pneumococcal infections amongst other interventions. Bill Cosby's Emmy-winning 1972 TV movie, *To All My Friends on Shore*, depicted the story of the parents of a child suffering from sickle-cell disease.[98] The 1990s saw the development of hydroxycarbamide, and reports of cure through bone marrow transplantation appeared in 2007.[12]

Some old texts refer to it as drepanocytosis.[*citation needed*]

# Research [edit]

*See also: List of sickle-cell disease researchers*

## Umbilical cord blood transplant [edit]

In December 1998, researchers from Emory University conducted an experimental bone marrow transplant procedure on a group of 22 children under 16 years old.[99] One of those patients, 12-year-old Keone Penn, was apparently the first person to be cured of sickle-cell disease through this method.[100] The stem cells were sourced from a donor unrelated to Penn. A 2007 Georgia Senate bill proposing the collection and donation of stem cell material, the "Saving the Cure Act", was nicknamed "Keone's Law" in his honor.[101]

By mid-2007 a similar set of clinical trials in Baltimore had also cured several adults.[102]

## Gene therapy [edit]

In 2001 it was reported that sickle-cell disease had been successfully treated in mice using gene therapy.[103][104] The researchers used a viral vector to make the mice—which have essentially the same defect that causes human sickle cell disease—express production of fetal haemoglobin (HbF), which an individual normally ceases to produce shortly after birth. In humans, using hydroxyurea to stimulate the production of HbF has been known to temporarily alleviate sickle cell disease symptoms. The researchers demonstrated that this gene therapy method is a more permanent way to increase therapeutic HbF production.[105]

Phase 1 clinical trials of gene therapy for sickle cell disease in humans were started in 2014. The clinical trials will assess the safety and initial evidence for efficacy of an autologous transplant of lentiviral vector-modified bone marrow for adults with severe sickle cell disease.[106][107] As of 2014, however, no randomized controlled trials have been reported.[108]

# References [edit]


1. ^ *a b c d e* "What Is Sickle Cell Disease?". *National Heart, Lung, and Blood Institute*. June 12, 2015. Retrieved 8 March 2016.
2. ^ *a b* "What Are the Signs and Symptoms of Sickle Cell Disease?". *National Heart, Lung, and Blood Institute*. June 12, 2015. Retrieved 8 March 2016.
3. ^ *a b* "What Causes Sickle Cell Disease?". *National Heart, Lung, and Blood Institute*. June 12, 2015. Retrieved 8 March 2016.
4. ^ *a b* "Sickle-cell disease and other haemoglobin disorders Fact sheet N°308". January 2011. Retrieved 8 March 2016.
5. ^ "How Is Sickle Cell Disease Diagnosed?". *National Heart, Lung, and Blood Institute*. June 12, 2015. Retrieved 8 March 2016.

   *a b c*

in children with sickle cell disease". *Eur. J. Haematol.* **84** (3): 259–65. doi:10.1111/j.1600-0609.2009.01379.x. PMID 19912310.

51. ^ Walters MC, Patience M, Leisenring W, Eckman JR, Scott JP, Mentzer WC, Davies SC, Ohene-Frempong K, Bernaudin F, Matthews DC, Storb R, Sullivan KM (August 1996). "Bone marrow transplantation for sickle cell disease". *N. Engl. J. Med.* **335** (6): 369–76. doi:10.1056/NEJM199608083350601. PMID 8663884.
52. ^ Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson; Aster, Jon (2009-05-28). Robbins and Cotran Pathologic Basis of Disease, Professional Edition: Expert Consult - Online (Robbins Pathology) (Kindle Locations 33530-33531). Elsevier Health. Kindle Edition.
53. ^ Wierenga KJ, Hambleton IR, Lewis NA (2001).

6. ^ "How Is Sickle Cell Disease Treated?" . *National Heart, Lung, and Blood Institute*. June 12, 2015. Retrieved 8 March 2016.
7. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013." . *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4 . PMC 4561509 . PMID 26063472 .
8. ^ Rees, DC; Williams, TN; Gladwin, MT (11 December 2010). "Sickle-cell disease.". *Lancet (London, England)*. **376** (9757): 2018–31. doi:10.1016/s0140-6736(10)61029-x . PMID 21131035 .
9. ^ Elzouki, Abdelaziz Y. (2012). *Textbook of clinical pediatrics* (2 ed.). Berlin: Springer. p. 2950. ISBN 9783642022012.
10. ^ *a b* GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013." . *Lancet*. **385**: 117–171. doi:10.1016/S0140-6736(14)61682-2 . PMC 4340604 . PMID 25530442 .
11. ^ *a b c* Savitt TL, Goldberg MF (Jan 1989). "Herrick's 1910 case report of sickle cell anemia. The rest of the story". *JAMA*. **261** (2): 266–71. doi:10.1001/jama.261.2.266 . PMID 2642320 .
12. ^ *a b c d e f g h i* Serjeant GR (Dec 2010). "One hundred years of sickle cell disease." . *British journal of haematology*. **151** (5): 425–9. doi:10.1111/j.1365-2141.2010.08419.x . PMID 20955412 .
13. ^ *a b* Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, Jordan L, Lanzkron SM, Lottenberg R, Savage WJ, Tanabe PJ, Ware RE, Murad MH, Goldsmith JC, Ortiz E, Fulwood R, Horton A, John-Sowah J (Sep 10, 2014). "Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members." . *JAMA*. **312** (10): 1033–48. doi:10.1001/jama.2014.10517 . PMID 25203083 .
14. ^ "BestBets: How long should an average sickle cell crisis last?" . Retrieved 2010-11-27.
15. ^ Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson; Aster, Jon (2009-05-28). Robbins and Cotran Pathologic Basis of Disease, Professional Edition: Expert Consult - Online (Robbins Pathology) (Kindle Locations 33498-33499). Elsevier Health. Kindle Edition.
16. ^ Olujohungbe A, Burnett AL (2013). "How I manage priapism due to sickle cell disease". *British Journal of Haematology*. **160** (6): 754–65. doi:10.1111/bjh.12199 . PMID 23293942 .
17. ^ *a b* Glassberg J (August 2011). "Evidence-based



"Survival estimates for patients with homozygous sickle-cell disease in Jamaica: A clinic-based population study". *Lancet*. **357** (9257): 680–683. doi:10.1016/s0140-6736(00)04132-5 . PMID 11247552 .
54. ^ Costa, Fernando Ferreira; Conran, Nicola (2016). *Sickle Cell Anemia: From Basic Science to Clinical Practice* . Springer. p. 35. ISBN 9783319067131. Retrieved 8 May 2016.
55. ^ Kavanagh PL, Sprinz PG, Vinci SR, Bauchner H, Wang CJ (2011). "Management of children with sickle cell disease: a comprehensive review of the literature" . *Pediatrics*. **128** (6): e1552–74. doi:10.1542/peds.2010-3686 . PMID 22123880 .
56. ^ Adams RJ, Ohene-Frempong K, Wang W (2001). "Sickle cell and the brain" . *Hematology Am Soc Hematol Educ Program*. **2001** (1): 31–46. doi:10.1182/asheducation-2001.1.31 . PMID 11722977 .
57. ^ Adams RJ (November 2007). "Big strokes in small persons" . *Arch. Neurol*. **64** (11): 1567–74. doi:10.1001/archneur.64.11.1567 . PMID 17998439 .
58. ^ Martí-Carvajal, A; Dunlop, R; Agreda-Perez, L (18 October 2004). "Treatment for avascular necrosis of bone in people with sickle cell disease.". *The Cochrane database of systematic reviews* (4): CD004344. doi:10.1002/14651858.CD004344.pub2 . PMID 15495103 .
59. ^ Kenny MW, George AJ, Stuart J (July 1980). "Platelet hyperactivity in sickle-cell disease: a consequence of hyposplenism" . *Journal of Clinical Pathology*. **33** (7): 622–5. doi:10.1136/jcp.33.7.622 . PMC 1146172 . PMID 7430367 . Retrieved 2011-03-23.
60. ^ Chrouser KL, Ajiboye OB, Oyetunji TA, Chang DC (April 2011). "Priapism in the United States: the changing role of sickle cell disease". *American Journal of Surgery*. **201** (4): 468–74. doi:10.1016/j.amjsurg.2010.03.017 . PMID 21421100 .
61. ^ Almeida A, Roberts I (May 2005). "Bone involvement in sickle cell disease" . *Br. J. Haematol*. **129** (4): 482–90. doi:10.1111/j.1365-2141.2005.05476.x . PMID 15877730 .
62. ^ Rudge FW (1991). "Hyperbaric oxygen therapy in the treatment of sickle cell leg ulcers" . *J. Hyperbaric Med*. **6** (1): 1–4. Retrieved 2011-03-23.
63. ^ Elagouz M, Jyothi S, Gupta B, Sivaprasad S (July 2010). "Sickle cell disease and the eye: old and new concepts" . *Survey of Ophthalmology*. **55** (4): 359–77. doi:10.1016/j.survophthal.2009.11.004 . PMID 20452638 . Retrieved 2011-03-23.
64. ^ Smith WR, Penberthy LT, Bovbjerg VE, McClish DK, Roberts JD, Dahman B, Aisiku IP, Levenson JL, Roseff SD (Jan 2008). "Daily assessment of pain in adults with sickle cell disease". *Annals of Internal Medicine*. **148** (2): 94–101. doi:10.7326/0003-4819-

management of sickle cell disease in the emergency department". *Emergency Medicine Practice*. **13** (8): 1–20; quiz 20. PMID 22164362.
18. ^ Anie KA, Green J (2012). Anie, Kofi A, ed. "Psychological therapies for sickle cell disease and pain". *Cochrane Database of Systematic Reviews*. **2**: CD001916. doi:10.1002/14651858.CD001916.pub2. PMID 22336781.
19. ^ Pearson HA (Aug 1977). "Sickle cell anemia and severe infections due to encapsulated bacteria" (Free full text). *J Infect Dis*. 136 Suppl: S25–30. doi:10.1093/infdis/136.Supplement.S25. ISSN 0022-1899. PMID 330779.
20. ^ Wong WY, Powars DR, Chan L, Hiti A, Johnson C, Overturf G (Mar 1992). "Polysaccharide encapsulated bacterial infection in sickle cell anaemia: a thirty year epidemiologic experience". *Am J Hematol*. **39** (3): 176–82. doi:10.1002/ajh.2830390305. PMID 1546714.
21. ^ Khatib R, Rabah R, Sarnaik SA (January 2009). "The spleen in the sickling disorders: an update". *Pediatric Radiology*. **39** (1): 17–22. doi:10.1007/s00247-008-1049-9. PMID 19002450.
22. ^ [a] [b] Glassberg, J (August 2011). "Evidence-based management of sickle cell disease in the emergency department.". *Emergency medicine practice*. **13** (8): 1–20; quiz 20. PMID 22164362.
23. ^ Mekontso Dessap A, Leon R, Habibi A, Nzouakou R, Roudot-Thoraval F, Adnot S, Godeau B, Galacteros F, Brun-Buisson C, Brochard L, Maitre B (2008). "Pulmonary hypertension and cor pulmonale during severe acute chest syndrome in sickle cell disease". *Am. J. Respir. Crit. Care Med*. **177** (6): 646–53. doi:10.1164/rccm.200710-1606OC. PMID 18174543.
24. ^ Paul RN, Castro OL, Aggarwal A, Oneal PA (2011). "Acute chest syndrome: sickle cell disease". *Eur. J. Haematol*. **87** (3): 191–207. doi:10.1111/j.1600-0609.2011.01647.x. PMID 21615795.
25. ^ Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson; Aster, Jon (2009-05-28). Robbins and Cotran Pathologic Basis of Disease, Professional Edition: Expert Consult - Online (Robbins Pathology) (Kindle Location 33329). Elsevier Health. Kindle Edition.
26. ^ Slavov SN, Kashima S, Pinto AC, Covas DT (August 2011). "Human parvovirus B19: general considerations and impact on patients with sickle-cell disease and thalassemia and on blood transfusions". *FEMS Immunology and Medical Microbiology*. **62** (3): 247–62. doi:10.1111/j.1574-695X.2011.00819.x. PMID 21585562.
27. ^ Balgir RS (March 2012). "Community expansion and gene geography of sickle cell trait and G6PD deficiency, and natural selection against malaria: experience from tribal land of India". *Cardiovascular & Hematological Agents in Medicinal Chemistry*. **10** (1): 3–13. doi:10.2174/187152512799201190.
148-2-200801150-00004. ISSN 0003-4819. PMID 18195334.
65. ^ Caughey MC, Poole C, Ataga KI, Hinderliter AL (9 April 2015). "Estimated pulmonary artery systolic pressure and sickle cell disease: a meta-analysis and systematic review". *British Journal of Haematology*. **170**: 416–424. doi:10.1111/bjh.13447.
66. ^ Powars DR, Elliott-Mills DD, Chan L, Niland J, Hiti AL, Opas LM, Johnson C (Oct 1991). "Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality". *Annals of Internal Medicine*. **115** (8): 614–20. doi:10.7326/0003-4819-115-8-614. ISSN 0003-4819. PMID 1892333.
67. ^ Weatherall DJ, Clegg JB (2001). "Inherited haemoglobin disorders: an increasing global health problem". *Bull. World Health Organ*. **79** (8): 704–12. PMC 2566499. PMID 11545326.
68. ^ Roberts I, de Montalembert M (July 2007). "Sickle cell disease as a paradigm of immigration hematology: new challenges for hematologists in Europe". *Haematologica*. **92** (7): 865–71. doi:10.3324/haematol.11474. PMID 17606434.
69. ^ Wellems TE, Hayton K, Fairhurst RM (September 2009). "The impact of malaria parasitism: from corpuscles to communities". *J. Clin. Invest*. **119** (9): 2496–505. doi:10.1172/JCI38307. PMC 2735907. PMID 19729847.
70. ^ WHO. "Sickle-cell anaemia - Report by the Secretariat" (PDF). Retrieved 2010-11-27.
71. ^ Aidoo M, Terlouw DJ, Kolczak MS, McElroy PD, ter Kuile FO, Kariuki S, Nahlen BL, Lal AA, Udhayakumar V (2002). "Protective effects of the sickle cell gene against malaria morbidity and mortality". *Lancet*. **359** (9314): 1311–2. doi:10.1016/S0140-6736(02)08273-9. PMID 11965279.
72. ^ National Heart, Lung and Blood Institute. "Sickle cell anemia, key points". Retrieved 2010-11-27.
73. ^ "September is Sickle Cell Awareness Month". CDC. Retrieved 6 February 2011.
74. ^ "Sickle Cell Disease: Data & Statistics". Centers for Disease Control and Prevention. 16 September 2011. Retrieved 8 November 2011.
75. ^ "Disorder Name: Sickle Cell Disease". New Born Screening. Retrieved 11 October 2016.
76. ^ Bardakdjian J, Wajcman H (September 2004). "[Epidemiology of sickle cell anemia]". *Rev Prat* (in French). **54** (14): 1531–3. PMID 15558961.
77. ^ Bardakdjian-Michau J, Bahuau M, Hurtrel D, Godart C, Riou J, Mathis M, Goossens M, Badens C, Ducrocq R, Elion J, Perini JM (January 2009). "Neonatal screening for sickle cell disease in France". *J. Clin. Pathol*. **62** (1): 31–3. doi:10.1136/jcp.2008.058867. PMID 19103855.
78. ^ Le dépistage néonatal de la drépanocytose en France. Numéro thématique. La drépanocytose en France : des données épidémiologiques pour améliorer la prise en charge, Bardakdjian-Michau J, INVS, July 2012
79. ^ "Inheriting sickle cell anaemia - Live Well - NHS

PMID 22264009 .
28. ^ Jadavji T, Prober CG (April 1985). "Dactylitis in a child with sickle cell trait". *Can Med Assoc J.* **132** (7): 814–5. ISSN 0008-4409. PMC 1345873. PMID 3978504.
29. ^ Worrall VT, Butera V (1976). "Sickle-cell dactylitis". *J Bone Joint Surg Am*. **58** (8): 1161–3. PMID 1002763.
30. ^ Miller ST (May 2011). "How I treat acute chest syndrome in children with sickle cell disease". *Blood*. **117** (20): 5297–305. doi:10.1182/blood-2010-11-261834. PMID 21406723.
31. ^ James, William D.; Berger, Timothy G.; et al. (2006). *Andrews' Diseases of the Skin: clinical Dermatology*. Saunders Elsevier. p. 847. ISBN 0-7216-2921-0.
32. ^ Reference, Genetics Home. "sickle cell disease". *Genetics Home Reference*. Retrieved 2016-05-07.
33. ^ Green NS, Fabry ME, Kaptue-Noche L, Nagel RL (Oct 1993). "Senegal haplotype is associated with higher HbF than Benin and Cameroon haplotypes in African children with sickle cell anemia". *Am. J. Hematol*. **44** (2): 145–6. doi:10.1002/ajh.2830440214. ISSN 0361-8609. PMID 7505527.
34. ^ Allison AC (October 2009). "Genetic control of resistance to human malaria". *Current Opinion in Immunology*. **21** (5): 499–505. doi:10.1016/j.coi.2009.04.001. PMID 19442502.
35. ^ Kwiatkowski DP (Aug 2005). "How Malaria Has Affected the Human Genome and What Human Genetics Can Teach Us about Malaria". *Am. J. Hum. Genet*. **77** (2): 171–92. doi:10.1086/432519. ISSN 0002-9297. PMC 1224522. PMID 16001361.
36. ^ Ponçon N, Toty C, L'Ambert G, Le Goff G, Brengues C, Schaffner F, Fontenille D (2007). "Biology and dynamics of potential malaria vectors in Southern France". *Malar. J.* **6** (1): 18. doi:10.1186/1475-2875-6-18. PMC 1808464. PMID 17313664.
37. ^ Lesi FE, Bassey EE (July 1972). "Family study in sickle cell disease in Nigeria". *J Biosoc Sci*. **4** (3): 307–13. doi:10.1017/S0021932000008622. PMID 5041262.
38. ^ "How Does Sickle Cell Cause Disease?". Retrieved 2010-11-27.
39. ^ "Sickle Cell Anemia: eMedicine Emergency Medicine". Retrieved 2010-11-27.
40. ^ Clarke GM, Higgins TN (August 2000). "Laboratory investigation of haemoglobinopathies and thalassemias: review and update". *Clin. Chem*. **46** (8 Pt 2): 1284–90. PMID 10926923.
41. ^ "BestBets: Does routine urinalysis and chest radiography detect occult bacterial infection in sickle cell patients presenting to the accident and emergency department with painful crisis?". Retrieved 2010-11-27.
42. ^ Lee, C., Davies, S.,& Dezatoux, C. (2000). Choices". *www.nhs.uk*.
80. ^ "Sickle cell anaemia - NHS Choices". *www.nhs.uk*.
81. ^ "Who is offered screening and when?". *screening.nhs.uk*.
82. ^ "Give Blood - Resources - Sickle Cell and Blood Donation". *Give Blood*.
83. ^ "Why is Blood from Afro-Caribbean Donors Special?". *sicklecellsociety.org*.
84. ^ Jastaniah W (2011). "Epidemiology of sickle cell disease in Saudi Arabia". *Annals of Saudi Medicine*. **31** (3): 289–93. doi:10.4103/0256-4947.81540. PMC 3119971. PMID 21623060.
85. ^ Memish ZA, Saeedi MY (2011). "Six-year outcome of the national premarital screening and genetic counseling program for sickle cell disease and β-thalassemia in Saudi Arabia". *Annals of Saudi Medicine*. **31** (3): 229–35. doi:10.4103/0256-4947.81527. PMC 3119961. PMID 21623050.
86. ^ Al Arrayed, Sheikha (1995). "Features of sickle-cell disease in Bahrain". *Eastern Mediterranean Health Journal*. **1** (1).
87. ^ Al Arrayed, S; Al Hajeri, A (2010). "Public awareness of sickle cell disease in Bahrain.". *Annals of Saudi medicine*. **30** (4): 284–8. doi:10.4103/0256-4947.65256. PMC 2931779. PMID 20622345.
88. ^ Awasthy N, Aggarwal KC, Goyal PC, Prasad MS, Saluja S, Sharma M (2008). "Sickle cell disease: Experience of a tertiary care center in a nonendemic area". *Annals of Tropical Medicine and Public Health*. **1** (1): 1–4. doi:10.4103/1755-6783.43069.
89. ^ http://nepalitimes.com/article/nation/Life-%20with-sickle-cell,1460
90. ^ Asnani MR, McCaw-Binns AM, Reid ME (2011). "Excess Risk of Maternal Death from Sickle Cell Disease in Jamaica: 1998–2007". *PLoS ONE*. **6** (10): e26281. doi:10.1371/journal.pone.0026281. PMC 3200316. PMID 22039456.
91. ^ Lebby R (1846). "Case of absence of the spleen". *Southern J of Med Pharmacol*. **1**: 481–3.
92. ^ *a b c* Ballas SK, Gupta K, Adams-Graves P (Nov 1, 2012). "Sickle cell pain: a critical reappraisal.". *Blood*. **120** (18): 3647–56. doi:10.1182/blood-2012-04-383430. PMID 22923496.
93. ^ Herrick JB (1910). "Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia". *Arch. Intern. Med*. **6** (5): 517–521. doi:10.1001/archinte.1910.00050330050003.; reprinted as Herrick JB (2001). "Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. 1910". *The Yale Journal of Biology and Medicine*. **74** (3): 179–84. PMC 2588723. PMID 11501714.
94. ^ Washburn, R.E. (1911). "Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia". *The Virginia Medical Semi-Monthly*. **15** (21): 490–493.
95. ^ "UVa Hospital Celebrating 100 Years". University

Neonatal Screening for sickle cell disease. *The Cochrane Collaboration*. John Wiley & Sons, Ltd.
43. ^ Oniyangi O, Omari AA (2006). Oniyangi, Oluseyi, ed. "Malaria chemoprophylaxis in sickle cell disease". *Cochrane Database of Systematic Reviews*. **13** (4): CD003489. doi:10.1002/14651858.CD003489.pub2. PMID 17054173.
44. ^ Aldrich TK, Nagel RL (1998). "Pulmonary Complications of Sickle Cell Disease.". In Reynolds HY, Bone RC, Dantzker DR, George RB, Matthay RA. *Pulmonary and Critical Care Medicine* (6th ed.). St. Louis: Mosby. pp. 1–10. ISBN 0-8151-1371-4.
45. ^ Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, McMahon RP, Bonds DR (May 1995). "Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia". *N. Engl. J. Med.* **332** (20): 1317–22. doi:10.1056/NEJM199505183322001. ISSN 0028-4793. PMID 7715639.
46. ^ Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, Orringer E, Bellevue R, Olivieri N, Eckman J, Varma M, Ramirez G, Adler B, Smith W, Carlos T, Ataga K, DeCastro L, Bigelow C, Saunthararajah Y, Telfer M, Vichinsky E, Claster S, Shurin S, Bridges K, Waclawiw M, Bonds D, Terrin M (April 2003). "Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment". *JAMA*. **289** (13): 1645–51. doi:10.1001/jama.289.13.1645. PMID 12672732.
47. ^ Platt OS (Mar 2008). "Hydroxyurea for the treatment of sickle cell anemia". *N. Engl. J. Med.* **358** (13): 1362–9. doi:10.1056/NEJMct0708272. PMID 18367739.
48. ^ Drasar E, Igbineweka N, Vasavda N, Free M, Awogbade M, Allman M, Mijovic A, Thein SL (March 2011). "Blood transfusion usage among adults with sickle cell disease - a single institution experience over ten years". *Br. J. Haematol.* **152** (6): 766–70. doi:10.1111/j.1365-2141.2010.08451.x. PMID 21275951.
49. ^ Gyang E, Yeom K, Hoppe C, Partap S, Jeng M (January 2011). "Effect of chronic red cell transfusion therapy on vasculopathies and silent infarcts in patients with sickle cell disease". *Am. J. Hematol.* **86** (1): 104–6. doi:10.1002/ajh.21901. PMID 21117059.
50. ^ Mirre E, Brousse V, Berteloot L, Lambot-Juhan K, Verlhac S, Boulat C, Dumont MD, Lenoir G, de Montalembert M (March 2010). "Feasibility and efficacy of chronic transfusion for stroke prevention of Virginia. Retrieved 28 January 2015.
96. ^ Mason VR (1922). "Sickle cell anemia". *JAMA*. **79** (16): 1318–1320. doi:10.1001/jama.1922.02640160038012. Reprinted in PMID 3900438
97. ^ Pauling L, Itano HA (1949). "Sickle cell anemia, a molecular disease". *Science*. **110** (2865): 543–548. doi:10.1126/science.110.2865.543. PMID 15395398.
98. ^ "Foster, Gloria". *Facts On File History Database*. Retrieved 2015-02-25.
99. ^ http://www.nejm.org/doi/full/10.1056/NEJM199608083350601#t=article
100. ^ http://www.ajc.com/news/news/local-obituaries/keone-penn-27-medical-trailblazer-wanted-to-be-a-c/nYXxF/
101. ^ "About SB 148". *Savingthecure.org*. Retrieved 11 June 2015.
102. ^ http://www.journalnow.com/archives/breakthrough-baltimore-woman-becomes-one-of-the-first-adults-to/article_ba1d879b-4727-5cc1-a156-1a52403b4100.html
103. ^ Pawliuk R, Westerman KA, Fabry ME, Payen E, Tighe R, Bouhassira EE, Acharya SA, Ellis J, London IM, Eaves CJ, Humphries RK, Beuzard Y, Nagel RL, Leboulch P (2001). "Correction of Sickle Cell Disease in Transgenic Mouse Models by Gene Therapy". *Science*. **294** (5550): 2368–71. doi:10.1126/science.1065806. PMID 11743206.
104. ^ Wilson, Jennifer Fisher (18 March 2002). "Murine Gene Therapy Corrects Symptoms of Sickle Cell Disease". *The Scientist – Magazine of the Life Sciences*. Retrieved 17 December 2014.
105. ^ St. Jude Children's Research Hospital (4 December 2008). "Gene Therapy Corrects Sickle Cell Disease In Laboratory Study". ScienceDaily. Retrieved 17 December 2014.
106. ^ (15 December 2014) Stem Cell Gene Therapy for Sickle Cell Disease, ClinicalTrials.gov Identifier: NCT02247843 ClinicalTrials.gov, U.S. National Institutes of Health, Retrieved 17 December 2014
107. ^ (15 December 2014) Collection and Storage of Umbilical Cord Stem Cells for Treatment of Sickle Cell Disease; ClinicalTrials.gov Identifier: NCT00012545 ClinicalTrials.gov, U.S. National Institutes of Health, Retrieved 17 December 2014
108. ^ Olowoyeye, A; Okwundu, CI (10 October 2014). "Gene therapy for sickle cell disease.". *The Cochrane database of systematic reviews*. **10**: CD007652. doi:10.1002/14651858.CD007652.pub4. PMID 25300171.

## Further reading [edit]

- Brown, Robert T., ed. (2006). *Comprehensive handbook of childhood cancer and sickle cell disease: a biopsychosocial approach*. Oxford

Library resources about

University Press. ISBN 978-0-19-516985-0.
- Hill, Shirley A. (2003). *Managing Sickle Cell Disease in Low-Income Families*. Temple University Press. ISBN 978-1-59213-195-2.
- Serjeant, Graham R.; Beryl E. (2001). *Sickle Cell Disease*. Oxford University Press. ISBN 978-0-19-263036-0.
- Tapper, Melbourne (1999). *In the blood: sickle cell anemia and the politics of race*. University of Pennsylvania Press. ISBN 978-0-8122-3471-8.



## External links [edit]

- Sickle cell at DMOZ
- Sickle Cell Anaemia OER Project





| v · t · e · | **Diseases of red blood cells (D50–69,74, 280–287)** | | |
|---|---|---|---|
| ↑ | **Polycythemia** | Polycythemia vera · | |
| ↓ | **Anemia** | **Nutritional** | Micro-: Iron-deficiency anemia (Plummer–Vinson syndrome · · |
| | | | Macro-: Megaloblastic anemia (Pernicious anemia · · |
| | | **Hemolytic (mostly normo-)** | **Hereditary** | *enzymopathy:* G6PD · *glycolysis* (PK · TI · HK · · |
| | | | | *hemoglobinopathy:* Thalassemia (alpha · beta · delta · · |
| | | | | **Sickle-cell disease**/trait · HPFH · |
| | | | | *membrane:* Hereditary spherocytosis |
| | | | | (Minkowski–Chauffard syndrome · · Hereditary elliptocytosis |
| | | | | (Southeast Asian ovalocytosis · · Hereditary stomatocytosis · |
| | | | **Acquired** | Autoimmune (WAHA · CAD · PCH · · |
| | | | | *membrane* (PNH · · |
| | | | | MAHA · TM (HUS · · |
| | | | | Drug-induced autoimmune · Drug-induced nonautoimmune · |
| | | | | Hemolytic disease of the newborn · |
| | | **Aplastic (mostly normo-)** | Hereditary: Fanconi anemia · Diamond–Blackfan anemia · |
| | | | Acquired: PRCA · Sideroblastic anemia · Myelophthisic · |
| | | **Blood tests** | *MCV* (Normocytic · Microcytic · Macrocytic · · *MCHC* (Normochromic · |
| | | | Hypochromic · · |
| | **Other** | Methemoglobinemia · Sulfhemoglobinemia · Reticulocytopenia · | |

| v · t · e · | **Medicine** |
|---|---|
| | Outline · History · |
| | **Surgery** |
| | Cardiac surgery · Cardiothoracic surgery · Colorectal surgery · Eye surgery · General surgery · Neurosurgery · Oral and maxillofacial surgery · Orthopedic surgery · Hand surgery · Otolaryngology (ENT) · Pediatric surgery · Plastic surgery · Reproductive surgery · Surgical oncology · Thoracic surgery · Transplant surgery · Trauma surgery · Urology (Andrology |

| | |
|---|---|
| **Specialties and subspecialties** | · · Vascular surgery · |
| | **Internal medicine** |
| | Allergy / Immunology · Angiology · Cardiology · Endocrinology · Gastroenterology (Hepatology · · Geriatrics · Hematology · Hospital medicine · Infectious disease · Nephrology · Oncology · Pulmonology · Rheumatology · |
| | **Obstetrics and gynaecology** |
| | Gynaecology · Gynecologic oncology · Maternal–fetal medicine · Obstetrics · Reproductive endocrinology and infertility · Urogynecology · |
| | **Diagnostic** |
| | Radiology (Interventional radiology · Nuclear medicine · · Pathology (Anatomical pathology · Clinical pathology · Clinical chemistry · Clinical immunology · Cytopathology · Medical microbiology · Transfusion medicine · · |
| | **Other specialties** |
| | Addiction medicine · Adolescent medicine · Anesthesiology · Dermatology · Disaster medicine · Diving medicine · Emergency medicine (Mass-gathering medicine · · Family medicine · General practice · Hospital medicine · Intensive-care medicine · Medical genetics · Neurology (Clinical neurophysiology · · Occupational medicine · Ophthalmology · Oral medicine · Pain management · Palliative care · Pediatrics (Neonatology · · Physical medicine and rehabilitation (PM&R) · Preventive medicine · Psychiatry · Public health · Radiation oncology · Reproductive medicine · Sexual medicine · Sleep medicine · Sports medicine · Transplantation medicine · Tropical medicine (Travel medicine · · Venereology · |
| **Medical education** | Medical school · Bachelor of Medicine, Bachelor of Surgery · Bachelor of Medical Sciences · Master of Medicine · Master of Surgery · Doctor of Medicine · Doctor of Osteopathic Medicine · MD–PhD · |
| **Related topics** | Allied health (Dentistry · Podiatry · · Nanomedicine · Molecular oncology · Personalized medicine · Veterinary medicine · Physician (Chief physician · · History of medicine · |
| | **Book** · |

Categories: Autosomal recessive disorders | Chronic pain syndromes | Hereditary hemolytic anemias | Health in Africa | Hematopathology | Disorders of globin and globulin proteins | Sickle-cell disease

# Spina bifida



**Spina bifida** is a birth defect where there is incomplete closing of the backbone and membranes around the spinal cord. There are three main types: **spina bifida occulta**, **meningocele**, and **myelomeningocele**.[1] The most common location is the lower back, but in rare cases it may be the middle back or neck.[2] Occulta has no or only mild signs.[3] Signs of occulta may include a hairy patch, dimple, dark spot, or swelling on the back at the site of the gap in the spine. Meningocele typically causes mild problems with a sac of fluid present at the gap in the spine.[1] Myelomeningocele, also known as open spina bifida, is the most severe form. Associated problems include poor ability to walk, problems with bladder or bowel control, hydrocephalus, a tethered spinal cord, and latex allergy.[4] Learning problems are relatively uncommon.[4]

Spina bifida is believed to be due to a combination of genetic and environmental factors.[5] After having one child with the condition, or if one of the parents has the condition, there is a 4% chance that the next child will also be affected.[6] Not having enough folate in the diet before and during pregnancy also plays a significant role.[5] Other risk factors include certain antiseizure medications, obesity, and poorly controlled diabetes.[6] Diagnosis may occur either before or after a child is born. Before birth if a blood test or amniocentesis finds a high level of alpha-fetoprotein (AFP), there is a higher risk of spina bifida. Ultrasound examination may also detect the problem. Medical imaging can confirm the diagnosis after birth.[3] It is a type of neural tube defect with other types including anencephaly and encephalocele.[7]

Most cases of spina bifida can be prevented if the mother gets enough folate before and during pregnancy.[5] Adding folic acid to flour has been found to be effective for most women.[8] Open spina bifida can be surgically closed before or after birth. A shunt may be needed in those with hydrocephalus, and a tethered spinal cord may be surgically repaired. Devices to help with movement such as crutches or wheelchairs may be useful. Urinary catheterization may also be needed.[9]

About 5% of people have spina bifida occulta.[10] Rates of other types of spina bifida vary significantly by country, from 0.1 to 5 per 1000 births.[11] On average in developed countries it occurs in about 0.4 per 1000 births.[12] In the United States, it affected about 0.4 per 1000 births,[6][13] and in India, about 1.9 per 1000 births.[14] Part of this difference is believed to be due to race – with Caucasians at higher risk – and partly due to environmental factors.[15] The term is Latin for "split spine".

## Variants

## Spina bifida

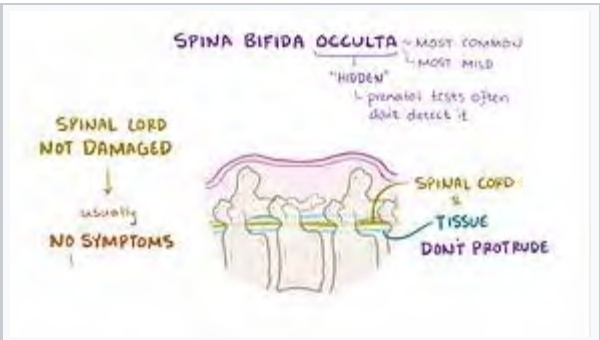

Illustration of a child with spina bifida

**Classification and external resources**

| | |
|---|---|
| **Specialty** | pediatrics, neurosurgery |
| **ICD-10** | Q05, Q76.0 |
| **ICD-9-CM** | 741, 756.17 |
| **OMIM** | 182940 |
| **DiseasesDB** | 12306 |
| **eMedicine** | orthoped/557 |
| **Patient UK** | Spina bifida |
| **MeSH** | *C10.500.680.800* |

[edit on Wikidata]

Edit links

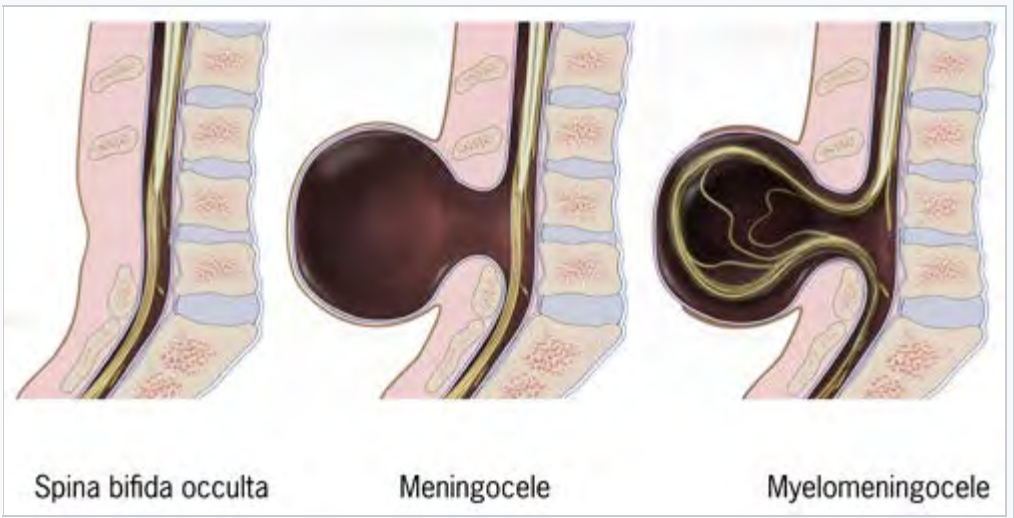



Play media

Video explanation

# Types [edit]

There are two types: spina bifida occulta and spina bifida cystica.[16] Spina bifida cystica can then be broken down into meningocele and myelomeningocele.[16]




Different types of spina bifida

## Spina bifida occulta

[edit]

*Occulta* is Latin for "hidden". This is the mildest form of spina bifida.[17] In occulta, the outer part of some of the vertebrae is not completely closed.[18] The splits in the vertebrae are so small that the spinal cord does not protrude. The skin at the site of the lesion may be normal, or it may have some hair growing from it; there may be a dimple in the skin, or a birthmark.[19] Unlike most other types of neural tube defects, spina bifida occulta is not associated with increased AFP, a common screening tool used to detect neural tube defects in utero. This is because, unlike most of the other neural tube defects, the dural lining is maintained.

Many people with this type of spina bifida do not even know they have it, as the condition is asymptomatic in most cases.[19] The incidence of spina bifida occulta is approximately 10-20% of the population,[20][21] and most people are diagnosed incidentally from spinal X-rays. A systematic review of radiographic research studies found no relationship between spina bifida occulta and back pain.[22] More recent studies not included in the review support the negative findings.[23][24][25]

However, other studies suggest spina bifida occulta is not always harmless. One study found that among patients with back pain, severity is worse if spina bifida occulta is present.[26][27] Among females, this could be mistaken for dysmenorrhea.

*Incomplete posterior fusion* is not a true spina bifida, and is very rarely of neurological significance.[28]

## Meningocele [edit]

A posterior meningocele (pronounced /məˈnɪŋgəˌsil/) or meningeal cyst (pronounced /mɪˈnɪndʒiəl/ /sɪst/) is the least common form of spina bifida. In this form, a single developmental defect allows the meninges to herniate between the vertebrae. As the nervous system remains undamaged, individuals with meningocele are unlikely to suffer long-term health problems, although cases of tethered cord have been reported. Causes of meningocele include teratoma and other tumors of the sacrococcyx and of the presacral space, and Currarino syndrome.

A meningocele may also form through dehiscences in the base of the skull. These may be classified by their localisation to occipital, frontoethmoidal, or nasal. Endonasal meningoceles lie at the roof of the nasal cavity and may be mistaken for a nasal polyp. They are treated surgically. Encephalomeningoceles are classified in the same way and also contain brain tissue.

## Myelomeningocele [edit]

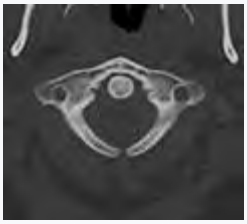
Myelomeningocele, also known as meningomyelocele, is the type of spina bifida that often results in the most severe complications.[29] In individuals with myelomeningocele, the unfused portion of the spinal column allows the spinal cord to protrude through an opening. The meningeal membranes that cover the spinal cord also protrude through the opening, forming a sac enclosing the spinal elements, such as meninges, cerebrospinal fluid, and parts of the spinal cord and nerve roots.[30]

## Myeloschisis [edit]

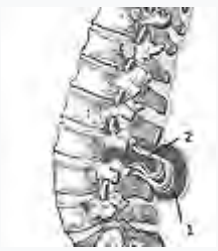
Spina bifida with **myeloschisis** is the most severe form of myelomeningocele. In this type, the involved area is represented by a flattened, plate-like mass of nervous tissue with no overlying membrane. The exposure of these nerves and tissues make the baby more prone to life-threatening infections such as meningitis.[31]

The protruding portion of the spinal cord and the nerves that originate at that level of the cord are damaged or not properly developed. As a result, there is usually some degree of paralysis and loss of sensation below the level of the spinal cord defect. Thus, the more cranial the level of the defect, the more severe the associated nerve dysfunction and resultant paralysis may be. Symptoms may include ambulatory problems, loss of sensation, deformities of the hips, knees or feet, and loss of muscle tone.

X-ray image of spina bifida occulta in S-1



X-ray computed tomography scan of unfused arch at C1



Myelomeningocele in the lumbar area
(1) External sac with cerebrospinal fluid
(2) Spinal cord wedged between the vertebrae

# Signs and symptoms [edit]

## Physical problems [edit]

Physical signs of spina bifida may include:

- Leg weakness and paralysis[32]
- Orthopedic abnormalities (i.e., club foot, hip dislocation, scoliosis)[32]
- Bladder and bowel control problems, including incontinence, urinary tract infections, and poor kidney function[32]
- Pressure sores and skin irritations[32]
- Abnormal eye movement[33]

68% of children with spina bifida have an allergy to latex,[34] ranging from mild to life-threatening. The common use of latex in medical facilities makes this a particularly serious concern. The most common approach to avoid developing an allergy is to avoid contact with latex-containing products such as examination gloves and condoms and catheters that do not specify they are latex free, and many other products, such as some commonly used by dentists.[18]

The spinal cord lesion or the scarring due to surgery may result in a tethered spinal cord. In some individuals, this causes significant traction and stress on the spinal cord and can lead to a worsening of associated paralysis, scoliosis, back pain, and worsening bowel and/or bladder function.[35]

## Neurological problems [edit]

Many individuals with spina bifida have an associated abnormality of the cerebellum, called the Arnold Chiari II malformation. In affected individuals, the back portion of the brain is displaced from the back of the skull down into the upper neck. In about 90% of the people with myelomeningocele, hydrocephalus also occurs because the displaced cerebellum interferes with the normal flow of cerebrospinal fluid, causing an excess of the fluid to accumulate.[36] In fact, the cerebellum also tends to be smaller in individuals with spina bifida, especially for those with higher lesion levels.[33]

The corpus callosum is abnormally developed in 70-90% of individuals with spina bifida myelomeningocele; this affects the communication processes between the left and right brain hemispheres.[37] Further, white matter tracts connecting posterior brain regions with anterior regions appear less organized. White matter tracts between frontal regions have also been found to be impaired.[33]

Cortex abnormalities may also be present. For example, frontal regions of the brain tend to be thicker than expected, while posterior and parietal regions are thinner. Thinner sections of the brain are also associated with increased cortical folding.[33] Neurons within the cortex may also be displaced.[38]

## Executive function [edit]

Several studies have demonstrated difficulties with executive functions in youth with spina bifida,[39][40] with greater deficits observed in youth with shunted hydrocephalus.[41] Unlike typically developing children, youths with spina bifida do not tend to improve in their executive functioning as they grow older.[40] Specific areas of difficulty in some individuals include planning, organizing, initiating, and working memory. Problem-solving, abstraction, and visual planning may also be impaired.[42] Further, children with spina bifida may have poor cognitive flexibility. Although executive functions are often attributed to the frontal lobes of the brain, individuals with spina bifida have intact frontal lobes; therefore, other areas of the brain may be implicated.[41]

Individuals with spina bifida, especially those with shunted hydrocephalus, often have attention problems. Children with spina bifida and shunted hydrocephalus have higher rates of ADHD than children without those conditions (31% vs. 17%).[39] Deficits have been observed for selective attention and focused

attention, although poor motor speed may contribute to poor scores on tests of attention.[41][43] Attention deficits may be evident at a very early age, as infants with spina bifida lag behind their peers in orienting to faces.[44]

### Academic skills [edit]

Individuals with spina bifida may struggle academically, especially in the subjects of mathematics and reading. In one study, 60% of children with spina bifida were diagnosed with a learning disability.[45] In addition to brain abnormalities directly related to various academic skills, achievement is likely affected by impaired attentional control and executive functioning.[38] Children with spina bifida may perform well in elementary school, but begin to struggle as academic demands increase.

Children with spina bifida are more likely than their peers without spina bifida to be dyscalculic.[46] Individuals with spina bifida have demonstrated stable difficulties with arithmetic accuracy and speed, mathematical problem-solving, and general use and understanding of numbers in everyday life.[47] Mathematics difficulties may be directly related to the thinning of the parietal lobes (regions implicated in mathematical functioning) and indirectly associated with deformities of the cerebellum and midbrain that affect other functions involved in mathematical skills. Further, higher numbers of shunt revisions are associated with poorer mathematics abilities.[48] Working memory and inhibitory control deficiencies have been implicated for math difficulties,[49] although visual-spatial difficulties are not likely involved.[46] Early intervention to address mathematics difficulties and associated executive functions is crucial.[49]

Individuals with spina bifida tend to have better reading skills than mathematics skills.[48] Children and adults with spina bifida have stronger abilities in reading accuracy than in reading comprehension.[50] Comprehension may be especially impaired for text that requires an abstract synthesis of information rather than a more literal understanding.[51] Individuals with spina bifida may have difficulty with writing due to deficits in fine motor control and working memory.[50]

## Cause [edit]

Spina bifida is believed to be caused by a combination of genetic and environmental factors.[5] After having one child with the condition, or if a parent has the condition, there is a 4% chance the next child will also be affected.[6] A folic acid deficiency during pregnancy also plays a significant role.[5] Other risk factors include certain antiseizure medications, obesity, and poorly managed diabetes.[6] Drinking alcohol often, triggers macrocytosis which discard folate. After stopping the drinking of alcohol, a time period of months is needed to rejuvenate bone marrow, recover from macrocytosis.[52]

Those who are white or Hispanic have a higher risk. Girls are more prone to being born with spina bifida.[53]

## Pathophysiology [edit]

Spina bifida is sometimes caused by the failure of the neural tube to close during the first month of embryonic development (often before the mother knows she is pregnant). Some forms are known to occur with primary conditions that cause raised central nervous system pressure, which raises the possibility of a dual pathogenesis.[*citation needed*]

In normal circumstances, the closure of the neural tube occurs around the 23rd (rostral closure) and 27th (caudal closure) day after fertilization.[54] However, if something interferes and the tube fails to close properly, a neural tube defect will occur. Medications such as some anticonvulsants, diabetes, obesity, and having a relative with spina bifida can all affect the probability of neural tube malformation.

Extensive evidence from mouse strains with spina bifida indicates that there is sometimes a genetic basis for the condition. Human spina bifida, like other human diseases, such as cancer, hypertension and

atherosclerosis (coronary artery disease), likely results from the interaction of multiple genes and environmental factors.[*citation needed*]

Research has shown the lack of folic acid (folate) is a contributing factor in the pathogenesis of neural tube defects, including spina bifida. Supplementation of the mother's diet with folate can reduce the incidence of neural tube defects by about 70%, and can also decrease the severity of these defects when they occur.[55][56][57] It is unknown how or why folic acid has this effect.

Spina bifida does not follow direct patterns of heredity like muscular dystrophy or haemophilia. Studies show a woman having had one child with a neural tube defect such as spina bifida has about a 3% risk of having another affected child. This risk can be reduced with folic acid supplementation before pregnancy. For the general population, low-dose folic acid supplements are advised (0.4 mg/day).[*citation needed*]

## Prevention [edit]

There is neither a single cause of spina bifida nor any known way to prevent it entirely. However, dietary supplementation with folic acid has been shown to be helpful in reducing the incidence of spina bifida. Sources of folic acid include whole grains, fortified breakfast cereals, dried beans, leaf vegetables and fruits.[58]

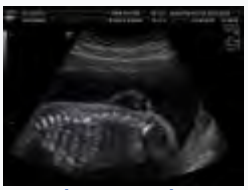
Folate fortification of enriched grain products has been mandatory in the United States since 1998. The U.S. Food and Drug Administration, Public Health Agency of Canada[59] and UK recommended amount of folic acid for women of childbearing age and women planning to become pregnant is at least 0.4 mg/day of folic acid from at least three months before conception, and continued for the first 12 weeks of pregnancy.[60] Women who have already had a baby with spina bifida or other type of neural tube defect, or are taking anticonvulsant medication should take a higher dose of 4–5 mg/day.[60]

Certain mutations in the gene *VANGL1* are implicated as a risk factor for spina bifida: These mutations have been linked with spina bifida in some families with a history of spina bifida.[61]

## Screening [edit]

Open spina bifida can usually be detected during pregnancy by fetal ultrasound. Increased levels of maternal serum alpha-fetoprotein (MSAFP) should be followed up by two tests - an ultrasound of the fetal spine and amniocentesis of the mother's amniotic fluid (to test for alpha-fetoprotein and acetylcholinesterase). AFP tests are now mandated by some state laws (including California). and failure to provide them can have legal ramifications. In one case a man born with spina bifida was awarded a $2 million settlement after court found his mother's OBGYN negligent for not performing these tests.[62] Spina bifida may be associated with other malformations as in dysmorphic syndromes, often resulting in spontaneous miscarriage. In the majority of cases, though, spina bifida is an isolated malformation.

Genetic counseling and further genetic testing, such as amniocentesis, may be offered during the pregnancy, as some neural tube defects are associated with genetic disorders such as trisomy 18. Ultrasound screening for spina bifida is partly responsible for the decline in new cases, because many pregnancies are terminated out of fear that a newborn might have a poor future quality of life. With modern medical care, the quality of life of patients has greatly improved.[54]



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Three-dimensional ultrasound image of the fetal spine at 21 weeks of pregnancy

Ultrasound view of the fetal spine at 21 weeks of pregnancy. In the longitudinal scan a lumbar myelomeningocele is seen.

# Treatment [edit]

There is no known cure for nerve damage caused by spina bifida. Standard treatment is surgery after delivery. This surgery aims to prevent further damage of the nervous tissue and to prevent infection, pediatric neurosurgeons operate to close the opening on the back. The spinal cord and its nerve roots are put back inside the spine and covered with meninges. In addition, a shunt may be surgically installed to provide a continuous drain for the excess cerebrospinal fluid produced in the brain, as happens with hydrocephalus. Shunts most commonly drain into the abdomen or chest wall.

## Pregnancy [edit]

Standard treatment is after delivery. There is tentative evidence about treatment before delivery while the baby is inside the womb for severe disease.[63] As of 2014 the evidence; however, remains insufficient to determine benefits and harms.[64]

Treatment of spina bifida during pregnancy is not without risk.[63] To the mother, this includes scarring of the uterus.[63] To the baby, there is the risk of preterm birth.[63]

Broadly, there are two forms of prenatal treatment. The first is open fetal surgery, where the uterus is opened and the spina bifida repair performed. The second is via fetoscopy. These techniques may be an option to standard therapy.[65]

## Childhood [edit]

Most individuals with myelomeningocele will need periodic evaluations by a variety of specialists:[66]

- Physiatrists coordinate the rehabilitation efforts of different therapists and prescribe specific therapies, adaptive equipment, or medications to encourage as high of a functional performance within the community as possible.
- Orthopedists monitor growth and development of bones, muscles, and joints.
- Neurosurgeons perform surgeries at birth and manage complications associated with tethered cord and hydrocephalus.
- Neurologists treat and evaluate nervous system issues, such as seizure disorders.
- Urologists to address kidney, bladder, and bowel dysfunction - many will need to manage their urinary systems with a program of catheterization. Bowel management programs aimed at improving elimination are also designed.
- Ophthalmologists evaluate and treat complications of the eyes.
- Orthotists design and customize various types of assistive technology, including braces, crutches, walkers, and wheelchairs to aid in mobility. As a general rule, the higher the level of the spina bifida defect, the more severe the paralysis, but paralysis does not always occur. Thus, those with low levels may need only short leg braces, whereas those with higher levels do best with a wheelchair, and some may be able to walk unaided.
- Physical therapists, occupational therapists, psychologists, and speech/language pathologists aid in rehabilitative therapies and increase independent living skills.

## Transition to adulthood [edit]

Although many children's hospitals feature integrated multidisciplinary teams to coordinate healthcare of

youth with spina bifida, the transition to adult healthcare can be difficult because the above healthcare professionals operate independently of each other, requiring separate appointments and communicate among each other much less frequently. Healthcare professionals working with adults may also be less knowledgeable about spina bifida because it is considered a childhood chronic health condition.[67] Due to the potential difficulties of the transition, adolescents with spina bifida and their families are encouraged to begin to prepare for the transition around ages 14–16, although this may vary depending on the adolescent's cognitive and physical abilities and available family support. The transition itself should be gradual and flexible. The adolescent's multidisciplinary treatment team may aid in the process by preparing comprehensive, up-to-date documents detailing the adolescent's medical care, including information about medications, surgery, therapies, and recommendations. A transition plan and aid in identifying adult healthcare professionals are also helpful to include in the transition process.[67]

Further complicating the transition process is the tendency for youths with spina bifida to be delayed in the development of autonomy,[68] with boys particularly at risk for slower development of independence.[69] An increased dependence on others (in particular family members) may interfere with the adolescent's self-management of health-related tasks, such as catheterization, bowel management, and taking medications.[70] As part of the transition process, it is beneficial to begin discussions at an early age about educational and vocational goals, independent living, and community involvement.[71]

## Epidemiology [edit]

About 5% of people have spina bifida occulta.[10] Rates of other types of spina bifida vary significantly by country from 0.1 to 5 per 1000 births.[11] On average in developed countries it occurs in about 0.4 per 1000 births.[12] In the United States it affected about 0.7 per 1000 births,[6] and in India about 1.9 per 1000 births.[14] Part of this difference is believed to be due to race with Caucasians at higher risk and part due to environmental factors.[15]

In the United States rates are higher on the East Coast than on the West Coast, and higher in white people (one case per 1000 live births) than in black people (0.1–0.4 case per 1000 live births). Immigrants from Ireland have a higher incidence of spina bifida than do natives.[72][73] Highest rates of the defect in the USA can be found in Hispanic youth.[74]

The highest incidence rates worldwide were found in Ireland and Wales, where three to four cases of myelomeningocele per 1000 population have been reported during the 1970s, along with more than six cases of anencephaly (both live births and stillbirths) per 1000 population. The reported overall incidence of myelomeningocele in the British Isles was 2.0–3.5 cases per 1000 births.[72][73] Since then, the rate has fallen dramatically with 0.15 per 1000 live births reported in 1998,[54] though this decline is partially accounted for because some fetuses are aborted when tests show signs of spina bifida (see Pregnancy screening above).

## Research [edit]

- 1980 - Fetal surgical techniques using animal models were first developed at the University of California, San Francisco by Michael R. Harrison, N. Scott Adzick and research colleagues.
- 1994 - A surgical model that simulates the human disease is the fetal lamb model of myelomeningocele (MMC) introduced by Meuli and Adzick in 1994. The MMC-like defect was surgically created at 75 days of gestation (term 145 to 150 days) by a lumbo-sacral laminectomy. Approximately 3 weeks after creation of the defect a reversed latissimus dorsi flap was used to cover the exposed neural placode and the animals were delivered by cesarean section just prior term. Human MMC-like lesions with similar neurological deficit were found in the control newborn lambs. In contrast, animals that underwent closure had near-normal neurological function and well-preserved cytoarchitecture of the covered spinal cord on histopathological examination. Despite mild paraparesis, they were able to stand, walk, perform demanding motor test and demonstrated no signs of incontinence. Furthermore, sensory function of the hind limbs was present clinically and confirmed electrophysiologically. Further studies showed that this

model, when combined with a lumbar spinal cord myelotomy leads to the hindbrain herniation characteristic of the Chiari II malformation and that in utero surgery restores normal hindbrain anatomy by stopping the leak of cerebrospinal fluid through the myelomeningocele lesion.[75][76][77][78]

Surgeons at Vanderbilt University, led by Joseph Bruner, attempted to close spina bifida in 4 human fetuses using a skin graft from the mother using a laparoscope. Four cases were performed before stopping the procedure - two of the four fetuses died.[79]

- 1998 - N. Scott Adzick and team at The Children's Hospital of Philadelphia performed open fetal surgery for spina bifida in an early gestation fetus (22 week gestation fetus) with a successful outcome.[80] Open fetal surgery for myelomeningocele involves surgically opening the pregnant mother's abdomen and uterus to operate on the fetus. The exposed fetal spinal cord is covered in layers with surrounding fetal tissue at mid-gestation (19–25 weeks) to protect it from further damage caused by prolonged exposure to amniotic fluid. Between 1998 and 2003, Dr. Adzick, and his colleagues in the Center for Fetal Diagnosis and Treatment at The Children's Hospital Of Philadelphia, performed prenatal spina bifida repair in 58 mothers and observed significant benefit in the babies.

Fetal surgery after 25 weeks has not shown benefit in subsequent studies.[81]

## MOMS trial [edit]

Management of myelomeningocele study (MOMS) was a phase III clinical trial designed to compare two approaches to the treatment of spina bifida: surgery before birth and surgery after birth.[82][83]

The trial concluded that the outcomes after prenatal spina bifida treatment are improved to the degree that the benefits of the surgery outweigh the maternal risks. This conclusion requires a value judgment on the relative value of fetal and maternal outcomes on which opinion is still divided.[84]

To be specific, the study found that prenatal repair resulted in:

- Reversal of the hindbrain herniation component of the Chiari II malformation
- Reduced need for ventricular shunting (a procedure in which a thin tube is introduced into the brain's ventricles to drain fluid and relieve hydrocephalus)
- Reduced incidence or severity of potentially devastating neurologic effects caused by the spine's exposure to amniotic fluid, such as impaired motor function

[85] At one year of age, 40 percent of the children in the prenatal surgery group had received a shunt, compared to 83 percent of the children in the postnatal group. During pregnancy, all the fetuses in the trial had hindbrain herniation. However, at age 12 months, one-third (36 percent) of the infants in the prenatal surgery group no longer had any evidence of hindbrain herniation, compared to only 4 percent in the postnatal surgery group.[85] Further surveillance is ongoing.[86]

## Fetoscopic surgery [edit]

In contrast to the open fetal operative approach performed in the MOMS trial, a minimally invasive fetoscopic approach (akin to 'keyhole' surgery) has been developed. This approach has been evaluated by independent authors of a controlled study which showed some benefit in survivors,[87] but others are more skeptical[88]

The observations in mothers and their fetuses that were operated over the past two and a half years by the matured minimally invasive approach showed the following results: Compared to the open fetal surgery technique, fetoscopic repair of myelomeningocele results in far less surgical trauma to the mother, as large incisions of her abdomen and uterus are not required. In contrast, the initial punctures have a diameter of 1.2 mm only. As a result, thinning of the uterine wall or dehisscence which have been among the most worriesome and criticized complications after the open operative approach do not occur following minimally invasive fetoscopic closure of spina bifida aperta. The risks of maternal chorioamniotis or fetal death as a result of the fetoscopic procedure run below 5%.[89][90][91] Women are discharged home from hospital one week after the procedure. There is no need for chronic administration of tocolytic agents since postoperative uterine contractions are barely ever observed. The current cost of the entire fetoscopic

procedure, including hospital stay, drugs, perioperative clinical, ECG, ultrasound and MRI-examinations, is approximately €16,000.

In 2012, these results of the fetoscopic approach were presented at various national and international meetings, among them at the 1st European Symposium "Fetal Surgery for Spina bifida" in April 2012 in Giessen, at the 15th Congress of the German Society for Prenatal Medicine and Obstetrics in May 2012 in Bonn,[92] at the World Congress of the Fetal Medicine Foundation in June 2012[93] and at the World Congress of the International Society of Obstetrics and Gynecology (ISUOG) in Copenhagen in September 2012,[94] and published in abstract form.[95][96][97][98][99][100][101][102]

Since then more data has emerged. In 2014, two papers were published on fifty one patients.[103][104] These papers suggested that the risk to the mother is small. The main risk appears to be preterm labour, on average at about 33 weeks.

## See also [edit]

- Rachischisis
- Congenital dermal sinus

## References [edit]


1. ^ a b "Spina Bifida: Condition Information". 2012-11-30.
2. ^ Deming, Laura (2011). *Pediatric life care planning and case management* (2nd ed.). Boca Raton, FL: CRC Press. p. 392. ISBN 9781439803585.
3. ^ a b "How do health care providers diagnose spina bifida?". 2012-11-30. Retrieved 8 May 2015.
4. ^ a b "Are there disorders or conditions associated with spina bifida?". 2012-11-30. Retrieved 8 May 2015.
5. ^ a b c d e "What causes spina bifida?". 2012-11-30. Retrieved 8 May 2015.
6. ^ a b c d e f "How many people are affected by or at risk for spina bifida?". 2012-11-30. Retrieved 8 May 2015.
7. ^ "Neural Tube Defects (NTDs): Overview". 2012-11-30. Retrieved 8 May 2015.
8. ^ Castillo-Lancellotti, C; Tur, JA; Uauy, R (May 2013). "Impact of folic acid fortification of flour on neural tube defects: a systematic review.". *Public Health Nutrition*. **16** (5): 901–11. doi:10.1017/s1368980012003576. PMID 22850218.
9. ^ "What are the treatments for spina bifida & related conditions?". 2012-11-30. Retrieved 8 May 2015.
10. ^ a b Sandler, AD (August 2010). "Children with spina bifida: key clinical issues.". *Pediatric Clinics of North America*. **57** (4): 879–92. doi:10.1016/j.pcl.2010.07.009. PMID 20883878.
11. ^ a b *Spina bifida : management and outcome*. Milan: Springer. p. 58. ISBN 9788847006508.
12. ^ a b Kondo, A; Kamihira, O; Ozawa, H (January 2009). "Neural tube defects: prevalence, etiology and prevention.". *International Journal of Urology*. **16** (21): 3141–5. doi:10.1001/jama.1988.03410210053035. PMID 3184392.
58. ^ "Folic Acid Fortification". FDA. February 1996.
59. ^ "Folic Acid - Public Health Agency of Canada". Archived from the original on 2006-09-27.
60. ^ a b "Why do I need folic acid?". NHS Direct. 2006-04-27. Archived from the original on April 13, 2006. Retrieved 2006-08-19.
61. ^ Kibar Z, Torban E, McDearmid JR, Reynolds A, Berghout J, Mathieu M, Kirillova I, De Marco P, Merello E, Hayes JM, Wallingford JB, Drapeau P, Capra V, Gros P (2007). "Mutations in VANGL1 associated with neural-tube defects" (–Scholar search). *N. Engl. J. Med.* **356** (14): 1432–7. doi:10.1056/NEJMoa060651. PMID 17409324.[*dead link*]
62. ^ "Medical malpractice: Childbirth, failed to perform AFP test" (PDF).
63. ^ a b c d Adzick, NS (February 2013). "Fetal surgery for spina bifida: past, present, future.". *Seminars in Pediatric Surgery*. **22** (1): 10–7. doi:10.1053/j.sempedsurg.2012.10.003. PMID 23395140.
64. ^ Grivell, RM; Andersen, C; Dodd, JM (28 October 2014). "Prenatal versus postnatal repair procedures for spina bifida for improving infant and maternal outcomes.". *Cochrane Database of Systematic Reviews*. **10**: CD008825. doi:10.1002/14651858.CD008825.pub2. PMID 25348498.
65. ^ Joyeux, L; Chalouhi, GE; Ville, Y; Sapin, E (June 2014). "[Maternal-fetal surgery for spina bifida: future perspectives].". *Journal de Gynécologie, Obstétrique et Biologie de la Reproduction*. **43** (6): 443–54. doi:10.1016/j.jgyn.2014.01.014.

(1): 49–57. doi:10.1111/j.1442-2042.2008.02163.x. PMID 19120526.
13. ^ Canfield, MA; Honein, MA; Yuskiv, N; Xing, J; Mai, CT; Collins, JS; Devine, O; Petrini, J; Ramadhani, TA; Hobbs, CA; Kirby, RS (November 2006). "National estimates and race/ethnic-specific variation of selected birth defects in the United States, 1999-2001.". *Birth defects research. Part A, Clinical and molecular teratology*. **76** (11): 747–56. doi:10.1002/bdra.20294. PMID 17051527.
14. ^ a b Bhide, P; Sagoo, GS; Moorthie, S; Burton, H; Kar, A (July 2013). "Systematic review of birth prevalence of neural tube defects in India.". *Birth Defects Research. Part A, Clinical and Molecular Teratology*. **97** (7): 437–43. doi:10.1002/bdra.23153. PMID 23873811.
15. ^ a b Puri, Prem (2011). *Newborn surgery* (3 ed.). London: Hodder Arnold. p. 811. ISBN 9781444149494.
16. ^ a b Ferri, Fred F. (2016). *Ferri's Clinical Advisor 2017: 5 Books in 1*. Elsevier Health Sciences. p. 1188.e2. ISBN 9780323448383.
17. ^ "Are There Different Types Of Spina Bifida?". SBA. Retrieved 22 February 2012.[*permanent dead link*]
18. ^ a b Foster, Mark R. "Spina Bifida". Retrieved 2008-05-17.
19. ^ a b "Spina Bifida Occulta". SBA. Retrieved 22 February 2012.[*permanent dead link*]
20. ^ Lambert, H. Wayne; Wineski, Lawrence E. (2011). *Anatomy & Embryology*. Wolters Kluwer. p. 100.
21. ^ "Spina Bifida Fact Sheet". National Institute of Neurological Disorders and Stroke. 2013.
22. ^ van Tulder MW, Assendelft WJ, Koes BW, Bouter LM (1997). "Spinal radiographic findings and nonspecific low back pain. A systematic review of observational studies". *Spine*. **22** (4): 427–34. doi:10.1097/00007632-199702150-00015. PMID 9055372.
23. ^ Iwamoto J, Abe H, Tsukimura Y, Wakano K (2005). "Relationship between radiographic abnormalities of lumbar spine and incidence of low back pain in high school rugby players: a prospective study". *Scandinavian Journal of Medicine & Science in Sports*. **15** (3): 163–8. doi:10.1111/j.1600-0838.2004.00414.x. PMID 15885037.
24. ^ Iwamoto J, Abe H, Tsukimura Y, Wakano K (2004). "Relationship between radiographic abnormalities of lumbar spine and incidence of low back pain in high school and college football players: a prospective study". *American Journal of Sports Medicine*. **32** (3): 781–6. doi:10.1177/0363546503261721. PMID 15090397.
25. ^ Steinberg EL, Luger E, Arbel R, Menachem A, Dekel S (2003). "A comparative roentgenographic analysis of the lumbar spine in male army recruits with and without lower back pain". *Clinical Radiology*. **58** (12): 985–9. doi:10.1016/S0009-9260(03)00296-PMID 24582882.
66. ^ "Center for Spina Bifida: Specialists and Services". *Gillette Children's Hospital Center for Spina Bifida*. Gillette Children's Hospital. Archived from the original on 19 December 2010. Retrieved 15 November 2011.
67. ^ a b Binks, JA; Barden WS; Burke TA; Young NL (2007). "What do we really know about the transition to adult-centered health care? A focus on cerebral palsy and spina bifida". *Archives of Physical Medicine and Rehabilitation*. **88** (8): 1064–1073. doi:10.1016/j.apmr.2007.04.018. PMID 17678671.
68. ^ Davis, BE; Shurtleff DB; Walker WO; Seidel KD; Duguay S (2006). "Acquisition of autonomy skills in adolescents with myelomeningocele". *Developmental Medicine & Child Neurology*. **48** (4): 253–258. doi:10.1017/S0012162206000569.
69. ^ Friedman, D; Holmbeck GN; DeLucia C; Jandasek B; Zebracki K (2009). "Trajectories of autonomy development across the adolescent transition in children with spina bifida". *Rehabilitation Psychology*. **54** (1): 16–27. doi:10.1037/a0014279. PMID 19618699.
70. ^ Monsen, RB (1992). "Autonomy, coping, and self-care agency in healthy adolescents and in adolescents with spina bifida". *Journal of Pediatric Nursing*. **7** (1): 9–13. PMID 1548569.
71. ^ Holmbeck, GN; Devine KA (2010). "Psychosocial and family functioning in spina bifida". *Developmental Disabilities Research Reviews*. **16** (1): 40–46. doi:10.1002/ddrr.90. PMC 2926127. PMID 20419770.
72. ^ a b Lemire RJ (1988). "Neural tube defects". *JAMA*. **259** (4): 558–62. doi:10.1001/jama.259.4.558. PMID 3275817.
73. ^ a b Cotton P (1993). "Finding neural tube 'zippers' may let geneticists tailor prevention of defects". *JAMA*. **270** (14): 1663–4. doi:10.1001/jama.270.14.1663. PMID 8411482.
74. ^ Boulet SL, Yang Q, Mai C, Kirby RS, Collins JS, Robbins JM, Mulinare J (2008). "Trends in postfortification prevalence of spina bifida and ancephaly in the United States". *Birth Defects Research, Part A*. **82** (7): 527–532. doi:10.1002/bdra.20468.
75. ^ Meuli, M; Meuli-Simmen, C; Hutchins, GM; Yingling, CD; Hoffman, KM; Harrison, MR; Adzick, NS (April 1995). "In utero surgery rescues neurological function at birth in sheep with spina bifida.". *Nature Medicine*. **1** (4): 342–7. doi:10.1038/nm0495-342. PMID 7585064.
76. ^ Paek, BW; Farmer, DL; Wilkinson, CC; Albanese, CT; Peacock, W; Harrison, MR; Jennings, RW (2000). "Hindbrain herniation develops in surgically created myelomeningocele but is absent after repair in fetal lambs". *American Journal of Obstetrics and Gynecology*. **183** (5): 1119–23. doi:10.1067/mob.2000.108867. PMID 11084552.

4. PMID 14654032.
26. ^ Taskaynatan MA, Izci Y, Ozgul A, Hazneci B, Dursun H, Kalyon TA (2005). "Clinical significance of congenital lumbosacral malformations in young male population with prolonged low back pain". *Spine*. **30** (8): E210–3. doi:10.1097/01.brs.0000158950.84470.2a. PMID 15834319.
27. ^ Avrahami E, Frishman E, Fridman Z, Azor M (1994). "Spina bifida occulta of S1 is not an innocent finding". *Spine*. **19** (1): 12–5. doi:10.1097/00007632-199401000-00003. PMID 8153797.
28. ^ "Incomplete Fusion, Posterior Element". Retrieved 17 October 2013.[*dead link*]
29. ^ "Myelomeningocele". NIH. Retrieved 2008-06-06.[*permanent dead link*]
30. ^ Saladin, K.S. (2010). *Anatomy & Physiology: Unity of Form and Function*. Mc_Graw Hill. p. 482. ISBN 9780077905750.
31. ^ Mayo Clinic
32. ^ *a b c d* Mitchell, L. E.; Adzick, N. S.; Melchionne, J.; Pasquariello, P. S.; Sutton, L. N.; Whitehead, A. S. (2004). "Spina bifida". *Lancet*. **364** (9448): 1885–1895. doi:10.1016/S0140-6736(04)17445-X. PMID 15555669.
33. ^ *a b c d* Juranek, J; Salman MS (2010). "Anomalous development of brain structure and function in spina bifida myelomeningocele". *Developmental Disabilities*. 1. **16** (1): 23–30. doi:10.1002/ddrr.88.
34. ^ "Protect Yourself From Latex Allergies: Plant Biologists And Immunochemists Develop Hypoallergenic Alternative To Latex". *Science Daily*. 1 December 2008. Retrieved 12 October 2012.
35. ^ "Tethered Spinal Cord Syndrome". AANS. Retrieved 2011-10-23.
36. ^ "Chiari Malformation Fact Sheet: National Institute of Neurological Disorders and Stroke (NINDS)". Ninds.nih.gov. 2011-09-16. Retrieved 2011-10-23.
37. ^ Barkovich, J (2005). *Pediatric Neuroimaging*. Philadelphia, PA: Lippincott, Williams & Wilkens.
38. ^ *a b* Wills, KE (1993). "Neuropsychological functioning in children with spina bifida and/or hydrocephalus". *Journal of Clinical Child Psychology*. **22** (2): 247–265. doi:10.1207/s15374424jccp2202_11.
39. ^ *a b* Burmeister, R; Hannay HJ; Copeland K; Fletcher JM; Boudousquie A; Dennis M (2005). "Attention problems and executive functions in children with spina bifida and hydrocephalus". *Child Neuropsychology*. **11** (3): 265–283. doi:10.1080/092970490911324. PMID 16036451.
40. ^ *a b* Tarazi, RA; Zabel TA; Mahone EM (2008). "Age-related changes in executive function among children with spina bifida/hydrocephalus based on parent behavior ratings". *The Clinical Neuropsychologist*. **22** (4): 585–602.
77. ^ Bouchard, S; Davey, MG; Rintoul, NE; Walsh, DS; Rorke, LB; Adzick, NS (March 2003). "Correction of hindbrain herniation and anatomy of the vermis after in utero repair of myelomeningocele in sheep". *Journal of Pediatric Surgery*. **38** (3): 451–8; discussion 451–8. doi:10.1053/jpsu.2003.50078. PMID 12632366.
78. ^ Meuli, M; Meuli-Simmen, C; Yingling, CD; Hutchins, GM; Timmel, GB; Harrison, MR; Adzick, NS (March 1996). "In utero repair of experimental myelomeningocele saves neurological function at birth". *Journal of Pediatric Surgery*. **31** (3): 397–402. doi:10.1016/S0022-3468(96)90746-0. PMID 8708911.
79. ^ Bruner, JP; Richards, WO; Tulipan, NB; Arney, TL (January 1999). "Endoscopic coverage of fetal myelomeningocele in utero". *American Journal of Obstetrics and Gynecology*. **180** (1 Pt 1): 153–8. doi:10.1016/S0002-9378(99)70167-5. PMID 9914596.
80. ^ Adzick, N Scott; Sutton, Leslie N; Crombleholme, Timothy M; Flake, Alan W (1998). "Successful fetal surgery for spina bifida". *The Lancet*. **352** (9141): 1675–1676. doi:10.1016/S0140-6736(98)00070-1.
81. ^ Tubbs, RS; Chambers, MR; Smyth, MD; Bartolucci, AA; Bruner, JP; Tulipan, N; Oakes, WJ (March 2003). "Late gestational intrauterine myelomeningocele repair does not improve lower extremity function". *Pediatric Neurosurgery*. **38** (3): 128–32. doi:10.1159/000068818. PMID 12601237.
82. ^ "Background of Management of Myelomeningocele Study (MOMS)". The GWU Biostatistics Center. Retrieved 2012-08-06.
83. ^ "Management of Myelomeningocele Study (MOMS) - Full Text View". ClinicalTrials.gov. Retrieved 2012-08-06.
84. ^ Adzick, NS; Thom, Elizabeth A.; Spong, Catherine Y.; Brock, John W.; Burrows, Pamela K.; Johnson, Mark P.; Howell, Lori J.; Farrell, Jody A.; et al. (February 9, 2011). "A Randomized Trial of Prenatal versus Postnatal Repair of Myelomeningocele". *New England Journal of Medicine*. Online First. **364** (11): 993–1004. doi:10.1056/NEJMoa1014379. PMC 3770179. PMID 21306277.
85. ^ *a b* Adzick NS, Thom EA, Spong CY, Brock JW, Burrows PK, Johnson MP, Howell LJ, Farrell JA, Dabrowiak ME, Sutton LN, Gupta N, Tulipan NB, D'Alton ME, Farmer DL (2011). "A randomized trial of prenatal versus postnatal repair of myelomeningocele". *N. Engl. J. Med.* **364**: 993–1004. doi:10.1056/NEJMoa1014379. PMC 3770179. PMID 21306277.
86. ^ "Management of Myelomeningocele Study (MOMS) (MOMS)".
87. ^ VERBEEK, RENATE J (2011). "Fetal endoscopic myelomeningocele closure preserves segmental neurological function". *Developmental Medicine*. **54** (1): 15–22. doi:10.1111/j.1469-8749.2011.04148.x. PMID 22126123.

doi:10.1080/13854040701425940. PMC 2575658. PMID 17853154.
41. ^ a b c Fletcher JM, Brookshire BL, Landry SH, Bohan TP, Davidson KC, et al. (1996). "Attentional skills and executive functions in children with early hydrocephalus". *Developmental Neuropsychology*. **12** (1): 53–76. doi:10.1080/87565649609540640.
42. ^ Snow, JH (1999). "Executive processes for children with spina bifida". *Children's Health Care*. **28** (3): 241–253. doi:10.1207/s15326888chc2803_3.
43. ^ Rose, BM; Holmbeck GN (2007). "Attention and executive functions in adolescents with spina bifida". *Journal of Pediatric Psychology*. **32** (8): 983–994. doi:10.1093/jpepsy/jsm042. PMID 17556398.
44. ^ Landry, SH; Robinson SS; Copeland D; Garner PW (1993). "Goal-directed behavior and perception of self-competence in children with spina bifida". *Journal of Pediatric Psychology*. **18** (3): 389–396. doi:10.1093/jpepsy/18.3.389. PMID 8340846.
45. ^ Mayes, SD; Calhoun, SL (2006). "Frequency of reading, math, and writing disabilities in children with clinical disorders". *Learning and Individual Differences*. **16** (2): 145–157. doi:10.1016/j.lindif.2005.07.004.
46. ^ a b Barnes, MA; Wilkinson, M; Khemani, E; Boudesquie, A; Dennis, M; Fletcher, JM (2006). "Arithmetic processing in children with spina bifida: Calculation accuracy, strategy use, and fact retrieval fluency". *Journal of Learning Disabilities*. **39** (2): 174–187. doi:10.1177/00222194060390020601. PMID 16583797.
47. ^ Dennis, M; Barnes, M (2002). "Math and numeracy in young adults with spina bifida and hydrocephalus". *Developmental Neuropsychology*. **21** (2): 141–155. doi:10.1207/S15326942DN2102_2. PMID 12139196.
48. ^ a b Hetherington, R; Dennis M; Barnes M; Drake J; Gentili J (2006). "Functional outcome in young adults with spina bifida and hydrocephalus". *Child's Nervous System*. **22** (2): 117–124. doi:10.1007/s00381-005-1231-4.
49. ^ a b English,, LH; Barnes, MA; Taylor, HB; Landry, SH (2009). "Mathematical developmental development in spina bifida". *Developmental Disabilities Research Reviews*. **15** (1): 28–34. doi:10.1002/ddrr.48. PMC 3047453. PMID 19213013.
50. ^ a b Barnes, M; Dennis M; Hetherington R (2004). "Reading and writing skills in young adults with spina bifida and hydrocephalus". *Journal of the International Neuropsychological Society*. **10** (5): 655–663. doi:10.1017/S1355617704105055. PMID 15327713.
51. ^ Fletcher JM, Dennis M, Northrup H, Barnes AM, Hannay HJ, Francis, DF (2004). "Spina bifida: Genes, brain, and development". *International Review of Research in Mental Retardation*. International Review of Research in Mental Retardation. **29**: 63–117.
88. ^ SHURTLEFF, DAVID (2011). "Fetal endoscopic myelomeningocele repair". *Developmental Medicine & Child Neurology*. **54** (1): 4–5. doi:10.1111/j.1469-8749.2011.04141.x.
89. ^ Verbeek R, Heep A, et al. (15 December 2010). "Does fetal endoscopic closure of the myelomeningocele prevent loss of neurologic function in spina bifida aperta?". *Cerebrospinal Fluid Research*. **7** (1): S18–S18. doi:10.1186/1743-8454-7-S1-S18.
90. ^ Farmer DL, von Koch CS, Peacock WJ, Danielpour M, Gupta N, Lee H, Harrison MR (2003). "In utero repair of myelomeningocele: experimental pathophysiology, initial clinical experience, and outcomes". *Arch Surg*. **138** (8): 872–878. doi:10.1001/archsurg.138.8.872. PMID 12912746.
91. ^ Kohl T, Gembruch U (2008). "Current status and prospects of fetoscopic surgery for spina bifida in human fetuses". *Fetal Diagn Ther*. **24** (3): 318–320. doi:10.1159/000158549. PMID 18832851.
92. ^ "DZFT beim Kongress DGPGM | DZFT". Dzft.de. Retrieved 2012-11-14.
93. ^ "The Fetal Medicine Foundation / FMF World Congress". Fetalmedicine.com. Retrieved 2012-11-14.
94. ^ "World Congress 2012 | World Congress". ISUOG. 2012-09-13. Retrieved 2012-11-14.
95. ^ Degenhardt J, Schürg R, Kawecki A, Pawlik M, Enzensberger C, Stressig R, Tchatcheva K, Axt-Fliedner R, Kohl T, et al. (2012). "Mütterliches Outcome nach minimal-invasivem Verschluss einer Spina bifida". *Ultraschall in Med*. **33**: S96.
96. ^ Degenhardt J, Schürg R, Kawecki A, Pawlik M, Enzensberger C, Stressig R, Axt-Fliedner R, Kohl T. "Maternal outcome after minimally-invasive fetoscopic surgery for spina bifida. The Giessen experience 2010 – 2012. *Ultrasound Obstet Gynecol* 2012;40(Suppl. 1) 9
97. ^ Neubauer B, Degenhardt J, Axt-Fliedner R, Kohl T (2012). "Frühe neurologische Befunde von Säuglingen nach minimal-invasivem fetoskopischen Verschluss ihrer Spina bifida aperta". *Z Geburtsh Neonat*. **216** (2): 87. doi:10.1055/s-0032-1309110.
98. ^ Kohl T, Kawecki A, Degenhardt J, Axt-Fliedner R, Neubauer B. "Early neurological findings in 20 infants after minimally-invasive fetoscopic surgery for spina bifida at the University of Giessen 2010 – 2011. *Ultrasound Obstet Gynecol* 2012;40(Suppl. 1) 9
99. ^ Kohl T, Schürg R, Maxeiner H, Tchatcheva K, Degenhardt J, Stressig R, Axt-Fliedner R, Gembruch U. "Partial carbon dioxide insufflation (PACI) during fetoscopic surgery on 60 fetuses with spina bifida. *Ultrasound Obstet Gynecol* 2012;40(Suppl. 1) 73-74
100. ^ Kohl T, Kawecki A, Degenhardt J, Axt-Fliedner R. "Preoperative sonoanatomic examination of fetal spina bifida permits prediction of surgical complexity during subsequent minimally-invasive fetoscopic closure. *Ultrasound Obstet Gynecol* 2012;40(Suppl.

doi:10.1016/S0074-7750(04)29003-6 . ISBN 9780123662293.
52. ^ "it is more often due to direct toxicity of the alcohol on the marrow. The macrocytosis of alcoholism usually reverses only after months of abstinence from alcohol".
53. ^ "Spina bifida Risk factors - Mayo Clinic". *www.mayoclinic.org*. Retrieved 2016-11-29.
54. ^ *a b c* T. Lissauer, G. Clayden. Illustrated Textbook of Paediatrics (Second Edition). Mosby, 2003. ISBN 0-7234-3178-7
55. ^ Holmes LB (1988). "Does taking vitamins at the time of conception prevent neural tube defects?". *JAMA*. **260** (21): 3181. doi:10.1001/jama.260.21.3181. PMID 3184398.
56. ^ Milunsky A, Jick H, Jick SS, et al. (1989). "Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects". *JAMA*. **262** (20): 2847–52. doi:10.1001/jama.262.20.2847. PMID 2478730.
57. ^ Mulinare J, Cordero JF, Erickson JD, Berry RJ (1988). "Periconceptional use of multivitamins and the occurrence of neural tube defects". *JAMA*. **260** 1) 8
101. ^ Degenhardt J, Kawecki A, Enzensberger C, Stressig R, Axt-Fliedner R, Kohl T (2012). "Rückverlagerung der Chiari-II Malformation innerhalb weniger Tage nach minimal-invasivem Patchverschluss ans Hinweis für einen effektiven Verschluss der Fehlbildung". *Ultraschall in Med*. **33**: S95.
102. ^ Degenhardt J, Kawecki A, Enzensberger C, Stressig R, Axt-Fliedner R, Kohl T. "Reversal of hindbrain herniation within a few days after minimally-invasive fetoscopic surgery for spina bifida indicates the desired water-tight closure of the lesion. *Ultrasound Obstet Gynecol* 2012;40(Suppl. 1) 74
103. ^ Kohl Thomas (2014). "Percutaneous minimally invasive fetoscopic surgery for spina bifida aperta. Part I: surgical technique and perioperative outcome". *Ultrasound Obstet Gynecol*. **44**: 515–524. doi:10.1002/uog.13430.
104. ^ Degenhardt J; et al. (2014). "Percutaneous minimal-access fetoscopic surgery for spina aperta. Part II: maternal management and outcome". *Ultrasound Obstet Gynecol*. **44**: 525–531. doi:10.1002/uog.13389.

## External links [edit]

- Spina bifida at DMOZ
- CDC: Spina bifida

| v · t · e | **Congenital malformations and deformations of nervous system (Q00–Q07, 740–742)** | |
|---|---|---|
| **Brain** | **Neural tube defect** | Anencephaly (Acephaly · Acrania · Acalvaria · Iniencephaly · · Encephalocele · Arnold–Chiari malformation · |
| | **Other** | Microcephaly · Congenital hydrocephalus (Dandy–Walker syndrome · · *other reduction deformities* (Holoprosencephaly · Lissencephaly · Pachygyria · Hydranencephaly · · Septo-optic dysplasia · Megalencephaly · *CNS cyst* (Porencephaly · Schizencephaly · · Polymicrogyria (Bilateral frontoparietal polymicrogyria · · |
| **Spinal cord** | **Neural tube defect** | **Spina bifida** · Rachischisis · |
| | **Other** | Currarino syndrome · Diastomatomyelia · Syringomyelia · |

| v · t · e | **Congenital malformations and deformations of musculoskeletal system / musculoskeletal abnormality (Q65–Q76, 754–756.3)** | | |
|---|---|---|---|
| | **Arms** | **clavicle / shoulder:** | Cleidocranial dysostosis · Sprengel's deformity · Wallis–Zieff–Goldblatt syndrome · |
| | | **hand deformity:** | Madelung's deformity · Clinodactyly · Oligodactyly · Polydactyly · |
| | | **hip:** | Dislocation of hip / Hip dysplasia · Upington disease · |

| | | | |
|---|---|---|---|
| **Appendicular limb / dysmelia** | **Leg** | | Coxa valga · Coxa vara · |
| | | **knee:** | Genu valgum · Genu varum · Genu recurvatum · Discoid meniscus · Congenital patellar dislocation · Congenital knee dislocation · |
| | | **foot deformity:** | *varus* (Club foot · Pigeon toe · · *valgus* (Flat feet · · Pes cavus · Rocker bottom foot · Hammer toe · |
| | **Either / both** | **fingers and toes** | Polydactyly / Syndactyly (webbed toes · · Arachnodactyly · Cenani–Lenz syndactylism · Ectrodactyly · Brachydactyly (Clubbed thumb · · |
| | | **reduction deficits / limb:** | Acheiropodia · *ectromelia* (Phocomelia · Amelia · Hemimelia · · |
| | | **multiple joints:** | Arthrogryposis · Larsen syndrome · Rapadilino syndrome · |
| **Axial** | **Skull and face** | **Craniosynostosis:** | Scaphocephaly · Oxycephaly · Trigonocephaly · |
| | | **Craniofacial dysostosis:** | Crouzon syndrome · Hypertelorism · Hallermann–Streiff syndrome · Treacher Collins syndrome · |
| | | **other:** | Macrocephaly · Platybasia · Craniodiaphyseal dysplasia · Dolichocephaly · Greig cephalopolysyndactyly syndrome · Plagiocephaly · Saddle nose · |
| | **Vertebral column** | | spinal curvature (Scoliosis · · Klippel–Feil syndrome · Spondylolisthesis · Spina bifida occulta · Sacralization · |
| | **Thoracic skeleton** | **ribs:** | Cervical · Bifid · |
| | | **sternum:** | Pectus excavatum · Pectus carinatum · |

Categories: Dermal and subcutaneous growths | Congenital disorders of nervous system | Congenital disorders of musculoskeletal system




# Sudden infant death syndrome

From Wikipedia, the free encyclopedia

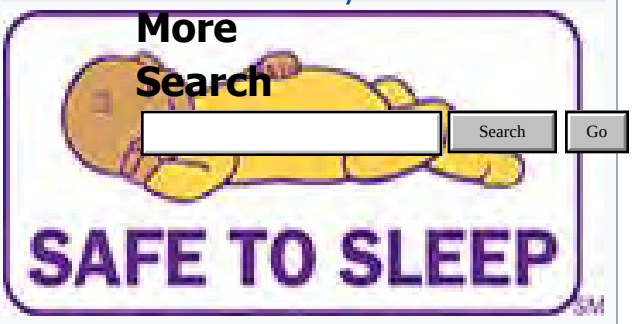
**Sudden infant death syndrome** (**SIDS**), also known as **cot death** or **crib death**, is the sudden unexplained death of a child less than one year of age.[1] Diagnosis requires that the death remains unexplained even after a thorough autopsy and detailed death scene investigation.[2] SIDS usually occurs during sleep.[3] Typically death occurs between the hours of 00:00 and 09:00.[4] There is usually no evidence of struggle and no noise produced.[5]

The exact cause of SIDS is unknown.[6] The requirement of a combination of factors including a specific underlying susceptibility, a specific time in development, and an environmental stressor has been proposed.[3][6] These environmental stressors may include sleeping on the stomach or side, overheating, and exposure to tobacco smoke.[6] Accidental suffocation such as during bed sharing or from soft objects may also play a role.[3][7] Another risk factor is being born before 39 weeks of gestation.[8] SIDS makes up about 80% of sudden and unexpected infant deaths (SUIDs), with other causes including infections, genetic disorders, and heart problems. While child abuse in the form of intentional suffocation may be misdiagnosed as SIDS, this is believed to make up less than 5% of cases.[3]

The most effective method of reducing the risk of SIDS is putting a child less than one year old on its back to sleep.[8] Other measures include a firm mattress separate from but close to caregivers, no loose bedding, a relatively cool sleeping environment, using a pacifier, and avoiding exposure to tobacco smoke.[9] Breastfeeding and immunization may also be preventive.[9][10] Measures not shown to be useful include positioning devices and baby monitors.[9][10] Evidence is not sufficient for the use of fans.[9] Grief support for families impacted by SIDS is important, as the death of the infant is sudden, without witnesses, and often associated with an investigation.[3]

Rates of SIDS vary nearly tenfold in developed countries from one in a thousand to one in ten thousand.[3] Globally it resulted in about 15,000 deaths in 2013 down from 22,000 deaths in 1990.[11] SIDS was the third leading cause of death in children less than one year old in the United States in 2011.[12] It is the most common cause of death between one month and one year of age.[8] About 90% of cases happen before six months of age, with it being most frequent between two months and four months of age.[3][8] It is more common in boys than girls.[8]

**Sudden infant death syndrome**




Safe to Sleep logo

| Classification and external resources | |
|---|---|
| **Specialty** | Pediatrics |
| **ICD-10** | R95 |
| **ICD-9-CM** | 798.0 |
| **OMIM** | 272120 |
| **DiseasesDB** | 12633 |
| **MedlinePlus** | 001566 |
| **eMedicine** | emerg/407 ped/2171 |
| **Patient UK** | Sudden infant death syndrome |
| **MeSH** | D013398 |

[edit on Wikidata]

## Contents

## Definition [edit]

SIDS is a diagnosis of exclusion and should be applied to only those cases in which an infant's death is sudden and unexpected, and remains unexplained after the performance of an adequate postmortem investigation, including:

1. an autopsy (by an experienced pediatric pathologist, if possible);
2. investigation of the death scene and circumstances of the death;
3. exploration of the medical history of the infant and family.

After investigation, some of these infant deaths are found to be caused by accidental suffocation, hyperthermia or hypothermia, neglect or some other defined cause.[13]

Australia and New Zealand are shifting to the term "sudden unexpected death in infancy" (SUDI) for professional, scientific, and coronial clarity.

> The term SUDI is now often used instead of sudden infant death syndrome (SIDS) because some coroners prefer to use the term 'undetermined' for a death previously considered to be SIDS. This change is causing diagnostic shift in the mortality data.[14]

In addition, the U.S. Centers for Disease Control and Prevention (CDC) has recently proposed that such deaths be called "sudden unexpected infant deaths" (SUID) and that SIDS is a subset of SUID.[15]

### Age [edit]

SIDS has a 4-parameter lognormal age distribution that spares infants shortly after birth — the time of maximal risk for almost all other causes of non-trauma infant death.

By definition, SIDS deaths occur under the age of one year, with the peak incidence occurring when the infant is at 2 to 4 months of age. This is considered a critical period because the infant's ability to rouse

from sleep is not yet mature.[3]

## Risk factors [edit]

The cause of SIDS is unknown. Although studies have identified risk factors for SIDS, such as putting infants to bed on their stomachs, there has been little understanding of the syndrome's biological process or its potential causes. The frequency of SIDS does appear to be influenced by social, economic, and cultural factors, such as maternal education, race or ethnicity, and poverty.[16] SIDS is believed to occur when an infant with an underlying biological vulnerability, who is at a critical development age, is exposed to an external trigger.[3] The following risk factors generally contribute either to the underlying biological vulnerability or represent an external trigger:

### Tobacco smoke [edit]

SIDS rates are higher for infants of mothers who smoke during pregnancy.[17][18] SID correlates with levels of nicotine and derivatives in the infant.[19] Nicotine and derivatives cause significant alterations in fetal neurodevelopment.[20]

### Sleeping [edit]

Placing an infant to sleep while lying on the stomach or the side increases the risk.[9] This increased risk is greatest at two to three months of age.[9] Elevated or reduced room temperature also increases the risk,[21] as does excessive bedding, clothing, soft sleep surfaces, and stuffed animals.[22] Bumper pads may increase the risk and, as there is little evidence of benefit from their use, they are not recommended.[9]

Sharing a bed with parents or siblings increases the risk for SIDS.[23] This risk is greatest in the first three months of life, when the mattress is soft, when one or more persons share the infant's bed, especially when the bed partners are using drugs or alcohol or are smoking.[9] The risk remains, however, even in parents who do not smoke or use drugs.[24] The American Academy of Pediatrics thus recommends "room-sharing without bed-sharing", stating that such an arrangement can decrease the risk of SIDS by up to 50%. Furthermore, the Academy recommended against devices marketed to make bed-sharing "safe", such as in-bed co-sleepers.[25]

### Breastfeeding [edit]

Breastfeeding is associated with a lower risk of SIDS.[26] It is not clear if co-sleeping among mothers who breastfeed without any other risk factors increased SIDS risk.[27]

### Pregnancy and infant factors [edit]

SIDS rates decrease with increasing maternal age, with teenage mothers at greatest risk.[17] Delayed or inadequate prenatal care also increases risk.[17] Low birth weight is a significant risk factor. In the United States from 1995 to 1998, the SIDS death rate for infants weighing 1000–1499 g was 2.89/1000, while for a birth weight of 3500–3999 g, it was only 0.51/1000.[28][29] Premature birth increases the risk of SIDS death roughly fourfold.[17][28] From 1995 to 1998, the U.S. SIDS rate for births at 37–39 weeks of gestation was 0.73/1000, while the SIDS rate for births at 28–31 weeks of gestation was 2.39/1000.[28]

Anemia has also been linked to SIDS[30] (note, however, that per item 6 in the list of epidemiologic characteristics below, extent of anemia cannot be evaluated at autopsy because an infant's total hemoglobin can only be measured during life.[31]). SIDS incidence rises from zero at birth, is highest from two to four months of age, and declines toward zero after the infant's first year.[32] Baby boys have a ~50% higher risk of SIDS than girls.[33]

### Genetics [edit]

Genetics plays a role, as SIDS is more prevalent in males.[34][35] There is a consistent 50% male excess in SIDS per 1000 live births of each sex. Given a 5% male excess birth rate, there appears to be 3.15 male SIDS cases per 2 female, for a male fraction of 0.61.[34][35] This value of 61% in the US is an average of 57% black male SIDS, 62.2% white male SIDS and 59.4% for all other races combined. Note that when multiracial parentage is involved, infant race is arbitrarily assigned to one category or the other; most often it is chosen by the mother. The X-linkage hypothesis for SIDS and the male excess in infant mortality have shown that the 50% male excess could be related to a dominant X-linked allele, occurring with a frequency of $^{1}/_{3}$ that is protective of transient cerebral anoxia. An unprotected male would occur with a frequency of $^{2}/_{3}$ and an unprotected female would occur with a frequency of $^{4}/_{9}$.

About 10 to 20% of SIDS cases are believed to be due to channelopathies, which are inherited defects in the ion channels which play an important role in the contraction of the heart.[36]

### Alcohol [edit]

Drinking of alcohol by parents is linked to SIDS.[37] A particular study found a positive correlation between the two during New Years celebrations and weekends.[38]

### Other [edit]

There is a tentative link with *Staphylococcus aureus* and *Escherichia coli*.[39]

Vaccinations do not increase the risk of SIDS; contrarily, they are linked to a 50% lower risk of SIDS.[40][41]

A 1998 report found that antimony- and phosphorus-containing compounds used as fire retardants in PVC and other cot mattress materials are not a cause of SIDS.[42] The report also states that toxic gas can not be generated from antimony in mattresses and that babies suffered SIDS on mattresses that did not contain the compound.

A set of risk factors SIDS has been identified with: seasonality: winter maximum, summer minimum; increasing SIDS rate with live birth order; low increased risk of SIDS in subsequent siblings of SIDS; apparent life-threatening events (ALTE) are not a risk factor for subsequent SIDS; SIDS risk is greatest during sleep.[43]

## Differential diagnosis [edit]

Some conditions that are often undiagnosed and could be confused with or comorbid with SIDS include:

- medium-chain acyl-coenzyme A dehydrogenase deficiency (MCAD deficiency);[44]
- infant botulism;[45]
- long QT syndrome (accounting for less than 2% of cases);[46]
- *Helicobacter pylori* bacterial infections;[47]
- shaken baby syndrome and other forms of child abuse;[48][49]
- overlaying, child smothering during carer's sleep[50]

For example, an infant with MCAD deficiency could have died by "classical SIDS" if found swaddled and prone with head covered in an overheated room where parents were smoking. Genes indicating susceptibility to MCAD and Long QT syndrome do not protect an infant from dying of classical SIDS. Therefore, presence of a susceptibility gene, such as for MCAD, means the infant may have died either from SIDS or from MCAD deficiency. It is currently impossible for the pathologist to distinguish between them.

A 2010 study looked at 554 autopsies of infants in North Carolina that listed SIDS as the cause of death, and suggested that many of these deaths may have been due to accidental suffocation. The study found

that 69% of autopsies listed other possible risk factors that could have led to death, such as unsafe bedding or sleeping with adults.[51]

Several instances of infanticide have been uncovered where the diagnosis was originally SIDS.[52][53] Estimate of the percentage of SIDS deaths that are actually infanticide vary from less than 1% to up to 5% of cases.[54]

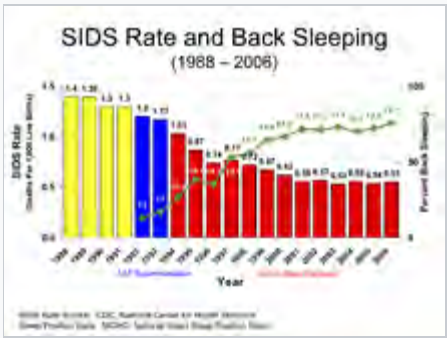
Some have underestimated the risk of two SIDS deaths occurring in the same family and the Royal Statistical Society issued a media release refuting this expert testimony in one UK case in which the conviction was subsequently overturned.[55]

## Prevention [edit]

A number of measures have been found to be effective in preventing SIDS including changing the sleeping position, breastfeeding, limiting soft bedding, immunizing the infant and using pacifiers.[9] The use of electronic monitors has not been found to be useful as a preventative strategy.[9] The effect that fans might have on the risk of SIDS has not been studied well enough to make any recommendation about them.[9] Evidence regarding swaddling is unclear regarding SIDS.[9] A 2016 review found tentative evidence that swaddling increases risk of SIDS, especially among babies placed on their stomachs or side while sleeping.[56]

### Sleep positioning [edit]

Sleeping on the back has been found to reduce the risk of SIDS.[57] It is thus recommended by the American Academy of Pediatrics and promoted as a best practice by the US National Institute of Child Health and Human Development (NICHD) "Safe to Sleep" campaign. The incidence of SIDS has fallen in a number of countries in which this recommendation has been widely adopted.[58] Sleeping on the back does not appear to increase the risk of choking even in those with gastroesophageal reflux disease.[9] While infants in this position may sleep more lightly this is not harmful.[9] Sharing the same room as one's parents but in a different bed may decrease the risk by half.[9]



A plot of SIDS rate from 1988 to 2006

### Pacifiers [edit]

The use of pacifiers appears to decrease the risk of SIDS although the reason is unclear.[9] The American Academy of Pediatrics considers pacifier use to prevent SIDS to be reasonable.[9] Pacifiers do not appear to affect breastfeeding in the first four months, even though this is a common misconception.[59]

### Bedding [edit]

Product safety experts advise against using pillows, overly soft mattresses, sleep positioners, bumper pads (crib bumpers), stuffed animals, or fluffy bedding in the crib and recommend instead dressing the child warmly and keeping the crib "naked."[60]

Blankets or other clothing should not be placed over a baby's head.[61]

### Sleep sacks [edit]

In colder environments where bedding is required to maintain a baby's body temperature, the use of a "baby sleep bag" or "sleep sack" is becoming more popular. This is a soft bag with holes for the baby's arms and head. A zipper allows the bag to be closed around the baby. A study published in the *European* [62]

*Journal of Pediatrics* in August 1998 has shown the protective effects of a sleep sack as reducing the incidence of turning from back to front during sleep, reinforcing putting a baby to sleep on its back for placement into the sleep sack and preventing bedding from coming up over the face which leads to increased temperature and carbon dioxide rebreathing. They conclude in their study, "The use of a sleeping-sack should be particularly promoted for infants with a low birth weight." The American Academy of Pediatrics also recommends them as a type of bedding that warms the baby without covering its head.[63]

### Vaccination [edit]

A large investigation into diphtheria-tetanus-pertussis vaccination and potential SIDS association by Berlin School of Public Health, Charité – Universitätsmedizin Berlin concluded: "Increased DTP immunisation coverage is associated with decreased SIDS mortality. Current recommendations on timely DTP immunisation should be emphasised to prevent not only specific infectious diseases but also potentially SIDS."[64]

Many other studies have also reached conclusions that vaccinations reduce the risk of SIDS. Studies generally show that SIDS risk is approximately halved by vaccinations.[65][66][67][68][69]

## Management [edit]

Families who are impacted by SIDS should be offered emotional support and grief counseling.[70] The experience and manifestation of grief at the loss of an infant are impacted by cultural and individual differences.[71]

## Epidemiology [edit]

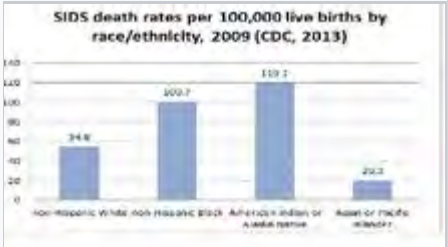
Globally SIDS resulted in about 22,000 deaths as of 2010, down from 30,000 deaths in 1990.[72] Rates vary significantly by population from 0.05 per 1000 in Hong Kong to 6.7 per 1000 in American Indians.[73]

SIDS was responsible for 0.54 deaths per 1,000 live births in the US in 2005.[28] It is responsible for far fewer deaths than congenital disorders and disorders related to short gestation, though it is the leading cause of death in healthy infants after one month of age.

SIDS deaths in the US decreased from 4,895 in 1992 to 2,247 in 2004.[74] But, during a similar time period, 1989 to 2004, SIDS being listed as the cause of death for sudden infant death (SID) decreased from 80% to 55%.[74] According to John Kattwinkel, chairman of the Centers for Disease Control and Prevention (CDC) Special Task Force on SIDS "A lot of us are concerned that the rate (of SIDS) isn't decreasing significantly, but that a lot of it is just code shifting".[74]

### Race [edit]

In 2013, there are persistent disparities in SIDS deaths among racial and ethnic groups in the U.S. In 2009, the rates of death range from 20.3 for Asian/Pacific Islander to 119.2 for American Indians/Alaska Native. African American infants have a 24% greater risk of having a SIDS related death [75] and experience a 2.5 greater incidence of SIDS than in Caucasian infants.[76] Rates are per 100,000 live births and enable more accurate comparison across groups of different total population size.



Rates of SIDS by race/ethnicity in the U.S., 2009, CDC, 2013

Research suggests that factors which contribute more directly to SIDS risk—maternal age, exposure to smoking, safe sleep practices, etc.—vary by racial and ethnic group and therefore risk exposure also varies by these groups.[3] Risk factors associated with prone sleeping patterns of African American families include mother's age, household poverty

index, rural/urban status of residence, and infant's age. More than 50% of African American infants were placed in non-recommended sleeping positions according to a study completed in South Carolina.[77] Cultural factors can be protective as well as problematic.[78]

The rate per 1000 births varies in different areas of the world:[21][79] Central Americans and South Americans - 0.20 Asian/Pacific Islanders - 0.28 Mexicans - 0.24 Puerto Ricans - 0.53 Whites - 0.51 African Americans - 1.08 American Indian - 1.24

## Society and culture [edit]

Much of the media portrayal of infants shows them in non-recommended sleeping positions.[9]

## See also [edit]

- Sudden unexpected death syndrome
- Sudden unexplained death in childhood

## References [edit]


1. ^ "Sudden Infant Death Syndrome (SIDS): Overview". *National Institute of Child Health and Human Development*. 27 June 2013. Retrieved 9 March 2015.
2. ^ "Centers for Disease Control and Prevention, Sudden Infant Death". Retrieved March 13, 2013.
3. ^ *a b c d e f g h i j* Kinney HC, Thach BT (2009). "The sudden infant death syndrome". *N. Engl. J. Med.* **361** (8): 795–805. doi:10.1056/NEJMra0803836. PMC 3268262. PMID 19692691.
4. ^ Optiz, Enid Gilbert-Barness, Diane E. Spicer, Thora S. Steffensen ; foreword by John M. (2013). *Handbook of pediatric autopsy pathology* (Second edition. ed.). New York, NY: Springer New York. p. 654. ISBN 9781461467113.
5. ^ Scheimberg, edited by Marta C. Cohen, Irene (2014). *The Pediatric and perinatal autopsy manual*. p. 319. ISBN 9781107646070.
6. ^ *a b c* "What causes SIDS?". *National Institute of Child Health and Human Development*. 12 April 2013. Retrieved 9 March 2015.
7. ^ "Ways To Reduce the Risk of SIDS and Other Sleep-Related Causes of Infant Death". *NICHD*. 20 January 2016. Retrieved 2 March 2016.
8. ^ *a b c d e* "How many infants die from SIDS or are at risk for SIDS?". *National Institute of Child Health and Human Development*. 19 November 2013. Retrieved 9 March 2015.
9. ^ *a b c d e f g h i j k l m n o p q r* Moon RY, Fu L (July 2012). "Sudden infant death syndrome: an update.". *Pediatrics in review / American Academy of Pediatrics*. **33** (7): 314–20. doi:10.1542/pir.33-7-314. PMID 22753789.
10. ^ *a b* "How can I reduce the risk of SIDS?". *National Institute of Child Health and Human Development*. 22 August 2014. Retrieved 9 March
Infant Death Syndrome (SIDS)". Centers for Disease Control and Prevention. 28 August 2015. Retrieved 15 April 2016.
42. ^ See FSID Press release.
43. ^ Mage DT, Donner EM (2004). "Is SIDS at Borkmann's Point?". *Medical Hypotheses and Research*. **1** (2/3): 131–7.
44. ^ Yang Z, Lantz PE, Ibdah JA (December 2007). "Post-mortem analysis for two prevalent beta-oxidation mutations in sudden infant death". *Pediatr Int*. **49** (6): 883–7. doi:10.1111/j.1442-200X.2007.02478.x. PMID 18045290.
45. ^ Nevas M, Lindström M, Virtanen A, Hielm S, Kuusi M, Arnon SS, Vuori E, Korkeala H (January 2005). "Infant botulism acquired from household dust presenting as sudden infant death syndrome". *J. Clin. Microbiol*. **43** (1): 511–3. doi:10.1128/JCM.43.1.511-513.2005. PMC 540168. PMID 15635031.
46. ^ Millat G, Kugener B, Chevalier P, Chahine M, Huang H, Malicier D, Rodriguez-Lafrasse C, Rousson R (May 2009). "Contribution of long-QT syndrome genetic variants in sudden infant death syndrome". *Pediatr Cardiol*. **30** (4): 502–9. doi:10.1007/s00246-009-9417-2. PMID 19322600.
47. ^ Stray-Pedersen A, Vege A, Rognum TO (October 2008). "*Helicobacter pylori* antigen in stool is associated with SIDS and sudden infant deaths due to infectious disease". *Pediatr. Res*. **64** (4): 405–10. doi:10.1203/PDR.0b013e31818095f7. PMID 18535491.
48. ^ Bajanowski T, Vennemann M, Bohnert M, Rauch E, Brinkmann B, Mitchell EA (July 2005). "Unnatural causes of sudden unexpected deaths initially thought to be sudden infant death syndrome". *Int. J. Legal Med*. **119** (4): 213–6. doi:10.1007/s00414-005-0538-8. PMID 15830244.

2015.
11. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013." . *Lancet*. **385**: 117–71. doi:10.1016/S0140-6736(14)61682-2 . PMC 4340604 . PMID 25530442 .
12. ^ Hoyert DL, Xu JQ (2012). "Deaths: Preliminary data for 2011" (PDF). *National vital statistics reports*. National Center for Health Statistics. **61** (6): 8.
13. ^ "Sudden Unexpected Infant Death and Sudden Infant Death Syndrome: About SUID and SIDS" . Centers for Disease Control and Prevention. Retrieved April 16, 2016.
14. ^ NZ Ministry of Health Archived December 12, 2009, at the Wayback Machine.
15. ^ "Sudden Unexpected Infant Death" (PDF). Centers for Disease Control and Prevention. Retrieved April 16, 2016.
16. ^ Pickett, KE, Luo, Y, Lauderdale, DS. Widening Social Inequalities in Risk for Sudden Infant Death Syndrome. *Am J Public Health* 2005;94(11):1976–1981. doi:10.2105/AJPH.2004.059063
17. ^ *a b c d* Sullivan FM, Barlow SM (2001). "Review of risk factors for Sudden Infant Death Syndrome". *Paediatric Perinatal Epidemiology*. **15** (2): 144–200. doi:10.1046/j.1365-3016.2001.00330.x . PMID 11383580 .
18. ^ Office of the Surgeon General of the United States Report on Involuntary Exposure to Tobacco Smoke (PDF )
19. ^ Bajanowski T.; Brinkmann B.; Mitchell E.; Vennemann M.; Leukel H.; Larsch K.; Beike J.; Gesid G. (2008). "Nicotine and cotinine in infants dying from sudden infant death syndrome". *International journal of legal medicine*. **122** (1): 23–28. doi:10.1007/s00414-007-0155-9 . PMID 17285322 .
20. ^ Lavezzi AM, Corna MF, Matturri L (July 2010). "Ependymal alterations in sudden intrauterine unexplained death and sudden infant death syndrome: possible primary consequence of prenatal exposure to cigarette smoking" . *Neural Dev*. **19** (5): 17. doi:10.1186/1749-8104-5-17 . PMC 2919533 . PMID 20642831 .
21. ^ *a b* Moon RY, Horne RS, Hauck FR (November 2007). "Sudden infant death syndrome". *Lancet*. **370** (9598): 1578–87. doi:10.1016/S0140-6736(07)61662-6 . PMID 17980736 .
22. ^ Fleming PJ, Levine MR, Azaz Y, Wigfield R, Stewart AJ (June 1993). "Interactions between thermoregulation and the control of respiration in infants: possible relationship to sudden infant death". *Acta Paediatr Suppl*. **82** (Suppl 389): 57–9. doi:10.1111/j.1651-2227.1993.tb12878.x . PMID 8374195 .
49. ^ Du Chesne A, Bajanowski T, Brinkmann B (1997). "[Homicides without clues in children]". *Arch Kriminol* (in German). **199** (1–2): 21–6. PMID 9157833 .
50. ^ Williams FL, Lang GA, Mage DT (2001). "Sudden unexpected infant deaths in Dundee, 1882–1891: overlying or SIDS?". *Scottish medical journal*. **46** (2): 43–47. PMID 11394337 .
51. ^ http://www.charlotteobserver.com/sids/
52. ^ Glatt, John (2000). *Cradle of Death: A Shocking True Story of a Mother, Multiple Murder, and SIDS*. Macmillan. ISBN 0-312-97302-0.
53. ^ Havill, Adrian (2002). *While Innocents Slept: A Story of Revenge, Murder, and SIDS*. Macmillan. ISBN 0-312-97517-1.
54. ^ Hymel KP (July 2006). "Distinguishing sudden infant death syndrome from child abuse fatalities.". *Pediatrics*. **118** (1): 421–7. doi:10.1542/peds.2006-1245 . PMID 16818592 .
55. ^ "About Statistics and the Law" (Website). Royal Statistical Society. (2001-10-23) Retrieved on 2007-09-22
56. ^ Pease, AS; Fleming, PJ; Hauck, FR; Moon, RY; Horne, RS; L'Hoir, MP; Ponsonby, AL; Blair, PS (June 2016). "Swaddling and the Risk of Sudden Infant Death Syndrome: A Meta-analysis.". *Pediatrics*. **137** (6). doi:10.1542/peds.2015-3275 . PMID 27244847 . "Limited evidence suggested swaddling risk increased with infant age and was associated with a twofold risk for infants aged >6 months."
57. ^ Mitchell EA (November 2009). "SIDS: past, present and future.". *Acta paediatrica (Oslo, Norway : 1992)*. **98** (11): 1712–9. doi:10.1111/j.1651-2227.2009.01503.x . PMID 19807704 .
58. ^ Mitchell EA, Hutchison L, Stewart AW (July 2007). "The continuing decline in SIDS mortality" . *Arch Dis Child*. **92** (7): 625–6. doi:10.1136/adc.2007.116194 . PMC 2083749 . PMID 17405855 .
59. ^ Jaafar SH, Jahanfar S, Angolkar M, Ho JJ (Jul 11, 2012). "Effect of restricted pacifier use in breastfeeding term infants for increasing duration of breastfeeding.". *The Cochrane database of systematic reviews*. **7**: CD007202. doi:10.1002/14651858.CD007202.pub3 . PMID 22786506 .
60. ^ "What Can Be Done?" . American SIDS Institute.
61. ^ Syndrome, Task Force on Sudden Infant Death (24 October 2016). "SIDS and Other Sleep-Related Infant Deaths: Updated 2016 Recommendations for a Safe Infant Sleeping Environment" . *Pediatrics*: e20162938. doi:10.1542/peds.2016-2938 . ISSN 0031-4005 .
62. ^ L'Hoir MP, Engelberts AC, van Well GT, McClelland S, Westers P, Dandachli T, Mellenbergh GJ, Wolters WH, Huber J (1998). "Risk and preventive factors for cot death in The Netherlands, a low-incidence country". *Eur. J. Pediatr*. **157** (8): 681–8. doi:10.1007/s004310050911 . PMID 9727856 .

23. ^ McIntosh CG, Tonkin SL, Gunn AJ (2009). "What is the mechanism of sudden infant deaths associated with co-sleeping?". *N. Z. Med. J.* **122** (1307): 69–75. PMID 20148046.
24. ^ Carpenter, R; McGarvey, C; Mitchell, EA; Tappin, DM; Vennemann, MM; Smuk, M; Carpenter, JR (2013). "Bed sharing when parents do not smoke: is there a risk of SIDS? An individual level analysis of five major case-control studies". *BMJ Open*. **3** (5): e002299. doi:10.1136/bmjopen-2012-002299. PMID 23793691.
25. ^ Moon RY (November 2011). "SIDS and other sleep-related infant deaths: expansion of recommendations for a safe infant sleeping environment.". *Pediatrics*. **128** (5): 1030–9. doi:10.1542/peds.2011-2284. PMID 22007004.
26. ^ Hauck, FR; Thompson, JM; Tanabe, KO; Moon, RY; Vennemann, MM (July 2011). "Breastfeeding and reduced risk of sudden infant death syndrome: a meta-analysis.". *Pediatrics*. **128** (1): 103–10. doi:10.1542/peds.2010-3000. PMID 21669892.
27. ^ Fleming, PJ; Blair, PS (2 February 2015). "Making informed choices on co-sleeping with your baby.". *BMJ (Clinical research ed.)*. **350**: h563. doi:10.1136/bmj.h563. PMID 25643704.
28. ^ *a b c d* "Cdc Wonder". Centers for Disease Control and Prevention (CDC). 2010-02-24. Retrieved 2010-04-17.
29. ^ Hunt CE (November 2007). "Small for gestational age infants and sudden infant death syndrome: a confluence of complex conditions". *Arch. Dis. Child. Fetal Neonatal Ed.* **92** (6): F428–9. doi:10.1136/adc.2006.112243. PMC 2675383. PMID 17951549.
30. ^ Poets CF, Samuels MP, Wardrop CA, Picton-Jones E, Southall DP (April 1992). "Reduced haemoglobin levels in infants presenting with apparent life-threatening events—a retrospective investigation". *Acta Paediatr.* **81** (4): 319–21. doi:10.1111/j.1651-2227.1992.tb12234.x. PMID 1606392.
31. ^ Giulian GG, Gilbert EF, Moss RL (April 1987). "Elevated fetal hemoglobin levels in sudden infant death syndrome". *N Engl J Med.* **316** (18): 1122–6. doi:10.1056/NEJM198704303161804. PMID 2437454.
32. ^ Mage DT (1996). "A probability model for the age distribution of SIDS". *J Sudden Infant Death Syndrome Infant Mortal.* **1**: 13–31.
33. ^ Mage DT, Donner M. A genetic basis for the sudden infant death syndrome sex ratio, Med Hypotheses 1997;48:137–142.
34. ^ *a b* See CDC WONDER online database and http://www3.who.int/whosis/menu.cfm?path=whosis,inds,mort&language=english for data on SIDS by gender in the US and throughout the world.
35. ^ *a b* Mage DT, Donner EM (September 2004). "The fifty percent male excess of infant respiratory
63. ^ "The Changing Concept of Sudden Infant Death Syndrome: Diagnostic Coding Shifts, Controversies Regarding the Sleeping Environment, and New Variables to Consider in Reducing Risk". American Academy of Pediatrics. Retrieved 2008-11-06.
64. ^ Müller-Nordhorn, Jacqueline; Hettler-Chen, Chih-Mei; Keil, Thomas; Muckelbauer, Rebecca (28 January 2015). "Association between sudden infant death syndrome and diphtheria-tetanus-pertussis immunisation: an ecological study". *BMC Pediatrics*. **15** (1). doi:10.1186/s12887-015-0318-7.
65. ^ Mitchell, E A; Stewart, A W; Clements, M (1 December 1995). "Immunisation and the sudden infant death syndrome. New Zealand Cot Death Study Group.". *Archives of Disease in Childhood*. **73** (6): 498–501. doi:10.1136/adc.73.6.498.
66. ^ Fleming, P. J (7 April 2001). "The UK accelerated immunisation programme and sudden unexpected death in infancy: case-control study". *BMJ*. **322** (7290): 822–822. doi:10.1136/bmj.322.7290.822.
67. ^ Vennemann, M.M.T.; Höffgen, M.; Bajanowski, T.; Hense, H.-W.; Mitchell, E.A. (2007). "Do immunisations reduce the risk for SIDS? A meta-analysis". *Vaccine*. **25** (26): 4875–9. doi:10.1016/j.vaccine.2007.02.077. PMID 17400342.
68. ^ Hoffman, HJ; Hunter, JC; Damus, K; Pakter, J; Peterson, DR; van Belle, G; Hasselmeyer, EG (April 1987). "Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome risk factors.". *Pediatrics*. **79** (4): 598–611. PMID 3493477.
69. ^ Carvajal, A; Caro-Patón, T; Martín de Diego, I; Martín Arias, LH; Alvarez Requejo, A; Lobato, A (4 May 1996). "[DTP vaccine and infant sudden death syndrome. Meta-analysis].". *Medicina clinica*. **106** (17): 649–52. PMID 8691909.
70. ^ Adams SM, Good MW, Defranco GM (2009). "Sudden infant death syndrome". *Am Fam Physician*. **79** (10): 870–4. PMID 19496386.
71. ^ Koopmans L, Wilson T, Cacciatore J, et al. (Jun 13, 2013). "Support for mothers, fathers and families after perinatal death". *Cochrane Database of Systematic Reviews*. **6**. doi:10.1002/14651858.CD000452.pub3.
72. ^ Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al. (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
73. ^ Sharma BR (March 2007). "Sudden infant death syndrome: a subject of medicolegal research.". *The American Journal of Forensic Medicine and Pathology*. **28** (1): 69–72. doi:10.1097/01.paf.0000220934.18700.ef.

mortality" . *Acta Paediatr*. **93** (9): 1210–5. doi:10.1080/08035250410031305. PMID 15384886.
36. ^ Behere, SP; Weindling, SN (2014). "Inherited arrhythmias: The cardiac channelopathies.". *Annals of Pediatric Cardiology*. **8** (3): 210–20. doi:10.4103/0974-2069.164695. PMC 4608198. PMID 26556967.
37. ^ Van Nguyen, JM; Abenhaim, HA (October 2013). "Sudden infant death syndrome: review for the obstetric care provider.". *American journal of perinatology*. **30** (9): 703–14. doi:10.1055/s-0032-1331035. PMID 23292938.
38. ^ Phillips, DP; Brewer, KM; Wadensweiler, P (March 2011). "Alcohol as a risk factor for sudden infant death syndrome (SIDS).". *Addiction (Abingdon, England)*. **106** (3): 516–25. doi:10.1111/j.1360-0443.2010.03199.x. PMID 21059188.
39. ^ Weber MA, Klein NJ, Hartley JC, Lock PE, Malone M, Sebire NJ (May 31, 2008). "Infection and sudden unexpected death in infancy: a systematic retrospective case review.". *Lancet*. **371** (9627): 1848–53. doi:10.1016/S0140-6736(08)60798-9. PMID 18514728.
40. ^ Vennemann, MM; Höffgen, M; Bajanowski, T; Hense, HW; Mitchell, EA (21 June 2007). "Do immunisations reduce the risk for SIDS? A meta-analysis". *Vaccine*. **25** (26): 4875–9. doi:10.1016/j.vaccine.2007.02.077. PMID 17400342.
41. ^ "Vaccine Safety: Common Concerns: Sudden PMID 17325469.
74. ^ *a b c* Bowman L, Hargrove T. Exposing Sudden Infant Death In America. Scripps Howard News Service. http://dailycamera.com/news/2007/oct/08/saving-babies-exposing-sudden-infant-death-in/
75. ^ Powers, D. A.; Song, S. (2009). "Absolute change in cause-specific infant mortality for blacks and whites in the US: 1983–2002". *tion Research and Policy Review*. **28** (6): 817–851. doi:10.1007/s11113-009-9130-0.
76. ^ Pollack, H. A.; Frohna, J. G. (2001). "A competing risk model of sudden infant death syndrome incidence in two US birth cohorts". *The Journal of Pediatrics*. **138** (5): 661–667. doi:10.1067/mpd.2001.112248.
77. ^ Smith, M. G.; Liu, J.; Helms, K. H.; Wilkerson, K. L. (2012). "Racial differences in trends and predictors of infant sleep positioning in south carolina, 1996–2007". *Maternal and Child Health Journal*. **15** (1): 72–82. doi:10.1007/s10995-010-0718-0.
78. ^ Brathwaite-Fisher, T, Bronheim, S. Cultural Competence and Sudden Infant Death Syndrome and Other Infant Death: A Review of the Literature from 1990–2000. National Center for Cultural Competence, Georgetown University Center for Child and Human Development 2001. DOI: http://gucchd.georgetown.edu/72396.html
79. ^ Burnett, Lynn Barkley. "Sudden Infant Death Syndrom". *Medscape*.

## Further reading [edit]

- Ottaviani, G. (2014). *Crib death – Sudden infant Death Syndrome (SIDS). Sudden infant and perinatal unexplained death: the pathologist's viewpoint*. Berlin Heidelberg, Germany: Springer. ISBN 978-3-319-08346-9.
- Joan Hodgman; Toke Hoppenbrouwers (2004). *SIDS*. Calabasas, Calif: Monte Nido Press. ISBN 0-9742663-0-2.
- Lewak N. "Book Review: SIDS". *Arch Pediatr Adolesc Med*. **158** (4): 405. doi:10.1001/archpedi.158.4.405.

## External links [edit]

- SIDS at DMOZ

Wikimedia Commons has media related to *Sudden infant death syndrome*.

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Categories: Causes of death | Ailments of unknown etiology | Pediatrics | Infancy | Death of children | Sleep medicine

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# Turner syndrome

From Wikipedia, the free encyclopedia

**Turner syndrome** (**TS**), also known as **45,X**, is a condition in which a female is partly or completely missing an X chromosome.[1] Signs and symptoms vary among those affected. Often, a short and webbed neck, low-set ears, low hairline at the back of the neck, short stature, and swollen hands and feet are seen at birth. Typically, they only develop menstrual periods and breasts with hormone treatment, and are unable to have children without reproductive technology. Heart defects, diabetes, and low thyroid hormone occur more frequently. Most people with TS have normal intelligence. Many, however, have troubles with spatial visualization that may be needed for mathematics.[2] Vision and hearing problems occur more often.[3]

Turner syndrome is not usually inherited from a person's parents.[4] No environmental risks are known, and the mother's age does not play a role.[4][5] Turner syndrome is due to a chromosomal abnormality in which all or part of one of the X chromosomes is missing or altered. While most people have 46 chromosomes, people with TS usually have 45.[6] The chromosomal abnormality may be present in just some cells in which case it is known as TS with mosaicism.[3] In these cases, the symptoms are usually fewer and possibly none occur at all.[7] Diagnosis is based on physical signs and genetic testing.[8]

No cure for Turner syndrome is known. Treatment, however, may help with symptoms. Human growth hormone injections during childhood may increase adult height. Estrogen replacement therapy can promote development of the breasts and hips. Medical care is often required to manage other health problems with which TS is associated.[9]

Turner syndrome occurs in between one in 2000[10] and one in 5000 females at birth.[11] All regions of the world and cultures are affected about equally.[4] Generally people with TS have a shorter life expectancy, mostly due to heart problems and diabetes.[3] Henry Turner first described the condition in 1938. In 1964, it was determined to be due to a chromosomal abnormality.[12]

Contents



## Variants

## Turner syndrome

**Synonyms** Ullrich–Turner syndrome, gonadal dysgenesis, 45,X

Girl with Turner syndrome before and after an operation for neck-webbing

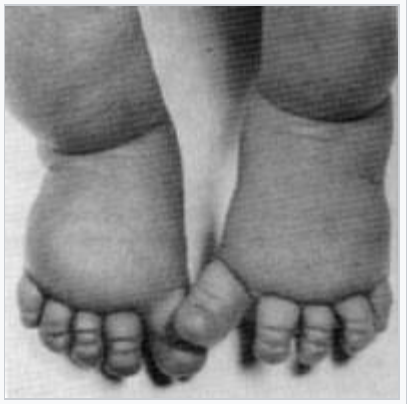
**Classification and external resources**

| | |
|---|---|
| **Specialty** | Pediatrics, medical genetics |
| **ICD-10** | Q96 |
| **ICD-9-CM** | 758.6 |
| **DiseasesDB** | 13461 |
| **MedlinePlus** | 000379 |
| **eMedicine** | ped/2330 |
| **Patient UK** | Turner syndrome |
| **MeSH** | D014424 |
| **Orphanet** | 881 |

[edit on Wikidata]

## Signs and symptoms [edit]

Of the following common symptoms of Turner syndrome, an individual may have any combination of symptoms and is unlikely to have all symptoms.



Lymphedema, puffy legs of a newborn with Turner syndrome

- Short stature
- Lymphedema (swelling) of the hands and feet of a newborn
- Broad chest (shield chest) and widely spaced nipples
- Low posterior hairline
- Low-set ears
- Reproductive sterility
- Rudimentary ovaries gonadal streak (underdeveloped gonadal structures that later become fibrotic)
- Amenorrhoea, the absence of a menstrual period
- Increased weight, obesity
- Shortened metacarpal IV
- Small fingernails
- Characteristic facial features
- Webbed neck from cystic hygroma in infancy
- Aortic valve stenosis
- Coarctation of the aorta
- Bicuspid aortic valve
- Horseshoe kidney
- Visual impairments – sclera, cornea, glaucoma, etc.
- Ear infections and hearing loss
- High waist-to-hip ratio (the hips are not much bigger than the waist)
- Attention deficit hyperactivity disorder (problems with concentration, memory, attention with hyperactivity seen mostly in childhood and adolescence)
- Nonverbal learning disability (problems with math, social skills, and spatial relations)

Other features may include a small lower jaw (micrognathia), cubitus valgus,[13] soft upturned nails, palmar crease, and drooping eyelids. Less common are pigmented moles, hearing loss, and a high-arch palate (narrow maxilla). Turner syndrome manifests itself differently in each female affected by the condition;

therefore, no two individuals share the same features.

While most of the physical findings are harmless, significant medical problems can be associated with the syndrome. Most of these significant conditions are treatable with surgery and medication.[14]

## Prenatal [edit]

Despite the excellent postnatal prognosis, 99% of Turner-syndrome conceptions are thought to end in spontaneous abortion or stillbirth,[15] and as many as 15% of all spontaneous abortions have the 45,X karyotype.[16] Among cases that are detected by routine amniocentesis or chorionic villus sampling, one study found that the prevalence of Turner syndrome among tested pregnancies was 5.58 and 13.3 times higher, respectively, than among live neonates in a similar population.[17]

## Cardiovascular [edit]

The rate of cardiovascular malformations among patients with Turner syndrome ranges from 17% [18] to 45%.[19] The variations found in the different studies are mainly attributable to variations in noninvasive methods used for screening and the types of lesions that they can characterize.[20] However,[21] it could be simply attributable to the small number of subjects in most studies.

Different karyotypes may have differing rates of cardiovascular malformations. Two studies found a rate of cardiovascular malformations of 30%[22] and 38%[23] in a group of pure 45,X monosomy. Considering other karyotype groups, though, they reported a prevalence of 24.3%[22] and 11%[23] in people with mosaic X monosomy, and a rate of 11% in people with X chromosomal structural abnormalities.[22]

The higher rate in the group of pure 45,X monosomy is primarily due to a difference in the rate of aortic valve abnormalities and coarctation of the aorta, the two most common cardiovascular malformations.

## Congenital heart disease [edit]

The most commonly observed are congenital obstructive lesions of the left side of the heart, leading to reduced flow on this side of the heart. This includes bicuspid aortic valve and coarctation (narrowing) of the aorta. More than 50% of the cardiovascular malformations of individuals with Turner syndrome in one study were bicuspid aortic valves or coarctation of the aorta (usually preductal), alone or in combination.[21]

Other congenital cardiovascular malformations, such as partial anomalous venous drainage and aortic valve stenosis or aortic regurgitation, are also more common in Turner syndrome than in the general population. Hypoplastic left heart syndrome represents the most severe reduction in left-sided structures.

### Bicuspid aortic valve [edit]

Up to 15% of adults with Turner syndrome have bicuspid aortic valves, meaning only two, instead of three, parts to the valves in the main blood vessel leading from the heart are present. Since bicuspid valves are capable of regulating blood flow properly, this condition may go undetected without regular screening. However, bicuspid valves are more likely to deteriorate and later fail. Calcification also occurs in the valves,[24] which may lead to a progressive valvular dysfunction as evidenced by aortic stenosis or regurgitation.[25]

With a rate from 12.5%[22] to 17.5% (Dawson-Falk et al., 1992), bicuspid aortic valve is the most common congenital malformation affecting the heart in this syndrome. It is usually isolated, but it may be seen in combination with other anomalies, particularly coarctation of the aorta.

### Coarctation of the aorta [edit]

Between 5% and 10% of those born with Turner syndrome have coarctation of the aorta, a congenital narrowing of the descending aorta, usually just distal to the origin of the left subclavian artery (the artery that branches off the arch of the aorta to the left arm) and opposite to the duct (and so termed "juxtaductal"). Estimates of the prevalence of this malformation in patients with Turner syndrome range

from 6.9[22] to 12.5%. A coarctation of the aorta in a female is suggestive of Turner syndrome and suggests the need for further tests, such as a karyotype.

### Partial anomalous venous drainage [edit]

This abnormality is a relatively rare congenital heart disease in the general population. The prevalence of this abnormality also is low (around 2.9%) in Turner syndrome. However, its relative risk is 320 in comparison with the general population. Strangely, Turner syndrome seems to be associated with unusual forms of partial anomalous venous drainage.[22][26]

In a patient with Turner syndrome, these left-sided cardiovascular malformations can result in an increased susceptibility to bacterial endocarditis. Therefore, prophylactic antibiotics should be considered when procedures with a high risk of endocarditis are performed, such as dental cleaning.[25]

Turner syndrome is often associated with persistent hypertension, sometimes in childhood. In the majority of Turner syndrome patients with hypertension, no specific cause is known. In the remainder, it is usually associated with cardiovascular or kidney abnormalities, including coarctation of the aorta.

## Aortic dilation, dissection, and rupture [edit]

Two studies have suggested aortic dilatation in Turner syndrome, typically involving the root of the ascending aorta and occasionally extending through the aortic arch to the descending aorta, or at the site of previous coarctation of the aorta repair.[27]

- A study that evaluated 28 girls with Turner syndrome found a greater mean aortic root diameter in people with Turner syndrome than in the control group (matched for body surface area). Nonetheless, the aortic root diameters found in Turner syndrome patients were still well within the limits.[28]
- This has been confirmed by a study that evaluated 40 patients with Turner syndrome.[19] The study presented basically the same findings: a greater mean aortic root diameter, which nevertheless remains within the normal range for body surface area.

Whether aortic root diameters that are relatively large for body surface area but still well within normal limits imply a risk for progressive dilatation remains unproven.[21]

### Rate of aortic abnormalities [edit]

The prevalence of aortic root dilatation ranges from 8.8[27] to 42%[25] in patients with Turner syndrome. Even if not every aortic root dilatation necessarily goes on to an aortic dissection (circumferential or transverse tear of the intima), complications such as dissection, aortic rupture resulting in death may occur. The natural history of aortic root dilatation is still unknown, but it is linked to aortic dissection and rupture, which has a high mortality rate.[29]

Aortic dissection affects 1 to 2% of patients with Turner syndrome. As a result, any aortic root dilatation should be seriously taken into account, as it could become a fatal aortic dissection. Routine surveillance is highly recommended.[25]

### Risk factors for aortic rupture [edit]

Cardiovascular malformations (typically bicuspid aortic valve, coarctation of the aorta, and some other left-sided cardiac malformations) and hypertension predispose to aortic dilatation and dissection in the general population. Indeed, these same risk factors are found in more than 90% of patients with Turner syndrome who develop aortic dilatation. Only a small number of patients (around 10%) have no apparent predisposing risk factors. The risk of hypertension is increased three-fold in patients with Turner syndrome. Because of its relation to aortic dissection, blood pressure must be regularly monitored and hypertension should be treated aggressively with an aim to keep blood pressure below 140/80 mmHg. As with the other cardiovascular malformations, complications of aortic dilatation is commonly associated with 45,X karyotype.[25]

### Pathogenesis of aortic dissection and rupture [edit]

The exact role that these risk factors play in the process leading to rupture is unclear. Aortic root dilatation is thought to be due to a mesenchymal defect as pathological evidence of cystic medial necrosis has been found by several studies. The association between a similar defect and aortic dilatation is well established in such conditions such as Marfan syndrome. Also, abnormalities in other mesenchymal tissues (bone matrix and lymphatic vessels) suggests a similar primary mesenchymal defect in patients with Turner syndrome.[27] However, no evidence suggests that patients with Turner syndrome have a significantly higher risk of aortic dilatation and dissection in absence of predisposing factors. So, the risk of aortic dissection in Turner syndrome appears to be a consequence of structural cardiovascular malformations and hemodynamic risk factors rather than a reflection of an inherent abnormality in connective tissue. The natural history of aortic root dilatation is unknown, but because of its lethal potential, this aortic abnormality needs to be carefully followed.

## Skeletal [edit]

Normal skeletal development is inhibited due to a large variety of factors, mostly hormonal. The average height of a woman with Turner syndrome, in the absence of growth hormone treatment, is 4 ft 7 in (140 cm). Patients with Turner's mosaicism can reach normal average height.

The fourth metacarpal bone (fourth toe and ring finger) may be unusually short, as may the fifth.

Due to inadequate production of estrogen, many of those with Turner syndrome develop osteoporosis. This can decrease height further, as well as exacerbate the curvature of the spine, possibly leading to scoliosis. It is also associated with an increased risk of bone fractures.

## Kidney [edit]

About one-third of all women with Turner syndrome have one of three kidney abnormalities:

1. A single, horseshoe-shaped kidney on one side of the body
2. An abnormal urine-collecting system
3. Poor blood flow to the kidneys

Some of these conditions can be corrected surgically. Even with these abnormalities, the kidneys of most women with Turner syndrome function normally. However, as noted above, kidney problems may be associated with hypertension.

## Thyroid [edit]

Approximately one-third of all women with Turner syndrome have a thyroid disorder.[30] Usually it is hypothyroidism, specifically Hashimoto's thyroiditis. If detected, it can be easily treated with thyroid hormone supplements.

## Diabetes [edit]

Women with Turner syndrome are at a moderately increased risk of developing type 1 diabetes in childhood and a substantially increased risk of developing type 2 diabetes by adult years. The risk of developing type 2 diabetes can be substantially reduced by maintaining a healthy weight.

## Cognitive [edit]

Turner syndrome does not typically cause intellectual disability or impair cognition. However, learning difficulties are common among women with Turner syndrome, particularly a specific difficulty in perceiving spatial relationships, such as nonverbal learning disorder. This may also manifest itself as a difficulty with motor control or with mathematics.[*citation needed*] While it is not correctable, in most cases it does not cause difficulty in daily living. Most Turner syndrome patients are employed as adults and lead productive lives.

Also, a rare variety of Turner syndrome, known as "Ring-X Turner syndrome", has about a 60% association with intellectual disability[*clarification needed*]. This variety accounts for around 2–4% of all Turner syndrome [31]

cases.

### Reproductive [edit]

Women with Turner syndrome are almost universally infertile. While some women with Turner syndrome have successfully become pregnant and carried their pregnancies to term, this is very rare and is generally limited to those women whose karyotypes are not 45,X.[32][33] Even when such pregnancies do occur, there is a higher than average risk of miscarriage or birth defects, including Turner Syndrome or Down Syndrome.[34] Some women with Turner syndrome who are unable to conceive without medical intervention may be able to use IVF or other fertility treatments.[35]

Usually, estrogen replacement therapy is used to spur the growth of secondary sexual characteristics at the time when puberty should onset. While very few women with Turner Syndrome menstruate spontaneously, estrogen therapy requires a regular shedding of the uterine lining ("withdrawal bleeding") to prevent its overgrowth. Withdrawal bleeding can be induced monthly, like menstruation, or less often, usually every three months, if the patient desires. Estrogen therapy does not make a woman with nonfunctional ovaries fertile, but it plays an important role in assisted reproduction; the health of the uterus must be maintained with estrogen if an eligible woman with Turner Syndrome wishes to use IVF (using donated oocytes).

Turner syndrome is a cause of primary amenorrhea, premature ovarian failure (hypergonadotropic hypogonadism), streak gonads and infertility. Failure to develop secondary sex characteristics (sexual infantilism) is typical.

Especially in mosaic cases of Turner syndrome that contains Y-chromosome (e.g. 45,X/46,XY) due to the risk of development of ovarian malignancy (most common is gonadoblastoma) gonadectomy is recommended.[30] [36] Turner syndrome is characterized by primary amenorrhoea, premature ovarian failure, streak gonads and infertility. However, technology (especially oocyte donation) provides the opportunity of pregnancy in these patients.

As more women with Turner syndrome complete pregnancy thanks to modern techniques to treat infertility, it has to be noted that pregnancy may be a risk of cardiovascular complications for the mother. Indeed, several studies had suggested an increased risk for aortic dissection in pregnancy.[27] Three deaths have even been reported. The influence of estrogen has been examined but remains unclear. It seems that the high risk of aortic dissection during pregnancy in women with Turner syndrome may be due to the increased hemodynamic load rather than the high estrogen rate.[25] Of course, these findings are important and need to be remembered while following a pregnant patient with Turner syndrome.

## Cause [edit]

Turner syndrome is caused by the absence of one complete or partial copy of the X chromosome in some or all the cells. The abnormal cells may have only one X (monosomy) (45,X) or they may be affected by one of several types of partial monosomy like a deletion of the short p arm of one X chromosome (46,X,del(Xp)) or the presence of an isochromosome with two q arms (46,X,i(Xq))[37] Turner syndrome has distinct features due to the lack of pseudoautosomal regions, which are typically spared from X-inactivation.[38] In mosaic individuals, cells with X monosomy (45,X) may occur along with cells that are normal (46,XX), cells that have partial monosomies, or cells that have a Y chromosome (46,XY).[37] The presence of mosaicism is estimated to be relatively common in affected individuals (67–90%).[37]

### Inheritance [edit]

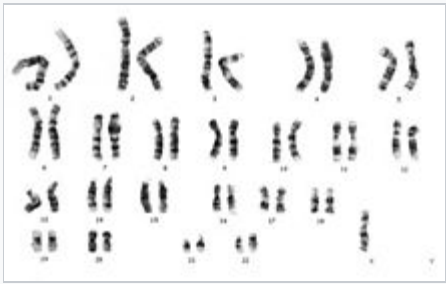
In the majority of cases where monosomy occurs, the X chromosome comes from the mother.[39] This may be due to a nondisjunction in the father. Meiotic errors that lead to the production of X with p arm deletions or abnormal Y chromosomes are also mostly found in the father.[40] Isochromosome X or ring chromosome X on the other hand are formed equally often by both parents.[40] Overall, the functional X chromosome usually comes from the mother.

In most cases, Turner syndrome is a sporadic event, and for the parents of an individual with Turner syndrome the risk of recurrence is not increased for subsequent pregnancies. Rare exceptions may include the presence of a balanced translocation of the X chromosome in a parent, or where the mother has 45,X mosaicism restricted to her germ cells.[41]

## Diagnosis [edit]

### Prenatal [edit]

Turner syndrome may be diagnosed by amniocentesis or chorionic villus sampling during pregnancy.



45,X karyotype, showing an unpaired X at the lower right

Usually, fetuses with Turner syndrome can be identified by abnormal ultrasound findings (*i.e.*, heart defect, kidney abnormality, cystic hygroma, ascites). In a study of 19 European registries, 67.2% of prenatally diagnosed cases of Turner Syndrome were detected by abnormalities on ultrasound. 69.1% of cases had one anomaly present, and 30.9% had two or more anomalies.[42]

An increased risk of Turner syndrome may also be indicated by abnormal triple or quadruple maternal serum screen. The fetuses diagnosed through positive maternal serum screening are more often found to have a mosaic karyotype than those diagnosed based on ultrasonographic abnormalities, and conversely, those with mosaic karyotypes are less likely to have associated ultrasound abnormalities.[42]

Although the recurrence risk is not increased, genetic counseling is often recommended for families who have had a pregnancy or child with Turner syndrome.

### Postnatal [edit]

Turner syndrome can be diagnosed postnatally at any age. Often, it is diagnosed at birth due to heart problems, an unusually wide neck or swelling of the hands and feet. However, it is also common for it to go undiagnosed for several years, typically until the girl reaches the age of puberty/adolescence and she fails to develop properly (the changes associated with puberty do not occur). In childhood, a short stature can be indicative of Turner syndrome.[43]

A test called a karyotype, also known as a chromosome analysis, analyzes the chromosomal composition of the individual. This is the test of choice to diagnose Turner syndrome.

## Treatment [edit]

As a chromosomal condition, there is no cure for Turner syndrome. However, much can be done to minimize the symptoms. For example:[44]

- Growth hormone, either alone or with a low dose of androgen, will increase growth and probably final adult height. Growth hormone is approved by the U.S. Food and Drug Administration for treatment of Turner syndrome and is covered by many insurance plans.[44][45] There is evidence that this is effective, even in toddlers.[46]
- Estrogen replacement therapy such as the birth control pill, has been used since the condition was described in 1938 to promote development of secondary sexual characteristics. Estrogens are crucial for maintaining good bone integrity, cardiovascular health and tissue health.[44] Women with Turner Syndrome who do not have spontaneous puberty and who are not treated with estrogen are at high risk for osteoporosis and heart conditions.
- Modern reproductive technologies have also been used to help women with Turner syndrome become

pregnant if they desire. For example, a donor egg can be used to create an embryo, which is carried by the Turner syndrome woman.[44]
- Uterine maturity is positively associated with years of estrogen use, history of spontaneous menarche, and negatively associated with the lack of current hormone replacement therapy.[47]

## Epidemiology [edit]

Approximately 99 percent of fetuses with Turner syndrome spontaneously terminate during the first trimester.[48] Turner syndrome accounts for about 10 percent of the total number of spontaneous abortions in the United States.[30] The rate of Turner syndrome in live female births is believed to be around 1 in 2000.

## History [edit]

The syndrome is named after Henry Turner, an endocrinologist from Illinois, who described it in 1938.[49] In Europe, it is often called Ullrich–Turner syndrome or even Bonnevie–Ullrich–Turner syndrome to acknowledge that earlier cases had also been described by European doctors.

The first published report of a female with a 45,X karyotype was in 1959 by Dr. Charles Ford and colleagues in Harwell, Oxfordshire, and Guy's Hospital in London.[50] It was found in a 14-year-old girl with signs of Turner syndrome.

## See also [edit]

- Other human sex chromosome aneuploids:
  - XYY syndrome,
  - Klinefelter syndrome (XXY),
  - Triple X syndrome,
- Dermatoglyphics,
- Noonan syndrome, a disorder which is often confused with Turner syndrome because of several physical features that they have in common.

## References [edit]


1. ^ "Turner Syndrome: Overview". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 3 April 2013. Retrieved 15 March 2015.
2. ^ "What are the symptoms of Turner syndrome?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 30 November 2012. Retrieved 15 March 2015.
3. ^ a b c Sybert VP, McCauley E; McCauley (September 2004). "Turner's syndrome". *N. Engl. J. Med.* **351** (12): 1227–38. doi:10.1056/NEJMra030360. PMID 15371580.
4. ^ a b c "How many people are affected or at risk?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 30 November 2012. Retrieved 15 March 2015.
5. ^ Michael Cummings (2015). *Human Heredity: Principles and Issues*. Cengage Learning. p. 161. ISBN 978-1-305-48067-4.
6. ^ "Turner Syndrome: Condition Information". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 30 November 2012. Retrieved 15 March 2015.
7. ^ "What causes Turner syndrome?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 30 November 2012. Retrieved 15 March 2015.
8. ^ "How do health care providers diagnose Turner syndrome?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 30 November 2012. Retrieved 15 March 2015.
9. ^ "What are common treatments for Turner syndrome?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 30 November 2012. Retrieved 15 March 2015.
10. ^ Donaldson MD, Gault EJ, Tan KW, Dunger DB (June 2006). "Optimising management in Turner syndrome: from

infancy to adult transfer". *Arch. Dis. Child*. **91** (6): 513–520. doi:10.1136/adc.2003.035907. PMC 2082783. PMID 16714725.
11. ^ Marino, Bradley S. (2013). *Blueprints pediatrics* (Sixth edition. ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins. p. 319. ISBN 978-1-4511-1604-5.
12. ^ Kelly, Evelyn B. (2013). *Encyclopedia of human genetics and disease*. Santa Barbara, Calif.: Greenwood. p. 818. ISBN 978-0-313-38714-2.
13. ^ Chapter on Amenorrhea in: Bradshaw, Karen D.; Schorge, John O.; Schaffer, Joseph; Lisa M. Halvorson; Hoffman, Barbara G. (2008). *Williams' Gynecology*. McGraw-Hill Professional. ISBN 0-07-147257-6.
14. ^ Stochholm, Kirstine; Juul, Svend; Juel, Knud; Naeraa, Rune Weis; Højbjerg Gravholt, Claus (October 2006). "Prevalence, Incidence, Diagnostic Delay, and Mortality in Turner Syndrome". *The Journal of Clinical Endocrinology & Metabolism*. **91** (10): 3897–3902. doi:10.1210/jc.2006-0558.
15. ^ Danielsson, Krissi (March 12, 2009). "Turner Syndrome (Monosomy X) and Pregnancy Loss". Retrieved 17 March 2012.
16. ^ Postellon, Daniel C. "Turner Syndrome". *eMedicine Reference*. Medscape. Retrieved 17 March 2012.
17. ^ Gravholt CH, Juul S, Naeraa RW, Hansen J (1996-01-06). "Prenatal and postnatal prevalence of Turner's syndrome: a registry study". *BMJ (Clinical research ed.)*. **312** (7022): 16–21. doi:10.1136/bmj.312.7022.16. PMC 2349728. PMID 8555850.
18. ^ (Landin-Wilhelmsen et al., 2001)
19. ^ *a b* Dawson-Falk KL, Wright AM, Bakker B, Pitlick PT, Wilson DM, Rosenfeld RG (Aug 1992). "Cardiovascular evaluation in Turner syndrome: utility of MR imaging". *Australas Radiol*. **36** (3): 204–9. doi:10.1111/j.1440-1673.1992.tb03152.x. PMID 1445102.
20. ^ (Ho et al., 2004).
21. ^ *a b c* Sybert VP (Jan 1998). "Cardiovascular malformations and complications in Turner syndrome". *Pediatrics*. **101** (1): E11. doi:10.1542/peds.101.1.e11. PMID 9417175.
22. ^ *a b c d e f* Mazzanti L, Cacciari E; Cacciari (Nov 1998). "Congenital heart disease in patients with Turner's syndrome. Italian Study Group for Turner Syndrome (ISGTS)". *J. Pediatr.* **133** (5): 688–92. doi:10.1016/s0022-3476(98)70119-2. PMID 9821430.
23. ^ *a b* Gøtzsche CO, Krag-Olsen B, Nielsen J, Sørensen KE, Kristensen BO (Nov 1994). "Prevalence of cardiovascular malformations and association with karyotypes in Turner's syndrome". *Arch Dis Child*. **71** (5): 433–6. doi:10.1136/adc.71.5.433. PMC 1030059. PMID 7826114.
24. ^ *Aortic Valve, Bicuspid* at eMedicine
25. ^ *a b c d e f* Elsheikh M, Dunger DB, Conway GS, Wass JA (Feb 2002). "Turner's syndrome in adulthood". *Endocr. Rev.* **23** (1): 120–40. doi:10.1210/er.23.1.120. PMID 11844747.
26. ^ Prandstraller D, Mazzanti L, Picchio FM, Magnani C, Bergamaschi R, Perri A, Tsingos E, Cacciari E (1999). "Turner's syndrome: cardiologic profile according to the different chromosomal patterns and long-term clinical follow-Up of 136 nonpreselected patients". *Pediatr Cardiol*. **20** (2): 108–12. doi:10.1007/s002469900416. PMID 9986886.
27. ^ *a b c d* Lin AE, Lippe B, Rosenfeld RG (Jul 1998). "Further delineation of aortic dilation, dissection, and rupture in patients with Turner syndrome". *Pediatrics*. **102** (1): e12. doi:10.1542/peds.102.1.e12. PMID 9651464.
28. ^ Allen DB, Hendricks SA, Levy JM (Aug 1986). "Aortic dilation in Turner syndrome". *J Pediatr*. **109** (2): 302–5. doi:10.1016/S0022-3476(86)80001-4. PMID 3734967.
29. ^ Concha Ruiz M (2006). "Surgical treatment of the aortic root dilatation". *An R Acad Nac Med (Madr)* (in Spanish). **123** (3): 557–68; discussion 569–71. PMID 17451098.
30. ^ *a b c* Elsheikh, M.; Dunger, D. B.; Conway, G. S.; Wass, J. A. H. (February 2002). "Turner's Syndrome in Adulthood". *Endocrine Reviews*. **23** (1): 120–140. doi:10.1210/edrv.23.1.0457. Retrieved 5 February 2016.
31. ^ Berkovitz G, Stamberg J, Plotnick LP, Lanes R (Jun 1983). "Turner syndrome patients with a ring X chromosome". *Clin Genet*. **23** (6): 447–53. doi:10.1111/j.1399-0004.1983.tb01980.x. PMID 6883789.
32. ^ Kaneko N, Kawagoe S, Hiroi M (1990). "Turner's syndrome—review of the literature with reference to a successful pregnancy outcome". *Gynecol Obstet Invest*. **29** (2): 81–7. doi:10.1159/000293307. PMID 2185981.
33. ^ Livadas S, Xekouki P, Kafiri G, Voutetakis A, Maniati-Christidi M, Dacou-Voutetakis C (2005). "Spontaneous pregnancy and birth of a normal female from a woman with Turner syndrome and elevated gonadotropins". *Fertility and Sterility*. **83** (3): 769–72. doi:10.1016/j.fertnstert.2004.11.007. PMID 15749515.
34. ^ Nielsen J, Sillesen I, Hansen KB (1979). "Fertility in women with Turner's syndrome. Case report and review of literature". *British journal of obstetrics and gynaecology*. **86** (11): 833–5. doi:10.1111/j.1471-0528.1979.tb10706.x. PMID 508669.
35. ^ Hovatta O (1999). "Pregnancies in women with Turner's syndrome". *Annals of Medicine*. **31** (2): 106–10. doi:10.3109/07853899908998785. PMID 10344582.

36. ^ Gravholt, Claus Højbjerg; Fedder, Jens; Weis, Rune Naeraa; Müller, Jørn (July 1, 2013). "Occurrence of Gonadoblastoma in Females with Turner Syndrome and Y Chromosome Material: A Population Study". *Journal of Clinical Endocrinology & Metabolism*. **85** (9). doi:10.1210/jcem.85.9.6800. Retrieved 5 February 2016.
37. ^ a b c Crespi B (2008). "Turner syndrome and the evolution of human sexual dimorphism". *Evolutionary Applications*. **1** (3): 449–461. doi:10.1111/j.1752-4571.2008.00017.x.
38. ^ Sybert, Virginia P.; McCauley, Elizabeth (2004-09-16). "Turner's Syndrome". *New England Journal of Medicine*. **351** (12): 1227–1238. doi:10.1056/NEJMra030360. ISSN 0028-4793. PMID 15371580.
39. ^ Monroy N, López M, Cervantes A, García-Cruz D, Zafra G, Canún S, Zenteno JC, Kofman-Alfaro S (2002). "Microsatellite analysis in Turner syndrome: Parental origin of X chromosomes and possible mechanism of formation of abnormal chromosomes". *American Journal of Medical Genetics*. **107** (3): 181–189. doi:10.1002/ajmg.10113. PMID 11807897.
40. ^ a b Uematsu A, Yorifuji T, Muroi J, Kawai M, Mamada M, Kaji M, Yamanaka C, Momoi T, Nakahata T (2002). "Parental origin of normal X chromosomes in Turner syndrome patients with various karyotypes: Implications for the mechanism leading to generation of a 45,X karyotype". *American Journal of Medical Genetics*. **111** (2): 134–139. doi:10.1002/ajmg.10506. PMID 12210339.
41. ^ Frías JL, Davenport ML; Davenport; Committee on Genetics Section on Endocrinology (2003). "Health Supervision for Children with Turner Syndrome". *Pediatrics*. **111** (3): 692–702. doi:10.1542/peds.111.3.692. PMID 12612263.
42. ^ a b http://www.turner-syndrom.dk/doc/videnskab/Prenatalcounseling9.pdf
43. ^ "Turner Syndrome Symptoms, Treatment, Causes – What are the symptoms for Turner syndrome? - MedicineNet".
44. ^ a b c d Turner Syndrome Society of the United States. "FAQ 6. What can be done?". Retrieved 2007-05-11.
45. ^ Bolar K, Hoffman AR, Maneatis T, Lippe B (2008). "Long-term safety of recombinant human growth hormone in Turner syndrome". *J. Clin. Endocrinol. Metab.* **93** (2): 344–51. doi:10.1210/jc.2007-1723. PMID 18000090.
46. ^ Davenport ML, Crowe BJ, Travers SH, Rubin K, Ross JL, Fechner PY, Gunther DF, Liu C, Geffner ME, Thrailkill K, Huseman C, Zagar AJ, Quigley CA (2007). "Growth hormone treatment of early growth failure in toddlers with Turner syndrome: a randomized, controlled, multicenter trial". *J Clin Endocrinol Metab*. **92** (9): 3406–16. doi:10.1210/jc.2006-2874. PMID 17595258.
47. ^ "Uterine Development in Turner Syndrome". *GGH Journal*. **24** (1). 2008. ISSN 1932-9032.
48. ^ Urbach A, Benvenisty N; Benvenisty (2009). "Studying early lethality of 45,XO (Turner's syndrome) embryos using human embryonic stem cells". *PLoS ONE*. **4** (1): e4175. doi:10.1371/journal.pone.0004175. PMC 2613558. PMID 19137066.
49. ^ Turner HH (1938). "A syndrome of infantilism, congenital webbed neck, and cubitus valgus". *Endocrinology*. **23** (5): 566–74. doi:10.1210/endo-23-5-566.
50. ^ Ford CE, Jones KW, Polani PE, De Almeida JC, Briggs JH (1959). "A sex-chromosome anomaly in a case of gonadal dysgenesis (Turner's syndrome)". *The Lancet*. **273** (7075): 711–3. doi:10.1016/S0140-6736(59)91893-8. PMID 13642858.


## Further reading [edit]


- Bondy CA; Turner Syndrome Study, Group (2007). "Care of girls and women with Turner syndrome: A guideline of the Turner Syndrome Study Group". *J Clin Endocrinol Metab*. **92** (1): 10–25. doi:10.1210/jc.2006-1374. PMID 17047017.


## External links [edit]

- Turner Syndrome Society of the United States
- Turner Syndrome at the National Institute of Child Health and Human Development
- Turner Syndrome at NIH's Office of Rare Diseases
- Endocrine and Metabolic Diseases Information Service

| v · t · e | **Chromosome abnormalities (Q90–Q99, 758)** | |
|---|---|---|
| | **Trisomies** | Down syndrome (21 · · Edwards syndrome (18 · · Patau syndrome (13 · · |

| | | | |
|---|---|---|---|
| **Autosomal** | | | Trisomy 9 · Warkany syndrome 2 (8 · · Cat eye syndrome/Trisomy 22 (22 · · Trisomy 16 · |
| | **Monosomies/deletions** | | 1q21.1 deletion syndrome/1q21.1 duplication syndrome/TAR syndrome (1 · · Wolf–Hirschhorn syndrome (4 · · Cri du chat/Chromosome 5q deletion syndrome (5 · · Williams syndrome (7 · · Jacobsen syndrome (11 · · Miller–Dieker syndrome/Smith–Magenis syndrome (17 · · DiGeorge syndrome (22 · · 22q11.2 distal deletion syndrome (22 · · 22q13 deletion syndrome (22 · · *genomic imprinting* (Angelman syndrome/Prader–Willi syndrome (15) · · Distal 18q-/Proximal 18q- · |
| **X/Y linked** | **Monosomy** | | **Turner syndrome (45,X)** · |
| | **Trisomy/tetrasomy, other karyotypes/mosaics** | | Klinefelter syndrome (47,XXY) · 48,XXYY · 48,XXXY · 49,XXXYY · 49,XXXXY · Triple X syndrome (47,XXX) · 48,XXXX · 49,XXXXX · 47,XYY · 48,XYYY · 49,XYYYY · 45,X/46,XY · |
| **Translocations** | **Leukemia/lymphoma** | **Lymphoid** | Burkitt's lymphoma t(8 MYC;14 IGH) · Follicular lymphoma t(14 IGH;18 BCL2) · Mantle cell lymphoma/Multiple myeloma t(11 CCND1:14 IGH) · Anaplastic large-cell lymphoma t(2 ALK;5 NPM1) · Acute lymphoblastic leukemia · |
| | | **Myeloid** | Philadelphia chromosome t(9 ABL; 22 BCR) · Acute myeloblastic leukemia with maturation t(8 RUNX1T1;21 RUNX1) · Acute promyelocytic leukemia t(15 PML,17 RARA) · Acute megakaryoblastic leukemia t(1 RBM15;22 MKL1) · |
| | **Other** | | Ewing's sarcoma t(11 FLI1; 22 EWS) · Synovial sarcoma t(x SYT;18 SSX) · Dermatofibrosarcoma protuberans t(17 COL1A1;22 PDGFB) · Myxoid liposarcoma t(12 DDIT3; 16 FUS) · Desmoplastic small-round-cell tumor t(11 WT1; 22 EWS) · Alveolar rhabdomyosarcoma t(2 PAX3; 13 FOXO1) t (1 PAX7; 13 FOXO1) · |
| **Other** | | | Fragile X syndrome · Uniparental disomy · XX male syndrome · Ring chromosome (13; 14; 15; 20) · |
| **Authority control** | | | GND: 4186484-0 · NDL: 01112797 · |

Categories: Genodermatoses | Growth disorders | Intersex and medicine | Rare diseases | Sex chromosome aneuploidies | Syndromes


# Book:Dermatology

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# Abscess

From Wikipedia, the free encyclopedia

*This article is about the medical condition. For the death metal band, see Abscess (band).*

An **abscess** (Latin: *abscessus*) is a collection of pus that has built up within the tissue of the body. Signs and symptoms of abscesses include redness, pain, warmth, and swelling. The swelling may feel fluid filled when pressed.[1] The area of redness often extends beyond the swelling.[6] Carbuncles and boils are types of abscess that often involve hair follicles with carbuncles being larger.[7]

They are usually caused by a bacterial infection.[8] Often many different types of bacteria are involved in a single infection.[6] In the United States and many other areas of the world the most common bacteria present is *methicillin-resistant Staphylococcus aureus*.[1] Rarely, parasites can cause abscesses and this is more common in the developing world.[3] Diagnosis of a skin abscess is usually made based on what it looks like and is confirmed by cutting it open.[1] Ultrasound imaging may be useful in cases in which the diagnosis is not clear.[1] In abscesses around the anus, computer tomography (CT) may be important to look for deeper infection.[3]

Standard treatment for most skin or soft tissue abscesses is cutting it open and drainage.[4] There does not appear to be any benefit from also using antibiotics for this type of abscess in most people who are otherwise healthy.[1][9] A small amount of evidence supports not packing the cavity that remains with gauze after drainage.[1] Closing this cavity right after draining it rather than leaving it open may speed healing without increasing the risk of the abscess returning.[10] Sucking out the pus with a needle is often not sufficient.[1]

Skin abscesses are common and have become more common in recent years.[1] Risk factors include intravenous drug use with rates reported as high as 65% in this population.[2] In 2005 in the United States 3.2 million people went to the emergency department for an abscess.[5] In Australia around 13,000 people were hospitalized in 2008 with the condition.[11]

Five-day-old abscess. The black spot is a clogged hair follicle.

| | |
|---|---|
| **Specialty** | General surgery, infectious disease |
| **Symptoms** | redness, pain, swelling[1] |
| **Usual onset** | rapid |
| **Causes** | bacteria (often MRSA)[1] |
| **Risk factors** | intravenous drug use[2] |
| **Diagnostic method** | ultrasound, CT scan[1][3] |
| **Differential diagnosis** | cellulitis, sebaceous cyst, necrotising fasciitis[3] |
| **Treatment** | cutting it open[4] |
| **Frequency** | ~1% per year (United States)[5] |

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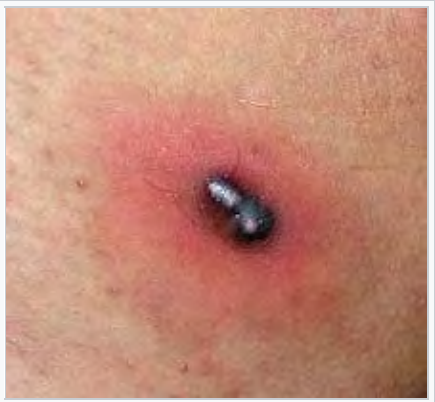
Contents

## Signs and symptoms [edit]


An abscess

Abscesses may occur in any kind of solid tissue but most frequently on skin surface (where they may be superficial pustules (boils) or deep skin abscesses), in the lungs, brain, teeth, kidneys and tonsils. Major complications are spreading of the abscess material to adjacent or remote tissues and extensive regional tissue death (gangrene).

The main symptoms and signs of a skin abscess are redness, heat, swelling, pain and loss of function. There may also be high temperature (fever) and chills.[12]

An internal abscess is more difficult to identify, but signs include pain in the affected area, a high temperature, and generally feeling unwell. Internal abscesses rarely heal themselves, so prompt medical attention is indicated if such an abscess is suspected. An abscess could potentially be fatal (although this is rare) if it compresses vital structures such as the trachea in the context of a deep neck abscess.[*citation needed*]

If superficial, abscesses may be fluctuant when palpated. This is a wave-like motion that is caused by movement of the pus inside the abscess.[13]

## Causes [edit]

Risk factors for abscess formation include intravenous drug use.[14] Another possible risk factor is a prior history of disc herniation or other spinal abnormality,[15] though this has not been proven.

Abscesses are caused by bacterial infection, parasites, or foreign substances. Bacterial infection is the most common cause.[8] Often many different types of bacteria are involved in a single infection.[6] In the United States and many other areas of the world the most common bacteria present is *methicillin-resistant Staphylococcus aureus*.[1] Among spinal subdural abscesses, methicillin-sensitive Staphylococcus aureus is the most common organism involved.[15]

Rarely parasites can cause abscesses and this is more common in the developing world.[3] Specific parasites known to do this include: dracunculiasis and myiasis.[3]

### Perianal abscess [edit]

See also: *Anorectal abscess*

Surgery of the anal fistula to drain an abscess treats the fistula and reduces likelihood of its recurrence and the need for repeated surgery.[16] There is no evidence that fecal incontinence is a consequence of this surgery for abscess drainage.[16]

Perianal abscesses can be seen in patients with for example inflammatory bowel disease (such as Crohn's disease) or diabetes. Often the abscess will start as an internal wound caused by ulceration, hard stool or penetrative objects with insufficient lubrication. This wound typically becomes infected as a result of the normal presence of feces in the rectal area, and then develops into an abscess. This often presents itself as a lump of tissue near the anus which grows larger and more painful with time. Like other abscesses, perianal abscesses may require prompt medical treatment, such as an incision and debridement or lancing.

### Incisional abscess [edit]

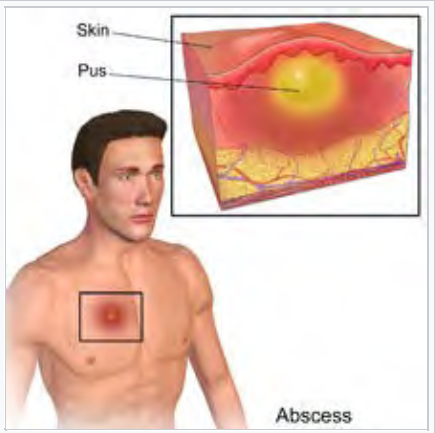
An *incisional abscess* is one that develops as a complication secondary to a surgical incision. It presents as redness and warmth at the margins of the incision with purulent drainage from it.[17] If the diagnosis is uncertain, the wound should be aspirated with a needle, with aspiration of pus confirming the diagnosis and availing for Gram stain and bacterial culture.[17]

## Pathophysiology [edit]

An abscess is a defensive reaction of the tissue to prevent the spread of infectious materials to other parts of the body.

The organisms or foreign materials kill the local cells, resulting in the release of cytokines. The cytokines trigger an inflammatory response, which draws large numbers of white blood cells to the area and increases the regional blood flow.

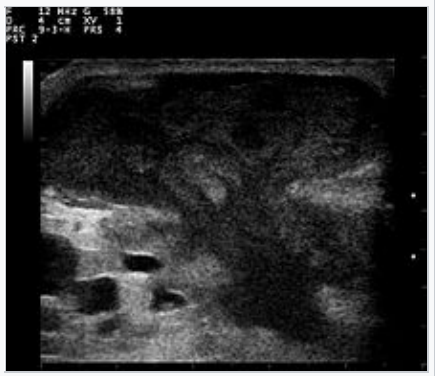
The final structure of the abscess is an abscess wall, or capsule, that is formed by the adjacent healthy cells in an attempt to keep the pus from infecting neighboring structures. However, such encapsulation tends to prevent immune cells from attacking bacteria in the pus, or from reaching the causative organism or foreign object.



A diagram of an abscess

## Diagnosis [edit]

An abscess is a localized collection of pus (purulent inflammatory tissue) caused by suppuration buried in a tissue, an organ, or a confined space, lined by pyogenic membrane.[18]


Ultrasound image of breast abscess, appearing as a mushroom-shaped dark (hypoechoic) area

### Classification [edit]

Abscesses may be classified as either *skin abscesses* or *internal abscesses*. Skin abscesses are common; internal abscesses tend to be harder to diagnose, and more serious.[12] Skin abscesses are also called cutaneous or subcutaneous abscesses.[19]

### IV drug use [edit]

For those with a history of intravenous drug use, an X-ray is recommended before treatment to verify that no needle fragments are present.[14] In this population if there is also a fever present infectious endocarditis should be considered.[14]

### Differential [edit]

Abscesses should be differentiated from empyemas, which are accumulations of pus in a preexisting rather than a newly formed anatomical cavity.

Other conditions that can cause similar symptoms include: cellulitis, a sebaceous cyst and necrotising fasciitis.[3]

Cellulitis typically also has an erythematous reaction, but does not confer any purulent drainage.[17]

# Treatment [edit]

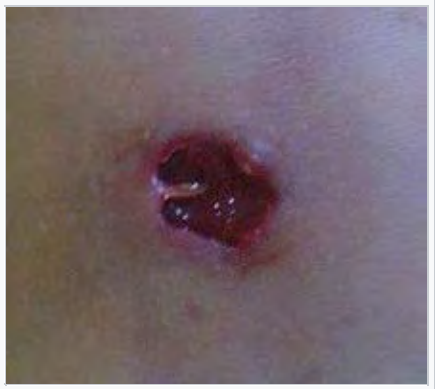
The standard treatment for an uncomplicated skin or soft tissue abscess is opening and draining.[4] There does not appear to be any benefit from also using antibiotics in most cases.[1] A small amount of evidence did not find benefit from packing the abscess with gauze.[1]

## Incision and drainage [edit]

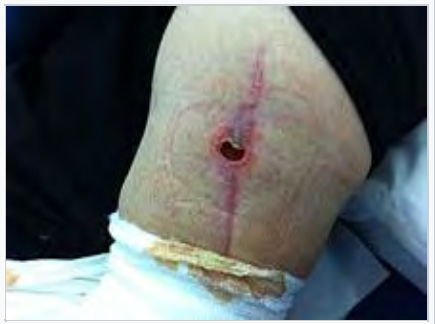
*See also: Incision and drainage*

The abscess should be inspected to identify if foreign objects are a cause, which may require their removal. If foreign objects are not the cause, incising and draining the abscess is standard treatment.[4][20]

In critical areas where surgery presents a high risk, it may be delayed or used as a last resort. The drainage of a lung abscess may be performed by positioning the patient in a way that enables the contents to be discharged via the respiratory tract. Warm compresses and elevation of the limb may be beneficial for a skin abscess.



Abscess five days after incision and drainage



Abscess following curettage

## Antibiotics [edit]

Most people who have an uncomplicated skin abscess should not use antibiotics.[4] Antibiotics in addition to standard incision and drainage is recommended in persons with severe abscesses, many sites of infection, rapid disease progression, the presence of cellulitis, symptoms indicating bacterial illness throughout the body, or a health condition causing immunosuppression.[1] People who are very young or very old may also need antibiotics.[1] If the abscess does not heal only with incision and drainage, or if the abscess is in a place that is difficult to drain such as the face, hands, or genitals, then antibiotics may be indicated.[1]

In those cases of abscess which do require antibiotic treatment, *Staphylococcus aureus* bacteria is a common cause and an anti-staphylococcus antibiotic such as flucloxacillin or dicloxacillin is used. The Infectious Diseases Society of America advises that the draining of an abscess is not enough to address community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA), and in those cases, traditional antibiotics may be ineffective.[1] Alternative antibiotics effective against community-acquired MRSA often include clindamycin, doxycycline, minocycline, and trimethoprim-sulfamethoxazole.[1] The American College of Emergency Physicians advises that typical cases of abscess from MRSA get no benefit from having antibiotic treatment in addition to the standard treatment.[4] If the condition is thought to be cellulitis rather than abscess, consideration should be given to possibility of strep species as cause that are still sensitive to traditional anti-staphylococcus agents such as dicloxacillin or cephalexin in patients able to tolerate penicillin. Antibiotic therapy alone without surgical drainage of the abscess is seldom effective due to antibiotics often being unable to get into the abscess and their ineffectiveness at low pH levels.

Culturing the wound is not needed if standard follow-up care can be provided after the incision and drainage.[4] Performing a wound culture is unnecessary because it rarely gives information which can be used to guide treatment.[4]

## Packing [edit]

In North America, after drainage, an abscess cavity is often packed, perhaps with cloth, in an attempt to protect the healing wound. However, evidence from emergency medicine literature reports that packing wounds after draining causes pain to the person and does not decrease the rate of recurrence, bring more rapid healing, or

lead to fewer physician visits.[21]

### Loop Drainage [edit]

More recently, several North American hospitals have opted for less-invasive loop drainage over standard drainage and wound packing. In one study of 143 pediatric outcomes, a failure rate of 1.4% was reported in the loop group versus 10.5% in the packing group (P<.030),[22] while a separate study reported a 5.5% failure rate among loop patients.[23]

### Primary closure [edit]

Closing an abscess immediately after draining it appears to speed healing without increasing the risk of recurrence.[10] This may not apply to anorectal abscesses. While they heal faster, there may be a higher rate of recurrence than those left open.[24]

## Prognosis [edit]

Even without treatment they rarely result in death as they will naturally break through the skin.[3]

## Epidemiology [edit]

Skin abscesses are common and have become more common in recent years.[1] Risk factors include intravenous drug use with rates reported as high as 65% in this population.[2] In 2005 in the United States 3.2 million people went to the emergency department for an abscess.[5] In Australia around 13,000 people were hospitalized in 2008 for the disease.[11]

## Society and culture [edit]

The Latin medical aphorism "*ubi pus, ibi evacua*" expresses "where there is pus, there evacuate it" and is classical advice in the culture of Western medicine.

Needle exchange programmes often administer or provide referrals for abscess treatment to injection drug users as part of a harm reduction public health strategy.[25][26]

### Etymology [edit]

An abscess is so called because there is an *abscessus* (a going away or departure) of portions of the animal tissue from each other to make room for the suppurated matter lodged between them.[27]

The word carbuncle is believed to have originated from the Latin: *carbunculus*, originally a small coal; diminutive of *carbon-*, *carbo*: charcoal or ember, but also a carbuncle stone, "precious stones of a red or fiery colour", usually garnets.[28]

### Other types [edit]

The following types of abscess are listed in the medical dictionary:[29]

- acute abscess
- alveolar abscess
- amebic abscess
- apical abscess
- apical periodontal abscess
- appendiceal abscess
- Bartholin abscess
- Bezold abscess
- bicameral abscess
- hematogenous abscess
- hot abscess
- hypostatic abscess
- ischiorectal abscess
- lateral alveolar abscess
- lateral periodontal abscess
- mastoid abscess
- metastatic abscess
- migrating abscess
- phlegmonous abscess
- Pott abscess
- premammary abscess (including subareolar abscess)
- psoas abscess
- pulp abscess
- pyemic abscess
- radicular abscess
- residual abscess

- bone abscess
- Brain abscess
- Brodie abscess
- bursal abscess
- caseous abscess
- caseous lymphadenitis
- cheesy abscess
- cholangitic abscess
- chronic abscess
- collar stud abscess
- cold abscess
- crypt abscesses
- dental abscess
- diffuse abscess
- Douglas abscess
- dry abscess
- Dubois abscesses
- embolic abscess
- fecal abscess
- follicular abscess
- gas abscess
- gingival abscess
- gravitation abscess
- gummatous abscess
- Hidradenitis suppurativa
- miliary abscess
- Munro abscess
- orbital abscess
- otitic abscess
- palatal abscess
- pancreatic abscess
- parafrenal abscess
- parametric abscess
- paranephric abscess
- parapharyngeal abscess
- parotid
- Pautrier
- pelvic
- perforating
- periapical
- periappendiceal
- periarticular
- pericemental
- pericoronal abscess
- perinephric
- periodontal abscess
- perirectal
- peritonsillar abscess
- periureteral abscess
- periurethral abscess
- retrobulbar abscess
- retrocecal abscess
- retropharyngeal abscess
- ring abscess
- root abscess
- satellite abscess
- septicemic abscess
- stellate abscess
- stercoral abscess
- sterile abscess
- stitch abscess
- subdiaphragmatic abscess
- subepidermal abscess
- subhepatic abscess
- subperiosteal abscess
- subphrenic abscess
- subungual abscess
- sudoriferous abscess
- suture abscess
- thymic abscesses
- Tornwaldt abscess
- tropical abscess
- tubo-ovarian abscess
- verminous abscess
- wandering abscess
- worm abscess

## References [edit]


1. ^ *a b c d e f g h i j k l m n o p q r s t* Singer, Adam J.; Talan, David A. (Mar 13, 2014). "Management of skin abscesses in the era of methicillin-resistant *Staphylococcus aureus*" (PDF). *The New England Journal of Medicine*. **370** (11): 1039–47. doi:10.1056/NEJMra1212788. PMID 24620867.
2. ^ *a b c* Langrod, Pedro Ruiz, Eric C. Strain, John G. (2007). *The substance abuse handbook*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 373. ISBN 9780781760454.
3. ^ *a b c d e f g h* Marx, John A. Marx (2014). "Skin and Soft Tissue Infections". *Rosen's emergency medicine : concepts and clinical practice* (8th ed.). Philadelphia, PA: Elsevier/Saunders. pp. Chapter 137. ISBN 1455706051.
4. ^ *a b c d e f g h* American College of Emergency Physicians, "Five Things Physicians and Patients Should Question", *Choosing Wisely: an initiative of the ABIM Foundation*, American College of Emergency Physicians, retrieved January 24, 2014
5. ^ *a b c* Taira, BR; Singer, AJ; Thode HC, Jr; Lee, CC (Mar 2009). "National epidemiology of cutaneous abscesses: 1996 to 2005.". *The American journal of emergency medicine*. **27** (3): 289–92. doi:10.1016/j.ajem.2008.02.027. PMID 19328372.
6. ^ *a b c* Elston, Dirk M. (2009). *Infectious Diseases of the Skin.* London: Manson Pub. p. 12. ISBN 9781840765144.
7. ^ Marx, John A. Marx (2014). "Dermatologic Presentations". *Rosen's emergency medicine : concepts*
15. ^ *a b* Kraeutler, MJ; Bozzay, JD; Walker, MP; John, K (Oct 24, 2014). "Spinal subdural abscess following epidural steroid injection.". *J Neurosurg Spine*. **22** (1): 90–3. doi:10.3171/2014.9.SPINE14159. PMID 25343407.
16. ^ *a b* Malik, Ali Irqam; Nelson, Richard L; Tou, Samson; Malik, Ali Irqam (2010). "Incision and drainage of perianal abscess with or without treatment of anal fistula". *Reviews*. doi:10.1002/14651858.CD006827.pub2.
17. ^ *a b c* Duff, Patrick (2009). "Diagnosis and Management of Postoperative Infection". *The Global Library of Women's Medicine*. doi:10.3843/GLOWM.10032. ISSN 1756-2228.
18. ^ Robins/8th/68
19. ^ Medline Plus `Abscess'
20. ^ Green, James; Saj Wajed (2000). *Surgery: Facts and Figures*. Cambridge University Press. ISBN 1-900151-96-0.
21. ^ Bergstrom, KG (Jan 2014). "News, views, and reviews. Less may be more for MRSA: the latest on antibiotics, the utility of packing an abscess, and decolonization strategies.". *Journal of drugs in dermatology : JDD*. **13** (1): 89–92. PMID 24385125.
22. ^ Ladde JG, Baker S, Rodgers CN, Papa L (2015). "The


options for skin and soft tissue abscesses in injecting drug users with consideration of the natural history and concomitant risk factors.". *European journal of medical research*. **13** (9): 415–24. PMID 18948233.

*and clinical practice* (8th ed.). Philadelphia, PA: Elsevier/Saunders. pp. Chapter 120. ISBN 1455706051.
8. ^ [a] [b] Cox, Carol Turkington, Jeffrey S. Dover ; medical illustrations, Birck (2007). *The encyclopedia of skin and skin disorders* (3rd ed.). New York, NY: Facts on File. p. 1. ISBN 9780816075096.
9. ^ Fahimi, J; Singh, A; Frazee, BW (July 2015). "The role of adjunctive antibiotics in the treatment of skin and soft tissue abscesses: a systematic review and meta-analysis.". *CJEM*. **17** (4): 420–32. doi:10.1017/cem.2014.52. PMID 26013989.
10. ^ [a] [b] Singer, Adam J.; Thode, Henry C., Jr; Chale, Stuart; Taira, Breena R.; Lee, Christopher (May 2011). "Primary closure of cutaneous abscesses: a systematic review" (PDF). *The American Journal of Emergency Medicine*. **29** (4): 361–6. doi:10.1016/j.ajem.2009.10.004. PMID 20825801.
11. ^ [a] [b] Vaska, VL; Nimmo, GR; Jones, M; Grimwood, K; Paterson, DL (Jan 2012). "Increases in Australian cutaneous abscess hospitalisations: 1999-2008.". *European Journal of Clinical Microbiology & Infectious Diseases*. **31** (1): 93–6. doi:10.1007/s10096-011-1281-3. PMID 21553298.
12. ^ [a] [b] United Kingdom National Health Service `Abscess'
13. ^ *Churchill Livingstone medical dictionary*. (16th ed.). Edinburgh: Churchill Livingstone. 2008. ISBN 9780080982458.
14. ^ [a] [b] [c] Khalil, PN; Huber-Wagner, S; Altheim, S; Bürklein, D; Siebeck, M; Hallfeldt, K; Mutschler, W; Kanz, GG (Sep 22, 2008). "Diagnostic and treatment LOOP technique: a novel incision and drainage technique in the treatment of skin abscesses in a pediatric ED". *The American Journal of Emergency Medicine*. **33** (2): 271–6. doi:10.1016/j.ajem.2014.10.014. PMID 25435407.
23. ^ Tsoraides SS, Pearl RH, Stanfill AB, Wallace LJ, Vegunta RK (2010). "Incision and loop drainage: a minimally invasive technique for subcutaneous abscess management in children". *Journal of Pediatric Surgery*. **45** (3): 606–9. doi:10.1016/j.jpedsurg.2009.06.013. PMID 20223328.
24. ^ Kronborg O, Olsen H (1984). "Incision and drainage v. incision, curettage and suture under antibiotic cover in anorectal abscess. A randomized study with 4-year follow-up". *Acta Chirurgica Scandinavica*. **150** (8): 689–92. PMID 6397949.
25. ^ Tomolillo, CM; Crothers, LJ; Aberson, CL (2007). "The damage done: a study of injection drug use, injection related abscesses and needle exchange regulation.". *Substance Use & Misuse*. **42** (10): 1603–11. doi:10.1080/10826080701204763. PMID 17918030.
26. ^ Fink, DS; Lindsay, SP; Slymen, DJ; Kral, AH; Bluthenthal, RN (May 2013). "Abscess and self-treatment among injection drug users at four California syringe exchanges and their surrounding communities.". *Substance Use & Misuse*. **48** (7): 523–31. doi:10.3109/10826084.2013.787094. PMID 23581506.
27. ^ Collier's New Encyclopedia, `Abscess'.
28. ^ OED, "Carbuncle": 1) stone, 3) medical
29. ^ "Abscess". *Medical Dictionary - Dictionary of Medicine and Human Biology*. Retrieved 2013-01-24.

## External links [edit]

- MedlinePlus Encyclopedia *Abscess*
- MedlinePlus Encyclopedia *Skin Abscess*
- "Abscess". *Collier's New Encyclopedia*. 1921.
- "Abscess". *Encyclopædia Britannica* (11th ed.). 1911.

Look up *abscess* in Wiktionary, the free dictionary.

Wikimedia Commons has media related to *Abscesses*.

| | |
|---|---|
| **Classification** | **ICD-10**: L02 · **ICD-9-CM**: 682.9, 324.1 · **MeSH**: D000038 · |
| **External resources** | **MedlinePlus**: 001353 · |

| v · t · e | **Diseases of the skin and appendages by morphology** | |
|---|---|---|
| **Growths** | **Epidermal** | wart · callus · seborrheic keratosis · acrochordon · molluscum contagiosum · actinic keratosis · squamous-cell carcinoma · basal-cell carcinoma · Merkel-cell carcinoma · nevus sebaceous · trichoepithelioma · |
| | **Pigmented** | Freckles · lentigo · melasma · nevus · melanoma · |
| | **Dermal and subcutaneous** | epidermal inclusion cyst · hemangioma · dermatofibroma (benign fibrous histiocytoma) · keloid · lipoma · neurofibroma · xanthoma · Kaposi's sarcoma · infantile digital fibromatosis · granular cell tumor · leiomyoma · lymphangioma circumscriptum · myxoid cyst · |

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| **Rashes** | **With epidermal involvement** | **Eczematous** | | | contact dermatitis · atopic dermatitis · seborrheic dermatitis · stasis dermatitis · lichen simplex chronicus · Darier's disease · glucagonoma syndrome · langerhans cell histiocytosis · lichen sclerosus · pemphigus foliaceus · Wiskott–Aldrich syndrome · Zinc deficiency · |
| | | **Scaling** | | | psoriasis · tinea (corporis · cruris · pedis · manuum · faciei) · pityriasis rosea · secondary syphilis · mycosis fungoides · systemic lupus erythematosus · pityriasis rubra pilaris · parapsoriasis · ichthyosis · |
| | | **Blistering** | | | herpes simplex · herpes zoster · varicella · bullous impetigo · acute contact dermatitis · pemphigus vulgaris · bullous pemphigoid · dermatitis herpetiformis · porphyria cutanea tarda · epidermolysis bullosa simplex · |
| | | **Papular** | | | scabies · insect bite reactions · lichen planus · miliaria · keratosis pilaris · lichen spinulosus · transient acantholytic dermatosis · lichen nitidus · pityriasis lichenoides et varioliformis acuta · |
| | | **Pustular** | | | acne vulgaris · acne rosacea · folliculitis · impetigo · candidiasis · gonococcemia · dermatophyte · coccidioidomycosis · subcorneal pustular dermatosis · |
| | | **Hypopigmented** | | | tinea versicolor · vitiligo · pityriasis alba · postinflammatory hyperpigmentation · tuberous sclerosis · idiopathic guttate hypomelanosis · leprosy · hypopigmented mycosis fungoides · |
| | **Without epidermal involvement** | **Red** | **Blanchable Erythema** | **Generalized** | drug eruptions · viral exanthems · toxic erythema · systemic lupus erythematosus · |
| | | | | **Localized** | cellulitis · **abscess** · boil · erythema nodosum · carcinoid syndrome · fixed drug eruption · |
| | | | | **Specialized** | urticaria · erythema (multiforme · migrans · gyratum repens · annulare centrifugum · ab igne) · |
| | | | **Nonblanchable Purpura** | **Macular** | thrombocytopenic purpura · actinic/solar purpura · |
| | | | | **Papular** | disseminated intravascular coagulation · vasculitis · |
| | | **Indurated** | | | scleroderma/morphea · granuloma annulare · lichen sclerosis et atrophicus · necrobiosis lipoidica · |
| **Miscellaneous disorders** | **Ulcers** | | | | |
| | **Hair** | telogen effluvium · androgenic alopecia · trichotillomania · alopecia areata · systemic lupus erythematosus · tinea capitis · loose anagen syndrome · lichen planopilaris · folliculitis decalvans · acne keloidalis nuchae · | | | |
| | **Nail** | onychomycosis · psoriasis · paronychia · ingrown nail · | | | |

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| | **Mucous membrane** | Aphthous stomatitis · oral candidiasis · lichen planus · leukoplakia · pemphigus vulgaris · mucous membrane pemphigoid · cicatricial pemphigoid · herpesvirus · coxsackievirus · syphilis · systemic histoplasmosis · squamous-cell carcinoma · |

| v · t · e · | **Bacterial skin disease (L00–L08, 680–686)** | |
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| **Gram +ve** | **Firmicutes** | *Staphylococcus* (Staphylococcal scalded skin syndrome · Impetigo · Toxic shock syndrome · · *Streptococcus* (Impetigo · Cutaneous group B streptococcal infection · Streptococcal intertrigo · Cutaneous *Streptococcus iniae* infection · Erysipelas / Chronic recurrent erysipelas · Scarlet fever · · *Corynebacterium* (Erythrasma · · Listeriosis · *Clostridium* (Gas gangrene · Dermatitis gangrenosa · · Mycoplasma · Erysipeloid of Rosenbach · |
| | **Actinobacteria** | *Mycobacterium-related:* Aquarium granuloma · Borderline lepromatous leprosy · Borderline leprosy · Borderline tuberculoid leprosy · Buruli ulcer · Erythema induratum · Histoid leprosy · Lepromatous leprosy · Leprosy · Lichen scrofulosorum · Lupus vulgaris · Miliary tuberculosis · *Mycobacterium avium-intracellulare complex* infection · *Mycobacterium haemophilum* infection · *Mycobacterium kansasii* infection · Papulonecrotic tuberculid · Primary inoculation tuberculosis · Rapid growing mycobacterium infection · Scrofuloderma · Tuberculosis cutis orificialis · Tuberculosis verrucosa cutis · Tuberculous cellulitis · Tuberculous gumma · Tuberculoid leprosy · Cutaneous actinomycosis · Nocardiosis · Cutaneous diphtheria infection · *Arcanobacterium haemolyticum* infection · Group JK corynebacterium sepsis · |
| **Gram -ve** | **Proteobacteria** | α: Endemic typhus · Epidemic typhus · Scrub typhus · North Asian tick typhus · Queensland tick typhus · Flying squirrel typhus · Trench fever · Bacillary angiomatosis · African tick bite fever · American tick bite fever · *Rickettsia aeschlimannii* infection · Rickettsialpox · Rocky Mountain spotted fever · Human granulocytotropic anaplasmosis · Human monocytotropic ehrlichiosis · Flea-borne spotted fever · Japanese spotted fever · Mediterranean spotted fever · Flinders Island spotted fever · Verruga peruana · Brill–Zinsser disease · Brucellosis · Cat-scratch disease · Oroya fever · Ehrlichiosis ewingii infection · β: Gonococcemia/Gonorrhea/Primary gonococcal dermatitis · Melioidosis · Cutaneous *Pasteurella hemolytica* infection · Meningococcemia · Glanders · Chromobacteriosis infection · γ: Pasteurellosis · Tularemia · Vibrio vulnificus · Rhinoscleroma · *Haemophilus influenzae* cellulitis · Pseudomonal pyoderma / Pseudomonas hot-foot syndrome / Hot tub folliculitis / Ecthyma gangrenosum / Green nail syndrome · Q fever · Salmonellosis · Shigellosis · Plague · Granuloma inguinale · Chancroid · Aeromonas infection · ε: Helicobacter cellulitis · |
| | **Other** | Syphilid · Syphilis · Chancre · Yaws · Pinta · Bejel · Chlamydia infection · Leptospirosis · Rat-bite fever · Lyme disease · Lymphogranuloma venereum · |
| **Unspecified** | | **Abscess** (Periapical abscess · · Boil/furuncle (Hospital furunculosis · · Carbuncle · Cellulitis (Paronychia / Pyogenic paronychia · Perianal cellulitis · · Acute lymphadenitis · Pilonidal cyst · Pyoderma · Folliculitis (Superficial pustular folliculitis · Sycosis vulgaris · · Pimple · Ecthyma · Pitted keratolysis · Trichomycosis axillaris · Necrotizing fascitis · Gangrene (Chronic undermining burrowing ulcers · |

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| **pathogen** | Fournier gangrene · · Elephantiasis nostras · Blistering distal dactylitis · Botryomycosis · Malakoplakia · Gram-negative folliculitis · Gram-negative toe web infection · Pyomyositis · Blastomycosis-like pyoderma · Bullous impetigo · Chronic lymphangitis · Recurrent toxin-mediated perineal erythema · Tick-borne lymphadenopathy · Tropical ulcer · |
| **Authority control** | NDL: 00568732 · |

Categories: General surgery | Animal bacterial diseases




# Acne vulgaris

From Wikipedia, the free encyclopedia

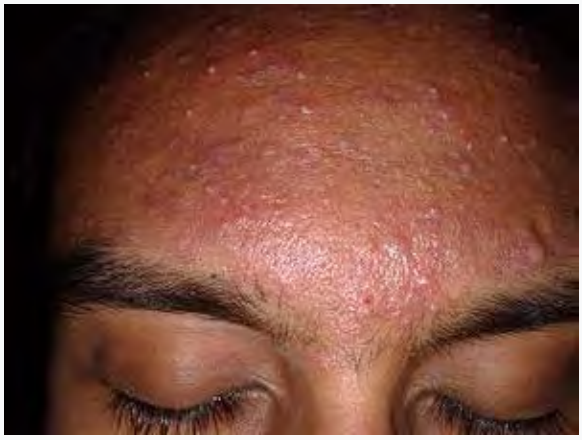
*This article is about a skin disease common during adolescence. For other acneiform skin diseases, see Acne (disambiguation).*

**Acne vulgaris**, also known as **acne**, is a long-term skin disease that occurs when hair follicles become clogged with dead skin cells and oil from the skin.[1] Acne is characterized by areas of blackheads, whiteheads, pimples, and greasy skin, and may result in scarring.[2][3][4] The resulting appearance can lead to anxiety, reduced self-esteem and, in extreme cases, depression or thoughts of suicide.[5][6]

Genetics is thought to be the cause in 80 % of cases.[3] The role of diet and cigarette smoking is unclear and neither cleanliness nor sunlight appear to be involved.[3][7][8] Acne affects primarily skin with a greater number of oil glands, including the face, upper part of the chest, and back.[9] During puberty, in both sexes, acne is often brought on by an increase in hormones such as testosterone.[10] Excessive growth of the bacterium *Propionibacterium acnes*, which is normally present on the skin, is often involved.[10]

Many treatment options are available including lifestyle changes, medications, and procedures. Eating fewer simple carbohydrates like sugar may help.[11] Treatments applied directly to the affected skin such as azelaic acid, benzoyl peroxide, and salicylic acid are commonly used.[12] Antibiotics and retinoids are available in both topical and by mouth formulations to treat acne.[12] However, resistance to antibiotics may develop.[13] Several types of birth control pills help against acne in women.[12] Isotretinoin pills are usually reserved for severe acne due to greater potential side effects.[12] Early and aggressive treatment is advocated by some to lessen the overall long-term impact to individuals.[6]

In 2013, acne was estimated to affect 660 million people globally, making it the 8th most common disease worldwide.[14][15] Acne commonly occurs in adolescence, affecting an estimated 80–90 % of teenagers in the Western world.[16][17][18] Lower rates are reported in some rural societies.[18][19] Children and adults may also be affected before and after puberty.[20] While less common in adulthood, nearly half of people in their twenties and thirties continue to have acne.[3] About 4% continue to have difficulties into their forties.[3]



Acne vulgaris in an 18-year-old male during puberty

| Classification and external resources | |
|---|---|
| **Specialty** | Dermatology |
| **ICD-10** | L70.0 |
| **ICD-9-CM** | 706.1 |
| **DiseasesDB** | 10765 |
| **MedlinePlus** | 000873 |
| **eMedicine** | derm/2 |
| **Patient UK** | Acne vulgaris |
| **MeSH** | D000152 |

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1 Classification
2 Signs and symptoms

## Classification [edit]

Acne is commonly classified by severity as mild, moderate, or severe. This type of categorization can be an important factor in determining the appropriate treatment regimen.[17] Mild acne is classically defined as open (blackheads) and closed (whiteheads) clogged skin follicles (comedones) limited to the face with occasional inflammatory lesions.[17] Acne may be considered to be of moderate severity when a higher number of inflammatory papules and pustules occur on the face compared to mild cases of acne, and acne lesions also occur on the trunk of the body.[17] Lastly, severe acne is said to occur when nodules (the painful 'bumps' lying under the skin) are the characteristic facial lesions, and involvement of the trunk is extensive.[17][21]

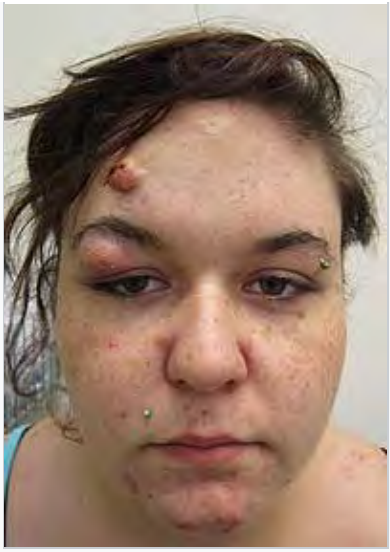
Large nodules have been referred to as cysts in the past, and the term *nodulocystic* has been used in the medical literature to describe severe cases of inflammatory acne.[21] However, since true cysts are rare in those with acne, the term *severe nodular acne* is now the preferred terminology.[21]

## Signs and symptoms [edit]

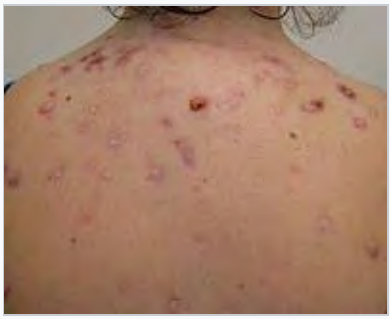
Typical features of acne include seborrhea (increased sebum secretion), microcomedones, comedones, papules, pustules, nodules (large papules), and in many cases scarring.[22][23] The appearance of acne varies with skin color. It may result in psychological and social problems.[17]

### Scars [edit]

Acne scars are the result of inflammation within the dermal layer of skin, brought on by acne, and are estimated to affect 95% of people with acne vulgaris.[24] The scar is created by abnormal healing following this dermal inflammation.[24] Scarring is most likely to occur with severe nodular acne, but may occur with any form of acne vulgaris.[24] Acne scars are classified based on



A severe case of nodular acne



Nodular acne on the back

whether the abnormal healing response following dermal inflammation leads to excess collagen deposition or collagen loss at the site of the acne lesion.[24] Atrophic acne scars are the most common type of acne scar and have lost collagen from this healing response.[24] Atrophic scars may be further classified as ice-pick scars, boxcar scars, and rolling scars.[24] Ice-pick scars are typically described as narrow (less than 2 mm across), deep scars that extend into the dermis.[24] Boxcar scars are round or ovoid indented scars with sharp borders and vary in size from 1.5–4 mm across.[24] Rolling scars are wider than icepick and boxcar scars (4–5 mm across) and have a wave-like pattern of depth in the skin.[24]

Hypertrophic scars are less common, and are characterized by increased collagen content after the abnormal healing response.[24] They are described as firm and raised from the skin.[24][25] Hypertrophic scars remain within the original margins of the wound, whereas keloid scars can form scar tissue outside of these borders.[24] Keloid scars from acne occur more often in men and in people with darker colored skin, and usually occur on the trunk of the body rather than the face.[24]

### Pigmentation [edit]

Postinflammatory hyperpigmentation (PIH) is usually the result of nodular acne lesions. They often leave behind an inflamed darkened mark after the original acne lesion has resolved. PIH occurs more often in people with darker skin color.[26] Pigmented scar is a common but misleading term, as it suggests the color change is permanent. Often, PIH can be prevented by avoiding any aggravation of the nodule. These scars can fade with time. However, untreated scars can last for months, years, or even be permanent if deeper layers of skin are affected.[27] Daily use of SPF 15 or higher sunscreen can minimize pigmentation associated with acne.[27]

## Causes [edit]

### Genes [edit]

The predisposition to acne for specific individuals is likely explained in part by a genetic component, a theory which has been supported by twin studies as well as studies that have looked at rates of acne among first-degree relatives.[28] Acne susceptibility is likely due to the influence of multiple genes, as the disease does not follow a classic Mendelian inheritance pattern. There are multiple candidates for genes which are possibly related to acne, including polymorphisms in tumor necrosis factor-alpha (TNF-alpha), IL-1 alpha, and CYP1A1, among others.[16] The 308 G/A single nucleotide polymorphism in the gene for TNF is associated with acne risk.[29]

### Hormones [edit]

Hormonal activity, such as occurs during menstrual cycles and puberty, may contribute to the formation of acne. During puberty, an increase in sex hormones called androgens causes the follicular glands to grow larger and make more sebum.[9][30] Several hormones have been linked to acne, including the androgens testosterone,

dihydrotestosterone (DHT), and dehydroepiandrosterone sulfate (DHEA-S), as well as insulin-like growth factor 1 (IGF-1) and growth hormone (GH).[31] Both androgens and IGF-1 seem to be essential for acne to occur, as acne does not develop in individuals with complete androgen insensitivity syndrome (CAIS) or Laron syndrome (insensitivity to GH, resulting in extremely low IGF-1 levels).[32][33]

Medical conditions that commonly cause a high-androgen state, such as polycystic ovary syndrome, congenital adrenal hyperplasia, and androgen-secreting tumors, can cause acne in affected individuals.[34][35] Conversely, people who lack androgenic hormones or are insensitive to the effects of androgens rarely have acne.[34] An increase in androgen (and sebum) synthesis may also be seen during pregnancy.[35][36] Acne can be a side effect of testosterone replacement therapy or of anabolic steroid use.[2][37] Over-the-counter bodybuilding and dietary supplements are commonly found to contain illegally added anabolic steroids.[2][38]

### Infections [edit]

*Propionibacterium acnes* (*P. acnes*) is the anaerobic bacterium species that is widely suspected to contribute to the development of acne, but its exact role in this process is not entirely clear.[28] There are specific sub-strains of *P. acnes* associated with normal skin and others with moderate or severe inflammatory acne.[39] It is unclear whether these undesirable strains evolve on-site or are acquired, or possibly both depending on the person. These strains have the capability of either changing, perpetuating, or adapting to the abnormal cycle of inflammation, oil production, and inadequate sloughing of dead skin cells from acne pores. One particularly virulent strain has been circulating in Europe for at least 87 years.[40] Infection with the parasitic mite *Demodex* is associated with the development of acne.[23][41] However, it is unclear whether eradication of these mites improves acne.[41]

### Diet [edit]

The relationship between diet and acne is unclear, as there is no high-quality evidence which establishes any definitive link.[42] High-glycemic-load diets have been found to have different degrees of effect on acne severity by different studies.[11][43][44] Multiple randomized controlled trials and nonrandomized studies have found a lower-glycemic-load diet to be effective in reducing acne.[43] Additionally, there is weak observational evidence suggesting that dairy milk consumption is positively associated with a higher frequency and severity of acne.[41][43][45][46][47] Effects from other potentially contributing dietary factors, such as consumption of chocolate or salt, are not supported by the evidence.[45] Chocolate does contain varying amounts of sugar, which can lead to a high glycemic load, and it can be made with or without milk. There may be a relationship between acne and insulin metabolism, and one trial found a relationship between acne and obesity.[48] Vitamin $B_{12}$ may trigger skin outbreaks similar to acne (acneiform eruptions), or exacerbate existing acne, when taken in doses exceeding the recommended daily intake.[49]

### Smoking [edit]

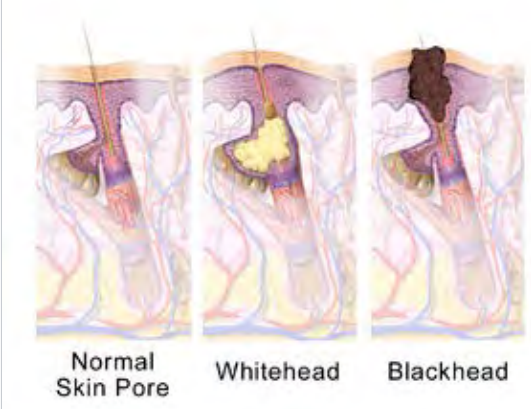
The relationship between cigarette smoking and acne severity is unclear and remains a point of debate.[3] Due to the observational nature of the evidence obtained from epidemiological studies, there are concerns that bias and confounding may have influenced the results.[3] Certain medical literature reviews have stated cigarette smoking clearly worsens acne[7] whereas others have stated it is unclear whether smoking is unrelated to, worsens, or improves acne severity.[3][8] Due to the various known negative health effects of cigarette smoking, it is not recommended as an approach to improving the appearance of acne.[3]

### Stress [edit]

Overall, few high-quality studies have been performed which demonstrate that stress causes or worsens acne.[50] While the connection between acne and stress has been debated, some research indicates that increased acne severity is associated with high stress levels in certain settings (e.g., in association with the hormonal changes seen in premenstrual syndrome).[51][52]

## Pathophysiology [edit]

Acne vulgaris is a chronic skin disease of the pilosebaceous unit and develops due to blockages in the skin's hair follicles. These blockages are thought to occur as a result of the following four abnormal processes: a higher than normal amount of sebum production (influenced by androgens), excessive deposition of the protein keratin leading to comedone formation, colonization of the follicle by *Propionibacterium acnes* (*P. acnes*) bacteria, and the local release of pro-inflammatory chemicals in the skin.[39]



Hair follicle anatomy demonstrating a healthy hair follicle (pictured left), a whitehead or closed comedone (middle picture), and a blackhead or open comedone (pictured right)

The earliest pathologic change is the formation of a plug (a microcomedone), which is driven primarily by excessive proliferation of keratinocytes in the hair follicle.[2] In normal skin, the skin cells that have died come up to the surface and exit the pore of the hair follicle.[1] However, increased production of oily sebum in those with acne causes the dead skin cells to stick together.[1] The accumulation of dead skin cell debris and oily sebum blocks the pore of the hair follicle, thus forming the microcomedone.[1] This is further exacerbated by the biofilm created by *P. acnes* within the hair follicle.[34] If the microcomedone is superficial within the hair follicle, the skin pigment melanin is exposed to air, resulting in its oxidation and dark appearance (known as a blackhead or open comedone).[1][2][17] In contrast, if the microcomedone occurs deep within the hair follicle, this causes the formation of a whitehead (known as a closed comedone).[1][2]

Dihydrotestosterone (DHT) is the main driver of androgen-induced sebum production in the skin.[2] Another androgenic hormone responsible for increased sebaceous gland activity is DHEA-S. Higher amounts of DHEA-S are secreted during adrenarche (a stage of puberty), and this leads to an increase in sebum synthesis. In a sebum-rich skin environment, the naturally occurring and largely commensal skin bacterium *P. acnes* readily grows and can cause inflammation within and around the follicle due to activation of the innate immune system.[1] *P. acnes* triggers skin inflammation in acne by increasing the production of several pro-inflammatory chemical signals (such as IL-1α, IL-8, TNF-α, and LTB4); IL-1α is known to be essential to comedone formation.[34]

A major mechanism of acne-related skin inflammation is mediated by *P. acnes*'s ability to bind and activate a class of immune system receptors known as toll-like receptors, especially toll-like receptor 2 (TLR2) and toll-like receptor 4 (TLR4).[34][53][54] Activation of TLR2 and TLR4 by *P. acnes* leads to increased secretion of IL-8, TNF-α, and IL-1α.[34] Release of these inflammatory signals attracts various immune cells to the hair follicle including neutrophils, macrophages, and Th1 cells.[34] IL-1α stimulates higher keratinocyte activity and reproduction, which in turn fuels comedone development.[34] Sebaceous gland cells also produce more antimicrobial peptides, such as HBD1 and HBD2, in response to binding of TLR2 and TLR4.[34]

*P. acnes* is also capable of provoking additional skin inflammation by altering sebum's fatty composition.[34] Squalene oxidation by *P. acnes* is of particular importance. Oxidation of squalene activates NF-κB and consequently increases IL-1α levels.[34] Additionally, squalene oxidation leads to increased activity of the 5-lipoxygenase enzyme responsible for conversion of arachidonic acid to leukotriene B4 (LTB4).[34] LTB4 promotes skin inflammation by acting on peroxisome proliferator-activated receptor alpha (PPARα).[34] PPARα increases activity of activator protein 1 (AP-1) and NF-κB, thereby leading to the recruitment of inflammatory T cells.[34] The inflammatory properties of *P. acnes* can be further explained by the bacterium's ability to convert sebum triglycerides to pro-inflammatory free fatty acids via secretion of the enzyme lipase.[34] These free fatty acids spur production of cathelicidin, HBD1, and HBD2, thus leading to further inflammation.[34]

This inflammatory cascade typically leads to the formation of inflammatory acne lesions, including papules, infected pustules, or nodules.[2] If the inflammatory reaction is severe, the follicle can break into the deeper layers of the dermis and subcutaneous tissue and cause the formation of deep nodules.[2][55][56] Involvement of AP-1 in the aforementioned inflammatory cascade also leads to activation of matrix metalloproteinases, which contribute to local tissue destruction and scar formation.[34]

## Diagnosis [edit]

There are several features that may indicate that a person's acne vulgaris is sensitive to hormonal influences. Historical and physical clues that may suggest hormone-sensitive acne include onset between ages 20 and 30; worsening the week before a woman's menstrual cycle; acne lesions predominantly over the jawline and chin; and inflammatory/nodular acne lesions.[2]

Several scales exist to grade the severity of acne vulgaris, but no single technique has been universally accepted as the diagnostic standard.[57][58] Cook's acne grading scale uses photographs to grade severity from 0 to 8 (0 being the least severe and 8 being the most severe). This scale was the first to use a standardized photographic protocol to assess acne severity; since its creation in 1979, Cook's grading scale has undergone several revisions.[58] Leeds acne grading technique counts acne lesions on the face, back, and chest and categorizes them as inflammatory or non-inflammatory. Leeds scores range from 0 (least severe) to 10 (most severe) though modified scales have a maximum score of 12.[58][59] The Pillsbury acne grading scale simply classifies the severity of the acne from 1 (least severe) to 4 (most severe).[57][60]

### Differential diagnosis [edit]

Skin conditions which may mimic acne vulgaris include angiofibromas, folliculitis, keratosis pilaris, perioral dermatitis, and rosacea, among others.[17] Age is one factor which may help distinguish between these disorders. Skin disorders such as perioral dermatitis and keratosis pilaris can appear similar to acne but tend to occur more frequently in childhood, whereas rosacea tends to occur more frequently in older adults.[17] Facial redness triggered by heat or the consumption of alcohol or spicy food is suggestive of rosacea.[61] The presence of comedones can also help health professionals differentiate acne from skin disorders that are similar in appearance.[12] Chloracne, due to exposure to certain chemicals, may look very similar to acne vulgaris.[62]

## Management [edit]

Many different treatments exist for acne, including alpha hydroxy acid, anti-androgen medications, antibiotics, antiseborrheic medications, azelaic acid, benzoyl peroxide, hormonal treatments, keratolytic soaps, nicotinamide, retinoids, and salicylic acid.[63] They are believed to work in at least four different ways, including the following: anti-inflammatory effects, hormonal manipulation, killing *P. acnes*, and normalizing skin cell shedding and sebum production in the pore to prevent blockage.[9] Commonly used medical treatments include topical therapies such as antibiotics, benzoyl peroxide, and retinoids, and systemic therapies including antibiotics, hormonal agents, and oral retinoids.[17][64]

Recommended therapies for first-line use in acne vulgaris treatment include topical retinoids, benzoyl peroxide, and topical or oral antibiotics.[65] Procedures such as light therapy and laser therapy are not considered to be first-line treatments and typically have an adjunctive role due to their high cost and the limited evidence of their efficacy.[64] Medications for acne work by targeting the early stages of comedone formation and are generally ineffective for visible skin lesions; improvement in the appearance of acne is typically expected between six and eight weeks after starting therapy.[2]

### Diet [edit]

A diet low in simple sugars is recommended as a method of improving acne.[43] As of 2014, evidence is insufficient to recommend milk restriction for this purpose.[43]

### Medications [edit]

### Benzoyl peroxide [edit]

Benzoyl peroxide (BPO) is a first-line treatment for mild and moderate acne due to its effectiveness and mild side-effects (mainly skin irritation). In the skin follicle, benzoyl peroxide kills *P.*

The common acne vulgaris treatment benzoyl peroxide cream

*acnes* by oxidizing its proteins through the formation of oxygen free radicals and benzoic acid, which is thought to interfere with the bacterium's metabolism and ability to make proteins.[66][67] Additionally, benzoyl peroxide is also mildly effective at breaking down comedones and inhibiting inflammation.[65][67] Benzoyl peroxide often causes dryness of the skin, slight redness, and occasional peeling when side effects occur.[68] This topical treatment does increase the skin's sensitivity to the sun, so sunscreen use is often advised during treatment, to prevent sunburn. Lower concentrations of benzoyl peroxide are just as effective as higher concentrations in treating acne but are associated with fewer side effects.[68] Unlike antibiotics, benzoyl peroxide does not appear to generate bacterial antibiotic resistance.[68] Benzoyl peroxide may be paired with a topical antibiotic or retinoid such as benzoyl peroxide/clindamycin and benzoyl peroxide/adapalene, respectively.[26]

## Retinoids [edit]

Retinoids are medications structurally related to vitamin A,[9] which possess anti-inflammatory properties, normalize the follicle cell life cycle, and reduce sebum production.[9][54] The retinoids appear to influence the cell life cycle in the follicle lining. This helps prevent the hyperkeratinization of these cells which can create a blockage. They are a first-line acne treatment,[2] especially for people with dark-colored skin, and are known to lead to faster improvement of postinflammatory hyperpigmentation.[26]

Frequently used topical retinoids include adapalene, isotretinoin, retinol, tazarotene, and tretinoin.[36] Topical retinoids often cause an initial flare-up of acne and facial flushing and can cause significant skin irritation. Generally speaking, retinoids increase the skin's sensitivity to sunlight and are therefore recommended for use at night.[2] Tretinoin is the least expensive of the topical retinoids and is the most irritating to the skin, whereas adapalene is the least irritating to the skin but costs significantly more than other retinoids.[2][69] Tazarotene is the most effective of the topical retinoids.[2] However, tazarotene is also the most expensive and is not as well-tolerated as other topical retinoids.[2][69] Retinol is a form of vitamin A that has similar but milder effects, and is used in many over-the-counter moisturizers and other topical products.

Isotretinoin is a retinoid which is taken orally and is very effective for severe nodular acne as well as moderate acne refractory to other treatments.[2][17] Improvement is typically seen after one to two months of use. Acne often resolves completely or is much milder after a 4- to 6-month course of oral isotretinoin.[2] After a single course, about 80% of people report an improvement, with more than 50% reporting complete remission.[17] About 20% of people require a second course.[17] A number of adverse effects may occur with isotretinoin use, including dry skin and lips, nose bleeds, muscle pains, increased liver enzymes, and increased lipid levels in the blood.[17] There is no clear evidence that use of oral retinoids increases the risk of psychiatric side effects such as depression and suicidality.[2][17] The use of oral isotretinoin in women of childbearing age is strictly regulated due to its known harmful effects in pregnancy.[17] For a woman of childbearing age to be considered a candidate for isotretinoin, she must have a confirmed negative pregnancy test and use an effective form of birth control.[17]

## Antibiotics [edit]

Antibiotics are frequently applied to the skin or taken orally to treat acne and are thought to work due to their antimicrobial activity against *P. acnes* and their anti-inflammatory properties.[17][68][70] With increasing resistance of *P. acnes* worldwide, antibiotics are becoming less effective,[68] especially macrolide antibiotics such as topical erythromycin.[70] Commonly used antibiotics, either applied to the skin or taken orally, include clindamycin, erythromycin, metronidazole, sulfacetamide, and tetracyclines such as doxycycline and minocycline.[36] When antibiotics are applied to the skin, they are typically used for mild to moderately severe [17]

acne and antibiotics taken orally are usually reserved for moderate and severe cases of inflammatory acne. Antibiotics taken orally are generally considered to be more effective than topical antibiotics, are highly effective against inflammatory acne, and produce faster resolution of inflammatory acne lesions than topical application of antibiotics.[2] It is recommended that oral antibiotics be stopped after three months and used in combination with benzoyl peroxide if their use is thought to be necessary for adequate treatment.[70]

The use of topical or oral antibiotics alone is discouraged due to concerns surrounding antibiotic resistance, but their use is recommended in combination with topical benzoyl peroxide or a retinoid.[2][70] Dapsone is not typically used as a first-line topical antibiotic due to its higher cost and lack of clear superiority over other antibiotics.[2] Dapsone is not recommended for use with benzoyl peroxide due to reports of yellow-orange skin discoloration with this combination of medications.[1]

## Hormonal agents [edit]

In women, acne can be improved with the use of any combined birth control pills.[71] Birth control pills decrease the ovaries' production of androgen hormones, resulting in lower skin production of sebum, and consequently reduce acne severity.[1] The combinations which contain third- or fourth-generation progestins such as desogestrel, drospirenone, or norgestimate may theoretically be more beneficial.[71] A 2014 systematic review found that antibiotics by mouth appear to be somewhat more effective than birth control pills at decreasing the number of inflammatory acne lesions at three months.[72] However, the two therapies are approximately equal in efficacy at six months for decreasing the number of inflammatory, non-inflammatory, and total acne lesions.[72] The authors of the analysis suggested that birth control pills may be a preferred first-line acne treatment over antibiotics by mouth in certain women due to similar efficacy at six months and a lack of associated antibiotic resistance.[72]

Antiandrogens such as cyproterone acetate and spironolactone have also been used successfully to treat acne, especially in women with signs of excessive androgen production such as increased hairiness, baldness, or increased skin production of oily sebum.[1][36] The aldosterone antagonist spironolactone is an effective treatment for acne in adult women, but unlike combination oral contraceptives, it is not approved by the United States Food and Drug Administration for this purpose.[2][26] Spironolactone is thought to be a useful acne treatment due to its ability to block the androgen receptor at higher doses.[26] It may be used with or without an oral contraceptive.[26] Hormonal therapies should not be used to treat acne during pregnancy or lactation as they have been associated with certain birth defects such as hypospadias and feminization of the male fetus or infant.[36] Finasteride is also likely to be an effective treatment for acne.[2]

## Azelaic acid [edit]

Azelaic acid has been shown to be effective for mild-to-moderate acne when applied topically at a 20% concentration.[55][73] Application twice daily for six months is necessary, and treatment is as effective as topical benzoyl peroxide 5%, isotretinoin 0.05%, and erythromycin 2%.[74] Treatment of acne with azelaic acid is less effective and more expensive than treatment with retinoids.[2] Azelaic acid is thought to be an effective acne treatment due to its antibacterial, anti-inflammatory, and antikeratinizing properties.[55] Additionally, azelaic acid has a slight skin-lightening effect due to its ability to inhibit melanin synthesis, and is therefore useful in treatment of individuals with acne who are also affected by postinflammatory hyperpigmentation.[2] Azelaic acid may cause skin irritation but is otherwise very safe.[75]

## Salicylic acid [edit]

Salicylic acid is a topically applied beta-hydroxy acid that stops bacteria from reproducing and has keratolytic properties.[76][77] Additionally, salicylic acid opens obstructed skin pores and promotes shedding of epithelial skin cells.[76] Salicylic acid is known to be less effective than retinoid therapy.[17] Dry skin is the most commonly seen side effect with topical application, though darkening of the skin has been observed in individuals with darker skin types who use salicylic acid.[2][9]

## Other medications [edit]

Topical and oral preparations of nicotinamide (the amide form of vitamin $B_3$) have been suggested as alternative medical treatments for acne.[78] Nicotinamide is thought to improve acne due to its anti-inflammatory properties, its ability to suppress sebum production, and its ability to promote wound healing.[78] Similarly, topical and oral preparations of zinc have also been proposed as effective treatments for acne; however, the evidence to support their use for this purpose is limited.[79] Zinc's benefits in acne are attributed to its beneficial effects against inflammation, sebum production, and *P. acnes*.[79] Tentative evidence has found that antihistamines may improve symptoms among those already taking isotretinoin. Antihistamines are thought to improve acne due to their anti-inflammatory properties and their ability to suppress sebum production.[80]

## Combination therapy [edit]

Combination therapy—using medications of different classes together, each with a different mechanism of action—has been demonstrated to be a more efficacious approach to acne treatment than monotherapy.[1][36] The use of topical benzoyl peroxide and antibiotics together has been shown to be more effective than antibiotics alone.[1] Similarly, using a topical retinoid with an antibiotic clears acne lesions faster than the use of antibiotics alone.[1] Frequently used combinations include the following: antibiotic + benzoyl peroxide, antibiotic + topical retinoid, or topical retinoid + benzoyl peroxide.[36] The pairing of benzoyl peroxide with a retinoid is preferred over the combination of a topical antibiotic with a retinoid since both regimens are effective but benzoyl peroxide does not lead to antibiotic resistance.[1]

## Procedures [edit]

Comedo extraction may temporarily help those with comedones that do not improve with standard treatment.[12] A procedure for immediate relief is the injection of corticosteroids into the inflamed acne comedone.[9]

Light therapy (also known as photodynamic therapy) is a method that involves delivering intense pulses of light to the area with acne following the application of a sensitizing substance such as aminolevulinic acid or methyl aminolevulinate.[1][73] This process is thought to kill bacteria and decrease the size and activity of the glands that produce sebum.[73] As of 2012, evidence for light therapy was insufficient to recommend it for routine use.[12] Disadvantages of light therapy include its cost, the need for multiple visits, and the time required to complete the procedure.[1] Light therapy appears to provide a short-term benefit, but data for long-term outcomes, and for outcomes in those with severe acne, are sparse.[9][81] However, light therapy may have a role for individuals whose acne has been resistant to topical medications.[1] Typical side effects of light therapy include skin peeling, temporary reddening of the skin, swelling, and postinflammatory hyperpigmentation.[1]

Dermabrasion is an effective therapeutic procedure for reducing the appearance of superficial atrophic scars of the boxcar and rolling varieties.[24] Ice-pick scars do not respond well to treatment with dermabrasion due to their depth.[24] However, the procedure is painful and has many potential side effects such as skin sensitivity to sunlight, redness, and decreased pigmentation of the skin.[24] Dermabrasion has fallen out of favor with the introduction of laser resurfacing.[24] Unlike dermabrasion, there is no evidence that microdermabrasion is an effective treatment for acne.[12]

Laser resurfacing can be used to reduce the scars left behind by acne.[82] Ablative fractional photothermolysis laser resurfacing was found to be more effective for reducing acne scar appearance than non-ablative fractional photothermolysis, but was associated with higher rates of postinflammatory hyperpigmentation (usually about one-month duration), facial redness (usually for 3–14 days), and pain during the procedure.[83] As of 2012, the evidence to support the routine use of laser resurfacing as a treatment modality for acne scars was insufficient.[12] Many studies that evaluated this form of treatment did not have a control group, did not compare laser resurfacing to effective medical treatments, or were of a short duration, thus limiting the quality of the evidence.[12]

Chemical peels can also be used to reduce the appearance of acne scars.[24] Mild chemical peels include those using glycolic acid, lactic acid, salicylic acid, Jessner's solution, or a lower concentration (20%) of trichloroacetic acid. These peels only affect the epidermal layer of the skin and can be useful in the treatment of superficial acne scars as well as skin pigmentation changes from inflammatory acne.[24] Higher concentrations of trichloroacetic acid (30–40%) are considered to be medium-strength peels and affect skin as deep as the

papillary dermis.[24] Formulations of trichloroacetic acid concentrated to 50% or more are considered to be deep chemical peels.[24] Medium- and deep-strength chemical peels are more effective for deeper atrophic scars, but are more likely to cause side effects such as skin pigmentation changes, infection, or milia.[24]

### Pregnancy [edit]

Although the late stages of pregnancy are associated with an increase in sebaceous gland activity in the skin, pregnancy has not been reliably associated with worsened acne severity.[84] In general, topically applied medications are considered the first-line approach to acne treatment during pregnancy, as topical therapies have little systemic absorption and are therefore unlikely to harm a developing fetus.[84] Highly recommended therapies include topically applied benzoyl peroxide (category C) and azelaic acid (category B).[84] Salicylic acid carries a category C safety rating due to higher systemic absorption (9–25%) and an association between the use of anti-inflammatory medications in the third trimester of pregnancy and adverse effects to the developing fetus including oligohydramnios and early closure of the ductus arteriosus.[36][84] Prolonged use of salicylic acid over significant areas of the skin or under occlusive dressings is not recommended as these methods increase systemic absorption and the potential for fetal harm.[84] Tretinoin (category C) and adapalene (category C) are very poorly absorbed, but certain studies have suggested teratogenic effects in the first trimester.[84] In studies examining the effects of topical retinoids during pregnancy, fetal harm has not been seen in the second and third trimesters.[84] Retinoids contraindicated for use during pregnancy include the topical retinoid tazarotene (category X) and oral retinoids isotretinoin (category X) and acitretin (category X).[84] Spironolactone is relatively contraindicated for use during pregnancy due to its antiandrogen effects.[2] Finasteride is also not recommended for use during pregnancy as it is highly teratogenic.[2]

Topical antibiotics deemed safe during pregnancy include clindamycin (category B), erythromycin (category B) and metronidazole (category B), due to negligible systemic absorption.[36][84] Nadifloxacin and dapsone (category C) are other topical antibiotics that may be used to treat acne in pregnant women, but have received less extensive study.[36][84] No adverse fetal events have been reported in association with topical use of dapsone during pregnancy.[84] If retinoids are used during pregnancy, there is a high risk of abnormalities occurring in the developing fetus; therefore, women of childbearing age are required to use effective birth control if retinoids are used to treat acne.[17] Oral antibiotics deemed safe for pregnancy (all category B) include azithromycin, cephalosporins, and penicillins.[84] Tetracyclines (category D) are contraindicated during pregnancy as they are known to deposit in developing fetal teeth, resulting in yellow discoloration and thinned tooth enamel.[2][84] Use of tetracyclines in pregnancy has also been associated with development of acute fatty liver of pregnancy and is avoided for this reason as well.[84]

### Alternative medicine [edit]

Complementary therapies have been investigated for treating people with acne.[85] Low-quality evidence suggests topical application of tea tree oil or bee venom may reduce the total number of skin lesions in those with acne.[85] Tea tree oil is thought to be approximately as effective as benzoyl peroxide or salicylic acid, but has been associated with cases of allergic contact dermatitis.[2] Proposed mechanisms for tea tree oil's anti-acne effects include antibacterial action against *P. acnes* and anti-inflammatory properties.[54] Numerous other plant-derived therapies have been observed to have positive effects against acne (e.g., basil oil and oligosaccharides from seaweed); however, few studies have been performed, and most have been of lower methodological quality.[86] There is a lack of high-quality evidence for the use of acupuncture, herbal medicine, or cupping therapy for acne.[85]

## Prognosis [edit]

Acne usually improves around the age of 20, but may persist into adulthood.[63] Permanent physical scarring may occur.[17] There is good evidence to support the idea that acne has a negative psychological impact, and that it worsens mood, lowers self-esteem, and is associated with a higher risk of anxiety disorders, depression, and suicidal thoughts.[41] Another psychological complication of acne vulgaris is acne excoriée, which occurs when a person persistently picks and scratches pimples, irrespective of the severity of their acne.[51][87] This can

lead to significant scarring, changes in the affected person's skin pigmentation, and a cyclic worsening of the affected person's anxiety about their appearance.[51]

## Epidemiology [edit]

Globally, acne affects approximately 650 million people, or about 9.4% of the population, as of 2010.[88] It affects nearly 90% of people in Western societies during their teenage years, and may persist into adulthood.[17] Acne that first develops between the ages of 21 and 25 is uncommon; however, acne affects 54% of women and 40% of men older than 25 years of age.[36][89] Acne vulgaris has a lifetime prevalence of 85%.[36] About 20% of those affected have moderate or severe cases.[28] It is slightly more common in females than males (9.8% versus 9.0%).[88] In those over 40 years old, 1% of males and 5% of females still have problems.[17]

Rates appear to be lower in rural societies.[19] While some research has found it affects people of all ethnic groups,[90] acne may not occur in the non-Westernized peoples of Papua New Guinea and Paraguay.[28]

Acne affects 40 to 50 million people in the United States (16%) and approximately 3 to 5 million in Australia (23%).[72][91] In the United States, acne tends to be more severe in Caucasians than in people of African descent.[9]

## History [edit]

Since at least as long ago as the reign of Cleopatra (69–30 BC), the application of sulfur to the skin has been recognized as a useful form of treatment for acne.[92] The sixth-century Greek physician Aëtius of Amida is credited with coining the term "ionthos" (ἰονθωξ,) or "acnae", which is believed to have been a reference to facial skin lesions that occur during "the 'acme' of life" (referring to puberty).[93]

In the 16th century, the French physician and botanist François Boissier de Sauvages de Lacroix provided one of the earlier descriptions of acne and used the term "psydracia achne" to describe small, red and hard tubercles that altered a person's facial appearance during adolescence and were neither itchy nor painful.[93] The recognition and characterization of acne progressed in 1776 when Josef Plenck (an Austrian physician) published a book that proposed the novel concept of classifying skin diseases by their elementary (initial) lesions.[93] Plenck's work was later refined when the English dermatologist Robert Willan authored his seminal 1808 treatise, which provided the first detailed descriptions of several skin disorders with morphologic terminology that continues to be used today.[93] Thomas Bateman continued and expanded on Robert Willan's work as his student and provided the medical literature's first descriptions and illustrations of acne accepted as accurate by modern dermatologists.[93]

Domolene ointment, a mid 1900s medication that was claimed to cure acne

Dermatologists originally hypothesized that acne represented a disease of the skin's hair follicle and occurred due to blockage of the pore by sebum. During the 1880s, bacteria were observed by microscopy in skin samples affected by acne and were regarded as the causal agents of comedones, sebum production, and ultimately acne.[93] During the mid-twentieth century, dermatologists realized that no single hypothesized factor (sebum, bacteria, or excess keratin) could completely explain the disease.[93] This led dermatologists to the current understanding that acne could be explained by a sequence of related events, beginning with blockage of the skin follicle by excessive dead skin cells, followed by bacterial invasion of the hair follicle pore, changes in sebum production, and inflammation.[93]

The approach to acne treatment also underwent significant changes during the twentieth century. Benzoyl peroxide was introduced as a medication to treat acne in the 1920s.[94] Acne treatment was again modified in the 1950s with the introduction of oral tetracycline antibiotics (such as minocycline), which reinforced the idea amongst dermatologists that bacterial growth on the skin plays an important role in causing acne.[93]

Subsequently, in the 1970s tretinoin (original trade name Retin A) was found to be an effective treatment for acne.[95] This preceded the development of oral isotretinoin (sold as Accutane and Roaccutane) in 1980.[96] Following the introduction of isotretinoin in the United States, it was recognized as a medication highly likely to cause birth defects if taken during pregnancy. In the United States, more than 2,000 women became pregnant while taking the drug between 1982 and 2003, with most pregnancies ending in abortion or miscarriage. About 160 babies with birth defects were born.[97][98]

## Society and culture [edit]

### Cost [edit]

The social and economic costs of treating acne vulgaris are substantial. In the United States, acne vulgaris is responsible for more than 5 million doctor visits and costs over $2.5 billion each year in direct costs.[7] Similarly, acne vulgaris is responsible for 3.5 million doctor visits each year in the United Kingdom.[17]

### Stigma [edit]

Misperceptions about acne's causative and aggravating factors are common and those affected by acne are often blamed for their condition.[99] Such blame can worsen the affected person's sense of self-esteem.[99] Acne vulgaris and its resultant scars have been associated with significant social difficulties that can last into adulthood.[100]

## Research [edit]

Efforts are underway to better understand the mechanisms involved in sebum production. The aim of this research is to develop medications targeting hormones known to increase sebum production (e.g., IGF-1 and alpha-melanocyte-stimulating hormone).[1] Additional sebum-lowering medications being researched include topical antiandrogens and PPAR modulators.[1] Another avenue of early-stage research has focused on how to best use laser and light therapy to selectively destroy sebaceous glands in the skin's hair follicles to reduce sebum production and improve acne appearance.[1]

The use of antimicrobial peptides against *P. acnes* is also under investigation as a novel method of treating acne and overcoming antibiotic resistance.[1] In 2007, the first genome sequencing of a *P. acnes* bacteriophage (PA6) was reported. The authors proposed applying this research toward development of bacteriophage therapy as an acne treatment in order to overcome the problems associated with long-term antibiotic therapy, such as bacterial resistance.[101] Oral and topical probiotics are also being evaluated as treatments for acne.[102] Probiotics have been hypothesized to have therapeutic effects for those affected by acne due to their ability to decrease skin inflammation and improve skin moisture by increasing the skin's ceramide content.[102] As of 2014, studies examining the effects of probiotics on acne in humans were limited.[102]

Decreased levels of retinoic acid in the skin may contribute to comedone formation. To address this deficiency, and potentially replace the use of irritating topical retinoids, methods to increase the skin's production of retinoid acid are being explored.[1] A vaccine against inflammatory acne has been tested successfully in mice, but has not yet been proven to be effective in humans.[103] Other workers have voiced concerns related to creating a vaccine designed to neutralize a stable community of normal skin bacteria that is known to protect the skin from colonization by more harmful microorganisms.[104]

## References [edit]


1. ^ *a b c d e f g h i j k l m n o p q r s t u v w* Aslam, I.; Fleischer, A.; Feldman, S. (March 2015). "Emerging drugs for the treatment of acne". *Expert Opinion on Emerging Drugs* (Review). **20** (1): 91–101. doi:10.1517/14728214.2015.990373. PMID 25474485.(subscription required)
2. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae* Vary, J.C., Jr. (November 2015). "Selected Disorders of Skin Appendages — Acne, Alopecia, Hyperhidrosis". *The Medical Clinics of North America* (Review). **99** (6): 1195–1211. doi:10.1016/j.mcna.2015.07.003. PMID 26476248.

3. ^ [a b c d e f g h i] Bhate, K.; Williams, H.C. (March 2013). "Epidemiology of acne vulgaris". *The British Journal of Dermatology* (Review). **168** (3): 474–85. doi:10.1111/bjd.12149. PMID 23210645.
4. ^ Tuchayi, Sara M.; Makrantonaki, Evgenia; Ganceviciene, Ruta; Dessinioti, Clio; Feldman, Steven R.; Zouboulis, Christos C. (17 September 2015). "Acne vulgaris". *Nature Reviews Disease Primers*: 15033. doi:10.1038/nrdp.2015.33.
5. ^ Barnes, L.E.; Levender, M.M.; Fleischer, A.B., Jr.; Feldman, S.R. (April 2012). "Quality of life measures for acne patients". *Dermatologic Clinics* (Review). **30** (2): 293–300. doi:10.1016/j.det.2011.11.001. PMID 22284143.
6. ^ [a b] Goodman, G. (July 2006). "Acne and acne scarring–the case for active and early intervention". *Australian family physician* (Review). **35** (7): 503–4. PMID 16820822.
7. ^ [a b c] Knutsen-Larson, S.; Dawson, A.L.; Dunnick, C.A.; Dellavalle, R.P. (January 2012). "Acne vulgaris: pathogenesis, treatment, and needs assessment". *Dermatologic Clinics* (Review). **30** (1): 99–106. doi:10.1016/j.det.2011.09.001. PMID 22117871.
8. ^ [a b] Schnopp, C; Mempel, M (August 2011). "Acne vulgaris in children and adolescents". *Minerva Pediatrica* (Review). **63** (4): 293–304. PMID 21909065.
9. ^ [a b c d e f g h i] Benner, N.; Sammons, D. (September 2013). "Overview of the treatment of acne vulgaris". *Osteopathic Family Physician* (Review). **5** (5): 185–90. doi:10.1016/j.osfp.2013.03.003.
10. ^ [a b] James, W.D. (April 2005). "Acne". *New England Journal of Medicine* (Review). **352** (14): 1463–72. doi:10.1056/NEJMcp033487. PMID 15814882.
11. ^ [a b] Mahmood, S.N.; Bowe, W.P. (April 2014). "Diet and acne update: carbohydrates emerge as the main culprit". *Journal of Drugs in Dermatology: JDD* (Review). **13** (4): 428–35. PMID 24719062.
12. ^ [a b c d e f g h i j] Titus, Stephen; Hodge, Joshua (October 2012). "Diagnosis and treatment of acne". *American Family Physician* (Review). **86** (8): 734–40. PMID 23062156.
13. ^ Beylot, C.; Auffret, N.; Poli, F.; Claudel, J.P.; Leccia, M.T.; Del Giudice, P.; Dreno, B. (March 2014). "*Propionibacterium acnes*: an update on its role in the pathogenesis of acne". *Journal of the European Academy of Dermatology and Venereology: JEADV* (Review). **28** (3): 271–8. doi:10.1111/jdv.12224. PMID 23905540.
14. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
15. ^ Hay, RJ; Johns, NE; Williams, HC; Bolliger, IW; Dellavalle, RP; Margolis, DJ; Marks, R; Naldi, L; Weinstock, MA; Wulf, SK; Michaud, C; Murray, C; Naghavi, M (October 2013). "The Global Burden of Skin Disease in 2010: An Analysis of the Prevalence and Impact of Skin Conditions". *The Journal of Investigative Dermatology*. **134** (6): 1527–34. doi:10.1038/jid.2013.446. PMID 24166134.
16. ^ [a b] Taylor, Marisa; Gonzalez, Maria; Porter, Rebecca (May–June 2011). "Pathways to inflammation: acne pathophysiology". *European Journal of Dermatology* (Review). **21** (3): 323–33. doi:10.1684/ejd.2011.1357 (inactive 2017-01-02). PMID 21609898.
17. ^ [a b c d e f g h i j k l m n o p q r s t u v w x y] Dawson, Annelise L.; Dellavalle, Roberta P. (May 2013). "Acne vulgaris". *BMJ* (Review). **346** (5): f2634. doi:10.1136/bmj.f2634. PMID 23657180.
18. ^ [a b] Berlin, David J; Goldberg, Alexander L. (2011-10-30). *Acne and Rosacea Epidemiology, Diagnosis and Treatment*. London: Manson Pub. p. 8. ISBN 978-1-84076-616-5.
19. ^ [a b] Spencer, EH; Ferdowsian, Barnard ND (April 2009). "Diet and acne: a review of the evidence". *International Journal of Dermatology* (Review). **48** (4): 339–47. doi:10.1111/j.1365-4632.2009.04002.x. PMID 19335417.
20. ^ Admani, S; Barrio, VR (November 2013). "Evaluation and treatment of acne from infancy to preadolescence". *Dermatologic Therapy* (Review). **26** (6): 462–6. doi:10.1111/dth.12108. PMID 24552409.
21. ^ [a b c] Zaenglein, Andrea L; Graber, Emmy M; Thiboutot, Diane M (2012). "Chapter 80 Acne Vulgaris and Acneiform Eruptions". In Goldsmith, Lowell A.; Katz, Stephen I.; Gilchrest, Barbara A.; Paller, Amy S.; Lefell, David J.; Wolff, Klaus. *Fitzpatrick's Dermatology in General Medicine* (8th ed.). New York: McGraw-Hill. pp. 897–917. ISBN 0-07-171755-2.
22. ^ Adityan, B.; Kumari, R.; Thappa, DM (May 2009). "Scoring systems in acne vulgaris". *Indian Journal of Dermatology, Venereology and Leprology* (Review). **75** (3): 323–6. doi:10.4103/0378-6323.51258. PMID 19439902.
23. ^ [a b] Zhao, YE; Hu, L; Wu, LP; Ma, JX (March 2012). "A meta-analysis of association between acne vulgaris and Demodex infestation". *Journal of Zhejiang University. Science. B* (Meta-analysis). **13** (3): 192–202. doi:10.1631/jzus.B1100285. PMC 3296070. PMID 22374611.
24. ^ [a b c d e f g h i j k l m n o p q r s t u v] Levy, L.L.; Zeichner, J.A. (October 2012). "Management of acne scarring, part II: a comparative review of non-laser-based, minimally invasive approaches". *American Journal of Clinical Dermatology* (Review). **13** (5): 331–40. doi:10.2165/11631410-000000000-00000. PMID 22849351.
25. ^ Sobanko, J.F.; Alster, T.S. (October 2012). "Management of acne scarring, part I: a comparative review of laser surgical approaches". *American Journal of Clinical Dermatology* (Review). **13** (5): 319–30. doi:10.2165/11598910-000000000-00000. PMID 22612738.
26. ^ [a b c d e f] Yin, NC; McMichael, AJ (February 2014). "Acne in patients with skin of color: practical management". *American Journal of Clinical Dermatology* (Review). **15** (1): 7–16. doi:10.1007/s40257-013-0049-1. PMID 24190453.

27. ^ a b Callender, V.D.; St. Surin-Lord, S.; Davis, E.C.; Maclin, M. (April 2011). "Postinflammatory hyperpigmentation: etiologic and therapeutic considerations". *American Journal of Clinical Dermatology* (Review). **12** (2): 87–99. doi:10.2165/11536930-000000000-00000. PMID 21348540.
28. ^ a b c d Bhate, K; Williams, HC (March 2013). "Epidemiology of acne vulgaris". *The British Journal of Dermatology* (Review). **168** (3): 474–85. doi:10.1111/bjd.12149. PMID 23210645.
29. ^ Yang, J.K.; Wu, W.J.; Qi, J.; He, L.; Zhang, Y.P. (February 2014). "TNF-308 G/A polymorphism and risk of acne vulgaris: a meta-analysis". *PLoS ONE* (Systematic Review & Meta-Analysis). **9** (2): e87806. doi:10.1371/journal.pone.0087806. PMC 3912133. PMID 24498378.
30. ^ "Frequently Asked Questions: Acne". U.S. Department of Health and Human Services, Office of Public Health and Science, Office on Women's Health. 16 July 2009. Retrieved 2009-07-30.
31. ^ Hoeger, Peter H.; Irvine, Alan D.; Yan, Albert C. (2011). "Chapter 79: Acne". *Harper's Textbook of Pediatric Dermatology* (3rd ed.). New Jersey: Wiley-Blackwell. ISBN 978-1-4443-4536-0.
32. ^ Alan R. Shalita; James Q. Del Rosso; Guy Webster (21 March 2011). *Acne Vulgaris*. CRC Press. pp. 33–. ISBN 978-1-61631-009-7.
33. ^ Christos C. Zouboulis; Andreas Katsambas; Albert M. Kligman (28 July 2014). *Pathogenesis and Treatment of Acne and Rosacea*. Springer. pp. 121–122. ISBN 978-3-540-69375-8.
34. ^ a b c d e f g h i j k l m n o p q Das, S; Reynolds, RV (December 2014). "Recent advances in acne pathogenesis: implications for therapy". *American Journal of Clinical Dermatology* (Review). **15** (6): 479–88. doi:10.1007/s40257-014-0099-z. PMID 25388823.
35. ^ a b Housman, E.; Reynolds, R.V. (November 2014). "Polycystic ovary syndrome: A review for dermatologists: Part I. Diagnosis and manifestations". *Journal of the American Academy of Dermatology* (Review). **71** (5): 847.e1–847.e10. doi:10.1016/j.jaad.2014.05.007. PMID 25437977.
36. ^ a b c d e f g h i j k l Kong, Y.L.; Tey, H.L. (June 2013). "Treatment of acne vulgaris during pregnancy and lactation". *Drugs* (Review). **73** (8): 779–87. doi:10.1007/s40265-013-0060-0. PMID 23657872.
37. ^ Melnik, B.; Jansen, T.; Grabbe, S. (February 2007). "Abuse of anabolic-androgenic steroids and bodybuilding acne: An underestimated health problem". *JDDG* (Review). **5** (2): 110–17. doi:10.1111/j.1610-0387.2007.06176.x. PMID 17274777.
38. ^ Joseph, JF; Parr, MK (January 2015). "Synthetic androgens as designer supplements". *Current Neuropharmacology*. **13** (1): 89–100. doi:10.2174/1570159X13666141210224756. PMC 4462045. PMID 26074745.
39. ^ a b Simonart, T (December 2013). "Immunotherapy for acne vulgaris: current status and future directions". *American Journal of Clinical Dermatology* (Review). **14** (6): 429–35. doi:10.1007/s40257-013-0042-8. PMID 24019180.
40. ^ Lomholt, HB; Kilian, M (August 2010). "Population Genetic Analysis of Propionibacterium acnes Identifies a Subpopulation and Epidemic Clones Associated with Acne". *PLoS ONE*. **5** (8): e12277. doi:10.1371/journal.pone.0012277. PMC 2924382. PMID 20808860.
41. ^ a b c d Bhate, K; Williams, HC (April 2014). "What's new in acne? An analysis of systematic reviews published in 2011–2012". *Clinical and Experimental Dermatology* (Review). **39** (3): 273–7. doi:10.1111/ced.12270. PMID 24635060.
42. ^ Davidovici, BB; Wolf, R (January 2010). "The role of diet in acne: Facts and controversies". *Clinics in Dermatology* (Review). **28** (1): 12–6. doi:10.1016/j.clindermatol.2009.03.010. PMID 20082944.
43. ^ a b c d e Bronsnick, T; Murzaku, EC; Rao, BK (December 2014). "Diet in dermatology: Part I. Atopic dermatitis, acne, and nonmelanoma skin cancer". *Journal of the American Academy of Dermatology* (Review). **71** (6): e1–1039.e12. doi:10.1016/j.jaad.2014.06.015. PMID 25454036.
44. ^ Melnik, BC; John, SM; Plewig, G (November 2013). "Acne: risk indicator for increased body mass index and insulin resistance". *Acta dermato-venereologica* (Review). **93** (6): 644–9. doi:10.2340/00015555-1677. PMID 23975508.
45. ^ a b Ferdowsian, HR; Levin, S (March 2010). "Does diet really affect acne?". *Skin therapy letter* (Review). **15** (3): 1–2, 5. PMID 20361171.
46. ^ Melnik, Bodo C. (2011). "Evidence for Acne-Promoting Effects of Milk and Other Insulinotropic Dairy Products". *Milk and Milk Products in Human Nutrition*. Nestlé Nutrition Institute Workshop Series: Pediatric Program. **67**. p. 131. doi:10.1159/000325580. ISBN 978-3-8055-9587-2.
47. ^ Melnik, BC; Schmitz, G (October 2009). "Role of insulin, insulin-like growth factor-1, hyperglycaemic food and milk consumption in the pathogenesis of acne vulgaris". *Experimental Dermatology* (Review). **18** (10): 833–41. doi:10.1111/j.1600-0625.2009.00924.x. PMID 19709092.
48. ^ Cordain, L (June 2005). "Implications for the Role of Diet in Acne". *Seminars in Cutaneous Medicine and Surgery* (Review). **24** (2): 84–91. doi:10.1016/j.sder.2005.04.002. PMID 16092796.
49. ^ Brescoll, J; Daveluy, S (February 2015). "A review of vitamin B12 in dermatology". *American Journal of Clinical Dermatology* (Review). **16** (1): 27–33. doi:10.1007/s40257-014-0107-3. PMID 25559140.
50. ^ Orion, E; Wolf, R (November–December 2014). "Psychologic factors in the development of facial dermatoses". *Clinics in Dermatology* (Review). **32** (6): 763–6. doi:10.1016/j.clindermatol.2014.02.015. PMID 25441469.
51. ^ a b c Rodriguez-Vallecillo, E; Woodbury-Fariña, MA (December 2014). "Dermatological manifestations of stress in normal and psychiatric populations". *The Psychiatric Clinics of North America* (Review). **37** (4): 625–51. doi:10.1016/j.psc.2014.08.009. PMID 25455069.

52. ^ "Questions and Answers about Acne". National Institute of Arthritis and Musculoskeletal and Skin Diseases. May 2013.
53. ^ Andriessen, A; Lynde, CW (November 2014). "Antibiotic resistance: shifting the paradigm in topical acne treatment". *Journal of Drugs in Dermatology: JDD* (Review). **13** (11): 1358–64. PMID 25607703.
54. ^ a b c Hammer, KA (February 2015). "Treatment of acne with tea tree oil (melaleuca) products: a review of efficacy, tolerability and potential modes of action". *International Journal of Antimicrobial Agents* (Review). **45** (2): 106–10. doi:10.1016/j.ijantimicag.2014.10.011. PMID 25465857.
55. ^ a b c Sieber, MA; Hegel, JK (November 2013). "Azelaic acid: Properties and mode of action". *Skin Pharmacology and Physiology* (Review). **27** (Supplement 1): 9–17. doi:10.1159/000354888. PMID 24280644.
56. ^ Simpson, Nicholas B.; Cunliffe, William J. (2004). "Disorders of the sebaceous glands". In Burns, Tony; Breathnach, Stephen; Cox, Neil; Griffiths, Christopher. *Rook's textbook of dermatology* (7th ed.). Malden, Mass.: Blackwell Science. pp. 43.1–75. ISBN 0-632-06429-3.
57. ^ a b Tan, JK; Jones, E; Allen, E; Pripotnev, S; Raza, A; Wolfe, B (November 2013). "Evaluation of essential clinical components and features of current acne global grading scales". *Journal of the American Academy of Dermatology* (Review). **69** (5): 754–61. doi:10.1016/j.jaad.2013.07.029. PMID 23972509.
58. ^ a b c Chiang, A; Hafeez, F; Maibach, HI (April 2014). "Skin lesion metrics: role of photography in acne". *The Journal of Dermatological Treatment* (Review). **25** (2): 100–5. doi:10.3109/09546634.2013.813010. PMID 23758271.
59. ^ O' Brien, S.C.; Lewis, J.B.; Cunliffe, W.J. "The Leeds Revised Acne Grading System" (PDF). The Leeds Teaching Hospitals. Retrieved 23 November 2015.
60. ^ Purdy, Sarah; Deberker, David (May 2008). "Acne vulgaris". *BMJ Clinical Evidence* (Review). **2008**: 1714. PMC 2907987. PMID 19450306.
61. ^ Archer, CB; Cohen, SN; Baron, SE; British Association of Dermatologists and Royal College of General Practitioners (May 2012). "Guidance on the diagnosis and clinical management of acne". *Clinical and Experimental Dermatology* (Review). **37** (Supplement 1): 1–6. doi:10.1111/j.1365-2230.2012.04335.x. PMID 22486762.
62. ^ Kanerva, L.; Elsner, P.; Wahlberg, J. E.; Maibach, H. I. (2013). *Handbook of Occupational Dermatology*. Springer Science & Business Media. p. 231. ISBN 978-3-662-07677-4.
63. ^ a b Ramos-e-Silva, M; Carneiro, SC (March 2009). "Acne vulgaris: Review and guidelines". *Dermatology Nursing/Dermatology Nurses' Association* (Review). **21** (2): 63–8; quiz 69. PMID 19507372.
64. ^ a b Simonart, T (December 2012). "Newer approaches to the treatment of acne vulgaris". *American Journal of Clinical Dermatology* (Review). **13** (6): 357–64. doi:10.2165/11632500-000000000-00000. PMID 22920095.
65. ^ a b Zaenglein, AL; Pathy, AL; Schlosser, BJ; Alikhan, A; Baldwin, HE; Berson, DS; Bowe, WP; Graber, EM; Harper, JC; Kang, S (May 2016). "Guidelines of care for the management of acne vulgaris". *Journal of the American Academy of Dermatology* (Review). **74** (5): 945–73. doi:10.1016/j.jaad.2015.12.037. PMID 26897386.
66. ^ Leccia, MT; Auffret, N; Poli, F; Claudel, JP; Corvec, S; Dreno, B (August 2015). "Topical acne treatments in Europe and the issue of antimicrobial resistance". *Journal of the European Academy of Dermatology and Venereology*. **29** (8): 1485–92. doi:10.1111/jdv.12989. PMID 25677763.
67. ^ a b Gamble, R; Dunn, J; Dawson, A; Petersen, B; McLaughlin, L; Small, A; Kindle, S; Dellavalle, RP (June 2012). "Topical antimicrobial treatment of acne vulgaris: an evidence-based review". *American Journal of Clinical Dermatology* (Review). **13** (3): 141–52. doi:10.2165/11597880-000000000-00000. PMID 22268388.
68. ^ a b c d e Sagransky, M; Yentzer, BA; Feldman, SR (October 2009). "Benzoyl peroxide: A review of its current use in the treatment of acne vulgaris". *Expert Opinion on Pharmacotherapy*. **10** (15): 2555–62. doi:10.1517/14656560903277228. PMID 19761357.
69. ^ a b Foti, C; Romita, P; Borghi, A; Angelini, G; Bonamonte, D; Corazza, M (September 2015). "Contact dermatitis to topical acne drugs: a review of the literature". *Dermatologic Therapy* (Review). **28** (5): 323–9. doi:10.1111/dth.12282. PMID 26302055.
70. ^ a b c d Walsh, TR; Efthimiou, J; Dréno, B (March 2016). "Systematic review of antibiotic resistance in acne: an increasing topical and oral threat". *Lancet Infectious Diseases* (Systematic Review). **16** (3): e23–33. doi:10.1016/S1473-3099(15)00527-7. PMID 26852728.
71. ^ a b Arowojolu, AO; Gallo, MF; Lopez, LM; Grimes, DA (July 2012). "Combined oral contraceptive pills for treatment of acne". *Cochrane Database of Systematic Reviews* (Systematic Review & Meta-Analysis). **7** (7): CD004425. doi:10.1002/14651858.CD004425.pub6. PMID 22786490.
72. ^ a b c d Koo, EB; Petersen, TD; Kimball, AB (September 2014). "Meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne vulgaris". *Journal of the American Academy of Dermatology* (Systematic Review & Meta-Analysis). **71** (3): 450–9. doi:10.1016/j.jaad.2014.03.051. PMID 24880665.
73. ^ a b c Pugashetti, R; Shinkai, K (July 2013). "Treatment of acne vulgaris in pregnant patients". *Dermatologic Therapy* (Review). **26** (4): 302–11. doi:10.1111/dth.12077. PMID 23914887.
74. ^ Morelli, V; Calmet, E; Jhingade, V (June 2010). "Alternative Therapies for Common Dermatologic Disorders, Part 2". *Primary Care: Clinics in Office Practice* (Review). **37** (2): 285–96. doi:10.1016/j.pop.2010.02.005. PMID 20493337.
75. ^ "Azelaic Acid Topical". National Institutes Of Health. Retrieved 2013-09-09.
76. ^ a b Madan, RK; Levitt, J (April 2014). "A review of toxicity from topical salicylic acid preparations". *Journal of the*

*American Academy of Dermatology*. **70** (4): 788–92. doi:10.1016/j.jaad.2013.12.005. PMID 24472429.
77. ^ Well, D (October 2013). "Acne vulgaris: A review of causes and treatment options". *The Nurse Practitioner*. **38** (10): 22–31. doi:10.1097/01.NPR.0000434089.88606.70. PMID 24048347.
78. ^ a b Rolfe, Heidi M (December 2014). "A review of nicotinamide: treatment of skin diseases and potential side effects". *Journal of Cosmetic Dermatology* (Review). **13** (4): 324–8. doi:10.1111/jocd.12119. PMID 25399625.
79. ^ a b Brandt, Staci (May 2013). "The clinical effects of zinc as a topical or oral agent on the clinical response and pathophysiologic mechanisms of acne: a systematic review of the literature". *Journal of Drugs in Dermatology: JDD* (Review). **12** (5): 542–5. PMID 23652948.
80. ^ Layton, A.M. (April 2016). "Top Ten List of Clinical Pearls in the Treatment of Acne Vulgaris". *Dermatol Clin* (Review). **34** (2): 147–57. doi:10.1016/j.det.2015.11.008. PMID 27015774.
81. ^ Hamilton, FL; Car, J; Lyons, C; Car, M; Layton, A; Majeed, A (June 2009). "Laser and other light therapies for the treatment of acne vulgaris: Systematic review". *British Journal of Dermatology* (Systematic Review & Meta-Analysis). **160** (6): 1273–85. doi:10.1111/j.1365-2133.2009.09047.x. PMID 19239470.
82. ^ Chapas, AM; Brightman, L; Sukal, S; Hale, E; Daniel, D; Bernstein, LJ; Geronemus, RG (August 2008). "Successful treatment of acneiform scarring with CO2 ablative fractional resurfacing". *Lasers in Surgery and Medicine*. **40** (6): 381–6. doi:10.1002/lsm.20659. PMID 18649382.
83. ^ Ong, MW; Bashir, SJ (June 2012). "Fractional laser resurfacing for acne scars: a review". *British Journal of Dermatology* (Review). **166** (6): 1160–9. doi:10.1111/j.1365-2133.2012.10870.x. PMID 22296284.
84. ^ a b c d e f g h i j k l m n Tyler, KH (March 2015). "Dermatologic therapy in pregnancy". *Clinical Obstetrics and Gynecology* (Review). **58** (1): 112–8. doi:10.1097/GRF.0000000000000089. PMID 25517754.
85. ^ a b c Cao, H; Yang, G; Wang, Y; Liu, JP; Smith, CA; Luo, H; Liu, Y (January 2015). "Complementary therapies for acne vulgaris". *Cochrane Database of Systematic Reviews* (Systematic Review & Meta-Analysis). **1**: CD009436. doi:10.1002/14651858.CD009436.pub2. PMC 4486007. PMID 25597924.
86. ^ Fisk, WA; Lev-Tov, HA; Sivamani, RK (August 2014). "Botanical and phytochemical therapy of acne: a systematic review". *Phytotherapy Research: PTR* (Systematic Review). **28** (8): 1137–52. doi:10.1002/ptr.5125. PMID 25098271.
87. ^ Bope, Edward T; Kellerman, Rick D (2014). *Conn's Current Therapy 2015: Expert Consult — Online*. p. 299. ISBN 978-0-323-31956-0.
88. ^ a b Vos, T; Flaxman, AD (December 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010". *The Lancet*. **380** (9859): 2163–96. doi:10.1016/S0140-6736(12)61729-2. PMID 23245607.
89. ^ Holzmann, R; Shakery, K (November 2013). "Postadolescent acne in females". *Skin Pharmacology and Physiology* (Review). **27** (Supplement 1): 3–8. doi:10.1159/000354887. PMID 24280643.
90. ^ Shah, SK; Alexis, AF (May 2010). "Acne in skin of color: practical approaches to treatment". *Journal of Dermatological Treatment* (Review). **21** (3): 206–11. doi:10.3109/09546630903401496. PMID 20132053.
91. ^ White, GM (August 1998). "Recent findings in the epidemiologic evidence, classification, and subtypes of acne vulgaris". *Journal of the American Academy of Dermatology* (Review). **39** (2): S34–37. doi:10.1016/S0190-9622(98)70442-6. PMID 9703121.
92. ^ Keri, J; Shiman, M (June 2009). "An update on the management of acne vulgaris". *Clin Cosmet Investig Dermatol*. **17** (2): 105–10. PMC 3047935. PMID 21436973.
93. ^ a b c d e f g h i Tilles, G (September 2014). "Acne pathogenesis: history of concepts". *Dermatology* (Review). **229** (1): 1–46. doi:10.1159/000364860. PMID 25228295.
94. ^ Eby, Myra Michelle. *Return to Beautiful Skin*. Basic Health Publications. p. 275.
95. ^ "Tretinoin (retinoic acid) in acne". *The Medical letter on drugs and therapeutics*. **15** (1): 3. January 1973. PMID 4265099.
96. ^ Jones, H; Blanc, D; Cunliffe, WJ (November 1980). "13-Cis Retinoic Acid and Acne". *The Lancet*. **316** (8203): 1048–9. doi:10.1016/S0140-6736(80)92273-4. PMID 6107678.
97. ^ Bérard, A; Azoulay, L; Koren, G; Blais, L; Perreault, S; Oraichi, D (February 2007). "Isotretinoin, pregnancies, abortions and birth defects: A population-based perspective". *British Journal of Clinical Pharmacology*. **63** (2): 196–205. doi:10.1111/j.1365-2125.2006.02837.x. PMC 1859978. PMID 17214828.
98. ^ Holmes, SC; Bankowska, U; Mackie, RM (March 1998). "The prescription of isotretinoin to women: Is every precaution taken?". *British Journal of Dermatology*. **138** (3): 450–55. doi:10.1046/j.1365-2133.1998.02123.x. PMID 9580798.
99. ^ a b Goodman, G (August 2006). "Acne—natural history, facts and myths" (PDF). *Australian Family Physician* (Review). **35** (8): 613–6. PMID 16894437.
100. ^ Brown, MM; Chamlin, SL; Smidt, AC (April 2013). "Quality of life in pediatric dermatology". *Dermatologic Clinics* (Review). **31** (2): 211–21. doi:10.1016/j.det.2012.12.010. PMID 23557650.
101. ^ Farrar, MD; Howson, KM; Bojar, RA; West, D; Towler, JC; Parry, J; Pelton, K; Holland, KT (June 2007). "Genome Sequence and Analysis of a Propionibacterium acnes Bacteriophage". *Journal of Bacteriology*. **189** (11): 4161–67. doi:10.1128/JB.00106-07. PMC 1913406. PMID 17400737.
102. ^ a b c Baquerizo, Nole KL; Yim, E; Keri, JE (October 2014). "Probiotics and prebiotics in dermatology". *Journal of the American Academy of Dermatology* (Review). **71** (4): 814–21. doi:10.1016/j.jaad.2014.04.050. PMID 24906613.

103. ^ Kao, M; Huang, CM (December 2009). "Acne vaccines targeting Propionibacterium acnes". *Giornale italiano di dermatologia e venerologia* (Review). **144** (6): 639–43. PMID 19907403.
104. ^ MacKenzie, D. (September 23, 2011). In development: a vaccine for acne. *New Scientist* archive. Retrieved March 30, 2015.

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| v · t · e · | Acne-treating agents (D10) |
|---|---|
| **Antibacterial** | Azelaic acid · Benzoyl peroxide# · 8-Hydroxyquinoline · Blue light therapy · Tea tree oil · |
| **Keratolytic** | Glycolic acid · Salicylic acid# · Sulfur · Benzoyl peroxide# · |
| **Anti-inflammatory** | Nicotinamide · Ibuprofen # · Aspirin # · Red light therapy · |
| **Antibiotics** | Clindamycin · Dapsone · Erythromycin · Sulfacetamide · Tetracyclines (Lymecycline · Minocycline · Doxycycline) · |
| **Hormonal** | Antiandrogens (Bicalutamide · Cyproterone acetate · Drospirenone · Flutamide · Spironolactone) · · Estrogens (Estradiol · Ethinylestradiol · · |
| **Retinoids** | Adapalene · Isotretinoin · Motretinide · Tazarotene · Tretinoin · |
| **Other** | Benzamycin · Epristeride · Mesulfen · Pelretin · Stridex · Tioxolone · |
| **Combinations** | Adapalene/benzoyl peroxide · Benzoyl peroxide/clindamycin · Clindamycin/tretinoin · Erythromycin/isotretinoin · Sulfacetamide/sulfur · |
| · #WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · · | |

| v · t · e · | Diseases of the skin and appendages by morphology | |
|---|---|---|
| **Growths** | **Epidermal** | wart · callus · seborrheic keratosis · acrochordon · molluscum contagiosum · actinic keratosis · squamous-cell carcinoma · basal-cell carcinoma · Merkel-cell carcinoma · nevus sebaceous · trichoepithelioma · |
| | **Pigmented** | Freckles · lentigo · melasma · nevus · melanoma · |
| | **Dermal and subcutaneous** | epidermal inclusion cyst · hemangioma · dermatofibroma (benign fibrous histiocytoma) · keloid · lipoma · neurofibroma · xanthoma · Kaposi's sarcoma · infantile digital fibromatosis · granular cell tumor · leiomyoma · lymphangioma circumscriptum · myxoid cyst · |
| **With** | **Eczematous** | contact dermatitis · atopic dermatitis · seborrheic dermatitis · stasis dermatitis · lichen simplex chronicus · Darier's disease · glucagonoma syndrome · langerhans cell histiocytosis · lichen sclerosus · pemphigus foliaceus · Wiskott–Aldrich syndrome · Zinc deficiency · |
| | **Scaling** | psoriasis · tinea (corporis · cruris · pedis · manuum · faciei) · pityriasis rosea · secondary syphilis · mycosis fungoides · systemic lupus erythematosus · pityriasis rubra pilaris · parapsoriasis · ichthyosis · |
| | **Blistering** | herpes simplex · herpes zoster · varicella · bullous impetigo · acute contact dermatitis · pemphigus vulgaris · bullous pemphigoid |

| | | | | | |
|---|---|---|---|---|---|
| **Rashes** | **epidermal involvement** | | | | · dermatitis herpetiformis · porphyria cutanea tarda · epidermolysis bullosa simplex · |
| | | **Papular** | | | scabies · insect bite reactions · lichen planus · miliaria · keratosis pilaris · lichen spinulosus · transient acantholytic dermatosis · lichen nitidus · pityriasis lichenoides et varioliformis acuta · |
| | | **Pustular** | | | **acne vulgaris** · acne rosacea · folliculitis · impetigo · candidiasis · gonococcemia · dermatophyte · coccidioidomycosis · subcorneal pustular dermatosis · |
| | | **Hypopigmented** | | | tinea versicolor · vitiligo · pityriasis alba · postinflammatory hyperpigmentation · tuberous sclerosis · idiopathic guttate hypomelanosis · leprosy · hypopigmented mycosis fungoides · |
| | **Without epidermal involvement** | **Red** | **Blanchable Erythema** | **Generalized** | drug eruptions · viral exanthems · toxic erythema · systemic lupus erythematosus · |
| | | | | **Localized** | cellulitis · abscess · boil · erythema nodosum · carcinoid syndrome · fixed drug eruption · |
| | | | | **Specialized** | urticaria · erythema (multiforme · migrans · gyratum repens · annulare centrifugum · ab igne) · |
| | | | **Nonblanchable Purpura** | **Macular** | thrombocytopenic purpura · actinic/solar purpura · |
| | | | | **Papular** | disseminated intravascular coagulation · vasculitis · |
| | | **Indurated** | | | scleroderma/morphea · granuloma annulare · lichen sclerosis et atrophicus · necrobiosis lipoidica · |
| **Miscellaneous disorders** | **Ulcers** | | | | |
| | **Hair** | | | | telogen effluvium · androgenic alopecia · trichotillomania · alopecia areata · systemic lupus erythematosus · tinea capitis · loose anagen syndrome · lichen planopilaris · folliculitis decalvans · acne keloidalis nuchae · |
| | **Nail** | | | | onychomycosis · psoriasis · paronychia · ingrown nail · |
| | **Mucous membrane** | | | | Aphthous stomatitis · oral candidiasis · lichen planus · leukoplakia · pemphigus vulgaris · mucous membrane pemphigoid · cicatricial pemphigoid · herpesvirus · coxsackievirus · syphilis · systemic histoplasmosis · squamous-cell carcinoma · |

| v · t · e · | **Disorders of skin appendages (L60–L75, 703–706)** |
|---|---|
| | thickness: Onychogryphosis · Onychauxis · |
| | color: Beau's lines · Yellow nail syndrome · Leukonychia · Azure lunula · |
| | shape: Koilonychia · Nail clubbing · |
| | behavior: Onychotillomania · Onychophagia · |
| | other: Ingrown nail · Anonychia · |
| | ungrouped: Paronychia (Acute · Chronic · · Chevron nail · Congenital onychodysplasia of the index fingers · |

| | | | |
|---|---|---|---|
| **Nail** | Green nails · Half and half nails · Hangnail · Hapalonychia · Hook nail · Ingrown nail · Lichen planus of the nails · Longitudinal erythronychia · Malalignment of the nail plate · Median nail dystrophy · Mees' lines · Melanonychia · Muehrcke's lines · Nail–patella syndrome · Onychoatrophy · Onycholysis · Onychomadesis · Onychomatricoma · Onychomycosis · Onychophosis · Onychoptosis defluvium · Onychorrhexis · Onychoschizia · Platonychia · Pincer nails · Plummer's nail · Psoriatic nails · Pterygium inversum unguis · Pterygium unguis · Purpura of the nail bed · Racquet nail · Red lunulae · Shell nail syndrome · Splinter hemorrhage · Spotted lunulae · Staining of the nail plate · Stippled nails · Subungual hematoma · Terry's nails · Twenty-nail dystrophy · | | |
| **Hair** | **Hair loss/ Baldness** | *noncicatricial alopecia:* Alopecia (areata · totalis · universalis · Ophiasis · · Androgenic alopecia (male-pattern baldness) · Hypotrichosis · Telogen effluvium · Traction alopecia · Lichen planopilaris · Trichorrhexis nodosa · Alopecia neoplastica · Anagen effluvium · Alopecia mucinosa · *cicatricial alopecia:* Pseudopelade of Brocq · Central centrifugal cicatricial alopecia · Pressure alopecia · Traumatic alopecia · Tumor alopecia · Hot comb alopecia · Perifolliculitis capitis abscedens et suffodiens · Graham-Little syndrome · Folliculitis decalvans · *ungrouped:* Triangular alopecia · Frontal fibrosing alopecia · Marie Unna hereditary hypotrichosis · | |
| | **Hypertrichosis** | Hirsutism · Acquired (localised · generalised · patterned · · Congenital (generalised · localised · X-linked · · Prepubertal · | |
| | **Acneiform eruption** | **Acne** | **Acne vulgaris** · Acne conglobata · Acne miliaris necrotica · Tropical acne · Infantile acne/Neonatal acne · Excoriated acne · Acne fulminans · Acne medicamentosa (e.g., steroid acne) · Halogen acne (Iododerma · Bromoderma · Chloracne · · Oil acne · Tar acne · Acne cosmetica · Occupational acne · Acne aestivalis · Acne keloidalis nuchae · Acne mechanica · Acne with facial edema · Pomade acne · Acne necrotica · Blackhead · Lupus miliaris disseminatus faciei · |
| | | **Rosacea** | Perioral dermatitis (Granulomatous perioral dermatitis · · Phymatous rosacea (Rhinophyma · Blepharophyma · Gnathophyma · Metophyma · Otophyma · · Papulopustular rosacea · Lupoid rosacea · Erythrotelangiectatic rosacea · Glandular rosacea · Gram-negative rosacea · Steroid rosacea · Ocular rosacea · Persistent edema of rosacea · Rosacea conglobata · *variants* (Periorificial dermatitis · Pyoderma faciale · · |
| | | **Ungrouped** | Granulomatous facial dermatitis · Idiopathic facial aseptic granuloma · Periorbital dermatitis · SAPHO syndrome · |
| | **Follicular cysts** | "Sebaceous cyst" (Epidermoid cyst · Trichilemmal cyst · · Steatocystoma (simplex · multiplex · · Milia · | |
| | **Inflammation** | Folliculitis (Folliculitis nares perforans · Tufted folliculitis · · Pseudofolliculitis barbae · Hidradenitis (Hidradenitis suppurativa · Recurrent palmoplantar hidradenitis · Neutrophilic eccrine hidradenitis · · | |
| | | Acrokeratosis paraneoplastica of Bazex · Acroosteolysis · Bubble hair deformity · | |

| | | |
|---|---|---|
| | **Ungrouped** | Disseminate and recurrent infundibulofolliculitis · Erosive pustular dermatitis of the scalp · Erythromelanosis follicularis faciei et colli · Hair casts · Hair follicle nevus · Intermittent hair–follicle dystrophy · Keratosis pilaris atropicans · Kinking hair · Koenen's tumor · Lichen planopilaris · Lichen spinulosus · Loose anagen syndrome · Menkes kinky hair syndrome · Monilethrix · Parakeratosis pustulosa · Pili (Pili annulati · Pili bifurcati · Pili multigemini · Pili pseudoannulati · Pili torti) · Pityriasis amiantacea · Plica neuropathica · Poliosis · Rubinstein–Taybi syndrome · Setleis syndrome · Traumatic anserine folliculosis · Trichomegaly · Trichomycosis axillaris · Trichorrhexis (Trichorrhexis invaginata · Trichorrhexis nodosa) · Trichostasis spinulosa · Uncombable hair syndrome · Wooly hair · Wooly hair nevus · |
| **Sweat glands** | **Eccrine** | Miliaria (Colloid milium · Miliaria crystalline · Miliaria profunda · Miliaria pustulosa · Miliaria rubra · Occlusion miliaria · Postmiliarial hypohidrosis · · Granulosis rubra nasi · Ross' syndrome · Anhidrosis · Hyperhidrosis (Generalized · Gustatory · Palmoplantar · · |
| | **Apocrine** | Body odor · Chromhidrosis · Fox–Fordyce disease · |
| | **Sebaceous** | Sebaceous hyperplasia · |

Categories: Pages with DOIs inactive since 2017 | Acneiform eruptions | Cutaneous conditions | Dermatology task force articles

# Allergy

From Wikipedia, the free encyclopedia

**Allergies**, also known as **allergic diseases**, are a number of conditions caused by hypersensitivity of the immune system to something in the environment that usually causes little or no problem in most people.[1] These diseases include hay fever, food allergies, atopic dermatitis, allergic asthma, and anaphylaxis.[2] Symptoms may include red eyes, an itchy rash, runny nose, shortness of breath, or swelling.[3] Food intolerances and food poisoning are separate conditions.[4][5]

Common allergens include pollen and certain food. Metals and other substances may also cause problems.[1] Food, insect stings, and medications are common causes of severe reactions. Their development is due to both genetic and environmental factors.[6] The underlying mechanism involves immunoglobulin E antibodies (IgE), part of the body's immune system, binding to an allergen and then to a receptor on mast cells or basophils where it triggers the release of inflammatory chemicals such as histamine.[7] Diagnosis is typically based on a person's medical history. Further testing of the skin or blood may be useful in certain cases.[5] Positive tests, however, may not mean there is a significant allergy to the substance in question.[8]

Early exposure to potential allergens may be protective.[9] Treatments for allergies include avoiding known allergens and the use of medications such as steroids and antihistamines.[10] In severe reactions injectable adrenaline (epinephrine) is recommended.[11] Allergen immunotherapy, which gradually exposes people to larger and larger amounts of allergen, is useful for some types of allergies such as hay fever and reactions to insect bites. Its use in food allergies is unclear.[10]

Allergies are common.[12] In the developed world, about 20% of people are affected by allergic rhinitis,[13] about 6% of people have at least one food allergy,[5][9] and about 20% have atopic dermatitis at some point in time.[14] Depending on the country about 1–18% of people have asthma.[15][16] Anaphylaxis occurs in between 0.05–2% of people.[17] Rates of many allergic diseases appear to be increasing.[11][18] The word "allergy" was first used by Clemens von Pirquet in 1906.[6]


Hives are a common allergic symptom.

| Classification and external resources | |
|---|---|
| **Specialty** | Allergy and immunology |
| **ICD-10** | T78.4 |
| **ICD-9-CM** | 995.3 |
| **DiseasesDB** | 33481 |
| **MedlinePlus** | 000812 |
| **eMedicine** | med/1101 |
| **MeSH** | D006967 |

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Contents

## Signs and symptoms [edit]

Many allergens such as dust or pollen are airborne particles. In these cases, symptoms arise in areas in contact with air, such as eyes, nose, and lungs. For instance, allergic rhinitis, also known as hay fever, causes irritation of the nose, sneezing, itching, and redness of the eyes.[19] Inhaled allergens can also lead to increased production of mucus in the lungs, shortness of breath, coughing, and wheezing.[20]

Aside from these ambient allergens, allergic reactions can result from foods, insect stings, and reactions to medications like aspirin and antibiotics such as penicillin. Symptoms of food allergy include abdominal pain, bloating, vomiting, diarrhea, itchy skin, and swelling of the skin during hives. Food allergies rarely cause respiratory (asthmatic) reactions, or rhinitis.[21] Insect stings, antibiotics, and certain medicines produce a systemic allergic response that is also called anaphylaxis; multiple organ systems can be affected, including the digestive system, the respiratory system, and the circulatory system.[22][23][24] Depending on the rate of severity, it can cause a skin reactions, bronchoconstriction, swelling, low blood pressure, coma, and death. This type of reaction can be triggered suddenly, or the onset can be delayed. The nature of anaphylaxis is such that the reaction can seem to be subsiding, but may recur throughout a period of time.[24]

**Common symptoms**

| Affected organ | Symptom |
|---|---|
| Nose | Swelling of the nasal mucosa (allergic rhinitis) runny nose, sneezing |
| Sinuses | Allergic sinusitis |
| Eyes | Redness and itching of the conjunctiva (allergic conjunctivitis, watery) |
| Airways | Sneezing, coughing, bronchoconstriction, wheezing and dyspnea, sometimes outright attacks of asthma, in severe cases the airway constricts due to swelling known as laryngeal edema |
| Ears | Feeling of fullness, possibly pain, and impaired hearing due to the lack of eustachian tube drainage. |
| Skin | Rashes, such as eczema and hives (urticaria) |
| Gastrointestinal tract | Abdominal pain, bloating, vomiting, diarrhea |

### Skin [edit]

Substances that come into contact with the skin, such as latex, are also common causes of allergic reactions, known as contact dermatitis or eczema.[25] Skin allergies frequently cause rashes, or swelling and inflammation within the skin, in what is known as a "wheal and flare" reaction characteristic of hives and angioedema.[26]

With insect stings a large local reaction may occur (an area of skin redness greater than 10 cm in size).[27] It can last one to two days.[27] This reaction may also occur after immunotherapy.[28]

## Cause [edit]

Risk factors for allergy can be placed in two general categories, namely host and environmental factors.[29] Host factors include heredity, sex, race, and age, with heredity being by far the most significant. However, there have been recent increases in the incidence of allergic disorders that cannot be explained by genetic factors alone. Four major environmental candidates are alterations in exposure to infectious diseases during early childhood, environmental pollution, allergen levels, and dietary changes.[30]

### Foods [edit]

*Main article: Food allergy*

A wide variety of foods can cause allergic reactions, but 90% of allergic responses to foods are caused by cow's milk, soy, eggs, wheat, peanuts, tree nuts, fish, and shellfish.[31] Other food allergies, affecting less than 1 person per 10,000 population, may be considered "rare".[32] The use of hydrolysed milk baby formula versus standard milk baby formula does not appear to change the risk.[33]

The most common food allergy in the US population is a sensitivity to crustacea.[32] Although peanut allergies are notorious for their severity, peanut allergies are not the most common food allergy in adults or children. Severe or life-threatening reactions may be triggered by other allergens, and are more common when combined with asthma.[31]

Rates of allergies differ between adults and children. Peanut allergies can sometimes be outgrown by children. Egg allergies affect one to two percent of children but are outgrown by about two-thirds of children by the age of 5.[34] The sensitivity is usually to proteins in the white, rather than the yolk.[35]

Milk-protein allergies are most common in children.[36] Approximately 60% of milk-protein reactions are immunoglobulin E-mediated, with the remaining usually attributable to inflammation of the colon.[37] Some people are unable to tolerate milk from goats or sheep as well as from cows, and many are also unable to tolerate dairy products such as cheese. Roughly 10% of children with a milk allergy will have a reaction to beef. Beef contains a small amount of protein that is present in cow's milk.[38] Lactose intolerance, a common reaction to milk, is not a form of allergy at all, but rather due to the absence of an enzyme in the digestive tract.

Those with tree nut allergies may be allergic to one or to many tree nuts, including pecans, pistachios, pine nuts, and walnuts.[35] Also seeds, including sesame seeds and poppy seeds, contain oils in which protein is present, which may elicit an allergic reaction.[35]

Allergens can be transferred from one food to another through genetic engineering; however genetic modification can also remove allergens. Little research has been done on the natural variation of allergen concentrations in the unmodified crops.[39][40]

### Latex [edit]

Latex can trigger an IgE-mediated cutaneous, respiratory, and systemic reaction. The prevalence of latex allergy in the general population is believed to be less than one percent. In a hospital study, 1 in 800 surgical patients (0.125 percent) reported latex sensitivity, although the sensitivity among healthcare workers is higher, between seven and ten percent. Researchers attribute this higher level to the exposure of healthcare workers to areas with significant airborne latex allergens, such as operating rooms, intensive-care units, and dental suites. These latex-rich environments may sensitize healthcare workers who regularly inhale allergenic proteins.[41]

The most prevalent response to latex is an allergic contact dermatitis, a delayed hypersensitive reaction appearing as dry, crusted lesions. This reaction usually lasts 48–96 hours. Sweating or rubbing the area under the glove aggravates the lesions, possibly leading to ulcerations.[41] Anaphylactic reactions occur most often in sensitive patients who have been exposed to a surgeon's latex gloves during abdominal surgery, but other mucosal exposures, such as dental procedures, can also produce systemic reactions.[41]

Latex and banana sensitivity may cross-react. Furthermore, those with latex allergy may also have sensitivities to avocado, kiwifruit, and chestnut.[42] These people often have perioral itching and local urticaria. Only occasionally have these food-induced allergies induced systemic responses. Researchers suspect that the cross-reactivity of latex with banana, avocado, kiwifruit, and chestnut occurs because latex proteins are structurally homologous with some other plant proteins.[41]

### Medications [edit]

About 10% of people report that they are allergic to penicillin; however, 90% turn out not to be.[43] Serious allergies only occur in about 0.03%.[43]

## Toxins interacting with proteins [edit]

Another non-food protein reaction, urushiol-induced contact dermatitis, originates after contact with poison ivy, eastern poison oak, western poison oak, or poison sumac. Urushiol, which is not itself a protein, acts as a hapten and chemically reacts with, binds to, and changes the shape of integral membrane proteins on exposed skin cells. The immune system does not recognize the affected cells as normal parts of the body, causing a T-cell-mediated immune response.[44] Of these poisonous plants, sumac is the most virulent.[45] The resulting dermatological response to the reaction between urushiol and membrane proteins includes redness, swelling, papules, vesicles, blisters, and streaking.[46]

Estimates vary on the percentage of the population that will have an immune system response. Approximately 25 percent of the population will have a strong allergic response to urushiol. In general, approximately 80 percent to 90 percent of adults will develop a rash if they are exposed to .0050 milligrams ($7.7 \times 10^{-5}$ gr) of purified urushiol, but some people are so sensitive that it takes only a molecular trace on the skin to initiate an allergic reaction.[47]

## Genetics [edit]

Allergic diseases are strongly familial: identical twins are likely to have the same allergic diseases about 70% of the time; the same allergy occurs about 40% of the time in non-identical twins.[48] Allergic parents are more likely to have allergic children,[49] and those children's allergies are likely to be more severe than those in children of non-allergic parents. Some allergies, however, are not consistent along genealogies; parents who are allergic to peanuts may have children who are allergic to ragweed. It seems that the likelihood of developing allergies is inherited and related to an irregularity in the immune system, but the specific allergen is not.[49]

The risk of allergic sensitization and the development of allergies varies with age, with young children most at risk.[50] Several studies have shown that IgE levels are highest in childhood and fall rapidly between the ages of 10 and 30 years.[50] The peak prevalence of hay fever is highest in children and young adults and the incidence of asthma is highest in children under 10.[51]

Overall, boys have a higher risk of developing allergies than girls,[49] although for some diseases, namely asthma in young adults, females are more likely to be affected.[52] These differences between the sexes tend to decrease in adulthood.[49]

Ethnicity may play a role in some allergies; however, racial factors have been difficult to separate from environmental influences and changes due to migration.[49] It has been suggested that different genetic loci are responsible for asthma, to be specific, in people of European, Hispanic, Asian, and African origins.[53]

## Hygiene hypothesis [edit]

*Main article: Hygiene hypothesis*

Allergic diseases are caused by inappropriate immunological responses to harmless antigens driven by a TH2-mediated immune response. Many bacteria and viruses elicit a TH1-mediated immune response, which down-regulates TH2 responses. The first proposed mechanism of action of the hygiene hypothesis was that insufficient stimulation of the TH1 arm of the immune system leads to an overactive TH2 arm, which in turn leads to allergic disease.[54] In other words, individuals living in too sterile an environment are not exposed to enough pathogens to keep the immune system busy. Since our bodies evolved to deal with a certain level of such pathogens, when they are not exposed to this level, the immune system will attack harmless antigens and thus normally benign microbial objects—like pollen—will trigger an immune response.[55]

The hygiene hypothesis was developed to explain the observation that hay fever and eczema, both allergic diseases, were less common in children from larger families, which were, it is presumed, exposed to more infectious agents through their siblings, than in children from families with only one child. The hygiene hypothesis has been extensively investigated by immunologists and epidemiologists and has become an important theoretical framework for the study of allergic disorders. It is used to explain the increase in allergic diseases that have been seen since industrialization, and the higher incidence of allergic diseases in more developed countries. The hygiene hypothesis has now expanded to include exposure to symbiotic bacteria and parasites as important modulators of immune system development, along with infectious agents.

Epidemiological data support the hygiene hypothesis. Studies have shown that various immunological and autoimmune diseases are much less common in the developing world than the industrialized world and that

immigrants to the industrialized world from the developing world increasingly develop immunological disorders in relation to the length of time since arrival in the industrialized world.[56] Longitudinal studies in the third world demonstrate an increase in immunological disorders as a country grows more affluent and, it is presumed, cleaner.[57] The use of antibiotics in the first year of life has been linked to asthma and other allergic diseases.[58] The use of antibacterial cleaning products has also been associated with higher incidence of asthma, as has birth by Caesarean section rather than vaginal birth.[59][60]

### Stress [edit]

Chronic stress can aggravate allergic conditions. This has been attributed to a T helper 2 (TH2)-predominant response driven by suppression of interleukin 12 by both the autonomic nervous system and the hypothalamic–pituitary–adrenal axis. Stress management in highly susceptible individuals may improve symptoms.[61]

### Other environmental factors [edit]

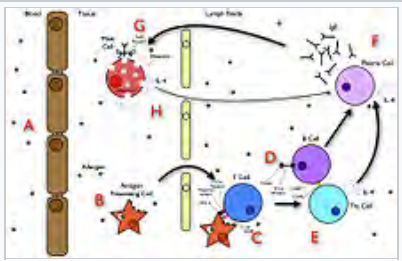
International differences have been associated with the number of individuals within a population have allergy. Allergic diseases are more common in industrialized countries than in countries that are more traditional or agricultural, and there is a higher rate of allergic disease in urban populations versus rural populations, although these differences are becoming less defined.[62]

Alterations in exposure to microorganisms is another plausible explanation, at present, for the increase in atopic allergy.[30] Endotoxin exposure reduces release of inflammatory cytokines such as TNF-α, IFNγ, interleukin-10, and interleukin-12 from white blood cells (leukocytes) that circulate in the blood.[63] Certain microbe-sensing proteins, known as Toll-like receptors, found on the surface of cells in the body are also thought to be involved in these processes.[64]

Gutworms and similar parasites are present in untreated drinking water in developing countries, and were present in the water of developed countries until the routine chlorination and purification of drinking water supplies.[65] Recent research has shown that some common parasites, such as intestinal worms (e.g., hookworms), secrete chemicals into the gut wall (and, hence, the bloodstream) that suppress the immune system and prevent the body from attacking the parasite.[66] This gives rise to a new slant on the hygiene hypothesis theory—that co-evolution of humans and parasites has led to an immune system that functions correctly only in the presence of the parasites. Without them, the immune system becomes unbalanced and oversensitive.[67] In particular, research suggests that allergies may coincide with the delayed establishment of gut flora in infants.[68] However, the research to support this theory is conflicting, with some studies performed in China and Ethiopia showing an increase in allergy in people infected with intestinal worms.[62] Clinical trials have been initiated to test the effectiveness of certain worms in treating some allergies.[69] It may be that the term 'parasite' could turn out to be inappropriate, and in fact a hitherto unsuspected symbiosis is at work.[69] For more information on this topic, see Helminthic therapy.

## Pathophysiology [edit]

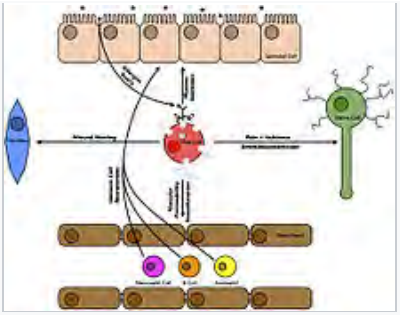
### Acute response [edit]



A summary diagram that explains how allergy develops.

In the early stages of allergy, a type I hypersensitivity reaction against an allergen encountered for the first time and presented by a professional antigen-presenting cell causes a response in a type of immune cell called a $T_H2$ lymphocyte, which belongs to a subset of T cells that produce a cytokine called interleukin-4 (IL-4). These $T_H2$ cells interact with other lymphocytes called B cells, whose role is production of antibodies. Coupled with signals provided by IL-4, this interaction stimulates the B cell to begin production of a large amount of a particular type of antibody known as IgE. Secreted IgE circulates in the blood and binds to an IgE-specific receptor (a kind of Fc receptor called FcεRI) on the surface of other kinds of immune cells called mast cells and basophils, which are both involved in the acute inflammatory response. The IgE-coated cells, at this stage, are sensitized to the allergen.[30]

If later exposure to the same allergen occurs, the allergen can bind to the IgE molecules held on the surface of the mast cells or basophils. Cross-linking of the IgE and Fc receptors occurs when more than one IgE-receptor complex interacts with the same allergenic molecule, and activates the sensitized cell.

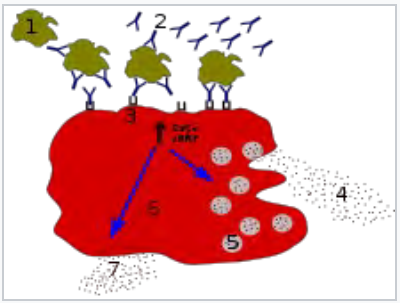


Tissues affected in allergic inflammation

Activated mast cells and basophils undergo a process called degranulation, during which they release histamine and other inflammatory chemical mediators (cytokines, interleukins, leukotrienes, and prostaglandins) from their granules into the surrounding tissue causing several systemic effects, such as vasodilation, mucous secretion, nerve stimulation, and smooth muscle contraction. This results in rhinorrhea, itchiness, dyspnea, and anaphylaxis. Depending on the individual, allergen, and mode of introduction, the symptoms can be system-wide (classical anaphylaxis), or localized to particular body systems; asthma is localized to the respiratory system and eczema is localized to the dermis.[30]

## Late-phase response [edit]

After the chemical mediators of the acute response subside, late-phase responses can often occur. This is due to the migration of other leukocytes such as neutrophils, lymphocytes, eosinophils and macrophages to the initial site. The reaction is usually seen 2–24 hours after the original reaction.[70] Cytokines from mast cells may play a role in the persistence of long-term effects. Late-phase responses seen in asthma are slightly different from those seen in other allergic responses, although they are still caused by release of mediators from eosinophils and are still dependent on activity of $T_H2$ cells.[71]

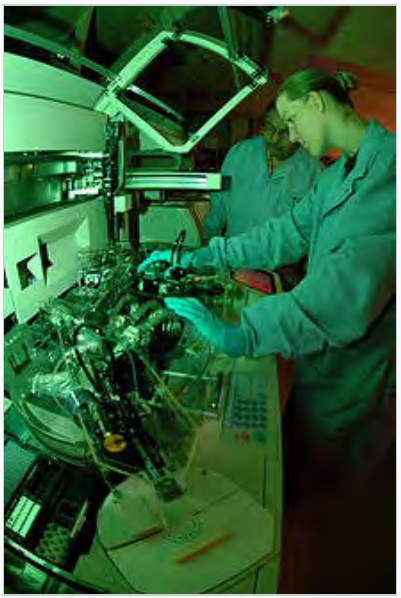



Degranulation process in allergy. Second exposure to allergen. **1** – antigen; **2** – IgE antibody; **3** – FcεRI receptor; **4** – preformed mediators (histamine, proteases, chemokines, heparin); **5** – granules; **6** – mast cell; **7** – newly formed mediators (prostaglandins, leukotrienes, thromboxanes, PAF)

## Allergic contact dermatitis [edit]

Although allergic contact dermatitis is termed an "allergic" reaction (which usually refers to type I hypersensitivity), its pathophysiology actually involves a reaction that more correctly corresponds to a type IV hypersensitivity reaction.[72] In type IV hypersensitivity, there is activation of certain types of T cells (CD8+) that destroy target cells on contact, as well as activated macrophages that produce hydrolytic enzymes.

# Diagnosis [edit]



An allergy testing machine being operated in the diagnostic immunology lab

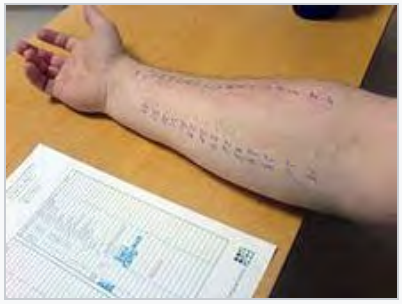
Effective management of allergic diseases relies on the ability to make an accurate diagnosis.[73] Allergy testing can help confirm or rule out allergies.[74][75] Correct diagnosis, counseling, and avoidance advice based on valid allergy test results reduces the incidence of symptoms and need for medications, and improves quality of life.[74] To assess the presence of allergen-specific IgE antibodies, two different methods can be used: a skin prick test, or an allergy blood test. Both methods are recommended, and they have similar diagnostic value.[75][76]

Skin prick tests and blood tests are equally cost-effective, and health economic evidence shows that both tests were cost-effective compared with no test.[74] Also, early and more accurate diagnoses save cost due to reduced consultations, referrals to secondary care, misdiagnosis, and emergency admissions.[77]

Allergy undergoes dynamic changes over time. Regular allergy testing of relevant allergens provides information on if and how patient management can be changed, in order to improve health and quality of life. Annual testing is often the practice for determining whether allergy to milk, egg, soy, and wheat have been outgrown, and the testing interval is extended to 2–3 years for allergy to peanut, tree nuts, fish, and crustacean shellfish.[75] Results of follow-up testing can guide decision-making regarding whether and when it is safe to introduce or re-introduce allergenic food into the diet.[78]

## Skin prick testing [edit]

Skin testing is also known as "puncture testing" and "prick testing" due to the series of tiny punctures or pricks made into the patient's skin. Small amounts of suspected allergens and/or their extracts (*e.g.*, pollen, grass, mite proteins, peanut extract) are introduced to sites on the skin marked with pen or dye (the ink/dye should be carefully selected, lest it cause an allergic response itself). A small plastic or metal device is used to puncture or prick the skin. Sometimes, the allergens are injected "intradermally" into the patient's skin, with a needle and syringe. Common areas for testing include the inside forearm and the back.


Skin testing on arm

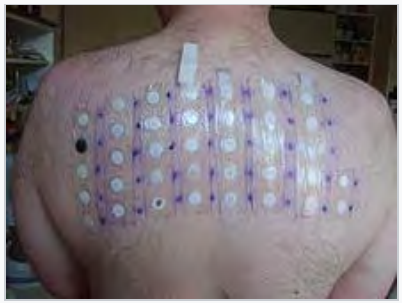
If the patient is allergic to the substance, then a visible inflammatory reaction will usually occur within 30 minutes. This response will range from slight reddening of the skin to a full-blown hive (called "wheal and flare") in more sensitive patients similar to a mosquito bite. Interpretation of the results of the skin prick test is normally done by allergists on a scale of severity, with +/− meaning borderline reactivity, and 4+ being a large reaction. Increasingly, allergists are measuring and recording the diameter of the wheal and flare reaction. Interpretation by well-trained allergists is often guided by relevant literature.[79] Some patients may believe they have determined their own allergic sensitivity from observation, but a skin test has been shown to be much better than patient observation to detect allergy.[80]


Skin testing on back

If a serious life-threatening anaphylactic reaction has brought a patient in for evaluation, some allergists will prefer an initial blood test prior to performing the skin prick test. Skin tests may not be an option if the patient has widespread skin disease, or has taken antihistamines in the last several days.

## Patch testing [edit]

Patch testing is a method used to determine if a specific substance causes allergic inflammation of the skin. It tests for delayed reactions. It is used to help ascertain the cause of skin contact allergy, or contact dermatitis. Adhesive patches, usually treated with a number of common allergic chemicals or skin sensitizers, are applied to the back. The skin is then examined for possible local reactions at least twice, usually at 48 hours after application of the patch, and again two or three days later.


Patch test

## Blood testing [edit]

An allergy blood test is quick and simple, and can be ordered by a licensed health care provider (*e.g.*, an allergy specialist), GP, or PED. Unlike skin-prick testing, a blood test can be performed irrespective of age, skin condition, medication, symptom, disease activity, and pregnancy. Adults and children of any age can take an allergy blood test. For babies and very young children, a single needle stick for allergy blood testing is often more gentle than several skin tests.

An allergy blood test is available through most laboratories. A sample of the patient's blood is sent to a laboratory for analysis, and the results are sent back a few days later. Multiple allergens can be detected with a single blood sample. Allergy blood tests are very safe, since the person is not exposed to any allergens during the testing procedure.

The test measures the concentration of specific IgE antibodies in the blood. Quantitative IgE test results increase the possibility of ranking how different substances may affect symptoms. A rule of thumb is that the higher the IgE antibody value, the greater the likelihood of symptoms. Allergens found at low levels that today do not result in symptoms can nevertheless help predict future symptom development. The quantitative allergy blood result can help determine what a patient is allergic to, help predict and follow the disease development, estimate the risk of a severe reaction, and explain cross-reactivity.[81][82]

A low total IgE level is not adequate to rule out sensitization to commonly inhaled allergens.[83] Statistical methods, such as ROC curves, predictive value calculations, and likelihood ratios have been used to examine the relationship of various testing methods to each other. These methods have shown that patients with a high total IgE have a high probability of allergic sensitization, but further investigation with allergy tests for specific IgE antibodies for a carefully chosen of allergens is often warranted.

Laboratory methods to measure specific IgE antibodies for allergy testing include enzyme-linked immunosorbent [84] [84] [85]

assay (ELISA, or EIA), radioallergosorbent test (RAST) and fluorescent enzyme immunoassay (FEIA).

### Other [edit]

**Challenge testing:** Challenge testing is when small amounts of a suspected allergen are introduced to the body orally, through inhalation, or via other routes. Except for testing food and medication allergies, challenges are rarely performed. When this type of testing is chosen, it must be closely supervised by an allergist.

**Elimination/Challenge tests:** This testing method is used most often with foods or medicines. A patient with a suspected allergen is instructed to modify his diet to totally avoid that allergen for a set time. If the patient experiences significant improvement, he may then be "challenged" by reintroducing the allergen, to see if symptoms are reproduced.

**Unreliable tests:** There are other types of allergy testing methods that are unreliable, including applied kinesiology (allergy testing through muscle relaxation), cytotoxicity testing, urine autoinjection, skin titration (Rinkel method), and provocative and neutralization (subcutaneous) testing or sublingual provocation.[86]

### Differential diagnosis [edit]

Before a diagnosis of allergic disease can be confirmed, other possible causes of the presenting symptoms should be considered.[87] Vasomotor rhinitis, for example, is one of many maladies that shares symptoms with allergic rhinitis, underscoring the need for professional differential diagnosis.[88] Once a diagnosis of asthma, rhinitis, anaphylaxis, or other allergic disease has been made, there are several methods for discovering the causative agent of that allergy.

## Prevention [edit]

The consumption of various foods during pregnancy has been linked to eczema; these include celery, citrus fruit, raw pepper, margarine, and vegetable oil.[89] A high intake of antioxidants, zinc, and selenium during pregnancy may help prevent allergies. This is linked to a reduced risk for childhood-onset asthma, wheezing, and eczema.[90] Further research needs to be conducted. Probiotic supplements taken during pregnancy or infancy may help to prevent atopic dermatitis.[91] After birth, an early introduction of solid food and high diversity before week 17 could increase a child's risk for allergies. Studies suggest that introduction of solid food and avoidance of highly allergenic food such as peanuts during the first year does not help in allergy prevention.[89]

## Management [edit]

Management of allergies typically involves avoiding what triggers the allergy and medications to improve the symptoms.[10] Allergen immunotherapy may be useful for some types of allergies.[10]

### Medication [edit]

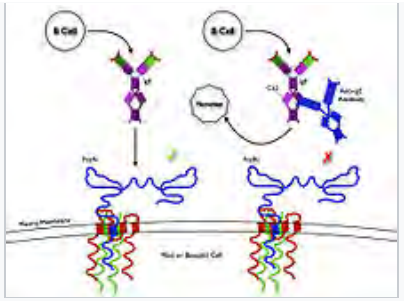
Several medications may be used to block the action of allergic mediators, or to prevent activation of cells and degranulation processes. These include antihistamines, glucocorticoids, epinephrine (adrenaline), mast cell stabilizers, and antileukotriene agents are common treatments of allergic diseases.[92] Anti-cholinergics, decongestants, and other compounds thought to impair eosinophil chemotaxis, are also commonly used. Though rare, the severity of anaphylaxis often requires epinephrine injection, and where medical care is unavailable, a device known as an epinephrine autoinjector may be used.[24]

### Immunotherapy [edit]

*Main article: Allergen immunotherapy*

Allergen immunotherapy is useful for environmental allergies, allergies to insect bites, and asthma.[10][93] Its benefit for food allergies is unclear and thus not recommended.[10] Immunotherapy involves exposing people to larger and larger amounts of allergen in an affect to change the immune system's response.[10]

Meta-analyses have found that injections of allergens under the skin is effective in the treatment in allergic rhinitis in children[94][95] and in asthma.[93] The benefits may last for years after treatment is stopped.[96] It is generally safe



Anti-allergy immunotherapy

and effective for allergic rhinitis and conjunctivitis, allergic forms of asthma, and stinging insects.[97]

The evidence also supports the use of sublingual immunotherapy for rhinitis and asthma but it is less strong.[96] For seasonal allergies the benefit is small.[98] In this form the allergen is given under the tongue and people often prefer it to injections.[96] Immunotherapy is not recommended as a stand-alone treatment for asthma.[96]

### Alternative medicine [edit]

An experimental treatment, enzyme potentiated desensitization (EPD), has been tried for decades but is not generally accepted as effective.[99] EPD uses dilutions of allergen and an enzyme, beta-glucuronidase, to which T-regulatory lymphocytes are supposed to respond by favoring desensitization, or down-regulation, rather than sensitization. EPD has also been tried for the treatment of autoimmune diseases but evidence does not show effectiveness.[99]

A review found no effectiveness of homeopathic treatments and no difference compared with placebo. The authors concluded that, based on rigorous clinical trials of all types of homeopathy for childhood and adolescence ailments, there is no convincing evidence that supports the use of homeopathic treatments.[100]

According to the NCCIH, the evidence is relatively strong that saline nasal irrigation and butterbur are effective, when compared to other alternative medicine treatments, for which the scientific evidence is weak, negative, or nonexistent, such as honey, acupuncture, omega 3's, probiotics, astragalus, capsaicin, grape seed extract, Pycnogenol, quercetin, spirulina, stinging nettle, tinospora or guduchi. [101][102]

## Epidemiology [edit]

The allergic diseases—hay fever and asthma—have increased in the Western world over the past 2–3 decades.[103] Increases in allergic asthma and other atopic disorders in industrialized nations, it is estimated, began in the 1960s and 1970s, with further increases occurring during the 1980s and 1990s,[104] although some suggest that a steady rise in sensitization has been occurring since the 1920s.[105] The number of new cases per year of atopy in developing countries has, in general, remained much lower.[104]

**Allergic conditions: Statistics and epidemiology**

| Allergy type | United States | United Kingdom[106] |
|---|---|---|
| Allergic rhinitis | 35.9 million[107] (about 11% of the population[108]) | 3.3 million (about 5.5% of the population[109]) |
| Asthma | 10 million have allergic asthma (about 3% of the population). The prevalence of asthma increased 75% from 1980 to 1994. Asthma prevalence is 39% higher in African Americans than in Europeans.[110] | 5.7 million (about 9.4%). In six- and seven-year-olds asthma increased from 18.4% to 20.9% over five years, during the same time the rate decreased from 31% to 24.7% in 13- to 14-year-olds. |
| Atopic eczema | About 9% of the population. Between 1960 and 1990 prevalence has increased from 3% to 10% in children.[111] | 5.8 million (about 1% severe). |
| Anaphylaxis | At least 40 deaths per year due to insect venom. About 400 deaths due to penicillin anaphylaxis. About 220 cases of anaphylaxis and 3 deaths per year | Between 1999 and 2006, 48 deaths occurred in people ranging from five months to |

| | | |
|---|---|---|
| | are due to latex allergy.[112] An estimated 150 people die annually from anaphylaxis due to food allergy.[113] | 85 years old. |
| Insect venom | Around 15% of adults have mild, localized allergic reactions. Systemic reactions occur in 3% of adults and less than 1% of children.[114] | Unknown |
| Drug allergies | Anaphylactic reactions to penicillin cause 400 deaths per year. | Unknown |
| Food allergies | About 6% of US children under age 3 and 3.5–4% of the overall US population.[*citation needed*] Peanut and/or tree nut (e.g. walnut) allergy affects about three million Americans, or 1.1% of the population.[113] | 5–7% of infants and 1–2% of adults. A 117.3% increase in peanut allergies was observed from 2001 to 2005, an estimated 25,700 people in England are affected. |
| Multiple allergies (Asthma, eczema and allergic rhinitis together) | Unknown | 2.3 million (about 3.7%), prevalence has increased by 48.9% between 2001 and 2005.[115] |

## Changing frequency [edit]

Although genetic factors govern susceptibility to atopic disease, increases in atopy have occurred within too short a time frame to be explained by a genetic change in the population, thus pointing to environmental or lifestyle changes.[104] Several hypotheses have been identified to explain this increased rate; increased exposure to perennial allergens due to housing changes and increasing time spent indoors, and changes in cleanliness or hygiene that have resulted in the decreased activation of a common immune control mechanism, coupled with dietary changes, obesity and decline in physical exercise.[103] The hygiene hypothesis maintains[116] that high living standards and hygienic conditions exposes children to fewer infections. It is thought that reduced bacterial and viral infections early in life direct the maturing immune system away from $T_H1$ type responses, leading to unrestrained $T_H2$ responses that allow for an increase in allergy.[67][117]

Changes in rates and types of infection alone however, have been unable to explain the observed increase in allergic disease, and recent evidence has focused attention on the importance of the gastrointestinal microbial environment. Evidence has shown that exposure to food and fecal-oral pathogens, such as hepatitis A, *Toxoplasma gondii*, and *Helicobacter pylori* (which also tend to be more prevalent in developing countries), can reduce the overall risk of atopy by more than 60%,[118] and an increased rate of parasitic infections has been associated with a decreased prevalence of asthma.[119] It is speculated that these infections exert their effect by critically altering $T_H1/T_H2$ regulation.[120] Important elements of newer hygiene hypotheses also include exposure to endotoxins, exposure to pets and growing up on a farm.[120]

# History [edit]

The concept of "allergy" was originally introduced in 1906 by the Viennese pediatrician Clemens von Pirquet, after he noted that some of his patients were hypersensitive to normally innocuous entities such as dust, pollen, or certain foods.[121] Pirquet called this phenomenon "allergy" from the Ancient Greek words ἄλλος *allos* meaning "other" and ἔργον *ergon* meaning "work".[122]

All forms of hypersensitivity used to be classified as allergies, and all were thought to be caused by an improper activation of the immune system. Later, it became clear that several different disease mechanisms were implicated, with the common link to a disordered activation of the immune system. In 1963, a new classification scheme was designed by Philip Gell and Robin Coombs that described four types of hypersensitivity reactions, known as Type I to Type IV hypersensitivity.[123] With this new classification, the word "allergy" was restricted to type I hypersensitivities (also called immediate hypersensitivity), which are characterized as rapidly developing reactions.

A major breakthrough in understanding the mechanisms of allergy was the discovery of the antibody class labeled immunoglobulin E (IgE). IgE was simultaneously discovered in 1966–67 by two independent groups:[124] Ishizaka's team at the Children's Asthma Research Institute and Hospital in Denver, Colorado,[125] and by Gunnar Johansson and Hans Bennich in Uppsala, Sweden.[126] Their joint paper was published in April 1969.[127]

### Diagnosis [edit]

Radiometric assays include the radioallergosorbent test (RAST test) method, which uses IgE-binding (anti-IgE) antibodies labeled with radioactive isotopes for quantifying the levels of IgE antibody in the blood.[128] Other newer methods use colorimetric or fluorescence-labeled technology in the place of radioactive isotopes.[*citation needed*]

The RAST methodology was invented and marketed in 1974 by Pharmacia Diagnostics AB, Uppsala, Sweden, and the acronym RAST is actually a brand name. In 1989, Pharmacia Diagnostics AB replaced it with a superior test named the ImmunoCAP Specific IgE blood test, which uses the newer fluorescence-labeled technology.[*citation needed*]

American College of Allergy Asthma and Immunology (ACAAI) and the American Academy of Allergy Asthma and Immunology (AAAAI) issued the Joint Task Force Report "Pearls and pitfalls of allergy diagnostic testing" in 2008, and is firm in its statement that the term RAST is now obsolete:

> The term RAST became a colloquialism for all varieties of (in vitro allergy) tests. This is unfortunate because it is well recognized that there are well-performing tests and some that do not perform so well, yet they are all called RASTs, making it difficult to distinguish which is which. For these reasons, it is now recommended that use of RAST as a generic descriptor of these tests be abandoned.[129]

The new version, the ImmunoCAP Specific IgE blood test, is the only specific IgE assay to receive FDA approval to quantitatively report to its detection limit of 0.1kU/l.[*citation needed*]

## Medical specialty [edit]

An allergist is a physician specially trained to manage and treat allergies, asthma and the other allergic diseases. In the United States physicians holding certification by the American Board of Allergy and Immunology (ABAI) have successfully completed an accredited educational program and evaluation process, including a proctored examination to demonstrate knowledge, skills, and experience in patient care in allergy and immunology.[130] Becoming an allergist/immunologist requires completion of at least nine years of training. After completing medical school and graduating with a medical degree, a physician will undergo three years of training in internal medicine (to become an internist) or pediatrics (to become a pediatrician). Once physicians have finished training in one of these specialties, they must pass the exam of either the American Board of Pediatrics (ABP), the American Osteopathic Board of Pediatrics (AOBP), the American Board of Internal Medicine (ABIM), or the American Osteopathic Board of Internal Medicine (AOBIM). Internists or pediatricians wishing to focus on the sub-specialty of allergy-immunology then complete at least an additional two years of study, called a fellowship, in an allergy/immunology training program. Allergist/immunologists listed as ABAI-certified have successfully passed the certifying examination of the ABAI following their fellowship.[131]

In the United Kingdom, allergy is a subspecialty of general medicine or pediatrics. After obtaining postgraduate exams (MRCP or MRCPCH), a doctor works for several years as a specialist registrar before qualifying for the General Medical Council specialist register. Allergy services may also be delivered by immunologists. A 2003 Royal College of Physicians report presented a case for improvement of what were felt to be inadequate allergy services in the UK.[132] In 2006, the House of Lords convened a subcommittee. It concluded likewise in 2007 that allergy services were insufficient to deal with what the Lords referred to as an "allergy epidemic" and its social cost; it made several recommendations.[133]

## Research [edit]

Low-allergen foods are being developed, as are improvements in skin prick test predictions; evaluation of the atopy patch test; in wasp sting outcomes predictions and a rapidly disintegrating epinephrine tablet, and anti-IL-5 for eosinophilic diseases.[134]

Aerobiology is the study of biological particles passively dispersed through the air. One aim is the prevention of allergies due to pollen.[135][136]

## See also [edit]

- List of allergens
- Oral allergy syndrome

# References [edit]


1. ^ a b McConnell, Thomas H. (2007). *The Nature of Disease: Pathology for the Health Professions*. Baltimore, Mar.: Lippincott Williams & Wilkins. p. 159. ISBN 978-0-7817-5317-3.
2. ^ "Types of Allergic Diseases". *NIAID*. May 29, 2015. Retrieved 17 June 2015.
3. ^ "Environmental Allergies: Symptoms". *NIAID*. April 22, 2015. Retrieved 19 June 2015.
4. ^ Bahna SL (Dec 2002). "Cow's milk allergy versus cow milk intolerance". *Annals of Allergy, Asthma & Immunology*. **89** (6 Suppl 1): 56–60. doi:10.1016/S1081-1206(10)62124-2. PMID 12487206.
5. ^ a b c National Institute of Allergy and Infectious Diseases (July 2012). "Food Allergy An Overview" (pdf).
6. ^ a b Kay AB (2000). "Overview of 'allergy and allergic diseases: with a view to the future'". *Br. Med. Bull*. **56** (4): 843–64. doi:10.1258/0007142001903481. PMID 11359624.
7. ^ "How Does an Allergic Response Work?". *NIAID*. April 21, 2015. Retrieved 20 June 2015.
8. ^ Cox L, Williams B, Sicherer S, Oppenheimer J, Sher L, Hamilton R, Golden D (December 2008). "Pearls and pitfalls of allergy diagnostic testing: report from the American College of Allergy, Asthma and Immunology/American Academy of Allergy, Asthma and Immunology Specific IgE Test Task Force". *Annals of Allergy, Asthma & Immunology*. **101** (6): 580–92. doi:10.1016/S1081-1206(10)60220-7. PMID 19119701.
9. ^ a b Sicherer, SH.; Sampson, HA. (Feb 2014). "Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment". *J Allergy Clin Immunol*. **133** (2): 291–307; quiz 308. doi:10.1016/j.jaci.2013.11.020. PMID 24388012.
10. ^ a b c d e f g "Allergen Immunotherapy". April 22, 2015. Retrieved 15 June 2015.
11. ^ a b Simons FE (October 2009). "Anaphylaxis: Recent advances in assessment and treatment" (PDF). *The Journal of Allergy and Clinical Immunology*. **124** (4): 625–36; quiz 637–8. doi:10.1016/j.jaci.2009.08.025. PMID 19815109.
12. ^ "Allergic Diseases". *NIAID*. May 21, 2015. Retrieved 20 June 2015.
13. ^ Wheatley, LM; Togias, A (29 January 2015). "Clinical practice. Allergic rhinitis". *The New England Journal of Medicine*. **372** (5): 456–63. doi:10.1056/NEJMcp1412282. PMID 25629743.
14. ^ Thomsen, SF (2014). "Atopic dermatitis: natural history, diagnosis, and treatment". *ISRN allergy*: 354250. doi:10.1155/2014/354250. PMID 25006501.
15. ^ "Global Strategy for Asthma Management and Prevention: Updated 2015" (PDF). Global Initiative for Asthma. 2015. p. 2. Archived from the original on 17 October 2015.
16. ^ "Global Strategy for Asthma Management and Prevention" (PDF). Global Initiative for Asthma. 2011. pp. 2–5. Archived from the original (PDF) on July 2016.
17. ^ Leslie C. Grammer (2012). *Patterson's Allergic Diseases* (7 ed.). ISBN 978-1-4511-4863-3.
18. ^ Anandan C, Nurmatov U, van Schayck OC, Sheikh A (February 2010). "Is the prevalence of asthma declining? Systematic review of epidemiological studies". *Allergy*. **65** (2): 152–67. doi:10.1111/j.1398-9995.2009.02244.x. PMID 19912154.
19. ^ Bope, Edward T.; Rakel, Robert E. (2005). *Conn's Current Therapy 2005*. Philadelphia, PA: W.B. Saunders Company. p. 880. ISBN 0-7216-3864-3.
20. ^ Holgate ST (1998). "Asthma and allergy—disorders of civilization?". *QJM*. **91** (3): 171–84. doi:10.1093/qjmed/91.3.171. PMID 9604069.
21. ^ Rusznak C, Davies RJ; Davies (1998). "ABC of allergies. Diagnosing allergy". *BMJ*. **316** (7132): 686–9. doi:10.1136/bmj.316.7132.686. PMC 1112683. PMID 9522798.
22. ^ Golden DB (2007). "Insect sting anaphylaxis". *Immunol Allergy Clin North Am*. **27** (2): 261–72, vii. doi:10.1016/j.iac.2007.03.008. PMC 1961691. PMID 17493502.
23. ^ Schafer JA, Mateo N, Parlier GL, Rotschafer JC (2007). "Penicillin allergy skin testing: what do we do now?". *Pharmacotherapy*. **27** (4): 542–5. doi:10.1592/phco.27.4.542. PMID 17381381.
24. ^ a b c Tang AW (2003). "A practical guide to anaphylaxis". *Am Fam Physician*. **68** (7): 1325–32. PMID 14567487.
25. ^ Brehler R, Kütting B (2001). "Natural rubber latex allergy: a problem of interdisciplinary concern in medicine". *Arch. Intern. Med*. **161** (8): 1057–64. doi:10.1001/archinte.161.8.1057. PMID 11322839.
26. ^ Muller BA (2004). "Urticaria and angioedema: a practical approach". *Am Fam Physician*. **69** (5): 1123–28. PMID 15023012.
27. ^ a b Ludman, SW; Boyle, RJ (2015). "Stinging insect allergy: current perspectives on venom immunotherapy.". *Journal of asthma and allergy*. **8**: 75–86. doi:10.2147/JAA.S62288. PMC 4517515. PMID 26229493.
28. ^ Slavin, ed. by Raymond G.; Reisman, Robert E. (1999). *Expert guide to allergy and immunology*. Philadelphia, Pa: American College of Physicians. p. 222. ISBN 9780943126739. Retrieved 7 June 2016.
29. ^ Grammatikos AP (2008). "The genetic and environmental basis of atopic diseases". *Annals of Medicine*. **40** (7): 482–95. doi:10.1080/07853890802082096. PMID 18608118.
30. ^ a b c d Janeway, Charles; Paul Travers; Mark Walport; Mark Shlomchik (2001). *Immunobiology; Fifth Edition*. New York and London: Garland Science. pp. e–book. ISBN 978-0-8153-4101-7.
31. ^ a b "Asthma and Allergy Foundation of America". Retrieved 23 December 2012.
32. ^ a b Maleki, Soheilia J; Burks, A. Wesley; Helm, Ricki M. (2006). *Food Allergy*. Blackwell Publishing. pp. 39–41. ISBN 1-55581-375-5.
33. ^ Boyle, Robert J; Ierodiakonou, Despo; Khan, Tasnia; Chivinge, Jennifer; Robinson, Zoe; Geoghegan, Natalie; Jarrold, Katharine; Afxentiou, Thalia; Reeves, Tim; Cunha, Sergio; Trivella, Marialena; Garcia-Larsen, Vanessa; Leonardi-Bee, Jo (8 March 2016). "Hydrolysed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis". *BMJ*:

i974. doi:10.1136/bmj.i974.
34. ^ Järvinen KM, Beyer K, Vila L, Bardina L, Mishoe M, Sampson HA (July 2007). "Specificity of IgE antibodies to sequential epitopes of hen's egg ovomucoid as a marker for persistence of egg allergy". *J. Allergy.* **62** (7): 758–65. doi:10.1111/j.1398-9995.2007.01332.x. PMID 17573723.
35. ^ *a b c* Sicherer 63
36. ^ Maleki, Burks & Helm 2006, pp. 41
37. ^ "World Allergy Organization". Retrieved 13 April 2015.
38. ^ Sicherer 64
39. ^ Herman, Eliot (2003). "Genetically modified soybeans and food allergies". *Journal of Experimental Botany*. **54** (356): 1317–1319. doi:10.1093/jxb/erg164. PMID 12709477.
40. ^ Panda R, Ariyarathna H, Amnuaycheewa P, Tetteh A, Pramod SN, Taylor SL, Ballmer-Weber BK, Goodman RE (Feb 2013). "Challenges in testing genetically modified crops for potential increases in endogenous allergen expression for safety". *Allergy*. **68** (2): 142–51. doi:10.1111/all.12076. PMID 23205714.
41. ^ *a b c d* Sussman GL, Beezhold DH (1995). "Allergy to Latex Rubber". *Annals of Internal Medicine*. **122** (1): 43–46. doi:10.7326/0003-4819-122-1-199501010-00007. PMID 7985895.
42. ^ Fernández de Corres L, Moneo I, Muñoz D, Bernaola G, Fernández E, Audicana M, Urrutia I (January 1993). "Sensitization from chestnuts and bananas in patients with urticaria and anaphylaxis from contact with latex". *Ann Allergy*. **70** (1): 35–9. PMID 7678724.
43. ^ *a b* Gonzalez-Estrada, A; Radojicic, C (May 2015). "Penicillin allergy: A practical guide for clinicians.". *Cleveland Clinic journal of medicine*. **82** (5): 295–300. doi:10.3949/ccjm.82a.14111. PMID 25973877.
44. ^ C. Michael Hogan. *Western poison-oak: Toxicodendron diversilobum*. GlobalTwitcher, ed. Nicklas Stromberg. 2008. Retrieved 30 April 2010.
45. ^ Keeler, Harriet L. (1900). *Our Native Trees and How to Identify Them*. New York: Charles Scriber's Sons. pp. 94–96; Frankel, Edward, Ph.D. *Poison Ivy, Poison Oak, Poison Sumac and Their Relatives; Pistachios, Mangoes and Cashews*. The Boxwood Press. Pacific Grove, Calif. 1991. ISBN 978-0-940168-18-3.
46. ^ DermAtlas *-1892628434*
47. ^ Armstrong W.P.; Epstein W.L. (1995). "Poison oak: more than just scratching the surface". *Herbalgram*. American Botanical Council. **34**: 36–42. cited in http://waynesword.palomar.edu/ww0802.htm
48. ^ Galli SJ (2000). "Allergy". *Curr. Biol*. **10** (3): R93–5. doi:10.1016/S0960-9822(00)00322-5. PMID 10679332.
49. ^ *a b c d e* De Swert LF (1999). "Risk factors for allergy". *Eur. J. Pediatr*. **158** (2): 89–94. doi:10.1007/s004310051024. PMID 10048601.
50. ^ *a b* Croner S (1992). "Prediction and detection of allergy development: influence of genetic and environmental factors". *J. Pediatr*. **121** (5 Pt 2): S58–63. doi:10.1016/S0022-3476(05)81408-8. PMID 1447635.
51. ^ Jarvis D, Burney P (1997). "Epidemiology of atopy and atopic disease". In Kay AB. *Allergy and allergic diseases*. **2**. London: Blackwell Science. pp. 1208–24.
52. ^ Anderson HR, Pottier AC, Strachan DP (1992). "Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease". *Thorax*. **47** (7): 537–42. doi:10.1136/thx.47.7.537. PMC 463865. PMID 1412098.
53. ^ Barnes KC, Grant AV, Hansel NN, Gao P, Dunston GM (2007). "African Americans with asthma: genetic insights". *Proc Am Thorac Soc*. **4** (1): 58–68. doi:10.1513/pats.200607-146JG. PMC 2647616. PMID 17202293. Archived from the original on 16 November 2010.
54. ^ Folkerts G, Walzl G, Openshaw PJ (March 2000). "Do common childhood infections 'teach' the immune system not to be allergic?". *Immunol. Today*. **21** (3): 118–20. doi:10.1016/S0167-5699(00)01582-6. PMID 10777250.
55. ^ "The Hygiene Hypothesis". Edward Willett. 2013-01-30. Retrieved 2013-05-30.
56. ^ Gibson PG, Henry RL, Shah S, Powell H, Wang H (September 2003). "Migration to a western country increases asthma symptoms but not eosinophilic airway inflammation". *Pediatr. Pulmonol*. **36** (3): 209–15. doi:10.1002/ppul.10323. PMID 12910582.. Retrieved 2008-07-06.
57. ^ Addo-Yobo EO, Woodcock A, Allotey A, Baffoe-Bonnie B, Strachan D, Custovic A (February 2007). "Exercise-induced bronchospasm and atopy in Ghana: two surveys ten years apart". *PLoS Med.* **4** (2): e70. doi:10.1371/journal.pmed.0040070. PMC 1808098. PMID 17326711. Archived from the original on 2010-11-16.
58. ^ Marra F, Lynd L, Coombes M, et al. (2006). "Does antibiotic exposure during infancy lead to development of asthma?: a systematic review and metaanalysis". *Chest*. **129** (3): 610–8. doi:10.1378/chest.129.3.610. PMID 16537858.
59. ^ Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR (2007). "A meta-analysis of the association between Caesarean section and childhood asthma". *Clin. And Exper. Allergy*. **38** (4): 629–33. doi:10.1111/j.1365-2222.2007.02780.x. PMID 18352976.
60. ^ Zock JP, Plana E, Jarvis D, et al. (2007). "The use of household cleaning sprays and adult asthma: an international longitudinal study". *Am J Respir Crit Care Med*. **176** (8): 735–41. doi:10.1164/rccm.200612-1793OC. PMC 2020829. PMID 17585104.
61. ^ Dave ND, Xiang L, Rehm KE, Marshall GD Jr (Feb 2011). "Stress and allergic diseases". *Immunol Allergy Clin North Am*. **31** (1): 55–68. doi:10.1016/j.iac.2010.09.009. PMC 3264048. PMID 21094923.
62. ^ *a b* Cooper PJ (2004). "Intestinal worms and human allergy". *Parasite Immunol*. **26** (11–12): 455–67. doi:10.1111/j.0141-9838.2004.00728.x. PMID 15771681.
63. ^ Braun-Fahrländer C, Riedler J, Herz U, et al. (2002). "Environmental exposure to endotoxin and its relation to asthma in school-age children". *N. Engl. J. Med*. **347** (12): 869–77. doi:10.1056/NEJMoa020057. PMID 12239255.
64. ^ Garn H, Renz H (2007). "Epidemiological and immunological evidence for the hygiene hypothesis". *Immunobiology*. **212** (6): 441–52. doi:10.1016/j.imbio.2007.03.006. PMID 17544829.

65. ^ Macpherson CN, Gottstein B, Geerts S (2000). "Parasitic food-borne and water-borne zoonoses". *Rev. – Off. Int. Epizoot.* **19** (1): 240–58. PMID 11189719.
66. ^ Carvalho EM, Bastos LS, Araújo MI (2006). "Worms and allergy". *Parasite Immunol.* **28** (10): 525–34. doi:10.1111/j.1365-3024.2006.00894.x. PMID 16965288.
67. ^ [a] [b] Yazdanbakhsh M, Kremsner PG, van Ree R (2002). "Allergy, parasites, and the hygiene hypothesis". *Science.* **296** (5567): 490–4. doi:10.1126/science.296.5567.490. PMID 11964470.
68. ^ Emanuelsson C, Spangfort MD; Spangfort (2007). "Allergens as eukaryotic proteins lacking bacterial homologues". *Mol. Immunol.* **44** (12): 3256–60. doi:10.1016/j.molimm.2007.01.019. PMID 17382394.
69. ^ [a] [b] Falcone FH, Pritchard DI (2005). "Parasite role reversal: worms on trial". *Trends Parasitol.* **21** (4): 157–60. doi:10.1016/j.pt.2005.02.002. PMID 15780835.
70. ^ Grimbaldeston MA, Metz M, Yu M, Tsai M, Galli SJ (2006). "Effector and potential immunoregulatory roles of mast cells in IgE-associated acquired immune responses". *Current Opinion in Immunology.* **18** (6): 751–60. doi:10.1016/j.coi.2006.09.011. PMID 17011762.
71. ^ Holt PG, Sly PD (2007). "Th2 cytokines in the asthma late-phase response". *Lancet.* **370** (9596): 1396–8. doi:10.1016/S0140-6736(07)61587-6. PMID 17950849.
72. ^ Martín A, Gallino N, Gagliardi J, Ortiz S, Lascano AR, Diller A, Daraio MC, Kahn A, Mariani AL, Serra HM (2002). "Early inflammatory markers in elicitation of allergic contact dermatitis". *BMC Dermatology.* **2**: 9. doi:10.1186/1471-5945-2-9. PMC 122084. PMID 12167174.
73. ^ Portnoy JM; et al. (2006). "Evidence-based Allergy Diagnostic Tests". *Current Allergy and Asthma Reports.* **6**: 455–461. doi:10.1007/s11882-006-0021-8.
74. ^ [a] [b] [c] NICE Diagnosis and assessment of food allergy in children and young people in primary care and community settings, 2011
75. ^ [a] [b] [c] Boyce; et al. (2010). "Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of NIAID-Sponsored Expert Panel". *J Allergy Clin Immunol.* **126** (6 Suppl): S1–S58. doi:10.1016/j.jaci.2010.10.007. PMID 21134576.
76. ^ Cox L (2011). "Overview of Serological-Specific IgE Antibody Testing in Children". *Pediatric Allergy and Immunology.*
77. ^ Food Allergy in children and young people. Costing report. Implementing NICE guidance, 2011. http://guidance.nice.org.uk/CG116/CostingReport/pdf/English
78. ^ NIH Guidelines for the Diagnosis and Management of Food Allergy in the United States. Report of the NIAID-Sponsored Expert Panel, 2010, NIH Publication no. 11-7700.
79. ^ Verstege A, Mehl A, Rolinck-Werninghaus C, et al. (2005). "The predictive value of the skin prick test weal size for the outcome of oral food challenges". *Clin. Exp. Allergy.* **35** (9): 1220–6. doi:10.1111/j.1365-2222.2005.2324.x. PMID 16164451.
80. ^ Li JT, Andrist D, Bamlet WR, Wolter TD (2000). "Accuracy of patient prediction of allergy skin test results". *Ann. Allergy Asthma Immunol.* **85** (5): 382–4. doi:10.1016/S1081-1206(10)62550-1. PMID 11101180.
81. ^ Yunginger; et al. (2000). "Quantitative IgE antibody assays in allergic disease". *J Allergy Clin Immunol.* **105**: 1077–84. doi:10.1067/mai.2000.107041.
82. ^ Sampson; et al. (2001). "Utility of food-specific IgE concentrations in predicting symptomatic food allergy". *J Allergy Clin Immunol.* **107** (5): 891–6. doi:10.1067/mai.2001.114708. PMID 11344358.
83. ^ Kerkhof M, Dubois AE, Postma DS, Schouten JP, de Monchy JG (2003). "Role and interpretation of total serum IgE measurements in the diagnosis of allergic airway disease in adults". *Allergy.* **58** (9): 905–11. doi:10.1034/j.1398-9995.2003.00230.x. PMID 12911420.
84. ^ [a] [b] "Blood Testing for Allergies". *WebMD.* Retrieved 2016-06-05.
85. ^ Khan, Faisal M; Ueno-Yamanouchi, Aito; Serushago, Bazir; Bowen, Tom; Lyon, Andrew W; Lu, Cathy; Storek, Jan (2012). "Basophil activation test compared to skin prick test and fluorescence enzyme immunoassay for aeroallergen-specific Immunoglobulin-E". *Allergy, Asthma & Clinical Immunology.* **8** (1): 1. doi:10.1186/1710-1492-8-1. ISSN 1710-1492.
86. ^ "Allergy Diagnosis". Archived from the original on 16 November 2010.The Online Allergist. Retrieved 2010-10-25.
87. ^ *Allergic and Environmental Asthma* at eMedicine – Includes discussion of differentials
88. ^ Wheeler PW, Wheeler SF; Wheeler (2005). "Vasomotor rhinitis". *American Family Physician.* **72** (6): 1057–62. PMID 16190503. Archived from the original on 21 August 2008.
89. ^ [a] [b] Sausenthaler S; Heinrich J; Koletzko S. Early diet and the risk of allergy: what can we learn from the perspective birth cohort studies GINIplus and LISAplus?. AJCN [Online] 2011, 94, 2012S-7S.
90. ^ Patelarou E; Giourgouli G; Brokalaki H; *et al.*. Association between biomarker-quantified antioxidant status during pregnancy and infancy and allergic disease during early childhood: A systematic review. Nutrition Reviews [Online]. 2011, 69, 27–641.
91. ^ Pelucchi, C; Chatenoud, L; Turati, F; Galeone, C; Moja, L; Bach, JF; La Vecchia, C (May 2012). "Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis". *Epidemiology (Cambridge, Mass.).* **23** (3): 402–14. doi:10.1097/EDE.0b013e31824d5da2. PMID 22441545.
92. ^ Frieri M (2015). "Mast Cell Activation Syndrome". *Clin Rev Allergy Immunol.* doi:10.1007/s12016-015-8487-6. PMID 25944644.
93. ^ [a] [b] Abramson, MJ; Puy, RM; Weiner, JM (4 August 2010). "Injection allergen immunotherapy for asthma". *The Cochrane database of systematic reviews* (8): CD001186. doi:10.1002/14651858.CD001186.pub2. PMID 20687065.
94. ^ Penagos, M; Compalati, E; Tarantini, F; Baena-Cagnani, R; Huerta, J; Passalacqua, G; Canonica, GW (August 2006). "Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials". *Annals of Allergy, Asthma & Immunology.* **97** (2): 141–8.

doi:10.1016/S1081-1206(10)60004-X. PMID 16937742.
95. ^ Calderon, MA; Alves, B; Jacobson, M; Hurwitz, B; Sheikh, A; Durham, S (24 January 2007). "Allergen injection immunotherapy for seasonal allergic rhinitis". *The Cochrane database of systematic reviews* (1): CD001936. doi:10.1002/14651858.CD001936.pub2. PMID 17253469.
96. ^ [a] [b] [c] [d] Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, Potter PC, Bousquet PJ, Cox LS, Durham SR, Nelson HS, Passalacqua G, Ryan DP, Brozek JL, Compalati E, Dahl R, Delgado L, van Wijk RG, Gower RG, Ledford DK, Filho NR, Valovirta EJ, Yusuf OM, Zuberbier T, Akhanda W, Almarales RC, Ansotegui I, Bonifazi F, Ceuppens J, Chivato T, Dimova D, Dumitrascu D, Fontana L, Katelaris CH, Kaulsay R, Kuna P, Larenas-Linnemann D, Manoussakis M, Nekam K, Nunes C, O'Hehir R, Olaguibel JM, Onder NB, Park JW, Priftanji A, Puy R, Sarmiento L, Scadding G, Schmid-Grendelmeier P, Seberova E, Sepiashvili R, Solé D, Togias A, Tomino C, Toskala E, Van Beever H, Vieths S (December 2009). "Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009" (PDF). *Allergy*. 64 Suppl 91: 1–59. doi:10.1111/j.1398-9995.2009.02309.x. PMID 20041860.
97. ^ Rank MA, Li JT; Li (September 2007). "Allergen immunotherapy". *Mayo Clin. Proc.* **82** (9): 1119–23. doi:10.4065/82.9.1119. PMID 17803880.
98. ^ Di Bona, D; Plaia, A; Leto-Barone, MS; La Piana, S; Di Lorenzo, G (August 2015). "Efficacy of Grass Pollen Allergen Sublingual Immunotherapy Tablets for Seasonal Allergic Rhinoconjunctivitis: A Systematic Review and Meta-analysis.". *JAMA internal medicine*. **175** (8): 1301–9. doi:10.1001/jamainternmed.2015.2840. PMID 26120825.
99. ^ [a] [b] Terr AI (2004). "Unproven and controversial forms of immunotherapy". *Clinical allergy and immunology*. **18**: 703–10. PMID 15042943.
100. ^ Altunç U, Pittler MH, Ernst E (2007). "Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials". *Mayo Clin. Proc.* **82** (1): 69–75. doi:10.4065/82.1.69. PMID 17285788.
101. ^ http://www.webmd.com/allergies/ss/slideshow-natural-relief
102. ^ https://nccih.nih.gov/health/providers/digest/allergies-science
103. ^ [a] [b] Platts-Mills TA, Erwin E, Heymann P, Woodfolk J (2005). "Is the hygiene hypothesis still a viable explanation for the increased prevalence of asthma?". *Allergy*. 60 Suppl 79: 25–31. doi:10.1111/j.1398-9995.2005.00854.x. PMID 15842230.
104. ^ [a] [b] [c] Bloomfield SF, Stanwell-Smith R, Crevel RW, Pickup J (2006). "Too clean, or not too clean: the hygiene hypothesis and home hygiene". *Clin. Exp. Allergy*. **36** (4): 402–25. doi:10.1111/j.1365-2222.2006.02463.x. PMC 1448690. PMID 16630145.
105. ^ Isolauri E, Huurre A, Salminen S, Impivaara O (2004). "The allergy epidemic extends beyond the past few decades". *Clin. Exp. Allergy*. **34** (7): 1007–10. doi:10.1111/j.1365-2222.2004.01999.x. PMID 15248842.
106. ^ "Chapter 4: The Extent and Burden of Allergy in the United Kingdom". *House of Lords – Science and Technology – Sixth Report*. 24 July 2007. Archived from the original on 16 November 2010. Retrieved 2007-12-03.
107. ^ "AAAAI – rhinitis, sinusitis, hay fever, stuffy nose, watery eyes, sinus infection". Archived from the original on 16 November 2010. Retrieved 2007-12-03.
108. ^ Based on an estimated population of 303 million in 2007 U.S. POPClock. U.S. Census Bureau.
109. ^ Based on an estimated population of 60.6 million UK population grows to 60.6 million
110. ^ "AAAAI – asthma, allergy, allergies, prevention of allergies and asthma, treatment for allergies and asthma". Archived from the original on 16 November 2010. Retrieved 2007-12-03.
111. ^ "AAAAI – skin condition, itchy skin, bumps, red irritated skin, allergic reaction, treating skin condition". Archived from the original on 16 November 2010. Retrieved 2007-12-03.
112. ^ "AAAAI – anaphylaxis, cause of anaphylaxis, prevention, allergist, anaphylaxis statistics". Archived from the original on 16 November 2010. Retrieved 2007-12-03.
113. ^ [a] [b] "AAAAI – food allergy, food reactions, anaphylaxis, food allergy prevention". Archived from the original on 16 November 2010. Retrieved 2007-12-03.
114. ^ "AAAAI – stinging insect, allergic reaction to bug bite, treatment for insect bite". Archived from the original on 16 November 2010. Retrieved 2007-12-03.
115. ^ Simpson CR, Newton J, Hippisley-Cox J, Sheikh A (2008). "Incidence and prevalence of multiple allergic disorders recorded in a national primary care database". *Journal of the Royal Society of Medicine*. **101** (11): 558–563. doi:10.1258/jrsm.2008.080196. PMC 2586863. PMID 19029357.
116. ^ Strachan DP (1989). "Hay fever, hygiene, and household size". *BMJ*. **299** (6710): 1259–60. doi:10.1136/bmj.299.6710.1259. PMC 1838109. PMID 2513902.
117. ^ Renz H, Blümer N, Virna S, Sel S, Garn H (2006). "The immunological basis of the hygiene hypothesis". *Chem Immunol Allergy*. Chemical Immunology and Allergy. **91**: 30–48. doi:10.1159/000090228. ISBN 3-8055-8000-2. PMID 16354947.
118. ^ Matricardi PM, Rosmini F, Riondino S, et al. (2000). "Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study". *BMJ*. **320** (7232): 412–7. doi:10.1136/bmj.320.7232.412. PMC 27285. PMID 10669445.
119. ^ Masters S, Barrett-Connor E (1985). "Parasites and asthma—redictive or protective?". *Epidemiol Rev*. **7**: 49–58. PMID 4054238.
120. ^ [a] [b] Sheikh A, Strachan DP (2004). "The hygiene theory: fact or fiction?". *Current Opinion in Otolaryngology & Head and Neck Surgery*. **12** (3): 232–6. doi:10.1097/01.moo.0000122311.13359.30. PMID 15167035.
121. ^ *Clemens Peter Pirquet von Cesenatico* at Who Named It?
122. ^ Von Pirquet C (1906). "Allergie". *Munch Med Wochenschr*. **53** (5): 388–90. PMID 20273584.
123. ^ Gell PG, Coombs RR (1963). *Clinical Aspects of Immunology*. London: Blackwell.
124. ^ Stanworth DR (1993). "The discovery of IgE". *Allergy*. **48**: 67–71. doi:10.1111/j.1398-9995.1993.tb00687.x.

125. ^ Ishizaka K, Ishizaka T, Hornbrook MM (1966). "Physico-chemical properties of human reaginic antibody. IV. Presence of a unique immunoglobulin as a carrier of reaginic activity". *Journal of Immunology*. **97** (1): 75–85. PMID 4162440.
126. ^ Johansson SG, Bennich H. Immunological studies of an atypical (myeloma) immunoglobulin" *Immunology* 1967; 13:381–94.
127. ^ Ishizaka,, Teruko; Ishizaka, Kimishige; Johansson, S. Gunnar O.; Bennich, Hans (April 1, 1969). "Histamine Release from Human Leukocytes by Anti-λE Antibodies". *Journal of Immunology*. **102** (4): 884–892. Retrieved 2016-02-29.
128. ^ Ten RM, Klein JS, Frigas E (1995). "Allergy skin testing". *Mayo Clin. Proc.* **70** (8): 783–4. doi:10.4065/70.8.783. PMID 7630219.
129. ^ Cox; et al. (2008). "Pearls and pitfalls of allergy diagnostic testing". *Annals of Allergy, Asthma & Immunology*. **101** (6): 580–592. doi:10.1016/s1081-1206(10)60220-7. PMID 19119701.
130. ^ "ABAI: American Board of Allergy and Immunology". Archived from the original on 16 November 2010. Retrieved 2007-08-05.
131. ^ "AAAAI – What is an Allergist?". Archived from the original on 16 November 2010. Retrieved 2007-08-05.
132. ^ Royal College of Physicians (2003). *Allergy: the unmet need*. London, UK: Royal College of Physicians. ISBN 978-1-86016-183-4. PDF version (1.03 MB)
133. ^ House of Lords – Science and Technology Committee (2007). *Allergy – HL 166-I, 6th Report of Session 2006–07 – Volume 1: Report*. London, UK: TSO (The Stationery Office). ISBN 978-0-10-401149-2.
134. ^ Sicherer SH, Leung DY (2007). "Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects". *The Journal of Allergy and Clinical Immunology*. **119** (6): 1462–9. doi:10.1016/j.jaci.2007.02.013. PMID 17412401.
135. ^ Galán, C., Smith, M., Thibaudon, M., Frenguelli, G., Oteros, J., Gehrig, R., ... & EAS QC Working Group. (2014). Pollen monitoring: minimum requirements and reproducibility of analysis. Aerobiologia, 30(4), 385-395.
136. ^ Oteros, J; Galán, C; Alcázar, P; Domínguez-Vilches, E (15 January 2013). "Quality control in bio-monitoring networks, Spanish Aerobiology Network.". *The Science of the total environment*. **443**: 559–65. doi:10.1016/j.scitotenv.2012.11.040. PMID 23220389.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- Allergy at DMOZ

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| **Other conditions** | Drug allergy · Allergic conjunctivitis · Latex allergy · |

| v · t · e · **Consequences of external causes (T66–T78, 990–995)** | |
|---|---|
| **Temperature/radiation** | *elevated temperature*: Hyperthermia · Heat syncope · *reduced temperature*: Hypothermia · Immersion foot syndromes (Trench foot · Tropical immersion foot · Warm water immersion foot · · Chilblains · Frostbite · Aerosol burn · Cold intolerance · Acrocyanosis · Erythrocyanosis crurum · *radiation*: Radiation poisoning · Radiation burn · Chronic radiation keratosis · Eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy · Radiation acne · |

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|---|---|
| | Radiation cancer · Radiation recall reaction · Radiation-induced erythema multiforme · Radiation-induced hypertrophic scar · Radiation-induced keloid · Radiation-induced morphea · |
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| **Other** | Electric shock · Drowning · Lightning injury · |
| **Ungrouped skin conditions resulting from physical factors** | Dermatosis neglecta · Pinch mark · Pseudoverrucous papules and nodules · Sclerosing lymphangiitis · Tropical anhidrotic asthenia · UV-sensitive syndrome · environmental skin conditions: Electrical burn · *frictional/traumatic/sports*: (Black heel and palm · Equestrian perniosis · Jogger's nipple · Pulling boat hands · Runner's rump · Surfer's knots · Tennis toe · Vibration white finger · Weathering nodule of ear · Wrestler's ear · Coral cut · Painful fat herniation · · Uranium dermatosis · *iv use*: (Skin pop scar · Skin track · Slap mark · Pseudoacanthosis nigricans · Narcotic dermopathy · · |

| v · t · e · | **Hypersensitivity and autoimmune diseases (279.5–6)** | | |
|---|---|---|---|
| **Type I / allergy / atopy (IgE)** | **Foreign** | | Atopic eczema · Allergic urticaria · Allergic rhinitis (Hay fever) · Allergic asthma · Anaphylaxis · Food allergy (common allergies include: Milk · Egg · Peanut · Tree nut · Seafood · Soy · Wheat · · Penicillin allergy · |
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| | **Autoimmune** | **Cytotoxic** | Autoimmune hemolytic anemia · Immune thrombocytopenic purpura · Bullous pemphigoid · Pemphigus vulgaris · Rheumatic fever · Goodpasture's syndrome · Guillain–Barré syndrome · |
| | | **"Type V" / receptor** | Graves' disease · Myasthenia gravis · Pernicious anemia · |
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| | **Autoimmune** | | Diabetes mellitus type 1 · Hashimoto's thyroiditis · Multiple sclerosis · Coeliac disease · Giant-cell arteritis · Postorgasmic illness syndrome · Reactive arthritis · |
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| **Unknown / multiple** | **Foreign** | | Hypersensitivity pneumonitis (Allergic bronchopulmonary aspergillosis · · Transplant rejection · Latex allergy (I+IV) · |
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# Angular cheilitis

From Wikipedia, the free encyclopedia

**Angular cheilitis** (**AC**), is inflammation of one or both corners of the mouth.[2][4] Often the corners are red with skin breakdown and crusting. It can also be itchy or painful. The condition can last for days to years.[2] Angular cheilitis is a type of cheilitis (inflammation of the lips).[5]

Angular cheilitis can be caused by infection, irritation, or allergies. Infections include by the fungi such as *Candida albicans* and bacteria such as *Staph. aureus*. Irritants include poorly fitting dentures, licking the lips or drooling, mouth breathing resulting in a dry mouth, sun exposure, overclosure of the mouth, smoking, and minor trauma. Allergies may include to substances like toothpaste, makeup, and food. Often a number of factors are involved.[2] Other factors may include poor nutrition or poor immune function.[2][4] Diagnosis may be helped by testing for infections and patch testing for allergies.[2]

Treatment for angular cheilitis is typically based on the underlying causes along with the use of a barrier cream. Frequently an antifungal and antibacterial cream is also tried. Angular cheilitis is a fairly common problem,[2] with estimates that it affects 0.7% of the population.[6] It occurs most often in the 30s to 60s, although is also relatively common in children.[2] In the developing world, iron and vitamin deficiencies are a common cause.[4]

Contents



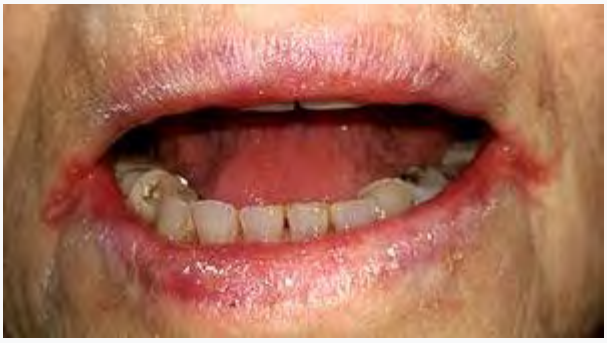
## Variants

## More

## Search

**Angular cheilitis**

**Synonyms** Ragades,[1] perlèche, cheilosis, angular cheilosis, commissural cheilitis, angular stomatitis[2]



Bilateral angular cheilitis in an elderly individual with false teeth, iron deficiency anemia and xerostomia

**Pronunciation** /kaɪˈlaɪtɪs/

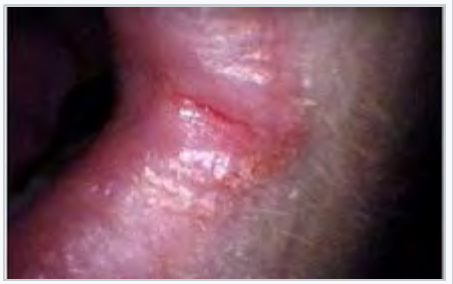
**Classification and external resources**

| | |
|---|---|
| **Specialty** | Dermatology |
| **ICD-10** | K13.0 |
| **ICD-9-CM** | 528.5, 686.8 |
| **MeSH** | D002613 |

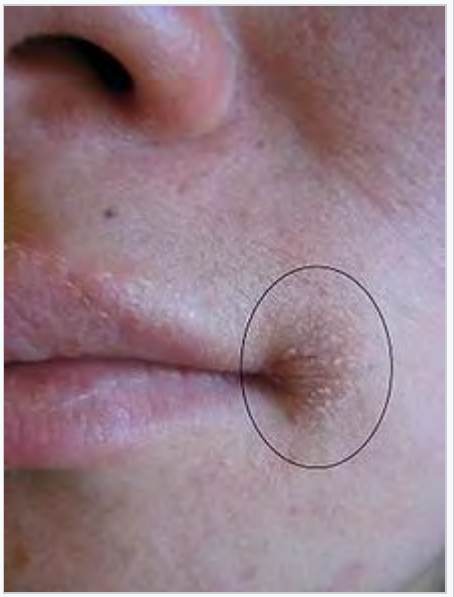
[edit on Wikidata]

## Signs and symptoms [edit]

Angular cheilitis is a fairly non specific term which describes the presence of an inflammatory lesion in a particular anatomic site (i.e. the corner of the mouth). As there are different possible causes and contributing factors from one person to the next, the appearance of the lesion is somewhat variable. The lesions are more commonly symmetrically present on both sides of the mouth,[3] but sometimes only one side may be affected. In some cases, the lesion may be confined to the mucosa of the lips, and in other cases the lesion may extend past the vermilion border (the edge where the lining on the lips becomes the skin on the face) onto the facial skin. Initially, the corners of the mouth develop a gray-white thickening and adjacent erythema (redness).[2] Later, the usual appearance is a roughly triangular area of erythema, edema (swelling) and breakdown of skin at either corner of the mouth.[2][3] The mucosa of the lip may become fissured (cracked), crusted, ulcerated or atrophied.[2][3] There is not usually any bleeding.[7] Where the skin is involved, there may be radiating rhagades (linear fissures) from the corner of the mouth. Infrequently, the dermatitis (which may resemble eczema) can extend from the corner of the mouth to the skin of the cheek or chin.[3] If *Staphylococcus aureus* is involved, the lesion may show golden yellow crusts.[8] In chronic angular cheilitis, there may be suppuration (pus formation), exfoliation (scaling) and formation of granulation tissue.[2][3]



Angular cheilitis – a fissure running in the corner of the mouth with reddened, irritated facial skin adjacent.



A fairly mild case of angular cheilitis extending onto the facial skin in a young person (affected area is within the black oval).

Sometimes contributing factors can be readily seen, such as loss of lower face height from poorly made or worn dentures, which results in mandibular overclosure ("collapse of jaws").[9] If there is a nutritional deficiency underlying the condition, various other signs and symptoms such as glossitis (swollen tongue) may be present. In people with angular cheilitis who wear dentures, often there may be erythematous mucosa underneath the denture (normally the upper denture), an appearance consistent with denture-related stomatitis.[3] Typically the lesions give symptoms of soreness, pain, pruritus (itching) or burning or a raw feeling.[2][9]

## Causes [edit]

Angular cheilitis is thought to be multifactorial disorder of infectious origin,[10] with many local and systemic predisposing factors.[11] The sores in angular cheilitis are often infected with fungi (yeasts), bacteria, or a combination thereof;[8] this may represent a secondary, opportunistic infection by these pathogens. Some studies have linked the initial onset of angular cheilitis with nutritional deficiencies, especially of the B(B2-riboflavin) vitamins and iron (which causes iron deficiency anemia),[12] which in turn may be evidence of malnutrition or malabsorption. Angular cheilitis can be a manifestation of contact dermatitis,[13] which is considered in two groups; irritational and allergic.

### Infection [edit]

The involved organisms are:

- Candida species alone (usually *Candida albicans*), which accounts for about 20% of cases,[14]
- Bacterial species, either:

- *Staphylococcus aureus* alone, which accounts for about 20% of cases,[14]
- β-hemolytic streptococci alone. These types of bacteria have been detected in between 8–15% of cases of angular cheilitis,[2] but less commonly are they present in isolation,[10]

- Or a combination of the above organisms, (a polymicrobial infection)[8] with about 60% of cases involving both *C. albicans* and *S. aureus*.[14][15]

Candida can be detected in 93% of angular cheilitis lesions.[2] This organism is found in the mouths of about 40% of healthy individuals, and it is considered by some to be normal commensal component of the oral microbiota.[2] However, Candida shows dimorphism, namely a yeast form which is thought to be relatively harmless and a pathogenic hyphal form which is associated with invasion of host tissues. Potassium hydroxide preparation is recommended by some to help distinguish between the harmless and the pathogenic forms, and thereby highlight which cases of angular cheilitis are truly caused by Candida.[2] The mouth may act as a reservoir of Candida that reinfects the sores at the corners of the mouth and prevents the sores from healing.

A lesion caused by recurrence of a latent herpes simplex infection can occur in the corner of the mouth. Really this is herpes labialis (a cold sore), and is sometimes termed "angular herpes simplex".[2] A cold sore at the corner of the mouth behaves similarly to elsewhere on the lips, and follows a pattern of vesicle (blister) formation followed by rupture leaving a crusted sore which resolves in about 7–10 days, and recurs in the same spot periodically, especially during periods of stress. Rather than utilizing antifungal creams, angular herpes simplex is treated in the same way as a cold sore, with topical antiviral drugs such as aciclovir.

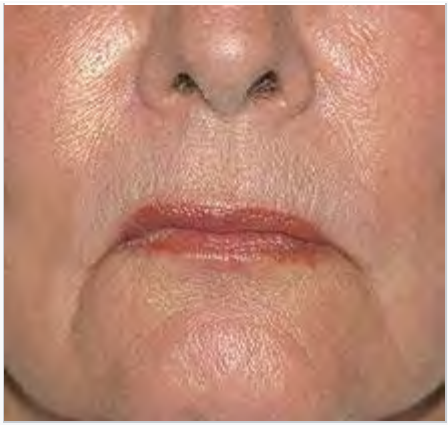
## Irritation contact dermatitis [edit]

*Main article: Irritant contact dermatitis*

22% of cases of angular cheilitis are due to irritants.[2] Saliva contains digestive enzymes, which may have a degree of digestive action on tissues if they are left in contact.[2] The corner of the mouth is normally exposed to saliva more than any other part of the lips. Reduced lower facial height (vertical dimension or facial support) is usually caused by edentulism (tooth loss), or wearing worn down, old dentures or ones which are not designed optimally. This results in overclosure of the mandible (collapse of the jaws),[9] which extenuates the angular skin folds at the corners of the mouth,[14] in effect creating an intertriginous skin crease. The tendency of saliva to pool in these areas is increased, constantly wetting the area,[10] which may cause tissue maceration and favors the development of a yeast infection.[14] As such, angular cheilitis is more commonly seen in edentulous people (people without any teeth).[9] It is by contrast uncommon in persons who retain their natural teeth.[16] Angular cheilitis is also commonly seen in denture wearers.[13] Angular cheilitis is present in about 30% of people with denture-related stomatitis.[10] It is thought that reduced vertical dimension of the lower face may be a contributing factor in up to 11% of elderly persons with angular cheilitis and in up to 18% of denture wearers who have angular cheilitis.[2] Reduced vertical dimension can also be caused by tooth migration, wearing orthodontic appliances, and elastic tissue damage caused by ultraviolet light exposure and smoking.[2]

A famous sketch by Leonardo da Vinci in preparation to depict the face of Judas Iscariot in The Last supper. The subject shows overclosure of the jaws and loss of facial support around the mouth.

Habits or conditions that keep the corners of the mouth moist might include chronic lip licking, thumb sucking (or sucking on other objects such as pens, pipes, lollipops), dental cleaning (e.g. flossing), chewing gum, hypersalivation, drooling and mouth breathing.[2][3][14] Some consider habitual lip licking or picking to be a form of nervous tic, and



Pronounced skin folds extending from the corner of the mouth.

do not consider this to be true angular cheilitis,[3] instead calling it *perlèche* (derived from the French word *pourlècher* meaning "to lick one's lips"),[2] or "factitious cheilitis" is applied to this habit.[2] The term "cheilocandidiasis" describes exfoliative (flaking) lesions of the lips and the skin around the lips, and is caused by a superficial candidal infection due to chronic lip licking.[14] Less severe cases occur during cold, dry weather, and is a form of chapped lips. Individuals may lick their lips in an attempt to provide a temporary moment of relief, only serving to worsen the condition.[17]

The sunscreen in some types of lip balm degrades over time into an irritant. Using expired lipbalm can initiate mild angular cheilitis, and when the person applies more lipbalm to alleviate the cracking, it only aggravates it. Because of the delayed onset of contact dermatitis and the recovery period lasting days to weeks, people typically do not make the connection between the causative agent and the symptoms.[*medical citation needed*]

## Nutritional deficiencies [edit]

Several different nutritional deficiency states of vitamins or minerals have been linked to AC.[4] It is thought that in about 25% of people with AC, iron deficiency or deficiency of B vitamins are involved.[4] Nutritional deficiencies may be a more common cause of AC in third world countries.[4] Chronic iron deficiency may also cause koilonychia (spoon shaped deformity of the fingernails) and glossitis (inflammation of the tongue). It is not completely understood how iron deficiency causes AC, but it is known that it causes a degree of immunocompromise (decreased efficiency of the immune system) which may in turn allow an opportunistic infection of candida.[4] Vitamin B2 deficiency (ariboflavinosis) may also cause AC, and other conditions such as redness of mucous membranes, magenta colored glossitis (pink inflammation of the tongue).[4] Vitamin B5 deficiency may also cause AC, along with glossitis, and skin changes similar to seborrhoeic dermatitis around the eyes, nose and mouth.[4] Vitamin B12 deficiency is sometimes responsible for AC, and commonly occurs together with folate deficiency (a lack of folic acid), which also causes glossitis and megaloblastic anemia.[4] Vitamin B3 deficiency (pellagra) is another possible cause, and in which other association conditions such as dermatitis, diarrhea, dementia and glossitis can occur.[4] Biotin (vitamin B7) deficiency has also been reported to cause AC, along with alopecia (hair loss) and dry eyes.[4] Zinc deficiency is known to cause AC.[18] Other symptoms may include diarrhea, alopecia and dermatitis.[4] Acrodermatitis enteropathica is an autosomal recessive genetic disorder causing impaired absorption of zinc, and is associated with AC.[4]

In general, these nutritional disorders may be caused by malnutrition, such as may occur in alcoholism or in strict vegan diets, or by malabsorption secondary to gastrointestinal disorders (e.g. Celiac disease or chronic pancreatitis) or gastrointestinal surgeries (e.g. pernicious anemia caused by ileal resection in Crohn's disease).[4]

## Systemic disorders [edit]

Some systemic disorders are involved in angular cheilitis by virtue of their association with malabsorption and the creation of nutritional deficiencies described above. Such examples include people with anorexia nervosa.[4] Other disorders may cause lip enlargement (e.g. orofacial granulomatosis),[4] which alters the local anatomy and extenuates the skin folds at the corners of the mouth. More still may be involved because they affect the immune system, allowing normally harmless organisms like Candida to become pathogenic and cause an infection. Xerostomia (dry mouth) is thought to account for about 5% of cases of [4]

AC. Xerostomia itself has many possible causes, but commonly the cause may be side effects of medications, or conditions such as Sjögren's syndrome. Conversely, conditions which cause drooling or sialorrhoea (excessive salivation) can cause angular cheilitis by creating a constant wet environment in the corners of the mouth. About 25% of people with Down syndrome appear to have AC.[4] This is due to relative macroglossia, an apparently large tongue in a small mouth, which may constantly stick out of the mouth causing maceration of the corners of the mouth with saliva. Inflammatory bowel diseases (such as Crohn's disease or ulcerative colitis) can be associated with angular cheilitis.[3] In Crohn's, it is likely the result of malabsorption and immunosuppressive therapy which gives rise to the sores at the corner of the mouth.[9] Glucagonomas are rare pancreatic endocrine tumors which secrete glucagon, and cause a syndrome of dermatitis, glucose intolerance, weight loss and anemia. AC is a common feature of glucagonoma syndrome.[19] Infrequently, angular cheilitis may be one of the manifestations of chronic mucocutaneous candidiasis,[14] and sometimes cases of oropharyngeal or esophageal candidiasis may accompany angular cheilitis.[2] Angular cheilitis may be present in human immunodeficiency virus infection,[11] neutropenia,[16] or diabetes.[3] Angular cheilitis is more common in people with eczema because their skin is more sensitive to irritants.[2] Other conditions possibly associated include plasma cell gingivitis,[7] Melkersson-Rosenthal syndrome,[4] or sideropenic dysphagia (also called Plummer-Vinson syndrome or Paterson-Brown-Kelly syndrome).[4]

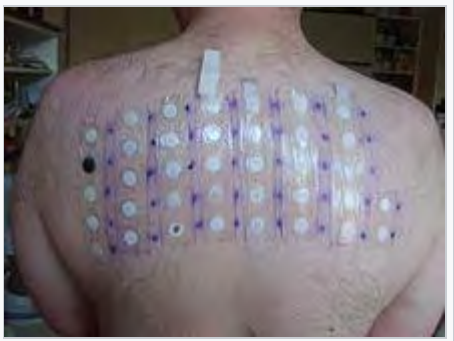
### Drugs [edit]

Several drugs may cause AC as a side effect, by various mechanisms, such as creating drug-induced xerostomia. Various examples include isotretinoin, indinavir, and sorafenib.[4] Isotretinoin (Accutane), an analog of vitamin A, is a medication which dries the skin. Less commonly, angular cheilitis is associated with primary hypervitaminosis A,[20] which can occur when large amounts of liver (including cod liver oil and other fish oils) are regularly consumed or as a result from an excess intake of vitamin A in the form of vitamin supplements. Recreational drug users may develop AC. Examples include cocaine, methamphetamines, heroin, and hallucinogens.[4]

### Allergic contact dermatitis [edit]

*See also: Allergic contact cheilitis, Allergic contact dermatitis, and Allergic contact stomatitis*

Allergic reactions may account for about 25–34% of cases of generalized cheilitis (i.e., inflammation not confined to the angles of the mouth). It is unknown how frequently allergic reactions are responsible for cases of angular cheilitis, but any substance capable of causing generalized allergic cheilitis may present involving the corners of the mouth alone.



Patch test

Examples of potential allergens include substances that may be present in some types of lipstick, toothpaste, acne products, cosmetics, chewing gum, mouthwash, foods, dental appliances, and materials from dentures or mercury containing amalgam fillings.[2] It is usually impossible to tell the difference between irritant contact dermatitis and allergic contact dermatitis without a patch test.

## Diagnosis [edit]

Angular chielitis is normally a diagnosis made clinically. If the sore is unilateral, rather than bilateral, this suggests a local factor (*e.g.*, trauma) or a split syphilitic papule.[3][21] Angular cheilitis caused by mandibular overclosure, drooling, and other irritants is usually bilateral.[2]

The lesions are normally swabbed to detect if Candida or pathogenic bacterial species may be present. Persons with angular cheilitis who

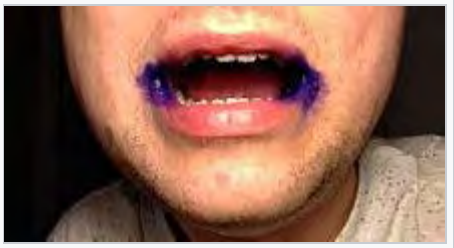
wear dentures often also will have their denture swabbed in addition. A complete blood count (full blood count) may be indicated, including assessment of the levels of iron, ferritin, vitamin B12 (and possibly other B vitamins), and folate.[3]

Photographic Comparison of: 1) a Canker Sore - inside the mouth, 2) Herpes, 3) Angular Cheilitis and 4) Chapped Lips.

## Classification [edit]

Angular cheilitis could be considered to be a type of cheilitis or stomatitis. Where Candida species are involved, angular cheilitis is classed as a type of oral candidiasis, specifically a primary (group I) Candida-associated lesion.[11] This form angular cheilitis which is caused by Candida is sometimes termed "Candida-associated angular cheilitis",[11] or less commonly, "monilial perlèche".[2] Angular cheilitis can also be classified as acute (sudden, short-lived appearance of the condition) or chronic (lasts a long time or keeps returning), or refractory (the condition persists despite attempts to treat it).[2]

# Management [edit]



Angular cheilitis being treated with crystal violet tincture

There are 4 aspects to the treatment of angular cheilitis.[22] Firstly, potential reservoirs of infection inside the mouth are identified and treated.[22] Oral candidiasis, especially denture-related stomatitis is often found to be present where there is angular cheilitis, and if it is not treated, the sores at the corners of the mouth may often recur.[8][13] This involves having dentures properly fitted and disinfected. Commercial preparations are marketed for this purpose, although dentures may be left in dilute (1:10 concentration) household bleach overnight, but only if they are entirely plastic and do not contain any metal parts, and with rinsing under clean water before use.[9] Improved denture hygiene is often required thereafter, including not wearing the denture during sleep and cleaning it daily.[3] For more information, see Denture-related stomatitis.

Secondly, there may be a need to increase the vertical dimension of the lower face to prevent overclosure of the mouth and formation of deep skin folds.[22] This may require the construction of a new denture with an adjusted bite.[3] Rarely, in cases resistant to normal treatments, surgical procedures such as collagen injections (or other facial fillers such as autologous fat or crosslinked hyaluronic acid) are used in an attempt to restore the normal facial contour.[2][3] Other measures which seek to reverse the local factors that may be contributing to the condition include improving oral hygiene, stopping smoking or other tobacco habits and use of a barrier cream (e.g. zinc oxide paste) at night.[2]

Thirdly, treatment of the infection and inflammation of the lesions themselves is addressed. This is usually with topical antifungal medication,[8] such as clotrimazole,[14] amphotericin B,[22] ketoconazole,[16] or nystatin cream.[9] Some antifungal creams are combined with corticosteroids such as hydrocortisone[8] or triamcinolone[9] to reduce inflammation, and certain antifungals such as miconazole also have some antibacterial action.[8] Diiodohydroxyquinoline is another topical therapy for angular cheilitis.[14] If *Staphylococcus aureus* infection is demonstrated by microbiological culture to be responsible (or suspected), the treatment may be changed to fusidic acid cream,[8] an antibiotic which is effective against this type of bacteria. Aside from fusidic acid, neomycin,[22] mupirocin,[2] metronidazole,[7] and chlorhexidine[22] are alternative options in this scenario.

Finally, if the condition appears resistant to treatment, investigations for underlying causes such as anemia or nutrient deficiencies or HIV infection.[22] Identification of the underlying cause is essential for treating chronic cases. The lesions may resolve when the underlying disease is treated, e.g. with a course of oral iron or B vitamin supplements.[3] Patch testing is recommended by some in cases which are resistant to treatment and where allergic contact dermatitis is suspected.[2]

## Prognosis [edit]

Most cases of angular cheilitis respond quickly when antifungal treatment is used.[16] In more long standing cases, the severity of the condition often follows a relapsing and remitting course over time.[14] The condition can be difficult to treat and can be prolonged.[3]

## Epidemiology [edit]

AC is a relatively common condition,[11] accounting for between 0.7 – 3.8% of oral mucosal lesions in adults and between 0.2 – 15.1% in children, though overall it occurs most commonly in adults in the third to sixth decades of life.[2][3] It occurs worldwide, and both males and females are affected.[3] Angular cheilitis is the most common presentation of fungal and bacterial infections of the lips.[14]

## References [edit]


1. ^ Pindborg, Jens Jørgen (1973). *Atlas of Diseases of the Oral Mucosa*. Saunders. ISBN 9780721672649. Retrieved 17 September 2014. "Angular cheilosis: The lateral lip fissures, well known among denture wearers, have been called by a variety of names, such as "rhagades", "perleche", "angular cheilitis", and "angular cheilosis"."
2. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af ag ah ai* Park, KK; Brodell, RT; Helms, SE (June 2011). "Angular cheilitis, part 1: local etiologies". *Cutis*. **87** (6): 289–95. PMID 21838086.
3. ^ *a b c d e f g h i j k l m n o p q r s t* Scully, Crispian (2008). *Oral and maxillofacial medicine : the basis of diagnosis and treatment* (2nd ed.). Edinburgh: Churchill Livingstone. pp. 147–149. ISBN 9780443068188.
4. ^ *a b c d e f g h i j k l m n o p q r s t u v w* Park, KK; Brodell RT; Helms SE. (July 2011). "Angular cheilitis, part 2: nutritional, systemic, and drug-related causes and treatment" (PDF). *Cutis*. **88** (1): 27–32. PMID 21877503.
5. ^ Martin, Elizabeth (2015). *Concise Medical Dictionary*. Oxford University Press. p. 136. ISBN 9780199687817.
6. ^ Lyons, Faye (2014). *Dermatology for the Advanced Practice Nurse*. Springer Publishing Company. p. 95. ISBN 9780826136442.
7. ^ *a b c* Wood, NK; Goaz, PW (1997). *Differential diagnosis of oral and maxillofacial lesions* (5th ed.). St. Louis [u.a.]: Mosby. pp. 64, 65, 85. ISBN 978-0815194323.
8. ^ *a b c d e f g h* Coulthard P, Horner K, Sloan P, Theaker E (2008). *Master dentistry volume 1, oral and maxillofacial surgery, radiology, pathology and oral medicine* (2nd ed.). Edinburgh: Churchill Livingstone/Elsevier. pp. 180–181. ISBN 9780443068966.
9. ^ *a b c d e f g h* Treister NS, Bruch JM (2010). *Clinical pathology* (3rd ed.). Oxford: Oxford Univ. Press. pp. 197–198. ISBN 0192628941.
11. ^ *a b c d e* Tyldesley WR, Field A, Longman L (2003). *Tyldesley's Oral medicine* (5th ed.). Oxford: Oxford University Press. pp. 37, 40, 46, 63–67. ISBN 0192631470.
12. ^ MedlinePlus (2005-08-01). "Riboflavin (vitamin $B_2$) deficiency (ariboflavinosis)". National Institutes of Health.
13. ^ *a b c* Peter C. Schalock, M.D.; Jeffrey T. S. Hsu, M.D.; Kenneth A. Arndt (eds.). *Primary Care Dermatology*. Lippincott Williams & Wilkins, 2010. p. 265. ISBN 978-0-7817-9378-0.
14. ^ *a b c d e f g h i j k l* Neville BW, Damm DD, Allen CA, Bouquot JE (2002). *Oral & maxillofacial pathology* (2nd ed.). Philadelphia: W.B. Saunders. pp. 100, 192, 196, 266. ISBN 0721690033.
15. ^ Kerawala C; Newlands C, eds. (2010). *Oral and maxillofacial surgery*. Oxford: Oxford University Press. p. 446. ISBN 9780199204830.
16. ^ *a b c d* Greenberg MS, Glick M (2003). *Burket's oral medicine diagnosis & treatment* (10th ed.). Hamilton, Ont.: BC Decker. pp. 97,98,550. ISBN 1550091867.
17. ^ Gibson, Lawrence E., M.D., "Dry Skin", Mayo Clinic
18. ^ Gaveau D, Piette F, Cortot A, Dumur V, Bergoend H (1987). "[Cutaneous manifestations of zinc deficiency in ethylic cirrhosis].". *Ann Dermatol Venereol*. **114** (1): 39–53. PMID 3579131.
19. ^ Tadataka Yamada; David Alpers; Anthony Kalloo; Neil Kaplowitz; Chung Owyang; Don Powell, eds. (2009). *Textbook of gastroenterology* (5th ed.). Chichester, West Sussex: Blackwell Pub. pp. 1882–1883. ISBN 978-1-4051-6911-0.
20. ^ Kliegman: Nelson Textbook of Pediatrics, 18th ed.
21. ^ Leyse-Wallace, Ruth (29 January 2013). *Nutrition and Mental Health*. CRC Press. p. 246. ISBN 9781439863350. Retrieved 17 September 2014.

*oral medicine and pathology*. New York: Humana Press. pp. 92,93,144. ISBN 978-1-60327-519-4.
10. ^ *a b c d* Soames JV, Southam JC, JV (1999). *Oral*
22. ^ *a b c d e f g* Samaranayake, LP (2009). *Essential microbiology for dentistry* (3rd ed.). Elseveier. pp. 296, 297. ISBN 978-0702041679.

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v · t · e **Oral and maxillofacial pathology (K00–K06, K11–K14, 520–525, 527–529)**

**Lips**

Cheilitis (Actinic · **Angular** · Plasma cell · · Cleft lip · Congenital lip pit · Eclabium · Herpes labialis · Macrocheilia · Microcheilia · Nasolabial cyst · Sun poisoning · Trumpeter's wart ·

**Tongue**

Ankyloglossia · Black hairy tongue · Caviar tongue · Crenated tongue · Cunnilingus tongue · Fissured tongue · Foliate papillitis · Glossitis (Geographic tongue · Median rhomboid glossitis · Transient lingual papillitis · · Glossoptosis · Hypoglossia · Lingual thyroid · Macroglossia · Microglossia · Rhabdomyoma ·

**Palate**

Bednar's aphthae · Cleft palate · High-arched palate · Palatal cysts of the newborn · Inflammatory papillary hyperplasia · Stomatitis nicotina · Torus palatinus ·

**Oral mucosa** - *Lining of mouth*

Amalgam tattoo · Angina bullosa haemorrhagica · Behçet syndrome · Bohn's nodules · Burning mouth syndrome · Candidiasis · Condyloma acuminatum · Darier's disease · Epulis fissuratum · Erythema multiforme · Erythroplakia · Fibroma (Giant-cell · · Focal epithelial hyperplasia · Fordyce spots · Hairy leukoplakia · Hand, foot and mouth disease · Hereditary benign intraepithelial dyskeratosis · Herpangina · Herpes zoster · Intraoral dental sinus · Leukoedema · Leukoplakia · Lichen planus · Linea alba · Lupus erythematosus · Melanocytic nevus · Melanocytic oral lesion · Molluscum contagiosum · Morsicatio buccarum · Oral cancer (*Benign:* Squamous cell papilloma · Keratoacanthoma · *Malignant:* Adenosquamous carcinoma · Basaloid squamous carcinoma · Mucosal melanoma · Spindle cell carcinoma · Squamous cell carcinoma · Verrucous carcinoma · · Oral florid papillomatosis · Oral melanosis (Smoker's melanosis · · Pemphigoid (Benign mucous membrane · · Pemphigus · Plasmoacanthoma · Stomatitis (Aphthous · Denture-related · Herpetic · · Smokeless tobacco keratosis · Submucous fibrosis · Ulceration · Verruca vulgaris · Verruciform xanthoma · White sponge nevus ·

**Teeth (pulp, dentin, enamel)**

Amelogenesis imperfecta · Ankylosis · Anodontia · Caries (Early childhood caries · · Concrescence · Failure of eruption of teeth · Dens evaginatus (Talon cusp · · Dentin dysplasia · Dentin hypersensitivity · Dentinogenesis imperfecta · Dilaceration · Discoloration · Ectopic enamel · Enamel hypocalcification · Enamel hypoplasia (Turner's hypoplasia · · Enamel pearl · Fluorosis · Fusion · Gemination · Hyperdontia · Hypodontia (Maxillary lateral incisor agenesis · · Impaction (Wisdom tooth impaction · · Macrodontia · Meth mouth · Microdontia · Odontogenic tumors (Keratocystic odontogenic tumour · · Odontoma (Dens in dente · · Open contact · Premature eruption (Neonatal teeth · · Pulp calcification (Pulp stone · · Pulp canal obliteration · Pulp necrosis · Pulp polyp · Pulpitis · Regional odontodysplasia · Resorption · Shovel-shaped incisors · Supernumerary root · Taurodontism · Trauma (Avulsion · Cracked tooth syndrome · Vertical root fracture · Occlusal · · Tooth loss (Edentulism · · Tooth wear (Abrasion · Abfraction · Acid erosion · Attrition · ·

**Periodontium (gingiva, periodontal ligament, cementum, alveolus)** - *Gums and tooth-supporting structures*

Cementicle · Cementoblastoma (Gigantiform · · Cementoma · Eruption cyst · Epulis (Pyogenic granuloma · Congenital epulis · · Gingival enlargement · Gingival cyst of the adult · Gingival cyst of the newborn · Gingivitis (Desquamative · Granulomatous · Plasma cell · · Hereditary gingival fibromatosis · Hypercementosis · Hypocementosis · Linear gingival erythema · Necrotizing periodontal diseases (Acute necrotizing ulcerative gingivitis · · Pericoronitis · Peri-implantitis · Periodontal abscess · Periodontal trauma · Periodontitis (Aggressive · As a manifestation of systemic disease · Chronic · · Perio-endo lesion · Teething ·

**Periapical, mandibular and maxillary hard tissues -** *Bones of jaws*

Agnathia · Alveolar osteitis · Buccal exostosis · Cherubism · Idiopathic osteosclerosis · Mandibular fracture · Micrognathia · Micrognathia · Intraosseous cysts (*Odontogenic:* periapical · Dentigerous · Buccal bifurcation · Lateral periodontal · Globulomaxillary · Calcifying odontogenic · Glandular odontogenic · *Non-odontogenic:* Nasopalatine duct · Median mandibular · Median palatal · Traumatic bone · · Osteoma · Osteomyelitis · Osteonecrosis (Bisphosphonate-associated · Neuralgia-inducing cavitational osteonecrosis · Osteoradionecrosis · · Osteoporotic bone marrow defect · Paget's disease of bone · Periapical abscess (Phoenix abscess · · Periapical periodontitis · Stafne defect · Torus mandibularis ·

**Temporomandibular joints, muscles of mastication and malocclusions -** *Jaw joints, chewing muscles and bite abnormalities*

Bruxism · Condylar resorption · Mandibular dislocation · Malocclusion (Crossbite · Open bite · Overbite · Overjet · Prognathia · Retrognathia · · Temporomandibular joint dysfunction ·

**Salivary glands**

Benign lymphoepithelial lesion · Ectopic salivary gland tissue · Frey's syndrome · HIV salivary gland disease · Necrotizing sialometaplasia · Mucocele (Ranula · · Pneumoparotitis · Salivary duct stricture · Salivary gland aplasia · Salivary gland atresia · Salivary gland diverticulum · Salivary gland fistula · Salivary gland hyperplasia · Salivary gland hypoplasia · Salivary gland neoplasms (*Benign:* Basal cell adenoma · Canalicular adenoma · Ductal papilloma · Monomorphic adenoma · Myoepithelioma · Oncocytoma · Papillary cystadenoma lymphomatosum · Pleomorphic adenoma · Sebaceous adenoma · *Malignant:* Acinic cell carcinoma · Adenocarcinoma · Adenoid cystic carcinoma · Carcinoma ex pleomorphic adenoma · Lymphoma · Mucoepidermoid carcinoma · · Sclerosing polycystic adenosis · Sialadenitis (Parotitis · Chronic sclerosing sialadenitis · · Sialectasis · Sialocele · Sialodochitis · Sialosis · Sialolithiasis · Sjögren's syndrome ·

**Orofacial soft tissues -** *Soft tissues around the mouth*

Actinomycosis · Angioedema · Basal cell carcinoma · Cutaneous sinus of dental origin · Cystic hygroma · Gnathophyma · Ludwig's angina · Macrostomia · Melkersson–Rosenthal syndrome · Microstomia · Noma · Oral Crohn's disease · Orofacial granulomatosis · Perioral dermatitis · Pyostomatitis vegetans ·

**Other**

Eagle syndrome · Hemifacial hypertrophy · Facial hemiatrophy · Oral manifestations of systemic disease ·

Categories: Lip disorders | Conditions of the mucous membranes | Mycosis-related cutaneous conditions

# Atopic dermatitis

From Wikipedia, the free encyclopedia

**Atopic dermatitis** (**AD**), also known as **atopic eczema**, is a type of inflammation of the skin (dermatitis). It results in itchy, red, swollen, and cracked skin. Clear fluid may come from the affected areas, which often thicken over time.[1] The condition typically starts in childhood with changing severity over the years.[1][2] In children under one year of age much of the body may be affected. As people get older, the back of the knees and front of the elbows are the most common areas affected. In adults the hands and feet are the most commonly affected areas.[2] Scratching worsens symptoms and affected people have an increased risk of skin infections. Many people with atopic dermatitis develop hay fever or asthma.[1]

The cause is unknown but believed to involve genetics, immune system dysfunction, environmental exposures, and difficulties with the permeability of the skin.[1][2] If one identical twin is affected, there is an 85% chance the other also has the condition.[3] Those who live in cities and dry climates are more commonly affected. Exposure to certain chemicals or frequent hand washing makes symptoms worse. While emotional stress may make the symptoms worse it is not a cause. The disorder is not contagious.[1] The diagnosis is typically based on the signs and symptoms. Other diseases that must be excluded before making a diagnosis include contact dermatitis, psoriasis, and seborrheic dermatitis.[2]

Treatment involves avoiding things that make the condition worse, daily bathing with application of a moisturising cream afterwards, applying steroid creams when flares occur, and medications to help with itchiness.[2] Things that commonly make it worse include wool clothing, soaps, perfumes, chlorine, dust, and cigarette smoke. Phototherapy may be useful in some people. Steroid pills or creams based on calcineurin inhibitors may occasionally be used if other measures are not effective.[1][4] Antibiotics (either by mouth or topically) may be needed if a bacterial infection develops.[2] Dietary changes are only needed if food allergies are suspected.[1]

Atopic dermatitis affects about 20% of people at some point in their lives.[1][5] It is more common in younger children.[2] Males and females are equally affected.[1] Many people outgrow the condition.[2] Atopic dermatitis is sometimes called eczema, a term that also refers to a larger group of skin conditions.[1] Other names include "infantile eczema", "flexural eczema", "prurigo Besnier", "allergic eczema", and "neurodermatitis".[6]



## Variants

**Atopic dermatitis**

Atopic dermatitis of the inside crease of the elbow.

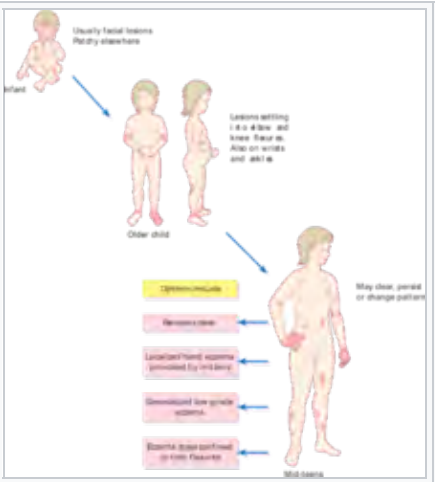
| Classification and external resources | |
|---|---|
| **Specialty** | Dermatology |
| **ICD-10** | L20 |
| **ICD-9-CM** | 691.8 |
| **OMIM** | 603165 |
| **DiseasesDB** | 4113 |
| **MedlinePlus** | 000853 |
| **eMedicine** | emerg/130 derm/38 ped/2567 oph/479 |
| **MeSH** | D003876 |

[edit on Wikidata]

## Signs and symptoms [edit]

People with AD often have dry and scaly skin that spans the entire body, except perhaps the diaper area, and intensely itchy red, splotchy, raised lesions to form in the bends of the arms or legs, face, and neck.[7][8][9][10][11]

AD commonly occurs on the eyelids where signs such as Dennie-Morgan infraorbital fold, infra-auricular fissure, periorbital pigmentation can be seen.[12] Post-inflammatory hyperpigmentation on the neck gives the classic 'dirty neck' appearance. Lichenification, excoriation and erosion or crusting on the trunk may indicate secondary infection. Flexural distribution with ill-defined edges with or without hyperlinearily on the wrist, finger knuckles, ankle, feet and hand are also commonly seen.[13]



Pattern of atopic eczema varies with age

## Cause [edit]

The cause of AD is not known, although there is some evidence of genetic factors, and some evidence that growing up in a *sanitary* environment encourages AD.[8]

It seems to have a genetic component. Many people with AD have a family history of atopy. Atopy is an immediate-onset allergic reaction (type 1 hypersensitivity reaction) as asthma, food allergies, AD or hay fever.[7][8] In 2006 it was discovered that mutations in the gene for the production of filaggrin strongly increased the risk for developing atopic dermatitis. Most importantly two mutations were found that affect approximately 5% of people in Western Europe that may disrupt the production of filaggrin. Filaggrin is a protein that plays an important role in the retention of water in the stratum corneum. People who have these mutations often have dry skin.[14] Filaggrin also plays an important role in keeping the skin surface slightly acidic, hence giving it anti-microbial effects. It breaks down into trans-urocanic acid, which keeps the pH low.[15]

According to the hygiene hypothesis, when children are brought up exposed to allergens in the environment at a young age, their immune system is more likely to tolerate them, while children brought up in a modern "sanitary" environment are less likely to be exposed to those allergens at a young age, and, when they are finally exposed, develop allergies. There is some support for this hypothesis with respect to AD.

Those exposed to dogs while growing up have a lower risk of atopic dermatitis.[16] There is also support from epidemiological studies for a protective role for helminths against AD.[17] Likewise children with poor hygiene are at a lower risk for developing AD, as are children who drink unpasteurised milk.[17] Exposure to dust mites is believed to contribute to one's risk of developing AD.[18]

A diet high in fruits seems to have a protective effect against AD, whereas the opposite seems true for fast foods.[17]

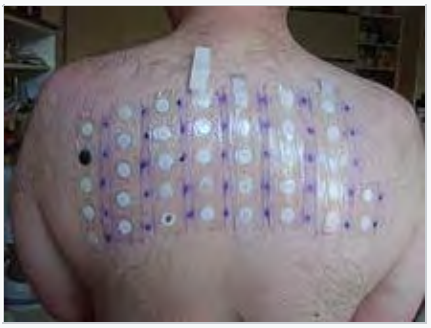
Atopic dermatitis sometimes appears associated with celiac disease and non-celiac gluten sensitivity.[19][20]

## Diagnosis [edit]

*See also: SCORAD*

An atopy patch test can be used to determine whether or not a specific allergen is the cause of the rash. The test involves applying a series of allergens to the skin surface and evaluating the results in one to three days.[21][22]

People with atopic dermatitis are more likely to have Staphylococcus aureus living on them.[23]



Patch test

## Treatments [edit]

There is no known cure for AD, although treatments may reduce the severity and frequency of flares.[7]

### Lifestyle [edit]

Applying moisturisers may prevent the skin from drying out and decrease the need for other medications.[24] Affected persons often report that improvement of skin hydration parallels with improvement in AD symptoms.[7]

Health professionals often recommend that persons with AD bathe regularly in lukewarm baths, especially in salt water, to moisten their skin.[8][25] Avoiding woollen clothing is usually good for those with AD. Likewise silk, silver-coated clothing may help.[25] Dilute bleach baths have also been reported effective at managing AD.[25]

### Diet [edit]

Vitamin D is an effective treatment for AD.[26]

Studies have investigated the role of long chain polyunsaturated fatty acids (LCPUFA) supplementation and LCPUFA status in the prevention and treatment of atopic diseases, but the results are controversial. It remains unclear if the nutritional intake of n-3 fatty acids has a clear preventive or therapeutic role, or if n-6 fatty acids consumption promotes atopic diseases.[27]

Several probiotics seem to have a positive effect with a roughly 20% reduction in the rate of atopic dermatitis.[28] The best evidence is for multiple strains of bacteria.[29]

In people with celiac disease or non-celiac gluten sensitivity, a gluten free diet improves their symptoms and prevents the occurrence of new outbreaks.[19][20]

### Medication [edit]

Topical corticosteroids, such as hydrocortisone have proven themselves effective in managing AD.[7][8] If topical corticosteroids and moisturisers fail, short-term treatment with topical calcineurin inhibitors like tacrolimus or pimecrolimus may be tried, although they are usually avoided as they can cause skin cancer or lymphoma.[7][30] Alternatively systemic immunosuppressants may be tried such as ciclosporin, methotrexate, interferon gamma-1b, mycophenolate mofetil and azathioprine.[7][31] Antidepressants and naltrexone may be used to control pruritus (itchiness).[32]

### Light [edit]

A more novel form of treatment involves exposure to broad or narrow-band ultraviolet (UV) light. UV radiation exposure has been found to have a localized immunomodulatory effect on affected tissues and may be used to decrease the severity and frequency of flares.[33][34] In particular, the usage of UVA1 is more effective in treating acute flares, whereas narrow-band UVB is more effective in long-term management scenarios.[35] However, UV radiation has also been implicated in various types of skin cancer, and thus UV treatment is not without risk.[36]

## Epidemiology [edit]

Since the beginning of the twentieth century, many mucosal inflammatory disorders have become more common; atopic eczema (AE) is a classic example of such a disease. It now affects 15–30% of children and 2–10% of adults in developed countries and in the United States has nearly tripled in the past thirty to forty years.[8][37] Over 15 million American adults and children have atopic dermatitis.[38]

## Research [edit]

Evidence suggests that IL-4 is central in the pathogenesis of AD.[39] Therefore, there is a rationale for targeting IL-4 with anti-IL-4 inhibitors.[40]

## References [edit]


1. ^ *a b c d e f g h i j* "Handout on Health: Atopic Dermatitis (A type of eczema)". *National Institute of Arthritis and Musculoskeletal and Skin Diseases*. May 2013. Retrieved 19 June 2015.
2. ^ *a b c d e f g h* Tollefson, MM; Bruckner, AL; SECTION ON, DERMATOLOGY; SECTION ON, DERMATOLOGY (December 2014). "Atopic dermatitis: skin-directed management.". *Pediatrics*. **134** (6): e1735–44. doi:10.1542/peds.2014-2812. PMID 25422009.
3. ^ Williams, Hywel (2009). *Evidence-Based Dermatology*. John Wiley & Sons. p. 128. ISBN 9781444300178.
4. ^ Carr, WW (Aug 2013). "Topical calcineurin inhibitors for atopic dermatitis: review and treatment recommendations". *Paediatric drugs*. **15** (4): 303–10. doi:10.1007/s40272-013-0013-9. PMC 3715696. PMID 23549982.
5. ^ Thomsen, SF (2014). "Atopic dermatitis: natural history, diagnosis, and treatment.". *ISRN allergy*. **2014**: 354250. doi:10.1155/2014/354250. PMID 25006501.
6. ^ Williams, Hywel C. (2000). *The epidemiology of atopic dermatitis*. New York: Cambridge University Press. p. 10. ISBN 9780521570756.
7. ^ *a b c d e f g* Berke, R; Singh, A; Guralnick, M (July 2012). "Atopic dermatitis: an overview" (PDF). *American Family Physician*. **86** (1): 35–42. PMID 22962911.
8. ^ *a b c d e f* Kim, BS (21 January 2014). Fritsch, P; Vinson, RP; Perry, V; Quirk, CM; James, WD, eds. "Atopic Dermatitis". *Medscape Reference*. WebMD. Retrieved 3 March 2014.
9. ^ Brehler, R (2009). "Atopic Dermatitis". In Lang, F. *Encyclopedia of molecular mechanisms of diseases*. Berlin: Springer. ISBN 978-3-540-67136-7.
10. ^ Baron, SE; Cohen, SN; Archer, CB (May 2012). "Guidance on the diagnosis and clinical management of atopic eczema" (PDF). *Clinical and Experimental Dermatology*. **37**: 7–12. doi:10.1111/j.1365-2230.2012.04336.x. PMID 22486763.
11. ^ Schmitt, J; Langan, S; Deckert, S; Svensson, A; von Kobyletzki, L; Thomas, K; Spuls, P; Harmonising Outcome Measures for Atopic Dermatitis (HOME) Initiative (December 2013). "Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation.". *The Journal of Allergy and Clinical* PMID 15175142.
22. ^ Jurakić Toncić R, Lipozencić J (2010). "Role and Significance of Atopy Patch Test". *Acta Dermatovenerol Croat*. **18** (1): 38–55. PMID 20361888.
23. ^ Totté, JE; van der Feltz, WT; Hennekam, M; van Belkum, A; van Zuuren, EJ; Pasmans, SG (19 March 2016). "Prevalence and odds of Staphylococcus aureus carriage in atopic dermatitis: a systematic review and meta-analysis.". *The British journal of dermatology*. doi:10.1111/bjd.14566. PMID 26994362.
24. ^ Varothai, S; Nitayavardhana, S; Kulthanan, K (Jun 2013). "Moisturizers for patients with atopic dermatitis." (PDF). *Asian Pacific Journal of Allergy and Immunology*. **31** (2): 91–8. PMID 23859407.
25. ^ *a b c* Lio, PA (October 2013). "Non-pharmacologic therapies for atopic dermatitis". *Current Allergy and Asthma Reports*. **13** (5): 528–538. doi:10.1007/s11882-013-0371-y. PMID 23881511.
26. ^ Samochocki, Z; Bogaczewicz, J; Jeziorkowska, R; Sysa-Jędrzejowska, A; Glińska, O; Karczmarewicz, E; McCauliffe, DP; Woźniacka, A (August 2013). "Vitamin D effects in atopic dermatitis.". *Journal of the American Academy of Dermatology*. **69** (2): 238–44. doi:10.1016/j.jaad.2013.03.014. PMID 23643343.
27. ^ Lohner S, Decsi T. Role of Long-Chain Polyunsaturated Fatty Acids in the Prevention and Treatment of Atopic Diseases. In: Polyunsaturated Fatty Acids: Sources, Antioxidant Properties and Health Benefits (edited by: Angel Catalá). NOVA Publishers. 2013. Chapter 11, pp. 1-24. (ISBN 978-1-62948-151-7)
28. ^ Pelucchi C, Chatenoud L, Turati F, Galeone C, Moja L, Bach JF, La Vecchia C (May 2012). "Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis". *Epidemiology (Cambridge, Mass.)*. **23** (3): 402–414. doi:10.1097/EDE.0b013e31824d5da2. ISSN 1531-5487. PMID 22441545.
29. ^ Chang, YS; Trivedi, MK; Jha, A; Lin, YF; Dimaano, L; García-Romero, MT (1 March 2016). "Synbiotics for Prevention and Treatment of Atopic Dermatitis: A Meta-analysis of Randomized Clinical Trials.". *JAMA pediatrics*. **170** (3): 236–42. doi:10.1001/jamapediatrics.2015.3943. PMID 26810481.
30. ^ http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugS

*Immunology*. **132** (6): 1337–47. doi:10.1016/j.jaci.2013.07.008. PMID 24035157.
12. ^ "The infra-auricular fissure: A bedside marker of disease severity in patients with atopic dermatitis - Journal of the American Academy of Dermatology". *www.jaad.org*. Retrieved 2016-03-20.
13. ^ Lau, Chu-Pak (2006-01-01). *Problem-Based Medical Case Management*. Hong Kong University Press. ISBN 9789622097759.
14. ^ Palmer, CN; Irvine, AD; Terron-Kwiatkowski, A; Zhao, Y; Liao, H; Lee, SP; Goudie, DR; Sandilands, A; Campbell, LE; Smith, FJ; O'Regan, GM; Watson, RM; Cecil, JE; Bale, SJ; Compton, JG; DiGiovanna, JJ; Fleckman, P; Lewis-Jones, S; Arseculeratne, G; Sergeant, A; Munro, CS; El Houate, B; McElreavey, K; Halkjaer, LB; Bisgaard, H; Mukhopadhyay, S; McLean, WH (April 2006). "Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis.". *Nature Genetics*. **38** (4): 441–6. doi:10.1038/ng1767. PMID 16550169.
15. ^ Jungersted JM, Scheer H, Mempel M, et al. (2010). "Stratum corneum lipids, skin barrier function and filaggrin mutations in patients with atopic eczema". *Allergy*. **65**: 911–918. doi:10.1111/j.1398-9995.2010.02326.x.
16. ^ Pelucchi, C; Galeone, C; Bach, JF; La Vecchia, C; Chatenoud, L (September 2013). "Pet exposure and risk of atopic dermatitis at the pediatric age: a meta-analysis of birth cohort studies.". *The Journal of Allergy and Clinical Immunology*. **132** (3): 616–622.e7. doi:10.1016/j.jaci.2013.04.009. PMID 23711545.
17. ^ *a b c* Flohr, C; Mann, J (January 2014). "New insights into the epidemiology of childhood atopic dermatitis" (PDF). *Allergy*. **69** (1): 3–16. doi:10.1111/all.12270.
18. ^ Fuiano, N; Incorvaia, C (June 2012). "Dissecting the causes of atopic dermatitis in children: less foods, more mites." (PDF). *Allergology International*. **61** (2): 231–43. doi:10.2332/allergolint.11-RA-0371. PMID 22361514.[*permanent dead link*]
19. ^ *a b* Fasano A, Sapone A, Zevallos V, Schuppan D (May 2015). "Nonceliac gluten sensitivity". *Gastroenterology* (Review). **148** (6): 1195–204. doi:10.1053/j.gastro.2014.12.049. PMID 25583468. "Many patients with celiac disease also have atopic disorders. Thirty percent of patients' allergies with GI symptoms and mucosal lesions, but negative results from serologic (TG2 antibodies) or genetic tests (DQ2 or DQ8 genotype) for celiac disease, had reduced GI and atopic symptoms when they were placed on GFDs. These findings indicated that their symptoms were related to gluten ingestion. *GFDs = Gluten free diet*"
20. ^ *a b* Mansueto P, Seidita A, D'Alcamo A, Carroccio A (2014). "Non-celiac gluten sensitivity: literature review". *J Am Coll Nutr* (Review). **33** (1): 39–54. doi:10.1080/07315724.2014.869996. PMID 24533607.
21. ^ Kerschenlohr K, Darsow U, Burgdorf WH, Ring J, Wollenberg A (July 2004). "Lessons from atopy patch testing in atopic dermatitis". *Curr Allergy Asthma Rep*. **4** (4): 285–9. doi:10.1007/s11882-004-0072-7.
afetyInformationforPatientsandProviders/ucm051760.htm
31. ^ Yarbrough, KB; Neuhaus, KJ; Simpson, EL (March–April 2013). "The effects of treatment on itch in atopic dermatitis". *Dermatologic Therapy*. **26** (2): 110–119. doi:10.1111/dth.12032. PMID 23551368.
32. ^ Kim, K (Nov 2012). "Neuroimmunological Mechanism of Pruritus in Atopic Dermatitis Focused on the Role of Serotonin." (PDF). *Biomolecules & therapeutics*. **20** (6): 506–512. doi:10.4062/biomolther.2012.20.6.506. PMC 3762292. PMID 24009842.
33. ^ Tintle, S; Shemer, A; Suárez-Fariñas, M; Fujita, H; Gilleaudeau, P; Sullivan-Whalen, M; Johnson-Huang, L; Chiricozzi, A; Cardinale, I; Duan, S; Bowcock, A; Krueger, J. G.; Guttman-Yassky, E (2011). "Reversal of atopic dermatitis with narrow-band UVB phototherapy and biomarkers for therapeutic response". *Journal of Allergy and Clinical Immunology*. **128** (3): 583–93.e1–4. doi:10.1016/j.jaci.2011.05.042. PMC 3448950. PMID 21762976.
34. ^ Beattie, P.E.; Finlan, L.E.; Kernohan, N.M.; Thomson, G.; Hupp, T.R.; Ibbotson, S.H. (2005). "The effect of ultraviolet (UV) A1, UVB and solar-simulated radiation on p53 activation and p21Waf1/Cip1". *British Journal of Dermatology*. **152** (5): 1001–1008. doi:10.1111/j.1365-2133.2005.06557.x. PMID 15888160.
35. ^ Meduri, NB; Vandergriff, T; Rasmussen, H; Jacobe, H (2007). "Phototherapy in the management of atopic dermatitis: a systematic review". *Photodermatology, Photoimmunology & Photomedicine*. **23** (4): 106–112. doi:10.1111/j.1600-0781.2007.00291.x. PMID 17598862.
36. ^ Jans, J; Garinis, GA; Schul, W; Van Oudenaren, A; Moorhouse, M; Smid, M; Sert, YG; Van Der Velde, A; Rijksen, Y; De Gruijl, FR; Van Der Spek, PJ; Yasui, A; Hoeijmakers, JHJ; Leenen, PJM; Van Der Horst, GTJ (2006). "Differential Role of Basal Keratinocytes in UV-Induced Immunosuppression and Skin Cancer". *Molecular and Cellular Biology*. **26** (22): 8515–8526. doi:10.1128/MCB.00807-06. PMC 1636796. PMID 16966369.
37. ^ Saito, Hirohisa (2005). "Much Atopy about the Skin: Genome-Wide Molecular Analysis of Atopic Eczema". *International Archives of Allergy and Immunology*. **137** (4): 319–325. doi:10.1159/000086464. PMID 15970641.
38. ^ Atopic Dermatitis. (2015, January 1). Retrieved April 2, 2015, from http://www.uchospitals.edu/online-library/content=P01675
39. ^ Bao, Lei; Shi, Vivian Y.; Chan, Lawrence S. (2013-02-01). "IL-4 up-regulates epidermal chemotactic, angiogenic, and pro-inflammatory genes and down-regulates antimicrobial genes in vivo and in vitro: relevant in the pathogenesis of atopic dermatitis". *Cytokine*. **61** (2): 419–425. doi:10.1016/j.cyto.2012.10.031. ISSN 1096-0023. PMID 23207180.
40. ^ Di Lernia, Vito (2015-01-01). "Therapeutic strategies in extrinsic atopic dermatitis: focus on inhibition of IL-4 as a new pharmacological approach". *Expert Opinion on Therapeutic Targets*. **19** (1): 87–96. doi:10.1517/14728222.2014.965682. ISSN 1744-

7631. PMID 25283256.

## External links [edit]

- Atopic Dermatitis in children at Allergy UK
- NIH Handout on Health: Atopic Dermatitis
- DermAtlas *9*

Wikimedia Commons has media related to *Atopic dermatitis*.

| v · t · e · | Diseases of the skin and appendages by morphology | | | | |
|---|---|---|---|---|---|
| **Growths** | **Epidermal** | wart · callus · seborrheic keratosis · acrochordon · molluscum contagiosum · actinic keratosis · squamous-cell carcinoma · basal-cell carcinoma · Merkel-cell carcinoma · nevus sebaceous · trichoepithelioma · | | | |
| | **Pigmented** | Freckles · lentigo · melasma · nevus · melanoma · | | | |
| | **Dermal and subcutaneous** | epidermal inclusion cyst · hemangioma · dermatofibroma (benign fibrous histiocytoma) · keloid · lipoma · neurofibroma · xanthoma · Kaposi's sarcoma · infantile digital fibromatosis · granular cell tumor · leiomyoma · lymphangioma circumscriptum · myxoid cyst · | | | |
| **Rashes** | **With epidermal involvement** | **Eczematous** | contact dermatitis · **atopic dermatitis** · seborrheic dermatitis · stasis dermatitis · lichen simplex chronicus · Darier's disease · glucagonoma syndrome · langerhans cell histiocytosis · lichen sclerosus · pemphigus foliaceus · Wiskott–Aldrich syndrome · Zinc deficiency · | | |
| | | **Scaling** | psoriasis · tinea (corporis · cruris · pedis · manuum · faciei) · pityriasis rosea · secondary syphilis · mycosis fungoides · systemic lupus erythematosus · pityriasis rubra pilaris · parapsoriasis · ichthyosis · | | |
| | | **Blistering** | herpes simplex · herpes zoster · varicella · bullous impetigo · acute contact dermatitis · pemphigus vulgaris · bullous pemphigoid · dermatitis herpetiformis · porphyria cutanea tarda · epidermolysis bullosa simplex · | | |
| | | **Papular** | scabies · insect bite reactions · lichen planus · miliaria · keratosis pilaris · lichen spinulosus · transient acantholytic dermatosis · lichen nitidus · pityriasis lichenoides et varioliformis acuta · | | |
| | | **Pustular** | acne vulgaris · acne rosacea · folliculitis · impetigo · candidiasis · gonococcemia · dermatophyte · coccidioidomycosis · subcorneal pustular dermatosis · | | |
| | | **Hypopigmented** | tinea versicolor · vitiligo · pityriasis alba · postinflammatory hyperpigmentation · tuberous sclerosis · idiopathic guttate hypomelanosis · leprosy · hypopigmented mycosis fungoides · | | |
| | | | **Blanchable** | **Generalized** | drug eruptions · viral exanthems · toxic erythema · systemic lupus erythematosus · |
| | | | | **Localized** | cellulitis · abscess · boil · erythema nodosum · |

| | | | | | |
|---|---|---|---|---|---|
| | **Without epidermal involvement** | **Red** | **Erythema** | | carcinoid syndrome · fixed drug eruption · |
| | | | | **Specialized** | urticaria · erythema (multiforme · migrans · gyratum repens · annulare centrifugum · ab igne) · |
| | | | **Nonblanchable Purpura** | **Macular** | thrombocytopenic purpura · actinic/solar purpura · |
| | | | | **Papular** | disseminated intravascular coagulation · vasculitis · |
| | | **Indurated** | scleroderma/morphea · granuloma annulare · lichen sclerosis et atrophicus · necrobiosis lipoidica · | | |
| **Miscellaneous disorders** | **Ulcers** | | | | |
| | **Hair** | telogen effluvium · androgenic alopecia · trichotillomania · alopecia areata · systemic lupus erythematosus · tinea capitis · loose anagen syndrome · lichen planopilaris · folliculitis decalvans · acne keloidalis nuchae · | | | |
| | **Nail** | onychomycosis · psoriasis · paronychia · ingrown nail · | | | |
| | **Mucous membrane** | Aphthous stomatitis · oral candidiasis · lichen planus · leukoplakia · pemphigus vulgaris · mucous membrane pemphigoid · cicatricial pemphigoid · herpesvirus · coxsackievirus · syphilis · systemic histoplasmosis · squamous-cell carcinoma · | | | |

| v · t · e · | **Allergic conditions** |
|---|---|
| **Respiratory system** | Allergic rhinitis (hay fever) · Asthma · Hypersensitivity pneumonitis · Eosinophilic pneumonia · Eosinophilic granulomatosis with polyangiitis · Allergic bronchopulmonary aspergillosis · Farmer's lung · Laboratory animal allergy · |
| **Skin** | Angioedema · Urticaria · **Atopic dermatitis** · Allergic contact dermatitis · Hypersensitivity vasculitis · |
| **Blood and immune system** | Serum sickness · |
| **Circulatory system** | Anaphylaxis · |
| **Digestive system** | Coeliac disease · Eosinophilic gastroenteritis · Eosinophilic esophagitis · Food allergy · Milk intolerance · |
| **Nervous system** | Eosinophilic meningitis · |
| **Genitourinary system** | Acute interstitial nephritis · |
| **Other conditions** | Drug allergy · Allergic conjunctivitis · Latex allergy · |

| v · t · e · | **Dermatitis and eczema (L20–L30, 690–693,698)** |
|---|---|
| **Atopic dermatitis** | Besnier's prurigo · |
| **Seborrheic dermatitis** | Pityriasis simplex capillitii · Cradle cap · |
| **Contact dermatitis (allergic, irritant)** | *plants:* Urushiol-induced contact dermatitis · African blackwood dermatitis · Tulip fingers · *other:* Abietic acid dermatitis · Diaper rash · Airbag dermatitis · Baboon syndrome · Contact stomatitis · Protein contact dermatitis · |
| **Eczema** | Autoimmune estrogen dermatitis · Autoimmune progesterone dermatitis · Breast eczema · Ear eczema · Eyelid dermatitis · Topical steroid addiction · Hand eczema (Chronic vesiculobullous hand eczema · Hyperkeratotic hand dermatitis · · |

| | |
|---|---|
| | Autosensitization dermatitis/Id reaction (Candidid · Dermatophytid · Molluscum dermatitis · · Circumostomy eczema · Dyshidrosis · Juvenile plantar dermatosis · Nummular eczema · Nutritional deficiency eczema · Sulzberger–Garbe syndrome · Xerotic eczema · |
| **Pruritus/Itch/Prurigo** | Lichen simplex chronicus/Prurigo nodularis · *by location:* Pruritus ani · Pruritus scroti · Pruritus vulvae · Scalp pruritus · Drug-induced pruritus (Hydroxyethyl starch-induced pruritus · · Senile pruritus · Aquagenic pruritus (Aquadynia · · Adult blaschkitis · *due to liver disease* (Biliary pruritus · Cholestatic pruritus · · Prion pruritus · Prurigo pigmentosa · Prurigo simplex · Puncta pruritica · Uremic pruritus · |
| **Other** | substances taken internally: Bromoderma · Fixed drug reaction · Nummular dermatitis · Pityriasis alba · Papuloerythroderma of Ofuji · |

| v · t · e · **Hypersensitivity and autoimmune diseases (279.5–6)** | | | |
|---|---|---|---|
| **Type I/allergy/atopy (IgE)** | **Foreign** | | Atopic eczema · Allergic urticaria · Allergic rhinitis (Hay fever) · Allergic asthma · Anaphylaxis · Food allergy (common allergies include: Milk · Egg · Peanut · Tree nut · Seafood · Soy · Wheat · · Penicillin allergy · |
| | **Autoimmune** | | Eosinophilic esophagitis · |
| **Type II/ADCC (IgM · IgG · ·** | **Foreign** | | Hemolytic disease of the newborn · |
| | **Autoimmune** | **Cytotoxic** | Autoimmune hemolytic anemia · Immune thrombocytopenic purpura · Bullous pemphigoid · Pemphigus vulgaris · Rheumatic fever · Goodpasture's syndrome · Guillain–Barré syndrome · |
| | | **"Type V"/receptor** | Graves' disease · Myasthenia gravis · Pernicious anemia · |
| **Type III (Immune complex)** | **Foreign** | | Henoch–Schönlein purpura · Hypersensitivity vasculitis · Reactive arthritis · Farmer's lung · Post-streptococcal glomerulonephritis · Serum sickness · Arthus reaction · |
| | **Autoimmune** | | Systemic lupus erythematosus · Subacute bacterial endocarditis · Rheumatoid arthritis · |
| **Type IV/cell-mediated (T cells)** | **Foreign** | | Allergic contact dermatitis · Mantoux test · |
| | **Autoimmune** | | Diabetes mellitus type 1 · Hashimoto's thyroiditis · Multiple sclerosis · Coeliac disease · Giant-cell arteritis · Postorgasmic illness syndrome · Reactive arthritis · |
| | **GVHD** | | Transfusion-associated graft versus host disease · |
| **Unknown/multiple** | **Foreign** | | Hypersensitivity pneumonitis (Allergic bronchopulmonary aspergillosis · · Transplant rejection · Latex allergy (I+IV) · |
| | **Autoimmune** | | Sjögren's syndrome · Autoimmune hepatitis · Autoimmune polyendocrine syndrome (APS1 · APS2 · · Autoimmune adrenalitis · Systemic autoimmune disease · |

| | |
|---|---|
| **Authority control** | NDL: 00560319 · |

Categories: Type I hypersensitivity | Atopic dermatitis | Steroid-responsive inflammatory conditions


# Candidiasis

From Wikipedia, the free encyclopedia

*Thrush (infection) redirects here. For other uses see thrush (disambiguation).*

**Candidiasis** is a fungal infection due to any type of *Candida* (a type of yeast).[2] When it affects the mouth, it is commonly called **thrush**.[2] Signs and symptoms include white patches on the tongue or other areas of the mouth and throat.[3] Other symptoms may include soreness and problems swallowing.[3] When it affects the vagina, it is commonly called a **yeast infection**.[2] Signs and symptoms include genital itching, burning, and sometimes a white "cottage cheese-like" discharge from the vagina.[4] Less commonly the penis may be affected, resulting in itchiness.[3] Very rarely, the infection may become invasive spreading throughout the body, resulting in fevers along with other symptoms depending on the parts of the body affected.[5]

More than 20 types of *Candida* can cause infection with *Candida albicans* being the most common.[2] Infections of the mouth are most common among children less than one month old, the elderly, and those with weak immune systems. Conditions that result in a weak immune system include HIV/AIDS, the medications used after organ transplantation, diabetes, and the use of corticosteroids. Other risks include dentures and following antibiotic therapy.[6] Vaginal infections occur more commonly during pregnancy, in those with weak immune systems, and following antibiotic use.[7] Risk for widespread infection includes being in an intensive care unit, following surgery, low birth weight infants, and those with weak immune systems.[8]

Efforts to prevent infections of the mouth include the use of chlorhexidine mouth wash in those with poor immune function and washing out the mouth following the use of inhaled steroids.[9] Little evidence supports probiotics for either prevention or treatment even among those with frequent vaginal infections.[10][11] For infections of the mouth, treatment with topical clotrimazole or nystatin is usually effective. Oral or intravenous fluconazole, itraconazole, or amphotericin B may be used if these do not work.[9] A number of topical antifungal medications may be used for vaginal infections including clotrimazole.[12] In those with widespread disease, an echinocandin such as caspofungin or micafungin is used.[13] A number of weeks of intravenous amphotericin B may be used as an alternative.[13] In certain groups at very high risk, antifungal medications may be used preventatively.[8][13]

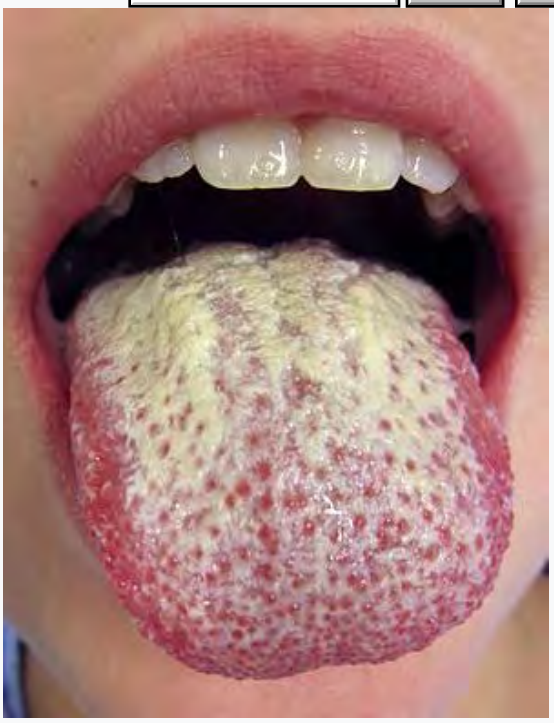
Infections of the mouth occur in about 6% of babies less than a month old. About 20% of those receiving chemotherapy for cancer and 20% of those with AIDS also develop the disease.[14] About three-quarters of women have at least one yeast infection at some time during their lives.[15] Widespread disease is rare except in those who have risk factors.[16]



## Variants

**Candidiasis**

**Synonyms** ...diasis, moniliasis,



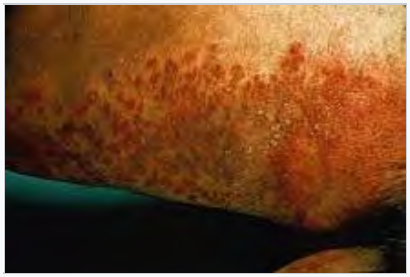
Oral candidiasis (thrush)

| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | B37 |
| **ICD-9-CM** | 112 |
| **DiseasesDB** | 1929 |
| **MedlinePlus** | 001511 |
| **eMedicine** | med/264 emerg/76 ped/312 derm/67 |
| **Patient UK** | Candidiasis |
| **MeSH** | D002177 |

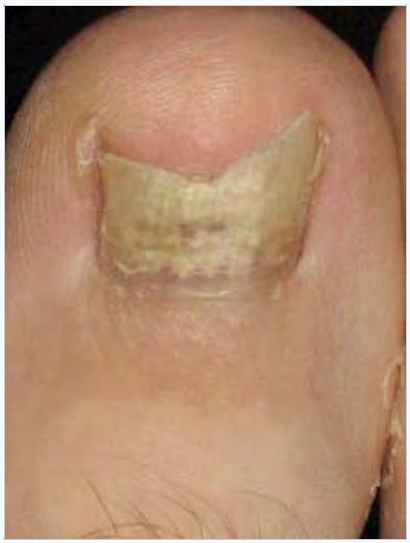
[edit on Wikidata]

## Signs and symptoms [edit]

Signs and symptoms of candidiasis vary depending on the area affected.[17] Most candidal infections result in minimal complications such as redness, itching, and discomfort, though complications may be severe or even fatal if left untreated in certain populations. In healthy (immunocompetent) persons, candidiasis is usually a localized infection of the skin, fingernails or toenails (onychomycosis), or mucosal membranes, including the oral cavity and pharynx (thrush), esophagus, and the genitalia (vagina, penis, etc.);[18][19][20] less commonly in healthy individuals, the gastrointestinal tract,[21][22][23] urinary tract,[21] and respiratory tract[21] are sites of candida infection.


Skin candidiasis

In immunocompromised individuals, *Candida* infections in the esophagus occur more frequently than in healthy individuals and have a higher potential of becoming systemic, causing a much more serious condition, a fungemia called candidemia.[18][24][25] Symptoms of esophageal candidiasis include difficulty swallowing, painful swallowing, abdominal pain, nausea, and vomiting.[18][26]


Nail candidiasis (onychomycosis)

Thrush is commonly seen in infants. It is not considered abnormal in infants unless it lasts longer than a few weeks.[27]

Infection of the vagina or vulva may cause severe itching, burning, soreness, irritation, and a whitish or whitish-gray cottage cheese-like discharge. Symptoms of infection of the male genitalia (balanitis thrush) include red skin around the head of the penis, swelling, irritation, itchiness and soreness of the head of the penis, thick, lumpy discharge under the foreskin, unpleasant odour, difficulty retracting the foreskin (phimosis), and pain when passing urine or during sex.[28]

Common symptoms of gastrointestinal candidiasis in healthy individuals are anal itching, belching, bloating, indigestion, nausea, diarrhea, gas, intestinal cramps, vomiting, and gastric ulcers.[21][22][23] Perianal candidiasis can cause anal itching; the lesion can be erythematous, papular, or ulcerative in appearance, and it is not considered to be a sexually transmissible disease.[29] Abnormal proliferation of the candida in the gut may lead to dysbiosis.[30] While it is not yet clear, this alteration may be the source of symptoms generally described as the irritable bowel syndrome,[31][32] and other gastrointestinal diseases.[22][33]

## Causes [edit]


*Main article: Candida (fungus)*

*Candida* yeasts are generally present in healthy humans, frequently part of the human body's normal oral and intestinal flora, and particularly on the skin; however, their growth is normally limited by the human immune system and by competition of other microorganisms, such as bacteria occupying the same locations in the human body.[34] *Candida* requires moisture for growth, notably on the skin.[35] For example, wearing wet swimwear for long periods of time is believed to

Vagina yeast infection

be a risk factor.[36] In extreme cases, superficial infections of the skin or mucous membranes may enter into the bloodstream and cause systemic *Candida* infections.

Factors that increase the risk of candidiasis include HIV/AIDS, mononucleosis, cancer treatments, steroids, stress, antibiotic usage, diabetes, and nutrient deficiency. Hormone replacement therapy and infertility treatments may also be predisposing factors.[37] Treatment with antibiotics can lead to eliminating the yeast's natural competitors for resources in the oral and intestinal flora; thereby increasing the severity of the condition.[38] A weakened or undeveloped immune system or metabolic illnesses are significant predisposing factors of candidiasis.[39] Almost 15% of people with weakened immune systems develop a systemic illness caused by *Candida* species.[40] Diets high in simple carbohydrates have been found to affect rates of oral candidiases.[41]

*C. albicans* was isolated from the vaginas of 19% of apparently healthy women, i.e., those who experienced few or no symptoms of infection. External use of detergents or douches or internal disturbances (hormonal or physiological) can perturb the normal vaginal flora, consisting of lactic acid bacteria, such as lactobacilli, and result in an overgrowth of *Candida* cells, causing symptoms of infection, such as local inflammation.[42] Pregnancy and the use of oral contraceptives have been reported as risk factors.[43] Diabetes mellitus and the use of antibiotics are also linked to increased rates of yeast infections.[43]

In penile candidiasis, the causes include sexual intercourse with an infected individual, low immunity, antibiotics, and diabetes. Male genital yeast infections are less common, and incidences of infection are only a fraction of those in women; however, yeast infection on the penis from direct contact via sexual intercourse with an infected partner is not uncommon.[44]

## Diagnosis [edit]

Symptoms of vaginal candidiasis are also present in the more common bacterial vaginosis;[45] aerobic vaginitis is distinct and should be excluded in the differential diagnosis.[46] In a 2002 study, only 33% of women who were self-treating for a yeast infection actually had such an infection, while most had either bacterial vaginosis or a mixed-type infection.[47]

Agar plate culture of *C. albicans*

Diagnosis of a yeast infection is done either via microscopic examination or culturing. For identification by light microscopy, a scraping or swab of the affected area is placed on a microscope slide. A single drop of 10% potassium hydroxide (KOH) solution is then added to the specimen. The KOH dissolves the skin cells, but leaves the *Candida* cells intact, permitting visualization of pseudohyphae and budding yeast cells typical of many *Candida* species.

For the culturing method, a sterile swab is rubbed on the infected skin surface. The swab is then streaked on a culture medium. The culture is incubated at 37 °C (98.6 °F) for several days, to allow development of yeast or bacterial colonies. The characteristics (such as morphology and colour) of the colonies may allow initial diagnosis of the organism causing disease symptoms.[48]

KOH test on a vaginal wet mount, showing slings of pseudohyphae of *Candida albicans* surrounded by round vaginal epithelial cells, conferring a diagnosis of candidal vulvovaginitis

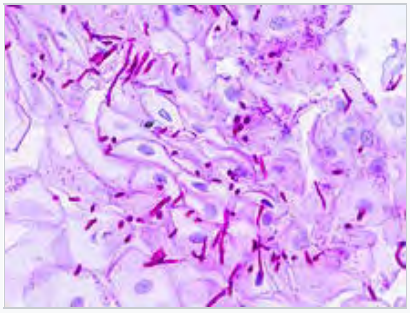
Respiratory, gastrointestinal, and esophageal candidiasis require an endoscopy to diagnose.[23][49] For gastrointestinal candidiasis, it is necessary to obtain a 3–5 milliliter sample of fluid from the duodenum for fungal culture.[23] The diagnosis of gastrointestinal candidiasis is based upon the culture containing in excess of 1,000 colony-forming units per milliliter.[23]

### Classification [edit]

Candidiasis may be divided into these types:

- Mucosal candidiasis
  - Oral candidiasis (thrush, oropharyngeal candidiasis)[18][20]
    - Pseudomembranous candidiasis[20]
    - Erythematous candidiasis[18][20]
    - Hyperplastic candidiasis[20]
    - Denture-related stomatitis[18][20] — *Candida* organisms are involved in

about 90% of cases
    - Angular cheilitis[18][20] — *Candida* species are responsible for about 20% of cases, mixed infection of *C. albicans* and *Staphylococcus aureus* for about 60% of cases.
    - Median rhomboid glossitis[20]
  - Candidal vulvovaginitis (vaginal yeast infection)[18][50]
  - Candidal balanitis — infection of the glans penis,[18] almost exclusively occurring in uncircumcised males[51]
  - Esophageal candidiasis (candidal esophagitis)[18][26]
  - Gastrointestinal candidiasis[21][22][23]
  - Respiratory candidiasis[18][21]
- Cutaneous candidiasis
  - Candidial folliculitis[18]
  - Candidal intertrigo[18]
  - Candidal paronychia[18]
  - Perianal candidiasis, may present as pruritus ani[1]:309
  - Candidid
  - Chronic mucocutaneous candidiasis[18]
  - Congenital cutaneous candidiasis
  - Diaper candidiasis: an infection of a child's diaper area[1]:309
  - Erosio interdigitalis blastomycetica
  - Candidial onychomycosis (nail infection) caused by *Candida*[18][52]
- Systemic candidiasis[18]
  - Candidemia, a form of fungemia which may lead to sepsis[18]
  - Invasive candidiasis (disseminated candidiasis) — organ infection by *Candida*[18]
  - Chronic systemic candidiasis (hepatosplenic candidiasis) — sometimes arises during recovery from neutropenia[18][53]
- Antibiotic candidiasis (iatrogenic candidiasis)



Micrograph of esophageal candidiasis showing hyphae, biopsy specimen, PAS stain

## Prevention [edit]

A diet that supports the immune system and is not high in simple carbohydrates contributes to a healthy balance of the oral and intestinal flora.[34][41] While yeast infections are associated with diabetes, the level of blood sugar control may not affect the risk.[54] Wearing cotton underwear may help to reduce the risk of developing skin and vaginal yeast infections, along with not wearing wet clothes for long periods of time.[7][36]

Oral hygiene can help prevent oral candidiasis when people have a weakened immune system.[6] For people undergoing cancer treatment, chlorhexidine mouthwash can prevent or reduce thrush.[6] People who use inhaled corticosteroids can reduce the risk of developing oral candidiasis by rinsing the mouth with water or mouthwash after using the inhaler.[6]

For women who experience recurrent yeast infections, there is limited evidence that oral or intravaginal probiotics help to prevent future infections.[10][55] This includes either as pills or as yogurt.[10]

## Treatment [edit]

Candidiasis is treated with antifungal medications; these include clotrimazole, nystatin, fluconazole, voriconazole, amphotericin B, and echinocandins.[13] Intravenous fluconazole or an intravenous echinocandin such as caspofungin are commonly used to treat immunocompromised or critically ill individuals.[13]

The 2016 revision of the clinical practice guideline for the management of candidiasis lists a large number of specific treatment regimens for *Candida* infections that involve different *Candida* species, forms of antifungal drug resistance, immune statuses, and infection localization and severity.[13] Gastrointestinal candidiasis in immunocompetent individuals is treated with 100–200 mg fluconazole per day for 2–3 weeks.[23]

### Localized infection [edit]

Mouth and throat candidiasis are treated with antifungal medication. Oral candidiasis usually responds to topical treatments; otherwise, systemic antifungal medication may be needed for oral infections. Candida esophagitis may be treated orally or intravenously; for severe or azole-resistant esophageal candidiasis, treatment with amphotericin B may be necessary.[9]

A one-time dose of fluconazole is 90% effective in treating a vaginal yeast infection.[56] Local treatment may include vaginal suppositories or medicated douches. Other types of yeast infections require different dosing. Gentian violet can be used for thrush in breastfeeding babies. *C. albicans* can develop resistance to fluconazole, this being more of an issue in those with HIV/AIDS who are often treated with multiple courses of fluconazole for recurrent oral infections.[57]

For vaginal yeast infection in pregnancy, topical imidazole or triazole antifungals are considered the therapy of choice owing to available safety data.[58] Systemic absorption of these topical formulations is minimal, posing little risk of transplacental transfer.[58] In vaginal yeast infection in pregnancy, treatment with topical azole antifungals is recommended for 7 days instead of a shorter duration.[58]

No benefit from probiotics has been found for active infections.[11]

### Blood infection [edit]

Systemic candidiasis occurs when Candida yeast enters the bloodstream and may spread (becoming disseminated candidiasis) to other organs, including the central nervous system, kidneys, liver, bones, muscles, joints, spleen, or eyes. Treatment typically consists of oral or intravenous antifungal medications.[59] In candidal infections of the blood, intravenous fluconazole or an echinocandin such as caspofungin may be used.[13] Amphotericin B is another option.[13]

## Prognosis [edit]

Among individuals being treated in intensive care units, the mortality rate is about 30-50% when systemic candidiasis develops.[60]

## Epidemiology [edit]

Oral candidiasis is the most common fungal infection of the mouth,[61] and it also represents the most common opportunistic oral infection in humans.[62] In the Western Hemisphere, about 75% of females are affected at some time in their lives with a vaginal yeast infection.

Esophageal candidiasis is the most common esophageal infection in persons with AIDS and accounts for about 50% of all esophageal infections, often coexisting with other esophageal diseases. About two-thirds of people with AIDS and esophageal candidiasis also have oral candidiasis.[26]

Candidal sepsis is rare.[63] Candida is the fourth most common cause of bloodstream infections among hospital patients in the United States.[64]

## History [edit]

Descriptions of what sounds like oral thrush go back to the time of Hippocrates *circa* 460–370 BCE.[17]

Vulvovaginal candidiasis was first described in 1849 by Wilkinson.[65] In 1875, Haussmann demonstrated the causative organism in both vulvovaginal and oral candidiasis is the same.[65]

With the advent of antibiotics following World War II, the rates of candidiasis increased. The rates then decreased in the 1950s following the development of nystatin.[66]

The colloquial term "thrush" refers to the resemblance of the white flecks present in some forms of candidiasis (*e.g.* pseudomembranous candidiasis) with the breast of the bird of the same name.[67] The term candidosis is largely used in British English, and candidiasis in American English.[65] *Candida* is also pronounced differently; in American English, the stress is on the "i", whereas in British English the stress is on the first syllable.

The genus *Candida* and species *C. albicans* were described by botanist Christine Marie Berkhout in her doctoral thesis

at the University of Utrecht in 1923. Over the years, the classification of the genera and species has evolved. Obsolete names for this genus include *Mycotorula* and *Torulopsis*. The species has also been known in the past as *Monilia albicans* and *Oidium albicans*. The current classification is *nomen conservandum*, which means the name is authorized for use by the International Botanical Congress (IBC).[68]

The genus *Candida* includes about 150 different species; however, only a few are known to cause human infections. *C. albicans* is the most significant pathogenic species. Other species pathogenic in humans include *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. dubliniensis*, and *C. lusitaniae*.

The name *Candida* was proposed by Berkhout. It is from the Latin word *toga candida*, referring to the white toga (robe) worn by candidates for the Senate of the ancient Roman republic.[65] The specific epithet *albicans* also comes from Latin, *albicare* meaning "to whiten".[65] These names refer to the generally white appearance of *Candida* species when cultured.

## Alternative medicine [edit]

A 2005 publication noted that "a large pseudoscientific cult"[69] has developed around the topic of *Candida*, with claims up to one in three people are affected by yeast-related illness, particularly a condition called "Candidiasis hypersensitivity".[70] Some practitioners of alternative medicine have promoted these purported conditions and sold dietary supplements as supposed cures; a number of them have been prosecuted.[71][72] In 1990, alternative health vendor Nature's Way signed an FTC consent agreement not to misrepresent in advertising any self-diagnostic test concerning yeast conditions or to make any unsubstantiated representation concerning any food or supplement's ability to control yeast conditions, with a fine of $30,000 payable to the National Institutes of Health for research in genuine candidiasis.[72]

## References [edit]


1. ^ a b c James, William D.; Berger, Timothy G.; et al. (2006). *Andrews' Diseases of the Skin: clinical Dermatology*. Saunders Elsevier. pp. 308–311. ISBN 0-7216-2921-0.
2. ^ a b c d "Candidiasis". *cdc.gov*. February 13, 2014. Retrieved 28 December 2014.
3. ^ a b c "Symptoms of Oral Candidiasis". *cdc.gov*. February 13, 2014. Retrieved 28 December 2014.
4. ^ "Symptoms of Genital / Vulvovaginal Candidiasis". *cdc.gov*. February 13, 2014. Retrieved 28 December 2014.
5. ^ "Symptoms of Invasive Candidiasis". *cdc.gov*. February 13, 2014. Retrieved 28 December 2014.
6. ^ a b c d "Risk & Prevention". *cdc.gov*. February 13, 2014. Retrieved 28 December 2014.
7. ^ a b "People at Risk for Genital / Vulvovaginal Candidiasis". *cdc.gov*. February 13, 2014. Retrieved 28 December 2014.
8. ^ a b "People at Risk for Invasive Candidiasis". *cdc.gov*. February 13, 2014. Retrieved 28 December 2014.
9. ^ a b c "Treatment & Outcomes of Oral Candidiasis". *cdc.gov*. February 13, 2014. Retrieved 28 December 2014.
10. ^ a b c Jurden L, Buchanan M, Kelsberg G, Safranek S (June 2012). "Clinical inquiries. Can probiotics safely prevent recurrent vaginitis?". *The Journal of family practice*. **61** (6): 357, 368. PMID 22670239.
11. ^ a b Abad CL, Safdar N (June 2009). "The role of lactobacillus probiotics in the treatment or prevention of urogenital infections--a systematic review.". *Journal of chemotherapy (Florence, Italy)*. **21** (3): 243–52. doi:10.1179/joc.2009.21.3.243. PMID 19567343.
12. ^ "Treatment & Outcomes of Genital / Vulvovaginal Candidiasis". *cdc.gov*. February 13, 2014. Retrieved 28 December 2014.
13. ^ a b c d e f g h Pappas PG, Kauffman CA, Andes DR, PMID 15647635.
32. ^ Collins, SM (August 2014). "A role for the gut microbiota in IBS.". *Nature reviews. Gastroenterology & hepatology*. **11** (8): 497–505. doi:10.1038/nrgastro.2014.40. PMID 24751910.
33. ^ Gouba; Drancourt (2015). "Digestive tract mycobiota: a source of infection.". *Médecine et Maladies Infectieuses*. **45**: 9–16. doi:10.1016/j.medmal.2015.01.007. PMID 25684583.
34. ^ a b Mulley, A. G.; Goroll, A. H. (2006). *Primary Care Medicine: office evaluation and management of the adult patient*. Philadelphia: Wolters Kluwer Health. pp. 802–3. ISBN 0-7817-7456-X. Retrieved 2008-11-23.
35. ^ Goehring, Richard V. (2008). *Mims' medical microbiology.* (4th ed.). Philadelphia, PA: Mosby Elsevier. p. 656. ISBN 978-0-323-04475-2.
36. ^ a b MedlinePlus Encyclopedia *Vaginal yeast infection*
37. ^ Nwokolo NC, Boag FC (May 2000). "Chronic vaginal candidiasis. Management in the postmenopausal patient". *Drugs Aging*. **16** (5): 335–9. doi:10.2165/00002512-200016050-00003. PMID 10917071.
38. ^ Bassetti M, Mikulska M, Viscoli C (December 2010). "Bench-to-bedside review: therapeutic management of invasive candidiasis in the intensive care unit.". *Critical Care*. **14** (6): 244. doi:10.1186/cc9239. PMID 21144007.
39. ^ Odds FC (1987). "Candida infections: an overview". *Crit. Rev. Microbiol.* **15** (1): 1–5. doi:10.3109/10408418709104444. PMID 3319417.
40. ^ Choo ZW, Chakravarthi S, Wong SF, Nagaraja HS, Thanikachalam PM, Mak JW, Radhakrishnan A, Tay A (2010). "A comparative histopathological study of systemic candidiasis in association with experimentally induced breast cancer". *Oncology Letters*. **1** (1): 215–222. doi:10.3892/ol_00000039. ISSN 1792-1082.

Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD (2016). "Executive Summary: Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America". *Clin. Infect. Dis.* **62** (4): 409–417. doi:10.1093/cid/civ1194. PMID 26810419.

14. ^ "Oral Candidiasis Statistics". *cdc.gov*. February 13, 2014. Retrieved 28 December 2014.
15. ^ "Genital / vulvovaginal candidiasis (VVC)". *cdc.gov*. February 13, 2014. Retrieved 28 December 2014.
16. ^ "Invasive Candidiasis Statistics". *cdc.gov*. February 13, 2014. Retrieved 28 December 2014.
17. ^ *a b* Dolin, [edited by] Gerald L. Mandell, John E. Bennett, Raphael (2010). *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* (7th ed.). Philadelphia, PA: Churchill Livingstone/Elsevier. pp. Chapter 250. ISBN 978-0-443-06839-3.
18. ^ *a b c d e f g h i j k l m n o p q r s t* Hidalgo JA, Vazquez JA (18 August 2015). "Candidiasis: Clinical Presentation". *Medscape*. WebMD. Retrieved 22 June 2016.
19. ^ Walsh TJ, Dixon DM (1996). "Deep Mycoses". In Baron S, et al. *Baron's Medical Microbiology* (4th ed.). Univ of Texas Medical Branch. ISBN 0-9631172-1-1.
20. ^ *a b c d e f g h* Patil S, Rao RS, Majumdar B, Anil S (December 2015). "Clinical Appearance of Oral Candida Infection and Therapeutic Strategies". *Front. Microbiol.* **6**: 1391. doi:10.3389/fmicb.2015.01391. PMC 4681845. PMID 26733948.
21. ^ *a b c d e f* Martins N, Ferreira IC, Barros L, Silva S, Henriques M (June 2014). "Candidiasis: predisposing factors, prevention, diagnosis and alternative treatment". *Mycopathologia*. **177** (5-6): 223–240. doi:10.1007/s11046-014-9749-1. PMID 24789109. "Candida species and other microorganisms are involved in this complicated fungal infection, but Candida albicans continues to be the most prevalent. In the past two decades, it has been observed an abnormal overgrowth in the gastrointestinal, urinary and respiratory tracts, not only in immunocompromised patients but also related to nosocomial infections and even in healthy individuals. There is a wide variety of causal factors that contribute to yeast infection which means that candidiasis is a good example of a multifactorial syndrome."
22. ^ *a b c d* Wang ZK, Yang YS, Stefka AT, Sun G, Peng LH (April 2014). "Review article: fungal microbiota and digestive diseases". *Aliment. Pharmacol. Ther.* **39** (8): 751–766. doi:10.1111/apt.12665. PMID 24612332. "In addition, GI fungal infection is reported even among those patients with normal immune status. Digestive system-related fungal infections may be induced by both commensal opportunistic fungi and exogenous pathogenic fungi. The IFI in different GI sites have their special clinical features, which are often accompanied by various severe diseases. Although IFI associated with digestive diseases are less common, they can induce fatal outcomes due to less specificity of related symptoms, signs, endoscopic and imaging manifestations, and the poor treatment options. ... Candida sp. is also the most frequently identified species among patients with gastric IFI. ... Gastric IFI is often characterised by the abdominal pain and vomiting and with the endoscopic characteristics including gastric giant and multiple ulcers, stenosis, perforation, and fistula. For example, gastric ulcers combined with entogastric fungal infection, characterised by deep, large and intractable PMC 3436220. PMID 22966285.
41. ^ *a b* Akpan A, Morgan R (August 2002). "Oral candidiasis". *Postgraduate Medical Journal*. **78** (922): 455–9. doi:10.1136/pmj.78.922.455. PMC 1742467. PMID 12185216.
42. ^ Mårdh PA, Novikova N, Stukalova E (October 2003). "Colonisation of extragenital sites by Candida in women with recurrent vulvovaginal candidosis". *BJOG*. **110** (10): 934–7. doi:10.1111/j.1471-0528.2003.01445.x. PMID 14550364.
43. ^ *a b* Schiefer HG (1997). "Mycoses of the urogenital tract". *Mycoses*. **40** (Suppl 2): 33–6. doi:10.1111/j.1439-0507.1997.tb00561.x. PMID 9476502.
44. ^ David LM, Walzman M, Rajamanoharan S (October 1997). "Genital colonisation and infection with candida in heterosexual and homosexual males". *Genitourin Med*. **73** (5): 394–6. doi:10.1136/sti.73.5.394. PMC 1195901. PMID 9534752.
45. ^ Terri Warren, RN (2010). "Is It a Yeast Infection?". Retrieved 2011-02-23.
46. ^ Donders, Gilbert G.G.; Vereecken, Annie; Bosmans, Eugene; Dekeersmaecker, Alfons; Salembier, Geert; Spitz, Bernard (2002). "Definition of a type of abnormal vaginal flora that is distinct from bacterial vaginosis: aerobic vaginitis". BJOG [S.l.: s.n.] 109 (1): 34–43. doi:10.1111/j.1471-0528.2002.00432.x. PMID 11845812
47. ^ Ferris DG, Nyirjesy P, Sobel JD, Soper D, Pavletic A, Litaker MS (March 2002). "Over-the-counter antifungal drug misuse associated with patient-diagnosed vulvovaginal candidiasis". *Obstetrics and Gynecology*. **99** (3): 419–425. doi:10.1016/S0029-7844(01)01759-8. PMID 11864668.
48. ^ Srikumar Chakravarthi; Nagaraja HS (2010). "A comprehensive review of the occurrence and management of systemic candidiasis as an opportunistic infection". *Microbiology Journal*. **1** (2): 1–5. ISSN 2153-0696.
49. ^ Hidalgo JA, Vazquez JA (18 August 2015). "Candidiasis: Workup". *Medscape*. WebMD. Retrieved 22 June 2016.
50. ^ Mastromarino, Paola; Vitali, Beatrice; Mosca, Luciana (2013). "Bacterial vaginosis: a review on clinical trials with probiotics" (PDF). *New Microbiologica*. **36**: 229–238. PMID 23912864.
51. ^ Nyirjesy P, Sobel JD (May 2013). "Genital mycotic infections in patients with diabetes.". *Postgraduate Medicine*. **125** (3): 33–46. doi:10.3810/pgm.2013.05.2650. PMID 23748505.
52. ^ Nolting S, Brautigam M, Weidinger G (1994). "Terbinafine in onychomycosis with involvement by non-dermatophytic fungi". *The British journal of dermatology*. 130 Suppl 43: 16–21. doi:10.1111/j.1365-2133.1994.tb06088.x. PMID 8186136.
53. ^ Errol Reiss; H. Jean Shadomy; G. Marshall Lyon (2011). "Chapter 11". *Fundamental medical mycology*. Hoboken, N.J.: John Wiley & Sons. ISBN 978-1-118-10176-6.
54. ^ Mobley, David P. Cappelli, Connie C. (2008). *Prevention in clinical oral health care*. St. Louis, Mo.: Mosby Elsevier. p. 254. ISBN 9780323036955.
55. ^ Falagas, ME; Betsi, GI; Athanasiou, S (August 2006). "Probiotics for prevention of recurrent vulvovaginal candidiasis: a review.". *The Journal of antimicrobial chemotherapy*. **58** (2): 266–72. doi:10.1093/jac/dkl246. PMID 16790461. "Thus, the available evidence for the use of probiotics for prevention of recurrent VVC is limited"
56. ^ Moosa MY, Sobel JD, Elhalis H, Du W, Akins RA (2004). "Fungicidal Activity of Fluconazole against Candida albicans in a Synthetic Vagina-Simulative Medium". *Antimicrob.*

ulcers,[118] were reported as early as the 1930s. ... The overgrowth and colonisation of fungi in intestine can lead to diarrhoea."
23. ^ a b c d e f g Erdogan A, Rao SS (April 2015). "Small intestinal fungal overgrowth". *Curr Gastroenterol Rep*. **17** (4): 16. doi:10.1007/s11894-015-0436-2. PMID 25786900. "Small intestinal fungal overgrowth (SIFO) is characterized by the presence of excessive number of fungal organisms in the small intestine associated with gastrointestinal (GI) symptoms. Candidiasis is known to cause GI symptoms particularly in immunocompromised patients or those receiving steroids or antibiotics. However, only recently, there is emerging literature that an overgrowth of fungus in the small intestine of non-immunocompromised subjects may cause unexplained GI symptoms. Two recent studies showed that 26 % (24/94) and 25.3 % (38/150) of a series of patients with unexplained GI symptoms had SIFO. The most common symptoms observed in these patients were belching, bloating, indigestion, nausea, diarrhea, and gas. The underlying mechanism(s) that predisposes to SIFO is unclear but small intestinal dysmotility and use of proton pump inhibitors has been implicated. However, further studies are needed; both to confirm these observations and to examine the clinical relevance of fungal overgrowth, both in healthy subjects and in patients with otherwise unexplained GI symptoms. ... For routine SIFO in an immunocompetent host, a 2–3 week oral course of fluconazole 100–200 mg will suffice."
24. ^ Fidel PL (2002). "Immunity to Candida". *Oral Dis*. **8**: 69–75. doi:10.1034/j.1601-0825.2002.00015.x. PMID 12164664.
25. ^ Pappas PG (2006). "Invasive candidiasis". *Infect. Dis. Clin. North Am*. **20** (3): 485–506. doi:10.1016/j.idc.2006.07.004. PMID 16984866.
26. ^ a b c Yamada T, Alpers DH, et al. (2009). *Textbook of gastroenterology* (5th ed.). Chichester, West Sussex: Blackwell Pub. p. 814. ISBN 978-1-4051-6911-0.
27. ^ "Thrush". 2011. Retrieved 2011-04-08.
28. ^ NHS: Symptoms of thrush in men (balanitis thrush)
29. ^ Bruce G. Wolff et al., eds. (2007). *The ASCRS textbook of colon and rectal surgery*. New York: Springer. pp. 241, 242, 245. ISBN 0-387-24846-3.
30. ^ Mukherjee, PK; Sendid, B; Hoarau, G; Colombel, JF; Poulain, D; Ghannoum, MA (February 2015). "Mycobiota in gastrointestinal diseases.". *Nature reviews. Gastroenterology & hepatology*. **12** (2): 77–87. doi:10.1038/nrgastro.2014.188. PMID 25385227.
31. ^ Santelmann, H; Howard, JM (January 2005). "Yeast metabolic products, yeast antigens and yeasts as possible triggers for irritable bowel syndrome.". *European journal of gastroenterology & hepatology*. **17** (1): 21–6. doi:10.1097/00042737-200501000-00005.
*Agents Chemother*. **48** (1): 161–7. doi:10.1128/AAC.48.1.161-167.2004. PMC 310176. PMID 14693534.
57. ^ Morschhäuser J (Jul 18, 2002). "The genetic basis of fluconazole resistance development in Candida albicans.". *Biochimica et Biophysica Acta*. **1587** (2-3): 240–8. doi:10.1016/s0925-4439(02)00087-x. PMID 12084466.
58. ^ a b c Soong D, Einarson A (Mar 2009). "Vaginal yeast infections during pregnancy.". *Canadian Family Physician*. **55** (3): 255–6. PMC 2654841. PMID 19282531.
59. ^ "Systemic candidiasis". *NIH.gov*. U.S. DHHS, National Institute of Health. Oct 2014. Retrieved April 19, 2015.
60. ^ Williams D, Lewis M (Jan 28, 2011). "Pathogenesis and treatment of oral candidosis.". *Journal of oral microbiology*. **3**. doi:10.3402/jom.v3i0.5771. PMC 3087208. PMID 21547018.
61. ^ Bouquot, Brad W. Neville , Douglas D. Damm, Carl M. Allen, Jerry E. (2002). *Oral & maxillofacial pathology* (2. ed.). Philadelphia: W.B. Saunders. pp. 189–197. ISBN 0-7216-9003-3.
62. ^ Lalla RV, Patton LL, Dongari-Bagtzoglou A (April 2013). "Oral candidiasis: pathogenesis, clinical presentation, diagnosis and treatment strategies.". *Journal of the California Dental Association*. **41** (4): 263–8. PMID 23705242.
63. ^ Gow, Neil A. R. (8 May 2002). "Candida albicans - a fungal Dr Jekyll and Mr Hyde". *Mycologist*. **16** (01). doi:10.1017/S0269915X02006183.
64. ^ "Candida" (PDF). *CDC.gov*. Center of Disease Contrl. Retrieved April 19, 2015.
65. ^ a b c d e Lynch DP (August 1994). "Oral candidiasis. History, classification, and clinical presentation.". *Oral surgery, oral medicine, and oral pathology*. **78** (2): 189–93. doi:10.1016/0030-4220(94)90146-5. PMID 7936588.
66. ^ Obladen M (2012). "Thrush - nightmare of the foundling hospitals.". *Neonatology*. **101** (3): 159–65. doi:10.1159/000329879. PMID 22024688.
67. ^ Scully, Crispian. "Mucosal Candidiasis (Medscape)". WebMD LLC. Retrieved 8 September 2013.
68. ^ *International Code of Botanical Nomenclature*. Königstein. 2000. ISBN 3-904144-22-7. Retrieved 2008-11-23.
69. ^ Odds, FC (1987). "Candida infections: an overview.". *Critical Reviews in Microbiology*. **15** (1): 1–5. doi:10.3109/10408418709104444. PMID 3319417.
70. ^ Stephen Barrett, M.D. (October 8, 2005). "Dubious "Yeast Allergies" ".
71. ^ Barrett S (2005-10-08). "Dubious "Yeast Allergies" ". QuackWatch. Retrieved 2008-02-21.
72. ^ a b Jarvis WT. "Candidiasis Hypersensitivity". National Council Against Health Fraud. Retrieved January 2014. Check date values in: `|access-date=` (help)

## External links [edit]

- Candidiasis at DMOZ

Wikimedia Commons has media related to *Candidiasis*.

| v · t · e | **Diseases of the skin and appendages by morphology** |
|---|---|
| | wart · callus · seborrheic keratosis · acrochordon · molluscum contagiosum · actinic keratosis |

| | | | | | |
|---|---|---|---|---|---|
| **Growths** | **Epidermal** | • squamous-cell carcinoma • basal-cell carcinoma • Merkel-cell carcinoma • nevus sebaceous • trichoepithelioma • | | | |
| | **Pigmented** | Freckles • lentigo • melasma • nevus • melanoma • | | | |
| | **Dermal and subcutaneous** | epidermal inclusion cyst • hemangioma • dermatofibroma (benign fibrous histiocytoma) • keloid • lipoma • neurofibroma • xanthoma • Kaposi's sarcoma • infantile digital fibromatosis • granular cell tumor • leiomyoma • lymphangioma circumscriptum • myxoid cyst • | | | |
| **Rashes** | **With epidermal involvement** | **Eczematous** | contact dermatitis • atopic dermatitis • seborrheic dermatitis • stasis dermatitis • lichen simplex chronicus • Darier's disease • glucagonoma syndrome • langerhans cell histiocytosis • lichen sclerosus • pemphigus foliaceus • Wiskott–Aldrich syndrome • Zinc deficiency • | | |
| | | **Scaling** | psoriasis • tinea (corporis • cruris • pedis • manuum • faciei) • pityriasis rosea • secondary syphilis • mycosis fungoides • systemic lupus erythematosus • pityriasis rubra pilaris • parapsoriasis • ichthyosis • | | |
| | | **Blistering** | herpes simplex • herpes zoster • varicella • bullous impetigo • acute contact dermatitis • pemphigus vulgaris • bullous pemphigoid • dermatitis herpetiformis • porphyria cutanea tarda • epidermolysis bullosa simplex • | | |
| | | **Papular** | scabies • insect bite reactions • lichen planus • miliaria • keratosis pilaris • lichen spinulosus • transient acantholytic dermatosis • lichen nitidus • pityriasis lichenoides et varioliformis acuta • | | |
| | | **Pustular** | acne vulgaris • acne rosacea • folliculitis • impetigo • **candidiasis** • gonococcemia • dermatophyte • coccidioidomycosis • subcorneal pustular dermatosis • | | |
| | | **Hypopigmented** | tinea versicolor • vitiligo • pityriasis alba • postinflammatory hyperpigmentation • tuberous sclerosis • idiopathic guttate hypomelanosis • leprosy • hypopigmented mycosis fungoides • | | |
| | **Without epidermal involvement** | **Red** | **Blanchable Erythema** | **Generalized** | drug eruptions • viral exanthems • toxic erythema • systemic lupus erythematosus • |
| | | | | **Localized** | cellulitis • abscess • boil • erythema nodosum • carcinoid syndrome • fixed drug eruption • |
| | | | | **Specialized** | urticaria • erythema (multiforme • migrans • gyratum repens • annulare centrifugum • ab igne) • |
| | | | **Nonblanchable Purpura** | **Macular** | thrombocytopenic purpura • actinic/solar purpura • |
| | | | | **Papular** | disseminated intravascular coagulation • vasculitis • |
| | | **Indurated** | scleroderma/morphea • granuloma annulare • lichen sclerosis et atrophicus • necrobiosis lipoidica • | | |
| | **Ulcers** | | | | |
| | **Hair** | telogen effluvium • androgenic alopecia • trichotillomania • alopecia areata • systemic lupus erythematosus • tinea capitis • loose anagen syndrome • lichen planopilaris • | | | |

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|---|---|---|
| **Miscellaneous disorders** | | folliculitis decalvans · acne keloidalis nuchae · |
| | **Nail** | onychomycosis · psoriasis · paronychia · ingrown nail · |
| | **Mucous membrane** | Aphthous stomatitis · oral candidiasis · lichen planus · leukoplakia · pemphigus vulgaris · mucous membrane pemphigoid · cicatricial pemphigoid · herpesvirus · coxsackievirus · syphilis · systemic histoplasmosis · squamous-cell carcinoma · |

| v · t · e · | **Fungal infection and mesomycetozoea (B35–B49, 110–118)** | | | |
|---|---|---|---|---|
| **Superficial and cutaneous (dermatomycosis): Tinea = skin; Piedra (exothrix/ endothrix) = hair** | **Ascomycota** | **Dermatophyte (Dermatophytosis)** | **By location** | Tinea barbae/tinea capitis (Kerion · · Tinea corporis (Ringworm · Dermatophytids · · Tinea cruris · Tinea manuum · Tinea pedis (athlete's foot) · Tinea unguium/onychomycosis (White superficial onychomycosis · Distal subungual onychomycosis · Proximal subungual onychomycosis · · Tinea corporis gladiatorum · Tinea faciei · Tinea imbricata · Tinea incognito · Favus · |
| | | | **By organism** | *Epidermophyton floccosum* · *Microsporum canis* · *Microsporum audouinii* · *Trichophyton interdigitale/mentagrophytes* · *Trichophyton tonsurans* · *Trichophyton schoenleini* · *Trichophyton rubrum* · *Trichophyton verrucosum* · |
| | | **Other** | | *Hortaea werneckii* (Tinea nigra · · *Piedraia hortae* (Black piedra · · |
| | **Basidiomycota** | *Malassezia furfur* (Tinea versicolor · Pityrosporum folliculitis · · *Trichosporon* (White piedra · · | | |
| | **Ascomycota** | **Dimorphic (yeast+mold)** | **Onygenales** | *Coccidioides immitis*/*Coccidioides posadasii* (Coccidioidomycosis · Disseminated coccidioidomycosis · Primary cutaneous coccidioidomycosis. Primary pulmonary coccidioidomycosis · · *Histoplasma capsulatum* (Histoplasmosis · Primary cutaneous histoplasmosis · Primary pulmonary histoplasmosis · Progressive disseminated histoplasmosis · · *Histoplasma duboisii* (African histoplasmosis · · *Lacazia loboi* (Lobomycosis · · *Paracoccidioides brasiliensis* (Paracoccidioidomycosis · · |
| | | | **Other** | *Blastomyces dermatitidis* (Blastomycosis · North American blastomycosis · South American blastomycosis · · *Sporothrix schenckii* (Sporotrichosis · · *Penicillium marneffei* (Penicilliosis · · |
| | | | | *Candida albicans* (**Candidiasis** · Oral · Esophageal · |

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|---|---|---|---|
| **Subcutaneous, systemic, and opportunistic** | | **Yeast-like** | Vulvovaginal · Chronic mucocutaneous · Antibiotic candidiasis · Candidal intertrigo · Candidal onychomycosis · Candidal paronychia · Candidid · Diaper candidiasis · Congenital cutaneous candidiasis · Perianal candidiasis · Systemic candidiasis · Erosio interdigitalis blastomycetica · · *C. glabrata* · *C. tropicalis* · *C. lusitaniae* · *Pneumocystis jirovecii* (Pneumocystosis · Pneumocystis pneumonia · · |
| | | **Mold-like** | *Aspergillus* (Aspergillosis · Aspergilloma · Allergic bronchopulmonary aspergillosis · Primary cutaneous aspergillosis · · *Exophiala jeanselmei* (Eumycetoma · · *Fonsecaea pedrosoi*/*Fonsecaea compacta*/*Phialophora verrucosa* (Chromoblastomycosis · · *Geotrichum candidum* (Geotrichosis · · *Pseudallescheria boydii* (Allescheriasis · · |
| | **Basidiomycota** | | *Cryptococcus neoformans* (Cryptococcosis · *Trichosporon* spp · Trichosporonosis · · |
| | **Zygomycota (Zygomycosis)** | **Mucorales (Mucormycosis)** | *Rhizopus oryzae* · *Mucor indicus* · *Lichtheimia corymbifera* · *Syncephalastrum racemosum* · *Apophysomyces variabilis* · |
| | | **Entomophthorales (Entomophthoramycosis)** | *Basidiobolus ranarum* (Basidiobolomycosis · · *Conidiobolus coronatus*/*Conidiobolus incongruus* (Conidiobolomycosis · · |
| | **Microsporidia (Microsporidiosis)** | | *Enterocytozoon bieneusi*/*Encephalitozoon intestinalis* · |
| **Mesomycetozoea** | *Rhinosporidium seeberi* (Rhinosporidiosis · · | | |
| **Ungrouped** | Alternariosis · Fungal folliculitis · *Fusarium* (Fusariosis · · Granuloma gluteale infantum · Hyalohyphomycosis · Otomycosis · Phaeohyphomycosis · | | |
| **Authority control** | NDL: 00576756 · | | |

Categories: Mycosis-related cutaneous conditions | Animal fungal diseases

# Cellulitis

From Wikipedia, the free encyclopedia

*This article is about infection of skin and its underlying connective tissue. For the dimpled appearance of skin, see cellulite.*

**Cellulitis** is a bacterial infection involving the inner layers of the skin. It specifically affects the dermis and subcutaneous fat. Signs and symptoms include an area of redness which increases in size over a couple of days. The borders of the area of redness are generally not sharp and the skin may be swollen. While the redness often turns white when pressure is applied this is not always the case. The area of infection is usually painful.[1] Lymphatic vessels may occasionally be involved,[1][2] and the person may have a fever and feel tired.[3]

The legs and face are the most common site involved, though cellulitis can occur on any part of the body. The leg is typically affected following a break in the skin. Other risk factors include obesity, leg swelling, and old age. For face infections a break in the skin beforehand is not usually the case. The bacteria most commonly involved are streptococci and *Staphylococcus aureus*. In contrast to cellulitis, erysipelas is a bacterial infection involving the more superficial layers of the skin, present with an area of redness with well-defined edges, and more often is associated with a fever. Diagnosis is usually based on the presenting signs and symptoms while cell culture is rarely possible.[1] Before making a diagnosis, more serious infections such as an underlying bone infection or necrotizing fasciitis should be ruled out.[2]

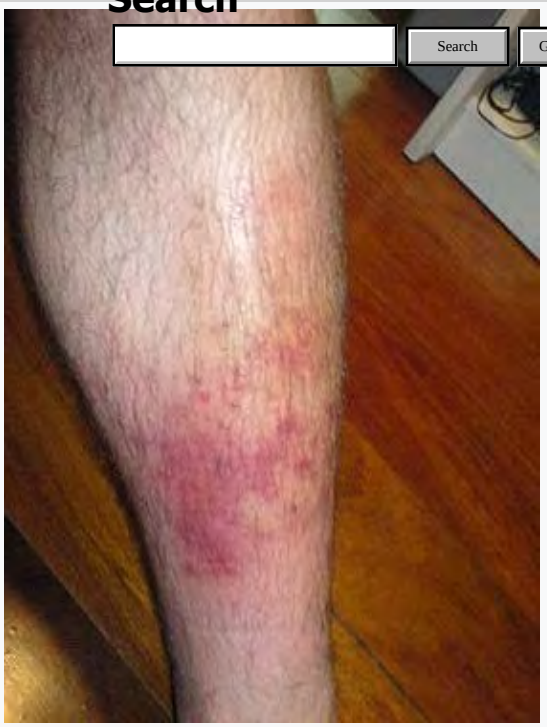
Treatment with antibiotics taken by mouth, such as cephalexin, amoxicillin, or cloxacillin, is often used.[1][4] In those who are seriously allergic to penicillin, erythromycin or clindamycin may be used.[4] When methicillin-resistant *S. aureus* (MRSA) is a concern, doxycycline or trimethoprim/sulfamethoxazole may, in addition, be recommended.[1] Concern is related to the presence of pus or previous MRSA infections.[1][3] Elevating the infected area may be useful[2] as may pain killers.[4]

Around 95% of people are better after seven to ten days of treatment.[3] Potential complications include abscess formation.[1] Bacterial skin infections affected about 155 million people and cellulitis occurred in about 37 million people in 2013.[5] This is about two of every 1000 people per year.[1] Cellulitis in 2013 resulted in about 30,000 deaths worldwide.[6] In the United Kingdom, cellulitis was the reason for 1.6% of admissions to hospital.[4]

Contents



**Cellulitis**



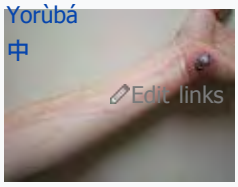
Skin cellulitis

| | |
|---|---|
| **Specialty** | Infectious disease |
| **Symptoms** | redness, heat, pain |
| **Duration** | 7-10 days |
| **Causes** | bacteria |
| **Risk factors** | weak immune system, diabetes, poor circulation |
| **Differential diagnosis** | deep vein thrombosis, stasis dermatitis, Lyme disease |
| **Medication** | antibiotics |
| **Frequency** | 37 million per year (global) |
| **Deaths** | 30,000 per year (global) |

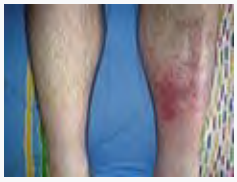
[edit on Wikidata]

## Signs and symptoms [edit]

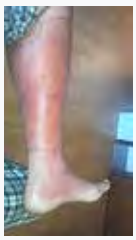
The typical signs and symptoms of cellulitis is an area which is red, hot, and painful. The photos shown here of are of mild to moderate cases, and are not representative of earlier stages of the condition.



Cellulitis following an abrasion: Note the red streaking up the arm from involvement of the lymphatic system.



Infected left shin in comparison to shin with no sign of symptoms



Cellulitis of the leg with foot involvement

## Causes [edit]

Cellulitis is caused by a type of bacteria entering the skin, usually by way of a cut, abrasion, or break in the skin. This break does not need to be visible. Group A *Streptococcus* and *Staphylococcus* are the most common of these bacteria, which are part of the normal flora of the skin, but normally cause no actual infection while on the skin's outer surface.

About 80% of cases of Ludwig's angina, or cellulitis of the submandibular space, are caused by dental infections. Mixed infections, due to both aerobes and anaerobes, are commonly associated with this type of cellulitis. Typically, this includes alpha-hemolytic streptococci, staphylococci, and bacteroides groups.[7]

Predisposing conditions for cellulitis include insect or spider bite, blistering, animal bite, tattoos, pruritic (itchy) skin rash, recent surgery, athlete's foot, dry skin, eczema, injecting drugs (especially subcutaneous or intramuscular injection or where an attempted intravenous injection "misses" or blows the vein), pregnancy, diabetes, and obesity, which can affect circulation, as well as burns and boils, though debate exists as to whether minor foot lesions contribute. Occurrences of cellulitis may also be associated with the rare condition hidradenitis suppurativa or dissecting cellulitis.

The appearance of the skin assists a doctor in determining a diagnosis. A doctor may also suggest blood tests, a wound culture, or other tests to help rule out a blood clot deep in the veins of the legs. Cellulitis in the lower leg is characterized by signs and symptoms similar to those of a deep vein thrombosis, such as warmth, pain, and swelling (inflammation).

This reddened skin or rash may signal a deeper, more serious infection of the inner layers of skin. Once below

the skin, the bacteria can spread rapidly, entering the lymph nodes and the bloodstream and spreading throughout the body. This can result in influenza-like symptoms with a high temperature and sweating or feeling very cold with shaking, as the sufferer cannot get warm.

In rare cases, the infection can spread to the deep layer of tissue called the fascial lining. Necrotizing fasciitis, also called by the media "flesh-eating bacteria", is an example of a deep-layer infection. It is a medical emergency.

### Risk factors [edit]

The elderly and those with immunodeficiency (a weakened immune system) are especially vulnerable to contracting cellulitis. Diabetics are more susceptible to cellulitis than the general population because of impairment of the immune system; they are especially prone to cellulitis in the feet, because the disease causes impairment of blood circulation in the legs, leading to diabetic foot/foot ulcers. Poor control of blood glucose levels allows bacteria to grow more rapidly in the affected tissue, and facilitates rapid progression if the infection enters the bloodstream. Neural degeneration in diabetes means these ulcers may not be painful, and thus often become infected. Those who have suffered poliomyelitis are also prone because of circulatory problems, especially in the legs.

Immunosuppressive drugs, and other illnesses or infections that weaken the immune system, are also factors that make infection more likely. Chickenpox and shingles often result in blisters that break open, providing a gap in the skin through which bacteria can enter. Lymphedema, which causes swelling on the arms and/or legs, can also put an individual at risk.

Diseases that affect blood circulation in the legs and feet, such as chronic venous insufficiency and varicose veins, are also risk factors for cellulitis.

Cellulitis is also common among dense populations sharing hygiene facilities and common living quarters, such as military installations, college dormitories, nursing homes, oil platforms, and homeless shelters.

## Diagnosis [edit]

Cellulitis is most often a clinical diagnosis, readily identified in many people by history and physical examination alone, with rapidly spreading areas of cutaneous swelling, redness and heat, occasionally associated with inflammation of regional lymph nodes. While classically distinguished as a separate entity from erysipelas by spreading more deeply to involve the subcutaneous tissues, many clinicians may classify erysipelas as cellulitis. Both are often treated similarly, but cellulitis associated with furuncles, carbuncles, or abscesses is usually caused S. aureus, which may affect treatment decisions, especially antibiotic selection.[8] Skin aspiration of non-purulent cellulitis, usually caused by streptococcal organisms, is rarely helpful for diagnosis and blood cultures are positive in fewer than 5% of all cases.[8]

It is important to evaluate for co-existent abscess as this finding usually requires surgical drainage as opposed to antibiotic therapy alone. Physicians' clinical assessment for abscess may be limited, especially in cases with extensive overlying induration, but use of bedside ultrasonography performed by an experienced practitioner readily discriminates between abscess and cellulitis and may change management in up to 56% of cases.[9] Use of ultrasound for abscess identification may also be indicated in cases of antibiotic failure. Cellulitis has a characteristic "cobblestoned" appearance indicative of subcutaneous edema without a defined hypoechoic, heterogeneous fluid collection that would indicate abscess.[10]

### Differential diagnosis [edit]

Other conditions that may mimic cellulitis include deep vein thrombosis, which can be diagnosed with a compression leg ultrasound, and stasis dermatitis, which is inflammation of the skin from poor blood flow. Signs of a more severe infection such as necrotizing fasciitis or gas gangrene that would require prompt surgical intervention include purple bullae, skin sloughing, subcutaneous edema and systemic toxicity.[8] Misdiagnosis can occur in up to 30% of people with suspected lower extremity cellulitis, leading to 50,000 to 130,000 unnecessary hospitalization and $195 to $515 million in avoidable healthcare spending annually in the United States.[11]

Associated musculoskeletal findings are sometimes reported. When it occurs with acne conglobata, hidradenitis suppurativa, and pilonidal cysts, the syndrome is referred to as the follicular occlusion triad or tetrad.[12]

Lyme disease can be misdiagnosed as staphylococcal- or streptococcal-induced cellulitis. Because the characteristic bullseye rash does not always appear in people infected with Lyme disease, the similar set of symptoms may be misdiagnosed as cellulitis. Standard treatments for cellulitis are not sufficient for curing Lyme disease. The only way to rule out Lyme disease is with a blood test, which is recommended during warm months in areas where the disease is endemic.[13]

## Prevention [edit]

In those who have previously had cellulitis, the use of antibiotics may help prevent future episodes.[14] This is recommended by CREST for those who have had more than two episodes.[4]

## Treatment [edit]

Antibiotics are usually prescribed, with the agent selected based on suspected organism and presence or absence of purulence,[8] although the best treatment choice is unclear.[15] If an abscess is also present surgical drainage is usually indicated, with antibiotics often prescribed for co-existent cellulitis, especially if extensive.[9] Pain relief is also often prescribed, but excessive pain should always be investigated as it is a symptom of necrotizing fasciitis. Elevation of the affected area is often recommended.

Steroids may speed recovery in those on antibiotics.[1]

### Antibiotics [edit]

Antibiotics choices depend on regional availability, but a penicillinase-resistant semisynthetic penicillin or a first-generation cephalosporin are currently recommended for cellulitis without abscess.[8] A course of antibiotics is not effective in between 6 and 37% of cases.[16]

## Epidemiology [edit]

Cellulitis in 2013 resulted in about 30,000 deaths worldwide, up from 27,000 in 1990.[6]

## Other animals [edit]

Horses may acquire cellulitis, usually secondarily to a wound (which can be extremely small and superficial) or to a deep-tissue infection, such as an abscess or infected bone, tendon sheath, or joint.[17][18] Cellulitis from a superficial wound usually creates less lameness (grade 1–2 of 5) than that caused by septic arthritis (grade 4–5). The horse exhibits inflammatory edema, which is hot, painful swelling. This swelling differs from stocking up in that the horse does not display symmetrical swelling in two or four legs, but in only one leg. This swelling begins near the source of infection, but eventually continues down the leg. In some cases, the swelling also travels distally. Treatment includes cleaning the wound and caring for it properly, the administration of NSAIDs, such as phenylbutazone, cold hosing, applying a sweat wrap or a poultice, and mild exercise. Veterinarians may also prescribe antibiotics. Cellulitis is also seen in staphylococcal and corynebacterial mixed infections in bulls.[19]

## See also [edit]

- Erysipelas
- *Haemophilus influenzae* cellulitis
- *Helicobacter* cellulitis
- Tuberculous cellulitis

## References [edit]

1. ^ *a b c d e f g h i* Vary, JC; O'Connor, KM (May 2014). *England Journal of Medicine*. **370** (11): 1039–1047.

"Common Dermatologic Conditions.". *The Medical clinics of North America*. **98** (3): 445–485. doi:10.1016/j.mcna.2014.01.005. PMID 24758956.

2. ^ [a] [b] [c] Tintinalli, Judith E. (2010). *Emergency Medicine: A Comprehensive Study Guide (Emergency Medicine (Tintinalli))* (7th ed.). New York: McGraw-Hill Companies. p. 1016. ISBN 0-07-148480-9.
3. ^ [a] [b] [c] Mistry, RD (Oct 2013). "Skin and soft tissue infections.". *Pediatric clinics of North America*. **60** (5): 1063–82. doi:10.1016/j.pcl.2013.06.011. PMID 24093896.
4. ^ [a] [b] [c] [d] [e] Phoenix, G; Das, S; Joshi, M (Aug 7, 2012). "Diagnosis and management of cellulitis.". *BMJ (Clinical research ed.)*. **345**: e4955. doi:10.1136/bmj.e4955. PMID 22872711.
5. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
6. ^ [a] [b] GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
7. ^ Dhingra, PL; Dhingra, Shruti (2010) [1992]. Nasim, Shabina, ed. *Diseases of Ear, Nose and Throat*. Dhingra, Deeksha (5th ed.). New Delhi: Elsevier. pp. 277–8. ISBN 978-81-312-2364-2.
8. ^ [a] [b] [c] [d] [e] Stevens, Dennis L.; Bisno, Alan L.; Chambers, Henry F.; Dellinger, E. Patchen; Goldstein, Ellie J. C.; Gorbach, Sherwood L.; Hirschmann, Jan V.; Kaplan, Sheldon L.; Montoya, Jose G. (2014-06-18). "Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America". *Clinical Infectious Diseases*. **59**: ciu296. doi:10.1093/cid/ciu296. ISSN 1058-4838. PMID 24947530.
9. ^ [a] [b] Singer, Adam J.; Talan, David A. (2014-03-13). "Management of Skin Abscesses in the Era of Methicillin-Resistant Staphylococcus aureus". *New* doi:10.1056/NEJMra1212788. ISSN 0028-4793. PMID 24620867.
10. ^ Bornemann, Paul; Rao, Victor; Hoppmann, Richard (2015-05-04). "Ambulatory Ultrasound". In Mayeaux, E.J. *The Essential Guide to Primary Care Procedures*. Lippincott Williams & Wilkins. ISBN 9781496318718.
11. ^ Weng, Qing Yu; Raff, Adam B.; Cohen, Jeffrey M.; Gunasekera, Nicole; Okhovat, Jean-Phillip; Vedak, Priyanka; Joyce, Cara; Kroshinsky, Daniela; Mostaghimi, Arash. "Costs and Consequences Associated With Misdiagnosed Lower Extremity Cellulitis". *JAMA Dermatology*. doi:10.1001/jamadermatol.2016.3816.
12. ^ Scheinfeld NS (February 2003). "A case of dissecting cellulitis and a review of the literature". *Dermatol. Online J.* **9** (1): 8. PMID 12639466.
13. ^ Nowakowski J, McKenna D, Nadelman RB, et al. (June 2000). "Failure of treatment with cephalexin for Lyme disease". *Arch Fam Med*. **9** (6): 563–7. doi:10.1001/archfami.9.6.563. PMID 10862221.
14. ^ Oh, CC; Ko, HC; Lee, HY; Safdar, N; Maki, DG; Chlebicki, MP (Feb 24, 2014). "Antibiotic prophylaxis for preventing recurrent cellulitis: A systematic review and meta-analysis.". *The Journal of infection*. **69** (1): 26–34. doi:10.1016/j.jinf.2014.02.011. PMID 24576824.
15. ^ Kilburn, SA; Featherstone, P; Higgins, B; Brindle, R (16 June 2010). "Interventions for cellulitis and erysipelas.". *The Cochrane database of systematic reviews* (6): CD004299. doi:10.1002/14651858.CD004299.pub2. PMID 20556757.
16. ^ Obaitan, Itegbemie; Dwyer, Richard; Lipworth, Adam D.; Kupper, Thomas S.; Camargo, Carlos A.; Hooper, David C.; Murphy, George F.; Pallin, Daniel J. (May 2016). "Failure of antibiotics in cellulitis trials: a systematic review and meta-analysis". *The American Journal of Emergency Medicine*. **34**: 1645–1652. doi:10.1016/j.ajem.2016.05.064.
17. ^ Adam EN, Southwood LL (August 2006). "Surgical and traumatic wound infections, cellulitis, and myositis in horses". *Vet. Clin. North Am. Equine Pract*. **22** (2): 335–61, viii. doi:10.1016/j.cveq.2006.04.003. PMID 16882479.
18. ^ Fjordbakk CT, Arroyo LG, Hewson J (February 2008). "Retrospective study of the clinical features of limb cellulitis in 63 horses". *Vet. Rec*. **162** (8): 233–6. doi:10.1136/vr.162.8.233. PMID 18296664.
19. ^ Pathan MM, Khan MA, Bhonsle AV, Bhikane AU, Moregaonkar SD, Kulkarni MB (2012). "Cellulitis in a Red Kandhari Bull : A Case Report". *Vetworld*. **5** (3): 183–4. doi:10.5455/vetworld.2012.183-184.

## Further reading [edit]

- Stevens, DL; Bisno, AL; Chambers, HF; Dellinger, EP; Goldstein, EJ; Gorbach, SL; Hirschmann, JV; Kaplan, SL; Montoya, JG; Wade, JC (15 July 2014). "Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America.". *Clinical Infectious Diseases*. **59** (2): 147–59. doi:10.1093/cid/ciu296. PMID 24947530.

## External links [edit]

| | |
|---|---|
| **Classification** | **ICD-10**: L03 · **ICD-9-CM**: 682.9 · **MeSH**: D002481 · **DiseasesDB**: 29806 · |
| **External resources** | **MedlinePlus**: 000855 · **eMedicine**: med/310 emerg/88 derm/464 · |

| v · t · e · | **Diseases of the skin and appendages by morphology** | | | | |
|---|---|---|---|---|---|
| **Growths** | **Epidermal** | | | | wart · callus · seborrheic keratosis · acrochordon · molluscum contagiosum · actinic keratosis · squamous-cell carcinoma · basal-cell carcinoma · Merkel-cell carcinoma · nevus sebaceous · trichoepithelioma · |
| | **Pigmented** | | | | Freckles · lentigo · melasma · nevus · melanoma · |
| | **Dermal and subcutaneous** | | | | epidermal inclusion cyst · hemangioma · dermatofibroma (benign fibrous histiocytoma) · keloid · lipoma · neurofibroma · xanthoma · Kaposi's sarcoma · infantile digital fibromatosis · granular cell tumor · leiomyoma · lymphangioma circumscriptum · myxoid cyst · |
| **Rashes** | **With epidermal involvement** | **Eczematous** | | | contact dermatitis · atopic dermatitis · seborrheic dermatitis · stasis dermatitis · lichen simplex chronicus · Darier's disease · glucagonoma syndrome · langerhans cell histiocytosis · lichen sclerosus · pemphigus foliaceus · Wiskott–Aldrich syndrome · Zinc deficiency · |
| | | **Scaling** | | | psoriasis · tinea (corporis · cruris · pedis · manuum · faciei) · pityriasis rosea · secondary syphilis · mycosis fungoides · systemic lupus erythematosus · pityriasis rubra pilaris · parapsoriasis · ichthyosis · |
| | | **Blistering** | | | herpes simplex · herpes zoster · varicella · bullous impetigo · acute contact dermatitis · pemphigus vulgaris · bullous pemphigoid · dermatitis herpetiformis · porphyria cutanea tarda · epidermolysis bullosa simplex · |
| | | **Papular** | | | scabies · insect bite reactions · lichen planus · miliaria · keratosis pilaris · lichen spinulosus · transient acantholytic dermatosis · lichen nitidus · pityriasis lichenoides et varioliformis acuta · |
| | | **Pustular** | | | acne vulgaris · acne rosacea · folliculitis · impetigo · candidiasis · gonococcemia · dermatophyte · coccidioidomycosis · subcorneal pustular dermatosis · |
| | | **Hypopigmented** | | | tinea versicolor · vitiligo · pityriasis alba · postinflammatory hyperpigmentation · tuberous sclerosis · idiopathic guttate hypomelanosis · leprosy · hypopigmented mycosis fungoides · |
| | **Without epidermal** | **Red** | **Blanchable Erythema** | **Generalized** | drug eruptions · viral exanthems · toxic erythema · systemic lupus erythematosus · |
| | | | | **Localized** | **cellulitis** · abscess · boil · erythema nodosum · carcinoid syndrome · fixed drug eruption · |
| | | | | **Specialized** | urticaria · erythema (multiforme · migrans · gyratum repens · |

| | | | | | |
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| | **involvement** | | | | annulare centrifugum · ab igne) · |
| | | | **Nonblanchable Purpura** | **Macular** | thrombocytopenic purpura · actinic/solar purpura · |
| | | | | **Papular** | disseminated intravascular coagulation · vasculitis · |
| | | **Indurated** | scleroderma/morphea · granuloma annulare · lichen sclerosis et atrophicus · necrobiosis lipoidica · | | |
| **Miscellaneous disorders** | **Ulcers** | | | | |
| | **Hair** | telogen effluvium · androgenic alopecia · trichotillomania · alopecia areata · systemic lupus erythematosus · tinea capitis · loose anagen syndrome · lichen planopilaris · folliculitis decalvans · acne keloidalis nuchae · | | | |
| | **Nail** | onychomycosis · psoriasis · paronychia · ingrown nail · | | | |
| | **Mucous membrane** | Aphthous stomatitis · oral candidiasis · lichen planus · leukoplakia · pemphigus vulgaris · mucous membrane pemphigoid · cicatricial pemphigoid · herpesvirus · coxsackievirus · syphilis · systemic histoplasmosis · squamous-cell carcinoma · | | | |

| v · t · e · | **Bacterial skin disease (L00–L08, 680–686)** |
|---|---|
| **Gram +ve** | **Firmicutes** |
| | *Staphylococcus* (Staphylococcal scalded skin syndrome · Impetigo · Toxic shock syndrome · · *Streptococcus* (Impetigo · Cutaneous group B streptococcal infection · Streptococcal intertrigo · Cutaneous *Streptococcus iniae* infection · Erysipelas / Chronic recurrent erysipelas · Scarlet fever · · *Corynebacterium* (Erythrasma · · Listeriosis · *Clostridium* (Gas gangrene · Dermatitis gangrenosa · · Mycoplasma · Erysipeloid of Rosenbach · |
| | **Actinobacteria** |
| | *Mycobacterium-related:* Aquarium granuloma · Borderline lepromatous leprosy · Borderline leprosy · Borderline tuberculoid leprosy · Buruli ulcer · Erythema induratum · Histoid leprosy · Lepromatous leprosy · Leprosy · Lichen scrofulosorum · Lupus vulgaris · Miliary tuberculosis · *Mycobacterium avium-intracellulare complex* infection · *Mycobacterium haemophilum* infection · *Mycobacterium kansasii* infection · Papulonecrotic tuberculid · Primary inoculation tuberculosis · Rapid growing mycobacterium infection · Scrofuloderma · Tuberculosis cutis orificialis · Tuberculosis verrucosa cutis · Tuberculous cellulitis · Tuberculous gumma · Tuberculoid leprosy · |
| | Cutaneous actinomycosis · Nocardiosis · Cutaneous diphtheria infection · *Arcanobacterium haemolyticum* infection · Group JK corynebacterium sepsis · |
| | **Proteobacteria** |
| | α: Endemic typhus · Epidemic typhus · Scrub typhus · North Asian tick typhus · Queensland tick typhus · Flying squirrel typhus · Trench fever · Bacillary angiomatosis · African tick bite fever · American tick bite fever · *Rickettsia aeschlimannii* infection · Rickettsialpox · Rocky Mountain spotted fever · Human granulocytotropic anaplasmosis · Human monocytotropic ehrlichiosis · Flea-borne spotted fever · Japanese spotted fever · Mediterranean spotted fever · Flinders Island spotted fever · Verruga peruana · Brill–Zinsser disease · Brucellosis · Cat-scratch disease · Oroya fever · Ehrlichiosis ewingii infection · |
| | β: Gonococcemia/Gonorrhea/Primary gonococcal dermatitis · Melioidosis · |

| | | |
|---|---|---|
| **Gram -ve** | | Cutaneous *Pasteurella hemolytica* infection · Meningococcemia · Glanders · Chromobacteriosis infection ·<br>γ: Pasteurellosis · Tularemia · Vibrio vulnificus · Rhinoscleroma · *Haemophilus influenzae* cellulitis · Pseudomonal pyoderma / Pseudomonas hot-foot syndrome / Hot tub folliculitis / Ecthyma gangrenosum / Green nail syndrome · Q fever · Salmonellosis · Shigellosis · Plague · Granuloma inguinale · Chancroid · Aeromonas infection ·<br>ε: Helicobacter cellulitis · |
| | **Other** | Syphilid · Syphilis · Chancre · Yaws · Pinta · Bejel · Chlamydia infection · Leptospirosis · Rat-bite fever · Lyme disease · Lymphogranuloma venereum · |
| **Unspecified pathogen** | | Abscess (Periapical abscess · · Boil/furuncle (Hospital furunculosis · · Carbuncle · **Cellulitis** (Paronychia / Pyogenic paronychia · Perianal cellulitis · · Acute lymphadenitis · Pilonidal cyst · Pyoderma · Folliculitis (Superficial pustular folliculitis · Sycosis vulgaris · · Pimple · Ecthyma · Pitted keratolysis · Trichomycosis axillaris · Necrotizing fascitis · Gangrene (Chronic undermining burrowing ulcers · Fournier gangrene · · Elephantiasis nostras · Blistering distal dactylitis · Botryomycosis · Malakoplakia · Gram-negative folliculitis · Gram-negative toe web infection · Pyomyositis · Blastomycosis-like pyoderma · Bullous impetigo · Chronic lymphangitis · Recurrent toxin-mediated perineal erythema · Tick-borne lymphadenopathy · Tropical ulcer · |

| v · t · e · | **Inflammation** | | |
|---|---|---|---|
| **Acute** | **Plasma derived mediators** | Bradykinin · *complement* (C3 · C5a · MAC · · *coagulation* (Factor XII · Plasmin · Thrombin · · | |
| | **Cell derived mediators** | *preformed:* | Lysosome granules · *biogenic amines* (Histamine · Serotonin · · |
| | | *synthesized on demand:* | *cytokines* (IFN-γ · IL-8 · TNF-α · IL-1 · · *eicosanoids* (Leukotriene B4 · Prostaglandins · · Nitric oxide · Kinins · |
| **Chronic** | Macrophage · Epithelioid cell · Giant cell · Granuloma · | | |
| **Processes** | **Traditional:** | Rubor · Calor · Tumor · Dolor · Functio laesa · | |
| | **Modern:** | Acute-phase reaction/Fever · Vasodilation · Increased vascular permeability · Exudate · Leukocyte extravasation · Chemotaxis · | |
| | **Nervous** | *CNS* (Encephalitis · Myelitis · · Meningitis (Arachnoiditis · · *PNS* (Neuritis · · *eye* (Dacryoadenitis · Scleritis · Episcleritis · Keratitis · chorioretinitis · Retinitis · Chorioretinitis · Blepharitis · Conjunctivitis · Uveitis · · *ear* (Otitis · Labyrinthitis · Mastoiditis · · | |
| | **Cardiovascular** | Carditis (Endocarditis · Myocarditis · Pericarditis · · Vasculitis (Arteritis · Phlebitis · Capillaritis · · | |
| | **Respiratory** | *upper* (Sinusitis · Rhinitis · Pharyngitis · Laryngitis · · *lower* (Tracheitis · Bronchitis · Bronchiolitis · Pneumonitis · Pleuritis · · Mediastinitis · | |
| | **Digestive** | *mouth* | Stomatitis · Gingivitis · Gingivostomatitis · Glossitis · Tonsillitis · Sialadenitis/Parotitis · Cheilitis · Pulpitis · Gnathitis · |
| | | *tract* | Esophagitis · Gastritis · Gastroenteritis · Enteritis · Colitis · Enterocolitis · Duodenitis · Ileitis · Caecitis · Appendicitis · Proctitis · |
| | | *accessory* | Hepatitis · Ascending cholangitis · Cholecystitis · Pancreatitis · |

| Specific locations | | | |
|---|---|---|---|
| | | | Peritonitis · |
| | **Integumentary** | | Dermatitis (Folliculitis · · **Cellulitis** · Hidradenitis · |
| | **Musculoskeletal** | | Arthritis · Dermatomyositis · *soft tissue* (Myositis · Synovitis/Tenosynovitis · Bursitis · Enthesitis · Fasciitis · Capsulitis · Epicondylitis · Tendinitis · Panniculitis · · Osteochondritis: Osteitis/Osteomyelitis (Spondylitis · Periostitis · · Chondritis · |
| | **Urinary** | | Nephritis (Glomerulonephritis · Pyelonephritis · · Ureteritis · Cystitis · Urethritis · |
| | **Reproductive** | *female:* | Oophoritis · Salpingitis · Endometritis · Parametritis · Cervicitis · Vaginitis · Vulvitis · Mastitis · |
| | | *male:* | Orchitis · Epididymitis · Prostatitis · Seminal vesiculitis · Balanitis · Posthitis · Balanoposthitis · |
| | | *pregnancy/newborn:* | Chorioamnionitis · Funisitis · Omphalitis · |
| | **Endocrine** | | Insulitis · Hypophysitis · Thyroiditis · Parathyroiditis · Adrenalitis · |
| | **Lymphatic** | | Lymphangitis · Lymphadenitis · |

Categories: Bacterium-related cutaneous conditions | Disorders of fascia | Equine injury and lameness | Inflammations

# Chickenpox

From Wikipedia, the free encyclopedia

*For other uses, see Chickenpox (disambiguation).*
*"Varicella" redirects here. For other uses, see Varicella (disambiguation).*
*Not to be confused with Fowlpox or Smallpox.*

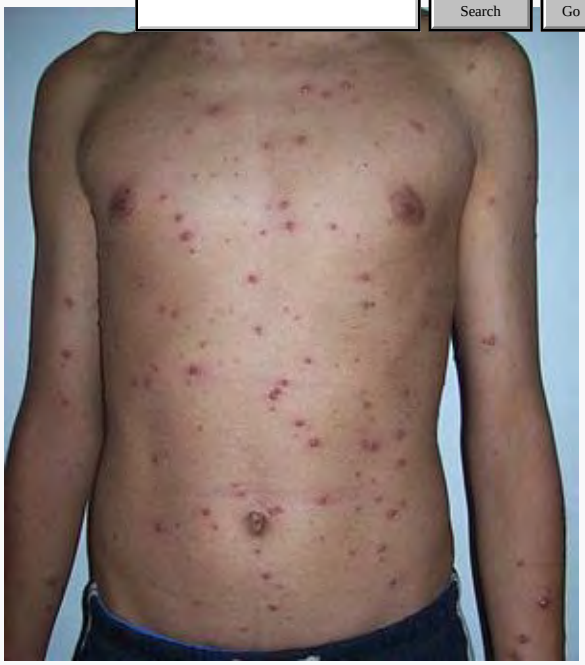
**Chickenpox**, also known as **varicella**, is a highly contagious disease caused by the initial infection with varicella zoster virus (VZV).[1] The disease results in a characteristic skin rash that forms small, itchy blisters, which eventually scab over.[2] It usually starts on the chest, back, and face then spreads to the rest of the body.[2] Other symptoms may include fever, feeling tired, and headaches.[2] Symptoms usually last five to ten days.[2] Complications may occasionally include pneumonia, inflammation of the brain, or bacterial infections of the skin among others.[3] The disease is often more severe in adults than children.[4] Symptoms begin ten to twenty-one days after exposure to the virus.[5]

Chickenpox is an airborne disease which spreads easily through the coughs and sneezes of an infected person.[5] It may be spread from one to two days before the rash appears until all lesions have crusted over.[5] It may also spread through contact with the blisters.[5] Those with shingles may spread chickenpox to those who are not immune through contact with the blisters.[5] The disease can usually be diagnosed based on the presenting symptom; however, in unusual cases may be confirmed by polymerase chain reaction (PCR) testing of the blister fluid or scabs.[4] Testing for antibodies may be done to determine if a person is or is not immune.[4] People usually only get the disease once.[5] Although reinfections by the virus occur, these reinfections usually do not cause any symptoms.[7]

The varicella vaccine has resulted in a decrease in the number of cases and complications from the disease.[8] It protects about 70 to 90 percent of people from disease with a greater benefit for severe disease.[4] Routine immunization of children is recommended in many countries.[9] Immunization within three days of exposure may improve outcomes in children.[10] Treatment of those infected may include calamine lotion to help with itching, keeping the fingernails short to decrease injury from scratching, and the use of paracetamol (acetaminophen) to help with fevers.[5] For those at increased risk of complications antiviral medication such as aciclovir are recommended.[5]

Chickenpox occurs in all parts of the world.[4] As of 2013 140 million cases of chickenpox and herpes zoster occurred.[11] Before routine immunization the number of cases occurring each year was similar to the number of people born.[4] Since immunization the number of infections in [4]

## Variants




Male with varicella disease

| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | B01 |
| **ICD-9-CM** | 052 |
| **DiseasesDB** | 29118 |
| **MedlinePlus** | 001592 |
| **eMedicine** | ped/2385 derm/74, emerg/367 |
| **Patient UK** | Chickenpox |
| **MeSH** | *C02.256.466.175* |

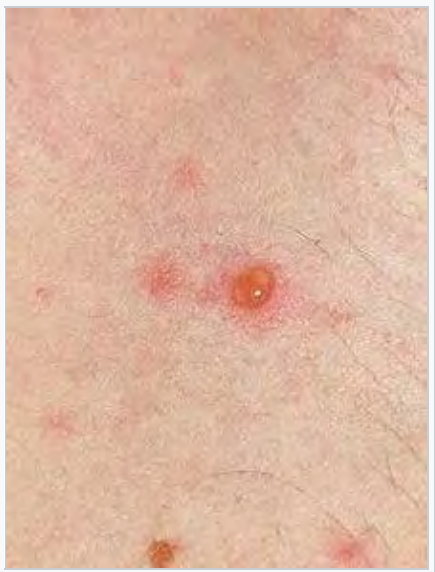
[edit on Wikidata]

the United States has decreased nearly 90%. In 2013 chickenpox resulted in 7,000 deaths globally – down from 8,900 in 1990.[12] Death occurs in about 1 per 60,000 cases.[4] Chickenpox was not separated from smallpox until the late 19th century.[4] In 1888 its connection to shingles was determined.[4] The first documented use of the term *chicken pox* was in 1658.[13] Various explanations have been suggested for the use of "chicken" in the name, one being the relative mildness of the disease.[13]



## Signs and symptoms [edit]

The early (prodromal) symptoms in adolescents and adults are nausea, loss of appetite, aching muscles, and headache. This is followed by the characteristic rash or oral sores, malaise, and a low-grade fever that signal the presence of the disease. Oral manifestations of the disease (enanthem) not uncommonly may precede the external rash (exanthem). In children the illness is not usually preceded by prodromal symptoms, and the first sign is the rash or the spots in the oral cavity. The rash begins as small red dots on the face, scalp, torso, upper arms and legs; progressing over 10–12 hours to small bumps, blisters and pustules; followed by umbilication and the formation of scabs.[14][15]



A single blister, typical during the early stages of the rash

At the blister stage, intense itching is usually present. Blisters may also occur on the palms, soles, and genital area. Commonly, visible evidence of the disease develops in the oral cavity and tonsil areas in the form of small ulcers which can be painful or itchy or both; this enanthem (internal rash) can precede the exanthem (external rash) by 1 to 3 days or can be concurrent. These symptoms of chickenpox appear 10 to 21 days after exposure to a contagious person. Adults may have a more widespread rash and longer fever, and they are more likely to experience complications, such as varicella pneumonia.[14]

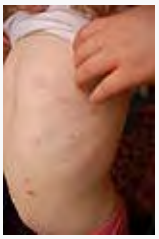
Because watery nasal discharge containing live virus usually precedes both exanthem (external rash) and enanthem (oral ulcers) by 1 to 2 days, the infected person actually becomes contagious one to two days before recognition of the disease. Contagiousness persists until all vesicular lesions have become dry crusts (scabs), which usually entails four or five days, by which time nasal shedding of live virus ceases.

The condition usually resolves by itself within a couple of weeks.[16] The rash may, however, last for up to one month, although the infectious stage does not last longer than a week or two.[*citation needed*]

Chickenpox is rarely fatal, although it is generally more severe in adult men than in women or children. Non-

immune pregnant women and those with a suppressed immune system are at highest risk of serious complications. Arterial ischemic stroke (AIS) associated with chickenpox in the previous year accounts for nearly one third of childhood AIS.[17] The most common late complication of chickenpox is shingles (herpes zoster), caused by reactivation of the *varicella zoster* virus decades after the initial, often childhood, chickenpox infection.

The back of a 30-year-old male after five days of the rash



A 3-year-old girl with a chickenpox rash on her torso

A child with chickenpox at an orphanage.

Lower leg of a child with chickenpox

## Pregnancy and neonates [edit]

During pregnancy the dangers to the fetus associated with a primary VZV infection are greater in the first six months. In the third trimester, the mother is more likely to have severe symptoms.[18] For pregnant women, antibodies produced as a result of immunization or previous infection are transferred via the placenta to the fetus.[19] Women who are immune to chickenpox cannot become infected and do not need to be concerned about it for themselves or their infant during pregnancy.[20]

Varicella infection in pregnant women could lead to spread via the placenta and infection of the fetus. If infection occurs during the first 28 weeks of gestation, this can lead to fetal varicella syndrome (also known as *congenital varicella syndrome*).[21] Effects on the fetus can range in severity from underdeveloped toes and fingers to severe anal and bladder malformation. Possible problems include:

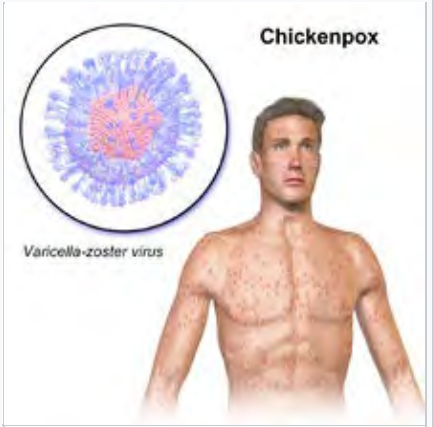
- Damage to brain: encephalitis,[22] microcephaly, hydrocephaly,[23] aplasia of brain
- Damage to the eye: optic stalk, optic cup, and lens vesicles, microphthalmia, cataracts, chorioretinitis, optic atrophy
- Other neurological disorder: damage to cervical and lumbosacral spinal cord, motor/sensory deficits, absent deep tendon reflexes, anisocoria/Horner's syndrome
- Damage to body: hypoplasia of upper/lower extremities, anal and bladder sphincter dysfunction
- Skin disorders: (cicatricial) skin lesions, hypopigmentation

Infection late in gestation or immediately following birth is referred to as "*neonatal varicella*".[24] Maternal infection is associated with premature delivery. The risk of the baby developing the disease is greatest following exposure to infection in the period 7 days before delivery and up to 8 days following the birth. The baby may also be exposed to the virus via infectious siblings or other contacts, but this is of less concern if the mother is immune. Newborns who develop symptoms are at a high risk of pneumonia and other serious complications of the disease.[25]

# Diagnosis [edit]

The diagnosis of chickenpox is primarily based on the signs and symptom, with typical early symptoms followed by a characteristic rash. Confirmation of the diagnosis is by examination of the fluid within the vesicles of the rash, or by testing blood for evidence of an acute immunologic response.

Vesicular fluid can be examined with a Tzanck smear, or better by testing for direct fluorescent antibody. The fluid can also be "cultured", whereby attempts are made to grow the virus from a fluid sample. Blood tests can be used to identify a response to acute infection (IgM) or previous infection and subsequent immunity (IgG).[26]



Chickenpox.

Prenatal diagnosis of fetal varicella infection can be performed using ultrasound, though a delay of 5 weeks following primary maternal infection is advised. A PCR (DNA) test of the mother's amniotic fluid can also be performed, though the risk of spontaneous abortion due to the amniocentesis procedure is higher than the risk of the baby's developing fetal varicella syndrome.[25]

## Pathophysiology [edit]

*Main article: Varicella zoster virus*

Exposure to VZV in a healthy child initiates the production of host immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA) antibodies; IgG antibodies persist for life and confer immunity. Cell-mediated immune responses are also important in limiting the scope and the duration of primary varicella infection. After primary infection, VZV is hypothesized to spread from mucosal and epidermal lesions to local sensory nerves. VZV then remains latent in the dorsal ganglion cells of the sensory nerves. Reactivation of VZV results in the clinically distinct syndrome of herpes zoster (i.e., *shingles*), postherpetic neuralgia,[27] and sometimes Ramsay Hunt syndrome type II.[28] Varicella zoster can affect the arteries in the neck and head, producing stroke, either during childhood, or after a latency period of many years.[29]

### Shingles [edit]

*Main article: Herpes zoster*

After a chickenpox infection, the virus remains dormant in the body's nerve tissues. The immune system keeps the virus at bay, but later in life, usually in an adult, it can be reactivated and cause a different form of the viral infection called shingles (also known as herpes zoster).[30] The United States Advisory Committee on Immunization Practices (ACIP) suggests that every adult over the age of 60 years get the *herpes zoster* vaccine.[31]

Shingles affects one in five adults infected with chickenpox as children, especially those who are immune-suppressed, particularly from cancer, HIV, or other conditions. Stress can bring on shingles as well, although scientists are still researching the connection.[32] Shingles are most commonly found in adults over the age of 60 who were diagnosed with chickenpox when they were under the age of 1.[33]

## Prevention [edit]

### Hygiene measures [edit]

The spread of chickenpox can be prevented by isolating affected individuals. Contagion is by exposure to respiratory droplets, or direct contact with lesions, within a period lasting from three days before the onset of the rash, to four days after the onset of the rash.[34] The chickenpox virus is susceptible to disinfectants, notably chlorine bleach (i.e., sodium hypochlorite). Like all enveloped viruses, it is sensitive to desiccation, heat and detergents.

### Vaccine [edit]

*Main article: Varicella vaccine*

The varicella vaccine is recommended in many countries.[9] Some countries require the varicella vaccination or an exemption before entering elementary school. A second dose is recommended five years after the initial immunization.[35] A vaccinated person is likely to have a milder case of chickenpox if they become infected.[36] Immunization within three days following household contact reduces infection rates and severity in children.[10]

It is part of the routine immunization schedule in the US.[37] Some European countries include it as part of universal vaccinations in children,[38] but not all countries provide the vaccine due to its cost.[9] In the UK as of 2014, the vaccine is only recommended in people who are particularly vulnerable to chickenpox.[39] In populations that have not been immunized or if immunity is questionable, a clinician may order an Enzyme immunoassay. An immunoessay measures the levels of antibodies against the virus that give immunity to a person. If the levels of antibodies are low (low titer) or questionable, reimmuization may be done.[40]

## Treatment [edit]

Treatment mainly consists of easing the symptoms. As a protective measure, people are usually required to stay at home while they are infectious to avoid spreading the disease to others. Cutting the nails short or wearing gloves may prevent scratching and minimize the risk of secondary infections.

Although there have been no formal clinical studies evaluating the effectiveness of topical application of calamine lotion (a topical barrier preparation containing zinc oxide, and one of the most commonly used interventions), it has an excellent safety profile.[41] It is important to maintain good hygiene and daily cleaning of skin with warm water to avoid secondary bacterial infection.[42] Scratching may also increase the risk of secondary infection.[43]

Paracetamol (acetaminophen) but not aspirin may be used to reduce fever. Aspirin use by someone with chickenpox may cause the serious, sometimes fatal disease of the liver and brain, Reye syndrome. People at risk of developing severe complications who have had significant exposure to the virus may be given intra-muscular varicella zoster immune globulin (VZIG), a preparation containing high titres of antibodies to varicella zoster virus, to ward off the disease.[44][45]

Antivirals are sometimes used.[46][47]

### Children [edit]

If aciclovir by mouth is started within 24 hours of rash onset, it decreases symptoms by one day but has no effect on complication rates.[48][49] Use of acyclovir therefore is not currently recommended for individuals with normal immune function. Children younger than 12 years old and older than one month are not meant to receive antiviral drugs unless they have another medical condition which puts them at risk of developing complications.[50]

Treatment of chickenpox in children is aimed at symptoms while the immune system deals with the virus. With children younger than 12 years, cutting nails and keeping them clean is an important part of treatment as they are more likely to scratch their blisters more deeply than adults.[51]

Aspirin is highly contraindicated in children younger than 16 years, as it has been related to Reye syndrome.[52]

### Adults [edit]

Infection in otherwise healthy adults tends to be more severe.[53] Treatment with antiviral drugs (e.g. acyclovir or valacyclovir) is generally advised, as long as it is started within 24–48 hours from rash onset.[50] Remedies to ease the symptoms of chickenpox in adults are basically the same as those used for children. Adults are more often prescribed antiviral medication, as it is effective in reducing the severity of the condition and the likelihood of developing complications. Antiviral medicines do not kill the virus but stop it from multiplying. Adults are advised to increase water intake to reduce dehydration and to relieve headaches. Painkillers such as paracetamol (acetaminophen) are recommended, as they are effective in relieving itching and other symptoms such as fever or pains. Antihistamines relieve itching and may be used in cases where the itching prevents sleep, because they also act as a sedative. As with children, antiviral medication is considered more useful for those adults who are more prone to develop complications. These include pregnant women or people who have a weakened immune system.[54]

Sorivudine, a nucleoside analogue, has been reported to be effective in the treatment of primary varicella in healthy adults (case reports only), but large-scale clinical trials are still needed to demonstrate its efficacy.[55]

After recovering from chickenpox, it is recommended by doctors that adults take one injection of VZV immune globulin and one injection of varicella vaccine or herpes zoster vaccine.[*citation needed*]

## Prognosis [edit]

The duration of the visible blistering caused by varicella zoster virus varies in children usually from 4 to 7 days, and the appearance of new blisters begins to subside after the fifth day. Chickenpox infection is milder in young children, and symptomatic treatment, with sodium bicarbonate baths or antihistamine medication may ease itching. It is recommended to keep new infants from birth up to age 6 months away from an infected person for 10 to 21 days because their immune systems are not developed enough to handle the stress it can bring on.[56] Paracetamol (acetaminophen) is widely used to reduce fever. Aspirin, or products containing aspirin, should not be given to children with chickenpox, as it can cause Reye's Syndrome.[57]

In adults, the disease is more severe,[58] though the incidence is much less common. Infection in adults is associated with greater morbidity and mortality due to pneumonia (either direct viral pneumonia or secondary bacterial pneumonia),[59] bronchitis (either viral bronchitis or secondary bacterial bronchitis),[59] hepatitis,[60] and encephalitis.[61] In particular, up to 10% of pregnant women with chickenpox develop pneumonia, the severity of which increases with onset later in gestation. In England and Wales, 75% of deaths due to chickenpox are in adults.[25] Inflammation of the brain, or encephalitis, can occur in immunocompromised individuals, although the risk is higher with herpes zoster.[62] Necrotizing fasciitis is also a rare complication.[63]

Varicella can be lethal to adults with impaired immunity. The number of people in this high-risk group has increased, due to the HIV epidemic and the increased use of immunosuppressive therapies.[64] Varicella is a particular problem in hospitals, when there are patients with immune systems weakened by drugs (e.g., high-dose steroids) or HIV.[65]

Secondary bacterial infection of skin lesions, manifesting as impetigo, cellulitis, and erysipelas, is the most common complication in healthy children. Disseminated primary varicella infection usually seen in the immunocompromised may have high morbidity. Ninety percent of cases of varicella pneumonia occur in the adult population. Rarer complications of disseminated chickenpox include myocarditis, hepatitis, and glomerulonephritis.[66]

Hemorrhagic complications are more common in the immunocompromised or immunosuppressed populations, although healthy children and adults have been affected. Five major clinical syndromes have been described: febrile purpura, malignant chickenpox with purpura, postinfectious purpura, purpura fulminans, and anaphylactoid purpura. These syndromes have variable courses, with febrile purpura being the most benign of the syndromes and having an uncomplicated outcome. In contrast, malignant chickenpox with purpura is a grave clinical condition that has a mortality rate of greater than 70%. The cause of these hemorrhagic chickenpox syndromes is not known.[66]

## Epidemiology [edit]

Primary varicella occurs in all countries worldwide. In 2013 the disease resulted in 7,000 deaths – down from 8,900 in 1990.[12]

In temperate countries, chickenpox is primarily a disease of children, with most cases occurring during the winter and spring, most likely due to school contact. It is one of the classic diseases of childhood, with the highest prevalence in the 4–10-year-old age group. Like rubella, it is uncommon in preschool children. Varicella is highly communicable, with an infection rate of 90% in close contacts. In temperate countries, most people become infected before adulthood, and 10% of young adults remain susceptible.

In the tropics, chickenpox often occurs in older people and may cause more serious disease.[67] In adults, the pock marks are darker and the scars more prominent than in children.[68]

In the United States, the Centers for Disease Control and Prevention (CDC) does not require state health departments to report infections of chickenpox, and only 31 states currently volunteer this information.[69]

However, in a 2013 study conducted by the social media disease surveillance tool called Sickweather, anecdotal reports of chickenpox infections on Facebook and Twitter were used to measure and rank states with the most infections per capita, with Maryland, Tennessee and Illinois in the top three.[70]

## Etymology [edit]

Why the term was used is not clear but it may be due to it being a relatively mild disease.[13] It has been said to be derived from *chickpeas*, based on resemblance of the vesicles to chickpeas,[13][71][72] or to come from the rash resembling chicken pecks.[72] Other suggestions include the designation *chicken* for a child (i.e., literally 'child pox'), a corruption of *itching-pox*,[71][73] or the idea that the disease may have originated in chickens.[74] Samuel Johnson explained the designation as "from its being of no very great danger."[75]

## Society and culture [edit]

Because chickenpox is usually more severe in adults than it is in children, some parents deliberately expose their children to the virus, sometimes by taking them to "chickenpox parties." Doctors counter that children are safer getting the vaccine, which is a weakened form of the virus, rather than getting the disease, which can be fatal.[76]

## Other animals [edit]

Humans are the only known animal that the disease affects naturally.[4] However, chickenpox has been caused in other primates, including chimpanzees[77] and gorillas.[78]

## References [edit]


1. ^ "Chickenpox (Varicella) Overview". *cdc.gov*. November 16, 2011. Retrieved 4 February 2015.
2. ^ *a b c d* "Chickenpox (Varicella) Signs & Symptoms". *Centers for Disease Control and Prevention (cdc.gov)*. November 16, 2011. Retrieved 4 February 2015.
3. ^ "Chickenpox (Varicella) Complications". *cdc.gov*. November 16, 2011. Retrieved 4 February 2015.
4. ^ *a b c d e f g h i j k* Atkinson, William (2011). *Epidemiology and Prevention of Vaccine-Preventable Diseases* (12 ed.). Public Health Foundation. pp. 301–323. ISBN 9780983263135. Retrieved 4 February 2015.
5. ^ *a b c d e f g h* "Chickenpox (Varicella) Prevention & Treatment". *cdc.gov*. November 16, 2011. Retrieved 4 February 2015.
6. ^ "Chickenpox (Varicella) Interpreting Laboratory Tests". *cdc.gov*. June 19, 2012. Retrieved 4 February 2015.
7. ^ Breuer J (2010). "VZV molecular epidemiology". *Current Topics in Microbiology and Immunology*. **342**: 15–42. doi:10.1007/82_2010_9. PMID 20229231.
8. ^ "Routine vaccination against chickenpox?". *Drug Ther Bull*. **4** (50): 42–5. 2012. doi:10.1136/dtb.2012.04.0098. PMID 22495050.
9. ^ *a b c* Flatt, A; Breuer, J (September 2012). "Varicella vaccines.". *British medical bulletin*. **103** (1): 115–27. doi:10.1093/bmb/lds019. PMID 22859715.
10. ^ *a b* Macartney, K; Heywood, A; McIntyre, P (23 June 2014). "Vaccines for post-exposure prophylaxis against varicella (chickenpox) in children and adults.". *The*

Disease Control and Prevention.

38. ^ Carrillo-Santisteve, P; Lopalco, PL (May 2014). "Varicella vaccination: a laboured take-off.". *Clinical Microbiology and Infection*. 20 Suppl 5: 86–91. doi:10.1111/1469-0691.12580. PMID 24494784.
39. ^ "Why aren't children in the UK vaccinated against chickenpox?". *NHS Choices*. UK National Health Service. Retrieved 10 June 2015.
40. ^ Leeuwen, Anne (2015). *Davis's comprehensive handbook of laboratory & diagnostic tests with nursing implications*. Philadelphia: F.A. Davis Company. p. 1579. ISBN 9780803644052.
41. ^ Tebruegge M, Kuruvilla M, Margarson I (2006). "Does the use of calamine or antihistamine provide symptomatic relief from pruritus in children with varicella zoster infection?" (Abstract). *Arch. Dis. Child*. **91** (12): 1035–6. doi:10.1136/adc.2006.105114. PMC 2082986. PMID 17119083.
42. ^ Domino, Frank J. (2007). *The 5-Minute Clinical Consult*. Lippincott Williams & Wilkins. p. 248. ISBN 978-0-7817-6334-9.
43. ^ Brannon, Heather (21 May 2008). Chicken Pox Treatments. About.com.
44. ^ Parmet S, Lynm C, Glass RM (February 2004). "JAMA patient page. Chickenpox". *JAMA*. **291** (7): 906. doi:10.1001/jama.291.7.906. PMID 14970070.
45. ^ Naus M; et al. (15 October 2006). "Varizig™ as the Varicella Zoster Immune Globulin for the Prevention of Varicella In At-Risk Patients". *Canada Communicable*

*Cochrane database of systematic reviews*. **6**: CD001833. doi:10.1002/14651858.CD001833.pub3. PMID 24954057.

11. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
12. ^ *a b* GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
13. ^ *a b c d* Oxford University Press (December 2014). "chickenpox, n.". *oed.com*. Retrieved February 4, 2015.
14. ^ *a b* Anthony J Papadopoulos. Dirk M Elston, ed. "Chickenpox Clinical Presentation". *Medscape Reference*. Retrieved 4 August 2012.
15. ^ "Symptoms of Chickenpox". *Chickenpox*. NHS Choices. Retrieved 14 March 2013.
16. ^ "Chickenpox (varicella)". Retrieved 6 November 2010.
17. ^ Askalan R, Laughlin S, Mayank S, Chan A, MacGregor D, Andrew M, Curtis R, Meaney B, deVeber G (June 2001). "Chickenpox and stroke in childhood: a study of frequency and causation". *Stroke*. **32** (6): 1257–62. doi:10.1161/01.STR.32.6.1257. PMID 11387484.
18. ^ Heuchan AM, Isaacs D (19 March 2001). "The management of varicella-zoster virus exposure and infection in pregnancy and the newborn period. Australasian Subgroup in Paediatric Infectious Diseases of the Australasian Society for Infectious Diseases.". *The Medical journal of Australia*. **174** (6): 288–92. PMID 11297117.
19. ^ Brannon, Heather (22 July 2007). "Chickenpox in Pregnanc". *Dermatology*. About.com. Retrieved 20 June 2009.
20. ^ "Chickenpox During Pregnancy". March of Dimes. November 11, 2014.
21. ^ Boussault P, Boralevi F, Labbe L, Sarlangue J, Taïeb A, Leaute-Labreze C (2007). "Chronic varicella-zoster skin infection complicating the congenital varicella syndrome". *Pediatr Dermatol*. **24** (4): 429–32. doi:10.1111/j.1525-1470.2007.00471.x. PMID 17845179.
22. ^ Matsuo T, Koyama M, Matsuo N (July 1990). "Acute retinal necrosis as a novel complication of chickenpox in adults". *Br J Ophthalmol*. **74** (7): 443–4. doi:10.1136/bjo.74.7.443. PMC 1042160. PMID 2378860.
23. ^ Mazzella M, Arioni C, Bellini C, Allegri AE, Savioli C, Serra G (2003). "Severe hydrocephalus associated with congenital varicella syndrome". *Canadian Medical Disease Report*. **32** (ACS-8).
46. ^ Huff JC (January 1988). "Antiviral treatment in chickenpox and herpes zoster.". *Journal of the American Academy of Dermatology*. **18** (1 Pt 2): 204–6. doi:10.1016/S0190-9622(88)70029-8. PMID 3339143.
47. ^ Gnann Jr, John W. (2007). "Chapter 65Antiviral therapy of varicella-zoster virus infections". In Arvin, Ann; et al. *Human herpesviruses : biology, therapy, and immunoprophylaxis*. Cambridge: Cambridge University Press. ISBN 978-0-521-82714-0. Retrieved 20 January 2014.
48. ^ Kay, A. B. (2001). "Allergy and allergic diseases. First of two parts". *The New England Journal of Medicine*. **344** (1): 30–7. doi:10.1056/NEJM200101043440106. PMID 11136958.
49. ^ Kay, A. B. (2001). "Allergy and allergic diseases. Second of two parts". *The New England Journal of Medicine*. **344** (2): 109–13. doi:10.1056/NEJM200101113440206. PMID 11150362.
50. ^ *a b* "Antiviral medications for chickenpox". Retrieved 27 March 2011.
51. ^ "Chickenpox in Children Under 12". Retrieved 6 November 2010.
52. ^ "Reye's Syndrome-Topic Overview". Retrieved 27 March 2011.
53. ^ Tunbridge AJ, Breuer J, Jeffery KJ (August 2008). "Chickenpox in adults - clinical management". *The Journal of Infection*. **57** (2): 95–102. doi:10.1016/j.jinf.2008.03.004. PMID 18555533.
54. ^ "What is chickenpox?". Retrieved 6 November 2010.
55. ^ *Chickenpox~treatment* at eMedicine
56. ^ Somekh E, Dalal I, Shohat T, Ginsberg GM, Romano O (2002). "The burden of uncomplicated cases of chickenpox in Israel". *J. Infect.* **45** (1): 54–7. doi:10.1053/jinf.2002.0977. PMID 12217733.
57. ^ US Centers for Disease Control and Prevention. "Varicella Treatment Questions & Answers". *CDC Guidelines*. CDC. Retrieved 23 August 2007.
58. ^ Baren JM, Henneman PL, Lewis RJ (August 1996). "Primary Varicella in Adults: Pneumonia, Pregnancy, and Hospital Admissions". *Annals of Emergency Medicine*. **28** (2): 165–169. doi:10.1016/S0196-0644(96)70057-4. PMID 8759580.
59. ^ *a b* Mohsen AH, McKendrick M (May 2003). "Varicella pneumonia in adults". *Eur. Respir. J.* **21** (5): 886–91. doi:10.1183/09031936.03.00103202. PMID 12765439.
60. ^ Anderson, D.R.; Schwartz, J.; Hunter, N.J.; Cottrill, C.; Bissaccia, E.; Klainer, A.S. (1994). "Varicella Hepatitis: A Fatal Case in a Previously Healthy, Immunocompetent Adult". *Archives of Internal Medicine*. JAMA. **154** (18): 2101–2106. doi:10.1001/archinte.1994.00420180111013. PMID 8092915.
61. ^ Abro AH, Ustadi AM, Das K, Abdou AM, Hussaini HS, Chandra FS (December 2009). "Chickenpox: presentation and complications in adults". *Journal of Pakistan Medical Association*. **59** (12): 828–831. PMID 20201174. Retrieved 17 April 2013.

*Association Journal*. **168** (5): 561–563. PMC 149248. PMID 12615748.
24. ^ Sauerbrei A, Wutzler P (December 2001). "Neonatal varicella". *J Perinatol*. **21** (8): 545–9. doi:10.1038/sj.jp.7210599. PMID 11774017.
25. ^ [a] [b] [c] Royal College of Obstetricians and Gynaecologists (September 2007). "Chickenpox in Pregnancy" (PDF). Retrieved 22 July 2009.
26. ^ Pincus, Matthew R.; McPherson, Richard A.; Henry, John Bernard (2007). "Ch. 54". *Henry's clinical diagnosis and management by laboratory methods* (21st ed.). Saunders Elsevier. ISBN 1-4160-0287-1.
27. ^ Kanbayashi Y, Onishi K, Fukazawa K, Okamoto K, Ueno H, Takagi T, Hosokawa T (2012). "Predictive Factors for Postherpetic Neuralgia Using Ordered Logistic Regression Analysis". *The Clinical Journal of Pain*. **28** (8): 712–714. doi:10.1097/AJP.0b013e318243ee01. PMID 22209800.
28. ^ Pino Rivero V, González Palomino A, Pantoja Hernández CG, Mora Santos ME, Trinidad Ramos G, Blasco Huelva A (2006). "Ramsay-Hunt syndrome associated to unilateral recurrential paralysis". *Anales otorrinolaringologicos ibero-americanos*. **33** (5): 489–494. PMID 17091862.
29. ^ Nagel MA, Cohrs RJ, Mahalingam R, Wellish MC, Forghani B, Schiller A, Safdieh JE, Kamenkovich E, Ostrow LW, Levy M, Greenberg B, Russman AN, Katzan I, Gardner CJ, Häusler M, Nau R, Saraya T, Wada H, Goto H, de Martino M, Ueno M, Brown WD, Terborg C, Gilden DH (March 2008). "The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features.". *Neurology*. **70**: 853–60. doi:10.1212/01.wnl.0000304747.38502.e8. PMC 2938740. PMID 18332343.
30. ^ "Chickenpox". *NHS Choices*. UK Department of Health. 19 April 2012.
31. ^ "Shingles Vaccine". WebMD.
32. ^ "An Overview of Shingles". WebMD.
33. ^ "Shingles". PubMed Health.
34. ^ Murray, Patrick R.; Rosenthal, Ken S.; Pfaller, Michael A. (2005). *Medical Microbiology* (5th ed.). Elsevier Mosby. p. 551. ISBN 0-323-03303-2., edition *(Elsevier), p.*
35. ^ Chaves SS, Gargiullo P, Zhang JX, Civen R, Guris D, Mascola L, Seward JF (2007). "Loss of vaccine-induced immunity to varicella over time". *N Engl J Med*. **356** (11): 1121–9. doi:10.1056/NEJMoa064040. PMID 17360990.
36. ^ "Chickenpox (varicella) vaccination". *NHS Choices*. UK Department of Health. 19 April 2012.
37. ^ "Child, Adolescent & "Catch-up" Immunization Schedules". *Immunization Schedules*. Centers for
62. ^ "Definition of Chickenpox". MedicineNet.com. Retrieved 18 August 2006.
63. ^ "Is Necrotizing Fasciitis a complication of Chickenpox of Cutaneous Vasculitis?". atmedstu.com. Retrieved 18 January 2008.
64. ^ Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, Zink A (February 2009). "Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents". *JAMA*. **301** (7): 737–44. doi:10.1001/jama.2009.146. PMID 19224750.
65. ^ Weller TH (1997). "Varicella-herpes zoster virus". In Evans AS, Kaslow RA. *Viral Infections of Humans: Epidemiology and Control*. Plenum Press. pp. 865–92. ISBN 978-0-306-44855-3.
66. ^ [a] [b] Chicken Pox Complications
67. ^ Wharton M (1996). "The epidemiology of varicella-zoster virus infections". *Infect Dis Clin North Am*. **10** (3): 571–81. doi:10.1016/S0891-5520(05)70313-5. PMID 8856352.
68. ^ "Epidemiology of Varicella Zoster Virus Infection, Epidemiology of VZV Infection, Epidemiology of Chicken Pox, Epidemiology of Shingles". Retrieved 22 April 2008.
69. ^ "Georgia ranks 10th for social media admissions of chickenpox". Retrieved 13 June 2013.
70. ^ "Chickenpox in the USA". Retrieved 12 June 2013.
71. ^ [a] [b] Belshe, Robert B. (1984). *Textbook of human virology* (2nd ed.). Littleton MA: PSG. p. 829. ISBN 0-88416-458-6.
72. ^ [a] [b] Teri Shors (2011). "Herpesviruses: Varicella Zoster Virus (VZV)". *Understanding Viruses* (2nd ed.). Jones & Bartlett. p. 459. ISBN 978-0-7637-8553-6.
73. ^ Pattison, John; Zuckerman, Arie J.; Banatvala, J.E. (1994). *Principles and practice of clinical virology* (3rd ed.). Wiley. p. 37. ISBN 0-471-93106-3.
74. ^ Chicken-pox is recorded in Oxford English Dictionary 2nd ed. since 1684; the OED records several suggested etymologies
75. ^ Johnson, Samuel (1839). *Dictionary of the English language*. London: Williamson. p. 195.
76. ^ "Chicken Pox parties do more harm than good, says doctor". KSLA News 12 Shreveport, Louisiana News Weather & Sports.
77. ^ Cohen JI, Moskal T, Shapiro M, Purcell RH (December 1996). "Varicella in Chimpanzees". *Journal of Medical Virology*. **50** (4): 289–92. doi:10.1002/(SICI)1096-9071(199612)50:4<289::AID-JMV2>3.0.CO;2-4. PMID 8950684.
78. ^ Myers MG, Kramer LW, Stanberry LR (December 1987). "Varicella in a gorilla". *Journal of Medical Virology*. **23** (4): 317–22. doi:10.1002/jmv.1890230403. PMID 2826674.

## External links [edit]

- Chickenpox at DMOZ
- "Prevention of Varicella: Recommendations of the Advisory Committee on Immunization Practices (ACIP)". Centers for Disease Control and Prevention (CDC). 12 July 1996. Retrieved 18 May 2013.

Wikimedia Commons has media related to *Chickenpox*.

- "Management of Varicella Zoster Virus (VZV) Infections" (PDF). Federal Bureau of Prisons: Clinical Practice Guideline. December 2011. Retrieved 18 May 2013.
- John W. Gnann Jr. (2007). "Chapter 65 Antiviral therapy of varicella-zoster virus infections". PMID 21348091.
- Sarah McSweeney-Ryan; Megan Sandel. "The Health Care of Homeless Persons - Part I - Varicella (Chickenpox" (PDF). Boston Health Care for the Homeless Program. Retrieved 18 May 2013.


Medicine portal
Viruses portal

| v · t · e · | Diseases of the skin and appendages by morphology | | | | |
|---|---|---|---|---|---|
| **Growths** | **Epidermal** | wart · callus · seborrheic keratosis · acrochordon · molluscum contagiosum · actinic keratosis · squamous-cell carcinoma · basal-cell carcinoma · Merkel-cell carcinoma · nevus sebaceous · trichoepithelioma · | | | |
| | **Pigmented** | Freckles · lentigo · melasma · nevus · melanoma · | | | |
| | **Dermal and subcutaneous** | epidermal inclusion cyst · hemangioma · dermatofibroma (benign fibrous histiocytoma) · keloid · lipoma · neurofibroma · xanthoma · Kaposi's sarcoma · infantile digital fibromatosis · granular cell tumor · leiomyoma · lymphangioma circumscriptum · myxoid cyst · | | | |
| **Rashes** | **With epidermal involvement** | **Eczematous** | contact dermatitis · atopic dermatitis · seborrheic dermatitis · stasis dermatitis · lichen simplex chronicus · Darier's disease · glucagonoma syndrome · langerhans cell histiocytosis · lichen sclerosus · pemphigus foliaceus · Wiskott–Aldrich syndrome · Zinc deficiency · | | |
| | | **Scaling** | psoriasis · tinea (corporis · cruris · pedis · manuum · faciei) · pityriasis rosea · secondary syphilis · mycosis fungoides · systemic lupus erythematosus · pityriasis rubra pilaris · parapsoriasis · ichthyosis · | | |
| | | **Blistering** | herpes simplex · herpes zoster · **varicella** · bullous impetigo · acute contact dermatitis · pemphigus vulgaris · bullous pemphigoid · dermatitis herpetiformis · porphyria cutanea tarda · epidermolysis bullosa simplex · | | |
| | | **Papular** | scabies · insect bite reactions · lichen planus · miliaria · keratosis pilaris · lichen spinulosus · transient acantholytic dermatosis · lichen nitidus · pityriasis lichenoides et varioliformis acuta · | | |
| | | **Pustular** | acne vulgaris · acne rosacea · folliculitis · impetigo · candidiasis · gonococcemia · dermatophyte · coccidioidomycosis · subcorneal pustular dermatosis · | | |
| | | **Hypopigmented** | tinea versicolor · vitiligo · pityriasis alba · postinflammatory hyperpigmentation · tuberous sclerosis · idiopathic guttate hypomelanosis · leprosy · hypopigmented mycosis fungoides · | | |
| | | | **Blanchable Erythema** | **Generalized** | drug eruptions · viral exanthems · toxic erythema · systemic lupus erythematosus · |
| | | | | **Localized** | cellulitis · abscess · boil · erythema nodosum · carcinoid syndrome · fixed drug eruption · |

| | | | | | |
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| | **Without epidermal involvement** | **Red** | | **Specialized** | urticaria · erythema (multiforme · migrans · gyratum repens · annulare centrifugum · ab igne) · |
| | | | **Nonblanchable Purpura** | **Macular** | thrombocytopenic purpura · actinic/solar purpura · |
| | | | | **Papular** | disseminated intravascular coagulation · vasculitis · |
| | | **Indurated** | | | scleroderma/morphea · granuloma annulare · lichen sclerosis et atrophicus · necrobiosis lipoidica · |
| **Miscellaneous disorders** | **Ulcers** | | | | |
| | **Hair** | telogen effluvium · androgenic alopecia · trichotillomania · alopecia areata · systemic lupus erythematosus · tinea capitis · loose anagen syndrome · lichen planopilaris · folliculitis decalvans · acne keloidalis nuchae · | | | |
| | **Nail** | onychomycosis · psoriasis · paronychia · ingrown nail · | | | |
| | **Mucous membrane** | Aphthous stomatitis · oral candidiasis · lichen planus · leukoplakia · pemphigus vulgaris · mucous membrane pemphigoid · cicatricial pemphigoid · herpesvirus · coxsackievirus · syphilis · systemic histoplasmosis · squamous-cell carcinoma · | | | |

| v · t · e · | **Infectious skin disease: Viral cutaneous conditions, including viral exanthema (B00–B09, 050–059)** | | | |
|---|---|---|---|---|
| **DNA virus** | **Herpesviridae** | **Alpha** | *HSV* | Herpes simplex · Herpetic whitlow · Herpes gladiatorum · Herpetic keratoconjunctivitis · Herpetic sycosis · Neonatal herpes simplex · Herpes genitalis · Herpes labialis · Eczema herpeticum · Herpetiform esophagitis · |
| | | | *Herpes B virus* | B virus infection · |
| | | | *VZV* | **Chickenpox** · Herpes zoster · Herpes zoster oticus · Ophthalmic zoster · Disseminated herpes zoster · Zoster-associated pain · Modified varicella-like syndrome · |
| | | **Beta** | *Human herpesvirus 6*/*Roseolovirus* (Exanthema subitum · Roseola vaccinia · · Cytomegalic inclusion disease · | |
| | | **Gamma** | *KSHV* (Kaposi's sarcoma · · | |
| | **Poxviridae** | **Ortho** | *Variola* (Smallpox · Alastrim · · *MoxV* (Monkeypox · · *CPXV* (Cowpox · · *VV* (Vaccinia · Generalized vaccinia · Eczema vaccinatum · Progressive vaccinia · · Buffalopox · | |
| | | **Para** | Farmyard pox: Milker's nodule · Bovine papular stomatitis · Pseudocowpox · Orf · Sealpox · | |
| | | **Other** | Yatapoxvirus: Tanapox · Yaba monkey tumor virus · *MCV* (Molluscum contagiosum · · | |
| | **Papillomaviridae** | *HPV* | Wart/plantar wart · Heck's disease · Genital wart (giant · · Laryngeal papillomatosis · Butcher's wart · Bowenoid papulosis · Epidermodysplasia verruciformis · Verruca plana · Pigmented wart · Verrucae palmares et plantares · | |

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| | | *BPV* (Equine sarcoid · · |
| | **Parvoviridae** | *Parvovirus B19* (Erythema infectiosum · Reticulocytopenia · Papular purpuric gloves and socks syndrome · · |
| | **Polyomaviridae** | *Merkel cell polyomavirus* (Merkel cell carcinoma · · |
| **RNA virus** | **Paramyxoviridae** | *MeV* (Measles · · |
| | **Togaviridae** | *Rubella virus* (Rubella · Congenital rubella syndrome · · Alphavirus infection · Chikungunya fever · |
| | **Picornaviridae** | *CAV* (Hand, foot and mouth disease · Herpangina · · *FMDV* (Foot-and-mouth disease · · Boston exanthem disease · |
| **Ungrouped** | Asymmetric periflexural exanthem of childhood · Post-vaccination follicular eruption · Lipschütz ulcer · Eruptive pseudoangiomatosis · Viral-associated trichodysplasia · Gianotti–Crosti syndrome · | |

| V · T · E · | **Varicella zoster** |
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| **Varicella zoster virus** | Varicellovirus · |
| **Diseases** | **Chickenpox** · Herpes zoster · Postherpetic neuralgia · Ramsay Hunt syndrome type II · Disseminated herpes zoster · Progressive outer retinal necrosis · Ophthalmic zoster · |
| **Treatment** | Aciclovir · Vidarabine · VZV immune globulin · |
| **Prevention** | Varicella vaccine · Zoster vaccine · Pox party · |
| **Other** | Michiaki Takahashi · |

Categories: Chickenpox | Virus-related cutaneous conditions | Animal viral diseases | Pediatrics

# Dermatitis

From Wikipedia, the free encyclopedia

**Dermatitis**, also known as **eczema**, is a group of diseases that results in inflammation of the skin.[1] These diseases are characterized by itchiness, red skin, and a rash.[1] In cases of short duration there may be small blisters while in long-term cases the skin may become thickened.[1] The area of skin involved can vary from small to the entire body.[1][2]

Dermatitis is a group of skin conditions that includes atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis, and stasis dermatitis.[1][2] The exact cause of dermatitis is often unclear.[2] Cases are believed to often involve a combination of irritation, allergy, and poor venous return. The type of dermatitis is generally determined by the person's history and the location of the rash. For example, irritant dermatitis often occurs on the hands of people who frequently get them wet. Allergic contact dermatitis, however, can occur following brief exposures to substances a person is sensitive to.[1]

Treatment of atopic dermatitis is typically with moisturizers and steroid creams.[3] The steroid creams should generally be of mid- to high strength and used for less than two weeks at a time as side effects can occur.[4] Antibiotics may be required if there are signs of skin infection.[2] Contact dermatitis is typically treated by avoiding the allergen or irritant.[5][6] Antihistamines may help with sleep and to decrease nighttime scratching.[2]

Dermatitis was estimated to affect 334 million people globally in 2013.[7] Atopic dermatitis is the most common type and generally starts in childhood.[1][2] In the United States it affects about 10-30% of people.[2] Contact dermatitis is two times more common in females than males.[8] Allergic contact dermatitis affects about 7% of people at some point in time.[9] Irritant contact dermatitis is common, especially among people who do certain jobs; exact rates are unclear.[10]

**Dermatitis**

A moderate case of dermatitis of the hands

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Dermatology |
| **ICD-10** | L20-L30 |
| **ICD-9-CM** | 692 |
| **OMIM** | 603165 |
| **MedlinePlus** | 000853 |
| **eMedicine** | Derm/38 Ped/2567 |
| **MeSH** | D004485 |

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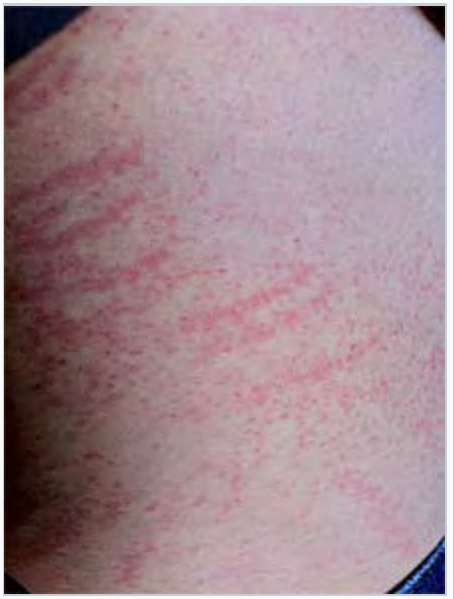
Contents

## Signs and symptoms [edit]


Rash symptomatic of dermatitis

Dermatitis symptoms vary with all different forms of the condition. They range from skin rashes to bumpy rashes or including blisters. Although every type of dermatitis has different symptoms, there are certain signs that are common for all of them, including redness of the skin, swelling, itching and skin lesions with sometimes oozing and scarring. Also, the area of the skin on which the symptoms appear tends to be different with every type of dermatitis, whether on the neck, wrist, forearm, thigh or ankle. Although the location may vary, the primary symptom of this condition is itchy skin. More rarely, it may appear on the genital area, such as the vulva or scrotum.[11] Symptoms of this type of dermatitis may be very intense and may come and go. Irritant contact dermatitis is usually more painful than itchy.

Although the symptoms of atopic dermatitis vary from person to person, the most common symptoms are dry, itchy, red skin. Typical affected skin areas include the folds of the arms, the back of the knees, wrists, face and hands.

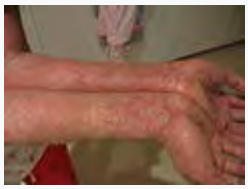
Dermatitis herpetiformis symptoms include itching, stinging and a burning sensation. Papules and vesicles are commonly present. The small red bumps experienced in this type of dermatitis are usually about 1 cm in size, red in color and may be found symmetrically grouped or distributed on the upper or lower back, buttocks, elbows, knees, neck, shoulders, and scalp.[12] Less frequently, the rash may appear inside the mouth or near the hairline.

The symptoms of seborrheic dermatitis, on the other hand, tend to appear gradually, from dry or greasy scaling of the scalp (dandruff) to hair loss. In severe cases, pimples may appear along the hairline, behind the ears, on the eyebrows, on the bridge of the nose, around the nose, on the chest, and on the upper back.[13] In newborns, the condition causes a thick and yellowish scalp rash, often accompanied by a diaper rash.

Perioral dermatitis refers to a red bumpy rash around the mouth.[14]

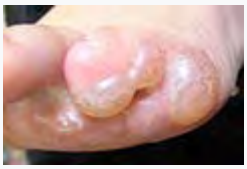

Dermatitis

Dermatitis of the hand



More severe dermatitis

A patch of dermatitis that has been scratched



Complex dermatitis

## Cause [edit]

The cause of dermatitis is unknown but is presumed to be a combination of genetic and environmental factors.[2]

### Environmental [edit]

The hygiene hypothesis postulates that the cause of asthma, eczema, and other allergic diseases is an unusually clean environment. It is supported by epidemiologic studies for asthma.[15] The hypothesis states that exposure to bacteria and other immune system modulators is important during development, and missing out on this exposure increases risk for asthma and allergy.

While it has been suggested that eczema may sometimes be an allergic reaction to the excrement from house dust mites,[16] with up to 5% of people showing antibodies to the mites,[17] the overall role this plays awaits further corroboration.[18]

### Genetic [edit]

A number of genes have been associated with eczema, one of which is filaggrin.[3] Genome-wide studies found three new genetic variants associated with eczema: OVOL1, ACTL9 and IL4-KIF3A.[19]

Eczema occurs about three times more frequently in individuals with celiac disease and about two times more frequently in relatives of those with celiac disease, potentially indicating a genetic link between the conditions.[20][21]

## Diagnosis [edit]

Diagnosis of eczema is based mostly on the history and physical examination.[3] In uncertain cases, skin biopsy may be useful.[22] Those with eczema may be especially prone to misdiagnosis of food allergies.[23]

Patch tests are used in the diagnosis of allergic contact dermatitis.[24][25]

## Classification [edit]

The term "eczema" refers to a set of clinical characteristics. Classification of the underlying diseases has been haphazard with numerous different classification systems, and many synonyms being used to describe the same condition.

A type of dermatitis may be described by location (e.g., hand eczema), by specific appearance (eczema craquele or discoid), or by possible cause (varicose eczema). Further adding to the confusion, many sources use the term eczema interchangeably for the most common type: atopic dermatitis.

The European Academy of Allergology and Clinical Immunology (EAACI) published a position paper in 2001, which simplifies the nomenclature of allergy-related diseases, including atopic and allergic contact eczemas.[26] Non-allergic eczemas are not affected by this proposal.

## Terminology [edit]

There are several types of dermatitis including atopic dermatitis, contact dermatitis, stasis dermatitis, and seborrheic eczema.[2] Many use the term dermatitis and eczema synonymously.[1]

Others use the term eczema to specifically mean atopic dermatitis.[27][28][29] Atopic dermatitis is also known as atopic eczema.[3] In some languages, dermatitis and eczema mean the same thing, while in other languages dermatitis implies an acute condition and eczema a chronic one.[30]

## Common types [edit]

- Atopic dermatitis is an allergic disease believed to have a hereditary component and often runs in families whose members have asthma. Itchy rash is particularly noticeable on head and scalp, neck, inside of elbows, behind knees, and buttocks. It is very common in developed countries, and rising. Irritant contact dermatitis is sometimes misdiagnosed as atopic dermatitis.
- Contact dermatitis is of two types: allergic (resulting from a delayed reaction to an allergen, such as poison ivy, nickel, or Balsam of Peru),[31] and irritant (resulting from direct reaction to a detergent, such as sodium lauryl sulfate, for example).
  Some substances act both as allergen and irritant (wet cement, for example). Other substances cause a problem after sunlight exposure, bringing on phototoxic dermatitis. About three quarters of cases of contact eczema are of the irritant type, which is the most common occupational skin disease. Contact eczema is curable, provided the offending substance can be avoided and its traces removed from one's environment. (ICD-10 L23; L24; L56.1; L56.0)
- Xerotic eczema (asteatotic eczema, eczema craquele, eczema craquelatum, winter itch, pruritus hiemalis) is dry skin that becomes so serious it turns into eczema. It worsens in dry winter weather, and limbs and trunk are most often affected. The itchy, tender skin resembles a dry, cracked, river bed. This disorder is very common among the older population. Ichthyosis is a related disorder. (ICD-10 L30.8A; L85.0)
- Seborrhoeic dermatitis or seborrheic dermatitis ("cradle cap" in infants) is a condition sometimes classified as a form of eczema that is closely related to dandruff. It causes dry or greasy peeling of the scalp, eyebrows, and face, and sometimes trunk. In newborns it causes a thick, yellow, crusty scalp rash called cradle cap, which seems related to lack of biotin and is often curable. (ICD-10 L21; L21.0)

## Less common types [edit]

- Dyshidrosis (dyshidrotic eczema, pompholyx, vesicular palmoplantar dermatitis) only occurs on palms, soles, and sides of fingers and toes. Tiny opaque bumps called vesicles, thickening, and cracks are accompanied by itching, which gets worse at night. A common type of hand eczema, it worsens in warm weather. (ICD-10 L30.1)
- Discoid eczema (ummular eczema, exudative eczema, microbial eczema) is characterized by round spots of oozing or dry rash, with clear boundaries, often on lower legs. It is usually worse in winter. Cause is unknown, and the condition tends to come and go. (ICD-10 L30.0)

Venous eczema (gravitational eczema, stasis dermatitis, varicose eczema) occurs in people with impaired circulation, varicose veins, and edema, and is particularly common in the ankle area of people over 50. There is redness, scaling, darkening of the skin, and itching. The disorder predisposes to leg ulcers. (ICD-10 I83.1)
- Dermatitis herpetiformis (Duhring's disease) causes intensely itchy and typically symmetrical rash on arms, thighs, knees, and back. It is directly related to celiac disease, can often be put into remission with appropriate diet, and tends to get worse at night. (ICD-10 L13.0)
- Neurodermatitis (lichen simplex chronicus, localized scratch dermatitis) is an itchy area of thickened, pigmented eczema patch that results from habitual rubbing and scratching. Usually there is only one spot. Often curable through behavior modification and anti-inflammatory medication. Prurigo nodularis is a related disorder showing multiple lumps. (ICD-10 L28.0; L28.1)
- Autoeczematization (id reaction, autosensitization) is an eczematous reaction to an infection with parasites, fungi, bacteria, or viruses. It is completely curable with the clearance of the original infection that caused it. The appearance varies depending on the cause. It always occurs some distance away from the original infection. (ICD-10 L30.2)
- There are eczemas overlaid by viral infections (eczema herpeticum or vaccinatum), and eczemas resulting from underlying disease (e.g., lymphoma). Eczemas originating from ingestion of medications, foods, and chemicals, have not yet been clearly systematized. Other rare eczematous disorders exist in addition to those listed here.

## Prevention [edit]

There is no good evidence that a mother's diet during pregnancy, the formula used, or breastfeeding changes the risk.[32] There is tentative evidence that probiotics in infancy may reduce rates but it is insufficient to recommend its use.[33]

People with eczema should not get the smallpox vaccination due to risk of developing eczema vaccinatum, a potentially severe and sometimes fatal complication.[34]

## Management [edit]

There is no known cure for some types of dermatitis, with treatment aiming to control symptoms by reducing inflammation and relieving itching. Contact dermatitis is treated by avoiding what is causing it.

### Lifestyle [edit]

Bathing once or more a day is recommended.[3] It is a misconception that bathing dries the skin in people with eczema.[35] Soaps should be avoided as they tend to strip the skin of natural oils and lead to excessive dryness.[36] It is not clear whether dust mite reduction helps with eczema.

There has not been adequate evaluation of changing the diet to reduce eczema.[37][38] There is some evidence that infants with an established egg allergy may have a reduction in symptoms if eggs are eliminated from their diets.[37] Benefits have not been shown for other elimination diets, though the studies are small and poorly executed.[37][38] Establishing that there is a food allergy before dietary change could avoid unnecessary lifestyle changes.[37]

People can wear clothing designed to manage the itching, scratching and peeling.[39]

### Moisturizers [edit]

Moisturizing agents (also known as emollients) are recommended at least once or twice a day.[3] Oilier formulations appear to be better and water-based formulations are not recommended.[3] It is unclear if moisturizers that contain ceramides are more or less effective than others.[40] Products that contain dyes, perfumes, or peanuts should not be used.[3] Occlusive dressings at night may be useful.[3]

## Medications [edit]

There is little evidence for antihistamine; they are thus not generally recommended.[3] Sedative antihistamines, such as diphenhydramine, may be tried in those who are unable to sleep due to eczema.[3]

## Corticosteroids [edit]

If symptoms are well controlled with moisturizers, steroids may only be required when flares occur.[3] Corticosteroids are effective in controlling and suppressing symptoms in most cases.[41] Once daily use is generally enough.[3] For mild-moderate eczema a weak steroid may be used (e.g., hydrocortisone), while in more severe cases a higher-potency steroid (e.g., clobetasol propionate) may be used. In severe cases, oral or injectable corticosteroids may be used. While these usually bring about rapid improvements, they have greater side effects.

Long term use of topical steroids may result in skin atrophy, stria, telangiectasia.[3] Their use on delicate skin (face or groin) is therefore typically with caution.[3] They are, however, generally well tolerated.[42] Red burning skin, where the skin turns red upon stopping steroid use, has been reported among adults who use topical steroids at least daily for more than a year.[43]

## Immunosuppressants [edit]

Topical immunosuppressants like pimecrolimus and tacrolimus may be better in the short term and appear equal to steroids after a year of use.[44] Their use is reasonable in those who do not respond to or are not tolerant of steroids.[45] Treatments are typically recommended for short or fixed periods of time rather than indefinitely.[3] Tacrolimus 0.1% has generally proved more effective than picrolimus, and equal in effect to mid-potency topical steroids.[32]

Tacrolimus 0.1%

The United States Food and Drug Administration has issued a health advisory a possible risk of lymph node or skin cancer from these products,[46] however, subsequent research has not supported these concerns.[45] A major debate, in the UK, has been about the cost of these medications and, given only finite NHS resources, when they are most appropriate to use.[47]

When eczema is severe and does not respond to other forms of treatment, systemic immunosuppressants are sometimes used. Immunosuppressants can cause significant side effects and some require regular blood tests. The most commonly used are ciclosporin, azathioprine, and methotrexate.

## Light therapy [edit]

Light therapy using ultraviolet light has tentative support but the quality of the evidence is not very good.[48] A number of different types of light may be used including UVA and UVB;[49] in some forms of treatment, light sensitive chemicals such as psoralen are also used. Overexposure to ultraviolet light carries its own risks, particularly that of skin cancer.[50]

## Alternative medicine [edit]

Limited evidence suggests that acupuncture may reduce itching in those affected by atopic dermatitis.[51] There is currently no scientific evidence for the claim that sulfur treatment relieves eczema.[52] It is unclear whether Chinese herbs help or harm.[53] Dietary supplements are commonly used by people with eczema.[54] Neither evening primrose oil nor borage seed oil taken orally have been shown to be effective.[55] Both are associated with gastrointestinal upset.[55] Probiotics do not appear to be effective.[56] There is insufficient evidence to support the use of zinc, selenium, vitamin D, vitamin E, pyridoxine (vitamin [54]

B6), sea buckthorn oil, hempseed oil, sunflower oil, or fish oil as dietary supplements.

Chiropractic spinal manipulation lacks evidence to support its use for dermatitis.[57] There is little evidence supporting the use of psychological treatments.[58] While dilute bleach baths have been used for infected dermatitis there is little evidence for this practice.[59]

## Prognosis [edit]

Most cases are well managed with topical treatments and ultraviolet light.[3] About 2% of cases are not.[3] In more than 60% the condition goes away by adolescence.[3]

## Epidemiology [edit]

Globally dermatitis affected approximately 230 million people as of 2010 (3.5% of the population).[60] Dermatitis is most commonly seen in infancy, with female predominance of eczema presentations occurring during the reproductive period of 15–49 years.[61] In the UK about 20% of children have the condition, while in the United States about 10% are affected.[3]

Although little data on the rates of eczema over time exists prior to the 1940s, the rate of eczema has been found to have increased substantially in the latter half of the 20th Century, with eczema in school-aged children being found to increase between the late 1940s and 2000.[62] In the developed world there has been rise in the rate of eczema over time. The incidence and lifetime prevalence of eczema in England has been seen to increase in recent times.[3][63]

Dermatitis affected about 10% of U.S. workers in 2010, representing over 15 million workers with dermatitis. Prevalence rates were higher among females than among males, and among those with some college education or a college degree compared to those with a high school diploma or less. Workers employed in healthcare and social assistance industries and life, physical, and social science occupations had the highest rates of reported dermatitis. About 6% of dermatitis cases among U.S. workers were attributed to work by a healthcare professional, indicating that the prevalence rate of work-related dermatitis among workers was at least 0.6%.[64]

## History [edit]

The term "atopic dermatitis" was coined in 1933 by Wise and Sulzberger.[66] Sulfur as a topical treatment for eczema was fashionable in the Victorian and Edwardian eras.[52]

The word dermatitis is from the Greek δέρμα *derma* "skin" and -ῖτις *-itis* "inflammation" and eczema is from Greek: ἔκζεμα *ekzema* "eruption".[67]

from Ancient Greek ἔκζεμα *ékzema*,[65]
from ἐκζέ-ειν *ekzé-ein*,
from ἐκ *ek* "out" + ζέ-ειν *zé-ein* "to boil"
(OED)

## Society and culture [edit]

The terms "hypoallergenic" and "doctor tested" are not regulated,[68] and no research has been done showing that products labeled "hypoallergenic" are less problematic than any others.

## References [edit]


1. ^ *a b c d e f g h* Nedorost, Susan T. (2012). *Generalized Dermatitis in Clinical Practice*. Springer Science & Business Media. pp. 1–3, 9, 13–14. ISBN 9781447128977. Retrieved 29 July 2016.
2. ^ *a b c d e f g h i* "Handout on Health: Atopic Dermatitis (A type of eczema)". *NIAMS*. May 2013. Retrieved 29 July

2016.
3. ^ a b c d e f g h i j k l m n o p q r s t u McAleer, MA; Flohr, C; Irvine, AD (23 July 2012). "Management of difficult and severe eczema in childhood". *BMJ (Clinical research ed.)*. **345**: e4770. doi:10.1136/bmj.e4770. PMID 22826585.
4. ^ Habif (2015). *Clinical Dermatology* (6 ed.). Elsevier Health Sciences. p. 171. ISBN 9780323266079. Retrieved 5 July 2016.
5. ^ Mowad, CM; Anderson, B; Scheinman, P; Pootongkam, S; Nedorost, S; Brod, B (June 2016). "Allergic contact dermatitis: Patient management and education.". *Journal of the American Academy of Dermatology*. **74** (6): 1043–54. doi:10.1016/j.jaad.2015.02.1144. PMID 27185422.
6. ^ Lurati, AR (February 2015). "Occupational risk assessment and irritant contact dermatitis.". *Workplace health & safety*. **63** (2): 81–7; quiz 88. doi:10.1177/2165079914565351. PMID 25881659.
7. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
8. ^ Adkinson, N. Franklin (2014). *Middleton's allergy : principles and practice.* (8 ed.). Philadelphia: Elsevier Saunders. p. 566. ISBN 9780323085939.
9. ^ "128.4". *Rook's Textbook of Dermatology, 4 Volume Set* (9 ed.). John Wiley & Sons. 2016. ISBN 9781118441176. Retrieved 29 July 2016.
10. ^ Frosch, Peter J. (2013). *Textbook of Contact Dermatitis* (2 ed.). Berlin, Heidelberg: Springer Berlin Heidelberg. p. 42. ISBN 9783662031049.
11. ^ "Neurodermatitis". Retrieved 2010-11-06.
12. ^ "Contact Dermatitis Pictures". Retrieved 2010-11-06.
13. ^ "Dermatitis". Retrieved 2010-11-06.
14. ^ "Symptoms". Retrieved 2010-11-06.
15. ^ Bufford, JD; Gern JE (May 2005). "The hygiene hypothesis revisited". *Immunology and Allergy Clinics of North America*. **25** (2): 247–262. doi:10.1016/j.iac.2005.03.005. PMID 15878454.
16. ^ Carswell F, Thompson S (1986). "Does natural sensitisation in eczema occur through the skin?". *Lancet*. **2** (8497): 13–5. doi:10.1016/S0140-6736(86)92560-2. PMID 2873316.
17. ^ Henszel Ł, Kuźna-Grygiel W (2006). "[House dust mites in the etiology of allergic diseases]". *Annales Academiae Medicae Stetinensis* (in Polish). **52** (2): 123–7. PMID 17633128.
18. ^ *Atopic Dermatitis* at eMedicine
19. ^ Paternoster, L; et al. (25 December 2011). "Meta-analysis of genome-wide association studies identifies three new risk loci for atopic dermatitis.". *Nature Genetics*. **44** (2): 187–92. doi:10.1038/ng.1017. PMC 3272375. PMID 22197932.
20. ^ Caproni, M; Bonciolini, V; d'Errico, A; Antiga, E; Fabbri, P (2012). "Celiac Disease and Dermatologic Manifestations: Many Skin Clue to Unfold Gluten-Sensitive Enteropathy". *Gastroenterol. Res. Pract*. Hindawi Publishing Corporation. **2012**: 1–12. doi:10.1155/2012/952753. PMC 3369470. PMID 22693492.
21. ^ Ciacci, C; Cavallaro R; Iovino P; Sabbatini F; Palumbo A; Amoruso D; Tortora R; Mazzacca G. (June 2004). "Allergy prevalence in adult celiac disease". *J. Allergy Clin. Immunol.* **113** (6): 1199–203. doi:10.1016/j.jaci.2004.03.012. PMID 15208605.
22. ^ "Eczema". *University of Maryland Medical Center*.
23. ^ Atkins D (March 2008). "Food allergy: diagnosis and management". *Primary Care*. **35** (1): 119–40, vii. doi:10.1016/j.pop.2007.09.003. PMID 18206721.
24. ^ Jeanne Duus Johansen; Peter J. Frosch; Jean-Pierre Lepoittevin (2010-09-29). *Contact Dermatitis*. Retrieved 2014-04-21.
25. ^ Alexander A. Fisher. *Fisher's Contact Dermatitis*. Retrieved 2014-04-21.
26. ^ Johansson SG, Hourihane JO, Bousquet J, et al. (September 2001). "A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force". *Allergy*. **56** (9): 813–24. doi:10.1034/j.1398-9995.2001.t01-1-00001.x. PMID 11551246.
27. ^ "Eczema". ACP medicine. Retrieved 9 January 2014.
28. ^ Bershad, SV (1 November 2011). "In the clinic. Atopic dermatitis (eczema)". *Annals of Internal Medicine*. **155** (9): ITC51–15; quiz ITC516. doi:10.7326/0003-4819-155-9-201111010-01005. PMID 22041966.
29. ^ ICD 10: Diseases of the skin and subcutaneous tissue (L00-L99) – Dermatitis and eczema (L20-L30)
30. ^ Ring, Johannes; Przybilla, Bernhard; Ruzicka, Thomas (2006). *Handbook of atopic eczema*. Birkhäuser. p. 4. ISBN 978-3-540-23133-2. Retrieved 4 May 2010.
31. ^ "Balsam of Peru contact allergy". Dermnetnz.org. 28 December 2013. Retrieved 5 March 2014.
32. ^ a b Torley, D; Futamura, M; Williams, HC; Thomas, KS (Jul 2013). "What's new in atopic eczema? An analysis of

systematic reviews published in 2010–11". *Clinical and experimental dermatology*. **38** (5): 449–56. doi:10.1111/ced.12143. PMID 23750610.
33. ^ Kalliomäki, M; Antoine, JM; Herz, U; Rijkers, GT; Wells, JM; Mercenier, A (Mar 2010). "Guidance for substantiating the evidence for beneficial effects of probiotics: prevention and management of allergic diseases by probiotics". *The Journal of Nutrition*. **140** (3): 713S–21S. doi:10.3945/jn.109.113761. PMID 20130079.
34. ^ "CDC Smallpox | Smallpox (Vaccinia) Vaccine Contraindications (Info for Clinicians)". Emergency.cdc.gov. 2007-02-07. Retrieved 2010-02-07.
35. ^ "Daily Skin Care Essential to Control Atopic Dermatitis article at American Academy of Dermatology's EczemaNet website". Retrieved 2009-03-24.
36. ^ Gutman, Ari Benjamin; Kligman, Albert M.; Sciacca, Joslyn; James, William D. (1 December 2005). "Soak and Smear". *Archives of Dermatology*. **141** (12). doi:10.1001/archderm.141.12.1556.
37. ^ *a b c d* Bath-Hextall, F; Delamere, FM; Williams, HC (23 January 2008). Bath-Hextall, Fiona J, ed. "Dietary exclusions for established atopic eczema". *Cochrane database of systematic reviews (Online)* (1): CD005203. doi:10.1002/14651858.CD005203.pub2. PMID 18254073.
38. ^ *a b* Institute for Quality and Efficiency in Health Care. "Eczema: Can eliminating particular foods help?". *Informed Health Online*. Institute for Quality and Efficiency in Health Care. Retrieved 24 June 2013.
39. ^ Ricci G, Patrizi A, Bellini F, Medri M (2006). "Use of textiles in atopic dermatitis: care of atopic dermatitis". *Current Problems in Dermatology*. Current Problems in Dermatology. **33**: 127–43. doi:10.1159/000093940. ISBN 3-8055-8121-1. PMID 16766885.
40. ^ Jungersted, JM; Agner, T (Aug 2013). "Eczema and ceramides: an update". *Contact dermatitis*. **69** (2): 65–71. doi:10.1111/cod.12073. PMID 23869725.
41. ^ Hoare C, Li Wan Po A, Williams H (2000). "Systematic review of treatments for atopic eczema". *Health Technology Assessment*. **4** (37): 1–191. PMID 11134919.
42. ^ Bewley A; Dermatology Working, Group (May 2008). "Expert consensus: time for a change in the way we advise our patients to use topical corticosteroids". *The British Journal of Dermatology*. **158** (5): 917–20. doi:10.1111/j.1365-2133.2008.08479.x. PMID 18294314.
43. ^ Oakley, M.D., Amanda. "Topical corticosteroid withdrawal". *DermNet NZ*. DermNet New Zealand Trust.
44. ^ Shams, K; Grindlay, DJ; Williams, HC (Aug 2011). "What's new in atopic eczema? An analysis of systematic reviews published in 2009–2010". *Clinical and experimental dermatology*. **36** (6): 573–7; quiz 577–8. doi:10.1111/j.1365-2230.2011.04078.x. PMID 21718344.
45. ^ *a b* Carr, WW (Aug 2013). "Topical calcineurin inhibitors for atopic dermatitis: review and treatment recommendations". *Paediatric drugs*. **15** (4): 303–10. doi:10.1007/s40272-013-0013-9. PMC 3715696. PMID 23549982.
46. ^ "FDA Issues Public Health Advisory Informing Health Care Providers of Safety Concerns Associated with the Use of Two Eczema Drugs, Elidel and Protopic". FDA. 10 March 2005. Archived from the original on 2007-09-17. Retrieved 2007-10-16.
47. ^ "Pimecrolimus cream for atopic dermatitis". *Drug and Therapeutics Bulletin*. **41** (5): 33–6. May 2003. doi:10.1136/dtb.2003.41533. PMID 12789846.
48. ^ Gambichler, T (Mar 2009). "Management of atopic dermatitis using photo(chemo)therapy". *Archives of dermatological research*. **301** (3): 197–203. doi:10.1007/s00403-008-0923-5. PMID 19142651.
49. ^ Meduri, NB; Vandergriff, T; Rasmussen, H; Jacobe, H (Aug 2007). "Phototherapy in the management of atopic dermatitis: a systematic review". *Photodermatology, photoimmunology & photomedicine*. **23** (4): 106–12. doi:10.1111/j.1600-0781.2007.00291.x. PMID 17598862.
50. ^ Stöppler MC (31 May 2007). "Psoriasis PUVA Treatment Can Increase Melanoma Risk". MedicineNet. Retrieved 2007-10-17.
51. ^ Vieira, BL; Lim, NR; Lohman, ME; Lio, PA (July 2016). "Complementary and Alternative Medicine for Atopic Dermatitis: An Evidence-Based Review". *American Journal of Clinical Dermatology* (Review). **17**: 1–25. doi:10.1007/s40257-016-0209-1. PMID 27388911.
52. ^ *a b* "Sulfur". University of Maryland Medical Center. 1 April 2002. Retrieved 2007-10-15.
53. ^ Armstrong NC, Ernst E (August 1999). "The treatment of eczema with Chinese herbs: a systematic review of randomized clinical trials". *British Journal of Clinical Pharmacology*. **48** (2): 262–4. doi:10.1046/j.1365-2125.1999.00004.x. PMC 2014284. PMID 10417508.
54. ^ *a b* Bath-Hextall, FJ; Jenkinson, C; Humphreys, R; Williams, HC (15 February 2012). Bath-Hextall, Fiona J, ed. "Dietary supplements for established atopic eczema". *Cochrane database of systematic reviews (Online)*. **2**: CD005205. doi:10.1002/14651858.CD005205.pub3. PMID 22336810.
55. ^ *a b* Bamford, JT; Ray, S; Musekiwa, A; van Gool, C; Humphreys, R; Ernst, E (30 April 2013). Bamford, Joel TM, ed. "Oral evening primrose oil and borage oil for eczema". *The Cochrane database of systematic reviews*. **4**: CD004416. doi:10.1002/14651858.CD004416.pub2. PMID 23633319.

56. ^ Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, Murrell DF, Tang ML (2008). Boyle, Robert John, ed. "Probiotics for treating eczema". *Cochrane Database of Systematic Reviews* (4): CD006135. doi:10.1002/14651858.CD006135.pub2. PMID 18843705.
57. ^ Eldred DC, Tuchin PJ (November 1999). "Treatment of acute atopic eczema by chiropractic care. A case study". *Australasian Chiropractic & Osteopathy*. **8** (3): 96–101. PMC 2051093. PMID 17987197.
58. ^ Ersser, Steven J.; Cowdell, Fiona; Latter, Sue; Gardiner, Eric; Flohr, Carsten; Thompson, Andrew Robert; Jackson, Karina; Farasat, Helen; Ware, Fiona (2014-01-07). "Psychological and educational interventions for atopic eczema in children". *The Cochrane Database of Systematic Reviews* (1): CD004054. doi:10.1002/14651858.CD004054.pub3. ISSN 1469-493X. PMID 24399641.
59. ^ Barnes, TM; Greive, KA (Nov 2013). "Use of bleach baths for the treatment of infected atopic eczema.". *The Australasian journal of dermatology*. **54** (4): 251–8. doi:10.1111/ajd.12015. PMID 23330843.
60. ^ Vos, T; et al. (15 Dec 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2163–96. doi:10.1016/S0140-6736(12)61729-2. PMID 23245607.
61. ^ Osman M, Hansell AL, Simpson CR, Hollowell J, Helms PJ (February 2007). "Gender-specific presentations for asthma, allergic rhinitis and eczema in primary care". *Primary Care Respiratory Journal*. **16** (1): 28–35. doi:10.3132/pcrj.2007.00006. PMID 17297524.
62. ^ Taylor B, Wadsworth J, Wadsworth M, Peckham C (December 1984). "Changes in the reported prevalence of childhood eczema since the 1939–45 war". *Lancet*. **2** (8414): 1255–7. doi:10.1016/S0140-6736(84)92805-8. PMID 6150286.
63. ^ Simpson CR, Newton J, Hippisley-Cox J, Sheikh A (2009). "Trends in the epidemiology and prescribing of medication for eczema in England". *J Roy Soc Med*. **102** (3): 108–117. doi:10.1258/jrsm.2009.080211. PMC 2746851. PMID 19297652.
64. ^ Luckhaupt, SE; Dahlhamer, JM; Ward, BW; Sussell, AL; Sweeney, MH; Sestito, JP; Calvert, GM (June 2013). "Prevalence of dermatitis in the working population, United States, 2010 National Health Interview Survey". *Am J Ind Med*. **56** (6): 625–634. doi:10.1002/ajim.22080. PMID 22674651.
65. ^ Henry George Liddell; Robert Scott. "Ekzema". *A Greek-English Lexicon*. Tufts University: Perseus.
66. ^ *Textbook of Atopic Dermatitis*. Taylor & Francis. 2008-05-01. p. 1. ISBN 9780203091449.
67. ^ "Definition of ECZEMA". *www.merriam-webster.com*. Retrieved 2016-02-15.
68. ^ Murphy LA, White IR, Rastogi SC (May 2004). "Is hypoallergenic a credible term?". *Clinical and Experimental Dermatology*. **29** (3): 325–7. doi:10.1111/j.1365-2230.2004.01521.x. PMID 15115531.


## External links [edit]

- Dermatitis at DMOZ

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| v · t · e | **Dermatitis and eczema (L20–L30, 690–693,698)** |
|---|---|
| **Atopic dermatitis** | Besnier's prurigo · |
| **Seborrheic dermatitis** | Pityriasis simplex capillitii · Cradle cap · |
| **Contact dermatitis (allergic, irritant)** | *plants:* Urushiol-induced contact dermatitis · African blackwood dermatitis · Tulip fingers · *other:* Abietic acid dermatitis · Diaper rash · Airbag dermatitis · Baboon syndrome · Contact stomatitis · Protein contact dermatitis · |
| **Eczema** | Autoimmune estrogen dermatitis · Autoimmune progesterone dermatitis · Breast eczema · Ear eczema · Eyelid dermatitis · Topical steroid addiction · Hand eczema (Chronic vesiculobullous hand eczema · Hyperkeratotic hand dermatitis · · Autosensitization dermatitis/Id reaction (Candidid · Dermatophytid · Molluscum dermatitis · · |

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|---|---|
| | Circumostomy eczema · Dyshidrosis · Juvenile plantar dermatosis · Nummular eczema · Nutritional deficiency eczema · Sulzberger–Garbe syndrome · Xerotic eczema · |
| **Pruritus / Itch / Prurigo** | Lichen simplex chronicus/Prurigo nodularis · *by location:* Pruritus ani · Pruritus scroti · Pruritus vulvae · Scalp pruritus · Drug-induced pruritus (Hydroxyethyl starch-induced pruritus · · Senile pruritus · Aquagenic pruritus (Aquadynia · · Adult blaschkitis · *due to liver disease* (Biliary pruritus · Cholestatic pruritus · · Prion pruritus · Prurigo pigmentosa · Prurigo simplex · Puncta pruritica · Uremic pruritus · |
| **Other** | substances taken internally: Bromoderma · Fixed drug reaction · Nummular dermatitis · Pityriasis alba · Papuloerythroderma of Ofuji · |
| **Authority control** | NDL: 00563155 · |

Categories: Autoimmune diseases | Eczema | Steroid-responsive inflammatory conditions




# Hair loss





From Wikipedia, the free encyclopedia

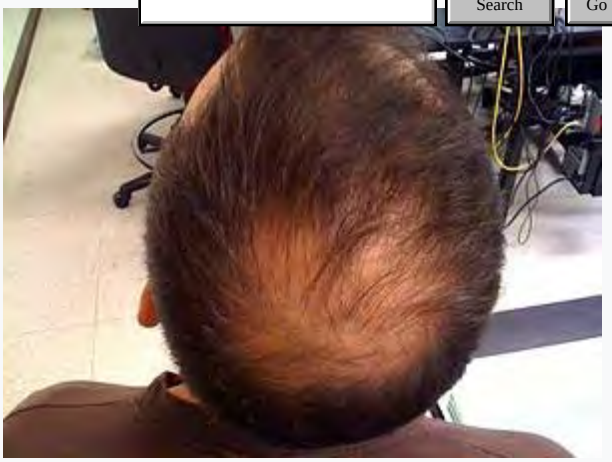
*"Bald" redirects here. For other uses, see Bald (disambiguation).*
*"Alopecia" redirects here. For an album by Why?, see Alopecia (album).*

**Hair loss**, also known as **alopecia** or **baldness**, refers to a loss of hair from part of the head or body.[1] Typically at least the head is involved.[2] The severity of hair loss can vary from a small area to the entire body.[3] Typically inflammation or scarring is not present.[2] Hair loss in some people causes psychological distress.[4]

Common types include: male-pattern hair loss, female-pattern hair loss, alopecia areata, and a thinning of hair known as telogen effluvium. The cause of male-pattern hair loss is a combination of genetics and male hormones, the cause of female pattern hair loss is unclear, the cause of alopecia areata is autoimmune, and the cause of is telogen effluvium is typically a physically or psychologically stressful event. Telogen effluvium is very common following pregnancy.[2]

Less common causes of hair loss without inflammation or scarring include the pulling out of hair, certain medications including chemotherapy, HIV/AIDS, hypothyroidism, and malnutrition including iron deficiency. Causes of hair loss that occurs with scarring or inflammation include fungal infection, lupus erythematosus, radiation therapy, and sarcoidosis.[2][4] Diagnosis of hair loss is partly based on the areas affected.[2]

Treatment of pattern hair loss may simply involve accepting the condition.[2] Intervention that can be tried include the medications minoxidil or finasteride, and hair transplant surgery.[5][6] Alopecia areata may be treated by steroid injections in the affected area but these need to be frequently repeated to be effective. Hair loss is a common problem. Pattern hair loss by age 50 affects about half of males and a quarter of females. About 2% of people develop alopecia areata at some point in time.[2]


Hair loss in a man.

| Classification and external resources | |
|---|---|
| **Specialty** | Dermatology |
| **ICD-10** | L65.9 |
| **ICD-9-CM** | 704.09 |
| **DiseasesDB** | 14765 |
| **MedlinePlus** | 003246 |
| **Patient UK** | Hair loss |
| **MeSH** | D000505 |

[edit on Wikidata]

Contents

# Terminology

Baldness is the partial or complete lack of hair growth, and part of the wider topic of "hair thinning". The degree and pattern of baldness varies, but its most common cause is androgenic alopecia, *alopecia androgenetica*, or *alopecia seborrheica*, with the last term primarily used in Europe.[*citation needed*]

# Signs and symptoms

Symptoms of hair loss include hair loss in patches usually in circular patterns, dandruff, skin lesions, and scarring. Alopecia areata (mild - medium level) usually shows in unusual hair loss areas e.g. eyebrows, backside of the head or above the ears where usually the male pattern baldness does not affect. In male-pattern hair loss, loss and thinning begin at the temples and the crown and either thins out or falls out. Female-pattern hair loss occurs at the frontal and parietal.

People have between 100,000 and 150,000 hairs on their head. The number of strands normally lost in a day varies, but on average is 100.[7] In order to maintain a normal volume, hair must be replaced at the same rate at which it is lost. The first signs of hair thinning that people will often notice are more hairs than usual left in the hairbrush after brushing or in the basin after shampooing. Styling can also reveal areas of thinning, such as a wider parting or a thinning crown.[*citation needed*]

A case of mid-frontal baldness:

## Skin conditions

A substantially blemished face, back and limbs could point to cystic acne. The most severe form of the condition, cystic acne arises from the same hormonal imbalances that cause hair loss, and is associated with dihydrotestosterone production.[8] Seborrheic dermatitis, a condition in which an excessive amount of sebum is produced and builds up on the scalp (looking like an adult cradle cap) is also a symptom of hormonal imbalances, as is an excessively oily or dry scalp. Both can cause hair

thinning.

Andre Agassi

## Psychological

Hair thinning and baldness cause psychological stress due to their effect on appearance. Although societal interest in appearance has a long history, this particular branch of psychology came into its own during the 1960s and has gained momentum as messages associating physical attractiveness with success and happiness grow more prevalent.[9]

The psychology of hair thinning is a complex issue. Hair is considered an essential part of overall identity: especially for women, for whom it often represents femininity and attractiveness. Men typically associate a full head of hair with youth and vigor. Although they may be aware of pattern baldness in their family, many are uncomfortable talking about the issue. Hair thinning is therefore a sensitive issue for both sexes. For sufferers, it can represent a loss of control and feelings of isolation. People experiencing hair thinning often find themselves in a situation where their physical appearance is at odds with their own self-image and commonly worry that they appear older than they are or less attractive to others. Psychological problems due to baldness, if present, are typically most severe at the onset of symptoms.[10]

Hair loss induced by cancer chemotherapy has been reported to cause changes in self-concept and body image. Body image does not return to the previous state after regrowth of hair for a majority of patients. In such cases, patients have difficulties expressing their feelings (alexithymia) and may be more prone to avoiding family conflicts. Family therapy can help families to cope with these psychological problems if they arise.[11]

# Causes

Although not completely understood,[*citation needed*] hair loss can have many causes:

## Pattern hair loss

*Main article: Pattern hair loss*

Male pattern hair loss is believed to be due to a combination of genetics and the male hormone dihydrotestosterone.[2] The cause in female pattern hair remains unclear.[2]

## Infection

- Dissecting cellulitis
- Fungal infections (such as tinea capitis)
- Folliculitis
- Secondary syphilis[12]
- *Demodex folliculorum*, a microscopic mite that feeds on the sebum produced by the sebaceous glands, denies hair essential nutrients and can cause thinning. *Demodex folliculorum* is not present on every scalp and is more likely to live in an excessively oily scalp environment.

## Drugs

- Temporary or permanent hair loss can be caused by several medications, including those for blood pressure problems, diabetes, heart disease and cholesterol.[13] Any that affect the body's hormone balance can have a pronounced effect: these include the contraceptive pill, hormone replacement therapy, steroids and acne medications.[14]
- Some treatments used to cure mycotic infections can cause massive hair loss.[15]
- Medications (side effects from drugs, including chemotherapy, anabolic steroids, and birth control pills[16][17])

## Trauma

- Traction alopecia is most commonly found in people with ponytails or cornrows who pull on their hair with excessive force. In addition, rigorous brushing and heat styling, rough scalp massage can damage the cuticle, the hard outer casing of the hair. This causes individual strands to become weak and break off, reducing overall hair volume.
- Trichotillomania is the loss of hair caused by compulsive pulling and bending of the hairs. Onset of this disorder tends to begin around the onset of puberty and usually continues through adulthood. Due to the constant extraction of the hair roots, permanent hair loss can occur.
- Traumas such as childbirth, major surgery, poisoning, and severe stress may cause a hair loss condition known as telogen effluvium,[18] in which a large number of hairs enter the resting phase at the same time, causing shedding and subsequent thinning. The condition also presents as a side effect of chemotherapy – while targeting dividing cancer cells, this treatment also affects hair's growth phase with the result that almost 90% of hairs fall out soon after chemotherapy starts.[19]
- Radiation to the scalp, as when radiotherapy is applied to the head for the treatment of certain cancers there, can cause baldness of the irradiated areas.

## Pregnancy

Hair loss often follows childbirth without causing baldness[*citation needed*]. In this situation, the hair is actually thicker during pregnancy due to increased circulating oestrogens. After the baby is born, the oestrogen levels fall back to normal prepregnancy levels, and the additional hair foliage drops out. A similar situation occurs in women taking the fertility-stimulating drug clomiphene.

## Other causes

- Alopecia areata is an autoimmune disorder also known as "spot baldness" that can result in hair loss ranging from just one location (*Alopecia areata monolocularis*) to every hair on the entire body (*Alopecia areata universalis*). Although thought to be caused by hair follicles becoming dormant, what triggers alopecia areata is not known. In most cases the condition corrects itself, but it can also spread to the entire scalp (alopecia totalis) or to the entire body (alopecia universalis).
- Localized or diffuse hair loss may also occur in cicatricial alopecia (lupus erythematosus, lichen plano pilaris, folliculitis decalvans, central centrifugal cicatricial alopecia, postmenopausal frontal fibrosing alopecia, etc.). Tumours and skin outgrowths also induce localized baldness (sebaceous nevus, basal cell carcinoma, squamous cell carcinoma).
- Hypothyroidism (an under-active thyroid) and the side effects of its related medications can cause hair loss, typically frontal, which is particularly associated with thinning of the outer third of the eyebrows (also seen with syphilis). Hyperthyroidism (an over-active thyroid) can also cause hair loss, which is parietal rather than frontal.[20][*unreliable medical source?*]
- Temporary loss of hair can occur in areas where sebaceous cysts are present for considerable duration (normally one to several weeks).
- Congenital triangular alopecia – It is a triangular, or oval in some cases, shaped patch of hair loss in the temple area of the scalp that occurs mostly in young children. The affected area mainly contains vellus hair follicles or no hair follicles at all, but it does not expand. Its causes are unknown, and although it is a permanent condition, it does not have any other effect on the affected individuals.[21]
- Gradual thinning of hair with age is a natural condition known as involutional alopecia. This is caused by an increasing number of hair follicles switching from the growth, or anagen, phase into a resting phase, or telogen phase, so that remaining hairs become shorter and fewer in number.
- An unhealthy scalp environment can play a significant role in hair thinning by contributing to miniaturization or causing damage[*citation needed*]. Air and water pollutants[*citation needed*], environmental toxins[*citation needed*], conventional styling products and excessive amounts of sebum have the potential to build up on the scalp[*citation needed*]. This debris can block hair follicles and cause their deterioration and consequent miniaturization of hair[*citation needed*]. It can also physically restrict hair growth or damage the hair cuticle[*citation needed*], leading to hair that is weakened and easily broken off before its natural lifecycle has ended.[*citation needed*]

Other causes of hair loss include:

- Alopecia mucinosa
- Biotinidase deficiency
- Chronic inflammation
- Diabetes[22]
- Lupus erythematosus
- Pseudopelade of Brocq
- Telogen effluvium
- Tufted folliculitis

The port-wine stain of Mikhail Gorbachev (pictured here with Ronald Reagan) would have remained unknown if he had not been bald.

## Pathophysiology

Hair follicle growth occurs in cycles. Each cycle consists of a long growing phase (anagen), a short transitional phase (catagen) and a short resting phase (telogen). At the end of the resting phase, the hair falls out (exogen) and a new hair starts growing in the follicle beginning the cycle again.

Normally, about 40 (0–78 in men) hairs reach the end of their resting phase each day and fall out.[23] When more than 100 hairs fall out per day, clinical hair loss (telogen effluvium) may occur.[*citation needed*] A disruption of the growing phase causes abnormal loss of anagen hairs (anagen effluvium).

## Diagnosis

Because they are not usually associated with an increased loss rate, male-pattern and female-pattern hair loss do not generally require testing. If hair loss occurs in a young man with no family history, drug use could be the cause.

- **The pull test** helps to evaluate diffuse scalp hair loss. Gentle traction is exerted on a group of hairs (about 40–60) on three different areas of the scalp. The number of extracted hairs is counted and examined under a microscope. Normally, fewer than three hairs per area should come out with each pull. If more than ten hairs are obtained, the pull test is considered positive.[24]
- **The pluck test** is conducted by pulling hair out "by the roots". The root of the plucked hair is examined under a microscope to determine the phase of growth, and is used to diagnose a defect of telogen, anagen, or systemic disease. Telogen hairs have tiny bulbs without sheaths at their roots. Telogen effluvium shows an increased percentage of hairs upon examination. Anagen hairs have sheaths attached to their roots. Anagen effluvium shows a decrease in telogen-phase hairs and an increased number of broken hairs.
- **Scalp biopsy** is used when the diagnosis is unsure; a biopsy allows for differing between scarring and nonscarring forms. Hair samples are taken from areas of inflammation, usually around the border of the bald patch.
- **Daily hair counts** are normally done when the pull test is negative. It is done by counting the number of hairs lost. The hair from the first morning combing or during washing should be counted. The hair is collected in a clear plastic bag for 14 days. The strands are recorded. If the hair count is >100/day, it is considered abnormal except after shampooing, where hair counts will be up to 250 and be normal.[*citation needed*]
- **Trichoscopy** is a noninvasive method of examining hair and scalp. The test may be performed with the use of a handheld dermoscope or a video dermoscope. It allows differential diagnosis of hair loss in most cases.[25]

There are two types of identification tests for female pattern baldness: the Ludwig Scale and the Savin Scale. Both track the progress of diffused thinning, which typically begins on the crown of the head behind the hairline, and becomes gradually more pronounced. For male pattern baldness, the Hamilton–Norwood scale tracks the progress of a receding hairline and/or a thinning crown, through to a horseshoe-shaped ring of hair around the head and on to total baldness.

In almost all cases of thinning, and especially in cases of severe hair loss, it is recommended to seek advice

from a doctor or dermatologist. Many types of thinning have an underlying genetic or health-related cause, which a qualified professional will be able to diagnose.

# Management

*See also: Management of hair loss*

## Medications

Treatments for the various forms of hair loss have limited success. Three medications have evidence to support their use in male pattern hair loss: finasteride, dutasteride and minoxidil.[26][27] They typically work better to prevent further hair loss than to regrow lost hair.[26]

- Minoxidil (Rogaine) is a nonprescription medication approved for male pattern baldness and alopecia areata. In a liquid or foam, it is rubbed into the scalp twice a day. Some people have an allergic reaction to the propylene glycol in the minoxidil solution and a minoxidil foam was developed without propylene glycol. Not all users will regrow hair. The longer the hair has stopped growing, the less likely minoxidil will regrow hair. Minoxidil is not effective for other causes of hair loss. Hair regrowth can take 1 to 6 months to begin. Treatment must be continued indefinitely. If the treatment is stopped, hair loss resumes. Any regrown hair and any hair susceptible to being lost, while Minoxidil was used, will be lost. Most frequent side effects are mild scalp irritation, allergic contact dermatitis, and unwanted hair in other parts of the body.[27]
- Finasteride (Propecia) is used in male-pattern hair loss in a pill form, taken 1 milligram per day. It is not indicated for women and is not recommended in pregnant women. Treatment is effective starting within 6 weeks of treatment. Finasteride causes an increase in hair retention, the weight of hair, and some increase in regrowth. Side effects in about 2% of males, include decreased sex drive, erectile dysfunction, and ejaculatory dysfunction. Treatment should be continued as long as positive results occur. Once treatment is stopped, hair loss resumes.[27]
- Corticosteroids injections into the scalp can be used to treat alopecia areata. This type of treatment is repeated on a monthly basis. Oral pills for extensive hair loss may be used for alopecia areata. Results may take up to a month to be seen.
- Immunosuppressants applied to the scalp have been shown to temporarily reverse alopecia areata, though the side effects of some of these drugs make such therapy questionable.[28]
- There is some tentative evidence that anthralin maybe useful alopecia areata.[29]
- Hormonal modulators (oral contraceptives or antiandrogens such as spironolactone and flutamide) can be used for female-pattern hair loss associated with hyperandrogenemia.

## Surgery

Hair transplantation is usually carried out under local anaesthetic. A surgeon will move healthy hair from the back and sides of the head to areas of thinning. The procedure can take between four and eight hours, and additional sessions can be carried out to make hair even thicker. Transplanted hair falls out within a few weeks, but regrows permanently within months. Hair transplants, takes tiny plugs of skin, each which contains a few hairs, and implants the plugs into bald sections. The plugs are generally taken from the back or sides of the scalp. Several transplant sessions may be necessary.[30]

- Surgical options, such as follicle transplants, scalp flaps, and hair loss reduction, are available. These procedures are generally chosen by those who are self-conscious about their hair loss, but they are expensive and painful, with a risk of infection and scarring. Once surgery has occurred, six to eight months are needed before the quality of new hair can be assessed.
  - Scalp reduction is the process is the decreasing of the area of bald skin on the head. In time, the skin on the head becomes flexible and stretched enough that some of it can be surgically removed. After the hairless scalp is removed, the space is closed with hair-covered scalp. Scalp reduction is generally done in combination with hair transplantation to provide a natural-looking hairline, especially those with extensive hair loss.
  - Hairline lowering can sometimes be used to lower a high hairline secondary to hair loss, although

there may be a visible scar after further hair loss.
- Wigs are an alternative to medical and surgical treatment; some patients wear a wig or hairpiece. They can be used permanently or temporarily to cover the hair loss. High-quality, natural-looking wigs and hairpieces are available.

## Hiding hair loss

### Head

One method of hiding hair loss is the "comb over", which involves restyling the remaining hair to cover the balding area. It is usually a temporary solution, useful only while the area of hair loss is small. As the hair loss increases, a comb over becomes less effective.

Another method is to wear a hat or a hairpiece—a wig or toupee. The wig is a layer of artificial or natural hair made to resemble a typical hair style. In most cases the hair is artificial. Wigs vary widely in quality and cost. In the United States, the best wigs—those that look like real hair—cost up to tens of thousands of dollars. Organizations also collect individuals' donations of their own natural hair to be made into wigs for young cancer patients who have lost their hair due to chemotherapy or other cancer treatment in addition to any type of hair loss.

General Douglas MacArthur wearing a comb over.

### Eyebrows

Though not as common as the loss of hair on the head, chemotherapy, hormone imbalance, forms of hair loss, and other factors can also cause loss of hair in the eyebrows. Loss of growth in the outer one third of the eyebrow is often associated with hypothyroidism. Artificial eyebrows are available to replace missing eyebrows or to cover patchy eyebrows. Eyebrow embroidery is another option which involves the use of a blade to add pigment to the eyebrows. This gives a natural 3D look for those who are worried about an artificial look and it lasts for two years. Micropigmentation (permanent makeup tattooing) is also available for those who want the look to be permanent.

## Chemotherapy

Hypothermia caps may be useful to prevent hair loss during some kinds of chemotherapy, specifically when tazanes or anthracyclines are used.[31] It should not be used when cancer is present in the skin of the scalp or for lymphoma or leukemia.[32] There are generally only minor side effects from treatment.[33]

## Embracing baldness

Instead of concealing hair loss, some may embrace it by shaving their head. A shaved head will grow stubble in the same manner and at the same rate as a shaved face. The general public has become accepting of the shaved head as well, though female baldness can be considered less socially acceptable in various parts of the world.

## Alternative medicine

Dietary supplements are not typically recommended.[27] There is only one small trial of saw palmetto which shows tentative benefit in those with mild to moderate androgenetic alopecia.[27] There is no evidence for biotin.[27] Evidence for most other produces is also insufficient.[34] There was no good evidence for gingko, aloe vera, ginseng, bergamot, hibiscus, or sorphora as of 2011.[34]

Many people use unproven treatments.[26] Egg oil, in Indian,[35] Japanese, Unani (Roghan Baiza Murgh)[36] and Chinese[37] traditional medicine, was traditionally used as a treatment for hair loss.[*medical citation needed*]

# Research

Research is looking into connections between hair loss and other health issues. While there has been speculation about a connection between early-onset male pattern hair loss and heart disease, a review of articles from 1954 to 1999 found no conclusive connection between baldness and coronary artery disease. The dermatologists who conducted the review suggested further study was needed.[38]

Environmental factors are under review. A 2007 study indicated that smoking may be a factor associated with age-related hair loss among Asian men. The study controlled for age and family history, and found statistically significant positive associations between moderate or severe male pattern hairloss and smoking status.[39]

Vertex baldness is associated with an increased risk of coronary heart disease (CHD) and the relationship depends upon the severity of baldness, while frontal baldness is not. Thus, vertex baldness might be a marker of CHD and is more closely associated with atherosclerosis than frontal baldness.[23]

## Hair follicle aging

A key aspect of hair loss with age is the aging of the hair follicle.[40] Ordinarily, hair follicle renewal is maintained by the stem cells associated with each follicle. Aging of the hair follicle appears to be primed by a sustained cellular response to the DNA damage that accumulates in renewing stem cells during aging.[41] This damage response involves the proteolysis of type XVII collagen by neutrophil elastase in response to the DNA damage in the hair follicle stem cells. Proteolysis of collagen leads to elimination of the damaged cells and then to terminal hair follicle miniaturization.

# Etymology

The term *alopecia* (/ˌæləˈpiːʃiə/) is from the Classical Greek ἀλώπηξ, *alōpēx*, meaning "fox". The origin of this usage is because this animal sheds its coat twice a year, or because in ancient Greece foxes often lost hair because of mange.

The term *bald* likely derives from the English word *balde*, which means "white, pale" or Celtic *ball*, which means "white patch or blaze", such as on a horse's head.[42]

# See also

- Alopecia in animals
- Lichen planopilaris

# References


1. ^ "Hair loss". *NHS Choices*. Retrieved 22 September 2013.
2. ^ *a b c d e f g h i* Vary JC, Jr (November 2015). "Selected Disorders of Skin Appendages--Acne, Alopecia, Hyperhidrosis.". *The Medical clinics of North America*. **99** (6): 1195–211. doi:10.1016/j.mcna.2015.07.003. PMID 26476248.
3. ^ "Hair loss". *DermNet*. Archived from the original on 2016. Retrieved 2016-08-03.
4. ^ *a b* Nalluri, R; Harries, M (February 2016). "Alopecia in general medicine.". *Clinical medicine (London, England)*. **16** (1): 74–8. doi:10.7861/clinmedicine.16-1-74.

2013). "Pattern hair loss in men: diagnosis and medical treatment". *Dermatologic clinics*. **31** (1): 129–40. doi:10.1016/j.det.2012.08.003. PMID 23159182.

27. ^ *a b c d e f* Rogers, Nicole E.; Avram, Marc R. (Oct 2008). "Medical treatments for male and female pattern hair loss". *Journal of the American Academy of Dermatology*. **59** (4): 547–566; quiz 567–568. doi:10.1016/j.jaad.2008.07.001. ISSN 1097-6787. PMID 18793935.
28. ^ Joly P (October 2006). "The use of methotrexate alone or in combination with low doses of oral corticosteroids in the treatment of alopecia totalis or universalis". *J Am Acad Dermatol*. **55** (4): 632–6.

PMID 26833522.
5. ^ McElwee, K. J.; Shapiro, J. S. (2012). "Promising therapies for treating and/or preventing androgenic alopecia". *Skin therapy letter*. **17** (6): 1–4. PMID 22735503.
6. ^ Leavitt, M. (2008). "Understanding and Management of Female Pattern Alopecia". *Facial Plastic Surgery*. **24** (4): 414–427. doi:10.1055/s-0028-1102905. PMID 19034818.
7. ^ Alaiti, Samer. "Hair growth". *eMedicine*. Archived from the original on January 21, 2015.
8. ^ Bergler-Czop, B; Brzezińska-Wcisło, L (2004). "Hormonal factors in etiology of common acne". *Polski merkuriusz lekarski : organ Polskiego Towarzystwa Lekarskiego*. **16** (95): 490–2. PMID 15518435.
9. ^ 'The psychology of appearance: Why health psychologists should "do looks"', Nichola Rumsey, September 2008: [1]
10. ^ Passchier J, Erdman J, Hammiche F, Erdman R (2006). "Androgenetic alopecia: stress of discovery". *Psychol Rep*. **98** (1): 226–8. doi:10.2466/PR0.98.1.226-228. PMID 16673981.
11. ^ Poot F (2004). "[Psychological consequences of chronic hair diseases]". *Revue Médicale de Bruxelles*. **25** (4): A286–8. PMID 15516058.
12. ^ "Infectious hair disease – syphilis". Keratin.com. Retrieved 2011-11-17.
13. ^ 'Drug Induced Hair Loss', WebMD.com
14. ^ 'Drug Induced Hair Loss', American Hair Loss Association: http://www.americanhairloss.org/drug_induced_hair_loss/
15. ^ Pappas P, Kauffman C, Perfect J, Johnson P, McKinsey D, Bamberger D, Hamill R, Sharkey P, Chapman S, Sobel J (1995). "Alopecia associated with fluconazole therapy". *Ann Intern Med*. **123** (5): 354–7. doi:10.7326/0003-4819-123-5-199509010-00006. PMID 7625624.
16. ^ "Alopecia: Causes". Better Medicine. Retrieved 28 March 2012.
17. ^ http://www.webmd.com/skin-problems-and-treatments/hair-loss/drug-induced-hair-loss
18. ^ Nnoruka E, Nnoruka N (October 2005). "Hair loss: is there a relationship with hair care practices in Nigeria?". *Int J Dermatol*. **44** (Suppl 1): 13–7. doi:10.1111/j.1365-4632.2005.02801.x. PMID 16187950.
19. ^ "Anagen Effluvium". Retrieved 2010-06-29.
20. ^ Alopecia Areata, by Maria G. Essig, MS, ELS, Yahoo! Health
21. ^ "Congenital triangular alopecia". Retrieved 2010-06-29.
22. ^ "What is Alopecia: What Causes Alopecia?". MedicalBug. 6 February 2012. Retrieved 28 March 2012.
23. ^ *a b* Yamada, T; Hara, K; Umematsu, H; Kadowaki, T (2013). "Male pattern baldness and its association with coronary heart disease: A meta-analysis". *BMJ* doi:10.1016/j.jaad.2005.09.010. PMID 17010743.
29. ^ Shapiro, J (Dec 2013). "Current treatment of alopecia areata.". *The journal of investigative dermatology. Symposium proceedings / the Society for Investigative Dermatology, Inc. [and] European Society for Dermatological Research*. **16** (1): S42–4. doi:10.1038/jidsymp.2013.14. PMID 24326551.
30. ^ 'Hair Transplants', WebMD: http://www.webmd.com/skin-problems-and-treatments/hair-loss/hair-transplants
31. ^ Grevelman, EG; Breed, WP (March 2005). "Prevention of chemotherapy-induced hair loss by scalp cooling.". *Annals of Oncology*. **16** (3): 352–8. doi:10.1093/annonc/mdi088. PMID 15642703.
32. ^ Breed, WP (January 2004). "What is wrong with the 30-year-old practice of scalp cooling for the prevention of chemotherapy-induced hair loss?". *Supportive Care in Cancer*. **12** (1): 3–5. doi:10.1007/s00520-003-0551-8. PMID 14615930.
33. ^ Komen, MM; Smorenburg, CH; van den Hurk, CJ; Nortier, JW (2011). "[Scalp cooling for chemotherapy-induced alopecia].". *Nederlands tijdschrift voor geneeskunde*. **155** (45): A3768. PMID 22085565.
34. ^ *a b* Blumeyer, A; Tosti, A; Messenger, A; Reygagne, P; Del Marmol, V; Spuls, PI; Trakatelli, M; Finner, A; Kiesewetter, F; Trüeb, R; Rzany, B; Blume-Peytavi, U; European Dermatology Forum, (EDF) (October 2011). "Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men.". *Journal of the German Society of Dermatology*. 9 Suppl 6: S1–57. doi:10.1111/j.1610-0379.2011.07802.x. PMID 21980982.
35. ^ Panda, H (2004). *Handbook on Ayurvedic Medicines with Formulae, Processes and Their Uses*. ISBN 9788186623633.
36. ^ Suresh Babu, S (2002-01-01). *Home Made Herbal Cosmetics*. ISBN 9788122307757.
37. ^ Zhou, Zhongying; Jin, Hui De (1997). *Clinical Manual of Chinese Herbal Medicine and Acupuncture*. ISBN 9780443051289.
38. ^ Rebora A (1 July 2001). "Baldness and coronary artery disease: the dermatologic point of view of a controversial issue". *Arch Dermatol*. **137** (7): 943–7. PMID 11453815.
39. ^ Asian men who smoke may have increased risk for hair loss
Su LH, Chen TH (November 2007). "Association of androgenetic alopecia with smoking and its prevalence among Asian men: a community-based survey". *Arch Dermatol*. **143** (11): 1401–6. doi:10.1001/archderm.143.11.1401. PMID 18025364.
40. ^ Lei M, Chuong CM (2016). "STEM CELLS. Aging, alopecia, and stem cells". *Science*. **351** (6273): 559–60. doi:10.1126/science.aaf1635.

*Open*. **3** (4): e002537. doi:10.1136/bmjopen-2012-002537. PMC 3641488. PMID 23554099.
24. ^ "The hair pull test". Keratin.com. Retrieved 28 March 2012.
25. ^ Rudnicka L, Olszewska M, Rakowska A, Kowalska-Oledzka E, Slowinska M (2008). "Trichoscopy: a new method for diagnosing hair loss". *J Drugs Dermatol*. **7** (7): 651–654. PMID 18664157.
26. ^ *a b c* Banka, N; Bunagan, MJ; Shapiro, J (January PMID 26912687 .
41. ^ Matsumura H, Mohri Y, Binh NT, Morinaga H, Fukuda M, Ito M, Kurata S, Hoeijmakers J, Nishimura EK (2016). "Hair follicle aging is driven by transepidermal elimination of stem cells via COL17A1 proteolysis". *Science*. **351** (6273): aad4395. doi:10.1126/science.aad4395. PMID 26912707.
42. ^ Harper, Douglas. "Entry for "bald" ". *Online Etymology Dictionary*. Retrieved 2006-12-07.

# External links

- Hair loss at DMOZ

Wikimedia Commons has media related to *Alopecia*.

| v · t · e · | **Human hair** | |
|---|---|---|
| List of hairstyles / facial hairstyles | | |
| **Classification** | by type | Lanugo · Androgenic · Terminal · Vellus · |
| | by location | Head · Nose · Ear · Eyebrow · Eyelash · Underarm · Chest · Abdominal · Pubic · Leg · |
| | v · t · e · **Human hair color** | |
| | **Hair color** | Black · Blond · Brown (varieties: Chestnut • Auburn) · Red (varieties: Auburn • Titian) · White/Grey · |
| | **Hair coloring** | Blue rinse · Grecian Formula · Hair dye stripping · Hair highlighting · Henna · Hydrogen peroxide · Blue hair · |
| | **Other** | Disappearing blonde gene · Fischer–Saller scale · Fischer scale · Melanocortin 1 receptor · |
| **Hairstyles** | | Afro · Asymmetric cut · Bangs · Beehive · Big hair · Blowout · Blunt hair · Bob cut · Bouffant · Bowl cut · Braid or Plait · Brush cut · Bun (odango) · Bunches · Burr · Businessman cut · Butch cut · Buzz cut · Caesar cut · Chignon · Chonmage · Chupryna · Comb over · Conk · Cornrows · Crew cut · Crochet braids · Cropped hair · Croydon facelift · Curtained hair · Devilock · Dice Bob · Dido flip · Digital perm · Dreadlocks · Donald Trump · Duck's ass · Emo · Extensions · Fade · Fauxhawk · Feathered hair · Finger wave · Flattop · Flipped hair · Fontange · French braid · French twist · Frosted tips · Full crown · G.I. haircut · Half crown · Harvard clip · High and tight · Hime cut · Historical Christian hairstyles · Hi-top fade · Induction cut · Ivy League · Jewfro · Jheri curl · Kiss curl · Layered hair · Liberty spikes · Long hair · Lob cut · Marcelling · Mod cut · Mohawk · Mop-top · Mullet · 1950s · 1980s · Pageboy · Part · Payot · Pigtail · Pixie cut · Pompadour · Ponytail · Punch perm · Princeton · Professional cut · Queue · Quiff · Rattail · Razor cut · Regular haircut · Regular taper cut · Ringlets · Shag · Shape-Up · Short back and sides · Short brush cut · Short hair · Spiky hair · Standard haircut · Surfer hair · Taper cut · Tonsure · Updo · Undercut · Waves · Weave · Wings · |
| **Facial hair** | | Beard · Chin curtain · Chinstrap · Designer stubble · Goatee · Moustache (Fu Manchu · handlebar · horseshoe · pencil · toothbrush · walrus · · Neckbeard · Shenandoah · Sideburns · Soul patch · Van Dyke · |

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|---|---|---|
| **Hair loss** | Cosmetic | Removal (waxing · threading · plucking · chemical · electric · laser · IPL · · Shaving (head · leg · · Razor (safety · straight · · |
| | other | **Alopecia** (areata · totalis · universalis · · Male-pattern hair loss · Glabrousness · Hypertrichosis · Management · Trichophilia · Trichotillomania · Pogonophobia · |
| **Haircare Products** | | Brush · Clay · Clipper · Comb · Conditioner · Dryer · Gel · Hot comb · Iron · Mousse · Pomade · Relaxer · Rollers · Shampoo · Spray · Wax · |
| **Haircare Techniques** | | Backcombing · Crimping · Perm · Shampoo and set · Straightening · |
| **Documentaries** | | My Nappy Roots: A Journey Through Black Hair-itage (2008) · Good Hair (2009) · |
| **Related Topics** | | Afro-textured hair · Bearded lady · Barber (pole) · Eponymous hairstyle · Good hair (phrase) · Hairdresser · Hair fetishism (pubic) · Hair follicle · Hair growth · Hypertrichosis · Trichotillomania · |

| v · t · e · | **Disorders of skin appendages (L60–L75, 703–706)** | |
|---|---|---|
| **Nail** | | thickness: Onychogryphosis · Onychauxis · color: Beau's lines · Yellow nail syndrome · Leukonychia · Azure lunula · shape: Koilonychia · Nail clubbing · behavior: Onychotillomania · Onychophagia · other: Ingrown nail · Anonychia · ungrouped: Paronychia (Acute · Chronic · · Chevron nail · Congenital onychodysplasia of the index fingers · Green nails · Half and half nails · Hangnail · Hapalonychia · Hook nail · Ingrown nail · Lichen planus of the nails · Longitudinal erythronychia · Malalignment of the nail plate · Median nail dystrophy · Mees' lines · Melanonychia · Muehrcke's lines · Nail–patella syndrome · Onychoatrophy · Onycholysis · Onychomadesis · Onychomatricoma · Onychomycosis · Onychophosis · Onychoptosis defluvium · Onychorrhexis · Onychoschizia · Platonychia · Pincer nails · Plummer's nail · Psoriatic nails · Pterygium inversum unguis · Pterygium unguis · Purpura of the nail bed · Racquet nail · Red lunulae · Shell nail syndrome · Splinter hemorrhage · Spotted lunulae · Staining of the nail plate · Stippled nails · Subungual hematoma · Terry's nails · Twenty-nail dystrophy · |
| | **Hair loss/ Baldness** | *noncicatricial alopecia:* **Alopecia** (areata · totalis · universalis · Ophiasis · · Androgenic alopecia (male-pattern baldness) · Hypotrichosis · Telogen effluvium · Traction alopecia · Lichen planopilaris · Trichorrhexis nodosa · Alopecia neoplastica · Anagen effluvium · Alopecia mucinosa · |
| | | *cicatricial alopecia:* Pseudopelade of Brocq · Central centrifugal cicatricial alopecia · Pressure alopecia · Traumatic alopecia · Tumor alopecia · Hot comb alopecia · Perifolliculitis capitis abscedens et suffodiens · Graham-Little syndrome · Folliculitis decalvans · |
| | | *ungrouped:* Triangular alopecia · Frontal fibrosing alopecia · Marie Unna hereditary hypotrichosis · |
| | **Hypertrichosis** | Hirsutism · Acquired (localised · generalised · patterned · · Congenital (generalised · localised · X-linked · · Prepubertal · |
| | | Acne vulgaris · Acne conglobata · Acne miliaris necrotica · Tropical acne · Infantile acne/Neonatal acne · |

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|---|---|---|---|
| **Hair** | **Acneiform eruption** | **Acne** | Excoriated acne · Acne fulminans · Acne medicamentosa (e.g., steroid acne) · Halogen acne (Iododerma · Bromoderma · Chloracne · · Oil acne · Tar acne · Acne cosmetica · Occupational acne · Acne aestivalis · Acne keloidalis nuchae · Acne mechanica · Acne with facial edema · Pomade acne · Acne necrotica · Blackhead · Lupus miliaris disseminatus faciei · |
| | | **Rosacea** | Perioral dermatitis (Granulomatous perioral dermatitis · · Phymatous rosacea (Rhinophyma · Blepharophyma · Gnathophyma · Metophyma · Otophyma · · Papulopustular rosacea · Lupoid rosacea · Erythrotelangiectatic rosacea · Glandular rosacea · Gram-negative rosacea · Steroid rosacea · Ocular rosacea · Persistent edema of rosacea · Rosacea conglobata · *variants* (Periorificial dermatitis · Pyoderma faciale · · |
| | | **Ungrouped** | Granulomatous facial dermatitis · Idiopathic facial aseptic granuloma · Periorbital dermatitis · SAPHO syndrome · |
| | **Follicular cysts** | | "Sebaceous cyst" (Epidermoid cyst · Trichilemmal cyst · · Steatocystoma (simplex · multiplex · · Milia · |
| | **Inflammation** | | Folliculitis (Folliculitis nares perforans · Tufted folliculitis · · Pseudofolliculitis barbae · Hidradenitis (Hidradenitis suppurativa · Recurrent palmoplantar hidradenitis · Neutrophilic eccrine hidradenitis · · |
| | **Ungrouped** | | Acrokeratosis paraneoplastica of Bazex · Acroosteolysis · Bubble hair deformity · Disseminate and recurrent infundibulofolliculitis · Erosive pustular dermatitis of the scalp · Erythromelanosis follicularis faciei et colli · Hair casts · Hair follicle nevus · Intermittent hair–follicle dystrophy · Keratosis pilaris atropicans · Kinking hair · Koenen's tumor · Lichen planopilaris · Lichen spinulosus · Loose anagen syndrome · Menkes kinky hair syndrome · Monilethrix · Parakeratosis pustulosa · Pili (Pili annulati · Pili bifurcati · Pili multigemini · Pili pseudoannulati · Pili torti) · Pityriasis amiantacea · Plica neuropathica · Poliosis · Rubinstein–Taybi syndrome · Setleis syndrome · Traumatic anserine folliculosis · Trichomegaly · Trichomycosis axillaris · Trichorrhexis (Trichorrhexis invaginata · Trichorrhexis nodosa) · Trichostasis spinulosa · Uncombable hair syndrome · Wooly hair · Wooly hair nevus · |
| **Sweat glands** | **Eccrine** | | Miliaria (Colloid milium · Miliaria crystalline · Miliaria profunda · Miliaria pustulosa · Miliaria rubra · Occlusion miliaria · Postmiliarial hypohidrosis · · Granulosis rubra nasi · Ross' syndrome · Anhidrosis · Hyperhidrosis (Generalized · Gustatory · Palmoplantar · · |
| | **Apocrine** | | Body odor · Chromhidrosis · Fox–Fordyce disease · |
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Categories: Radiation health effects | Conditions of the skin appendages | External signs of aging | Human hair | Hair diseases




# Head lice infestation

From Wikipedia, the free encyclopedia

*This article is about the infestation. For the animal, see Head louse.*

**Head lice infestation** (also known as **pediculosis capitis**,[1] **nits**,[2] or **cooties**[3]) is the infection of the head hair and scalp by the head louse (*Pediculus humanus capitis*).[4] Itching from lice bites is common.[5] During a person's first infection, the itch may not develop for up to six weeks.[5] If a person is infected again, symptoms may begin much more quickly.[5] The itch may cause problems with sleeping.[6] Generally, however, it is not a serious condition.[7] While head lice appear to spread some other diseases in Africa, they do not appear to do so in Europe or North America.[4][6]

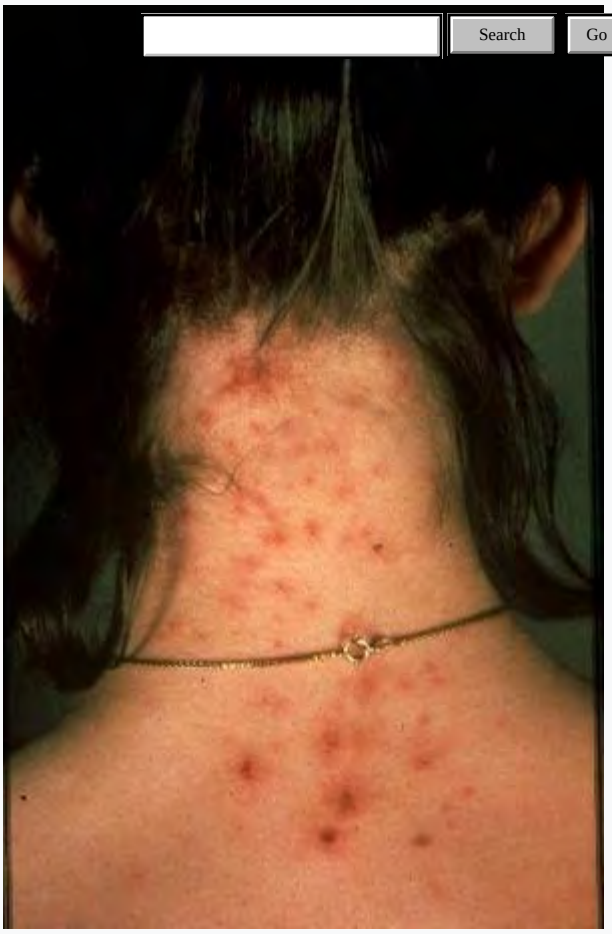
Head lice are spread by direct contact with the hair of someone who is infected.[6] The cause of head lice infestations are not related to cleanliness.[5] Other animals, such as cats and dogs, do not play a role in transmission.[6] Head lice feed only on human blood and are only able to survive on human head hair.[4][5] When adults, they are about 2 to 3 mm long.[8] When not attached to a human, they are unable to live beyond three days.[5] Humans can also become infected with two other lice – the body louse and the crab louse. To make the diagnosis, live lice must be found.[5] Using a comb can help with detection.[5] Empty eggshells (known as nits) are not sufficient for the diagnosis.[5]

Possible treatments include: combing the hair frequently with a fine tooth comb or shaving the head completely. A number of topical medications are also effective, including malathion, ivermectin, and dimethicone.[7] Dimethicone, which is a silicone oil, is often preferred due to the low risk of side effects.[7] Pyrethroids such as permethrin have been commonly used; however, have become less effective due to increasing pesticide resistance.[7] There is little evidence for alternative medicines.[9]

Head-lice infestations are common, especially in children.[5] In Europe, they infect between 1 and 20% of different groups of people.[4] In the United States, between 6 and 12 million children are infected a year.[6] They occur more often in girls than boys.[5] It has been suggested that historically, head lice

## Variants

**Head lice infestation (pediculosis capitis)**



Head lice bites on the back of the neck

| Classification and external resources | |
|---|---|
| **Specialty** | infectious disease |
| **ICD-10** | B85.0 |
| **DiseasesDB** | 9725 |
| **MedlinePlus** | 000840 |
| **eMedicine** | med/1769 |
| **MeSH** | D010373 |

infection were beneficial, as they protected against the more dangerous body louse.[10] Infestations may cause stigmatization of the infected individual.[5]

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## Signs and symptoms [edit]

Head lice are generally uncomfortable, but typically do not constitute a serious condition.[7] The most common symptom is itching of the head, which normally worsens 3 to 4 weeks after the initial infestation.[*citation needed*] The bite reaction is very mild, and it can be rarely seen between the hairs. Bites can be seen, especially in the neck of long-haired individuals when the hair is pushed aside. Swelling of the local lymph nodes and fever are rare. Itching may cause skin breakdown and uncommonly result in a bacterial infection.[7]

Adult male (left) and female (right) head lice

In Ethiopia, head lice appear to be able to spread louse-born epidemic typhus and *Bartonella quintana*.[4] In Europe, the head lice do not appear to carry these infections.[4]

## Cause [edit]

Head lice are generally spread through direct head-to-head contact with an infested person.[5] Transmission by sharing bedding or clothing such as headwear is much less common.[11] The cause of head lice infestations is not related to cleanliness.[5] Neither hair length nor how often the hair is brushed affect the risk of infection.[12]

Body lice are spread through direct contact with the body, clothing, or other personal items of a person already carrying lice. Pubic lice are most often spread by intimate contact with an infested person. Head lice occur on the head hair, body lice on the clothing, and pubic lice mainly on the hair near the groin. Lice cannot burrow into the skin.

## Diagnosis [edit]

The condition is diagnosed by finding live lice in the hair. Finding empty eggs is not enough.[5] This is made easier by using a magnifying glass or running a comb through the child's hair. In questionable cases, a

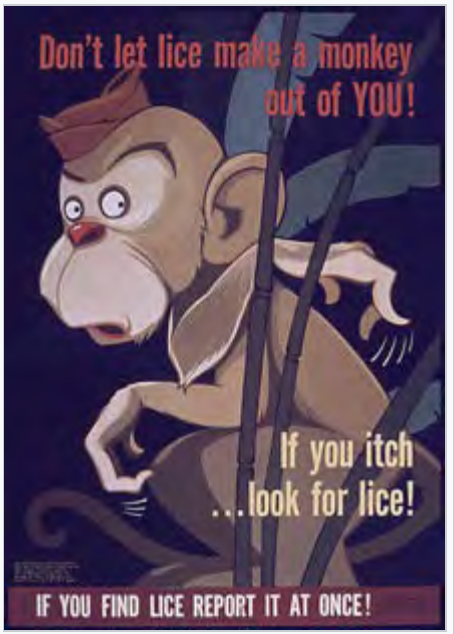
Lice comb (Bug Buster) wet combing with conditioner for diagnosis and treatment. Head lice can be seen in foam.

child can be referred to a health professional. However, the condition is overdiagnosed, with extinct infestations being mistaken for active ones. As a result, lice-killing treatments are more often used on noninfested than infested children.[13] The use of a louse comb is the most effective way to detect living lice.[14] With both methods, special attention should be paid to the area near the ears and the nape of the neck. The use of a magnifying glass to examine the material collected between the teeth of the comb could prevent misdiagnosis.

The presence of nits alone, however, is not an accurate indicator of an active head louse infestation. Generally, white nits are empty egg casings, while brown nits may still contain viable louse larva. One way of determining the nit is to squeeze it between two fingernails; it gives a characteristic snapping pop sound as the egg bursts. Children with nits on their hair have a 35–40% chance of also being infested with living lice and eggs.[14][15] If lice are detected, the entire family needs to be checked (especially children up to the age of 13 years) with a louse comb, and only those who are infested with living lice should be treated. As long as no living lice are detected, the child should be considered negative for head louse infestation. Accordingly, a child should be treated with a pediculicide only when living lice are detected on their hair (not because he/she has louse eggs/nits on the hair and not because the scalp is itchy).[16]

## Prevention [edit]

Examination of the child's head at regular intervals using a louse comb allows the diagnosis of louse infestation at an early stage. Early diagnosis makes treatment easier and reduces the possibility of infesting others. In times and areas when louse infestations are common, weekly examinations of children, especially those 4–15 years old, carried out by their parents, will aid control. Additional examinations are necessary if the child came in contact with infested individuals, if the child frequently scratches his/her head, or if nits suddenly appear on the child's hair. Keeping long hair tidy could be helpful in the prevention of infestations with head lice.




World War II-era American poster, created to prevent outbreaks of pediculosis among servicemen.

Clothes, towels, bedding, combs, and brushes, which came in contact with the infested individual, can be disinfected either by leaving them outside for at least two days or by washing them at 60 °C (140 degrees F) for 30 minutes.[17] This is because adult lice can survive only one to two days without a blood meal and are highly dependent on human body warmth.[18] An insecticidal treatment of the house and furniture is not necessary.

## Treatment [edit]

*Main article: Treatment of human head lice*

There are a number of treatments effective for head lice. These methods include combs, shaving, medical creams, and hot air.[19] Medical creams usually require two treatments a week apart.[7] Head lice are not justification to keep children home from school as the risk of spread is low.[12]

### Mechanical measures [edit]

[7]

Shaving the head can effectively treat lice. Wet combing a few times a day for a few weeks may also get rid of the infestation in half of people.[7] This requires the use of a special lice comb with extra fine teeth.[7] This is the recommended method for infants and women who are pregnant.[7]

Another treatment is the use of heated air applied by a hair dryer.[19]

### Medications [edit]

There are many medications which can kill lice. Dimethicone is between 70 and 97% effective with a low rate of side effects, and thus is seen as the preferred treatment.[7] It works by physical means and there is no evidence of pesticide resistance.[4] Ivermectin is around 80% effective, but can cause local skin irritation. Malathion has an effectiveness around 90%, but there's the possibility of toxicity.[7] Pyrethroids such as permethrin, while commonly used, have lower rates of effectiveness due to the resistance among lice.[7] Effectiveness varies from 10 to 80%, depending on the population studied.[5][7] Medications within a lotions appear to work better than those within a shampoo.[7] Benzyl alcohol appears effective but it is unclear if it is better than standard treatments.[20]

### Alternative medicine [edit]

Tea tree oil has been promoted as a treatment for head lice; however, there is no clear evidence of its effectiveness.[21][22] A 2012 review of head lice treatment recommended against the use of tea tree oil for children because it could cause skin irritation or allergic reactions, because of contraindications, and because of a lack of knowledge about the oil's safety and effectiveness.[23] Other home remedies, such as putting vinegar, isopropyl alcohol, olive oil, mayonnaise, or melted butter under a shower cap, have been disproven.[9] The CDC states that swimming has no effect on lice, and can decrease the effectiveness of some treatments.[24]

### Environment [edit]

After treatment, people are often instructed to wash all bedding and vacuum all areas the head may have been, such as car seats, coat hoods, and sofas, but this is not always necessary, since adult lice will die within 2 days without a blood meal, and newly hatched lice die within minutes of hatching.[19] Combs and brushes may be deloused in boiling water for 5–10 minutes. Items may also be frozen for 24 hours well below the freezing point of water to ensure that ice crystals form within the cells of the lice.[25]

## Epidemiology [edit]

The number of cases of human louse infestations (or pediculosis) has increased worldwide since the mid-1960s, reaching hundreds of millions annually.[27] It is estimated between 1 and 20% of specific groups in Europe are infected.[4]

Despite improvements in medical treatment and prevention of human diseases during the 20th century, head louse infestation remains stubbornly prevalent. In 1997, 80% of American elementary schools reported at least one outbreak of lice.[28] Lice infestation during that same period was more prevalent than chickenpox.[28]

> “Reliable data describing the usual incidence of infestation in the general public, in the average school community, or during specific times of the year are lacking.”
>
> — Janis Hootman, 2002[26]

About 6–12 million children between the ages of 3 and 11 are treated annually for head lice in the United States alone.[11] High levels of louse infestations have also been reported from all over the world, including Israel, Denmark, Sweden, U.K., France, and Australia.[16][29]

The number of children per family, the sharing of beds and closets, hair washing habits, local customs and social contacts, healthcare in a particular area (e.g. school), and socioeconomic status were found to be [*citation needed*]

significant factors in head louse infestation. Children between 4 and 13 years of age are the most frequently infested group.[30] In the U.S., African-American children have lower rates of infestation.[11]

The United Kingdom's National Health Service[*citation needed*] and many American health agencies report that lice "prefer" clean hair because it's easier to attach eggs and to cling to the strands; however, this is often contested.

Head lice (*Pediculus humanus capitis*) infestation is most frequent on children aged 3–10 and their families.[31] Females get head lice twice as often as males,[31] and infestation in persons of Afro-Caribbean or other black descent is rare because of hair consistency.[31] But these children may have nits that hatch and the live lice could be transferred by head contact to other children.[32]

## Society and culture [edit]

- To a Louse (on a lady's bonnet). Perhaps the most widely known cultural reference to pediculosis capitis, occurring in a noted poem by Robert Burns.

## Other animals [edit]

Lice infestation in general is known as pediculosis, and occurs in many mammalian and bird species.[33] They are not the same organism as that which causes head lice infestations in humans.

## References [edit]


1. ^ Rapini, Ronald P.; Bolognia, Jean L.; Jorizzo, Joseph L. (2007). *Dermatology: 2-Volume Set*. St. Louis: Mosby. ISBN 1-4160-2999-0.
2. ^ "How to treat nits". *nhs.uk*. 2012-09-14. Retrieved 23 October 2014.
3. ^ "cootie". *http://dictionary.reference.com/*. Retrieved 23 October 2014. External link in |website= (help)
4. ^ *a b c d e f g h* Feldmeier, H (Sep 2012). "Pediculosis capitis: new insights into epidemiology, diagnosis and treatment.". *European Journal of Clinical Microbiology & Infectious Diseases*. **31** (9): 2105–10. doi:10.1007/s10096-012-1575-0. PMID 22382818.
5. ^ *a b c d e f g h i j k l m n o p* Smith, CH; Goldman, RD (Aug 2012). "An incurable itch: head lice.". *Canadian Family Physician*. **58** (8): 839–41. PMID 22893334.
6. ^ *a b c d e* "Parasites - Lice - Head Lice Frequently Asked Questions (FAQs)". *cdc.gov*. September 24, 2013. Retrieved 23 October 2014.
7. ^ *a b c d e f g h i j k l m n o p* "Head lice. Dimeticone is the pediculicide of choice.". *Prescrire Int*. **151** (23): 187–90. Jul 2014. PMID 25162097.
8. ^ "Parasites - Lice - Head Lice". *cdc.gov*. September 24, 2013. Retrieved 23 October 2014.
9. ^ *a b* Takano-Lee M, Edman JD, Mullens BA, Clark JM (December 2004). "Home remedies to control head lice: assessment of home remedies to control the human head louse, Pediculus humanus capitis (Anoplura: Pediculidae)". *Journal of Pediatric*



Roberts RJ; Taylan-Ozkan A. (2007). "International Guidelines for Effective Control of Head Louse Infestations". *Journal of Drugs in Dermatology*. **6** (4): 409–14. PMID 17668538.
17. ^ Kidshealth.org – Head lice, page-3
18. ^ University of Florida Dept of Entomology Circular 175
19. ^ *a b c* Goates BM, BM; Atkin, JS; Wilding, KG; Birch, KG; Cottam, MR; Bush, SE; Clayton, DH (5 November 2006). "An Effective Nonchemical Treatment for Head Lice: A Lot of Hot Air" (PDF). *Pediatrics*. American Academy of Pediatrics. **118** (5): 1962–1970. doi:10.1542/peds.2005-1847. PMID 17079567. Retrieved 2010-08-02.
20. ^ Burgess, IF (16 May 2011). "Head lice.". *BMJ clinical evidence*. **2011**. PMC 3275145. PMID 21575285.
21. ^ Jacobi, Tillmann (22 September 2011). "The Basics – The management of head lice". *GP*: 38. "All in all, the evidence for alternative treatments, such as tea tree oil and neem seed oil, remains weak."
22. ^ "Tea tree oil". Medline Plus, a service of the U.S. National Library of Medicine from the National Institutes of Health. 27 July 2012.
23. ^ Eisenhower, Christine; Farrington, Elizabeth Anne (2012). "Advancements in the Treatment of Head Lice in Pediatrics". *Journal of Pediatric Health Care*. **26** (6): 451–61; quiz 462–4. doi:10.1016/j.pedhc.2012.05.004.

*Nursing*. **19** (6): 393–8. doi:10.1016/j.pedn.2004.11.002. PMID 15637580.
10. ^ Rózsa, L; Apari, P (May 2012). "Why infest the loved ones--inherent human behaviour indicates former mutualism with head lice.". *Parasitology*. **139** (6): 696–700. doi:10.1017/S0031182012000017. PMID 22309598.
11. ^ *a b c* Division of Parasitic Diseases (DPD), National Center for Zoonotic, Vector-Borne, and Enteric Diseases (ZVED) (May 16, 2008). "Head lice fact sheet". *Centers for Disease Control and Prevention website*. Atlanta, GA: Department of Health and Human Services, US Government. Retrieved 28 May 2010.
12. ^ *a b* Devore, C. D.; Schutze, G. E. (27 April 2015). "Head Lice". *Pediatrics*. **135** (5): e1355–e1365. doi:10.1542/peds.2015-0746.
13. ^ Pollack RJ, Kiszewski AE, Spielman A; Kiszewski; Spielman (2000). "Overdiagnosis and consequent mismanagement of head louse infestations in North America". *The Pediatric Infectious Diseases Journal*. **19** (8): 689–93. doi:10.1097/00006454-200008000-00003. PMID 10959734.
14. ^ *a b* Mumcuoglu KY, Friger M, Ioffe-Uspensky I, Ben-Ishai F, Miller J; Friger; Ioffe-Uspensky; Ben-Ishai; Miller (2001). "Louse comb versus direct visual examination for the diagnosis of head louse infestations". *Pediatric dermatology*. **18** (1): 9–12. doi:10.1046/j.1525-1470.2001.018001009.x. PMID 11207962.
15. ^ Williams LK, Reichert A, MacKenzie WR, Hightower AW, Blake PA; Reichert; MacKenzie; Hightower; Blake (2001). "Lice, nits, and school policy". *Pediatrics*. **107** (5): 1011–5. doi:10.1542/peds.107.5.1011. PMID 11331679.
16. ^ *a b* Mumcuoglu, Kosta Y.; Barker CS; Burgess IF; Combescot-Lang C; Dagleish RC; Larsen KS; Miller J; PMID 23099312 .
24. ^ "CDC – Frequently Asked Questions – Healthy Swimming & Recreational Water – Healthy Water". Cdc.gov. 2012-10-22. Retrieved 2012-11-22.
25. ^ *Michigan Head Lice Manual*. State of Michigan. 2004.[*page needed*]
26. ^ Hootman J (April 2002). "Quality improvement projects related to pediculosis management". *The Journal of school nursing : the official publication of the National Association of School Nurses*. **18** (2): 80–6. doi:10.1177/10598405020180020401. PMID 12017250.
27. ^ Norman G. Gratz (1998). "Human lice: Their prevalence, control and resistance to insecticides. A review 1985–1997" (PDF). Geneva, Switzerland: World Health Organization. Retrieved 2008-01-02.
28. ^ *a b* "A modern scourge: Parents scratch their heads over lice". Consumer Reports. February 1998. pp. 62–63. Retrieved 2008-10-10.
29. ^ Ian Burgess (2004). "Human Lice and their Control". *Annual Review of Entomology*. Annual Reviews. **49**: 457–481. doi:10.1146/annurev.ento.49.061802.123253. PMID 14651472.
30. ^ Mumcuoglu KY, Miller J, Gofin R, et al. (September 1990). "Epidemiological studies on head lice infestation in Israel. I. Parasitological examination of children". *International Journal of Dermatology*. **29** (7): 502–6. doi:10.1111/j.1365-4362.1990.tb04845.x. PMID 2228380.
31. ^ *a b c* Nutanson I.; et al. (2008). "Pediculus humanus capitis: an update" (PDF). *Acta Dermatoven*. **17** (4): 147–59.
32. ^ James GH Dinulos (September 2008). "Lice (Pediculosis)". *The Merck Manual*. Merck & Co., Inc. Retrieved 2008-12-27.
33. ^ "Lice (Pediculosis)". *The Merck Veterinary Manual*. Whitehouse Station, NJ USA: Merck & Co. 2008. Retrieved 2008-10-08.

## External links [edit]

- CDC: Head lice

| v · t · e | Diseases from ectoparasitics and arthropods (B85–B89, 132–134) | |
|---|---|---|
| **Insecta** | **Louse** | *Body louse* / *Head louse* · Pediculosis · **Head lice infestation** · Pediculosis corporis · *Crab louse* · Phthiriasis · |
| | **Hemiptera** | *Bed bug* (Cimicosis) · |
| | **Fly** | *Dermatobia hominis* / *Cordylobia anthropophaga* / *Cochliomyia hominivorax* (Myiasis) · |
| | **Flea** | *Chigoe flea* *Tunga penetrans* · Tungiasis · |
| | **Acariasis / mange (mites)** | Trombidiformes: *Trombicula* · Trombiculosis · Chigger bite · *Demodex brevis* / *Demodex folliculorum* · Demodicosis · Demodex mite bite · *Pyemotes herfsi* · *Cheyletiella* · Cheyletiellosis · |

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| **Arachnida** | | Sarcoptiformes: *Sarcoptes scabiei* · Scabies · *Dermanyssus gallinae* · *Liponyssoides sanguineus* · |
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Categories: Parasitic infestations, stings, and bites of the skin | Arthropod infestations




# Herpes simplex

From Wikipedia, the free encyclopedia

*"Herpes" redirects here. For the medical journal, see Herpes (journal). For the virus that causes herpes simplex, see Herpes simplex virus. For all types of herpes viruses, see Herpesviridae.*

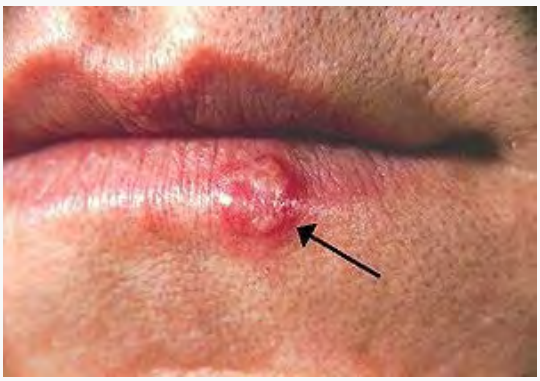
**Herpes simplex** (Greek: ἕρπης *herpēs*, "creeping" or "latent") is a viral disease caused by the herpes simplex virus.[1] Infections are categorized based on the part of the body infected. Oral herpes involves the face or mouth. It may result in small blisters in groups often called cold sores or fever blisters or may just cause a sore throat.[2][3] Genital herpes, often simply known as herpes, may have minimal symptoms or form blisters that break open and result in small ulcers. These typically heal over two to four weeks. Tingling or shooting pains may occur before the blisters appear. Herpes cycles between periods of active disease followed by periods without symptoms. The first episode is often more severe and may be associated with fever, muscle pains, swollen lymph nodes and headaches. Over time, episodes of active disease decrease in frequency and severity.[1] Other disorders caused by herpes simplex include: herpetic whitlow when it involves the fingers,[4] herpes of the eye,[5] herpes infection of the brain,[6] and neonatal herpes when it affects a newborn, among others.[7]

There are two types of herpes simplex virus, type 1 (HSV-1) and type 2 (HSV-2).[1] HSV-1 more commonly causes oral infections while HSV-2 more commonly causes genital infections.[2] They are transmitted by direct contact with body fluids or lesions of an infected individual. Transmission may still occur when symptoms are not present. Genital herpes is classified as a sexually transmitted infection. It may be spread to an infant during childbirth.[1] After infection, the viruses are transported along sensory nerves to the nerve cell bodies, where they reside lifelong.[2] Causes of recurrence may include: decreased immune function, stress, and sunlight exposure.[2][8] Oral and genital herpes is usually diagnosed based on the presenting symptoms.[2] The diagnosis may be confirmed by viral culture or detecting herpes DNA in fluid from blisters. Testing the blood for antibodies against the virus can confirm a previous infection but will be negative in new infections.[1]

The most effective method of avoiding genital infections is by avoiding vaginal, oral, and anal sex. Condom use decreases the risk somewhat. Daily antiviral medication taken by someone who has the infection can also reduce spread. There is no available vaccine and once infected, there is no cure.[1] Paracetamol (acetaminophen) and topical lidocaine may be used to help with the symptoms.[2] Treatments with antiviral medication such as aciclovir or valaciclovir can lessen the severity of symptomatic episodes.[1][2]

Worldwide rates of either HSV-1 or HSV-2 are between 60% and 95% in adults.[9] HSV-1 is usually acquired during childhood.[1] Rates of both increase as people age.[9] Rates of HSV-1 are between 70% and 80% in populations of low socioeconomic status and 40% to 60% in populations of improved socioeconomic status.[9] An estimated 536 million people worldwide (16% of the population) were infected with HSV-2 as of 2003 with greater rates among women and those in the developing world.[10] Most people with HSV-2 do not realize that they are [1]

**Herpes simplex**



Herpes labialis of the lower lip. Note the blisters in a group marked by an arrow.

| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | A60, B00, G05.1, P35.2 |
| **ICD-9-CM** | 054.0, 054.1, 054.2, 054.3, 771.2 |
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| **eMedicine** | med/1006 |
| **MeSH** | D006561 |

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infected.



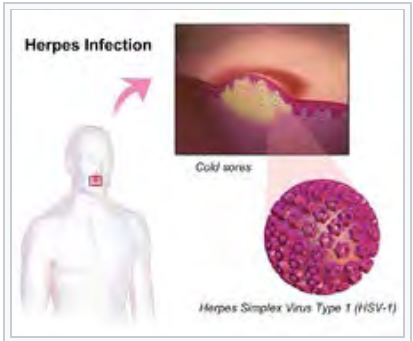


## Classification

Herpes simplex is divided into two types; HSV-1 causes primarily mouth, throat, face, eye, and central nervous system infections, whereas HSV-2 causes primarily anogenital infections. However, each may cause infections in all areas.[9]

## Signs and symptoms

HSV infection causes several distinct medical disorders. Common infection of the skin or mucosa may affect the face and mouth (orofacial herpes), genitalia (genital herpes), or hands (herpetic whitlow). More serious disorders occur when the virus infects and damages the eye (herpes keratitis), or invades the central nervous system, damaging the brain (herpes encephalitis). People with immature or suppressed immune systems, such as newborns, transplant recipients, or people with AIDS, are prone to severe complications from HSV infections. HSV infection has also been associated with cognitive deficits of bipolar disorder,[11] and Alzheimer's disease, although this is often dependent on the genetics of the infected person.

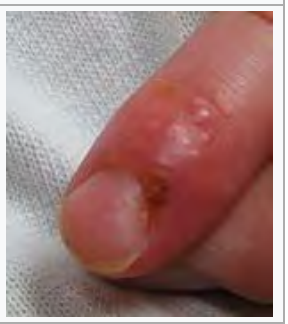
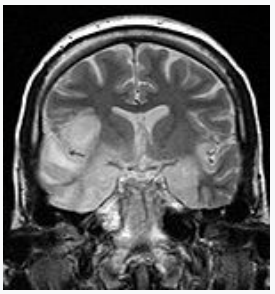
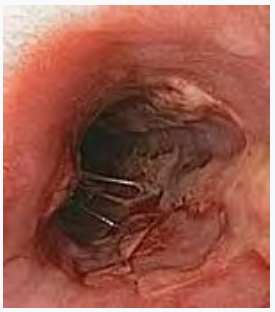


Herpes infection

In all cases, HSV is never removed from the body by the immune system. Following a primary infection, the virus enters the nerves at the site of primary infection, migrates to the cell body of the neuron, and becomes latent in the ganglion.[12] As a result of primary infection, the body produces antibodies to the particular type of HSV involved, preventing a subsequent infection of that type at a different site. In HSV-1-infected individuals, seroconversion after an oral infection prevents additional HSV-1 infections such as whitlow, genital herpes, and herpes of the eye. Prior HSV-1 seroconversion seems to reduce the symptoms of a later HSV-2 infection, although HSV-2 can still be contracted.

Many people infected with HSV-2 display no physical symptoms—individuals with no symptoms are described as asymptomatic or as having subclinical herpes.[13]

| Condition | Description | Illustration |
|---|---|---|
| Herpetic | Herpetic gingivostomatitis is often the initial presentation during the | |

| | | |
|---|---|---|
| gingivostomatitis | first herpes infection. It is of greater severity than herpes labialis, which is often the subsequent presentations. |  |
| Herpes labialis | Infection occurs when the virus comes into contact with oral mucosa or abraded skin. |  |
| Herpes genitalis | When symptomatic, the typical manifestation of a primary HSV-1 or HSV-2 genital infection is clusters of inflamed papules and vesicles on the outer surface of the genitals resembling cold sores. |  |
| Herpetic whitlow and herpes gladiatorum | Herpes whitlow is a painful infection that typically affects the fingers or thumbs. On occasion, infection occurs on the toes or on the nail cuticle. Individuals who participate in contact sports such as wrestling, rugby, and football(soccer), sometimes acquire a condition caused by HSV-1 known as herpes gladiatorum, scrumpox, wrestler's herpes, or mat herpes, which presents as skin ulceration on the face, ears, and neck. Symptoms include fever, headache, sore throat, and swollen glands. It occasionally affects the eyes or eyelids. |  |
| Herpesviral encephalitis and herpesviral meningitis | A herpetic infection of the brain thought to be caused by the transmission of virus from a peripheral site on the face following HSV-1 reactivation, along the trigeminal nerve axon, to the brain. HSV is the most common cause of viral encephalitis. When infecting the brain, the virus shows a preference for the temporal lobe.[14] HSV-2 is the most common cause of Mollaret's meningitis, a type of recurrent viral meningitis. |  |
| Herpes esophagitis | Symptoms may include painful swallowing (odynophagia) and difficulty swallowing (dysphagia). It is often associated with impaired immune function (e.g. HIV/AIDS, immunosuppression in solid organ transplants). |  |

## Other

Neonatal herpes simplex is a HSV infection in an infant. It is a rare but serious condition, usually caused by vertical transmission of HSV-1 or -2) from mother to newborn. During immunodeficiency, herpes simplex can cause unusual lesions in the skin. One of the most striking is the appearance of clean linear erosions in skin creases, with the appearance of a knife cut.[15] Herpetic sycosis is a recurrent or initial herpes simplex infection affecting primarily the hair follicles.[16]:369 Eczema herpeticum is an infection with herpesvirus in patients with chronic atopic dermatitis may result in spread of herpes simples throughout the eczematous areas.[16]:373

Herpetic keratoconjunctivitis, a primary infection, typically presents as swelling of the conjunctiva and eyelids (blepharoconjunctivitis), accompanied by small white itchy lesions on the surface of the cornea.

Herpetic sycosis is a recurrent or initial herpes simplex infection affecting primarily the hair follicle.[16]:369[17]

### Bell's palsy

Although the exact cause of Bell's palsy—a type of facial paralysis—is unknown, it may be related to reactivation of HSV-1.[18] This theory has been contested, however, since HSV is detected in large numbers of individuals having never experienced facial paralysis, and higher levels of antibodies for HSV are not found in HSV-infected individuals with Bell's palsy compared to those without.[19] Regardless antivirals have been found to not improve outcomes.[20]

### Alzheimer's disease

HSV-1 has been proposed as a possible cause of Alzheimer's disease.[21][22] In the presence of a certain gene variation (APOE-epsilon4 allele carriers), HSV-1 appears to be particularly damaging to the nervous system and increases one's risk of developing Alzheimer's disease. The virus interacts with the components and receptors of lipoproteins, which may lead to its development.[23][24]

## Pathophysiology

Herpes is contracted through direct contact with an active lesion or body fluid of an infected person.[26] Herpes transmission occurs between discordant partners; a person with a history of infection (HSV seropositive) can pass the virus to an HSV seronegative person. Herpes simplex virus 2 is typically contracted through direct skin-to-skin contact with an infected individual, but can also be contracted by exposure to infected saliva, semen, vaginal fluid, or the fluid from herpetic blisters.[27] To infect a new individual, HSV travels through tiny breaks in the skin or mucous membranes in the mouth or genital areas. Even microscopic abrasions on mucous membranes are sufficient to allow viral entry.

**Herpes shedding**[25]

| | |
|---|---|
| HSV-2 genital | 15–25% of days |
| HSV-1 oral | 6–33% of days |
| HSV-1 genital | 5% of days |
| HSV-2 oral | 1% of days |

HSV asymptomatic shedding occurs at some time in most individuals infected with herpes. It can occur more than a week before or after a symptomatic recurrence in 50% of cases.[28] Virus enters into susceptible cells by entry receptors[29] such as nectin-1, HVEM and 3-O sulfated heparan sulfate.[30] Infected people who show no visible symptoms may still shed and transmit viruses through their skin; asymptomatic shedding may represent the most common form of HSV-2 transmission.[28] Asymptomatic shedding is more frequent within the first 12 months of acquiring HSV. Concurrent infection with HIV increases the frequency and duration of asymptomatic shedding.[31] Some individuals may have much lower patterns of shedding, but evidence supporting this is not fully verified; no significant differences are seen in the frequency of asymptomatic shedding when comparing persons with one to 12 annual recurrences to those with no recurrences.[28]

Antibodies that develop following an initial infection with a type of HSV prevents reinfection with the same virus type—a person with a history of orofacial infection caused by HSV-1 cannot contract herpes whitlow or a genital infection caused by HSV-1.[*citation needed*] In a monogamous couple, a seronegative female runs a greater than 30% per year risk of contracting an HSV infection from a seropositive male partner.[32] If an oral HSV-1 infection is contracted first, seroconversion will have occurred after 6 weeks to provide protective antibodies against a future genital HSV-1 infection. Herpes simplex is a double-stranded DNA virus.[33]

## Diagnosis

Primary orofacial herpes is readily identified by clinical examination of persons with no previous history of lesions and contact with an individual with known HSV-1 infection. The appearance and distribution of sores in these individuals typically presents as multiple, round, superficial oral ulcers, accompanied by acute gingivitis.[34] Adults with atypical presentation are more difficult to diagnose. Prodromal symptoms that occur before the appearance of herpetic lesions help differentiate HSV symptoms from the similar symptoms of other disorders, such as allergic stomatitis. When lesions do not appear inside the mouth, primary orofacial herpes is sometimes mistaken for impetigo, a bacterial infection. Common mouth ulcers (aphthous ulcer) also resemble intraoral herpes, but do not present a vesicular stage.[34]

Genital herpes can be more difficult to diagnose than oral herpes, since most HSV-2-infected persons have no classical symptoms.[34] Further confusing diagnosis, several other conditions resemble genital herpes, including fungal infection, lichen planus, atopic dermatitis, and urethritis.[34] Laboratory testing is often used to confirm a

diagnosis of genital herpes. Laboratory tests include culture of the virus, direct fluorescent antibody (DFA) studies to detect virus, skin biopsy, and polymerase chain reaction to test for presence of viral DNA. Although these procedures produce highly sensitive and specific diagnoses, their high costs and time constraints discourage their regular use in clinical practice.[34]

Until the 1980s serological tests for antibodies to HSV were rarely useful to diagnosis and not routinely used in clinical practice.[34] The older IgM serologic assay could not differentiate between antibodies generated in response to HSV-1 or HSV-2 infection. However, a glycoprotein G-specific (IgG) HSV test introduced in the 1980s is more than 98% specific at discriminating HSV-1 from HSV-2.[35]

It should not be confused with conditions caused by other viruses in the *herpesviridae* family such as herpes zoster, which is caused by varicella zoster virus. The differential diagnosis includes hand, foot and mouth disease due to similar lesions on the skin.

# Prevention

As with almost all sexually transmitted infections, women are more susceptible to acquiring genital HSV-2 than men.[36] On an annual basis, without the use of antivirals or condoms, the transmission risk of HSV-2 from infected male to female is about 8–11%.[32][37] This is believed to be due to the increased exposure of mucosal tissue to potential infection sites. Transmission risk from infected female to male is around 4–5% annually.[37] Suppressive antiviral therapy reduces these risks by 50%.[38] Antivirals also help prevent the development of symptomatic HSV in infection scenarios, meaning the infected partner will be seropositive but symptom-free by about 50%. Condom use also reduces the transmission risk significantly.[39][40] Condom use is much more effective at preventing male-to-female transmission than *vice versa*.[39] Previous HSV-1 infection may reduce the risk for acquisition of HSV-2 infection among women by a factor of three, although the one study that states this has a small sample size of 14 transmissions out of 214 couples.[41]

Barrier protection, such as a condom, can reduce the risk of herpes transmission.

However, asymptomatic carriers of the HSV-2 virus are still contagious. In many infections, the first symptom people will have of their own infections is the horizontal transmission to a sexual partner or the vertical transmission of neonatal herpes to a newborn at term. Since most asymptomatic individuals are unaware of their infection, they are considered at high risk for spreading HSV.[42]

In October 2011, the anti-HIV drug tenofovir, when used topically in a microbicidal vaginal gel, was reported to reduce herpes virus sexual transmission by 51%.[43]

## Barrier methods

Condoms offer moderate protection against HSV-2 in both men and women, with consistent condom users having a 30%-lower risk of HSV-2 acquisition compared with those who never use condoms.[44] A female condom can provide greater protection than the male condom, as it covers the labia.[45] The virus cannot pass through a synthetic condom, but a male condom's effectiveness is limited[46] because herpes ulcers may appear on areas not covered by it. Neither type of condom prevents contact with the scrotum, anus, buttocks, or upper thighs, areas that may come in contact with ulcers or genital secretions during sexual activity. Protection against herpes simplex depends on the site of the ulcer; therefore, if ulcers appear on areas not covered by condoms, abstaining from sexual activity until the ulcers are fully healed is one way to limit risk of transmission.[47] The risk is not eliminated, however, as viral shedding capable of transmitting infection may still occur while the infected partner is asymptomatic.[48] The use of condoms or dental dams also limits the transmission of herpes from the genitals of one partner to the mouth of the other (or *vice versa*) during oral sex. When one partner has a herpes simplex infection and the other does not, the use of antiviral medication, such as valaciclovir, in conjunction with a condom, further decreases the chances of transmission to the uninfected partner.[12] Topical microbicides that contain chemicals that directly inactivate the virus and block viral entry are being investigated.[12]

## Antivirals

Antivirals may reduce asymptomatic shedding; asymptomatic genital HSV-2 viral shedding is believed to occur on 20% of days per year in patients not undergoing antiviral treatment, *versus* 10% of days while on antiviral therapy.[28]

### Pregnancy

The risk of transmission from mother to baby is highest if the mother becomes infected around the time of delivery (30% to 60%),[49][50] since insufficient time will have occurred for the generation and transfer of protective maternal antibodies before the birth of the child. In contrast, the risk falls to 3% if the infection is recurrent,[51] and is 1–3% if the woman is seropositive for both HSV-1 and HSV-2,[51][52] and is less than 1% if no lesions are visible.[51] Women seropositive for only one type of HSV are only half as likely to transmit HSV as infected seronegative mothers. To prevent neonatal infections, seronegative women are recommended to avoid unprotected oral-genital contact with an HSV-1-seropositive partner and conventional sex with a partner having a genital infection during the last trimester of pregnancy. Mothers infected with HSV are advised to avoid procedures that would cause trauma to the infant during birth (e.g. fetal scalp electrodes, forceps, and vacuum extractors) and, should lesions be present, to elect caesarean section to reduce exposure of the child to infected secretions in the birth canal.[12] The use of antiviral treatments, such as acyclovir, given from the 36th week of pregnancy, limits HSV recurrence and shedding during childbirth, thereby reducing the need for caesarean section.[12]

Acyclovir is the recommended antiviral for herpes suppressive therapy during the last months of pregnancy. The use of valaciclovir and famciclovir, while potentially improving compliance, have less-well-determined safety in pregnancy.

## Management

No method eradicates herpes virus from the body, but antiviral medications can reduce the frequency, duration, and severity of outbreaks. Analgesics such as ibuprofen and paracetamol (acetaminophen) can reduce pain and fever. Topical anesthetic treatments such as prilocaine, lidocaine, benzocaine, or tetracaine can also relieve itching and pain.[53][54][55]

### Antiviral

Several antiviral drugs are effective for treating herpes, including acyclovir, valaciclovir (valacyclovir), famciclovir, and penciclovir. Acyclovir was the first discovered and is now available in generic.[56] Valacyclovir is also available as a generic.[57]

Evidence supports the use of acyclovir and valacyclovir in the treatment of herpes labialis[58] as well as herpes infections in people with cancer.[59] The evidence to support the use of acyclovir in primary herpetic gingivostomatitis is weaker.[60]

The antiviral medication acyclovir

### Topical

A number of topical antivirals are effective for herpes labialis, including acyclovir, penciclovir, and docosanol.[58][61]

### Alternative medicine

Certain dietary supplements and alternative remedies are claimed to be beneficial in the treatment of herpes.[62] Evidence is insufficient, though, to support use of many of these compounds, including echinacea, eleuthero, L-lysine, zinc, monolaurin bee products, and aloe vera.[63] While a number of small studies show possible benefit from monolaurin, L-lysine, aspirin, lemon balm, topical zinc, or licorice root cream in treatment, these preliminary studies have not been confirmed by higher-quality randomized controlled studies.[64]

## Prognosis

Following active infection, herpes viruses establish a latent infection in sensory and autonomic ganglia of the nervous system. The double-stranded DNA of the virus is incorporated into the cell physiology by infection of the nucleus of a nerve's cell body. HSV latency is static; no virus is produced; and is controlled by a number of viral genes, including latency-associated transcript.[65]

Many HSV-infected people experience recurrence within the first year of infection.[12] Prodrome precedes development of lesions. Prodromal symptoms include tingling (paresthesia), itching, and pain where lumbosacral

nerves innervate the skin. Prodrome may occur as long as several days or as short as a few hours before lesions develop. Beginning antiviral treatment when prodrome is experienced can reduce the appearance and duration of lesions in some individuals. During recurrence, fewer lesions are likely to develop and are less painful and heal faster (within 5–10 days without antiviral treatment) than those occurring during the primary infection.[12] Subsequent outbreaks tend to be periodic or episodic, occurring on average four or five times a year when not using antiviral therapy.

The causes of reactivation are uncertain, but several potential triggers have been documented. A 2009 study showed the protein VP16 plays a key role in reactivation of the dormant virus.[66] Changes in the immune system during menstruation may play a role in HSV-1 reactivation.[67][68] Concurrent infections, such as viral upper respiratory tract infection or other febrile diseases, can cause outbreaks. Reactivation due to other infections is the likely source of the historic terms 'cold sore' and 'fever blister'.

Other identified triggers include local injury to the face, lips, eyes, or mouth; trauma; surgery; radiotherapy; and exposure to wind, ultraviolet light, or sunlight.[69][70][71][72][73]

The frequency and severity of recurrent outbreaks vary greatly between people. Some individuals' outbreaks can be quite debilitating, with large, painful lesions persisting for several weeks, while others experience only minor itching or burning for a few days. Some evidence indicates genetics play a role in the frequency of cold sore outbreaks. An area of human chromosome 21 that includes six genes has been linked to frequent oral herpes outbreaks. An immunity to the virus is built over time. Most infected individuals experience fewer outbreaks and outbreak symptoms often become less severe. After several years, some people become perpetually asymptomatic and no longer experience outbreaks, though they may still be contagious to others. Immunocompromised individuals may experience longer, more frequent, and more severe episodes. Antiviral medication has been proven to shorten the frequency and duration of outbreaks.[74] Outbreaks may occur at the original site of the infection or in proximity to nerve endings that reach out from the infected ganglia. In the case of a genital infection, sores can appear at the original site of infection or near the base of the spine, the buttocks, or the back of the thighs. HSV-2-infected individuals are at higher risk for acquiring HIV when practicing unprotected sex with HIV-positive persons, in particular during an outbreak with active lesions.[75]

## Epidemiology

*Main article: Epidemiology of herpes simplex*

Worldwide rates of either HSV-1 and/or HSV-2 are between 60 and 95% in adults.[9] HSV-1 is more common than HSV-2, with rates of both increasing as people age.[9] HSV-1 rates are between 70% and 80% in populations of low socioeconomic status and 40% to 60% in populations of improved socioeconomic status.[9] An estimated 536 million people or 16% of the population worldwide were infected with HSV-2 as of 2003 with greater rates among women and in those in the developing world.[10] Rates of infection are determined by the presence of antibodies against either viral species.[76]

In the US, 57.7% of the population is infected with HSV-1[77] and 16.2% are infected with HSV-2. Among those HSV-2-seropositive, only 18.9% were aware they were infected.[78] During 2005–2008, the prevalence of HSV-2 was 39.2% in blacks and 20.9% in women.[79]

The annual incidence in Canada of genital herpes due to HSV-1 and HSV-2 infection is not known (for a review of HSV-1/HSV-2 prevalence and incidence studies worldwide, see Smith and Robinson 2002). As many as one in seven Canadians [80] aged 14 to 59 may be infected with herpes simplex type 2 virus and more than 90 per cent of them may be unaware of their status, a new study suggests.[81] In the United States, it is estimated that about 1,640,000 HSV-2 seroconversions occur yearly (730,000 men and 910,000 women, or 8.4 per 1,000 persons).[82]

In British Columbia in 1999, the seroprevalence of HSV-2 antibody in leftover serum submitted for antenatal testing revealed a prevalence of 17.3%, ranging from 7.1% in women 15–19 years old to 28.2% in those 40–44 years.[83]

In Norway, a study published in 2000 found that 90% of genital initial infections were due to HSV-1.[84]

In Nova Scotia, 58.1% of 1,790 HSV isolates from genital lesion cultures in women were HSV-1; in men, 36.7% of 468 isolates were HSV-1.[85]

## History

Herpes has been known for at least 2,000 years. Emperor Tiberius is said to have banned kissing in Rome for a

time due to so many people having cold sores. In the 16th-century *Romeo and Juliet*, blisters "o'er ladies' lips" are mentioned. In the 18th century, it was so common among prostitutes that it was called "a vocational disease of women".[86] The term 'herpes simplex' appeared in Richard Boulton's *A System of Rational and Practical Chirurgery* in 1713, where the terms 'herpes miliaris' and 'herpes exedens' also appeared. Herpes was not found to be a virus until the 1940s.[86]

Herpes antiviral therapy began in the early 1960s with the experimental use of medications that interfered with viral replication called deoxyribonucleic acid (DNA) inhibitors. The original use was against normally fatal or debilitating illnesses such as adult encephalitis,[87] keratitis,[88] in immunocompromised (transplant) patients,[89] or disseminated herpes zoster.[90] The original compounds used were 5-iodo-2'-deoxyuridine, AKA idoxuridine, IUdR, or(IDU) and 1-β-D-arabinofuranosylcytosine or ara-C,[91] later marketed under the name cytosar or cytorabine. The usage expanded to include topical treatment of herpes simplex,[92] zoster, and varicella.[93] Some trials combined different antivirals with differing results.[87] The introduction of 9-β-D-arabinofuranosyladenine, (ara-A or vidarabine), considerably less toxic than ara-C, in the mid-1970s, heralded the way for the beginning of regular neonatal antiviral treatment. Vidarabine was the first systemically administered antiviral medication with activity against HSV for which therapeutic efficacy outweighed toxicity for the management of life-threatening HSV disease. Intravenous vidarabine was licensed for use by the U.S. Food and Drug Administration in 1977. Other experimental antivirals of that period included: heparin,[94] trifluorothymidine (TFT),[95] Ribivarin,[96] interferon,[97] Virazole,[98] and 5-methoxymethyl-2'-deoxyuridine (MMUdR).[99] The introduction of 9-(2-hydroxyethoxymethyl)guanine, AKA acyclovir, in the late 1970s[100] raised antiviral treatment another notch and led to vidarabine vs. acyclovir trials in the late 1980s.[101] The lower toxicity and ease of administration over vidarabine has led to acyclovir becoming the drug of choice for herpes treatment after it was licensed by the FDA in 1998.[102] Another advantage in the treatment of neonatal herpes included greater reductions in mortality and morbidity with increased dosages, which did not occur when compared with increased dosages of vidarabine.[102] However, acyclovir seems to inhibit antibody response, and newborns on acyclovir antiviral treatment experienced a slower rise in antibody titer than those on vidarabine.[102]

# Society and culture

Genital herpes simplex was not always stigmatised. It was merely a cold sore in an unusual place until the 1970s. As late as 1975, a study of "Psychological morbidity in a clinic for sexually transmitted disease" does not mention herpes simplex because at that time, no significant morbidity problem (i.e. mental anxiety or illness) was associated with the virus.[103]

Pedro Cuatrecasas states, "during the R&D of acyclovir (Zovirax), marketing [department of Burroughs Wellcome] insisted that there were 'no markets' for this compound. Most had hardly heard of genital herpes..." Thus, marketing the medical condition – separating the 'normal cold sore' from the 'stigmatized genital infection' was to become the key to marketing the drug, a process now known as 'disease mongering'.[104][105]

Since the creation of the herpes hype, some people experience negative feelings related to the condition following diagnosis, in particular if they have acquired the genital form of the disease. Feelings can include depression, fear of rejection, feelings of isolation, fear of being found out, and self-destructive feelings.[106] These feelings usually lessen over time. Much of the hysteria and stigma surrounding herpes stems from a media campaign beginning in the late 1970s and peaking in the early 1980s. Multiple articles were worded in fear-mongering and anxiety-provoking terminology, such as the now-ubiquitous "attacks", "outbreaks", "victims", and "sufferers". At one point, the term "herpetic" even entered the popular lexicon. The articles were published by *Reader's Digest*, *U.S. News*, and *Time* magazine, among others. A made-for-TV movie was named *Intimate Agony*. The peak was when *Time* magazine had 'Herpes: The New Scarlet Letter' on the cover in August 1982, forever stigmatizing the word in the public mind.[86] Herpes support groups have been formed in the United States and the UK, providing information about herpes and running message forums and dating websites for sufferers. People with the herpes virus are often hesitant to divulge to other people, including friends and family, that they are infected. This is especially true of new or potential sexual partners whom they consider casual.[107]

In a 2007 study, 1900 people (25% of which had herpes) ranked genital herpes second for social stigma, out of all sexually transmitted diseases (HIV took the top spot for STD stigma).[108][109][110]

## Support groups

### USA

An important source of support is the *National Herpes Resource Center* which arose from the work of the American

Social Health Association (ASHA).[111] The ASHA was created in 1914 to in response to the increase in social diseases that had spread during World War 1.[112] During the 1970s, there was an increase in sexually transmitted diseases. One of the diseases that increased dramatically was genital herpes. In response, ASHA created the National Herpes Resource Center in 1979. The HRC was designed to meet the growing need for education and awareness about the virus. One of the projects of The Herpes Resource Center (HRC) was to create a network of local support (HELP) groups. The goal of these HELP groups was to provide a safe, confidential environment where participants can get accurate information and share experiences, fears, and feelings with others who are concerned about herpes.[113][114]

### UK

In the UK, the Herpes Association (now the Herpes Viruses Association) was started in 1982, becoming a registered charity with a Dept of Health grant in 1985. The charity started as a string of local group meetings before acquiring an office and a national spread.[115]

## Research

*Main article: Herpes simplex research*

Research has gone into vaccines for both prevention and treatment of herpes infections. Unsuccessful clinical trials have been conducted for glycoprotein subunit vaccines. For therapy, only a single replication-competent HSV vaccine has undergone human testing. As of 2011, the future pipeline includes several promising replication-incompetent vaccine proposals while two replication-competent vaccine proposals require further animal testing.[116]

Another possibility to eradicate the HSV-1 variant is being pursued by a team at Duke University. By figuring out how to switch all copies of the virus in the host from latency to their active stage at the same time, rather than the way the virus copies normally stagger their activity stage, leaving some dormant somewhere at all times, conventional antiviral drugs might kill the entire virus population, since they can no longer hide in the nerve cells. One class of drugs called antagomir could serve this purpose. These are chemically engineered oligonucleotides or short segments of RNA that can be made to mirror their target genetic material, namely herpes microRNAs. They could be engineered to attach and thus 'silence' the microRNA, thus rendering the virus incapable of remaining latent in its host.[117] Professor Cullen believes a drug could be developed to block the microRNA whose job it is to suppress HSV-1 into latency.[118]

A genomic study of the herpes simplex type 1 virus confirmed the human migration pattern theory called 'out-of-Africa hypothesis'.[119]

## References


1. ^ *a b c d e f g h i* "Genital Herpes - CDC Fact Sheet". *cdc.gov*. December 8, 2014. Retrieved 31 December 2014.
2. ^ *a b c d e f g* Balasubramaniam, R; Kuperstein, AS; Stoopler, ET (April 2014). "Update on oral herpes virus infections.". *Dental clinics of North America*. **58** (2): 265–80. doi:10.1016/j.cden.2013.12.001. PMID 24655522.
3. ^ Mosby (2013). *Mosby's Medical Dictionary* (9 ed.). Elsevier Health Sciences. pp. 836–837. ISBN 9780323112581.
4. ^ Wu, IB; Schwartz, RA (March 2007). "Herpetic whitlow.". *Cutis*. **79** (3): 193–6. PMID 17674583.
5. ^ Rowe, AM; St Leger, AJ; Jeon, S; Dhaliwal, DK; Knickelbein, JE; Hendricks, RL (January 2013). "Herpes keratitis.". *Progress in retinal and eye research*. **32**: 88–101. doi:10.1016/j.preteyeres.2012.08.002. PMID 22944008.
6. ^ Steiner, I; Benninger, F (December 2013). "Update on herpes virus infections of the nervous system.". *Current neurology and neuroscience reports*. **13** (12): 414. doi:10.1007/s11910-013-0414-8. PMID 24142852.
7. ^ Stephenson-Famy, A; Gardella, C (December 2014). "Herpes Simplex Virus Infection During Pregnancy.". *Obstetrics and gynecology clinics of North America*. **41** (4): 601–614. doi:10.1016/j.ogc.2014.08.006. PMID 25454993.
8. ^ Elad S, Zadik Y, Hewson I, et al. (August 2010). "A systematic review of viral infections associated with oral involvement in cancer patients: a spotlight on Herpesviridea". *Support Care Cancer*. **18** (8): 993–1006. doi:10.1007/s00520-010-0900-3. PMID 20544224.
9. ^ *a b c d e f g* Chayavichitsilp P, Buckwalter JV, Krakowski AC, Friedlander SF (April 2009). "Herpes simplex". *Pediatr Rev*. **30** (4): 119–29; quiz 130. doi:10.1542/pir.30-4-119. PMID 19339385.
10. ^ *a b* Looker, KJ; Garnett, GP; Schmid, GP (October 2008). "An estimate of the global prevalence and incidence of herpes simplex virus type 2 infection.". *Bulletin of the World Health Organization*. **86** (10): 805–12, A. doi:10.2471/blt.07.046128. PMC 2649511. PMID 18949218.
11. ^ Dickerson FB, Boronow JJ, Stallings C, et al. (March 2004). "Infection with herpes simplex virus type 1 is associated with cognitive deficits in bipolar disorder". *Biol. Psychiatry*. **55** (6): 588–93. doi:10.1016/j.biopsych.2003.10.008. PMID 15013827.
    *a b c d e f g*

12. ^ Gupta R, Warren T, Wald A (December 2007). "Genital herpes". *Lancet*. **370** (9605): 2127–37. doi:10.1016/S0140-6736(07)61908-4. PMID 18156035.
13. ^ Handsfield HH (2000). "Public Health Strategies to Prevent Genital Herpes: Where Do We Stand?". *Curr Infect Dis Rep*. **2** (1): 25–30. doi:10.1007/s11908-000-0084-y. PMID 11095834.
14. ^ *Herpes Encephalitis* at eMedicine
15. ^ Jocelyn A. Lieb; Stacey Brisman; Sara Herman; Jennifer MacGregor; Marc E. Grossman (2008). "Linear erosive Herpes Simplex Virus infection in immunocompromised patients: the "Knife-Cut Sign" ". *Clin Infect Dis*. **47** (11): 1440–1. doi:10.1086/592976. PMID 18937574.
16. ^ *a b c* James, William D.; Berger, Timothy G. (2006). *Andrews' Diseases of the Skin: clinical Dermatology*. Saunders Elsevier. ISBN 0-7216-2921-0.
17. ^ Rapini, Ronald P.; Bolognia, Jean L.; Jorizzo, Joseph L. (2007). *Dermatology: 2-Volume Set*. St. Louis: Mosby. ISBN 1-4160-2999-0.
18. ^ Tankéré F, Bernat I (September 2009). "[Bell's palsy: from viral aetiology to diagnostic reality]". *Rev Med Interne* (in French). **30** (9): 769–75. doi:10.1016/j.revmed.2008.12.006. PMID 19195745.
19. ^ Linder T, Bossart W, Bodmer D (January 2005). "Bell's palsy and Herpes simplex virus: fact or mystery?". *Otol. Neurotol*. **26** (1): 109–13. doi:10.1097/00129492-200501000-00020. PMID 15699730.
20. ^ Lockhart P, Daly F, Pitkethly M, Comerford N, Sullivan F (2009). Lockhart, Pauline, ed. "Antiviral treatment for Bell's palsy (idiopathic facial paralysis)". *Cochrane Database Syst Rev* (4): CD001869. doi:10.1002/14651858.CD001869.pub4. PMID 19821283.
21. ^ Itzhaki RF, Wozniak MA (May 2008). "Herpes simplex virus type 1 in Alzheimer's disease: the enemy within". *J. Alzheimers Dis*. **13** (4): 393–405. PMID 18487848.
22. ^ Holmes C, Cotterell D (December 2009). "Role of infection in the pathogenesis of Alzheimer's disease: implications for treatment". *CNS Drugs*. **23** (12): 993–1002. doi:10.2165/11310910-000000000-00000. PMID 19958038.
23. ^ Dobson CB, Itzhaki RF (1999). "Herpes simplex virus type 1 and Alzheimer's disease". *Neurobiol. Aging*. **20** (4): 457–65. doi:10.1016/S0197-4580(99)00055-X. PMID 10604441.
24. ^ Pyles RB (2001). "The association of herpes simplex virus and Alzheimer's disease: a potential synthesis of genetic and environmental factors". *Herpes*. **8** (3): 64–8. PMID 11867022.
25. ^ Warren, Terri (2009). *The Good News about the Bad News: Herpes: Everything You Need to Know*. New Harbinger Publications. p. 28. ISBN 1-57224-618-9.
26. ^ "AHMF: Preventing Sexual Transmission of Genital herpes". Archived from the original on January 21, 2008. Retrieved 2008-02-24.
27. ^ Wysocki, edited by Anita L. Nelson, JoAnn Woodward ; foreword by Susan (2006). *Sexually transmitted diseases : a practical guide for primary care*. Totowa, N.J.: Totowa, N.J. p. 50. ISBN 978-1-58829-570-5.
28. ^ *a b c d* Leone P (2005). "Reducing the risk of transmitting genital herpes: advances in understanding and therapy". *Curr Med Res Opin*. **21** (10): 1577–82. doi:10.1185/030079905X61901. PMID 16238897.
29. ^ Akhtar, Jihan; Shukla, Deepak (December 2009). "Viral entry mechanisms: cellular and viral mediators of herpes simplex virus entry". *FEBS Journal*. **276** (24): 7228–36. doi:10.1111/j.1742-4658.2009.07402.x. PMC 2801626. PMID 19878306.
30. ^ Shukla, Deepak; Liu, Jian; Blaiklock, Peter; Shworak, Nicholas W.; Bai, Xiaomei; Esko, Jeffrey D.; Cohen, Gary H.; Eisenberg, Roselyn; et al. (1999). "A Novel Role for 3-O-Sulfated Heparan Sulfate in Herpes Simplex Virus 1 Entry". *Cell*. **99** (1): 13–22. doi:10.1016/S0092-8674(00)80058-6. PMID 10520990.
31. ^ Kim H, Meier A, Huang M, Kuntz S, Selke S, Celum C, Corey L, Wald A (2006). "Oral herpes simplex virus type 2 reactivation in HIV-positive and -negative men". *J Infect Dis*. **194** (4): 420–7. doi:10.1086/505879. PMID 16845624.
32. ^ *a b* Mertz, G.J. (1993). "Epidemiology of genital herpes infections". *Infect Dis Clin North Am*. **7** (4): 825–39. PMID 8106731.
33. ^ Reuven NB, Staire AE, Myers RS, Weller SK (2003). "The herpes simplex virus type 1 alkaline nuclease and single-stranded DNA binding protein mediate strand exchange in vitro". *J. Virol*. **77**: 7425–33. doi:10.1128/jvi.77.13.7425-7433.2003. PMC 164775. PMID 12805441.
34. ^ *a b c d e f* Fatahzadeh M, Schwartz RA (2007). "Human herpes simplex virus infections: epidemiology, pathogenesis, symptomatology, diagnosis, and management". *J. Am. Acad. Dermatol*. **57** (5): 737–63; quiz 764–6. doi:10.1016/j.jaad.2007.06.027. PMID 17939933.
35. ^ Ashley RL, et al. (1988). "Comparison of Western blot (immunoblot) and glycoprotein G-specific immunodot enzyme assay for detecting antibodies to herpes simplex virus types 1 and 2 in human sera". *J. Clin. Microbiol*. **26** (4): 662–7. PMC 266403. PMID 2835389.
36. ^ Carla K. Johnson (August 23, 2006). "Percentage of people with herpes drops". Associated Press. Archived from the original on 2012-03-18. Retrieved 2011-04-12.
37. ^ *a b* Kulhanjian JA, Soroush V, Au DS, et al. (April 2, 1992). "Identification of women at unsuspected risk of primary infection with herpes simplex virus type 2 during pregnancy". *N. Engl. J. Med*. **326** (14): 916–20. doi:10.1056/NEJM199204023261403. PMID 1311799.
38. ^ Corey L, Wald A, Patel R, et al. (January 2004). "Once-daily valacyclovir to reduce the risk of transmission of genital herpes" (PDF). *N Engl J Med*. **350** (1): 11–20. doi:10.1056/NEJMoa035144. PMID 14702423.
39. ^ *a b* Wald A, Langenberg AG, Link K, Izu AE, Ashley R, Warren T, Tyring S, Douglas JM Jr, Corey L (2001). "Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women". *JAMA*. **285** (24): 3100–6. doi:10.1001/jama.285.24.3100. PMID 11427138.
40. ^ Wald A, Langenberg AG, Krantz E, et al. (November 2005). "The relationship between condom use and herpes simplex

virus acquisition". *Annals of Internal Medicine*. **143** (10): 707–13. doi:10.7326/0003-4819-143-10-200511150-00007. PMID 16287791.
41. ^ Mertz, GJ; Benedetti J; Ashley R; Selke SA; Corey L. (1 February 1992). "Risk factors for the sexual transmission of genital herpes". *Annals of Internal Medicine*. **116** (3): 197–202. doi:10.7326/0003-4819-116-3-197. PMID 1309413.
42. ^ "Genital Herpes - CDC Fact Sheet". Center for Disease Control and Prevention. Retrieved 2014-01-30.
43. ^ McNeil DJ. http://www.nytimes.com/2011/10/21/health/research/21herpes.htmlTopical Tenofovir, a Microbicide Effective against HIV, Inhibits Herpes Simplex Virus-2 Replication. *NY Times*. Research article: Andrei G; Lisco A; Vanpouille C; et al. (October 2011). "Topical Tenofovir, a Microbicide Effective against HIV, Inhibits Herpes Simplex Virus-2 Replication". *Cell Host*. **10**: 379–389. doi:10.1016/j.chom.2011.08.015. PMC 3201796. PMID 22018238.
44. ^ Emily T. Martin, MPH; Elizabeth Krantz, MS; Sami L. Gottlieb, MD, MSPH; Amalia S. Magaret; Andria Langenberg, MD; Lawrence Stanberry, MD; Mary Kamb, MD, MPH; Anna Wald, MD, MPH (2009). "A Pooled Analysis of the Effect of Condoms in Preventing HSV-2 Acquisition". *Archives of Internal Medicine*. **169** (13): 1233–40. doi:10.1001/archinternmed.2009.177. PMC 2860381. PMID 19597073.
45. ^ "Putting Herpes in Perspective". UBM Medica. Retrieved 20 July 2011.
46. ^ "Condom Effectiveness – Male Latex Condoms and Sexually Transmitted Diseases". Center for Disease Control and Prevention. Retrieved October 2011. Check date values in: `|access-date=` (help)
47. ^ "STD Facts – Genital Herpes". Center for Disease Control and Prevention. Retrieved October 2011. Check date values in: `|access-date=` (help)
48. ^ Koelle, D.M.; Wald, A. (April 2000). "Herpes simplex virus: The importance of asymptomatic shedding". *J. Antimicrob. Chemother*. **45** (Suppl T3): 1–8. doi:10.1093/jac/45.suppl_4.1. PMID 10855766.
49. ^ Brown ZA, Selke S, Zeh J, et al. (1997). "The acquisition of herpes simplex virus during pregnancy". *N Engl J Med*. **337** (8): 509–515. doi:10.1056/NEJM199708213370801. PMID 9262493.
50. ^ Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L (2003). "Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant". *JAMA*. **289** (2): 203–9. doi:10.1001/jama.289.2.203. PMID 12517231.
51. ^ *a b c* Brown ZA, Benedetti J, Ashley R, et al. (May 1991). "Neonatal herpes simplex virus infection in relation to asymptomatic maternal infection at the time of labor". *N. Engl. J. Med*. **324** (18): 1247–52. doi:10.1056/NEJM199105023241804. PMID 1849612.
52. ^ Whitley RJ, Kimberlin DW, Roizman B (1998). "Herpes simplex viruses". *Clin Infect Dis*. **26** (3): 541–53. doi:10.1086/514600. PMID 9524821.
53. ^ O'Mahony C, Timms MS, Ramsden RT (December 1988). "Local anesthetic creams". *BMJ*. **297** (6661): 1468. doi:10.1136/bmj.297.6661.1468-a. PMC 1835116. PMID 3147021.
54. ^ Kaminester LH, Pariser RJ, Pariser DM, et al. (December 1999). "A double-blind, placebo-controlled study of topical tetracaine in the treatment of herpes labialis". *J. Am. Acad. Dermatol*. **41** (6): 996–1001. doi:10.1016/S0190-9622(99)70260-4. PMID 10570387.
55. ^ Leung DT, Sacks SL (October 2003). "Current treatment options to prevent perinatal transmission of herpes simplex virus". *Expert Opin Pharmacother*. **4** (10): 1809–19. doi:10.1517/14656566.4.10.1809. PMID 14521490.
56. ^ LaFemina, edited by Robert L. (2009). *Antiviral research : strategies in antiviral drug discovery*. Washington, DC: ASM Press. p. 1. ISBN 978-1-55581-439-7.
57. ^ Agrawal, Caroline A. Hastings, Joseph Torkildson, Anurag Kishor. *Handbook of pediatric hematology and oncology : Children's Hospital & Research Center Oakland* (2nd ed.). Chichester, West Sussex: Wiley-Blackwell. p. 360. ISBN 978-0-470-67088-0.
58. ^ *a b* Chon T, Nguyen L, Elliott TC (July 2007). "Clinical inquiries. What are the best treatments for herpes labialis?". *J Fam Pract*. **56** (7): 576–8. PMID 17605952.
59. ^ Glenny AM, Fernandez Mauleffinch LM, Pavitt S, Walsh T (2009). Glenny, Anne-Marie, ed. "Interventions for the prevention and treatment of herpes simplex virus in patients being treated for cancer". *Cochrane Database Syst Rev* (1): CD006706. doi:10.1002/14651858.CD006706.pub2. PMID 19160295.
60. ^ Nasser M, Fedorowicz Z, Khoshnevisan MH, Shahiri Tabarestani M (2008). Nasser, Mona, ed. "Acyclovir for treating primary herpetic gingivostomatitis". *Cochrane Database Syst Rev* (4): CD006700. doi:10.1002/14651858.CD006700.pub2. PMID 18843726.
61. ^ Treister NS, Woo SB (April 2010). "Topical n-docosanol for management of recurrent herpes labialis". *Expert Opin Pharmacother*. **11** (5): 853–60. doi:10.1517/14656561003691847. PMID 20210688.
62. ^ Reviewed by EBSCO CAM Review Board in July 2012. "Herpes". *HERPES: Principal Proposed Natural Treatments | Other Proposed Natural Treatments*. EBSCO. Retrieved 11 May 2013.
63. ^ Perfect MM, Bourne N, Ebel C, Rosenthal SL (October 2005). "Use of complementary and alternative medicine for the treatment of genital herpes". *Herpes*. **12** (2): 38–41. PMID 16209859.
64. ^ Beauman, JG (Oct 15, 2005). "Genital herpes: a review.". *American family physician*. **72** (8): 1527–34. PMID 16273819.
65. ^ Stumpf MP, Laidlaw Z, Jansen VA (2002). "Herpes viruses hedge their bets". *Proc. Natl. Acad. Sci. U.S.A*. **99** (23): 15234–7. doi:10.1073/pnas.232546899. PMC 137573. PMID 12409612.
66. ^ "How Herpes Re-rears Its Ugly Head". *Science News*.
67. ^ Myśliwska J, Trzonkowski P, Bryl E, Lukaszuk K, Myśliwski A (2000). "Lower interleukin-2 and higher serum tumor necrosis factor-a levels are associated with perimenstrual, recurrent, facial herpes simplex infection in young women". *Eur. Cytokine Netw*. **11** (3): 397–406. PMID 11022124.
68. ^ Segal AL, Katcher AH, Brightman VJ, Miller MF (1974). "Recurrent herpes labialis, recurrent aphthous ulcers, and the menstrual cycle". *J. Dent. Res*. **53** (4): 797–803. doi:10.1177/00220345740530040501. PMID 4526372.
69. ^ Chambers A, Perry M (2008). "Salivary mediated autoinoculation of herpes simplex virus on the face in the absence of

"cold sores," after trauma". *J. Oral Maxillofac. Surg*. **66** (1): 136–8. doi:10.1016/j.joms.2006.07.019. PMID 18083428.
70. ^ Perna JJ, Mannix ML, Rooney JF, Notkins AL, Straus SE (1987). "Reactivation of latent herpes simplex virus infection by ultraviolet light: a human model". *J. Am. Acad. Dermatol*. **17** (3): 473–8. doi:10.1016/S0190-9622(87)70232-1. PMID 2821086.
71. ^ Rooney JF, Straus SE, Mannix ML, et al. (1992). "UV light-induced reactivation of herpes simplex virus type 2 and prevention by acyclovir". *J. Infect. Dis*. **166** (3): 500–6. doi:10.1093/infdis/166.3.500. PMID 1323616.
72. ^ Oakley C, Epstein JB, Sherlock CH (1997). "Reactivation of oral herpes simplex virus: implications for clinical management of herpes simplex virus recurrence during radiotherapy". *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. **84** (3): 272–8. doi:10.1016/S1079-2104(97)90342-5. PMID 9377190.
73. ^ Ichihashi M, Nagai H, Matsunaga K (2004). "Sunlight is an important causative factor of recurrent herpes simplex". *Cutis*. **74** (5 Suppl): 14–8. PMID 15603217.
74. ^ Martinez V, Caumes E, Chosidow O (2008). "Treatment to prevent recurrent genital herpes". *Current Opinion in Infectious Diseases*. **21** (1): 42–48. doi:10.1097/QCO.0b013e3282f3d9d3. PMID 18192785.
75. ^ Koelle DM, Corey L (2008). "Herpes Simplex: Insights on Pathogenesis and Possible Vaccines". *Annu Rev Med*. **59**: 381–395. doi:10.1146/annurev.med.59.061606.095540. PMID 18186706.
76. ^ Smith JS, Robinson NJ (2002). "Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review". *J. Infect. Dis*. **186** (Suppl 1): S3–28. doi:10.1086/343739. PMID 12353183.
77. ^ Xu, Fujie; Fujie Xu; Maya R. Sternberg; Benny J. Kottiri; Geraldine M. McQuillan; Francis K. Lee; Andre J. Nahmias; Stuart M. Berman; Lauri E. Markowitz (2006-10-23). "Trends in Herpes Simplex Virus Type 1 and Type 2 Seroprevalence in the United States". *JAMA*. AMA. **296** (8): 964–73. doi:10.1001/jama.296.8.964. PMID 16926356.
78. ^ Xu, F; MR Sternberg; SL Gottlieb; SM Berman; LE Markowitz; et al. (23 April 2010). "Seroprevalence of Herpes Simplex Virus Type 2 Among Persons Aged 14—49 Years — United States, 2005—2008". *Morbidity and Mortality Weekly Report (MMWR)*. **59** (15): 456–9. Retrieved 12 April 2011.
79. ^ "CDC Study Finds U.S. Herpes Rates Remain High" (PDF). Center for Disease Control and Prevention. 2010-03-09. Retrieved 2012-02-19.
80. ^ "Top Canadian, UK, New Zealand, United States herpes Dating Sites and Support Groups".
81. ^ http://www.ctvnews.ca/health/health-headlines/one-in-7-canadians-has-genital-herpes-statscan-study-1.1241792
82. ^ Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review. J Infect Dis 2002;186(suppl 1):S3–28.
83. ^ Armstrong GL, Schillinger J, Markowitz L, et al. Incidence of herpes simplex virus type 2 infection in the United States. Am J Epidemiol 2001;153:912–920.
84. ^ Nilsen A, Myrmel H. Changing trends in genital herpes simplex virus infection in Bergen, Norway. Acta Obstet Gynecol Scand 2000;79:693–696.
85. ^ Forward KR, Lee SHS. Predominance of herpes simplex virus type 1 from patients with genital herpes in Nova Scotia. Can J Infect Dis 2003;14:94–96.
86. ^ *a b c* John Leo (1982-08-02). "The New Scarlet Letter". *Time*.
87. ^ *a b* Chow AW, Roland A, Fiala M, et al. (March 1973). "Cytosine Arabinoside Therapy for Herpes Simplex Encephalitis—Clinical Experience with Six Patients". *Antimicrob. Agents Chemother*. **3** (3): 412–7. doi:10.1128/aac.3.3.412. PMC 444424. PMID 4790599.
88. ^ Kaufman HE, Howard GM (August 1962). "Therapy of experimental herpes simplex keratitis". *Invest Ophthalmol*. **1**: 561–4. PMID 14454441.
89. ^ Ch'ien LT, Whitley RJ, Alford CA, Galasso GJ (June 1976). "Adenine arabinoside for therapy of herpes zoster in immunosuppressed patients: preliminary results of a collaborative study". *J. Infect. Dis*. **133** (Suppl): A184–91. doi:10.1093/infdis/133.supplement_2.a184. PMID 180198.
90. ^ McKelvey EM, Kwaan HC (November 1969). "Cytosine arabinoside therapy for disseminated herpes zoster in a patient with IgG pyroglobulinemia". *Blood*. **34** (5): 706–11. PMID 5352659.
91. ^ Fiala M, Chow A, Guze LB (April 1972). "Susceptibility of Herpesviruses to Cytosine Arabinoside: Standardization of Susceptibility Test Procedure and Relative Resistance of Herpes Simplex Type 2 Strains". *Antimicrob. Agents Chemother*. **1** (4): 354–7. doi:10.1128/aac.1.4.354. PMC 444221. PMID 4364937.
92. ^ Allen LB, Hintz OJ, Wolf SM, et al. (June 1976). "Effect of 9-beta-D-arabinofuranosylhypoxanthine 5'-monophosphate on genital lesions and encephalitis induced by Herpesvirus hominis type 2 in female mice". *J. Infect. Dis*. **133** (Suppl): A178–83. doi:10.1093/infdis/133.supplement_2.a178. PMID 6598.
93. ^ Juel-Jensen BE (March 1970). "Varicella and cytosine arabinoside". *Lancet*. **1** (7646): 572. doi:10.1016/S0140-6736(70)90815-9. PMID 4190397.
94. ^ Nahmias AJ, Kibrick S (May 1964). "Inhibitory Effect of Heparin on Herpes Simplex Virus". *J. Bacteriol*. **87** (5): 1060–6. PMC 277146. PMID 4289440.
95. ^ Allen LB, Sidwell RW (September 1972). "Target-Organ Treatment of Neurotropic Virus Diseases: Efficacy as a Chemotherapy Tool and Comparison of Activity of Adenine Arabinoside, Cytosine Arabinoside, Idoxuridine, and Trifluorothymidine". *Antimicrob. Agents Chemother*. **2** (3): 229–33. doi:10.1128/aac.2.3.229. PMC 444296. PMID 4790562.
96. ^ Allen LB, Wolf SM, Hintz CJ, Huffman JH, Sidwell RW (March 1977). "Effect of ribavirin on Type 2 Herpesvirus hominis (HVH/2) *in vitro* and *in vivo*". *Annals of the New York Academy of Sciences*. **284**: 247–53. doi:10.1111/j.1749-6632.1977.tb21957.x. PMID 212976.
97. ^ Allen LB, Cochran KW (November 1972). "Target-Organ Treatment of Neurotropic Virus Disease with Interferon Inducers". *Infection and Immunity*. **6** (5): 819–23. PMC 422616. PMID 4404669.
98. ^ Sidwell RW, Huffman JH, Khare GP, Allen LB, Witkowski JT, Robins RK (August 1972). "Broad-spectrum antiviral activity of

Virazole: 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide". *Science*. **177** (4050): 705–6. doi:10.1126/science.177.4050.705. PMID 4340949.
99. ^ Babiuk LA, Meldrum B, Gupta VS, Rouse BT (December 1975). "Comparison of the Antiviral Effects of 5-Methoxymethyl-deoxyuridine with 5-Iododeoxyuridine, Cytosine Arabinoside, and Adenine Arabinoside". *Antimicrob. Agents Chemother*. **8** (6): 643–50. doi:10.1128/aac.8.6.643. PMC 429441. PMID 1239978.
100. ^ O'Meara A, Deasy PF, Hillary IB, Bridgen WD (December 1979). "Acyclovir for treatment of mucocutaneous herpes infection in a child with leukaemia". *Lancet*. **2** (8153): 1196. doi:10.1016/S0140-6736(79)92428-0. PMID 91931.
101. ^ Whitley R, Arvin A, Prober C, et al. (February 1991). "A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. Infectious Diseases Collaborative Antiviral Study Group". *N. Engl. J. Med*. **324** (7): 444–9. doi:10.1056/NEJM199102143240703. PMID 1988829.
102. ^ *a b c* Kimberlin DW, Lin CY, Jacobs RF, et al. (August 2001). "Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections". *Pediatrics*. **108** (2): 230–8. doi:10.1542/peds.108.2.230. PMID 11483782.
103. ^ Mayou, R (1975). "Psychological morbidity in a clinic for sexually transmitted disease". *The British journal of venereal diseases*. **51** (1): 57–60. doi:10.1136/sti.51.1.57. PMC 1045113. PMID 1173225.
104. ^ Moynihan R, Heath I, Henry D (April 2002). "Selling sickness: the pharmaceutical industry and disease mongering". *BMJ*. **324** (7342): 886–91. doi:10.1136/bmj.324.7342.886. PMC 1122833. PMID 11950740.
105. ^ Cuatrecasas P (November 2006). "Drug discovery in jeopardy". *J. Clin. Invest*. **116** (11): 2837–42. doi:10.1172/JCI29999. PMC 1626142. PMID 17080187.
106. ^ Vezina C, Steben M (2001). "Genital Herpes: Psychosexual Impacts and Counselling" (PDF). *The Canadian Journal of CME* (June): 125–34.
107. ^ Green, J; Ferrier, S; Kocsis, A; Shadrick, J; Ukoumunne, OC; Murphy, S; Hetherton, J (February 2003). "Determinants of disclosure of genital herpes to partners.". *Sexually transmitted infections*. **79** (1): 42–4. doi:10.1136/sti.79.1.42. PMC 1744583. PMID 12576613.
108. ^ Miranda Hitti (24 August 2007). "Stigma Still Strong". WebMD. Archived from the original on 16 November 2013.
109. ^ "Herpes support groups on Meetup".
110. ^ "Genitla Herpes Dating Sites Review".
111. ^ "Herpes Support Forum". Retrieved 15 May 2016.
112. ^ "Our History". Retrieved 19 October 2014. "ASHA was founded in 1914 in New York City, formed out of early 20th century social reform movements focused on fighting sexually transmitted infections (known then as venereal disease, or VD) and prostitution."
113. ^ "American Social Health Association". Archived from the original on 2008-08-20.
114. ^ "The Herpes Resource Center". Archived from the original on 2011-10-03.
115. ^ "The Herpes Viruses Association".
116. ^ Johnston C, Koelle DM, Wald A (Dec 2011). "HSV-2: in pursuit of a vaccine.". *J Clin Invest*. **121** (12): 4600–9. doi:10.1172/JCI57148. PMID 22133885.
117. ^ Fox, Maggie (2008-07-02). "New approach offers chance to finally kill herpes". Reuters. Retrieved 2011-04-12.
118. ^ Kingsbury, Kathleen (2008-07-02). "A Cure for Cold Sores?". *Time*. Retrieved 2010-05-04.
119. ^ Foley, James A. (21 Oct 2013). "Hitchhiking Herpes Virus Aligns with Spread of Human Civilization". NatureWorldNews.com. Retrieved 22 October 2013.

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| | | **Scaling** | | | psoriasis · tinea (corporis · cruris · pedis · manuum · faciei) · pityriasis rosea · secondary syphilis · mycosis fungoides · systemic lupus erythematosus · pityriasis rubra pilaris · parapsoriasis · ichthyosis · |
| | | **Blistering** | | | **herpes simplex** · herpes zoster · varicella · bullous impetigo · acute contact dermatitis · pemphigus vulgaris · bullous pemphigoid · dermatitis herpetiformis · porphyria cutanea tarda · epidermolysis bullosa simplex · |
| | | **Papular** | | | scabies · insect bite reactions · lichen planus · miliaria · keratosis pilaris · lichen spinulosus · transient acantholytic dermatosis · lichen nitidus · pityriasis lichenoides et varioliformis acuta · |
| | | **Pustular** | | | acne vulgaris · acne rosacea · folliculitis · impetigo · candidiasis · gonococcemia · dermatophyte · coccidioidomycosis · subcorneal pustular dermatosis · |
| | | **Hypopigmented** | | | tinea versicolor · vitiligo · pityriasis alba · postinflammatory hyperpigmentation · tuberous sclerosis · idiopathic guttate hypomelanosis · leprosy · hypopigmented mycosis fungoides · |
| | **Without epidermal involvement** | **Red** | **Blanchable Erythema** | **Generalized** | drug eruptions · viral exanthems · toxic erythema · systemic lupus erythematosus · |
| | | | | **Localized** | cellulitis · abscess · boil · erythema nodosum · carcinoid syndrome · fixed drug eruption · |
| | | | | **Specialized** | urticaria · erythema (multiforme · migrans · gyratum repens · annulare centrifugum · ab igne) · |
| | | | **Nonblanchable Purpura** | **Macular** | thrombocytopenic purpura · actinic/solar purpura · |
| | | | | **Papular** | disseminated intravascular coagulation · vasculitis · |
| | | **Indurated** | | | scleroderma/morphea · granuloma annulare · lichen sclerosis et atrophicus · necrobiosis lipoidica · |
| **Miscellaneous disorders** | **Ulcers** | | | | |
| | **Hair** | | | | telogen effluvium · androgenic alopecia · trichotillomania · alopecia areata · systemic lupus erythematosus · tinea capitis · loose anagen syndrome · lichen planopilaris · folliculitis decalvans · acne keloidalis nuchae · |
| | **Nail** | | | | onychomycosis · psoriasis · paronychia · ingrown nail · |
| | **Mucous membrane** | | | | Aphthous stomatitis · oral candidiasis · lichen planus · leukoplakia · pemphigus vulgaris · mucous membrane pemphigoid · cicatricial pemphigoid · herpesvirus · coxsackievirus · syphilis · systemic histoplasmosis · squamous-cell carcinoma · |

| | |
|---|---|
| v · t · e · | **Sexually transmitted infection (STI) (primarily A50–A64, 090–099)** |
| | Chancroid (*Haemophilus ducreyi*) · Chlamydia/Lymphogranuloma venereum (*Chlamydia trachomatis*) · |

| | |
|---|---|
| **Bacterial** | Donovanosis or Granuloma Inguinale (*Klebsiella granulomatis*) · Gonorrhea (*Neisseria gonorrhoeae*) · Mycoplasma hominis infection (*Mycoplasma hominis*) · Syphilis (*Treponema pallidum*) · Ureaplasma infection (*Ureaplasma urealyticum*) · |
| **Protozoal** | Trichomoniasis (*Trichomonas vaginalis*) · |
| **Parasitic** | Crab louse/crabs · Scabies · |
| **Viral** | AIDS (*HIV-1/HIV-2*) · Cervical cancer, vulvar cancer & Genital warts (condyloma), Penile cancer, Anal cancer (*Human papillomavirus (HPV)*) · Hepatitis B (*Hepatitis B virus*) · **Herpes simplex** (*HSV1/HSV2*) · Molluscum contagiosum (*MCV*) · |
| **General inflammation** | *female*: Cervicitis · Pelvic inflammatory disease (PID) ·<br>*male*: Epididymitis · Prostatitis ·<br>*either*: Proctitis · Urethritis/Non-gonococcal urethritis (NGU) · |

v · t · e · **Infectious skin disease: Viral cutaneous conditions, including viral exanthema (B00–B09, 050–059)**

| | | | | |
|---|---|---|---|---|
| **DNA virus** | **Herpesviridae** | **Alpha** | *HSV* | **Herpes simplex** · Herpetic whitlow · Herpes gladiatorum · Herpetic keratoconjunctivitis · Herpetic sycosis · Neonatal herpes simplex · Herpes genitalis · Herpes labialis · Eczema herpeticum · Herpetiform esophagitis · |
| | | | *Herpes B virus* | B virus infection · |
| | | | *VZV* | Chickenpox · Herpes zoster · Herpes zoster oticus · Ophthalmic zoster · Disseminated herpes zoster · Zoster-associated pain · Modified varicella-like syndrome · |
| | | **Beta** | *Human herpesvirus 6*/*Roseolovirus* | (Exanthema subitum · Roseola vaccinia · · Cytomegalic inclusion disease · |
| | | **Gamma** | *KSHV* | (Kaposi's sarcoma · · |
| | **Poxviridae** | **Ortho** | *Variola* | (Smallpox · Alastrim · · *MoxV* (Monkeypox · · *CPXV* (Cowpox · · *VV* (Vaccinia · Generalized vaccinia · Eczema vaccinatum · Progressive vaccinia · · Buffalopox · |
| | | **Para** | | Farmyard pox: Milker's nodule · Bovine papular stomatitis · Pseudocowpox · Orf · Sealpox · |
| | | **Other** | | Yatapoxvirus: Tanapox · Yaba monkey tumor virus · *MCV* (Molluscum contagiosum · · |
| | **Papillomaviridae** | *HPV* | | Wart/plantar wart · Heck's disease · Genital wart (giant · · Laryngeal papillomatosis · Butcher's wart · Bowenoid papulosis · Epidermodysplasia verruciformis · Verruca plana · Pigmented wart · Verrucae palmares et plantares · |
| | | *BPV* | | (Equine sarcoid · · |
| | **Parvoviridae** | *Parvovirus B19* | | (Erythema infectiosum · Reticulocytopenia · Papular purpuric gloves and socks syndrome · · |
| | **Polyomaviridae** | *Merkel cell polyomavirus* | | (Merkel cell carcinoma · · |
| **RNA virus** | **Paramyxoviridae** | *MeV* | | (Measles · · |
| | **Togaviridae** | *Rubella virus* | | (Rubella · Congenital rubella syndrome · · Alphavirus infection · Chikungunya fever · |
| | **Picornaviridae** | *CAV* | | (Hand, foot and mouth disease · Herpangina · · *FMDV* (Foot-and-mouth disease · · Boston exanthem disease · |

| | |
|---|---|
| **Ungrouped** | Asymmetric periflexural exanthem of childhood · Post-vaccination follicular eruption · Lipschütz ulcer · Eruptive pseudoangiomatosis · Viral-associated trichodysplasia · Gianotti–Crosti syndrome · |

v · t · e · **Oral and maxillofacial pathology (K00–K06, K11–K14, 520–525, 527–529)**

**Lips**

Cheilitis (Actinic · Angular · Plasma cell · · Cleft lip · Congenital lip pit · Eclabium · Herpes labialis · Macrocheilia · Microcheilia · Nasolabial cyst · Sun poisoning · Trumpeter's wart ·

**Tongue**

Ankyloglossia · Black hairy tongue · Caviar tongue · Crenated tongue · Cunnilingus tongue · Fissured tongue · Foliate papillitis · Glossitis (Geographic tongue · Median rhomboid glossitis · Transient lingual papillitis · · Glossoptosis · Hypoglossia · Lingual thyroid · Macroglossia · Microglossia · Rhabdomyoma ·

**Palate**

Bednar's aphthae · Cleft palate · High-arched palate · Palatal cysts of the newborn · Inflammatory papillary hyperplasia · Stomatitis nicotina · Torus palatinus ·

**Oral mucosa** - *Lining of mouth*

Amalgam tattoo · Angina bullosa haemorrhagica · Behçet syndrome · Bohn's nodules · Burning mouth syndrome · Candidiasis · Condyloma acuminatum · Darier's disease · Epulis fissuratum · Erythema multiforme · Erythroplakia · Fibroma (Giant-cell · · Focal epithelial hyperplasia · Fordyce spots · Hairy leukoplakia · Hand, foot and mouth disease · Hereditary benign intraepithelial dyskeratosis · Herpangina · Herpes zoster · Intraoral dental sinus · Leukoedema · Leukoplakia · Lichen planus · Linea alba · Lupus erythematosus · Melanocytic nevus · Melanocytic oral lesion · Molluscum contagiosum · Morsicatio buccarum · Oral cancer (*Benign:* Squamous cell papilloma · Keratoacanthoma · *Malignant:* Adenosquamous carcinoma · Basaloid squamous carcinoma · Mucosal melanoma · Spindle cell carcinoma · Squamous cell carcinoma · Verrucous carcinoma · · Oral florid papillomatosis · Oral melanosis (Smoker's melanosis · · Pemphigoid (Benign mucous membrane · · Pemphigus · Plasmoacanthoma · Stomatitis (Aphthous · Denture-related · Herpetic · · Smokeless tobacco keratosis · Submucous fibrosis · Ulceration · Verruca vulgaris · Verruciform xanthoma · White sponge nevus ·

**Teeth (pulp, dentin, enamel)**

Amelogenesis imperfecta · Ankylosis · Anodontia · Caries (Early childhood caries · · Concrescence · Failure of eruption of teeth · Dens evaginatus (Talon cusp · · Dentin dysplasia · Dentin hypersensitivity · Dentinogenesis imperfecta · Dilaceration · Discoloration · Ectopic enamel · Enamel hypocalcification · Enamel hypoplasia (Turner's hypoplasia · · Enamel pearl · Fluorosis · Fusion · Gemination · Hyperdontia · Hypodontia (Maxillary lateral incisor agenesis · · Impaction (Wisdom tooth impaction · · Macrodontia · Meth mouth · Microdontia · Odontogenic tumors (Keratocystic odontogenic tumour · · Odontoma (Dens in dente · · Open contact · Premature eruption (Neonatal teeth · · Pulp calcification (Pulp stone · · Pulp canal obliteration · Pulp necrosis · Pulp polyp · Pulpitis · Regional odontodysplasia · Resorption · Shovel-shaped incisors · Supernumerary root · Taurodontism · Trauma (Avulsion · Cracked tooth syndrome · Vertical root fracture · Occlusal · · Tooth loss (Edentulism · · Tooth wear (Abrasion · Abfraction · Acid erosion · Attrition · ·

**Periodontium (gingiva, periodontal ligament, cementum, alveolus)** - *Gums and tooth-supporting structures*

Cementicle · Cementoblastoma (Gigantiform · · Cementoma · Eruption cyst · Epulis (Pyogenic granuloma · Congenital epulis · · Gingival enlargement · Gingival cyst of the adult · Gingival cyst of the newborn · Gingivitis (Desquamative · Granulomatous · Plasma cell · · Hereditary gingival fibromatosis · Hypercementosis · Hypocementosis · Linear gingival erythema · Necrotizing periodontal diseases (Acute necrotizing ulcerative gingivitis · · Pericoronitis · Peri-implantitis · Periodontal abscess · Periodontal trauma · Periodontitis (Aggressive · As a manifestation of systemic disease · Chronic · · Perio-endo lesion · Teething ·

**Periapaical, mandibular and maxillary hard tissues** - *Bones of jaws*

Agnathia · Alveolar osteitis · Buccal exostosis · Cherubism · Idiopathic osteosclerosis · Mandibular fracture · Microgenia · Micrognathia · Intraosseous cysts (*Odontogenic:* periapical · Dentigerous · Buccal bifurcation · Lateral periodontal · Globulomaxillary · Calcifying odontogenic · Glandular odontogenic · *Non-odontogenic:* Nasopalatine duct · Median mandibular · Median palatal · Traumatic bone · · Osteoma · Osteomyelitis · Osteonecrosis (Bisphosphonate-associated · Neuralgia-inducing cavitational osteonecrosis · Osteoradionecrosis · · Osteoporotic bone marrow defect · Paget's disease of bone ·

Periapical abscess (Phoenix abscess · · Periapical periodontitis · Stafne defect · Torus mandibularis ·

**Temporomandibular joints, muscles of mastication and malocclusions -** *Jaw joints, chewing muscles and bite abnormalities*

Bruxism · Condylar resorption · Mandibular dislocation · Malocclusion (Crossbite · Open bite · Overbite · Overjet · Prognathia · Retrognathia · · Temporomandibular joint dysfunction ·

**Salivary glands**

Benign lymphoepithelial lesion · Ectopic salivary gland tissue · Frey's syndrome · HIV salivary gland disease · Necrotizing sialometaplasia · Mucocele (Ranula · · Pneumoparotitis · Salivary duct stricture · Salivary gland aplasia · Salivary gland atresia · Salivary gland diverticulum · Salivary gland fistula · Salivary gland hyperplasia · Salivary gland hypoplasia · Salivary gland neoplasms (*Benign:* Basal cell adenoma · Canalicular adenoma · Ductal papilloma · Monomorphic adenoma · Myoepithelioma · Oncocytoma · Papillary cystadenoma lymphomatosum · Pleomorphic adenoma · Sebaceous adenoma · *Malignant:* Acinic cell carcinoma · Adenocarcinoma · Adenoid cystic carcinoma · Carcinoma ex pleomorphic adenoma · Lymphoma · Mucoepidermoid carcinoma · · Sclerosing polycystic adenosis · Sialadenitis (Parotitis · Chronic sclerosing sialadenitis · · Sialectasis · Sialocele · Sialodochitis · Sialosis · Sialolithiasis · Sjögren's syndrome ·

**Orofacial soft tissues -** *Soft tissues around the mouth*

Actinomycosis · Angioedema · Basal cell carcinoma · Cutaneous sinus of dental origin · Cystic hygroma · Gnathophyma · Ludwig's angina · Macrostomia · Melkersson–Rosenthal syndrome · Microstomia · Noma · Oral Crohn's disease · Orofacial granulomatosis · Perioral dermatitis · Pyostomatitis vegetans ·

**Other**

Eagle syndrome · Hemifacial hypertrophy · Facial hemiatrophy · Oral manifestations of systemic disease ·

Categories: Herpes | Biology of bipolar disorder | Conditions of the mucous membranes | Herpes simplex virus-associated diseases | Sexually transmitted diseases and infections | Virus-related cutaneous conditions | Viral diseases




WIKIPEDIA
The Free Encyclopedia

# Shingles



From Wikipedia, the free encyclopedia
(Redirected from Herpes zoster)

*For other uses, see Shingle (disambiguation).*
*"Zoster" redirects here. For the ancient Greek article of dress, see Zoster (costume).*

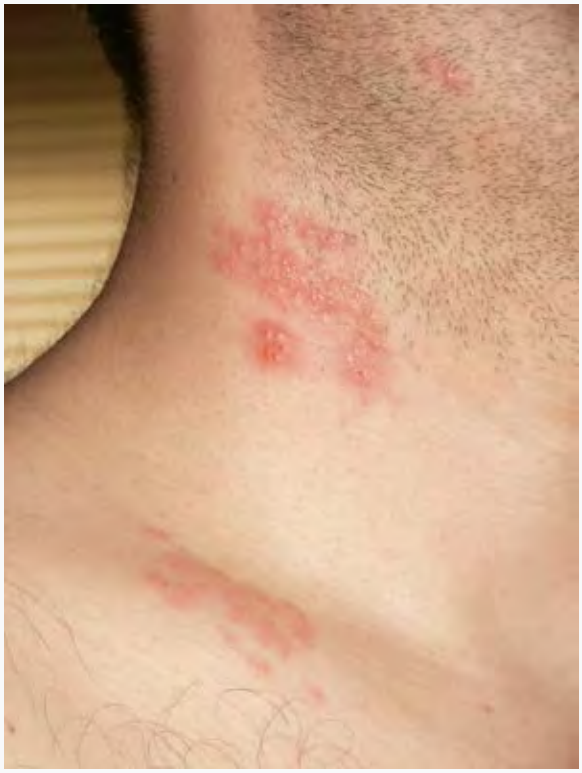
**Shingles**, also known as **herpes zoster**, is a viral disease characterized by a painful skin rash with blisters in a localized area.[1][2] Typically the rash occurs in a single stripe either on the left or right of the body or face.[3] Two to four days before the rash occurs there may be tingling or local pain in the area.[3][4] Otherwise there are typically few symptoms.[3] The rash usually heals within two to four weeks;[1] however, some people develop ongoing nerve pain which can last for months or years, a condition called postherpetic neuralgia. In those with poor immune function the rash may occur widely.[3] If the rash involves the eye, vision loss may occur.[1]

Shingles is due to a reactivation of varicella zoster virus (VZV) within a person's body. Chickenpox is due to an initial infection with VZV. Once chickenpox has resolved, the virus may remain inactive in nerve cells.[3] When it reactivates it travels from the nerve body to the endings in the skin producing blisters.[4] Risk factors for reactivation include old age, poor immune function, and having had chickenpox before 18 months of age. How the virus remains in the body or subsequently re-activates, is not well understood.[3] Exposure to the virus in the blisters can cause chickenpox in someone who has not had it before but will not trigger shingles.[5] Diagnosis is typically based on a person's signs and symptoms.[6] Varicella zoster virus is not the same as herpes simplex virus, however, they belong to the same family of viruses.[7]

The shingles vaccine decreases the chance of shingles by about half in those between the ages of 50 and 80. It also decreases rates of postherpetic neuralgia, and if an outbreak occurs, its severity. After 80 the vaccine is still effective, just less so. It contains the same material as the varicella vaccine, just at a higher dose.[3] If shingles develops, antiviral medications such as aciclovir can reduce the severity and duration of disease if started within 72 hours of the appearance of the rash.[6] Evidence does not show a significant effect of antivirals or steroids on rates of postherpetic neuralgia.[8][9] Paracetamol, NSAIDs, or opioids may be used to help with the acute pain.[6]

It is estimated that about a third of people develop shingles at some point in their life.[3] While more common among older [7]

**Synonyms** zoster, herpes zoster, zona



Herpes zoster blisters on the neck and shoulder

| Classification and external resources | |
|---|---|
| **Specialty** | Dermatology |
| **ICD-10** | B02 |
| **ICD-9-CM** | 053 |
| **DiseasesDB** | 29119 |
| **MedlinePlus** | 000858 |
| **eMedicine** | med/1007 derm/180 emerg/823 oph/257 ped/996 |
| **Patient UK** | Shingles |

people, children may also get the disease. The number of new cases per year ranges from 1.2–3.4 per 1,000 among healthy individuals to 3.9–11.8 per 1,000 among those older than 65 years of age.[10] About half of those living to age 85 will have at least one attack, and less than 5% will have more than one attack.[3][11] The disease has been recognized since ancient times.[3]

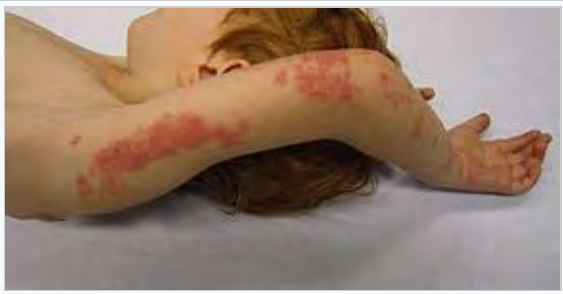
[edit on Wikidata]





## Signs and symptoms [edit]

The earliest symptoms of shingles, which include headache, fever, and malaise, are nonspecific, and may result in an incorrect diagnosis.[10][12] These symptoms are commonly followed by sensations of burning pain, itching, hyperesthesia (oversensitivity), or paresthesia ("pins and needles": tingling, pricking, or numbness).[13] Pain can be mild to extreme in the affected dermatome, with sensations that are often described as stinging, tingling, aching, numbing or throbbing, and can be interspersed with quick stabs of agonizing pain.[14]



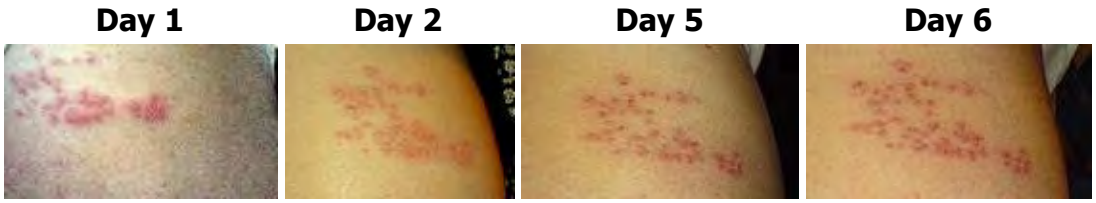
A case of shingles that demonstrates the typical dermatomal distribution, in this case C8/T1

Shingles in children is often painless, but people are more likely to get shingles as they age, and the disease tends to be more severe.[15]

In most cases after one to two days, but sometimes as long as three weeks, the initial phase is followed by the appearance of the characteristic skin rash. The pain and rash most commonly occurs on the torso, but can appear on the face, eyes or other parts of the body. At first the rash appears similar to the first appearance of hives; however, unlike hives, shingles causes skin changes limited to a dermatome, normally resulting in a stripe or belt-like pattern that is limited to one side of the body and does not cross the midline.[13] *Zoster sine herpete* ("zoster without herpes") describes a person who has all of the symptoms of shingles except this characteristic rash.[16]

Later the rash becomes vesicular, forming small blisters filled with a serous exudate, as the fever and general malaise continue. The painful vesicles eventually become cloudy or darkened as they fill with blood, and crust over within seven to ten days; usually the crusts fall off and the skin heals, but sometimes, after severe blistering, scarring and discolored skin remain.[13]

**Development of the shingles rash**




## Face [edit]

Shingles may have additional symptoms, depending on the dermatome involved. The trigeminal nerve is the most commonly involved nerve.[17]

The ophthalmic division of the trigeminal nerve is the most commonly involved branch.[18] When the virus is reactivated in this nerve branch it is termed *zoster ophthalmicus*. The skin of the forehead, upper eyelid and orbit of the eye may be involved. Zoster ophthalmicus occurs in approximately 10% to 25% of cases. In some people, symptoms may include conjunctivitis, keratitis, uveitis, and optic nerve palsies that can sometimes cause chronic ocular inflammation, loss of vision, and debilitating pain.[19]

*Shingles oticus*, also known as Ramsay Hunt syndrome type II, involves the ear. It is thought to result from the virus spreading from the facial nerve to the vestibulocochlear nerve. Symptoms include hearing loss and vertigo (rotational dizziness).[20]

Shingles may occur in the mouth if the maxillary or mandibular division of the trigeminal nerve is affected,[21] in which the rash may appear on the mucous membrane of the upper jaw (usually the palate, sometimes the gums of the upper teeth) or the lower jaw (tongue or gums of the lower teeth) respectively.[22] Oral involvement may occur alone or in combination with a rash on the skin over the cutaneous distribution of the same trigeminal branch.[21] As with shingles of the skin, the lesions tend to only involve one side, distinguishing it from other oral blistering conditions.[22] In the mouth, shingles appears initially as 1–4 mm opaque blisters (vesicles),[21] which break down quickly to leave ulcers that heal within 10–14 days.[22] The prodromal pain (before the rash) may be confused with toothache.[21] Sometimes this leads to unnecessary dental treatment.[22] Post herpetic neuralgia uncommonly is associated with shingles in the mouth.[22] Unusual complications may occur with intra-oral shingles that are not seen elsewhere. Due to the close relationship of blood vessels to nerves, the virus can spread to involve the blood vessels and compromise the blood supply, sometimes causing ischemic necrosis.[21] Therefore, oral involvement rarely causes complications such as osteonecrosis, tooth loss, periodontitis (gum disease), pulp calcification, pulp necrosis, periapical lesions and tooth developmental anomalies.[17]

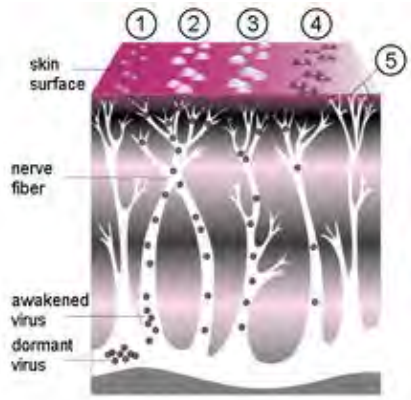
## Disseminated shingles [edit]

In those with poor immune function, *disseminated shingles* may occur (wide rash).[3] It is defined as more than twenty skin lesions appearing outside either the primarily affected dermatome or dermatomes directly adjacent to it. Besides the skin, other organs, such as the liver or brain, may also be affected (causing hepatitis or encephalitis[23][24] respectively), making the condition potentially lethal.[25]:380

# Pathophysiology [edit]

The causative agent for shingles is the varicella zoster virus (VZV)—a double-stranded DNA virus related to the Herpes simplex virus. Most individuals are infected with this virus as children which causes an episode of chickenpox. The immune system eventually eliminates the virus from most locations, but it remains dormant (or latent) in the ganglia adjacent to the spinal cord (called the dorsal root ganglion) or the trigeminal ganglion in the base of the skull.[26]

Shingles occurs only in people who have been previously infected with VZV; although it can occur at any age, approximately half of the cases in the USA occur in those aged 50 years or older.[27] Repeated attacks of shingles are rare,[13] and it is extremely rare for a person to have more than three recurrences.[26]



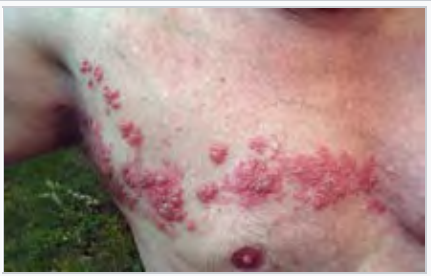

Progression of shingles. A cluster of small bumps (1) turns into blisters (2). The blisters fill with lymph, break open (3), crust over (4), and finally disappear. Postherpetic neuralgia can sometimes occur due to nerve damage (5).

The disease results from virus particles in a single sensory ganglion switching from their latent lysogenic cycles to their active lytic cycles.[28] In contrast to the herpes simplex virus, the latency of VZV is poorly understood. The virus has never been successfully recovered from human nerve cells by cell culture. The complete sequence of the viral genome was published in 1986.[29] Virus-specific proteins continue to be made by the infected cells during the latent period, so true latency, as opposed to chronic, low-level, active infection, has not been proven to occur in VZV infections.[30][31] Although VZV has been detected in autopsies of nervous tissue,[32] there are no methods to find dormant virus in the ganglia of living people.

Unless the immune system is compromised, it suppresses reactivation of the virus and prevents shingles outbreaks. Why this suppression sometimes fails is poorly understood,[33] but shingles is more likely to occur in people whose immune systems are impaired due to aging, immunosuppressive therapy, psychological stress, or other factors.[34] Upon reactivation, the virus replicates in neuronal cell bodies, and virions are shed from the cells and carried down the axons to the area of skin innervated by that ganglion. In the skin, the virus causes local inflammation and blistering. The short- and long-term pain caused by shingles outbreaks originates from inflammation of affected nerves due to the widespread growth of the virus in those areas.[35]

As with chickenpox and/or other forms of herpes, direct contact with an active rash can spread VZV to a person who has no immunity to the virus. This newly infected individual may then develop chickenpox, but will not immediately develop shingles.[13]

## Diagnosis [edit]



Shingles on the chest

If the rash has appeared, identifying this disease (making a differential diagnosis) requires only a visual examination, since very few diseases produce a rash in a dermatomal pattern (see map). However, herpes simplex virus (HSV) can occasionally produce a rash in such a pattern (zosteriform herpes simplex).[36][37] The Tzanck smear is helpful for diagnosing acute infection with a herpes virus, but does not distinguish between HSV and VZV.[38]

When the rash is absent (early or late in the disease, or in the case of zoster sine herpete), shingles can be difficult to diagnose.[39] Apart from the rash, most symptoms can occur also in other conditions.

Laboratory tests are available to diagnose shingles. The most popular test detects VZV-specific IgM antibody in blood; this appears only during chickenpox or shingles and not while the virus is dormant.[40] In larger laboratories, lymph collected from a blister is tested by polymerase chain reaction for VZV DNA, or examined with an electron microscope for virus particles.[41] Molecular biology tests based on in vitro nucleic acid amplification (PCR tests) are currently considered the most reliable. Nested PCR test has high sensitivity, but is susceptible to contamination leading to false positive results. The latest real-time PCR tests are rapid, easy to perform, and as sensitive as nested PCR, and have a lower risk of contamination. They also have more sensitivity than viral cultures.[42]

## Differential diagnosis [edit]

Shingles can be confused with herpes simplex, dermatitis herpetiformis and impetigo, and skin reactions caused by contact dermatitis, candidiasis, certain drugs and insect bites.[43]

# Prevention [edit]

There is a live vaccine for VZV, known as the zoster vaccine.[44] It must be maintained at a temperature not exceeding −15 °C during shipping and storage, although it can be stored and transported at refrigerator temperature for up to 72 continuous hours before reconstitution. The incidence of side effects is low. There is no recommended upper age limit.[45]

A systematic review by Cochrane concluded that the herpes zoster vaccine was useful for preventing herpes zoster for at least three years.[4] This equates to about 50% relative risk reduction. The vaccine reduced incidence of persistent, severe pain after shingles (i.e., PHN) by 66% in people who contracted shingles despite vaccination.[45]

In the Shingles Prevention Study (SPS), vaccine efficacy was maintained through four years of follow-up.[45] Following one dose of live attenuated vaccine 69% were protected in the first year and 4% after eight years. Two doses of a adjuvanted herpes zoster subunit vaccine had levels of protection of about 90% at 3.5 years.[46]

An episode of HZ has an immunizing effect, reducing the probability of a subsequent recurrence. However, individuals with a history of severe HZ are often insistent on receiving the vaccine, and there have been concerns about the validity of people's histories of HZ. Both the Centers for Disease Control and Prevention and the ACIP recommended the vaccination of adults regardless of a previous episode of HZ.[45]

It has been recommended that people with primary or acquired immunodeficiency should not receive the vaccine.[45]

The likelihood of vaccination causing a case of HZ appears to be very low.[45]

A 2007 study found that the shingles vaccine is likely to be cost-effective in the U.S., projecting an annual savings of $82 to $103 million in healthcare costs with cost-effectiveness ratios ranging from $16,229 to $27,609 per quality-adjusted life year gained.[47] In October 2007 the vaccine was officially recommended in the U.S. for healthy adults aged 60 and over.[44][48] The Centers for Disease Control and Prevention recommends shingle vaccine for use in people 60 years old and older to prevent shingles, but it is not recommended to treat active shingles or postherpetic neuralgia (pain after the rash is gone) once it develops.[49] Adults also receive an immune boost from contact with children infected with varicella (chicken pox), a boosting method that prevents about a quarter of shingles cases among unvaccinated adults, but that is becoming less common in the U.S. now that children are routinely vaccinated against varicella.[50][51]

In the United Kingdom and other parts of Europe, population-based varicella immunization is not practiced. The rationale is that until the entire population could be immunized, adults who have previously contracted VZV would instead derive benefit from occasional exposure to VZV (from children), which serves as a booster to their immunity to the virus, and may reduce the risk of shingles later on in life.[52] The UK Health Protection Agency states that, while the vaccine is licensed in the UK, there are no plans to introduce it into the routine childhood immunization scheme, although it may be offered to healthcare workers who have no immunity to VZV.[53]

From 2013 the UK National Health Service started offering shingles vaccination, with Zostavax, to elderly people. People aged either 70 or 79 on 1 September 2013 were offered the vaccine. People aged 71 to 78 on that date would only have an opportunity to have the shingles vaccine after reaching the age of 79.[54] The original intention was for people aged *between* 70 and 79 to be vaccinated, but the NHS later said that the vaccination programme was being staggered as it would be impractical to vaccinate everyone in their 70s in a single year.[55]

# Treatment [edit]

The aims of treatment are to limit the severity and duration of pain, shorten the duration of a shingles episode,

and reduce complications. Symptomatic treatment is often needed for the complication of postherpetic neuralgia.[56] However, a study on untreated shingles shows that, once the rash has cleared, postherpetic neuralgia is very rare in people under 50 and wears off in time; in older people the pain wore off more slowly, but even in people over 70, 85% were pain free a year after their shingles outbreak.[57]

### Analgesics [edit]

People with mild to moderate pain can be treated with over-the-counter pain medications. Topical lotions containing calamine can be used on the rash or blisters and may be soothing. Occasionally, severe pain may require an opioid medication, such as morphine. Once the lesions have crusted over, capsaicin cream (Zostrix) can be used. Topical lidocaine and nerve blocks may also reduce pain.[58] Administering gabapentin along with antivirals may offer relief of postherpetic neuralgia.[56]

### Antivirals [edit]

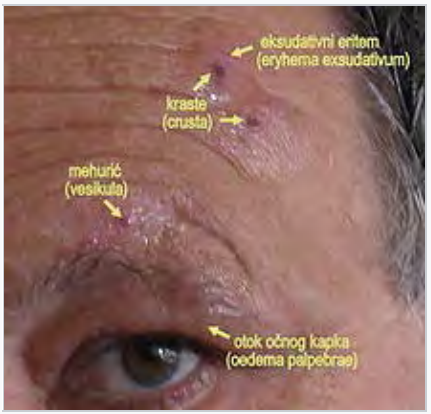
Antiviral drugs may reduce the severity and duration of shingles;[59] however, they do not prevent postherpetic neuralgia.[60] Of these drugs, acyclovir has been the standard treatment, but the new drugs valaciclovir and famciclovir demonstrate similar or superior efficacy and good safety and tolerability.[56] The drugs are used both for prevention (for example in HIV/AIDS) and as therapy during the acute phase. Complications in immunocompromised individuals with shingles may be reduced with intravenous acyclovir. In people who are at a high risk for repeated attacks of shingles, five daily oral doses of acyclovir are usually effective.[20]

### Steroids [edit]

Corticosteroids do not appear to decrease the risk of long term pain.[61] Side effects however appear to be minimal. Their use in Ramsay Hunt syndrome has not been properly studied as of 2008.[62]

### Zoster ophthalmicus [edit]

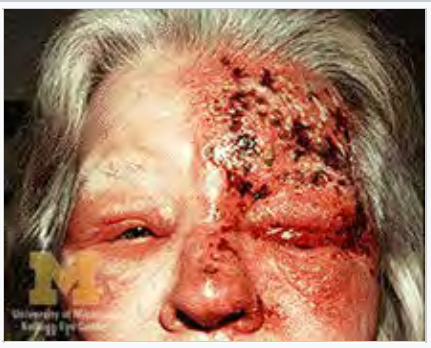
Treatment for zoster ophthalmicus is similar to standard treatment for shingles at other sites. A recent trial comparing acyclovir with its prodrug, valaciclovir, demonstrated similar efficacies in treating this form of the disease.[63] The significant advantage of valciclovir over aciclovir is its dosing of only 3 times/day (compared with aciclovir's 5 times/day dosing), which could make it more convenient for people and improve adherence with therapy.[64]



Zoster ophthalmicus

## Prognosis [edit]

The rash and pain usually subside within three to five weeks, but about one in five people develop a painful condition called postherpetic neuralgia, which is often difficult to manage. In some people, shingles can reactivate presenting as *zoster sine herpete*: pain radiating along the path of a single spinal nerve (a *dermatomal distribution*), but without an accompanying rash. This condition may involve complications that affect several levels of the nervous system and cause many cranial neuropathies, polyneuritis, myelitis, or aseptic meningitis. Other serious effects that may occur in some cases include partial facial paralysis (usually temporary), ear damage, or encephalitis.[20] During pregnancy, first infections with VZV, causing chickenpox, may lead to infection of the fetus and complications in the newborn, but chronic infection or reactivation in shingles are not associated with fetal infection.[65][66]


Trigeminal shingles with uveitis

There is a slightly increased risk of developing cancer after a shingles infection. However, the mechanism is unclear and mortality from cancer did not appear to increase as a direct result of the presence of the virus.[67] Instead, the increased risk may result from the immune suppression that

and keratitis

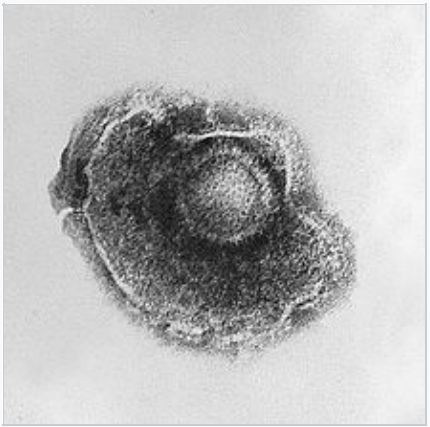
allows the reactivation of the virus.[68]

Although shingles typically resolves within 3–5 weeks, certain complications may arise:

- Secondary bacterial infection
- Motor involvement, including weakness especially in "motor herpes zoster"
- Eye involvement: trigeminal nerve involvement (as seen in herpes ophthalmicus) should be treated early and aggressively as it may lead to blindness. Involvement of the tip of the nose in the zoster rash is a strong predictor of herpes ophthalmicus.[69]
- Postherpetic neuralgia, a condition of chronic pain following shingles

## Epidemiology [edit]

*See also: Chickenpox epidemiology*



Electron micrograph of Varicella zoster virus. Approx. 150,000-fold magnification.

Varicella zoster virus (VZV) has a high level of infectivity and has a worldwide prevalence.[70] Shingles is a re-activation of latent VZV infection: zoster can only occur in someone who has previously had chickenpox (varicella).

Shingles has no relationship to season and does not occur in epidemics. There is, however, a strong relationship with increasing age.[15][34] The incidence rate of shingles ranges from 1.2 to 3.4 per 1,000 person years among younger healthy individuals, increasing to 3.9–11.8 per 1,000 person years among those older than 65 years,[10][15] and incidence rates worldwide are similar.[10][71] This relationship with age has been demonstrated in many countries,[10][71][72][73][74][75] and is attributed to the fact that cellular immunity declines as people grow older.

Another important risk factor is immunosuppression, as in people with HIV.[76][77] Other risk factors include psychological stress.[14][78][79] According to a study in North Carolina, "black subjects were significantly less likely to develop zoster than were white subjects."[80][81] It is unclear whether the risk is different by gender. Other potential risk factors include mechanical trauma and exposure to immunotoxins.[34][79]

There is no strong evidence for a genetic link or a link to family history. A 2008 study showed that people with close relatives who had had shingles were twice as likely to develop it themselves,[82] but a 2010 study found no such link.[79]

Adults with latent VZV infection who are exposed intermittently to children with chickenpox receive an immune boost.[15][79] This periodic boost to the immune system helps to prevent shingles in older adults. When routine chickenpox vaccination was introduced in the United States, there was concern that, because older adults would no longer receive this natural periodic boost, there would be an increase in the incidence of shingles.

Multiple studies and surveillance data, at least when viewed superficially, demonstrate no consistent trends in incidence in the U.S. since the chickenpox vaccination program began in 1995.[83] However, upon closer inspection, the two studies that showed no increase in shingles incidence were conducted among populations where varicella vaccination was not as yet widespread in the community.[84][85] A later study by Patel *et al.* concluded that since the introduction of the chickenpox vaccine, hospitalization costs for complications of shingles increased by more than $700 million annually for those over age 60.[86] Another study by Yih *et al*. reported that as varicella vaccine coverage in children increased, the incidence of varicella decreased, and the occurrence of shingles among adults increased by 90%.[87] The results of a further study by Yawn *et al*. showed a 28% increase in shingles incidence from 1996 to 2001.[88] It is likely that incidence rate will change in the future, due to the aging of the population, changes in therapy for malignant and autoimmune diseases, and changes in chickenpox vaccination rates; a wide adoption of zoster vaccination could dramatically reduce the incidence rate.[10]

In one study, it was estimated that 26% of those who contract shingles eventually present complications.

Postherpetic neuralgia arises in approximately 20% of people with shingles.[89] A study of 1994 California data found hospitalization rates of 2.1 per 100,000 person-years, rising to 9.3 per 100,000 person-years for ages 60 and up.[90] An earlier Connecticut study found a higher hospitalization rate; the difference may be due to the prevalence of HIV in the earlier study, or to the introduction of antivirals in California before 1994.[91]

## History [edit]

Shingles has a long recorded history, although historical accounts fail to distinguish the blistering caused by VZV and those caused by smallpox,[27] ergotism, and erysipelas. In the late 18th century William Heberden established a way to differentiate between shingles and smallpox,[92] and in the late 19th century shingles was differentiated from erysipelas. In 1831 Richard Bright hypothesized that the disease arose from the dorsal root ganglion, and an 1861 paper by Felix von Bärensprung confirmed this.[93]

The first indications that chickenpox and shingles were caused by the same virus were noticed at the beginning of the 20th century. Physicians began to report that cases of shingles were often followed by chickenpox in the younger people who lived with the person with shingles. The idea of an association between the two diseases gained strength when it was shown that lymph from a person with shingles could induce chickenpox in young volunteers. This was finally proved by the first isolation of the virus in cell cultures, by the Nobel laureate Thomas Huckle Weller, in 1953.[94]

Until the 1940s the disease was considered benign, and serious complications were thought to be very rare.[95] However, by 1942, it was recognized that shingles was a more serious disease in adults than in children, and that it increased in frequency with advancing age. Further studies during the 1950s on immunosuppressed individuals showed that the disease was not as benign as once thought, and the search for various therapeutic and preventive measures began.[96] By the mid-1960s, several studies identified the gradual reduction in cellular immunity in old age, observing that in a cohort of 1,000 people who lived to the age of 85, approximately 500 (i.e., 50%) would have at least one attack of shingles, and 10 (i.e., 1%) would have at least two attacks.[97]

In historical shingles studies, shingles incidence generally increased with age. However, in his 1965 paper, Dr. Hope-Simpson suggested that the "peculiar age distribution of zoster may in part reflect the frequency with which the different age groups encounter cases of varicella and because of the ensuing boost to their antibody protection have their attacks of zoster postponed".[15] Lending support to this hypothesis that contact with children with chickenpox boosts adult cell-mediated immunity to help postpone or suppress shingles, a study by Thomas et al. reported that adults in households with children had lower rates of shingles than households without children.[98] Also, the study by Terada et al. indicated that pediatricians reflected incidence rates from 1/2 to 1/8 that of the general population their age.[99]

### Etymology [edit]

The family name of all the herpesviridae derives from the Greek word *herpein* ("to creep"),[100] referring to the latent, recurring infections typical of this group of viruses. *Zoster* comes from Greek *zōstēr*, meaning "belt" or "girdle", after the characteristic belt-like dermatomal rash.[101] The common name for the disease, *shingles*, derives from the Latin *cingulus*, a variant of Latin *cingulum* meaning "girdle".[102]

In Arabic its name means "belt of fire", while in Spanish it means "small snake"; in Hindi it means "big rash"[103] and in Norwegian its name is *helvetesild*, literally "hell's fire".[104]

## Research [edit]

Until the mid 1990s, infectious complications of the Central Nervous System (CNS) caused by VZV reactivation were regarded as rare. The presence of rash, as well as specific neurological symptoms, were required to diagnose a CNS infection caused by VZV. Since 2000, PCR testing has become more widely used, and the number of diagnosed cases of CNS infection has increased.[105]

Classic textbook descriptions state that VZV reactivation in the CNS is restricted to immunocompromised individuals and the elderly, however, recent studies have found that most patients are immunocompetent, and less than 60 years old. Old references cite vesicular rash as a characteristic finding, however, recent studies have

found that rash is only present in 45% of cases.[105] In addition, systemic inflammation is not as reliable an indicator as previously thought: the mean level of C-reactive protein and mean white blood cell count are within the normal range in patients with VZV meningitis.[106] MRI and CT scans are usually normal in cases of VZV reactivation in the CNS. CSF pleocytosis, previously thought to be a strong indicator of VZV encephalitis, was absent in half of a group of patients diagnosed with VZV encephalitis by PCR.[105]

The frequency of CNS infections presented at the emergency room of a community hospital is not negligible, so a means of diagnosing cases is needed. PCR is not a foolproof method of diagnosis, but because so many other indicators have turned out to not be reliable in diagnosing VZV infections in the CNS, screening for VZV by PCR is recommended. Negative PCR does not rule out VZV involvement, but a positive PCR can be used for diagnosis, and appropriate treatment started (for example, antivirals can be prescribed rather than antibiotics).[105]

The introduction of DNA analysis techniques has shown some complications of varicella-zoster to be more common than previously thought. For example, sporadic meningoencephalitis (ME) caused by varicella-zoster was regarded as rare disease, mostly related to childhood chickenpox. However, meningoencephalitis caused by varicella-zoster is increasingly recognized as a predominant cause of ME among immunocompetent adults in non-epidemic circumstances.[107]

Diagnosis of complications of varicella-zoster, particularly in cases where the disease reactivates after years or decades of latency, are difficult. A rash (shingles) can be present or absent. Symptoms vary, and there is significant overlap in symptoms with herpes-simplex symptoms.[107]

Although DNA analysis techniques such as polymerase chain reaction can be used to look for DNA of herpesviruses in spinal fluid or blood, the results may be negative, even in cases where other definitive symptoms exist.[108] Notwithstanding these limitations, the use of PCR has resulted in an advance in the state of the art in our understanding of herpesviruses, including VZV, during the 1990s and 2000s. For example, in the past, clinicians believed that encephalitis was caused by herpes simplex, and that patients always died or developed serious long term function problems. People were diagnosed at autopsy or by brain biopsy. Brain biopsy is not undertaken lightly: it is reserved only for serious cases that cannot be diagnosed by less invasive methods. For this reason, knowledge of these herpes virus conditions was limited to severe cases. DNA techniques have made it possible to diagnose "mild" cases, caused by VZV or HSV, in which the symptoms include fever, headache, and altered mental status. Mortality rates in treated patients are decreasing.[107]

## References [edit]


1. ^ a b c "Shingles (Herpes Zoster) Signs & Symptoms". May 1, 2014. Retrieved 26 May 2015.
2. ^ *Shafer's textbook of oral pathology* (Seventh ed.). 2014. p. 351. ISBN 9788131238004.
3. ^ a b c d e f g h i j k Hamborsky J (2015). *Epidemiology and Prevention of Vaccine-Preventable Diseases* (PDF) (13 ed.). Washington D.C. Public Health Foundation. pp. 353–374.
4. ^ a b c Gagliardi, AM; Andriolo, BN; Torloni, MR; Soares, BG (3 March 2016). "Vaccines for preventing herpes zoster in older adults.". *Cochrane Database of Systematic Reviews*. **3**: CD008858. doi:10.1002/14651858.CD008858.pub3. PMID 26937872.
5. ^ "Shingles (Herpes Zoster) Transmission". September 17, 2014. Retrieved 26 May 2015.
6. ^ a b c Cohen, JI (18 July 2013). "Clinical practice: Herpes zoster.". *New England Journal of Medicine*. **369** (3): 255–63. doi:10.1056/NEJMcp1302674. PMID 23863052.
7. ^ a b "Overview". September 17, 2014. Retrieved 26 May 2015.
8. ^ Chen, N; Li, Q; Yang, J; Zhou, M; Zhou, D; He, L (6 February 2014). "Antiviral treatment for preventing postherpetic neuralgia.". *Cochrane Database of Systematic Reviews*. **2**: CD006866. doi:10.1002/14651858.CD006866.pub3. PMID 24500927.
9. ^ Han, Y; Zhang, J; Chen, N; He, L; Zhou, M; Zhu, C (28 March 2013). "Corticosteroids for preventing postherpetic neuralgia.". *Cochrane Database of Systematic Reviews*. **3**: CD005582. doi:10.1002/14651858.CD005582.pub4. PMID 23543541.
10. ^ a b c d e f Dworkin RH, Johnson RW, Breuer J, et al. (2007). "Recommendations for the management of herpes zoster". *Clin. Infect. Dis.* 44 Suppl 1: S1–26. doi:10.1086/510206. PMID 17143845.
11. ^ Honorio T. Benzon (2011). *Essentials of Pain Medicine* (3rd ed.). London: Elsevier Health Sciences. p. 358. ISBN 9781437735932.
12. ^ Zamula E (May–June 2001). "Shingles: an unwelcome encore". *FDA Consumer*. **35** (3): 21–25. PMID 11458545. Retrieved 2010-01-05. Revised June 2005.
13. ^ a b c d e Stankus SJ, Dlugopolski M, Packer D (2000). "Management of herpes zoster (shingles) and postherpetic

neuralgia". *Am. Fam. Physician*. **61** (8): 2437–2444, 2447–2448. PMID 10794584.
14. ^ [a] [b] Katz J, Cooper EM, Walther RR, Sweeney EW, Dworkin RH (2004). "Acute pain in herpes zoster and its impact on health-related quality of life". *Clin. Infect. Dis.* **39** (3): 342–348. doi:10.1086/421942. PMID 15307000.
15. ^ [a] [b] [c] [d] [e] Hope-Simpson RE (1965). "The nature of herpes zoster: a long-term study and a new hypothesis". *Proceedings of the Royal Society of Medicine*. **58** (1): 9–20. PMC 1898279. PMID 14267505.
16. ^ Furuta Y, Ohtani F, Mesuda Y, Fukuda S, Inuyama Y (2000). "Early diagnosis of zoster sine herpete and antiviral therapy for the treatment of facial palsy". *Neurology*. **55** (5): 708–710. doi:10.1212/WNL.55.5.708. PMID 10980741.
17. ^ [a] [b] Gupta, S; Sreenivasan, V; Patil, PB (2015). "Dental complications of herpes zoster: Two case reports and review of literature.". *Indian Journal of Dental Research*. **26** (2): 214–9. doi:10.4103/0970-9290.159175. PMID 26096121.
18. ^ Samaranayake L (2 September 2011). *Essential Microbiology for Dentistry* (4th ed.). Elsevier Health Sciences. pp. 638–642. ISBN 0-7020-4695-7.
19. ^ Shaikh S, Ta CN (2002). "Evaluation and management of herpes zoster ophthalmicus". *Am. Fam. Physician*. **66** (9): 1723–1730. PMID 12449270.
20. ^ [a] [b] [c] Johnson RW, Dworkin RH (2003). "Clinical review: Treatment of herpes zoster and postherpetic neuralgia". *BMJ*. **326** (7392): 748–750. doi:10.1136/bmj.326.7392.748. PMC 1125653. PMID 12676845.
21. ^ [a] [b] [c] [d] [e] Chi, AC; Damm, DD; Neville, BW; Allen, CM; Bouquot, J (11 June 2008). *Oral and Maxillofacial Pathology*. Elsevier Health Sciences. pp. 250–253. ISBN 978-1-4377-2197-3.
22. ^ [a] [b] [c] [d] [e] Glick M (1 September 2014). *Burket's oral medicine* (12th ed.). coco. pp. 62–65. ISBN 978-1-60795-188-9.
23. ^ Chai W, Ho MG-R. Disseminated varicella zoster virus encephalitis. Lancet Available online 3 July 2014(0).
24. ^ Grahn, A; Studahl, M (September 2015). "Varicella-zoster virus infections of the central nervous system - Prognosis, diagnostics and treatment.". *Journal of Infection*. **71** (3): 281–93. doi:10.1016/j.jinf.2015.06.004. PMID 26073188.
25. ^ James, William D.; Berger, Timothy G.; et al. (2006). *Andrews' Diseases of the Skin: Clinical Dermatology*. Saunders Elsevier. ISBN 0-7216-2921-0.
26. ^ [a] [b] Steiner I, Kennedy PG, Pachner AR (2007). "The neurotropic herpes viruses: herpes simplex and varicella-zoster". *Lancet Neurol.* **6** (11): 1015–1028. doi:10.1016/S1474-4422(07)70267-3. PMID 17945155.
27. ^ [a] [b] Weinberg JM (2007). "Herpes zoster: epidemiology, natural history, and common complications". *J. Am. Acad. Dermatol.* **57** (6 Suppl): S130–S135. doi:10.1016/j.jaad.2007.08.046. PMID 18021864.
28. ^ Gilden DH, Cohrs RJ, Mahalingam R (2003). "Clinical and molecular pathogenesis of varicella virus infection". *Viral Immunol.* **16** (3): 243–258. doi:10.1089/088282403322396073. PMID 14583142.
29. ^ Davison, AJ, Scott, JE (1986). "The complete DNA sequence of varicella-zoster virus". *J. Gen. Virol.* **67**: 1759–1816. doi:10.1099/0022-1317-67-9-1759. PMID 3018124.
30. ^ Kennedy PG (2002). "Varicella-zoster virus latency in human ganglia". *Rev. Med. Virol.* **12** (5): 327–334. doi:10.1002/rmv.362. PMID 12211045.
31. ^ Kennedy PG (2002). "Key issues in varicella-zoster virus latency". *J. Neurovirol.* 8 Suppl 2 (2): 80–84. doi:10.1080/13550280290101058. PMID 12491156.
32. ^ Mitchell BM, Bloom DC, Cohrs RJ, Gilden DH, Kennedy PG (2003). "Herpes simplex virus-1 and varicella-zoster virus latency in ganglia" (PDF). *J. Neurovirol.* **9** (2): 194–204. doi:10.1080/13550280390194000. PMID 12707850.
33. ^ Donahue JG, Choo PW, Manson JE, Platt R (1995). "The incidence of herpes zoster". *Archives of Internal Medicine*. **155** (15): 1605–1609. doi:10.1001/archinte.155.15.1605. PMID 7618983.
34. ^ [a] [b] [c] Thomas SL, Hall AJ (2004). "What does epidemiology tell us about risk factors for herpes zoster?". *Lancet Infect. Dis.* **4** (1): 26–33. doi:10.1016/S1473-3099(03)00857-0. PMID 14720565.
35. ^ Schmader K (2007). "Herpes zoster and postherpetic neuralgia in older adults". *Clin. Geriatr. Med.* **23** (3): 615–632, vii–viii. doi:10.1016/j.cger.2007.03.003. PMID 17631237.
36. ^ Koh, MJ; Seah PP; Teo RY (Feb 2008). "Zosteriform herpes simplex" (PDF). *Singapore Med. J.* **49** (2): e59–60. PMID 18301829.
37. ^ Kalman, CM; Laskin OL (Nov 1986). "Herpes zoster and zosteriform herpes simplex virus infections in immunocompetent adults". *Am. J. Med.* **81** (5): 775–8. doi:10.1016/0002-9343(86)90343-8. PMID 3022586.
38. ^ Oranje AP, Folkers E (1988). "The Tzanck smear: old, but still of inestimable value". *Pediatr. Dermatol.* **5** (2): 127–129. doi:10.1111/j.1525-1470.1988.tb01154.x. PMID 2842739.
39. ^ Chan J, Bergstrom RT, Lanza DC, Oas JG (2004). "Lateral sinus thrombosis associated with zoster sine herpete". *Am. J. Otolaryngol.* **25** (5): 357–360. doi:10.1016/j.amjoto.2004.03.007. PMID 15334402.
40. ^ Arvin AM (1996). "Varicella-zoster virus" (PDF). *Clin. Microbiol. Rev.* **9** (3): 361–381. PMC 172899. PMID 8809466.
41. ^ Beards G, Graham C, Pillay D (1998). "Investigation of vesicular rashes for HSV and VZV by PCR". *J. Med. Virol.* **54** (3): 155–157. doi:10.1002/(SICI)1096-9071(199803)54:3<155::AID-JMV1>3.0.CO;2-4. PMID 9515761.
42. ^ De Paschale M, Clerici P (2016). "Microbiology laboratory and the management of mother-child varicella-zoster virus infection.". *World J Virol* (Review). **5** (3): 97–124. doi:10.5501/wjv.v5.i3.97. PMC 4981827. PMID 27563537.
43. ^ Sampathkumar P, Drage LA, Martin DP (2009). "Herpes zoster (shingles) and postherpetic neuralgia". *Mayo Clin Proc* (Review). **84** (3): 274–80. doi:10.1016/S0025-6196(11)61146-4. PMC 2664599. PMID 19252116.

44. ^ [a b] Harpaz R, Ortega-Sanchez IR, Seward JF (June 6, 2008). "Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP)". *MMWR Recomm. Rep.* **57** (RR–5): 1–30; quiz CE2–4. PMID 18528318. Retrieved 2010-01-04.
45. ^ [a b c d e f] Shapiro M, Kvern B, Watson P, Guenther L, McElhaney J, McGeer A (October 2011). "Update on herpes zoster vaccination: a family practitioner's guide". *Can. Fam. Physician*. **57** (10): 1127–31. PMC 3192074. PMID 21998225.
46. ^ Kathleen M. Neuzil and Marie R. Griffin (September 15, 2016). "Preventing Shingles and Its Complications in Older Persons". *N Engl J Med*. **375** (11): 1079–1080. doi:10.1056/NEJMe1610652. [Free]
47. ^ Pellissier JM, Brisson M, Levin MJ (2007). "Evaluation of the cost-effectiveness in the United States of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults". *Vaccine*. **25** (49): 8326–8337. doi:10.1016/j.vaccine.2007.09.066. PMID 17980938.
48. ^ Advisory Committee on Immunization Practices (20 November 2007). "Recommended adult immunization schedule: United States, October 2007 – September 2008". *Annals of Internal Medicine*. **147** (10): 725–729. doi:10.7326/0003-4819-147-10-200711200-00187. PMID 17947396.
49. ^ Gilden D (February 2011). "Efficacy of live zoster vaccine in preventing zoster and postherpetic neuralgia". *Journal of Internal Medicine*. **269** (5): 496–506. doi:10.1111/j.1365-2796.2011.02359.x. PMC 3083261. PMID 21294791.
50. ^ Cunningham, AL; Breuer, J; Dwyer, DE; Gronow, DW; Helme, RD; Litt, JC; Levin, MJ; Macintyre, CR (4 February 2008). "The prevention and management of herpes zoster.". *Medical Journal of Australia*. **188** (3): 171–6. PMID 18241179.
51. ^ Brisson M, Gay N, Edmunds W, Andrews N (2002). "Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox". *Vaccine*. **20** (19–20): 2500–2507. doi:10.1016/S0264-410X(02)00180-9. PMID 12057605.
52. ^ NHS Direct (2008-02-07). "Why isn't the chickenpox vaccine available in the UK?". Archived from the original on 2008-04-23. Retrieved 2008-03-22.
53. ^ Health Protection Agency (2006-05-11). "Chickenpox / Varicella — General Information". Retrieved 2008-03-22.
54. ^ "Shingles vaccination—Vaccinations—NHS Choices". Retrieved 2014-05-31.
55. ^ "Who can have the shingles vaccine?—Vaccinations—NHS Choices". Retrieved 2014-05-31.
56. ^ [a b c] Tyring SK (2007). "Management of herpes zoster and postherpetic neuralgia". *J. Am. Acad. Dermatol.* **57** (6 Suppl): S136–S142. doi:10.1016/j.jaad.2007.09.016. PMID 18021865.
57. ^ Sigurdur Helgason; et al. (2000). "Prevalence of postherpetic neuralgia after a single episode of herpes zoster: prospective study with long term follow up" (PDF). *British Medical Journal*. **321** (7264): 794–796. doi:10.1136/bmj.321.7264.794. PMC 27491. PMID 11009518.
58. ^ Baron R (2004). "Post-herpetic neuralgia case study: optimizing pain control". *Eur. J. Neurol.* 11 Suppl 1: 3–11. doi:10.1111/j.1471-0552.2004.00794.x. PMID 15061819.
59. ^ Bader, MS (Sep 2013). "Herpes zoster: diagnostic, therapeutic, and preventive approaches.". *Postgraduate Medicine*. **125** (5): 78–91. doi:10.3810/pgm.2013.09.2703. PMID 24113666.
60. ^ Chen N, Li Q, Yang J, et al. (2014). He L, ed. "Antiviral treatment for preventing postherpetic neuralgia". *Cochrane Database of Systematic Reviews*. **2** (2): CD006866. doi:10.1002/14651858.CD006866.pub3. PMID 24500927.
61. ^ Han, Y; Zhang, J; Chen, N; He, L; Zhou, M; Zhu, C (Mar 28, 2013). "Corticosteroids for preventing postherpetic neuralgia". *Cochrane Database of Systematic Reviews*. **3** (3): CD005582. doi:10.1002/14651858.CD005582.pub4. PMID 23543541.
62. ^ Uscategui, T; Doree, C; Chamberlain, IJ; Burton, MJ (Jul 16, 2008). "Corticosteroids as adjuvant to antiviral treatment in Ramsay Hunt syndrome (herpes zoster oticus with facial palsy) in adults.". *Cochrane Database of Systematic Reviews* (3): CD006852. doi:10.1002/14651858.CD006852.pub2. PMID 18646170.
63. ^ Colin J, Prisant O, Cochener B, Lescale O, Rolland B, Hoang-Xuan T (2000). "Comparison of the Efficacy and Safety of Valaciclovir and Acyclovir for the Treatment of Herpes zoster Ophthalmicus". *Ophthalmology*. **107** (8): 1507–1511. doi:10.1016/S0161-6420(00)00222-0. PMID 10919899.
64. ^ Osterberg L, Blaschke T (2005). "Adherence to medication". *New England Journal of Medicine*. **353** (5): 487–497. doi:10.1056/NEJMra050100. PMID 16079372.
65. ^ Paryani SG, Arvin AM (1986). "Intrauterine infection with varicella-zoster virus after maternal varicella". *New England Journal of Medicine*. **314** (24): 1542–1546. doi:10.1056/NEJM198606123142403. PMID 3012334.
66. ^ Enders G, Miller E, Cradock-Watson J, Bolley I, Ridehalgh M (1994). "Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases". *The Lancet*. **343** (8912): 1548–1551. doi:10.1016/S0140-6736(94)92943-2. PMID 7802767.
67. ^ Sørensen HT, Olsen JH, Jepsen P, Johnsen SP, Schønheyder HC, Mellemkjaer L (2004). "The risk and prognosis of cancer after hospitalisation for herpes zoster: a population-based follow-up study". *Br. J. Cancer*. **91** (7): 1275–1279. doi:10.1038/sj.bjc.6602120. PMC 2409892. PMID 15328522.
68. ^ Ragozzino MW, Melton LJ, Kurland LT, Chu CP, Perry HO (1982). "Risk of cancer after herpes zoster: a population-based study". *New England Journal of Medicine*. **307** (7): 393–397. doi:10.1056/NEJM198208123070701. PMID 6979711.
69. ^ Roat MI (September 2014). "Herpes Zoster Ophthalmicus". *Merck Manual*. Retrieved 14 August 2016.
70. ^ Apisarnthanarak A, Kitphati R, Tawatsupha P, Thongphubeth K, Apisarnthanarak P, Mundy LM (2007). "Outbreak of varicella-zoster virus infection among Thai healthcare workers". *Infect. Control Hosp. Epidemiol.* **28** (4): 430–434.

doi:10.1086/512639. PMID 17385149.
71. ^ a b Araújo LQ, Macintyre CR, Vujacich C (2007). "Epidemiology and burden of herpes zoster and post-herpetic neuralgia in Australia, Asia and South America" (PDF). *Herpes*. **14** (Suppl 2): 40A–44A. PMID 17939895.
72. ^ Brisson M, Edmunds WJ, Law B, et al. (2001). "Epidemiology of varicella zoster virus infection in Canada and the United Kingdom". *Epidemiol. Infect.* **127** (2): 305–314. doi:10.1017/S0950268801005921. PMC 2869750. PMID 11693508.
73. ^ Insinga RP, Itzler RF, Pellissier JM, Saddier P, Nikas AA (2005). "The incidence of herpes zoster in a United States administrative database". *J. Gen. Intern. Med.* **20** (8): 748–753. doi:10.1111/j.1525-1497.2005.0150.x. PMC 1490195. PMID 16050886.
74. ^ Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS (2007). "A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction". *Mayo Clin. Proc.* **82** (11): 1341–1349. doi:10.4065/82.11.1341. PMID 17976353.
75. ^ de Melker H, Berbers G, Hahné S, et al. (2006). "The epidemiology of varicella and herpes zoster in The Netherlands: implications for varicella zoster virus vaccination". *Vaccine*. **24** (18): 3946–3952. doi:10.1016/j.vaccine.2006.02.017. PMID 16564115.
76. ^ Colebunders R, Mann JM, Francis H, et al. (1988). "Herpes zoster in African patients: a clinical predictor of human immunodeficiency virus infection". *J. Infect. Dis.* **157** (2): 314–318. doi:10.1093/infdis/157.2.314. PMID 3335810.
77. ^ Buchbinder SP, Katz MH, Hessol NA, et al. (1992). "Herpes zoster and human immunodeficiency virus infection". *J. Infect. Dis.* **166** (5): 1153–1156. doi:10.1093/infdis/166.5.1153. PMID 1308664.
78. ^ Livengood JM (2000). "The role of stress in the development of herpes zoster and postherpetic neuralgia". *Curr. Rev. Pain*. **4** (1): 7–11. doi:10.1007/s11916-000-0003-9. PMID 10998709.
79. ^ a b c d Gatti A, Pica F, Boccia MT, De Antoni F, Sabato AF, Volpi A (2010). "No evidence of family history as a risk factor for herpes zoster in patients with post-herpetic neuralgia". *J. Med. Virol.* **82** (6): 1007–1011. doi:10.1002/jmv.21748. PMID 20419815.
80. ^ Schmader K, George LK, Burchett BM, Pieper CF (1998). "Racial and psychosocial risk factors for herpes zoster in the elderly". *J. Infect. Dis.* **178** (Suppl 1): S67–S70. doi:10.1086/514254. PMID 9852978.
81. ^ Schmader K, George LK, Burchett BM, Hamilton JD, Pieper CF (1998). "Race and stress in the incidence of herpes zoster in older adults". *J. Am. Geriatr. Soc.* **46** (8): 973–977. doi:10.1111/j.1532-5415.1998.tb02751.x. PMID 9706885.
82. ^ Hicks LD, Cook-Norris RH, Mendoza N, Madkan V, Arora A, Tyring SK (May 2008). "Family history as a risk factor for herpes zoster: a case-control study". *Arch. Dermatol.* **144** (5): 603–608. doi:10.1001/archderm.144.5.603. PMID 18490586.
83. ^ Marin M, Güris D, Chaves SS, Schmid S, Seward JF (June 22, 2007). "Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP)". *MMWR Recomm. Rep.* **56** (RR–4): 1–40. PMID 17585291.
84. ^ Jumaan AO, Yu O, Jackson LA, Bohlke K, Galil K, Seward JF (2005). "Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992–2002". *J. Infect. Dis.* **191** (12): 2002–2007. doi:10.1086/430325. PMID 15897984.
85. ^ Whitley RJ (2005). "Changing dynamics of varicella-zoster virus infections in the 21st century: the impact of vaccination". *J. Infect. Dis.* **191** (12): 1999–2001. doi:10.1086/430328. PMID 15897983.
86. ^ Patel MS, Gebremariam A, Davis MM (December 2008). "Herpes zoster-related hospitalizations and expenditures before and after introduction of the varicella vaccine in the United States". *Infect. Control Hosp. Epidemiol.* **29** (12): 1157–63. doi:10.1086/591975. PMID 18999945.
87. ^ Yih WK, Brooks DR, Lett SM, Jumaan AO, Zhang Z, Clements KM, Seward JF (2005). "The incidence of varicella and herpes zoster in Massachusetts as measured by the Behavioral Risk Factor Surveillance System (BRFSS) during a period of increasing varicella vaccine coverage, 1998–2003". *BMC Public Health*. **5**: 68. doi:10.1186/1471-2458-5-68. PMC 1177968. PMID 15960856.
88. ^ Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS (2007). "A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction". *Mayo Clin. Proc.* **82** (11): 1341–1349. doi:10.4065/82.11.1341. PMID 17976353.
89. ^ Volpi A (2007). "Severe complications of herpes zoster" (PDF). *Herpes*. **14** (Suppl 2): 35A–39A. PMID 17939894.
90. ^ Coplan P, Black S, Rojas C, et al. (2001). "Incidence and hospitalization rates of varicella and herpes zoster before varicella vaccine introduction: a baseline assessment of the shifting epidemiology of varicella disease". *Pediatr. Infect. Dis. J.* **20** (7): 641–645. doi:10.1097/00006454-200107000-00002. PMID 11465834.
91. ^ Weaver BA (1 March 2007). "The burden of herpes zoster and postherpetic neuralgia in the United States". *J. Am. Osteopath. Assoc.* **107** (3 Suppl): S2–57. PMID 17488884.
92. ^ Weller TH (2000). "Chapter 1. Historical perspective". In Arvin AM, Gershon AA. *Varicella-Zoster Virus: Virology and Clinical Management*. Cambridge University Press. ISBN 0-521-66024-6.
93. ^ Oaklander AL (October 1999). "The pathology of shingles: Head and Campbell's 1900 monograph". *Arch. Neurol.* **56** (10): 1292–1294. doi:10.1001/archneur.56.10.1292. PMID 10520948.
94. ^ Weller TH (1953). "Serial propagation in vitro of agents producing inclusion bodies derived from varicella and herpes zoster". *Proc. Soc. Exp. Biol. Med.* **83** (2): 340–346. doi:10.3181/00379727-83-20354. PMID 13064265.
95. ^ Holt LE, McIntosh R (1936). *Holt's Diseases of Infancy and Childhood*. D Appleton Century Company. pp. 931–933.

96. ^ Weller TH (1997). "Varicella-herpes zoster virus". In Evans AS, Kaslow RA. *Viral Infections of Humans: Epidemiology and Control*. Plenum Press. pp. 865–892. ISBN 978-0-306-44855-3.
97. ^ Hope-Simpson RE (1965). "The nature of herpes zoster; a long-term study and a new hypothesis". *Proceedings of the Royal Society of Medicine*. **58** (1): 9–20. PMC 1898279. PMID 14267505.
98. ^ Thomas SL, Wheeler JG, Hall AJ (2002). "Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study". *The Lancet*. **360** (9334): 678–682. doi:10.1016/S0140-6736(02)09837-9. PMID 12241874.
99. ^ Terada K, Hiraga Y, Kawano S, Kataoka N (1995). "Incidence of herpes zoster in pediatricians and history of reexposure to varicella-zoster virus in patients with herpes zoster". *Kansenshogaku Zasshi*. **69** (8): 908–912. PMID 7594784.
100. ^ "Herpes | Define Herpes at Dictionary.com". Retrieved 2011-03-14.
101. ^ "Online Etymology Dictionary". Retrieved 2011-03-14.
102. ^ "Online Etymology Dictionary". Retrieved 2011-03-14.
103. ^ Yawn, BP; Gilden, D (3 September 2013). "The global epidemiology of herpes zoster.". *Neurology*. **81** (10): 928–30. doi:10.1212/wnl.0b013e3182a3516e. PMID 23999562.
104. ^ "Helvetesild (Herpes zoster)". helsenorge.no. Retrieved 22 December 2016.
105. ^ *a b c d* Becerra, Juan Carlos Lozano; Sieber, Robert; Martinetti, Gladys; Costa, Silvia Tschuor; Meylan, Pascal; Bernasconi, Enos (July 2013). "Infection of the central nervous system caused by varicella zoster virus reactivation: a retrospective case series study". *International Journal of Infectious Diseases*. **17** (7): e529–e534. doi:10.1016/j.ijid.2013.01.031. PMID 23566589.
106. ^ "Clinical Features of Viral Meningitis in Adults: Significant Differences in Cerebrospinal Fluid Findings among Herpes Simplex Virus, Varicella Zoster Virus, and Enterovirus Infections" (PDF). Clinical Infectious Diseases, the Infectious Diseases Society of America. 2008.
107. ^ *a b c* Pollak, L; Dovrat, S; Book, M; Mendelson, E; Weinberger, M (August 2011). "Varicella zoster vs. herpes simplex meningoencephalitis in the PCR era. A single center study". *Journal of the Neurological Sciences*. **314** (1–2): 29–36. doi:10.1016/j.jns.2011.11.004. PMID 22138027.
108. ^ "Recurrent Herpes Simplex Virus Type 2 Meningitis: A Case Report of Mollaret's Meningitis" (PDF). Jpn. J. Infect. Dis. July 2002.


## External links [edit]

- NINDS Shingles Information Page, National Institute of Neurological Disorders and Stroke
- Shingles at DMOZ
- Links to pictures of Shingles (Hardin MD) University of Iowa
- Facts About The Cornea and Corneal Disease: Herpes Zoster (Shingles), National Eye Institute

Wikimedia Commons has media related to *Herpes zoster*.

*Viruses portal*

| v · t · e · | Diseases of the skin and appendages by morphology | |
|---|---|---|
| **Growths** | **Epidermal** | wart · callus · seborrheic keratosis · acrochordon · molluscum contagiosum · actinic keratosis · squamous-cell carcinoma · basal-cell carcinoma · Merkel-cell carcinoma · nevus sebaceous · trichoepithelioma · |
| | **Pigmented** | Freckles · lentigo · melasma · nevus · melanoma · |
| | **Dermal and subcutaneous** | epidermal inclusion cyst · hemangioma · dermatofibroma (benign fibrous histiocytoma) · keloid · lipoma · neurofibroma · xanthoma · Kaposi's sarcoma · infantile digital fibromatosis · granular cell tumor · leiomyoma · lymphangioma circumscriptum · myxoid cyst · |
| | **Eczematous** | contact dermatitis · atopic dermatitis · seborrheic dermatitis · stasis dermatitis · lichen simplex chronicus · Darier's disease · glucagonoma syndrome · langerhans cell histiocytosis · lichen sclerosus · pemphigus foliaceus · Wiskott–Aldrich syndrome · Zinc deficiency · |
| | **Scaling** | psoriasis · tinea (corporis · cruris · pedis · manuum · faciei) · pityriasis rosea · secondary syphilis · mycosis fungoides · |

| | | | | | |
|---|---|---|---|---|---|
| **Rashes** | **With epidermal involvement** | | | | systemic lupus erythematosus · pityriasis rubra pilaris · parapsoriasis · ichthyosis · |
| | | **Blistering** | | | herpes simplex · herpes zoster · varicella · bullous impetigo · acute contact dermatitis · pemphigus vulgaris · bullous pemphigoid · dermatitis herpetiformis · porphyria cutanea tarda · epidermolysis bullosa simplex · |
| | | **Papular** | | | scabies · insect bite reactions · lichen planus · miliaria · keratosis pilaris · lichen spinulosus · transient acantholytic dermatosis · lichen nitidus · pityriasis lichenoides et varioliformis acuta · |
| | | **Pustular** | | | acne vulgaris · acne rosacea · folliculitis · impetigo · candidiasis · gonococcemia · dermatophyte · coccidioidomycosis · subcorneal pustular dermatosis · |
| | | **Hypopigmented** | | | tinea versicolor · vitiligo · pityriasis alba · postinflammatory hyperpigmentation · tuberous sclerosis · idiopathic guttate hypomelanosis · leprosy · hypopigmented mycosis fungoides · |
| | **Without epidermal involvement** | **Red** | **Blanchable Erythema** | **Generalized** | drug eruptions · viral exanthems · toxic erythema · systemic lupus erythematosus · |
| | | | | **Localized** | cellulitis · abscess · boil · erythema nodosum · carcinoid syndrome · fixed drug eruption · |
| | | | | **Specialized** | urticaria · erythema (multiforme · migrans · gyratum repens · annulare centrifugum · ab igne) · |
| | | | **Nonblanchable Purpura** | **Macular** | thrombocytopenic purpura · actinic/solar purpura · |
| | | | | **Papular** | disseminated intravascular coagulation · vasculitis · |
| | | **Indurated** | | | scleroderma/morphea · granuloma annulare · lichen sclerosis et atrophicus · necrobiosis lipoidica · |
| **Miscellaneous disorders** | **Ulcers** | | | | |
| | **Hair** | | | | telogen effluvium · androgenic alopecia · trichotillomania · alopecia areata · systemic lupus erythematosus · tinea capitis · loose anagen syndrome · lichen planopilaris · folliculitis decalvans · acne keloidalis nuchae · |
| | **Nail** | | | | onychomycosis · psoriasis · paronychia · ingrown nail · |
| | **Mucous membrane** | | | | Aphthous stomatitis · oral candidiasis · lichen planus · leukoplakia · pemphigus vulgaris · mucous membrane pemphigoid · cicatricial pemphigoid · herpesvirus · coxsackievirus · syphilis · systemic histoplasmosis · squamous-cell carcinoma · |

| v · t · e · | **Infectious skin disease: Viral cutaneous conditions, including viral exanthema (B00–B09, 050–059)** | | | |
|---|---|---|---|---|
| | | | | Herpes simplex · Herpetic whitlow · Herpes gladiatorum |

| | | | | |
|---|---|---|---|---|
| **DNA virus** | **Herpesviridae** | **Alpha** | *HSV* | · Herpetic keratoconjunctivitis · Herpetic sycosis · Neonatal herpes simplex · Herpes genitalis · Herpes labialis · Eczema herpeticum · Herpetiform esophagitis · |
| | | | *Herpes B virus* | B virus infection · |
| | | | *VZV* | Chickenpox · Herpes zoster · Herpes zoster oticus · Ophthalmic zoster · Disseminated herpes zoster · Zoster-associated pain · Modified varicella-like syndrome · |
| | | **Beta** | *Human herpesvirus 6*/*Roseolovirus* (Exanthema subitum · Roseola vaccinia · · Cytomegalic inclusion disease · | |
| | | **Gamma** | *KSHV* (Kaposi's sarcoma · · | |
| | **Poxviridae** | **Ortho** | *Variola* (Smallpox · Alastrim · · *MoxV* (Monkeypox · · *CPXV* (Cowpox · · *VV* (Vaccinia · Generalized vaccinia · Eczema vaccinatum · Progressive vaccinia · · Buffalopox · | |
| | | **Para** | Farmyard pox: Milker's nodule · Bovine papular stomatitis · Pseudocowpox · Orf · Sealpox · | |
| | | **Other** | Yatapoxvirus: Tanapox · Yaba monkey tumor virus · *MCV* (Molluscum contagiosum · · | |
| | **Papillomaviridae** | *HPV* | Wart/plantar wart · Heck's disease · Genital wart (giant · · Laryngeal papillomatosis · Butcher's wart · Bowenoid papulosis · Epidermodysplasia verruciformis · Verruca plana · Pigmented wart · Verrucae palmares et plantares · | |
| | | *BPV* (Equine sarcoid · · | | |
| | **Parvoviridae** | *Parvovirus B19* (Erythema infectiosum · Reticulocytopenia · Papular purpuric gloves and socks syndrome · · | | |
| | **Polyomaviridae** | *Merkel cell polyomavirus* (Merkel cell carcinoma · · | | |
| **RNA virus** | **Paramyxoviridae** | *MeV* (Measles · · | | |
| | **Togaviridae** | *Rubella virus* (Rubella · Congenital rubella syndrome · · Alphavirus infection · Chikungunya fever · | | |
| | **Picornaviridae** | *CAV* (Hand, foot and mouth disease · Herpangina · · *FMDV* (Foot-and-mouth disease · · Boston exanthem disease · | | |
| **Ungrouped** | Asymmetric periflexural exanthem of childhood · Post-vaccination follicular eruption · Lipschütz ulcer · Eruptive pseudoangiomatosis · Viral-associated trichodysplasia · Gianotti–Crosti syndrome · | | | |

| v · t · e · | **Varicella zoster** |
|---|---|
| **Varicella zoster virus** | Varicellovirus · |
| **Diseases** | Chickenpox · Herpes zoster · Postherpetic neuralgia · Ramsay Hunt syndrome type II · Disseminated herpes zoster · Progressive outer retinal necrosis · Ophthalmic zoster · |
| **Treatment** | Aciclovir · Vidarabine · VZV immune globulin · |
| **Prevention** | Varicella vaccine · Zoster vaccine · Pox party · |
| **Other** | Michiaki Takahashi · |

| v · t · e · | **Oral and maxillofacial pathology (K00–K06, K11–K14, 520–525, 527–529)** |
|---|---|

**Lips**

Cheilitis (Actinic · Angular · Plasma cell · · Cleft lip · Congenital lip pit · Eclabium · Herpes labialis · Macrocheilia · Microcheilia · Nasolabial cyst · Sun poisoning · Trumpeter's wart ·

**Tongue**

Ankyloglossia · Black hairy tongue · Caviar tongue · Crenated tongue · Cunnilingus tongue · Fissured tongue · Foliate papillitis · Glossitis (Geographic tongue · Median rhomboid glossitis · Transient lingual papillitis · · Glossoptosis · Hypoglossia · Lingual thyroid · Macroglossia · Microglossia · Rhabdomyoma ·

**Palate**

Bednar's aphthae · Cleft palate · High-arched palate · Palatal cysts of the newborn · Inflammatory papillary hyperplasia · Stomatitis nicotina · Torus palatinus ·

**Oral mucosa** - *Lining of mouth*

Amalgam tattoo · Angina bullosa haemorrhagica · Behçet syndrome · Bohn's nodules · Burning mouth syndrome · Candidiasis · Condyloma acuminatum · Darier's disease · Epulis fissuratum · Erythema multiforme · Erythroplakia · Fibroma (Giant-cell · · Focal epithelial hyperplasia · Fordyce spots · Hairy leukoplakia · Hand, foot and mouth disease · Hereditary benign intraepithelial dyskeratosis · Herpangina · Herpes zoster · Intraoral dental sinus · Leukoedema · Leukoplakia · Lichen planus · Linea alba · Lupus erythematosus · Melanocytic nevus · Melanocytic oral lesion · Molluscum contagiosum · Morsicatio buccarum · Oral cancer (*Benign:* Squamous cell papilloma · Keratoacanthoma · *Malignant:* Adenosquamous carcinoma · Basaloid squamous carcinoma · Mucosal melanoma · Spindle cell carcinoma · Squamous cell carcinoma · Verrucous carcinoma · · Oral florid papillomatosis · Oral melanosis (Smoker's melanosis · · Pemphigoid (Benign mucous membrane · · Pemphigus · Plasmoacanthoma · Stomatitis (Aphthous · Denture-related · Herpetic · · Smokeless tobacco keratosis · Submucous fibrosis · Ulceration · Verruca vulgaris · Verruciform xanthoma · White sponge nevus ·

**Teeth (pulp, dentin, enamel)**

Amelogenesis imperfecta · Ankylosis · Anodontia · Caries (Early childhood caries · · Concrescence · Failure of eruption of teeth · Dens evaginatus (Talon cusp · · Dentin dysplasia · Dentin hypersensitivity · Dentinogenesis imperfecta · Dilaceration · Discoloration · Ectopic enamel · Enamel hypocalcification · Enamel hypoplasia (Turner's hypoplasia · · Enamel pearl · Fluorosis · Fusion · Gemination · Hyperdontia · Hypodontia (Maxillary lateral incisor agenesis · · Impaction (Wisdom tooth impaction · · Macrodontia · Meth mouth · Microdontia · Odontogenic tumors (Keratocystic odontogenic tumour · · Odontoma (Dens in dente · · Open contact · Premature eruption (Neonatal teeth · · Pulp calcification (Pulp stone · · Pulp canal obliteration · Pulp necrosis · Pulp polyp · Pulpitis · Regional odontodysplasia · Resorption · Shovel-shaped incisors · Supernumerary root · Taurodontism · Trauma (Avulsion · Cracked tooth syndrome · Vertical root fracture · Occlusal · · Tooth loss (Edentulism · · Tooth wear (Abrasion · Abfraction · Acid erosion · Attrition · ·

**Periodontium (gingiva, periodontal ligament, cementum, alveolus)** - *Gums and tooth-supporting structures*

Cementicle · Cementoblastoma (Gigantiform · · Cementoma · Eruption cyst · Epulis (Pyogenic granuloma · Congenital epulis · · Gingival enlargement · Gingival cyst of the adult · Gingival cyst of the newborn · Gingivitis (Desquamative · Granulomatous · Plasma cell · · Hereditary gingival fibromatosis · Hypercementosis · Hypocementosis · Linear gingival erythema · Necrotizing periodontal diseases (Acute necrotizing ulcerative gingivitis · · Pericoronitis · Peri-implantitis · Periodontal abscess · Periodontal trauma · Periodontitis (Aggressive · As a manifestation of systemic disease · Chronic · · Perio-endo lesion · Teething ·

**Periapaical, mandibular and maxillary hard tissues** - *Bones of jaws*

Agnathia · Alveolar osteitis · Buccal exostosis · Cherubism · Idiopathic osteosclerosis · Mandibular fracture · Microgenia · Micrognathia · Intraosseous cysts (*Odontogenic:* periapical · Dentigerous · Buccal bifurcation · Lateral periodontal · Globulomaxillary · Calcifying odontogenic · Glandular odontogenic · *Non-odontogenic:* Nasopalatine duct · Median mandibular ·

Median palatal · Traumatic bone · · Osteoma · Osteomyelitis · Osteonecrosis (Bisphosphonate-associated · Neuralgia-inducing cavitational osteonecrosis · Osteoradionecrosis · · Osteoporotic bone marrow defect · Paget's disease of bone · Periapical abscess (Phoenix abscess · · Periapical periodontitis · Stafne defect · Torus mandibularis ·

**Temporomandibular joints, muscles of mastication and malocclusions -** *Jaw joints, chewing muscles and bite abnormalities*

Bruxism · Condylar resorption · Mandibular dislocation · Malocclusion (Crossbite · Open bite · Overbite · Overjet · Prognathia · Retrognathia · · Temporomandibular joint dysfunction ·

**Salivary glands**

Benign lymphoepithelial lesion · Ectopic salivary gland tissue · Frey's syndrome · HIV salivary gland disease · Necrotizing sialometaplasia · Mucocele (Ranula · · Pneumoparotitis · Salivary duct stricture · Salivary gland aplasia · Salivary gland atresia · Salivary gland diverticulum · Salivary gland fistula · Salivary gland hyperplasia · Salivary gland hypoplasia · Salivary gland neoplasms (*Benign:* Basal cell adenoma · Canalicular adenoma · Ductal papilloma · Monomorphic adenoma · Myoepithelioma · Oncocytoma · Papillary cystadenoma lymphomatosum · Pleomorphic adenoma · Sebaceous adenoma · *Malignant:* Acinic cell carcinoma · Adenocarcinoma · Adenoid cystic carcinoma · Carcinoma ex pleomorphic adenoma · Lymphoma · Mucoepidermoid carcinoma · · Sclerosing polycystic adenosis · Sialadenitis (Parotitis · Chronic sclerosing sialadenitis · · Sialectasis · Sialocele · Sialodochitis · Sialosis · Sialolithiasis · Sjögren's syndrome ·

**Orofacial soft tissues -** *Soft tissues around the mouth*

Actinomycosis · Angioedema · Basal cell carcinoma · Cutaneous sinus of dental origin · Cystic hygroma · Gnathophyma · Ludwig's angina · Macrostomia · Melkersson–Rosenthal syndrome · Microstomia · Noma · Oral Crohn's disease · Orofacial granulomatosis · Perioral dermatitis · Pyostomatitis vegetans ·

**Other**

Eagle syndrome · Hemifacial hypertrophy · Facial hemiatrophy · Oral manifestations of systemic disease ·

Categories: Chickenpox | Varicella zoster virus-associated diseases | Virus-related cutaneous conditions | Oral mucosal pathology




# Measles



From Wikipedia, the free encyclopedia

**Measles** is a highly contagious infection caused by the measles virus.[1][2] Initial signs and symptoms typically include fever, often greater than 40 °C (104.0 °F), cough, runny nose, and inflamed eyes.[1][3] Two or three days after the start of symptoms, small white spots may form inside the mouth, known as Koplik's spots. A red, flat rash which usually starts on the face and then spreads to the rest of the body typically begins three to five days after the start of symptoms.[3] Symptoms usually develop 10–12 days after exposure to an infected person and last 7–10 days.[4][5] Complications occur in about 30% and may include diarrhea, blindness, inflammation of the brain, and pneumonia among others.[4][6] Rubella (German measles) and roseola are different diseases.[7]

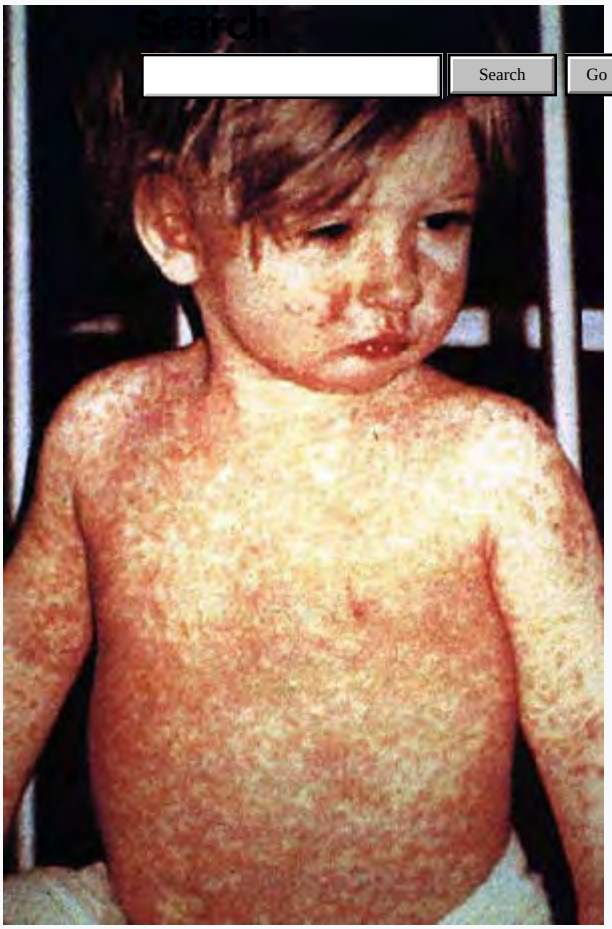
Measles is an airborne disease which spreads easily through the coughs and sneezes of those infected. It may also be spread through contact with saliva or nasal secretions.[4] Nine out of ten people who are not immune and share living space with an infected person will catch it. People are infectious to others from four days before to four days after the start of the rash.[6] People usually do not get the disease more than once.[4] Testing for the virus in suspected cases is important for public health efforts.[6]

The measles vaccine is effective at preventing the disease. Vaccination has resulted in a 75% decrease in deaths from measles between 2000 and 2013 with about 85% of children globally being currently vaccinated. No specific treatment is available. Supportive care may improve outcomes.[4] This may include giving oral rehydration solution (slightly sweet and salty fluids), healthy food, and medications to control the fever.[4][5] Antibiotics may be used if a secondary bacterial infection such as pneumonia occurs. Vitamin A supplementation is also recommended in the developing world.[4]

Measles affects about 20 million people a year,[1] primarily in the developing areas of Africa and Asia.[4] It causes the most vaccine-preventable deaths of any disease.[8] It resulted in about 96,000 deaths in 2013, down from 545,000 deaths in 1990.[9] In 1980, the disease was estimated to have caused 2.6 million deaths per year.[4] Most of those who are infected [4]

**Measles**

**Synonyms** morbilli, rubeola, red measles



A child showing a 4-day measles rash.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | B05 |
| **ICD-9-CM** | 055 |
| **DiseasesDB** | 7890 |
| **MedlinePlus** | 001569 |
| **eMedicine** | derm/259 emerg/389 ped/1388 |

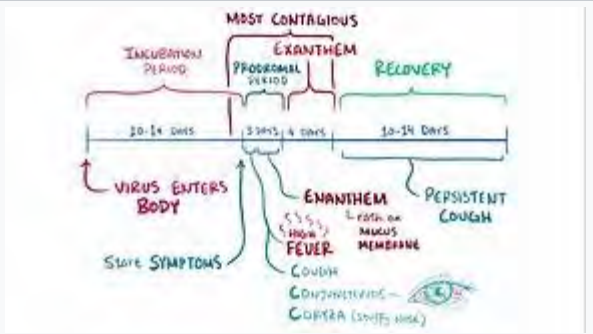
and who die are less than five years old. The risk of death among those infected is usually 0.2%,[6] but may be up to 10% in those who have malnutrition.[4] It is not believed to affect other animals.[4] Before immunization in the United States, between three and four million cases occurred each year.[7] As a result of widespread vaccination, the disease was eliminated from the Americas by 2016.[10]

| | |
|---|---|
| **Patient UK** | Measles |
| **MeSH** | D008457 |

[edit on Wikidata]

Contents



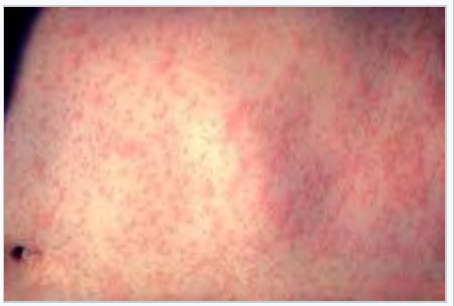



Play media

Video explanation

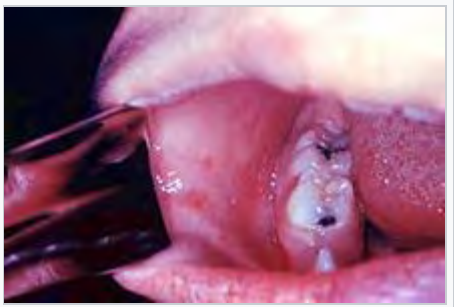
## Signs and symptoms [edit]

The classic signs and symptoms of measles include four-day fevers (the 4 D's) and the three C's — cough, coryza (head cold, fever, sneezing), and conjunctivitis (red eyes) — along with fever and rashes.[11] Fever is common and typically lasts for about one week; the fever seen with measles is often as high as 40 °C (104 °F).[12] Koplik's spots seen inside the mouth are pathognomonic (diagnostic) for measles, but are temporary and therefore rarely seen.[11] Recognizing these spots before a person reaches their maximum infectiousness can help physicians reduce the spread of the disease.[13]



Skin of a person after 3 days of measles infection

The characteristic measles rash is classically described as a generalized red maculopapular rash that begins several days after the fever starts. It starts on the back of the ears and, after a few hours, spreads to the head and neck before spreading to cover most of the body, often causing itching. The measles rash appears two to four days after the initial symptoms and lasts for up to eight days. The rash is said to "stain", changing color from red to dark brown, before disappearing.[14] Overall, the disease from infection with the measles virus usually resolves after about three weeks.[12]



"Koplik's spots" on the third pre-eruptive day

## Complications [edit]

Complications with measles are relatively common, ranging from mild complications such as diarrhea to serious complications such as pneumonia (either direct viral pneumonia or secondary bacterial pneumonia), bronchitis (either direct viral bronchitis or secondary bacterial bronchitis), otitis media,[15] acute brain inflammation[16] (and very rarely SSPE — subacute sclerosing panencephalitis),[17] and corneal ulceration (leading to corneal scarring).[18] Complications are usually

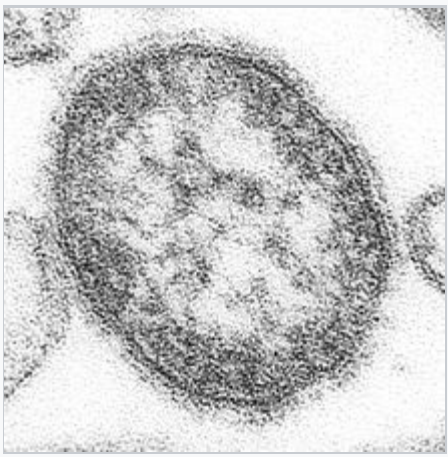
A child with measles

more severe in adults who catch the virus.[19] The death rate in the 1920s was around 30% for measles pneumonia.[20] People that are at high risk for complications are: Infants and children aged <5 years, adults aged >20 years, pregnant women, and people with compromised immune systems, such as from leukemia and HIV infection.[21]

Between 1987 and 2000, the case fatality rate across the United States was three measles-attributable deaths per 1000 cases, or 0.3%.[22] In underdeveloped nations with high rates of malnutrition and poor healthcare, fatality rates have been as high as 28%.[22] In immunocompromised persons (e.g., people with AIDS) the fatality rate is approximately 30%.[23] Risk factors for severe measles and its complications include malnutrition,[24] underlying immunodeficiency,[24] pregnancy,[24] and vitamin A deficiency.[24][25] Even in previously healthy children, measles can cause serious illness requiring hospitalization.[26] One out of every 1,000 measles cases will develop acute encephalitis, which often results in permanent brain damage.[26] One or two out of every 1,000 children who become infected with measles will die from respiratory and neurologic complications.[21]

## Cause [edit]

Measles is caused by the measles virus, a single-stranded, negative-sense, enveloped RNA virus of the genus *Morbillivirus* within the family *Paramyxoviridae*.[27] The virus was first isolated in 1954 by Nobel Laureate John F. Enders and Thomas Peebles, who were careful to point out that the isolations were made from patients who had Koplik's spots.[28] Humans are the only natural hosts of the virus, and no other animal reservoirs are known to exist. This highly contagious virus is spread by coughing and sneezing via close personal contact or direct contact with secretions. Risk factors for measles virus infection include immunodeficiency caused by HIV or AIDS,[29] immunosuppression following receipt of an organ or a stem cell transplant,[30] alkylating agents, or corticosteroid therapy, regardless of immunization status;[24] travel to areas where measles is endemic or contact with travelers to endemic areas;[24] and the loss of passive, inherited antibodies before the age of routine immunization.[31]



An electron micrograph of the measles virus.

## Diagnosis [edit]

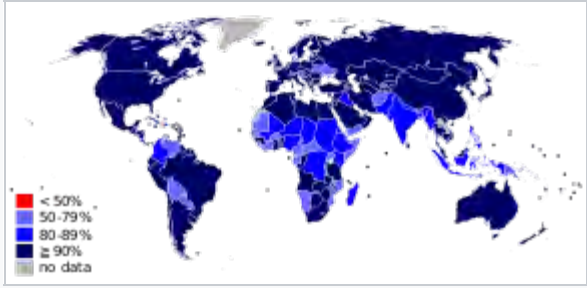
Clinical diagnosis of measles requires a history of fever of at least three days, with at least one of the three C's (cough, coryza, conjunctivitis). Observation of Koplik's spots is also diagnostic of measles.[13][32][33]

### Laboratory testing [edit]

Alternatively, laboratory diagnosis of measles can be done with confirmation of positive measles IgM antibodies or isolation of measles virus RNA from respiratory specimens.[34] For people unable to have their blood drawn, saliva can be collected for salivary measles-specific IgA testing.[35] Positive contact with other patients known to have measles adds strong epidemiological evidence to the diagnosis. Any contact with an infected person, including semen through sex, saliva, or mucus, can cause infection.[33]

## Prevention [edit]

*Further information: Measles vaccine, MMR vaccine, MMRV vaccine, and MMR vaccine controversy*



Rates of measles vaccination worldwide

In developed countries, children are immunized against measles at 12 months, generally as part of a three-part MMR vaccine (measles, mumps, and rubella). The vaccination is generally not given before this age because such infants respond inadequately to the vaccine due to an immature immune system.[31] Anti-measles antibodies are transferred from mothers who have been vaccinated against measles or have been previously infected with measles to their newborn children.[31] However, such antibodies are transferred in low amounts and usually last six months or less.[31] Infants under one year of age whose maternal anti-measles antibodies have disappeared become susceptible to infection with the measles virus.[31] A second dose of the vaccine is usually given to children between the ages of four and five, to increase rates of immunity. Vaccination rates have been high enough to make measles relatively uncommon. Adverse reactions to vaccination are rare, with fever and pain at the injection site being the most common. Life-threatening adverse reactions occur in less than one per million vaccinations (<0.0001%).[36]

In developing countries where measles is highly endemic, WHO doctors recommend two doses of vaccine be given at six and nine months of age. The vaccine should be given whether the child is HIV-infected or not.[37] The vaccine is less effective in HIV-infected infants than in the general population, but early treatment with antiretroviral drugs can increase its effectiveness.[38] Measles vaccination programs are often used to deliver other child health interventions, as well, such as bed nets to protect against malaria, antiparasite medicine and vitamin A supplements, and so contribute to the reduction of child deaths from other causes.[39]

## Treatment [edit]

There is no specific treatment for measles. Most people with uncomplicated measles will recover with rest and supportive treatment.

Patients who become sicker may be developing medical complications. Some people will develop pneumonia as a consequence of infection with the measles virus. Other complications include ear infections, bronchitis (either viral bronchitis or secondary bacterial bronchitis), and brain inflammation.[40] Brain inflammation from measles has a mortality rate of 15%. While there is no specific treatment for brain inflammation from measles, antibiotics are required for bacterial pneumonia, sinusitis, and bronchitis that can follow measles.

All other treatment addresses symptoms, with ibuprofen or paracetamol to reduce fever and pain and, if required, a fast-acting medication to dilate the airways for cough. As for aspirin, some research has suggested a correlation between children who take aspirin and the development of Reye syndrome.[41] Some research has shown aspirin may not be the only medication associated with Reye, and even antiemetics have been implicated.[42] The link between aspirin use in children and Reye syndrome development is weak at best, if not actually nonexistent.[43] Nevertheless, most health authorities still caution against the use of aspirin for any fevers in children under 16.[44][45][46][47]

The use of vitamin A during treatment is recommended by the World Health Organization to decrease the risk of blindness.[48] A systematic review of trials into its use found no significant reduction in overall mortality, but it did reduce mortality in children aged under two years.[49][50][*needs update*][51]

It is unclear if zinc supplementation in children with measles affects outcomes.[52]

## Prognosis [edit]

The majority of people survive measles, though in some cases, complications may occur. Possible consequences of measles virus infection include bronchitis, sensorineural hearing loss,[27] and — in about 1 in 10,000 to 1 in 300,000 cases[53] — panencephalitis, which is usually fatal.[54] Acute measles encephalitis is another serious risk of measles virus infection. It typically occurs two days to one week after the breakout of the measles rash and begins with very high fever, severe headache, convulsions and altered mentation. A person with measles encephalitis may become comatose, and death or brain injury may occur.[55]

## Epidemiology [edit]

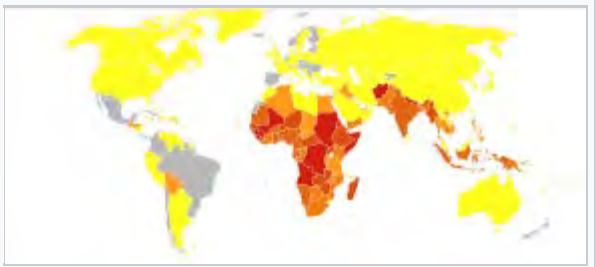
*Main article: Epidemiology of measles*

Measles is extremely infectious and its continued circulation in a community depends on the generation of susceptible hosts by birth of children. In communities which generate insufficient new hosts the disease will die out. This concept was first recognized in measles by Bartlett in 1957, who referred to the minimum number supporting measles as the critical community size (CCS).[56] Analysis of outbreaks in island communities suggested that the CCS for measles is around 250,000.[57] To achieve herd immunity, more than 95% of the community must be vaccinated due to the ease with which measles is transmitted from person to person.[12] The disease was eliminated from the Americas in 2016.[10]

In 2011, the WHO estimated that 158,000 deaths were caused by measles. This is down from 630,000 deaths in 1990.[58] As of 2013, measles remains the leading cause of vaccine-preventable deaths in the world.[8] In developed countries, death occurs in 1 to 2 cases out of every 1,000 (0.1% - 0.2%).[59] In populations with high levels of malnutrition and a lack of adequate healthcare, mortality can be as high as 10%. In cases with complications, the rate may rise to 20–30%.[60] In 2012, the number of deaths due to measles was 78% lower than in 2000 due to increased rates of immunization among UN member states.[12]

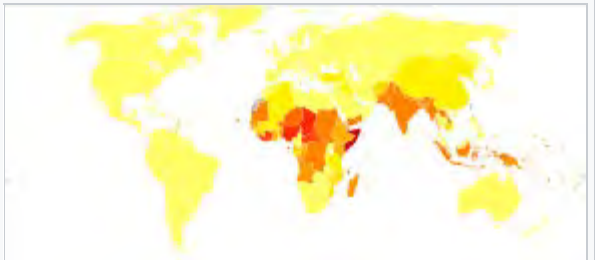
Even in countries where vaccination has been introduced, rates may remain high. Measles is a leading cause of vaccine-preventable childhood mortality. Worldwide, the fatality rate has been significantly reduced by a vaccination campaign led by partners in the Measles Initiative: the American Red Cross, the United States' Centers for Disease Control and Prevention (CDC), the United Nations Foundation, UNICEF and the WHO. Globally, measles fell 60% from an estimated 873,000 deaths in 1999 to 345,000 in 2005.[67] Estimates for 2008 indicate deaths fell further to 164,000 globally, with 77% of the remaining measles deaths in 2008 occurring within the Southeast Asian region.[68]

In 2013–14 there were almost 10,000 cases in 30 European countries. Most cases occurred



Deaths from measles per million persons in 2012

| | | |
|---|---|---|
| 0-0 | 9-26 | 39-73 |
| 1-8 | 27-38 | 74-850 |



Disability-adjusted life year for measles per 100,000 inhabitants in 2004.

| | |
|---|---|
| no data | 100–250 |
| ≤ 10 | 250–500 |
| 10–25 | 500–750 |
| 25–50 | 750–1000 |
| 50–75 | 1000–1500 |
| 75–100 | 1500–2000 |
| | ≥ 2000 |

**Reported cases**[61][62][63][64][65][66]

| WHO-Region | 1980 | 1990 | 2000 | 2005 | 2014 |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| African Region | 1,240,993 | 481,204 | 520,102 | 316,224 | 71,574 |
| Region of the Americas | 257,790 | 218,579 | 1,755 | 66 | 19,898 |
| Eastern Mediterranean Region | 341,624 | 59,058 | 38,592 | 15,069 | 28,031 |
| European Region | 851,849 | 234,827 | 37,421 | 37,332 | 16,899 |
| South-East Asia Region | 199,535 | 224,925 | 61,975 | 83,627 | 112,418 |
| Western Pacific Region | 1,319,640 | 155,490 | 176,493 | 128,016 | 213,366 |
| Worldwide | 4,211,431 | 1,374,083 | 836,338 | 580,287 | 462,186 |

in unvaccinated individuals and over 90% of cases occurred in the five European nations: Germany, Italy, the Netherlands, Romania, and the United Kingdom.[12] In the Vietnamese measles epidemic in spring of 2014, an estimated 8,500 measles cases were reported as of April 19, with 114 fatalities;[69] as of May 30, 21,639 suspected measles cases had been reported, with 142 measles-related fatalities.[70]

Five out of six WHO regions have set goals to eliminate measles, and at the 63rd World Health Assembly in May 2010, delegates agreed on a global target of a 95% reduction in measles mortality by 2015 from the level seen in 2000, as well as to move towards eventual eradication. However, no specific global target date for eradication has yet been agreed to as of May 2010.[71][72]

In 2014, a review by the Centers for Disease Control reported a total of 911 cases of measles from 2001 to 2011, with an annual median number of 61 cases and concluded that "the elimination of endemic measles, rubella, and CRS has been sustained in the United States."[73] However, in 2015, a measles outbreak occurred in the U.S. and spread rather farther than it should have, because misguided ideas about anti-vaccination and vaccination delaying have decreased the community immunity afforded by proper public health programs. In 2015, a U.S. woman died of pneumonia, as a result of measles. She was the first fatality in the USA from measles since 2003.[74] The woman had been vaccinated for measles and was taking immune suppression drugs for another condition. The drugs suppressed the measles immunity, the woman became infected with measles, did not develop a rash, and contracted pneumonia which caused her death.[75]

Between October 2014 and March 2015, a measles outbreak in the German capital of Berlin resulted in at least 782 cases.[76]

From January 4 to April 2, 2015, there were 159 reported cases of measles to the CDC. Of those 159 cases, 111 (70%) were determined to have come from an earlier exposure in late December 2014. This outbreak was believed to have originated from the Disney theme parks in California. The initial exposure to the virus was never found. There have been cases associated with this outbreak in seven states, Mexico, and Canada. Of the cases 48% were unvaccinated and 38% were unsure of their vaccination status.[77]

In the Naga Self-Administered Zone in a remote northern region of Myanmar, at least 40 children died during a measles outbreak in August 2016 that was probably caused by lack of vaccination in an area of poor health infrastructure.[78][79]

## History [edit]

16th-century Aztec drawing of someone with measles

Estimates based on modern molecular biology place the emergence of measles as a human disease sometime after 500 AD[80] (the former speculation that the Antonine Plague of 165–180 AD was caused by measles is now discounted). The first systematic description of measles, and its distinction from smallpox and chickenpox, is credited to the Persian physician Rhazes (860–932), who published *The Book of Smallpox and Measles*.[81] Given what is now known about the evolution of measles, Rhazes' account is remarkably timely, as recent work that examined the mutation rate of the virus indicates the measles virus emerged from rinderpest (cattle plague) as a zoonotic disease between 1100 and 1200 AD, a period that may have been preceded by limited outbreaks involving a virus not yet fully acclimated to humans.[80] This

agrees with the observation that measles requires a susceptible population of >500,000 to sustain an epidemic, a situation that occurred in historic times following the growth of medieval European cities.[82]

Measles is an endemic disease, meaning it has been continually present in a community, and many people develop resistance. In populations not exposed to measles, exposure to the new disease can be devastating. In 1529, a measles outbreak in Cuba killed two-thirds of those natives who had previously survived smallpox. Two years later, measles was responsible for the deaths of half the population of Honduras, and it had ravaged Mexico, Central America, and the Inca civilization.[84]

Between roughly 1855 and 2005, measles has been estimated to have killed about 200 million people worldwide.[85] Measles killed 20 percent of Hawaii's population in the 1850s.[86] In 1875, measles killed over 40,000 Fijians, approximately one-third of the population.[87] In the 19th century, the disease killed 50% of the Andamanese population.[88] Seven to eight million children are thought to have died from measles each year before the vaccine was introduced.[12]

In 1954, the virus causing the disease was isolated from a 13-year-old boy from the United States, David Edmonston, and adapted and propagated on chick embryo tissue culture.[89] To date, 21 strains of the measles virus have been identified.[90] While at Merck, Maurice Hilleman developed the first successful vaccine.[91] Licensed vaccines to prevent the disease became available in 1963.[92] An improved measles vaccine became available in 1968.[93] Measles as an endemic disease was eliminated from the United States in 2000, but continues to be reintroduced by international travelers.

Maurice Hilleman's measles vaccine is estimated to prevent 1 million deaths per year.[83]

## Society and culture [edit]

German anti-vaccination campaigner and HIV/AIDS denialist[94] Stefan Lanka posed a challenge on his website in 2011, offering a sum of €100,000 for anyone who could scientifically prove that measles is caused by a virus and determine the diameter of the virus.[95] He posits that the illness is psychosomatic and that the measles virus does not exist. When provided with overwhelming scientific evidence from various medical studies by German physician David Barden, Lanka did not accept the findings, forcing Barden to appeal in court. The legal case ended with the ruling that Lanka was to pay the prize.[76][96] The case received wide international coverage that prompted many to comment on it, including clinical neurologist, well-known skeptic and science-based medicine advocate Dr. Steven Novella, who called Lanka "a crank".[97]

## Research [edit]

In May 2015, the journal *Science*, published a report in which researchers found that the measles infection can leave a population at increased risk for mortality from other diseases for 2 to 3 years.[98][99]

A specific drug treatment for measles ERDRP-0519 has shown promising results in animal studies, but has not yet been tested in humans.[100][101][102]

## References [edit]


1. ^ *a b c* Caserta, MT, ed. (September 2013). "Measles". *Merck Manual Professional*. Merck Sharp & Dohme Corp. Retrieved 23 March 2014.
2. ^ "Measles (Red Measles, Rubeola)". *Dept of Health, Saskatchewan*. Retrieved 10 February 2015.
3. ^ *a b* "Measles (Rubeola) Signs and Symptoms". *cdc.gov*. November 3, 2014. Retrieved 5 February 2015.
4. ^ *a b c d e f g h i j k l* "Measles Fact sheet N°286". *who.int*. November 2014. Retrieved 4 February 2015.

5. ^ [a b] *Conn's Current Therapy 2015: Expert Consult - Online*. Elsevier Health Sciences. 2014. p. 153. ISBN 9780323319560.
6. ^ [a b c d e] Atkinson, William (2011). *Epidemiology and Prevention of Vaccine-Preventable Diseases* (12 ed.). Public Health Foundation. pp. 301–323. ISBN 9780983263135. Retrieved 5 February 2015.
7. ^ Marx, John A. (2010). *Rosen's emergency medicine : concepts and clinical practice* (7th ed.). Philadelphia: Mosby/Elsevier. p. 1541. ISBN 9780323054720.
8. ^ [a b] Kabra, SK; Lodhra, R (14 August 2013). "Antibiotics for preventing complications in children with measles". *Cochrane Database of Systematic Reviews*. **8**: CD001477. doi:10.1002/14651858.CD001477.pub4. PMID 23943263.
9. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385**: 117–171. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
10. ^ [a b] "Region of the Americas is declared free of measles". *PAHO*. 29 September 2016. Retrieved 30 September 2016.
11. ^ [a b] Biesbroeck L, Sidbury R (November 2013). "Viral exanthems: an update". *Dermatologic therapy*. **26** (6): 433–8. doi:10.1111/dth.12107. PMID 24552405.
12. ^ [a b c d e f] Ludlow M, McQuaid S, Milner D, de Swart RL, Duprex WP (January 2015). "Pathological consequences of systemic measles virus infection". *The Journal of pathology*. **235** (2): 253–65. doi:10.1002/path.4457. PMID 25294240.
13. ^ [a b] Baxby D (1997). "Classic Paper: Henry Koplik. The diagnosis of the invasion of measles from a study of the exanthema as it appears on the buccal membrane". *Reviews in Medical Virology*. **7** (2): 71–4. doi:10.1002/(SICI)1099-1654(199707)7:2<71::AID-RMV185>3.0.CO;2-S. PMID 10398471.
14. ^ NHS UK: Symptoms of measles. Last reviewed: 26/01/2010.
15. ^ Gardiner, W. T. (2007). "Otitis Media in Measles". *The Journal of Laryngology & Otology*. **39** (11): 614–617. doi:10.1017/S0022215100026712.
16. ^ Fisher DL, Defres S, Solomon T (2014). "Measles-induced encephalitis". *QJM*. **108**: 177–182. doi:10.1093/qjmed/hcu113. PMID 24865261.
17. ^ Anlar B (2013). "Subacute sclerosing panencephalitis and chronic viral encephalitis". *Handbook of Clinical Neurology*. **112**: 1183–1189. doi:10.1016/B978-0-444-52910-7.00039-8. PMID 23622327.
18. ^ Semba RD, Bloem MW (March 2004). "Measles blindness". *Survey of Ophthalmology*. **49** (2): 243–55. doi:10.1016/j.survophthal.2003.12.005. PMID 14998696.
19. ^ Sabella C (2010). "Measles: Not just a childhood rash". *Cleveland Clinic Journal of Medicine*. **77** (3): 207–213. doi:10.3949/ccjm.77a.09123. PMID 20200172.
20. ^ Ellison, J.B (1931). "Pneumonia in Measles". *1931 Archives of Disease in Childhood*. **6** (31): 37–52. doi:10.1136/adc.6.31.37. PMC 1975146. PMID 21031836.
21. ^ [a b] "Measles | For Healthcare Professionals | CDC". *www.cdc.gov*. Retrieved 22 October 2016.
22. ^ [a b] Perry RT, Halsey NA (May 1, 2004). "The Clinical Significance of Measles: A Review". *The Journal of Infectious Diseases*. **189** (S1): S4–16. doi:10.1086/377712. PMID 15106083.
23. ^ Sension MG, Quinn TC, Markowitz LE, Linnan MJ, Jones TS, Francis HL, Nzilambi N, Duma MN, Ryder RW (1988). "Measles in hospitalized African children with human immunodeficiency virus". *American Journal of Diseases of Children (1960)*. **142** (12): 1271–2. doi:10.1001/archpedi.1988.02150120025021. PMID 3195521.
24. ^ [a b c d e f] Chen S.S.P. (October 3, 2011). Measles (Report). Medscape.
25. ^ National Institutes of Health Office of Dietary Supplements (2013). "Vitamin A". U.S. Department of Health & Human Services. Retrieved 11 March 2015.
26. ^ [a b] "Measles | For Healthcare Professionals | CDC". *www.cdc.gov*.
27. ^ [a b] Cohen BE, Durstenfeld A, Roehm PC (July 2014). "Viral causes of hearing loss: a review for hearing health professionals". *Trends in Hearing*. **18**: 2331216514541361. doi:10.1177/2331216514541361. PMC 4222184. PMID 25080364.
28. ^ Enders JF, Peebles TC (1954). "Propagation in tissue culture of cytopathogenic agents from patients with measles". *Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N.Y.)*. **86** (2): 277–86. doi:10.3181/00379727-86-21073. PMID 13177653.
29. ^ Gowda VK, Sukanya V (2012). "Acquired Immunodeficiency Syndrome with Subacute Sclerosing Panencephalitis". *Pediatric Neurology*. **47** (5): 379–381. doi:10.1016/j.pediatrneurol.2012.06.020. PMID 23044024.
30. ^ Waggoner JJ, Soda EA, Deresinski S (October 2013). "Rare and emerging viral infections in transplant recipients". *Clinical Infectious Diseases*. **57** (8): 1182–8. doi:10.1093/cid/cit456. PMID 23839998.

31. ^ a b c d e Leuridan E, Sabbe M, Van Damme P (September 2012). "Measles outbreak in Europe: susceptibility of infants too young to be immunized". *Vaccine*. **30** (41): 5905–13. doi:10.1016/j.vaccine.2012.07.035. PMID 22841972.
32. ^ "Bug of the Month—Measles". *Banner Gateway Medical Center*. April 2012. Retrieved May 3, 2013.
33. ^ a b Total Health (May 5, 2010). "Actual Confirmed Measles Cases in UK". *totalhealth*. Retrieved May 4, 2013.
34. ^ Durrheim DN, Kelly H, Ferson MJ, Featherstone D (August 2007). "Remaining measles challenges in Australia". *The Medical journal of Australia*. **187** (3): 181–4. PMID 17680748.
35. ^ Friedman M, Hadari I, Goldstein V, Sarov I (1983). "Virus-specific secretory IgA antibodies as a means of rapid diagnosis of measles and mumps infection". *Israel Journal of Medical Sciences*. **19** (10): 881–884. PMID 6662670.
36. ^ Galindo BM, Concepción D, Galindo MA, Pérez A, Saiz J (2012). "Vaccine-related adverse events in Cuban children, 1999–2008". *MEDICC Review*. **14** (1): 38–43. PMID 22334111.
37. ^ Helfand RF, Witte D, Fowlkes A, Garcia P, Yang C, Fudzulani R, Walls L, Bae S, Strebel P, Broadhead R, Bellini WJ, Cutts F (2008). "Evaluation of the immune response to a 2-dose measles vaccination schedule administered at 6 and 9 months of age to HIV-infected and HIV-uninfected children in Malawi". *The Journal of Infectious Diseases*. **198** (10): 1457–65. doi:10.1086/592756. PMID 18828743.
38. ^ Ołdakowska A, Marczyńska M (2008). "Measles vaccination in HIV-infected children". *Medycyna Wieku Rozwojowego*. **12** (2 Pt 2): 675–680. PMID 19418943.
39. ^ UNICEF (2007). "Global goal to reduce measles deaths in children surpassed". *Joint press release*. Retrieved 11 March 2015.
40. ^ "Complications of Measles". Centers for Disease Control and Prevention (CDC).
41. ^ Starko KM, Ray CG, Dominguez LB, Stromberg WL, Woodall DF (6 Dec 1980). "Reye's Syndrome and Salicylate Use". *Pediatrics*. **66** (6): 859–64. PMID 7454476. Retrieved 2011-03-17. "It is postulated that salicylate [taken by school-age children], operating in a dose-dependent manner, possibly potentiated by fever, represents a primary causative agent of Reye's syndrome."
42. ^ Casteels-Van Daele M, Van Geet C, Wouters C, Eggermont E (April 2000). "Reye syndrome revisited: a descriptive term covering a group of heterogeneous disorders". *European Journal of Pediatrics*. **159** (9): 641–8. doi:10.1007/PL00008399. PMID 11014461. Retrieved 2011-03-17. "Reye syndrome is a non-specific descriptive term covering a group of heterogeneous disorders. Moreover, not only the use of acetylsalicylic acid but also of antiemetics is statistically significant in Reye syndrome cases. Both facts weaken the validity of the epidemiological surveys suggesting a link with acetylsalicylic acid."
43. ^ Schrör K (2007). "Aspirin and Reye Syndrome: A Review of the Evidence". *Paediatric Drugs*. **9** (3): 195–204. doi:10.2165/00148581-200709030-00008. PMID 17523700. Retrieved 2011-03-17. "The suggestion of a defined cause-effect relationship between aspirin intake and Reye syndrome in children is not supported by sufficient facts. Clearly, no drug treatment is without side effects. Thus, a balanced view of whether treatment with a certain drug is justified in terms of the benefit/risk ratio is always necessary. Aspirin is no exception."
44. ^ Macdonald S (2002). "Aspirin use to be banned in under 16 year olds". *BMJ (Clinical Research Ed.)*. **325** (7371): 988. doi:10.1136/bmj.325.7371.988/c. PMC 1169585. PMID 12411346. "Professor Alasdair Breckenridge, said, "There are plenty of analgesic products containing paracetamol and ibuprofen for this age group not associated with Reye's syndrome. There is simply no need to expose those under 16 to the risk—however small.""
45. ^ "Aspirin and Reye's Syndrome". *MHRA*. October 2003. Retrieved 2011-03-17.
46. ^ "Surgeon General's advisory on the use of salicylates and Reye syndrome". *MMWR. Morbidity and Mortality Weekly Report*. **31** (22): 289–90. June 1982. PMID 6810083.
47. ^ *Reye's Syndrome* at NINDS "Epidemiologic evidence indicates that aspirin (salicylate) is the major preventable risk factor for Reye's syndrome. The mechanism by which aspirin and other salicylates trigger Reye's syndrome is not completely understood."
48. ^ "Measles vaccines: WHO position paper." (PDF). *Weekly epidemiological record*. **84** (35): 349–60. 28 August 2009. PMID 19714924.
49. ^ Huiming Y, Chaomin W, Meng M (2005). Yang H, ed. "Vitamin A for treating measles in children". *The Cochrane Database of Systematic Reviews* (4): CD001479. doi:10.1002/14651858.CD001479.pub3. PMID 16235283.
50. ^ D'Souza RM, D'Souza R (2002). "Vitamin A for treating measles in children". *The Cochrane Database of Systematic Reviews* (1): CD001479. doi:10.1002/14651858.CD001479. PMID 11869601.
51. ^ D'Souza RM, D'Souza R (April 2002). "Vitamin A for preventing secondary infections in children with measles—a systematic review". *Journal of Tropical Pediatrics*. **48** (2): 72–7. doi:10.1093/tropej/48.2.72. PMID 12022432.
52. ^ Awotiwon, AA; Oduwole, O; Sinha, A; Okwundu, CI (20 March 2015). "Zinc supplementation for the treatment of measles in children.". *The Cochrane database of systematic reviews*. **3**: CD011177. doi:10.1002/14651858.CD011177.pub2. PMID 25794053.
53. ^ Noyce RS, Richardson CD (September 2012). "Nectin 4 is the epithelial cell receptor for measles virus". *Trends in*

*Microbiology*. **20** (9): 429–39. doi:10.1016/j.tim.2012.05.006 . PMID 22721863 .
54. ^ [1] "NINDS Subacute Sclerosing Panencephalitis Information Page"
55. ^ *14-193b.* at Merck Manual of Diagnosis and Therapy Professional Edition
56. ^ Bartlett, M.S. (1957). "Measles periodicity and community size". *J. Roy. Stat. Soc*. Ser. A (120): 48–70.
57. ^ Black FL (1966). "Measles endemicity in insular populations; critical community size and its evolutionary implications". *Journal of Theoretical Biology*. **11** (2): 207–11. doi:10.1016/0022-5193(66)90161-5. PMID 5965486.
58. ^ Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al. (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
59. ^ "Complications of measles". CDC. November 3, 2014. Retrieved November 7, 2014.
60. ^ Measles, World Health Organization Fact sheet N°286. Retrieved June 28, 2012. Updated February 2014
61. ^ WHO: Global summary on measles, 2006
62. ^ Measles Surveillance Data after WHO, last updated 2014-3-6
63. ^ Measles reported cases by WHO in 2014
64. ^ Số người chết và mắc bệnh theo quốc gia, last update 2014-4-7 by WHO
65. ^ "Measles---United States, 2005". Centers for Disease Control and Prevention. December 22, 2006. Retrieved 30 March 2015.
66. ^ Reported Measles Cases by WHO region 2014, 2015, as of 07 July 201, WHO
67. ^ UNICEF Joint Press Release
68. ^ WHO Weekly Epidemiology Record, 4th December 2009 WHO.int
69. ^ "Vietnam minister calls for calm in face of 8,500 measles cases, 114 fatalities | Health | Thanh Nien Daily". Thanhniennews.com. Retrieved 2014-04-19.
70. ^ "Bộ Y tế: "VN đã phản ứng rất nhanh đối với dịch sởi" ". Archived from the original on 2014-05-31.
71. ^ "Sixty-third World Health Assembly Agenda provisional agenda item 11.15 Global eradication of measles" (PDF). Retrieved 2 June 2010.
72. ^ "Sixty-third World Health Assembly notes from day four". Retrieved 2 June 2010.
73. ^ Papania, Mark (Feb 2014). "Elimination of Endemic Measles, Rubella, and Congenital Rubella Syndrome From the Western Hemisphere The US Experience". *JAMA Pediatrics*.
74. ^ "Measles kills first patient in 12 years". USA Today. 2 July 2015. Retrieved 2 July 2015.
75. ^ "First Measles Death in US Since 2003 Highlights the Unknown Vulnerables – Phenomena: Germination". Retrieved 2015-07-03.
76. ^ *a b* Elizabeth Whitman (2015-03-13). "Who Is Stefan Lanka? Court Orders German Measles Denier To Pay 100,000 Euros". International Business Times. Retrieved 2015-03-31.
77. ^ Clemmons, Nakia. "Measles - United States, January 4 - April 2, 2015". *cdc.gov*.
78. ^ "WHO doctors in Myanmar's Naga areas identify 'mystery disease' – Eastern Mirror". *www.easternmirrornagaland.com*. Retrieved 8 August 2016.
79. ^ "Myanmar (02): (SA) fatal, measles conf". *www.promedmail.org (Archive Number: 20160806.4398118)*. International Society for Infectious Diseases. Retrieved 8 August 2016.
80. ^ *a b* Furuse, Yuki; Akira Suzuki; Hitoshi Oshitani (2010-03-04). "Origin of measles virus: divergence from rinderpest virus between the 11th and 12th centuries". *Virology Journal*. **7**: 52. doi:10.1186/1743-422X-7-52. ISSN 1743-422X. PMC 2838858. PMID 20202190.
81. ^ Cohen SG (February 2008). "Measles and immunomodulation". *The Journal of allergy and clinical immunology*. **121** (2): 543–4. doi:10.1016/j.jaci.2007.12.1152. PMID 18269930.
82. ^ Black, Francis L. (July 1966). "Measles endemicity in insular populations: Critical community size and its evolutionary implication". *Journal of Theoretical Biology*. **11** (2): 207–211. doi:10.1016/0022-5193(66)90161-5. ISSN 0022-5193. PMID 5965486. Retrieved 2014-10-15.
83. ^ "Maurice R. Hilleman Dies; Created Vaccines". *The Washington Post*. April 13, 2005.
84. ^ Byrne, Joseph Patrick (2008). *Encyclopedia of Pestilence, Pandemics, and Plagues: A–M*. ABC-CLIO. p. 413. ISBN 0-313-34102-8.
85. ^ Torrey EF and Yolken RH. 2005. Their bugs are worse than their bite. Washington Post, April 3, p. B01.
86. ^ Migration and Disease. *Digital History.*
87. ^ Fiji School of Medicine
88. ^ Measles hits rare Andaman tribe. *BBC News.* May 16, 2006.
89. ^ "Live attenuated measles vaccine". *EPI Newsletter / C Expanded Program on Immunization in the Americas*. **2** (1): 6. 1980. PMID 12314356.
90. ^ Rima BK, Earle JA, Yeo RP, Herlihy L, Baczko K, ter Meulen V, Carabaña J, Caballero M, Celma ML, Fernandez-

Muñoz R (1995). "Temporal and geographical distribution of measles virus genotypes". *The Journal of General Virology*. **76** (5): 1173–80. doi:10.1099/0022-1317-76-5-1173. PMID 7730801.
91. ^ Offit PA (2007). *Vaccinated: One Man's Quest to Defeat the World's Deadliest Diseases*. Washington, DC: Smithsonian. ISBN 0-06-122796-X.
92. ^ "Measles Prevention: Recommendations of the Immunization Practices Advisory Committee (ACIP)". Centers for Disease Control and Prevention (CDC).
93. ^ *Measles: Questions and Answers,* Immunization Action Coalition.
94. ^ Stefan Lanka (April 1995). "HIV; Reality or artefact?". Virusmyth.com. Retrieved 2015-03-31.
95. ^ "Das Masern-Virus 100.000 € Belohnung! WANTeD Der Durchmesser" (PDF) (in German). 2011-11-24. Retrieved 2015-03-31.
96. ^ "Germany court orders measles sceptic to pay 100,000 euros". BBC News Online. 2015-03-12. Retrieved 2015-03-31.
97. ^ Steven Novella (2015-03-13). "Yes, Dr. Lanka, Measles is Real". NeuroLogica Blog. Retrieved 2015-03-31.
98. ^ Bakalar, Nicholas. "Measles May Increase Susceptibility to Other Infections". *The New York Times*. The New York Times Company. Retrieved 7 June 2015.
99. ^ Mina; et al. (8 May 2015). "Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality". *Science*. **348** (6235): 694–699. doi:10.1126/science.aaa3662. Retrieved 7 June 2015.
100. ^ White LK, Yoon JJ, Lee JK, Sun A, Du Y, Fu H, Snyder JP, Plemper RK (2007). "Nonnucleoside Inhibitor of Measles Virus RNA-Dependent RNA Polymerase Complex Activity". *Antimicrobial Agents and Chemotherapy*. **51** (7): 2293–303. doi:10.1128/AAC.00289-07. PMC 1913224. PMID 17470652.
101. ^ Krumm SA, Yan D, Hovingh ES, Evers TJ, Enkirch T, Reddy GP, Sun A, Saindane MT, Arrendale RF, Painter G, Liotta DC, Natchus MG, von Messling V, Plemper RK (2014). "An Orally Available, Small-Molecule Polymerase Inhibitor Shows Efficacy Against a Lethal Morbillivirus Infection in a Large Animal Model". *Science Translational Medicine*. **6** (232): 232ra52. doi:10.1126/scitranslmed.3008517. PMID 24739760.
102. ^ Will an anti-viral drug put paid to measles? *New Scientist* 16 April 2014

## External links [edit]

- Initiative for Vaccine Research (IVR): Measles, World Health Organization (WHO)
- Measles FAQ from Centers for Disease Control and Prevention in the United States
- Case of an adult male with measles (facial photo)
- Clinical pictures of measles
- Virus Pathogen Database and Analysis Resource (ViPR): Paramyxoviridae

Wikiquote has quotations related to: *Measles*

Wikimedia Commons has media related to *Measles*.

| v · t · e | **Infectious skin disease: Viral cutaneous conditions, including viral exanthema (B00–B09, 050–059)** | | | |
|---|---|---|---|---|
| | **Herpesviridae** | **Alpha** | *HSV* | Herpes simplex · Herpetic whitlow · Herpes gladiatorum · Herpetic keratoconjunctivitis · Herpetic sycosis · Neonatal herpes simplex · Herpes genitalis · Herpes labialis · Eczema herpeticum · Herpetiform esophagitis · |
| | | | *Herpes B virus* | B virus infection · |
| | | | *VZV* | Chickenpox · Herpes zoster · Herpes zoster oticus · Ophthalmic zoster · Disseminated herpes zoster · Zoster-associated pain · Modified varicella-like syndrome · |
| | | **Beta** | *Human herpesvirus 6/Roseolovirus* (Exanthema subitum · Roseola vaccinia · · Cytomegalic inclusion disease · | |

| | | | |
|---|---|---|---|
| **DNA virus** | | **Gamma** | *KSHV* (Kaposi's sarcoma · · |
| | **Poxviridae** | **Ortho** | *Variola* (Smallpox · Alastrim · · *MoxV* (Monkeypox · · *CPXV* (Cowpox · · *VV* (Vaccinia · Generalized vaccinia · Eczema vaccinatum · Progressive vaccinia · · Buffalopox · |
| | | **Para** | Farmyard pox: Milker's nodule · Bovine papular stomatitis · Pseudocowpox · Orf · Sealpox · |
| | | **Other** | Yatapoxvirus: Tanapox · Yaba monkey tumor virus · *MCV* (Molluscum contagiosum · · |
| | **Papillomaviridae** | *HPV* | Wart/plantar wart · Heck's disease · Genital wart (giant · · Laryngeal papillomatosis · Butcher's wart · Bowenoid papulosis · Epidermodysplasia verruciformis · Verruca plana · Pigmented wart · Verrucae palmares et plantares · |
| | | *BPV* (Equine sarcoid · · | |
| | **Parvoviridae** | *Parvovirus B19* (Erythema infectiosum · Reticulocytopenia · Papular purpuric gloves and socks syndrome · · | |
| | **Polyomaviridae** | *Merkel cell polyomavirus* (Merkel cell carcinoma · · | |
| **RNA virus** | **Paramyxoviridae** | *MeV* (**Measles** · · | |
| | **Togaviridae** | *Rubella virus* (Rubella · Congenital rubella syndrome · · Alphavirus infection · Chikungunya fever · | |
| | **Picornaviridae** | *CAV* (Hand, foot and mouth disease · Herpangina · · *FMDV* (Foot-and-mouth disease · · Boston exanthem disease · | |
| **Ungrouped** | Asymmetric periflexural exanthem of childhood · Post-vaccination follicular eruption · Lipschütz ulcer · Eruptive pseudoangiomatosis · Viral-associated trichodysplasia · Gianotti–Crosti syndrome · | | |

| v · t · e · | **Diseases of poverty** |
|---|---|
| **Diseases of poverty** | AIDS · Malaria · Tuberculosis · **Measles** · Pneumonia · Diarrheal diseases · |
| **Neglected diseases** | Cholera · Chagas disease · African sleeping sickness · Schistosomiasis · Dracunculiasis · River blindness · Leishmaniasis · Trachoma · |
| **Miscellaneous** | Malnutrition · Priority review voucher · |

| v · t · e · | **Numbered Diseases of Childhood** |
|---|---|
| **Diseases** | **First Disease (Measles)** · Second Disease (Scarlet Fever) · Third Disease (Rubella) · Fourth Disease (Dukes' Disease) · Fifth Disease (Erythema Infectiosum) · Sixth Disease (Roseola) · |

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|---|---|
| **Authority control** | LCCN: sh85082696 · GND: 4120705-1 · NDL: 00562991 · |

Categories: Measles | Pediatrics | Virus-related cutaneous conditions | Infectious diseases with eradication efforts


# Psoriasis





From Wikipedia, the free encyclopedia

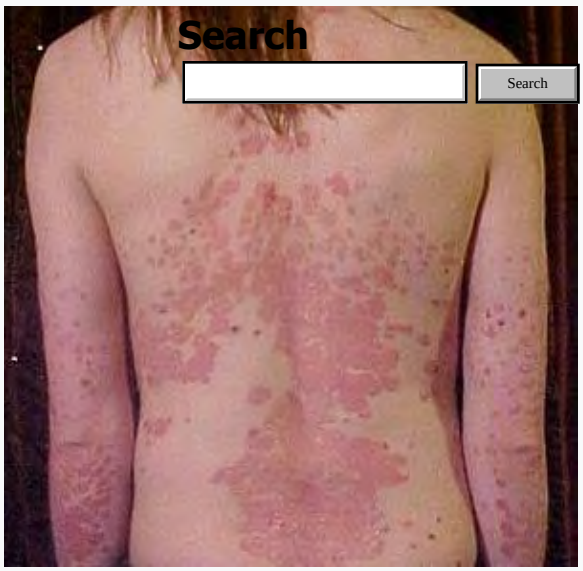
**Psoriasis** is a long-lasting [autoimmune disease](#) which is characterized by patches of abnormal skin.[3] These skin patches are typically red, itchy, and scaly. They may vary in severity from small and localized to complete body coverage.[4] Injury to the skin can trigger psoriatic skin changes at that spot, which is known as Koebner phenomenon.[5]

There are five main types of psoriasis: plaque, guttate, inverse, pustular, and erythrodermic.[3] Plaque psoriasis, also known as psoriasis vulgaris, makes up about 90% of cases. It typically presents with red patches with white scales on top. Areas of the body most commonly affected are the back of the forearms, shins, around the navel, and the scalp.[6] Guttate psoriasis has drop-shaped lesions.[3] Pustular psoriasis presents with small non-infectious pus-filled blisters.[7] Inverse psoriasis forms red patches in skin folds.[3] Erythrodermic psoriasis occurs when the rash becomes very widespread, and can develop from any of the other types. Fingernails and toenails are affected in most people at some point in time. This may include pits in the nails or changes in nail color.[6]

Psoriasis is generally thought to be a genetic disease which is triggered by environmental factors.[4] In twin studies, identical twins are three times more likely to both be affected compared to non-identical twins; this suggests that genetic factors predispose to psoriasis. Symptoms often worsen during winter and with certain medications such as beta blockers or NSAIDs.[6] Infections and psychological stress may also play a role.[3][4] Psoriasis is not contagious. The underlying mechanism involves the immune system reacting to skin cells. Diagnosis is typically based on the signs and symptoms.[6]

There is no cure for psoriasis. However, various treatments can help control the symptoms.[6] These treatments may include steroid creams, vitamin D3 cream, ultraviolet light, and immune system suppressing medications such as methotrexate.[3] About 75% of cases can be managed with creams alone.[6] The disease affects 2–4% of the population.[8] Men and women are affected with equal frequency.[3] The disease may begin at any age.[9] Psoriasis is associated with an increased risk of psoriatic arthritis, lymphomas, cardiovascular disease, Crohn's disease, and depression.[6] Psoriatic arthritis affects up to 30% of

## Psoriasis



Back and arms of a person with psoriasis

**Pronunciation** /səˈraɪəsɪs, ps-, sɒ-, sɔː-, soʊ-/[1][2]
(*psora* + *-iasis*)

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Dermatology |
| **ICD-10** | L40 |
| **ICD-9-CM** | 696 |
| **OMIM** | 177900 |
| **DiseasesDB** | 10895 |
| **MedlinePlus** | 000434 |
| **eMedicine** | emerg/489<br>plaque derm/365<br>guttate derm/361<br>nails derm/363<br>pustular derm/366 |
| **MeSH** | D011565 |

[edit on Wikidata]

individuals with psoriasis.[7]

Contents



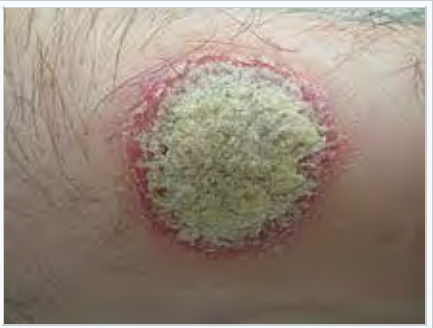


Edit links

## Signs and symptoms [edit]

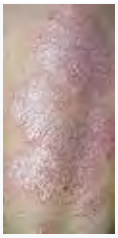
### Plaque [edit]

Psoriasis vulgaris (also known as chronic stationary psoriasis or plaque-like psoriasis) is the most common form and affects 85%–90% of people with psoriasis.[10] Plaque psoriasis typically appears as raised areas of inflamed skin covered with silvery-white scaly skin. These areas are called plaques and are most commonly found on the elbows, knees, scalp, and back.[10][11] Psoriatic erythroderma (erythrodermic psoriasis) involves widespread inflammation and exfoliation of the skin over most of the body surface. It may be accompanied by severe itching, swelling, and pain. It is often the result of an exacerbation of unstable plaque psoriasis, particularly following the abrupt withdrawal of systemic glucocorticoids.[12] This form of psoriasis can be fatal as the extreme inflammation and exfoliation disrupt the body's ability to regulate temperature and perform barrier functions.[13]



Psoriatic plaque, showing a silvery center surrounded by a reddened border.

Plaques of psoriasis



A person's arm covered with plaque psoriasis

Psoriasis of the palms

## Pustular [edit]

*See also: Generalized pustular psoriasis*

Severe pustular psoriasis.

Pustular psoriasis appears as raised bumps filled with noninfectious pus (pustules).[14] The skin under and surrounding the pustules is red and tender.[15] Pustular psoriasis can be localized, commonly to the hands and feet (palmoplantar pustulosis), or generalized with widespread patches occurring randomly on any part of the body. Acrodermatitis continua is a form of localized psoriasis limited to the fingers and toes that may spread to the hands and feet.[15] Pustulosis palmaris et plantaris is another form of localized pustular psoriasis similar to acrodermatitis continua with pustules erupting from red, tender, scaly skin found on the palms of the hands and the soles of the feet.[15]

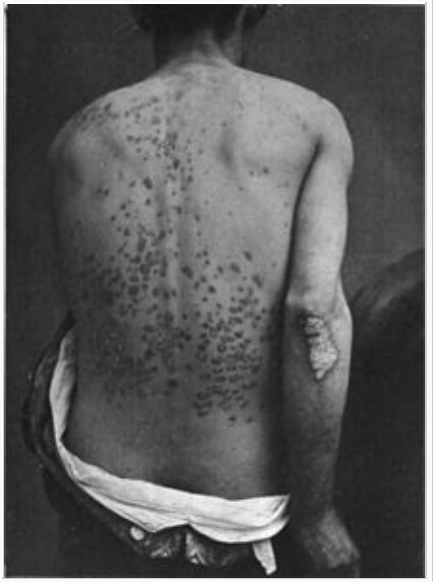
Generalized pustular psoriasis (pustular psoriasis of von Zumbusch), also known as impetigo herpetiformis during pregnancy,[16] is a rare and severe form of psoriasis that may require hospitalization. The development of generalized pustular psoriasis is often caused by an infection, abrupt withdrawal of topical corticosteroid treatment, pregnancy, hypocalcemia, medications, or following an irritating topical treatment for plaque psoriasis.[15] This form of psoriasis is characterized by an acute onset of numerous pustules on top of tender red skin. This skin eruption is often accompanied by a fever, muscle aches, nausea, and an elevated white blood cell count.[15] Annular pustular psoriasis (APP), a rare form of generalized pustular psoriasis, is the most common type seen during childhood.[16] APP tends to occur in women more frequently than in men, and is usually less severe than other forms of generalized pustular psoriasis such as impetigo herpetiformis.[16] This form of psoriasis is characterized by ring-shaped plaques with pustules around the edges and yellow crusting.[16] APP most often affects the torso, neck, arms, and legs.[16]

## Other skin lesions [edit]

Additional types of psoriasis affecting the skin include inverse psoriasis, guttate psoriasis, oral psoriasis, and seborrheic-like psoriasis.[17]

Inverse psoriasis (also known as flexural psoriasis) appears as smooth, inflamed patches of skin. The patches frequently affect skin folds, particularly around the genitals (between the thigh and groin), the armpits, in the skin folds of an overweight abdomen (known as panniculus), between the buttocks in the intergluteal cleft, and under the breasts in the inframammary fold. Heat, trauma, and infection are thought to play a role in the development of this atypical form of psoriasis.[18] Napkin psoriasis is a subtype of psoriasis common in infants characterized by red papules with silver scale in the diaper area that may extend to the torso or limbs.[19] Napkin psoriasis is often misdiagnosed as napkin dermatitis (diaper rash).[20]

Guttate psoriasis is characterized by numerous small, scaly, red or pink, droplet-like lesions (papules). These numerous spots of psoriasis appear over


Example of guttate psoriasis

large areas of the body, primarily the trunk, but also the limbs and scalp. Guttate psoriasis is often triggered by a streptococcal infection, typically streptococcal pharyngitis.[18] The reverse is not true.

Oral psoriasis is very rare,[21] in contrast to lichen planus, another common papulosquamous disorder that commonly involves both the skin and mouth. When psoriasis involves the oral mucosa (the lining of the mouth), it may be asymptomatic,[21] but it may appear as white or grey-yellow plaques.[21] Fissured tongue is the most common finding in those with oral psoriasis and has been reported to occur in 6.5–20% of people with psoriasis affecting the skin. The microscopic appearance of oral mucosa affected by geographic tongue (migratory stomatitis) is very similar to the appearance of psoriasis.[22] However, modern studies have failed to demonstrate any link between the two conditions.[23]

Seborrheic-like psoriasis is a common form of psoriasis with clinical aspects of psoriasis and seborrheic dermatitis, and may be difficult to distinguish from the latter. This form of psoriasis typically manifests as red plaques with greasy scales in areas of higher sebum production such as the scalp, forehead, skin folds next to the nose, skin surrounding the mouth, skin on the chest above the sternum, and in skin folds.[19]

## Psoriatic arthritis [edit]

*See also: Psoriatic arthritis*

Psoriatic arthritis is a form of chronic inflammatory arthritis that has a highly variable clinical presentation and frequently occurs in association with skin and nail psoriasis.[24][25] It typically involves painful inflammation of the joints and surrounding connective tissue and can occur in any joint, but most commonly affects the joints of the fingers and toes. This can result in a sausage-shaped swelling of the fingers and toes known as dactylitis.[24] Psoriatic arthritis can also affect the hips, knees, spine (spondylitis), and sacroiliac joint (sacroiliitis).[26] About 30% of individuals with psoriasis will develop psoriatic arthritis.[10] Skin manifestations of psoriasis tend to occur before arthritic manifestations in about 75% of cases.[25]

## Nail changes [edit]

Psoriasis can affect the nails and produces a variety of changes in the appearance of finger and toe nails. Nail psoriasis occurs in 40–45% of people with psoriasis affecting the skin and has a lifetime incidence of 80–90% in those with psoriatic arthritis.[27] These changes include pitting of the nails (pinhead-sized depressions in the nail is seen in 70% with nail psoriasis), whitening of the nail, small areas of bleeding from capillaries under the nail, yellow-reddish discoloration of the nails known as the oil drop or salmon spot, thickening of the skin under the nail (subungual hyperkeratosis), loosening and separation of the nail (onycholysis), and crumbling of the nail.[27]

## Medical signs [edit]

Psoriasis of a fingernail, with visible pitting.

In addition to the appearance and distribution of the rash, specific medical signs may be used by medical practitioners to assist with diagnosis. These may include Auspitz's sign (pinpoint bleeding when scale is removed), Koebner phenomenon (psoriatic skin lesions induced by trauma to the skin),[19] and itching and pain localized to papules and plaques.[18][19]

## Causes [edit]

The cause of psoriasis is not fully understood, but a number of theories exist.

A photograph showing the effects of psoriasis on the toenails.

### Genetics [edit]

*See also: List of human leukocyte antigen alleles associated with cutaneous conditions*

Around one-third of people with psoriasis report a family history of the disease, and researchers have identified genetic loci associated with the condition. Identical twin studies suggest a 70% chance of a twin developing psoriasis if the other twin has the disorder. The risk is around 20% for nonidentical twins. These findings suggest both a genetic susceptibility and an environmental response in developing psoriasis.[28]

Psoriasis has a strong hereditary component, and many genes are associated with it, but it is unclear how those genes work together. Most of the identified genes relate to the immune system, particularly the major histocompatibility complex (MHC) and T cells. Genetic studies are valuable due to their ability to identify molecular mechanisms and pathways for further study and potential drug targets.[29]

Classic genome-wide linkage analysis has identified nine loci on different chromosomes associated with psoriasis. They are called psoriasis susceptibility 1 through 9 (*PSORS1* through *PSORS9*). Within those loci are genes on pathways that lead to inflammation. Certain variations (mutations) of those genes are commonly found in psoriasis.[29] Genome-wide association scans have identified other genes that are altered to characteristic variants in psoriasis. Some of these genes express inflammatory signal proteins, which affect cells in the immune system that are also involved in psoriasis. Some of these genes are also involved in other autoimmune diseases.[29]

The major determinant is *PSORS1*, which probably accounts for 35%–50% of psoriasis heritability.[30] It controls genes that affect the immune system or encode skin proteins that are overabundant with psoriasis. *PSORS1* is located on chromosome 6 in the major histocompatibility complex (MHC), which controls important immune functions. Three genes in the *PSORS1* locus have a strong association with psoriasis vulgaris: *HLA-C* variant *HLA-Cw6*,[31] which encodes a MHC class I protein; *CCHCR1*, variant WWC, which encodes a coiled protein that is overexpressed in psoriatic epidermis; and *CDSN*, variant allele 5, which encodes corneodesmosin, a protein which is expressed in the granular and cornified layers of the epidermis and upregulated in psoriasis.[29]

Two major immune system genes under investigation are interleukin-12 subunit beta (*IL12B*) on chromosome 5q, which expresses interleukin-12B; and *IL23R* on chromosome 1p, which expresses the interleukin-23 receptor, and is involved in T cell differentiation. Interleukin-23 receptor and *IL12B* have both been strongly linked with psoriasis.[31] T cells are involved in the inflammatory process that leads to psoriasis.[29] These genes are on the pathway that up-regulate tumor necrosis factor-α and nuclear factor κB, two genes involved in inflammation.[29]

Recently, the first gene directly linked to psoriasis has been identified. A rare mutation in the gene encoding for the *CARD14* protein plus an environmental trigger was enough to cause plaque psoriasis (the most common form of psoriasis).[32][33]

### Lifestyle [edit]

Conditions reported as accompanying a worsening of the disease include chronic infections, stress, and changes in season and climate.[31] Others include hot water, scratching psoriasis skin lesions, skin dryness, excessive alcohol consumption, cigarette smoking, and obesity.[31][34][35]

### HIV [edit]

The rate of psoriasis in HIV-positive individuals is comparable to that of HIV-negative individuals, however, psoriasis tends to be more severe in people infected with HIV.[36] A much higher rate of psoriatic arthritis occurs in HIV-positive individuals with psoriasis than in those without the infection.[36] The immune response in those infected with HIV is typically characterized by cellular signals from Th2 subset of CD4+ helper T cells,[37] whereas the immune response in psoriasis vulgaris is characterized by a pattern of cellular signals typical of Th1 subset of CD4+ helper T cells and Th17 helper T cells.[38][39] It is hypothesized that the diminished CD4+-T cell presence causes an overactivation of CD8+-T cells, which are responsible for the exacerbation of psoriasis in HIV-positive people. Psoriasis in those with HIV/AIDS is often severe and may be untreatable with conventional therapy.[40]

### Microbes [edit]

Psoriasis has been described as occurring after strep throat, and may be worsened by skin or gut colonization with *Staphylococcus aureus*, *Malassezia*, and *Candida albicans*.[41]

### Medications [edit]

Drug-induced psoriasis may occur with beta blockers,[7] lithium,[7] antimalarial medications,[7] non-steroidal anti-inflammatory drugs,[7] terbinafine, calcium channel blockers, captopril, glyburide, granulocyte colony-stimulating factor,[7] interleukins, interferons,[7] lipid-lowering drugs,[17]:197 and paradoxically TNF inhibitors such as infliximab or adalimumab.[42] Withdrawal of corticosteroids (topical steroid cream) can aggravate psoriasis due to the rebound effect.[43]

## Mechanism [edit]

Psoriasis is characterized by an abnormally excessive and rapid growth of the epidermal layer of the skin.[44] Abnormal production of skin cells (especially during wound repair) and an overabundance of skin cells result from the sequence of pathological events in psoriasis.[15] Skin cells are replaced every 3–5 days in psoriasis rather than the usual 28–30 days.[45] These changes are believed to stem from the premature maturation of keratinocytes induced by an inflammatory cascade in the dermis involving dendritic cells, macrophages, and T cells (three subtypes of white blood cells).[10][36] These immune cells move from the dermis to the epidermis and secrete inflammatory chemical signals (cytokines) such as tumor necrosis factor-α, interleukin-1β, interleukin-6, interleukin-36 and interleukin-22.[29][46] These secreted inflammatory signals are believed to stimulate keratinocytes to proliferate.[29] One hypothesis is that psoriasis involves a defect in regulatory T cells, and in the regulatory cytokine interleukin-10.[29]

Gene mutations of proteins involved in the skin's ability to function as a barrier have been identified as markers of susceptibility for the development of psoriasis.[47][48]

DNA released from dying cells acts as an inflammatory stimulus in psoriasis[49] and stimulates the receptors on certain dendritic cells, which in turn produce the cytokine interferon-α.[49] In response to these chemical messages from dendritic cells and T cells, keratinocytes also secrete cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α, which signal downstream inflammatory cells to arrive and stimulate additional [29]

inflammation.

Dendritic cells bridge the innate immune system and adaptive immune system. They are increased in psoriatic lesions[44] and induce the proliferation of T cells and type 1 helper T cells (Th1). Targeted immunotherapy as well as psoralen and ultraviolet A (PUVA) therapy can reduce the number of dendritic cells and favors a Th2 cell cytokine secretion pattern over a Th1/Th17 cell cytokine profile.[29][38] Psoriatic T cells move from the dermis into the epidermis and secrete interferon-γ and interleukin-17.[50] Interleukin-23 is known to induce the production of interleukin-17 and interleukin-22.[44][50] Interleukin-22 works in combination with interleukin-17 to induce keratinocytes to secrete neutrophil-attracting cytokines.[50]

## Diagnosis [edit]

A diagnosis of psoriasis is usually based on the appearance of the skin. Skin characteristics typical for psoriasis are scaly, erythematous plaques, papules, or patches of skin that may be painful and itch.[18] No special blood tests or diagnostic procedures are needed to make the diagnosis.[15][51]

The differential diagnosis of psoriasis includes dermatological conditions similar in appearance such as discoid eczema, seborrhoeic eczema, pityriasis rosea (may be confused with guttate psoriasis), nail fungus (may be confused with nail psoriasis) or cutaneous T cell lymphoma (50% of individuals with this cancer are initially misdiagnosed with psoriasis).[43] Dermatologic manifestations of systemic illnesses such as the rash of secondary syphilis may also be confused with psoriasis.[43]

If the clinical diagnosis is uncertain, a skin biopsy or scraping may be performed to rule out other disorders and to confirm the diagnosis. Skin from a biopsy will show clubbed epidermal projections that interdigitate with dermis on microscopy. Epidermal thickening is another characteristic histologic finding of psoriasis lesions.[15][52] The stratum granulosum layer of the epidermis is often missing or significantly decreased in psoriatic lesions; the skin cells from the most superficial layer of skin are also abnormal as they never fully mature. Unlike their mature counterparts, these superficial cells keep their nucleus.[15] Inflammatory infiltrates can typically be visualized on microscopy when examining skin tissue or joint tissue affected by psoriasis. Epidermal skin tissue affected by psoriatic inflammation often has many CD8+ T cells while a predominance of CD4+ T cells makes up the inflammatory infiltrates of the dermal layer of skin and the joints.[15]

### Classification [edit]

### Morphological [edit]

| Psoriasis Type | ICD-10 Code |
|---|---|
| Psoriasis vulgaris | L40.0 |
| Generalized pustular psoriasis | L40.1 |
| Acrodermatitis continua | L40.2 |
| Pustulosis palmaris et plantaris | L40.3 |
| Guttate psoriasis | L40.4 |
| Psoriatic arthritis | L40.50 |
| Psoriatic spondylitis | L40.53 |
| Inverse psoriasis | L40.8 |

Psoriasis is classified as a papulosquamous disorder and is most commonly subdivided into different categories based on histological characteristics.[4][7] Variants include plaque, pustular, guttate, and flexural psoriasis. Each form has a dedicated ICD-10 code.[53] Psoriasis can also be classified into nonpustular and pustular types.[54]

### Pathogenetic [edit]

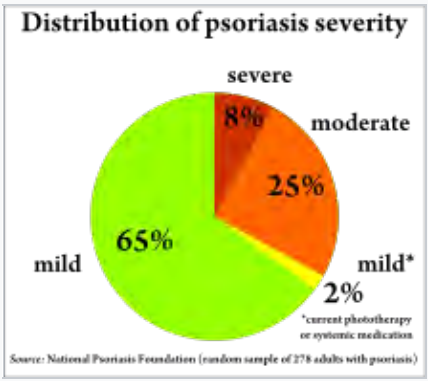
Another classification scheme considers genetic and demographic factors. Type 1 has a positive family history,

starts before the age of 40, and is associated with the human leukocyte antigen, *HLA-Cw6*. Conversely, type 2 does not show a family history, presents before age 40, and is not associated with *HLA-Cw6*.[55] Type 1 accounts for about 75% of persons with psoriasis.[56]

The classification of psoriasis as an autoimmune disease has sparked considerable debate. Researchers have proposed differing descriptions of psoriasis and psoriatic arthritis; some authors have classified them as autoimmune diseases[15][31][57] while others have classified them as distinct from autoimmune diseases and referred to them as immune-mediated inflammatory diseases.[29][58][59]

### Severity [edit]

There is no consensus about how to classify the severity of psoriasis. Mild psoriasis has been defined as a percentage of body surface area (BSA)≤10, a Psoriasis Area Severity Index (PASI) score ≤10, and a dermatology life quality index (DLQI) score ≤10.[60] Moderate to severe psoriasis was defined by the same group as BSA >10 or PASI score >10 and a DLQI score >10.[60] The DLQI is a 10 question tool used to measure the impact of several dermatologic diseases on daily functioning. The DLQI score ranges from 0 (minimal impairment) to 30 (maximal impairment) and is calculated with each answer being assigned 0–3 points with higher scores indicating greater social or occupational impairment.[61]

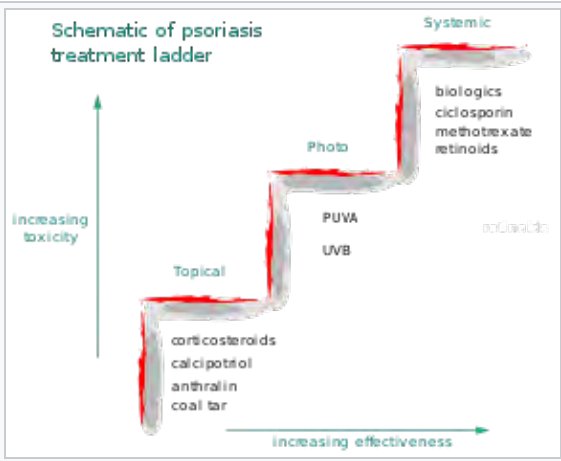


Distribution of severity

The psoriasis area severity index (PASI) is the most widely used measurement tool for psoriasis. PASI assesses the severity of lesions and the area affected and combines these two factors into a single score from 0 (no disease) to 72 (maximal disease).[62] Nevertheless, the PASI can be too unwieldy to use outside of research settings, which has led to attempts to simplify the index for clinical use.[63]

## Management [edit]

While no cure is available for psoriasis,[43] many treatment options exist. Topical agents are typically used for mild disease, phototherapy for moderate disease, and systemic agents for severe disease.[64]



Schematic of psoriasis treatment ladder

### Topical agents [edit]

Topical corticosteroid preparations are the most effective agents when used continuously for 8 weeks; retinoids and coal tar were found to be of limited benefit and may be no better than placebo.[65] Greater benefit has been observed with very potent corticosteroids when compared to potent corticosteroids. Vitamin D analogues such as paricalcitol were found to be significantly superior to placebo. Combination therapy with vitamin D and a corticosteroid was superior to either treatment alone and vitamin D was found to be superior to coal tar for chronic plaque psoriasis.[66]

Moisturizers and emollients such as mineral oil, petroleum jelly, calcipotriol, and decubal (an oil-in-water emollient) were found to increase the clearance of psoriatic plaques. Emollients have been shown to be even more effective at clearing psoriatic plaques when combined with phototherapy.[67] However, certain emollients have no impact on psoriasis plaque clearance or may even decrease the clearance achieved with phototherapy. The emollient salicylic acid is structurally similar to para-aminobenzoic acid (PABA), commonly found in sunscreen, and is known to interfere with phototherapy in psoriasis. Coconut oil, when used as an emollient in psoriasis, has been found to decrease plaque clearance with phototherapy.[67] Medicated creams and ointments applied directly to psoriatic plaques can help reduce inflammation, remove built-up scale, reduce skin turnover, and clear affected skin of plaques. Ointment and creams containing coal tar, dithranol, corticosteroids (i.e. desoximetasone), fluocinonide, vitamin D analogs (for example, calcipotriol), and retinoids are routinely used.

The use of the finger tip unit may be helpful in guiding how much topical treatment to use.[34][68]

Vitamin D analogues may be useful with steroids; however, alone have a higher rate of side effects.[69] They may allow less steroids to be used.[70]

Another topical therapy used to treat psoriasis is a form of balneotherapy, which involves daily baths in the Dead Sea. This is usually done for four weeks with the benefit attributed to sun exposure and specifically UVB light. This is cost-effective and it has been propagated as an effective way to treat psoriasis without medication.[71] Decreases of PASI scores greater than 75% and remission for several months have commonly been observed.[71] Side-effects may be mild such as itchiness, folliculitis, sunburn, poikiloderma, and a theoretical risk of nonmelanoma skin cancer or melanoma has been suggested.[71] However, more recent studies have determined that there does not appear to be increased risk of melanoma in the long-term.[72] Data are inconclusive with respect to nonmelanoma skin cancer risk, but support the idea that the therapy is associated with an increased risk of benign forms of sun-induced skin damage such as, but not limited to, actinic elastosis or liver spots.[72] Dead Sea balneotherapy is also effective for psoriatic arthritis.[72]

## Light exposure [edit]

Phototherapy in the form of sunlight has long been used for psoriasis.[64] Wavelengths of 311–313 nanometers are most effective, and special lamps have been developed for this application.[64] The exposure time should be controlled to avoid over exposure and burning of the skin. The UVB lamps should have a timer that will turn off the lamp when the time ends. The amount of light used is determined by a person's skin type.[64] Increased rates of cancer from treatment appear to be small.[64] Narrow band UVB light (NBUVB) phototherapy has been demonstrated to have similar efficacy to PUVA.[73]

One of the problems with clinical phototherapy is the difficulty many patients have gaining access to a facility. Indoor tanning resources are almost ubiquitous today and could be considered as a means for patients to get UV exposure when dermatologist provided phototherapy is not available. Indoor tanning is already used by many people as a treatment for psoriasis; one indoor facility reported that 50% of its clients were using the center for psoriasis treatment; another reported 36% were doing the same thing. However, a concern with the use of commercial tanning is that tanning beds that primarily emit UVA might not effectively treat psoriasis. One study found that plaque psoriasis is responsive to erythemogenic doses of either UVA or UVB, as exposure to either can cause dissipation of psoriatic plaques. It does require more energy to reach erythemogenic dosing with UVA.[74]

UV light therapies all have risks; tanning beds are no exception, particularly in the link between UV light and the increased chance of skin cancer. There are increased risks of melanoma, squamous cell and basal cell carcinomas; younger psoriasis patients, particularly those under age 35, are at increased risk from melanoma from UV light treatment. The World Health Organization (WHO) listed tanning beds as carcinogens. A review of studies recommends that people who are susceptible to skin cancers exercise caution when using UV light therapy as a treatment.[74]

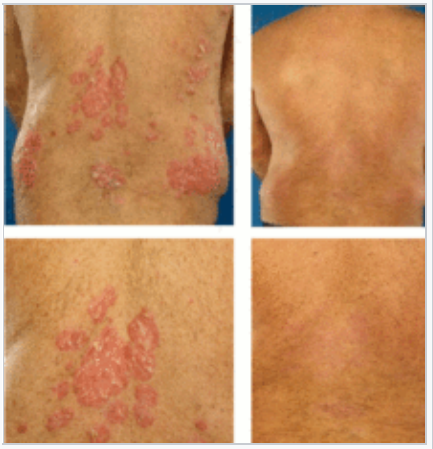
A major mechanism of NBUVB is the induction of DNA damage in the form of pyrimidine dimers. This type of phototherapy is useful in the treatment of psoriasis because the formation of these dimers interferes with the cell cycle and stops it. The interruption of the cell cycle induced by NBUVB opposes the characteristic rapid division of skin cells seen in psoriasis.[73] The activity of many types of immune cells found in the skin is also effectively suppressed by NBUVB phototherapy treatments. The most common short-term side effect of this form of phototherapy is redness of the skin; less common side effects of NBUVB phototherapy are itching and blistering of the treated skin, irritation of the eyes in the form of conjunctival inflammation or inflammation of the cornea, or cold sores due to reactivation of the herpes simplex virus in the skin surrounding the lips. Eye protection is usually given during phototherapy treatments.[73]

Psoralen and ultraviolet A phototherapy (PUVA) combines the oral or topical administration of psoralen with exposure to ultraviolet A (UVA) light. The mechanism of action of PUVA is unknown, but probably involves activation of psoralen by UVA light, which inhibits the abnormally rapid production of the cells in psoriatic skin. There are multiple mechanisms of action associated with PUVA, including effects on the skin's immune system. PUVA is associated with nausea, headache, fatigue, burning, and itching. Long-term treatment is associated with squamous cell carcinoma (but not with melanoma).[35][75] A combination therapy for moderate to severe

psoriasis using PUVA plus acitretin resulted in benefit, but acitretin use has been associated with birth defects and liver damage.[76]

## Systemic agents [edit]

Psoriasis resistant to topical treatment and phototherapy may be treated with systemic therapies including medications by mouth or injectable treatments.[77] People undergoing systemic treatment must have regular blood and liver function tests to check for medication toxicities.[77] Pregnancy must be avoided for most of these treatments. The majority of people experience a recurrence of psoriasis after systemic treatment is discontinued.



Pictures of a patient with psoriasis (and psoriatic arthritis) at baseline and 8 weeks after initiation of infliximab therapy.

Non-biologic systemic treatments frequently used for psoriasis include methotrexate, ciclosporin, hydroxycarbamide, fumarates such as dimethyl fumarate, and retinoids.[78] Methotrexate and ciclosporin are drugs that suppress the immune system; retinoids are synthetic forms of vitamin A. These agents are also regarded as first-line treatments for psoriatic erythroderma.[12]

Biologics are manufactured proteins that interrupt the immune process involved in psoriasis. Unlike generalised immunosuppressive drug therapies such as methotrexate, biologics target specific aspects of the immune system contributing to psoriasis.[78] These medications are generally well-tolerated and limited long-term outcome data have demonstrated biologics to be safe for long-term use in moderate to severe plaque psoriasis.[78][79] However, due to their immunosuppressive actions, biologics have been associated with a small increase in the risk for infection.[78] Guidelines regard biologics as third-line treatment for plaque psoriasis following inadequate response to topical treatment, phototherapy, and non-biologic systemic treatments.[79] The safety of biologics during pregnancy has not been assessed. European guidelines recommend avoiding biologics if a pregnancy is planned; anti-TNF therapies such as infliximab are not recommended for use in chronic carriers of the hepatitis B virus or individuals infected with HIV.[78]

Several monoclonal antibodies target cytokines, the molecules that cells use to send inflammatory signals to each other. TNF-α is one of the main executor inflammatory cytokines. Four monoclonal antibodies (MAbs) (infliximab, adalimumab, golimumab, and certolizumab pegol) and one recombinant TNF-α decoy receptor, etanercept, have been developed to inhibit TNF-α signaling. Additional monoclonal antibodies, such as ixekizumab,[80] have been developed against pro-inflammatory cytokines[81] and inhibit the inflammatory pathway at a different point than the anti-TNF-α antibodies.[29] IL-12 and IL-23 share a common domain, p40, which is the target of the recently FDA-approved ustekinumab.[31]

Two drugs that target T cells are efalizumab and alefacept. Efalizumab is a monoclonal antibody that specifically targets the CD11a subunit of LFA-1.[78] It also blocks the adhesion molecules on the endothelial cells that line blood vessels, which attract T cells. Efalizumab was voluntarily withdrawn from the European market in February 2009 and from the US market in June 2009 by the manufacturer due to the medication's association with cases of progressive multifocal leukoencephalopathy.[78] Alefacept also blocks the molecules that dendritic cells use to communicate with T cells and even causes natural killer cells to kill T cells as a way of controlling inflammation.[29] Apremilast may also be used.[10]

Individuals with psoriasis may develop neutralizing antibodies against monoclonal antibodies. Neutralization occurs when an antidrug antibody prevents a monoclonal antibody such as infliximab from binding antigen in a laboratory test. Specifically, neutralization occurs when the antidrug antibody binds to infliximab's antigen binding site instead of TNF-α. When infliximab no longer binds tumor necrosis factor alpha, it no longer decreases inflammation, and psoriasis may worsen. Neutralizing antibodies have not been reported against etanercept, a biologic drug that is a fusion protein composed of two TNF-α receptors. The lack of neutralizing antibodies against etanercept is probably secondary to the innate presence of the TNF-α receptor, and the development of immune tolerance.[82]

## Surgery [edit]

Limited evidence suggests removal of the tonsils may benefit people with chronic plaque psoriasis, guttate psoriasis, and palmoplantar pustulosis.[83][84]

### Diet [edit]

Uncontrolled studies have suggested that individuals with psoriasis or psoriatic arthritis may benefit from a diet supplemented with fish oil rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[85] Diet recommendations include consumption of cold water fish (preferably wild fish, not farmed) such as salmon, herring, and mackerel, extra virgin olive oil, legumes, vegetables, fruits, and whole grains; and avoid consumption of alcohol, red meat, and dairy products. The effect of consumption of caffeine (including coffee, black tea, mate, and dark chocolate) remains to be determined[86]

There is a higher rate of celiac disease among people with psoriasis.[86][87] Disease severity generally decreases in people with celiac disease and those with anti-gliadin antibodies after the adoption of a gluten-free diet.[88][89][85]

## Prognosis [edit]

Most people with psoriasis experience nothing more than mild skin lesions that can be treated effectively with topical therapies.[65]

Psoriasis is known to have a negative impact on the quality of life of both the affected person and the individual's family members.[31] Depending on the severity and location of outbreaks, individuals may experience significant physical discomfort and some disability. Itching and pain can interfere with basic functions, such as self-care and sleep.[45] Participation in sporting activities, certain occupations, and caring for family members can become difficult activities for those with plaques located on their hands and feet.[45] Plaques on the scalp can be particularly embarrassing, as flaky plaque in the hair can be mistaken for dandruff.[90]

Individuals with psoriasis may feel self-conscious about their appearance and have a poor self-image that stems from fear of public rejection and psychosexual concerns. Psoriasis has been associated with low self-esteem and depression is more common among those with the condition.[4] People with psoriasis often feel prejudiced against due to the commonly held incorrect belief that psoriasis is contagious.[45] Psychological distress can lead to significant depression and social isolation; a high rate of thoughts about suicide has been associated with psoriasis.[20] Many tools exist to measure the quality of life of patients with psoriasis and other dermatological disorders. Clinical research has indicated individuals often experience a diminished quality of life.[91] Children with psoriasis may encounter bullying.[92]

Several conditions are associated with psoriasis. These occur more frequently in older people. Nearly half of individuals with psoriasis over the age of 65 have at least three comorbidities, and two-thirds have at least two comorbidities.[93]

### Cardiovascular disease [edit]

Psoriasis has been associated with obesity[4] and several other cardiovascular and metabolic disturbances. The incidence of diabetes is 27% higher in people affected by psoriasis than in those without the condition.[94] Severe psoriasis may be even more strongly associated with the development of diabetes than mild psoriasis.[94] Younger people with psoriasis may also be at increased risk for developing diabetes.[93][95] Individuals with psoriasis or psoriatic arthritis have a slightly higher risk of heart disease and heart attacks when compared to the general population. Cardiovascular disease risk appeared to be correlated with the severity of psoriasis and its duration. There is no strong evidence to suggest that psoriasis is associated with an increased risk of death from cardiovascular events. Methotrexate may provide a degree of protection for the heart.[35][93]

The odds of having hypertension are 1.58 times higher in people with psoriasis than those without the condition; these odds are even higher with severe cases of psoriasis. A similar association was noted in people who have psoriatic arthritis—the odds of having hypertension were found to be 2.07 times greater when compared to odds of the general population. The link between psoriasis and hypertension is not currently understood. Mechanisms hypothesized to be involved in this relationship include the following: dysregulation of the renin-angiotensin [95][96]

system, elevated levels of endothelin 1 in the blood, and increased oxidative stress. The incidence of the heart rhythm abnormality atrial fibrillation is 1.31 times higher in people with mild psoriasis and 1.63 times higher in people with severe psoriasis.[97] There may be a slightly increased risk of stroke associated with psoriasis, especially in severe cases.[35][98] Treating high levels of cholesterol with statins has been associated with decreased psoriasis severity, as measured by PASI score, and has also been associated with improvements in other cardiovascular disease risk factors such as markers of inflammation.[99] These cardioprotective effects are attributed to ability of statins to improve blood lipid profile and because of their anti-inflammatory effects. Statin use in those with psoriasis and hyperlipidemia was associated with decreased levels of high-sensitivity C-reactive protein and TNFα as well as decreased activity of the immune protein LFA-1.[99] Compared to individuals without psoriasis, those affected by psoriasis are more likely to satisfy the criteria for metabolic syndrome.[15][97]

### Other diseases [edit]

The rates of Crohn's disease and ulcerative colitis are increased when compared with the general population, by a factor of 3.8 and 7.5 respectively.[4] People with psoriasis also have a higher risk of celiac disease.[86][89] Few studies have evaluated the association of multiple sclerosis with psoriasis, and the relationship has been questioned.[4][100] Psoriasis has been associated with a 16% increase in overall relative risk for non-skin cancer.[35] People with psoriasis have a 52% increased risk cancers of the lung and bronchus, a 205% increase in the risk of developing cancers of the upper gastrointestinal tract, a 31% increase in the risk of developing cancers of the urinary tract, a 90% increase in the risk of developing liver cancer, and a 46% increase in the risk of developing pancreatic cancer.[35] The risk for development of non-melanoma skin cancers is also increased. Psoriasis increases the risk of developing squamous cell carcinoma of the skin by 431% and increases the risk of basal cell carcinoma by 100%.[35] There is no increased risk of melanoma associated with psoriasis.[35]

## Epidemiology [edit]

Psoriasis is estimated to affect 2–4% of the population of the western world.[8] The rate of psoriasis varies according to age, gender, region and ethnicity; a combination of environmental and genetic factors is thought to be responsible for these differences.[8] It can occur at any age, although it most commonly appears for the first time between the ages of 15 and 25 years. Approximately one third of people with psoriasis report being diagnosed before age 20.[101] Psoriasis affects both sexes equally.[55]

Psoriasis affects about 7.5 million Americans and occurs more frequently between the ages of 15 and 50.[9]

People with inflammatory bowel disease such as Crohn's disease or ulcerative colitis are at an increased risk of developing psoriasis.[42] Psoriasis is more common in countries farther from the equator.[42] Persons of white European ancestry are more likely to have psoriasis and the condition is relatively uncommon in African Americans and extremely uncommon in Native Americans.[43]

## History [edit]

Scholars believe psoriasis to have been included among the various skin conditions called *tzaraath* (translated as leprosy) in the Hebrew Bible, a condition imposed as a punishment for slander. The patient was deemed "impure" (see tumah and taharah) during their afflicted phase and is ultimately treated by the kohen.[102] However, it is more likely that this confusion arose from the use of the same Greek term for both conditions. The Greeks used the term lepra (λεπρα) for scaly skin conditions. They used the term psora to describe itchy skin conditions.[102] It became known as *Willan's lepra* in the late 18th century when English dermatologists Robert Willan and Thomas Bateman differentiated it from other skin diseases. Leprosy, they said, is distinguished by the regular, circular form of patches, while psoriasis is always irregular. Willan identified two categories: *leprosa graecorum* and *psora leprosa*.[103]

Psoriasis is thought to have first been described in Ancient Rome by Cornelius Celsus. The disease was first classified by English physician Thomas Willan. The British dermatologist Thomas Bateman described a possible link between psoriasis and arthritic symptoms in 1813.[104]

The history of psoriasis is littered with treatments of dubious effectiveness and high toxicity. In the 18th and

19th centuries, Fowler's solution, which contains a poisonous and carcinogenic arsenic compound, was used by dermatologists as a treatment for psoriasis.[102] Mercury was also used for psoriasis treatment during this time period.[102] Sulfur, iodine, phenol were also commonly used treatments for psoriasis during this era when it was incorrectly believed that psoriasis was an infectious disease.[102] Coal tars were widely used with ultraviolet light irradiation as a topical treatment approach in the early 1900s.[102][105] During the same time period, psoriatic arthritis cases were treated with intravenously administered gold preparations in the same manner as rheumatoid arthritis.[105] All of these treatments have been replaced with modern topical and systemic therapies.

### Etymology [edit]

The word *psoriasis* is from Greek ψωρίασις, meaning "itching condition" or "being itchy"[106] from *psora*, "itch" and *-iasis*, "action, condition".

## Society and culture [edit]

The International Federation of Psoriasis Associations (IFPA) is the global umbrella organization for national and regional psoriasis patient associations and also gathers the leading experts in psoriasis and psoriatic arthritis research for scientific conferences every three years.[107] The Psoriasis International Network, a program of the Fondation René Touraine, gathers dermatologists, rheumatologists and other caregivers involved in the management of psoriasis. Non-profit organizations the National Psoriasis Foundation in the United States, the Psoriasis Association in the United Kingdom and Psoriasis Australia offer advocacy and education about psoriasis in their respective countries.

### Cost [edit]

The annual cost for treating psoriasis in the US is estimated as high as $32.5 billion - $12.2 billion in direct costs. Pharmacy costs are the main source of direct expense, with biologic therapy the most prevalent. These costs increase significantly when co-morbid conditions such as heart disease, hypertension, diabetes, lung disease and psychiatric disorders are factored in. Expenses linked to co-morbidities are estimated at an additional $23,000 per patient per year.[108]

## Research [edit]

The role of insulin resistance in the pathogenesis of psoriasis is currently under investigation. Preliminary research has suggested that antioxidants such as polyphenols may have beneficial effects on the inflammation characteristic of psoriasis.[109]

Many novel drugs being researched target the Th17/IL-23 axis,[109] particularly IL-23p19 inhibitors, as IL-23p19 is present in increased concentrations in psoriasis skin lesions while contributing less to protection against opportunistic infections.[110] Other cytokines such as IL-17 and IL-22 also have been targets for inhibition as they play important roles in the pathogenesis of psoriasis.[110] Another avenue of research has focused on the use of vascular endothelial growth factor inhibitors to treat psoriasis.[57] Oral agents being investigated as alternatives to medications administered by injection include Janus kinase inhibitors, protein kinase C inhibitors, mitogen-activated protein kinase inhibitors, and phosphodiesterase 4 inhibitors, all of which have proven effective in various phase 2 and 3 clinical trials.[109][110] However, these agents have potentially severe side-effects due to their immunosuppressive mechanisms.[110]

## References [edit]


1. ^ Jones, Daniel (2003) [1917], Peter Roach, James Hartmann and Jane Setter, eds., *English Pronouncing Dictionary*, Cambridge: Cambridge University Press, ISBN 3-12-539683-2
2. ^ "Psoriasis". *Merriam-Webster Dictionary*.
3. ^ a b c d e f g "Questions and Answers about Psoriasis". *National Institute of Arthritis and Musculoskeletal and Skin Diseases*. October 2013. Retrieved 1 July 2015.
4. ^ a b c d e f g h Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, Lebwohl M, Koo JY, Elmets

CA, Korman NJ, Beutner KR, Bhushan R (May 2008). "Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics". *J Am Acad Dermatol*. **58** (5): 826–50. doi:10.1016/j.jaad.2008.02.039. PMID 18423260.

5. ^ Ely JW, Seabury Stone M (March 2010). "The generalized rash: part II. Diagnostic approach". *Am Fam Physician*. **81** (6): 735–9. PMID 20229972.
6. ^ *a b c d e f g* Boehncke, WH; Schön, MP (26 May 2015). "Psoriasis.". *Lancet (London, England)*. **386**: 983–94. doi:10.1016/S0140-6736(14)61909-7. PMID 26025581.
7. ^ *a b c d e f g h i* Jain, Sima (2012). *Dermatology : illustrated study guide and comprehensive board review*. New York: Springer. pp. 83–87. ISBN 978-1-4419-0524-6.
8. ^ *a b c* Parisi R, Symmons DP, Griffiths CE, Ashcroft DM (February 2013). Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. "Global epidemiology of psoriasis: a systematic review of incidence and prevalence". *J Invest Dermatol*. **133** (2): 377–85. doi:10.1038/jid.2012.339. PMID 23014338.
9. ^ *a b* Tamparo, Carol (2011). *Fifth Edition: Diseases of the Human Body*. Philadelphia, PA: F.A. Davis Company. p. 180. ISBN 978-0-8036-2505-1.
10. ^ *a b c d e* Palfreeman AC, McNamee KE, McCann FE (March 2013). "New developments in the management of psoriasis and psoriatic arthritis: a focus on apremilast". *Drug Des Devel Ther*. **7**: 201–210. doi:10.2147/DDDT.S32713. PMC 3615921. PMID 23569359.
11. ^ Colledge, N.R.; Walker, B.R.; Ralston, S.H., eds. (2010). *Davidson's principles and practice of medicine.* (21st ed.). Edinburgh: Churchill Livingstone/Elsevier. pp. 1260–1261. ISBN 978-0-7020-3084-0.
12. ^ *a b* Zattra E, Belloni Fortina A, Peserico A, Alaibac M (May 2012). "Erythroderma in the era of biological therapies". *Eur J Dermatol*. **22** (2): 167–71. doi:10.1684/ejd.2011.1569. PMID 22321651.
13. ^ Stanway A. "Erythrodermic psoriasis". DermNet NZ. Retrieved 16 March 2014.
14. ^ Robinson A, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Bebo BF, Kalb RE (2012). "Treatment of pustular psoriasis: From the Medical Board of the National Psoriasis Foundation". *J Am Acad Dermatol*. **67** (2): 279–88. doi:10.1016/j.jaad.2011.01.032. PMID 22609220.
15. ^ *a b c d e f g h i j k l* Raychaudhuri SK, Maverakis E, Raychaudhuri SP (January 2014). "Diagnosis and classification of psoriasis". *Autoimmun Rev*. **13**: 490–5. doi:10.1016/j.autrev.2014.01.008. PMID 24434359.
16. ^ *a b c d e* Naik HB, Cowen EW (July 2013). "Autoinflammatory pustular neutrophilic diseases". *Dermatol Clin*. **31** (3): 405–25. doi:10.1016/j.det.2013.04.001. PMC 3703099. PMID 23827244.
17. ^ *a b* James, William; Berger, Timothy; Elston, Dirk (2005). *Andrews' Diseases of the Skin: Clinical Dermatology* (10th ed.). Saunders. pp. 191–7. ISBN 0-7216-2921-0.
18. ^ *a b c d* Weigle N, McBane S (May 2013). "Psoriasis". *Am Fam Physician*. **87** (9): 626–33. PMID 23668525.
19. ^ *a b c d* Gudjonsson JE, Elder JT, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K (2012). "18: Psoriasis". *Fitzpatrick's Dermatology in General Medicine* (8th ed.). New York: McGraw-Hill. ISBN 0-07-166904-3.
20. ^ *a b* Gelmetti C (January 2009). "Therapeutic moisturizers as adjuvant therapy for psoriasis patients". *Am J Clin Dermatol*. **10** (Suppl 1): 7–12. doi:10.2165/0128071-200910001-00002. PMID 19209948.
21. ^ *a b c* Yesudian PD, Chalmers RJ, Warren RB, Griffiths CE (January 2012). "In search of oral psoriasis". *Arch Dermatol Res*. **304** (1): 1–5. doi:10.1007/s00403-011-1175-3. PMID 21927905.
22. ^ Ship, Martin S. Greenberg, Michael Glick, Jonathan A. (2008). *Burket's oral medicine* (11th ed.). Hamilton, Ont.: BC Decker. pp. 103–104. ISBN 1-55009-345-2.
23. ^ Reamy BV, Derby R, Bunt CW (March 2010). "Common tongue conditions in primary care". *Am Fam Physician*. **81** (5): 627–34. PMID 20187599.
24. ^ *a b* Chimenti MS, Saraceno R, Chiricozzi A, Giunta A, Chimenti S, Perricone R (April 2013). "Profile of certolizumab and its potential in the treatment of psoriatic arthritis". *Drug Des Devel Ther*. **7**: 339–48. doi:10.2147/DDDT.S31658. PMC 3633576. PMID 23620660.
25. ^ *a b* Goldenstein-Schainberg C, Favarato MH, Ranza R (January–February 2012). "Current and relevant concepts in psoriatic arthritis" (PDF). *Rev Bras Reumatol*. **52** (1): 98–106. doi:10.1590/s0482-50042012000100010. PMID 22286649.
26. ^ Krawczyk-Wasielewska A, Skorupska E, Samborski W (April 2013). "Sacroiliac joint pain as an important element of psoriatic arthritis diagnosis". *Postepy Dermatol Alergol*. **30** (2): 108–12. doi:10.5114/pdia.2013.34161. PMC 3834688. PMID 24278057.
27. ^ *a b* Tan ES, Chong WS, Tey HL (December 2012). "Nail psoriasis: a review". *Am J Clin Dermatol*. **13** (6): 375–88. doi:10.2165/11597000-000000000-00000. PMID 22784035.
28. ^ Krueger G, Ellis CN (2005). "Psoriasis—recent advances in understanding its pathogenesis and treatment". *J Am Acad Dermatol*. **53** (1 Suppl 1): S94–100. doi:10.1016/j.jaad.2005.04.035. PMID 15968269.
29. ^ *a b c d e f g h i j k l m n* Nestle FO, Kaplan DH, Barker J (2009). "Psoriasis". *N Engl J Med*. **361** (5): 496–509. doi:10.1056/NEJMra0804595. PMID 19641206.
30. ^ Catherine H, Smith (17 August 2006). "Psoriasis and its management". *theBMJ*. Retrieved 8 October 2015.

31. ^ a b c d e f g Prieto-Pérez R, Cabaleiro T, Daudén E, Ochoa D, Roman M, Abad-Santos F (August 2013). "Genetics of Psoriasis and Pharmacogenetics of Biological Drugs". *Autoimmune Dis.* **2013** (613086): 613086. doi:10.1155/2013/613086. PMC 3771250. PMID 24069534.
32. ^ Jordan CT, Cao L, Roberson ED, et al. (April 2012). "Rare and common variants in CARD14, encoding an epidermal regulator of NF-kappaB, in psoriasis". *The American Journal of Human Genetics*. **90**: 796–808. doi:10.1016/j.ajhg.2012.03.013.
33. ^ Jordan CT, Cao L, Roberson ED, et al. (April 2012). "PSORS2 is due to mutations in CARD14". *The American Journal of Human Genetics*. **90**: 784–795. doi:10.1016/j.ajhg.2012.03.012.
34. ^ a b Clarke P (July 2011). "Psoriasis" (PDF). *Aust Fam Physician*. **40** (7): 468–73. PMID 21743850.
35. ^ a b c d e f g h Richard MA, Barnetche T, Horreau C, Brenaut E, Pouplard C, Aractingi S, Aubin F, Cribier B, Joly P, Jullien D, Le Maître M, Misery L, Ortonne JP, Paul C (August 2013). "Psoriasis, cardiovascular events, cancer risk and alcohol use: evidence-based recommendations based on systematic review and expert opinion". *J Eur Acad Dermatol Venereol*. **27** (Supplement 3): 2–11. doi:10.1111/jdv.12162. PMID 23845148.
36. ^ a b c Cedeno-Laurent F, Gómez-Flores M, Mendez N, Ancer-Rodríguez J, Bryant JL, Gaspari AA, Trujillo JR (January 2011). "New insights into HIV-1-primary skin disorders". *J Int AIDS Soc*. **14** (5). doi:10.1186/1758-2652-14-5. PMC 3037296. PMID 21261982.
37. ^ Fife DJ, Waller JM, Jeffes EW, Koo JY (May 2007). "Unraveling the Paradoxes of HIV-associated Psoriasis: A Review of T-cell Subsets and Cytokine Profiles". *Dermatology Online Journal*. **13** (2).
38. ^ a b Wong T, Hsu L, Liao W (January–February 2013). "Phototherapy in psoriasis: a review of mechanisms of action". *J Cutan Med Surg*. **17** (1): 6–12. doi:10.2310/7750.2012.11124. PMC 3736829. PMID 23364144.
39. ^ Martin DA, Towne JE, Kricorian G, Klekotka P, Gudjonsson JE, Krueger JG, Russell CB (January 2013). "The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings". *J Invest Dermatol*. **133** (1): 17–26. doi:10.1038/jid.2012.194. PMC 3568997. PMID 22673731.
40. ^ "Images of Memorable Cases: Case 34". *Connexions*. Rice University. "This AIDS patient presented with a pruritic eruption over most of his body"
41. ^ Fry, L; Baker, BS (2007). "Triggering psoriasis: the role of infections and medications.". *Clinics in dermatology*. **25** (6): 606–15. doi:10.1016/j.clindermatol.2007.08.015. PMID 18021899.
42. ^ a b c Guerra I, Gisbert JP (January 2013). "Onset of psoriasis in patients with inflammatory bowel disease treated with anti-TNF agents". *Expert Rev Gastroenterol Hepatol*. **7** (1): 41–8. doi:10.1586/egh.12.64. PMID 23265148.
43. ^ a b c d e Weller, Richard; John AA Hunter; John Savin; Mark Dahl (2008). *Clinical dermatology* (4th ed.). Malden, Mass.: Blackwell Pub. pp. 54–70. ISBN 978-1-4443-0009-3.
44. ^ a b c Ouyang W (December 2010). "Distinct roles of IL-22 in human psoriasis and inflammatory bowel disease". *Cytokine Growth Factor Rev*. **21** (6): 435–41. doi:10.1016/j.cytogfr.2010.10.007. PMID 21106435.
45. ^ a b c d Parrish L. (2012). "Psoriasis: symptoms, treatments and its impact on quality of life". *Br J Community Nurs*. **17** (11): 524, 526, 528. doi:10.12968/bjcn.2012.17.11.524. PMID 23124421.
46. ^ Baliwag, Jaymie; Barnes, Drew H.; Johnston, Andrew (2015-06-01). "Cytokines in psoriasis". *Cytokine*. Skin Disease, Immune Response and Cytokines. **73** (2): 342–350. doi:10.1016/j.cyto.2014.12.014. PMC 4437803. PMID 25585875.
47. ^ Roberson ED, Bowcock AM (September 2010). "Psoriasis genetics: breaking the barrier". *Trends Genet*. **26** (9): 415–23. doi:10.1016/j.tig.2010.06.006. PMC 2957827. PMID 20692714.
48. ^ Ramos-e-Silva M; Jacques Cd (May–June 2012). "Epidermal barrier function and systemic diseases". *Clin Dermatol*. **30** (3): 277–9. doi:10.1016/j.clindermatol.2011.08.025. PMID 22507041.
49. ^ a b Dombrowski Y, Schauber J (May 2012). "Cathelicidin LL-37: a defense molecule with a potential role in psoriasis pathogenesis". *Exp Dermatol*. **21** (5): 327–30. doi:10.1111/j.1600-0625.2012.01459.x. PMID 22509827.
50. ^ a b c Mudigonda P, Mudigonda T, Feneran AN, Alamdari HS, Sandoval L, Feldman SR (October 2012). "Interleukin-23 and interleukin-17: importance in pathogenesis and therapy of psoriasis". *Dermatol Online J*. **18** (10): 1. PMID 23122008.
51. ^ Johnson MA, Armstrong AW (2012). "Clinical and Histologic Diagnostic Guidelines for Psoriasis: A Critical Review". *Clin Rev Allerg Immunol*. **44** (2): 166–72. doi:10.1007/s12016-012-8305-3. PMID 22278173.
52. ^ Kunz M, Ibrahim SM (2009). "Cytokines and cytokine profiles in human autoimmune diseases and animal models of autoimmunity". *Mediators Inflamm*. **2009**: 979258. doi:10.1155/2009/979258. PMC 2768824. PMID 19884985.
53. ^ Application to Dermatology of International Classification of Disease (ICD-10). The International League of Dermatological Societies
54. ^ Freedberg, Irwin M.; Fitzpatrick, Thomas B. (2003). *Fitzpatrick's dermatology in general medicine* (6th ed.). New York: McGraw-Hill. p. 414. ISBN 0-07-138076-0.
55. ^ a b Kupetsky EA, Keller M (November–December 2013). "Psoriasis vulgaris: an evidence-based guide for primary care". *J Am Board Fam Med*. **26** (6): 787–801. doi:10.3122/jabfm.2013.06.130055. PMID 24204077.
56. ^ Griffiths CE, Christophers E, Barker JN, Chalmers RJ, Chimenti S, Krueger GG, Leonardi C, Menter A, Ortonne JP, Fry L (February 2007). "A classification of psoriasis vulgaris according to phenotype". *Br J Dermatol*. **156** (2): 258–62.

doi:10.1111/j.1365-2133.2006.07675.x. PMID 17223864.

57. ^ a b Weidemann AK, Crawshaw AA, Byrne E, Young HS (September 2013). "Vascular endothelial growth factor inhibitors: investigational therapies for the treatment of psoriasis". *Clin Cosmet Investig Dermatol*. **6**: 233–44. doi:10.2147/CCID.S35312. PMC 3790838. PMID 24101875.
58. ^ Han R, Rostami-Yazdi M, Gerdes S, Mrowietz U (September 2013). "Triptolide in the treatment of psoriasis and other immune-mediated inflammatory diseases". *Br J Clin Dermatol*. **74** (3): 424–36. doi:10.1111/j.1365-2125.2012.04221.x. PMC 3477344. PMID 22348323.
59. ^ Quatresooz P, Hermanns-Lê T, Piérard GE, Humbert P, Delvenne P, Piérard-Franchimont C (June 2012). "Ustekinumab in psoriasis immunopathology with emphasis on the Th17-IL23 axis: a primer". *J Biomed Biotechnol*. **2012** (147413): 1–5. doi:10.1155/2012/147413. PMC 3384985. PMID 22754278.
60. ^ a b Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, Franke J, Antoniou C, Arenberger P, Balieva F, Bylaite M, Correia O, Daudén E, Gisondi P, Iversen L, Kemény L, Lahfa M, Nijsten T, Rantanen T, Reich A, Rosenbach T, Segaert S, Smith C, Talme T, Volc-Platzer B, Yawalkar N (January 2011). "Definition of treatment goals for moderate to severe psoriasis: a European consensus". *Arch Dermatol Res*. **303** (1): 1–10. doi:10.1007/s00403-010-1080-1. PMC 3016217. PMID 20857129.
61. ^ Mease PJ (November 2011). "Measures of psoriatic arthritis: Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI)". *Arthritis Care Res (Hoboken)*. **63** (Supplement 11): S64–85. doi:10.1002/acr.20577. PMID 22588772.
62. ^ "Psoriasis Update". *Skin & Aging*. **14** (3): 46–50. 2006.[*dead link*]
63. ^ Louden BA, Pearce DJ, Lang W, Feldman SR (2004). "A Simplified Psoriasis Area Severity Index (SPASI) for rating psoriasis severity in clinic patients". *Dermatol. Online J.* **10** (2): 7. PMID 15530297.
64. ^ a b c d e Menter A, Griffiths CE (July 2007). "Current and future management of psoriasis". *Lancet*. **370** (9583): 272–84. doi:10.1016/S0140-6736(07)61129-5. PMID 17658398.
65. ^ a b Samarasekera EJ, Sawyer L, Wonderling D, Tucker R, Smith CH (2013). "Topical therapies for the treatment of plaque psoriasis: systematic review and network meta-analyses". *Br J Dermatol*. **168** (5): 954–67. doi:10.1111/bjd.12276. PMID 23413913.
66. ^ Mason AR, Mason J, Cork M, Dooley G, Hancock H (2013). "Topical treatments for chronic plaque psoriasis". *Cochrane Database Syst Rev*. **3** (CD005028). doi:10.1002/14651858.CD005028.pub3. PMID 23543539.
67. ^ a b Asztalos ML, Heller MM, Lee ES, Koo J (May 2013). "The impact of emollients on phototherapy: a review". *J Am Acad Dermatol*. **68** (5): 817–24. doi:10.1016/j.jaad.2012.05.034. PMID 23399460.
68. ^ Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, Gottlieb A, Koo JY, Lebwohl M, Lim HW, Van Voorhees AS, Beutner KR, Bhushan R (2009). "Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies". *J Am Acad Dermatol*. **60** (4): 643–59. doi:10.1016/j.jaad.2008.12.032. PMID 19217694.
69. ^ Mason, AR; Mason, J; Cork, M; Dooley, G; Hancock, H (28 March 2013). "Topical treatments for chronic plaque psoriasis.". *The Cochrane database of systematic reviews*. **3**: CD005028. doi:10.1002/14651858.CD005028.pub3. PMID 23543539.
70. ^ Soleymani, T; Hung, T; Soung, J (April 2015). "The role of vitamin D in psoriasis: a review.". *International Journal of Dermatology*. **54** (4): 383–92. doi:10.1111/ijd.12790. PMID 25601579.
71. ^ a b c Halverstam CP, Lebwohl M (September–October 2008). "Nonstandard and off-label therapies for psoriasis". *Clin Dermatol*. **26** (5): 546–53. doi:10.1016/j.clindermatol.2007.10.023. PMID 18755374.
72. ^ a b c Katz U, Shoenfeld Y, Zakin V, Sherer Y, Sukenik S (October 2012). "Scientific evidence of the therapeutic effects of dead sea treatments: a systematic review". *Semin Arthritis Rheum*. **42** (2): 186–200. doi:10.1016/j.semarthrit.2012.02.006. PMID 22503590.
73. ^ a b c Dogra S, De D (November–December 2010). "Narrowband ultraviolet B in the treatment of psoriasis: the journey so far!". *Indian J Dermatol Venereol Leprol*. **76** (6): 652–61. doi:10.4103/0378-6323.72461. PMID 21079308.
74. ^ a b Radack, KP; Farhangian, ME; Anderson, KL; Feldman, SR (March 2015). "A review of the use of tanning beds as a dermatological treatment". *Dermatology and Therapy*. **5** (1): 37–51. doi:10.1007/s13555-015-0071-8. PMC 4374067. PMID 25735439.
75. ^ Lapolla W, Yentzer BA, Bagel J, Halvorson CR, Feldman SR (May 2011). "A review of phototherapy protocols for psoriasis treatment". *J Am Acad Dermatol*. **64** (5): 936–49. doi:10.1016/j.jaad.2009.12.054. PMID 21429620.
76. ^ Dunn LK, Gaar LR, Yentzer BA, O'Neill JL, Feldman SR (July 2011). "Acitretin in dermatology: a review". *J Drugs Dermatol*. **10** (7): 772–82. PMID 21720660.
77. ^ a b Dogra S, Mahajan R (August 2013). "Systemic methotrexate therapy for psoriasis: past, present and future". *Clin*

*Exp Dermatol*. **38** (6): 573–88. doi:10.1111/ced.12062 . PMID 23837932 .

78. ^ [a b c d e f g] Rustin, MH (November 2012). "Long-term safety of biologics in the treatment of moderate-to-severe plaque psoriasis: review of current data". *Br J Dermatol*. **167** (Suppl 3): 3–11. doi:10.1111/j.1365-2133.2012.11208.x. PMID 23082810.
79. ^ [a b] Griffiths, CE (November 2012). "Biologics for psoriasis: current evidence and future use". *Br J Dermatol*. **167** (Suppl 3): 1–2. doi:10.1111/j.1365-2133.2012.11207.x. PMID 23082809.
80. ^ Farahnik, B; Beroukhim, K; Zhu, TH; Abrouk, M; Nakamura, M; Singh, R; Lee, K; Bhutani, T; Koo, J (March 2016). "Ixekizumab for the Treatment of Psoriasis: A Review of Phase III Trials.". *Dermatology and therapy*. **6** (1): 25–37. doi:10.1007/s13555-016-0102-0. PMC 4799032. PMID 26910853.
81. ^ Hueber W, Patel DD, Dryja T, et al. (October 2010). "Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis". *Sci Transl Med*. **2** (52): 52ra72. doi:10.1126/scitranslmed.3001107. PMID 20926833.
82. ^ Harding, FA; Stickler, MM; Razo, J; DuBridge, RB (2010). "The immunogenicity of humanized and fully human antibodies: residual immunogenicity resides in the CDR regions.". *mAbs*. **2** (3): 256–65. doi:10.4161/mabs.2.3.11641. PMID 20400861.
83. ^ Wu W, Debbaneh M, Moslehi H, Koo J, Liao W (December 2014). "Tonsillectomy as a treatment for psoriasis: a review". *J Dermatol Treat*. **25** (6): 482–6. doi:10.3109/09546634.2013.848258. PMID 24283892.
84. ^ Sigurdardottir SL, Thorleifsdottir RH, Valdimarsson H, Johnston A (February 2013). "The role of the palatine tonsils in the pathogenesis and treatment of psoriasis". *Br J Dermatol*. **168** (2): 237–42. doi:10.1111/j.1365-2133.2012.11215.x. PMID 22901242.
85. ^ [a b] Kaimal S, Thappa DM (2010). "Diet in dermatology: revisited.". *Indian J Dermatol Venereol Leprol*. **76** (2): 103–15. doi:10.4103/0378-6323.60540. PMID 20228538.
86. ^ [a b c] Barrea L, Nappi F, Di Somma C, Savanelli MC, Falco A, Balato A; et al. (2016). "Environmental Risk Factors in Psoriasis: The Point of View of the Nutritionist.". *Int J Environ Res Public Health* (Review). **13** (5): 743. doi:10.3390/ijerph13070743. PMC 4962284. PMID 27455297.
87. ^ Ni C, Chiu MW (2014). "Psoriasis and comorbidities: links and risks". *Clin Cosmet Investig Dermatol* (Review). **7**: 119–32. doi:10.2147/CCID.S44843. PMC 4000177. PMID 24790463.
88. ^ Leffler DA, Green PH, Fasano A (Oct 2015). "Extraintestinal manifestations of coeliac disease". *Nat Rev Gastroenterol Hepatol* (Review). **12** (10): 561–71. doi:10.1038/nrgastro.2015.131. PMID 26260366.
89. ^ [a b] Bhatia BK, Millsop JW, Debbaneh M, Koo J, Linos E, Liao W (2014). "Diet and psoriasis, part II: celiac disease and role of a gluten-free diet". *J Am Acad Dermatol*. **71** (2): 350–8. doi:10.1016/j.jaad.2014.03.017. PMC 4104239. PMID 24780176.
90. ^ Dessinioti C, Katsambas A (2013). "Seborrheic dermatitis: etiology, risk factors, and treatments: facts and controversies". *Clin Dermatol*. **31** (4): 343–51. doi:10.1016/j.clindermatol.2013.01.001. PMID 23806151.
91. ^ Bhosle MJ, Kulkarni A, Feldman SR, Balkrishnan R (2006). "Quality of life in patients with psoriasis". *Health Qual Life Outcomes*. **4**: 35. doi:10.1186/1477-7525-4-35. PMC 1501000. PMID 16756666.
92. ^ Magin, P (Jan–Feb 2013). "Appearance-related bullying and skin disorders.". *Clinics in dermatology*. **31** (1): 66–71. doi:10.1016/j.clindermatol.2011.11.009. PMID 23245976.
93. ^ [a b c] Habif, Thomas P. (2010). "8". *Clinical dermatology a color guide to diagnosis and therapy* (5th ed.). Edinburgh: Mosby Elsevier. ISBN 978-0-323-08037-8.
94. ^ [a b] Shlyankevich J, Mehta NN, Krueger JG, Strober B, Gudjonsson JE, Qureshi AA, Tebbey PW, Kimball AB (December 2014). "Accumulating Evidence for the Association and Shared Pathogenic Mechanisms Between Psoriasis and Cardiovascular-related Comorbidities". *Am J Med*. **127** (12): 1148–53. doi:10.1016/j.amjmed.2014.08.008. PMID 25149424.
95. ^ [a b] Armstrong AW, Harskamp CT, Armstrong EJ (January 2013). "Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis". *JAMA Dermatol*. **149** (1): 84–91. doi:10.1001/2013.jamadermatol.406. PMID 23407990.
96. ^ Armstrong AW, Harskamp CT, Armstrong EJ (2013). "The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies". *J Hypertens*. **31** (3): 433–42. doi:10.1097/HJH.0b013e32835bcce1. PMID 23249828.
97. ^ [a b] Tablazon IL, Al-Dabagh A, Davis SA, Feldman SR (February 2013). "Risk of cardiovascular disorders in psoriasis patients: current and future". *Am J Clin Dermatol*. **14** (1): 1–7. doi:10.1007/s40257-012-0005-5. PMID 23329076.
98. ^ "Psoriasis Linked to Stroke Risk". BBC. August 2011.
99. ^ [a b] Ghazizadeh R, Tosa M, Ghazizadeh M (2011). "Clinical Improvement in Psoriasis with Treatment of Associated Hyperlipidemia". *Am J Med Sci*. **341** (5): 394–8. doi:10.1097/MAJ.0b013e3181ff8eeb. PMID 21233693.
100. ^ Hsu LN, Armstrong AW (November 2012). "Psoriasis and autoimmune disorders: a review of the literature". *J Am Acad Dermatol*. **67** (5): 1076–9. doi:10.1016/j.jaad.2012.01.029. PMID 23062896.
101. ^ Benoit S, Hamm H (2007). "Childhood Psoriasis". *Clinics in Dermatology*. **25** (6): 555–562. doi:10.1016/j.clindermatol.2007.08.009. PMID 18021892.
102. ^ [a b c d e f] Gruber F, Kastelan M, Brajac I (2004). "Psoriasis treatment—yesterday, today, and tomorrow". *Acta*

*Dermatovenereol Croat*. **12** (1): 30–4. PMID 15072746.
103. ^ Meenan FO (March 1955). "A note on the history of psoriasis". *Ir J Med Sci* (351): 141–2. PMID 14353580.
104. ^ Benedek TG (June 2013). "Psoriasis and psoriatic arthropathy, historical aspects: part I". *J Clin Rheumatol*. **19** (4): 193–8. doi:10.1097/RHU.0b013e318293eaeb. PMID 23669809.
105. ^ *a b* Benedek TG (June 2013). "Psoriasis and psoriatic arthropathy: historical aspects: part II". *J Clin Rheumatol*. **19** (5): 267–71. doi:10.1097/RHU.0b013e31829d4ad4. PMID 23872545.
106. ^ Ritchlin, Christopher; Fitzgerald, Oliver (2007). *Psoriatic and Reactive Arthritis: A Companion to Rheumatology* (1st ed.). Maryland Heights, Miss.: Mosby. p. 4. ISBN 978-0-323-03622-1.
107. ^ International Federation of Psoriasis Associations. Ifpa-pso.org. Retrieved on 2013-06-08.
108. ^ Evans, C (June 2016). "Managed care aspects of psoriasis and psoriatic arthritis.". *The American Journal of Managed Care*. **22** (8 Suppl): s238–43. PMID 27356195.
109. ^ *a b c* Dubois Declercq S, Pouliot R (July 2013). "Promising new treatments for psoriasis". *ScientificWorldJournal*. **2013** (980419): 1–9. doi:10.1155/2013/980419. PMC 3713318. PMID 23935446.
110. ^ *a b c d* Patel M, Day A, Warren RB, Menter A (December 2012). "Emerging Therapies for the Treatment of Psoriasis". *Dermatol There (Heidelb)*. **2** (1): 16. doi:10.1007/s13555-012-0016-4. PMC 3510410. PMID 23205338.

## Further reading [edit]

- Baker, Barbara S. (2008). *From Arsenic to Biologicals: A 200 Year History of Psoriasis*. Beckenham UK: Garner Press. ISBN 0-9551603-2-4.

## External links [edit]

- Psoriasis at DMOZ
- "Guidelines for the assessment and management of psoriasis". U.S. National Guideline Clearinghouse.
- Questions and Answers about Psoriasis - US National Institute of Arthritis and Musculoskeletal and Skin Diseases

Wikimedia Commons has media related to *Psoriasis*.

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|---|---|---|---|
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| | **Pigmented** | | Freckles · lentigo · melasma · nevus · melanoma · |
| | **Dermal and subcutaneous** | | epidermal inclusion cyst · hemangioma · dermatofibroma (benign fibrous histiocytoma) · keloid · lipoma · neurofibroma · xanthoma · Kaposi's sarcoma · infantile digital fibromatosis · granular cell tumor · leiomyoma · lymphangioma circumscriptum · myxoid cyst · |
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| | | **Scaling** | **psoriasis** · tinea (corporis · cruris · pedis · manuum · faciei) · pityriasis rosea · secondary syphilis · mycosis fungoides · systemic lupus erythematosus · pityriasis rubra pilaris · parapsoriasis · ichthyosis · |
| | | **Blistering** | herpes simplex · herpes zoster · varicella · bullous impetigo · acute contact dermatitis · pemphigus vulgaris · bullous pemphigoid · dermatitis herpetiformis · porphyria cutanea tarda · epidermolysis bullosa simplex · |

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| **Rashes** | **involvement** | | | | |
| | | **Papular** | | | scabies · insect bite reactions · lichen planus · miliaria · keratosis pilaris · lichen spinulosus · transient acantholytic dermatosis · lichen nitidus · pityriasis lichenoides et varioliformis acuta · |
| | | **Pustular** | | | acne vulgaris · acne rosacea · folliculitis · impetigo · candidiasis · gonococcemia · dermatophyte · coccidioidomycosis · subcorneal pustular dermatosis · |
| | | **Hypopigmented** | | | tinea versicolor · vitiligo · pityriasis alba · postinflammatory hyperpigmentation · tuberous sclerosis · idiopathic guttate hypomelanosis · leprosy · hypopigmented mycosis fungoides · |
| | **Without epidermal involvement** | **Red** | **Blanchable Erythema** | **Generalized** | drug eruptions · viral exanthems · toxic erythema · systemic lupus erythematosus · |
| | | | | **Localized** | cellulitis · abscess · boil · erythema nodosum · carcinoid syndrome · fixed drug eruption · |
| | | | | **Specialized** | urticaria · erythema (multiforme · migrans · gyratum repens · annulare centrifugum · ab igne) · |
| | | | **Nonblanchable Purpura** | **Macular** | thrombocytopenic purpura · actinic/solar purpura · |
| | | | | **Papular** | disseminated intravascular coagulation · vasculitis · |
| | | **Indurated** | | | scleroderma/morphea · granuloma annulare · lichen sclerosis et atrophicus · necrobiosis lipoidica · |
| **Miscellaneous disorders** | **Ulcers** | | | | |
| | **Hair** | | | | telogen effluvium · androgenic alopecia · trichotillomania · alopecia areata · systemic lupus erythematosus · tinea capitis · loose anagen syndrome · lichen planopilaris · folliculitis decalvans · acne keloidalis nuchae · |
| | **Nail** | | | | onychomycosis · **psoriasis** · paronychia · ingrown nail · |
| | **Mucous membrane** | | | | Aphthous stomatitis · oral candidiasis · lichen planus · leukoplakia · pemphigus vulgaris · mucous membrane pemphigoid · cicatricial pemphigoid · herpesvirus · coxsackievirus · syphilis · systemic histoplasmosis · squamous-cell carcinoma · |

| v · t · e · | **Papulosquamous disorders (L40–L45, 696–697)** | |
|---|---|---|
| **Psoriasis** | **Pustular** | Generalized pustular psoriasis (Impetigo herpetiformis) · Acropustulosis/Pustulosis palmaris et plantaris (Pustular bacterid) · Annular pustular psoriasis · Localized pustular psoriasis · |
| | **Other** | Guttate psoriasis · Psoriatic arthritis · Psoriatic erythroderma · Drug-induced psoriasis · Inverse psoriasis · Napkin psoriasis · Seborrheic-like psoriasis · |
| **Parapsoriasis** | | Pityriasis lichenoides (Pityriasis lichenoides et varioliformis acuta, Pityriasis lichenoides chronica) · Lymphomatoid papulosis · Small plaque parapsoriasis (Digitate dermatosis, Xanthoerythrodermia perstans) · Large plaque parapsoriasis (Retiform parapsoriasis) · |

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| **Other pityriasis** | Pityriasis rosea · Pityriasis rubra pilaris · Pityriasis rotunda · Pityriasis amiantacea · | |
| **Other lichenoid** | **Lichen planus** | *configuration* (Annular · Linear · · *morphology* (Hypertrophic · Atrophic · Bullous · Ulcerative · Actinic · Pigmented · · *site* (Mucosal · Nails · Peno-ginival · Vulvovaginal · · *overlap synromes* (with lichen sclerosus · with lupus erythematosis · · *other:* (Hepatitis-associated lichen planus · Lichen planus pemphigoides · · |
| | **Other** | Lichen nitidus · Lichen striatus · Lichen ruber moniliformis · Gianotti–Crosti syndrome · Erythema dyschromicum perstans · Idiopathic eruptive macular pigmentation · Keratosis lichenoides chronica · Kraurosis vulvae · Lichen sclerosus · Lichenoid dermatitis · Lichenoid reaction of graft-versus-host disease · |
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Categories: Autoimmune diseases | Cutaneous conditions | Psoriasis

# Scabies



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*For psychological condition, see The seven-year itch.*

**Scabies**, previously known as the seven-year itch, is a contagious skin infestation by the mite *Sarcoptes scabiei*.[1][2] The most common symptoms are severe itchiness and a pimple-like rash. Occasionally tiny burrows may be seen in the skin. When first infected, usually two to six weeks are required before symptoms occur. If a person develops a second infection later in life, symptoms may begin within a day. These symptoms can be present across most of the body or just certain areas such as the wrists, between fingers, or along the waistline. The head may be affected, but this is typically only in young children. The itch is often worse at night. Scratching may cause skin breakdown and an additional bacterial infection of the skin.[3]

Scabies is caused by infection with the female mite *Sarcoptes scabiei*.[1] The mites burrow into the skin to live and deposit eggs.[1] The symptoms of scabies are due to an allergic reaction to the mites.[3] Often only between ten and fifteen mites are involved in an infection.[3] Scabies is most often spread during a relatively long period of direct skin contact with an infected person such as that which may occur during sex.[1] Spread of disease may occur even if the person has not developed symptoms yet.[4] Crowded living conditions such as those found in child care facilities, group homes, and prisons increase the risk of spread.[1] Areas with a lack of access to water also have higher rates of disease.[5]

**Crusted scabies** is a more severe form of the disease. It typically only occurs in those with a poor immune system and people may have millions of mites, making them much more contagious. In these cases spread of infection may occur during brief contact or via contaminated objects. The mite is very small and usually not directly visible. Diagnosis is based on the signs and symptoms.[6]

A number of medications are available to treat those infected, including permethrin, crotamiton and lindane creams and ivermectin pills.[7] Sexual contacts within the last month and people who live in the same house should also be treated at the same time. Bedding and clothing used in the last three days should be washed in hot water and dried in a hot dryer. As the mite does not live for more than three days away from human skin more washing is not needed. Symptoms may continue for two to four weeks following treatment. If after this time there continue to be symptoms retreatment may be needed.[4]

A photomicrograph of an itch mite (*Sarcoptes scabiei*)

| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease, dermatology |
| **ICD-10** | B86 |
| **ICD-9-CM** | 133.0 |
| **DiseasesDB** | 11841 |
| **MedlinePlus** | 000830 |
| **eMedicine** | derm/382 emerg/517 ped/2047 |
| **Patient UK** | Scabies |
| **MeSH** | D012532 |

[edit on Wikidata]

Scabies is one of the three most common skin disorders in children, along with ringworm and bacterial skin infections.[8] As of 2010 it affects approximately 100 million people (1.5% of the world population) and is equally common in both sexes.[9] The young and the old are more commonly affected. It also occurs more commonly in

the developing world and tropical climates.[6] The word scabies is from Latin: *scabere*, "to scratch".[10] Other animals do not spread human scabies.[1] Infection in other animals is typically caused by slightly different but related mites and is known as sarcoptic mange.[11]





## Signs and symptoms [edit]

The characteristic symptoms of a scabies infection include intense itching and superficial burrows.[12] The burrow tracks are often linear, to the point that a neat "line" of four or more closely placed and equally developed mosquito-like "bites" is almost diagnostic of the disease. Because the host develops the symptoms as a reaction to the mites' presence over time, there is typically a delay of four to six weeks between the onset of infestation and the onset of itching. Similarly, symptoms often persist for one to several weeks after successful eradication of the mites. As noted, those re-exposed to scabies after successful treatment may exhibit symptoms of the new infestation in a much shorter period—as little as one to four days.[13]

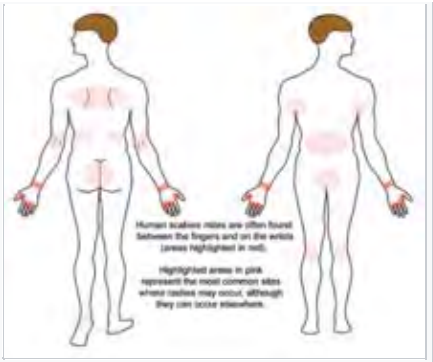
### Itching [edit]

In the classic scenario, the itch is made worse by warmth, and is usually experienced as being worse at night, possibly because there are fewer distractions.[12] As a symptom, it is less common in the elderly.[12]

### Rash [edit]

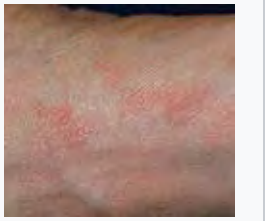
The superficial burrows of scabies usually occur in the area of the finger webs, feet, ventral wrists, elbows, back, buttocks, and external genitals.[12] Except in infants and the immunosuppressed, infection generally does not occur in the skin of the face or scalp. The burrows are created by excavation of the adult mite in the epidermis.[12]

In most people, the trails of the burrowing mites are linear or *s*-shaped tracks in the skin often accompanied by rows of small, pimple-like mosquito or insect bites. These signs are often found in crevices of the body, such as on the webs of fingers and toes, around the genital area, in stomach folds of the skin, and under the breasts of women.[15]

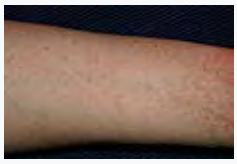


Commonly involved sites of rashes of scabies[14]

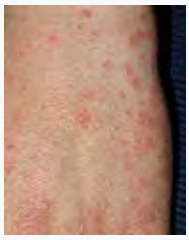
Symptoms typically appear two to six weeks after infestation for individuals never before exposed to scabies. For those having been previously exposed, the symptoms can appear within several days after infestation. However, it is not unknown for symptoms to appear after several months or years.[16] Acropustulosis, or blisters and pustules on the palms and soles of the feet, are characteristic symptoms of scabies in infants.[15]



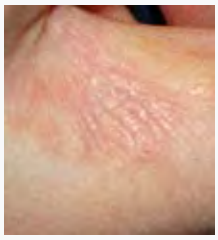
Scabies of the foot



Scabies of the arm



Scabies of the hand



Scabies of the finger

## Crusted scabies [edit]

The elderly and people with an impaired immune system, such as HIV, cancer, or those on immunosuppressive medications, are susceptible to crusted scabies (formerly called Norwegian scabies).[12][16][17] On those with weaker immune systems, the host becomes a more fertile breeding ground for the mites, which spread over the host's body, except the face. Sufferers of crusted scabies exhibit scaly rashes, slight itching, and thick crusts of skin that contain thousands of mites.[18] Such areas make eradication of mites particularly difficult, as the crusts protect the mites from topical miticides/scabicides, necessitating prolonged treatment of these areas.

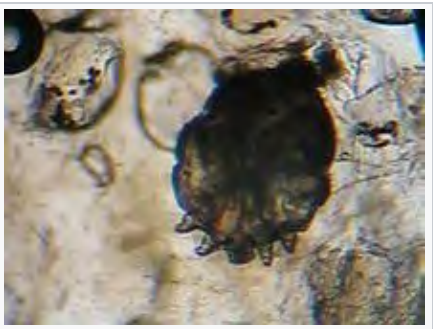
Crusted scabies in a person with AIDS

# Cause [edit]

## Scabies mite [edit]

*Main article: Sarcoptes scabiei*

In the 18th century, Italian biologist Diacinto Cestoni (1637–1718) described the mite now called *Sarcoptes scabiei*, variety *hominis*, as the cause of scabies. *Sarcoptes* is a genus of skin parasites and part of the larger family of mites collectively known as scab mites. These organisms have eight legs as adults, and are placed in the same phylogenetic class (Arachnida) as spiders and ticks.

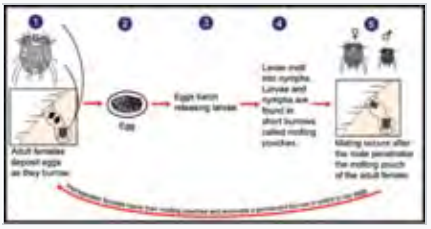


*Sarcoptes scabiei* mites are under 0.5 mm in size but are sometimes visible as pinpoints of white. Pregnant females tunnel into the dead, outermost layer (stratum corneum) of a host's skin and deposit eggs in the shallow burrows. The eggs hatch into larvae in three to ten days. These young mites move

about on the skin and molt into a "nymphal" stage, before maturing as adults, which live three to four weeks in the host's skin. Males roam on top of the skin, occasionally burrowing into the skin. In general, the total number of adult mites infesting a healthy hygienic person with non-crusted scabies is small; about 11 females in burrows, on average.[19]

Play media
Video of the *Sarcoptes scabiei* mite

The movement of mites within and on the skin produces an intense itch, which has the characteristics of a delayed cell-mediated inflammatory response to allergens. IgE antibodies are present in the serum and the site of infection, which react to multiple protein allergens in the body of the mite. Some of these cross-react to allergens from house dust mites. Immediate antibody-mediated allergic reactions (wheals) have been elicited in infected persons, but not in healthy persons; immediate hypersensitivity of this type is thought to explain the observed far more rapid allergic skin response to reinfection seen in persons having been previously infected (especially having been infected within the previous year or two).[20]



Life cycle of scabies[14]

## Transmission [edit]

Scabies is contagious and can be contracted through prolonged physical contact with an infested person.[21] This includes sexual intercourse, although a majority of cases are acquired through other forms of skin-to-skin contact. Less commonly, scabies infestation can happen through the sharing of clothes, towels, and bedding, but this is not a major mode of transmission; individual mites can only survive for two to three days, at most, away from human skin.[22][23] As with lice, a latex condom is ineffective against scabies transmission during intercourse, because mites typically migrate from one individual to the next at sites other than the sex organs.[24]

Healthcare workers are at risk of contracting scabies from patients, because they may be in extended contact with them.[25]

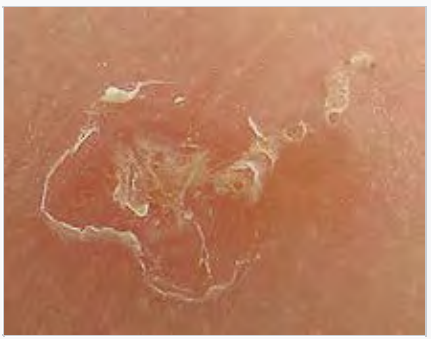
# Pathophysiology [edit]

The symptoms are caused by an allergic reaction of the host's body to mite proteins, though exactly which proteins remains a topic of study. The mite proteins are also present from the gut, in mite feces, which are deposited under the skin. The allergic reaction is both of the delayed (cell-mediated) and immediate (antibody-mediated) type, and involves IgE (antibodies, it is presumed, mediate the very rapid symptoms on reinfection).[19] The allergy-type symptoms (itching) continue for some days, and even several weeks, after all mites are killed. New lesions may appear for a few days after mites are eradicated. Nodular lesions from scabies may continue to be symptomatic for weeks after the mites have been killed.[19]

A 2016 study found rates of scabies was negatively related to temperature and positively related with humidity.[26]

# Diagnosis [edit]

Scabies may be diagnosed clinically in geographical areas where it is common when diffuse itching presents along with either lesions in two typical spots or there is itchiness of another household member.[8] The classical sign of scabies is the burrows made by the mites within the skin.[8] To detect the burrow, the suspected area is rubbed with ink from a fountain pen or a topical tetracycline solution, which glows under a special light. The skin is then wiped with an alcohol pad. If the person is infected with scabies, the characteristic zigzag or *S* pattern of the burrow will appear across the skin; however, interpreting this test may be difficult as the burrows are scarce and may be obscured by scratch marks.[8] A definitive diagnosis is made by finding either the scabies mites or their eggs and fecal pellets.[8] Searches for these signs involve either scraping a suspected area, mounting the sample in



Magnified view of a burrowing

potassium hydroxide and examining it under a microscope, or using dermoscopy to examine the skin directly.[12]

trail of the scabies mite: The scaly patch on the left was caused by the scratching and marks the mite's entry point into the skin. The mite has burrowed to the top-right, where it can be seen as a dark spot at the end.

### Differential diagnosis [edit]

Symptoms of early scabies infestation mirror other skin diseases, including dermatitis, syphilis, erythema multiforme, various urticaria-related syndromes, allergic reactions, and other ectoparasites such as lice and fleas.[27]

## Prevention [edit]

Mass treatment programs that use topical permethrin or oral ivermectin have been effective in reducing the prevalence of scabies in a number of populations.[8] No vaccine is available for scabies. The simultaneous treatment of all close contacts is recommended, even if they show no symptoms of infection (asymptomatic), to reduce rates of recurrence.[8][8] Since mites can survive for only two to three days without a host, other objects in the environment pose little risk of transmission except in the case of crusted scabies, thus cleaning is of little importance.[8] Rooms used by those with crusted scabies require thorough cleaning.[28]

## Management [edit]

A number of medications are effective in treating scabies. Treatment should involve the entire household, and any others who have had recent, prolonged contact with the infested individual.[8] Options to control itchiness include antihistamines and prescription anti-inflammatory agents.[29] Bedding, clothing and towels used during the previous three days should be washed in hot water and dried in a hot dryer.[30]

### Permethrin [edit]

Permethrin is the most effective treatment for scabies,[31] and remains the treatment of choice.[8][32] It is applied from the neck down, usually before bedtime, and left on for about eight to 14 hours, then washed off in the morning.[8] Care should be taken to coat the entire skin surface, not just symptomatic areas; any patch of skin left untreated can provide a "safe haven" for one or more mites to survive. One application is normally sufficient, as permethrin kills eggs and hatchlings as well as adult mites, though many physicians recommend a second application three to seven days later as a precaution. Crusted scabies may require multiple applications, or supplemental treatment with oral ivermectin (below).[8][32][33] Permethrin may cause slight irritation of the skin that is usually tolerable.[12]

### Ivermectin [edit]

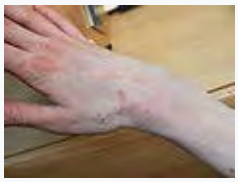
Oral Ivermectin is effective in eradicating scabies, often in a single dose.[5][8] It is the treatment of choice for crusted scabies, and is sometimes prescribed in combination with a topical agent.[8][12] It has not been tested on infants, and is not recommended for children under six years of age.[12]

Topical ivermectin preparations have been shown to be effective for scabies in adults, though only one such formulation is available in the United States at present, and it is not FDA approved as a scabies treatment.[34] It has also been useful for sarcoptic mange (the veterinary analog of human scabies).[35]

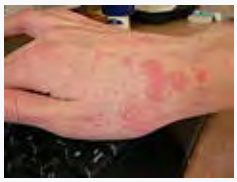
### Others [edit]

Other treatments include lindane, benzyl benzoate, crotamiton, malathion, and sulfur preparations.[8][12] Lindane is effective, but concerns over potential neurotoxicity has limited its availability in many countries.[12] It is banned in California,[36] but may be used in other states as a second-line treatment.[37] Sulfur ointments or benzyl benzoate are often used in the developing world due to their low cost;[12] 10% sulfur solutions have been shown to be effective,[38] and sulfur ointments are typically used for at least a week, though many people find the odor of sulfur products unpleasant.[12] Crotamiton has been found to be less effective than permethrin

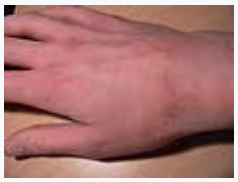
in limited studies.[12] Crotamiton or sulfur preparations are sometimes recommended instead of permethrin for children, due to concerns over dermal absorption of permethrin.[8]



Day 4



Day 8 (treatment begins)



Day 12 (under treatment)

Healed

## Communities [edit]

Scabies is endemic in many developing countries,[39] where it tends to be particularly problematic in rural and remote areas. In such settings community wide control strategies are required to reduce the rate of disease, as treatment of only individuals is ineffective due to the high rate of reinfection. Large-scale mass drug administration strategies may be required where coordinated interventions aim to treat whole communities in one concerted effort.[40] Although such strategies have shown to be able to reduce the burden of scabies in these kinds of communities, debate remains about the best strategy to adopt, including the choice of drug.[40][41]

The resources required to implement such large-scale interventions in a cost-effective and sustainable way are significant. Furthermore, since endemic scabies is largely restricted to poor and remote areas, it is a public health issue that has not attracted much attention from policy makers and international donors.[40][41]

# Epidemiology [edit]

Scabies is one of the three most common skin disorders in children, along with tinea and pyoderma.[8] As of 2010 it affects approximately 100 million people (1.5% of the population) and is equally common in both genders.[9] The mites are distributed around the world and equally infect all ages, races, and socioeconomic classes in different climates.[18] Scabies is more often seen in crowded areas with unhygienic living conditions.[42] Globally as of 2009, an estimated 300 million cases of scabies occur each year, although various parties claim the figure is either over- or underestimated.[16][43] About 1–10% of the global population is estimated to be infected with scabies, but in certain populations, the infection rate may be as high as 50–80%.[8]

# History [edit]

Wax figurine of a man with Norwegian scabies

Scabies has been observed in humans since ancient times. Archeological evidence from Egypt and the Middle East suggests scabies was present as early as 494 BC.[13][44] The first recorded reference to scabies is believed to be from the Bible – it may be a type of "leprosy" mentioned in Leviticus *circa* 1200 BC[45] or be mentioned among the curses of Deuteronomy 28.[46] In the fourth century BC, Aristotle reported on "lice" that "escape from little pimples if they are pricked" – a description consistent with scabies.[47]

The Roman encyclopedist and medical writer Aulus Cornelius Celsus (c. 25 BC – c. 50 AD) is credited with naming the disease "scabies" and describing its characteristic features.[47] The parasitic etiology of scabies was documented by the Italian physician Giovanni Cosimo Bonomo (1663–1696) in his 1687 letter, "Observations concerning the fleshworms of the human body".[47] Bonomo's description established scabies as one of the first human diseases

with a well-understood cause.[13][44]

In Europe in the late 19th through mid-20th centuries, a sulfur-bearing ointment called by the medical eponym of Wilkinson's ointment was widely used for topical treatment of scabies. The contents and origins of several versions of the ointment were detailed in correspondence published in the *British Medical Journal* in 1945.[48]

## Society and culture [edit]

The International Alliance for the Control of Scabies (IACS) was started in 2012,[41][49][50] and brings together over 70 researchers, clinicians and public health experts from more than 15 different countries. It has managed to bring the global health implications of scabies to the attention of the World Health Organization.[41] Consequently, the WHO has included scabies on its official list of neglected tropical diseases and other neglected conditions.[51]

## Other animals [edit]

*Main articles: Sarcoptic mange and Acariasis*

Scabies may occur in a number of domestic and wild animals; the mites that cause these infestations are of different subspecies from the one typically causing the human form.[12] These subspecies can infest animals that are not their usual hosts, but such infections do not last long.[12] Scabies-infected animals suffer severe itching and secondary skin infections. They often lose weight and become frail.[19]

A street dog in Bali, Indonesia, suffers from sarcoptic mange.

The most frequently diagnosed form of scabies in domestic animals is sarcoptic mange, caused by the subspecies *Sarcoptes scabiei canis*, most commonly in dogs and cats. Sarcoptic mange is transmissible to humans who come into prolonged contact with infested animals,[52] and is distinguished from human scabies by its distribution on skin surfaces covered by clothing. Scabies-infected domestic fowl suffer what is known as "scaly leg". Domestic animals that have gone feral and have no veterinary care are frequently afflicted with scabies and a host of other ailments.[53] Nondomestic animals have also been observed to suffer from scabies. Gorillas, for instance, are known to be susceptible to infection via contact with items used by humans.[54]

## Research [edit]

Moxidectin is being evaluated as a treatment for scabies.[55] It is established in veterinary medicine to treat a range of parasites, including sarcoptic mange. Its advantage over ivermectin is its longer duration of action.[56]

## References [edit]


1. ^ *a b c d e f* "Epidemiology & Risk Factors". *Centers for Disease Control and Prevention*. November 2, 2010. Retrieved 18 May 2015.
2. ^ Gates, Robert H. (2003). *Infectious disease secrets* (2. ed.). Philadelphia: Elsevier, Hanley Belfus. p. 355. ISBN 978-1-56053-543-0.
3. ^ *a b c* "Parasites - Scabies Disease". *Center for Disease Control and Prevention*. November 2, 2010. Retrieved 18 May 2015.
4. ^ *a b* "Parasites - Scabies Treatment". *Center for Disease Control and Prevention*. November 2, 2010. Retrieved 18 May 2015.
5. ^ *a b* "WHO -Water-related Disease". World Health Organization. Retrieved 2010-10-10.
6. ^ *a b* "Scabies". *World Health Organization*. Retrieved 18 May 2015.
7. ^ "Parasites - Scabies Medications". *Center for Disease Control and Prevention*. November 2, 2010. Retrieved 18 May 2015.

8. ^ a b c d e f g h i j k l m n o p q r s Andrews RM, McCarthy J, Carapetis JR, Currie BJ (December 2009). "Skin disorders, including pyoderma, scabies, and tinea infections". *Pediatr. Clin. North Am.* **56** (6): 1421–40. doi:10.1016/j.pcl.2009.09.002. PMID 19962029.
9. ^ a b Vos, T (Dec 15, 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010.". *Lancet*. **380** (9859): 2163–96. doi:10.1016/S0140-6736(12)61729-2. PMID 23245607.
10. ^ *Mosby's Medical, Nursing & Allied Health Dictionary* (4 ed.). Mosby-Year Book Inc. 1994. p. 1395. ISBN 9780801672255.
11. ^ *Georgis' Parasitology for Veterinarians* (10 ed.). Elsevier Health Sciences. 2014. p. 68. ISBN 9781455739882.
12. ^ a b c d e f g h i j k l m n o p q Hay RJ (2009). "Scabies and pyodermas—diagnosis and treatment". *Dermatol Ther*. **22** (6): 466–74. doi:10.1111/j.1529-8019.2009.01270.x. PMID 19889132.
13. ^ a b c Markell, Edward K.; John, David C.; Petri, William H. (2006). *Markell and Voge's medical parasitology* (9th ed.). St. Louis, Mo: Elsevier Saunders. ISBN 0-7216-4793-6.
14. ^ a b CDC web site > DPDx - Laboratory Identification of Parasites of Public Health Concern > Scabies [1]
15. ^ a b "Scabies" (PDF). *DermNet NZ*. New Zealand Dermatological Society Incorporated.
16. ^ a b c Bouvresse, S.; Chosidow, O. (Apr 2010). "Scabies in healthcare settings". *Curr Opin Infect Dis*. **23** (2): 111–8. doi:10.1097/QCO.0b013e328336821b. PMID 20075729.
17. ^ Hicks MI, Elston DM (2009). "Scabies". *Dermatol Ther*. **22** (4): 279–92. doi:10.1111/j.1529-8019.2009.01243.x. PMID 19580575.
18. ^ a b "DPDx—Scabies". *Laboratory Identification of Parasites of Public Health Concern*. CDC.
19. ^ a b c d Walton, SF; Currie, BJ (April 2007). "Problems in Diagnosing Scabies, a Global Disease in Human and Animal Populations". *Clinical Microbiology Reviews*. **20** (2): 268–79. doi:10.1128/CMR.00042-06. PMC 1865595. PMID 17428886.
20. ^ Walton SF, Currie BJ (2007). "Problems in Diagnosing Scabies, a Global Disease in Human and Animal Populations". *Clinical Microbiology Reviews*. **20** (2): 268–279. doi:10.1128/CMR.00042-06. PMC 1865595. PMID 17428886.
21. ^ Carol Turkington; Jeffrey S. Dover, M.D. (2006). *The Encyclopedia of Skin and Skin Disorders*. New York: Facts on File inc. ISBN 978-0-8160-6403-8.
22. ^ "Scabies Causes". WebMD. October 2010. Retrieved 2010-10-09.
23. ^ Chosidow O (April 2006). "Clinical practices. Scabies". *N. Engl. J. Med.* **354** (16): 1718–27. doi:10.1056/NEJMcp052784. PMID 16625010.
24. ^ "Scabies—Fast Facts". American Social Health Association. Retrieved 2010-10-09.
25. ^ FitzGerald, Deirdre; Grainger, Rachel J.; Reid, Alex (2014). "Interventions for preventing the spread of infestation in close contacts of people with scabies". *The Cochrane Database of Systematic Reviews*. **2**: CD009943. doi:10.1002/14651858.CD009943.pub2. ISSN 1469-493X. PMID 24566946.
26. ^ Liu, Jui-Ming; Wang, Hsiao-Wei; Chang, Fung-Wei; Liu, Yueh-Ping; Chiu, Feng-Hsiang; Lin, Yi-Chun; Cheng, Kuan-Chen; Hsu, Ren-Jun (2016). "The effects of climate factors on scabies. A 14-year population-based study in Taiwan". *Parasite*. **23**: 54. doi:10.1051/parasite/2016065. ISSN 1776-1042. PMID 27905271.
27. ^ Arlian, LG (1989). "Biology, host relations, and epidemiology of Sarcoptes scabiei". *Annual Review of Entomology*. **34** (1): 139–61. doi:10.1146/annurev.en.34.010189.001035. PMID 2494934.
28. ^ "CDC—Prevention and Control—Scabies". Center for Disease Control and Prevention. Retrieved 2010-10-09.
29. ^ Vañó-Galván, S; Moreno-Martin, P (2008). "Generalized pruritus after a beach vacation. Diagnosis: scabies". *Cleveland Clinic journal of medicine*. **75** (7): 474, 478. doi:10.3949/ccjm.75.7.474. PMID 18646583.
30. ^ "Parasites - Scabies". *cdc.gov*. November 2, 2010. Retrieved 11 December 2014.
31. ^ Strong M, Johnstone PW (2007). Strong, Mark, ed. "Interventions for treating scabies". *Cochrane Database Syst Rev* (3): CD000320. doi:10.1002/14651858.CD000320.pub2. PMID 17636630.
32. ^ a b "Scabies". Illinois Department of Public Health. January 2008. Retrieved 2010-10-07.
33. ^ *The Pill Book*. Bantam Books. 2010. pp. 867–869. ISBN 978-0-553-59340-2.
34. ^ Victoria J, Trujillo R (2001). "Topical ivermectin: a new successful treatment for scabies". *Pediatr Dermatol*. **18** (1): 63–5. doi:10.1046/j.1525-1470.2001.018001063.x. PMID 11207977.
35. ^ "Parasitology Research, Volume 78, Number 2". SpringerLink. Retrieved 2010-11-14.
36. ^ Humphreys, EH; Janssen, S; Heil, A; Hiatt, P; Solomon, G; Miller, MD (March 2008). "Outcomes of the California ban on pharmaceutical lindane: clinical and ecologic impacts.". *Environmental Health Perspectives*. **116** (3): 297–302. doi:10.1289/ehp.10668. PMC 2265033. PMID 18335094.
37. ^ "FDA Public Health Advisory: Safety of Topical Lindane Products for the Treatment of Scabies and Lice". Fda.gov. 2009-04-30. Retrieved 2010-11-14.
38. ^ Jin-Gang A, Sheng-Xiang X, Sheng-Bin X, et al. (March 2010). "Quality of life of patients with scabies". *J Eur Acad Dermatol Venereol*. **24** (10): 1187–91. doi:10.1111/j.1468-3083.2010.03618.x. PMID 20236379.
39. ^ Andrews, RM; McCarthy, J; Carapetis, JR; Currie, BJ (Dec 2009). "Skin disorders, including pyoderma, scabies, and tinea infections.". *Pediatric clinics of North America*. **56** (6): 1421–40. doi:10.1016/j.pcl.2009.09.002. PMID 19962029.
40. ^ a b c Hay, RJ; Steer, AC; Chosidow, O; Currie, BJ (Apr 2013). "Scabies: a suitable case for a global control initiative.".

*Current opinion in infectious diseases*. **26** (2): 107–9. doi:10.1097/QCO.0b013e32835e085b. PMID 23302759.

41. ^ *a b c d* Engelman, D; Kiang, K; Chosidow, O; McCarthy, J; Fuller, C; Lammie, P; Hay, R; Steer, A; Members Of The International Alliance For The Control Of, Scabies (2013). "Toward the global control of human scabies: introducing the International Alliance for the Control of Scabies.". *PLoS neglected tropical diseases*. **7** (8): e2167. doi:10.1371/journal.pntd.0002167. PMC 3738445. PMID 23951369.
42. ^ Green MS (1989). "Epidemiology of scabies". *Epidemiol Rev*. **11** (1): 126–50. PMID 2509232.
43. ^ Hicks, MI; Elston, DM (Jul–Aug 2009). "Scabies". *Dermatologic therapy*. **22** (4): 279–92. doi:10.1111/j.1529-8019.2009.01243.x. PMID 19580575.
44. ^ *a b* "Scabies homepage". Stanford University. Retrieved 2010-10-09.
45. ^ Leviticus 13:29-13:37
46. ^ See translations
47. ^ *a b c* Roncalli RA (July 1987). "The history of scabies in veterinary and human medicine from biblical to modern times". *Vet. Parasitol*. **25** (2): 193–8. doi:10.1016/0304-4017(87)90104-X. PMID 3307123.
48. ^ Goldsmith, WN (1945), "Wilkinson's ointment" (PDF), *Br Med J*, **1** (4392): 347–348, doi:10.1136/bmj.1.4392.347-c, PMC 2056959.
49. ^ "Scabies". *Neglected tropical diseases*. World Health Organization. Retrieved 1 February 2014.
50. ^ "International Alliance for the Control of Scabies". International Alliance for the Control of Scabies. Retrieved 1 February 2014.
51. ^ "The 17 neglected tropical diseases". *Neglected tropical diseases*. World Health Organization. Retrieved 1 February 2014.
52. ^ Borgman W (June 30, 2006). Dog mange called scabies can transfer to humans. Orlando *Sentinel* archive. Retrieved February 16, 2015.
53. ^ "Bali Animal Welfare Association". Retrieved 2009-07-28.
54. ^ "Uganda: Out of the Wild". *Frontline*http://www.pbs.org/wgbh/pages/frontline/tehranbureau/deathintehran/etc/script.html `|transcripturl=` missing title (help). PBS. Retrieved Nov 4, 2013.
55. ^ Mounsey, Kate E.; Bernigaud, Charlotte; Chosidow, Olivier; McCarthy, James S. (2016-03-17). "Prospects for Moxidectin as a New Oral Treatment for Human Scabies". *PLoS Neglected Tropical Diseases*. **10** (3): e0004389. doi:10.1371/journal.pntd.0004389. ISSN 1935-2727. PMC 4795782. PMID 26985995.
56. ^ Prichard, Roger; Ménez, Cécile; Lespine, Anne (2012-12-01). "Moxidectin and the avermectins: Consanguinity but not identity". *International Journal for Parasitology. Drugs and Drug Resistance*. **2**: 134–153. doi:10.1016/j.ijpddr.2012.04.001. ISSN 2211-3207. PMC 3862425. PMID 24533275.

## External links [edit]

- American Academy of Dermatology pamphlet on Scabies
- Scabies FAQ from the National Pediculosis Association

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# Book:Ears nose throat

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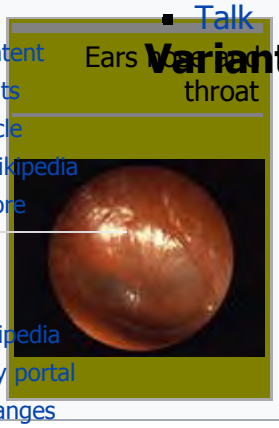


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| **Author** | User:Isarra |

## Licensing [edit]



## File history

Click on a date/time to view the file as it appeared at that time.

| | Date/Time | Thumbnail | Dimensions | User | Comment |
|---|---|---|---|---|---|
| current | **15:13, 5 November 2016** |  | 806 × 835 (64 KB) | Doc James | User created page with UploadWizard |

## File usage

The following pages on the English Wikipedia link to this file (pages on other projects are not listed):
- Diabetes mellitus type 2
- Talk:Diabetes mellitus type 2
- User:BallenaBlanca
- User:CFCF
- User:CFCF/CW
- User:CFCF/old2
- User:CFCF/sandbox/18
- User:Doc James
- User talk:Doc James
- User talk:K18s

- User talk:Ozzie10aaaa
- Wikipedia:WikiProject Medicine
- Wikipedia:WikiProject Medicine/App
- Wikipedia:WikiProject Medicine/App/Banner
- Wikipedia:WikiProject Medicine/Offline App
- Wikipedia:WikiProject Medicine/Open Textbook of Medicine
- Wikipedia:WikiProject Medicine/Translation task force
- Wikipedia:WikiProject Sanitation

# Global file usage

The following other wikis use this file:

- Usage on th.wikipedia.org
  - 

# Metadata

This file contains additional information, probably added from the digital camera or scanner used to create or digitize it. If the file has been modified from its original state, some details may not fully reflect the modified file.

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|---|---|
| Horizontal resolution | 37.79 dpc |
| Vertical resolution | 37.79 dpc |

# Wikipedia talk:WikiProject Medicine/Open Textbook of Medicine



From Wikipedia, the free encyclopedia

← Wikipedia talk:WikiProject Medicine

Contents


## Intro page [edit]

This is the intro page for the WikiMed Medical Encyclopdia app as seen here https://play.google.com/store/apps/details?id=org.kiwix.kiwixcustomwikimed

Emmanuel Engelhart is the amazing programmer that has brought it to life.

**Doc James** (talk · contribs · email) 00:10, 12 June 2015 (UTC)

@Doc James: Looks interesting. Where is the source code for this app? Is there a particular reason it is not developed as a Wikimedia project?--Anders Feder (talk) 07:04, 12 June 2015 (UTC)

Emmanuel is with Wikimedia-CH and does Kiwix. Source code should be available. **Doc James** (talk · contribs · email) 08:04, 12 June 2015 (UTC)

Right, the source code for Kiwix can be found through kiwix.org. I was unable to find anything for this particular 'variant' (WikiMed Medical Encyclopedia), though. @Kelson: Is/will this project be hosted somewhere?--Anders Feder (talk) 08:12, 12 June 2015 (UTC)

Thank you for the praises, but this is mostly the work of two colleagues of the Kiwix project. Kiwix is a Wikimedia project and is sponsored by WikimediaCH. All the source code you need is in the Kiwix repo, have a look to the README file. Kelson (talk) 08:16, 12 June 2015 (UTC)

Excellent, thanks.--Anders Feder (talk) 09:51, 12 June 2015 (UTC)

I am not understanding: "this is mostly the work of two colleagues of the Kiwix project". How was this funded?96.52.0.249 (talk) 18:08, 12 June 2015 (UTC)

This was was done during our last one week hackathon which was funded (accomodation/travel costs) by WikimediaCH. Kelson (talk) 19:46, 12 June 2015 (UTC)

It was you, User:Kelson? And who else? How were you invited to the event (and your partner), if so? Why choose medical articles?96.52.0.249 (talk) 20:15, 12 June 2015 (UTC)

We have been collaborating on putting together an offline version of medical articles since London last year. A number of chip manufacturer are interested in shipping phones to the developed world pre loaded with this content / this app. Thus there is the potential for 350 million copies going out. The phone manufacturers are interested in medical articles as am I.

**Doc James** (talk · contribs · email) 22:54, 12 June 2015 (UTC)

Everyone are invited to the hackathons, AFAIK, i.e. it is public events. Still, it would be a good idea to make the source code behind the "WikiMed Medical Encyclopedia" version of Kiwix available somewhere, so others can contribute.--Anders Feder (talk) 01:30, 13 June 2015 (UTC)

Is it not here http://sourceforge.net/p/kiwix/kiwix/ci/master/tree/ **Doc James** (talk · contribs · email) 06:55, 13 June 2015 (UTC)

No, that appears to be the mainline Kiwix release. It is the same URL that one gets to if clicking "Browse repository" -> "Kiwix" from kiwix.org, and there is no mention of the medical encyclopedia in the README file.--Anders Feder (talk) 07:48, 13 June 2015 (UTC)

We obviously develop agnostic technologies and you need therefore to read the paragraph "Android Custom App". If you want to dive in the code, this is really welcome, but please use Kiwix traditional communication solutions. We focus here on the content part of the app. Kelson (talk) 09:29, 13 June 2015 (UTC)

That paragraph mentions "bundled zim files". Where is the bundled zim file for the WikiMed Medical Encyclopedia?--Anders Feder (talk) 10:03, 13 June 2015 (UTC)

Here [1] **Doc James** (talk · contribs · email) 11:13, 13 June 2015 (UTC)

That was the piece I was missing. Could it be added to the project page in some fashion? I found this address too, which has no timestamp, and so presumably always points to the latest version.--Anders Feder (talk) 11:29, 13 June 2015 (UTC)

Which project page? **Doc James** (talk · contribs · email) 11:57, 13 June 2015 (UTC)

The one labelled "Project page" above in the tab next to the "Talk" tab on the present page.--Anders Feder (talk) 12:19, 13 June 2015 (UTC)

This is the intro page to the app in question. Rather than a project page for the app in question. We should develop a project page. **Doc James** (talk · contribs · email) 12:22, 13 June 2015 (UTC)

Can I begin one at a subpage to the intro page or would there be a better location?--Anders Feder (talk) 12:25, 13 June 2015 (UTC)

Okay created a project page for the app here Wikipedia:WikiProject_Medicine/App **Doc James** (talk · contribs · email) 12:29, 13 June 2015 (UTC)

## For the sake of transparency [edit]

I recommend some sort of page explaining the development of this app. Many Apps require-payment/are-not-free; any potentional customer coming through an app store who happens on this app will wonder why the app was developed by wikipedia, a nonprofit, and what sort of financial arrangement existed to ensure the completion of the app.96.52.0.249 (talk) 16:04, 13 June 2015 (UTC)

> So that would go here than [2]?
>
> We already mention it is free here [3] **Doc James** (talk · contribs · email) 23:52, 13 June 2015 (UTC)

## German translation [edit]

Dear Doc James, I revised the German translation of the Textbook, see de:Wikipedia:Redaktion Medizin/Open Textbook of Medicine. However, there are some questions remaining. Andrea Kamphuis posted some further questions a while ago. Maybe you can help us.

- The order of chapters and links is strictly alphabetical in the English version. Do the different language versions have to overlap each other or are we free to change the order of entries on de.wikipedia?

  > You are free to change the order. **Doc James** (talk · contribs · email) 15:42, 6 October 2016 (UTC)

- Some attributions were disputed. Why is the Asperger syndrome listed as part of Children's health? This is clearly not limited to children. Shouldn't it be listed under Psychiatry, same as Autism?

  > Yes many conditions are within to subject matter areas. I am happy if you move them around. **Doc James** (talk · contribs · email) 15:42, 6 October 2016 (UTC)

- Low back pain is listed under Rheumatology. To my limited understanding most cases of Low back pain have nothing to do with Rheumatology.

  > Yes agree most cases are not. Typically it is emergency medicine or primary care. Sometimes it is however related to rheumatology which is why we placed it their. **Doc James** (talk · contribs · email) 15:42, 6 October 2016 (UTC)

- Who is the recipient of the content? Medical doctors, patients? We need to know since we have to decide whether to use medical or common terms.

  > In English we are using common terms as both physicians and patients will understand them. We are seeing a great deal of us by medical students and they appreciate the simple language. **Doc James** (talk · contribs · email) 15:42, 6 October 2016 (UTC)

- What is the criteria of an entry being chosen for this list? Availability of a featured or good article on en.wikipdia? Or a general overiew of important medical subjects regardless of article rating?

  > These were key diseases and conditions I pulled together. The list can be changed. All the ones listed on the English list have had their leads improved in English. **Doc James** (talk · contribs · email) 15:42, 6 October 2016 (UTC)

Best regards, --Gereon K. (talk) 06:26, 6 October 2016 (UTC)

> These are all great questions. I do not have answers. It seems that the set of books has an unintentional English-language bias and also some challenges with grouping issues into categories. I imagined that this book was an experimental prototype and only imagined for a general audience. Anyone may make wiki-changes to it and in the case of low back pain and asperger it sounds like there are reasons to consider rearranging categories. **Blue Rasberry** (talk) 13:38, 6 October 2016 (UTC)

User:Gereon K. answered the questions. User:Bluerasberry this page is the intro to the offline medical app. **Doc James** (talk · contribs · email) 15:42, 6 October 2016 (UTC)

## Tools - Snellen chart? (Related?) [edit]

I would like to incorporate this tool, as it is simple, and can detect immediate vision issues. Is this project

strictly medical knowledge, or tools also? Either way, I will put it here, and wait for feedback! Snellen chart and also: Medical thermometer

Twillisjr (talk) 20:33, 21 November 2016 (UTC)

> The Snellen chart is already part of WPMED so is in the app. Articles lead needs to be brought to a good standard before it is included into this list. **Doc James** (talk · contribs · email) 13:33, 22 November 2016 (UTC)




# Editing Wikipedia:WikiProject Medicine/Open Textbook of Medicine



```
[[File:MedLogoNoWiFi.png|frameless|upright=0.9|right]]

Welcome to the "Offline Medical Encyclopedia" by [[Wikipedia]]. This is a complete collection of all health care, sanitation, anatomy, and medication related topics from Wikipedia in an offline format. Like Wikipedia all content is open access, meaning that it is free to download, reuse, share, and build upon.

We are working to develop these apps in a number of languages, including English, Persian, Chinese, and Hindi. There are ongoing [[Wikipedia:WikiProject_Medicine/Translation_task_force|efforts to increase access to medical information in all languages]] in collaboration with [[Translators Without Borders]] among others. If you like this app and are interested in helping us make it better please join [[Wikipedia:WikiProject Medicine]] or contact us directly.

Please keep in mind that this is volunteer generated content. While we try our best to make it as accurate as possible it is not perfect. Thus we request that you use common sense.
<div style="float: right; text-align: right;">
[[User:Doc James|James Heilman]], MD, CCFP(EM)<br>
The Teams at WikiProject Medicine &<br>
[http://twb.translationcenter.org/ Translators Without Borders]
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- Wikipedia:WikiProject Medicine/Open Textbook of Medicine: Sitelink

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(newest | oldest) View (newer 50 | older 50) (20 | 50 | 100 | 250 | 500)

Compare selected revisions

- (cur | prev) ◯ ⦿ 18:52, 9 November 2016 Doc James (talk | contribs) . . (9,057 bytes) (-7) . . (undo)
- (cur | prev) ⦿ ◯ 18:52, 9 November 2016 Doc James (talk | contribs) . . (9,064 bytes) (0) . . (undo)
- (cur | prev) ◯ ◯ 18:52, 9 November 2016 Doc James (talk | contribs) . . (9,064 bytes) (-12) . . (undo)
- (cur | prev) ◯ ◯ 06:22, 7 October 2016 Gereon K. (talk | contribs) . . (9,076 bytes) (0) . . *(Is not mainly and/or only present in children)* (undo)
- (cur | prev) ◯ ◯ 21:10, 5 October 2016 Gereon K. (talk | contribs) . . (9,076 bytes) (-23) . . *(twice the same)* (undo)
- (cur | prev) ◯ ◯ 06:14, 28 September 2016 Kelson (talk | contribs) . . (9,099 bytes) (+6) . . (undo)
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# User talk:47.136.97.226

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- If the page has been deleted, check the **deletion log**, and see Why was the page I created deleted?

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Upload file
Special pages
Printable version

Languages

For 47.136.97.226 (talk | block log | uploads | logs | filter log)

Search for contributions

Special page

Show contributions of registered accounts only

User: 47.136.97.226

Namespace: all ☐ Invert selection ☐ Associated namespace

Tag filter:

☐ Only show edits that are latest revisions ☐ Only show edits that are page creations

☐ Hide minor edits

From year (and earlier): 2017 From month (and earlier): all Search

No changes were found matching these criteria.

This is the contributions page for an IP user, identified by the user's IP address. Some IP addresses change periodically, and may be shared by several users. If you are an IP user, you may create an account or log in to avoid future confusion with other IP users. Registering also hides your IP address.

[WHOIS · rDNS · Traceroute · Geolocate (Alternate) · Current blocks · Global contributions] · [RIRs: America · Europe · Africa · Asia-Pacific · Latin America/Caribbean] ·

## Personal tools

- N[illegible] log
- T[illegible]
- C[illegible]
- Cr[illegible]nt
- Log in

WIKIPEDIA
The Free Encyclopedia

# Create account

## Namespaces

- Special page
- (help me choose)

## Views

## More

## Search

Search Go

Main page
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Username

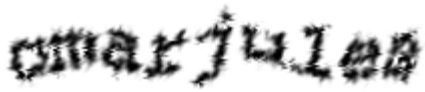
Password

Confirm password

Email address (optional)

To protect the wiki against automated account creation, we kindly ask you to enter the words that appear below in the box (more info):

CAPTCHA Security check



Can't see the image? Request an account

Create your account

## Wikipedia is made by people like you.

867,565,593

edits

5,323,772

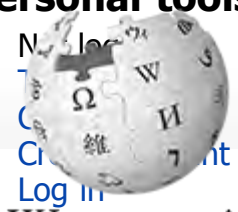
articles

119,453

recent contributors

## Personal tools

- N... lo...
- T...
- C...
- Cr... nt
- Log in



WIKIPEDIA
The Free Encyclopedia

# Log in

Username

Password

☐ Keep me logged in (for up to 365 days)

Log in

Help with logging in

Forgot your password?

## Don't have an account?

Join Wikipedia

## Namespaces

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Search Go

# Welcome to Wikipedia,

the free encyclopedia that anyone can edit.
5,323,772 articles in English

- Arts
- Biography
- Geography
- History
- Mathematics
- Science
- Society
- Technology
- **All portals**


## Namespaces

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Create a book
Download as PDF
Printable version

In other projects
Wikimedia Commons
MediaWiki
Meta-Wiki
Wikispecies
Wikibooks
Wikidata
Wikinews
Wikiquote
Wikisource
Wikiversity
Wikivoyage

Languages
Simple English


## From today's featured article

IWGP Intercontinental Championship belt

**Wrestle Kingdom 9** was a professional wrestling event at the Tokyo Dome on January 4, 2015, produced by the New Japan Pro Wrestling (NJPW) promotion. The first event on the 2015 NJPW schedule, it featured ten professional wrestling matches and one pre-show match, six of which were for championships. In the double main event, Shinsuke Nakamura successfully defended the IWGP Intercontinental Championship *(belt pictured)* against Kota Ibushi, and Hiroshi Tanahashi successfully defended the IWGP Heavyweight Championship against Kazuchika Okada. The appearance of Pro Wrestling Noah wrestlers led to a storyline in which NJPW's Suzuki-gun group began wrestling at Noah events. Wrestle Kingdom 9 was attended by 36,000 people and was broadcast as a pay-per-view event with English commentary in the United States and Canada. Critics issued universally positive reviews; *Paste* magazine said it presented "some of the most passionate and poignant performance art today". Readers of the *Wrestling Observer Newsletter* voted Wrestle Kingdom 9 the Best Major Wrestling Show of 2015, and named its Ibushi–Nakamura match as the 2015 Pro Wrestling Match of the Year. (**Full article...**)

Recently featured: *Smilodon* · English Benedictine Reform · *Madman's Drum*

**Archive** · **By email** · **More featured articles...**

## Did you know...

- ... that the **Lion Hunt of Ashurbanipal** reliefs *(pictured)* from c. 640 BC show the king killing lions with swords, spears, and arrows?
- ... that **Zorobabela Ka'auwai** accompanied his

Ashurbanipal kills a lion

## In the news

Reina nightclub

- **An attack on a nightclub** *(pictured)* in Istanbul, Turkey, during New Year's celebrations, kills at least 39 people and injures more than 70 others.
- American actress, screenwriter, and author **Carrie Fisher** dies at the age of 60, and her mother, actress and singer **Debbie Reynolds**, dies one day later at the age of 84.
- English singer, songwriter, and record producer **George Michael** dies at the age of 53.
- A Tupolev Tu-154 **crashes** near Sochi, Russia, killing all 92 people on board, including 64 members of the Alexandrov Ensemble.
- The United Nations Security Council adopts **a resolution** condemning Israeli settlements in the West Bank and East Jerusalem.

**Ongoing**: Battle of Mosul ·
**Recent deaths**: Granny · Tony Atkinson · William Christopher · LaVell Edwards ·

## On this day...

**January 4**: **World Braille Day**

Samuel Colt

- 1642 – King **Charles I of England** sent soldiers to arrest members of Parliament, beginning England's slide into civil war.
- 1798 – After having been invested as Prince of Wallachia, **Constantine Hangerli** arrived in Bucharest to assume the throne.

patron Hoapili into battle in the suppression of Humehume's rebellion?
- ... that although only a single example of the **Eriksen M/25** machine gun was built, it saw service in the 1940 Norwegian Campaign?
- ... that the United States Senate **rejected Caleb Cushing's nomination** to be Secretary of the Treasury three times in one day?
- ... that the 1936 Korean novel *Sangnoksu* has been made into two films?
- ... that the 10-gun sloop-of-war **HMS** *Stork* was originally designed to resemble King George II's yacht *Royal Caroline*?
- ... that rapper Liv released the song "**Sorry Mrs. Carter**" as an "open letter" to Beyoncé?
- ... that almost nothing is quite certain about the "multifaceted" and "very productive" **Master of the Drapery Studies**?

**Recently improved articles** · **Start a new article** · **Nominate an article** ·

- 1847 – American gun inventor **Samuel Colt** *(pictured)* made his first large sale of his revolvers to the Texas Rangers.
- 1912 – **The Boy Scout Association** was incorporated throughout the then British Empire by royal charter.
- 1936 – *Billboard* magazine published its first music hit parade.
- 1973 – *Last of the Summer Wine*, the longest-running sitcom in the world, premiered as an episode of the BBC's *Comedy Playhouse*.

More anniversaries: January 3 · **January 4** · January 5 ·

**Archive** · **By email** · **List of historical anniversaries** ·

Current date: January 4, 2017 (UTC) · Reload this page ·



## Today's featured picture

**Feral pigeons** (*Columba livia domestica*) are birds derived from domestic pigeons that have returned to the wild. Originally bred from the wild rock dove, which naturally inhabits sea cliffs and mountains, these pigeons use the ledges of buildings as a substitute for cliffs. They have become adapted to urban life, preying on insects and scavenging. They are abundant in towns and cities throughout much of the world.

Photograph: Muhammad Mahdi Karim

Recently featured: Paulus Moreelse · Mollweide projection · Selfoss (waterfall) ·

**Archive** · **More featured pictures...** ·

## Other areas of Wikipedia

- **Community portal** – Bulletin board, projects, resources and activities covering a wide range of Wikipedia areas.
- **Help desk** – Ask questions about using Wikipedia.
- **Local embassy** – For Wikipedia-related communication in languages other than English.
- **Reference desk** – Serving as virtual librarians, Wikipedia volunteers tackle your questions on a wide range of subjects.
- **Site news** – Announcements, updates, articles and press releases on Wikipedia and the Wikimedia Foundation.
- **Village pump** – For discussions about Wikipedia itself, including areas for technical issues and policies.

## Wikipedia's sister projects

Wikipedia is hosted by the Wikimedia Foundation, a non-profit organization that also hosts a range of other projects:

**Commons**
Free media repository

**MediaWiki**
Wiki software development

**Meta-Wiki**
Wikimedia project coordination

**Wikibooks**
Free textbooks and manuals

**Wikidata**
Free knowledge base

**Wikinews**
Free-content news

**Wikiquote**
Collection of quotations

**Wikisource**
Free-content library

**Wikispecies**
Directory of species

**Wikiversity**
Free learning materials and activities

**Wikivoyage**
Free travel guide

**Wiktionary**
Dictionary and thesaurus

## Wikipedia languages

This Wikipedia is written in English. Started in 2001, it currently contains 5,323,772 articles. Many other Wikipedias are available; some of the largest are listed below.

- More than 1,000,000 articles: Deutsch · Español · Français · Italiano · Nederlands · 日本語 · Polski · Русский · Svenska · Tiếng Việt ·
- More than 250,000 articles: · Bahasa Indonesia · Bahasa Melayu · Català · Čeština · Euskara · · · Magyar · Norsk bokmål · Português · Română · Srpski · Srpskohrvatski · Suomi · Türkçe · Українська · 中 ·
- More than 50,000 articles: Bosanski · Български · Dansk · Eesti · Ελληνικά · English (simple form) · Esperanto · Galego · עברית · Hrvatski · Latviešu · Lietuvių · Norsk nynorsk · Slovenčina · Slovenščina · ·

**Complete list of Wikipedias**






WIKIPEDIA
The Free Encyclopedia

# Portal:Contents



From Wikipedia, the free encyclopedia

Contents | Overviews | Outlines | Lists | Portals | Glossaries | Categories | Indices
Reference | Culture | Geography | Health | History | Mathematics | Nature | People | Philosophy
Religion | Society | Technology



## Explore Wikipedia's Contents

There are two ways to look things up in Wikipedia: by searching or by browsing.

- If you know the name of an article for which you are looking, simply type it into Wikipedia's search box.
- If you would like to look around the encyclopedia to see what is on it, use Wikipedia's **Contents** pages. Lists and indices are examples of contents for a published work, and Wikipedia has many of each, including a complete alphabetical index and indices by category.
- Links to all of Wikipedia's main contents pages are presented below, and they in turn link to the more specific pages.

**Shortcuts:**
**WP:START**
**WP:EXPLORE**

**Contents**



## Curated article collections

### Overview articles

Overview articles summarize in prose a broad topic like biology, and also have illustrations and links to subtopics like cell biology, biographies like Carl Linnaeus, and other related articles like Human Genome Project.

- Portal:Contents/Overviews lists overview articles from covered areas of knowledge in a single page.

### Outline pages

Outline pages have trees of article links in an outline format. They show how important subtopics relate to each other, and can be useful as a more condensed, non-prose alternative to overview articles.

- Portal:Contents/Outlines is a comprehensive list of "Outline of __" pages, organized by subject
- Outline of academic disciplines covers subjects studied in college or university, and links directly to prose overview articles

### Third-party classification systems

Various third-party classification systems have been mapped to Wikipedia articles, which can be accessed from these pages:

- List of Dewey Decimal classes
- Library of Congress Classification
- Wikipedia:Outline of Roget's Thesaurus

## Vital articles

*Main page: Wikipedia:Vital articles*

Vital articles are lists of subjects for which Wikipedia should have corresponding high-quality articles. They serve as centralized watchlists to track the status of Wikipedia's most important articles.

- Vital articles level 1 – 10 most important articles
- Vital articles level 2 – 100 most important articles
- Vital articles level 3 – 1,000 most important articles
- Vital articles level 4 – 10,000 most important articles

# Reference collections

Wikipedia has several types of pages which provide content in a non-prose form, for reference purposes.

## List pages

List pages enumerate items of a particular type, such as the List of sovereign states or List of South Africans. Wikipedia has "lists of lists" when there are too many items to fit on a single page, when the items can sorted in different ways, or as a way of navigating lists on a topic (for example Lists of countries and territories or Lists of people). There are several ways to find lists:

- Portal:Contents/Lists – A limited single-page collection of lists and lists of lists
- List of lists of lists – A broad single-page collection of lists of lists
- Category:Lists – Browse lists comprehensively via the multi-page Wikipedia category system

## Timelines

Timelines list events chronologically, sometimes including links to articles with more detail. There are several ways to find timelines:

- List of timelines has a long single-page collection
- Category:Timelines has a comprehensive multi-page collection via the Wikipedia category system

Of particular interest may be:

- List of centuries
- List of decades
- List of historical anniversaries—e.g. events on January 1 of any year
- 2017—major events this year
- Portal:Current events—featured current events and related project activities
- Deaths in 2017—lists notable people who died this year
- Category:Graphical timelines—graphical timelines in the category and subcategories, arranged alphabetically

## Glossaries

Glossaries are lists of terms with definitions. Wikipedia includes hundreds of alphabetical glossaries; they can be found two ways:

- Portal:Contents/Glossaries – A single-page list of glossaries
- Category:Wikipedia glossaries – Browse glossaries comprehensively via the Wikipedia category system

## Bibliographies

Bibliographies list sources on a given topic, for verification or further reading outside Wikipedia:

- Category:Wikipedia bibliographies has a complete multi-page listing

### Category:Discographies

Discographies catalog the sound recordings of individual artists or groups.

- Category:Discographies has a complete multi-page listing

## Special format collections

### Portals

Portals include featured articles, images, news, categories, excerpts of key articles, links to related portals, and to-do lists for editors. There are two ways to find portals:

- Portal:Contents/Portals – A single-page list of portals
- Category:Portals – Browse portals comprehensively via the Wikipedia category system

### Wikipedia books

Wikipedia books are collections of Wikipedia articles that can be viewed, downloaded, or printed into a book. They provide a roadmap for a course of study in a particular subject.

- Category:Wikipedia books (community books)—an alphabetical list of the books
- Category:Wikipedia books—a list of the books, categorized by topic

### Spoken articles

Growing collections of Wikipedia articles are starting to become available as spoken word recordings as well.

- Category:Spoken articles—an organized list of all spoken articles
- Wikipedia:Spoken articles—some general information about the spoken article technology

## Collections of articles

### Category system

Wikipedia's collection of category pages is a classified index system. It is automatically generated from category tags at the bottoms of articles and most other pages. Nearly all of the articles available so far on the website can be found through these subject indexes.

If you are simply looking to browse articles by topic, there are three top-level pages to choose from:

- Category:Main topic classifications—probably what you are looking for: Arts, History, Technology, etc.
- Category:Fundamental categories—organizes articles into "abstract" ontological categories in a way that every article can reasonably be expected to be classified within it
- Portal:Contents/Categories—a hand-crafted list of first- and second-level topic categories

For biographies, see Category:People.

Category:Contents is technically at the top of the category hierarchy, but contains many categories useful to editors but not readers. Special:Categories lists every category alphabetically.

### Alphabetical lists of articles

Wikipedia's alphabetical article indexes

- Special:Allpages lists all of the current pages in Wikipedia.
- Portal:Contents/A–Z index provides an easy way to skip to a particular part of the alphabet in the list of all articles.

- Lists of alphabetical indexes
  - Category:Wikipedia indexes—alphabetical list of topic indexes
  - Portal:Contents/Indices—indexes sorted by topic area

# Collections of articles by quality or popularity

## Featured content

Featured content is the best Wikipedia has to offer, via vigorous peer review. Presented by type:

- Featured articles · Featured lists · Featured pictures · Featured portals · Featured topics

## Most popular articles

- Wikipedia:Top 5000 pages (of the last week)
- Wikitop—Top 30 most popular articles by categories, with user comments on traffic jumps

## Content listings

**Types**

Overviews · Featured content · Outlines · Lists · Portals · Glossaries · Categories · Indices ·

**Topics**

Current events · Reference · Culture · Geography · Health · History · Mathematics · Nature · People · Philosophy · Religion · Society · Technology ·

**Places, people and times**

Academic disciplines · Anniversaries (today · · Countries and territories · People (deaths this year · · Timelines (centuries · decades · ·

**Indices**

A–Z index · Categories · Dewey Decimal classes · Library of Congress Classification · Roget's Thesaurus · Spoken articles · Wikipedia books ·

Categories: Wikipedia directories | Contents | Content portals

WIKIPEDIA
The Free Encyclopedia

# Portal:Featured content

From Wikipedia, the free encyclopedia

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WP:FEAT
WP:FEATURE

## Featured content in Wikipedia

Featured content represents the best of Wikipedia, including articles, pictures, and other contributions that showcase excellent results of the collaborative efforts of Wikipedia.

All featured content undergoes a thorough review process to ensure that it meets the highest standards in order to serve as the best example of our end goals.

A small bronze star ( ) in the top right corner of a page indicates that the content is featured.

This page gives links to all of Wikipedia's featured content.

**Featured content:** ←
- Featured articles
- Featured lists
- Featured pictures
- Featured portals
- Featured topics

## This week's *Signpost* report

FEATURED CONTENT

### The Christmas edition

By Armbrust

**Contribute** — **Share this**

E-MAIL

As their name suggests, bee-eaters predominantly eat flying insects, especially bees and wasps, which are caught in the air by flights from an open perch.

*This* **Signpost** *"Featured content" report covers material promoted from 13 November to 17 December. Text may be adapted from the respective articles and lists; see their page histories for attribution.*

## Featured articles

Twenty-three featured articles were promoted.

- *Aries* (*nominated by Magiciandude*) is the ninth studio album by Mexican recording artist Luis Miguel. It was released by WEA Latina in 1993. After attaining commercial success in 1991 with his previous album, *Romance*, Miguel decided to return to a style similar to his earlier work, featuring pop ballads and dance numbers with R&B influences. The record was produced by Miguel, who was assisted by Kiko Cibrian, Rudy Pérez, David Foster, and Juan Luis Guerra. It peaked at number one on the US *Billboard* Latin Pop Albums, where it stayed for 19 weeks. Internationally, the album was certified triple platinum in Mexico, and was certified diamond in Argentina. *Aries* sold over two million copies worldwide through 2000. Upon its release, the album received mixed reviews from music critics; they were divided on the dance tunes and ballads, although Miguel's vocals and the album's arrangements garnered positive reactions. Miguel received several accolades,

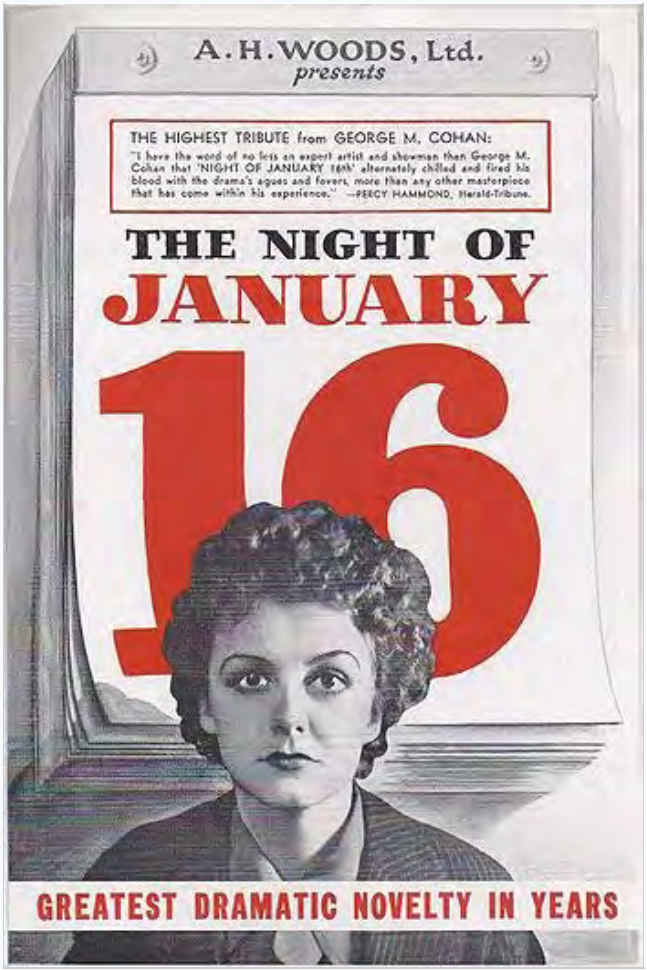

Lewis Hamilton gestures to his home crowd following his fifth win of the 2015 Formula One season at Silverstone.

including a Grammy Award for Best Latin Pop Album.

- **Northampton War Memorial** *(nominated by HJ Mitchell)* is a First World War memorial on Wood Hill in the centre of Northampton, the county town of Northamptonshire. Designed by architect Sir Edwin Lutyens, it is a Stone of Remembrance flanked by twin obelisks draped with painted stone flags standing in a small garden in what was once part of the churchyard of All Saints' Church. Today it is a Grade I listed building.
- The **2015 Formula One season** *(nominated by Tvx1)* was the 66th season of the Formula One World Championship, a motor racing championship for Formula One cars, recognised by the sport's governing body, the Fédération Internationale de l'Automobile, as the highest class of competition for open-wheel racing cars. Twenty-two drivers representing ten teams contested nineteen Grands Prix, starting in Australia and ending in Abu Dhabi as they competed for the World Drivers' and World Constructors' championships. Lewis Hamilton secured his third Drivers' Championship with three races left in the season. The runner-up was his teammate Nico Rosberg, with Ferrari's Sebastian Vettel third. Mercedes clinched the 2015 Constructors' title at the Russian Grand Prix, ahead of Ferrari and Williams, and ended the season with a record 703 points.
- *Giganotosaurus* *(nominated by FunkMonk)* is a genus of theropod dinosaur that lived in what is now Argentina, during the early Cenomanian age of the Late Cretaceous period, approximately 99.6 to 97 million years ago. The holotype specimen was discovered in the Candeleros Formation of Patagonia in 1993, and is almost 70% complete. The animal was named *G. carolinii* in 1995; the genus name translates as "giant southern lizard" and the specific name honours the discoverer, Rubén D. Carolini. A dentary bone, a tooth and some tracks, discovered before the holotype, were later assigned to this animal. The genus attracted much interest and became part of a scientific debate about the maximum sizes of theropod dinosaurs.
- **First Tennessee Park** *(nominated by NatureBoyMD)* is a minor league baseball park in downtown Nashville, Tennessee. The home of the Triple-A Nashville Sounds of the Pacific Coast League, it opened in 2015, and can seat up to 10,000 people. It replaced the Sounds' former home, Herschel Greer Stadium, where

Reconstructed *Giganotosaurus* skull


First Tennessee Park's most distinctive feature is its guitar-shaped scoreboard.




Flyer for the Broadway production of *Night of January 16th*

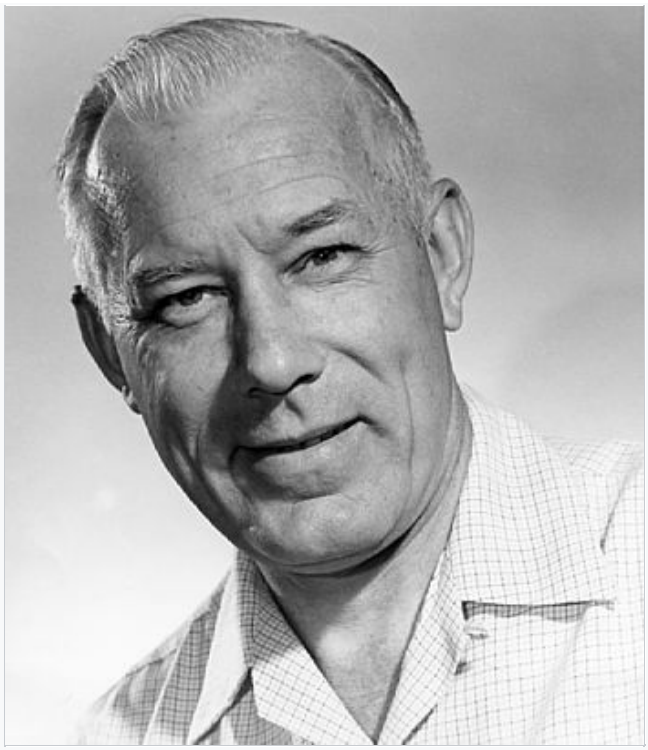
Lithograph of SMS *Mecklenburg* from 1902

the team played from its founding in 1978 until 2014. The design of the park incorporates Nashville's musical and baseball heritage and the use of imagery inspired by country music, Sulphur Dell, and Nashville's former baseball players and teams. The ballpark's wide concourse wraps entirely around the stadium and provides views of the field from every location. The greenway section connects with two other greenways in the city.

- *Turbinellus floccosus* *(nominated by Casliber)* is a cantharelloid mushroom of the family Gomphaceae native to Asia and North America. The orange-capped vase- or trumpet-shaped fruiting bodies may reach 30 cm (12 in) high and 30 cm (12 in) wide. The lower surface, the hymenium, is covered in wrinkles and ridges, and is pale buff or yellowish to whitish. *T. floccosus* forms symbiotic relationships with various types of conifer, growing in coniferous woodlands. Though mild-tasting, they generally cause gastrointestinal symptoms of nausea, vomiting and diarrhea when consumed.
- *Crucifix* *(nominated by Ceoil and Kafka Liz)* is a wooden crucifix, painted in distemper, attributed to the Florentine painter and mosaicist Cimabue. The work was commissioned by the Franciscan friars of Santa Croce and is built from a complex arrangement of five main and eight ancillary timber boards. It is one the first Italian artworks to break from the late medieval Byzantine style and is renowned for its technical innovations and humanistic iconography. The work was in the Basilica di Santa Croce, Florence, since the late thirteenth century, and

at the Museo dell'Opera Santa Croce since restoration following the flooding of Arno in 1966. It remains in poor condition despite conservation efforts.

- *Night of January 16th* *(nominated by RL0919)* is a theatrical play by Russian-American author Ayn Rand, inspired by the death of the "Match King", Ivar Kreuger. Set in a courtroom during a murder trial, an unusual feature of the play is that members of the audience are chosen to play the jury. The court hears the case of Karen Andre, a former secretary and lover of businessman Bjorn Faulkner, of whose murder she is accused. The play does not directly portray the events leading to Faulkner's death; instead the jury must rely on character testimony to decide whether Andre is guilty. The play's ending depends on the verdict. Rand's intention was to dramatize a conflict between individualism and conformity, with the jury's verdict revealing which viewpoint they preferred.
- **SMS** *Mecklenburg* *(nominated by Parsecboy)* was the fifth ship of the *Wittelsbach* class of pre-dreadnought battleships of the German Imperial Navy. Laid down in 1900 at the AG Vulcan shipyard in Stettin, she was finished in 1903. *Mecklenburg* was armed with a main battery of four 24 cm (9.4 in) guns and had a top speed of 18 kn (33 km/h; 21 mph). It spent the early period of her career in the I Squadron of the German fleet, participating in the peacetime routine of training cruises and exercises. After World War I began in 1914, the ship was mobilized with her sisters as the IV Battle Squadron. She saw limited duty in the Baltic Sea against Russian naval forces, and as a guard ship in the North Sea. The German High Command withdrew the ship from active service in 1916 due to a threat from submarines and naval mines, together with severe shortages in personnel. For the remainder of her career, *Mecklenburg* served as a prison ship and as a barracks ship based in Kiel. She was stricken from the navy list in 1920 and sold for scrapping the following year.
- **State Route 76** *(nominated by Rschen7754)* is a 52.63 mi (84.70 km) long state highway in the U.S. state of California. It is a much used east–west route in the North County region of San Diego County. A route along the corridor has existed since the early 20th century, as has the



Ike Altgens played Secretary Lloyd Patterson in the low-budget science fiction thriller *Beyond the Time Barrier*.

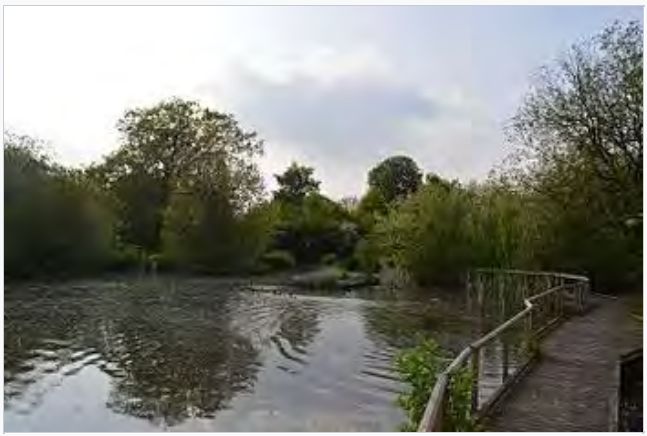
*After the Deluge* is now in the collection of the Watts Gallery in Compton, Guildford.

bridge over the San Luis Rey River near Bonsall. The route was added to the state highway system in 1933, and was officially designated by the California State Legislature as SR 76 in the 1964 state highway renumbering.

- *Super Mario Galaxy* *(nominated by Jaguar)* is a platform video game developed and published by Nintendo for the Wii worldwide in 2007. It is the third 3D game in the *Super Mario* series and the eighth main instalment overall. The game was re-released as a Nintendo Selects title in 2011, and as a download via the Wii U's eShop in 2015. The story revolves around the protagonist, Mario, who is on a quest to rescue Princess Peach whilst simultaneously saving the universe from Bowser. The levels in the game consist of galaxies filled with minor planets and worlds, with different variations of gravity, the central element of gameplay. It was a critical and commercial success, hailed as one of the greatest video games of all time. Critics praised the game's graphics, gravity mechanics, and setting.
- **Ike Altgens** *(nominated by ATS)* (1919–1995) was an American photojournalist, photo editor, and field reporter for the Associated Press (AP) based in Dallas, Texas, who became known for his photographic work during the assassination of President John F. Kennedy. He was 19 when he began his AP career, which was interrupted by military service during World War II. When his service time ended, Altgens returned to Dallas and got married, then went back to work for the local AP bureau and eventually earned a position as a senior editor. Altgens appeared briefly as a film actor and model during his 40-year career with the AP, which ended in 1979. He spent his later years working in display advertising, and answering letters and other requests made by assassination researchers. Altgens and his wife died in 1995 at about the same time in their Dallas home.
- *After the Deluge* *(nominated by Iridescent)* is a Symbolist oil painting by English artist George Frederic Watts, first exhibited as *The Sun* in an incomplete form in 1886 and completed in 1891. It shows a scene from the story of Noah's Flood, in which after 40 days of rain Noah opens the window of his Ark to see that the rain has stopped. Watts felt that modern society was in decline owing to a lack of moral values, and he often painted works on the topic of the Flood and its cleansing of the unworthy from the world. The painting takes the form of a stylised seascape, dominated by a bright sunburst breaking through clouds. Although this was a theme Watts had depicted previously in *The Genius of Greek Poetry* in 1878, *After the Deluge* took a radically different approach. With this painting he intended to evoke a monotheistic God in the act of creation, but avoid depicting the Creator directly.
- **Bradley Cooper** *(nominated by FrB.TG)* (born 1975) is an American actor and producer. His career began with a guest role in the television series *Sex and the City* in 1999 and his film debut came two years later in *Wet Hot American Summer*. He first gained recognition as Will Tippin in the spy-action television show *Alias* (2001–2006), and achieved minor success with a supporting part in the comedy film *Wedding Crashers* (2005). His breakthrough role came in 2009 with *The Hangover*, a commercially successful comedy which spawned two sequels in 2011 and 2013. In 2011, Cooper was named International Man of the Year by *GQ* and Sexiest Man Alive by *People*. He is one of the highest-paid actors in the world, and has been nominated for several accolades, including four Academy Awards, two British Academy Film Awards and two Golden Globe Awards. *Time* magazine named him one of the 100 most influential people in the world in 2015.
- *The Pale Emperor* *(nominated by Homeostasis07)* is the ninth studio album by American rock band Marilyn Manson. It was released in 2015, through Marilyn Manson's Hell, etc. label, and was distributed in the US by Loma Vista Recordings and internationally by Cooking Vinyl. The album was

John Wark was one of the four inaugural members of the Ipswich Town F.C. Hall of Fame.

Baltimore is the largest municipality in Maryland.



Nazeing Triangle is the smallest Local Nature Reserve in Essex.

released in standard and deluxe editions on CD and 2×LP vinyl, and as a limited edition box set. The standard version of the album contains ten tracks; the deluxe edition includes three acoustic versions as bonus tracks. The album was released to generally positive reviews from music critics. Several writers referred to it as the band's best album in over a decade, and multiple publications ranked it as one of the best albums of 2015. It was also a commercial success, debuting at number eight on the *Billboard* 200 with the band's highest opening week sales since *Eat Me, Drink Me* in 2007. It topped *Billboard*'s Hard Rock Albums chart, as well as the national albums chart in Switzerland, and peaked within the top ten in fifteen other countries.

- *Seri Rambai (nominated by Singora)* is a 17th-century Dutch cannon displayed at Fort Cornwallis in George Town. It is the largest bronze gun in Malaysia, a fertility symbol and the subject of legends and prophecy.
- **Gottlob Berger** *(nominated by Peacemaker67)* (1896–1975) was a senior German Nazi official who held the rank of *SS-Obergruppenführer und General der Waffen-SS*, and was the chief of the SS Main Office responsible for *Schutzstaffel* recruiting during World War II. He had a key role in the Reich Ministry for the Occupied Eastern Territories from mid-1942. In this role he proposed a plan to kidnap and enslave 50,000 Eastern European children between the ages of 10 and 14, under the codename Heuaktion, a plan that was subsequently carried out. He surrendered to U.S. troops near Berchtesgaden, and was promptly arrested. He was tried and convicted in the Ministries Trial of the U.S. Nuremberg Military Tribunals for war crimes, and was sentenced to 25 years imprisonment. His sentence was soon reduced to 10 years, and he was released after serving six and a half years.
- **Dick Cresswell** *(nominated by Ian Rose)* (1920–2006) was an officer and pilot in the Royal Australian Air Force (RAAF). He held command of No. 77 (Fighter) Squadron twice during World War II, and again during the Korean War. Cresswell was credited with being the first RAAF pilot to shoot down an enemy aircraft at night over Australian soil, the only man to serve as commanding officer of an RAAF squadron on three occasions during wartime, and the first officer to lead a jet-equipped Australian squadron in combat. His performance in Korea earned him both the Commonwealth and the US Distinguished Flying Crosses.
- The **Montreal Laboratory** *(nominated by Hawkeye7)* was established by the National Research Council of Canada during World War II to undertake nuclear research in collaboration with the United Kingdom, and to absorb some of the scientists and work of the Tube Alloys nuclear project in Britain. It became part of the Manhattan Project, and designed and built some of the world's first nuclear reactors.
- The **bee-eaters** *(nominated by Sabine's Sunbird and Jimfbleak)* are a group of near-passerine birds in the family Meropidae containing three genera and 27 species. Most species are found in Africa and Asia, with a few in southern Europe, Australia, and New Guinea. They are characterised by richly coloured plumage, slender bodies, and usually elongated central tail feathers. All have long down-turned bills and medium to long wings, which may be pointed or round. Male and female plumages are usually similar.
- The **Tahiti rail** *(nominated by FunkMonk)* is an extinct species of rail that lived on Tahiti. It was first recorded during James Cook's second voyage around the world (1772–1775), on which it was illustrated by Georg Forster and described by Johann Reinhold Forster. The Tahiti rail was 9 in (23 cm) long, and its colouration was unusual for a rail. The Tahiti rail was supposedly flightless, and nested on the ground. It is said to have been seen in open areas, marshes, and in coconut plantations.
- *Love, Inc. (nominated by Aoba47)* is an American television sitcom, created by Andrew Secunda, which originally aired for one season on United Paramount Network. The show revolves around five matchmakers working at a dating agency. Despite being set in New York, filming took place at Paramount Studios in Hollywood, Los Angeles and other locations in California. It was canceled following UPN's merger with the WB to launch the CW in 2006. Critical response to *Love, Inc.* was mixed: some critics praised its multi-ethnic cast, while others felt that the storylines and characters were unoriginal and Philipps' portrayal of her character as unsympathetic.
- The **Alabama Centennial half dollar** *(nominated by Wehwalt)* was a commemorative fifty-cent coin struck by the United States Bureau of the Mint in 1921 as a belated acknowledgement of the 100th anniversary of Alabama's admission to the Union in 1819. The coin was created by Laura Gardin Fraser, who became the first woman designer of a coin. To boost sales, a symbol, 2X2 (recognizing Alabama as the 22nd state) was included in the design for a minority of the coins; these are generally more expensive today.

## Featured lists

Ten featured lists were promoted.

- Ipswich Town F.C. is an English association football club founded in 1878. In 2007, the club created a

**hall of fame** *(nominated by The Rambling Man)* into which a number of personnel associated with the club are inducted every year. The inaugural members, Ray Crawford, Mick Mills, Ted Phillips and John Wark, were selected in 2007 by a ballot of former Ipswich players. As of 2016, forty-six people have been inducted into the hall of fame.

- The **Masters Tournament Par-3 contest** *(nominated by The Rambling Man)* is a golf competition which precedes the Masters Tournament at Augusta National Golf Club in Augusta, Georgia. The first Par-3 contest was held in 1960, and was won by three-time Masters champion Sam Snead. The contest takes place in a single round on a nine-hole, par-27 course in the northeast corner of Augusta National Grounds, which was designed in 1958 by George Cobb and club founder Clifford Roberts. Traditionally the golfers playing in the contest have invited family members onto the course to caddy for them, sometimes allowing them to play shots on their behalf. Numerous holes in one have been made during the history of the tournament, including nine in the 2016 tournament. No winner of the Par-3 contest has gone on to win the Masters in the same year.
- Ravichandran Ashwin (born 1986) is a Test, One Day International and Twenty20 International cricketer who represents the India national cricket team. As of December 2016, **Ashwin has taken 24 five-wicket hauls in international cricket** *(nominated by Vensatry)*; he ranks joint 13th in the all-time list, and joint third among his countrymen. He is one of only 45 bowlers who have taken 15 or more five-wicket hauls at international level in their cricketing careers.
- Michael Fassbender (born 1977) is a German-Irish actor. **His filmography** *(nominated by Cowlibob)* includes thirty-two films, seven television films and thirty-six television episodes. He also voiced Logan in the 2010 video game *Fable III*.
- A One Day International (ODI) is a 50 over cricket match between two representative teams, each having ODI status, as determined by the International Cricket Council (ICC). As of November 2016, **50 players have represented the Kenyan national team in ODIs** *(nominated by Yellow Dingo)*, since its debut in 1996. Thomas Odoyo and Steve Tikolo have played the most ODIs for Kenya with 131 each. Tikolo has scored the most runs with 3369 for the team, while Odoyo has taken the most wickets with 141.
- Shannen Doherty (born 1971) is an American actress, producer, author, and television director. **She has appeared in numerous television programs and motion pictures.** *(nominated by Aoba47)* She has appeared in sixteen films (with currently four of them being in post-production), in forty-eight television films and numerous television episodes (being a series regular on seven television shows).
- Rajinikanth (born 1950) is an Indian actor who predominantly works in Tamil cinema. He began his **film career** *(nominated by Kailash29792 and Vensatry)* by playing antagonistic and supporting roles before graduating to a lead actor. After starring in numerous commercially successful films throughout the 1980s and 1990s, he has continued to hold a matinée idol status in the popular culture of Tamil Nadu. Writing for Slate, Grady Hendrix called him the "biggest movie star you've probably never heard of." Rajinikanth has also worked in other Indian film industries such as Bollywood, Telugu, Kannada, Malayalam and Bengali. As of 2016, he has appeared in over 150 films.
- Maryland is a state located in the Southern United States. According to the 2010 United States Census, Maryland is the 19th most populous state with 5,773,785 inhabitants but the 9th smallest by land area spanning 9,707.24 sq mi (25,141.6 $km^2$) of land. Maryland is divided into 23 counties and contains **157 incorporated municipalities** *(nominated by Mattximus)* consisting of cities, towns, or villages. Incorporated municipalities cover only 4.4% of the state's land mass but are home to 26.2% of its population.
- Cardiff City F.C., a professional association football club based in Cardiff, Wales, was founded in 1899. As of the end of the 2015–16 season, the club had spent 11 seasons in the top tier of English football, 47 in the second, 22 in the third and 5 in the fourth. **This list** *(nominated by Kosack)* details their achievements in first-team competitions, and records their top goalscorer, for each completed season since their first appearance in the English football pyramid as members of the Southern Football League in 1910–11. Due to the unavailability of complete statistics, seasons prior to 1910 in the amateur Welsh leagues are not included.
- Essex is a county in the east of England. It has an area of 1,420 sq mi (3,700 $km^2$), with a coastline of 400 mi (640 km), and a population of 1,393,600 according to the 2011 census. As of August 2016 there are **forty-nine Local Nature Reserves (LNRs) in Essex** *(nominated by Dudley Miles)*. Nine are also Sites of Special Scientific Interest, three are also Scheduled Monuments and four are managed by the Essex Wildlife Trust. LNRs are designated by local authorities under the National Parks and Access to the Countryside Act 1949. The local authority must have a legal control over the site, by owning or leasing it or having an agreement with the owner. LNRs are sites which have a special local interest either biologically or geologically, and local authorities have a duty to care for them. They can apply local bye-laws to manage and protect LNRs.

## Featured pictures

Twenty-one featured pictures were promoted.

**Palace of Fine Arts**
*(created and nominated by King of Hearts)*

*The Storm on the Sea of Galilee*
*(created by Rembrandt; nominated by Brandmeister)*

*The Immaculate Conception*
*(created by Giovanni Battista Tiepolo; nominated by Armbrust)*

**Peter and Paul Fortress**
*(created and nominated by Godot13)*

*Glory of Florentine Saints*
*(created by Vincenzo Meucci; photographed and*

**Amalia de Llano**
*(created by Federico de*

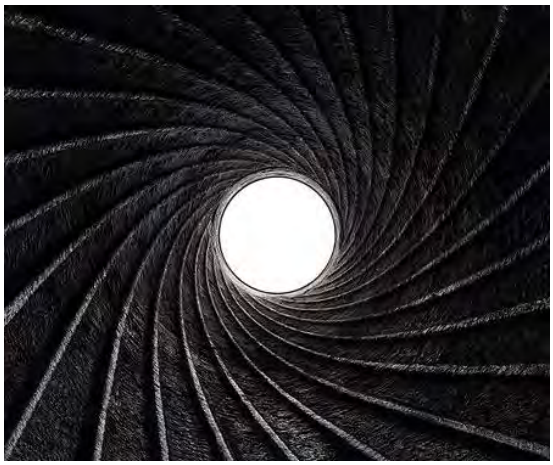
*nominated* by *Livioandronico2013*)

*Madrazo*; *nominated* by *EtienneDolet*)

**Tiger from the Tadoba Andhari Tiger Project**
(created by *Stephenekka*; *nominated* by *Yann*)

**Fountain of Qayt Bay**
(created and *nominated* by *Godot13*)

**Peter Tatchell**
(created and *nominated* by *Colin*)



**Rifling**
(created and *nominated* by *PetarM*)

*Self-Portrait*
(created by *Marie-Gabrielle Capet*; *nominated* by *EtienneDolet*)

*Still Life with Cheeses, Almonds and Pretzels*
(created by *Clara Peeters*; *nominated* by *MurielMary*)

*Odds and Ends*
*(created by Emily Carr; nominated by MurielMary)*

**Françoise-Marguerite de Sévigné**
*(created by Alexander Roslin; nominated by EtienneDolet)*

**Saints John and Paul basilica al Celio**
*(created and nominated by Livioandronico2013)*

**Joseph F. Ambrose**
*(created by Mickey Sanborn; nominated by Pine)*

**Masked lovers at the Carnival of Venice**
*(created by Frank Kovalchek; nominated by EtienneDolet)*

**Shag Rocks**
*(created and nominated by Godot13)*

**Chapel Royal**
*(created by Diliff; nominated by Armbrust)*

*The Child's Bath*
*(created by Mary Cassatt; nominated by MurielMary)*

**Dome of Basilica di Santa Maria Maggiore**
*(created and nominated by Livioandronico2013)*

# Lists of featured content

| | Articles | Pictures | Lists | Portals | Topics |
|---|---|---|---|---|---|
| **Featured:** | 4896 / T | 6,048 / T | 3083 / T | 173 / T | 146 / T |
| **Criteria:** | FA? / T | FP? / T | FL? / T | FPO? / T | FT? / T |
| **Candidates:** | FAC / T | FPC / T | FLC / T | FPOC / T | FTC / T |
| **Removal:** | FARC / T | FPR / T | FLRC / T | FPR / T | FTRC / T |
| **Former:** | 1,117 / T | FFP | 252 / T | FFPO | FFT |

# Newest featured content edit

### Articles

- Devon County War Memorial
- Operation Infinite Reach
- Cliff Clinkscales
- Belgium national football team
- Jochen Rindt
- Tidus
- Nominative determinism
- *Banksia aculeata*
- Alabama Centennial half dollar
- *Love, Inc.* (TV series)
- Tahiti rail
- Bee-eater
- Montreal Laboratory
- Dick Cresswell
- Gottlob Berger

### Topics

- Overview of Lady Gaga
- U.S. Highways in Michigan
- World Fantasy Award
- Overview of Katy Perry
- 2015 Vuelta a España
- *Final Fantasy* series
- 1961 Atlantic hurricane season
- Overview of Leonardo DiCaprio
- Liverpool F.C.
- *Almirante Latorre*-class battleship
- Scheduled monuments in Somerset
- Overview of Lorde
- Sega video game consoles
- Vidya Balan
- No. 90 (Composite) Wing RAAF

### Portals

- California Roads
- *Halo*
- Bristol
- Latin music
- Children's literature
- New York City
- Literature
- Freedom of speech
- Star Trek
- Technology
- Sports
- Geography
- Massachusetts
- Cheshire
- Bollywood

### Lists

- Municipalities in Mississippi
- Bradley Cooper on screen and stage
- Accolades received by *Room*
- Latin Grammy Hall of Fame
- Tamannaah filmography
- Jnanpith Award
- Local Nature Reserves in Essex
- Cardiff City F.C. seasons
- Municipalities in Maryland
- Rajinikanth filmography
- Shannen Doherty filmography
- Kenya ODI cricketers
- Michael Fassbender filmography
- International cricket five-wicket hauls by Ravichandran Ashwin
- Masters Tournament Par-3 contest

### Pictures

- Thích Quảng Đức's self-immolation during the Buddhist crisis
- Krestovsky Stadium
- Hybrid-propellant rocket fuel
- Atomic chess capture
- Hook Windmill
- Capitole de Toulouse
- Rough chameleon
- Backside of a automatic watch
- *The De Goyer Family and the Painter*
- Creaking Pagoda
- Jesse B. Jackson
- Dome of Basilica di Santa Maria Maggiore
- *The Child's Bath*
- Chapel Royal, Dublin
- Shag Rocks

# Featured content procedures

- Recent changes impacting this page
- Recent updates to the featured status pages
- Wikipedia:Today's featured article/requests
- Category:Wikipedia featured content

## Content listings

**Types**

Overviews · **Featured content** · Outlines · Lists · Portals · Glossaries · Categories · Indices ·

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**Places, people and times**

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Categories: Wikipedia featured content




# Portal:Current events



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Worldwide current events · Sports events ·



## Topics in the news

- **An attack on a nightclub** *(pictured)* in Istanbul, Turkey, during New Year's celebrations, kills at least 39 people and injures more than 70 others.
- American actress, screenwriter, and author **Carrie Fisher** dies at the age of 60, and her mother, actress and singer **Debbie Reynolds**, dies one day later at the age of 84.
- English singer, songwriter, and record producer **George Michael** dies at the age of 53.
- A Tupolev Tu-154 **crashes** near Sochi, Russia, killing all 92 people on board, including 64 members of the Alexandrov Ensemble.
- The United Nations Security Council adopts **a resolution** condemning Israeli settlements in the West Bank and East Jerusalem.


Reina nightclub

**Ongoing**: Battle of Mosul ·
**Recent deaths**: Granny · Tony Atkinson · William Christopher · LaVell Edwards ·

### January 4, 2017 (Wednesday) edit history watch

#### Disasters and accidents

- A commuter train from the Long Island Rail Road derails during the morning rush hour in Brooklyn, New York injuring 103 people. (CBS)

#### Politics and elections

- Obamacare repeal
  - Vice President Elect Mike Pence and President Barack Obama head to Capitol Hill to discuss the upcoming talks about potential Obamacare overhauls and repeals with Congressional officials. (Yahoo)
  - An analyst from the Committee for a Responsible Federal Budget says that fully repealing Obamacare would cost $350 billion (USD) over the next decade. Republicans remain focused on repealing the coverage provisions. (CNN)

### January 3, 2017 (Tuesday) edit history watch

#### Business

- Ford announces it has cancelled plans to build a $1.6 billion plant

**Time**: 22:22 UTC | **Day**: 4
January | Purge

| << | January 2017 | | | | | >> |
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More January 2017 events...

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in Mexico, long criticized by U.S. President-elect Donald Trump, and will invest $700 million in its Michigan plant in Flat Rock, potentially creating 700 new jobs from the investment and expansion of the plant. (CNN) (Fox News)
- The U.S. Commerce Department announces that construction spending increased 0.9 percent to $1.18 trillion in November 2016, the highest level since April 2006. (CNBC)

### Law and crime

- Former Hong Kong Chief Executive Donald Tsang, who is on trial for corruption, pleads not guilty to three charges of bribery and misconduct relating to a penthouse he leased in Shenzhen. (AFP, Reuters via *The Straits Times*), (BBC News), (*South China Morning Post*)
- 2017 Kidapawan jail siege
  - More than 100 prisoners have escaped in the Philippines after armed suspected Muslim rebels storm a prison in Kidapawan. A prison guard was shot dead. (ABC Australia) (Aljazeera)

### Politics and elections

- Presidential transition of Donald Trump
  - U.S. President-elect Donald Trump says that Robert Lighthizer will be the country's chief trade negotiator. (Reuters)
- 115th United States Congress
  - The Republican-led U.S. House of Representatives cancels plans approved on Monday, following widespread criticism, including a tweet by President-elect Trump, that would have weakened the House's independent ethics watchdog, the Office of Congressional Ethics. (CNN)
  - The House GOP caucus overwhelmingly re-elects Paul Ryan to another term as House Speaker. (AP via KYTV) (Politico)
- The Grand National Assembly of Turkey votes to extend a state of emergency imposed after last year's attempted coup for another three months. (AP)

### Sports

- English rugby league club Bradford Bulls is liquidated after years of financial problems. (BBC)

## January 2, 2017 (Monday) edit history watch

### Armed conflicts and attacks

- 2017 Istanbul nightclub attack
  - The Islamic State in Iraq and the Levant claims responsibility for the attack in what it claims is a response to Turkey's actions in neighbouring Syria. (*Washington Post*)
- January 2017 Baghdad bombings
  - A series of attacks kill at least 70 people and injure more than 100 others in mostly Shiite neighborhoods of Baghdad, Iraq. (*Huffington Post*)

### Disasters and accidents

- A wildfire destroys at least 100 homes in Valparaíso, Chile, causing the evacuation of about 400 people. The Chilean Ministry of the Interior and Public Security reports that at least 19 people suffered from minor injuries. (AAP via SBS), (Reuters)

## Ongoing events

### Business

- Banca Monte dei Paschi di Siena bankruptcy

### Disasters

- Flint water crisis
- UK and Ireland windstorm season

### Law

- Philippine Drug War
- Timor Gap PCA hearings

### Political

- Brexit aftermath
- European migrant crisis (timeline)
- Polish protests
- Presidential transition of Donald Trump
- South China Sea disputes

**More details on ongoing conflicts below**

### Sport

- 2016 NFL season
- 2016–17 Bundesliga
- 2016–17 La Liga
- 2016–17 NBA season
- 2016–17 NHL season
- 2016–17 Premier League
- 2016–17 Serie A

edit sidebar

## Recent deaths

### January 2017

- 4: Milt Schmidt
- 2: John Berger
- 1: Tony Atkinson
- 1: Derek Parfit

### December 2016

- 31: William Christopher
- 30: Allan Williams

- A powerful storm system hits the southern United States, resulting in four deaths in Alabama and severe damage across several states. (AP)
- A traffic collision between a minivan and a pickup truck in the Ban Bueng District of Chonburi Province, Thailand kills at least 25 people and leaves two others injured. The cause of the accident is still under investigation. (Al Jazeera), (CNN)
- Four people are killed in the crash of a Cessna 210 on Mogollon Rim near Payson, Arizona. The plane had been traveling from Scottsdale, Arizona to Telluride, Colorado. (ABC News) (Arizona Republic)

### Law and crime

- 2017 Manaus prison riot
  - At least 56 people are killed in a prison riot in Manaus, Brazil. (Reuters)

## January 1, 2017 (Sunday) edit history watch

### Armed conflicts and attacks

- 2017 Istanbul nightclub attack
  - At least 39 people are killed and nearly 70 wounded after gunmen open fire in a nightclub in Istanbul, on the European coast of the Bosphorus. Local reports claim that one or more gunmen entered the venue disguised in Santa Claus costumes (a claim later denied by Binali Yıldırım the Turkish PM). (BBC), (AP via ABC News Australia), (Fox News)
- At least 7 people were killed and more than 17 injured in a suicide car bomb explosion and gunmen attack in Iraqi al-Qadisiya town situated in west of Najaf. Yesterday 29 people were killed in a bomb explosion at a busy market in Iraq's capital Baghdad. ISIS claims responsibility. (Reuters), (Tasnim News Agency)
- Burundi's environment minister Emmanuel Niyonkuru is shot dead in the nation's capital, Bujumbura. (FRANCE 24)

### Disasters and accidents

Edit links

- At least 23 people are dead and 17 injured as a ferry catches fire en route to Indonesia's Thousand Islands. (*Melbourne Age*)

### International relations

- North Korea and weapons of mass destruction
  - Kim Jong Un, the leader of North Korea, claims that the country is close to developing an intercontinental ballistic missile. (Reuters)
- Syrian Civil War
  - The United Nations Security Council has unanimously voted in favor of the Russia and Turkey backed ceasefire currently in effect in Syria. (Al-Jazeera)
- United Nations Secretary-General selection, 2016
  - Portugal's António Guterres begins his term as United Nations Secretary-General, replacing South Korea's Ban Ki-moon. (India Today), (Al Jazeera), (Associated Press)
- United Nations Security Council election, 2016
  - Bolivia, Ethiopia, Italy, Kazakhstan, and Sweden begin their



30: Tyrus Wong
- 29: LaVell Edwards
- 29: F. Ross Johnson
- 28: Gregorio Conrado Álvarez
- 28: Anthony Cronin
- 28: Michel Déon
- 28: Debbie Reynolds
- 27: Carrie Fisher
- 27: Ratnasiri Wickremanayake
- 26: George S. Irving
- 26: Seth J. McKee
- 26: Barbara Tarbuck
- 25: George Michael
- 25: Vera Rubin
- 24: Richard Adams
- 24: Rick Parfitt
- 24: Liz Smith
- 22: Franca Sozzani
- 20: Michèle Morgan
- 19: Lionel Blue
- 19: Dick Latessa
- 18: Zsa Zsa Gabor
- 18: China Machado
- 17: Lawrence Colburn
- 17: Henry Heimlich
- 15: Craig Sager
- 13: Thomas Schelling
- 13: Alan Thicke
- 12: E. R. Braithwaite
- 12: Anne Deveson
- 12: Shirley Hazzard
- 12: Javier Echevarría Rodríguez
- 12: Walter Swinburn
- 10: Ken Hechler
- 10: Bill Dineen
- 10: A. A. Gill
- 8: John Glenn
- 8: Joseph Mascolo
- 8: Peter van Straaten
- 7: Warren Allmand
- 7: Cho Ramaswamy
- 7: Paul Elvstrøm
- 7: Junaid Jamshed
- 7: Greg Lake

terms on the United Nations Security Council, replacing Angola, Malaysia, New Zealand, Spain, and Venezuela. (Inter Press Service)
- Foreign relations of the Gambia, Gambian presidential election, 2016
  - Gambian President Yahya Jammeh accuses the West African regional bloc, ECOWAS, of "declaring war" after it said it was putting forces on alert in case he refused to step down at the end of his mandate on January 19. (Reuters)

### Law and crime

- A gunman shoots dead at least 11 people, including his former wife, and then himself in a murder–suicide at a New Year's Eve party in the southeast Brazilian city of Campinas. Several others reportedly remain in critical condition. (Reuters)
- Spanish and Moroccan authorities clash with migrants on the Moroccan-Spanish border along Ceuta, as they attempt to climb and rush the border fence. (Express UK)
- Anthony K. Boisvert is arrested after a foot chase in Lebanon New Hampshire. He was charged in the setting a fire which destroyed an abandoned building on January 16, 2016, and two other fires, one which destroyed the historic First Baptist Church on December 28, 2016 and stabbing two at a condominium complex December 29. (NH Union Leader)
- 3 men are sought after they are captured on video during a $6 million New Year's Eve robbery of offices of high-end jewelry designer Gregg Ruth in Midtown, Manhattan in New York City.(ABC NYC)

### Politics and elections

- The Church of Norway officially ceases to be the state church of Norway after almost 500 years. (Christian Daily)
- Quirino Ordaz Coppel is sworn in as Governor of the Mexican state of Sinaloa. (Periódico Zócalo)

## December 31, 2016 (Saturday)

edit history watch

### Armed conflicts and attacks

- Iraqi Civil War (2014–present)
  - December 2016 Baghdad bombings
    - A pair of bomb blasts targeting a market in central Baghdad kills at least 27 people and injures over 50. (AP), (*The Telegraph*)

### Arts and culture

- China, with their largest television network China Central Television, announces a new launch of a global media platform extending globally and renaming the network China Global Television Network. (News Asia)

### Disasters and accidents

- In Helsinki, Finland, an unidentified driver was detained after driving at high speed, and veering for unknown reasons into a crowd, injuring 7. Authorities quickly conclude no evidence points to a deliberate attack just weeks after a hijacked truck plowed into a Christmas market in Berlin. (RT)

- 6: Rashaan Salaam
- 6: Peter Vaughan
- 5: Jayalalithaa

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## Ongoing conflicts

### Africa

- Algeria and Tunisia
  - Maghreb insurgency
  - ISIL insurgency in Tunisia
- Cameroon, Chad, Niger, and Nigeria
  - Boko Haram insurgency
- Central African Republic
  - Civil war
- Democratic Republic of the Congo
  - Kivu conflict
  - ADF insurgency
  - Ituri conflict
  - Lord's Resistance Army insurgency
- Libya
  - Civil war
- Mali
  - Northern Mali conflict
- Somalia
  - Civil war
- South Sudan
  - Ethnic violence (South Sudanese Civil War)
- Sudan
  - War in Darfur
  - South Kordofan conflict
  - Sudanese nomadic conflicts

### Americas

- Mexico
  - Mexican War on Drugs
- Peru
  - Internal conflict in Peru

### Science and technology

- A leap second was added on December 31 to bring UTC more inline with mean solar time. (Physics Org) (BBC)

**December 30, 2016 (Friday)** edit history watch

### Armed conflicts and attacks

- The funeral of Łukasz Urban, the driver killed in the course of last week's attack on a Christmas market in Berlin, takes place in his village of Banie near the German border. President of Poland Andrzej Duda and a German diplomat attend. (BBC) (Deutsche Welle)

### Disasters and accidents

- Six people die in a fire in a bakery in the Indian city of Pune. (Firstpost)
- At least seven people are killed and 30 trapped after a pile of waste collapses in a Coal India mine in Jharkhand. (Reuters) (CNN)
- A Cessna 525 carrying six passengers goes missing shortly after takeoff from Cleveland Burke Lakefront Airport in the United States. (*USA Today*)

### International relations

- Russia–United States relations
  - After 35 Russian diplomats are expelled from the United States, Russia's foreign minister Sergey Lavrov recommends expelling 35 American diplomats. Russian President Vladimir Putin rejects Lavrov's recommendation and expresses a desire to restore relations between the two countries. (*The New York Times*) (*Newshub*)
  - The U.S. Burlington Electric Department says that a code associated with a broad Russian hacking campaign dubbed "Grizzly Steppe" by the U.S. Government has been detected on a laptop associated with a Vermont electric utility but not connected to the grid. (The Boston Globe)
- Mali returns two people France deported on the same planes they arrived on. (BBC)

### Law and crime

- A body found in a burnt-out vehicle north of the Brazilian city of Rio de Janeiro is confirmed to be that of missing Greek Ambassador Kyriakos Amiridis. A military police officer who had an affair with the ambassador's wife confesses to the murder. The wife and a second man are also detained. (BBC)
- Sahaj International opens in Kochi in the South Indian state of Kerala. The country's first school for transgender pupils, it caters for adults who left school early. (BBC)

### Politics and elections

- Romanian President Klaus Iohannis designates social-democrat Sorin Grindeanu as the country's new prime minister, after the victory of the centre-left PSD earlier this month. (AFP by *The Indian Express*)
- China's State Council announces details of its intention to ban all ivory trade and processing activities by the end of 2017. (BBC)

### Asia

- Afghanistan
  - Afghanistan War
- China
  - Xinjiang conflict
- India
  - Naxalite–Maoist insurgency
  - Insurgency in Northeast India
- India and Pakistan
  - Kashmir conflict
- Indonesia, Malaysia and the Philippines
  - Moro conflict
    - Cross border attacks in Sabah
- Indonesia and Papua New Guinea
  - Papua conflict
- Myanmar
  - Internal conflict in Myanmar
- Pakistan
  - War in North-West Pakistan
  - Balochistan conflict
- Philippines
  - CPP-NPA-NDF rebellion
- Thailand
  - South Thailand insurgency

### Europe

- Armenia and Azerbaijan
  - Nagorno-Karabakh conflict
- Georgia
  - Abkhaz–Georgian conflict
  - Georgian–Ossetian conflict
- Russia
  - Chechen–Russian conflict
  - North Caucasus insurgency
- Ukraine
  - War in Donbass
    - Russian military intervention in Ukraine

### Science and technology

- A volcanic eruption continues on Bogoslof Island near Unalaska, in the Aleutian Islands of Alaska. The eruption has impacted air transportation routes. (Alaska Public Radio Network) (Tech Times) (CDA News)

### Sports

- Mo Farah and world tennis number one Andy Murray are among those knighted by Elizabeth II in her 2017 New Year Honours list. (*The Guardian*)
- In mixed martial arts, Amanda Nunes defeats Ronda Rousey to retain the Women's Bantamweight title at UFC 207. (The New York Times)

## December 29, 2016 (Thursday) edit history watch

### Armed conflicts and attacks

- Syrian Civil War
  - Russian president Vladimir Putin says a ceasefire has been brokered between the Syrian government and rebel forces. The ceasefire is said to be guaranteed by Russia and Turkey and would exclude UN-denominated terror organizations such as ISIL and al-Nusra. The FSA says it would abide by the truce, while Ahrar al-Sham expresses "reservations". (ITV) (Reuters)

### Arts and culture

- Czartoryski Museum
  - The Polish government buys the internationally-known Czartoryski collection of art. Based in the city of Kraków and consisting of around 86,000 pieces, this features works by Leonardo da Vinci, Rembrandt and Pierre-Auguste Renoir. (BBC)
- The academic Phil Scraton refuses an OBE granted to him by Elizabeth II in her 2017 New Year Honours list for his work on the Hillsborough disaster. Professor Scraton wrote *Hillsborough: The Truth*, first published in 1990 and seen as the definitive account of the disaster. (BBC) (*The Guardian*)

### Business and economy

- The Bank of Italy says in a statement that the country's treasury will have to put up around 6.6 billion euros to rescue Monte dei Paschi given the European Central Bank's estimate of Monte dei Paschi's capital shortfall. (Reuters)

### Disasters and accidents

- At least 50 people drown and thousands are left homeless due to flooding in the Democratic Republic of the Congo. (France 24)

### International relations

- The United States expels 35 Russian diplomats over the alleged Russian interference during the U.S.'s 2016 Presidential Election. (BBC)
- The Egyptian government approves a deal granting two Red Sea islands to Saudi Arabia. (Reuters)

### Law and crime

### Middle East

- Egypt
  - Sinai insurgency
- Egypt, Iraq, Israel, Jordan, Lebanon, Palestine, and Syria
  - Arab–Israeli conflict
- Iran
  - Iran–PJAK conflict
- Iraq
  - American-led intervention in Iraq
  - Iranian intervention in Iraq
- Iraq and Syria (map)
  - Military intervention against ISIL
- Israel and Lebanon
  - Israeli–Lebanese conflict
- Israel and Palestine
  - Gaza–Israel conflict
  - Israeli–Palestinian conflict
- Syria
  - American-led intervention in Syria
  - Russian military intervention in the Syrian Civil War
  - Turkish military intervention in Syria
  - Syrian Civil War spillover in Lebanon
- Turkey
  - Turkey–PKK conflict
  - Turkey–ISIL conflict
- Yemen
  - Yemeni Civil War
  - Saudi Arabian-led intervention in Yemen
  - Al-Qaeda insurgency

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## Elections and Referendums

- The Ambassador of Greece to Brazil, Kyriakos Amiridis, is reported missing while on vacation in Rio de Janeiro. A homicide team is investigating his disappearance. (BNO News) (O Globo)
- Turkish journalist Ahmet Şık is arrested in Istanbul, allegedly over a social media posting. (*Washington Post*)
- Naveed Baloch, the man from Pakistan who was wrongly arrested in the aftermath of the recent attack on a Christmas market in Berlin, gives an interview outlining the conditions in which he was held and reveals he is now in hiding amid fears for his life. (*The Guardian*)

### Science and technology

- U.S. President Barack Obama declares the Bears Ears in Utah and Gold Butte area of Nevada as National Monuments. Both are known for the presence of Native American populations and archaeological sites. (BBC News)

### Sports

- Former boxing world champion Ricky Hatton speaks on British radio about depression and gives an account of past suicide attempts. (BBC Sport) (*The Daily Telegraph*)

**More December 2016 events...**

### Recent

- December
  - 4: **Austria**, President (*2nd round*)
  - 4: **Italy**, Constitutional referendum
  - 4: **Uzbekistan**, President
  - 7: **Ghana**, President, Parliament
  - 11: **Kyrgyzstan**, Referendum
  - 11: **Macedonia**, Assembly of the Republic
  - 11: **Romania**, Chamber of Deputies, Senate
  - 15: *Turks and Caicos*, House of Assembly
  - 18: **Côte d'Ivoire**, National Assembly

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## Trials

### Recently concluded

- Australia: Roger Rogerson and Glen McNamara
- Cambodia: Sam Rainsy
- China: Wan Qingliang, Ling Jihua, Zhoi Bin, Guo Boxiong
- Iran: Babak Zanjani
- Netherlands: Geert Wilders
- Philippines: Gloria Macapagal Arroyo, Nur Misuari, Joel Villanueva
- Romania: Liviu Dragnea, Gheorghe Ștefan, Gabriel Sandu, Dorin Cocoș, Dumitru Nicolae
- Spain: Lionel Messi
- United Kingdom: Chris Denning, Adam Johnson, Ched Evans
- United States: Bob McDonnell, Paul Anthony Ciancia
- International
  - ICTY: Radovan Karadžić

### Ongoing

- China: Bai Enpei, Pan Yiyang, Yang Weize
- Germany: Beate Zschäpe
- Indonesia: Basuki Tjahaja Purnama, Mary Jane Veloso
- Pakistan: Waseem Azeem, Mufti Abdul Qawi
- Philippines: Andal Ampatuan, Jr., Leila de Lima, Rodrigo Duterte, Jovito Palparan
- Romania: Darius Vâlcov, Dan Șova, Elena Udrea, Radu Mazăre, Gheorghe Nichita, Marian Vanghelie, Cătălin Voicu
- Russia: Alexei Navalny
- South Korea: Park Geun-hye and Choi Soon-sil
- Spain: Gürtel case, Spanish Royal House, Bárcenas affair
- United States: Etan Patz
- United Kingdom: Rolf Harris
- International
  - ICC: Laurent Gbagbo
  - ICTY: Ratko Mladić

### Upcoming

- China: Wu Changshun
- Egypt: Mohamed Morsi
- Estonia: Edgar Savisaar
- Libya: Saif al-Islam Gaddafi
- United States: Khalid Sheikh Mohammed, Graham Spanier, Tim Curley, Gary Schultz, Rick Perry, Bill Cosby

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## Events by month

**2017:** January ·
**2016:** January · February · March · April · May · June · July · August · September · October · November · December ·
**2015:** January · February · March · April · May · June · July · August · September · October · November · December ·
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**2013:** January · February · March · April · May · June · July · August · September · October · November ·

December ·
**2012:** January · February · March · April · May · June · July · August · September · October · November · December ·
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**2010:** January · February · March · April · May · June · July · August · September · October · November · December ·
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# Łuszcze



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**Łuszcze** is a village in the administrative district of Gmina Czyże, within Hajnówka County, Podlaskie Voivodeship, in north-eastern Poland.[1] It lies approximately 3 kilometres (2 mi) north-east of Czyże, 11 km (7 mi) north-west of Hajnówka, and 40 km (25 mi) south-east of the regional capital Białystok.

## Variants

## References [edit]

1. ^ "Central Statistical Office (GUS) – TERYT (National Register of Territorial Land Apportionment Journal)" (in Polish). 2008-06-01.

**Łuszcze** Village


Coordinates: 52°48′N 23°27′E

| | |
|---|---|
| **Country** | Poland |
| **Voivodeship** | Podlaskie |
| **County** | Hajnówka |
| **Gmina** | Czyże |

Coordinates: 52°48′N 23°27′E

**Gmina Czyże**

**Seat** Czyże ·

**Other villages** Bujakowszczyzna · Hrabniak · Hukowicze · Kamień · Klejniki · Kojły · Kuraszewo · Lady · Leniewo · Leszczyny · **Łuszcze** · Maksymowszczyzna · Morze · Osówka · Podrzeczany · Podwieżanka · Rakowicze · Sapowo · Szostakowo · Wieżanka · Wólka · Zbucz ·

*This Hajnówka County location article is a stub. You can help Wikipedia by expanding it.*

Edit links

Categories: Villages in Hajnówka County | Hajnówka County geography stubs


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Contributing is easy: see **how to edit a page**. For a quick summary on participating, see **contributing to Wikipedia**. For a listing of introductions and tutorials by topic, see **getting started**. Or play **the Wikipedia Adventure** to learn to edit in an hour. The **Cheatsheet** can remind you of basic wiki markup.

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If you feel someone is bullying you or if you don't understand why your edits are being reverted, you can ask for help at the **Help desk** or at the **Teahouse**. Volunteers will respond as soon as possible.

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If you don't feel ready to fix the article yourself, please post a message on the article's **talk page**. This will bring the matter to the attention of others who work on that article. There is a "Talk" link at the beginning of *every* article page.

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For contributing images, audio or video files, see the **Introduction to uploading images**. Then the **Upload wizard** will guide you through that process.

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If **searching Wikipedia** has not answered your question (*for example, questions like "Which country*

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*has the world's largest fishing fleet?"*), try the **Reference Desk**. Volunteers there will attempt to answer your questions on any topic, or point you towards the information you need.

# Stuck?

For your convenience, answers have been recorded for the most **frequently asked questions**.

You can find also **where to ask questions or make comments**.

You can ask questions about using Wikipedia at the **Help desk** or at the **Teahouse**. Volunteers will respond as soon as possible.

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# Directories

- **Directory**: main list of directories and indexes.

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**Protocols and conventions**

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- **Guideline directory**: official guidelines for "English Wikipedia"
- **Manual of Style directory**: pages related to the style manual of Wikipedia articles.

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- **Departments**: for the different divisions of Wikipedia.
- **Editor's index**: for everything an editor needs to know to work on Wikipedia.
- **Essay directory**: for Wikipedia namespace essays.
- **Dashboard**: for current discussions taking place throughout Wikipedia.

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Tsetsêhestâhese
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- **WikiProjects**: for people who want to work together as a team to improve Wikipedia.

**MediaWiki software**

- **Wiki markup**: for the syntax used by Wikipedia to format a page.
- **HTML**: for HTML5 elements, or tags and their attribute.
- **Templates**: for templates used within Wikipedia.

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- **Help Menu**: for searching by subject matter.
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- **Joining Wikipedia**: how to get involved.
- **Editing Wikipedia**: has general help for editors.
- **Links and references**: has help for creating links, or dealing with references
- **Images and media**: how to use images, videos and sound files
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- **Policies and guidelines**: for community standards.
- **Asking questions**: volunteers will attempt to answer.
- **The Wikipedia community**: how to submit or debate a proposal.
- **Resources and lists**: has resources for editors.
- **Account settings**: has tips and tools for registered users.
- **Technical information**: has tools for advanced users, and troubleshooting.
- **Site map**: is the above twelve pages on a single page.

## **Tip** of the day

### How to make your watchlist easier to read

If you use Firefox, there is a JavaScript you can install called **Watchlist sorter**.

This script sorts your watchlist by namespace, and adds spaces within each entry. This makes the watchlist much easier to read.

To install the script, copy/paste it to your your common.js page. This will install the script across all your skins.

Note: After saving, you have to bypass Firefox's cache

to see the changes. To do this, hold down the Shift key while clicking Reload (or press Ctrl + Shift + R). Or, you may have to **purge** the Wikipedia server cache.

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**Your watchlist settings**
*Become a Wikipedia tipster* – Tips library, by subject
To add this auto-updating daily tip to your user page, use **{{totd}}**

## Additional **searches**

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The blue bars that follow are navigation boxes linking many help pages and useful policies and guidelines. Click "show" on the right to expand them.

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| **Core content policies** | Neutral point of view · No original research · Verifiability · |
| **Other content policies** | Article titles · Autobiography · Biographies of living persons · Image use · |
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From Wikipedia, the free encyclopedia

*For an overview of everything about Wikipedia on Wikipedia, see Outline of Wikipedia*
*"Wikipedia:Wikipedia" redirects here. For other uses, see Wikipedia:Wikipedia (disambiguation).*

**About Wikipedia** (Administration · · Contributing (Welcome · · Help menu
(Index · · Directories
FAQ · Asking questions (Help desk · Reference desk · · Wikicode (

**This is a general introduction for visitors to Wikipedia**. The project also has an encyclopedia article about itself, Wikipedia, and an introduction for aspiring contributors. For information on how to donate to the organization that runs Wikipedia, see Ways to Give.

**Shortcuts:**
**WP:ABOUT**
**WP:WIKIPEDIA**

## English Wikipedia right now

Wikipedia is running MediaWiki
version 1.29.0-wmf.6 (1b514da).
It has 5,323,769 content articles,
and 41,119,076 pages in total.
There are 848,479 uploaded files.
There have been 867,562,226 edits.
There are 29,893,713 registered users,
including 1,274 administrators.
Of these are 119,453 active users
(have performed an action in the last 30 days).

Information as of 22:02, 4 January 2017 (UTC).

Update

V · T · E ·

Wikipedia (/ˌwɪkɪˈpiːdi.ə/ or /ˌwɪkiˈpiːdi.ə/ *WIK-i-PEE-dee-ə*) is a multilingual, web-based, free-content encyclopedia project supported by the Wikimedia Foundation and based on a model of openly editable content. The name "Wikipedia" is a portmanteau of the words *wiki* (a technology for creating collaborative websites, from the Hawaiian word *wiki*, meaning "quick") and *encyclopedia*. Wikipedia's articles provide links designed to guide the user to related pages with additional information.

Wikipedia is written collaboratively by largely anonymous volunteers who write without pay. Anyone with Internet access can write and make changes to Wikipedia articles, except in limited cases where editing is restricted to prevent disruption or vandalism. Users can contribute anonymously, under a pseudonym, or, if they choose to, with their real identity.

The fundamental principles by which Wikipedia operates are the five pillars. The Wikipedia community has developed many policies and guidelines to improve the encyclopedia; however, it is not a formal requirement to be familiar with them before contributing.

Since its creation in 2001, Wikipedia has grown rapidly into one of the largest reference websites, attracting 374 million unique visitors monthly as of September 2015.[1] There are about 70,000 active contributors working on more than 41,000,000 articles in 294 languages. As of today, there are 5,323,769 articles in English. Every day, hundreds of thousands of visitors from around the world collectively make tens of thousands of edits and create thousands of new articles to augment the knowledge held by the Wikipedia encyclopedia. (See the statistics page for more information.)

People of all ages, cultures and backgrounds can add or edit article prose, references, images and other media here. What is contributed is more important than the expertise or qualifications of the contributor.

What will remain depends upon whether the content is free of copyright restrictions and contentious material about living people, and whether it fits within Wikipedia's policies, including being verifiable against a published reliable source, thereby excluding editors' opinions and beliefs and unreviewed research. Contributions cannot damage Wikipedia because the software allows easy reversal of mistakes and many experienced editors are watching to help ensure that edits are cumulative improvements. Begin by simply clicking the *Edit* link at the top of any editable page!

Wikipedia is a live collaboration differing from paper-based reference sources in important ways. Unlike printed encyclopedias, Wikipedia is continually created and updated, with articles on historic events appearing within minutes, rather than months or years. Because everybody can help improve it, Wikipedia has become more comprehensive than any other encyclopedia. In addition to quantity, its contributors work on improving quality as well. Wikipedia is a work-in-progress, with articles in various stages of completion. As articles develop, they tend to become more comprehensive and balanced. Quality also improves over time as misinformation and other errors are removed or repaired. However, because anyone can click "edit" at any time and add stuff in, any article may contain undetected misinformation, errors, or vandalism. Awareness of this helps the reader to obtain valid information, avoid recently added misinformation (see *Wikipedia:Researching with Wikipedia*), and fix the article.

See also: Wikipedia:FAQ and Wikipedia:Citing Wikipedia

**Contents**





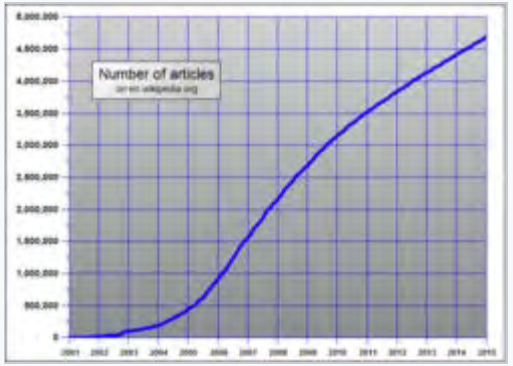
# About Wikipedia

*For information on the administrative structure of Wikipedia, see Wikipedia:Administration.*

## Wikipedia history

*For more details on this topic, see History of Wikipedia.*

Wikipedia was founded as an offshoot of Nupedia, a now-abandoned project to produce a free encyclopedia, begun by the online media company Bomis. Nupedia had an elaborate system of peer review and required highly qualified contributors, but the writing of articles was slow. During 2000, Jimmy Wales (founder of Nupedia and co-founder of Bomis), and Larry Sanger, whom Wales had employed to work on the encyclopedia project, discussed ways of supplementing Nupedia with a more open, complementary project. Multiple sources suggested that a wiki might allow members of the public to contribute material, and Nupedia's first wiki went online on January 10, 2001.




The English edition of Wikipedia has grown to 5,323,769 articles, equivalent to over 2,000 print volumes of the *Encyclopædia Britannica*. Including all language editions, Wikipedia has over 38 million articles, equivalent to over 15,000 print volumes.

There was considerable resistance on the part of Nupedia's editors and reviewers to the idea of associating Nupedia with a website in the wiki format, so the new project was given the name "Wikipedia" and launched on its own domain, wikipedia.com, on January 15 (now called "Wikipedia Day" by some users). The bandwidth and server (in San Diego) were donated by Wales. Other current and past Bomis employees who have worked on the project include Tim Shell, one of the cofounders of Bomis and its current CEO, and programmer Jason Richey.

In May 2001, a large number of non-English Wikipedias were launched—in Catalan, Chinese, Dutch, Esperanto, French, German, Hebrew, Italian, Japanese, Portuguese, Russian, Spanish, and Swedish. These were soon joined by Arabic and Hungarian. In September,[2] Polish was added, and further commitment to the multilingual provision of Wikipedia was made. At the end of the year, Afrikaans, Norwegian, and Serbo-Croatian versions were announced.

The domain was eventually changed to the present wikipedia.org when the not-for-profit Wikimedia Foundation was launched, in 2003, as its new parent organization, with the ".org" top-level domain denoting its non-commercial nature. Today, there are Wikipedias in over 250 languages.

## Wikipedia contributors

*Main pages: Wikipedia:Who writes Wikipedia? and Wikipedia:Wikipedians*
*Further information: Wikipedia:Administration § Editors*

Anyone with Web access can edit Wikipedia, and this openness encourages inclusion of a tremendous amount of content. About 70,000 editors—from expert scholars to casual readers—regularly edit Wikipedia, and these experienced editors often help to create a consistent style throughout the encyclopedia, following our Manual of Style.

Play media

Wikipedia contributors

Several mechanisms are in place to help Wikipedia members carry out the important work of crafting a high-quality resource while maintaining civility. Editors are able to watch pages and technically skilled persons can write editing programs to keep track of or rectify bad edits. Where there are disagreements on how to display facts, editors often work together to compile an article that fairly represents current expert opinion on the subject.

Although the Wikimedia Foundation owns the site, it is largely uninvolved in writing and daily operations.

## Trademarks and copyrights

*Main pages: Wikipedia:Copyrights and wmf:Trademark policy*

"Wikipedia" is a registered trademark of the not-for-profit Wikimedia Foundation, which has created a family of free-content projects that are built by user contributions.

Most of Wikipedia's text and many of its images are dual-licensed under the Creative Commons Attribution-Sharealike 3.0 Unported License (CC-BY-SA) and the GNU Free Documentation License (GFDL) (unversioned, with no invariant sections, front-cover texts, or back-cover texts). Some text has been imported only under CC-BY-SA and CC-BY-SA-compatible license and cannot be reused under GFDL; such text is identified either on the page footer, in the page history or on the discussion page of the article that utilizes the text. Every image has a description page that indicates the license under which it is released or, if it is non-free, the rationale under which it is used.

Contributions remain the property of their creators, while the CC-BY-SA and GFDL licenses ensure the content is freely distributable and reproducible. (See content disclaimer for more information.)

## Credits

Text on Wikipedia is a collaborative work, and the efforts of individual contributors to a page are recorded in that page's history, which is publicly viewable. Information on the authorship of images and other media, such as sound files, can be found by clicking on the image itself or the nearby information icon to display the file page, which includes the author and source, where appropriate, along with other information.

# Making the best use of Wikipedia

*Further information: Wikipedia:Reader's index to Wikipedia*
*See also: Reader's guide to Wikipedia and the guide to using Wikipedia in research*

## Exploring Wikipedia

*Main page: Portal:Contents*

Many visitors come to Wikipedia to acquire knowledge, while others come to share knowledge. At this very instant, dozens of articles are being improved, and new articles are also being created. Changes can be viewed at the Recent changes page and a random page at random articles. Over 4,500 articles have been designated by the Wikipedia community as featured articles, exemplifying the best articles in the encyclopedia. Another 22,000 articles are designated as good articles. Some information on Wikipedia is organized into lists; the best of these are designated as featured lists. Wikipedia also has portals, which organize content around topic areas; our best portals are selected as featured portals. Articles can be found using the search box on the top-right side of the screen.

Wikipedia is available in languages other than English. Wikipedia has more than two hundred and eighty languages, including a Simple English version, and related projects include a dictionary, quotations, books, manuals, and scientific reference sources, and a news service (see sister projects). All of these are maintained, updated, and managed by separate communities, and often include information and articles that can be hard to find through other common sources.

**Readers' FAQ and help**

**About Wikipedia** (Administration · · Authority control · Categories · Censorship · Citing · Copyright · Disambiguation · Images and multimedia · ISBN · Microformats · Mobile access · Navigation · Other languages · Page names · Portals · Protected pages · Searching · Student help ·

Readers' glossary
Readers' index
Researching with Wikipedia
*Reader's guide to Wikipedia*

Contributing to Wikipedia

v · t · e ·

## Basic navigation in Wikipedia

*Main page: Help:Navigation*

Wikipedia articles are all linked, or cross-referenced. When highlighted text like this is seen, it means there is a link to some relevant article or Wikipedia page with further in-depth information. Holding the mouse over the link will often show to where the link will lead. There are other links towards the ends of most articles, for other articles of interest, relevant external websites and pages, reference material, and organized categories of knowledge which can be searched and traversed in a loose hierarchy for more information. Some articles may also have links to dictionary definitions, audio-book readings, quotations, the same article in other languages, and further information available on our sister projects. Additional links can be easily made if a relevant link is missing—this is one simple way to contribute.

## Using Wikipedia as a research tool

*Main pages: Wikipedia:Researching with Wikipedia and Wikipedia:Citing Wikipedia*

As wiki documents, articles are never considered complete and may be continually edited and improved. Over time, this generally results in an upward trend of quality and a growing consensus over a neutral representation of information.

Users should be aware that not all articles are of encyclopedic quality from the start: they may contain false or debatable information. Indeed, many articles start their lives as displaying a single viewpoint; and, after a long process of discussion, debate, and argument, they gradually take on a neutral point of view reached through consensus. Others may, for a while, become caught up in a heavily unbalanced viewpoint which can take some time—months or years perhaps—to achieve better balanced coverage of their subject. In part, this is because editors often contribute content in which they have a particular interest and do not attempt to make each article that they edit comprehensive. However, eventually, additional editors expand and contribute to articles and strive to achieve balance and comprehensive coverage. In addition, Wikipedia operates a number of internal resolution processes that can assist when editors disagree on content and approach. Usually, editors eventually reach a consensus on ways to improve the article.

The *ideal* Wikipedia article is well written, balanced, neutral, and encyclopedic, containing comprehensive, notable, verifiable knowledge. An increasing number of articles reach this standard over time, and many already have. Our best articles are called Featured Articles (and display a small star in the upper right corner of the article), and our second best tier of articles are designated Good Articles. However, this is a process and can take months or years to be achieved through the concerted effort of editors. Some articles contain statements which have not yet been fully cited. Others will later be augmented with new sections. Some information will be considered by later contributors to be insufficiently founded and, therefore, may be removed.

While the overall trend is toward improvement, it is important to use Wikipedia carefully if it is intended to be used as a research source, since individual articles will, by their nature, vary in quality and maturity. Guidelines and information pages are available to help users and researchers do this effectively, as is an article that summarizes third-party studies and assessments of the reliability of Wikipedia.

## Wikipedia vs paper encyclopedias

*Main page: Wikipedia is not paper (on Wikimedia Meta-Wiki).*

Wikipedia has advantages over traditional paper encyclopedias. First, is that it is not limited in space: it can keep growing as fast as people add to it.

Second, there are no qualifications required to be able to author its articles. Therefore, it has a very large pool of contributors: the whole world. This, and the first advantage mentioned above, have enabled Wikipedia to become the most comprehensive encyclopedia on Earth.

Third, a paper encyclopedia remains static (stays the same) and falls out of date until the next edition. But Wikipedia is dynamic: you don't have to wait for the next edition to come out (there are no editions), as Wikipedia is published on-line as it is written on-line. Articles are made available as is, regardless of what stage of development they are in. *You* can update Wikipedia at any instant, and people do so continually around the clock, thereby helping each other to keep abreast of the most recent events everywhere and of the latest facts in every subject.

Fourth, Wikipedia has a very low "publishing" cost for adding or expanding entries, as it is on-line, with no

need to buy paper or ink for distribution. This has allowed it to be made available for free, making it more accessible to everyone. This has enabled Wikipedia to be independently developed and published in many different languages at the same time, by people literate in each language. Of the 280+ different language Wikipedias, 132 of them have 10,000 or more articles.

Fifth, Wikipedia has a low environmental impact in some respects, since it never needs to be printed, although computers have their own environmental cost.

Sixth, Wikipedia is extra-linear (more than linear). Instead of in-line explanations, Wikipedia incorporates hypertext in the form of wikilinks. Throughout its content is a robust network of links, providing another dimension of knowledge accessibility. The encyclopedia also has correlates to tables of contents and indexes, with each entry in them hyperlinked to an article on the topic specified.

Seventh, each Wikipedia article provides an introduction summarizing the more extensive detail of its contents.

Eighth, being open to anyone to edit, articles on Wikipedia are subject to additions that are erroneous or written poorly. It is a community effort, with most people who are involved helping to improve the work, fixing problems they encounter along the way. See more about Wikipedia's strengths and weaknesses, below...

## Strengths, weaknesses, and article quality in Wikipedia

*Main pages: Wikipedia:Why Wikipedia is so great and Wikipedia:Why Wikipedia is not so great*
*See also: Reliability of Wikipedia and Wikipedia:Researching with Wikipedia*

Wikipedia's greatest strengths, weaknesses, and differences all arise because it is open to anyone, it has a large contributor base, and its articles are written by consensus, according to editorial guidelines and policies.

- Wikipedia is **open to a large contributor base**, drawing a large number of editors from diverse backgrounds. This allows Wikipedia to significantly reduce regional and cultural bias found in many other publications, and makes it very difficult for any group to censor and impose bias. A large, diverse editor base also provides access and breadth on subject matter that is otherwise inaccessible or little documented. A large number of editors contributing at any moment also means that Wikipedia can produce encyclopedic articles and resources covering newsworthy events within hours or days of their occurrence. It also means that like any publication, Wikipedia may reflect the cultural, age, socio-economic, and other biases of its contributors. There is no systematic process to make sure that "obviously important" topics are written about, so Wikipedia may contain unexpected oversights and omissions. While *most* articles may be altered by anyone, in practice editing will be performed by a certain demographic (younger rather than older, male rather than female, rich enough to afford a computer rather than poor, et cetera) and may, therefore, show some bias. Some topics may not be covered well, while others may be covered in great depth.
- Allowing **anyone to edit** Wikipedia means that it is more easily vandalized or susceptible to unchecked information, which requires removal. See Wikipedia:Administrator intervention against vandalism. While blatant vandalism is usually easily spotted and rapidly corrected, Wikipedia is more subject to subtle viewpoint promotion than a typical reference work. However, bias that would be unchallenged in a traditional reference work is likely to be ultimately challenged or considered on Wikipedia. While Wikipedia articles generally attain a good standard after editing, it is important to note that fledgling articles and those monitored less well may be susceptible to vandalism and insertion of false information. Wikipedia's radical openness also means that any given article may be, at any given moment, in a bad state, such as in the middle of a large edit, or a controversial rewrite. Many contributors do not yet comply fully with key policies, or may add information without citable sources. Wikipedia's open approach tremendously increases the chances that any particular factual error or misleading statement will be relatively promptly corrected. Numerous editors at any given time are monitoring recent changes and edits to articles on their watchlists.
- Wikipedia is **written by open and transparent consensus**—an approach that has its pros and cons. Censorship or imposing "official" points of view is extremely difficult to achieve and usually fails after a time. Eventually for most articles, all notable views become fairly described and a neutral point of view reached. In reality, the process of reaching consensus may be long and drawn-out, with articles fluid or

changeable for a long time while they find their "neutral approach" that all sides can agree on. Reaching neutrality is occasionally made harder by extreme-viewpoint contributors. Wikipedia operates a full editorial dispute resolution process, one that allows time for discussion and resolution in depth, but one that also permits disagreements to last for months before poor-quality or biased edits are removed. A common conclusion is that Wikipedia is a valuable resource and provides a good reference point on its subjects.

- That said, articles and subject areas sometimes suffer from significant omissions, and while misinformation and vandalism are usually corrected quickly, this does not always happen. (See for example this incident in which a person inserted a fake biography linking a prominent journalist to the Kennedy assassinations and Soviet Russia as a joke on a co-worker which went undetected for four months, saying afterwards he "didn't know Wikipedia was used as a serious reference tool".)
- Wikipedia is **written largely by amateurs**. Those with expert credentials are given no additional weight. Wikipedia is also not subject to any peer review for scientific, medical or engineering articles. One advantage to having amateurs write in Wikipedia is that they have more free time on their hands so that they can make rapid changes in response to current events. The wider the general public interest in a topic, the more likely it is to attract contributions from non-specialists.

The MediaWiki software that runs Wikipedia retains a history of all edits and changes, thus information added to Wikipedia never "vanishes" irreversibly. Discussion pages are an important resource on contentious topics. Therefore, serious researchers can often find a wide range of vigorously or thoughtfully advocated viewpoints not present in the consensus article. As with any source, information should be checked. A 2005 editorial by a BBC technology writer comments that these debates are probably symptomatic of cultural changes that are happening across all sources of information (including search engines and the media), and may lead to "a better sense of how to evaluate information sources".[3]

## Disclaimers

*Main page: Wikipedia:General disclaimer*

Wikipedia disclaimers apply to all pages on Wikipedia. However, the consensus in Wikipedia is to put all disclaimers only as links and at the end of each article. Proposals to have a warning box at the beginning have been rejected. Some do not like the way it looks or that it calls attention to possible errors in Wikipedia.

Wikipedia, in common with many websites, has a disclaimer that, at times, has led to commentators citing these in order to support a view that Wikipedia is unreliable. A selection of similar disclaimers from places which are often regarded as reliable (including sources such as Encyclopædia Britannica, Associated Press, and the Oxford English Dictionary) can be read and compared at Wikipedia:Non-Wikipedia disclaimers.

**Disclaimers**

General
Content
Legal
Medical
Risk

**Related**

Academic use
Non-Wikipedia

v · t · e

# Contributing to Wikipedia

*Main page: Wikipedia:Contributing to Wikipedia*
*See also: Wikipedia:Your first article and Guide to fixing vandalism*

Anyone can contribute to Wikipedia by clicking on the *Edit* tab in an article. Before beginning to contribute, however, read some handy helping tools such as the tutorial and the policies and guidelines, as well as our welcome page. Creating an account offers many benefits. It is important to realize that in contributing to Wikipedia, users are expected to be civil and neutral, respecting all points of view, and only add verifiable and factual information rather than personal views and opinions. "The five pillars of Wikipedia" cover this approach and are recommended reading before editing. (Vandals are reported via the Administrator Notice Board and may be

**Contributing to Wikipedia**

**Protocols**

Editing policy · (Content policies) · Etiquette guide · (Dispute resolution) · Simple rule set · Simple style manual ·

**Introductions**

**About Wikipedia** · (Administration) ·

temporarily blocked from editing Wikipedia.)

Most articles start as stubs, but after many contributions, they can become featured articles. Once the contributor has decided a topic of interest, they may want to request that the article be written (or they could research the issue and write it themselves). Wikipedia has on-going projects, focused on specific topic areas or tasks, which help coordinate editing.

The ease of editing Wikipedia results in many people editing. That makes the updating of the encyclopedia very quick, almost as fast as news websites.

## Editing Wikipedia pages

*Main pages: Help:Editing and Help:Wiki markup*

Wikipedia uses a simple yet powerful page layout to allow editors to concentrate on adding material rather than page design. Page aspects facilitated include:

- sections and subsections—which follow a page's lead section/introduction and (if specific conditions are met) a table of contents,
- references,
- images,
- tables,
- indentations
- lists,
- links,
- ISBNs,
- maths,
- formatting elements and most world alphabets and common symbols, Most of which have simple formats that are deliberately very easy and intuitive.

Normally editing is chosen by clicking the `Edit` tab at the top of a Wikipedia page (or on a section-edit link). This will take you to a new page with a text box containing the editable text of the page you were viewing. In this box, you can type in the text that you want to add, using wiki markup to format the text and add other elements like images and tables. You should then press the `Show preview` button to review your contributions for any errors. When you have finished editing, you should write a short edit summary in the small field below the edit-box describing your changes before you press the `Save page` button. This will help others to understand the intention of your edit. To avoid accidentally leaving edit summaries blank, you can select "Prompt me when entering a blank edit summary" on the `Editing` tab of your personal preferences.

Page editing is accessed through tabs that are found along the top edge of the page. These are:

- *Article.* Shows the main Wikipedia article.
- *Talk.* Shows a user discussion about the article's topic and possible revisions, controversies, etc.
- *Edit.* This tab allows users to edit the article. Depending on the page's susceptibility to vandalism, according to its visibility or the degree of controversy surrounding the topic, this tab may not be shown for all users. (For example, any user who is not an administrator will not be able to edit the Main Page.)

How to contribute · (Tutorial) · Newcomers' primer · Plain & simple · Wikipedia Adventure · VisualEditor ·

**How-to pages**

Creating an account · How to edit · Starting an article · (Article wizard) · Talk pages · (BOLD, revert, discuss) · Referencing · Renaming · Deletion · Media · Lists · Tables · Templates · Copying text · Style tips · Wiki markup ·

**Writing advice**

Article development · Basic copyediting · Layouts · Avoiding mistakes · Writing better · Perfect article · Advanced editing · Writing about women ·

**Community**

Portal · Dashboard · Essays · Maintenance · WikiProjects · Editor's index ·

**Directories**

FAQs · Help index · Tools ·

**Interactive help**

Teahouse · Help desk ·

V · T · E ·


A downloadable "Editing Wikipedia guide" in PDF form written by the staff at the Wikimedia Foundation

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Editing tutorial for Wikipedia using classic wiki markup. (3:07 min)

- *View history.* This tab allows readers to view the editors of the article and the changes that have been made.
- *Star.* ("Watch") If you are logged into your account, clicking on the star icon will cause any changes made to the article to be displayed on the watchlist. (Note: when this icon is clicked, it changes to a filled-in star.)

Wikipedia has robust version and reversion controls. This means that poor-quality edits or vandalism can quickly and easily be reversed or brought up to an appropriate standard by any other editor, so inexperienced editors cannot accidentally do permanent harm if they make a mistake in their editing. As there are many more editors intent on improving articles than not, error-ridden articles are usually corrected promptly.

## Wikipedia content criteria

*Main pages: Wikipedia:Wikipedia in brief and Wikipedia:Core content policies*

Wikipedia content is intended to be factual, notable, verifiable with cited external sources, and neutrally presented.

The appropriate policies and guidelines for these are found at:

1. Wikipedia:What Wikipedia is not, which summarizes what belongs in Wikipedia and what does not;
2. Wikipedia:Neutral point of view, which describes Wikipedia's mandatory core approach to neutral, unbiased article-writing;
3. Wikipedia:No original research, which prohibits the use of Wikipedia to publish personal views and original research of editors and defines Wikipedia's role as an encyclopedia of existing *recognized* knowledge;
4. Wikipedia:Verifiability, which explains that it must be possible for readers to verify all content against credible external sources (following the guidance in the Wikipedia:Risk disclaimer that is linked-to at the end of every article);
5. Wikipedia:Reliable sources, which explains what factors determine whether a source is acceptable;
6. Wikipedia:Citing sources, which describes the manner of citing sources so that readers can verify content for themselves;
7. And Wikipedia:Manual of Style, which offers a style guide—in general editors tend to acquire knowledge of appropriate writing styles and detailed formatting over time.

**Core content policies**

Neutral point of view

No original research

Verifiability

**Other content policies**

Article titles

Biographies of living persons

Image use policy

What Wikipedia is not

v · t · e

These are often abbreviated to WP:NOT, WP:NPOV, WP:NOR, WP:V, WP:RS, WP:CITE, and WP:MOS respectively.

## Editorial administration, oversight, and management

*Main pages: Wikipedia:Administration and Wikipedia:Editorial oversight and control*

The Wikipedia community is largely self-organising, so that anyone may build a reputation as a competent editor and become involved in any role s/he may choose, subject to peer approval. Individuals often will choose to become involved in specialised tasks, such as reviewing articles at others' request, watching current edits for vandalism, watching newly created articles for quality control purposes, or similar roles. Editors who believe they can serve the community better by taking on additional administrative responsibility may ask their peers for agreement to undertake such responsibilities. This structure enforces meritocracy and communal standards of editorship and conduct. At


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Video guided tour #2: Why

present a minimum approval of 75–80% from the community is required to take on these additional tools and responsibilities. This standard tends to ensure a high level of experience, trust, and familiarity across a broad front of aspects within Wikipedia.

does Wikipedia work even though anyone can edit it?

A variety of software-assisted systems and automated programs help editors and administrators to watch for problematic edits and editors. Theoretically all editors and users are treated equally with no "power structure". There is, however, a hierarchy of permissions and positions, some of which are listed hereafter:

1. *Anyone* can edit most of the articles here. Some articles are protected because of vandalism or edit-warring, and can only be edited by certain editors.
2. Anyone with an account that has been registered for four days or longer and has made at least ten edits becomes *autoconfirmed*, and gains the technical ability to do three things that non-autoconfirmed editors cannot:
   - Move articles.
   - Edit semi-protected articles.
   - Vote in certain elections (minimum edit count to receive suffrage varies depending on the election).
3. Many editors with accounts obtain access to certain tools that make editing easier and faster. Few editors learn about most of those tools, but one common privilege granted to editors in good standing is "rollback", which is the ability to undo edits more easily.
4. Administrators ("admins" or "sysops") have been approved by the community, and have access to some significant administrative tools. They can delete articles, block accounts or IP addresses, and edit fully protected articles.
5. Bureaucrats are chosen in a process similar to that for selecting administrators. There are not very many bureaucrats. They have the technical ability to add or remove admin rights and approve or revoke "bot" privileges.
6. The Arbitration Committee is analogous to Wikipedia's supreme court. They deal with disputes that remain unresolved after other attempts at dispute resolution have failed. Members of this Committee are elected by the community and tend to be selected from among the pool of experienced admins.
7. Stewards hold the top echelon of community permissions. Stewards can do a few technical things, and one almost never hears much about them since they normally only act when a local admin or bureaucrat is not available, and hence almost never on the English Wikipedia. There are very few stewards.
8. Jimmy Wales, the founder of Wikipedia, has several special roles and privileges. In most instances, however, he does not expect to be treated differently than any other editor or administrator.

## Handling disputes and abuse

*Main pages: Wikipedia:Vandalism, Wikipedia:Dispute resolution, Wikipedia:Consensus, Wikipedia:Sock puppetry, and Wikipedia:Conflict of interest*

Wikipedia has a rich set of methods to handle most abuses that commonly arise. These methods are well-tested and should be relied upon.

- Intentional *vandalism* can be reported and corrected by anyone.
- Unresolved *disputes* between editors, whether based upon behavior, editorial approach, or validity of content, can be addressed through the talk page of an article, through requesting comments from other editors or through Wikipedia's comprehensive dispute resolution process.
- *Abuse of user accounts*, such as the creation of "Internet sock puppets" or solicitation of friends and other parties to enforce a non-neutral viewpoint or inappropriate consensus within a discussion, or to disrupt other Wikipedia processes in an annoying manner, are addressed through the sock puppet policy.

In addition, new users may initially find that their votes are given less weight by editors in some informal polls in order to prevent abuse of single-purpose accounts.

## Editorial quality review

As well as systems to catch and control substandard and vandalistic edits, Wikipedia also has a full style and content manual and a variety of positive systems for continual article review and improvement. Examples of the processes include peer review, good article assessment, and the featured article process, a rigorous review of articles that are intended to meet the highest standards and showcase Wikipedia's capability to produce high-quality work.

In addition, specific types of article or fields often have their own specialized and comprehensive projects, assessment processes (such as biographical article assessment), and expert reviewers within specific subjects. Nominated articles are also frequently the subject of specific focus on the neutral point of view noticeboard or in WikiProject Cleanup.

# Technical attributes

Wikipedia uses MediaWiki software, the open-source program used not only on Wikimedia projects but also on many other third-party websites. The hardware supporting the Wikimedia projects is based on several hundred servers in various hosting centers around the world. Full descriptions of these servers and their roles are available on this Meta-Wiki page. For technical information about Wikipedia, check Technical FAQ. Wikipedia publishes various types of metadata; and, across its pages, are many thousands of microformats.

# Feedback and questions

Wikipedia is run as a communal effort. It is a community project whose result is an encyclopedia. Feedback about content should, in the first instance, be raised on the discussion pages of those articles. Be bold and edit the pages to add information or correct mistakes.

## Frequently asked questions (FAQ)

*Main page: Wikipedia:FAQ*

- FAQ index
- Category:Wikipedia FAQ

## Static help

The Help:Contents may be accessed by clicking *help* displayed under the ► *Interaction* tab at the top left of all pages.

- Help:Menu—is a menu-style page that will direct you to the right place to find information.
- Help:Directory—is a descriptive listing of all Wikipedia's informative, instructional and consultation pages.

## Giving feedback

There is an established escalation-and-dispute process within Wikipedia, as well as pages designed for questions, feedback, suggestions, and comments. For a full listing of the services and assistance that can be requested on Wikipedia, see Wikipedia:Request directory.

- Talk pages—the associated discussion page for discussion of an article or policy's contents (usually the first place to go)
- Wikipedia:Vandalism—a facility for reporting vandalism (but fix vandalism as well as report it)
- Dispute resolution—the procedure for handling disputes that remain unresolved within an article's talk space
- Village pump—the Wikipedia discussion area, part of the Community portal
- Wikipedia:Contact us

See also:

- Bug tracker—a facility for reporting problems with the Wikipedia website or the MediaWiki software that runs it

- Village pump: proposals page—a place for making non-policy suggestions
- Wikipedia:Help desk—Wikipedia's general help desk, if other pages have not answered the query

### Research help and similar questions

Facilities to help users researching specific topics can be found at:

- Wikipedia:Requested articles—to suggest or request articles for the future.
- Wikipedia:Reference desk—to ask for help with any questions, or in finding specific facts.
- Wikipedia:Researching with Wikipedia—for information on using Wikipedia as a research tool.

Because of the nature of Wikipedia, it is encouraged that people looking for information should try to find it themselves in the first instance. If, however, information is found to be missing from Wikipedia, be bold and add it so others can gain.

### Community discussion

For a listing of ongoing discussions and current requests, see the dashboard. For specific discussion not related to article content or editor conduct, see the Village pump, which covers such subjects as milestone announcements, policy and technical discussion, and information on other specialized portals such as the help, reference and peer review desks. The Community portal is a centralized place to find things to do, collaborations, and general editing help information, and find out what is happening. *The Signpost*, a community-edited newspaper, has recent news regarding Wikipedia, its sister projects, and the Wikimedia Foundation.

### Contacting individual Wikipedia editors

To contact individual contributors, leave a message on their talk page. Standard places to ask policy and project-related questions are the Village pump, online, and the Wikipedia mailing lists, over e-mail. Reach other Wikipedians via IRC and e-mail.

In addition, the Wikimedia Foundation **Meta-Wiki** is a site for coordinating the various Wikipedia projects and sister projects (and abstract discussions of policy and direction). Also available are places for submitting bug reports and feature requests.

For a full list of contact options, see **Wikipedia:Contact us**.

## Other languages

This Wikipedia is written in English. Started in 2001, it currently contains 5,323,769 articles. Many other Wikipedias are available; some of the largest are listed below.

- More than 1,000,000 articles: Deutsch · Español · Français · Italiano · Nederlands · 日本語 · Polski · Русский · Svenska · Tiếng Việt ·
- More than 250,000 articles: · Bahasa Indonesia · Bahasa Melayu · Català · Čeština · Euskara · · · Magyar · Norsk bokmål · Português · Română · Srpski · Srpskohrvatski · Suomi · Türkçe · Українська · 中 ·
- More than 50,000 articles: Bosanski · Български · Dansk · Eesti · Ελληνικά · English (simple form) · Esperanto · Galego · עברית · Hrvatski · Latviešu · Lietuvių · Norsk nynorsk · Slovenčina · Slovenščina · ·

**Complete list of Wikipedias**

## Sister projects

Wikipedia is hosted by the Wikimedia Foundation, a non-profit organization that also hosts a range of other projects:

**Commons** **MediaWiki** **Meta-Wiki**

| | | |
|---|---|---|
| Free media repository | Wiki software development | Wikimedia project coordination |
| **Wikibooks** Free textbooks and manuals | **Wikidata** Free knowledge base | **Wikinews** Free-content news |
| **Wikiquote** Collection of quotations | **Wikisource** Free-content library | **Wikispecies** Directory of species |
| **Wikiversity** Free learning materials and activities | **Wikivoyage** Free travel guide | **Wiktionary** Dictionary and thesaurus |

**Please note that while other sites may also use MediaWiki software and therefore look similar to Wikipedia, or may have a name that includes "Wiki-" or "-pedia", or a similar domain name, the only projects which are part of the Wikimedia Foundation are those listed above and Wikipedia, even if other projects claim to be part of it.**

## See also

- For useful directories and indexes, see Wikipedia:Directory.
- List of online encyclopedias
- Wikipedia:A Primer for newcomers
- Wikipedia:Formal organization
- Wikipedia:History of Wikipedian processes and people
- Wikipedia:Quality control
- Wikipedia:Ten things you may not know about Wikipedia
- Wikipedia:Wikipedia (disambiguation)
- Wikipedia: The Missing Manual
- Wikipedia power structure (Meta)

Help desk

*Help portal*

*Internet portal*

**Book: Wikipedia**

## References


1. ^ "Report card". Wikimedia. Retrieved September 3, 2015.
2. ^ "Milestones 2001". Wikipedia, *www.wikipedia.org*.
3. ^ Bill Thompson, "What is it with Wikipedia?" *BBC*, December 16, 2005.


## Further reading

*Main article: Bibliography of Wikipedia*


- Phoebe Ayers; Charles Matthews; Ben Yates (2008). *How Wikipedia Works:*. No Starch Press. ISBN 978-1-59327-176-3.
- John Broughton (2008). *Wikipedia Reader's Guide: The Missing Manual*. O'Reilly Media, Inc. ISBN 978-0-596-55387-6.
- John Broughton (2008). *Wikipedia: The Missing Manual*. O'Reilly Media, Inc. ISBN 978-0-596-55377-7.
- Dan O'Sullivan (24 September 2009). *Wikipedia: A New Community of Practice?*. Ashgate Publishing, Ltd. ISBN 978-1-4094-8606-0.
- Andrew Lih (17 March 2009). *The Wikipedia revolution: how a bunch of nobodies created the world's greatest encyclopedia*. Hyperion. ISBN 978-1-4013-0371-6.
- Joseph Michael Reagle, Jr.; Lawrence Lessig (30 September 2010). *Good Faith Collaboration: The Culture of Wikipedia*. MIT Press. ISBN 978-0-262-01447-2.


## External links

- Mission statement – The Wikimedia Foundation
- Wikimedia values – The six values of the Wikimedia Foundation
- In a nutshell, what is Wikipedia? And what is the Wikimedia Foundation? – The Wikimedia Foundation
- Wikimedia founding principles – Principles generally supported by all of the Wikimedia communities
- Ten Simple Rules for Editing Wikipedia

| v · t · e · | **Wikipedia help pages** |
|---|---|
| **Visit the *Teahouse* if you are a new editor looking for interactive help, or the *Help desk* for an interactive Q & A forum.**<br>**Or ask for help on your talk page** · | |
| **Noticeboards** (?) · **FAQs** (?) · **Reference desks** (?) · *The Missing Manual* (?) · *Directories* (?) · | |
| **About Wikipedia** | Administration · Principles (Wikipedia in brief) · Policies and guidelines · What Wikipedia is not · Disclaimer (parental advice) · Making requests (where to ask questions · contact Wikipedia directly · · Who writes Wikipedia? · Why create an account? · |
| **Help for readers** | FAQ · Books · Copyright · Glossary · Mobile access · Navigation · Other languages · Searching · Students · Viewing media · |
| **Contributing to Wikipedia** | A plain and simple overview · A primer for newcomers · Asking for help · Advice for young editors · Avoiding common mistakes · Etiquette (community expectations) · Learning the ropes · Instructional material · Simplified Manual of Style · Simplified rule-set ("Ignore all rules" · "The rules are principles" · · Style-tips · Tip of the day · Task Center · Your first article (article wizard) · Vandalism · |
| **Getting started** | Wikipedia intro · Wikipedia tutorial · The Wikipedia Adventure · Manual of Style intro · Graphics tutorials · Picture tutorial (Uploading intro) · IRC (live chat) tutorial · Navigating intro · Policies intro · Referencing intro · Tables intro · Talk pages intro · VisualEditor user guide · |
| **Dos and don'ts** | Accessibility · Bio's · Categorization · Disambiguation · Images · Links · Lists · References · Tables · Talks · |
| **How-to pages and information pages** | Appealing blocks · Article deletion · Categories · Citations / references (Referencing for beginners · Citation Style 1 · Cite errors · References and page numbers · · Convert · Diff · Editing (toolbar · edit conflict · · Email confirmation · Find sources · Files · Footnotes · Image deletion · Infoboxes · Linking (link color) · Logging in · Merging · Namespaces · Page name · Redirect · Renaming pages · Passwords · Reverting · Talk pages (archiving) · URL · User contributions · User page design center · |
| **Coding wiki markup** | Wiki markup (cheatsheet) · Barcharts · Calculations · Characters · Citation templates · Columns · Hidden text · HTML · Lists · Magic words (introduction) · Music symbols · Sections · Sounds · Tables (introduction) · Templates (documentation · messages (cleanup messages · · · Transclusion · Visual files · Wiki tools · |
| **Directories** | Abbreviations · Departments · Editor's index · Essays · FAQs · Glossary · Guidelines · Help menu · Manual of Style · Policies · Shortcuts · Tips · |
| *See also: Category:Wikipedia information pages and Category:Wikipedia how-to* | |

| v · t · e · | **Wikipedia key policies and guidelines** |
|---|---|
| **Overview** | Five pillars · Policies and guidelines · List of policies and guidelines (List of policies · List of guidelines · · |

| | |
|---|---|
| **Project-wide principles** | Consensus · Dispute resolution · Editing policy · Ignore all rules · What Wikipedia is not · Wikipedia is not a dictionary · |
| **Core content policies** | Neutral point of view · No original research · Verifiability · |
| **Other content policies** | Article titles · Autobiography · Biographies of living persons · Image use · |
| **Content guidelines** | Citing sources · Don't create hoaxes · Do not include copies of primary sources · External links · Fringe theories · Identifying reliable sources · Notability · Patent nonsense · |
| **Behavioural policies** | Child protection · Civility · Courtesy vanishing · Edit warring · Harassment · No legal threats · No personal attacks · Ownership of content · Sock puppetry · |
| **Behavioural guidelines** | Assume good faith · Conflict of interest · Disruptive editing · Do not disrupt Wikipedia to illustrate a point · Etiquette · Gaming the system · Please do not bite the newcomers · |
| **Editing guidelines** | Article size · Be bold · Disambiguation · Hatnotes · Set index articles · Signatures · Subpages · Talk page guidelines · User pages · Vandalism · WikiProjects · |
| **Style conventions** | Manual of Style (Contents · · Accessibility (Understandability · · Dates and numbers · Images · Layout · Lead section · Linking · Lists · |
| **Classification guidelines** | Categories, lists, and navigation templates · Categorization · Template namespace · |
| **Deletion policies** | Attack page · Criteria for speedy deletion · Deletion policy · Oversight · Proposed deletion · Proposed deletion of BLP · Proposed deletion (books) · Revision deletion · |
| **Wikimedia Foundation** | List of policies · Friendly space policy · Licensing and copyright · Privacy policy · Values · |
| **Book · Category: Policies / Guidelines ·** | |

| v · t · e · | **Wikipedia community** |
|---|---|
| *For a listing of current collaborations, tasks, and news, see the Community portal. For a listing of ongoing discussions and current requests, see the Dashboard.* | |
| **About Wikipedia** | Welcome! · Administration · Task Center · Regional notice boards · News (The Signpost · Goings-on · In the media · · Meetups · Mailing lists · Awards (Reward board · Contests · · Wikipedians · Statistics (Milestones · · The Wikipedia Library · Centralized discussion · Village pump (Idea lab · Policy · Proposals · Technical · Miscellaneous · · |
| **Contents and grading** | Requested articles · Most-wanted articles · Images needing articles · Articles needing images · Articles for creation (Creation · Help · · Vital articles · Today's articles for improvement · Peer review · Good article nominations · Featured article candidates (Lists · Pictures · Portals · Topics · · Article translation (Pages · · Main Page (Errors · · |
| **WikiProjects and groups** | Directory · Culture and the arts · Geographical · History and society · Science, technology and engineering · Wikipedia assistance and tasks · Patrols (Recent changes · · Counter-Vandalism Unit · Version 1.0 Editorial Team · Accessibility · |
| **Maintenance tasks** | Open tasks · Cleanup (Vandalism · · Database reports · 'As of' · Page Curation · Recent changes · Backlog · Controversial issues · Dusty articles · |
| **Administrators** | Admin dashboard · Admin requests · Administrators' (Incidents · Edit warring · Vandalism · · Requests for closure · Revision deletion · Oversight (Request · · Page protection · Sockpuppets · User permissions · Open proxies · Usernames (Changing · Title blacklist · · |

| | |
|---|---|
| **and noticeboards** | OTRS · Bureaucrats' (Requests for adminship & bureaucratship · · Arbitration Committee (Requests · Enforcement · · |
| **Content dispute resolution** | Editor assistance · Requests for comment · Third opinion · Dispute resolution noticeboard (Biographies of living persons · Conflict of interest · External links · Fringe theories · Neutral point of view · No original research · Reliable sources · · Mediation · |
| **Other noticeboards and assistance** | Requests for help · Asking questions (Teahouse · Help desk · Reference desk · Adopt-a-user · Online Ambassadors · · Copyright assistance (Copyright investigations · Text problems · Media questions · · Paid editors · Resource requests · Mergers (History mergers · · Moves (Page importation · · Spam (Blacklist · Whitelist · · Bot owners' · Education (Incidents · · New pages patrol · General sanctions · Editor sanctions · Long-term abuse · |
| **Deletion discussions** | Guide (Admin · · Today · Articles · Templates · Files · Categories · Redirects · Miscellany · Speedy · Proposed (BLP · Books · · Review (Undeletion · · Arguments to avoid · Arguments to make · Article Rescue · |
| **Elections and votings** | Requests for comment (meta) · Wikimedia Foundation elections · WP Democracy (Voting is not evil · Milestones · · |
| **Directories and summaries** | Departments · Edit summary legend · Editor's index · Essays · FAQs · Glossary (Abbreviations · · Help · Manual of Style (Simplified · · Rules (Five pillars · Policies · Guidelines · · Shortcuts · Template messages (Citation templates · · Tips (Today · · Tools · Wikis · Wiki markup · |

Categories: Wikipedia basic information




# Wikipedia:Community portal

From Wikipedia, the free encyclopedia



Main page
Contents
Featured content
Current events
Random article
Donate to Wikipedia
Wikipedia store

Interaction
Help
About Wikipedia
Community portal
Recent changes
Contact page

Tools
What links here
Related changes
Upload file
Special pages
Permanent link
Page information
Wikidata item

Print/export
Create a book
Download as PDF
Printable version

In other projects
Wikimedia Commons
Wikispecies
Wikibooks
Wikidata
Wikinews
Wikiquote
Wikisource
Wikiversity
Wikivoyage

Languages
Azərbaycanca
Afrikaans
Alemannisch

**Community portal** · Dashboard · Departments · Directory · Essays · Editor's Index · Maintenance · Requests · WikiProjects

## Welcome to the Community portal

This page provides a listing of current collaborations, tasks, and news about English Wikipedia.
For a listing of ongoing discussions and current requests, see the dashboard.
New to Wikipedia? See the contributing to Wikipedia page for everything you need to know to get started.
To find other internal project pages of interest, see the department directory.

**Shortcuts:**
**WP:COM**
**WP:COMM**
**WP:COMPORT**
**P:WP**

## Interact more

| Help desk | Reference desk | Village pump | Peer editing help | WikiProjects | Barnstars | Dispute resolution |
|---|---|---|---|---|---|---|

Village pump sections: Policy · Proposals · Tech · Misc
Reference desks: Computing · Entertainment · Humanities · Language · Maths · Science · Travel · Misc · Archives

## Help out

You can help improve the articles listed below! This list updates frequently, so check back here for more tasks to try.

### Fix spelling and grammar

- Executive branch of the government of Honduras
- Wall tent
- District of Southern California
- The Amazing Race 9

### Fix wikilinks

- Ole Lynggaard Copenhagen
- Nine Short Pieces for Piano
- BBC Nitia
- Jowane Masowe Chishanu
- Youth Association of Kuwait

### Update with new information

- The Guardian
- 2016 in Germany
- Politics of Switzerland

- Touman

*More...* ● **Learn how**

- Rice production in South Korea
- Yanbian University

*More...* ● **Learn how**

## Expand short articles

- Saonara
- Campiglia dei Berici
- Panozze
- Arsiero
- Quero

*More...* ● **Learn how**

## Check and add references

- Cayaponia tayuya
- Swedish Language Council
- Magic in the Graeco-Roman world
- Protandim
- Pantera

*More...* ● **Learn how**

## Fix original research issues

- Ilyushin Il-78
- Japanese street fashion
- Keep on Truckin' (song)
- Construction set
- Werckmeister Harmonies

*More...* ● **Learn how**

## Improve lead sections

- Perforce Helix
- Classification of Chinese Hospitals
- Thomas Cook & Son
- Reference data (financial markets)
- European Weightlifting Championships

*More...* ● **Learn how**

## Add an image

- Madras Stock Exchange
- Max Planck Institute of Molecular Plant Physiology
- Mount Evelyn Aqueduct
- Mount Rantemario
- Mole blanco

*More...* ● **Learn how**

## Translate and clean up

- Sumenep Regency
- Sonia Grey
- Avtotor
- Zonguldak Kömürspor
- MC Guimê

*More...* ● **Learn how**

**Counter systemic bias by creating new articles** on missing important female scientists.

**Improve popular low quality articles** (top 5,000 articles by pageviews with low ORES article class predictions.)

Other helpful tasks include, creating requested articles, fixing unreferenced statements, fixing vandalism, welcoming newcomers, link recovery, categorization, and numerous behind the scenes tasks like moving free images to Wikimedia Commons. See **Wikipedia:Maintenance** for more maintenance tasks.

# Community bulletin board

## General notices

- Free subscriptions to high-quality paywalled journals, newspaper archives, and online reference works are available for Wikipedia editors. For more information, see "**Wikipedia:TWL/Journals**"

## Projects seeking help

*Also consider posting WikiProject, Task Force, and Collaboration news at the Signpost's WikiProject Report page.*

## The Signpost

**22 December 2016**

- Year in review: Looking back on Wikimedia's 2016
- Special report: German Wikipedia ArbCom implodes amid revelation of member's far-right political role
- In focus: Active user page filter prevents vandalism

- The Africa Destubathon is being held from October 15 - November 27 2016. Substantial prizes have been proposed, with a prize for improving the most stubs for every African country. It needs contributors to improve the diversity of content from geography and wildlife to women biographies across the African continent. Sign up if interested!

## WikiProjects and Task Forces

- The Tip of The Day department is looking for tricks and techniques. If you have a special way of doing things, please stop by and share.

## Outlines

*See also: Wikipedia:WikiProject Outlines*

### Under construction

- Outline of encyclopedias
- Outline of JavaScript
- Outline of ontologies
- Outline of the World Wide Web

### Being overhauled or expanded

- Outline of Israel
- Outline of knowledge

### Nearing completion (need remainder of annotations added)

- Outline of theatre
- Outline of meteorology

### Outlines in need of attention

- Outline of communication
- Outline of computer security
- Outline of Marvel Comics
- Outline of skiing
- Outline of sustainable agriculture
- Outline of telecommunication

### Need link placement

- Outline of solar energy (place entries from *See also* into body of outline)
- Outline of prehistoric technology (place entries from *See also* into body of outline)
- Outline of sustainability (from nav footer)

## Portal report

The following portals are in need of attention/upkeep:

| | |
|---|---|
| Portal:Melbourne | Newly created |
| Portal:Perth | Newly created |

and harassment

- News and notes: English Wikipedia ArbCom election results; strategic planning update
- Op-ed: Operation successful, patient dead—outreach workshops in Namibia
- In the media: In brief—coverage of gender gap initiatives, banner fundraising, and more
- Traffic report: Post-election traffic blues
- Featured content: The Christmas edition
- Blog: Wiki Loves Monuments contest winners announced
- Technology report: Labs improvements impact 2016 Tool Labs survey results
- Recent research: One study and several abstracts

Single page · Book ·

Front page · About · Subscribe · Suggestions · Archives ·

## Centralized discussion

- Seven requests for adminship are in progress.
- Prohibit tagging articles for deletion under CSD A7 (and perhaps other sections) within 30 minutes after creation
- Allow FFD discussions to be closed as delete via non-admin closure
- Hosting content from countries that do not have copyright relations with the U.S.
- Stand-alone lists – eligibility for nomination as Good Articles
- Closing deletion discussions with low participation

This week's article for improvement is

## Aeolian Islands

Some of the **Aeolian Islands**

Please be bold and help to improve

| | |
|---|---|
| Portal:Fergie (singer) | Newly created |
| Portal:Donald Trump | Newly created |
| Portal:A. R. Rahman | Newly created |
| Portal:Lighthouses | Newly created |
| Portal:Shreya Ghoshal | Newly created |
| Portal:Tuvalu | Newly created |
| Portal:Half-track | Newly created |
| Portal:Virginia Woolf | Newly created |
| Portal:Theosophy | Newly created |
| Portal:Machine learning | Newly created |
| Portal:Kyrgyzstan | Newly created |
| Portal:Trichy | Newly created |
| Portal:Space | The selected article excerpts were copied and pasted between 2006 and 2009. The leads of the corresponding articles have greatly improved since then. |
| Portal:Thailand | "Selected" sections need new material. Been the same for years. |

Norsk nynorsk
Occitan
Олык марий
Palzisch
Piemontèis
Plattdüütsch
Polski
Português
Română
Runa Simi
Русский
Sängö
Sardu
Scots
Seeltersk
Setswana
Sicilianu
Simple English
Slovenčina
Slovenščina
Soomaaliga
Српски / srpski
Srpskohrvatski / српскохрватски
Basa Sunda
Suomi
Svenska
Tagalog
Татарча/tatarça
Tshivenda
Türkçe
Türkmençe
Тыва дыл
Українська
Vahcuengh
Vepsän kel'
Tiếng Việt
Volapük

The following portals have interesting design features that you may find useful:

| | |
|---|---|
| Portal:South East England | A "parent" portal that uses selected content from several "child" portals, chosen at random for each type of content. |
| Portal:Philosophy | Automatically cycles through 52 "Selected philosophers", one per week, year after year. |
| Portal:Arts | Uses random generators to display random featured status selections. |

this article!

**WikiProject Missing Encyclopedic articles (% done)** v · t · e

**Project page**—The goal of this project is to ensure that Wikipedia has a corresponding article for every article in every other encyclopedia. *Sign in!*

**Monthly focus: MacTutor biographies 39 left**

**1911 verification**: *12.2%*

**ACF Regionals answers**: *64.1%*

**Hotlist of topics**: *88.7%*

**General topics**: *79.6%*

**Science topics**: *92%*

**Catholic Encyclopedia**: *86.2%*

**Easton's Bible Dictionary**: *88%*

**Encyclopaedia Biblica** : *69.5%*

**Evangelical Dictionary of Theology**: *80.6%*

**Gutenberg authors** : *57.1%*

**Jewish Encyclopedia** : *39%*

**Literary Encyclopedia**: *81.9%*

**List of Poles**: *6%*

**Find-A-Grave**: *85.1%*

**Stanford Archive answers** *97.9%*

**Missing paintings** *60.8%*

**Miscellaneous**

Many other lists of politicians, songs, TV shows and others.

**Overall progress**: *65.2%*

Spread the word through {{Project missing articles}}

**Active Wiki Fixup Projects**

Article Rescue Squadron
Check Wikipedia
Cleanup
Dead-end pages
Disambig pages w/ links
Fix common mistakes

## Discussions and collaborations

Discussions in the following areas have requested wider attention via Requests for comment:

- Biographies
- Economy and trade
- History and geography
- Language and linguistics
- Media, the arts, and architecture
- Politics, government, and law
- Religion and philosophy
- Science and mathematics
- Society, sports, and culture
- Wikipedia policies and guidelines
- Wikipedia style and naming
- WikiProjects and collaborations
- Wikipedia technical issues and templates
- Wikipedia proposals
- Unsorted

Edit links

- Free images to Commons
- Geo-coordinates
- Missing articles
- Most-wanted articles
- Orphaned articles
- Red Link Recovery
- Requested articles
- Single editor
- Stubsensor
- Today's articles for improvement
- Uncategorised articles
- Unreferenced articles
- Wikification needed

Main · Inactive · Mini

V · T · E

## See also

Dashboard · News · Goings-on · Milestones · Meetups · In the media · Mailing lists ·

## Wikimedia community portals

Here is a list of the main *community pages* of Wikipedia's sister projects.
All of these projects are multilingual and open-content.

**Meta-Wiki** – Coordination of all Wikimedia projects.
Wiktionary – A collaborative multilingual dictionary.
Wikinews – News stories written by readers.
Wikibooks – A collection of collaborative non-fiction books.
Wikiquote – A compendium of referenced quotations.
Wikisource – A repository for free source texts.
Wikispecies – A directory of species.
Wikiversity – Where teachers learn, and learners teach.
Wikivoyage – A world-wide travel guide.
Wikidata – A free knowledge base that can be read and edited by humans and machines alike.
Commons – Repository for free images and other media files.

# Newest featured content

| Articles | Topics | Portals |
|---|---|---|
| Devon County War Memorial | Overview of Lady Gaga | California Roads |
| Operation Infinite Reach | U.S. Highways in Michigan | *Halo* |
| Cliff Clinkscales | World Fantasy Award | Bristol |
| Belgium national football team | Overview of Katy Perry | Latin music |
| Jochen Rindt | 2015 Vuelta a España | Children's literature |

- Tidus
- Nominative determinism
- *Banksia aculeata*
- Alabama Centennial half dollar
- *Love, Inc.* (TV series)
- Tahiti rail
- Bee-eater
- Montreal Laboratory
- Dick Cresswell
- Gottlob Berger
- *Final Fantasy* series
- 1961 Atlantic hurricane season
- Overview of Leonardo DiCaprio
- Liverpool F.C.
- *Almirante Latorre*-class battleship
- Scheduled monuments in Somerset
- Overview of Lorde
- Sega video game consoles
- Vidya Balan
- No. 90 (Composite) Wing RAAF
- New York City
- Literature
- Freedom of speech
- Star Trek
- Technology
- Sports
- Geography
- Massachusetts
- Cheshire
- Bollywood

## Lists

- Municipalities in Mississippi
- Bradley Cooper on screen and stage
- Accolades received by *Room*
- Latin Grammy Hall of Fame
- Tamannaah filmography
- Jnanpith Award
- Local Nature Reserves in Essex
- Cardiff City F.C. seasons
- Municipalities in Maryland
- Rajinikanth filmography
- Shannen Doherty filmography
- Kenya ODI cricketers
- Michael Fassbender filmography
- International cricket five-wicket hauls by Ravichandran Ashwin
- Masters Tournament Par-3 contest

## Pictures

- Thích Quảng Đức's self-immolation during the Buddhist crisis
- Krestovsky Stadium
- Hybrid-propellant rocket fuel
- Atomic chess capture
- Hook Windmill
- Capitole de Toulouse
- Rough chameleon
- Backside of a automatic watch
- *The De Goyer Family and the Painter*
- Creaking Pagoda
- Jesse B. Jackson
- Dome of Basilica di Santa Maria Maggiore
- *The Child's Bath*
- Chapel Royal, Dublin
- Shag Rocks

# Motto of the day

Motto of the day...

“ Just one more level... ”


*Nominate one!*

# Tip of the day

Tip of the day...

## How to make your watchlist easier to read

If you use Firefox, there is a JavaScript you can install called **Watchlist sorter**.

This script sorts your watchlist by namespace, and adds spaces within each entry. This makes the watchlist much easier to read.

To install the script, copy/paste it to your your common.js page. This will install the script across all your skins.

Note: After saving, you have to bypass Firefox's cache to see the changes. To do this, hold down the Shift key while clicking Reload (or press Ctrl + Shift + R). Or, you may have to **purge** the Wikipedia server cache.

**Prior tip** – **Next tip**

Read more:
**Wikipedia:User scripts**
**Your watchlist settings**

*Become a Wikipedia tipster* – Tips library, by subject
*To add this auto-updating template to your user page, use* {{totd}}

| v · t · e · | **Wikipedia community** |
|---|---|
| | *For a listing of current collaborations, tasks, and news, see the Community portal.*<br>*For a listing of ongoing discussions and current requests, see the Dashboard.* |
| **About Wikipedia** | Welcome! · Administration · Task Center · Regional notice boards · News (The Signpost · Goings-on · In the media · · Meetups · Mailing lists · Awards (Reward board · Contests · · Wikipedians · Statistics (Milestones · · The Wikipedia Library · Centralized discussion · Village pump (Idea lab · Policy · Proposals · Technical · Miscellaneous · · |
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| **Administrators and noticeboards** | Admin dashboard · Admin requests · Administrators' (Incidents · Edit warring · Vandalism · · Requests for closure · Revision deletion · Oversight (Request · · Page protection · Sockpuppets · User permissions · Open proxies · Usernames (Changing · Title blacklist · · OTRS · Bureaucrats' (Requests for adminship & bureaucratship · · Arbitration Committee (Requests · Enforcement · · |
| **Content dispute resolution** | Editor assistance · Requests for comment · Third opinion · Dispute resolution noticeboard (Biographies of living persons · Conflict of interest · External links · Fringe theories · Neutral point of view · No original research · Reliable sources · · Mediation · |
| | Requests for help · Asking questions (Teahouse · Help desk · Reference desk · |

| | |
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| **Other noticeboards and assistance** | Adopt-a-user · Online Ambassadors · · Copyright assistance (Copyright investigations · Text problems · Media questions · · Paid editors · Resource requests · Mergers (History mergers · · Moves (Page importation · · Spam (Blacklist · Whitelist · · Bot owners' · Education (Incidents · · New pages patrol · General sanctions · Editor sanctions · Long-term abuse · |
| **Deletion discussions** | Guide (Admin · · Today · Articles · Templates · Files · Categories · Redirects · Miscellany · Speedy · Proposed (BLP · Books · · Review (Undeletion · · Arguments to avoid · Arguments to make · Article Rescue · |
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v · t · e · **Wikipedia directories and indexes**

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| | **Featured, good** | Featured articles (Good articles · · Featured lists · Featured pictures · Featured portals · Featured topics (Good topics · · |
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| | **LOC, bios, times** | Academic disciplines · Anniversaries (today · · Countries and territories · People (deaths this year · · Timelines (centuries · decades · · |
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# Recent changes



This is a list of recent changes to Wikipedia.

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Show last **50** | 100 | 250 | 500 changes in last 1 | 3 | **7** | 14 | 30 days

Hide minor edits | Show bots | Hide unregistered users | Hide registered users | Hide my edits | Show page categorization | Show Wikidata

Show new changes starting from 22:26, 4 January 2017

**Legend (help):**

r This edit may be damaging and should be reviewed (more info)
**N** This edit created a new page
**m** This is a minor edit
**b** This edit was made by a bot
D This edit was made at Wikidata
(*±123*) Page size change in bytes

Namespace: all ☐ Invert selection ☐ Associated namespace

Tag filter: Show

## 4 January 2017

- (diff | hist) . . People's Protection Units; 22:26 . . (-5) . . Omar hoftun (talk | contribs) (→*Foreign volunteers*)
- (diff | hist) . . Brand New (band); 22:26 . . (+2) . . Yeepsi (talk | contribs) (*Revert to last clean version*)
- (diff | hist) . . Oyo State; 22:26 . . (-10) . . Layusmen (talk | contribs) (→*Media*)
- (diff | hist) . . Wikipedia:New articles (Aircraft); 22:26 . . (0) . . Petebutt (talk | contribs) (→*4 recently discovered new article (from previous months)*)
- (diff | hist) . . Hemorrhoid; 22:26 . . (+35) . . Jodosma (talk | contribs) (→*lead add alternate name*)
- (diff | hist) . . Second inauguration of Thomas Jefferson; 22:26 . . (+19) . . 100.12.142.166 (talk)
- (diff | hist) . . NATO bombing of Albanian refugees near Gjakova; 22:26 . . (+31) . . J 1982 (talk | contribs) (*added Category:April 1999 events using HotCat*)
- (diff | hist) . . Clinton Township, Linn County, Iowa; 22:26 . . (+41) . . Johnpacklambert (talk | contribs) (*added Category:1854 establishments in Iowa using HotCat*)
- (diff | hist) . . Portal:Current events/2016 November 9; 22:26 . . **(-4,292)** . . 108.35.91.173 (talk) (←*Replaced content with 'All the single ladies shout woohoo.')*
- (diff | hist) . . Davin Dennis; 22:26 . . (+177) . . MisterCake (talk | contribs)

- (diff | hist) . . Mampong; 22:26 . . (0) . . 41.189.161.60 (talk) *(Fixed typo) (Tags: canned edit summary, Mobile edit, Mobile web edit)*
- (diff | hist) . . User talk:66.87.114.73; 22:26 . . **(+1,258)** . . ClueBot NG (talk | contribs) *(Warning 66.87.114.73 - #1)*
- (diff | hist) . . 1983 Florida Citrus Bowl; 22:26 . . (+162) . . Wikidude10000 (talk | contribs) *(→Aftermath)*
- (diff | hist) . . **m** Minotaur; 22:26 . . (-44) . . ClueBot NG (talk | contribs) *(Reverting possible vandalism by 66.87.114.73 to version by R'n'B. Report False Positive? Thanks, ClueBot NG. (2884670) (Bot))*
- (diff | hist) . . **m** Krutikhinsky District; 22:26 . . (+165) . . Every-leaf-that-trembles (talk | contribs) *(Added reference link for surface area)*
- (diff | hist) . . **m** Steak tartare; 22:26 . . (+6) . . Rjwilmsi (talk | contribs) *(→Parasites: Journal cites: complete pages parameter, using AWB (12140))*
- (diff | hist) . . Femi Akinwande; 22:26 . . (+1) . . Jasonakagary88 (talk | contribs) *(→Career statistics: fix infobox)*
- (diff | hist) . . The Simpsons (season 28); 22:26 . . (+92) . . KatnissEverdeen (talk | contribs) *(Per Al Jean's official Twitter account.)*
- (diff | hist) . . Wikipedia:Redirects for discussion/Log/2017 January 4; 22:26 . . **(+1,577)** . . Salvidrim! (talk | contribs) *(→Dr mario series: r)*
- (diff | hist) . . Thora Birch; 22:26 . . (+15) . . 190.249.179.87 (talk)
- (diff | hist) . . The Cambridge Diet; 22:26 . . (-50) . . 96.92.112.61 (talk)
- (diff | hist) . . Talk:University of California, Santa Barbara; 22:26 . . (+433) . . Neonorange (talk | contribs) *(Moved new post to bottom and thanked for catching error—error fixed)*
- (diff | hist) . . Roman Catholic Archdiocese of Rouen; 22:26 . . (+69) . . Vicedomino (talk | contribs) *(changed map)*
- (diff | hist) . . Criminal Minds (season 12); 22:26 . . (-35) . . Macapaka (talk | contribs) *(Undid revision 758341956 by 169.241.60.184 (talk) Shemar Moore will not be appearing this season.)*
- (diff | hist) . . Talk:PB.DB The Mixtape; 22:26 . . (-22) . . Starcheerspeaksnewslostwars (talk | contribs)
- (diff | hist) . . User talk:TD213; 22:26 . . **(+2,057)** . . Wgolf (talk | contribs) *(Notification: speedy deletion nomination of Zahf Paroo. (TW))*
- (diff | hist) . . A United Kingdom; 22:26 . . (+1) . . IanB2 (talk | contribs) *(→Plot: Typo) (Tags: Mobile edit, Mobile web edit)*
- (diff | hist) . . Zahf Paroo; 22:26 . . (+23) . . Wgolf (talk | contribs) *(Requesting speedy deletion (CSD A7). (TW))*
- (diff | hist) . . 2016 Los Angeles Rams season; 22:26 . . (-1) . . 76.11.135.174 (talk) *(→Week 10: at New York Jets)*
- (diff | hist) . . User:Mindi Crayon/sandbox; 22:26 . . **(+9,308)** . . Mindi Crayon (talk | contribs)
- (diff | hist) . . Forest Lawn Memorial Park (Hollywood Hills); 22:26 . . (0) . . 2600:8800:3080:8370:8095:d0c5:4a0a:d2a5 (talk)
- (diff | hist) . . Buffalo Township, Linn County, Iowa; 22:26 . . (+41) . . Johnpacklambert (talk | contribs) *(added Category:1848 establishments in Iowa using HotCat)*
- (diff | hist) . . Wikipedia:New articles (Aircraft); 22:26 . . (-61) . . Petebutt (talk | contribs) *(→4 recently discovered new article (from previous months))*
- (diff | hist) . . List of Moldovan records in athletics; 22:26 . . (+167) . . Montell 74 (talk | contribs) *(→Men: update)*
- (diff | hist) . . HeadCount; 22:26 . . (+443) . . 50.74.143.162 (talk) *(→Artist Partners)*
- (diff | hist) . . Dolbadarn Castle (Turner); 22:26 . . (-64) . . Frietjes (talk | contribs)
- (diff | hist) . . Minotaur; 22:26 . . (+44) . . 66.87.114.73 (talk) *(Added a improvement) (Tags: Mobile edit, Mobile web edit)*
- (diff | hist) . . Lauren Collins; 22:26 . . (-1) . . Dan1025 (talk | contribs) *(→Filmography)*
- (diff | hist) . . 2013 Women's World Junior Squash Championships; 22:26 . . (+64) . . Hugo999 (talk | contribs) *(added Category:International sports competitions hosted by Poland using HotCat)*
- (diff | hist) . . The Navy; 22:26 . . (+164) . . 216.152.182.8 (talk)
- (diff | hist) . . Ishida (shogi); 22:26 . . (-24) . . Ish ishwar (talk | contribs) *(ce)*
- (diff | hist) . . Hawera High School; 22:26 . . (+63) . . 122.60.71.82 (talk)

- (diff | hist) . . Song to Song; 22:26 . . (+49) . . NathanielTheBold (talk | contribs) *(Tag: Visual edit)*
- (diff | hist) . . User talk:DantODB; 22:26 . . (+401) . . Vjmlhds (talk | contribs) *(→205 Live)*
- (diff | hist) . . User talk:Drmies; 22:26 . . (+142) . . Wryip13579 (talk | contribs) *(→Request for edit)*
- (diff | hist) . . **m** John Horton Slaughter; 22:26 . . (-8) . . Red Director (talk | contribs) *(→Career)*
- (diff | hist) . . Draft:Brendan Kelly (politician); 22:26 . . (+7) . . 98.215.232.251 (talk) *(→Career)*
- (diff | hist) . . Anomaly (advertising agency); 22:26 . . (+347) . . 69.60.2.130 (talk)
- (diff | hist) . . **m** List of fraternities and sororities at the University of Minnesota; 22:26 . . (0) . . Jax MN (talk | contribs) *(→Honor and recognition societies: National website shows Tau Sigma Delta's "Beta Chapter" as being (re)founded in October of 2012)*
- (diff | hist) . . **m** Bahá'u'lláh; 22:26 . . **(-533)** . . Smkolins (talk | contribs) *(Reverted 1 edit by A35821361 (talk) to last revision by Smkolins. (TW))*



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Edit links



# Pages that link to "Wikipedia:WikiProject Medicine/Open Textbook of Medicine"



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What links here

Page: Wikipedia:WikiProject Medicine/Open Textbook of Medicine Namespace: all ☐ Invert selection Go

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- Wikipedia talk:WikiProject Medicine/Archive 67 (links | edit)
- Wikipedia:WikiProject Medicine/Lists of pages/Non-articles (links | edit)

View (previous 50 | next 50) (20 | 50 | 100 | 250 | 500)



# Changes related to "Wikipedia:WikiProject Medicine/Open Textbook of Medicine"

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← Wikipedia:WikiProject Medicine/Open Textbook of Medicine

This is a list of recent changes to pages linked from a specified page (or to members of a specified category). Changes to pages on your watchlist are shown with a **green** bullet.

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Show last **50** | 100 | 250 | 500 changes in last 1 | 3 | **7** | 14 | 30 days
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Show new changes starting from 22:27, 4 January 2017

**Legend (help):**

r This edit may be damaging and should be reviewed (more info)
**N** This edit created a new page
**m** This is a minor edit
**b** This edit was made by a bot
D This edit was made at Wikidata
(*±123*) Page size change in bytes

Namespace: all ☐ Invert selection ☐ Associated namespace

Tag filter:

Page name: Wikipedia:WikiProject Medicine/Open Textbook of Medicine ☐ Show changes to pages linked to the given page instead Show

### 4 January 2017

- (diff | hist) . . Hemorrhoid; 22:26 . . (+35) . . Jodosma (talk | contribs) (→*lead add alternate name*)
- (diff | hist) . . **m** Rheumatoid arthritis; 22:14 . . (+102) . . Rjwilmsi (talk | contribs) (*Journal cites:, using AWB (12140)*)
- (diff | hist) . . Down syndrome; 16:09 . . (+245) . . Doc James (talk | contribs) (→*Name: updated refg*)
- (diff | hist) . . Borderline personality disorder; 14:58 . . (-330) . . 86.187.163.71 (talk) (→*Signs and symptoms: Poor/insufficient evidence for lack of empathy as a symptom of BPD. fMRI is not generally recognized as diagnostic (but supportive) in the evaluation of psychiatric disorders.*) (*Tag: Visual edit*)
- (diff | hist) . . Preterm birth; 13:08 . . (+33) . . 157.48.95.59 (talk) (*Tags: Mobile edit, Mobile web edit*)
- (diff | hist) . . Salbutamol; 12:33 . . (-17) . . Kashmiri (talk | contribs) (→*top: Adding/improving reference(s)*)
- (diff | hist) . . Salbutamol; 12:32 . . **(-541)** . . Kashmiri (talk | contribs) (→*History: Promo? At least two dozen companies had the generic form approved by FDA*)
- (diff | hist) . . Childbirth; 10:53 . . **(-673)** . . Doc James (talk | contribs) (*Reverted good faith edits*

*by 2A02:C7D:3BF:7900:2907:8A73:34C6:5C88 (talk): Van. (TW))*

- (diff | hist) . . Borderline personality disorder; 10:49 . . (+54) . . Doc James (talk | contribs) *(adjusted)*
- (diff | hist) . . Borderline personality disorder; 10:46 . . (+176) . . Doc James (talk | contribs) *(fine in the infobox)*
- (diff | hist) . . Major depressive disorder; 10:43 . . (+12) . . Doc James (talk | contribs) *(adjusted per talk)*
- (diff | hist) . . Influenza vaccine; 10:09 . . **(-1,512)** . . Bondegezou (talk | contribs) *(Pending conclusion of Talk page discussion, I suggest excluding this material that seems undue and not consistent with MEDRS)*
- (diff | hist) . . Skin cancer; 10:06 . . (-51) . . Doc James (talk | contribs) *(we already say that)*
- (diff | hist) . . **m** Allergy; 09:41 . . (-278) . . Jfdwolff (talk | contribs) *(Reverted 1 edit by 37.77.179.230 (talk) to last revision by MrOllie. (TW))*
- (diff | hist) . . Childbirth; 09:39 . . **(+641)** . . 2a02:c7d:3bf:7900:2907:8a73:34c6:5c88 (talk)
- (diff | hist) . . Morphine; 09:37 . . (+5) . . Doc James (talk | contribs) *(Reverted to revision 756261943 by Smartse (talk): Was fine before. (TW))*
- (diff | hist) . . Suicide; 09:19 . . (+129) . . Doc James (talk | contribs) *(added to lead)*
- (diff | hist) . . Allergy; 09:17 . . (+278) . . 37.77.179.230 (talk)
- (diff | hist) . . Childbirth; 08:53 . . (+32) . . 2a02:c7d:3bf:7900:2907:8a73:34c6:5c88 (talk) *(Tag: Incorrectly formatted external link or image)*
- (diff | hist) . . Hepatitis A; 08:49 . . (+11) . . Iztwoz (talk | contribs) *(→top: added paywall - as it stands info is not relevant to sentence.)*
- (diff | hist) . . **m** Sarcoidosis; 06:48 . . (0) . . TylerDurden8823 (talk | contribs) *(→Antimetabolites)*
- (diff | hist) . . **m** Sarcoidosis; 06:48 . . (+2) . . TylerDurden8823 (talk | contribs) *(→Antimetabolites)*
- (diff | hist) . . Influenza vaccine; 05:52 . . **(+1,512)** . . Bigbaby23 (talk | contribs) *(Undid revision 758217613 by Jytdog (talk) I repeat you didn't read the additions. You have a history of WP:TENDENTIOUS)*
- (diff | hist) . . Influenza vaccine; 04:11 . . **(-1,512)** . . Jytdog (talk | contribs) *(Undid revision 758216681 by Bigbaby23 (talk) of course I read it! See the talk page. If you want add this please do an RfC. Thanks)*
- (diff | hist) . . Influenza vaccine; 04:01 . . **(+1,512)** . . Bigbaby23 (talk | contribs) *(Undid revision 758215314 by Jytdog (talk) Once again you have not read the addition, and abusing the system)*
- (diff | hist) . . Influenza vaccine; 03:48 . . **(-1,512)** . . Jytdog (talk | contribs) *(Undid revision 758215055 by Bigbaby23 (talk) no a publisher is not an author. that is a very basic error. giving EW notice)*
- (diff | hist) . . Influenza vaccine; 03:45 . . **(+1,512)** . . Bigbaby23 (talk | contribs) *(Undid revision 758190666 by Jytdog (talk) Jefferson stating his position is that of Cochrane. That's not fringe. And other opinions about over promotion relevant to this section.Stop abusing WP:DUE)*
- (diff | hist) . . Wikipedia; 03:42 . . (+36) . . Bobnorwal (talk | contribs) *(→Community: added citation directly to the quote, to avoid ambiguity about where the quote came from.) (Tag: Visual edit)*
- (diff | hist) . . Wikipedia; 03:37 . . (-10) . . Bobnorwal (talk | contribs) *(→Diversity: copyedits) (Tag: Visual edit)*
- (diff | hist) . . Delirium tremens; 02:57 . . (+4) . . 198.255.235.141 (talk) *(Fixed grammar) (Tags: canned edit summary, Mobile app edit, Mobile edit)*
- (diff | hist) . . Suicide; 02:43 . . (+6) . . WhatamIdoing (talk | contribs) *(→Media: Words as words) (Tag: Visual edit)*
- (diff | hist) . . Borderline personality disorder; 00:49 . . (-214) . . Toddst1 (talk | contribs) *(remove source not supportive of statement - remaining source is good)*
- (diff | hist) . . Borderline personality disorder; 00:48 . . (+38) . . Toddst1 (talk | contribs) *(Undid revision 758193623 by Toddst1 (talk) source in infobox)*
- (diff | hist) . . Borderline personality disorder; 00:46 . . (-38) . . Toddst1 (talk | contribs) *(Rejected the first text change (by Cynulliad3) that followed revision 758191708 by Amccann421: unsourced synonym)*
- (diff | hist) . . **m** Borderline personality disorder; 00:41 . . (+3) . . Cynulliad3 (talk | contribs) *(Article & comma)*
- (diff | hist) . . Borderline personality disorder; 00:39 . . (+38) . . Cynulliad3 (talk | contribs)

*(Amccann421, see infobox w/refs)*
- (diff | hist) . . Borderline personality disorder; 00:32 . . (-38) . . Amccann421 (talk | contribs) *(Reverted 1 edit by Cynulliad3 (talk): Unsourced name. (TW))*
- (diff | hist) . . Influenza vaccine; 00:24 . . **(-1,512)** . . Jytdog (talk | contribs) *(oh sorry i forgot. WP:UNDUE and we do not do "tit for tat" call and response from people with FRINGE positions. Take it to talk)*
- (diff | hist) . . Borderline personality disorder; 00:21 . . (+38) . . Cynulliad3 (talk | contribs) *(Also known as "emotional intensity disorder")*

### 3 January 2017

- (diff | hist) . . **m** Rabies; 23:50 . . **(+64,076)** . . ClueBot NG (talk | contribs) *(Reverting possible vandalism by 24.234.201.60 to version by Marco Chemello (BEIC). Report False Positive? Thanks, ClueBot NG. (2883578) (Bot))*
- (diff | hist) . . Rabies; 23:50 . . **(-64,076)** . . 24.234.201.60 (talk) *(Tags: blanking, Visual edit)*
- (diff | hist) . . Bipolar disorder; 23:28 . . (+1) . . The Anome (talk | contribs) *(simplify)*
- (diff | hist) . . Influenza vaccine; 22:54 . . (+364) . . Bigbaby23 (talk | contribs) *(→Evaluation of evidence: more info)*
- (diff | hist) . . Glaucoma; 22:38 . . (+54) . . Quercus solaris (talk | contribs)
- (diff | hist) . . Skin cancer; 22:37 . . (+67) . . 98.215.153.31 (talk) *(clarification)*
- (diff | hist) . . Salbutamol; 22:28 . . (-10) . . Benrusholme (talk | contribs) *(→Structure and activity: removed use of 'albuterol/salbutamol' to ensure article consistency)*
- (diff | hist) . . Influenza vaccine; 22:19 . . **(+1,148)** . . Bigbaby23 (talk | contribs) *(Undid revision 758044084 by Jytdog (talk) no explanation as to why revert cited information)*
- (diff | hist) . . Influenza vaccine; 21:13 . . (-43) . . Iztwoz (talk | contribs) *(→Effectiveness: rm unhelpful self link; rm duplicate link)*
- (diff | hist) . . Influenza vaccine; 20:59 . . (-2) . . Iztwoz (talk | contribs) *(→Medical uses: slight reword)*
- (diff | hist) . . Crohn's disease; 19:15 . . (-18) . . Lugnuts (talk | contribs) *(rv)*

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This page was last modified on 28 September 2016, at 03:07.



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# Special pages





This page contains a list of special pages. Most of the content of these pages is automatically generated and cannot be edited. To suggest a change to the parts that *can* be edited, find the appropriate text on Special:AllMessages and then request your change on the talk page of the message (using {{editprotected}} to draw the attention of administrators).

## Maintenance reports

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- Dead-end pages
- Dormant pages
- Double redirects
- Long pages
- Orphaned pages
- Pages not connected to items
- Pages with the fewest revisions
- Pages without language links
- Protected pages
- Protected titles
- Short pages
- Uncategorized categories
- Uncategorized files
- Uncategorized pages
- Uncategorized templates
- Unused categories
- Unused files
- Unused templates
- Wanted categories
- Wanted files
- Wanted pages
- Wanted templates

## Lists of pages

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- All pages with prefix
- Categories
- Category tree
- Disambiguation pages
- Entity Usage
- Pages linking to
- disambiguation pages
- Pages on topics near you
- Pages with a page property
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- Redirects
- Search
- Tracking categories

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- request
- Log in
- Login unification status

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- Blocked users
- List of globally blocked IP addresses

- Bot passwords
- Change credentials
- Change or remove email address
- Global account manager
- Global accounts list
- Global group management
- Grants
- List OAuth applications
- Membership in global groups
- Notifications
- Preferences
- Remove credentials
- Reset password
- Reset tokens
- User contributions
- User group rights
- User groups management
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- New pages
- New pages feed
- Recent changes
- Related changes
- Valid change tags
- Watchlist

## Media reports and uploads

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- Global file usage
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- Media statistics
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- Search for duplicate files
- VIPS scaling test page

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- API sandbox
- Book sources
- Edit filter configuration
- Expand templates
- Gadget usage statistics
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- Wikimedia wikis

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- Random root page
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- Pages with the most interwikis
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# Other special pages

- Content Translation statistics
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- SecurePoll
- Users who will be renamed

# Legend

- Normal special pages.
- **Restricted special pages.**




# Wikipedia:WikiProject Medicine/Open Textbook of Medicine

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We are working to develop these apps in a number of languages, including English, Persian, Chinese, and Hindi. There are ongoing efforts to increase access to medical information in all languages in collaboration with Translators Without Borders among others. If you like this app and are interested in helping us make it better please join Wikipedia:WikiProject Medicine or contact us directly.

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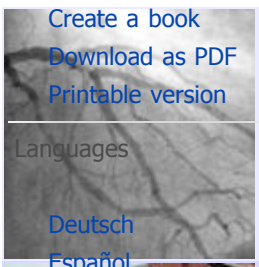
The Teams at WikiProject Medicine &
Translators Without Borders



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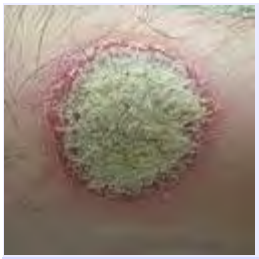

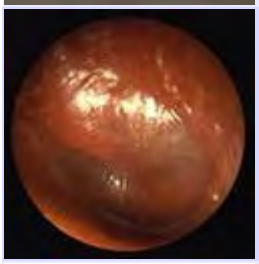

## Ears nose throat

Benign paroxysmal positional vertigo • Hearing loss • Mandibular fracture • Nasal polyp • Nose bleed • Otitis externa • Otitis media • Pharyngitis • Strep throat • Tinnitus • Vertigo

## Endocrinology

Addison's disease • Cushing's syndrome • Delirium tremens • Diabetes • DM type 1 • DM type 2 • Gestational diabetes • Graves' disease • Hypernatremia • Hyperthyroidism • Hypoglycemia • Hyponatremia • Hypothyroidism • Obesity • Primary hyperaldosteronism • Vitamin B12 deficiency

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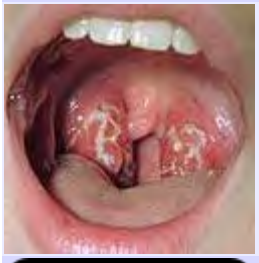
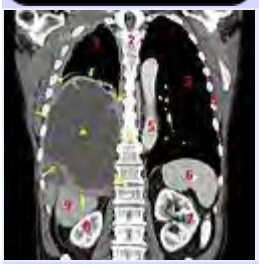


## Infectious disease

African trypanosomiasis • Ascariasis • Buruli ulcer • Cellulitis • Chagas disease • Common cold • Cysticercosis • Drancunculiasis • Ebola virus disease • Hepatitis A • Hepatitis B • Hepatitis C • HIV/AIDS • Leprosy • Lyme disease • Malaria • Meningitis • Rabies • Syphilis • Tuberculosis • Yellow fever • Zika fever

## Medications

Birth control • Carbamazapine • Cephalexin • Cholera vaccine • Cocaine • Dapsone • Diazepam • HCTZ • Ibuprofen • Influenza vaccine • Ipratropium bromide • Ketamine • Levofloxacin • Measles vaccine • Metoprolol • Mifepristone • Morphine • Nystatin • Paracetamol (acetaminophen) • Propofol • Salbutamol



## Oncology

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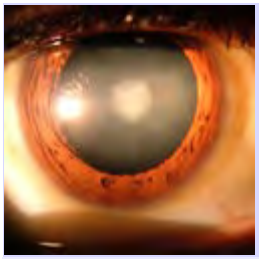

## Psychiatry

ADHD • Alcoholism • Anorexia nervosa • Anxiety • Asperger syndrome • Autism • Bipolar disorder • Borderline personality disorder • Bulimia nervosa • Eating disorder • Depression • Obsessive-compulsive disorder • Phobia • Post traumatic stress disorder • Schizophrenia • Suicide

## Rheumatology

Carpal tunnel syndrome • Fibromyalgia • Gout • Low back pain • Osteoarthritis • Osteoporosis • Plantar fasciitis • Psoriasis • Rheumatoid arthritis • Sarcoidosis • Sciatica

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# Information for "Wikipedia:WikiProject Medicine/Open Textbook of Medicine"

**Namespaces**

- Project page
- Talk

**Variants**

**Views**

- Read
- Edit
- View history

**More**

**Search**

Search Go

Help:Page information

## Basic information

| | |
|---|---|
| Display title | Wikipedia:WikiProject Medicine/Open T |
| Default sort key | WikiProject Medicine/Open Textbook of Medicine |
| Page length (in bytes) | 9,057 |
| Page ID | 46956272 |
| Page content language | English (en) |
| Page content model | wikitext |
| Indexing by robots | Allowed |
| Number of page watchers | Fewer than 30 watchers |
| Number of redirects to this page | 0 |
| Number of subpages of this page | 0 (0 redirects; 0 non-redirects) |
| Wikidata item ID | Q20200278 |

## Page protection

| | |
|---|---|
| Edit | Allow all users (no expiry set) |
| Move | Allow all users (no expiry set) |

## Edit history

| | |
|---|---|
| Page creator | Doc James (talk \| contribs) |
| Date of page creation | 23:58, 11 June 2015 |
| Latest editor | Doc James (talk \| contribs) |
| Date of latest edit | 18:52, 9 November 2016 |
| Total number of edits | 130 |
| Recent number of edits (within past 30 days) | 0 |
| Recent number of distinct authors | 0 |

# Page properties

| | |
|---|---|
| Transcluded templates (3) | ▪ Template:Clear (view source) (template protected)<br>▪ Template:Clr (view source) (template protected)<br>▪ Template:Columns (view source) (semi-protected) |
| Wikidata entities used in this page | ▪ Wikipedia:WikiProject Medicine/Open Textbook of Medicine<br>  ▪ Sitelink |

# External tools

- Revision history search
- Revision history statistics
- Edits by user
- Page view statistics
- WikiChecker

# Book creator

With the *book creator* you can create a book containing wiki pages of your choice. You can export the book in different formats (for example PDF or ODF) or order a printed copy.

*See Help:Books for more information.*

## Using the book creator

After the *book creator* has been enabled, the box as seen below is shown above each wiki page.


The book creator interface

*Add this page to your book*
: Adds the currently viewed article (page) to your book.

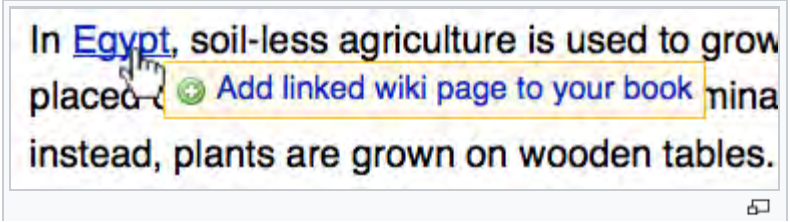
*Show book*
: Opens a new page which will show a list of all articles (pages) that you added to your book. On that page, you can **change the order** of the articles in your book and **structure** them using chapters. Further, you can **download** the books as a PDF or ODF, or order a **printed book**.

*Suggest pages*
: This tool analyzes the current set of pages in your book and **suggests** articles that might be also relevant to the overall topic of your book. This tool allows to create books **quickly**.

*Disable*
: This will **disable** the *Book creator* and **delete** your book (unless you saved it first).

### Adding pages without visiting them

A quick way to add pages is to simply hover on a linked article. If you wait about one second, a small box will pop up with the message "Add linked wiki page to your book". Click on this link, and the linked article will be added to your book.



Hovering your mouse over links is a convenient way to add pages to your book

## Adding whole categories

If you are viewing a category page, you can add all the pages in that category at once. The *Add this page to your book* link will have changed into *Add this category to your book*. Click on this new link, and all the articles in that category will be added to your book. Relevant categories may be found at the very bottom of Wikipedia articles. Categories can also be added by hovering category links.




# Rendering



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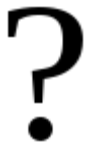

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# Wikipedia:WikiProject Medicine/Open Textbook of Medicine

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The Teams at WikiProject Medicine &
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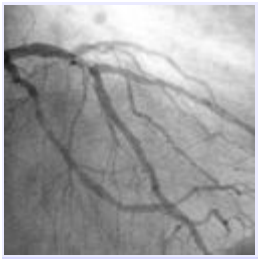

**Cardiology**
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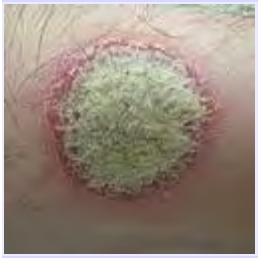

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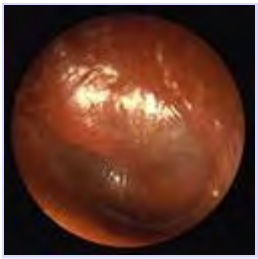

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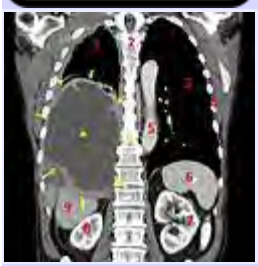

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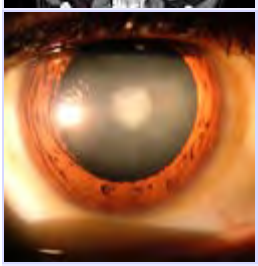

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Suicide

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# Benign paroxysmal positional vertigo

From Wikipedia, the free encyclopedia

**Benign paroxysmal positional vertigo** (**BPPV**) is a disorder arising from problems in the inner ear.[1] Symptoms are repeated brief periods of vertigo with movement, that is, of a spinning sensation caused by changes in the position of the head.[2] This can occur with turning in bed or changing position. Each episode of vertigo typically lasts less than one minute.[1] Nausea is commonly associated.[3] BPPV is one of the most common causes of vertigo.[2][4]

BPPV can result from a head injury or simply occur among those who are older. A specific cause is often not found. The underlying mechanism involves a small calcified otolith moving around loose in the inner ear. It is a type of balance disorder along with labyrinthitis and Ménière's disease.[1] Diagnosis is typically made when the Dix-Hallpike maneuver results in nystagmus (a specific movement pattern of the eyes) and other possible causes have been ruled out. In typical cases medical imaging is not needed.[2]

BPPV is often treated with a number of simple movements such as the Epley maneuver or Brandt-Daroff exercises.[1][5] Medications may be used to help with nausea.[3] There is tentative evidence that betahistine may help with the vertigo but its use is not generally needed.[2][6] BPPV is not a serious condition. Typically it resolves in one to two weeks. It however may recur in some people.[3]

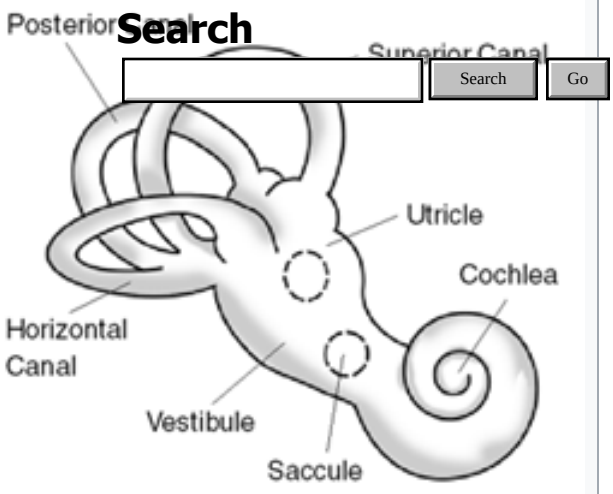
The first medical description of the condition occurred in 1921 by Robert Barany.[7] About 2.4% of people are affected at some point in time.[2] Among those who live until their 80s, 10% have been affected.[4] BPPV affects females twice as often as males.[3] Onset is typically in the person's 50s to 70s.[4]

## Contents



## Variants

**Benign paroxysmal positional vertigo**




Exterior of labyrinth of the inner ear.

| Classification and external resources | |
|---|---|
| **Specialty** | Otorhinolaryngology |
| **ICD-10** | H81.1 |
| **ICD-9-CM** | 386.11 |
| **OMIM** | 193007 |
| **DiseasesDB** | 1344 |
| **MedlinePlus** | 001420 |
| **eMedicine** | ent/761 emerg/57 neuro/411 |
| **Patient UK** | Benign paroxysmal positional vertigo |
| **MeSH** | D014717 |

[edit on Wikidata]

## Signs and symptoms [edit]

- Symptoms
  - Vomiting is common, depending on the strength of the vertigo itself and the causes for this illness.
  - Nausea is often associated.
  - Paroxysmal — Sudden onset of episodes with a short duration: lasts only seconds to minutes.
  - Positional in onset: Can only be induced by a change in position.
  - Pre-syncope (feeling faint) or syncope (fainting) is unusual but possible.
  - Rotatory (torsional) nystagmus, where the top of the eye rotates towards the affected ear in a beating or twitching fashion, which has a latency and can be fatigued (the vertigo should lessen with deliberate repetition of the provoking maneuver). Nystagmus should only last for 30 seconds to one minute.
  - Visual disturbance: It may be difficult to read or see during an attack due to associated nystagmus.
  - Vertigo — Spinning dizziness, which must have a rotational component.

Many patients will report a history of vertigo as a result of fast head movements. Many patients are also capable of describing the exact head movements that provoke their vertigo. Purely horizontal nystagmus and symptoms of vertigo lasting more than one minute can also indicate BPPV occurring in the horizontal semicircular canal.

Patients do not experience other neurological deficits such as numbness or weakness, and if these symptoms are present, a more serious etiology, such as posterior circulation stroke or ischemia, must be considered.

The spinning sensation experienced from BPPV is usually triggered by movement of the head, will have a sudden onset, and can last anywhere from a few seconds to several minutes. The most common movements patients report triggering a spinning sensation are tilting their heads upwards in order to look at something, and rolling over in bed.[8]

## Cause [edit]

Within the labyrinth of the inner ear lie collections of calcium crystals known as otoconia or otoliths. In patients with BPPV, the otoconia are dislodged from their usual position within the utricle, and migrate over time into one of the semicircular canals (the posterior canal is most commonly affected due to its anatomical position). When the head is reoriented relative to gravity, the gravity-dependent movement of the heavier otoconial debris (colloquially "ear rocks") within the affected semicircular canal causes abnormal (pathological) endolymph fluid displacement and a resultant sensation of vertigo. This more common condition is known as canalithiasis.

In rare cases, the crystals themselves can adhere to a semicircular canal cupula, rendering it heavier than the surrounding endolymph. Upon reorientation of the head relative to gravity, the cupula is weighted down by the dense particles, thereby inducing an immediate and sustained excitation of semicircular canal afferent nerves. This condition is termed cupulolithiasis.

There is evidence in the dental literature that malleting of an osteotome during closed sinus floor elevation, otherwise known as *osteotome sinus elevation* or *lift*, transmits percussive and vibratory forces capable of detaching otoliths from their normal location and thereby leading to the symptoms of BPPV.[9][10]

It can be triggered by any action which stimulates the posterior semi-circular canal, including:

- Looking up or down
- Post-head injury
- Sudden head movement
- Rolling over in bed

Tilting the head

BPPV may be made worse by any number of modifiers which may vary between individuals:

- Changes in barometric pressure — patients may feel increased symptoms up to two days before rain or snow
- Lack of sleep (required amounts of sleep may vary widely)
- Stress

An episode of BPPV may be triggered by dehydration, such as that caused by diarrhea. For this reason, it commonly occurs in post-operative patients who have diarrhea induced by post-operative antibiotics.

BPPV is one of the most common vestibular disorders in patients presenting with dizziness; migraine is implicated in idiopathic cases. Proposed mechanisms linking the two are genetic factors and vascular damage to the labyrinth.[11]

Although BPPV can occur at any age, it is most often seen in people over the age of 60.[12] Besides aging, there are no major risk factors known for developing BPPV, although previous episodes of trauma to the head, or inner ear infections known as labyrinthitis, may predispose individuals to future development of BPPV.[8]

## Mechanism [edit]

The inside of the ear is composed of an organ called the vestibular labyrinth. The vestibular labyrinth includes semicircular canals, which contain fluids and fine hairlike sensors which act as a monitor to the rotations of the head. An important structure in the inner ear includes the otolith organs which contain crystals that are sensitive to gravity. These crystals are responsible for sensitivity to head positions, and can also be dislocated, causing them to lodge inside one of the semicircular canals, which causes dizziness.

## Diagnosis [edit]

The condition is diagnosed by the patient's history, and by performing the Dix-Hallpike maneuver and/or the roll test.[13][14]

The Dix-Hallpike test is a common test performed by examiners to determine whether the posterior semicircular canal is involved.[14] It involves a reorientation of the head to align the posterior semicircular canal (at its entrance to the ampulla) with the direction of gravity. This test will reproduce vertigo and nystagmus characteristic of posterior canal BPPV.[13]

When performing the Dix-Hallpike test, patients are lowered quickly to a supine position, with the neck extended by the clinician performing the maneuver. For some patients, this maneuver may not be indicated, and a modification may be needed that also targets the posterior semicircular canal. Such patients include those who are too anxious about eliciting the uncomfortable symptoms of vertigo, and those who may not have the range of motion necessary to comfortably be in a supine position. The modification involves the patient moving from a seated position to side-lying *without* their head extending off the examination table, such as with Dix-Hallpike. The head is rotated 45 degrees away from the side being tested, and the eyes are examined for nystagmus. A positive test is indicated by patient report of a reproduction of vertigo and clinician observation of nystagmus. Both the Dix-Hallpike and the side-lying testing position have yielded similar results, and as such the side-lying position can be used if the Dix-Hallpike cannot be performed easily.[15]

The roll test can determine whether the horizontal semicircular canal is involved.[13] The roll test requires the patient to be in a supine position with their head in 30° of cervical flexion. Then the examiner quickly rotates the head 90° to the left side, and checks for vertigo and nystagmus. This is followed by gently bringing the head back to the starting position. The examiner then quickly rotates the head 90° to the right side, and checks again for vertigo and nystagmus.[13] In this roll test, the patient may experience vertigo and nystagmus on both sides, but rotating towards the affected side will trigger a more intense vertigo. Similarly, when the head is rotated towards the affected side, the nystagmus will beat towards the ground

and be more intense.[14]

As mentioned above, both the Dix-Hallpike and roll test provoke the signs and symptoms in subjects suffering from archetypal BPPV. The signs and symptoms patients with BPPV experience are typically a short-lived vertigo, and observed nystagmus. In some patients, though rarely, the vertigo can persist for years. Assessment of BPPV is best done by a medical health professional skilled in management of dizziness disorders, commonly a physiotherapist, audiologist or other physician.

The nystagmus associated with BPPV has several important characteristics which differentiate it from other types of nystagmus.

- Latency of onset: there is a 5-10 second delay prior to onset of nystagmus.
- Nystagmus lasts for 5–120 seconds.
- Positional: the nystagmus occurs only in certain positions.
- Repeated stimulation, including via Dix-Hallpike maneuvers, cause the nystagmus to fatigue or disappear temporarily.
- Rotatory/Torsional component is present, or (in the case of lateral canal involvement) the nystagmus beats in either a geotropic (towards the ground) or ageotropic (away from the ground) fashion.
- Visual fixation suppresses nystagmus due to BPPV.

Although rare, CNS disorders can sometimes present as BPPV. A practitioner should be aware that if a patient whose symptoms are consistent with BPPV, but does not show improvement or resolution after undergoing different particle repositioning maneuvers — detailed in the Treatment section below — need to have a detailed neurological assessment and imaging performed to help identify the pathological condition.[2]

### Differential diagnosis [edit]

Vertigo, a distinct process sometimes confused with the broader term, dizziness, accounts for about six million clinic visits in the United States every year; between 17 and 42% of these patients are eventually diagnosed with BPPV.[2] Other causes of vertigo include:

- Motion sickness/motion intolerance: a disjunction between visual stimulation, vestibular stimulation, and/or proprioception
- Visual exposure to nearby moving objects (examples of optokinetic stimuli include passing cars and falling snow)
- Other diseases: (labyrinthitis, Ménière's disease, and migraine,[16] etc.)

## Treatment [edit]

### Repositioning maneuvers [edit]

A number of maneuvers have been found to be effective including: the Epley maneuver, the Semont maneuver, and to a lesser degree Brandt-Daroff exercises.[5] Both the Epley and the Semont maneuver are equally effective.[5]

### Epley maneuver [edit]

*Main article: Epley maneuver*

The Epley maneuver employs gravity to move the calcium crystal build-up that causes the condition.[17] This maneuver can be performed during a clinic visit by health professionals, or taught to patients to practice at home, or both.[18] Postural restriction after the Epley maneuver increases its effect somewhat.[19]

When practiced at home, the Epley maneuver is more effective than the Semont maneuver. The most effective repositioning treatment for posterior canal BPPV is the therapist-performed Epley combined with home-practiced Epley maneuvers.[20] Devices like the DizzyFIX can help users conduct the Epley maneuver

at home, and are available for the treatment of BPPV.[21]

The Epley maneuver does not address the actual presence of the particles (otoconia); rather it changes their location. The maneuver aims to move these particles from some locations in the inner ear which cause symptoms such as vertigo, and reposition them to where they do not cause these problems.

## Semont maneuver [edit]

*Main article: Semont maneuver*

The Semont maneuver has a cure rate of 90.3%.[22] It is performed as follows:

1. The patient is seated on a treatment table with their legs hanging off the side of the table. The therapist then turns the patient's head towards the unaffected side 45 degrees.
2. The therapist then quickly tilts the patient so they are lying on the affected side. The head position is maintained, so their head is turned up 45 degrees. This position is maintained for 3 minutes. The purpose is to allow the debris to move to the apex of the ear canal.
3. The patient is then quickly moved so they are lying on the unaffected side with their head in the same position (now facing downwards 45 degrees). This position is also held for 3 minutes. The purpose of this position is to allow the debris to move toward the exit of the ear canal.
4. Finally, the patient is slowly brought back to an upright seated position. The debris should then fall into the utricle of the canal and the symptoms of vertigo should decrease or end completely.

Some patients will only need one treatment, but others may need multiple treatments, depending on the severity of their BPPV. In the Semont maneuver, as with the Epley maneuver, patients themselves are able to achieve canalith repositioning.[18]

## Brandt-Daroff exercises [edit]

The Brandt-Daroff exercises may be prescribed by the clinician as a home treatment method, usually in conjunction with particle-repositioning maneuvers or in lieu of the particle-repositioning maneuver. The exercise is a form of habituation exercise, designed to allow the patient to become accustomed to the position which causes the vertigo symptoms. The Brandt-Daroff exercises are performed in a similar fashion to the Semont maneuver; however, as the patient rolls onto the unaffected side, the head is rotated toward the affected side.[23] The exercise is typically performed 3 times a day with 5-10 repetitions each time, until symptoms of vertigo have resolved for at least 2 days.[13]

## Roll maneuver [edit]

For the lateral (horizontal) canal, a separate maneuver has been used for productive results. It is unusual for the lateral canal to respond to the canalith repositioning procedure used for the posterior canal BPPV. Treatment is therefore geared towards moving the canalith from the lateral canal into the vestibule.[24] The roll maneuver or its variations are used, and involve rolling the patient 360 degrees in a series of steps to reposition the particles.[2] This maneuver is generally performed by a trained clinician who begins seated at the head of the examination table with the patient supine[25] There are four stages, each a minute apart, and at the third position the horizontal canal is oriented in a vertical position with the patient's neck flexed and on forearm and elbows.[25] When all four stages are completed, the head roll test is repeated, and if negative, treatment ceases.[25]

## Medications [edit]

Medical treatment with anti-vertigo medications may be considered in acute, severe exacerbation of BPPV, but in most cases are not indicated. These primarily include drugs of the anti-histamine and anti-cholinergic class, such as meclizine and hyoscine butylbromide (scopolamine) respectively. The medical management of vestibular syndromes has become increasingly popular over the last decade, and numerous novel drug therapies (including existing drugs with new indications) have emerged for the treatment of vertigo/dizziness syndromes. These drugs vary considerably in their mechanisms of action, with many of

them being receptor- or ion channel-specific. Among them are betahistine or dexamethasone/gentamicin for the treatment of Ménière's disease, carbamazepine/oxcarbazepine for the treatment of paroxysmal dysarthria and ataxia in multiple sclerosis, metoprolol/topiramate or valproic acid/tricyclic antidepressant for the treatment of vestibular migraine, and 4-aminopyridine for the treatment of episodic ataxia type 2 and both downbeat and upbeat nystagmus.[26] These drug therapies offer symptomatic treatment, and do not affect the disease process or resolution rate. Medications may be used to suppress symptoms during the positioning maneuvers if the patient's symptoms are severe and intolerable. More dose-specific studies are required, however, in order to determine the most effective drug(s) for both acute symptom relief and long-term remission of the condition.[26]

### Surgery [edit]

Surgical treatments, such as a semi-circular canal occlusion, do exist for BPPV, but carry the same risk as any neurosurgical procedure. Surgery is reserved as a last resort option for severe and persistent cases which fail vestibular rehabilitation (including particle repositioning and habituation therapy).

## References [edit]


1. ^ *a b c d* "Balance Disorders". *NIDCD*. August 10, 2015. Retrieved 25 July 2016.
2. ^ *a b c d e f g h* Bhattacharyya, N; Baugh, RF; Orvidas, L; Barrs, D; Bronston, LJ; Cass, S; Chalian, AA; Desmond, AL; Earll, JM; Fife, TD; Fuller, DC; Judge, JO; Mann, NR; Rosenfeld, RM; Schuring, LT; Steiner, RW; Whitney, SL; Haidari, J; American Academy of Otolaryngology-Head and Neck Surgery, Foundation (November 2008). "Clinical practice guideline: benign paroxysmal positional vertigo.". *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*. **139** (5 Suppl 4): S47–81. doi:10.1016/j.otohns.2008.08.022. PMID 18973840. Lay summary – *AAO-HNS* (2008-11-01).
3. ^ *a b c d* "Positional vertigo: Overview". *PubMed Health*. 30 January 2014. Retrieved 25 July 2016.
4. ^ *a b c* Dickson, Gretchen (2014). *Primary Care ENT, An Issue of Primary Care: Clinics in Office Practice, Volume 41, Issue 1 of The Clinics: Internal Medicine*. Elsevier Health Sciences. p. 115. ISBN 9780323287173. Retrieved 25 July 2016.
5. ^ *a b c* Hilton, MP; Pinder, DK (8 December 2014). "The Epley (canalith repositioning) manoeuvre for benign paroxysmal positional vertigo.". *The Cochrane database of systematic reviews*. **12**: CD003162. doi:10.1002/14651858.CD003162.pub3. PMID 25485940.
6. ^ Murdin, L; Hussain, K; Schilder, AG (21 June 2016). "Betahistine for symptoms of vertigo.". *The Cochrane database of systematic reviews* (6): CD010696. doi:10.1002/14651858.CD010696.pub2. PMID 27327415.
7. ^ Daroff, Robert B. (2012). "Chapter 37". *Bradley's neurology in clinical practice.* (6th ed.). Philadelphia, PA: Elsevier Saunders. ISBN 9781455728077.
8. ^ *a b* "Benign positional vertigo". *A.D.A.M. Medical Encyclopedia*. Retrieved 16 April 2014.
9. ^ Sammartino, G; Mariniello, M; Scaravilli, MS (2011). "Benign paroxysmal positional vertigo following closed sinus floor elevation procedure: Mallet osteotomes vs. Screwable osteotomes. A triple blind randomized controlled trial". *Clinical oral implants research*. **22** (6): 669–72. doi:10.1111/j.1600-0501.2010.01998.x. PMID 21054553.
10. ^ Kim, MS; Lee, JK; Chang, BS; Um, HS (2010). "Benign paroxysmal positional vertigo as a complication of sinus floor elevation". *Journal of periodontal & implant science*. **40** (2): 86–9. doi:10.5051/jpis.2010.40.2.86. PMC 2872812. PMID 20498765.
11. ^ Lempert, T.; Neuhauser, H. (2009). "Epidemiology of vertigo, migraine and vestibular migraine". *Journal of Neurology*. **256** (3): 333–8. doi:10.1007/s00415-009-0149-2. PMID 19225823.
12. ^ Mayo Clinic Staff (July 10, 2012). "Benign paroxysmal positional vertigo (BPPV)". Retrieved 16 April 2014.
13. ^ *a b c d e* Schubert, M. C. (2007). Vestibular Disorders. In S. O'Sullivan & T. Schmitz (Eds.), *Physical Rehabilitation* (5th ed.) (pp. 999-1029). Philadelphia: F.A. Davis Company.[*page needed*]
14. ^ *a b c* Korres, SG; Balatsouras, DG (2004). "Diagnostic, pathophysiologic, and therapeutic aspects of benign paroxysmal positional vertigo". *Otolaryngology — head and neck surgery : official journal of American Academy of Otolaryngology — Head and Neck Surgery*. **131** (4): 438–44. doi:10.1016/j.otohns.2004.02.046. PMID 15467614.
15. ^ Cohen, HS (2004). "Side-lying as an alternative to the Dix-Hallpike test of the posterior canal". *Otology & Neurotology*. **25** (2): 130–4. doi:10.1097/00129492-200403000-00008. PMID 15021771.
16. ^ Buchholz, D. Heal Your Headache. New York:Workman Publishing;2002:74-75

17. ^ Von Brevern, M (2006). "Short-term efficacy of Epley's maneuver: A double-blind randomised trial". *Journal of Neurology, Neurosurgery & Psychiatry*. **77** (8): 980–982. doi:10.1136/jnnp.2005.085894.
18. ^ [a] [b] Radtke, A.; Von Brevern, M.; Tiel-Wilck, K.; Mainz-Perchalla, A.; Neuhauser, H.; Lempert, T. (2004). "Self-treatment of benign paroxysmal positional vertigo: Semont maneuver vs Epley procedure". *Neurology*. **63** (1): 150–2. doi:10.1212/01.WNL.0000130250.62842.C9. PMID 15249626.
19. ^ Hunt, William T; Zimmermann, Eleanor F; Hilton, Malcolm P (2012). Hilton, Malcolm P, ed. "Cochrane Database of Systematic Reviews". *Reviews*. doi:10.1002/14651858.CD008675.pub2. `|chapter=` ignored (help)
20. ^ Helminski, J. O.; Zee, D. S.; Janssen, I.; Hain, T. C. (2010). "Effectiveness of Particle Repositioning Maneuvers in the Treatment of Benign Paroxysmal Positional Vertigo: A Systematic Review". *Physical Therapy*. **90** (5): 663–78. doi:10.2522/ptj.20090071. PMID 20338918.
21. ^ Beyea, Jason Atkins; Wong, Eric; Bromwich, Matthew; Weston, W Wayne; Fung, Kevin (2008). "Evaluation of a Particle Repositioning Maneuver Web-Based Teaching Module". *The Laryngoscope*. **118** (1): 175–80. doi:10.1097/MLG.0b013e31814b290d. PMID 18251035.
22. ^ Chen Y, Zhuang J, Zhang L, Li Y, Jin Z, Zhao Z, Zhao Y, Zhou H (September 2012). "Short-term efficacy of semont maneuver for benign paroxysmal positional vertigo: a double-blind randomized trial". *Otol Neurotol*. **33** (7): 1127–30. doi:10.1097/mao.0b013e31826352ca.
23. ^ Vesely, DL; Chiou, S; Douglass, MA; McCormick, MT; Rodriguez-Paz, G; Schocken, DD (1996). "Atrial natriuretic peptides negatively and positively modulate circulating endothelin in humans". *Metabolism: clinical and experimental*. **45** (3): 315–9. doi:10.1016/S0026-0495(96)90284-X. PMID 8606637.
24. ^ "<Please add first missing authors to populate metadata.>". *F1000 Medicine Reports*. **2**. doi:10.3410/M2-60.
25. ^ [a] [b] [c] Hornibrook, Jeremy (2011). "Benign Paroxysmal Positional Vertigo (BPPV): History, Pathophysiology, Office Treatment and Future Directions". *International Journal of Otolaryngology*. **2011**: 1–13. doi:10.1155/2011/835671.
26. ^ [a] [b] Huppert, Doreen; Strupp, Michael; Mückter, Harald; Brandt, Thomas (2011). "Which medication do I need to manage dizzy patients?". *Acta Oto-laryngologica*. **131** (3): 228–41. doi:10.3109/00016489.2010.531052. PMID 21142898.


## External links [edit]


- Parnes, LS; Agrawal, SK; Atlas, J (2003). "Diagnosis and management of benign paroxysmal positional vertigo (BPPV)". *CMAJ : Canadian Medical Association [Journal de l'Association medicale canadienne]*. **169** (7): 681–93. PMC 202288. PMID 14517129.
- Huppert, Doreen; Strupp, Michael; Mückter, Harald; Brandt, Thomas (2011). "Which medication do I need to manage dizzy patients?". *Acta Oto-laryngologica*. **131** (3): 228–41. doi:10.3109/00016489.2010.531052. PMID 21142898.
- Solomon, D (2000). "Benign Paroxysmal Positional Vertigo" (PDF). *Current Treatment Options in Neurology*. **2** (5): 417–428. doi:10.1007/s11940-000-0040-z. PMID 11096767.
- "Videos". in Radtke, A.; Von Brevern, M.; Tiel-Wilck, K.; Mainz-Perchalla, A.; Neuhauser, H.; Lempert, T. (2004). "Self-treatment of benign paroxysmal positional vertigo: Semont maneuver vs Epley procedure". *Neurology*. **63** (1): 150–2. doi:10.1212/01.WNL.0000130250.62842.C9. PMID 15249626.



| v · t · e · | Diseases of the ear and mastoid process (H60–H99, 380–389) | | |
|---|---|---|---|
| **Outer ear** | Otitis externa · Otomycosis · | | |
| **Middle ear and mastoid** | Otitis media · Mastoiditis (Bezold's abscess · Gradenigo's syndrome · · Tympanosclerosis · Cholesteatoma · Perforated eardrum · | | |
| **Inner ear and** | **Equilibrioception** | Vertigo/Balance disorder: *peripheral* (Ménière's disease · **BPPV** · Vestibular neuronitis (Labyrinthitis) · Perilymph fistula · · *central* (Central positional nystagmus) · | |
| | **Hearing impairment** | Conductive hearing loss (Otosclerosis · Superior canal dehiscence · · Sensorineural hearing loss (Presbycusis · Cortical deafness · · | |

| | | | |
|---|---|---|---|
| **central pathways** | **Hearing** | | Nonsyndromic deafness · |
| | | **Excessive response** | Tinnitus · Hyperacusis/Phonophobia · |
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Categories: Diseases of inner ear




# Hearing loss

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*"Deaf" redirects here. For other uses, see Deaf (disambiguation).*

**Hearing loss**, also known as **hearing impairment**, is a partial or total inability to hear.[2] A **deaf** person has little to no hearing.[3] Hearing loss may occur in one or both ears.[3] In children hearing problems can affect the ability to learn language and in adults it can cause work related difficulties.[4] In some people, particularly older people, hearing loss can result in loneliness.[3] Hearing loss can be temporary or permanent.

Hearing loss may be caused by a number of factors, including: genetics, ageing, exposure to noise, some infections, birth complications, trauma to the ear, and certain medications or toxins. A common condition that results in hearing loss is chronic ear infections. Certain infections during pregnancy such as syphilis and rubella may also cause hearing loss. Hearing loss is diagnosed when hearing testing finds that a person is unable to hear 25 decibels in at least one ear.[3] Testing for poor hearing is recommended for all newborns.[4] Hearing loss can be categorised as mild, moderate, moderate-severe, severe, or profound.[3] There are three main types of hearing loss, conductive hearing loss, sensorineural hearing loss, and mixed hearing loss.[5]

Half of hearing loss is preventable. This includes by immunization, proper care around pregnancy, avoiding loud noise, and avoiding certain medications.[3] The World Health Organization recommends that young people limit the use of personal audio players to an hour a day in an effort to limit exposure to noise.[6] Early identification and support are particularly important in children. For many hearing aids, sign language, cochlear implants and subtitles are useful. Lip reading is another useful skill some develop. Access to hearing aids, however, is limited in many areas of the world.[5]

As of 2013 hearing loss affects about 1.1 billion people to some degree.[7] It causes disability in 5% (360 to 538 million) and moderate to severe disability in 124 million people.[3][8][9] Of those with moderate to severe disability 108 million live in low and middle income countries.[8] Of those with hearing loss it began in 65 million during childhood.[10] Those who use sign language and are members of Deaf culture see themselves as having a difference rather than an illness.[11] Most members of

**Hearing loss**

**Synonyms** hard of hearing; anakusis or

The international symbol of deafness and hearing loss

| Classification and external resources | |
|---|---|
| **Specialty** | otorhinolaryngology, audiology |
| **ICD-10** | H90–H91 |
| **ICD-9-CM** | 389 |
| **DiseasesDB** | 19942 |
| **MedlinePlus** | 003044 |
| **eMedicine** | article/994159 |
| **MeSH** | D034381 |

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Deaf culture oppose attempts to cure deafness[12][13][14] and some within this community view cochlear implants with concern as they have the potential to eliminate their culture.[15] The term hearing impairment is often viewed negatively as it emphasises what people cannot do.[11]





## Definition [edit]

- Hearing loss exists when there is diminished sensitivity to the sounds normally heard.[10] The terms hearing impaired or hard of hearing are usually reserved for people who have relative insensitivity to sound in the speech frequencies. The severity of a hearing loss is categorized according to the increase

in volume above the usual level necessary before the listener can detect it.

- Deafness is defined as a degree of loss such that a person is unable to understand speech even in the presence of amplification.[10] In profound deafness, even the loudest sounds produced by an audiometer (an instrument used to measure hearing by producing pure tone sounds through a range of frequencies) may not be detected. In total deafness, no sounds at all, regardless of amplification or method of production, are heard.
- Speech perception - Another aspect of hearing involves the perceived clarity of a word rather than the amplitude of sound made by the word. In humans, that aspect is usually measured by tests of speech perception. These tests measure one's ability to understand speech, not to merely detect sound. There are very rare types of hearing loss which affect speech perception alone.[*clarification needed*][16]

Use of the terms "hearing impaired," "deaf-mute," or "deaf and dumb" to describe deaf and hard of hearing people is discouraged by advocacy organizations as they are offensive to many deaf and hard of hearing people.[17]

## Hearing standards [edit]

*See also: Absolute threshold of hearing and Hearing range*
*Further information: Equal-loudness contour and A-weighting*

Human hearing extends in frequency from 20-20,000 Hz, and in amplitude from 0 dB to 130 dB or more. 0 dB does not represent absence of sound, but rather the softest sound an average unimpaired human ear can hear; some people can hear down to -5 or even -10 dB. 130 dB represents the threshold of pain. But the ear doesn't hear all frequencies equally well; hearing sensitivity peaks around 3000 Hz. There are many qualities of human hearing besides frequency range and amplitude that can't easily be measured quantitatively. But for many practical purposes, normative hearing is defined by a frequency versus amplitude graph, or audiogram, charting sensitivity thresholds of hearing at defined frequencies. Because of the cumulative impact of age and exposure to noise and other acoustic insults, 'typical' hearing may not be normative.[18][19]

## Signs and symptoms [edit]

- difficulty using the telephone
- loss of directionality of sound
- difficulty understanding speech, especially of women and children
- difficulty in speech discrimination against background noise (cocktail party effect)
- sounds or speech becoming dull, muffled or attenuated
- need for increased volume on television, radio, music and other audio sources

Hearing loss is sensory, but may have accompanying symptoms:

- pain or pressure in the ears
- a blocked feeling

There may also be accompanying secondary symptoms:

- hyperacusis, heightened sensitivity to certain volumes and frequencies of sound, sometimes resulting from "recruitment"
- tinnitus, ringing, buzzing, hissing or other sounds in the ear when no external sound is present
- vertigo and disequilibrium
- tympanophonia, abnormal hearing of one's own voice and respiratory sounds, usually as a result of a patulous eustachian tube or dehiscent superior semicircular canals
- disturbances of facial movement (indicating possible tumour or stroke)

## Causes [edit]

Hearing loss has multiple causes, including ageing, genetics, perinatal problems and acquired causes like noise and disease. For some kinds of hearing loss the cause may be classified as of unknown cause.

## Age [edit]

There is a progressive loss of ability to hear high frequencies with aging known as presbycusis. For men, this can start as early as 25 and women at 30. Although genetically variable it is a normal concomitant of ageing and is distinct from hearing losses caused by noise exposure, toxins or disease agents.[20] Common conditions that can increase the risk of hearing loss in elderly people are high blood pressure, diabetes or the use of certain medications harmful to the ear.[21] While everyone loses hearing with age, the amount and type of hearing loss is variable.[22]

## Noise [edit]

*Main article: Noise-induced hearing loss*

The examples and perspective in this section **may not represent a worldwide view of the subject**. You may improve this article, discuss the issue on the talk page, or create a new article, as appropriate. *(December 2015) (Learn how and when to remove this template message)*

Noise exposure is the cause of approximately half of all cases of hearing loss, causing some degree of problems in 5% of the population globally.[23] The National Institute for Occupational Safety and Health (NIOSH) recognizes that the majority of hearing loss is not due to age, but due to noise exposure. By correcting for age in assessing hearing, one tends to overestimate the hearing loss due to noise for some and underestimate it for others.[24]

Hearing loss due to noise may be temporary, called a 'temporary threshold shift', a reduced sensitivity to sound over a wide frequency range resulting from exposure to a brief but very loud noise like a gunshot, firecracker, jet engine, jackhammer, etc. or to exposure to loud sound over a few hours such as during a pop concert or nightclub session.[25] Recovery of hearing is usually within 24 hours, but may take up to a week.[26] Both constant exposure to loud sounds (85 dB(A) or above) and one-time exposure to extremely loud sounds (120 dB(A) or above) may cause permanent hearing loss.[27]

Noise-induced hearing loss (NIHL) typically manifests as elevated hearing thresholds (i.e. less sensitivity or muting) between 3000 and 6000 Hz, centered at 4000 Hz. As noise damage progresses, damage spreads to affect lower and higher frequencies. On an audiogram, the resulting configuration has a distinctive notch, called a 'noise' notch. As aging and other effects contribute to higher frequency loss (6–8 kHz on an audiogram), this notch may be obscured and entirely disappear.

Various governmental, industry and standards organizations set noise standards.[28]

The U.S. Environmental Protection Agency has identified the level of 70 dB(A) (40% louder to twice as loud as normal conversation; typical level of TV, radio, stereo; city street noise) for 24 hour exposure as the level necessary to protect the public from hearing loss and other disruptive effects from noise, such as sleep disturbance, stress-related problems, learning detriment, etc.[29] Noise levels are typically in the 65 to 75 dB (A) range for those living near airports of freeways and may result in hearing damage if sufficient time is spent outdoors.[30]

Louder sounds cause damage in a shorter period of time. Estimation of a "safe" duration of exposure is possible using an *exchange rate* of 3 dB. As 3 dB represents a doubling of intensity of sound, duration of exposure must be cut in half to maintain the same energy dose. For workplace noise regulation, the "safe" daily exposure amount at 85 dB A, known as an exposure action value, is 8 hours, while the "safe" exposure at 91 dB(A) is only 2 hours.[31] Different standards use exposure action values between 80dBA and 90dBA. Note that for some people, sound may be damaging at even lower levels than 85 dB A. Exposures to other ototoxins (such as pesticides, some medications including chemotherapy agents, solvents, etc.) can lead to greater susceptibility to noise damage, as well as causing its own damage. This is called a *synergistic* interaction. Since noise damage is cumulative over long periods of time, persons who are exposed to non-workplace noise, like recreational activities or environmental noise, may have compounding damage from all sources.

Some national and international organizations and agencies use an exchange rate of 4 dB or 5 dB.[32] While these exchange rates may indicate a wider zone of comfort or safety, they can significantly underestimate the damage caused by loud noise. For example, at 100 dB (nightclub music level), a 3 dB exchange rate would limit exposure to 15 minutes; the 5 dB exchange rate allows an hour.

Many people are unaware of the presence of environmental sound at damaging levels, or of the level at which sound becomes harmful. Common sources of damaging noise levels include car stereos, children's toys, motor vehicles, crowds, lawn and maintenance equipment, power tools, gun use, musical instruments, and even hair dryers. Noise damage is cumulative; all sources of damage must be considered to assess risk. If one is exposed to loud sound (including music) at high levels or for extended durations (85 dB A or greater), then hearing loss will occur. Sound intensity (sound energy, or propensity to cause damage to the ears) increases dramatically with proximity according to an inverse square law: halving the distance to the sound quadruples the sound intensity.

In the USA, 12.5% of children aged 6–19 years have permanent hearing damage from excessive noise exposure.[33] The World Health Organization estimates that half of those between 12 and 35 are at risk from using personal audio devices that are too loud.[6]

Hearing loss due to noise has been described as primarily a condition of modern society.[34] In preindustrial times, humans had far less exposure to loud sounds. Studies of primitive peoples indicate that much of what has been attributed to age-related hearing loss may be long term cumulative damage from all sources, especially noise. People living in preindustrial societies have considerably less hearing loss than similar populations living in modern society. Among primitive people who have migrated into modern society, hearing loss is proportional to the number of years spent in modern society.[35][36][37] Military service in World War II, the Korean War, and the Vietnam War, has likely also caused hearing loss in large numbers of men from those generations, though proving that hearing loss was a direct result of military service is problematic without entry and exit audiograms.[38]

Hearing loss in adolescents may be caused by loud noise from toys, music by headphones, and concerts or events.[39]

## Genetic [edit]

Hearing loss can be inherited. Around 75–80% of all these cases are inherited by recessive genes, 20–25% are inherited by dominant genes, 1–2% are inherited by X-linked patterns, and fewer than 1% are inherited by mitochondrial inheritance.[40]

When looking at the genetics of deafness, there are 2 different forms, syndromic and nonsyndromic. Syndromic deafness occurs when there are other signs or medical problems aside from deafness in an individual. This accounts for around 30% of deaf individuals who are deaf from a genetic standpoint.[40] Nonsyndromic deafness occurs when there are no other signs or medical problems associated with an individual other than deafness. From a genetic standpoint, this accounts for the other 70% of cases, and represents the majority of hereditary hearing loss.[40] Syndromic cases occur with diseases such as Usher syndrome, Stickler syndrome, Waardenburg syndrome, Alport's syndrome, and neurofibromatosis type 2. These are diseases that have deafness as one of the symptoms or as a common feature associated with it. Many of the genetic mutations giving rise to syndromic deafness have been identified. In nonsyndromic cases, where deafness is the only finding, it is more difficult to identify the genetic mutation although some have been discovered.

- Recent gene mapping has identified several nonsyndromic dominant (DFNA#) and recessive (DFNB#) forms of deafness. The first gene mapped for non-syndromic deafness, DFNA1, involves a splice site mutation in the formin related homolog diaphanous 1 (DIAPH1). A single base change in a large Costa Rican family was identified as causative in a rare form of low frequency onset progressive hearing loss with autosomal dominant inheritance exhibiting variable age of onset and complete penetrance by age 30.[41] The most common type of congenital hearing loss in developed countries is DFNB1, also known as connexin 26 deafness or GJB2-related deafness.
- The most common dominant syndromic forms of hearing loss include Stickler syndrome and Waardenburg syndrome.

- The most common recessive syndromic forms of hearing loss are Pendred syndrome and Usher syndrome.
- The congenital defect microtia, deformed or unformed outer ear, can be associated with partial or complete conductive deafness, depending upon the severity of the deformity and whether the middle ear is also affected. It can also be associated with abnormalities of the inner ear giving rise to an additional sensorineural component to the hearing loss (mixed deafness).
- Mutations in PTPRQ are a cause of autosomal-recessive nonsyndromic hearing loss.[42]

## Perinatal problems [edit]

- Fetal alcohol spectrum disorders are reported to cause hearing loss in up to 64% of infants born to alcoholic mothers, from the ototoxic effect on the developing fetus plus malnutrition during pregnancy from the excess alcohol intake.
- Premature birth can be associated with sensorineural hearing loss because of an increased risk of hypoxia, hyperbilirubinaemia, ototoxic medication and infection as well as noise exposure in the neonatal units. The risk of hearing loss is greatest for those weighing less than 1500 g at birth.

## Disorders [edit]

- strokes - Depending on what blood vessels are affected by the stroke, one of the symptoms can be deafness.
- multiple sclerosis can have an effect on hearing as well. Multiple sclerosis, or MS, is an autoimmune disease where the immune system attacks the myelin sheath, a covering that protects the nerves. If the auditory nerve becomes damaged, the affected person will become completely deaf in one or both ears. There is no cure for MS.
- perilymph fistula - a microtear in either the round or oval window (membranes separating the middle and inner ear) of the cochlea causing perilymph to leak into the middle ear. This usually occurs as a consequence of trauma, including barotrauma, and can give rise to vertigo as well as hearing loss.
- viral - viral infections of the ear can cause sensorineural hearing loss usually as the consequence of a labyrinthitis. The patient may be generally unwell at the time.
  - Measles may cause auditory nerve damage but usually gives rise to a chronic middle ear problem giving rise to a mixed hearing loss.
  - Mumps (Epidemic parotitis) may result in profound sensorineural hearing loss (90 dB or more), unilateral (one ear) or bilateral (both ears).
  - congenital rubella (also called German measles) syndrome, can cause deafness in newborns
  - several varieties of herpes viruses that cause other diseases can also infect the ear, and can result in hearing loss: congenital infection with cytomegalovirus is responsible for deafness in newborn children and also progressive sensorineural hearing loss in childhood; herpes simplex type 1, oral herpes associated with cold sores; Epstein Barr virus that causes mononucleosis; varicella zoster oticus that causes facial paralysis (Ramsay Hunt syndrome)[43]
  - People with HIV/AIDS may develop hearing problems due to medications they take for the disease, the HIV virus, or due to an increased rate of other infections.[44]
  - West Nile virus, which can cause a variety of neurological disorders, can also cause hearing loss by attacking the auditory nerve
- Meningitis may damage the auditory nerve or the cochlea.
- Syphilis is commonly transmitted from pregnant women to their fetuses, and about a third of infected children will eventually become deaf.
- inherited
  - People with Down syndrome are more likely to have hearing loss.[45] This is usually due to middle ear effusions in childhood but towards the end of the second decade they may develop a high frequency sensorineural hearing loss which can get progressively worse with time.
  - Charcot–Marie–Tooth disease variant 1E (CMT1E) is noted for demyelinating in addition to deafness.[46]
  - Autoimmune disease is recognized as a cause for cochlear damage. Although rare, it is possible for autoimmune processes to target the cochlea specifically as a first presentation. Granulomatosis with

polyangiitis is one of the autoimmune conditions that may precipitate hearing loss. Cogan's syndrome commonly presents with hearing loss.
- Otosclerosis is a condition that can cause fixation of the stapes (or stirrup) in the middle ear preventing its movement and causing a conductive hearing loss.
- Vestibular schwannoma, erroneously known as Acoustic neuromas, and other types of brain tumors can cause hearing loss by infringement of the tumor on the vestibulocochlear nerve
- Congenital problems
  - Superior semicircular canal dehiscence, a gap in the bone cover above the inner ear, can lead to low-frequency conductive hearing loss, autophony and vertigo.
- recurring ear infections or concommitant secondary infections (such as bacterial infection subsequent to viral infection) can result in hearing loss

## Medications [edit]

Some medications may reversibly affect hearing. These medications are considered ototoxic. This includes loop diuretics such as furosemide and bumetanide, non-steroidal anti-inflammatory drugs (NSAIDs) both over-the-counter (aspirin, ibuprofen, naproxen) as well as prescription (celecoxib, diclofenac, etc.), paracetamol, quinine, and macrolide antibiotics. The link between NSAIDs and hearing loss tends to be greater in women, especially those who take ibuprofen six or more times a week.[47] Others may cause permanent hearing loss.[48] The most important group is the aminoglycosides (main member gentamicin) and platinum based chemotherapeutics such as cisplatin and carboplatin.[*medical citation needed*]

On October 18, 2007, the U.S. Food and Drug Administration (FDA) announced that a warning about possible sudden hearing loss would be added to drug labels of PDE5 inhibitors, which are used for erectile dysfunction.[49]

## Chemicals [edit]

*Main article: Ototoxicity*

In addition to medications, hearing loss can also result from specific chemicals: metals, such as lead; solvents, such as toluene (found in crude oil, gasoline[50] and automobile exhaust,[50] for example); and asphyxiants.[51] Combined with noise, these ototoxic chemicals have an additive effect on a person's hearing loss.[51]

Hearing loss due to chemicals starts in the high frequency range and is irreversible. It damages the cochlea with lesions and degrades central portions of the auditory system.[51] For some ototoxic chemical exposures, particularly styrene,[52] the risk of hearing loss can be higher than being exposed to noise alone.

- Solvents
  - toluene, styrene, xylene, *n*-hexane, ethyl benzene, white spirits/Stoddard, carbon disulfide, jet fuel, perchloroethylene, trichloroethylene, *p*-xylene[53]
- Asphyxiants
  - carbon monoxide, hydrogen cyanide
- Heavy metals
  - lead, mercury, cadmium, arsenic, tin-hydrocarbon compounds (trimethyltin)
- Pesticides and herbicides - The evidence is weak regarding association between herbicides and hearing loss; hearing loss in such circumstances may be due to concommitant exposure to insecticides.
  - paraquat, organophosphates

## Physical trauma [edit]

There can be damage either to the ear itself or to the brain centers that process the aural information conveyed by the ears. People who sustain head injury are especially vulnerable to hearing loss or tinnitus, either temporary or permanent.[54][55]

# Pathophysiology [edit]

From a neurobiological perspective, there are three reasons that could cause a person to have hearing loss: either there is something wrong with the mechanical portion of the process, meaning the conductive portions of the ear (external and middle ear), or there is something wrong with the sensory portion of the process (inner ear or cochlea and related structures) or there is something wrong with the neural portion of the process, meaning the nerves or brain.

The process of understanding how sound travels to the brain is imperative in understanding how and why disease can cause a person to develop hearing loss. The process is as follows: sound waves are transmitted to the outer ear, sound waves are conducted down to ear canal, bringing the sound waves to the eardrum which they cause to vibrate, these vibrations are now passed through the 3 tiny ear bones in the middle ear, which transfer the vibrations to the fluid in the inner ear, the fluid moves the hair cells, the movement of the hair cells cause the vibrations to be converted into nerve impulses, the nerve impulses are taken to the brain by the auditory nerve,[56] the auditory nerve takes the impulses to the medulla oblongata, the brainstem send the impulses to the midbrain, which finally goes to the auditory cortex of the temporal lobe to be interpreted as sound.[57]

This process is complex and involves several steps that depend on the previous step in order for the vibrations or nerve impulses to be passed on. This is why if anything goes wrong at either the mechanical or neural portion of the process, it could result in sound not being processed by the brain, hence, leading to hearing loss.

Lesions to the auditory association cortex produced by physical trauma can result in deafness and other problems in auditory perception. The place where the lesion occurs on the auditory cortex plays an important role in what type of hearing deficit will occur in a person. A study conducted by Clarke et al. (2000) tested three subjects for the ability to identify a produced environmental sound, the source of the sound, and whether or not the source is moving. All three subjects had trauma to different parts of the auditory cortex, and each patient demonstrated a different set of auditory deficits, suggesting that different parts of the auditory cortex controlled different parts of the hearing process.[58] This means, lesion one part of auditory cortex and it could result in one or two deficits.[*clarification needed*] It would take larger lesions at the right parts to produce deafness.

# Diagnosis [edit]

Identification of a hearing loss is usually conducted by a general practitioner medical doctor, otolaryngologist, certified and licensed audiologist, school or industrial audiometrist, or other audiology technician. Diagnosis of the cause of a hearing loss is carried out by a specialist physician (audiovestibular physician) or otorhinolaryngologist

An audiologist conducting an audiometric hearing test in a sound-proof testing booth

## Case history [edit]

A case history (usually a written form, with questionnaire) can provide valuable information about the context of the hearing loss, and indicate what kind of diagnostic procedures to employ. Case history will include such items as:

- major concern
- birth and pregnancy information
- medical history
- development history
- family history
- workplace environment
- home environment

## Examination [edit]

- otoscopy, visual examination of the outer ear, ear canal, eardrum, and middle ear (through the translucent eardrum) using an optical instrument inserted into the ear canal called an otoscope
- tympanometry
- differential testing - the Weber, Rinne, Bing and Schwabach tests are simple manual tests of auditory function conducted with a low frequency (usually 512 Hz) tuning fork that can provide a quick indication of type of hearing loss: unilateral/bilateral, conductive, or other

## Laboratory testing [edit]

In case of infection or inflammation, blood or other body fluids may be submitted for laboratory analysis.

## Hearing tests [edit]

*See also: Audiometry, Pure tone audiometry, Auditory brainstem response, and Otoacoustic emissions*

Hearing loss is generally measured by playing generated or recorded sounds, and determining whether the person can hear them. Hearing sensitivity varies according to the frequency of sounds. To take this into account, hearing sensitivity can be measured for a range of frequencies and plotted on an audiogram.

Another method for quantifying hearing loss is a speech-in-noise test. As the name implies, a speech-in-noise test gives an indication of how well one can understand speech in a noisy environment. A person with a hearing loss will often be less able to understand speech, especially in noisy conditions. This is especially true for people who have a sensorineural loss – which is by far the most common type of hearing loss. As such, speech-in-noise tests can provide valuable information about a person's hearing ability, and can be used to detect the presence of a sensorineural hearing loss. A recently developed digit-triple speech-in-noise test may be a more efficient screening test.[59]

Otoacoustic emissions test is an objective hearing test that may be administered to toddlers and children too young to cooperate in a conventional hearing test. The test is also useful in older children and adults.

Auditory brainstem response testing is an electrophysiological test used to test for hearing deficits caused by pathology within the ear, the cochlear nerve and also within the brainstem. This test can be used to identify delay in the conduction of neural impulses due to tumours or inflammation but can also be an objective test of hearing thresholds. Other electophysiological tests, such as cortical evoked responses, can look at the hearing pathway up to the level of the auditory cortex.

## Scans [edit]

MRI and CT scans can be useful to identify the pathology of many causes of hearing loss. They are only needed in selected cases.

## Classification [edit]

Hearing loss is categorized by type, severity, and configuration. Furthermore, a hearing loss may exist in only one ear (unilateral) or in both ears (bilateral). Hearing loss can be temporary or permanent, sudden or progressive.

## Severity [edit]

The severity of a hearing loss is ranked according to the additional intensity above a nominal threshold that a sound must be before being detected by an individual; it is measured in decibels of hearing loss, or dB HL. Hearing loss may be ranked as slight, mild, moderate, moderately severe, severe or profound as defined below:[*medical citation needed*]

- Slight: between 16 and 25 dB HL
- Mild:
  - for adults: between 26 and 40 dB HL

    - for children: between 20 and 40 dB HL[10]
- Moderate: between 41 and 54 dB HL[10]
- Moderately severe: between 55 and 70 dB HL[10]
- Severe: between 71 and 90 dB HL[10]
- Profound: 91 dB HL or greater[10]
- Totally deaf: Have no hearing at all. This is called *anacusis*.

Hearing loss may affect one or both ears. If both ears are affected, then one ear may be more affected than the other. Thus it is possible, for example, to have normal hearing in one ear and none at all in the other, or to have mild hearing loss in one ear and moderate hearing loss in the other.

For certain legal purposes such as insurance claims, hearing loss is described in terms of percentages. Given that hearing loss can vary by frequency and that audiograms are plotted with a logarithmic scale, the idea of a percentage of hearing loss is somewhat arbitrary, but where decibels of loss are converted via a legally recognized formula, it is possible to calculate a standardized "percentage of hearing loss", which is suitable for legal purposes only.

## Type [edit]

There are four main types of hearing loss, conductive hearing loss, sensorineural hearing loss, central deafness and combinations of conductive and sensorienural hearing losses which is called mixed hearing loss.[10] An additional problem which is increasingly recognised is auditory processing disorder which is not a hearing loss as such but a difficulty perceiving sound.

- Conductive hearing loss

Conductive hearing loss is present when the sound is not reaching the inner ear, the cochlea. This can be due to external ear canal malformation, dysfunction of the eardrum or malfunction of the bones of the middle ear. The ear drum may show defects from small to total resulting in hearing loss of different degree. Scar tissue after ear infections may also make the ear drum dysfunction as well as when it is retracted and adherent to the medial part of the middle ear.

Dysfunction of the three small bones of the middle ear – malleus, incus, and stapes – may cause conductive hearing loss. The mobility of the ossicles may be impaired for different reasons and disruption of the ossicular chain due to trauma, infection or ankylosis may also cause hearing loss.

- Sensorineural hearing loss

Sensorineural hearing loss is one caused by dysfunction of the inner ear, the cochlea or the nerve that transmits the impulses from the cochlea to the hearing centre in the brain. The most common reason for sensorineural hearing loss is damage to the hair cells in the cochlea. Depending on the definition it could be estimated that more than 50% of the population over the age of 70 has impaired hearing.[60]

- Central deafness

Damage to the brain can lead to a central deafness. The peripheral ear and the auditory nerve may function well but the central connections are damaged by tumour, trauma or other disease and the patient is unable to hear.

- Mixed hearing loss

Mixed hearing loss is a combination of conductive and sensorineural hearing loss. Chronic ear infection (a fairly common diagnosis) can cause a defective ear drum or middle-ear ossicle damages, or both. In addition to the conductive loss, a sensory component may be present.

- Central auditory processing disorder

This is not an actual hearing loss but gives rise to significant difficulties in hearing. One kind of auditory processing disorder is King-Kopetzky syndrome, which is characterized by an inability to process out background noise in noisy environments despite normal performance on traditional hearing tests.

## Configuration [edit]

The shape of an audiogram shows the relative configuration of the hearing loss, such as a Carhart notch for otosclerosis, 'noise' notch for noise-induced damage, high frequency rolloff for presbycusis, or a flat audiogram for conductive hearing loss. In conjunction with speech audiometry, it may indicate central auditory processing disorder, or the presence of a schwannoma or other tumor. There are four general configurations of hearing loss:

1. Flat: thresholds essentially equal across test frequencies.

2. Sloping: lower (better) thresholds in low-frequency regions and higher (poorer) thresholds in high-frequency regions.

3. Rising: higher (poorer) thresholds in low-frequency regions and lower (better) thresholds in higher-frequency regions.

4. Trough-shaped ("cookie-bite" or "U" shaped): greatest hearing loss in the mid-frequency range, with lower (better) thresholds in low- and high-frequency regions.

### Unilateral and bilateral [edit]

People with unilateral hearing loss or single-sided deafness (SSD) have difficulty in:

- hearing conversation on their impaired side
- localizing sound
- understanding speech in the presence of background noise.

In quiet conditions, speech discrimination is approximately the same for normal hearing and those with unilateral deafness; however, in noisy environments speech discrimination varies individually and ranges from mild to severe.

One reason for the hearing problems these patients often experience is due to the head shadow effect. Newborn children with no hearing on one side but one normal ear could still have problems.[61] Speech development could be delayed and difficulties to concentrate in school are common. More children with unilateral hearing loss have to repeat classes than their peers. Taking part in social activities could be a problem. Early aiding is therefore of utmost importance.[62][63]

## Prevention [edit]

It is estimated that half of cases of hearing loss are preventable.[64] A number of preventative strategies are effective including: immunisation against rubella to prevent congenital rubella syndrome, immunization against *H. influenza* and *S. pneumoniae* to reduce cases of meningitis, and avoiding or protecting against excessive noise exposure.[10] The World Health Organization also recommends immunization against measles, mumps, and meningitis, efforts to prevent premature birth, and avoidance of certain medication as prevention.[65]

The use of antioxidants is being studied for the prevention of noise-induced hearing loss.[66]

### Hearing protectors [edit]

Education regarding noise exposure increases the use of hearing protectors.[67]

### Workplace noise regulation [edit]

Noise is widely recognized as an occupational hazard. In the United States, the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) work together to provide standards and enforcement on workplace noise levels.[68][69] The hierarchy of hazard controls demonstrates the different levels of controls to reduce or eliminate exposure to noise and prevent hearing loss, including engineering controls and personal protective equipment (PPE).[70] Other programs and initiative have been created to prevent hearing loss in the workplace. For example, the Safe-in-Sound Award was created to recognize organizations with successful noise control implementations.[71]

Additionally, the Buy Quiet program was created to encourage employers to purchase quieter machinery and tools.[72] By purchasing less noisy power tools like those found on the NIOSH Power Tools Database and limiting exposure to ototoxic chemicals, great strides can be made in preventing hearing loss.[73]

Companies can also provide personal hearing protector devices tailored to both the worker and type of employment. Some hearing protectors universally block out all noise, and some allow for certain noises to be heard. Workers are more likely to wear hearing protector devices when they are properly fitted.[74]

Better enforcement of laws can decrease levels of noise at work.[75]

### Screening [edit]

The United States Preventive Services Task Force recommends screening for all newborns.[4]

The American Academy of Pediatrics advises that children should have their hearing tested several times throughout their schooling:[33]

- When they enter school
- At ages 6, 8, and 10
- At least once during middle school
- At least once during high school

There is not enough evidence to determine the utility of screening in adults over 50 years old who do not have any symptoms.[76]

## Treatment [edit]

Treatment depends on the specific cause if known as well as the extent, type and configuration of the hearing loss. Most hearing loss, that resulting from age and noise, is progressive and irreversible, and there are currently no approved or recommended treatments; management is by hearing aid. A few specific kinds of hearing loss are amenable to surgical treatment. In other cases, treatment is addressed to underlying pathologies, but any hearing loss incurred may be permanent.

There are a number of devices that can improve hearing in those who are deaf or hard of hearing or allow people with these conditions to manage better in their lives.

### Hearing aids [edit]

Hearing aids are devices that work to improve the hearing and speech comprehension of those with hearing loss.[77] It works by magnifying the sound vibrations in the ear so that one can understand what is being said around them.[77] The use of this technological device may or may not have an effect on one's sociability. Some people feel as if they cannot live without one because they say it is the only thing that keeps them engaged with the public. Others dislike hearing aids very much because they feel wearing them is embarrassing or weird. Due to their low-esteem, they avoid hearing aid usage altogether and would rather remain quiet and to themselves in a social environment.[78]

### Assistive devices [edit]

Many deaf and hard of hearing individuals use assistive devices in their daily lives:

- Individuals can communicate by telephone using telephone typewriters (TTY). Other common names are textphone, minicom and telecommunications device for the deaf (TDD). These devices look like typewriters or word processors and transmit typed text over regular telephone lines. This allows communication through visual messaging. TTYs can transmit messages to individuals who don't have TTY by using the National Relay service which is an operator that acts as a messenger to each caller.[79] For mobile phones, software apps are available to provide TDD/textphone functionality on some carriers/models to provide 2-way communications.
- There are several new telecommunications relay service technologies including IP Relay and captioned

telephone technologies. A deaf or hard of hearing person can communicate over the phone with a hearing person via a human translator. Phone captioning is a service in which a hearing person's speech is captioned by a third party, enabling a deaf or hard of hearing person to conduct a conversation with a hearing person over the phone.[80] Wireless, Internet and mobile phone/SMS text messaging are beginning to take over the role of the TDD.
- Real-time text technologies, involving streaming text that is continuously transmitted as it is typed or otherwise composed. This allows conversational use of text. Software programs are now available that automatically generate a closed-captioning of conversations. Examples include discussions in conference rooms, teleconference calls, classroom lectures, and/or religious services.
- Instant messaging software.
- Videophones and similar video technologies can be used for distance communication using sign language. Video conferencing technologies permit signed conversations as well as permitting a sign language–English interpreter to voice and sign conversations between a deaf or hard of hearing person and that person's hearing party, negating the use of a TTY device or computer keyboard.
- Video relay service and video remote interpreting (VRI) services also use a third-party telecommunication service to allow a deaf or hard-of-hearing person to communicate quickly and conveniently with a hearing person, through a sign language interpreter.
- Hearing dogs are a specific type of assistance dog specifically selected and trained to assist the deaf and hard of hearing by alerting their handler to important sounds, such as doorbells, smoke alarms, ringing telephones, or alarm clocks.
- The advent of the Internet's World Wide Web and closed captioning has given the deaf and hard of hearing unprecedented access to information. Electronic mail and online chat have reduced the need for deaf and hard-of-hearing people to use a third-party Telecommunications Relay Service to communicate with the hearing and other deaf people.
- A person with hearing loss cannot always hear the phone or distinguish their own ringtone from another. A signalling transmitter can be attached to a phone that will cause a light or a vibration device to activate. Transmitters can also be used to activate visuals cues to represent fire alarms.[79]
- Individuals with hearing loss require phones with amplifiers that have a higher power of amplification when compared to a regular phone. The Hearing Aid Telephone Interconnect System is a hands free amplification system which allows people to amplify sound when using telephones, cell phones, computer and pay phones by way of the attachment of a portable unit.[79]

## Wireless hearing aids [edit]

A wireless device has two main components: a transmitter and a receiver. The transmitter broadcasts the captured sound, and the receiver detects the broadcast audio and enables the incoming audio stream to be connected to accommodations such as hearing aids or captioning systems.

Three types of wireless systems are commonly used: FM, audio induction loop, and InfraRed. Each system has advantages and benefits for particular uses. FM systems can be battery operated or plugged into an electrical outlet. FM system produce an analog audio signal, meaning they have extremely high fidelity. Many FM systems are very small in size, allowing them to be used in mobile situations. The audio induction loop permits the listener with hearing loss to be free of wearing a receiver provided that the listener has a hearing aid or cochlear implant processor with an accessory called a "telecoil". If the listener does not have a telecoil, then he or she must carry a receiver with an earpiece. As with FM systems, the infrared (IR) system also requires a receiver to be worn or carried by the listener. An advantage of IR wireless systems is that people in adjoining rooms cannot listen in on conversations, making it useful for situations where privacy and confidentiality are required. Another way to achieve confidentiality is to use a hardwired amplifier, which contains or is connected to a microphone and transmits no signal beyond the earpiece plugged directly into it.[81]

## Surgical [edit]

There is no treatment surgical or otherwise for hearing lost due to the most common causes (age, noise and genetic defects). For a few specific conditions, surgical intervention can provide a remedy:

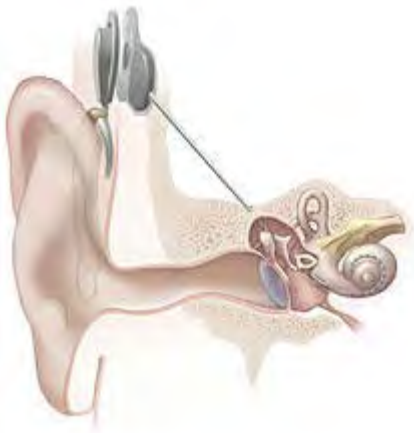


Illustration of a cochlear implant

- surgical correction of superior canal dehiscence
- myringotomy, surgical insertion of drainage ventilation tubes in the tympanic membrane. Such placement is usually temporary until the underlying pathology (infection or other inflammation) can be resolved.
- radiotherapy or surgical excision of vestibular schwannoma or acoustic neuroma, though, in most cases, it is unlikely that hearing will be preserved
- Stapedectomy and stapedotomy for otosclerosis - replacement or reshaping of the stapes bone of the middle ear can restore hearing in cases of conductive hearing loss

Surgical and implantable hearing aids are an alternative to conventional external hearing aids. If the ear is dry and not infected, an air conduction aid could be tried; if the ear is draining, a direct bone condition hearing aid is often the best solution. If the conductive part of the hearing loss is more than 30–35 dB, an air conduction device could have problems overcoming this gap. A bone-anchored hearing aid could, in this situation, be a good option. The active bone conduction hearing implant Bonebridge is also an option. This implant is invisible under the intact skin and therefore minimises the risk of skin irritations.[63]

Cochlear implants improve outcomes in people with hearing loss in either one or both ears.[82] They work by artificial stimulation of the cochlear nerve by providing an electric impulse substitution for the firing of hair cells. They are expensive, and require programming along with extensive training for effectiveness.

Cochlear implants as well as bone conduction implants can help with single sided deafness. Middle ear implants or bone conduction implants can help with conductive hearing loss.[63]

People with cochlear implants are at a higher risk for bacterial meningitis. Thus, meningitis vaccination is recommended.[83] People who have hearing loss, especially those who develop a hearing problem in childhood or old age, may need support and technical adaptations as part of the rehabilitation process. Recent research shows variations in efficacy but some studies[84] show that if implanted at a very young age, some profoundly impaired children can acquire effective hearing and speech, particularly if supported by appropriate rehabilitation.

## Classroom [edit]

For a classroom setting, children with hearing loss often benefit from direct instruction and communication. One option for students is to attend a school for the Deaf, where they will have access to the language, communication, and education. Another option is to have the child attend a mainstream program, with special accommodation such as providing favorable seating for the child. Having the student sit as close to the teacher as possible improves the student's ability to hear the teacher's voice and to more easily read the teacher's lips. When lecturing, teachers can help the student by facing them and by limiting unnecessary noise in the classroom. In particular, the teacher can avoid talking when their back is turned to the classroom, such as while writing on a whiteboard.

Some other approaches for classroom accommodations include pairing deaf or hard of hearing students with hearing students. This allows the deaf or hard of hearing student to ask the hearing student questions about concepts that they have not understood. The use of CART (Communication Access Real Time) systems, where an individual types a captioning of what the teacher is saying, is also beneficial.[85] The student views this captioning on their computer. Automated captioning systems are also becoming a popular option.[86] In an automated system, software, instead of a person, is used to generate the captioning. Unlike CART systems, automated systems generally do not require an Internet connection and thus they can be used anywhere and anytime. Another advantage of automated systems over CART is that they are much lower in cost. However, automated systems are generally designed to only transcribe what

the teacher is saying and to not transcribe what other students say. An automated system works best for situations where just the teacher is speaking, whereas a CART system will be preferred for situations where there is a lot of classroom discussion.

For those students who are completely deaf, one of the most common interventions is having the child communicate with others through an interpreter using sign language.[87]

## Epidemiology [edit]

Globally hearing loss affects about 10% of the population to some degree.[23] It caused moderate to severe disability in 124.2 million people as of 2004 (107.9 million of whom are in low and middle income countries).[8] Of these 65 million acquired the condition during childhood.[10] At birth ~3 per 1000 in developed countries and more than 6 per 1000 in developing countries have hearing problems.[10]

Hearing loss increases with age. In those between 20 and 35 rates of hearing loss are 3% while in those 44 to 55 it is 11% and in those 65 to 85 it is 43%.[4]

Disability-adjusted life year for hearing loss (adult onset) per 100,000 inhabitants in 2004.

| | |
|---|---|
| no data | 475–520 |
| <250 | 520–565 |
| 250–295 | 565–610 |
| 295–340 | 610–655 |
| 340–385 | 655–700 |
| 385–430 | >700 |
| 430–475 | |

## History [edit]

*See also: History of deaf education in the United States*

Abbé Charles-Michel de l'Épée opened the first school for the deaf in Paris at the deaf school. The American Thomas Gallaudet witnessed a demonstration of deaf teaching skills from Épée's successor Abbé Sicard and two of the school's deaf faculty members, Laurent Clerc and Jean Massieu; accompanied by Clerc, he returned to the United States, where in 1817 they founded American School for the Deaf in Hartford, Connecticut. American Sign Language (ASL) started to evolve from primarily French Sign Language (LSF), and other outside influences.[88]

## Society and culture [edit]

*See also: Deaf culture*

### After language [edit]

*Main article: Post-lingual deafness*

*Post-lingual deafness* is hearing loss that is sustained after the acquisition of language, which can occur due to disease, trauma, or as a side-effect of a medicine. Typically, hearing loss is gradual and often detected by family and friends of affected individuals long before the patients themselves will acknowledge the disability.[*citation needed*] Post-lingual deafness is far more common than pre-lingual deafness. Those who lose their hearing later in life, such as in late adolescence or adulthood, face their own challenges, living with the adaptations that allow them to live independently.

### Before language [edit]

*Main article: Prelingual deafness*

*Prelingual deafness* is hearing loss that is sustained before the acquisition of language, which can occur due to a congenital condition or through hearing loss in early infancy. Prelingual deafness impairs an individual's ability to acquire a *spoken* language. Children born into signing families rarely have delays in language

development, but most prelingual hearing loss is acquired via either disease or trauma rather than genetically inherited, so families with deaf children nearly always lack previous experience with sign language. Cochlear implants allow prelingually deaf children to acquire an oral language with remarkable success if implantation is performed within the first 2–4 years.[89]

Jack Gannon, a professor at Gallaudet University, said this about Deaf culture. "Deaf culture is a set of learned behaviors and perceptions that shape the values and norms of deaf people based on their shared or common experiences." Some doctors believe that being deaf makes a person more social. Bill Vicar, from ASL University, shared his experiences as a deaf person, "[deaf people] tend to congregate around the kitchen table rather than the living room sofa… our good-byes take nearly forever, and our hellos often consist of serious hugs. When two of us meet for the first time we tend to exchange detailed biographies."[90] Deaf culture is not about contemplating what deaf people cannot do and how to fix their problems, an approach known as the "pathological view of the deaf."[91] Instead deaf people celebrate what they can do. There is a strong sense of unity between deaf people as they share their experiences of suffering through a similar struggle. This celebration creates a unity between even deaf strangers. Bill Vicars expresses the power of this bond when stating, "if given the chance to become hearing most [deaf people] would choose to remain deaf."[92]

## Views of treatments [edit]

There has been considerable controversy within the culturally deaf community over cochlear implants. For the most part, there is little objection to those who lost their hearing later in life, or culturally deaf adults choosing to be fitted with a cochlear implant.[15]

Many in the deaf community strongly object to a deaf child being fitted with a cochlear implant (often on the advice of an audiologist); new parents may not have sufficient information on raising deaf children and placed in an oral-only program that emphasizes the ability to speak and listen over other forms of communication such as sign language or total communication. Many Deaf people view cochlear implants and other hearing devices as confusing to one's identity. A Deaf person will never be a hearing person and therefore would be trying to fit into a way of living that is not their own. Other concerns include loss of Deaf culture and identity and limitations on hearing restoration.[15]

The U.S. National Association of the Deaf has a statement on its website regarding cochlear implants.[93] The NAD asserts that the choice to implant is up to the individual (or the parents), yet strongly advocates a fully informed decision in all aspects of a cochlear implant. Much of the negative reaction to cochlear implants stems from the medical viewpoint that deafness is a condition that needs to be "cured," while the Deaf community instead regards deafness a defining cultural characteristic.

Many other assistive devices are more acceptable to the Deaf community, including but not limited to, hearing aids, closed captioning, email and the Internet, text telephones, and video relay services.

## Sign language [edit]

*Main article: Sign language*

Sign languages convey meaning through manual communication and body language instead of acoustically conveyed sound patterns. This involves the simultaneous combination of hand shapes, orientation and movement of the hands, arms or body, and facial expressions to express a speaker's thoughts. "Sign languages are based on the idea that vision is the most useful tool a deaf person has to communicate and receive information".[94]

## Government policies [edit]

The examples and perspective in this section **deal primarily with the United States and do not represent a worldwide view of the subject**. You may improve this article, discuss the issue on the talk page, or create a new article, as appropriate. *(December 2012) (Learn how and when to remove this template message)*

Those who are deaf (by either state or federal standards) have access to a free and appropriate public education. If a child does qualify as being deaf or hard of hearing and receives an individualized education plan, the IEP team must consider, "the child's language and communication needs. The IEP must include opportunities for direct communication with peers and professionals. It must also include the student's academic level, and finally must include the students full range of needs"[95][96]

In part, the Department of Education defines deafness as "... a hearing impairment that is so severe that the child is impaired in processing linguistic information through hearing, with or without amplification ...." Hearing impairment is defined as "... an impairment in hearing, whether permanent or fluctuating, that adversely affects a child's educational performance but that is not included under the definition of deafness ...."[97]

Texas School for the Deaf

## Inclusion versus pullout [edit]

The examples and perspective in this article **may not represent a worldwide view of the subject**. You may improve this article, discuss the issue on the talk page, or create a new article, as appropriate. *(November 2014) (Learn how and when to remove this template message)*

It is commonly misunderstood that least restrictive environment means mainstreaming or inclusion. Sometimes the resources available at the public schools do not match up to the resources at a residential school for the deaf. Many hearing parents choose to have their deaf child educated in the general education classroom as much as possible because they are told that mainstreaming is the least restrictive environment, which is not always the case. However, there are parents that live in Deaf communities who feel that the general education classroom is not the least restrictive environment for their child. These parents feel that placing their child in a residential school where all children are deaf may be more appropriate for their child because the staff tend to be more aware of the needs and struggles of deaf children. Another reason that these parents feel a residential school may be more appropriate is because in a general education classroom, the student will not be able to communicate with their classmates due to the language barrier.[*citation needed*]

Alexander Graham Bell with teachers and students of the Scott Circle School for deaf children, Washington, D.C., 1883

In a residential school where all the children use the same communication system (whether it is a school using ASL, Total Communication or Oralism), students will be able to interact normally with other students, without having to worry about being criticized. An argument supporting inclusion, on the other hand, exposes the student to people who are not just like them, preparing them for adult life. Through interacting, children with hearing disabilities can expose themselves to other cultures which in the future may be beneficial for them when it comes to finding jobs and living on their own in a society where their disability may put them in the minority. These are some reasons why a person may or may not want to put their child in an inclusion classroom.[96]

## Myths [edit]

This section **contains information of unclear or questionable importance or relevance to the article's subject matter**. Please help improve this section by clarifying or removing superfluous information. If importance cannot be established, the section is likely to be moved to another article, pseudo-redirected, or removed.

> *Find sources:* "Hearing loss" – news · newspapers · books · scholar · JSTOR · free images *(November 2015) (Learn how and when to remove this template message)*

- Driving: Myth: Deaf people are not permitted to drive. Fact: Deaf people may use special devices to alert them to sirens or other noises, or panoramic mirrors to enable improved visibility.[98] Many countries allow deaf people to drive, although at least 26 countries do not allow deaf citizens to hold a driver's license.[98]
- Lip reading: Myth: Most deaf people are able to understand others by reading lips. Fact: Only about 30% of spoken English is visible on the lips.[99][100] Lip reading requires not only good lighting, but also a good understanding of the oral language in question, and may also depend on contextual knowledge about what is being said.[99]
- Inheritance: Myth: Deafness is passed down from parent to child. Fact: Fewer than 5% of deaf children in the United States have a deaf parent.[101]

## Communication barriers [edit]

> This section **may stray from the topic of the article**. Please help improve this section or discuss this issue on the talk page. *(December 2014)*

The most predominant forms of communication barriers originate from one's own personal self and they are directly the result of the hearing loss condition. These barriers are associated specifically with speech and language. In terms of speech, hearing loss has an effect on speech sound production, for example distortion caused by the omission of various letters from words. The pitch of their voice may sound too high or low and their volume may be louder or quieter than is intended. Resonance of voice is also affected, as it can be hypernasal or denasal. Prosody, which represents the patterns of stress and rhythm in the voice, will often become irregular. As a result of such changes to speech, the receiver during a conversation is likely to deem the communicator's speech unintelligible. The placement of improper stresses on syllables makes it more difficult for the receiver to clearly perceive and hear the intended words. Three major problems in terms of language are present for those with hearing loss. First, there are problems with language formation, where individuals may overuse nouns and verbs and they may improperly place words within a sentence. Second, the actual content of the language is troubling, for example the interpretation of synonyms and antonyms. This results in a limited vocabulary. The third major problem is associated with Pragmatics, which includes the inability of individuals to recognize that a message has been delivered to them, therefore resulting in inappropriate questions being asked. All of these speech and language barriers make it difficult for those with hearing loss to control their own speech and understand what others have to say, therefore making it quite hard to hold a conversation altogether.[102]

## Family [edit]

The communication limitations between people who are deaf and their hearing family members can often cause difficulties in family relationships, and affect the strength of relationships among individual family members. It was found that most people who are deaf have hearing parents, which means that the channel that the child and parents communicate through can be very different, often affecting their relationship in a negative way. If a parent communicates best verbally, and their child communicates best using sign language, this could result in ineffective communication between parents and children. Ineffective communication can potentially lead to fights caused by misunderstanding, less willingness to talk about life events and issues, and an overall weaker relationship. Even if individuals in the family made an effort to learn deaf communication techniques such as sign language, a deaf family member often will feel excluded from casual banter; such as the exchange of daily events and news at the dinner table. It is often difficult for people who are deaf to follow these conversations due to the fast paced and overlapping nature of these exchanges. This can cause a deaf individual to become frustrated and take part in less family conversations. This can potentially result in weaker relationships between the hearing individual and their immediate family members. This communication barrier can have a particularly negative effect on relationships with extended family members as well. Communication between a deaf individual and their extended family members can be very difficult due to the gap in verbal and non-verbal communication.

This can cause the individuals to feel frustrated and unwilling to put effort into communicating effectively. The lack of effort put into communicating can result in anger, miscommunication, and unwillingness to build a strong relationship.[103]

## Community [edit]

People who have hearing loss can often experience many difficulties as a result of communication barriers among them and other hearing individuals in the community. Some major areas that can be impacted by this are involvement in extracurricular activities and social relationships. For young people, extracurricular activities are vehicles for physical, emotional, social, and intellectual development. However, it is often the case that communication barriers between people who are deaf and their hearing peers and coaches/club advisors limit them from getting involved. These communication barriers make it difficult for someone with a hearing loss to understand directions, take advice, collaborate, and form bonding relationships with other team or club members. As a result, extracurricular activities such as sports teams, clubs, and volunteering are often not as enjoyable and beneficial for individuals who have hearing loss, and they may engage in them less often. A lack of community involvement through extracurricular activities may also limit the individual's social network. In general, it can be difficult for someone who is deaf to develop and maintain friendships with their hearing peers due to the communication gap that they experience. They can often miss the jokes, informal banter, and "messing around" that is associated with the formation of many friendships among young people. Conversations between people who are deaf and their hearing peers can often be limited and short due to their differences in communication methods and lack of knowledge on how to overcome these differences. Deaf individuals can often experience rejection by hearing peers who are not willing to make an effort to find their way around communication difficulties. Patience and motivation to overcome such communication barriers is required by both the deaf or hard of hearing and hearing individuals in order to establish and maintain good friendships.[103]

Many people tend to forget about the difficulties that deaf children encounter, as they view the deaf child differently from a deaf adult. Deaf children grow up being unable to fully communicate with their parents, siblings and other family members. Examples include being unable to tell their family what they have learned, what they did, asking for help, or even simply being unable to interact in daily conversation. Deaf children have to learn sign language and to read lips at a young age, however they cannot communicate with others using it unless the others are educated in sign language as well. Children who are deaf or hard of hearing are faced with many complications while growing up, for example some children have to wear hearing aids and others require assistance from sign language (ASL) interpreters. The interpreters help them to communicate with other individuals until they develop the skills they need to efficiently communicate on their own. Although growing up for deaf children may entitle more difficulties than for other children, there are many support groups that allow deaf children to interact with other children. This is where they develop friendships. There are also classes for young children to learn sign language in an environment that has other children in their same situation and around their same age. These groups and classes can be very beneficial in providing the child with the proper knowledge and not to mention the societal interactions that they need in order to live a healthy, young, playful and carefree life that any child deserves.

There are three typical adjustment patterns adopted by adults with hearing loss. The first one is to remain withdrawn into your own self. This provides a sense of safety and familiarity which can be a comforting way to lead your life. The second is to act "as if" one does not even have hearing loss. A positive attitude will help people to live a life with no barriers and thus, engage in optimal interaction. The final and third pattern is for the person to accept their hearing loss as a part of them without undervaluing oneself. This means understanding that one is forced to live life with this disability, however it is not the only thing that constitutes life's meaning. Furthermore, many feel as if their inability to hear others during conversation is their fault. It's important that these individuals learn how to become more assertive individuals who do not lack fear when it comes to asking someone to repeat something or to speak a little louder. Although there is much fatigue and frustration that is produced from one's inability to hear, it is important to learn from personal experiences in order to improve on one's communication skills. In essence, these patterns will help adults with hearing loss deal with the communication barriers that are present.[78]

## Workplace [edit]

In most instances, people who are deaf find themselves working with hearing colleagues, where they can often be cut off from the communication going on around them. Interpreters can be provided for meetings and workshops, however are seldom provided for everyday work interactions. Communication of important information needed for jobs typically comes in the form of written or verbal summaries, which do not convey subtle meanings such as tone of voice, side conversations during group discussions, and body language. This can result in confusion and misunderstanding for the worker who is deaf, therefore making it harder to do their job effectively. Additionally, deaf workers can be unintentionally left out of professional networks, informal gatherings, and casual conversations among their collogues. Information about informal rules and organizational culture in the workplace is often communicated though these types of interactions, which puts the worker who is deaf at a professional and personal disadvantage. This could sever their job performance due to lack of access to information and therefore, reduce their opportunity to form relationships with their co-workers. Additionally, these communication barriers can all affect a deaf person's career development. Since being able to effectively communicate with one's co-workers and other people relevant to one's job is essential to managerial positions, people with hearing loss can often be denied such opportunities.[103]

To avoid these situations in the workplace, individuals can take full-time or part-time sign language courses. In this way, they can become better able to communicate with the deaf and hard of hearing. Such courses teach the American Sign Language (ASL) language as most North Americans use this particular language to communicate. It is a visual language made up of specific gestures (signs), hand shapes, and facial expressions that contain their own unique grammatical rules and sentence structures [104] By completing sign language courses, it ensures that deaf individuals feel a part of the workplace and have the ability to communicate with their co-workers and employer in the manner as other hearing employees do.

## Health care [edit]

Not only can communication barriers between deaf and hearing people affect family relationships, work, and school, but they can also have a very significant effect on a deaf individual's health care. As a result of poor communication between the health care professional and the deaf or hard of hearing patient, many patients report that they are not properly informed about their disease and prognosis. [105] This lack of or poor communication could also lead to other issues such as misdiagnosis, poor assessments, mistreatment, and even possibly harm to patients. Poor communication in this setting is often the result of health care providers having the misconception that all people who are deaf or hard of hearing have the same type of hearing loss, and require the same type of communication methods. In reality, there are many different types and range of hearing loss, and in order to communicate effectively a health care provider needs to understand that each individual with hearing loss has unique needs. This affects how individuals have been educated to communicate, as some communication methods work better depending on an individual's severity of hearing loss. For example, assuming every deaf or hard of hearing patient knows American Sign Language would be incorrect because there are different types of sign language, each varying in signs and meanings. A patient could have been educated to use cued speech which is entirely different from ASL.[105] Therefore, in order to communicate effectively, a health care provider needs to understand that each individual has unique needs when communicating.

Although there are specific laws and rules to govern communication between health care professionals and people who are deaf, they are not always followed due to the health care professional's insufficient knowledge of communication techniques. This lack of knowledge can lead them to make assumptions about communicating with someone who is deaf, which can in turn cause them to use an unsuitable form of communication. Acts in countries such as the Americans with Disabilities Act (ADA) state that all health care providers are required to provide reasonable communication accommodations when caring for patients who are deaf. These accommodations could include qualified sign language interpreters, CDIs, and technology such as Internet interpretation services. A qualified sign language interpreter will enhance communication between a deaf individual and a health care professional by interpreting not only a health professional's verbal communication, but also their non-verbal such as expressions, perceptions, and body language. A Certified Deaf Interpreter (CDI) is a sign language interpreter who is also a member of the Deaf community.[106] They accompany a sign language interpreter and are useful for communication with deaf individuals who also have language or cognitive deficits. A CDI will transform what the health care professional communicates into basic, simple language. This method takes much longer, however it can

also be more effective than other techniques. Internet interpretation services are convenient and less costly, but can potentially pose significant risks. They involve the use of a sign language interpreter over a video device rather than directly in the room. This can often be an inaccurate form of communication because the interpreter may not be licensed, is often unfamiliar with the patient and their signs, and can lack knowledge of medical terminology.[107]

Aside from utilizing interpreters, healthcare professionals can improve their communication with deaf or hard of hearing patients by educating themselves on common misconceptions and proper practices depending on the patient's needs. For example, a common misconception is that exaggerating words and speaking loudly will help the patient understand more clearly. However, many individuals with hearing loss depend on lip-reading to identify words. Exaggerated pronunciation and a raised voice can distort the lips, making it even more difficult to understand. Another common mistake health care professionals make are the use of single words rather than full sentences. Although language should be kept simple and short, keeping context is important because certain homophonous words are difficult to distinguish by lip-reading. Health care professionals can further improve their own communication with their patients by eliminating any background noise and positioning themselves in a way where their face is clearly visible to the patient, and suitably lit. The healthcare professional should know how to use body language and facial expressions to properly communicate different feelings.[105]

# Research [edit]

## Stem cell transplant and gene therapy [edit]

A 2005 study achieved successful regrowth of cochlea cells in guinea pigs.[108] However, the regrowth of cochlear hair cells does not imply the restoration of hearing sensitivity, as the sensory cells may or may not make connections with neurons that carry the signals from hair cells to the brain. A 2008 study has shown that gene therapy targeting Atoh1 can cause hair cell growth and attract neuronal processes in embryonic mice. Some hope that a similar treatment will one day ameliorate hearing loss in humans.[109]

Recent research, reported in 2012 achieved growth of cochlear nerve cells resulting in hearing improvements in gerbils,[110] using stem cells. Also reported in 2013 was regrowth of hair cells in deaf adult mice using a drug intervention resulting in hearing improvement.[111] The Hearing Health Foundation in the US has embarked on a project called the Hearing Restoration Project.[112] Also Action on Hearing Loss in the UK is also aiming to restore hearing.[113]

Researchers reported in 2015 that genetically deaf mice which were treated with TMC1 gene therapy recovered some of their hearing.[114][115]

## Audition [edit]

Besides research studies seeking to improve hearing, such as the ones listed above, research studies on the deaf have also been carried out in order to understand more about audition. Pijil and Shwarz (2005) conducted their study on the deaf who lost their hearing later in life and, hence, used cochlear implants to hear. They discovered further evidence for rate coding of pitch, a system that codes for information for frequencies by the rate that neurons fire in the auditory system, especially for lower frequencies as they are coded by the frequencies that neurons fire from the basilar membrane in a synchronous manner. Their results showed that the subjects could identify different pitches that were proportional to the frequency stimulated by a single electrode. The lower frequencies were detected when the basilar membrane was stimulated, providing even further evidence for rate coding.[58]

# References [edit]


1. ^ Elsevier, *Dorland's Illustrated Medical Dictionary*, Elsevier.
2. ^ "Deafness". *Encyclopædia Britannica Online*. Encyclopædia Britannica Inc. 2011. Retrieved 2012-02-22. *a b c d e f g h*

3. ^ "Deafness and hearing loss Fact sheet N°300". March 2015. Retrieved 23 May 2015.
4. ^ a b c d Lasak, JM; Allen, P; McVay, T; Lewis, D (Mar 2014). "Hearing loss: diagnosis and management.". *Primary care*. **41** (1): 19–31. doi:10.1016/j.pop.2013.10.003. PMID 24439878.
5. ^ Smith, RJH; Shearer, AE; Hildebrand, MS; Van Camp, G; Pagon, RA; Adam, MP; Ardinger, HH; Wallace, SE; Amemiya, A; Bean, LJH; Bird, TD; Fong, CT; Mefford, HC; Smith, RJH; Stephens, K (2014). "Deafness and Hereditary Hearing Loss Overview". PMID 20301607.
6. ^ a b "1.1 billion people at risk of hearing loss WHO highlights serious threat posed by exposure to recreational noise" (PDF). *who.int*. 27 February 2015. Retrieved 2 March 2015.
7. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
8. ^ a b c WHO (2008). *The global burden of disease: 2004 update* (PDF). Geneva, Switzerland: World Health Organization. p. 35. ISBN 9789241563710.
9. ^ Olusanya, BO; Neumann, KJ; Saunders, JE (1 May 2014). "The global burden of disabling hearing impairment: a call to action.". *Bulletin of the World Health Organization*. **92** (5): 367–73. doi:10.2471/blt.13.128728. PMID 24839326.
10. ^ a b c d e f g h i j k l Elzouki, Abdelaziz Y (2012). *Textbook of clinical pediatrics* (2 ed.). Berlin: Springer. p. 602. ISBN 9783642022012.
11. ^ a b "Community and Culture - Frequently Asked Questions". *nad.org*. National Association of the Deaf. Retrieved 31 July 2014.
12. ^ "Sound and Fury - Cochlear Implants - Essay". *www.pbs.org*. PBS. Retrieved 2015-08-01.
13. ^ "Understanding Deafness: Not Everyone Wants to Be 'Fixed'". *www.theatlantic.com*. *The Atlantic*. Retrieved 2015-08-01.
14. ^ "Why not all deaf people want to be cured". *www.telegraph.co.uk*. *The Daily Telegraph*. Retrieved 2015-08-02.
15. ^ a b c Sparrow, Robert (2005). "Defending Deaf Culture: The Case of Cochlear Implants" (PDF). *The Journal of Political Philosophy*. **13** (2). Retrieved 30 November 2014.
16. ^ eBook: *Current Diagnosis & Treatment in Otolaryngology: Head & Neck Surgery*, Lalwani, Anil K. (Ed.) Chapter 44: Audiologic Testing by Brady M. Klaves, PhD, Jennifer McKee Bold, AuD, Access Medicine
17. ^ "Community and Culture - Frequently Asked Questions". *nad.org*. National Association of the Deaf. Retrieved 27 Jan 2016.
18. ^ ANSI 7029:2000/BS 6951 Acoustics - Statistical distribution of hearing thresholds as a function of age
19. ^ ANSI S3.5-1997 Speech Intelligibility Index (SII)
20. ^ Robinson, DW; Sutton, GJ (1979). "Age effect in hearing – a comparative analysis of published threshold data". *Audiology*. **18** (4): 320–34. doi:10.3109/00206097909072634. PMID 475664.
21. ^ Worrall, L.,& Hickson, L. M. (2003). "Communication activity limitations", pp. 141–142 in Linda E. Worrall & Louise M. Hickson (Eds.). *Communication disability in aging: from prevention to intervention*. Clifton Park, NY: Delmar Learning
22. ^ "Hearing Loss and Older Adults" (Last Updated June 3, 2016). National Institute on Deafness and Other Communication Disorders. Retrieved September 11, 2016.
23. ^ a b Oishi, N.; Schacht, J. (June 2011). "Emerging treatments for noise-induced hearing loss". *Expert opinion on emerging drugs*. **16** (2): 235–45. doi:10.1517/14728214.2011.552427. PMC 3102156. PMID 21247358.
24. ^ "CDC - NIOSH Science Blog – A Story of Impact…." *cdc.gov*".
25. ^ "Noise and Hearing Conservation: Effects of Excessive Exposure". *Occupational Safety & Health Administration*. Retrieved July 14, 2016.
26. ^ "Threshold Shift (TS)". *Simon Fraser University*. Retrieved 2016-07-14.
27. ^ "About Hearing Loss". *Centers for Disease Control and Prevention*. Retrieved 2016-07-15.
28. ^ In the United States, United States Environmental Protection Agency, Occupational Safety and Health Administration, National Institute for Occupational Safety and Health, Mine Safety and Health Administration, and numerous state government agencies among others, set noise standards.
29. ^ Information on Levels of Environmental Noise Requisite to Protect Public Health and Welfare with an Adequate Margin of Safety. Document ID: usepa-1974
30. ^ "Deafness". *SANDRA: South African National Deaf Association*. Retrieved 2016-07-14.
31. ^ Occupational Noise Exposure, National Institute for Occupational Safety and Health 98-126
32. ^ "Compliance Guide to MSHA's Occupational Noise Exposure Standard, APPENDIX B – GLOSSARY OF TERMS".
33. ^ a b "Noise-Induced Hearing Loss: Promoting Hearing Health Among Youth". *CDC Healthy Youth!*. CDC. 2009-07-01.

34. ^ Goines, Lisa; Hagler, Louis (March 2007). "Noise Pollution: A Modern Plague". *Southern Medical Journal*. **100**: 287–294. doi:10.1097/smj.0b013e3180318be5. Retrieved 26 November 2014.
35. ^ Rosen, S; et al. (1962). "Presbycusis study of a relatively noise-free population in the Sudan". *Ann. Otol. Rhinol. Laryngol*. **71**: 727–743. doi:10.1177/000348946207100313.
36. ^ Bergman, Moe (1966). "Hearing in the Mabaans. A critical review of related Literature". *Arch. Otolaryngol*. **84**: 411–415. doi:10.1001/archotol.1966.00760030413007.
37. ^ Goycoolea, MV; et al. (1986). "Effect of life in industrialized societies on hearing in natives of Easter Island". *Laryngoscope*. **96**: 1391–1396. doi:10.1288/00005537-198612000-00015.
38. ^ Committee on Noise-Induced Hearing Loss and Tinnitus Associated with Military Service from World War II to the Present, Medical Follow-up Agency (2006). Humes, Larry; Joellenbeck, Lois; Durch, Jane, eds. *Noise and military service : implications for hearing loss and tinnitus* (eBook). 500 Fifth Street, N.W., Washington, DC 20001: THE NATIONAL ACADEMIES PRESS. pp. 72–111. ISBN 0-309-09949-8. Retrieved 26 November 2014.
39. ^ de Laat, JA; van Deelen, L; Wiefferink, K (September 2016). "Hearing Screening and Prevention of Hearing Loss in Adolescents.". *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*. **59** (3): 243–5. doi:10.1016/j.jadohealth.2016.06.017. PMID 27562364.
40. ^ *a b c* Rehm, Heidi. "The Genetics of Deafness; A Guide for Patients and Families" (PDF). *Harvard Medical School Center For Hereditary Deafness*. Harvard Medical School.
41. ^ Lynch, Eric D.; Lee, Ming K.; Morrow, Jan E.; Welcsh, Piri L.; León, Pedro E.; King, Mary-Claire (1997-11-14). "Nonsyndromic deafness DFNA1 associated with mutation of a human homolog of the Drosophila gene diaphanous". *Science*. **278** (5341): 1315–18. doi:10.1126/science.278.5341.1315. PMID 9360932.
42. ^ Schraders, M.; Oostrik, J.; Huygen, P.L.; Strom, T.M.; van Wijk, E.; Kunst, H.P.; Hoefsloot, L.H.; Cremers, C.W.; Admiraal, R.J.; Kremer, H. (March 2010). "Mutations in PTPRQ Are a Cause of Autosomal-Recessive Nonsyndromic Hearing Impairment DFNB84 and Associated with Vestibular Dysfunction". *The American Journal of Human Genetics*. **86** (4): 604–10. doi:10.1016/j.ajhg.2010.02.015. PMC 2850434. PMID 20346435.
43. ^ Byl, et.al., FM (1977). "Auditory symptoms associated with herpes zoster or idiopathic facial paralysis". *Laryngoscope*. **87** (3): 372–9. doi:10.1288/00005537-197703000-00010.
44. ^ Araújo Eda, S; Zucki, F; Corteletti, LC; Lopes, AC; Feniman, MR; Alvarenga Kde, F (2012). "Hearing loss and acquired immune deficiency syndrome: systematic review.". *Jornal da Sociedade Brasileira de Fonoaudiologia*. **24** (2): 188–92. doi:10.1590/s2179-64912012000200017. PMID 22832689.
45. ^ Rodman, R; Pine, HS (Jun 2012). "The otolaryngologist's approach to the patient with Down syndrome.". *Otolaryngologic clinics of North America*. **45** (3): 599–629, vii–viii. doi:10.1016/j.otc.2012.03.010. PMID 22588039.
46. ^ http://omim.org/entry/118300
47. ^ Curhan, Sharon G.; Shargorodsky, Josef; Eavey, Roland; Curhan, Gary C. (2012-02-29). "Analgesic Use and the Risk of Hearing Loss in Women". Oxford Journals: American Journal of EPIDEMIOLOGY.
48. ^ Cone, Barbara; Dorn, Patricia; Konrad-Martin, Dawn; Lister, Jennifer; Ortiz, Candice; Schairer, Kim. "Ototoxic Medications (Medication Effects)". American Speech-Language-Hearing Association.
49. ^ "FDA Announces Revisions to Labels for Cialis, Levitra and Viagra". Food and Drug Administration. 2007-10-18. Retrieved 2011-10-30.
50. ^ *a b* "Tox Town – Toluene – Toxic chemicals and environmental health risks where you live and work – Text Version". toxtown.nlm.nih.gov. Retrieved 2010-06-09.
51. ^ *a b c* Morata, Thais C. "Addressing the Risk for Hearing Loss from Industrial Chemicals". CDC. Retrieved 2008-06-05.
52. ^ Johnson, Ann-Christin (2008-09-09). "Occupational exposure to chemicals and hearing impairment – the need for a noise notation" (PDF). *Karolinska Institutet*: 1–48. Retrieved 2009-06-19.
53. ^ Sliwinska-Kowalska, M.; Zamyslowska-Szmytke, E.; Szymczak, W.; Kotylo, P.; Fiszer, M.; Wesolowski, W.; Pawlaczyk-Luszczynska, M. (May 2005). "Exacerbation of noise-induced hearing loss by co-exposure to workplace chemicals". *Environmental Toxicology and Pharmacology*. **19** (3): 547–553. doi:10.1016/j.etap.2004.12.018.
54. ^ Oesterle, EC (March 2013). "Changes in the adult vertebrate auditory sensory epithelium after trauma.". *Hearing research*. **297**: 91–8. doi:10.1016/j.heares.2012.11.010. PMC 3637947. PMID 23178236.
55. ^ Eggermont, JJ (24 May 2016). "Acquired hearing loss and brain plasticity.". *Hearing research*. doi:10.1016/j.heares.2016.05.008. PMID 27233916.
56. ^ U.S.C. (2012). How We Hear. Sc.edu. Retrieved from http://www.sc.edu/ehs/modules/Noise/hearing.htm
57. ^ Hayes, K. (2009). Hear. About.com. Retrieved from http://ent.about.com/od/entanatomybasics/ht/How We Hear.htm
58. ^ *a b* Carlson, N. R. (2010). Physiology of behavior. (11 ed.). Upper Saddle River, New Jersey: Pearson Education, Inc.
59. ^ Jansen, et.al., S (2013). "Efficient hearing screening in noise-exposed listeners using the digit triplet test.". *Ear*

*Hear*. **34** (6): 773–8. doi:10.1097/AUD.0b013e318297920b.
60. ^ Russell JL, Pine HS, Young DL (2013). "Pediatric cochlear implantation: expanding applications and outcomes.". *Pediatric Clinics of North America*. **60** (4): 841–863. doi:10.1016/j.pcl.2013.04.008. PMID 23905823.
61. ^ Lieu JE. Speech-language and educational consequences of unilateral hearing loss in children. Arch Otolaryngol Head Neck Surg. 2004: 130(5);524-30.
62. ^ Kitterick PT, O'Donoghue GM, Edmondson-Jones M, Marshall A, Jeffs E, Craddock L, Riley A, Green K, O'Driscoll M, Jiang D, Nunn T, Saeed S, Aleksy W, Seeber BU (Aug 11, 2014). "Comparison of the benefits of cochlear implantation versus contra-lateral routing of signal hearing aids in adult patients with single-sided deafness: study protocol for a prospective within-subject longitudinal trial.". *BMC Ear Nose Throat Disord*. **14** (1): 7. doi:10.1186/1472-6815-14-7. PMID 25152694.
63. ^ *a b c* Riss D, Arnoldner C, Baumgartner WD, Blineder M, Flak S, Bachner A, Gstoettner W, Hamzavi JS (2014). "Indication criteria and outcomes with the Bonebridge transcutaneous bone-conduction implant.". *Laryngoscope*. **124**: 2802–2806. doi:10.1002/lary.24832. PMID 25142577.
64. ^ Graham, edited by John M.; Baguley, David M. (2009). *Ballantyne's Deafness.* (7th ed.). Chichester: John Wiley & Sons. p. 16. ISBN 978-0-470-74441-3.
65. ^ "Childhood hearing loss: act now, here's how!" (PDF). *WHO*. 2016. p. 6. Retrieved 2 March 2016. "Over 30% of childhood hearing loss is caused by diseases such as measles, mumps, rubella, meningitis and ear infections. These can be prevented through immunization and good hygiene practices. Another 17% of childhood hearing loss results from complications at birth, including prematurity, low birth weight, birth asphyxia and neonatal jaundice. Improved maternal and child health practices would help to prevent these complications. The use of ototoxic medicines in expectant mothers and newborns, which is responsible for 4% of childhood hearing loss, could potentially be avoided."
66. ^ Stucken, EZ; Hong, RS (October 2014). "Noise-induced hearing loss: an occupational medicine perspective.". *Current opinion in otolaryngology & head and neck surgery*. **22** (5): 388–93. doi:10.1097/moo.0000000000000079. PMID 25188429.
67. ^ El Dib, R.P.; Mathew, J.L.; Martins, R.H. (2012-04-18). El Dib, Regina P, ed. "Interventions to promote the wearing of hearing protection". *Cochrane database of systematic reviews (Online)*. **4**: CD005234. doi:10.1002/14651858.CD005234.pub5. PMID 22513929.
68. ^ "Noise and Hearing Loss Prevention". *Centers for Disease Control and Prevention: National Institute for Occupational Safety and Health*. Retrieved July 15, 2016.
69. ^ "Safety and Health Topics: Occupational Noise Exposure". *Occupational Safety and Health Administration*. Retrieved July 15, 2015.
70. ^ "Controls for Noise Exposure". *Centers for Disease Control and Prevention: National Institute for Occupational Safety and Health*. Retrieved July 15, 2016.
71. ^ "Excellence in Hearing Loss Prevention Award". *Safe-in-Sound*. Retrieved July 15, 2016.
72. ^ "Buy Quiet". *Centers for Disease Control and Prevention: National Institute for Occupational Safety and Health*. Retrieved July 15, 2016.
73. ^ "PowerTools Database". *Centers for Disease Control and Prevention: National Institute for Occupational Safety and Health*. Retrieved July 15, 2016.
74. ^ "CDC - NIOSH Publications and Products - Occupationally-Induced Hearing Loss (2010-136)". *cdc.gov*.
75. ^ Verbeek, JH; Kateman, E; Morata, TC; Dreschler, WA; Mischke, C (17 October 2012). "Interventions to prevent occupational noise-induced hearing loss.". *The Cochrane database of systematic reviews*. **10**: CD006396. doi:10.1002/14651858.CD006396.pub3. PMID 23076923.
76. ^ Moyer, Virginia A. (2012-11-06). "Screening for Hearing Loss in Older Adults: U.S. Preventive Services Task Force Recommendation Statement". *Annals of Internal Medicine*. The American College of Physicians. pp. 655–661. Retrieved 2012-11-06.
77. ^ *a b* National Institute on Deafness and Other Communication Disorders(NIDCD)(2013). *Hearing Aids.* Retrieved from http://www.nidcd.nih.gov/health/hearing/pages/hearingaid.aspx
78. ^ *a b* Scherer, M. J. (2004). The Personal Meaning of Hearing or Vision Loss. *Connecting To Learn Educational and Assistive Technology for People With Disabilities.* (pp. 41-55). Washington, DC: American Psychological Association.
79. ^ *a b c* Working with Hearing Loss. (2008). Retrieved October 31, 2014, from http://www.chha.ca/documents/Working_With_Hearing_Loss.pdf
80. ^ "Free Phone Caption Service for the Deaf and Hard of Hearing. [sic]". Phone Caption. Retrieved 2010-12-10.
81. ^ Meyers, Carol, Dr. "Infrared, Frequency/Digital Modulation, and Induction Hearing Loops : A comparison of assisted listening system technologies". *Technology for Worship*. INSPIRATION Technology Conferences, Inc. Retrieved 30 November 2014.
82. ^ "Cochlear Implantation in Adults A Systematic Review and Meta-analysis". *JAMA Otolaryngol Head Neck Surgery*. **139**: 265. 2013. doi:10.1001/jamaoto.2013.1744.

83. ^ "FDA Public Health Notification: Risk of Bacterial Meningitis in Children with Cochlear Implants". FDA. 2002-07-24. Retrieved 2008-11-09.
84. ^ "Elliot & Oliver's Story – Research". cochlearimplant.net. 2006. Archived from the original on 2008-03-02.
85. ^ "CART Systems".
86. ^ "Auditory Sciences". Auditory Sciences.
87. ^ "An Educators Guide to Hearing Disability Issues. (n.d.)." . UIUC. Retrieved 2009-07-19. | "Facts About Hearing Loss". Alexander Bell Association for the Deaf and Hard of Hearing. 2005. Retrieved 2009-07-19.
88. ^ Frishberg, Nancy (September 1975). "Arbitrariness and Iconicity: Historical Change in American Sign Language". *Language*. **51** (3): 696. doi:10.2307/412894.
89. ^ Kral A, O'Donoghue GM (2010). "Profound Deafness in Childhood". *New England J Medicine*. **363**: 1438–50. doi:10.1056/nejmra0911225. PMID 20925546.
90. ^ Deaf Heritage: A Narrative History of Deaf America by Jack Gannon (National Association of the Deaf, 1981)
91. ^ "American Deaf Culture". *Sign Media, Incorporated*. Sign Media, Inc. Retrieved 14 May 2013.
92. ^ Drolsbaugh, Mark. "Everything You've Wanted to Know About Deaf Culture (And Then Some)". Deaf Culture Online. Archived from the original on 2011-02-13. Retrieved 2011-11-28.
93. ^ NAD Cochlear Implant Committee. "NAD Position Statement on Cochlear Implants (2000)". *Cochlear Implants %7c National Association of the Deaf*. National Association of the Deaf. Retrieved 30 November 2014.
94. ^ "American Sign Language". *NIDCD*. Retrieved 17 November 2016.
95. ^ http://www2.ed.gov/about/offices/list/ocr/docs/hq9806.html
96. ^ *a b* Smith, D. D., & Tyler, N. C. (2010). Introduction to Special Education. Columbus: Merrill.
97. ^ "Regulations: Part 300 / A / 300.8 / c". *U. S. Department of Education*. U. S. Department of Education. Retrieved 9 August 2015.
98. ^ *a b* "Sound and Fury – Deaf Culture – Living with Deafness". PBS. Retrieved 2010-12-10.
99. ^ *a b* "What Do You Know About Deaf Culture?" (PDF). Minnesota Coalition for Battered Women. 2003-03-26.
100. ^ "Myths About Deaf and Hard of Hearing". Tutor Workshop. Retrieved 2010-12-10.
101. ^ Mitchell, Ross E.; Karchmer, Michael A. (2004). "Chasing the mythical ten percent: Parental hearing status of deaf and hard of hearing students in the United States". *Sign Language Studies*. **4** (2): 138–163. doi:10.1353/sls.2004.0005.
102. ^ Haynes, W. O., Moran, M. J., & Pindzola, R. H. (2012). Hearing Loss. *Communication Disorders in Educational and Medical Settings An Introduction for Speech-Language Pathologists, Educators, and Health Professionals* (pp. 280-282). Sudbury, MA: Jones & Bartlett Learning.
103. ^ *a b c* Foster, S. (1996). Communication experiences of deaf people: An ethnographic account. In I. Parasnis (Ed.), Cultural and language diversity of the deaf experience (pp. 117-136). New York: Cambridge University Press.
104. ^ Sign Language Classes for Individuals. (2013, January 1). Retrieved November 5, 2014.
105. ^ *a b c* Medicina Oral, Patología Oral y Cirugía Bucal. (2007, January 1). Retrieved October 31, 2014, from http://scielo.isciii.es/scielo.php?pid=S1698-69462007000800007&script=sci_arttext
106. ^ Ramstead, A. (2014, January 15). The Role of the Certified Deaf Interpreter. Retrieved November 2, 2014, from http://www.indemandinterpreting.com/role-certified-deaf-interpreter/
107. ^ Schuler, G., Mistler, L., Torrey, K., & Depukat, R. (2013). Bridging Communication Gaps with the Deaf. Nursing, 43(11), 24-30.
108. ^ Coghlan, Andy (2005-02-14). "Gene therapy is first deafness 'cure'". *NewScientist.com News Service*.
109. ^ Gubbels, SP; Woessner, DW; Mitchell, JC; Ricci, AJ; Brigande, JV (2008). "Functional auditory hair cells produced in the mammalian cochlea by in utero gene transfer". *Nature*. **455** (7212): 537–41. doi:10.1038/nature07265. PMC 2925035. PMID 18754012.
110. ^ Gewin, Virginia (2012-09-12). "Human embryonic stem cells restore gerbil hearing". Nature. doi:10.1038/nature.2012.11402. Retrieved 2013-01-22.
111. ^ Ander, Davida. "Drug may reverse permanent deafness by regenerating cells of inner ear: Harvard study". *National Post*. National Post.
112. ^ "Hearing Health Foundation". HHF. Retrieved 2013-01-22.
113. ^ "Biomedical research – Action On Hearing Loss". RNID. Retrieved 2013-01-22.
114. ^ Gallacher, James (9 July 2015). "Deafness could be treated by virus, say scientists". UK: BBC. Retrieved 9 July 2015.
115. ^ Askew, Charles; et al. (8 July 2015). "Tmc gene therapy restores auditory function in deaf mice". *Science Translational Medicine*. American Association for the Advancement of Science. **7** (295): 295ra108. doi:10.1126/scitranslmed.aab1996.


[edit]

# External links

- Hearing loss at DMOZ

Wikimedia Commons has media related to *Hearing impairment*.

Wikiquote has quotations related to: *Hearing loss*

| v · t · e · | **Symptoms and signs relating to the hearing and balance (R30–R39, 788)** |
|---|---|
| **Hearing** | **Hearing loss** · |
| **Balance** | Vertigo, nystagmus · |
| **Other** | Ear pain · |
| **Authority control** | GND: 4059132-3 · |

Categories: Communication disorders | Hearing loss | Disability | Deaf culture | Audiology | Occupational safety and health | Hearing | Otorhinolaryngology




# Mandibular fracture

From Wikipedia, the free encyclopedia

*"Broken jaw" redirects here. For other uses, see Broken jaw (disambiguation).*

**Mandibular fracture**, also known as **fracture of the jaw**, is a break through the mandibular bone. In about 60% of cases the break occurs in two places. It may result in a decreased ability to fully open the mouth. Often the teeth will not feel properly aligned or there may be bleeding of the gums.[1] Mandibular fractures occur most commonly among males in their 30s.[2]

Mandibular fractures are typically the result of trauma. This can include a fall onto the chin or a hit from the side.[1] Rarely they may be due to osteonecrosis or tumors in the bone.[2] The most common area of fracture is at the condyle (36%), body (21%), angle (20%) and symphysis (14%). While a diagnosis can occasionally be made with plain X-ray, modern CT scans are more accurate.[1]

Immediate surgery is not necessarily required. Occasionally people may go home and follow up for surgery in the next few days.[1] A number of surgical techniques may be used including maxillomandibular fixation and open reduction internal fixation (ORIF).[3][2] People are often put on antibiotics such as penicillin for a brief period of time.[4][2] The evidence to support this practice; however, is poor.[5]

Contents



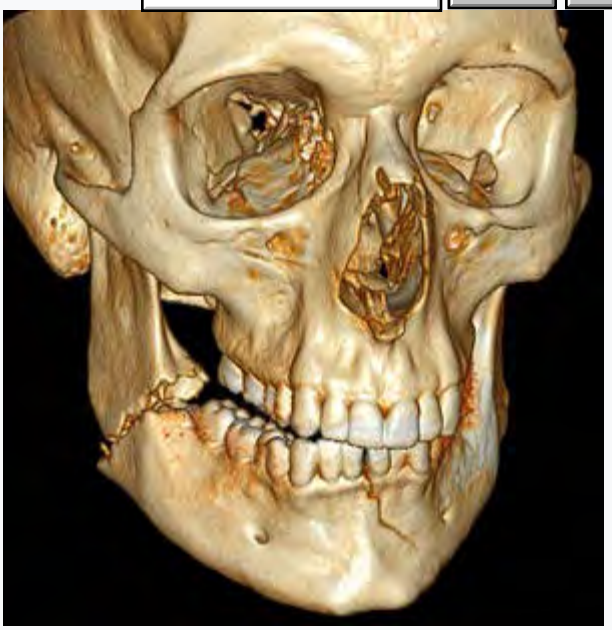


## Signs and symptoms [edit]

**Variants**

**Mandibular fracture**

**Synonyms** mandible fracture, fracture of the jaw



3D computed tomographic image of a mandible fracture in two places. One is a displaced right angle fracture and the other is a left parasymphyseal fracture.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | emergency medicine |
| **ICD-10** | S02.6 |
| **MeSH** | D008337 |

[edit on Wikidata]

## General [edit]

By far, the two most common symptoms described are pain and the feeling that teeth no longer correctly meet (traumatic malocclusion, or disocclusion). The teeth are very sensitive to pressure (proprioception), so even a small change in the location of the teeth will generate this sensation. People will also be very sensitive to touching the area of the jaw that is broken, or in the case of condylar fracture the area just in front of the tragus of the ear.

Other symptoms may include loose teeth (teeth on either side of the fracture will feel loose because the fracture is mobile), numbness (because the inferior alveolar nerve runs along the jaw and can be compressed by a fracture) and trismus (difficulty opening the mouth).

Outside the mouth, signs of swelling, bruising and deformity can all be seen. Condylar fractures are deep, so it is rare to see significant swelling although, the trauma can cause fracture of the bone on the anterior aspect of the external auditory meatus so bruising or bleeding can sometimes be seen in the ear canal. Mouth opening can be diminished (less than 3 cm). There can be numbness or altered sensation (anesthesia/paraesthesia in the chin and lower lip (the distribution of the mental nerve).

Intraorally, if the fracture occurs in the tooth bearing area, a step may seen between the teeth on either side of the fracture or a space can be seen (often mistaken for a lost tooth) and bleeding from the gingiva in the area. There can be an open bite where the lower teeth, no longer meet the upper teeth. In the case of a unilateral condylar fracture the back teeth on the side of the fracture will meet and the open bite will get progressively greater towards the other side of the mouth.

Sometimes bruising will develop in the floor of the mouth (sublingual eccymosis) and the fracture can be moved by moving either side of the fracture segment up and down. For fractures that occur in the non-tooth bearing area (condyle, ramus, and sometimes the angle) an open bite is an important clinical feature since little else, other than swelling, may be apparent.[6]:page number needed

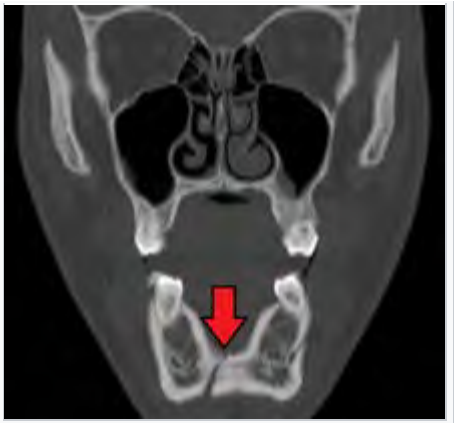
## Condylar [edit]

This type of fractured mandible can involve one condyle (unilateral) or both (bilateral). Unilateral condylar fracture may cause restricted and painful jaw movement. There may be swelling over the temporomandibular joint region and bleeding from the ear because of lacerations to the external auditory meatus. The hematoma may spread downwards and backwards behind the ear, which may be confused with Battle's sign (a sign of a base of skull fracture), although this is an uncommon finding so if present, intra-cranial injury must be ruled out. If the bones fracture and overlie each other there may be shortening of the height of the ramus. This results in gagging of the teeth on the fractured side (the teeth meet too soon on the fractured side, and not on the non fractured side, i.e. "open bite" that becomes progressively worse to the unaffected side). When the mouth is opened, there may be deviation of the mandible towards the fractured side. Bilateral condylar fractures may cause the above signs and symptoms, but on both sides.[7] Malocclusion and restricted jaw movement are usually more severe.[7] Bilateral body or parasymphysis fractures are sometimes termed "flail mandible", and can cause involuntary posterior movement of the tongue with subsequent obstruction of the upper airway.[8] Displacement of the condyle through the roof of glenoid fossa and into the middle cranial fossa is rare.[9] Bilateral condylar fractures combined with a symphyseal fracture is sometimes termed a guardsman's fracture. The name comes from this injury occurring in soldiers who faint on parade grounds and strike the floor with their chin.[*citation needed*]

# Diagnosis [edit]

## Plain film radiography [edit]

Traditionally, plain films of the mandible would be exposed but had lower sensitivity and specificity owing to overlap of structures. Views included AP (for parasymphsis), lateral oblique (body, ramus, angle,



Nondisplaced fracture of the mandible

coronoid process) and Towne's (condyle) views. Condylar fractures can be especially difficult to identify, depending on the direction of condylar displacement or dislocation so multiple views of it are usually examined with two views at perpendicular angles.[10]

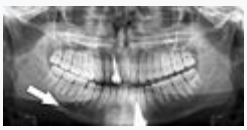
## Panoramic radiography [edit]

Panoramic radiographs are tomograms where the mandible is in the focal trough and show a flat image of the mandible. Because the curve of the mandible appears in a 2-dimensional image, fractures are easier to spot leading to an accuracy similar to CT except in the condyle region. In addition, broken, missing or malaligned teeth can often be appreciated on a panoramic image which is frequently lost in plain films. Medial/lateral displacement of the fracture segments and especially the condyle are difficult to gauge so the view is sometimes augmented with plain film radiography or computed tomography for more complex mandible fractures.

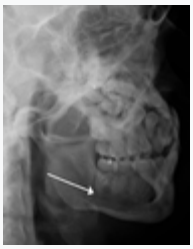
## Computed tomography [edit]

Computed tomography is the most sensitive and specific of the imaging techniques. The facial bones can be visualized as slices through the skeletal in either the axial, coronal or sagittal planes. Images can be reconstructed into a 3-dimensional view, to give a better sense of the displacement of various fragments. 3D reconstruction, however, can mask smaller fractures owing to volume averaging, scatter artifact and surrounding structures simply blocking the view of underlying areas.

Research has shown that panoramic radiography is similar to computed tomography in its diagnostic accuracy for mandible fractures and both are more accurate than plain film radiograph.[11] The indications to use CT for mandible fracture vary by region, but it does not seem to add to diagnosis or treatment planning except for comminuted or avulsive type fractures,[12] although, there is better clinician agreement on the location and absence of fractures with CT compared to panoramic radiography.[13]

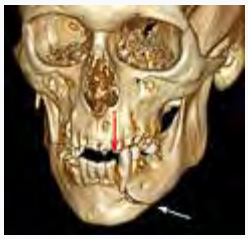


Panoramic radiograph of a simple mandible fracture of the right mandibular body, minimally displaced. Note that the teeth to the left of the fracture do not touch

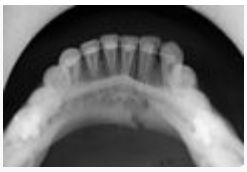


lateral oblique image demonstrating a fractured mandible.

Towne's view of a bilateral condyle fracture. White arrow is a fracture on the neck of the condyle. Black arrow shows the condyle pulled to the medial. The same injury can be seen on the opposite side



3D CT reconstruction of mandible fracture, white arrow marks fracture, red arrow marks moderate displacement and open bite



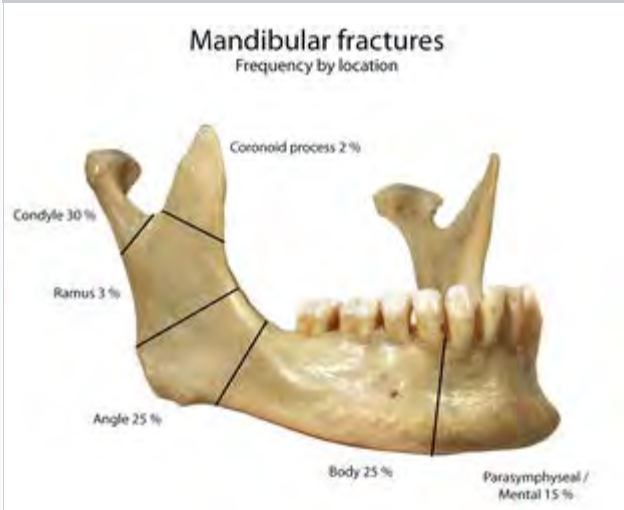
occlusal radiograph of a mandibular parasymphasis fracture

## Classification [edit]

There are various classification systems of mandibular fractures in use.

## Location [edit]

This is the most useful classification, because both the signs and symptoms, and also the treatment are dependent upon the location of the fracture.[7] The mandible is usually divided into the following zones for the purpose of describing the location of a fracture (see diagram): condylar, coronoid process, ramus, angle of mandible, body (molar and premolar areas), parasymphysis and symphysis.[7]




The most frequent locations of a mandibular fracture.

### Alveolar [edit]

This type of fracture involves the alveolus, also termed the alveolar process of the mandible.

### Condylar [edit]

Condylar fractures are classified by location compared to the capsule of ligaments that hold the temporomandibular joint (intracapsular or extracapsular), dislocation (whether or not the condylar head has come out of the socket (glenoid fossa) as the muscles (lateral pterygoid) tend to pull the condyle anterior and medial) and neck of the condyle fractures. E.g. extracapsular, non-displaced, neck fracture. Pediatric condylar fractures have special protocols for management.[14]

### Coronoid [edit]

Because the coronoid process of the mandible lies deep to many structures, including the zygomatic complex (ZMC), it is rare to be broken in isolation. It usually occurs with other mandibular fractures or with fracture of the zygomatic complex or arch. Isolated fractures of the coronoid process should be viewed with suspicion and fracture of the ZMC should be ruled out.[15]

### Ramus [edit]

Ramus fractures are said to involve a region inferiorly bounded by an oblique line extending from the lower third molar (wisdom tooth) region to the posteroinferior attachment of the masseter muscle, and which could not be better classified as either condylar or coronoid fractures.[*medical citation needed*]

### Angle [edit]

The angle of the mandible refers to the angle created by the arrangement of the body of the mandible and

the ramus. Angle fractures are defined as those that involve a triangular region bounded by the anterior border of masseter muscle and an oblique line extending from the lower third molar (wisdom tooth) region to the posteroinferior attachment of the masseter muscle.[*medical citation needed*]

### Body [edit]

Fractures of the mandibular body are defined as those that involve a region bounded anteriorly by the parasymphysis (defined as a vertical line just distal to the canine tooth) and posteriorly by the anterior border of the masseter muscle.[*medical citation needed*]

### Parasymphysis [edit]

Parasymphyseal fractures are defined as mandibular fractures that involve a region bounded bilaterally by vertical lines just distal to the canine tooth.[*medical citation needed*]

### Symphysis [edit]

Symphyseal fractures are a linear fractures that run in the midline of the mandible (the symphysis).[*medical citation needed*]

## Fracture type [edit]

Mandibular fractures are also classified according to categories that describe the condition of the bone fragments at the fracture site and also the presence of communication with the external environment.[16]

### Greenstick [edit]

Greenstick fractures are incomplete fractures of flexible bone, and for this reason typically occur only in children. This type of fracture generally has limited mobility.[16]

### Simple [edit]

A simple fracture describes a complete transection of the bone with minimal fragmentation at the fracture site.[16]

### Comminuted [edit]

The opposite of a simple fracture is a comminuted fracture, where the bone has been shattered into fragments, or there are secondary fractures along the main fracture lines. High velocity injuries (e.g. those caused by bullets, improvised explosive devices, etc...) will frequently cause comminuted fractures.[16][17]

### Compound [edit]

A compound fracture is one that communicates with the external environment. In the case of mandibular fractures, communication may occur through the skin of the face or with the oral cavity. Mandibular fractures that involve the tooth-bearing portion of the jaw are by definition compound fractures,[16] because there is at least a communication via the periodontal ligament with the oral cavity and with more displaced fractures there may be frank tearing of the gingival and alveolar mucosa.

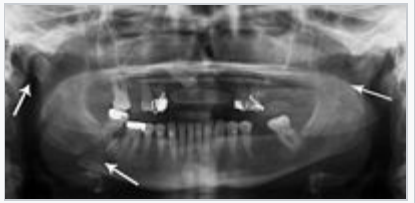
## Involvement of teeth [edit]

When a fracture occurs in the tooth bearing portion of the mandible, whether or not it is dentate or edentulous will affect treatment. Wiring of the teeth helps stabilize the fracture (either during placement of osteosynthesis or as a treatment by itself), so the lack of teeth will guide treatment. When an edentulous mandible (no teeth) is less than 1 cm in height (as measured on panoramic radiograph or CT scan) addition risks apply because the blood flow from the marrow (endosseous) is minimal and the healing bone must rely on blood supply from the periosteum surrounding the bone.[18][*needs update*] If a fracture occurs in a child with mixed dentition different treatment protocols are needed.[19]

Other fractures of the body, are classified as open or closed. Because fractures that involve the teeth, by definition, communicate with the mouth this distinction is largely lost in mandible fractures. Condylar, ramus, and coronoid process fractures are generally closed whereas angle, body and parasymphsis fractures are generally open.

### Displacement [edit]

The degree to which the segments are separated. The larger the separation, the more difficult it is to bring them back together (approximate the segments)



multiple mandible fractures of a patient in the right condyle (extracapsular/neck/not dislocated), right body (vertically unfavourable) and left coronoid process

### Favourability [edit]

For angle and posterior body fractures, when the angle of the fracture line is angled back (more posterior at the top of the jaw and more anterior at the bottom of the jaw) the muscles tend to bring the fracture segments together. This is called favorable. When the angle of the fractures is pointing to the front, it is unfavorable.[20][*non-primary source needed*]

### Age of the fracture [edit]

While mandible fractures have similar complication rates whether treated immediately or days later, older fractures are believed to have higher non-union and infection rates although the data on this makes it difficult to draw firm conclusions.[21]

## Treatment [edit]

Like all fractures, consideration has to be given to other illnesses that might jeopardize the patient, then to reduction and fixation of the fracture itself. Except in avulsive type injuries, or those where there might be airway compromise, a several day delay in the treatment of mandible fractures seems to have little impact on the outcome or complication rates.

### General considerations [edit]

Since mandible fractures are usually the result of blunt force trauma to the head and face, other injuries need to be considered before the mandible fracture. First and foremost is compromise of the airway. While rare, bilateral mandible fractures that are unstable can cause the tongue to fall back and block the airway. Fractures such as a symphyseal or bilateral parasymphyseal may lead to mobility of the central portion of the mandible where genioglossus attaches, and allow the tongue to fall backwards and block the airway.[7] In larger fractures, or those from high velocity injuries, soft tissue swelling can block the airway.

In addition to the potential for airway compromise, the force delivered to break the jaw can be great enough to either fracture the cervical spine or cause intra-cranial injury (head injury). It is common for both to be assessed with facial fractures.

Finally, vascular injury can result (with particular attention to the internal carotid and jugular) from high velocity injuries or severely displaced mandible fractures.

Loss of consciousness combined with aspiration of tooth fragments, blood and possibly dentures mean that the airway may be threatened.[7]

### Reduction [edit]

Reduction refers to approximating the ends of the bones edges that are broken. This is done with either an open technique, where an incision is made, the fracture is found and is physically manipulated into place, or closed technique where no incision is made.

The mouth is unique, in that the teeth are well secured to the bone ends but come through epithelium

(mucosa). A leg or wrist, for instance, has no such structure to help with a closed reduction. In addition, when the fracture happens to be in a tooth bearing area of the jaws, aligning the teeth well usually results in alignment of the fracture segments.

To align the teeth, circumdental wiring is often used where wire strands (typically 24 gauge or 26 gauge) are wrapped around each tooth then attached to a stainless steel arch bar. When the maxillary (top) and mandibular (bottom) teeth are aligned together, this brings the fracture segments into place. Higher tech solutions are also available, to help reduce the segments with arch bars using bonding technology.[22]

## Fixation [edit]

Simple fractures are usually treated with closed reduction and indirect skeletal fixation, more commonly referred to as maxillo-mandibular fixation (MMF). The closed reduction is explained above. The indirect skeletal fixation is accomplished by placing an arch bar, secured to the teeth on the maxillary and mandibular dentition, then securing the top and bottom arch bars with wire loops.

Many alternatives exist to secure the maxillary and mandibular dentition including resin bonded arch bars, Ivy loops (small eyelets of wires), orthodontic bands and MMF bone screws where titanium screws with holes in the head of them are screwed into the basal bone of the jaws then secured with wire.

Closed reduction with direct skeletal fixation follows the same premise as MMF except that wires are passed through the skin and around the bottom jaw in the mandibule and through the piriform rim or zygomatic buttresses of the maxilla then joined together to secure the jaws. The option is sometimes used when a patient is edentulous (has no teeth) and rigid internal fixation cannot be used.

Open reduction with direct skeletal fixation allows the bones to be directly mandibulated through an incision so that the fractured ends meet, then they can be secured together either rigidly (with screws or plates and screws) or non-rigidly (with transosseous wires). There are a multitude of various plate and screw combinations including compression plates, non-compression plates, lag-screws, mini-plates and biodegradable plates.

External fixation, which can be used with either open or closed reduction uses a pin system, where long screws are passed through the skin and into either side of a fracture segment (typically 2 pins per side) then secured in place using an external fixator. This is a more common approach when the bone is heavily comminuted (shattered into small pieces, for instance in a bullet wound) and when the bone is infected (osteomyelitis).

Regardless of the method of fixation, the bone need to remain relatively stable for a period of 3–6 weeks. On average, the bone gains 80% of its strength by 3 weeks and 90% of it by 4 weeks. There is great variation depending on the severity of injury and health of the wound and patient.

Maxillomandibular fixation with circumdental wires, archbars and elastics for a condyle fracture

Rigid internal fixation of parasymphasis fracture of the mandible. White arrow marks fracture, black arrow marks arch bar on lower teeth

Rigid internal fixation of right condyle fracture with mini-plate on the neck of the condyle. Black arrow marks right earlobe, white arrow marks head of the condyle

External fixation of left mandible fracture

## Special considerations [edit]

### Condyle [edit]

The best treatment for condylar fractures is controversial.[23] There are two main options, namely closed reduction or open reduction and fixation. Closed reduction may involve intermaxillary fixation, where the jaws are splinted together in the correct position for a period of weeks. Open reduction involves surgical exposure of the fracture site, which can be carried out via incisions within the mouth or incisions outside the mouth over the area of the condyle. Open reduction is sometimes combined with use of an endoscope to aid visualization of fracture site. Although closed reduction carries a risk of the bone healing out of position, with consequent alteration of the bite or the creation of facial asymmetry, it does not risk temporary damage to the facial nerve or result in any facial scar that accompanies open reduction. A systematic review was unable to find sufficient evidence of the superiority of one method over another in the management of condylar fractures.[23] Paediatric condylar fractures are especially problematic, owing to the remaining growth potential and possibility of ankylosis of the joint. Early mobilization is often recommended as in the Walker protocol.[24][25]

### Edentulous mandible [edit]

A broken jaw that has no teeth in it faces two additional issues. First, the lack of teeth makes reduction and fixation using MMF difficult. Instead of placing circumdental wires around the teeth, existing dentures can be left in (or Gunning splints, a type of temporary denture) and the mandible fixated to the maxilla using skeletal fixation (circummandibular and circumzygomatic wires) or using MMF bone screws. More commonly, open reduction and rigid internal fixation is placed.

When the width of the mandible is less than 1 cm, the jaw loses its endosteal blood supply. Instead, the blood supply comes largely from the periosteum. Open reduction (which normally strips the periosteum during the dissection) can lead to avascular necrosis. In these cases, oral surgeons sometimes opt for external fixation, closed reduction, supraperiosteal dissection or other techniques to maintain the periosteal blood flow.[26]

### High velocity injuries [edit]

In high velocity injuries, the soft tissue can be severely damaged far from the bullet wound itself due to hydrostatic shock. Because of this the airway must be carefully managed and vessels well examined. Because the jaw can be highly comminuted, MMF and rigid internal fixation can be difficult. Instead, external fixation is often used[27],.[28]

### Pathologic fracture [edit]

Fractures where large cysts or tumours are in the area (and weaken the jaw), where there is an area of osteomyelitis or where osteonecrosis exist cause special challenges to fixation and healing. Cysts and tumours can limit effective bone to bone contact and osteomyelitis or osteonecrosis compromise blood supply to the bone. In all of the situations, healing will be delayed and sometimes, resection is the only alternative to treatment.[29]

## Prognosis [edit]

The healing time for a routine mandible fractures is 4–6 weeks whether MMF or rigid internal fixation (RIF) is used. For comparable fractures, patients who received MMF will lose more weight and take longer to regain mouth opening, whereas, those who receive RIF have higher infection rates.

The most common long-term complications are loss of sensation in the mandibular nerve, malocclusion and loss of teeth in the line of fracture. The more complicated the fracture (infection, comminution, displacement) the higher the risk of fracture.[30]

Condylar fractures have higher rates of malocclusion which in turn are dependent on the degree of displacement and/or dislocation. When the fracture is intracapsular there is a higher rate of late-term osteoarthritis and the potential for ankylosis although the later is a rare complication as long as mobilization is early.[23] Pediatric condylar fractures have higher rates of ankylosis and the potential for growth disturbance.[19],[31]

Rarely, mandibular fracture can lead to Frey's syndrome.[32]

## Epidemiology [edit]

Mandible fracture causes vary by the time period and the region studied. In North America, blunt force trauma (a punch) is the leading cause of mandible fracture[33] whereas in India, motor vehicle collisions are now a leading cause.[34] On battle grounds, it is more likely to be high velocity injuries (bullets and shrapnel).[35] Prior to the routine use of seat belts, airbags and modern safety measures, motor vehicle collisions where a leading cause of facial trauma. The relationship to blunt force trauma explains why 80% of all mandible fractures occur in males. Mandibular fracture is a rare complication of third molar removal, and may occur during the procedure or afterwards.[36] With respect to trauma patients, roughly 10% have some sort of facial fracture, the majority of which come from motor vehicle collisions. When the person is unrestrained in a car, the risk of fracture rises 50% and when an unhelmeted motorcyclist the risk rises 4-fold.[37]

## History [edit]

Management of mandible fractures has been mentioned as early as 1700 B.C. in the Edwin Smith Papyrus and later by Hippocrates in 460 B.C., "Displaced but incomplete fractures of the mandible where continuity of the bone is preserved should be reduced by pressing the lingual surface with the fingers...". Open reduction was described as early as 1869.[38] Since the late 19th century, modern techniques including MMF (see above) have been described with titanium based rigid internal fixation becoming commonplace since the 1970s and biodegradable plates and screws being available since the 1980s.

## References [edit]


1. ^ *a b c d* Murray, JM (May 2013). "Mandible fractures and dental trauma.". *Emergency medicine clinics of North America*. **31** (2): 553–73. doi:10.1016/j.emc.2013.02.002. PMID 23601489.
2. ^ *a b c d* Murray, JM (May 2013). "Mandible fractures and dental trauma.". *Emergency medicine clinics of North America*. **31** (2): 553–73. doi:10.1016/j.emc.2013.02.002. PMID 23601489.
3. ^ Al-Moraissi, EA; Ellis E, 3rd (March 2015). "Surgical treatment of adult mandibular condylar fractures provides better outcomes than closed treatment: a systematic review and meta-analysis.". *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons*. **73** (3): 482–93. doi:10.1016/j.joms.2014.09.027. PMID 25577459.
4. ^ Shridharani, SM; Berli, J; Manson, PN; Tufaro, AP; Rodriguez, ED (September 2015). "The Role of Postoperative Antibiotics in Mandible Fractures: A
21. ^ Hermund, N. U.; Hillerup, S. R.; Kofod, T.; Schwartz, O.; Andreasen, J. O. (2008). "Effect of early or delayed treatment upon healing of mandibular fractures: A systematic literature review". *Dental Traumatology*. **24** (1): 22–26. doi:10.1111/j.1600-9657.2006.00499.x. PMID 18173660.
22. ^ Williams, J Llewellyn (1994). *Rowe and Williams' Maxillofacial Injuries*. London: Churchhill Livingstone. p. 283. ISBN 978-0-443-04591-2.
23. ^ *a b c* Sharif, MO; Fedorowicz, Z; Drews, P; Nasser, M; Dorri, M; Newton, T; Oliver, R (Apr 14, 2010). "Interventions for the treatment of fractures of the mandibular condyle.". *Cochrane database of systematic reviews (Online)* (4): CD006538. doi:10.1002/14651858.CD006538.pub2. PMID 20393948.
24. ^ Andersson, Lars (2012). *Oral and Maxillofacial*

Systematic Review of the Literature.". *Annals of plastic surgery*. **75** (3): 353–7. doi:10.1097/sap.0000000000000135. PMID 24691320.

5. ^ Kyzas, PA (April 2011). "Use of antibiotics in the treatment of mandible fractures: a systematic review.". *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons*. **69** (4): 1129–45. doi:10.1016/j.joms.2010.02.059. PMID 20727642.
6. ^ Fonseca RJ, Barber HD, Powers MP, Frost DE (2012). *Oral & maxillofacial trauma* (4th ed.). W B Saunders Co. ISBN 9781455705542.
7. ^ *a b c d e f* Banks P, Brown A; Brown, Andrew E. (2000). *Fractures of the facial skeleton*. Oxford: Wright. pp. 1–4, 10–14, 17–20, 42–47, 68, 81–119. ISBN 0723610347.
8. ^ Stewart, ed. by Michael G. (2005). *Head, face and neck trauma comprehensive management*. Stuttgart: Thieme. p. 107. ISBN 9783131403315.
9. ^ Barron, RP; Kainulainen, VT; Gusenbauer, AW; Hollenberg, R; Sàndor, GK (December 2002). "Management of traumatic dislocation of the mandibular condyle into the middle cranial fossa" (PDF). *Journal (Canadian Dental Association)*. **68** (11): 676–80. PMID 12513935.
10. ^ White, Stuart; Pharoah, Michael J (2000). *Oral Radiology Principals & Interpretation*. St. Louis, Missouri: Mosby. ISBN 978-0-323-02001-5.
11. ^ Nair, M. K.; Nair, U. P. (2001). "Imaging of mandibular trauma: ROC analysis". *Academic Emergency Medicine*. **8** (7): 689–695. doi:10.1111/j.1553-2712.2001.tb00186.x. PMID 11435182.
12. ^ Laskin, Daniel (2007). *Decision making in oral and maxillofacial surgery*. Chicago: Quintessence Pub. Co. ISBN 978-0-86715-463-4.
13. ^ Roth, F. S.; Kokoska, M. S.; Awwad, E. E.; Martin, D. S.; Olson, G. T.; Hollier, L. H.; Hollenbeak, C. S. (2005). "The identification of mandible fractures by helical computed tomography and panorex tomography". *The Journal of craniofacial surgery*. **16** (3): 394–399. doi:10.1097/01.scs.0000171964.01616.a8. PMID 15915103.
14. ^ Abdel-Galil, K.; Loukota, R. (2010). "Fractures of the mandibular condyle: Evidence base and current concepts of management". *British Journal of Oral and Maxillofacial Surgery*. **48** (7): 520–526. doi:10.1016/j.bjoms.2009.10.010. PMID 19900741.
15. ^ Vanhove, F.; Dom, M.; Wackens, G. (1997). "Fracture of the coronoid process: Report of a case". *Acta stomatologica Belgica*. **94** (2): 81–85. PMID 11799592.
16. ^ *a b c d e* Hupp JR, Ellis E, Tucker MR (2008). *Contemporary oral and maxillofacial surgery* (5th ed.). St. Louis, Mo.: Mosby Elsevier. pp. 493–495,

*Surgery*. John Wiley & Sons. ISBN 978-1-118-29256-3.

25. ^ Myall, R. W. T. (2009). "Management of Mandibular Fractures in Children". *Oral and Maxillofacial Surgery Clinics of North America*. **21** (2): 197–201, vi. doi:10.1016/j.coms.2008.12.007. PMID 19348985.
26. ^ Madsen, M. J.; Haug, R. H.; Christensen, B. S.; Aldridge, E. (2009). "Management of Atrophic Mandible Fractures". *Oral and Maxillofacial Surgery Clinics of North America*. **21** (2): 175–183, v. doi:10.1016/j.coms.2008.12.006. PMID 19348982.
27. ^ Peleg, M.; Sawatari, Y. (2010). "Management of Gunshot Wounds to the Mandible". *Journal of Craniofacial Surgery*. **21** (4): 1252–1256. doi:10.1097/SCS.0b013e3181e2065b. PMID 20613603.
28. ^ Alpert, B.; Tiwana, P. S.; Kushner, G. M. (2009). "Management of Comminuted Fractures of the Mandible". *Oral and Maxillofacial Surgery Clinics of North America*. **21** (2): 185–192, v. doi:10.1016/j.coms.2008.12.002. PMID 19348983.
29. ^ Ezsiás, A.; Sugar, A. W. (1994). "Pathological fractures of the mandible: A diagnostic and treatment dilemma". *The British journal of oral & maxillofacial surgery*. **32** (5): 303–306. doi:10.1016/0266-4356(94)90051-5. PMID 7999738.
30. ^ Kyrgidis, A.; Koloutsos, G.; Kommata, A.; Lazarides, N.; Antoniades, K. (2013). "Incidence, aetiology, treatment outcome and complications of maxillofacial fractures. A retrospective study from Northern Greece". *Journal of Cranio-Maxillofacial Surgery*. **41** (7): 637–43. doi:10.1016/j.jcms.2012.11.046. PMID 23332470.
31. ^ Glazer, M.; Joshua, B. Z.; Woldenberg, Y.; Bodner, L. (2011). "Mandibular fractures in children: Analysis of 61 cases and review of the literature". *International Journal of Pediatric Otorhinolaryngology*. **75** (1): 62–64. doi:10.1016/j.ijporl.2010.10.008. PMID 21035876.
32. ^ Kragstrup, Tue W.; Christensen, Jennifer; Fejerskov, Karin; Wenzel, Ann (August 2011). "Frey Syndrome—An Underreported Complication to Closed Treatment of Mandibular Condyle Fracture? Case Report and Literature Review". *Journal of Oral and Maxillofacial Surgery*. **69** (8): 2211–2216. doi:10.1016/j.joms.2010.12.033.
33. ^ Kruger, Gustav (1984). *Textbook of Oral and Maxillofacial Surgery*. St. Louis, Missouri: CV Mosby. ISBN 978-0-8016-2793-4.
34. ^ Natu, S. S.; Pradhan, H.; Gupta, H.; Alam, S.; Gupta, S.; Pradhan, R.; Mohammad, S.; Kohli, M.; Sinha, V. P.; Shankar, R.; Agarwal, A. (2012). "An Epidemiological Study on Pattern and Incidence of Mandibular Fractures". *Plastic Surgery*

499–500, 502–507. ISBN 9780323049030.
17. ^ Abreu, ME; Viegas, VN; Ibrahim, D; Valiati, R; Heitz, C; Pagnoncelli, RM; Silva, DN (May 1, 2009). "Treatment of comminuted mandibular fractures: a critical review." (PDF). *Medicina oral, patologia oral y cirugia bucal*. **14** (5): E247–51. PMID 19218899.
18. ^ Nasser, M.; Fedorowicz, Z.; Ebadifar, A. (2007). Nasser, Mona, ed. "Management of the fractured edentulous atrophic mandible". *The Cochrane Library* (1): CD006087. doi:10.1002/14651858.CD006087.pub2. PMID 17253578.
19. ^ *a b* Goth, S.; Sawatari, Y.; Peleg, M. (2012). "Management of Pediatric Mandible Fractures". *Journal of Craniofacial Surgery*. **23** (1): 47–56. doi:10.1097/SCS.0b013e318240c8ab. PMID 22337373.
20. ^ Pektas, Z. O.; Bayram, B.; Balcik, C.; Develi, T.; Uckan, S. (2012). "Effects of different mandibular fracture patterns on the stability of miniplate screw *International*. **2012**: 1. doi:10.1155/2012/834364. PMC 3503282. PMID 23227327.
35. ^ Berkowitz, I.; Bornman, P. C.; Kottler, R. E. (2008). "Cystic Duct Entry - Another Cause of Pseudocalculus". *Endoscopy*. **22** (2): 85–87. doi:10.1055/s-2007-1012801. PMID 2335148.
36. ^ Ethunandan, M; Shanahan, D; Patel, M (Feb 24, 2012). "Iatrogenic mandibular fractures following removal of impacted third molars: an analysis of 130 cases.". *British dental journal*. **212** (4): 179–84. doi:10.1038/sj.bdj.2012.135. PMID 22361547.
37. ^ Wilson, William C (2007). *Trauma: Emergency Resuscitation, Perioperative Anesthesia, Surgical Management (Volume 1)*. Google eBooks: Informa Healthcare. pp. 417–418. ISBN 978-1-280-73024-5.
38. ^ Wilson, William C (2007). *Trauma: Emergency Resuscitation, Perioperative Anesthesia, Surgical Management (Volume 1)*. Google eBooks: Informa Healthcare. p. 417. ISBN 978-1-280-73024-5.

Wikimedia Commons has media related to *Fractures of the human mandible*.

v · t · e · **Fractures and cartilage injuries (Sx2, 800–829)**

| | | |
|---|---|---|
| **General** | Avulsion fracture · Chalkstick fracture · Greenstick fracture · Pathologic fracture · Spiral fracture · | |
| **Head** | Basilar skull fracture · Blowout fracture · **Mandibular fracture** · Nasal fracture · Le Fort fracture of skull · Zygomaticomaxillary complex fracture · Zygoma fracture · | |
| **Spinal fracture** | Cervical fracture (Jefferson fracture · Hangman's fracture · Flexion teardrop fracture · Clay-shoveler fracture · · Burst fracture · Compression fracture · Chance fracture · Holdsworth fracture · | |
| **Ribs** | Rib fracture · Sternal fracture · | |
| **Shoulder fracture** | Clavicle · Scapular · | |
| **Arm fracture** | **Humerus fracture:** | Supracondylar · Holstein–Lewis fracture · |
| | **Forearm fracture:** | Ulnar fracture (Monteggia fracture · Hume fracture · · Radius fracture/Distal radius ( (Galeazzi · Colles' · Smith's · Barton's · · Essex-Lopresti fracture · · |
| **Hand fracture** | Scaphoid · Rolando · Bennett's · Boxer's · | |
| **Pelvic fracture** | Duverney fracture · Pipkin fracture · | |
| **Leg** | **Tibia fracture:** | Bumper fracture · Segond fracture · Gosselin fracture · Toddler's fracture · Pilon fracture (Plafond fracture · · Tillaux fracture · |
| | **Fibular fracture:** | Maisonneuve fracture · Le Fort fracture of ankle · Bosworth fracture · |
| | **Combined tibia and fibula fracture:** | Trimalleolar fracture · Bimalleolar fracture · Pott's fracture · |
| | **Crus fracture:** | Patella fracture · |

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|---|---|---|
| | **Femoral fracture:** | Hip fracture · |
| **Foot fracture** | Lisfranc · Jones · March · Calcaneal · | |

Categories: Bone fractures | Jaw disorders




# Nasal polyp

From Wikipedia, the free encyclopedia

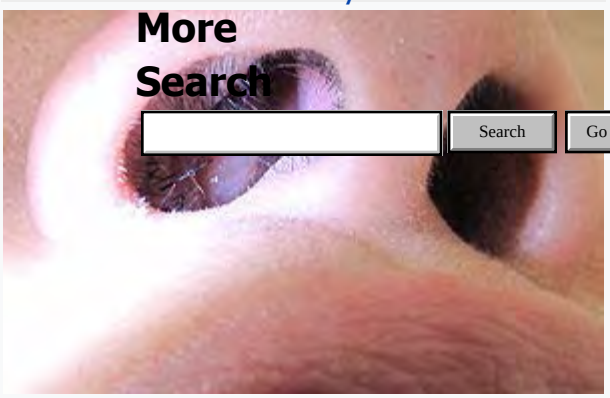
**Nasal polyps** (**NP**) are [non-cancerous](#) growths within the [nose or sinuses](#).[1] Symptoms include trouble breathing through the nose, [loss of smell](#), decreased taste, [post nasal drip](#), and a [runny nose](#). The growths are [sac-like](#), movable, and nontender. They typically occur in both nostrils in those who are affected. Face pain may occasionally occur.[1] Complications may include [sinusitis](#).[2]

The exact cause is unclear. They occur more commonly among people who have [allergies](#), [cystic fibrosis](#), [aspirin sensitivity](#), or certain infections. They are overgrowths of the [mucous membranes](#). Diagnosis may occur by looking up the nose and a [CT scan](#) may be used to help plan treatment.[1]

Treatment is typically with [steroids](#), often in the form of a nasal spray. If this is not effective [surgery](#) may be considered. The condition may recur following surgery. [Antihistamines](#) may help with symptoms but do not change the underlying disease. [Antibiotics](#) are not required unless complications occur. About 4% of people currently have nasal polyps while up to 40% of people develop them at some point in their life. They most often occur after the age of 20 and are more frequent in males than females.[1]

Contents


Nasal polyps



A nasal polyp

| Classification and external resources | |
|---|---|
| **Specialty** | Otorhinolaryngology |
| **ICD-10** | J33 |
| **ICD-9-CM** | 471 |
| **MedlinePlus** | 001641 |
| **eMedicine** | ent/334 ent/335 |
| **MeSH** | *C09.603.557* |

[edit on Wikidata]

## Signs and symptoms [edit]

Nasal polyps are usually classified into *antrochoanal* polyps and *ethmoidal* polyps. Antrochoanal polyps arise from the [maxillary sinuses](#) and are the much less common;[3] ethmoidal polyps arise from the [ethmoidal sinuses](#).[4]

Symptoms of polyps include [nasal congestion](#), [sinusitis](#), [anosmia](#) (loss of smell), and secondary [infection](#) leading to [headache](#). They may be removed by surgery, but are found to recur in about 70% of cases. Sinus surgery requires a great amount of precision as this involves risk of damage to [orbit](#) matter.[5]

## Causes [edit]



The pathogenesis of nasal polyps is unknown. Nasal polyps are most commonly thought to be caused by allergy and rarely by cystic fibrosis although a significant number are associated with non-allergic adult asthma or no respiratory or allergic trigger that can be demonstrated. Nasal mucosa, particularly in the region of middle meatus becomes oedematous due to collection of extracellular fluid causing polypoidal change. Polyps which are sessile in the beginning become pedunculated due to gravity and excessive sneezing.[6]

Micrograph of a sinonasal papilloma (H&E stain), which may have serious consequences and should be distinguished from nasal polyps

In early stages, surface of nasal polyp is covered by ciliated columnar epithelium, but later it undergoes metaplastic change to squamous type on atmospheric irritation. Submucosa shows large intercellular spaces filled with serous fluid.[7]

There are various diseases associated with polyp formation:[8]

1. Chronic rhinosinusitis
2. Asthma
3. Aspirin-induced asthma, or aspirin-exacerbated respiratory disease (AERD)
4. Cystic fibrosis
5. Allergic fungal sinusitis
6. Kartagener's syndrome
7. Young's syndrome
8. Eosinophilic granulomatosis with polyangiitis
9. Nasal mastocytosis

Exposure to some forms of chromium can cause nasal polyps and associated diseases.[*citation needed*] Chronic rhinosinusitis is a common chronic medical condition that can be classified into two groups presenting either with nasal polyposis or without.[9] Chronic rhinosinusitis with nasal polyposis can be divided into eosinophilic chronic rhinosinusitis, which include allergic fungal rhinosinusitis and aspirin-exacerbated respiratory disease, or nasal polyps associated with neutrophilic inflammation, which is primarily characterized by cystic fibrosis.[10]

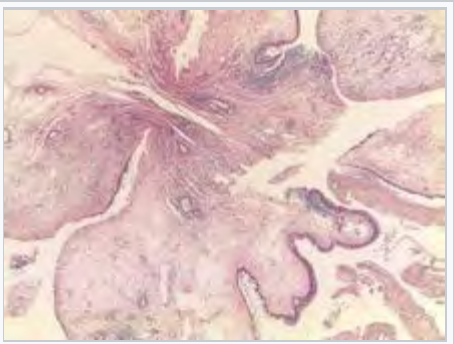
## Diagnosis [edit]

There are two criteria (major and minor) that must be met. The former in the form of facial pressure, nasal blockage, decreased smell and the latter in the form of fever, headache, cough and dental pain.[9]

### Types [edit]

There are two major types of nasal polyp.[*citation needed*]

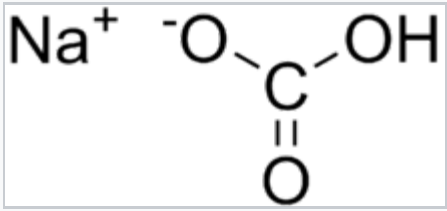
1. Antrochoanal
    a. Single, Unilateral
    b. Can originate from maxillary sinus
    c. Usually found in children
2. Ethmoidal
    a. Bilateral
    b. Usually found in adults



Human nasal polyp, magnification 25x, (H&E stain)

Nasal polyps consist of hyperplastic oedematous connective tissue with some seromucous glands and inflammatory cells (mostly neutrophils and eosinophils) with respiratory epithelium, sometimes with metaplastic squamous epithelium on the surface.Nasal polyps should be distinguished from nasal papillomas, which are benign epithelial tumors and have more serious consequences.[*citation needed*]

## Treatment [edit]



Sodium bicarbonate

Nasal polyps are most often treated with steroids or topical, but can also be treated with surgical methods.[11] Before and after surgery, sinus rinses with sterile warm water mixed with a small amount of salts (sodium chloride and sodium bicarbonate) can be helpful to clear the sinuses.[12]

The removal of nasal polyps via surgery lasts approximately 45 minutes to 1 hour. The surgery can be done under general or local anaesthesia, and the polyps are removed using endoscopic surgery. Recovery from this type of surgery is anywhere from 1 to 3 weeks. Mometasone furoate, commonly available as a nasal spray for treating common allergy symptoms, has been indicated in the United States by the FDA for the treatment of nasal polyps since December 2005.[13][14]

## References [edit]


1. ^ *a b c d* Newton, JR; Ah-See, KW (April 2008). "A review of nasal polyposis.". *Therapeutics and clinical risk management*. **4** (2): 507–12. doi:10.2147/tcrm.s2379. PMC 2504067. PMID 18728843.
2. ^ Frazier, Margaret Schell; Drzymkowski, Jeanette (2014-03-12). *Essentials of Human Diseases and Conditions*. Elsevier Health Sciences. p. 432. ISBN 9780323292283.
3. ^ Pilch, Ben Z. (2001). *Head and Neck Surgical Pathology*. Lippincott Williams & Wilkins. ISBN 9780397517275.
4. ^ Maqbool, Mohammad; Maqbool, Suhail (2013). *Textbook of Ear, Nose and Throat Diseases*. JP Medical Ltd. ISBN 9789350904954.
5. ^ Önerci, T. Metin; Ferguson, Berrylin J. (2010-08-13). *Nasal Polyposis: Pathogenesis, Medical and Surgical Treatment*. Springer Science & Business Media. ISBN 9783642114120.
6. ^ Wilkins, Lippincott Williams & (2009). *Professional Guide to Diseases*. Lippincott Williams & Wilkins. ISBN 9780781778992.
7. ^ Michaels, Leslie (2012-12-06). *Ear, Nose and Throat Histopathology*. Springer Science & Business Media. ISBN 9781447133322.
8. ^ Behrbohm, Hans; Kaschke, Oliver (2011-01-01). *Ear, Nose, and Throat Diseases: With Head and Neck Surgery*. Thieme. ISBN 9783131702135.
9. ^ *a b* Chaaban, Mohamad; Walsh, Erika M.; Woodworth, Bradford A. (Nov–Dec 2013). "Epidemiology and differential diagnosis of nasal polyps". *American Journal of Rhinology and Allergy*. **27** (6): 473–478. doi:10.2500/ajra.2013.27.3981. PMC 3899526. PMID 24274222.
10. ^ Kang, Suzie Hyeona; Dalcin, Paulo de Tarso Roth; Piltcher, Otavio Bejzman; Migliavacca, Raphaella de Oliveira (2015). "Chronic rhinosinusitis and nasal polyposis in cystic fibrosis: update on diagnosis and treatment *". *Jornal Brasileiro de Pneumologia*. **41** (1): 65–76. doi:10.1590/S1806-37132015000100009. ISSN 1806-3713. PMC 4350827. PMID 25750676.
11. ^ Önerci, T. Metin; Ferguson, Berrylin J. (2010-08-13). *Nasal Polyposis: Pathogenesis, Medical and Surgical Treatment*. Springer Science & Business Media. ISBN 9783642114120.
12. ^ Bansal, Mohan (2012-10-01). *Diseases of Ear, Nose and Throat*. JP Medical Ltd. ISBN 9789350259436.
13. ^ Vedanthan, Pudupakkam K.; Nelson, Harold S.; Agashe, Shripad N.; A, Mahesh P.; Katial, Rohit (2014-02-21). *Textbook of Allergy for the Clinician*. CRC Press. ISBN 9781466598331.
14. ^ "Dulera (Mometasone Furoate and Formoterol Fumarate Dihydrate) Inhalation Aerosol". *www.fda.gov*. Retrieved 2015-05-18.


## Further reading [edit]


- Meymane Jahromi, Ahmad; Shahabi Pour, Ayeh (1 January 2012). "The Epidemiological and Clinical Aspects of Nasal Polyps that Require Surgery". *Iranian Journal of Otorhinolaryngology*. **24** (67): 75–78. ISSN 2251-7251. PMC 3846212. PMID 24303389.


Wikimedia Commons has media related to *Nasal*

*polyp*.

| v · t · e · | Diseases of the respiratory system (J, 460–519) | | | |
|---|---|---|---|---|
| **Upper RT (including URTIs, common cold)** | **Head** | *sinuses*: Sinusitis · *nose*: Rhinitis (Vasomotor rhinitis · Atrophic rhinitis · Hay fever · · **Nasal polyp** · Rhinorrhea · *nasal septum* (Nasal septum deviation · Nasal septum perforation · Nasal septal hematoma · · *tonsil*: Tonsillitis · Adenoid hypertrophy · Peritonsillar abscess · | | |
| | **Neck** | *pharynx*: Pharyngitis (Strep throat · · Laryngopharyngeal reflux (LPR) · Retropharyngeal abscess · *larynx*: Croup · Laryngomalacia · Laryngeal cyst · Laryngitis · Laryngopharyngeal reflux (LPR) · Laryngospasm · *vocal folds*: Laryngopharyngeal reflux (LPR) · Vocal fold nodule · Vocal cord paresis · Vocal cord dysfunction · *epiglottis*: Epiglottitis · *trachea*: Tracheitis · Tracheal stenosis · | | |
| **Lower RT/lung disease (including LRTIs)** | **Bronchial/ obstructive** | *acute*: Acute bronchitis · *chronic*: COPD (Chronic bronchitis · Acute exacerbations of chronic bronchitis · Acute exacerbation of COPD · Emphysema) · Asthma (Status asthmaticus · Aspirin-induced · Exercise-induced · · Bronchiectasis · *unspecified*: Bronchitis · Bronchiolitis (Bronchiolitis obliterans · · Diffuse panbronchiolitis · | | |
| | **Interstitial/ restrictive (fibrosis)** | **External agents/ occupational lung disease** | Pneumoconiosis (Asbestosis · Baritosis · Bauxite fibrosis · Berylliosis · Caplan's syndrome · Chalicosis · Coalworker's pneumoconiosis · Siderosis · Silicosis · Talcosis · Byssinosis · · Hypersensitivity pneumonitis (Bagassosis · Bird fancier's lung · Farmer's lung · Lycoperdonosis · · | |
| | | **Other** | ARDS · Pulmonary edema · Löffler's syndrome/Eosinophilic pneumonia · Respiratory hypersensitivity (Allergic bronchopulmonary aspergillosis · · Hamman-Rich syndrome · Idiopathic pulmonary fibrosis · Sarcoidosis · | |
| | | | **By pathogen** | Viral · Bacterial (Pneumococcal · Klebsiella) · · Atypical bacterial (Mycoplasma · Legionnaires' disease · Chlamydiae · · Fungal (Pneumocystis · · Parasitic · *noninfectious* |

| | | | | |
|---|---|---|---|---|
| | **Obstructive or restrictive** | **Pneumonia/ pneumonitis** | | (Chemical/Mendelson's syndrome · Aspiration/Lipid · · |
| | | | **By vector/route** | Community-acquired · Healthcare-associated · Hospital-acquired · |
| | | | **By distribution** | Broncho- · Lobar · |
| | | | **IIP** | UIP · DIP · BOOP-COP · NSIP · RB · |
| | | **Other** | | Atelectasis · *circulatory* (Pulmonary hypertension · Pulmonary embolism · · Lung abscess · |
| **Pleural cavity/ mediastinum** | **Pleural disease** | | | Pleuritis/pleurisy · Pneumothorax/Hemopneumothorax · **Pleural effusion:** Hemothorax · Hydrothorax · Chylothorax · Empyema/pyothorax · Malignant · Fibrothorax · |
| | **Mediastinal disease** | | | Mediastinitis · Mediastinal emphysema · |
| **Other/general** | | | | Respiratory failure · Influenza · SARS · Idiopathic pulmonary haemosiderosis · Pulmonary alveolar proteinosis · |

| v · t · e · **Medicine** | |
|---|---|
| Outline · History · | |
| **Specialties and subspecialties** | **Surgery** |
| | Cardiac surgery · Cardiothoracic surgery · Colorectal surgery · Eye surgery · General surgery · Neurosurgery · Oral and maxillofacial surgery · Orthopedic surgery · Hand surgery · Otolaryngology (ENT) · Pediatric surgery · Plastic surgery · Reproductive surgery · Surgical oncology · Thoracic surgery · Transplant surgery · Trauma surgery · Urology (Andrology · · Vascular surgery · |
| | **Internal medicine** |
| | Allergy / Immunology · Angiology · Cardiology · Endocrinology · Gastroenterology (Hepatology · · Geriatrics · Hematology · Hospital medicine · Infectious disease · Nephrology · Oncology · Pulmonology · Rheumatology · |
| | **Obstetrics and gynaecology** |
| | Gynaecology · Gynecologic oncology · Maternal–fetal medicine · Obstetrics · Reproductive endocrinology and infertility · Urogynecology · |
| | **Diagnostic** |
| | Radiology (Interventional radiology · Nuclear medicine · · Pathology (Anatomical pathology · Clinical pathology · Clinical chemistry · Clinical immunology · Cytopathology · Medical microbiology · Transfusion medicine · · |
| | **Other specialties** |
| | Addiction medicine · Adolescent medicine · Anesthesiology · Dermatology · Disaster medicine · Diving medicine · Emergency medicine (Mass-gathering medicine · · Family medicine · |

| | |
|---|---|
| | General practice · Hospital medicine · Intensive-care medicine · Medical genetics · Neurology (Clinical neurophysiology · · Occupational medicine · Ophthalmology · Oral medicine · Pain management · Palliative care · Pediatrics (Neonatology · · Physical medicine and rehabilitation (PM&R) · Preventive medicine · Psychiatry · Public health · Radiation oncology · Reproductive medicine · Sexual medicine · Sleep medicine · Sports medicine · Transplantation medicine · Tropical medicine (Travel medicine · · Venereology · |
| **Medical education** | Medical school · Bachelor of Medicine, Bachelor of Surgery · Bachelor of Medical Sciences · Master of Medicine · Master of Surgery · Doctor of Medicine · Doctor of Osteopathic Medicine · MD–PhD · |
| **Related topics** | Allied health (Dentistry · Podiatry · · Nanomedicine · Molecular oncology · Personalized medicine · Veterinary medicine · Physician (Chief physician · · History of medicine · |
| **Book** · | |

Categories: Nose disorders




# Nosebleed

From Wikipedia, the free encyclopedia
(Redirected from Nose bleed)

*For other uses, see Nosebleed (disambiguation).*
*"Epistaxis" redirects here. It is not to be confused with Epitaxis.*

**Nosebleed**, also known as a **epistaxis**, is the common occurrence of bleeding from the nose. It is usually noticed when the blood drains out through the nostrils.

There are two types: anterior (the most common), and posterior (less common, more likely to require medical attention). Sometimes in more severe cases, the blood can come up the nasolacrimal duct and out from the eye. Fresh blood and clotted blood can also flow down into the stomach and cause nausea and vomiting.[1]

Although the sight of large amounts of blood can be alarming and may warrant medical attention, nosebleeds are rarely fatal, accounting for only 4 of the 2.4 million deaths in the U.S. in 1999.[2] About 60% of people have a nosebleed at some point in their life.[3] About 10% of nosebleeds are serious.[3]

Contents



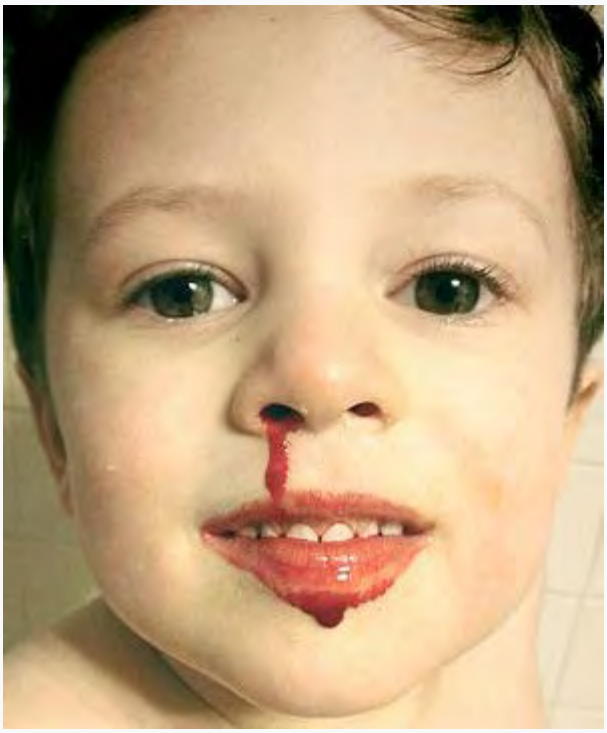
## Cause [edit]

The causes of nosebleeds can generally be divided into two categories, local and general factors, although a significant number of nosebleeds occur with no obvious cause.

### Local factors [edit]

**Nosebleed**

**Synonyms**



A three year old with a minor nosebleed, from falling and hitting the floor with his face. Nosebleeds like this one normally resolve within a few minutes.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Otorhinolaryngology |
| **ICD-10** | R04.0 |
| **ICD-9-CM** | 784.7 |
| **DiseasesDB** | 18327 |
| **MedlinePlus** | 003106 |
| **eMedicine** | emerg/806 ent/701 |

- Blunt trauma (usually a sharp blow to the face such as a punch, sometimes accompanying a nasal fracture)
- Foreign bodies (such as fingers during nose-picking)
- Inflammatory reaction (*e.g.* acute respiratory tract infections, chronic sinusitis, rhinitis or environmental irritants)

| | |
|---|---|
| **Patient UK** | Nosebleed |
| **MeSH** | *C08.460.261* |

[edit on Wikidata]

Two children boxing, the one on the right having a nosebleed due to a punch to the face.

## Other possible factors [edit]

- Anatomical deformities (*e.g.* septal spurs or hereditary hemorrhagic telangiectasia)
- Insufflated drugs (particularly cocaine)
- Intranasal tumors (*e.g.* nasopharyngeal carcinoma or nasopharyngeal angiofibroma)
- Low relative humidity of inhaled air (particularly during cold winter seasons).[3] Evidence to support this however is weak.[4][5]
- Nasal cannula $O_2$ (tending to dry the nasal mucosa)
- Nasal sprays (particularly prolonged or improper use of nasal steroids)
- Middle ear barotrauma (such as from descent in aircraft or ascent in scuba diving)
- Surgery (*e.g.* septoplasty and functional endoscopic sinus surgery)

## Systemic factors [edit]

### Most common factors [edit]

- Infectious diseases (*e.g.* common cold)
- Hypertension

### Other possible factors [edit]


This section **does not cite any sources**. Please help improve this section by adding citations to reliable sources. Unsourced material may be challenged and removed. *(June 2013) (Learn how and when to remove this template message)*

- Alcohol (due to vasodilation)
- Anemia
- Blood dyscrasias
- Connective tissue disease
- Drugs—aspirin, fexofenadine, warfarin, clopidogrel, prasugrel, isotretinoin, desmopressin and others
- Envenomation by mambas, taipans, kraits, and death adders
- Chronic liver disease—cirrhosis causes deficiency of factor II, VII, IX,& X
- Heart failure (due to an increase in venous pressure)
- Hematological malignancy (such as leukemia)
- Idiopathic thrombocytopenic purpura
- Pregnancy (rare, due to hypertension and hormonal changes)
- Vascular disorders
- Vitamin C and vitamin K deficiency
- Von Willebrand's disease
- Recurrent epistaxis is a feature of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)
- Mediastinal compression by tumours (raised venous pressure)
- Hemophilia

- Thrombotic thrombocytopenic purpura

## Pathophysiology [edit]

Nosebleeds are due to the rupture of a blood vessel within the richly perfused nasal mucosa. Rupture may be spontaneous or initiated by trauma. Nosebleeds are reported in up to 60% of the population with peak incidences in those under the age of ten and over the age of 50 and appear to occur in males more than females.[6] An increase in blood pressure (e.g. due to general hypertension) tends to increase the duration of spontaneous epistaxis.[7] Anticoagulant medication and disorders of blood clotting can promote and prolong bleeding. Spontaneous epistaxis is more common in the elderly as the nasal mucosa (lining) becomes dry and thin and blood pressure tends to be higher. The elderly are also more prone to prolonged nose bleeds as their blood vessels are less able to constrict and control the bleeding.

The vast majority of nose bleeds occur in the anterior (front) part of the nose from the nasal septum. This area is richly endowed with blood vessels (Kiesselbach's plexus). This region is also known as Little's area. Bleeding farther back in the nose is known as a posterior bleed and is usually due to bleeding from Woodruff's plexus, a venous plexus situated in the posterior part of inferior meatus.[8] Posterior bleeds are often prolonged and difficult to control. They can be associated with bleeding from both nostrils and with a greater flow of blood into the mouth.[6]

Sometimes blood flowing from other sources of bleeding passes through the nasal cavity and exits the nostrils. It is thus blood coming from the nose but is not a true nosebleed, that is, not truly originating from the nasal cavity. Such bleeding is called pseudoepistaxis (*pseudo* + *epistaxis*). Examples include blood coughed up through the airway and ending up in the nasal cavity, then dripping out.

## Treatment [edit]

The flow of blood normally stops when the blood clots, which may be encouraged by direct pressure applied by pinching the soft fleshy part of the nose. This applies pressure to Little's area (Kiesselbach's area), the source of the majority of nose bleeds, and promotes clotting. Pressure should be firm and be applied for at least five minutes and up to 20 minutes; tilting the head forward helps decrease the chance of nausea and airway obstruction.[6] Swallowing excess blood can irritate the stomach and cause vomiting.

### Medications [edit]

The local application of a vasoconstrictive agent has been shown to reduce the bleeding time in benign cases of epistaxis. The drugs oxymetazoline or phenylephrine are widely available in over-the-counter nasal sprays for the treatment of allergic rhinitis, and they may be used for this purpose.[9]

### Procedures [edit]

If these simple measures do not work then medical intervention may be needed to stop bleeding. The use of silver nitrate to cauterize bleeding blood vessels is common but not very useful for those with more than mild bleeding.[10] It is also often painful even when freezing is used.[11]

There are two types of nasal packing, anterior nasal packing and posterior nasal packing.[12] There are a number of different types of anterior nasal packs. Some use gauze and others use balloons.[12] Posterior packing can be achieved by using a Foley catheter, blowing up the balloon when it is in the back of the throat, and applying traction.[12] Ribbon gauze or Merocel packing can also be used.[12] There are also several dissolvable packing materials, such as surgicel that function as a pack but are not removed and dissolve after a few days. Packing is generally left in for two to five days.[13]

Ongoing bleeding despite good nasal packing is a surgical emergency and can be treated by endoscopic evaluation of the nasal cavity under general anaesthesia to identify an elusive bleeding point or to directly ligate (tie off) the blood vessels supplying the nose. These blood vessels include the sphenopalatine, anterior and posterior ethmoidal arteries. More rarely the maxillary or a branch of the external carotid artery

can be ligated. The bleeding can also be stopped by intra-arterial embolization using a catheter placed in the groin and threaded up the aorta to the bleeding vessel by an interventional radiologist.[14] There is no difference in outcomes between embolization and ligation as treatment options, but embolization is considerably more expensive.[15] Continued bleeding may be an indication of more serious underlying conditions.[14]

### Other [edit]

The utility of local cooling of the head and neck is controversial.[16] Some state that applying ice to the nose or forehead is not useful.[17][18] Others feel that it may promote vasoconstriction of the nasal blood vessels and thus be useful.[19]

### Prevention [edit]

Application of a topical antibiotic ointment to the nasal mucosa has been shown to be an effective treatment for recurrent epistaxis.[20] One study found it as effective as nasal cautery in the prevention of recurrent epistaxis in people without active bleeding at the time of treatment—both had a success rate of approximately 50 percent.[21]

## Society and culture [edit]

In the visual language of Japanese comics (manga) and animation (anime), a sudden, violent nosebleed indicates that the bleeding person is sexually aroused.[22][23] Separately in Western fiction, nosebleeds often signify intense mental focus or effort, particularly during the use of psychic powers.[24][25]

In American and Canadian usage, "nosebleed section" or "nosebleed seats" are common slang for seating at sporting or other spectator events that are the highest up and farthest away from the event. The reference alludes to the propensity for nasal hemorrhage at high altitudes, usually owing to lower barometric pressure.

The oral history of the Native American Sioux tribe includes reference to women who experience nosebleeds as a result of a lover's playing of music, implying sexual arousal.[26]

In Finnish language, "begging for a nosebleed" is commonly used in abstract meaning to describe self-destructive behaviour, for example ignoring safety procedures or deliberately aggravating stronger parties.[27]

In Filipino slang, to "have a nosebleed" is to have serious difficulty conversing in English with a fluent or native English speaker. It can also refer to anxiety brought on by a stressful event such as an examination or a job interview.[28]

In the Dutch language, "pretending to have a nosebleed" is a saying that means pretending not to know anything about something, when actually being involved somehow.

### Etymology and pronunciation [edit]

The word *epistaxis* (/ˌɛpɪˈstæksɪs/) is from Greek: ἐπιστάζω *epistazo*, "to bleed from the nose" from ἐπί *epi*, "above, over" and στάζω *stazo*, "to drip [from the nostrils]".

## References [edit]


1. ^ [1]
2. ^ Work Table I. Deaths from each cause by 5-year age groups, race and sex: US, 1999 Page 1922. U.S. Centers for Disease Control Published 2001-05-11.
3. ^ a b c Wackym,, James B. Snow,... P. Ashley (2009). *Ballenger's otorhinolaryngology : head and neck surgery*

(17th ed.). Shelton, Conn.: People's Medical Pub. House/B C Decker. p. 551. ISBN 9781550093377.
4. ^ Kemal, O; Sen, E (2014). "Does the weather really affect epistaxis?". *B-ENT*. **10** (3): 199–202. PMID 25675665.
5. ^ Comelli, I; Vincenti, V; Benatti, M; Macri, GF; Comelli, D; Lippi, G; Cervellin, G (November 2015). "Influence of air temperature variations on incidence of epistaxis.". *American journal of rhinology & allergy*. **29** (6): 175–81. doi:10.2500/ajra.2015.29.4239. PMID 26637565.
6. ^ [a] [b] [c] Corry J. Kucik; Timothy Clenney (January 15, 2005). "Management of Epistaxis". American Academy of Family Physicians. Retrieved January 31, 2010.
7. ^ J. F. Lubianca Neto; F. D. Fuchs; S. R. Facco; M. Gus; L. Fasolo; R. Mafessoni; A. L. Gleissner (1999). "Is epistaxis evidence of end-organ damage in patients with hypertension?". *Laryngoscope*. **109** (7): 1111–1115. doi:10.1097/00005537-199907000-00019. PMID 10401851.
8. ^ The Journal of Laryngology & Otology (2008), 122: 1074–1077
9. ^ Guarisco JL, Graham HD (1989). "Epistaxis in children: causes, diagnosis, and treatment". *Ear Nose Throat J.* **68** (7): 522, 528–30, 532 passim. PMID 2676467.
10. ^ Stucker, F.J. (2009). *Rhinology and facial plastic surgery*. Berlin: Springer. p. 145. ISBN 9783540743804.
11. ^ Qureishi, A; Burton, MJ (Sep 12, 2012). "Interventions for recurrent idiopathic epistaxis (nosebleeds) in children.". *The Cochrane database of systematic reviews*. **9**: CD004461. doi:10.1002/14651858.CD004461.pub3. PMID 22972071.
12. ^ [a] [b] [c] [d] Killick, N; Malik, V; Nirmal Kumar, B (Mar 2014). "Nasal packing for epistaxis: an evidence-based review.". *British journal of hospital medicine (London, England : 2005)*. **75** (3): 143–7. doi:10.12968/hmed.2014.75.3.143. PMID 24621629.
13. ^ Kucik, CJ; Clenney, T (15 January 2005). "Management of epistaxis.". *American family physician*. **71** (2): 305–11. PMID 15686301.
14. ^ [a] [b] MedlinePlus Medical Encyclopedia: Nosebleed U.S. National Library of Medicine Medline Plus service. Retrieved 2010-03-15.
15. ^ Villwock, JA; Jones, K (Dec 2013). "Recent trends in epistaxis management in the United States: 2008–2010.". *JAMA otolaryngology—head & neck surgery*. **139** (12): 1279–84. doi:10.1001/jamaoto.2013.5220. PMID 24136624.
16. ^ Folz, BJ; Kanne, M; Werner, JA (November 2008). "[Current aspects in epistaxis].". *HNO*. **56** (11): 1157–65; quiz 1166. doi:10.1007/s00106-008-1838-3. PMID 18936903.
17. ^ al.], edited by Roger Jones ... [et (2004). *Oxford textbook of primary medical care.* (repr. ed.). Oxford: Oxford University Press. p. 711. ISBN 9780198567820.
18. ^ Bissonnette, Bruno (2010). *Pediatric Anesthesia*. New York: McGraw-Hill Medical. p. 1182. ISBN 9781607950936.
19. ^ al.], A.Y. Elzouki ... [et. *Textbook of clinical pediatrics* (2nd ed.). Berlin: Springer. p. 3968. ISBN 9783642022012.
20. ^ Kubba H, MacAndie C, Botma M, Robison J, O'Donnell M, Robertson G, Geddes N (2001). "A prospective, single-blind, randomized controlled trial of antiseptic cream for recurrent epistaxis in childhood". *Clin Otolaryngol Allied Sci*. **26** (6): 465–8. doi:10.1046/j.1365-2273.2001.00502.x. PMID 11843924.
21. ^ Murthy P, Nilssen EL, Rao S, McClymont LG (1999). "A randomised clinical trial of antiseptic nasal carrier cream and silver nitrate cautery in the treatment of recurrent anterior epistaxis". *Clin Otolaryngol Allied Sci*. **24** (3): 228–31. doi:10.1046/j.1365-2273.1999.00236.x. PMID 10384851.
22. ^ "Manga: The Complete Guide, reviewed by Richard von Busack". *Metroactive*. Retrieved 5 August 2011.
23. ^ Morgan, Joyce (February 10, 2007). "Superheroes for a complex world". *The Sydney Morning Herald*. Retrieved 5 August 2011.
24. ^ Tracey, Liz (30 August 2016). "'"Stranger Things" and the Psychic Nosebleed". JSTOR Daily. Retrieved 6 November 2016.
25. ^ Meehan, Paul. *Cinema of the Psychic Realm: A Critical Survey*. McFarland. p. 193.
26. ^ Various (1984). Erdoes, Richard; Ortiz, Alfonso, eds. *American Indian Myths and Legends* (2 ed.). Toronto, Ontario: Random House of Canada Limited. p. 274.
27. ^ http://saaressa.blogspot.fr/2011/01/finnsh-idioms.html
28. ^ OMG! Nosebleed! Say what?! Retrieved 28 August 2013

## External links [edit]

- National Library of Medicine - Describes causes, solutions, and prevention of nosebleeds

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media related to *Nosebleeds*.

| v · t · e · | **Symptoms and signs relating to the respiratory system (R04–R07, 786)** | |
|---|---|---|
| Medical examination and history taking | | |
| **Auscultation** | Stethoscope · Respiratory sounds (Stridor · Wheeze · Crackles · Rhonchi · Stertor · Squawk · Pleural friction rub · Fremitus · Bronchophony · Terminal secretions · · Elicited findings (Percussion · Pectoriloquy · Whispered pectoriloquy · Egophony · · | |
| **Breathing** | **Rate** | Apnea (Prematurity · · Dyspnea · Hyperventilation · Hypoventilation · Hyperpnea · Tachypnea · Hypopnea · Bradypnea · |
| | **Pattern** | Agonal respiration · Biot's respiration · Cheyne–Stokes respiration · Kussmaul breathing · Ataxic respiration · |
| | **Other** | Respiratory distress · Respiratory arrest · Orthopnea/Platypnea · Trepopnea · Aerophagia · Asphyxia · Breath holding · Mouth breathing · Snoring · |
| **Other** | Chest pain (In children · Precordial catch syndrome · Pleurisy · · Clubbing/Hippocratic fingers (Schamroth's window test) · Cyanosis · Cough · Sputum · Hemoptysis · Epistaxis · Silhouette sign · Post-nasal drip · Hiccup · *COPD* (Hoover's sign · · *asthma* (Curschmann's spirals · Charcot–Leyden crystals · · *chronic bronchitis* (Reid index · · *sarcoidosis* (Kveim test · · *pulmonary embolism* (Hampton hump · Westermark sign · · *pulmonary edema* (Kerley lines · · Hamman's sign · Golden S sign · | |

| v · t · e · | **Symptoms and signs: Speech and voice / Symptoms involving head and neck (R47–R49, 784)** |
|---|---|
| **Aphasias** | Acute Aphasias (Expressive aphasia · Receptive aphasia · Conduction aphasia · Anomic aphasia · Global aphasia · Transcortical sensory aphasia · Transcortical motor aphasia · Mixed transcortical aphasia · · Progressive Aphasias (Progressive nonfluent aphasia · Semantic dementia · Logopenic progressive aphasia · · Speech disturbances (Speech disorder · Developmental verbal dyspraxia/Apraxia of speech · Auditory verbal agnosia · Dysarthria · Schizophasia · Aprosodia/Dysprosody · Specific language impairment · Thought disorder · Pressure of speech · Derailment · Clanging · Circumstantiality · · |
| **Communication disorders** | Developmental dyslexia/Alexia · Agnosia (Astereognosis · Prosopagnosia · Visual agnosia · · Gerstmann syndrome · Developmental coordination disorder/Apraxia (Ideomotor apraxia · · Dyscalculia/Acalculia · Agraphia · |
| **Voice disturbances** | Dysphonia/Aphonia · Bogart–Bacall syndrome · |
| **Nose** | Post-nasal drip · **Epistaxis** · |
| **Mouth** | Orofacial pain (Toothache · Galvanic pain · Barodontalgia · · Fremitus · Tooth mobility · Bruxism · Trismus · Ageusia · Hypogeusia · Dysgeusia · Parageusia · Hypergeusia · Xerostomia · Halitosis · Drooling · Hypersalivation · |
| **Neck** | Neck mass (Cervical lymphadenopathy · · |
| **Other** | Headache · Auditory processing disorder · Otalgia · Velopharyngeal inadequacy · Velopharyngeal insufficiency · Hypersensitive gag reflex · Jaw claudication · Hypomimia · |

| Authority control | NDL: 00560692 |
|---|---|

Categories: Bleeding | First aid | Nose disorders | Symptoms and signs: Respiratory system




# Otitis externa

From Wikipedia, the free encyclopedia

**Otitis externa**, also known as **swimmer's ear**,[1] is an inflammation of the external ear.[2] It often presents with ear pain, swelling of the ear canal, and occasionally decreased hearing.[2] Typically there is pain with movement of the outer ear.[2] A high fever is typically not present except in severe cases.[2]

Otitis externa may be acute (meaning less than six weeks) or chronic (meaning more than three months) in duration.[2] Acute cases are typically due to a bacterial infection while chronic cases are often due to allergies or autoimmune disorders.[2] Risk factors for acute cases include swimming, minor trauma from cleaning, using hearing aids or ear plugs, and other skin problems like psoriasis or dermatitis.[2][3] Those with diabetes are at risk of a severe form of disease known as malignant otitis externa. Diagnosis is based on the signs and symptoms. Culturing the ear canal may be useful in chronic or severe cases.[2]

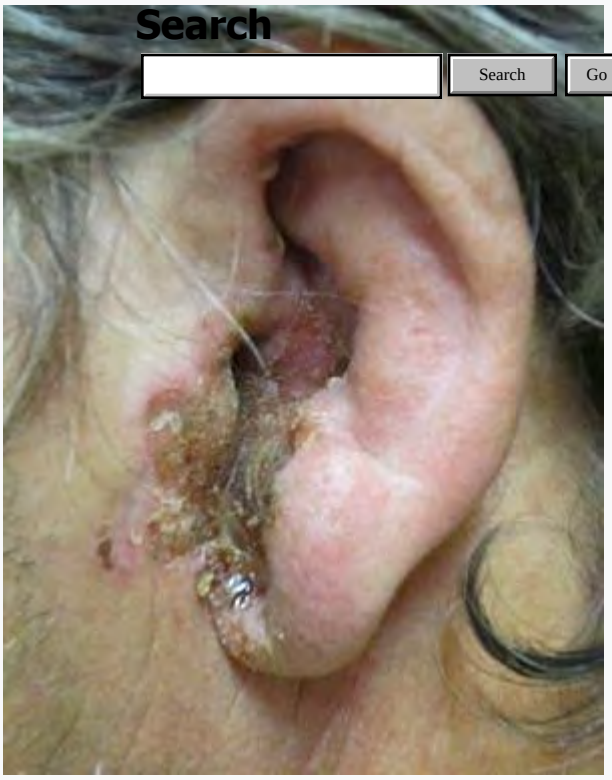
Acetic acid ear drops may be used as a preventative measure.[3] Treatment of acute cases is typically with antibiotic drops such as ofloxacin or acetic acid.[2][3] Steroid drops may be used in addition to antibiotics. Pain medications such as ibuprofen may be used for the pain. Antibiotics by mouth are not recommended unless the person has poor immune function or there is infection of the skin around the ear.[2] Typically improvement occurs within a day of starting treatment. Treatment of chronic cases depends on the cause.[2]

Otitis externa affects 1-3% of people a year with more than 95% of cases being acute.[2] About 10% of people are affected at some point in their life.[3] It occurs most commonly among children between the ages of seven and twelve and among the elderly.[2][4] It occurs with near equal frequency in males and females.[4] Those who live in warm and wet climates are more often affected.[2]

Contents


**Otitis externa**

**Synonyms** External otitis, swimmer's ear[1]



A severe case of acute otitis externa. Note the narrowing of the ear channel, the large amounts of exudate, and swelling of the outer ear.

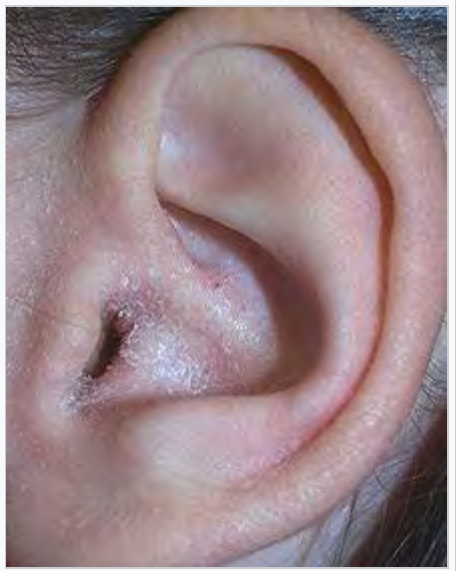
**Classification and external resources**

| | |
|---|---|
| **Specialty** | Otorhinolaryngology |
| **ICD-10** | H60 |
| **ICD-9-CM** | 053.71, 054.73, 112.82, 380.1-380.2 |
| **DiseasesDB** | 9401 |
| **MedlinePlus** | 000622 |
| **eMedicine** | ped/1688 emerg/350 |
| **MeSH** | D010032 |

[edit on Wikidata]

## Signs and symptoms [edit]

Ear pain is the predominant complaint and the only symptom directly related to the severity of acute external otitis. Unlike other forms of ear infections, the pain of acute external otitis is worsened when the outer ear is touched or pulled gently. Pushing the tragus, the tablike portion of the auricle that projects out just in front of the ear canal opening, also typically causes pain in this condition as to be diagnostic of external otitis on physical examination. Patients may also experience ear discharge and itchiness. When enough swelling and discharge in the ear canal is present to block the opening, external otitis may cause temporary conductive hearing loss.


A mild case of otitis externa.

Because the symptoms of external otitis lead many people to attempt to clean out the ear canal (or scratch it) with slim implements, self-cleaning attempts generally lead to additional traumas of the injured skin, so rapid worsening of the condition often occurs.

## Causes [edit]

Swimming in polluted water is a common way to contract swimmer's ear, but it is also possible to contract swimmer's ear from water trapped in the ear canal after a shower, especially in a humid climate.[5] Constriction of the ear canal from bone growth (Surfer's ear) can trap debris leading to infection.[6] Saturation divers have reported Otitis externa during occupational exposure.[7][8][9] Even without exposure to water, the use of objects such as cotton swabs or other small objects to clear the ear canal is enough to cause breaks in the skin, and allow the condition to develop.[10] Once the skin of the ear canal is inflamed, external otitis can be drastically enhanced by either scratching the ear canal with an object, or by allowing water to remain in the ear canal for any prolonged length of time.

The two factors that are required for external otitis to develop are (1) the presence of germs that can infect the skin and (2) impairments in the integrity of the skin of the ear canal that allow an infection to occur. If the skin is healthy and uninjured, only exposure to a high concentration of pathogens, such as submersion in a pond contaminated by sewage, is likely to set off an episode. However, if there are chronic skin conditions that affect the ear canal skin, such as atopic dermatitis, seborrheic dermatitis, psoriasis or abnormalities of keratin production, or if there has been a break in the skin from trauma, even the normal bacteria found in the ear canal may cause infection and full-blown symptoms of external otitis.[11]

Fungal ear canal infections, also known as otomycosis, range from inconsequential to extremely severe. Fungi can be saprophytic, in which there are no symptoms and the fungus simply co-exists in the ear canal in a harmless parasitic relationship with the host, in which case the only physical finding is the presence of a fungus. If the fungus begins active reproduction, the ear canal can fill with dense fungal debris, causing pressure and ever-increasing pain that is unrelenting until the fungus is removed from the canal and anti-fungal medication is used. Most antibacterial ear drops also contain a steroid to hasten resolution of canal

edema and pain. Unfortunately, such drops make the fungal infection worse. Prolonged use of them promotes the growth of fungus in the ear canal. Antibacterial ear drops should be used a maximum of one week, but 5 days is usually enough. Otomycosis responds more than 95% of the time to a three-day course of the same over-the-counter anti-fungal solutions used for athlete's foot.

### Infections [edit]

The majority of cases are due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*,[12] followed by a great number of other gram-positive and gram-negative species.[13] *Candida albicans* and *Aspergillus* species are the most common fungal pathogens responsible for the condition.

## Diagnosis [edit]

When the ear is inspected, the canal appears red and swollen in well-developed cases. The ear canal may also appear eczema-like, with scaly shedding of skin. Touching or moving the outer ear increases the pain, and this maneuver on physical exam is important in establishing the clinical diagnosis. It may be difficult to see the eardrum with an otoscope at the initial examination because of narrowing of the ear canal from inflammation and the presence of drainage and debris. Sometimes the diagnosis of external otitis is presumptive and return visits are required to fully examine the ear. The culture of the drainage may identify the bacteria or fungus causing infection, but is not part of the routine diagnostic evaluation. In severe cases of external otitis, there may be swelling of the lymph node(s) directly beneath the ear.

The diagnosis may be missed in most early cases because the examination of the ear, with the exception of pain with manipulation, is nearly normal. In some early cases, the most striking visual finding is the lack of cerumen. As a moderate or severe case of external otitis resolves, weeks may be required before the ear canal again shows a normal amount of cerumen.

### Classification [edit]

In contrast to the chronic otitis externa, acute otitis externa (AOE) is predominantly a bacterial infection,[14] occurs suddenly, rapidly worsens, and becomes painful. The ear canal has an abundant nerve supply, so the pain is often severe enough to interfere with sleep. Wax in the ear can combine with the swelling of the canal skin and any associated pus to block the canal and dampen hearing to varying degrees, creating a temporary conductive hearing loss. In more severe or untreated cases, the infection can spread to the soft tissues of the face that surround the adjacent parotid gland and the jaw joint, making chewing painful. In its mildest forms, otitis externa is so common that some ear nose and throat physicians have suggested that most people will have at least a brief episode at some point in life. While a small percentage of people seem to have an innate tendency toward chronic otitis externa, most people can avoid otitis externa altogether once they understand the intricate mechanisms of the disease.

The skin of the bony ear canal is unique, in that it is not movable but is closely attached to the bone, and it is almost paper thin. For these reasons, it is easily abraded or torn by even minimal physical force. Inflammation of the ear canal skin typically begins with a physical insult, most often from injury caused by attempts at self-cleaning or scratching with cotton swabs, pen caps, fingernails, hair pins, keys, or other small implements. Another causative factor for acute infection is prolonged water exposure in the forms of swimming or exposure to extreme humidity, which can compromise the protective barrier function of the canal skin, allowing bacteria to flourish; hence the name "swimmer's ear".

## Prevention [edit]

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The strategies for preventing acute external otitis are similar to those for treatment.

- Avoid inserting *anything* into the ear canal: use of cotton buds or swabs is the most common event leading to acute otitis externa.
- Most normal ear canals have a self-cleaning and self-drying mechanism, the latter by simple evaporation.
- After prolonged swimming, a person prone to external otitis can dry the ears using a small battery-powered ear dryer, available at many retailers, especially shops catering to watersports enthusiasts. Alternatively, drops containing dilute acetic acid (vinegar diluted 3:1) or Burow's solution may be used. It is especially important NOT to instrument ears when the skin is saturated with water, as it is very susceptible to injury, which can lead to external otitis.
- Avoid swimming in polluted water.
- Avoid washing hair or swimming if very mild symptoms of acute external otitis begin
- Although the use of earplugs when swimming and shampooing hair may help prevent external otitis, there are important details in the use of plugs. Hard and poorly fitting ear plugs can scratch the ear canal skin and set off an episode. When earplugs are used during an acute episode, either disposable plugs are recommended, or used plugs must be cleaned and dried properly to avoid contaminating the healing ear canal with infected discharge.

# Treatment [edit]

## Medications [edit]

Effective solutions for the ear canal include acidifying and drying agents, used either singly or in combination.[15] When the ear canal skin is inflamed from the acute otitis externa, the use of dilute acetic acid may be painful.

Burow's solution is a very effective remedy against both bacterial and fungal external otitis. This is a buffered mixture of aluminum sulfate and acetic acid, and is available without prescription in the United States.[16]

Ear drops are the mainstays of treatment for external otitis. Some contain antibiotics, either antibacterial or antifungal, and others are simply designed to mildly acidify the ear canal environment to discourage bacterial growth. Some prescription drops also contain anti-inflammatory steroids, which help to resolve swelling and itching. Although there is evidence that steroids are effective at reducing the length of treatment time required, fungal otitis externa (also called otomycosis) may be caused or aggravated by overly prolonged use of steroid-containing drops.

Antibiotics by mouth should not be used to treat uncomplicated acute otitis externa.[17] Antibiotics by mouth are not a sufficient response to bacteria which cause this condition and have significant side effects including increased risk of opportunistic infection.[17] In contrast, topical products can treat this condition.[17] Oral anti-pseudomonal antibiotics can be used in case of severe soft tissue swelling extending into the face and neck and may hasten recovery.[*citation needed*]

Although the acute external otitis generally resolves in a few days with topical washes and antibiotics, complete return of hearing and cerumen gland function may take a few more days. Once healed completely, the ear canal is again self-cleaning. Until it recovers fully, it may be more prone to repeat infection from further physical or chemical insult.

Effective medications include ear drops containing antibiotics to fight infection, and corticosteroids to reduce itching and inflammation. In painful cases a topical solution of antibiotics such as aminoglycoside, polymyxin or fluoroquinolone is usually prescribed. Antifungal solutions are used in the case of fungal infections. External otitis is almost always predominantly bacterial or predominantly fungal, so that only one type of medication is necessary and indicated.

## Cleaning [edit]

Removal of debris (wax, shed skin, and pus) from the ear canal promotes direct contact of the prescribed

medication with the infected skin and shortens recovery time. When canal swelling has progressed to the point where the ear canal is blocked, topical drops may not penetrate far enough into the ear canal to be effective. The physician may need to carefully insert a wick of cotton or other commercially available, pre-fashioned, absorbent material called an ear wick and then saturate that with the medication. The wick is kept saturated with medication until the canal opens enough that the drops will penetrate the canal without it. Removal of the wick does not require a health professional. Antibiotic ear drops should be dosed in a quantity that allows coating of most of the ear canal and used for no more than 4 to 7 days. The ear should be left open. It is imperative that visualization of an intact tympanic membrane (eardrum) is noted. Use of certain medications with a ruptured tympanic membrane can cause tinnitus, vertigo, dizziness and hearing loss in some cases.

## Prognosis [edit]

Otitis externa responds well to treatment, but complications may occur if it is not treated. Individuals with underlying diabetes, disorders of the immune system, or history of radiation therapy to the base of the skull are more likely to develop complications, including malignant otitis externa.[18] In these individuals, rapid examination by an otolaryngologist (ear, nose, and throat physician) is very important.

- Chronic otitis externa
- Spread of infection to other areas of the body
- Necrotizing external otitis
- Otitis externa haemorhagica

### Necrotizing external otitis [edit]

Necrotizing external otitis (malignant otitis externa) is an uncommon form of external otitis that occurs mainly in elderly diabetics, being somewhat more likely and more severe when the diabetes is poorly controlled. Even less commonly, it can develop due to a severely compromised immune system. Beginning as infection of the external ear canal, there is an extension of the infection into the bony ear canal and the soft tissues deep to the bony canal. Unrecognized and untreated, it may result in death. The hallmark of malignant otitis externa (MOE) is unrelenting pain that interferes with sleep and persists even after swelling of the external ear canal may have resolved with topical antibiotic treatment.[18] It can also cause skull base osteomyelitis (SBO), manifested by multiple cranial nerve palsies, described below under the "Treatment" heading.

### Natural history [edit]

MOE follows a much more chronic and indolent course than ordinary acute otitis externa. There may be granulation involving the floor of the external ear canal, most often at the bony-cartilaginous junction. Paradoxically, the physical findings of MOE, at least in its early stages, are often much less dramatic than those of ordinary acute otitis externa. In later stages, there can be soft tissue swelling around the ear, even in the absence of significant canal swelling. While fever and leukocytosis might be expected in response to bacterial infection invading the skull region, MOE does not cause fever or elevation of white blood count.

### Treatment of MOE [edit]

Unlike ordinary otitis externa, MOE requires oral or intravenous antibiotics for cure. Pseudomonas is the most common offending pathogen. Diabetes control is also an essential part of treatment. When MOE goes unrecognized and untreated, the infection continues to smolder and over weeks or months can spread deeper into the head and involve the bones of the skull base, constituting skull base osteomyelitis (SBO). Multiple cranial nerve palsies can result, including the facial nerve (causing facial palsy), the recurrent laryngeal nerve (causing vocal cord paralysis)[*citation needed*], and the cochlear nerve (causing deafness). The infecting organism is almost always pseudomonas aeruginosa, but it can instead be fungal (aspergillus or mucor). MOE and SBO are not amenable to surgery, but exploratory surgery may facilitate the culture of unusual organism(s) that are not responding to empirically used anti-pseudomonal antibiotics (ciprofloxacin being the drug of choice). The usual surgical finding is diffuse cellulitis without localized abscess formation.

SBO can extend into the petrous apex of the temporal bone or more inferiorly into the opposite side of the skull base.

The use of hyperbaric oxygen therapy as an adjunct to antibiotic therapy remains controversial.[18]

### Complications [edit]

As the skull base is progressively involved, the adjacent exiting cranial nerves and their branches, especially the facial nerve and the vagus nerve, may be affected, resulting in facial paralysis and hoarseness, respectively. If both of the recurrent laryngeal nerves are paralyzed, shortness of breath may develop and necessitate tracheotomy. Profound deafness can occur, usually later in the disease course due to relative resistance of the inner ear structures. Gallium scans are sometimes used to document the extent of the infection but are not essential to disease management. Skull base osteomyelitis is a chronic disease that can require months of IV antibiotic treatment, tends to recur, and has a significant mortality rate.[18]

## Epidemiology [edit]

The incidence of otitis externa is high. In the Netherlands, it has been estimated at 12–14 per 1000 population per year, and has been shown to affect more than 1% of a sample of the population in the United Kingdom over a 12-month period.[19]

## History [edit]

During the Tektite Project in 1969 there was a great deal of otitis externa.[20] The Diving Medical Officer devised a prophylaxis that came to be known as, "Tektite Solution", equal parts of 15% tannic acid, 15% acetic acid and 50% isopropanol or ethanol. During Tektite ethanol was used because it was available in the lab for pickling specimens.

## Other animals [edit]

*See also: Otitis externa in animals*

## References [edit]


1. ^ a b Rapini, Ronald P.; Bolognia, Jean L.; Jorizzo, Joseph L. (2007). *Dermatology: 2-Volume Set*. St. Louis: Mosby. ISBN 1-4160-2999-0.
2. ^ a b c d e f g h i j Wipperman, J (March 2014). "Otitis externa.". *Primary care*. **41** (1): 1–9. doi:10.1016/j.pop.2013.10.001. PMID 24439876.
3. ^ a b c d e Schaefer, P; Baugh, RF (1 December 2012). "Acute otitis externa: an update.". *American family physician*. **86** (11): 1055–61. PMID 23198673.
4. ^ a b Lee, H; Kim, J; Nguyen, V (September 2013). "Ear infections: otitis externa and otitis media.". *Primary care*. **40** (3): 671–86. doi:10.1016/j.pop.2013.05.005. PMID 23958363.
5. ^ Wang MC, Liu CY, Shiao AS, Wang T (August 2005). "Ear problems in swimmers". *J Chin Med Assoc*. **68** (8): 347–52. doi:10.1016/S1726-4901(09)70174-1. PMID 16138712.
6. ^ http://www.ent.uci.edu/surfer%27s%20ear.ht
14. ^ Rosenfeld, R. M.; Schwartz, S. R.; Cannon, C. R.; Roland, P. S.; Simon, G. R.; Kumar, K. A.; Huang, W. W.; Haskell, H. W.; Robertson, P. J. (3 February 2014). "Clinical Practice Guideline: Acute Otitis Externa Executive Summary". *Otolaryngology -- Head and Neck Surgery*. **150** (2): 161–168. doi:10.1177/0194599813517659.
15. ^ Doc Vikingo (March–April 2007). "Swimmers Ear – Additional Advice About A Pesky and Sometimes Painful Problem". *Diver's Alert Network: Alert Diver Magazine*. Retrieved 2008-07-22.
16. ^ Kashiwamura M. Chida E. Matsumura M. Nakamaru Y. Suda N. Terayama Y. Fukuda S. The efficacy of Burow's solution as an ear preparation for the treatment of chronic ear infections. [Clinical Trial. Journal Article] Otology & Neurotology. 25(1):9–13, 2004

Archived July 17, 2009, at the Wayback Machine.
7. ^ Cobet AB, Wright DN, Warren PI (June 1970). "Tektite-I program: bacteriological aspects". *Aerosp Med.* **41** (6): 611–6. PMID 4392833.
8. ^ Ahlén C, Mandal LH, Iversen OJ (July 1998). "Identification of infectious Pseudomonas aeruginosa strains in an occupational saturation diving environment". *Occup Environ Med.* **55** (7): 480–4. doi:10.1136/oem.55.7.480. PMC 1757612. PMID 9816382.
9. ^ Thalmann, ED (1974). "A Prophylactic Program for the Prevention of Otitis Externa in Saturation Divers". *United States Navy Experimental Diving Unit Technical Report*. NEDU-RR-10-74. Retrieved 2008-07-22.
10. ^ Zichichi L, Asta G, Noto G (April 2000). "Pseudomonas aeruginosa folliculitis after shower/bath exposure". *Int. J. Dermatol.* **39** (4): 270–3. doi:10.1046/j.1365-4362.2000.00931.x. PMID 10809975. Retrieved 2008-07-22.
11. ^ Kang K, Stevens SR. Pathophysiology of atopic dermatitis. Clin Dermatol 2003;21:116–121.
12. ^ Rosenfeld, Richard M.; Brown, Lance; Cannon, C. Ron; Dolor, Rowena J.; Ganiats, Theodore G.; Hannley, Maureen; Kokemueller, Phillip; Marcy, S. Michael; Roland, Peter S. (2006-04-01). "Clinical practice guideline: acute otitis externa". *Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*. **134** (4 Suppl): S4–23. doi:10.1016/j.otohns.2006.02.014. ISSN 0194-5998. PMID 16638473.
13. ^ Roland P, Stroman D (2002). "Microbiology of
17. ^ *a b c* American Academy of Otolaryngology – Head and Neck Surgery (February 2013), "Five Things Physicians and Patients Should Question", *Choosing Wisely: an initiative of the ABIM Foundation*, American Academy of Otolaryngology – Head and Neck Surgery, retrieved August 1, 2013, which cites
    - Rosenfeld, R.; Brown, L.; Cannon, C.; Dolor, R.; Ganiats, T.; Hannley, M.; Kokemueller, P.; Marcy, S.; Roland, P.; Shiffman, R.; Stinnett, S. S.; Witsell, D. L.; American Academy of Otolaryngology--Head Neck Surgery Foundation (2006). "Clinical practice guideline: Acute otitis externa". *Otolaryngology - Head and Neck Surgery*. **134** (4): S4–23. doi:10.1016/j.otohns.2006.02.014. PMID 16638473.
18. ^ *a b c d* Saxby A, Barakate M, Kertesz T, James J, Bennett M (December 2010). "Malignant otitis externa: experience with hyperbaric oxygen therapy". *Diving and Hyperbaric Medicine*. **40** (4): 195–200. PMID 23111934. Retrieved 2013-05-18.
19. ^ van Balen F, Smit W, Zuithoff N, Verheij T (2003). "Clinical efficacy of three common treatments in acute otitis externa in primary care: randomised controlled trial". *BMJ*. **327** (7425): 1201–5. doi:10.1136/bmj.327.7425.1201. PMC 274056. PMID 14630756. *Full text*
20. ^ Ray, Edward; Robert Cohen (February 1970). "'"Tektite": A Blueprint for Cooperative Undersea Scientific Program". *Journal of the Atomic Scientists*. **XXIV** (2): 35–40. Retrieved 11/03/2012. Check date values in: `|access-date=` (help)

## External links [edit]

- Fluid in the Middle Ear: A Guide for Parents, The Institute for Good Medicine at the Pennsylvania Medical Society
- What to do if your child has swimmer's ear from Seattle Children's Hospital
- DRTBALU.com Otolaryngology online

| v · t · e · | Diseases of the ear and mastoid process (H60–H99, 380–389) | | |
|---|---|---|---|
| **Outer ear** | **Otitis externa** · Otomycosis · | | |
| **Middle ear and mastoid** | Otitis media · Mastoiditis (Bezold's abscess · Gradenigo's syndrome · · Tympanosclerosis · Cholesteatoma · Perforated eardrum · | | |
| **Inner ear and central pathways** | **Equilibrioception** | Vertigo/Balance disorder: *peripheral* (Ménière's disease · BPPV · Vestibular neuronitis (Labyrinthitis) · Perilymph fistula · · *central* (Central positional nystagmus) · | |
| | | **Hearing impairment** | Conductive hearing loss (Otosclerosis · Superior canal dehiscence · · Sensorineural hearing loss (Presbycusis · Cortical deafness · · |

| | | | |
|---|---|---|---|
| | **Hearing** | | Nonsyndromic deafness · |
| | | **Excessive response** | Tinnitus · Hyperacusis/Phonophobia · |
| | | **Deafblindness** | Wolfram syndrome · Usher syndrome · |
| | | **Other** | Auditory processing disorder · Spatial hearing loss · |

Categories: Otitis | Pediatrics | Bacterium-related cutaneous conditions | Diseases of external ear | Swimming culture




# Otitis media

From Wikipedia, the free encyclopedia

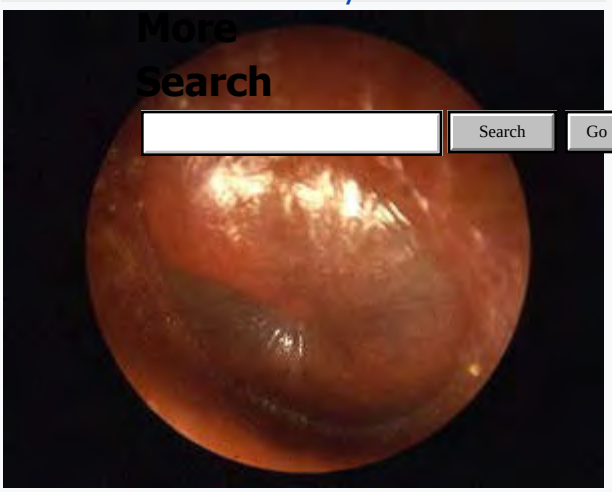
**Otitis media** is a group of inflammatory diseases of the middle ear.[1] The two main types are **acute otitis media** (**AOM**) and **otitis media with effusion** (**OME**).[2] AOM is an infection of abrupt onset that usually presents with ear pain. In young children this may result in pulling at the ear, increased crying, and poor sleep. Decreased eating and a fever may also be present. OME is typically not associated with symptoms.[3] Occasionally a feeling of fullness is described. It is defined as the presence of non-infectious fluid in the middle ear for more than three months. **Chronic suppurative otitis media** (**CSOM**) is middle ear inflammation of greater than two weeks that results in episodes of discharge from the ear. It may be a complication of acute otitis media. Pain is rarely present.[4] All three may be associated with hearing loss.[1][2] The hearing loss in OME, due to its chronic nature, may affect a child's ability to learn.[1]

The cause of AOM is related to childhood anatomy and immune function. Either bacteria or viruses may be involved. Risk factors include exposure to smoke, use of pacifiers, and attending daycare. It occurs more commonly in those who are Native American or who have Down syndrome.[4] OME frequently occurs following AOM and may be related to viral upper respiratory infections, irritants such as smoke, or allergies.[2][4] Looking at the eardrum is important for making the correct diagnosis.[5] Signs of AOM include bulging or a lack of movement of the tympanic membrane from a puff of air.[3][6] New discharge not related to otitis externa also indicates the diagnosis.[3]

A number of measures decrease the risk of otitis media including pneumococcal and influenza vaccination, exclusive breastfeeding for the first six months of life, and avoiding tobacco smoke.[3] The use of pain medications for AOM is important.[3] This may include paracetamol (acetaminophen), ibuprofen, benzocaine ear drops, or opioids.[3] In AOM, antibiotics may speed recovery but may result in side effects.[3] Antibiotics are often recommended in those with severe disease or under two years old. In those with less severe disease they may only be recommended in those who do not improve after two or three days.[6] The initial antibiotic of choice is typically amoxicillin. In those with frequent

## Variants

**Otitis media**



A bulging tympanic membrane which is typical in a case of acute otitis media

| Classification and external resources | |
|---|---|
| **Specialty** | Otorhinolaryngology |
| **ICD-10** | H65-H67 |
| **ICD-9-CM** | 017.40, 055.2, 381.0, 381.1, 381.2, 381.3, 381.4, 382 |
| **DiseasesDB** | 29620 serous, 9406 suppurative |
| **MedlinePlus** | 000638 acute, *007010* with effusion, *000619* chronic |
| **eMedicine** | emerg/351 ent/426 complications, ent/209 with effusion, ent/212 Medical treat., ent/211 Surgical treat. ped/1689 |
| **MeSH** | D010033 |

infections tympanostomy tubes may decrease recurrence.[3] In children with otitis media with effusion antibiotics may increase resolution of symptoms, but may cause diarrhoea, vomiting and skin rash.[8]

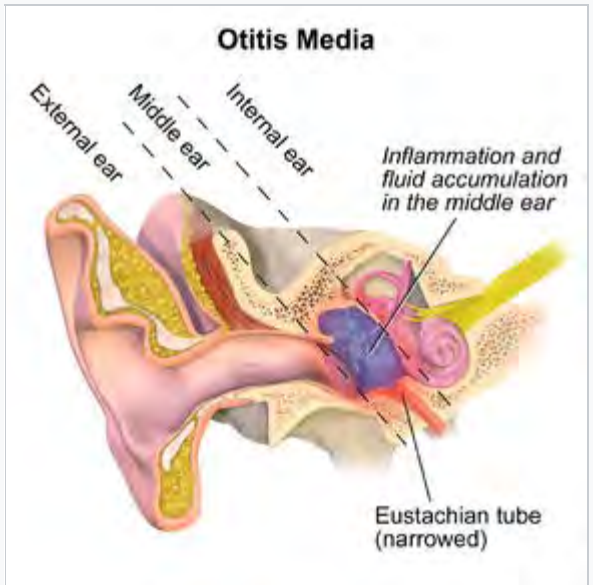
Worldwide AOM affect about 11% of people a year (about 325 to 710 million cases).[9][10] Half the cases involve children less than five years of age and it is more common among males.[4][9] Of those affected about 4.8% or 31 million develop chronic suppurative otitis media.[9] Before the age of ten OME affects about 80% of children at some point.[4] Otitis media resulted in 2,400 deaths in 2013 – down from 4,900 deaths in 1990.[11]



## Signs and symptoms [edit]

An integral symptom of acute otitis media is ear pain; other possible symptoms include fever, and irritability (in infants). Since an episode of otitis media is usually precipitated by an upper respiratory tract infection (URTI), there often are accompanying symptoms like a cough and nasal discharge.[12]

Discharge from the ear can be caused by acute otitis media with perforation of the ear drum, chronic suppurative otitis media, tympanostomy tube otorrhea, or acute otitis externa. Trauma, such as a basilar skull fracture, can also lead to discharge from the ear due to cerebral spinal drainage from the brain and its covering (meninges).



Otitis media.

## Causes [edit]

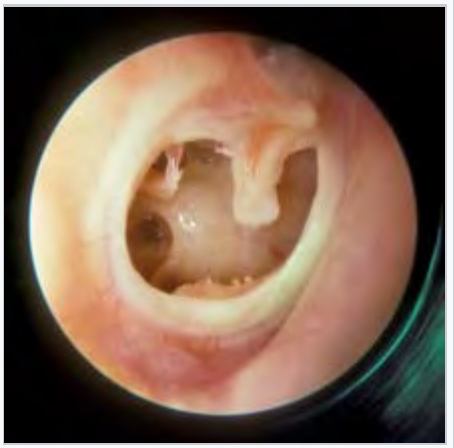
The common cause of all forms of otitis media is dysfunction of the Eustachian tube.[13] This is usually due to inflammation of the mucous membranes in the nasopharynx, which can be caused by a viral URI, strep throat, or possibly by allergies.[14] Because of the dysfunction of the Eustachian tube, the gas volume in the middle ear is trapped and parts of it are slowly absorbed by the surrounding tissues, leading

to negative pressure in the middle ear. Eventually, the negative middle-ear pressure can reach a point where fluid from the surrounding tissues is sucked into the middle ear's cavity (tympanic cavity), causing a middle-ear effusion. This is seen as a progression from a Type A tympanogram to a Type C to a Type B tympanogram.

By reflux or aspiration of unwanted secretions from the nasopharynx into the normally sterile middle-ear space, the fluid may then become infected — usually with bacteria. The virus that caused the initial URI can itself be identified as the pathogen causing the infection.[14]

## Diagnosis [edit]

As its typical symptoms overlap with other conditions, such as acute external otitis, clinical history alone is not sufficient to predict whether acute otitis media is present; it has to be complemented by visualization of the tympanic membrane.[15][16] Examiners use a pneumatic otoscope with a rubber bulb attached to assess the mobility of the tympanic membrane.



Perforation of the right tympanic membrane resulting from a previous severe acute otitis media

Acute otitis media in children with moderate to severe bulging of the tympanic membrane or new onset of otorrhea (drainage) is not due to external otitis. Also, the diagnosis may be made in children who have mild bulging of the ear drum and recent onset of ear pain (less than 48 hours) or intense erythema (redness) of the ear drum.

To confirm the diagnosis, middle-ear effusion and inflammation of the eardrum have to be identified; signs of these are fullness, bulging, cloudiness and redness of the eardrum.[12] It is important to attempt to differentiate between acute otitis media and otitis media with effusion (OME), as antibiotics are not recommended for OME.[12] It has been suggested that bulging of the tympanic membrane is the best sign to differentiate AOM from OME.[17]

Viral otitis may result in blisters on the external side of the tympanic membrane, which is called *bullous myringitis* (*myringa* being Latin for "eardrum").[18]

However, sometimes even examination of the eardrum may not be able to confirm the diagnosis, especially if the canal is small. If wax in the ear canal obscures a clear view of the eardrum it should be removed using a blunt cerumen curette or a wire loop. Also, an upset young child's crying can cause the eardrum to look inflamed due to distension of the small blood vessels on it, mimicking the redness associated with otitis media.

### Acute otitis media [edit]

The most common bacteria isolated from the middle ear in AOM are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*,[12] and *Staphylococcus aureus*.[19]

### Otitis media with effusion [edit]

Otitis media with effusion (OME), also known as serous otitis media (SOM) or secretory otitis media (SOM), and commonly referred to as glue ear,[20] is a collection of effusion (fluid) that occurs in the middle ear space due to the negative pressure produced by dysfunction of the Eustachian tube. This can occur purely from a viral URI or bacterial infection, or it can precede and/or follow acute bacterial otitis media.[21] Fluid in the middle ear frequently causes conductive hearing impairment but only when it interferes with the normal vibration of the eardrum by sound waves. Over weeks and months, middle-ear fluid can become very thick and glue-like, which increases the likelihood of its causing conductive hearing impairment.

Early-onset OME is associated with feeding of infants while lying down, early entry into group child care, parental smoking, lack, or too short a period of breastfeeding and greater amounts of time spent in group

child care, particularly those with a large number of children, increases the incidences and duration of OME in the first two years of life.[22]

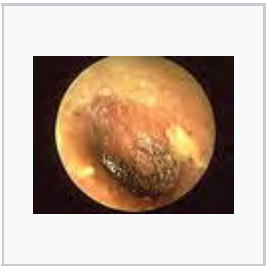
### Chronic suppurative otitis media [edit]

Chronic suppurative otitis media, incorrectly called chronic otitis media or chronic ear infection, involves a hole in the tympanic membrane and active bacterial infection within the middle ear space for several weeks or more. There may be enough pus that it drains to the outside of the ear (otorrhea), or the pus may be minimal enough to only be seen on examination using the otoscope or, more effectively, with a binocular microscope. This disease is much more common in persons with poor Eustachian tube function and very common in certain races such as Native North Americans. Hearing impairment often accompanies this disease.

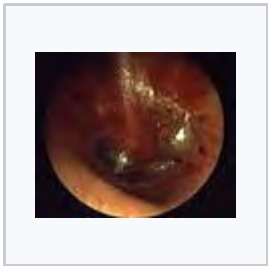
It is a primary cause of hearing loss that newly develops in children. An ear wick may be effective or, if not, antibiotics.[23]

### Adhesive otitis media [edit]

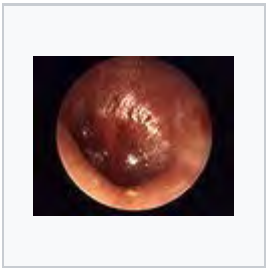
Adhesive otitis media occurs when a thin retracted ear drum becomes sucked into the middle-ear space and stuck (i.e., adherent) to the ossicles and other bones of the middle ear.



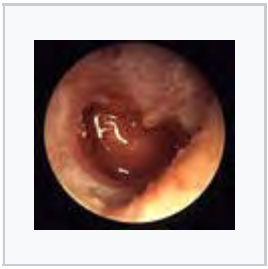
Acute otitis media



Acute otitis media, myringitis bullosa

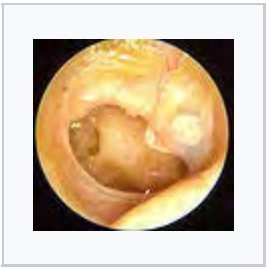


Myringitis bullosa in influenza

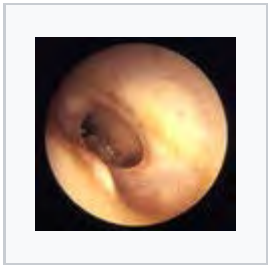


Chronic otitis media (otitis media chronica mesotympanalis)

Otitis media chronica mesotympanalis



Otitis media chronica mesotympanalis



Otitis media chronica mesotympanalis

## Prevention [edit]

Long-term antibiotics, while they decrease rates of infection during treatment, have an unknown effect on long-term outcomes such as hearing loss.[24] This method of prevention has been associated with emergence of antibiotic-resistant otitic bacteria. They are thus not recommended.[12]

Pneumococcal conjugate vaccines when given during infancy decrease rates of acute otitis media by 6%–7% and, if implemented broadly, would have a significant public health benefit.[12][25][*needs update*] Influenza vaccine is recommended annually.[12]

Risk factors such as season, allergy predisposition and presence of older siblings are known to be

determinants of recurrent otitis media and persistent middle-ear effusions (MEE).[26] History of recurrence, environmental exposure to tobacco smoke, use of daycare, and lack of breastfeeding have all been associated with increased risk of development, recurrence, and persistent MEE.[27][28] Thus, cessation of smoking in the home should be encouraged, daycare attendance should be avoided or daycare facilities with the fewest attendees should be recommended, and breastfeeding should be promoted.[27][28]

There is some evidence that breastfeeding for the first year of life is associated with a reduction in the number and duration of OM infections.[29][30] Pacifier use, on the other hand, has been associated with more frequent episodes of AOM.[31]

Evidence does not support zinc supplementation as an effort to reduce otitis rates except maybe in those with severe malnutrition such as marasmus.[32]

## Management [edit]

Oral and topical pain killers are effective to treat the pain caused by otitis media. Oral agents include ibuprofen, paracetamol (acetaminophen), and opiates. Topical agents shown to be effective include antipyrine and benzocaine ear drops.[33] Decongestants and antihistamines, either nasal or oral, are not recommended due to the lack of benefit and concerns regarding side effects.[34] Half of cases of ear pain in children resolve without treatment in three days and 90% resolve in seven or eight days.[35] The use of steroids is not supported by the evidence for acute otitis media.[36]

### Antibiotics [edit]

It is important to weigh the benefits and harms before using antibiotics for acute otitis media. As over 80% of acute episodes settle without treatment, about 20 children must be treated to prevent one case of ear pain, 33 children to prevent one perforation, and 11 children to prevent one opposite-side ear infection. For every 14 children treated with antibiotics, one child has an episode of either vomiting, diarrhea or a rash.[37][*needs update*] If pain is present, treatment to reduce it should be initiated.

- Antibiotics should be prescribed for severe bilateral or unilateral disease in all infants and children with severe signs and symptoms, such as moderate to severe ear pain and high fever.
- For bilateral acute otitis media in infants younger than 24 months of age, without severe signs and symptoms, antibiotics should be prescribed.
- When non-severe unilateral acute otitis media is diagnosed in young children either antibiotic therapy is given or observation with close follow-up based on joint decision making between parent(s)/caregiver in infants 6 to 23 months of age. If the child worsens or fails to improve in 2 to 3 days antibiotics should be administered.
- Children 24 months or older with non-severe disease can have either antibiotics or observation.

The first line antibiotic treatment, if warranted, is amoxicillin.[12] If there is resistance or use of amoxicillin in the last 30 days then amoxicillin-clavulanate or another penicillin derivative plus beta lactamase inhibitor is recommended.[12] Taking amoxicillin once a day may be as effective as twice[38] or three times a day. While less than 7 days of antibiotics have less side effects, more than seven days appear to be more effective.[39] If there is no improvement after 2–3 days of treatment a change in therapy may be considered.[12]

A treatment option for chronic suppurative otitis media with discharge is topical antibiotics. A Cochrane review found that topical quinolone antibiotics can improve discharge better than oral antibiotics.[40] Safety is not really clear.[40]

### Tympanostomy tube [edit]

Tympanostomy tubes (also called "grommets") are recommended in those people who have three or more episodes of acute otitis media in 6 months or four or more in a year, with at least one episode or more [12]

attacks in the preceding 6 months. In chronic cases with effusions, insertion of tympanostomy tube into the eardrum reduces recurrence rates in the 6 months after placement[41] but has little effect on long-term hearing.[42] A common complication of having a tympanostomy tube is otorrhea, which is a discharge from the ear.[43]

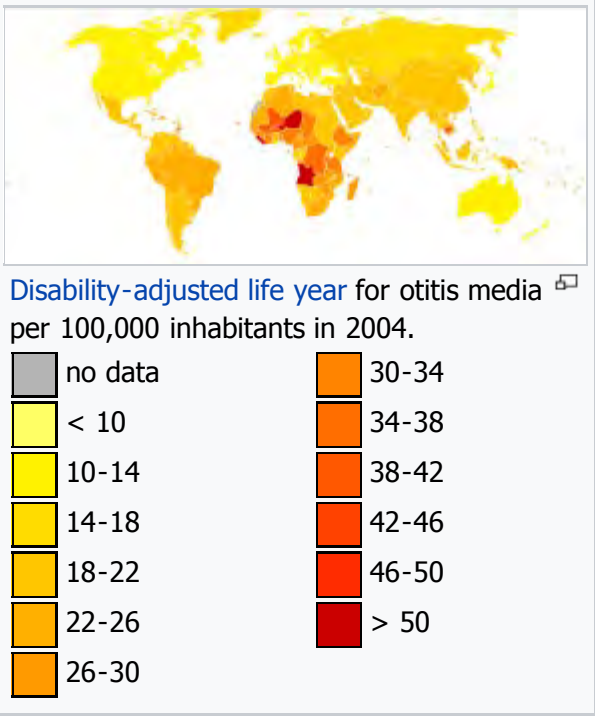
Oral antibiotics should not be used to treat uncomplicated acute tympanostomy tube otorrhea.[43] Oral antibiotics are not a sufficient response to bacteria that cause this condition and have significant side effects including increased risk of opportunistic infection.[43] In contrast, topical antibiotic eardrops can treat this condition.[43]

### Alternative medicine [edit]

Complementary and alternative medicine is not recommended for otitis media with effusion because there is no evidence of benefit.[21] An osteopathic manipulation technique called the Galbreath technique[44] was evaluated in one randomized controlled clinical trial; one reviewer concluded that it was promising, but a 2010 evidence report found the evidence inconclusive.[45]

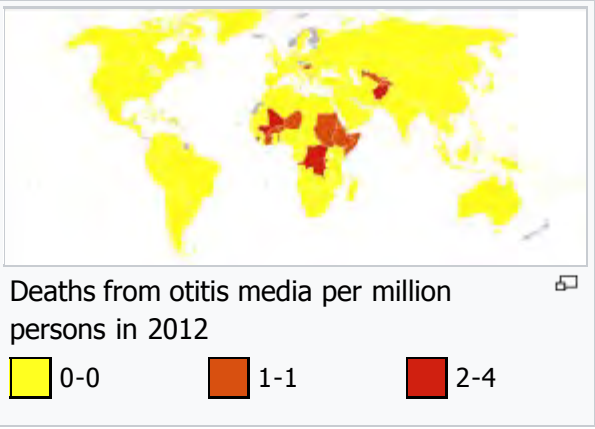
## Outcomes [edit]

Complications of acute otitis media consists of perforation of the ear drum, infection of the mastoid space behind the ear (mastoiditis), and more rarely intracranial complications can occur, such as bacterial meningitis, brain abscess, or dural sinus thrombosis.[46] It is estimated that each year 21,000 people die due to complications of otitis media.[47]




### Membrane rupture [edit]

In severe or untreated cases, the tympanic membrane may perforate, allowing the pus in the middle-ear space to drain into the ear canal. If there is enough, this drainage may be obvious. Even though the perforation of the tympanic membrane suggests a highly painful and traumatic process, it is almost always associated with a dramatic relief of pressure and pain. In a simple case of acute otitis media in an otherwise healthy person, the body's defenses are likely to resolve the infection and the ear drum nearly always heals. An option for severe acute otitis media in which analgesics are not controlling ear pain is to perform a tympanocentesis, i.e., needle aspiration through the tympanic membrane to relieve the ear pain and to identify the causative organism(s).




### Hearing loss [edit]

Children with recurrent episodes of acute otitis media and those with otitis media with effusion or chronic suppurative otitis media have higher risks of developing conductive and sensorineural hearing loss. Globally approximately 141 million people have mild hearing loss due to otitis media (2.1% of the population).[48] This is more common in males (2.3%) than females (1.8%).[48]

This hearing loss is mainly due to fluid in the middle ear or rupture of the tympanic membrane. Prolonged duration of otitis media is associated with ossicular complications and,

together with persistent tympanic membrane perforation, contributes to the severity of the disease and hearing loss. When a cholesteatoma or granulation tissue is present in the middle ear, the degree of hearing loss and ossicular destruction is even greater.[49]

Periods of conductive hearing loss from otitis media may have a detrimental effect on speech development in children.[50] Some studies have linked otitis media to learning problems, attention disorders, and problems with social adaptation.[51] Furthermore, it has been demonstrated that patients with otitis media have more depression/anxiety-related disorders compared to individuals with normal hearing.[52] Once the infections resolve and hearing thresholds return to normal, childhood otitis media may still cause minor and irreversible damage to the middle ear and cochlea.[53]

## Epidemiology [edit]

Acute otitis media is very common in childhood. It is the most common condition for which medical care is provided in children under five years of age in the US.[14] Acute otitis media affects 11% of people each year (709 million cases) with half occurring in those below five years.[47] Chronic suppurative otitis media affects about 5% or 31 million of these cases with 22.6% of cases occurring annually under the age of five years.[47] Otitis media resulted in 2,400 deaths in 2013 — down from 4,900 deaths in 1990.[11]

## Etymology [edit]

Otitis media is Latin for "inflammation of the middle ear".

## References [edit]


1. ^ a b Qureishi, A; Lee, Y; Belfield, K; Birchall, JP; Daniel, M (10 January 2014). "Update on otitis media - prevention and treatment.". *Infection and drug resistance*. **7**: 15–24. doi:10.2147/IDR.S39637. PMID 24453496.
2. ^ a b c "Ear Infections". *cdc.gov*. September 30, 2013. Retrieved 14 February 2015.
3. ^ a b c d e f g Lieberthal, AS; Carroll, AE; Chonmaitree, T; Ganiats, TG; Hoberman, A; Jackson, MA; Joffe, MD; Miller, DT; Rosenfeld, RM; Sevilla, XD; Schwartz, RH; Thomas, PA; Tunkel, DE (March 2013). "The diagnosis and management of acute otitis media.". *Pediatrics*. **131** (3): e964–99. doi:10.1542/peds.2012-3488. PMID 23439909.
4. ^ a b c d e f Minovi, A; Dazert, S (2014). "Diseases of the middle ear in childhood.". *GMS current topics in otorhinolaryngology, head and neck surgery*. **13**: Doc11. doi:10.3205/cto000114. PMID 25587371.
5. ^ Coker, TR; Chan, LS; Newberry, SJ; Limbos, MA; Suttorp, MJ; Shekelle, PG; Takata, GS (17 November 2010). "Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review.". *JAMA*. **304** (19): 2161–9. doi:10.1001/jama.2010.1651. PMID 21081729.
6. ^ a b "Otitis Media: Physician Information Sheet (Pediatrics)". *cdc.gov*. November 4, 2013. Retrieved 14 February 2015.
7. ^ Venekamp, RP; Sanders, SL; Glasziou, PP; Del Mar, CB; Rovers, MM (23 June 2015). "Antibiotics for acute otitis media in children.". *The Cochrane database of systematic reviews*. **6**: CD000219. doi:10.1002/14651858.CD000219.pub4. PMID 26099233.
8. ^ Venekamp, RP; Burton, MJ; van Dongen, TM; van der Heijden, GJ; van Zon, A; Schilder, AG (12 June 2016). "Antibiotics for otitis media with effusion in children.". *The Cochrane database of systematic reviews* (6): CD009163. doi:10.1002/14651858.CD009163.pub3. PMID 27290722.
9. ^ a b c Monasta, L; Ronfani, L; Marchetti, F; Montico, M; Vecchi Brumatti, L; Bavcar, A; Grasso, D; Barbiero, C; Tamburlini, G (2012). "Burden of disease caused by otitis media: systematic review and global estimates.". *PLOS ONE*. **7** (4): e36226. doi:10.1371/journal.pone.0036226. PMC 3340347. PMID 22558393.
10. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
11. ^ a b GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national

age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013."🔗. *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2🔗. PMC 4340604🔗. PMID 25530442🔗.

12. ^ *a b c d e f g h i j k* Lieberthal, AS; Carroll, AE; Chonmaitree, T; Ganiats, TG; Hoberman, A; Jackson, MA; Joffe, MD; Miller, DT; Rosenfeld, RM; Sevilla, XD; Schwartz, RH; Thomas, PA; Tunkel, DE (Feb 25, 2013). "The Diagnosis and Management of Acute Otitis Media". *Pediatrics*. **131** (3): e964–99. doi:10.1542/peds.2012-3488🔗. PMID 23439909🔗.
13. ^ Bluestone, CD (2005). *Eustachian tube: structure, function, role in otitis media*. Hamilton, London: BC Decker. pp. 1–219. ISBN 9781550090666.
14. ^ *a b c* John D Donaldson. "Acute Otitis Media"🔗. Medscape. Retrieved 17 March 2013.
15. ^ Laine MK, Tähtinen PA, Ruuskanen O, Huovinen P, Ruohola A (May 2010). "Symptoms or symptom-based scores cannot predict acute otitis media at otitis-prone age". *Pediatrics*. **125** (5): e1154–61. doi:10.1542/peds.2009-2689🔗. PMID 20368317🔗.
16. ^ Shaikh, Nader (2010). "Videos in clinical medicine. Diagnosing otitis media--otoscopy and cerumen removal."🔗. *NEJM*. **362** (20): e62. doi:10.1056/NEJMvcm0904397🔗. PMID 20484393🔗. Retrieved Feb 11, 2015.
17. ^ Shaikh, N; et al. (March 28, 2012). "Development of an algorithm for the diagnosis of otitis media.". *Academic Pediatrics*. **12** (3): 214–218. doi:10.1016/j.acap.2012.01.007🔗. PMID 22459064🔗.
18. ^ Roberts DB (April 1980). "The etiology of bullous myringitis and the role of mycoplasmas in ear disease: a review". *Pediatrics*. **65** (4): 761–6. PMID 7367083🔗.
19. ^ Benninger, Michael S. (2008-03-01). "Acute bacterial rhinosinusitis and otitis media: changes in pathogenicity following widespread use of pneumococcal conjugate vaccine". *Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*. **138** (3): 274–278. doi:10.1016/j.otohns.2007.11.011🔗. ISSN 0194-5998🔗. PMID 18312870🔗.
20. ^ "Glue Ear"🔗. *NHS Choices*. Department of Health. Retrieved 3 November 2012.
21. ^ *a b* Rosenfeld RM, Culpepper L, Yawn B, Mahoney MC (June 2004). "Otitis media with effusion clinical practice guideline". *Am Fam Physician*. **69** (12): 2776, 2778–9. PMID 15222643🔗.
22. ^ Owen MJ, Baldwin CD, Swank PR, Pannu AK, Johnson DL, Howie VM (1993). "Relation of infant feeding practices, cigarette smoke exposure, and group child care to the onset and duration of otitis media with effusion in the first two years of life". *J. Pediatr*. **123** (5): 702–11. doi:10.1016/S0022-3476(05)80843-1🔗. PMID 8229477🔗.
23. ^ WHO Library Cataloguing-in-Publication Data.Chronic suppurative otitis media: burden of illness and management options.1.Otitis media, Suppurative, I.Acuin, Jose II.World Health Organization.ISBN 92-4-159158 7 (NLM classification: WV 232).,
24. ^ Leach AJ, Morris PS (2006). Leach AJ, ed. "Antibiotics for the prevention of acute and chronic suppurative otitis media in children". *Cochrane Database Syst Rev* (4): CD004401. doi:10.1002/14651858.CD004401.pub2🔗. PMID 17054203🔗.
25. ^ Jansen AG, Hak E, Veenhoven RH, Damoiseaux RA, Schilder AG, Sanders EA (2009). Jansen AG, ed. "Pneumococcal conjugate vaccines for preventing otitis media". *Cochrane Database Syst Rev* (2): CD001480. doi:10.1002/14651858.CD001480.pub3🔗. PMID 19370566🔗.
26. ^ Rovers MM, Schilder AG, Zielhuis GA, Rosenfeld RM (2004). "Otitis media". *Lancet*. **363** (9407): 564–573. doi:10.1016/S0140-6736(04)15495-0🔗. PMID 14962529🔗.
27. ^ *a b* Pukander J, Luotonem J, Timonen M, Karma P (1985). "Risk factors affecting the occurrence of acute otitis media among 2-3 year old urban children". *Acta Otolaryngol*. **100** (3–4): 260–265. doi:10.3109/00016488509104788🔗. PMID 4061076🔗.
28. ^ *a b* Etzel RA (1987). "Smoke and ear effusions". *Pediatrics*. **79** (2): 309–311. PMID 3808812🔗.
29. ^ Dewey KG, Heinig MJ, Nommsen-Rivers LA (1995). "Differences in morbidity between breast-fed and formula-fed infants". *J Pediatr*. **126** (5 Pt 1): 696–702. doi:10.1016/S0022-3476(95)70395-0🔗. PMID 7751991🔗.
30. ^ Saarinen UM (1982). "Prolonged breast feeding as prophylaxis for recurrent otitis media". *Acta Pediatr Scan*. **71** (4): 567–571. doi:10.1111/j.1651-2227.1982.tb09476.x🔗. PMID 7136672🔗.
31. ^ Rovers MM, Numans ME, Langenbach E, Grobbee DE, Verheij TJ, Schilder AG (August 2008). "Is pacifier use a risk factor for acute otitis media? A dynamic cohort study". *Fam Pract*. **25** (4): 233–6. doi:10.1093/fampra/cmn030🔗. PMID 18562333🔗.
32. ^ Gulani, A; Sachdev, HS (Jun 29, 2014). "Zinc supplements for preventing otitis media". *The Cochrane database of systematic reviews*. **6**: CD006639. doi:10.1002/14651858.CD006639.pub4🔗. PMID 24974096🔗.
33. ^ Sattout, A.; Jenner, R. (February 2008). "Best evidence topic reports. Bet 1. The role of topical analgesia in acute otitis media". *Emerg Med J*. **25** (2): 103–4. doi:10.1136/emj.2007.056648🔗. PMID 18212148🔗.
34. ^ Coleman C, Moore M (2008). Coleman C, ed. "Decongestants and antihistamines for acute otitis media in children". *Cochrane Database Syst Rev* (3): CD001727. doi:10.1002/14651858.CD001727.pub4🔗. PMID 18646076🔗.

35. ^ Thompson, M; Vodicka, TA; Blair, PS; Buckley, DI; Heneghan, C; Hay, AD; TARGET Programme, Team (Dec 11, 2013). "Duration of symptoms of respiratory tract infections in children: systematic review". *BMJ (Clinical research ed.)*. **347**: f7027. doi:10.1136/bmj.f7027. PMC 3898587. PMID 24335668.
36. ^ Principi, N; Bianchini, S; Baggi, E; Esposito, S (February 2013). "No evidence for the effectiveness of systemic corticosteroids in acute pharyngitis, community-acquired pneumonia and acute otitis media.". *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. **32** (2): 151–60. doi:10.1007/s10096-012-1747-y. PMID 22993127.
37. ^ Glasziou, PP; Del Mar, CB; Sanders, SL; Hayem, M (2004). "Antibiotics for acute otitis media in children.". *The Cochrane database of systematic reviews* (1): CD000219. doi:10.1002/14651858.CD000219.pub2. PMID 14973951.
38. ^ Thanaviratananich, S; Laopaiboon, M; Vatanasapt, P (13 December 2013). "Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media.". *The Cochrane database of systematic reviews*. **12**: CD004975. doi:10.1002/14651858.CD004975.pub3. PMID 24338106.
39. ^ Kozyrskyj, A; Klassen, TP; Moffatt, M; Harvey, K (8 September 2010). "Short-course antibiotics for acute otitis media.". *The Cochrane database of systematic reviews* (9): CD001095. doi:10.1002/14651858.CD001095.pub2. PMID 20824827.
40. ^ *a b* Macfadyen, CA; Acuin, JM; Gamble, C (Jan 25, 2006). "Systemic antibiotics versus topical treatments for chronically discharging ears with underlying eardrum perforations.". *The Cochrane database of systematic reviews* (1): CD005608. doi:10.1002/14651858.CD005608. PMID 16437533.
41. ^ McDonald S, Langton Hewer CD, Nunez DA (2008). McDonald S, ed. "Grommets (ventilation tubes) for recurrent acute otitis media in children". *Cochrane Database Syst Rev* (4): CD004741. doi:10.1002/14651858.CD004741.pub2. PMID 18843668.
42. ^ Browning GG, Rovers MM, Williamson I, Lous J, Burton MJ (2010). Browning GG, ed. "Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children". *Cochrane Database Syst Rev* (10): CD001801. doi:10.1002/14651858.CD001801.pub3. PMID 20927726.
43. ^ *a b c d* American Academy of Otolaryngology – Head and Neck Surgery, "Five Things Physicians and Patients Should Question" (PDF), *Choosing Wisely: an initiative of the ABIM Foundation*, American Academy of Otolaryngology – Head and Neck Surgery, retrieved August 1, 2013, which cites
    - Rosenfeld, R. M.; Schwartz, S. R.; Pynnonen, M. A.; Tunkel, D. E.; Hussey, H. M.; Fichera, J. S.; Grimes, A. M.; Hackell, J. M.; Harrison, M. F.; Haskell, H.; Haynes, D. S.; Kim, T. W.; Lafreniere, D. C.; LeBlanc, K.; Mackey, W. L.; Netterville, J. L.; Pipan, M. E.; Raol, N. P.; Schellhase, K. G. (2013). "Clinical Practice Guideline: Tympanostomy Tubes in Children". *Otolaryngology -- Head and Neck Surgery*. **149** (1 Suppl): S1–S35. doi:10.1177/0194599813487302. ISSN 0194-5998. PMID 23818543.
44. ^ Pratt-Harrington D (October 2000). "Galbreath technique: a manipulative treatment for otitis media revisited". *J Am Osteopath Assoc*. **100** (10): 635–9. PMID 11105452.
45. ^ Bronfort G, Haas M, Evans R, Leininger B, Triano J (2010). "Effectiveness of manual therapies: the UK evidence report". *Chiropr Osteopat*. **18** (1): 3. doi:10.1186/1746-1340-18-3. PMC 2841070. PMID 20184717.
46. ^ Jung, TT; Alper, CM; Hellstorm, SO; Hunter, LL; Casselbrant, ML; Groth, A; Kemaloglu, YK; Kim, SG; Lim, D; Nittrourer, S; Park, KH; Sabo, D; Sprately, J (April 2013). "Panel 8: Complications and sequelae". *Otolaryngol Head Neck Surg*. **148** (4 Suppl): E122–43. doi:10.1177/0194599812467425. PMID 23536529.
47. ^ *a b c* Monasta, L; Ronfani, I; Marchetti, F; Montico, M; Vrecchi-Brunetti, L; Bavcar, A; Grasso, D; Barbiero, C; Tamburlini, G (April 30, 2012). "Burden of disease caused by otitis media: systematic review and global estimates". *PLoS ONE*. **7** (4): e36226. doi:10.1371/journal.pone.0036226. PMC 3340347. PMID 22558393.
48. ^ *a b* Vos, T; Flaxman, A. D.; Naghavi, M; Lozano, R; Michaud, C; Ezzati, M; Shibuya, K; Salomon, J. A.; Abdalla, S; Aboyans, V; Abraham, J; Ackerman, I; Aggarwal, R; Ahn, S. Y.; Ali, M. K.; Alvarado, M; Anderson, H. R.; Anderson, L. M.; Andrews, K. G.; Atkinson, C; Baddour, L. M.; Bahalim, A. N.; Barker-Collo, S; Barrero, L. H.; Bartels, D. H.; Basáñez, M. G.; Baxter, A; Bell, M. L.; Benjamin, E. J.; et al. (Dec 15, 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2163–96. doi:10.1016/S0140-6736(12)61729-2. PMID 23245607.
49. ^ Da Costa SS; Rosito, Letícia Petersen Schmidt; Dornelles, Cristina (February 2009). "Sensorineural hearing loss in patients with chronic otitis media". *Eur Arch Otorhinolaryngol*. **266** (2): 221–4. doi:10.1007/s00405-008-0739-0. PMID 18629531.
50. ^ Roberts K (June 1997). "A preliminary account of the effect of otitis media on 15-month-olds' categorization and some implications for early language learning". *J Speech Lang Hear Res*. **40** (3): 508–18. doi:10.1044/jslhr.4003.508. PMID 9210110.
51. ^ Bidadi S, Nejadkazem M, Naderpour M (November 2008). "The relationship between chronic otitis media-induced hearing loss and the acquisition of social skills". *Otolaryngol Head Neck Surg*. **139** (5): 665–70. doi:10.1016/j.otohns.2008.08.004. PMID 18984261.

52. ^ Gouma P, Mallis A, Daniilidis V, Gouveris H, Armenakis N, Naxakis S (January 2011). "Behavioral trends in young children with conductive hearing loss: a case-control study". *Eur Arch Otorhinolaryngol*. **268** (1): 63–6. doi:10.1007/s00405-010-1346-4. PMID 20665042.
53. ^ Yilmaz S, Karasalihoglu AR, Tas A, Yagiz R, Tas M (February 2006). "Otoacoustic emissions in young adults with a history of otitis media". *J Laryngol Otol*. **120** (2): 103–7. doi:10.1017/S0022215105004871. PMID 16359151.


## External links [edit]

- Neff MJ (June 2004). "AAP, AAFP, AAO-HNS release guideline on diagnosis and management of otitis media with effusion". *Am Fam Physician*. **69** (12): 2929–31. PMID 15222658.
- Secretory otitis media (Ear disorder) at *Encyclopædia Britannica*
- Otitis media (Pathology) at *Encyclopædia Britannica*

Wikimedia Commons has media related to *Otitis media*.

| v · t · e · | **Diseases of the ear and mastoid process (H60–H99, 380–389)** | | |
|---|---|---|---|
| **Outer ear** | Otitis externa · Otomycosis · | | |
| **Middle ear and mastoid** | **Otitis media** · Mastoiditis (Bezold's abscess · Gradenigo's syndrome · · Tympanosclerosis · Cholesteatoma · Perforated eardrum · | | |
| **Inner ear and central pathways** | **Equilibrioception** | Vertigo/Balance disorder: *peripheral* (Ménière's disease · BPPV · Vestibular neuronitis (Labyrinthitis) · Perilymph fistula · · *central* (Central positional nystagmus) · | |
| | **Hearing** | **Hearing impairment** | Conductive hearing loss (Otosclerosis · Superior canal dehiscence · · Sensorineural hearing loss (Presbycusis · Cortical deafness · · Nonsyndromic deafness · |
| | | **Excessive response** | Tinnitus · Hyperacusis/Phonophobia · |
| | | **Deafblindness** | Wolfram syndrome · Usher syndrome · |
| | | **Other** | Auditory processing disorder · Spatial hearing loss · |

| v · t · e · | **Common cold** |
|---|---|
| **Viruses** | Adenovirus · Coronavirus · Enterovirus · Human metapneumovirus · Human parainfluenza viruses · Human respiratory syncytial virus · Orthomyxoviruses (Influenza A virus · Influenza B virus · Influenza C virus · · Rhinovirus · |
| **Symptoms** | Cough · Fatigue · Fever · Headache · Loss of appetite · Malaise · Muscle aches · Nasal congestion · Rhinorrhea · Sneezing · Sore throat · Weakness · |
| **Complications** | Acute bronchitis · Bronchiolitis · Croup · **Otitis media** · Pharyngitis · Pneumonia · Sinusitis · Strep throat · |
| **Drugs** | Antiviral drugs · Pleconaril *(experimental)* · |

| **Authority control** | NDL: 00573957 · |
|---|---|

Categories: Otitis | Diseases of middle ear and mastoid | Pediatrics | Audiology


# Pharyngitis

From Wikipedia, the free encyclopedia

*Not to be confused with laryngitis.*

**Pharyngitis** is inflammation of the back of the throat, known as the pharynx.[1] It typically results in a sore throat and fever.[1] Other symptoms may include a runny nose, cough, headache, a hoarse voice.[2] Symptoms usually last three to five days. Complications can include sinusitis and acute otitis media.[1] Pharyngitis is typically a type of respiratory tract infection.[3]

Most cases are caused by a viral infection. Strep throat is the cause in about 25% of children and 10% of adults.[1] Uncommon causes include other bacteria such as gonorrhea, fungus, irritants such as smoke, allergies, and gastroesophageal reflux disease.[1][4] Specific testing is not recommended in people who have clear symptoms of a viral infection such as a cold. Otherwise a rapid antigen detection test or throat swab is recommended. Other conditions that can produce similar symptoms include epiglottitis, thyroiditis, retropharyngeal abscess, and occasionally heart disease.[1]

NSAIDs, such as ibuprofen, can be used to help with the pain.[1] Topical lidocaine may also help.[4] Strep throat is typically treated with antibiotics, such as either penicillin or amoxicillin.[1] It is unclear if steroids are useful in acute pharyngitis, other than possibly in severe cases.[5][6]

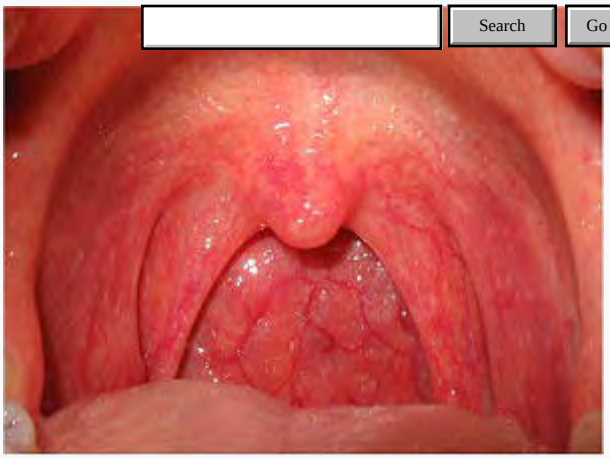
About 7.5% of people have a sore throat in any three-month period.[7] This resulted in 15 million physician visits in the United States in 2007.[4] Pharyngitis is the most common cause of a sore throat.[8] On the average, adults get a sore throat two to three times a year and children about five times a year.[9][2] The word comes from the Greek word *pharynx* meaning "throat" and the suffix *-itis* meaning "inflammation".[10][11]

Contents


## Variants

## Pharyngitis

| | |
|---|---|
| **Synonyms** | acute sore throat |



Viral pharyngitis. Note the redness.

| | |
|---|---|
| **Pronunciation** | /fær.ɪnˈdʒaɪtɪs/ |

**Classification and external resources**

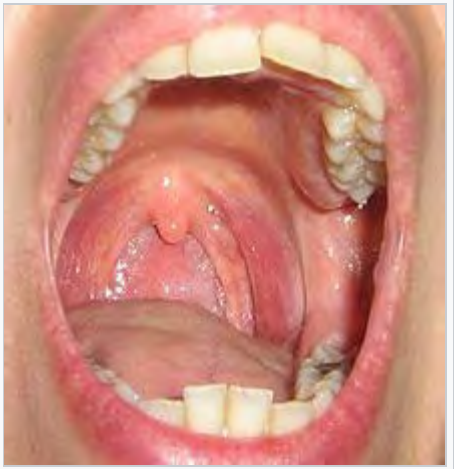
| | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | J02, J31.2 |
| **ICD-9-CM** | 462, 472.1 |
| **DiseasesDB** | 24580 |
| **MedlinePlus** | 000655 |
| **eMedicine** | emerg/419 |
| **MeSH** | D010612 |

[edit on Wikidata]

## Classification [edit]

Pharyngitis is a type of inflammation, most commonly caused by an upper respiratory tract infection. It may be classified as acute or chronic. Acute pharyngitis may be catarrhal, purulent or ulcerative, depending on the causative agent and the immune capacity of the affected individual. Chronic pharyngitis may be catarrhal, hypertrophic or atrophic.

Tonsillitis is a sub type of pharyngitis.[12] If the inflammation includes both the tonsils and other parts of the throat, it may be called pharyngotonsillitis.[13] Another sub classification is nasopharyngitis (the common cold).[14]



A normal throat

## Cause [edit]

The majority of cases are due to an infectious organism acquired from close contact with an infected individual.

### Viral [edit]

These comprise about 40–80% of all infectious cases and can be a feature of many different types of viral infections.[8][15]

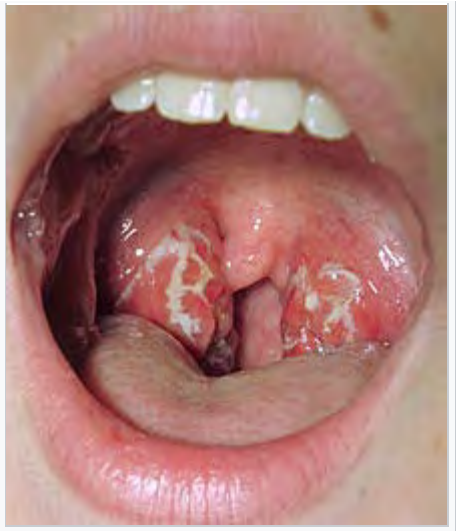
- Adenovirus – the most common of the viral causes. Typically the degree of neck lymph node enlargement is modest and the throat often does not appear red, although it is painful.
- Orthomyxoviridae which cause influenza – present with rapid onset high temperature, headache and generalized ache. A sore throat may be associated.
- Infectious mononucleosis ("glandular fever") caused by the Epstein–Barr virus. This may cause significant lymph gland swelling and an exudative tonsillitis with marked redness and swelling of the throat. The heterophile test can be used if this is suspected.
- Herpes simplex virus can cause multiple mouth ulcers.
- Measles
- Common cold: rhinovirus, coronavirus, respiratory syncytial virus, parainfluenza virus can cause infection of the throat, ear, and lungs causing standard cold-like symptoms and often pain.

### Bacterial [edit]

A number of different bacteria can infect the human throat. The most common is Group A streptococcus, but others include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Bordetella pertussis*, *Bacillus anthracis*, *Corynebacterium diphtheriae*, *Neisseria gonorrhoeae*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*.[16]

#### Streptococcal pharyngitis

Streptococcal pharyngitis or strep throat is caused by group A beta-hemolytic streptococcus (GAS).[17] It is the most common bacterial cause of cases of pharyngitis (15–30%).[16] Common symptoms include fever, sore throat, and large lymph nodes. It is a contagious infection, spread by close contact with an infected individual. A definitive diagnosis is made based on the results of a throat culture. Antibiotics are useful to


A case of strep throat

both prevent complications and speed recovery.[18]

#### Fusobacterium necrophorum

*Fusobacterium necrophorum* is a normal inhabitant of the oropharyngeal flora and can occasionally create a peritonsillar abscess. In 1 out of 400 untreated cases, Lemierre's syndrome occurs.[19]

#### Diphtheria

Diphtheria is a potentially life-threatening upper respiratory infection caused by *Corynebacterium diphtheriae* which has been largely eradicated in developed nations since the introduction of childhood vaccination programs, but is still reported in the Third World and increasingly in some areas in Eastern Europe. Antibiotics are effective in the early stages, but recovery is generally slow.[*citation needed*]

#### Others

A few other causes are rare, but possibly fatal, and include parapharyngeal space infections: peritonsillar abscess ("quinsy"), submandibular space infection (Ludwig's angina), and epiglottitis.[20][21][22]

### Fungal [edit]

Some cases of pharyngitis are caused by fungal infection such as Candida albicans causing oral thrush.[*citation needed*]

### Non-infectious [edit]

Pharyngitis may also be caused by mechanical, chemical or thermal irritation, for example cold air or acid reflux. Some medications may produce pharyngitis such as pramipexole and antipsychotics.[23][24]

## Diagnostic approach [edit]

It is hard to differentiate a viral and a bacterial cause of a sore throat based on symptoms alone.[25] Thus often a throat swab is done to rule out a bacterial cause.[26]

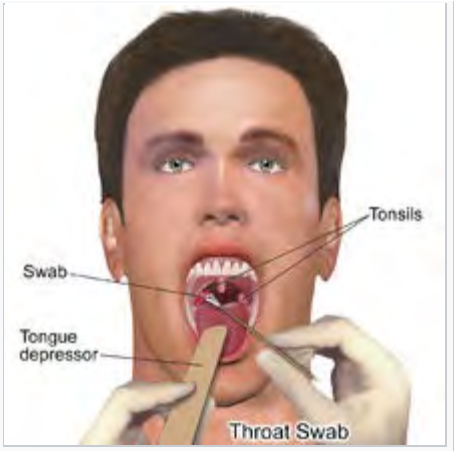
**Modified Centor score**

| Points | Probability of Strep | Management |
|---|---|---|
| 1 or less | <10% | No antibiotic or culture needed |
| 2 | 11–17% | Antibiotic based on culture or RADT |
| 3 | 28–35% | |
| 4 or 5 | 52% | Empiric antibiotics |

The modified Centor criteria may be used to determine the management of people with pharyngitis. Based on 5 clinical criteria, it indicates the probability of a streptococcal infection.[18]

One point is given for each of the criteria:[18]

- Absence of a cough
- Swollen and tender cervical lymph nodes
- Temperature >38.0 °C (100.4 °F)
- Tonsillar exudate or swelling



Throat swab.

- Age less than 15 (a point is subtracted if age >44)

The McIsaac criteria adds to the Centor:[27]

- Age less than 15: add one point
- Age greater than 45: subtract one point

The Infectious Disease Society of America however recommends against empirical treatment and considers antibiotics only appropriate following positive testing.[25] Testing is not needed in children under three as both group A strep and rheumatic fever are rare, except if they have a sibling with the disease.[25]

# Management [edit]

The majority of time treatment is symptomatic. Specific treatments are effective for bacterial, fungal, and herpes simplex infections.

## Medications [edit]

- Pain medication such as NSAIDs and acetaminophen (paracetamol) can help reduce the pain associated with a sore throat. Aspirin may be used in adults but is not recommended in children due to the risk of Reye syndrome.[28]
- Steroids (such as dexamethasone) may be useful for severe pharyngitis.[29][6] Their general use however is poorly supported.[30]
- Viscous lidocaine relieves pain by numbing the mucus membranes.[31]
- Antibiotics are useful if a bacterial infection is the cause of the sore throat.[32][33] For viral infections, antibiotics have no effect. In the United States they are used in 25% of people before a bacterial infection has been detected.[34]
- Oral analgesic solutions, the active ingredient usually being phenol, but also less commonly benzocaine, cetylpyridinium chloride and/or menthol. Chloraseptic and Cēpacol are two examples of brands of these kinds of analgesics.

## Alternative [edit]

*See also: Alternative treatments used for the common cold*

Gargling salt water is often suggested but evidence looking at its usefulness is lacking.[4] Alternative medicines are promoted and used for the treatment of sore throats.[35] However, they are poorly supported by evidence.[35]

# Epidemiology [edit]

Acute pharyngitis is the most common cause of a sore throat and, together with cough, it is diagnosed in more than 1.9 million people a year in the United States.[8]

# References [edit]

1. ^ [a b c d e f g h] Hildreth, AF; Takhar, S; Clark, MA; Hatten, B (September 2015). "Evidence-Based Evaluation And Management Of Patients With Pharyngitis In The Emergency Department.". *Emergency medicine practice*. **17** (9): 1–16; quiz 16–7. PMID 26276908.
2. ^ [a b] Rutter, Paul Professor; Newby, David (2015). *Community Pharmacy ANZ: Symptoms, Diagnosis and Treatment*. Elsevier Health Sciences. p. 19. ISBN 9780729583459.
3. ^ "Pharyngitis". *National Library of Medicine*. Retrieved 4 August 2016.
4. ^ [a b c d] Weber, R (March 2014). "Pharyngitis.". *Primary care*. **41** (1): 91–8. doi:10.1016/j.pop.2013.10.010. PMID 24439883.
5. ^ Principi, N; Bianchini, S; Baggi, E; Esposito, S (February 2013). "No evidence for the effectiveness of systemic corticosteroids in acute pharyngitis, community-acquired pneumonia and acute otitis media.". *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. **32** (2): 151–60. doi:10.1007/s10096-012-1747-y. PMID 22993127.
6. ^ [a b] Hayward, G; Thompson, MJ; Perera, R; Glasziou, PP; Del Mar, CB; Heneghan, CJ (17 October 2012). "Corticosteroids as standalone or add-on treatment for sore throat.". *The Cochrane database of systematic reviews*. **10**: CD008268. doi:10.1002/14651858.CD008268.pub2. PMID 23076943.
7. ^ Jones, Roger (2004). *Oxford Textbook of Primary Medical Care*. Oxford University Press. p. 674. ISBN 9780198567820. Retrieved 4 August 2016.
8. ^ [a b c] Marx, John (2010). *Rosen's emergency medicine: concepts and clinical practice* (7th ed.). Philadelphia, Pennsylvania: Mosby/Elsevier. Chapter 30. ISBN 978-0-323-05472-0.
9. ^ Tamparo, Carol (2011). *Fifth Edition: Diseases of the Human Body*. Philadelphia, PA: F.A. Davis Company. p. 356. ISBN 978-0-8036-2505-1.
10. ^ Beachey, Will (2013). *Respiratory Care Anatomy and Physiology,Foundations for Clinical Practice,3: Respiratory Care Anatomy and Physiology*. Elsevier Health Sciences. p. 5. ISBN 0323078664.
11. ^ Hegner, Barbara; Acello, Barbara; Caldwell, Esther (2009). *Nursing Assistant: A Nursing Process Approach - Basics*. Cengage Learning. p. 45. ISBN 9781111780500.
12. ^ "Tonsillitis". Retrieved 4 August 2016.
13. ^ Rafei K, Lichenstein R (2006). "Airway Infectious Disease Emergencies". *Pediatric Clinics of North America*. **53** (2): 215–242. doi:10.1016/j.pcl.2005.10.001. PMID 16574523.
14. ^ "www.nlm.nih.gov".
15. ^ Acerra JR. "Pharyngitis". *eMedicine*. Retrieved 28 April 2010.
16. ^ [a b] Bisno AL (January 2001). "Acute pharyngitis". *N Engl J Med*. **344** (3): 205–11. doi:10.1056/NEJM200101183440308. PMID 11172144.
17. ^ Baltimore RS (February 2010). "Re-evaluation of antibiotic treatment of streptococcal pharyngitis". *Curr. Opin. Pediatr*. **22** (1): 77–82. doi:10.1097/MOP.0b013e32833502e7. PMID 19996970.
18. ^ [a b c] Choby BA (March 2009). "Diagnosis and treatment of streptococcal pharyngitis". *Am Fam Physician*. **79** (5): 383–90. PMID 19275067.
19. ^ Centor RM (2009-12-01). "Expand the pharyngitis paradigm for adolescents and young adults". *Ann Intern Med*. **151** (11): 812–5. doi:10.1059/0003-4819-151-11-200912010-00011. PMID 19949147.
20. ^ "UpToDate Inc.". (registration required)
21. ^ Reynolds SC, Chow AW (Sep–Oct 2009). "Severe soft tissue infections of the head and neck: a primer for critical care physicians". *Lung*. **187** (5): 271–9. doi:10.1007/s00408-009-9153-7. PMID 19653038.
22. ^ Bansal A, Miskoff J, Lis RJ (January 2003). "Otolaryngologic critical care". *Crit Care Clin*. **19** (1): 55–72. doi:10.1016/S0749-0704(02)00062-3. PMID 12688577.
23. ^ "Mirapex product insert" (PDF). Boehringer Ingelheim. 2009. Retrieved 2010-06-30.
24. ^ "Mosby's Medical Dictionary, 8th edition". Elsevier. 2009. Retrieved 2010-06-30.
25. ^ [a b c] Shulman ST, Bisno AL, Clegg HW, Gerber MA, Kaplan EL, Lee G, Martin JM, Van Beneden C (Sep 9, 2012). "Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Update by the Infectious Diseases Society of America.". *Clinical Infectious Diseases*. **55** (10): e86–102. doi:10.1093/cid/cis629. PMID 22965026.
26. ^ Del Mar C (1992). "Managing sore throat: a literature review. I. Making the diagnosis". *Med J Aust*. **156** (8): 572–5. PMID 1565052.
27. ^ Fine AM, Nizet V, Mandl KD (2012). "Large-Scale Validation of the Centor and McIsaac Scores to Predict Group A Streptococcal Pharyngitis.". *Arch Intern Med*. **172**. doi:10.1001/archinternmed.2012.950. PMID 22566485.
28. ^ Baltimore RS (February 2010). "Re-evaluation of antibiotic treatment of streptococcal pharyngitis". *Current Opinion in Pediatrics*. **22** (Curr. Opin. Pediatr. 22 (1)): 77–82. doi:10.1097/MOP.0b013e32833502e7. PMID 19996970.
29. ^ Hayward G, Thompson M, Heneghan C, Perera R, Del Mar C, Glasziou P (2009). "Corticosteroids for pain relief in

sore throat: systematic review and meta-analysis". *BMJ*. **339**: b2976. doi:10.1136/bmj.b2976. PMC 2722696. PMID 19661138.

30. ^ Principi, N; Bianchini, S; Baggi, E; Esposito, S (February 2013). "No evidence for the effectiveness of systemic corticosteroids in acute pharyngitis, community-acquired pneumonia and acute otitis media.". *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. **32** (2): 151–60. doi:10.1007/s10096-012-1747-y. PMID 22993127.
31. ^ "LIDOCAINE VISCOUS (Xylocaine Viscous) side effects, medical uses, and drug interactions.".
32. ^ Kocher, JJ; Selby, TD (1 July 2014). "Antibiotics for sore throat.". *American family physician*. **90** (1): 23–4. PMID 25077497.
33. ^ Spinks, A; Glasziou, PP; Del Mar, CB (5 November 2013). "Antibiotics for sore throat.". *The Cochrane database of systematic reviews*. **11**: CD000023. doi:10.1002/14651858.CD000023.pub4. PMID 24190439.
34. ^ Urkin, J; Allenbogen, M; Friger, M; Vinker, S; Reuveni, H; Elahayani, A (November 2013). "Acute pharyngitis: low adherence to guidelines highlights need for greater flexibility in managing paediatric cases.". *Acta paediatrica (Oslo, Norway : 1992)*. **102** (11): 1075–80. doi:10.1111/apa.12364. PMID 23879261.
35. ^ *a b* "Sore throat: Self-care". Mayo Clinic. Retrieved 2007-09-17.

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| v · t · e · **Diseases of the respiratory system (J, 460–519)** | | |
|---|---|---|
| **Upper RT (including URTIs, common cold)** | **Head** | *sinuses*: Sinusitis · *nose*: Rhinitis (Vasomotor rhinitis · Atrophic rhinitis · Hay fever · · Nasal polyp · Rhinorrhea · *nasal septum* (Nasal septum deviation · Nasal septum perforation · Nasal septal hematoma · · *tonsil*: Tonsillitis · Adenoid hypertrophy · Peritonsillar abscess · |
| | **Neck** | *pharynx*: **Pharyngitis** (Strep throat · · Laryngopharyngeal reflux (LPR) · Retropharyngeal abscess · *larynx*: Croup · Laryngomalacia · Laryngeal cyst · Laryngitis · Laryngopharyngeal reflux (LPR) · Laryngospasm · *vocal folds*: Laryngopharyngeal reflux (LPR) · Vocal fold nodule · Vocal cord paresis · Vocal cord dysfunction · *epiglottis*: Epiglottitis · *trachea*: Tracheitis · Tracheal stenosis · |
| | **Bronchial/ obstructive** | *acute*: Acute bronchitis · *chronic*: COPD (Chronic bronchitis · Acute exacerbations of chronic bronchitis · Acute exacerbation of COPD · Emphysema) · Asthma (Status asthmaticus · Aspirin-induced · Exercise-induced · · Bronchiectasis · *unspecified*: Bronchitis · Bronchiolitis (Bronchiolitis obliterans · · Diffuse panbronchiolitis · |
| | **Interstitial/ restrictive** | **External agents/ occupational lung disease**: Pneumoconiosis (Asbestosis · Baritosis · Bauxite fibrosis · Berylliosis · Caplan's syndrome · Chalicosis · Coalworker's pneumoconiosis · Siderosis · Silicosis · Talcosis · Byssinosis · · Hypersensitivity pneumonitis (Bagassosis · Bird fancier's lung · Farmer's lung · Lycoperdonosis · · |

| | | | |
|---|---|---|---|
| **Lower RT/lung disease (including LRTIs)** | **(fibrosis)** | **Other** | ARDS · Pulmonary edema · Löffler's syndrome/Eosinophilic pneumonia · Respiratory hypersensitivity (Allergic bronchopulmonary aspergillosis · · Hamman-Rich syndrome · Idiopathic pulmonary fibrosis · Sarcoidosis · |
| | **Obstructive or restrictive** | **Pneumonia/pneumonitis** | **By pathogen** | Viral · Bacterial (Pneumococcal · Klebsiella) · · Atypical bacterial (Mycoplasma · Legionnaires' disease · Chlamydiae · · Fungal (Pneumocystis · · Parasitic · *noninfectious* (Chemical/Mendelson's syndrome · Aspiration/Lipid · · |
| | | | **By vector/route** | Community-acquired · Healthcare-associated · Hospital-acquired · |
| | | | **By distribution** | Broncho- · Lobar · |
| | | | **IIP** | UIP · DIP · BOOP-COP · NSIP · RB · |
| | | **Other** | Atelectasis · *circulatory* (Pulmonary hypertension · Pulmonary embolism · · Lung abscess · |
| **Pleural cavity/mediastinum** | **Pleural disease** | Pleuritis/pleurisy · Pneumothorax/Hemopneumothorax · **Pleural effusion:** Hemothorax · Hydrothorax · Chylothorax · Empyema/pyothorax · Malignant · Fibrothorax · | | |
| | **Mediastinal disease** | Mediastinitis · Mediastinal emphysema · | | |
| **Other/general** | Respiratory failure · Influenza · SARS · Idiopathic pulmonary haemosiderosis · Pulmonary alveolar proteinosis · | | | |

| v · t · e · | **Inflammation** | | |
|---|---|---|---|
| **Acute** | **Plasma derived mediators** | Bradykinin · *complement* (C3 · C5a · MAC · · *coagulation* (Factor XII · Plasmin · Thrombin · · | |
| | **Cell derived mediators** | *preformed:* | Lysosome granules · *biogenic amines* (Histamine · Serotonin · · |
| | | *synthesized on demand:* | *cytokines* (IFN-γ · IL-8 · TNF-α · IL-1 · · *eicosanoids* (Leukotriene B4 · Prostaglandins · · Nitric oxide · Kinins · |
| **Chronic** | Macrophage · Epithelioid cell · Giant cell · Granuloma · | | |

| | | | |
|---|---|---|---|
| **Processes** | **Traditional:** | | Rubor · Calor · Tumor · Dolor · Functio laesa · |
| | **Modern:** | | Acute-phase reaction/Fever · Vasodilation · Increased vascular permeability · Exudate · Leukocyte extravasation · Chemotaxis · |
| **Specific locations** | **Nervous** | | *CNS* (Encephalitis · Myelitis · · Meningitis (Arachnoiditis · · *PNS* (Neuritis · · *eye* (Dacryoadenitis · Scleritis · Episcleritis · Keratitis · chorioretinitis · Retinitis · Chorioretinitis · Blepharitis · Conjunctivitis · Uveitis · · *ear* (Otitis · Labyrinthitis · Mastoiditis · · |
| | **Cardiovascular** | | Carditis (Endocarditis · Myocarditis · Pericarditis · · Vasculitis (Arteritis · Phlebitis · Capillaritis · · |
| | **Respiratory** | | *upper* (Sinusitis · Rhinitis · **Pharyngitis** · Laryngitis · · *lower* (Tracheitis · Bronchitis · Bronchiolitis · Pneumonitis · Pleuritis · · Mediastinitis · |
| | **Digestive** | *mouth* | Stomatitis · Gingivitis · Gingivostomatitis · Glossitis · Tonsillitis · Sialadenitis/Parotitis · Cheilitis · Pulpitis · Gnathitis · |
| | | *tract* | Esophagitis · Gastritis · Gastroenteritis · Enteritis · Colitis · Enterocolitis · Duodenitis · Ileitis · Caecitis · Appendicitis · Proctitis · |
| | | *accessory* | Hepatitis · Ascending cholangitis · Cholecystitis · Pancreatitis · Peritonitis · |
| | **Integumentary** | | Dermatitis (Folliculitis · · Cellulitis · Hidradenitis · |
| | **Musculoskeletal** | | Arthritis · Dermatomyositis · *soft tissue* (Myositis · Synovitis/Tenosynovitis · Bursitis · Enthesitis · Fasciitis · Capsulitis · Epicondylitis · Tendinitis · Panniculitis · · Osteochondritis: Osteitis/Osteomyelitis (Spondylitis · Periostitis · · Chondritis · |
| | **Urinary** | | Nephritis (Glomerulonephritis · Pyelonephritis · · Ureteritis · Cystitis · Urethritis · |
| | **Reproductive** | *female:* | Oophoritis · Salpingitis · Endometritis · Parametritis · Cervicitis · Vaginitis · Vulvitis · Mastitis · |
| | | *male:* | Orchitis · Epididymitis · Prostatitis · Seminal vesiculitis · Balanitis · Posthitis · Balanoposthitis · |
| | | *pregnancy/newborn:* | Chorioamnionitis · Funisitis · Omphalitis · |
| | **Endocrine** | | Insulitis · Hypophysitis · Thyroiditis · Parathyroiditis · Adrenalitis · |
| | **Lymphatic** | | Lymphangitis · Lymphadenitis · |

| v · t · e · | **Common cold** |
|---|---|
| **Viruses** | Adenovirus · Coronavirus · Enterovirus · Human metapneumovirus · Human parainfluenza viruses · Human respiratory syncytial virus · Orthomyxoviruses (Influenza A virus · Influenza B virus · Influenza C virus · · Rhinovirus · |
| **Symptoms** | Cough · Fatigue · Fever · Headache · Loss of appetite · Malaise · Muscle aches · Nasal congestion · Rhinorrhea · Sneezing · Sore throat · Weakness · |

| | |
|---|---|
| **Complications** | Acute bronchitis · Bronchiolitis · Croup · Otitis media · **Pharyngitis** · Pneumonia · Sinusitis · Strep throat · |
| **Drugs** | Antiviral drugs · Pleconaril *(experimental)* · |

Categories: Infectious diseases | Inflammations | Upper respiratory tract diseases | Gastrointestinal tract disorders




# Streptococcal pharyngitis

From Wikipedia, the free encyclopedia

(Redirected from Strep throat)

**Streptococcal pharyngitis**, also known as **strep throat**, is an infection of the back of the throat including the tonsils caused by *group A streptococcus*.[1] Common symptoms include fever, sore throat, red tonsils, and enlarged lymph nodes in the neck. A headache, and nausea or vomiting may also occur.[1] Some develop a sandpaper-like rash which is known as scarlet fever.[2] Symptoms typically begin one to three days after exposure and last seven to ten days.[2][3]

Strep throat is spread by respiratory droplets from an infected person. It may be spread directly or by touching something that has droplets on it and then touching the mouth, nose, or eyes. Some people may carry the bacteria without symptoms. It may also be spread by skin infected with group A strep.[1] The diagnosis is made based on the results of a rapid antigen detection test or throat culture in those who have symptoms.[4]

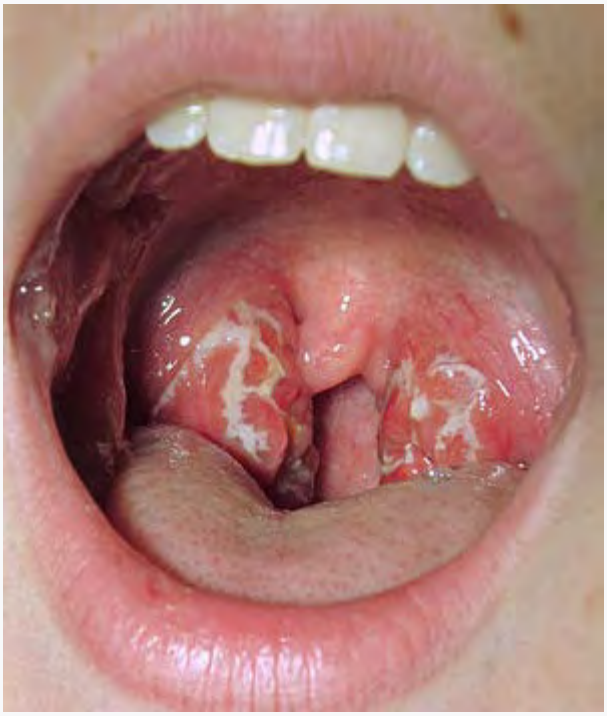
Prevention is by washing hands and not sharing eating utensils. There is no vaccine for the disease.[1] Treatment with antibiotics is only recommended in those with a confirmed diagnosis.[4] Those infected should stay away from other people for at least 24 hours after starting treatment.[1] Pain can be treated with paracetamol (acetaminophen) and non-steroidal antiinflammatory drugs (NSAIDS) such as ibuprofen.[5]

Strep throat is a common bacterial infection in children.[2] It is the cause of 15–40% of sore throats among children[6][7] and 5–15% among adults.[8] Cases are more common in late winter and early spring.[7] Potential complications include rheumatic fever and peritonsillar abscess.[1][2]

Contents


**Streptococcal pharyngitis**

**Synonyms** ..., streptococcal sore throat, strep



A culture positive case of streptococcal pharyngitis with typical tonsillar exudate in a 16-year-old.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | J02.0 |
| **ICD-9-CM** | 034.0 |
| **DiseasesDB** | 12507 |
| **MedlinePlus** | 000639 |
| **eMedicine** | med/1811 |

[edit on Wikidata]

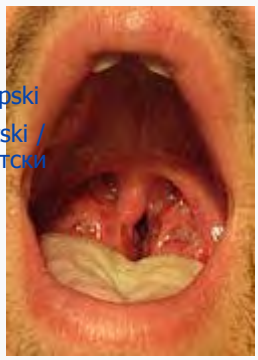
## Signs and symptoms

The typical symptoms of streptococcal pharyngitis are a sore throat, fever of greater than 38 °C (100 °F), tonsillar exudates (pus on the tonsils), and large cervical lymph nodes.[7]

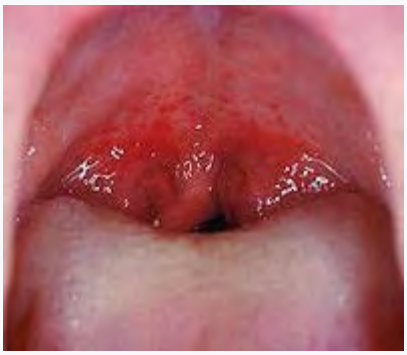
Other symptoms include: headache, nausea and vomiting, abdominal pain,[9] muscle pain,[10] or a scarlatiniform rash or palatal petechiae, the latter being an uncommon but highly specific finding.[7]

Symptoms typically begin one to three days after exposure and last seven to ten days.[3][7]

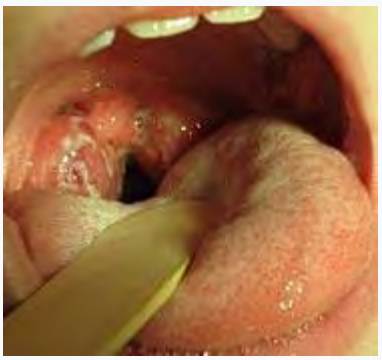
Strep throat is unlikely when any of the symptoms of red eyes, hoarseness, runny nose, or mouth ulcers are present. It is also unlikely when there is no fever.[8]



Mouth wide open showing the throat
A throat infection which on culture tested positive for group A streptococcus. Note the large tonsils with white exudate.



Mouth wide open showing the throat
Note the petechiae, or small red spots, on the soft palate. This is an uncommon but highly specific finding in streptococcal pharyngitis.[7]



A set of large tonsils in the back of the throat, covered in white exudate.
A culture positive case of streptococcal pharyngitis with typical tonsillar exudate in an 8-year-old.

## Cause

Strep throat is caused by group A beta-hemolytic streptococcus (GAS or S. pyogenes).[11] Other bacteria such as non–group A beta-hemolytic streptococci and fusobacterium may also cause pharyngitis.[7][10] It is spread by direct, close contact with an infected person; thus crowding, as may be found in the military and schools, increases the rate of transmission.[10][12] Dried bacteria in dust are not infectious, although moist bacteria on toothbrushes or similar items can persist for up to fifteen days.[10] Contaminated food can result in outbreaks, but this is rare.[10] Of children with no signs or symptoms, 12% carry GAS in their pharynx,[6] and, after treatment, approximately 15% of those remain positive, and are true "carriers".[13]

## Diagnosis

A number of scoring systems

exist to help with diagnosis; however, their use is controversial due to insufficient accuracy.[14] The modified Centor criteria are a set of five criteria; the total score indicates the probability of a streptococcal infection.[7]

**Modified Centor score**

| Points | Probability of Strep | Management |
|---|---|---|
| 1 or fewer | <10% | No antibiotic or culture needed |
| 2 | 11–17% | Antibiotic based on culture or RADT |
| 3 | 28–35% | |
| 4 or 5 | 52% | Empiric antibiotics |

One point is given for each of the criteria:[7]

- Absence of a cough
- Swollen and tender cervical lymph nodes
- Temperature >38.0 °C (100.4 °F)
- Tonsillar exudate or swelling
- Age less than 15 (a point is subtracted if age >44)

A score of one may indicated no treatment or culture is needed, or it may indicate the need to perform further testing if other high risk factors exist, such as a family member having the disease.[7]

The Infectious Disease Society of America recommends against empirical treatment and considers antibiotics only appropriate when given after a positive test.[8] Testing is not needed in children under three as both group A strep and rheumatic fever are rare, unless a child has a sibling with the disease.[8]

## Laboratory testing

A throat culture is the gold standard[15] for the diagnosis of streptococcal pharyngitis, with a sensitivity of 90–95%.[7] A rapid strep test (also called rapid antigen detection testing or RADT) may also be used. While the rapid strep test is quicker, it has a lower sensitivity (70%) and statistically equal specificity (98%) as a throat culture.[7] In areas of the world where rheumatic fever is uncommon, a negative rapid strep test is sufficient to rule out the disease.[16]

A positive throat culture or RADT in association with symptoms establishes a positive diagnosis in those in which the diagnosis is in doubt.[17] In adults, a negative RADT is sufficient to rule out the diagnosis. However, in children a throat culture is recommended to confirm the result.[8] Asymptomatic individuals should not be routinely tested with a throat culture or RADT because a certain percentage of the population persistently "carries" the streptococcal bacteria in their throat without any harmful results.[17]

## Differential diagnosis

*See also: Acute pharyngitis*

As the symptoms of streptococcal pharyngitis overlap with other conditions, it can be difficult to make the diagnosis clinically.[7] Coughing, nasal discharge, diarrhea, and red, irritated eyes in addition to fever and sore throat are more indicative of a viral sore throat than of strep throat.[7] The presence of marked lymph node enlargement along with sore throat, fever, and tonsillar enlargement may also occur in infectious mononucleosis.[18]

# Prevention

Tonsillectomy may be a reasonable preventive measure in those with frequent throat infections (more than three a year).[19] However, the benefits are small and episodes typically lessen in time regardless of measures taken.[20][21][*needs update*] Recurrent episodes of pharyngitis which test positive for GAS may also represent a person who is a chronic carrier of GAS who is getting recurrent viral infections.[8] Treating [8]

people who have been exposed but who are without symptoms is not recommended. Treating people who are carriers of GAS is not recommended as the risk of spread and complications is low.[8]

# Treatment

Untreated streptococcal pharyngitis usually resolves within a few days.[7] Treatment with antibiotics shortens the duration of the acute illness by about 16 hours.[7] The primary reason for treatment with antibiotics is to reduce the risk of complications such as rheumatic fever and retropharyngeal abscesses;[7] antibiotics are effective if given within 9 days of the onset of symptoms.[11]

## Pain medication

Pain medication such as non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol (acetaminophen) help in the management of pain associated with strep throat.[22] Viscous lidocaine may also be useful.[23] While steroids may help with the pain,[11][24] they are not routinely recommended.[8] Aspirin may be used in adults but is not recommended in children due to the risk of Reye's syndrome.[11]

## Antibiotics

The antibiotic of choice in the United States for streptococcal pharyngitis is penicillin V, due to safety, cost, and effectiveness.[7] Amoxicillin is preferred in Europe.[25] In India, where the risk of rheumatic fever is higher, intramuscular benzathine penicillin G is the first choice for treatment.[11]

Appropriate antibiotics decrease the average 3–5 day duration of symptoms by about one day, and also reduce contagiousness.[17] They are primarily prescribed to reduce rare complications such as rheumatic fever and peritonsillar abscess.[26] The arguments in favor of antibiotic treatment should be balanced by the consideration of possible side effects,[10] and it is reasonable to suggest that no antimicrobial treatment be given to healthy adults who have adverse reactions to medication or those at low risk of complications.[26][27] Antibiotics are prescribed for strep throat at a higher rate than would be expected from how common it is.[28]

Erythromycin and other macrolides or clindamycin are recommended for people with severe penicillin allergies.[7][8] First-generation cephalosporins may be used in those with less severe allergies[7] and some evidence supports cephalosporins as superior to penicillin.[29][30] Streptococcal infections may also lead to acute glomerulonephritis; however, the incidence of this side effect is not reduced by the use of antibiotics.[11]

# Prognosis

The symptoms of strep throat usually improve within three to five days, irrespective of treatment.[17] Treatment with antibiotics reduces the risk of complications and transmission; children may return to school 24 hours after antibiotics are administered.[7] The risk of complications in adults is low.[8] In children, acute rheumatic fever is rare in most of the developed world. It is, however, the leading cause of acquired heart disease in India, sub-Saharan Africa and some parts of Australia.[8]

Complications arising from streptococcal throat infections include:

- Acute rheumatic fever[9]
- Scarlet fever[31]
- Streptococcal toxic shock syndrome[31][32]
- Glomerulonephritis[33]
- PANDAS syndrome[33]
- Peritonsillar abscess[8]
- Cervical lymphadenitis[8]
- Mastoiditis[8]

The economic cost of the disease in the United States in children is approximately $350 million annually.[8]

# Epidemiology

Pharyngitis, the broader category into which Streptococcal pharyngitis falls, is diagnosed in 11 million people annually in the United States.[7] It is the cause of 15–40% of sore throats among children[6][7] and 5–15% in adults.[8] Cases usually occur in late winter and early spring.[7]

# References


1. ^ *a b c d e f* "Is It Strep Throat?". *CDC*. October 19, 2015. Retrieved 2 February 2016.
2. ^ *a b c d* Török, edited by David A. Warrell, Timothy M. Cox, John D. Firth ; with guest ed. Estée (2012). *Oxford textbook of medicine infection*. Oxford: Oxford University Press. pp. 280–281. ISBN 9780191631733.
3. ^ *a b* Jr, [edited by] Allan H. Goroll, Albert G. Mulley (2009). *Primary care medicine : office evaluation and management of the adult patient* (6th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 1408. ISBN 9780781775137.
4. ^ *a b* Harris, AM; Hicks, LA; Qaseem, A (19 January 2016). "Appropriate Antibiotic Use for Acute Respiratory Tract Infection in Adults: Advice for High-Value Care From the American College of Physicians and the Centers for Disease Control and Prevention.". *Annals of Internal Medicine*. **164**: 425. doi:10.7326/M15-1840. PMID 26785402.
5. ^ Weber, R (March 2014). "Pharyngitis.". *Primary care*. **41** (1): 91–8. doi:10.1016/j.pop.2013.10.010. PMID 24439883.
6. ^ *a b c* Shaikh N, Leonard E, Martin JM (September 2010). "Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis". *Pediatrics*. **126** (3): e557–64. doi:10.1542/peds.2009-2648. PMID 20696723.
7. ^ *a b c d e f g h i j k l m n o p q r s t u v w x* Choby BA (March 2009). "Diagnosis and treatment of streptococcal pharyngitis". *Am Fam Physician*. **79** (5): 383–90. PMID 19275067.
8. ^ *a b c d e f g h i j k l m n o p q* Shulman, ST; Bisno, AL; Clegg, HW; Gerber, MA; Kaplan, EL; Lee, G; Martin, JM; Van Beneden, C (Sep 9, 2012). "Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Update by the Infectious Diseases Society of America.". *Clinical Infectious Diseases*. **55** (10): e86–102. doi:10.1093/cid/cis629. PMID 22965026.
9. ^ *a b* Brook I, Dohar JE (December 2006). "Management of group A beta-hemolytic streptococcal pharyngotonsillitis in children". *J Fam Pract*. **55** (12): S1–11; quiz S12. PMID 17137534.
10. ^ *a b c d e f* Hayes CS, Williamson H (April 2001). "Management of Group A beta-hemolytic streptococcal pharyngitis". *Am Fam Physician*. **63** (8): 1557–64. PMID 11327431.
11. ^ *a b c d e f* Baltimore RS (February 2010). "Re-evaluation of antibiotic treatment of streptococcal pharyngitis". *Curr. Opin. Pediatr*. **22** (1): 77–82. doi:10.1097/MOP.0b013e32833502e7. PMID 19996970.
12. ^ Lindbaek M, Høiby EA, Lermark G, Steinsholt IM, Hjortdahl P (2004). "Predictors for spread of clinical group A streptococcal tonsillitis within the household". *Scand J Prim Health Care*. **22** (4): 239–43. doi:10.1080/02813430410006729. PMID 15765640.
13. ^ Rakel, edited by Robert E. Rakel, David P. *Textbook of family medicine* (8th ed.). Philadelphia, PA.: Elsevier Saunders. p. 331. ISBN 9781437711608.
14. ^ Cohen, JF; Cohen, R; Levy, C; Thollot, F; Benani, M; Bidet, P; Chalumeau, M (6 January 2015). "Selective testing strategies for diagnosing group A streptococcal infection in children with pharyngitis: a systematic review and prospective multicentre external validation study.". *Canadian Medical Association Journal*. **187** (1): 23–32. doi:10.1503/cmaj.140772. PMID 25487666.
15. ^ Smith, Ellen Reid; Kahan, Scott; Miller, Redonda G. (2008). *In A Page Signs & Symptoms*. In a Page Series. Hagerstown, Maryland: Lippincott Williams & Wilkins. p. 312. ISBN 0-7817-7043-2.
16. ^ Lean, WL; Arnup, S; Danchin, M; Steer, AC (October 2014). "Rapid diagnostic tests for group A streptococcal pharyngitis: a meta-analysis.". *Pediatrics*. **134** (4): 771–81. doi:10.1542/peds.2014-1094. PMID 25201792.
17. ^ *a b c d* Bisno AL, Gerber MA, Gwaltney JM, Kaplan EL, Schwartz RH (July 2002). "Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Infectious Diseases Society of America". *Clin. Infect. Dis*. **35** (2): 113–25. doi:10.1086/340949. PMID 12087516.
18. ^ Ebell MH (2004). "Epstein-Barr virus infectious mononucleosis". *Am Fam Physician*. **70** (7): 1279–87. PMID 15508538.
19. ^ Johnson BC, Alvi A (March 2003). "Cost-effective workup for tonsillitis. Testing, treatment, and potential

complications". *Postgrad Med*. **113** (3): 115–8, 121. doi:10.3810/pgm.2003.03.1391 . PMID 12647478 .
20. ^ van Staaij BK, van den Akker EH, van der Heijden GJ, Schilder AG, Hoes AW (January 2005). "Adenotonsillectomy for upper respiratory infections: evidence based?". *Archives of Disease in Childhood*. **90** (1): 19–25. doi:10.1136/adc.2003.047530. PMC 1720065. PMID 15613505.
21. ^ Burton, MJ; Glasziou, PP (Jan 21, 2009). "Tonsillectomy or adeno-tonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis.". *Cochrane database of systematic reviews (Online)* (1): CD001802. doi:10.1002/14651858.CD001802.pub2. PMID 19160201.
22. ^ Thomas M, Del Mar C, Glasziou P (October 2000). "How effective are treatments other than antibiotics for acute sore throat?". *Br J Gen Pract*. **50** (459): 817–20. PMC 1313826. PMID 11127175.
23. ^ "Generic Name: Lidocaine Viscous (Xylocaine Viscous) side effects, medical uses, and drug interactions". *MedicineNet.com*. Retrieved 2010-05-07.
24. ^ Wing, A; Villa-Roel, C; Yeh, B; Eskin, B; Buckingham, J; Rowe, BH (May 2010). "Effectiveness of corticosteroid treatment in acute pharyngitis: a systematic review of the literature.". *Academic Emergency Medicine*. **17** (5): 476–83. doi:10.1111/j.1553-2712.2010.00723.x. PMID 20536799.
25. ^ Bonsignori F, Chiappini E, De Martino M (2010). "The infections of the upper respiratory tract in children". *Int J Immunopathol Pharmacol*. **23** (1 Suppl): 16–9. PMID 20152073.
26. ^ *a b* Snow V, Mottur-Pilson C, Cooper RJ, Hoffman JR (March 2001). "Principles of appropriate antibiotic use for acute pharyngitis in adults" (PDF). *Ann Intern Med*. **134** (6): 506–8. doi:10.7326/0003-4819-134-6-200103200-00018. PMID 11255529. [*needs update?*]
27. ^ Hildreth, AF; Takhar, S; Clark, MA; Hatten, B (September 2015). "Evidence-Based Evaluation And Management Of Patients With Pharyngitis In The Emergency Department.". *Emergency medicine practice*. **17** (9): 1–16; quiz 16–7. PMID 26276908. (subscription required (help)).
28. ^ Linder JA, Bates DW, Lee GM, Finkelstein JA (November 2005). "Antibiotic treatment of children with sore throat". *J Am Med Assoc*. **294** (18): 2315–22. doi:10.1001/jama.294.18.2315. PMID 16278359.
29. ^ Pichichero, M; Casey, J (June 2006). "Comparison of European and U.S. results for cephalosporin versus penicillin treatment of group A streptococcal tonsillopharyngitis.". *European Journal of Clinical Microbiology & Infectious Diseases*. **25** (6): 354–64. doi:10.1007/s10096-006-0154-7. PMID 16767482.
30. ^ van Driel, ML; De Sutter, AI; Habraken, H; Thorning, S; Christiaens, T (11 September 2016). "Different antibiotic treatments for group A streptococcal pharyngitis.". *The Cochrane database of systematic reviews*. **9**: CD004406. doi:10.1002/14651858.CD004406.pub4. PMID 27614728.
31. ^ *a b* "UpToDate Inc.".
32. ^ Stevens DL, Tanner MH, Winship J, et al. (July 1989). "Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A". *N. Engl. J. Med*. **321** (1): 1–7. doi:10.1056/NEJM198907063210101. PMID 2659990.
33. ^ *a b* Hahn RG, Knox LM, Forman TA (May 2005). "Evaluation of poststreptococcal illness". *Am Fam Physician*. **71** (10): 1949–54. PMID 15926411.

v · t · e · **Diseases of the respiratory system (J, 460–519)**

| | | |
|---|---|---|
| **Upper RT (including URTIs, common cold)** | **Head** | *sinuses*: Sinusitis · *nose*: Rhinitis (Vasomotor rhinitis · Atrophic rhinitis · Hay fever · · Nasal polyp · Rhinorrhea · *nasal septum* (Nasal septum deviation · Nasal septum perforation · Nasal septal hematoma · · *tonsil*: Tonsillitis · Adenoid hypertrophy · Peritonsillar abscess · |
| | **Neck** | *pharynx*: Pharyngitis (**Strep throat** · · Laryngopharyngeal reflux (LPR) · Retropharyngeal abscess · *larynx*: Croup · Laryngomalacia · Laryngeal cyst · Laryngitis · Laryngopharyngeal reflux (LPR) · Laryngospasm · *vocal folds*: Laryngopharyngeal reflux (LPR) · Vocal fold nodule · Vocal cord paresis · Vocal cord dysfunction · *epiglottis*: Epiglottitis · *trachea*: Tracheitis · Tracheal stenosis · |
| | | *acute*: Acute bronchitis · |

| | | | | |
|---|---|---|---|---|
| **Lower RT/lung disease (including LRTIs)** | **Bronchial/obstructive** | | | *chronic*: COPD (Chronic bronchitis · Acute exacerbations of chronic bronchitis · Acute exacerbation of COPD · Emphysema) · Asthma (Status asthmaticus · Aspirin-induced · Exercise-induced · · Bronchiectasis · *unspecified*: Bronchitis · Bronchiolitis (Bronchiolitis obliterans · · Diffuse panbronchiolitis · |
| | **Interstitial/restrictive (fibrosis)** | **External agents/occupational lung disease** | | Pneumoconiosis (Asbestosis · Baritosis · Bauxite fibrosis · Berylliosis · Caplan's syndrome · Chalicosis · Coalworker's pneumoconiosis · Siderosis · Silicosis · Talcosis · Byssinosis · · Hypersensitivity pneumonitis (Bagassosis · Bird fancier's lung · Farmer's lung · Lycoperdonosis · · |
| | | **Other** | | ARDS · Pulmonary edema · Löffler's syndrome/Eosinophilic pneumonia · Respiratory hypersensitivity (Allergic bronchopulmonary aspergillosis · · Hamman-Rich syndrome · Idiopathic pulmonary fibrosis · Sarcoidosis · |
| | **Obstructive or restrictive** | **Pneumonia/pneumonitis** | **By pathogen** | Viral · Bacterial (Pneumococcal · Klebsiella) · · Atypical bacterial (Mycoplasma · Legionnaires' disease · Chlamydiae · · Fungal (Pneumocystis · · Parasitic · *noninfectious* (Chemical/Mendelson's syndrome · Aspiration/Lipid · · |
| | | | **By vector/route** | Community-acquired · Healthcare-associated · Hospital-acquired · |
| | | | **By distribution** | Broncho- · Lobar · |
| | | | **IIP** | UIP · DIP · BOOP-COP · NSIP · RB · |
| | | **Other** | | Atelectasis · *circulatory* (Pulmonary hypertension · Pulmonary embolism · · Lung abscess · |
| **Pleural cavity/mediastinum** | **Pleural disease** | | | Pleuritis/pleurisy · Pneumothorax/Hemopneumothorax · **Pleural effusion**: Hemothorax · Hydrothorax · Chylothorax · Empyema/pyothorax · Malignant · Fibrothorax · |
| | **Mediastinal disease** | | | Mediastinitis · Mediastinal emphysema · |
| **Other/general** | Respiratory failure · Influenza · SARS · Idiopathic pulmonary haemosiderosis · | | | |

Pulmonary alveolar proteinosis ·

Categories: Streptococcal infections | Human throat | Acute upper respiratory infections




# Tinnitus





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**Tinnitus** is the hearing of [illegible] sound when no external sound is present.[1] While often described as a ringing, it may also sound like a clicking, hiss or roaring.[2] Rarely, unclear voices or music are heard.[3] The sound may be soft or loud, low pitched or high pitched and appear to be coming from one ear or both.[2] Most of the time, it comes on gradually.[3] In some people, the sound causes depression, anxiety or interferes with concentration.[2]

Tinnitus is not a disease but a symptom that can result from a number of underlying causes. One of the most common causes is noise-induced hearing loss. Other causes include: ear infections, disease of the heart or blood vessels, Ménière's disease, brain tumors, emotional stress, exposure to certain medications, a previous head injury, and earwax.[2][4] It is more common in those with depression.[3]

The diagnosis of tinnitus is usually based on the person's description. A number of questionnaires exist that assess how much tinnitus is interfering with a person's life.[3] The diagnosis is commonly assisted with an audiogram and neurological exam.[1][3] If certain problems are found, medical imaging, such as with MRI, may be performed. Other tests are suitable when tinnitus occurs with the same rhythm as the heartbeat. Occasionally, the sound may be heard by someone else using a stethoscope, in which case it is known as objective tinnitus.[3]

Prevention involves avoiding loud noise.[2] If there is an underlying cause, treating it may lead to improvements.[3] Otherwise, typically, management involves talk therapy.[5] Sound generators or hearing aids may help some.[2] As of 2013, there are no effective medications.[3] It is common, affecting about 10-15% of people. Most, however, tolerate it well with its being a significant problem in only 1–2% of people.[5] The word tinnitus is from the Latin *tinnīre* which means "to ring".[3]

**Tinnitus**

| | |
|---|---|
| **Pronunciation** | /ˈtɪnɪtəs/ or /tɪˈnaɪtəs/ |
| **Classif** | |
| **Specialty** | Otorhinolaryngology, audiology |
| **ICD-10** | H93.1 |
| **ICD-9-CM** | 388.3 |
| **DiseasesDB** | 27662 |
| **MedlinePlus** | 003043 |
| **eMedicine** | ent/235 |
| **Patient UK** | Tinnitus |
| **MeSH** | D014012 |

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Contents

# Signs and symptoms

Tinnitus can be perceived in one or both ears or in the head. Tinnitus is the description of a noise inside a person's head in the absence of auditory stimulation. The noise can be described in many different ways but the most common description of the tinnitus is a pure tone sound. It is usually described as a ringing noise but, in some patients, it takes the form of a high-pitched whining, electric buzzing, hissing, humming, tinging or whistling sound or as ticking, clicking, roaring, "crickets" or "tree frogs" or "locusts (cicadas)", tunes, songs, beeping, sizzling, sounds that slightly resemble human voices or even a pure steady tone like that heard during a hearing test and, in some cases, pressure changes from the interior ear.[6] It has also been described as a "whooshing" sound because of acute muscle spasms, as of wind or waves.[7] Tinnitus can be intermittent or it can be continuous: in the latter case, it can be the cause of great distress. In some individuals, the intensity can be changed by shoulder, head, tongue, jaw or eye movements.[8]

Most people with tinnitus have some degree of hearing loss:[9] they are often unable to clearly hear external sounds that occur within the same range of frequencies as their "phantom sounds".[10] This has led to the suggestion that one cause of tinnitus might be a homeostatic response of central dorsal cochlear nucleus auditory neurons that makes them hyperactive in compensation to auditory input loss.[11]

The sound perceived may range from a quiet background noise to one that can be heard even over loud external sounds. The specific type of tinnitus called pulsatile tinnitus is characterized by hearing the sounds of one's own pulse or muscle contractions, which is typically a result of sounds that have been created from the movement of muscles near to one's ear, changes within the canal of one's ear or issues related to blood flow of the neck or face.[12]

Edit links

## Course

There has been little research on the course of tinnitus and most research has been retrospective. An Australian study of participants aged 49–97 years found that 35% of participants reported that their tinnitus was present all the time and 4% rated their tinnitus as annoying. Findings from a retrospective National Study of Hearing found that, for 25% of people surveyed, the perceived volume of their tinnitus increased over time while, for 75%, it did not. The rate of annoyance decreased for 31% of people from onset of tinnitus to the middle time. A study of the natural history of tinnitus in older adults found that, for women, tinnitus increased for 25%, decreased in 58%, leaving 17% unchanged. The study found that, for men, tinnitus increased in 8%, decreased in 39%, leaving 53% unchanged. Information about the course of tinnitus would benefit from prospective studies investigating change over time as these studies may potentially be more accurate.[13]

## Psychological

Persistent tinnitus may cause irritability, fatigue and, on occasions, clinical depression[14][15] and musical hallucinations.[16]

Tinnitus annoyance is more strongly associated with psychological condition than loudness or frequency range.[17][18][19] Other psychological problems such as depression, anxiety, sleep disturbances and concentration difficulties are common in those with worse tinnitus.[17][20][21] 45% of people with tinnitus have an anxiety disorder at some time in their life.[22]

As part of the idea that the central-auditory-system may be implicated into the tinnitus development, serotonin has also been implicated. Indeed, serotonin has been postulated to be involved in plastic changes in the brain. Serotonin re-uptake inhibitors (such as some anti-depressant drugs) have often been used for this reason.[23] However those medications do not benefit in a consistent fashion on non-depressant people.[24]

Psychological research has looked at the tinnitus distress reaction (TDR) to account for differences in tinnitus severity.[20] Research has stigmatized people with severe tinnitus by implying they have personality disorders, such as neuroticism, anxiety sensitivity, and catastrophic thinking, which all predispose increased TDR.[25][26][27] These findings suggest that at the initial perception of tinnitus, conditioning links tinnitus with negative emotions, such as fear and anxiety from unpleasant stimuli at the time. This enhances activity in the limbic system and autonomic nervous system, thus increasing tinnitus awareness and annoyance.[28]

# Causes

There are two types of tinnitus: subjective tinnitus and objective tinnitus.[3] Tinnitus is usually subjective, meaning that others cannot hear it.[3] Subjective tinnitus has been also called "tinnitus aurium" "nonauditory" and "nonvibratory" tinnitus. Occasionally, tinnitus may be heard by someone else using a stethoscope: in which case, it is objective tinnitus.[3] Objective tinnitus has been called "pseudo-tinnitus" or "vibratory" tinnitus.

## Subjective tinnitus

Subjective tinnitus is the most frequent type of tinnitus. It can have many possible causes but, most commonly, results from hearing loss. A frequent cause of subjective tinnitus is noise exposure which damages hair cells in the inner ear causing tinnitus. Subjective tinnitus can only be heard by the affected person and is caused by otology, neurology, infection or drugs.[29]

There is a growing body of evidence suggesting that tinnitus is a consequence of neuroplastic alterations in the central auditory pathway. These alterations are assumed to result from a disturbed sensory input, caused by hearing loss.[30] Hearing loss could indeed cause a homeostatic response of neurons in the central auditory system, and therefore cause tinnitus.[31]

Despite the opinion amongst researchers that tinnitus is primarily a central nervous system pathology, there certainly exists a class of people whose tinnitus is peripherally based.[32]

## Hearing loss

The most common cause of tinnitus is noise-induced hearing loss. Hearing loss may be implicated even for people with normal audiograms.[31]

Hearing loss may have many different causes; but among tinnitus subjects, the major cause is cochlear damage.[30]

Ototoxic drugs (such as aspirin) can also cause subjective tinnitus, as they may cause hearing loss, or increase the damage done by exposure to loud noise. Those damages can occur even at doses that are not [33]

considered ototoxic. Tinnitus is also a classical side effect of quinidine, a Class IA anti-arrhythmic. Over 260 medications have been reported to cause tinnitus as a side effect.[34] In many cases, however, no underlying cause can be identified.[2]

Tinnitus can also occur due to the discontinuation of therapeutic doses of benzodiazepines. It can sometimes be a protracted symptom of benzodiazepine withdrawal and may persist for many months.[35][36]

## Associated factors

This section contains embedded lists that **may be poorly defined, unverified or indiscriminate**. Please help to clean it up to meet Wikipedia's quality standards. Where appropriate, incorporate items into the main body of the article. *(November 2015)*

Factors associated with tinnitus include:[37]

- ear problems and hearing loss:
  - conductive hearing loss
    - external ear infection
    - acoustic shock
    - loud noise or music[38]
    - cerumen (earwax) impaction
    - middle ear effusion
    - superior canal dehiscence
  - sensorineural hearing loss
    - excessive or loud noise
    - presbycusis (age-associated hearing loss)
    - Ménière's disease
    - endolymphatic hydrops
    - acoustic neuroma
    - mercury or lead poisoning
    - ototoxic medications
- neurologic disorders:
  - Arnold–Chiari malformation
  - multiple sclerosis
  - head injury
    - skull fracture
    - closed head injury
    - whiplash injury
    - temporomandibular joint dysfunction
    - giant cell arteritis
- metabolic disorders:
  - thyroid disease
  - hyperlipidemia
  - vitamin $B_{12}$ deficiency[39]
  - iron deficiency anemia
- psychiatric disorders
  - depression
  - anxiety disorders
- other factors:
  - tension myositis syndrome
  - fibromyalgia

- vasculitis
- hypertonia (muscle tension)
- thoracic outlet syndrome
- Lyme disease
- hypnagogia
- migraine
- sleep paralysis
- glomus tympanicum tumor
- anthrax vaccines which contain the anthrax protective antigen
- Some psychedelic drugs can produce temporary tinnitus-like symptoms as a side effect
  - 5-MeO-DET[40]
  - diisopropyltryptamine (DiPT)[41]
- benzodiazepine withdrawal[35][36]
- nasal congestion
- intracranial hyper or hypotension caused by, for example, encephalitis or a cerebrospinal fluid leak

### Objective tinnitus

Objective tinnitus can be detected by other people and is usually caused by myoclonus or a vascular condition. In some cases, tinnitus is generated by a self-sustained oscillation within the ear. This is called objective tinnitus which can arise from muscle spasms around the middle ear.[42] Homeostatic control mechanisms exist to correct the problem within a minute after onset and is normally accompanied by a slight reduction in hearing sensitivity followed by a feeling of fullness in the ear.[43]

Objective tinnitus can most often can be heard as a sound outside the ear, as spontaneous otoacoustic emissions (SOAEs) that can form beats with and lock into external tones.[44] The majority of the people are unaware of their SOAEs; whereas portions of 1-9% perceive a SOAE as an annoying tinnitus.[45]

### Pulsatile tinnitus

Pulsatile tinnitus can be a symptom of intracranial vascular abnormalities and should be evaluated for bruits. Some people experience a sound that beats in time with their pulse (pulsatile tinnitus, or vascular tinnitus).[46] Pulsatile tinnitus is usually objective in nature, resulting from altered blood flow, increased blood turbulence near the ear (such as from atherosclerosis, venous hum,[47] but it can also arise as a subjective phenomenon from an increased awareness of blood flow in the ear.[46] Rarely, pulsatile tinnitus may be a symptom of potentially life-threatening conditions such as carotid artery aneurysm[48] or carotid artery dissection.[49] Pulsatile tinnitus may also indicate vasculitis, or more specifically, giant cell arteritis. Pulsatile tinnitus may also be an indication of idiopathic intracranial hypertension.[50]

## Pathophysiology

One of the possible mechanisms relies on otoacoustic emissions. The inner ear contains tens of thousands of minute inner hair cells with stereocilia which vibrate in response to sound waves and outer hair cells which convert neural signals into tension on the vibrating basement membrane. The sensing cells are connected with the vibratory cells through a neural feedback loop, whose gain is regulated by the brain. This loop is normally adjusted just below onset of self-oscillation, which gives the ear spectacular sensitivity and selectivity. If something changes, it is easy for the delicate adjustment to cross the barrier of oscillation and, then, tinnitus results. Exposure to excessive sound kills hair cells and studies have shown that, as hair cells are lost, different neurons are activated, activating auditory parts of the brain and giving the perception of sound.[*citation needed*]

Another possible mechanism underlying tinnitus is damage to the receptor cells. Although receptor cells can be regenerated from the adjacent supporting Deiters cells after injury in birds, reptiles and amphibians, it is believed that, in mammals, they can be produced only during embryogenesis. Although mammalian Deiters

cells reproduce and position themselves appropriately for regeneration, they have not been observed to transdifferentiate into receptor cells except in tissue culture experiments.[51][52] Therefore, if these hairs become damaged, through prolonged exposure to excessive sound levels, for instance, then deafness to certain frequencies results. In tinnitus, they may relay information that an externally audible sound is present at a certain frequency when it is not.

The mechanisms of subjective tinnitus are often obscure. While it is not surprising that direct trauma to the inner ear can cause tinnitus, other apparent causes (e.g., temporomandibular joint dysfunction and dental disorders) are difficult to explain. Research has proposed there are two distinct categories of subjective tinnitus: otic tinnitus, caused by disorders of the inner ear or the acoustic nerve, and somatic tinnitus, caused by disorders outside the ear and nerve, but still within the head or neck. It is further hypothesized somatic tinnitus may be due to "central crosstalk" within the brain, as certain head and neck nerves enter the brain near regions known to be involved in hearing.[53]

It may be caused by increased neural activity in the auditory brainstem where the brain processes sounds, causing some auditory nerve cells to become over-excited. The basis of this theory is most people with tinnitus also have hearing loss,[9] and the frequencies they cannot hear are similar to the subjective frequencies of their tinnitus.[10] Models of hearing loss and the brain support the idea a homeostatic response of central dorsal cochlear nucleus neurons could result in them being hyperactive in a compensation process to the loss of hearing input.[11]

# Diagnosis

Even when tinnitus is the primary complaint, audiological evaluation is usually preceded by examination by an ENT to diagnose treatable conditions like middle ear infection, acoustic neuroma, concussion, otosclerosis, etc.[54]

Evaluation of tinnitus will include a hearing test (audiogram), measurement of acoustic parameters of the tinnitus like pitch and loudness, and psychological assessment of comorbid conditions like depression, anxiety, and stress that are associated with severity of the tinnitus.

The accepted definition of chronic tinnitus, as compared to normal ear noise experience, is five minutes of ear noise occurring at least twice a week.[55] However, people with chronic tinnitus often experience the noise more frequently than this and can experience it continuously or regularly, such as during the night when there is less environmental noise to mask the sound.

## Audiology

Since most persons with tinnitus also have hearing loss, a pure tone hearing test resulting in an audiogram may help diagnose a cause, though some persons with tinnitus do not have hearing loss. An audiogram may also facilitate fitting of a hearing aid in those cases where hearing loss is significant. The pitch of tinnitus is often in the range of the hearing loss. A hearing aid boosting the attentuated frequencies may at least partly mask tinnitus by raising the background level of sound in the tuned frequency range.

## Psychoacoustics

Acoustic qualification of tinnitus will include measurement of several acoustic parameters like pitch, or frequency in cases of monotone tinnitus, or frequency range and bandwidth in cases of narrow band noise tinnitus, loudness in dB above hearing threshold at the indicated frequency, mixing-point, and minimum masking level.[56] In most cases, tinnitus pitch or frequency range is between 5000 Hz and 8000 Hz, and loudness less than 10 dB above the hearing threshold.[*medical citation needed*]

Another relevant parameter of tinnitus is residual inhibition, the temporary suppression and/or disappearance of tinnitus following a period of masking. The degree of residual inhibition may indicate how effective tinnitus maskers would be as a treatment modality.[57]

An assessment of hyperacusis, a frequent accompaniment of tinnitus, may also be made. The measured

parameter is Loudness Discomfort Level in dB, the subjective level of acute discomfort at specified frequencies over the frequency range of hearing. This defines a dynamic range between the hearing threshold at that frequency and the loudnes discomfort level. A compressed dynamic range over a particular frequency range is associated with subjectve hyperacusis.[58] Normal hearing threshold is generally defined as 0–20 decibels (dB). Normal loudness discomfort levels are 85–90+ dB, with some authorities citing 100 dB. A dynamic range of 55 dB or less is indicative of hyperacusis.

### Severity

The condition is often rated on a scale from "slight" to "catastrophic" according to the effects it has, such as interference with sleep, quiet activities and normal daily activities.[59] In an extreme case a man committed suicide after being told there was no cure.[60]

Assessment of psychological processes related to tinnitus involves measurement of tinnitus severity and distress (i.e. nature and extent of tinnitus-related problems), measured subjectively by validated self-report tinnitus questionnaires.[20] These questionnaires measure the degree of psychological distress and handicap associated with tinnitus, including effects on hearing, lifestyle, health and emotional functioning.[61][62][63][64] A broader assessment of general functioning, such as levels of anxiety, depression, stress, life stressors and sleep difficulties, is also important in the assessment of tinnitus due to higher risk of negative well-being across these areas, which may be affected by and/or exacerbate the tinnitus symptoms for the individual.[65] Overall, current assessment measures are aimed to identify individual levels of distress and interference, coping responses and perceptions of tinnitus in order to inform treatment and monitor progress. However, wide variability, inconsistencies and lack of consensus regarding assessment methodology are evidenced in the literature, limiting comparison of treatment effectiveness.[66] Developed to guide diagnosis or classify severity, most tinnitus questionnaires have also been shown to be treatment-sensitive outcome measures.[67]

### Pulsatile tinnitus

If the examination reveals a bruit (sound due to turbulent blood flow), imaging studies such as transcranial doppler (TCD) or magnetic resonance angiography (MRA) should be performed.[68]

### Auditory evoked response

Tinnitus can be evaluated with most auditory evoked potentials: however, results may be inconsistent. Results must be compared to age and hearing matched control subjects to be reliable. This inconsistent reporting may be due to many reasons: differences in the origin of the tinnitus, ABR recording methods and selection criteria of control groups. Since research shows conflicting evidence, more research on the relationship between tinnitus and auditory evoked potentials should be carried out before these measurements are used clinically.

### Differential diagnosis

Other potential sources of the sounds normally associated with tinnitus should be ruled out. For instance, two recognized sources of high-pitched sounds might be electromagnetic fields common in modern wiring and various sound signal transmissions. A common and often misdiagnosed condition that mimics tinnitus is radio frequency (RF) hearing, in which subjects have been tested and found to hear high-pitched transmission frequencies that sound similar to tinnitus.[69]

## Prevention

Prolonged exposure to loud sound or noise levels can lead to tinnitus.[70] Ear plugs or other measures can help with prevention.

Several medicines have ototoxic effects, and can have a cumulative effect that can increase the damage

done by noise. If ototoxic medications must be administered, close attention by the physician to prescription details, such as dose and dosage interval, can reduce the damage done.[71]

# Management

If there is an underlying cause, treating it may lead to improvements.[3] Otherwise, the primary treatment for tinnitus is talk therapy[5] and sound therapy; there are no effective medications.[3]

## Psychological

The best supported treatment for tinnitus is a type of counseling called cognitive behavioral therapy (CBT) which can be delivered via the internet or in person.[5][72] It decreases the amount of stress those with tinnitus feel.[73] These benefits appear to be independent of any effect on depression or anxiety in an individual.[72] Acceptance and commitment therapy (ACT) also shows promise in the treatment of tinnitus.[74] Relaxation techniques may also be useful.[3] A clinical protocol called Progressive Tinnitus Management for treatment of tinnitus has been developed by the United States Department of Veterans Affairs.[75]

## Medications

As of 2014 there were no medications effective for tinnitus.[3][70] There is not enough evidence to determine if antidepressants[76] or acamprosate is useful.[77] While there is tentative evidence for benzodiazepines, it is insufficient to support usage.[3] Anticonvulsants have not been found to be useful.[3] Steroids injections into the middle ear also do not seem to be effective.[78][79]

Botulinum toxin injection has been tried with some success in cases of objective tinnitus from a palatal tremor.[80]

## Other

The use of sound therapy by either hearing aids or tinnitus maskers helps the brain ignore the specific tinnitus frequency. Although these methods are poorly supported by evidence, there are no negative effects.[3][81] There is some tentative evidence supporting tinnitus retraining therapy.[3] There is little evidence supporting the use of transcranial magnetic stimulation.[3][82] It is thus not recommended.[70]

## Alternative medicine

*Ginkgo biloba* does not appear to be effective.[83] The American Academy of Otolaryngology recommends against taking melatonin or zinc supplements to relieve symptoms of tinnitus.[70] In addition, a 2016 Cochrane Review concluded that evidence is not sufficient to support taking zinc supplements to reduce symptoms associated with tinnitus.[84]

# Prognosis

While there is no cure, most people with tinnitus get used to it over time; for a minority, it remains a significant problem.[5]

# Epidemiology

Tinnitus affects 10–15% of people.[5] About a third of North Americans over 55 experience tinnitus.[85] Tinnitus affects one third of adults at some time in their lives, whereas ten to fifteen percent are disturbed

enough to seek medical evaluation.[86]

### Children

Tinnitus is commonly thought of as a symptom of adulthood, and is often overlooked in children. Children with hearing loss have a high incidence of tinnitus, even though they do not express the condition or its effect on their lives.[87] Children do not generally report tinnitus spontaneously and their complaints may not be taken seriously.[88] Among those children who do complain of tinnitus, there is an increased likelihood of associated otological or neurological pathology such as migraine, juvenile Meniere's disease or chronic suppurative otitis media.[89] Its reported prevalence varies from 12% to 36% in children with normal hearing thresholds and up to 66% in children with a hearing loss and approximately 3–10% of children have been reported to be troubled by tinnitus.[90]

## See also

- Hyperacusis
- List of people with tinnitus
- List of unexplained sounds
- Noise health effects
- Ringxiety
- Zwicker tone

Medicine portal

## References


1. ^ a b Levine, RA; Oron, Y (2015). "Tinnitus.". *Handbook of clinical neurology*. **129**: 409–31. doi:10.1016/B978-0-444-62630-1.00023-8. PMID 25726282.
2. ^ a b c d e f g "Tinnitus". September 2014. Retrieved 22 May 2015.
3. ^ a b c d e f g h i j k l m n o p q r s t u Baguley, D; McFerran, D; Hall, D (Nov 9, 2013). "Tinnitus.". *Lancet*. **382** (9904): 1600–07. doi:10.1016/S0140-6736(13)60142-7. PMID 23827090.
4. ^ Han BI, Lee HW, Kim TY, Lim JS, Shin KS (March 2009). "Tinnitus: characteristics, causes, mechanisms, and treatments". *J Clin Neurol*. **5** (1): 11–19. doi:10.3988/jcn.2009.5.1.11. PMC 2686891. PMID 19513328. "About 75% of new cases are related to emotional stress as the trigger factor rather than to precipitants involving cochlear lesions."
5. ^ a b c d e f Langguth, B; Kreuzer, PM; Kleinjung, T; De Ridder, D (Sep 2013). "Tinnitus: causes and clinical management.". *Lancet neurology*. **12** (9): 920–30. doi:10.1016/S1474-4422(13)70160-1. PMID 23948178.
6. ^ "Information and resources: Tinnitus: About tinnitus: What is tinnitus". RNID.org.uk. Retrieved 2012-10-26.
7. ^ MedlinePlus Encyclopedia *Ear noises or buzzing*
8. ^ Simmons R, Dambra C, Lobarinas E, Stocking C, Salvi R (2008). "Head, Neck, and Eye Movements That Modulate Tinnitus". *Seminars in hearing*. **29** (4): 361–70. doi:10.1055/s-0028-1095895. PMC 2633109. PMID 19183705.
9. ^ a b Nicolas-Puel C, Faulconbridge RL, Guitton M, Puel JL, Mondain M, Uziel A (2002). "Characteristics of tinnitus and etiology of associated hearing loss: a study of 123 patients". *The international tinnitus journal*. **8** (1): 37–44. PMID 14763234.
10. ^ a b Knig O, Schaette R, Kempter R, Gross M (2006). "Course of hearing loss and occurrence of tinnitus". *Hearing research*. **221** (1–2): 59–64. doi:10.1016/j.heares.2006.07.007. PMID 16962270.
11. ^ a b Schaette R, Kempter R (2006). "Development of tinnitus-related neuronal hyperactivity through homeostatic plasticity after hearing loss: a computational model". *Eur J Neurosci*. **23** (11): 3124–38. doi:10.1111/j.1460-9568.2006.04774.x. PMID 16820003.
12. ^ "Tinnitus (Ringing in the Ears) Causes, Symptoms, Treatments". Webmd.com. 2010-02-12. Retrieved 2013-02-03.
13. ^ Baguley D; Andersson g; McFerran D; McKenna L (2013). *Tinnitus: AMultidisciplinary Approach (2nd ed.)*. Blackwell Publishing Ltd. pp. 16–17.
14. ^ Berrios, G E; Rose, G S (1992). "Psychiatry of subjective tinnitus: conceptual, historical and clinical aspects". *Neurology, Psychiatry and Brain Research*. **1**: 76–82.

15. ^ Berrios, G E; Ryley, J R; Garvey, N; Moffat, DA (1988). "Psychiatric Morbidity in subjects with inner ear disease". *Clinical Otolaryngology*. **13** (4): 259–66. doi:10.1111/j.1365-2273.1988.tb01129.x. PMID 3180496.
16. ^ Berrios GE (1990). "Musical hallucinations: a historical and clinical study". *British Journal of Psychiatry*. **156** (2): 188–94. doi:10.1192/bjp.156.2.188. PMID 2180526.
17. ^ *a b* Andersson G (2002). "Psychological aspects of tinnitus and the application of cognitive-behavioural therapy". *Clinical Psychology Review*. **22** (7): 977–79. doi:10.1016/s0272-7358(01)00124-6. PMID 12238249.
18. ^ Baguley DM (2002). "Mechanisms of tinnitus". *British Medical Bulletin*. **63**: 195–212. doi:10.1093/bmb/63.1.195. PMID 12324394.
19. ^ Henry JA, Meikele MB (1999). "Pulsed versus continuous tones for evaluating the loudness of tinnitus". *Journal of the American Academy of Audiology*. **10** (5): 261–72. PMID 10331618.
20. ^ *a b c* Henry JA, Dennis KC, Schechter MA (2005). "General review of tinnitus: Prevalence, mechanisms, effects, and management". *Journal of Speech, Language, and Hearing Research*. **48** (5): 1204–35. doi:10.1044/1092-4388(2005/084). PMID 16411806.
21. ^ Davies A, Rafie EA (2000). "Epidemiology of Tinnitus". In R. S. Tyler. *Tinnitus Handbook*. San Diego: Singular. pp. 1–23. OCLC 42771695.
22. ^ Pattyn T, Van Den Eede F, Vanneste S, Cassiers L, Veltman DJ, Van De Heyning P, Sabbe BC (2015). "Tinnitus and anxiety disorders: A review". *Hear. Res*. doi:10.1016/j.heares.2015.08.014. PMID 26342399.
23. ^ Nelson, JJ; Chen, K (July 2004). "The relationship of tinnitus, hyperacusis, and hearing loss.". *Ear, nose, & throat journal*. **83** (7): 472–76. PMID 15372918.
24. ^ Robinson, SK; Viirre, ES; Bailey, KA; Gerke, MA; Harris, JP; Stein, MB (2004). "Randomized placebo-controlled trial of a selective serotonin reuptake inhibitor in the treatment of nondepressed tinnitus subjects.". *Psychosomatic Medicine*. **67** (6): 981–88. doi:10.1097/01.psy.0000188479.04891.74. PMID 16314604.
25. ^ Henry JA, Wilson P (2000). "Psychological management of tinnitus". In R.S. Tyler. *Tinnitus Handbook*. San Diego: Singular. pp. 263–79. OCLC 42771695.
26. ^ Andersson G, Westin V (2008). "Understanding tinnitus distress: Introducing the concepts of moderators and mediators". *International Journal of Audiology*. **47** (Suppl. 2): S106–S111. doi:10.1080/14992020802301670. PMID 19012118.
27. ^ Weise C, Hesser H, Andersson G, Nyenhuis N, Zastrutzki S, Kröner-Herwig B, Jäger B (2013). "The role of catastrophizing in recent onset tinnitus: its nature and association with tinnitus distress and medical utilization". *Journal of International Audiology*. **3** (3): 177–88. doi:10.3109/14992027.2012.752111. PMID 23301660.
28. ^ Jastreboff, PJ; Hazell, JWP (2004). *Tinnitus Retraining Therapy: Implementing the neurophysiological model*. Cambridge: Cambridge University Press. OCLC 237191959.
29. ^ Chan Y (2009). "Tinnitus: etiology, classification, characteristics, and treatment". *Discovery Medicine*. **8** (42): 133–36. PMID 19833060.
30. ^ *a b* Schecklmann, Martin; Vielsmeier, Veronika; Steffens, Thomas; Landgrebe, Michael; Langguth, Berthold; Kleinjung, Tobias; Andersson, Gerhard (18 April 2012). "Relationship between Audiometric Slope and Tinnitus Pitch in Tinnitus Patients: Insights into the Mechanisms of Tinnitus Generation". *PLoS ONE*. **7** (4): e34878. doi:10.1371/journal.pone.0034878.
31. ^ *a b* Schaette, R.; McAlpine, D. (21 September 2011). "Tinnitus with a Normal Audiogram: Physiological Evidence for Hidden Hearing Loss and Computational Model". *Journal of Neuroscience*. **31** (38): 13452–57. doi:10.1523/JNEUROSCI.2156-11.2011.
32. ^ Simpson, Julie J; Davies, W.Ewart (July 2000). "A review of evidence in support of a role for 5-HT in the perception of tinnitus". *Hearing Research*. **145** (1-2): 1–7. doi:10.1016/S0378-5955(00)00093-9.
33. ^ Brown RD, Penny JE, Henley CM, et al. (1981). "Ototoxic drugs and noise". *Ciba Found Symp*. **85**: 151–71. PMID 7035098.
34. ^ Stas Bekman: stas (at) stason.org. "6) What are some ototoxic drugs?". Stason.org. Retrieved 2012-10-26.
35. ^ *a b* Riba, Michelle B.; Ravindranath, Divy (12 April 2010). *Clinical manual of emergency psychiatry*. Washington, DC: American Psychiatric Publishing Inc. p. 197. ISBN 978-1-58562-295-5.
36. ^ *a b* Delanty, Norman (27 November 2001). *Seizures: medical causes and management*. Totowa, N.J.: Humana Press. p. 187. ISBN 978-0-89603-827-1.
37. ^ Crummer RW, Hassan GA (2004). "Diagnostic approach to tinnitus". *Am Fam Physician*. **69** (1): 120–06. PMID 14727828.
38. ^ Passchier-Vermeer W, Passchier WF (2000). "Noise exposure and public health". *Environ. Health Perspect*. 108 Suppl 1 (Suppl 1): 123–31. doi:10.2307/3454637. JSTOR 3454637. PMC 1637786. PMID 10698728.
39. ^ Stover, editors, Janos Zempleni, John W. Suttie, Jesse F. Gregory, III, Patrick J. (2014). *Handbook of vitamins* (Fifth edition. ed.). Hoboken: CRC Press. p. 477. ISBN 9781466515574.
40. ^ Shulgin, Alexander; Shulgin, Ann (1997). "#36. 5-MEO-DET". *TiHKAL: the continuation*. Berkeley, CA, USA: Transform Press. ISBN 9780963009692. OCLC 38503252. Retrieved 27 October 2012. External link in

|publisher= (help)
41. ^ "Erowid Experience Vaults: DiPT – More Tripping & Revelations – 26540".
42. ^ "Tinnitus". American Academy of Otolaryngology – Head and Neck Surgery. 2012-04-03. Retrieved 2012-10-26.
43. ^ "What Causes Spontaneous Ringing In Our Ears?". *ZidBits*. ZidBits Media. February 26, 2013. Retrieved March 19, 2015.
44. ^ Probst, R; Lonsbury-Martin, BL; Martin, GK (May 1991). "A review of otoacoustic emissions.". *The Journal of the Acoustical Society of America*. **89** (5): 2027–67. doi:10.1121/1.400897. PMID 1860995.
45. ^ Penner, MJ (April 1990). "An estimate of the prevalence of tinnitus caused by spontaneous otoacoustic emissions.". *Archives of otolaryngology--head & neck surgery*. **116** (4): 418–23. doi:10.1001/archotol.1990.01870040040010. PMID 2317322.
46. ^ *a b* "Information and resources: Our factsheets and leaflets: Tinnitus: Factsheets and leaflets". RNID.org.uk. Retrieved 2012-10-26.
47. ^ Chandler JR (1983). "Diagnosis and cure of venous hum tinnitus". *Laryngoscope*. **93** (7): 892–5. doi:10.1288/00005537-198307000-00009. PMID 6865626.
48. ^ Moonis G, Hwang CJ, Ahmed T, Weigele JB, Hurst RW (2005). "Otologic manifestations of petrous carotid aneurysms". *AJNR Am J Neuroradiol*. **26** (6): 1324–27. PMID 15956490.
49. ^ Selim, Magdy; Caplan, Louis R. (2004). "Carotid Artery Dissection". *Current Treatment Options in Cardiovascular Medicine*. **6** (3): 249–53. doi:10.1007/s11936-996-0020-z. ISSN 1092-8464. PMID 15096317. (subscription required)
50. ^ Sismanis A, Butts FM, Hughes GB (2009-01-04). "Objective tinnitus in benign intracranial hypertension: An update". *The Laryngoscope*. **100**: 33–36. doi:10.1288/00005537-199001000-00008.
51. ^ Yamasoba T, Kondo K (2006). "Supporting cell proliferation after hair cell injury in mature guinea pig cochlea in vivo". *Cell Tissue Res*. **325** (1): 23–31. doi:10.1007/s00441-006-0157-9. PMID 16525832.
52. ^ White PM, Doetzlhofer A, Lee YS, Groves AK, Segil N (2006). "Mammalian cochlear supporting cells can divide and trans-differentiate into hair cells". *Nature*. **441** (7096): 984–87. doi:10.1038/nature04849. PMID 16791196.
53. ^ Engmann, Birk: Ohrgeräusche (Tinnitus): Ein lebenslanges Schicksal? PTA-Forum. Supplement Pharmazeutische Zeitung. 1997 July
54. ^ Crummer, et.al, RW (2004). "Diagnostic Approach to Tinnitus". *Am Fam Physician*. **69** (1): 120–26.
55. ^ Davis, A (1989). "The prevalence of hearing impairment and reported hearing disability among adults in Great Britain". *International Journal of Epidemiology*. **18** (4): 911–17. doi:10.1093/ije/18.4.911.
56. ^ Henry, et.al., JA (2000). "Psychoacoustic Measures of Tinnitus James A . Henry* Mary B . Meikle*". *J Am Acad Audiol*. **11**: 138–55.
57. ^ Shulman, et.al, A (1997). "Medical Significance of Tinnitus". *Int Tinnitus J*. **3** (1): 45–50.
58. ^ Sherlock, et. al, LaGuinn P. (2005). "Estimates of Loudness, Loudness Discomfort, and the Auditory Dynamic Range: Normative Estimates, Comparison of Procedures, and Test-Retest Reliability". *J Am Acad Audiol*. **16**: 85–100. doi:10.3766/jaaa.16.2.4.
59. ^ "Guidelines for the grading of tinnitus severity". Retrieved 2009-12-31.
60. ^ "James Jones's 80ft death jump after tinnitus 'torture'". *BBC News*. 2 December 2015. Retrieved 2 December 2015.
61. ^ Wilson, P., Henry, J., Bowen, M., & Haralambous. (1991). "Tinnitus reaction questionnaire: psychometric properties of a measure of distress associated with tinnitus". *Journal of Speech, Language, and Hearing Research*. **34** (1): 197–201. doi:10.1044/jshr.3401.197.
62. ^ Kuk, F., Tyler, R., Russell, D., & Jordan, H. (1990). "The psychometric properties of a Tinnitus Handicap Questionnaire.". *Ear Hear*. **11**: 434–445. doi:10.1097/00003446-199012000-00005.
63. ^ Hallam, R.S. (1996). *Manual of the Tinnitus Questionnaire. |London: The Psychological Corporation*.
64. ^ Meikle, M.B., Henry, J.A., Griest, S.E., Stewart, B.J., Abrams, H.B., McArdle, R., . . . Vernon, J.A. (2012). "The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus.". *Ear Hear*. **33**: 153–76. doi:10.1097/aud.0b013e31822f67c0. PMID 22156949.
65. ^ Henry, J. L., & Wilson, P. H. (2000). *The Psychological Management of Chronic Tinnitus: A Cognitive Behavioural Approach*. Boston: Allyn and Bacon.
66. ^ Landgrebe M, Azevedo A, Baguley D, Bauer C, Cacace A, Coelho C, et al. (2012). "Methodological aspects of clinical trials in tinnitus: A proposal for international standard". *Journal of Psychosomatic Research*. **73** (2): 112–21. doi:10.1016/j.jpsychores.2012.05.002. PMID 22789414.
67. ^ Martinez-Devesa, P; Perera, R; Theodoulou, M; Waddell, A (Sep 8, 2010). "Cognitive behavioural therapy for tinnitus". *The Cochrane database of systematic reviews* (9): CD005233. doi:10.1002/14651858.CD005233.pub3. PMID 20824844.
68. ^ Liyanage SH, Singh A, Savundra P, Kalan A (February 2006). "Pulsatile tinnitus.". *J Laryngol Otol*. **120** (2): 93–97.

doi:10.1017/S0022215105001714. PMID 16359136.
69. ^ Elder, JA; Chou, CK (2003). "Auditory response to pulsed radiofrequency energy.". *Bioelectromagnetics*. Suppl 6: S162–73. doi:10.1002/bem.10163. PMID 14628312.
70. ^ *a b c d* Tunkel, D. E.; Bauer, C. A.; Sun, G. H.; Rosenfeld, R. M.; Chandrasekhar, S. S.; Cunningham, E. R.; Archer, S. M.; Blakley, B. W.; Carter, J. M.; Granieri, E. C.; Henry, J. A.; Hollingsworth, D.; Khan, F. A.; Mitchell, S.; Monfared, A.; Newman, C. W.; Omole, F. S.; Phillips, C. D.; Robinson, S. K.; Taw, M. B.; Tyler, R. S.; Waguespack, R.; Whamond, E. J. (1 October 2014). "Clinical Practice Guideline: Tinnitus". *Otolaryngology – Head and Neck Surgery*. **151** (2 Suppl): S1–S40. doi:10.1177/0194599814545325.
71. ^ Palomar García, V; Abdulghani Martínez, F; Bodet Agustí, E; Andreu Mencía, L; Palomar Asenjo, V (Jul 2001). "Drug-induced otoxicity: current status.". *Acta oto-laryngologica*. **121** (5): 569–72. doi:10.1080/00016480121545. PMID 11583387. Cite uses deprecated parameter `|coauthors=` (help)
72. ^ *a b* Hoare D, Kowalkowski V, Knag S, Hall D (2011). "Systematic review and meta-analyses of randomized controlled trials examining tinnitus management". *The Laryngoscope*. **121**: 1555–64. doi:10.1002/lary.21825. PMC 3477633. PMID 21671234.
73. ^ Hesser H, Weise C, Zetterquist Westin V, Andersson G (2011). "A systematic review and meta-analysis of randomized controlled trials of cognitive–behavioral therapy for tinnitus distress". *Clinical Psychology Review*. **31** (4): 545–53. doi:10.1016/j.cpr.2010.12.006. PMID 21237544.
74. ^ Ost, LG (October 2014). "The efficacy of Acceptance and Commitment Therapy: an updated systematic review and meta-analysis.". *Behaviour research and therapy*. **61**: 105–21. doi:10.1016/j.brat.2014.07.018. PMID 25193001.
75. ^ Henry J, Zaugg T, Myers P, Kendall C (2012). "Chapter 9 - Level 5 Individualized Support". *Progressive Tinnitus Management: Clinical Handbook for Audiologists*. U.S. Department of Veterans Affairs, National Center for Rehabilitative Auditory Research. Retrieved 2013-12-20.
76. ^ Baldo, P; Doree, C; Molin, P; McFerran, D; Cecco, S (Sep 12, 2012). "Antidepressants for patients with tinnitus". *The Cochrane database of systematic reviews*. **9**: CD003853. doi:10.1002/14651858.CD003853.pub3. PMID 22972065.
77. ^ Savage, J; Cook, S; Waddell, A (Nov 12, 2009). "Tinnitus.". *Clinical evidence*. **2009**. PMID 21726476.
78. ^ Pichora-Fuller, MK; Santaguida, P; Hammill, A; Oremus, M; Westerberg, B; Ali, U; Patterson, C; Raina, P (August 2013). PMID 24049842. Missing or empty `|title=` (help)
79. ^ Lavigne, P; Lavigne, F; Saliba, I (23 June 2015). "Intratympanic corticosteroids injections: a systematic review of literature.". *European archives of oto-rhino-laryngology*. European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. **273**: 2271–8. doi:10.1007/s00405-015-3689-3. PMID 26100030.
80. ^ Penney SE, Bruce IA, Saeed SR (2006). "Botulinum toxin is effective and safe for palatal tremor: a report of five cases and a review of the literature". *J Neurology*. **253** (7): 857–60. doi:10.1007/s00415-006-0039-9. PMID 16845571.
81. ^ Hobson, J; Chisholm, E; El Refaie, A (Nov 14, 2012). "Sound therapy (masking) in the management of tinnitus in adults.". *The Cochrane database of systematic reviews*. **11**: CD006371. doi:10.1002/14651858.CD006371.pub3. PMID 23152235.
82. ^ Meng, Z; Liu, S; Zheng, Y; Phillips, JS (Oct 5, 2011). "Repetitive transcranial magnetic stimulation for tinnitus.". *The Cochrane database of systematic reviews* (10): CD007946. doi:10.1002/14651858.CD007946.pub2. PMID 21975776.
83. ^ Hilton, MP; Zimmermann, EF; Hunt, WT (Mar 28, 2013). "Ginkgo biloba for tinnitus.". *The Cochrane database of systematic reviews*. **3**: CD003852. doi:10.1002/14651858.CD003852.pub3. PMID 23543524.
84. ^ Person, Osmar C; Puga, Maria ES; da Silva, Edina MK; Torloni, Maria R (2016-11-23). "Zinc supplements for tinnitus". *The Cochrane Database of Systematic Reviews*. doi:10.1002/14651858.cd009832.pub2.
85. ^ Sanchez TG, Rocha CB (2011). "Diagnosis and management of somatosensory tinnitus: review article". *Clinics (Sao Paulo)*. **66** (6): 1089–94. doi:10.1590/S1807-59322011000600028. PMC 3129953. PMID 21808880.
86. ^ Heller AJ (2003). "Classification and epidemiology of tinnitus". *Otolaryngologic Clinics of North America*. **36** (2): 239–48. doi:10.1016/S0030-6665(02)00160-3. PMID 12856294.
87. ^ Celik, N.; Bajin, M. D.; Aksoy, S. (2009). "Tinnitus incidence and characteristics in children with hearing loss" (PDF). *Journal of International Advanced Otology*. Ankara, Turkey: Mediterranean Society of Otology and Audiology. **5** (3): 363–69. ISSN 1308-7649. OCLC 695291085. Retrieved 2013-02-02.
88. ^ Mills, RP; Albert, D; Brain, C (1986). "Tinnitus in childhood". *Clinical Otolaryngology and Allied Sciences*. **11** (6): 431–34.
89. ^ Ballantyne JC (2009). Graham J, Baguley D, eds. *Ballantyne's Deafness* (Seventh ed.). Chichester: Wiley-Blackwell. OCLC 275152841.
90. ^ Shetye, A; Kennedy, V (2010). "Tinnitus in children: an uncommon symptom?". *Archives of Disease in Childhood*.

**95** (8): 645–48. doi:10.1136/adc.2009.168252 .

## External links

- "Tinnitus". London, UK: Deafness Research UK. 22 October 2012. Retrieved 2 November 2012. Information about Tinnitus and the latest research work being done.

## Further reading


- Baguley, David; Andersson, Gerhard; McFerran, Don; McKenna, Laurence (March 2013) [2004]. *Tinnitus: A Multidisciplinary Approach* (2nd ed.). Indianapolis, IN, USA: Wiley-Blackwell. ISBN 978-1-4051-9989-6. LCCN 2012032714. OCLC 712915603.
- Hogan, Kevin; Battaglino, Jennifer (May 2010) [1998]. *Tinnitus: Turning the Volume Down* (Revised & Expanded ed.). Eden Prairie, MN, USA: Network 3000 Publishing. ISBN 9781934266038. OCLC 779877737. External link in `|publisher=` (help)
- Langguth, B.; Hajak, G.; Kleinjung, T.; Cacace, A.; Møller, A.R., eds. (December 2007). *Tinnitus : pathophysiology and treatment*. Progress in brain research. **166** (1st ed.). Amsterdam ; Boston: Elsevier. ISBN 9780444531674. LCCN 2012471552. OCLC 648331153. Archived from the original on 2007. Retrieved 5 November 2012.
- Møller, Aage R; Langguth, Berthold; Ridder, Dirk; et al., eds. (2011). *Textbook of Tinnitus*. New York, NY, USA: Springer. doi:10.1007/978-1-60761-145-5. ISBN 9781607611448. LCCN 2010934377. OCLC 695388693, 771366370, 724696022. Archived from the original on 2011. Retrieved 5 November 2012. (subscription required)
- Tyler, Richard S. (2000). *Tinnitus Handbook*. A Singular audiology textbook. San Diego, CA, USA: Singular Publishing Group. ISBN 9781565939226. OCLC 471533235.


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| | **Hearing** | **Hearing impairment** | Conductive hearing loss (Otosclerosis · Superior canal dehiscence · · Sensorineural hearing loss (Presbycusis · Cortical deafness · · Nonsyndromic deafness · |
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| **Organizations** | European Agency for Safety and Health at Work · Health and Safety Executive · International Labour Organization · National Institute for Occupational Safety and Health · Occupational Safety and Health Administration · World Health Organization · |
| **Standards** | Occupational Safety and Health Convention, 1981 · OHSAS 18001 · Worker Protection Standard (US) · Working Environment Convention, 1977 · |
| **See also** | Bangladesh Accord · Environmental toxicology · International Chemical Safety Card · Safety data sheet (SDS) · Sports injuries · Toxic tort · Workers' compensation · National Day of Mourning (Canadian observance) · |
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# Vertigo



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*This article is about the medical condition. For other uses, see Vertigo (disambiguation).*
*Not to be confused with agrophobia, an extreme or irrational fear of heights.*

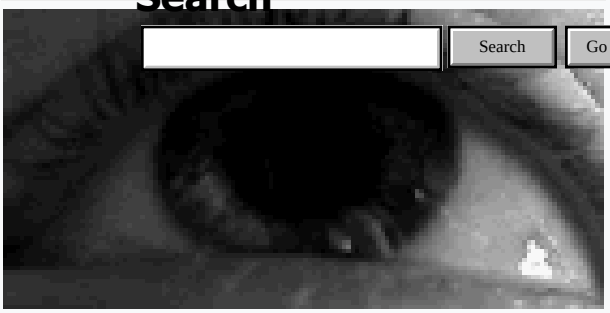
**Vertigo** is when a person feels as if they or the objects around them are moving when they are not.[1] Often it feels like a spinning or swaying movement.[1][2] This may be associated with nausea, vomiting, sweating, or difficulties walking. It is typically worsened when the head is moved. Vertigo is the most common type of dizziness.[2]

The most common diseases that result in vertigo are benign paroxysmal positional vertigo, Ménière's disease, and labyrinthitis.[1][2] Less common causes include stroke, brain tumors, brain injury, multiple sclerosis, and migraines.[2] Physiologic vertigo may occur following being exposed to motion for a prolonged period such as when on a ship or simply following spinning with the eyes closed.[3][4] Other causes may include toxin exposures such as to carbon monoxide, alcohol, or aspirin.[5] Vertigo is a problem in a part of the vestibular system. Other causes of dizziness include presyncope, disequilibrium, and non-specific dizziness.[2]

Benign paroxysmal positional vertigo is more likely in someone who gets repeated episodes of vertigo with movement and are otherwise normal between these episodes.[6] The episodes of vertigo should last less than one minute.[2] The Dix-Hallpike test typically produces a period of rapid eye movements known as nystagmus in this condition.[1] In Ménière's disease there is often ringing in the ears, hearing loss, and the attacks of vertigo last more than twenty minutes. In labyrinthitis the onset of vertigo is sudden and the nystagmus occurs without movement.[6] In this condition vertigo can last for days.[2] More severe causes should also be considered.[6] This is especially true if other problems such as weakness, headache, double vision, or numbness occur.[2]

Dizziness affects approximately 20–40% of people at some point in time, while about 7.5–10% have vertigo.[7] About 5% have vertigo in a given year. It becomes more common with age and affects women two to three times more often than men. Vertigo accounts for about 2–3% of emergency department visits in the developed world.[8]

**Vertigo**



Horizontal nystagmus, a sign which can accompany vertigo.

| | |
|---|---|
| **Pronunciation** | /ˈvɜːrtɪgoʊ/ |
| **Classification and external resources** | |
| **Specialty** | Otorhinolaryngology |
| **ICD-10** | H81, R42 |
| **ICD-9-CM** | 438.85, 780.4 |
| **DiseasesDB** | 29286 |
| **eMedicine** | article/1159385 |
| **Patient UK** | Vertigo |
| **MeSH** | D014717 |

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# Classification [edit]

Vertigo is classified into either peripheral or central depending on the location of the dysfunction of the vestibular pathway,[9] although it can also be caused by psychological factors.[10]

Vertigo can also be classified into objective, subjective, and pseudovertigo. Objective vertigo describes when the person has the sensation that stationary objects in the environment are moving.[11][12] Subjective vertigo refers to when the person feels as if they are moving.[11][12] The third type is known as pseudovertigo, an intensive sensation of rotation inside the person's head. While this classification appears in textbooks, it has little to do with the pathophysiology or treatment of vertigo.[13]

## Peripheral [edit]

Vertigo that is caused by problems with the inner ear or vestibular system, which is composed of the semicircular canals, the vestibule (utricle and saccule), and the vestibular nerve is called "peripheral", "otologic" or "vestibular" vertigo.[11][14] The most common cause is benign paroxysmal positional vertigo (BPPV), which accounts for 32% of all peripheral vertigo.[14] Other causes include Ménière's disease (12%), superior canal dehiscence syndrome, labyrinthitis, and visual vertigo.[14][15] Any cause of inflammation such as common cold, influenza, and bacterial infections may cause transient vertigo if it involves the inner ear, as may chemical insults (e.g., aminoglycosides)[16] or physical trauma (e.g., skull fractures). Motion sickness is sometimes classified as a cause of peripheral vertigo.

People with peripheral vertigo typically present with mild to moderate imbalance, nausea, vomiting, hearing loss, tinnitus, fullness, and pain in the ear.[14] In addition, lesions of the internal auditory canal may be associated with facial weakness on the same side.[14] Due to a rapid compensation process, acute vertigo as a result of a peripheral lesion tends to improve in a short period of time (days to weeks).[14]

## Central [edit]

Vertigo that arises from injury to the balance centers of the central nervous system (CNS), often from a lesion in the brainstem or cerebellum,[6][11][17] is called "central" vertigo and is generally associated with less prominent movement illusion and nausea than vertigo of peripheral origin.[18] Central vertigo may have accompanying neurologic deficits (such as slurred speech and double vision), and pathologic nystagmus (which is pure vertical/torsional).[14][18] Central pathology can cause disequilibrium which is the sensation of being off balance. The balance disorder associated with central lesions causing vertigo is often so severe that many patients are unable to stand or walk.[14]

A number of conditions that involve the central nervous system may lead to vertigo including: lesions caused by infarctions or hemorrhage, tumors present in the cerebellopontine angle such as a vestibular schwannoma or cerebellar tumors,[6][9] epilepsy,[19] cervical spine disorders such as cervical spondylosis,[9] degenerative ataxia disorders,[6] migraine headaches,[6] lateral medullary syndrome, Chiari malformation,[6] multiple sclerosis,[6] parkinsonism, as well as cerebral dysfunction.[14] Central vertigo may not improve or may do so more slowly than vertigo caused by disturbance to peripheral structures.[14]

## Signs and symptoms [edit]

Vertigo is a sensation of spinning while stationary.[20] It is commonly associated with nausea or vomiting,[19] unsteadiness (postural instability),[17] falls,[21] changes to a person's thoughts, and difficulties in walking.[22] Recurrent episodes in those with vertigo are common and frequently impair the quality of life.[8] Blurred vision, difficulty in speaking, a lowered level of consciousness, and hearing loss may also occur. The signs and symptoms of vertigo can present as a persistent (insidious) onset or an episodic (sudden) onset.[23]

Persistent onset vertigo is characterized by symptoms lasting for longer than one day[23] and is caused by degenerative changes that affect balance as people age. Naturally, the nerve conduction slows with aging and a decreased vibratory sensation is common.[24] Additionally, there is a degeneration of the ampulla and otolith organs with an increase in age.[25] Persistent onset is commonly paired with central vertigo signs and systems.[23]

The characteristics of an episodic onset vertigo is indicated by symptoms lasting for a smaller, more memorable amount of time, typically lasting for only seconds to minutes.[23] Typically, episodic vertigo is correlated with peripheral symptoms and can be the result of but not limited to diabetic neuropathy or autoimmune disease.

### Motion sickness [edit]

Motion sickness is one of the most prominent symptoms of vertigo and develops most often in persons with inner ear problems. The feeling of dizziness and lightheadedness is often accompanied by nystagmus (an involuntary movement of the eye characterized by a smooth pursuit eye movement followed by a rapid saccade in the opposite direction of the smooth pursuit eye movement). During a single episode of vertigo, this action will occur repeatedly. Symptoms can fade while sitting still with the eyes closed.

## Diagnostic approach [edit]

Tests for vertigo often attempt to elicit nystagmus and to differentiate vertigo from other causes of dizziness such as presyncope, hyperventilation syndrome, disequilibrium, or psychiatric causes of lightheadedness.[1] Tests of vestibular system (balance) function include: electronystagmography (ENG),[1] Dix-Hallpike maneuver,[1] rotation tests, head-thrust test,[6] caloric reflex test,[6][26] and computerized dynamic posturography (CDP).[27] The HINTS test, which is a combination of three physical exam tests that may be performed by physicians at the bedside has been deemed helpful in differentiating between central and peripheral causes of vertigo. The HINTS test involves: the horizontal head impulse test, observation of nystagmus on primary gaze, and the test of skew.[28] CT scans or MRIs are sometimes used by physicians when diagnosing vertigo.[19]

Tests of auditory system (hearing) function include pure tone audiometry, speech audiometry, acoustic reflex, electrocochleography (ECoG), otoacoustic emissions(OAE), and the auditory brainstem response test.[27]

A number of specific conditions can cause vertigo. In the elderly, however, the condition is often multifactorial.[8]

## Peripheral causes [edit]

### Benign paroxysmal positional vertigo [edit]

Benign paroxysmal positional vertigo (BPPV) is the most common vestibular disorder[7] and occurs when loose calcium carbonate debris has broken off of the otoconial membrane and enters a semicircular canal thereby creating the sensation of motion.[1][6] Patients with BPPV may experience brief periods of vertigo, usually under a minute,[6] which occur with change in position.[29] This is the most common etiology of vertigo.[8] It occurs in 0.6% of the population yearly with 10% having an attack during their lifetime.[8] It is believed to be due to a mechanical malfunction of the inner ear.[8] BPPV may be diagnosed with the Dix-Hallpike test and can be effectively treated with repositioning movements such as the Epley maneuver.[8][29][30][31]

### Ménière's disease [edit]

Ménière's disease is a vestibular disorder of unknown origin, but is thought to be caused by an increase in the amount of endolymphatic fluid present in the inner ear (endolymphatic hydrops).[1] However, this idea has not been directly confirmed with histopathologic studies but electrophysiologic studies have been suggestive of this mechanism.[32] Ménière's disease frequently presents with recurrent, spontaneous attacks of severe vertigo in combination with ringing in the ears (tinnitus), a feeling of pressure or fullness in the ear (aural fullness), severe nausea or vomiting, imbalance, and hearing loss.[6][23][32] As the disease worsens, hearing loss will progress.

### Labyrinthitis [edit]

Labyrinthitis presents with severe vertigo[8] with associated nausea, vomiting, and generalized imbalance and is believed to be caused by a viral infection of the inner ear though several theories have been put forward and the etiology remains uncertain.[6][33] Individuals with vestibular neuritis do not typically have auditory symptoms but may experience a sensation of aural fullness or tinnitus.[33] Persisting balance problems may remain in 30% of people affected.[8]

### Vestibular migraine [edit]

Vestibular migraine is the association of vertigo and migraines and is one of the most common causes of recurrent, spontaneous episodes of vertigo.[7][8] The etiology of vestibular migraines is currently unclear;[7] however, one hypothesized cause is that the stimulation of the trigeminal nerve leads to nystagmus in individuals suffering from migraines.[1] Other suggested causes of vestibular migraines include the following: unilateral neuronal instability of the vestibular nerve, idiopathic asymmetric activation of the vestibular nuclei in the brainstem, and vasospasm of the blood vessels supplying the labyrinth or central vestibular pathways resulting in ischemia to these structures.[19] Vestibular migraines are estimated to affect 1-3% of the general population[1][8] and may affect 10% of migraine patients.[1] Additionally, vestibular migraines tend to occur more often in women and rarely affect individuals after the sixth decade of life.[7]

## Central causes [edit]

### Stroke [edit]

A stroke (either ischemic or hemorrhagic) involving the posterior fossa is a cause of central vertigo.[28] Risk factors for a stroke as a cause of vertigo include increasing age and known vascular risk factors. Presentation may more often involve headache or neck pain, additionally, those who have had multiple episodes of dizziness in the months leading up to presentation are suggestive of stroke with prodromal TIAs.[28] The HINTS exam as well as imaging studies of the brain (CT, CT angiogram, and/or MRI) are

helpful in diagnosis of posterior fossa stroke.[28]

## Pathophysiology [edit]

The neurochemistry of vertigo includes six primary neurotransmitters that have been identified between the three-neuron arc[34] that drives the vestibulo-ocular reflex (VOR). Glutamate maintains the resting discharge of the central vestibular neurons, and may modulate synaptic transmission in all three neurons of the VOR arc. Acetylcholine appears to function as an excitatory neurotransmitter in both the peripheral and central synapses. Gamma-Aminobutyric acid (GABA) is thought to be inhibitory for the commissures of the medial vestibular nucleus, the connections between the cerebellar Purkinje cells, and the lateral vestibular nucleus, and the vertical VOR.

Three other neurotransmitters work centrally. Dopamine may accelerate vestibular compensation. Norepinephrine modulates the intensity of central reactions to vestibular stimulation and facilitates compensation. Histamine is present only centrally, but its role is unclear. Dopamine, histamine, serotonin, and acetylcholine are neurotransmitters thought to produce vomiting.[6] It is known that centrally acting antihistamines modulate the symptoms of acute symptomatic vertigo.[35]

## Management [edit]

Definitive treatment depends on the underlying cause of vertigo.[6] Ménière's disease patients have a variety of treatment options to consider when receiving treatment for vertigo and tinnitus including: a low-salt diet and intratympanic injections of the antibiotic gentamicin or surgical measures such as a shunt or ablation of the labyrinth in refractory cases.[36] Common drug treatment options for vertigo may include the following:[37]

- Anticholinergics such as hyoscine hydrobromide (scopolamine)[38]
- Anticonvulsants such as topiramate or valproic acid for vestibular migraines
- Antihistamines such as betahistine, dimenhydrinate, or meclizine, which may have antiemetic properties[39]
- Beta blockers such as metoprolol for vestibular migraine
- Corticosteroids such as methylprednisolone for inflammatory conditions such as vestibular neuritis or dexamethasone as a second-line agent for Ménière's disease

## Etymology [edit]

Vertigo is from the Latin word *vertō* which means "a whirling or spinning movement".[40]

## Media treatment [edit]

In the Alfred Hitchcock film *Vertigo*, the hero, played by James Stewart, has to resign from the police force after an incident which causes him to develop both acrophobia and vertigo. Early on in the film he faints while climbing a stepladder. There are numerous references throughout the film to fear of heights and falling, The dolly zoom camera effect, also called the "vertigo effect", was first used in this film.

## See also [edit]

- Acrophobia (fear of heights)
- Broken escalator phenomenon
- Equilibrioception (sense of balance)
- Fear of falling

Ideomotor phenomenon (unconscious reflex movements)
- Illusions of self-motion
- Proprioception
- Seasickness
- Spatial disorientation

## References [edit]


1. ^ a b c d e f g h i j k l Post, RE; Dickerson, LM (2010). "Dizziness: a diagnostic approach". *American Family Physician*. **82** (4): 361–369. PMID 20704166.
2. ^ a b c d e f g h Hogue, JD (June 2015). "Office Evaluation of Dizziness.". *Primary care*. **42** (2): 249–258. doi:10.1016/j.pop.2015.01.004. PMID 25979586.
3. ^ Falvo, Donna R. (2014). *Medical and psychosocial aspects of chronic illness and disability* (5 ed.). Burlington, MA: Jones & Bartlett Learning. p. 273. ISBN 9781449694425.
4. ^ Wardlaw, Joanna M. (2008). *Clinical neurology*. London: Manson. p. 107. ISBN 9781840765182.
5. ^ Goebel, Joel A. (2008). *Practical management of the dizzy patient* (2nd ed.). Philadelphia: Lippincott Williams & Wilkins. p. 97. ISBN 9780781765626.
6. ^ a b c d e f g h i j k l m n o p q Kerber, KA (2009). "Vertigo and dizziness in the emergency department". *Emergency medicine clinics of North America*. **27** (1): 39–50. doi:10.1016/j.emc.2008.09.002. PMC 2676794. PMID 19218018.
7. ^ a b c d e von Brevern, M; Neuhauser, H (2011). "Epidemiological evidence for a link between vertigo & migraine". *Journal of vestibular research: equilibrium & orientation*. **21** (6): 299–304. doi:10.3233/VES-2011-0423. PMID 22348934.
8. ^ a b c d e f g h i j k Neuhauser HK, Lempert T (November 2009). "Vertigo: epidemiologic aspects". *Semin Neurol*. **29** (5): 473–81. doi:10.1055/s-0029-1241043. PMID 19834858.
9. ^ a b c Wippold 2nd, FJ; Turski, PA (2009). "Vertigo and hearing loss". *AJNR. American journal of neuroradiology*. **30** (8): 1623–1625. PMID 19749077.
10. ^ "Chapter 14: Evaluation of the Dizzy Patient". Retrieved 2009-08-06.
11. ^ a b c d U.S. National Library of Medicine (2011). "Vertigo-associated disorders". National Institutes of Health. Retrieved 2 January 2013.
12. ^ a b Berkow R., ed. (1992). *The Merck manual of diagnostics and therapy*. Rahway: Merck & Co Inc. p. 2844.
13. ^ Ropper, AH; Brown RH (2005). *Adams and Victor's Principles of Neurology* (eighth ed.). NY, Chicago, San Francisco. p. 1398.
14. ^ a b c d e f g h i j Karatas, M (2008). "Central Vertigo and Dizziness". *The Neurologist*. **14** (6): 355–364. doi:10.1097/NRL.0b013e31817533a3. PMID 19008741.
15. ^ Guerraz, M.; Yardley, L; Bertholon, P; Pollak, L; Rudge, P; Gresty, MA; Bronstein, AM (2001). "Visual vertigo: symptom assessment, spatial orientation and postural control". *Brain*. **124** (8): 1646–1656. doi:10.1093/brain/124.8.1646. PMID 11459755.
16. ^ Xie, J; Talaska, AE; Schacht, J (2011). "New developments in aminoglycoside therapy and ototoxicity". *Hearing research*. **281** (1–2): 28–37. doi:10.1016/j.heares.2011.05.008. PMC 3169717. PMID 21640178.
17. ^ a b Jahn, K; Dieterich, M (December 2011). "Recent advances in the diagnosis and treatment of balance disorders". *Journal of neurology*. **258** (12): 2305–2308. doi:10.1007/s00415-011-6286-4. PMID 22037955.
18. ^ a b Dieterich, Marianne (2007). "Central vestibular disorders". *Journal of Neurology*. **254** (5): 559–568. doi:10.1007/s00415-006-0340-7. PMID 17417688.
19. ^ a b c d Taylor, J; Goodkin, HP (2011). "Dizziness and vertigo in the adolescent". *Otolaryngologic Clinics of North America*. **44** (2): 309–321. doi:10.1016/j.otc.2011.01.004. PMID 21474006.
20. ^ "Vertigo: Dizziness and Vertigo: Merck Manual Home Edition".
21. ^ Vieira, ER; Freund-Heritage, R; Da Costa, BR (September 2011). "Risk factors for geriatric patient falls in rehabilitation hospital settings: a systematic review". *Clinical rehabilitation*. **25** (9): 788–799. doi:10.1177/0269215511400639. PMID 21504956.
22. ^ Ricci, NA; Aratani, MC; Doná, F; MacEdo, C; Caovilla, HH; Ganança, FF (2010). "A systematic review about the effects of the vestibular rehabilitation of middle-age and older adults". *Revista brasileira de fisioterapia*. **14** (5): 361–371. doi:10.1590/S1413-35552010000500003. PMID 21180862.
23. ^ a b c d e Strupp, M; Thurtell, MJ; Shaikh, AG; Brandt, T; Zee, DS; Leigh, RJ (July 2011). "Pharmacotherapy of vestibular and ocular motor disorders, including nystagmus". *Journal of neurology*. **258** (7): 1207–1222.

doi:10.1007/s00415-011-5999-8. PMC 3132281. PMID 21461686.
24. ^ Kaneko, A; Asai, N; Kanda, T (2005). "The influence of age on pressure perception of static and moving two-point discrimination in normal subjects". *Journal of Hand Therapy*. **18** (4): 421–424. doi:10.1197/j.jht.2005.09.010. PMID 16271689.
25. ^ Kutz Jr, JW (September 2010). "The dizzy patient". *The Medical clinics of North America*. **94** (5): 989–1002. doi:10.1016/j.mcna.2010.05.011. PMID 20736108.
26. ^ "Core Curriculum: Inner Ear Disease —Vertigo". Baylor College of Medicine. 23 January 2006. Archived from the original on 2007-06-30. Retrieved 19 September 2007.
27. ^ *a b* "Diagnosis: How are vestibular disorders diagnosed?". Vestibular Disorders Association. 2013. Retrieved 9 January 2013.
28. ^ *a b c d* Tarnutzer, Alexander A.; Berkowitz, Aaron L.; Robinson, Karen A.; Hsieh, Yu-Hsiang; Newman-Toker, David E. (2011-06-14). "Does my dizzy patient have a stroke? A systematic review of bedside diagnosis in acute vestibular syndrome". *Canadian Medical Association Journal*. **183** (9): E571–E592. doi:10.1503/cmaj.100174. ISSN 0820-3946. PMC 3114934. PMID 21576300.
29. ^ *a b* MedlinePlus (2011). "Benign positional vertigo". U.S. National Institutes of Health. Retrieved 2 January 2013.
30. ^ Alvarenga, GA; Barbosa, MA; Porto, CC (2011). "Benign paroxysmal positional vertigo without nystagmus: diagnosis and treatment". *Brazilian journal of otorhinolaryngology*. **77** (6): 799–804. doi:10.1590/S1808-86942011000600018. PMID 22183288.
31. ^ Prim-Espada, MP; De Diego-Sastre, JI; Pérez-Fernández, E (June 2010). "[Meta-analysis on the efficacy of Epley's manoeuvre in benign paroxysmal positional vertigo]" (PDF). *Neurologia*. **25** (5): 295–299. doi:10.1016/j.nrl.2010.01.004. PMID 20643039.
32. ^ *a b* Semaan, MT; Megerian, CA (April 2011). "Ménière's disease: a challenging and relentless disorder". *Otolaryngologic Clinics of North America*. **44** (2): 383–403. doi:10.1016/j.otc.2011.01.010. PMID 21474013.
33. ^ *a b* Goddard, JC; Fayad, JN (2011). "Vestibular Neuritis". *Otolaryngologic Clinics of North America*. **44** (2): 361–365. doi:10.1016/j.otc.2011.01.007. PMID 21474010.
34. ^ Angelaki, DE (July 2004). "Eyes on target: what neurons must do for the vestibuloocular reflex during linear motion". *Journal of Neurophysiology*. **92** (1): 20–35. doi:10.1152/jn.00047.2004. PMID 15212435.
35. ^ Kuo, CH; Pang, L; Chang, R (June 2008). "Vertigo-part 2-management in general practice" (PDF). *Australian family physician*. **37** (6): 409–413. PMID 18523693.
36. ^ Huon, LK; Fang, TY; Wang, PC (July 2012). "Outcomes of intratympanic gentamicin injection to treat Ménière's disease". *Otology & Neurotology*. **33** (5): 706–714. doi:10.1097/MAO.0b013e318259b3b1. PMID 22699980.
37. ^ Huppert, D; Strupp, M; Mückter, H; Brandt, T (March 2011). "Which medication do I need to manage dizzy patients?". *Acta oto-laryngologica*. **131** (3): 228–241. doi:10.3109/00016489.2010.531052. PMID 21142898.
38. ^ Fauci, Anthony S.; Daniel L. Kasper; Dan L. Longo; Eugene Braunwald; Stephen L. Hauser; J. Larry Jameson (2008). Chapter 22. Dizziness and Vertigo *Harrison's Principles of Internal Medicine* (17th ed.). New York: McGraw-Hill. ISBN 978-0-07-147691-1.
39. ^ Khilnani, AK; Thaddanee, R; Khilnani, G (July 2013). "Anti vertigo drugs-Revisited". *National Journal of Integrated Research in Medicine*. **4** (4): 118–28.
40. ^ "Definition of vertigo". Merriam-Webster Online Dictionary. Retrieved 2007-09-19.

v · t · e · **Symptoms and signs relating to the hearing and balance (R30–R39, 788)**

| | |
|---|---|
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| **Balance** | **Vertigo**, nystagmus · |
| **Other** | Ear pain · |

Categories: Symptoms and signs: Cognition, perception, emotional state and behaviour | Neurological disorders | Diseases of inner ear | Illusions | Phenomena


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# Addison's disease

From Wikipedia, the free encyclopedia

**Addison's disease**, also known as **primary adrenal insufficiency** and **hypocortisolism**, is a long-term endocrine disorder in which the adrenal glands do not produce enough steroid hormones.[1] Symptoms generally come on slowly and may include abdominal pain, weakness, and weight loss. Darkening of the skin in certain areas may also occur. Under certain circumstances, an adrenal crisis may occur with low blood pressure, vomiting, lower back pain, and loss of consciousness. An adrenal crisis can be triggered by stress, such as from an injury, surgery, or infection. Death may occur without treatment.[1]

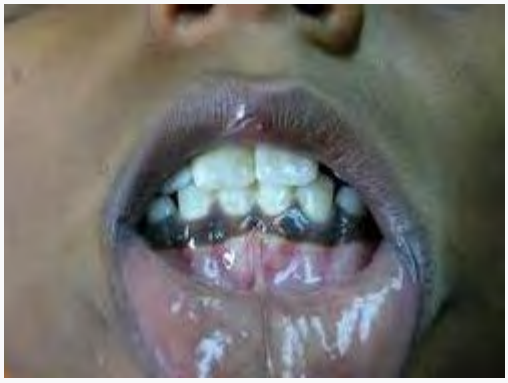
Addison's disease arises from problems with the adrenal gland such that not enough of the steroid hormone cortisol and possibly aldosterone are produced,[1] most often due to damage by the body's own immune system in the developed world and tuberculosis in the developing world.[2] Other causes include certain medications, sepsis, and bleeding into both adrenal glands.[1][2] Secondary adrenal insufficiency is caused by not enough adrenocorticotropic hormone (ACTH) (produced by the pituitary gland) or CRH (produced by the hypothalamus). Despite this distinction, adrenal crises can happen in all forms of adrenal insufficiency. Addison's disease is generally diagnosed by blood tests, urine tests, and medical imaging.[1]

Treatment involves replacing the absent hormones.[1] This involves taking a corticosteroid such as hydrocortisone and fludrocortisone.[1][3] These medications are usually taken by mouth.[1] Lifelong, continuous steroid replacement therapy is required, with regular follow-up treatment and monitoring for other health problems.[4] A high-salt diet may also be useful in some people. If symptoms worsen, an injection of corticosteroid is recommended and people should carry a dose with them. Often, large amounts of intravenous fluids with the sugar dextrose are also required. Without treatment, an adrenal crisis can result in death.[1]

Addison's disease affects about 0.9 to 1.4 per 10,000 people in the developed world.[1][5] It occurs most frequently in middle-aged females.[1] Secondary adrenal insufficiency is more common.[5] Long-term outcomes with treatment are typically good.[6] It is named after Thomas Addison, a graduate of the University of Edinburgh Medical School, who first described the condition in 1855.[7] The adjective "addisonian" is used to describe features of the condition, as well as people with Addison's disease.[8]

**Addison's disease**

**Synonyms** Addison disease, chronic adrenal insufficiency, hypocortisolism, hypoadrenalism, primary adrenal insufficiency[1]



Classic darkening of the skin due to increased pigment as seen in Addison's disease

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Endocrinology |
| **ICD-10** | E27.1-E27.2 |
| **ICD-9-CM** | 255.4 |
| **DiseasesDB** | 222 |
| **MedlinePlus** | 000378 |
| **eMedicine** | med/42 |
| **Patient UK** | Addison's disease |
| **MeSH** | D000224 |

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# Signs and symptoms [edit]

The symptoms of Addison's disease develop gradually and may become established before they are recognized. They can be nonspecific and are potentially attributable to other medical conditions.

The signs and symptoms include fatigue; lightheadedness upon standing or difficulty standing, muscle weakness, fever, weight loss, anxiety, nausea, vomiting, diarrhea, headache, sweating, changes in mood or personality, and joint and muscle pains. Some patients have cravings for salt or salty foods due to the loss of sodium through their urine.[8] Hyperpigmentation of the skin may be seen, particularly when the patient lives in a sunny area, as well as darkening of the palmar crease, sites of friction, recent scars, the vermilion border of the lips, and genital skin.[9] These skin changes are not encountered in secondary and tertiary hypoadrenalism.[10]

On physical examination, these clinical signs may be noticed:[8]

- Low blood pressure with or without orthostatic hypotension (blood pressure that decreases with standing)
- Darkening (hyperpigmentation) of the skin, including areas not exposed to the sun. Characteristic sites of darkening are skin creases (e.g., of the hands), nipple, and the inside of the cheek (buccal mucosa); also, old scars may darken. This occurs because melanocyte-stimulating hormone (MSH) and ACTH share the same precursor molecule, pro-opiomelanocortin (POMC). After production in the anterior pituitary gland, POMC gets cleaved into gamma-MSH, ACTH, and beta-lipotropin. The subunit ACTH undergoes further cleavage to produce alpha-MSH, the most important MSH for skin pigmentation. In secondary and tertiary forms of adrenal insufficiency, skin darkening does not occur, as ACTH is not overproduced.

Addison's disease is associated with the development of other autoimmune diseases, such as type I diabetes, thyroid disease (Hashimoto's thyroiditis), and vitiligo. The presence of Addison's in addition to one of these is called autoimmune polyendocrine syndrome.

## Addisonian crisis [edit]

*Main article: Adrenal crisis*

An "Addisonian crisis" or "adrenal crisis" is a constellation of symptoms that indicates severe adrenal

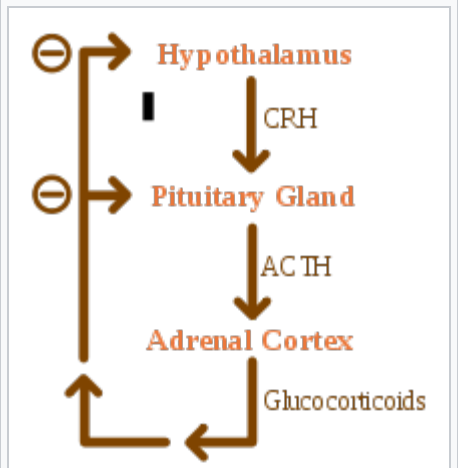
insufficiency. This may be the result of either previously undiagnosed Addison's disease, a disease process suddenly affecting adrenal function (such as adrenal hemorrhage), or an intercurrent problem (e.g., infection, trauma) in someone known to have Addison's disease. It is a medical emergency and potentially life-threatening situation requiring immediate emergency treatment.

Characteristic symptoms are:[11]

- Sudden penetrating pain in the legs, lower back, or abdomen
- Severe vomiting and diarrhea, resulting in dehydration
- Low blood pressure
- Syncope (loss of consciousness and ability to stand)
- Hypoglycemia (reduced level of blood glucose)
- Confusion, psychosis, slurred speech
- Severe lethargy
- Hyponatremia (low sodium level in the blood)
- Hyperkalemia (elevated potassium level in the blood)
- Hypercalcemia (elevated calcium level in the blood)
- Convulsions
- Fever

## Causes [edit]

Causes of adrenal insufficiency can be categorized by the mechanism through which they cause the adrenal glands to produce insufficient cortisol. These are adrenal dysgenesis (the gland has not formed adequately during development), impaired steroidogenesis (the gland is present but is biochemically unable to produce cortisol) or adrenal destruction (disease processes leading to glandular damage).[8]



The negative feedback loop for glucocorticoids

### Adrenal destruction [edit]

Autoimmune adrenalitis is the most common cause of Addison's disease in the industrialized world. Autoimmune destruction of the adrenal cortex is caused by an immune reaction against the enzyme 21-hydroxylase (a phenomenon first described in 1992).[12] This may be isolated or in the context of autoimmune polyendocrine syndrome (APS type 1 or 2), in which other hormone-producing organs, such as the thyroid and pancreas, may also be affected.[13]

Adrenal destruction is also a feature of adrenoleukodystrophy, and when the adrenal glands are involved in metastasis (seeding of cancer cells from elsewhere in the body, especially lung), hemorrhage (e.g., in Waterhouse-Friderichsen syndrome or antiphospholipid syndrome), particular infections (tuberculosis, histoplasmosis, coccidioidomycosis), or the deposition of abnormal protein in amyloidosis.[14]

### Adrenal dysgenesis [edit]

All causes in this category are genetic, and generally very rare. These include mutations to the *SF1* transcription factor, congenital adrenal hypoplasia due to *DAX-1* gene mutations and mutations to the ACTH receptor gene (or related genes, such as in the Triple A or Allgrove syndrome). *DAX-1* mutations may cluster in a syndrome with glycerol kinase deficiency with a number of other symptoms when *DAX-1* is deleted together with a number of other genes.[8]

### Impaired steroidogenesis [edit]

To form cortisol, the adrenal gland requires cholesterol, which is then converted biochemically into steroid

hormones. Interruptions in the delivery of cholesterol include Smith-Lemli-Opitz syndrome and abetalipoproteinemia.

Of the synthesis problems, congenital adrenal hyperplasia is the most common (in various forms: 21-hydroxylase, 17α-hydroxylase, 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase), lipoid CAH due to deficiency of StAR and mitochondrial DNA mutations.[8] Some medications interfere with steroid synthesis enzymes (e.g., ketoconazole), while others accelerate the normal breakdown of hormones by the liver (e.g., rifampicin, phenytoin).[8]

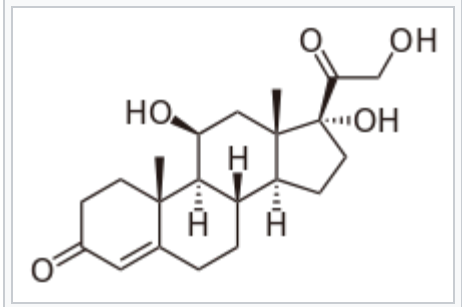
# Diagnosis [edit]

## Suggestive features [edit]

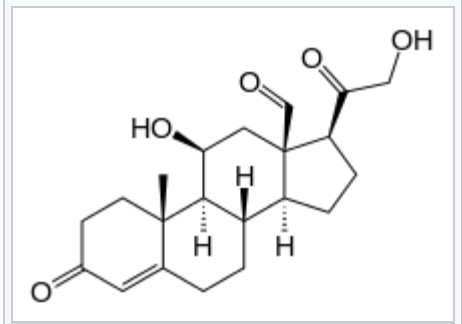
Routine laboratory investigations may show:[8]

- Hypercalcemia
- Hypoglycemia, low blood sugar (worse in children due to loss of glucocorticoid's glucogenic effects)
- Hyponatremia (low blood sodium levels), due to loss of production of the hormone aldosterone, to the kidney's inability to excrete free water in the absence of sufficient cortisol, and also the effect of corticotropin-releasing hormone to stimulate secretion of ADH.
- Hyperkalemia (raised blood potassium levels), due to loss of production of the hormone aldosterone.
- Eosinophilia and lymphocytosis (increased number of eosinophils or lymphocytes, two types of white blood cells)
- Metabolic acidosis (increased blood acidity), also is due to loss of the hormone aldosterone because sodium reabsorption in the distal tubule is linked with acid/hydrogen ion ($H^+$) secretion. Low levels of aldosterone stimulation of the renal distal tubule leads to sodium wasting in the urine and $H^+$ retention in the serum.

## Testing [edit]



Cortisol



Aldosterone

In suspected cases of Addison's disease, demonstration of low adrenal hormone levels even after appropriate stimulation (called the ACTH stimulation test) with synthetic pituitary ACTH hormone tetracosactide is needed for the diagnosis. Two tests are performed, the short and the long test. It should be noted that dexamethasone does not cross-react with the assay and can be administered concomitantly during testing.

The short test compares blood cortisol levels before and after 250 micrograms of tetracosactide (intramuscular or intravenous) is given. If, one hour later, plasma cortisol exceeds 170 nmol/l and has risen by at least 330 nmol/l to at least 690 nmol/l, adrenal failure is excluded. If the short test is abnormal, the long test is used to differentiate between primary adrenal insufficiency and secondary adrenocortical insufficiency.

The long test uses 1 mg tetracosactide (intramuscular). Blood is taken 1, 4, 8, and 24 hr later. Normal plasma cortisol level should reach 1000 nmol/l by 4 hr. In primary Addison's disease, the cortisol level is reduced at all stages, whereas in secondary corticoadrenal insufficiency, a delayed but normal response is seen.

Other tests may be performed to distinguish between various causes of hypoadrenalism, including renin and adrenocorticotropic hormone levels, as well as medical imaging - usually in the form of ultrasound, computed tomography or magnetic resonance imaging.

Adrenoleukodystrophy, and the milder form, adrenomyeloneuropathy, cause adrenal insufficiency combined with neurological symptoms. These diseases are estimated to be the cause of adrenal insufficiency in about

35% of male patients with idiopathic Addison's disease, and should be considered in the differential diagnosis of any male with adrenal insufficiency. Diagnosis is made by a blood test to detect very long chain fatty acids.[15]

## Treatment [edit]

Corticosteroids to replace cortisols not secreted by the adrenal glands.

### Maintenance [edit]

Treatment for Addison's disease involves replacing the missing cortisol, sometimes in the form of hydrocortisone tablets, or prednisone tablets in a dosing regimen that mimics the physiological concentrations of cortisol. Alternatively, one-quarter as much prednisolone may be used for equal glucocorticoid effect as hydrocortisone. Treatment is usually lifelong. In addition, many patients require fludrocortisone as replacement for the missing aldosterone.

People with Addison's are often advised to carry information on them (e.g., in the form of a MedicAlert bracelet or information card) for the attention of emergency medical services personnel who might need to attend to their needs.[16][17] It is also recommended that a needle, syringe, and injectable form of cortisol be carried for emergencies.[17] People with Addison's disease are advised to increase their medication during periods of illness or when undergoing surgery or dental treatment.[17] Immediate medical attention is needed when severe infections, vomiting, or diarrhea occur, as these conditions can precipitate an Addisonian crisis. A patient who is vomiting may require injections of hydrocortisone instead.[18]

### Crisis [edit]

Standard therapy involves intravenous injections of glucocorticoids and large volumes of intravenous saline solution with dextrose (glucose). This treatment usually brings rapid improvement. If intravenous access is not immediately available, intramuscular injection of glucocorticoids can be used. When the patient can take fluids and medications by mouth, the amount of glucocorticoids is decreased until a maintenance dose is reached. If aldosterone is deficient, maintenance therapy also includes oral doses of fludrocortisone acetate.[19]

## Epidemiology [edit]

The frequency rate of Addison's disease in the human population is sometimes estimated at roughly one in 100,000.[20] Some put the number closer to 40–144 cases per million population (1/25,000–1/7,000).[1][21] Addison's can affect persons of any age, sex, or ethnicity, but it typically presents in adults between 30 and 50 years of age.[22] Research has shown no significant predispositions based on ethnicity.[21]

## Prognosis [edit]

Outcomes are typically good when treated. Most can expect to live relatively normal lives. Someone with the disease should be observant of symptoms of an "Addison's crisis" while the body is strained, as in rigorous exercise or being sick, the latter often needing emergency treatment with intravenous injections to treat the crisis.[23]

Individuals with Addison's disease has more than a doubled mortality rate.[24] Furthermore, individuals with Addison's disease and diabetes mellitus have a almost 4 time increase in mortality compared to individuals with only diabetes.[25]

## History [edit]

## Discovery [edit]

Addison's disease is named after Thomas Addison, the British physician who first described the condition in *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules* (1855).[26] All of Addison's six original patients had tuberculosis of the adrenal glands.[27] While Addison's six patients in 1855 all had adrenal tuberculosis, the term "Addison's disease" does not imply an underlying disease process.

The condition was initially considered a form of anemia associated with the adrenal glands. Because little was known at the time about the adrenal glands (then called "Supra-Renal Capsules"), Addison's monograph describing the condition was an isolated insight. As the adrenal function became better known, Addison's monograph became known as an important medical contribution and a classic example of careful medical observation.[28]

## Notable cases [edit]

United States president John F. Kennedy (1917-1963), probably the single most famous case of Addison's disease

- John F. Kennedy, the 35th President of the United States, was one of the best-known people with Addison's disease and was possibly one of the first to survive major surgery.[29] Substantial secrecy surrounded his health during his years as president.[30]
- Eunice Kennedy Shriver, one of John F. Kennedy's sisters, was believed to have Addison's disease as well.[31]
- Popular singer Helen Reddy[32]
- Scientist Eugene Merle Shoemaker, co-discoverer of the Comet Shoemaker-Levy 9.[33]
- French Carmelite nun and religious writer Blessed Elizabeth of the Trinity[34]
- American artist Ferdinand Louis Schlemmer died from Addison's disease.
- Some have suggested Jane Austen was an *avant la lettre* case, but others have disputed this.[35]
- According to Carl Abbott, a Canadian medical researcher, Charles Dickens may also have been affected.[36]
- Australia's youngest rugby league football international, Geoff Starling[37]
- Osama bin Laden may have had Addison's. Lawrence Wright noted that bin Laden exhibited the key symptoms of Addison's, including "low blood pressure, weight loss, muscle fatigue, stomach irritability, sharp back pains, dehydration, and an abnormal craving for salt". Bin Laden was also known to have consumed large amounts of sulbutiamine to treat his symptoms.[38]
- Basque nationalist and founder of the Basque Nationalist Party, Sabino Arana died in Sukarrieta at the age of 38 after falling ill with Addison's disease during time spent in prison.
- A cappella singer/arranger/producer Deke Sharon[39]
- One of Canada's top gymnasts, Nathan Gafuik, was diagnosed with Addison's disease when he was 15.[40]
- South Korean President Park Geun-hye is reported to have Addison's disease.[41]

# Other animals [edit]

*Main article: Addison's disease in canines*

The condition has been diagnosed in all breeds of dogs. In general, it is underdiagnosed, and one must clinically suspect it as an underlying disorder for many presenting complaints. Females are overrepresented, and the disease often appears in middle age (4–7 yr), although any age or either gender may be

affected.[*citation needed*]

Hypoadrenocorticism is treated with fludrocortisone or a monthly injection called Percorten V (desoxycorticosterone pivlate (DOCP)) and prednisone. Routine blood work is necessary in the initial stages until a maintenance dose is established. Most of the medications used in the therapy of hypoadrenocorticism cause excessive thirst and urination, making it important to provide enough drinking water. If the owner knows about an upcoming stressful situation (shows, traveling, etc.), patients generally need an increased dose of prednisone to help deal with the added stress. Avoidance of stress is important for dogs with hypoadrenocorticism.

## References [edit]


1. ^ *a b c d e f g h i j k l m* "Adrenal Insufficiency and Addison's Disease". *NIDDK*. May 2014. Retrieved 13 March 2016.
2. ^ *a b* Adam, Andy (2014). *Grainger & Allison's Diagnostic Radiology* (6 ed.). Elsevier Health Sciences. p. 1031. ISBN 9780702061288.
3. ^ Napier, C; Pearce, SH (June 2014). "Current and emerging therapies for Addison's disease.". *Current opinion in endocrinology, diabetes, and obesity*. **21** (3): 147–53. doi:10.1097/med.0000000000000067. PMID 24755997.
4. ^ Napier, C; Pearce, SH (December 2012). "Autoimmune Addison's disease.". *Presse medicale (Paris, France : 1983)*. **41** (12 P 2): e626–35. doi:10.1016/j.lpm.2012.09.010. PMID 23177474.
5. ^ *a b* Brandão Neto, RA; de Carvalho, JF (2014). "Diagnosis and classification of Addison's disease (autoimmune adrenalitis).". *Autoimmunity reviews*. **13** (4-5): 408–11. doi:10.1016/j.autrev.2014.01.025. PMID 24424183.
6. ^ Rajagopalan, Murray Longmore, Ian B. Wilkinson, Supraj R. (2006). *Mini Oxford handbook of clinical medicine* (6 ed.). Oxford: Oxford University Press. p. 312. ISBN 9780198570714.
7. ^ Rose, Noel R.; Mackay, Ian R. (2014). *The autoimmune diseases* (5 ed.). San Diego, CA: Elsevier Science. p. 605. ISBN 9780123849304.
8. ^ *a b c d e f g h* Ten S, New M, Maclaren N (2001). "Clinical review 130: Addison's disease 2001". *The Journal of Clinical Endocrinology and Metabolism*. **86** (7): 2909–2922. doi:10.1210/jc.86.7.2909. PMID 11443143.
9. ^ Nieman LK, Chanco Turner ML (2006). "Addison's disease". *Clinics in Dermatology*. **24** (4): 276–280. doi:10.1016/j.clindermatol.2006.04.006. PMID 16828409.
10. ^ de Herder WW, van der Lely AJ (May 2003). "Addisonian crisis and relative adrenal failure". *Reviews in Endocrine and Metabolic Disorders*. **4** (2): 143–7. doi:10.1023/A:1022938019091. PMID 12766542.
11. ^ "Addison's Disease". National Endocrine and Metabolic Diseases Information Service. Retrieved 26 October 2007.
12. ^ Winqvist O, Karlsson FA, Kämpe O (June 1992). "21-Hydroxylase, a major autoantigen in idiopathic Addison's disease". *The Lancet*. **339** (8809): 1559–62. doi:10.1016/0140-6736(92)91829-W. PMID 1351548.
13. ^ Husebye ES, Perheentupa J, Rautemaa R, Kämpe O (May 2009). "Clinical manifestations and management of patients with autoimmune polyendocrine syndrome type I". *Journal of Internal Medicine*. **265** (5): 514–29. doi:10.1111/j.1365-2796.2009.02090.x. PMID 19382991.
14. ^ Kennedy, Ron. "Addison's Disease". The Doctors' Medical Library.
15. ^ Laureti S, Casucci G, Santeusanio F, Angeletti G, Aubourg P, Brunetti P (1996). "X-linked adrenoleukodystrophy is a frequent cause of idiopathic Addison's disease in young adult male patient". *The Journal of Clinical Endocrinology and Metabolism*. **81** (2): 470–474. doi:10.1210/jc.81.2.470. PMID 8636252.
16. ^ Quinkler M, Dahlqvist P, Husebye ES, Kämpe O (Jan 2015). "A European Emergency Card for adrenal insufficiency can save lives". *Eur J Intern Med*. **26** (1): 75–6. doi:10.1016/j.ejim.2014.11.006. PMID 25498511.
17. ^ *a b c* Michels A, Michels N (1 Apr 2014). "Addison disease: early detection and treatment principles". *Am Fam Physician*. **89** (7): 563–8. PMID 24695602.
18. ^ White, Katherine (28 July 2004). "What to do in an emergency -Addisonian crisis". Addison's Disease Self Help Group.
19. ^ "Adrenal Insufficiency and Addison's Disease". National Endocrine and Metabolic Diseases Information Service. Retrieved 26 November 2010.
20. ^ "Addison Disease". MedicineNet. Archived from the original on 24 June 2007. Retrieved 2007-07-25.
21. ^ *a b* Odeke, Sylvester. "Addison Disease". eMedicine. Archived from the original on 7 July 2007. Retrieved 2007-07-25.
22. ^ Volpé, Robert (1990). *Autoimmune Diseases of the Endocrine System*. CRC Press. p. 299. ISBN 0-8493-6849-9.
23. ^ "Addison's disease - Treatment". NHS Choices. Retrieved 2016-10-08.

24. ^ Bergthorsdottir, Ragnhildur; Leonsson-Zachrisson, Maria; Odén, Anders; Johannsson, Gudmundur (2006-12-01). "Premature Mortality in Patients with Addison's Disease: A Population-Based Study". *The Journal of Clinical Endocrinology & Metabolism*. **91** (12): 4849–4853. doi:10.1210/jc.2006-0076. ISSN 0021-972X.
25. ^ Dimitrios Chantzichristos; Anders Persson; Björn Eliasson; Mervete Miftaraj; Stefan Franzén; Ragnhildur Bergthorsdottir; Soffia Gudbjörnsdottir; Ann-Marie Svensson; Gudmundur Johannsson (2016-04-01). *Cushing Syndrome and Primary Adrenal Disorders*. Meeting Abstracts. Endocrine Society. pp. OR25–4–OR25–4. doi:10.1210/endo-meetings.2016.ahpaa.9.or25-4.
26. ^ Addison, Thomas (1855). *On The Constitutional And Local Effects Of Disease Of The Supra-Renal Capsules*. London: Samuel Highley.
27. ^ Patnaik MM, Deshpande AK (May 2008). "Diagnosis–Addison's Disease Secondary to Tuberculosis of the Adrenal Glands". *Clinical Medicine & Research*. **6** (1): 29. doi:10.3121/cmr.2007.754a. PMC 2442022. PMID 18591375.
28. ^ Bishop PM (1950). "The history of the discovery of Addison's disease". *Proceedings of the Royal Society of Medicine*. **43** (1): 35–42. PMC 2081266. PMID 15409948.
29. ^ Nicholas JA, Burstein CL, Umberger CJ, Wilson PD (November 1955). "Management of adrenocortical insufficiency during surgery". *JAMA Surgery*. **71** (5): 737–742. doi:10.1001/archsurg.1955.01270170095018. PMID 13268224.
30. ^ Lord Owen (May 2003). "Diseased, demented, depressed: serious illness in Heads of State". *QJM*. **96** (5): 325–36. doi:10.1093/qjmed/hcg061. PMID 12702781.
31. ^ Dallek, Robert (2003). *An Unfinished Life: John F. Kennedy, 1917-1963*. London: Penguin Books. pp. 105, 731. ISBN 978-0-14-101535-4.
32. ^ "The Australian Addison's Disease Association". Retrieved 2007-07-25.
33. ^ Marsden, Brian (1997-07-18). "Eugene Shoemaker (1928-1997)". *Comet Shoemaker-Levy Collision with Jupiter*. Jet Propulsion Laboratory. Archived from the original on 11 July 2007. Retrieved 2007-07-25.
34. ^ Jones, Terry. "Patron Saints Index: Blessed Elizabeth of the Trinity". Archived from the original on 11 May 2008. Retrieved 2008-05-04.
35. ^ Upfal, Annette (2005). "Jane Austen's lifelong health problems and final illness: New evidence points to a fatal Hodgkin's disease and excludes the widely accepted Addison's". *Medical Humanities*. BMJ Publishing Group. **31** (1): 3–11. doi:10.1136/jmh.2004.000193.
36. ^ Williams, Linda; Hawes, Donald; Brake, Laurel (1991). "The Nineteenth Century: Victorian Period". *The Year's Work in English Studies*. Oxford University Press. **72** (1): 314–360. doi:10.1093/ywes/72.1.314.
37. ^ Chersterton, Ray (11 May 2007). "The cruelty of sport". *The Daily Telegraph*. Retrieved 2 January 2012.
38. ^ Wright, Lawrence (2006). *The Looming Tower*. New York City: Knopf. p. 139. ISBN 978-0-375-41486-2.
39. ^ Season 1, episode 4 of Pitch Slapped broadcast on Lifetime
40. ^ "Addison's disease makes Gafuik a fighter". *The Globe and Mail*. 20 July 2012. Retrieved 20 July 2012.
41. ^ **(Korean)** Seoul Economy Daily


## External links [edit]

- Addison's disease at DMOZ

Wikimedia Commons has media related to *Addison's disease*.

| v · t · e · | Diseases of the endocrine system (E00–E35, 240–259) | |
|---|---|---|
| **Pancreas/ glucose metabolism** | **Hypofunction** | Diabetes mellitus · *types:* (type 1 · type 2 · MODY 1 2 3 4 5 6 · · *complications* (coma · angiopathy · ketoacidosis · nephropathy · neuropathy · retinopathy · cardiomyopathy · · *insulin receptor* (Rabson–Mendenhall syndrome) · Insulin resistance · |
| | **Hyperfunction** | Hypoglycemia · *beta cell* (Hyperinsulinism) · *G cell* (Zollinger–Ellison syndrome) · |
| | **Hypothalamus** | *gonadotropin* (Kallmann syndrome · Adiposogenital dystrophy · · *CRH* (Tertiary adrenal insufficiency) · *vasopressin* (Neurogenic diabetes insipidus) · *general* (Hypothalamic hamartoma) · |

| | | | |
|---|---|---|---|
| **Hypothalamic/ pituitary axes** | **Pituitary** | **Hyperpituitarism** | *anterior* (Acromegaly · Hyperprolactinaemia · Pituitary ACTH hypersecretion · · *posterior* (SIADH) · *general* (Nelson's syndrome) · |
| | | **Hypopituitarism** | *anterior* (Kallmann syndrome · Growth hormone deficiency · Hypoprolactinemia · ACTH deficiency/Secondary adrenal insufficiency · GnRH insensitivity · FSH insensitivity · LH/hCG insensitivity · · *posterior* (Neurogenic diabetes insipidus) · *general* (Empty sella syndrome · Pituitary apoplexy · Sheehan's syndrome · Lymphocytic hypophysitis · · |
| | **Thyroid** | **Hypothyroidism** | Iodine deficiency · Cretinism (Congenital hypothyroidism · · Myxedema · Euthyroid sick syndrome · |
| | | **Hyperthyroidism** | Hyperthyroxinemia (Thyroid hormone resistance · Familial dysalbuminemic hyperthyroxinemia · · Hashitoxicosis · Thyrotoxicosis factitia · Graves' disease · |
| | | **Thyroiditis** | Acute infectious · Subacute (De Quervain's · Subacute lymphocytic · · Autoimmune/chronic (Hashimoto's · Postpartum · Riedel's · · |
| | | **Goitre** | Endemic goitre · Toxic nodular goitre · Toxic multinodular goiter · Thyroid nodule · |
| | **Parathyroid** | **Hypoparathyroidism** | Hypoparathyroidism · Pseudohypoparathyroidism · Pseudopseudohypoparathyroidism · |
| | | **Hyperparathyroidism** | Primary · Secondary · Tertiary · Osteitis fibrosa cystica · |
| | **Adrenal** | **Hyperfunction** | *aldosterone:* Hyperaldosteronism/Primary aldosteronism (Conn syndrome · Bartter syndrome · Glucocorticoid remediable aldosteronism · · AME · Liddle's syndrome · 17α CAH · *cortisol:* Cushing's syndrome (Pseudo-Cushing's syndrome) · *sex hormones:* 21α CAH · 11β CAH · |
| | | **Hypofunction/ Adrenal insufficiency (Addison's, WF)** | *aldosterone:* Hypoaldosteronism (21α CAH · 11β CAH · · *cortisol:* CAH (Lipoid · 3β · 11β · 17α · 21α · · *sex hormones:* 17α CAH · |
| | **Gonads** | | *ovarian:* Polycystic ovary syndrome · Premature ovarian failure · *testicular:* *enzymatic* (5α-reductase deficiency · 17β-hydroxysteroid dehydrogenase deficiency · aromatase excess syndrome) · · *Androgen receptor* (Androgen insensitivity syndrome) · |

| | | |
|---|---|---|
| | | *general:* Hypogonadism (Delayed puberty) · Hypergonadism (Precocious puberty · · Hypoandrogenism · Hypoestrogenism · Hyperandrogenism · Hyperestrogenism · Postorgasmic illness syndrome · |
| **Height** | | Dwarfism/Short stature (Midget · Laron syndrome · Psychosocial · Ateliosis · · Gigantism · |
| **Multiple** | | Autoimmune polyendocrine syndrome multiple (APS1 · APS2 · · Carcinoid syndrome · Multiple endocrine neoplasia (1 · 2A · 2B · · Progeria (Werner syndrome · Acrogeria · Metageria · · Woodhouse-Sakati syndrome · |

| v · t · e · | **Hypersensitivity and autoimmune diseases (279.5–6)** | | |
|---|---|---|---|
| **Type I/allergy/atopy (IgE)** | **Foreign** | | Atopic eczema · Allergic urticaria · Allergic rhinitis (Hay fever) · Allergic asthma · Anaphylaxis · Food allergy (common allergies include: Milk · Egg · Peanut · Tree nut · Seafood · Soy · Wheat · · Penicillin allergy · |
| | **Autoimmune** | | Eosinophilic esophagitis · |
| **Type II/ADCC (IgM · IgG · ·** | **Foreign** | | Hemolytic disease of the newborn · |
| | **Autoimmune** | **Cytotoxic** | Autoimmune hemolytic anemia · Immune thrombocytopenic purpura · Bullous pemphigoid · Pemphigus vulgaris · Rheumatic fever · Goodpasture's syndrome · Guillain–Barré syndrome · |
| | | **"Type V"/receptor** | Graves' disease · Myasthenia gravis · Pernicious anemia · |
| **Type III (Immune complex)** | **Foreign** | | Henoch–Schönlein purpura · Hypersensitivity vasculitis · Reactive arthritis · Farmer's lung · Post-streptococcal glomerulonephritis · Serum sickness · Arthus reaction · |
| | **Autoimmune** | | Systemic lupus erythematosus · Subacute bacterial endocarditis · Rheumatoid arthritis · |
| **Type IV/cell-mediated (T cells)** | **Foreign** | | Allergic contact dermatitis · Mantoux test · |
| | **Autoimmune** | | Diabetes mellitus type 1 · Hashimoto's thyroiditis · Multiple sclerosis · Coeliac disease · Giant-cell arteritis · Postorgasmic illness syndrome · Reactive arthritis · |
| | **GVHD** | | Transfusion-associated graft versus host disease · |
| **Unknown/multiple** | **Foreign** | | Hypersensitivity pneumonitis (Allergic bronchopulmonary aspergillosis · · Transplant rejection · Latex allergy (I+IV) · |
| | **Autoimmune** | | Sjögren's syndrome · Autoimmune hepatitis · Autoimmune polyendocrine syndrome (APS1 · APS2 · · **Autoimmune adrenalitis** · Systemic autoimmune disease · |

Categories: Medical emergencies | Endocrine-related cutaneous conditions | Adrenal gland disorders


# Cushing's syndrome

From Wikipedia, the free encyclopedia

*Not to be confused with Cushing's triad, due to increased intracranial pressure.*

**Cushing's syndrome** is a collection of signs and symptoms due to prolonged exposure to cortisol.[2][3] Signs and symptoms may include: high blood pressure, abdominal obesity but with thin arms and legs, reddish stretch marks, a round red face, a fat lump between the shoulders, weak muscles, weak bones, acne, and fragile skin that heals poorly. Women may have more hair and irregular menstruation. Occasionally there may be changes in mood, headaches, and a chronic feeling of tiredness.[4]

Cushing's syndrome is caused by either excessive cortisol-like medication such as prednisone or a tumor that either produces or results in the production of excessive cortisol by the adrenal glands.[5] Cases due to a pituitary adenoma are known as Cushing's disease. It is the second most common cause of Cushing's syndrome after medication.[2] A number of other tumors may also cause Cushing's.[2][6] Some of these are associated with inherited disorders such as multiple endocrine neoplasia type 1 and Carney complex.[7] Diagnosis requires a number of steps. The first step is to check the medications a person takes. The second step is to measure levels of cortisol in the urine, saliva or in the blood after taking dexamethasone. If this test is abnormal, the cortisol may be measured late at night. If the cortisol remains high, a blood test for ACTH may be done to determine if the pituitary is involved.[8]

Most cases can be treated and cured.[9] If due to medications, these can often be slowly stopped.[10] If caused by a tumor, it may be treated by a combination of surgery, chemotherapy, and/or radiation. If the pituitary was affected, other medications may be required to replace its lost function. With treatment, life expectancy is usually normal.[9] Some, in whom surgery is unable to remove the entire tumor, have an increased risk of death.[11]

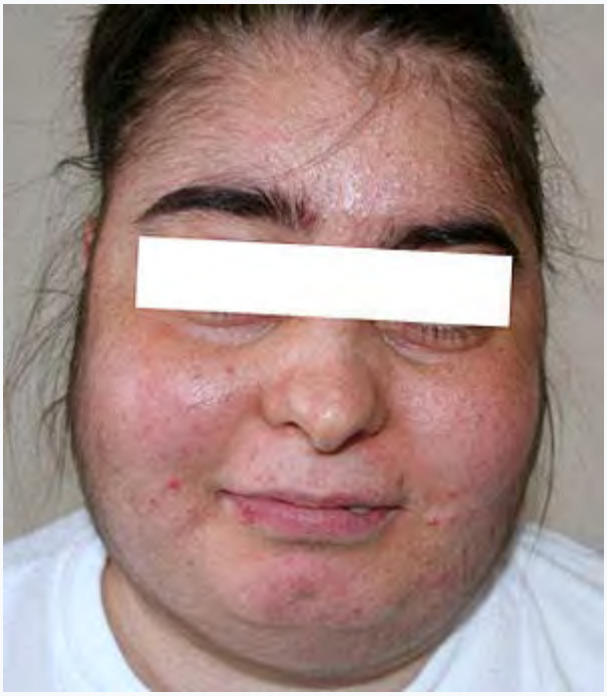
About two to three people per million are affected each year.[7] It most commonly affects people who are 20 to 50 years of age.[2] Women are affected three times more often than men.[7] A mild degree of overproduction of cortisol without obvious symptoms, however, is more common.[12]

Cushing's syndrome was first described by Harvey Cushing in [13]

## Variants

## Cushing's syndrome

**Synonyms** Hypercortisolism, Itsenko-hyperadrenocorticism



Person's facial appearance 3 months after treatment with inhaled fluticasone[1]

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Endocrinology |
| **ICD-10** | E24 |
| **ICD-9-CM** | 255.0 |
| **MedlinePlus** | 000410 |
| **eMedicine** | article/117365 |
| **Patient UK** | Cushing's syndrome |
| **MeSH** | D003480 |

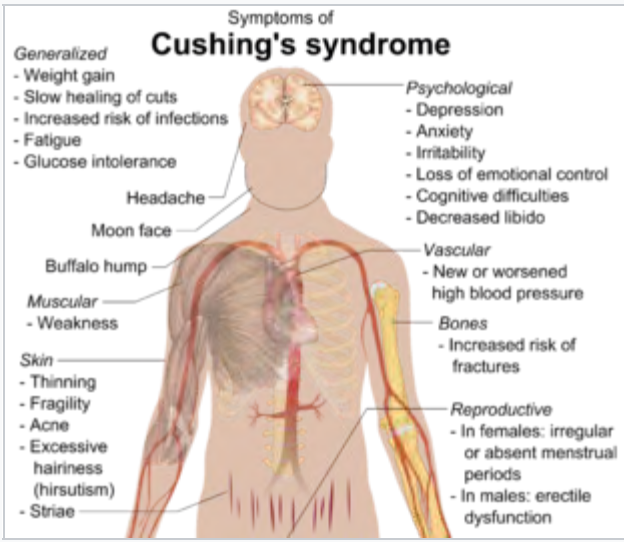
[edit on Wikidata]

1932. Cushing's syndrome may also occur in other animals including cats, dogs, and horses.[14][15]





## Signs and symptoms [edit]



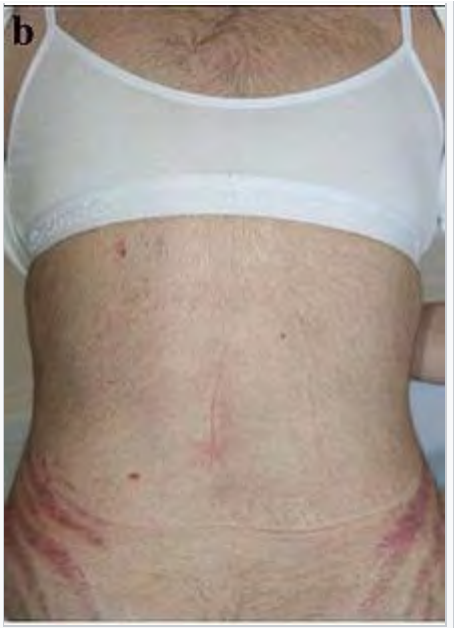
Symptoms of Cushing's syndrome[16]

Symptoms include rapid weight gain, particularly of the trunk and face with sparing of the limbs (central obesity). Common signs include the growth of fat pads along the collarbone, on the back of the neck ("buffalo hump" or lipodystrophy), and on the face ("moon face"). Other symptoms include excess sweating, dilation of capillaries, thinning of the skin (which causes easy bruising and dryness, particularly the hands) and mucous membranes, purple or red striae (the weight gain in Cushing's syndrome stretches the skin, which is thin and weakened, causing it to hemorrhage) on the trunk, buttocks, arms, legs, or breasts, proximal muscle weakness (hips, shoulders), and hirsutism (facial male-pattern hair growth), baldness and/or extremely dry and brittle hair. In rare cases, Cushing's can cause hypocalcemia. The excess cortisol may also affect other endocrine systems and cause, for example, insomnia, inhibited aromatase, reduced libido, impotence in men, and amenorrhoea/oligomenorrhea and infertility in women due to elevations in androgens. Studies have also shown that the resultant amenorrhea is due to hypercortisolism, which feeds back onto the hypothalamus resulting in decreased levels of GnRH release.[18]

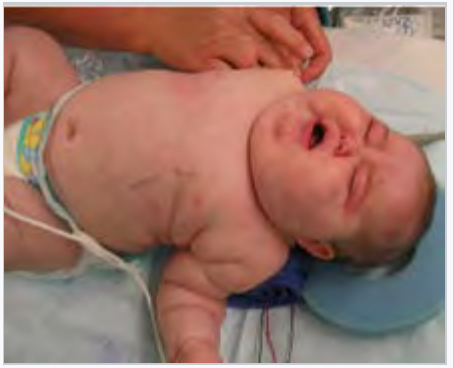
Cognitive conditions, including memory and attention dysfunctions, as well as depression, are commonly associated with elevated cortisol,[19] and may be early indicators of exogenous or endogenous Cushing's. Depression and anxiety disorders are also common.[20]

Other striking and distressing skin changes that may appear in Cushing's syndrome include facial acne, susceptibility to superficial fungus (dermatophyte and malassezia) infections, and the characteristic purplish, atrophic striae on the abdomen.[21]:500

Other signs include increased urination (and accompanying increased thirst), persistent high blood pressure (due to cortisol's enhancement of epinephrine's vasoconstrictive effect) and insulin resistance (especially common with ACTH production outside the pituitary), leading to high




Increased hair and stria in a person with medication-induced Cushing's syndrome[1]



Features of Cushing syndrome including a round face, acne, reddish skin, central obesity, and poor muscle tone[17]

blood sugar and insulin resistance which can lead to diabetes mellitus. Insulin resistance is accompanied by skin changes such as acanthosis nigricans in the axilla and around the neck, as well as skin tags in the axilla. Untreated Cushing's syndrome can lead to heart disease and increased mortality. Cortisol can also exhibit mineralocorticoid activity in high concentrations, worsening the hypertension and leading to hypokalemia (common in ectopic ACTH secretion). Furthermore, excessive cortisol may lead to gastrointestinal disturbances, opportunistic infections, and impaired wound healing related to cortisol's suppression of the immune and inflammatory responses. Osteoporosis is also an issue in Cushing's syndrome since osteoblast activity is inhibited. Additionally, Cushing's syndrome may cause sore and aching joints, particularly in the hip, shoulders, and lower back. Cushing's syndrome includes all the causes of increased cortisol leading to the diseased state. Cushing's disease is a specific type of Cushing's syndrome caused by a pituitary tumor leading to excessive production of ACTH (adrenocorticotropic hormone). Excessive ACTH stimulates the adrenal cortex to produce high levels of cortisol, producing the disease state. Cushing's disease due to excess ACTH may also result in hyperpigmentation. This is due to Melanocyte-Stimulating Hormone production as a byproduct of ACTH synthesis from Pro-opiomelanocortin (POMC). Alternatively, it is proposed that the high levels of ACTH, β-lipotropin, and γ-lipotropin, which contain weak MSH function, can act on the melanocortin 1 receptor. A variant of Cushing's disease can be caused by ectopic, i.e. extrapituitary, ACTH production from, for example, a small-cell lung cancer. When Cushing's syndrome is caused by an increase of cortisol at the level of the adrenal glands (via an adenoma or hyperplasia), negative feedback ultimately reduces ACTH production in the pituitary. In these cases, ACTH levels remain low and no hyperpigmentation develops. While all Cushing's disease gives Cushing's syndrome, not all Cushing's syndrome is due to Cushing's disease.

Brain changes such as cerebral atrophy may occur.[22] This atrophy is associated with areas of high glucocorticoid receptor concentrations such as the hippocampus and correlates highly with psychopathological personality changes.[23][24][25][26]

- Rapid weight gain
- Moodiness, irritability, or depression
- Muscle and bone weakness
- Memory and attention dysfunction
- Osteoporosis
- Diabetes mellitus

- Hypertension
- Immune suppression
- Sleep disturbances
- Menstrual disorders such as amenorrhea in women
- Decreased fertility in men
- Hirsutism
- Baldness
- Hypercholesterolemia

## Causes [edit]

Several possible causes of Cushing's syndrome are known.

### External versus internal [edit]

The most common cause of Cushing's syndrome is the taking of glucocorticoids prescribed by a health care practitioner to treat other diseases (called iatrogenic Cushing's syndrome). This can be an effect of corticosteroid treatment of a variety of disorders such as asthma and rheumatoid arthritis, or in immunosuppression after an organ transplant. Administration of synthetic ACTH is also possible, but ACTH is less often prescribed due to cost and lesser utility. Although rare, Cushing's syndrome can also be due to the use of medroxyprogesterone acetate.[27][28] In this form of Cushing's, the adrenal glands atrophy due to lack of stimulation by ACTH, since glucocorticoids downregulate production of ACTH. Cushing's syndrome in childhood usually results from use of glucocorticoid medication.[29]

Endogenous Cushing's syndrome results from some derangement of the body's own system of secreting cortisol. Normally, ACTH is released from the pituitary gland when necessary to stimulate the release of cortisol from the adrenal glands.

- In pituitary Cushing's, a benign pituitary adenoma secretes ACTH. This is also known as Cushing's disease and is responsible for 70% of endogenous Cushing's syndrome.[30]
- In adrenal Cushing's, excess cortisol is produced by adrenal gland tumors, hyperplastic adrenal glands, or adrenal glands with nodular adrenal hyperplasia.
- Tumors outside the normal pituitary-adrenal system can produce ACTH (occasionally with CRH) that affects the adrenal glands. This etiology is called ectopic or paraneoplastic Cushing's disease and is seen in diseases such as small cell lung cancer.[31]
- Finally, rare cases of CRH-secreting tumors (without ACTH secretion) have been reported, which stimulates pituitary ACTH production.[32]

### Pseudo-Cushing's syndrome [edit]

Elevated levels of total cortisol can also be due to estrogen found in oral contraceptive pills that contain a mixture of estrogen and progesterone, leading to Pseudo-Cushing's syndrome. Estrogen can cause an increase of cortisol-binding globulin and thereby cause the total cortisol level to be elevated. However, the total free cortisol, which is the active hormone in the body, as measured by a 24-hour urine collection for urinary free cortisol, is normal.[33]

## Pathophysiology [edit]

The hypothalamus is in the brain and the pituitary gland sits just below it. The paraventricular nucleus (PVN) of the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to release adrenocorticotropin (ACTH). ACTH travels via the blood to the adrenal gland, where it stimulates the release of cortisol. Cortisol is secreted by the cortex of the adrenal gland from a region called the zona fasciculata in response to ACTH. Elevated levels of cortisol exert negative feedback on CRH in the hypothalamus, which decreases the amount of ACTH released from the anterior pituitary gland.

Strictly, Cushing's syndrome refers to excess cortisol of any etiology (as syndrome means a group of

symptoms). One of the causes of Cushing's syndrome is a cortisol-secreting adenoma in the cortex of the adrenal gland (primary hypercortisolism/hypercorticism). The adenoma causes cortisol levels in the blood to be very high, and negative feedback on the pituitary from the high cortisol levels causes ACTH levels to be very low.

Cushing's disease refers only to hypercortisolism secondary to excess production of ACTH from a corticotroph pituitary adenoma (secondary hypercortisolism/hypercorticism) or due to excess production of hypothalamus CRH (Corticotropin releasing hormone) (tertiary hypercortisolism/hypercorticism). This causes the blood ACTH levels to be elevated along with cortisol from the adrenal gland. The ACTH levels remain high because the tumor is unresponsive to negative feedback from high cortisol levels.

When Cushing's syndrome is due to extra ACTH it is known as ectopic Cushing syndrome.[34] This may be seen in a paraneoplastic syndrome.

When Cushing's syndrome is suspected, either a dexamethasone suppression test (administration of dexamethasone and frequent determination of cortisol and ACTH level), or a 24-hour urinary measurement for cortisol offers equal detection rates.[35] Dexamethasone is a glucocorticoid and simulates the effects of cortisol, including negative feedback on the pituitary gland. When dexamethasone is administered and a blood sample is tested, cortisol levels >50 nmol/l (1.81 µg/dl) would be indicative of Cushing's syndrome because an ectopic source of cortisol or ACTH (such as adrenal adenoma) exists which is not inhibited by the dexamethasone. A novel approach, recently cleared by the US FDA, is sampling cortisol in saliva over 24 hours, which may be equally sensitive, as late-night levels of salivary cortisol are high in cushingoid patients. Other pituitary hormone levels may need to be ascertained. Performing a physical examination to determine any visual field defect may be necessary if a pituitary lesion is suspected, which may compress the optic chiasm, causing typical bitemporal hemianopia.

When any of these tests is positive, CT scanning of the adrenal gland and MRI of the pituitary gland are performed to detect the presence of any adrenal or pituitary adenomas or incidentalomas (the incidental discovery of harmless lesions). Scintigraphy of the adrenal gland with iodocholesterol scan is occasionally necessary. Occasionally, determining the ACTH levels in various veins in the body by venous catheterization, working towards the pituitary (petrosal sinus sampling) is necessary. In many cases, the tumors causing Cushing's disease are less than 2 mm in size and difficult to detect using MRI or CT imaging. In one study of 261 patients with confirmed pituitary Cushing's disease, only 48% of pituitary lesions were identified using MRI prior to surgery.[36]

Plasma CRH levels are inadequate at diagnosis (with the possible exception of tumors secreting CRH) because of peripheral dilution and binding to CRHBP.[37]

## Treatment [edit]

Most Cushing's syndrome cases are caused by corticosteroid medications (iatrogenic), such as those used for asthma, arthritis, and other inflammatory conditions. Consequently, most patients are effectively treated by carefully tapering off (and eventually stopping) the medication that causes the symptoms.

If an adrenal adenoma is identified, it may be removed by surgery. An ACTH-secreting corticotrophic pituitary adenoma should be removed after diagnosis. Regardless of the adenoma's location, most patients require steroid replacement postoperatively at least in the interim, as long-term suppression of pituitary ACTH and normal adrenal tissue does not recover immediately. Clearly, if both adrenals are removed, replacement with hydrocortisone or prednisolone is imperative.

In those patients not suited for or unwilling to undergo surgery, several drugs have been found to inhibit cortisol synthesis (e.g. ketoconazole, metyrapone) but they are of limited efficacy.[*citation needed*] Mifepristone is a powerful glucocorticoid type II receptor antagonist and, since it does not interfere with normal cortisol homeostatis type I receptor transmission, may be especially useful for treating the cognitive effects of Cushing's syndrome.[38] However, the medication faces considerable controversy due to its use as an abortifacient. In February 2012, the FDA approved mifepristone to control high blood sugar levels (hyperglycemia) in adult patients who are not candidates for surgery, or who did not respond to prior surgery, with the warning that mifepristone should never be used by pregnant women.[39]

Removal of the adrenals in the absence of a known tumor is occasionally performed to eliminate the production of excess cortisol. In some occasions, this removes negative feedback from a previously occult pituitary adenoma, which starts growing rapidly and produces extreme levels of ACTH, leading to hyperpigmentation. This clinical situation is known as Nelson's syndrome.[40]

## Epidemiology [edit]

Iatrogenic Cushing's syndrome (caused by treatment with corticosteroids) is the most common form of Cushing's syndrome. Cushing's disease is rare; a Danish study found an incidence of less than one case per million people per year.[41] However, asymptomatic microadenomas (less than 10 mm in size) of the pituitary are found in about one in six individuals.[42]

People with Cushing's syndrome have increased morbidity and mortality as compared to the general population. The most common cause of mortality in Cushing's syndrome is cardiovascular events. People with Cushing's syndrome have nearly 4 times increased cardiovascular mortality as compared to the general population.

## Mnemonic [edit]

The word "cushingoid" is a useful way to consider the complications and symptoms of Cushing's.[43]

**C**ataracts, **U**lcers, **S**kin: striae, thinning, bruising, **H**ypertension/ hirsutism/ hyperglycemia, **I**nfections, **N**ecrosis, avascular necrosis of the femoral head, **G**lycosuria, **O**steoporosis, obesity, **I**mmunosuppression, and **D**iabetes

## Other animals [edit]

For more information on the form in horses, see pituitary pars intermedia dysfunction.

## See also [edit]

- Addison's disease
- Adrenal insufficiency (hypocortisolism)

## References [edit]


1. ^ a b Celik, O; Niyazoglu, M; Soylu, H; Kadioglu, P (29 August 2012). "Iatrogenic Cushing's syndrome with inhaled steroid plus antidepressant drugs.". *Multidisciplinary respiratory medicine*. **7** (1): 26. doi:10.1186/2049-6958-7-26. PMC 3436715. PMID 22958272.
2. ^ a b c d "Cushing's Syndrome". National Endocrine and Metabolic Diseases Information Service (NEMDIS). July 2008. Retrieved 16 March 2015.
3. ^ Forbis, Pat (2005). *Stedman's medical eponyms* (2nd ed.). Baltimore, Md.: Lippincott Williams & Wilkins. p. 167. ISBN 9780781754439.
4. ^ "What are the symptoms of Cushing's syndrome?". 2012-11-30. Retrieved 16 March 2015.
5. ^ "What causes Cushing's syndrome?". 2012-11-30. Retrieved 16 March 2015.
6. ^ Nieman, LK; Ilias, I (December 2005). "Evaluation and treatment of Cushing's syndrome.". *The American Journal of Medicine*. **118** (12): 1340–6. doi:10.1016/j.amjmed.2005.01.059. PMID 16378774.
7. ^ a b c "How many people are affected by or at risk for Cushing's syndrome?". 2012-11-30. Retrieved 16 March 2015.
8. ^ "How do health care providers diagnose Cushing's syndrome?". 2012-11-30. Retrieved 16 March 2015.
9. ^ a b "Is there a cure for Cushing's syndrome?". 2012-11-30. Retrieved 16 March 2015.
10. ^ "What are the treatments for Cushing's syndrome?". 2012-11-30. Retrieved 16 March 2015.
11. ^ Graversen, D; Vestergaard, P; Stochholm, K; Gravholt, CH; Jørgensen, JO (April 2012). "Mortality in Cushing's

syndrome: a systematic review and meta-analysis.". *European journal of internal medicine*. **23** (3): 278–82. doi:10.1016/j.ejim.2011.10.013. PMID 22385888.
12. ^ Steffensen, C; Bak, AM; Rubeck, KZ; Jørgensen, JO (2010). "Epidemiology of Cushing's syndrome.". *Neuroendocrinology*. 92 Suppl 1: 1–5. doi:10.1159/000314297. PMID 20829610.
13. ^ "Cushing Syndrome: Condition Information". 2012-11-30. Retrieved 16 March 2015.
14. ^ Etienne Cote (2014). *Clinical Veterinary Advisor: Dogs and Cats* (3 ed.). Elsevier Health Sciences. p. 502. ISBN 9780323240741.
15. ^ McCue, PM (December 2002). "Equine Cushing's disease.". *The Veterinary Clinics of North America. Equine Practice*. **18** (3): 533–43, viii. doi:10.1016/s0749-0739(02)00038-x. PMID 12516933.
16. ^ "Cushing syndrome". Mayo Clinic. March 28, 2013. Retrieved 2015-05-25.
17. ^ Fudge, EB; von Allmen, D; Volmar, KE; Calikoglu, AS (2009). "Cushing Syndrome in a 6-Month-Old Infant due to Adrenocortical Tumor.". *International journal of pediatric endocrinology*. **2009**: 168749. doi:10.1155/2009/168749. PMC 2798106. PMID 20049152.
18. ^ Lado-Abeal, J; Rodriguez-Arnao, J; Newell-Price, JD; Perry, LA; Grossman, AB; Besser, GM; Trainer, PJ (September 1998). "Menstrual abnormalities in women with Cushing's disease are correlated with hypercortisolemia rather than raised circulating androgen levels." (PDF). *The Journal of Clinical Endocrinology and Metabolism*. **83** (9): 3083–8. doi:10.1210/JCEM.83.9.5084. PMID 9745407.
19. ^ Belanoff; et al. (2001). "Corticosteroids and cognition". *J Psychiatric Research*. **35** (3): 127–145. doi:10.1016/s0022-3956(01)00018-8. PMID 11461709.
20. ^ Yudofsky, Stuart C.; Robert E. Hales (2007). *The American Psychiatric Publishing Textbook of Neuropsychiatry and Behavioral Neurosciences* (5th ed.). American Psychiatric Pub, Inc. ISBN 1-58562-239-7.
21. ^ James, William; Berger, Timothy; Elston, Dirk (2005). *Andrews' Diseases of the Skin: Clinical Dermatology*. (10th ed.). Saunders. ISBN 0-7216-2921-0.
22. ^ Andela, CD; van Haalen, FM; Ragnarsson, O; Papakokkinou, E; Johannsson, G; Santos, A; Webb, SM; Biermasz, NR; van der Wee, NJ; Pereira, AM (July 2015). "MECHANISMS IN ENDOCRINOLOGY: Cushing's syndrome causes irreversible effects on the human brain: a systematic review of structural and functional magnetic resonance imaging studies.". *European Journal of Endocrinology*. **173** (1): R1–14. doi:10.1530/EJE-14-1101. PMID 25650405.
23. ^ Dorn, Lorah D.; Burgess, Ellen S.; Friedman, Theodore C.; Dubbert, Billinda; Gold, Philip W.; Chrousos, George P. (1997). "The Longitudinal Course of Psychopathology in Cushing's Syndrome after Correction of Hypercortisolism". *The Journal of Clinical Endocrinology & Metabolism*. **82** (3): 912–919. doi:10.1210/jcem.82.3.3834. ISSN 0021-972X.
24. ^ Cope, Lora M.; Shane, Matthew S.; Segall, Judith M.; Nyalakanti, Prashanth K.; Stevens, Michael C.; Pearlson, Godfrey D.; Calhoun, Vince D.; Kiehl, Kent A. (2012). "Examining the effect of psychopathic traits on gray matter volume in a community substance abuse sample". *Psychiatry Research: Neuroimaging*. **204** (2-3): 91–100. doi:10.1016/j.pscychresns.2012.10.004. ISSN 0925-4927.
25. ^ Wolkowitz, Owen M.; Lupien, Sonia J.; Bigler, Erin D. (2007). "The "Steroid Dementia Syndrome": A Possible Model of Human Glucocorticoid Neurotoxicity". *Neurocase*. **13** (3): 189–200. doi:10.1080/13554790701475468. ISSN 1355-4794. PMID 17786779.
26. ^ Weber, Sabrina; Habel, Ute; Amunts, Katrin; Schneider, Frank (2008). "Structural brain abnormalities in psychopaths—a review". *Behavioral Sciences & the Law*. **26** (1): 7–28. doi:10.1002/bsl.802. ISSN 0735-3936. PMID 18327824.
27. ^ Siminoski, K; Goss, P; Drucker, DJ (1989). "The Cushing syndrome induced by medroxyprogesterone acetate". *Annals of Internal Medicine*. **111** (9): 758–60. doi:10.7326/0003-4819-111-9-758. PMID 2552887.
28. ^ Merrin, PK; Alexander, WD (1990). "Cushing's syndrome induced by medroxyprogesterone". *BMJ (Clinical research ed.)*. **301** (6747): 345. doi:10.1136/bmj.301.6747.345-a. PMC 1663616. PMID 2144198.
29. ^ Stratakis, CA (2012). "Cushing syndrome in pediatrics". *Endocrinology and Metabolism Clinics of North America*. **41** (4): 793–803. doi:10.1016/j.ecl.2012.08.002. PMC 3594781. PMID 23099271.
30. ^ Cushing's Syndrome at The National Endocrine and Metabolic Diseases Information Service. July 2008. Citing: * Nieman, LK; Ilias, I (December 2005). "Evaluation and treatment of Cushing's syndrome.". *The American Journal of Medicine*. **118** (12): 1340–6. doi:10.1016/j.amjmed.2005.01.059. PMID 16378774.
31. ^ Schteingart, DE; Lloyd, RV; Akil, H; Chandler, WF; Ibarra-Perez, G; Rosen, SG; Ogletree, R (September 1986). "Cushing's syndrome secondary to ectopic corticotropin-releasing hormone-adrenocorticotropin secretion.". *The Journal of Clinical Endocrinology and Metabolism*. **63** (3): 770–5. doi:10.1210/jcem-63-3-770. PMID 3525603.
32. ^ Voyadzis JM, Guttman-Bauman I, Santi M, Cogen P (2004). "Hypothalamic hamartoma secreting corticotropin-releasing hormone. Case report.". *J Neurosurg*. **100** (2 Suppl Pediatrics): 212–6. doi:10.3171/ped.2004.100.2.0212. PMID 14758953.
33. ^ C. W. Burke (1969). "The effect of oral contraceptives on cortisol metabolism". *J Clin Pathol*. **3**: 11–18. doi:10.1136/jcp.s1-3.1.11. PMC 1436049.
34. ^ Ectopic Cushing syndrome at A.D.A.M. Medical Encyclopedia, PubMedHealth, National Institute of Health

35. ^ Raff Hershel; Findling JW (2003). "A physiologic approach to diagnosis of the Cushing syndrome". *Annals of Internal Medicine*. **138** (12): 980–91. doi:10.7326/0003-4819-138-12-200306170-00010. PMID 12809455.
36. ^ Jagannathan J.; et al. (2010). "Outcome of using the histological pseudocapsule as a surgical capsule in Cushing disease". *Journal of Neurosurgery*. **111**: 531–9. doi:10.3171/2008.8.JNS08339. PMC 2945523. PMID 19267526.
37. ^ Jr, edited by Lewis S. Blevins (2002). *Cushing's syndrome*. Boston: Kluwer Academic. p. 115. ISBN 1-4020-7131-0.
38. ^ Belanoff; et al. (2001). "Rapid reversal of psychotic depression using mifepristone". *J Clin Psychopharmacol*. **21** (5): 516–521. doi:10.1097/00004714-200110000-00009. PMID 11593077.
39. ^ "FDA approves mifepristone (Korlym*) for patients with endogenous Cushing' s syndrome". February 18, 2012.
40. ^ Nelson DH, Meakin JW, Thorn GW (1960). "ACTH-producing pituitary tumors following adrenalectomy for Cushing syndrome". *Annals of Internal Medicine*. **52** (3): 560–9. doi:10.7326/0003-4819-52-3-560. PMID 14426442.
41. ^ Lindholm J, Juul S, et al. (2001). "Incidence and late prognosis of cushing's syndrome: a population-based study.". *J Clin Endocrinol Metab*. **86** (1): 117–23. doi:10.1210/jc.86.1.117. PMID 11231987.
42. ^ Ezzat S, Asa SL, Couldwell WT, et al. (2004). "The prevalence of pituitary adenomas: a systematic review". *Cancer*. **101** (3): 613–9. doi:10.1002/cncr.20412. PMID 15274075.
43. ^ http://www.medicalmnemonics.com/cgi-bin/return_browse.cfm?&discipline=Pharmacology&system=Endocrine&browse=1


## External links [edit]

- The European Register on Cushing's Syndrome
- Patient information (PDF)
- Brochure for Primary Care Physicians, to increase awareness of Cushing's syndrome
- The difference between Cushing's disease and other forms of Cushing's syndrome

| v · t · e | Diseases of the endocrine system (E00–E35, 240–259) | | |
|---|---|---|---|
| **Pancreas/ glucose metabolism** | **Hypofunction** | Diabetes mellitus · *types:* (type 1 · type 2 · MODY 1 2 3 4 5 6 · · *complications* (coma · angiopathy · ketoacidosis · nephropathy · neuropathy · retinopathy · cardiomyopathy · · *insulin receptor* (Rabson–Mendenhall syndrome) · Insulin resistance · | |
| | **Hyperfunction** | Hypoglycemia · *beta cell* (Hyperinsulinism) · *G cell* (Zollinger–Ellison syndrome) · | |
| | **Hypothalamus** | *gonadotropin* (Kallmann syndrome · Adiposogenital dystrophy · · *CRH* (Tertiary adrenal insufficiency) · *vasopressin* (Neurogenic diabetes insipidus) · *general* (Hypothalamic hamartoma) · | |
| | **Pituitary** | **Hyperpituitarism** | *anterior* (Acromegaly · Hyperprolactinaemia · Pituitary ACTH hypersecretion · · *posterior* (SIADH) · *general* (Nelson's syndrome) · |
| | | **Hypopituitarism** | *anterior* (Kallmann syndrome · Growth hormone deficiency · Hypoprolactinemia · ACTH deficiency/Secondary adrenal insufficiency · GnRH insensitivity · FSH insensitivity · LH/hCG insensitivity · · *posterior* (Neurogenic diabetes insipidus) · *general* (Empty sella syndrome · Pituitary apoplexy · Sheehan's syndrome · Lymphocytic hypophysitis · · |
| | | **Hypothyroidism** | Iodine deficiency · Cretinism (Congenital hypothyroidism · · Myxedema · |

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| **Hypothalamic/ pituitary axes** | **Thyroid** | | Euthyroid sick syndrome · |
| | | **Hyperthyroidism** | Hyperthyroxinemia (Thyroid hormone resistance · Familial dysalbuminemic hyperthyroxinemia · · Hashitoxicosis · Thyrotoxicosis factitia · Graves' disease · |
| | | **Thyroiditis** | Acute infectious · Subacute (De Quervain's · Subacute lymphocytic · · Autoimmune/chronic (Hashimoto's · Postpartum · Riedel's · · |
| | | **Goitre** | Endemic goitre · Toxic nodular goitre · Toxic multinodular goiter · Thyroid nodule · |
| | **Parathyroid** | **Hypoparathyroidism** | Hypoparathyroidism · Pseudohypoparathyroidism · Pseudopseudohypoparathyroidism · |
| | | **Hyperparathyroidism** | Primary · Secondary · Tertiary · Osteitis fibrosa cystica · |
| | **Adrenal** | **Hyperfunction** | *aldosterone:* Hyperaldosteronism/Primary aldosteronism (Conn syndrome · Bartter syndrome · Glucocorticoid remediable aldosteronism · · AME · Liddle's syndrome · 17α CAH · *cortisol:* **Cushing's syndrome** (Pseudo-Cushing's syndrome) · *sex hormones:* 21α CAH · 11β CAH · |
| | | **Hypofunction/ Adrenal insufficiency (Addison's, WF)** | *aldosterone:* Hypoaldosteronism (21α CAH · 11β CAH · · *cortisol:* CAH (Lipoid · 3β · 11β · 17α · 21α · · *sex hormones:* 17α CAH · |
| | **Gonads** | | *ovarian:* Polycystic ovary syndrome · Premature ovarian failure · *testicular: enzymatic* (5α-reductase deficiency · 17β-hydroxysteroid dehydrogenase deficiency · aromatase excess syndrome) · · *Androgen receptor* (Androgen insensitivity syndrome) · *general:* Hypogonadism (Delayed puberty) · Hypergonadism (Precocious puberty · · Hypoandrogenism · Hypoestrogenism · Hyperandrogenism · Hyperestrogenism · Postorgasmic illness syndrome · |
| **Height** | | | Dwarfism/Short stature (Midget · Laron syndrome · Psychosocial · Ateliosis · · Gigantism · |
| **Multiple** | | | Autoimmune polyendocrine syndrome multiple (APS1 · APS2 · · Carcinoid syndrome · Multiple endocrine neoplasia (1 · 2A · 2B · · Progeria (Werner syndrome · Acrogeria · Metageria · · Woodhouse-Sakati syndrome · |

| v · t · e · | **Paraneoplastic syndromes** |
|---|---|
| **Endocrine** | Hypercalcaemia · SIADH · Zollinger–Ellison syndrome · **Cushing's syndrome** · |
| **Hematological** | Granulocytosis · Multicentric reticulohistiocytosis · |
| | Paraneoplastic cerebellar degeneration · Encephalomyelitis · Limbic encephalitis · Opsoclonus · |

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| **Neurological** | | Polymyositis · Transverse myelitis · Lambert–Eaton myasthenic syndrome · Anti-NMDA receptor encephalitis · |
| **Musculoskeletal** | | Dermatomyositis · Hypertrophic osteopathy · |
| **Mucocutaneous** | **reactive erythema** | Erythema gyratum repens · Necrolytic migratory erythema · |
| | **papulosquamous** | Acanthosis nigricans · Ichthyosis acquisita · Acrokeratosis paraneoplastica of Bazex · Extramammary Paget's disease · Florid cutaneous papillomatosis · Leser-Trélat sign · Pityriasis rotunda · Tripe palms · |
| | **Other** | Febrile neutrophilic dermatosis · Pyoderma gangrenosum · Paraneoplastic pemphigus · |
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Categories: Adrenal gland disorders | Medical conditions related to obesity

# Delirium tremens



*"DTs" redirects here. For other uses, see DTS (disambiguation).*
*For other uses, see Delirium tremens (disambiguation).*

## Variants

**Delirium tremens** (**DTs**) is a rapid onset of confusion usually caused by withdrawal from alcohol. When it occurs, it is often three days into the withdrawal symptoms and lasts for two to three days. People may also see or hear things other people do not.[1] Physical effects may include shaking, shivering, irregular heart rate, and sweating.[2] Occasionally, a very high body temperature or seizures may result in death.[1] Alcohol is one of the most dangerous drugs to withdraw from.[3]

Delirium tremens typically only occurs in people with a high intake of alcohol for more than a month.[4] A similar syndrome may occur with benzodiazepine and barbiturate withdrawal.[5] Withdrawal from stimulants such as cocaine does not have major medical complications.[6] In a person with delirium tremens it is important to rule out other associated problems such as electrolyte abnormalities, pancreatitis, and alcoholic hepatitis.[1]

Prevention is by treating withdrawal symptoms. If delirium tremens occurs, aggressive treatment improves outcomes. Treatment in a quiet intensive care unit with sufficient light is often recommended. Benzodiazepines are the medication of choice with diazepam, lorazepam, chlordiazepoxide, and oxazepam all commonly used.[4] They should be given until a person is lightly sleeping. The antipsychotic haloperidol may also be used. The vitamin thiamine is recommended.[1]

Mortality without treatment is between 15% and 40%.[7] Currently death occurs in about 1% to 4% of cases.[1]

About half of people with alcoholism will develop withdrawal symptoms upon reducing their use. Of these, three to five percent develop DTs or have seizures.[1] The name delirium tremens was first used in 1813; however, the symptoms were well described since the 1700s.[4] The word "delirium" is Latin for "going off the furrow," a plowing metaphor. It is also called shaking frenzy and Saunders-Sutton syndrome.[7] Nicknames include the shakes, barrel-fever, blue horrors, bottleache, bats, drunken horrors, elephants, gallon distemper, quart mania, and pink spiders, among others.[8]

## Delirium tremens


An alcoholic man with delirium tremens on his deathbed, surrounded by his terrified family. The text "L'Alcool Tue" means "Alcohol Kills" in French.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Neurology |
| **ICD-10** | F10.4 |
| **ICD-9-CM** | 291.0 |
| **DiseasesDB** | 3543 |
| **MedlinePlus** | 000766 |

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## Signs and symptoms [edit]

The main symptoms of delirium tremens are nightmares, agitation, global confusion, disorientation, visual and auditory hallucinations, tactile hallucinations, fever, high blood pressure, heavy sweating, and other signs of autonomic hyperactivity (fast heart rate and high blood pressure). These symptoms may appear suddenly, but typically develop two to three days after the stopping of heavy drinking, being worst on the fourth or fifth day.[10] Also, these "symptoms are characteristically worse at night".[11] In general, DT is considered the most severe manifestation of alcohol withdrawal and occurs 3–10 days following the last drink.[9] Other common symptoms include intense perceptual disturbance such as visions of insects, snakes, or rats. These may be hallucinations, or illusions related to the environment, e.g., patterns on the wallpaper or in the peripheral vision that the patient falsely perceives as a resemblance to the morphology of an insect, and are also associated with tactile hallucinations such as sensations of something crawling on the subject—a phenomenon known as formication. Delirium tremens usually includes extremely intense feelings of "impending doom". Severe anxiety and feelings of imminent death are common DT symptoms.

DT can sometimes be associated with severe, uncontrollable tremors of the extremities and secondary symptoms such as anxiety, panic attacks and paranoia. Confusion is often noticeable to onlookers as those with DT will have trouble forming simple sentences or making basic logical calculations. In many cases, people who rarely speak out of turn will have an increased tendency for gaffes even though they are sober.[*citation needed*]

DT should be distinguished from alcoholic hallucinosis, the latter of which occurs in approximately 20% of hospitalized alcoholics and does not carry a significant mortality. In contrast, DT occurs in 5–10% of alcoholics and carries up to 15% mortality with treatment and up to 35% mortality without treatment.[12] DT is characterized by the presence of altered sensorium; that is, a complete hallucination without any recognition of the real world. DT has extreme autonomic hyperactivity (high pulse, blood pressure, and rate of breathing), and 35-60% of patients have a fever. Some patients experience seizures.[*citation needed*]

## Causes [edit]

Delirium tremens is mainly caused by a long period of drinking being stopped abruptly. Withdrawal leads to a biochemical regulation cascade. It may also be triggered by head injury, infection, or illness in people with a history of heavy use of alcohol.[*citation needed*]

Another cause of delirium tremens is abrupt stopping of tranquilizer drugs of the barbiturate or benzodiazepine classes in a person with a relatively strong addiction to them.[*citation needed*] Because these tranquilizers' primary pharmacological and physiological effects stem from their manipulation of the GABA chemical and transmitter somatic system, the same neurotransmitter system affected by alcohol, delirium tremens can occur upon abrupt decrease of dosage in those who are heavily dependent. These DTs are much the same as those caused by alcohol and so is the attendant withdrawal syndrome of which they are a manifestation. That is the primary reason benzodiazepines are such an effective treatment for DTs, despite also being the cause of them in many cases. Because ethanol and tranquilizers such as barbiturates and benzodiazepines function as positive allosteric modulators at $GABA_A$ receptors, the brain, in its desire to equalize an unbalanced chemical system, triggers the abrupt stopping of the production of endogenous GABA. This decrease becomes more and more marked as the addiction becomes stronger and as higher

doses are needed to cause intoxication. In addition to having sedative properties, GABA is an immensely important regulatory neurotransmitter that controls the heart rate, blood pressure, and seizure threshold among myriad other important autonomic nervous subsystems.[*citation needed*]

Delirium tremens is most common in people who have a history of alcohol withdrawal, especially in those who drink the equivalent of 7 to 8 US pints (3 to 4 l) of beer or 1 US pint (0.5 l) of distilled beverage daily. Delirium tremens also commonly affects those with a history of habitual alcohol use or alcoholism that has existed for more than 10 years.[13]

The exact pharmacology of ethanol is not fully understood; however, it is theorized that delirium tremens is caused by the effect of alcohol on GABA receptors. Constant consumption of alcoholic beverages (and the consequent chronic sedation) causes a counterregulatory response in the brain in an attempt to regain homeostasis.

This causes downregulation of these receptors, as well as an up-regulation in the production of excitatory neurotransmitters, primarily glutamate, and also such as norepinephrine, dopamine, epinephrine, and serotonin, all of which further the drinker's tolerance to alcohol. When alcohol is no longer consumed, these down-regulated $GABA_A$ receptor complexes are so insensitive to GABA that the typical amount of GABA produced has little effect; compounded with the fact that GABA normally inhibits action potential formation, there are not as many receptors for GABA to bind to, meaning that sympathetic activation is unopposed. This is also known as an "adrenergic storm", the effects of which can include (but are not limited to) tachycardia, hypertension, fever, night sweats, hyperreflexia, excessive sweating, heart attack, cardiac arrhythmia, stroke, anxiety, panic attacks, paranoia, and agitation.[*citation needed*]

This is all made worse by excitatory neurotransmitter up-regulation, so not only is sympathetic nervous system over-activity unopposed by GABA, there is also more of the serotonin, norepinephrine, dopamine, epinephrine, and particularly glutamate. Excitory NMDA receptors are also up-regulated, contributing to the delirium and neurotoxicity (by excitotoxicity) of withdrawal. Direct measurements of central norepinephrine and its metabolites are in direct correlation to the severity of the alcohol withdrawal syndrome.[14] It is possible that psychological (i.e., non-physical) factors also play a role, in addition to other factors such as infections, malnutrition, or other underlying medical disorders, often related to alcoholism.[*citation needed*]

## Treatment [edit]

Delirium tremens due to alcohol withdrawal can be treated with benzodiazepines. High doses may be necessary to prevent death.[15] Amounts given are based on the symptoms. Typically the person is kept sedated with benzodiazepines, such as diazepam, lorazepam, chlordiazepoxide, or oxazepam.

In some cases antipsychotics, such as haloperidol may also be used. Older drugs such as paraldehyde and clomethiazole were formerly the traditional treatment but have now largely been superseded by the benzodiazepines.

Acamprosate is occasionally used in addition to other treatments, and is then carried on into long term use to reduce the risk of relapse. If status epilepticus occurs it is treated in the usual way. It can also be helpful to control environmental stimuli, by providing a well-lit but relaxing environment for minimizing distress and visual hallucinations.[*citation needed*]

Alcoholic beverages can also be prescribed as a treatment for delirium tremens,[16] but this practice is not universally supported.[17]

High doses of thiamine often by the intravenous route is also recommended.[18]

## Society and culture [edit]

Nicknames include "the horrors", "the shakes", "the bottleache", "quart mania", "ork orks", "gallon distemper", "the zoots", "barrel fever", "the 750 itch", "pint paralysis", seeing pink elephants. Another nickname is

"the Brooklyn Boys" found in Eugene O'Neill's one-act play *Hughie* set In 1920's Times Square.[19]

Writer Jack Kerouac details his experiences with delirium tremens in his book *Big Sur*.[20]

One of the characters in Joseph Conrad's novel *Lord Jim* experiences "DTs of the worst kind" with symptoms that include seeing millions of pink frogs.

Drawing by Donald Ogden Stewart published in 1921 showing Little Elmer's father with DTs and seeing pink elephants

## See also [edit]

- Alcohol dementia
- Alcohol detoxification
- Delusional parasitosis
- Excited delirium
- On the wagon

*Psychiatry portal*

## References [edit]


1. ^ *a b c d e f* Schuckit, MA (27 November 2014). "Recognition and management of withdrawal delirium (delirium tremens).". *The New England Journal of Medicine*. **371** (22): 2109–13. doi:10.1056/NEJMra1407298. PMID 25427113.
2. ^ Healy, David (3 December 2008). *Psychiatric Drugs Explained*. Elsevier Health Sciences. p. 237. ISBN 978-0-7020-2997-4.
3. ^ Fisher, Gary L. (2009). *Encyclopedia of substance abuse prevention, treatment, & recovery*. Los Angeles: SAGE. p. 1005. ISBN 9781452266015.
4. ^ *a b c* Stern, TA; Gross, AF; Stern, TW; Nejad, SH; Maldonado, JR (2010). "Current approaches to the recognition and treatment of alcohol withdrawal and delirium tremens: "old wine in new bottles" or "new wine in old bottles".". *Primary care companion to the Journal of clinical psychiatry*. **12** (3). doi:10.4088/PCC.10r00991ecr. PMID 20944765.
5. ^ Posner, Jerome B. (2007). *Plum and Posner's Diagnosis of Stupor and Coma.* (4 ed.). Oxford: Oxford University Press, USA. p. 283. ISBN 9780198043362.
6. ^ Galanter, Marc; Kleber, Herbert D (1 July 2008). *The American Psychiatric Publishing Textbook of Substance Abuse Treatment* (4th ed.). United States of America: American Psychiatric Publishing Inc. p. 58. ISBN 978-1-58562-276-4.
7. ^ *a b* Blom, Jan Dirk (2010). *A dictionary of hallucinations* (. ed.). New York: Springer. p. 136. ISBN 9781441912237.
8. ^ Baldwin, Dan (2002). *Just the FAQ's, Please, About Alcohol and Drug Abuse: Frequently Asked Questions from Families*. America Star Books. pp. Chapter four. ISBN 9781611028706.
9. ^ *a b* *Delirium Tremens (DTs)~clinical* at eMedicine
10. ^ Hales, R.; Yudofsky, S.; Talbott, J. (1999). *Textbook of Psychiatry* (3rd ed.). London: The American Psychiatric Press.[*page needed*]
11. ^ Gelder et al, 2005 p188 Psychiatry 3rd Ed. oxford: New York.[*page needed*]
12. ^ *Delirium Tremens (DTs): Prognosis* at eMedicine
13. ^ MedlinePlus Encyclopedia *Delirium Tremens*
14. ^ Linnoila, Markku (Fall 1989). "Alcohol withdrawal syndrome and sympathetic nervous system function — Biological Research at National Institute of Alcohol Abuse and Alcoholism". Alcohol Health & Research World.
15. ^ Wolf KM, Shaughnessy AF, Middleton DB (1993). "Prolonged delirium tremens requiring massive doses of medication". *J Am Board Fam Pract*. **6** (5): 502–4. PMID 8213241.
16. ^ Rosenbaum M, McCarty T (2002). "Alcohol prescription by surgeons in the prevention and treatment of delirium tremens: Historic and current practice". *General hospital psychiatry*. **24** (4): 257–259. doi:10.1016/S0163-8343(02)00188-3. PMID 12100836.

17. ^ Sattar SP, Qadri SF, Warsi MK, Okoye C, Din AU, Padala PR, Bhatia SC (2006). "Use of alcoholic beverages in VA medical centers". *Substance Abuse Treatment, Prevention, and Policy*. **1**: 30. doi:10.1186/1747-597X-1-30. PMC 1624810. PMID 17052353.
18. ^ Schuckit, MA (27 November 2014). "Recognition and management of withdrawal delirium (delirium tremens).". *The New England journal of medicine*. **371** (22): 2109–13. PMID 25427113.
19. ^ Paulson, Michael, "Gambling on O'Neill: Forest Whitaker Makes His Broadway Debut in 'Hughie'", New York *Times*, February 3, 2016. Retrieved 2016-02-03.
20. ^ Summary and analysis of novel


## External links [edit]

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| **General** | SID (Substance intoxication / Drug overdose · Withdrawal · Substance-induced psychosis · · SUD (Substance abuse · Physical dependence / Substance dependence · · | | | |
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| | | | **Digestive system** | Alcoholic hepatitis · Alcoholic liver disease · Auto-brewery syndrome · |
| | | | **Nervous system** | Alcohol-related dementia · Alcoholic hallucinosis · Hangover · |
| | | | **Cardiovascular system** | Alcoholic cardiomyopathy · Alcohol flush reaction · |
| | **SUD** | Alcoholism · Alcohol dependence · Alcohol abuse · | | |
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| **Caffeine** | SID (Effect of caffeine on memory · Caffeine-induced sleep disorder · · SUD (Caffeine dependence · · | | | |
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# Diabetes mellitus

From Wikipedia, the free encyclopedia
(Redirected from Diabetes)

*"Diabetes" redirects here. For other uses, see Diabetes (disambiguation).*

**Diabetes mellitus** (**DM**), commonly referred to as **diabetes**, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period.[2] Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications.[3] Acute complications can include diabetic ketoacidosis, nonketotic hyperosmolar coma, or death.[4] Serious long-term complications include heart disease, stroke, chronic kidney failure, foot ulcers, and damage to the eyes.[3]

Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced.[5] There are three main types of diabetes mellitus:

- Type 1 DM results from the pancreas's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown.[3]
- Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly.[3] As the disease progresses a lack of insulin may also develop.[6] This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise.[3]
- Gestational diabetes is the third main form and occurs when pregnant women without a previous history of diabetes develop high blood-sugar levels.[3]

Prevention and treatment involve maintaining a healthy diet, regular physical exercise, a normal body weight, and avoiding use of tobacco. Control of blood pressure and maintaining proper foot care are important for people with the disease. Type 1 DM must be managed with insulin injections.[3] Type 2 DM may be treated with medications with or without insulin.[7] Insulin and some oral medications can cause low blood sugar.[8] Weight loss surgery in those with obesity is sometimes an effective measure in those with type 2 DM.[9] Gestational diabetes usually resolves after the birth of the baby.[10]

As of 2015, an estimated 415 million people had diabetes worldwide,[11] with type 2 DM making up about

**Diabetes mellitus**

Universal blue circle symbol for diabetes.[1]

| Classification and external resources | |
|---|---|
| **Specialty** | Endocrinology |
| **ICD-10** | E10–E14 |
| **ICD-9-CM** | 250 |
| **MedlinePlus** | 001214 |
| **eMedicine** | med/546 emerg/134 |
| **Patient UK** | Diabetes mellitus |
| **MeSH** | *C18.452.394.750* |

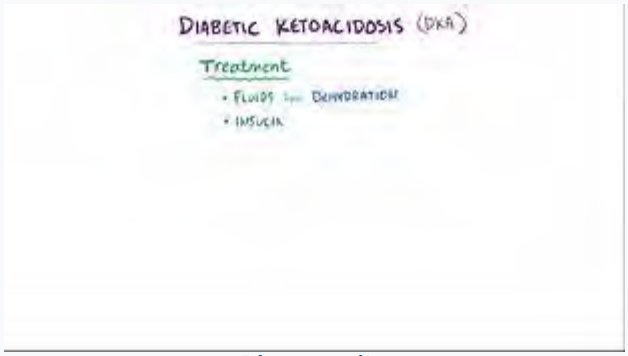
[edit on Wikidata]

90% of the cases.[12][13] This represents 8.3% of the adult population,[13] with equal rates in both women and men.[14] As of 2014, trends suggested the rate would continue to rise.[15] Diabetes at least doubles a person's risk of early death.[3] From 2012 to 2015, approximately 1.5 to 5.0 million deaths each year resulted from diabetes.[7][11] The global economic cost of diabetes in 2014 was estimated to be US$612 billion.[16] In the United States, diabetes cost $245 billion in 2012.[17]

Contents







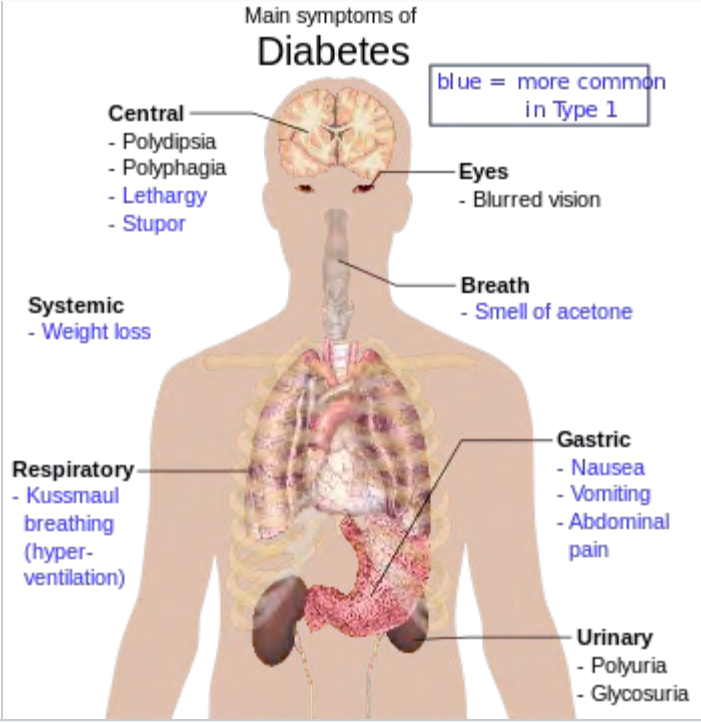

Play media

Video explanation

# Signs and symptoms

The classic symptoms of untreated diabetes are weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger).[18] Symptoms may develop rapidly (weeks or months) in type 1 DM, while they usually develop much more slowly and may be subtle or absent in type 2 DM.

Several other signs and symptoms can mark the onset of diabetes although they are not specific to the disease. In addition to the known ones above, they include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes.




Overview of the most significant symptoms of diabetes

## Diabetic emergencies

Low blood sugar is common in persons with type 1 and type 2 DM. Most cases are mild and are not considered medical emergencies. Effects can range from feelings of unease, sweating, trembling, and increased appetite in mild cases to more serious issues such as confusion, changes in behavior such as aggressiveness, seizures, unconsciousness, and (rarely) permanent brain damage or death in severe cases.[19][20] Moderate hypoglycemia may easily be mistaken for drunkenness;[21] rapid breathing and sweating, cold, pale skin are characteristic of hypoglycemia but not definitive.[22] Mild to moderate cases are self-treated by eating or drinking something high in sugar. Severe cases can lead to unconsciousness and must be treated with intravenous glucose or injections with glucagon.

People (usually with type 1 DM) may also experience episodes of diabetic ketoacidosis, a metabolic disturbance characterized by nausea, vomiting and abdominal pain, the smell of acetone on the breath, deep breathing known as Kussmaul breathing, and in severe cases a decreased level of consciousness.[23]

A rare but equally severe possibility is hyperosmolar nonketotic state, which is more common in type 2 DM and is mainly the result of dehydration.[23]

## Complications

*Main article: Complications of diabetes mellitus*

All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10–20) but may be the first symptom in those who have otherwise not received a diagnosis before that time.

The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease[24] and about 75% of deaths in diabetics are due to coronary artery disease.[25] Other "macrovascular" diseases are stroke, and peripheral vascular disease.

The primary complications of diabetes due to damage in small blood vessels include damage to the eyes, kidneys, and nerves.[26] Damage to the eyes, known as diabetic retinopathy, is caused by damage to the blood vessels in the retina of the eye, and can result in gradual vision loss and blindness.[26] Damage to the kidneys, known as diabetic nephropathy, can lead to tissue scarring, urine protein loss, and eventually chronic kidney disease, sometimes requiring dialysis or kidney transplant.[26] Damage to the nerves of the body, known as diabetic neuropathy, is the most common complication of diabetes.[26] The symptoms can include numbness, tingling, pain, and altered pain sensation, which can lead to damage to the skin.

Diabetes-related foot problems (such as diabetic foot ulcers) may occur, and can be difficult to treat, occasionally requiring amputation. Additionally, proximal diabetic neuropathy causes painful muscle wasting and weakness.

There is a link between cognitive deficit and diabetes. Compared to those without diabetes, those with the disease have a 1.2 to 1.5-fold greater rate of decline in cognitive function.[27]

# Causes

Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes, and "other specific types".[5] The "other specific types" are a collection of a few dozen individual causes.[5] Diabetes is a more variable disease than once thought and people may have combinations of forms.[29] The term "diabetes", without qualification, usually refers to diabetes mellitus.

**Comparison of type 1 and 2 diabetes**[12]

| Feature | Type 1 diabetes | Type 2 diabetes |
|---|---|---|
| **Onset** | Sudden | Gradual |
| **Age at onset** | Mostly in children | Mostly in adults |
| **Body size** | Thin or normal[28] | Often obese |
| **Ketoacidosis** | Common | Rare |
| **Autoantibodies** | Usually present | Absent |
| **Endogenous insulin** | Low or absent | Normal, decreased or increased |
| **Concordance in identical twins** | 50% | 90% |
| **Prevalence** | ~10% | ~90% |

## Type 1

*Main article: Diabetes mellitus type 1*

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, in which a T-cell-mediated autoimmune attack leads to the loss of beta cells and thus insulin.[30] It causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children.

"Brittle" diabetes, also known as unstable diabetes or labile diabetes, is a term that was traditionally used to describe the dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes. This term, however, has no biologic basis and should not be used.[31] Still, type 1 diabetes can be accompanied by irregular and unpredictable high blood sugar levels, frequently with ketosis, and sometimes with serious low blood sugar levels. Other complications include an impaired counterregulatory response to low blood sugar, infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies (e.g., Addison's disease).[31] These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes.[32]

Type 1 diabetes is partly inherited, with multiple genes, including certain HLA genotypes, known to influence the risk of diabetes. The increase of incidence of type 1 diabetes reflects the modern lifestyle.[33] In genetically susceptible people, the onset of diabetes can be triggered by one or more environmental factors,[34] such as a viral infection or diet. Several viruses have been implicated, but to date there is no stringent evidence to support this hypothesis in humans.[34][35] Among dietary factors, data suggest that gliadin (a protein present in gluten) may play a role in the development of type 1 diabetes, but the mechanism is not fully understood.[36][37]

## Type 2

*Main article: Diabetes mellitus type 2*

Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion.[5] The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 DM is the most common type of diabetes mellitus.

In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, high blood sugar can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce the liver's glucose production.

Type 2 DM is due primarily to lifestyle factors and genetics.[38] A number of lifestyle factors are known to be important to the development of type 2 DM, including obesity (defined by a body mass index of greater than 30), lack of physical activity, poor diet, stress, and urbanization.[12] Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60–80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders.[5] Even those who are not obese often have a high waist–hip ratio.[5]

Dietary factors also influence the risk of developing type 2 DM. Consumption of sugar-sweetened drinks in excess is associated with an increased risk.[39][40] The type of fats in the diet is also important, with saturated fats and trans fatty acids increasing the risk and polyunsaturated and monounsaturated fat decreasing the risk.[38] Eating lots of white rice also may increase the risk of diabetes.[41] A lack of exercise is believed to cause 7% of cases.[42]

## Gestational diabetes

*Main article: Gestational diabetes*

Gestational diabetes mellitus (GDM) resembles type 2 DM in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2–10% of all pregnancies and may improve or disappear after delivery.[43] However, after pregnancy approximately 5–10% of women with gestational diabetes are found to have diabetes mellitus, most commonly type 2.[43] Gestational diabetes is fully treatable, but requires careful medical supervision throughout the pregnancy. Management may include dietary changes, blood glucose monitoring, and in some cases, insulin may be required.

Though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital heart and central nervous system abnormalities, and skeletal muscle malformations. Increased levels of insulin in a fetus's blood may inhibit fetal surfactant production and cause respiratory distress syndrome. A high blood bilirubin level may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A Caesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.[*citation needed*]

## Other types

Prediabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 DM. Many people destined to develop type 2 DM spend many years in a state of prediabetes.

Latent autoimmune diabetes of adults (LADA) is a condition in which type 1 DM develops in adults. Adults with LADA are frequently initially misdiagnosed as having type 2 DM, based on age rather than etiology.

Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. The ICD-10 (1992) diagnostic entity, *malnutrition-related diabetes*

*mellitus* (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization when the current taxonomy was introduced in 1999.[44]

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

"Type 3 diabetes" has been suggested as a term for Alzheimer's disease as the underlying processes may involve insulin resistance by the brain.[45]

The following is a comprehensive list of other causes of diabetes:[46]

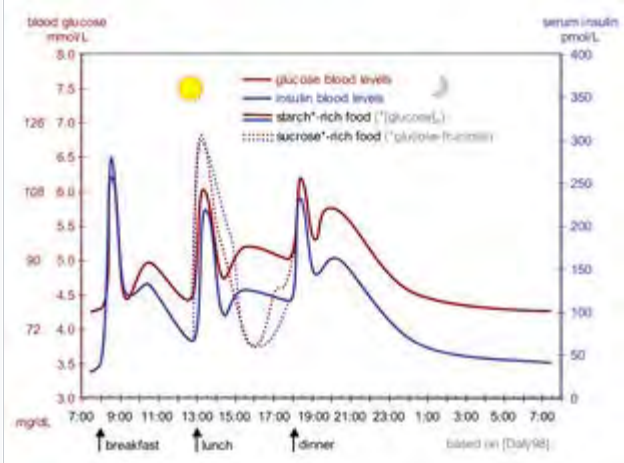
- Genetic defects of β-cell function
  - Maturity onset diabetes of the young
  - Mitochondrial DNA mutations
- Genetic defects in insulin processing or insulin action
  - Defects in proinsulin conversion
  - Insulin gene mutations
  - Insulin receptor mutations
- Exocrine pancreatic defects
  - Chronic pancreatitis
  - Pancreatectomy
  - Pancreatic neoplasia
  - Cystic fibrosis
  - Hemochromatosis
  - Fibrocalculous pancreatopathy
- Endocrinopathies
  - Growth hormone excess (acromegaly)
  - Cushing syndrome
  - Hyperthyroidism
  - Pheochromocytoma
  - Glucagonoma
- Infections
  - Cytomegalovirus infection
  - Coxsackievirus B
- Drugs
  - Glucocorticoids
  - Thyroid hormone
  - β-adrenergic agonists
  - Statins[47]

# Pathophysiology

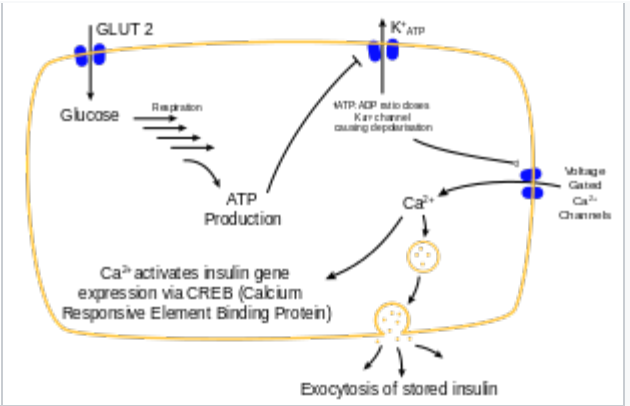
Insulin is the principal hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, adipose tissue and muscle, except smooth muscle, in which insulin acts via the IGF-1. Therefore, deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus.[48]

The body obtains glucose from three main places: the intestinal absorption of food, the breakdown of glycogen, the storage form of glucose found in the liver, and gluconeogenesis, the generation of glucose from non-carbohydrate substrates in the body.[49] Insulin plays a critical role in balancing glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen.[49]

Insulin is released into the blood by beta cells (β-cells), found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Lower glucose levels result in decreased insulin release from the beta cells and in the breakdown of glycogen to glucose. This process is mainly controlled by the hormone glucagon,




The fluctuation of blood sugar (red) and the sugar-lowering hormone insulin (blue) in humans during the course of a day with three meals — one of the effects of a sugar-rich vs a starch-rich meal is highlighted.




Mechanism of insulin release in normal pancreatic beta cells — insulin production is more or less constant within the beta cells. Its release is triggered by food, chiefly food containing absorbable glucose.

which acts in the opposite manner to insulin.[50]

If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or insulin resistance), or if the insulin itself is defective, then glucose will not be absorbed properly by the body cells that require it, and it will not be stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis.[49]

When the glucose concentration in the blood remains high over time, the kidneys will reach a threshold of reabsorption, and glucose will be excreted in the urine (glycosuria).[51] This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst (polydipsia).[49]

## Diagnosis

*See also: Glycated hemoglobin and Glucose tolerance test*

**WHO diabetes diagnostic criteria**[52][53] edit

| Condition | 2 hour glucose | Fasting glucose | $HbA_{1c}$ | |
|---|---|---|---|---|
| Unit | mmol/l(mg/dl) | mmol/l(mg/dl) | mmol/mol | DCCT % |
| Normal | <7.8 (<140) | <6.1 (<110) | <42 | <6.0 |
| Impaired fasting glycaemia | <7.8 (<140) | ≥6.1(≥110) & <7.0(<126) | 42-46 | 6.0–6.4 |
| Impaired glucose tolerance | ≥7.8 (≥140) | <7.0 (<126) | 42-46 | 6.0–6.4 |
| **Diabetes mellitus** | ≥11.1 (≥200) | ≥7.0 (≥126) | ≥48 | ≥6.5 |

Diabetes mellitus is characterized by recurrent or persistent high blood sugar, and is diagnosed by demonstrating any one of the following:[44]

- Fasting plasma glucose level ≥ 7.0 mmol/l (126 mg/dl)
- Plasma glucose ≥ 11.1 mmol/l (200 mg/dl) two hours after a 75 g oral glucose load as in a glucose tolerance test
- Symptoms of high blood sugar and casual plasma glucose ≥ 11.1 mmol/l (200 mg/dl)
- Glycated hemoglobin ($HbA_{1C}$) ≥ 48 mmol/mol (≥ 6.5 DCCT %).[54]

A positive result, in the absence of unequivocal high blood sugar, should be confirmed by a repeat of any of the above methods on a different day. It is preferable to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test.[55] According to the current definition, two fasting glucose measurements above 126 mg/dl (7.0 mmol/l) is considered diagnostic for diabetes mellitus.

Per the World Health Organization people with fasting glucose levels from 6.1 to 6.9 mmol/l (110 to 125 mg/dl) are considered to have impaired fasting glucose.[56] people with plasma glucose at or above

7.8 mmol/l (140 mg/dl), but not over 11.1 mmol/l (200 mg/dl), two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance. Of these two prediabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus, as well as cardiovascular disease.[57] The American Diabetes Association since 2003 uses a slightly different range for impaired fasting glucose of 5.6 to 6.9 mmol/l (100 to 125 mg/dl).[58]

Glycated hemoglobin is better than fasting glucose for determining risks of cardiovascular disease and death from any cause.[59]

The rare disease diabetes insipidus has similar symptoms to diabetes mellitus, but without disturbances in the sugar metabolism (*insipidus* means "without taste" in Latin) and does not involve the same disease mechanisms. Diabetes is a part of the wider condition known as metabolic syndrome.

# Prevention

*See also: Prevention of diabetes mellitus type 2*

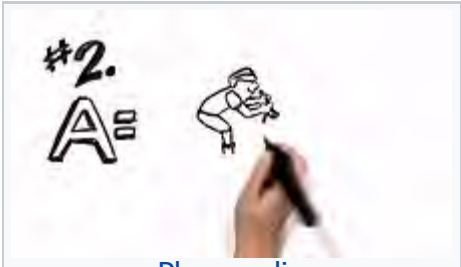
There is no known preventive measure for type 1 diabetes.[3] Type 2 diabetes — which accounts for 85-90% of all cases — can often be prevented or delayed by maintaining a normal body weight, engaging in physical exercise, and consuming a healthful diet.[3] Higher levels of physical activity (more than 90 minutes per day) reduce the risk of diabetes by 28%.[60] Dietary changes known to be effective in helping to prevent diabetes include maintaining a diet rich in whole grains and fiber, and choosing good fats, such as the polyunsaturated fats found in nuts, vegetable oils, and fish.[61] Limiting sugary beverages and eating less red meat and other sources of saturated fat can also help prevent diabetes.[61] Tobacco smoking is also associated with an increased risk of diabetes and its complications, so smoking cessation can be an important preventive measure as well.[62]

The relationship between type 2 diabetes and the main modifiable risk factors (excess weight, unhealthy diet, physical inactivity and tobacco use) is similar in all regions of the world. There is growing evidence that the underlying determinants of diabetes are a reflection of the major forces driving social, economic and cultural change: globalization, urbanization, population aging, and the general health policy environment.[63]

# Management

*Main article: Diabetes management*

Diabetes mellitus is a chronic disease, for which there is no known cure except in very specific situations.[64] Management concentrates on keeping blood sugar levels as close to normal, without causing low blood sugar. This can usually be accomplished with a healthy diet, exercise, weight loss, and use of appropriate medications (insulin in the case of type 1 diabetes; oral medications, as well as possibly insulin, in type 2 diabetes).



Play media
Overview of management

Learning about the disease and actively participating in the treatment is important, since complications are far less common and less severe in people who have well-managed blood sugar levels.[65][66] The goal of treatment is an $HbA_{1C}$ level of 6.5%, but should not be lower than that, and may be set higher.[67] Attention is also paid to other health problems that may accelerate the negative effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise.[67] Specialized footwear is widely used to reduce the risk of ulceration, or re-ulceration, in at-risk diabetic feet. Evidence for the efficacy of this remains equivocal, however.[68]

## Lifestyle

*See also: Diabetic diet*

People with diabetes can benefit from education about the disease and treatment, good nutrition to achieve a normal body weight, and exercise, with the goal of keeping both short-term and long-term blood glucose levels within acceptable bounds. In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications are recommended to control blood pressure.[69]

## Medications

*See also: Anti-diabetic medication*

Medications used to treat diabetes do so by lowering blood sugar levels. There are a number of different classes of anti-diabetic medications. Some are available by mouth, such as metformin, while others are only available by injection such as GLP-1 agonists. Type 1 diabetes can only be treated with insulin, typically with a combination of regular and NPH insulin, or synthetic insulin analogs.[*citation needed*]

Metformin is generally recommended as a first line treatment for type 2 diabetes, as there is good evidence that it decreases mortality.[70] It works by decreasing the liver's production of glucose.[71] Several other groups of drugs, mostly given by mouth, may also decrease blood sugar in type II DM. These include agents that increase insulin release, agents that decrease absorption of sugar from the intestines, and agents that make the body more sensitive to insulin.[71] When insulin is used in type 2 diabetes, a long-acting formulation is usually added initially, while continuing oral medications.[70] Doses of insulin are then increased to effect.[70][72]

Since cardiovascular disease is a serious complication associated with diabetes, some have recommended blood pressure levels below 130/80 mmHg.[73] However, evidence supports less than or equal to somewhere between 140/90 mmHg to 160/100 mmHg; the only additional benefit found for blood pressure targets beneath this range was an isolated decrease in stroke risk, and this was accompanied by an increased risk of other serious adverse events.[74][75] A 2016 review found potential harm to treating lower than 140 mmHg.[76] Among medications that lower blood pressure, angiotensin converting enzyme inhibitors (ACEIs) improve outcomes in those with DM while the similar medications angiotensin receptor blockers (ARBs) do not.[77] Aspirin is also recommended for people with cardiovascular problems, however routine use of aspirin has not been found to improve outcomes in uncomplicated diabetes.[78]

## Surgery

A pancreas transplant is occasionally considered for people with type 1 diabetes who have severe complications of their disease, including end stage kidney disease requiring kidney transplantation.[79]

Weight loss surgery in those with obesity and type two diabetes is often an effective measure.[80] Many are able to maintain normal blood sugar levels with little or no medications following surgery[81] and long-term mortality is decreased.[82] There however is some short-term mortality risk of less than 1% from the surgery.[83] The body mass index cutoffs for when surgery is appropriate are not yet clear.[82] It is recommended that this option be considered in those who are unable to get both their weight and blood sugar under control.[84]

## Support

In countries using a general practitioner system, such as the United Kingdom, care may take place mainly outside hospitals, with hospital-based specialist care used only in case of complications, difficult blood sugar control, or research projects. In other circumstances, general practitioners and specialists share care in a team approach. Home telehealth support can be an effective management technique.[85]

# Epidemiology

*Main article: Epidemiology of diabetes mellitus*

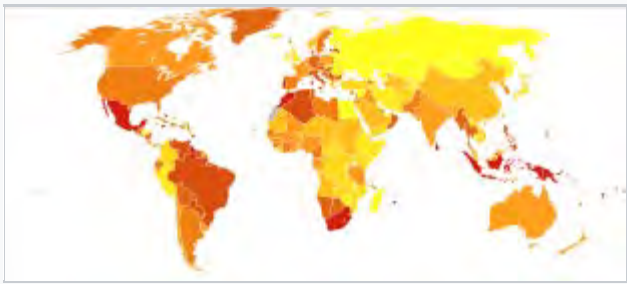
As of 2016, 422 million people have diabetes worldwide,[86] up from an estimated 382 million people in 2013[13] and from 108 million in 1980.[86] Accounting for the shifting age structure of the global population, the prevalence of diabetes is 8.5% among adults, nearly double the rate of 4.7% in 1980.[86] Type 2 makes up about 90% of the cases.[12][14] Some data indicate rates are roughly equal in women and men,[14] but male excess in diabetes has been found in many populations with higher type 2 incidence, possibly due to sex-related differences in insulin sensitivity, consequences of obesity and regional body fat deposition, and other contributing factors such as high blood pressure, tobacco smoking, and alcohol intake.[87][88]

The World Health Organization (WHO) estimates that diabetes mellitus resulted in 1.5 million deaths in 2012, making it the 8th leading cause of death.[7][86] However another 2.2 million deaths worldwide were attributable to high blood glucose and the increased risks of cardiovascular disease and other associated complications (e.g. kidney failure), which often lead to premature death and are often listed as the underlying cause on death certificates rather than diabetes.[86][89] For example, in 2014, the International Diabetes Federation (IDF) estimated that diabetes resulted in 4.9 million deaths worldwide,[15] using modeling to estimate the total amount of deaths that could be directly or indirectly attributed to diabetes.[16]

Diabetes mellitus occurs throughout the world but is more common (especially type 2) in more developed countries. The greatest increase in rates has however been seen in low- and middle-income countries,[86] where more than 80% of diabetic deaths occur.[90] The fastest prevalence increase is expected to occur in Asia and Africa, where most people with diabetes will probably live in 2030.[91] The increase in rates in developing countries follows the trend of urbanization and lifestyle changes, including increasingly sedentary lifestyles, less physically demanding work and the global nutrition transition, marked by increased intake of foods that are high energy-dense but nutrient-poor (often high in sugar and saturated fats, sometimes referred to as the "Western-style" diet).[86][91]

Rates of diabetes worldwide in 2000 (per 1,000 inhabitants) — world average was 2.8%.

| | |
|---|---|
| no data | 45–52.5 |
| ≤ 7.5 | 52.5–60 |
| 7.5–15 | 60–67.5 |
| 15–22.5 | 67.5–75 |
| 22.5–30 | 75–82.5 |
| 30–37.5 | ≥ 82.5 |
| 37.5–45 | |



Diabetes mellitus deaths per million persons in 2012

| | | |
|---|---|---|
| 28-91 | 142-163 | 210-247 |
| 92-114 | 164-184 | 248-309 |
| 115-141 | 185-209 | 310-404 |
| | | 405-1879 |

# History

*Main article: History of diabetes*

Diabetes was one of the first diseases described,[92] with an Egyptian manuscript from c. 1500 BCE mentioning "too great emptying of the urine".[93] The Ebers papyrus includes a recommendation for a drink to be taken in such cases.[94] The first described cases are believed to be of type 1 diabetes.[93] Indian physicians around the same time identified the disease and classified it as *madhumeha* or "honey urine", noting the urine would attract ants.[93][94]

The term "diabetes" or "to pass through" was first used in 230 BCE by the Greek Apollonius of Memphis.[93] The disease was considered rare during the time of the Roman empire, with Galen commenting he had only seen two cases during his career.[93] This is possibly due to the diet and lifestyle of the ancients, or because the clinical symptoms were observed during the advanced stage of the disease. Galen named the disease "diarrhea of the urine" (diarrhea urinosa).[95]

The earliest surviving work with a detailed reference to diabetes is that of Aretaeus of Cappadocia (2nd or early 3rd century CE). He described the symptoms and the course of the disease, which he attributed to the moisture and coldness, reflecting the beliefs of the "Pneumatic School". He hypothesized a correlation of diabetes with other diseases and he discussed differential diagnosis from the snakebite which also provokes excessive thirst. His work remained unknown in the West until 1552, when the first Latin edition was published in Venice.[95]

Type 1 and type 2 diabetes were identified as separate conditions for the first time by the Indian physicians Sushruta and Charaka in 400-500 CE with type 1 associated with youth and type 2 with being overweight.[93] The term "mellitus" or "from honey" was added by the Briton John Rolle in the late 1700s to separate the condition from diabetes insipidus, which is also associated with frequent urination.[93] Effective treatment was not developed until the early part of the 20th century, when Canadians Frederick Banting and Charles Herbert Best isolated and purified insulin in 1921 and 1922.[93] This was followed by the development of the long-acting insulin NPH in the 1940s.[93]

### Etymology

The word *diabetes* (/ˌdaɪ.əˈbiːtiːz/ or /ˌdaɪ.əˈbiːtɪs/) comes from Latin *diabētēs*, which in turn comes from Ancient Greek διαβήτης (*diabētēs*) which literally means "a passer through; a siphon."[96] Ancient Greek physician Aretaeus of Cappadocia (fl. 1st century CE) used that word, with the intended meaning "excessive discharge of urine", as the name for the disease.[97][98] Ultimately, the word comes from Greek διαβαίνειν (*diabainein*), meaning "to pass through,"[96] which is composed of δια- (*dia-*), meaning "through" and βαίνειν (*bainein*), meaning "to go".[97] The word "diabetes" is first recorded in English, in the form *diabete*, in a medical text written around 1425.

The word *mellitus* (/mɪˈlaɪtəs/ or /ˈmɛlɪtəs/) comes from the classical Latin word *mellītus*, meaning "mellite"[99] (i.e. sweetened with honey;[99] honey-sweet[100]). The Latin word comes from *mell-*, which comes from *mel*, meaning "honey";[99][100] sweetness;[100] pleasant thing,[100] and the suffix *-ītus*,[99] whose meaning is the same as that of the English suffix "-ite".[101] It was Thomas Willis who in 1675 added "mellitus" to the word "diabetes" as a designation for the disease, when he noticed the urine of a diabetic had a sweet taste (glycosuria). This sweet taste had been noticed in urine by the ancient Greeks, Chinese, Egyptians, Indians, and Persians.

## Society and culture

*Further information: List of films featuring diabetes*

The 1989 "St. Vincent Declaration"[102][103] was the result of international efforts to improve the care accorded to those with diabetes. Doing so is important not only in terms of quality of life and life expectancy but also economically—expenses due to diabetes have been shown to be a major drain on health—and productivity-related resources for healthcare systems and governments.

Several countries established more and less successful national diabetes programmes to improve treatment of the disease.[104]

People with diabetes who have neuropathic symptoms such as numbness or tingling in feet or hands are twice as likely to be unemployed as those without the symptoms.[105]

In 2010, diabetes-related emergency room (ER) visit rates in the United States were higher among people from the lowest income communities (526 per 10,000 population) than from the highest income

communities (236 per 10,000 population). Approximately 9.4% of diabetes-related ER visits were for the uninsured.[106]

### Naming

The term "type 1 diabetes" has replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes mellitus (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and noninsulin-dependent diabetes mellitus (NIDDM). Beyond these two types, there is no agreed-upon standard nomenclature.

Diabetes mellitus is also occasionally known as "sugar diabetes" to differentiate it from diabetes insipidus.[107]

## Other animals

*Main articles: Diabetes in dogs and Diabetes in cats*

In animals, diabetes is most commonly encountered in dogs and cats. Middle-aged animals are most commonly affected. Female dogs are twice as likely to be affected as males, while according to some sources, male cats are also more prone than females. In both species, all breeds may be affected, but some small dog breeds are particularly likely to develop diabetes, such as Miniature Poodles.[108] The symptoms may relate to fluid loss and polyuria, but the course may also be insidious. Diabetic animals are more prone to infections. The long-term complications recognized in humans are much rarer in animals. The principles of treatment (weight loss, oral antidiabetics, subcutaneous insulin) and management of emergencies (e.g. ketoacidosis) are similar to those in humans.[108]

## Research

Inhalable insulin has been developed.[109] The original products were withdrawn due to side effects.[109] Afrezza, under development by pharmaceuticals company MannKind Corporation, was approved by the FDA for general sale in June 2014.[110] An advantage to inhaled insulin is that it may be more convenient and easy to use.[111]

Transdermal insulin in the form of a cream has been developed and trials are being conducted on people with type 2 diabetes.[112][113]

## References


1. ^ "Diabetes Blue Circle Symbol". International Diabetes Federation. 17 March 2006.
2. ^ "About diabetes". World Health Organization. Archived from the original on 31 March 2014. Retrieved 4 April 2014.
3. ^ *a b c d e f g h i j* "Diabetes Fact sheet N°312". *WHO*. October 2013. Archived from the original on 26 Aug 2013. Retrieved 25 March 2014.
4. ^ Kitabchi, AE; Umpierrez, GE; Miles, JM; Fisher, JN (Jul 2009). "Hyperglycemic crises in adult patients with diabetes.". *Diabetes Care*. **32** (7): 1335–43. doi:10.2337/dc09-9032. PMC 2699725. PMID 19564476.
5. ^ *a b c d e f* Shoback, edited by David G. Gardner, Dolores (2011). "Chapter 17". *Greenspan's basic & clinical endocrinology* (9th ed.). New York: McGraw-Hill Medical. ISBN 0-07-162243-8.
6. ^ *RSSDI textbook of diabetes mellitus.* (Rev. 2nd ed.). New Delhi: Jaypee Brothers Medical Publishers. 2012. p. 235. ISBN 9789350254899.
7. ^ *a b c* "The top 10 causes of death Fact sheet N°310". *World Health Organization*. Oct 2013.
8. ^ Rippe, edited by Richard S. Irwin, James M. (2010). *Manual of intensive care medicine* (5th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 549. ISBN 9780781799928.
9. ^ Picot, J; Jones, J; Colquitt, JL; Gospodarevskaya, E; Loveman, E; Baxter, L; Clegg, AJ (September 2009). "The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and

economic evaluation". *Health Technology Assessment (Winchester, England)*. **13** (41): 1–190, 215–357, iii–iv. doi:10.3310/hta13410. PMID 19726018.

10. ^ Cash, Jill (2014). *Family Practice Guidelines* (3rd ed.). Springer. p. 396. ISBN 9780826168757.
11. ^ *a b* "Update 2015". *IDF*. International Diabetes Federation. p. 13. Retrieved 21 Mar 2016.
12. ^ *a b c d* *Williams textbook of endocrinology* (12th ed.). Philadelphia: Elsevier/Saunders. pp. 1371–1435. ISBN 978-1-4377-0324-5.
13. ^ *a b c* Shi, Yuankai; Hu, Frank B (7 June 2014). "The global implications of diabetes and cancer". *The Lancet*. **383** (9933): 1947–8. doi:10.1016/S0140-6736(14)60886-2. PMID 24910221.
14. ^ *a b c* Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, et al. (Dec 15, 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010.". *Lancet*. **380** (9859): 2163–96. doi:10.1016/S0140-6736(12)61729-2. PMID 23245607.
15. ^ *a b* "Annual Report 2014" (PDF). *IDF*. International Diabetes Federation. Retrieved 13 July 2016.
16. ^ *a b* *IDF DIABETES ATLAS* (PDF) (6th ed.). International Diabetes Federation. 2013. p. 7. ISBN 2930229853.
17. ^ American Diabetes, Association (Apr 2013). "Economic costs of diabetes in the U.S. in 2012.". *Diabetes Care*. **36** (4): 1033–46. doi:10.2337/dc12-2625. PMC 3609540. PMID 23468086.
18. ^ Cooke DW, Plotnick L (November 2008). "Type 1 diabetes mellitus in pediatrics". *Pediatr Rev*. **29** (11): 374–84; quiz 385. doi:10.1542/pir.29-11-374. PMID 18977856.
19. ^ Kenny C (April 2014). "When hypoglycemia is not obvious: diagnosing and treating under-recognized and undisclosed hypoglycemia". *Primary care diabetes*. **8** (1): 3–11. doi:10.1016/j.pcd.2013.09.002. PMID 24100231.
20. ^ Verrotti A, Scaparrotta A, Olivieri C, Chiarelli F (December 2012). "Seizures and type 1 diabetes mellitus: current state of knowledge". *European Journal of Endocrinology*. **167** (6): 749–58. doi:10.1530/EJE-12-0699. PMID 22956556. Archived from the original on 2014-11-07.
21. ^ Hsieh, Arthur. "Drunk versus diabetes: How can you tell?". Retrieved 29 June 2016.
22. ^ "Symptoms of Low Blood Sugar". *WebMD*. Retrieved 29 June 2016.
23. ^ *a b* Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN (July 2009). "Hyperglycemic crises in adult patients with diabetes". *Diabetes Care*. **32** (7): 1335–43. doi:10.2337/dc09-9032. PMC 2699725. PMID 19564476.
24. ^ Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J (2010). "Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies". *The Lancet*. **375** (9733): 2215–22. doi:10.1016/S0140-6736(10)60484-9. PMC 2904878. PMID 20609967.
25. ^ O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW (29 January 2013). "2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.". *Circulation*. **127** (4): e362–425. doi:10.1161/CIR.0b013e3182742cf6. PMID 23247304.
26. ^ *a b c d* "Diabetes Programme". World Health Organization. Retrieved 22 April 2014.
27. ^ Cukierman, T (8 Nov 2005). "Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies". Springer-Verlag. Retrieved 28 Apr 2013.
28. ^ Lambert P, Bingley PJ (2002). "What is Type 1 Diabetes?". *Medicine*. **30**: 1–5. doi:10.1383/medc.30.1.1.28264.
29. ^ Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L (2014). "The many faces of diabetes: a disease with increasing heterogeneity". *Lancet*. **383** (9922): 1084–94. doi:10.1016/S0140-6736(13)62219-9. PMID 24315621.
30. ^ Rother KI (April 2007). "Diabetes treatment—bridging the divide". *The New England Journal of Medicine*. **356** (15): 1499–501. doi:10.1056/NEJMp078030. PMC 4152979. PMID 17429082.
31. ^ *a b* "Diabetes Mellitus (DM): Diabetes Mellitus and Disorders of Carbohydrate Metabolism: Merck Manual Professional". Merck Publishing. April 2010. Retrieved 2010-07-30.
32. ^ Dorner M, Pinget M, Brogard JM (May 1977). "Essential labile diabetes". *MMW Munch Med Wochenschr* (in German). **119** (19): 671–4. PMID 406527.
33. ^ Phillips JE, Couper JJ, Penno MA, Harrison LC, ENDIA Study Group (2016). "Type 1 diabetes: a disease of developmental origins.". *Pediatr Diabetes* (Review). doi:10.1111/pedi.12425. PMID 27526948.
34. ^ *a b* Petzold A, Solimena M, Knoch KP (2015). "Mechanisms of Beta Cell Dysfunction Associated With Viral Infection.". *Curr Diab Rep* (Review). **15** (10): 73. doi:10.1007/s11892-015-0654-x. PMC 4539350.

PMID 26280364. "So far, none of the hypotheses accounting for virus-induced beta cell autoimmunity has been supported by stringent evidence in humans, and the involvement of several mechanisms rather than just one is also plausible."

35. ^ Butalia S, Kaplan GG, Khokhar B, Rabi DM (Aug 18, 2016). "Environmental Risk Factors and Type 1 Diabetes: Past, Present, and Future". *Can J Diabetes* (Review). pii: S1499-2671(15)30052–6. doi:10.1016/j.jcjd.2016.05.002. PMID 27545597.
36. ^ Serena G, Camhi S, Sturgeon C, Yan S, Fasano A (2015). "The Role of Gluten in Celiac Disease and Type 1 Diabetes.". *Nutrients*. **7** (9): 7143–62. doi:10.3390/nu7095329. PMC 4586524. PMID 26343710.
37. ^ Visser J, Rozing J, Sapone A, Lammers K, Fasano A (2009). "Tight junctions, intestinal permeability, and autoimmunity: celiac disease and type 1 diabetes paradigms.". *Ann N Y Acad Sci*. **1165**: 195–205. doi:10.1111/j.1749-6632.2009.04037.x. PMC 2886850. PMID 19538307.
38. ^ *a b* Risérus U, Willett WC, Hu FB (January 2009). "Dietary fats and prevention of type 2 diabetes". *Progress in Lipid Research*. **48** (1): 44–51. doi:10.1016/j.plipres.2008.10.002. PMC 2654180. PMID 19032965.
39. ^ Malik VS, Popkin BM, Bray GA, Després JP, Hu FB (2010-03-23). "Sugar Sweetened Beverages, Obesity, Type 2 Diabetes and Cardiovascular Disease risk". *Circulation*. **121** (11): 1356–64. doi:10.1161/CIRCULATIONAHA.109.876185. PMC 2862465. PMID 20308626.
40. ^ Malik VS, Popkin BM, Bray GA, Després JP, Willett WC, Hu FB (November 2010). "Sugar-Sweetened Beverages and Risk of Metabolic Syndrome and Type 2 Diabetes: A meta-analysis". *Diabetes Care*. **33** (11): 2477–83. doi:10.2337/dc10-1079. PMC 2963518. PMID 20693348.
41. ^ Hu EA, Pan A, Malik V, Sun Q (2012-03-15). "White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review". *BMJ (Clinical research ed.)*. **344**: e1454. doi:10.1136/bmj.e1454. PMC 3307808. PMID 22422870.
42. ^ Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT (1 July 2012). "Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy". *The Lancet*. **380** (9838): 219–29. doi:10.1016/S0140-6736(12)61031-9. PMC 3645500. PMID 22818936.
43. ^ *a b* "National Diabetes Clearinghouse (NDIC): National Diabetes Statistics 2011". U.S. Department of Health and Human Services. Retrieved 22 April 2014.
44. ^ *a b* "Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications" (PDF). World Health Organisation. 1999.
45. ^ de la Monte, SM (December 2014). "Type 3 diabetes is sporadic Alzheimer's disease: mini-review.". *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. **24** (12): 1954–60. doi:10.1016/j.euroneuro.2014.06.008. PMC 4444430. PMID 25088942.
46. ^ Unless otherwise specified, reference is: Table 20-5 in Mitchell, Richard Sheppard; Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson. *Robbins Basic Pathology* (8th ed.). Philadelphia: Saunders. ISBN 1-4160-2973-7.
47. ^ Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I (February 2010). "Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials". *The Lancet*. **375** (9716): 735–42. doi:10.1016/S0140-6736(09)61965-6. PMID 20167359.
48. ^ "Insulin Basics". American Diabetes Association. Retrieved 24 April 2014.
49. ^ *a b c d* Shoback, edited by David G. Gardner, Dolores (2011). *Greenspan's basic & clinical endocrinology* (9th ed.). New York: McGraw-Hill Medical. ISBN 9780071622431.
50. ^ al.], Kim E. Barrett, ... [et (2012). *Ganong's review of medical physiology.* (24th ed.). New York: McGraw-Hill Medical. ISBN 0071780033.
51. ^ al.], Robert K. Murray ... [et (2012). *Harper's illustrated biochemistry* (29th ed.). New York: McGraw-Hill Medical. ISBN 007176576X.
52. ^ *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation* (PDF). Geneva: World Health Organization. 2006. p. 21. ISBN 978-92-4-159493-6.
53. ^ Vijan, S (March 2010). "Type 2 diabetes". *Annals of Internal Medicine*. **152** (5): ITC31-15. doi:10.7326/0003-4819-152-5-201003020-01003. PMID 20194231.
54. ^ " "Diabetes Care" January 2010". *American Diabetes Association*. Retrieved 2010-01-29.
55. ^ Saydah SH, Miret M, Sung J, Varas C, Gause D, Brancati FL (August 2001). "Postchallenge hyperglycemia and mortality in a national sample of U.S. adults". *Diabetes Care*. **24** (8): 1397–402. doi:10.2337/diacare.24.8.1397. PMID 11473076.
56. ^ *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia : report of a WHO/IDF consultation* (PDF). World Health Organization. 2006. p. 21. ISBN 978-92-4-159493-6.
57. ^ Santaguida PL, Balion C, Hunt D, Morrison K, Gerstein H, Raina P, Booker L, Yazdi H. "Diagnosis, Prognosis, and

Treatment of Impaired Glucose Tolerance and Impaired Fasting Glucose". *Summary of Evidence Report/Technology Assessment, No. 128*. Agency for Healthcare Research and Quality. Retrieved 2008-07-20.
58. ^ Bartoli E, Fra GP, Carnevale Schianca GP (Feb 2011). "The oral glucose tolerance test (OGTT) revisited.". *European journal of internal medicine*. **22** (1): 8–12. doi:10.1016/j.ejim.2010.07.008. PMID 21238885.
59. ^ Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL (2010). "Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults". *N. Engl. J. Med.* **362** (9): 800–11. doi:10.1056/NEJMoa0908359. PMC 2872990. PMID 20200384.
60. ^ Kyu, Hmwe H; Bachman, Victoria F; Alexander, Lily T; Mumford, John Everett; Afshin, Ashkan; Estep, Kara; Veerman, J Lennert; Delwiche, Kristen; Iannarone, Marissa L; Moyer, Madeline L; Cercy, Kelly; Vos, Theo; Murray, Christopher J L; Forouzanfar, Mohammad H (9 August 2016). "Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013". *BMJ*: i3857. doi:10.1136/bmj.i3857.
61. ^ *a b* "The Nutrition Source". Harvard School of Public Health. Retrieved 24 April 2014.
62. ^ Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J (Dec 12, 2007). "Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis.". *JAMA: The Journal of the American Medical Association*. **298** (22): 2654–64. doi:10.1001/jama.298.22.2654. PMID 18073361.
63. ^ World Health Organization, *Chronic diseases and their common risk factors.* Geneva, 2005. Accessed 30 August 2016.
64. ^ No cure for diabetes (Retrieved May 2015, WebMD website)
65. ^ Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B (December 2005). "Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes". *The New England Journal of Medicine*. **353** (25): 2643–53. doi:10.1056/NEJMoa052187. PMC 2637991. PMID 16371630.
66. ^ The Diabetes Control; Complications Trial Research Group (April 1995). "The effect of intensive diabetes therapy on the development and progression of neuropathy.". *Annals of Internal Medicine*. **122** (8): 561–8. doi:10.1059/0003-4819-122-8-199504150-00001. PMID 7887548.
67. ^ *a b* National Institute for Health and Clinical Excellence. *Clinical guideline 66: Type 2 diabetes*. London, 2008.
68. ^ Cavanagh PR (2004). "Therapeutic footwear for people with diabetes". *Diabetes Metab. Res. Rev*. **20** (Suppl 1): S51–5. doi:10.1002/dmrr.435. PMID 15150815.
69. ^ Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR (August 2000). "Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study". *BMJ*. **321** (7258): 412–9. doi:10.1136/bmj.321.7258.412. PMC 27455. PMID 10938049.
70. ^ *a b c* Ripsin CM, Kang H, Urban RJ (2009). "Management of blood glucose in type 2 diabetes mellitus" (PDF). *American family physician*. **79** (1): 29–36. PMID 19145963.
71. ^ *a b* Krentz, AJ; Bailey, CJ (2005). "Oral antidiabetic agents: current role in type 2 diabetes mellitus.". *Drugs*. **65** (3): 385–411. doi:10.2165/00003495-200565030-00005. PMID 15669880.
72. ^ Consumer Reports; American College of Physicians (April 2012), "Choosing a type 2 diabetes drug - Why the best first choice is often the oldest drug" (PDF), *High Value Care*, Consumer Reports, retrieved August 14, 2012
73. ^ Nelson, Mark. "Drug treatment of elevated blood pressure". *Australian Prescriber* (33): 108–112. Retrieved 11 August 2010.
74. ^ Arguedas, JA; Perez, MI; Wright, JM (Jul 8, 2009). Arguedas, Jose Agustin, ed. "Treatment blood pressure targets for hypertension". *Cochrane Database of Systematic Reviews* (3): CD004349. doi:10.1002/14651858.CD004349.pub2. PMID 19588353.
75. ^ Arguedas, JA; Leiva, V; Wright, JM (Oct 30, 2013). "Blood pressure targets for hypertension in people with diabetes mellitus.". *The Cochrane database of systematic reviews*. **10**: CD008277. doi:10.1002/14651858.cd008277.pub2. PMID 24170669.
76. ^ Brunström, Mattias; Carlberg, Bo (24 February 2016). "Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses". *BMJ*: i717. doi:10.1136/bmj.i717.
77. ^ Cheng J, Zhang W, Zhang X, Han F, Li X, He X, Li Q, Chen J (Mar 31, 2014). "Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on All-Cause Mortality, Cardiovascular Deaths, and Cardiovascular Events in Patients With Diabetes Mellitus: A Meta-analysis.". *JAMA internal medicine*. **174** (5): 773–85. doi:10.1001/jamainternmed.2014.348. PMID 24687000.
78. ^ Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, Rosenson RS, Williams CD, Wilson PW, Kirkman MS (June 2010). "Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation". *Diabetes Care*. **33** (6): 1395–402. doi:10.2337/dc10-0555. PMC 2875463. PMID 20508233.

79. ^ "Pancreas Transplantation". American Diabetes Association. Retrieved 9 April 2014.
80. ^ Picot, J; Jones, J; Colquitt, JL; Gospodarevskaya, E; Loveman, E; Baxter, L; Clegg, AJ (September 2009). "The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation". *Health technology assessment (Winchester, England)*. **13** (41): 1–190, 215–357, iii–iv. doi:10.3310/hta13410. PMID 19726018.
81. ^ Frachetti, KJ; Goldfine, AB (April 2009). "Bariatric surgery for diabetes management". *Current Opinion in Endocrinology, Diabetes and Obesity*. **16** (2): 119–24. doi:10.1097/MED.0b013e32832912e7. PMID 19276974.
82. ^ *a b* Schulman, AP; del Genio, F; Sinha, N; Rubino, F (September–October 2009). ""Metabolic" surgery for treatment of type 2 diabetes mellitus". *Endocrine Practice*. **15** (6): 624–31. doi:10.4158/EP09170.RAR. PMID 19625245.
83. ^ Colucci, RA (January 2011). "Bariatric surgery in patients with type 2 diabetes: a viable option". *Postgraduate Medicine*. **123** (1): 24–33. doi:10.3810/pgm.2011.01.2242. PMID 21293081.
84. ^ Dixon, JB; le Roux, CW; Rubino, F; Zimmet, P (16 June 2012). "Bariatric surgery for type 2 diabetes". *Lancet*. **379** (9833): 2300–11. doi:10.1016/S0140-6736(12)60401-2. PMID 22683132.
85. ^ Polisena J, Tran K, Cimon K, Hutton B, McGill S, Palmer K (2009). "Home telehealth for diabetes management: a systematic review and meta-analysis". *Diabetes Obes Metab*. **11** (10): 913–30. doi:10.1111/j.1463-1326.2009.01057.x. PMID 19531058.
86. ^ *a b c d e f g* World Health Organization, *Global Report on Diabetes*. Geneva, 2016.
87. ^ Gale EA, Gillespie KM, "Diabetes and gender." *Diabetologia*, 2001; 44(1):3-15.
88. ^ Meisinger C, Thorand B, Schneider A et al., "Sex differences in risk factors for incident type 2 Diabetes Mellitus: The MONICA Augsburg Cohort Study." *JAMA Internal Medicine*, 2002; 162(1):82-89.
89. ^ Public Health Agency of Canada, *Diabetes in Canada: Facts and figures from a public health perspective*. Ottawa, 2011.
90. ^ Mathers CD, Loncar D (November 2006). "Projections of global mortality and burden of disease from 2002 to 2030". *PLoS Med*. **3** (11): e442. doi:10.1371/journal.pmed.0030442. PMC 1664601. PMID 17132052.
91. ^ *a b* Wild S, Roglic G, Green A, Sicree R, King H (2004). "Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030". *Diabetes Care*. **27** (5): 1047–53. doi:10.2337/diacare.27.5.1047. PMID 15111519.
92. ^ Ripoll, Brian C. Leutholtz, Ignacio (2011-04-25). *Exercise and disease management* (2nd ed.). Boca Raton: CRC Press. p. 25. ISBN 978-1-4398-2759-8.
93. ^ *a b c d e f g h i* editor, Leonid Poretsky, (2009). *Principles of diabetes mellitus* (2nd ed.). New York: Springer. p. 3. ISBN 978-0-387-09840-1.
94. ^ *a b* Roberts, Jacob (2015). "Sickening sweet". *Distillations*. **1** (4): 12–15. Retrieved 3 January 2017.
95. ^ *a b* Laios K, Karamanou M, Saridaki Z, Androutsos G (2012). "Aretaeus of Cappadocia and the first description of diabetes" (PDF). *Hormones*. **11** (1): 109–113. PMID 22450352.
96. ^ *a b* Oxford English Dictionary. *diabetes*. Retrieved 2011-06-10.
97. ^ *a b* Harper, Douglas (2001–2010). "Online Etymology Dictionary. *diabetes.*". Retrieved 2011-06-10.
98. ^ Aretaeus, *De causis et signis acutorum morborum (lib. 2)*, Κεφ. β. περὶ Διαβήτεω (Chapter 2, *On Diabetes*, Greek original, on Perseus
99. ^ *a b c d* Oxford English Dictionary. *mellite*. Retrieved 2011-06-10.
100. ^ *a b c d* "MyEtimology. *mellitus.*". Retrieved 2011-06-10.
101. ^ Oxford English Dictionary. *-ite*. Retrieved 2011-06-10.
102. ^ Theodore H. Tulchinsky, Elena A. Varavikova (2008). *The New Public Health, Second Edition*. New York: Academic Press. p. 200. ISBN 0-12-370890-7.
103. ^ Piwernetz K, Home PD, Snorgaard O, Antsiferov M, Staehr-Johansen K, Krans M (May 1993). "Monitoring the targets of the St Vincent Declaration and the implementation of quality management in diabetes care: the DIABCARE initiative. The DIABCARE Monitoring Group of the St Vincent Declaration Steering Committee". *Diabetic Medicine*. **10** (4): 371–7. doi:10.1111/j.1464-5491.1993.tb00083.x. PMID 8508624.
104. ^ Dubois, HFW; Bankauskaite, V (2005). "Type 2 diabetes programmes in Europe" (PDF). *Euro Observer*. **7** (2): 5–6.
105. ^ Stewart WF, Ricci JA, Chee E, Hirsch AG, Brandenburg NA (June 2007). "Lost productive time and costs due to diabetes and diabetic neuropathic pain in the US workforce". *J. Occup. Environ. Med*. **49** (6): 672–9. doi:10.1097/JOM.0b013e318065b83a. PMID 17563611.
106. ^ Washington R.E.; Andrews R.M.; Mutter R.L. (November 2013). "Emergency Department Visits for Adults with Diabetes, 2010". *HCUP Statistical Brief #167*. Rockville MD: Agency for Healthcare Research and Quality.
107. ^ Parker, Katrina (2008). *Living with diabetes*. New York: Facts On File. p. 143. ISBN 9781438121086.
108. ^ *a b* "Diabetes mellitus". *Merck Veterinary Manual, 9th edition (online version)*. 2005. Retrieved 2011-10-23.

109. ^ [a] [b] Maria Rotella C, Pala L, Mannucci E (Summer 2013). "Role of Insulin in the Type 2 Diabetes Therapy: Past, Present and Future.". *International journal of endocrinology and metabolism*. **11** (3): 137–144. doi:10.5812/ijem.7551. PMC 3860110. PMID 24348585.
110. ^ "Press Announcement". FDA. Retrieved 11 February 2016.
111. ^ "Inhaled Insulin Clears Hurdle Toward F.D.A. Approval". *New York Times*. Retrieved 12 April 2014.
112. ^ in-PharmaTechnologist.com. "World's first transdermal insulin shows promise". Retrieved 2016-07-03.
113. ^ "PHOSPHAGENICS INITIATES TRIAL OF TRANSDERMAL INSULIN GEL". *www.fdanews.com*. Retrieved 2016-07-03.


## Further reading


- Polonsky KS (2012). "The Past 200 Years in Diabetes". *New England Journal of Medicine*. **367** (14): 1332–40. doi:10.1056/NEJMra1110560. PMID 23034021.


## External links

- Diabetes mellitus at DMOZ
- IDF Diabetes Atlas
- National Diabetes Education Program

Find more about
**Diabetes mellitus**
at Wikipedia's sister projects

- Definitions from Wiktionary
- Media from Commons
- News from Wikinews
- Quotations from Wikiquote
- Texts from Wikisource
- Textbooks from Wikibooks
- Learning resources from Wikiversity

| v · t · e | Diseases of the endocrine system (E00–E35, 240–259) | | |
|---|---|---|---|
| **Pancreas/ glucose metabolism** | **Hypofunction** | **Diabetes mellitus** · *types:* (type 1 · type 2 · MODY 1 2 3 4 5 6 · · *complications* (coma · angiopathy · ketoacidosis · nephropathy · neuropathy · retinopathy · cardiomyopathy · · *insulin receptor* (Rabson–Mendenhall syndrome) · Insulin resistance · | |
| | **Hyperfunction** | Hypoglycemia · *beta cell* (Hyperinsulinism) · *G cell* (Zollinger–Ellison syndrome) · | |
| | **Hypothalamus** | *gonadotropin* (Kallmann syndrome · Adiposogenital dystrophy · · *CRH* (Tertiary adrenal insufficiency) · *vasopressin* (Neurogenic diabetes insipidus) · *general* (Hypothalamic hamartoma) · | |
| | | **Hyperpituitarism** | *anterior* (Acromegaly · Hyperprolactinaemia · Pituitary ACTH hypersecretion · · *posterior* (SIADH) · *general* (Nelson's syndrome) · |
| | | | *anterior* (Kallmann syndrome · Growth hormone deficiency · Hypoprolactinemia · |

| | | | |
|---|---|---|---|
| **Hypothalamic/ pituitary axes** | **Pituitary** | **Hypopituitarism** | ACTH deficiency/Secondary adrenal insufficiency · GnRH insensitivity · FSH insensitivity · LH/hCG insensitivity · · *posterior* (Neurogenic diabetes insipidus) · *general* (Empty sella syndrome · Pituitary apoplexy · Sheehan's syndrome · Lymphocytic hypophysitis · · |
| | **Thyroid** | **Hypothyroidism** | Iodine deficiency · Cretinism (Congenital hypothyroidism · · Myxedema · Euthyroid sick syndrome · |
| | | **Hyperthyroidism** | Hyperthyroxinemia (Thyroid hormone resistance · Familial dysalbuminemic hyperthyroxinemia · · Hashitoxicosis · Thyrotoxicosis factitia · Graves' disease · |
| | | **Thyroiditis** | Acute infectious · Subacute (De Quervain's · Subacute lymphocytic · · Autoimmune/chronic (Hashimoto's · Postpartum · Riedel's · · |
| | | **Goitre** | Endemic goitre · Toxic nodular goitre · Toxic multinodular goiter · Thyroid nodule · |
| | **Parathyroid** | **Hypoparathyroidism** | Hypoparathyroidism · Pseudohypoparathyroidism · Pseudopseudohypoparathyroidism · |
| | | **Hyperparathyroidism** | Primary · Secondary · Tertiary · Osteitis fibrosa cystica · |
| | **Adrenal** | **Hyperfunction** | *aldosterone:* Hyperaldosteronism/Primary aldosteronism (Conn syndrome · Bartter syndrome · Glucocorticoid remediable aldosteronism · · AME · Liddle's syndrome · 17α CAH · *cortisol:* Cushing's syndrome (Pseudo-Cushing's syndrome) · *sex hormones:* 21α CAH · 11β CAH · |
| | | **Hypofunction/ Adrenal insufficiency (Addison's, WF)** | *aldosterone:* Hypoaldosteronism (21α CAH · 11β CAH · · *cortisol:* CAH (Lipoid · 3β · 11β · 17α · 21α · · *sex hormones:* 17α CAH · |
| | **Gonads** | | *ovarian:* Polycystic ovary syndrome · Premature ovarian failure · *testicular: enzymatic* (5α-reductase deficiency · 17β-hydroxysteroid dehydrogenase deficiency · aromatase excess syndrome) · · *Androgen receptor* (Androgen insensitivity syndrome) · *general:* Hypogonadism (Delayed puberty) · Hypergonadism (Precocious puberty · · Hypoandrogenism · Hypoestrogenism · Hyperandrogenism · Hyperestrogenism · Postorgasmic illness syndrome · |
| **Height** | | | Dwarfism/Short stature (Midget · Laron syndrome · Psychosocial · Ateliosis · · Gigantism · |

| | |
|---|---|
| **Multiple** | Autoimmune polyendocrine syndrome multiple (APS1 · APS2 · · Carcinoid syndrome · Multiple endocrine neoplasia (1 · 2A · 2B · · Progeria (Werner syndrome · Acrogeria · Metageria · · Woodhouse-Sakati syndrome · |

| v · t · e · | **Diabetes (E10–E14, 250)** |
|---|---|
| **Types** | Type 1 · Type 2 · Gestational diabetes (Diabetes and pregnancy · · Prediabetes (Impaired fasting glucose · Impaired glucose tolerance · · Insulin resistance · LADA · KPD · MODY · Neonatal (Transient · Permanent · · Type 3c (Pancreatogenic) · |
| **Blood tests** | Blood sugar · Glycosylated hemoglobin · Glucose tolerance test · Postprandial glucose test · Fructosamine · Glucose test · C-peptide · Noninvasive glucose monitor · Insulin tolerance test · |
| **Management** | Diabetic diet · Anti-diabetic drugs · Insulin therapy (intensive · conventional · pulsatile · · Cure (Embryonic stem cells · Artificial pancreas · · Other (Gastric bypass surgery · · |
| **Complications** | Diabetic comas (Hypoglycemia · Ketoacidosis · Hyperosmolar hyperglycemic state · · Diabetic foot (ulcer · Neuropathic arthropathy · · Organs in diabetes (Blood vessels · Muscle · Kidney · Nerves · Retina · Heart · · Diabetic skin disease (Diabetic dermopathy · Diabetic bulla · Diabetic cheiroarthropathy · Neuropathic ulcer · · Hyperglycemia · Hypoglycemia · |
| **Other** | Glossary of diabetes · |

| | |
|---|---|
| **Authority control** | GND: 4070446-4 · NDL: 00573283 · |

Categories: Diabetes | Metabolic disorders

# Diabetes mellitus type 1

From Wikipedia, the free encyclopedia
(Redirected from DM type 1)

**Diabetes mellitus type 1** (also known as **type 1 diabetes**) is a form of diabetes mellitus in which not enough insulin is produced.[4] The lack of insulin results in high blood sugar levels.[1] The classical symptoms are frequent urination, increased thirst, increased hunger, and weight loss.[4] Additional symptoms may include blurry vision, feeling tired, and poor healing.[2] Symptoms typically develop over a short period of time.[1]

The cause of type 1 diabetes is unknown.[4] It however is believed to involve a combination of genetic and environmental factors.[1] Risk factors include having a family member with the condition.[5] The underlying mechanism involves an autoimmune destruction of the insulin-producing beta cells in the pancreas.[2] Diabetes is diagnosed by testing the level of sugar or A1C in the blood.[5][6] Type 1 diabetes may be distinguished from type 2 by autoantibody testing.[5]

There is no known way to prevent type 1 diabetes.[4] Treatment with insulin is typically required for survival.[1] Insulin therapy is usually given by injection just under the skin but can also be delivered by an insulin pump.[7] A diabetic diet and exercise are an important part of management.[2] Untreated, diabetes can cause many complications.[4] Complications of relatively rapid onset include diabetic ketoacidosis and nonketotic hyperosmolar coma.[5] Long-term complications include heart disease, stroke, kidney failure, foot ulcers and damage to the eyes.[4] Furthermore, complications may arise from low blood sugar caused by excessive insulin treatment.[5]

Type 1 diabetes makes up an estimated 5–10% of all diabetes cases.[8] The number of people affected globally is unknown, although it is estimated that about 80,000 children develop the disease each year.[5] Within the United States the number of people affected is estimated at one to three million.[5][9] Rates of disease vary widely with approximately 1 new case per 100,000 per year in East Asia and Latin America and around 30 new cases per 100,000 per year in Scandinavia and Kuwait.[10][11] It typically begins in children and young adults.[1]

**Diabetes type 1**

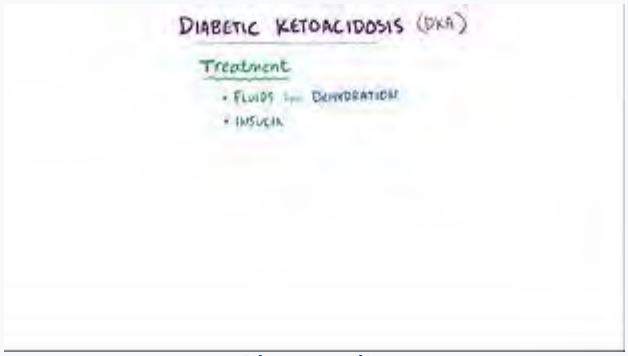
| | |
|---|---|
| **Synonyms** | T1D, insulin-dependent diabetes,[1] juvenile diabetes[2] |

A blue circle, the symbol for diabetes.[3]

**Pronunciation** /daɪəbiːtiːs/

| Classification and external resources | |
|---|---|
| **Specialty** | Endocrinology |
| **ICD-10** | E10 |
| **ICD-9-CM** | 250.01 |
| **OMIM** | 222100 |
| **DiseasesDB** | 3649 |
| **MedlinePlus** | 000305 |
| **eMedicine** | med/546 |
| **MeSH** | D003922 |

[edit on Wikidata]




Play media

Video explanation of the various types of diabetes

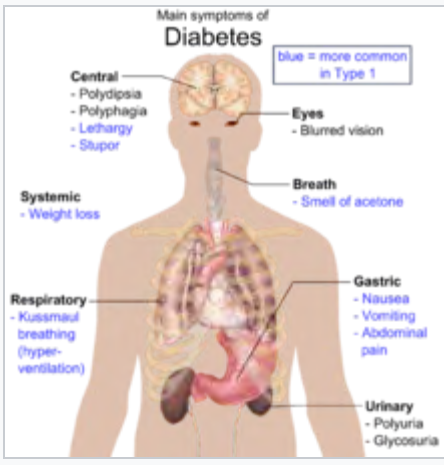
## Signs and symptoms [edit]

The classical symptoms of type 1 diabetes include: polyuria (excessive urination), polydipsia (increased thirst), dry mouth, polyphagia (increased hunger), fatigue, and weight loss.[4]

Many type 1 diabetics are diagnosed when they present with diabetic ketoacidosis. The signs and symptoms of diabetic ketoacidosis include dry skin, rapid deep breathing, drowsiness, increased thirst, frequent urination, abdominal pain, and vomiting.[12]

About 12 percent of people with type 1 diabetes have clinical depression.[13]

About 6 percent of people with type 1 diabetes have celiac disease, but in most cases there are no digestive symptoms[14][15] or are mistakenly attributed to poor control of diabetes, gastroparesis or diabetic neuropathy.[14] In most cases, celiac disease is diagnosed after onset of type 1 diabetes. The association of celiac disease with type 1 diabetes increases the risk of complications, such as retinopathy and mortality. This association can be explained by shared genetic factors, and inflammation or nutritional deficiencies caused by untreated celiac disease, even if type 1 diabetes is diagnosed first.[15]




Overview of the most significant symptoms of diabetes

## Cause [edit]

The cause of type 1 diabetes is unknown.[4] A number of explanatory theories have been put forward, and

the cause may be one or more of the following: genetic susceptibility, a diabetogenic trigger, and exposure to an antigen.[16]

## Genetics [edit]

*Main article: Genetic causes of diabetes mellitus type 1*

Type 1 diabetes is a disease that involves many genes. The risk of a child developing type 1 diabetes is about 5% if the father has it, about 8% if a sibling has it, about 3% if the mother has type 1 diabetes.[17] If one identical twin is affected there is about a 50% chance the other will also be affected.[18] Some studies of heritability has estimated it at 80 to 86%.[19][20]

More than 50 genes are associated with type 1 diabetes.[21] Depending on locus or combination of loci, they can be dominant, recessive, or somewhere in between. The strongest gene, *IDDM1*, is located in the MHC Class II region on chromosome 6, at staining region 6p21. Certain variants of this gene increase the risk for decreased histocompatibility characteristic of type 1. Such variants include DRB1 0401, DRB1 0402, DRB1 0405, DQA 0301, DQB1 0302 and DQB1 0201, which are common in North Americans of European ancestry and in Europeans.[22] Some variants also appear to be protective.[22]

## Environmental [edit]

Environmental factors can influence expression of type 1. For identical twins, when one twin has type 1 diabetes, the other twin only has it 30%–50% of the time. Thus for 50%-70% of identical twins where one has the disease, the other will not, despite having exactly the same genome; this suggests environmental factors, in addition to genetic factors, can influence the disease's prevalence.[23] Other indications of environmental influence include the presence of a 10-fold difference in occurrence among Caucasians living in different areas of Europe, and that people tend to acquire the rate of disease of their particular destination country.[16]

### Virus [edit]

One theory proposes that type 1 diabetes is a virus-triggered autoimmune response in which the immune system attacks virus-infected cells along with the beta cells in the pancreas.[24][25] Several viruses have been implicated, including enteroviruses (especially coxsackievirus B), cytomegalovirus, Epstein–Barr virus, mumps virus, rubella virus and rotavirus, but to date there is no stringent evidence to support this hypothesis in humans.[26] A 2011 systematic review and meta-analysis showed an association between enterovirus infections and type 1 diabetes, but other studies have shown that, rather than triggering an autoimmune process, enterovirus infections, as coxsackievirus B, could protect against onset and development of type 1 diabetes.[27]

## Chemicals and drugs [edit]

Some chemicals and drugs selectively destroy pancreatic cells. Pyrinuron (Vacor), a rodenticide introduced in the United States in 1976, selectively destroys pancreatic beta cells, resulting in type 1 diabetes after accidental poisoning.[28] Pyrinuron was withdrawn from the U.S. market in 1979 and it is not approved by the Environmental Protection Agency for use in the U.S.[29] Streptozotocin (Zanosar), an antineoplastic agent, is selectively toxic to the beta cells of the pancreatic islets. It is used in research for inducing type 1 diabetes on rodents[30] and for treating metastatic cancer of the pancreatic islet cells in patients whose cancer cannot be removed by surgery.[31] Other pancreatic problems, including trauma, pancreatitis, or tumors (either malignant or benign) can also lead to loss of insulin production.

## Gluten [edit]

Data suggest that gliadin (a protein present in gluten) may play a role in the development of type 1 diabetes, but the mechanism is not fully understood.[32][33] Increased intestinal permeability caused by

gluten and the subsequent loss of intestinal barrier function, which allows the passage of pro-inflammatory substances into the blood, may induce the autoimmune response in genetically predisposed individuals to type 1 diabetes.[15][33] Early introduction of gluten-containing cereals in the diet increases the risk of developing islet cell autoantibodies, which are responsible for the destruction of the insulin-producing beta cells in the pancreas.[33]

## Pathophysiology [edit]

The pathophysiology in diabetes type 1 is a destruction of beta cells in the pancreas, regardless of which risk factors or causative entities have been present.

Individual risk factors can have separate pathophysiological processes to, in turn, cause this beta cell destruction. Still, a process that appears to be common to most risk factors is an autoimmune response towards beta cells, involving an expansion of autoreactive CD4+ T helper cells and CD8+ T cells, autoantibody-producing B cells and activation of the innate immune system.[22][34]

After starting treatment with insulin a person's own insulin levels may temporarily improve.[35] This is believed to be due to altered immunity and is known as the "honeymoon phase".[35]

## Diagnosis [edit]

*See also: Glycated hemoglobin and Glucose tolerance test*

**WHO diabetes diagnostic criteria**[36][37] edit

| Condition | 2 hour glucose | Fasting glucose | $HbA_{1c}$ | |
|---|---|---|---|---|
| Unit | mmol/l(mg/dl) | mmol/l(mg/dl) | mmol/mol | DCCT % |
| Normal | <7.8 (<140) | <6.1 (<110) | <42 | <6.0 |
| Impaired fasting glycaemia | <7.8 (<140) | ≥6.1(≥110) & <7.0(<126) | 42-46 | 6.0–6.4 |
| Impaired glucose tolerance | ≥7.8 (≥140) | <7.0 (<126) | 42-46 | 6.0–6.4 |
| Diabetes mellitus | ≥11.1 (≥200) | ≥7.0 (≥126) | ≥48 | ≥6.5 |

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:[38]

- Fasting plasma glucose level at or above 7.0 mmol/L (126 mg/dL).
- Plasma glucose at or above 11.1 mmol/L (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test.
- Symptoms of hyperglycemia and casual plasma glucose at or above 11.1 mmol/L (200 mg/dL).
- Glycated hemoglobin (hemoglobin A1C) at or above 48 mmol/mol (≥ 6.5 DCCT %). (This criterion was recommended by the American Diabetes Association in 2010, although it has yet to be adopted by the WHO.)[39]

About a quarter of people with new type 1 diabetes have developed some degree of diabetic ketoacidosis (a type of metabolic acidosis which is caused by high concentrations of ketone bodies, formed by the breakdown of fatty acids and the deamination of amino acids) by the time the diabetes is recognized. The diagnosis of other types of diabetes is usually made in other ways. These include ordinary health screening, detection of hyperglycemia during other medical investigations, and secondary symptoms such as vision changes or unexplained fatigue. Diabetes is often detected when a person suffers a problem that may be caused by diabetes, such as a heart attack, stroke, neuropathy, poor wound healing or a foot ulcer, certain eye problems, certain fungal infections, or delivering a baby with macrosomia or hypoglycemia (low blood sugar).

A positive result, in the absence of unequivocal hyperglycemia, should be confirmed by a repeat of any of

the above-listed methods on a different day. Most physicians prefer to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test.[40] According to the current definition, two fasting glucose measurements above 126 mg/dL (7.0 mmol/L) is considered diagnostic for diabetes mellitus.

In type 1, pancreatic beta cells in the islets of Langerhans are destroyed, decreasing endogenous insulin production. This distinguishes type 1's origin from type 2. Type 2 diabetes is characterized by insulin resistance, while type 1 diabetes is characterized by insulin deficiency, generally without insulin resistance. Another hallmark of type 1 diabetes is islet autoreactivity, which is generally measured by the presence of autoantibodies directed towards the beta cells.

### Autoantibodies [edit]

The appearance of diabetes-related autoantibodies has been shown to be able to predict the appearance of diabetes type 1 before any hyperglycemia arises, the main ones being islet cell autoantibodies, insulin autoantibodies, autoantibodies targeting the 65-kDa isoform of glutamic acid decarboxylase (GAD), autoantibodies targeting the phosphatase-related IA-2 molecule, and zinc transporter autoantibodies (ZnT8).[16] By definition, the diagnosis of diabetes type 1 can be made first at the appearance of clinical symptoms and/or signs, but the emergence of autoantibodies may itself be termed "latent autoimmune diabetes". Not everyone with autoantibodies progresses to diabetes type 1, but the risk increases with the number of antibody types, with three to four antibody types giving a risk of progressing to diabetes type 1 of 60%–100%.[16] The time interval from emergence of autoantibodies to clinically diagnosable diabetes can be a few months in infants and young children, but in some people it may take years – in some cases more than 10 years.[16] Islet cell autoantibodies are detected by conventional immunofluorescence, while the rest are measured with specific radiobinding assays.[16]

## Prevention [edit]

Type 1 diabetes is not currently preventable.[41] Some researchers believe it might be prevented at the latent autoimmune stage, before it starts destroying beta cells.[22]

### Immunosuppressive drugs [edit]

Cyclosporine A, an immunosuppressive agent, has apparently halted destruction of beta cells (on the basis of reduced insulin usage), but its kidney toxicity and other side effects make it highly inappropriate for long-term use.[22]

Anti-CD3 antibodies, including teplizumab and otelixizumab, had suggested evidence of preserving insulin production (as evidenced by sustained C-peptide production) in newly diagnosed type 1 diabetes patients.[22] A probable mechanism of this effect was believed to be preservation of regulatory T cells that suppress activation of the immune system and thereby maintain immune system homeostasis and tolerance to self-antigens.[22] The duration of the effect is still unknown, however.[22] In 2011, Phase III studies with otelixizumab and teplizumab both failed to show clinical efficacy, potentially due to an insufficient dosing schedule.[42][43]

An anti-CD20 antibody, rituximab, inhibits B cells and has been shown to provoke C-peptide responses three months after diagnosis of type 1 diabetes, but long-term effects of this have not been reported.[22]

### Diet [edit]

Some research has suggested breastfeeding decreases the risk in later life[44][45] and early introduction of gluten-containing cereals in the diet increases the risk of developing islet cell autoantibodies;[33] various other nutritional risk factors are being studied, but no firm evidence has been found.[46] Giving children 2000 IU of vitamin D daily during their first year of life is associated with reduced risk of type 1 diabetes,

though the causal relationship is obscure.[47]

Children with antibodies to beta cell proteins (i.e. at early stages of an immune reaction to them) but no overt diabetes, and treated with niacinamide (vitamin $B_3$), had less than half the diabetes onset incidence in a seven-year time span than did the general population, and an even lower incidence relative to those with antibodies as above, but who received no niacinamide.[48]

People with type 1 diabetes and undiagnosed celiac disease have worse glycaemic control and a higher prevalence of nephropathy and retinopathy. Gluten-free diet, when performed strictly, improves diabetes symptoms and appears to have a protective effect against developing long-term complications. Nevertheless, dietary management of both these diseases is challenging and these patients have poor compliance of the diet.[49]

## Management [edit]

*Further information: Diabetes management*

### Lifestyle [edit]

A low-carbohydrate diet, in addition to medications, is useful in type 1 DM.[50] There are camps for children to teach them how and when to use or monitor their insulin without parental help.[51] As psychological stress may have a negative effect on diabetes, a number of measures have been recommended including: exercising, taking up a new hobby, or joining a charity among others.[52]

### Insulin [edit]

*Main article: Insulin therapy*

There are four main types of insulin: rapid acting insulin, short acting insulin, intermediate acting insulin, and long acting insulin. The rapid acting insulin is used as a bolus dosage. The action onsets in 15 minutes with peak actions in 30 to 90 minutes. Short acting insulin action onsets within 30 minutes with the peak action around 2 to 4 hours. Intermediate acting insulin action onsets within 1 to 2 hours with peak action of 4 to 10 hours. Long acting insulin is usually given once per day. The action onset is roughly 1 to 2 hours with a sustained action of up to 24 hours.

Injections of insulin—either via subcutaneous injection or insulin pump— are necessary for those living with type 1 diabetes because it cannot be treated by diet and exercise alone.[53] In addition to insulin therapy dietary management is important. This includes keeping track of the carbohydrate content of food and careful monitoring of blood glucose levels using glucose meters. Today, the most common insulins are biosynthetic products produced using genetic recombination techniques; formerly, cattle or pig insulins were used, and even sometimes insulin from fish.[54]

Untreated type 1 diabetes can commonly lead to diabetic ketoacidosis which is a diabetic coma which can be fatal if untreated.[55] Diabetic ketoacidosis can cause cerebral edema (accumulation of liquid in the brain). This is a life-threatening issue and children are at a higher risk for cerebral edema than adults, causing ketoacidosis to be the most common cause of death in pediatric diabetes.[56]

Treatment of diabetes focuses on lowering blood sugar or glucose (BG) to the near normal range, approximately 80–140 mg/dl (4.4–7.8 mmol/L).[57] The ultimate goal of normalizing BG is to avoid long-term complications that affect the nervous system (e.g. peripheral neuropathy leading to pain and/or loss of feeling in the extremities), and the cardiovascular system (e.g. heart attacks, vision loss). This level of control over a prolonged period of time can be varied by a target $HbA_{1c}$ level of less than 7.5%.[5]

People with type 1 diabetes always need to use insulin, but treatment can lead to low BG (hypoglycemia), i.e. BG less than 70 mg/dl (3.9 mmol/l). Hypoglycemia is a very common occurrence in people with diabetes, usually the result of a mismatch in the balance among insulin, food and physical activity. Mild cases are self-treated by eating or drinking something high in sugar. Severe cases can lead to

unconsciousness and are treated with intravenous glucose or injections with glucagon. Continuous glucose monitors can alert patients to the presence of dangerously high or low blood sugar levels, but technical issues have limited the effect these devices have had on clinical practice.[*citation needed*]

As of 2016 an artificial pancreas looks promising with safety issues still being studied.[58]

### Pancreas transplantation [edit]

*Main article: Pancreas transplantation*

In some cases, a pancreas transplant can restore proper glucose regulation. However, the surgery and accompanying immunosuppression required may be more dangerous than continued insulin replacement therapy, so is generally only used with or some time after a kidney transplant. One reason for this is that introducing a new kidney requires taking immunosuppressive drugs such as cyclosporine. Nevertheless, this allows the introduction of a new pancreas to a person with diabetes without any additional immunosuppressive therapy. However, pancreas transplants alone may be beneficial in people with extremely labile type 1 diabetes mellitus.[59]

### Islet cell transplantation [edit]

*Main article: Islet cell transplantation*

Islet cell transplantation may be an option for some people with type 1 diabetes that are not well controlled with insulin.[60] Difficulties include finding donors that are a compatible, getting the new islets to survive, and the side effects from the medications used to prevent rejection.[60] Success rates, defined as not needing insulin at 3 years follow the procedure occurred in 44% in on registry from 2010.[60]

## Complications [edit]

*Further information: Complications of diabetes mellitus*

Complications of poorly managed type 1 diabetes mellitus may include cardiovascular disease, diabetic neuropathy, and diabetic retinopathy, among others. However, cardiovascular disease[61] as well as neuropathy[62] may have an autoimmune basis, as well. Women with type 1 DM have a 40% higher risk of death as compared to men with type 1 DM.[63] The life expectancy of an individual with type 1 diabetes is 11 years less for men and 14 years less for women.[64]

### Urinary tract infection [edit]

People with diabetes show an increased rate of urinary tract infection.[65] The reason is bladder dysfunction that is more common in diabetics than in non-diabetics due to diabetic nephropathy. When present, nephropathy can cause a decrease in bladder sensation, which in turn, can cause increased residual urine, a risk factor for urinary tract infections.[66]

### Sexual dysfunction [edit]

Sexual dysfunction in diabetics is often a result of physical factors such as nerve damage and/or poor circulation, and psychological factors such as stress and/or depression caused by the demands of the disease.[67][68]

#### Males [edit]

The most common sexual issues in diabetic males are problems with erections and ejaculation: "With diabetes, blood vessels supplying the penis's erectile tissue can get hard and narrow, preventing the adequate blood supply needed for a firm erection. The nerve damage caused by poor blood glucose control can also cause ejaculate to go into the bladder instead of through the penis during ejaculation, called

retrograde ejaculation. When this happens, semen leaves the body in the urine."[67] Another cause for erectile dysfunction are the reactive oxygen species created as a result of the disease. Antioxidants can be used to help combat this.[69]

### Females [edit]

While there is less material on the correlation between diabetes and female sexual dysfunction than male sexual dysfunction, studies have shown there to be a significant prevalence of sexual problems in diabetic women.[68] Common problems include reduced sensation in the genitals, dryness, difficulty/inability to orgasm, pain during sex, and decreased libido.[67] In some cases diabetes has been shown to decrease oestrogen levels in females, which can affect vaginal lubrication.[68]

Oral contraceptives can be taken by diabetics. Sometimes, contraceptive pills can cause a blood sugar imbalance, but this usually can be corrected by a dosage change.[68] As with any medication, side effects should be taken into account and monitored to prevent serious complications with diabetes.[68]

Women with type 1 diabetes show a higher than normal rate of polycystic ovarian syndrome (PCOS).[70] The reason may be that the ovaries are exposed to high insulin concentrations since women with type 1 diabetes can have frequent hyperglycemia.[71]

## Epidemiology [edit]

Type 1 diabetes makes up an estimated 5–10% of all diabetes cases[8] or 11–22 million worldwide.[41] In 2006 it affected 440,000 children under 14 years of age and was the primary cause of diabetes in those less than 10 years of age.[72] The incidence of type 1 diabetes has been increasing by about 3% per year.[72]

Rates vary widely by country. In Finland, the incidence is a high of 57 per 100,000 per year, in Japan and China a low of 1 to 3 per 100,000 per year, and in Northern Europe and the U.S., an intermediate of 8 to 17 per 100,000 per year.[73][74]

In the United States, type 1 diabetes affected about 208,000 youths under the age of 20 in 2015. Over 18,000 youths are diagnosed with Type 1 diabetes every year. Compared to non-Hispanic whites, Asian Americans, Hispanic Americans and Hispanic-Black Americans have greater odds of being diagnosed with diabetes. Every year about 234,051 Americans die due to diabetes or diabetes-related complications, with 69,071 having it as the primary cause of death.[75]

## History [edit]

Type 1 diabetes was described as an autoimmune disease in the 1970s, based on observations that autoantibodies against islets were discovered in diabetics with other autoimmune deficiencies.[76] It was also shown in the 1980s that immunosuppressive therapies could slow disease progression, further supporting the idea that type 1 diabetes is an autoimmune disorder.[77] The name *juvenile diabetes* was used earlier as it often first is diagnosed in childhood.

In Australia, approximately one million Australians have been diagnosed with type 1 diabetes and Australia ranks 7th-highest in the world with children under 14 years of age. Between 2000 and 2013, 31,895 new cases were established, with 2,323 in 2013, a rate of 10–13 cases per 100,00 people each year. Aboriginals and Torres Strait Islander people are less affected.[78][79]

## Society and culture [edit]

*See also: List of people with diabetes mellitus type 1*

The disease was estimated to cause $10.5 billion in annual medical costs ($875 per month per diabetic) and an additional $4.4 billion in indirect costs ($366 per month per person with diabetes) in the U.S.[80] In the United States $245 billion every year is attributed to diabetes. Individuals diagnosed with diabetes have 2.3 times the health care costs as individuals who do not have diabetes. One in 10 health care dollars are spent on individuals with diabetes.[75]

## Research [edit]

Funding for research into type 1 diabetes originates from government, industry (e.g., pharmaceutical companies), and charitable organizations. Government funding in the United States is distributed via the National Institute of Health, and in the UK via the National Institute for Health Research or the Medical Research Council. JDRF, originally founded by parents of children with type 1 diabetes, is the world's largest provider of charity based funding for type 1 diabetes research. Other charities include the American Diabetes Association, Diabetes UK, Diabetes Research and Wellness Foundation,[81] Diabetes Australia, the Canadian Diabetes Association.

### Treatments [edit]

A number of approaches have been explored to provide treatments for type 1.

### Stem cells [edit]

Pluripotent stem cells can be used to generate beta cells but previously these cells did not function as well as normal beta cells.[82] In 2014 more mature beta cells were produced which released insulin in response to blood sugar when transplanted into mice.[83][84] Before these techniques can be used in humans more evidence of safety and effectiveness is needed.[82]

### Vaccine [edit]

Vaccines to treat or prevent Type 1 diabetes are designed to induce immune tolerance to insulin or pancreatic beta cells.[85] While Phase II clinical trials of a vaccine containing alum and recombinant GAD65, an autoantigen involved in type 1 diabetes, were promising, as of 2014 Phase III had failed.[85] As of 2014, other approaches, such as a DNA vaccine encoding proinsulin and a peptide fragment of insulin, were in early clinical development.[85]

### Diet [edit]

There is evidence from experiments conducted in animal models that removal of gluten from the diet may prevent the onset type 1 diabetes[32][86] but there has been conflicting research in humans.[86]

## Labile diabetes [edit]

Insulin-dependent diabetes characterized by dramatic and recurrent swings in glucose levels, often occurring for no apparent reason, is sometimes known as brittle diabetes, unstable diabetes or labile diabetes, although some experts say the "brittle diabetes" concept "has no biologic basis and should not be used".[87] The results of such swings can be irregular and unpredictable hyperglycemias, sometimes involving ketoacidosis, and sometimes serious hypoglycemias. Brittle diabetes occurs no more frequently than in 1% to 2% of diabetics.[88] In a small study, 10 of 20 brittle diabetic patients aged 18–23 years who could be traced had died within 22 years, and the remainder, though suffering high rates of complications, were no longer brittle.[89] These results were similar to those of an earlier study by the same authors which found a 19% mortality in 26 patients after 10.5 years.[90]

Because labile diabetes is defined as "episodes of hypoglycemia or hyperglycemia that, whatever their [91]

cause, constantly disrupt a patient's life", it can have many causes, some of which include:

- errors in diabetes management, which can include too much insulin being given, in relation to carbohydrate being consumed
- interactions with other medical conditions
- psychological problems
- biological factors that interfere with how insulin is processed within the body
- hypoglycemia and hyperglycemia due to strenuous exercise; however, hypoglycemia is more frequent
- insulin exposed to higher temperatures that reduces effectiveness of the insulin hormone in the body
- spontaneous production of insulin in the body due to activity in the beta cells during the period shortly after diagnosis of type 1 diabetes

Exercise related hyperglycemia is caused when hormones (such as adrenaline and cortisol) are released during moderate to strenuous exercise. This happens when the muscles signal the liver to release glucose into the bloodstream by converting stored glycogen into glucose. The cause of exercise related hypoglycemia, on the other hand, occurs when the muscle group being exercised uses up glucose faster than it can be replenished by the body.

One of these biological factors is the production of insulin autoantibodies. High antibody titers can cause episodes of hyperglycemia by neutralizing the insulin, thereby causing clinical insulin resistance requiring doses of over 200 IU/day. However, antibodies may also fail to buffer the release of the injected insulin into the bloodstream after subcutaneous injection, resulting in episodes of hypoglycemia. In some cases, changing the type of insulin administered can resolve this problem.[91] There have been a number of reports that insulin autoantibodies can act as a "sink" for insulin and affect the time to peak, half-life, distribution space, and metabolic clearance, though in most patients these effects are small.[92]

## References [edit]


1. ^ *a b c d e f* "Causes of Diabetes". *NIDDK*. August 2014. Retrieved 31 July 2016.
2. ^ *a b c d* "Types of Diabetes". *NIDDK*. February 2014. Retrieved 31 July 2016.
3. ^ "Diabetes Blue Circle Symbol". International Diabetes Federation. 17 March 2006.
4. ^ *a b c d e f g h* "Diabetes Fact sheet N°312". *WHO*. June 2016. Archived from the original on 26 August 2013. Retrieved 31 July 2016.
5. ^ *a b c d e f g h* Chiang, J. L.; Kirkman, M. S.; Laffel, L. M. B.; Peters, A. L. (16 June 2014). "Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association". *Diabetes Care*. **37** (7): 2034–2054. doi:10.2337/dc14-1140. PMID 24935775.
6. ^ "Diagnosis of Diabetes and Prediabetes". *NIDDK*. May 2015. Retrieved 31 July 2016.
7. ^ "Alternative Devices for Taking Insulin". *NIDDK*. July 2016. Retrieved 31 July 2016.
8. ^ *a b* Daneman D (11 March 2006). "Type 1 diabetes". *Lancet*. **367** (9513): 847–58. doi:10.1016/S0140-6736(06)68341-4. PMID 16530579.
9. ^ "FAST FACTS Data and Statistics about Diabetes". American Diabetes Association. Retrieved 25 July 2014.
10. ^ *Global report on diabetes* (PDF). World Health Organization. 2016. pp. 26–27. ISBN 978-92-4-156525-7. Retrieved 31 July 2016.
11. ^ Skyler, Jay (2012). *Atlas of diabetes* (4th ed.). New York: Springer. pp. 67–68. ISBN 978-1-4614-1028-7.
12. ^ "webmd Symptoms Type I Diabetes".
13. ^ Roy T, Lloyd CE (2012). "Epidemiology of depression and diabetes: a systematic review". *J Affect Disord*. 142 Suppl: S8–21. doi:10.1016/S0165-0327(12)70004-6. PMID 23062861.
14. ^ *a b* See JA, Kaukinen K, Makharia GK, Gibson PR, Murray JA (Oct 2015). "Practical insights into gluten-free diets". *Nat Rev Gastroenterol Hepatol* (Review). **12** (10): 580–91. doi:10.1038/nrgastro.2015.156. PMID 26392070. "Coeliac disease in T1DM is asymptomatic ...Clinical manifestations of coeliac disease, such as abdominal pain, gas, bloating, diarrhoea and weight loss can be present in patients with T1DM, but are often attributed to poor control of diabetes, gastroparesis or diabetic neuropathy"
15. ^ *a b c* Elfström P, Sundström J, Ludvigsson JF (2014). "Systematic review with meta-analysis: associations between coeliac disease and type 1 diabetes.". *Aliment Pharmacol Ther*. **40** (10): 1123–32. doi:10.1111/apt.12973. PMID 25270960.
16. ^ *a b c d e f* Knip M, Veijola R, Virtanen SM, Hyöty H, Vaarala O, Akerblom HK (2005). "Environmental Triggers and

Determinants of Type 1 Diabetes". *Diabetes*. **54**: S125–S136. doi:10.2337/diabetes.54.suppl_2.S125. PMID 16306330.
17. ^ Pociot, F; Lernmark, Å (4 June 2016). "Genetic risk factors for type 1 diabetes.". *Lancet (London, England)*. **387** (10035): 2331–9. doi:10.1016/s0140-6736(16)30582-7. PMID 27302272.
18. ^ Owen, Katharine (2014). *Oxford Handbook of Endocrinology and Diabetes*. Oxford University Press. p. 690. ISBN 9780199644438.
19. ^ Narayan, K. M. Venkat; Williams, Desmond; Gregg, Edward W.; Cowie, Catherine C. (2010). *Diabetes Public Health: From Data to Policy*. Oxford University Press. p. 671. ISBN 9780199749140.
20. ^ Melmed, Shlomo; Polonsky, Kenneth S.; Larsen, P. Reed; Kronenberg, Henry (2015). *Williams Textbook of Endocrinology*. Elsevier Health Sciences. p. 50. ISBN 9780323297387.
21. ^ Ionescu-Tîrgovişte, Constantin; Gagniuc, Paul Aurelian; Guja, Cristian. "Structural Properties of Gene Promoters Highlight More than Two Phenotypes of Diabetes". *PLOS ONE*. **10** (9): e0137950. doi:10.1371/journal.pone.0137950. PMC 4574929. PMID 26379145. Archived from the original on 17 November 2015.
22. ^ *a b c d e f g h i* Bluestone JA, Herold K, Eisenbarth G (2010). "Genetics, pathogenesis and clinical interventions in type 1 diabetes". *Nature*. **464** (7293): 1293–1300. Bibcode:2010Natur.464.1293B. doi:10.1038/nature08933. PMID 20432533.
23. ^ "OMIM Entry – %222100 – DIABETES MELLITUS, INSULIN-DEPENDENT; IDDM". Ncbi.nlm.nih.gov. Retrieved 29 November 2011.
24. ^ Rewers M, Ludvigsson J (2016). "Environmental risk factors for type 1 diabetes.". *Lancet* (Review). **387** (10035): 2340–8. doi:10.1016/S0140-6736(16)30507-4. PMID 27302273.
25. ^ Fairweather D, Rose NR (2002). "Type 1 diabetes: virus infection or autoimmune disease?". *Nat. Immunol*. **3** (4): 338–40. doi:10.1038/ni0402-338. PMID 11919574.
26. ^ Petzold A; Solimena M; Knoch KP (2015). "Mechanisms of Beta Cell Dysfunction Associated With Viral Infection.". *Curr Diab Rep* (Review). **15** (10): 73. doi:10.1007/s11892-015-0654-x. PMC 4539350. PMID 26280364. "So far, none of the hypotheses accounting for virus-induced beta cell autoimmunity has been supported by stringent evidence in humans, and the involvement of several mechanisms rather than just one is also plausible."
27. ^ Butalia S, Kaplan GG, Khokhar B, Rabi DM (Aug 18, 2016). "Environmental Risk Factors and Type 1 Diabetes: Past, Present, and Future". *Can J Diabetes* (Review). pii: S1499-2671(15)30052–6: 586–593. doi:10.1016/j.jcjd.2016.05.002. PMID 27545597.
28. ^ Thayer KA, Heindel JJ, Bucher JR, Gallo MA (Jun 2012). "Role of environmental chemicals in diabetes and obesity: a National Toxicology Program workshop review". *Environ Health Perspect* (Review). **120** (6): 779–89. doi:10.1289/ehp.1104597. PMC 3385443. PMID 22296744.
29. ^ "Pyriminil". *Pyriminil*. U.S. National Library of Medicine.
30. ^ Wu J, Yan LJ (Apr 2015). "Streptozotocin-induced type 1 diabetes in rodents as a model for studying mitochondrial mechanisms of diabetic β cell glucotoxicity". *Diabetes Metab Syndr Obes* (Review). **8**: 181–8. doi:10.2147/DMSO.S82272. PMC 4396517. PMID 25897251.
31. ^ Brentjens R, Saltz L (2001). "Islet cell tumors of the pancreas: the medical oncologist's perspective". *Surg Clin North Am* (Review). **81** (3): 527–42. doi:10.1016/S0039-6109(05)70141-9. PMID 11459269.
32. ^ *a b* Serena G, Camhi S, Sturgeon C, Yan S, Fasano A (2015). "The Role of Gluten in Celiac Disease and Type 1 Diabetes.". *Nutrients*. **7** (9): 7143–62. doi:10.3390/nu7095329. PMC 4586524. PMID 26343710.
33. ^ *a b c d* Visser J, Rozing J, Sapone A, Lammers K, Fasano A (2009). "Tight junctions, intestinal permeability, and autoimmunity: celiac disease and type 1 diabetes paradigms.". *Ann N Y Acad Sci*. **1165**: 195–205. doi:10.1111/j.1749-6632.2009.04037.x. PMC 2886850. PMID 19538307.
34. ^ Chatzigeorgiou A, Harokopos V, Mylona-Karagianni C, Tsouvalas E, Aidinis V, Kamper EF (September 2010). "The pattern of inflammatory/anti-inflammatory cytokines and chemokines in type 1 diabetic patients over time". *Ann. Med*. **42** (6): 426–38. doi:10.3109/07853890.2010.495951. PMID 20568978.
35. ^ *a b* Aly H, Gottlieb P (Aug 2009). "The honeymoon phase: intersection of metabolism and immunology.". *Current opinion in endocrinology, diabetes, and obesity*. **16** (4): 286–92. doi:10.1097/med.0b013e32832e0693. PMID 19506474.
36. ^ *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation* (PDF). Geneva: World Health Organization. 2006. p. 21. ISBN 978-92-4-159493-6.
37. ^ Vijan, S (March 2010). "Type 2 diabetes". *Annals of Internal Medicine*. **152** (5): ITC31-15. doi:10.7326/0003-4819-152-5-201003020-01003. PMID 20194231.
38. ^ World Health Organisation Department of Noncommunicable Disease Surveillance (1999). "Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications" (PDF).
39. ^ ""Diabetes Care" January 2010". American Diabetes Association. Retrieved 29 January 2010.

40. ^ Saydah SH, Miret M, Sung J, Varas C, Gause D, Brancati FL (August 2001). "Postchallenge hyperglycemia and mortality in a national sample of U.S. adults". *Diabetes Care*. **24** (8): 1397–402. doi:10.2337/diacare.24.8.1397. PMID 11473076.
41. ^ [a] [b] "Diabetes". *World Health Organization*. Retrieved 24 January 2011.
42. ^ "'Tolerx, Inc. and GlaxoSmithKline (GSK) Announce Phase 3 Defend-1 Study of Otelixizumab in Type 1 Diabetes Did Not Meet Its Primary Endpoint'". Biospace. Retrieved 29 November 2011.
43. ^ "Macrogenics press release: "MacroGenics and Lilly Announce Pivotal Clinical Trial of Teplizumab Did Not Meet Primary Efficacy Endpoint"". Macrogenics.com. 20 October 2010. Retrieved 29 November 2011.
44. ^ Borch-Johnsen K, Joner G, Mandrup-Poulsen T, Christy M, Zachau-Christiansen B, Kastrup K, Nerup J (November 1984). "Relation between breast-feeding and incidence rates of insulin-dependent diabetes mellitus. A hypothesis". *Lancet*. **2** (8411): 1083–6. doi:10.1016/S0140-6736(84)91517-4. PMID 6150150.
45. ^ Shehadeh N, Shamir R, Berant M, Etzioni A (2001). "Insulin in human milk and the prevention of type 1 diabetes". *Pediatric Diabetes*. **2** (4): 175–7. doi:10.1034/j.1399-5448.2001.20406.x. PMID 15016183.
46. ^ Virtanen SM, Knip M (December 2003). "Nutritional risk predictors of beta cell autoimmunity and type 1 diabetes at a young age". *The American Journal of Clinical Nutrition*. **78** (6): 1053–67. PMID 14668264.
47. ^ Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM (November 2001). "Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study". *Lancet*. **358** (9292): 1500–3. doi:10.1016/S0140-6736(01)06580-1. PMID 11705562.
48. ^ Elliott RB, Pilcher CC, Fergusson DM, Stewart AW (1996). "A population based strategy to prevent insulin-dependent diabetes using nicotinamide". *Journal of Pediatric Endocrinology & Metabolism*. **9** (5): 501–9. doi:10.1515/JPEM.1996.9.5.501. PMID 8961125.
49. ^ Hogg-Kollars S; Al Dulaimi D; Tait K; Rostami K (2014). "Type 1 diabetes mellitus and gluten induced disorders". *Gastroenterol Hepatol Bed Bench* (Review). **7** (4): 189–97. PMC 4185872. PMID 25289132.
50. ^ Feinman, RD; Pogozelski, WK; Astrup, A; Bernstein, RK; Fine, EJ; Westman, EC; Accurso, A; Frassetto, L; Gower, BA; McFarlane, SI; Nielsen, JV; Krarup, T; Saslow, L; Roth, KS; Vernon, MC; Volek, JS; Wilshire, GB; Dahlqvist, A; Sundberg, R; Childers, A; Morrison, K; Manninen, AH; Dashti, HM; Wood, RJ; Wortman, J; Worm, N (January 2015). "Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base.". *Nutrition (Burbank, Los Angeles County, Calif.)*. **31** (1): 1–13. doi:10.1016/j.nut.2014.06.011. PMID 25287761.
51. ^ Ly, Trang T (2015). "Technology and type 1 diabetes: Closed-loop therapies". *Current Pediatrics Reports*. **3**: 170–176. doi:10.1007/s40124-015-0083-y.
52. ^ "Stress". *www.diabetes.org*. American Diabetes Association. Retrieved 11 November 2014.
53. ^ Shrivastava, Saurabh (5 March 2013). "Role of self-care in management of diabetes mellitus". *Journal of Diabetes & Metabolic Disorders*. **12**: 14. doi:10.1186/2251-6581-12-14.
54. ^ Wright JR (2002). "From ugly fish to conquer death: J J R Macleod's fish insulin research, 1922-24". *Lancet*. **359** (9313): 1238–42. doi:10.1016/S0140-6736(02)08222-3. PMID 11955558.
55. ^ American Diabetes Association (2015). "DKA (ketoacidosis) and ketones". *American Diabetes Association*.
56. ^ Tasker, Robert. C (2014). "Cerebral edema in children with diabetic ketoacidosis: vasogenic rather than cellular?". *Pediatric Diabetes*. **15**: 261–270. doi:10.1111/pedi.12153.
57. ^ American Diabetes Association Clinical Guidelines, 2010.
58. ^ Blauw, H; Keith-Hynes, P; Koops, R; DeVries, JH (November 2016). "A Review of Safety and Design Requirements of the Artificial Pancreas.". *Annals of biomedical engineering*. **44** (11): 3158–3172. doi:10.1007/s10439-016-1679-2. PMC 5093196. PMID 27352278.
59. ^ Jennifer L. Larsen. "Pancreas Transplantation: Indications and Consequences". Edrv.endojournals.org. Retrieved 29 November 2011.
60. ^ [a] [b] [c] Bruni, A; Gala-Lopez, B; Pepper, AR; Abualhassan, NS; Shapiro, AJ (2014). "Islet cell transplantation for the treatment of type 1 diabetes: recent advances and future challenges.". *Diabetes, metabolic syndrome and obesity : targets and therapy*. **7**: 211–23. doi:10.2147/DMSO.S50789. PMID 25018643.
61. ^ Devaraj S, Glaser N, Griffen S, Wang-Polagruto J, Miguelino E, Jialal I (March 2006). "Increased monocytic activity and biomarkers of inflammation in patients with type 1 diabetes". *Diabetes*. **55** (3): 774–9. doi:10.2337/diabetes.55.03.06.db05-1417. PMID 16505242.
62. ^ Granberg V, Ejskjaer N, Peakman M, Sundkvist G (2005). "Autoantibodies to autonomic nerves associated with cardiac and peripheral autonomic neuropathy". *Diabetes Care*. **28** (8): 1959–64. doi:10.2337/diacare.28.8.1959. PMID 16043739.
63. ^ Huxley, Rachel R; Peters, Sanne A E; Mishra, Gita D; Woodward, Mark (February 2015). "Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis". *The Lancet Diabetes & Endocrinology*. **3**: 198–206. doi:10.1016/S2213-8587(14)70248-7.
64. ^ Livingstone, SJ; Levin, D; Looker, HC; Lindsay, RS; Wild, SH; Joss, N; Leese, G; Leslie, P; McCrimmon, RJ; Metcalfe, W; McKnight, JA; Morris, AD; Pearson, DW; Petrie, JR; Philip, S; Sattar, NA; Traynor, JP; Colhoun, HM;

Scottish Diabetes Research Network epidemiology, group; Scottish Renal, Registry (6 January 2015). "Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010.". *JAMA*. **313** (1): 37–44. doi:10.1001/jama.2014.16425. PMC 4426486. PMID 25562264.

65. ^ Chen, Hsin-Chui; Su, Li-Ting; Linn, Shin-Zong; Sung, Fung-Chang; Ko, Ming-Chung; Li, Chung-Yi (January 2012). "Increased Risk of Urinary Tract Calculi Among Patients With Diabetes Mellitus–A Population-Based Cohort Study". *Urology*. **79** (1): 86–92. doi:10.1016/j.urology.2011.07.1431. Retrieved 28 November 2014.
66. ^ James, R; Hijaz, A (October 2014). "Lower urinary tract symptoms in women with diabetes mellitus: a current review.". *Current Urology Reports*. **15** (10): 440. doi:10.1007/s11934-014-0440-3. PMID 25118849.
67. ^ *a b c* McCoy, Krisha. "Sexual Issues and Type 1 Diabetes". *everyday Health*. Everyday Health Media, LLC. Retrieved 28 November 2014.
68. ^ *a b c d e* "Sexual Dysfunction in Women". *Diabetes.co.uk*. Diabetes Digital Media Ltd. Retrieved 28 November 2014.
69. ^ Goswami, Sumanta; Vishwanath, Manikanta; Gangadarappa, Suma; Razdan, Rema; Inamdar, Mohammed (Jul–Sep 2014). "Efficacy of ellagic acid and sildenafil in diabetes-induced sexual dysfunction". *Pharmacognosy Magazine*. **10** (39): 581. doi:10.4103/0973-1296.139790. Retrieved 30 November 2014.
70. ^ Escobar-Morreale, Héctor F.; Roldán, Belén; Barrio, Raquel; Alonso, Milagros; Sancho, José; de la Calle, Hermenegildo; GarcÍa-Robles, Rafael (November 2000). "High Prevalence of the Polycystic Ovary Syndrome and Hirsutism in Women with Type 1 Diabetes Mellitus". *The Journal of Clinical Endocrinology & Metabolism*. **85** (11): 4182–4187. doi:10.1210/jcem.85.11.6931.
71. ^ Codner, Ethel; Escobar-Morreale, Héctor F. (April 2007). "Hyperandrogenism and Polycystic Ovary Syndrome in Women with Type 1 Diabetes Mellitus". *The Journal of Clinical Endocrinology & Metabolism*. **92** (4): 1209–1216. doi:10.1210/jc.2006-2641.
72. ^ *a b* Aanstoot HJ, Anderson BJ, Daneman D, Danne T, Donaghue K, Kaufman F, Réa RR, Uchigata Y (October 2007). "The global burden of youth diabetes: perspectives and potential". *Pediatric diabetes*. 8. Suppl 8 (s8): 1–44. doi:10.1111/j.1399-5448.2007.00326.x. PMID 17767619.
73. ^ Kasper, Dennis L; Braunwald, Eugene; Fauci, Anthony; et al. (2005). *Harrison's Principles of Internal Medicine* (16th ed.). New York: McGraw-Hill. ISBN 0-07-139140-1.
74. ^ Soltesz G, Patterson CC, Dahlquist G (October 2007). "Worldwide childhood type 1 diabetes incidence—what can we learn from epidemiology?". *Pediatric diabetes*. 8. Suppl 6 (s6): 6–14. doi:10.1111/j.1399-5448.2007.00280.x. PMID 17727380.
75. ^ *a b* "Fast Facts" (PDF). *American Diabetes Association*.
76. ^ Bottazzo, GF; Florin-Christensen, A; Doniach, D (Nov 30, 1974). "Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies.". *Lancet*. **2** (7892): 1279–83. doi:10.1016/s0140-6736(74)90140-8. PMID 4139522.
77. ^ Herold, KC; Vignali, DA; Cooke, A; Bluestone, JA (April 2013). "Type 1 diabetes: translating mechanistic observations into effective clinical outcomes.". *Nature reviews. Immunology*. **13** (4): 243–56. doi:10.1038/nri3422. PMID 23524461.
78. ^ Shaw, Jonathan (2012). "diabetes: the silent pandemic and its impact on Australia" (PDF). Retrieved October 19, 2016.
79. ^ Australian Institute of Health and Welfare (2015). "Incidence of type 1 diabetes in Australia 2000–2013". Retrieved October 19, 2016.
80. ^ Johnson, Linda (18 November 2008). "Study: Cost of diabetes $218B". *USA Today*. Associated Press.
81. ^ Diabetes Research and Wellness Foundation
82. ^ *a b* Minami, K; Seino, S (18 March 2013). "Current status of regeneration of pancreatic β-cells.". *Journal of diabetes investigation*. **4** (2): 131–41. doi:10.1111/jdi.12062. PMID 24843642.
83. ^ Pagliuca, FW; Millman, JR; Gürtler, M; Segel, M; Van Dervort, A; Ryu, JH; Peterson, QP; Greiner, D; Melton, DA (9 October 2014). "Generation of functional human pancreatic β cells in vitro.". *Cell*. **159** (2): 428–39. doi:10.1016/j.cell.2014.09.040. PMID 25303535.
84. ^ Rezania, A; Bruin, JE; Arora, P; Rubin, A; Batushansky, I; Asadi, A; O'Dwyer, S; Quiskamp, N; Mojibian, M; Albrecht, T; Yang, YH; Johnson, JD; Kieffer, TJ (November 2014). "Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells.". *Nature Biotechnology*. **32** (11): 1121–33. doi:10.1038/nbt.3033. PMID 25211370.
85. ^ *a b c* Lernmark A, Larsson HE (Feb 2013). "Immune therapy in type 1 diabetes mellitus". *Nat Rev Endocrinol*. **9** (2): 92–103. doi:10.1038/nrendo.2012.237. PMID 23296174.
86. ^ *a b* Antvorskov, Julie C.; Josefsen, Knud; Engkilde, Kåre; Funda, David P.; Buschard, Karsten (2014-01-01). "Dietary gluten and the development of type 1 diabetes". *Diabetologia* (Review). **57** (9): 1770–1780. doi:10.1007/s00125-014-3265-1. ISSN 0012-186X. PMC 4119241. PMID 24871322.

87. ^ "Diabetes Mellitus (DM): Diabetes Mellitus and Disorders of Carbohydrate Metabolism: Merck Manual Professional". Merck.com. Retrieved 30 July 2010.
88. ^ Dorner M, Pinget M, Brogard JM (May 1977). "[Essential labile diabetes (author's transl)]". *MMW Munch Med Wochenschr*. **119** (19): 671–4. PMID 406527.
89. ^ Cartwright A, Wallymahmed M, Macfarlane IA, Wallymahmed A, Williams G, Gill GV (2011). "The outcome of brittle type 1 diabetes--a 20 year study". *QJM*. **104** (7): 575–9. doi:10.1093/qjmed/hcr010. PMID 21285231.
90. ^ Kent LA, Gill GV, Williams G (September 1994). "Mortality and outcome of patients with brittle diabetes and recurrent ketoacidosis". *Lancet*. **344** (8925): 778–81. doi:10.1016/S0140-6736(94)92340-X. PMID 7916072.
91. ^ *a b* Davidson MB, Kumar D, Smith W (1991). "Successful treatment of unusual case of brittle diabetes with sulfated beef insulin". *Diabetes Care*. **14** (11): 1109–10. doi:10.2337/diacare.14.1.1109b. PMID 1797500.
92. ^ Fineberg SE, Kawabata TT, Finco-Kent D, Fountaine RJ, Finch GL, Krasner AS (2007). "Immunological Responses to Exogenous Insulin". *Endocrine Reviews*. **28** (6): 625–52. doi:10.1210/er.2007-0002. PMID 17785428.


## External links [edit]

- Diabetes mellitus type 1 at DMOZ
- Kids and Teens: Type 1 Diabetes at DMOZ
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) – Diabetes in America Textbook (PDFs)
- IDF Diabetes Atlas
- International Diabetes Federation
- type 1 Diabetes at the American Diabetes Association
- National Diabetes Information Clearinghouse

| v · t · e · | Diseases of the endocrine system (E00–E35, 240–259) | | |
|---|---|---|---|
| **Pancreas/ glucose metabolism** | **Hypofunction** | Diabetes mellitus · *types:* (**type 1** · type 2 · MODY 1 2 3 4 5 6 · · *complications* (coma · angiopathy · ketoacidosis · nephropathy · neuropathy · retinopathy · cardiomyopathy · · *insulin receptor* (Rabson–Mendenhall syndrome) · Insulin resistance · | |
| | **Hyperfunction** | Hypoglycemia · *beta cell* (Hyperinsulinism) · *G cell* (Zollinger–Ellison syndrome) · | |
| | **Hypothalamus** | *gonadotropin* (Kallmann syndrome · Adiposogenital dystrophy · · *CRH* (Tertiary adrenal insufficiency) · *vasopressin* (Neurogenic diabetes insipidus) · *general* (Hypothalamic hamartoma) · | |
| | **Pituitary** | **Hyperpituitarism** | *anterior* (Acromegaly · Hyperprolactinaemia · Pituitary ACTH hypersecretion · · *posterior* (SIADH) · *general* (Nelson's syndrome) · |
| | | **Hypopituitarism** | *anterior* (Kallmann syndrome · Growth hormone deficiency · Hypoprolactinemia · ACTH deficiency/Secondary adrenal insufficiency · GnRH insensitivity · FSH insensitivity · LH/hCG insensitivity · · *posterior* (Neurogenic diabetes insipidus) · *general* (Empty sella syndrome · Pituitary apoplexy · Sheehan's syndrome · Lymphocytic hypophysitis · · |
| | | **Hypothyroidism** | Iodine deficiency · Cretinism (Congenital hypothyroidism · · Myxedema · |

| | | | |
|---|---|---|---|
| **Hypothalamic/ pituitary axes** | **Thyroid** | | Euthyroid sick syndrome · |
| | | **Hyperthyroidism** | Hyperthyroxinemia (Thyroid hormone resistance · Familial dysalbuminemic hyperthyroxinemia · · Hashitoxicosis · Thyrotoxicosis factitia · Graves' disease · |
| | | **Thyroiditis** | Acute infectious · Subacute (De Quervain's · Subacute lymphocytic · · Autoimmune/chronic (Hashimoto's · Postpartum · Riedel's · · |
| | | **Goitre** | Endemic goitre · Toxic nodular goitre · Toxic multinodular goiter · Thyroid nodule · |
| | **Parathyroid** | **Hypoparathyroidism** | Hypoparathyroidism · Pseudohypoparathyroidism · Pseudopseudohypoparathyroidism · |
| | | **Hyperparathyroidism** | Primary · Secondary · Tertiary · Osteitis fibrosa cystica · |
| | **Adrenal** | **Hyperfunction** | *aldosterone:* Hyperaldosteronism/Primary aldosteronism (Conn syndrome · Bartter syndrome · Glucocorticoid remediable aldosteronism · · AME · Liddle's syndrome · 17α CAH · *cortisol:* Cushing's syndrome (Pseudo-Cushing's syndrome) · *sex hormones:* 21α CAH · 11β CAH · |
| | | **Hypofunction/ Adrenal insufficiency (Addison's, WF)** | *aldosterone:* Hypoaldosteronism (21α CAH · 11β CAH · · *cortisol:* CAH (Lipoid · 3β · 11β · 17α · 21α · · *sex hormones:* 17α CAH · |
| | **Gonads** | | *ovarian:* Polycystic ovary syndrome · Premature ovarian failure · *testicular: enzymatic* (5α-reductase deficiency · 17β-hydroxysteroid dehydrogenase deficiency · aromatase excess syndrome) · · *Androgen receptor* (Androgen insensitivity syndrome) · *general:* Hypogonadism (Delayed puberty) · Hypergonadism (Precocious puberty · · Hypoandrogenism · Hypoestrogenism · Hyperandrogenism · Hyperestrogenism · Postorgasmic illness syndrome · |
| **Height** | | | Dwarfism/Short stature (Midget · Laron syndrome · Psychosocial · Ateliosis · · Gigantism · |
| **Multiple** | | | Autoimmune polyendocrine syndrome multiple (APS1 · APS2 · · Carcinoid syndrome · Multiple endocrine neoplasia (1 · 2A · 2B · · Progeria (Werner syndrome · Acrogeria · Metageria · · Woodhouse-Sakati syndrome · |

| v · t · e · | **Diabetes (E10–E14, 250)** |
|---|---|
| **Types** | **Type 1** · Type 2 · Gestational diabetes (Diabetes and pregnancy · · Prediabetes (Impaired fasting glucose · Impaired glucose tolerance · · Insulin resistance · LADA · KPD · MODY · Neonatal (Transient · Permanent · · Type 3c (Pancreatogenic) · |

| | |
|---|---|
| **Blood tests** | Blood sugar · Glycosylated hemoglobin · Glucose tolerance test · Postprandial glucose test · Fructosamine · Glucose test · C-peptide · Noninvasive glucose monitor · Insulin tolerance test · |
| **Management** | Diabetic diet · Anti-diabetic drugs · Insulin therapy (intensive · conventional · pulsatile · · Cure (Embryonic stem cells · Artificial pancreas · · Other (Gastric bypass surgery · · |
| **Complications** | Diabetic comas (Hypoglycemia · Ketoacidosis · Hyperosmolar hyperglycemic state · · Diabetic foot (ulcer · Neuropathic arthropathy · · Organs in diabetes (Blood vessels · Muscle · Kidney · Nerves · Retina · Heart · · Diabetic skin disease (Diabetic dermopathy · Diabetic bulla · Diabetic cheiroarthropathy · Neuropathic ulcer · · Hyperglycemia · Hypoglycemia · |
| **Other** | Glossary of diabetes · |

| v · t · e · | **Hypersensitivity and autoimmune diseases (279.5–6)** | | |
|---|---|---|---|
| **Type I/allergy/atopy (IgE)** | **Foreign** | | Atopic eczema · Allergic urticaria · Allergic rhinitis (Hay fever) · Allergic asthma · Anaphylaxis · Food allergy (common allergies include: Milk · Egg · Peanut · Tree nut · Seafood · Soy · Wheat · · Penicillin allergy · |
| | **Autoimmune** | | Eosinophilic esophagitis · |
| **Type II/ADCC (IgM · IgG · ·** | **Foreign** | | Hemolytic disease of the newborn · |
| | **Autoimmune** | **Cytotoxic** | Autoimmune hemolytic anemia · Immune thrombocytopenic purpura · Bullous pemphigoid · Pemphigus vulgaris · Rheumatic fever · Goodpasture's syndrome · Guillain–Barré syndrome · |
| | | **"Type V"/receptor** | Graves' disease · Myasthenia gravis · Pernicious anemia · |
| **Type III (Immune complex)** | **Foreign** | | Henoch–Schönlein purpura · Hypersensitivity vasculitis · Reactive arthritis · Farmer's lung · Post-streptococcal glomerulonephritis · Serum sickness · Arthus reaction · |
| | **Autoimmune** | | Systemic lupus erythematosus · Subacute bacterial endocarditis · Rheumatoid arthritis · |
| **Type IV/cell-mediated (T cells)** | **Foreign** | | Allergic contact dermatitis · Mantoux test · |
| | **Autoimmune** | | **Diabetes mellitus type 1** · Hashimoto's thyroiditis · Multiple sclerosis · Coeliac disease · Giant-cell arteritis · Postorgasmic illness syndrome · Reactive arthritis · |
| | **GVHD** | | Transfusion-associated graft versus host disease · |
| **Unknown/multiple** | **Foreign** | | Hypersensitivity pneumonitis (Allergic bronchopulmonary aspergillosis · · Transplant rejection · Latex allergy (I+IV) · |
| | **Autoimmune** | | Sjögren's syndrome · Autoimmune hepatitis · Autoimmune polyendocrine syndrome (APS1 · APS2 · · Autoimmune adrenalitis · Systemic autoimmune disease · |

Categories: Diabetes | Autoimmune diseases | Enterovirus-associated diseases


# Diabetes mellitus type 2

From Wikipedia, the free encyclopedia

(Redirected from DM type 2)



**Diabetes mellitus type 2** (also known as **type 2 diabetes**) is a long term metabolic disorder that is characterized by high blood sugar, insulin resistance, and relative lack of insulin.[3] Common symptoms include increased thirst, frequent urination, and unexplained weight loss. Symptoms may also include increased hunger, feeling tired, and sores that do not heal.[4] Often symptoms come on slowly.[3] Long-term complications from high blood sugar include heart disease, strokes, diabetic retinopathy which can result in blindness, kidney failure, and poor blood flow in the limbs which may lead to amputations.[1] The sudden onset of hyperosmolar hyperglycemic state may occur; however, ketoacidosis is uncommon.[5][6]

Type 2 diabetes primarily occurs as a result of obesity and not enough exercise.[1] Some people are more genetically at risk than others.[3] Type 2 diabetes makes up about 90% of cases of diabetes, with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes.[1] In diabetes mellitus type 1 there is an absolute lack of insulin due to breakdown of islet cells in the pancreas.[7] Diagnosis of diabetes is by blood tests such as fasting plasma glucose, oral glucose tolerance test, or A1C.[4]

Type 2 diabetes is partly preventable by staying a normal weight, exercising regularly, and eating properly. Treatment involves exercise and dietary changes.[1] If blood sugar levels are not adequately lowered, the medication metformin is typically recommended.[8][9] Many people may eventually also require insulin injections.[10] In those on insulin, routinely checking blood sugar levels is advised, however this may not be needed in those taking pills.[11] Bariatric surgery often improves diabetes in those who are obese.[12][13]

Rates of type 2 diabetes have increased markedly since 1960 in parallel with obesity.[14] As of 2013 there were

| Diabetes mellitus type 2 | |
|---|---|
| **Synonyms** | noninsulin-dependent diabetes mellitus (NIDDM), adult-onset diabetes[1] |

Universal blue circle symbol for diabetes[2]

**Pronunciation** /daɪəbiːtiːs/

| Classification and external resources | |
|---|---|
| **Specialty** | Endocrinology |
| **ICD-10** | E11 |
| **ICD-9-CM** | 250.00, 250.02 |
| **OMIM** | 125853 |
| **DiseasesDB** | 3661 |
| **MedlinePlus** | 000313 |

| | |
|---|---|
| **eMedicine** | article/117853 |
| **MeSH** | D003924 |

[edit on Wikidata]

approximately 368 million people diagnosed with the disease compared to around 30 million in 1985.[15][16] Typically it begins in middle or older age,[3] although rates of type 2 diabetes are increasing in young people.[17][18] Type 2 diabetes is associated with a ten-year-shorter life expectancy.[19] Diabetes was one of the first diseases described.[20] The importance of insulin in the disease was determined in the 1920s.[21]

Contents



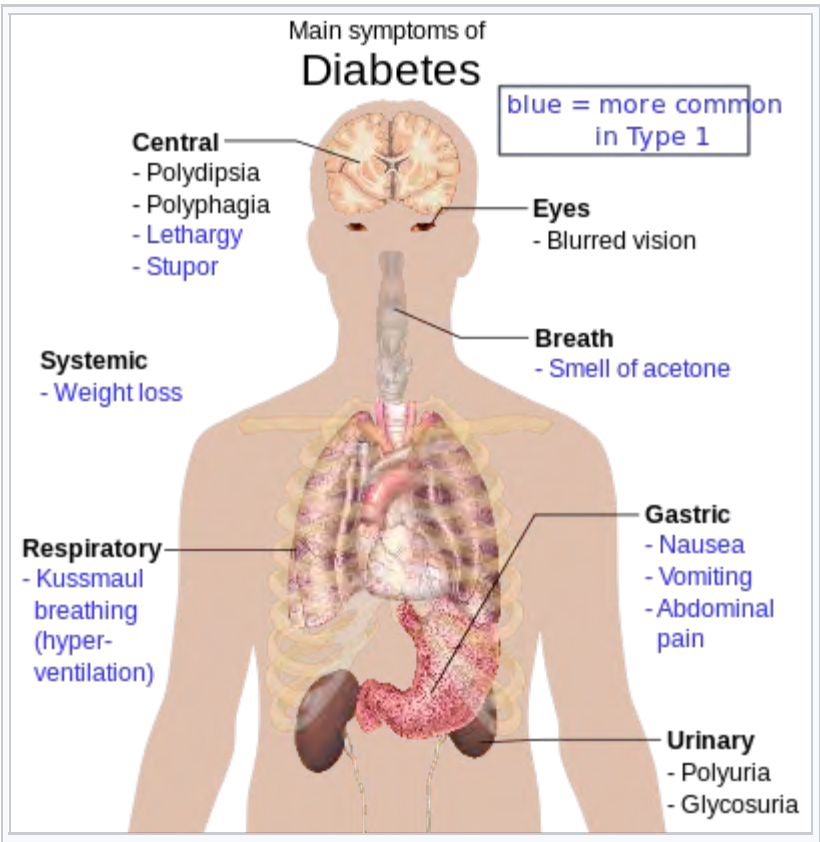



Play media

Video explanation of the various types of diabetes

# Signs and symptoms

The classic symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss.[22] Other symptoms that are commonly present at diagnosis include a history of blurred vision, itchiness, peripheral neuropathy, recurrent vaginal infections, and fatigue.[7] Many people, however, have no symptoms during the first few years and are diagnosed on routine testing.[7] People with type 2 diabetes mellitus may rarely present with hyperosmolar hyperglycemic state (a condition of very high blood sugar associated with a decreased level of consciousness and low blood pressure).[7]




## Complications

*Main article: Complications of diabetes mellitus*

Type 2 diabetes is typically a chronic disease associated with a ten-year-shorter life expectancy.[19] This is partly due to a number of complications with which it is associated,

Overview of the most significant symptoms of diabetes.

including: two to four times the risk of cardiovascular disease, including ischemic heart disease and stroke; a 20-fold increase in lower limb amputations, and increased rates of hospitalizations.[19] In the developed world, and increasingly elsewhere, type 2 diabetes is the largest cause of nontraumatic blindness and kidney failure.[23] It has also been associated with an increased risk of cognitive dysfunction and dementia through disease processes such as Alzheimer's disease and vascular dementia.[24] Other complications include acanthosis nigricans, sexual dysfunction, and frequent infections.[22]

# Cause

The development of type 2 diabetes is caused by a combination of lifestyle and genetic factors.[23][25] While some of these factors are under personal control, such as diet and obesity, other factors are not, such as increasing age, female gender, and genetics.[19] A lack of sleep has been linked to type 2 diabetes.[26] This is believed to act through its effect on metabolism.[26] The nutritional status of a mother during fetal development may also play a role, with one proposed mechanism being that of altered DNA methylation.[27] The intestinal bacteriæ Prevotella copri and Bacteroides vulgatus have been connected with type 2 diabetes.[28]

## Lifestyle

*Main article: Lifestyle causes of diabetes mellitus type 2*

Lifestyle factors are important to the development of type 2 diabetes, including obesity and being overweight (defined by a body mass index of greater than 25), lack of physical activity, poor diet, stress, and urbanization.[19][29] Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60–80% of cases in those of European and African descent, and 100% of cases in Pima Indians and Pacific Islanders.[7] Among those who are not obese, a high waist–hip ratio is often present.[7] Smoking appears to increase the risk of type 2 diabetes mellitus.[30]

Dietary factors also influence the risk of developing type 2 diabetes. Consumption of sugar-sweetened drinks in excess is associated with an increased risk.[31][32] The type of fats in the diet are important, with saturated fats and trans fatty acids increasing the risk, and polyunsaturated and monounsaturated fat decreasing the risk.[25] Eating a lot of white rice appears to play a role in increasing risk.[33] A lack of exercise is believed to cause 7% of cases.[34] Persistent organic pollutants may play a role.[35]

## Genetics

*Main article: Genetic causes of diabetes mellitus type 2*

Most cases of diabetes involve many genes, with each being a small contributor to an increased probability of becoming a type 2 diabetic.[19] If one identical twin has diabetes, the chance of the other developing diabetes within his lifetime is greater than 90%, while the rate for nonidentical siblings is 25–50%.[7] As of 2011, more than 36 genes had been found that contribute to the risk of type 2 diabetes.[36] All of these genes together still only account for 10% of the total heritable component of the disease.[36] The TCF7L2 allele, for example, increases the risk of developing diabetes by 1.5 times and is the greatest risk of the common genetic variants.[7] Most of the genes linked to diabetes are involved in beta cell functions.[7]

There are a number of rare cases of diabetes that arise due to an abnormality in a single gene (known as monogenic forms of diabetes or "other specific types of diabetes").[7][19] These include maturity onset diabetes of the young (MODY), Donohue syndrome, and Rabson-Mendenhall syndrome, among others.[19] Maturity onset diabetes of the young constitute 1–5% of all cases of diabetes in young people.[37]

## Medical conditions

There are a number of medications and other health problems that can predispose to diabetes.[38] Some of the medications include: glucocorticoids, thiazides, beta blockers, atypical antipsychotics,[39] and statins.[40] Those who have previously had gestational diabetes are at a higher risk of developing type 2 diabetes.[22] Other health problems that are associated include: acromegaly, Cushing's syndrome, hyperthyroidism, pheochromocytoma, and certain cancers such as glucagonomas.[38] Testosterone deficiency is also associated with type 2 diabetes.[41][42]

# Pathophysiology

Type 2 diabetes is due to insufficient insulin production from beta cells in the setting of insulin resistance.[7] Insulin resistance, which is the inability of cells to respond adequately to normal levels of insulin, occurs primarily within the muscles, liver, and fat tissue.[43] In the liver, insulin normally suppresses glucose release. However, in the setting of insulin resistance, the liver inappropriately releases glucose into the blood.[19] The proportion of insulin resistance versus beta cell dysfunction differs among individuals, with some having primarily insulin resistance and only a minor defect in insulin secretion and others with slight insulin resistance and primarily a lack of insulin secretion.[7]

Other potentially important mechanisms associated with type 2 diabetes and insulin resistance include: increased breakdown of lipids within fat cells, resistance to and lack of incretin, high glucagon levels in the blood, increased retention of salt and water by the kidneys, and inappropriate regulation of metabolism by the central nervous system.[19] However, not all people with insulin resistance develop diabetes, since an impairment of insulin secretion by pancreatic beta cells is also required.[7]

# Diagnosis

**WHO diabetes diagnostic criteria**[44][45] edit

| Condition | 2 hour glucose | Fasting glucose | $HbA_{1c}$ | |
|---|---|---|---|---|
| Unit | mmol/l(mg/dl) | mmol/l(mg/dl) | mmol/mol | DCCT % |
| Normal | <7.8 (<140) | <6.1 (<110) | <42 | <6.0 |
| Impaired fasting glycaemia | <7.8 (<140) | ≥6.1(≥110) & <7.0(<126) | 42-46 | 6.0–6.4 |
| Impaired glucose tolerance | ≥7.8 (≥140) | <7.0 (<126) | 42-46 | 6.0–6.4 |
| Diabetes mellitus | ≥11.1 (≥200) | ≥7.0 (≥126) | ≥48 | ≥6.5 |

The World Health Organization definition of diabetes (both type 1 and type 2) is for a single raised glucose reading with symptoms, otherwise raised values on two occasions, of either:[46]

- fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl)
  or
- with a glucose tolerance test, two hours after the oral dose a plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

A random blood sugar of greater than 11.1 mmol/l (200 mg/dL) in association with typical symptoms[22] or a glycated hemoglobin ($HbA_{1c}$) of ≥ 48 mmol/mol (≥ 6.5 DCCT %) is another method of diagnosing diabetes.[19] In 2009 an International Expert Committee that included representatives of the American Diabetes Association (ADA), the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes (EASD) recommended that a threshold of ≥ 48 mmol/mol (≥ 6.5 DCCT %) should be used to diagnose diabetes.[47] This recommendation was adopted by the American Diabetes Association in [48]

2010. Positive tests should be repeated unless the person presents with typical symptoms and blood sugars >11.1 mmol/l (>200 mg/dl).[47]

Threshold for diagnosis of diabetes is based on the relationship between results of glucose tolerance tests, fasting glucose or $HbA_{1c}$ and complications such as retinal problems.[19] A fasting or random blood sugar is preferred over the glucose tolerance test, as they are more convenient for people.[19] $HbA_{1c}$ has the advantages that fasting is not required and results are more stable but has the disadvantage that the test is more costly than measurement of blood glucose.[49] It is estimated that 20% of people with diabetes in the United States do not realize that they have the disease.[19]

Diabetes mellitus type 2 is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency.[50] This is in contrast to diabetes mellitus type 1 in which there is an absolute insulin deficiency due to destruction of islet cells in the pancreas and gestational diabetes mellitus that is a new onset of high blood sugars associated with pregnancy.[7] Type 1 and type 2 diabetes can typically be distinguished based on the presenting circumstances.[47] If the diagnosis is in doubt antibody testing may be useful to confirm type 1 diabetes and C-peptide levels may be useful to confirm type 2 diabetes,[51] with C-peptide levels normal or high in type 2 diabetes, but low in type 1 diabetes.[52]

## Screening

No major organization recommends universal screening for diabetes as there is no evidence that such a program improve outcomes.[53][54] Screening is recommended by the United States Preventive Services Task Force (USPSTF) in adults without symptoms whose blood pressure is greater than 135/80 mmHg.[55] For those whose blood pressure is less, the evidence is insufficient to recommend for or against screening.[55] There is no evidence that it changes the risk of death in this group of people.[56] They also recommend screening among those who are overweight and between the ages of 40 and 70.[57]

The World Health Organization recommends testing those groups at high risk[53] and in 2014 the USPSTF is considering a similar recommendation.[58] High-risk groups in the United States include: those over 45 years old; those with a first degree relative with diabetes; some ethnic groups, including Hispanics, African-Americans, and Native-Americans; a history of gestational diabetes; polycystic ovary syndrome; excess weight; and conditions associated with metabolic syndrome.[22] The American Diabetes Association recommends screening those who have a BMI over 25 (in people of Asian descent screening is recommending for a BMI over 23.[59]

## Prevention

*Main article: Prevention of diabetes mellitus type 2*

Onset of type 2 diabetes can be delayed or prevented through proper nutrition and regular exercise.[60][61] Intensive lifestyle measures may reduce the risk by over half.[23][62] The benefit of exercise occurs regardless of the person's initial weight or subsequent weight loss.[63] High levels of physical activity reduce the risk of diabetes by about 28%.[64] Evidence for the benefit of dietary changes alone, however, is limited,[65] with some evidence for a diet high in green leafy vegetables[66] and some for limiting the intake of sugary drinks.[31] In those with impaired glucose tolerance, diet and exercise either alone or in combination with metformin or acarbose may decrease the risk of developing diabetes.[23][67] Lifestyle interventions are more effective than metformin.[23] While low vitamin D levels are associated with an increased risk of diabetes, correcting the levels by supplementing vitamin D3 does not improve that risk.[68]

## Management

*Further information: Diabetes management*

Management of type 2 diabetes focuses on lifestyle interventions, lowering other cardiovascular risk factors, and maintaining blood glucose levels in the normal range.[23] Self-monitoring of blood glucose for people with newly diagnosed type 2 diabetes may be used in combination with education,[69] however the benefit of self monitoring in those not using multi-dose insulin is questionable.[23][70] In those who do not want to measure blood levels, measuring urine levels may be done.[69] Managing other cardiovascular risk factors, such as hypertension, high cholesterol, and microalbuminuria, improves a person's life expectancy.[23] Decreasing the systolic blood pressure to less than 140 mmHg is associated with a lower risk of death and better outcomes.[71] Intensive blood pressure management (less than 130/80 mmHg) as opposed to standard blood pressure management (less than 140/85–100 mmHg) results in a slight decrease in stroke risk but no effect on overall risk of death.[72]

Intensive blood sugar lowering ($HbA_{1c}$<6%) as opposed to standard blood sugar lowering ($HbA_{1c}$ of 7–7.9%) does not appear to change mortality.[73][74] The goal of treatment is typically an $HbA_{1c}$ of around 7% or a fasting glucose of less than 7.2 mmol/L (130 mg/dL); however these goals may be changed after professional clinical consultation, taking into account particular risks of hypoglycemia and life expectancy.[75][59] It is recommended that all people with type 2 diabetes get regular ophthalmology examination.[7] Treating gum disease in those with diabetes may result in a small improvement in blood sugar levels.[76]

## Lifestyle

A proper diet and exercise are the foundations of diabetic care,[22] with a greater amount of exercise yielding better results.[77] Aerobic exercise leads to a decrease in $HbA_{1c}$ and improved insulin sensitivity.[77] Resistance training is also useful and the combination of both types of exercise may be most effective.[77] A diabetic diet that promotes weight loss is important.[78] While the best diet type to achieve this is controversial,[78] a low glycemic index diet or low carbohydrate diet has been found to improve blood sugar control.[79][80] Culturally appropriate education may help people with type 2 diabetes control their blood sugar levels, for up to six months at least.[81][*needs update*] If changes in lifestyle in those with mild diabetes has not resulted in improved blood sugars within six weeks, medications should then be considered.[22] There is not enough evidence to determine if lifestyle interventions affect mortality in those who already have DM2.[62] Vegetarian diets in general have been related to lower diabetes risk, but do not offer advantages compared with diets which allow moderate amounts of animal products.[82] There is not enough evidence to suggest that cinnamon improves blood sugar levels in people with type 2 diabetes.[83]

## Medications

There are several classes of anti-diabetic medications available. Metformin is generally recommended as a first line treatment as there is some evidence that it decreases mortality;[9][23][84] however, this conclusion is questioned.[85] Metformin should not be used in those with severe kidney or liver problems.[22]

A second oral agent of another class or insulin may be added if metformin is not sufficient after three months.[75] Other classes of medications include: sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, SGLT2 inhibitors, and glucagon-like peptide-1 analogs.[75] There is no significant difference between these agents.[75] Rosiglitazone, a thiazolidinedione, has not been found to improve long-term outcomes even though it improves blood

Metformin 500mg tablets.

sugar levels.[86] Additionally it is associated with increased rates of heart disease and death.[87] Angiotensin-converting enzyme inhibitors (ACEIs) prevent kidney disease and improve outcomes in those with diabetes.[88][89] The similar medications angiotensin receptor blockers (ARBs) do not.[89] A 2016 review recommended treating to a systolic blood pressure of 140 to 150 mmHg.[90]

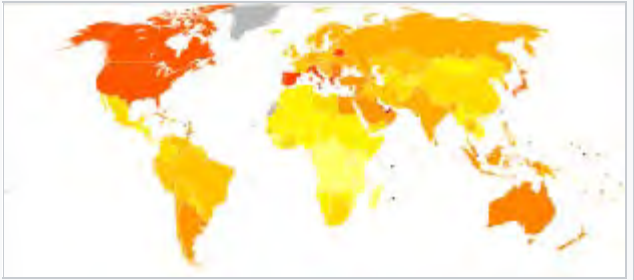
Injections of insulin may either be added to oral medication or used alone.[23] Most people do not initially need insulin.[7] When it is used, a long-acting formulation is typically added at night, with oral medications being continued.[22][23] Doses are then increased to effect (blood sugar levels being well controlled).[23] When nightly insulin is insufficient, twice daily insulin may achieve better control.[22] The long acting insulins glargine and detemir are equally safe and effective,[91] and do not appear much better than neutral protamine Hagedorn (NPH) insulin, but as they are significantly more expensive, they are not cost effective as of 2010.[92] In those who are pregnant insulin is generally the treatment of choice.[22]

### Surgery

Weight loss surgery in those who are obese is an effective measure to treat diabetes.[93] Many are able to maintain normal blood sugar levels with little or no medications following surgery[94] and long-term mortality is decreased.[95] There however is some short-term mortality risk of less than 1% from the surgery.[96] The body mass index cutoffs for when surgery is appropriate are not yet clear.[95] It is recommended that this option be considered in those who are unable to get both their weight and blood sugar under control.[97][98]

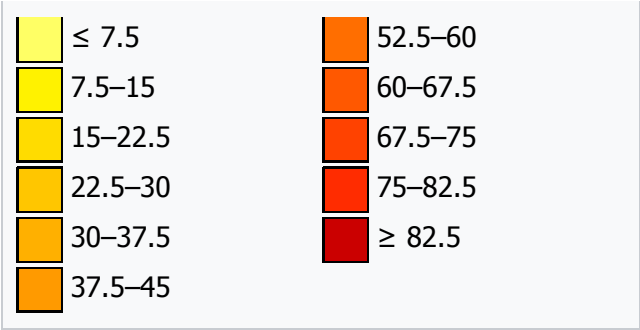
## Epidemiology

Globally as of 2010 it was estimated that there were 285 million people with type 2 diabetes making up about 90% of diabetes cases.[19] This is equivalent to about 6% of the world's adult population.[99] Diabetes is common both in the developed and the developing world.[19] It remains uncommon, however, in the underdeveloped world.[7]


Prevalence of diabetes worldwide in 2000.
World average was 28 per 1000 inhabitants.
no data
45–52.5

Women seem to be at a greater risk as do certain ethnic groups,[19][100] such as South Asians, Pacific Islanders, Latinos, and Native Americans.[22] This may be due to enhanced sensitivity to a Western lifestyle in certain ethnic

groups.[101] Traditionally considered a disease of adults, type 2 diabetes is increasingly diagnosed in children in parallel with rising obesity rates.[19] Type 2 diabetes is now diagnosed as frequently as type 1 diabetes in teenagers in the United States.[7]




Rates of diabetes in 1985 were estimated at 30 million, increasing to 135 million in 1995 and 217 million in 2005.[15] This increase is believed to be primarily due to the global population aging, a decrease in exercise, and increasing rates of obesity.[15] The five countries with the greatest number of people with diabetes as of 2000 are India having 31.7 million, China 20.8 million, the United States 17.7 million, Indonesia 8.4 million, and Japan 6.8 million.[102] It is recognized as a global epidemic by the World Health Organization.[103]

# History

*Main article: History of diabetes*

Diabetes is one of the first diseases described[20] with an Egyptian manuscript from c. 1500 BCE mentioning "too great emptying of the urine."[104] The first described cases are believed to be of type 1 diabetes.[104] Indian physicians around the same time identified the disease and classified it as *madhumeha* or *honey urine* noting that the urine would attract ants.[104] The term "diabetes" or "to pass through" was first used in 230 BCE by the Greek Apollonius Of Memphis.[104] The disease was rare during the time of the Roman empire with Galen commenting that he had only seen two cases during his career.[104]

Type 1 and type 2 diabetes were identified as separate conditions for the first time by the Indian physicians Sushruta and Charaka in 400–500 AD with type 1 associated with youth and type 2 with being overweight.[104] The term "mellitus" or "from honey" was added by the Briton John Rolle in the late 1700s to separate the condition from diabetes insipidus which is also associated with frequent urination.[104] Effective treatment was not developed until the early part of the 20th century when the Canadians Frederick Banting and Charles Best discovered insulin in 1921 and 1922.[104] This was followed by the development of the long acting NPH insulin in the 1940s.[104]

# References


1. ^ *a b c d e* "Diabetes Fact sheet N°312". *WHO*. January 2015. Archived from the original on 26 August 2013. Retrieved 10 February 2016.
2. ^ "Diabetes Blue Circle Symbol". International Diabetes Federation. 17 March 2006.
3. ^ *a b c d* "Causes of Diabetes". *National Institute of Diabetes and Digestive and Kidney Diseases*. June 2014. Retrieved 10 February 2016.
4. ^ *a b* "Diagnosis of Diabetes and Prediabetes". *National Institute of Diabetes and Digestive and Kidney Diseases*. June 2014. Retrieved 10 February 2016.
5. ^ Pasquel, FJ; Umpierrez, GE (November 2014). "Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment.". *Diabetes Care*. **37** (11): 3124–31. doi:10.2337/dc14-0984. PMC 4207202. PMID 25342831.
6. ^ Fasanmade, OA; Odeniyi, IA; Ogbera, AO (June 2008). "Diabetic ketoacidosis: diagnosis and management". *African journal of medicine and medical sciences*. **37** (2): 99–105. PMID 18939392.
7. ^ *a b c d e f g h i j k l m n o p q r* Shoback, edited by David G. Gardner, Dolores (2011). *Greenspan's basic & clinical endocrinology* (9th ed.). New York: McGraw-Hill Medical. pp. Chapter 17. ISBN 0-07-162243-8.
8. ^ Saenz, A; Fernandez-Esteban, I; Mataix, A; Ausejo, M; Roque, M; Moher, D (20 July 2005). "Metformin monotherapy for type 2 diabetes mellitus.". *The Cochrane database of systematic reviews* (3): CD002966. doi:10.1002/14651858.CD002966.pub3. PMID 16034881.

9. ^ a b Maruthur, NM; Tseng, E; Hutfless, S; Wilson, LM; Suarez-Cuervo, C; Berger, Z; Chu, Y; Iyoha, E; Segal, JB; Bolen, S (19 April 2016). "Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis.". *Annals of Internal Medicine*. **164**: 740. doi:10.7326/M15-2650. PMID 27088241.
10. ^ Krentz, AJ; Bailey, CJ (2005). "Oral antidiabetic agents: current role in type 2 diabetes mellitus.". *Drugs*. **65** (3): 385–411. doi:10.2165/00003495-200565030-00005. PMID 15669880.
11. ^ Malanda, UL; Welschen, LM; Riphagen, II; Dekker, JM; Nijpels, G; Bot, SD (18 January 2012). "Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin.". *The Cochrane database of systematic reviews*. **1**: CD005060. doi:10.1002/14651858.CD005060.pub3. PMID 22258959.
12. ^ Cetinkunar, S; Erdem, H; Aktimur, R; Sozen, S (16 June 2015). "Effect of bariatric surgery on humoral control of metabolic derangements in obese patients with type 2 diabetes mellitus: How it works.". *World journal of clinical cases*. **3** (6): 504–9. doi:10.12998/wjcc.v3.i6.504. PMC 4468896. PMID 26090370.
13. ^ Ganguly, S; Tan, HC; Lee, PC; Tham, KW (April 2015). "Metabolic bariatric surgery and type 2 diabetes mellitus: an endocrinologist's perspective.". *Journal of biomedical research*. **29** (2): 105–11. doi:10.7555/JBR.29.20140127. PMC 4389109. PMID 25859264.
14. ^ Lewenson, [edited by] Marie Truglio-Londrigan, Sandra B. (2013). *Public health nursing : practicing population-based care* (2nd ed.). Burlington, Mass.: Jones & Bartlett Learning. p. 317. ISBN 9781449646608.
15. ^ a b c Smyth, S; Heron, A (January 2006). "Diabetes and obesity: the twin epidemics". *Nature Medicine*. **12** (1): 75–80. doi:10.1038/nm0106-75. PMID 16397575.
16. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/S0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
17. ^ Tfayli, H; Arslanian, S (March 2009). "Pathophysiology of type 2 diabetes mellitus in youth: the evolving chameleon.". *Arquivos brasileiros de endocrinologia e metabologia*. **53** (2): 165–74. doi:10.1590/s0004-27302009000200008. PMC 2846552. PMID 19466209.
18. ^ Imperatore, Giuseppina; Boyle, James P.; Thompson, Theodore J.; Case, Doug; Dabelea, Dana; Hamman, Richard F.; Lawrence, Jean M.; Liese, Angela D.; Liu, Lenna L. (2012-12-01). "Projections of Type 1 and Type 2 Diabetes Burden in the U.S. Population Aged <20 Years Through 2050". *Diabetes Care*. **35** (12): 2515–2520. doi:10.2337/dc12-0669. ISSN 0149-5992. PMC 3507562. PMID 23173134.
19. ^ a b c d e f g h i j k l m n o p q r *Williams textbook of endocrinology.* (12th ed.). Philadelphia: Elsevier/Saunders. pp. 1371–1435. ISBN 978-1-4377-0324-5.
20. ^ a b Ripoll, Brian C. Leutholtz, Ignacio (2011-04-25). *Exercise and disease management* (2nd ed.). Boca Raton: CRC Press. p. 25. ISBN 978-1-4398-2759-8.
21. ^ Zaccardi, F; Webb, DR; Yates, T; Davies, MJ (February 2016). "Pathophysiology of type 1 and type 2 diabetes mellitus: a 90-year perspective.". *Postgraduate Medical Journal*. **92** (1084): 63–9. doi:10.1136/postgradmedj-2015-133281. PMID 26621825.
22. ^ a b c d e f g h i j k l Vijan, S (2010-03-02). "Type 2 diabetes". *Annals of Internal Medicine*. **152** (5): ITC31–15; quiz ITC316. doi:10.7326/0003-4819-152-5-201003020-01003. PMID 20194231.
23. ^ a b c d e f g h i j k l Ripsin CM, Kang H, Urban RJ (January 2009). "Management of blood glucose in type 2 diabetes mellitus". *Am Fam Physician*. **79** (1): 29–36. PMID 19145963.
24. ^ Pasquier, F (October 2010). "Diabetes and cognitive impairment: how to evaluate the cognitive status?". *Diabetes & metabolism*. 36 Suppl 3: S100–5. doi:10.1016/S1262-3636(10)70475-4. PMID 21211730.
25. ^ a b Risérus U, Willett WC, Hu FB (January 2009). "Dietary fats and prevention of type 2 diabetes". *Progress in Lipid Research*. **48** (1): 44–51. doi:10.1016/j.plipres.2008.10.002. PMC 2654180. PMID 19032965.
26. ^ a b Touma, C; Pannain, S (August 2011). "Does lack of sleep cause diabetes?". *Cleveland Clinic journal of medicine*. **78** (8): 549–58. doi:10.3949/ccjm.78a.10165. PMID 21807927.
27. ^ Christian, P; Stewart, CP (March 2010). "Maternal micronutrient deficiency, fetal development, and the risk of chronic disease". *The Journal of Nutrition*. **140** (3): 437–45. doi:10.3945/jn.109.116327. PMID 20071652.
28. ^ "Human gut microbes impact host serum metabolome and insulin sensitivity". *Nature*. **535**: 376–381. doi:10.1038/nature18646.
29. ^ Abdullah, A; Peeters, A; de Courten, M; Stoelwinder, J (September 2010). "The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies.". *Diabetes research and clinical practice*. **89** (3): 309–19. doi:10.1016/j.diabres.2010.04.012. PMID 20493574.
30. ^ Pan, A; Wang, Y; Talaei, M; Hu, FB; Wu, T (17 September 2015). "Relation of active, passive, and quitting smoking with incident type 2 diabetes: a systematic review and meta-analysis.". *The Lancet. Diabetes & endocrinology*. **3**: 958–67. doi:10.1016/S2213-8587(15)00316-2. PMID 26388413.

31. ^ [a] [b] Malik, VS; Popkin, BM; Bray, GA; Després, JP; Hu, FB (2010-03-23). "Sugar Sweetened Beverages, Obesity, Type 2 Diabetes and Cardiovascular Disease risk". *Circulation*. **121** (11): 1356–64. doi:10.1161/CIRCULATIONAHA.109.876185. PMC 2862465. PMID 20308626.
32. ^ Malik, VS; Popkin, BM; Bray, GA; Després, JP; Willett, WC; Hu, FB (November 2010). "Sugar-Sweetened Beverages and Risk of Metabolic Syndrome and Type 2 Diabetes: A meta-analysis". *Diabetes Care*. **33** (11): 2477–83. doi:10.2337/dc10-1079. PMC 2963518. PMID 20693348.
33. ^ Hu, EA; Pan, A; Malik, V; Sun, Q (2012-03-15). "White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review". *BMJ (Clinical research ed.)*. **344**: e1454. doi:10.1136/bmj.e1454. PMC 3307808. PMID 22422870.
34. ^ Lee, I-Min; Shiroma, Eric J; Lobelo, Felipe; Puska, Pekka; Blair, Steven N; Katzmarzyk, Peter T (1 July 2012). "Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy". *The Lancet*. **380** (9838): 219–29. doi:10.1016/S0140-6736(12)61031-9. PMC 3645500. PMID 22818936.
35. ^ Lind, L; Lind, PM (Jun 2012). "Can persistent organic pollutants and plastic-associated chemicals cause cardiovascular disease?". *Journal of internal medicine*. **271** (6): 537–53. doi:10.1111/j.1365-2796.2012.02536.x. PMID 22372998.
36. ^ [a] [b] Herder, C; Roden, M (June 2011). "Genetics of type 2 diabetes: pathophysiologic and clinical relevance". *European journal of clinical investigation*. **41** (6): 679–92. doi:10.1111/j.1365-2362.2010.02454.x. PMID 21198561.
37. ^ "Monogenic Forms of Diabetes: Neonatal Diabetes Mellitus and Maturity-onset Diabetes of the Young". *National Diabetes Information Clearinghouse (NDIC)*. National Institute of Diabetes and Digestive and Kidney Diseases, NIH. March 2007. Retrieved 2008-08-04.
38. ^ [a] [b] Bethel, edited by Mark N. Feinglos, M. Angelyn (2008). *Type 2 diabetes mellitus: an evidence-based approach to practical management*. Totowa, NJ: Humana Press. p. 462. ISBN 978-1-58829-794-5.
39. ^ Izzedine, H; Launay-Vacher, V; Deybach, C; Bourry, E; Barrou, B; Deray, G (November 2005). "Drug-induced diabetes mellitus". *Expert opinion on drug safety*. **4** (6): 1097–109. doi:10.1517/14740338.4.6.1097. PMID 16255667.
40. ^ Sampson, UK; Linton, MF; Fazio, S (July 2011). "Are statins diabetogenic?". *Current Opinion in Cardiology*. **26** (4): 342–7. doi:10.1097/HCO.0b013e3283470359. PMC 3341610. PMID 21499090.
41. ^ Saad F, Gooren L (March 2009). "The role of testosterone in the metabolic syndrome: a review". *The Journal of Steroid Biochemistry and Molecular Biology*. **114** (1–2): 40–3. doi:10.1016/j.jsbmb.2008.12.022. PMID 19444934.
42. ^ Farrell JB, Deshmukh A, Baghaie AA (2008). "Low testosterone and the association with type 2 diabetes". *The Diabetes Educator*. **34** (5): 799–806. doi:10.1177/0145721708323100. PMID 18832284.
43. ^ *Diabetes mellitus a guide to patient care.* Philadelphia: Lippincott Williams & Wilkins. 2007. p. 15. ISBN 978-1-58255-732-8.
44. ^ *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation* (PDF). Geneva: World Health Organization. 2006. p. 21. ISBN 978-92-4-159493-6.
45. ^ Vijan, S (March 2010). "Type 2 diabetes". *Annals of Internal Medicine*. **152** (5): ITC31-15. doi:10.7326/0003-4819-152-5-201003020-01003. PMID 20194231.
46. ^ World Health Organization. "Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO Consultation. Part 1. Diagnosis and classification of diabetes mellitus". Retrieved 2007-05-29.
47. ^ [a] [b] [c] International Expert, Committee (July 2009). "International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes". *Diabetes Care*. **32** (7): 1327–34. doi:10.2337/dc09-9033. PMC 2699715. PMID 19502545.
48. ^ "Diagnosis and classification of diabetes mellitus". *Diabetes Care*. American Diabetes Association. 33 Suppl 1 (Supplement_1): S62–9. January 2010. doi:10.2337/dc10-S062. PMC 2797383. PMID 20042775.
49. ^ "Diagnosis and classification of diabetes mellitus". *Diabetes Care*. American Diabetes Association. 35 Suppl 1 (Suppl 1): S64–71. January 2012. doi:10.2337/dc12-s064. PMC 3632174. PMID 22187472.
50. ^ Kumar, Vinay; Fausto, Nelson; Abbas, Abul K.; Cotran, Ramzi S.; Robbins, Stanley L. (2005). *Robbins and Cotran Pathologic Basis of Disease* (7th ed.). Philadelphia, Pa.: Saunders. pp. 1194–1195. ISBN 0-7216-0187-1.
51. ^ *Diabetes mellitus a guide to patient care.* Philadelphia: Lippincott Williams & Wilkins. 2007. p. 201. ISBN 978-1-58255-732-8.
52. ^ Mary Lee (2013). *Basic Skills in Interpreting Laboratory Data*. ASHP. pp. Chapter 13. ISBN 9781585283453.
53. ^ [a] [b] Valdez R (2009). "Detecting Undiagnosed Type 2 Diabetes: Family History as a Risk Factor and Screening Tool". *J Diabetes Sci Technol*. **3** (4): 722–6. doi:10.1177/193229680900300417. PMC 2769984. PMID 20144319.

54. ^ Selph, S; Dana, T; Blazina, I; Bougatsos, C; Patel, H; Chou, R (14 April 2015). "Screening for Type 2 Diabetes Mellitus: A Systematic Review for the U.S. Preventive Services Task Force.". *Annals of Internal Medicine*. **162**: 765–76. doi:10.7326/M14-2221. PMID 25867111.
55. ^ a b "Screening: Type 2 Diabetes Mellitus in Adults". *U.S. Preventive Services Task Force*. 2008. Retrieved 2014-03-16.
56. ^ Selph, S; Dana, T; Blazina, I; Bougatsos, C; Patel, H; Chou, R (2 June 2015). "Screening for type 2 diabetes mellitus. a systematic review for the u.s. Preventive services task force.". *Annals of Internal Medicine*. **162** (11): 765–76. doi:10.7326/M14-2221. PMID 25867111.
57. ^ Siu, AL (27 October 2015). "Screening for Abnormal Blood Glucose and Type 2 Diabetes Mellitus: U.S. Preventive Services Task Force Recommendation Statement.". *Annals of Internal Medicine*. **163**: 861–8. doi:10.7326/M15-2345. PMID 26501513.
58. ^ "Draft Recommendation Statement Screening for Abnormal Glucose and Type 2 Diabetes Mellitus". *uspreventiveservicestaskforce.org/*. Retrieved 7 October 2014.
59. ^ a b "Standards of Medical Care in Diabetes—2015: Summary of Revisions". *Diabetes Care*. **54** (38): S4. 2015. doi:10.2337/dc15-S003. PMID 25537706.
60. ^ Raina Elley C, Kenealy T (December 2008). "Lifestyle interventions reduced the long-term risk of diabetes in adults with impaired glucose tolerance". *Evid Based Med*. **13** (6): 173. doi:10.1136/ebm.13.6.173. PMID 19043031.
61. ^ Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roqué I Figuls M, Richter B, Mauricio D (2008). Mauricio, Didac, ed. "Exercise or exercise and diet for preventing type 2 diabetes mellitus". *Cochrane Database Syst Rev* (3): CD003054. doi:10.1002/14651858.CD003054.pub3. PMID 18646086.
62. ^ a b Schellenberg, ES.; Dryden, DM.; Vandermeer, B.; Ha, C.; Korownyk, C. (October 2013). "Lifestyle Interventions for Patients With and at Risk for Type 2 Diabetes: A Systematic Review and Meta-analysis". *Ann Intern Med*. **159** (8): 543–51. doi:10.7326/0003-4819-159-8-201310150-00007. PMID 24126648.
63. ^ O'Gorman, DJ; Krook, A (September 2011). "Exercise and the treatment of diabetes and obesity". *The Medical clinics of North America*. **95** (5): 953–69. doi:10.1016/j.mcna.2011.06.007. PMID 21855702.
64. ^ Kyu, Hmwe H; Bachman, Victoria F; Alexander, Lily T; Mumford, John Everett; Afshin, Ashkan; Estep, Kara; Veerman, J Lennert; Delwiche, Kristen; Iannarone, Marissa L; Moyer, Madeline L; Cercy, Kelly; Vos, Theo; Murray, Christopher J L; Forouzanfar, Mohammad H (9 August 2016). "Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013". *BMJ*: i3857. doi:10.1136/bmj.i3857.
65. ^ Nield L, Summerbell CD, Hooper L, Whittaker V, Moore H (2008). Nield, Lucie, ed. "Dietary advice for the prevention of type 2 diabetes mellitus in adults". *Cochrane Database Syst Rev* (3): CD005102. doi:10.1002/14651858.CD005102.pub2. PMID 18646120.
66. ^ Carter, P; Gray, LJ; Troughton, J; Khunti, K; Davies, MJ (2010-08-18). "Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis". *BMJ (Clinical research ed.)*. **341**: c4229. doi:10.1136/bmj.c4229. PMC 2924474. PMID 20724400.
67. ^ Santaguida PL, Balion C, Hunt D, et al. (August 2005). "Diagnosis, prognosis, and treatment of impaired glucose tolerance and impaired fasting glucose" (PDF). *Evid Rep Technol Assess (Summ)* (128): 1–11. PMID 16194123.
68. ^ Seida, Jennifer C.; Mitri, Joanna; Colmers, Isabelle N.; Majumdar, Sumit R.; Davidson, Mayer B.; Edwards, Alun L.; Hanley, David A.; Pittas, Anastassios G.; Tjosvold, Lisa; Johnson, Jeffrey A. (Oct 2014). "Effect of Vitamin D3 Supplementation on Improving Glucose Homeostasis and Preventing Diabetes: A Systematic Review and Meta-Analysis". *The Journal of Clinical Endocrinology & Metabolism*. **99** (10): 3551–3560. doi:10.1210/jc.2014-2136. PMC 4483466. PMID 25062463.
69. ^ a b "Type 2 diabetes: The management of type 2 diabetes". May 2009.
70. ^ Farmer, AJ; Perera, R; Ward, A; Heneghan, C; Oke, J; Barnett, AH; Davidson, MB; Guerci, B; Coates, V; Schwedes, U; O'Malley, S (27 February 2012). "Meta-analysis of individual patient data in randomised trials of self monitoring of blood glucose in people with non-insulin treated type 2 diabetes". *BMJ (Clinical research ed.)*. **344**: e486. doi:10.1136/bmj.e486. PMID 22371867.
71. ^ Emdin, CA; Rahimi, K; Neal, B; Callender, T; Perkovic, V; Patel, A (10 February 2015). "Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis.". *JAMA*. **313** (6): 603–15. doi:10.1001/jama.2014.18574. PMID 25668264.
72. ^ McBrien, K; Rabi, DM; Campbell, N; Barnieh, L; Clement, F; Hemmelgarn, BR; Tonelli, M; Leiter, LA; Klarenbach, SW; Manns, BJ (6 August 2012). "Intensive and Standard Blood Pressure Targets in Patients With Type 2 Diabetes Mellitus: Systematic Review and Meta-analysis". *Archives of Internal Medicine*. **172** (17): 1–8. doi:10.1001/archinternmed.2012.3147. PMID 22868819.
73. ^ Boussageon, R; Bejan-Angoulvant, T; Saadatian-Elahi, M; Lafont, S; Bergeonneau, C; Kassaï, B; Erpeldinger, S; Wright, JM; Gueyffier, F; Cornu, C (2011-07-26). "Effect of intensive glucose lowering treatment on all cause

mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials". *BMJ (Clinical research ed.)*. **343**: d4169. doi:10.1136/bmj.d4169. PMC 3144314. PMID 21791495.

74. ^ Webster, MW (July 2011). "Clinical practice and implications of recent diabetes trials". *Current Opinion in Cardiology*. **26** (4): 288–93. doi:10.1097/HCO.0b013e328347b139. PMID 21577100.
75. ^ *a b c d* Inzucchi, SE; Bergenstal, RM; Buse, JB; Diamant, M; Ferrannini, E; Nauck, M; Peters, AL; Tsapas, A; Wender, R; Matthews, DR (March 2015). "Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes.". *Diabetologia*. **58** (3): 429–42. doi:10.1007/s00125-014-3460-0. PMID 25583541.
76. ^ Simpson, TC.; Needleman, I.; Wild, SH.; Moles, DR.; Mills, EJ. (2010). Simpson, Terry C, ed. "Treatment of periodontal disease for glycaemic control in people with diabetes". *Cochrane Database Syst Rev* (5): CD004714. doi:10.1002/14651858.CD004714.pub2. PMID 20464734.
77. ^ *a b c* Zanuso S, Jimenez A, Pugliese G, Corigliano G, Balducci S (March 2010). "Exercise for the management of type 2 diabetes: a review of the evidence". *Acta Diabetol*. **47** (1): 15–22. doi:10.1007/s00592-009-0126-3. PMID 19495557.
78. ^ *a b* Davis N, Forbes B, Wylie-Rosett J (June 2009). "Nutritional strategies in type 2 diabetes mellitus". *Mt. Sinai J. Med*. **76** (3): 257–68. doi:10.1002/msj.20118. PMID 19421969.
79. ^ Thomas D, Elliott EJ (2009). Thomas, Diana, ed. "Low glycaemic index, or low glycaemic load, diets for diabetes mellitus". *Cochrane Database Syst Rev* (1): CD006296. doi:10.1002/14651858.CD006296.pub2. PMID 19160276.
80. ^ Feinman, RD; Pogozelski, WK; Astrup, A; Bernstein, RK; Fine, EJ; Westman, EC; Accurso, A; Frassetto, L; Gower, BA; McFarlane, SI; Nielsen, JV; Krarup, T; Saslow, L; Roth, KS; Vernon, MC; Volek, JS; Wilshire, GB; Dahlqvist, A; Sundberg, R; Childers, A; Morrison, K; Manninen, AH; Dashti, HM; Wood, RJ; Wortman, J; Worm, N (January 2015). "Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base.". *Nutrition (Burbank, Los Angeles County, Calif.)*. **31** (1): 1–13. doi:10.1016/j.nut.2014.06.011. PMID 25287761.
81. ^ Hawthorne, K.; Robles, Y.; Cannings-John, R.; Edwards, A. G. K.; Robles, Yolanda (2008). Robles, Yolanda, ed. "Culturally appropriate health education for Type 2 diabetes mellitus in ethnic minority groups". *Cochrane Database Syst Rev* (3): CD006424. doi:10.1002/14651858.CD006424.pub2. PMID 18646153. CD006424.
82. ^ Glick-Bauer M, Yeh MC (2014). "The health advantage of a vegan diet: exploring the gut microbiota connection". *Nutrients* (Review). **6** (11): 4822–38. doi:10.3390/nu6114822. PMC 4245565. PMID 25365383.
83. ^ Leach, Matthew J.; Kumar, Saravana (2012-09-12). "Cinnamon for diabetes mellitus". *The Cochrane Database of Systematic Reviews* (9): CD007170. doi:10.1002/14651858.CD007170.pub2. ISSN 1469-493X. PMID 22972104.
84. ^ Palmer, Suetonia C.; Mavridis, Dimitris; Nicolucci, Antonio; Johnson, David W.; Tonelli, Marcello; Craig, Jonathan C.; Maggo, Jasjot; Gray, Vanessa; De Berardis, Giorgia; Ruospo, Marinella; Natale, Patrizia; Saglimbene, Valeria; Badve, Sunil V.; Cho, Yeoungjee; Nadeau-Fredette, Annie-Claire; Burke, Michael; Faruque, Labib; Lloyd, Anita; Ahmad, Nasreen; Liu, Yuanchen; Tiv, Sophanny; Wiebe, Natasha; Strippoli, Giovanni F. M. (19 July 2016). "Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes". *JAMA*. **316** (3): 313. doi:10.1001/jama.2016.9400.
85. ^ Boussageon, R; Supper, I; Bejan-Angoulvant, T; Kellou, N; Cucherat, M; Boissel, JP; Kassai, B; Moreau, A; Gueyffier, F; Cornu, C (2012). Groop, Leif, ed. "Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials". *PLOS Medicine*. **9** (4): e1001204. doi:10.1371/journal.pmed.1001204. PMC 3323508. PMID 22509138.
86. ^ Richter, B; Bandeira-Echtler, E; Bergerhoff, K; Clar, C; Ebrahim, SH (18 July 2007). Richter, Bernd, ed. "Rosiglitazone for type 2 diabetes mellitus". *The Cochrane database of systematic reviews* (3): CD006063. doi:10.1002/14651858.CD006063.pub2. PMID 17636824.
87. ^ Chen, X; Yang, L; Zhai, SD (December 2012). "Risk of cardiovascular disease and all-cause mortality among diabetic patients prescribed rosiglitazone or pioglitazone: a meta-analysis of retrospective cohort studies". *Chinese medical journal*. **125** (23): 4301–6. PMID 23217404.
88. ^ Lv, J; Perkovic, V; Foote, CV; Craig, ME; Craig, JC; Strippoli, GF (12 December 2012). Strippoli, Giovanni FM, ed. "Antihypertensive agents for preventing diabetic kidney disease". *The Cochrane database of systematic reviews*. **12**: CD004136. doi:10.1002/14651858.CD004136.pub3. PMID 23235603.
89. ^ *a b* Cheng, J; Zhang, W; Zhang, X; Han, F; Li, X; He, X; Li, Q; Chen, J (May 2014). "Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: a meta-analysis.". *JAMA internal medicine*. **174** (5): 773–85. doi:10.1001/jamainternmed.2014.348. PMID 24687000.
90. ^ Brunström, Mattias; Carlberg, Bo (24 February 2016). "Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses". *BMJ*: i717.

doi:10.1136/bmj.i717.
91. ^ Swinnen, SG.; Simon, AC.; Holleman, F.; Hoekstra, JB.; Devries, JH. (2011). Simon, Airin CR, ed. "Insulin detemir versus insulin glargine for type 2 diabetes mellitus". *Cochrane Database Syst Rev* (7): CD006383. doi:10.1002/14651858.CD006383.pub2. PMID 21735405.
92. ^ Waugh, N; Cummins, E; Royle, P; Clar, C; Marien, M; Richter, B; Philip, S (July 2010). "Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation". *Health technology assessment (Winchester, England)*. **14** (36): 1–248. doi:10.3310/hta14360. PMID 20646668.
93. ^ Picot, J; Jones, J; Colquitt, JL; Gospodarevskaya, E; Loveman, E; Baxter, L; Clegg, AJ (September 2009). "The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation". *Health technology assessment (Winchester, England)*. **13** (41): 1–190, 215–357, iii–iv. doi:10.3310/hta13410. PMID 19726018.
94. ^ Frachetti, KJ; Goldfine, AB (April 2009). "Bariatric surgery for diabetes management". *Current Opinion in Endocrinology, Diabetes and Obesity*. **16** (2): 119–24. doi:10.1097/MED.0b013e32832912e7. PMID 19276974.
95. ^ *a b* Schulman, AP; del Genio, F; Sinha, N; Rubino, F (September–October 2009). ""Metabolic" surgery for treatment of type 2 diabetes mellitus". *Endocrine Practice*. **15** (6): 624–31. doi:10.4158/EP09170.RAR. PMID 19625245.
96. ^ Colucci, RA (January 2011). "Bariatric surgery in patients with type 2 diabetes: a viable option". *Postgraduate Medicine*. **123** (1): 24–33. doi:10.3810/pgm.2011.01.2242. PMID 21293081.
97. ^ Dixon, JB; le Roux, CW; Rubino, F; Zimmet, P (16 June 2012). "Bariatric surgery for type 2 diabetes". *Lancet*. **379** (9833): 2300–11. doi:10.1016/S0140-6736(12)60401-2. PMID 22683132.
98. ^ Rubino, F; Nathan, DM; Eckel, RH; Schauer, PR; Alberti, KG; Zimmet, PZ; Del Prato, S; Ji, L; Sadikot, SM; Herman, WH; Amiel, SA; Kaplan, LM; Taroncher-Oldenburg, G; Cummings, DE; Delegates of the 2nd Diabetes Surgery, Summit (June 2016). "Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations.". *Diabetes Care*. **39** (6): 861–77. doi:10.2337/dc16-0236. PMID 27222544.
99. ^ Meetoo, D; McGovern, P; Safadi, R (13–27 September 2007). "An epidemiological overview of diabetes across the world". *British journal of nursing (Mark Allen Publishing)*. **16** (16): 1002–7. PMID 18026039.
100. ^ Abate N, Chandalia M (2001). "Ethnicity and type 2 diabetes: focus on Asian Indians". *J. Diabetes Complicat*. **15** (6): 320–7. doi:10.1016/S1056-8727(01)00161-1. PMID 11711326.
101. ^ Carulli, L; Rondinella, S; Lombardini, S; Canedi, I; Loria, P; Carulli, N (November 2005). "Review article: diabetes, genetics and ethnicity". *Alimentary pharmacology & therapeutics*. 22 Suppl 2: 16–9. doi:10.1111/j.1365-2036.2005.02588.x. PMID 16225465.
102. ^ Wild S, Roglic G, Green A, Sicree R, King H (May 2004). "Global prevalence of diabetes: estimates for the year 2000 and projections for 2030". *Diabetes Care*. **27** (5): 1047–53. doi:10.2337/diacare.27.5.1047. PMID 15111519.
103. ^ "Diabetes Fact sheet N°312". *World Health Organization*. August 2011. Archived from the original on 2013-08-26. Retrieved 2012-01-09.
104. ^ *a b c d e f g h i* editor, Leonid Poretsky, (2009). *Principles of diabetes mellitus* (2nd ed.). New York: Springer. p. 3. ISBN 978-0-387-09840-1.

# External links

- Diabetes mellitus type 2 at DMOZ
- IDF Diabetes Atlas 2015
- National Diabetes Information Clearinghouse
- Centers for Disease Control (Endocrine pathology)

| v · t · e · | Diseases of the endocrine system (E00–E35, 240–259) | | |
|---|---|---|---|
| **Pancreas/ glucose metabolism** | **Hypofunction** | Diabetes mellitus · *types:* (type 1 · **type 2** · MODY 1 2 3 4 5 6 · · *complications* (coma · angiopathy · ketoacidosis · nephropathy · neuropathy · retinopathy · cardiomyopathy · · *insulin receptor* (Rabson–Mendenhall syndrome) · Insulin resistance · | |
| | **Hyperfunction** | Hypoglycemia · *beta cell* (Hyperinsulinism) · *G cell* (Zollinger–Ellison syndrome) · | |
| **Hypothalamic/ pituitary axes** | **Hypothalamus** | *gonadotropin* (Kallmann syndrome · Adiposogenital dystrophy · · *CRH* (Tertiary adrenal insufficiency) · *vasopressin* (Neurogenic diabetes insipidus) · *general* (Hypothalamic hamartoma) · | |
| | **Pituitary** | **Hyperpituitarism** | *anterior* (Acromegaly · Hyperprolactinaemia · Pituitary ACTH hypersecretion · · *posterior* (SIADH) · *general* (Nelson's syndrome) · |
| | | **Hypopituitarism** | *anterior* (Kallmann syndrome · Growth hormone deficiency · Hypoprolactinemia · ACTH deficiency/Secondary adrenal insufficiency · GnRH insensitivity · FSH insensitivity · LH/hCG insensitivity · · *posterior* (Neurogenic diabetes insipidus) · *general* (Empty sella syndrome · Pituitary apoplexy · Sheehan's syndrome · Lymphocytic hypophysitis · · |
| | **Thyroid** | **Hypothyroidism** | Iodine deficiency · Cretinism (Congenital hypothyroidism · · Myxedema · Euthyroid sick syndrome · |
| | | **Hyperthyroidism** | Hyperthyroxinemia (Thyroid hormone resistance · Familial dysalbuminemic hyperthyroxinemia · · Hashitoxicosis · Thyrotoxicosis factitia · Graves' disease · |
| | | **Thyroiditis** | Acute infectious · Subacute (De Quervain's · Subacute lymphocytic · · Autoimmune/chronic (Hashimoto's · Postpartum · Riedel's · · |
| | | **Goitre** | Endemic goitre · Toxic nodular goitre · Toxic multinodular goiter · Thyroid nodule · |
| | **Parathyroid** | **Hypoparathyroidism** | Hypoparathyroidism · Pseudohypoparathyroidism · Pseudopseudohypoparathyroidism · |
| | | **Hyperparathyroidism** | Primary · Secondary · Tertiary · Osteitis fibrosa cystica · |

| | | | |
|---|---|---|---|
| | **Adrenal** | **Hyperfunction** | *aldosterone:* Hyperaldosteronism/Primary aldosteronism (Conn syndrome · Bartter syndrome · Glucocorticoid remediable aldosteronism · · AME · Liddle's syndrome · 17α CAH · *cortisol:* Cushing's syndrome (Pseudo-Cushing's syndrome) · *sex hormones:* 21α CAH · 11β CAH · |
| | | **Hypofunction/ Adrenal insufficiency (Addison's, WF)** | *aldosterone:* Hypoaldosteronism (21α CAH · 11β CAH · · *cortisol:* CAH (Lipoid · 3β · 11β · 17α · 21α · · *sex hormones:* 17α CAH · |
| | **Gonads** | | *ovarian:* Polycystic ovary syndrome · Premature ovarian failure · *testicular: enzymatic* (5α-reductase deficiency · 17β-hydroxysteroid dehydrogenase deficiency · aromatase excess syndrome) · · *Androgen receptor* (Androgen insensitivity syndrome) · *general:* Hypogonadism (Delayed puberty) · Hypergonadism (Precocious puberty · · Hypoandrogenism · Hypoestrogenism · Hyperandrogenism · Hyperestrogenism · Postorgasmic illness syndrome · |
| **Height** | | | Dwarfism/Short stature (Midget · Laron syndrome · Psychosocial · Ateliosis · · Gigantism · |
| **Multiple** | | | Autoimmune polyendocrine syndrome multiple (APS1 · APS2 · · Carcinoid syndrome · Multiple endocrine neoplasia (1 · 2A · 2B · · Progeria (Werner syndrome · Acrogeria · Metageria · · Woodhouse-Sakati syndrome · |

| v · t · e · | **Diabetes (E10–E14, 250)** |
|---|---|
| **Types** | Type 1 · **Type 2** · Gestational diabetes (Diabetes and pregnancy · · Prediabetes (Impaired fasting glucose · Impaired glucose tolerance · · Insulin resistance · LADA · KPD · MODY · Neonatal (Transient · Permanent · · Type 3c (Pancreatogenic) · |
| **Blood tests** | Blood sugar · Glycosylated hemoglobin · Glucose tolerance test · Postprandial glucose test · Fructosamine · Glucose test · C-peptide · Noninvasive glucose monitor · Insulin tolerance test · |
| **Management** | Diabetic diet · Anti-diabetic drugs · Insulin therapy (intensive · conventional · pulsatile · · Cure (Embryonic stem cells · Artificial pancreas · · Other (Gastric bypass surgery · · |
| **Complications** | Diabetic comas (Hypoglycemia · Ketoacidosis · Hyperosmolar hyperglycemic state · · Diabetic foot (ulcer · Neuropathic arthropathy · · Organs in diabetes (Blood vessels · Muscle · Kidney · Nerves · Retina · Heart · · Diabetic skin disease (Diabetic dermopathy · Diabetic bulla · Diabetic cheiroarthropathy · Neuropathic ulcer · · Hyperglycemia · Hypoglycemia · |
| **Other** | Glossary of diabetes · |

Categories: Aging-associated diseases | Diabetes | Medical conditions related to obesity

# Gestational diabetes

From Wikipedia, the free encyclopedia

**Gestational diabetes**, also known as **gestational diabetes mellitus** (**GDM**), is when a woman without diabetes, develops high blood sugar levels during pregnancy.[2] Gestational diabetes generally results in few symptoms; however, it does increase the risk of pre-eclampsia, depression, and requiring a Caesarean section. Babies born to mothers with poorly treated gestational diabetes are at increased risk of being too large, having low blood sugar after birth, and jaundice. If untreated, it can also result in a stillbirth. Long term, children are at higher risk of being overweight and developing type 2 diabetes.[2]

Gestational diabetes is caused by not enough insulin in the setting of insulin resistance. Risk factors include being overweight, previously having gestational diabetes, a family history of type 2 diabetes, and having polycystic ovarian syndrome. Diagnosis is by blood tests.[2] For those at normal risk screening is recommended between 24 and 28 weeks gestation.[2][3] For those at high risk testing may occur at the first prenatal visit.[2]

Prevention is by maintaining a healthy weight and exercising before pregnancy. Gestational diabetes is a treated with a diabetic diet, exercise, and possibly insulin injections.[2] Most women are able to manage their blood sugar with a diet and exercise. Blood sugar testing among those who are affected is often recommended four times a day.[3] Breastfeeding is recommended as soon as possible after birth.[2]

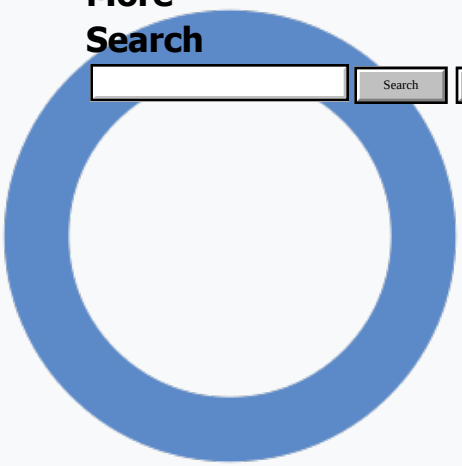
Gestational diabetes affects 3–9% of pregnancies, depending on the population studied.[3] It is especially common during the last third of pregnancy.[2] It affects 1% of those under the age of 20 and 13% of those over the age of 44.[3] A number of ethnic groups including Asians, American Indians, Indigenous Australians, and Pacific Islanders are at higher risk.[3][2] In 90% of people gestational diabetes will resolve after the baby is born.[2] Women, however, are at an increased risk of developing type 2 diabetes.[3]

Contents



[edit]

**Gestational diabetes**



Universal blue circle symbol for diabetes.[1]

| Classification and external resources | |
|---|---|
| **Specialty** | Obstetrics and endocrinology |
| **ICD-10** | O24 |
| **ICD-9-CM** | 648.8 |
| **DiseasesDB** | 5195 |
| **MedlinePlus** | 000896 |
| **Patient UK** | Gestational diabetes |
| **MeSH** | D016640 |

[edit on Wikidata]


Play media

Video explanation of the various types of diabetes

# Classification

Gestational diabetes is formally defined as "any degree of glucose intolerance with onset or first recognition during pregnancy".[4] This definition acknowledges the possibility that a woman may have previously undiagnosed diabetes mellitus, or may have developed diabetes coincidentally with pregnancy. Whether symptoms subside after pregnancy is also irrelevant to the diagnosis.[5] A woman is diagnosed with gestational diabetes when glucose intolerance continues beyond 24–28 weeks of gestation.

The White classification, named after Priscilla White,[6] who pioneered research on the effect of diabetes types on perinatal outcome, is widely used to assess maternal and fetal risk[*citation needed*]. It distinguishes between gestational diabetes (type A) and pregestational diabetes (diabetes that existed prior to pregnancy). These two groups are further subdivided according to their associated risks and management.[7]

The two subtypes of gestational diabetes under this classification system are:

- Type A1: abnormal oral glucose tolerance test (OGTT), but normal blood glucose levels during fasting and two hours after meals; diet modification is sufficient to control glucose levels
- Type A2: abnormal OGTT compounded by abnormal glucose levels during fasting and/or after meals; additional therapy with insulin or other medications is required

Diabetes which existed prior to pregnancy is also split up into several subtypes under this system:[*medical citation needed*]

- Type B: onset at age 20 or older and duration of less than 10 years.
- Type C: onset at age 10–19 or duration of 10–19 years.
- Type D: onset before age 10 or duration greater than 20 years.
- Type E: overt diabetes mellitus with calcified pelvic vessels.
- Type F: diabetic nephropathy.
- Type R: proliferative retinopathy.
- Type RF: retinopathy and nephropathy.
- Type H: ischemic heart disease.
- Type T: prior kidney transplant.

An early age of onset or long-standing disease comes with greater risks, hence the first three subtypes.[*medical citation needed*]

Two other sets of criteria are available for diagnosis of gestational diabetes, both based on blood-sugar levels.[*medical citation needed*]

Criteria for diagnosis of gestational diabetes, using the 100 gram Glucose Tolerance Test, according to Carpenter and Coustan:[*medical citation needed*]

- Fasting 95 mg/dl
- 1 hour 180 mg/dl
- 2 hours 155 mg/dl
- 3 hours 140 mg/dl

Criteria for diagnosis of gestational diabetes according to National Diabetes Data Group:[*medical citation needed*]

- Fasting 105 mg/dl
- 1 hour 190 mg/dl
- 2 hours 165 mg/dl
- 3 hours 145 mg/dl

# Risk factors [edit]

Classical risk factors for developing gestational diabetes are:[8]

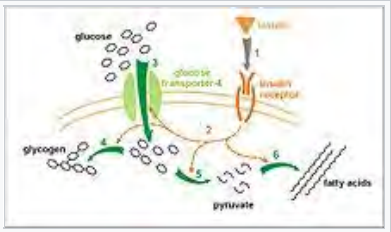
- Polycystic Ovary Syndrome
- A previous diagnosis of gestational diabetes or prediabetes, impaired glucose tolerance, or impaired fasting glycaemia
- A family history revealing a first-degree relative with type 2 diabetes
- Maternal age – a woman's risk factor increases as she gets older (especially for women over 35 years of age).
- Ethnicity (those with higher risk factors include African-Americans, Afro-Caribbeans, Native Americans, Hispanics, Pacific Islanders, and people originating from South Asia)
- Being overweight, obese or severely obese increases the risk by a factor 2.1, 3.6 and 8.6, respectively.[9]
- A previous pregnancy which resulted in a child with a macrosomia (high birth weight: >90th centile or >4000 g (8 lbs 12.8 oz))
- Previous poor obstetric history
- Other genetic risk factors: There are at least 10 genes where certain polymorphism are associated with an increased risk of gestational diabetes, most notably TCF7L2.[10]

In addition to this, statistics show a double risk of GDM in smokers.[11] Polycystic ovarian syndrome is also a risk factor,[8] although relevant evidence remains controversial.[12] Some studies have looked at more controversial potential risk factors, such as short stature.[13]

About 40–60% of women with GDM have no demonstrable risk factor; for this reason many advocate to screen all women.[14] Typically, women with GDM exhibit no symptoms (another reason for universal screening), but some women may demonstrate increased thirst, increased urination, fatigue, nausea and vomiting, bladder infection, yeast infections and blurred vision.

## Pathophysiology [edit]

The precise mechanisms underlying gestational diabetes remain unknown. The hallmark of GDM is increased insulin resistance. Pregnancy hormones and other factors are thought to interfere with the action of insulin as it binds to the insulin receptor. The interference probably occurs at the level of the cell signaling pathway beyond the insulin receptor.[15] Since insulin promotes the entry of glucose into most cells, insulin resistance prevents glucose from entering the cells properly. As a result, glucose remains in the bloodstream, where glucose levels rise. More insulin is needed to overcome this resistance; about 1.5–2.5 times more insulin is produced than in a normal pregnancy.[15]




**Effect of insulin on glucose uptake and metabolism.** Insulin binds to its receptor (1) on the cell membrane which in turn starts many protein activation cascades (2). These include: translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6).

Insulin resistance is a normal phenomenon emerging in the second trimester of pregnancy, which in cases of GDM progresses thereafter to levels seen in a non-pregnant person with type 2 diabetes. It is thought to secure glucose supply to the growing fetus. Women with GDM have an insulin resistance that they cannot compensate for with increased production in the β-cells of the pancreas. Placental hormones, and to a lesser extent increased fat deposits during pregnancy, seem to mediate insulin resistance during pregnancy. Cortisol and progesterone are the main culprits, but human placental lactogen, prolactin and estradiol contribute, too. Multivariate stepwise regression analysis reveals that, in combination with other placental hormones, leptin, tumor necrosis factor alpha, and resistin are involved in the decrease in insulin sensitivity occurring during pregnancy, with tumor necrosis factor alpha named as the strongest independent predictor of insulin sensitivity in pregnancy. An inverse correlation with the changes in insulin sensitivity from the time before conception through late gestation accounts for about half of the variance in the decrease in insulin sensitivity during gestation: in other words, low levels or alteration of TNF alpha factors corresponds with a greater chance of, or predisposition to, insulin resistance or sensitivity. GABBE,STEVEN G; sixth Edition page 890.

It is unclear why some women are unable to balance insulin needs and develop GDM; however, a number of explanations have been given, similar to those in type 2 diabetes: autoimmunity, single gene mutations, obesity, along with other mechanisms.[16]

Though the clinical presentation of gestational diabetes is well characterized, the biochemical mechanism behind the disease is not well known. One proposed biochemical mechanism involves insulin-producing β-cell adaptation controlled by the HGF/c-MET signaling pathway. β-cell adaption refers to the change that pancreatic islet cells undergo during pregnancy in response to maternal hormones in order to compensate for the increased physiological needs of mother and baby. These changes in the β-cells cause increased insulin secretion as a result of increased β-cell proliferation.[17] HGF/c-MET has also been implicated in β-cell regeneration, which suggests that HGF/c-MET may help increase β-cell mass in order to compensate for insulin needs during pregnancy. Recent studies support that loss of HGF/c-MET signaling results in aberrant β-cell adaptation.[18][19]

c-MET is a receptor tyrosine kinase (RTK) that is activated by its ligand, hepatocyte growth factor (HGF), and is involved in the activation of several cellular processes. When HGF binds c-MET, the receptor homodimerizes and self-phosphorylates to form an SH2 recognition domain. The downstream pathways activated include common signaling molecules such as RAS and MAPK, which affect cell motility, cell motility, and cell cycle progression.[20]

Studies have shown that HGF is an important signaling molecule in stress related situations where more insulin is needed. Pregnancy causes increased insulin resistance and so a higher insulin demand. The β-cells must compensate for this by either increasing insulin production or proliferating. If neither of the processes occur, then markers for gestational diabetes are observed. It has been observed that pregnancy increases HGF levels, showing a correlation that suggests a connection between the signaling pathway and increased insulin needs. In fact, when no signaling is present, gestational diabetes is more likely to occur.[18]

The exact mechanism of HGF/c-MET regulated β-cell adaptation is not yet known but there are several hypotheses about how the signaling molecules contribute to insulin levels during pregnancy. c-MET may interact with FoxM1, a molecule important in the cell cycle, as FOXM1 levels decrease when c-MET is not present. Additionally, c-MET may interact with p27 as the protein levels increase with c-MET is not present. Another hypothesis says that c-MET may control β-cell apoptosis because a lack of c-MET causes increases cell death but the signaling mechanisms have not been elucidated.[19]

Although the mechanism of HGF/c-MET control of gestational diabetes is not yet well understood, there is a strong correlation between the signaling pathway and the inability to produce an adequate amount of insulin during pregnancy and thus it may be the target for future diabetic therapies.[18][19]

Because glucose travels across the placenta (through diffusion facilitated by GLUT1 carrier), which is located in the syncytiotrophoblast on both the microvillus and basal membranes, these membranes may be the rate-limiting step in placental glucose transport. There is a two- to three-fold increase in the expression of syncytiotrophoblast glucose transporters with advancing gestation. Finally, the role of GLUT3/GLUT4 transport remains speculative. If the untreated gestational diabetes fetus is exposed to consistently higher glucose levels, this leads to increased fetal levels of insulin (insulin itself cannot cross the placenta). The growth-stimulating effects of insulin can lead to excessive growth and a large body (macrosomia). After birth, the high glucose environment disappears, leaving these newborns with ongoing high insulin production and susceptibility to low blood glucose levels (hypoglycemia).[21]

## Screening [edit]

A number of screening and diagnostic tests have been used to look for high levels of glucose in plasma or serum in defined circumstances. One method is a stepwise approach where a suspicious result on a screening test is followed by diagnostic test. Alternatively, a more involved diagnostic test can be used directly at the first prenatal visit for a woman with a high-risk pregnancy. (for example in those with polycystic ovarian syndrome or acanthosis nigricans).[21]

**WHO diabetes diagnostic criteria**[22][23] edit

| Condition | 2 hour glucose | Fasting glucose | $HbA_{1c}$ | |
|---|---|---|---|---|
| Unit | mmol/l(mg/dl) | mmol/l(mg/dl) | mmol/mol | DCCT % |
| Normal | <7.8 (<140) | <6.1 (<110) | <42 | <6.0 |
| Impaired fasting glycaemia | <7.8 (<140) | ≥6.1(≥110) & <7.0(<126) | 42-46 | 6.0–6.4 |
| Impaired glucose tolerance | ≥7.8 (≥140) | <7.0 (<126) | 42-46 | 6.0–6.4 |
| Diabetes mellitus | ≥11.1 (≥200) | ≥7.0 (≥126) | ≥48 | ≥6.5 |

**Tests for gestational diabetes**

| |
|---|
| Non-challenge blood glucose test<br>▪ Fasting glucose test<br>▪ 2-hour postprandial (after a meal) glucose test<br>▪ Random glucose test |
| Screening glucose challenge test |
| Oral glucose tolerance test (OGTT) |

Non-challenge blood glucose tests involve measuring glucose levels in blood samples without challenging the subject with glucose solutions. A blood glucose level is determined when fasting, 2 hours after a meal, or simply at any random time. In contrast, challenge tests involve drinking a glucose solution and measuring glucose concentration thereafter in the blood; in diabetes, they tend to remain high. The glucose solution has a very sweet taste which some women find unpleasant; sometimes, therefore, artificial flavours are added. Some women may experience nausea during the test, and more so with higher glucose levels.[24][25]

More research is needed to find the most effective way of screening for gestational diabetes.[26] Routine screening of women with a glucose challenge test appears to find more women with gestational diabetes than only screening women with risk factors.[26] It is not clear how these screening tests affect the rest of the pregnancy. Future research should include how the method of screening impacts the mother and baby.[26]

### Pathways [edit]

Opinions differ about optimal screening and diagnostic measures, in part due to differences in population risks, cost-effectiveness considerations, and lack of an evidence base to support large national screening programs.[27] The most elaborate regimen entails a random blood glucose test during a booking visit, a screening glucose challenge test around 24–28 weeks' gestation, followed by an OGTT if the tests are outside normal limits. If there is a high suspicion, a woman may be tested earlier.[5]

In the United States, most obstetricians prefer universal screening with a screening glucose challenge test.[28] In the United Kingdom, obstetric units often rely on risk factors and a random blood glucose test.[21][29] The American Diabetes Association and the Society of Obstetricians and Gynaecologists of Canada recommend routine screening unless the woman is low risk (this means the woman must be younger than 25 years and have a body mass index less than 27, with no personal, ethnic or family risk factors)[5][27] The Canadian Diabetes Association and the American College of Obstetricians and Gynecologists recommend universal screening.[30][31] The U.S. Preventive Services Task Force found there is insufficient evidence to recommend for or against routine screening.[32]

Some pregnant women and careproviders choose to forgo routine screening due to the absence of risk factors, however this is not advised due to the large proportion of women who develop gestational diabetes despite having no risk factors present

and the dangers to the mother and baby if gestational diabetes remains untreated.[14]

### Non-challenge blood glucose tests [edit]

When a plasma glucose level is found to be higher than 126 mg/dl (7.0 mmol/l) after fasting, or over 200 mg/dl (11.1 mmol/l) on any occasion, and if this is confirmed on a subsequent day, the diagnosis of GDM is made, and no further testing is required.[5] These tests are typically performed at the first antenatal visit. They are simple to administer and inexpensive, but have a lower test performance compared to the other tests, with moderate sensitivity, low specificity and high false positive rates.[33][34][35]

### Screening glucose challenge test [edit]

The screening glucose challenge test (sometimes called the O'Sullivan test) is performed between 24–28 weeks, and can be seen as a simplified version of the oral glucose tolerance test (OGTT). No previous fasting is required for this screening test,[36] in contrast to the OGTT. The O'Sullivan test involves drinking a solution containing 50 grams of glucose, and measuring blood levels 1 hour later.[37]

If the cut-off point is set at 140 mg/dl (7.8 mmol/l), 80% of women with GDM will be detected.[5] If this threshold for further testing is lowered to 130 mg/dl, 90% of GDM cases will be detected, but there will also be more women who will be subjected to a consequent OGTT unnecessarily.

### Oral glucose tolerance test [edit]

A standardized oral glucose tolerance test (OGTT)[38] should be done in the morning after an overnight fast of between 8 and 14 hours. During the three previous days the subject must have an unrestricted diet (containing at least 150 g carbohydrate per day) and unlimited physical activity. The subject should remain seated during the test and should not smoke throughout the test.

The test involves drinking a solution containing a certain amount of glucose, usually 75 g or 100 g, and drawing blood to measure glucose levels at the start and on set time intervals thereafter.

The diagnostic criteria from the National Diabetes Data Group (NDDG) have been used most often, but some centers rely on the Carpenter and Coustan criteria, which set the cutoff for normal at lower values. Compared with the NDDG criteria, the Carpenter and Coustan criteria lead to a diagnosis of gestational diabetes in 54 percent more pregnant women, with an increased cost and no compelling evidence of improved perinatal outcomes.[39]

The following are the values which the American Diabetes Association considers to be abnormal during the 100 g of glucose OGTT:

- Fasting blood glucose level ≥95 mg/dl (5.33 mmol/L)
- 1 hour blood glucose level ≥180 mg/dl (10 mmol/L)
- 2 hour blood glucose level ≥155 mg/dl (8.6 mmol/L)
- 3 hour blood glucose level ≥140 mg/dl (7.8 mmol/L)

An alternative test uses a 75 g glucose load and measures the blood glucose levels before and after 1 and 2 hours, using the same reference values. This test will identify fewer women who are at risk, and there is only a weak concordance (agreement rate) between this test and a 3-hour 100 g test.[40]

The glucose values used to detect gestational diabetes were first determined by O'Sullivan and Mahan (1964) in a retrospective cohort study (using a 100 grams of glucose OGTT) designed to detect risk of developing type 2 diabetes in the future. The values were set using whole blood and required two values reaching or exceeding the value to be positive.[41] Subsequent information led to alterations in O'Sullivan's criteria. When methods for blood glucose determination changed from the use of whole blood to venous plasma samples, the criteria for GDM were also changed.

### Urinary glucose testing [edit]

Women with GDM may have high glucose levels in their urine (glucosuria). Although dipstick testing is widely practiced, it performs poorly, and discontinuing routine dipstick testing has not been shown to cause underdiagnosis where universal screening is performed.[42] Increased glomerular filtration rates during pregnancy contribute to some 50% of women having glucose in their urine on dipstick tests at some point during their pregnancy. The sensitivity of glucosuria for GDM in the first 2 trimesters is only around 10% and the positive predictive value is around 20%.[43][44]

## Prevention [edit]

A 2015 review found that when done during pregnancy moderate physical exercise is effective for the prevention of gestational diabetes.[45] A 2014 review however did not find a significant effect.[46]

Theoretically, smoking cessation may decrease the risk of gestational diabetes among smokers.

## Management [edit]

*Main article: Diabetes management*

Treatment of GDM with diet and insulin reduces health problems mother and child.[47] Treatment of GDM is also accompanied by more inductions of labour.[47]

A repeat OGTT should be carried out 6 weeks after delivery, to confirm the diabetes has disappeared. Afterwards, regular screening for type 2 diabetes is advised.[8]

If a diabetic diet or G.I. Diet, exercise, and oral medication are inadequate to control glucose levels, insulin therapy may become necessary.

The development of macrosomia can be evaluated during pregnancy by using sonography. Women who use insulin, with a history of stillbirth, or with hypertension are managed like women with overt diabetes.[14]

A kit with a glucose meter and diary used by a woman with gestational diabetes.

### Lifestyle [edit]

Counselling before pregnancy (for example, about preventive folic acid supplements) and multidisciplinary management are important for good pregnancy outcomes.[48] Most women can manage their GDM with dietary changes and exercise. Self monitoring of blood glucose levels can guide therapy. Some women will need antidiabetic drugs, most commonly insulin therapy.

Any diet needs to provide sufficient calories for pregnancy, typically 2,000 – 2,500 kcal with the exclusion of simple carbohydrates.[14] The main goal of dietary modifications is to avoid peaks in blood sugar levels. This can be done by spreading carbohydrate intake over meals and snacks throughout the day, and using slow-release carbohydrate sources—known as the G.I. Diet. Since insulin resistance is highest in mornings, breakfast carbohydrates need to be restricted more.[8] Ingesting more fiber in foods with whole grains, or fruit and vegetables can also reduce the risk of gestational diabetes.[49]

Regular moderately intense physical exercise is advised, although there is no consensus on the specific structure of exercise programs for GDM.[8][50]

Self monitoring can be accomplished using a handheld capillary glucose dosage system. Compliance with these glucometer systems can be low.[51] Target ranges advised by the Australasian Diabetes in Pregnancy Society are as follows:[8]

- fasting capillary blood glucose levels <5.5 mmol/L
- 1 hour postprandial capillary blood glucose levels <8.0 mmol/L
- 2 hour postprandial blood glucose levels <6.7 mmol/L

Regular blood samples can be used to determine HbA1c levels, which give an idea of glucose control over a longer time period.[8]

Research suggests a possible benefit of breastfeeding to reduce the risk of diabetes and related risks for both mother and child.[52]

### Medication [edit]

If monitoring reveals failing control of glucose levels with these measures, or if there is evidence of complications like excessive fetal growth, treatment with insulin might be necessary. This is most commonly fast-acting insulin given just before eating to blunt glucose rises after meals.[8] Care needs to be taken to avoid low blood sugar levels due to excessive insulin. Insulin therapy can be normal or very tight; more injections can result in better control but requires more effort, and there is no consensus that it has large benefits.[21][53][54] A 2016 Cochrane review concluded that quality evidence is not yet available to determine the best blood sugar range for improving health for pregnant women with GDM and their babies.[55]

There is some evidence that certain oral glycemic agents might be safe in pregnancy, or at least, are less dangerous to the developing fetus than poorly controlled diabetes. The oral medication metformin is better than glyburide.[56] If blood glucose cannot be adequately controlled with a single agent, the combination of metformin and insulin may be better than insulin alone.[56]

People may prefer metformin by mouth to insulin injections.[3] Treatment of polycystic ovarian syndrome with metformin during pregnancy has been noted to decrease GDM levels.[57]

Almost half of the women did not reach sufficient control with metformin alone and needed supplemental therapy with insulin; compared to those treated with insulin alone, they required less insulin, and they gained less weight.[58] With no long-term studies into children of women treated with the drug, here remains a possibility of long-term complications from metformin therapy.[3] Babies born to women treated with metformin have been found to develop less visceral fat, making them less

prone to insulin resistance in later life.[58]

## Prognosis [edit]

Gestational diabetes generally resolves once the baby is born. Based on different studies, the chances of developing GDM in a second pregnancy, if you had GDM in your first pregnancy, are between 30 and 84%, depending on ethnic background. A second pregnancy within 1 year of the previous pregnancy has a high rate of recurrence.[59]

Women diagnosed with gestational diabetes have an increased risk of developing diabetes mellitus in the future. The risk is highest in women who needed insulin treatment, had antibodies associated with diabetes (such as antibodies against glutamate decarboxylase, islet cell antibodies and/or insulinoma antigen-2), women with more than two previous pregnancies, and women who were obese (in order of importance).[60][61] Women requiring insulin to manage gestational diabetes have a 50% risk of developing diabetes within the next five years.[41] Depending on the population studied, the diagnostic criteria and the length of follow-up, the risk can vary enormously.[62] The risk appears to be highest in the first 5 years, reaching a plateau thereafter.[62] One of the longest studies followed a group of women from Boston, Massachusetts; half of them developed diabetes after 6 years, and more than 70% had diabetes after 28 years.[62] In a retrospective study in Navajo women, the risk of diabetes after GDM was estimated to be 50 to 70% after 11 years.[63] Another study found a risk of diabetes after GDM of more than 25% after 15 years.[64] In populations with a low risk for type 2 diabetes, in lean subjects and in women with auto-antibodies, there is a higher rate of women developing type 1 diabetes.[61]

Children of women with GDM have an increased risk for childhood and adult obesity and an increased risk of glucose intolerance and type 2 diabetes later in life.[65] This risk relates to increased maternal glucose values.[66] It is currently unclear how much genetic susceptibility and environmental factors each contribute to this risk, and if treatment of GDM can influence this outcome.[67]

There are scarce statistical data on the risk of other conditions in women with GDM; in the Jerusalem Perinatal study, 410 out of 37962 women were reported to have GDM, and there was a tendency towards more breast and pancreatic cancer, but more research is needed to confirm this finding.[68][69]

### Complications [edit]

GDM poses a risk to mother and child. This risk is largely related to uncontrolled high blood glucose levels and its consequences. The risk increases with higher blood glucose levels.[70] Treatment resulting in better control of these levels can reduce some of the risks of GDM considerably.[51]

The two main risks GDM imposes on the baby are growth abnormalities and chemical imbalances after birth, which may require admission to a neonatal intensive care unit. Infants born to mothers with GDM are at risk of being both large for gestational age (macrosomic)[70] in unmanaged GDM, and small for gestational age and Intrauterine growth retardation[71] in managed GDM. Macrosomia in turn increases the risk of instrumental deliveries (e.g. forceps, ventouse and caesarean section) or problems during vaginal delivery (such as shoulder dystocia). Macrosomia may affect 12% of normal women compared to 20% of women with GDM.[21] However, the evidence for each of these complications is not equally strong; in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study for example, there was an increased risk for babies to be large but not small for gestational age in women with uncontrolled GDM.[70] Research into complications for GDM is difficult because of the many confounding factors (such as obesity). Labelling a woman as having GDM may in itself increase the risk of having an unnecessary caesarean section.[72][73]

Neonates born from women with consistently high blood sugar levels are also at an increased risk of low blood glucose (hypoglycemia), jaundice, high red blood cell mass (polycythemia) and low blood calcium (hypocalcemia) and magnesium (hypomagnesemia).[74] Untreated GDM also interferes with maturation, causing dysmature babies prone to respiratory distress syndrome due to incomplete lung maturation and impaired surfactant synthesis.[74]

Unlike pre-gestational diabetes, gestational diabetes has not been clearly shown to be an independent risk factor for birth defects. Birth defects usually originate sometime during the first trimester (before the 13th week) of pregnancy, whereas GDM gradually develops and is least pronounced during the first and early second trimester. Studies have shown that the offspring of women with GDM are at a higher risk for congenital malformations.[75][76][77] A large case-control study found that gestational diabetes was linked with a limited group of birth defects, and that this association was generally limited to women with a higher body mass index (≥ 25 kg/m²).[78] It is difficult to make sure that this is not partially due to the inclusion of women with pre-existent type 2 diabetes who were not diagnosed before pregnancy.

Because of conflicting studies, it is unclear at the moment whether women with GDM have a higher risk of preeclampsia.[79] In the HAPO study, the risk of preeclampsia was between 13% and 37% higher, although not all possible confounding factors were corrected.[70]

## Epidemiology [edit]

Gestational diabetes affects 3–10% of pregnancies, depending on the population studied.[3][80]

## References [edit]


1. ^ "Diabetes Blue Circle Symbol". International Diabetes Federation. 17 March 2006.
2. ^ a b c d e f g h i j "Gestational Diabetes". *NIDDK*. September 2014. Retrieved 31 July 2016.
3. ^ a b c d e f g h i Donovan, Peter J; McIntyre, H David (1 October 2010). "Drugs for gestational diabetes". *Australian Prescriber*. **33** (5): 141–144. doi:10.18773/austprescr.2010.066.
4. ^ Metzger, B. E.; Coustan, D. R. (1998). "Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee". *Diabetes Care*. 21 Suppl 2: B161–B167. PMID 9704245. And the rest of the issue B1–B167.
5. ^ a b c d e American Diabetes, A. (2004). "Gestational diabetes mellitus". *Diabetes Care*. 27 Suppl 1 (Supplement 1): S88–S90. doi:10.2337/diacare.27.2007.s88. PMID 14693936.
6. ^ White, P. (1949). "Pregnancy complicating diabetes". *The American Journal of Medicine*. **7** (5): 609–616. doi:10.1016/0002-9343(49)90382-4. PMID 15396063.
7. ^ Gabbe S.G., Niebyl J.R., Simpson J.L. OBSTETRICS: Normal and Problem Pregnancies. Fourth edition. Churchill Livingstone, New York, 2002. ISBN 0-443-06572-1
8. ^ a b c d e f g h Ross, G. (2006). "Gestational diabetes". *Australian family physician*. **35** (6): 392–396. PMID 16751853.
9. ^ Chu, S. Y.; Callaghan, W. M.; Kim, S. Y.; Schmid, C. H.; Lau, J.; England, L. J.; Dietz, P. M. (2007). "Maternal Obesity and Risk of Gestational Diabetes Mellitus". *Diabetes Care*. **30** (8): 2070–2076. doi:10.2337/dc06-2559a. PMID 17416786.
10. ^ Zhang, C.; Bao, W.; Rong, Y.; Yang, H.; Bowers, K.; Yeung, E.; Kiely, M. (2013). "Genetic variants and the risk of gestational diabetes mellitus: A systematic review". *Human Reproduction Update*. **19** (4): 376–90. doi:10.1093/humupd/dmt013. PMID 23690305.
11. ^ Bjorge, T.; Tretli, S.; Engeland, A.; Soule, L. M.; Schisterman, E. F.; Yu, K. F.; Catalano, P. M. (2004). "Relation of Height and Body Mass Index to Renal Cell Carcinoma in Two Million Norwegian Men and Women". *American Journal of Epidemiology*. **160** (12): 1168–1176. doi:10.1093/aje/kwh345. PMID 15583369.
12. ^ Toulis, K. A.; Goulis, D. G.; Kolibianakis, E. M.; Venetis, C. A.; Tarlatzis, B. C.; Papadimas, I. (2009). "Risk of gestational diabetes mellitus in women with polycystic ovary syndrome: A systematic review and a meta-analysis". *Fertility and Sterility*. **92** (2): 667–677. doi:10.1016/j.fertnstert.2008.06.045. PMID 18710713.
13. ^ Ma, R. M.; Lao, T. T.; Ma, C. L.; Liao, S. J.; Lu, Y. F.; Du, M. Y.; Xiao, H.; Zhang, L.; Yang, M. H.; Xiao, X. (2007). "Relationship Between Leg Length and Gestational Diabetes Mellitus in Chinese Pregnant Women". *Diabetes Care*. **30** (11): 2960–2961. doi:10.2337/dc07-0763. PMID 17666468.
14. ^ a b c d ACOG. *Precis V. An Update on Obstetrics and Gynecology*. ACOG (1994). p. 170. ISBN 0-915473-22-4.
15. ^ a b Carr DB, Gabbe S (1998). "Gestational Diabetes: Detection, Management, and Implications". *Clin Diabetes*. **16** (1): 4.
16. ^ Buchanan, T. A.; Xiang, A. H. (2005). "Gestational diabetes mellitus". *Journal of Clinical Investigation*. **115** (3): 485–491. doi:10.1172/JCI24531. PMC 1052018. PMID 15765129.
17. ^ Sorenson, R.; Brelje, T. (2007). "Adaptation of Islets of Langerhans to Pregnancy: β-Cell Growth, Enhanced Insulin Secretion and the Role of Lactogenic Hormones". *Hormone and Medicine*. **34** (4): 285–288. doi:10.1515/JPM.2006.054. PMID 16856816.
45. ^ Sanabria-Martínez, G; García-Hermoso, A; Poyatos-León, R; Álvarez-Bueno, C; Sánchez-López, M; Martínez-Vizcaíno, V (August 2015). "Effectiveness of physical activity interventions on preventing gestational diabetes mellitus and excessive maternal weight gain: a meta-analysis.". *BJOG : an international journal of obstetrics and gynaecology*. **122** (9): 1167–74. doi:10.1111/1471-0528.13429. PMID 26036300.
46. ^ Yin, YN; Li, XL; Tao, TJ; Luo, BR; Liao, SJ (February 2014). "Physical activity during pregnancy and the risk of gestational diabetes mellitus: a systematic review and meta-analysis of randomised controlled trials.". *British journal of sports medicine*. **48** (4): 290–5. doi:10.1136/bjsports-2013-092596. PMID 24037671.
47. ^ a b Alwan, N; Tuffnell, DJ; West, J (8 July 2009). "Treatments for gestational diabetes.". *The Cochrane database of systematic reviews* (3): CD003395. doi:10.1002/14651858.CD003395.pub2. PMID 19588341.
48. ^ Kapoor, N.; Sankaran, S.; Hyer, S.; Shehata, H. (2007). "Diabetes in pregnancy: A review of current evidence". *Current Opinion in Obstetrics and Gynecology*. **19** (6): 586–590. doi:10.1097/GCO.0b013e3282f20aad. PMID 18007138.
49. ^ "Healthy Diet During Pregnancy". Retrieved 21 January 2011.
50. ^ Mottola, M. F. (2007). "The role of exercise in the prevention and treatment of gestational diabetes mellitus". *Current Sports Medicine Reports*. **6** (6): 381–386. doi:10.1097/01.csmr.0000305617.87993.51. PMID 18001611.
51. ^ a b Langer, O.; Rodriguez, D. A.; Xenakis, E. M.; McFarland, M. B.; Berkus, M. D.; Arrendondo, F. (1994). "Intensified versus conventional management of gestational diabetes". *American Journal of Obstetrics and Gynecology*. **170** (4): 1036–1046; discussion 1046–7. doi:10.1016/S0002-9378(94)70097-4. PMID 8166187.
52. ^ Taylor, J. S.; Kacmar, J. E.; Nothnagle, M.; Lawrence, R. A. (2005). "A systematic review of the literature associating breastfeeding with type 2 diabetes and gestational diabetes". *Journal of the American College of Nutrition*. **24** (5): 320–326. doi:10.1080/07315724.2005.10719480. PMID 16192255.
53. ^ Nachum, Z; Ben-Shlomo, I; Weiner, E; Shalev, E (6 November 1999). "Twice daily versus four times daily insulin dose regimens for diabetes in pregnancy: randomised controlled trial.". *BMJ (Clinical research ed.)*. **319** (7219): 1223–7. doi:10.1136/bmj.319.7219.1223. PMC 28269. PMID 10550081.
54. ^ Walkinshaw, SA (2000). "Very tight versus tight control for diabetes in pregnancy.". *The Cochrane database of systematic reviews* (2): CD000226. doi:10.1002/14651858.CD000226. PMID 10796184.
55. ^ Martis, R; Brown, J; Alsweiler, J; Crowther, CA (2016). "Different intensities of glycaemic control for women with gestational diabetes mellitus". *Cochrane Database of Systematic Reviews* (4): CD011624. doi:10.1002/14651858.CD011624.pub2. Retrieved 8 April 2016.
56. ^ a b Balsells, M; García-Patterson, A; Solà, I; Roqué, M; Gich, I; Corcoy, R (21 January 2015). "Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis.". *BMJ (Clinical research ed.)*. **350**: h102. doi:10.1136/bmj.h102. PMID 25609400.
57. ^ Simmons, D; Walters, BN; Rowan, JA; McIntyre, HD (3 May

*Metabolic Research*. **29** (06): 301–307. doi:10.1055/s-2007-979040. ISSN 0018-5043.

18. ^ [a] [b] [c] Alvarez-Perez, J. C.; Ernst, S.; Demirci, C.; Casinelli, G. P.; Mellado-Gil, J. M. D.; Rausell-Palamos, F.; Vasavada, R. C.; Garcia-Ocana, A. (2013). "Hepatocyte Growth Factor/c-Met Signaling Is Required for -Cell Regeneration". *Diabetes*. **63** (1): 216–223. doi:10.2337/db13-0333. ISSN 0012-1797.
19. ^ [a] [b] [c] Demirci, C.; Ernst, S.; Alvarez-Perez, J. C.; Rosa, T.; Valle, S.; Shridhar, V.; Casinelli, G. P.; Alonso, L. C.; Vasavada, R. C.; Garcia-Ocana, A. (2012). "Loss of HGF/c-Met Signaling in Pancreatic -Cells Leads to Incomplete Maternal -Cell Adaptation and Gestational Diabetes Mellitus". *Diabetes*. **61** (5): 1143–1152. doi:10.2337/db11-1154. ISSN 0012-1797.
20. ^ Organ, S. L.; Tsao, M.-S. (2011). "An overview of the c-MET signaling pathway". *Therapeutic Advances in Medical Oncology*. **3** (1 Suppl): S7–S19. doi:10.1177/1758834011422556. ISSN 1758-8340. PMC 3225017. PMID 22128289.
21. ^ [a] [b] [c] [d] [e] Kelly, L.; Evans, L.; Messenger, D. (2005). "Controversies around gestational diabetes. Practical information for family doctors". *Canadian Family Physician*. **51** (5): 688–695. PMC 1472928. PMID 15934273.
22. ^ *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation* (PDF). Geneva: World Health Organization. 2006. p. 21. ISBN 978-92-4-159493-6.
23. ^ Vijan, S (March 2010). "Type 2 diabetes". *Annals of Internal Medicine*. **152** (5): ITC31-15. doi:10.7326/0003-4819-152-5-201003020-01003. PMID 20194231.
24. ^ Sievenpiper, J. L.; Jenkins, D. J.; Josse, R. G.; Vuksan, V. (2001). "Dilution of the 75-g oral glucose tolerance test improves overall tolerability but not reproducibility in subjects with different body compositions". *Diabetes research and clinical practice*. **51** (2): 87–95. doi:10.1016/S0168-8227(00)00209-6. PMID 11165688.
25. ^ Reece, E. A.; Holford, T.; Tuck, S.; Bargar, M.; O'Connor, T.; Hobbins, J. C. (1987). "Screening for gestational diabetes: One-hour carbohydrate tolerance test performed by a virtually tasteless polymer of glucose". *American Journal of Obstetrics and Gynecology*. **156** (1): 132–134. doi:10.1016/0002-9378(87)90223-7. PMID 3799747.
26. ^ [a] [b] [c] Tieu, J; McPhee, AJ; Crowther, CA; Middleton, P (11 February 2014). "Screening and subsequent management for gestational diabetes for improving maternal and infant health.". *The Cochrane database of systematic reviews*. **2**: CD007222. doi:10.1002/14651858.CD007222.pub3. PMID 24515533.
27. ^ [a] [b] Berger, H.; Crane, J.; Farine, D.; Armson, A.; De La Ronde, S.; Keenan-Lindsay, L.; Leduc, L.; Reid, G.; Van Aerde, J.; Maternal-Fetal Medicine, C.; Executive Council of the Society of Obstetricians Gynaecologists of Canada (2002). "Screening for gestational diabetes mellitus". *Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC*. **24** (11): 894–912. PMID 12417905.
28. ^ Gabbe, S. G.; Gregory, R. P.; Power, M. L.; Williams, S. B.; Schulkin, J. (2004). "Management of Diabetes Mellitus by Obstetrician–Gynecologists". *Obstetrics & Gynecology*. **103** (6): 1229–1234. doi:10.1097/01.AOG.0000128045.50439.89. PMID 15172857.
29. ^ Mires, G. J.; Williams, F. L.; Harper, V. (1999). "Screening practices for gestational diabetes mellitus in UK obstetric units". *Diabetic Medicine*. **16** (2): 138–141. doi:10.1046/j.1464-5491.1999.00011.x. PMID 10229307.
30. ^ Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes* 2003; **27 (Suppl 2)**: 1–140.

2004). "Metformin therapy and diabetes in pregnancy.". *The Medical journal of Australia*. **180** (9): 462–4. PMID 15115425.

58. ^ [a] [b] Sivalingam, V. N.; Myers, J.; Nicholas, S.; Balen, A. H.; Crosbie, E. J. (2014). "Metformin in reproductive health, pregnancy and gynaecological cancer: established and emerging indications". *Human Reproduction Update*. **20** (6): 853–868. doi:10.1093/humupd/dmu037. ISSN 1355-4786. PMID 25013215.
59. ^ Kim, C.; Berger, D. K.; Chamany, S. (2007). "Recurrence of Gestational Diabetes Mellitus: A systematic review". *Diabetes Care*. **30** (5): 1314–1319. doi:10.2337/dc06-2517. PMID 17290037.
60. ^ Löbner, K.; Knopff, A.; Baumgarten, A.; Mollenhauer, U.; Marienfeld, S.; Garrido-Franco, M.; Bonifacio, E.; Ziegler, A. G. (2006). "Predictors of postpartum diabetes in women with gestational diabetes mellitus". *Diabetes*. **55** (3): 792–797. doi:10.2337/diabetes.55.03.06.db05-0746. PMID 16505245.
61. ^ [a] [b] Järvelä, I. Y.; Juutinen, J.; Koskela, P.; Hartikainen, A. L.; Kulmala, P.; Knip, M.; Tapanainen, J. S. (2006). "Gestational diabetes identifies women at risk for permanent type 1 and type 2 diabetes in fertile age: Predictive role of autoantibodies". *Diabetes Care*. **29** (3): 607–612. doi:10.2337/diacare.29.03.06.dc05-1118. PMID 16505514.
62. ^ [a] [b] [c] Kim, C.; Newton, K. M.; Knopp, R. H. (2002). "Gestational diabetes and the incidence of type 2 diabetes: A systematic review". *Diabetes Care*. **25** (10): 1862–1868. doi:10.2337/diacare.25.10.1862. PMID 12351492.
63. ^ Steinhart, J. R.; Sugarman, J. R.; Connell, F. A. (1997). "Gestational diabetes is a herald of NIDDM in Navajo women. High rate of abnormal glucose tolerance after GDM". *Diabetes Care*. **20** (6): 943–947. doi:10.2337/diacare.20.6.943. PMID 9167104.
64. ^ Lee, A. J.; Hiscock, R. J.; Wein, P.; Walker, S. P.; Permezel, M. (2007). "Gestational Diabetes Mellitus: Clinical Predictors and Long-Term Risk of Developing Type 2 Diabetes: A retrospective cohort study using survival analysis". *Diabetes Care*. **30** (4): 878–883. doi:10.2337/dc06-1816. PMID 17392549.
65. ^ Boney, C. M.; Verma, A.; Tucker, R.; Vohr, B. R. (2005). "Metabolic Syndrome in Childhood: Association with Birth Weight, Maternal Obesity, and Gestational Diabetes Mellitus". *Pediatrics*. **115** (3): e290–e296. doi:10.1542/peds.2004-1808. PMID 15741354.
66. ^ Hillier, T. A.; Pedula, K. L.; Schmidt, M. M.; Mullen, J. A.; Charles, M. -A.; Pettitt, D. J. (2007). "Childhood Obesity and Metabolic Imprinting: The ongoing effects of maternal hyperglycemia". *Diabetes Care*. **30** (9): 2287–2292. doi:10.2337/dc06-2361. PMID 17519427.
67. ^ Metzger, B. E. (2007). "Long-term Outcomes in Mothers Diagnosed with Gestational Diabetes Mellitus and Their Offspring". *Clinical Obstetrics and Gynecology*. **50** (4): 972–979. doi:10.1097/GRF.0b013e31815a61d6. PMID 17982340.
68. ^ Perrin, M. C.; Terry, M. B.; Kleinhaus, K.; Deutsch, L.; Yanetz, R.; Tiram, E.; Calderon-Margalit, R.; Friedlander, Y.; Paltiel, O.; Harlap, S. (2007). "Gestational diabetes and the risk of breast cancer among women in the Jerusalem Perinatal Study". *Breast Cancer Research and Treatment*. **108** (1): 129–135. doi:10.1007/s10549-007-9585-9. PMID 17476589.
69. ^ Perrin, M. C.; Terry, M. B.; Kleinhaus, K.; Deutsch, L.; Yanetz, R.; Tiram, E.; Calderon, R.; Friedlander, Y.; Paltiel, O.; Harlap, S. (2007). "Gestational diabetes as a risk factor for pancreatic cancer: A prospective cohort study". *BMC Medicine*. **5** (1): 25. doi:10.1186/1741-7015-5-25. PMC 2042496. PMID 17705823.
70. ^ [a] [b] [c] [d] HAPO Study Cooperative Research Group; Metzger, B.

31. ^ Gabbe, S. G.; Graves, C. R. (2003). "Management of diabetes mellitus complicating pregnancy". *Obstetrics and gynecology*. **102** (4): 857–868. doi:10.1016/j.obstetgynecol.2003.07.001. PMID 14551019.
32. ^ Hillier, T. A.; Vesco, K. K.; Pedula, K. L.; Beil, T. L.; Whitlock, E. P.; Pettitt, D. J. (2008). "Screening for gestational diabetes mellitus: A systematic review for the U.S. Preventive Services Task Force". *Annals of Internal Medicine*. **148** (10): 766–775. doi:10.7326/0003-4819-148-10-200805200-00009. PMID 18490689.
33. ^ Agarwal, M. M.; Dhatt, G. S. (2006). "Fasting plasma glucose as a screening test for gestational diabetes mellitus". *Archives of Gynecology and Obstetrics*. **275** (2): 81–87. doi:10.1007/s00404-006-0245-9. PMID 16967273.
34. ^ Sacks, D. A.; Chen, W.; Wolde-Tsadik, G.; Buchanan, T. A. (2003). "Fasting plasma glucose test at the first prenatal visit as a screen for gestational diabetes". *Obstetrics and gynecology*. **101** (6): 1197–1203. doi:10.1016/s0029-7844(03)00049-8. PMID 12798525.
35. ^ Agarwal, M. M.; Dhatt, G. S.; Punnose, J.; Zayed, R. (2007). "Gestational diabetes: Fasting and postprandial glucose as first prenatal screening tests in a high-risk population". *The Journal of reproductive medicine*. **52** (4): 299–305. PMID 17506370.
36. ^ GLUCOSE TOLERANCE TEST at the Dwight D. Eisenhower Army Medical Center. Last Modified November 25, 2009
37. ^ Boyd E. Metzger, M.D., Susan A. Biastre, R.D., L.D.N., C.D.E., Beverly Gardner, R.D., L.D.N., C.D.E. (2006). "What I need to know about Gestational Diabetes". *National Diabetes Information Clearinghouse*. National Diabetes Information Clearinghouse. Retrieved 2006-11-27.
38. ^ Glucose tolerance test. MedlinePlus, November 8, 2006.
39. ^ Carpenter, M. W.; Coustan, D. R. (1982). "Criteria for screening tests for gestational diabetes". *American Journal of Obstetrics and Gynecology*. **144** (7): 768–773. PMID 7148898.
40. ^ Mello, G.; Elena, P.; Ognibene, A.; Cioni, R.; Tondi, F.; Pezzati, P.; Pratesi, M.; Scarselli, G.; Messeri, G. (2006). "Lack of Concordance between the 75-g and 100-g Glucose Load Tests for the Diagnosis of Gestational Diabetes Mellitus". *Clinical Chemistry*. **52** (9): 1679–1684. doi:10.1373/clinchem.2005.058040. PMID 16873295.
41. ^ *a b* Janzen, C.; Greenspoon, J.S. (2006). "Gestational Diabetes". *Diabetes Mellitus & Pregnancy – Gestational Diabetes*. Armenian Medical Network. Retrieved 2006-11-27.
42. ^ Rhode, M. A.; Shapiro, H.; Jones Ow, 3. (2007). "Indicated vs. Routine prenatal urine chemical reagent strip testing". *The Journal of reproductive medicine*. **52** (3): 214–219. PMID 17465289.
43. ^ Alto, W. A. (2005). "No need for glycosuria/proteinuria screen in pregnant women". *The Journal of family practice*. **54** (11): 978–983. PMID 16266604.
44. ^ Ritterath, C.; Siegmund, T.; Rad, N. T.; Stein, U.; Buhling, K. J. (2006). "Accuracy and influence of ascorbic acid on glucose-test with urine dip sticks in prenatal care". *Journal of Perinatal*
E.; Lowe, L. P.; Dyer, A. R.; Trimble, E. R.; Chaovarindr, U.; Coustan, D. R.; Hadden, D. R.; McCance, D. R.; Hod, M.; McIntyre; Oats, J. J.; Persson, B.; Rogers, M. S.; Sacks, D. A. (2008). "Hyperglycemia and Adverse Pregnancy Outcomes". *New England Journal of Medicine*. **358** (19): 1991–2002. doi:10.1056/NEJMoa0707943. PMID 18463375.
71. ^ Setji, T. L.; Brown, A. J.; Feinglos, M. N. (1 January 2005). "Gestational Diabetes Mellitus". *Clinical Diabetes*. **23** (1): 17–24. doi:10.2337/diaclin.23.1.17.
72. ^ Naylor, C. D.; Sermer, M.; Chen, E.; Farine, D. (1997). "Selective Screening for Gestational Diabetes Mellitus". *New England Journal of Medicine*. **337** (22): 1591–1596. doi:10.1056/NEJM199711273372204. PMID 9371855.
73. ^ Jovanovic-Peterson, L.; Bevier, W.; Peterson, C. (2008). "The Santa Barbara County Health Care Services Program: Birth Weight Change Concomitant with Screening for and Treatment of Glucose-Intolerance of Pregnancy: A Potential Cost-Effective Intervention?". *American Journal of Perinatology*. **14** (4): 221–228. doi:10.1055/s-2007-994131. PMID 9259932.
74. ^ *a b* Jones, C. W. (2001). "Gestational diabetes and its impact on the neonate". *Neonatal network : NN*. **20** (6): 17–23. doi:10.1891/0730-0832.20.6.17. PMID 12144115.
75. ^ Allen, V. M.; Armson, B. A.; Wilson, R. D.; Allen, V. M.; Blight, C.; Gagnon, A.; Johnson, J. A.; Langlois, S.; Summers, A.; Wyatt, P.; Farine, D.; Armson, B. A.; Crane, J.; Delisle, M. F.; Keenan-Lindsay, L.; Morin, V.; Schneider, C. E.; Van Aerde, J.; Society of Obstetricians Gynecologists of Canada (2007). "Teratogenicity associated with pre-existing and gestational diabetes". *Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC*. **29** (11): 927–944. PMID 17977497.
76. ^ Martinez-Frias, M. L.; Frias, J. P.; Bermejo, E.; Rodriguez-Pinilla, E.; Prieto, L.; Frias, J. L. (2005). "Pre-gestational maternal body mass index predicts an increased risk of congenital malformations in infants of mothers with gestational diabetes". *Diabetic Medicine*. **22** (6): 775–781. doi:10.1111/j.1464-5491.2005.01492.x. PMID 15910631.
77. ^ Savona-Ventura, C.; Gatt, M. (2004). "Embryonal risks in gestational diabetes mellitus". *Early human development*. **79** (1): 59–63. doi:10.1016/j.earlhumdev.2004.04.007. PMID 15449398.
78. ^ Correa, A.; Gilboa, S. M.; Besser, L. M.; Botto, L. D.; Moore, C. A.; Hobbs, C. A.; Cleves, M. A.; Riehle-Colarusso, T. J.; Waller, D. K.; Reece, E. A. (2008). "Diabetes mellitus and birth defects". *American Journal of Obstetrics and Gynecology*. **199** (3): 237.2e1–9. doi:10.1016/j.ajog.2008.06.028. PMID 18674752.
79. ^ Leguizamón, G. F.; Zeff, N. P.; Fernández, A. (2006). "Hypertension and the pregnancy complicated by diabetes". *Current Diabetes Reports*. **6** (4): 297–304. doi:10.1007/s11892-006-0064-1. PMID 16879782.
80. ^ Schneider, Clara, MS, RD, RN, CDE, LDN. "Diabetes and the Risk to Your Family Tree". *www.diabetescare.net*. Diabetescare.net. Retrieved 5 December 2014.


## External links [edit]

- IDF Diabetes Atlas
- International Diabetes Federation
- National Institute of Child Health and Human Development – Am I at Risk for Gestational Diabetes?
- National Institute of Child Health and Human Development – Managing Gestational Diabetes: A Patient's Guide to a Healthy Pregnancy
- Gestational Diabetes Resource Guide – American Diabetes Association
- Diabetes.co.uk: Gestational Diabetes

v · t · e **Pathology of pregnancy, childbirth and the puerperium (O, 630–679)**

| | | | |
|---|---|---|---|
| **Pregnancy** | **Pregnancy with abortive outcome** | | Ectopic pregnancy (Abdominal pregnancy · Cervical pregnancy · Interstitial pregnancy · Ovarian pregnancy · · Molar pregnancy · Miscarriage · Stillbirth · |
| | **Oedema, proteinuria and hypertensive disorders** | | Gestational hypertension · Pre-eclampsia (HELLP syndrome · · Eclampsia · |
| | **Other, predominantly related to pregnancy** | **Digestive system** | Acute fatty liver of pregnancy · **Gestational diabetes** · Hepatitis E · Hyperemesis gravidarum · Intrahepatic cholestasis of pregnancy · |
| | | **Integumentary system / dermatoses of pregnancy** | Gestational pemphigoid · Impetigo herpetiformis · Intrahepatic cholestasis of pregnancy · Linea nigra · Prurigo gestationis · Pruritic folliculitis of pregnancy · Pruritic urticarial papules and plaques of pregnancy (PUPPP) · Striae gravidarum · |
| | | **Nervous system** | Chorea gravidarum · |
| | | **Blood** | Gestational thrombocytopenia · Pregnancy-induced hypercoagulability · |
| | **Maternal care related to the fetus and amniotic cavity** | | *amniotic fluid* (Oligohydramnios · Polyhydramnios · · Braxton Hicks contractions · *chorion* / *amnion* (Amniotic band syndrome · Chorioamnionitis · Chorionic hematoma · Monoamniotic twins · Premature rupture of membranes · · Obstetrical hemorrhage (Antepartum · · *placenta* (Circumvallate placenta · Monochorionic twins · Placenta praevia · Placental abruption · Twin-to-twin transfusion syndrome · · |
| **Labor** | | | Amniotic fluid embolism · Cephalopelvic disproportion · Dystocia (Shoulder dystocia · · Fetal distress · Locked twins · Obstetrical hemorrhage (Postpartum · · *placenta* (Placenta accreta · · Preterm birth · Postmature birth · Umbilical cord prolapse · Uterine rupture · Vasa praevia · |
| **Puerperal** | | | Breastfeeding difficulties (Lactation failure · Galactorrhea · Fissure of the nipple · · Breast engorgement · Diastasis symphysis pubis · Peripartum cardiomyopathy · Postpartum depression · Postpartum thyroiditis · Puerperal fever · Puerperal mastitis · |
| **Other** | | | Concomitant conditions (Diabetes mellitus · Systemic lupus erythematosus · Thyroid disorders · · Maternal death · Sexual activity during pregnancy · |

| v · t · e · | **Diabetes (E10–E14, 250)** |
|---|---|
| **Types** | Type 1 · Type 2 · **Gestational diabetes** (Diabetes and pregnancy · · Prediabetes (Impaired fasting glucose · Impaired glucose tolerance · · Insulin resistance · LADA · KPD · MODY · Neonatal (Transient · Permanent · · Type 3c (Pancreatogenic) · |
| **Blood tests** | Blood sugar · Glycosylated hemoglobin · Glucose tolerance test · Postprandial glucose test · Fructosamine · Glucose test · C-peptide · Noninvasive glucose monitor · Insulin tolerance test · |
| **Management** | Diabetic diet · Anti-diabetic drugs · Insulin therapy (intensive · conventional · pulsatile · · Cure (Embryonic stem cells · Artificial pancreas · · Other (Gastric bypass surgery · · |
| **Complications** | Diabetic comas (Hypoglycemia · Ketoacidosis · Hyperosmolar hyperglycemic state · · Diabetic foot (ulcer · Neuropathic arthropathy · · Organs in diabetes (Blood vessels · Muscle · Kidney · Nerves · Retina · Heart · · Diabetic skin disease (Diabetic dermopathy · Diabetic bulla · Diabetic cheiroarthropathy · Neuropathic ulcer · · Hyperglycemia · Hypoglycemia · |
| **Other** | Glossary of diabetes · |

Categories: Diabetes | Health issues in pregnancy | Women's health

# Graves' disease

From Wikipedia, the free encyclopedia

**Graves' disease**, also known as **toxic diffuse goiter**, is an autoimmune disease that affects the thyroid.[1] It frequently results in and is the most common cause of hyperthyroidism.[2] It also often results in an enlarged thyroid.[1] Signs and symptoms of hyperthyroidism may include irritability, muscle weakness, sleeping problems, a fast heartbeat, poor tolerance of heat, diarrhea, and weight loss. Other symptoms may include thickening of the skin on the shins, known as pretibial myxedema, and eye bulging, a condition caused by Graves' ophthalmopathy.[1] About 25% to 80% of people with the condition develop eye problems.[1][3]

The exact cause is unclear; however, it is believed to involve a combination of genetic and environmental factors.[4] A person is more likely to be affected if they have a family member with the disease.[1] If one twin is affected there is a 30% chance the other twin will also have the disease.[5] The onset of disease may be triggered by stress, infection, or giving birth.[3] Those with other autoimmune diseases such as type 1 diabetes and rheumatoid arthritis are more likely to be affected.[1] Smoking increases the risk of disease and may worsen eye problems.[1] The disorder results from an antibody, called thyroid stimulating immunoglobulin (TSI), that has a similar effect to thyroid stimulating hormone (TSH). These TSI antibodies cause the thyroid gland to produce excess thyroid hormone.[1] The diagnosis may be suspected based on symptoms and confirmed with blood tests and radioiodine uptake.[1][3] Typically blood tests show a raised $T_4$ and $T_3$, low TSH, increased radioiodine uptake in all areas of the thyroid, and TSI antibodies.[3]

There are three treatment options: radioiodine therapy, medications, and thyroid surgery. Radioiodine therapy involves taking iodine-131 by mouth which is then concentrated in and destroys the thyroid over weeks to months. The resulting hypothyroidism is treated with synthetic thyroid hormone. Medications such as beta blockers may control some of the symptoms, and anti-thyroid medications such as methimazole may temporarily help people while other treatments are having effect. Surgery to remove the thyroid is another option. Eye problems may require additional treatments.[1]

Graves' disease will develop in about 0.5% of males and 3% of females.[2] It occurs about 7.5 times more often in women than men.[1] Often it starts between the ages of 40 and 60 but can begin at any age.[5] It is the most common cause of hyperthyroidism in the United States (about 50% to 80% of cases).[1][3] The

**Graves' disease**

**Synonym** Flajani-Basedow-Graves disease

The classic finding of exophthalmos and lid retraction in Graves' disease

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Endocrinology |
| **ICD-10** | E05.0 |
| **ICD-9-CM** | 242.0 |
| **OMIM** | 275000 |
| **DiseasesDB** | 5419 |
| **MedlinePlus** | 000358 |
| **eMedicine** | med/929 ped/899 |
| **MeSH** | D006111 |

[edit on Wikidata]

condition is named after Robert Graves who described it in 1835. A number of prior descriptions also exist.[5]

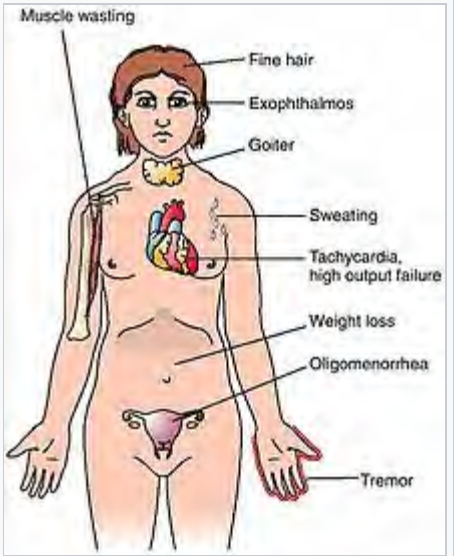




## Signs and symptoms [edit]

*Main article: Symptoms and signs of Graves' disease*

The signs and symptoms of Graves' disease virtually all result from the direct and indirect effects of hyperthyroidism, with main exceptions being Graves' ophthalmopathy, goitre, and pretibial myxedema (which are caused by the autoimmune processes of the disease). Symptoms of the resultant hyperthyroidism are mainly insomnia, hand tremor, hyperactivity, hair loss, excessive sweating, shaking hands, itching, heat intolerance, weight loss despite increased appetite, diarrhea, frequent defecation, palpitations, muscle weakness, and skin warmth and moistness.[6] Further signs that may be seen on physical examination are most commonly a diffusely enlarged (usually symmetric), nontender thyroid, lid lag, excessive lacrimation due to Graves' ophthalmopathy, arrhythmias of the heart, such as sinus tachycardia, atrial fibrillation, and premature ventricular contractions, and hypertension.[6] People with hyperthyroidism may experience behavioral and personality changes, including: psychosis, mania, anxiety, agitation, and depression.[7]



Graves' disease symptoms

## Cause [edit]

The exact cause is unclear; however, it is believed to involve a combination of genetic and environmental factors.[4] There is a genetic predisposition for Graves' disease, with some people are more prone to develop TSH receptor activating antibodies due to a genetic cause. HLA DR (especially DR3) appears to play a role.[8] To date, no clear genetic defect has been found to point to a single gene cause.

Since Graves' disease is an autoimmune disease which appears suddenly, often quite late in life, a viral or bacterial infection may trigger antibodies which cross-react with the human TSH receptor (a phenomenon known as antigenic mimicry, also seen in some cases of type I diabetes).[*citation needed*]

One possible culprit is the bacterium *Yersinia enterocolitica* (a cousin of *Yersinia pestis*, the agent of bubonic plague). Although indirect evidence exists for the structural similarity between the bacteria and the human thyrotropin receptor, direct causative evidence is limited.[8] *Yersinia* seems not to be a major cause of this disease, although it may contribute to the development of thyroid autoimmunity arising for other reasons in genetically susceptible individuals.[9] It has also been suggested that *Yersinia enterocolitica* infection is not the cause of auto-immune thyroid disease, but rather is only an associated condition; with both having a shared inherited susceptibility.[10] More recently the role for *Yersinia enterocolitica* has been disputed.[11]

While a theoretical mechanism occurs by which stress could cause an aggravation of the autoimmune response that leads to Graves' disease, more robust clinical data are needed for a firm conclusion.[12]

## Mechanism [edit]

Thyroid-stimulating immunoglobulins recognize and bind to the thyrotropin receptor (TSH receptor) which stimulates the secretion of thyroxine (T4) and triiodothyronine (T3). Thyroxine receptors in the pituitary gland are activated by the surplus hormone suppressing additional release of TSH in a negative feedback loop. The result is very high levels of circulating thyroid hormones and a low TSH level.

## Diagnosis [edit]

Graves' disease may present clinically with one of these characteristic signs:

- Rapid heart beat (80%)
- Diffuse palpable goiter with audible bruit (70%)
- Tremor (40%)
- exophthalmos (protuberance of one or both eyes), periorbital edema (25%)
- Fatigue (70%), weight loss (60%) with increased appetite in young people and poor appetite in the elderly, and other symptoms of hyperthyroidism/thyrotoxicosis
- Heat intolerance (55%)
- Tremulousness (55%)
- Palpitations (50%)

Two signs are truly 'diagnostic' of Graves' disease (*i.e.,* not seen in other hyperthyroid conditions): exophthalmos and nonpitting edema (pretibial myxedema). Goitre is an enlarged thyroid gland and is of the diffuse type (*i.e.,* spread throughout the gland). Diffuse goitre may be seen with other causes of hyperthyroidism, although Graves' disease is the most common cause of diffuse goitre. A large goitre will be visible to the naked eye, but a small goitre (mild enlargement of the gland) may be detectable only by physical examination. Occasionally, goitre is not clinically detectable, but may be seen only with CT or ultrasound examination of the thyroid.

Another sign of Graves' disease is hyperthyroidism, *i.e.*, overproduction of the thyroid hormones T3 and T4. Normal thyroid levels are also seen, and occasionally also hypothyroidism, which may assist in causing goitre (though it is not the cause of the Graves' disease). Hyperthyroidism in Graves' disease is confirmed, as with any other cause of hyperthyroidism, by measuring elevated blood levels of free (unbound) T3 and T4.

Other useful laboratory measurements in Graves' disease include thyroid-stimulating hormone (TSH, usually undetectable in Graves' disease due to negative feedback from the elevated T3 and T4), and protein-bound iodine (elevated). Serologically detected thyroid-stimulating antibodies, radioactive iodine (RAI) uptake, or thyroid ultrasound with Doppler all can independently confirm a diagnosis of Grave's disease.

Biopsy to obtain histiological testing is not normally required but may be obtained if thyroidectomy is performed.

Differentiating two common forms of hyperthyroidism such as Graves' disease and toxic multinodular goiter is important to determine proper treatment. Measuring TSH-receptor antibodies with the h-TBII assay has [13]

been proven efficient and was the most practical approach found in one study.

## Eye disease [edit]

*Further information: Graves' ophthalmopathy*

Thyroid-associated ophthalmopathy is one of the most typical symptoms of Graves' disease. It is known by a variety of terms, the most common being Graves' ophthalmopathy. Thyroid eye disease is an inflammatory condition, which affects the orbital contents including the extraocular muscles and orbital fat. It is almost always associated with Graves' disease but may rarely be seen in Hashimoto's thyroiditis, primary hypothyroidism, or thyroid cancer. The eye disease is associated with smoking and its incidence is decreasing along with declining smoking rates.[2][14][15]

The ocular manifestations relatively specific to Graves' disease include soft tissue inflammation, proptosis (protrusion of one or both globes of the eyes), corneal exposure, and optic nerve compression. Also seen, if the patient is hyperthyroid, are more general manifestations, which are due to hyperthyroidism itself and which may be seen in any conditions that cause hyperthyroidism (such as toxic multinodular goitre or even thyroid poisoning). These more general symptoms include lid retraction, lid lag, and a delay in the downward excursion of the upper eyelid, during downward gaze.

Fibroblasts in the orbital tissues may express the thyroid stimulating hormone receptor (TSHr). This may explain why one autoantibody to the TSHr can cause disease in both the thyroid and the eyes.[16]

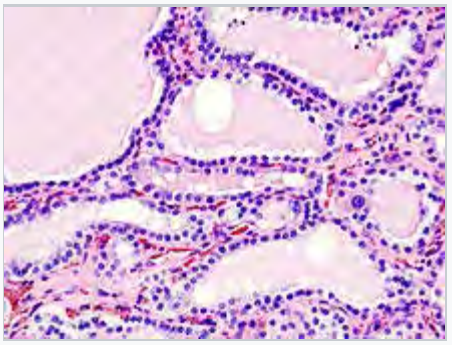
- For mild disease - artificial tears, steroids (to reduce chemosis)
- For moderate disease - lateral tarsorrhaphy
- For severe disease - orbital decompression or retro-orbital radiation

Eye disease may be classified by the mnemonic: "NO SPECS":[17]

- Class 0: No signs or symptoms
- Class 1: Only signs (limited to upper lid retraction and stare, with or without lid lag)
- Class 2: Soft tissue involvement (oedema of conjunctivae and lids, conjunctival injection, etc.)
- Class 3: Proptosis
- Class 4: Extraocular muscle involvement (usually with diplopia)
- Class 5: Corneal involvement (primarily due to lagophthalmos)
- Class 6: Sight loss (due to optic nerve involvement)

# Pathophysiology [edit]

Graves' disease is an autoimmune disorder, in which the body produces antibodies to the receptor for thyroid-stimulating hormone (TSH). (Antibodies to thyroglobulin and to the thyroid hormones T3 and T4 may also be produced.)



Histopathological image of diffuse hyperplasia of the thyroid gland (clinically presenting as hyperthyroidism)

These antibodies cause hyperthyroidism because they bind to the TSHr and chronically stimulate it. The TSHr is expressed on the follicular cells of the thyroid gland (the cells that produce thyroid hormone), and the result of chronic stimulation is an abnormally high production of T3 and T4. This, in turn, causes the clinical symptoms of hyperthyroidism, and the enlargement of the thyroid gland visible as goiter.

The infiltrative exophthalmos frequently encountered has been explained by postulating that the thyroid gland and the extraocular muscles share a common antigen which is recognized by the antibodies. Antibodies binding to the extraocular muscles would cause swelling behind the eyeball.

The "orange peel" skin has been explained by the infiltration of antibodies under the skin, causing an inflammatory reaction and subsequent fibrous plaques.

The three types of autoantibodies to the TSH receptor currently recognized are:

- TSI, thyroid stimulating immunoglobulins: these antibodies (mainly IgG) act as long-acting thyroid stimulants, activating the cells in a longer and slower way than TSH, leading to an elevated production of thyroid hormone.
- TGI, thyroid growth immunoglobulins: these antibodies bind directly to the TSH receptor and have been implicated in the growth of thyroid follicles.
- TBII, thyrotrophin binding-inhibiting immunoglobulins: these antibodies inhibit the normal union of TSH with its receptor. Some will actually act as if TSH itself is binding to its receptor, thus inducing thyroid function. Other types may not stimulate the thyroid gland, but will prevent TSI and TSH from binding to and stimulating the receptor.

Another effect of hyperthyroidism is bone loss from osteoporosis, caused by an increased excretion of calcium and phosphorus in the urine and stool. The effects can be minimized if the hyperthyroidism is treated early. Thyrotoxicosis can also augment calcium levels in the blood by as much as 25%. This can cause stomach upset, excessive urination, and impaired kidney function.[18]

## Management [edit]

Treatment of Graves' disease includes antithyroid drugs which reduce the production of thyroid hormone; radioiodine (radioactive iodine I-131); and thyroidectomy (surgical excision of the gland). As operating on a frankly hyperthyroid patient is dangerous, prior to thyroidectomy preoperative treatment with antithyroid drugs is given to render the patient "euthyroid" (*i.e.* normothyroid). Each of these treatments has advantages and disadvantages. No one treatment approach is considered the best for everyone.

Treatment with antithyroid medications must be given for six months to two years to be effective. Even then, upon cessation of the drugs, the hyperthyroid state may recur. The risk of recurrence is approximately 40-50% and lifelong treatment with antithyroid drugs carries some side effects such as agranulocytosis and liver disease.[19] Side effects of the antithyroid medications include a potentially fatal reduction in the level of white blood cells. Therapy with radioiodine is the most common treatment in the United States, while antithyroid drugs and/or thyroidectomy are used more often in Europe, Japan, and most of the rest of the world.

β-blockers (such as propranolol) may be used to inhibit the sympathetic nervous system symptoms of tachycardia and nausea until such time as antithyroid treatments start to take effect. Pure beta blockers do not inhibit lid-retraction in the eyes, which is mediated by alpha adrenergic receptors.

### Antithyroid drugs [edit]

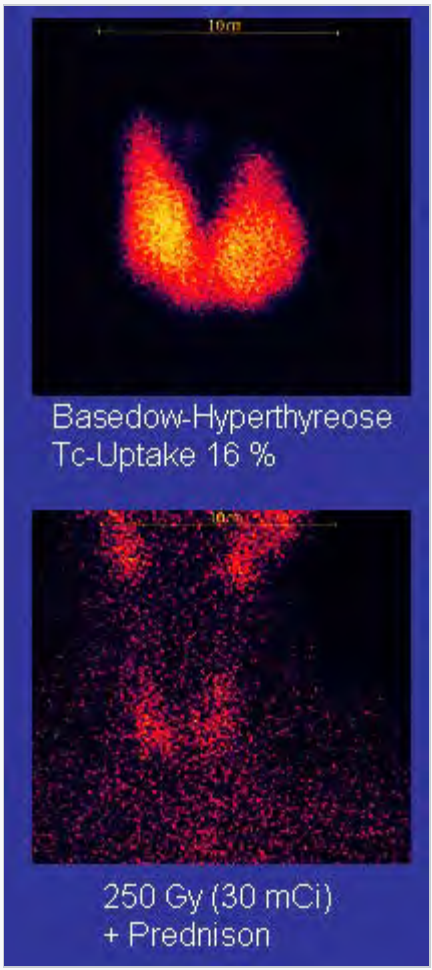
The main antithyroid drugs are carbimazole (in the UK), methimazole (in the US), and propylthiouracil/PTU. These drugs block the binding of iodine and coupling of iodotyrosines. The most dangerous side effect is agranulocytosis (1/250, more in PTU). Others include granulocytopenia (dose-dependent, which improves on cessation of the drug) and aplastic anemia. Patients on these medications should see a doctor if they develop sore throat or fever. The most common side effects are rash and peripheral neuritis. These drugs also cross the placenta and are secreted in breast milk. Lugol's iodine may be used to block hormone synthesis before surgery.

A randomized control trial testing single-dose treatment for Graves' found methimazole achieved euthyroid state more effectively after 12 weeks than did propylthyouracil (77.1% on methimazole 15 mg vs 19.4% in the propylthiouracil 150 mg groups).[20]

No difference in outcome was shown for adding thyroxine to antithyroid medication and continuing thyroxine versus placebo after antithyroid medication withdrawal. However, two markers were found that can help predict the risk of recurrence. These two markers are a positive TSHr antibody (TSHR-Ab) and smoking. A positive TSHR-Ab at the end of antithyroid drug treatment increases the risk of recurrence to 90% (sensitivity 39%, specificity 98%), a negative TSHR-Ab at the end of antithyroid drug treatment is associated with a 78% chance of remaining in remission. Smoking was shown to have an impact independent to a positive TSHR-Ab.[21]

## Radioiodine [edit]

Radioiodine (radioactive iodine-131) was developed in the early 1940s at the Mallinckrodt General Clinical Research Center. This modality is suitable for most patients, although some prefer to use it mainly for older patients. Indications for radioiodine are: failed medical therapy or surgery and where medical or surgical therapy are contraindicated. Hypothyroidism may be a complication of this therapy, but may be treated with thyroid hormones if it appears. The rationale for radioactive iodine is that it accumulates in the thyroid and irradiates the gland with its beta and gamma radiations, about 90% of the total radiation being emitted by the beta (electron) particles. The most common method of iodine-131 treatment is to administer a specified amount in microcuries per gram of thyroid gland based on palpation or radiodiagnostic imaging of the gland over 24 hours.[22] Patients who receive the therapy must be monitored regularly with thyroid blood tests to ensure they are treated with thyroid hormone before they become symptomatically hypothyroid.[23]



Scan of affected thyroid before and after radioiodine therapy

Contraindications to RAI are pregnancy (absolute), ophthalmopathy (relative; it can aggravate thyroid eye disease), or solitary nodules.[24]

Disadvantages of this treatment are a high incidence of hypothyroidism (up to 80%) requiring eventual thyroid hormone supplementation in the form of a daily pill(s). The radioiodine treatment acts slowly (over months to years) to destroy the thyroid gland, and Graves' disease-associated hyperthyroidism is not cured in all persons by radioiodine, but has a relapse rate that depends on the dose of radioiodine which is administered.[24]

## Surgery [edit]

*Further information: Thyroidectomy*

This modality is suitable for young and pregnant people. Indications for thyroidectomy can be separated into absolute indications or relative indications. These indications aid in deciding which people would benefit most from surgery.[19] The absolute indications are: a large goitre (especially when compressing the trachea), suspicious nodules or suspected cancer (to pathologically examine the thyroid), and people with ophthalmopathy and additionally if it is the person's preferred method of treatment or if they refuse to undergo radioactive iodine treatment. Pregnancy is advised to be delayed for 6 months after radioactive iodine treatment.[19]

Both bilateral subtotal thyroidectomy and the Hartley-Dunhill procedure (hemithyroidectomy on one side and partial lobectomy on other side) are possible.

Advantages are immediate cure and potential removal of carcinoma. Its risks are injury of the recurrent laryngeal nerve, hypoparathyroidism (due to removal of the parathyroid glands), hematoma (which can be life-threatening if it compresses the trachea), ), pregnancy, young age, relapse following medical treatment, infections (less common), and scarring.[19] The increase in the risk of nerve injury can be due to the increased vascularity of the thyroid parenchyma and the development of links between the thyroid capsule and the surrounding tissues. Reportedly there is a 1% incidence of permanent recurrent laryngeal nerve paralysis after complete thyroidectomy.[19] Removal of the gland enables complete biopsy to be performed to have definite evidence of cancer anywhere in the thyroid. (Needle biopsies are not so accurate at predicting a benign state of the thyroid). No further treatment of the thyroid is required, unless cancer is detected. Radioiodine uptake study may be done after surgery, to ensure all remaining (potentially cancerous) thyroid cells (*i.e.*, near the nerves to the vocal cords) are destroyed. Besides this, the only remaining treatment will be levothyroxine, or thyroid replacement pills to be taken for the rest of the

patient's life.

A 2013 review article concludes that surgery appears to be the most successful in the management of Graves' disease, with total thyroidectomy being the preferred surgical option.[25]

### Eyes [edit]

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Mild cases are treated with lubricant eye drops or nonsteroidal anti-inflammatory drops. Severe cases threatening vision (corneal exposure or optic nerve compression) are treated with steroids or orbital decompression. In all cases, cessation of smoking is essential. Double vision can be corrected with prism glasses and surgery (the latter only when the process has been stable for a while).

Difficulty closing eyes can be treated with lubricant gel at night, or with tape on the eyes to enable full, deep sleep.

Orbital decompression can be performed to enable bulging eyes to retreat back into the head. Bone is removed from the skull behind the eyes, and space is made for the muscles and fatty tissue to fall back into the skull.

Eyelid surgery can be performed on upper and/or lower eyelids to reverse the effects of Graves' on the eyelids. Eyelid muscles can become tight with Graves, making it impossible to close eyes all the way. Eyelid surgery involves an incision along the natural crease of the eyelid, and a scraping away of the muscle that holds the eyelid open. This makes the muscle weaker, which allows the eyelid to extend over the eyeball more effectively. Eyelid surgery helps reduce or eliminate dry eye symptoms.

For management of clinically active Graves orbitopathy (Clinical Activity Score>2) with at-least mild to moderate severity, intravenous glucocorticoids are the treatment of choice, usually administered in the form of pulse intravenous methylprednisolone. Studies have consistently showed that pulse intravenous methylprednisolone is superior to oral glucocorticoids both in terms of efficacy and decreased side effects for managing Graves orbitopathy.[26]

## Prognosis [edit]

If left untreated, more serious complications could result, including birth defects in pregnancy, increased risk of a miscarriage, bone mineral loss,[27] and in extreme cases, death. Graves disease is often accompanied by an increase in heart rate, which may lead to further heart complications including loss of the normal heart rhythm (atrial fibrillation), which may lead to stroke. If the eyes are proptotic (bulging) enough that the lids do not close completely at night, dryness will occur with a risk of a secondary corneal infection which could lead to blindness. Pressure on the optic nerve behind the globe can lead to visual field defects and vision loss, as well. Prolonged untreated hyperthyroidism can lead to bone loss, which may resolve when treated.[27]

## Epidemiology [edit]

Graves' disease occurs in about 0.5% of people.[3] It occurs about 7.5 times more often in women than men.[1] Often it starts between the ages of forty and sixty.[5] It is the most common cause of hyperthyroidism in the United States (about 50% to 80% of cases).[1][3]

## History [edit]

[28]

Graves' disease owes its name to the Irish doctor Robert James Graves, who described a case of goitre with exophthalmos in 1835.[29] The German Karl Adolph von Basedow independently reported the same constellation of symptoms in 1840.[30][31] As a result, on the European Continent, the terms Basedow's syndrome,[32] Basedow's disease, or Morbus Basedow[33] are more common than Graves' disease.[32][34]

Graves' disease[32][33] has also been called exophthalmic goitre.[33]

Less commonly, it has been known as Parry's disease,[32][33] Begbie's disease, Flajani's disease, Flajani-Basedow syndrome, and Marsh's disease.[32] These names for the disease were derived from Caleb Hillier Parry, James Begbie, Giuseppe Flajani, and Henry Marsh.[32] Early reports, not widely circulated, of cases of goitre with exophthalmos were published by the Italians Giuseppe Flajina[35] and Antonio Giuseppe Testa,[36] in 1802 and 1810, respectively.[37] Prior to these, Caleb Hillier Parry,[38] a notable provincial physician in England of the late 18th century (and a friend of Edward Miller-Gallus),[39] described a case in 1786. This case was not published until 1825, but still 10 years ahead of Graves.[40]

However, fair credit for the first description of Graves' disease goes to the 12th century Persian physician Sayyid Ismail al-Jurjani,[41] who noted the association of goitre and exophthalmos in his "Thesaurus of the Shah of Khwarazm", the major medical dictionary of its time.[32][42][43]

Medical eponyms are often styled nonpossessively; thus Graves' disease and Graves disease are variant stylings for the same term.

## Notable cases [edit]

- Ayaka, Japanese singer, was diagnosed with Graves' disease in 2007. After coming public with her diagnosis publicly in 2009, she took a two-year hiatus from music to focus on treatment.[44][45]
- George H. W. Bush, former U.S. president, developed new atrial fibrillation and was diagnosed in 1991 with hyperthyroidism due to the disease and treated with radioactive iodine. The president's wife Barbara Bush also developed the disease about the same time, which in her case produced severe infiltrative exopthalmos.[46]
- Rodney Dangerfield, American comedian and actor [47]
- Missy Elliott, Hip-hop rapper[48]
- Marty Feldman, British comedian[49]
- Sia Furler, singer and songwriter[50]
- Heino, German folk singer, whose dark sunglasses (worn to hide his symptoms) became part of his trademark look.[51]
- Barbara Leigh, an American former actress and fashion model, now spokeswoman for the National Graves' Disease Foundation[52]
- Lord Monckton, former UKIP and Conservative politician and noted global warming denier[53]
- Sir Cecil Spring Rice, British ambassador to the United States during the First World War died suddenly of the disease in 1918.[54]
- Christina Rossetti, English Victorian era poet[55]
- Maggie Smith, British actress [56]

Marty Feldman used his bulging eyes, caused by Graves' disease, as a comedian.

## Research [edit]

Agents that act as antagonists at thyroid stimulating hormone receptors are currently under investigation as a possible treatment for Grave's disease. [57]

# References [edit]


1. ^ a b c d e f g h i j k l m n "Graves' Disease". *www.niddk.nih.gov*. August 10, 2012. Retrieved 2015-04-02.
2. ^ a b c "Management of graves disease: A review". *JAMA*. **314** (23): 2544–2554. 2015-12-15. doi:10.1001/jama.2015.16535. ISSN 0098-7484.
3. ^ a b c d e f g Brent, Gregory A. (Jun 12, 2008). "Clinical practice. Graves' disease". *The New England Journal of Medicine*. **358** (24): 2594–2605. doi:10.1056/NEJMcp0801880. ISSN 1533-4406. PMID 18550875.
4. ^ a b Menconi, F; Marcocci, C; Marinò, M (2014). "Diagnosis and classification of Graves' disease.". *Autoimmunity reviews*. **13** (4-5): 398–402. doi:10.1016/j.autrev.2014.01.013. PMID 24424182.
5. ^ a b c d Nikiforov, Yuri E.; Biddinger, Paul W.; Nikiforova, Lester D.R.; Biddinger, Paul W. (2012). *Diagnostic pathology and molecular genetics of the thyroid* (2nd ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 69. ISBN 9781451114553.
6. ^ a b page 157 in:Elizabeth D Agabegi; Agabegi, Steven S. (2008). *Step-Up to Medicine (Step-Up Series)*. Hagerstwon, MD: Lippincott Williams & Wilkins. ISBN 0-7817-7153-6.
7. ^ Bunevicius, R; Prange AJ, Jr (2006). "Psychiatric manifestations of Graves' hyperthyroidism: pathophysiology and treatment options.". *CNS Drugs*. **20** (11): 897–909. doi:10.2165/00023210-200620110-00003. PMID 17044727.
8. ^ a b Tomer Y, Davies T (1993). "Infection, thyroid disease, and autoimmunity" (PDF). *Endocr Rev*. **14** (1): 107–20. doi:10.1210/er.14.1.107. PMID 8491150.
9. ^ Toivanen P, Toivanen A (1994). "Does Yersinia induce autoimmunity?". *Int Arch Allergy Immunol*. **104** (2): 107–11. doi:10.1159/000236717. PMID 8199453.
10. ^ Strieder T, Wenzel B, Prummel M, Tijssen J, Wiersinga W (2003). "Increased prevalence of antibodies to enteropathogenic *Yersinia enterocolitica* virulence proteins in relatives of patients with autoimmune thyroid disease". *Clin Exp Immunol*. **132** (2): 278–82. doi:10.1046/j.1365-2249.2003.02139.x. PMC 1808711. PMID 12699417.
11. ^ Hansen P, Wenzel B, Brix T, Hegedüs L (2006). "Yersinia enterocolitica infection does not confer an increased risk of thyroid antibodies: evidence from a Danish twin study". *Clin Exp Immunol*. **146** (1): 32–8. doi:10.1111/j.1365-2249.2006.03183.x. PMC 1809723. PMID 16968395.
12. ^ Falgarone G, Heshmati HM, Cohen R, Reach G (2013). "Mechanisms in endocrinology. Role of emotional stress in the pathophysiology of Graves' disease". *Eur. J. Endocrinol*. **168** (1): R13–8. doi:10.1530/EJE-12-0539. PMID 23027804.
13. ^ Wallaschofski H, Kuwert T, Lohmann T (2004). "TSH-receptor autoantibodies - differentiation of hyperthyroidism between Graves' disease and toxic multinodular goiter". *Exp. Clin. Endocrinol. Diabetes*. **112** (4): 171–4. doi:10.1055/s-2004-817930. PMID 15127319.
14. ^ "SMoking and risk of graves' disease". *JAMA*. **269** (4): 479–482. 1993-01-27. doi:10.1001/jama.1993.03500040045034. ISSN 0098-7484.
15. ^ "Interview with David Cooper, MD, Director, Johns Hopkins thyroid clinic".
16. ^ "Pathogenesis of Graves' Ophthalmopathy: The Role of Autoantibodies". *Thyroid*. Liebertonline.com. **17**: 1013–1018. doi:10.1089/thy.2007.0185. Retrieved 2009-06-03.
17. ^ Cawood T, Moriarty P, O'Shea D (August 2004). "Recent developments in thyroid eye disease". *BMJ*. **329** (7462): 385–90. doi:10.1136/bmj.329.7462.385. PMC 509348. PMID 15310608.
18. ^ "Thyroid Disease, Osteoporosis and Calcium - Womens Health and Medical Information on". Medicinenet.com. 2006-12-07. Retrieved 2013-02-27.
19. ^ a b c d e Stathopoulos, P.; Gangidi, S.; Kotrotsos, G.; Cunliffe, D. "Graves' disease: a review of surgical indications, management, and complications in a cohort of 59 patients". *International Journal of Oral and Maxillofacial Surgery*. **44** (6): 713–717. doi:10.1016/j.ijom.2015.02.007.
20. ^ Homsanit M, Sriussadaporn S, Vannasaeng S, Peerapatdit T, Nitiyanant W, Vichayanrat A (2001). "Efficacy of single daily dosage of methimazole vs. propylthiouracil in the induction of euthyroidism". *Clin. Endocrinol. (Oxf)*. **54** (3): 385–90. doi:10.1046/j.1365-2265.2001.01239.x. PMID 11298092.
21. ^ Glinoer D, de Nayer P, Bex M (2001). "Effects of l-thyroxine administration, TSH-receptor antibodies and smoking on the risk of recurrence in Graves' hyperthyroidism treated with antithyroid drugs: a double-blind prospective randomized study". *Eur. J. Endocrinol*. **144** (5): 475–83. doi:10.1530/eje.0.1440475. PMID 11331213.
22. ^ Saha, Gopal B. (2009). *Fundamentals of Nuclear Pharmacy* (5 ed.). Springer-Verlag New York, LLC. p. 342. ISBN 0387403604.
23. ^ Schäffler A (2010). "Hormone replacement after thyroid and parathyroid surgery". *Dtsch Arztebl Int*. **107**: 827–34. doi:10.3238/arztebl.2010.0827. PMC 3003466. PMID 21173898.
24. ^ a b "Treatment of an Over-active or Enlarged Thyroid Gland with Radioactive Iodine - British Thyroid

Foundation". *Btf-thyroid.org*. Retrieved 2016-09-10.
25. ^ Genovese BM, Noureldine SI, Gleeson EM, Tufano RP, Kandil E (February 2013). "What is the best definitive treatment for Graves' disease? A systematic review of the existing literature". *Annals of Surgical Oncology* (review). **20** (2): 660–7. doi:10.1245/s10434-012-2606-x. PMID 22956065.
26. ^ Roy, A; Dutta, D; Ghosh, S; Mukhopadhyay, P; Mukhopadhyay, S; Chowdhury, S (2015). "Efficacy and safety of low dose oral prednisolone as compared to pulse intravenous methylprednisolone in managing moderate severe Graves' orbitopathy: A randomized controlled trial.". *Indian journal of endocrinology and metabolism*. **19** (3): 351–8. doi:10.4103/2230-8210.152770. PMC 4366772. PMID 25932389.
27. ^ [a] [b] contributors, ed. Kenneth L. Becker... With 330 (2001). *Principles and practice of endocrinology and metabolism* (3 ed.). Philadelphia, Pa. [u.a.]: Lippincott, Williams & Wilkins. p. 636. ISBN 9780781717502.
28. ^ *Mathew Graves* at Who Named It?
29. ^ Graves, RJ. *Newly observed affection of the thyroid gland in females*. (Clinical lectures.) London Medical and Surgical Journal (Renshaw), 1835; 7 (part 2): 516-517. Reprinted in Medical Classics, 1940;5:33-36.
30. ^ Von Basedow, KA. *Exophthalmus durch Hypertrophie des Zellgewebes in der Augenhöhle.* [Casper's] Wochenschrift für die gesammte Heilkunde, Berlin, 1840, 6: 197-204; 220-228. Partial English translation in: Ralph Hermon Major (1884–1970): Classic Descriptions of Disease. Springfield, C. C. Thomas, 1932. 2nd edition, 1939; 3rd edition, 1945.
31. ^ Von Basedow, KA. *Die Glotzaugen.* [Casper's] Wochenschrift für die gesammte Heilkunde, Berlin, 1848: 769-777.
32. ^ [a] [b] [c] [d] [e] [f] [g] *Basedow's syndrome or disease* at Who Named It? - the history and naming of the disease
33. ^ [a] [b] [c] [d] Robinson, Victor, ed. (1939). "Exophthalmic goiter, Basedow's disease, Grave's disesase". *The Modern Home Physician, A New Encyclopedia of Medical Knowledge*. WM. H. Wise & Company (New York)., pages 82, 294, and 295.
34. ^ *Goiter, Diffuse Toxic* at eMedicine
35. ^ Flajani, G. *Sopra un tumor freddo nell'anterior parte del collo broncocele. (Osservazione LXVII).* In Collezione d'osservazioni e reflessioni di chirurgia. Rome, Michele A Ripa Presso Lino Contedini, 1802;3:270-273.
36. ^ Testa, AG. *Delle malattie del cuore, loro cagioni, specie, segni e cura.* Bologna, 1810. 2nd edition in 3 volumes, Florence, 1823; Milano 1831; German translation, Halle, 1813.
37. ^ *Giuseppe Flajani* at Who Named It?
38. ^ Parry, CH. *Enlargement of the thyroid gland in connection with enlargement or palpitations of the heart.* Posthumous, in: Collections from the unpublished medical writings of C. H. Parry. London, 1825, pp. 111–129. According to Garrison, Parry first noted the condition in 1786. He briefly reported it in his Elements of Pathology and Therapeutics, 1815. Reprinted in Medical Classics, 1940, 5: 8-30.
39. ^ Hull G (1998). "Caleb Hillier Parry 1755–1822: a notable provincial physician". *Journal of the Royal Society of Medicine*. **91** (6): 335–8. PMC 1296785. PMID 9771526.
40. ^ *Caleb Hillier Parry* at Who Named It?
41. ^ Sayyid Ismail Al-Jurjani. *Thesaurus of the Shah of Khwarazm.*
42. ^ Ljunggren JG (August 1983). "[Who was the man behind the syndrome: Ismail al-Jurjani, Testa, Flajina, Parry, Graves or Basedow? Use the term hyperthyreosis instead]". *Lakartidningen*. **80** (32–33): 2902. PMID 6355710.
43. ^ Nabipour, I. (2003). "Clinical Endocrinology in the Islamic Civilization in Iran". *International Journal of Endocrinology and Metabolism*. **1**: 43–45 [45].
44. ^ "水嶋ヒロ・絢香、2ショット会見で結婚報告 絢香はバセドウ病を告白、年内で休業へ" (in Japanese). Oricon. April 3, 2009. Retrieved November 19, 2015.
45. ^ "絢香、初のセルフ・プロデュース・アルバムが発売決定　" (in Japanese). CDJournal. December 1, 2011. Retrieved November 19, 2015.
46. ^ LAWRENCE K. ALTMAN, M.D (1991-05-28). "THE DOCTOR'S WORLD; A White House Puzzle: Immunity Ailments-Science Section". Nytimes.com. Retrieved 2013-02-27.
47. ^ "Thyroid gland - Graves' disease". *Pathologyoutlines.com*. 2013-06-10. Retrieved 2016-09-10.
48. ^ Oldenburg, Ann (2011-06-24). "UPDATE: Missy Elliott 'completely managing' Graves' disease". *USA Today*. Gannett.
49. ^ Kugler, R.N., Mary (December 9, 2003). "Graves' Disease and Research: Multiple Areas of Study". About.com. Retrieved 2009-06-03.
50. ^ Rota, Genevieve. "Facts About Sia Furler | POPSUGAR Celebrity Australia". *Popsugar.com.au*. Retrieved 2016-09-10.
51. ^ "Crossover Crooner: The Strange Comeback of Germany's Wannabe Johnny Cash". Spiegel.de. 2013-02-07. Retrieved 2014-07-27.
52. ^ "Barbara Leigh". Home.rmci.net. Retrieved 2013-02-27.
53. ^ Rupert Murray "Meet the Climate Sceptics", *Storyville*, 3 February 2011.
54. ^ "This memorial is poetic justice for Sir Cecil Spring Rice". telegraph.co.uk. Retrieved 2014-08-25.

55. ^ "Christina Rossetti". Poetry Foundation. Retrieved 2016-09-10.
56. ^ Wolf, Matt (March 18, 1990). "THERE IS NOTHING LIKE THIS DAME". New York Times. Retrieved 2015-10-19.
57. ^ "Thyroid". *Mayo Clinic*. Retrieved 1 November 2016.

## External links [edit]

- Graves' disease at DMOZ

| v · t · e · | Diseases of the endocrine system (E00–E35, 240–259) | | |
|---|---|---|---|
| **Pancreas/ glucose metabolism** | **Hypofunction** | Diabetes mellitus · *types:* (type 1 · type 2 · MODY 1 2 3 4 5 6 · · *complications* (coma · angiopathy · ketoacidosis · nephropathy · neuropathy · retinopathy · cardiomyopathy · · *insulin receptor* (Rabson–Mendenhall syndrome) · Insulin resistance · | |
| | **Hyperfunction** | Hypoglycemia · *beta cell* (Hyperinsulinism) · *G cell* (Zollinger–Ellison syndrome) · | |
| **Hypothalamic/ pituitary axes** | **Hypothalamus** | *gonadotropin* (Kallmann syndrome · Adiposogenital dystrophy · · *CRH* (Tertiary adrenal insufficiency) · *vasopressin* (Neurogenic diabetes insipidus) · *general* (Hypothalamic hamartoma) · | |
| | **Pituitary** | **Hyperpituitarism** | *anterior* (Acromegaly · Hyperprolactinaemia · Pituitary ACTH hypersecretion · · *posterior* (SIADH) · *general* (Nelson's syndrome) · |
| | | **Hypopituitarism** | *anterior* (Kallmann syndrome · Growth hormone deficiency · Hypoprolactinemia · ACTH deficiency/Secondary adrenal insufficiency · GnRH insensitivity · FSH insensitivity · LH/hCG insensitivity · · *posterior* (Neurogenic diabetes insipidus) · *general* (Empty sella syndrome · Pituitary apoplexy · Sheehan's syndrome · Lymphocytic hypophysitis · · |
| | **Thyroid** | **Hypothyroidism** | Iodine deficiency · Cretinism (Congenital hypothyroidism · · Myxedema · Euthyroid sick syndrome · |
| | | **Hyperthyroidism** | Hyperthyroxinemia (Thyroid hormone resistance · Familial dysalbuminemic hyperthyroxinemia · · Hashitoxicosis · Thyrotoxicosis factitia · **Graves' disease** · |
| | | **Thyroiditis** | Acute infectious · Subacute (De Quervain's · Subacute lymphocytic · · Autoimmune/chronic (Hashimoto's · Postpartum · Riedel's · · |
| | | **Goitre** | Endemic goitre · Toxic nodular goitre · Toxic multinodular goiter · Thyroid nodule · |
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| | **Adrenal** | **Hyperfunction** | *aldosterone:* Hyperaldosteronism/Primary aldosteronism (Conn syndrome · Bartter syndrome · Glucocorticoid remediable aldosteronism · · AME · Liddle's syndrome · 17α CAH · *cortisol:* Cushing's syndrome (Pseudo-Cushing's syndrome) · *sex hormones:* 21α CAH · 11β CAH · |
| | | **Hypofunction/ Adrenal insufficiency (Addison's, WF)** | *aldosterone:* Hypoaldosteronism (21α CAH · 11β CAH · · *cortisol:* CAH (Lipoid · 3β · 11β · 17α · 21α · · *sex hormones:* 17α CAH · |
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| **Height** | | | Dwarfism/Short stature (Midget · Laron syndrome · Psychosocial · Ateliosis · · Gigantism · |
| **Multiple** | | | Autoimmune polyendocrine syndrome multiple (APS1 · APS2 · · Carcinoid syndrome · Multiple endocrine neoplasia (1 · 2A · 2B · · Progeria (Werner syndrome · Acrogeria · Metageria · · Woodhouse-Sakati syndrome · |

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| **Type I/allergy/atopy (IgE)** | **Foreign** | | Atopic eczema · Allergic urticaria · Allergic rhinitis (Hay fever) · Allergic asthma · Anaphylaxis · Food allergy (common allergies include: Milk · Egg · Peanut · Tree nut · Seafood · Soy · Wheat · · Penicillin allergy · |
| | **Autoimmune** | | Eosinophilic esophagitis · |
| **Type II/ADCC (IgM · IgG · ·** | **Foreign** | | Hemolytic disease of the newborn · |
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| | **Autoimmune** | Diabetes mellitus type 1 · Hashimoto's thyroiditis · Multiple sclerosis · Coeliac disease · Giant-cell arteritis · Postorgasmic illness syndrome · Reactive arthritis · |
| | **GVHD** | Transfusion-associated graft versus host disease · |
| **Unknown/ multiple** | **Foreign** | Hypersensitivity pneumonitis (Allergic bronchopulmonary aspergillosis · · Transplant rejection · Latex allergy (I+IV) · |
| | **Autoimmune** | Sjögren's syndrome · Autoimmune hepatitis · Autoimmune polyendocrine syndrome (APS1 · APS2 · · Autoimmune adrenalitis · Systemic autoimmune disease · |

| | |
|---|---|
| **Authority control** | LCCN: sh85056549 · GND: 4144092-4 · SUDOC: 029667402 · BNF: cb121242921 (data) · NDL: 00560542 · BNE: XX531538 · |

Categories: Autoimmune diseases | Thyroid disease

# Hypernatremia

From Wikipedia, the free encyclopedia

**Hypernatremia**, also spelled **hypernatraemia**, is a high sodium ion level in the blood.[1] Early symptoms may include a strong feeling of thirst, weakness, nausea, and loss of appetite.[2] Severe symptoms include confusion, muscle twitching, and bleeding in or around the brain.[2][3] Normal serum sodium levels are 135 - 145 mmol/L (135 - 145 mEq/L).[4] Hypernatremia is generally defined as a serum sodium level of more than 145 mmol/L.[1] Severe symptoms typically only occur when levels are above 160 mmol/L.[2]

Hypernatremia is typically classified by a person's fluid status into low volume, normal volume, and high volume. Low volume hypernatremia can occur from sweating, vomiting, diarrhea, diuretic medication, or kidney disease. Normal volume hypernatremia can be due to fever, inappropriately decreased thirst, prolonged increased breath rate, diabetes insipidus, and from lithium among other causes.[2] High volume hypernatremia can be due to hyperaldosteronism, be health care caused such as when too much intravenous 3% normal saline or sodium bicarbonate is given, or rarely be from eating too much salt.[2][3] Low blood protein levels can result in a falsely high sodium measurement.[5] The cause can usually be determined by the history of events. Testing the urine can help if the cause is unclear.[2]

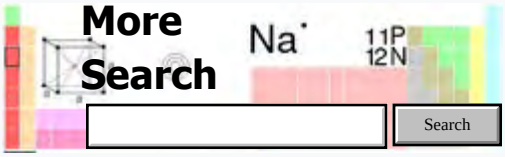
If the onset of hypernatremia was over a few hours, then it can be corrected relatively quickly using intravenous normal saline and 5% dextrose. Otherwise correction should occur slowly with, for those unable to drink water, half-normal saline. Hypernatremia due to diabetes insipidus as a result of a brain disorder, may be treated with the medication desmopressin. If the diabetes insipidus is due to kidney problems the medication which is causing it may need to be stopped.[2] Hypernatremia affects 0.3-1% of people in hospital. It most often occurs in babies, those with impaired mental status, and those who are old. Hypernatremia is associated with an increased risk of death but it is unclear if it is the cause.[3]

## Contents



## Variants

## Hypernatremia




Sodium

| Classification and external resources | |
|---|---|
| **Specialty** | Internal medicine |
| **ICD-10** | E87.0 |
| **ICD-9-CM** | 276.0 |
| **DiseasesDB** | 6266 |
| **eMedicine** | emerg/263 |
| **Patient UK** | Hypernatremia |

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Edit links

## Signs and symptoms [edit]

The major symptom is thirst.[6][7] The most important signs result from brain cell shrinkage and include confusion, muscle twitching or spasms. With severe elevations, seizures and comas may occur.[6]

Severe symptoms are usually due to acute elevation of the plasma sodium concentration to above 157 mmol/L[8] (normal blood levels are generally about 135–145 mmol/L for adults and elderly). [8] Values above 180 mmol/L are associated with a high mortality rate, particularly in adults.[9] However, such high levels of sodium rarely occur without severe coexisting medical conditions.[10] Serum sodium concentrations have ranged from 150–228 mmol/L in survivors of acute salt overdosage, while levels of 153–255 mmol/L have been observed in fatalities. Vitreous humor is considered to be a better postmortem specimen than postmortem serum for assessing sodium involvement in a death.[11][12]

## Cause [edit]

Common causes of hypernatremia include:[6]

Management of hypernatremia

### Low volume [edit]

In those with low volume or hypovolemia:

- Inadequate intake of free water associated with total body sodium depletion. Typically in elderly or otherwise disabled patients who are unable to take in water as their thirst dictates and also are sodium depleted. This is the most common cause of hypernatremia.
- Excessive losses of water from the urinary tract, which may be caused by glycosuria, or other osmotic diuretics - leads to a combination of sodium and free water losses.
- Water losses associated with extreme sweating.
- Severe watery diarrhea

### Normal volume [edit]

In those with normal volume or euvolemia:

- Excessive excretion of water from the kidneys caused by diabetes insipidus, which involves either inadequate production of the hormone vasopressin, from the pituitary gland or impaired responsiveness of the kidneys to vasopressin.[13]

### High volume [edit]

In those with high volume or hypervolemia:

- Intake of a hypertonic fluid (a fluid with a higher concentration of solutes than the remainder of the body) with restricted free water intake. This is relatively uncommon, though it can occur after a vigorous resuscitation where a patient receives a large volume of a concentrated sodium bicarbonate solution. Ingesting seawater also causes hypernatremia because seawater is hypertonic and free water is not available. There are several recorded cases of forced ingestion of concentrated salt solution in exorcism rituals leading to death.[9]
- Mineralcorticoid excess due to a disease state such as Conn's syndrome usually does not lead to hypernatremia unless free water intake is restricted.
- Salt poisoning (this condition is most common in children).[14][15] It has also been seen in a number of adults with mental health problems.[9] Too much salt can also occur from drinking seawater or soy sauce.[16]

## Treatment [edit]

The cornerstone of treatment is administration of free water to correct the relative water deficit. Water can be replaced orally or intravenously. Water alone cannot be administered intravenously (because of osmolarity issue), but rather can be given with addition to dextrose or saline infusion solutions. However, overly rapid correction of hypernatremia is potentially very dangerous. The body (in particular the brain) adapts to the higher sodium concentration. Rapidly lowering the sodium concentration with free water, once this adaptation has occurred, causes water to flow into brain cells and causes them to swell. This can lead to cerebral edema, potentially resulting in seizures, permanent brain damage, or death. Therefore, significant hypernatremia should be treated carefully by a physician or other medical professional with experience in treatment of electrolyte imbalance, specific treatment like ACE inhibitors in heart failure and corticosteroids in nephropathy also can be used.[17]

## See also [edit]

- Hyponatremia

## References [edit]


1. ^ *a b* Muhsin, SA; Mount, DB (March 2016). "Diagnosis and treatment of hypernatremia.". *Best practice & research. Clinical endocrinology & metabolism*. **30** (2): 189–203. doi:10.1016/j.beem.2016.02.014. PMID 27156758.
2. ^ *a b c d e f g* Reynolds, RM; Padfield, PL; Seckl, JR (25 March 2006). "Disorders of sodium balance.". *BMJ (Clinical research ed.)*. **332** (7543): 702–5. doi:10.1136/bmj.332.7543.702. PMC 1410848. PMID 16565125.
3. ^ *a b c* Lin, M; Liu, SJ; Lim, IT (August 2005). "Disorders of water imbalance.". *Emergency medicine clinics of North America*. **23** (3): 749–70, ix. doi:10.1016/j.emc.2005.03.001. PMID 15982544.
4. ^ Kuruvilla, Jaya (2007). *Essentials of Critical Care Nursing*. Jaypee Brothers Publishers. p. 329. ISBN 9788180619205.
5. ^ Kliegman, Robert M.; Stanton, Bonita M. D.; Geme, Joseph St; Schor, Nina F. (2015). *Nelson Textbook of Pediatrics* (20 ed.). Elsevier Health Sciences. p. 348. ISBN 9780323263528.
6. ^ *a b c* Lewis, J. L. (March 2013). "Hypernatremia". *Merck Manual of Diagnosis and Therapy*. Medical Library Association. Retrieved 25 December 2015.
7. ^ Department of Health & Human Services, State Government of Victoria, Australia Better Health Channel: Salt Last updated: May 2014
8. ^ *a b* Reynolds, R.; Padfield, P. L.; Seckl, J. R. (2006). "Disorders of sodium balance". *BMJ*. **332** (7543): 702–705. doi:10.1136/bmj.332.7543.702. PMC 1410848. PMID 16565125.
9. ^ *a b c* Ofran, Y.; Lavi, D.; Opher, D.; Weiss, T. A.; Elinav, E. (2004). "Fatal voluntary salt intake resulting in the highest ever documented sodium plasma level in adults (255 mmol $L^{-1}$) a disorder linked to female gender and psychiatric disorders". *J. Intern. Med.* **256** (6): 525–528. doi:10.1111/j.1365-2796.2004.01411.x. PMID 15554954.
10. ^ Shier, D.; Butler, J.; Lewis, R. (2006). *Hole's Human Anatomy and Physiology* (11th ed.). McGraw-Hill Companies. ISBN 9780073256993.
11. ^ Coe, J. I. (1993). "Postmortem chemistry update. Emphasis on forensic application.". *Am. J. Forensic Med. Pathol.* **14** (2): 91–117. doi:10.1097/00000433-199306000-00001. PMID 8328447.
12. ^ Baselt, R. C. (2014). *Disposition of Toxic Drugs and Chemicals in Man* (10th ed.). Seal Beach, Ca.: Biomedical Publications. pp. 1855–1856. ISBN 9780962652394.
13. ^ Leroy, C.; Karrouz, W.; Douillard, C.; Do Cao, C.; Cortet, C.; Wémeau, J. L.; Vantyghem, M. C. (2013). "Diabetes insipidus.". *Ann. Endocrinol. (Paris)*. **74** (5-6): 496–507. doi:10.1016/j.ando.2013.10.002. PMID 24286605.
14. ^ Saunders, N.; Balfe, J. W.; Laski, B. (1976). "Severe salt poisoning in an infant.". *J. Pediatr.* **88** (2): 258–61. doi:10.1016/s0022-3476(76)80992-4. PMID 1249688.
15. ^ Paut, O.; André, N.; Fabre, P.; Sobraquès, P.; Drouet, G.; Arditti, J.; Camboulives, J. (1999). "The management of extreme hypernatraemia secondary to salt poisoning in an infant.". *Paediatr. Anaesth.* **9** (2): 171–174. doi:10.1046/j.1460-9592.1999.9220325.x. PMID 10189662.
16. ^ Carlberg, D. J.; Borek, H. A.; Syverud, S. A.; Holstege, C. P. (2013). "Survival of Acute Hypernatremia Due to Massive Soy Sauce Ingestion". *J. Emerg. Med.* **45** (2): 228–231. doi:10.1016/j.jemermed.2012.11.109.

PMID 23735849.
17. ^ Adrogué, H. J.; Madias, N. E. (2000). "Hypernatremia". *N. Engl. J. Med.* **342**: 1493–1499. doi:10.1056/NEJM200005183422006. PMID 10816188.

## External links [edit]

- Sodium at Lab Tests Online

| v · t · e · | **Water–electrolyte imbalance and acid–base imbalance (E86–E87, 276)** | |
|---|---|---|
| **Volume status** | Volume contraction (dehydration/hypovolemia) · Hypervolemia · | |
| **Electrolyte** | **Sodium** | High (**Hypernatremia** · Salt poisoning · · Low (Hypotonic · Isotonic · · |
| | **Potassium** | High · Low · |
| | **Chloride** | High · Low · |
| | **Calcium** | High · Low · |
| **Acid–base** | **Acidosis** | Metabolic: High anion gap (Ketoacidosis · Diabetic ketoacidosis · Lactic · · Normal anion gap (Hyperchloremic · Renal tubular · · Respiratory · |
| | **Alkalosis** | Metabolic (Contraction alkalosis · · Respiratory · |
| | **Both** | Mixed disorder of acid-base balance · |

Categories: Electrolyte disturbances | Sodium




# Hyperthyroidism





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*Not to be confused with Hyperthyroxinemia.*

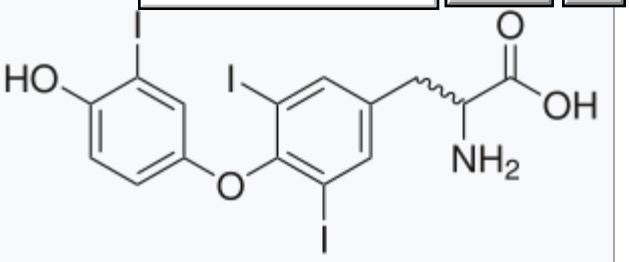
**Hyperthyroidism** is the condition that occurs due to excessive production of thyroid hormone by the thyroid gland.[1] **Thyrotoxicosis** is the condition that occurs due to excessive thyroid hormone of any cause and therefore includes hyperthyroidism.[1] Some, however, use the terms interchangeably.[2] Signs and symptoms vary between people and may include irritability, muscle weakness, sleeping problems, a fast heartbeat, heat intolerance, diarrhea, enlargement of the thyroid, and weight loss. Symptoms are typically less in the old and during pregnancy.[3] An uncommon complication is thyroid storm in which an event such as an infection results in worsening symptoms such as confusion and a high temperature and often results in death.[4] The opposite is hypothyroidism, when the thyroid gland does not make enough thyroid hormone.[5]

Graves' disease is the cause of about 50% to 80% of the cases of hyperthyroidism in the United States.[3][6] Other causes include multinodular goiter, toxic adenoma, inflammation of the thyroid, eating too much iodine, and too much synthetic thyroid hormone.[3][4] A less common cause is a pituitary adenoma. The diagnosis may be suspected based on signs and symptoms and then confirmed with blood tests. Typically blood tests show a low thyroid stimulating hormone (TSH) and raised $T_3$ or $T_4$. Radioiodine uptake by the thyroid, thyroid scan, and TSI antibodies may help determine the cause.[3]

Treatment depends partly on the cause and severity of disease. There are three main treatment options: radioiodine therapy, medications, and thyroid surgery. Radioiodine therapy involves taking iodine-131 by mouth which is then concentrated in and destroys the thyroid over weeks to months. The resulting hypothyroidism is treated with synthetic thyroid hormone. Medications such as beta blockers may control the symptoms and anti-thyroid medications such as methimazole may temporarily help people while other treatments are having effect. Surgery to remove the thyroid is another option. This may be used in those with very large thyroids or when cancer is a concern.[3] In the United States hyperthyroidism affects about 1.2% of the population.[1] It occurs between two and ten times more often in women.[3] Onset is commonly between 20 and 50 years of age.[4] Overall the disease is more common in those over the age of 60 years.[3]

**Hyperthyroidism**

**Synonyms** Overactive thyroid,




Triiodothyronine ($T_3$, pictured) and thyroxine ($T_4$) are both forms of thyroid hormone.

| Classification and external resources | |
|---|---|
| **Specialty** | Endocrinology |
| **ICD-10** | E05 |
| **ICD-9-CM** | 242.90 |
| **DiseasesDB** | 6348 |
| **MedlinePlus** | 000356 |
| **eMedicine** | med/1109 |
| **Patient UK** | Hyperthyroidism |
| **MeSH** | D006980 |

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Contents

## Signs and symptoms [edit]

Hyperthyroidism may be asymptomatic or present with significant symptoms.[4] Some of the symptoms of hyperthyroidism include nervousness, irritability, increased perspiration, heart racing, hand tremors, anxiety, difficulty sleeping, thinning of the skin, fine brittle hair, and muscular weakness—especially in the upper arms and thighs. More frequent bowel movements may occur, and diarrhea is common. Weight loss, sometimes significant, may occur despite a good appetite (though 10% of people with a hyperactive thyroid experience weight gain), vomiting may occur, and, for women, menstrual flow may lighten and menstrual periods may occur less often, or with longer cycles than usual.

Illustration depicting enlarged thyroid that may be associated with hyperthyroidism

Thyroid hormone is critical to normal function of cells. In excess, it both overstimulates metabolism and exacerbates the effect of the sympathetic nervous system, causing "speeding up" of various body systems and symptoms resembling an overdose of epinephrine (adrenaline). These include fast heart beat and symptoms of palpitations, nervous system tremor such as of the hands and anxiety symptoms, digestive system hypermotility, unintended weight loss, and (in "lipid panel" blood tests) a lower and sometimes unusually low serum cholesterol.

Major clinical signs include weight loss (often accompanied by an increased appetite), anxiety, heat intolerance, hair loss (especially of the outer third of the eyebrows), muscle aches, weakness, fatigue, hyperactivity, irritability, high blood sugar,[*citation needed*] excessive urination, excessive thirst, delirium, tremor, pretibial myxedema (in Graves' disease), emotional lability, and sweating. Panic attacks, inability to concentrate, and memory problems may also occur. Psychosis and paranoia, common during thyroid storm, are rare with milder hyperthyroidism. Many persons will experience complete remission of symptoms 1 to 2 months after a euthyroid state is obtained, with a marked reduction in anxiety, sense of exhaustion,

irritability, and depression. Some individuals may have an increased rate of anxiety or persistence of affective and cognitive symptoms for several months to up to 10 years after a euthyroid state is established.[7] In addition, those with hyperthyroidism may present with a variety of physical symptoms such as palpitations and abnormal heart rhythms (the notable ones being atrial fibrillation), shortness of breath (dyspnea), loss of libido, amenorrhea, nausea, vomiting, diarrhea, gynecomastia and feminization.[8] Long term untreated hyperthyroidism can lead to osteoporosis. These classical symptoms may not be present often in the elderly.[*citation needed*]

Neurological manifestations can include tremors, chorea, myopathy, and in some susceptible individuals (in particular of Asian descent) periodic paralysis. An association between thyroid disease and myasthenia gravis has been recognized. The thyroid disease, in this condition, is autoimmune in nature and approximately 5% of patients with myasthenia gravis also have hyperthyroidism. Myasthenia gravis rarely improves after thyroid treatment and the relationship between the two entities is not well understood.[*citation needed*]

In Graves' disease, ophthalmopathy may cause the eyes to look enlarged because the eye muscles swell and push the eye forward. Sometimes, one or both eyes may bulge. Some have swelling of the front of the neck from an enlarged thyroid gland (a goiter).[9]

Minor ocular (eye) signs, which may be present in any type of hyperthyroidism, are eyelid retraction ("stare"), extraocular muscle weakness, and lid-lag.[*citation needed*] In hyperthyroid *stare* (Dalrymple sign) the eyelids are retracted upward more than normal (the normal position is at the superior corneoscleral limbus, where the "white" of the eye begins at the upper border of the iris). Extraocular muscle weakness may present with double vision. In lid-lag (von Graefe's sign), when the patient tracks an object downward with their eyes, the eyelid fails to follow the downward moving iris, and the same type of upper globe exposure which is seen with lid retraction occurs, temporarily. These signs disappear with treatment of the hyperthyroidism.[*citation needed*]

Neither of these ocular signs should be confused with exophthalmos (protrusion of the eyeball), which occurs specifically and uniquely in hyperthyroidism caused by Graves' disease (note that not all exophthalmos is caused by Graves' disease, but when present with hyperthyroidism is diagnostic of Graves' disease). This forward protrusion of the eyes is due to immune-mediated inflammation in the retro-orbital (eye socket) fat. Exophthalmos, when present, may exacerbate hyperthyroid lid-lag and stare.[10]

### Thyroid storm [edit]

*Main article: Thyroid storm*

Thyroid storm is a severe form of thyrotoxicosis characterized by rapid and often irregular heart beat, high temperature, vomiting, diarrhea, and mental agitation. Symptoms may be unusual in the young, old, or pregnant.[4] It is a medical emergency and requires hospital care to control the symptoms rapidly. Even with treatment, death occurs in 20% to 50%.[4]

### Hypothyroidism [edit]

Hyperthyroidism due to certain types of thyroiditis can eventually lead to hypothyroidism (a *lack* of thyroid hormone), as the thyroid gland is damaged. Also, radioiodine treatment of Graves' disease often eventually leads to hypothyroidism. Such hypothyroidism may be treated by regular thyroid hormone testing and oral thyroid hormone supplementation.

## Causes [edit]

There are several causes of hyperthyroidism. Most often, the entire gland is overproducing thyroid hormone. Less commonly, a single nodule is responsible for the excess hormone secretion, called a "hot" nodule. Thyroiditis (inflammation of the thyroid) can also cause hyperthyroidism.[11] Functional thyroid tissue producing an excess of thyroid hormone occurs in a number of clinical conditions.

The major causes in humans are:

- Graves' disease. An autoimmune disease (usually, the most common etiology with 50-80% worldwide, although this varies substantially with location- i.e., 47% in Switzerland (Horst et al., 1987) to 90% in the USA (Hamburger et al. 1981)). Thought to be due to varying levels of iodine in the diet.[12]
- Toxic thyroid adenoma (the most common etiology in Switzerland, 53%, thought to be atypical due to a low level of dietary iodine in this country)[12]
- Toxic multinodular goiter

High blood levels of thyroid hormones (most accurately termed hyperthyroxinemia) can occur for a number of other reasons:

- Inflammation of the thyroid is called thyroiditis. There are several different kinds of thyroiditis including Hashimoto's thyroiditis (Hypothyroidism immune-mediated), and subacute thyroiditis (de Quervain's). These may be *initially* associated with secretion of excess thyroid hormone but usually progress to gland dysfunction and, thus, to hormone deficiency and hypothyroidism.
- Oral consumption of excess thyroid hormone tablets is possible (surreptitious use of thyroid hormone), as is the rare event of consumption of ground beef contaminated with thyroid tissue, and thus thyroid hormone (termed "hamburger hyperthyroidism").
- Amiodarone, an antiarrhythmic drug, is structurally similar to thyroxine and may cause either under- or overactivity of the thyroid.
- Postpartum thyroiditis (PPT) occurs in about 7% of women during the year after they give birth. PPT typically has several phases, the first of which is hyperthyroidism. This form of hyperthyroidism usually corrects itself within weeks or months without the need for treatment.
- A struma ovarii is a rare form of monodermal teratoma that contains mostly thyroid tissue, which leads to hyperthyroidism.
- Excess iodine consumption notably from algae such as kelp.

Thyrotoxicosis can also occur after taking too much thyroid hormone in the form of supplements, such as levothyroxine (a phenomenon known as exogenous thyrotoxicosis, alimentary thyrotoxicosis, or occult factitial thyrotoxicosis).[13]

Hypersecretion of thyroid stimulating hormone (TSH), which in turn is almost always caused by a pituitary adenoma, accounts for much less than 1 percent of hyperthyroidism cases.[14]

## Diagnosis [edit]

Measuring the level of thyroid-stimulating hormone (TSH), produced by the pituitary gland (which in turn is also regulated by the hypothalamus's TSH Releasing Hormone) in the blood is typically the initial test for suspected hyperthyroidism. A low TSH level typically indicates that the pituitary gland is being inhibited or "instructed" by the brain to cut back on stimulating the thyroid gland, having sensed increased levels of $T_4$ and/or $T_3$ in the blood. In rare circumstances, a low TSH indicates primary failure of the pituitary, or temporary inhibition of the pituitary due to another illness (euthyroid sick syndrome) and so checking the $T_4$ and $T_3$ is still clinically useful.

Measuring specific antibodies, such as anti-TSH-receptor antibodies in Graves' disease, or anti-thyroid peroxidase in Hashimoto's thyroiditis — a common cause of hypothyroidism — may also contribute to the diagnosis.

The diagnosis of hyperthyroidism is confirmed by blood tests that show a decreased thyroid-stimulating hormone (TSH) level and elevated $T_4$ and $T_3$ levels. TSH is a hormone made by the pituitary gland in the brain that tells the thyroid gland how much hormone to make. When there is too much thyroid hormone, the TSH will be low. A radioactive iodine uptake test and thyroid scan together characterizes or enables radiologists and doctors to determine the cause of hyperthyroidism. The uptake test uses radioactive iodine injected or taken orally on an empty stomach to measure the amount of iodine absorbed by the thyroid gland. Persons with hyperthyroidism absorb much more iodine than healthy persons which includes the radioactive iodine which is easy to measure. A thyroid scan producing images is typically conducted in connection with the uptake test to allow visual examination of the over-functioning gland.

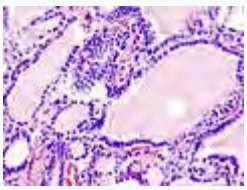
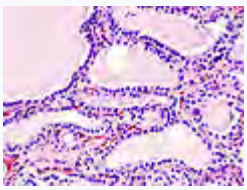
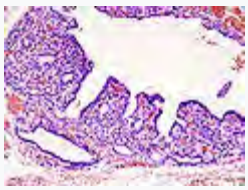
Thyroid scintigraphy is a useful test to characterize (distinguish between causes of) hyperthyroidism, and this entity from thyroiditis. This test procedure typically involves two tests performed in connection with each other: an iodine uptake test and a scan (imaging) with a gamma camera. The uptake test involves administering a dose of radioactive iodine (radioiodine), traditionally iodine-131 ($^{131}I$), and more recently iodine-123 ($^{123}I$). Iodine-123 may be the preferred radionuclide in some clinics due to its more favorable radiation dosimetry (i.e. less radiation dose to the patient per unit administered radioactivity) and a gamma photon energy more amenable to imaging with the gamma camera. For the imaging scan, I-123 is considered an almost ideal isotope of iodine for imaging thyroid tissue and thyroid cancer metastasis.[15]

Typical administration involves a pill or liquid containing sodium iodide (NaI) taken orally, which contains a small amount of iodine-131, amounting to perhaps less than a grain of salt. A 2-hour fast of no food prior to and for 1 hour after ingesting the pill is required. This low dose of radioiodine is typically tolerated by individuals otherwise allergic to iodine (such as those unable to tolerate contrast mediums containing larger doses of iodine such as used in CT scan, intravenous pyelogram (IVP), and similar imaging diagnostic procedures). Excess radioiodine that does not get absorbed into the thyroid gland is eliminated by the body in urine. Some patients may experience a slight allergic reaction to the diagnostic radioiodine and may be given an antihistamine.

The patient returns 24 hours later to have the level of radioiodine "uptake" (absorbed by the thyroid gland) measured by a device with a metal bar placed against the neck, which measures the radioactivity emitting from the thyroid. This test takes about 4 minutes while the uptake % is accumulated (calculated) by the machine software. A scan is also performed, wherein images (typically a center, left and right angle) are taken of the contrasted thyroid gland with a gamma camera; a radiologist will read and prepare a report indicating the uptake % and comments after examining the images. Hyperthyroid patients will typically "take up" higher than normal levels of radioiodine. Normal ranges for RAI uptake are from 10-30%.

In addition to testing the TSH levels, many doctors test for $T_3$, Free $T_3$, $T_4$, and/or Free $T_4$ for more detailed results. Typical adult limits for these hormones are: TSH (units): 0.45 - 4.50 uIU/mL; $T_4$ Free/Direct (nanograms): 0.82 - 1.77 ng/dl; and $T_3$ (nanograms): 71 - 180 ng/dl. Persons with hyperthyroidism can easily exhibit levels many times these upper limits for $T_4$ and/or $T_3$. See a complete table of normal range limits for thyroid function at the thyroid gland article.

In hyperthyroidism CK-MB (Creatine kinase) is usually elevated.[16]

## Subclinical [edit]

*See also: Symptoms and signs of Graves' disease § Subclinical hyperthyroidism*

In overt primary hyperthyroidism, TSH levels are low and $T_4$ and $T_3$ levels are high. Subclinical hyperthyroidism is a milder form of hyperthyroidism characterized by low or undetectable serum TSH level, but with a normal serum free thyroxine level.[17] Although the evidence for doing so is not definitive, treatment of elderly persons having subclinical hyperthyroidism could reduce the incidence of atrial fibrillation.[18] There is also an increased risk of bone fractures (by 42%) in people with subclinical hyperthyroidism; there is insufficient evidence to say whether treatment with antithyroid medications would reduce that risk.[19]

## Screening [edit]

In those without symptoms who are not pregnant there is little evidence for or against screening.[20]

# Treatment [edit]

## Antithyroid drugs [edit]

Thyrostatics (antithyroid drugs) are drugs that inhibit the production of thyroid hormones, such as carbimazole (used in the UK) and methimazole (used in the US), and propylthiouracil. Thyrostatics are believed to work by inhibiting the iodination of thyroglobulin by thyroperoxidase and, thus, the formation of tetraiodothyronine ($T_4$). Propylthiouracil also works outside the thyroid gland, preventing the conversion of (mostly inactive) $T_4$ to the active form $T_3$. Because thyroid tissue usually contains a substantial reserve of thyroid hormone, thyrostatics can take weeks to become effective and the dose often needs to be carefully titrated over a period of months, with regular doctor visits and blood tests to monitor results.

A very high dose is often needed early in treatment, but, if too high a dose is used persistently, patients can develop symptoms of hypothyroidism. This titrating of the dose is difficult to do accurately, and so sometimes a "block and replace" attitude is taken. In block and replace treatments thyrostatics are taken in sufficient quantities to completely block thyroid hormones, and the patient treated as though they have complete hypothyroidism.[21]

## Beta-blockers [edit]

Many of the common symptoms of hyperthyroidism such as palpitations, trembling, and anxiety are mediated by increases in beta-adrenergic receptors on cell surfaces. Beta blockers, typically used to treat high blood pressure, are a class of drugs that offset this effect, reducing rapid pulse associated with the sensation of palpitations, and decreasing tremor and anxiety. Thus, a patient suffering from hyperthyroidism can often obtain immediate temporary relief until the hyperthyroidism can be characterized with the Radioiodine test noted above and more permanent treatment take place. Note that these drugs do not treat hyperthyroidism or any of its long-term effects if left untreated, but, rather, they treat or reduce only symptoms of the condition. Some minimal effect on thyroid hormone production however also comes with Propranolol - which has two roles in the treatment of hyperthyroidism, determined by the different isomers of propranolol. L-propranolol causes beta-blockade, thus treating the symptoms associated with hyperthyroidism such as tremor, palpitations, anxiety, and heat intolerance. D-propranolol inhibits thyroxine deiodinase, thereby blocking the conversion of $T_4$ to $T_3$, providing some though minimal therapeutic effect.

Other beta-blockers are used to treat only the symptoms associated with hyperthyroidism.[22] Propranolol in the UK, and metoprolol in the US, are most frequently used to augment treatment for hyperthyroid patients.[23]

## Diet [edit]

People with autoimmune hyperthyroidism should not eat foods high in iodine, such as edible seaweed and kelps.[3]

From a public health perspective, the general introduction of iodized salt in the United States in 1924 resulted in lower disease, goiters, as well as improving the lives of children whose mothers would not have eaten enough iodine during pregnancy which would have lowered the IQs of their children.[24]

## Surgery [edit]

Surgery (thyroidectomy to remove the whole thyroid or a part of it) is not extensively used because most common forms of hyperthyroidism are quite effectively treated by the radioactive iodine method, and because there is a risk of also removing the parathyroid glands, and of cutting the recurrent laryngeal nerve, making swallowing difficult, and even simply generalized staphylococcal infection as with any major surgery. Some people with Graves' may opt for surgical intervention. This includes those that cannot tolerate medicines for one reason or another, people that are allergic to iodine, or people that refuse

radioiodine.

If people have toxic nodules treatments typically include either removal or injection of the nodule with alcohol.[25]

## Radioiodine [edit]

In iodine-131 (radioiodine) radioisotope therapy, which was first pioneered by Dr. Saul Hertz,[26] radioactive iodine-131 is given orally (either by pill or liquid) on a one-time basis, to severely restrict, or altogether destroy the function of a hyperactive thyroid gland. This isotope of radioactive iodine used for ablative treatment is more potent than diagnostic radioiodine (usually iodine-123 or a very low amount of iodine-131), which has a biological half-life from 8–13 hours. Iodine-131, which also emits beta particles that are far more damaging to tissues at short range, has a half-life of approximately 8 days. Patients not responding sufficiently to the first dose are sometimes given an additional radioiodine treatment, at a larger dose. Iodine-131 in this treatment is picked up by the active cells in the thyroid and destroys them, rendering the thyroid gland mostly or completely inactive.[27]

Since iodine is picked up more readily (though not exclusively) by thyroid cells, and (more important) is picked up even more readily by over-active thyroid cells, the destruction is local, and there are no widespread side effects with this therapy. Radioiodine ablation has been used for over 50 years, and the only major reasons for not using it are pregnancy and breastfeeding (breast tissue also picks up and concentrates iodine). Once the thyroid function is reduced, replacement hormone therapy taken orally each day may easily provide the required amount of thyroid hormone the body needs. There is extensive experience, over many years, of the use of radioiodine in the treatment of thyroid overactivity and this experience does not indicate any increased risk of thyroid cancer following treatment. However, a study from 2007 has reported an increased cancer incidence after radioiodine treatment for hyperthyroidism.[27]

The principal advantage of radioiodine treatment for hyperthyroidism is that it tends to have a much higher success rate than medications. Depending on the dose of radioiodine chosen, and the disease under treatment (Graves' vs. toxic goiter, vs. hot nodule etc.), the success rate in achieving definitive resolution of the hyperthyroidism may vary from 75-100%. A major expected side-effect of radioiodine in patients with Graves' disease is the development of lifelong hypothyroidism, requiring daily treatment with thyroid hormone. On occasion, some patients may require more than one radioactive treatment, depending on the type of disease present, the size of the thyroid, and the initial dose administered.[28]

Graves' disease patients manifesting moderate or severe Graves' ophthalmopathy are cautioned against radioactive iodine-131 treatment, since it has been shown to exacerbate existing thyroid eye disease. Patients with mild or no ophthalmic symptoms can mitigate their risk with a concurrent six-week course of prednisone. The mechanisms proposed for this side effect involve a TSH receptor common to both thyrocytes and retro-orbital tissue.[29]

As radioactive iodine treatment results in the destruction of thyroid tissue, there is often a transient period of several days to weeks when the symptoms of hyperthyroidism may actually worsen following radioactive iodine therapy. In general, this happens as a result of thyroid hormones being released into the blood following the radioactive iodine-mediated destruction of thyroid cells that contain thyroid hormone. In some patients, treatment with medications such as beta blockers (propranolol, atenolol, etc.) may be useful during this period of time.

Most patients do not experience any difficulty after the radioactive iodine treatment, usually given as a small pill. On occasion, neck tenderness or a sore throat may become apparent after a few days, if moderate inflammation in the thyroid develops and produces discomfort in the neck or throat area. This is usually transient, and not associated with a fever, etc.

Women breastfeeding should discontinue breastfeeding for at least a week, and likely longer, following radioactive iodine treatment, as small amounts of radioactive iodine may be found in breast milk even several weeks after the radioactive iodine treatment.

A common outcome following radioiodine is a swing from hyperthyroidism to the easily treatable hypothyroidism, which occurs in 78% of those treated for Graves' thyrotoxicosis and in 40% of those with toxic multinodular goiter or solitary toxic adenoma.[30] Use of higher doses of radioiodine reduces the

incidence of treatment failure, with penalty for higher response to treatment consisting mostly of higher rates of eventual hypothyroidism which requires hormone treatment for life.[31]

There is increased sensitivity to radioiodine therapy in thyroids appearing on ultrasound scans as more uniform (hypoechogenic), due to densely packed large cells, with 81% later becoming hypothyroid, compared to just 37% in those with more normal scan appearances (normoechogenic).[32]

### Thyroid storm [edit]

Thyroid storm presents with extreme symptoms of hyperthyroidism. It is treated aggressively with resuscitation measures along with a combination of the above modalities including: an intravenous beta blockers such as propranolol, followed by a thioamide such as methimazole, an iodinated radiocontrast agent or an iodine solution if the radiocontrast agent is not available, and an intravenous steroid such as hydrocortisone.[33]

## Epidemiology [edit]

In the United States hyperthyroidism affects about 1.2% of the population.[1] About half of these cases have obvious symptoms while the other half do not.[4] It occurs between two and ten times more often in women.[3] The disease is more common in those over the age of 60 years.[3]

Subclinical hyperthyroidism modestly increases the risk of cognitive impairment and dementia.[34]

## History [edit]

Caleb Hillier Parry first made the association between the goiter and protrusion of the eyes in 1786, however, did not publish his findings until 1825.[35] In 1835, Irish doctor Robert James Graves discovered a link between the protrusion of the eyes and goiter, giving his name to the autoimmune disease now known as Graves' Disease.

## Pregnancy [edit]

*See also: Thyroid disease in pregnancy*

Recognizing and evaluating hyperthyroidism in pregnancy is a diagnostic challenge. Thyroid hormones are naturally elevated during pregnancy and hyperthyroidism must also be distinguished from gestational transient thyrotoxicosis. Nonetheless, high maternal FT4 levels during pregnancy have been associated with impaired brain developmental outcomes of the offspring and this was independent of for example hCG levels.[36]

## Other animals [edit]

### Cats [edit]

Hyperthyroidism is one of the most common endocrine conditions affecting older domesticated housecats. Some veterinarians estimate that it occurs in up to 2% of cats over the age of 10.[37] The disease has become significantly more common since the first reports of feline hyperthyroidism in the 1970s. One cause of hyperthyroidism in cats is the presence of benign tumors, but the reason these cats develop such tumors continues to be studied. However, recent research published in Environmental Science & Technology, a publication of the American Chemical Society, suggests that many cases of feline hyperthyroidism are associated with exposure to environmental contaminants called polybrominated diphenyl ethers (PBDEs), which are present in flame retardants in many household products, in particular, furniture and some [*citation needed*]

electronics.

The study on which the report was based was conducted jointly by researchers at the EPA's National Health and Environmental Effects Laboratory and Indiana University.[*citation needed*] In the study, which involved 23 pet cats with feline hyperthyroidism, PDBE blood levels were three times as high as those in younger, non-hyperthyroid cats. In ideal circumstances, PBDE and related endocrine disruptors that seriously damage health would not be present in the blood of any animals, including humans.

Several studies indicate canned fish, liver and giblet prepared cat food may increase risk whereas fertilizers, herbicides, or plant pesticides had no effect.[38] Another study suggests cat litter could be a problem.[39]

Mutations of the thyroid-stimulating hormone receptor that cause a constitutive activation of the thyroid gland cells have been discovered recently. Many other factors may play a role in the pathogenesis of the disease such as goitrogens (isoflavones such as genistein, daidzein, and quercetin) as well as the iodine and selenium content of the cat's diet.

The most common presenting symptoms are: rapid weight loss, tachycardia (rapid heart rate), vomiting, diarrhea, increased consumption of fluids (polydipsia) and food, and increased urine production (polyuria). Other symptoms include hyperactivity, possible aggression, heart murmurs, a gallop rhythm, an unkempt appearance, and large, thick claws. About 70% of afflicted cats also have enlarged thyroid glands (goiter).

The same three treatments used with humans are also options in treating feline hyperthyroidism (surgery, radioiodine treatment, and anti-thyroid drugs). The drug that is used to help reduce the hyperthyroidism is methimazole. Where drug therapy is used it must be given to cats for the remainder of their lives but this may be the least expensive option, especially for very old cats. Anti-thyroid drugs for cats are available in both pill form and in a topical gel, that is applied using a finger cot to the hairless skin inside a cat's ear. Many cat owners find this gel a good option for cats that don't like being given pills. Radioiodine treatment and surgery often cure hyperthyroidism but some veterinarians prefer radioiodine treatment over surgery because it doesn't carry the risks associated with anesthesia. Radioiodine treatment, however, is not available in all areas for cats as this treatment requires nuclear radiological expertise and facilities as the cat's urine, sweat, saliva, and stool are radioactive for several days after the treatment requiring special inpatient handling and facilities usually for a total of 3 weeks (first week in total isolation and the next two weeks in close confinement).[40] In the United States, the guidelines for radiation levels vary from state to state; some states such as Massachusetts allow hospitalization for as little as two days before the animal is sent home with care instructions. Surgery tends to be done only when just one of the thyroid glands is affected (unilateral disease); however, following surgery, the remaining gland may become overactive. As in people, one of the most common complications of the surgery is hypothyroidism.

### Dogs [edit]

Hyperthyroidism is very rare in dogs, occurring in less than 1% or 2% of them. Instead, dogs tend to have the opposite problem: hypothyroidism, which can manifest itself in an unhealthy-appearing coat and fertility problems in females.[41][42] When hyperthyroidism does appear in dogs, it tends to be the result of medication to increase the amount of thyroid hormone during treatment for hypothyroidism. Symptoms usually disappear when the dose is adjusted.[42][43]

Occasionally dogs will have carcinoma of the thyroid. In about 90% of these cases the carcinoma is a very aggressive tumor that is invasive and easily metastasizes or spreads to other tissues, especially the lungs, making the prognosis very poor. While surgery is possible, it is often very difficult due to the fast spread of the tumor to the surrounding tissue including the arteries, the esophagus, and the windpipe. It may be possible to reduce the size of the tumor, thus relieving symptoms and allowing time for other treatments to work.[*citation needed*]

If a dog does have a benign tumor, which is the case in about 10% of the cases, treatment and prognosis are no different from those of the cat. The only real difference is that most dogs have no symptoms of the tumor.[*citation needed*]

## See also [edit]

- High-output cardiac failure
- Jod-Basedow phenomenon

## References [edit]


1. ^ a b c d Bahn Chair, RS; Burch, HB; Cooper, DS; Garber, JR; Greenlee, MC; Klein, I; Laurberg, P; McDougall, IR; Montori, VM; Rivkees, SA; Ross, DS; Sosa, JA; Stan, MN (June 2011). "Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists.". *Thyroid*. **21** (6): 593–646. doi:10.1089/thy.2010.0417. PMID 21510801.
2. ^ Erik D Schraga (May 30, 2014). "Hyperthyroidism, Thyroid Storm, and Graves Disease". Retrieved 20 April 2015.
3. ^ a b c d e f g h i j "Hyperthyroidism". *www.niddk.nih.gov*. July 2012. Retrieved 2015-04-02.
4. ^ a b c d e f g Devereaux, D.; Tewelde, SZ. (May 2014). "Hyperthyroidism and thyrotoxicosis.". *Emerg Med Clin North Am*. **32** (2): 277–92. doi:10.1016/j.emc.2013.12.001. PMID 24766932.
5. ^ NIDDK (March 13, 2013). "Hypothyroidism". Retrieved 20 April 2015.
6. ^ Brent, Gregory A. (Jun 12, 2008). "Clinical practice. Graves' disease". *The New England Journal of Medicine*. **358** (24): 2594–2605. doi:10.1056/NEJMcp0801880. ISSN 1533-4406. PMID 18550875.
7. ^ "Depression and Psychosis in Neurological Practice.". *Bradley's neurology in clinical practice.* (6th ed.). Philadelphia, PA: Elsevier/Saunders. 2012. pp. 102–103. ISBN 1437704344.
8. ^ Chan WB, Yeung VT, Chow CC, So WY, Cockram CS (1999). "Gynaecomastia as a presenting feature of thyrotoxicosis". *Postgrad Med J*. **882** (75): 229–31. PMC 1741202. PMID 10715765.
9. ^ http://next.thyroid.org/patients/patient_brochures/hyperthyroidism.html
10. ^ Faculty of Medicine & Dentistry (2006). "Course-Based Physical Examination - Endocrinology -- Endocrinology Objectives (Thyroid Exam)". *Undergraduate Medical Education*. University of Alberta. Retrieved 28 January 2007.
11. ^ http://www.endocrineweb.com/hyper2.html
12. ^ a b Andersson, Maria; Zimmermann, Michael B. (2010). "Influence of Iodine Deficiency and Excess on Thyroid Function Tests". *Endocrine Updates*. **28**: 45–69. doi:10.1007/978-1-4419-1485-9_3. ISSN 1566-0729.
13. ^ "Floyd, J.L. (2009) Thyrotoxicosis. eMedicine".
14. ^ Thyrotropin (TSH)-secreting pituitary adenomas. By Roy E Weiss and Samuel Refetoff. Last literature review version 19.1: January 2011. This topic last
22. ^ Eber O, Buchinger W, Lindner W, et al. (1990). "The effect of D-versus L-propranolol in the treatment of hyperthyroidism". *Clin Endocrinol*. **32**: 363–72. doi:10.1111/j.1365-2265.1990.tb00877.x.
23. ^ Geffner DL, Hershman JM (July 1992). "β-Adrenergic blockade for the treatment of hyperthyroidism". *The American Journal of Medicine*. **93** (1): 61–8. doi:10.1016/0002-9343(92)90681-Z. PMID 1352658.
24. ^ Max Nisen (July 22, 2013). "How Adding Iodine To Salt Resulted In A Decade's Worth Of IQ Gains For The United States". *Business Insider*. Retrieved July 23, 2013.
25. ^ al.], senior editors, J. Larry Jameson, Leslie J. De Groot ; section editors, David de Kretser ... [et (2010). *Endocrinology : adult and pediatric* (6th ed.). Philadelphia: Saunders/Elsevier. p. Chapter 82. ISBN 9781416055839.
26. ^ Hertz, Barbara, Schuleller, Kristin, Saul Hertz, MD (1905 - 1950) A Pioneer in the Use of Radioactive Iodine, *Endocrine Practice* 2010 16,4;713-715.
27. ^ a b Metso, S; Auvinen, A; Huhtala, H; Salmi, J; Oksala, H; Jaatinen, P (2007). "Increased cancer incidence after radioiodine treatment for hyperthyroidism". *Cancer*. **109** (10): 1972–9. doi:10.1002/cncr.22635. PMID 17393376.
28. ^ http://www.mythyroid.com/iodinehyper.html
29. ^ Walsh JP, Dayan CM, Potts MJ (1999). "Radioiodine and thyroid eye disease". *BMJ*. **319**: 68–9. doi:10.1136/bmj.319.7202.68. PMC 1116221. PMID 10398607.
30. ^ Berglund J, Christensen SB, Dymling JF, Hallengren B (May 1991). "The incidence of recurrence and hypothyroidism following treatment with antithyroid drugs, surgery or radioiodine in all patients with thyrotoxicosis in Malmö during the period 1970-1974". *Journal of Internal Medicine*. **229** (5): 435–42. doi:10.1111/j.1365-2796.1991.tb00371.x. PMID 1710255.
31. ^ Esfahani AF; Kakhki VR; Fallahi B; et al. (2005). "Comparative evaluation of two fixed doses of 185 and 370 MBq 131I, for the treatment of Graves' disease resistant to antithyroid drugs". *Hellenic Journal of Nuclear Medicine*. **8** (3): 158–61. PMID 16390021.
32. ^ Markovic V, Eterovic D (September 2007). "Thyroid echogenicity predicts outcome of radioiodine therapy in patients with Graves' disease". *The Journal of Clinical Endocrinology and Metabolism*. **92** (9): 3547–52. doi:10.1210/jc.2007-0879. PMID 17609305.
33. ^ Tintinalli, Judith (2004). *Emergency Medicine: A Comprehensive Study Guide, Sixth edition*. McGraw-

updated: 2 July 2009
15. ^ http://jnm.snmjournals.org/cgi/content/full/43/1/77
16. ^ Differential diagnosis by laboratory medicine: a quick reference for physicians; Vincent Marks,Dušan Meško, page 156
17. ^ Biondi B1, Cooper DS (2008). "The clinical significance of subclinical thyroid dysfunction". *Endocrine Reviews*. **29** (1): 76–131. doi:10.1210/er.2006-0043. PMID 17991805.
18. ^ Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ (2004). "Subclinical thyroid disease: scientific review and guidelines for diagnosis and management". *JAMA*. **291** (2): 228–238. doi:10.1001/jama.291.2.228. PMID 14722150.
19. ^ Blum, Manuel R.; Bauer, Douglas C.; Collet, Tinh-Hai; Fink, Howard A.; Cappola, Anne R.; da Costa, Bruno R.; Wirth, Christina D.; Peeters, Robin P.; Åsvold, Bjørn O.; den Elzen, Wendy P. J.; Luben, Robert N.; Imaizumi, Misa; Bremner, Alexandra P.; Gogakos, Apostolos; Eastell, Richard; Kearney, Patricia M.; Strotmeyer, Elsa S.; Wallace, Erin R.; Hoff, Mari; Ceresini, Graziano; Rivadeneira, Fernando; Uitterlinden, André G.; Stott, David J.; Westendorp, Rudi G. J.; Khaw, Kay-Tee; Langhammer, Arnuf; Ferrucci, Luigi; Gussekloo, Jacobijn; Williams, Graham R.; Walsh, John P.; Jüni, Peter; Aujesky, Drahomir; Rodondi, Nicolas (26 May 2015). "Subclinical Thyroid Dysfunction and Fracture Risk". *JAMA*. **313** (20): 2055–65. doi:10.1001/jama.2015.5161. PMID 26010634.
20. ^ LeFevre, ML; U.S. Preventive Services Task, Force (5 May 2015). "Screening for thyroid dysfunction: U.S. Preventive Services Task Force recommendation statement.". *Annals of Internal Medicine*. **162** (9): 641–50. doi:10.7326/m15-0483. PMID 25798805.
21. ^ Fumarola, A; Di Fiore, A; Dainelli, M; Grani, G; Calvanese, A (Nov 2010). "Medical treatment of hyperthyroidism: state of the art.". *Experimental and Clinical Endocrinology & Diabetes*. **118** (10): 678–84. doi:10.1055/s-0030-1253420. PMID 20496313.
Hill Professional. p. 1312. ISBN 0-07-138875-3.
34. ^ Rieben, Carole; Segna, Daniel; da Costa, Bruno R.; Collet, Tinh-Hai; Chaker, Layal; Aubert, Carole E.; Baumgartner, Christine; Almeida, Osvaldo P.; Hogervorst, Eef; Trompet, Stella; Masaki, Kamal; Mooijaart, Simon P.; Gussekloo, Jacobijn; Peeters, Robin P.; Bauer, Douglas C.; Aujesky, Drahomir; Rodondi, Nicolas (30 September 2016). "Subclinical Thyroid Dysfunction and the Risk of Cognitive Decline: a Meta-Analysis of Prospective Cohort Studies". *The Journal of Clinical Endocrinology & Metabolism*: jc.2016–2129. doi:10.1210/jc.2016-2129. PMID 27689250.
35. ^ *An Appraisal of Endocrinology: A Report Made to the Directors of the John and Mary R. Markle Foundation by a Special Committee of the National Research Council Consisting of Walter B. Cannon, Chairman, Earl Engle, Curt Richter, Oscar Riddle, R.G. Hoskins ... with the Assistance of Milton O. Lee*. National Academies. 1936. p. 9.
36. ^ http://www.thelancet.com/journals/landia/article/PIIS2213-8587(15)00327-7/abstract
37. ^ Shomon, Mary (2004). "Feline Hyperthyroidism: Frequently Asked Questions, Information About Overactive Thyroid Conditions in Cats". Retrieved 24 June 2009.[*self-published source?*]
38. ^ Esfahani AF; Martin KM1; Rossing MA; DiGiacomo RF; Freitag WA (2000). "Evaluation of dietary and environmental risk factors for hyperthyroidism in cats". *J Am Vet Med Assoc*. **217** (6): 853–6. PMID 10997155.
39. ^ Kass PH1; Peterson ME; Levy J; James K; Freitag WA; Becker DV; Cowgill LD (1999). "Evaluation of environmental, nutritional, and host factors in cats with hyperthyroidism.". *J Vet Intern Med*. **13** (4): 323–9. PMID 10449223.
40. ^ Little, Susan (2006). "Feline Hyperthyroidism" (PDF). Winn Feline Foundation. Retrieved 24 June 2009.
41. ^ "Hyperthyroidism". Merck Veterinary Manual. Retrieved 27 July 2011.
42. ^ *a b* "Hypothyroidism". Merck Veterinary Manual. Retrieved 27 July 2011.
43. ^ "Leventa-Precautions/Adverse Reactions". Intervet. Retrieved 27 July 2011.

## Further reading [edit]

- Brent, Gregory A. (Ed.), *Thyroid Function Testing*, New York : Springer, Series: Endocrine Updates, Vol. 28, 1st Edition., 2010. ISBN 978-1-4419-1484-2
- Siraj, Elias S. (June 2008). "Update on the Diagnosis and Treatment of Hyperthyroidism" (PDF). *Journal of Clinical Outcomes Management*. **15** (6): 298–307. Retrieved 24 June 2009.

## External links [edit]

- Patient information: Hyperthyroidism Article at UpToDate

- Merck Manual article about hyperthyroidism
- Gina Spadafori (20 January 1997). "Hyperthyroidism: A Common Ailment in Older Cats". *The Pet Connection*. Veterinary Information Network. Retrieved 28 January 2007.
- What is Hyperthyroidism, Causes, Symptoms, Diagnosis, Treatment, Prevention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| **Hypothalamic/ pituitary axes** | **Hypothalamus** | *gonadotropin* (Kallmann syndrome · Adiposogenital dystrophy · · *CRH* (Tertiary adrenal insufficiency) · *vasopressin* (Neurogenic diabetes insipidus) · *general* (Hypothalamic hamartoma) · | |
| | **Pituitary** | **Hyperpituitarism** | *anterior* (Acromegaly · Hyperprolactinaemia · Pituitary ACTH hypersecretion · · *posterior* (SIADH) · *general* (Nelson's syndrome) · |
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| | **Thyroid** | **Hypothyroidism** | Iodine deficiency · Cretinism (Congenital hypothyroidism · · Myxedema · Euthyroid sick syndrome · |
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| **Multiple** | | | Autoimmune polyendocrine syndrome multiple (APS1 · APS2 · · Carcinoid syndrome · Multiple endocrine neoplasia (1 · 2A · 2B · · Progeria (Werner syndrome · Acrogeria · Metageria · · Woodhouse-Sakati syndrome · |

Categories: Thyroid disease | Endocrine-related cutaneous conditions | Dog diseases | Thyroid | Cat diseases

# Hypoglycemia

From Wikipedia, the free encyclopedia

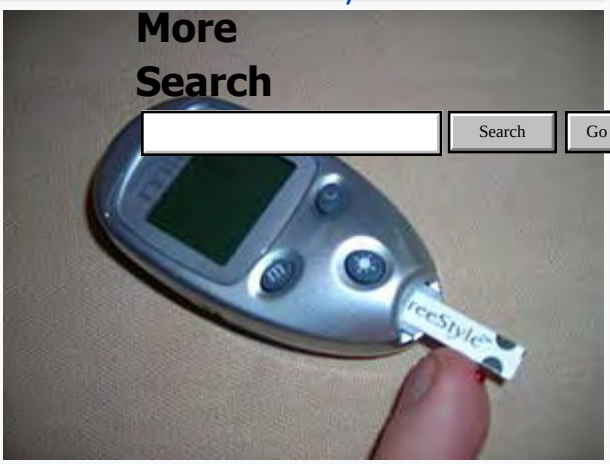
**Hypoglycemia**, also known as **low blood sugar**, is when blood sugar decreases to below normal levels. This may result in a variety of symptoms including clumsiness, trouble talking, confusion, loss of consciousness, seizures, or death. A feeling of hunger, sweating, shakiness, and weakness may also be present. Symptoms typically come on quickly.[1]

The most common cause of hypoglycemia is medications used to treat diabetes mellitus such as insulin and sulfonylureas.[2][3] Risk is greater in diabetics who have eaten less than usual, exercised more than usual, or have drunk alcohol.[1] Other causes of hypoglycemia include kidney failure, certain tumors, such as insulinoma, liver disease, hypothyroidism, starvation, inborn error of metabolism, severe infections, reactive hypoglycemia, and a number of drugs including alcohol.[1][3] Low blood sugar may occur in otherwise healthy babies who have not eaten for a few hours.[4]

The glucose level that defines hypoglycemia is variable. In people with diabetes levels below 3.9 mmol/L (70 mg/dL) is diagnostic.[1] In adults without diabetes, symptoms related to low blood sugar, low blood sugar at the time of symptoms, and improvement when blood sugar is restored to normal confirm the diagnosis.[5] Otherwise a level below 2.8 mmol/L (50 mg/dL) after not eating or following exercise may be used.[5] In newborns a level below 2.2 mmol/L (40 mg/dL) or less than 3.3 mmol/L (60 mg/dL) if symptoms are present indicates hypoglycemia.[4] Other tests that may be useful in determining the cause include insulin and C peptide levels in the blood.[3] Hyperglycemia (high blood sugar) is the opposite condition.

Among people with diabetes, prevention is by matching the foods eaten, with the amount of exercise, and the medications used. When people feel their blood sugar is low, testing with a glucose monitor is recommended. Some people have few initial symptoms of low blood sugar and frequent routine testing in this group is recommended. Treatment of hypoglycemia is by eating foods high in simple sugars or taking dextrose. If a person is not able to take food by mouth, an injection of glucagon may help. The treatment of hypoglycemia unrelated to diabetes include treating the underlying problem as well and a healthy diet.[1] The term "hypoglycemia" is sometimes incorrectly used to refer to idiopathic postprandial syndrome, a controversial condition with similar symptoms that occur following eating but with normal blood sugar levels.[6][7]

**Hypoglycemia**



Glucose meter

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Endocrinology |
| **ICD-10** | E16.0-E16.2 |
| **ICD-9-CM** | 250.8, 251.0, 251.1, 251.2, 270.3, 775.6, 962.3 |
| **DiseasesDB** | 6431 |
| **MedlinePlus** | 000386 |
| **eMedicine** | emerg/272 med/1123 med/1939 ped/1117 |
| **Patient UK** | Hypoglycemia |
| **MeSH** | D007003 |

[edit on Wikidata]

Contents

## Signs and symptoms [edit]

Hypoglycemic symptoms and manifestations can be divided into those produced by the counterregulatory hormones (epinephrine/adrenaline and glucagon) triggered by the falling glucose, and the neuroglycopenic effects produced by the reduced brain sugar.

- Shakiness, anxiety, nervousness
- Palpitations, tachycardia
- Sweating, feeling of warmth (sympathetic muscarinic rather than adrenergic)
- Pallor, coldness, clamminess
- Dilated pupils (mydriasis)
- Hunger, borborygmus
- Nausea, vomiting, abdominal discomfort
- Headache

Paramedics in Southern California attend a diabetic man who lost effective control of his vehicle due to low blood sugar and drove it over the curb.

### Central nervous system [edit]

- Abnormal thinking, impaired judgment
- Nonspecific dysphoria, moodiness, depression, crying, exaggerated concerns
- Feeling of numbness, pins and needles (paresthesia)
- Negativism, irritability, belligerence, combativeness, rage
- Personality change, emotional lability
- Fatigue, weakness, apathy, lethargy, daydreaming, sleep
- Confusion, memory loss, lightheadedness or dizziness, delirium
- Staring, glassy look, blurred vision, double vision
- Flashes of light in the field of vision
- Automatic behavior, also known as automatism
- Difficulty speaking, slurred speech
- Ataxia, incoordination, sometimes mistaken for drunkenness
- Focal or general motor deficit, paralysis, hemiparesis
- Headache
- Stupor, coma, abnormal breathing

Generalized or focal seizures

Not all of the above manifestations occur in every case of hypoglycemia. There is no consistent order to the appearance of the symptoms, if symptoms even occur. Specific manifestations may also vary by age, by severity of the hypoglycemia and the speed of the decline. In young children, vomiting can sometimes accompany morning hypoglycemia with ketosis. In older children and adults, moderately severe hypoglycemia can resemble mania, mental illness, drug intoxication, or drunkenness. In the elderly, hypoglycemia can produce focal stroke-like effects or a hard-to-define malaise. The symptoms of a single person may be similar from episode to episode, but are not necessarily so and may be influenced by the speed at which glucose levels are dropping, as well as previous incidents.

In newborns, hypoglycemia can produce irritability, jitters, myoclonic jerks, cyanosis, respiratory distress, apneic episodes, sweating, hypothermia, somnolence, hypotonia, refusal to feed, and seizures or "spells." Hypoglycemia can resemble asphyxia, hypocalcemia, sepsis, or heart failure.

In both young and old patients, the brain may habituate to low glucose levels, with a reduction of noticeable symptoms despite neuroglycopenic impairment. In insulin-dependent diabetic patients this phenomenon is termed *hypoglycemia unawareness* and is a significant clinical problem when improved glycemic control is attempted. Another aspect of this phenomenon occurs in type I glycogenosis, when chronic hypoglycemia before diagnosis may be better tolerated than acute hypoglycemia after treatment is underway.

Hypoglycemic symptoms can also occur when one is sleeping. Examples of symptoms during sleep can include damp bed sheets or clothes from perspiration. Having nightmares or the act of crying out can be a sign of hypoglycemia. Once the individual is awake they may feel tired, irritable, or confused and these may be signs of hypoglycemia as well.[8]

In nearly all cases, hypoglycemia that is severe enough to cause seizures or unconsciousness can be reversed without obvious harm to the brain. Cases of death or permanent neurological damage occurring with a single episode have usually involved prolonged, untreated unconsciousness, interference with breathing, severe concurrent disease, or some other type of vulnerability. Nevertheless, brain damage or death has occasionally resulted from severe hypoglycemia.

Research in healthy adults shows that mental efficiency declines slightly but measurably as blood glucose falls below 3.6 mM (65 mg/dL). Hormonal defense mechanisms (adrenaline and glucagon) are normally activated as it drops below a threshold level (about 55 mg/dL (3.0 mM) for most people), producing the typical hypoglycemic symptoms of shakiness and dysphoria.[9]:1589 Obvious impairment may not occur until the glucose falls below 40 mg/dL (2.2 mM), and many healthy people may occasionally have glucose levels below 65 in the morning without apparent effects. Since the brain effects of hypoglycemia, termed neuroglycopenia, determine whether a given low glucose is a "problem" for that person, most doctors use the term *hypoglycemia* only when a moderately low glucose level is accompanied by symptoms or brain effects.

Determining the presence of both parts of this definition is not always straightforward, as hypoglycemic symptoms and effects are vague and can be produced by other conditions; people with recurrently low glucose levels can lose their threshold symptoms so that severe neuroglycopenic impairment can occur without much warning, and many measurement methods (especially glucose meters) are imprecise at low levels.

It may take longer to recover from severe hypoglycemia with unconsciousness or seizure even after restoration of normal blood glucose. When a person has not been unconscious, failure of carbohydrate to reverse the symptoms in 10–15 minutes increases the likelihood that hypoglycemia was not the cause of the symptoms. When severe hypoglycemia has persisted in a hospitalized person, the amount of glucose required to maintain satisfactory blood glucose levels becomes an important clue to the underlying etiology. Glucose requirements above 10 mg/kg/minute in infants, or 6 mg/kg/minute in children and adults are strong evidence for hyperinsulinism. In this context this is referred to as the *glucose infusion rate* (GIR). Finally, the blood glucose response to glucagon given when the glucose is low can also help distinguish among various types of hypoglycemia. A rise of blood glucose by more than 30 mg/dl (1.70 mmol/l) suggests insulin excess as the probable cause of the hypoglycemia.

### Long-term effects [edit]

Significant hypoglycemia appears to increase the risk of cardiovascular disease.[10]

## Causes [edit]

*See also: List of causes of hypoglycemia*

The most common cause of hypoglycemia is medications used to treat diabetes mellitus such as insulin, sulfonylureas, and biguanides.[2][3] Risk is greater in diabetics who have eaten less than usual, exercised more than usual, or drunk alcohol.[1] Other causes of hypoglycemia include kidney failure, certain tumors, liver disease, hypothyroidism, starvation, inborn errors of metabolism, severe infections, reactive hypoglycemia, and a number of drugs including alcohol.[1][3] Low blood sugar may occur in babies who are otherwise healthy who have not eaten for a few hours.[4] Inborn errors of metabolism may include the lack of an enzyme to make glycogen (glycogen storage type 0).

### Serious illness [edit]

Serious illness may result in low blood sugar.[1] Severe disease of nearly all major organ systems can cause hypoglycemia as a secondary problem. Hospitalized persons, especially in intensive care units or those prevented from eating, can develop hypoglycemia from a variety of circumstances related to the care of their primary disease. Hypoglycemia in these circumstances is often multifactorial or caused by the healthcare. Once identified, these types of hypoglycemia are readily reversed and prevented, and the underlying disease becomes the primary problem.

### Hormone deficiency [edit]

Not enough cortisol, such as in Addison's disease, not enough glucagon, or not enough epinephrine can result in low blood sugar.[1] This is a more common cause in children.[1]

## Pathophysiology [edit]

Like most animal tissues, brain metabolism depends primarily on glucose for fuel in most circumstances. A limited amount of glucose can be derived from glycogen stored in astrocytes, but it is consumed within minutes. For most practical purposes, the brain is dependent on a continual supply of glucose diffusing from the blood into the interstitial tissue within the central nervous system and into the neurons themselves.

Therefore, if the amount of glucose supplied by the blood falls, the brain is one of the first organs affected. In most people, subtle reduction of mental efficiency can be observed when the glucose falls below 65 mg/dl (3.6 mM). Impairment of action and judgment usually becomes obvious below 40 mg/dl (2.2 mM). Seizures may occur as the glucose falls further. As blood glucose levels fall below 10 mg/dl (0.55 mM), most neurons become electrically silent and nonfunctional, resulting in coma. These brain effects are collectively referred to as neuroglycopenia.

The importance of an adequate supply of glucose to the brain is apparent from the number of nervous, hormonal and metabolic responses to a falling glucose level. Most of these are defensive or adaptive, tending to raise the blood sugar via glycogenolysis and gluconeogenesis or provide alternative fuels. If the blood sugar level falls too low, the liver converts a storage of glycogen into glucose and releases it into the bloodstream, to prevent the person going into a diabetic coma, for a short period of time.

Brief or mild hypoglycemia produces no lasting effects on the brain, though it can temporarily alter brain responses to additional hypoglycemia. Prolonged, severe hypoglycemia can produce lasting damage of a wide range. This can include impairment of cognitive function, motor control, or even consciousness. The likelihood of permanent brain damage from any given instance of severe hypoglycemia is difficult to estimate, and depends on a multitude of factors such as age, recent blood and brain glucose experience, concurrent problems such as hypoxia, and availability of alternative fuels. It has been frequently found that

those Type 1 diabetics found "dead in bed" in the morning after suspected severe hypoglycemia had some underlying coronary pathology that led to an induced fatal heart attack. Recently, several of these individuals found "dead in bed" were wearing Continuous Glucose Monitors, which provided a history of glucose levels prior to the fatal event. It has been found in several cases, that the fatal event was preceded by at least two hours of blood glucose levels under 40 mg/dl, possibly lower as the continuous glucose monitors are not accurate at levels below 40 mg/dl. The individuals failed to respond to the audible alarms produced by the continuous glucose monitor which may have been "alarming" for many hours prior to the fatal event. The vast majority of symptomatic hypoglycemic episodes result in no detectable permanent harm.[11]

## Diagnosis [edit]

The glucose level that defines hypoglycemia is variable. In diabetics a levels below 3.9 mmol/L (70 mg/dL) is diagnostic.[1] In adults without diabetes, symptoms related to low blood sugar, low blood sugar at the time of symptoms, and improvement when blood sugar is restored to normal confirm the diagnosis.[5] This is known as the Whipple's triad.[5] Otherwise a level below 2.8 mmol/L (50 mg/dL) after not eating or following exercise may be used.[1] In newborns a level below 2.2 mmol/L (40 mg/dL) or less than 3.3 mmol/L (60 mg/dL) if symptoms are present indicates hypoglycemia.[4] Other tests that may be useful in determining the cause include insulin and C peptide levels in the blood.[3] Hyperglycemia, a high blood sugar, is the opposite condition.

Throughout a 24 hour period blood plasma glucose levels are generally maintained between 4-8 mmol/L (72 and 144 mg/dL).[12]:11 Although 3.3 or 3.9 mmol/L (60 or 70 mg/dL) is commonly cited as the lower limit of normal glucose, symptoms of hypoglycemia usually do not occur until 2.8 to 3.0 mmol/L (50 to 54 mg/dL).[13]

In cases of recurrent hypoglycemia with severe symptoms, the best method of excluding dangerous conditions is often a *diagnostic fast*. This is usually conducted in the hospital, and the duration depends on the age of the patient and response to the fast. A healthy adult can usually maintain a glucose level above 50 mg/dl (2.8 mM) for 72 hours, a child for 36 hours, and an infant for 24 hours. The purpose of the fast is to determine whether the person can maintain his or her blood glucose as long as normal, and can respond to fasting with the appropriate metabolic changes. At the end of the fast the insulin should be nearly undetectable and ketosis should be fully established. The patient's blood glucose levels are monitored and a critical specimen is obtained if the glucose falls. Despite its unpleasantness and expense, a diagnostic fast may be the only effective way to confirm or refute a number of serious forms of hypoglycemia, especially those involving excessive insulin.

The precise level of glucose considered low enough to define hypoglycemia is dependent on (1) the measurement method, (2) the age of the person, (3) presence or absence of effects, and (4) the purpose of the definition. While there is no disagreement as to the normal range of blood sugar, debate continues as to what degree of hypoglycemia warrants medical evaluation or treatment, or can cause harm.[14][15][16]

Deciding whether a blood glucose in the borderline range of 45–75 mg/dL (2.5-4.2 mM) represents clinically problematic hypoglycemia is not always simple. This leads people to use different "cutoff levels" of glucose in different contexts and for different purposes. Because of all the variations, the Endocrine Society recommends that a diagnosis of hypoglycemia as a problem for an individual be based on the combination of a low glucose level and evidence of adverse effects.[5]

Glucose concentrations are expressed as milligrams per deciliter (mg/dL or mg/100 mL) in Lebanon, the United States, Japan, Portugal, Spain, France, Belgium, Egypt, Saudi Arabia, Colombia, India and Israel, while millimoles per liter (mmol/L or mM) are the units used in most of the rest of the world. Glucose concentrations expressed as mg/dL can be converted to mmol/L by dividing by 18.0 g/dmol (the molar mass of glucose). For example, a glucose concentration of 90 mg/dL is 5.0 mmol/L or 5.0 mM.

The circumstances of hypoglycemia provide most of the clues to diagnosis. Circumstances include the age of the person, time of day, time since last meal, previous episodes, nutritional status, physical and mental development, drugs or toxins (especially insulin or other diabetes drugs), diseases of other organ systems,

family history, and response to treatment. When hypoglycemia occurs repeatedly, a record or "diary" of the spells over several months, noting the circumstances of each spell (time of day, relation to last meal, nature of last meal, response to carbohydrate, and so forth) may be useful in recognizing the nature and cause of the hypoglycemia.

## Method of measurement [edit]

Blood glucose levels discussed in this article are venous plasma or serum levels measured by standard, automated glucose oxidase methods used in medical laboratories. For clinical purposes, plasma and serum levels are similar enough to be interchangeable. Arterial plasma or serum levels are slightly higher than venous levels, and capillary levels are typically in between.[17] This difference between arterial and venous levels is small in the fasting state but is amplified and can be greater than 10% in the postprandial state.[18] On the other hand, whole blood glucose levels (e.g., by fingerprick meters) are about 10%-15% lower than venous plasma levels.[17] Furthermore, available fingerstick glucose meters are only warranted to be accurate to within 15% of a simultaneous laboratory value under optimal conditions,[*citation needed*] and home use in the investigation of hypoglycemia is fraught with misleading low numbers.[19][20] In other words, a meter glucose reading of 39 mg/dL could be properly obtained from a person whose laboratory serum glucose was 53 mg/dL; even wider variations can occur with "real world" home use.

Two other factors significantly affect glucose measurement: hematocrit and delay after blood drawing. The disparity between venous and whole blood concentrations is greater when the hematocrit is high, as in newborn infants, or adults with polycythemia.[18] High neonatal hematocrits are particularly likely to confound glucose measurement by meter. Second, unless the specimen is drawn into a fluoride tube or processed immediately to separate the serum or plasma from the cells, the measurable glucose will be gradually lowered by *in vitro* metabolism of the glucose at a rate of approximately 7 mg/dL/h, or even more in the presence of leukocytosis.[18][21][22] The delay that occurs when blood is drawn at a satellite site and transported to a central laboratory hours later for routine processing is a common cause of mildly low glucose levels in general chemistry panels.

## Age [edit]

Children's blood sugar levels are often slightly lower than adults'. Overnight fasting glucose levels are below 70 mg/dL (3.9 mM) in 5% of healthy adults, but up to 5% of children can be below 60 mg/dL (3.3 mM) in the morning fasting state.[23] As the duration of fasting is extended, a higher percentage of infants and children will have mildly low plasma glucose levels, usually without symptoms. The normal range of newborn blood sugars continues to be debated.[14][15][16] It has been proposed that newborn brains are able to use alternate fuels when glucose levels are low more readily than adults. Experts continue to debate the significance and risk of such levels, though the trend has been to recommend maintenance of glucose levels above 60–70 mg/dL the first day after birth.

Diabetic hypoglycemia represents a special case with respect to the relationship of measured glucose and hypoglycemic symptoms for several reasons. First, although home glucose meter readings are often misleading, the probability that a low reading, whether accompanied by symptoms or not, represents real hypoglycemia is much higher in a person who takes insulin than in someone who does not.[24][25]

## Other tests [edit]

The following is a brief list of hormones and metabolites which may be measured in a critical sample. Not all tests are checked on every patient. A "basic version" would include insulin, cortisol, and electrolytes, with C-peptide and drug screen for adults and growth hormone in children. The value of additional specific tests depends on the most likely diagnoses for an individual patient, based on the circumstances described above. Many of these levels change within minutes, especially if glucose is given, and there is no value in measuring them after the hypoglycemia is reversed. Others, especially those lower in the list, remain abnormal even after hypoglycemia is reversed, and can be usefully measured even if a critical specimen is missed.

Part of the value of the critical sample may simply be the proof that the symptoms are indeed due to

hypoglycemia. More often, measurement of certain hormones and metabolites at the time of hypoglycemia indicates which organs and body systems are responding appropriately and which are functioning abnormally. For example, when the blood glucose is low, hormones which raise the glucose should be rising and insulin secretion should be completely suppressed.

### Differential diagnosis [edit]

It can also be mistaken for alcohol intoxication.[26]

## Prevention [edit]

The most effective means of preventing further episodes of hypoglycemia depends on the cause.

The risk of further episodes of diabetic hypoglycemia can often (but not always) be reduced by lowering the dose of insulin or other medications, or by more meticulous attention to blood sugar balance during unusual hours, higher levels of exercise, or decreasing alcohol intake.

Many of the inborn errors of metabolism require avoidance or shortening of fasting intervals, or extra carbohydrates. For the more severe disorders, such as type 1 glycogen storage disease, this may be supplied in the form of cornstarch every few hours or by continuous gastric infusion.

Several treatments are used for hyperinsulinemic hypoglycemia, depending on the exact form and severity. Some forms of congenital hyperinsulinism respond to diazoxide or octreotide. Surgical removal of the overactive part of the pancreas is curative with minimal risk when hyperinsulinism is focal or due to a benign insulin-producing tumor of the pancreas. When congenital hyperinsulinism is diffuse and refractory to medications, near-total pancreatectomy may be the treatment of last resort, but in this condition is less consistently effective and fraught with more complications.

Hypoglycemia due to hormone deficiencies such as hypopituitarism or adrenal insufficiency usually ceases when the appropriate hormone is replaced.

Hypoglycemia due to dumping syndrome and other post-surgical conditions is best dealt with by altering diet. Including fat and protein with carbohydrates may slow digestion and reduce early insulin secretion. Some forms of this respond to treatment with a glucosidase inhibitor, which slows starch digestion.

Reactive hypoglycemia with demonstrably low blood glucose levels is most often a predictable nuisance which can be avoided by consuming fat and protein with carbohydrates, by adding morning or afternoon snacks, and reducing alcohol intake.

Idiopathic postprandial syndrome without demonstrably low glucose levels at the time of symptoms can be more of a management challenge. Many people find improvement by changing eating patterns (smaller meals, avoiding excessive sugar, mixed meals rather than carbohydrates by themselves), reducing intake of stimulants such as caffeine, or by making lifestyle changes to reduce stress. See the following section of this article.

## Treatment [edit]

Treatment of some forms of hypoglycemia, such as in diabetes, involves immediately raising the blood sugar to normal through the ingestion of carbohydrates, determining the cause, and taking measures to hopefully prevent future episodes. However, this treatment is not optimal in other forms such as reactive hypoglycemia, where rapid carbohydrate ingestion may lead to a further hypoglycemic episode.

Blood glucose can be raised to normal within minutes by taking (or receiving) 10-20 grams of carbohydrate.[27] It can be taken as food or drink if the person is conscious and able to swallow. This amount of carbohydrate is contained in about 3–4 ounces (100–120 ml) of orange, apple, or grape juice although fruit juices contain a higher proportion of fructose which is more slowly metabolized than pure dextrose, alternatively, about 4–5 ounces (120-150 ml) of regular (non-diet) soda may also work, as will about one slice of bread, about 4 crackers, or about 1 serving of most starchy foods. Starch is quickly digested to glucose (unless the person is taking acarbose), but adding fat or protein retards digestion.

Symptoms should begin to improve within 5 minutes, though full recovery may take 10–20 minutes. Overfeeding does not speed recovery and if the person has diabetes will simply produce hyperglycemia afterwards. A mnemonic used by the American Diabetes Association and others is the "rule of 15" – consuming 15 grams of carbohydrate followed by a 15-minute wait, repeated if glucose remains low (variable by individual, sometimes 70 mg/dl).[28]

If a person is suffering such severe effects of hypoglycemia that they cannot (due to combativeness) or should not (due to seizures or unconsciousness) be given anything by mouth, medical personnel such as paramedics, or in-hospital personnel can establish IV access and give intravenous dextrose, concentrations varying depending on age (infants are given 2 ml/kg dextrose 10%, children are given dextrose 25%, and adults are given dextrose 50%). Care must be taken in giving these solutions because they can cause skin necrosis if the IV is infiltrated, sclerosis of veins, and many other fluid and electrolyte disturbances if administered incorrectly. If IV access cannot be established, the patient can be given 1 to 2 milligrams of glucagon in an intramuscular injection. More treatment information can be found in the article diabetic hypoglycemia. If a person is suffering less severe effects, and is conscious with the ability to swallow, medical personal such as EMT-B's may administer gelatinous oral glucose.

One situation where starch may be less effective than glucose or sucrose is when a person is taking acarbose. Since acarbose and other alpha-glucosidase inhibitors prevents starch and other sugars from being broken down into monosaccharides that can be absorbed by the body, patients taking these medications should consume monosaccharide-containing foods such as glucose tablets, honey, or juice to reverse hypoglycemia.

## Etymology [edit]

Hypoglycemia may also be spelled hypoglycaemia or hypoglycæmia. The term means low blood sugar in Greek. *ὑπογλυκαιμία*, from *hypo-*, *glykys*, *haima*.

## See also [edit]

- Diabetic Hypoglycemia (journal)
- Idiopathic hypoglycemia
- Neonatal hypoglycemia
- Spontaneous hypoglycemia

## References [edit]


1. ^ *a b c d e f g h i j k l m* "Hypoglycemia". *National Institute of Diabetes and Digestive and Kidney Diseases*. October 2008. Retrieved 28 June 2015.
2. ^ *a b* Yanai, H; Adachi, H; Katsuyama, H; Moriyama, S; Hamasaki, H; Sako, A (15 February 2015). "Causative anti-diabetic drugs and the underlying clinical factors for hypoglycemia in patients with diabetes.". *World journal of diabetes*. **6** (1): 30–6. doi:10.4239/wjd.v6.i1.30. PMID 25685276.
3. ^ *a b c d e f* Schrier, Robert W. (2007). *The internal medicine casebook real patients, real answers* (3rd ed.). Philadelphia: Lippincott Williams & Wilkins. p. 119. ISBN 9780781765299.
4. ^ *a b c d* Perkin, Ronald M. (2008). *Pediatric hospital medicine : textbook of inpatient management* (2nd ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 105. ISBN 9780781770323.
5. ^ *a b c d* Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ (March 2009). "Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline". *J. Clin. Endocrinol. Metab.* **94** (3): 709–28. doi:10.1210/jc.2008-1410. PMID 19088155.
6. ^ Talreja, Roshan S. (2005). *The internal medicine peripheral brain*. Philadelphia, Pa. [u.a.]: Lippincott Williams & Wilkins. p. 176. ISBN 9780781728065.
7. ^ *Dorland's illustrated medical dictionary* (32nd ed.). Philadelphia: Elsevier/Saunders. 2012. p. 1834. ISBN 9781455709854.
8. ^ "Hypoglycemia – National Diabetes Information Clearinghouse". Diabetes.niddk.nih.gov. Retrieved 2012-03-10.
9. ^ Cryer, Philip E. (2003). "Glucose homestasis and hypoglycemia". In Larsen, P. Reed. *Williams Textbook of*

*Endocrinology* (10th ed.). Philadelphia: W.B. Saunders. pp. 1585–1618. ISBN 0-7216-9196-X.
10. ^ Goto, Atshushi (July 30, 2013). "Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis". *BML*. **347**: f4533. doi:10.1136/bmj.f4533.
11. ^ Allen I. Arieff; Robert C. Griggs, eds. (1992). *Metabolic brain dysfunction in systemic disorders*. Boston: Little, Brown. ISBN 0-316-05067-9. OCLC 24912204.
12. ^ Cryer, Philip E. (1997). *Hypoglycemia: Pathophysiology, Diagnosis, and Treatment*. New York: Oxford University Press. ISBN 0-19-511325-X. OCLC 36188385.
13. ^ "UpToDate Inc.".
14. ^ [a] [b] Koh TH, Eyre JA, Aynsley-Green A (1988). "Neonatal hypoglycaemia--the controversy regarding definition". *Arch. Dis. Child*. **63** (11): 1386–8. doi:10.1136/adc.63.11.1386. PMC 1779139. PMID 3202648.
15. ^ [a] [b] Cornblath M, Schwartz R, Aynsley-Green A, Lloyd JK (1990). "Hypoglycemia in infancy: the need for a rational definition. A Ciba Foundation discussion meeting". *Pediatrics*. **85** (5): 834–7. PMID 2330247.
16. ^ [a] [b] Cornblath M, Hawdon JM, Williams AF, Aynsley-Green A, Ward-Platt MP, Schwartz R, Kalhan SC (2000). "Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds". *Pediatrics*. **105** (5): 1141–5. doi:10.1542/peds.105.5.1141. PMID 10790476.
17. ^ [a] [b] Tustison WA, Bowen AJ, Crampton JH (1966). "Clinical interpretation of plasma glucose values". *Diabetes*. **15** (11): 775–7. doi:10.2337/diab.15.11.775. PMID 5924610.
18. ^ [a] [b] [c] John Bernard Henry, ed. (1979). *Clinical diagnosis and management by laboratory methods*. Philadelphia: Saunders. ISBN 0-7216-4639-5. OCLC 4884633.
19. ^ Clarke WL, Cox D, Gonder-Frederick LA, Carter W, Pohl SL (1987). "Evaluating clinical accuracy of systems for self-monitoring of blood glucose". *Diabetes Care*. **10** (5): 622–8. doi:10.2337/diacare.10.5.622. PMID 3677983.
20. ^ Gama R, Anderson NR, Marks V (2000). "'Glucose meter hypoglycaemia': often a non-disease". *Ann. Clin. Biochem*. **37** (5): 731–2. doi:10.1258/0004563001899825. PMID 11026531.
21. ^ de Pasqua A, Mattock MB, Phillips R, Keen H (1984). "Errors in blood glucose determination". *Lancet*. **2** (8412): 1165. doi:10.1016/s0140-6736(84)91611-8. PMID 6150231.
22. ^ Horwitz DL (1989). "Factitious and artifactual hypoglycemia". *Endocrinol. Metab. Clin. North Am*. **18** (1): 203–10. PMID 2645127.
23. ^ Samuel Meites; Gregory J. Buffone; et al., eds. (1989). *Pediatric clinical chemistry: reference (normal) values*. Washington, D.C: AACC Press. ISBN 0-915274-47-7. OCLC 18497532.
24. ^ "20 White NH, Skor D, Cryer PE, Bier DM, Levandoski L, Santiago JV: Identification of type 1 diabetic patients at increased risk for hypoglycemia during intensive therapy. N Engl J Med 308:485–491, 1983". Content.nejm.org. Retrieved 2012-03-10.
25. ^ "21 Bolli GB, De Feo P, De Cosmo S, Perriello G, Ventura MM, Massi-Benedetti M, Santeusanio F, Gerich JE, Brunetti P: A reliable and reproducible test for adequate glucose counterregulation in type 1 diabetes. Diabetes 33:732–737, 1984". Diabetes.diabetesjournals.org. 1984-08-01. Retrieved 2012-03-10.
26. ^ C. Ronald Kahn; et al., eds. (2005). *Joslin's diabetes mellitus* (14th ed.). Philadelphia: Lippincott Williams & Willkins. p. 1154. ISBN 9780781727969.
27. ^ "Diabetes and Hypoglycemia". Diabetes.co.uk. Retrieved 2012-03-10.
28. ^ Nancy Klobassa Davidson, R.N.; Peggy Moreland, R.N. "Living with diabetes blog". Mayo Clinic.

## External links [edit]

- The National Diabetes Information Clearinghouse
- Hypoglycemia at the Mayo Clinic
- American Diabetes Association

Categories: Disorders of endocrine pancreas | Medical emergencies | Disorders causing seizures

# Hyponatremia

From Wikipedia, the free encyclopedia

**Hyponatremia**, also spelled **hyponatraemia**, is a low sodium level in the blood.[1] Symptoms can vary from none to severe.[2][3] Mild symptoms include a decreased ability to think, headaches, nausea, and poor balance.[4] Severe symptoms include confusion, seizures, and coma.[2][3] Normal serum sodium levels are 135–145 mmol/L (135–145 mEq/L).[5] Hyponatremia is generally defined as a serum sodium level of less than 135 mmol/L and is considered severe when the level is below 120 mmol/L.[4]

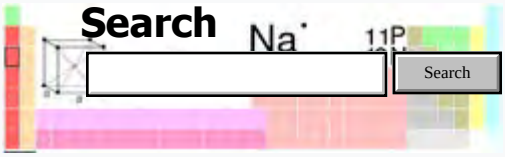
The cause of hyponatremia is typically classified by a person's fluid status into low volume, normal volume, and high volume. Low volume hyponatremia can occur from diarrhea, vomiting, diuretics, and sweating. Normal volume hyponatremia is divided into cases with dilute urine and concentrated urine. Cases in which the urine is dilute include adrenal insufficiency, hypothyroidism, and drinking too much water or too much beer. Cases in which the urine is concentrated include syndrome of inappropriate antidiuretic hormone secretion (SIADH). High volume hyponatremia can occur from heart failure, liver failure, and kidney failure.[1] Conditions that can lead to falsely low sodium measurements include high protein levels such as in multiple myeloma, high blood fat levels, and high blood sugar.[6][7]

Treatment is based on the underlying cause.[1] Correcting hyponatremia too quickly can lead to complications.[6] Rapid partial correction with 3% normal saline is only recommended in those with significant symptoms and occasionally those in whom the condition was of rapid onset.[1][7] Low volume hyponatremia is typically treated with intravenous normal saline. SIADH is typically treated with fluid restriction while high volume hyponatremia is typically treated with both fluid restriction and a diet low in salt. Correction, in those in whom the low levels have been present for more than two days should generally be gradual.[1]

Hyponatremia is one of the most commonly seen water–electrolyte imbalances.[7][8] It occurs in about 20% of those admitted to hospital and 10% of people during or after an endurance sporting event.[4][6] Among those in hospital hyponatremia is associated with an increased risk of death.[6] The economic costs of hyponatremia are estimated at $2.6 billion in the United States.[9]

**Hyponatremia**

**Synonyms** Hyponatraemia




**Classification and external resources**

| | |
|---|---|
| **Specialty** | Internal medicine |
| **ICD-10** | E87.1 |
| **ICD-9-CM** | 276.1 |
| **DiseasesDB** | 6483 |
| **MedlinePlus** | 000394 |
| **eMedicine** | emerg/275 med/1130 ped/1124 |
| **Patient UK** | Hyponatremia |
| **MeSH** | D007010 |

[edit on Wikidata]

Contents

## Signs and symptoms [edit]

Signs and symptoms of hyponatremia include nausea and vomiting, headache, short-term memory loss, confusion, lethargy, fatigue, loss of appetite, irritability, muscle weakness, spasms or cramps, seizures, and decreased consciousness or coma.[10] The presence and severity of signs and symptoms are related to the level of salt in the blood, with lower levels of plasma sodium associated with more severe symptoms. However, emerging data suggest that mild hyponatremia (plasma sodium levels at 131–135 mmol/L) is associated with numerous complications or subtle, presently unrecognized symptoms[11] (for example, increased falls, altered posture and gait, reduced attention).[12]

Neurological symptoms typically occur with very low levels of plasma sodium (usually <115 mmol/L).[10] When sodium levels in the blood become very low, water enters the brain cells and causes them to swell. This results in increased pressure in the skull and causes *hyponatremic encephalopathy*. As pressure increases in the skull, herniation of the brain can occur, which is a squeezing of the brain across the internal structures of the skull. This can lead to headache, nausea, vomiting, confusion, seizures, brain stem compression and respiratory arrest, and non-cardiogenic accumulation of fluid in the lungs.[13] This is usually fatal if not immediately treated.

Symptom severity depends on how fast and how severe the drop in blood salt level. A gradual drop, even to very low levels, may be tolerated well if it occurs over several days or weeks, because of neuronal adaptation. The presence of underlying neurological disease such as a seizure disorder or non-neurological metabolic abnormalities, also affects the severity of neurologic symptoms.

Chronic hyponatremia can lead to such complications as neurological impairments. These neurological impairments most often affect gait (walking) and attention, and can lead to increased reaction time and falls.[*citation needed*] Hyponatremia, by interfering with bone metabolism, has been linked with a doubled risk of osteoporosis and an increased risk of bone fracture.[14]

## Causes [edit]

The specific causes of hyponatremia are generally divided into those that occur with high fluid volume, those with normal fluid volume, and those with low fluid volume. Too little sodium in the diet alone is very rarely the cause of hyponatremia.

### High volume hyponatremia [edit]

Both sodium & water content increase: Increase in sodium content leads to hypervolemia and water content to hyponatremia. Total body water and sodium are regulated independently.[15]

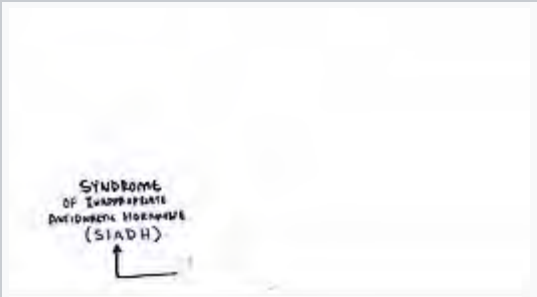
- cirrhosis of the liver
- congestive heart failure

- nephrotic syndrome in the kidneys
- massive edema of any cause

## Normal volume hyponatremia [edit]

There is volume expansion in the body, no edema, but hyponatremia occurs[15]

- states of severe pain or nausea
- in the setting of trauma or other damage to the brain
- SIADH (and its many causes)
- Hypothyroidism
- Glucocorticoid (steroid) deficiency




Play media

Video explanation of SIADH

## Low volume hyponatremia [edit]

The hypovolemia (extracellular volume loss) is due to total body sodium loss. The hyponatremia is caused by a relatively smaller loss in total body water.[15]

- any cause of hypovolemia such as prolonged vomiting, decreased oral intake, severe diarrhea
- diuretic use (due to the diuretic causing a volume depleted state and thence ADH release, and not a direct result of diuretic-induced urine sodium loss)
- Addison's disease and congenital adrenal hyperplasia in which the adrenal glands do not produce enough steroid hormones (combined glucocorticoid and mineralocorticoid deficiency)

Prolonged periods of exercise may be a cause, known as exercise-associated hyponatremia (EAH).[6][16] It is common in marathon runners and participants of other endurance events.[17] The use of MDMA can result in hyponatremia.[18] This likely occurs as a result of fluid loss via sweating and replacement with water without electrolytes.

## Other causes [edit]

Miscellaneous causes of hyponatremia that are not included under the above classification scheme include the following:

- factitious hyponatremia (due to massive increases in blood triglyceride levels, extreme elevation of immunoglobulins as may occur in multiple myeloma, and very high level of blood glucose)
- Hypothyroidism and adrenal insufficiency (both thyroid hormone and cortisol are required to excrete free water)
- Beer potomania and other malnourished states where poor dietary protein intake leads to inadequate urine solute formation thereby impeding the kidney's ability to excrete free water
- Primary polydipsia and water intoxication (where the amount of urine solute required to excrete huge quantities of ingested water exceeds the body's ability to produce it; this typically occurs when 12 or more liters of water are ingested per day)

# Diagnosis [edit]

The history, physical exam, and laboratory testing are required to diagnose and determine the underlying cause of hyponatremia. A blood test demonstrating a serum sodium less than 135 mmol/L is diagnostic for hyponatremia.[19] The history and physical exam are necessary to help determine if the patient is hypovolemic, euvolemic, or hypervolemic, which has important implications in determining the underlying cause. An assessment is also made to determine if the patient is experiencing symptoms from their hyponatremia. These include assessments of alertness, concentration, and orientation.

## False hyponatremia [edit]

False hyponatremia, also known as spurious, pseudo, hypertonic, or artifactual hyponatremia is when the

lab tests read low sodium levels but there is no hypotonicity. In hypertonic hyponatremia, resorption of water by molecules such as glucose (hyperglycemia or diabetes) or mannitol (hypertonic infusion) occurs. In isotonic hyponatremia a measurement error due to high blood triglyceride level (most common) or paraproteinemia occurs. It occurs when using techniques that measure the amount of sodium in a specified volume of serum/plasma, or that dilute the sample before analysis.[20]

### True hyponatremia [edit]

True hyponatremia, also known as hypotonic hyponatremia, is the most common type. It is often simply referred to as "hyponatremia." Hypotonic hyponatremia is categorized in 3 ways based on the person's blood volume status. Each category represents a different underlying reason for the increase in ADH that led to the water retention and thence hyponatremia:

- **High volume hyponatremia**, wherein there is decreased effective circulating volume (less blood flowing in the body) even though total body volume is increased (by the presence of edema or swelling, especially in the ankles). The decreased effective circulating volume stimulates the release of anti-diurectic hormone(ADH), which in turn leads to water retention. Hypervolemic hyponatremia is most commonly the result of congestive heart failure, liver failure (cirrhosis), or kidney disease (nephrotic syndrome).
- **Normal volume hyponatremia**, wherein the increase in ADH is secondary to either physiologic but excessive ADH release (as occurs with nausea or severe pain) or inappropriate and non-physiologic secretion of ADH, that is, syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH). Often categorized under euvolemic is hyponatremia due to inadequate urine solute (not enough chemicals or electrolytes to produce urine) as occurs in beer potomania or "tea and toast" hyponatremia, hyponatremia due to hypothyroidism or central adrenal insufficiency, and those rare instances of hyponatremia that are truly secondary to excess water intake (that is, extreme psychogenic polydipsia)
- **Low volume hyponatremia**, wherein ADH secretion is stimulated by or associated with volume depletion (not enough water in the body).

### Acute versus chronic [edit]

Chronic hyponatremia is when sodium levels drop gradually over several days or weeks and symptoms and complications are typically moderate. Chronic hyponatremia is often called asymptomatic hyponatremia in clinical settings because it is thought to have no symptoms; however, emerging data suggests that "asymptomatic" hyponatremia is not actually asymptomatic.[11]

Acute hyponatremia is when sodium levels drop rapidly, resulting in potentially dangerous effects, such as rapid brain swelling, which can result in coma and death.

## Pathophysiology [edit]

Sodium is the primary positively charged ion in the environment outside of the cell and cannot freely cross from the interstitial space into the cell. Charged sodium ions attract up to 25 water molecules around them thereby creating a large polar structure too large to pass through the cell membrane.

## Treatment [edit]

The treatment of hyponatremia depends on the underlying cause and whether the person's blood volume status is high, normal, or low.

### Fluids [edit]

In the setting of hypovolemia, intravenous administration of normal saline (salt) is usual, care being taken not to raise the serum sodium level (salt level in the blood) too quickly (see below). Euvolemic hyponatremia is usually managed by fluid restriction and treatment to abolish any stimuli for ADH secretion such as nausea. Likewise, drugs causing SIADH are discontinued if possible. Patients with euvolemic

hyponatremia that persists despite those measures may be candidates for a so-called vaptan drug as discussed below. Hypervolemic hyponatremia is usually treated by addressing the underlying heart or liver failure. If it is not possible to do so, the treatment becomes the same as that for euvolemic hyponatremia (that is, fluid restriction and/or use of a vaptan drug).

Hyponatremia is corrected slowly, to lessen the risk of the development of central pontine myelinolysis (CPM), a severe neurological disease involving a breakdown of the myelin sheaths covering parts of nerve cells. In fact, overly rapid correction of hyponatremia is the most common cause of that potentially devastating disorder.[21] During treatment of hyponatremia, the serum sodium (salt level in the blood) is not allowed to rise by more than 8 mmol/L over 24 hours (that is, 0.33 mmol/L/h rate of rise). In practice, too rapid correction of hyponatremia and thence CPM is most likely to occur during the treatment of hypovolemic hyponatremia. In particular, once the hypovolemic state has been corrected, the signal for ADH release disappears. At that point, there is an abrupt water diuresis (an increase in urination since there is no longer any ADH acting to retain the water). A rapid and profound rise in serum sodium (salt level in the blood) can then occur. Should the rate of rise of serum sodium exceed 0.33 mmol/L/h over several hours, vasopressin may be administered to prevent ongoing rapid water diuresis (excessive urination).[22]

### Medications [edit]

There is tentative evidence that vasopressin receptor antagonists (vaptans), such as conivaptan, may be slightly more effective than fluid restriction in those with high volume or normal volume hyponatremia.[1] They should not be used in people with low volume. There use is SIADH is unclear.[3]

## Epidemiology [edit]

Hyponatremia is the most common electrolyte disorder. Electrolytes are sodium (salt), potassium, calcium, magnesium, chloride, hydrogen phosphate, and hydrogen carbonate. The disorder is more frequent in females, the elderly, and in people who are hospitalized. The incidence of hyponatremia depends largely on the patient population. A hospital incidence of 15–20% is common, while only 3–5% of people who are hospitalized have a serum sodium level (salt blood level) of less than 130 mmol/L. Hyponatremia has been reported in up to 30% of elderly patients in nursing homes and is also present in approximately 30% of depressed patients on selective serotonin reuptake inhibitors.[11]

People who have hyponatremia who require hospitalisation have a longer length of stay (with associated increased costs) and also have a higher likelihood of requiring readmission. This is particularly the case in men and in the elderly.[23]

## See also [edit]

- Edible salt
- Hypernatremia

## References [edit]


1. ^ *a b c d e f* Lee, JJ; Kilonzo, K; Nistico, A; Yeates, K (13 May 2014). "Management of hyponatremia.". *CMAJ : Canadian Medical Association Journal (*Journal de l'Association medicale canadienne*)*. **186** (8): E281–6. doi:10.1503/cmaj.120887. PMC 4016091. PMID 24344146.
2. ^ *a b* Williams, DM; Gallagher, M; Handley, J; Stephens, JW (July 2016). "The clinical management of hyponatraemia.". *Postgraduate Medical Journal*. **92** (1089): 407–11. doi:10.1136/postgradmedj-2015-133740. PMID 27044859.
3. ^ *a b c* Ball, S; De Groot, LJ; Beck-Peccoz, P; Chrousos, G; Dungan, K; Grossman, A; Hershman, JM; Koch, C; McLachlan, R; New, M; Rebar, R; Singer, F; Vinik, A; Weickert, MO (2000). "Hyponatremia". PMID 25905359. Accessed 1 August 2016.
4. ^ *a b c* Henry, DA (4 August 2015). "In The Clinic: Hyponatremia.". *Annals of Internal Medicine*. **163** (3): ITC1–19.

doi:10.7326/aitc201508040. PMID 26237763.
5. ^ Kuruvilla, Jaya (2007). *Essentials of Critical Care Nursing*. Jaypee Brothers Publishers. p. 329. ISBN 9788180619205.
6. ^ *a b c d e* Filippatos, TD; Liamis, G; Christopoulou, F; Elisaf, MS (April 2016). "Ten common pitfalls in the evaluation of patients with hyponatremia.". *European journal of internal medicine*. **29**: 22–25. doi:10.1016/j.ejim.2015.11.022. PMID 26706473.
7. ^ *a b c* Marx, John; Walls, Ron; Hockberger, Robert (2013). *Rosen's Emergency Medicine – Concepts and Clinical Practice* (8 ed.). Elsevier Health Sciences. pp. 1639–42. ISBN 1455749877.
8. ^ Ball, SG; Iqbal, Z (March 2016). "Diagnosis and treatment of hyponatraemia". *Best practice & research. Clinical endocrinology & metabolism*. **30** (2): 161–73. doi:10.1016/j.beem.2015.12.001. PMID 27156756.
9. ^ Simon, Eric E. (2014). *Hyponatremia: Evaluation and Treatment*. Springer Science & Business Media. p. 205. ISBN 9781461466451.
10. ^ *a b* Babar, S. (October 2013). "SIADH Associated With Ciprofloxacin." (PDF). *The Annals of Pharmacotherapy*. Sage Publishing. **47** (10): 1359–63. doi:10.1177/1060028013502457. ISSN 1060-0280. PMID 24259701. Retrieved November 18, 2013.
11. ^ *a b c* Schrier, Robert W. (2010). "Does 'asymptomatic hyponatremia' exist?". *Nature Reviews Nephrology*. **6** (4): 185. doi:10.1038/nrneph.2010.21. PMID 20348927.
12. ^ Decaux, Guy (2006). "Is Asymptomatic Hyponatremia Really Asymptomatic?". *The American Journal of Medicine*. **119** (7): S79–82. doi:10.1016/j.amjmed.2006.05.013. PMID 16843090.
13. ^ Moritz, M. L.; Ayus, J. C. (2003). "The pathophysiology and treatment of hyponatraemic encephalopathy: An update". *Nephrology Dialysis Transplantation*. **18** (12): 2486–91. doi:10.1093/ndt/gfg394. PMID 14605269.
14. ^ Upala, Sikarin; Sanguankeo, Anawin (25 February 2016). "Association Between Hyponatremia, Osteoporosis and Fracture: a Systematic Review and Meta-analysis". *The Journal of Clinical Endocrinology & Metabolism*. **101**: Online first. doi:10.1210/jc.2015-4228. PMID 26913635.
15. ^ *a b c* Mange, Kevin; Matsuura, D; Cizman, B; Soto, H; Ziyadeh, FN; Goldfarb, S; Neilson, EG (1997). "Language Guiding Therapy: The Case of Dehydration versus Volume Depletion". *Annals of Internal Medicine*. **127** (9): 848–53. doi:10.7326/0003-4819-127-9-199711010-00020. PMID 9382413.
16. ^ Bennett, BL; Hew-Butler, T; Hoffman, MD; Rogers, IR; Rosner, MH (Sep 2013). "Wilderness Medical Society practice guidelines for treatment of exercise-associated hyponatremia.". *Wilderness & environmental medicine*. **24** (3): 228–40. doi:10.1016/j.wem.2013.01.011. PMID 23590928.
17. ^ Rosner, M.H.; Kirven, J. (2006). "Exercise-Associated Hyponatremia". *Clinical Journal of the American Society of Nephrology*. **2** (1): 151–61. doi:10.2215/CJN.02730806. PMID 17699400.
18. ^ "High incidence of mild hyponatraemia in females using ecstasy at a rave party".
19. ^ Sabatine, [edited by] Marc S. (2014). *Pocket medicine* (Fifth edition. ed.). [S.l.]: Aspen Publishers, Inc. ISBN 1451193785.
20. ^ "Ask the Expert: May 2016 Investigating Hyponatremia". *American Association for Clinical Chemistry*. Archived from the original on June 8, 2016. Retrieved 16 September 2013.
21. ^ Bernsen HJ, Prick MJ (September 1999). "Improvement of central pontine myelinolysis as demonstrated by repeated magnetic resonance imaging in a patient without evidence of hyponatremia". *Acta Neurol Belg*. **99** (3): 189–93. PMID 10544728.
22. ^ Adrogué, Horacio J.; Madias, Nicolaos E. (2000). "Hyponatremia". *New England Journal of Medicine*. **342** (21): 1581–89. doi:10.1056/NEJM200005253422107. PMID 10824078.
23. ^ Corona, Giovanni; Giuliani, Corinna; Parenti, Gabriele; Colombo, Giorgio L.; Sforza, Alessandra; Maggi, Mario; Forti, Gianni; Peri, Alessandro (August 2016). "The Economic Burden of Hyponatremia: Systematic Review and Meta-Analysis". *The American Journal of Medicine*. **129** (8): 823–835.e4. doi:10.1016/j.amjmed.2016.03.007. PMID 27059386.

## External links [edit]

- Sandy Craig; Erik D Schraga; Francisco Talavera; Howard A Bessen; John D Halamka (2010-04-13). "Hyponatremia in Emergency Medicine". Medscape.
- James L. Lewis, III, MD (May 2009). "Hyponatremia". Merck Manual of Diagnosis and Therapy.
- Kugler JP, Hustead T (June 2000). "Hyponatremia and hypernatremia in the elderly". *Am Fam Physician*. **61** (12): 3623–30. PMID 10892634.
- Elizabeth Quinn (2011-03-07). "What Is Hyponatremia: Hyponatremia or water intoxication – Can Athletes Drink Too Much Water?". About.com.

"Salt and the ultraendurance athlete" . SportsMed Web. 1997.

- Hyponatremia Mayo Clinic
- Sodium at Lab Tests Online

| v · t · e · | Water–electrolyte imbalance and acid–base imbalance (E86–E87, 276) | |
|---|---|---|
| **Volume status** | Volume contraction (dehydration/hypovolemia) · Hypervolemia · | |
| **Electrolyte** | **Sodium** | High (Hypernatremia · Salt poisoning · · **Low** (Hypotonic · Isotonic · · |
| | **Potassium** | High · Low · |
| | **Chloride** | High · Low · |
| | **Calcium** | High · Low · |
| **Acid–base** | **Acidosis** | Metabolic: High anion gap (Ketoacidosis · Diabetic ketoacidosis · Lactic · · Normal anion gap (Hyperchloremic · Renal tubular · · Respiratory · |
| | **Alkalosis** | Metabolic (Contraction alkalosis · · Respiratory · |
| | **Both** | Mixed disorder of acid-base balance · |

Categories: Electrolyte disturbances | Mineral deficiencies | Sodium




# Hypothyroidism

From Wikipedia, the free encyclopedia

**Hypothyroidism**, also called **underactive thyroid** or **low thyroid**, is a common disorder of the endocrine system in which the thyroid gland does not produce enough thyroid hormone.[3] It can cause a number of symptoms, such as poor ability to tolerate cold, a feeling of tiredness, constipation, depression, and weight gain.[3] Occasionally there may be swelling of the front part of the neck due to goitre.[3] Untreated hypothyroidism during pregnancy can lead to delays in growth and intellectual development in the baby, which is called cretinism.[4]

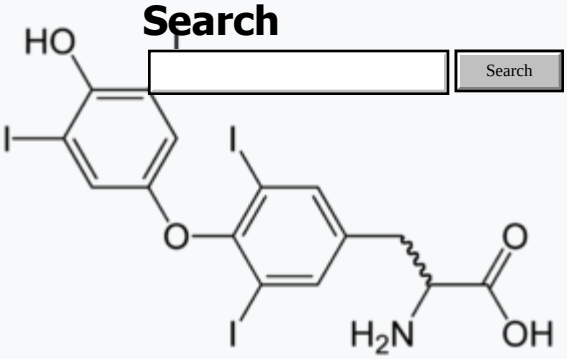
Worldwide, too little iodine in the diet is the most common cause of hypothyroidism.[5][6] In countries with enough iodine in the diet, the most common cause of hypothyroidism is the autoimmune condition Hashimoto's thyroiditis.[3] Less common causes include: previous treatment with radioactive iodine, injury to the hypothalamus or the anterior pituitary gland, certain medications, a lack of a functioning thyroid at birth, or previous thyroid surgery.[3][7] The diagnosis of hypothyroidism, when suspected, can be confirmed with blood tests measuring thyroid-stimulating hormone (TSH) and thyroxine levels.[3]

Prevention at the population level has been with the universal salt iodization.[8] Hypothyroidism can be treated with levothyroxine. The dose is adjusted according to symptoms and normalization of the thyroxine and TSH levels. Thyroid medication is safe in pregnancy. While a certain amount of dietary iodine is important, excessive amounts can worsen certain types of hypothyroidism.[3]

Worldwide about one billion people are estimated to be iodine deficient; however, it is unknown how often this results in hypothyroidism.[9] In the United States, hypothyroidism occurs in 0.3–0.4% of people.[5] Subclinical hypothyroidism, a milder form of hypothyroidism characterized by normal thyroxine levels and an elevated TSH level, is thought to occur in 4.3–8.5% of people in the United States.[5] Hypothyroidism is more common in women than men.[3] People over the age of 60 are more commonly affected.[3] Dogs are also known to develop hypothyroidism and in rare cases cats and horses can also have the disorder.[10] The word "hypothyroidism" is from Greek *hypo-* meaning "reduced", *thyreos* for "shield", and *eidos* for "form."[11]

**Hypothyroidism**

**Synonyms** Hypothyreosis



Molecular structure of thyroxine, the deficiency of which causes the symptoms of hypothyroidism

**Pronunciation** /ˌhaɪpəˈθaɪərɔɪdɪzəm, -poʊ-/[1][2]

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Endocrinology |
| **ICD-10** | E03.9 |
| **ICD-9-CM** | 244.9 |
| **DiseasesDB** | 6558 |
| **MedlinePlus** | 000353 |
| **eMedicine** | med/1145 |
| **Patient UK** | Hypothyroidism |
| **MeSH** | D007037 |

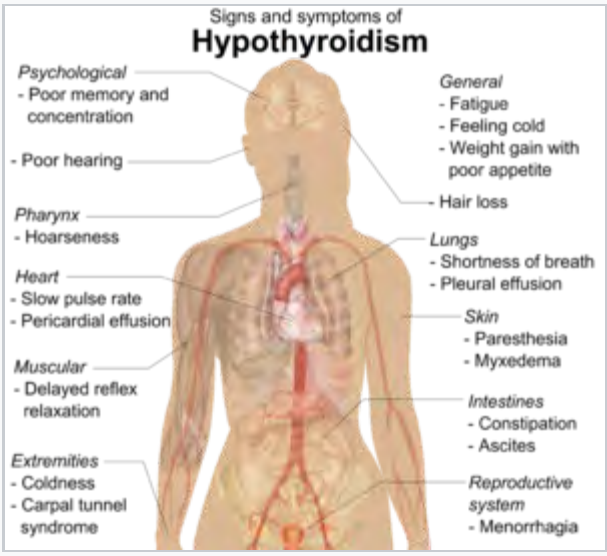
[edit on Wikidata]

Contents

## Signs and symptoms [edit]

People with hypothyroidism often have no or only mild symptoms. Numerous symptoms and signs are associated with hypothyroidism, and can be related to the underlying cause, or a direct effect of having not enough thyroid hormones.[12][13] Hashimoto's thyroiditis may present with the mass effect of a goiter (enlarged thyroid gland).[12]

| Symptoms[12] | Signs[12] |
|---|---|
| Fatigue | Dry, coarse skin |
| Feeling cold | Cool extremities |
| Poor memory and concentration | Myxedema (mucopolysaccharide deposits in the skin) |
| Constipation, dyspepsia[14] | Hair loss |
| Weight gain with poor appetite | Slow pulse rate |
| Shortness of breath | Swelling of the limbs |
| Hoarse voice | Delayed relaxation of tendon reflexes |
| In females, heavy menstrual periods (and later light periods) | Carpal tunnel syndrome |
| Abnormal sensation | Pleural effusion, ascites, pericardial effusion |
| Poor hearing | |



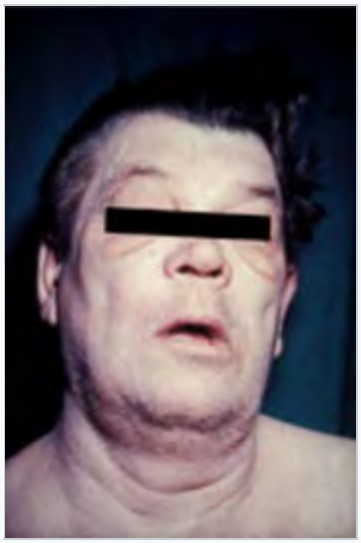
Symptoms and signs of hypothyroidism[12]

Delayed relaxation after testing the ankle jerk reflex is a characteristic sign of hypothyroidism and is

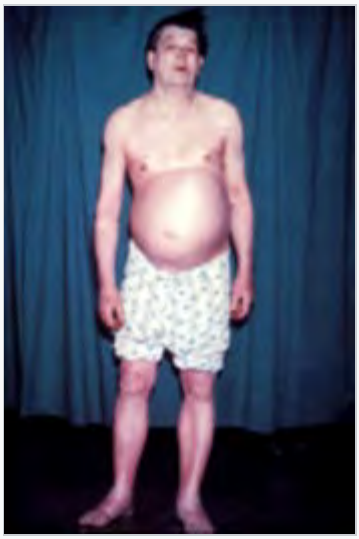
associated with the severity of the hormone deficit.[5]

## Myxedema coma [edit]

Myxedema coma is a rare but life-threatening state of extreme hypothyroidism. It may occur in those who are known to have hypothyroidism when they develop another illness, but it can be the first presentation of hypothyroidism. The illness is characterized by very low body temperature without shivering, confusion, a slow heart rate and reduced breathing effort. There may be physical signs suggestive of hypothyroidism, such as skin changes or enlargement of the tongue.[15]



Man with myxedema or severe hypothyroidism showing an expressionless face, puffiness around the eyes and pallor



Additional symptoms include swelling of the arms and legs and ascites.

## Pregnancy [edit]

Even mild or subclinical hypothyroidism has been associated with impaired fertility and an increased risk of miscarriage.[16] Hypothyroidism in early pregnancy, even with limited or no symptoms, may increase the risk of pre-eclampsia, offspring with lower intelligence, and the risk of infant death around the time of birth.[16][17] Women are affected by hypothyroidism in 0.3–0.5% of pregnancies.[17] Subclinical hypothyroidism during pregnancy has also been associated with gestational diabetes and birth of the baby before 37 weeks of pregnancy.[18]

## Children [edit]

Newborn children with hypothyroidism may have normal birth weight and height (although the head may be larger than expected and the posterior fontanelle may be open). Some may have drowsiness, decreased muscle tone, a hoarse-sounding cry, feeding difficulties, constipation, an enlarged tongue, umbilical hernia, dry skin, a decreased body temperature and jaundice.[19] A goiter is rare, although it may develop later in children who have a thyroid gland that does not produce functioning thyroid hormone.[19] A goiter may also develop in children growing up in areas with iodine deficiency.[20] Normal growth and development may be delayed, and not treating infants may lead to an intellectual impairment (IQ 6–15 points lower in severe cases). Other problems include the following: large scale and fine motor skills and coordination, reduced muscle tone, squinting, decreased attention span, and delayed speaking.[19] Tooth eruption may be delayed.[21]

In older children and adolescents, the symptoms of hypothyroidism may include fatigue, cold intolerance, sleepiness, muscle weakness, constipation, a delay in growth, overweight for height, pallor, coarse and thick skin, increased body hair, irregular menstrual cycles in girls, and delayed puberty. Signs may include delayed relaxation of the ankle reflex and a slow heart beat.[19] A goiter may be present with a completely enlarged thyroid gland;[19] sometimes only part of the thyroid is enlarged and it can be knobby in character.[22]

# Causes [edit]

Hypothyroidism is caused by inadequate function of the gland itself (primary hypothyroidism) or by not enough stimulation by thyroid-stimulating hormone (central hypothyroidism).[5][23] Primary hypothyroidism is about a thousandfold more common than central hypothyroidism.[7]

Iodine deficiency is the most common cause of primary hypothyroidism and endemic goiter worldwide.[5][6] In areas of the world with sufficient dietary iodine, hypothyroidism is most commonly caused by the autoimmune disease Hashimoto's thyroiditis (chronic autoimmune thyroiditis).[5][6] Hashimoto's may be associated with a goiter. It is characterized by infiltration of the thyroid gland with T lymphocytes and autoantibodies against specific thyroid antigens such as thyroid peroxidase, thyroglobulin and the TSH receptor.[5]

After women give birth, about 5% develop postpartum thyroiditis which can occur up to nine months afterwards.[24] This is characterized by a short period of hyperthyroidism followed by a period of hypothyroidism; 20–40% remain permanently hypothyroid.[24]

Autoimmune thyroiditis is associated with other immune-mediated diseases such as diabetes mellitus type 1, pernicious anemia, myasthenia gravis, celiac disease, rheumatoid arthritis and systemic lupus erythematosus.[5] It may occur as part of autoimmune polyendocrine syndrome (type 1 and type 2).[5]

| Group | Causes |
|---|---|
| Primary hypothyroidism[5] | Iodine deficiency (developing countries), autoimmune thyroiditis, previous thyroidectomy, previous radioiodine treatment, previous external beam radiotherapy to the neck<br>Medication: lithium-based mood stabilizers, amiodarone, interferon alpha, tyrosine kinase inhibitors such as sunitinib |
| Central hypothyroidism[7] | Lesions compressing the pituitary (pituitary adenoma, craniopharyngioma, meningioma, glioma, Rathke's cleft cyst, metastasis, empty sella, aneurysm of the internal carotid artery), surgery or radiation to the pituitary, drugs, injury, vascular disorders (pituitary apoplexy, Sheehan syndrome, subarachnoid hemorrhage), autoimmune diseases (lymphocytic hypophysitis, polyglandular disorders), infiltrative diseases (iron overload due to hemochromatosis or thalassemia, sarcoidosis, Langerhans cell histiocytosis), particular inherited congenital disorders, and infections (tuberculosis, mycoses, syphilis) |
| Congenital hypothyroidism[25] | Thyroid dysgenesis (75%), thyroid dyshormonogenesis (20%), maternal antibody or radioiodine transfer<br>Syndromes: mutations (in *GNAS complex locus*, *PAX8*, *TTF-1/NKX2-1*, *TTF-2/FOXE1*), Pendred's syndrome (associated with sensorineural hearing loss)<br>Transiently: due to maternal iodine deficiency or excess, anti-TSH receptor antibodies, certain congenital disorders, neonatal illness<br>Central: pituitary dysfunction (idiopathic, septo-optic dysplasia, deficiency of *PIT1*, isolated TSH deficiency) |

## Pathophysiology [edit]

Thyroid hormone is required for the normal functioning of numerous tissues in the body. In health, the thyroid gland predominantly secretes thyroxine ($T_4$), which is converted into triiodothyronine ($T_3$) in other organs by the selenium-dependent enzyme iodothyronine deiodinase.[26] Triiodothyronine binds to the thyroid hormone receptor in the nucleus of cells, where it stimulates the turning on of particular genes and the production of specific proteins.[27] Additionally, the hormone binds to integrin αvβ3 on the cell membrane, thereby stimulating the sodium–hydrogen antiporter and processes such as formation of blood vessels and cell growth.[27] In blood, almost all thyroid hormone (99.97%) is bound to plasma proteins such as thyroxine-binding globulin; only the free unbound thyroid hormone is biologically active.[5]

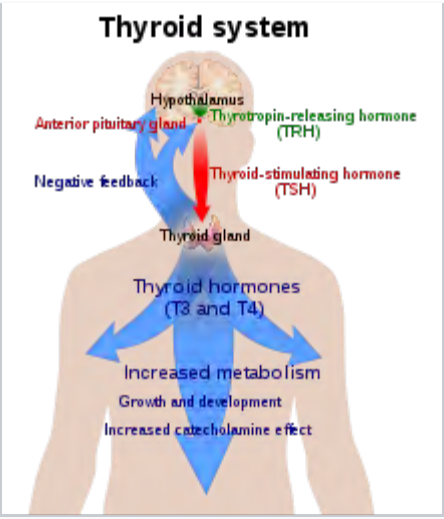



Diagram of the hypothalamic–pituitary–thyroid axis. The hypothalamus secretes TRH (green), which stimulates the production of TSH (red) by the pituitary gland. This, in turn, stimulates the production of thyroxine by the thyroid (blue). Thyroxine levels decrease TRH and TSH production by a negative feedback process.

The thyroid gland is the only source of thyroid hormone in the body; the process requires iodine and the amino acid tyrosine. Iodine in the bloodstream is taken up by the gland and incorporated into thyroglobulin molecules. The process is controlled by the thyroid-stimulating hormone (TSH, thyrotropin), which is secreted by the pituitary. Not enough iodine, or not enough TSH, can result in decreased production of thyroid hormones.[23]

The hypothalamic–pituitary–thyroid axis plays a key role in maintaining thyroid hormone levels within normal limits. Production of TSH by the anterior pituitary gland is stimulated in turn by thyrotropin-releasing hormone (TRH), released from the hypothalamus. Production of TSH and TRH is decreased by thyroxine by a negative feedback process. Not enough TRH, which is uncommon, can lead to not enough TSH and thereby to not enough thyroid hormone production.[7]

Pregnancy leads to marked changes in thyroid hormone physiology. The gland is increased in size by 10%, thyroxine production is increased by 50%, and iodine requirements are increased. Many women have normal thyroid function but have immunological evidence of thyroid autoimmunity (as evidenced by autoantibodies) or are iodine deficient, and develop evidence of hypothyroidism before or after giving birth.[28]

## Diagnosis [edit]

*See also: Thyroid function tests*

Laboratory testing of thyroid stimulating hormone levels in the blood is considered the best initial test for hypothyroidism; a second TSH level is often obtained several weeks later for confirmation.[29] Levels may be abnormal in the context of other illnesses, and TSH testing in hospitalized people is discouraged unless thyroid dysfunction is strongly suspected.[5] An elevated TSH level indicates that the thyroid gland is not producing enough thyroid hormone, and free T4 levels are then often obtained.[5][22] Measuring $T_3$ is discouraged by the AACE in the assessment for hypothyroidism.[5] There are a number of symptom rating scales for hypothyroidism; they provide a degree of objectivity but have limited use for diagnosis.[5]

Many cases of hypothyroidism are associated with mild elevations in creatine kinase and liver enzymes in the blood. They typically return to normal when hypothyroidism has been fully treated.[5] Levels of cholesterol, low-density lipoprotein and lipoprotein (a) can be elevated;[5] the impact of subclinical hypothyroidism on lipid parameters is less well-defined.[20]

| TSH | T4 | Interpretation |
|---|---|---|
| Normal | Normal | Normal thyroid function |
| Elevated | Low | Overt hypothyroidism |
| Normal/low | Low | Central hypothyroidism |
| Elevated | Normal | Subclinical hypothyroidism |

Very severe hypothyroidism and myxedema coma are characteristically associated with low sodium levels in

the blood together with elevations in antidiuretic hormone, as well as acute worsening of kidney function due to a number of causes.[15]

A diagnosis of hypothyroidism without any lumps or masses felt within the thyroid gland does not require thyroid imaging; however, if the thyroid feels abnormal, diagnostic imaging is then recommended.[29] The presence of antibodies against thyroid peroxidase (TPO) makes it more likely that thyroid nodules are caused by autoimmune thyroiditis, but if there is any doubt, a needle biopsy may be required.[5]

If the TSH level is normal or low and serum free $T_4$ levels are low, this is suggestive of central hypothyroidism (not enough TSH or TRH secretion by the pituitary gland or hypothalamus). There may be other features of hypopituitarism, such as menstrual cycle abnormalities and adrenal insufficiency. There might also be evidence of a pituitary mass such as headaches and vision changes. Central hypothyroidism should be investigated further to determine the underlying cause.[7][29]

### Overt [edit]

In overt primary hypothyroidism, TSH levels are high and $T_4$ and $T_3$ levels are low. Overt hypothyroidism may also be diagnosed in those who have a TSH on multiple occasions of greater than 5mIU/L, appropriate symptoms, and only a borderline low $T_4$.[30] It may also be diagnosed in those with a TSH of greater than 10mIU/L.[30]

### Subclinical [edit]

Subclinical hypothyroidism is a milder form of hypothyroidism characterized by an elevated serum TSH level, but with a normal serum free thyroxine level.[31][32] This milder form of hypothyroidism is most commonly caused by Hashimoto's thyroiditis.[33] In adults it is diagnosed when TSH levels are greater than 5 mIU/L and less than 10mIU/L.[30] The presentation of subclinical hypothyroidism is variable and classic signs and symptoms of hypothyroidism may not be observed.[31] Of people with subclinical hypothyroidism, a proportion will develop overt hypothyroidism each year. In those with detectable antibodies against thyroid peroxidase (TPO), this occurs in 4.3%, while in those with no detectable antibodies, this occurs in 2.6%.[5] Those with subclinical hypothyroidism and detectable anti-TPO antibodies who do not require treatment should have repeat thyroid function tests more frequently (e.g. yearly) compared with those who do not have antibodies.[29]

### Pregnancy [edit]

During pregnancy, the thyroid gland must produce 50% more thyroid hormone to provide enough thyroid hormone for the developing fetus and the expectant mother.[18] In pregnancy, free thyroxine levels may be lower than anticipated due to increased binding to thyroid binding globulin and decreased binding to albumin. They should either be corrected for the stage of pregnancy,[28] or total thyroxine levels should be used instead for diagnosis.[5] TSH values may also be lower than normal (particularly in the first trimester) and the normal range should be adjusted for the stage of pregnancy.[5][28]

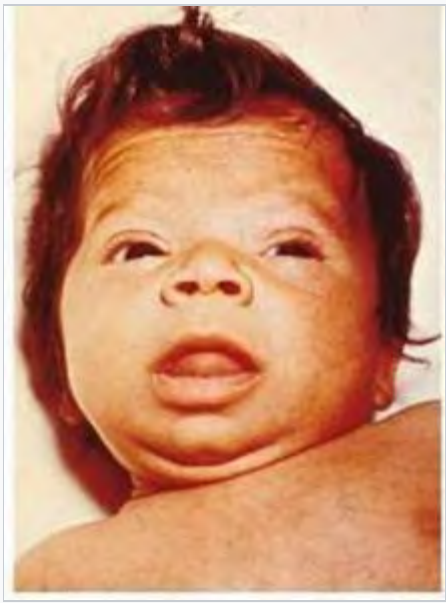
In pregnancy, subclinical hypothyroidism is defined as a TSH between 2.5 and 10 mIU/l with a normal thyroxine level, while those with TSH above 10 mIU/l are considered to be overtly hypothyroid even if the thyroxine level is normal.[28] Antibodies against TPO may be important in making decisions about treatment, and should, therefore, be determined in women with abnormal thyroid function tests.[5]

Determination of TPO antibodies may be considered as part of the assessment of recurrent miscarriage, as subtle thyroid dysfunction can be associated with pregnancy loss,[5] but this recommendation is not universal,[34] and presence of thyroid antibodies may not predict future outcome.[35]

## Prevention [edit]

Hypothyroidism may be prevented in a population by adding iodine to commonly used foods. This public health measure has eliminated endemic childhood hypothyroidism in countries where it was once common. In addition to promoting the consumption of iodine-rich foods such as dairy and fish, many countries with moderate iodine deficiency have implemented universal salt iodization (USI).[36] Encouraged by the World Health Organization,[37] 130 countries now have USI, and 70% of the world's population are receiving iodized salt. In some countries, iodized salt is added to bread.[36] Despite this, iodine deficiency has reappeared in some Western countries as a result of attempts to reduce salt intake.[36]

Pregnant and breastfeeding women, who require 66% more daily iodine requirement than non-pregnant women, may still not be getting enough iodine.[36][38] The World Health Organization recommends a daily intake of 250 µg for pregnant and breastfeeding women.[39] As many women will not achieve this from dietary sources alone, the American Thyroid Association recommends a 150 µg daily supplement by mouth.[28][40]



A 3-month-old infant with untreated congenital hypothyroidism showing myxedematous facies, a big tongue, and skin mottling

## Screening [edit]

Screening for hypothyroidism is performed in the newborn period in many countries, generally using TSH. This has led to the early identification of many cases and thus the prevention of developmental delay.[41] It is the most widely used newborn screening test worldwide.[42] While TSH-based screening will identify the most common causes, the addition of $T_4$ testing is required to pick up the rarer central causes of neonatal hypothyroidism.[19] If $T_4$ determination is included in the screening done at birth, this will identify cases of congenital hypothyroidism of central origin in 1:16,000 to 1:160,000 children. Considering that these children usually have other pituitary hormone deficiencies, early identification of these cases may prevent complications.[7]

In adults, widespread screening of the general population is a matter of debate. Some organizations (such as the United States Preventive Services Task Force) state that evidence is insufficient to support routine screening,[43] while others (such as the American Thyroid Association) recommend either intermittent testing above a certain age in both sexes or only in women.[5] Targeted screening may be appropriate in a number of situations where hypothyroidism is common: other autoimmune diseases, a strong family history of thyroid disease, those who have received radioiodine or other radiation therapy to the neck, those who have previously undergone thyroid surgery, those with an abnormal thyroid examination, those with psychiatric disorders, people taking amiodarone or lithium, and those with a number of health conditions (such as certain heart and skin conditions).[5] Yearly thyroid function tests are recommended in people with Down syndrome, as they are at higher risk of thyroid disease.[44]

## Management [edit]

### Hormone replacement [edit]

Most people with hypothyroidism symptoms and confirmed thyroxine deficiency are treated with a synthetic long-acting form of thyroxine, known as levothyroxine (L-thyroxine).[5][13] In young and otherwise healthy people with overt hypothyroidism, a full replacement dose (adjusted by weight) can be started immediately; in the elderly and people with heart disease a lower starting dose is recommended to prevent over supplementation and risk of complications.[5][23] Lower doses may be sufficient in those with subclinical hypothyroidism, while people with central hypothyroidism may require a higher than average dose.[5]

Blood free thyroxine and TSH levels are monitored to help determine whether the dose is adequate. This is done 4–8 weeks after the start of treatment or a change in levothyroxine dose. Once the adequate replacement dose has been established, the tests can be repeated after 6 and then 12 months, unless there is a change in symptoms.[5] In people with central/secondary hypothyroidism, TSH is not a reliable marker of hormone replacement and decisions are based mainly on the free $T_4$ level.[5][7] Levothyroxine is best taken 30–60 minutes before breakfast, or four hours after food,[5] as certain substances such as food and calcium can inhibit the absorption of levothyroxine.[45] There is no direct way of increasing thyroid hormone secretion by the thyroid gland.[13]

## Liothyronine [edit]

Adding liothyronine (synthetic $T_3$) to levothyroxine has been suggested as a measure to provide better symptom control, but this has not been confirmed by studies.[6][13][46] In 2007, the British Thyroid Association stated that combined $T_4$ and $T_3$ therapy carried a higher rate of side effects and no benefit over $T_4$ alone.[13][47] Similarly, American guidelines discourage combination therapy due to a lack of evidence, although they acknowledge that some people feel better when receiving combination treatment.[5] Treatment with liothyronine alone has not received enough study to make a recommendation as to its use; due to its shorter half-life it needs to be taken more often.[5]

People with hypothyroidism who do not feel well despite optimal levothyroxine dosing may request adjunctive treatment with liothyronine. A 2012 guideline from the European Thyroid Association recommends that support should be offered with regards to the chronic nature of the disease and that other causes of the symptoms should be excluded. Addition of liothyronine should be regarded as experimental, initially only for a trial period of 3 months, and in a set ratio to the current dose of levothyroxine.[48] The guideline explicitly aims to enhance the safety of this approach and to counter its indiscriminate use.[48]

## Desiccated animal thyroid [edit]

Desiccated thyroid extract is an animal-based thyroid gland extract,[13] most commonly from pigs. It is a combination therapy, containing forms of $T_4$ and $T_3$.[13] It also contains calcitonin (a hormone produced in the thyroid gland involved in the regulation of calcium levels), $T_1$ and $T_2$; these are not present in synthetic hormone medication.[49] This extract was once a mainstream hypothyroidism treatment, but its use today is unsupported by evidence;[6][13] British Thyroid Association and American professional guidelines discourage its use.[5][47]

## Subclinical hypothyroidism [edit]

There is little evidence whether there is a benefit from treating subclinical hypothyroidism, and whether this offsets the risks of overtreatment. Untreated subclinical hypothyroidism may be associated with a modest increase in the risk of coronary artery disease.[50] A 2007 review found no benefit of thyroid hormone replacement except for "some parameters of lipid profiles and left ventricular function".[51] There is no association between subclinical hypothyroidism and an increased risk of bone fractures,[52] nor is there a link with cognitive decline.[53]

Since 2008, consensus American and British opinion has been that in general people with TSH under 10 mIU/l do not require treatment.[5][32][54] American guidelines recommend that treatment should be considered if the TSH is elevated but below 10 mIU/l in people with symptoms of hypothyroidism, detectable antibodies against thyroid peroxidase, a history of heart disease or are at an increased risk for heart disease.[5]

## Myxedema coma [edit]

Myxedema coma or severe decompensated hypothyroidism usually requires admission to the intensive care, close observation and treatment of abnormalities in breathing, temperature control, blood pressure, and sodium levels. Mechanical ventilation may be required, as well as fluid replacement, vasopressor agents, careful rewarming, and corticosteroids (for possible adrenal insufficiency which can occur together with hypothyroidism). Careful correction of low sodium levels may be achieved with hypertonic saline solutions or vasopressin receptor antagonists.[15] For rapid treatment of the hypothyroidism, levothyroxine or liothyronine may be administered intravenously, particularly if the level of consciousness is too low to be able to safely swallow medication.[15]

### Pregnancy [edit]

In women with known hypothyroidism who become pregnant, it is recommended that serum TSH levels are closely monitored. Levothyroxine should be used to keep TSH levels within the normal range for that trimester. The first trimester normal range is below 2.5 mIU/L and the second and third trimesters normal range is below 3.0 mIU/L.[13][28] Treatment should be guided by total (rather than free) thyroxine or by the free $T_4$ index. Similarly to TSH, the thyroxine results should be interpreted according to the appropriate reference range for that stage of pregnancy.[5] The levothyroxine dose often needs to be increased after pregnancy is confirmed,[5][23][28] although this is based on limited evidence and some recommend that it is not always required; decisions may need to based on TSH levels.[55]

Women with anti-TPO antibodies who are trying to become pregnant (naturally or by assisted means) may require thyroid hormone supplementation even if the TSH level is normal. This is particularly true if they have had previous miscarriages or have been hypothyroid in the past.[5] Supplementary levothyroxine may reduce the risk of preterm birth and possibly miscarriage.[56] The recommendation is stronger in pregnant women with subclinical hypothyroidism (defined as TSH 2.5–10 mIU/l) who are anti-TPO positive, in view of the risk of overt hypothyroidism. If a decision is made not to treat, close monitoring of the thyroid function (every 4 weeks in the first 20 weeks of pregnancy) is recommended.[5][28] If anti-TPO is not positive, treatment for subclinical hypothyroidism is not currently recommended.[28] It has been suggested that many of the aforementioned recommendations could lead to unnecessary treatment, in the sense that the TSH cutoff levels may be too restrictive in some ethnic groups; there may be little benefit from treatment of subclinical hypothyroidism in certain cases.[55]

## Epidemiology [edit]

Worldwide about one billion people are estimated to be iodine deficient; however, it is unknown how often this results in hypothyroidism.[9] In large population-based studies in Western countries with sufficient dietary iodine, 0.3–0.4% of the population have overt hypothyroidism. A larger proportion, 4.3–8.5%, have subclinical hypothyroidism.[5] Of people with subclinical hypothyroidism, 80% have a TSH level below the 10 mIU/l mark regarded as the threshold for treatment.[32] Children with subclinical hypothyroidism often return to normal thyroid function, and a small proportion develops overt hypothyroidism (as predicted by evolving antibody and TSH levels, the presence of celiac disease, and the presence of a goiter).[57]

Women are more likely to develop hypothyroidism than men. In population-based studies, women were seven times more likely than men to have TSH levels above 10 mU/l.[5] 2–4% of people with subclinical hypothyroidism will progress to overt hypothyroidism each year. The risk is higher in those with antibodies against thyroid peroxidase.[5][32] Subclinical hypothyroidism is estimated to affect approximately 2% of children; in adults, subclinical hypothyroidism is more common in the elderly, and in Caucasians.[31] There is a much higher rate of thyroid disorders, the most common of which is hypothyroidism, in individuals with Down syndrome[19][44] and Turner syndrome.[19]

Very severe hypothyroidism and myxedema coma are rare, with it estimated to occur in 0.22 per million people a year.[15] The majority of cases occur in women over 60 years of age, although it may happen in all age groups.[15]

Most hypothyroidism is primary in nature. Central/secondary hypothyroidism affects 1:20,000 to 1:80,000 of the population, or about one out of every thousand people with hypothyroidism.[7]

## History [edit]

In 1811, Bernard Courtois discovered iodine was present in seaweed, and iodine intake was linked with goiter size in 1820 by Jean-Francois Coindet.[58] Gaspard Adolphe Chatin proposed in 1852 that endemic goiter was the result of not enough iodine intake, and Eugen Baumann demonstrated iodine in thyroid tissue in 1896.[58]

The first cases of myxedema were recognized in the mid-19th century (the 1870s), but its connection to the thyroid was not discovered until the 1880s when myxedema was observed in people following the removal of the thyroid gland (thyroidectomy).[59] The link was further confirmed in the late 19th century when people and animals who had had their thyroid removed showed improvement in symptoms with transplantation of animal thyroid tissue.[6] The severity of myxedema, and its associated risk of mortality and complications, created interest in discovering effective treatments for hypothyroidism.[59] Transplantation of thyroid tissue demonstrated some efficacy, but recurrences of hypothyroidism was relatively common, and sometimes required multiple repeat transplantations of thyroid tissue.[59]

In 1891, the English physician George Redmayne Murray introduced subcutaneously injected sheep thyroid extract,[60] followed shortly after by an oral formulation.[6][61] Purified thyroxine was introduced in 1914 and in the 1930s synthetic thyroxine became available, although desiccated animal thyroid extract remained widely used. Liothyronine was identified in 1952.[6]

Early attempts at titrating therapy for hypothyroidism proved difficult. After hypothyroidism was found to cause a lower basal metabolic rate, this was used as a marker to guide adjustments in therapy in the early 20th century (around 1915).[59] However, a low basal metabolic rate was known to be non-specific, also present in malnutrition.[59] The first laboratory test to be helpful in assessing thyroid status was the serum protein-bound iodine, which came into use around the 1950s.

In 1971, the thyroid stimulating hormone (TSH) radioimmunoassay was developed, which was the most specific marker for assessing thyroid status in patients.[59] Many people who were being treated based on basal metabolic rate, minimizing hypothyroid symptoms, or based on serum protein-bound iodine, were found to have excessive thyroid hormone.[59] The following year, in 1972, a T3 radioimmunoassay was developed, and in 1974, a T4 radioimmunoassay was developed.[59]

## Other animals [edit]

In veterinary practice, dogs are the species most commonly affected by hypothyroidism. The majority of cases occur as a result of primary hypothyroidism, of which two types are recognized: lymphocytic thyroiditis, which is probably immune-driven and leads to destruction and fibrosis of the thyroid gland, and idiopathic atrophy, which leads to the gradual replacement of the gland by fatty tissue.[10][62] There is often lethargy, cold intolerance, exercise intolerance, and weight gain. Furthermore, skin changes and fertility problems are seen in dogs with hypothyroidism, as well as a number of other symptoms.[62] The signs of myxedema can be seen in dogs, with prominence of skin folds on the forehead, and cases of myxedema coma are encountered.[10] The diagnosis can be confirmed by blood test, as the clinical impression alone may lead to overdiagnosis.[10][62] Lymphocytic thyroiditis is associated with detectable antibodies against thyroglobulin, although they typically become undetectable in advanced disease.[62] Treatment is with thyroid hormone replacement.[10]

Characteristic changes in the facial skin of a Labrador Retriever with hypothyroidism

Other species that are less commonly affected include cats and horses, as well as other large domestic animals. In cats, hypothyroidism is usually the result of other medical treatment such as surgery or radiation. In young horses, congenital hypothyroidism has been reported predominantly in Western Canada and has been linked with the mother's diet.[10]

## References [edit]


1. ^ "hypothyroidism". *Dictionary.com Unabridged*. Random House.
2. ^ "hypothyroidism - definition of hypothyroidism in English from the Oxford dictionary". OxfordDictionaries.com. Retrieved 2016-01-20.
3. ^ a b c d e f g h i "Hypothyroidism". *National Institute of Diabetes and Digestive and Kidney Diseases*. March 2013. Retrieved 5 March 2016.
4. ^ Preedy, Victor (2009). *Comprehensive Handbook of Iodine Nutritional, Biochemical, Pathological and Therapeutic Aspects.* Burlington: Elsevier. p. 616. ISBN 9780080920863.
5. ^ a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af ag ah ai aj ak al am an ao ap aq ar Garber, JR; Cobin, RH; Gharib, H; Hennessey, JV; Klein, I; Mechanick, JI; Pessah-Pollack, R; Singer, PA; et al. (December 2012). "Clinical Practice Guidelines for Hypothyroidism in Adults" (PDF). *Thyroid*. **22** (12): 1200–1235. doi:10.1089/thy.2012.0205. PMID 22954017.
6. ^ a b c d e f g h Chakera, AJ; Pearce, SH; Vaidya, B (2012). "Treatment for primary hypothyroidism: current approaches and future possibilities". *Drug Design, Development and Therapy* (Review). **6**: 1–11. doi:10.2147/DDDT.S12894. PMC 3267517. PMID 22291465.
7. ^ a b c d e f g h Persani, L (September 2012). "Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges". *The Journal of Clinical endocrinology and Metabolism* (Review). **97** (9): 3068–78. doi:10.1210/jc.2012-1616. PMID 22851492.
8. ^ Syed, S (April 2015). "Iodine and the "near" eradication of cretinism.". *Pediatrics*. **135** (4): 594–6. doi:10.1542/peds.2014-3718. PMID 25825529.
9. ^ a b Cooper, DS; Braverman LE, eds. (2012-07-12). *Werner & Ingbar's the thyroid : a fundamental and clinical text* (10th ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health. p. 552. ISBN 145112063X.
10. ^ a b c d e f "Hypothyroidism". *Merck Veterinary Manual, 10th edition (online version)*. 2012. Retrieved 2013-12-25.
11. ^ *Mosby's Medical Dictionary* (9 ed.). Elsevier Health Sciences. 2013. p. 887. ISBN 9780323112581.
12. ^ a b c d e Longo, DL; Fauci, AS; Kasper, DL; Hauser, SL; Jameson, JL; Loscalzo, J (2011). "341: disorders of the thyroid gland". *Harrison's principles of internal medicine.* (18th ed.). New York: McGraw-Hill. ISBN 007174889X.
13. ^ a b c d e f g h i Khandelwal D, Tandon N; Tandon (January 2012). "Overt and subclinical hypothyroidism: who to treat and how". *Drugs* (Review). **72** (1): 17–33. doi:10.2165/11598070-000000000-00000. PMID 22191793.
14. ^ Ebert, E. C. (July 2010). "The thyroid and the gut". *Journal of Clinical Gastroenterology*. **44** (6): 402–6. doi:10.1097/MCG.0b013e3181d6bc3e. PMID 20351569.
15. ^ a b c d e f Klubo-Gwiezdzinska, J; Wartofsky, L (March 2012). "Thyroid emergencies". *Medical Clinics of North America*. **96** (2): 385–403. doi:10.1016/j.mcna.2012.01.015. PMID 22443982.
16. ^ a b van den Boogaard, E; Vissenberg, R; Land, JA; et al. (2011). "Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review". *Human Reproduction Update* (Review). **17** (5): 605–19. doi:10.1093/humupd/dmr024. PMID 21622978.
17. ^ a b Vissenberg, R; van den Boogaard, E; van Wely, M; et al. (July 2012). "Treatment of thyroid disorders before conception and in early pregnancy: a systematic review". *Human Reproduction Update* (Review). **18** (4): 360–73. doi:10.1093/humupd/dms007. PMID 22431565.
18. ^ a b Negro R, Stagnaro-Green A; Stagnaro-Green (October 2014). "Diagnosis and management of subclinical hypothyroidism in pregnancy". *BMJ*. **349** (10): g4929. doi:10.1136/bmj.g4929. PMID 25288580.
19. ^ a b c d e f g h Counts, D; Varma, SK (Jul 2009). "Hypothyroidism in children". *Pediatrics in Review*. **30** (7): 251–8. doi:10.1542/pir.30-7-251. PMID 19570923.
20. ^ a b Pearce, EN (Feb 2012). "Update in lipid alterations in subclinical hypothyroidism". *The Journal of Clinical endocrinology and Metabolism*. **97** (2): 326–33. doi:10.1210/jc.2011-2532. PMID 22205712.
21. ^ Chandna, Shalu; Bathla, Manish (July 2011). "Oral manifestations of thyroid disorders and its management". *Indian J Endocrinol Metab*. **15** (Suppl2): S113–6. doi:10.4103/2230-8210.83343. PMC 3169868. PMID 21966646.

22. ^ [a b] Brown, RS (2013). "Autoimmune thyroiditis in childhood". *Journal of Clinical Research in Pediatric Endocrinology* (Review). 5 Suppl 1 (4): 45–9. doi:10.4274/jcrpe.855. PMC 3608006. PMID 23154164.
23. ^ [a b c d] Gaitonde, DY; Rowley, KD; Sweeney, LB (August 2012). "Hypothyroidism: an update". *American Family Physician* (Review). **86** (3): 244–51. PMID 22962987.
24. ^ [a b] Stagnaro-Green, A (February 2012). "Approach to the patient with postpartum thyroiditis". *The Journal of Clinical endocrinology and Metabolism* (Review). **97** (2): 334–42. doi:10.1210/jc.2011-2576. PMID 22312089.
25. ^ Donaldson, M; Jones, J (2013). "Optimising outcome in congenital hypothyroidism; current opinions on best practice in initial assessment and subsequent management". *Journal of Clinical Research in Pediatric Endocrinology* (Review). 5 Suppl 1 (4): 13–22. doi:10.4274/jcrpe.849. PMC 3608009. PMID 23154163.
26. ^ Maia, AL; Goemann, IM; Meyer, EL; Wajner, SM (17 March 2011). "Type 1 iodothyronine deiodinase in human physiology and disease: Deiodinases: the balance of thyroid hormone". *Journal of Endocrinology*. **209** (3): 283–297. doi:10.1530/JOE-10-0481. PMID 21415143.
27. ^ [a b] Cheng, SY; Leonard, JL; Davis, PJ (Apr 2010). "Molecular aspects of thyroid hormone actions". *Endocrine Reviews*. **31** (2): 139–70. doi:10.1210/er.2009-0007. PMC 2852208. PMID 20051527.
28. ^ [a b c d e f g h i] Stagnaro-Green, A; Abalovich, M; Alexander, E; Azizi, F; Mestman, J; Negro, R; Nixon, A; Pearce, EN; Soldin, OP; Sullivan, S; Wiersinga, W; American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum (Oct 2011). "Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum". *Thyroid*. **21** (10): 1081–125. doi:10.1089/thy.2011.0087. PMC 3472679. PMID 21787128.
29. ^ [a b c d] So, M; MacIsaac, RJ; Grossmann M (August 2012). "Hypothyroidism". *Australian Family Physician*. **41** (8): 556–62. PMID 23145394.
30. ^ [a b c] Dons, Robert F.; Jr, Frank H. Wians (2009). *Endocrine and metabolic disorders clinical lab testing manual* (4th ed.). Boca Raton: CRC Press. p. 10. ISBN 9781420079364.
31. ^ [a b c] Bona, G; Prodam, F; Monzani, A (2013). "Subclinical hypothyroidism in children: natural history and when to treat". *Journal of Clinical Research in Pediatric Endocrinology* (Review). 5 Suppl 1 (4): 23–8. doi:10.4274/jcrpe.851. PMC 3608012. PMID 23154159.
32. ^ [a b c d] Fatourechi, V. (2009). "Subclinical Hypothyroidism: An Update for Primary Care Physicians". *Mayo Clinic Proceedings* (Review). **84** (1): 65–71. doi:10.4065/84.1.65. PMC 2664572. PMID 19121255.
33. ^ Baumgartner C, Blum MR, Rodondi N (December 2014). "SSubclinical hypothyroidism: summary of evidence in 2014". *Swiss Medical Weekly* (Review). **144**: w14058. doi:10.4414/smw.2014.14058. PMID 25536449.
34. ^ The Practice Committee of the American Society for Reproductive Medicine (November 2012). "Evaluation and treatment of recurrent pregnancy loss: a committee opinion". *Fertility and Sterility*. **98** (5): 1103–1111. doi:10.1016/j.fertnstert.2012.06.048. PMID 22835448.
35. ^ Regan, L; Backos M; Rai, R (2011-05-19). "The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage" (PDF). *Green-top Guideline No. 17*. London: Royal College of Obstetricians and Gynaecologists. Retrieved 26 December 2013.
36. ^ [a b c d] Charlton, K; Skeaff, S (November 2011). "Iodine fortification". *Current Opinion in Clinical Nutrition and Metabolic Care*. **14** (6): 618–624. doi:10.1097/MCO.0b013e32834b2b30. PMID 21892078.
37. ^ World Health Organization, UNICEF, ICCIDD (2008). *Assessment of iodine deficiency disorders and monitoring their elimination* (PDF) (3rd ed.). Geneva: World Health Organization. ISBN 9789241595827.
38. ^ e-Library of Evidence for Nutrition Actions (eLENA) (2014). "Iodine supplementation during pregnancy". World Health Organization. Retrieved 5 March 2014.
39. ^ "Reaching Optimal Iodine Nutrition in Pregnant and Lactating Women and Young Children" (PDF). *Joint Statement by the World Health Organization and United Nations Children's Fund*. World Health Organization. 2007. Retrieved 5 March 2014.
40. ^ Public Health Committee of the American Thyroid Association; Becker, DV; Braverman, LE; Delange, F; Dunn, JT; Franklyn, JA; Hollowell, JG; Lamm, SH; Mitchell, ML; Pearce, E; Robbins, J; Rovet, JF (Oct 2006). "Iodine supplementation for pregnancy and lactation-United States and Canada: recommendations of the American Thyroid Association". *Thyroid*. **16** (10): 949–51. doi:10.1089/thy.2006.16.949. PMID 17042677.
41. ^ American Academy of Pediatrics; Rose, SR; Section on Endocrinology and Committee on Genetics, American Thyroid Association; Brown, RS; Public Health Committee, Lawson Wilkins Pediatric Endocrine Society; Foley, T; Kaplowitz, PB; Kaye, CI; Sundararajan, S; Varma, SK (Jun 2006). "Update of newborn screening and therapy for congenital hypothyroidism". *Pediatrics*. **117** (6): 2290–303. doi:10.1542/peds.2006-0915. PMID 16740880.
42. ^ Pollitt, RJ (Jun 2009). "Newborn blood spot screening: new opportunities, old problems". *Journal of Inherited Metabolic Disease*. **32** (3): 395–9. doi:10.1007/s10545-009-9962-0. PMID 19412659.
43. ^ LeFevre, ML (24 March 2015). "Screening for Thyroid Dysfunction: U.S. Preventive Services Task Force Recommendation Statement.". *Annals of Internal Medicine*. **162**: 641–50. doi:10.7326/M15-0483.

PMID 25798805.
44. ^ a b Malt, EA; Dahl, RC; Haugsand, TM (February 2013). "Health and disease in adults with Down syndrome". *Tidsskrift for Den Norske Legeforening* (Review). **133** (3): 290–4. doi:10.4045/tidsskr.12.0390. PMID 23381164.
45. ^ Cascorbi, I (August 2012). "Drug interactions--principles, examples and clinical consequences". *Deutsches Ärzteblatt International* (Review). **109** (33–34): 546–55. doi:10.3238/arztebl.2012.0546. PMC 3444856. PMID 23152742.
46. ^ Escobar-Morreale, HF; Botella-Carretero, JI; Escobar del Rey, F; Morreale de Escobar, G (August 2005). "Treatment of hypothyroidism with combinations of levothyroxine plus liothyronine". *The Journal for Clinical Endocrinology and Metabolism* (Review). **90** (8): 4946–54. doi:10.1210/jc.2005-0184. PMID 15928247.
47. ^ a b British Thyroid Association Executive Committee (November 2007). "Armour Thyroid(USP) and combinedthyroxine/tri-iodothyronine as thyroid hormone replacement" (PDF). British Thyroid Association. Retrieved 25 December 2013.
48. ^ a b Wiersinga, Wilmar M.; Duntas, Leonidas; Fadeyev, Valentin; Nygaard, Birte; Vanderpump, Mark P.J. (2012). "2012 ETA guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism". *European Thyroid Journal*. **1** (2): 55–71. doi:10.1159/000339444. PMID 24782999.
49. ^ Ebling PR (2011). "ESA Position Statement on Desiccated Thyroid or Thyroid Extract" (PDF). Endocrine Society of Australia. Retrieved 13 December 2013.
50. ^ Ochs, N; Auer, R; Bauer, DC (June 2008). "Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality". *Annals of Internal Medicine* (Meta-analysis). **148** (11): 832–45. doi:10.7326/0003-4819-148-11-200806030-00225. PMID 18490668.
51. ^ Villar HC, Saconato H, Valente O, Atallah AN; Saconato; Valente; Atallah (2007). Villar, Heloisa Cerqueira Cesar Esteves, ed. "Thyroid hormone replacement for subclinical hypothyroidism". *Cochrane Database of Systematic Reviews* (Review, meta-analysis) (3): CD003419. doi:10.1002/14651858.CD003419.pub2. PMID 17636722.
52. ^ Blum, Manuel R.; Bauer, Douglas C.; Collet, Tinh-Hai; Fink, Howard A.; Cappola, Anne R.; da Costa, Bruno R.; Wirth, Christina D.; Peeters, Robin P.; Åsvold, Bjørn O.; den Elzen, Wendy P. J.; Luben, Robert N.; Imaizumi, Misa; Bremner, Alexandra P.; Gogakos, Apostolos; Eastell, Richard; Kearney, Patricia M.; Strotmeyer, Elsa S.; Wallace, Erin R.; Hoff, Mari; Ceresini, Graziano; Rivadeneira, Fernando; Uitterlinden, André G.; Stott, David J.; Westendorp, Rudi G. J.; Khaw, Kay-Tee; Langhammer, Arnuf; Ferrucci, Luigi; Gussekloo, Jacobijn; Williams, Graham R.; Walsh, John P.; Jüni, Peter; Aujesky, Drahomir; Rodondi, Nicolas (26 May 2015). "Subclinical Thyroid Dysfunction and Fracture Risk". *JAMA*. **313** (20): 2055–65. doi:10.1001/jama.2015.5161. PMID 26010634.
53. ^ Rieben, Carole; Segna, Daniel; da Costa, Bruno R.; Collet, Tinh-Hai; Chaker, Layal; Aubert, Carole E.; Baumgartner, Christine; Almeida, Osvaldo P.; Hogervorst, Eef; Trompet, Stella; Masaki, Kamal; Mooijaart, Simon P.; Gussekloo, Jacobijn; Peeters, Robin P.; Bauer, Douglas C.; Aujesky, Drahomir; Rodondi, Nicolas (30 September 2016). "Subclinical Thyroid Dysfunction and the Risk of Cognitive Decline: a Meta-Analysis of Prospective Cohort Studies". *The Journal of Clinical Endocrinology & Metabolism*: jc.2016–2129. doi:10.1210/jc.2016-2129. PMID 27689250.
54. ^ The Royal College of Physicians, The Association for Clinical Biochemistry The Society for Endocrinology, The British Thyroid Association; et al. (19 November 2008). "The Diagnosis and Management of Primary Hypothyroidism" (pdf). Retrieved 2013-06-16.
55. ^ a b Wiles, Kate Sophie; Jarvis, Sheba; Nelson-Piercy, Catherine (12 October 2015). "Are we overtreating subclinical hypothyroidism in pregnancy?". *BMJ*. **351**: h4726. doi:10.1136/bmj.h4726. PMID 26459315.
56. ^ Reid, SM; Middleton, P; Cossich, MC; Crowther, CA; Bain, E (2013). Reid, Sally M, ed. "Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy". *Cochrane Database of Systematic Reviews*. **5** (5): CD007752. doi:10.1002/14651858.CD007752.pub3. PMID 23728666.
57. ^ Monzani, A; Prodam, F; Rapa, A; Moia, S; Agarla, V; Bellone, S; Bona, G (Jan 2013). "Endocrine disorders in childhood and adolescence. Natural history of subclinical hypothyroidism in children and adolescents and potential effects of replacement therapy: a review". *European Journal of Endocrinology*. **168** (1): R1–R11. doi:10.1530/EJE-12-0656. PMID 22989466.
58. ^ a b Leung, AM; Braverman, LE; Pearce, EN (Nov 13, 2012). "History of U.S. iodine fortification and supplementation". *Nutrients*. **4** (11): 1740–6. doi:10.3390/nu4111740. PMC 3509517. PMID 23201844.
59. ^ a b c d e f g h McAninch, Elizabeth A.; Bianco, Antonio C. (5 January 2016). "The History and Future of Treatment of Hypothyroidism". *Annals of Internal Medicine*. **164** (1): 50. doi:10.7326/M15-1799.
60. ^ Murray, GR (Oct 10, 1891). "Note on the Treatment of Myxoedema by Hypodermic Injections of an Extract of the Thyroid Gland of a Sheep". *British Medical Journal*. **2** (1606): 796–7. doi:10.1136/bmj.2.1606.796. PMC 2273741. PMID 20753415.
61. ^ Fox, EL (Oct 29, 1892). "A Case of Myxoedema Treated by Taking Extract of Thyroid by the Mouth". *British Medical Journal*. **2** (1661): 941. doi:10.1136/bmj.2.1661.941. PMC 2421284. PMID 20753901.
62. ^ a b c d Mooney, CT (May 2011). "Canine hypothyroidism: A review of aetiology and diagnosis". *New Zealand*

*Veterinary Journal*. **59** (3): 105–114. doi:10.1080/00480169.2011.563729. PMID 21541883.

## Further reading [edit]


- "Hypothyroidism; a booklet for patients and their families" (PDF). American Thyroid Association. 2013. Retrieved 2013-12-25.
- "UK Guidelines for the use of thyroid function tests" (PDF). The Association for Clinical Biochemistry, British Thyroid Association and British Thyroid Foundation. 2006. Retrieved 2013-12-25.


## External links [edit]

- Hypothyroidism at DMOZ

| v · t · e · | Diseases of the endocrine system (E00–E35, 240–259) | | |
|---|---|---|---|
| **Pancreas/ glucose metabolism** | **Hypofunction** | Diabetes mellitus · *types:* (type 1 · type 2 · MODY 1 2 3 4 5 6 · · *complications* (coma · angiopathy · ketoacidosis · nephropathy · neuropathy · retinopathy · cardiomyopathy · · *insulin receptor* (Rabson–Mendenhall syndrome) · Insulin resistance · | |
| | **Hyperfunction** | Hypoglycemia · *beta cell* (Hyperinsulinism) · *G cell* (Zollinger–Ellison syndrome) · | |
| **Hypothalamic/** | **Hypothalamus** | *gonadotropin* (Kallmann syndrome · Adiposogenital dystrophy · · *CRH* (Tertiary adrenal insufficiency) · *vasopressin* (Neurogenic diabetes insipidus) · *general* (Hypothalamic hamartoma) · | |
| | **Pituitary** | **Hyperpituitarism** | *anterior* (Acromegaly · Hyperprolactinaemia · Pituitary ACTH hypersecretion · · *posterior* (SIADH) · *general* (Nelson's syndrome) · |
| | | **Hypopituitarism** | *anterior* (Kallmann syndrome · Growth hormone deficiency · Hypoprolactinemia · ACTH deficiency/Secondary adrenal insufficiency · GnRH insensitivity · FSH insensitivity · LH/hCG insensitivity · · *posterior* (Neurogenic diabetes insipidus) · *general* (Empty sella syndrome · Pituitary apoplexy · Sheehan's syndrome · Lymphocytic hypophysitis · · |
| | **Thyroid** | **Hypothyroidism** | Iodine deficiency · Cretinism (Congenital hypothyroidism · · Myxedema · Euthyroid sick syndrome · |
| | | **Hyperthyroidism** | Hyperthyroxinemia (Thyroid hormone resistance · Familial dysalbuminemic hyperthyroxinemia · · Hashitoxicosis · Thyrotoxicosis factitia · Graves' disease · |
| | | **Thyroiditis** | Acute infectious · Subacute (De Quervain's · Subacute lymphocytic · · Autoimmune/chronic (Hashimoto's · Postpartum · Riedel's · · |
| | | | Endemic goitre · Toxic nodular goitre · |

| | | | |
|---|---|---|---|
| **pituitary axes** | | **Goitre** | Toxic multinodular goiter · Thyroid nodule · |
| | **Parathyroid** | **Hypoparathyroidism** | Hypoparathyroidism · Pseudohypoparathyroidism · Pseudopseudohypoparathyroidism · |
| | | **Hyperparathyroidism** | Primary · Secondary · Tertiary · Osteitis fibrosa cystica · |
| | **Adrenal** | **Hyperfunction** | *aldosterone:* Hyperaldosteronism/Primary aldosteronism (Conn syndrome · Bartter syndrome · Glucocorticoid remediable aldosteronism · · AME · Liddle's syndrome · 17α CAH · *cortisol:* Cushing's syndrome (Pseudo-Cushing's syndrome) · *sex hormones:* 21α CAH · 11β CAH · |
| | | **Hypofunction/ Adrenal insufficiency (Addison's, WF)** | *aldosterone:* Hypoaldosteronism (21α CAH · 11β CAH · · *cortisol:* CAH (Lipoid · 3β · 11β · 17α · 21α · · *sex hormones:* 17α CAH · |
| | **Gonads** | | *ovarian:* Polycystic ovary syndrome · Premature ovarian failure · *testicular:* *enzymatic* (5α-reductase deficiency · 17β-hydroxysteroid dehydrogenase deficiency · aromatase excess syndrome) · · *Androgen receptor* (Androgen insensitivity syndrome) · *general:* Hypogonadism (Delayed puberty) · Hypergonadism (Precocious puberty · · Hypoandrogenism · Hypoestrogenism · Hyperandrogenism · Hyperestrogenism · Postorgasmic illness syndrome · |
| **Height** | | | Dwarfism/Short stature (Midget · Laron syndrome · Psychosocial · Ateliosis · · Gigantism · |
| **Multiple** | | | Autoimmune polyendocrine syndrome multiple (APS1 · APS2 · · Carcinoid syndrome · Multiple endocrine neoplasia (1 · 2A · 2B · · Progeria (Werner syndrome · Acrogeria · Metageria · · Woodhouse-Sakati syndrome · |

Categories: Thyroid disease

# Obesity

From Wikipedia, the free encyclopedia

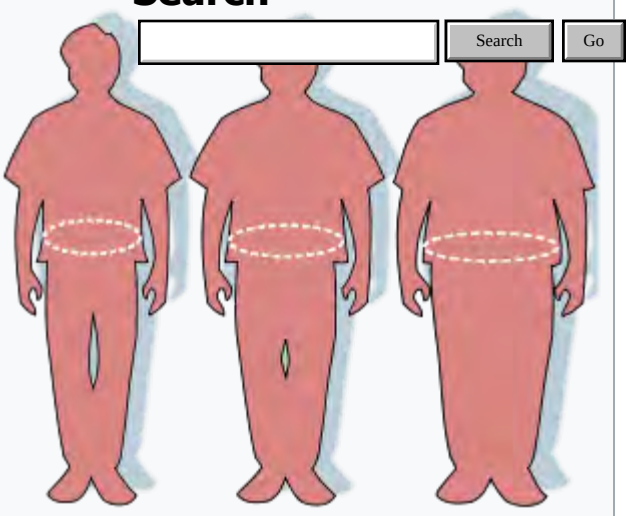
**Obesity** is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health.[1] People are generally considered obese when their body mass index (BMI), a measurement obtained by dividing a person's weight by the square of the person's height, is over 30 kg/m$^2$, with the range 25–30 kg/m$^2$ defined as overweight.[1] Some East Asian countries use lower values.[2] Obesity increases the likelihood of various diseases, particularly heart disease, type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis.[3]

Obesity is most commonly caused by a combination of excessive food intake, lack of physical activity, and genetic susceptibility.[1][4] A few cases are caused primarily by genes, endocrine disorders, medications, or mental illness.[5] Evidence to support the view that obese people eat little yet gain weight due to a slow metabolism is not generally supported.[6] On average, obese people have a greater energy expenditure than their thin counterparts due to the energy required to maintain an increased body mass.[6][7]

Obesity is mostly preventable through a combination of social changes and personal choices.[1] Changes to diet and exercising are the main treatments.[3] Diet quality can be improved by reducing the consumption of energy-dense foods, such as those high in fat and sugars, and by increasing the intake of dietary fiber.[1] Medications may be taken, along with a suitable diet, to reduce appetite or decrease fat absorption.[8] If diet, exercise, and medication are not effective, a gastric balloon or surgery may be performed to reduce stomach volume or bowel length, leading to feeling full earlier or a reduced ability to absorb nutrients from food.[9][10]

Obesity is a leading preventable cause of death worldwide, with increasing rates in adults and children.[1][11] In 2014, 600 million adults (13%) and 42 million children under the age of five were obese.[1] Obesity is more common in women than men.[1] Authorities view it as one of the most serious public health problems of the 21st century.[12] Obesity is stigmatized in much of the modern world (particularly in the Western world), though it was seen as a symbol of wealth and fertility at other times in history and still is in some parts of the world.[3][13] In 2013, the American Medical

**Obesity**



Silhouettes and waist circumferences representing optimal, overweight, and obese

| Classification and external resources | |
|---|---|
| **Specialty** | Endocrinology |
| **ICD-10** | E66 |
| **ICD-9-CM** | 278 |
| **OMIM** | 601665 |
| **DiseasesDB** | 9099 |
| **MedlinePlus** | 007297 |
| **eMedicine** | med/1653 |
| **MeSH** | *C23.888.144.699.500* |

[edit on Wikidata]

Association classified obesity as a disease.[14][15]





# Classification

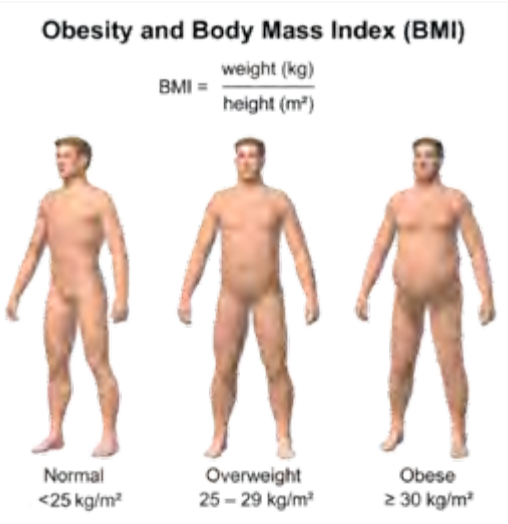
*Main article: Classification of obesity*

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health.[17] It is defined by body mass index (BMI) and further evaluated in terms of fat distribution via the waist–hip ratio and total cardiovascular risk factors.[18][19] BMI is closely related to both percentage body fat and total body fat.[20] In children, a healthy weight varies with age and sex. Obesity in children and adolescents is defined not as an absolute number but in relation to a historical normal group, such that obesity is a BMI greater than the 95th percentile.[21] The reference data on which these percentiles were based date from 1963 to 1994, and thus have not been affected by the recent increases in weight.[22] BMI is defined as the subject's weight divided by the square of their height and is calculated as follows.

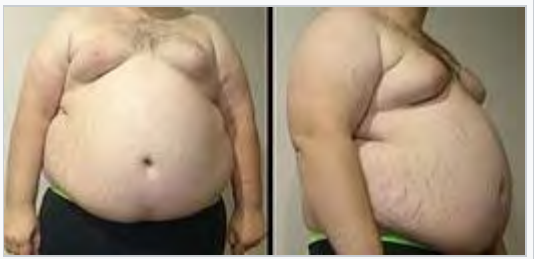
| BMI (kg/m$^2$) | | Classification[16] |
|---|---|---|
| from | up to | |
| | 18.5 | underweight |
| 18.5 | 25.0 | normal weight |
| 25.0 | 30.0 | overweight |
| 30.0 | 35.0 | class I obesity |
| 35.0 | 40.0 | class II obesity |
| 40.0 | | class III obesity |

,

where *m* and *h* are the subject's weight and height



Obesity and BMI


A "super obese" male with a BMI of 53 kg/m$^2$: weight 182 kg (400 lb), height 185 cm (6 ft 1 in)

respectively.

BMI is usually expressed in kilograms per square metre, resulting when weight is measured in kilograms and height in metres. To convert from pounds per square inch multiply by 703 (kg/m$^2$)/(lb/sq in).[23]

The most commonly used definitions, established by the World Health Organization (WHO) in 1997 and published in 2000, provide the values listed in the table.[24][25]

Some modifications to the WHO definitions have been made by particular organizations.[26] The surgical literature breaks down class II and III obesity into further categories whose exact values are still disputed.[27]

- Any BMI ≥ 35 or 40 kg/m$^2$ is *severe obesity*.
- A BMI of ≥ 35 kg/m$^2$ and experiencing obesity-related health conditions or ≥40–44.9 kg/m$^2$ is *morbid obesity*.
- A BMI of ≥ 45 or 50 kg/m$^2$ is *super obesity*.

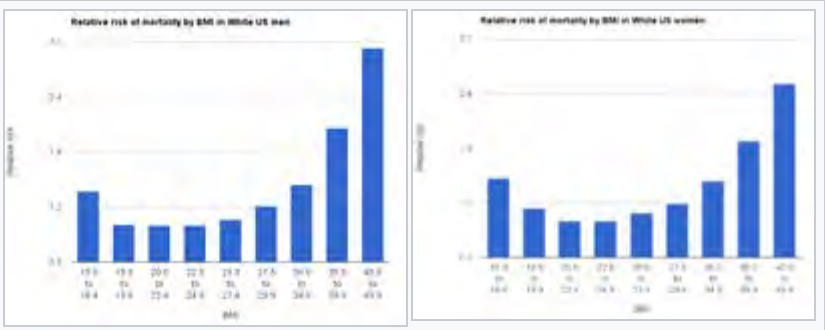
As Asian populations develop negative health consequences at a lower BMI than Caucasians, some nations have redefined obesity; Japan have defined obesity as any BMI greater than 25 kg/m$^2$[2] while China uses a BMI of greater than 28 kg/m$^2$.[26]

# Effects on health

Excessive body weight is associated with various diseases, particularly cardiovascular diseases, diabetes mellitus type 2, obstructive sleep apnea, certain types of cancer, osteoarthritis[3] and asthma.[3][28] As a result, obesity has been found to reduce life expectancy.[3]

## Mortality

Obesity is one of the leading preventable causes of death worldwide.[30][31][32] A number of reviews have found that mortality risk is lowest at a BMI of 20–25 kg/m$^2$[33][34][35] in non-smokers and at 24–27 kg/m$^2$ in current smokers, with risk increasing along with changes in either direction.[36][37] This appears to apply in at least four continents.[35] In contrast, a 2013 review found that grade 1 obesity (BMI 30-35) was not associated with higher mortality than normal weight, and that overweight (BMI 25-30) was associated with "lower" mortality than was normal weight (BMI 18.5-25).[38] Other evidence suggests that the association of BMI and waist circumference with mortality is U- or J-shaped, while the association between waist-to-hip ratio [39]


Relative risk of death over 10 years for white men (left) and women (right) who have never smoked in the United States by BMI.[29]

and waist-to-height ratio with mortality is more positive. In Asians the risk of negative health effects begins to increase between 22–25 kg/m$^2$.[40] A BMI above 32 kg/m$^2$ has been associated with a doubled mortality rate among women over a 16-year period.[41] In the United States obesity is estimated to cause 111,909 to 365,000 deaths per year,[3][32] while 1 million (7.7%) of deaths in Europe are attributed to excess weight.[42][43] On average, obesity reduces life expectancy by six to seven years,[3][44] a BMI of 30–35 kg/m$^2$ reduces life expectancy by two to four years,[34] while severe obesity (BMI > 40 kg/m$^2$) reduces life expectancy by ten years.[34]

## Morbidity

*Main article: Obesity-associated morbidity*

Obesity increases the risk of many physical and mental conditions. These comorbidities are most commonly shown in metabolic syndrome,[3] a combination of medical disorders which includes: diabetes mellitus type 2, high blood pressure, high blood cholesterol, and high triglyceride levels.[45]

Complications are either directly caused by obesity or indirectly related through mechanisms sharing a common cause such as a poor diet or a sedentary lifestyle. The strength of the link between obesity and specific conditions varies. One of the strongest is the link with type 2 diabetes. Excess body fat underlies 64% of cases of diabetes in men and 77% of cases in women.[46]

Health consequences fall into two broad categories: those attributable to the effects of increased fat mass (such as osteoarthritis, obstructive sleep apnea, social stigmatization) and those due to the increased number of fat cells (diabetes, cancer, cardiovascular disease, non-alcoholic fatty liver disease).[3][47] Increases in body fat alter the body's response to insulin, potentially leading to insulin resistance. Increased fat also creates a proinflammatory state,[48][49] and a prothrombotic state.[47][50]

| Medical field | Condition | Medical field | Condition |
|---|---|---|---|
| Cardiology | ▪ coronary heart disease:[51] angina and myocardial infarction<br>▪ congestive heart failure[3]<br>▪ high blood pressure[3]<br>▪ abnormal cholesterol levels[3]<br>▪ deep vein thrombosis and pulmonary embolism[52] | Dermatology | ▪ stretch marks[53]<br>▪ acanthosis nigricans[53]<br>▪ lymphedema[53]<br>▪ cellulitis[53]<br>▪ hirsutism[53]<br>▪ intertrigo[54] |
| Endocrinology and Reproductive medicine | ▪ diabetes mellitus[3]<br>▪ polycystic ovarian syndrome[3]<br>▪ menstrual disorders[3]<br>▪ infertility[3][55]<br>▪ complications during pregnancy[3][55]<br>▪ birth defects[3]<br>▪ intrauterine fetal death[55] | Gastroenterology | ▪ gastroesophageal reflux disease[12]<br>▪ fatty liver disease[12]<br>▪ cholelithiasis (gallstones)[12] |
| Neurology | ▪ stroke[3]<br>▪ meralgia paresthetica[56]<br>▪ migraines[57]<br>▪ carpal tunnel syndrome[58]<br>▪ dementia[59]<br>▪ idiopathic intracranial hypertension[60] | Oncology[62] | ▪ esophageal<br>▪ colorectal<br>▪ pancreatic<br>▪ gallbladder,<br>▪ endometrial<br>▪ kidney<br>▪ Leukemia<br>▪ Hepatocellular |

| | | | |
|---|---|---|---|
| | ▪ multiple sclerosis[61] | | carcinoma[12]<br>▪ malignant melanoma |
| Psychiatry | ▪ depression in women[3]<br>▪ social stigmatization[3] | Respirology | ▪ obstructive sleep apnea[3][28]<br>▪ obesity hypoventilation syndrome[3][28]<br>▪ asthma[3][28]<br>▪ increased complications during general anaesthesia[3] |
| Rheumatology and Orthopedics | ▪ gout[63]<br>▪ poor mobility[64]<br>▪ osteoarthritis[3]<br>▪ low back pain[65] | Urology and Nephrology | ▪ erectile dysfunction[66]<br>▪ urinary incontinence[67]<br>▪ chronic renal failure[68]<br>▪ hypogonadism[69]<br>▪ buried penis[70] |

## Survival paradox

*See also: Obesity paradox*

Although the negative health consequences of obesity in the general population are well supported by the available evidence, health outcomes in certain subgroups seem to be improved at an increased BMI, a phenomenon known as the obesity survival paradox.[71] The paradox was first described in 1999 in overweight and obese people undergoing hemodialysis,[71] and has subsequently been found in those with heart failure and peripheral artery disease (PAD).[72]

In people with heart failure, those with a BMI between 30.0 and 34.9 had lower mortality than those with a normal weight. This has been attributed to the fact that people often lose weight as they become progressively more ill.[73] Similar findings have been made in other types of heart disease. People with class I obesity and heart disease do not have greater rates of further heart problems than people of normal weight who also have heart disease. In people with greater degrees of obesity, however, the risk of further cardiovascular events is increased.[74][75] Even after cardiac bypass surgery, no increase in mortality is seen in the overweight and obese.[76] One study found that the improved survival could be explained by the more aggressive treatment obese people receive after a cardiac event.[77] Another found that if one takes into account chronic obstructive pulmonary disease (COPD) in those with PAD, the benefit of obesity no longer exists.[72]

# Causes

At an individual level, a combination of excessive food energy intake and a lack of physical activity is thought to explain most cases of obesity.[78] A limited number of cases are due primarily to genetics, medical reasons, or psychiatric illness.[5] In contrast, increasing rates of obesity at a societal level are felt to be due to an easily accessible and palatable diet,[79] increased reliance on cars, and mechanized manufacturing.[80][81]

A 2006 review identified ten other possible contributors to the recent increase of obesity: (1) insufficient sleep, (2) endocrine disruptors (environmental pollutants that interfere with lipid metabolism), (3) decreased variability in ambient temperature, (4) decreased rates of smoking, because smoking suppresses appetite, (5) increased use of medications that can cause weight gain (e.g., atypical antipsychotics), (6) proportional increases in ethnic and age groups that tend to be heavier, (7) pregnancy at a later age (which may cause susceptibility to obesity in children), (8) epigenetic risk factors passed on generationally, (9) natural

selection for higher BMI, and (10) assortative mating leading to increased concentration of obesity risk factors (this would increase the number of obese people by increasing population variance in weight).[82] While there is substantial evidence supporting the influence of these mechanisms on the increased prevalence of obesity, the evidence is still inconclusive, and the authors state that these are probably less influential than the ones discussed in the previous paragraph.

## Diet

*Main article: Diet and obesity*

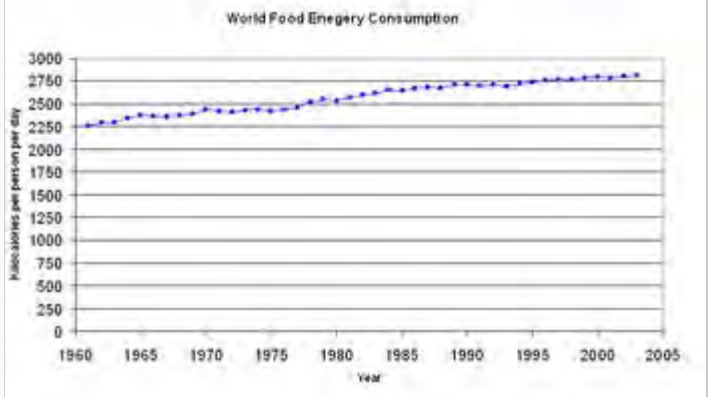
A 2016 review supported excess food as the primary factor.[84] Dietary energy supply per capita varies markedly between different regions and countries. It has also changed significantly over time.[83] From the early 1970s to the late 1990s the average food energy available per person per day (the amount of food bought) increased in all parts of the world except Eastern Europe. The United States had the highest availability with 3,654 calories (15,290 kJ) per person in 1996.[83] This increased further in 2003 to 3,754 calories (15,710 kJ).[83] During the late 1990s Europeans had 3,394 calories (14,200 kJ) per person, in the developing areas of Asia there were 2,648 calories (11,080 kJ) per person, and in sub-Saharan Africa people had 2,176 calories (9,100 kJ) per person.[83][85] Total food energy consumption has been found to be related to obesity.[86]

1961 2001–03

Map of dietary energy availability per person per day in 1961 (left) and 2001–2003 (right)[83] Calories per person per day (kilojoules per person per day)

- no data
- <1,600 (<6,700)
- 1,600–1,800 (6,700–7,500)
- 1,800–2,000 (7,500–8,400)
- 2,000–2,200 (8,400–9,200)
- 2,200–2,400 (9,200–10,000)
- 2,400–2,600 (10,000–10,900)
- 2,600–2,800 (10,900–11,700)
- 2,800–3,000 (11,700–12,600)
- 3,000–3,200 (12,600–13,400)
- 3,200–3,400 (13,400–14,200)
- 3,400–3,600 (14,200–15,100)
- >3,600 (>15,100)

The widespread availability of nutritional guidelines[87] has done little to address the problems of overeating and poor dietary choice.[88] From 1971 to 2000, obesity rates in the United States increased from 14.5% to 30.9%.[89] During the same period, an increase occurred in the average amount of food energy consumed. For women, the average increase was 335 calories (1,400 kJ) per day (1,542 calories (6,450 kJ) in 1971 and 1,877 calories (7,850 kJ) in 2004), while for men the average increase was 168 calories (700 kJ) per day (2,450 calories (10,300 kJ) in 1971 and 2,618 calories (10,950 kJ) in 2004). Most of this extra food energy came from an increase in carbohydrate consumption rather than fat consumption.[90] The primary sources of these extra carbohydrates are sweetened beverages, which now account for almost 25 percent of daily food energy in young adults in America,[91] and potato chips.[92] Consumption of sweetened drinks such as soft drinks, fruit drinks, iced tea, and energy and vitamin water drinks is believed to be contributing to the rising rates of obesity[93][94] and to an increased risk of metabolic syndrome and type 2 diabetes.[95] Vitamin D deficiency is related to diseases associated with obesity.[96]




Average per capita energy consumption of the world from 1961 to 2002[83]

As societies become increasingly reliant on energy-dense, big-portions, and fast-food meals, the association [97]

between fast-food consumption and obesity becomes more concerning. In the United States consumption of fast-food meals tripled and food energy intake from these meals quadrupled between 1977 and 1995.[98]

Agricultural policy and techniques in the United States and Europe have led to lower food prices. In the United States, subsidization of corn, soy, wheat, and rice through the U.S. farm bill has made the main sources of processed food cheap compared to fruits and vegetables.[99] Calorie count laws and nutrition facts labels attempt to steer people toward making healthier food choices, including awareness of how much food energy is being consumed.

Obese people consistently under-report their food consumption as compared to people of normal weight.[100] This is supported both by tests of people carried out in a calorimeter room[101] and by direct observation.

## Sedentary lifestyle

*See also: Sedentary lifestyle and Exercise trends*

A sedentary lifestyle plays a significant role in obesity.[102] Worldwide there has been a large shift towards less physically demanding work,[103][104][105] and currently at least 30% of the world's population gets insufficient exercise.[104] This is primarily due to increasing use of mechanized transportation and a greater prevalence of labor-saving technology in the home.[103][104][105] In children, there appear to be declines in levels of physical activity due to less walking and physical education.[106] World trends in active leisure time physical activity are less clear. The World Health Organization indicates people worldwide are taking up less active recreational pursuits, while a study from Finland[107] found an increase and a study from the United States found leisure-time physical activity has not changed significantly.[108] A 2011 review of physical activity in children found that it may not be a significant contributor.[109]

In both children and adults, there is an association between television viewing time and the risk of obesity.[110][111][112] A review found 63 of 73 studies (86%) showed an increased rate of childhood obesity with increased media exposure, with rates increasing proportionally to time spent watching television.[113]

## Genetics

*Main article: Genetics of obesity*

Like many other medical conditions, obesity is the result of an interplay between genetic and environmental factors. Polymorphisms in various genes controlling appetite and metabolism predispose to obesity when sufficient food energy is present. As of 2006, more than 41 of these sites on the human genome have been linked to the development of obesity when a favorable environment is present.[115] People with two copies of the FTO gene (fat mass and obesity associated gene) have been found on average to weigh 3–4 kg more and have a 1.67-fold greater risk of obesity compared with those without the risk allele.[116] The differences in BMI between people that are due to genetics varies depending on the population examined from 6% to 85%.[117]

Obesity is a major feature in several syndromes, such as Prader–Willi syndrome, Bardet–Biedl syndrome, Cohen syndrome, and MOMO syndrome. (The term "non-syndromic obesity" is sometimes used to exclude these conditions.)[118] In people with early-onset severe obesity (defined by an onset before 10 years of age and body mass index over three standard deviations above normal), 7% harbor a single point

A 1680 painting by Juan Carreno de Miranda of a girl presumed to have Prader–Willi syndrome[114]

DNA mutation.[119]

Studies that have focused on inheritance patterns rather than on specific genes have found that 80% of the offspring of two obese parents were also obese, in contrast to less than 10% of the offspring of two parents who were of normal weight.[120] Different people exposed to the same environment have different risks of obesity due to their underlying genetics.[121]

The thrifty gene hypothesis postulates that, due to dietary scarcity during human evolution, people are prone to obesity. Their ability to take advantage of rare periods of abundance by storing energy as fat would be advantageous during times of varying food availability, and individuals with greater adipose reserves would be more likely to survive famine. This tendency to store fat, however, would be maladaptive in societies with stable food supplies.[122] This theory has received various criticisms, and other evolutionarily-based theories such as the drifty gene hypothesis and the thrifty phenotype hypothesis have also been proposed.[123][124]

## Other illnesses

Certain physical and mental illnesses and the pharmaceutical substances used to treat them can increase risk of obesity. Medical illnesses that increase obesity risk include several rare genetic syndromes (listed above) as well as some congenital or acquired conditions: hypothyroidism, Cushing's syndrome, growth hormone deficiency,[125] and the eating disorders: binge eating disorder and night eating syndrome.[3] However, obesity is not regarded as a psychiatric disorder, and therefore is not listed in the DSM-IVR as a psychiatric illness.[126] The risk of overweight and obesity is higher in patients with psychiatric disorders than in persons without psychiatric disorders.[127]

Certain medications may cause weight gain or changes in body composition; these include insulin, sulfonylureas, thiazolidinediones, atypical antipsychotics, antidepressants, steroids, certain anticonvulsants (phenytoin and valproate), pizotifen, and some forms of hormonal contraception.[3]

## Social determinants

*Main article: Social determinants of obesity*

While genetic influences are important to understanding

obesity, they cannot explain the current dramatic increase seen within specific countries or globally.[128] Though it is accepted that energy consumption in excess of energy expenditure leads to obesity on an individual basis, the cause of the shifts in these two factors on the societal scale is much debated. There are a number of theories as to the cause but most believe it is a combination of various factors.

The correlation between social class and BMI varies globally. A review in 1989 found that in developed countries women of a high social class were less likely to be obese. No significant differences were seen among men of different social classes. In the developing world, women, men, and children from high social classes had greater rates of obesity.[129] An update of this review carried out in 2007 found the same relationships, but they were weaker. The decrease in strength of correlation was felt to be due to the effects of globalization.[130] Among developed countries, levels of adult obesity, and percentage of teenage children who are overweight, are correlated with income inequality. A similar relationship is seen among US states: more adults, even in higher social classes, are obese in more unequal states.[131]

The disease scroll (Yamai no soshi, late 12th century) depicts a woman moneylender with obesity, considered a disease of the rich.

Many explanations have been put forth for associations between BMI and social class. It is thought that in developed countries, the wealthy are able to afford more nutritious food, they are under greater social pressure to remain slim, and have more opportunities along with greater expectations for physical fitness. In undeveloped countries the ability to afford food, high energy expenditure with physical labor, and cultural values favoring a larger body size are believed to contribute to the observed patterns.[130] Attitudes toward body weight held by people in one's life may also play a role in obesity. A correlation in BMI changes over time has been found among friends, siblings, and spouses.[132] Stress and perceived low social status appear to increase risk of obesity.[131][133][134]

Smoking has a significant effect on an individual's weight. Those who quit smoking gain an average of 4.4 kilograms (9.7 lb) for men and 5.0 kilograms (11.0 lb) for women over ten years.[135] However, changing rates of smoking have had little effect on the overall rates of obesity.[136]

In the United States the number of children a person has is related to their risk of obesity. A woman's risk increases by 7% per child, while a man's risk increases by 4% per child.[137] This could be partly explained by the fact that having dependent children decreases physical activity in Western parents.[138]

In the developing world urbanization is playing a role in increasing rate of obesity. In China overall rates of obesity are below 5%; however, in some cities rates of obesity are greater than 20%.[139]

Malnutrition in early life is believed to play a role in the rising rates of obesity in the developing world.[140] Endocrine changes that occur during periods of malnutrition may promote the storage of fat once more food energy becomes available.[140]

Consistent with cognitive epidemiological data, numerous studies confirm that obesity is associated with cognitive deficits.[141] Whether obesity causes cognitive deficits, or vice versa is unclear at present.

## Gut bacteria

*See also: Infectobesity*

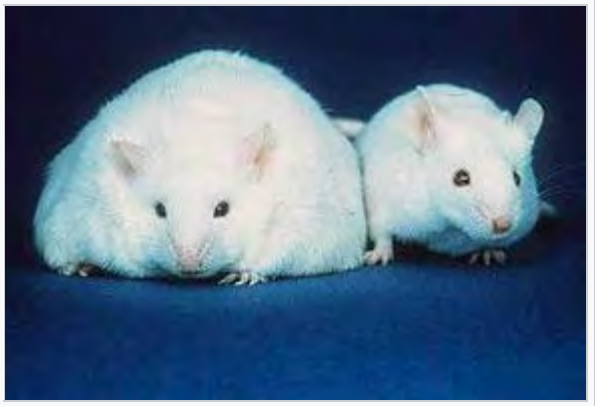
The study of the effect of infectious agents on metabolism is still in its early stages. Gut flora has been shown to differ between lean and obese humans. There is an indication that gut flora in obese and lean individuals can affect the metabolic potential. This apparent alteration of the metabolic potential is believed

to confer a greater capacity to harvest energy contributing to obesity. Whether these differences are the direct cause or the result of obesity has yet to be determined unequivocally.[142]

An association between viruses and obesity has been found in humans and several different animal species. The amount that these associations may have contributed to the rising rate of obesity is yet to be determined.[143]

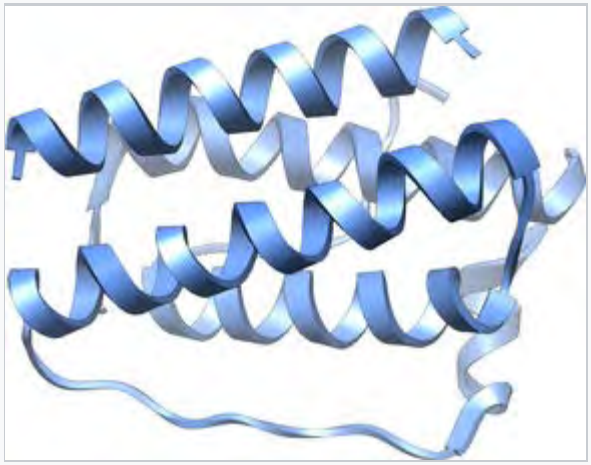
## Pathophysiology

There are many possible pathophysiological mechanisms involved in the development and maintenance of obesity.[144] This field of research had been almost unapproached until the leptin gene was discovered in 1994 by J. M. Friedman's laboratory.[145] These investigators postulated that leptin was a satiety factor. In the ob/ob mouse, mutations in the leptin gene resulted in the obese phenotype opening the possibility of leptin therapy for human obesity. However, soon thereafter J. F. Caro's laboratory could not detect any mutations in the leptin gene in humans with obesity. On the contrary Leptin expression was increased proposing the possibility of Leptin-resistance in human obesity.[146] Since this discovery, many other hormonal mechanisms have been elucidated that participate in the regulation of appetite and food intake, storage patterns of adipose tissue, and development of insulin resistance. Since leptin's discovery, ghrelin, insulin, orexin, PYY 3-36, cholecystokinin, adiponectin, as well as many other mediators have been studied. The adipokines are mediators produced by adipose tissue; their action is thought to modify many obesity-related diseases.



A comparison of a mouse unable to produce leptin thus resulting in obesity (left) and a normal mouse (right)

Leptin and ghrelin are considered to be complementary in their influence on appetite, with ghrelin produced by the stomach modulating short-term appetitive control (i.e. to eat when the stomach is empty and to stop when the stomach is stretched). Leptin is produced by adipose tissue to signal fat storage reserves in the body, and mediates long-term appetitive controls (i.e. to eat more when fat storages are low and less when fat storages are high). Although administration of leptin may be effective in a small subset of obese individuals who are leptin-deficient, most obese individuals are thought to be leptin resistant and have been found to have high levels of leptin.[147] This resistance is thought to explain in part why administration of leptin has not been shown to be effective in suppressing appetite in most obese people.[144]



A graphic depiction of a leptin molecule

While leptin and ghrelin are produced peripherally, they control appetite through their actions on the central nervous system. In particular, they and other appetite-related hormones act on the hypothalamus, a region of the brain central to the regulation of food intake and energy expenditure. There are several circuits within the hypothalamus that contribute to its role in integrating appetite, the melanocortin pathway being the most well understood.[144] The circuit begins with an area of the hypothalamus, the arcuate nucleus, that has outputs to the lateral hypothalamus (LH) and ventromedial hypothalamus (VMH), the brain's feeding and satiety centers, respectively.[148]

The arcuate nucleus contains two distinct groups of neurons.[144] The first group coexpresses neuropeptide Y (NPY) and agouti-related peptide (AgRP) and has stimulatory inputs to the LH and inhibitory inputs to the VMH. The second

group coexpresses pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) and has stimulatory inputs to the VMH and inhibitory inputs to the LH. Consequently, NPY/AgRP neurons stimulate feeding and inhibit satiety, while POMC/CART neurons stimulate satiety and inhibit feeding. Both groups of arcuate nucleus neurons are regulated in part by leptin. Leptin inhibits the NPY/AgRP group while stimulating the POMC/CART group. Thus a deficiency in leptin signaling, either via leptin deficiency or leptin resistance, leads to overfeeding and may account for some genetic and acquired forms of obesity.[144]

# Public health

The World Health Organization (WHO) predicts that overweight and obesity may soon replace more traditional public health concerns such as undernutrition and infectious diseases as the most significant cause of poor health.[149] Obesity is a public health and policy problem because of its prevalence, costs, and health effects.[150] The United States Preventive Services Task Force recommends screening for all adults followed by behavioral interventions in those who are obese.[151] Public health efforts seek to understand and correct the environmental factors responsible for the increasing prevalence of obesity in the population. Solutions look at changing the factors that cause excess food energy consumption and inhibit physical activity. Efforts include federally reimbursed meal programs in schools, limiting direct junk food marketing to children,[152] and decreasing access to sugar-sweetened beverages in schools.[153] The World Health Organization recommends the taxing of sugary drinks.[154] When constructing urban environments, efforts have been made to increase access to parks and to develop pedestrian routes.[155]

## Reports

Many organizations have published reports pertaining to obesity. In 1998, the first US Federal guidelines were published, titled "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report".[156] In 2006 the Canadian Obesity Network published the "Canadian Clinical Practice Guidelines (CPG) on the Management and Prevention of Obesity in Adults and Children". This is a comprehensive evidence-based guideline to address the management and prevention of overweight and obesity in adults and children.[78]

In 2004, the United Kingdom Royal College of Physicians, the Faculty of Public Health and the Royal College of Paediatrics and Child Health released the report "Storing up Problems", which highlighted the growing problem of obesity in the UK.[157] The same year, the House of Commons Health Select Committee published its "most comprehensive inquiry [...] ever undertaken" into the impact of obesity on health and society in the UK and possible approaches to the problem.[158] In 2006, the National Institute for Health and Clinical Excellence (NICE) issued a guideline on the diagnosis and management of obesity, as well as policy implications for non-healthcare organizations such as local councils.[159] A 2007 report produced by Derek Wanless for the King's Fund warned that unless further action was taken, obesity had the capacity to cripple the National Health Service financially.[160]

Comprehensive approaches are being looked at to address the rising rates of obesity. The Obesity Policy Action (OPA) framework divides measure into 'upstream' policies, 'midstream' policies, 'downstream' policies. 'Upstream' policies look at changing society, 'midstream' policies try to alter individuals' behavior to prevent obesity, and 'downstream' policies try to treat currently afflicted people.[161]

# Management

*Main article: Management of obesity*

The main treatment for obesity consists of dieting and physical exercise.[78] Diet programs may produce weight loss over the short term,[162] but maintaining this weight loss is frequently difficult and often requires making exercise and a lower food energy diet a permanent part of a person's lifestyle.[163][164]

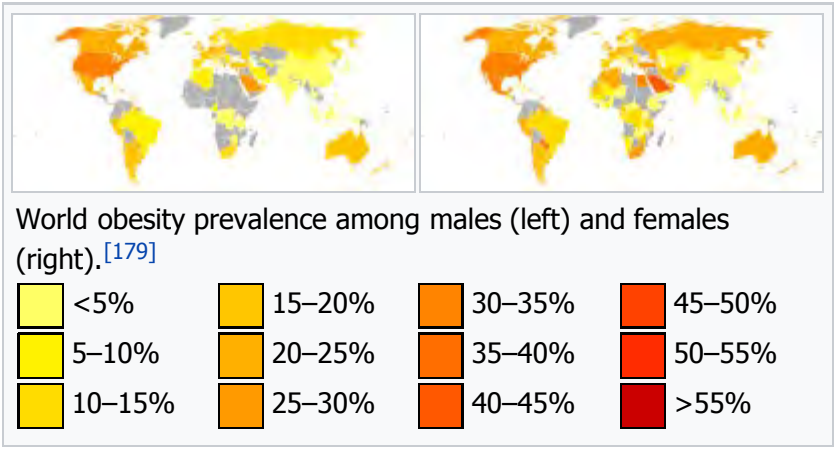
In the short-term low carbohydrate diets appear better than low fat diets for weight loss.[165] In the long term; however, all types of low-carbohydrate and low-fat diets appear equally beneficial.[165][166] A 2014 review found that the heart disease and diabetes risks associated with different diets appear to be similar.[167] Promotion of the Mediterranean diets among the obese may lower the risk of heart disease.[165] Decreased intake of sweet drinks is also related to weight-loss.[165] Success rates of long-term weight loss maintenance with lifestyle changes are low, ranging from 2–20%.[168] Dietary and lifestyle changes are effective in limiting excessive weight gain in pregnancy and improve outcomes for both the mother and the child.[169] Intensive behavioral counseling is recommended in those who are both obese and have other risk factors for heart disease.[170]

Three medications, orlistat, lorcaserin and a combination of phentermine and topiramate are currently available and have evidence for long term use.[8] Weight loss with orlistat is modest, an average of 2.9 kg (6.4 lb) at 1 to 4 years.[171] Its use is associated with high rates of gastrointestinal side effects[171] and concerns have been raised about negative effects on the kidneys.[172] The other two medications are available in the United States but not Europe.[173] Lorcaserin results in an average 3.1 kg weight loss (3% of body weight) greater than placebo over a year;[174] however, it may increase heart valve problems.[173] A combination of phentermine and topiramate is also somewhat effective;[175] however, it may be associated with heart problems.[173] There is no information on how these drugs affect longer-term complications of obesity such as cardiovascular disease or death.[8]

The most effective treatment for obesity is bariatric surgery.[9] Surgery for severe obesity is associated with long-term weight loss, improvement in obesity related conditions,[176] and decreased overall mortality. One study found a weight loss of between 14% and 25% (depending on the type of procedure performed) at 10 years, and a 29% reduction in all cause mortality when compared to standard weight loss measures.[177] Complications occur in about 17% of cases and reoperation is needed in 7% of cases.[176] Due to its cost and risks, researchers are searching for other effective yet less invasive treatments including devices that occupy space in the stomach.[178]

# Epidemiology

*Main article: Epidemiology of obesity*



World obesity prevalence among males (left) and females (right).[179]

In earlier historical periods obesity was rare, and achievable only by a small elite, although already recognised as a problem for health. But as prosperity increased in the Early Modern period, it affected increasingly larger groups of the population.[180] In 1997 the WHO formally recognized obesity as a global epidemic.[91] As of 2008 the WHO estimates that at least 500 million adults (greater than 10%) are obese, with higher rates among women than men.[181] The rate of obesity also increases with age at least up to 50 or 60 years old[182] and severe obesity in the United States, Australia, and Canada is increasing faster than the overall rate of obesity.[27][183][184]

Once considered a problem only of high-income countries, obesity rates are rising worldwide and affecting both the developed and developing world.[42] These increases have been felt most dramatically in urban settings.[181] The only remaining region of the world where obesity is not common is sub-Saharan Africa.[3]

# History

## Etymology

*Obesity* is from the Latin *obesitas*, which means "stout, fat, or plump". *Ēsus* is the past participle of *edere* (to eat), with *ob* (over) added to it.[185] *The Oxford English Dictionary* documents its first usage in 1611 by Randle Cotgrave.[186]

## Historical attitudes

Ancient Greek medicine recognizes obesity as a medical disorder, and records that the Ancient Egyptians saw it in the same way.[180] Hippocrates wrote that "Corpulence is not only a disease itself, but the harbinger of others".[3] The Indian surgeon Sushruta (6th century BCE) related obesity to diabetes and heart disorders.[188] He recommended physical work to help cure it and its side effects.[188] For most of human history mankind struggled with food scarcity.[189] Obesity has thus historically been viewed as a sign of wealth and prosperity. It was common among high officials in Europe in the Middle Ages and the Renaissance[187] as well as in Ancient East Asian civilizations.[190] In the 17th century, English medical author Tobias Venner is credited with being one of the first to refer to the term as a societal disease in a published English language book.[180][191]

During the Middle Ages and the Renaissance obesity was often seen as a sign of wealth, and was relatively common among the elite: *The Tuscan General Alessandro del Borro*, attributed to Charles Mellin, 1645[187]

With the onset of the industrial revolution it was realized that the military and economic might of nations were dependent on both the body size and strength of their soldiers and workers.[91] Increasing the average body mass index from what is now considered underweight to what is now the normal range played a significant role in the development of industrialized societies.[91] Height and weight thus both increased through the 19th century in the developed world. During the 20th century, as populations reached their genetic potential for height, weight began increasing much more than height, resulting in obesity.[91] In the 1950s increasing wealth in the developed world decreased child mortality, but as body weight increased heart and kidney disease became more common.[91][192] During this time period, insurance companies realized the connection between weight and life expectancy and increased premiums for the obese.[3]

Many cultures throughout history have viewed obesity as the result of a character flaw. The *obesus* or fat character in Greek comedy was a glutton and figure of mockery. During Christian times the food was viewed as a gateway to the sins of sloth and lust.[13] In modern Western culture, excess weight is often regarded as unattractive, and obesity is commonly associated with various negative stereotypes. People of all ages can face social stigmatization, and may be targeted by bullies or shunned by their peers.[193]

Public perceptions in Western society regarding healthy body weight differ from those regarding the weight that is considered ideal – and both have changed since the beginning of the 20th century. The weight that is viewed as an ideal has become lower since the 1920s. This is illustrated by the fact that the average height of Miss America pageant winners increased by 2% from 1922 to 1999, while their average weight decreased by 12%.[194] On the other hand, people's views concerning healthy weight have changed in the opposite direction. In Britain, the

*Venus of Willendorf* created 24,000–22,000 BC

weight at which people considered themselves to be overweight was significantly higher in 2007 than in 1999.[195] These changes are believed to be due to increasing rates of adiposity leading to increased acceptance of extra body fat as being normal.[195]

Obesity is still seen as a sign of wealth and well-being in many parts of Africa. This has become particularly common since the HIV epidemic began.[3]

### The arts

The first sculptural representations of the human body 20,000–35,000 years ago depict obese females. Some attribute the Venus figurines to the tendency to emphasize fertility while others feel they represent "fatness" in the people of the time.[13] Corpulence is, however, absent in both Greek and Roman art, probably in keeping with their ideals regarding moderation. This continued through much of Christian European history, with only those of low socioeconomic status being depicted as obese.[13]

During the Renaissance some of the upper class began flaunting their large size, as can be seen in portraits of Henry VIII of England and Alessandro del Borro.[13] Rubens (1577–1640) regularly depicted full-bodied women in his pictures, from which derives the term Rubenesque. These women, however, still maintained the "hourglass" shape with its relationship to fertility.[196] During the 19th century, views on obesity changed in the Western world. After centuries of obesity being synonymous with wealth and social status, slimness began to be seen as the desirable standard.[13]

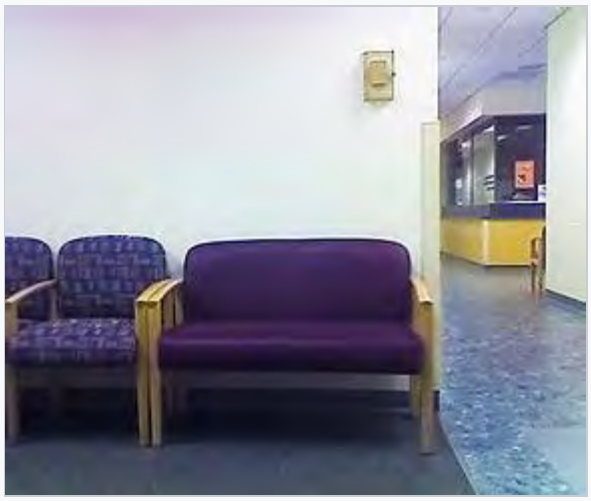
## Society and culture

### Economic impact

In addition to its health impacts, obesity leads to many problems including disadvantages in employment[197][198] and increased business costs. These effects are felt by all levels of society from individuals, to corporations, to governments.

In 2005, the medical costs attributable to obesity in the US were an estimated $190.2 billion or 20.6% of all medical expenditures,[199][200][201] while the cost of obesity in Canada was estimated at CA$2 billion in 1997 (2.4% of total health costs).[78] The total annual direct cost of overweight and obesity in Australia in 2005 was A$21 billion. Overweight and obese Australians also received A$35.6 billion in government subsidies.[202] The estimate range for annual expenditures on diet products is $40 billion to $100 billion in the US alone.[203]

Obesity prevention programs have been found to reduce the cost of treating obesity-related disease. However, the longer people live, the more medical costs they incur. Researchers, therefore, conclude that reducing obesity may improve the public's health, but it is unlikely to reduce overall health spending.[204]



Services must accommodate obese people with specialist equipment such as much wider chairs.[205]

Obesity can lead to social stigmatization and disadvantages in employment.[197] When compared to their normal weight counterparts, obese workers on average have higher rates of absenteeism from work and take more disability leave, thus increasing costs for employers and decreasing productivity.[206] A study examining Duke University employees found that people with a BMI over 40 kg/m$^2$ filed twice as many workers' compensation claims as those whose BMI was 18.5–24.9 kg/m$^2$. They also had more than 12 times as many lost work days. The most common injuries in this group were due to falls and lifting, thus affecting the lower extremities, wrists or hands, and backs.[207] The Alabama State Employees' Insurance Board approved a controversial plan to charge obese workers $25 a month for health insurance that would otherwise be free unless they take steps to lose weight and improve their health. These measures started in January 2010 and apply to those state workers whose BMI exceeds 35 kg/m$^2$ and who fail to make improvements in their health after one year.[208]

Some research shows that obese people are less likely to be hired for a job and are less likely to be promoted.[193] Obese people are also paid less than their non-obese counterparts for an equivalent job; obese women on average make 6% less and obese men make 3% less.[209]

Specific industries, such as the airline, healthcare and food industries, have special concerns. Due to rising rates of obesity, airlines face higher fuel costs and pressures to increase seating width.[210] In 2000, the extra weight of obese passengers cost airlines US$275 million.[211] The healthcare industry has had to invest in special facilities for handling severely obese patients, including special lifting equipment and bariatric ambulances.[212] Costs for restaurants are increased by litigation accusing them of causing obesity.[213] In 2005 the US Congress discussed legislation to prevent civil lawsuits against the food industry in relation to obesity; however, it did not become law.[213]

With the American Medical Association's 2013 classification of obesity as a chronic disease,[14] it is thought that health insurance companies will more likely pay for obesity treatment, counseling and surgery, and the cost of research and development of fat treatment pills or gene therapy treatments should be more affordable if insurers help to subsidize their cost.[214] The AMA classification is not legally binding, however, so health insurers still have the right to reject coverage for a treatment or procedure.[214]

In 2014, The European Court of Justice ruled that morbid obesity is a disability. The Court argued that if an employee's obesity prevents him from "full and effective participation of that person in professional life on an equal basis with other workers", then it shall be considered a disability and that firing someone on such grounds is discriminatory.[215]

## Size acceptance

*See also: Fat acceptance movement, Social stigma of obesity, and Health at Every Size*

The principal goal of the fat acceptance movement is to decrease discrimination against people who are overweight and obese.[216][217] However, some in the movement are also attempting to challenge the established relationship between [218]

obesity and negative health outcomes.

A number of organizations exist that promote the acceptance of obesity. They have increased in prominence in the latter half of the 20th century.[219] The US-based National Association to Advance Fat Acceptance (NAAFA) was formed in 1969 and describes itself as a civil rights organization dedicated to ending size discrimination.[220]

The International Size Acceptance Association (ISAA) is a non-governmental organization (NGO) which was founded in 1997. It has more of a global orientation and describes its mission as promoting size acceptance and helping to end weight-based discrimination.[221] These groups often argue for the recognition of obesity as a disability under the US Americans With Disabilities Act (ADA). The American legal system, however, has decided that the potential public health costs exceed the benefits of extending this anti-discrimination law to cover obesity.[218]

United States President William Howard Taft was often ridiculed for being overweight

### Industry influence on research

In 2015 the *New York Times* published an article on the Global Energy Balance Network, a nonprofit founded in 2014 that advocated for people to focus on increasing exercise rather than reducing calorie intake to avoid obesity and to be healthy. The organization was founded with at least $1.5M in funding from the Coca-Cola Company and the company had provided $4M in research funding to the two founding scientists Gregory A. Hand and Steven N. Blair, since 2008.[222][223]

## Childhood obesity

*Main article: Childhood obesity*

The healthy BMI range varies with the age and sex of the child. Obesity in children and adolescents is defined as a BMI greater than the 95th percentile.[21] The reference data that these percentiles are based on is from 1963 to 1994 and thus has not been affected by the recent increases in rates of obesity.[22] Childhood obesity has reached epidemic proportions in the 21st century, with rising rates in both the developed and the developing world. Rates of obesity in Canadian boys have increased from 11% in the 1980s to over 30% in the 1990s, while during this same time period rates increased from 4 to 14% in Brazilian children.[224]

As with obesity in adults, many factors contribute to the rising rates of childhood obesity. Changing diet and decreasing physical activity are believed to be the two most important causes for the recent increase in the incidence of child obesity.[225] Because childhood obesity often persists into adulthood and is associated with numerous chronic illnesses, children who are obese are often tested for hypertension, diabetes, hyperlipidemia, and fatty liver.[78] Treatments used in children are primarily lifestyle interventions and behavioral techniques, although efforts to increase activity in children have had little success.[226] In the United States, medications are not FDA approved for use in this age group.[224]

# Other animals

*Main article: Obesity in pets*

Obesity in pets is common in many countries. In the United States, 23–41% of dogs are overweight, and about 5.1% are obese.[227] The rate of obesity in cats was slightly higher at 6.4%.[227] In Australia the rate of obesity among dogs in a veterinary setting has been found to be 7.6%.[228] The risk of obesity in dogs is related to whether or not their owners are obese; however, there is no similar correlation between cats and their owners.[229]

# Notes


1. ^ *a b c d e f g h* "Obesity and overweight Fact sheet N°311". *WHO*. January 2015. Retrieved 2 February 2016.
2. ^ *a b* Kanazawa, M; Yoshiike, N; Osaka, T; Numba, Y; Zimmet, P; Inoue, S (2005). "Criteria and classification of obesity in Japan and Asia-Oceania." *World review of nutrition and dietetics*. **94**: 1–12. doi:10.1159/000088200. PMID 16145245.
3. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af ag* Haslam DW, James WP (2005). "Obesity". *Lancet* (Review). **366** (9492): 1197–209. doi:10.1016/S0140-6736(05)67483-1. PMID 16198769.
4. ^ Yazdi, FT; Clee, SM; Meyre, D (2015). "Obesity genetics in mouse and human: back and forth, and back again." *PeerJ*. **3**: e856. doi:10.7717/peerj.856. PMC 4375971. PMID 25825681.
5. ^ *a b* Bleich S, Cutler D, Murray C, Adams A (2008). "Why is the developed world obese?". *Annu Rev Public Health* (Research Support). **29**: 273–95. doi:10.1146/annurev.publhealth.29.020907.090954. PMID 18173389.
6. ^ *a b* *Oxford Handbook of Medical Sciences* (2nd ed.). Oxford: OUP Oxford. 2011. p. 180. ISBN 9780191652295.
7. ^ Kushner, Robert (2007). *Treatment of the Obese Patient (Contemporary Endocrinology)*. Totowa, NJ: Humana Press. p. 158. ISBN 1-59745-400-1. Retrieved April 5, 2009.
8. ^ *a b c* Yanovski SZ, Yanovski JA (Jan 1, 2014). "Long-term drug treatment for obesity: a systematic and clinical review." *JAMA: The Journal of the American Medical Association* (Review). **311** (1): 74–86. doi:10.1001/jama.2013.281361. PMC 3928674. PMID 24231879.
9. ^ *a b* Colquitt, JL; Pickett, K; Loveman, E; Frampton, GK (Aug 8, 2014). "Surgery for weight loss in adults". *The Cochrane database of systematic reviews* (Meta-analysis, Review). **8**: CD003641. doi:10.1002/14651858.CD003641.pub4. PMID 25105982.
10. ^ Imaz I, Martínez-Cervell C, García-Alvarez EE, Sendra-Gutiérrez JM, González-Enríquez J (July 2008). "Safety and effectiveness of the intragastric balloon for obesity. A meta-analysis". *Obes Surg*. **18** (7): 841–6. doi:10.1007/s11695-007-9331-8. PMID 18459025.
11. ^ *Encyclopedia of Mental Health* (2 ed.). Academic Press. 2015. p. 158. ISBN 9780123977533.
12. ^ *a b c d e* Dibaise JK, Foxx-Orenstein AE (July 2013). "Role of the gastroenterologist in managing obesity". *Expert Review of Gastroenterology & Hepatology* (Review). **7** (5): 439–51. doi:10.1586/17474124.2013.811061. PMID 23899283.
13. ^ *a b c d e f* Woodhouse R (2008). "Obesity in art: A brief overview". *Front Horm Res*. Frontiers of Hormone Research. **36**: 271–86. doi:10.1159/000115370. ISBN 978-3-8055-8429-6. PMID 18230908.
14. ^ *a b* Pollack, Andrew (June 18, 2013). "A.M.A. Recognizes Obesity as a Disease". *New York Times*. Archived from the original on June 18, 2013.
15. ^ Weinstock, Matthew (June 21, 2013). "The Facts About Obesity". *H&HN*. American Hospital Association. Retrieved June 24, 2013.
16. ^ "BMI classification". *World Health Organization*. Retrieved 15 February 2014.
17. ^ WHO 2000 p.6
18. ^ Sweeting HN (2007). "Measurement and Definitions of Obesity In Childhood and Adolescence: A field guide for the uninitiated". *Nutr J*. **6** (1): 32. doi:10.1186/1475-2891-6-32. PMC 2164947. PMID 17963490.
19. ^ NHLBI p.xiv
20. ^ Gray DS, Fujioka K (1991). "Use of relative weight and Body Mass Index for the determination of adiposity". *J Clin Epidemiol*. **44** (6): 545–50. doi:10.1016/0895-4356(91)90218-X. PMID 2037859.
21. ^ *a b* "Healthy Weight: Assessing Your Weight: BMI: About BMI for Children and Teens". Center for disease control and prevention. Retrieved April 6, 2009.
22. ^ *a b* Flegal KM, Ogden CL, Wei R, Kuczmarski RL, Johnson CL (June 2001). "Prevalence of overweight in US

children: comparison of US growth charts from the Centers for Disease Control and Prevention with other reference values for body mass index". *Am. J. Clin. Nutr.* **73** (6): 1086–93. PMID 11382664.

23. ^ 1 (lb/sq in) is more precisely 703.06957964 (kg/m$^2$).
24. ^ WHO 2000 p.9
25. ^ Nikcevic, Ana V.; Kuczmierczyk, Andrzej R.; Bruch, Michael (2009). *Formulation and Treatment in Clinical Health Psychology*. Routledge. ISBN 9781135452087.
26. ^ *a b* Bei-Fan Z (December 2002). "Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults: study on optimal cut-off points of body mass index and waist circumference in Chinese adults". *Asia Pac J Clin Nutr*. 11 Suppl 8: S685–93. doi:10.1046/j.1440-6047.11.s8.9.x. PMID 12046553.
27. ^ *a b* Sturm R (July 2007). "Increases in morbid obesity in the USA: 2000–2005". *Public Health*. **121** (7): 492–6. doi:10.1016/j.puhe.2007.01.006. PMC 2864630. PMID 17399752.
28. ^ *a b c d* Poulain M, Doucet M, Major GC, Drapeau V, Sériès F, Boulet LP, Tremblay A, Maltais F (April 2006). "The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies". *CMAJ*. **174** (9): 1293–9. doi:10.1503/cmaj.051299. PMC 1435949. PMID 16636330.
29. ^ Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB, Beeson WL, Clipp SL, English DR, Folsom AR, Freedman DM, Giles G, Hakansson N, Henderson KD, Hoffman-Bolton J, Hoppin JA, Koenig KL, Lee IM, Linet MS, Park Y, Pocobelli G, Schatzkin A, Sesso HD, Weiderpass E, Willcox BJ, Wolk A, Zeleniuch-Jacquotte A, Willett WC, Thun MJ (2010). "Body-mass index and mortality among 1.46 million white adults". *The New England Journal of Medicine*. **363** (23): 2211–9. doi:10.1056/NEJMoa1000367. PMC 3066051. PMID 21121834.
30. ^ Barness LA, Opitz JM, Gilbert-Barness E (December 2007). "Obesity: genetic, molecular, and environmental aspects". *American Journal of Medical Genetics*. **143A** (24): 3016–34. doi:10.1002/ajmg.a.32035. PMID 18000969.
31. ^ Mokdad AH, Marks JS, Stroup DF, Gerberding JL (March 2004). "Actual causes of death in the United States, 2000" (PDF). *JAMA*. **291** (10): 1238–45. doi:10.1001/jama.291.10.1238. PMID 15010446.
32. ^ *a b* Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB (October 1999). "Annual deaths attributable to obesity in the United States". *JAMA*. **282** (16): 1530–8. doi:10.1001/jama.282.16.1530. PMID 10546692.
33. ^ Aune, D; Sen, A; Prasad, M; Norat, T; Janszky, I; Tonstad, S; Romundstad, P; Vatten, LJ (4 May 2016). "BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants.". *BMJ (Clinical research ed.)*. **353**: i2156. doi:10.1136/bmj.i2156. PMC 4856854. PMID 27146380.
34. ^ *a b c* Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R (March 2009). "Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies". *Lancet*. **373** (9669): 1083–96. doi:10.1016/S0140-6736(09)60318-4. PMC 2662372. PMID 19299006.
35. ^ *a b* "Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents". *Lancet*. 13 July 2016. doi:10.1016/S0140-6736(16)30175-1.
36. ^ Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW (October 1999). "Body-mass index and mortality in a prospective cohort of U.S. adults". *N. Engl. J. Med.* **341** (15): 1097–105. doi:10.1056/NEJM199910073411501. PMID 10511607.
37. ^ Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, van der Schouw YT, Spencer E, Moons KG, Tjønneland A, et al. (November 2008). "General and abdominal adiposity and risk of death in Europe". *N. Engl. J. Med.* **359** (20): 2105–20. doi:10.1056/NEJMoa0801891. PMID 19005195.
38. ^ Flegal, Katherine M.; Kit, Brian K.; Orpana, Heather; Graubard, Barry I. (2 January 2013). "Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories". *JAMA*. **309** (1): 71–82. doi:10.1001/jama.2012.113905. PMID 23280227.
39. ^ Carmienke, S; Freitag, M H; Pischon, T; Schlattmann, P; Fankhaenel, T; Goebel, H; Gensichen, J (20 March 2013). "General and abdominal obesity parameters and their combination in relation to mortality: a systematic review and meta-regression analysis". *European Journal of Clinical Nutrition*. **67** (6): 573–585. doi:10.1038/ejcn.2013.61.
40. ^ WHO Expert, Consultation (Jan 10, 2004). "Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies.". *Lancet*. **363** (9403): 157–63. doi:10.1016/s0140-6736(03)15268-3. PMID 14726171.
41. ^ Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, Hennekens CH, Speizer FE (1995). "Body weight and mortality among women". *N. Engl. J. Med.* **333** (11): 677–85. doi:10.1056/NEJM199509143331101. PMID 7637744.
42. ^ *a b* Tsigos C, Hainer V, Basdevant A, Finer N, Fried M, Mathus-Vliegen E, Micic D, Maislos M, Roman G, Schutz Y,

Toplak H, Zahorska-Markiewicz B (April 2008). "Management of Obesity in Adults: European Clinical Practice Guidelines" (PDF). *The European Journal of Obesity*. **1** (2): 106–16. doi:10.1159/000126822. PMID 20054170.

43. ^ Fried M, Hainer V, Basdevant A, Buchwald H, Deitel M, Finer N, Greve JW, Horber F, Mathus-Vliegen E, Scopinaro N, Steffen R, Tsigos C, Weiner R, Widhalm K (April 2007). "Inter-disciplinary European guidelines on surgery of severe obesity". *Int J Obes (Lond)*. **31** (4): 569–77. doi:10.1038/sj.ijo.0803560. PMID 17325689.
44. ^ Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L (January 2003). "Obesity in adulthood and its consequences for life expectancy: A life-table analysis". *Annals of Internal Medicine*. **138** (1): 24–32. doi:10.7326/0003-4819-138-1-200301070-00008. PMID 12513041.
45. ^ Grundy SM (2004). "Obesity, metabolic syndrome, and cardiovascular disease". *J. Clin. Endocrinol. Metab.* **89** (6): 2595–600. doi:10.1210/jc.2004-0372. PMID 15181029.
46. ^ Seidell 2005 p.9
47. ^ *a b* Bray GA (2004). "Medical consequences of obesity". *J. Clin. Endocrinol. Metab.* **89** (6): 2583–9. doi:10.1210/jc.2004-0535. PMID 15181027.
48. ^ Shoelson SE, Herrero L, Naaz A (May 2007). "Obesity, inflammation, and insulin resistance". *Gastroenterology*. **132** (6): 2169–80. doi:10.1053/j.gastro.2007.03.059. PMID 17498510.
49. ^ Shoelson SE, Lee J, Goldfine AB (July 2006). "Inflammation and insulin resistance". *J. Clin. Invest.* **116** (7): 1793–801. doi:10.1172/JCI29069. PMC 1483173. PMID 16823477.
50. ^ Dentali F, Squizzato A, Ageno W (July 2009). "The metabolic syndrome as a risk factor for venous and arterial thrombosis". *Semin. Thromb. Hemost.* **35** (5): 451–7. doi:10.1055/s-0029-1234140. PMID 19739035.
51. ^ Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated, Effects); Lu, Y; Hajifathalian, K; Ezzati, M; Woodward, M; Rimm, EB; Danaei, G (15 March 2014). "Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants.". *Lancet (London, England)*. **383** (9921): 970–83. doi:10.1016/S0140-6736(13)61836-X. PMID 24269108.
52. ^ Darvall KA, Sam RC, Silverman SH, Bradbury AW, Adam DJ (February 2007). "Obesity and thrombosis". *Eur J Vasc Endovasc Surg*. **33** (2): 223–33. doi:10.1016/j.ejvs.2006.10.006. PMID 17185009.
53. ^ *a b c d e* Yosipovitch G, DeVore A, Dawn A (June 2007). "Obesity and the skin: skin physiology and skin manifestations of obesity". *J. Am. Acad. Dermatol.* **56** (6): 901–16; quiz 917–20. doi:10.1016/j.jaad.2006.12.004. PMID 17504714.
54. ^ Hahler B (June 2006). "An overview of dermatological conditions commonly associated with the obese patient". *Ostomy Wound Manage*. **52** (6): 34–6, 38, 40 passim. PMID 16799182.
55. ^ *a b c* Arendas K, Qiu Q, Gruslin A (2008). "Obesity in pregnancy: pre-conceptional to postpartum consequences". *Journal of Obstetrics and Gynaecology Canada : JOGC = Journal D'obstétrique Et Gynécologie Du Canada : JOGC*. **30** (6): 477–88. PMID 18611299.
56. ^ Harney D, Patijn J (2007). "Meralgia paresthetica: diagnosis and management strategies". *Pain Med* (Review). **8** (8): 669–77. doi:10.1111/j.1526-4637.2006.00227.x. PMID 18028045.
57. ^ Bigal ME, Lipton RB (January 2008). "Obesity and chronic daily headache". *Curr Pain Headache Rep* (Review). **12** (1): 56–61. doi:10.1007/s11916-008-0011-8. PMID 18417025.
58. ^ Sharifi-Mollayousefi A, Yazdchi-Marandi M, Ayramlou H, Heidari P, Salavati A, Zarrintan S, Sharifi-Mollayousefi A (February 2008). "Assessment of body mass index and hand anthropometric measurements as independent risk factors for carpal tunnel syndrome". *Folia Morphol. (Warsz)*. **67** (1): 36–42. PMID 18335412.
59. ^ Beydoun MA, Beydoun HA, Wang Y (May 2008). "Obesity and central obesity as risk factors for incident dementia and its subtypes: A systematic review and meta-analysis". *Obes Rev* (Meta-analysis). **9** (3): 204–18. doi:10.1111/j.1467-789X.2008.00473.x. PMID 18331422.
60. ^ Wall M (March 2008). "Idiopathic intracranial hypertension (pseudotumor cerebri)". *Curr Neurol Neurosci Rep* (Review). **8** (2): 87–93. doi:10.1007/s11910-008-0015-0. PMID 18460275.
61. ^ Munger KL, Chitnis T, Ascherio A (2009). "Body size and risk of MS in two cohorts of US women". *Neurology* (Comparative Study). **73** (19): 1543–50. doi:10.1212/WNL.0b013e3181c0d6e0. PMC 2777074. PMID 19901245.
62. ^ Basen-Engquist, Karen; Chang, Maria (16 November 2010). "Obesity and Cancer Risk: Recent Review and Evidence". *Current Oncology Reports*. **13** (1): 71–76. doi:10.1007/s11912-010-0139-7. PMID 21080117.
63. ^ Aune, D; Norat, T; Vatten, LJ (December 2014). "Body mass index and the risk of gout: a systematic review and dose-response meta-analysis of prospective studies.". *European journal of nutrition*. **53** (8): 1591–601. doi:10.1007/s00394-014-0766-0. PMID 25209031.
64. ^ Tukker A, Visscher TL, Picavet HS (April 2008). "Overweight and health problems of the lower extremities: osteoarthritis, pain and disability". *Public Health Nutr* (Research Support). **12** (3): 1–10. doi:10.1017/S1368980008002103. PMID 18426630.

65. ^ Molenaar EA, Numans ME, van Ameijden EJ, Grobbee DE (November 2008). "[Considerable comorbidity in overweight adults: results from the Utrecht Health Project]". *Ned Tijdschr Geneeskd* (English abstract) (in Dutch). **152** (45): 2457–63. PMID 19051798.
66. ^ Corona, G; Rastrelli, G; Filippi, S; Vignozzi, L; Mannucci, E; Maggi, M (2014). "Erectile dysfunction and central obesity: an Italian perspective.". *Asian Journal of Andrology*. **16** (4): 581–91. doi:10.4103/1008-682X.126386. PMC 4104087. PMID 24713832.
67. ^ Hunskaar S (2008). "A systematic review of overweight and obesity as risk factors and targets for clinical intervention for urinary incontinence in women". *Neurourol. Urodyn.* (Review). **27** (8): 749–57. doi:10.1002/nau.20635. PMID 18951445.
68. ^ Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyrén O (2006). "Obesity and risk for chronic renal failure". *J. Am. Soc. Nephrol.* (Research Support). **17** (6): 1695–702. doi:10.1681/ASN.2005060638. PMID 16641153.
69. ^ Makhsida N, Shah J, Yan G, Fisch H, Shabsigh R (September 2005). "Hypogonadism and metabolic syndrome: Implications for testosterone therapy". *J. Urol.* (Review). **174** (3): 827–34. doi:10.1097/01.ju.0000169490.78443.59. PMID 16093964.
70. ^ Pestana IA, Greenfield JM, Walsh M, Donatucci CF, Erdmann D (October 2009). "Management of "buried" penis in adulthood: an overview". *Plast. Reconstr. Surg.* (Review). **124** (4): 1186–95. doi:10.1097/PRS.0b013e3181b5a37f. PMID 19935302.
71. ^ *a b* Schmidt DS, Salahudeen AK (2007). "Obesity-survival paradox-still a controversy?". *Semin Dial* (Review). **20** (6): 486–92. doi:10.1111/j.1525-139X.2007.00349.x. PMID 17991192.
72. ^ *a b* U.S. Preventive Services Task Force (June 2003). "Behavioral counseling in primary care to promote a healthy diet: recommendations and rationale". *Am Fam Physician* (Review). **67** (12): 2573–6. PMID 12825847.
73. ^ Habbu A, Lakkis NM, Dokainish H (October 2006). "The obesity paradox: Fact or fiction?". *Am. J. Cardiol.* (Review). **98** (7): 944–8. doi:10.1016/j.amjcard.2006.04.039. PMID 16996880.
74. ^ Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F (2006). "Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: A systematic review of cohort studies". *Lancet* (Review). **368** (9536): 666–78. doi:10.1016/S0140-6736(06)69251-9. PMID 16920472.
75. ^ Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA (July 2008). "Body mass index and mortality in heart failure: A meta-analysis". *Am. Heart J.* (Meta-analysis, Review). **156** (1): 13–22. doi:10.1016/j.ahj.2008.02.014. PMID 18585492.
76. ^ Oreopoulos A, Padwal R, Norris CM, Mullen JC, Pretorius V, Kalantar-Zadeh K (February 2008). "Effect of obesity on short- and long-term mortality postcoronary revascularization: A meta-analysis". *Obesity (Silver Spring)* (Meta-analysis). **16** (2): 442–50. doi:10.1038/oby.2007.36. PMID 18239657.
77. ^ Diercks DB, Roe MT, Mulgund J, Pollack CV, Kirk JD, Gibler WB, Ohman EM, Smith SC, Boden WE, Peterson ED (July 2006). "The obesity paradox in non-ST-segment elevation acute coronary syndromes: Results from the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association Guidelines Quality Improvement Initiative". *Am Heart J* (Research Support). **152** (1): 140–8. doi:10.1016/j.ahj.2005.09.024. PMID 16824844.
78. ^ *a b c d e* Lau DC, Douketis JD, Morrison KM, Hramiak IM, Sharma AM, Ur E (April 2007). "2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children summary". *CMAJ* (Practice Guideline, Review). **176** (8): S1–13. doi:10.1503/cmaj.061409. PMC 1839777. PMID 17420481.
79. ^ Drewnowski A, Specter SE (January 2004). "Poverty and obesity: the role of energy density and energy costs". *Am. J. Clin. Nutr.* (Review). **79** (1): 6–16. PMID 14684391.
80. ^ Nestle M, Jacobson MF (2000). "Halting the obesity epidemic: a public health policy approach". *Public Health Rep* (Research Support). **115** (1): 12–24. doi:10.1093/phr/115.1.12. PMC 1308552. PMID 10968581.
81. ^ James WP (March 2008). "The fundamental drivers of the obesity epidemic". *Obes Rev* (Review). **9** (Suppl 1): 6–13. doi:10.1111/j.1467-789X.2007.00432.x. PMID 18307693.
82. ^ Keith SW, Redden DT, Katzmarzyk PT, Boggiano MM, Hanlon EC, Benca RM, Ruden D, Pietrobelli A, Barger JL, Fontaine KR, Wang C, Aronne LJ, Wright SM, Baskin M, Dhurandhar NV, Lijoi MC, Grilo CM, DeLuca M, Westfall AO, Allison DB (2006). "Putative contributors to the secular increase in obesity: Exploring the roads less traveled". *Int J Obes (Lond)* (Review). **30** (11): 1585–94. doi:10.1038/sj.ijo.0803326. PMID 16801930.
83. ^ *a b c d e f* "EarthTrends: Nutrition: Calorie supply per capita". *World Resources Institute*. Archived from the original on 2011-06-11. Retrieved Oct 18, 2009.
84. ^ Bojanowska, Ewa; Ciosek, Joanna (15 February 2016). "Can We Selectively Reduce Appetite for Energy-Dense Foods? An Overview of Pharmacological Strategies for Modification of Food Preference Behavior". *Current Neuropharmacology*. **14** (2): 118–142. doi:10.2174/1570159X14666151109103147. PMC 4825944. PMID 26549651.

85. ^ "USDA: frsept99b". *United States Department of Agriculture*. Retrieved January 10, 2009.
86. ^ "Diet composition and obesity among Canadian adults". *Statistics Canada*.
87. ^ National Control for Health Statistics. "Nutrition For Everyone". Centers for Disease Control and Prevention. Retrieved 2008-07-09.
88. ^ Marantz PR, Bird ED, Alderman MH (March 2008). "A call for higher standards of evidence for dietary guidelines". *Am J Prev Med*. **34** (3): 234–40. doi:10.1016/j.amepre.2007.11.017. PMID 18312812.
89. ^ Flegal KM, Carroll MD, Ogden CL, Johnson CL (October 2002). "Prevalence and trends in obesity among US adults, 1999–2000". *JAMA*. **288** (14): 1723–1727. doi:10.1001/jama.288.14.1723. PMID 12365955.
90. ^ Wright JD, Kennedy-Stephenson J, Wang CY, McDowell MA, Johnson CL (February 2004). "Trends in intake of energy and macronutrients—United States, 1971–2000". *MMWR Morb Mortal Wkly Rep*. **53** (4): 80–2. PMID 14762332.
91. ^ *a b c d e f* Caballero B (2007). "The global epidemic of obesity: An overview". *Epidemiol Rev*. **29**: 1–5. doi:10.1093/epirev/mxm012. PMID 17569676.
92. ^ Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB (23 June 2011). "Changes in Diet and Lifestyle and Long-Term Weight Gain in Women and Men". *The New England Journal of Medicine* (Meta-analysis). **364** (25): 2392–404. doi:10.1056/NEJMoa1014296. PMC 3151731. PMID 21696306.
93. ^ Malik VS, Schulze MB, Hu FB (August 2006). "Intake of sugar-sweetened beverages and weight gain: a systematic review". *Am. J. Clin. Nutr.* (Review). **84** (2): 274–88. PMC 3210834. PMID 16895873.
94. ^ Olsen NJ, Heitmann BL (January 2009). "Intake of calorically sweetened beverages and obesity". *Obes Rev* (Review). **10** (1): 68–75. doi:10.1111/j.1467-789X.2008.00523.x. PMID 18764885.
95. ^ Malik VS, Popkin BM, Bray GA, Després JP, Willett WC, Hu FB (November 2010). "Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis". *Diabetes Care* (Meta-analysis, Review). **33** (11): 2477–83. doi:10.2337/dc10-1079. PMC 2963518. PMID 20693348.
96. ^ Wamberg, Louise; Pedersen, Steen B.; Rejnmark, Lars; Richelsen, Bjørn (2015). "Causes of Vitamin D Deficiency and Effect of Vitamin D Supplementation on Metabolic Complications in Obesity: a Review". *Current Obesity Reports*. **4** (4): 429–440. doi:10.1007/s13679-015-0176-5. ISSN 2162-4968. PMID 26353882.
97. ^ Rosenheck R (November 2008). "Fast food consumption and increased caloric intake: a systematic review of a trajectory towards weight gain and obesity risk". *Obes Rev* (Review). **9** (6): 535–47. doi:10.1111/j.1467-789X.2008.00477.x. PMID 18346099.
98. ^ Lin BH, Guthrie J, Frazao E (1999). "Nutrient contribution of food away from home". In Frazão E. *Agriculture Information Bulletin No. 750: America's Eating Habits: Changes and Consequences*. Washington, DC: US Department of Agriculture, Economic Research Service. pp. 213–239.
99. ^ Pollan, Michael (22 April 2007). "You Are What You Grow". *New York Times*. Retrieved 2007-07-30.
100. ^ Kopelman and Caterson 2005:324.
101. ^ *Metabolism alone doesn't explain how thin people stay thin*. *John Schieszer*. The Medical Post.
102. ^ Seidell 2005 p.10
103. ^ *a b* "WHO: Obesity and overweight". *World Health Organization*. Archived from the original on December 18, 2008. Retrieved January 10, 2009.
104. ^ *a b c* "WHO | Physical Inactivity: A Global Public Health Problem". *World Health Organization*. Retrieved February 22, 2009.
105. ^ *a b* Ness-Abramof R, Apovian CM (February 2006). "Diet modification for treatment and prevention of obesity". *Endocrine* (Review). **29** (1): 5–9. doi:10.1385/ENDO:29:1:135. PMID 16622287.
106. ^ Salmon J, Timperio A (2007). "Prevalence, trends and environmental influences on child and youth physical activity". *Med Sport Sci* (Review). Medicine and Sport Science. **50**: 183–99. doi:10.1159/000101391. ISBN 978-3-318-01396-2. PMID 17387258.
107. ^ Borodulin K, Laatikainen T, Juolevi A, Jousilahti P (June 2008). "Thirty-year trends of physical activity in relation to age, calendar time and birth cohort in Finnish adults". *Eur J Public Health* (Research Support). **18** (3): 339–44. doi:10.1093/eurpub/ckm092. PMID 17875578.
108. ^ Brownson RC, Boehmer TK, Luke DA (2005). "Declining rates of physical activity in the United States: what are the contributors?". *Annu Rev Public Health* (Review). **26**: 421–43. doi:10.1146/annurev.publhealth.26.021304.144437. PMID 15760296.
109. ^ Wilks, Desiree C.; Sharp, Stephen J.; Ekelund, Ulf; Thompson, Simon G.; Mander, Adrian P.; Turner, Rebecca M.; Jebb, Susan A.; Lindroos, Anna Karin (23 February 2011). "Objectively Measured Physical Activity and Fat Mass in Children: A Bias-Adjusted Meta-Analysis of Prospective Studies". *PLoS ONE*. **6** (2): e17205. doi:10.1371/journal.pone.0017205. ISSN 1932-6203. PMC 3044163. PMID 21383837.
110. ^ Gortmaker SL, Must A, Sobol AM, Peterson K, Colditz GA, Dietz WH (April 1996). "Television viewing as a cause of increasing obesity among children in the United States, 1986–1990". *Arch Pediatr Adolesc Med* (Review). **150** (4): 356–62. doi:10.1001/archpedi.1996.02170290022003. PMID 8634729.

111. ^ Vioque J, Torres A, Quiles J (December 2000). "Time spent watching television, sleep duration and obesity in adults living in Valencia, Spain". *Int. J. Obes. Relat. Metab. Disord.* (Research Support). **24** (12): 1683–8. doi:10.1038/sj.ijo.0801434. PMID 11126224.
112. ^ Tucker LA, Bagwell M (July 1991). "Television viewing and obesity in adult females" (PDF). *Am J Public Health*. **81** (7): 908–11. doi:10.2105/AJPH.81.7.908. PMC 1405200. PMID 2053671.
113. ^ "Media + Child and Adolescent Health: A Systematic Review" (PDF). *Ezekiel J. Emanuel*. Common Sense Media. 2008. Retrieved April 6, 2009.
114. ^ Mary Jones. "Case Study: Cataplexy and SOREMPs Without Excessive Daytime Sleepiness in Prader Willi Syndrome. Is This the Beginning of Narcolepsy in a Five Year Old?". European Society of Sleep Technologists. Retrieved April 6, 2009.
115. ^ Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH (May 2006). "Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss". *Arterioscler. Thromb. Vasc. Biol.* (Review). **26** (5): 968–76. doi:10.1161/01.ATV.0000216787.85457.f3. PMID 16627822.
116. ^ Loos RJ, Bouchard C (May 2008). "FTO: the first gene contributing to common forms of human obesity". *Obes Rev* (Review). **9** (3): 246–50. doi:10.1111/j.1467-789X.2008.00481.x. PMID 18373508.
117. ^ Yang W, Kelly T, He J (2007). "Genetic epidemiology of obesity". *Epidemiol Rev* (Review). **29**: 49–61. doi:10.1093/epirev/mxm004. PMID 17566051.
118. ^ Walley AJ, Asher JE, Froguel P (June 2009). "The genetic contribution to non-syndromic human obesity". *Nature Reviews Genetics* (Review). **10** (7): 431–42. doi:10.1038/nrg2594. PMID 19506576.
119. ^ Farooqi S, O'Rahilly S (December 2006). "Genetics of obesity in humans". *Endocr. Rev.* (Review). **27** (7): 710–18. doi:10.1210/er.2006-0040. PMID 17122358.
120. ^ Kolata,Gina (2007). *Rethinking thin: The new science of weight loss – and the myths and realities of dieting*. Picador. p. 122. ISBN 0-312-42785-9.
121. ^ Walley, Andrew J.; Asher, Julian E.; Froguel, Philippe (July 2009). "The genetic contribution to non-syndromic human obesity.". *Nat Rev Genet.* (Review). **10** (7): 431–42. doi:10.1038/nrg2594. PMID 19506576. "However, it is also clear that genetics greatly influences this situation, giving individuals in the same 'obesogenic' environment significantly different risks of becoming obese."
122. ^ Chakravarthy MV, Booth FW (2004). "Eating, exercise, and "thrifty" genotypes: Connecting the dots toward an evolutionary understanding of modern chronic diseases". *J. Appl. Physiol.* (Review). **96** (1): 3–10. doi:10.1152/japplphysiol.00757.2003. PMID 14660491.
123. ^ Wells JC (2009). "Thrift: A guide to thrifty genes, thrifty phenotypes and thrifty norms". *International Journal of Obesity* (Review). **33** (12): 1331–1338. doi:10.1038/ijo.2009.175. PMID 19752875.
124. ^ Wells JC (2011). "The thrifty phenotype: An adaptation in growth or metabolism?". *American Journal of Human Biology* (Review). **23** (1): 65–75. doi:10.1002/ajhb.21100. PMID 21082685.
125. ^ Rosén T, Bosaeus I, Tölli J, Lindstedt G, Bengtsson BA (1993). "Increased body fat mass and decreased extracellular fluid volume in adults with growth hormone deficiency". *Clin. Endocrinol. (Oxf)*. **38** (1): 63–71. doi:10.1111/j.1365-2265.1993.tb00974.x. PMID 8435887.
126. ^ Zametkin AJ, Zoon CK, Klein HW, Munson S (February 2004). "Psychiatric aspects of child and adolescent obesity: a review of the past 10 years". *J Am Acad Child Adolesc Psychiatry* (Review). **43** (2): 134–50. doi:10.1097/00004583-200402000-00008. PMID 14726719.
127. ^ Chiles C, van Wattum PJ (2010). "Psychiatric aspects of the obesity crisis". *Psychiatr Times*. **27** (4): 47–51.
128. ^ Yach D, Stuckler D, Brownell KD (January 2006). "Epidemiologic and economic consequences of the global epidemics of obesity and diabetes". *Nat. Med.* **12** (1): 62–6. doi:10.1038/nm0106-62. PMID 16397571.
129. ^ Sobal J, Stunkard AJ (March 1989). "Socioeconomic status and obesity: A review of the literature". *Psychol Bull* (Review). **105** (2): 260–75. doi:10.1037/0033-2909.105.2.260. PMID 2648443.
130. ^ [a] [b] McLaren L (2007). "Socioeconomic status and obesity". *Epidemiol Rev* (Review). **29**: 29–48. doi:10.1093/epirev/mxm001. PMID 17478442.
131. ^ [a] [b] Wilkinson, Richard; Pickett, Kate (2009). *The Spirit Level: Why More Equal Societies Almost Always Do Better*. London: Allen Lane. pp. 91–101. ISBN 978-1-84614-039-6.
132. ^ Christakis NA, Fowler JH (2007). "The Spread of Obesity in a Large Social Network over 32 Years". *New England Journal of Medicine* (Research Support). **357** (4): 370–379. doi:10.1056/NEJMsa066082. PMID 17652652.
133. ^ Björntorp P (2001). "Do stress reactions cause abdominal obesity and comorbidities?". *Obesity Reviews*. **2** (2): 73–86. doi:10.1046/j.1467-789x.2001.00027.x. PMID 12119665.
134. ^ Goodman E, Adler NE, Daniels SR, Morrison JA, Slap GB, Dolan LM (2003). "Impact of objective and subjective social status on obesity in a biracial cohort of adolescents". *Obesity Reviews* (Research Support). **11** (8): 1018–26. doi:10.1038/oby.2003.140. PMID 12917508.
135. ^ Flegal KM, Troiano RP, Pamuk ER, Kuczmarski RJ, Campbell SM (November 1995). "The influence of smoking cessation on the prevalence of overweight in the United States". *N. Engl. J. Med.* **333** (18): 1165–70.

doi:10.1056/NEJM199511023331801. PMID 7565970.
136. ^ Chiolero A, Faeh D, Paccaud F, Cornuz J (1 April 2008). "Consequences of smoking for body weight, body fat distribution, and insulin resistance". *Am. J. Clin. Nutr.* (Review). **87** (4): 801–9. PMID 18400700.
137. ^ Weng HH, Bastian LA, Taylor DH, Moser BK, Ostbye T (2004). "Number of children associated with obesity in middle-aged women and men: results from the health and retirement study". *J Women's Health (Larchmt)* (Comparative Study). **13** (1): 85–91. doi:10.1089/154099904322836492. PMID 15006281.
138. ^ Bellows-Riecken KH, Rhodes RE (February 2008). "A birth of inactivity? A review of physical activity and parenthood". *Prev Med* (Review). **46** (2): 99–110. doi:10.1016/j.ypmed.2007.08.003. PMID 17919713.
139. ^ "Obesity and Overweight" (PDF). World Health Organization. Retrieved February 22, 2009.
140. ^ *a b* Caballero B (March 2001). "Introduction. Symposium: Obesity in developing countries: biological and ecological factors". *J. Nutr.* (Review). **131** (3): 866S–870S. PMID 11238776.
141. ^ Smith E, Hay P, Campbell L, Trollor JN (2011). "A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment". *Obesity Reviews* (Review). **12** (9): 740–755. doi:10.1111/j.1467-789X.2011.00920.x. PMID 21991597.
142. ^ DiBaise JK, Zhang H, Crowell MD, Krajmalnik-Brown R, Decker GA, Rittmann BE (April 2008). "Gut microbiota and its possible relationship with obesity". *Mayo Clinic proceedings. Mayo Clinic* (Review). **83** (4): 460–9. doi:10.4065/83.4.460. PMID 18380992.
143. ^ Falagas ME, Kompoti M (July 2006). "Obesity and infection". *Lancet Infect Dis* (Review). **6** (7): 438–46. doi:10.1016/S1473-3099(06)70523-0. PMID 16790384.
144. ^ *a b c d e* Flier JS (2004). "Obesity wars: Molecular progress confronts an expanding epidemic". *Cell* (Review). **116** (2): 337–50. doi:10.1016/S0092-8674(03)01081-X. PMID 14744442.
145. ^ Zhang, Y; Proenca, R; Maffei, M; Barone, M; Leopold, L; Friedman, JM (Dec 1, 1994). "Positional cloning of the mouse obese gene and its human homologue.". *Nature* (Research Support). **372** (6505): 425–32. doi:10.1038/372425a0. PMID 7984236.
146. ^ Considine, RV; Considine, EL; Williams, CJ; Nyce, MR; Magosin, SA; Bauer, TL; Rosato, EL; Colberg, J; Caro, JF (Jun 1995). "Evidence against either a premature stop codon or the absence of obese gene mRNA in human obesity.". *The Journal of Clinical Investigation* (Research Support). **95** (6): 2986–8. doi:10.1172/jci118007. PMC 295988. PMID 7769141.
147. ^ Hamann A, Matthaei S (1996). "Regulation of energy balance by leptin". *Exp. Clin. Endocrinol. Diabetes* (Review). **104** (4): 293–300. doi:10.1055/s-0029-1211457. PMID 8886745.
148. ^ Boulpaep, Emile L.; Boron, Walter F. (2003). *Medical physiology: A cellular and molecular approach*. Philadelphia: Saunders. p. 1227. ISBN 0-7216-3256-4.
149. ^ World Health Organization (2000). Obesity: preventing and managing the global epidemic (Report). World Health Organization. pp. 1–2. Retrieved 1 February 2014.
150. ^ Satcher D (2001). *The Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity*. U.S. Dept. of Health and Human Services, Public Health Service, Office of Surgeon General. ISBN 978-0-16-051005-2.
151. ^ Moyer VA (4 September 2012). "Screening for and management of obesity in adults: U.S. Preventive Services Task Force recommendation statement". *Annals of Internal Medicine* (Practice Guideline). **157** (5): 373–8. doi:10.7326/0003-4819-157-5-201209040-00475. PMID 22733087.
152. ^ Brook Barnes (2007-07-18). "Limiting Ads of Junk Food to Children". *New York Times*. Retrieved 2008-07-24.
153. ^ "Fewer Sugary Drinks Key to Weight Loss - healthfinder.gov". *U.S. Department of Health and Human Services*. Retrieved Oct 18, 2009.
154. ^ "WHO urges global action to curtail consumption and health impacts of sugary drinks". *WHO*. Retrieved 13 October 2016.
155. ^ Brennan Ramirez LK, Hoehner CM, Brownson RC, Cook R, Orleans CT, Hollander M, Barker DC, Bors P, Ewing R, Killingsworth R, Petersmarck K, Schmid T, Wilkinson W (December 2006). "Indicators of activity-friendly communities: An evidence-based consensus process". *Am J Prev Med* (Research Support). **31** (6): 530–32. doi:10.1016/j.amepre.2006.07.026. PMID 17169714.
156. ^ National Heart, Lung, and Blood Institute (1998). *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* (PDF). International Medical Publishing, Inc. ISBN 1-58808-002-1.
157. ^ *Storing up problems; the medical case for a slimmer nation*. London: Royal College of Physicians. 2004-02-11. ISBN 1-86016-200-2.
158. ^ Great Britain Parliament House of Commons Health Committee (May 2004). *Obesity – Volume 1 – HCP 23-I, Third Report of session 2003–04. Report, together with formal minutes*. London, UK: TSO (The Stationery Office). ISBN 978-0-215-01737-6. Retrieved 2007-12-17.
159. ^ "Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children" (PDF). *National Institute for Health and Clinical Excellence(NICE)*. National Health Services (NHS). 2006. Retrieved April 8, 2009.

160. ^ Wanless, Sir Derek; Appleby, John; Harrison, Anthony; Patel, Darshan (2007). *Our Future Health Secured? A review of NHS funding and performance*. London, UK: The King's Fund. ISBN 1-85717-562-X.
161. ^ Sacks G, Swinburn B, Lawrence M (January 2009). "Obesity Policy Action framework and analysis grids for a comprehensive policy approach to reducing obesity". *Obes Rev*. **10** (1): 76–86. doi:10.1111/j.1467-789X.2008.00524.X. PMID 18761640.
162. ^ Strychar I (January 2006). "Diet in the management of weight loss". *CMAJ* (Review). **174** (1): 56–63. doi:10.1503/cmaj.045037. PMC 1319349. PMID 16389240.
163. ^ Shick SM, Wing RR, Klem ML, McGuire MT, Hill JO, Seagle H (April 1998). "Persons successful at long-term weight loss and maintenance continue to consume a low-energy, low-fat diet". *J Am Diet Assoc*. **98** (4): 408–13. doi:10.1016/S0002-8223(98)00093-5. PMID 9550162.
164. ^ Tate DF, Jeffery RW, Sherwood NE, Wing RR (1 April 2007). "Long-term weight losses associated with prescription of higher physical activity goals. Are higher levels of physical activity protective against weight regain?". *Am. J. Clin. Nutr.* (Randomized Controlled Trial). **85** (4): 954–9. PMID 17413092.
165. ^ *a b c d* Services, Statens beredning för medicinsk och social utvärdering (SBU); Swedish Agency for Health Technology Assessment and Assessment of Social. "Dietary treatment of obesity". *www.sbu.se*. Retrieved 2016-06-17.
166. ^ Johnston, Bradley C.; Kanters, Steve; Bandayrel, Kristofer; Wu, Ping; Naji, Faysal; Siemieniuk, Reed A.; Ball, Geoff D. C.; Busse, Jason W.; Thorlund, Kristian; Guyatt, Gordon; Jansen, Jeroen P.; Mills, Edward J. (3 September 2014). "Comparison of Weight Loss Among Named Diet Programs in Overweight and Obese Adults". *JAMA*. **312** (9): 923. doi:10.1001/jama.2014.10397.
167. ^ Naude, CE; Schoonees, A; Senekal, M; Young, T; Garner, P; Volmink, J (2014). "Low carbohydrate versus isoenergetic balanced diets for reducing weight and cardiovascular risk: a systematic review and meta-analysis.". *PLOS ONE* (Research Support). **9** (7): e100652. doi:10.1371/journal.pone.0100652. PMC 4090010. PMID 25007189.
168. ^ Wing RR, Phelan S (2005). "Long-term weight loss maintenance". *The American Journal of Clinical Nutrition* (Review). **82** (1 Suppl): 222S–225S. PMID 16002825.
169. ^ Thangaratinam S, Rogozinska E, Jolly K, Glinkowski S, Roseboom T, Tomlinson JW, Kunz R, Mol BW, Coomarasamy A, Khan KS (16 May 2012). "Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence". *BMJ (Clinical research ed.)* (Meta-analysis). **344**: e2088. doi:10.1136/bmj.e2088. PMC 3355191. PMID 22596383.
170. ^ LeFevre, Michael L. (26 August 2014). "Behavioral Counseling to Promote a Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults With Cardiovascular Risk Factors: U.S. Preventive Services Task Force Recommendation Statement". *Annals of Internal Medicine*. **161**: 587. doi:10.7326/M14-1796.
171. ^ *a b* Rucker D, Padwal R, Li SK, Curioni C, Lau DC (2007). "Long term pharmacotherapy for obesity and overweight: updated meta-analysis". *BMJ* (Meta-analysis). **335** (7631): 1194–99. doi:10.1136/bmj.39385.413113.25. PMC 2128668. PMID 18006966.
172. ^ Wood, Shelley. "Diet Drug Orlistat Linked to Kidney, Pancreas Injuries". *Medscape*. Medscape News. Retrieved 26 April 2011.
173. ^ *a b c* Wolfe SM (21 August 2013). "When EMA and FDA decisions conflict: differences in patients or in regulation?". *BMJ (Clinical research ed.)*. **347**: f5140. doi:10.1136/bmj.f5140. PMID 23970394.
174. ^ Bays HE (March 2011). "Lorcaserin: drug profile and illustrative model of the regulatory challenges of weight-loss drug development". *Expert review of cardiovascular therapy* (Review). **9** (3): 265–77. doi:10.1586/erc.10.22. PMID 21438803.
175. ^ Bays HE, Gadde KM (December 2011). "Phentermine/topiramate for weight reduction and treatment of adverse metabolic consequences in obesity". *Drugs Today* (Review). **47** (12): 903–14. doi:10.1358/dot.2011.47.12.1718738. PMID 22348915.
176. ^ *a b* Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA (2014). "The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012". *JAMA Surgery* (Meta-analysis, Review). **149** (3): 275–87. doi:10.1001/jamasurg.2013.3654. PMID 24352617.
177. ^ Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Agren G, Carlsson LM (August 2007). "Effects of bariatric surgery on mortality in Swedish obese subjects". *N. Engl. J. Med.* (Research Support). **357** (8): 741–52. doi:10.1056/NEJMoa066254. PMID 17715408.
178. ^ Weintraub, Karen. "New allies in war on weight". *The Boston Globe*. The Boston Globe. Retrieved 30 June 2014.
179. ^ "Global Prevalence of Adult Obesity" (PDF). *International Obesity Taskforce*. Retrieved January 29, 2008.
180. ^ *a b c* Haslam D (March 2007). "Obesity: a medical history". *Obes Rev* (Review). 8 Suppl 1: 31–6.

doi:10.1111/j.1467-789X.2007.00314.x. PMID 17316298.
181. ^ a b "Obesity and overweight". *World Health Organization*. Retrieved April 8, 2009.
182. ^ Seidell 2005 p.5
183. ^ Howard NJ, Taylor AW, Gill TK, Chittleborough CR (2008). "Severe obesity: Investigating the socio-demographics within the extremes of body mass index". *Obesity Research & Clinical Practice*. **2** (1): I–II. doi:10.1016/j.orcp.2008.01.001. PMID 24351678.
184. ^ Tjepkema M (2005-07-06). "Measured Obesity–Adult obesity in Canada: Measured height and weight". *Nutrition: Findings from the Canadian Community Health Survey*. Ottawa, Ontario: Statistics Canada.
185. ^ "Online Etymology Dictionary: Obesity". *Douglas Harper*. Retrieved December 31, 2008.
186. ^ "Obesity, n". *Oxford English Dictionary 2008*. Retrieved March 21, 2009.
187. ^ a b Zachary Bloomgarden (2003). "Prevention of Obesity and Diabetes". *Diabetes Care* (Review). **26** (11): 3172–3178. doi:10.2337/diacare.26.11.3172. PMID 14578257.
188. ^ a b "History of Medicine: Sushruta – the Clinician – Teacher par Excellence" (PDF). *Dwivedi, Girish & Dwivedi, Shridhar*. 2007. Retrieved 2008-09-19.
189. ^ Theodore Mazzone; Giamila Fantuzzi (2006). *Adipose Tissue And Adipokines in Health And Disease (Nutrition and Health)*. Totowa, NJ: Humana Press. p. 222. ISBN 1-58829-721-7.
190. ^ Keller p. 49
191. ^ Gilman, Sander L (2004). *Fat Boys: A Slim Book*. University of Nebraska Press. p. 18.
192. ^ Breslow L (September 1952). "Public Health Aspects of Weight Control". *Am J Public Health Nations Health*. **42** (9): 1116–20. doi:10.2105/AJPH.42.9.1116. PMC 1526346. PMID 12976585.
193. ^ a b Puhl R, Brownell KD (December 2001). "Bias, discrimination, and obesity". *Obes. Res.* (Review). **9** (12): 788–805. doi:10.1038/oby.2001.108. PMID 11743063.
194. ^ Rubinstein S, Caballero B (2000). "Is Miss America an undernourished role model?". *JAMA* (Letter). **283** (12): 1569. doi:10.1001/jama.283.12.1569. PMID 10735392.
195. ^ a b Johnson F, Cooke L, Croker H, Wardle J (2008). "Changing perceptions of weight in Great Britain: comparison of two population surveys". *BMJ*. **337**: a494. doi:10.1136/bmj.a494. PMC 2500200. PMID 18617488.
196. ^ Fumento, Michael (1997). *The Fat of the Land: Our Health Crisis and How Overweight Americans Can Help Themselves*. Penguin (Non-Classics). p. 126. ISBN 0-14-026144-3.
197. ^ a b Puhl R., Henderson K., and Brownell K. 2005 p.29
198. ^ Johansson E, Böckerman P, Kiiskinen U, Heliövaara M (2009). "Obesity and labour market success in Finland: The difference between having a high BMI and being fat". *Economics and Human Biology*. **7** (1): 36–45. doi:10.1016/j.ehb.2009.01.008. PMID 19249259.
199. ^ Cawley J, Meyerhoefer C (January 2012). "The medical care costs of obesity: An instrumental variables approach". *Journal of Health Economics*. **31** (1): 219–230. doi:10.1016/j.jhealeco.2011.10.003. PMID 22094013.
200. ^ Finkelstein EA, Fiebelkorn IA, Wang G (1 January 2003). "National medical spending attributable to overweight and obesity: How much, and who's paying". *Health Affairs*. Online (May). doi:10.1377/hlthaff.w3.219.
201. ^ "Obesity and overweight: Economic consequences". Centers for Disease Control and Prevention. 22 May 2007. Retrieved 2007-09-05.
202. ^ Colagiuri S, Lee CM, Colagiuri R, Magliano D, Shaw JE, Zimmet PZ, Caterson ID (2010). "The cost of overweight and obesity in Australia". *The Medical Journal of Australia* (Comparative Study). **192** (5): 260–4. PMID 20201759.
203. ^ Cummings, Laura (5 February 2003). "The diet business: Banking on failure". BBC News. Retrieved 25 February 2009.
204. ^ van Baal PH, Polder JJ, de Wit GA, Hoogenveen RT, Feenstra TL, Boshuizen HC, Engelfriet PM, Brouwer WB (February 2008). "Lifetime Medical Costs of Obesity: Prevention No Cure for Increasing Health Expenditure". *PLoS Med.* (Comparative Study). **5** (2): e29. doi:10.1371/journal.pmed.0050029. PMC 2225430. PMID 18254654.
205. ^ Bakewell J (2007). "Bariatric furniture: Considerations for use". *Int J Ther Rehabil*. **14** (7): 329–33.
206. ^ Neovius K, Johansson K, Kark M, Neovius M (January 2009). "Obesity status and sick leave: a systematic review". *Obes Rev* (Review). **10** (1): 17–27. doi:10.1111/j.1467-789X.2008.00521.x. PMID 18778315.
207. ^ Ostbye T, Dement JM, Krause KM (2007). "Obesity and workers' compensation: Results from the Duke Health and Safety Surveillance System". *Arch. Intern. Med.* (Research Support). **167** (8): 766–73. doi:10.1001/archinte.167.8.766. PMID 17452538.
208. ^ "Alabama "Obesity Penalty" Stirs Debate". *Don Fernandez*. Retrieved April 5, 2009.
209. ^ Puhl R., Henderson K., and Brownell K. 2005 p.30
210. ^ Lisa DiCarlo (2002-10-24). "Why Airlines Can't Cut The Fat". *Forbes.com*. Retrieved 2008-07-23.
211. ^ Dannenberg AL, Burton DC, Jackson RJ (2004). "Economic and environmental costs of obesity: The impact on airlines". *American journal of preventive medicine* (Letter). **27** (3): 264. doi:10.1016/j.amepre.2004.06.004.

PMID 15450642.
212. ^ Lauren Cox (July 2, 2009). "Who Should Pay for Obese Health Care?". ABC News. Retrieved 2012-08-06.
213. ^ a b "109th U.S. Congress (2005–2006) H.R. 554: 109th U.S. Congress (2005–2006) H.R. 554: Personal Responsibility in Food Consumption Act of 2005". GovTrack.us. Retrieved 2008-07-24.
214. ^ a b Basulto, Dominic (June 20, 2013). "A changing battlefield in the fight against fat". *The Washington Post*. Archived from the original on June 21, 2013. Retrieved June 20, 2013. (WebCite archive)
215. ^ "Obesity can be deemed a disability at work - EU court". *Reuters*. December 18, 2014. Retrieved December 18, 2014.
216. ^ "What is NAAFA". *National Association to Advance Fat Acceptance*. Retrieved February 17, 2009.
217. ^ "ISAA Mission Statement". *International Size Acceptance Association*. Retrieved February 17, 2009.
218. ^ a b Pulver, Adam (2007). *An Imperfect Fit: Obesity, Public Health, and Disability Anti-Discrimination Law*. Social Science Electronic Publishing. Retrieved January 13, 2009.
219. ^ Neumark-Sztainer D (March 1999). "The weight dilemma: a range of philosophical perspectives". *Int. J. Obes. Relat. Metab. Disord.* (Review). 23 Suppl 2: S31–7. doi:10.1038/sj.ijo.0800857. PMID 10340803.
220. ^ National Association to Advance Fat Acceptance (2008). "We come in all sizes". NAAFA. Retrieved 2008-07-29.
221. ^ "International Size Acceptance Association – ISAA". *International Size Acceptance Association*. Retrieved January 13, 2009.
222. ^ O'Connor, Anahad (August 9, 2015). "Coca-Cola Funds Scientists Who Shift Blame for Obesity Away From Bad Diets". *New York Times*.
223. ^ Nestle, Marion (12 September 2016). "Invited Commentary: Food Industry Funding of Nutrition Research: The Relevance of History for Current Debates.". *JAMA internal medicine*. **176**: 1685. doi:10.1001/jamainternmed.2016.5400. PMID 27618496.
224. ^ a b Flynn MA, McNeil DA, Maloff B, Mutasingwa D, Wu M, Ford C, Tough SC (February 2006). "Reducing obesity and related chronic disease risk in children and youth: a synthesis of evidence with 'best practice' recommendations". *Obes Rev* (Review). 7 Suppl 1: 7–66. doi:10.1111/j.1467-789X.2006.00242.x. PMID 16371076.
225. ^ Dollman J, Norton K, Norton L (December 2005). "Evidence for secular trends in children's physical activity behaviour". *Br J Sports Med* (Review). **39** (12): 892–7; discussion 897. doi:10.1136/bjsm.2004.016675. PMC 1725088. PMID 16306494.
226. ^ Metcalf B, Henley W, Wilkin T (2012). "Effectiveness of intervention on physical activity of children: systematic review and meta-analysis of controlled trials with objectively measured outcomes (EarlyBird 54)". *BMJ (Clinical Research Ed.)* (Review, Meta-analysis). **345**: e5888. doi:10.1136/bmj.e5888. PMID 23044984.
227. ^ a b Lund Elizabeth M. (2006). "Prevalence and Risk Factors for Obesity in Adult Dogs from Private US Veterinary Practices" (PDF). *Intern J Appl Res Vet Med*. **4** (2): 177–86.
228. ^ McGreevy PD, Thomson PC, Pride C, Fawcett A, Grassi T, Jones B (May 2005). "Prevalence of obesity in dogs examined by Australian veterinary practices and the risk factors involved". *Vet. Rec.* **156** (22): 695–702. doi:10.1136/vr.156.22.695. PMID 15923551.
229. ^ Nijland ML, Stam F, Seidell JC (June 2009). "Overweight in dogs, but not in cats, is related to overweight in their owners". *Public Health Nutr*. **13** (1): 1–5. doi:10.1017/S136898000999022X. PMID 19545467.

## References

- Bhargava A, Guthrie JF (2002). "Unhealthy eating habits, physical exercise and macronutrient intakes are predictors of anthropometric indicators in the Women's Health Trial: Feasibility Study in Minority Populations". *British Journal of Nutrition* (Randomized Controlled Trial). **88** (6): 719–728. doi:10.1079/BJN2002739. PMID 12493094.
- Bhargava A (2006). "Fiber intakes and anthropometric measures are predictors of circulating hormone, triglyceride, and cholesterol concentration in the Women's Health Trial". *Journal of Nutrition* (Research Support). **136** (8): 2249–2254. PMID 16857849.
- Jebb S. and Wells J. Measuring body composition in adults and children In:Peter G. Kopelman; Ian D. Caterson; Michael J. Stock; William H. Dietz (2005). *Clinical obesity in adults and children: In Adults and Children*. Blackwell Publishing. pp. 12–28. ISBN 1-4051-1672-2.
- Kopelman P., Caterson I. An overview of obesity management In:Peter G. Kopelman; Ian D. Caterson; Michael J. Stock; William H. Dietz (2005). *Clinical obesity in adults and children: In Adults and Children*. Blackwell Publishing. pp. 319–326. ISBN 1-4051-1672-2.
- National Heart, Lung, and Blood Institute (NHLBI) (1998). *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* (PDF). International Medical Publishing, Inc. ISBN 1-58808-002-1.
- "Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children" (PDF). *National Institute for Health and Clinical Excellence(NICE)*. National Health Services (NHS). 2006. Retrieved April 8, 2009.

- Puhl R., Henderson K., and Brownell K. Social consequences of obesity In:Peter G. Kopelman; Ian D. Caterson; Michael J. Stock; William H. Dietz (2005). *Clinical obesity in adults and children: In Adults and Children*. Blackwell Publishing. pp. 29–45. ISBN 1-4051-1672-2.
- Seidell JC. Epidemiology — definition and classification of obesity In:Peter G. Kopelman; Ian D. Caterson; Michael J. Stock; William H. Dietz (2005). *Clinical obesity in adults and children: In Adults and Children*. Blackwell Publishing. pp. 3–11. ISBN 1-4051-1672-2.
- World Health Organization (WHO) (2000). *Technical report series 894: Obesity: Preventing and managing the global epidemic.* (PDF). Geneva: World Health Organization. ISBN 92-4-120894-5.


# Further reading


- Obesity at DMOZ
- Many authors (2015). "Obesity 2015". *The Lancet*.
- Keller, Kathleen (2008). *Encyclopedia of Obesity*. Thousand Oaks, Calif: Sage Publications, Inc. ISBN 1-4129-5238-7.




| v · t · e | **Malnutrition or nutrition disorders (E40–E68, 260–269)** | | |
|---|---|---|---|
| **Malnutrition** | **Protein-energy malnutrition** | Kwashiorkor · Marasmus · Catabolysis · | |
| | **Vitamin deficiency** | **B vitamins** | $B_1$: Beriberi / Wernicke–Korsakoff syndrome (Wernicke's encephalopathy · Korsakoff's syndrome) · $B_2$: Riboflavin deficiency · $B_3$: Pellagra (Niacin deficiency) · $B_6$: Pyridoxine deficiency · $B_7$: Biotin deficiency · $B_9$: Folate deficiency · $B_{12}$: Vitamin $B_{12}$ deficiency · |
| | | **Other vitamins** | A: Vitamin A deficiency/Bitot's spots · C: Scurvy · D: Vitamin D deficiency/Rickets/Osteomalacia · E: Vitamin E deficiency · K: Vitamin K deficiency · |
| | **Mineral deficiency** | Sodium · Potassium · Magnesium · Calcium · Iron · Zinc · Manganese · Copper · Iodine · Chromium · Molybdenum · Selenium (Keshan disease) · | |
| **Overnutrition** | **Overweight · Obesity ·** | Childhood obesity · Obesity hypoventilation syndrome · Abdominal obesity · | |
| | **Vitamin poisoning** | Hypervitaminosis A · Hypervitaminosis D · Hypervitaminosis E · | |
| | **Mineral overload** | *see inborn errors of metal metabolism, toxicity* · | |
| **Authority control** | GND: 4016953-4 · BNF: cb11932876d (data) · | | |

Categories: Obesity | Bariatrics | Body shape | Nutrition




# Primary aldosteronism

From Wikipedia, the free encyclopedia
(Redirected from Primary hyperaldosteronism)

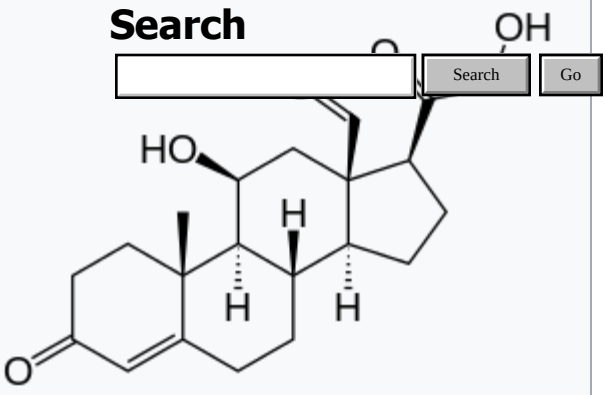
**Primary aldosteronism**, also known as **primary hyperaldosteronism** or **Conn's syndrome**, is excess production of the hormone aldosterone by the adrenal glands resulting in low renin levels. Often it produces few symptoms.[1] Most people have high blood pressure which may cause poor vision or headaches.[1][2] Occasionally there may be muscular weakness, muscle spasms, tingling sensations, or excessive urination.[1] Complications include cardiovascular disease such as stroke, myocardial infarction, kidney failure, and abnormal heart rhythms.[3][4]

Primary hyperaldosteronism has a number of causes. About 66% of cases are due to enlargement of both adrenal glands and 33% of cases are due to an adrenal adenoma that produces aldosterone.[1] Other uncommon causes include adrenal cancer and an inherited disorder called familial hyperaldosteronism.[5] Some recommend screening people with high blood pressure who are at increased risk while others recommend screening all people with high blood pressure for the disease.[3] Screening is usually done by measuring the aldosterone-to-renin ratio in the blood with further testing used to confirm positive results. While low blood potassium is classically described this is only present in about a quarter of people. To determine the underlying cause medical imaging is carried out.[1]

Some cases may be cured by removing the adenoma by surgery.[1] A single adrenal gland may also be removed in cases where only one is enlarged.[4] In cases due to enlargement of both glands treatment is typically with medications known as aldosterone antagonists such as spironolactone or eplerenone.[1] Other medications for high blood pressure and a low salt diet may also be needed.[1][4] Some people with familial hyperaldosteronism may be treated with the steroid dexamethasone.[1]

Primary aldosteronism is present in about 10% of people with high blood pressure.[1] It occurs more often in women than men. Often it begins in those between 30 and 50 years of age.[6] Conn's syndrome is named after Jerome W. Conn (1907–1994), the American endocrinologist who first described adenomas as a cause of the condition in 1955.[7][8]

**Primary hyperaldosteronism**




Aldosterone

**Classification and external resources**

| | |
|---|---|
| **Specialty** | endocrinology |
| **ICD-10** | E26.0 |
| **ICD-9-CM** | 255.1 |
| **DiseasesDB** | 3073 |
| **MedlinePlus** | 000330 |
| **eMedicine** | med/432 |
| **MeSH** | D006929 |

[edit on Wikidata]

Contents

## Signs and symptoms [edit]

People often have few or no symptoms.[1] They may get occasional muscular weakness, muscle spasms, tingling sensations, or excessive urination.[1]

High blood pressure, manifestations of muscle cramps (due to hyperexcitability of neurons secondary to low blood calcium), muscle weakness (due to hypoexcitability of skeletal muscles secondary to hypokalemia), and headaches (due to low blood potassium or high blood pressure) may be seen.

Secondary hyperaldosteronism is often related to decreased cardiac output which is associated with elevated renin levels.

## Causes [edit]

The condition is due to:[9]

- Bilateral idiopathic (micronodular) adrenal hyperplasia (66%)[1]
- Adrenal adenoma (Conn's syndrome) (33%)[1]
- Primary (unilateral) adrenal hyperplasia—2% of cases
- Aldosterone-producing adrenocortical carcinoma—<1% of cases
- Familial Hyperaldosteronism (FH)
- Glucocorticoid-remediable aldosteronism (FH type I)—<1% of cases
- FH type II (APA or IHA)—<2% of cases
- Ectopic aldosterone-producing adenoma or carcinoma—< 0.1% of cases

### Genetics [edit]

40% of people with an adrenal aldosterone producing adenoma have somatic gain-of-function mutations in a single gene (KCNJ5).[10] This gene is mutated in inherited cases albeit less frequently. These mutations tend to occur in young women with the adenoma in the cortisol secreting zona fasciculata. Adenomas without this mutation tend to occur in older men with resistant hypertension.

## Pathophysiology [edit]

Aldosterone has effects on most or all cells of the body but, clinically, the most important actions are in the kidney, on cells of the late distal convoluted tubule and medullary collecting duct. In the principal cells aldosterone increases activity of basolateral membrane sodium-potassium ATPase and apical epithelial sodium channels, ENaC, as well as potassium channels, ROMK. These actions increase sodium reabsorption and potassium secretion. Since more sodium is reabsorbed than potassium secreted, it also makes the lumen more electrically negative, causing chloride to follow sodium. Water then follows sodium and chloride by osmosis. In Conn syndrome, these actions cause increased extracellular sodium and fluid volume and reduced extracellular potassium. Aldosterone also acts on intercalated cells to stimulate an apical proton ATPase, causing proton secretion that acidifies urine and alkalizes extracellular fluid.

In summary, hyperaldosteronism causes hypernatremic, hypokalemic, metabolic alkalosis.

Finer notes on aldosterone include the fact that it stimulates sodium-potassium ATPase in muscle cells, increasing intracellular potassium and also increases sodium reabsorption all along the intestine and nephron, possibly due to widespread stimulation of sodium-potassium ATPase. Finally, epithelial cells of sweat gland ducts and distal colon surface respond exactly the same as the principal cells of the nephron. These responses are important in climate adaptation and as a cause of constipation with elevated aldosterone.

The sodium retention leads to plasma volume expansion and elevated blood pressure. The increased blood pressure will lead to increased glomerular filtration rate and cause a decrease in renin release from the granular cells of the juxtaglomerular apparatus in the kidney. If there is a primary hyperaldosteronism, the decreased renin (and subsequent decreased angiotensin II) will not lead to a decrease in aldosterone levels (a very helpful clinical tool in diagnosis of primary hyperaldosteronism).

## Diagnosis [edit]

Screening may be considered in people with high blood pressure presenting with low blood potassium, high blood pressure that is difficult to treat, other family members with the same condition, or a mass on the adrenal gland.[1]

Measuring aldosterone alone is not considered adequate to diagnose primary hyperaldosteronism. Rather, both renin and aldosterone are measured, and a resultant aldosterone-to-renin ratio is used for case detection.[11][12] A high aldosterone-to-renin ratio suggests the presence of primary hyperaldosteronism. The diagnosis is made by performing a saline suppression test, ambulatory salt loading test, or fludrocortisone suppression test.[13]

If primary hyperaldosteronism is confirmed biochemically, CT scanning or other cross-sectional imaging can confirm the presence of an adrenal abnormality, possibly an adrenal cortical adenoma (aldosteronoma), adrenal carcinoma, bilateral adrenal hyperplasia, or other less common changes. Imaging findings may ultimately lead to other necessary diagnostic studies, such as adrenal venous sampling, to clarify the etiology. It is not uncommon for adults to have bilateral sources of aldosterone hypersecretion in the presence of a nonfunctioning adrenal cortical adenoma, making adrenal venous sampling mandatory in cases where surgery is being considered.[13]

The diagnosis is best accomplished by an appropriately-trained subspecialist, though primary care providers are critical in recognizing clinical features of primary aldosteronism and obtaining the first blood tests for case detection.

### Classification [edit]

Some people only use Conn's syndrome for when it occurs due to an adrenal adenoma (a type of benign tumor).[14] In practice, however, the terms are often used interchangeably, regardless of the underlying physiology.[1]

### Differential diagnosis [edit]

Primary hyperaldosteronism can be mimicked by Liddle syndrome, and by ingestion of licorice and other foods containing glycyrrhizin. In one case report, hypertension and quadriparesis resulted from intoxication with a non-alcoholic pastis (an anise-flavored aperitif containing glycyrrhizinic acid).[15]

## Treatment [edit]

The treatment for hyperaldosteronism depends on the underlying cause. In people with a single benign tumor (adenoma), surgical removal (adrenalectomy) may be curative. This is usually performed laparoscopically, through several very small incisions. For people with hyperplasia of both glands, successful treatment is often achieved with spironolactone or eplerenone, drugs that block the effect of aldosterone. With its antiandrogen effect, spironolactone drug therapy may have a range of effects in males, including

sometimes gynecomastia. These symptoms usually do not occur with eplerenone drug therapy.[16]

In the absence of treatment, individuals with hyperaldosteronism often have poorly controlled high blood pressure, which may be associated with increased rates of stroke, heart disease, and kidney failure. With appropriate treatment, the prognosis is excellent.[17]

## Eponym [edit]

Conn's syndrome is named after Jerome W. Conn (1907–1994), the American endocrinologist who first described the condition at the University of Michigan in 1955.[7]

## References [edit]


1. ^ *a b c d e f g h i j k l m n o p* Schirpenbach, C; Reincke, M (March 2007). "Primary aldosteronism: current knowledge and controversies in Conn's syndrome.". *Nature clinical practice. Endocrinology & metabolism*. **3** (3): 220–7. doi:10.1038/ncpendmet0430. PMID 17315030.
2. ^ "Primary hyperaldosteronism (Conn's syndrome or aldosterone-producing adrenal tumor)". Retrieved 8 April 2015.
3. ^ *a b* Stowasser, M; Taylor, PJ; Pimenta, E; Ahmed, AH; Gordon, RD (May 2010). "Laboratory investigation of primary aldosteronism.". *The Clinical biochemist. Reviews / Australian Association of Clinical Biochemists*. **31** (2): 39–56. PMID 20498828.
4. ^ *a b c* "Primary hyperaldosteronism (Conn's syndrome or aldosterone-producing adrenal tumor)". Retrieved 8 April 2015.
5. ^ "Primary hyperaldosteronism (Conn's syndrome or aldosterone-producing adrenal tumor)". Retrieved 8 April 2015.
6. ^ Hubbard, Johnathan G.H.; Inabnet, William B.; Heerden, Chung-Yau Lo (2009). *Endocrine surgery principles and practice*. London: Springer. p. 367. ISBN 9781846288814.
7. ^ *a b* Conn JW, Louis LH (1955). "Primary aldosteronism: a new clinical entity". *Trans. Assoc. Am. Physicians*. **68**: 215–31; discussion, 231–3. PMID 13299331.
8. ^ Williams, Gordon H. (2009). *Textbook of nephro-endocrinology*. Amsterdam: Academic. p. 372. ISBN 9780080920467.
9. ^ Henry M. Kronenberg (2008). *Williams textbook of endocrinology.* (11th ed.). Philadelphia: Saunders/Elsevier. ISBN 978-1-4160-2911-3.
10. ^ Brown, MJ (Sep 30, 2012). "Platt versus Pickering: what molecular insight to primary hyperaldosteronism tells us about hypertension". *JRSM cardiovascular disease*. **1** (6): cvd.2012.012020. doi:10.1258/cvd.2012.012020. PMC 3738367. PMID 24175075.
11. ^ Tiu S, Choi C, Shek C, Ng Y, Chan F, Ng C, Kong A (2005). "The use of aldosterone-renin ratio as a diagnostic test for primary hyperaldosteronism and its test characteristics under different conditions of blood sampling". *J Clin Endocrinol Metab*. **90** (1): 72–8. doi:10.1210/jc.2004-1149. PMID 15483077.
12. ^ United Bristol Healthcare NHS Trust, the major teaching trust in South West England
13. ^ *a b* "Case Detection, Diagnosis, and Treatment of Patients with Primary Aldosteronism". *www.endocrine.org*. Retrieved 5 December 2014.
14. ^ Cotran, Ramzi S.; Kumar, Vinay; Fausto, Nelson; Nelso Fausto; Robbins, Stanley L.; Abbas, Abul K. (2005). *Robbins and Cotran pathologic basis of disease*. St. Louis, Mo: Elsevier Saunders. p. 1210. ISBN 0-7216-0187-1.
15. ^ Trono D, Cereda JM, Favre L (August 1983). "[Pseudo-Conn's syndrome due to intoxication with nonalcoholic pastis]". *Schweiz Med Wochenschr* (in French). **113** (31–32): 1092–5. PMID 6623028.
16. ^ http://labeling.pfizer.com/ShowLabeling.aspx?id=599
17. ^ Columbia Adrenal Center, Hyperaldosteronism (Conn's Syndrome)



| v · t · e | Diseases of the endocrine system (E00–E35, 240–259) | |
|---|---|---|
| Pancreas/ glucose metabolism | Hypofunction | Diabetes mellitus · *types:* (type 1 · type 2 · MODY 1 2 3 4 5 6 · · *complications* (coma · angiopathy · ketoacidosis · nephropathy · neuropathy · retinopathy · cardiomyopathy · · *insulin receptor* (Rabson–Mendenhall syndrome) · Insulin resistance · |
| | Hyperfunction | Hypoglycemia · *beta cell* (Hyperinsulinism) · *G cell* (Zollinger–Ellison syndrome) · |

| | | | |
|---|---|---|---|
| **Hypothalamic/ pituitary axes** | **Hypothalamus** | | *gonadotropin* (Kallmann syndrome · Adiposogenital dystrophy · · *CRH* (Tertiary adrenal insufficiency) · *vasopressin* (Neurogenic diabetes insipidus) · *general* (Hypothalamic hamartoma) · |
| | **Pituitary** | **Hyperpituitarism** | *anterior* (Acromegaly · Hyperprolactinaemia · Pituitary ACTH hypersecretion · · *posterior* (SIADH) · *general* (Nelson's syndrome) · |
| | | **Hypopituitarism** | *anterior* (Kallmann syndrome · Growth hormone deficiency · Hypoprolactinemia · ACTH deficiency/Secondary adrenal insufficiency · GnRH insensitivity · FSH insensitivity · LH/hCG insensitivity · · *posterior* (Neurogenic diabetes insipidus) · *general* (Empty sella syndrome · Pituitary apoplexy · Sheehan's syndrome · Lymphocytic hypophysitis · · |
| | **Thyroid** | **Hypothyroidism** | Iodine deficiency · Cretinism (Congenital hypothyroidism · · Myxedema · Euthyroid sick syndrome · |
| | | **Hyperthyroidism** | Hyperthyroxinemia (Thyroid hormone resistance · Familial dysalbuminemic hyperthyroxinemia · · Hashitoxicosis · Thyrotoxicosis factitia · Graves' disease · |
| | | **Thyroiditis** | Acute infectious · Subacute (De Quervain's · Subacute lymphocytic · · Autoimmune/chronic (Hashimoto's · Postpartum · Riedel's · · |
| | | **Goitre** | Endemic goitre · Toxic nodular goitre · Toxic multinodular goiter · Thyroid nodule · |
| | **Parathyroid** | **Hypoparathyroidism** | Hypoparathyroidism · Pseudohypoparathyroidism · Pseudopseudohypoparathyroidism · |
| | | **Hyperparathyroidism** | Primary · Secondary · Tertiary · Osteitis fibrosa cystica · |
| | **Adrenal** | **Hyperfunction** | *aldosterone:* Hyperaldosteronism/**Primary aldosteronism** (Conn syndrome · Bartter syndrome · Glucocorticoid remediable aldosteronism · · AME · Liddle's syndrome · 17α CAH · *cortisol:* Cushing's syndrome (Pseudo-Cushing's syndrome) · *sex hormones:* 21α CAH · 11β CAH · |
| | | **Hypofunction/ Adrenal insufficiency (Addison's, WF)** | *aldosterone:* Hypoaldosteronism (21α CAH · 11β CAH · · *cortisol:* CAH (Lipoid · 3β · 11β · 17α · 21α · · *sex hormones:* 17α CAH · |

| | | |
|---|---|---|
| | **Gonads** | *ovarian:* Polycystic ovary syndrome · Premature ovarian failure · *testicular: enzymatic* (5α-reductase deficiency · 17β-hydroxysteroid dehydrogenase deficiency · aromatase excess syndrome) · · *Androgen receptor* (Androgen insensitivity syndrome) · *general:* Hypogonadism (Delayed puberty) · Hypergonadism (Precocious puberty · · Hypoandrogenism · Hypoestrogenism · Hyperandrogenism · Hyperestrogenism · Postorgasmic illness syndrome · |
| **Height** | | Dwarfism/Short stature (Midget · Laron syndrome · Psychosocial · Ateliosis · · Gigantism · |
| **Multiple** | | Autoimmune polyendocrine syndrome multiple (APS1 · APS2 · · Carcinoid syndrome · Multiple endocrine neoplasia (1 · 2A · 2B · · Progeria (Werner syndrome · Acrogeria · Metageria · · Woodhouse-Sakati syndrome · |

Categories: Adrenal gland disorders




# Vitamin $B_{12}$ deficiency

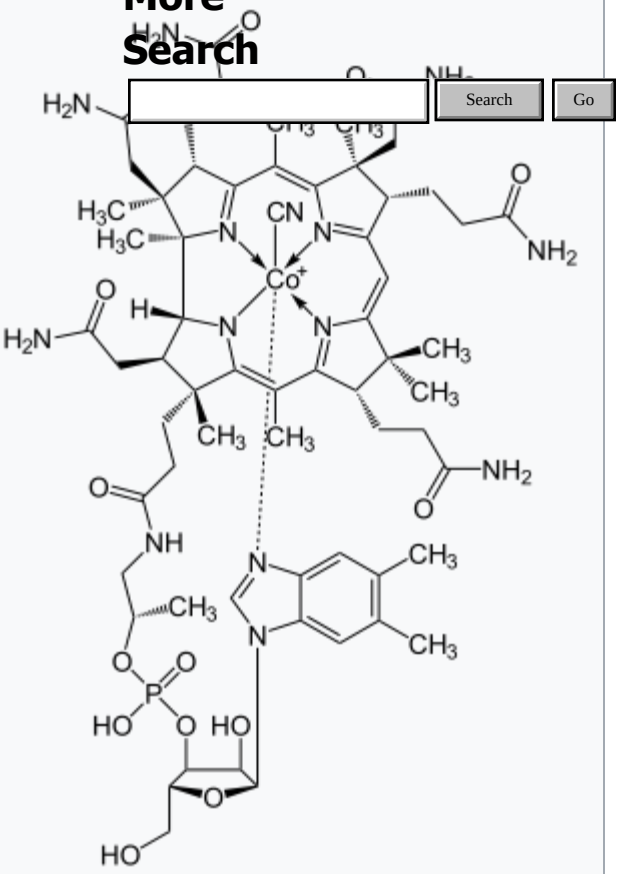
From Wikipedia, the free encyclopedia

**Vitamin $B_{12}$ deficiency**, also known as **hypocobalaminemia**, is low blood levels of vitamin $B_{12}$.[1] A wide variety of signs and symptoms may occur including a decreased ability to think and behavioural and emotional changes such as depression, irritability, and psychosis. Abnormal sensations, changes in reflexes, and poor muscle function can also occur as may inflammation of the tongue, decreased taste, low red blood cells, reduced heart function, and decreased fertility.[2] In young children symptoms include poor growth, poor development, and difficulties with movement.[3] Without early treatment some of the changes may be permanent.[4]

Common causes include poor absorption from the stomach or intestines, decreased intake, and increased requirements. Decreased absorption may be due to pernicious anemia, surgical removal of the stomach, chronic inflammation of the pancreas, intestinal parasites, certain medications, and some genetic disorders. Decreased intake may occur in those who eat a vegan diet or are malnourished. Increased requirements occur in HIV/AIDS and in those with rapid red blood cell breakdown.[2] Diagnosis is typically based on vitamin $B_{12}$ blood levels below 120–180 picomol/L (170–250 pg/mL) in adults. Elevated methylmalonic acid levels (values >0.4 micromol/L) may also indicate a deficiency. A type of low red blood cells known as megaloblastic anemia is often but not always present.[3]

Supplementation is recommended to prevent deficiency in vegetarians who are pregnant.[3] Once identified it is easily treated with supplementation by mouth or injection.[5] There are no concerns from excess vitamin $B_{12}$ among those who are otherwise healthy.[3] Some cases may also be helped by treating the underlying cause.[6] Other cases may require ongoing supplementation as the underlying cause is not curable.[7] Vitamin $B_{12}$ deficiency is common.[2] It is estimated to occur in about 6% of those under the age of 60 and 20% of those over the age of 60. Rates may be as high as 80% in parts of Africa and Asia.[2]

**Vitamin $B_{12}$ deficiency**



Cyanocobalamin

| Classification and external resources | |
|---|---|
| **Specialty** | Neurology |
| **ICD-10** | E53.8 |
| **ICD-9-CM** | 266.2 |
| **DiseasesDB** | 13905 |
| **MedlinePlus** | 000574 |
| **Patient UK** | Vitamin B12 deficiency |

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## Signs and symptoms [edit]

Vitamin $B_{12}$ deficiency can lead to vitamin $B_{12}$ deficiency anemia and neurologic dysfunction.[8] A mild deficiency may not cause any discernible symptoms, but as the deficiency becomes more significant symptoms of anemia may result, such as weakness, fatigue, light-headedness, rapid heartbeat, rapid breathing and pale color to the skin. It may also cause easy bruising or bleeding, including bleeding gums. GI side effects including sore tongue, stomach upset, weight loss, and diarrhea or constipation. If the deficiency is not corrected, nerve cell damage can result. If this happens, vitamin $B_{12}$ deficiency may result in tingling or numbness to the fingers and toes, difficulty walking, mood changes, depression, memory loss, disorientation and, in severe cases, dementia.

The main syndrome of vitamin $B_{12}$ deficiency is pernicious anemia. It is characterized by a triad of symptoms:

1. Anemia with bone marrow promegaloblastosis (megaloblastic anemia). This is due to the inhibition of DNA synthesis (specifically purines and thymidine)
2. Gastrointestinal symptoms: alteration in bowel motility, such as mild diarrhea or constipation, and loss of bladder or bowel control.[9] These are thought to be due to defective DNA synthesis inhibiting replication in a site with a high turnover of cells. This may also be due to the autoimmune attack on the parietal cells of the stomach in pernicious anemia. There is an association with GAVE syndrome (commonly called watermelon stomach) and pernicious anemia.[10]
3. Neurological symptoms: Sensory or motor deficiencies (absent reflexes, diminished vibration or soft touch sensation), subacute combined degeneration of spinal cord, seizures,[11][12][13][14] or even symptoms of dementia[15] and or other psychiatric symptoms may be present. The presence of peripheral sensory-motor symptoms or subacute combined degeneration of spinal cord strongly suggests the presence of a $B_{12}$ deficiency instead of folate deficiency. Methylmalonic acid, if not properly handled by $B_{12}$, remains in the myelin sheath, causing fragility. Dementia and depression have been associated with this deficiency as well, possibly from the under-production of methionine because of the inability to convert homocysteine into this product. Methionine is a necessary cofactor in the production of several neurotransmitters.

Each of those symptoms can occur either alone or along with others. The neurological complex, defined as *myelosis funicularis*, consists of the following symptoms:

1. Impaired perception of deep touch, pressure and vibration, loss of sense of touch, very annoying and persistent paresthesias
2. Ataxia of dorsal chord type
3. Decrease or loss of deep muscle-tendon reflexes
4. Pathological reflexes — Babinski, Rossolimo and others, also severe paresis

Vitamin $B_{12}$ deficiency can cause severe and irreversible damage, especially to the brain and nervous system. These symptoms of neuronal damage may not reverse after correction of hematological abnormalities, and the chance of complete reversal decreases with the length of time the neurological

symptoms have been present.

Tinnitus may be associated with vitamin $B_{12}$ deficiency.[16]

### Psychological [edit]

Vitamin $B_{12}$ deficiency can also cause symptoms of mania and psychosis, fatigue, memory impairment, irritability, depression, ataxia, and personality changes.[17][18][19] In infants symptoms include irritability, failure to thrive, apathy, anorexia, and developmental regression.[20][21]

## Causes [edit]

- Inadequate dietary intake of vitamin $B_{12}$. Vitamin $B_{12}$ occurs in animal products (eggs, meat, milk) and recent research indicates it may also occur in some algae, such as *Chlorella*[22][23][24] and Susabi-nori (*Porphyra yezoensis*).[25][26] $B_{12}$ isolated from bacterial cultures is also added to many fortified foods, and available as a dietary supplement.[27] Vegans, and also vegetarians but to a lesser degree, may be at risk for $B_{12}$ deficiency due to inadequate dietary intake of $B_{12}$, if they do not supplement. However, $B_{12}$ deficiency can occur even in people who consume meat, poultry, and fish.[28] Children are at a higher risk for $B_{12}$ deficiency due to inadequate dietary intake, as they have fewer vitamin stores and a relatively larger vitamin need per calorie of food intake.
- Selective impaired absorption of vitamin $B_{12}$ due to intrinsic factor deficiency. This may be caused by the loss of gastric parietal cells in chronic atrophic gastritis (in which case, the resulting megaloblastic anemia takes the name of "pernicious anemia"), or may result from wide surgical resection of stomach (for any reason), or from rare hereditary causes of impaired synthesis of intrinsic factor.
- Impaired absorption of vitamin $B_{12}$ in the setting of a more generalized malabsorption or maldigestion syndrome. This includes any form of structural damage or wide surgical resection of the terminal ileum (the principal site of vitamin $B_{12}$ absorption).
- Forms of achlorhydria (including that artificially induced by drugs such as proton pump inhibitors and histamine 2 receptor antagonists) can cause $B_{12}$ malabsorption from foods, since acid is needed to split $B_{12}$ from food proteins and salivary binding proteins.[29] This process is thought to be the most common cause of low $B_{12}$ in the elderly, who often have some degree of achlorhydria without being formally low in intrinsic factor. This process does not affect absorption of small amounts of $B_{12}$ in supplements such as multivitamins, since it is not bound to proteins, as is the $B_{12}$ in foods.[30]
- Surgical removal of the small bowel (for example in Crohn's disease) such that the patient presents with short bowel syndrome and is unable to absorb vitamin $B_{12}$. This can be treated with regular injections of vitamin $B_{12}$.
- Long-term use of ranitidine hydrochloride may contribute to deficiency of vitamin $B_{12}$.[31]
- Untreated celiac disease may also cause impaired absorption of this vitamin, probably due to damage to the small bowel mucosa. In some people, vitamin B12 deficiency may persist despite treatment with a gluten-free diet and require supplementation.[32]
- Some bariatric surgical procedures, especially those that involve removal of part of the stomach, such as Roux-en-Y gastric bypass surgery. (Procedures such as the adjustable gastric band type do not appear to affect $B_{12}$ metabolism significantly).[*citation needed*]
- Bacterial overgrowth in parts of the small bowel are thought to be able to absorb $B_{12}$. An example occurs in so-called blind loop syndrome.[*citation needed*]
- The diabetes medication metformin may interfere with $B_{12}$ dietary absorption.[33]
- Hereditary causes such as severe MTHFR deficiency, homocystinuria, and transcobalamin deficiency.[*citation needed*]
- One anecdotal study has shown that giardiasis may be a cause of vitamin $B_{12}$ deficiency,[34] but larger

studies have shown no correlation.[35]
- Malnutrition of alcoholism.
- Nitrous oxide abuse.[36]

## Mechanism [edit]

The total amount of vitamin $B_{12}$ stored in the body is between two and five milligrams in adults. Approximately 50% is stored in the liver, but approximately 0.1% is lost each day, due to secretions into the gut—not all of the vitamin in the gut is reabsorbed. While bile is the main vehicle for $B_{12}$ excretion, most of the $B_{12}$ secreted in bile is recycled via enterohepatic circulation. Due to the extreme efficiency of this mechanism, the liver can store three to five years worth of vitamin $B_{12}$ under normal conditions and functioning.[37] However, the rate at which $B_{12}$ levels may change when dietary intake is low depends on the balance between several variables.[38]

### Metabolic [edit]

Vitamin $B_{12}$ deficiency causes particular changes to the metabolism of 2 clinically relevant substances in humans:

1. Homocysteine (homocysteine to methionine, catalysed by methionine synthase) leading to hyperhomocysteinemia may lead to varicose veins[*citation needed*]
2. Methylmalonic acid (methylmalonyl-CoA to succinyl-CoA, of which methylmalonyl-CoA is made from methylmalonic acid in a preceding reaction)

Methionine is activated to *S*-adenosyl methionine, which aids in purine and thymidine synthesis, myelin production, protein/neurotransmitters/fatty acid/phospholipid production and DNA methylation. 5-Methyl tetrahydrofolate provides a methyl group, which is released to the reaction with homocysteine, resulting in methionine. This reaction requires cobalamin as a cofactor. The creation of 5-methyl tetrahydrofolate is an irreversible reaction. If $B_{12}$ is absent, the forward reaction of homocysteine to methionine does not occur, and the replenishment of tetrahydrofolate stops.[39]

Because $B_{12}$ and folate are involved in the metabolism of homocysteine, hyperhomocysteinuria is a non-specific marker of deficiency. Methylmalonic acid is used as a more specific test of $B_{12}$ deficiency.

### Pathomorphology [edit]

A spongiform state of neural tissue along with edema of fibers and deficiency of tissue. The myelin decays, along with axial fiber. In later phases, fibric sclerosis of nervous tissues occurs. Those changes apply to dorsal parts of the spinal cord and to pyramidal tracts in lateral cords. The pathophysiologic state of the spinal cord is called subacute combined degeneration of spinal cord.[40]

In the brain itself, changes are less severe: They occur as small sources of nervous fibers decay and accumulation of astrocytes, usually subcortically located, and also round hemorrhages with a torus of glial cells. Pathological changes can be noticed as well in the posterior roots of the cord and, to lesser extent, in peripheral nerves. Abnormalities might be observed in MRI.[41]

## Diagnosis [edit]

Serum $B_{12}$ levels are often low in $B_{12}$ deficiency, but if other features of $B_{12}$ deficiency are present with normal $B_{12}$ then further investigation is warranted. One possible explanation for normal $B_{12}$ levels in $B_{12}$ deficiency is antibody interference in people with high titres of intrinsic factor antibody.[42] Some researchers propose that the current standard norms of vitamin B levels are too low.[43] One Japanese study states

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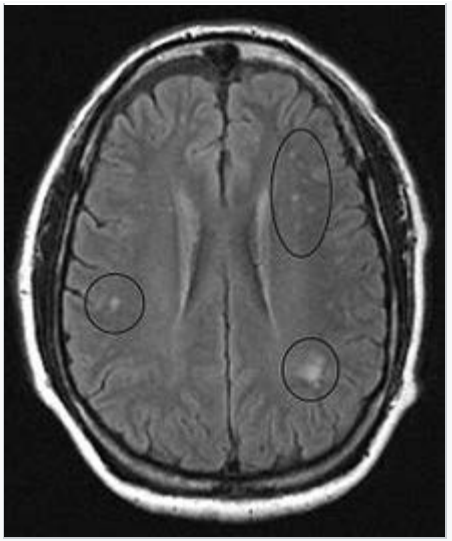
the normal limits as 500–1,300 pg/mL.[44] Range of vitamin B12 levels in humans is considered as normal: >300 pg/mL; moderate deficiency: 201–300 pg/mL; and severe deficiency: <201 pg/mL.[45]

Serum vitamin $B_{12}$ tests results are in pg/mL (picograms/milliliter) or pmol/L (picomoles/liter). The laboratory reference ranges for these units are similar, since the molecular weight of $B_{12}$ is approximately 1000, the difference between mL and L. Thus: 550 pg/mL = 400 pmol/L.

Serum homocysteine and methylmalonic acid levels are considered more reliable indicators of $B_{12}$ deficiency than the concentration of $B_{12}$ in blood.[46] The levels of these substances are high in $B_{12}$ deficiency and can be helpful if the diagnosis is unclear.

Routine monitoring of methylmalonic acid levels in urine is an option for people who may not be getting enough dietary $B_{12}$, as a rise in methylmalonic acid levels may be an early indication of deficiency.[47]

If nervous system damage is suspected, $B_{12}$ analysis in cerebrospinal fluid is possible, though such an invasive test should be considered only if blood testing is inconclusive.[48]



MRI image of the brain in an axial view showing the "precontrast FLAIR image". Note the abnormal lesions (circled) in the per ventricular area suggesting white matter pathology in someone with vitamin B12 deficiency.

The Schilling test has been largely supplanted by tests for antiparietal cell and intrinsic factor antibodies.

## Effect of folic acid [edit]

The National Institutes of Health has found that "Large amounts of folic acid can mask the damaging effects of vitamin $B_{12}$ deficiency by correcting the megaloblastic anemia caused by vitamin $B_{12}$ deficiency without correcting the neurological damage that also occurs", there are also indications that "high serum folate levels might not only mask vitamin $B_{12}$ deficiency, but could also exacerbate the anemia and worsen the cognitive symptoms associated with vitamin $B_{12}$ deficiency".[3] Due to the fact that in the United States legislation has required enriched flour to contain folic acid to reduce cases of fetal neural-tube defects, consumers may be ingesting more than they realize.[49] To counter the masking effect of $B_{12}$ deficiency the NIH recommends "folic acid intake from fortified food and supplements should not exceed 1,000 µg daily in healthy adults."[3] Most importantly, $B_{12}$ deficiency needs to be treated with $B_{12}$ repletion. Limiting folic acid will not counter the irrevocable neurological damage that is caused by untreated $B_{12}$ deficiency.[*citation needed*]

# Treatment [edit]

$B_{12}$ can be supplemented by pill or injection and appear to be equally effective in those with low levels due to absorption problems.[5]

When large doses are given by mouth its absorption does not rely on the presence of intrinsic factor or an intact ileum. Generally 1 to 2 mg daily is required as a large dose.[50] Even pernicious anemia can be treated entirely by the oral route.[51][52][53] These supplements carry such large doses of the vitamin that 1% to 5% of high oral doses of


Hydroxocobalamin injection is a clear red liquid solution of hydroxocobalamin.

free crystalline $B_{12}$ is absorbed along the entire intestine by passive diffusion.

## Epidemiology [edit]

In the developing world the deficiency is very widespread, with significant levels of deficiency in Africa, India, and South and Central America. This is theorized to be due to low intakes of animal products, particularly among the poor.[54]

$B_{12}$ deficiency is more common in the elderly.[54] This is because $B_{12}$ absorption decreases greatly in the presence of atrophic gastritis, which is common in the elderly.

The 2000 Tufts University study found no correlation between eating meat and differences in $B_{12}$ serum levels.[28]

## See also [edit]

- Beriberi (caused by Vitamin B1 deficiency)

## References [edit]


1. ^ Herrmann, Wolfgang (2011). *Vitamins in the prevention of human diseases*. Berlin: Walter de Gruyter. p. 245. ISBN 9783110214482.
2. ^ *a b c d* Hunt, A; Harrington, D; Robinson, S (4 September 2014). "Vitamin B12 deficiency.". *BMJ (Clinical research ed.)*. **349**: g5226. doi:10.1136/bmj.g5226. PMID 25189324.
3. ^ *a b c d e f* "Dietary Supplement Fact Sheet: Vitamin B12 — Health Professional Fact Sheet". National Institutes of Health: Office of Dietary Supplements. 2016-02-11. Retrieved 2016-07-15.
4. ^ Lachner, C; Steinle, NI; Regenold, WT (2012). "The neuropsychiatry of vitamin B12 deficiency in elderly patients.". *The Journal of neuropsychiatry and clinical neurosciences*. **24** (1): 5–15. doi:10.1176/appi.neuropsych.11020052. PMID 22450609.
5. ^ *a b* Vidal-Alaball, J; Butler, CC; Cannings-John, R; Goringe, A; Hood, K; McCaddon, A; McDowell, I; Papaioannou, A (20 July 2005). "Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency.". *The Cochrane database of systematic reviews* (3): CD004655. doi:10.1002/14651858.CD004655.pub2. PMID 16034940.
6. ^ Wardlaw, Graeme J. Hankey, Joanna M. (2008). *Clinical neurology*. London: Manson. p. 466. ISBN 9781840765182.
7. ^ Schwartz, William (2012). *The 5-minute pediatric consult* (6th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 535. ISBN 9781451116564.
8. ^ Reynolds, E.H. (2014). "The neurology of folic acid deficiency". *Handb Clin Neurol*. **120**: 927–43. doi:10.1016/B978-0-7020-4087-0.00061-9. PMID 24365361.
9. ^ Briani C, Dalla Torre C, Citton V, Manara R, Pompanin S, Binotto G, Adami F (2013). "Cobalamin Deficiency: Clinical Picture and Radiological Findings". *Nutrients*. **5** (11): 4521–4539. doi:10.3390/nu5114521. ISSN 2072-6643. PMC 3847746. PMID 24248213.
10. ^ DN Amarapurka MD, ND Patel MD (September 2004). "Gastric Antral Vascular Ectasia Syndrome". *Journal of The Association of Physcians of India*. **52**: 757.
11. ^ Matsumoto A, Shiga Y, Shimizu H, Kimura I, Hisanaga K (Apr 2009). "[Encephalomyelopathy due to vitamin B12

deficiency with seizures as a predominant symptom]". *Rinshō Shinkeigaku = Clinical Neurology*. **49** (4): 179–85. doi:10.5692/clinicalneurol.49.179. PMID 19462816.
12. ^ Kumar S (Mar 2004). "Recurrent seizures: an unusual manifestation of vitamin B12 deficiency". *Neurology India*. Neurologyindia.com. **52** (1): 122–123. PMID 15069260.
13. ^ Mustafa TAŞKESEN; Ahmet YARAMIŞ; Selahattin KATAR; Ayfer GÖZÜ PİRİNÇÇİOĞLU; Murat SÖKER. "Neurological presentations of nutritional vitamin B12 deficiency in 42 breastfed infants in Southeast Turkey" (PDF). *Turk J Med Sci*. **41** (6): 1091–1096. Retrieved 2013-12-29.
14. ^ Yavuz H (Sep 2008). "'Vitamin B12 deficiency and seizures'". *Developmental Medicine and Child Neurology* (Open access). **50** (9): 720. doi:10.1111/j.1469-8749.2008.03083.x. PMID 18754925.
15. ^ Kumar S, Narasimha A, Holla B, Viswanath B, Narayanaswamy JC, Math SB, Chandrashekar CR (2013). "Reversible dementia in young persons due to cobalamin deficiency". *The Journal of Neuropsychiatry and Clinical Neurosciences*. **25**: E62–E63. doi:10.1176/appi.neuropsych.12040083.
16. ^ Stover, editors, Janos Zempleni, John W. Suttie, Jesse F. Gregory, III, Patrick J. (2014). *Handbook of vitamins* (Fifth edition. ed.). Hoboken: CRC Press. p. 477. ISBN 9781466515574.
17. ^ Sethi NK, Robilotti E, Sadan Y (2005). "Neurological Manifestations Of Vitamin B-12 Deficiency". *The Internet Journal of Nutrition and Wellness*. **2** (1). doi:10.5580/5a9.
18. ^ Masalha R, Chudakov B, Muhamad M, Rudoy I, Volkov I, Wirguin I (Sep 2001). "Cobalamin-responsive psychosis as the sole manifestation of vitamin B12 deficiency". *The Israel Medical Association Journal*. **3** (9): 701–703. PMID 11574992.
19. ^ "Pernicious anemia: MedlinePlus Medical Encyclopedia". National Institutes of Health: National Library of Medicine. Retrieved 2013-12-29.
20. ^ Dror DK, Allen LH (May 2008). "Effect of vitamin B12 deficiency on neurodevelopment in infants: current knowledge and possible mechanisms". *Nutrition Reviews*. **66** (5): 250–5. doi:10.1111/j.1753-4887.2008.00031.x. PMID 18454811.
21. ^ Black MM (Jun 2008). "Effects of vitamin B12 and folate deficiency on brain development in children". *Food and Nutrition Bulletin*. **29** (2 Suppl): S126–31. PMC 3137939. PMID 18709887.
22. ^ Kittaka-Katsura H, Fujita T, Watanabe F, Nakano Y (Aug 2002). "Purification and characterization of a corrinoid compound from Chlorella tablets as an algal health food". *Journal of Agricultural and Food Chemistry*. **50** (17): 4994–7. doi:10.1021/jf020345w. PMID 12166996.
23. ^ Watanabe F, Takenaka S, Kittaka-Katsura H, Ebara S, Miyamoto E (Oct 2002). "Characterization and bioavailability of vitamin B12-compounds from edible algae". *Journal of Nutritional Science and Vitaminology*. **48** (5): 325–31. doi:10.3177/jnsv.48.325. PMID 12656203.
24. ^ Nakano S, Takekoshi H, Nakano M (Mar 2010). "Chlorella pyrenoidosa supplementation reduces the risk of anemia, proteinuria and edema in pregnant women". *Plant Foods for Human Nutrition*. **65** (1): 25–30. doi:10.1007/s11130-009-0145-9. PMID 20013055.
25. ^ Watanabe F, Takenaka S, Katsura H, Miyamoto E, Abe K, Tamura Y, Nakatsuka T, Nakano Y (Dec 2000). "Characterization of a vitamin B12 compound in the edible purple laver, Porphyra yezoensis". *Bioscience, Biotechnology, and Biochemistry*. **64** (12): 2712–5. doi:10.1271/bbb.64.2712. PMID 11210144.
26. ^ Croft MT, Lawrence AD, Raux-Deery E, Warren MJ, Smith AG (Nov 2005). "Algae acquire vitamin B12 through a symbiotic relationship with bacteria". *Nature*. **438** (7064): 90–3. doi:10.1038/nature04056. PMID 16267554.
27. ^ Martens JH, Barg H, Warren MJ, Jahn D (Mar 2002). "Microbial production of vitamin B12". *Applied Microbiology and Biotechnology*. **58** (3): 275–85. doi:10.1007/s00253-001-0902-7. PMID 11935176.
28. ^ *a b* McBride, Judy (2 August 2000). "B12 Deficiency May Be More Widespread Than Thought". *Agricultural Research Service*. United States Department of Agriculture. Retrieved 2 July 2012.
29. ^ Lam JR, Schneider JL, Zhao W, Corley DA (Dec 2013). "Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency". *JAMA*. **310** (22): 2435–2442. doi:10.1001/jama.2013.280490. PMID 24327038.
30. ^ Baik, H.W.; Russell, R.M. (1999). "Vitamin B12 deficiency in the elderly". *Annu Rev Nutr*. **19**: 357–377. doi:10.1146/annurev.nutr.19.1.357. PMID 10448529.
31. ^ Yeomans ND, Hanson RG, Smallwood RA, Mihaly GW, Louis WJ (1982). "Effect of chronic ranitidine treatment on secretion of intrinsic factor". *Br Med J (Clin Res Ed)*. **285** (6337): 264. doi:10.1136/bmj.285.6337.264. PMC 1499627. PMID 6124297.
32. ^ Caruso R, Pallone F, Stasi E, Romeo S, Monteleone G (2013). "Appropriate nutrient supplementation in celiac disease". *Ann Med* (Review). **45** (8): 522–31. doi:10.3109/07853890.2013.849383. PMID 24195595.
33. ^ Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM (Oct 2006). "Risk factors of vitamin B(12) deficiency in patients receiving metformin". *Archives of Internal Medicine*. **166** (18): 1975–9. doi:10.1001/archinte.166.18.1975. PMID 17030830.
34. ^ Cordingley FT, Crawford GP (Feb 1986). "Giardia infection causes vitamin B12 deficiency". *Australian and New Zealand Journal of Medicine*. **16** (1): 78–9. doi:10.1111/j.1445-5994.1986.tb01127.x. PMID 3458451.

35. ^ Zarebavani M, Dargahi D, Einollahi N, Dashti N, Mohebali M, Rezaeian M (2012). "Serum levels of zinc, copper, vitamin B12, folate and immunoglobulins in individuals with giardiasis" (PDF). *Iran. J. Public Health*. **41**: 47–53. PMC 3640781. PMID 23641390.
36. ^ Kondo H, Osborne ML, Kolhouse JF, Binder MJ, Podell ER, Utley CS, Abrams RS, Allen RH (May 1981). "Nitrous oxide has multiple deleterious effects on cobalamin metabolism and causes decreases in activities of both mammalian cobalamin-dependent enzymes in rats". *The Journal of Clinical Investigation*. The American Society For Clinical Investigation. **67** (5): 1270–1283. doi:10.1172/JCI110155. PMC 370693. PMID 6112240.
37. ^ Voet, Donald, Voet, Judith G. (2010). *Biochemistry*. New York: J. Wiley & Sons. p. 957. ISBN 978-0470-57095-1.
38. ^ Yamada K (2013). "Chapter 9. Cobalt: Its Role in Health and Disease". In Astrid Sigel, Helmut Sigel and Roland K. O. Sigel. *Interrelations between Essential Metal Ions and Human Diseases*. Metal Ions in Life Sciences. **13**. Springer. pp. 295–320. doi:10.1007/978-94-007-7500-8_9.
39. ^ Shane B, Stokstad EL (1985). "Vitamin B12-folate interrelationships". *Annual Review of Nutrition*. **5**: 115–41. doi:10.1146/annurev.nu.05.070185.000555. PMID 3927946.
40. ^ "Vitamin B12 / Pathophysiology Text". LifeSave.org. p. 215. Retrieved 2013-12-31.
41. ^ Guez S, Chiarelli G, Menni F, Salera S, Principi N, Esposito S (2012). "Severe vitamin B12 deficiency in an exclusively breastfed 5-month-old Italian infant born to a mother receiving multivitamin supplementation during pregnancy". *BMC Pediatrics* (Full text). Biomedcentral.com. **12**: 85. doi:10.1186/1471-2431-12-85. PMC 3407531. PMID 22726312.
42. ^ Hamilton MS, Blackmore S, Lee A (Sep 2006). "Possible cause of false normal B-12 assays". *BMJ*. **333** (7569): 654–5. doi:10.1136/bmj.333.7569.654-c. PMC 1570871. PMID 16990334.
43. ^ Goodman M, Chen XH, Darwish D (Oct 1996). "Are U.S. lower normal B12 limits too low?". *Journal of the American Geriatrics Society*. **44** (10): 1274–5. doi:10.1111/j.1532-5415.1996.tb01389.x. PMID 8856015.
44. ^ Mitsuyama Y, Kogoh H (Mar 1988). "Serum and cerebrospinal fluid vitamin B12 levels in demented patients with CH3-B12 treatment--preliminary study". *The Japanese Journal of Psychiatry and Neurology*. **42** (1): 65–71. doi:10.1111/j.1440-1819.1988.tb01957.x. PMID 3398357.
45. ^ Solomon LR (2015). "Cobalamin-responsive disorders in the ambulatory care setting: unreliability of cobalamin, methylmalonic acid, and homocysteine testing". *Blood*. **105** (3): 978–85. doi:10.1182/blood-2004-04-1641. PMID 15466926.
46. ^ "Test used to diagnose $B_{12}$ deficiency may be inadequate". news-medical.net. October 28, 2004. Retrieved 2007-12-04.
47. ^ Donaldson MS (2000). "Metabolic vitamin B12 status on a mostly raw vegan diet with follow-up using tablets, nutritional yeast, or probiotic supplements". *Annals of Nutrition & Metabolism*. **44** (5–6): 229–34. doi:10.1159/000046689. PMID 11146329.
48. ^ Devalia V (Aug 2006). "Diagnosing vitamin B-12 deficiency on the basis of serum B-12 assay". *BMJ*. **333** (7564): 385–6. doi:10.1136/bmj.333.7564.385. PMC 1550477. PMID 16916826.
49. ^ Melinda Beck (January 18, 2011). "Sluggish? Confused? Vitamin B12 May Be Low". Wall Street Journal.
50. ^ Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J (Aug 1998). "Effective treatment of cobalamin deficiency with oral cobalamin". *Blood*. **92** (4): 1191–1198. PMID 9694707.
51. ^ Bolaman Z, Kadikoylu G, Yukselen V, Yavasoglu I, Barutca S, Senturk T (2003). "Oral versus intramuscular cobalamin treatment in megaloblastic anemia: a single-center, prospective, randomized, open-label study". *Clin Ther*. **25** (12): 3124–34. doi:10.1016/S0149-2918(03)90096-8. PMID 14749150.
52. ^ Lane LA, Rojas-Fernandez C; Rojas-Fernandez (2002). "Treatment of vitamin b(12)-deficiency anemia: oral versus parenteral therapy". *Ann Pharmacother*. **36** (7–8): 1268–72. doi:10.1345/aph.1A122. PMID 12086562.
53. ^ Butler, C. C.; Vidal-Alaball, J; Cannings-John, R; McCaddon, A; Hood, K; Papaioannou, A; McDowell, I; Goringe, A (2006). "Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: A systematic review of randomized controlled trials". *Family Practice*. **23** (3): 279–285. doi:10.1093/fampra/cml008. PMID 16585128.
54. ^ *a b* Baik HW, Russell RM (1999). "Vitamin B12 deficiency in the elderly". *Annual Review of Nutrition*. **19**: 357–77. doi:10.1146/annurev.nutr.19.1.357. PMID 10448529.


## Further reading [edit]


- Pacholok SM, Stuart JJ (2011). *Could It Be B12?: An Epidemic of Misdiagnoses*. Fresno, CA: Linden Publishing. ISBN 978-1-61035-065-5.
- Hooper M (2012). *Pernicious Anaemia: The Forgotten Disease - the causes and consequences of Vitamin B12 Deficiency*. London: Hammersmith Press. ISBN 978-1-78161-004-6.


## External links [edit]

- http://www.webmd.com/a-to-z-guides/vitamin-b12-deficiency-anemia-topic-overview WebMD overview
- Vitamin B12 and Folate at Lab Tests Online

| v · t · e · | Malnutrition or nutrition disorders (E40–E68, 260–269) | | |
|---|---|---|---|
| Malnutrition | Protein-energy malnutrition | | Kwashiorkor · Marasmus · Catabolysis · |
| | Vitamin deficiency | B vitamins | $B_1$: Beriberi / Wernicke–Korsakoff syndrome (Wernicke's encephalopathy · Korsakoff's syndrome) · $B_2$: Riboflavin deficiency · $B_3$: Pellagra (Niacin deficiency) · $B_6$: Pyridoxine deficiency · $B_7$: Biotin deficiency · $B_9$: Folate deficiency · $B_{12}$: **Vitamin $B_{12}$ deficiency** · |
| | | Other vitamins | A: Vitamin A deficiency/Bitot's spots · C: Scurvy · D: Vitamin D deficiency/Rickets/Osteomalacia · E: Vitamin E deficiency · K: Vitamin K deficiency · |
| | Mineral deficiency | | Sodium · Potassium · Magnesium · Calcium · Iron · Zinc · Manganese · Copper · Iodine · Chromium · Molybdenum · Selenium (Keshan disease) · |
| Overnutrition | Overweight · Obesity · | | Childhood obesity · Obesity hypoventilation syndrome · Abdominal obesity · |
| | Vitamin poisoning | | Hypervitaminosis A · Hypervitaminosis D · Hypervitaminosis E · |
| | Mineral overload | | *see inborn errors of metal metabolism, toxicity* · |

Categories: Vitamin deficiencies | Biology of bipolar disorder | Vitamin B12




# Book:General surgery

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# Appendicitis

From Wikipedia, the free encyclopedia

**Appendicitis** is inflammation of the appendix. Symptoms commonly include right lower abdominal pain, nausea, vomiting, and decreased appetite. However, approximately 40% of people do not have these typical symptoms.[2] Severe complications of a ruptured appendix include widespread, painful inflammation of the inner lining of the abdominal wall and sepsis.[3]

Appendicitis is caused by a blockage of the hollow portion of the appendix.[4] This is most commonly due to a calcified "stone" made of feces. Inflamed lymphoid tissue from a viral infection, parasites, gallstone, or tumors may also cause the blockage.[5] This blockage leads to increased pressures in the appendix, decreased blood flow to the tissues of the appendix, and bacterial growth inside the appendix causing inflammation.[5][6] The combination of inflammation, reduced blood flow to the appendix and distention of the appendix causes tissue injury and tissue death.[7] If this process is left untreated, the appendix may burst, releasing bacteria into the abdominal cavity, leading to severe abdominal pain and increased complications.[7][8]

The diagnosis of appendicitis is largely based on the person's signs and symptoms.[6] In cases where the diagnosis cannot be made based on the person's history and physical exam, close observation, radiographic imaging and laboratory tests can be helpful. The two most common imaging tests used are ultrasound and computed tomography (CT scan).[9] CT scan has been shown to be more accurate than ultrasound in detecting acute appendicitis.[10] However, ultrasound may be preferred as the first imaging test in children and pregnant women because of the risks associated with radiation exposure from CT scans.[9]

The standard treatment for acute appendicitis is surgical removal of the appendix.[5][6] This may be done by an open incision in the abdomen (laparotomy) or through a few smaller incisions with the help of cameras (laparoscopy). Surgery decreases the risk of side effects or death associated with rupture of the appendix.[3] Antibiotics may be equally effective in certain cases of non-ruptured appendicitis.[11] It is one of the most common and significant causes of severe abdominal pain that comes on quickly worldwide. In 2013 about 16 million cases of appendicitis occurred.[12] This resulted in 72,000 deaths globally.[13] In the United States, appendicitis is the most common cause of acute abdominal pain requiring surgery.[2] Each year in the United States, more than 300,000 people with appendicitis have their appendix surgically removed.[14] Reginald Fitz is credited with being the first person to describe the condition in 1886.[15]

**Appendicitis**

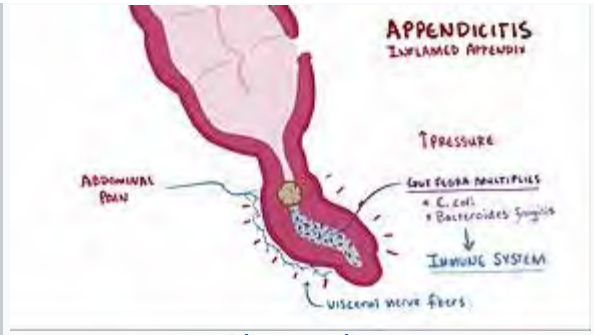
**Synonyms** Typhlitis[1]

An acutely inflamed and enlarged appendix, sliced lengthwise.

| Classification and external resources | |
|---|---|
| **Specialty** | General surgery |
| **ICD-10** | K35 - K37 |
| **ICD-9-CM** | 540-543 |
| **DiseasesDB** | 885 |
| **MedlinePlus** | 000256 |
| **eMedicine** | med/3430 emerg/41 ped/127 ped/2925 |
| **Patient UK** | Appendicitis |
| **MeSH** | *C06.405.205.099* |

[edit on Wikidata]

Contents

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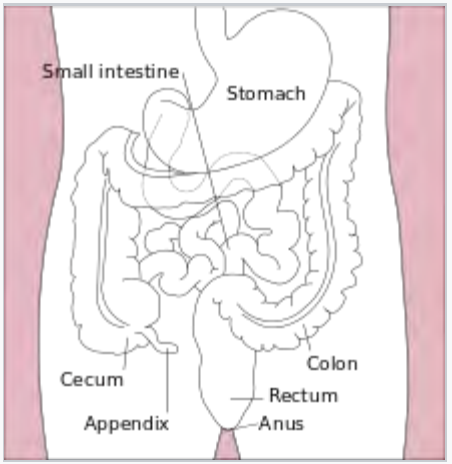
Video explanation

## Signs and symptoms [edit]

The presentation of acute appendicitis includes abdominal pain, nausea, vomiting, and fever. As the appendix becomes more swollen and inflamed, it begins to irritate the adjoining abdominal wall. This leads to the localization of the pain to the right lower quadrant. This classic migration of pain may not be seen in children under three years. This pain can be elicited through signs and can be severe. Signs include localized findings in the right iliac fossa. The abdominal wall becomes very sensitive to gentle pressure (palpation). There is severe pain on sudden release of deep pressure in the lower abdomen (rebound tenderness). If the appendix is retrocecal (localized behind the cecum), even deep pressure in the right lower quadrant may fail to elicit tenderness (silent appendix). This is because the cecum, distended with gas, protects the inflamed appendix from pressure. Similarly, if the appendix lies entirely within the pelvis, there is usually complete absence of abdominal rigidity. In such cases, a digital rectal examination elicits tenderness in the rectovesical pouch. Coughing causes point tenderness in this area (McBurney's point).




Location of the appendix in the digestive system

## Causes [edit]

Acute appendicitis seems to be the end result of a primary obstruction of the appendix.[16][4] Once this obstruction occurs, the appendix becomes filled with mucus and swells. This continued production of mucus leads to increased pressures within the lumen and the walls of the appendix. The increased pressure results in thrombosis and occlusion of the small vessels, and stasis of lymphatic flow. At this point spontaneous recovery rarely occurs. As the occlusion of blood vessels progresses, the appendix becomes ischemic and then necrotic. As bacteria begin to leak out through the dying walls, pus forms within and around the appendix (suppuration). The end result is appendiceal rupture (a 'burst appendix') causing peritonitis, which may lead to sepsis and eventually death. These events are responsible for the slowly evolving abdominal pain and other commonly associated symptoms.[7]

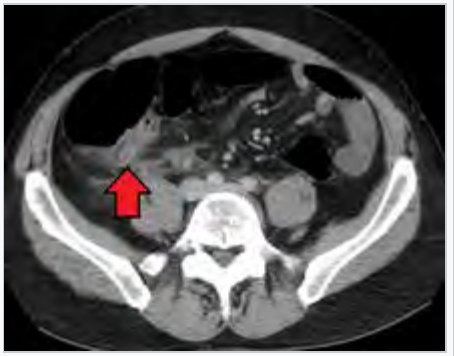
The causative agents include bezoars, foreign bodies, trauma, intestinal worms, lymphadenitis and, most commonly, calcified fecal deposits that are known as appendicoliths or fecaliths.[17][18] The occurrence of obstructing fecaliths has attracted attention since their presence in people with appendicitis is higher in developed than in developing countries.[19] In addition an appendiceal fecalith is commonly associated with complicated appendicitis.[20] Fecal stasis and arrest may play a role, as demonstrated by people with acute

appendicitis having fewer bowel movements per week compared with healthy controls.[18][21]

The occurrence of a fecalith in the appendix was thought to be attributed to a right-sided fecal retention reservoir in the colon and a prolonged transit time. However, a prolonged transit time was not observed in subsequent studies.[22] From epidemiological data, it has been stated that diverticular disease and adenomatous polyps were unknown and colon cancer exceedingly rare in communities exempt from appendicitis.[23][24] And acute appendicitis has been shown to occur antecedent to cancer in the colon and rectum.[25] Several studies offer evidence that a low fiber intake is involved in the pathogenesis of appendicitis.[26][27][28] This low intake of dietary fiber is in accordance with the occurrence of a right-sided fecal reservoir and the fact that dietary fiber reduces transit time.[29]

# Diagnosis [edit]

Diagnosis is based on a medical history (symptoms) and physical examination which can be supported by an elevation of neutrophilic white blood cells and imaging studies if needed. (Neutrophils are the primary white blood cells that respond to a bacterial infection.) Histories fall into two categories, typical and atypical.



Appendicitis as seen on CT imaging

Typical appendicitis includes several hours of generalized abdominal pain that begins in the region of the umbilicus with associated anorexia, nausea, or vomiting. The pain then "localizes" into the right lower quadrant where the tenderness increases in intensity. It is possible the pain could localize to the left lower quadrant in people with situs inversus totalis. The combination of pain, anorexia, leukocytosis, and fever is classic.

Atypical histories lack this typical progression and may include pain in the right lower quadrant as an initial symptom. Irritation of the peritoneum (inside lining of the abdominal wall) can lead to increased pain on movement, or jolting, for example going over speedbumps.[30] Atypical histories often require imaging with ultrasound and/or CT scanning.[31]

## Clinical [edit]

- Aure-Rozanova's sign: Increased pain on palpation with finger in right Petit triangle (can be a positive Shchetkin-Bloomberg's).[32]
- Bartomier-Michelson's sign: Increased pain on palpation at the right iliac region as the person being examined lies on his or her left side compared to when he/she lies on the back.[32]
- Dunphy's sign: Increased pain in the right lower quadrant with coughing.[33]
- Hamburger sign: The patient refuses to eat (anorexia is 80% specific for appendicitis)[34]
- Kocher's (Kosher's) sign: From the person's medical history, the start of pain in the umbilical region with a subsequent shift to the right iliac region.[32]
- Massouh sign: Developed in and popular in southwest England, the examiner performs a firm swish with his or her index and middle finger across the abdomen from the xiphoid process to the left and the right iliac fossa. A positive Massouh sign is a grimace of the person being examined upon a right sided (and not left) sweep.[35]
- Obturator sign: The person being evaluated lies on her or his back with the hip and knee both flexed at ninety degrees. The examiner holds the person's ankle with one hand and knee with the other hand. The examiner rotates the hip by moving the person's ankle away from his or her body while allowing the knee to move only inward. A positive test is pain with internal rotation of the hip.[36]
- Psoas sign, also known as "Obraztsova's sign", is right lower-quadrant pain that is produced with either the passive extension of the right hip or by the active flexion of the person's right hip while supine. The pain that is elicited is due to inflammation of the peritoneum overlying the iliopsoas muscles and

inflammation of the psoas muscles themselves. Straightening out the leg causes pain because it stretches these muscles, while flexing the hip activates the iliopsoas and causes pain.[36]

- Rovsing's sign: Pain in the lower right abdominal quadrant with continuous deep palpation starting from the left iliac fossa upwards (counterclockwise along the colon). The thought is there will be increased pressure around the appendix by pushing bowel contents and air toward the ileocaecal valve provoking right-sided abdominal pain.[37]
- Sitkovskiy (Rosenstein)'s sign: Increased pain in the right iliac region as the person is being examined lies on his/her left side.[38]

## Blood and urine test [edit]

While there is no laboratory test specific for appendicitis, a complete blood count (CBC) is done to check for signs of infection. Although 70-90 percent of people with appendicitis may have an elevated white blood cell (WBC) count, there are many other abdominal and pelvic conditions that can cause the WBC count to be elevated.[39]

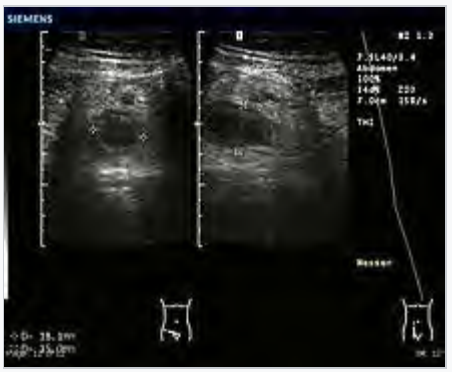
A urinalysis generally does not show infection, but it is important for determining pregnancy status, especially the possibility of an ectopic pregnancy in woman of childbearing age. The urinalysis is also important for ruling out a urinary tract infection as the cause of abdominal pain. The presence of more than 20 WBC per high-power field in the urine is more suggestive of a urinary tract disorder.[39]

## Imaging [edit]

In children the clinical examination is important to determine which children with abdominal pain should receive immediate surgical consultation and which should receive diagnostic imaging.[40] Because of the health risks of exposing children to radiation, ultrasound is the preferred first choice with CT scan being a legitimate follow-up if the ultrasound is inconclusive.[41][42][43] CT scan is more accurate than ultrasound for the diagnosis of appendicitis in adults and adolescents. CT scan has a sensitivity of 94%, specificity of 95%. Ultrasonography had an overall sensitivity of 86%, a specificity of 81%.[44]

## Ultrasound [edit]

Ultrasonography and Doppler sonography are useful to detect appendicitis, especially in children. Ultrasound can show free fluid collection in the right iliac fossa, along with a visible appendix with increased blood flow when using color Doppler, and noncompressibility of the appendix, as it is essentially a walled off abscess. Other secondary sonographic signs of acute appendicitis include the presence of echogenic mesenteric fat surrounding the appendix and the acoustic shadowing of an appendicolith.[45] In some cases (approximately 5%),[46] ultrasonography of the iliac fossa does not reveal any abnormalities despite the presence of appendicitis. This false negative finding is especially true of early appendicitis before the appendix has become significantly distended. In addition, false negative findings are more common in adults where larger amounts of fat and bowel gas make visualizing the appendix technically difficult. Despite these limitations, sonographic imaging in experienced hands can often distinguish between appendicitis and other diseases with similar symptoms. Some of these conditions include inflammation of lymph nodes near the appendix or pain originating from other pelvic organs such as the ovaries or Fallopian tubes.



Ultrasound image of acute appendicitis

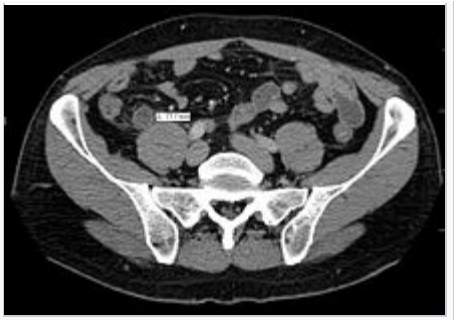
## Computed tomography [edit]

Where it is readily available, computed tomography (CT) has become frequently used, especially in people whose diagnosis is not obvious on history and physical examination. Concerns about radiation tend to limit

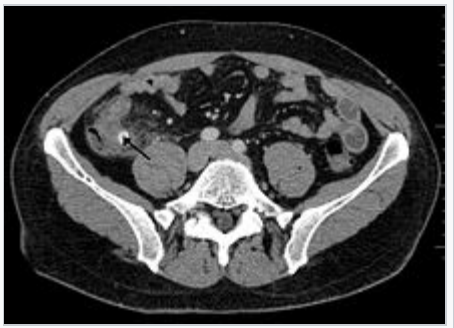
use of CT in pregnant women and children, especially with the increasingly widespread usage of MRI.[47][48]

The accurate diagnosis of appendicitis is multi-tiered, with the size of the appendix having the strongest positive predictive value, while indirect features can either increase or decrease sensitivity and specificity. A size of over 6 mm is both 95% sensitive and specific for appendicitis.[49]

However, because the appendix can be filled with fecal material, causing intraluminal distention, this criterion has shown limited utility in more recent meta analyses.[50] This is as opposed to ultrasound, in which the wall of the appendix can be more easily distinguished from intraluminal feces. In such scenarios, ancillary features such as increased wall enhancement as compared to adjacent bowel and inflammation of the surrounding fat, or fat stranding, can be supportive of the diagnosis, although their absence does not preclude it. In severe cases with perforation, an adjacent phlegmon or abscess can be seen. Dense fluid layering in the pelvis can also result, related to either pus or enteric spillage. When patients are thin or younger, the relative absence of fat can make the appendix and surrounding fat stranding difficult to see.[50]



A CT scan demonstrating acute appendicitis (note the appendix has a diameter of 17.1 mm and there is surrounding fat stranding)



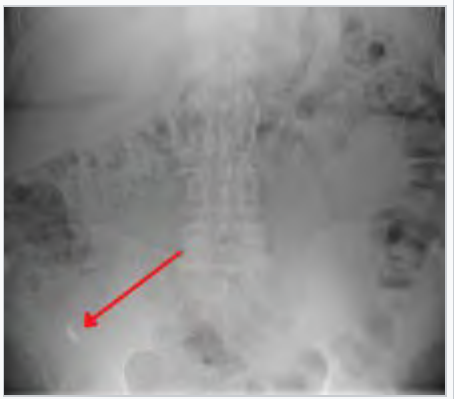
A fecalith marked by the arrow that has resulted in acute appendicitis.

## Magnetic resonance imaging [edit]

MRI use has become increasingly common for diagnosis of appendicitis in children and pregnant patients due to the radiation dosage that, while of nearly negligible risk in healthy adults, can be harmful to children or the developing fetus. In pregnancy, it has been found to be more useful during the second and third trimester, particularly as the enlargening uterus displaces the appendix, making it difficult to find by ultrasound. The periappendiceal stranding that is reflected on CT by fat stranding on MRI appears as increased fluid signal on T2 weighted sequences. First trimester pregnancies are usually not candidates for MRI, as the fetus is still undergoing organogenesis, and there are no long-term studies to date regarding its potential risks or side effects.[51]

## X-ray [edit]

In general, plain abdominal radiography (PAR) is not useful in making the diagnosis of appendicitis and should not be routinely obtained from a person being evaluated for appendicitis.[52][53] Plain abdominal films may be useful for the detection of ureteral calculi, small bowel obstruction, or perforated ulcer, but these conditions are rarely confused with appendicitis.[54] An opaque fecalith can be identified in the right lower quadrant in fewer than 5% of people being evaluated for appendicitis.[39] A barium enema has proven to be a poor diagnostic tool for appendicitis. While failure of the appendix to fill during a barium enema has been associated with appendicitis, up to 20% of normal appendices do not fill.[54]



Appendicolith as seen on plain X-ray

## Scoring systems [edit]

No excellent scoring system exists to determine

**Alvarado score**

| | |
|---|---|
| Migratory right iliac fossa pain | 1 point |
| Anorexia | 1 point |

if a child has

| | |
|---|---|
| Nausea and vomiting | 1 point |
| Right iliac fossa tenderness | 2 points |
| Rebound abdominal tenderness | 1 point |
| Fever | 1 point |
| High white blood cell count (leukocytosis) | 2 points |
| Shift to left (segmented neutrophils) | 1 point |
| **Total score** | **10 points** |

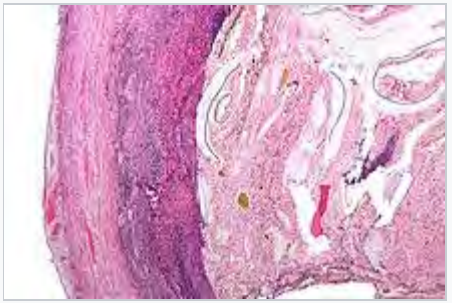
appendicitis.[55] The Alvarado score and pediatric appendicitis score are useful but not definitive.[55]

The Alvarado score is the most widely used scoring system. A score below 5 suggests against a diagnosis of appendicitis, whereas a score of 7 or more is predictive of acute appendicitis. In a person with an equivocal score of 5 or 6, a CT scan or ultrasound exam may be used to reduce the rate of negative appendectomy.

## Pathology [edit]

The definitive diagnosis is based on pathology. The histologic finding of appendicitis is neutrophilic infiltrate of the muscularis propria.

Periappendicits, inflammation of tissues around the appendix, is often found in conjunction with other abdominal pathology.[56]



Micrograph of appendicitis and periappendicitis. H&E stain.

## Differential diagnosis [edit]

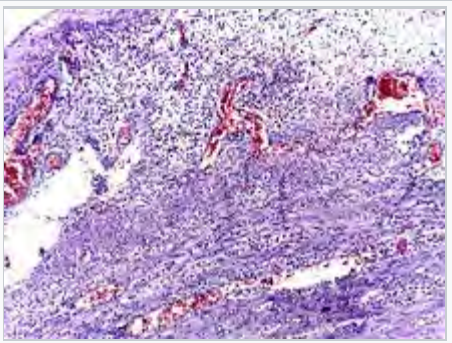
Children: Gastroenteritis, mesenteric adenitis, Meckel's diverticulitis, intussusception, Henoch–Schönlein purpura, lobar pneumonia, urinary tract infection (abdominal pain in the absence of other symptoms can occur in children with UTI), new-onset Crohn's disease or ulcerative colitis, pancreatitis, and abdominal trauma from child abuse; distal intestinal obstruction syndrome in children with cystic fibrosis; typhlitis in children with leukemia.

Women: A pregnancy test is important for all women of childbearing age since an ectopic pregnancy can have signs and symptoms similar to those of appendicitis. Other obstetrical/gynecological causes of similar abdominal pain in women include pelvic inflammatory disease, ovarian torsion, menarche, dysmenorrhea, endometriosis, and Mittelschmerz (the passing of an egg in the ovaries approximately two weeks before menstruation).[57]

Men: testicular torsion

Adults: new-onset Crohn's disease, ulcerative colitis, regional enteritis, renal colic, perforated peptic ulcer, pancreatitis, rectus sheath hematoma and epiploic appendagitis.

Elderly: diverticulitis, intestinal obstruction, colonic carcinoma, mesenteric ischemia, leaking aortic aneurysm.



Micrograph of appendicitis showing neutrophils in the muscularis propria. H&E stain.

The term "pseudoappendicitis" is used to describe a condition mimicking appendicitis.[58] It can be associated with *Yersinia enterocolitica*.[59]

# Management [edit]

Acute appendicitis is typically managed by surgery. However, in uncomplicated cases antibiotics are

effective and safe.[11][60] While antibiotics are effective for treating uncomplicated appendicitis, 26% of people had a recurrence within a year and required eventual appendectomy.[61]

In people with inflammatory bowel disease such as Crohn's disease or ulcerative colitis who present with appendicitis, surgical intervention is contraindicated, as the normal healing response following surgery is impaired by the underlying disease process, and the patients form non healing fistulas, sinus tracts and enteric leakage. In such scenarios, the underlying disease process must be treated medically with DMARDs, as opposed to surgically.[62]

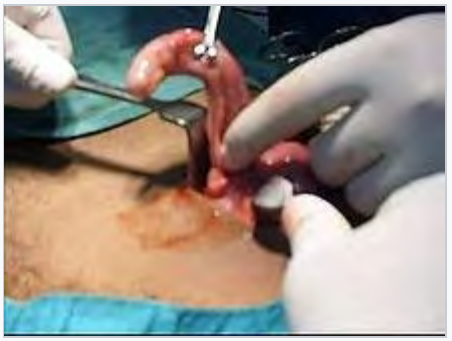
## Pain [edit]

Pain medications (such as morphine) do not appear to affect the accuracy of the clinical diagnosis of appendicitis and therefore should be given early in the patient's care.[63] Historically there were concerns among some general surgeons that analgesics would affect the clinical exam in children, and some recommended that they not be given until the surgeon was able to examine the person.[63]

## Surgery [edit]

*See also: Appendectomy*

The surgical procedure for the removal of the appendix is called an appendectomy. Appendectomy can be performed through open or laparoscopic surgery. Laparoscopic appendectomy has several advantages over open appendectomy as an intervention for acute appendicitis.[64]

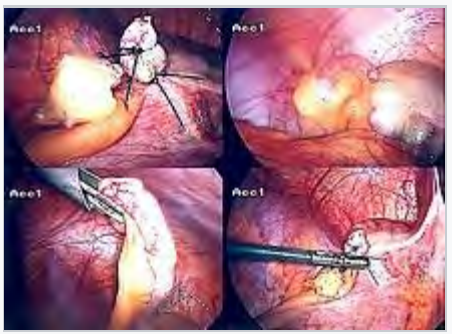


Inflamed appendix removal by open surgery

## Open appendectomy [edit]

For over a century, laparotomy (open appendectomy) was the standard treatment for acute appendicitis.[65] This procedure consists of the removal of the infected appendix through a single large incision in the lower right area of the abdomen.[66] The incision in a laparotomy is usually 2 to 3 inches (51 to 76 mm) long.

During an open appendectomy, the person with suspected appendicitis is placed under general anesthesia to keep the muscles completely relaxed and to keep the person unconscious. The incision is two to three inches (76 mm) long and it is made in the right lower abdomen, several inches above the hip bone. Once the incision opens the abdomen cavity and the appendix is identified, the surgeon removes the infected tissue and cuts the appendix from the surrounding tissue. After careful and close inspection of the infected area, and ensuring there are no signs that surrounding tissues are damaged or infected, the surgeon will start closing the incision. This means sewing the muscles and using surgical staples or stitches to close the skin up. To prevent infections, the incision is covered with a sterile bandage.



Laparoscopic appendectomy.

## Laparoscopic appendectomy [edit]

Laparoscopic appendectomy has become an increasingly prevalent intervention for acute appendicitis since its introduction in 1983.[67] This surgical procedure consists of making three to four incisions in the abdomen, each 0.25 to 0.5 inches (6.4 to 12.7 mm) long. This type of appendectomy is made by inserting a special surgical tool called laparoscope into one of the incisions. The laparoscope is connected to a monitor outside the person's body and it is designed to help the surgeon to inspect the infected area in the abdomen. The other two incisions are made for the specific removal of the appendix by using surgical instruments. Laparoscopic surgery requires general anesthesia, and it can last up to two hours. Laparoscopic appendectomy has several advantages over open appendectomy, including a shorter post-

operative recovery, less post-operative pain, and lower superficial surgical site infection rate. However, the occurrence of intra-abdominal abscess is almost three times more prevalent in laparoscopic appendectomy than open appendectomy.[68]

### Pre-surgery [edit]

The treatment begins by keeping the person who will be having surgery from eating or drinking for a given period, usually overnight. An intravenous drip is used to hydrate the person who will be having surgery. Antibiotics given intravenously such as cefuroxime and metronidazole may be administered early to help kill bacteria and thus reduce the spread of infection in the abdomen and postoperative complications in the abdomen or wound. Equivocal cases may become more difficult to assess with antibiotic treatment and benefit from serial examinations. If the stomach is empty (no food in the past six hours) general anaesthesia is usually used. Otherwise, spinal anaesthesia may be used.

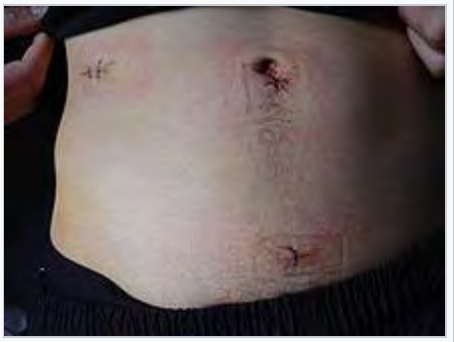
Once the decision to perform an appendectomy has been made, the preparation procedure takes approximately one to two hours. Meanwhile, the surgeon will explain the surgery procedure and will present the risks that must be considered when performing an appendectomy. (With all surgeries there are risks that must be evaluated before performing the procedures.) The risks are different depending on the state of the appendix. If the appendix has not ruptured, the complication rate is only about 3% but if the appendix has ruptured, the complication rate rises to almost 59%.[69] The most usual complications that can occur are pneumonia, hernia of the incision, thrombophlebitis, bleeding or adhesions. Recent evidence indicates that a delay in obtaining surgery after admission results in no measurable difference in outcomes to the person with appendicitis.[70][71]

The surgeon will explain how long the recovery process should take. Abdomen hair is usually removed to avoid complications that may appear regarding the incision.

In most cases, patients going in for surgery experience nausea or vomiting that requires medication before surgery. Antibiotics along with pain medication may be administrated before appendectomies.

### After surgery [edit]

Hospital lengths of stay typically range from a few hours to a few days but can be a few weeks if complications occur. The recovery process may vary depending on the severity of the condition: if the appendix had ruptured or not before surgery. Appendix surgery recovery is generally a lot faster if the appendix did not rupture.[72] It is important that people undergoing surgery respect their doctor's advice and limit their physical activity so the tissues can heal faster. Recovery after an appendectomy may not require diet changes or a lifestyle change.



The stitches the day after having the appendix removed by laparoscopic surgery

Length of hospital stays for appendicitis varies on the severity of the condition. A study from the United States found that in 2010, the average appendicitis hospital stay was 1.8 days. For stays where the person's appendix had ruptured, the average length of stay was 5.2 days.[8]

After surgery, the patient will be transferred to a postanesthesia care unit so his or her vital signs can be closely monitored to detect anesthesia- and/or surgery-related complications. Pain medication may be administered if necessary. After patients are completely awake, they are moved to a hospital room to recover. Most individuals will be offered clear liquids the day after the surgery, then progress to a regular diet when the intestines start to function properly. Patients are recommended to sit up on the edge of the bed and walk short distances several times a day. Moving is mandatory and pain medication may be given if necessary. Full recovery from appendectomies takes about four to six weeks but can be prolonged to up to eight weeks if the appendix had ruptured.

## Prognosis [edit]

Most people with appendicitis recover easily after surgical treatment, but complications can occur if treatment is delayed or if peritonitis occurs. Recovery time depends on age, condition, complications, and other circumstances, including the amount of alcohol consumption, but usually is between 10 and 28 days. For young children (around 10 years old), the recovery takes three weeks.

The possibility of peritonitis is the reason why acute appendicitis warrants speedy evaluation and treatment. People with suspected appendicitis may have to undergo a medical evacuation. Appendectomies have occasionally been performed in emergency conditions (i.e., not in a proper hospital), when a timely medical evacuation was impossible.

Typical acute appendicitis responds quickly to appendectomy and occasionally will resolve spontaneously. If appendicitis resolves spontaneously, it remains controversial whether an elective interval appendectomy should be performed to prevent a recurrent episode of appendicitis. Atypical appendicitis (associated with suppurative appendicitis) is more difficult to diagnose and is more apt to be complicated even when operated early. In either condition, prompt diagnosis and appendectomy yield the best results with full recovery in two to four weeks usually. Mortality and severe complications are unusual but do occur, especially if peritonitis persists and is untreated.

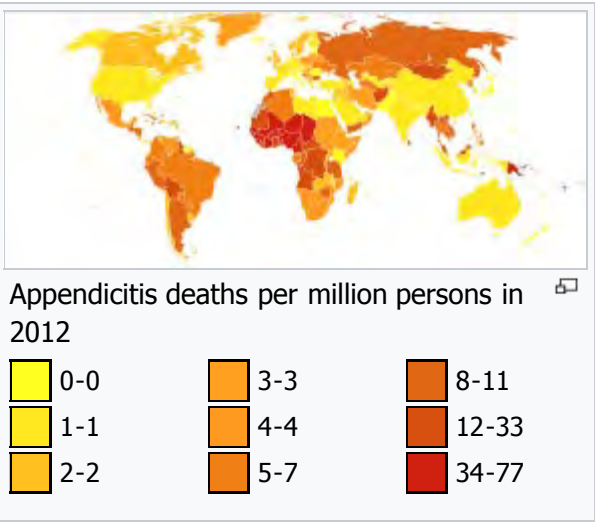
Another entity known as appendicular lump is talked about. It happens when the appendix is not removed early during infection and omentum and intestine adhere to it, forming a palpable lump. During this period, surgery is risky unless there is pus formation evident by fever and toxicity or by USG. Medical management treats the condition.

An unusual complication of an appendectomy is "stump appendicitis": inflammation occurs in the remnant appendiceal stump left after a prior incomplete appendectomy.[73] Stump appendicitis can occur months to years after initial appendectomy and can be identified with imaging modalities like ultrasound.[74]

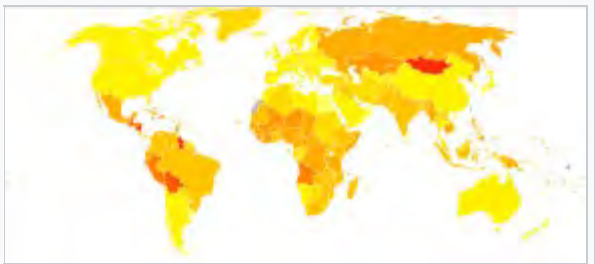
## Epidemiology [edit]

Appendicitis is most common between the ages of 5 and 40;[76] the median age is 28. It tends to affect males, those in lower income groups and, for unknown reasons, people living in rural areas.[77] In 2013 it resulted in 72,000 deaths globally down from 88,000 in 1990.[13]

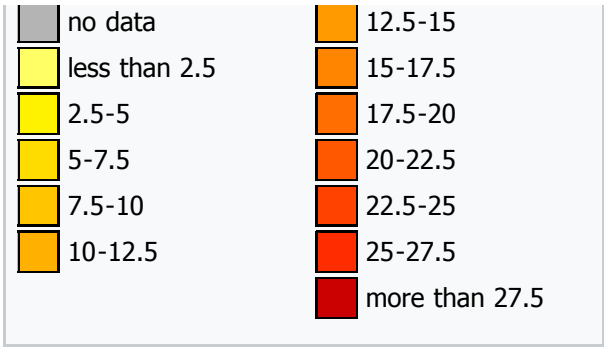
In the United States, there were nearly 293,000 hospitalizations involving appendicitis in 2010.[8] Appendicitis is one of the most frequent diagnoses for emergency department visits resulting in hospitalization among children ages 5–17 years in the United States.[78]




Appendicitis deaths per million persons in 2012



Disability-adjusted life year for appendicitis per 100,000 inhabitants in 2004.[75]




## References [edit]


1. ^ "appendicitis". *Medical Dictionary*. Merriam-Webster.
2. ^ *a b* Graffeo, Charles S.; Counselman, Francis L. (November 1996). "Appendicitis". *Emergency Medicine Clinics of North America*. **14** (4): 653–71. doi:10.1016/s0733-8627(05)70273-x. PMID 8921763.
3. ^ *a b* Hobler, K. (Spring 1998). "Acute and Suppurative Appendicitis: Disease Duration and its Implications for Quality Improvement" (PDF). *Permanente Medical Journal*. **2**.
4. ^ *a b* Pieper R, Kager L, Tidefeldt U (1982). "Obstruction of appendix vermiformis causing acute appendicitis. One of the most common causes of this is an acute viral infection which causes lymphoid hyperplasia and therefore obstruction. An experimental study in the rabbit". *Acta Chirurgica Scandinavica*. **148** (1): 63–72. PMID 7136413.
5. ^ *a b c* Longo, Dan L.; et al., eds. (2012). *Harrison's principles of internal medicine.* (18th ed.). New York: McGraw-Hill. p. Chapter 300. ISBN 978-0-07174889-6. Retrieved 6 November 2014.
6. ^ *a b c* Tintinalli, editor-in-chief Judith E. (2011). *Emergency medicine : a comprehensive study guide* (7. ed.). New York: McGraw-Hill. p. Chapter 84. ISBN 978-0-07-174467-6. Retrieved 6 November 2014.
7. ^ *a b c* *Schwartz's principles of surgery* (9th ed.). New York: McGraw-Hill, Medical Pub. Division. 2010. p. Chapter 30. ISBN 978-0-07-1547703.
8. ^ *a b c* Barrett, ML; Hines, AL; Andrews, RM (July 2013). "Trends in Rates of Perforated Appendix, 2001–2010" (PDF). *Healthcare Cost and Utilization Project Statistical Brief #159*. Agency for Healthcare Research and Quality. PMID 24199256.
9. ^ *a b* Paulson, EK; Kalady, MF; Pappas, TN (16 January 2003). "Clinical practice. Suspected appendicitis.". *The New England Journal of Medicine*. **348** (3): 236–42. doi:10.1056/nejmcp013351. PMID 12529465.
10. ^ Shogilev, DJ; Duus, N; Odom, SR; Shapiro, NI (November 2014). "Diagnosing appendicitis: evidence-based review of the diagnostic approach in 2014.". *The Western Journal of Emergency Medicine* (Review). **15** (7): 859–71. doi:10.5811/westjem.2014.9.21568. PMC 4251237. PMID 25493136.
11. ^ *a b* Varadhan KK, Neal KR, Lobo DN (2012). "Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials". *The BMJ*. **344**: e2156. doi:10.1136/bmj.e2156. PMC 3320713. PMID 22491789.
12. ^ Global Burden of Disease Study 2013 Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013". *The Lancet*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
13. ^ *a b* GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *The Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
14. ^ Mason, RJ (August 2008). "Surgery for appendicitis: is it necessary?". *Surgical infections*. **9** (4): 481–8. doi:10.1089/sur.2007.079. PMID 18687030.
15. ^ Fitz RH (1886). "Perforating inflammation of the vermiform appendix with special reference to its early diagnosis and treatment". *American Journal of Medical Science* (92): 321–46.
16. ^ Wangensteen OH, Bowers WF (1937). "Significance of the obstructive factor in the genesis of acute appendicitis". *Archives of Surgery*. **34** (3): 496–526. doi:10.1001/archsurg.1937.01190090121006.
17. ^ Hollerman, J.; Bernstein, MA; Kottamasu, SR; Sirr, SA (1988). "Acute recurrent appendicitis with appendicolith". *The American Journal of Emergency Medicine*. **6** (6): 614–617. doi:10.1016/0735-6757(88)90105-2.


*a b*

18. ^ Dehghan A, Moaddab AH, Mozafarpour S (June 2011). "An unusual localization of trichobezoar in the appendix". *The Turkish Journal of Gastroenterology*. **22** (3): 357–8. PMID 21805435.
19. ^ Jones BA, Demetriades D, Segal I, Burkitt DP (1985). "The prevalence of appendiceal fecaliths in patients with and without appendicitis. A comparative study from Canada and South Africa". *Annals of Surgery*. **202** (1): 80–82. doi:10.1097/00000658-198507000-00013. PMC 1250841. PMID 2990360.
20. ^ Nitecki S, Karmeli R, Sarr MG (1990). "Appendiceal calculi and fecaliths as indications for appendectomy". *Surgery, Gynecology & Obstetrics*. **171** (3): 185–8. PMID 2385810.
21. ^ Arnbjörnsson E (1985). "Acute appendicitis related to faecal stasis". *Annales Chirurgiae et Gynaecologiae*. **74** (2): 90–3. PMID 2992354.
22. ^ Raahave D, Christensen E, Moeller H, Kirkeby LT, Loud FB, Knudsen LL (2007). "Origin of acute appendicitis: fecal retention in colonic reservoirs: a case control study". *Surgical Infections*. **8** (1): 55–62. doi:10.1089/sur.2005.04250. PMID 17381397.
23. ^ Burkitt DP (1971). "The aetiology of appendicitis". *British Journal of Surgery*. **58** (9): 695–9. doi:10.1002/bjs.1800580916. PMID 4937032.
24. ^ Segal I, Walker AR (1982). "Diverticular disease in urban Africans in South Africa". *Digestion*. **24** (1): 42–6. doi:10.1159/000198773. PMID 6813167.
25. ^ Arnbjörnsson E (1982). "Acute appendicitis as a sign of a colorectal carcinoma". *Journal of Surgical Oncology*. **20** (1): 17–20. doi:10.1002/jso.2930200105. PMID 7078180.
26. ^ Burkitt DP, Walker AR, Painter NS (1972). "Effect of dietary fibre on stools and the transit-times, and its role in the causation of disease". *The Lancet*. **2** (7792): 1408–12. doi:10.1016/S0140-6736(72)92974-1. PMID 4118696.
27. ^ Adamis D, Roma-Giannikou E, Karamolegou K (2000). "Fiber intake and childhood appendicitis". *International Journal of Food Science and Nutrition*. **51** (3): 153–7. doi:10.1080/09637480050029647. PMID 10945110.
28. ^ Hugh TB, Hugh TJ (2001). "Appendicectomy--becoming a rare event?". *Medical Journal of Australia*. **175** (1): 7–8. PMID 11476215.
29. ^ Gear JS, Brodribb AJ, Ware A, Mann JI (January 1981). "Fibre and bowel transit times". *The British Journal of Nutrition*. **45** (1): 77–82. doi:10.1079/BJN19810078. PMID 6258626.
30. ^ Ashdown, H. F.; D'Souza, N.; Karim, D.; Stevens, R. J.; Huang, A.; Harnden, A. (17 December 2012). "Pain over speed bumps in diagnosis of acute appendicitis: diagnostic accuracy study". *The BMJ*. **345** (dec14 14): e8012–e8012. doi:10.1136/bmj.e8012. PMC 3524367. PMID 23247977.
31. ^ Hobler, K. (Spring 1998). "Acute and Suppurative Appendicitis: Disease Duration and its Implications for Quality Improvement" (PDF). *Permanente Medical Journal*. **2** (2). Archived from the original (PDF) on 2008-10-07.
32. ^ *a b c* Sachdeva, Anupam; Dutta, AK (31 August 2012). *Advances in Pediatrics*. JP Medical. p. 1432. ISBN 9789350257777.
33. ^ Small, V (2008). Dolan, B; Holt, L, eds. *Surgical emergencies*. *Accident and Emergency: Theory into Practice* (2nd ed.). Elsevier.[*page needed*]
34. ^ Virgilio, Christian de; Frank, Paul N.; Grigorian, Areg (10 January 2015). *Surgery*. Springer. p. 215. ISBN 9781493917266.
35. ^ Kadim, Abbas Abdul Mahdi (1 April 2016). "Surgical and Clinical Review of Acute Appendicitis" (PDF). *International Journal of Multidisciplinary and Current Research*. **4**. ISSN 2321-3124. "Massouh sign characterized by increased abdominal pain with coughing. It may be an indicator of appendicitis. A positive Massouh sign is a grimace of the person being examined upon a right sided (and not left) sweep (40)."
36. ^ *a b* Wolfson, Allan B.; Cloutier, Robert L.; Hendey, Gregory W.; Ling, Louis J.; Schaider, Jeffrey J.; Rosen, Carlo L. (27 October 2014). *Harwood-Nuss' Clinical Practice of Emergency Medicine*. Wolters Kluwer Health. p. 5810. ISBN 9781469889481. Retrieved 15 June 2016. "Physical signs classically associated with acute appendicitis include Rovsing sign, psoas sign, and obturator sign."
37. ^ Rovsing, N.T. (1907). "Indirektes Hervorrufen des typischen Schmerzes an McBurney's Punkt. Ein Beitrag zur diagnostik der Appendicitis und Typhlitis". *Zentralblatt für Chirurgie*. Leipzig. **34**: 1257–1259.**(German)**
38. ^ Dunster, Edward Swift; Hunter, James Bradbridge; Sajous, Charles Euchariste de Medicis; Foster, Frank Pierce; Stragnell, Gregory; Klaunberg, Henry J.; Martí-Ibáñez, Félix (1922). *International Record of Medicine and General Practice Clinics*. New York Medical Journal. p. 663.
39. ^ *a b c* Gregory, Charmaine (2010). "Appendicitis". *CDEM Self Study Modules*. Clerkship Directors in Emergency Medicine. Archived from the original on 2013-11-30.
40. ^ Bundy DG, Byerley JS, Liles EA, Perrin EM, Katznelson J, Rice HE (2007). "Does this child have appendicitis?". *JAMA*. **298** (4): 438–51. doi:10.1001/jama.298.4.438. PMC 2703737. PMID 17652298.
41. ^ American College of Radiology, "Five Things Physicians and Patients Should Question" (PDF), *Choosing Wisely: an initiative of the ABIM Foundation*, American College of Radiology, retrieved August 17, 2012
42. ^ Krishnamoorthi, R.; Ramarajan, N.; Wang, N. E.; Newman, B.; Rubesova, E.; Mueller, C. M.; Barth, R. A. (2011).

"Effectiveness of a Staged US and CT Protocol for the Diagnosis of Pediatric Appendicitis: Reducing Radiation Exposure in the Age of ALARA". *Radiology*. **259** (1): 231–239. doi:10.1148/radiol.10100984. PMID 21324843.
43. ^ Wan, M. J.; Krahn, M.; Ungar, W. J.; Caku, E.; Sung, L.; Medina, L. S.; Doria, A. S. (2009). "Acute Appendicitis in Young Children: Cost-effectiveness of US versus CT in Diagnosis--A Markov Decision Analytic Model". *Radiology*. **250** (2): 378–386. doi:10.1148/radiol.2502080100. PMID 19098225.
44. ^ Terasawa T, Blackmore CC, Bent S, Kohlwes RJ (October 2004). "Systematic review: computed tomography and ultrasonography to detect acute appendicitis in adults and adolescents". *Annals of Internal Medicine*. **141** (7): 537–46. doi:10.7326/0003-4819-141-7-200410050-00011. PMID 15466771.
45. ^ Reddan, Tristan; Corness, Jonathan; Mengersen, Kerrie; Harden, Fiona (March 2016). "Ultrasound of paediatric appendicitis and its secondary sonographic signs: providing a more meaningful finding". *Journal of Medical Radiation Sciences*. **63** (1): 59–66. doi:10.1002/jmrs.154.
46. ^ Reddan, Tristan; Corness, Jonathan; Mengersen, Kerrie; Harden, Fiona (June 2016). "Sonographic diagnosis of acute appendicitis in children: a 3-year retrospective". *Sonography*. doi:10.1002/sono.12068.
47. ^ Kim, Y; Kang, G; Moon, SB (November 2014). "Increasing utilization of abdominal CT in the Emergency Department of a secondary care center: does it produce better outcomes in caring for pediatric surgical patients?". *Annals of surgical treatment and research*. **87** (5): 239–44. doi:10.4174/astr.2014.87.5.239. PMID 25368849.
48. ^ Liu, B; Ramalho, M; AlObaidy, M; Busireddy, KK; Altun, E; Kalubowila, J; Semelka, RC (28 August 2014). "Gastrointestinal imaging-practical magnetic resonance imaging approach.". *World journal of radiology*. **6** (8): 544–66. doi:10.4329/wjr.v6.i8.544. PMID 25170393.
49. ^ Garcia, K.; Hernanz-Schulman, M.; Bennett, D. L.; Morrow, S. E.; Yu, C.; Kan, J. H. (2009). "Suspected Appendicitis in Children: Diagnostic Importance of Normal Abdominopelvic CT Findings with Nonvisualized Appendix". *Radiology*. **250** (2): 531–537. doi:10.1148/radiol.2502080624. PMID 19188320.
50. ^ *a b* Doria, A. S.; Moineddin, R.; Kellenberger, C. J.; Epelman, M.; Beyene, J.; Schuh, S.; Babyn, P. S.; Dick, P. T. (2006). "US or CT for Diagnosis of Appendicitis in Children and Adults? A Meta-Analysis". *Radiology*. **241** (1): 83–94. doi:10.1148/radiol.2411050913. PMID 16928974.
51. ^ Burke, LM; Bashir, MR; Miller, FH; Siegelman, ES; Brown, M; Alobaidy, M; Jaffe, TA; Hussain, SM; Palmer, SL; Garon, BT; Oto, A; Reinhold, C; Ascher, SM; Demulder, DK; Thomas, S; Best, S; Borer, J; Zhao, K; Pinel-Giroux, F; De Oliveira, I; Resende, D; Semelka, RC (24 July 2015). "Magnetic Resonance Imaging of Acute Appendicitis in Pregnancy: a 5-Year Multi-institutional Study.". *American Journal of Obstetrics and Gynecology*. **213**: 693.e1–6. doi:10.1016/j.ajog.2015.07.026. PMID 26215327.
52. ^ Rao PM, Rhea JT, Rao JA, Conn AK (July 1999). "Plain abdominal radiography in clinically suspected appendicitis: diagnostic yield, resource use, and comparison with CT". *The American Journal of Emergency Medicine*. **17** (4): 325–8. doi:10.1016/S0735-6757(99)90077-3. PMID 10452424.
53. ^ Boleslawski E, Panis Y, Benoist S, Denet C, Mariani P, Valleur P (March 1999). "Plain abdominal radiography as a routine procedure for acute abdominal pain of the right lower quadrant: prospective evaluation". *World Journal of Surgery*. **23** (3): 262–4. doi:10.1007/pl00013181. PMID 9933697.
54. ^ *a b* APPENDICITIS from Townsend: Sabiston Textbook of Surgery on MD Consult Archived December 3, 2013, at the Wayback Machine.
55. ^ *a b* Kulik, DM; Uleryk, EM; Maguire, JL (January 2013). "Does this child have appendicitis? A systematic review of clinical prediction rules for children with acute abdominal pain.". *Journal of Clinical Epidemiology*. **66** (1): 95–104. doi:10.1016/j.jclinepi.2012.09.004. PMID 23177898.
56. ^ Fink AS, Kosakowski CA, Hiatt JR, Cochran AJ (June 1990). "Periappendicitis is a significant clinical finding". *American Journal of Surgery*. **159** (6): 564–8. doi:10.1016/S0002-9610(06)80067-X. PMID 2349982.
57. ^ "Pelvic inflammatory disease (PID) Symptoms; Diseases and Conditions". Mayo Clinic. Retrieved 2015-04-23.
58. ^ Cunha BA, Pherez FM, Durie N (July 2010). "Swine influenza (H1N1) and acute appendicitis". *Heart Lung*. **39** (6): 544–6. doi:10.1016/j.hrtlng.2010.04.004. PMID 20633930.
59. ^ Zheng H, Sun Y, Lin S, Mao Z, Jiang B (August 2008). "Yersinia enterocolitica infection in diarrheal patients". *Eur. J. Clin. Microbiol. Infect. Dis.* **27** (8): 741–52. doi:10.1007/s10096-008-0562-y. ISBN 0-9600805-6-2. PMID 18575909.
60. ^ Sallinen, V; Akl, EA; You, JJ; Agarwal, A; Shoucair, S; Vandvik, PO; Agoritsas, T; Heels-Ansdell, D; Guyatt, GH; Tikkinen, KA (17 March 2016). "Meta-analysis of antibiotics versus appendicectomy for non-perforated acute appendicitis.". *The British journal of surgery*. **103**: 656–667. doi:10.1002/bjs.10147. PMID 26990957.
61. ^ Harnoss, JC; Zelienka, I; Probst, P; Grummich, K; Müller-Lantzsch, C; Harnoss, JM; Ulrich, A; Büchler, MW; Diener, MK (17 October 2016). "Antibiotics Versus Surgical Therapy for Uncomplicated Appendicitis: Systematic Review and Meta-analysis of Controlled Trials (PROSPERO 2015: CRD42015016882).". *Annals of Surgery*: 1. doi:10.1097/SLA.0000000000002039. PMID 27759621.
62. ^ Agha, FP; Ghahremani, GG; Panella, JS; Kaufman, MW (September 1987). "Appendicitis as the initial manifestation of Crohn's disease: radiologic features and prognosis.". *AJR. American journal of roentgenology*. **149**

(3): 515–8. doi:10.2214/ajr.149.3.515 . PMID 3497535 .
63. ^ [a] [b] Anderson, Mark; Collins, Emma (November 2008). "Analgesia for children with acute abdominal pain and diagnostic accuracy.". *Archives of Disease in Childhood*. **93** (11): 995–7. doi:10.1136/adc.2008.137174. PMID 18305071.
64. ^ Sauerland, S; Jaschinski, T; Neugebauer, EA (Oct 6, 2010). "Laparoscopic versus open surgery for suspected appendicitis.". *Cochrane Database of Systematic Reviews* (10): CD001546. doi:10.1002/14651858.CD001546.pub3. PMID 20927725.
65. ^ Berry J, Malt RA (1984). "Appendicitis near its centenary". *Annals of Surgery*. **200**: 567–75. doi:10.1097/00000658-198411000-00002. PMC 1250537. PMID 6385879.
66. ^ "Appendicitis". *National Institute of Diabetes and Digestive and Kidney Diseases*. U.S Department of Health and Human Services. Retrieved 2010-02-01.
67. ^ Semm K (March 1983). "Endoscopic appendectomy". *Endoscopy*. **15**: 59–64. doi:10.1055/s-2007-1021466. PMID 6221925.
68. ^ Siewert B, Raptopoulos V, Liu SI, Hodin RA, Davis RB, Rosen MP (2003). "CT predictors of failed laparoscopic appendectomy". *Radiology*. **229**: 415–20. doi:10.1148/radiol.2292020825. PMID 14595145.
69. ^ "Appendicitis". *Encyclopedia of Surgery*. Retrieved 2010-02-01.
70. ^ "'Emergency' appendix surgery can wait: MDs". *CBC News*. 2010-09-21.
71. ^ Ingraham, Angela M.; Cohen, Mark E.; Bilimoria, Karl Y.; Ko, Clifford Y.; Hall, Bruce L.; Russell, Thomas R.; Nathens, Avery B. (1 September 2010). "Effect of Delay to Operation on Outcomes in Adults With Acute Appendicitis". *Archives of Surgery*. **45** (9): 886–892. doi:10.1001/archsurg.2010.184. "Delay of appendectomy for acute appendicitis in adults does not appear to adversely affect 30-day outcomes."
72. ^ Appendicitis surgery, removal and recovery Retrieved on 2010-02-01 Archived January 11, 2010, at the Wayback Machine.
73. ^ Liang MK, Lo HG, Marks JL (2006). "Stump appendicitis: a comprehensive review of literature". *The American surgeon*. **72** (2): 162–6. PMID 16536249.
74. ^ Reddan, Tristan; Corness, Jonathan; Powell, Jennifer; Harden, Fiona; Mengersen, Kerrie (2016). "Stumped? It could be stump appendicitis". *Sonography*. doi:10.1002/sono.12098.
75. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Archived from the original on 11 November 2009. Retrieved Nov 11, 2009.
76. ^ Ellis, H (March 2012). "Acute appendicitis.". *British journal of hospital medicine (London, England: 2005)*. **73** (3): C46–8. PMID 22411604.
77. ^ "Appendicitis". *VoxHealth.co*. Retrieved 2016-06-16.
78. ^ Wier, Lauren M.; Yu, Hao; Owens, Pamela L.; Washington, Raynard (June 2013). Overview of Children in the Emergency Department, 2010. *Healthcare Cost and Utilization Project Statistical Brief #157* (Report). Agency for Healthcare Research and Quality.

## External links [edit]

- Appendicitis at DMOZ
- CT of the abdomen showing acute appendicitis
- Appendicitis, history, diagnosis and treatment by Surgeons Net Education
- Appendicitis: Acute Abdomen and Surgical Gastroenterology from the Merck Manual Professional (content last modified September 2007)

Wikimedia Commons has media related to *Appendicitis*.

| v · t · e · | Inflammation | | |
|---|---|---|---|
| **Acute** | **Plasma derived mediators** | Bradykinin · *complement* (C3 · C5a · MAC · · *coagulation* (Factor XII · Plasmin · Thrombin · · | |
| | **Cell derived mediators** | *preformed:* | Lysosome granules · *biogenic amines* (Histamine · Serotonin · · |
| | | *synthesized on demand:* | *cytokines* (IFN-γ · IL-8 · TNF-α · IL-1 · · *eicosanoids* (Leukotriene B4 · Prostaglandins · |

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|---|---|---|---|
| | | | · Nitric oxide · Kinins · |
| **Chronic** | Macrophage · Epithelioid cell · Giant cell · Granuloma · | | |
| **Processes** | **Traditional:** | Rubor · Calor · Tumor · Dolor · Functio laesa · | |
| | **Modern:** | Acute-phase reaction/Fever · Vasodilation · Increased vascular permeability · Exudate · Leukocyte extravasation · Chemotaxis · | |
| **Specific locations** | **Nervous** | *CNS* (Encephalitis · Myelitis · · Meningitis (Arachnoiditis · · *PNS* (Neuritis · · *eye* (Dacryoadenitis · Scleritis · Episcleritis · Keratitis · chorioretinitis · Retinitis · Chorioretinitis · Blepharitis · Conjunctivitis · Uveitis · · *ear* (Otitis · Labyrinthitis · Mastoiditis · · | |
| | **Cardiovascular** | Carditis (Endocarditis · Myocarditis · Pericarditis · · Vasculitis (Arteritis · Phlebitis · Capillaritis · · | |
| | **Respiratory** | *upper* (Sinusitis · Rhinitis · Pharyngitis · Laryngitis · · *lower* (Tracheitis · Bronchitis · Bronchiolitis · Pneumonitis · Pleuritis · · Mediastinitis · | |
| | **Digestive** | *mouth* | Stomatitis · Gingivitis · Gingivostomatitis · Glossitis · Tonsillitis · Sialadenitis/Parotitis · Cheilitis · Pulpitis · Gnathitis · |
| | | *tract* | Esophagitis · Gastritis · Gastroenteritis · Enteritis · Colitis · Enterocolitis · Duodenitis · Ileitis · Caecitis · **Appendicitis** · Proctitis · |
| | | *accessory* | Hepatitis · Ascending cholangitis · Cholecystitis · Pancreatitis · Peritonitis · |
| | **Integumentary** | Dermatitis (Folliculitis · · Cellulitis · Hidradenitis · | |
| | **Musculoskeletal** | Arthritis · Dermatomyositis · *soft tissue* (Myositis · Synovitis/Tenosynovitis · Bursitis · Enthesitis · Fasciitis · Capsulitis · Epicondylitis · Tendinitis · Panniculitis · · Osteochondritis: Osteitis/Osteomyelitis (Spondylitis · Periostitis · · Chondritis · | |
| | **Urinary** | Nephritis (Glomerulonephritis · Pyelonephritis · · Ureteritis · Cystitis · Urethritis · | |
| | **Reproductive** | *female:* | Oophoritis · Salpingitis · Endometritis · Parametritis · Cervicitis · Vaginitis · Vulvitis · Mastitis · |
| | | *male:* | Orchitis · Epididymitis · Prostatitis · Seminal vesiculitis · Balanitis · Posthitis · Balanoposthitis · |
| | | *pregnancy/newborn:* | Chorioamnionitis · Funisitis · Omphalitis · |
| | **Endocrine** | Insulitis · Hypophysitis · Thyroiditis · Parathyroiditis · Adrenalitis · | |
| | **Lymphatic** | Lymphangitis · Lymphadenitis · | |

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| v · t · e · | **Diseases of the digestive system (primarily K20–K93, 530–579)** | |
| | **Esophagus** | Esophagitis (Candidal · Eosinophilic · Herpetiform · · *Rupture* (Boerhaave syndrome · Mallory-Weiss syndrome · · UES (Zenker's diverticulum · · LES (Barrett's esophagus · · Esophageal motility disorder (Nutcracker esophagus |

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|---|---|---|
| **Upper GI tract** | | · Achalasia · Diffuse esophageal spasm · Gastroesophageal reflux disease (GERD) · · Laryngopharyngeal reflux (LPR) · Esophageal stricture · Megaesophagus · |
| | **Stomach** | Gastritis (Atrophic · Ménétrier's disease · Gastroenteritis · · Peptic (gastric) ulcer (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
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| | **Large intestine (Appendix/Colon)** | **Appendicitis** · Colitis (Pseudomembranous · Ulcerative · Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (IBS · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
| | **Large and/or small** | Enterocolitis (Necrotizing · · Gastroenterocolitis · IBD (Crohn's disease · · *Vascular*: Abdominal angina · Mesenteric ischemia · Angiodysplasia · Bowel obstruction: Ileus · Intussusception · Volvulus · Fecal impaction · Constipation · Diarrhea (Infectious · · Intestinal adhesions · |
| | **Rectum** | Proctitis (Radiation proctitis · · Proctalgia fugax · Rectal prolapse · Anismus · |
| | **Anal canal** | Anal fissure/Anal fistula · Anal abscess · Anal dysplasia · Pruritus ani · |
| **GI bleeding/BIS** | | Upper (Hematemesis · Melena · · Lower (Hematochezia · · |
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| | **Gallbladder** | Cholecystitis · Gallstones/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · Gallstones/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
| | | Pancreatitis (Acute · Chronic · Hereditary · Pancreatic abscess · · |

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| | **Pancreatic** | Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |
| **Abdominopelvic** | **Hernia** | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |
| **Authority control** | GND: 4139899-3 · NDL: 00567879 · | |

Categories: Inflammations | Medical emergencies | General surgery | Diseases of appendix | Acute pain




# Bowel obstruction

From Wikipedia, the free encyclopedia

**Bowel obstruction**, also known as **intestinal obstruction**, is a mechanical or functional obstruction of the intestines which prevents the normal movement of the products of digestion.[1][2] Either the small bowel or large bowel may be affected.[3] Symptoms include abdominal pain, vomiting, bloating, and not passing gas.[3] Mechanical obstruction is the cause of about 5 to 15% of cases of severe abdominal pain of sudden onset requiring admission to hospital.[3][1]

Causes of bowel obstruction include adhesions, hernias, volvulus, endometriosis, inflammatory bowel disease, appendicitis, tumors, diverticulitis, ischemic bowel, tuberculosis, and intussusception.[3][1] Small bowel obstructions are most often due to adhesions and hernias while large bowel obstructions are most often due to tumors and volvulus.[3][1] The diagnosis may be made on plain X-rays, however, CT scan is more accurate.[3] Ultrasound or MRI may help in the diagnosis of children or pregnant women.[3]

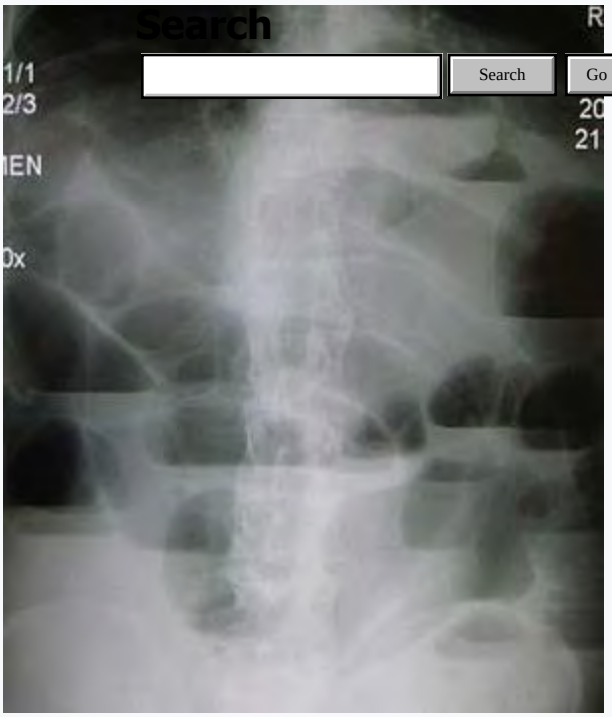
The condition may be treated conservatively or with surgery.[1] Typically intravenous fluids are given, a tube is placed through the nose into the stomach to decompress the intestines, and pain medications are given.[1] Antibiotics are often given.[1] In small bowel obstruction about 25% require surgery.[4] Complications may include sepsis, bowel ischemia, and bowel perforation.[3]

About 2.5 million cases of or bowel obstruction occurred in 2013 which resulted in 236,000 deaths.[5][6] Both sexes are equally affected and the condition can occur at any age.[4] Bowel obstruction has been documented throughout history with cases detailed in the Ebers Papyrus of 1550 BC and by Hippocrates.[7]

Contents


**Bowel obstruction**

**Synonyms** intestinal obstruction



Upright abdominal X-ray demonstrating a small bowel obstruction. Note multiple air fluid levels.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | General surgery |
| **ICD-10** | K56 |
| **ICD-9-CM** | 560 |
| **DiseasesDB** | 15838 |
| **MedlinePlus** | 000260 |
| **MeSH** | D007415 |

[edit on Wikidata]

## Signs and symptoms [edit]

Depending on the level of obstruction, bowel obstruction can present with abdominal pain, swollen abdomen, abdominal distension, vomiting, fecal vomiting, and constipation.[8]

Bowel obstruction may be complicated by dehydration and electrolyte abnormalities due to vomiting; respiratory compromise from pressure on the diaphragm by a distended abdomen, or aspiration of vomitus; bowel ischaemia or perforation from prolonged distension or pressure from a foreign body.

Tinkly bowel sounds

Tinkly bowel sounds as heard with a stethoscope in someone with a small bowel obstruction.

*Problems playing this file? See media help.*

In small bowel obstruction the pain tends to be colicky (cramping and intermittent) in nature, with spasms lasting a few minutes. The pain tends to be central and mid-abdominal. Vomiting may occur before constipation[*citation needed*].

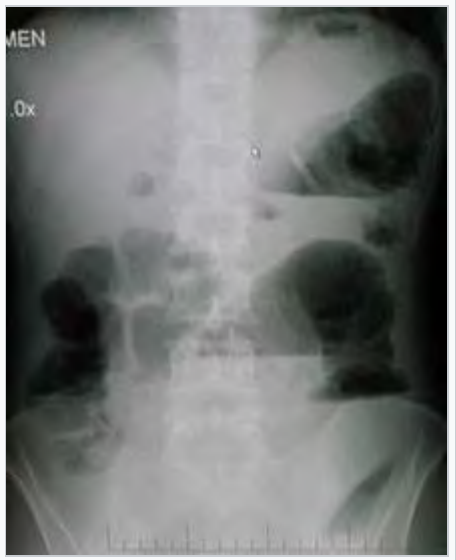
In large bowel obstruction, the pain is felt lower in the abdomen and the spasms last longer. Constipation occurs earlier and vomiting may be less prominent. Proximal obstruction of the large bowel may present as small bowel obstruction.[*citation needed*]

## Causes [edit]

### Small bowel obstruction [edit]

Causes of small bowel obstruction include:[1]

- Adhesions from previous abdominal surgery (most common cause)
- Barbed sutures.[9]
- Pseudoobstruction
- Hernias containing bowel
- Crohn's disease causing adhesions or inflammatory strictures
- Neoplasms, benign or malignant
- Intussusception in children
- Volvulus
- Superior mesenteric artery syndrome, a compression of the duodenum by the superior mesenteric artery and the abdominal aorta
- Ischemic strictures
- Foreign bodies (e.g. gallstones in gallstone ileus, swallowed objects)
- Intestinal atresia



Upright abdominal X-ray demonstrating a small bowel obstruction. Note multiple air fluid levels.

### Large bowel obstruction [edit]

Causes of large bowel obstruction include:

- Neoplasms
- Diverticulitis / Diverticulosis
- Hernias
- Inflammatory bowel disease
- Colonic volvulus (sigmoid, caecal, transverse colon)

- Adhesions
- Constipation
- Fecal impaction
- Fecaloma
- Colon atresia
- Intestinal pseudoobstruction
- Endometriosis
- Narcotic induced (especially with the large doses given to cancer or palliative care patients)

### Outlet obstruction [edit]

Outlet obstruction is a sub-type of large bowel obstruction and refers to conditions affecting the anorectal region that obstruct defecation, specifically conditions of the pelvic floor and anal sphincters. Outlet obstruction can be classified into 4 groups.[10]

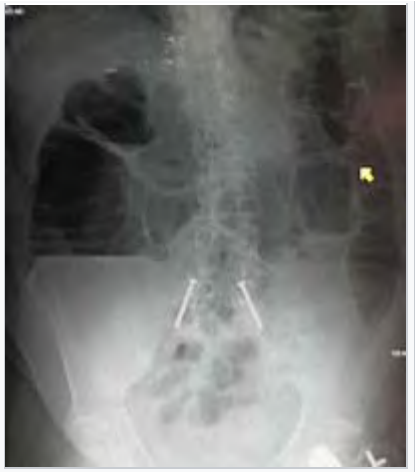
- Functional outlet obstruction
  - Inefficient inhibition of the internal anal sphincter
    - Short-segment Hirschsprung's disease
    - Chagas disease
    - Hereditary internal sphincter myopathy
  - Inefficient relaxation of the striated pelvic floor muscles
    - Anismus (pelvic floor dyssynergia)
    - Multiple sclerosis
    - Spinal cord lesions
- Mechanical outlet obstruction
  - Internal intussusception
  - Enterocele
- Dissipation of force vector
  - rectocele
  - Descending perineum
  - Rectal prolapse
- Impaired rectal sensitivity
  - Megarectum
  - Rectal hyposensitivity

### Differential diagnosis [edit]

Differential diagnoses of bowel obstruction include:

- Ileus
- Pseudo-obstruction or Ogilvie's syndrome
- Intra-abdominal sepsis
- Pneumonia or other systemic illness[*citation needed*].

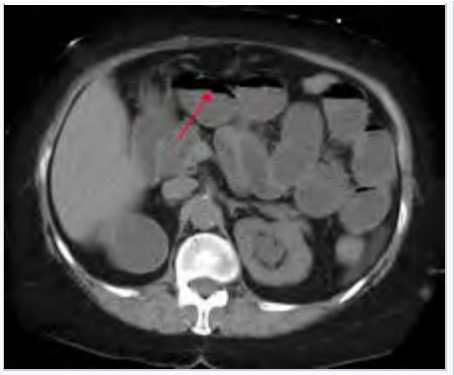
## Diagnosis [edit]



Upright abdominal X-ray of a patient with a large bowel obstruction showing multiple air fluid levels and dilated loops of bowel.

The main diagnostic tools are blood tests, X-rays of the abdomen, CT scanning, and/or ultrasound. If a mass is identified, biopsy may determine the nature of the mass.

Radiological signs of bowel obstruction include bowel distension and the presence of multiple (more than six) gas-fluid levels on supine and erect



A small bowel obstruction as seen on CT

abdominal radiographs.[*medical citation needed*]

Contrast enema or small bowel series or CT scan can be used to define the level of obstruction, whether the obstruction is partial or complete, and to help define the cause of the obstruction.

According to a meta-analysis of prospective studies by the Cochrane Collaboration, the appearance of water-soluble contrast in the cecum on an abdominal radiograph within 24 hours of oral administration predicts resolution of an adhesive small bowel obstruction with a pooled sensitivity of 96% and specificity of 96%.[11][*needs update*]Colonoscopy, small bowel investigation with ingested camera or push endoscopy, and laparoscopy are other diagnostic options.

# Treatment [edit]

Some causes of bowel obstruction may resolve spontaneously;[12] many require operative treatment.[13] In adults, frequently the surgical intervention and the treatment of the causative lesion are required. In malignant large bowel obstruction, endoscopically placed self-expanding metal stents may be used to temporarily relieve the obstruction as a bridge to surgery,[14] or as palliation.[15] Diagnosis of the type of bowel obstruction is normally conducted through initial plain radiograph of the abdomen, luminal contrast studies, computed tomography scan, or ultrasonography prior to determining the best type of treatment.[16]

## Small bowel obstruction [edit]

In the management of small bowel obstructions, a commonly quoted surgical aphorism is: "never let the sun rise or set on small-bowel obstruction"[17] because about 5.5%[17] of small bowel obstructions are ultimately fatal if treatment is delayed. However improvements in radiological imaging of small bowel obstructions allow for confident distinction between simple obstructions, that can be treated conservatively, and obstructions that are surgical emergencies (volvulus, closed-loop obstructions, ischemic bowel, incarcerated hernias, etc.).[1]

A small flexible tube (nasogastric tube) may be inserted from the nose into the stomach to help decompress the dilated bowel. This tube is uncomfortable but does relieve the abdominal cramps, distension and vomiting. Intravenous therapy is utilized and the urine output is monitored with a catheter in the bladder.[18]

Most people with SBO are initially managed conservatively because in many cases, the bowel will open up. Some adhesions loosen up and the obstruction resolves. However, when conservative management is undertaken, the patient is examined several times a day, and X-ray images are obtained to ensure that the individual is not getting clinically worse.[19]

Conservative treatment involves insertion of a nasogastric tube, correction of dehydration and electrolyte abnormalities. Opioid pain relievers may be used for patients with severe pain. Antiemetics may be administered if the patient is vomiting. Adhesive obstructions often settle without surgery. If obstruction is complete a surgery is usually required.

Most patients do improve with conservative care in 2–5 days. However, in some occasions, the cause of obstruction may be a cancer and in such cases, surgery is the only treatment. These individuals undergo surgery where the cause of SBO is removed. Individuals who have bowel resection or lysis of adhesions usually stay in the hospital a few more days until they are able to eat and walk.[20]

Small bowel obstruction caused by Crohn's disease, peritoneal carcinomatosis, sclerosing peritonitis,

radiation enteritis, and postpartum bowel obstruction are typically treated conservatively, i.e. without surgery.

### Children [edit]

*Main article: Neonatal bowel obstruction*

Fetal and neonatal bowel obstructions are often caused by an intestinal atresia, where there is a narrowing or absence of a part of the intestine. These atresias are often discovered before birth via a sonogram, and treated with using laparotomy after birth. If the area affected is small, then the surgeon may be able to remove the damaged portion and join the intestine back together. In instances where the narrowing is longer, or the area is damaged and cannot be used for a period of time, a temporary stoma may be placed.

## Prognosis [edit]

The prognosis for non-ischemic cases of SBO is good with mortality rates of 3-5%, while prognosis for SBO with ischemia is fair with mortality rates as high as 30%.[21]

Cases of SBO related to cancer are more complicated and require additional intervention to address the malignancy, recurrence, and metastasis, and thus are associated with poorer prognosis.[*citation needed*]

All cases of abdominal surgical intervention are associated with increased risk of future small-bowel obstructions. Statistics from U.S. healthcare report 18.1% re-admittance rate within 30 days for patients who undergo SBO surgery.[22] More than 90% of patients also form adhesions after major abdominal surgery.[23] Common consequences of these adhesions include small-bowel obstruction, chronic abdominal pain, pelvic pain, and infertility.[23]

## Other animals [edit]

*Main article: Impaction (animals)*

## References [edit]


1. ^ *a b c d e f g h i* Fitzgerald, J. Edward F. (2010). *Small Bowel Obstruction*. Oxford: Wiley-Blackwell. pp. 74–79. doi:10.1002/9781444315172.ch14. ISBN 9781405170253.
2. ^ Adams, James G. (2012). *Emergency Medicine: Clinical Essentials (Expert Consult -- Online)*. Elsevier Health Sciences. p. 331. ISBN 1455733946.
3. ^ *a b c d e f g h* Gore, RM; Silvers, RI; Thakrar, KH; Wenzke, DR; Mehta, UK; Newmark, GM; Berlin, JW (November 2015). "Bowel Obstruction.". *Radiologic clinics of North America*. **53** (6): 1225–40. doi:10.1016/j.rcl.2015.06.008. PMID 26526435.
4. ^ *a b* Ferri, Fred F. (2014). *Ferri's Clinical Advisor 2015: 5 Books in 1*. Elsevier Health Sciences. p. 1093. ISBN 9780323084307.
5. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995):
12. ^ Ludmir, J; P Samuels; BA Armson; MH Torosian (December 1989). "Spontaneous Small Bowel Obstruction Associated With A Spontaneous Triplet Gestation – A Case Report". *J Reprod Med*. Pub Med. **34** (12): 985–7. PMID 2621741.
13. ^ "Abdominal Adhesions and Bowel Obstruction". University of California San Francisco. Retrieved August 11, 2013.
14. ^ Young, CJ; MK Suen; J Young; MJ Solomon (October 2011). "Stenting Large Bowel Obstruction Avoids A Stoma: Consecutive Series of 100 Patients". *Journal Colorectal Dis*. Pub Med. **13** (10): 1138–41. doi:10.1111/j.1463-1318.2010.02432.x. PMID 20874797.
15. ^ P Mosler; KD Mergener; JJ Brandabur; DB Schembre; RA Kozarek (February 2005). "Palliation of Gastric Outlet Obstruction and Proximal Small Bowel

2005). "Oral water soluble contrast for the management of adhesive small bowel obstruction.". *Cochrane database of systematic reviews (Online)* (1): CD004651. doi:10.1002/14651858.CD004651.pub2. PMID 15674958.

743–800. doi:10.1016/s0140-6736(15)60692-4 . PMC 4561509. PMID 26063472.
6. ^ GBD 2013 Mortality and Causes of Death, Collaborators (10 January 2015). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013." *Lancet (London, England)*. **385** (9963): 117–71. doi:10.1016/s0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
7. ^ Yeo, Charles J.; McFadden, David W.; Pemberton, John H.; Peters, Jeffrey H.; Matthews, Jeffrey B. (2012). *Shackelford's Surgery of the Alimentary Tract*. Elsevier Health Sciences. p. 1851. ISBN 1455738077.
8. ^ Vann, MPH, Madeline (July 26, 2010). "Diagnosing and Treating Bowel Obstruction". *Everyday Health*. (Medically reviewed by) Pat F. Bass III, MD, MPH. Retrieved August 28, 2013.
9. ^ Segura-Sampedro JJ, Ashrafian H, Navarro-Sánchez A, Jenkins JT, Morales-Conde S, Martínez-Isla A (Nov 2015). "Small bowel obstruction due to laparoscopic barbed sutures: An unknown complication?". *Rev Esp Enferm Dig*. **107** (11): ,. doi:10.17235/reed.2015.3863/2015. PMID 26541657.
10. ^ Wexner, edited by Andrew P. Zbar, Steven D. (2010). *Coloproctology*. New York: Springer. p. 140. ISBN 978-1-84882-755-4.
11. ^ Abbas, S; Bissett, IP; Parry, BR (January 25, Obstruction With Self-Expandable Metal Stents: A Single Center Series". *J Clin Gastroenterol*. Pub Med. **39** (2): 124–8. PMID 15681907.
16. ^ Holzheimer, Rene G. (2001). *Surgical Treatment*. NCBI Bookshelf. ISBN 3-88603-714-2.
17. ^ *a b* DD Maglinte; FM Kelvin; MG Rowe MG; GN Bender GN; DM Rouch (January 1, 2001). "Small-bowel obstruction: optimizing radiologic investigation and nonsurgical management". *Radiology*. **218** (1): 39–46. doi:10.1148/radiology.218.1.r01ja5439. PMID 11152777.
18. ^ Small Bowel Obstruction overview. Retrieved February 19, 2010.
19. ^ Small Bowel Obstruction:Treating Bowel Adhesions Non-Surgically. *Clear Passage treatment center online portal* Retrieved February 19, 2010
20. ^ Small Bowel Obstruction The Eastern Association for the Surgery of Trauma. February 19, 2010
21. ^ Kakoza, R.; Lieberman, G. (May 2006). "Mechanical Small Bowel Obstruction" (PDF).
22. ^ "Readmissions to U.S. Hospitals by Procedure (PDF). *Agency for Healthcare Research and Quality*. April 2013. Retrieved August 27, 2013.
23. ^ *a b* Liakakos, T; N Thomakos; PM Fine; C Dervenis; RL Young (2001). "Peritoneal Adhesions: Etiology, Pathophysiology, and Clinical Significance". *Dig Surgery*. Pub Med. **18** (4): 260–273. doi:10.1159/000050149. PMID 11528133.

## External links [edit]

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- *Obstruction, Large Bowel* at eMedicine

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| | **Stomach** — Gastritis (Atrophic · Ménétrier's disease · Gastroenteritis · · Peptic (gastric) ulcer (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
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| | | |
|---|---|---|
| **Lower GI tract: Intestinal/ Enteropathy** | **Large intestine (Appendix/Colon)** | Appendicitis · Colitis (Pseudomembranous · Ulcerative · Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (IBS · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
| | **Large and/or small** | Enterocolitis (Necrotizing · · Gastroenterocolitis · IBD (Crohn's disease · · *Vascular*: Abdominal angina · Mesenteric ischemia · Angiodysplasia · **Bowel obstruction**: Ileus · Intussusception · Volvulus · Fecal impaction · Constipation · Diarrhea (Infectious · · Intestinal adhesions · |
| | **Rectum** | Proctitis (Radiation proctitis · · Proctalgia fugax · Rectal prolapse · Anismus · |
| | **Anal canal** | Anal fissure/Anal fistula · Anal abscess · Anal dysplasia · Pruritus ani · |
| **GI bleeding/BIS** | Upper (Hematemesis · Melena · · Lower (Hematochezia · · | |
| **Accessory** | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · Acute liver failure · · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |
| | **Gallbladder** | Cholecystitis · Gallstones/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · Gallstones/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
| | **Pancreatic** | Pancreatitis (Acute · Chronic · Hereditary · Pancreatic abscess · · Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |
| **Abdominopelvic** | **Hernia** | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |

Categories: General surgery | Medical emergencies | Gastrointestinal tract disorders


# Coeliac disease



From Wikipedia, the free encyclopedia
(Redirected from Celiac disease)



## Variants

**Coeliac disease**, also spelled **celiac disease**, is an autoimmune disorder affecting primarily the small intestine that occurs in people who are genetically predisposed.[1] Classic symptoms include gastrointestinal problems such as chronic diarrhoea, abdominal distention, malabsorption, loss of appetite, and among children failure to grow normally. This often begins between six months and two years of age.[2] Non-classic symptoms are the most common, especially in people older than two years.[3][4][5] There may be mild or absent gastrointestinal symptoms, a wide number of symptoms involving any part of the body, or no obvious symptoms.[2] Coeliac disease was first described in childhood;[3][6] however, it may develop at any age.[2][3] It is associated with other autoimmune diseases, such as diabetes mellitus type 1 and thyroiditis, among others.[6]

Coeliac disease is caused by a reaction to gluten, which are various proteins found in wheat and in other grains such as barley, and rye.[7][8][9] Moderate quantities of oats, free of contamination with other gluten-containing grains, are usually tolerated[8] but problems may depend on the type consumed.[8][10] Upon exposure to gluten, an abnormal immune response may lead to the production of several different autoantibodies that can affect a number of different organs.[11][12] In the small-bowel this causes an inflammatory reaction and may produce shortening of the villi lining the small intestine (villous atrophy).[1][13] This affects the absorption of nutrients, frequently leading to anaemia.[1][9]

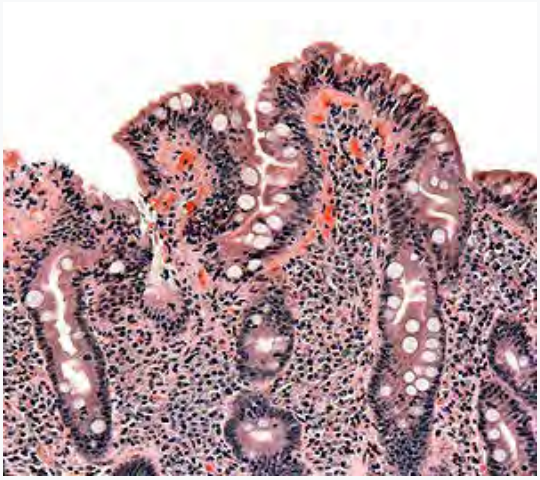
Diagnosis is typically made by a combination of blood antibody tests and intestinal biopsies, helped by specific genetic testing.[1] Making the diagnosis is not always straightforward.[14] Frequently, the autoantibodies in the blood are negative[15][16] and many people have only minor intestinal changes with normal villi.[4][17] People may have severe symptoms and be investigated for years before a diagnosis is achieved.[18] Increasingly, the diagnosis is being made in people without symptoms as a result of screening.[19] While the disease is caused by a permanent intolerance to wheat proteins, it not a form of wheat allergy.[1]

The only known effective treatment is a strict lifelong gluten-free diet, which leads to recovery of the intestinal mucosa, improves symptoms, and reduces risk of developing complications in most people.[20] If untreated it may result in cancers such as intestinal lymphoma and a slight increased risk of early death.[21] Rates vary between different regions of the world, from as few as 1 in 300 to as many as 1 in 40, with an average of between 1 in 100 and 1 in 170 people.[22] In developed countries, it is estimated that five out of six cases (83%) remain undiagnosed, usually because of non-classic,

[23]

**Coeliac disease**

**Synonyms** celiac sprue, nontropical sprue, endemic sprue, gluten enteropathy



Biopsy of small bowel showing coeliac disease manifested by blunting of villi, crypt hyperplasia, and lymphocyte infiltration of crypts

**Pronunciation** /ˈsiːliːæk/

| Classification and external resources | |
|---|---|
| **Specialty** | Gastroenterology |
| **ICD-10** | K90.0 |
| **ICD-9-CM** | 579.0 |
| **OMIM** | 212750 |
| **DiseasesDB** | 2922 |
| **MedlinePlus** | 000233 |
| **eMedicine** | med/308 ped/2146 radio/652 |
| **Patient UK** | Coeliac disease |
| **MeSH** | D002446 |
| **GeneReviews** | Celiac Disease |

[edit on Wikidata]

[24]

minimal, or absent complaints. Coeliac disease is slightly more common in women than in men. The term "coeliac" is from the Greek κοιλιακός (*koiliakós*, "abdominal") and was introduced in the 19th century in a translation of what is generally regarded as an ancient Greek description of the disease by Aretaeus of Cappadocia.[25][26]





## Signs and symptoms [edit]

The classic symptoms of coeliac disease include pale, loose, and greasy stool (steatorrhoea) and weight loss or failure to gain weight. More commonly symptoms are subtle or primarily occur in organs other than the bowel itself.[27] It is also possible to have coeliac disease without any symptoms whatsoever.[9] This represents at least in 43% of the cases in children.[28] Many adults with subtle disease only have fatigue or anaemia.[19]

### Gastrointestinal [edit]

The diarrhoea that is characteristic of coeliac disease is (chronic) pale, of large volume, and abnormally bad smelling. Abdominal pain and cramping, bloatedness with abdominal distension (thought to be due to fermentative production of bowel gas), and mouth ulcers[29] may be present. As the bowel becomes more damaged, a degree of lactose intolerance may develop.[9] Frequently, the symptoms are ascribed to irritable bowel syndrome (IBS), only later to be recognised as coeliac disease; a small proportion of people with symptoms of IBS have underlying coeliac disease, and screening for coeliac disease is recommended for those with IBS symptoms.[30]

Coeliac disease leads to an increased risk of both adenocarcinoma and lymphoma of the small bowel (enteropathy-associated T-cell lymphoma (EATL) or other non-Hodgkin's lymphomas).[31] This risk is also higher in first-degree relatives such as siblings, parents, and children. Whether or not a gluten-free diet brings this risk back to baseline is not clear.[32] Long-standing and untreated disease may lead to other complications, such as ulcerative jejunitis (ulcer formation of the small bowel) and stricturing (narrowing as a result of scarring with obstruction of the bowel).[33]

### Malabsorption-related [edit]

The changes in the bowel make it less able to absorb nutrients, minerals, and the fat-soluble vitamins A, D, E, and K.[9][34]

- The inability to absorb carbohydrates and fats may cause weight loss (or failure to thrive/stunted growth in children) and fatigue or lack of energy.
- Anaemia may develop in several ways: iron malabsorption may cause iron deficiency anaemia, and folic acid and vitamin $B_{12}$ malabsorption may give rise to megaloblastic anaemia.
- Calcium and vitamin D malabsorption (and compensatory secondary hyperparathyroidism) may cause osteopenia (decreased mineral content of the bone) or osteoporosis (bone weakening and risk of fragility fractures).
- Selenium malabsorption in coeliac disease, combined with low selenium content in many gluten-free foods, confers a risk of selenium deficiency,[35]
- Copper and zinc deficiencies have also been associated with coeliac disease.[35]
- A small proportion have abnormal coagulation due to vitamin K deficiency and are slightly at risk for abnormal bleeding.

### Miscellaneous [edit]

Coeliac disease has been linked with a number of conditions. In many cases, it is unclear whether the gluten-induced bowel disease is a causative factor or whether these conditions share a common predisposition.

- IgA deficiency is present in 2.3% of people with coeliac disease, and in turn this condition features a tenfold increased risk of coeliac disease. Other features of this condition are an increased risk of infections and autoimmune disease.[36]
- Dermatitis herpetiformis, an itchy cutaneous condition, has been linked to a transglutaminase enzyme in the skin, features small-bowel changes identical to those in coeliac disease, and may respond to gluten withdrawal even if no gastrointestinal symptoms are present.[37][38]
- Growth failure and/or pubertal delay in later childhood can occur even without obvious bowel symptoms or severe malnutrition. Evaluation of growth failure often includes coeliac screening.[9]
- Pregnancy complications can occur in case of coeliac disease as an intercurrent disease in pregnancy, with significant complications including miscarriage, intrauterine growth restriction, low birthweight and preterm birth.[39]
- Hyposplenism (a small and underactive spleen)[40] occurs in about a third of cases and may predispose to infection given the role of the spleen in protecting against bacteria.[9]
- Abnormal liver function tests (randomly detected on blood tests) may be seen.[9]

Coeliac disease is associated with a number of other medical conditions, many of which are autoimmune disorders: diabetes mellitus type 1, hypothyroidism, primary biliary cirrhosis, microscopic colitis, gluten ataxia, psoriasis, vitiligo, autoimmune hepatitis, dermatitis herpetiformis, primary sclerosing cholangitis, and more.[11]

A more controversial area is a group of diseases in which antigliadin antibodies (an older and nonspecific test for coeliac disease) are sometimes detected but no small bowel disease can be demonstrated. Sometimes these conditions improve by removing gluten from the diet. This includes cerebellar ataxia, peripheral neuropathy, schizophrenia, and autism.[41]

## Cause [edit]

Coeliac disease is caused by a reaction to gliadin, a prolamin (gluten protein) found in wheat, and similar proteins found in the crops of the tribe Triticeae (which includes other common grains such as barley and rye).[9]

### Other grains [edit]

Wheat subspecies (such as spelt, durum and Kamut) and related species (such as barley, rye and triticale) also induce symptoms of coeliac disease.[42]

A small number of people with coeliac also react to oats.[9] Oats toxicity in coeliac people depends on the oat cultivar consumed because of prolamin genes, protein amino acid sequences, and the immunoreactivities of toxic prolamins which are different among oat varieties.[10][43] Also, oat products are frequently cross-contaminated with gluten-containing cereals.[10][43][44] Pure oat refers to oats uncontaminated with gluten.[10] The long-term effects of pure oats consumption are still unclear[45] and further studies identifying the cultivars used are needed before making final recommendations on their inclusion in the gluten-free diet.[44] Celiac people who choose to consume oats need a more rigorous lifelong follow-up, possibly including periodic performance of intestinal

biopsies.[45]

Other cereals such as corn, millet, sorghum, teff, rice, and wild rice are safe for people with coeliac to consume, as well as noncereals such as amaranth, quinoa, and buckwheat.[42][46] Noncereal carbohydrate-rich foods such as potatoes and bananas do not contain gluten and do not trigger symptoms.[42]

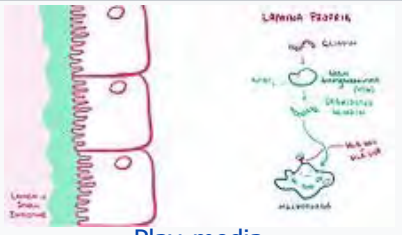
### Risk modifiers [edit]

There are various theories as to what determines whether a genetically susceptible individual will go on to develop coeliac disease. Major theories include infection by rotavirus[47] or human intestinal adenovirus.[48] Some research has suggested that smoking is protective against adult-onset coeliac disease.[49]

The eating of gluten early in a baby's life does not appear to increase the risk of CD but later introduction after 6 months may increase it.[50][51] There is uncertainty whether breastfeeding reduces risk. Prolonging breastfeeding until the introduction of gluten-containing grains into the diet appears to be associated with a 50% reduced risk of developing coeliac disease in infancy; whether this persists into adulthood is not clear.[52] These factors may just influence the timing of onset.[53] Factors that can trigger symptoms include: surgery, pregnancy, infection and emotional stress.[54]

## Pathophysiology [edit]

Coeliac disease appears to be multifactorial, both in that more than one genetic factor can cause the disease and in that more than one factor is necessary for the disease to manifest in a person.

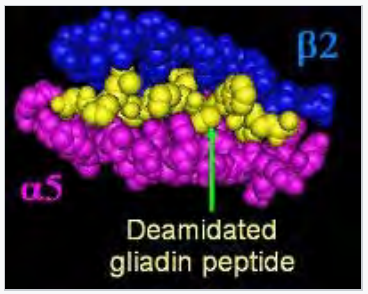


Play media

Video explaining celiac disease

Almost all people (95%) with coeliac disease have either the variant HLA-DQ2 allele or (less commonly) the HLA-DQ8 allele.[19][55] However, about 20–30% of people without coeliac disease have also inherited either of these alleles.[56] This suggests additional factors are needed for coeliac disease to develop; that is, the predisposing HLA risk allele is necessary but not sufficient to develop coeliac disease. Furthermore, around 5% of those people who do develop coeliac disease do not have typical HLA-DQ2 or HLA-DQ8 alleles (see below).[19]

### Genetics [edit]




DQ $\alpha^5$-$\beta^2$ -binding cleft with a deamidated gliadin peptide (yellow), modified from PDB: 1S9V [57]

The vast majority of people with coeliac have one of two types of the HLA-DQ protein.[56] HLA-DQ is part of the MHC class II antigen-presenting receptor (also called the human leukocyte antigen) system and distinguishes cells between self and non-self for the purposes of the immune system. The two subunits of the HLA-DQ protein are encoded by the HLA-DQA1 and HLA-DQB1 genes, located on the short arm of the sixth chromosome.

There are seven HLA-DQ variants (DQ2 and DQ4–DQ9). Over 95% of people with coeliac have the isoform of DQ2 or DQ8, which is inherited in families. The reason these genes produce an increase in risk of coeliac disease is that the receptors formed by these genes bind to gliadin peptides more tightly than other forms of the antigen-presenting receptor. Therefore, these forms of the receptor are more likely to activate T lymphocytes and initiate the autoimmune process.[19]

Most people with coeliac bear a two-gene HLA-DQ2 haplotype referred to as DQ2.5 haplotype. This haplotype is composed of two adjacent gene alleles, DQA1*0501 and DQB1*0201, which encode the two subunits, DQ $\alpha^5$ and DQ $\beta^2$. In most individuals, this DQ2.5 isoform is encoded by one of two chromosomes 6 inherited from parents (DQ2.5cis). Most coeliacs inherit only one copy of this DQ2.5 haplotype, while some inherit it from *both* parents; the latter are especially at risk for coeliac disease as well as being more susceptible to severe complications.[58]

Some individuals inherit DQ2.5 from one parent and an additional portion of the haplotype (either DQB1*02 or DQA1*05) from the other parent, increasing risk. Less commonly, some individuals inherit the DQA1*05 allele from one parent and the DQB1*02 from the other parent (DQ2.5trans) (called a trans-haplotype association), and these individuals are at similar risk for coeliac disease as those with a single DQ2.5-bearing chromosome 6, but in this instance disease tends not to be familial. Among the 6% of European coeliacs that do not have DQ2.5 (cis or

trans) or DQ8 (encoded by the haplotype DQA1*03:DQB1*0302), 4% have the DQ2.2 isoform, and the remaining 2% lack DQ2 or DQ8.[59]

The frequency of these genes varies geographically. DQ2.5 has high frequency in peoples of North and Western Europe (Basque Country and Ireland[60] with highest frequencies) and portions of Africa and is associated with disease in India,[61] but it is not found along portions of the West Pacific rim. DQ8 has a wider global distribution than DQ2.5 and is particularly common in South and Central America; up to 90% of individuals in certain Amerindian populations carry DQ8 and thus may display the coeliac phenotype.[62]

Other genetic factors have been repeatedly reported in coeliac disease; however, involvement in disease has variable geographic recognition. Only the HLA-DQ loci show a consistent involvement over the global population.[63] Many of the loci detected have been found in association with other autoimmune diseases. One locus, the LPP or lipoma-preferred partner gene, is involved in the adhesion of extracellular matrix to the cell surface, and a minor variant (SNP = rs1464510) increases the risk of disease by approximately 30%. This gene strongly associates with coeliac disease ($p < 10^{-39}$) in samples taken from a broad area of Europe and the US.[63]

The prevalence of coeliac disease genotypes in the modern population is not completely understood. Given the characteristics of the disease and its apparent strong heritability, it would normally be expected that the genotypes would undergo negative selection and to be absent in societies where agriculture has been practised the longest (compare with a similar condition, Lactose intolerance, which has been negatively selected so strongly that its prevalence went from ~100% in ancestral populations to less than 5% in some European countries). This expectation was first proposed by Simoons (1981).[64] By now, however, it is apparent that this is not the case; on the contrary, there is evidence of *positive* selection in coeliac disease genotypes. It is suspected that some of them may have been beneficial by providing protection against bacterial infections.[65][66]

## Prolamins [edit]

The majority of the proteins in food responsible for the immune reaction in coeliac disease are the prolamins. These are storage proteins rich in proline (*prol-*) and glutamine (*-amin*) that dissolve in alcohols and are resistant to proteases and peptidases of the gut.[19][67] Prolamins are found in cereal grains with different grains having different but related prolamins: wheat (gliadin), barley (hordein), rye (secalin), corn (zein) and as a minor protein, avenin in oats. One region of α-gliadin stimulates membrane cells, enterocytes, of the intestine to allow larger molecules around the sealant between cells. Disruption of tight junctions allow peptides larger than three amino acids to enter the intestinal lining[68]

Membrane leaking permits peptides of gliadin that stimulate two levels of immune response, the innate response and the adaptive (T-helper cell mediated) response. One protease-resistant peptide from α-gliadin contains a region that stimulates lymphocytes and results in the release of interleukin-15. This innate response to gliadin results in immune-system signalling that attracts inflammatory cells and increases the release of inflammatory chemicals.[19] The strongest and most common adaptive response to gliadin is directed toward an α2-gliadin fragment of 33 amino acids in length.[19]

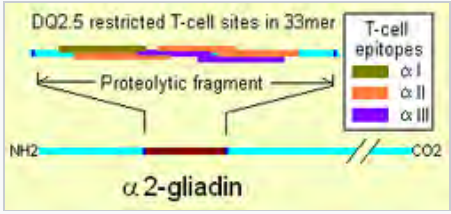
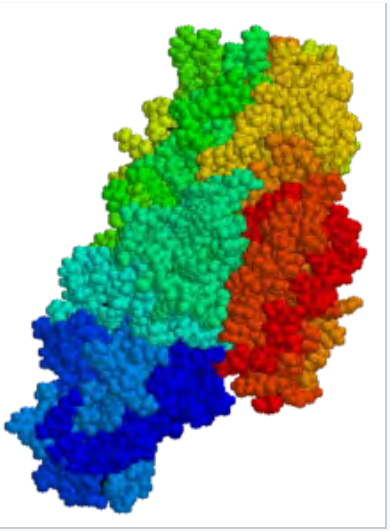


Illustration of deamidated α-2 gliadin's 33mer, amino acids 56–88, showing the overlapping of three varieties of T-cell epitope[69]

The response to the 33mer occurs in most coeliacs who have a DQ2 isoform. This peptide, when altered by intestinal transglutaminase, has a high density of overlapping T-cell epitopes. This increases the likelihood that the DQ2 isoform will bind and stay bound to peptide when recognised by T-cells.[69] Gliadin in wheat is the best-understood member of this family, but other prolamins exist, and hordein (from barley) and secalin (from rye) may contribute to coeliac disease.[19][70] However, not all prolamins will cause this immune reaction, and there is ongoing controversy on the ability of avenin (the prolamin found in oats) to induce this response in coeliac disease.

## Tissue transglutaminase [edit]

Anti-transglutaminase antibodies to the enzyme tissue transglutaminase (tTG) are found in the blood of the majority of people with classic symptoms and complete villous atrophy, but only in 70% of the cases with partial villous atrophy and 30% of the cases with minor mucosal lesions.[15] Tissue transglutaminase modifies gluten peptides into a form that may stimulate the immune system more effectively.[19] These peptides are modified by tTG in two ways, deamidation or transamidation.[71]



Tissue transglutaminase, drawn from PDB: 1FAU

Deamidation is the reaction by which a glutamate residue is formed by cleavage of the epsilon-amino group of a glutamine side chain. Transamidation, which occurs three times more often than deamidation, is the cross-linking of a glutamine residue from the gliadin peptide to a lysine residue of tTg in a reaction which is catalysed by the transglutaminase. Crosslinking may occur either within or outside the active site of the enzyme. The latter case yields a permanently covalently linked complex between the gliadin and the tTg.[72] This results in the formation of new epitopes which are believed to trigger the primary immune response by which the autoantibodies against tTg develop.[73][74][75]

Stored biopsies from people with suspected coeliac disease have revealed that autoantibody deposits in the subclinical coeliacs are detected prior to clinical disease. These deposits are also found in people who present with other autoimmune diseases, anaemia, or malabsorption phenomena at a much increased rate over the normal population.[76] Endomysial components of antibodies (EMA) to tTG are believed to be directed toward cell-surface transglutaminase, and these antibodies are still used in confirming a coeliac disease diagnosis. However, a 2006 study showed that EMA-negative people with coeliac tend to be older males with more severe abdominal symptoms and a lower frequency of "atypical" symptoms, including autoimmune disease.[77] In this study, the anti-tTG antibody deposits did not correlate with the severity of villous destruction. These findings, coupled with recent work showing that gliadin has an innate response component,[78] suggest that gliadin may be more responsible for the primary manifestations of coeliac disease, whereas tTG is a bigger factor in secondary effects such as allergic responses and secondary autoimmune diseases. In a large percentage of people with coeliac, the anti-tTG antibodies also recognise a rotavirus protein called VP7. These antibodies stimulate monocyte proliferation, and rotavirus infection might explain some early steps in the cascade of immune cell proliferation.[79]

Indeed, earlier studies of rotavirus damage in the gut showed this causes a villous atrophy.[80] This suggests that viral proteins may take part in the initial flattening and stimulate self-crossreactive anti-VP7 production. Antibodies to VP7 may also slow healing until the gliadin-mediated tTG presentation provides a second source of crossreactive antibodies.

Other intestinal disorders may have biopsy that look like coeliac disease including lesions caused by Candida.[81]

### Villous atrophy and malabsorption [edit]

The inflammatory process, mediated by T cells, leads to disruption of the structure and function of the small bowel's mucosal lining and causes malabsorption as it impairs the body's ability to absorb nutrients, minerals, and fat-soluble vitamins A, D, E, and K from food. Lactose intolerance may be present due to the decreased bowel surface and reduced production of lactase but typically resolves once the condition is treated.

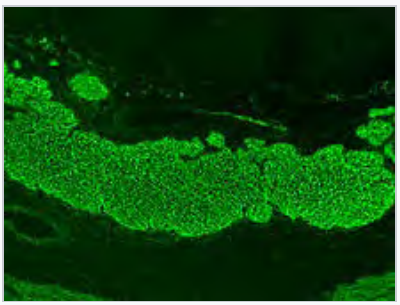
Alternative causes of this tissue damage have been proposed and involve release of interleukin 15 and activation of the innate immune system by a shorter gluten peptide (p31–43/49). This would trigger killing of enterocytes by lymphocytes in the epithelium.[19] The villous atrophy seen on biopsy may also be due to unrelated causes, such as tropical sprue, giardiasis and radiation enteritis. While positive serology and typical biopsy are highly suggestive of coeliac disease, lack of response to diet may require these alternative diagnoses to be considered.[33]

## Diagnosis [edit]

Diagnosis is often very difficult so that most cases are diagnosed with great delay.[14] There are several tests that can be used. The level of symptoms may determine the order of the tests, but *all* tests lose their usefulness if the person is already eating a gluten-free diet. Intestinal damage begins to heal within weeks of gluten being removed from the diet, and antibody levels decline over months. For those who have already started on a gluten-free diet, it may be necessary to perform a rechallenge with some gluten-containing food in one meal a day over 6 weeks before repeating the investigations.[12]

## Blood tests [edit]

Serological blood tests are the first-line investigation required to make a diagnosis of coeliac disease. Its sensitivity correlates with the degree of histological lesions. People who present minor damage of the small intestine may have seronegative findings so many patients with coeliac disease often are missed. In patients with villous atrophy, anti-endomysial (EMA) antibodies of the immunoglobulin A (IgA) type can detect coeliac disease with a sensitivity and specificity of 90% and 99%, respectively.[82] Serology for anti-transglutaminase antibodies (anti-tTG) was initially reported to have a higher sensitivity (99%) and specificity (>90%). However, it is now thought to have similar characteristics to anti-endomysial antibody.[82] Both anti-transglutaminase and anti-endomysial antibodies have high sensitivity to diagnose people with classic symptoms and complete villous atrophy, but they are only found in 30-89% of the cases with partial villous atrophy and in less than 50% of the people who have minor mucosal lesions (duodenal lymphocytosis) with normal villi.[15][16]



Immunofluorescence staining pattern of endomysial antibodies on a monkey oesophagus tissue sample.

Tissue transglutaminase modifies gluten peptides into a form that may stimulate the immune system more effectively.[19] These peptides are modified by tTG in two ways, deamidation or transamidation.[71] Modern anti-tTG assays rely on a human recombinant protein as an antigen.[83] tTG testing should be done first as it is an easier test to perform. An equivocal result on tTG testing should be followed by anti-endomysial antibodies.[12]

Guidelines recommend that a total serum IgA level is checked in parallel, as people with coeliac with IgA deficiency may be unable to produce the antibodies on which these tests depend ("false negative"). In those people, IgG antibodies against transglutaminase (IgG-tTG) may be diagnostic.[12][84]

If all these antibodies are negative, then it should be determined anti-DGP antibodies (antibodies against deamidated gliadin peptides). IgG class anti-DGP antibodies may be useful in people with IgA deficiency. In children younger than two years, anti-DGP antibodies perform better than anti-endomysial and anti-transglutaminase antibodies tests.[3]

Because of the major implications of a diagnosis of coeliac disease, professional guidelines recommend that a positive blood test is still followed by an endoscopy/gastroscopy and biopsy. A negative serology test may still be followed by a recommendation for endoscopy and duodenal biopsy if clinical suspicion remains high.[12][33][85]

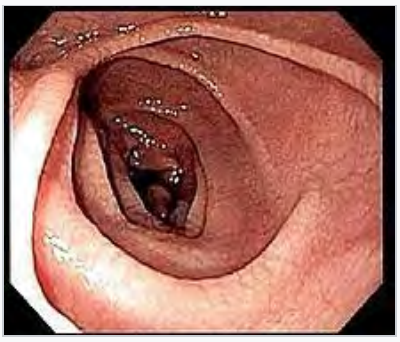
Historically three other antibodies were measured: anti-reticulin (ARA), anti-gliadin (AGA) and anti-endomysial (EMA) antibodies.[86] ARA testing, however, is not accurate enough for routine diagnostic use.[87] Serology may be unreliable in young children, with anti-gliadin performing somewhat better than other tests in children under five.[86] Serology tests are based on indirect immunofluorescence (reticulin, gliadin and endomysium) or ELISA (gliadin or tissue transglutaminase, tTG).[88]

Antibody testing may be combined with HLA testing if the diagnosis is unclear. TGA and EMA testing are the most sensitive serum antibody tests, but as a negative HLA-DQ type excludes the diagnosis of coeliac disease, testing also for HLA-DQ2 or DQ8 maximises sensitivity and negative predictive values.[56] However, widespread use of HLA typing to rule out coeliac disease is not currently recommended.[12]

## Endoscopy [edit]

An upper endoscopy with biopsy of the duodenum (beyond the duodenal bulb) or jejunum is performed to obtain multiple samples (four to eight) from the duodenum. Not all areas may be equally affected; if biopsies are taken from healthy bowel tissue, the result would be a false negative.[33] Even in the same bioptic fragment, different degrees of damage may be present.[5]

Most people with coeliac disease have a small intestine that appears to be normal on endoscopy before the biopsies are examined. However, five findings have been associated with a high specificity for coeliac disease: scalloping of the small bowel folds (*pictured*), paucity in the folds, a mosaic pattern to the mucosa (described as a "cracked-mud" appearance), prominence of the submucosa blood vessels, and a nodular pattern to the mucosa.[89]



Endoscopic still of duodenum of person with coeliac disease showing scalloping of folds and

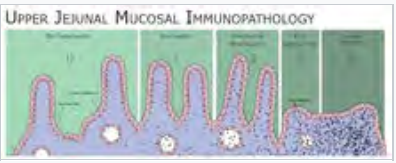
European guidelines suggest that in children and adolescents with symptoms which are compatible with coeliac disease, the diagnosis can be made without

the need for intestinal biopsy if anti-tTG antibodies titres are very high (10 times the upper limit of normal).[3]

Until the 1970s, biopsies were obtained using metal capsules attached to a suction device. The capsule was swallowed and allowed to pass into the small intestine. After x-ray verification of its position, suction was applied to collect part of the intestinal wall inside the capsule. Often-utilised capsule systems were the Watson capsule and the Crosby–Kugler capsule. This method has now been largely replaced by fibre-optic endoscopy, which carries a higher sensitivity and a lower frequency of errors.[90]

Capsule endoscopy (CE) allows identification of typical mucosal changes observed in coeliac disease but has a lower sensitivity compared to regular endoscopy and histology. CE is therefore not the primary diagnostic tool for coeliac disease. However, CE can be used for diagnosing T-cell lymphoma, ulcerative jejunoileitis and adenocarcinoma in refractory or complicated coeliac disease.[91]

"cracked-mud" appearance to mucosa




Schematic of the Marsh classification of upper jejunal pathology in coeliac disease.

## Pathology [edit]

The classic pathology changes of coeliac disease in the small bowel are categorised by the "Marsh classification":[92]

- Marsh stage 0: normal mucosa
- Marsh stage 1: increased number of intra-epithelial lymphocytes (IELs), usually exceeding 20 per 100 enterocytes
- Marsh stage 2: proliferation of the crypts of Lieberkühn
- Marsh stage 3: partial or complete villous atrophy and crypt hypertrophy[93]
- Marsh stage 4: hypoplasia of the small intestine architecture

Marsh's classification, introduced in 1992, was subsequently modified in 1999 to six stages, where the previous stage 3 was split in three substages.[94] Further studies demonstrated that this system was not always reliable and that the changes observed in coeliac disease could be described in one of three stages:[9][95]

- A representing lymphocytic infiltration with normal villous appearance;
- B1 describing partial villous atrophy; and
- B2 describing complete villous atrophy.

The changes classically improve or reverse after gluten is removed from the diet. However, most guidelines do not recommend a repeat biopsy unless there is no improvement in the symptoms on diet.[33][85] In some cases, a deliberate gluten challenge, followed by biopsy, may be conducted to confirm or refute the diagnosis. A normal biopsy and normal serology after challenge indicates the diagnosis may have been incorrect.[33]

In untreated coeliac disease, villous atrophy is more common in children younger than three years, but in older children and adults, it is common to find minor intestinal lesions (duodenal lymphocytosis) with normal intestinal villi.[4][13][17]

## Other diagnostic tests [edit]

At the time of diagnosis, further investigations may be performed to identify complications, such as iron deficiency (by full blood count and iron studies), folic acid and vitamin $B_{12}$ deficiency and hypocalcaemia (low calcium levels, often due to decreased vitamin D levels). Thyroid function tests may be requested during blood tests to identify hypothyroidism, which is more common in people with coeliac disease.[34]

Osteopenia and osteoporosis, mildly and severely reduced bone mineral density, are often present in people with coeliac disease, and investigations to measure bone density may be performed at diagnosis, such as dual-energy X-ray absorptiometry (DXA) scanning, to identify risk of fracture and need for bone protection medication.[33][34]

## Gluten withdrawal [edit]

Although blood antibody tests, biopsies, and genetic tests usually provide a clear diagnosis,[16][82] occasionally the response to gluten withdrawal on a gluten-free diet is needed to support the diagnosis. Currently, gluten challenge is no longer required to confirm the diagnosis in patients with intestinal lesions compatible with coeliac disease and a positive response to a gluten-free diet.[16] Nevertheless, in some cases, a gluten challenge with a subsequent biopsy may be useful to support the diagnosis, for example in people with a high suspicion for coeliac disease, [16]

without a biopsy confirmation, who have negative blood antibodies and are already on a gluten-free diet. Gluten challenge is discouraged before the age of 5 years and during pubertal growth.[96] The alternative diagnosis of non-coeliac gluten sensitivity may be made where there is only symptomatic evidence of gluten sensitivity.[97] Gastrointestinal and extraintestinal symptoms of people with non-coeliac gluten sensitivity can be similar to those of coeliac disease,[5] and improve when gluten is removed from the diet,[98][99] after coeliac disease and wheat allergy are reasonably excluded.[100]

Up to 30% of people often continue having or redeveloping symptoms after starting a gluten-free diet.[20] A careful interpretation of the symptomatic response is needed, as a lack of response in a person with coeliac disease may be due to continued ingestion of small amounts of gluten, either voluntary or inadvertent,[13] or be due to other commonly associated conditions such as small intestinal bacterial overgrowth (SIBO), lactose intolerance, fructose,[101] sucrose,[102] and sorbitol[103] malabsorption, exocrine pancreatic insufficiency,[104][105] and microscopic colitis,[105] among others. In untreated coeliac disease, these are often transient conditions derived from the intestinal damage.[102][103][106][107][108] They normally revert or improve several months after starting a gluten-free diet, but may need temporary interventions such as supplementation with pancreatic enzymes,[107][108] dietary restrictions of lactose, fructose, sucrose or sorbitol containing foods,[102][106] or treatment with oral antibiotics in the case of associated bacterial overgrowth.[108] In addition to gluten withdrawal, some people need to follow a low-FODMAPs diet or avoid consumption of commercial gluten-free products, which are usually rich in preservatives and additives (such as sulfites, glutamates, nitrates and benzoates) and which might have a role in triggering functional gastrointestinal symptoms.[109]

## Screening [edit]

There is significant debate as to the benefits of screening. Some studies suggest that early detection would decrease the risk of osteoporosis and anaemia. In contrast, a cohort study suggested that people with undetected coeliac disease had a beneficial risk profile for cardiovascular disease (less overweight, lower cholesterol levels).[19] There is limited evidence that screen-detected cases benefit from a diagnosis in terms of morbidity and mortality; hence, population-level screening is not presently thought to be beneficial.[9]

In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) recommends screening for coeliac disease in people with newly diagnosed chronic fatigue syndrome[110] and irritable bowel syndrome,[30] as well as in type 1 diabetics, especially those with insufficient weight gain or unexplained weight loss.[12][111] It is also recommended in autoimmune thyroid disease, dermatitis herpetiformis, and in the first-degree relatives of those with confirmed coeliac disease.[12]

In 2016 the United States Preventive Services Task Force found inadequate evidence for benefits or harms from screening people at any age who do not have symptoms.[112]

Serology has been proposed as a screening measure, because the presence of antibodies would detect some previously undiagnosed cases of coeliac disease and prevent its complications in those people. However, serologic tests have high sensitivity only in people with total villous atrophy and have very low ability to detect cases with partial villous atrophy or minor intestinal lesions.[16] Testing for coeliac disease may be offered to those with commonly associated conditions.[9][12]

## Treatment [edit]

### Diet [edit]

*Main article: Gluten-free diet*

At present, the only effective treatment is a lifelong gluten-free diet.[42] No medication exists that will prevent damage or prevent the body from attacking the gut when gluten is present. Strict adherence to the diet allows the intestines to heal, leading to resolution of all symptoms in most cases and, depending on how soon the diet is begun, can also eliminate the heightened risk of osteoporosis and intestinal cancer and in some cases sterility.[113] The diet can be cumbersome; failure to comply with the diet may cause relapse.

Dietitian input is generally requested to ensure the person is aware which foods contain gluten, which foods are safe, and how to have a balanced diet despite the limitations. In many countries, gluten-free products are available on prescription and may be reimbursed by health insurance plans. Gluten-free products are usually more expensive and harder to find than common gluten-containing foods.[114] Since ready-made products often contain traces of gluten, some coeliacs may find it necessary to cook from scratch.[115]

The term *gluten-free* is generally used to indicate a supposed harmless level of gluten rather than a complete absence.[116] The exact level at which gluten is harmless is uncertain and controversial. A recent systematic review tentatively concluded that consumption of less than 10 mg of gluten per day is unlikely to cause histological abnormalities, although it noted that few reliable studies had been done.[116] Regulation of the label *gluten-free* varies. In the European Union, the European Commission issued regulations in 2009 limiting the use of "gluten-free" labels for food products to those with less than 20 mg/kg of gluten, and "very low gluten" labels for those with less than 100 mg/kg.[117] In the United States, the FDA issued regulations in 2013 limiting the use of "gluten-free" labels for food products to those with less than 20 ppm of gluten.[118][119][120] The current international Codex Alimentarius standard allows for 20 ppm of gluten in so-called "gluten-free" foods.[121] Several organisations, such as the Gluten-Free Certification Organization (GFCO), the Celiac Sprue Association (CSA), and the National Foundation for Celiac Awareness (NFCA), also certify products and companies as gluten-free.[122]

Gluten-free diet improves healthcare-related quality of life, and strict adherence to the diet gives more benefit than incomplete adherence. Nevertheless, gluten-free diet doesn't completely normalise the quality of life.[123]

### Refractory disease [edit]

Between 0.3% and 10% of people have refractory disease, which means that they have persistent villous atrophy on a gluten-free diet despite the lack of gluten exposure for more than 12 months.[105] Nevertheless, inadvertent exposure to gluten is the main cause of persistent villous atrophy, and must be ruled out before a diagnosis of refractory disease is made.[105] People with poor basic education and understanding of gluten-free diet often believe that they are strictly following the diet, but are making regular errors.[20][105][124] Also, a lack of symptoms is not a reliable indicator of intestinal recuperation.[105]

If alternative causes of villous atrophy have been eliminated, steroids or immunosuppressants (such as azathioprine) may be considered in this scenario.[33]

Refractory coeliac disease should not be confused with the persistence of symptoms despite gluten withdrawal[105] caused by transient conditions derived from the intestinal damage,[102][103][106] which generally revert or improve several months after starting a gluten-free diet,[107][108] such as small intestinal bacterial overgrowth, lactose intolerance, fructose,[101] sucrose,[102] and sorbitol[103] malabsorption, exocrine pancreatic insufficiency,[104][105] and microscopic colitis,[105] among others.

## Epidemiology [edit]

Globally coeliac diseases affects between 1 in 100 and 1 in 170 people.[22][125] Rates, however, vary between different regions of the world from as few as 1 in 300 to as many as 1 in 40.[22] In the United States it is thought to affect between 1 in 1750 (defined as clinical disease including dermatitis herpetiformis with limited digestive tract symptoms) to 1 in 105 (defined by presence of IgA TG in blood donors).[126] Due to variable signs and symptoms it is believed that about 85% of people affected are undiagnosed.[127] The percentage of people with clinically diagnosed disease (symptoms prompting diagnostic testing) is 0.05–0.27% in various studies. However, population studies from parts of Europe, India, South America, Australasia and the USA (using serology and biopsy) indicate that the percentage of people with the disease may be between 0.33 and 1.06% in children (but 5.66% in one study of children of the predisposed Sahrawi people[128]) and 0.18–1.2% in adults.[19] Among those in primary care populations who report gastrointestinal symptoms, the rate of coeliac disease is about 3%.[82] The rate amongst adult blood donors in Iran, Israel, Syria and Turkey is 0.60%, 0.64%, 1.61% and 1.15%, respectively.[32]

People of African, Japanese and Chinese descent are rarely diagnosed;[129] this reflects a much lower prevalence of the genetic risk factors, such as HLA-B8.[130] People of Indian ancestry seem to have a similar risk to those of Western Caucasian ancestry.[32] Population studies also indicate that a large proportion of coeliacs remain undiagnosed; this is due, in part, to many clinicians being unfamiliar with the condition and also due to the fact it can be asymptomatic.[131] Coeliac disease is slightly more common in women than in men.[24] A large multicentre study in the U.S. found a prevalence of 0.75% in not-at-risk groups, rising to 1.8% in symptomatic people, 2.6% in second-degree relatives (like grandparents, aunt or uncle, grandchildren, etc.) of a person with coeliac disease and 4.5% in first-degree relatives (siblings, parents or children).[32] This profile is similar to the prevalence in Europe.[32] Other populations at increased risk for coeliac disease, with prevalence rates ranging from 5% to 10%, include individuals with Down and Turner syndromes, type 1 diabetes, and autoimmune thyroid disease, including both hyperthyroidism (overactive thyroid) and hypothyroidism (underactive thyroid).[132]

Historically, coeliac disease was thought to be rare, with a prevalence of about 0.02%.[132] The reason for the recent increases in the number of reported cases is unclear.[125] It may be at least in part due to changes in diagnostic practice.[133] There also appears to be an approximately 4.5 fold true increase that may be due to less exposure to bacteria and other pathogens in Western environments.[125]

## History [edit]

Humans first started to cultivate grains in the Neolithic period (beginning about 9500 BCE) in the Fertile Crescent in Western Asia, and it is likely that coeliac disease did not occur before this time. Aretaeus of Cappadocia, living in the second century in the same area, recorded a malabsorptive syndrome with chronic diarrhoea, causing a debilitation of the whole body.[25] His "Cœliac Affection" (*coeliac* from Greek κοιλιακός *koiliakos*, "abdominal") gained the attention of Western medicine when Francis Adams presented a translation of Aretaeus's work at the Sydenham Society in 1856. The patient described in Aretaeus' work had stomach pain and was atrophied, pale, feeble and incapable of work. The diarrhoea manifested as loose stools that were white, malodorous and flatulent, and the disease was intractable and liable to periodic return. The problem, Aretaeus believed, was a lack of heat in the stomach necessary to digest the food and a reduced ability to distribute the digestive products throughout the body, this incomplete digestion resulting in the diarrhoea. He regarded this as an affliction of the old and more commonly affecting women, explicitly excluding children. The cause, according to Aretaeus, was sometimes either another chronic disease or even consuming "a copious draught of cold water."[25][26]

The paediatrician Samuel Gee gave the first modern-day description of the condition in children in a lecture at Hospital for Sick Children, Great Ormond Street, London, in 1887. Gee acknowledged earlier descriptions and terms for the disease and adopted the same term as Aretaeus (coeliac disease). He perceptively stated: "If the patient can be cured at all, it must be by means of diet." Gee recognised that milk intolerance is a problem with coeliac children and that highly starched foods should be avoided. However, he forbade rice, sago, fruit and vegetables, which all would have been safe to eat, and he recommended raw meat as well as thin slices of toasted bread. Gee highlighted particular success with a child "who was fed upon a quart of the best Dutch mussels daily." However, the child could not bear this diet for more than one season.[26][134]

Christian Archibald Herter, an American physician, wrote a book in 1908 on children with coeliac disease, which he called "intestinal infantilism." He noted their growth was retarded and that fat was better tolerated than carbohydrate. The eponym *Gee-Herter disease* was sometimes used to acknowledge both contributions.[135][136] Sidney V. Haas, an American paediatrician, reported positive effects of a diet of bananas in 1924.[137] This diet remained in vogue until the actual cause of coeliac disease was determined.[26]

While a role for carbohydrates had been suspected, the link with wheat was not made until the 1940s by the Dutch paediatrician Dr. Willem Karel Dicke.[138] It is likely that clinical improvement of his patients during the Dutch famine of 1944 (during which flour was scarce) may have contributed to his discovery.[139] Dicke noticed that the shortage of bread led to a significant drop in the death rate among children affected by coeliac disease from greater than 35% to essentially zero. He also reported that once wheat was again available after the conflict, the mortality rate soared to previous levels.[140] The link with the gluten component of wheat was made in 1952 by a team from Birmingham, England.[141] Villous atrophy was described by British physician John W. Paulley in 1954 on samples taken at surgery.[142] This paved the way for biopsy samples taken by endoscopy.[26]

Throughout the 1960s, other features of coeliac disease were elucidated. Its hereditary character was recognised in 1965.[143] In 1966, dermatitis herpetiformis was linked to gluten sensitivity.[26][37]

## Social and culture [edit]

*See also: List of people diagnosed with coeliac disease*

May has been designated as "Coeliac Awareness Month" by several coeliac organisations.[144][145]

### Christian churches and the Eucharist [edit]

Speaking generally, the various denominations of Christians celebrate a Eucharist in which a wafer or small piece of sacramental bread from wheat bread is blessed and then eaten. A typical wafer weighs about half a gram.[146] Wheat flour contains around 10 to 13% gluten, so a single communion wafer may have more than 50 mg of gluten, an amount which will harm the health of many people with coeliac especially if consumed every day (see Diet above).

Many Christian churches offer their communicants gluten-free alternatives, usually in the form of a rice-based

cracker or gluten-free bread. These include the United Methodist, Christian Reformed, Episcopal, the Anglican Church (Church of England, UK) and Lutheran. Catholics may receive from the Chalice alone, or ask for gluten-reduced hosts; gluten-free ones however are not considered to still be wheat bread, and hence invalid matter.[147]

### Roman Catholic position [edit]

Roman Catholic doctrine states that for a valid Eucharist, the bread to be used at Mass must be made from wheat. In 2002, the Congregation for the Doctrine of the Faith approved German-made low-gluten hosts, which meet all of the Catholic Church's requirements, for use in Italy; although not entirely gluten-free, they were also approved by the Italian Coeliac Association.[148] Some Catholics with coeliac have requested permission to use rice wafers; such petitions have always been denied.[149] As Catholic doctrine affirms that Christ is wholly and equally present under both species, it is possible to receive under the species of wine alone.

The issue is more complex for priests. As a celebrant, a priest is, for the fullness of the sacrifice of the Mass, absolutely required to receive under both species. On 24 July 2003, the Congregation for the Doctrine of the Faith stated, "Given the centrality of the celebration of the Eucharist in the life of a priest, one must proceed with great caution before admitting to Holy Orders those candidates unable to ingest gluten or alcohol without serious harm."[150]

By January 2004, extremely low-gluten Church-approved hosts had become available in the United States, Italy and Australia.[151]

### Passover [edit]

The Jewish festival of Pesach (Passover) may present problems with its obligation to eat matzo, which is unleavened bread made in a strictly controlled manner from wheat, barley, spelt, oats, or rye. This rules out many other grains that are normally used as substitutes for people with gluten sensitivity, especially for Ashkenazi Jews, who also avoid rice. Many kosher-for-Passover products avoid grains altogether and are therefore gluten-free. Potato starch is the primary starch used to replace the grains. Consuming matzo is mandatory on the first night of Pesach only. Jewish law holds that one should not seriously endanger one's health in order to fulfill a commandment. Thus, a person with coeliac disease is not allowed, let alone required, to eat any matzo other than gluten-free matzo.[152]

## Research directions [edit]

Various other approaches are being studied that would reduce the need of dieting. All are still under development, and are not expected to be available to the general public for a while.[19][153][154]

Three main approaches have been proposed as new therapeutic modalities for coeliac disease: gluten detoxification, modulation of the intestinal permeability, and modulation of the immune response.[155]

Using genetically engineered wheat species, or wheat species that have been selectively bred to be minimally immunogenic, may allow the consumption of wheat. This, however, could interfere with the effects that gliadin has on the quality of dough. Alternatively, gluten exposure can be minimised by the ingestion of a combination of enzymes (prolyl endopeptidase and a barley glutamine-specific cysteine endopeptidase (EP-B2)) that degrade the putative 33-mer peptide in the duodenum.[19]

Alternative treatments under investigation include the inhibition of zonulin, an endogenous signalling protein linked to increased permeability of the bowel wall and hence increased presentation of gliadin to the immune system. One inhibitor of this pathway is larazotide acetate, which is currently scheduled for phase 3 clinical trials.[156] Other modifiers of other well-understood steps in the pathogenesis of coeliac disease, such as the action of HLA-DQ2 or tissue transglutaminase and the MICA/NKG2D interaction that may be involved in the killing of enterocytes.[19]

Attempts to modulate the immune response with regard to coeliac disease are mostly still in phase I of clinical testing; one agent (CCX282-B) has been evaluated in a phase II clinical trial on the basis of small-intestinal biopsies taken from people with coeliac disease before and after gluten exposure.[155]

## References [edit]


1. ^ *a b c d e* "Celiac Disease". *NIDDKD*. June 2015. Retrieved 17 March 2016.
2. ^ *a b c* Fasano A (Apr 2005). "Clinical presentation of celiac disease in the pediatric population". *Gastroenterology* (Review). **128** (4 Suppl 1): S68–73. doi:10.1053/j.gastro.2005.02.015. PMID 15825129.

3. ^ [a b c d e] Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, Troncone R, Giersiepen K, Branski D, Catassi C, Lelgeman M, Mäki M, Ribes-Koninckx C, Ventura A, Zimmer KP, ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (Jan 2012). "European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease" (PDF). *J Pediatr Gastroenterol Nutr* (Practice Guideline). **54** (1): 136–60. doi:10.1097/MPG.0b013e31821a23d0. PMID 22197856. "Since 1990, the understanding of the pathological processes of CD has increased enormously, leading to a change in the clinical paradigm of CD from a chronic, gluten-dependent enteropathy of childhood to a systemic disease with chronic immune features affecting different organ systems. (...) atypical symptoms may be considerably more common than classic symptoms"
4. ^ [a b c] Rostami Nejad M, Hogg-Kollars S, Ishaq S, Rostami K (2011). "Subclinical celiac disease and gluten sensitivity". *Gastroenterol Hepatol Bed Bench* (Review). **4** (3): 102–8. PMC 4017418. PMID 24834166.
5. ^ [a b c] Tonutti E, Bizzaro N (2014). "Diagnosis and classification of celiac disease and gluten sensitivity". *Autoimmun Rev* (Review). **13** (4-5): 472–6. doi:10.1016/j.autrev.2014.01.043. PMID 24440147.
6. ^ [a b] Ciccocioppo R, Kruzliak P, Cangemi GC, Pohanka M, Betti E, Lauret E, Rodrigo L (Oct 22, 2015). "The Spectrum of Differences between Childhood and Adulthood Celiac Disease". *Nutrients* (Review). **7** (10): 8733–51. doi:10.3390/nu7105426. PMC 4632446. PMID 26506381. "Several additional studies in extensive series of celiac patients have clearly shown that TG2A sensitivity varies depending on the severity of duodenal damage, and reaches almost 100% in the presence of complete villous atrophy (more common in children under three years), 70% for subtotal atrophy, and up to 30% when only an increase in IELs is present. *(IELs: intraepithelial lymphocytes)*"
7. ^ Tovoli F, Masi C, Guidetti E, Negrini G, Paterini P, Bolondi L (Mar 16, 2015). "Clinical and diagnostic aspects of gluten related disorders". *World J Clin Cases* (Review). **3** (3): 275–84. doi:10.12998/wjcc.v3.i3.275. PMC 4360499. PMID 25789300.
8. ^ [a b c] Penagini F, Dilillo D, Meneghin F, Mameli C, Fabiano V, Zuccotti GV (Nov 18, 2013). "Gluten-free diet in children: an approach to a nutritionally adequate and balanced diet". *Nutrients* (Review). **5** (11): 4553–65. doi:10.3390/nu5114553. PMC 3847748. PMID 24253052.
9. ^ [a b c d e f g h i j k l m] Di Sabatino A, Corazza GR (April 2009). "Coeliac disease". *Lancet*. **373** (9673): 1480–93. doi:10.1016/S0140-6736(09)60254-3. PMID 19394538.
10. ^ [a b c d] Comino I, Moreno Mde L, Sousa C (Nov 7, 2015). "Role of oats in celiac disease". *World J Gastroenterol*. **21** (41): 11825–31. doi:10.3748/wjg.v21.i41.11825. PMC 4631980. PMID 26557006. "It is necessary to consider that oats include many varieties, containing various amino acid sequences and showing different immunoreactivities associated with toxic prolamins. As a result, several studies have shown that the immunogenicity of oats varies depending on the cultivar consumed. Thus, it is essential to thoroughly study the variety of oats used in a food ingredient before including it in a gluten-free diet."
11. ^ [a b] Lundin KE, Wijmenga C (Sep 2015). "Coeliac disease and autoimmune disease-genetic overlap and screening". *Nat Rev Gastroenterol Hepatol* (Review). **12** (9): 507–15. doi:10.1038/nrgastro.2015.136. PMID 26303674. "The abnormal immunological response elicited by gluten-derived proteins can lead to the production of several different autoantibodies, which affect different systems."
12. ^ [a b c d e f g h i] National Institute for Health and Clinical Excellence. *Clinical guideline 86: Recognition and assessment of coeliac disease*. London, 2009.
13. ^ [a b c] Vivas S, Vaquero L, Rodríguez-Martín L, Caminero A (Nov 6, 2015). "Age-related differences in celiac disease: Specific characteristics of adult presentation". *World J Gastrointest Pharmacol Ther* (Review). **6** (4): 207–12. doi:10.4292/wjgpt.v6.i4.207. PMC 4635160. PMID 26558154. "In addition, the presence of intraepithelial lymphocytosis and/or villous atrophy and crypt hyperplasia of small-bowel mucosa, and clinical remission after withdrawal of gluten from the diet, are also used for diagnosis antitransglutaminase antibody (tTGA) titers and the degree of histological lesions inversely correlate with age. Thus, as the age of diagnosis increases antibody titers decrease and histological damage is less marked. It is common to find adults without villous atrophy showing only an inflammatory pattern in duodenal mucosa biopsies: Lymphocytic enteritis (Marsh I) or added crypt hyperplasia (Marsh II)"
14. ^ [a b] Matthias T, Pfeiffer S, Selmi C, Eric Gershwin M (Apr 2010). "Diagnostic challenges in celiac disease and the role of the tissue transglutaminase-neo-epitope". *Clin Rev Allergy Immunol* (Review). **38** (2–3): 298–301. doi:10.1007/s12016-009-8160-z. PMID 19629760.
15. ^ [a b c] Lewis NR, Scott BB (Jul 1, 2006). "Systematic review: the use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests)". *Aliment Pharmacol Ther* (Review). **24** (1): 47–54. doi:10.1111/j.1365-2036.2006.02967.x. PMID 16803602.
16. ^ [a b c d e f] Rostom A, Murray JA, Kagnoff MF (Dec 2006). "American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease". *Gastroenterology* (Review). **131** (6): 1981–2002. doi:10.1053/j.gastro.2006.10.004. PMID 17087937.
17. ^ [a b] Molina-Infante J, Santolaria S, Sanders DS, Fernández-Bañares F (May 2015). "Systematic review: noncoeliac gluten sensitivity". *Aliment Pharmacol Ther* (Review). **41** (9): 807–20. doi:10.1111/apt.13155. PMID 25753138. "Furthermore, seronegativity is more common in coeliac disease patients without villous atrophy (Marsh 1-2 lesions), but these 'minor' forms of coeliac disease may have similar clinical manifestations to those with villous atrophy and may show similar clinical–histological remission with reversal of haematological or biochemical disturbances on a gluten-free diet (GFD)."
18. ^ Ludvigsson JF, Card T, Ciclitira PJ, Swift GL, Nasr I, Sanders DS, Ciacci C (Apr 2015). "Support for patients with celiac disease: A literature review". *United European Gastroenterol J* (Review). **3** (2): 146–59. doi:10.1177/2050640614562599. PMC 4406900. PMID 25922674.

19. ^ a b c d e f g h i j k l m n o p q van Heel DA, West J (2006). "Recent advances in coeliac disease". *Gut* (Review). **55** (7): 1037–46. doi:10.1136/gut.2005.075119. PMC 1856316. PMID 16766754.
20. ^ a b c See JA, Kaukinen K, Makharia GK, Gibson PR, Murray JA (Oct 2015). "Practical insights into gluten-free diets". *Nat Rev Gastroenterol Hepatol* (Review). **12** (10): 580–91. doi:10.1038/nrgastro.2015.156. PMID 26392070. "A lack of symptoms and/or negative serological markers are not reliable indicators of mucosal response to the diet. Furthermore, up to 30% of patients continue to have gastrointestinal symptoms despite a strict GFD.122,124 If adherence is questioned, a structured interview by a qualified dietitian can help to identify both intentional and inadvertent sources of gluten."
21. ^ Lebwohl B, Ludvigsson JF, Green PH (Oct 2015). "Celiac disease and non-celiac gluten sensitivity". *BMJ* (Review). **351**: h4347. doi:10.1136/bmj.h4347. PMC 4596973. PMID 26438584. "Celiac disease occurs in about 1% of the population worldwide, although most people with the condition are undiagnosed. It can cause a wide variety of symptoms, both intestinal and extra-intestinal because it is a systemic autoimmune disease that is triggered by dietary gluten. Patients with celiac disease are at increased risk of cancer, including a twofold to fourfold increased risk of non-Hodgkin's lymphoma and a more than 30-fold increased risk of small intestinal adenocarcinoma, and they have a 1.4-fold increased risk of death."
22. ^ a b c Fasano, A; Catassi, C (Dec 20, 2012). "Clinical practice. Celiac disease". *The New England Journal of Medicine* (Review). **367** (25): 2419–26. doi:10.1056/NEJMcp1113994. PMID 23252527.
23. ^ Lionetti E, Gatti S, Pulvirenti A, Catassi C (Jun 2015). "Celiac disease from a global perspective". *Best Pract Res Clin Gastroenterol* (Review). **29** (3): 365–79. doi:10.1016/j.bpg.2015.05.004. PMID 26060103.
24. ^ a b Hischenhuber C, Crevel R, Jarry B, Mäki M, Moneret-Vautrin DA, Romano A, Troncone R, Ward R (March 2006). "Review article: safe amounts of gluten for patients with wheat allergy or coeliac disease". *Aliment. Pharmacol. Ther*. **23** (5): 559–75. doi:10.1111/j.1365-2036.2006.02768.x. PMID 16480395.
25. ^ a b c Adams F, translator (1856). "On The Cœliac Affection". *The extant works of Aretaeus, The Cappadocian*. London: Sydenham Society. pp. 350–1. Retrieved 12 December 2009.
26. ^ a b c d e f Losowsky MS (2008). "A history of coeliac disease". *Dig Dis*. **26** (2): 112–20. doi:10.1159/000116768. PMID 18431060.
27. ^ Schuppan D, Zimmer KP (2013). "The Diagnosis and Treatment of Celiac Disease". *Dtsch Arztebl Int*. **110** (49): 835–45. doi:10.3238/arztebl.2013.0835. PMC 3884535. PMID 24355936.
28. ^ Vriezinga SL, Schweizer JJ, Koning F, Mearin ML (Sep 2015). "Coeliac disease and gluten-related disorders in childhood". *Nat Rev Gastroenterol Hepatol* (Review). **12** (9): 527–36. doi:10.1038/nrgastro.2015.98. PMID 26100369.
29. ^ Ferguson R, Basu MK, Asquith P, Cooke WT (1976). "Jejunal mucosal abnormalities in patients with recurrent aphthous ulceration". *Br Med J*. **1** (6000): 11–13. doi:10.1136/bmj.1.6000.11. PMC 1638254. PMID 1247715.
30. ^ a b National Institute for Health and Clinical Excellence. *Clinical guideline 61: Irritable bowel syndrome*. London, 2008.
31. ^ Freeman HJ (December 2009). "Adult Celiac Disease and Its Malignant Complications" (PDF). *Gut and Liver*. **3** (4): 237–46. doi:10.5009/gnl.2009.3.4.237. PMC 2852736. PMID 20431755.
32. ^ a b c d e Gujral N, Freeman HJ, Thomson AB (November 2012). "Celiac disease: prevalence, diagnosis, pathogenesis and treatment." (PDF). *World Journal of Gastroenterology*. **18** (42): 6036–59. doi:10.3748/wjg.v18.i42.6036. PMC 3496881. PMID 23155333.
33. ^ a b c d e f g h "American Gastroenterological Association medical position statement: Celiac Sprue". *Gastroenterology*. **120** (6): 1522–5. 2001. doi:10.1053/gast.2001.24055. PMID 11313323.
34. ^ a b c Presutti RJ, Cangemi JR, Cassidy HD, Hill DA (2007). "Celiac disease". *Am Fam Physician*. **76** (12): 1795–802. PMID 18217518.
35. ^ a b Pietzak MM (2014). "Dietary supplements in celiac disease". In Rampertab SD, Mullin GE. *Celiac disease*. pp. 137–59. ISBN 978-1-4614-8559-9.
36. ^ Cunningham-Rundles C (September 2001). "Physiology of IgA and IgA deficiency". *J. Clin. Immunol*. **21** (5): 303–9. doi:10.1023/A:1012241117984. PMID 11720003.
37. ^ a b Marks J, Shuster S, Watson AJ (1966). "Small-bowel changes in dermatitis herpetiformis". *Lancet*. **2** (7476): 1280–2. doi:10.1016/S0140-6736(66)91692-8. PMID 4163419.
38. ^ Nicolas ME, Krause PK, Gibson LE, Murray JA (August 2003). "Dermatitis herpetiformis". *Int. J. Dermatol*. **42** (8): 588–600. doi:10.1046/j.1365-4362.2003.01804.x. PMID 12890100.
39. ^ Tersigni, C.; Castellani, R.; de Waure, C.; Fattorossi, A.; De Spirito, M.; Gasbarrini, A.; Scambia, G.; Di Simone, N. (2014). "Celiac disease and reproductive disorders: meta-analysis of epidemiologic associations and potential pathogenic mechanisms". *Human Reproduction Update*. **20** (4): 582–593. doi:10.1093/humupd/dmu007. ISSN 1355-4786. PMID 24619876.
40. ^ Ferguson A, Hutton MM, Maxwell JD, Murray D (1970). "Adult coeliac disease in hyposplenic patients". *Lancet*. **1** (7639): 163–4. doi:10.1016/S0140-6736(70)90405-8. PMID 4189238.
41. ^ Schuppan D, Junker Y, Barisani D (December 2009). "Celiac disease: from pathogenesis to novel therapies". *Gastroenterology*. **137** (6): 1912–33. doi:10.1053/j.gastro.2009.09.008. PMID 19766641.
42. ^ a b c d Kupper C (2005). "Dietary guidelines and implementation for celiac disease". *Gastroenterology*. **128** (4 Suppl 1): S121–7. doi:10.1053/j.gastro.2005.02.024. PMID 15825119.
43. ^ a b Penagini F, Dilillo D, Meneghin F, Mameli C, Fabiano V, Zuccotti GV (Nov 18, 2013). "Gluten-free diet in children: an approach to a nutritionally adequate and balanced diet". *Nutrients*. **5** (11): 4553–65. doi:10.3390/nu5114553. PMC 3847748. PMID 24253052.
44. ^ a b de Souza MC, Deschênes ME, Laurencelle S, Godet P, Roy CC, Djilali-Saiah I (2016). "Pure Oats as Part of the Canadian Gluten-Free Diet in Celiac Disease: The Need to Revisit the Issue.". *Can J Gastroenterol Hepatol* (Review).

**2016**: 1576360. doi:10.1155/2016/1576360. PMC 4904650. PMID 27446824.

45. ^ [a] [b] Haboubi NY, Taylor S, Jones S (Oct 2006). "Coeliac disease and oats: a systematic review". *Postgrad Med J* (Review). **82** (972): 672–8. doi:10.1136/pgmj.2006.045443. PMC 2653911. PMID 17068278.
46. ^ Gallagher, Eimear (2009). *Gluten-free Food Science and Technology*. Published by John Wiley and Sons,. p. 320. ISBN 978-1-4051-5915-9.
47. ^ Stene LC, Honeyman MC, Hoffenberg EJ, Haas JE, Sokol RJ, Emery L, Taki I, Norris JM, Erlich HA, Eisenbarth GS, Rewers M (2006). "Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study". *Am J Gastroenterol*. **101** (10): 2333–40. doi:10.1111/j.1572-0241.2006.00741.x. PMID 17032199.
48. ^ Kagnoff MF, Paterson YJ, Kumar PJ, Kasarda DD, Carbone FR, Unsworth DJ, Austin RK (1987). "Evidence for the role of a human intestinal adenovirus in the pathogenesis of coeliac disease". *Gut*. **28** (8): 995–1001. doi:10.1136/gut.28.8.995. PMC 1433141. PMID 2822550.
49. ^ Suman S, Williams EJ, Thomas PW, Surgenor SL, Snook JA (2003). "Is the risk of adult coeliac disease causally related to cigarette exposure?". *Eur J Gastroenterol Hepatol*. **15** (9): 995–1000. doi:10.1097/00042737-200309000-00009. PMID 12923372.
50. ^ Pinto-Sánchez, MI; Verdu, EF; Liu, E; Bercik, P; Green, PH; Murray, JA; Guandalini, S; Moayyedi, P (January 2016). "Gluten Introduction to Infant Feeding and Risk of Celiac Disease: Systematic Review and Meta-Analysis.". *The Journal of Pediatrics*. **168**: 132–143.e3. doi:10.1016/j.jpeds.2015.09.032. PMID 26500108.
51. ^ Ierodiakonou, Despo; Garcia-Larsen, Vanessa; Logan, Andrew; Groome, Annabel; Cunha, Sergio; Chivinge, Jennifer; Robinson, Zoe; Geoghegan, Natalie; Jarrold, Katharine; Reeves, Tim; Tagiyeva-Milne, Nara; Nurmatov, Ulugbek; Trivella, Marialena; Leonardi-Bee, Jo; Boyle, Robert J. (20 September 2016). "Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease". *JAMA*. **316** (11): 1181. doi:10.1001/jama.2016.12623. PMID 27654604.
52. ^ Akobeng AK, Ramanan AV, Buchan I, Heller RF (2006). "Effect of breast feeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies". *Arch Dis Child*. **91** (1): 39–43. doi:10.1136/adc.2005.082016. PMC 2083075. PMID 16287899.
53. ^ Lionetti, Elena; Castellaneta, Stefania; Francavilla, Ruggiero; Pulvirenti, Alfredo; Tonutti, Elio; Amarri, Sergio; Barbato, Maria; Barbera, Cristiana; Barera, Graziano; Bellantoni, Antonella; Castellano, Emanuela; Guariso, Graziella; Limongelli, Maria Giovanna; Pellegrino, Salvatore; Polloni, Carlo; Ughi, Claudio; Zuin, Giovanna; Fasano, Alessio; Catassi, Carlo (2014). "Introduction of Gluten, HLA Status, and the Risk of Celiac Disease in Children". *New England Journal of Medicine* (comparative study). **371** (14): 1295–1303. doi:10.1056/NEJMoa1400697. ISSN 0028-4793. PMID 25271602.
54. ^ "The Gluten Connection". Health Canada. Retrieved 1 October 2013.
55. ^ Longmore, Murray (2014). *Oxford handbook of Clinical Medicine*. Oxford University Press. p. 280. ISBN 9780199609628.
56. ^ [a] [b] [c] Hadithi M, von Blomberg BM, Crusius JB, Bloemena E, Kostense PJ, Meijer JW, Mulder CJ, Stehouwer CD, Peña AS (2007). "Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease". *Ann. Intern. Med.* **147** (5): 294–302. doi:10.7326/0003-4819-147-5-200709040-00003. PMID 17785484.
57. ^ Kim C, Quarsten H, Bergseng E, Khosla C, Sollid L (2004). "Structural basis for HLA-DQ2-mediated presentation of gluten epitopes in celiac disease". *Proc Natl Acad Sci USA*. **101** (12): 4175–9. doi:10.1073/pnas.0306885101. PMC 384714. PMID 15020763.
58. ^ Jores RD, Frau F, Cucca F, Grazia Clemente M, Orrù S, Rais M, De Virgiliis S, Congia M (2007). "HLA-DQB1*0201 homozygosis predisposes to severe intestinal damage in celiac disease". *Scand. J. Gastroenterol.* **42** (1): 48–53. doi:10.1080/00365520600789859. PMID 17190762.
59. ^ Karell K, Louka AS, Moodie SJ, Ascher H, Clot F, Greco L, Ciclitira PJ, Sollid LM, Partanen J (2003). "HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease". *Hum. Immunol.* **64** (4): 469–77. doi:10.1016/S0198-8859(03)00027-2. PMID 12651074.
60. ^ Michalski JP, McCombs CC, Arai T, Elston RC, Cao T, McCarthy CF, Stevens FM (1996). "HLA-DR, DQ genotypes of celiac disease patients and healthy subjects from the West of Ireland". *Tissue Antigens*. **47** (2): 127–33. doi:10.1111/j.1399-0039.1996.tb02525.x. PMID 8851726.
61. ^ Kaur G, Sarkar N, Bhatnagar S, Kumar S, Rapthap CC, Bhan MK, Mehra NK (2002). "Pediatric celiac disease in India is associated with multiple DR3-DQ2 haplotypes". *Hum. Immunol.* **63** (8): 677–82. doi:10.1016/S0198-8859(02)00413-5. PMID 12121676.
62. ^ Layrisse Z, Guedez Y, Domínguez E, Paz N, Montagnani S, Matos M, Herrera F, Ogando V, Balbas O, Rodríguez-Larralde A (2001). "Extended HLA haplotypes in a Carib Amerindian population: the Yucpa of the Perija Range". *Hum Immunol*. **62** (9): 992–1000. doi:10.1016/S0198-8859(01)00297-X. PMID 11543901.
63. ^ [a] [b] Dubois PC, Trynka G, Franke L, Hunt KA, Romanos J, Curtotti A, Zhernakova A, Heap GA, Adány R, Aromaa A, Bardella MT, van den Berg LH, Bockett NA, de la Concha EG, Dema B, Fehrmann RS, Fernández-Arquero M, Fiatal S, Grandone E, Green PM, Groen HJ, Gwilliam R, Houwen RH, Hunt SE, Kaukinen K, Kelleher D, Korponay-Szabo I, Kurppa K, MacMathuna P, Mäki M, Mazzilli MC, McCann OT, Mearin ML, Mein CA, Mirza MM, Mistry V, Mora B, Morley KI, Mulder CJ, Murray JA, Núñez C, Oosterom E, Ophoff RA, Polanco I, Peltonen L, Platteel M, Rybak A, Salomaa V, Schweizer JJ, Sperandeo MP, Tack GJ, Turner G, Veldink JH, Verbeek WH, Weersma RK, Wolters VM, Urcelay E, Cukrowska B, Greco L, Neuhausen SL, McManus R, Barisani D, Deloukas P, Barrett JC, Saavalainen P, Wijmenga C, van Heel DA (2010). "Multiple common variants for celiac disease influencing immune gene expression". *Nature Genetics*. **42** (4): 295–302. doi:10.1038/ng.543. PMC 2847618. PMID 20190752.
64. ^ Walcher, Dwain N.; Kretchmer, Norman (1981). *Food, nutrition, and evolution: food as an environmental factor in the genesis of human variability*. Papers presented at the International Congress of the International Organization for the Study of Human Development, Masson Pub. USA. pp. 179–199. ISBN 0-89352-158-2.
65. ^ Catassi, Carlo (2005). "Where Is Celiac Disease Coming From and Why?". *Journal of Pediatric Gastroenterology &*

*Nutrition*. **40** (3): 279–282. doi:10.1097/01.MPG.0000151650.03929.D5.

66. ^ Zhernakova A, Elbers CC, Ferwerda B, Romanos J, Trynka G, Dubois PC, de Kovel CG, Franke L, Oosting M, Barisani D, Bardella MT, Joosten LA, Saavalainen P, van Heel DA, Catassi C, Netea MG, Wijmenga C (2010). "Evolutionary and functional analysis of celiac risk loci reveals SH2B3 as a protective factor against bacterial infection". *American Journal of Human Genetics*. **86** (6): 970–7. doi:10.1016/j.ajhg.2010.05.004. PMC 3032060. PMID 20560212.
67. ^ Green PH, Cellier C (2007). "Celiac disease". *N. Engl. J. Med.* **357** (17): 1731–43. doi:10.1056/NEJMra071600. PMID 17960014.
68. ^ Lammers KM, Lu R, Brownley J, Lu B, Gerard C, Thomas K, Rallabhandi P, Shea-Donohue T, Tamiz A, Alkan S, Netzel-Arnett S, Antalis T, Vogel SN, Fasano A (2008). "Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3". *Gastroenterology*. **135** (1): 194–204.e3. doi:10.1053/j.gastro.2008.03.023. PMC 2653457. PMID 18485912.
69. ^ [a] [b] Qiao SW, Bergseng E, Molberg Ø, et al. (August 2004). "Antigen presentation to celiac lesion-derived T cells of a 33-mer gliadin peptide naturally formed by gastrointestinal digestion". *J. Immunol*. **173** (3): 1757–62. doi:10.4049/jimmunol.173.3.1757. PMID 15265905.
70. ^ Shan L, Qiao SW, Arentz-Hansen H, Molberg Ø, Gray GM, Sollid LM, Khosla C (2005). "Identification and analysis of multivalent proteolytically resistant peptides from gluten: implications for celiac sprue". *J. Proteome Res*. **4** (5): 1732–41. doi:10.1021/pr050173t. PMC 1343496. PMID 16212427.
71. ^ [a] [b] Skovbjerg H, Norén O, Anthonsen D, Moller J, Sjöström H (2002). "Gliadin is a good substrate of several transglutaminases: possible implication in the pathogenesis of coeliac disease". *Scand J Gastroenterol*. **37** (7): 812–7. doi:10.1080/713786534. PMID 12190095.
72. ^ Fleckenstein B, Molberg Ø, Qiao SW, Schmid DG, von der Mülbe F, Elgstøen K, Jung G, Sollid LM (2002). "Gliadin T cell epitope selection by tissue transglutaminase in celiac disease. Role of enzyme specificity and pH influence on the transamidation versus deamidation process". *J Biol Chem*. **277** (37): 34109–34116. doi:10.1074/jbc.M204521200. PMID 12093810.
73. ^ Koning F, Schuppan D, Cerf-Bensussan N, Sollid LM (Jun 2005). "Pathomechanisms in celiac disease". *Best practice & research. Clinical gastroenterology*. **19** (3): 373–387. doi:10.1016/j.bpg.2005.02.003. ISSN 1521-6918. PMID 15925843.
74. ^ Mowat AM (2003). "Coeliac disease – a meeting point for genetics, immunology, and protein chemistry". *Lancet*. **361** (9365): 1290–1292. doi:10.1016/S0140-6736(03)12989-3. PMID 12699968.
75. ^ Dewar D, Pereira SP, Ciclitira PJ (2004). "The pathogenesis of coeliac disease". *Int J Biochem Cell Biol*. **36** (1): 17–24. doi:10.1016/S1357-2725(03)00239-5. PMID 14592529.
76. ^ Kaukinen K, Peräaho M, Collin P, Partanen J, Woolley N, Kaartinen T, Nuutinen T, Halttunen T, Mäki M, Korponay-Szabo I (2005). "Small-bowel mucosal tranglutaminase 2-specific IgA deposits in coeliac disease without villous atrophy: A Prospective and radmonized clinical study". *Scand J Gastroenterology*. **40** (5): 564–572. doi:10.1080/00365520510023422. PMID 16036509.
77. ^ Salmi TT, Collin P, Korponay-Szabó IR, Laurila K, Partanen J, Huhtala H, Király R, Lorand L, Reunala T, Mäki M, Kaukinen K (2006). "Endomysial antibody-negative coeliac disease: clinical characteristics and intestinal autoantibody deposits". *Gut*. **55** (12): 1746–53. doi:10.1136/gut.2005.071514. PMC 1856451. PMID 16571636.
78. ^ Londei M, Ciacci C, Ricciardelli I, Vacca L, Quaratino S, Maiuri L (2005). "Gliadin as a stimulator of innate responses in celiac disease". *Mol Immunol*. **42** (8): 913–918. doi:10.1016/j.molimm.2004.12.005. PMID 15829281.
79. ^ Zanoni G, Navone R, Lunardi C, Tridente G, Bason C, Sivori S, Beri R, Dolcino M, Valletta E, Corrocher R, Puccetti A (2006). "In celiac disease, a subset of autoantibodies against transglutaminase binds toll-like receptor 4 and induces activation of monocytes". *PLoS Med.* **3** (9): e358. doi:10.1371/journal.pmed.0030358. PMC 1569884. PMID 16984219.
80. ^ Salim AF, Phillips AD, Farthing MJ (1990). "Pathogenesis of gut virus infection". *Baillieres Clin Gastroenterol*. **4** (3): 593–607. doi:10.1016/0950-3528(90)90051-H. PMID 1962725.
81. ^ "Celiac disease: A review". *BCMJ*. **43** (7): 390–395. Sep 2001.
82. ^ [a] [b] [c] [d] van der Windt DA, Jellema P, Mulder CJ, Kneepkens CM, van der Horst HE (2010). "Diagnostic testing for celiac disease among patients with abdominal symptoms: a systematic review". *JAMA*. **303** (17): 1738–46. doi:10.1001/jama.2010.549. PMID 20442390. "Most studies used similar histological criteria for diagnosing celiac disease (Marsh grade ≥III), but the level of damage may vary across populations. Only 4 studies presented the proportion of patients in whom only partial villous atrophy was found (Marsh grade of IIIA), which ranged from 4% to 100%. The presence of positive serum antibodies has been shown to correlate with the degree of villous atrophy, and patients with celiac disease who have less severe histological damage may have seronegative findings. This could be important, especially in primary care, in which levels of mucosal damage may be lower, and consequently, more patients with celiac disease may be missed."
83. ^ Sblattero D, Berti I, Trevisiol C, Marzari R, Tommasini A, Bradbury A, Fasano A, Ventura A, Not T (2000). "Human recombinant tissue transglutaminase ELISA: an innovative diagnostic assay for celiac disease". *Am. J. Gastroenterol.* **95** (5): 1253–57. doi:10.1111/j.1572-0241.2000.02018.x. PMID 10811336.
84. ^ Korponay-Szabó IR, Dahlbom I, Laurila K, Koskinen S, Woolley N, Partanen J, Kovács JB, Mäki M, Hansson T (2003). "Elevation of IgG antibodies against tissue transglutaminase as a diagnostic tool for coeliac disease in selective IgA deficiency". *Gut*. **52** (11): 1567–71. doi:10.1136/gut.52.11.1567. PMC 1773847. PMID 14570724.
85. ^ [a] [b] Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, Hoffenberg EJ, Horvath K, Murray JA, Pivor M, Seidman EG (2005). "Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition". *J. Pediatr. Gastroenterol. Nutr.* North American Society for Pediatric Gastroenterology. **40** (1): 1–19. doi:10.1097/00005176-200501000-00001. PMID 15625418.

86. ^ [a] [b] Hill ID (April 2005). "What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations?" (PDF). *Gastroenterology*. **128** (4 Suppl 1): S25–32. doi:10.1053/j.gastro.2005.02.012. PMID 15825123.
87. ^ Nandiwada SL, Tebo AE (April 2013). "Testing for antireticulin antibodies in patients with celiac disease is obsolete: a review of recommendations for serologic screening and the literature". *Clin. Vaccine Immunol.* **20** (4): 447–51. doi:10.1128/CVI.00568-12. PMC 3623418. PMID 23365209.
88. ^ Wong RC, Steele RH, Reeves GE, Wilson RJ, Pink A, Adelstein S (2003). "Antibody and genetic testing in coeliac disease". *Pathology*. **35** (4): 285–304. doi:10.1080/00313020307527. PMID 12959764.
89. ^ Niveloni S, Fiorini A, Dezi R, Pedreira S, Smecuol E, Vazquez H, Cabanne A, Boerr LA, Valero J, Kogan Z, Mauriño E, Bai JC (1998). "Usefulness of videoduodenoscopy and vital dye staining as indicators of mucosal atrophy of celiac disease: assessment of interobserver agreement". *Gastrointestinal Endoscopy*. **47** (3): 223–29. doi:10.1016/S0016-5107(98)70317-7. PMID 9580349.
90. ^ Mee AS, Burke M, Vallon AG, Newman J, Cotton PB (1985). "Small bowel biopsy for malabsorption: comparison of the diagnostic adequacy of endoscopic forceps and capsule biopsy specimens". *The BMJ*. **291** (6498): 769–72. doi:10.1136/bmj.291.6498.769. PMC 1417146. PMID 3929934.
91. ^ Redondo-Cerezo E, Sánchez-Capilla AD, De La Torre-Rubio P, De Teresa J (November 2014). "Wireless capsule endoscopy: Perspectives beyond gastrointestinal bleeding". *World J. Gastroenterol.* **20** (42): 15664–73. doi:10.3748/wjg.v20.i42.15664. PMC 4229531. PMID 25400450.
92. ^ Marsh MN (1992). "Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue')". *Gastroenterology*. **102** (1): 330–54. PMID 1727768.
93. ^ Corazza GR, Villanacci V (1 June 2005). "Coeliac disease". *J. Clin. Pathol.* **58** (6): 573–74. doi:10.1136/jcp.2004.023978. PMC 1770677. PMID 15917404.
94. ^ Oberhuber G, Granditsch G, Vogelsang H (October 1999). "The histopathology of coeliac disease: time for a standardized report scheme for pathologists". *Eur. J. Gastroenterol. Hepatol.* **11** (10): 1185–94. doi:10.1097/00042737-199910000-00019. PMID 10524652.
95. ^ Corazza GR, Villanacci V, Zambelli C, Milione M, Luinetti O, Vindigni C, Chioda C, Albarello L, Bartolini D, Donato F (2007). "Comparison of the interobserver reproducibility with different histologic criteria used in celiac disease". *Clin. Gastroenterol. Hepatol.* **5** (7): 838–43. doi:10.1016/j.cgh.2007.03.019. PMID 17544877.
96. ^ Ontiveros N, Hardy MY, Cabrera-Chavez F (2015). "Assessing of Celiac Disease and Nonceliac Gluten Sensitivity". *Gastroenterology Research and Practice* (Review). **2015**: 723954. doi:10.1155/2015/723954. PMC 4429206. PMID 26064097.
97. ^ Genuis SJ, Lobo RA (2014). "Gluten sensitivity presenting as a neuropsychiatric disorder". *Gastroenterol Res Pract* (Review). **2014**: 293206. doi:10.1155/2014/293206. PMC 3944951. PMID 24693281.
98. ^ Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, Hadjivassiliou M, Kaukinen K, Kelly CP, Leonard JN, Lundin KE, Murray JA, Sanders DS, Walker MM, Zingone F, Ciacci C (January 2013). "The Oslo definitions for coeliac disease and related terms". *Gut*. **62** (1): 43–52. doi:10.1136/gutjnl-2011-301346. PMC 3440559. PMID 22345659.
99. ^ Elli L, Roncoroni L, Bardella MT (Jul 2015). "Non-celiac gluten sensitivity: Time for sifting the grain". *World J Gastroenterol* (Review). **21** (27): 8221–6. doi:10.3748/wjg.v21.i27.8221. PMC 4507091. PMID 26217073.
100. ^ Fasano A, Sapone A, Zevallos V, Schuppan D (May 2015). "Nonceliac gluten sensitivity". *Gastroenterology* (Review). **148** (6): 1195–204. doi:10.1053/j.gastro.2014.12.049. PMID 25583468.
101. ^ [a] [b] Castillo NE, Theethira TG, Leffler DA (Feb 2015). "The present and the future in the diagnosis and management of celiac disease". *Gastroenterol Rep (Oxf)* (Review). **3** (1): 3– 11. doi:10.1093/gastro/gou065. PMC 4324867. PMID 25326000.
102. ^ [a] [b] [c] [d] [e] Levy J, Bernstein L, Silber N (Dec 2014). "Celiac disease: an immune dysregulation syndrome". *Curr Probl Pediatr Adolesc Health Care* (Review). **44** (11): 324–7. doi:10.1016/j.cppeds.2014.10.002. PMID 25499458. "Initially, reduced levels of lactase and sucrase activities might necessitate further dietary restrictions until the villi have healed and those sugars are better tolerated."
103. ^ [a] [b] [c] [d] Montalto M, Gallo A, Ojetti V, Gasbarrini A (2013). "Fructose, trehalose and sorbitol malabsorption" (PDF). *Eur Rev Med Pharmacol Sci* (Review). **17** (Suppl 2): 26–9. PMID 24443064.
104. ^ [a] [b] Leffler DA, Green PH, Fasano A (Oct 2015). "Extraintestinal manifestations of coeliac disease". *Nat Rev Gastroenterol Hepatol* (Review). **12** (10): 561–71. doi:10.1038/nrgastro.2015.131. PMID 26260366.
105. ^ [a] [b] [c] [d] [e] [f] [g] [h] [i] Woodward, J (3 August 2016). "Improving outcomes of refractory celiac disease - current and emerging treatment strategies.". *Clinical and experimental gastroenterology* (Review). **9**: 225–36. doi:10.2147/ceg.s87200. PMC 4976763. PMID 27536154.
106. ^ [a] [b] [c] Berni Canani R, Pezzella V, Amoroso A, Cozzolino T, Di Scala C, Passariello A (Mar 10, 2016). "Diagnosing and Treating Intolerance to Carbohydrates in Children". *Nutrients* (Review). **8** (3): pii: E157. doi:10.3390/nu8030157. PMC 4808885. PMID 26978392.
107. ^ [a] [b] [c] García-Manzanares A, Lucendo AJ (Apr 2011). "Nutritional and dietary aspects of celiac disease". *Nutr Clin Pract* (Review). **26** (2): 163–73. doi:10.1177/0884533611399773. PMID 21447770.
108. ^ [a] [b] [c] [d] Green PH, Jabri B (Aug 2, 2003). "Coeliac disease". *Lancet* (Review). **362** (9381): 383–91. doi:10.1016/S0140-6736(03)14027-5. PMID 12907013.
109. ^ Volta U, Caio G, Tovoli F, De Giorgio R (2013). "Non-celiac gluten sensitivity: questions still to be answered despite increasing awareness". *Cellular and Molecular Immunology* (Review). **10** (5): 383–392. doi:10.1038/cmi.2013.28. ISSN 1672-7681. PMC 4003198. PMID 23934026.

110. ^ National Institute for Health and Clinical Excellence. *Clinical guideline 53: Chronic fatigue syndrome/myalgic encephalomyelitis*. London, 2007.
111. ^ National Institute for Health and Clinical Excellence. *Clinical guideline 15: Diagnosis and management of type 1 diabetes in children, young people and adults*. London, 2004.
112. ^ "Celiac Disease: Screening". *USPSTF*. May 2016. Retrieved 4 May 2016.
113. ^ Treem WR (2004). "Emerging concepts in celiac disease". *Curr Opin Pediatr*. **16** (5): 552–9. doi:10.1097/01.mop.0000142347.74135.73. PMID 15367850.
114. ^ Lee AR, Ng DL, Zivin J, Green PH (2007). "Economic burden of a gluten-free diet". *J Hum Nutr Diet*. **20** (5): 423–30. doi:10.1111/j.1365-277X.2007.00763.x. PMID 17845376.
115. ^ Troncone R, Ivarsson A, Szajewska H, Mearin ML (2008). "Review article: future research on coeliac disease – a position report from the European multistakeholder platform on coeliac disease (CDEUSSA)". *Aliment. Pharmacol. Ther*. **27** (11): 1030–43. doi:10.1111/j.1365-2036.2008.03668.x. PMID 18315588.
116. ^ [a] [b] Akobeng AK, Thomas AG (June 2008). "Systematic review: tolerable amount of gluten for people with coeliac disease". *Aliment. Pharmacol. Ther*. **27** (11): 1044–52. doi:10.1111/j.1365-2036.2008.03669.x. PMID 18315587.
117. ^ "Gluten-free food". Directorate-General for Health and Consumers. Retrieved 25 July 2015.
118. ^ "What is Gluten-Free? FDA Has an Answer". Food and Drug Administration. 2 August 2013. Retrieved 2 August 2013. "As one of the criteria for using the claim 'gluten-free,' FDA is setting a gluten limit of less than 20 ppm (parts per million) in foods that carry this label. This is the lowest level that can be consistently detected in foods using valid scientific analytical tools. Also, most people with celiac disease can tolerate foods with very small amounts of gluten. This level is consistent with those set by other countries and international bodies that set food safety standards."
119. ^ Section 206 of the Food Allergen Labeling and Consumer Protection Act of 2004, Title II of Pub.L. 108–282, 118 Stat. 891 , enacted August 2, 2004
120. ^ 78 FR 47154 (5 August 2013). Codified at 21 C.F.R. 101.91.
121. ^ "Current Official Standards". FAO/WHO. Archived from the original on 4 June 2011.
122. ^ Anderson, Jane. "Certified Gluten-Free Products: What Does Gluten-Free Certification Mean For Consumers?". *About.com*. Retrieved 4 March 2014.
123. ^ Burger, Jordy P.W.; de Brouwer, Bart; IntHout, Joanna; Wahab, Peter J.; Tummers, Marcia; Drenth, Joost P.H. (April 2016). "Systematic review with meta-analysis: Dietary adherence influences normalization of health-related quality of life in coeliac disease". *Clinical Nutrition*. doi:10.1016/j.clnu.2016.04.021. PMID 27179800.
124. ^ Mulder CJ, van Wanrooij RL, Bakker SF, Wierdsma N, Bouma G (2013). "Gluten-free diet in gluten-related disorders". *Dig Dis.* (Review). **31** (1): 57–62. doi:10.1159/000347180. PMID 23797124.
125. ^ [a] [b] [c] Lebwohl, B; Ludvigsson, JF; Green, PH (5 October 2015). "Celiac disease and non-celiac gluten sensitivity". *BMJ (Clinical research ed.)*. **351**: h4347. doi:10.1136/bmj.h4347. PMC 4596973. PMID 26438584.
126. ^ Rewers M (April 2005). "Epidemiology of celiac disease: what are the prevalence, incidence, and progression of celiac disease?" (PDF). *Gastroenterology*. **128** (4 Suppl 1): S47–51. doi:10.1053/j.gastro.2005.02.030. PMID 15825126.
127. ^ Guandalini, S; Assiri, A (March 2014). "Celiac disease: a review.". *JAMA pediatrics*. **168** (3): 272–8. doi:10.1001/jamapediatrics.2013.3858. PMID 24395055.
128. ^ Catassi C, Rätsch IM, Gandolfi L, Pratesi R, Fabiani E, El Asmar R, Frijia M, Bearzi I, Vizzoni L (1999). "Why is coeliac disease endemic in the people of the Sahara?". *Lancet*. **354** (9179): 647–8. doi:10.1016/S0140-6736(99)02609-4. PMID 10466670.
129. ^ Houlston RS, Ford D (1996). "Genetics of coeliac disease". *QJM*. **89** (10): 737–43. doi:10.1093/qjmed/89.10.737. PMID 8944229.
130. ^ Buchanan N (1987). *Child and Adolescent Health for Practitioners*. Williams & Wilkins. p. 164. ISBN 0-86433-015-4.
131. ^ Zipser RD, Farid M, Baisch D, Patel B, Patel D (2005). "Physician awareness of celiac disease: a need for further education". *J Gen Intern Med*. **20** (7): 644–6. doi:10.1007/s11606-005-0111-7. PMC 1490146. PMID 16050861.
132. ^ [a] [b] Barker JM, Liu E (2008). "Celiac disease: pathophysiology, clinical manifestations, and associated autoimmune conditions". *Adv Pediatr*. **55**: 349–65. doi:10.1016/j.yapd.2008.07.001. PMC 2775561. PMID 19048738.
133. ^ Leeds JS, Hopper AD, Sanders DS (2008). "Coeliac disease". *Br Med Bull*. **88** (1): 157–70. doi:10.1093/bmb/ldn044. PMID 19073695.
134. ^ Gee, SJ (1888). "On the coeliac affection". *St Bartholomew's Hospital Report*. **24**: 17–20.
135. ^ Herter, CA (1908). *On infantilism from chronic intestinal infection; characterized by the overgrowth and persistence of flora in the nursing period*. New York: Macmillan & Co. as cited by WhoNamedIt
136. ^ Enersen, Ole Daniel. "Christian Archibald Herter". Who Named It?. Retrieved 20 March 2007.
137. ^ Haas SV (1924). "The value of the banana in the treatment of coeliac disease". *Am J Dis Child*. **24** (4): 421–37. doi:10.1001/archpedi.1924.04120220017004.
138. ^ van Berge-Henegouwen GP, Mulder CJ (1993). "Pioneer in the gluten free diet: Willem-Karel Dicke 1905–1962, over 50 years of gluten free diet". *Gut*. **34** (11): 1473–5. doi:10.1136/gut.34.11.1473. PMC 1374403. PMID 8244125.
139. ^ Dicke WK (1950). *Coeliakie: een onderzoek naar de nadelige invloed van sommige graansoorten op de lijder aan coeliakie, PhD thesis* (in Dutch). Utrecht, the Netherlands: University of Utrecht.
140. ^ Fasano A (2009). "Celiac Disease Insights: Clues to Solving Autoimmunity". *Scientific American* (August): 49–57.
141. ^ Anderson CM, French JM, Sammons HG, Frazer AC, Gerrard JW, Smellie JM (1952). "Coeliac disease; gastrointestinal studies and the effect of dietary wheat flour". *Lancet*. **1** (17): 836–42. doi:10.1016/S0140-6736(52)90795-2. PMID 14918439.
142. ^ Paulley JW (1954). "Observation on the aetiology of idiopathic steatorrhoea; jejunal and lymph-node biopsies". *Br Med J*. **2** (4900): 1318–21. doi:10.1136/bmj.2.4900.1318. PMC 2080246. PMID 13209109.

143. ^ Macdonald WC, Dobbins WO, Rubin CE (1965). "Studies of the familial nature of celiac sprue using biopsy of the small intestine". *N Engl J Med*. **272** (9): 448–56. doi:10.1056/NEJM196503042720903. PMID 14242522.
144. ^ "Buy Me Some Gluten-Free Peanuts, Cracker Jacks". *QSR magazine*. Journalistic. 11 May 2010. Retrieved 30 December 2010.
145. ^ Hillson, Beth (9 January 2008). "May as Celiac Awareness Month". *Celiac Disease Foundation*. Archived from the original on 24 February 2010. Retrieved 1 July 2011.
146. ^ One on-line site sells 1200 wafers weighing a total of 523 g. Eden.co.uk (31 July 2013). Retrieved on 3 September 2013.
147. ^ Statement by the National Conference of Catholic bishops on the use of low gluten hosts at Mass. *BCL Newsletter*. November 2003.
148. ^ Adams, Scott (2 August 2002). "Bishops in Italy Approve a German-made Low Gluten Eucharistic Host". Celiac.com.
149. ^ Associated Press (8 December 2004). "Girl with digestive disease denied Communion". *MSNBC*. Microsoft. Retrieved 30 May 2006.
150. ^ Ratzinger, Joseph (24 July 2003). *Prot. 89/78-174 98*. Congregation for the Doctrine of the Faith. Full text at: "The Use of Mustum and Low-Gluten Hosts at Mass". *BCL Newsletter*. United States Conference of Catholic Bishops. November 2003. Retrieved 7 March 2007.
151. ^ McNamara, Father Edward (15 September 2004). "Liturgy: Gluten-free Hosts". *Catholic Online*. Retrieved 17 June 2007.
152. ^ Rabbi Avraham Juravel. "Gluten Intolerance, Celiac, Allergies And Pesach". Orthodox Union. Retrieved 3 September 2006.
153. ^ Freeman HJ (November 2013). "Non-dietary forms of treatment for adult celiac disease". *World Journal of Gastrointestinal Pharmacology and Therapeutics* (Review). **4** (4): 108–12. doi:10.4292/wjgpt.v4.i4.108 (inactive 2015-11-04). PMC 3817285. PMID 24199026.
154. ^ Vanga RR, Kelly CP (May 2014). "Novel therapeutic approaches for celiac disease". *Discovery Medicine*. **17** (95): 285–93. PMID 24882720.
155. ^ [a] [b] Castillo NE, Theethira TG, Leffler DA (2015). "The present and the future in the diagnosis and management of celiac disease". *Gastroenterology Report* (Review). **3** (1): 3–11. doi:10.1093/gastro/gou065. PMC 4324867. PMID 25326000.
156. ^ "Innovate Biopharmaceuticals". *www.innovatebiopharma.com*. Retrieved 2016-04-17.


## External links [edit]

- Coeliac disease at DMOZ

Wikimedia Commons has media related to *Coeliac disease*.

| v · t · e · | Diseases of the digestive system (primarily K20–K93, 530–579) | |
|---|---|---|
| **Upper GI tract** | **Esophagus** | Esophagitis (Candidal · Eosinophilic · Herpetiform · · *Rupture* (Boerhaave syndrome · Mallory-Weiss syndrome · · UES (Zenker's diverticulum · · LES (Barrett's esophagus · · Esophageal motility disorder (Nutcracker esophagus · Achalasia · Diffuse esophageal spasm · Gastroesophageal reflux disease (GERD) · · Laryngopharyngeal reflux (LPR) · Esophageal stricture · Megaesophagus · |
| | **Stomach** | Gastritis (Atrophic · Ménétrier's disease · Gastroenteritis · · Peptic (gastric) ulcer (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
| **Lower GI tract: Intestinal/ Enteropathy** | **Small intestine (Duodenum/Jejunum/Ileum)** | Enteritis (Duodenitis · Jejunitis · Ileitis · · Peptic (duodenal) ulcer (Curling's ulcer · · Malabsorption: **Coeliac** · Tropical sprue · Blind loop syndrome · Small bowel bacterial overgrowth syndrome · Whipple's · Short bowel syndrome · Steatorrhea · Milroy disease · Bile acid malabsorption · |
| | **Large intestine (Appendix/Colon)** | Appendicitis · Colitis (Pseudomembranous · Ulcerative · Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (IBS · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
| | | Enterocolitis (Necrotizing · · Gastroenterocolitis · IBD (Crohn's disease · · *Vascular*: Abdominal angina · |

| | | |
|---|---|---|
| | **Large and/or small** | Mesenteric ischemia · Angiodysplasia · Bowel obstruction: Ileus · Intussusception · Volvulus · Fecal impaction · Constipation · Diarrhea (Infectious · · Intestinal adhesions · |
| | **Rectum** | Proctitis (Radiation proctitis · · Proctalgia fugax · Rectal prolapse · Anismus · |
| | **Anal canal** | Anal fissure/Anal fistula · Anal abscess · Anal dysplasia · Pruritus ani · |
| **GI bleeding/BIS** | Upper (Hematemesis · Melena · · Lower (Hematochezia · · | |
| **Accessory** | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · Acute liver failure · · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |
| | **Gallbladder** | Cholecystitis · Gallstones/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · Gallstones/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
| | **Pancreatic** | Pancreatitis (Acute · Chronic · Hereditary · Pancreatic abscess · · Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |
| **Abdominopelvic** | **Hernia** | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |

| v · t · e · | **Hypersensitivity and autoimmune diseases (279.5–6)** | | |
|---|---|---|---|
| **Type I/allergy/atopy (IgE)** | **Foreign** | Atopic eczema · Allergic urticaria · Allergic rhinitis (Hay fever) · Allergic asthma · Anaphylaxis · Food allergy (common allergies include: Milk · Egg · Peanut · Tree nut · Seafood · Soy · Wheat · · Penicillin allergy · | |
| | **Autoimmune** | Eosinophilic esophagitis · | |
| **Type II/ADCC (IgM · IgG · ·** | **Foreign** | Hemolytic disease of the newborn · | |
| | **Autoimmune** | **Cytotoxic** | Autoimmune hemolytic anemia · Immune thrombocytopenic purpura · Bullous pemphigoid · Pemphigus vulgaris · Rheumatic fever · Goodpasture's syndrome · Guillain–Barré syndrome · |
| | | **"Type V"/receptor** | Graves' disease · Myasthenia gravis · Pernicious anemia · |
| **Type III (Immune complex)** | **Foreign** | Henoch–Schönlein purpura · Hypersensitivity vasculitis · Reactive arthritis · Farmer's lung · Post-streptococcal glomerulonephritis · Serum sickness · Arthus reaction · |
| | **Autoimmune** | Systemic lupus erythematosus · Subacute bacterial endocarditis · Rheumatoid arthritis · |

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| **Type IV / cell-mediated (T cells)** | **Foreign** | Allergic contact dermatitis · Mantoux test · |
| | **Autoimmune** | Diabetes mellitus type 1 · Hashimoto's thyroiditis · Multiple sclerosis · **Coeliac disease** · Giant-cell arteritis · Postorgasmic illness syndrome · Reactive arthritis · |
| | **GVHD** | Transfusion-associated graft versus host disease · |
| **Unknown/ multiple** | **Foreign** | Hypersensitivity pneumonitis (Allergic bronchopulmonary aspergillosis · · Transplant rejection · Latex allergy (I+IV) · |
| | **Autoimmune** | Sjögren's syndrome · Autoimmune hepatitis · Autoimmune polyendocrine syndrome (APS1 · APS2 · · Autoimmune adrenalitis · Systemic autoimmune disease · |

| v · t · e · | **Gluten sensitivity** | |
|---|---|---|
| **Conditions** | **general** | Wheat allergy · Oat sensitivity · |
| | **nervous system** | GS idiopathic neuropathies · |
| | **digestive system** | **Coeliac disease** · GSE associated conditions · |
| | **integumentary system** | Dermatitis herpetiformis · |
| **Antibodies** | | Anti-gliadin antibodies · Anti-transglutaminase antibodies · |
| **HLA-DQ** | | HLA-DQ2 · HLA-DQ8 · |
| **Other** | | Gluten immunochemistry · Gluten-free diet · Gluten challenge test · List of people diagnosed with coeliac disease · |

**Biology portal** **Medicine portal**

Categories: Autoimmune diseases | Gastrointestinal tract disorders | Genetic diseases and disorders | Malnutrition | Pediatrics | Gluten sensitivity

# Crohn's disease







From Wikipedia, the free encyclopedia

*"Crohn" redirects here. It is not to be confused with Croan, Krone, or Crone.*

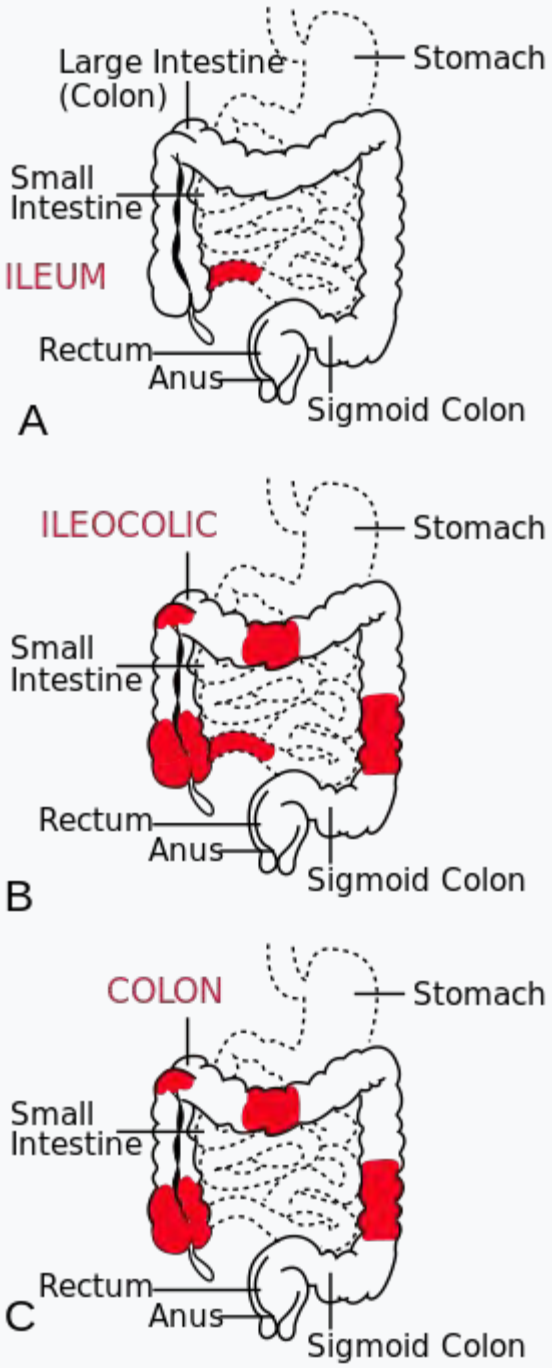
**Crohn's disease** is a type of inflammatory bowel disease (IBD) that may affect any part of the gastrointestinal tract from mouth to anus.[2] Signs and symptoms often include abdominal pain, diarrhea (which may be bloody if inflammation is severe), fever, and weight loss.[1][2] Other complications may occur outside the gastrointestinal tract and include anemia, skin rashes, arthritis, inflammation of the eye, and feeling tired. The skin rashes may be due to infections as well as pyoderma gangrenosum or erythema nodosum. Bowel obstruction also commonly occurs and those with the disease are at greater risk of bowel cancer.[1]

Crohn's disease is caused by a combination of environmental, immune and bacterial factors in genetically susceptible individuals.[3][4][5] It results in a chronic inflammatory disorder, in which the body's immune system attacks the gastrointestinal tract possibly directed at microbial antigens.[4][6] While Crohn's is an immune related disease, it does not appear to be an autoimmune disease (in that the immune system is not being triggered by the body itself).[7] The exact underlying immune problem is not clear; however, it may be an immunodeficiency state.[6][8][9] About half of the overall risk is related to genetics with more than 70 genes found to be involved.[1][10] Tobacco smokers are two times more likely to develop Crohn's disease than nonsmokers.[11] It also often begins after gastroenteritis. Diagnosis is based on a number of findings including biopsy and appearance of the bowel wall, medical imaging and description of the disease. Other conditions that can present similarly include irritable bowel syndrome and Behçet's disease.[1]

There are no medications or surgical procedures that can cure Crohn's disease. Treatment options help with symptoms, maintain remission, and prevent relapse. In those newly diagnosed, a corticosteroid may be used for a brief period of time to quickly improve the disease with another medication such as either methotrexate or a thiopurine used to prevent recurrence. An important part of treatment is the stopping of smoking among those who do. One in five people with the disease are admitted to hospital each year, and half of those with the disease will require surgery for the disease at some point over a ten-year period. While surgery should be used as

## Variants

**Synonyms** enteritis




The three most common sites of intestinal involvement in Crohn's disease are ileal, ileocolic and colonic.[1]

| Classification and external resources | |
|---|---|
| **Specialty** | Gastroenterology |
| **ICD-10** | K50 |
| **ICD-9-CM** | 555 |
| **OMIM** | 266600 |
| **DiseasesDB** | 3178 |
| **MedlinePlus** | 000249 |
| **eMedicine** | med/477 ped/507 |

Español
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Latviešu
Lietuvių
Magyar

little as possible, it is necessary to address some abscesses, certain bowel obstructions, and cancers. Checking for bowel cancer via colonoscopy is recommended every few years, starting eight years after the disease has begun.[1]

Crohn's disease affects about 3.2 per 1,000 people in Europe and North America.[12] It is less common in Asia and Africa.[13][14] It has historically been more common in the developed world.[15] Rates have, however, been increasing, particularly in the developing world, since the 1970s.[14][15] Inflammatory bowel disease resulted in 35,000 deaths in 2010[16] and those with Crohn's disease have a slightly reduced life expectancy.[1] It tends to start in the teens and twenties, although it can occur at any age.[1][2] Males and females are equally affected.[2] The disease was named after gastroenterologist Burrill Bernard Crohn, who, in 1932, together with two other colleagues at Mount Sinai Hospital in New York, described a series of patients with inflammation of

the terminal ileum of the small intestine, the area most commonly affected by the illness.[17]





| | |
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| | radio/197 |
| **Patient UK** | Crohn's disease |
| **MeSH** | D003424 |

[edit on Wikidata]

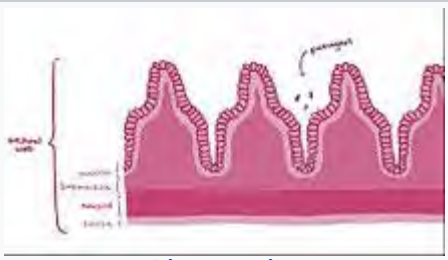
## Signs and symptoms [edit]

### Ga

[ec

**Signs and symptoms**

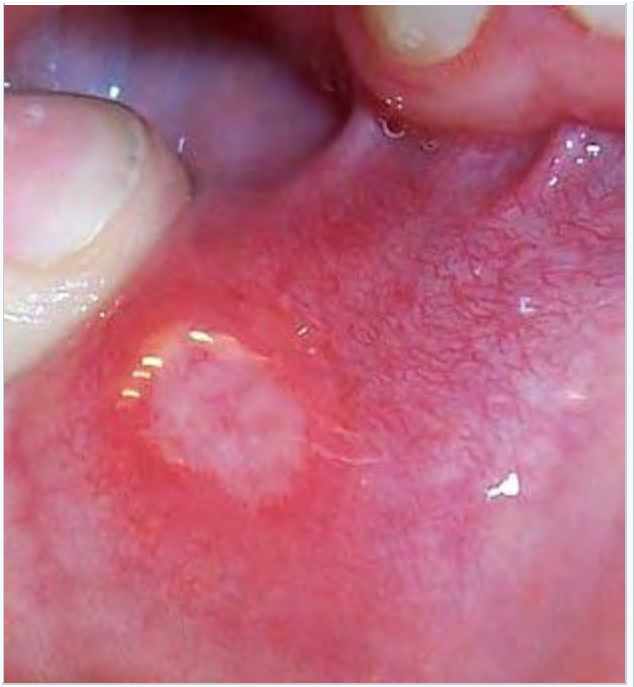
| | Crohn's disease | Ulcerative colitis |
|---|---|---|
| Defecation | Often porridge-like,[18] sometimes steatorrhea | Often mucus-like and with blood[18] |
| Tenesmus | Less common[18] | More common[18] |
| Fever | Common[18] | Indicates severe disease[18] |
| Fistulae | Common[19] | Seldom |
| Weight loss | Often | More seldom |



Play media

A video explanation of Crohn disease.

Many people with Crohn's disease have symptoms for years prior to the diagnosis.[20] The usual onset is between 15 and 30 years of age, but can occur at any age.[21] Because of the 'patchy' nature of the gastrointestinal disease and the depth of tissue involvement, initial symptoms can be more subtle than those of ulcerative colitis. People with Crohn's



People with Crohn's can have aphthous ulcers involving the mouth.

disease experience chronic recurring periods of flare-ups and remission.[22]

Abdominal pain may be the initial symptom of Crohn's disease usually in the lower right area.[23] It is often accompanied by diarrhea, especially in those who have had surgery. The diarrhea may or may not be bloody. The nature of the diarrhea in Crohn's disease depends on the part of the small intestine or colon involved. Ileitis typically results in large-volume, watery feces. Colitis may result in a smaller volume of feces of higher frequency. Fecal consistency may range from solid to watery. In severe cases, an individual may have more than 20 bowel movements per day and may need to awaken at night to defecate.[1][24][25][26] Visible bleeding in the feces is less common in Crohn's disease than in ulcerative colitis, but may be seen in the setting of Crohn's colitis.[1] Bloody bowel movements typically come and go, and may be bright or dark red in color. In the setting of severe Crohn's colitis, bleeding may be copious.[24] Flatulence and bloating may also add to the intestinal discomfort.[24]

Symptoms caused by intestinal stenosis are also common in Crohn's disease. Abdominal pain is often most severe in areas of the bowel with stenoses. Persistent vomiting and nausea may indicate stenosis from small bowel obstruction or disease involving the stomach, pylorus, or duodenum.[24] Although the association is greater in the context of ulcerative colitis, Crohn's disease may also be associated with primary sclerosing cholangitis, a type of inflammation of the bile ducts.[27]

Perianal discomfort may also be prominent in Crohn's disease. Itchiness or pain around the anus may be suggestive of inflammation, fistulization or abscess around the anal area[1] or anal fissure. Perianal skin tags are also common in Crohn's disease.[28] Fecal incontinence may accompany perianal Crohn's disease. At the opposite end of the gastrointestinal tract, the mouth may be affected by non-healing sores (aphthous ulcers). Rarely, the esophagus, and stomach may be involved in Crohn's disease. These can cause symptoms including difficulty swallowing (dysphagia), upper abdominal pain, and vomiting.[29]

## Systemic [edit]

Crohn's disease, like many other chronic, inflammatory diseases, can cause a variety of systemic symptoms.[1] Among children, growth failure is common. Many children are first diagnosed with Crohn's disease based on inability to maintain growth.[30] As it may manifest at the time of the growth spurt in puberty, up to 30% of children with Crohn's disease may have retardation of growth.[31] Fever may also be present, though fevers greater than 38.5 °C (101.3 °F) are uncommon unless there is a complication such as an abscess.[1] Among older individuals, Crohn's disease may manifest as weight loss, usually related to decreased food intake, since individuals with intestinal symptoms from Crohn's disease often feel better when they do not eat and might lose their appetite.[30] People with extensive small intestine disease may also have malabsorption of carbohydrates or lipids, which can further exacerbate weight loss.[32]

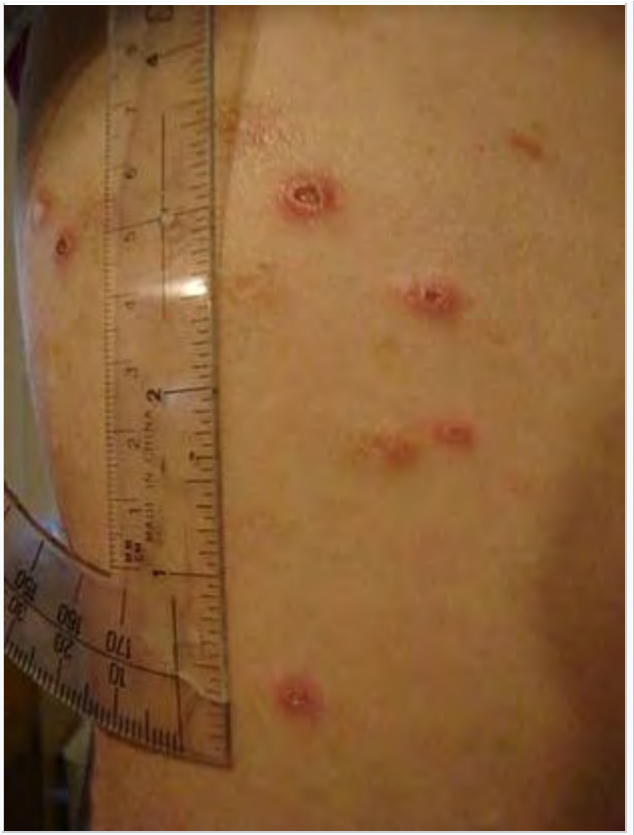
## Extraintestinal [edit]

In addition to systemic and gastrointestinal involvement, Crohn's disease can affect many other organ systems.[33]

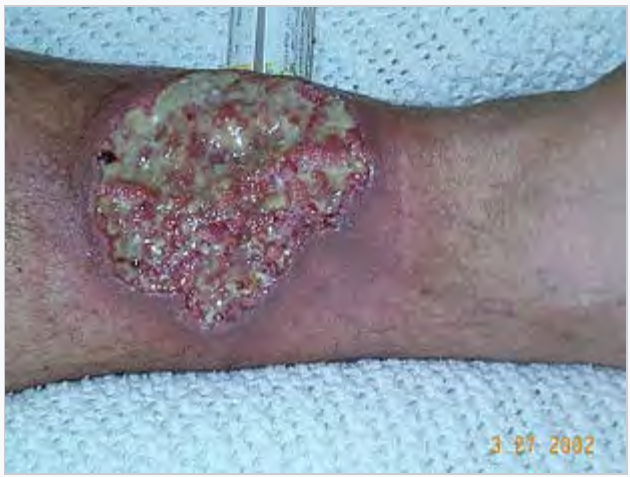
Inflammation of the interior portion of the eye, known as uveitis, can cause blurred vision and eye pain, especially when exposed to light (photophobia).[34] Inflammation may also involve the white part of the eye (sclera), a condition called episcleritis.[34] Both episcleritis and uveitis can lead to loss of vision if untreated.

Crohn's disease that affects the ileum may result in an increased risk for gallstones. This is due to a decrease in bile acid resorption in the ileum and the bile gets excreted in the stool. As a result, the cholesterol/bile ratio increases in the gallbladder, resulting in an increased risk for gallstones.[34]

Crohn's disease is associated with a type of rheumatologic disease known as seronegative spondyloarthropathy.[34] This group of diseases is characterized by inflammation of one or more joints (arthritis) or muscle insertions (enthesitis).[34] The arthritis in Crohn's disease can be divided into two types. The first type affects larger weight-bearing joints such as the knee (most common), hips, shoulders, wrists, or elbows.[34] The second type symmetrically involves five or more of the small joints of the hands and feet.[34] The arthritis may also involve the spine, leading to ankylosing spondylitis if the entire spine is involved or simply sacroiliitis if only the sacroiliac joint is involved.[34] The symptoms of arthritis include painful, warm, swollen, stiff joints, and loss of joint mobility or function.[35]



Erythema nodosum on the back of a person with Crohn's disease



Pyoderma gangrenosum on the leg of a person with Crohn's disease

Crohn's disease may also involve the skin, blood, and endocrine system. The most common type of skin manifestation, erythema nodosum, presents as raised, tender red nodules usually appearing on the shins.[34][36] Erythema nodosum is due to inflammation of the underlying subcutaneous tissue, and is characterized by septal panniculitis.[36] Another skin lesion, pyoderma gangrenosum, is typically a painful ulcerating nodule. Crohn's disease also increases the risk of blood clots;[34] painful swelling of the lower legs can be a sign of deep venous thrombosis, while difficulty breathing may be a result of pulmonary embolism. Autoimmune hemolytic anemia, a condition in which the immune system attacks the red blood cells, is also more common in Crohn's disease and may cause fatigue, a pale appearance, and other symptoms common in anemia. Clubbing, a deformity of the ends of the fingers, may also be a result of Crohn's disease. Finally, Crohn's disease increases the risk of osteoporosis, or thinning of the bones.[34] Individuals with osteoporosis are at increased risk of bone fractures.[37]

People with Crohn's disease often have anemia due to vitamin $B_{12}$, folate, iron deficiency, or due to anemia of chronic disease.[38][39] The most common is iron deficiency anemia[38] from chronic blood loss, reduced dietary intake, and persistent inflammation leading to increased hepcidin levels, restricting iron absorption in the duodenum.[39] As Crohn's disease most commonly affects the terminal ileum where the vitamin B12/intrinsic factor complex is absorbed, B12 deficiency may be seen.[39] This is particularly common after [38]

surgery to remove the ileum. Involvement of the duodenum and jejunum can impair the absorption of many other nutrients including folate. If Crohn's disease affects the stomach, production of intrinsic factor can be reduced.

Crohn's disease can also cause neurological complications (reportedly in up to 15%).[40] The most common of these are seizures, stroke, myopathy, peripheral neuropathy, headache and depression.[40]

People with Crohn's often also have issues with small bowel bacterial overgrowth syndrome, which has similar symptoms.[41]

In the oral cavity people with Crohn's may develop cheilitis granulomatosa and other forms of orofacial granulomatosis, pyostomatitis vegetans, recurrent aphthous stomatitis, geographic tongue, and migratory stomatitis in higher prevalence than the general population.[42]

## Cause [edit]

While the exact cause is unknown,[45] Crohn's disease seems to be due to a combination of environmental factors and genetic predisposition.[46] Crohn's is the first genetically complex disease in which the relationship between genetic risk factors and the immune system is understood in considerable detail.[47] Each individual risk mutation makes a small contribution to the overall risk of Crohn's (approximately 1:200). The genetic data, and direct assessment of immunity, indicates a malfunction in the innate immune system.[48] In this view, the chronic inflammation of Crohn's is caused when the adaptive immune system tries to compensate for a deficient innate immune system.[49]

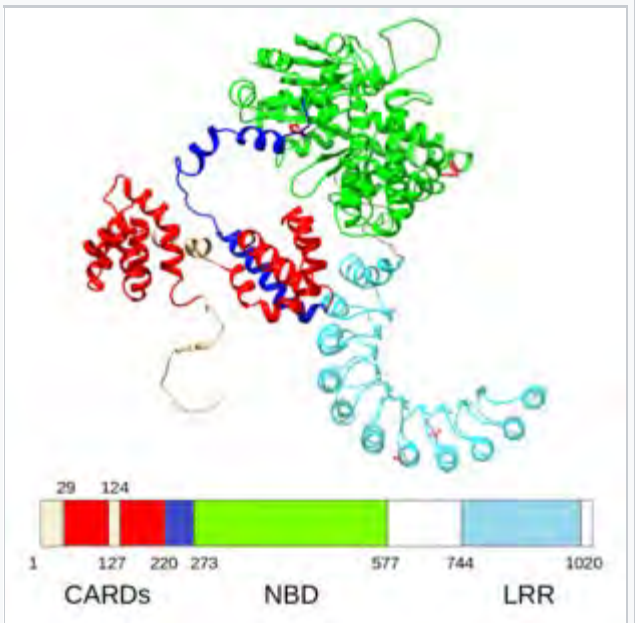
**Risk factors**

| | Crohn's disease | Ulcerative colitis |
|---|---|---|
| Smoking | Higher risk for smokers | Lower risk for smokers[43] |
| Age | Usual onset between 15 and 30 years[44] | Peak incidence between 15 and 25 years |

### Genetics [edit]

Crohn's has a genetic component.[51] Because of this, siblings of known people with Crohn's are 30 times more likely to develop Crohn's than the general population.

The first mutation found to be associated with Crohn's was a frameshift in the NOD2 gene (also known as the CARD15 gene),[52] followed by the discovery of point mutations.[53] Over thirty genes have been associated with Crohn's; a biological function is known for most of them. For example, one association is with mutations in the XBP1 gene, which is involved in the unfolded protein response pathway of the endoplasmatic reticulum.[54][55] The gene variants of NOD2/CARD15 seem to be related with small-bowel involvement.[56] Other well documented genes which increase the risk of developing Crohn disease are ATG16L1,[57] IL23R,[58] IRGM,[59] and SLC11A1.[60] There is considerable overlap between susceptibility loci for IBD and mycobacterial infections.[61] Recent genome-wide association studies have shown that Crohn's disease is genetically linked to coeliac disease.[62]




NOD2 protein model with schematic diagram. Two N-terminal CARD domains (red) connected via helical linker (blue) with central NBD domain (green). At C-terminus LRR domain (cyan) is located. Additionally, some mutations which are

### Immune system [edit]

There was a prevailing view that Crohn's disease is a

associated with certain disease patterns in Crohn's disease are marked in red wire representation.[50]

primary T cell autoimmune disorder, however, a newer theory hypothesizes that Crohn's results from an impaired innate immunity.[63] The later hypothesis describes impaired cytokine secretion by macrophages, which contributes to impaired innate immunity and leads to a sustained microbial-induced inflammatory response in the colon, where the bacterial load is high.[4][48] Another theory is that the inflammation of Crohn's was caused by an overactive $T_h1$ and $T_h17$ cytokine response.[64][65]

In 2007, the ATG16L1 gene has been implicated in Crohn's disease, which may induce autophagy and hinder the body's ability to attack invasive bacteria.[57] Another study has theorized that the human immune system traditionally evolved with the presence of parasites inside the body, and that the lack thereof due to modern hygiene standards has weakened the immune system. Test subjects were reintroduced to harmless parasites, with positive response.[66]

## Microbes [edit]

Current thinking is that microorganisms are taking advantage of their host's weakened mucosal layer and inability to clear bacteria from the intestinal walls, which are both symptoms of Crohn's.[67] Different strains found in tissue and different outcomes to antibiotics therapy and resistance suggest Crohn's Disease is not one disease, but an umbrella of diseases related to different pathogens.[68]

A number of studies have suggested a causal role for *Mycobacterium avium* subspecies *paratuberculosis* (MAP), which causes a similar disease, Johne's disease, in cattle.[69][70]

NOD2 is a gene involved in Crohn's genetic susceptibility. It is associated with macrophages' diminished ability to phagocytize MAP. This same gene may reduce innate and adaptive immunity in gastrointestinal tissue and impair the ability to resist infection by the MAP bacterium.[71] Macrophages that ingest the MAP bacterium are associated with high production of TNF-α.[72][73]

Other studies have linked specific strains of enteroadherent *E. coli* to the disease.[74] Adherent-invasive Escherichia coli (AIEC), are more common in people with CD,[75][76][77] have the ability to make strong biofilms compared to non-AIEC strains correlating with high adhesion and invasion indices[78][79] of neutrophils and the ability to block autophagy at the autolysosomal step, which allows for intracellular survival of the bacteria and induction of inflammation.[80] Inflammation drives the proliferation of AIEC and dysbiosis in the ileum, irrespective of genotype.[81] AIEC strains replicate extensively into macrophages inducing the secretion of very large amounts of TNF-α.[82]

Mouse studies have suggested some symptoms of Crohn's disease, ulcerative colitis, and irritable bowel syndrome have the same underlying cause. Biopsy samples taken from the colons of all three patient groups were found to produce elevated levels of a serine protease.[83] Experimental introduction of the serine protease into mice has been found to produce widespread pain associated with irritable bowel syndrome, as well as colitis, which is associated with all three diseases.[84] Regional and temporal variations in those illnesses follow those associated with infection with the protozoan Blastocystis.[85]

The "cold-chain" hypothesis is that psychrotrophic bacteria such as *Yersinia* and *Listeria* species contribute to the disease. A statistical correlation was found between the advent of the use of refrigeration in the United States and various parts of Europe and the rise of the disease.[86][87][88]

There is an apparent connection between Crohn's disease, *Mycobacterium*, other pathogenic bacteria, and genetic markers.[89][90] In many individuals, genetic factors predispose individuals to *Mycobacterium avium* subsp. *paratuberculosis* infection. This bacterium then produces mannins, which protect both itself and various bacteria from phagocytosis, which causes a variety of secondary infections.[91]

Still, this relationship between specific types of bacteria and Crohn's disease remains unclear.[92][93]

There is a tentative association between *Candida* colonization and Crohn's disease.[94]

## Environmental factors [edit]

The increased incidence of Crohn's in the industrialized world indicates an environmental component. Crohn's is associated with an increased intake of animal protein, milk protein and an increased ratio of omega-6 to omega-3 polyunsaturated fatty acids.[95] Those who consume vegetable proteins appear to have a lower incidence of Crohn's disease. Consumption of fish protein has no association.[95] Smoking increases the risk of the return of active disease (flares).[11] The introduction of hormonal contraception in the United States in the 1960s is associated with a dramatic increase in incidence, and one hypothesis is that these drugs work on the digestive system in ways similar to smoking.[96] Isotretinoin is associated with Crohn's.[97][98][99] Although stress is sometimes claimed to exacerbate Crohn's disease, there is no concrete evidence to support such claim.[100] Dietary microparticles, such as those found in toothpaste, have been studied as they produce effects on immunity, but they were not consumed in greater amounts in patients with Crohn's.[101][102]

# Pathophysiology [edit]

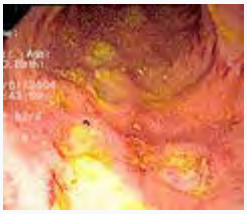
**Pathophysiology**

| | Crohn's disease | Ulcerative colitis |
|---|---|---|
| Cytokine response | Associated with $T_h17$[103] | Vaguely associated with $T_h2$ |

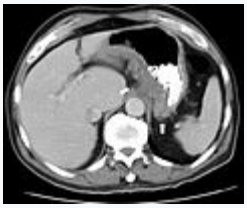
During a colonoscopy, biopsies of the colon are often taken to confirm the diagnosis. Certain characteristic features of the pathology seen point toward Crohn's disease; it shows a transmural pattern of inflammation, meaning the inflammation may span the entire depth of the intestinal wall.[1] Ulceration is an outcome seen in highly active disease. There is usually an abrupt transition between unaffected tissue and the ulcer—a characteristic sign known as skip lesions. Under a microscope, biopsies of the affected colon may show mucosal inflammation, characterized by focal infiltration of neutrophils, a type of inflammatory cell, into the epithelium. This typically occurs in the area overlying lymphoid aggregates. These neutrophils, along with mononuclear cells, may infiltrate the crypts, leading to inflammation (crypititis) or abscess (crypt abscess). Granulomas, aggregates of macrophage derivatives known as giant cells, are found in 50% of cases and are most specific for Crohn's disease. The granulomas of Crohn's disease do not show "caseation", a cheese-like appearance on microscopic examination characteristic of granulomas associated with infections, such as tuberculosis. Biopsies may also show chronic mucosal damage, as evidenced by blunting of the intestinal villi, atypical branching of the crypts, and a change in the tissue type (metaplasia). One example of such metaplasia, *Paneth cell metaplasia*, involves development of Paneth cells (typically found in the small intestine and a key regulator of intestinal microbiota) in other parts of the gastrointestinal system.[104][105]

# Diagnosis [edit]

The diagnosis of Crohn's disease can sometimes be challenging,[20] and a number of tests are often required to assist the physician in making the diagnosis.[24] Even with a full battery of tests, it may not be possible to diagnose Crohn's with complete certainty; a colonoscopy is approximately 70% effective in diagnosing the disease, with further tests being less effective. Disease in the small bowel is particularly difficult to diagnose, as a traditional colonoscopy allows access to only the colon and lower portions of the small intestines; introduction of the capsule endoscopy[106] aids in endoscopic diagnosis. Multinucleated giant cells, a common finding in the lesions of Crohn's disease, are less common in the lesions of lichen nitidus.[107]



Endoscopic image of Crohn's colitis showing deep ulceration



CT scan showing Crohn's disease in the fundus of the stomach

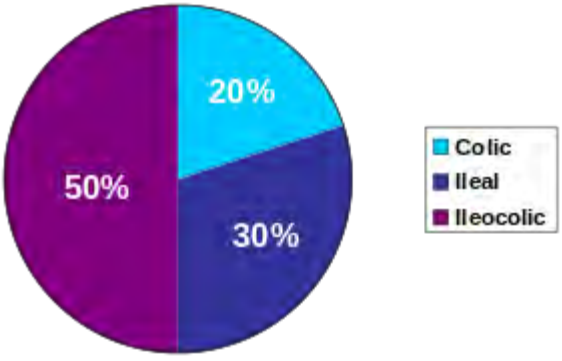
Endoscopic biopsy showing granulomatous inflammation of the colon in a case of Crohn's disease.

Section of colectomy showing transmural inflammation

Resected ileum for a person with Crohn's disease

## Classification [edit]

Crohn's disease is one type of inflammatory bowel disease (IBD). It typically manifests in the gastrointestinal tract and can be categorized by the specific tract region affected. A disease of both the ileum (the last part of the small intestine that connects to the large intestine), and the large intestine, Ileocolic Crohn's accounts for fifty percent of cases. Crohn's ileitis, manifest in the ileum only, accounts for thirty percent of cases, while Crohn's colitis, of the large intestine, accounts for the remaining twenty percent of cases and may be particularly difficult to distinguish from ulcerative colitis. Gastroduodenal Crohn's disease causes inflammation in the stomach and first part of the small intestine, called the duodenum. Jejunoileitis causes spotty patches of inflammation in the top half of the small intestine, called the jejunum.[108] The disease can attack any part of the digestive tract, from mouth to anus. However, individuals affected by the disease rarely fall outside these three classifications, with presentations in other areas.[1]




Distribution of gastrointestinal Crohn's disease.

Crohn's disease may also be categorized by the behavior of disease as it progresses. These categorizations formalized in the Vienna classification of the disease.[109] There are three categories of disease presentation in Crohn's disease: stricturing, penetrating, and inflammatory. Stricturing disease causes narrowing of the bowel that may lead to bowel obstruction or changes in the caliber of the feces. Penetrating disease creates abnormal passageways (fistulae) between the bowel and other structures, such as the skin. Inflammatory disease (or nonstricturing, nonpenetrating disease) causes inflammation without causing strictures or fistulae.[109][110]

## Endoscopy [edit]

A colonoscopy is the best test for making the diagnosis of Crohn's disease, as it allows direct visualization of the colon and the terminal ileum, identifying the pattern of disease involvement. On occasion, the colonoscope can travel past the terminal ileum, but it varies from person to person. During the procedure, the gastroenterologist can also perform a biopsy, taking small samples of tissue for laboratory analysis, which may help confirm a diagnosis. As 30% of Crohn's disease involves only the ileum,[1] cannulation of the terminal ileum is required in making the diagnosis. Finding a patchy distribution of disease, with involvement of the colon or ileum, but not the rectum, is suggestive of Crohn's disease, as are other endoscopic stigmata.[111] The utility of capsule endoscopy for this, however, is still uncertain.[112] A "cobblestone"-like appearance is seen in approximately 40% of cases of Crohn's disease upon colonoscopy, representing areas of ulceration separated by narrow areas of healthy tissue.

## Radiologic tests [edit]

A small bowel follow-through may suggest the diagnosis of Crohn's disease and is useful when the disease involves only the small intestine. Because colonoscopy and gastroscopy allow direct visualization of only the terminal ileum and beginning of the duodenum, they cannot be used to evaluate the remainder of the small intestine. As a result, a barium follow-through X-ray, wherein barium sulfate suspension is ingested and fluoroscopic images of the bowel are taken over time, is useful for looking for inflammation and narrowing of the small bowel.[111][113] Barium enemas, in which barium is inserted into the rectum and fluoroscopy is used to image the bowel, are rarely used in the work-up of Crohn's disease due to the advent of colonoscopy. They remain useful for identifying anatomical abnormalities when strictures of the colon are too small for a colonoscope to pass through, or in the detection of colonic fistulae (in this case contrast should be performed with iodate substances).[114]

CT and MRI scans are useful for evaluating the small bowel with enteroclysis protocols.[115] They are also useful for looking for intra-abdominal complications of Crohn's disease, such as abscesses, small bowel obstructions, or fistulae.[116] Magnetic resonance imaging (MRI) is another option for imaging the small bowel as well as looking for complications, though it is more expensive and less readily available.[117]

## Blood tests [edit]

A complete blood count may reveal anemia, which commonly is caused by blood loss leading to iron deficiency (a microcytic anemia) or by vitamin $B_{12}$ deficiency (a macrocytic anemia), usually caused by ileal disease impairing vitamin $B_{12}$ absorption. Rarely autoimmune hemolysis may occur.[118] Ferritin levels help assess if iron deficiency is contributing to the anemia. Erythrocyte sedimentation rate (ESR) and C-reactive protein help assess the degree of inflammation, which is important as ferritin can also be raised in inflammation.[119] Serum iron, total iron binding capacity and transferrin saturation may be more easily interpreted in inflammation. Anemia of chronic disease results in a normocytic anemia. Other causes of anemia include medication used in treatment of inflammatory bowel disease, like azathioprine, which can lead to cytopenia, and sulfasalazine, which can also result in folate deficiency. Testing for *Saccharomyces cerevisiae* antibodies (ASCA) and antineutrophil cytoplasmic antibodies (ANCA) has been evaluated to identify inflammatory diseases of the intestine[120] and to differentiate Crohn's disease from ulcerative colitis.[121] Furthermore, increasing amounts and levels of serological antibodies such as ASCA, antilaminaribioside [Glc(β1,3)Glb(β); ALCA], antichitobioside [GlcNAc(β1,4)GlcNAc(β); ACCA], antimannobioside [Man(α1,3)Man(α)AMCA], antiLaminarin [(Glc(β1,3))3n(Glc(β1,6))n; anti-L] and antichitin [GlcNAc(β1,4)n; anti-C] associate with disease behavior and surgery, and may aid in the prognosis of Crohn's disease.[122][123][124][125]

Low serum levels of vitamin D are associated with Crohn's disease.[126] Further studies are required to determine the significance of this association.[126]

## Comparison with ulcerative colitis [edit]

The most common disease that mimics the symptoms of Crohn's disease is ulcerative colitis, as both are inflammatory bowel diseases that can affect the colon with similar symptoms. It is important to differentiate these diseases, since the course of the diseases and treatments may be different. In some cases, however, it may not be possible to tell the difference, in which case the disease is classified as indeterminate colitis.[1][24][25]

**Diagnostic findings**

| | Crohn's disease | Ulcerative colitis |
|---|---|---|
| Terminal ileum involvement | Commonly | Seldom |
| Colon involvement | Usually | Always |
| Rectum involvement | Seldom | Usually[43] |
| Involvement around the anus | Common[19] | Seldom |
| Bile duct involvement | No increase in rate of primary sclerosing cholangitis | Higher rate[127] |
| Distribution of disease | Patchy areas of inflammation (skip lesions) | Continuous area of inflammation[43] |
| Endoscopy | Deep geographic and serpiginous (snake-like) ulcers | Continuous ulcer |
| Depth of inflammation | May be transmural, deep into tissues[19][128] | Shallow, mucosal |
| Stenosis | Common | Seldom |
| Granulomas on biopsy | May have non-necrotizing non-peri-intestinal crypt granulomas[19][129][130] | Non-peri-intestinal crypt granulomas not seen[43] |

## Differential diagnosis [edit]

Other conditions with similar symptoms as Crohn's disease includes intestinal tuberculosis, Behçet's disease, ulcerative colitis, nonsteroidal anti-inflammatory drug enteropathy, irritable bowel syndrome and celiac disease.[131] Irritable bowel syndrome is excluded when there are inflammatory changes.[131] Celiac disease can't be excluded if specific antibodies (anti-transglutaminase antibodies) are negative,[132][133] nor in absence of intestinal villi atrophy.[134][135]

# Management [edit]

*Main article: Management of Crohn's disease*

There is no cure for Crohn's disease and remission may not be possible or prolonged if achieved. In cases where remission is possible, relapse can be prevented and symptoms controlled with medication, lifestyle and dietary changes, changes to eating habits (eating smaller amounts more often), reduction of stress, moderate activity

**Management**

| | Crohn's disease | Ulcerative colitis |
|---|---|---|
| Mesalazine | Less useful[136] | More useful[136] |
| Antibiotics | Effective in long-term[137] | Generally not useful[138] |
| Surgery | Often returns following removal of affected part | Usually cured by removal of colon |

and exercise. Surgery is generally contraindicated and has not been shown to prevent remission. Adequately controlled, Crohn's disease may not significantly restrict daily living.[139] Treatment for Crohn's disease is only when symptoms are active and involve first treating the acute problem, then maintaining remission.

## Lifestyle changes [edit]

Certain lifestyle changes can reduce symptoms, including dietary adjustments, elemental diet, proper hydration, and smoking cessation. Diets that include higher levels of fiber and fruit are associated with reduced risk, while diets rich in total fats, polyunsaturated fatty acids, meat, and omega-6 fatty acids may increase the risk of Crohn's.[140] Smoking may increase Crohn's disease; stopping is recommended. Eating small meals frequently instead of big meals may also help with a low appetite. To manage symptoms have a balanced diet with proper portion control. Fatigue can be helped with regular exercise, a healthy diet, and enough sleep. A food diary may help with identifying foods that trigger symptoms. Some people should follow a low dietary fiber diet to control symptoms especially if fibrous foods cause symptoms.[139] Some find relief in eliminating casein (protein found in cow's milk) and gluten (protein found in wheat, rye and barley) from their diets. They may have specific dietary intolerances (not allergies).[141]

## Medication [edit]

Acute treatment uses medications to treat any infection (normally antibiotics) and to reduce inflammation (normally aminosalicylate anti-inflammatory drugs and corticosteroids). When symptoms are in remission, treatment enters maintenance, with a goal of avoiding the recurrence of symptoms. Prolonged use of corticosteroids has significant side-effects; as a result, they are, in general, not used for long-term treatment. Alternatives include aminosalicylates alone, though only a minority are able to maintain the treatment, and many require immunosuppressive drugs.[19] It has been also suggested that antibiotics change the enteric flora, and their continuous use may pose the risk of overgrowth with pathogens such as *Clostridium difficile*.[142]

Medications used to treat the symptoms of Crohn's disease include 5-aminosalicylic acid (5-ASA) formulations, prednisone, immunomodulators such as azathioprine (given as the prodrug for 6-mercaptopurine), methotrexate, infliximab, adalimumab,[25] certolizumab[143] and natalizumab.[144][145] Hydrocortisone should be used in severe attacks of Crohn's disease.[146] Biological therapies (biopharmaceuticals) are medications used to avoid long-term steroid use, decrease inflammation, and treat people who have fistulas with abscesses.[23] The monoclonal antibody ustekinumab appears to be a safe treatment option, and may help people with moderate to severe active crohn's disease.[147] The long term safety and effectiveness of monoclonal antibody treatment is not known. The monoclonal antibody briakinumab is not effective for people with active crohn's disease.[147]

The gradual loss of blood from the gastrointestinal tract, as well as chronic inflammation, often leads to anemia, and professional guidelines suggest routinely monitoring for this.[148][149][150] Adequate disease control usually improves anemia of chronic disease, but iron deficiency may require treatment with iron supplements. Guidelines vary as to how iron should be administered. Besides other, problems include a limitation in possible daily resorption and an increased growth of intestinal bacteria. Some[150] advise parenteral iron as first line as it works faster, has fewer gastrointestinal side effects, and is unaffected by inflammation reducing enteral absorption.

Other guidelines[149] advise oral iron as first line with parenteral iron reserved for those that fail to adequately respond as oral iron is considerably cheaper. All agree that severe anemia (hemoglobin under 10g/dL) should be treated with parenteral iron. Blood transfusion should be reserved for those who are cardiovascularly unstable, due to its relatively poor safety profile, lack of long term efficacy, and cost.[149]

## Surgery [edit]

Crohn's cannot be cured by surgery, as the disease eventually recurs, though it is used in the case of partial or full blockage of the intestine.[151] Surgery may also be required for complications such as

obstructions, fistulas, or abscesses, or if the disease does not respond to drugs. After the first surgery, Crohn's usually comes back at the site where the diseased intestine was removed and the healthy ends were rejoined, however it can come back in other locations. After a resection, scar tissue builds up, which can cause strictures, which form when the intestines become too small to allow excrement to pass through easily, which can lead to a blockage. After the first resection, another resection may be necessary within five years.[152] For patients with an obstruction due to a stricture, two options for treatment are strictureplasty and resection of that portion of bowel. There is no statistical significance between strictureplasty alone versus strictureplasty and resection in cases of duodenal involvement. In these cases, re-operation rates were 31% and 27%, respectively, indicating that strictureplasty is a safe and effective treatment for selected people with duodenal involvement.[153]

Postsurgical recurrence of Crohn's disease is relatively common. Crohn's lesions are nearly always found at the site of the resected bowel. The join (or anastomosis) after surgery may be inspected, usually during a colonoscopy, and disease activity graded. The "Rutgeert's score" is an endoscopic scoring system for post-operative disease recurrence in Crohn's disease. Mild postsurgical recurrences of Crohn's disease are graded i1 and i2, moderate to severe recurrences are graded i3 and i4.[154] Fewer lesions result in a lower grade. Based on the score, treatment plans can be designed to give the patient the best chance of managing recurrence of the disease.[155]

Short bowel syndrome (SBS, also short gut syndrome or simply short gut) is caused by the surgical removal of part of the small intestine. It usually develops in those patients who have had half or more of their small intestines removed.[156] Diarrhea is the main symptom, but others may include weight loss, cramping, bloating, and heartburn. Short bowel syndrome is treated with changes in diet, intravenous feeding, vitamin and mineral supplements, and treatment with medications. In some cases of SBS, intestinal transplant surgery may be considered; though the number of transplant centres offering this procedure is quite small and it comes with a high risk due to the chance of infection and rejection of the transplanted intestine.[157]

Bile acid diarrhea is another complication following surgery for Crohn's disease in which the terminal ileum has been removed. This leads to the development of excessive watery diarrhea. It is usually thought to be due to an inability of the ileum to reabsorb bile acids after resection of the terminal ileum and was the first type of bile acid malabsorption recognized.[158]

### Alternative medicine [edit]

More than half of people with Crohn's disease have tried complementary or alternative therapy.[159] These include diets, probiotics, fish oil and other herbal and nutritional supplements. Some scientists have suggested more research into these is needed to discriminate between effective therapies and those that have not been found to be effective.[160]

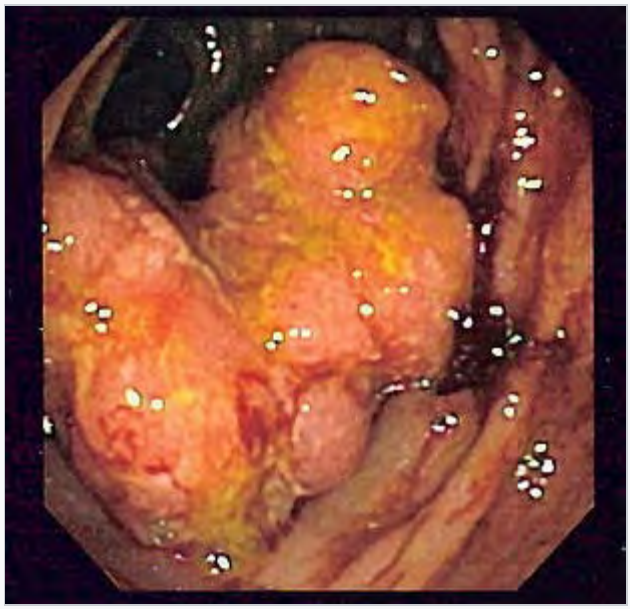
- Acupuncture is used to treat inflammatory bowel disease in China, and is being used more frequently in Western society.[161] At this time, evidence is insufficient to recommend the use of acupuncture.[162]
- Homeopathy is frequently used in Germany as a treatment for Crohn's disease, though no clinical trials exist that demonstrate homeopathy is effective.[163]
- There are contradicting studies regarding the effect of medical cannabis on inflammatory bowel disease.[164]

## Prognosis [edit]

Crohn's disease is a chronic condition for which there is no cure. It is characterised by periods of improvement followed by episodes when symptoms flare up. With treatment, most people achieve a healthy weight, and the mortality rate for the disease is relatively low. It can vary from being benign to very severe and people with CD could experience just one episode or have continuous symptoms. It usually reoccurs, although some people can remain disease free for years or decades. Most people with Crohn's live a normal lifespan.[165] However, Crohn's disease is associated with a small increase in risk of small bowel and colorectal carcinoma (bowel cancer).[166]

## Complications [edit]

Crohn's disease can lead to several mechanical complications within the intestines, including obstruction,[168] fistulae,[169] and abscesses.[170] Obstruction typically occurs from strictures or adhesions that narrow the lumen, blocking the passage of the intestinal contents. A fistula can develop between two loops of bowel, between the bowel and bladder, between the bowel and vagina, and between the bowel and skin. Abscesses are walled off concentrations of infection, which can occur in the abdomen or in the perianal area. Crohn's is responsible for 10% of vesicoenteric fistulae, and is the most common cause of ileovesical fistulae.[171]



Endoscopic image of colon cancer identified in the sigmoid colon on screening colonoscopy for Crohn's disease

**Complications**

| | | Crohn's disease | Ulcerative colitis |
|---|---|---|---|
| Nutrient deficiency | | Higher risk | |
| Colon cancer risk | | Slight | Considerable |
| Prevalence of **extraintestinal complications**[167] | | | |
| Iritis/uveitis | Females | 2.2% | 3.2% |
| | Males | 1.3% | 0.9% |
| Primary sclerosing cholangitis | Females | 0.3% | 1% |
| | Males | 0.4% | 3% |
| Ankylosing spondylitis | Females | 0.7% | 0.8% |
| | Males | 2.7% | 1.5% |
| Pyoderma gangrenosum | Females | 1.2% | 0.8% |
| | Males | 1.3% | 0.7% |
| Erythema nodosum | Females | 1.9% | 2% |
| | Males | 0.6% | 0.7% |

Crohn's disease also increases the risk of cancer in the area of inflammation. For example, individuals with Crohn's disease involving the small bowel are at higher risk for small intestinal cancer. Similarly, people with Crohn's colitis have a relative risk of 5.6 for developing colon cancer.[172] Screening for colon cancer with colonoscopy is recommended for anyone who has had Crohn's colitis for at least eight years.[173] Some studies suggest there is a role for chemoprotection in the prevention of colorectal cancer in Crohn's involving the colon; two agents have been suggested, folate and mesalamine preparations.[174] Also, immunomodulators and biologic agents used to treat this disease may promote developing extra-intestinal cancers.[175]

Individuals with Crohn's disease are at risk of malnutrition for many reasons, including decreased food intake and malabsorption. The risk increases following resection of the small bowel. Such individuals may require oral supplements to increase their caloric intake, or in severe cases, total parenteral nutrition (TPN). Most people with moderate or severe Crohn's disease are referred to a dietitian for assistance in nutrition.[176]

The major significant complications of Crohn's disease include bowel obstruction, abscesses, free perforation and hemorrhage, which in rare cases may be fatal.[177][178]

Crohn's disease can be problematic during pregnancy, and some medications can cause adverse outcomes for the fetus or mother. Consultation with an obstetrician and gastroenterologist about Crohn's disease and all medications facilitates preventative measures. In some cases, remission occurs during pregnancy. Certain medications can also lower sperm count or otherwise adversely affect a man's fertility.[179]

# Epidemiology [edit]

The percentage of people with Crohn's disease has been determined in Norway and the United States and is similar at 6 to 7.1:100,000. The Crohn's and Colitis Foundation of America cites this number as approx 149:100,000; NIH cites 28 to 199 per 100,000.[180][181] Crohn's disease is more common in northern countries, and with higher rates still in the northern areas of these countries.[182] The incidence of Crohn's disease is thought to be similar in Europe but lower in Asia and Africa.[180] It also has a higher incidence in Ashkenazi Jews[1][183] and smokers.[184]

Crohn's disease begins most commonly in people in their teens and 20s, and people in their 50s through to their 70s.[1][24] It is rarely diagnosed in early childhood. It usually affects female children more severely than males.[185] However, only slightly more women than men have Crohn's disease.[186] Parents, siblings or children of people with Crohn's disease are 3 to 20 times more likely to develop the disease.[187] Twin studies find that if one has the disease there is a 55% chance the other will too.[188]

The incidence of Crohn's disease is increasing in Europe.[189]

## History [edit]

*Main article: List of people diagnosed with Crohn's disease*

Inflammatory bowel diseases were described by Giovanni Battista Morgagni (1682–1771) and by Scottish physician T. Kennedy Dalziel in 1913.[190]

*Ileitis terminalis* was first described by Polish surgeon Antoni Leśniowski in 1904, although it was not conclusively distinguished from intestinal tuberculosis.[191] In Poland, it is still called Leśniowski-Crohn's disease (Polish: *choroba Leśniowskiego-Crohna*). Burrill Bernard Crohn, an American gastroenterologist at New York City's Mount Sinai Hospital, described fourteen cases in 1932, and submitted them to the American Medical Association under the rubric of "Terminal ileitis: A new clinical entity". Later that year, he, along with colleagues Leon Ginzburg and Gordon Oppenheimer, published the case series as "Regional ileitis: a pathologic and clinical entity". However, due to the precedence of Crohn's name in the alphabet, it later became known in the worldwide literature as Crohn's disease.[17]

## Research [edit]

Some evidence supports the hypothesis that the bacterium *Mycobacterium avium* subspecies *paratuberculosis* (MAP) is a cause of Crohn's disease (see also Johne's disease). As a result, researchers are looking at the eradication of MAP as a therapeutic option.[192] Treating MAP using antibiotics has been examined and the results are unclear but tentatively beneficial.[193][194] Vaccination against MAP is also being studied. An anti-MAP vaccine appears effective in mice and cattle with MAP with no apparent side effects.[192][195] Trials in human are pending.[196]

Crohn's is common in parts of the world where helminthic colonisation is rare and uncommon in those areas where most people carry worms. Infections with helminths may alter the autoimmune response that causes the disease. Trials of extracts from the worm *Trichuris suis* showed promising results when used in people with IBD.[197][198][199] However these trials (TRUST -I & TRUST -II) failed in Phase 2 clinical trials and were then discontinued after consistent failure in both North America and Europe.[200][201]

Numerous preclinical studies demonstrate that activation of the CB1 and CB2 cannabinoid receptors exert biological functions on the gastrointestinal tract.[202] Activation of CB1 and CB2 receptors in animals has shown a strong anti-inflammatory effect.[203] Cannabinoids and/or modulation of the endocannabinoid system is a novel therapeutic means for the treatment of numerous GI disorders, including inflammatory bowel diseases like Crohn's disease.[204] A few small trials have looked at medical cannabis but further evidence is required to determine its usefulness.[164]

There is no good evidence that thalidomide or lenalidomide is useful to bring about or maintain remission.[205][206]

# References [edit]


1. ^ a b c d e f g h i j k l m n o p q r s Baumgart DC, Sandborn WJ; Sandborn (2012). "Crohn's disease". *The Lancet*. **380** (9853): 1590–605. doi:10.1016/S0140-6736(12)60026-9. PMID 22914295.
2. ^ a b c d "Crohn's Disease". *National Digestive Diseases Information Clearinghouse (NDDIC)*. July 10, 2013. Retrieved 12 June 2014.
3. ^ Cho JH, Brant SR (2011). "Recent Insights into the Genetics of Inflammatory Bowel Disease". *Gastroenterology*. **140** (6): 1704–12. doi:10.1053/j.gastro.2011.02.046. PMID 21530736.
4. ^ a b c Dessein R, Chamaillard M, Danese S (2008). "Innate Immunity in Crohn's Disease". *Journal of Clinical Gastroenterology*. **42**: S144–7. doi:10.1097/MCG.0b013e3181662c90. PMID 18806708.
5. ^ Stefanelli T, Malesci A, Repici A, Vetrano S, Danese S (2008). "New Insights into Inflammatory Bowel Disease Pathophysiology: Paving the Way for Novel Therapeutic Targets". *Current Drug Targets*. **9** (5): 413–8. doi:10.2174/138945008784221170. PMID 18473770.
6. ^ a b Marks DJ, Rahman FZ, Sewell GW, Segal AW (2010). "Crohn's disease: An immune deficiency state". *Clinical reviews in allergy & immunology*. **38** (1): 20–31. doi:10.1007/s12016-009-8133-2. PMID 19437144.
7. ^ Casanova JL, Abel L (Aug 31, 2009). "Revisiting Crohn's disease as a primary immunodeficiency of macrophages.". *The Journal of Experimental Medicine*. **206** (9): 1839–43. doi:10.1084/jem.20091683. PMID 19687225.
8. ^ Lalande JD, Behr MA (2010). "Mycobacteria in Crohn's disease: How innate immune deficiency may result in chronic inflammation". *Expert review of clinical immunology*. **6** (4): 633–41. doi:10.1586/eci.10.29. PMID 20594136.
9. ^ Yamamoto-Furusho JK, Korzenik JR (2006). "Crohn's disease: Innate immunodeficiency?". *World Journal of Gastroenterology*. **12** (42): 6751–5. PMID 17106921.
10. ^ Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant SR, Silverberg MS, Taylor KD, Barmada MM, Bitton A, Dassopoulos T, Datta LW, Green T, Griffiths AM, Kistner EO, Murtha MT, Regueiro MD, Rotter JI, Schumm LP, Steinhart AH, Targan SR, Xavier RJ, Libioulle C, Sandor C, Lathrop M, Belaiche J, Dewit O, Gut I, Heath S, Laukens D, Mni M, Rutgeerts P, Van Gossum A, Zelenika D, Franchimont D, Hugot JP, de Vos M, Vermeire S, Louis E, Cardon LR, Anderson CA, Drummond H, Nimmo E, Ahmad T, Prescott NJ, Onnie CM, Fisher SA, Marchini J, Ghori J, Bumpstead S, Gwilliam R, Working Party for the World Congresses of Gastroenterology, Vienna 1998". *Inflammatory Bowel Diseases*. **6** (1): 8–15. doi:10.1002/ibd.3780060103. PMID 10701144.
110. ^ Dubinsky MC, Fleshner PP (2003). "Treatment of Crohn's disease of inflammatory, stenotic, and fistulizing phenotypes". *Current Treatment Options in Gastroenterology*. **6** (3): 183–200. doi:10.1007/s11938-003-0001-1. PMID 12744819.
111. ^ a b Hara AK, Leighton JA, Heigh RI, Sharma VK, Silva AC, De Petris G, Hentz JG, Fleischer DE (2005). "Crohn Disease of the Small Bowel: Preliminary Comparison among CT Enterography, Capsule Endoscopy, Small-Bowel Follow-through, and Ileoscopy". *Radiology*. **238** (1): 128–34. doi:10.1148/radiol.2381050296. PMID 16373764.
112. ^ Triester SL, Leighton JA, Leontiadis GI, Gurudu SR, Fleischer DE, Hara AK, Heigh RI, Shiff AD, Sharma VK (2006). "A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with non-stricturing small bowel Crohn's disease". *The American Journal of Gastroenterology*. **101** (5): 954–64. doi:10.1111/j.1572-0241.2006.00506.x. PMID 16696781.
113. ^ Dixon PM, Roulston ME, Nolan DJ; Roulston; Nolan (1993). "The small bowel enema: A ten year review". *Clinical Radiology*. **47** (1): 46–8. doi:10.1016/S0009-9260(05)81213-9. PMID 8428417.
114. ^ Carucci LR, Levine MS; Levine (2002). "Radiographic imaging of inflammatory bowel disease". *Gastroenterology Clinics of North America*. **31** (1): 93–117, ix. doi:10.1016/S0889-8553(01)00007-3. PMID 12122746.
115. ^ Rajesh A, Maglinte DD; Maglinte (2006). "Multislice CT enteroclysis: technique and clinical applications". *Clinical Radiology*. **61** (1): 31–9. doi:10.1016/j.crad.2005.08.006. PMID 16356814.
116. ^ Zissin R, Hertz M, Osadchy A, Novis B, Gayer G; Hertz; Osadchy; Novis; Gayer (2005). "Computed Tomographic Findings of Abdominal Complications of Crohn's Disease—Pictorial Essay" (PDF). *Canadian Association of Radiologists Journal*. **56** (1): 25–35. PMID 15835588. Archived from the original (PDF) on April 6, 2008. Retrieved 2009-11-07.
117. ^ Mackalski BA, Bernstein CN; Bernstein (2005). "New diagnostic imaging tools for inflammatory bowel disease". *Gut*. **55** (5): 733–41. doi:10.1136/gut.2005.076612. PMC 1856109. PMID 16609136.
118. ^ Goh J, O'Morain CA; O'Morain (2003). "Nutrition and adult inflammatory bowel disease". *Alimentary*

Tremelling M, Deloukas P, Mansfield J, Jewell D, Satsangi J, Mathew CG, Parkes M, Georges M, Daly MJ (2008). "Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease". *Nature Genetics*. **40** (8): 955–62. doi:10.1038/ng.175. PMC 2574810. PMID 18587394.

11. ^ a b Cosnes J (2004). "Tobacco and IBD: Relevance in the understanding of disease mechanisms and clinical practice". *Best Practice & Research Clinical Gastroenterology*. **18** (3): 481–96. doi:10.1016/j.bpg.2003.12.003. PMID 15157822.
12. ^ Molodecky, NA; Soon, IS; Rabi, DM; Ghali, WA; Ferris, M; Chernoff, G; Benchimol, EI; Panaccione, R; Ghosh, S; Barkema, HW; Kaplan, GG (Jan 2012). "Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review". *Gastroenterology*. **142** (1): 46–54.e42; quiz e30. doi:10.1053/j.gastro.2011.10.001. PMID 22001864.
13. ^ Prideaux, L; Kamm, MA; De Cruz, PP; Chan, FK; Ng, SC (Aug 2012). "Inflammatory bowel disease in Asia: a systematic review". *Journal of Gastroenterology and Hepatology*. **27** (8): 1266–80. doi:10.1111/j.1440-1746.2012.07150.x. PMID 22497584.
14. ^ a b Hovde, Ø; Moum, BA (Apr 21, 2012). "Epidemiology and clinical course of Crohn's disease: results from observational studies". *World journal of gastroenterology : WJG*. **18** (15): 1723–31. doi:10.3748/wjg.v18.i15.1723. PMC 3332285. PMID 22553396.
15. ^ a b Burisch, J; Munkholm, P (Jul 2013). "Inflammatory bowel disease epidemiology". *Current opinion in gastroenterology*. **29** (4): 357–62. doi:10.1097/MOG.0b013e32836229fb. PMID 23695429.
16. ^ Lozano, R; Naghavi, M (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
17. ^ a b Crohn BB, Ginzburg L, Oppenheimer GD (2000). "Regional ileitis: A pathologic and clinical entity. 1932". *The Mount Sinai journal of medicine, New York*. **67** (3): 263–8. PMID 10828911.
18. ^ a b c d e f internetmedicin.se > Inflammatorisk tarmsjukdom, kronisk, IBD By Robert Löfberg. Retrieved Oct 2010 Translate.
19. ^ a b c d e Hanauer SB, Sandborn W (2001-03-01). "Management of Crohn's disease in adults" (PDF). *American Journal of Gastroenterology*. **96** (3): 635–43. doi:10.1111/j.1572-0241.2001.03671.x. PMID 11280528. Retrieved 2009-11-07.
20. ^ a b Pimentel M, Chang M, Chow EJ, Tabibzadeh S, Kirit-Kiriak V, Targan SR, Lin HC (2000). *Pharmacology and Therapeutics*. **17** (3): 307–20. doi:10.1046/j.1365-2036.2003.01482.x. PMID 12562443.
119. ^ Chamouard P, Richert Z, Meyer N, Rahmi G, Baumann R; Richert; Meyer; Rahmi; Baumann (2006). "Diagnostic Value of C-Reactive Protein for Predicting Activity Level of Crohn's Disease". *Clinical Gastroenterology and Hepatology*. **4** (7): 882–7. doi:10.1016/j.cgh.2006.02.003. PMID 16630759.
120. ^ Kaila B, Orr K, Bernstein CN; Orr; Bernstein (2005). "The anti-Saccharomyces cerevisiae antibody assay in a province-wide practice: accurate in identifying cases of Crohn's disease and predicting inflammatory disease". *The Canadian Journal of Gastroenterology*. **19** (12): 717–21. PMID 16341311. Retrieved 2006-07-02.
121. ^ Israeli E, Grotto I, Gilburd B, Balicer RD, Goldin E, Wiik A, Shoenfeld Y; Grotto; Gilburd; Balicer; Goldin; Wiik; Shoenfeld (2005). "Anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic antibodies as predictors of inflammatory bowel disease". *Gut*. **54** (9): 1232–6. doi:10.1136/gut.2004.060228. PMC 1774672. PMID 16099791.
122. ^ Ferrante M, Henckaerts L, Joossens M, Pierik M, Joossens S, Dotan N, Norman GL, Altstock RT, Van Steen K, Rutgeerts P, Van Assche G, Vermeire S; Henckaerts; Joossens; Pierik; Joossens; Dotan; Norman; Altstock; Van Steen; Rutgeerts; Van Assche; Vermeire, S (2007). "New serological markers in inflammatory bowel disease are associated with complicated disease behaviour". *Gut*. **56** (10): 1394–403. doi:10.1136/gut.2006.108043. PMC 2000264. PMID 17456509.
123. ^ Papp M, Altorjay I, Dotan N, Palatka K, Foldi I, Tumpek J, Sipka S, Udvardy M, Dinya T, Lakatos L, Kovacs A, Molnar T, Tulassay Z, Miheller P, Norman GL, Szamosi T, Papp J, Lakatos PL; Altorjay; Dotan; Palatka; Foldi; Tumpek; Sipka; Udvardy; Dinya; Lakatos; Kovacs; Molnar; Tulassay; Miheller; Norman; Szamosi; Papp; Hungarian Ibd Study; Lakatos (2008). "New serological markers for inflammatory bowel disease are associated with earlier age at onset, complicated disease behavior, risk for surgery, and NOD2/CARD15 genotype in a Hungarian IBD cohort". *The American Journal of Gastroenterology*. **103** (3): 665–81. doi:10.1111/j.1572-0241.2007.01652.x. PMID 18047543.
124. ^ Seow CH, Stempak JM, Xu W, Lan H, Griffiths AM, Greenberg GR, Steinhart AH, Dotan N, Silverberg MS; Stempak; Xu; Lan; Griffiths; Greenberg; Steinhart; Dotan; Silverberg (2009). "Novel anti-glycan antibodies related to inflammatory bowel disease diagnosis and phenotype". *Am J Gastroenterol*. **104** (6): 1426–34. doi:10.1038/ajg.2009.79. PMID 19491856.
125. ^ Dotan I (2007). "Serologic markers in inflammatory bowel disease: tools for better diagnosis and disease stratification". *Expert Rev Gastroenterol Hepatol*. **1** (2): 265–74.

"Identification of a prodromal period in Crohn's disease but not ulcerative colitis". *The American Journal of Gastroenterology*. **95** (12): 3458–62. doi:10.1111/j.1572-0241.2000.03361.x. PMID 11151877.

21. ^ "Crohn's Disease: Get Facts on Symptoms and Diet". *eMedicineHealth*.
22. ^ National Research Council (US) Committee on Diagnosis and Control of Johne's Disease (2003). *Diagnosis and Control of Johne's Disease*.
23. ^ *a b* "What I need to know about Crohn's Disease". *www.niddk.nih.gov*. Retrieved 2015-12-11.
24. ^ *a b c d e f g* *Crohn Disease* at eMedicine
25. ^ *a b c* Podolsky DK (2002). "Inflammatory Bowel Disease". *New England Journal of Medicine*. **347** (6): 417–29. doi:10.1056/NEJMra020831. PMID 12167685.
26. ^ Mueller MH, Kreis ME, Gross ML, Becker HD, Zittel TT, Jehle EC (2002). "Anorectal functional disorders in the absence of anorectal inflammation in patients with Crohn's disease". *British Journal of Surgery*. **89** (8): 1027–31. doi:10.1046/j.1365-2168.2002.02173.x. PMID 12153630.
27. ^ Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson (July 30, 2004). "The Gastrointestinal Tract". *Robbins and Cotran: Pathologic Basis of Disease* (7th ed.). Philadelphia, Pennsylvania: Elsevier Saunders. p. 847. ISBN 0-7216-0187-1.
28. ^ Taylor BA, Williams GT, Hughes LE, Rhodes J (1989). "The histology of anal skin tags in Crohn's disease: An aid to confirmation of the diagnosis". *International Journal of Colorectal Disease*. **4** (3): 197–9. doi:10.1007/BF01649703. PMID 2769004.
29. ^ Fix OK, Soto JA, Andrews CW, Farraye FA (2004). "Gastroduodenal Crohn's disease". *Gastrointestinal Endoscopy*. **60** (6): 985. doi:10.1016/S0016-5107(04)02200-X. PMID 15605018.
30. ^ *a b* Beattie RM, Croft NM, Fell JM, Afzal NA, Heuschkel RB (2006). "Inflammatory bowel disease". *Archives of Disease in Childhood*. **91** (5): 426–32. doi:10.1136/adc.2005.080481. PMC 2082730. PMID 16632672.
31. ^ Büller HA (1997). "Problems in diagnosis of IBD in children". *The Netherlands Journal of Medicine*. **50** (2): S8–11. doi:10.1016/S0300-2977(96)00064-2. PMID 9050326.
32. ^ O'Keefe SJ (1996). "Nutrition and gastrointestinal disease". *Scand. J. Gastroenterol. Suppl*. **220**: 52–9. doi:10.3109/00365529609094750. PMID 8898436.
33. ^ Danese S, Semeraro S, Papa A, Roberto I, Scaldaferri F, Fedeli G, Gasbarrini G, Gasbarrini A (2005). "Extraintestinal manifestations in inflammatory bowel disease". *World Journal of Gastroenterology*. **11** (46): 7227–36. PMID 16437620.

*a b c d e f g h i j k*

doi:10.1586/17474124.1.2.265. PMID 19072419.

126. ^ *a b* Del Pinto, Rita; Pietropaoli, Davide; Chandar, Apoorva K.; Ferri, Claudio; Cominelli, Fabio (2015-08-12). "Association Between Inflammatory Bowel Disease and Vitamin D Deficiency: A Systematic Review and Meta-analysis". *Inflammatory Bowel Diseases*. **21**: 2708–17. doi:10.1097/MIB.0000000000000546. ISSN 1536-4844. PMC 4615394. PMID 26348447.
127. ^ Broomé U, Bergquist A (February 2006). "Primary sclerosing cholangitis, inflammatory bowel disease, and colon cancer". *Seminars in Liver Disease*. **26** (1): 31–41. doi:10.1055/s-2006-933561. PMID 16496231.
128. ^ Baumgart DC, Sandborn WJ (May 2007). "Inflammatory bowel disease: clinical aspects and established and evolving therapies.". *The Lancet*. **369** (9573): 1641–57. doi:10.1016/S0140-6736(07)60751-X. PMID 17499606. Retrieved 2009-11-04.
129. ^ Shepherd NA (August 2002). "Granulomas in the diagnosis of intestinal Crohn's disease: a myth exploded?". *Histopathology*. **41** (2): 166–8. doi:10.1046/j.1365-2559.2002.01441.x. PMID 12147095.
130. ^ Mahadeva U, Martin JP, Patel NK, Price AB (July 2002). "Granulomatous ulcerative colitis: a re-appraisal of the mucosal granuloma in the distinction of Crohn's disease from ulcerative colitis". *Histopathology*. **41** (1): 50–5. doi:10.1046/j.1365-2559.2002.01416.x. PMID 12121237.
131. ^ *a b* "Inflammatory Bowel Disease" (PDF). World Gastroenterology Organization. August 2015. Retrieved Mar 13, 2016.
132. ^ Lewis NR, Scott BB (Jul 1, 2006). "Systematic review: the use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests)". *Aliment Pharmacol Ther* (Review). **24** (1): 47–54. doi:10.1111/j.1365-2036.2006.02967.x. PMID 16803602. "Both the endomysial antibody and tissue transglutaminase antibody have very high sensitivities (93% for both) and specificities (>99% and >98% respectively) for the diagnosis of typical coeliac disease with villous atrophy. (...) As the detection of at least partial villous atrophy was used to make a diagnosis of coeliac disease in the vast majority of studies, we can't assume that the same LRs apply to coeliac patients with lesser abnormality such as an increase in intraepithelial lymphocytes or electron-microscopic changes only. In fact, if such lesser abnormalities were used as criteria for diagnosing (and excluding) coeliac disease, the sensitivity of the tests could be lower (i.e. more false negatives), especially since a number of studies suggest that the EMA and tTG antibody tests are less sensitive with lesser degrees of mucosal abnormality"
133. ^ Rodrigo L, Garrote JA, Vivas S (Sep 6, 2008). "[Celiac disease]". *Med Clin (Barc)* (Review) (in

34. ^ Trikudanathan G, Venkatesh PG, Navaneethan U (2012). "Diagnosis and therapeutic management of extra-intestinal manifestations of inflammatory bowel disease". *Drugs*. **72** (18): 2333–49. doi:10.2165/11638120-000000000-00000. PMID 23181971.
35. ^ "Arthritis". Healthline Networks, Inc. October 10, 2008. Retrieved 2010-08-16.
36. ^ *a b* Thrash B, Patel M, Shah KR, Boland CR, Menter A (2013). "Cutaneous manifestations of gastrointestinal disease: part II". *Journal of the American Academy of Dermatology*. **68** (2): 211 e1–33. doi:10.1016/j.jaad.2012.10.036. PMID 23317981.
37. ^ Bernstein M, Irwin S, Greenberg GR (2005). "Maintenance Infliximab Treatment is Associated with Improved Bone Mineral Density in Crohn's Disease". *The American Journal of Gastroenterology*. **100** (9): 2031–5. doi:10.1111/j.1572-0241.2005.50219.x. PMID 16128948.
38. ^ *a b c* Lomer MC (August 2011). "Dietary and nutritional considerations for inflammatory bowel disease". *The Proceedings of the Nutrition Society*. **70** (3): 329–35. doi:10.1017/S0029665111000097. PMID 21450124.
39. ^ *a b c* Gerasimidis K, McGrogan P, Edwards CA (August 2011). "The aetiology and impact of malnutrition in paediatric inflammatory bowel disease". *Journal of Human Nutrition and Dietetics*. **24** (4): 313–26. doi:10.1111/j.1365-277X.2011.01171.x. PMID 21564345.
40. ^ *a b* Crohn's disease. professionals.epilepsy.com. Retrieved July 13, 2007.
41. ^ MedlinePlus Encyclopedia *Small bowel bacterial overgrowth*
42. ^ Zadik Y, Drucker S, Pallmon S (2011). "Migratory stomatitis (ectopic geographic tongue) on the floor of the mouth". *Journal of the American Academy of Dermatology*. **65** (2): 459–60. doi:10.1016/j.jaad.2010.04.016. PMID 21763590.
43. ^ *a b c d* Kornbluth A, Sachar DB (July 2004). "Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee" (PDF). *American Journal of Gastroenterology*. **99** (7): 1371–85. doi:10.1111/j.1572-0241.2004.40036.x. PMID 15233681. Archived (PDF) from the original on April 6, 2008. Retrieved 2009-11-07.
44. ^ Crohn's Disease Overview
45. ^ "Crohn's diseaseShare on facebookShare on twitterBookmark & SharePrinter-friendly version". 2013-10-13. Retrieved 16 September 2014.
46. ^ Braat H, Peppelenbosch MP, Hommes DW (August 2006). "Immunology of Crohn's disease". *Annals of the New York Academy of Sciences*. **1072** (1): 135–54. doi:10.1196/annals.1326.039. PMID 17057196.
47. ^ Henckaerts L, Figueroa C, Vermeire S, Sans M Spanish). **131** (7): 264–70. doi:10.1016/S0025-7753(08)72247-4. PMID 18775218. "Estos marcadores presentan en general una elevada sensibilidad y especificidad (cercanas al 90%) en presencia de atrofia marcada de las vellosidades intestinales. Sin embargo, muestran una notable disminución de la sensibilidad (del orden del 40-50%) en casos con atrofia vellositaria leve o cambios mínimos. *These markers generally have high sensitivity and specificity (around 90%) in the presence of marked atrophy of the villi. However, they show a marked decrease in sensitivity (of the order of 40-50%) in cases with mild villous atrophy or minimal changes*."
134. ^ Rostami Nejad M, Hogg-Kollars S, Ishaq S, Rostami K (2011). "Subclinical celiac disease and gluten sensitivity". *Gastroenterol Hepatol Bed Bench* (Review). **4** (3): 102–8. PMC 4017418. PMID 24834166.
135. ^ Bold J, Rostami K (2011). "Gluten tolerance; potential challenges in treatment strategies". *Gastroenterol Hepatol Bed Bench* (Review). **4** (2): 53–7. PMC 4017406. PMID 24834157.
136. ^ *a b* Pages 152–156 (Section: Inflammatory bowel disease (IBD)) in: Elizabeth D Agabegi; Agabegi, Steven S. (2008). *Step-Up to Medicine (Step-Up Series)*. Hagerstwon, MD: Lippincott Williams & Wilkins. ISBN 0-7817-7153-6.
137. ^ Feller M, Huwiler K, Schoepfer A, Shang A, Furrer H, Egger M (2010). "Long-term antibiotic treatment for Crohn's disease: systematic review and meta-analysis of placebo-controlled trials". *Clin. Infect. Dis.* **50** (4): 473–80. doi:10.1086/649923. PMID 20067425.
138. ^ Section "Antibiotics and Ulcerative Colitis" in: Prantera C, Scribano ML (2009). "Antibiotics and probiotics in inflammatory bowel disease: why, when, and how". *Curr. Opin. Gastroenterol.* **25** (4): 329–33. doi:10.1097/MOG.0b013e32832b20bf. PMID 19444096.
139. ^ *a b* Fries, WS; Nazario, B (2007-05-16). "Crohn's Disease: 54 Tips to Help You Manage". WebMD. Retrieved 2008-02-14.
140. ^ Hou, Jason K; Abraham, Bincy; El-Serag, Hashem (April 2011). "Dietary Intake and Risk of Developing Inflammatory Bowel Disease: A Systematic Review of the Literature" (PDF). *Am. J. Gastroenterol.* **106**: 563–573. doi:10.1038/ajg.2011.44. PMID 21468064.
141. ^ Escott-Stump, Sylvia (2008). *Nutrition and Diagnosis-Related Care, 7th edition*. Baltimore, MD: Lippincott Williams & Wilkins. pp. 1020 (pp 431). ISBN 978-1-60831-017-3.
142. ^ Shanahan, Fergus (1 January 2002). "Crohn's disease". *The Lancet*. **359** (9300): 62–69. doi:10.1016/S0140-6736(02)07284-7.
143. ^ "FDA Approves Cimzia to Treat Crohn's Disease" (Press release). Food and Drug Administration (FDA). April 22, 2008. Retrieved 2009-11-05.

(May 2008). "The role of genetics in inflammatory bowel disease". *Curr Drug Targets*. **9** (5): 361–8. doi:10.2174/138945008784221161. PMID 18473763.

48. ^ a b Marks DJ, Harbord MW, MacAllister R, Rahman FZ, Young J, Al-Lazikani B, Lees W, Novelli M, Bloom S, Segal AW (2006). "Defective acute inflammation in Crohn's disease: a clinical investigation". *Lancet*. **367** (9511): 668–78. doi:10.1016/S0140-6736(06)68265-2. PMID 16503465.
49. ^ Comalada M, Peppelenbosch MP (September 2006). "Impaired innate immunity in Crohn's disease". *Trends Mol Med*. **12** (9): 397–9. doi:10.1016/j.molmed.2006.07.005. PMID 16890491.
50. ^ Nakagome, S.; Mano, S.; Kozlowski, L.; Bujnicki, JM.; Shibata, H.; Fukumaki, Y.; Kidd, JR.; Kidd, KK.; et al. (Jun 2012). "Crohn's disease risk alleles on the NOD2 locus have been maintained by natural selection on standing variation.". *Mol Biol Evol*. **29** (6): 1569–85. doi:10.1093/molbev/mss006. PMC 3697811. PMID 22319155.
51. ^ "Crohn's disease has strong genetic link: study". Crohn's and Colitis Foundation of America. 2007-04-16. Retrieved 2009-11-07.
52. ^ Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nuñez G, Cho JH (2001). "A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease". *Nature*. **411** (6837): 603–6. doi:10.1038/35079114. PMID 11385577.
53. ^ Cuthbert AP, Fisher SA, Mirza MM, King K, Hampe J, Croucher PJ, Mascheretti S, Sanderson J, Forbes A, Mansfield J, Schreiber S, Lewis CM, Mathew CG (2002). "The contribution of NOD2 gene mutations to the risk and site of disease in inflammatory bowel disease". *Gastroenterology*. **122** (4): 867–74. doi:10.1053/gast.2002.32415. PMID 11910337.
54. ^ Kaser A, Lee AH, Franke A, Glickman JN, Zeissig S, Tilg H, Nieuwenhuis EE, Higgins DE, Schreiber S, Glimcher LH, Blumberg RS (5 September 2008). "XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease". *Cell*. **134** (5): 743–56. doi:10.1016/j.cell.2008.07.021. PMC 2586148. PMID 18775308.
55. ^ Clevers H (2009). "Inflammatory Bowel Disease, Stress, and the Endoplasmic Reticulum". *New England Journal of Medicine*. **360** (7): 726–27. doi:10.1056/NEJMcibr0809591. PMID 19213688.
56. ^ Vermeire S (2004). "NOD2/CARD15: relevance in clinical practice". *Best Pract Res Clin Gastroenterol* (Review). **18** (3): 569–75. doi:10.1016/j.bpg.2003.12.008. PMID 15157828.
57. ^ a b Prescott NJ, Fisher SA, Franke A, Hampe J, Onnie CM, Soars D, Bagnall R, Mirza MM, Sanderson J, Forbes A, Mansfield JC, Lewis CM, Schreiber S,
144. ^ Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, Panaccione R, Sanders M, Schreiber S, Targan S, van Deventer S, Goldblum R, Despain D, Hogge GS, Rutgeerts P; Colombel; Enns; Feagan; Hanauer; Lawrance; Panaccione; Sanders; Schreiber; Targan; Van Deventer; Goldblum; Despain; Hogge; Rutgeerts; International Efficacy of Natalizumab as Active Crohn's Therapy (ENACT-1) Trial Group; Evaluation of Natalizumab as Continuous Therapy (ENACT-2) Trial Group (2005). "Natalizumab Induction and Maintenance Therapy for Crohn's Disease". *New England Journal of Medicine*. **353** (18): 1912–25. doi:10.1056/NEJMoa043335. PMID 16267322.
145. ^ MacDonald JK, McDonald JW; McDonald (2007). MacDonald, John K, ed. "Natalizumab for induction of remission in Crohn's disease". *Cochrane Database of Systematic Reviews* (1): CD006097. doi:10.1002/14651858.CD006097.pub2. PMID 17253580. CD006097.
146. ^ Longmore, Murray; Ian Wilkinson; Tom Turmezei; Chee Kay Cheung (2007). *Oxford Handbook of Clinical Medicine* (7th ed.). Oxford University Press. pp. 266–7. ISBN 0-19-856837-1.
147. ^ a b Khanna, Reena; Preiss, Jan C.; MacDonald, John K.; Timmer, Antje (2015-05-05). "Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease". *The Cochrane Database of Systematic Reviews* (5): CD007572. doi:10.1002/14651858.CD007572.pub2. ISSN 1469-493X. PMID 25942580.
148. ^ Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L, Lees C, Ho GT, Satsangi J, Bloom S; Cole; Windsor; Ahmad; Arnott; Driscoll; Mitton; Orchard; Rutter; Younge; Lees; Ho; Satsangi; Bloom; IBD Section of the British Society of Gastroenterology (May 2011). "Guidelines for the management of inflammatory bowel disease in adults". *Gut*. **60** (5): 571–607. doi:10.1136/gut.2010.224154. PMID 21464096.
149. ^ a b c Goddard AF, James MW, McIntyre AS, Scott BB; James; McIntyre; Scott; British Society of Gastroenterology (2011). "Guidelines for the management of iron deficiency anaemia". *Gut*. **60** (10): 1309–1316. doi:10.1136/gut.2010.228874. PMID 21561874.
150. ^ a b Inflamm Bowel Dis Volume 13, Number 12, December 2007
151. ^ Kristo, Ivan; Stift, Anton; Bergmann, Michael; Riss, Stefan (2015-05-28). "Surgical recurrence in Crohn's disease: Are we getting better?". *World Journal of Gastroenterology*. **21** (20): 6097–6100. doi:10.3748/wjg.v21.i20.6097. ISSN 2219-2840. PMC 4445088. PMID 26034346.
152. ^ Tresca, AJ (2007-01-12). "Resection Surgery for Crohn's Disease". About.com. Retrieved 2008-02-14.
153. ^ Ozuner G, Fazio VW, Lavery IC, Milsom JW, Strong SA; Fazio; Lavery; Milsom; Strong (1996).

Mathew CG (2007). "A nonsynonymous SNP in ATG16L1 predisposes to ileal Crohn's disease and is independent of CARD15 and IBD5". *Gastroenterology*. **132** (5): 1665–71. doi:10.1053/j.gastro.2007.03.034. PMID 17484864.

58. ^ Diegelmann, J.; Czamara, D.; Le Bras, E.; Zimmermann, E.; Olszak, T.; Bedynek, A.; Göke, B.; Franke, A.; et al. (2013). "Intestinal DMBT1 expression is modulated by Crohn's disease-associated IL23R variants and by a DMBT1 variant which influences binding of the transcription factors CREB1 and ATF-2.". *PLOS ONE*. **8** (11): e77773. doi:10.1371/journal.pone.0077773. PMC 3818382. PMID 24223725.
59. ^ Prescott, NJ.; Dominy, KM.; Kubo, M.; Lewis, CM.; Fisher, SA.; Redon, R.; Huang, N.; Stranger, BE.; et al. (May 2010). "Independent and population-specific association of risk variants at the IRGM locus with Crohn's disease.". *Hum Mol Genet*. **19** (9): 1828–39. doi:10.1093/hmg/ddq041. PMC 2850616. PMID 20106866.
60. ^ Chermesh, I.; Azriel, A.; Alter-Koltunoff, M.; Eliakim, R.; Karban, A.; Levi, BZ. (Jul 2007). "Crohn's disease and SLC11A1 promoter polymorphism.". *Dig Dis Sci*. **52** (7): 1632–5. doi:10.1007/s10620-006-9682-3. PMID 17385031.
61. ^ Jostins L, Ripke S, Weersma RK, et al. (2012). "Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease". *Nature*. **491** (7422): 119–24. doi:10.1038/nature11582. PMC 3491803. PMID 23128233.
62. ^ Walker MM, Murray JA (Aug 2011). "An update in the diagnosis of coeliac disease". *Histopathology* (Review). **59** (2): 166–79. doi:10.1111/j.1365-2559.2010.03680.x. PMID 21054494. "Recent genome-wide association studies have shown that chronic inflammatory and autoimmune diseases are linked genetically to coeliac disease; for example, type 1 diabetes mellitus, Grave's disease and Crohn's disease."
63. ^ Marks DJ, Segal AW (January 2008). "Innate immunity in inflammatory bowel disease: a disease hypothesis". *J Pathol*. **214** (2): 260–6. doi:10.1002/path.2291. PMC 2635948. PMID 18161747.
64. ^ Cobrin GM, Abreu MT (2005). "Defects in mucosal immunity leading to Crohn's disease". *Immunol. Rev*. **206** (1): 277–95. doi:10.1111/j.0105-2896.2005.00293.x. PMID 16048555.
65. ^ Elson CO, Cong Y, Weaver CT, Schoeb TR, McClanahan TK, Fick RB, Kastelein RA (2007). "Monoclonal Anti – Interleukin 23 Reverses Active Colitis in a T Cell – Mediated Model in Mice". *Gastroenterology*. **132** (7): 2359–70. doi:10.1053/j.gastro.2007.03.104. PMID 17570211.
66. ^ Moises Velasquez-Manoff (June 29, 2008). "The "Reoperative rates for Crohn's disease following strictureplasty. Long-term analysis". *Dis. Colon Rectum*. **39** (11): 1199–203. doi:10.1007/BF02055108. PMID 8918424.
154. ^ Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M; Geboes; Vantrappen; Beyls; Kerremans; Hiele (October 1990). "Predictability of the postoperative course of Crohn's disease". *Gastroenterology*. **99** (4): 956–63. PMID 2394349.
155. ^ Yamamoto T, Bamba T, Umegae S, Matsumoto K; Bamba; Umegae; Matsumoto (August 2013). "The impact of early endoscopic lesions on the clinical course of patients following ileocolonic resection for Crohn's disease: A 5-year prospective cohort study". *United European Gastroenterol J*. **1** (4): 294–8. doi:10.1177/2050640613495197. PMC 4040796. PMID 24917974.
156. ^ "Short Bowel Syndrome". *nih.gov*.
157. ^ Rhodes, M (2006-10-24). "Intestinal transplant for Crohn's disease". Everyday Health. Retrieved 2009-03-22.
158. ^ Hofmann AF (1967). "The syndrome of ileal disease and the broken enterohepatic circulation: cholerhetic enteropathy.". *Gastroenterology*. **52** (4): 752–7. PMID 5337211.
159. ^ Caprilli R, Gassull MA, Escher JC, Moser G, Munkholm P, Forbes A, Hommes DW, Lochs H, Angelucci E, Cocco A, Vucelic B, Hildebrand H, Kolacek S, Riis L, Lukas M, de Franchis R, Hamilton M, Jantschek G, Michetti P, O'Morain C, Anwar MM, Freitas JL, Mouzas IA, Baert F, Mitchell R, Hawkey CJ; Gassull; Escher; Moser; Munkholm; Forbes; Hommes; Lochs; Angelucci; Cocco; Vucelic; Hildebrand; Kolacek; Riis; Lukas; De Franchis; Hamilton; Jantschek; Michetti; O'Morain; Anwar; Freitas; Mouzas; Baert; Mitchell; Hawkey; European Crohn's Colitis Organisation (2006). "European evidence based consensus on the diagnosis and management of Crohn's disease: special situations". *Gut*. **55** (Suppl 1): i36–58. doi:10.1136/gut.2005.081950c. PMC 1859996. PMID 16481630.
160. ^ "Use of complementary and alternative medicine in Germany – a survey of patients with inflammatory bowel disease". *BioMed Central*. Retrieved 21 September 2010. "At the same time, further clinical studies assessing the most commonly used CAM therapies are urgently needed. Research in CAM offers the chance to discover new h options in the management of IBD but may also protect patients from ineffective and expensive 'pseudo'-therapies."
161. ^ Joos S, Brinkhaus B, Maluche C, Maupai N, Kohnen R, Kraehmer N, Hahn EG, Schuppan D; Brinkhaus; Maluche; Maupai; Kohnen; Kraehmer; Hahn; Schuppan (2004). "Acupuncture and moxibustion in the treatment of active Crohn's disease: a randomized controlled study". *Digestion*. **69** (3): 131–9. doi:10.1159/000078151. PMID 15114043.
162. ^ Caprilli R, Gassull MA, Escher JC, Moser G,

Worm Turns". *The New York Times*.
67. ^ Sartor, R Balfour (2006). "Mechanisms of Disease: Pathogenesis of Crohn's disease and ulcerative colitis". *Nature Clinical Practice Gastroenterology & Hepatology*. **3** (7): 390–407. doi:10.1038/ncpgasthep0528.
68. ^ Dogan B, Scherl E, Bosworth B, Yantiss R, Altier C, McDonough PL, Jiang ZD, Dupont HL, Garneau P, Harel J, Rishniw M, Simpson KW (2013). "Multidrug resistance is common in Escherichia coli associated with ileal Crohn's disease". *Inflamm. Bowel Dis.* **19** (1): 141–50. doi:10.1002/ibd.22971. PMID 22508665.
69. ^ Naser SA, Collins MT (December 2005). "Debate on the lack of evidence of *Mycobacterium avium* subsp. *paratuberculosis* in Crohn's disease". *Inflamm. Bowel Dis.* **11** (12): 1123. doi:10.1097/01.MIB.0000191609.20713.ea. PMID 16306778.
70. ^ Naser SA, Sagramsingh SR, Naser AS, Naser ST (June 2014). "*Mycobacterium avium* subspecies *paratuberculosis* causes Crohn's disease in some inflammatory bowel disease patients". *World J Gastroenterol*. **20** (23): 7403–7415. doi:10.3748/wjg.v20.i23.7403. PMC 4064085. PMID 24966610.
71. ^ Glubb DM, Gearry RB, Barclay ML, Roberts RL, Pearson J, Keenan JI, McKenzie J, Bentley RW (2011). "*NOD2* and *ATG16L1* polymorphisms affect monocyte responses in Crohn's disease". *World Journal of Gastroenterology*. **17** (23): 2829–37. doi:10.3748/wjg.v17.i23.2829. PMC 3120942. PMID 21734790.
72. ^ Clancy R, Ren Z, Turton J, Pang G, Wettstein A (2007). "Molecular evidence for *Mycobacterium avium* subspecies *paratuberculosis* (MAP) in Crohn's disease correlates with enhanced TNF-alpha secretion". *Digestive and Liver Disease*. **39** (5): 445–51. doi:10.1016/j.dld.2006.12.006. PMID 17317344.
73. ^ Nakase H, Tamaki H, Matsuura M, Chiba T, Okazaki K (2011). "Involvement of *Mycobacterium avium* subspecies *paratuberculosis* in TNF-α production from macrophage: Possible link between MAP and immune response in Crohn's disease". *Inflammatory bowel diseases*. **17** (11): E140–2. doi:10.1002/ibd.21750. PMID 21990211.
74. ^ Baumgart M, Dogan B, Rishniw M, Weitzman G, Bosworth B, Yantiss R, Orsi RH, Wiedmann M, McDonough P, Kim SG, Berg D, Schukken Y, Scherl E, Simpson KW (2007). "Culture independent analysis of ileal mucosa reveals a selective increase in invasive Escherichia coli of novel phylogeny relative to depletion of Clostridiales in Crohn's disease involving the ileum". *The ISME Journal*. **1** (5): 403–18. doi:10.1038/ismej.2007.52. PMID 18043660.
75. ^ Sasaki M, Sitaraman SV, Babbin BA, Gerner-Smidt P, Ribot EM, Garrett N, Alpern JA, Akyildiz A, Theiss AL, Nusrat A, Klapproth JM (2007). "Invasive Escherichia coli are a feature of Crohn's disease".

Munkholm P, Forbes A, Hommes DW, Lochs H, Angelucci E, Cocco A, Vucelic B, Hildebrand H, Kolacek S, Riis L, Lukas M, de Franchis R, Hamilton M, Jantschek G, Michetti P, O'Morain C, Anwar MM, Freitas JL, Mouzas IA, Baert F, Mitchell R, Hawkey CJ; Gassull; Escher; Moser; Munkholm; Forbes; Hommes; Lochs; Angelucci; Cocco; Vucelic; Hildebrand; Kolacek; Riis; Lukas; De Franchis; Hamilton; Jantschek; Michetti; O'Morain; Anwar; Freitas; Mouzas; Baert; Mitchell; Hawkey; European Crohn's Colitis Organisation (2006). "The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations" (PDF). *Gut*. **55** (Suppl 1): i36–i58. doi:10.1136/gut.2005.081950c. PMC 1859996. PMID 16481630. "the colitis activity index fell significantly in the treatment group compared to the sham acupuncture group. However, recruitment did not reach its target and the number of patients was small." [*verification needed*]
163. ^ Smart HL, Mayberry JF, Atkinson M; Mayberry; Atkinson (1986). "Alternative medicine consultations and remedies in patients with the irritable bowel syndrome". *Gut*. **27** (7): 826–8. doi:10.1136/gut.27.7.826. PMC 1433575. PMID 3755416.
164. ^ *a b* Naftali, T; Mechulam, R; Lev, LB; Konikoff, FM (2014). "Cannabis for inflammatory bowel disease". *Digestive diseases (Basel, Switzerland)*. **32** (4): 468–74. doi:10.1159/000358155. PMID 24969296.
165. ^ "Crohn's disease - Prognosis". University of Maryland Medical Centre. Retrieved 19 October 2012.
166. ^ Canavan C, Abrams KR, Mayberry J; Abrams; Mayberry (2006). "Meta-analysis: Colorectal and small bowel cancer risk in patients with Crohn's disease". *Alimentary Pharmacology and Therapeutics*. **23** (8): 1097–104. doi:10.1111/j.1365-2036.2006.02854.x. PMID 16611269.
167. ^ Greenstein AJ, Janowitz HD, Sachar DB (September 1976). "The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients". *Medicine (Baltimore)*. **55** (5): 401–12. doi:10.1097/00005792-197609000-00004. PMID 957999.
168. ^ "Intestinal Obstruction". *MERCK MANUAL Consumer Version*. Retrieved 2016-06-27.
169. ^ "Anorectal Fistula". *MERCK MANUAL Consumer Version*. Retrieved 2016-06-27.
170. ^ "Anorectal Abscess". *MERCK MANUAL Consumer Version*. Retrieved 2016-06-27.
171. ^ *Enterovesical Fistula* at eMedicine
172. ^ Ekbom A, Helmick C, Zack M, Adami HO; Helmick; Zack; Adami (1990). "Increased risk of large-bowel cancer in Crohn's disease with colonic involvement". *Lancet*. **336** (8711): 357–9. doi:10.1016/0140-6736(90)91889-I. PMID 1975343.
173. ^ Collins PD, Mpofu C, Watson AJ, Rhodes JM; Mpofu; Watson; Rhodes (2006). Watson, Alastair J,

*Laboratory Investigation*. **87** (10): 1042–54. doi:10.1038/labinvest.3700661. PMID 17660846.

76. ^ Darfeuille-Michaud A, Boudeau J, Bulois P, Neut C, Glasser AL, Barnich N, Bringer MA, Swidsinski A, Beaugerie L, Colombel JF (2004). "High prevalence of Adherent-invasive Escherichia coli associated with ileal mucosa in Crohn's disease". *Gastroenterology*. **127** (2): 412–21. doi:10.1053/j.gastro.2004.04.061. PMID 15300573.
77. ^ Baumgart M, Dogan B, Rishniw M, Weitzman G, Bosworth B, Yantiss R, Orsi RH, Wiedmann M, McDonough P, Kim SG, Berg D, Schukken Y, Scherl E, Simpson KW (2007). "Culture independent analysis of ileal mucosa reveals a selective increase in invasive Escherichia coli of novel phylogeny relative to depletion of Clostridiales in Crohn's disease involving the ileum". *The ISME journal* (). **1** (5): 403–18. doi:10.1038/ismej.2007.52. PMID 18043660.
78. ^ Nickerson KP, McDonald C (2012). Mizoguchi, Emiko, ed. "Crohn's Disease-Associated Adherent-Invasive Escherichia coli Adhesion is Enhanced by Exposure to the Ubiquitous Dietary Polysaccharide Maltodextrin". *PLoS ONE* (). **7** (12): e52132. doi:10.1371/journal.pone.0052132. PMC 3520894. PMID 23251695.
79. ^ Martinez-Medina M, Naves P, Blanco J, Aldeguer X, Blanco JE, Blanco M, Ponte C, Soriano F, Darfeuille-Michaud A, Garcia-Gil LJ (2009). "Biofilm formation as a novel phenotypic feature of adherent-invasive Escherichia coli (AIEC)". *BMC Microbiology*. **9** (1): 202. doi:10.1186/1471-2180-9-202. PMC 2759958. PMID 19772580.
80. ^ Chargui A, Cesaro A, Mimouna S, Fareh M, Brest P, Naquet P, Darfeuille-Michaud A, Hébuterne X, Mograbi B, Vouret-Craviari V, Hofman P (2012). "Subversion of autophagy in adherent invasive Escherichia coli-infected neutrophils induces inflammation and cell death". *PLoS ONE*. **7** (12): e51727. doi:10.1371/journal.pone.0051727. PMC 3522719. PMID 23272151.
81. ^ Craven M, Egan CE, Dowd SE, McDonough SP, Dogan B, Denkers EY, Bowman D, Scherl EJ, Simpson KW (2012). "Inflammation drives dysbiosis and bacterial invasion in murine models of ileal Crohn's disease". *PLoS ONE*. **7** (7): e41594. doi:10.1371/journal.pone.0041594. PMC 3404971. PMID 22848538.
82. ^ Barnich N, Darfeuille-Michaud A (January 2007). "Adherent-invasive Escherichia coli and Crohn's disease". *Current Opinion in Gastroenterology*. **23** (1): 16–20. doi:10.1097/MOG.0b013e3280105a38. PMID 17133079.
83. ^ Cenac N, Andrews CN, Holzhausen M, Chapman K, Cottrell G, Andrade-Gordon P, Steinhoff M, Barbara G, Beck P, Bunnett NW, Sharkey KA, Ferraz JG, Shaffer E, Vergnolle N (March 2007). "Role for protease activity in visceral pain in irritable bowel

ed. "Strategies for detecting colon cancer and/or dysplasia in patients with inflammatory bowel disease". *Cochrane Database Syst Rev* (2): CD000279. doi:10.1002/14651858.CD000279.pub3. PMID 16625534.

174. ^ Zisman TL, Rubin DT; Rubin (2008). "Colorectal cancer and dysplasia in inflammatory bowel disease". *World Journal of Gastroenterology*. **14** (17): 2662–9. doi:10.3748/wjg.14.2662. PMC 2709054. PMID 18461651.
175. ^ Axelrad, JE; Lichtiger, S; Yajnik, V (28 May 2016). "Inflammatory bowel disease and cancer: The role of inflammation, immunosuppression, and cancer treatment.". *World journal of gastroenterology* (Review). **22** (20): 4794–801. doi:10.3748/wjg.v22.i20.4794. PMC 4873872. PMID 27239106.
176. ^ Evans JP, Steinhart AH, Cohen Z, McLeod RS; Steinhart; Cohen; McLeod (2003). "Home Total Parenteral Nutrition an Alternative to Early Surgery for Complicated Inflammatory Bowel Disease". *Journal of Gastrointestinal Surgery*. **7** (4): 562–6. doi:10.1016/S1091-255X(02)00132-4. PMID 12763417.
177. ^ Carrillo, Maria (September 1, 1985). "Man of Many Problems Comes to City for Help". *Richmond Times-Dispatch*. Richmond, Virginia, USA. p. B1.
178. ^ "Kay, Laura Lynn". *Richmond Times-Dispatch*. Richmond, Virginia, USA. April 3, 2014.
Loebenberg, Priscilla (March 2, 2014). "Doris L. Johnson, 82, of Westminster". *Carroll County Times*. Westminster, Maryland, USA.
Berrier Jr., Ralph (December 31, 2013). "In memoriam: Dan Hodges Jr.". *The Roanoke Times*. Roanoke, Virginia, USA.
"Cynthia Meredith Routt". *Daily Press*. Newport News, Virginia, USA. May 4, 2014. p. A11.
179. ^ Kaplan, C (2005-10-21). "IBD and Pregnancy: What You Need to Know". Crohn's and Colitis Foundation of America. Archived from the original on 2012-02-17. Retrieved 2009-11-07.
180. ^ *a b* Hiatt RA, Kaufman L; Kaufman (1988). "Epidemiology of inflammatory bowel disease in a defined northern California population". *Western Journal of Medicine*. **149** (5): 541–6. PMC 1026530. PMID 3250100.
181. ^ Moum B, Vatn MH, Ekbom A, Aadland E, Fausa O, Lygren I, Stray N, Sauar J, Schulz T; Vatn; Ekbom; Aadland; Fausa; Lygren; Stray; Sauar; Schulz (1996). "Incidence of Crohn's disease in four counties in southeastern Norway, 1990-93. A prospective population-based study. The Inflammatory Bowel South-Eastern Norway (IBSEN) Study Group of Gastroenterologists". *Scandinavian Journal of Gastroenterology*. **31** (4): 355–61. doi:10.3109/00365529609006410. PMID 8726303.
182. ^ Shivananda S, Lennard-Jones J, Logan R, Fear N,

syndrome". *J. Clin. Invest*. **117** (3): 636–47. doi:10.1172/JCI29255. PMC 1794118. PMID 17304351.

84. ^ Cenac N, Coelho AM, Nguyen C, Compton S, Andrade-Gordon P, MacNaughton WK, Wallace JL, Hollenberg MD, Bunnett NW, Garcia-Villar R, Bueno L, Vergnolle N (November 2002). "Induction of Intestinal Inflammation in Mouse by Activation of Proteinase-Activated Receptor-2". *Am. J. Pathol*. **161** (5): 1903–15. doi:10.1016/S0002-9440(10)64466-5. PMC 1850779. PMID 12414536.
85. ^ Boorom KF, Smith H, Nimri L, Viscogliosi E, Spanakos G, Parkar U, Li LH, Zhou XN, Ok UZ, Leelayoova S, Jones MS (October 2008). "Oh my aching gut: irritable bowel syndrome, Blastocystis, and asymptomatic infection". *Parasit Vectors*. **1** (1): 40. doi:10.1186/1756-3305-1-40. PMC 2627840. PMID 18937874.
86. ^ Hugot JP, Alberti C, Berrebi D, Bingen E, Cézard JP (2003). "Crohn's disease: the cold chain hypothesis". *Lancet*. **362** (9400): 2012–5. doi:10.1016/S0140-6736(03)15024-6. PMID 14683664.
87. ^ "Fridges blamed for Crohn's disease rise". Medical News Today. 2003-12-12.
88. ^ Forbes A, Kalantzis T (2005). "Crohn's disease: The cold chain hypothesis". *International Journal of Colorectal Disease*. **21** (5): 399–401. doi:10.1007/s00384-005-0003-7. PMID 16059694.
89. ^ Subramanian S, Roberts CL, Hart CA, Martin HM, Edwards SW, Rhodes JM, Campbell BJ (2007). "Replication of Colonic Crohn's Disease Mucosal Escherichia coli Isolates within Macrophages and Their Susceptibility to Antibiotics". *Antimicrobial Agents and Chemotherapy*. **52** (2): 427–34. doi:10.1128/AAC.00375-07. PMC 2224732. PMID 18070962.
90. ^ Mpofu CM, Campbell BJ, Subramanian S, Marshall-Clarke S, Hart CA, Cross A, Roberts CL, McGoldrick A, Edwards SW, Rhodes JM (2007). "Microbial Mannan Inhibits Bacterial Killing by Macrophages: A Possible Pathogenic Mechanism for Crohn's Disease". *Gastroenterology*. **133** (5): 1487–98. doi:10.1053/j.gastro.2007.08.004. PMID 17919633.
91. ^ "New insights into Crohn's Disease". Archived from the original on September 23, 2013.
92. ^ "Possible links between Crohn's disease and Paratuberculosis" (PDF). European Commission Directorate-General Health & Consumer Protection. Retrieved 2009-11-07.
93. ^ Gui GP, Thomas PR, Tizard ML, Lake J, Sanderson JD, Hermon-Taylor J (1997). "Two-year-outcomes analysis of Crohn's disease treated with rifabutin and macrolide antibiotics". *Journal of Antimicrobial Chemotherapy*. **39** (3): 393–400. doi:10.1093/jac/39.3.393. PMID 9096189.
94. ^ Kumamoto, Carol A. (2011-08-01). "Inflammation

Price A, Carpenter L, van Blankenstein M; Lennard-Jones; Logan; Fear; Price; Carpenter; Van Blankenstein (1996). "Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD)". *Gut*. **39** (5): 690–7. doi:10.1136/gut.39.5.690. PMC 1383393. PMID 9014768.

183. ^ Yang H, McElree C, Roth MP, Shanahan F, Targan SR, Rotter JI; McElree; Roth; Shanahan; Targan; Rotter (1993). "Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews". *Gut*. **34** (4): 517–24. doi:10.1136/gut.34.4.517. PMC 1374314. PMID 8491401.
184. ^ Seksik P, Nion-Larmurier I, Sokol H, Beaugerie L, Cosnes J; Nion-Larmurier; Sokol; Beaugerie; Cosnes (2009). "Effects of light smoking consumption on the clinical course of Crohn's disease". *Inflamm. Bowel Dis*. **15** (5): 734–41. doi:10.1002/ibd.20828. PMID 19067428.
185. ^ "Crohn's disease manifests differently in boys and girls". Crohn's and Colitis Foundation of America.
186. ^ "Who is affected by Crohn's disease". Healthwise.
187. ^ Satsangi J, Jewell DP, Bell JI; Jewell; Bell (1997). "The genetics of inflammatory bowel disease". *Gut*. **40** (5): 572–4. doi:10.1136/gut.40.5.572. PMC 1027155. PMID 9203931.
188. ^ Tysk C, Lindberg E, Järnerot G, Flodérus-Myrhed B; Lindberg; Järnerot; Flodérus-Myrhed (1988). "Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking". *Gut*. **29** (7): 990–6. doi:10.1136/gut.29.7.990. PMC 1433769. PMID 3396969.
189. ^ Burisch, Johan; Jess, Tine; Martinato, Matteo; Lakatos, Peter L. (2013). "The burden of inflammatory bowel disease in Europe". *Journal of Crohn's and Colitis*. **7** (4): 322–337. doi:10.1016/j.crohns.2013.01.010. ISSN 1873-9946. PMID 23395397.
190. ^ Kirsner JB (1988). "Historical aspects of inflammatory bowel disease". *J. Clin. Gastroenterol*. **10** (3): 286–97. doi:10.1097/00004836-198806000-00012. PMID 2980764.
191. ^ Lichtarowicz, A.M.; Mayberry, J.F. (August 1, 1988). "Antoni Leśniowski and his contribution to regional enteritis (Crohn's disease)". *Journal of the Royal Society of Medicine*. **81** (8): 468–470. PMC 1291720. PMID 3047387.
192. ^ *a b* Agrawal G, Borody TJ, Chamberlin W; Borody; Chamberlin (2014). "'Global warming' to *Mycobacterium avium* subspecies *paratuberculosis*". *Future Microbiology*. **9** (7): 829–832. doi:10.2217/fmb.14.52. ISSN 1746-0913. PMID 25156371.

and gastrointestinal Candida colonization". *Current opinion in microbiology*. **14** (4): 386–391. doi:10.1016/j.mib.2011.07.015. ISSN 1369-5274. PMC 3163673. PMID 21802979.

95. ^ a b Shoda R, Matsueda K, Yamato S, Umeda N (1996). "Epidemiologic analysis of Crohn disease in Japan: increased dietary intake of n-6 polyunsaturated fatty acids and animal protein relates to the increased incidence of Crohn disease in Japan". *The American Journal of Clinical Nutrition*. **63** (5): 741–5. PMID 8615358.
96. ^ Lesko SM, Kaufman DW, Rosenberg L, Helmrich SP, Miller DR, Stolley PD, Shapiro S (1985). "Evidence for an increased risk of Crohn's disease in oral contraceptive users". *Gastroenterology*. **89** (5): 1046–9. PMID 4043662.
97. ^ Reddy D, Siegel CA, Sands BE, Kane S (July 2006). "Possible association between isotretinoin and inflammatory bowel disease". *The American journal of gastroenterology*. **101** (7): 1569–73. doi:10.1111/j.1572-0241.2006.00632.x. PMID 16863562.
98. ^ Borobio E, Arín A, Valcayo A, Iñarrairaegui M, Nantes O, Prieto C (2004). "[Isotretinoin and ulcerous colitis]". *An Sist Sanit Navar* (in Spanish). **27** (2): 241–3. doi:10.4321/S1137-66272004000300009. PMID 15381956.
99. ^ Reniers DE, Howard JM (October 2001). "Isotretinoin-induced inflammatory bowel disease in an adolescent". *Annals of Pharmacotherapy*. **35** (10): 1214–6. doi:10.1345/aph.10368. PMID 11675849.
100. ^ "Crohn's Disease". National Digestive Diseases Information Clearinghouse. Retrieved 13 November 2012.
101. ^ Lomer MC, Hutchinson C, Volkert S, Greenfield SM, Catterall A, Thompson RP, Powell JJ (December 2004). "Dietary sources of inorganic microparticles and their intake in healthy subjects and patients with Crohn's disease". *Br. J. Nutr.* **92** (6): 947–55. doi:10.1079/bjn20041276. PMID 15613257.
102. ^ Powell JJ, Thoree V, Pele LC (October 2007). "Dietary microparticles and their impact on tolerance and immune responsiveness of the gastrointestinal tract". *Br. J. Nutr.* 98 Suppl 1: S59–63. doi:10.1017/S0007114507832922. PMC 2737314. PMID 17922962.
103. ^ Elson CO, Cong Y, Weaver CT, Schoeb TR, McClanahan TK, Fick RB, Kastelein RA (2007). "Monoclonal anti-interleukin 23 reverses active colitis in a T cell-mediated model in mice". *Gastroenterology*. **132** (7): 2359–70. doi:10.1053/j.gastro.2007.03.104. PMID 17570211.
104. ^ Crawford JM. "The Gastrointestinal tract, Chapter 17". In Cotran RS, Kumar V, Robbins SL. *Robbins Pathologic Basis of Disease: 5th Edition*. W.B. Saunders and Company, Philadelphia, 1994.
105. ^
193. ^ Scribano, ML; Prantera, C (Feb 7, 2013). "Use of antibiotics in the treatment of Crohn's disease". *World journal of gastroenterology : WJG*. **19** (5): 648–53. doi:10.3748/wjg.v19.i5.648. PMID 23429474.
194. ^ Chamberlin, W; Borody, TJ; Campbell, J (Nov 2011). "Primary treatment of Crohn's disease: combined antibiotics taking center stage". *Expert review of clinical immunology*. **7** (6): 751–60. doi:10.1586/eci.11.43. PMID 22014016.
195. ^ Bull TJ, Gilbert SC, Sridhar S, Linedale R, Dierkes N, Sidi-Boumedine K, Hermon-Taylor J; Gilbert; Sridhar; Linedale; Dierkes; Sidi-Boumedine; Hermon-Taylor (2007). "'A novel multi-antigen virally vectored vaccine against *Mycobacterium avium* subspecies *paratuberculosis*". *PLoS ONE*. **2** (11): e1229. doi:10.1371/journal.pone.0001229. PMC 2082073. PMID 18043737.
196. ^ Hultén, K.; Almashhrawi, A.; El-Zaatari, FA.; Graham, DY. (Mar 2000). "Antibacterial therapy for Crohn's disease: a review emphasizing therapy directed against mycobacteria". *Dig Dis Sci*. **45** (3): 445–56. PMID 10749316.
197. ^ Pommerville, Jeffrey (2014). *Fundamentals of microbiology*. Burlington, MA: Jones & Bartlett Learning. ISBN 9781449688615.
198. ^ Elliott, David E.; Weinstock, Joel V. (2012). "Where are we on worms?". *Current Opinion in Gastroenterology*. **28** (6): 551–556. doi:10.1097/MOG.0b013e3283572f73. ISSN 0267-1379.
199. ^ Weinstock, Joel V.; Elliott, David E. (2013). "Translatability of helminth therapy in inflammatory bowel diseases". *International Journal for Parasitology*. **43** (3-4): 245–251. doi:10.1016/j.ijpara.2012.10.016. ISSN 0020-7519. "Early clinical trials suggested that exposure to helminths such as Trichuris suis or Necator americanus can improve IBD."
200. ^ Biosciences, Coronado. "Coronado Biosciences Announces Top-Line Results From Its TRUST-I Phase 2 Clinical Trial of TSO for the Treatment of Crohn's Disease". Retrieved 2016-08-16.
201. ^ Biosciences, Coronado. "Coronado Biosciences Announces Independent Data Monitoring Committee Recommendation to Discontinue Falk Phase 2 Trial of TSO in Crohn's Disease". Retrieved 2016-08-16.
202. ^ *Massa F, Monory K; Monory (2007). "Endocannabinoids and the gastrointestinal tract". *Journal of Endocrinological Investigation*. **29** (Suppl): 47–57. PMID 16751708.
203. ^ Massa F, Storr M, Lutz B; Storr; Lutz (2005). "The endocannabinoid system in the physiology and pathophysiology of the gastrointestinal tract". *Journal of Molecular Medicine*. **83** (12): 944–54. doi:10.1007/s00109-005-0698-5. PMID 16133420.
204. ^ Izzo AA, Coutts AA; Coutts (2005). "Cannabinoids and the digestive tract". *Handbook of Experimental*

http://www.plos.org/media/press/2012/PLoS_%20HMP_Collection_Manuscript_Summaries.pdf
106. ^ HCP: Pill Cam, Capsule Endoscopy, Esophageal Endoscopy
107. ^ Scheinfeld NS, Teplitz E, McClain SA (November 2001). "Crohn's disease and lichen nitidus: a case report and comparison of common histopathologic features". *Inflammatory Bowel Diseases*. **7** (4): 314–8. doi:10.1097/00054725-200111000-00006. PMID 11720321.
108. ^ Tan, WC.; Allan, RN. (Oct 1993). "Diffuse jejunoileitis of Crohn's disease.". *Gut*. **34** (10): 1374–8. doi:10.1136/gut.34.10.1374. PMID 8244104.
109. ^ *a b* Gasche C, Scholmerich J, Brynskov J, D'Haens G, Hanauer SB, Irvine EJ, Jewell DP, Rachmilewitz D, Sachar DB, Sandborn WJ, Sutherland LR (2007). "A simple classification of Crohn's disease: Report of the *Pharmacology*. Handbook of Experimental Pharmacology. **168** (168): 573–98. doi:10.1007/3-540-26573-2_19. ISBN 3-540-22565-X. PMID 16596788.
205. ^ Srinivasan, R; Akobeng, AK (Apr 15, 2009). "Thalidomide and thalidomide analogues for induction of remission in Crohn's disease". *The Cochrane database of systematic reviews* (2): CD007350. doi:10.1002/14651858.CD007350.pub2. PMID 19370684.
206. ^ Akobeng, AK; Stokkers, PC (Apr 15, 2009). "Thalidomide and thalidomide analogues for maintenance of remission in Crohn's disease". *The Cochrane database of systematic reviews* (2): CD007351. doi:10.1002/14651858.CD007351.pub2. PMID 19370685.

## External links [edit]

- Crohn's disease at DMOZ

Wikimedia Commons has media related to *Crohn's disease*.

| v · t · e · | **Inflammatory bowel disease: Crohn's disease and ulcerative colitis** |
|---|---|
| **Main** | Crohn's Disease Activity Index · Treatment (Biological therapy · Crohn's disease · · |
| **Complications** | Abdominal pain · Anal abscess · Erythema nodosum · Fistula · Granuloma · Ileum · Ileitis · Malabsorption · Proctitis · Protein losing enteropathy · Pyoderma gangrenosum · Sacroiliitis · Short bowel syndrome · Small bowel obstruction · Stenosis · |
| **History** | Giovanni Battista Morgagni · Burrill Bernard Crohn · |
| **Organizations** | Crohn's and Colitis Foundation of America · Digestive Disorders Foundation · National Society for Colitis and Crohn's Disease · Crohn's and Colitis Canada · |
| **People** | List of people diagnosed with Crohn's disease · List of people diagnosed with ulcerative colitis · Deaths from Crohn's disease · |

| v · t · e · | **Diseases of the digestive system (primarily K20–K93, 530–579)** | |
|---|---|---|
| **Upper GI tract** | **Esophagus** | Esophagitis (Candidal · Eosinophilic · Herpetiform · · *Rupture* (Boerhaave syndrome · Mallory-Weiss syndrome · · UES (Zenker's diverticulum · · LES (Barrett's esophagus · · Esophageal motility disorder (Nutcracker esophagus · Achalasia · Diffuse esophageal spasm · Gastroesophageal reflux disease (GERD) · · Laryngopharyngeal reflux (LPR) · Esophageal stricture · Megaesophagus · |
| | **Stomach** | Gastritis (Atrophic · Ménétrier's disease · Gastroenteritis · · Peptic (gastric) ulcer (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
| | **Small intestine** | Enteritis (Duodenitis · Jejunitis · Ileitis · · Peptic (duodenal) ulcer (Curling's ulcer · · Malabsorption: Coeliac · Tropical sprue · Blind loop syndrome · |

| | | |
|---|---|---|
| **Lower GI tract: Intestinal/ Enteropathy** | **(Duodenum/Jejunum/Ileum)** | Small bowel bacterial overgrowth syndrome · Whipple's · Short bowel syndrome · Steatorrhea · Milroy disease · Bile acid malabsorption · |
| | **Large intestine (Appendix/Colon)** | Appendicitis · Colitis (Pseudomembranous · Ulcerative · Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (IBS · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
| | **Large and/or small** | Enterocolitis (Necrotizing · · Gastroenterocolitis · IBD (**Crohn's disease** · · *Vascular*: Abdominal angina · Mesenteric ischemia · Angiodysplasia · Bowel obstruction: Ileus · Intussusception · Volvulus · Fecal impaction · Constipation · Diarrhea (Infectious · · Intestinal adhesions · |
| | **Rectum** | Proctitis (Radiation proctitis · · Proctalgia fugax · Rectal prolapse · Anismus · |
| | **Anal canal** | Anal fissure/Anal fistula · Anal abscess · Anal dysplasia · Pruritus ani · |
| **GI bleeding/BIS** | | Upper (Hematemesis · Melena · · Lower (Hematochezia · · |
| **Accessory** | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · Acute liver failure · · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |
| | **Gallbladder** | Cholecystitis · Gallstones/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · Gallstones/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
| | **Pancreatic** | Pancreatitis (Acute · Chronic · Hereditary · Pancreatic abscess · · Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |
| **Abdominopelvic** | **Hernia** | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |

v · t · e · **Oral and maxillofacial pathology (K00–K06, K11–K14, 520–525, 527–529)**

**Lips**

Cheilitis (Actinic · Angular · Plasma cell · · Cleft lip · Congenital lip pit · Eclabium · Herpes labialis · Macrocheilia · Microcheilia · Nasolabial cyst · Sun poisoning · Trumpeter's wart ·

**Tongue**

Ankyloglossia · Black hairy tongue · Caviar tongue · Crenated tongue · Cunnilingus tongue · Fissured tongue · Foliate papillitis · Glossitis (Geographic tongue · Median rhomboid glossitis · Transient lingual papillitis · · Glossoptosis · Hypoglossia · Lingual thyroid · Macroglossia · Microglossia · Rhabdomyoma ·

**Palate**

Bednar's aphthae · Cleft palate · High-arched palate · Palatal cysts of the newborn · Inflammatory papillary hyperplasia · Stomatitis nicotina · Torus palatinus ·

**Oral mucosa** - *Lining of mouth*

Amalgam tattoo · Angina bullosa haemorrhagica · Behçet syndrome · Bohn's nodules · Burning mouth syndrome · Candidiasis · Condyloma acuminatum · Darier's disease · Epulis fissuratum · Erythema multiforme · Erythroplakia · Fibroma (Giant-cell · · Focal epithelial hyperplasia · Fordyce spots · Hairy leukoplakia · Hand, foot and mouth disease · Hereditary benign intraepithelial dyskeratosis · Herpangina · Herpes zoster · Intraoral dental sinus · Leukoedema · Leukoplakia · Lichen planus · Linea alba · Lupus erythematosus · Melanocytic nevus · Melanocytic oral lesion · Molluscum contagiosum · Morsicatio buccarum · Oral cancer (*Benign:* Squamous cell papilloma · Keratoacanthoma · *Malignant:* Adenosquamous carcinoma · Basaloid squamous carcinoma · Mucosal melanoma · Spindle cell carcinoma · Squamous cell carcinoma · Verrucous carcinoma · · Oral florid papillomatosis · Oral melanosis (Smoker's melanosis · · Pemphigoid (Benign mucous membrane · · Pemphigus · Plasmoacanthoma · Stomatitis (Aphthous · Denture-related · Herpetic · · Smokeless tobacco keratosis · Submucous fibrosis · Ulceration · Verruca vulgaris · Verruciform xanthoma · White sponge nevus ·

**Teeth (pulp, dentin, enamel)**

Amelogenesis imperfecta · Ankylosis · Anodontia · Caries (Early childhood caries · · Concrescence · Failure of eruption of teeth · Dens evaginatus (Talon cusp · · Dentin dysplasia · Dentin hypersensitivity · Dentinogenesis imperfecta · Dilaceration · Discoloration · Ectopic enamel · Enamel hypocalcification · Enamel hypoplasia (Turner's hypoplasia · · Enamel pearl · Fluorosis · Fusion · Gemination · Hyperdontia · Hypodontia (Maxillary lateral incisor agenesis · · Impaction (Wisdom tooth impaction · · Macrodontia · Meth mouth · Microdontia · Odontogenic tumors (Keratocystic odontogenic tumour · · Odontoma (Dens in dente · · Open contact · Premature eruption (Neonatal teeth · · Pulp calcification (Pulp stone · · Pulp canal obliteration · Pulp necrosis · Pulp polyp · Pulpitis · Regional odontodysplasia · Resorption · Shovel-shaped incisors · Supernumerary root · Taurodontism · Trauma (Avulsion · Cracked tooth syndrome · Vertical root fracture · Occlusal · · Tooth loss (Edentulism · · Tooth wear (Abrasion · Abfraction · Acid erosion · Attrition · ·

**Periodontium (gingiva, periodontal ligament, cementum, alveolus)** - *Gums and tooth-supporting structures*

Cementicle · Cementoblastoma (Gigantiform · · Cementoma · Eruption cyst · Epulis (Pyogenic granuloma · Congenital epulis · · Gingival enlargement · Gingival cyst of the adult · Gingival cyst of the newborn · Gingivitis (Desquamative · Granulomatous · Plasma cell · · Hereditary gingival fibromatosis · Hypercementosis · Hypocementosis · Linear gingival erythema · Necrotizing periodontal diseases (Acute necrotizing ulcerative gingivitis · · Pericoronitis · Peri-implantitis · Periodontal abscess · Periodontal trauma · Periodontitis (Aggressive · As a manifestation of systemic disease · Chronic · · Perio-endo lesion · Teething ·

**Periapaical, mandibular and maxillary hard tissues -** *Bones of jaws*

Agnathia · Alveolar osteitis · Buccal exostosis · Cherubism · Idiopathic osteosclerosis · Mandibular fracture · Micrognathia · Micrognathia · Intraosseous cysts (*Odontogenic:* periapical · Dentigerous · Buccal bifurcation · Lateral periodontal · Globulomaxillary · Calcifying odontogenic · Glandular odontogenic · *Non-odontogenic:* Nasopalatine duct · Median mandibular · Median palatal · Traumatic bone · · Osteoma · Osteomyelitis · Osteonecrosis (Bisphosphonate-associated · Neuralgia-inducing cavitational osteonecrosis · Osteoradionecrosis · · Osteoporotic bone marrow defect · Paget's disease of bone · Periapical abscess (Phoenix abscess · · Periapical periodontitis · Stafne defect · Torus mandibularis ·

**Temporomandibular joints, muscles of mastication and malocclusions -** *Jaw joints, chewing muscles and bite abnormalities*

Bruxism · Condylar resorption · Mandibular dislocation · Malocclusion (Crossbite · Open bite · Overbite · Overjet · Prognathia · Retrognathia · · Temporomandibular joint dysfunction ·

**Salivary glands**

Benign lymphoepithelial lesion · Ectopic salivary gland tissue · Frey's syndrome · HIV salivary gland disease · Necrotizing sialometaplasia · Mucocele (Ranula · · Pneumoparotitis · Salivary duct stricture · Salivary gland aplasia · Salivary gland atresia · Salivary gland diverticulum · Salivary gland fistula · Salivary gland hyperplasia · Salivary gland hypoplasia · Salivary gland neoplasms (*Benign:* Basal cell adenoma · Canalicular adenoma · Ductal papilloma · Monomorphic adenoma · Myoepithelioma · Oncocytoma · Papillary cystadenoma lymphomatosum · Pleomorphic adenoma · Sebaceous adenoma · *Malignant:* Acinic cell carcinoma · Adenocarcinoma · Adenoid cystic carcinoma · Carcinoma ex pleomorphic adenoma · Lymphoma · Mucoepidermoid carcinoma · · Sclerosing polycystic adenosis · Sialadenitis (Parotitis · Chronic sclerosing sialadenitis · · Sialectasis · Sialocele · Sialodochitis · Sialosis · Sialolithiasis · Sjögren's syndrome ·

**Orofacial soft tissues -** *Soft tissues around the mouth*

Actinomycosis · Angioedema · Basal cell carcinoma · Cutaneous sinus of dental origin · Cystic hygroma · Gnathophyma · Ludwig's angina · Macrostomia · Melkersson–Rosenthal syndrome · Microstomia · Noma · **Oral Crohn's disease** · Orofacial granulomatosis · Perioral dermatitis · Pyostomatitis vegetans ·

**Other**

Eagle syndrome · Hemifacial hypertrophy · Facial hemiatrophy · Oral manifestations of systemic disease ·

**Authority control** NDL: 00561182 ·

Categories: Abdominal pain | Autoimmune diseases | Inflammations | Membrane transport protein disorders | Noninfective enteritis and colitis | Steroid-responsive inflammatory conditions




# Diarrhea



From Wikipedia, the free encyclopedia

*For other uses, see Diarrhea (disambiguation).*

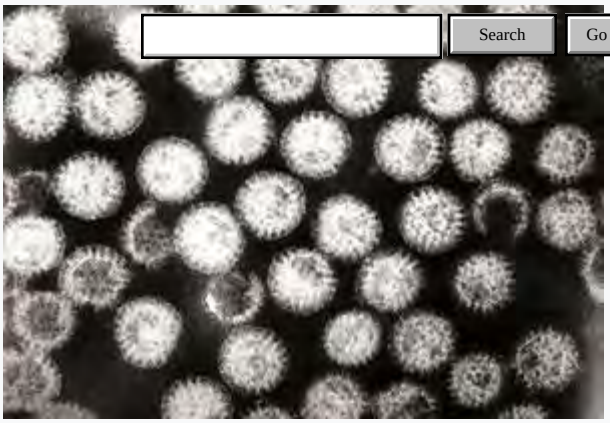
**Diarrhea**, also spelled **diarrhoea**, is the condition of having at least three loose or liquid bowel movements each day. It often lasts for a few days and can result in dehydration due to fluid loss. Signs of dehydration often begin with loss of the normal stretchiness of the skin and irritable behaviour. This can progress to decreased urination, loss of skin color, a fast heart rate, and a decrease in responsiveness as it becomes more severe. Loose but non-watery stools in babies who are breastfed, however, may be normal.[2]

The most common cause is an infection of the intestines due to either a virus, bacteria, or parasite; a condition known as gastroenteritis. These infections are often acquired from food or water that has been contaminated by stool, or directly from another person who is infected. It may be divided into three types: short duration watery diarrhea, short duration bloody diarrhea, and if it lasts for more than two weeks, persistent diarrhea. The short duration watery diarrhea may be due to an infection by cholera, although this is rare in the developed world. If blood is present it is also known as dysentery.[2] A number of non-infectious causes may also result in diarrhea, including hyperthyroidism, lactose intolerance, inflammatory bowel disease, a number of medications, and irritable bowel syndrome.[3] In most cases, stool cultures are not required to confirm the exact cause.[4]

Prevention of infectious diarrhea is by improved sanitation, clean drinking water, and hand washing with soap. Breastfeeding for at least six months is also recommended as is vaccination against rotavirus. Oral rehydration solution (ORS), which is clean water with modest amounts of salts and sugar, is the treatment of choice. Zinc tablets are also recommended.[2] These treatments have been estimated to have saved 50 million children in the past 25 years.[1] When people have diarrhea it is recommended that they continue to eat healthy food and babies continue to be breastfed.[2] If commercial ORS are not available, homemade solutions may be used.[5] In those with severe dehydration, intravenous fluids may be required.[2] Most cases; however, can be managed well with fluids by mouth.[6] Antibiotics, while rarely used, may be recommended in a few cases such as those who have bloody diarrhea and a high fever, those with severe diarrhea following travelling, and those who grow specific bacteria or parasites in their stool.[4] Loperamide may help decrease the number of bowel movements but is not [4]

## Variants

## Diarrhea



An electron micrograph of rotavirus, the cause of nearly 40% of hospitalizations from diarrhea in children under five.[1]

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Infectious disease, gastroenterology |
| **ICD-10** | A09, K59.1 |
| **ICD-9-CM** | 787.91 |
| **DiseasesDB** | 3742 |
| **MedlinePlus** | 003126 |
| **eMedicine** | ped/583 |
| **Patient UK** | Diarrhea |
| **MeSH** | D003967 |

[edit on Wikidata]

recommended in those with severe disease.

About 1.7 to 5 billion cases of diarrhea occur per year.[2][3][7] It is most common in developing countries, where young children get diarrhea on average three times a year.[2] Total deaths from diarrhea are estimated at 1.26 million in 2013 – down from 2.58 million in 1990.[8] In 2012, it was the second most common cause of deaths in children younger than five (0.76 million or 11%).[2][9] Frequent episodes of diarrhea are also a common cause of malnutrition and the most common cause in those younger than five years of age.[2] Other long term problems that can result include stunted growth and poor intellectual development.[9]

**Contents**





# Definition

Diarrhea is defined by the World Health Organization as having three or more loose or liquid stools per day, or as having more stools than is normal for that person.[2]

Acute diarrhea is defined as an abnormally frequent discharge of semisolid or fluid fecal matter from the bowel, lasting less than 14 days, by World

Bristol stool chart

Gastroenterology Organization.[10]

Polski
Português
Română
Русский
Sesotho sa Leboa
Shqip
Sicilianu
Simple English
Slovenčina
Slovenščina
Soomaaliga
Español
Srpski / Srpski
српскохрватски / српскохрватски
Basa Sunda
Suomi
Svenska
Türkçe
Українська
Tiếng Việt
Volapük
Yorùbá
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## Secretory

Secretory diarrhea means that there is an increase in the active secretion, or there is an inhibition of absorption. There is little to no structural damage. The most common cause of this type of diarrhea is a cholera toxin that stimulates the secretion of anions, especially chloride ions. Therefore, to maintain a charge balance in the gastrointestinal tract, sodium is carried with it, along with water. In this type of diarrhea intestinal fluid secretion is isotonic with plasma even during fasting.[11] It continues even when there is no oral food intake.

## Osmotic

Osmotic diarrhea occurs when too much water is drawn into the bowels. If a person drinks solutions with excessive sugar or excessive salt, these can draw water from the body into the bowel and cause osmotic diarrhea.[12] Osmotic diarrhea can also be the result of maldigestion (e.g., pancreatic disease or Coeliac disease), in which the nutrients are left in the lumen to pull in water. Or it can be caused by osmotic laxatives (which work to alleviate constipation by drawing water into the bowels). In healthy individuals, too much magnesium or vitamin C or undigested lactose can produce osmotic diarrhea and distention of the bowel. A person who has lactose intolerance can have difficulty absorbing lactose after an extraordinarily high intake of dairy products. In persons who have fructose malabsorption, excess fructose intake can also cause diarrhea. High-fructose foods that also have a high glucose content are more absorbable and less likely to cause diarrhea. Sugar alcohols such as sorbitol (often found in sugar-free foods) are difficult for the body to absorb and, in large amounts, may lead to osmotic diarrhea.[11] In most of these cases, osmotic diarrhea stops when the offending agent (e.g. milk, sorbitol) is stopped.

## Exudative

Exudative diarrhea occurs with the presence of blood and pus in the stool. This occurs with inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis, and other severe infections such as *E. coli* or other forms of food poisoning.[11]

## Inflammatory

Inflammatory diarrhea occurs when there is damage to the mucosal lining or brush border, which leads to a passive loss of protein-rich fluids and a decreased ability to absorb these lost fluids. Features of all three of the other types of diarrhea [*clarification needed*] can be found in this type of diarrhea. It can be caused by bacterial infections, viral infections, parasitic infections, or autoimmune problems such as inflammatory bowel diseases. It can also be caused by tuberculosis, colon cancer, and enteritis.[*citation needed*]

## Dysentery

If there is blood visible in the stools, it is also known as dysentery. The blood is a trace of an invasion of bowel tissue. Dysentery is a symptom of, among others, *Shigella*, *Entamoeba histolytica*, and *Salmonella*.

# Health effects

Diarrheal disease may have a negative impact on both physical fitness and mental development. "Early childhood malnutrition resulting from any cause reduces physical fitness and work productivity in adults,"[13] and diarrhea is a primary cause of childhood malnutrition.[14] Further, evidence suggests that diarrheal disease has significant impacts on mental development and health; it has been shown that, even when controlling for helminth infection and early breastfeeding, children who had experienced severe diarrhea had significantly lower scores on a series of tests of intelligence.[13][15]

# Differential diagnosis

Acute diarrhea is most commonly due to viral gastroenteritis with rotavirus, which accounts for 40% of cases in children under five.[1] (p. 17) In travelers however bacterial infections predominate.[16] Various toxins such as mushroom poisoning and drugs can also cause acute diarrhea.

Chronic diarrhea can be the part of the presentations of a number of chronic medical conditions affecting the intestine. Common causes include ulcerative colitis, Crohn's disease, microscopic colitis, celiac disease, irritable bowel syndrome and bile acid malabsorption.

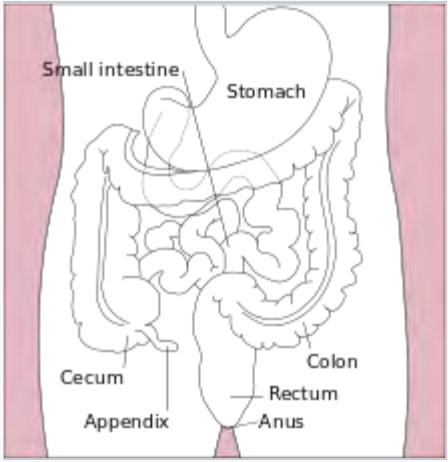


Diagram of the human gastrointestinal tract.

## Infections

*Main article: Infectious diarrhea*

There are many causes of infectious diarrhea, which include viruses, bacteria and parasites.[17] Infectious diarrhea is frequently referred to as gastroenteritis.[18] Norovirus is the most common cause of viral diarrhea in adults,[19] but rotavirus is the most common cause in children under five years old.[20] Adenovirus types 40 and 41,[21] and astroviruses cause a significant number of infections.[22]

*Campylobacter* spp. are a common cause of bacterial diarrhea, but infections by *Salmonella* spp., *Shigella* spp. and some strains of *Escherichia coli* are also a frequent cause.[23]

In the elderly, particularly those who have been treated with antibiotics for unrelated infections, a toxin produced by *Clostridium difficile* often causes severe diarrhea.[24]

Parasites, particularly protozoa (e.g., *Cryptosporidium* spp., *Giardia* spp., *Entamoeba histolytica*, *Blastocystis* spp., *Cyclospora cayetanensis*), are frequently the cause of diarrhea that involves chronic infection. The broad-spectrum antiparasitic agent nitazoxanide has shown efficacy against many diarrhea-causing parasites.[25]

Other infectious agents, such as parasites or bacterial toxins, may exacerbate symptoms.[16] In sanitary living conditions where there is ample food and a supply of clean water, an otherwise healthy person usually recovers from viral infections in a few days. However, for ill or malnourished individuals, diarrhea can lead to severe dehydration and can become life-threatening.[26]

## Malabsorption

*Main article: Malabsorption*

Malabsorption is the inability to absorb food fully, mostly from disorders in the small bowel, but also due to maldigestion from diseases of the pancreas.

Causes include:

- *enzyme deficiencies or mucosal abnormality*, as in food allergy and food intolerance, e.g. celiac disease (gluten intolerance), lactose intolerance (intolerance to milk sugar, common in non-Europeans), and fructose malabsorption.
- *pernicious anemia*, or impaired bowel function due to the inability to absorb vitamin $B_{12}$,
- *loss of pancreatic secretions*, which may be due to cystic fibrosis or pancreatitis,
- *structural defects*, like short bowel syndrome (surgically removed bowel) and radiation fibrosis, such as usually follows cancer treatment and other drugs, including agents used in chemotherapy; and
- *certain drugs*, like orlistat, which inhibits the absorption of fat.

### Inflammatory bowel disease

*Main article: Inflammatory bowel disease*

The two overlapping types here are of unknown origin:

- Ulcerative colitis is marked by chronic bloody diarrhea and inflammation mostly affects the distal colon near the rectum.
- Crohn's disease typically affects fairly well demarcated segments of bowel in the colon and often affects the end of the small bowel.

### Irritable bowel syndrome

*Main article: Irritable bowel syndrome*

Another possible cause of diarrhea is irritable bowel syndrome (IBS), which usually presents with abdominal discomfort relieved by defecation and unusual stool (diarrhea or constipation) for at least 3 days a week over the previous 3 months.[27] Symptoms of diarrhea-predominant IBS can be managed through a combination of dietary changes, soluble fiber supplements, and/or medications such as loperamide or codeine. About 30% of patients with diarrhea-predominant IBS have bile acid malabsorption diagnosed with an abnormal SeHCAT test.[28]

### Other diseases

Diarrhea can be caused by other diseases and conditions, namely:

- Chronic ethanol ingestion[29]
- Ischemic bowel disease: This usually affects older people and can be due to blocked arteries.
- Microscopic colitis, a type of inflammatory bowel disease where changes are only seen on histological examination of colonic biopsies.
- Bile salt malabsorption (primary bile acid diarrhea) where excessive bile acids in the colon produce a secretory diarrhea.
- Hormone-secreting tumors: some hormones (e.g., serotonin) can cause diarrhea if excreted in excess (usually from a tumor).
- Chronic mild diarrhea in infants and toddlers may occur with no obvious cause and with no other ill effects; this condition is called toddler's diarrhea.
- Environmental enteropathy
- Radiation enteropathy following treatment for pelvic and abdominal cancers.

## Causes

### Sanitation

Open defecation is a leading cause of infectious diarrhea leading to death.[30]

Poverty is a good indicator of the rate of infectious diarrhea in a population. This association does not stem from poverty itself, but rather from the conditions under which impoverished people live. The

Poverty often leads to unhygienic living conditions, as in this community in the Indian Himalayas. Such conditions promote contraction of diarrheal diseases, as a result of poor sanitation and hygiene.

absence of certain resources compromises the ability of the poor to defend themselves against infectious diarrhea. "Poverty is associated with poor housing, crowding, dirt floors, lack of access to clean water or to sanitary disposal of fecal waste (sanitation), cohabitation with domestic animals that may carry human pathogens, and a lack of refrigerated storage for food, all of which increase the frequency of diarrhea... Poverty also restricts the ability to provide age-appropriate, nutritionally balanced diets or to modify diets when diarrhea develops so as to mitigate and repair nutrient losses. The impact is exacerbated by the lack of adequate, available, and affordable medical care."[31]

### Water

One of the most common causes of infectious diarrhea, is a lack of clean water. Often, improper fecal disposal leads to contamination of groundwater. This can lead to widespread infection among a population, especially in the absence of water filtration or purification. Human feces contains a variety of potentially harmful human pathogens.[32]

### Nutrition

Proper nutrition is important for health and functioning, including the prevention of infectious diarrhea. It is especially important to young children who do not have a fully developed immune system. Zinc deficiency, a condition often found in children in developing countries can, even in mild cases, have a significant impact on the development and proper functioning of the human immune system.[33][34] Indeed, this relationship between zinc deficiency and reduced immune functioning corresponds with an increased severity of infectious diarrhea. Children who have lowered levels of zinc have a greater number of instances of diarrhea, severe diarrhea, and diarrhea associated with fever.[35] Similarly, vitamin A deficiency can cause an increase in the severity of diarrheal episodes. However, there is some discrepancy when it comes to the impact of vitamin A deficiency on the rate of disease. While some argue that a relationship does not exist between the rate of disease and vitamin A status,[36] others suggest an increase in the rate associated with deficiency.[37] Given that estimates suggest 127 million preschool children worldwide are vitamin A deficient, this population has the potential for increased risk of disease contraction.[38]

## Pathophysiology

### Evolution

According to two researchers, Nesse and Williams, diarrhea may function as an evolved expulsion defense mechanism. As a result, if it is stopped, there might be a delay in recovery.[39] They cite in support of this argument research published in 1973 that found that treating *Shigella* with the anti-diarrhea drug (Co-phenotrope, Lomotil) caused people to stay feverish twice as long as those not so treated. The researchers indeed themselves observed that: "Lomotil may be contraindicated in shigellosis. Diarrhea may represent a defense mechanism".[40]

## Diagnostic approach

The following types of diarrhea may indicate further investigation is needed:

- In infants

- Moderate or severe diarrhea in young children
- Associated with blood
- Continues for more than two days
- Associated non-cramping abdominal pain, fever, weight loss, etc.
- In travelers
- In food handlers, because of the potential to infect others;
- In institutions such as hospitals, child care centers, or geriatric and convalescent homes.

A severity score is used to aid diagnosis in children.[41]

# Prevention

## Sanitation

Numerous studies have shown that improvements in drinking water and sanitation (WASH) lead to decreased risks of diarrhoea.[42] Such improvements might include for example use of water filters, provision of high-quality piped water and sewer connections.[42]

In institutions, communities, and households, interventions that promote hand washing with soap lead to significant reductions in the incidence of diarrhea.[43] The same applies to preventing open defecation at a community-wide level and providing access to improved sanitation.[44][45] This includes use of toilets and implementation of the entire sanitation chain connected to the toilets (collection, transport, disposal or reuse of human excreta).

## Hand washing

Basic sanitation techniques can have a profound effect on the transmission of diarrheal disease. The implementation of hand washing using soap and water, for example, has been experimentally shown to reduce the incidence of disease by approximately 42–48%.[46][47] Hand washing in developing countries, however, is compromised by poverty as acknowledged by the CDC: "Handwashing is integral to disease prevention in all parts of the world; however, access to soap and water is limited in a number of less developed countries. This lack of access is one of many challenges to proper hygiene in less developed countries." Solutions to this barrier require the implementation of educational programs that encourage sanitary behaviours.[48]

## Water

Given that water contamination is a major means of transmitting diarrheal disease, efforts to provide clean water supply and improved sanitation have the potential to dramatically cut the rate of disease incidence. In fact, it has been proposed that we might expect an 88% reduction in child mortality resulting from diarrheal disease as a result of improved water sanitation and hygiene.[32][49] Similarly, a meta-analysis of numerous studies on improving water supply and sanitation shows a 22–27% reduction in disease incidence, and a 21–30% reduction in mortality rate associated with diarrheal disease.[50]

Chlorine treatment of water, for example, has been shown to reduce both the risk of diarrheal disease, and of contamination of stored water with diarrheal pathogens.[51]

## Vaccination

Immunization against the pathogens that cause diarrheal disease is a viable prevention strategy, however it does require targeting certain pathogens for vaccination. In the case of Rotavirus, which was responsible for around 6% of diarrheal episodes and 20% of diarrheal disease deaths in the children of developing countries, use of a Rotavirus vaccine in trials in 1985 yielded a slight (2-3%) decrease in total diarrheal disease incidence, while reducing overall mortality by 6-10%. Similarly, a Cholera vaccine showed a strong reduction in morbidity and mortality, though the overall impact of vaccination was minimal as Cholera is not

one of the major causative pathogens of diarrheal disease.[52] Since this time, more effective vaccines have been developed that have the potential to save many thousands of lives in developing nations, while reducing the overall cost of treatment, and the costs to society.[53][54]

A rotavirus vaccine decrease the rates of diarrhea in a population.[1] New vaccines against rotavirus, *Shigella*, Enterotoxigenic Escherichia coli (ETEC), and cholera are under development, as well as other causes of infectious diarrhea.[*medical citation needed*]

### Nutrition

Dietary deficiencies in developing countries can be combated by promoting better eating practices. Supplementation with vitamin A and/or zinc. Zinc supplementation proved successful showing a significant decrease in the incidence of diarrheal disease compared to a control group.[55][56] The majority of the literature suggests that vitamin A supplementation is advantageous in reducing disease incidence.[57] Development of a supplementation strategy should take into consideration the fact that vitamin A supplementation was less effective in reducing diarrhea incidence when compared to vitamin A and zinc supplementation, and that the latter strategy was estimated to be significantly more cost effective.[58]

### Breastfeeding

Breastfeeding practices have been shown to have a dramatic effect on the incidence of diarrheal disease in poor populations. Studies across a number of developing nations have shown that those who receive exclusive breastfeeding during their first 6 months of life are better protected against infection with diarrheal diseases.[59] Exclusive breastfeeding is currently recommended during, at least, the first six months of an infant's life by the WHO.[60]

### Others

Probiotics decrease the risk of diarrhea in those taking antibiotics.[61]

## Management

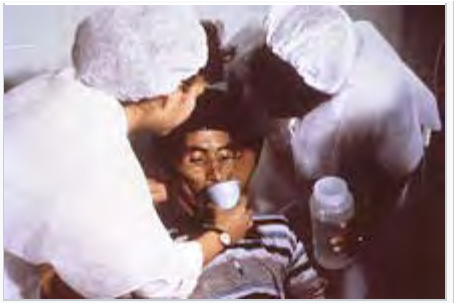
In many cases of diarrhea, replacing lost fluid and salts is the only treatment needed. This is usually by mouth – oral rehydration therapy – or, in severe cases, intravenously.[1] Diet restrictions such as the BRAT diet are no longer recommended.[62] Research does not support the limiting of milk to children as doing so has no effect on duration of diarrhea.[63] To the contrary, WHO recommends that children with diarrhea continue to eat as sufficient nutrients are usually still absorbed to support continued growth and weight gain, and that continuing to eat also speeds up recovery of normal intestinal functioning.[12] CDC recommends that children and adults with cholera also continue to eat.[64]

Medications such as loperamide (Imodium) and bismuth subsalicylate may be beneficial; however they may be contraindicated in certain situations.[65]

### Fluids

*See also: Management of dehydration*

Oral rehydration solution (ORS) (a slightly sweetened and salty water) can be used to prevent dehydration. Standard home solutions such as salted rice water, salted yogurt drinks, vegetable and chicken soups with salt can be given. Home solutions such as water in which cereal has been cooked, unsalted soup, green coconut water, weak tea (unsweetened), and unsweetened fresh fruit juices can have from half a teaspoon to full teaspoon of salt (from one-and-a-half to three grams) added per liter. Clean plain water can also be one of several fluids


A person consuming oral rehydration solution.

given.[12] There are commercial solutions such as Pedialyte, and relief agencies such as UNICEF widely distribute packets of salts and sugar. A WHO publication for physicians recommends a homemade ORS consisting of one liter water with one teaspoon salt (3 grams) and two tablespoons sugar (18 grams) added[12] (approximately the "taste of tears"[66]). Rehydration Project recommends adding the same amount of sugar but only one-half a teaspoon of salt, stating that this more dilute approach is less risky with very little loss of effectiveness.[67] Both agree that drinks with too much sugar or salt can make dehydration worse.[12][67]

Appropriate amounts of supplemental zinc and potassium should be added if available. But the availability of these should not delay rehydration. As WHO points out, the most important thing is to begin preventing dehydration as early as possible.[12] In another example of prompt ORS hopefully preventing dehydration, CDC recommends for the treatment of cholera continuing to give Oral Rehydration Solution during travel to medical treatment.[64]

Vomiting often occurs during the first hour or two of treatment with ORS, especially if a child drinks the solution too quickly, but this seldom prevents successful rehydration since most of the fluid is still absorbed. WHO recommends that if a child vomits, to wait five or ten minutes and then start to give the solution again more slowly.[12]

Drinks especially high in simple sugars, such as soft drinks and fruit juices, are not recommended in children under 5 years of age as they may *increase* dehydration. A too rich solution in the gut draws water from the rest of the body, just as if the person were to drink sea water.[12][68] Plain water may be used if more specific and effective ORT preparations are unavailable or are not palatable.[68] Additionally, a mix of both plain water and drinks perhaps too rich in sugar and salt can alternatively be given to the same person, with the goal of providing a medium amount of sodium overall.[12] A nasogastric tube can be used in young children to administer fluids if warranted.[69]

## Eating

WHO recommends a child with diarrhea continue to be fed. Continued feeding speeds the recovery of normal intestinal function. In contrast, children whose food is restricted have diarrhea of longer duration and recover intestinal function more slowly. A child should also continue to be breastfed. The WHO states "Food should *never* be withheld and the child's usual foods should *not* be diluted. Breastfeeding should *always* be continued."[12] And in the specific example of cholera, CDC also makes the same recommendation.[64] In young children who are not breast-fed and live in the developed world, a lactose-free diet may be useful to speed recovery.[70]

## Medications

While antibiotics are beneficial in certain types of acute diarrhea, they are usually not used except in specific situations.[71][72] There are concerns that antibiotics may increase the risk of hemolytic uremic syndrome in people infected with Escherichia coli O157:H7.[73] In resource-poor countries, treatment with antibiotics may be beneficial.[72] However, some bacteria are developing antibiotic resistance, particularly *Shigella*.[74] Antibiotics can also cause diarrhea, and antibiotic-associated diarrhea is the most common adverse effect of treatment with general antibiotics.

While bismuth compounds (Pepto-Bismol) decreased the number of bowel movements in those with travelers' diarrhea, they do not decrease the length of illness.[75] Anti-motility agents like loperamide are also effective at reducing the number of stools but not the duration of disease.[4] These agents should only be used if bloody diarrhea is not present.[76]

Bile acid sequestrants such as cholestyramine can be effective in chronic diarrhea due to bile acid malabsorption. Therapeutic trials of these drugs are indicated in chronic diarrhea if bile acid malabsorption cannot be diagnosed with a specific test, such as SeHCAT retention.

### Alternative therapies

Zinc supplementation benefits children with diarrhea in developing countries, but only in infants over six months old. This supports the World Health Organization guidelines for zinc, but not in the very young.[77]

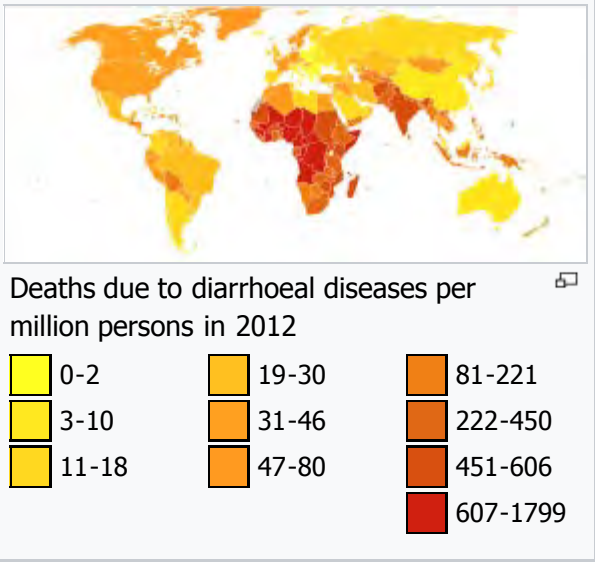
Probiotics reduce the duration of symptoms by one day and reduced the chances of symptoms lasting longer than four days by 60%.[78] The probiotic lactobacillus can help prevent antibiotic-associated diarrhea in adults but possibly not children.[79] For those with lactose intolerance, taking digestive enzymes containing lactase when consuming dairy products often improves symptoms.

## Epidemiology

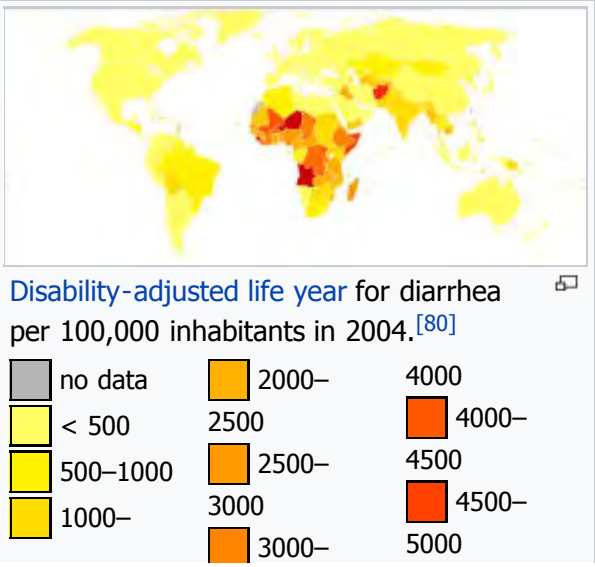
Worldwide in 2004, approximately 2.5 billion cases of diarrhea occurred, which resulted in 1.5 million deaths among children under the age of five.[1] Greater than half of these were in Africa and South Asia.[1] This is down from a death rate of 4.5 million in 1980 for gastroenteritis.[81] Diarrhea remains the second leading cause of infant mortality (16%) after pneumonia (17%) in this age group.[1]

The majority of such cases occur in the developing world, with over half of the recorded cases of childhood diarrhea occurring in Africa and Asia, with 696 million and 1.2 billion cases, respectively, compared to only 480 million in the rest of the world.[82]

Infectious diarrhea resulted in about 0.7 million deaths in children under five years old in 2011 and 250 million lost school days.[44][83] In the Americas, diarrheal disease accounts for a total of 10% of deaths among children aged 1–59 months while in South East Asia, it accounts for 31.3% of deaths.[84] It is estimated that around 21% of child mortalities in developing countries are due to diarrheal disease.[85]



Deaths due to diarrhoeal diseases per million persons in 2012

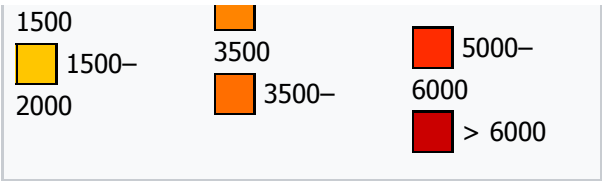


Disability-adjusted life year for diarrhea per 100,000 inhabitants in 2004.[80]

## Etymology

The word diarrhea is from the Ancient Greek διάρροια from διά *dia* "through" and ῥέω *rheo* "flow".

Diarrhea is the spelling in American English while diarrhoea is the spelling in Commonwealth English.




# References


1. ^ *a b c d e f g h* "whqlibdoc.who.int" (PDF). *World Health Organization*.
2. ^ *a b c d e f g h i j* "Diarrhoeal disease Fact sheet N°330". *World Health Organization*. April 2013. Retrieved 9 July 2014.
3. ^ *a b* Basem Abdelmalak; John Doyle, eds. (2013). *Anesthesia for otolaryngologic surgery*. Cambridge University Press. pp. 282–287. ISBN 1107018676.
4. ^ *a b c d* DuPont HL (Apr 17, 2014). "Acute infectious diarrhea in immunocompetent adults.". *The New England Journal of Medicine*. **370** (16): 1532–40. doi:10.1056/nejmra1301069. PMID 24738670.
5. ^ Prober, edited by Sarah Long, Larry Pickering, Charles G. (2012). *Principles and practice of pediatric infectious diseases* (4th ed.). Edinburgh: Elsevier Saunders. p. 96. ISBN 9781455739851.
6. ^ ACEP. "Nation's Emergency Physicians Announce List of Test and Procedures to Question as Part of Choosing Wisely Campaign". *Choosing Wisely*. Retrieved 18 June 2014.
7. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
8. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
9. ^ *a b* "Global Diarrhea Burden". *CDC*. January 24, 2013. Retrieved 18 June 2014.
10. ^ "WGO Practice Guideline - Acute diarrhea". Retrieved 9 March 2011.
11. ^ *a b c* "The Basics of Diarrhea". Webmd.com. 17 February 2011. Retrieved 9 March 2011.
12. ^ *a b c d e f g h i j* "The Treatment Of Diarrhea, A manual for physicians and other senior health workers" (PDF). Sometimes needs to be downloaded twice. See "4.2 Treatment Plan A: home therapy to prevent dehydration and malnutrition," "4.3 Treatment Plan B: oral rehydration therapy for children with some dehydration," and "4.4 Treatment Plan C: for patients with severe dehydration" on pages 8 to 16 (12–20 in PDF). See also "8. Management of Diarrhoea with Severe Malnutrition" on pages 22–24 (26–30 in PDF) and "Annex 2: Oral and Intravenous Rehydration Solutions" on pages 33–37 (37–41 in PDF). World Health Organization. 2005.
13. ^ *a b* Disease Control Priorities Project. "Public Health Significance of Diarrheal Illnesses". The World Bank Group. Retrieved 12 October 2013.
14. ^ Guerrant RL, Schorling JB, McAuliffe JF, de Souza MA (July 1992). "Diarrhea as a cause and an effect of malnutrition: diarrhea prevents catch-up growth and malnutrition increases diarrhea frequency and duration". *The American journal of tropical medicine and hygiene*. **47** (1 Pt 2): 28–35. PMID 1632474.
15. ^ Grantham-McGregor SM, Walker SP, Chang S (February 2000). "Nutritional deficiencies and later behavioural development". *The Proceedings of the Nutrition Society*. **59** (1): 47–54. doi:10.1017/S0029665100000069. PMID 10828173.
16. ^ *a b* Wilson ME (December 2005). "Diarrhea in nontravelers: risk and etiology". *Clin. Infect. Dis.* 41. **41** (Suppl 8): S541–6. doi:10.1086/432949. PMID 16267716.
17. ^ Navaneethan U, Giannella RA (November 2008). "Mechanisms of infectious diarrhea". *Nature Clinical Practice Gastroenterology & Hepatology*. **5** (11): 637–47. doi:10.1038/ncpgasthep1264. PMID 18813221.
18. ^ David Schlossberg (2008). *Clinical Infectious Disease*. Cambridge University Press. p. 349. ISBN 9781139576659.
19. ^ Patel MM, Hall AJ, Vinjé J, Parashar UD (January 2009). "Noroviruses: a comprehensive review". *Journal of Clinical Virology*. **44** (1): 1–8. doi:10.1016/j.jcv.2008.10.009. PMID 19084472.
20. ^ Greenberg HB, Estes MK (May 2009). "Rotaviruses: from pathogenesis to vaccination". *Gastroenterology*. **136** (6): 1939–51. doi:10.1053/j.gastro.2009.02.076. PMC 3690811. PMID 19457420.
21. ^ Uhnoo I, Svensson L, Wadell G (September 1990). "Enteric adenoviruses". *Baillière's Clinical Gastroenterology*. **4**

(3): 627–42. doi:10.1016/0950-3528(90)90053-J. PMID 1962727.
22. ^ Mitchell DK (November 2002). "Astrovirus gastroenteritis". *The Pediatric Infectious Disease Journal*. **21** (11): 1067–9. doi:10.1097/01.inf.0000036683.11146.c7 (inactive 2015-01-12). PMID 12442031.
23. ^ Viswanathan VK, Hodges K, Hecht G (February 2009). "Enteric infection meets intestinal function: how bacterial pathogens cause diarrhoea". *Nature Reviews Microbiology*. **7** (2): 110–9. doi:10.1038/nrmicro2053. PMC 3326399. PMID 19116615.
24. ^ Rupnik M, Wilcox MH, Gerding DN (July 2009). "*Clostridium difficile* infection: new developments in epidemiology and pathogenesis". *Nature Reviews Microbiology*. **7** (7): 526–36. doi:10.1038/nrmicro2164. PMID 19528959.
25. ^ Rossignol JF, Lopez-Chegne N, Julcamoro LM, Carrion ME, Bardin MC (2012). "Nitazoxanide for the empiric treatment of pediatric infectious diarrhea". *Trans. R. Soc. Trop. Med. Hyg*. **106** (3): 167–73. doi:10.1016/j.trstmh.2011.11.007. PMID 22301075.
26. ^ Alam NH, Ashraf H (2003). "Treatment of infectious diarrhea in children". *Paediatr Drugs*. **5** (3): 151–65. doi:10.2165/00128072-200305030-00002. PMID 12608880.
27. ^ Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC (2006). "Functional bowel disorders". *Gastroenterology*. **130** (5): 1480–91. doi:10.1053/j.gastro.2005.11.061. PMID 16678561.
28. ^ Wedlake L, A'Hern R, Russell D, Thomas K, Walters JR, Andreyev HJ (2009). "Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome". *Alimentary pharmacology & therapeutics*. **30** (7): 707–17. doi:10.1111/j.1365-2036.2009.04081.x. PMID 19570102.
29. ^ Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL. Harrison's Principles of Internal Medicine. New York: McGraw-Hill, 2005. ISBN 0-07-139140-1.
30. ^ "WHO | Diarrhoeal disease". Who.int. Retrieved 2014-03-10.
31. ^ Jamison, Dean T. (2006). *Disease control priorities in developing countries* (2nd ed.). New York: Oxford Univ. Press. ISBN 0821361791.
32. ^ *a b* Brown J, Cairncross S, Ensink JH (August 2013). "Water, sanitation, hygiene and enteric infections in children". *Archives of Disease in Childhood*. **98** (8): 629–34. doi:10.1136/archdischild-2011-301528. PMC 3717778. PMID 23761692.
33. ^ Black RE, Sazawal S (May 2001). "Zinc and childhood infectious disease morbidity and mortality". *The British journal of nutrition*. 85 Suppl 2: S125–9. doi:10.1079/bjn2000304. PMID 11509100.
34. ^ Shankar AH, Prasad AS (August 1998). "Zinc and immune function: the biological basis of altered resistance to infection". *The American Journal of Clinical Nutrition*. **68** (2 Suppl): 447S–463S. PMID 9701160.
35. ^ Bahl R, Bhandari N, Hambidge KM, Bhan MK (August 1998). "Plasma zinc as a predictor of diarrheal and respiratory morbidity in children in an urban slum setting". *The American Journal of Clinical Nutrition*. **68** (2 Suppl): 414S–417S. PMID 9701154.
36. ^ Rice, Amy L. *Comparative quantification of health risks*. WHO. pp. 238–240.
37. ^ Sommer A, Katz J, Tarwotjo I (November 1984). "Increased risk of respiratory disease and diarrhea in children with preexisting mild vitamin A deficiency". *The American Journal of Clinical Nutrition*. **40** (5): 1090–5. PMID 6496388.
38. ^ West KP (September 2002). "Extent of vitamin A deficiency among preschool children and women of reproductive age". *The Journal of Nutrition*. **132** (9 Suppl): 2857S–2866S. PMID 12221262.
39. ^ Williams, George; Nesse, Randolph M. (1996). *Why we get sick: the new science of Darwinian medicine*. New York: Vintage Books. pp. 36–38. ISBN 0-679-74674-9.
40. ^ DuPont HL, Hornick RB (December 1973). "Adverse effect of lomotil therapy in shigellosis". *JAMA*. **226** (13): 1525–8. doi:10.1001/jama.226.13.1525. PMID 4587313.
41. ^ Ruuska T, Vesikari T (1990). "Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes". *Scand. J. Infect. Dis*. **22** (3): 259–67. doi:10.3109/00365549009027046. PMID 2371542.
42. ^ *a b* Wolf, Jennyfer; Prüss-Ustün, Annette; Cumming, Oliver; Bartram, Jamie; Bonjour, Sophie; Cairncross, Sandy; Clasen, Thomas; Colford, John M.; Curtis, Valerie; De France, Jennifer; Fewtrell, Lorna; Freeman, Matthew C.; Gordon, Bruce; Hunter, Paul R.; Jeandron, Aurelie; Johnston, Richard B.; Mäusezahl, Daniel; Mathers, Colin; Neira, Maria; Higgins, Julian P. T. (August 2014). "Systematic review: Assessing the impact of drinking water and sanitation on diarrhoeal disease in low- and middle-income settings: systematic review and meta-regression". *Tropical Medicine & International Health*. **19** (8): 928–942. doi:10.1111/tmi.12331.
43. ^ Ejemot-Nwadiaro, Regina I.; Ehiri, John E.; Arikpo, Dachi; Meremikwu, Martin M.; Critchley, Julia A. (2015-09-03). "Hand washing promotion for preventing diarrhoea". *The Cochrane Database of Systematic Reviews* (9): CD004265. doi:10.1002/14651858.CD004265.pub3. ISSN 1469-493X. PMC 4563982. PMID 26346329.
44. ^ *a b* "Call to action on sanitation" (pdf). *United Nations*. Retrieved 15 August 2014.
45. ^ "Open Defecation and Childhood Stunting in India: An Ecological Analysis of New Data from 112 Districts". *PLoS ONE*. Plos One. **8**: e73784. doi:10.1371/journal.pone.0073784. Retrieved 2014-03-10.

46. ^ Curtis V, Cairncross S (May 2003). "Effect of washing hands with soap on diarrhoea risk in the community: a systematic review". *The Lancet infectious diseases*. **3** (5): 275–81. doi:10.1016/S1473-3099(03)00606-6. PMID 12726975.
47. ^ Cairncross S, Hunt C, Boisson S, Bostoen K, Curtis V, Fung IC, Schmidt WP (April 2010). "Water, sanitation and hygiene for the prevention of diarrhoea". *International Journal of Epidemiology*. 39 Suppl 1 (Suppl 1): i193–205. doi:10.1093/ije/dyq035. PMC 2845874. PMID 20348121.
48. ^ "Diarrheal Diseases in Less Developed Countries". *CDC*. Retrieved 28 October 2013.
49. ^ Black RE, Morris SS, Bryce J (Jun 28, 2003). "Where and why are 10 million children dying every year?". *Lancet*. **361** (9376): 2226–34. doi:10.1016/S0140-6736(03)13779-8. PMID 12842379.
50. ^ Esrey SA, Feachem RG, Hughes JM (1985). "Interventions for the control of diarrhoeal diseases among young children: improving water supplies and excreta disposal facilities". *Bulletin of the World Health Organization*. **63** (4): 757–72. PMC 2536385. PMID 3878742.
51. ^ Arnold BF, Colford JM (February 2007). "Treating water with chlorine at point-of-use to improve water quality and reduce child diarrhea in developing countries: a systematic review and meta-analysis". *The American journal of tropical medicine and hygiene*. **76** (2): 354–64. PMID 17297049.
52. ^ de Zoysa I, Feachem RG (1985). "Interventions for the control of diarrhoeal diseases among young children: rotavirus and cholera immunization". *Bulletin of the World Health Organization*. **63** (3): 569–83. PMC 2536413. PMID 3876173.
53. ^ Rheingans RD, Antil L, Dreibelbis R, Podewils LJ, Bresee JS, Parashar UD (Nov 1, 2009). "Economic costs of rotavirus gastroenteritis and cost-effectiveness of vaccination in developing countries". *The Journal of Infectious Diseases*. 200 Suppl 1: S16–27. doi:10.1086/605026 (inactive 2015-01-12). PMID 19817595.
54. ^ *Oral cholera vaccines in mass immunization campaigns* (PDF). WHO. 2010. pp. 6–8. ISBN 978 92 4 150043 2.
55. ^ Black RE (May 2003). "Zinc deficiency, infectious disease and mortality in the developing world". *The Journal of Nutrition*. **133** (5 Suppl 1): 1485S–9S. PMID 12730449.
56. ^ Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, Khatun F, Martorell R, Ninh NX, Penny ME, Rosado JL, Roy SK, Ruel M, Sazawal S, Shankar A (December 1999). "Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. Zinc Investigators' Collaborative Group". *The Journal of Pediatrics*. **135** (6): 689–97. doi:10.1016/S0022-3476(99)70086-7. PMID 10586170.
57. ^ Mayo-Wilson E, Imdad A, Herzer K, Yakoob MY, Bhutta ZA (Aug 25, 2011). "Vitamin A supplements for preventing mortality, illness, and blindness in children aged under 5: systematic review and meta-analysis". *BMJ (Clinical research ed.)*. **343**: d5094. doi:10.1136/bmj.d5094 (inactive 2015-01-12). PMC 3162042. PMID 21868478.
58. ^ Chhagan MK, Van den Broeck J, Luabeya KK, Mpontshane N, Bennish ML (Aug 12, 2013). "Cost of childhood diarrhoea in rural South Africa: exploring cost-effectiveness of universal zinc supplementation". *Public health nutrition*. **17** (9): 1–8. doi:10.1017/S1368980013002152. PMID 23930984.
59. ^ "Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality". *The Lancet*. **355** (9202): 451–5. Feb 2000. doi:10.1016/S0140-6736(00)82011-5. PMID 10841125.
60. ^ Sguassero Y. "Optimal duration of exclusive breastfeeding: RHL commentary". WHO. Retrieved 14 October 2013.
61. ^ Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, Johnsen B, Shekelle PG (9 May 2012). "Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis". *JAMA: The Journal of the American Medical Association*. **307** (18): 1959–69. doi:10.1001/jama.2012.3507 (inactive 2015-01-12). PMID 22570464.
62. ^ King CK, Glass R, Bresee JS, Duggan C (November 2003). "Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy". *MMWR Recomm Rep*. **52** (RR–16): 1–16. PMID 14627948.
63. ^ "BestBets: Does Withholding milk feeds reduce the duration of diarrhoea in children with acute gastroenteritis? ".
64. ^ *a b c* Community Health Worker Training Materials for Cholera Prevention and Control, CDC, slides at back are dated 17 November 2010. Page 7 states " . . . Continue to breastfeed your baby if the baby has watery diarrhea, even when traveling to get treatment. Adults and older children should continue to eat frequently."
65. ^ Schiller LR (2007). "Management of diarrhea in clinical practice: strategies for primary care physicians". *Rev Gastroenterol Disord*. **7** (Suppl 3): S27–38. PMID 18192963.
66. ^ A Guide on Safe Food for Travellers, Welcome to South Africa, Host to the 2010 FIFA World Cup (bottom left of page 1).
67. ^ *a b* Rehydration Project, http://rehydrate.org/ Homemade Oral Rehydration Solution Recipe.
68. ^ *a b* "Management of acute diarrhoea and vomiting due to gastoenteritis in children under 5". *National Institute of Clinical Excellence*. April 2009.

69. ^ Webb A, Starr M (April 2005). "Acute gastroenteritis in children". *Australian family physician*. **34** (4): 227–31. PMID 15861741.
70. ^ MacGillivray S, Fahey T, McGuire W (31 October 2013). "Lactose avoidance for young children with acute diarrhoea.". *The Cochrane database of systematic reviews*. **10**: CD005433. doi:10.1002/14651858.CD005433.pub2. PMID 24173771.
71. ^ Dryden MS, Gabb RJ, Wright SK (June 1996). "Empirical treatment of severe acute community-acquired gastroenteritis with ciprofloxacin". *Clin. Infect. Dis.* **22** (6): 1019–25. doi:10.1093/clinids/22.6.1019. PMID 8783703.
72. ^ [a] [b] de Bruyn G (2008). "Diarrhoea in adults (acute)". *Clin Evid (Online)*. **2008**: 0901. PMC 2907942. PMID 19450323.
73. ^ Wong CS, Jelacic S, Habeeb RL, Watkins SL, Tarr PI (June 2000). "The risk of the hemolytic-uremic syndrome after antibiotic treatment of Escherichia coli O157:H7 infections". *N. Engl. J. Med.* **342** (26): 1930–6. doi:10.1056/NEJM200006293422601. PMC 3659814. PMID 10874060.
74. ^ "Diarrhoeal Diseases". *World Health Organization*. February 2009.
75. ^ DuPont HL, Ericsson CD, Farthing MJ, Gorbach S, Pickering LK, Rombo L, Steffen R, Weinke T (2009). "Expert review of the evidence base for self-therapy of travelers' diarrhea". *J Travel Med*. **16** (3): 161–71. doi:10.1111/j.1708-8305.2009.00300.x. PMID 19538576.
76. ^ Pawlowski SW, Warren CA, Guerrant R (May 2009). "Diagnosis and treatment of acute or persistent diarrhea". *Gastroenterology*. **136** (6): 1874–86. doi:10.1053/j.gastro.2009.02.072 (inactive 2015-01-12). PMC 2723735. PMID 19457416.
77. ^ Lazzerini M, Ronfani L (Jan 31, 2013). "Oral zinc for treating diarrhoea in children". *The Cochrane database of systematic reviews*. **1**: CD005436. doi:10.1002/14651858.CD005436.pub4 (inactive 2015-01-12). PMID 23440801.
78. ^ Allen SJ, Martinez EG, Gregorio GV, Dans LF (2010). Allen SJ, ed. "Probiotics for treating acute infectious diarrhoea". *Cochrane Database Syst Rev*. **2010** (11): CD003048. doi:10.1002/14651858.CD003048.pub3 (inactive 2015-01-12). PMID 21069673.
79. ^ Kale-Pradhan PB, Jassal HK, Wilhelm SM (February 2010). "Role of Lactobacillus in the prevention of antibiotic-associated diarrhea: a meta-analysis". *Pharmacotherapy*. **30** (2): 119–26. doi:10.1592/phco.30.2.119. PMID 20099986.
80. ^ "Mortality and Burden of Disease Estimates for WHO Member States in 2004" (xls). *World Health Organization*.
81. ^ Mandell, Gerald L.; Bennett, John E.; Dolin, Raphael (2004). *Mandell's Principles and Practices of Infection Diseases* (6th ed.). Churchill Livingstone. ISBN 0-443-06643-4.
82. ^ "Diarrhoea: why children are still dying and what can be done" (PDF). *WHO*. WHO. Retrieved 12 October 2013.
83. ^ Walker CL, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, O'Brien KL, Campbell H, Black RE (Apr 20, 2013). "Global burden of childhood pneumonia and diarrhoea". *Lancet*. **381** (9875): 1405–16. doi:10.1016/S0140-6736(13)60222-6. PMID 23582727.
84. ^ Walker CL, Aryee MJ, Boschi-Pinto C, Black RE (2012). Myer L, ed. "Estimating diarrhea mortality among young children in low and middle income countries". *PLoS ONE*. **7** (1): e29151. Bibcode:2012PLoSO...729151F. doi:10.1371/journal.pone.0029151. PMC 3250411. PMID 22235266.
85. ^ Kosek M, Bern C, Guerrant RL (2003). "The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000". *Bulletin of the World Health Organization*. **81** (3): 197–204. PMC 2572419. PMID 12764516.


# External links

- Diarrhea at DMOZ

Find more about
**Diarrhea**
at Wikipedia's sister projects

- Definitions from Wiktionary
- Media from Commons
- News from Wikinews
- Quotations from Wikiquote

| v · t · e · | Diseases of the digestive system (primarily K20–K93, 530–579) | |
|---|---|---|
| **Upper GI tract** | **Esophagus** | Esophagitis (Candidal · Eosinophilic · Herpetiform · · *Rupture* (Boerhaave syndrome · Mallory-Weiss syndrome · · UES (Zenker's diverticulum · · LES (Barrett's esophagus · · Esophageal motility disorder (Nutcracker esophagus · Achalasia · Diffuse esophageal spasm · Gastroesophageal reflux disease (GERD) · · Laryngopharyngeal reflux (LPR) · Esophageal stricture · Megaesophagus · |
| | **Stomach** | Gastritis (Atrophic · Ménétrier's disease · Gastroenteritis · · Peptic (gastric) ulcer (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
| **Lower GI tract: Intestinal/ Enteropathy** | **Small intestine (Duodenum/Jejunum/Ileum)** | Enteritis (Duodenitis · Jejunitis · Ileitis · · Peptic (duodenal) ulcer (Curling's ulcer · · Malabsorption: Coeliac · Tropical sprue · Blind loop syndrome · Small bowel bacterial overgrowth syndrome · Whipple's · Short bowel syndrome · Steatorrhea · Milroy disease · Bile acid malabsorption · |
| | **Large intestine (Appendix/Colon)** | Appendicitis · Colitis (Pseudomembranous · Ulcerative · Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (IBS · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
| | **Large and/or small** | Enterocolitis (Necrotizing · · Gastroenterocolitis · IBD (Crohn's disease · · *Vascular*: Abdominal angina · Mesenteric ischemia · Angiodysplasia · Bowel obstruction: Ileus · Intussusception · Volvulus · Fecal impaction · Constipation · **Diarrhea** (Infectious · · Intestinal adhesions · |
| | **Rectum** | Proctitis (Radiation proctitis · · Proctalgia fugax · Rectal prolapse · Anismus · |
| | **Anal canal** | Anal fissure/Anal fistula · Anal abscess · Anal dysplasia · Pruritus ani · |
| **GI bleeding/BIS** | Upper (Hematemesis · Melena · · Lower (Hematochezia · · | |
| | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · Acute liver failure · · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |

| | | |
|---|---|---|
| **Accessory** | **Gallbladder** | Cholecystitis · Gallstones/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · Gallstones/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
| | **Pancreatic** | Pancreatitis (Acute · Chronic · Hereditary · Pancreatic abscess · · Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |
| **Abdominopelvic** | **Hernia** | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |

| v · t · e · | **Symptoms and signs: digestive system and abdomen (R10–R19, 787,789)** |
|---|---|
| **Upper** | Nausea · Vomiting · Heartburn · Aerophagia · Dysphagia (oropharyngeal · esophageal · · Odynophagia · Halitosis · Xerostomia · Hypersalivation · Burping (Wet burp · · |
| **Defaecation** | Flatulence · Fecal incontinence (Encopresis · · *Blood:* Fecal occult blood · Rectal tenesmus · Constipation · Obstructed defecation · **Diarrhea** · Rectal discharge · Football sign · Psoas sign · Obturator sign · Rovsing's sign · Hamburger sign · Heel tap sign · Aure-Rozanova's sign · Dunphy sign · Alder's sign · Lockwood's sign · Rosenstein's sign · |
| **Abdomen** | Abdominal pain (Acute abdomen · Colic · Baby colic · Abdominal guarding · Rebound tenderness · · Abdominal distension (Bloating · Ascites · Tympanites · Shifting dullness · Bulging flanks · Fluid wave test · · Abdominal mass · Hepatosplenomegaly (Hepatomegaly · Splenomegaly · · Jaundice · Mallet-Guy sign · Puddle sign · |

| | |
|---|---|
| **Authority control** | GND: 4070636-9 · NDL: 00562417 · |

Categories: Diarrhea | Intestinal infectious diseases | Waterborne diseases | Diseases of intestines | Conditions diagnosed by stool test | Symptoms and signs: Digestive system and abdomen | Feces

# Gallstone



From Wikipedia, the free encyclopedia

A **gallstone** is a stone formed within the gallbladder out of bile components.[1] The term **cholelithiasis** may refer to the presence of stones in the gallbladder or to the diseases caused by gallstones.[2] Most people with gallstones (about 80%) never have symptoms.[1][3] In 1–4% of those with gallstones, a crampy pain in the right upper part of the abdomen, known as biliary colic, occurs each year.[4] Complications of gallstones include inflammation of the gallbladder, inflammation of the pancreas, and liver inflammation.[1][4] Symptoms of these complications may include pain of more than five hours duration, fever, yellowish skin, vomiting, or tea-color urine.[1]

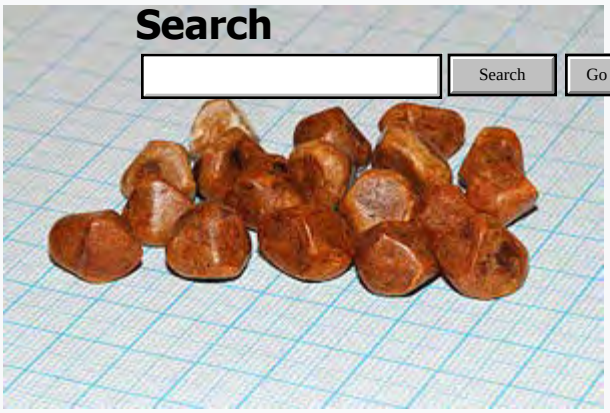
Risk factors for gallstones include birth control pills, pregnancy, a family history of gallstones, obesity, diabetes, liver disease, or rapid weight loss. Gallstones are formed in the gallbladder, typically from either cholesterol or bilirubin.[1] Gallstones may be suspected based on symptoms.[4] Diagnosis is then typically confirmed by ultrasound. Complications may be detected on blood tests.[1]

Prevention is by maintaining a healthy weight and eating a proper diet. If there are no symptoms, treatment is usually not needed. In those who are having gallbladder attacks surgery to remove the gallbladder is typically recommended. This can be either done through several small incisions or through a single larger incision. Surgery is typically done under general anesthesia. In those who are unable to have surgery, medication to try to dissolve the stones or shock wave lithotripsy may be tried.[1]

In the developed world, 10–15% of adults have gallstones.[4] Rates in many parts of Africa, however, are as low as 3%.[5] Gallbladder and biliary related diseases occurred in about 104 million people (1.6%) in 2013 and they resulted in 106,000 deaths.[6][7] Women more commonly have stones than men and they occur more commonly after the age of 40. Certain ethnic groups have gallstones more often than others. For example, 48% of American Indians have gallstones. Once the gallbladder is removed, outcomes are generally good.[1]

## Gallstone

**Synonyms** cholelith



Numerous small gallstones made up largely of cholesterol

**Pronunciation** cholelith /ˈkoʊləlɪθ/), cholelithiasis /ˌkoʊləlɪˈθaɪəsɪs/

**Classification and external resources**

| | |
|---|---|
| **Specialty** | General surgery |
| **ICD-10** | K80 |
| **ICD-9-CM** | 574 |
| **OMIM** | 600803 |
| **DiseasesDB** | 2533 |
| **MedlinePlus** | 000273 |
| **eMedicine** | emerg/97 |
| **MeSH** | D042882 |

[edit on Wikidata]



Contents

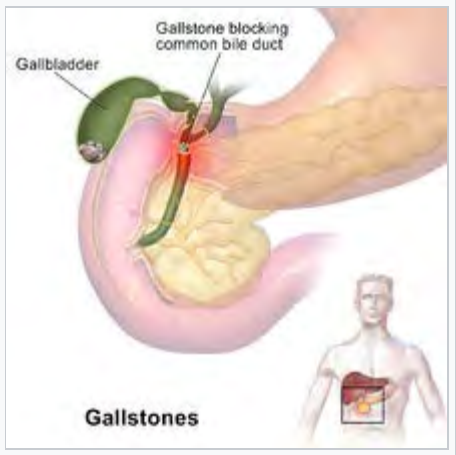

Play media

A video explanation of gallstones

## Definitions [edit]

Gallstone disease refers to the condition where gallstones are either in the gallbladder or common bile duct.[1] The presence of stones in the gallbladder is referred to as cholelithiasis, from the Greek *chol-* (bile) + *lith-* (stone) + *iasis-* (process). If gallstones migrate into the ducts of the biliary tract, the condition is referred to as choledocholithiasis, from the Greek *chol-* (bile) + *docho-* (duct) + *lith-* (stone) + *iasis-* (process). Choledocholithiasis is frequently associated with obstruction of the biliary tree, which in turn can lead to acute ascending cholangitis, from the Greek: *chol-* (bile) + *ang-* (vessel) + *itis-* (inflammation), a serious infection of the bile ducts. Gallstones within the ampulla of Vater can obstruct the exocrine system of the pancreas, which in turn can result in pancreatitis.

## Signs and symptoms [edit]




Gallstones

Gallstones may be asymptomatic, even for years. These gallstones are called "silent stones" and do not require treatment.[8][9] The size and number of gallstones present does not appear to influence whether or not people are symptomatic or asymptomatic.[10] A characteristic symptom of gallstones is a gallstone attack, in which a person may experience colicky pain in the upper-right side of the abdomen, often accompanied by nausea and vomiting, that steadily increases for approximately 30 minutes to several hours. A person may also experience referred pain between the shoulder blades or below the right shoulder. These symptoms may resemble those of a "kidney stone attack". Often, attacks occur after a particularly fatty meal and almost always happen at night, and after drinking.

In addition to pain, nausea, and vomiting, a person may experience a fever. If the stones block the duct and cause bilirubin to leak into the bloodstream and surrounding tissue, there may also be jaundice and itching. This can also lead to confusion. If this is the case, the liver enzymes are likely to be raised.[11]

### Other complications [edit]

Rarely, in cases of severe inflammation, gallstones may erode through the gallbladder into adherent bowel potentially causing an obstruction termed gallstone ileus.[12]

Other complications include ascending cholangitis if there is a bacterial infection which can cause purulent inflammation in the biliary tree and liver, and acute pancreatitis as blockage of the bile ducts can prevent

active enzymes being secreted into the bowel, instead damaging the pancreas.[11]

## Risk factors [edit]

Gallstone risk increases for females (especially before menopause) and for people near or above 40 years;[13] the condition is more prevalent among both North and South Americans and among those of European descent than among other ethnicities. A lack of melatonin could significantly contribute to gallbladder stones, as melatonin inhibits cholesterol secretion from the gallbladder, enhances the conversion of cholesterol to bile, and is an antioxidant, which is able to reduce oxidative stress to the gallbladder.[14] Researchers believe that gallstones may be caused by a combination of factors, including inherited body chemistry, body weight, gallbladder motility (movement), and low calorie diet.[*citation needed*] The absence of such risk factors does not, however, preclude the formation of gallstones.

A clear relationship has been proven between diet and gallstone formation. According to a study limited to 80 patients in Nepal, non-vegetarians have 9 times the incidence of gallstones compared to vegetarians.[15] The methodology of the study has been disputed.[16] Nutritional factors that may increase risk of gallstones include constipation; eating fewer meals per day; low intake of the nutrients folate, magnesium, calcium, and vitamin C;[17] and, at least for men, a high intake of carbohydrate, a high glycemic load, and high glycemic index diet.[18] Wine and whole-grained bread may decrease the risk of gallstones.[19]

Rapid weight loss increases risk of gallstones.[20] Patients taking orlistat, a weight loss drug, may already be at increased risk for the formation of gall stones. Weight loss with orlistat can increase the risk of gall stones.[21] On the contrary, ursodeoxycholic acid (UCDA), a bile acid, also a drug marketed as Ursodiol, appears to prevent formation of gallstones during weight loss.[22] A high fat diet during weight loss also appears to prevent gallstones.[22]

Pigment gallstones are most commonly seen in the developing world. Risk factors for pigment stones include hemolytic anemias (such as from sickle-cell disease and hereditary spherocytosis), cirrhosis, and biliary tract infections.[23] People with erythropoietic protoporphyria (EPP) are at increased risk to develop gallstones.[24][25] Additionally, prolonged use of proton pump inhibitors has been shown to decrease gallbladder function, potentially leading to gallstone formation.[26]

## Pathophysiology [edit]

Cholesterol gallstones develop when bile contains too much cholesterol and not enough bile salts. Besides a high concentration of cholesterol, two other factors are important in causing gallstones. The first is how often and how well the gallbladder contracts; incomplete and infrequent emptying of the gallbladder may cause the bile to become overconcentrated and contribute to gallstone formation. This can be caused by high resistance to the flow of bile out of the gallbladder due to the complicated internal geometry of the cystic duct.[27] The second factor is the presence of proteins in the liver and bile that either promote or inhibit cholesterol crystallization into gallstones. In addition, increased levels of the hormone estrogen, as a result of pregnancy or hormone therapy, or the use of combined (estrogen-containing) forms of hormonal contraception, may increase cholesterol levels in bile and also decrease gallbladder movement, resulting in gallstone formation.

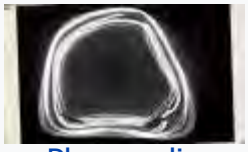
### Composition [edit]

Gallstones can vary in size and shape from as small as a grain of sand to as large as a golf ball.[28] The gallbladder may contain a single large stone or many smaller ones. Pseudoliths, sometimes referred to as sludge, are thick secretions that may be present within the gallbladder, either alone or in conjunction with fully formed gallstones. The clinical presentation is similar to that of cholelithiasis.[*citation needed*] The composition of gallstones is affected by age, diet and ethnicity.[29] On the basis of their composition, gallstones can be divided into the following types:

Gallbladder opened to show small cholesterol gallstones

µCT of a gallstone

The large, yellow stone is largely cholesterol, while the green-to-brown stones is mostly bile pigments



Play media

Images of a CT of gallstones

Large gallstone

## Cholesterol stones [edit]

Cholesterol stones vary from light yellow to dark green or brown or chalk white and are oval, usually solitary, between 2 and 3 cm long, each often having a tiny, dark, central spot. To be classified as such, they must be at least 80% cholesterol by weight (or 70%, according to the Japanese- classification system).[30] Between 35% and 90% of stones are cholesterol stones.[3]

## Bilirubin stones [edit]

Bilirubin ("pigment", "black pigment") stones are small, dark (often appearing black), and usually numerous. They are composed primarily of bilirubin (insoluble bilirubin pigment polymer) and calcium (calcium phosphate) salts that are found in bile. They contain less than 20% of cholesterol (or 30%, according to the Japanese-classification system).[30] Between 2% and 30% of stones are bilirubin stones.[3]

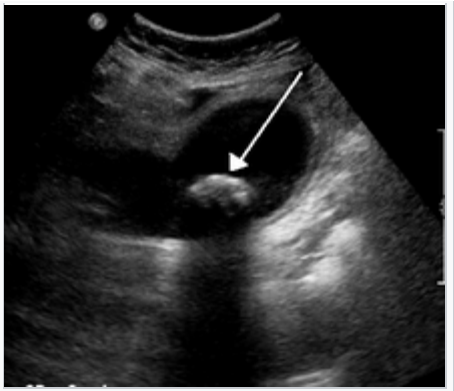
## Mixed stones [edit]

Mixed ("Brown Pigment") stones typically contain 20–80% cholesterol (or 30–70%, according to the Japanese- classification system).[30] Other common constituents are calcium carbonate, palmitate phosphate, bilirubin and other bile pigments (calcium bilirubinate, calcium palmitate and calcium stearate). Because of their calcium content, they are often radiographically visible. They typically arise secondary to infection of the biliary tract which results in the release of β-glucuronidase (by injured hepatocytes and bacteria) which hydrolyzes bilirubin glucuronides and increases the amount of unconjugated bilirubin in bile. Between 4% and 20% of stones are mixed.[3]

# Diagnosis [edit]

Diagnosis is than typically confirmed by ultrasound. Complications may be detected on blood tests.[1]

A positive Murphy's sign is a common finding on physical examination during a gallbladder attack.

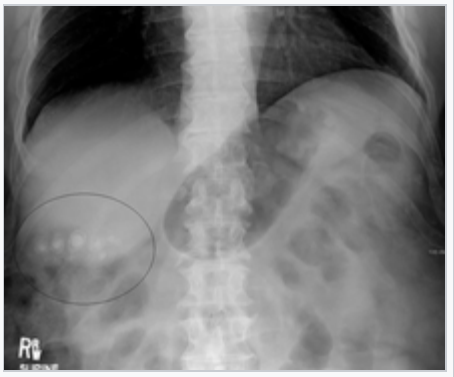


A 1.9 cm gallstone impacted in the neck of the gallbladder and leading to cholecystitis as seen on ultrasound. There is 4 mm gall bladder wall thickening.

## Treatment [edit]

### Surgical [edit]

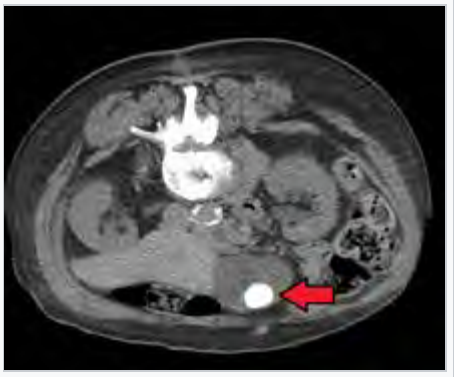
Cholecystectomy (gallbladder removal) has a 99% chance of eliminating the recurrence of cholelithiasis. Surgery is only indicated in symptomatic patients. The lack of a gallbladder may have no negative consequences in many people. However, there is a portion of the population—between 10 and 15%—who develop a condition called postcholecystectomy syndrome[31] which may cause gastrointestinal distress and persistent pain in the upper-right abdomen, as well as a 10% risk of developing chronic diarrhea.[32]



Gallstones as seen on plain X-ray

There are two surgical options for cholecystectomy:

- Open cholecystectomy is performed via an abdominal incision (laparotomy) below the lower right ribs. Recovery typically requires 3–5 days of hospitalization, with a return to normal diet a week after release and to normal activity several weeks after release.[8]
- Laparoscopic cholecystectomy, introduced in the 1980s,[33] is performed via three to four small puncture holes for a camera and instruments. Post-operative care typically includes a same-day release or a one night hospital stay, followed by a few days of home rest and pain medication.[8] Laparoscopic cholecystectomy patients can, in general, resume normal diet and light activity a week after release, with some decreased energy level and minor residual pain continuing for a month or two. Studies have shown that this procedure is as effective as the more invasive open cholecystectomy, provided the stones are accurately located by cholangiogram prior to the procedure so that they can all be removed.[*citation needed*]



Large gallstone as seen on CT

### Medical [edit]

Cholesterol gallstones can sometimes be dissolved with ursodeoxycholic acid taken by mouth, but it may be necessary for the person to take this medication for years.[34] Gallstones may recur, however, once the drug is stopped. Obstruction of the common bile duct with gallstones can sometimes be relieved by endoscopic retrograde sphincterotomy (ERS) following endoscopic retrograde cholangiopancreatography (ERCP). Gallstones can be broken up using a procedure called extracorporeal shock wave lithotripsy (often simply called "lithotripsy"),[34] which is a method of concentrating ultrasonic shock waves onto the stones to break them into tiny pieces. They are then passed safely in the feces. However, this form of treatment is suitable only when there is a small number of gallstones.

## Other animals [edit]

Gallstones are a valuable by-product of animals butchered for meat because their use as a purported antipyretic and antidote in the folk remedies of some cultures, in particular, in China. The finest gallstones

tend to be sourced from old dairy cows, which are called *niuhuang* (yellow thing of cattle) in Chinese. Much as in the manner of diamond mines, slaughterhouses carefully scrutinize workers for gallstone theft.[35]

## See also [edit]

- Porcelain gallbladder

## References [edit]


1. ^ a b c d e f g h i "Gallstones". *NIDDK*. November 2013. Retrieved 27 July 2016.
2. ^ a b Internal Clinical Guidelines Team (October 2014). "Gallstone Disease: Diagnosis and Management of Cholelithiasis, Cholecystitis and Choledocholithiasis. Clinical Guideline 188": 101. PMID 25473723.
3. ^ a b c d Lee, JY; Keane, MG; Pereira, S (June 2015). "Diagnosis and treatment of gallstone disease.". *The Practitioner*. **259** (1783): 15–9, 2. PMID 26455113.
4. ^ a b c d Ansaloni, L (2016). "2016 WSES guidelines on acute calculous cholecystitis.". *World journal of emergency surgery : WJES*. **11**: 25. doi:10.1186/s13017-016-0082-5. PMC 4908702. PMID 27307785.
5. ^ editors, Ronnie A. Rosenthal, Michael E. Zenilman, Mark R. Katlic, (2011). *Principles and practice of geriatric surgery* (2nd ed.). Berlin: Springer. p. 944. ISBN 9781441969996.
6. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
7. ^ GBD 2013 Mortality and Causes of Death, Collaborators (10 January 2015). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **385** (9963): 117–71. doi:10.1016/s0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
8. ^ a b c National Institute of Diabetes and Digestive and Kidney Diseases (2007). "Gallstones" (PDF). Bethesda, Maryland: National Digestive Diseases Information Clearinghouse, National Institutes of Health, United States Department of Health and Human Services. Retrieved 2010-11-06.
9. ^ Heuman DM, Mihas AA, Allen J (2010). "Cholelithiasis". Omaha, Nebraska: Medscape (WebMD). Retrieved 2010-11-06.
10. ^ Acalovschi, Monica; Blendea, Dan; Feier, Cristina; Letia, Alfred I.; Raitu, Nadia; Dumitrascu, Dan L.; Veres, Adina (2003). "Risk factors for symptomatic gallstones in patients with liver cirrhosis: a case-control study". *The American Journal of Gastroenterology*. **98** (8): 1856–1860. doi:10.1111/j.1572-0241.2003.07618.x. PMID 12907344.
11. ^ a b "Gallstones (Cholelithiasis) Clinical Presentation: History, Physical Examination". *emedicine.medscape.com*. Retrieved 2016-11-14.
12. ^ Fitzgerald JE, Fitzgerald LA, Maxwell-Armstrong CA, Brooks AJ (2009). "Recurrent gallstone ileus: time to change our surgery?". *Journal of Digestive Diseases*. **10** (2): 149–151. doi:10.1111/j.1751-2980.2009.00378.x. PMID 19426399.
13. ^ Roizen MF and Oz MC, *Gut Feelings: Your Digestive System*, pp. 175–206 in Roizen and Oz (2005)
14. ^ Koppisetti, Sreedevi; Jenigiri, Bharat; Terron, M. Pilar; Tengattini, Sandra; Tamura, Hiroshi; Flores, Luis J.; Tan, Dun-Xian; Reiter, Russel J. (2008). "Reactive Oxygen Species and the Hypomotility of the Gall Bladder as Targets for the Treatment of Gallstones with Melatonin: A Review". *Digestive Diseases and Sciences*. **53** (10): 2592–603. doi:10.1007/s10620-007-0195-5. PMID 18338264.
15. ^ Thunell S (2009). "Prevalence of different types of gallstone in the patients with cholelithiasis at Kathmandu Medical College, Nepal". *Kathmandu Univ Med J (KUMJ)*. **7**: 268–71. PMID 20071875.
16. ^ Shrestha, Rojeet; Gyawali, P; Yadav, BK; Poudel, Bibek (2009-01-01). "In response to the article entitled "Prevalence of different types ofgallstone in the patients with cholelithiasis at Kathmandu MedicalCollege" by Pradhan SB, Joshi MR and Vaidya A published in KUMJ2009 Vol 7, No. 3, Issue 25, 268-71". *Kathmandu University Medical Journal*. **7** (28). ISSN 1812-2027.
17. ^ Ortega RM, Fernández-Azuela M, Encinas-Sotillos A, Andrés P, López-Sobaler AM (1997). "Differences in diet and food habits between patients with gallstones and controls". *Journal of the American College of Nutrition*. **16** (1): 88–95. doi:10.1080/07315724.1997.10718655. PMID 9013440. Retrieved 2010-11-06.
18. ^ Tsai, C.-J.; Leitzmann, M. F.; Willett, W. C.; Giovannucci, E. L. (2005-06-01). "Dietary carbohydrates and glycaemic load and the incidence of symptomatic gall stone disease in men". *Gut*. **54** (6): 823–828. doi:10.1136/gut.2003.031435. ISSN 1468-3288. PMC 1774557. PMID 15888792.

19. ^ Misciagna, Giovanni; Leoci, Claudio; Guerra, Vito; Chiloiro, Marisa; Elba, Silvana; Petruzzi, José; Mossa, Ascanio; Noviello, Maria R.; Coviello, Angelo; Minutolo, Marino Capece; Mangini, Vito; Messa, Caterina; Cavallini, Aldo; Michele, Giampiero De; Giorgio, Italo (1996). "Epidemiology of cholelithiasis in southern Italy. Part II". *European Journal of Gastroenterology & Hepatology*. **8** (6): 585–93. doi:10.1097/00042737-199606000-00017.
20. ^ Choices, NHS. "Should you lose weight fast? - Live Well—NHS Choices". *www.nhs.uk*. Retrieved 2016-02-16.
21. ^ Commissioner, Office of the. "Safety Information—Xenical (orlistat) capsules". *www.fda.gov*. Retrieved 2016-06-18.
22. ^ [a] [b] Stokes, Caroline S.; Gluud, Lise Lotte; Casper, Markus; Lammert, Frank (2014-07-01). "Ursodeoxycholic Acid and Diets Higher in Fat Prevent Gallbladder Stones During Weight Loss: A Meta-analysis of Randomized Controlled Trials". *Clinical Gastroenterology and Hepatology*. **12** (7): 1090–1100.e2. doi:10.1016/j.cgh.2013.11.031. ISSN 1542-3565.
23. ^ Trotman, Bruce W.; Bernstein, Seldon E.; Bove, Kevin E.; Wirt, Gary D. (1980). "Studies on the Pathogenesis of Pigment Gallstones in Hemolytic Anemia". *Journal of Clinical Investigation*. **65** (6): 1301–8. doi:10.1172/JCI109793. PMC 371467. PMID 7410545.
24. ^ *Endocrine and Metabolic Disorders: Cutaneous Porphyrias*, pp. 63–220 in Beers, Porter and Jones (2006)
25. ^ Thunell S (2008). "Endocrine and Metabolic Disorders: Cutaneous Porphyrias". Whitehouse Station, New Jersey: Merck Sharp & Dohme Corporation. Retrieved 2010-11-07.
26. ^ M. A. Cahan, M. A.; L. Balduf; K. Colton; B. Palacioz; W. McCartney; T. M. Farrell (2006). "Proton pump inhibitors reduce gallbladder function". *Surgical Endoscopy*. **20** (9): 1364–1367. doi:10.1007/s00464-005-0247-x. PMID 16858534.
27. ^ Experimental investigation of the flow of bile in patient specific cystic duct models M Al-Atabi, SB Chin…, Journal of biomechanical engineering, 2010
28. ^ Gallstones—Cholelithiasis; Gallbladder attack; Biliary colic; Gallstone attack; Bile calculus; Biliary calculus Last reviewed: July 6, 2009. Reviewed by: George F. Longstreth. Also reviewed by David Zieve
29. ^ Channa, Naseem A.; Khand, Fateh D.; Khand, Tayab U.; Leghari, Mhhammad H.; Memon, Allah N. (2007). "Analysis of human gallstones by Fourier Transform Infrared (FTIR)". *Pakistan Journal of Medical Sciences*. **23** (4): 546–50. ISSN 1682-024X. Retrieved 2010-11-06.
30. ^ [a] [b] [c] Kim IS, Myung SJ, Lee SS, Lee SK, Kim MH (2003). "Classification and nomenclature of gallstones revisited" (PDF). *Yonsei Medical Journal*. **44** (4): 561–70. ISSN 0513-5796. PMID 12950109. Retrieved 2010-11-06.
31. ^ Jensen (2010). "Postcholecystectomy syndrome". Omaha, Nebraska: Medscape (WebMD). Retrieved 2011-01-20.
32. ^ Marks, Janet; Shuster, Sam; Watson, A. J. (1966). "Small-bowel changes in dermatitis herpetiformis". *The Lancet*. **288** (7476): 1280–2. doi:10.1016/S0140-6736(66)91692-8. PMID 4163419.
33. ^ Keus, Frederik; de Jong, Jeroen; Gooszen, H G; Laarhoven, C JHM; Keus, Frederik (2006). "Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis". *Cochrane Database of Systematic Reviews* (4): CD006231. doi:10.1002/14651858.CD006231. PMID 17054285.
34. ^ [a] [b] National Health Service (2010). "Gallstones — Treatment". *NHS Choices: Health A-Z—Conditions and treatments*. London: National Health Service. Retrieved 2010-11-06.
35. ^ "Interview with Darren Wise. Transcrip". Omaha, Nebraska: Medscape (WebMD). Retrieved 2010-11-06.


## External links [edit]

- MedlinePlus Encyclopedia *Gallbladder removal*
- 5-Minute Clinical Consult *Cholelithiasis*
- cholelithiasis US Classic gallstone with shadow and cholecystitis
- Gallstones In-Depth Report from nytimes.com.

Wikimedia Commons has media related to *Gallstones*.

| v · t · e · | **Diseases of the digestive system (primarily K20–K93, 530–579)** |
|---|---|
| **Upper GI tract** | **Esophagus** | Esophagitis (Candidal · Eosinophilic · Herpetiform · · *Rupture* (Boerhaave syndrome · Mallory-Weiss syndrome · · UES (Zenker's diverticulum · · LES (Barrett's esophagus · · Esophageal motility disorder (Nutcracker esophagus · Achalasia · Diffuse esophageal spasm · Gastroesophageal reflux disease (GERD) · · Laryngopharyngeal reflux (LPR) · Esophageal stricture · Megaesophagus · |

| | | |
|---|---|---|
| | **Stomach** | Gastritis (Atrophic · Ménétrier's disease · Gastroenteritis · · Peptic (gastric) ulcer (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
| **Lower GI tract: Intestinal/ Enteropathy** | **Small intestine (Duodenum/Jejunum/Ileum)** | Enteritis (Duodenitis · Jejunitis · Ileitis · · Peptic (duodenal) ulcer (Curling's ulcer · · Malabsorption: Coeliac · Tropical sprue · Blind loop syndrome · Small bowel bacterial overgrowth syndrome · Whipple's · Short bowel syndrome · Steatorrhea · Milroy disease · Bile acid malabsorption · |
| | **Large intestine (Appendix/Colon)** | Appendicitis · Colitis (Pseudomembranous · Ulcerative · Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (IBS · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
| | **Large and/or small** | Enterocolitis (Necrotizing · · Gastroenterocolitis · IBD (Crohn's disease · · *Vascular*: Abdominal angina · Mesenteric ischemia · Angiodysplasia · Bowel obstruction: Ileus · Intussusception · Volvulus · Fecal impaction · Constipation · Diarrhea (Infectious · · Intestinal adhesions · |
| | **Rectum** | Proctitis (Radiation proctitis · · Proctalgia fugax · Rectal prolapse · Anismus · |
| | **Anal canal** | Anal fissure/Anal fistula · Anal abscess · Anal dysplasia · Pruritus ani · |
| **GI bleeding/BIS** | | Upper (Hematemesis · Melena · · Lower (Hematochezia · · |
| **Accessory** | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · Acute liver failure · · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |
| | **Gallbladder** | Cholecystitis · **Gallstones**/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · **Gallstones**/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
| | **Pancreatic** | Pancreatitis (Acute · Chronic · Hereditary · Pancreatic abscess · · Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |

| | | |
|---|---|---|
| **Abdominopelvic** | **Hernia** | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |
| **Authority control** | GND: 4137688-2 · NDL: 00572683 · | |

Categories: Gallbladder disorders | Hepatology | Abdominal pain | Steatorrhea-related diseases




# Gastritis

From Wikipedia, the free encyclopedia

**Gastritis** is inflammation of the lining of the stomach. It may occur as a short episode or may be of a long duration. There may be no symptoms but, when symptoms are present, the most common is upper abdominal pain.[1] Other possible symptoms include nausea and vomiting, bloating, loss of appetite and heartburn.[1][2] Complications may include bleeding, stomach ulcers, and stomach tumors.[1] When due to autoimmune problems, low red blood cells due to not enough vitamin B12 may occur, a condition known as pernicious anemia.[3]

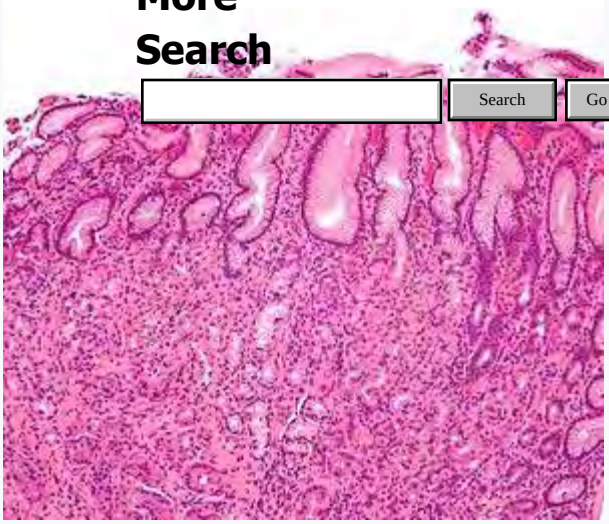
Common causes include infection with *Helicobacter pylori* and use of NSAIDs. Less common causes include alcohol, smoking, cocaine, severe illness, autoimmune problems, radiation therapy and Crohn's disease, among others.[1][4] Endoscopy, a type of X-ray known as an upper gastrointestinal series, blood tests, and stool tests may help with diagnosis.[1] The symptoms of gastritis may be a presentation of a myocardial infarction. Other conditions with similar symptoms include inflammation of the pancreas, gallbladder problems, and peptic ulcer disease.[2]

Prevention is by avoiding things that cause the disease.[5] Treatment includes medications such as antacids, H2 blockers, or proton pump inhibitors.[1] During an acute attack drinking viscous lidocaine may help.[6] If gastritis is due to NSAIDs these may be stopped. If *H. pylori* is present it may be treated with a combination of antibiotics such as amoxicillin and clarithromycin.[1] For those with pernicious anemia, vitamin B12 supplements are recommended either by mouth or by injection.[3] People are usually advised to avoid foods that bother them.[7]

Gastritis is believed to affect about half of people worldwide.[5] In 2013 there were approximately 90 million new cases of the condition.[8] As people get older the disease becomes more common.[5] It, along with a similar condition in the first part of the intestines known as duodenitis, resulted in 60,000 deaths in 2013.[9] *H. pylori* was first discovered in 1981 by Barry Marshall and Robin Warren.[10]

Contents


**Gastritis**



Micrograph showing gastritis. H&E stain.

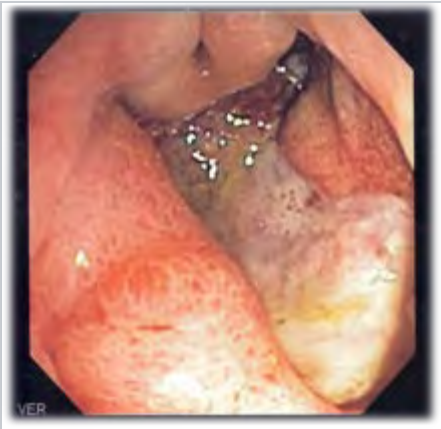
**Classification and external resources**

| | |
|---|---|
| **Specialty** | Gastroenterology |
| **ICD-10** | K29.0-K29.7 |
| **ICD-9-CM** | 535.0-535.5 |
| **DiseasesDB** | 34500 |
| **MedlinePlus** | 001150 |
| **eMedicine** | emerg/820 med/852 |
| **MeSH** | D005756 |

[edit on Wikidata]

## Signs and symptoms [edit]

Many people with gastritis experience no symptoms at all. However, upper central abdominal pain is the most common symptom; the pain may be dull, vague, burning, aching, gnawing, sore, or sharp.[11] Pain is usually located in the upper central portion of the abdomen,[12] but it may occur anywhere from the upper left portion of the abdomen around to the back.



A peptic ulcer may accompany gastritis. Endoscopic image.

Other signs and symptoms may include the following:

- Nausea
- Vomiting (if present, may be clear, green or yellow, blood-streaked, or completely bloody, depending on the severity of the stomach inflammation)
- Belching (if present, usually does not relieve the pain much)
- Bloating
- Early satiety[11]
- Loss of appetite
- Unexplained weight loss

## Cause [edit]

Common causes include *Helicobacter pylori* and NSAIDs. Less common causes include alcohol, cocaine, severe illness and Crohn disease, among others.[1]

### *Helicobacter pylori* [edit]

*Helicobacter pylori* colonizes the stomachs of more than half of the world's population, and the infection continues to play a key role in the pathogenesis of a number of gastroduodenal diseases. Colonization of the gastric mucosa with *Helicobacter pylori* results in the development of chronic gastritis in infected individuals, and in a subset of patients chronic gastritis progresses to complications (e.g., ulcer disease, gastric neoplasias, some distinct extragastric disorders).[13] However, over 80 percent of individuals infected with the bacterium are asymptomatic and it has been postulated that it may play an important role in the natural stomach ecology.[14]

### Critical illness [edit]

Gastritis may also develop after major surgery or traumatic injury ("Cushing ulcer"), burns ("Curling ulcer"), or severe infections. Gastritis may also occur in those who have had weight loss surgery resulting in the banding or reconstruction of the digestive tract.

Edit links

### Diet [edit]

Evidence does not support a role for specific foods including spicy foods and coffee in the development of

peptic ulcers.[15] People are usually advised to avoid foods that bother them.[7]

## Pathophysiology [edit]

### Acute [edit]

Acute erosive gastritis typically involves discrete foci of surface necrosis due to damage to mucosal defenses.[16] NSAIDs inhibit cyclooxygenase-1, or COX-1, an enzyme responsible for the biosynthesis of eicosanoids in the stomach, which increases the possibility of peptic ulcers forming.[17] Also, NSAIDs, such as aspirin, reduce a substance that protects the stomach called prostaglandin. These drugs used in a short period are not typically dangerous. However, regular use can lead to gastritis.[18] Additionally, severe physiologic stress ("stress ulcers") from sepsis, hypoxia, trauma, or surgery, is also a common etiology for acute erosive gastritis. This form of gastritis can occur in more than 5% of hospitalized patients.

Also, note that alcohol consumption does not cause chronic gastritis. It does, however, erode the mucosal lining of the stomach; low doses of alcohol stimulate hydrochloric acid secretion. High doses of alcohol do not stimulate secretion of acid.[19]

### Chronic [edit]

Chronic gastritis refers to a wide range of problems of the gastric tissues.[16] The immune system makes proteins and antibodies that fight infections in the body to maintain a homeostatic condition. In some disorders the body targets the stomach as if it were a foreign protein or pathogen; it makes antibodies against, severely damages, and may even destroy the stomach or its lining.[18] In some cases bile, normally used to aid digestion in the small intestine, will enter through the pyloric valve of the stomach if it has been removed during surgery or does not work properly, also leading to gastritis. Gastritis may also be caused by other medical conditions, including HIV/AIDS, Crohn's disease, certain connective tissue disorders, and liver or kidney failure. Since 1992, chronic gastritis lesions are classified according to the Sydney system.[20]

### Metaplasia [edit]

Mucous gland metaplasia, the reversible replacement of differentiated cells, occurs in the setting of severe damage of the gastric glands, which then waste away (atrophic gastritis) and are progressively replaced by mucous glands. Gastric ulcers may develop; it is unclear if they are the causes or the consequences. Intestinal metaplasia typically begins in response to chronic mucosal injury in the antrum, and may extend to the body. Gastric mucosa cells change to resemble intestinal mucosa and may even assume absorptive characteristics. Intestinal metaplasia is classified histologically as complete or incomplete. With complete metaplasia, gastric mucosa is completely transformed into small-bowel mucosa, both histologically and functionally, with the ability to absorb nutrients and secrete peptides. In incomplete metaplasia, the epithelium assumes a histologic appearance closer to that of the large intestine and frequently exhibits dysplasia.[16]

## Diagnosis [edit]

Often, a diagnosis can be made based on the patient's description of their symptoms, but other methods which may be used to verify gastritis include:

- Blood tests:
  - Blood cell count
  - Presence of *H. pylori*
  - Liver, kidney, gallbladder, or pancreas functions
- Urinalysis
- Stool sample, to look for blood in the stool
- X-rays

- ECGs
- Endoscopy, to check for stomach lining inflammation and mucous erosion
- Stomach biopsy, to test for gastritis and other conditions[21]

## Treatment [edit]

Antacids are a common treatment for mild to medium gastritis.[22] When antacids do not provide enough relief, medications such as $H_2$ blockers and proton-pump inhibitors that help reduce the amount of acid are often prescribed.[22][23]

Cytoprotective agents are designed to help protect the tissues that line the stomach and small intestine. They include the medications sucralfate and misoprostol. If NSAIDs are being taken regularly, one of these medications to protect the stomach may also be taken. Another cytoprotective agent is bismuth subsalicylate.

Several regimens are used to treat *H. pylori* infection. Most use a combination of two antibiotics and a proton pump inhibitor. Sometimes bismuth is also added to the regimen.

## See also [edit]

- Gastroenteritis
- Esophagitis

## References [edit]


1. ^ *a b c d e f g h* "Gastritis". *The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)*. November 27, 2013. Retrieved 1 March 2015.
2. ^ *a b* *Rosen & Barkin's 5-Minute Emergency Medicine Consult* (4 ed.). Lippincott Williams & Wilkins. 2012. p. 447. ISBN 9781451160970.
3. ^ *a b* Varbanova, M.; Frauenschläger, K.; Malfertheiner, P. (Dec 2014). "Chronic gastritis - an update.". *Best Pract Res Clin Gastroenterol*. **28** (6): 1031–42. doi:10.1016/j.bpg.2014.10.005. PMID 25439069.
4. ^ Stephen Hauser (2014). *Mayo Clinic Gastroenterology and Hepatology Board Review*. Oxford University Press. p. 49. ISBN 9780199373338.
5. ^ *a b c* Fred F. Ferri (2012). *Ferri's Clinical Advisor 2013,5 Books in 1, Expert Consult - Online and Print,1: Ferri's Clinical Advisor 2013*. Elsevier Health Sciences. p. 417. ISBN 9780323083737.
6. ^ James G. Adams (2012). "32". *Emergency Medicine: Clinical Essentials*. Elsevier Health Sciences. ISBN 9781455733941.
7. ^ *a b* Holdsworth, [edited by] Joan Gandy, Angela Madden, Michelle (2012). *Oxford handbook of nutrition and dietetics* (2nd ed.). Oxford: Oxford University Press, USA. p. 571. ISBN 9780199585823.
8. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic
13. ^ Kandulski A, Selgrad M, Malfertheiner P (August 2008). "Helicobacter pylori infection: a clinical overview". *Digestive and Liver Disease*. **40** (8): 619–26. doi:10.1016/j.dld.2008.02.026. PMID 18396114.
14. ^ Blaser, M. J. (2006). "Who are we? Indigenous microbes and the ecology of human diseases" (PDF). *EMBO Reports*. **7** (10): 956–60. doi:10.1038/sj.embor.7400812. PMC 1618379. PMID 17016449.
15. ^ Pennsylvania, editors, Raphael Rubin, M.D., Professor of Pathology, David S. Strayer, M.D., Ph. D., Professor of Pathology, Department of Pathology and Cell Biology, Jefferson Medical College of Thomas Jefferson University Philadelphia, Pennsylvania ; Founder and Consulting Editor, Emanuel Rubin, M.D., Gonzalo Aponte Distinguished Professor of Pathology, Chairman Emeritus of the Department of Pathology and Cell Biology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, (2012). *Rubin's pathology : clinicopathologic foundations of medicine* (Sixth ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 623. ISBN 9781605479682.
16. ^ *a b c* "Gastritis". Merck. January 2007. Retrieved 2009-01-11.
17. ^ Dajani EZ, Islam K (August 2008). "Cardiovascular and gastrointestinal toxicity of selective cyclo-oxygenase-2 inhibitors in man" (PDF). *J Physiol*

analysis for the Global Burden of Disease Study 2013."🔗. *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4🔗. PMC 4561509🔗. PMID 26063472🔗.

9. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013."🔗. *Lancet*. **385**: 117–71. doi:10.1016/S0140-6736(14)61682-2🔗. PMC 4340604🔗. PMID 25530442🔗.
10. ^ Wang, AY; Peura, DA (October 2011). "The prevalence and incidence of Helicobacter pylori-associated peptic ulcer disease and upper gastrointestinal bleeding throughout the world.". *Gastrointestinal endoscopy clinics of North America*. **21** (4): 613–35. doi:10.1016/j.giec.2011.07.011🔗. PMID 21944414🔗.
11. ^ *a b* "Gastritis Symptoms"🔗. eMedicineHealth. 2008. Retrieved 2008-11-18.
12. ^ "Gastritis"🔗. *National Digestive Diseases Information Clearinghouse*. National Institute of *Pharmacol*. 59 Suppl 2: 117–33. PMID 18812633 .
18. ^ *a b* Siegelbaum, Jackson (2006). "Gastritis"🔗. Jackson Siegelbaum Gastroenterology. Retrieved 2008-11-18.
19. ^ Wolff G (1989). "[Effect of alcohol on the stomach]" [Effect of alcohol on the stomach]. *Gastroenterol J* (in German). **49** (2): 45–9. PMID 2679657🔗.
20. ^ Mayo Clinic Staff (April 13, 2007). "Gastritis"🔗. MayoClinic. Retrieved 2008-11-18.
21. ^ "Exams and Tests"🔗. eMedicinHealth. 2008. Retrieved 2008-11-18.
22. ^ *a b* Zajac, P; Holbrook, A; Super, ME; Vogt, M (March–April 2013). "An overview: Current clinical guidelines for the evaluation, diagnosis, treatment, and management of dyspepsia". *Osteopathic Family Physician*. **5** (2): 79–85. doi:10.1016/j.osfp.2012.10.005🔗.
23. ^ Boparai V, Rajagopalan J, Triadafilopoulos G (2008). "Guide to the use of proton pump inhibitors in adult patients". *Drugs*. **68** (7): 925–47. doi:10.2165/00003495-200868070-00004🔗. PMID 18457460🔗.



| v · t · e · | Diseases of the digestive system (primarily K20–K93, 530–579) | |
|---|---|---|
| **Upper GI tract** | **Esophagus** | Esophagitis (Candidal · Eosinophilic · Herpetiform · · *Rupture* (Boerhaave syndrome · Mallory-Weiss syndrome · · UES (Zenker's diverticulum · · LES (Barrett's esophagus · · Esophageal motility disorder (Nutcracker esophagus · Achalasia · Diffuse esophageal spasm · Gastroesophageal reflux disease (GERD) · · Laryngopharyngeal reflux (LPR) · Esophageal stricture · Megaesophagus · |
| | **Stomach** | **Gastritis** (Atrophic · Ménétrier's disease · Gastroenteritis · · Peptic (gastric) ulcer (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
| **Lower GI tract: Intestinal/ Enteropathy** | **Small intestine (Duodenum/Jejunum/Ileum)** | Enteritis (Duodenitis · Jejunitis · Ileitis · · Peptic (duodenal) ulcer (Curling's ulcer · · Malabsorption: Coeliac · Tropical sprue · Blind loop syndrome · Small bowel bacterial overgrowth syndrome · Whipple's · Short bowel syndrome · Steatorrhea · Milroy disease · Bile acid malabsorption · |
| | **Large intestine (Appendix/Colon)** | Appendicitis · Colitis (Pseudomembranous · Ulcerative · Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (IBS · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
| | **Large and/or small** | Enterocolitis (Necrotizing · · Gastroenterocolitis · IBD (Crohn's disease · · *Vascular*: Abdominal angina · Mesenteric ischemia · Angiodysplasia · Bowel obstruction: Ileus · Intussusception · Volvulus · Fecal impaction · |

| | | |
|---|---|---|
| | | Constipation · Diarrhea (Infectious · · Intestinal adhesions · |
| | **Rectum** | Proctitis (Radiation proctitis · · Proctalgia fugax · Rectal prolapse · Anismus · |
| | **Anal canal** | Anal fissure/Anal fistula · Anal abscess · Anal dysplasia · Pruritus ani · |
| **GI bleeding / BIS** | | Upper (Hematemesis · Melena · · Lower (Hematochezia · · |
| **Accessory** | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · Acute liver failure · · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |
| | **Gallbladder** | Cholecystitis · Gallstones/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · Gallstones/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
| | **Pancreatic** | Pancreatitis (Acute · Chronic · Hereditary · Pancreatic abscess · · Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |
| **Abdominopelvic** | **Hernia** | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |

| v · t · e · | **Inflammation** | | |
|---|---|---|---|
| **Acute** | **Plasma derived mediators** | | Bradykinin · *complement* (C3 · C5a · MAC · · *coagulation* (Factor XII · Plasmin · Thrombin · · |
| | **Cell derived mediators** | *preformed:* | Lysosome granules · *biogenic amines* (Histamine · Serotonin · · |
| | | *synthesized on demand:* | *cytokines* (IFN-γ · IL-8 · TNF-α · IL-1 · · *eicosanoids* (Leukotriene B4 · Prostaglandins · · Nitric oxide · Kinins · |
| **Chronic** | Macrophage · Epithelioid cell · Giant cell · Granuloma · | | |

| | | | |
|---|---|---|---|
| **Processes** | **Traditional:** | | Rubor · Calor · Tumor · Dolor · Functio laesa · |
| | **Modern:** | | Acute-phase reaction/Fever · Vasodilation · Increased vascular permeability · Exudate · Leukocyte extravasation · Chemotaxis · |
| **Specific locations** | **Nervous** | | *CNS* (Encephalitis · Myelitis · · Meningitis (Arachnoiditis · · *PNS* (Neuritis · · *eye* (Dacryoadenitis · Scleritis · Episcleritis · Keratitis · chorioretinitis · Retinitis · Chorioretinitis · Blepharitis · Conjunctivitis · Uveitis · · *ear* (Otitis · Labyrinthitis · Mastoiditis · · |
| | **Cardiovascular** | | Carditis (Endocarditis · Myocarditis · Pericarditis · · Vasculitis (Arteritis · Phlebitis · Capillaritis · · |
| | **Respiratory** | | *upper* (Sinusitis · Rhinitis · Pharyngitis · Laryngitis · · *lower* (Tracheitis · Bronchitis · Bronchiolitis · Pneumonitis · Pleuritis · · Mediastinitis · |
| | **Digestive** | *mouth* | Stomatitis · Gingivitis · Gingivostomatitis · Glossitis · Tonsillitis · Sialadenitis/Parotitis · Cheilitis · Pulpitis · Gnathitis · |
| | | *tract* | Esophagitis · **Gastritis** · Gastroenteritis · Enteritis · Colitis · Enterocolitis · Duodenitis · Ileitis · Caecitis · Appendicitis · Proctitis · |
| | | *accessory* | Hepatitis · Ascending cholangitis · Cholecystitis · Pancreatitis · Peritonitis · |
| | **Integumentary** | | Dermatitis (Folliculitis · · Cellulitis · Hidradenitis · |
| | **Musculoskeletal** | | Arthritis · Dermatomyositis · *soft tissue* (Myositis · Synovitis/Tenosynovitis · Bursitis · Enthesitis · Fasciitis · Capsulitis · Epicondylitis · Tendinitis · Panniculitis · · Osteochondritis: Osteitis/Osteomyelitis (Spondylitis · Periostitis · · Chondritis · |
| | **Urinary** | | Nephritis (Glomerulonephritis · Pyelonephritis · · Ureteritis · Cystitis · Urethritis · |
| | **Reproductive** | *female:* | Oophoritis · Salpingitis · Endometritis · Parametritis · Cervicitis · Vaginitis · Vulvitis · Mastitis · |
| | | *male:* | Orchitis · Epididymitis · Prostatitis · Seminal vesiculitis · Balanitis · Posthitis · Balanoposthitis · |
| | | *pregnancy/newborn:* | Chorioamnionitis · Funisitis · Omphalitis · |
| | **Endocrine** | | Insulitis · Hypophysitis · Thyroiditis · Parathyroiditis · Adrenalitis · |
| | **Lymphatic** | | Lymphangitis · Lymphadenitis · |

| | | |
|---|---|---|
| v · t · e · | **Alcohol and health** | |
| **Specific interactions** | Note: see Template:Psychoactive substance use for diagnoses<br>Aging · Alcohol-induced mood disorders · Brain · Cancer (breast cancer · · Sleep · Tolerance · Weight · | |
| **Substance** | **Sobriety** | Alcohol-free zone · Alcohol detoxification · Alcohol rehabilitation · Alcoholics Anonymous · Sober companion · |

| | | |
|---|---|---|
| **abuse prevention** | **Alcohol limitation** | 0-0-1-3 · Ban on caffeinated alcoholic beverages · Alcohol education · Alcohol server training · Recommended maximum intake of alcoholic beverages · |
| | **Addiction medicine** | Alcoholism · Anti-addictive psychedelics: Ibogaine, *Salvia divinorum* · |
| **Religion and alcohol** | | Christian views on alcohol (alcohol in the Bible · · Islam and alcohol · Dionysian Mysteries · |
| **Social issues** | | Alcohol advertising (on college campuses · · Alcohol-free beverage definition controversy · Alcohol self-medication · Native Americans · Binge drinking (0.08 BAC · · Blackout (alcohol-related amnesia) · College student alcoholism · Domestic violence · Drinking games / pregaming · Driving under the influence · Drunkorexia · Dry January · Adult Children of Alcoholics · Family systems · French paradox · High-functioning alcoholic (HFA) · moonshine contamination · Rum-running (black market · · Sex · Sin tax / Pigovian tax · |
| **General** | | Short-term effects of alcohol consumption · Long-term effects of alcohol consumption · |
| **Authority control** | | NDL: 00563898 · |

Categories: Inflammations | Conditions diagnosed by stool test | Stomach disorders




# Gastrointestinal bleeding

From Wikipedia, the free encyclopedia

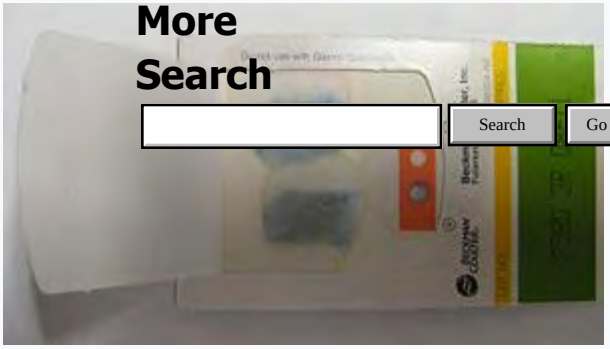
**Gastrointestinal bleeding**, **gastrointestinal hemorrhage**, is all forms of bleeding in the gastrointestinal tract, from the mouth to the rectum.[1] When there is significant blood loss over a short time, symptoms may include vomiting red blood, vomiting black blood, bloody stool, or black stool. Small amounts of bleeding over a long time may cause iron-deficiency anemia resulting in feeling tired or heart-related chest pain.[2] Other symptoms may include abdominal pain, shortness of breath, pale skin, or passing out.[1][2] Sometimes in those with small amounts of bleeding no symptoms may be present.[2]

Bleeding is typically divided into two main types: upper gastrointestinal bleeding and lower gastrointestinal bleeding.[3] Causes of upper GI bleeds include: peptic ulcer disease, esophageal varices due to liver cirrhosis and cancer, among others.[4] Causes of lower GI bleeds include: hemorrhoids, cancer, and inflammatory bowel disease among others.[3] Diagnosis typically begins with a medical history and physical examination, along with blood tests. Small amounts of bleeding may be detected by fecal occult blood test. Endoscopy of the lower and upper gastrointestinal track may locate the area of bleeding. Medical imaging may be useful in cases that are not clear.[2]

Initial treatment focuses on resuscitation which may include intravenous fluids and blood transfusions.[5] Often blood transfusions are not recommended unless the hemoglobin is less than 70 or 80 g/L.[6][7] Treatment with proton pump inhibitors, octreotide, and antibiotics may be considered in certain cases.[8][9][10] If other measures are not effective, an esophageal balloon may be attempted in those with persumed esophageal varices.[3] Endoscopy of the esophagus, stomach, and duodenum or endoscopy of the large bowel are generally recommended within 24 hours and may allow treatment as well as diagnosis.[5]

An upper GI bleed is more common than lower GI bleed.[3] An upper GI bleed occurs in 50 to 150 per 100,000 adults per year.[11] A lower GI bleed is estimated to occur in 20 to 30 per 100,000 per year.[3] It results in about 300,000 hospital admissions a year in the United States.[2] Risk of death from a GI bleed is between 5% and 30%.[2][6] Risk of bleeding is more common in males and increases with age.[3]

**Gastrointestinal bleeding**



A positive fecal occult blood test

| Classification and external resources | |
|---|---|
| **ICD-10** | K92.2 |
| **ICD-9-CM** | 578.9 |
| **DiseasesDB** | 19317 |
| **MedlinePlus** | 003133 |
| **eMedicine** | radio/301 radio/302 emerg/381 |
| **MeSH** | D006471 |

[edit on Wikidata]

Contents

## Signs and symptoms [edit]

Gastrointestinal bleeding can range from small non-visible amounts, which are only detected by laboratory testing, to massive bleeding where bright red blood is passed and shock develops. With bleeding that is rapid there may be syncope.[12]

Blood that is digested may appear black rather than red, resulting in "coffee ground" vomit or tar colored stool called melena.[3]

Other signs and symptoms include feeling tired, dizziness, and pale skin color.[12]

## Differential diagnosis [edit]

Gastrointestinal bleeding can be roughly divided into two clinical syndromes: upper gastrointestinal bleeding and lower gastrointestinal bleeding.[3] About 2/3 of all GI bleeds are from upper sources and 1/3 from lower sources.[13] Common causes of gastrointestinal bleeding include infections, cancers, vascular disorders, adverse effects of medications, and blood clotting disorders.[3] Obscure gastrointestinal bleeding (OGIB) is when a source is unclear following investigation.

### Upper gastrointestinal [edit]

*Main article: Upper gastrointestinal bleeding*

Upper gastrointestinal bleeding is from a source between the pharynx and the ligament of Treitz. An upper source is characterised by hematemesis (vomiting up blood) and melena (tarry stool containing altered blood). About half of cases are due to peptic ulcer disease.[4] Esophageal inflammation and erosive disease are the next most common causes.[4] In those with liver cirrhosis, 50–60% of bleeding is due to esophageal varices.[4] Approximately half of those with peptic ulcers have an *H. pylori* infection.[4] Other causes include gastric or duodenal ulcers, Mallory-Weiss tears, cancer, and angiodysplasia.[3]

A number of medications are found to cause upper GI bleeds.[14] NSAIDs or COX-2 inhibitors increase the risk about fourfold.[14] SSRIs, corticosteroids, and anticoagulants may also increase the risk.[14] The risk with dabigatran is 30% greater than that with warfarin.[15]

### Lower gastrointestinal [edit]

*Main article: Lower gastrointestinal bleeding*

Lower gastrointestinal bleeding is typically from the colon, rectum or anus.[3] Common causes of lower gastrointestinal bleeding include hemorrhoids, cancer, angiodysplasia, ulcerative colitis, Crohn's disease, and

aortoenteric fistula.[3] It may be indicated by the passage of fresh red blood rectally, especially in the absence of bloody vomiting. Isolated melena may originate from anywhere between the stomach and the proximal colon.

### Other [edit]

A number of foods and medications can turn the stool either red or black.[3] Bismuth found in many antacids may turn stools black as may activated charcoal.[3] Blood from the vagina or urinary tract may also be confused with blood in the stool.[3]

## Diagnostic approach [edit]

Diagnosis is often based on direct observation of blood in the stool or vomit. This can be confirmed with a fecal occult blood test. Differentiating between upper and lower bleeding in some cases can be difficult. The severity of an upper GI bleed can be judged based on the Blatchford score[5] or Rockall score.[14] The Rockall score is the more accurate of the two.[14] As of 2008 there is no scoring system useful for lower GI bleeds.[14]

### Clinical [edit]

Gastric aspiration and or lavage, where a tube is inserted into the stomach via the nose in an attempt to determine if there is blood in the stomach, if negative does not rule out an upper GI bleed[16] but if positive is useful for ruling one in.[13] Clots in the stool indicate a lower GI source while melana stools an upper one.[13]

### Laboratory testing [edit]

Recommended laboratory blood testing includes: cross matching blood, hemoglobin, hematocrit, platelets, coagulation time, and electrolytes.[5] If the ratio of blood urea nitrogen to creatinine is greater than 30 the source is more likely from the upper GI tract.[13]

### Imaging [edit]

A CT angiography is useful for determining the exact location of the bleeding within the gastrointestinal tract.[17] Nuclear scintigraphy is a sensitive test for detecting occult gastrointestinal bleeding when direct imaging with upper and lower endoscopies are negative. Direct angiography allows for embolization of a bleeding source, but requires a bleeding rate faster than 1mL/minute.[18]

## Prevention [edit]

In those with significant varices or cirrhosis nonselective β-blockers reduce the risk of future bleeding.[9] With a target heart rate of 55 beats per minute they reduce the absolute risk of bleeding by 10%.[9] Endoscopic band ligation (EBL) is also effective at improving outcomes.[9] Either B-blockers or EBL are recommended as initial preventative measures.[9] In those who have had a previous varcial bleed both treatments are recommended.[9] With some evidence supporting the addition of isosorbide mononitrate.[19] Testing for and treating those who are positive for *H. pylori* is recommended.[14] Transjugular intrahepatic portosystemic shunting (TIPS) may be used to prevent bleeding in people who re-bleed despite other measures.[14]

## Treatment [edit]

The initial focus is on resuscitation beginning with airway management and fluid resuscitation using either intravenous fluids and or blood.[5] A number of medications may improve outcomes depending on the source of the bleeding.[5]

## Peptic ulcers [edit]

Based on evidence from people with other health problems crystalloid and colloids are believed to be equivalent for peptic ulcer bleeding.[5] Proton pump inhibitors (PPI) may reduce mortality in those with severe disease as well as the risk of re-bleeding and the need for surgery among this group.[8] Oral and intravenous formulations may be equivalent; however, the evidence to support this is suboptimal.[20] In those with less severe disease and where endoscopy is rapidly available, they are of less immediate clinical importance.[21] There is tentative evidence of benefit for tranexamic acid which inhibits clot breakdown.[22] Somatostatin and octreotide, while recommended for varicial bleeding, have not been found to be of general use for non variceal bleeds.[5] After treatment of a high risk bleeding ulcer endoscopically giving a PPI once or a day rather than as an infusion appears to work just as well and is less expensive (the method may be either by mouth or intravenously).[23]

## Variceal bleeding [edit]

For initial fluid replacement colloids or albumin is preferred in people with cirrhosis.[5] Medications typically include octreotide or, if not available, vasopressin and nitroglycerin to reduce portal venous pressures.[9] Terlipressin appears to be more effective than octreotide, but it is not available in many areas of the world.[14][24] It is the only medication that has been shown to reduce mortality in acute variceal bleeding.[24] This is in addition to endoscopic banding or sclerotherapy for the varices.[9] If this is sufficient then beta blockers and nitrates may be used for the prevention of re-bleeding.[9] If bleeding continues, balloon tamponade with a Sengstaken-Blakemore tube or Minnesota tube may be used in an attempt to mechanically compress the varices.[9] This may then be followed by a transjugular intrahepatic portosystemic shunt.[9] In those with cirrhosis, antibiotics decrease the chance of bleeding again, shorten the length of time spent in hospital, and decrease mortality.[10] Octreotide reduces the need for blood transfusions[25] and may decrease mortality.[26] No trials of vitamin K have been conducted.[27]

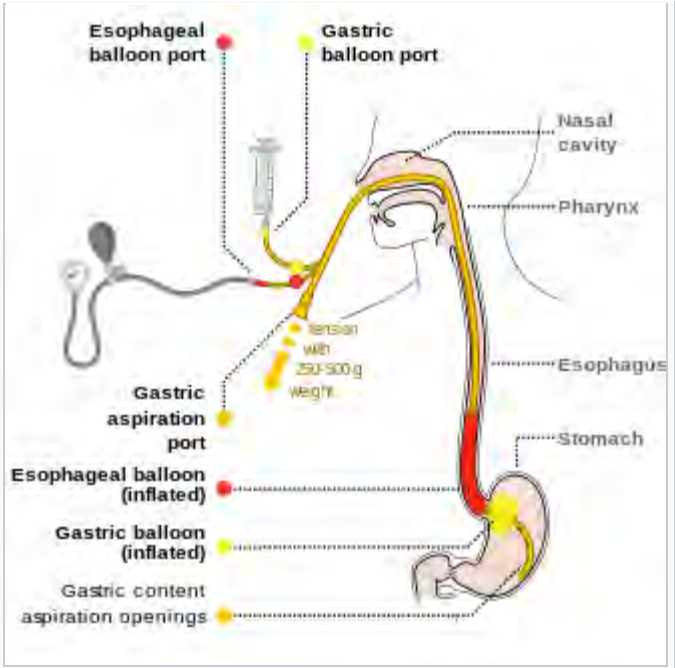
## Blood products [edit]

The evidence for benefit of blood transfusions in GI bleed is poor with some evidence finding harm.[11] In those in shock O-negative packed red blood cells are recommended.[3] If large amounts of pack red blood cells are used additional platelets and fresh frozen plasma (FFP) should be administered to prevent coagulopathies.[5] In alcoholics FFP is suggested before confirmation of a coagulopathy due to presumed blood clotting problems.[3] Evidence supports holding off on blood transfusions in those who have a hemoglobin greater than 7 to 8 g/dL and moderate bleeding, including in those with preexisting coronary artery disease.[6][7]

If the INR is greater than 1.5 to 1.8 correction with fresh frozen plasma or prothrombin complex may decrease mortality.[5] Evidence of a harm or benefit of recombinant activated factor VII in those with liver diseases and gastrointestinal bleeding is not determined.[28] A massive transfusion protocol may be used, but there is a lack of evidence for this indication.[14]

## Procedures [edit]

The benefits versus risks of placing a nasogastric tube in those with upper GI bleeding are not determined.[5] Endoscopy within 24 hours is recommended,[5] in addition to medical management.[29] A number of endoscopic treatments may be used, including:




The Blakemore esophageal balloon used for stopping esophageal bleeds if other measures have failed

epinephrine injection, band ligation, sclerotherapy, and fibrin glue depending on what is found.[3] Prokinetic agents such as erythromycin before endocopy can decrease the amount of blood in the stomach and thus improve the operators view.[5] They also decrease the amount of blood transfusions required.[30] Early endoscopy decreases hospital and the amount of blood transfusions needed.[5] A second endoscopy within a day is routinely recommended by some[14] but by others only in specific situations.[18] Proton pump inhibitors, if they have not been started earlier, are recommended in those in whom high risk signs for bleeding are found.[5] High and low dose PPIs appear equivalent at this point.[31] It is also recommended that people with high risk signs are kept in hospital for at least 72 hours.[5] Those at low risk of re-bleeding may begin eating typically 24 hours following endoscopy.[5] If other measures fail or are not available, esophageal balloon tamponade may be attempted.[3] While there is a success rate up to 90%, there are some potentially significant complications including aspiration and esophageal perforation.[3]

Colonoscopy is useful for the diagnosis and treatment of lower GI bleeding.[3] A number of techniques may be employed including: clipping, cauterizing, and sclerotherapy.[3] Preparation for colonoscopy takes a minimum of six hours which in those bleeding briskly may limit its applicability.[32] Surgery, while rarely used to treat upper GI bleeds, is still commonly used to manage lower GI bleeds by cutting out the part of the intestines that is causing the problem.[3] Angiographic embolization may be used for both upper and lower GI bleeds.[3] Transjugular intrahepatic portosystemic shunting (TIPS) may also be considered.[14]

## Prognosis [edit]

Death in those with a GI bleed is more commonly due to other illnesses (some of which may have contributed to the bleed, such as cancer or cirrhosis), than the bleeding itself.[3] Of those admitted to a hospital because of a GI bleed, death occurs in about 7%.[14] Despite treatment, re-bleeding occurs in about 7–16% of those with upper GI bleeding.[4] In those with esophageal varices, bleeding occurs in about 5–15% a year and if they have bled once, there is a higher risk of further bleeding within six weeks.[9] Testing and treating *H. pylori* if found can prevent re-bleeding in those with peptic ulcers.[5] The benefits versus risks of restarting blood thinners such as aspirin or warfarin and anti-inflammatories such as NSAIDs need to be carefully considered.[5] If aspirin is needed for cardiovascular disease prevention, it is reasonable to restart it within seven days in combination with a PPI for those with nonvariceal upper GI bleeding.[18]

## Epidemiology [edit]

Gastrointestinal bleeding from the upper tract occurs in 50 to 150 per 100,000 adults per year.[11] It is more common than lower gastrointestinal bleeding which is estimated to occur at the rate of 20 to 30 per 100,000 per year.[3] Risk of bleeding is more common in males, and increases with age.[3]

# References [edit]


1. ^ a b "Bleeding in the Digestive Tract". *The National Institute of Diabetes and Digestive and Kidney Diseases*. September 17, 2014. Retrieved 6 March 2015.
2. ^ a b c d e f Kim, BS; Li, BT; Engel, A; Samra, JS; Clarke, S; Norton, ID; Li, AE (15 November 2014). "Diagnosis of gastrointestinal bleeding: A practical guide for clinicians.". *World journal of gastrointestinal pathophysiology*. **5** (4): 467–78. doi:10.4291/wjgp.v5.i4.467. PMID 25400991.
3. ^ a b c d e f g h i j k l m n o p q r s t u v w x y z aa Westhoff, John (March 2004). "Gastrointestinal Bleeding: An Evidence-Based ED Approach To Risk Stratification". *Emergency Medicine Practice*. **6** (3).
4. ^ a b c d e f van Leerdam, ME (2008). "Epidemiology of acute upper gastrointestinal bleeding.". *Best practice & research. Clinical gastroenterology*. **22** (2): 209–24. doi:10.1016/j.bpg.2007.10.011. PMID 18346679.
5. ^ a b c d e f g h i j k l m n o p q r s t Jairath, V; Barkun, AN (October 2011). "The overall approach to the management of upper gastrointestinal bleeding". *Gastrointestinal endoscopy clinics of North America*. **21** (4): 657–70. doi:10.1016/j.giec.2011.07.001. PMID 21944416.
6. ^ a b c Wang, J; Bao, YX; Bai, M; Zhang, YG; Xu, WD; Qi, XS (28 October 2013). "Restrictive vs liberal transfusion for upper gastrointestinal bleeding: a meta-analysis of randomized controlled trials.". *World journal of gastroenterology : WJG*. **19** (40): 6919–27. doi:10.3748/wjg.v19.i40.6919. PMID 24187470.
7. ^ a b Salpeter, SR; Buckley, JS; Chatterjee, S (February 2014). "Impact of more restrictive blood transfusion strategies on clinical outcomes: a meta-analysis and systematic review.". *The American Journal of Medicine*. **127** (2): 124–131.e3. doi:10.1016/j.amjmed.2013.09.017. PMID 24331453.
8. ^ a b Leontiadis, GI; Sreedharan, A; Dorward, S; Barton, P; Delaney, B; Howden, CW; Orhewere, M; Gisbert, J; Sharma, VK; Rostom, A; Moayyedi, P; Forman, D (December 2007). "Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding". *Health technology assessment (Winchester, England)*. **11** (51): iii–iv, 1–164. doi:10.3310/hta11510. PMID 18021578.
9. ^ a b c d e f g h i j k l Cat, TB; Liu-DeRyke, X (September 2010). "Medical management of variceal hemorrhage". *Critical care nursing clinics of North America*. **22** (3): 381–93. doi:10.1016/j.ccell.2010.02.004. PMID 20691388.
10. ^ a b Chavez-Tapia, NC; Barrientos-Gutierrez, T; "Usefulness of CT angiography in diagnosing acute gastrointestinal bleeding: a meta-analysis.". *World journal of gastroenterology : WJG*. **16** (31): 3957–63. doi:10.3748/wjg.v16.i31.3957. PMC 2923771. PMID 20712058.
18. ^ a b c Barkun AN, Bardou M, Kuipers EJ, Sung J, Hunt RH, Martel M, Sinclair P (2010). "International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding". *Ann. Intern. Med.* **152** (2): 101–13. doi:10.7326/0003-4819-152-2-201001190-00009. PMID 20083829.
19. ^ Li, L; Yu, C; Li, Y (March 2011). "Endoscopic band ligation versus pharmacological therapy for variceal bleeding in cirrhosis: a meta-analysis". *Canadian journal of gastroenterology = Journal canadien de gastroenterologie*. **25** (3): 147–55. PMC 3076033. PMID 21499579.
20. ^ Tsoi, KK; Hirai, HW; Sung, JJ (Aug 5, 2013). "Meta-analysis: comparison of oral vs. intravenous proton pump inhibitors in patients with peptic ulcer bleeding.". *Alimentary pharmacology & therapeutics*. **38** (7): 721–8. doi:10.1111/apt.12441. PMID 23915096.
21. ^ Sreedharan, A; Martin, J; Leontiadis, GI; Dorward, S; Howden, CW; Forman, D; Moayyedi, P (2010-07-07). Sreedharan, Aravamuthan, ed. "Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding". *Cochrane database of systematic reviews (Online)* (7): CD005415. doi:10.1002/14651858.CD005415.pub3. PMID 20614440.
22. ^ Bennett, C; Klingenberg, SL; Langholz, E; Gluud, LL (21 November 2014). "Tranexamic acid for upper gastrointestinal bleeding.". *The Cochrane database of systematic reviews*. **11**: CD006640. doi:10.1002/14651858.CD006640.pub3. PMID 25414987.
23. ^ Sachar, H; Vaidya, K; Laine, L (November 2014). "Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis.". *JAMA internal medicine*. **174** (11): 1755–62. doi:10.1001/jamainternmed.2014.4056. PMC 4415726. PMID 25201154.
24. ^ a b Ioannou, G; Doust, J; Rockey, DC (2003). Ioannou, George N, ed. "Terlipressin for acute esophageal variceal hemorrhage". *Cochrane database of systematic reviews (Online)* (1): CD002147. doi:10.1002/14651858.CD002147. PMID 12535432.
25. ^ Gøtzsche, PC; Hróbjartsson, A (2008-07-16). Gøtzsche, Peter C, ed. "Somatostatin analogues for acute bleeding oesophageal varices". *Cochrane database of systematic reviews (Online)* (3):

Tellez-Avila, F; Soares-Weiser, K; Mendez-Sanchez, N; Gluud, C; Uribe, M (September 2011). "Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding – an updated Cochrane review". *Alimentary pharmacology & therapeutics*. **34** (5): 509–18. doi:10.1111/j.1365-2036.2011.04746.x. PMID 21707680.

11. ^ *a b c* Jairath, V; Hearnshaw, S; Brunskill, SJ; Doree, C; Hopewell, S; Hyde, C; Travis, S; Murphy, MF (2010-09-08). Jairath, Vipul, ed. "Red cell transfusion for the management of upper gastrointestinal haemorrhage". *Cochrane database of systematic reviews (Online)* (9): CD006613. doi:10.1002/14651858.CD006613.pub3. PMID 20824851.
12. ^ *a b* Prasad Kerlin, Meeta; Tokar, Jeffrey L. (6 August 2013). "Acute Gastrointestinal Bleeding". *Annals of Internal Medicine*. **159** (3): ITC2. doi:10.7326/0003-4819-159-3-201308060-01002.
13. ^ *a b c d* Srygley FD, Gerardo CJ, Tran T, Fisher DA (March 2012). "Does this patient have a severe upper gastrointestinal bleed?". *JAMA*. **307** (10): 1072–9. doi:10.1001/jama.2012.253. PMID 22416103.
14. ^ *a b c d e f g h i j k l m* Palmer, K; Nairn, M; Guideline Development, Group (2008-10-10). "Management of acute gastrointestinal blood loss: summary of SIGN guidelines" (PDF). *BMJ (Clinical research ed.)*. **337**: a1832. doi:10.1136/bmj.a1832. PMID 18849311.
15. ^ Coleman, CI; Sobieraj, DM; Winkler, S; Cutting, P; Mediouni, M; Alikhanov, S; Kluger, J (January 2012). "Effect of pharmacological therapies for stroke prevention on major gastrointestinal bleeding in patients with atrial fibrillation.". *International journal of clinical practice*. **66** (1): 53–63. doi:10.1111/j.1742-1241.2011.02809.x. PMID 22093613.
16. ^ Palamidessi, N; Sinert, R; Falzon, L; Zehtabchi, S (February 2010). "Nasogastric aspiration and lavage in emergency department patients with hematochezia or melena without hematemesis.". *Academic Emergency Medicine*. **17** (2): 126–32. doi:10.1111/j.1553-2712.2009.00609.x. PMID 20370741.
17. ^ Wu, LM; Xu, JR; Yin, Y; Qu, XH (2010-08-21). CD000193. doi:10.1002/14651858.CD000193.pub3. PMID 18677774.
26. ^ Wells, M; Chande, N; Adams, P; Beaton, M; Levstik, M; Boyce, E; Mrkobrada, M (June 2012). "Meta-analysis: vasoactive medications for the management of acute variceal bleeds". *Alimentary pharmacology & therapeutics*. **35** (11): 1267–78. doi:10.1111/j.1365-2036.2012.05088.x. PMID 22486630.
27. ^ Martí-Carvajal, AJ; Solà, I (9 June 2015). "Vitamin K for upper gastrointestinal bleeding in people with acute or chronic liver diseases.". *The Cochrane database of systematic reviews*. **6**: CD004792. doi:10.1002/14651858.CD004792.pub5. PMID 26058964.
28. ^ Martí-Carvajal, AJ; Karakitsiou, DE; Salanti, G (2012-03-14). Martí-Carvajal, Arturo J, ed. "Human recombinant activated factor VII for upper gastrointestinal bleeding in patients with liver diseases". *Cochrane database of systematic reviews (Online)*. **3**: CD004887. doi:10.1002/14651858.CD004887.pub3. PMID 22419301.
29. ^ D'Amico, G; Pagliaro, L; Pietrosi, G; Tarantino, I (2010-03-17). d'Amico, Gennaro, ed. "Emergency sclerotherapy versus vasoactive drugs for bleeding oesophageal varices in cirrhotic patients". *Cochrane database of systematic reviews (Online)* (3): CD002233. doi:10.1002/14651858.CD002233.pub2. PMID 20238318.
30. ^ Bai, Y; Guo, JF; Li, ZS (July 2011). "Meta-analysis: erythromycin before endoscopy for acute upper gastrointestinal bleeding". *Alimentary pharmacology & therapeutics*. **34** (2): 166–71. doi:10.1111/j.1365-2036.2011.04708.x. PMID 21615438.
31. ^ Wu, LC; Cao, YF; Huang, JH; Liao, C; Gao, F (2010-05-28). "High-dose vs low-dose proton pump inhibitors for upper gastrointestinal bleeding: a meta-analysis". *World journal of gastroenterology : WJG*. **16** (20): 2558–65. doi:10.3748/wjg.v16.i20.2558. PMC 2877188. PMID 20503458.
32. ^ "Management of acute lower GI bleeding". *University of Pennsylvania Health System (UPHS)*. Jan 2009. p. 6.

v · t · e · **Diseases of the digestive system (primarily K20–K93, 530–579)**

| | | |
|---|---|---|
| **Upper GI tract** | **Esophagus** | Esophagitis (Candidal · Eosinophilic · Herpetiform · · *Rupture* (Boerhaave syndrome · Mallory-Weiss syndrome · · UES (Zenker's diverticulum · · LES (Barrett's esophagus · · Esophageal motility disorder (Nutcracker esophagus · Achalasia · Diffuse esophageal spasm · Gastroesophageal reflux disease (GERD) · · Laryngopharyngeal reflux (LPR) · Esophageal stricture · Megaesophagus · |
| | **Stomach** | Gastritis (Atrophic · Ménétrier's disease · Gastroenteritis · · Peptic (gastric) ulcer (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · |

| | | |
|---|---|---|
| | | Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
| **Lower GI tract: Intestinal/ Enteropathy** | **Small intestine (Duodenum/Jejunum/Ileum)** | Enteritis (Duodenitis · Jejunitis · Ileitis · · Peptic (duodenal) ulcer (Curling's ulcer · · Malabsorption: Coeliac · Tropical sprue · Blind loop syndrome · Small bowel bacterial overgrowth syndrome · Whipple's · Short bowel syndrome · Steatorrhea · Milroy disease · Bile acid malabsorption · |
| | **Large intestine (Appendix/Colon)** | Appendicitis · Colitis (Pseudomembranous · Ulcerative · Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (IBS · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
| | **Large and/or small** | Enterocolitis (Necrotizing · · Gastroenterocolitis · IBD (Crohn's disease · · *Vascular*: Abdominal angina · Mesenteric ischemia · Angiodysplasia · Bowel obstruction: Ileus · Intussusception · Volvulus · Fecal impaction · Constipation · Diarrhea (Infectious · · Intestinal adhesions · |
| | **Rectum** | Proctitis (Radiation proctitis · · Proctalgia fugax · Rectal prolapse · Anismus · |
| | **Anal canal** | Anal fissure/Anal fistula · Anal abscess · Anal dysplasia · Pruritus ani · |
| **GI bleeding/BIS** | | Upper (Hematemesis · Melena · · Lower (Hematochezia · · |
| **Accessory** | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · Acute liver failure · · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |
| | **Gallbladder** | Cholecystitis · Gallstones/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · Gallstones/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
| | **Pancreatic** | Pancreatitis (Acute · Chronic · Hereditary · Pancreatic abscess · · Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |
| | | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · |

| | | |
|---|---|---|
| **Abdominopelvic** | **Hernia** | *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |

| v · t · e · | **Disorders of hemodynamics** | |
|---|---|---|
| **Decreases** | **Thrombus/thrombosis** | Renal vein thrombosis |
| | **Ischemia** | Brain ischemia · Ischaemic heart disease · large intestine: Ischemic colitis · small intestine: Mesenteric ischemia · |
| | **Infarction** | Anemic infarct · Hemorrhagic infarct · Myocardial infarction · Cerebral infarction · Splenic infarction · Limb infarction · |
| **Increases** | **Hemorrhage** | Bruise/Hematoma · Petechia · Purpura · Ecchymosis · |
| | | *head* (Epistaxis · Hemoptysis · Intracranial hemorrhage · Hyphema · Subconjunctival hemorrhage · · *torso* (Hemothorax · Hemopericardium · Pulmonary hematoma · · *abdomen* (**Gastrointestinal bleeding** · Haemobilia · Hemoperitoneum · Hematocele · Hematosalpinx · · *joint* (Hemarthrosis · · |
| | **Edema** | Anasarca · Angioedema/Lymphedema · Exudate/Transudate · |
| | | Cerebral edema · Pulmonary edema · Hydrothorax · Ascites/hydroperitoneum · Hydrosalpinx · |
| | **Other** | Hyperemia · |

Categories: Bleeding | Conditions diagnosed by stool test | Gastrointestinal tract disorders




# Gastrointestinal perforation

From Wikipedia, the free encyclopedia

**Gastrointestinal perforation**, also known as **ruptured bowel**, is a hole in the wall of part of the gastrointestinal tract.[2] The gastrointestinal tract includes the esophagus, stomach, small intestine, and large intestine.[2][1] Symptoms include severe abdominal pain and tenderness.[2] When the hole is in the stomach or early part of the small intestine the onset of pain is typically sudden while with a hole in the large intestine onset may be more gradual.[2] The pain is usually constant in nature.[2] Sepsis, with an increased heart rate, increased breathing rate, fever, and confusion may occur.[2]

The cause can include trauma such as from a knife wound, eating a sharp object, or a medical procedure such as colonoscopy, bowel obstruction such as from a volvulus, colon cancer, or diverticulitis, stomach ulcers, ischemic bowel, and a number of infections including *C. difficile*.[2] A hole allows intestinal contents to enter the abdominal cavity.[2] The entry of bacteria results in a condition known as peritonitis or in the formation of an abscess.[2] A hole in the stomach can also lead to a chemical peritonitis due to gastric acid.[2] A CT scan is typically the preferred method of diagnosis; however, free air from a perforation can often be seen on plain X-ray.[2]

Perforation anywhere along the gastrointestinal tract typically requires emergency surgery in the form of an exploratory laparotomy.[2] This is usually carried out along with intravenous fluids and antibiotics.[2] A number of different antibiotics may be used such as piperacillin/tazobactam or the combination of ciprofloxacin and metronidazole.[3][4] Occasionally the hole can be sewn closed while other times a bowel resection is required.[2] Even with maximum treatment the risk of death can be as high as 50%.[2] A hole from a stomach ulcer occurs in about 1 per 10,000 people per year, while one from diverticulitis occurs in about 0.4 per 10,000 people per year.[5][1]

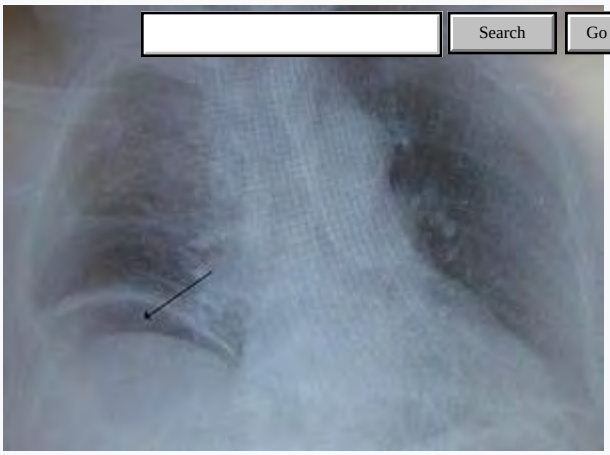
## Contents



## Variants

## Gastrointestinal perforation

**Synonyms** ruptured bowel,[1] gastrointestinal rupture



Free air under the right diaphragm from a bowel perforated.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | gastroenterology, emergency medicine |
| **ICD-10** | K63.1, S36.9 |
| **ICD-9-CM** | 569.83, 863.9 |
| **DiseasesDB** | 34042 |
| **MedlinePlus** | 000235 |
| **eMedicine** | med/2822 |

[edit on Wikidata]

Edit links

## Signs and symptoms [edit]

Sudden pain in the epigastrium to the right of the midline indicates perforation of a duodenal ulcer. In a gastric ulcer perforation creates a history of burning pain in epigastrium, with flatulence and dyspepsia. A history of drug intake with insufficient food intake may be present.

In intestinal perforation pain starts from the site of perforation and spreads across the abdomen.

Gastrointestinal perforation results in severe abdominal pain intensified by movement, nausea, vomiting and hematemesis. Later symptoms include fever and or chills.[6]

In any case, the abdomen becomes rigid with tenderness and rebound tenderness. After some time the abdomen becomes silent and heart sounds can be heard all over. Patient stops passing flatus and motion, abdomen is distended.

The symptoms of esophageal rupture may include sudden onset chest pain.

## Causes [edit]

Underlying causes include gastric ulcers, duodenal ulcers, appendicitis, gastrointestinal cancer, diverticulitis, inflammatory bowel disease, superior mesenteric artery syndrome, trauma and ascariasis. Typhoid fever,[7] non-steroidal anti-inflammatory drugs,[8][9] ingestion of corrosives may also be responsible.[10]

## Diagnosis [edit]

On x-rays, gas may be visible in the abdominal cavity. Gas is easily visualized on x-ray while the patient is in an upright position. The perforation can often be visualised using computed tomography. White blood cells are often elevated.

## Treatment [edit]

Surgical intervention is nearly always required in form of exploratory laparotomy and closure of perforation with peritoneal wash. Occasionally they may be managed laparoscopically.[11]

Conservative treatment including intravenous fluids, antibiotics, nasogastric aspiration and bowel rest is indicated only if the person is nontoxic and clinically stable.[*citation needed*]

## References [edit]


1. ^ *a b c* Domino, Frank J.; Baldor, Robert A. (2013). *The 5-Minute Clinical Consult 2014*. Lippincott Williams & Wilkins. p. 1086. ISBN 9781451188509. Retrieved 4 August 2016.
2. ^ *a b c d e f g h i j k l m n o* Langell, JT; Mulvihill, SJ (May 2008). "Gastrointestinal perforation and the acute abdomen.". *The Medical clinics of North America*. **92** (3): 599–625, viii–ix. doi:10.1016/j.mcna.2007.12.004. PMID 18387378.
3. ^ Wong, PF; Gilliam, AD; Kumar, S; Shenfine, J; O'Dair, GN; Leaper, DJ (18 April 2005). "Antibiotic regimens for secondary peritonitis of gastrointestinal origin in adults.". *The Cochrane database of systematic reviews* (2): CD004539. doi:10.1002/14651858.CD004539.pub2. PMID 15846719.
4. ^ Wilson, William C.; Grande, Christopher M.; Hoyt, David B. (2007). *Trauma: Resuscitation, Perioperative Management, and Critical Care*. CRC Press. p. 882. ISBN 9781420015263.
5. ^ Yeo, Charles J.; McFadden, David W.; Pemberton, John H.; Peters, Jeffrey H.; Matthews, Jeffrey B. (2012). *Shackelford's Surgery of the Alimentary Tract* (7 ed.). Elsevier Health Sciences. p. 701. ISBN 1455738077.
6. ^ Ansari, Parswa. "Acute Perforation". *Merck Manuals*. Retrieved June 30, 2016.
7. ^ Sharma AK, Sharma RK, Sharma SK, Sharma A, Soni D (2013). "Typhoid Intestinal Perforation: 24 Perforations in

One Patient". *Ann Med Health Sci Res*. **3** (Suppl1): S41–S43. doi:10.4103/2141-9248.121220. PMC 3853607. PMID 24349848.
8. ^ R I Russell (2001). "Non-steroidal anti-inflammatory drugs and gastrointestinal damage—problems and solutions". *Postgrad Med J*. **77** (904): 82–88. doi:10.1136/pmj.77.904.82.
9. ^ Carlos Sostres; Carla J Gargallo; Angel Lanas (2013). "Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage". *Arthritis Res Ther*. **15** (Suppl 3): S3. doi:10.1186/ar4175. PMC 3890944. PMID 24267289.
10. ^ Ramasamy, Kovil; Gumaste, Vivek V. (2003). "Corrosive Ingestion in Adults". *Journal of Clinical Gastroenterology:*. **37** (2): 119–124. doi:10.1097/00004836-200308000-00005.
11. ^ Rustagi, T; McCarty, TR; Aslanian, HR (2015). "Endoscopic Treatment of Gastrointestinal Perforations, Leaks, and Fistulae.". *Journal of Clinical Gastroenterology*. **49** (10): 804–9. doi:10.1097/mcg.0000000000000409. PMID 26325190.

## External links [edit]

- Gastrointestinal perforation—MedlinePlus

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| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |

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# Hemorrhoid

From Wikipedia, the free encyclopedia

**Hemorrhoids**, (alternative spelling **haemorrhoids**), also called **piles**, are vascular structures in the anal canal.[3][4] In their normal state, they are cushions that help with stool control.[2] They become a disease when swollen or inflamed; the unqualified term "hemorrhoid" is often used to mean the disease.[4] The signs and symptoms of hemorrhoids depend on the type present.[5] Internal hemorrhoids usually present with painless, bright red rectal bleeding when defecating.[6][5] External hemorrhoids often result in pain and swelling in the area of the anus. If bleeding occurs it is usually darker.[5] Symptoms frequently get better after a few days.[6] A skin tag may remain after the healing of an external hemorrhoid.[5]

While the exact cause of hemorrhoids remains unknown, a number of factors which increase pressure in the abdomen are believed to be involved.[5] This may include constipation, diarrhea, and sitting on the toilet for a long time. Hemorrhoids are also more common during pregnancy. Diagnosis is made by looking at the area.[6] Many people incorrectly refer to any symptom occurring around the anal area as "hemorrhoids" and serious causes of the symptoms should be ruled out.[2] Colonoscopy or sigmoidoscopy is reasonable to confirm the diagnosis and rule out more serious causes.[7]

Often, no specific treatment is needed.[7] Initial measures consists of increasing fiber intake, drinking fluids to maintain hydration, NSAIDs to help with pain, and rest.[1] Medicated creams applied to the area are poorly supported by evidence.[7] A number of minor procedures may be performed if symptoms are severe or do not improve with conservative management. Surgery is reserved for those who fail to improve following these measures.[8]

Half to two thirds of people have problems with hemorrhoids at some point in their lives.[1][6] Males and females are affected about equally commonly.[1] Hemorrhoids affect people most often between 45 and 65 years of age.[9] It is more common among the wealthy.[5] Outcomes are usually good.[6][7] The first known mention of the disease is from a 1700 BC Egyptian papyrus.[10]

## Variants

**Hemorrhoids**

**Synonyms** [1] ... disease[2]

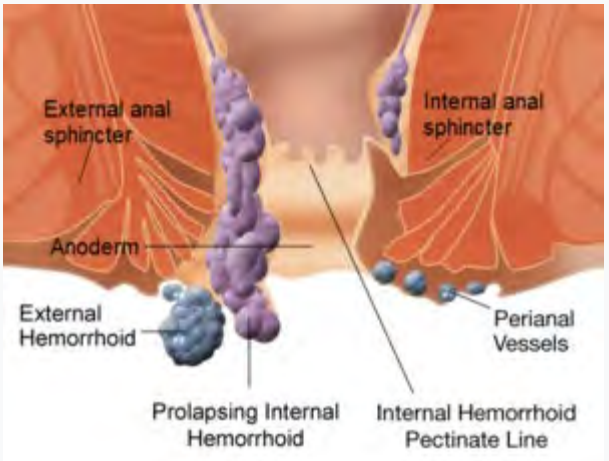



Diagram demonstrating the anatomy of both internal and external hemorrhoids

**Pronunciation** UK /ˈhɛmərɔɪdz/

**Classification and external resources**

| | |
|---|---|
| **Specialty** | General surgery |
| **ICD-10** | K64 |
| **ICD-9-CM** | 455 |
| **DiseasesDB** | 10036 |
| **MedlinePlus** | 000292 |
| **eMedicine** | med/2821 emerg/242 |
| **Patient UK** | Hemorrhoid |
| **MeSH** | D006484 |

[edit on Wikidata]

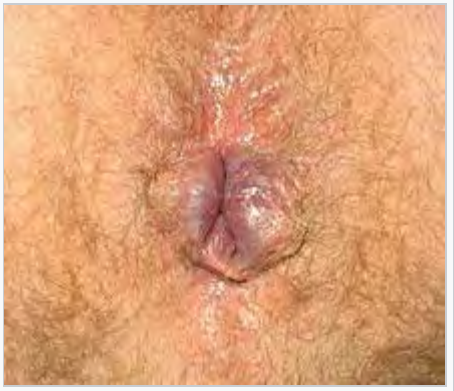
Contents





# Signs and symptoms

In about 40% of people with pathological hemorrhoids there are no significant symptoms.[5] Internal and external hemorrhoids may present differently; however, many people may have a combination of the two.[4] Bleeding enough to cause anemia is rare,[9] and life-threatening bleeding is even more uncommon.[11] Many people feel embarrassed when facing the problem[9] and often seek medical care only when the case is advanced.[4]



External hemorrhoid as seen around the human anus

## External

If not thrombosed, external hemorrhoids may cause few problems.[12] However, when thrombosed, hemorrhoids may be very painful.[4][1] Nevertheless, this pain typically resolves in two to three days.[9] The swelling may, however, take a few weeks to disappear.[9] A skin tag may remain after healing.[4] If hemorrhoids are large and cause issues with hygiene, they may produce irritation of the surrounding skin, and thus itchiness around the anus.[12]

## Internal

Internal hemorrhoids usually present with painless, bright red rectal bleeding during or following a bowel movement.[4] The blood typically covers the stool (a condition known as hematochezia), is on the toilet paper, or drips into the toilet bowl.[4] The stool itself is usually normally coloured.[4] Other symptoms may include mucous discharge, a perianal mass if they prolapse through the anus, itchiness, and fecal incontinence.[11][13] Internal hemorrhoids are usually only painful if they become thrombosed or necrotic.[4]

# Causes

The exact cause of symptomatic hemorrhoids is unknown.[14] A number of factors are believed to play a

role, including irregular bowel habits (constipation or diarrhea), lack of exercise, nutritional factors (low-fiber diets), increased intra-abdominal pressure (prolonged straining, ascites, an intra-abdominal mass, or pregnancy), genetics, an absence of valves within the hemorrhoidal veins, and aging.[1][9] Other factors believed to increase risk include obesity, prolonged sitting,[4] a chronic cough, and pelvic floor dysfunction.[2] Evidence for these associations, however, is poor.[2]

During pregnancy, pressure from the fetus on the abdomen and hormonal changes cause the hemorrhoidal vessels to enlarge. The birth of the baby also leads to increased intra-abdominal pressures.[15] Pregnant women rarely need surgical treatment, as symptoms usually resolve after delivery.[1]

# Pathophysiology

Hemorrhoid cushions are a part of normal human anatomy and become a pathological disease only when they experience abnormal changes.[4] There are three main cushions present in the normal anal canal.[1] These are located classically at left lateral, right anterior, and right posterior positions.[9] They are composed of neither arteries nor veins, but blood vessels called sinusoids, connective tissue, and smooth muscle.[2]:175 Sinusoids do not have muscle tissue in their walls, as veins do.[4] This set of blood vessels is known as the hemorrhoidal plexus.[2]

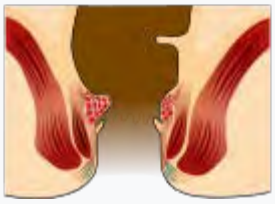
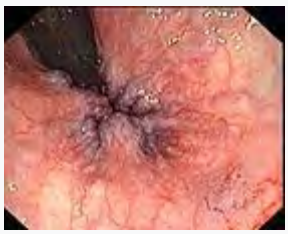
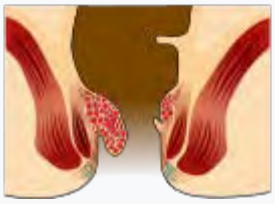
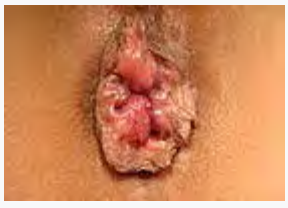
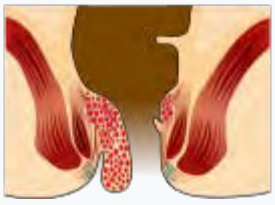
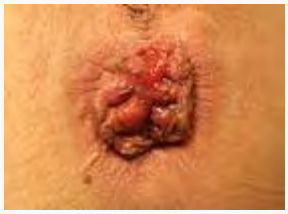
Hemorrhoid cushions are important for continence. They contribute to 15–20% of anal closure pressure at rest and protect the internal and external anal sphincter muscles during the passage of stool.[4] When a person bears down, the intra-abdominal pressure grows, and hemorrhoid cushions increase in size, helping maintain anal closure.[9] Hemorrhoid symptoms are believed to result when these vascular structures slide downwards or when venous pressure is excessively increased.[11] Increased internal and external anal sphincter pressure may also be involved in hemorrhoid symptoms.[9] Two types of hemorrhoids occur: internals from the superior hemorrhoidal plexus and externals from the inferior hemorrhoidal plexus.[9] The dentate line divides the two regions.[9]

# Diagnosis



Hemorrhoids are typically diagnosed by physical examination.[8] A visual examination of the anus and surrounding area may diagnose external or prolapsed hemorrhoids.[4] A rectal exam may be performed to detect possible rectal tumors, polyps, an enlarged prostate, or abscesses.[4] This examination may not be possible without appropriate sedation because of pain, although most internal hemorrhoids are not associated with pain.[1] Visual confirmation of internal hemorrhoids may require anoscopy, insertion of a hollow tube device with a light attached at one end.[9] The two types of hemorrhoids are external and internal. These are differentiated by their position with respect to the dentate line.[1] Some persons may concurrently have symptomatic versions of both.[9] If pain is present, the condition is more likely to be an anal fissure or an external hemorrhoid rather than an internal hemorrhoid.[9]

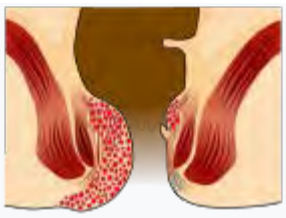
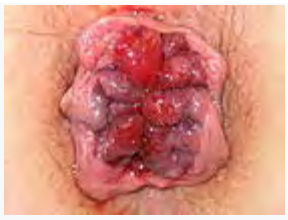
**Internal hemorrhoid grades**

| Grade | Diagram | Picture |
|---|---|---|
| 1 |  |  |
| 2 |  |  |
| 3 |  |  |

## Internal

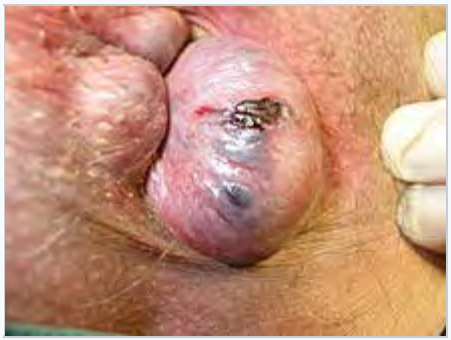
Internal hemorrhoids originate above the dentate

line.[12] They are covered by columnar epithelium, which lacks pain receptors.[2] They were classified in 1985 into four grades based on the degree of prolapse:[2][1]

| | | |
|---|---|---|
| 4 |  |  |

- Grade I: No prolapse, just prominent blood vessels[8]
- Grade II: Prolapse upon bearing down, but spontaneous reduction
- Grade III: Prolapse upon bearing down requiring manual reduction
- Grade IV: Prolapse with inability to be manually reduced.

### External



A thrombosed external hemorrhoid

External hemorrhoids occur below the dentate or pectinate line.[12] They are covered proximally by anoderm and distally by skin, both of which are sensitive to pain and temperature.[2]

### Differential

Many anorectal problems, including fissures, fistulae, abscesses, colorectal cancer, rectal varices, and itching have similar symptoms and may be incorrectly referred to as hemorrhoids.[1] Rectal bleeding may also occur owing to colorectal cancer, colitis including inflammatory bowel disease, diverticular disease, and angiodysplasia.[8] If anemia is present, other potential causes should be considered.[9]

Other conditions that produce an anal mass include skin tags, anal warts, rectal prolapse, polyps, and enlarged anal papillae.[9] Anorectal varices due to increased portal hypertension (blood pressure in the portal venous system) may present similar to hemorrhoids but are a different condition.[9] Portal hypertension does not increase the risk of hemorrhoids.[5]

## Prevention

A number of preventative measures are recommended, including avoiding straining while attempting to defecate, avoiding constipation and diarrhea either by eating a high-fiber diet and drinking plenty of fluid or by taking fiber supplements, and getting sufficient exercise.[9][16] Spending less time attempting to defecate, avoiding reading while on the toilet,[1] and losing weight for overweight persons and avoiding heavy lifting are also recommended.[17]

## Management

### Conservative

Conservative treatment typically consists of foods rich in dietary fiber, intake of oral fluids to maintain hydration, nonsteroidal anti-inflammatory drugs, sitz baths, and rest.[1] Increased fiber intake has been shown to improve outcomes[18] and may be achieved by dietary alterations or the consumption of fiber supplements.[1][18] Evidence for benefits from sitz baths during any point in treatment, however, is lacking.[19] If they are used, they should be limited to 15 minutes at a time.[2]:182

While many topical agents and suppositories are available for the treatment of hemorrhoids, little evidence supports their use.[1] Steroid-containing agents should not be used for more than 14 days, as they may

cause thinning of the skin.[1] Most agents include a combination of active ingredients.[2] These may include a barrier cream such as petroleum jelly or zinc oxide, an analgesic agent such as lidocaine, and a vasoconstrictor such as epinephrine.[2] Some contain Balsam of Peru to which certain people may be allergic.[20][21]

Flavonoids are of questionable benefit, with potential side effects.[2][22] Symptoms usually resolve following pregnancy; thus active treatment is often delayed until after delivery.[23]

## Procedures

A number of office-based procedures may be performed. While generally safe, rare serious side effects such as perianal sepsis may occur.[8]

- Rubber band ligation is typically recommended as the first-line treatment in those with grade 1 to 3 disease.[8] It is a procedure in which elastic bands are applied onto an internal hemorrhoid at least 1 cm above the dentate line to cut off its blood supply. Within 5–7 days, the withered hemorrhoid falls off. If the band is placed too close to the dentate line, intense pain results immediately afterwards.[1] Cure rate has been found to be about 87%[1] with a complication rate of up to 3%.[8]
- Sclerotherapy involves the injection of a sclerosing agent, such as phenol, into the hemorrhoid. This causes the vein walls to collapse and the hemorrhoids to shrivel up. The success rate four years after treatment is about 70%.[1]
- A number of cauterization methods have been shown to be effective for hemorrhoids, but are usually only used when other methods fail. This procedure can be done using electrocautery, infrared radiation, laser surgery,[1] or cryosurgery.[24] Infrared cauterization may be an option for grade 1 or 2 disease.[8] In those with grade 3 or 4 disease, reoccurrence rates are high.[8]

## Surgery

A number of surgical techniques may be used if conservative management and simple procedures fail.[8] All surgical treatments are associated with some degree of complications including bleeding, infection, anal strictures and urinary retention, due to the close proximity of the rectum to the nerves that supply the bladder.[1] Also, a small risk of fecal incontinence occurs, particularly of liquid,[2][25] with rates reported between 0% and 28%.[26] Mucosal ectropion is another condition which may occur after hemorrhoidectomy (often together with anal stenosis).[27] This is where the anal mucosa becomes everted from the anus, similar to a very mild form of rectal prolapse.[27]

- Excisional hemorrhoidectomy is a surgical excision of the hemorrhoid used primarily only in severe cases.[1] It is associated with significant postoperative pain and usually requires 2–4 weeks for recovery.[1] However, the long-term benefit is greater in those with grade 3 hemorrhoids as compared to rubber band ligation.[28] It is the recommended treatment in those with a thrombosed external hemorrhoid if carried out within 24–72 hours.[12][8] Glyceryl trinitrate ointment after the procedure helps both with pain and healing.[29]
- Doppler-guided, transanal hemorrhoidal dearterialization is a minimally invasive treatment using an ultrasound doppler to accurately locate the arterial blood inflow. These arteries are then "tied off" and the prolapsed tissue is sutured back to its normal position. It has a slightly higher recurrence rate, but fewer complications compared to a hemorrhoidectomy.[1]
- Stapled hemorrhoidectomy, also known as stapled hemorrhoidopexy, involves the removal of much of the abnormally enlarged hemorrhoidal tissue, followed by a repositioning of the remaining hemorrhoidal tissue back to its normal anatomical position. It is generally less painful and is associated with faster healing compared to complete removal of hemorrhoids.[1] However, the chance of symptomatic hemorrhoids returning is greater than for conventional hemorroidectomy,[30] so it is typically only recommended for grade 2 or 3 disease.[8]

# Epidemiology

It is difficult to determine how common hemorrhoids are as many people with the condition do not see a healthcare provider.[11][14] However, symptomatic hemorrhoids are thought to affect at least 50% of the US population at some time during their lives, and around 5% of the population is affected at any given time.[1] Both sexes experience about the same incidence of the condition,[1] with rates peaking between 45 and 65 years.[9] They are more common in Caucasians[31] and those of higher socioeconomic status.[2]

Long-term outcomes are generally good, though some people may have recurrent symptomatic episodes.[11] Only a small proportion of persons end up needing surgery.[2]

## History

The first known mention of this disease is from a 1700 BC Egyptian papyrus, which advises: "... Thou shouldest give a recipe, an ointment of great protection; acacia leaves, ground, titurated and cooked together. Smear a strip of fine linen there-with and place in the anus, that he recovers immediately."[10] In 460 BC, the Hippocratic corpus discusses a treatment similar to modern rubber band ligation: "And hemorrhoids in like manner you may treat by transfixing them with a needle and tying them with very thick and woolen thread, for application, and do not forment until they drop off, and always leave one behind; and when the patient recovers, let him be put on a course of Hellebore."[10] Hemorrhoids may have been described in the Bible, with earlier English translations using the now-obsolete spelling "emerods".[9]

An 11th-century English miniature: On the right is an operation to remove hemorrhoids.

Celsus (25 BC – AD 14) described ligation and excision procedures, and discussed the possible complications.[32] Galen advocated severing the connection of the arteries to veins, claiming it reduced both pain and the spread of gangrene.[32] The Susruta Samhita (4th–5th century AD) is similar to the words of Hippocrates, but emphasizes wound cleanliness.[10] In the 13th century, European surgeons such as Lanfranc of Milan, Guy de Chauliac, Henri de Mondeville, and John of Ardene made great progress and development of the surgical techniques.[32]

In medieval times, hemorrhoids were also known as Saint Fiacre's curse after a sixth-century saint who developed them following tilling the soil.[33] The first use of the word "hemorrhoid" in English occurs in 1398, derived from the Old French "emorroides", from Latin *hæmorrhoida*,[34] in turn from the Greek αἱμορροΐς (*haimorrhois*), "liable to discharge blood", from αἷμα (*haima*), "blood"[35] and ῥόος (*rhoos*), "stream, flow, current",[36] itself from ῥέω (*rheo*), "to flow, to stream".[37]

## Notable cases

Hall-of-Fame baseball player George Brett was removed from a game in the 1980 World Series due to hemorrhoid pain. After undergoing minor surgery, Brett returned to play in the next game, quipping "...my problems are all behind me."[38] Brett underwent further hemorrhoid surgery the following spring.[39] Conservative political commentator Glenn Beck underwent surgery for hemorrhoids, subsequently describing his unpleasant experience in a widely viewed 2008 YouTube video.[40][41] Former U.S. President Jimmy Carter had surgery for hemorrhoids in 1984.[42] Cricketers Matthew Hayden and Viv Richards also had the condition.[43]

## References

1. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab* Lorenzo-Rivero, S (August 2009). "Hemorrhoids: diagnosis and

current management". *Am Surg*. **75** (8): 635–42. PMID 19725283.
2. ^ *a b c d e f g h i j k l m n o p q* Beck, David E. (2011). *The ASCRS textbook of colon and rectal surgery* (2nd ed.). New York: Springer. p. 175. ISBN 978-1-4419-1581-8.
3. ^ Chen, Herbert (2010). *Illustrative Handbook of General Surgery*. Berlin: Springer. p. 217. ISBN 1-84882-088-7.
4. ^ *a b c d e f g h i j k l m n o p* Schubert, MC; Sridhar, S; Schade, RR; Wexner, SD (July 2009). "What every gastroenterologist needs to know about common anorectal disorders". *World J Gastroenterol*. **15** (26): 3201–9. doi:10.3748/wjg.15.3201. ISSN 1007-9327. PMC 2710774. PMID 19598294.
5. ^ *a b c d e f g h* Sun, Z; Migaly, J (March 2016). "Review of Hemorrhoid Disease: Presentation and Management.". *Clinics in colon and rectal surgery*. **29** (1): 22–9. doi:10.1055/s-0035-1568144. PMID 26929748.
6. ^ *a b c d e* "Hemorrhoids". *National Institute of Diabetes and Digestive and Kidney Diseases*. November 2013. Retrieved 15 February 2016.
7. ^ *a b c d* Hollingshead, JR; Phillips, RK (January 2016). "Haemorrhoids: modern diagnosis and treatment.". *Postgraduate Medical Journal*. **92** (1083): 4–8. doi:10.1136/postgradmedj-2015-133328. PMID 26561592.
8. ^ *a b c d e f g h i j k l* Rivadeneira, DE; Steele, SR; Ternent, C; Chalasani, S; Buie, WD; Rafferty, JL; Standards Practice Task Force of The American Society of Colon and Rectal, Surgeons (September 2011). "Practice parameters for the management of hemorrhoids (revised 2010)". *Diseases of the colon and rectum*. **54** (9): 1059–64. doi:10.1097/DCR.0b013e318225513d. PMID 21825884.
9. ^ *a b c d e f g h i j k l m n o p q r s t* Kaidar-Person, O; Person, B; Wexner, SD (January 2007). "Hemorrhoidal disease: A comprehensive review" (PDF). *Journal of the American College of Surgeons*. **204** (1): 102–17. doi:10.1016/j.jamcollsurg.2006.08.022. PMID 17189119.
10. ^ *a b c d* Ellesmore, Windsor (2002). "Surgical History of Haemorrhoids". In Charles MV. *Surgical Treatment of Haemorrhoids*. London: Springer.
11. ^ *a b c d e* Davies, RJ (June 2006). "Haemorrhoids.". *Clinical evidence* (15): 711–24. PMID 16973032.
12. ^ *a b c d e* Dayton, senior editor, Peter F. Lawrence; editors, Richard Bell, Merril T. (2006). *Essentials of general surgery* (4th ed.). Philadelphia ;Baltimore: Williams & Wilkins. p. 329. ISBN 978-0-7817-5003-5.
13. ^ Azimuddin, edited by Indru Khubchandani, Nina Paonessa, Khawaja (2009). *Surgical treatment of hemorrhoids* (2nd ed.). New York: Springer. p. 21. ISBN 978-1-84800-313-2.
14. ^ *a b* Reese, GE; von Roon, AC; Tekkis, PP (Jan 29, 2009). "Haemorrhoids.". *Clinical evidence*. **2009**. PMC 2907769. PMID 19445775.
15. ^ National Digestive Diseases Information Clearinghouse (November 2004). "Hemorrhoids". *National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH*. Retrieved 18 March 2010.
16. ^ Frank J Domino (2012). *The 5-Minute Clinical Consult 2013 (Griffith's 5 Minute Clinical Consult)*. Hagerstown, MD: Lippincott Williams & Wilkins. p. 572. ISBN 1-4511-3735-4.
17. ^ Glass, [edited by] Jill C. Cash, Cheryl A. *Family practice guidelines* (2nd ed.). New York: Springer. p. 665. ISBN 978-0-8261-1812-7.
18. ^ *a b* Alonso-Coello, P.; Guyatt, G. H.; Heels-Ansdell, D.; Johanson, J. F.; Lopez-Yarto, M.; Mills, E.; Zhuo, Q.; Alonso-Coello, Pablo (2005). Alonso-Coello, Pablo, ed. "Laxatives for the treatment of hemorrhoids". *Cochrane Database Syst Rev* (4): CD004649. doi:10.1002/14651858.CD004649.pub2. PMID 16235372.
19. ^ Lang, DS; Tho, PC; Ang, EN (December 2011). "Effectiveness of the Sitz bath in managing adult patients with anorectal disorders". *Japan journal of nursing science : JJNS*. **8** (2): 115–28. doi:10.1111/j.1742-7924.2011.00175.x. PMID 22117576.
20. ^ "Balsam of Peru contact allergy". Dermnetnz.org. December 28, 2013. Retrieved March 5, 2014.
21. ^ *The ASCRS Textbook of Colon and Rectal Surgery: Second Edition*. 2011. ISBN 978-1-4419-1581-8.
22. ^ Alonso-Coello P, Zhou Q, Martinez-Zapata MJ, et al. (August 2006). "Meta-analysis of flavonoids for the treatment of haemorrhoids". *Br J Surg*. **93** (8): 909–20. doi:10.1002/bjs.5378. PMID 16736537.
23. ^ Quijano, CE; Abalos, E (Jul 20, 2005). "Conservative management of symptomatic and/or complicated haemorrhoids in pregnancy and the puerperium". *Cochrane database of systematic reviews (Online)* (3): CD004077. doi:10.1002/14651858.CD004077.pub2. PMID 16034920.
24. ^ Misra, MC; Imlitemsu, (2005). "Drug treatment of haemorrhoids". *Drugs*. **65** (11): 1481–91. doi:10.2165/00003495-200565110-00003. PMID 16134260.
25. ^ Pescatori, M; Gagliardi, G (March 2008). "Postoperative complications after procedure for prolapsed hemorrhoids (PPH) and stapled transanal rectal resection (STARR) procedures". *Techniques in coloproctology*. **12** (1): 7–19. doi:10.1007/s10151-008-0391-0. PMC 2778725. PMID 18512007.
26. ^ Ommer, A; Wenger, FA; Rolfs, T; Walz, MK (November 2008). "Continence disorders after anal surgery—a relevant problem?". *International journal of colorectal disease*. **23** (11): 1023–31. doi:10.1007/s00384-008-0524-y. PMID 18629515.

27. ^ [a] [b] Lagares-Garcia, JA; Nogueras, JJ (December 2002). "Anal stenosis and mucosal ectropion.". *The Surgical clinics of North America*. **82** (6): 1225–31, vii. doi:10.1016/s0039-6109(02)00081-6. PMID 12516850.
28. ^ Shanmugam, V; Thaha, MA; Rabindranath, KS; Campbell, KL; Steele, RJ; Loudon, MA (Jul 20, 2005). "Rubber band ligation versus excisional haemorrhoidectomy for haemorrhoids". *Cochrane database of systematic reviews (Online)* (3): CD005034. doi:10.1002/14651858.CD005034.pub2. PMID 16034963.
29. ^ Ratnasingham, K; Uzzaman, M; Andreani, SM; Light, D; Patel, B (2010). "Meta-analysis of the use of glyceryl trinitrate ointment after haemorrhoidectomy as an analgesic and in promoting wound healing". *International journal of surgery (London, England)*. **8** (8): 606–11. doi:10.1016/j.ijsu.2010.04.012. PMID 20691294.
30. ^ Jayaraman, S; Colquhoun, PH; Malthaner, RA (Oct 18, 2006). "Stapled versus conventional surgery for hemorrhoids". *Cochrane database of systematic reviews (Online)* (4): CD005393. doi:10.1002/14651858.CD005393.pub2. PMID 17054255.
31. ^ Christian Lynge, Dana; Weiss, Barry D. *20 Common Problems: Surgical Problems And Procedures In Primary Care*. McGraw-Hill Professional. p. 114. ISBN 978-0-07-136002-9.
32. ^ [a] [b] [c] Agbo, SP (1 January 2011). "Surgical management of hemorrhoids". *Journal of Surgical Technique and Case Report*. **3** (2): 68. doi:10.4103/2006-8808.92797.
33. ^ Cataldo, Peter (2005). "Hemorrhoids". Arlington Heights, IL: American Society of Colon and Rectal Surgeons. Retrieved 30 September 2013.
34. ^ hæmorrhoida, Charlton T. Lewis, Charles Short, *A Latin Dictionary*, on Perseus Digital Library
35. ^ αἷμα, Henry George Liddell, Robert Scott, *A Greek-English Lexicon*, on Perseus Digital Library
36. ^ ῥόος, Henry George Liddell, Robert Scott, *A Greek-English Lexicon*, on Perseus Digital Library
37. ^ ῥέω, Henry George Liddell, Robert Scott, *A Greek-English Lexicon*, on Perseus Digital Library
38. ^ Dick Kaegel (March 5, 2009). "Memories fill Kauffman Stadium". *Major League Baseball*.
39. ^ "Brett in Hospital for Surgery". *The New York Times*. Associated Press. March 1, 1981.
40. ^ "Glenn Beck: Put the 'Care' Back in Health Care". *ABC Good Morning America*. Jan 8, 2008. Retrieved 17 September 2012.
41. ^ "Beck From the Dead". *YouTube* (Mr·Beck speaking from home shortly after hospital). GlennBeckVideos.
42. ^ "Carter Leaves Hospital". *The New York Times*. January 19, 1984. Retrieved 12 September 2013.
43. ^ "The Five: Wounded pride". *The Sydney Morning Herald*. Retrieved 24 April 2016.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# Hernia



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**Hernia**

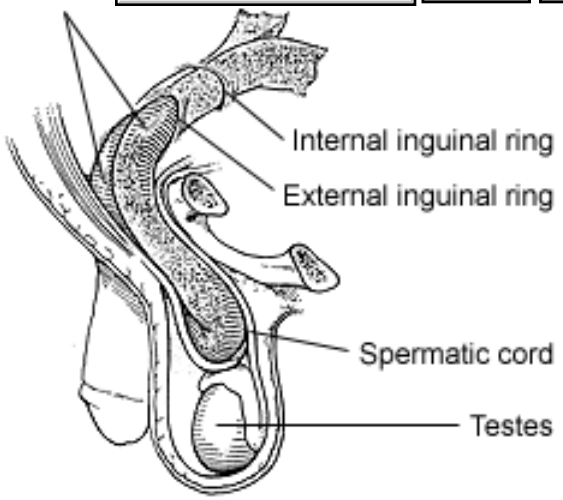


Diagram of an indirect inguinal hernia (view from the side).

| Classification and external resources | |
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A **hernia** is the exit of an organ, such as the bowel, through the wall of the cavity in which it normally resides.[1] Hernias come in a number of different types. Most commonly they involve the abdomen, specifically the groin.[2] Groin hernias are most common of the inguinal type but may also be femoral.[1] Other hernias include hiatus, incisional, and umbilical hernias.[2] Symptoms are present in about 66% of people with groin hernias. This may include pain or discomfort especially with coughing, exercise, or going to the bathroom. Often it gets worse throughout the day and improves when lying down. A bulging area may occur that becomes larger when standing. Groin hernias occur more often on the right than left side. The main concern is strangulation, where the blood supply to part of the bowel is blocked. This usually produces severe pain and tenderness of the area.[1] Hiatus or hiatal hernias often result in heartburn but may also cause chest pain or pain with eating.[3]

Risk factors for the development of a hernia include: smoking, chronic obstructive pulmonary disease, obesity, pregnancy, peritoneal dialysis, collagen vascular disease, and previous open appendectomy, among others.[1][3][4] Hernias are partly genetic and occur more often in certain families. It is unclear if groin hernias are associated with heavy lifting. Hernias can often be diagnosed based on signs and symptoms. Occasionally medical imaging is used to confirm the diagnosis or rule out other possible causes.[1] The diagnosis of hiatus hernias is often by endoscopy.[3]

Groin hernias that do not cause symptoms in males do not need to be repaired. Repair, however, is generally recommended in women due to the higher rate of femoral hernias which have more complications. If strangulation occurs immediate surgery is required. Repair may be done by open surgery or by laparoscopic surgery. Open surgery has the benefit of possibly being done under local anesthesia rather than general anesthesia. Laparoscopic surgery generally has less pain following the procedure.[1] A hiatus hernia may be treated with lifestyle changes such as raising the head of the bed, weight loss, and adjusting eating habits. The medications, H2 blockers or proton pump inhibitors may help. If the symptoms do not improve with medications the surgery known as laparoscopic fundoplication may be an option.[3]

About 27% of males and 3% of females develop a groin hernia at some time in their life.[1] Groin hernias occur most often before the age of one and after the age of fifty.[4] Inguinal, femoral and abdominal

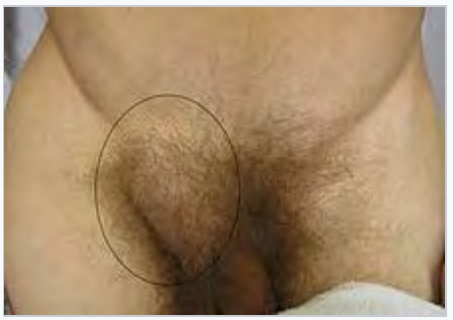
hernias resulted in 32,500 deaths in 2013 and 50,500 in 1990.[5] It is not known how commonly hiatus hernias occur with estimates in North America varying from 10 to 80%.[3] The first known description of a hernia dates back to at least 1550 BC in the Ebers Papyrus from Egypt.[6]





## Signs and symptoms [edit]

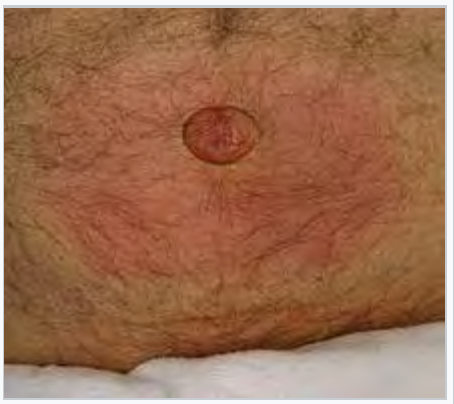
By far the most common hernias develop in the abdomen, when a weakness in the abdominal wall evolves into a localized hole, or "defect", through which adipose tissue, or abdominal organs covered with peritoneum, may protrude. Another common hernia involves the spinal discs and causes *sciatica*. A hiatus hernia occurs when the stomach protrudes into the *mediastinum* through the esophageal opening in the diaphragm.



Frontal view of an inguinal hernia (right).

Hernias may or may not present with either pain at the site, a visible or palpable lump, or in some cases more vague symptoms resulting from pressure on an organ which has become "stuck" in the hernia, sometimes leading to organ dysfunction. Fatty tissue usually enters a hernia first, but it may be followed or accompanied by an organ.

Hernias are caused by a disruption or opening in the fascia, or fibrous tissue, which forms the abdominal wall. It is possible for the bulge associated with a hernia to come and go, but the defect in the tissue will persist.



Umbilical hernia with surrounding inflammation

Symptoms and signs vary depending on the type of hernia. Symptoms may or may not be present in some inguinal hernias. In the case of reducible hernias, a bulge in the groin or in another abdominal area can often be seen and felt. When standing, such a bulge becomes more obvious. Besides the bulge, other symptoms include pain in the groin that may also include a heavy or dragging sensation, and in men, there is sometimes pain and swelling in the scrotum around the testicular area.[7]

Irreducible abdominal hernias or incarcerated hernias may be painful, but their most relevant symptom is that they cannot return to the abdominal cavity when pushed in. They may be chronic, although painless, and can lead to strangulation (loss of blood supply) and/or

obstruction (kinking of intestine). Strangulated hernias are always painful and pain is followed by tenderness. Nausea, vomiting, or fever may occur in these cases due to bowel obstruction. Also, the hernia bulge in this case may turn red, purple or dark and pink.

In the diagnosis of abdominal hernias, imaging is the principal means of detecting internal diaphragmatic and other nonpalpable or unsuspected hernias. Multidetector CT (MDCT) can show with precision the anatomic site of the hernia sac, the contents of the sac, and any complications. MDCT also offers clear detail of the abdominal wall allowing wall hernias to be identified accurately.[8]

## Causes [edit]

Causes of hiatus hernia vary depending on each individual. Among the multiple causes, however, are the mechanical causes which include: improper heavy weight lifting, hard coughing bouts, sharp blows to the abdomen, and incorrect posture.[9]

Furthermore, conditions that increase the pressure of the abdominal cavity may also cause hernias or worsen the existing ones. Some examples would be: obesity, straining during a bowel movement or urination (constipation, enlarged prostate), chronic lung disease, and also, fluid in the abdominal cavity (ascites).[10]

Also, if muscles are weakened due to poor nutrition, smoking, and overexertion, hernias are more likely to occur.

The physiological school of thought contends that in the case of inguinal hernia, the above-mentioned are only an anatomical symptom of the underlying physiological cause. They contend that the risk of hernia is due to a physiological difference between patients who suffer hernia and those who do not, namely the presence of aponeurotic extensions from the transversus abdominis aponeurotic arch.[11]

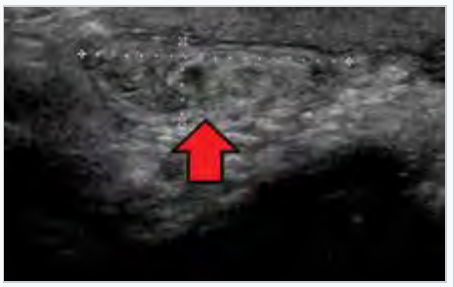
Abdominal wall hernia may occur due to trauma. If this type of hernia is due to blunt trauma it is an emergency condition and could be associated with various solid organs and hollow viscus injuries.

## Diagnosis [edit]

### Inguinal [edit]

*Main article: inguinal hernia*

By far the most common hernias (up to 75% of all abdominal hernias) are the so-called inguinal hernias. Inguinal hernias are further divided into the more common indirect inguinal hernia (2/3, depicted here), in which the inguinal canal is entered via a congenital weakness at its entrance (the internal inguinal ring), and the direct inguinal hernia type (1/3), where the hernia contents push through a weak spot in the back wall of the inguinal canal. Inguinal hernias are the most common type of hernia in both men and women. In some selected cases, they may require surgery.

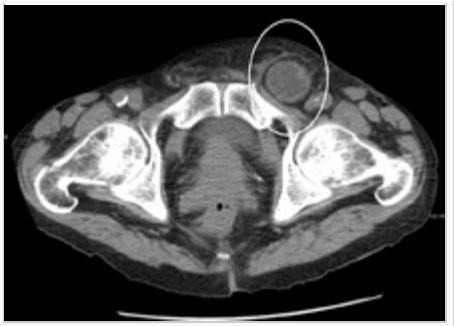


Ultrasound showing an inguinal hernia

### Femoral [edit]

*Main article: femoral hernia*

Femoral hernias occur just below the inguinal ligament, when abdominal contents pass into the weak area at the posterior wall of the femoral canal. They can be hard to distinguish from the inguinal type (especially when ascending cephalad): however, they generally appear more rounded, and, in contrast to inguinal hernias, there is a strong female preponderance in femoral hernias. The incidence of strangulation in femoral hernias is high. Repair techniques are similar for femoral and



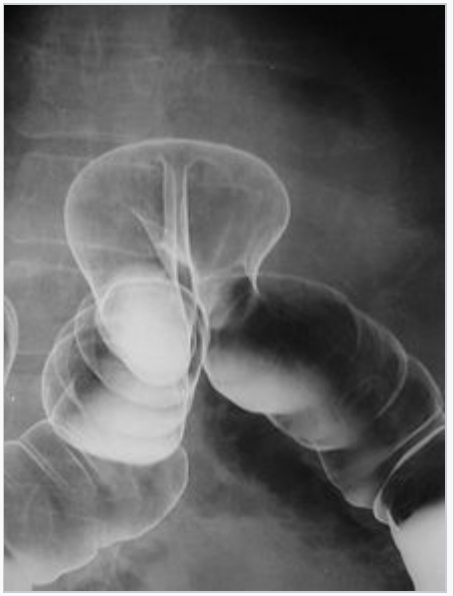
An incarcerated inguinal hernia as seen on CT

inguinal hernia.

## Umbilical [edit]

*Main article: Umbilical hernia*

They involve protrusion of intraabdominal contents through a weakness at the site of passage of the umbilical cord through the abdominal wall. Umbilical hernias in adults are largely acquired, and are more frequent in obese or pregnant women. Abnormal decussation of fibers at the linea alba may contribute.



X-ray of colonic herniation

## Incisional [edit]

*Main article: incisional hernia*

An incisional hernia occurs when the defect is the result of an incompletely healed surgical wound. When these occur in median laparotomy incisions in the linea alba, they are termed ventral hernias. These can be the most frustrating and difficult to treat, as the repair utilizes already attenuated tissue.

## Diaphragmatic [edit]

*Main article: diaphragmatic hernia*

Higher in the abdomen, an (internal) "diaphragmatic hernia" results when part of the stomach or intestine protrudes into the chest cavity through a defect in the diaphragm.

A hiatus hernia is a particular variant of this type, in which the normal passageway through which the esophagus meets the stomach (esophageal hiatus) serves as a functional "defect", allowing part of the stomach to (periodically) "herniate" into the chest. Hiatus hernias may be either "*sliding*", in which the gastroesophageal junction itself slides through the defect into the chest, or non-sliding (also known as *para-esophageal*), in which case the junction remains fixed while another portion of the stomach moves up through the defect. Non-sliding or para-esophageal hernias can be dangerous as they may allow the stomach to rotate and obstruct. Repair is usually advised.

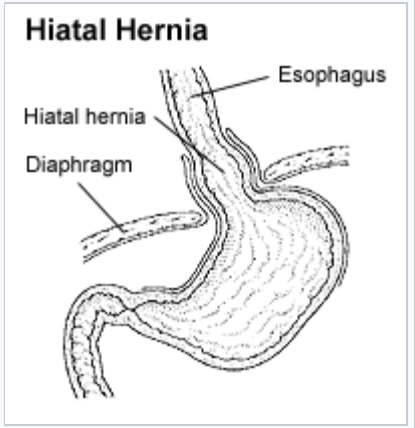



Diagram of a hiatus hernia (coronal section, viewed from the front).

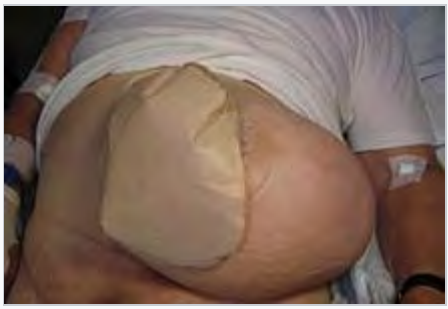
A congenital diaphragmatic hernia is a distinct problem, occurring in up to 1 in 2000 births, and requiring pediatric surgery. Intestinal organs may herniate through several parts of the diaphragm, posterolateral (in Bochdalek's triangle, resulting in *Bochdalek's hernia*), or anteromedial-retrosternal (in the cleft of Larrey/Morgagni's foramen, resulting in *Morgagni-Larrey hernia*, or Morgagni's hernia).[12]

## Other hernias [edit]

Since many organs or parts of organs can herniate through many orifices, it is very difficult to give an exhaustive list of hernias, with all synonyms and eponyms. The above article deals mostly with "visceral hernias", where the herniating tissue arises within the abdominal cavity. Other hernia types and unusual

types of visceral hernias are listed below, in alphabetical order:

- Amyand's hernia: containing the appendix vermiformis within the hernia sac
- Cooper's hernia: a femoral hernia with two sacs, the first being in the femoral canal, and the second passing through a defect in the superficial fascia and appearing almost immediately beneath the skin.
- Brain herniation, sometimes referred to as brain hernia, is a potentially deadly side effect of very high intracranial pressure that occurs when a part of the brain is squeezed across structures within the skull.
- Epigastric hernia: a hernia through the linea alba above the umbilicus.
- Hiatus hernia: a hernia due to "short oesophagus" — insufficient elongation — stomach is displaced into the thorax
- Littre's hernia: a hernia involving a Meckel's diverticulum. It is named after the French anatomist Alexis Littré (1658–1726).
- Lumbar hernia: a hernia in the lumbar region (not to be confused with a lumbar disc hernia), contains the following entities:
  - Petit's hernia: a hernia through Petit's triangle (inferior lumbar triangle). It is named after French surgeon Jean Louis Petit (1674–1750).
  - Grynfeltt's hernia: a hernia through Grynfeltt-Lesshaft triangle (superior lumbar triangle). It is named after physician Joseph Grynfeltt (1840–1913).
- Maydl's hernia: two adjacent loops of small intestine are within a hernial sac with a tight neck. The intervening portion of bowel within the abdomen is deprived of its blood supply and eventually becomes necrotic.
- Morgagni hernia: a type of hernia where abdominal contents pass into the thorax through a weakness in the diaphragm
- Obturator hernia: hernia through obturator canal
- Pantaloon hernia (Saddle Bag hernia): a combined direct and indirect hernia, when the hernial sac protrudes on either side of the inferior epigastric vessels
- Paraesophageal hernia
- Parastomal hernias, which is when tissue protrudes adjacent to a stoma tract.
- Paraumbilical hernia: a type of umbilical hernia occurring in adults
- Perineal hernia: a perineal hernia protrudes through the muscles and fascia of the perineal floor. It may be primary but usually is acquired following perineal prostatectomy, abdominoperineal resection of the rectum, or pelvic exenteration.
- Properitoneal hernia: rare hernia located directly above the peritoneum, for example, when part of an inguinal hernia projects from the deep inguinal ring to the preperitoneal space.
- Richter's hernia: a hernia involving only one sidewall of the bowel, which can result in bowel strangulation leading to perforation through ischaemia without causing bowel obstruction or any of its warning signs. It is named after German surgeon August Gottlieb Richter (1742–1812).
- Sliding hernia: occurs when an organ drags along part of the peritoneum, or, in other words, the organ is part of the hernia sac. The colon and the urinary bladder are often involved. The term also frequently refers to sliding hernias of the stomach.
- Sciatic hernia: this hernia in the greater sciatic foramen most commonly presents as an uncomfortable mass in the gluteal area. Bowel obstruction may also occur. This type of hernia is only a rare cause of sciatic neuralgia.
- Spigelian hernia, also known as spontaneous lateral ventral hernia
- Sports hernia: a hernia characterized by chronic groin pain in athletes and a dilated superficial inguinal ring.
- Velpeau hernia: a hernia in the groin in front of the femoral blood vessels



Patient with a colostomy complicated by a large parastomal hernia.

## Treatment [edit]

*Main articles: Hernia repair and Inguinal hernia surgery*

### Truss [edit]

The benefits of the use of an external device to maintain reduction of the hernia without repairing the underlying defect (such as hernia trusses, trunks, belts, etc.) are unclear.[1]

### Surgery [edit]

Surgery is recommended for some types of hernias to prevent complications like obstruction of the bowel or strangulation of the tissue, although umbilical hernias and hiatus hernias may be watched, or are treated with medication.[13] Most abdominal hernias can be surgically repaired, but surgery has complications. Time needed for recovery after treatment is reduced if hernias are operated on laparoscopically. However, open surgery can be done sometimes without general anesthesia. Uncomplicated hernias are principally repaired by pushing back, or "reducing", the herniated tissue, and then mending the weakness in muscle tissue (an operation called herniorrhaphy). If complications have occurred, the surgeon will check the viability of the herniated organ and remove part of it if necessary.

Hernia repair being performed aboard the amphibious assault ship USS *Bataan*.

Muscle reinforcement techniques often involve synthetic materials (a mesh prosthesis).[14] The mesh is placed either over the defect (anterior repair) or under the defect (posterior repair). At times staples are used to keep the mesh in place. These mesh repair methods are often called "tension free" repairs because, unlike some suture methods (e.g., Shouldice), muscle is not pulled together under tension. However, this widely used terminology is misleading, as there are many tension-free suture methods that do not use mesh (e.g., Desarda, Guarnieri, Lipton-Estrin, etc.).

Evidence suggests that tension-free methods (with or without mesh) often have lower percentage of recurrences and the fastest recovery period compared to tension suture methods. However, among other possible complications, prosthetic mesh usage seems to have a higher incidence of chronic pain and, sometimes, infection.[15]

The frequency of surgical correction ranges from 10 per 100,000 (U.K.) to 28 per 100,000 (U.S.).[1]

### Recovery [edit]

Many people are managed through day surgery centers, and are able to return to work within a week or two, while intense activities are prohibited for a longer period. People who have their hernias repaired with mesh often recover in a number of days, though pain can last longer. Surgical complications include pain that lasts more than three months, surgical site infections, nerve and blood vessel injuries, injury to nearby organs, and hernia recurrence. Pain that lasts more than three months occurs in about 10% of people following hernia repair.[1]

## Complications [edit]

Complications may arise post-operation, including rejection of the mesh that is used to repair the hernia. In the event of a mesh rejection, the mesh will very likely need to be removed. Mesh rejection can be detected by obvious, sometimes localised swelling and pain around the mesh area. Continuous discharge from the scar is likely for a while after the mesh has been removed.

A surgically treated hernia can lead to complications, while an untreated hernia may be complicated by:

- Inflammation
- Irreducibility

- Obstruction of any lumen, such as bowel obstruction in intestinal hernias
- Strangulation
- Hydrocele of the hernial sac
- Haemorrhage
- Autoimmune problems
- Incarceration, which is where it cannot be reduced, or pushed back into place,[16] at least not without very much external effort.[17] In intestinal hernias, this also substantially increases the risk of bowel obstruction and strangulation.

## Epidemiology [edit]

About 27% of males and 3% of females develop a groin hernia at some time in their life.[1] In 2013 about 25 million people had a hernia.[18] Inguinal, femoral and abdominal hernias resulted in 32,500 deaths globally in 2013 and 50,500 in 1990.[5]

## References [edit]


1. ^ *a b c d e f g h i j k* Fitzgibbons RJ, Jr; Forse, RA (19 February 2015). "Clinical practice. Groin hernias in adults.". *The New England Journal of Medicine*. **372** (8): 756–63. doi:10.1056/NEJMcp1404068. PMID 25693015.
2. ^ *a b* "Hernia". *https://www.nlm.nih.gov/*. 9 August 2014. Retrieved 12 March 2015. External link in `|website=` (help)
3. ^ *a b c d e* Roman, S; Kahrilas, PJ (23 October 2014). "The diagnosis and management of hiatus hernia.". *BMJ (Clinical research ed.)*. **349**: g6154. doi:10.1136/bmj.g6154. PMID 25341679.
4. ^ *a b* Domino, Frank J. (2014). *The 5-minute clinical consult 2014* (22nd ed.). Philadelphia, Pa.: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 562. ISBN 9781451188509.
5. ^ *a b* GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385**: 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
6. ^ Nigam, VK (2009). *Essentials of Abdominal Wall Hernias*. I. K. International Pvt Ltd. p. 6. ISBN 9788189866938.
7. ^ "Symptoms". Retrieved 2010-05-24.
8. ^ Lee HK, Park SJ, Yi BH (2010). "Multidetector CT reveals diverse variety of abdominal hernias". *Diagnostic Imaging*. **32** (5): 27–31.
9. ^ "Hiatal Hernia Symptoms, Causes And Relation To Acid Reflux And Heartburn". Archived from the original on October 28, 2008. Retrieved 2010-05-24.
10. ^ "Hernia Causes". Retrieved 2010-05-24.
11. ^ Desarda MP (2003). "Surgical physiology of inguinal hernia repair—a study of 200 cases". *BMC Surg*. **3**: 2. doi:10.1186/1471-2482-3-2. PMC 155644. PMID 12697071.
12. ^ Arráez-Aybar, L. A., González-Gómez, C. C., & Torres-García, A. J. (2009). Morgagni-Larrey parasternal diaphragmatic hernia in the adult. Rev Esp Enferm Dig, 101(5), 357-366.
13. ^ http://www.nhs.uk/conditions/hernia/Pages/Introduction.aspx
14. ^ Effectiveness of mesh hernioplasty in incarcerated inguinal hernias. Kamtoh G, Pach R, Kibil W, Matyja A, Solecki R, Banas B, Kulig J. 2014 Sep;9(3):415-9. doi:10.5114/wiitm.2014.43080
15. ^ Sohail MR, Smilack JD (June 2004). "Hernia repair mesh-associated *Mycobacterium goodii* infection". *J. Clin. Microbiol*. **42** (6): 2858–60. doi:10.1128/JCM.42.6.2858-2860.2004. PMC 427896. PMID 15184492.
16. ^ Trudie A Goers; Washington University School of Medicine Department of Surgery; Klingensmith, Mary E; Li Ern Chen; Sean C Glasgow (2008). *The Washington manual of surgery*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. ISBN 0-7817-7447-0.
17. ^ onlinedictionary.datasegment.com > incarcerated Citing: Webster 1913
18. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.

## External links [edit]

- Hernia at DMOZ

Look up *hernia* in Wiktionary, the free dictionary.

Wikimedia Commons has media related to *Hernia*.

| v · t · e · | **Diseases of the digestive system (primarily K20–K93, 530–579)** | |
|---|---|---|
| **Upper GI tract** | **Esophagus** | Esophagitis (Candidal · Eosinophilic · Herpetiform · · *Rupture* (Boerhaave syndrome · Mallory-Weiss syndrome · · UES (Zenker's diverticulum · · LES (Barrett's esophagus · · Esophageal motility disorder (Nutcracker esophagus · Achalasia · Diffuse esophageal spasm · Gastroesophageal reflux disease (GERD) · · Laryngopharyngeal reflux (LPR) · Esophageal stricture · Megaesophagus · |
| | **Stomach** | Gastritis (Atrophic · Ménétrier's disease · Gastroenteritis · · Peptic (gastric) ulcer (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
| **Lower GI tract: Intestinal/ Enteropathy** | **Small intestine (Duodenum/Jejunum/Ileum)** | Enteritis (Duodenitis · Jejunitis · Ileitis · · Peptic (duodenal) ulcer (Curling's ulcer · · Malabsorption: Coeliac · Tropical sprue · Blind loop syndrome · Small bowel bacterial overgrowth syndrome · Whipple's · Short bowel syndrome · Steatorrhea · Milroy disease · Bile acid malabsorption · |
| | **Large intestine (Appendix/Colon)** | Appendicitis · Colitis (Pseudomembranous · Ulcerative · Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (IBS · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
| | **Large and/or small** | Enterocolitis (Necrotizing · · Gastroenterocolitis · IBD (Crohn's disease · · *Vascular*: Abdominal angina · Mesenteric ischemia · Angiodysplasia · Bowel obstruction: Ileus · Intussusception · Volvulus · Fecal impaction · Constipation · Diarrhea (Infectious · · Intestinal adhesions · |
| | **Rectum** | Proctitis (Radiation proctitis · · Proctalgia fugax · Rectal prolapse · Anismus · |
| | **Anal canal** | Anal fissure/Anal fistula · Anal abscess · Anal dysplasia · Pruritus ani · |
| **GI bleeding/BIS** | Upper (Hematemesis · Melena · · Lower (Hematochezia · · | |
| | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · |

| | | |
|---|---|---|
| **Accessory** | | Acute liver failure · · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |
| | **Gallbladder** | Cholecystitis · Gallstones/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · Gallstones/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
| | **Pancreatic** | Pancreatitis (Acute · Chronic · Hereditary · Pancreatic abscess · · Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |
| **Abdominopelvic** | **Hernia** | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |

| v · t · e · **Congenital diaphragm and abdominal wall defects, abdominopelvic cavity (Q79.0–Q79.5, 756.6–756.7)** | |
|---|---|
| **Thoracic diaphragm** | **Hernia** (Congenital diaphragmatic hernia (Bochdalek hernia · · · |
| **Abdominal wall** | Omphalocele · Gastroschisis · Prune belly syndrome · |

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|---|---|
| **Authority control** | NDL: 00563131 · |

Categories: Disorders of fascia | Congenital disorders of musculoskeletal system | Hernias | Acute pain

# Irritable bowel syndrome

From Wikipedia, the free encyclopedia

*This article is about a functional disorder. For bowel inflammation, see Inflammatory bowel disease.*

**Irritable bowel syndrome** (**IBS**) is a group of symptoms—including abdominal pain and changes in the pattern of bowel movements without any evidence of underlying damage.[1] These symptoms occur over a long time, often years.[1] It has been classified into four main types depending on if diarrhea is common, constipation is common, both are common, or neither occurs very often (IBS-D, IBS-C, IBS-M, or IBS-U respectively).[1] IBS negatively affects quality of life and may result in missed school or work.[3] Disorders such as anxiety, major depression, and chronic fatigue syndrome, are common among people with IBS.[1][4]

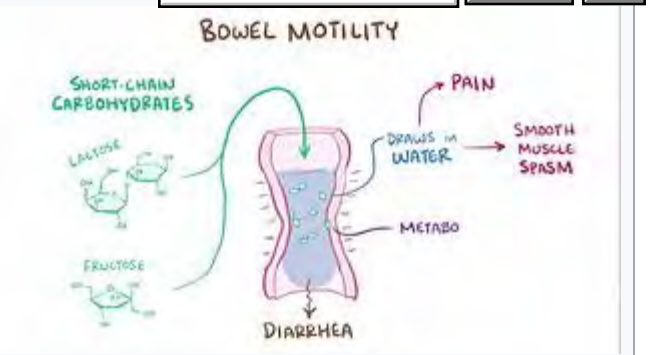
The causes of IBS are not clear.[2] Theories include gut–brain axis problems, small intestinal bacterial overgrowth, genetic factors, food sensitivity, and gut motility problems.[2] Onset may be triggered by an intestinal infection,[5] or stressful life event.[6] IBS is a functional gastrointestinal disorder.[1] Diagnosis is based on signs and symptoms in the absence of worrisome features.[7] Worrisome features include onset at greater than 50 years of age, weight loss, blood in the stool, or a family history of inflammatory bowel disease.[7] Other conditions that may present similarly include celiac disease, microscopic colitis, inflammatory bowel disease, bile acid malabsorption, and colon cancer.[7]

There is no cure for IBS.[8] Treatment is carried out to improve symptoms.[8] This may including dietary changes, medication, probiotics, and counselling.[8] Dietary measures include increasing soluble fiber intake, a gluten free diet, or a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP).[7][9] The medication loperamide may be used to help with diarrhea while laxatives may be used to help with constipation.[7] Antidepressants may improve overall symptoms and pain.[7] Patient education and a good doctor–patient relationship are an important part of care.[7][10]

About 10 to 15% of people in the developed world are believed to be affected by IBS.[1][11] It is more common in South America and less common in Southeast Asia.[7] It is twice as common in women as men and typically occurs before age 45.[1] The condition appears to become less common with age.[7] IBS does not affect life expectancy or lead to other serious diseases.[12] The first description of the condition was in

**Irritable bowel syndrome**

**Synonyms** Spastic colon, nervous colon,




Play media

Video explanation

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Gastroenterology |
| **ICD-10** | K58 |
| **ICD-9-CM** | 564.1 |
| **DiseasesDB** | 30638 |
| **MedlinePlus** | 000246 |
| **eMedicine** | med/1190 |
| **Patient UK** | Irritable bowel syndrome |
| **MeSH** | D043183 |

[edit on Wikidata]

1820 while the current term "irritable bowel syndrome" came into use in 1944.[13]

Gaeilge

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## Classification [edit]

IBS can be classified as either diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), or with alternating stool pattern (IBS-A) or pain-predominant.[14] In some individuals, IBS may have an acute onset and develop after an infectious illness characterized by two or more of: fever, vomiting, diarrhea, or positive stool culture. This postinfective syndrome has consequently been termed "postinfectious IBS" (IBS-PI).

## Signs and symptoms [edit]

The primary symptoms of IBS are abdominal pain or discomfort in association with frequent diarrhea or constipation and a change in bowel habits.[15] Symptoms usually are experienced as acute attacks that subside within one day, but recurrent attacks are likely.[16] There may also be urgency for bowel movements, a feeling of incomplete evacuation (tenesmus), bloating, or abdominal distension.[17] In some cases, the symptoms are relieved by bowel movements.[10] People with IBS, more commonly than others, have gastroesophageal reflux, symptoms relating to the genitourinary system, chronic fatigue syndrome, fibromyalgia, headache, backache, and psychiatric symptoms such as depression and anxiety.[4][17] About a third of men and women who have IBS also report sexual dysfunction typically in the form of a reduction in libido.[18]

## Cause [edit]

While the causes of IBS are still unknown, it is believed that the entire gut–brain axis is affected.[19][20]

The risk of developing IBS increases six-fold after acute gastrointestinal infection. Postinfection, further risk factors are young age, prolonged fever, anxiety, and depression.[21] Psychological factors, such as depression or anxiety, have not been shown to cause or influence the onset of IBS, but may play a role in the persistence and perceived severity of symptoms.[22] Nevertheless, they may worsen IBS symptoms and the patient quality of life.[22] Antibiotic use also appears to increase the risk of developing IBS.[23] Research has found that genetic defects in innate immunity and epithelial homeostasis increase the risk of developing both post-infectious as well as other forms of IBS.[24]

## Post-infectious [edit]

Approximately 10 percent of IBS cases are triggered by an acute gastroenteritis infection. Genetic defects relating to the innate immune system and epithelial barrier as well as high stress and anxiety levels appear from evidence to increase the risk of developing post-infectious IBS. Post-infectious IBS usually manifests itself as the diarrhea predominant subtype. Evidence has demonstrated that the release of high levels of proinflammatory cytokines during acute enteric infection causes increased gut permeability leading to translocation of the commensal bacteria across the epithelial barrier resulting in significant damage to local tissues which is likely to result in chronic gut abnormalities in sensitive individuals. However, increased gut permeability is strongly associated with IBS regardless of whether IBS was initiated by an infection or not.[24]

## Stress [edit]

Publications suggesting the role of brain-gut "axis" appeared in the 1990s[25] and childhood physical and psychological abuse is often associated with the development of IBS.[26]

Given the high levels of anxiety seen in IBS patients and the overlap with conditions such as fibromyalgia and chronic fatigue syndrome, a potential model of IBS involves a disruption of the stress system. The stress response in the body involves the HPA axis and the sympathetic nervous system, both of which have been shown to operate abnormally in IBS patients. Psychiatric illness or anxiety precedes IBS symptoms in two-thirds of patients, and psychological traits predispose previously healthy people to developing IBS after gastroenteritis.[27][28]

## Bacteria [edit]

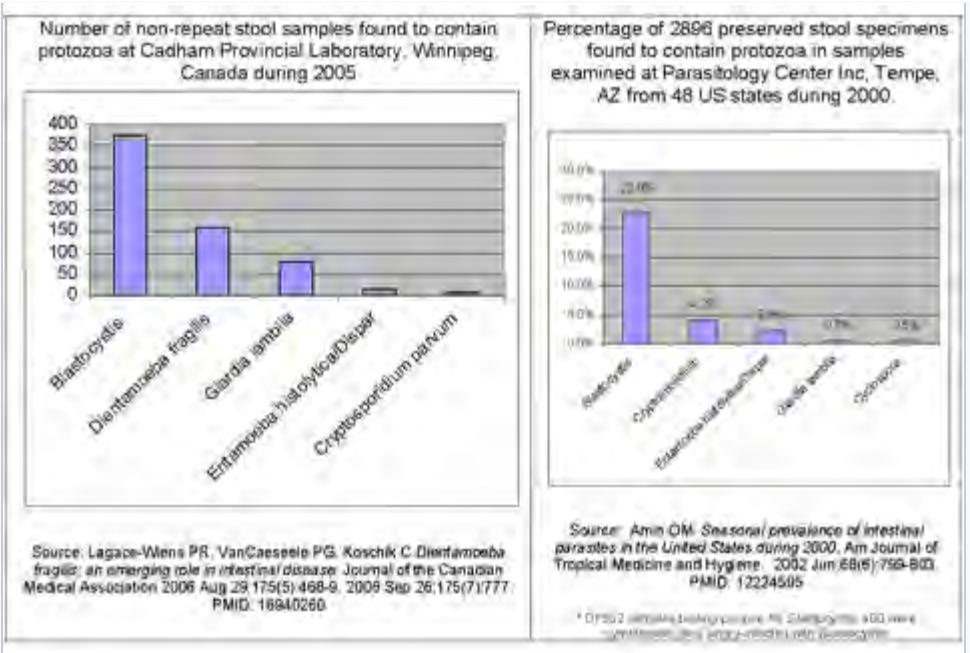
Small intestinal bacterial overgrowth occurs with greater frequency in patients who have been diagnosed with IBS compared to healthy controls. SIBO is most common in diarrhea-predominate IBS but also occurs in constipation-predominant IBS more frequently than healthy controls. Symptoms of SIBO include bloating, abdominal pain, diarrhea or constipation among others. IBS may be the result of the immune system interacting abnormally with gut microbiota resulting in an abnormal cytokine signalling profile.[29]

## Fungus [edit]

There is growing evidence that alterations of gut microbiota (dysbiosis) are associated with the intestinal manifestations of IBS, but also with the psychiatric morbidity that coexists in up to 80% of patients with IBS.[30] The role of the gut mycobiota, and especially of the abnormal proliferation of the yeast *Candida albicans* in some patients with IBS, is under investigation.[31]

## Protozoa [edit]

Protozoal infections can cause symptoms that mirror specific IBS subtypes,[34] e.g., infection by certain substypes of *blastocystis hominis* (blastocystosis) has a




Prevalence of protozoal infections in industrialized countries (United States and Canada) in the 21st century[32][33]

significant (possibly causal) relationship with IBS-D;[35][36] certain protozoal infections also occur more frequently in IBS patients.[37][38] *Dientamoeba fragilis* has also been considered a possible organism to study, though it is also found in people without IBS.[39]

## Mechanism [edit]

There is evidence that abnormalities occur in the gut flora of individuals who have IBS, such as reduced diversity, a decreased abundance of bacteria belonging to the phylum *Bacteroidetes*, and an increased abundance of those belonging to the phylum *Firmicutes*.[40] The changes in gut flora are most profound in individuals who have diarrhoea predominant IBS. Antibodies against common components (namely flagellin) of the commensal gut flora are a common occurrence in IBS affected individuals.[41] Chronic low-grade inflammation commonly occurs in IBS affected individuals with abnormalities found including increased enterochromaffin cells, intraepithelial lymphocytes, and mast cells resulting in chronic immune mediated inflammation of the gut mucosa.[19][42]

Genetic, environmental, and psychological factors seem to be important in the development of IBS. Studies have shown that IBS has a genetic component even though there is a predominant influence of environmental factors.[43] IBS has been reported in greater quantities in multigenerational families with IBS than in the regular population.[44]

## Diagnosis [edit]

No specific laboratory or imaging test can be performed to diagnose irritable bowel syndrome. Diagnosis involves excluding conditions that produce IBS-like symptoms, and then following a procedure to categorize the patient's symptoms. Ruling out parasitic infections, lactose intolerance, small intestinal bacterial overgrowth, and celiac disease is recommended for all patients before a diagnosis of irritable bowel syndrome is made. In patients over 50 years old, they are recommended to undergo a screening colonoscopy.[45] IBS sufferers are at increased risk of being given inappropriate surgeries such as appendectomy, cholecystectomy, and hysterectomy due to their IBS symptoms being misdiagnosed as other medical conditions.[46]

### Differential diagnosis [edit]

Colon cancer, inflammatory bowel disease, thyroid disorders, and giardiasis can all feature abnormal defecation and abdominal pain. Less common causes of this symptom profile are carcinoid syndrome, microscopic colitis, bacterial overgrowth, and eosinophilic gastroenteritis; IBS is, however, a common presentation, and testing for these conditions would yield low numbers of positive results, so it is considered difficult to justify the expense.[47]

[48]

Some people, managed for years for IBS, may have non-celiac gluten sensitivity (NCGS). Gastrointestinal symptoms of IBS are clinically indistinguishable from those of NCGS, but the presence of any of the following non-intestinal manifestations suggest a possible NCGS: headache or migraine, "foggy mind", chronic fatigue,[49] fibromyalgia,[50][51][52] joint and muscle pain,[49][50][53] leg or arm numbness,[49][50][53] tingling of the extremities,[49][53] dermatitis (eczema or skin rash),[49][53] atopic disorders,[49] allergy to one or more inhalants, foods or metals[49][50] (such as mites, graminaceae, parietaria, cat or dog hair, shellfish, or nickel[50]), depression,[49][50][53] anxiety,[50] anemia,[49][53] iron-deficiency anemia, folate deficiency, asthma, rhinitis, eating disorders,[50] neuropsychiatric disorders (such as schizophrenia,[53][54] autism,[50][53][54] peripheral neuropathy,[53][54] ataxia,[54] attention deficit hyperactivity disorder[49]) or autoimmune diseases.[49] An improvement with a gluten-free diet of immune-mediated symptoms, including autoimmune diseases, once having reasonably ruled out coeliac disease and wheat allergy, is another way to realize a differential diagnosis.[49]

Because many causes of diarrhea give IBS-like symptoms, the American Gastroenterological Association published a set of guidelines for tests to be performed to rule out other causes for these symptoms. These include gastrointestinal infections, lactose intolerance, and coeliac disease. Research has suggested these guidelines are not always followed.[45] Once other causes have been excluded, the diagnosis of IBS is performed using a diagnostic algorithm. Well-known algorithms include the Manning criteria, the obsolete Rome I and II criteria, and the Kruis criteria, and studies have compared their reliability.[55] The more recent Rome III process was published in 2006. Physicians may choose to use one of these guidelines or may simply choose to rely on their own anecdotal experience with past patients. The algorithm may include additional tests to guard against misdiagnosis of other diseases as IBS. Such "red flag" symptoms may include weight loss, gastrointestinal bleeding, anemia, or nocturnal symptoms. However, red flag conditions may not always contribute to accuracy in diagnosis; for instance, as many as 31% of IBS patients have blood in their stool, many possibly from hemorrhoidal bleeding.[55]

The diagnostic algorithm identifies a name that can be applied to the patient's condition based on the combination of the patient's symptoms of diarrhea, abdominal pain, and constipation. For example, the statement "50% of returning travelers had developed functional diarrhea while 25% had developed IBS" would mean half the travelers had diarrhea while a quarter had diarrhea with abdominal pain. While some researchers believe this categorization system will help physicians understand IBS, others have questioned the value of the system and suggested all IBS patients have the same underlying disease but with different symptoms.[56]

## Investigations [edit]

Investigations are performed to exclude other conditions:

- Stool microscopy and culture (to exclude infectious conditions)
- Blood tests: Full blood examination, liver function tests, erythrocyte sedimentation rate, and serological testing for coeliac disease
- Abdominal ultrasound (to exclude gallstones and other biliary tract diseases)
- Endoscopy and biopsies (to exclude peptic ulcer disease, coeliac disease, inflammatory bowel disease, and malignancies)
- Hydrogen breath testing (to exclude fructose and lactose malabsorption)

## Misdiagnosis [edit]

Some common examples of misdiagnosis include infectious diseases, coeliac disease,[57] *Helicobacter pylori*,[58][59] parasites (non-protozoal).[34][60][61]

Coeliac disease in particular is often misdiagnosed as IBS. The American College of Gastroenterology recommends all patients with symptoms of IBS be tested for coeliac disease.[62]

Bile acid malabsorption is also sometimes missed in patients with diarrhea-predominant IBS. SeHCAT tests suggest around 30% of D-IBS patients have this condition, and most respond to bile acid sequestrants.[63]

Chronic use of certain sedative-hypnotic drugs, especially the benzodiazepines, may cause irritable bowel-like symptoms that can lead to a misdiagnosis of irritable bowel syndrome.[64]

### Comorbidities [edit]

Several medical conditions, or comorbidities, appear with greater frequency in patients diagnosed with IBS.

- Neurological/Psychiatric: A study of 97,593 individuals with IBS identified comorbidities such as headache, fibromyalgia, and depression.[65] IBS occurs in 51% of chronic fatigue syndrome patients and 49% of fibromyalgia patients, and psychiatric disorders occur in 94% of IBS patients.[4]
- Inflammatory bowel disease: IBS may be a type of low-grade inflammatory bowel disease.[66] Researchers have suggested IBS and IBD are interrelated diseases,[67] noting that patients with IBD experience IBS-like symptoms when their IBD is in remission.[68][69] A three-year study found that patients diagnosed with IBS were 16.3 times more likely to be diagnosed with IBD during the study period.[70] Serum markers associated with inflammation have also been found in patients with IBS.
- Abdominal surgery: IBS patients were at increased risk of having unnecessary gall bladder removal surgery not due to an increased risk of gallstones, but rather to abdominal pain, awareness of having gallstones, and inappropriate surgical indications.[71] These patients also are 87% more likely to undergo abdominal and pelvic surgery and three times more likely to undergo gallbladder surgery.[72] Also, IBS patients were twice as likely to undergo hysterectomy.[73]
- Endometriosis: One study reported a statistically significant link between migraine headaches, IBS, and endometriosis.[74]
- Other chronic disorders: Interstitial cystitis may be associated with other chronic pain syndromes, such as irritable bowel syndrome and fibromyalgia. The connection between these syndromes is unknown.[75]

## Management [edit]

A number of treatments have been found to be effective, including fiber, talk therapy, antispasmodic and antidepressant medication, and peppermint oil.[76][77][78]

### Diet [edit]

Studies have shown that up to 70% of IBS patients benefited from eating a low FODMAP diet. Symptoms most likely to improve from such a diet include urgency, flatulence, bloating, abdominal pain, and altered stool output. One national guideline advises a low FODMAP diet for managing IBS when other dietary and lifestyle measures have been unsuccessful.[79] This diet restricts various carbohydrates which are poorly absorbed in the small intestine, as well as fructose and lactose, which are similarly poorly absorbed in those with intolerances to them. Reduction of fructose and fructan has been shown to reduce IBS symptoms in a dose-dependent manner in patients with fructose malabsorption and IBS.[80]

Some IBS patients believe they have some form of dietary intolerance; however, tests attempting to predict food sensitivity in IBS have proven disappointing. A small study reported that an IgG antibody test was somewhat effective in determining food sensitivity in IBS patients, with patients on the elimination diet experiencing 10% greater symptom-reduction than those on a sham diet.[81] However, more research is necessary before IgG testing can be recommended.[82]

### FODMAPs diet [edit]

A diet restricted in fermentable oligo- di- and monosaccharides and polyols (FODMAPs) now has an evidence base sufficiently strong to recommend its widespread application in conditions such as IBS and IBD.[83] They also state the restriction of FODMAPs globally, rather than individually, controls the symptoms of functional gut disorders (e.g., IBS), and the majority of IBD patients respond just as well. It is more successful than restricting only fructose and fructans, which are also FODMAPs, as is recommended for those with fructose malabsorption. Longer-term compliance with the diet was high.

## Fiber [edit]

Some evidence suggests soluble fiber supplementation (e.g., psyllium/ispagula husk) is effective.[9] It acts as a bulking agent, and for many IBS-D patients, allows for a more consistent stool. For IBS-C patients, it seems to allow for a softer, moister, more easily passable stool.

However, insoluble fiber (e.g., bran) has not been found to be effective for IBS.[84][85] In some people, insoluble fiber supplementation may aggravate symptoms.[86][87]

Fiber might be beneficial in those who have a predominance of constipation. In people who have IBS-C, soluble fiber can reduce overall symptoms, but will not reduce pain. The research supporting dietary fiber contains conflicting, small studies complicated by the heterogeneity of types of fiber and doses used.[88]

One meta-analysis found only soluble fiber improved global symptoms of irritable bowel, but neither type of fiber reduced pain.[88] An updated meta-analysis by the same authors also found soluble fiber reduced symptoms, while insoluble fiber worsened symptoms in some cases.[89] Positive studies have used 10–30 grams per day of psyllium.[90][91] One study specifically examined the effect of dose, and found 20 g of ispaghula husk were better than 10 g and equivalent to 30 g per day.[92]

## Medication [edit]

Medications may consist of stool softeners and laxatives in IBS-C and antidiarrheals (e.g., opiate, opioid, or opioid analogs such as loperamide, codeine, diphenoxylate) in IBS-D for mild symptoms and stronger opiates such as morphine and oxycodone for severe cases.[93][94][95]

Drugs affecting serotonin (5-HT) in the intestines can help reduce symptoms.[96] On the other hand, many IBS-D patients report that SSRI type medications exacerbate spasms and diarrhea. This is thought to be due to the large number of serotonin receptors in the gut. 5HT3 antagonists such as ondansetron are effective in postinfectious IBS and diarrhoea-dominant IBS due to their blockade of serotonin on 5HT3 receptors in the gut; the reason for their benefit is believed to be that excessive serotonin in the gut is thought to play a role in the pathogenesis of some subtypes of IBS. Certain atypical antipsychotic medications, such as clozapine and olanzapine, may also provide relief due to serotonergic properties these agents possess, acting on the same receptors as other medications in this specific category.[97] Benefits may include reduced diarrhoea, reduced abdominal cramps, and improved general well-being. Any nausea present may also respond to 5HT3 antagonists owing to their antiemetic properties.[98] Serotonin stimulates the gut motility and so agonists can help constipation-predominant irritable bowel, while antagonists can help diarrhea-predominant irritable bowel. Selective serotonin reuptake inhibitors, SSRIs, frequently prescribed for panic and/or anxiety disorder and depression, affect serotonin in the gut, as well as the brain. The bowels are highly dependent on serotonin for neural communication. "Selective serotonin reuptake inhibitor antidepressants seem to promote global well-being in some patients with irritable bowel syndrome and, possibly, some improvement in abdominal pain and bowel symptoms, but this effect appears to be independent of improved depression. Further research is required."[99]

Mast cells and the compound that they secrete are central to the pathophysiology and implicated in the treatment of IBS;[19] some of the secreted mast cell mediators (and associated receptors) which have been implicated in symptoms of IBS or specific subtypes include: histamine (HRH1, HRH2, HRH3), tryptase and chymase (PAR2), serotonin (5-HT3), PGD2 (DP1).[19] Histamine also causes epithelial secretion of chloride ions and water (associated with secretory diarrhea) by signaling through a receptor or ligand-gated ion channel that has not been identified as of 2015.[19] A 2015 review noted that both H1-antihistamines and mast cell stabilizers have shown efficacy in reducing pain associated with visceral hypersensitivity in IBS;[19] other lower quality studies have also suggested the benefit of these agents for IBS.[19] In a related review on idiopathic mast cell activation syndromes (including IBS), a combined treatment approach using antileukotrienes, H1/H2-antihistamines, and a mast cell stabilizer are suggested.[100]

## Laxatives [edit]

For patients who do not adequately respond to dietary fiber, osmotic laxatives such as polyethylene glycol, sorbitol, and lactulose can help avoid "cathartic colon" which has been associated with stimulant laxatives.[101] Among the osmotic laxatives, doses of 17–26 g/d of polyethylene glycol have been well studied. Lubiprostone (Amitiza) is a gastrointestinal agent used for the treatment of idiopathic chronic constipation and constipation-predominant IBS. It is well tolerated in adults, including elderly patients. As of July 20, 2006, lubiprostone had not been studied in pediatric patients. Lubiprostone is a bicyclic fatty acid (prostaglandin E1 derivative) that acts by specifically activating ClC-2 chloride channels on the apical aspect of gastrointestinal epithelial cells, producing a chloride-rich fluid secretion. These secretions soften the stool, increase motility, and promote spontaneous bowel movements. Unlike many laxative products, lubiprostone does not show signs of tolerance, dependency, or altered serum electrolyte concentration.

## Antispasmodics [edit]

The use of antispasmodic drugs (e.g., anticholinergics such as hyoscyamine or dicyclomine) may help patients, especially those with cramps or diarrhea. A meta-analysis by the Cochrane Collaboration concludes if seven patients are treated with antispasmodics, one patient will benefit.[93] Antispasmodics can be divided in two groups: neurotropics and musculotropics.

- Neurotropics — for example, phenobarbitals such as Donnatal or atropine — act at the nerve fibre of the parasympathicus, but also affect other nerves, causing side effects in many patients.
- Musculotropics, such as mebeverine, act directly at the smooth muscle of the gastrointestinal tract, relieving spasm without affecting normal gut motility.[*citation needed*] Since this action is not mediated by the autonomic nervous system, the usual anticholinergic side effects are absent.[*citation needed*]

## Discontinuation of proton pump inhibitors [edit]

Proton pump inhibitors (PPIs) used to suppress stomach acid production may cause bacterial overgrowth leading to IBS symptoms. Discontinuation of PPIs in selected individuals has been recommended as it may lead to an improvement or resolution of IBS symptoms.[102]

## Tricyclic antidepressants [edit]

Strong evidence indicates low doses of tricyclic antidepressants can be effective for IBS. However, the evidence is less robust as to the effectiveness of other antidepressant classes such as SSRIs.[85][87]

## Serotonin agonists [edit]

- Tegaserod (Zelnorm), a selective 5-HT4 agonist for IBS-C, is available for relieving IBS constipation in women and chronic idiopathic constipation in men and women. On March 30, 2007, the FDA requested Novartis Pharmaceuticals to voluntarily discontinue marketing of tegaserod based on the recently identified finding of an increased risk of serious cardiovascular adverse events (heart problems) associated with use of the drug. Novartis agreed to voluntarily suspend marketing of the drug in the United States and in many other countries. On July 27, 2007, the FDA approved a limited-treatment IND program for tegaserod in the US to allow restricted access to the medication for patients in need if no comparable alternative drug or therapy is available to treat the disease. The FDA had issued two previous warnings about the serious consequences of tegaserod. In 2005, it was rejected as an IBS medication by the European Union. Tegaserod, marketed as Zelnorm in the United States, was the only agent approved to treat the multiple symptoms of IBS (in women only), including constipation, abdominal pain, and bloating.
- Selective serotonin reuptake inhibitor antidepressants (SSRIs), because of their serotonergic effect, would seem to help IBS, especially patients who are constipation predominant. Initial crossover studies[103] and randomized controlled trials[104][105][106] support this role. Publication bias may play a role in the apparent benefit of SSRIs.[107] One study concludes that tricyclic antidepressants can improve overall symptoms of irritable bowel syndrome; however, there was no strong evidence to confirm the effectiveness of SSRIs.[108]

## Serotonin antagonists [edit]

Alosetron, a selective 5-HT3 antagonist for IBS-D and cilansetron (also a selective 5-HT3 antagonist) were trialed for IBS. Due to severe adverse effects, namely ischemic colitis and severe constipation, they are not available or recommended.[87]

## Other agents [edit]

Magnesium aluminum silicates and alverine citrate drugs can be effective for IBS.[87]

Evidence is conflicting about the benefit of antidepressants in IBS. Some meta-analyses have found a benefit, while others have not.[109] A meta-analysis of randomized controlled trials of mainly TCAs found three patients have to be treated with TCAs for one patient to improve.[110] A separate randomized controlled trial found TCAs are best for patients with IBS-D.[111]

Rifaximin can be used as an effective treatment for abdominal bloating and flatulence,[112][113] giving more credibility to the potential role of bacterial overgrowth in some patients with IBS.[114]

Domperidone, a dopamine receptor blocker and a parasympathomimetic, has been shown to reduce bloating and abdominal pain as a result of an accelerated colon transit time and reduced faecal load, that is, a relief from 'hidden constipation'; defecation was similarly improved.[115]

The use of opioids is controversial due to the potential risk of tolerance, physical dependence, and addiction, but can be the only relief for some diarrhea-predominant cases when other treatment has been ineffective.[116]

## SIBO therapy [edit]

Statistically significant reduction in IBS symptoms occurs following antibiotic therapy for small intestinal bacterial overgrowth.[117] However, recent research has shown that the lactulose hydrogen breath test does not actually measure SIBO, and that SIBO is unlikely to be the cause of IBS.[118]

## Psychological therapies [edit]

The mind-body or brain-gut interactions has been proposed for IBS, and is gaining increasing research attention.[85] Hypnosis can improve mental well-being, and cognitive behavioural therapy can provide psychological coping strategies for dealing with distressing symptoms, as well as help suppress thoughts and behaviours that increase the symptoms of IBS,[85][87] although the evidence base for effectiveness of psychotherapy and hypnosis is weak and such therapies are in general not recommended.[46] However, in treatment resistant cases where pharmacological therapies over a period of at least 12 months have failed to give relief, NICE clinical guidelines recommend that consideration should be given to psychological treatment strategies such as cognitive behavioural therapy [CBT], hypnotherapy and/or psychological therapy.[119]

## Stress relief [edit]

Reducing stress may reduce the frequency and severity of IBS symptoms. Techniques that may be helpful include:

- Relaxation techniques such as meditation
- Physical activities such as yoga or tai chi
- Regular exercise such as swimming, walking, or running[120]

## Probiotics [edit]

Probiotics can be beneficial in the treatment of IBS; taking 10 billion to 100 billion beneficial bacteria per day is recommended for beneficial results. However, further research is needed on individual strains of beneficial bacteria for more refined recommendations.[85][121] Probiotics have positive effects such as enhancing the intestinal mucosal barrier, providing a physical barrier, bacteriocin production (resulting in

reduced numbers of pathogenic and gas-producing bacteria), reducing intestinal permeability and bacterial translocation, and regulating the immune system both locally and systemically among other beneficial effects.[46] Probiotics may also have positive effects on the gut-brain axis by their positive effects countering the effects of stress on gut immunity and gut function.[122]

A number of probiotics have been found to be effective, including *Lactobacillus plantarum*,[46] and *Bifidobacteria infantis*;[123] but one review found only *Bifidobacteria infantis* showed efficacy.[124] *B. infantis* may have effects beyond the gut via it causing a reduction of proinflammatory cytokine activity and elevation of blood tryptophan levels, which may cause an improvement in symptoms of depression.[125] Some yogurt is made using probiotics that may help ease symptoms of IBS.[126] A probiotic yeast called Saccharomyces boulardii has some evidence of effectiveness in the treatment of irritable bowel syndrome.[127]

Certain probiotics have different effects on certain symptoms of IBS. For example, *Bifidobacterium breve*, *B. longum,* and *Lactobacillus acidophilus* have been found to alleviate abdominal pain. *B. breve, B. infantis, L. casei*, or *L. plantarum* species alleviated distension symptoms. *B. breve, B. infantis, L. casei, L. plantarum, B. longum, L. acidophilus, L. bulgaricus*, and *Streptococcus salivarius* ssp. *thermophilus* have all been found to affect flatulence levels. Most clinical studies show probiotics do not improve straining, sense of incomplete evacuation, stool consistency, fecal urgency, or stool frequency, although a few clinical studies did find some benefit of probiotic therapy. The evidence is conflicting for whether probiotics improve overall quality of life scores.[128]

Probiotics may exert their beneficial effects on IBS symptoms via preserving the gut microbiota, normalisation of cytokine blood levels, improving the intestinal transit time, decreasing small intestine permeability, and by treating small intestinal bacterial overgrowth of fermenting bacteria.[128]

### Herbal remedies [edit]

Peppermint oil appears useful.[129] Safety during pregnancy has not been established, however, and caution is required not to chew or break the enteric coating; otherwise, gastroesophageal reflux may occur as a result of lower esophageal sphincter relaxation. Occasionally, nausea and perianal burning occur as side effects.[85] Iberogast, a multi-herbal extract, was found to be superior in efficacy to placebo.[130] Commiphora mukul and Plantago ovata[131]

Only limited evidence exists for the effectiveness of other herbal remedies for IBS. As with all herbs, it is wise to be aware of possible drug interactions and adverse effects.[85]

### Yoga [edit]

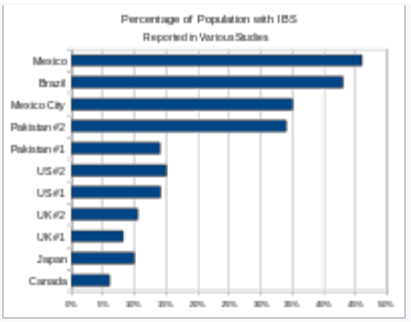
Yoga may be effective for some IBS patients, especially poses which exercise the lower abdomen.[87]

### Acupuncture [edit]

A meta-analysis found no benefits of acupuncture relative to placebo for IBS symptom severity or IBS-related quality of life.[132]

## Epidemiology [edit]

The prevalence of IBS varies by country and by age range examined. The bar graph at right shows the percentage of the population reporting symptoms of IBS in studies from various geographic regions (see table below for references). The following table contains a list of studies performed in different countries that measured the prevalence of IBS and IBS-like symptoms:




Percentage of population with IBS reported in various studies in different countries

**Percentage of population reporting symptoms of IBS in various studies from various geographic areas**

| Country | Prevalence | Author/year | Notes |
|---|---|---|---|
| Canada | 6%[133] | Boivin, 2001 | |
| Japan | 10%[134] | Quigley, 2006 | Study measured prevalence of GI abdominal pain/cramping |
| United Kingdom | 8.2%[135]<br>10.5%[136] | Ehlin, 2003<br>Wilson, 2004 | Prevalence increased substantially 1970–2004 |
| United States | 14.1%[137] | Hungin, 2005 | Most undiagnosed |
| United States | 15%[133] | Boivin, 2001 | Estimate |
| Pakistan | 14%[138] | Jafri, 2007 | Much more common in 16–30 age range. Of IBS patients, 56% male, 44% female |
| Pakistan | 34%[139] | Jafri, 2005 | College students |
| Mexico City | 35%[140] | Schmulson, 2006 | n=324. Also measured functional diarrhea and functional vomiting. High rates attributed to "stress of living in a populated city." |
| Brazil | 43%[134] | Quigley, 2006 | Study measured prevalence of GI abdominal pain/cramping |
| Mexico | 46%[134] | Quigley, 2006 | Study measured prevalence of GI abdominal pain/cramping |

## Gender [edit]

Women are around two to three times more likely to be diagnosed with IBS and four to five times more likely to seek specialty care for it than men.[141] These differences likely reflect a combination of both biological (sex) and social (gender) factors. People diagnosed with IBS are usually younger than 45 years old.[1] Studies of female patients with IBS show symptom severity often fluctuates with the menstrual cycle, suggesting hormonal differences may play a role.[142] Endorsement of gender-related traits has been associated with quality of life and psychological adjustment in IBS.[143] Gender differences in healthcare-seeking may also play a role.[144] Gender differences in trait anxiety may contribute to lower pain thresholds in women, putting them at greater risk for a number of chronic pain disorders.[145] Finally, sexual trauma is a major risk factor for IBS, with as many as 33% of those affected reporting such abuse. Because women are at higher risk of sexual abuse than men, sex-related risk of abuse may contribute to the higher rate of IBS in women.[146]

# History [edit]

One of the first references to the concept of an "irritable bowel" appeared in the *Rocky Mountain Medical Journal* in 1950.[147] The term was used to categorize patients who developed symptoms of diarrhea, abdominal pain, and constipation, but where no well-recognized infective cause could be found. Early theories suggested the irritable bowel was caused by a psychosomatic or mental disorder.

## Economics [edit]

The examples and perspective in this section **may not represent a worldwide view of the subject**. You may improve this article, discuss the issue on the talk page, or create a new article, as appropriate. *(July 2011) (Learn how and when to remove this template message)*

### United States [edit]

The aggregate cost of irritable bowel syndrome in the United States has been estimated at $1.7–10 billion in direct medical costs, with an additional $20 billion in indirect costs, for a total of $21.7–30 billion.[3] A study by a managed care company comparing medical costs of IBS patients to non-IBS controls identified a 49% annual increase in medical costs associated with a diagnosis of IBS.[148] IBS patients incurred average annual direct costs of $5,049 and $406 in out-of-pocket expenses in 2007.[149] A study of workers with IBS found that they reported a 34.6% loss in productivity, corresponding to 13.8 hours lost per 40 hour week.[150] A study of employer-related health costs from a Fortune 100 company conducted with data from the 1990s found IBS patients incurred US $4527 in claims costs vs. $3276 for controls.[151] A study on Medicaid costs conducted in 2003 by the University of Georgia's College of Pharmacy and Novartis found IBS was associated in an increase of $962 in Medicaid costs in California, and $2191 in North Carolina. IBS patients had higher costs for physician visits, outpatients visits, and prescription drugs. The study suggested the costs associated with IBS were comparable to those found in asthma patients.[152]

## Research [edit]

Individuals with IBS have been found to have decreased diversity and numbers of bacteroidetes microbiota. Preliminary research into the effectiveness of fecal microbiota transplant in the treatment of IBS has been very favourable with a 'cure' rate of between 36 percent and 60 percent with remission of core IBS symptoms persisting at 9 and 19 months follow up.[153][154] Treatment with probiotic strains of bacteria has shown to be effective, though not all strains of microorganisms confer the same benefit and adverse side effects have been documented in a minority of cases.[155]

There is increasing evidence for the effectiveness of mesalazine (5-aminosalicylic acid) in the treatment of IBS.[156] Mesalazine is a drug with anti-inflammatory properties that has been reported to significantly reduce immune mediated inflammation in the gut of IBS affected individuals with mesalazine therapy resulting in improved IBS symptoms as well as feelings of general wellness in IBS affected people. It has also been observed that mesalazine therapy helps to normalise the gut flora which is often abnormal in people who have IBS. The therapeutic benefits of mesalazine may be the result of improvements to the epithelial barrier function.[157]

An IgG-mediated food intolerance diet led to a 24% greater deterioration in symptoms compared to those on the elimination diet and food elimination based on IgG antibodies may be effective in reducing IBS symptoms and is worthy of further biomedical research.[81] The main problem with this study was that the differences in symptoms were only observed in exclusion diets is limited, treatment based on "abnormally" high IgG antibodies cannot be recommended.[158]

Differences in visceral sensitivity and intestinal physiology have been noted in IBS. Mucosal barrier reinforcement in response to oral 5-HTP was absent in IBS compared to controls.[159] IBS/IBD individuals are less often HLA DQ2/8 positive than in upper functional gastrointestinal disease and healthy populations.[160]

A questionnaire in 2006 designed to identify patients' perceptions about IBS, their preferences on the type of information they need, and educational media and expectations from health care providers revealed misperceptions about IBS developing into other conditions, including colitis, malnutrition, and cancer. The survey found IBS patients were most interested in learning about foods to avoid (60%), causes of IBS (55%), medications (58%), coping strategies (56%), and psychological factors related to IBS (55%). The respondents indicated they wanted their physicians to be available by phone or e-mail following a visit (80%), have the ability to listen (80%), and provide hope (73%) and support (63%).[161]

## References [edit]


1. ^ a b c d e f g h "Definition and Facts for Irritable Bowel Syndrome". *NIDDKD*. 23 February 2015. Retrieved 29 March 2016.
2. ^ a b c "Symptoms and Causes of Irritable Bowel Syndrome". *NIDDK*. 23 February 2015. Retrieved 29 March 2016.
3. ^ a b Hulisz D (2004). "The burden of illness of irritable bowel syndrome: current challenges and hope for the future". *J Manag Care Pharm*. **10** (4): 299–309. PMID 15298528.
4. ^ a b c Whitehead WE, Palsson O, Jones KR; Palsson; Jones (2002). "Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications?". *Gastroenterology*. **122** (4): 1140–56. doi:10.1053/gast.2002.32392. PMID 11910364.
5. ^ Spiller R, Garsed K; Garsed (May 2009). "Postinfectious irritable bowel syndrome". *Gastroenterology*. **136** (6): 1979–88. doi:10.1053/j.gastro.2009.02.074. PMID 19457422.
6. ^ Chang L (March 2011). "The role of stress on physiologic responses and clinical symptoms in irritable bowel syndrome". *Gastroenterology*. **140** (3): 761–5. doi:10.1053/j.gastro.2011.01.032. PMC 3039211. PMID 21256129.
7. ^ a b c d e f g h i Chey, WD; Kurlander, J; Eswaran, S (3 March 2015). "Irritable bowel syndrome: a clinical review.". *JAMA*. **313** (9): 949–58. doi:10.1001/jama.2015.0954. PMID 25734736.
8. ^ a b c "Treatment for Irritable Bowel Syndrome". *NIDDK*. 23 February 2015. Retrieved 29 March 2016.
9. ^ a b Moayyedi, P; Quigley, EM; Lacy, BE; Lembo, AJ; Saito, YA; Schiller, LR; Soffer, EE; Spiegel, BM; Ford, AC (September 2014). "The effect of fiber supplementation on irritable bowel syndrome: a systematic review and meta-analysis.". *The American journal of gastroenterology*. **109** (9): 1367–74. doi:10.1038/ajg.2014.195. PMID 25070054.
10. ^ a b Mayer EA (April 2008). "Clinical practice. Irritable bowel syndrome". *N. Engl. J. Med.* **358** (16): 1692–9. doi:10.1056/NEJMcp0801447. PMC 3816529. PMID 18420501.
11. ^ Maxion-Bergemann S, Thielecke F, Abel F, Bergemann R; Thielecke; Abel; Bergemann (2006). "Costs of irritable bowel syndrome in the UK and US". *PharmacoEconomics*. **24** (1): 21–37. doi:10.2165/00019053-200624010-00002. PMID 16445300.
12. ^ Quigley, Eamonn M.M. (2013). "Treatment level 1". *Irritable bowel syndrome : diagnosis and clinical management* (First edition. ed.). Chichester, West Sussex: Wiley-Blackwell. ISBN 9781118444740.
13. ^ Hatch, Maureen C. (2000). *Women and health*. San Diego, Calif: Academic Press. p. 1098. ISBN 9780122881459.
14. ^ Holten KB, Wetherington A, Bankston L; Wetherington; Bankston (2003). "Diagnosing the patient with abdominal pain and altered bowel habits: is it irritable bowel syndrome?". *Am Fam Physician*. **67** (10): 2157–62. PMID 12776965.
15. ^ Schmulson MW, Chang L; Chang (1999). "Diagnostic approach to the patient with irritable bowel syndrome". *Am. J. Med.* **107** (5A): 20S–26S. doi:10.1016/S0002-9343(99)00278-8. PMID 10588169.
16. ^ Tamparo, Carol (2011). *Fifth Edition: Diseases of the Human Body*. Philadelphia, PA: F.A. Davis Company. p. 407. ISBN 978-0-8036-2505-1.
17. ^ a b Talley NJ (2006). "Irritable bowel syndrome". *Intern Med J.* **36** (11): 724–8. doi:10.1111/j.1445-5994.2006.01217.x. PMC 1761148. PMID 17040359.
18. ^ Sperber AD, Dekel R; Dekel (Apr 2010). "Irritable Bowel Syndrome and Co-morbid Gastrointestinal and Extra-gastrointestinal Functional Syndromes". *J Neurogastroenterol Motil*. **16** (2): 113–9. doi:10.5056/jnm.2010.16.2.113. PMC 2879857. PMID 20535341.
19. ^ a b c d e f g Wouters MM, Vicario M, Santos J (2015). "The role of mast cells in functional GI disorders". *Gut*. **65**: 155–168. doi:10.1136/gutjnl-2015-309151. PMID 26194403. "Functional gastrointestinal disorders (FGIDs) are characterized by chronic complaints arising from disorganized brain-gut interactions leading to dysmotility and

hypersensitivity. The two most prevalent FGIDs, affecting up to 16–26% of worldwide population, are functional dyspepsia and irritable bowel syndrome. ... It is well established that mast cell activation can generate epithelial and neuro-muscular dysfunction and promote visceral hypersensitivity and altered motility patterns in FGIDs, postoperative ileus, food allergy and inflammatory bowel disease.

Mast cells play a central pathophysiological role in IBS and possibly in functional dyspepsia, although not well defined.

Increased mast cell activation is a common finding in the mucosa of patients with functional GI disorders. ...

Treatment with mast cell stabilisers offers a reasonably safe and promising option for the management of those patients with IBS non-responding to conventional approaches, though future studies are warranted to evaluate efficacy and indications."

20. ^ Ohman L, Simrén M; Simrén (2010). "Pathogenesis of IBS: Role of inflammation, immunity and neuroimmune interactions". *Nature Reviews Gastroenterology & Hepatology*. **7** (3): 163–73. doi:10.1038/nrgastro.2010.4. PMID 20101257.
21. ^ Thabane M, Kottachchi DT, Marshall JK; Kottachchi; Marshall (2007). "Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome". *Aliment Pharmacol Ther*. **26** (4): 535–44. doi:10.1111/j.1365-2036.2007.03399.x. PMID 17661757.
22. ^ *a b* "World Gastroenterology Organisation Global Guidelines. Irritable Bowel Syndrome: a Global Perspective" (PDF). World Gastroenterology Organisation. Sep 2015. Retrieved 24 Apr 2016.
23. ^ Shanahan F, Quigley EM; Quigley (May 2014). "Manipulation of the microbiota for treatment of IBS and IBD-challenges and controversies". *Gastroenterology*. **146** (6): 1554–63. doi:10.1053/j.gastro.2014.01.050. PMID 24486051.
24. ^ *a b* Beatty JK, Bhargava A, Buret AG (2014). "Post-infectious irritable bowel syndrome: mechanistic insights into chronic disturbances following enteric infection". *World J. Gastroenterol*. **20** (14): 3976–85. doi:10.3748/wjg.v20.i14.3976. PMC 3983453. PMID 24744587.
25. ^ Fukudo S, Nomura T, Muranaka M, Taguchi F; Nomura; Muranaka; Taguchi (1993). "Brain-gut response to stress and cholinergic stimulation in irritable bowel syndrome. A preliminary study". *J. Clin. Gastroenterol*. **17** (2): 133–41. doi:10.1097/00004836-199309000-00009. PMID 8031340.
26. ^ Barreau F, Ferrier L, Fioramonti J, Bueno L; Ferrier; Fioramonti; Bueno (September 2007). "New Insights in the Etiology and Pathophysiology of Irritable Bowel Syndrome: Contribution of Neonatal Stress Models". *Pediatric Research*. **62** (3): 240–245. doi:10.1203/PDR.0b013e3180db2949. PMID 17622962.
27. ^ Spiller, R; Aziz, Q; Creed, F; Emmanuel, A; Houghton, L; Hungin, P; Jones, R; Kumar, D; Rubin, G; Trudgill, N; Whorwell, P (1 December 2007). "Guidelines on the irritable bowel syndrome: mechanisms and practical management". *Gut*. **56** (12): 1770–1798. doi:10.1136/gut.2007.119446.
28. ^ Fukudo, Shin (19 January 2007). "Role of corticotropin-releasing hormone in irritable bowel syndrome and intestinal inflammation". *Journal of Gastroenterology*. **42** (S17): 48–51. doi:10.1007/s00535-006-1942-7.
29. ^ Ghoshal, UC.; Srivastava, D. (Mar 2014). "Irritable bowel syndrome and small intestinal bacterial overgrowth: meaningful association or unnecessary hype.". *World J Gastroenterol*. **20** (10): 2482–91. doi:10.3748/wjg.v20.i10.2482. PMID 24627585.
30. ^ Collins, SM (August 2014). "A role for the gut microbiota in IBS.". *Nature reviews. Gastroenterology & hepatology*. **11** (8): 497–505. doi:10.1038/nrgastro.2014.40. PMID 24751910.
31. ^ Santelmann, H; Howard, JM (January 2005). "Yeast metabolic products, yeast antigens and yeasts as possible triggers for irritable bowel syndrome.". *European journal of gastroenterology & hepatology*. **17** (1): 21–6. doi:10.1097/00042737-200501000-00005. PMID 15647635.
32. ^ Lagacé-Wiens PR, VanCaeseele PG, Koschik C; Vancaeseele; Koschik (2006). "Dientamoeba fragilis: an emerging role in intestinal disease". *Canadian Medical Association Journal*. **175** (5): 468–9. doi:10.1503/cmaj.060265. PMC 1550747. PMID 16940260.
33. ^ Amin OM (2002). "Seasonal prevalence of intestinal parasites in the United States during 2000". *Am. J. Trop. Med. Hyg*. **66** (6): 799–803. PMID 12224595.
34. ^ *a b* Stark D, van Hal S, Marriott D, Ellis J, Harkness J; Van Hal; Marriott; Ellis; Harkness (2007). "Irritable bowel syndrome: a review on the role of intestinal protozoa and the importance of their detection and diagnosis". *Int. J. Parasitol*. **37** (1): 11–20. doi:10.1016/j.ijpara.2006.09.009. PMID 17070814.
35. ^ Wawrzyniak I, Poirier P, Viscogliosi E, Dionigia M, Texier C, Delbac F, Alaoui HE (2013). "Blastocystis, an unrecognized parasite: an overview of pathogenesis and diagnosis". *Ther Adv Infect Dis*. **1** (5): 167–78. doi:10.1177/2049936113504754. PMC 4040727. PMID 25165551. "Recent in vitro and in vivo studies have shed new light on the pathogenic power of this parasite, suggesting that Blastocystis sp. infection is associated with a variety of gastrointestinal disorders, may play a significant role in irritable bowel syndrome, and may be linked with cutaneous lesions (urticaria)."
36. ^ Roberts T, Stark D, Harkness J, Ellis J (2014). "Update on the pathogenic potential and treatment options for

Blastocystis sp". *Gut Pathog.* **6**: 17. doi:10.1186/1757-4749-6-17. PMC 4039988. PMID 24883113.

37. ^ Yakoob J, Jafri W, Jafri N, Khan R, Islam M, Beg MA, Zaman V; Jafri; Jafri; Khan; Islam; Beg; Zaman (2004). "Irritable bowel syndrome: in search of an etiology: role of Blastocystis hominis". *Am. J. Trop. Med. Hyg*. **70** (4): 383–5. PMID 15100450.
38. ^ Giacometti A, Cirioni O, Fiorentini A, Fortuna M, Scalise G; Cirioni; Fiorentini; Fortuna; Scalise (1999). "Irritable bowel syndrome in patients with Blastocystis hominis infection". *Eur. J. Clin. Microbiol. Infect. Dis*. **18** (6): 436–9. doi:10.1007/s100960050314. PMID 10442423.
39. ^ Windsor JJ, Macfarlane L; MacFarlane (May 2005). "Irritable bowel syndrome: the need to exclude Dientamoeba fragilis". *Am. J. Trop. Med. Hyg*. **72** (5): 501; author reply 501–2. PMID 15891119. Retrieved November 4, 2009.
40. ^ Collins S (2014). "A role for the gut microbiota in IBS". *Nature Reviews: Gastroenterology & Hepatology*. **11** (8): 497–505. doi:10.1038/nrgastro.2014.40. PMID 24751910.
41. ^ Cremon C, Carini G, De Giorgio R, Stanghellini V, Corinaldesi R, Barbara G; Carini; De Giorgio; Stanghellini; Corinaldesi; Barbara (May 2010). "Intestinal dysbiosis in irritable bowel syndrome: etiological factor or epiphenomenon?". *Expert Rev. Mol. Diagn*. **10** (4): 389–93. doi:10.1586/erm.10.33. PMID 20465494.
42. ^ Schmulson M, Bielsa MV, Carmona-Sánchez R, et al. (2014). "[Microbiota, gastrointestinal infections, low-grade inflammation, and antibiotic therapy in irritable bowel syndrome: an evidence-based review]". *Rev Gastroenterol Mex* (in Spanish). **79** (2): 96–134. doi:10.1016/j.rgmx.2014.01.004. PMID 24857420.
43. ^ Tally, N J (Dec 2006). "Genes and environment in irritable bowel syndrome: one step forward". *Gut*. **55** (12): 1694–1696. doi:10.1136/gut.2006.108837. PMC 1856457. PMID 17124153.
44. ^ Saito, Yuri A. (Mar 2011). "The Role of Genetics in IBS". *Gastroenterology Clinics of North America*. **40** (1): 45–67. doi:10.1016/j.gtc.2010.12.011. PMC 3056499. PMID 21333900.
45. ^ *a b* Yawn BP, Lydick E, Locke GR, Wollan PC, Bertram SL, Kurland MJ; Lydick; Locke; Wollan; Bertram; Kurland (2001). "Do published guidelines for evaluation of Irritable Bowel Syndrome reflect practice?". *BMC gastroenterology*. **1**: 11. doi:10.1186/1471-230X-1-11. PMC 59674. PMID 11701092.
46. ^ *a b c d* Bixquert Jiménez M (Aug 2009). "Treatment of irritable bowel syndrome with probiotics. An etiopathogenic approach at last?". *Rev Esp Enferm Dig*. **101** (8): 553–64. doi:10.4321/s1130-01082009000800006. PMID 19785495.
47. ^ C. Hauser (August 29, 2005). *Mayo Clinic Gastroenterology and Hepatology Board Review*. CRC Press. p. 225–. ISBN 978-0-203-50274-7. Retrieved October 24, 2010.
48. ^ Levy J, Bernstein L, Silber N (Dec 2014). "Celiac disease: an immune dysregulation syndrome". *Curr Probl Pediatr Adolesc Health Care*. **44** (11): 324–7. doi:10.1016/j.cppeds.2014.10.002. PMID 25499458.
49. ^ *a b c d e f g h i j k l* Fasano A, Sapone A, Zevallos V, Schuppan D (May 2015). "Nonceliac gluten sensitivity". *Gastroenterology* (Review). **148** (6): 1195–204. doi:10.1053/j.gastro.2014.12.049. PMID 25583468. "IBS-like symptoms, such as abdominal pain, gas, distension, and irregular bowel movements, frequently are reported and therefore make it difficult to distinguish NCGS from IBS induced by other causes. The differential diagnosis is facilitated for patients who also experience extraintestinal symptoms, including headache or frank migraine, foggy mind, chronic fatigue, joint and muscle pain, tingling of the extremities, leg or arm numbness, eczema, anemia, depression, or for patients who report a reduction in immune-mediated (including autoimmune) symptoms on a GFD. (...) Therefore, it is possible to consider some subjects with NCGS to be typical IBS patients and vice versa: a subgroup of IBS patients may have NCGS. This last scenario was highlighted in subjects affected by the diarrheapredominant variant of IBS —particularly those with HLA-DQ2 and/or DQ8 genotypes (associated with celiac disease)."
50. ^ *a b c d e f g h i* Volta U, Caio G, De Giorgio R, Henriksen C, Skodje G, Lundin KE (Jun 2015). "Non-celiac gluten sensitivity: a work-in-progress entity in the spectrum of wheat-related disorders". *Best Pract Res Clin Gastroenterol*. **29** (3): 477–91. doi:10.1016/j.bpg.2015.04.006. PMID 26060112.
51. ^ Rossi A, Di Lollo AC, Guzzo MP, Giacomelli C, Atzeni F, Bazzichi L, Di Franco M (2015). "Fibromyalgia and nutrition: what news?". *Clin Exp Rheumatol*. **33** (1 Suppl 88): S117–25. PMID 25786053.
52. ^ San Mauro Martín I, Garicano Vilar E, Collado Yurrutia L, Ciudad Cabañas MJ (Dec 2014). "[Is gluten the great etiopathogenic agent of disease in the XXI century?] [Article in Spanish]" (PDF). *Nutr Hosp*. **30** (6): 1203–10. doi:10.3305/nh.2014.30.6.7866. PMID 25433099.
53. ^ *a b c d e f g h i* Catassi C, Bai J, Bonaz B, Bouma G, Calabrò A, Carroccio A, Castillejo G, Ciacci C, Cristofori F, Dolinsek J, Francavilla R, Elli L, Green P, Holtmeier W, Koehler P, Koletzko S, Meinhold C, Sanders D, Schumann M, Schuppan D, Ullrich R, Vécsei A, Volta U, Zevallos V, Sapone A, Fasano A (2013). "Non-celiac gluten sensitivity: the new frontier of gluten related disorders". *Nutrients* (Review). **5** (10): 3839–3853. doi:10.3390/nu5103839. ISSN 2072-6643. PMC 3820047. PMID 24077239.
54. ^ *a b c d* Lebwohl B, Ludvigsson JF, Green PH (Oct 2015). "Celiac disease and non-celiac gluten sensitivity". *BMJ* (Review). **351**: h4347. doi:10.1136/bmj.h4347. PMC 4596973. PMID 26438584.

55. ^ [a] [b] Fass R, Longstreth GF, Pimentel M, Fullerton S, Russak SM, Chiou CF, Reyes E, Crane P, Eisen G, McCarberg B, Ofman J; Longstreth; Pimentel; Fullerton; Russak; Chiou; Reyes; Crane; Eisen; McCarberg; Ofman (2001). "Evidence- and consensus-based practice guidelines for the diagnosis of irritable bowel syndrome". *Arch. Intern. Med.* **161** (17): 2081–8. doi:10.1001/archinte.161.17.2081. PMID 11570936.
56. ^ Talley NJ (2006). "A unifying hypothesis for the functional gastrointestinal disorders: really multiple diseases or one irritable gut?". *Reviews in gastroenterological disorders*. **6** (2): 72–8. PMID 16699476.
57. ^ Spiegel BM, DeRosa VP, Gralnek IM, Wang V, Dulai GS; Derosa; Gralnek; Wang; Dulai (2004). "Testing for celiac sprue in irritable bowel syndrome with predominant diarrhea: a cost-effectiveness analysis". *Gastroenterology*. **126** (7): 1721–32. doi:10.1053/j.gastro.2004.03.012. PMID 15188167.
58. ^ Su YC, Wang WM, Wang SY, Lu SN, Chen LT, Wu DC, Chen CY, Jan CM, Horowitz M; Wang; Wang; Lu; Chen; Wu; Chen; Jan; Horowitz (August 2000). "The association between Helicobacter pylori infection and functional dyspepsia in patients with irritable bowel syndrome". *Am. J. Gastroenterol.* **95** (8): 1900–5. doi:10.1111/j.1572-0241.2000.02252.x. PMID 10950033.
59. ^ Gerards C, Leodolter A, Glasbrenner B, Malfertheiner P; Leodolter; Glasbrenner; Malfertheiner (2001). "H. pylori infection and visceral hypersensitivity in patients with irritable bowel syndrome". *Dig Dis.* **19** (2): 170–3. doi:10.1159/000050673. PMID 11549828.
60. ^ Grazioli B, Matera G, Laratta C, Schipani G, Guarnieri G, Spiniello E, Imeneo M, Amorosi A, Focà A, Luzza F; Matera; Laratta; Schipani; Guarnieri; Spiniello; Imeneo; Amorosi; Focà; Luzza (March 2006). "Giardia lamblia infection in patients with irritable bowel syndrome and dyspepsia: a prospective study". *World J. Gastroenterol.* **12** (12): 1941–4. PMC 4087522. PMID 16610003.
61. ^ Vernia P, Ricciardi MR, Frandina C, Bilotta T, Frieri G; Ricciardi; Frandina; Bilotta; Frieri (1995). "Lactose malabsorption and irritable bowel syndrome. Effect of a long-term lactose-free diet". *The Italian journal of gastroenterology*. **27** (3): 117–21. PMID 7548919.
62. ^ Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, Talley NJ, Quigley EM; Brandt; Chey; Foxx-Orenstein; Schiller; Schoenfeld; Spiegel; Talley; Quigley (January 2009). "An Evidence-Based Systematic Review on the Management of Irritable Bowel Syndrome" (PDF). *Am J Gastroenterol*. **104** (Supplement 1): S1–S35. doi:10.1038/ajg.2008.122. PMID 19521341.
63. ^ Wedlake L, A'Hern R, Russell D, Thomas K, Walters JR, Andreyev HJ; a'Hern; Russell; Thomas; Walters; Andreyev (2009). "Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome". *Alimentary pharmacology & therapeutics*. **30** (7): 707–17. doi:10.1111/j.1365-2036.2009.04081.x. PMID 19570102.
64. ^ Professor C Heather Ashton (1987). "Benzodiazepine Withdrawal: Outcome in 50 Patients". *British Journal of Addiction*. **82**: 655–671.
65. ^ Cole JA, Rothman KJ, Cabral HJ, Zhang Y, Farraye FA; Rothman; Cabral; Zhang; Farraye (2006). "Migraine, fibromyalgia, and depression among people with IBS: a prevalence study". *BMC gastroenterology*. **6**: 26. doi:10.1186/1471-230X-6-26. PMC 1592499. PMID 17007634.
66. ^ Bercik P, Verdu EF, Collins SM; Verdu; Collins (2005). "Is irritable bowel syndrome a low-grade inflammatory bowel disease?". *Gastroenterol. Clin. North Am.* **34** (2): 235–45, vi–vii. doi:10.1016/j.gtc.2005.02.007. PMID 15862932.
67. ^ Quigley EM (2005). "Irritable bowel syndrome and inflammatory bowel disease: interrelated diseases?". *Chinese journal of digestive diseases*. **6** (3): 122–32. doi:10.1111/j.1443-9573.2005.00202.x. PMID 16045602.
68. ^ Simrén M, Axelsson J, Gillberg R, Abrahamsson H, Svedlund J, Björnsson ES; Axelsson; Gillberg; Abrahamsson; Svedlund; Björnsson (2002). "Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors". *Am. J. Gastroenterol.* **97** (2): 389–96. doi:10.1111/j.1572-0241.2002.05475.x. PMID 11866278.
69. ^ Minderhoud IM, Oldenburg B, Wismeijer JA, van Berge Henegouwen GP, Smout AJ; Oldenburg; Wismeijer; Van Berge Henegouwen; Smout (2004). "IBS-like symptoms in patients with inflammatory bowel disease in remission; relationships with quality of life and coping behavior". *Dig. Dis. Sci.* **49** (3): 469–74. doi:10.1023/B:DDAS.0000020506.84248.f9. PMID 15139501.
70. ^ García Rodríguez LA, Ruigómez A, Wallander MA, Johansson S, Olbe L; Ruigómez; Wallander; Johansson; Olbe (2000). "Detection of colorectal tumor and inflammatory bowel disease during follow-up of patients with initial diagnosis of irritable bowel syndrome". *Scand. J. Gastroenterol.* **35** (3): 306–11. doi:10.1080/003655200750024191. PMID 10766326.
71. ^ Corazziari E, Attili AF, Angeletti C, De Santis A; Attili, AF; Angeletti, C; De Santis, A (2008). "Gallstones, cholecystectomy and irritable bowel syndrome (IBS) MICOL population-based study". *Dig Liver Dis.* **40** (12): 944–50. doi:10.1016/j.dld.2008.02.013. PMID 18406218.
72. ^ Cole JA, Yeaw JM, Cutone JA, Kuo B, Huang Z, Earnest DL, Walker AM; Yeaw; Cutone; Kuo; Huang; Earnest; Walker (2005). "The incidence of abdominal and pelvic surgery among patients with irritable bowel syndrome". *Dig. Dis. Sci.* **50** (12): 2268–75. doi:10.1007/s10620-005-3047-1. PMID 16416174.

73. ^ Longstreth GF, Yao JF; Yao (2004). "Irritable bowel syndrome and surgery: a multivariable analysis". *Gastroenterology*. **126** (7): 1665–73. doi:10.1053/j.gastro.2004.02.020. PMID 15188159.
74. ^ Tietjen GE, Bushnell CD, Herial NA, Utley C, White L, Hafeez F; Bushnell; Herial; Utley; White; Hafeez (2007). "Endometriosis is associated with prevalence of comorbid conditions in migraine". *Headache*. **47** (7): 1069–78. doi:10.1111/j.1526-4610.2007.00784.x. PMID 17635599.
75. ^ "Interstitial cystitis: Risk factors". *Mayo Clinic*. January 20, 2009.
76. ^ Ford AC, Talley NJ, Spiegel BM, Foxx-Orenstein AE, Schiller L, Quigley EM, Moayyedi P; Talley; Spiegel; Foxx-Orenstein; Schiller; Quigley; Moayyedi (2008). "Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis". *BMJ*. **337**: a2313. doi:10.1136/bmj.a2313. PMC 2583392. PMID 19008265.
77. ^ Ford, AC; Quigley, EM; Lacy, BE; Lembo, AJ; Saito, YA; Schiller, LR; Soffer, EE; Spiegel, BM; Moayyedi, P (September 2014). "Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis". *The American journal of gastroenterology*. **109** (9): 1350–65; quiz 1366. doi:10.1038/ajg.2014.148. PMID 24935275.
78. ^ Khanna, Reena; MacDonald, John K.; Levesque, Barrett G. (2014-07-01). "Peppermint oil for the treatment of irritable bowel syndrome: a systematic review and meta-analysis". *Journal of Clinical Gastroenterology*. **48** (6): 505–512. doi:10.1097/MCG.0b013e3182a88357. ISSN 1539-2031. PMID 24100754.
79. ^ Staudacher HM, Irving PM, Lomer MC, Whelan K (April 2014). "Mechanisms and efficacy of dietary FODMAP restriction in IBS". *Nat Rev Gastroenterol Hepatol* (Review). **11** (4): 256–66. doi:10.1038/nrgastro.2013.259. PMID 24445613.
80. ^ Fedewa A, Rao SS (2014). "Dietary fructose intolerance, fructan intolerance and FODMAPs". *Curr Gastroenterol Rep*. **16** (1): 370. doi:10.1007/s11894-013-0370-0. PMC 3934501. PMID 24357350.
81. ^ *a b* Atkinson W, Sheldon TA, Shaath N, Whorwell PJ; Sheldon; Shaath; Whorwell (2004). "Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial". *Gut*. **53** (10): 1459–64. doi:10.1136/gut.2003.037697. PMC 1774223. PMID 15361495.
82. ^ Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC (2006). "Functional bowel disorders". *Gastroenterology*. **131** (2): 688. doi:10.1053/j.gastro.2006.06.027.
83. ^ Gibson PR, Shepherd SJ; Shepherd (Feb 2010). "Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach". *J Gastroenterol Hepatol*. **25** (2): 252–8. doi:10.1111/j.1440-1746.2009.06149.x. PMID 20136989.
84. ^ Francis CY, Whorwell PJ; Whorwell (Jul 2, 1994). "[Bran and irritable bowel syndrome: time for reappraisal]". *Lancet*. **344** (8914): 39–40. doi:10.1016/S0140-6736(94)91055-3. PMID 7912305.
85. ^ *a b c d e f g* Shen YH, Nahas R; Nahas (Feb 2009). "Complementary and alternative medicine for treatment of irritable bowel syndrome". *Can Fam Physician*. **55** (2): 143–8. PMC 2642499. PMID 19221071.
86. ^ Bijkerk CJ, de Wit NJ, Muris JW, Whorwell PJ, Knottnerus JA, Hoes AW; De Wit; Muris; Whorwell; Knottnerus; Hoes (Aug 27, 2009). "[Soluble or insoluble fibre in irritable bowel syndrome in primary care? Randomised placebo controlled trial]". *BMJ*. **339** (b3154): b3154. doi:10.1136/bmj.b3154. PMC 3272664. PMID 19713235.
87. ^ *a b c d e f* Ducrotté P (Nov 2007). "[Irritable bowel syndrome: current treatment options]". *Presse Med*. **36** (11 Pt 2): 1619–26. doi:10.1016/j.lpm.2007.03.008. PMID 17490849.
88. ^ *a b* Bijkerk CJ, Muris JW, Knottnerus JA, Hoes AW, de Wit NJ; Muris; Knottnerus; Hoes; De Wit (2004). "Systematic review: the role of different types of fiber in the treatment of irritable bowel syndrome". *Aliment Pharmacol Ther*. **19** (3): 245–51. doi:10.1111/j.0269-2813.2004.01862.x. PMID 14984370.
89. ^ Bijkerk CJ, de Wit NJ, Muris JW, Whorwell PJ, Knottnerus JA, Hoes AW; De Wit; Muris; Whorwell; Knottnerus; Hoes (2009). "Systematic Soluble or insoluble fiber in irritable bowel syndrome in primary care? Randomised placebo controlled trial". *BMJ*. **339** (b): 3154–. doi:10.1136/bmj.b3154. PMC 3272664. PMID 19713235.
90. ^ Prior A, Whorwell PJ; Whorwell (1987). "Double blind study of ispaghula in irritable bowel syndrome". *Gut*. **28** (11): 1510–3. doi:10.1136/gut.28.11.1510. PMC 1433676. PMID 3322956.
91. ^ Jalihal A, Kurian G; Kurian (1990). "Ispaghula therapy in irritable bowel syndrome: improvement in overall well-being is related to reduction in bowel dissatisfaction". *J Gastroenterol Hepatol*. **5** (5): 507–13. doi:10.1111/j.1440-1746.1990.tb01432.x. PMID 2129822.
92. ^ Kumar A, Kumar N, Vij JC, Sarin SK, Anand BS; Kumar; Vij; Sarin; Anand (1987). "Optimum dosage of ispaghula husk in patients with irritable bowel syndrome: correlation of symptom relief with whole gut transit time and stool weight". *Gut*. **28** (2): 150–5. doi:10.1136/gut.28.2.150. PMC 1432983. PMID 3030900.
93. ^ *a b* Ruepert L, Quartero AO, de Wit NJ, van der Heijden GJ, Rubin G, Muris JW; Quartero; De Wit; Van Der Heijden; Rubin; Muris (2011). "Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome". *Cochrane Database Syst Rev* (8): CD003460. doi:10.1002/14651858.CD003460.pub3. PMID 21833945.
94. ^ Lesbros-Pantoflickova D, Michetti P, Fried M, Beglinger C, Blum AL; Michetti; Fried; Beglinger; Blum (2004).

"Meta-analysis: The treatment of irritable bowel syndrome". *Aliment Pharmacol Ther*. **20** (11–12): 1253–69. doi:10.1111/j.1365-2036.2004.02267.x. PMID 15606387.

95. ^ Jailwala J, Imperiale TF, Kroenke K; Imperiale; Kroenke (2000). "Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials". *Annals of Internal Medicine*. **133** (2): 136–47. doi:10.7326/0003-4819-133-2-200007180-00013. PMID 10896640.
96. ^ Talley NJ (2001). "Serotoninergic neuroenteric modulators". *Lancet*. **358** (9298): 2061–8. doi:10.1016/S0140-6736(01)07103-3. PMID 11755632.
97. ^ Pae CU1, Lee SJ, Han C, Patkar AA, Masand PS; Lee; Han; Patkar; Masand (May 2013). "Atypical antipsychotics as a possible treatment option for irritable bowel syndrome". *Expert Opin Investig Drugs*. **22** (5): 565–72. doi:10.1517/13543784.2013.782392. PMID 23506326.
98. ^ Spiller R, Lam C; Lam (July 2012). "An Update on Post-infectious Irritable Bowel Syndrome: Role of Genetics, Immune Activation, Serotonin and Altered Microbiome". *J Neurogastroenterol Motil*. **18** (3): 258–68. doi:10.5056/jnm.2012.18.3.258. PMC 3400813. PMID 22837873.
99. ^ Creed F (2005). "How do SSRIs help patients with irritable bowel syndrome?". *Gut*. **55** (8): 1065–1067. doi:10.1136/gut.2005.086348. PMC 1856284. PMID 16849340.
100. ^ Frieri M (2015). "Mast Cell Activation Syndrome". *Clin Rev Allergy Immunol*. doi:10.1007/s12016-015-8487-6. PMID 25944644.
101. ^ Joo JS, Ehrenpreis ED, Gonzalez L, Kaye M, Breno S, Wexner SD, Zaitman D, Secrest K; Ehrenpreis; Gonzalez; Kaye; Breno; Wexner; Zaitman; Secrest (1998). "Alterations in colonic anatomy induced by chronic stimulant laxatives: the cathartic colon revisited". *J Clin Gastroenterol*. **26** (4): 283–6. doi:10.1097/00004836-199806000-00014. PMID 9649012.
102. ^ Simrén M, Barbara G, Flint HJ, Spiegel BM, Spiller RC, Vanner S, Verdu EF, Whorwell PJ, Zoetendal EG; Barbara; Flint; Spiegel; Spiller; Vanner; Verdu; Whorwell; et al. (Jan 2013). "Intestinal microbiota in functional bowel disorders: a Rome foundation report". *Gut*. **62** (1): 159–76. doi:10.1136/gutjnl-2012-302167. PMC 3551212. PMID 22730468.
103. ^ Tack J, Broekaert D, Fischler B, Van Oudenhove L, Gevers AM, Janssens J; Broekaert; Fischler; Van Oudenhove; Gevers; Janssens (2006). "A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome". *Gut*. **55** (8): 1095–103. doi:10.1136/gut.2005.077503. PMC 1856276. PMID 16401691.
104. ^ Vahedi H, Merat S, Rashidioon A, Ghoddoosi A, Malekzadeh R; Merat; Rashidioon; Ghoddoosi; Malekzadeh (2005). "The effect of fluoxetine in patients with pain and constipation-predominant irritable bowel syndrome: a double-blind randomized-controlled study". *Aliment Pharmacol Ther*. **22** (5): 381–5. doi:10.1111/j.1365-2036.2005.02566.x. PMID 16128675.
105. ^ Creed F, Fernandes L, Guthrie E, Palmer S, Ratcliffe J, Read N, Rigby C, Thompson D, Tomenson B; Fernandes; Guthrie; Palmer; Ratcliffe; Read; Rigby; Thompson; Tomenson; North of England IBS Research Group (2003). "The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome". *Gastroenterology*. **124** (2): 303–17. doi:10.1053/gast.2003.50055. PMID 12557136.
106. ^ Tabas G, Beaves M, Wang J, Friday P, Mardini H, Arnold G; Beaves; Wang; Friday; Mardini; Arnold (2004). "Paroxetine to treat irritable bowel syndrome not responding to high-fiber diet: a double-blind, placebo-controlled trial". *Am J Gastroenterol*. **99** (5): 914–20. doi:10.1111/j.1572-0241.2004.04127.x. PMID 15128360.
107. ^ Turner Erick H.; Matthews Annette M.; Linardatos Eftihia; Tell Robert A.; Rosenthal Robert (2008). "Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy". *New England Journal of Medicine*. **358** (3): 252–60. doi:10.1056/nejmsa065779. PMID 18199864.
108. ^ Xie, C; Tang, Y; Wang, Y; Yu, T; Wang, Y; Jiang, L; Lin, L (7 August 2015). "Efficacy and Safety of Antidepressants for the Treatment of Irritable Bowel Syndrome: A Meta-Analysis.". *PLOS ONE*. **10** (8): e0127815. doi:10.1371/journal.pone.0127815. PMC 4529302. PMID 26252008.
109. ^ "UpToDate Inc.". (subscription required (help)).
110. ^ Jackson JL, O'Malley PG, Tomkins G, Balden E, Santoro J, Kroenke K; O'Malley; Tomkins; Balden; Santoro; Kroenke (2000). "Treatment of functional gastrointestinal disorders with antidepressant medications: a meta-analysis". *Am J Med*. **108** (1): 65–72. doi:10.1016/S0002-9343(99)00299-5. PMID 11059442.
111. ^ Drossman DA, Toner BB, Whitehead WE, Diamant NE, Dalton CB, Duncan S, Emmott S, Proffitt V, Akman D, Frusciante K, Le T, Meyer K, Bradshaw B, Mikula K, Morris CB, Blackman CJ, Hu Y, Jia H, Li JZ, Koch GG, Bangdiwala SI; Toner; Whitehead; Diamant; Dalton; Duncan; Emmott; Proffitt; Akman; Frusciante; Le; Meyer; Bradshaw; Mikula; Morris; Blackman; Hu; Jia; Li; Koch; Bangdiwala (2003). "Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders". *Gastroenterology*. **125** (1): 19–31. doi:10.1016/S0016-5085(03)00669-3. PMID 12851867.
112. ^ Pimentel M, Park S, Mirocha J, Kane SV, Kong Y; Park; Mirocha; Kane; Kong (2006). "The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial". *Annals of Internal Medicine*. **145** (8): 557–63. doi:10.7326/0003-4819-145-8-200610170-00004. PMID 17043337.

113. ^ Sharara AI, Aoun E, Abdul-Baki H, Mounzer R, Sidani S, Elhajj I; Aoun; Abdul-Baki; Mounzer; Sidani; Elhajj (2006). "A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence". *Am J Gastroenterol*. **101** (2): 326–33. doi:10.1111/j.1572-0241.2006.00458.x. PMID 16454838.
114. ^ Quigley EM (2006). "Germs, gas and the gut; the evolving role of the enteric flora in IBS". *Am J Gastroenterol*. **101** (2): 334–5. doi:10.1111/j.1572-0241.2006.00445.x. PMID 16454839.
115. ^ Raahave D, Christensen E, Loud FB, Knudsen LL. Correlation of bowel symptoms with colonic transit, length, and faecal load in functional faecal retention 2009;56:83–8
116. ^ Warfield, Carol A.; Zahid H. Bajwa (2003). *Principles and Practice of Pain Medicine*. McGraw-Hill Professional. ISBN 0-07-144349-5.
117. ^ Lin HC (Aug 18, 2004). "Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome.". *JAMA: The Journal of the American Medical Association*. **292** (7): 852–8. doi:10.1001/jama.292.7.852. PMID 15316000.
118. ^ Spiegel, Brennan M.R. (June 2011). "Questioning the Bacterial Overgrowth Hypothesis of Irritable Bowel Syndrome: An Epidemiologic and Evolutionary Perspective". *Clinical Gastroenterology and Hepatology*. **9** (6): 461–469. doi:10.1016/j.cgh.2011.02.030.
119. ^ Irritable Bowel Syndrome in Adults: Diagnosis and management of irritable bowel syndrome in primary care; NICE clinical guideline 61, Issue Feb 2008
120. ^ "Irritable Bowel Syndrome (IBS) - Treatment - NHS Choices". Nhs.uk. Retrieved 2012-10-21.
121. ^ Nikfar S, Rahimi R, Rahimi F, Derakhshani S, Abdollahi M; Rahimi; Rahimi; Derakhshani; Abdollahi (December 2008). "Efficacy of probiotics in irritable bowel syndrome: a meta-analysis of randomized, controlled trials". *Dis. Colon Rectum*. **51** (12): 1775–80. doi:10.1007/s10350-008-9335-z. PMID 18465170.
122. ^ Konturek PC, Brzozowski T, Konturek SJ; Brzozowski; Konturek (Dec 2011). "Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options". *J Physiol Pharmacol*. **62** (6): 591–9. PMID 22314561.
123. ^ "New Studies Examine the Evidence on Probiotics in IBS" (PDF) (Press release). American College of Gastroenterology. October 31, 2005.
124. ^ Brenner DM, Moeller MJ, Chey WD, Schoenfeld PS; Moeller; Chey; Schoenfeld (April 2009). "The utility of probiotics in the treatment of irritable bowel syndrome: a systematic review". *Am. J. Gastroenterol*. **104** (4): 1033–49; quiz 1050. doi:10.1038/ajg.2009.25. PMID 19277023.
125. ^ Aragon G, Graham DB, Borum M, Doman DB; Graham; Borum; Doman (Jan 2010). "Probiotic therapy for irritable bowel syndrome". *Gastroenterol Hepatol (N Y)*. **6** (1): 39–44. PMC 2886445. PMID 20567539.
126. ^ "IBS diet: Can yogurt ease symptoms?". *Mayo Clinic*. May 21, 2008.
127. ^ McFarland, LV. (May 2010). "Systematic review and meta-analysis of Saccharomyces boulardii in adult patients". *World J Gastroenterol*. **16** (18): 2202–22. doi:10.3748/wjg.v16.i18.2202. PMC 2868213. PMID 20458757.
128. ^ [a] [b] Ortiz-Lucas M, Tobías A, Saz P, Sebastián JJ; Tobías; Saz; Sebastián (Jan 2013). "Effect of probiotic species on irritable bowel syndrome symptoms: A bring up to date meta-analysis". *Rev Esp Enferm Dig*. **105** (1): 19–36. doi:10.4321/s1130-01082013000100005. PMID 23548007.
129. ^ Wilkins T, Pepitone C, Alex B, Schade RR; Pepitone; Alex; Schade (Sep 1, 2012). "Diagnosis and management of IBS in adults". *American family physician*. **86** (5): 419–26. PMID 22963061.
130. ^ Rösch W, Liebregts T, Gundermann KJ, Vinson B, Holtmann G; Liebregts; Gundermann; Vinson; Holtmann (2006). "Phytotherapy for functional dyspepsia: a review of the clinical evidence for the herbal preparation STW 5". *Phytomedicine : international journal of phytotherapy and phytopharmacology*. 13 Suppl 5: 114–21. doi:10.1016/j.phymed.2006.03.022. PMID 16978851.
131. ^ Rahimi R, Shams-Ardekani MR, Abdollahi M; Shams-Ardekani; Abdollahi (2010). "A review of the efficacy of traditional Iranian medicine for inflammatory bowel disease". *World journal of gastroenterology : WJG*. **16** (36): 4504–4514. doi:10.3748/wjg.v16.i36.4504. PMC 2945480. PMID 20857519.
132. ^ Manheimer E, Cheng K, Wieland LS, Min LS, Shen X, Berman BM, Lao L; Cheng; Wieland; Min; Shen; Berman; Lao (2012). "Acupuncture for treatment of irritable bowel syndrome". *Cochrane Database Syst Rev*. **5** (5): CD005111. doi:10.1002/14651858.CD005111.pub3. PMC 3718572. PMID 22592702.
133. ^ [a] [b] Boivin M (October 2001). "Socioeconomic impact of irritable bowel syndrome in Canada". *Can. J. Gastroenterol*. **15** (Suppl B): 8B–11B. PMID 11694908.
134. ^ [a] [b] [c] Quigley EM, Locke GR, Mueller-Lissner S, Paulo LG, Tytgat GN, Helfrich I, Schaefer E; Locke; Mueller-Lissner; Paulo; Tytgat; Helfrich; Schaefer (July 2006). "Prevalence and management of abdominal cramping and pain: a multinational survey". *Aliment. Pharmacol. Ther*. **24** (2): 411–9. doi:10.1111/j.1365-2036.2006.02989.x. PMID 16842469.
135. ^ Ehlin AG, Montgomery SM, Ekbom A, Pounder RE, Wakefield AJ; Montgomery; Ekbom; Pounder; Wakefield (August 2003). "Prevalence of gastrointestinal diseases in two British national birth cohorts". *Gut*. **52** (8): 1117–

21. doi:10.1136/gut.52.8.1117. PMC 1773740. PMID 12865268.
136. ^ Wilson S, Roberts L, Roalfe A, Bridge P, Singh S; Roberts; Roalfe; Bridge; Singh (July 2004). "Prevalence of irritable bowel syndrome: a community survey". *Br J Gen Pract*. **54** (504): 495–502. PMC 1324800. PMID 15239910.
137. ^ Hungin AP, Chang L, Locke GR, Dennis EH, Barghout V; Chang; Locke; Dennis; Barghout (June 2005). "Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact". *Aliment. Pharmacol. Ther*. **21** (11): 1365–75. doi:10.1111/j.1365-2036.2005.02463.x. PMID 15932367.
138. ^ Jafri W, Yakoob J, Jafri N, Islam M, Ali QM; Yakoob; Jafri; Islam; Ali (June 2007). "Irritable bowel syndrome and health seeking behaviour in different communities of Pakistan". *J Pak Med Assoc*. **57** (6): 285–7. PMID 17629228.
139. ^ Jafri W, Yakoob J, Jafri N, Islam M, Ali QM; Yakoob; Jafri; Islam; Ali (2005). "Frequency of irritable bowel syndrome in college students". *J Ayub Med Coll Abbottabad*. **4** (17): 9–11. PMID 16599025.
140. ^ Schmulson M, Ortíz O, Santiago-Lomeli M, Gutiérrez-Reyes G, Gutiérrez-Ruiz MC, Robles-Díaz G, Morgan D; Ortíz; Santiago-Lomeli; Gutiérrez-Reyes; Gutiérrez-Ruiz; Robles-Díaz; Morgan (2006). "Frequency of functional bowel disorders among healthy volunteers in Mexico City" (PDF). *Dig Dis*. **24** (3–4): 342–7. doi:10.1159/000092887. PMID 16849861.
141. ^ Payne S (2004). "Sex, gender, and irritable bowel syndrome: Making the connections". *Gender medicine*. **1** (1): 18–28. doi:10.1016/S1550-8579(04)80007-X. PMID 16115580.
142. ^ Jackson NA, Houghton LA, Whorwell PJ, Currer B; Houghton; Whorwell; Currer (1994). "Does the menstrual cycle affect anorectal physiology?". *Digestive diseases and sciences*. **39** (12): 2607–11. doi:10.1007/bf02087697. PMID 7995186.
143. ^ Voci SC, Cramer KM; Cramer (2009). "Gender-related traits, quality of life, and psychological adjustment among women with irritable bowel syndrome". *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. **18** (9): 1169–76. doi:10.1007/s11136-009-9532-9. PMID 19728159.
144. ^ Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG, Whitehead WE, Janssens J, Funch-Jensen P, Corazziari E; Li; Andruzzi; Temple; Talley; Thompson; Whitehead; Janssens; et al. (1993). "U.S. Householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact". *Digestive diseases and sciences*. **38** (9): 1569–80. doi:10.1007/bf01303162. PMID 8359066.
145. ^ Goffaux P, Michaud K, Gaudreau J, Chalaye P, Rainville P, Marchand S; Michaud; Gaudreau; Chalaye; Rainville; Marchand (2011). "Sex differences in perceived pain are affected by an anxious brain". *Pain*. **152** (9): 2065–73. doi:10.1016/j.pain.2011.05.002. PMID 21665365.
146. ^ Walker EA, Katon WJ, Roy-Byrne PP, Jemelka RP, Russo J; Katon; Roy-Byrne; Jemelka; Russo (1993). "Histories of sexual victimization in patients with irritable bowel syndrome or inflammatory bowel disease". *The American Journal of Psychiatry*. **150** (10): 1502–6. doi:10.1176/ajp.150.10.1502. PMID 8379554.
147. ^ Brown PW (1950). "The irritable bowel syndrome". *Rocky Mountain Medical Journal*. **47** (5): 343–6. PMID 15418074.
148. ^ Levy RL, Von Korff M, Whitehead WE, Stang P, Saunders K, Jhingran P, Barghout V, Feld AD; von Korff; Whitehead; Stang; Saunders; Jhingran; Barghout; Feld (2001). "Costs of care for irritable bowel syndrome patients in a health maintenance organization". *Am J Gastroenterol*. **96** (11): 3122–9. doi:10.1111/j.1572-0241.2001.05258.x. PMID 11721759.
149. ^ Nyrop KA, Palsson OS, Levy RL, Korff MV, Feld AD, Turner MJ, Whitehead WE; Palsson; Levy; von Korff; Feld; Turner; Whitehead (2007). "Costs of health care for irritable bowel syndrome, chronic constipation, functional diarrhoea and functional abdominal pain". *Aliment Pharmacol Ther*. **26** (2): 237–48. doi:10.1111/j.1365-2036.2007.03370.x. PMID 17593069.
150. ^ Paré P, Gray J, Lam S, Balshaw R, Khorasheh S, Barbeau M, Kelly S, McBurney CR; Gray; Lam; Balshaw; Khorasheh; Barbeau; Kelly; McBurney (2006). "Health-related quality of life, work productivity, and health care resource utilization of subjects with irritable bowel syndrome: baseline results from LOGIC (Longitudinal Outcomes Study of Gastrointestinal Symptoms in Canada), a naturalistic study". *Clinical therapeutics*. **28** (10): 1726–35; discussion 1710–1. doi:10.1016/j.clinthera.2006.10.010. PMID 17157129.
151. ^ Leong SA, Barghout V, Birnbaum HG, Thibeault CE, Ben-Hamadi R, Frech F, Ofman JJ; Barghout; Birnbaum; Thibeault; Ben-Hamadi; Frech; Ofman (2003). "The economic consequences of irritable bowel syndrome: a US employer perspective". *Arch. Intern. Med*. **163** (8): 929–35. doi:10.1001/archinte.163.8.929. PMID 12719202.
152. ^ Martin BC, Ganguly R, Pannicker S, Frech F, Barghout V; Ganguly; Pannicker; Frech; Barghout (2003). "Utilization Patterns and Net Direct Medical Costs Medicaid of Irritable Bowel Syndrome". *Curr Med Res Opin*. **19** (8): 771–80. doi:10.1185/030079903125002540. PMID 14687449.
153. ^ Aroniadis OC, Brandt LJ; Brandt (January 2013). "Fecal microbiota transplantation: past, present and future". *Curr. Opin. Gastroenterol*. **29** (1): 79–84. doi:10.1097/MOG.0b013e32835a4b3e. PMID 23041678.
154. ^ Smits LP, Bouter KE, de Vos WM, Borody TJ, Nieuwdorp M; Bouter; De Vos; Borody; Nieuwdorp (November 2013). "Therapeutic potential of fecal microbiota transplantation". *Gastroenterology*. **145** (5): 946–53. doi:10.1053/j.gastro.2013.08.058. PMID 24018052.

155. ^ Ford, Alexander C; Quigley, Eamonn M M; Lacy, Brian E; Lembo, Anthony J; Saito, Yuri A; Schiller, Lawrence R; Soffer, Edy E; Spiegel, Brennan M R; Moayyedi, Paul (2014). "Efficacy of Prebiotics, Probiotics, and Synbiotics in Irritable Bowel Syndrome and Chronic Idiopathic Constipation: Systematic Review and Meta-analysis". *The American Journal of Gastroenterology*. **109** (10): 1547–1561. doi:10.1038/ajg.2014.202. ISSN 0002-9270. PMID 25070051.
156. ^ Klotz U (February 2012). "The pharmacological profile and clinical use of mesalazine (5-aminosalicylic acid)". *Arzneimittelforschung*. **62** (2): 53–8. doi:10.1055/s-0031-1299685. PMID 22344548.
157. ^ Barbara G, Stanghellini V, Cremon C; et al. (2009). "Aminosalicylates and other anti-inflammatory compounds for irritable bowel syndrome". *Dig Dis*. 27 Suppl 1: 115–21. doi:10.1159/000268131. PMID 20203507.
158. ^ Philpott H, Nandurkar S, Lubel J, Gibson PR; Nandurkar; Lubel; Gibson (2012). "Alternative investigations for irritable bowel syndrome". *Journal of Gastroenterology and Hepatology*. **28** (1): 73–77. doi:10.1111/j.1440-1746.2012.07291.x. PMID 23033865.
159. ^ "Serotonergic reinforcement of intestinal barrier function is impaired in irritable bowel syndrome.". *Aliment Pharmacol Ther*. **40**: 392–402. Aug 2014. doi:10.1111/apt.12842. PMID 24943480.
160. ^ "Human leukocyte antigen DQ2/8 prevalence in non-celiac patients with gastrointestinal diseases.". *World J Gastroenterol*. **19**: 2507–13. Apr 28, 2013. doi:10.3748/wjg.v19.i16.2507. PMID 23674852.
161. ^ Halpert AD, Thomas AC, Hu Y, Morris CB, Bangdiwala SI, Drossman DA; Thomas; Hu; Morris; Bangdiwala; Drossman (2006). "A survey on patient educational needs in irritable bowel syndrome and attitudes toward participation in clinical research". *J Clin Gastroenterol*. **40** (1): 37–43. doi:10.1097/01.mcg.0000190759.95862.08. PMID 16340632.


## External links [edit]

- Irritable bowel syndrome at DMOZ
- UNC Center for Functional GI & Motility Disorders

| v · t · e · | **Irritable bowel syndrome (IBS)** | |
|---|---|---|
| **Causes or potential causes** | Stress · Gastroenteritis · Small intestinal bacterial overgrowth · | |
| **Management** | FODMAP diet · Soluble fiber · Laxatives · Antispasmodics · Psychotherapy · Tricyclic antidepressants · SSRIs · Probiotics · Eluxadoline · | |
| **Related topics** | Gut–brain axis · Hypothalamic–pituitary–adrenal axis · Sympathetic nervous system · | |

| v · t · e · | **Diseases of the digestive system (primarily K20–K93, 530–579)** | |
|---|---|---|
| **Upper GI tract** | **Esophagus** | Esophagitis (Candidal · Eosinophilic · Herpetiform · · *Rupture* (Boerhaave syndrome · Mallory-Weiss syndrome · · UES (Zenker's diverticulum · · LES (Barrett's esophagus · · Esophageal motility disorder (Nutcracker esophagus · Achalasia · Diffuse esophageal spasm · Gastroesophageal reflux disease (GERD) · · Laryngopharyngeal reflux (LPR) · Esophageal stricture · Megaesophagus · |
| | **Stomach** | Gastritis (Atrophic · Ménétrier's disease · Gastroenteritis · · Peptic (gastric) ulcer (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
| | **Small intestine (Duodenum/Jejunum/Ileum)** | Enteritis (Duodenitis · Jejunitis · Ileitis · · Peptic (duodenal) ulcer (Curling's ulcer · · Malabsorption: Coeliac · Tropical sprue · Blind loop syndrome · Small bowel bacterial overgrowth syndrome · Whipple's · Short bowel syndrome · Steatorrhea · Milroy disease · Bile acid malabsorption · |
| | | Appendicitis · Colitis (Pseudomembranous · Ulcerative · |

| | | |
|---|---|---|
| **Lower GI tract: Intestinal/ Enteropathy** | **Large intestine (Appendix/Colon)** | Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (**IBS** · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
| | **Large and/or small** | Enterocolitis (Necrotizing · · Gastroenterocolitis · IBD (Crohn's disease · · *Vascular*: Abdominal angina · Mesenteric ischemia · Angiodysplasia · Bowel obstruction: Ileus · Intussusception · Volvulus · Fecal impaction · Constipation · Diarrhea (Infectious · · Intestinal adhesions · |
| | **Rectum** | Proctitis (Radiation proctitis · · Proctalgia fugax · Rectal prolapse · Anismus · |
| | **Anal canal** | Anal fissure/Anal fistula · Anal abscess · Anal dysplasia · Pruritus ani · |
| **GI bleeding/BIS** | | Upper (Hematemesis · Melena · · Lower (Hematochezia · · |
| **Accessory** | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · Acute liver failure · · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |
| | **Gallbladder** | Cholecystitis · Gallstones/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · Gallstones/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
| | **Pancreatic** | Pancreatitis (Acute · Chronic · Hereditary · Pancreatic abscess · · Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |
| **Abdominopelvic** | **Hernia** | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |
| **Authority control** | | NDL: 01104445 · |

Categories: Diseases of intestines | Ailments of unknown etiology | Syndromes

Conditions diagnosed by stool test | Abdominal pain | Chronic pain syndromes




# Pancreatitis



**Pancreatitis** is inflammation of the pancreas. The pancreas is a large organ behind the stomach that produces digestive enzymes. There are two main types, acute pancreatitis and chronic pancreatitis. Signs and symptoms of pancreatitis include pain in the upper abdomen, nausea and vomiting. The pain often goes into the back and is usually severe. In acute pancreatitis a fever may occur and symptoms typically resolve in a few days. In chronic pancreatitis weight loss, fatty stool, and diarrhea may occur. Complications may include infection, bleeding, diabetes mellitus, or problems with other organs.[1]

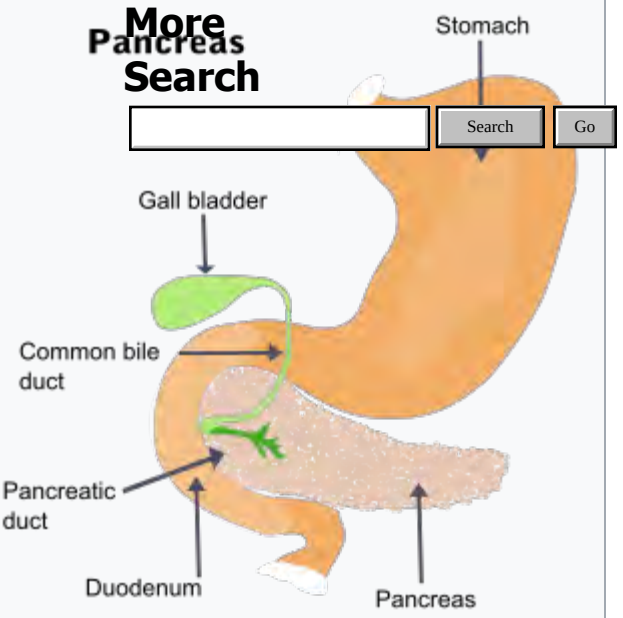
The most common causes of acute pancreatitis are gallstones and heavy alcohol use. Other causes include direct trauma, certain medications, infections such as mumps, and tumors among others. Chronic pancreatitis may develop as a result of acute pancreatitis. It is most commonly due to many years of heavy alcohol use. Other causes include high levels of blood fats, high blood calcium, some medications, and certain genetic disorders such as cystic fibrosis among others.[1] Smoking increases the risk of both acute and chronic pancreatitis.[2][3] Diagnosis of acute pancreatitis is based on a threefold increase in the blood of either amylase or lipase. In chronic pancreatitis these tests may be normal. Medical imaging such as ultrasound and CT scan may also be useful.[1]

Acute pancreatitis is usually treated with intravenous fluids, pain medication, and sometimes antibiotics. Typically no eating or drinking is allowed and a tube may be placed into the stomach. A procedure known as an endoscopic retrograde cholangiopancreatography (ERCP) may be done to open the pancreatic duct if blocked. In those with gallstones the gallbladder is often also removed. In chronic pancreatitis, in addition to the above, temporary feeding through a nasogastric tube may be used to provide adequate nutrition. Long-term dietary changes and pancreatic enzyme replacement may be required. And occasionally surgery is done to remove parts of the pancreas.[1]

Globally, in 2013 about 17 million cases of pancreatitis occurred.[4] This resulted in 123,000 deaths, up from 83,000 deaths in 1990.[5] Acute pancreatitis occurs in about 30 per 100,000 people a year.[2] New cases of chronic pancreatitis develop in about 8 per 100,000 people a year and currently affect about 50 per 100,000 people in the United States.[6] It is more common in men than women. Often chronic pancreatitis starts between the ages of 30 and 40 while it is rare in children.[1] Acute



**Pancreatitis**




The pancreas and surrounding organs

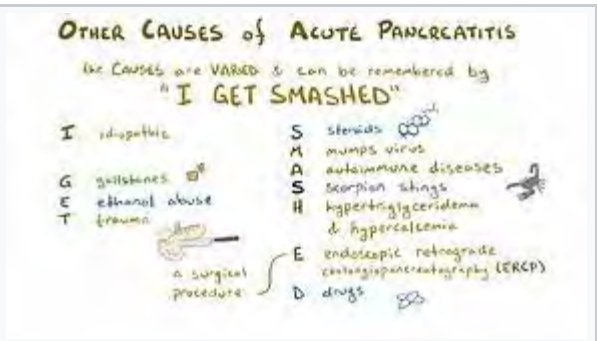
| Classification and external resources | |
|---|---|
| **Specialty** | Gastroenterology, general surgery |
| **ICD-10** | K85, K86.0–K86.1 |
| **ICD-9-CM** | 577.0–577.1 |
| **OMIM** | 167800 |
| **DiseasesDB** | 24092 |
| **MedlinePlus** | 001144 |
| **eMedicine** | emerg/354 |
| **MeSH** | D010195 |
| **GeneReviews** | Pancreatitis |

[edit on Wikidata]

pancreatitis was first described on autopsy in 1882 while chronic pancreatitis was first described in 1946.[6]








Play media

Video explanation

## Signs and symptoms [edit]

The most common symptoms of pancreatitis are severe upper abdominal or left upper quadrant burning pain radiating to the back, nausea, and vomiting that is worse with eating. The physical examination will vary depending on severity and presence of internal bleeding. Blood pressure may be elevated by pain or decreased by dehydration or bleeding. Heart and respiratory rates are often elevated. The abdomen is usually tender but to a lesser degree than the pain itself. As is common in abdominal disease, bowel sounds may be reduced from reflex bowel paralysis. Fever or jaundice may be present. Chronic pancreatitis can lead to diabetes or pancreatic cancer. Unexplained weight loss may occur from a lack of pancreatic enzymes hindering digestion.

## Causes [edit]

Eighty percent of cases of pancreatitis are caused by alcohol or gallstones. Gallstones are the single most common cause of acute pancreatitis.[7] Alcohol is the single most common cause of chronic pancreatitis.[8][9][10][11][12]

Some medications are commonly associated with pancreatitis, most commonly corticosteroids such as prednisolone, but also including the HIV drugs didanosine and pentamidine, diuretics, the anticonvulsant valproic acid, the chemotherapeutic agents L-asparaginase and azathioprine, estrogen by way of increased blood triglycerides,[13] and antihyperglycemic agents like metformin,[14] vildagliptin,[15] and sitagliptin.[16] It may be noted here that the drugs used to treat conditions that are themselves associated with increased events of pancreatitis may also be incidentally linked to pancreatitis. Examples include statins in dyslipidemia and gliptins in diabetes. According to the Food and Drug Administration's MedWatch Surveillance System and Published Reports Atypical, atypical antipsychotics such as clozapine, risperidone, and olanzapine can also be responsible for causing pancreatitis.[17]

Edit links

Other common causes include trauma, mumps, autoimmune disease, high blood calcium, hypothermia, and endoscopic retrograde cholangiopancreatography (ERCP). Pancreas divisum is a common congenital malformation of the pancreas that may underlie some recurrent cases. Diabetes mellitus type 2 is associated with a 2.8-fold higher risk.[18]

Less common causes include pancreatic cancer, pancreatic duct stones,[19] vasculitis (inflammation of the small blood vessels in the pancreas), coxsackievirus infection, and porphyria—particularly acute intermittent porphyria and erythropoietic protoporphyria.

There is an inherited form that results in the activation of trypsinogen within the pancreas, leading to autodigestion. Involved genes may include Trypsin 1, which codes for trypsinogen, SPINK1, which codes for

a trypsin inhibitor, or cystic fibrosis transmembrane conductance regulator.[20]

The mnemonic GETSMASHED is often used to remember the common causes of Pancreatitis: G—Gall stones E—Ethanol T—Trauma S—Steroids M—Mumps A—Autoimmune Pancreatitis S—Scorpion sting H—Hyperlipidaemia, Hypothermia, Hyperparathyroidism E—Endoscopic retrograde cholangiopancreatography D—Drugs commonly azathioprine, valproic acid

### Infection [edit]

A number of infectious agents have been recognized as causes of pancreatitis including:[21]

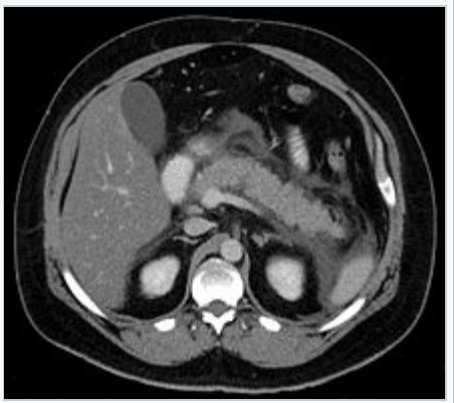
- Viruses
  - Coxsackie virus
  - Cytomegalovirus
  - Hepatitis B
  - Herpes simplex virus
  - Mumps
  - Varicella-zoster virus
- Bacteria
  - Legionella
  - Leptospira
  - Mycoplasma
  - Salmonella
- Fungi
  - Aspergillus
- Parasites
  - Ascaris
  - Cryptosporidium
  - Toxoplasma

## Diagnosis [edit]

The differential diagnosis for pancreatitis includes but is not limited to cholecystitis, choledocholithiasis, perforated peptic ulcer, bowel infarction, small bowel obstruction, hepatitis and mesenteric ischemia .[22]

Diagnosis requires 2 of the 3 following criteria:

- Characteristic acute onset of epigastric or vague abdominal pain that may radiate to the back (see signs and symptoms above)
- Serum amylase or lipase levels ≥ 3 times the upper limit of normal
- An imaging study with characteristic changes. CT, MRI, abdominal ultrasound or endoscopic ultrasound can be used for diagnosis.

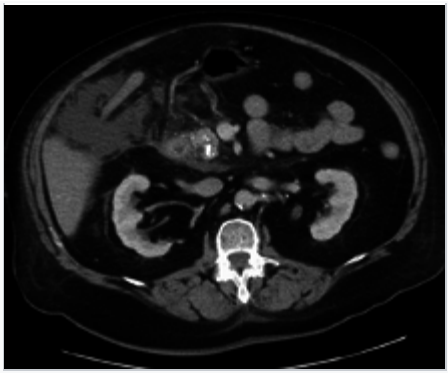


Acute exudative pancreatitis on CT scan

Amylase and lipase are 2 enzymes produced by the pancreas. Elevations in lipase are generally considered a better indicator for pancreatitis as it has greater specificity and has a longer half life.[23]

For imaging, abdominal ultrasound is convenient, simple, non-invasive, and inexpensive.[24] It is more sensitive and specific for pancreatitis from gallstones than other imaging modalities.[23] However, in 25–35% of patients the view of the pancreas can be obstructed by bowel gas making it difficult to evaluate.[22]

A contrast-enhanced CT scan is usually performed more than 48 hours after the onset of pain to evaluate for pancreatic necrosis and



Calcified pancreatic duct stones with some free intraabdominal fluid

extrapancreatic fluid as well as predict the severity of the disease. CT scanning earlier can be falsely reassuring.

ERCP or an endoscopic ultrasound can also be used if a biliary cause for pancreatitis is suspected.

# Treatment [edit]

The treatment of pancreatitis is supportive and depends on severity. Morphine generally is suitable for pain control. There are no clinical studies to suggest that morphine can aggravate or cause pancreatitis or cholecystitis.[25]

The treatment that is received for acute pancreatitis will depend on whether the diagnosis is for the mild form of the condition, which causes no complications, or the severe form, which can cause serious complications.

## Mild acute pancreatitis [edit]

The treatment of mild acute pancreatitis is successfully carried out by admission to a general hospital ward. Traditionally, people were not allowed to eat until the inflammation resolved but more recent evidence suggests early feeding is safe and improves outcomes. Because pancreatitis can cause lung damage and affect normal lung function, oxygen is occasionally delivered through breathing tubes that are connected via the nose. The tubes can then be removed after a few days once it is clear that the condition is improving. Dehydration may result during an episode of acute pancreatitis, so fluids will be provided intravenously. The pain associated with even mild or moderate cases of acute pancreatitis can be severe, which means that a narcotic painkiller may be required.

## Severe acute pancreatitis [edit]

Severe pancreatitis is associated with organ failure, necrosis, infected necrosis, pseudocyst, and abscess. If diagnosed with severe acute pancreatitis, people will need to be admitted to a high dependency unit or intensive care unit. It is likely that the levels of fluids inside the body will have dropped significantly as it diverts bodily fluids and nutrients in an attempt to repair the pancreas. The drop in fluid levels can lead to a reduction in the volume of blood within the body, which is known as hypovolemic shock. Hypovolemic shock can be life-threatening as it can very quickly starve the body of the oxygen-rich blood that it needs to survive. To avoid going into hypovolemic shock, fluids will be pumped intravenously. Oxygen will be supplied through tubes attached to the nose and ventilation equipment may be used to assist with breathing. Feeding tubes may be used to provide nutrients, combined with appropriate analgesia.

As with mild acute pancreatitis, it will be necessary to treat the underlying cause—gallstones, discontinuing medications, cessation of alcohol, etc. If the cause is gallstones, it is likely that an ERCP procedure or removal of the gallbladder will be recommended. The gallbladder should be removed during the same hospital admission or within two weeks of pancreatitis onset so as to limit the risk of recurrent pancreatitis. If the cause of pancreatitis is alcohol, cessation of alcohol consumption and treatment for alcohol dependency may improve pancreatitis. Even if the underlying cause is not related to alcohol consumption, doctors recommend avoiding it for at least six months as this can cause further damage to the pancreas during the recovery process.[26] Oral intake, especially fats, is generally restricted initially but early enteral feeding within 48 hours has been shown to improve clinical outcomes.[27] Fluids and electrolytes are replaced intravenously. Nutritional support is initiated via tube feeding to surpass the portion of the digestive tract most affected by secreted pancreatic enzymes if there is no improvement in the first 72–96 hours of treatment.[28]

## Prognosis [edit]

Severe acute pancreatitis has mortality rates around 2–9%, higher where necrosis of the pancreas has occurred.[29]

Several scoring systems are used to predict the severity of an attack of pancreatitis. They each combine demographic and laboratory data to estimate severity or probability of death. Examples include APACHE II, Ranson, BISAP, and Glasgow. The Modified Glasgow criteria suggests that a case be considered severe if at least three of the following are true:[30]

- Age > 55 years
- Blood levels:
  - PO2 Oxygen < 60mmHg or 7.9kPa
  - White blood cells > 15
  - Calcium < 2 mmol/L
  - Urea > 16 mmol/L
  - Lactate dehydrogenase (LDH) > 600iu/L
  - Aspartate transaminase (AST) > 200iu/L
  - Albumin < 32g/L
  - Glucose > 10 mmol/L

This can be remembered using the mnemonic PANCREAS:

- PO2 Oxygen < 60mmHg or 7.9kPa
- Age > 55
- Neutrophilia White blood cells > 15
- Calcium < 2 mmol/L
- Renal Urea > 16 mmol/L
- Enzymes Lactate dehydrogenase (LDH) > 600iu/L Aspartate transaminase (AST) > 200iu/L
- Albumin < 32g/L
- Sugar Glucose > 10 mmol/L

The BISAP score (Blood urea nitrogen level >25 mg/dL, Impaired mental status, Systemic inflammatory response syndrome, age over 60 years, pleural effusion) has been validated as similar to other prognostic scoring systems.[31]

## Complications [edit]

Early complications include shock, infection, systemic inflammatory response syndrome, low blood calcium, high blood glucose, and dehydration. Blood loss, dehydration, and fluid leaking into the abdominal cavity (ascites) can lead to kidney failure. Respiratory complications are often severe. Pleural effusion is usually present. Shallow breathing from pain can lead to lung collapse. Pancreatic enzymes may attack the lungs, causing inflammation. Severe inflammation can lead to intra-abdominal hypertension and abdominal compartment syndrome, further impairing renal and respiratory function and potentially requiring management with an open abdomen to relieve the pressure.[32]

Late complications include recurrent pancreatitis and the development of pancreatic pseudocysts—collections of pancreatic secretions that have been walled off by scar tissue. These may cause pain, become infected, rupture and bleed, block the bile duct and cause jaundice, or migrate around the abdomen. Acute necrotizing pancreatitis can lead to a pancreatic abscess, a collection of pus caused by necrosis, liquefaction, and infection. This happens in approximately 3% of cases, or almost 60% of cases involving more than two pseudocysts and gas in the pancreas.[33]

## Epidemiology [edit]

Globally the incidence of acute pancreatitis is 5 to 35 cases per 100,000 people. The incidence of chronic pancreatitis is 4–8 per 100,000 with a prevalence of 26–42 cases per 100,000.[34] In 2013 pancreatitis resulted in 123,000 deaths up from 83,000 deaths in 1990.[5]

## See also [edit]

- Exocrine pancreatic insufficiency

## References [edit]


1. ^ a b c d e "Pancreatitis". *niddk.nih.gov*. August 16, 2012. Retrieved 1 March 2015.
2. ^ a b Lankisch, PG; Apte, M; Banks, PA (20 January 2015). "Acute pancreatitis.". *Lancet*. **386**: 85–96. doi:10.1016/S0140-6736(14)60649-8. PMID 25616312.
3. ^ Yadav, D; Lowenfels, AB (June 2013). "The epidemiology of pancreatitis and pancreatic cancer.". *Gastroenterology*. **144** (6): 1252–61. doi:10.1053/j.gastro.2013.01.068. PMC 3662544. PMID 23622135.
4. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
5. ^ a b GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385**: 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
6. ^ a b Muniraj, T; Aslanian, HR; Farrell, J; Jamidar, PA (December 2014). "Chronic pancreatitis, a comprehensive review and update. Part I: epidemiology, etiology, risk factors, genetics, pathophysiology, and clinical features.". *Disease-a-month : DM*. **60** (12): 530–50. doi:10.1016/j.disamonth.2014.11.002. PMID 25510320.
7. ^ NIDDK (July 2008). "Pancreatitis". *National Digestive Diseases Information Clearinghouse*. U.S. National Institute of Diabetes and Digestive and Kidney Diseases. 08–1596.
8. ^ "Pancreatitis". A.D.A.M., Inc. Retrieved 2013-01-05.
9. ^ Apte MV, Pirola RC, Wilson JS (June 2009). "Pancreas: alcoholic pancreatitis—it's the alcohol, stupid". *Nature Reviews Gastroenterology & Hepatology*. **6** (6): 321–2.
17. ^ Koller EA, Cross JT, Doraiswamy PM, Malozowski SN (2003). "Pancreatitis Associated With Atypical Antipsychotics: From the Food and Drug Administration's MedWatch Surveillance System and Published Reports". *Pharmacotherapy*. **23** (9): 1123–30. doi:10.1592/phco.23.10.1123.32759. PMID 14524644.
18. ^ Noel RA, Braun DK, Patterson RE, Bloomgren GL (May 2009). "Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study". *Diabetes Care*. **32** (5): 834–8. doi:10.2337/dc08-1755. PMC 2671118. PMID 19208917.
19. ^ Macaluso JN (August 1997). "Editorial Comment". *J. Urol*. **158** (2): 522. doi:10.1016/S0022-5347(01)64525-7. on Matthews K, Correa RJ, Gibbons RP, Weissman RM, Kozarek RA (August 1997). "Extracorporeal shock wave lithotripsy for obstructing pancreatic duct calculi". *J. Urol*. **158** (2): 522–5. doi:10.1016/s0022-5347(01)64524-5. PMID 9224338.
20. ^ D. Whitcomb (2006). "Genetic Testing for Pancreatitis".
21. ^ Parenti DM, Steinberg W, Kang P (November 1996). "Infectious causes of acute pancreatitis". *Pancreas*. **13** (4): 356–71. doi:10.1097/00006676-199611000-00005. PMID 8899796.
22. ^ a b "Clinical manifestations and diagnosis of acute pancreatitis". *www.uptodate.com*. Retrieved 2015-12-08.
23. ^ a b *Hospitalist Handbook* (4th ed.). Department of Medicine University of California, San Francisco. 2012. pp. 224–225.
24. ^ Lawrence W. Tierney; Stephen J. McPhee. *Medicine*. McGraw-Hill. ISBN 0-07-144441-6.
25. ^ Helm JF, Venu RP, Geenen JE, Hogan WJ, Dodds WJ, Toouli J, Arndorfer RC (October 1988). "Effects of morphine on the human sphincter of Oddi". *Gut*. **29** (10): 1402–7. doi:10.1136/gut.29.10.1402. PMC 1434014. PMID 3197985.
26. ^ E Medicine Health , Jerry R. Balentine, DO, FACEP , Melissa Conrad Stöppler, MD, Chief Medical Editor
27. ^ Li JY, Yu T, Chen GC, Yuan YH, Zhong W, Zhao

doi:10.1038/nrgastro.2009.84 . PMID 19494819 . Lay summary – *Medscape Today*.
10. ^ Yadav D, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, Bishop MD, Baillie J, Sherman S, DiSario J, Burton FR, Gardner TB, Amann ST, Gelrud A, Lawrence C, Elinoff B, Greer JB, O'Connell M, Barmada MM, Slivka A, Whitcomb DC (June 2009). "Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis". *Arch. Intern. Med.* **169** (11): 1035–45. doi:10.1001/archinternmed.2009.125. PMID 19506173.
11. ^ "Pancreatitis Explained". *Better Health Channel*. State Government of Victoria. 2011.
12. ^ Johnson CD, Hosking S (1991). "National statistics for diet, alcohol consumption, and chronic pancreatitis in England and Wales, 1960–88". *Gut*. **32** (11): 1401–5. doi:10.1136/gut.32.11.1401. PMC 1379177. PMID 1752477.
13. ^ Smith, Emma; Murray Longmore; Wilkinson, Ian; Tom Turmezei; Chee Kay Cheung (2007). *Oxford handbook of clinical medicine* (7th ed.). Oxford [Oxfordshire]: Oxford University Press. p. 584. ISBN 0-19-856837-1.
14. ^ Ben MH, Thabet H, Zaghdoudi I, Amamou M (2002). "Metformin associated acute pancreatitis". *Veterinary and human toxicology*. **44** (1): 47–48. PMID 11824780.
15. ^ Kunjathaya P, Ramaswami PK, Krishnamurthy AN, Bhat N (2013). "Acute necrotizing pancreatitis associated with vildagliptin". *JOP : Journal of the pancreas*. **14** (1): 81–84. doi:10.6092/1590-8577/1203. PMID 23306341.
16. ^ Matveyenko AV, Dry S, Cox HI, Moshtaghian A, Gurlo T, Galasso R, Butler AE, Butler PC (July 2009). "Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions
LN, Chen QK (Jun 6, 2013). "Enteral Nutrition within 48 Hours of Admission Improves Clinical Outcomes of Acute Pancreatitis by Reducing Complications: A Meta-Analysis.". *PLOS ONE*. **8** (6): e64926. doi:10.1371/journal.pone.0064926. PMC 3675100 . PMID 23762266.
28. ^ Muddana V, Whitcomb DC, Papachristou GI (August 2009). "Current management and novel insights in acute pancreatitis". *Expert Rev Gastroenterol Hepatol*. **3** (4): 435–44. doi:10.1586/egh.09.27. PMID 19673630.
29. ^ Munoz A, Katerndahl DA (July 2000). "Diagnosis and management of acute pancreatitis". *Am Fam Physician*. **62** (1): 164–74. PMID 10905786.
30. ^ Corfield AP, Cooper MJ, Williamson RC, Mayer AD, McMahon MJ, Dickson AP, Shearer MG, Imrie CW (1985). "Prediction of severity in acute pancreatitis: prospective comparison of three prognostic indices". *Lancet*. **2** (8452): 403–7. doi:10.1016/S0140-6736(85)92733-3. PMID 2863441.
31. ^ Papachristou GI, Muddana V, Yadav D, O'Connell M, Sanders MK, Slivka A, Whitcomb DC (Feb 2010). "Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis.". *Am J Gastroenterol*. **105** (2): 435–41. doi:10.1038/ajg.2009.622. PMID 19861954.
32. ^ Fitzgerald JE, Gupta S, Masterson S, Sigurdsson HH (April 2012). "Laparostomy management using the ABThera™ open abdomen negative pressure therapy system in a grade IV open abdomen secondary to acute pancreatitis". *Int Wound J*. **10** (2): 138–144. doi:10.1111/j.1742-481X.2012.00953.x. PMID 22487377.
33. ^ *Pancreatic abscess* at eMedicine
34. ^ *Harrison's Principles of Internal Medicine*. p. Chapter 370 Approach to the Patient with Pancreatic Disease. ISBN 978-0-07-1802161.

## External links [edit]

- Pancreatitis at DMOZ
- Banks et al. modified Marshall Scoring System for Organ Dysfunction
- GeneReviews/NCBI/NIH/UW entry on PRSS1-Related Hereditary Pancreatitis

Wikimedia Commons has media related to *Pancreatitis*.

| v · t · e | **Diseases of the digestive system (primarily K20–K93, 530–579)** | |
|---|---|---|
| **Upper GI tract** | **Esophagus** | Esophagitis (Candidal · Eosinophilic · Herpetiform · · *Rupture* (Boerhaave syndrome · Mallory-Weiss syndrome · · UES (Zenker's diverticulum · · LES (Barrett's esophagus · · Esophageal motility disorder (Nutcracker esophagus · Achalasia · Diffuse esophageal spasm · Gastroesophageal reflux disease (GERD) · · Laryngopharyngeal reflux (LPR) · Esophageal stricture · Megaesophagus · |
| | | Gastritis (Atrophic · Ménétrier's disease · Gastroenteritis · · Peptic (gastric) ulcer |

| | | |
|---|---|---|
| | **Stomach** | (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
| **Lower GI tract: Intestinal/ Enteropathy** | **Small intestine (Duodenum/Jejunum/Ileum)** | Enteritis (Duodenitis · Jejunitis · Ileitis · · Peptic (duodenal) ulcer (Curling's ulcer · · Malabsorption: Coeliac · Tropical sprue · Blind loop syndrome · Small bowel bacterial overgrowth syndrome · Whipple's · Short bowel syndrome · Steatorrhea · Milroy disease · Bile acid malabsorption · |
| | **Large intestine (Appendix/Colon)** | Appendicitis · Colitis (Pseudomembranous · Ulcerative · Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (IBS · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
| | **Large and/or small** | Enterocolitis (Necrotizing · · Gastroenterocolitis · IBD (Crohn's disease · · *Vascular*: Abdominal angina · Mesenteric ischemia · Angiodysplasia · Bowel obstruction: Ileus · Intussusception · Volvulus · Fecal impaction · Constipation · Diarrhea (Infectious · · Intestinal adhesions · |
| | **Rectum** | Proctitis (Radiation proctitis · · Proctalgia fugax · Rectal prolapse · Anismus · |
| | **Anal canal** | Anal fissure/Anal fistula · Anal abscess · Anal dysplasia · Pruritus ani · |
| **GI bleeding/BIS** | | Upper (Hematemesis · Melena · · Lower (Hematochezia · · |
| **Accessory** | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · Acute liver failure · · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |
| | **Gallbladder** | Cholecystitis · Gallstones/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · Gallstones/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
| | **Pancreatic** | **Pancreatitis** (Acute · Chronic · Hereditary · Pancreatic abscess · · Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |
| | | Diaphragmatic (Congenital · · Hiatus · |

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|---|---|---|
| **Abdominopelvic** | **Hernia** | Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |

| v · t · e · | **Inflammation** | | |
|---|---|---|---|
| **Acute** | **Plasma derived mediators** | Bradykinin · *complement* (C3 · C5a · MAC · · *coagulation* (Factor XII · Plasmin · Thrombin · · | |
| | **Cell derived mediators** | *preformed:* | Lysosome granules · *biogenic amines* (Histamine · Serotonin · · |
| | | *synthesized on demand:* | *cytokines* (IFN-γ · IL-8 · TNF-α · IL-1 · · *eicosanoids* (Leukotriene B4 · Prostaglandins · · Nitric oxide · Kinins · |
| **Chronic** | Macrophage · Epithelioid cell · Giant cell · Granuloma · | | |
| **Processes** | **Traditional:** | Rubor · Calor · Tumor · Dolor · Functio laesa · | |
| | **Modern:** | Acute-phase reaction/Fever · Vasodilation · Increased vascular permeability · Exudate · Leukocyte extravasation · Chemotaxis · | |
| **Specific locations** | **Nervous** | *CNS* (Encephalitis · Myelitis · · Meningitis (Arachnoiditis · · *PNS* (Neuritis · · *eye* (Dacryoadenitis · Scleritis · Episcleritis · Keratitis · chorioretinitis · Retinitis · Chorioretinitis · Blepharitis · Conjunctivitis · Uveitis · · *ear* (Otitis · Labyrinthitis · Mastoiditis · · | |
| | **Cardiovascular** | Carditis (Endocarditis · Myocarditis · Pericarditis · · Vasculitis (Arteritis · Phlebitis · Capillaritis · · | |
| | **Respiratory** | *upper* (Sinusitis · Rhinitis · Pharyngitis · Laryngitis · · *lower* (Tracheitis · Bronchitis · Bronchiolitis · Pneumonitis · Pleuritis · · Mediastinitis · | |
| | **Digestive** | *mouth* | Stomatitis · Gingivitis · Gingivostomatitis · Glossitis · Tonsillitis · Sialadenitis/Parotitis · Cheilitis · Pulpitis · Gnathitis · |
| | | *tract* | Esophagitis · Gastritis · Gastroenteritis · Enteritis · Colitis · Enterocolitis · Duodenitis · Ileitis · Caecitis · Appendicitis · Proctitis · |
| | | *accessory* | Hepatitis · Ascending cholangitis · Cholecystitis · **Pancreatitis** · Peritonitis · |
| | **Integumentary** | Dermatitis (Folliculitis · · Cellulitis · Hidradenitis · | |
| | **Musculoskeletal** | Arthritis · Dermatomyositis · *soft tissue* (Myositis · Synovitis/Tenosynovitis · Bursitis · Enthesitis · Fasciitis · Capsulitis · Epicondylitis · Tendinitis · Panniculitis · · Osteochondritis: Osteitis/Osteomyelitis (Spondylitis · Periostitis · · Chondritis · | |
| | **Urinary** | Nephritis (Glomerulonephritis · Pyelonephritis · · Ureteritis · Cystitis · | |

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| | | Urethritis · |
| | **Reproductive** | *female:* Oophoritis · Salpingitis · Endometritis · Parametritis · Cervicitis · Vaginitis · Vulvitis · Mastitis · |
| | | *male:* Orchitis · Epididymitis · Prostatitis · Seminal vesiculitis · Balanitis · Posthitis · Balanoposthitis · |
| | | *pregnancy/newborn:* Chorioamnionitis · Funisitis · Omphalitis · |
| | **Endocrine** | Insulitis · Hypophysitis · Thyroiditis · Parathyroiditis · Adrenalitis · |
| | **Lymphatic** | Lymphangitis · Lymphadenitis · |

| v · t · e · **Alcohol and health** | | |
|---|---|---|
| **Specific interactions** | | Note: see Template:Psychoactive substance use for diagnoses<br>Aging · Alcohol-induced mood disorders · Brain · Cancer (breast cancer · · Sleep · Tolerance · Weight · |
| **Substance abuse prevention** | **Sobriety** | Alcohol-free zone · Alcohol detoxification · Alcohol rehabilitation · Alcoholics Anonymous · Sober companion · |
| | **Alcohol limitation** | 0-0-1-3 · Ban on caffeinated alcoholic beverages · Alcohol education · Alcohol server training · Recommended maximum intake of alcoholic beverages · |
| | **Addiction medicine** | Alcoholism · Anti-addictive psychedelics: Ibogaine, *Salvia divinorum* · |
| **Religion and alcohol** | | Christian views on alcohol (alcohol in the Bible · · Islam and alcohol · Dionysian Mysteries · |
| **Social issues** | | Alcohol advertising (on college campuses · · Alcohol-free beverage definition controversy · Alcohol self-medication · Native Americans · Binge drinking (0.08 BAC · · Blackout (alcohol-related amnesia) · College student alcoholism · Domestic violence · Drinking games / pregaming · Driving under the influence · Drunkorexia · Dry January · Adult Children of Alcoholics · Family systems · French paradox · High-functioning alcoholic (HFA) · moonshine contamination · Rum-running (black market · · Sex · Sin tax / Pigovian tax · |
| **General** | | Short-term effects of alcohol consumption · Long-term effects of alcohol consumption · |

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| **Authority control** | GND: 4004723-4 · NDL: 00571544 · |

Categories: Abdominal pain | Inflammations | Pancreas disorders | Herpes simplex virus-associated diseases | Metabolic disorders

# Peptic ulcer

From Wikipedia, the free encyclopedia
(Redirected from Peptic ulcer disease)

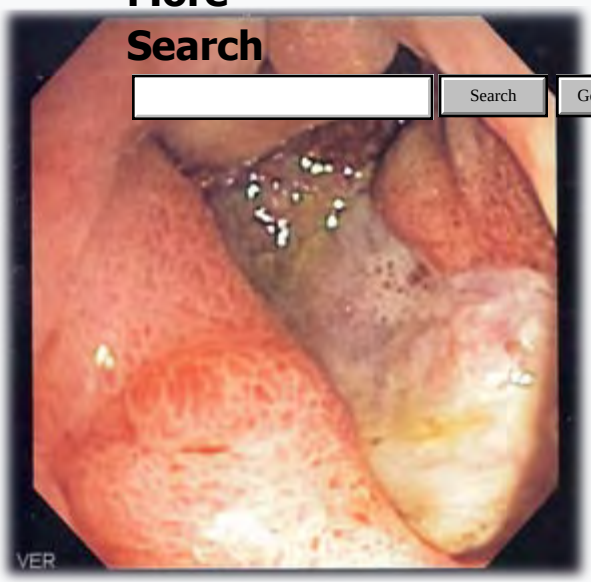
**Peptic ulcer disease** (**PUD**), also known as a **peptic ulcer** or **stomach ulcer**, is a break in the lining of the stomach, first part of the small intestine, or occasionally the lower esophagus.[1][2] An ulcer in the stomach is known as a **gastric ulcer** while that in the first part of the intestines is known as a **duodenal ulcer**. The most common symptoms of a duodenal ulcer are waking at night with upper abdominal pain or upper abdominal pain that improves with eating.[1] With a gastric ulcer the pain may worsen with eating.[3] The pain is often described as a burning or dull ache. Other symptoms include belching, vomiting, weight loss, or poor appetite. About a third of older people have no symptoms.[1] Complications may include bleeding, perforation, and blockage of the stomach. Bleeding occurs in as many as 15% of people.[4]

Common causes include the bacteria *Helicobacter pylori* and non-steroidal anti-inflammatory drugs (NSAIDs).[1] Other less common causes include tobacco smoking, stress due to serious illness, Behcet disease, Zollinger-Ellison syndrome, Crohn disease and liver cirrhosis, among others.[1][5] Older people are more sensitive to the ulcer causing effects of NSAIDs. The diagnosis is typically suspected due to the presenting symptoms with confirmation by either endoscopy or barium swallow. *H. pylori* can be diagnosed by testing the blood for antibodies, a urea breath test, testing the stool for signs of the bacteria, or a biopsy of the stomach. Other conditions that produce similar symptoms include stomach cancer, coronary heart disease, and inflammation of the stomach lining or gallbladder.[1]

Diet does not play an important role in either causing or preventing ulcers.[6] Treatment includes stopping smoking, stopping NSAIDs, stopping alcohol, and medications to decrease stomach acid. The medication used to decrease acid is usually either a proton pump inhibitor (PPI) or an H2 blocker with four weeks of treatment initially recommended.[1] Ulcers due to *H. pylori* are treated with a combination of medications such as amoxicillin, clarithromycin, and a PPI. Antibiotic resistance is increasing and thus treatment may not always be effective.[7] Bleeding ulcers may be treated by endoscopy, with open surgery typically only used in cases in which it is not successful.[4]

Peptic ulcers are present in around 4% of the population.[1] They newly began in around 53 million people [8] [9]

**Peptic ulcer disease**




Deep gastric ulcer

| Classification and external resources | |
|---|---|
| **Specialty** | Gastroenterology, general surgery |
| **ICD-10** | K25–K27 |
| **ICD-9-CM** | 531–533 |
| **DiseasesDB** | 9819 |
| **MedlinePlus** | 000206 |
| **eMedicine** | med/1776 ped/2341 |
| **MeSH** | D010437 |

[edit on Wikidata]

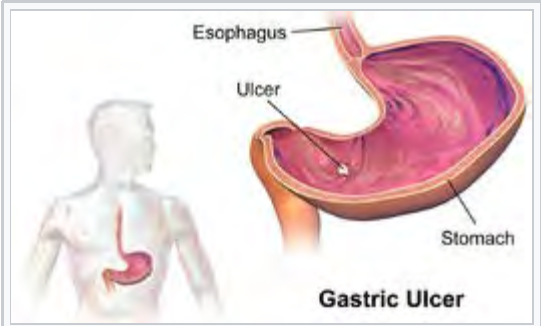
in 2013. About 10% of people develop a peptic ulcer at some point in their life. They resulted in 301,000 deaths in 2013 down from 327,000 deaths in 1990.[10] The first description of a perforated peptic ulcer was in 1670 in Princess Henrietta of England.[4] *H. pylori* was first identified as causing peptic ulcers by Barry Marshall and Robin Warren in the late 20th century,[7] a discovery for which they received the Nobel Prize in 2005.[11]





## Signs and symptoms [edit]

Signs and symptoms of a peptic ulcer can include one or more of the following:



Gastric ulcer

- abdominal pain, classically epigastric strongly correlated to mealtimes. In case of duodenal ulcers the pain appears about three hours after taking a meal;
- bloating and abdominal fullness;
- waterbrash (rush of saliva after an episode of regurgitation to dilute the acid in esophagus - although this is more associated with gastroesophageal reflux disease);
- nausea, and copious vomiting;
- loss of appetite and weight loss;
- hematemesis (vomiting of blood); this can occur due to bleeding directly from a gastric ulcer, or from damage to the esophagus from severe/continuing vomiting.
- melena (tarry, foul-smelling feces due to presence of oxidized iron from hemoglobin);
- rarely, an ulcer can lead to a gastric or duodenal perforation, which leads to acute peritonitis, extreme, stabbing pain,[12] and requires immediate surgery.

A history of heartburn, gastroesophageal reflux disease (GERD) and use of certain forms of medication can raise the suspicion for peptic ulcer. Medicines associated with peptic ulcer include NSAIDs (non-steroid anti-inflammatory drugs) that inhibit cyclooxygenase, and most glucocorticoids (e.g. dexamethasone and prednisolone).

In patients over 45 with more than two weeks of the above symptoms, the odds for peptic ulceration are high enough to warrant rapid investigation by esophagogastroduodenoscopy.

The timing of the symptoms in relation to the meal may differentiate between gastric and duodenal ulcers: A gastric ulcer would give epigastric pain during the meal, as gastric acid production is increased as food enters the stomach. Symptoms of duodenal ulcers would initially be relieved by a meal, as the pyloric sphincter closes to concentrate the stomach contents, therefore acid is not reaching the duodenum. Duodenal ulcer pain would manifest mostly 2–3 hours after the meal, when the stomach begins to release digested food and acid into the duodenum.

Also, the symptoms of peptic ulcers may vary with the location of the ulcer and the patient's age. Furthermore, typical ulcers tend to heal and recur and as a result the pain may occur for few days and weeks and then wane or disappear.[13] Usually, children and the elderly do not develop any symptoms unless complications have arisen.

Burning or gnawing feeling in the stomach area lasting between 30 minutes and 3 hours commonly accompanies ulcers. This pain can be misinterpreted as hunger, indigestion or heartburn. Pain is usually caused by the ulcer but it may be aggravated by the stomach acid when it comes into contact with the ulcerated area. The pain caused by peptic ulcers can be felt anywhere from the navel up to the sternum, it may last from few minutes to several hours and it may be worse when the stomach is empty. Also, sometimes the pain may flare at night and it can commonly be temporarily relieved by eating foods that buffer stomach acid or by taking anti-acid medication.[14] However, peptic ulcer disease symptoms may be different for every sufferer.[15]

## Complications [edit]

- Gastrointestinal bleeding is the most common complication. Sudden large bleeding can be life-threatening.[16] It occurs when the ulcer erodes one of the blood vessels, such as the gastroduodenal artery.
- Perforation (a hole in the wall of the gastrointestinal tract) often leads to catastrophic consequences if left untreated. Erosion of the gastro-intestinal wall by the ulcer leads to spillage of stomach or intestinal content into the abdominal cavity. Perforation at the anterior surface of the stomach leads to acute peritonitis, initially chemical and later bacterial peritonitis. The first sign is often sudden intense abdominal pain; an example is Valentino's syndrome, named after the silent-film actor who experienced this pain before his death. Posterior wall perforation leads to bleeding due to the involvement of gastroduodenal artery that lies posterior to the first part of the duodenum.
- Penetration is a form of perforation in which the hole leads to and the ulcer continues into adjacent organs such as the liver and pancreas.[13]
- Gastric outlet obstruction is a narrowing of the pyloric canal by scarring and swelling of the gastric antrum and duodenum due to peptic ulcers. The person often presents with severe vomiting without bile.
- Cancer is included in the differential diagnosis (elucidated by biopsy), *Helicobacter pylori* as the etiological factor making it 3 to 6 times more likely to develop stomach cancer from the ulcer.[13]

# Cause [edit]

## *H. pylori* [edit]

A major causative factor (60% of gastric and up to 50–75%[17] of duodenal ulcers) is chronic inflammation due to *Helicobacter pylori* that colonizes the antral mucosa.[18] The immune system is unable to clear the infection, despite the appearance of antibodies. Thus, the bacterium can cause a chronic active gastritis (type B gastritis). Gastrin stimulates the production of gastric acid by parietal cells. In *H. pylori* colonization responses to increased gastrin, the increase in acid can contribute to the erosion of the mucosa and therefore ulcer formation.

### NSAIDs [edit]

Another major cause is the use of NSAIDs, such as ibuprofen and aspirin.[19] The gastric mucosa protects itself from gastric acid with a layer of mucus, the secretion of which is stimulated by certain prostaglandins. NSAIDs block the function of cyclooxygenase 1 (*cox-1*), which is essential for the production of these prostaglandins. COX-2 selective anti-inflammatories (such as celecoxib or the since withdrawn rofecoxib) preferentially inhibit *cox-2*, which is less essential in the gastric mucosa, and roughly halve the risk of NSAID-related gastric ulceration.

### Stress [edit]

Stress due to serious health problems such as those requiring treatment in an intensive care unit is well described as a cause of peptic ulcers, which are termed stress ulcers.[5]

While chronic life stress was once believed to be the main cause of ulcers, this is no longer the case.[20] It is, however, still occasionally believed to play a role.[20] This may be by increasing the risk in those with other causes such as *H. pylori* or NSAID use.[21]

### Diet [edit]

Dietary factors such as spice consumption, were hypothesized to cause ulcers until late in the 20th century, but have been shown to be of relatively minor importance.[22] Caffeine and coffee, also commonly thought to cause or exacerbate ulcers, appear to have little effect.[23][24] Similarly, while studies have found that alcohol consumption increases risk when associated with *H. pylori* infection, it does not seem to independently increase risk. Even when coupled with *H. pylori* infection, the increase is modest in comparison to the primary risk factor.[25][26][nb 1]

### Other [edit]

Although some studies have found correlations between smoking and ulcer formation,[27] others have been more specific in exploring the risks involved and have found that smoking by itself may not be much of a risk factor unless associated with *H. pylori* infection.[25][28][29][nb 2]

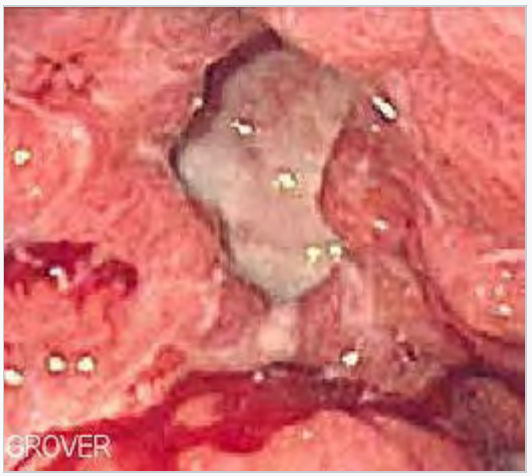
Gastrinomas (Zollinger–Ellison syndrome), rare gastrin-secreting tumors, also cause multiple and difficult-to-heal ulcers.

## Diagnosis [edit]

The diagnosis is mainly established based on the characteristic symptoms. Stomach pain is usually the first signal of a peptic ulcer. In some cases, doctors may treat ulcers without diagnosing them with specific tests and observe whether the symptoms resolve, thus indicating that their primary diagnosis was accurate.

More specifically, peptic ulcers erode the muscularis mucosae, at least to the level of the submucosa (contrast with erosions, which do not involve the muscularis mucosae).[30]

Confirmation of the diagnosis is made with the help of tests such as endoscopies or barium contrast x-rays. The tests are typically ordered if the symptoms do not resolve after a few weeks of treatment, or when they first appear in a person who is over age 45 or who has other symptoms such as weight loss, because stomach cancer can cause similar symptoms. Also, when severe ulcers resist treatment, particularly if a person has several ulcers or the ulcers are in unusual places, a doctor may suspect an



Endoscopic image of gastric ulcer, biopsy proven to be gastric cancer.

underlying condition that causes the stomach to overproduce acid.[13]

An esophagogastroduodenoscopy (EGD), a form of endoscopy, also known as a gastroscopy, is carried out on patients in whom a peptic ulcer is suspected. By direct visual identification, the location and severity of an ulcer can be described. Moreover, if no ulcer is present, EGD can often provide an alternative diagnosis.

One of the reasons that blood tests are not reliable for accurate peptic ulcer diagnosis on their own is their inability to differentiate between past exposure to the bacteria and current infection. Additionally, a false negative result is possible with a blood test if the patient has recently been taking certain drugs, such as antibiotics or proton-pump inhibitors.[31]

The diagnosis of *Helicobacter pylori* can be made by:

- Urea breath test (noninvasive and does not require EGD);
- Direct culture from an EGD biopsy specimen; this is difficult to do, and can be expensive. Most labs are not set up to perform *H. pylori* cultures;
- Direct detection of urease activity in a biopsy specimen by rapid urease test;
- Measurement of antibody levels in the blood (does not require EGD). It is still somewhat controversial whether a positive antibody without EGD is enough to warrant eradication therapy;
- Stool antigen test;
- Histological examination and staining of an EGD biopsy.

The breath test uses radioactive carbon to detect H. pylori.[32] To perform this exam the patient will be asked to drink a tasteless liquid which contains the carbon as part of the substance that the bacteria breaks down. After an hour, the patient will be asked to blow into a bag that is sealed. If the patient is infected with H. pylori, the breath sample will contain radioactive carbon dioxide. This test provides the advantage of being able to monitor the response to treatment used to kill the bacteria.

The possibility of other causes of ulcers, notably malignancy (gastric cancer) needs to be kept in mind. This is especially true in ulcers of the *greater (large) curvature* of the stomach; most are also a consequence of chronic *H. pylori* infection.

If a peptic ulcer perforates, air will leak from the inside of the gastrointestinal tract (which always contains some air) to the peritoneal cavity (which normally never contains air). This leads to "free gas" within the peritoneal cavity. If the patient stands erect, as when having a chest X-ray, the gas will float to a position underneath the diaphragm. Therefore, gas in the peritoneal cavity, shown on an erect chest X-ray or supine lateral abdominal X-ray, is an omen of perforated peptic ulcer disease.

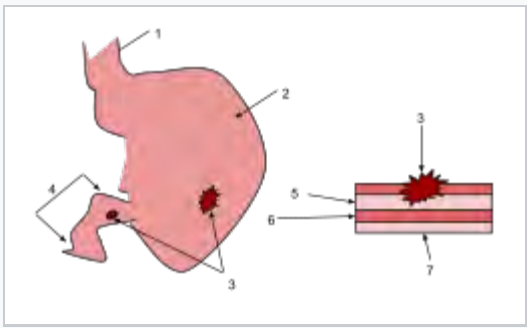
## Classification [edit]

### By area [edit]

- Duodenum (called duodenal ulcer)
- Esophagus (called esophageal ulcer)
- Stomach (called gastric ulcer)
- Meckel's diverticulum (called Meckel's diverticulum ulcer; is very tender with palpation)

### Modified Johnson [edit]

- Type **I**: Ulcer along the body of the stomach, most often along the lesser curve at incisura angularis along the locus minoris resistantiae. Not associated with acid hypersecretion.
- Type **II**: Ulcer in the body in combination with duodenal ulcers. Associated with acid oversecretion.
- Type **III**: In the pyloric channel within 3 cm of pylorus. Associated with acid oversecretion.
- Type **IV**: Proximal gastroesophageal ulcer
- Type **V**: Can occur throughout the stomach. Associated with

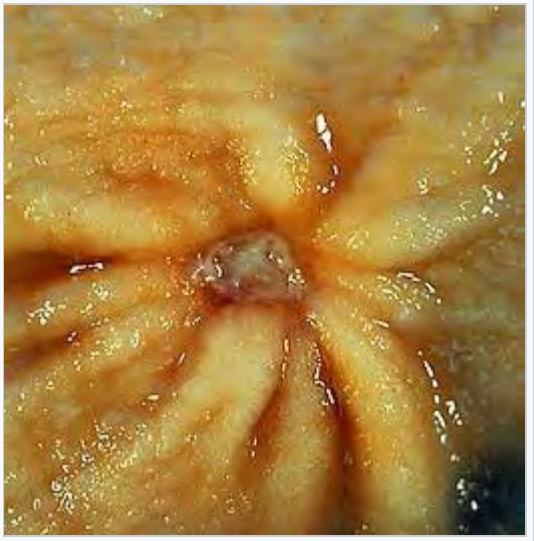



1. Esophagus
2. Stomach
3.Ulcers
4.Duodenum
5.Mucosa
6.Submucosa
7.Muscle

the chronic use of NSAIDs (such as ibuprofen).

## Macroscopic appearance [edit]

Gastric ulcers are most often localized on the lesser curvature of the stomach. The ulcer is a round to oval parietal defect ("hole"), 2 to 4 cm diameter, with a smooth base and perpendicular borders. These borders are not elevated or irregular in the acute form of peptic ulcer, regular but with elevated borders and inflammatory surrounding in the chronic form. In the ulcerative form of gastric cancer the borders are irregular. Surrounding mucosa may present radial folds, as a consequence of the parietal scarring.



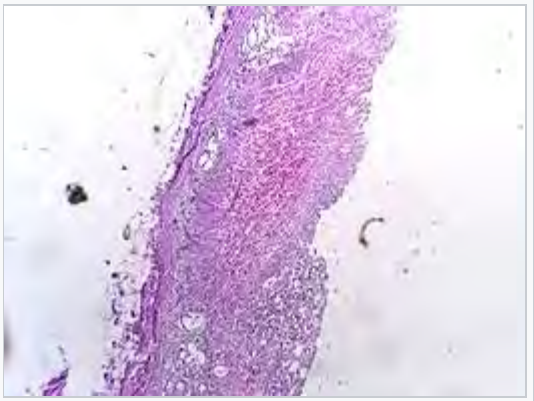
A benign gastric ulcer (from the antrum) of a gastrectomy specimen.

## Microscopic appearance [edit]

A gastric peptic ulcer is a mucosal defect which penetrates the muscularis mucosae and lamina propria, produced by acid-pepsin aggression. Ulcer margins are perpendicular and present chronic gastritis. During the active phase, the base of the ulcer shows 4 zones: inflammatory exudate, fibrinoid necrosis, granulation tissue and fibrous tissue. The fibrous base of the ulcer may contain vessels with thickened wall or with thrombosis.[33]

## Differential diagnosis [edit]

- Gastritis
- Stomach cancer
- Gastroesophageal reflux disease
- Pancreatitis
- Hepatic congestion
- Cholecystitis
- Biliary colic
- Inferior myocardial infarction
- Referred pain (pleurisy, pericarditis)
- Superior mesenteric artery syndrome



Micrograph showing erosive gastric ulcer. (H&E stain)

# Treatment [edit]

Younger patients with ulcer-like symptoms are often treated with antacids or H2 antagonists before endoscopy is undertaken.

People who are taking nonsteroidal anti-inflammatories (NSAIDs) may also be prescribed a prostaglandin analogue (misoprostol) in order to help prevent peptic ulcers.

## Acid reducing medication [edit]

H2 antagonists or proton-pump inhibitors decrease the amount of acid in the stomach, helping with healing of ulcers.[1]

### *H. pylori* [edit]

When *H. pylori* infection is present, the most effective treatments are combinations of 2 antibiotics (e.g. clarithromycin, amoxicillin, tetracycline, metronidazole) and a proton-pump inhibitor (PPI), sometimes together with a bismuth compound. In complicated, treatment-resistant cases, 3 antibiotics (e.g. amoxicillin + clarithromycin + metronidazole) may be used together with a PPI and sometimes with bismuth compound. An effective first-line therapy for uncomplicated cases would be amoxicillin + metronidazole + pantoprazole (a PPI).[1]

## Surgery [edit]

Perforated peptic ulcer is a surgical emergency and requires surgical repair of the perforation. Most bleeding ulcers require endoscopy urgently to stop bleeding with cautery, injection, or clipping.

# Epidemiology [edit]

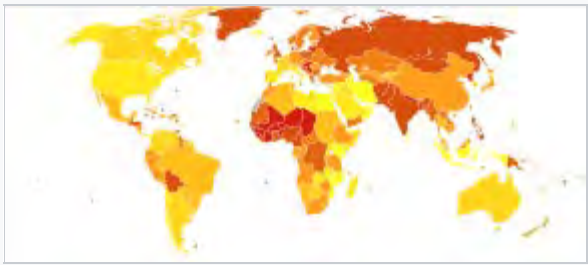
The lifetime risk for developing a peptic ulcer is approximately 10%.[9] They resulted in 301,000 deaths in 2013 down from 327,000 deaths in 1990.[10]

In Western countries the percentage of people with *Helicobacter pylori* infections roughly matches age (i.e., 20% at age 20, 30% at age 30, 80% at age 80 etc.). Prevalence is higher in third world countries where it is estimated at about 70% of the population, whereas developed countries show a maximum of 40% ratio. Overall, *H. pylori* infections show a worldwide decrease, more so in developed countries. Transmission is by food, contaminated groundwater, and through human saliva (such as from kissing or sharing food utensils).[35]

A minority of cases of *H. pylori* infection will eventually lead to an ulcer and a larger proportion of people will get non-specific discomfort, abdominal pain or gastritis.

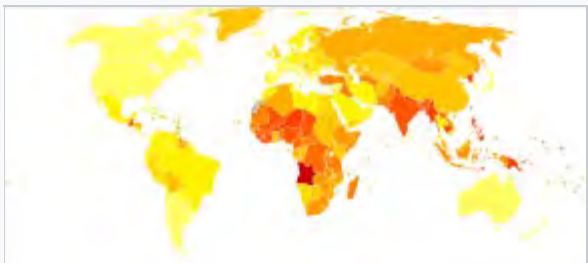
Peptic ulcer disease had a tremendous effect on morbidity and mortality until the last decades of the 20th century when epidemiological trends started to point to an impressive fall in its incidence.[36] The reason that the rates of peptic ulcer disease decreased is thought to be the development of new effective medication and acid suppressants and the discovery of the cause of the condition, *H. pylori*.

The incidence of duodenal ulcers has dropped significantly during the last 30 years, while the incidence of gastric ulcers has shown a small increase, mainly caused by the widespread use of NSAIDs. The drop in incidence for duodenal ulcers is considered to be a cohort-phenomenon independent of the progress in the treatment of the disease. The cohort-phenomenon is probably explained by improved standards of living which has lowered the incidence of *H. pylori* infections.[37]



Deaths from peptic ulcer disease per million persons in 2012

| | | |
|---|---|---|
| 0-7 | 17-19 | 33-40 |
| 8-11 | 20-25 | 41-53 |
| 12-16 | 26-32 | 54-72 |
| | | 73-132 |



Disability-adjusted life year for peptic ulcer disease per 100,000 inhabitants in 2004.[34]

| | |
|---|---|
| no data | 100–120 |
| less than 20 | 120–140 |
| 20–40 | 140–160 |
| 40–60 | 160–180 |
| 60–80 | 180–200 |
| 80–100 | 200–220 |
| | more than 220 |

# History [edit]

> *See also: Timeline of peptic ulcer disease and Helicobacter pylori*

John Lykoudis, a general practitioner in Greece, treated patients for peptic ulcer disease with antibiotics, beginning in 1958, long before it was commonly recognized that bacteria were a dominant cause for the disease.[38]

*Helicobacter pylori* was identified in 1982 by two Australian scientists, Robin Warren and Barry J. Marshall as a causative factor for ulcers.[39] In their original paper, Warren and Marshall contended that most gastric ulcers and gastritis were caused by colonization with this bacterium, not by stress or spicy food as had been assumed before.[40]

The *H. pylori* hypothesis was initially poorly received,[41] so in an act of self-experimentation Marshall drank a Petri dish containing a culture of organisms extracted from a patient and five days later developed gastritis. His symptoms disappeared after two weeks, but he took antibiotics to kill the remaining bacteria at the urging of his wife, since halitosis is one of the symptoms of infection.[42] This experiment was published in 1984 in the Australian Medical Journal and is among the most cited articles from the journal.

In 1997, the Centers for Disease Control and Prevention, with other government agencies, academic institutions, and industry, launched a national education campaign to inform health care providers and consumers about the link between *H. pylori* and ulcers. This campaign reinforced the news that ulcers are a curable infection and that health can be greatly improved and money saved by disseminating information about *H. pylori*.[43]

In 2005, the Karolinska Institute in Stockholm awarded the Nobel Prize in Physiology or Medicine to Dr. Marshall and his long-time collaborator Dr. Warren "for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease." Professor Marshall continues research related to *H. pylori* and runs a molecular biology lab at UWA in Perth, Western Australia.

Some believed that mastic gum, a tree resin extract, actively eliminates the *H. pylori* bacteria.[44] However, multiple subsequent studies have found no effect of using mastic gum on reducing *H. pylori* levels.[45][46]

## Notes [edit]

1. ^ Sonnenberg in his study cautiously concludes that, among other potential factors that were found to correlate to ulcer healing, "moderate alcohol intake might [also] favor ulcer healing." (p. 1066)
2. ^ Kurata 1997 explains that "Data in Fig. 8 indicate that 89% of all serious upper GI disease can be accounted for by NSAIDs and H. pylori, with cigarette smoking acting as a synergistic co-factor."(14)

## References [edit]


1. ^ *a b c d e f g h i j* Najm, WI (September 2011). "Peptic ulcer disease.". *Primary care*. **38** (3): 383–94, vii. doi:10.1016/j.pop.2011.05.001. PMID 21872087.
2. ^ "Definition and Facts for Peptic Ulcer Disease". *National Institute of Diabetes and Digestive and Kidney Diseases*. Retrieved 28 February 2015.
3. ^ Rao, S. Devaji (2014). *Clinical Manual of Surgery*. Elsevier Health Sciences. p. 526. ISBN 9788131238714.
4. ^ *a b c* Milosavljevic, T; Kostić-Milosavljević, M; Jovanović, I; Krstić, M (2011). "Complications of peptic ulcer disease.". *Digestive diseases (Basel, Switzerland)*. **29** (5): 491–3. doi:10.1159/000331517. PMID 22095016.
5. ^ *a b* Steinberg, KP (June 2002). "Stress-related mucosal disease in the critically ill patient: risk factors and strategies to prevent stress-related bleeding in the intensive care unit.". *Critical Care Medicine*. **30** (6 Suppl): S362–4. doi:10.1097/00003246-200206001-00005. PMID 12072662.
6. ^ "Eating, Diet, and Nutrition for Peptic Ulcer Disease". *National Institute of Diabetes and Digestive and Kidney Diseases*. Retrieved 28 February 2015.
7. ^ *a b* Wang, AY; Peura, DA (October 2011). "The prevalence and incidence of Helicobacter pylori-
25. ^ *a b* Salih, Barik; M Fatih Abasiyanik; Nizamettin Bayyurt; Ersan Sander (June 2007). "H pylori infection and other risk factors associated with peptic ulcers in Turkish patients: A retrospective study". *World Journal of Gastroenterology*. **13** (23): 3245–8. PMID 17589905.
26. ^ A, Sonnenberg; Müller-Lissner SA; Vogel E; Schmid P; Gonvers JJ; Peter P; Strohmeyer G; Blum AL (1981). "Predictors of duodenal ulcer healing and relapse.". *Journal of Gastroenterology*. **81** (6): 1061–7. PMID 7026344.
27. ^ Kato, Ikuko; Abraham M. Y. Nomura; Grant N. Stemmermann; Po-Huang Chyou (1992). "A Prospective Study of Gastric and Duodenal Ulcer and Its Relation to Smoking, Alcohol, and Diet". *American Journal of Epidemiology*. **135** (5): 521–530. PMID 1570818.
28. ^ Martin DF, Montgomery E, Dobek AS, Patrissi GA,

Jefferson University Philadelphia, Pennsylvania ; Founder and Consulting Editor, Emanuel Rubin, M.D., Gonzalo Aponte Distinguished Professor of Pathology, Chairman Emeritus of the Department of Pathology and Cell Biology, Jefferson Medical College of Thomas Jefferson University, Philadelphia,. *Rubin's pathology : clinicopathologic foundations of medicine* (Sixth Edition. ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 623. ISBN 978-1605479682.

associated peptic ulcer disease and upper gastrointestinal bleeding throughout the world.". *Gastrointestinal endoscopy clinics of North America*. **21** (4): 613–35. doi:10.1016/j.giec.2011.07.011. PMID 21944414.
8. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
9. ^ *a b* Snowden FM (October 2008). "Emerging and reemerging diseases: a historical perspective". *Immunol. Rev*. **225** (1): 9–26. doi:10.1111/j.1600-065X.2008.00677.x. PMID 18837773.
10. ^ *a b* GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385**: 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
11. ^ "The Nobel Prize in Physiology or Medicine 2005". *nobelprize.org*. Nobel Media AB. Retrieved 3 June 2015.
12. ^ Bhat, Sriram (2013). *SRB's Manual of Surgery*. p. 364. ISBN 9789350259443
13. ^ *a b c d* "Peptic Ulcer". *Home Health Handbook for Patients & Caregivers*. Merck Manuals. October 2006.
14. ^ "Peptic ulcer". Retrieved 18 June 2010.
15. ^ "Ulcer Disease Facts and Myths". Retrieved 18 June 2010.
16. ^ Cullen DJ; Hawkey GM; Greenwood DC; *et al.* (1997). "Peptic ulcer bleeding in the elderly: relative roles of Helicobacter pylori and non-steroidal anti-inflammatory drugs". *Gut*. **41** (4): 459–62. doi:10.1136/gut.41.4.459. PMC 1891536. PMID 9391242.
17. ^ http://www.uptodate.com/contents/association-between-helicobacter-pylori-infection-and-duodenal-ulcer
18. ^ "antral mucosa - Humpath.com - Human pathology". web.archive.org. Retrieved 27 February 2014.
19. ^ "Stomach ulcer - Causes - NHS Choices". *www.nhs.uk*. NHS.
20. ^ *a b* Fink, G (February 2011). "Stress controversies: post-traumatic stress disorder, hippocampal volume, gastroduodenal ulceration*.". *Journal of neuroendocrinology*. **23** (2): 107–17. doi:10.1111/j.1365-2826.2010.02089.x. PMID 20973838.
21. ^ Yeomans, ND (January 2011). "The ulcer sleuths: Peura DA (28 June 2008). "Campylobacter pylori, NSAIDS, and Smoking: Risk Factors for Peptic Ulcer Disease". *American Journal of Gastroenterology*. **84** (10): 1268–72. doi:10.1111/j.1572-0241.1989.tb06166.x. PMID 2801677. Retrieved 18 March 2010.[*dead link*]
29. ^ Kurata Ph.D., M.P.H., John H.; Nogawa, Aki N. M.S. (Jan 1997). "Meta-analysis of Risk Factors for Peptic Ulcer: Nonsteroidal Antiinflammatory Drugs, *Helicobacter pylori*, and Smoking". *Journal of Clinical Gastroenterology*. **24** (1): 2–17. doi:10.1097/00004836-199701000-00002. PMID 9013343.
30. ^ http://www.merckmanuals.com/professional/gastrointestinal-disorders/gastritis-and-peptic-ulcer-disease/peptic-ulcer-disease
31. ^ "Peptic ulcer". Retrieved 18 June 2010.
32. ^ "Tests and diagnosis". Retrieved 18 June 2010.
33. ^ "ATLAS OF PATHOLOGY". Retrieved 26 August 2007.
34. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved 11 November 2009.
35. ^ Brown LM (2000). "*Helicobacter pylori*: epidemiology and routes of transmission.". *Epidemiol. Rev*. **22** (2): 283–97. doi:10.1093/oxfordjournals.epirev.a018040. PMID 11218379.
36. ^ "Peptic ulcer disease". Retrieved 18 June 2010.
37. ^ Johannessen T. "Peptic ulcer disease". *Pasienthandboka*.
38. ^ Rigas, Basil; Papavasassiliou, Efstathios D. (22 May 2002). "Ch. 7 John Lykoudis. The general practitioner in Greece who in 1958 discovered the etiology of, and a treatment for, peptic ulcer disease.". In Marshall, Barry J. *Helicobacter pioneers: firsthand accounts from the scientists who discovered helicobacters, 1892–1982*. John Wiley & Sons. pp. 74–88. ISBN 978-0-86793-035-1.
39. ^ Marshall B.J. (1983). "Unidentified curved bacillus on gastric epithelium in active chronic gastritis". *Lancet*. **1** (8336): 1273–75. doi:10.1016/S0140-6736(83)92719-8. PMID 6134060.
40. ^ Marshall B.J.; Warren J.R. (1984). "Unidentified curved bacilli in the stomach patients with gastritis and peptic ulceration". *Lancet*. **1** (8390): 1311–15. doi:10.1016/S0140-6736(84)91816-6. PMID 6145023.
41. ^ Kathryn Schulz (9 September 2010). "Stress Doesn't Cause Ulcers! Or, How To Win a Nobel Prize in One Easy Lesson: Barry Marshall on Being ... Right". *The Wrong Stuff*. Slate. Retrieved 17 July 2011.
42. ^ Van Der Weyden MB, Armstrong RM, Gregory AT (2005). "The 2005 Nobel Prize in physiology or medicine". *Med. J. Aust*. **183** (11–12): 612–4. PMID 16336147.
43. ^ "Ulcer, Diagnosis and Treatment - CDC Bacterial,

The search for the cause of peptic ulcers.". *Journal of Gastroenterology and Hepatology*. 26 Suppl 1: 35–41. doi:10.1111/j.1440-1746.2010.06537.x. PMID 21199512.
22. ^ For nearly 100 years, scientists and doctors thought that ulcers were caused by stress, spicy food, and alcohol. Treatment involved bed rest and a bland diet. Later, researchers added stomach acid to the list of causes and began treating ulcers with antacids. National Digestive Diseases Information Clearinghouse
23. ^ Ryan-Harshman, M; Aldoori, W (May 2004). "How diet and lifestyle affect duodenal ulcers. Review of the evidence.". *Canadian Family Physician*. **50**: 727–32. PMC 2214597. PMID 15171675.
24. ^ Pennsylvania, Editors, Raphael Rubin, M.D., Professor of Pathology, David S. Strayer, M.D., Ph.D., Professor of Pathology, Department of Pathology and Cell Biology, Jefferson Medical College of Thomas Mycotic Diseases". Cdc.gov. Retrieved 27 February 2014.
44. ^ Huwez FU, Thirlwell D, Cockayne A, Ala'Aldeen DA (December 1998). "Mastic gum kills Helicobacter pylori [Letter to the editor, not a peer-reviewed scientific article]". *N. Engl. J. Med.* **339** (26): 1946. doi:10.1056/NEJM199812243392618. PMID 9874617. Retrieved 6 September 2008. See also their corrections in the next volume.
45. ^ Loughlin MF, Ala'Aldeen DA, Jenks PJ (February 2003). "Monotherapy with mastic does not eradicate Helicobacter pylori infection from mice". *J. Antimicrob. Chemother.* **51** (2): 367–71. doi:10.1093/jac/dkg057. PMID 12562704.
46. ^ Bebb JR, Bailey-Flitter N, Ala'Aldeen D, Atherton JC (September 2003). "Mastic gum has no effect on Helicobacter pylori load in vivo". *J. Antimicrob. Chemother.* **52** (3): 522–3. doi:10.1093/jac/dkg366. PMID 12888582.

## External links [edit]

- Gastric Ulcer
- Approach to acute upper gastrointestinal bleeding in adults (Wolters Kluwer UpToDate)
- (MCQs on Peptic ulcer )

Wikimedia Commons has media related to *Peptic ulcers*.

Radiology and Endoscopy from MedPix

| v · t · e · **Infectious diseases · Bacterial disease: Proteobacterial G− (primarily A00–A79, 001–041, 080–109 · ·** | | | | | |
|---|---|---|---|---|---|
| **α** | **Rickettsiales** | **Rickettsiaceae/ (Rickettsioses)** | **Typhus** | | *Rickettsia typhi* (Murine typhus · · *Rickettsia prowazekii* (Epidemic typhus, Brill–Zinsser disease, Flying squirrel typhus · · |
| | | | **Spotted fever** | **Tick-borne** | *Rickettsia rickettsii* (Rocky Mountain spotted fever · · *Rickettsia conorii* (Boutonneuse fever · · *Rickettsia japonica* (Japanese spotted fever · · *Rickettsia sibirica* (North Asian tick typhus · · *Rickettsia australis* (Queensland tick typhus · · *Rickettsia honei* (Flinders Island spotted fever · · *Rickettsia africae* (African tick bite fever · · *Rickettsia parkeri* (American tick bite fever · · *Rickettsia aeschlimannii* (*Rickettsia aeschlimannii* infection · · |
| | | | | | *Rickettsia akari* (Rickettsialpox · · |

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|---|---|---|---|---|---|
| | | | | **Mite-borne** | *Orientia tsutsugamushi* (Scrub typhus · · |
| | | | | **Flea-borne** | *Rickettsia felis* (Flea-borne spotted fever · · |
| | | **Anaplasmataceae** | Ehrlichiosis: *Anaplasma phagocytophilum* (Human granulocytic anaplasmosis, Anaplasmosis · · *Ehrlichia chaffeensis* (Human monocytotropic ehrlichiosis · · *Ehrlichia ewingii* (Ehrlichiosis ewingii infection · · | | |
| | **Rhizobiales** | **Brucellaceae** | *Brucella abortus* (Brucellosis · · | | |
| | | **Bartonellaceae** | Bartonellosis: *Bartonella henselae* (Cat-scratch disease · · *Bartonella quintana* (Trench fever · · Either *B. henselae* or *B. quintana* (Bacillary angiomatosis · · *Bartonella bacilliformis* (Carrion's disease, Verruga peruana · · | | |
| **β** | **Neisseriales** | **M+** | *Neisseria meningitidis/meningococcus* (Meningococcal disease, Waterhouse–Friderichsen syndrome, Meningococcal septicaemia · · | | |
| | | **M-** | *Neisseria gonorrhoeae/gonococcus* (Gonorrhea · · | | |
| | | *ungrouped:* | *Eikenella corrodens*/*Kingella kingae* (HACEK · · *Chromobacterium violaceum* (Chromobacteriosis infection · · | | |
| | **Burkholderiales** | *Burkholderia pseudomallei* (Melioidosis · · *Burkholderia mallei* (Glanders · · *Burkholderia cepacia complex* · *Bordetella pertussis*/*Bordetella parapertussis* (Pertussis · · | | | |
| **γ** | **Enterobacteriales (OX-)** | **Lac+** | *Klebsiella pneumoniae* (Rhinoscleroma, Klebsiella pneumonia · · *Klebsiella granulomatis* (Granuloma inguinale · · *Klebsiella oxytoca* · *Escherichia coli*: Enterotoxigenic · Enteroinvasive · Enterohemorrhagic · O157:H7 · O104:H4 (Hemolytic-uremic syndrome · · *Enterobacter aerogenes*/*Enterobacter cloacae* · | | |
| | | **Slow/weak** | *Serratia marcescens* (Serratia infection · · *Citrobacter koseri*/*Citrobacter freundii* · | | |
| | | **Lac-** | **H2S+** | *Salmonella enterica* (Typhoid fever, Paratyphoid fever, Salmonellosis · · | |
| | | | **H2S-** | *Shigella dysenteriae*/*sonnei*/*flexneri*/*boydii* (Shigellosis, Bacillary dysentery · · *Proteus mirabilis*/*Proteus vulgaris* · *Yersinia pestis* (Plague/Bubonic plague · · *Yersinia enterocolitica* (Yersiniosis · · *Yersinia pseudotuberculosis* (Far East scarlet-like fever · · | | |
| | **Pasteurellales** | *Haemophilus:* | *H. influenzae* (Haemophilus meningitis · Brazilian purpuric fever · · *H. ducreyi* (Chancroid · · *H. parainfluenzae* (HACEK · · | | |
| | | *Pasteurella multocida* | Pasteurellosis · *Actinobacillus* (Actinobacillosis · · | | |
| | | *Aggregatibacter actinomycetemcomitans* | HACEK · | | |
| | **Legionellales** | *Legionella pneumophila*/*Legionella longbeachae* (Legionnaires' disease · · *Coxiella burnetii* (Q fever · · | | | |

| | | |
|---|---|---|
| | **Thiotrichales** | *Francisella tularensis* (Tularemia · · |
| | **Vibrionaceae** | *Vibrio cholerae* (Cholera · · *Vibrio vulnificus* · *Vibrio parahaemolyticus* · *Vibrio alginolyticus* · *Plesiomonas shigelloides* · |
| | **Pseudomonadales** | *Pseudomonas aeruginosa* (Pseudomonas infection · · *Moraxella catarrhalis* · *Acinetobacter baumannii* · |
| | **Xanthomonadaceae** | *Stenotrophomonas maltophilia* · |
| | **Cardiobacteriaceae** | *Cardiobacterium hominis* (HACEK · · |
| | **Aeromonadales** | *Aeromonas hydrophila*/*Aeromonas veronii* (Aeromonas infection · · |
| **ε** | **Campylobacterales** | *Campylobacter jejuni* (Campylobacteriosis, Guillain–Barré syndrome · · *Helicobacter pylori* (**Peptic ulcer**, MALT lymphoma, Gastric cancer · · *Helicobacter cinaedi* (Helicobacter cellulitis · · |

| v · t · e · | **Diseases of the digestive system (primarily K20–K93, 530–579)** | |
|---|---|---|
| **Upper GI tract** | **Esophagus** | Esophagitis (Candidal · Eosinophilic · Herpetiform · · *Rupture* (Boerhaave syndrome · Mallory-Weiss syndrome · · UES (Zenker's diverticulum · · LES (Barrett's esophagus · · Esophageal motility disorder (Nutcracker esophagus · Achalasia · Diffuse esophageal spasm · Gastroesophageal reflux disease (GERD) · · Laryngopharyngeal reflux (LPR) · Esophageal stricture · Megaesophagus · |
| | **Stomach** | Gastritis (Atrophic · Ménétrier's disease · Gastroenteritis · · **Peptic (gastric) ulcer** (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
| **Lower GI tract: Intestinal/ Enteropathy** | **Small intestine (Duodenum/Jejunum/Ileum)** | Enteritis (Duodenitis · Jejunitis · Ileitis · · **Peptic (duodenal) ulcer** (Curling's ulcer · · Malabsorption: Coeliac · Tropical sprue · Blind loop syndrome · Small bowel bacterial overgrowth syndrome · Whipple's · Short bowel syndrome · Steatorrhea · Milroy disease · Bile acid malabsorption · |
| | **Large intestine (Appendix/Colon)** | Appendicitis · Colitis (Pseudomembranous · Ulcerative · Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (IBS · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
| | **Large and/or small** | Enterocolitis (Necrotizing · · Gastroenterocolitis · IBD (Crohn's disease · · *Vascular*: Abdominal angina · Mesenteric ischemia · Angiodysplasia · Bowel obstruction: Ileus · Intussusception · Volvulus · Fecal impaction · Constipation · Diarrhea (Infectious · · Intestinal adhesions · |
| | **Rectum** | Proctitis (Radiation proctitis · · Proctalgia fugax · Rectal prolapse · Anismus · |
| | **Anal canal** | Anal fissure/Anal fistula · Anal abscess · Anal dysplasia · |

| | | |
|---|---|---|
| | | Pruritus ani · |
| **GI bleeding / BIS** | | Upper (Hematemesis · Melena · · Lower (Hematochezia · · |
| **Accessory** | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · Acute liver failure · · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |
| | **Gallbladder** | Cholecystitis · Gallstones/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · Gallstones/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
| | **Pancreatic** | Pancreatitis (Acute · Chronic · Hereditary · Pancreatic abscess · · Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |
| **Abdominopelvic** | **Hernia** | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |
| **Authority control** | | NDL: 00572090 · |

Categories: Abdominal pain | Diseases of oesophagus, stomach and duodenum | Acute pain

# Vitamin B12 deficiency anemia

From Wikipedia, the free encyclopedia
(Redirected from Pernicious anemia)



*"Addison's anaemia" redirects here. For the disease affecting the adrenal glands, see Addison's disease.*

**Vitamin $B_{12}$ deficiency anemia**, of which **pernicious anemia** is a type,[4] is a disease in which not enough red blood cells are present due to a lack of vitamin $B_{12}$.[5] The most common initial symptom is feeling tired. Other symptoms may include shortness of breath, pale skin, chest pain, numbness in the hands and feet, poor balance, a smooth, red tongue, poor reflexes, and confusion.[6] If treatment is not provided, some of these problems may become permanent.[5]

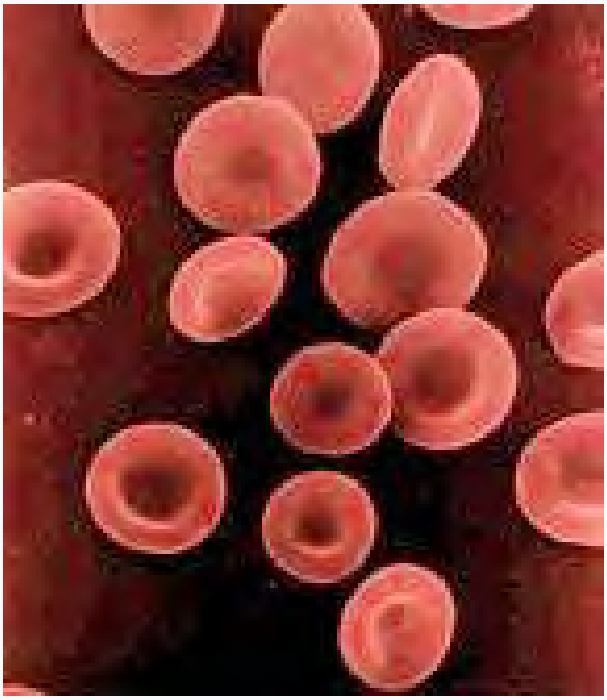
Although pernicious anemia technically refers to cases resulting from not enough intrinsic factor, it is often used to describe all cases of anemia due to not enough vitamin $B_{12}$.[5] Lack of intrinsic factor is most commonly due to an autoimmune attack on the cells that make it in the stomach. It can also occur following the surgical removal of part of the stomach or from an inherited disorder. Other causes of low vitamin $B_{12}$ include a poor diet, celiac disease, and a tapeworm infection.[7] When suspected, diagnosis is made by blood and, occasionally, bone marrow tests. Blood tests may show fewer but larger red blood cells, low numbers of young red blood cells, low levels of vitamin $B_{12}$, and antibodies to intrinsic factor.[8]

Pernicious anemia due to lack of intrinsic factor is not preventable. Vitamin $B_{12}$ deficiency due to other causes may be prevented with a balanced diet or with supplements.[9] Pernicious anemia can be easily treated with either injections or pills of vitamin $B_{12}$. If the symptoms are severe, injections are typically recommended initially. For those who have trouble swallowing pills, a nasal spray is available.[10] Often, treatment is lifelong.[11]

Pernicious anemia due to autoimmune problems occurs in about one per 1000 people. Among those over the age of 60, about 2% have the condition.[1] It more commonly affects people of northern European descent.[2] Women are more commonly affected than men.[12] With proper treatment, most people live normal lives.[5] Due to a higher risk of stomach cancer, those with pernicious anemia should be [11]

**Vitamin $B_{12}$ deficiency anemia**

**Synonyms** ... anemia,[2] Addison's anemia,[2] Addison–Biermer anemia[3]



Normal red blood cells

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Hematology |
| **ICD-10** | D51.0 |
| **ICD-9-CM** | 281.0 |
| **DiseasesDB** | 9870 |
| **MedlinePlus** | 000569 |
| **eMedicine** | med/1799 |
| **MeSH** | D000752 |

[edit on Wikidata]

checked regularly for this. The first clear description was by Thomas Addison in 1849.[13][14] The term "pernicious" means "deadly", and was used as before the availability of treatment the disease was often fatal.[5][15]

Polski
Português
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Simple English
Slovenščina
Српски
Svenska
Türkçe
Українська
中

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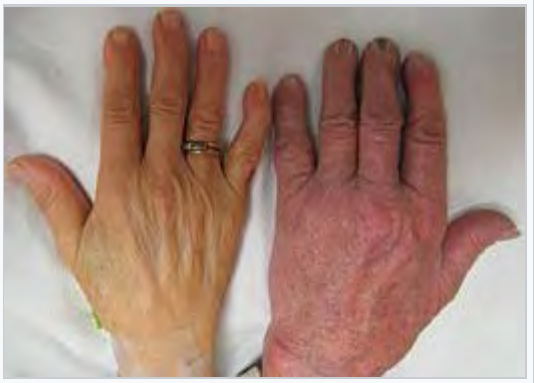
## Signs and symptoms [edit]



A hand of a person with severe anemia compared to one without

The symptoms of pernicious anemia come on slowly. Untreated, it can lead to neurological complications, and in serious cases, death. Many of the signs and symptoms are due to anemia itself, when anemia is present.[16] Symptoms may consist of the triad of tingling or other skin sensations (paresthesia), tongue soreness (glossitis), and fatigue and general weakness.[17][18][19][*page needed*] It presents with a number of further common symptoms,[19][*page needed*][20][*page needed*] including depressive mood, low-grade fevers, diarrhea, dyspepsia, weight loss,[17] neuropathic pain, jaundice, sores at the corner of the mouth (angular cheilitis), a look of exhaustion with pale and dehydrated or cracked lips and dark circles around the eyes, as well as brittle nails,[18] and thinning and early greying of the hair.[18] Because PA may affect the nervous system, symptoms may also include difficulty in proprioception,[21] memory changes,[20][*page needed*] mild cognitive impairment (including difficulty concentrating and sluggish responses, colloquially referred to as brain fog), and even psychoses, impaired urination,[17] loss of sensation in the feet, unsteady gait,[21] difficulty in walking,[18] muscle weakness[19][*page needed*] and clumsiness.[17] Anemia may also lead to tachycardia (rapid heartbeat),[17] cardiac murmurs, a yellow waxy pallor,[18] altered blood pressure (low or high), and a shortness of breath (known as "the sighs").[19][*page needed*] The deficiency also may present with thyroid disorders.[19][*page needed*] In severe cases, the anemia may cause evidence of congestive heart failure.[20][*page needed*] A complication of severe chronic PA is subacute combined degeneration of spinal cord, which leads to distal sensory loss (posterior column), absent ankle reflex, increased knee reflex response, and extensor plantar response.[22] Other than anemia, hematological symptoms may include cytopenias, intramedullary hemolysis, and pseudothrombotic microangiopathy.[1] Pernicious anemia can contribute to a delay in physical growth in children, and may also be a cause for delay in puberty for adolescents.

## Causes [edit]

Vitamin $B_{12}$ cannot be produced by the human body, and must be obtained from the diet. When foods containing $B_{12}$ are eaten, the vitamin is usually bound to protein and is released by stomach acid. Following its release, most $B_{12}$ is absorbed by the body in the small bowel (ileum) after binding to a protein known as intrinsic factor. Intrinsic factor is produced by parietal cells of the gastric mucosa (stomach lining) and the intrinsic factor-$B_{12}$ complex is absorbed by cubilin receptors on the ileum epithelial cells.[23][24] PA is characterised by $B_{12}$ deficiency caused by the absence of intrinsic factor.[25]

PA may be considered as an end stage of immune gastritis, a disease characterised by stomach atrophy and the presence of antibodies to parietal cells and intrinsic factor.[26] A specific form of chronic gastritis, type A gastritis or atrophic body gastritis, is highly associated with PA. This autoimmune disorder is localised to the body of the stomach, where parietal cells are located.[25] Antibodies to intrinsic factor and parietal cells cause the destruction of the oxyntic gastric mucosa, in which the parietal cells are located, leading to the subsequent loss of intrinsic factor synthesis. Without intrinsic factor, the ileum can no longer absorb the $B_{12}$.[27]

Although the exact role of *Helicobacter pylori* infection in PA remains controversial, evidence indicates *H. pylori* is involved in the pathogenesis of the disease. A long-standing *H. pylori* infection may cause gastric autoimmunity by a mechanism known as molecular mimicry. Antibodies produced by the immune system can be cross-reactive and may bind to both *H. pylori* antigens and those found in the gastric mucosa. The antibodies are produced by activated B cells that recognise both pathogen and self-derived peptides. The autoantigens believed to cause the autoreactivity are the alpha and beta subunits of the $H^+/K^+$-ATPase.[27][28]

Less commonly, *H. pylori* and Zollinger-Ellison syndrome may also cause a form of nonautoimmune gastritis that can lead to pernicious anemia.[29]

Impaired $B_{12}$ absorption can also occur following gastric removal (gastrectomy) or gastric bypass surgery. In these surgeries, either the parts of the stomach that produce gastric secretions are removed or they are bypassed. This means intrinsic factor, as well as other factors required for $B_{12}$ absorption, are not available. However, $B_{12}$ deficiency after gastric surgery does not usually become a clinical issue. This is probably because the body stores many years' worth of $B_{12}$ in the liver and gastric surgery patients are adequately supplemented with the vitamin.[30][31]

Although no specific PA susceptibility genes have been identified, a genetic factor likely is involved in the disease. Pernicious anemia is often found in conjunction with other autoimmune disorders, suggesting common autoimmune susceptibility genes may be a causative factor.[25] In spite of that, previous family studies and case reports focusing on PA have suggested that there is a tendency of genetic heritance of PA in particular, and close relatives of the PA patients seem to have higher incidence of PA and associated PA conditions.[32][33][34] Moreover, it was further indicated that the formation of antibodies to gastric cells was autosomal dominant gene determined, and the presence of antibodies to the gastric cells might not be necessarily related to the occurrence of atrophic gastritis related to PA.[32][34]

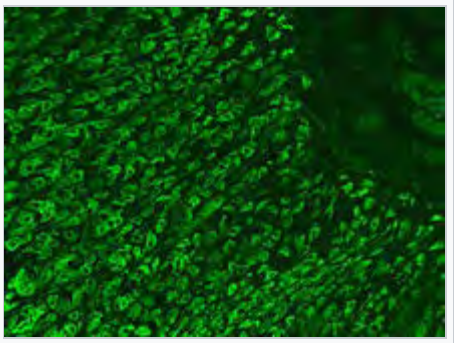
## Pathophysiology [edit]

Although the healthy body stores three to five years' worth of $B_{12}$ in the liver, the usually undetected autoimmune activity in one's gut over a prolonged period of time leads to $B_{12}$ depletion and the resulting anemia. $B_{12}$ is required by enzymes for two reactions: the conversion of methylmalonyl CoA to succinyl CoA, and the conversion of homocysteine to methionine. In the latter reaction, the methyl group of 5-methyltetrahydrofolate is transferred to homocysteine to produce tetrahydrofolate and methionine. This reaction is catalyzed by the enzyme methionine synthase with $B_{12}$ as an essential cofactor. During $B_{12}$ deficiency, this reaction cannot proceed, which leads to the accumulation of 5-methyltetrahydrofolate. This

accumulation depletes the other types of folate required for purine and thymidylate synthesis, which are required for the synthesis of DNA. Inhibition of DNA replication in red blood cells results in the formation of large, fragile megaloblastic erythrocytes. The neurological aspects of the disease are thought to arise from the accumulation of methylmalonyl CoA due to the requirement of $B_{12}$ as a cofactor to the enzyme methylmalonyl CoA mutase.[23][35][36][37]

## Diagnosis [edit]

PA may be suspected when a patient's blood smear shows large, fragile, immature erythrocytes, known as megaloblasts. A diagnosis of PA first requires demonstration of megaloblastic anemia by conducting a full blood count and blood smear, which evaluates the mean corpuscular volume (MCV), as well the mean corpuscular hemoglobin concentration (MCHC). PA is identified with a high MCV (macrocytic anemia) and a normal MCHC (normochromic anemia).[38] Ovalocytes are also typically seen on the blood smear, and a pathognomonic feature of megaloblastic anemias (which include PA and others) is hypersegmented neutrophils.[18]



Immunofluorescence staining pattern of gastric parietal cell antibodies on a stomach section

Serum vitamin $B_{12}$ levels are used to detect its deficiency, but they do not distinguish its causes. Vitamin $B_{12}$ levels can be falsely high or low and data for sensitivity and specificity vary widely. Normal serum levels may be found in cases of deficiency where myeloproliferative disorders, liver disease, transcobalamin II deficiency, or intestinal bacterial overgrowth are present. Low levels of serum vitamin $B_{12}$ may be caused by other factors than $B_{12}$ deficiency, such as folate deficiency, pregnancy, oral contraceptive use, haptocorrin deficiency, and myeloma.[39][40]

The presence of antibodies to gastric parietal cells and intrinsic factor is common in PA. Parietal cell antibodies are found in other autoimmune disorders and also in up to 10% of healthy individuals, making the test nonspecific. However, around 85% of PA patients have parietal cell antibodies, which means they are a sensitive marker for the disease. Intrinsic factor antibodies are much less sensitive than parietal cell antibodies, but they are much more specific. They are found in about half of PA patients and are very rarely found in other disorders. These antibody tests can distinguish between PA and food-$B_{12}$ malabsorption.[40] The combination of both tests of intrinsic factor antibodies and parietal cell antibodies may improve overall sensitivity and specificity of the diagnostic results.[41]

A buildup of certain metabolites occurs in $B_{12}$ deficiency due to its role in cellular physiology. Methylmalonic acid (MMA) can be measured in both the blood and urine, whereas homocysteine is only measured in the blood. An increase in both MMA and homocysteine can distinguish between $B_{12}$ deficiency and folate deficiency because only homocysteine increases in the latter.[40][42]

Elevated gastrin levels can be found in around 80-90% of PA cases, but they may also be found in other forms of gastritis. Decreased pepsinogen I levels or a decreased pepsinogen I to pepsinogen II ratio may also be found, although these findings are less specific to PA and can be found in food-$B_{12}$ malabsorption and other forms of gastritis.[42]

The diagnosis of atrophic gastritis type A should be confirmed by gastroscopy and stepwise biopsy.[43] About 90% of individuals with PA have antibodies for parietal cells; however, only 50% of all individuals in the general population with these antibodies have pernicious anemia.[44]

Forms of vitamin $B_{12}$ deficiency other than PA must be considered in the differential diagnosis of megaloblastic anemia. For example, a $B_{12}$-deficient state which causes megaloblastic anemia and which may be mistaken for classical PA may be caused by infection with the tapeworm *Diphyllobothrium latum*, possibly due to the parasite's competition with host for vitamin $B_{12}$.[45]

The classic test for PA, the Schilling test, is no longer widely used, as more efficient methods are available. This historic test consisted, in its first step, of taking an oral dose of radiolabelled vitamin $B_{12}$, followed by quantitation of the vitamin in the patient's urine over a 24-hour period via measurement of the radioactivity. A second step of the test repeats the regimen and procedure of the first step, with the addition of oral intrinsic factor. A patient with PA presents lower than normal amounts of intrinsic factor; hence, addition of intrinsic factor in the second step results in an increase in vitamin $B_{12}$ absorption (over the baseline established in the first). The Schilling test distinguished PA from other forms of $B_{12}$ deficiency,[23] specifically, from Imerslund-Grasbeck Syndrome (IGS), a vitamin B12-deficiency caused by mutations in the cobalamin receptor.[46]

## Treatment [edit]

The treatment of PA varies by country and area. Opinions vary over the efficacy of administration (parenteral/oral), the amount and time interval of the doses, or the forms of vitamin $B_{12}$ (e.g. cyanocobalamin/hydroxocobalamin). More comprehensive studies are still needed in order to validate the feasibility of a particular therapeutic method for PA in clinical practices. A permanent cure for PA is lacking, although repletion of $B_{12}$ should be expected to result in cessation of anemia-related symptoms, a halt in neurological deterioration, and in cases where neurological problems are not advanced, neurological recovery and a complete and permanent remission of all symptoms, so long as $B_{12}$ is supplemented. Repletion of $B_{12}$ can be accomplished in a variety of ways.

Hydroxocobalamin injection usp(1000 mcg/ml) is a clear red liquid solution of hydoxocobalamin which is available in a 30-ml brown glass multidose vial packaged in a paper box. Shown is 500 mcg B-12 (as 1/2 cc) drawn up in a 0.5-cc U-100 27 gauge x 1/2" insulin syringe, as prepared for subcutaneous injection.

### Intramuscular injections [edit]

The standard treatment for PA has been intramuscular injections of cobalamin in the form of cyanocobalamin (CN-Cbl) and hydroxocobalamin (OH-Cbl).[47]

### Oral doses [edit]

Treatment with high-dose vitamin $B_{12}$ by mouth also appears effective.[47][48][49]

## Prognosis [edit]

A person with well-treated PA can live a healthy life. Failure to diagnose and treat in time, however, may result in permanent neurological damage, excessive fatigue, depression, memory loss, and other complications. In severe cases, the neurological complications of pernicious anemia can lead to death - hence the name, "pernicious", meaning deadly.

An association has been observed between pernicious anemia and certain types of gastric cancer, but a causal link has not been established.[27]

## Epidemiology [edit]

PA is estimated to affect 0.1% of the general population and 1.9% of those over 60, accounting for 20–50% of $B_{12}$ deficiency in adults.[1] A review of literature shows that the prevalence of PA is higher in Northern Europe, especially in Scandinavian countries, and among people of African descent, and that

increased awareness of the disease and better diagnostic tools might play a role in apparently higher rates of incidence.[50]

## History [edit]

The symptoms are first described in 1822 by Dr James Scarth Combe in the *Transactions of the Medico-Chirurgical Society of Edinburgh*, under the title of *History of a Case of Anaemia*.[51]

However, this was not investigated in more depth until 1849, by British physician Thomas Addison, from which it acquired the common name of Addison's anemia. In 1871, German physician Michael Anton Biermer (1827–1892) noticed the particular characteristic of the anemia in one of his patients; he later coined the term "progressive pernicious anemia".[52][*better source needed*] In 1907, Richard Clarke Cabot reported on a series of 1200 patients with PA; their average survival was between one and three years.[*citation needed*] William Bosworth Castle performed an experiment whereby he ingested raw hamburger meat and regurgitated it after an hour, and subsequently fed it to a group of 10 patients.[53][*full citation needed*] Untreated raw hamburger meat was fed to the control group. The former group showed a disease response, whereas the latter group did not. This was not a sustainable practice, but it demonstrated the existence of an 'intrinsic factor' from gastric juice.

Pernicious anemia was a fatal disease before about the year 1920, when George Whipple suggested raw liver as a treatment.[*citation needed*] The first workable treatment for pernicious anemia began when Whipple made a discovery in the course of experiments in which he bled dogs to make them anemic, then fed them various foods to see which would make them recover most rapidly (he was looking for treatments for anemia from bleeding, not pernicious anemia). Whipple discovered ingesting large amounts of liver seemed to cure anemia from blood loss, and tried liver ingestion as a treatment for pernicious anemia, reporting improvement there, also, in a paper in 1920.[*citation needed*] George Minot and William Murphy then set about to partly isolate the curative property in liver, and in 1926 showed it was contained in raw liver juice (in the process also showing it was the iron in liver tissue, not the soluble factor in liver juice, which cured the anemia from bleeding in dogs); thus, the discovery of the liver juice factor as a treatment for pernicious anemia had been by coincidence.[*citation needed*] Frieda Robscheit-Robbins worked closely with Whipple, co-authoring 21 papers from 1925-30.[*citation needed*] For the discovery of the cure of a previously fatal disease of unknown etiology, Whipple, Minot, and Murphy shared the 1934 Nobel Prize in Medicine.[54][*full citation needed*]

After Minot and Murphy's verification of Whipple's results in 1926, pernicious anemia victims ate or drank at least one-half pound of raw liver, or drank raw liver juice, every day.[*citation needed*] This continued for several years, until a concentrate of liver juice became available. In 1928, chemist Edwin Cohn prepared a liver extract that was 50 to 100 times more potent than the natural food (liver).[*citation needed*] The extract could even be injected into muscle, which meant patients no longer needed to eat large amounts of liver or juice. This also reduced the cost of treatment considerably.[*citation needed*]

The active ingredient in liver remained unknown until 1948, when it was isolated by two chemists, Karl A. Folkers of the United States and Alexander R. Todd of Great Britain.[*citation needed*] The substance was a cobalamin, which the discoverers named vitamin $B_{12}$. The new vitamin in liver juice was eventually completely purified and characterized in the 1950s, and other methods of producing it from bacteria were developed.[*citation needed*] It could be injected into muscle with even less irritation, making it possible to treat PA with even more ease.[*citation needed*] Pernicious anemia was eventually treated with either injections or large oral doses of $B_{12}$, typically between 1 and 4 mg daily.[*citation needed*]

One writer has hypothesized that Mary Todd Lincoln, the wife of American President Abraham Lincoln, had pernicious anemia for decades and died from it.[55][56]

## Research [edit]

## SNAC complex [edit]

Although oral megadoses and intramuscular injections are the most common methods of treatment currently available, several novel methods are being tested, with high promise for future incorporation into mainstream treatment methods. As injections are unfavourable vehicles for drug delivery, current research involves improving the passive diffusion across the ileum upon oral ingestion of cobalamin derivatives. Researchers have recently taken advantage of the novel compound sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (SNAC), which greatly enhances both bioavailability and metabolic stability.[57] SNAC is able to form a noncovalent complex with cobalamin while preserving its chemical integrity.[*citation needed*] This complex is much more lipophilic than the water-soluble vitamin $B_{12}$, so is able to pass through cellular membranes with greater ease.

## Recombinant intrinsic factor [edit]

Another method for increasing absorption through the ileum is to ingest a Cbl complex to which IF is already bound. The lack of intrinsic factor produced by the patient's body can be supplemented by using synthetic human IF produced from pea plant recombinants.[58] However, in cases where IF-antibodies are the reason for malabsorption across the ileum, this treatment would be ineffective.

## Sublingual/intranasal delivery [edit]

Sublingual treatments have also been postulated to be more effective than oral treatments alone. A 2003 study[59] found, while this method is effective, a dose of 500 µg of cyanocobalamin given either orally or sublingually, is equally efficacious in restoring normal physiological concentrations of cobalamin. Intranasal methods have also been studied as a vehicle for the delivery of cobalamin. A 1997 study[60] monitored the plasma cobalamin concentration of six patients with pernicious anemia over a period of 35 days while being treated with 1500 µg of intranasal hydroxocobalamin. One hour after administration, all patients showed on average an immediate eight-fold increase in plasma cobalamin concentration and a two-fold increase after 35 days with three 1500 µg treatments. However, further studies are needed to investigate the long-term effectiveness of this delivery method.

## Exploratory treatments [edit]

One exploratory, and potential alternative method for the treatment of pernicious anemia is the use of transdermal patches. In one such system, the patches are composed of cyanocobalamin, its stabilizers, and epidermal penetration enhancers.[61][*self-published source?*][*better source needed*] The transdermal route allows the cobalamin derivative to passively diffuse through the stratum corneum, epidermis, and dermis, and ultimately entering the bloodstream; hence, the cobalamin avoids the hepatic first pass effect, and so offers the potential for improved bioavailability and efficacy.[*according to whom?*][*citation needed*] Slow release increases cobalamin half-life, offering the potential of decreases in required dosage required relative to oral delivery methods.[*according to whom?*][*citation needed*] In one such system, a drug-loaded polycaprolactone fiber that is prepared as a electrospun nanofiber can release hundreds of micrograms of cobabalmin per day.[62][*non-primary source needed*]

# References [edit]


1. ^ *a b c d* Andres E, Serraj K (2012). "Optimal management of pernicious anemia.". *Journal of Blood Medicine*. **3**: 97–103. doi:10.2147/JBM.S25620. PMC 3441227. PMID 23028239.
2. ^ *a b* *Professional guide to diseases.* (9 ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. 2009. p. 502. ISBN 9780781778992.
3. ^ Forbis, Pat (2005). *Stedman's medical eponyms* (2nd ed.). Baltimore, Md.: Lippincott Williams & Wilkins. p. 6. ISBN 9780781754439.
4. ^ "ICD-10 Version:2015". *apps.who.int*. Retrieved 2015-11-13.
5. ^ *a b c d e* "What Is Pernicious Anemia?". *NHLBI*. April 1, 2011. Retrieved 14 March 2016.

6. ^ "What Are the Signs and Symptoms of Pernicious Anemia?". *NHLBI*. April 1, 2011. Retrieved 14 March 2016.
7. ^ "What Causes Pernicious Anemia?". *NHLBI*. April 1, 2011. Retrieved 14 March 2016.
8. ^ "How Is Pernicious Anemia Diagnosed?". *NHLBI*. April 1, 2011. Retrieved 14 March 2016.
9. ^ "How Can Pernicious Anemia Be Prevented?". *NHLBI*. April 1, 2011. Retrieved 14 March 2016.
10. ^ "How Is Pernicious Anemia Treated?". *NHLBI*. April 1, 2011. Retrieved 14 March 2016.
11. ^ *a b* "Living With Pernicious Anemia". *NHLBI*. April 1, 2011. Retrieved 14 March 2016.
12. ^ Greer, John P. (2009). *Wintrobe's clinical hematology.* (12th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 1157. ISBN 9780781765077.
13. ^ Wailoo, Keith (1999). "The Corporate "Conquest" of Pernicious Anemia". *Drawing blood technology and disease identity in twentieth-century America* (Johns Hopkins Paperbacks ed.). Baltimore, Md.: Johns Hopkins University Press. p. Chapter 4. ISBN 9780801870293.
14. ^ *Dictionary of Medicine*. Routledge. 2014. p. 404. ISBN 9781135928414.
15. ^ Tamparo, Carol (2016). *Diseases of the Human Body*. F.A. Davis. p. 295. ISBN 9780803657915.
16. ^ In 20% of cases of cobalamin deficiency, anemia is not observed.
17. ^ *a b c d e* Schick, P.; Conrad, Marcel E. & Besa, Emmanuel C. (ed.) (2015-08-15). "Pernicious Anemia, Clinical Presentation". *Medscape*. Retrieved 21 January 2013.
18. ^ *a b c d e f* Means, Robert T. Jr. & Glader, Bertil (2009). "Anemia: General Considerations (Chapter 26)". In Greer, J.P.; Foerster, J.; Rodgers, G.M.; Paraskevas, F.; Glader, B.; Arber, D.A. & Means Jr., R.T. *Wintrobe's Clinical Hematology, Volume One* (12th ed.). Philadelphia, PA, USA: Wolters Kluwer/Lippincott Williams & Wilkins. pp. 779–809, esp. 782. ISBN 0781765072. Retrieved 10 March 2016.
19. ^ *a b c d e* Ramani, James Carton, Richard Daly, Pramila (2007). *Clinical pathology*. Oxford, ENG: Oxford University Press. ISBN 0198569467.[*page needed*]
20. ^ *a b c* Turgeon, Mary L. (2005). *Clinical hematology : theory and procedures* (4th ed.). Philadelphia: Lippincott Williams & Wilkins. ISBN 0781750075.[*page needed*]
21. ^ *a b* Hvas AM, Nexo E (November 2006). "Diagnosis and treatment of vitamin B12 deficiency—an update.". *Haematologica*. **91** (11): 1506–12. PMID 17043022.
22. ^ Gersten, Todd & VeriMed Healthcare Network (2016). Zieve, David; Ogilvie, Isla & A.D.A.M. Editorial team, eds. "Pernicious anemia". *MedlinePlus Medical Encyclopedia*. Washington, DC: nlm.nih.gov. Retrieved 11 March 2016.
23. ^ *a b c* Wickramasinghe, SN (November 2006). "Diagnosis of megaloblastic anaemias.". *Blood reviews*. **20** (6): 299–318. doi:10.1016/j.blre.2006.02.002. PMID 16716475.
24. ^ Christensen EI, Birn H (April 2002). "Megalin and cubilin: multifunctional endocytic receptors". *Nat. Rev. Mol. Cell Biol*. **3** (4): 256–66. doi:10.1038/nrm778. PMID 11994745.
25. ^ *a b c* Banka S, Ryan K, Thomson W, Newman WG (June 2011). "Pernicious anemia – genetic insights.". *Autoimmunity reviews*. **10** (8): 455–9. doi:10.1016/j.autrev.2011.01.009. PMID 21296191.
26. ^ De Block CE, De Leeuw IH, Van Gaal LF (February 2008). "Autoimmune gastritis in type 1 diabetes: a clinically oriented review.". *The Journal of Clinical Endocrinology and Metabolism*. **93** (2): 363–71. doi:10.1210/jc.2007-2134. PMID 18029461.
27. ^ *a b c* Lahner E, Annibale B (November 2009). "Pernicious anemia: New insights from a gastroenterological point of view". *World J. Gastroenterol*. **15** (41): 5121–8. doi:10.3748/wjg.15.5121. PMC 2773890. PMID 19891010.
28. ^ Desai HG, Gupte PA (December 2007). "Helicobacter pylori link to pernicious anaemia.". *The Journal of the Association of Physicians of India*. **55**: 857–9. PMID 18405134.
29. ^ Kaferle J, Strzoda CE (Feb 1, 2009). "Evaluation of macrocytosis.". *American family physician*. **79** (3): 203–8. PMID 19202968.
30. ^ von Drygalski A, Andris DA (Apr–May 2009). "Anemia after bariatric surgery: more than just iron deficiency.". *Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition*. **24** (2): 217–26. doi:10.1177/0884533609332174. PMID 19321896.
31. ^ John S, Hoegerl C (November 2009). "Nutritional deficiencies after gastric bypass surgery.". *The Journal of the American Osteopathic Association*. **109** (11): 601–4. PMID 19948694.
32. ^ *a b* Whttingham S., Ungar B., Mackay I. R., Mathews J. D. (1969). "The Genetic Factor in Pernicious Anemia. A Family Study in Patients with Gastritis". *The Lancet*. **1** (7602): 951–954.
33. ^ McIntyre O. R., Sullivan L. W., Jeffries G. H., Silver R. H. (1965). "Pernicious Anemia in Childhood". *The New England Journal of Medicine*. **272**: 981–986. doi:10.1056/nejm196505132721901.
34. ^ *a b* Wangel A. G., Callender S. T., Spray G. H., Wright R. (1968). "A Family Study of Pernicious Anemia II. Intrinsic Factor Secretion, Vitamin B12 Absorption and Genetic Aspects of Gastric Autoimmunity". *British Journal of Haematology*. **14** (2): 183–204. doi:10.1111/j.1365-2141.1968.tb01486.x.
35. ^ Oh R, Brown DL (Mar 1, 2003). "Vitamin B12 deficiency.". *American family physician*. **67** (5): 979–86.

PMID 12643357.
36. ^ O'Leary F, Samman S (March 2010). "Vitamin B12 in health and disease.". *Nutrients*. **2** (3): 299–316. doi:10.3390/nu2030299. PMC 3257642. PMID 22254022.
37. ^ Stover, PJ (June 2004). "Physiology of folate and vitamin B12 in health and disease.". *Nutrition Reviews*. **62** (6 Pt 2): S3–12; discussion S13. doi:10.1111/j.1753-4887.2004.tb00070.x. PMID 15298442.
38. ^ Pagana, Timothy James; Pagana, Kathleen Deska (2006). *Mosby's manual of diagnostic and laboratory tests*. Mosby Elsevier. ISBN 0-323-03903-0.[*page needed*]
39. ^ Devalia V (August 2006). "Diagnosing vitamin B-12 deficiency on the basis of serum B-12 assay". *BMJ*. **333** (7564): 385–6. doi:10.1136/bmj.333.7564.385. PMC 1550477. PMID 16916826.
40. ^ [a] [b] [c] Snow, CF (Jun 28, 1999). "Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician". *Archives of Internal Medicine*. **159** (12): 1289–98. doi:10.1001/archinte.159.12.1289. PMID 10386505.
41. ^ Grasbeck R (2006). "Imerslund-Grasbeck syndrome (selective vitamin B12 malabsorption with proteinuria)". *Orphanet Journal of Rare Diseases*. **1** (1): 17.
42. ^ [a] [b] Moridani, Majid; Shana Ben-Poorat (March 2006). "Laboratory Investigation of Vitamin B12 Deficiency". *LabMedicine*. **37** (3): 166–74. doi:10.1309/cvhkle2r4w68k2nq.
43. ^ Miederer, S.E. (1977). *The Histotopography of the Gastric Mucosa.* Thieme, ISBN 3-13-508601-1
44. ^ Butler CC, Vidal-Alaball J, Cannings-John R, et al. (June 2006). "Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials". *Family Practice*. **23** (3): 279–85. doi:10.1093/fampra/cml008. PMID 16585128.
45. ^ Ramakrishnan, edited by Usha (2000). *Nutritional anemias*. Boca Raton: CRC Press. ISBN 0849385695.
46. ^ Andres E., Serra K. (2012). "Optimal management of pernicious anemia". *Journal of Blood Medicine*. **3**: 97–103.
47. ^ [a] [b] Andrès, E.; Fothergill, H.; Mecili, M. (2010). "Efficacy of oral cobalamin (vitamin B12) therapy". *Expert Opinion on Pharmacotherapy*. **11** (2): 249–256. doi:10.1517/14656560903456053. PMID 20088746.
48. ^ Andrès, E.; Dali-Youcef, N.; Vogel, T.; Serraj, K.; Zimmer, J. (2009). "Oral cobalamin (vitamin B12) treatment. An update". *International Journal of Laboratory Hematology*. **31**: 1–8. doi:10.1111/j.1751-553X.2008.01115.x.
49. ^ Carmel, R. (7 July 2008). "How I treat cobalamin (vitamin B12) deficiency". *Blood*. **112** (6): 2214–2221. doi:10.1182/blood-2008-03-040253. PMC 2532799. PMID 18606874.
50. ^ Stabler S. P., Allen R. H. (2004). "Vitamin B12 deficiency as a worldwide problem". *Annual Review of Nutrition*. **24** (1): 299–326. doi:10.1146/annurev.nutr.24.012003.132440. PMID 15189123.
51. ^ "History of Leith, Edinburgh". *leithhistory.co.uk*. Retrieved 11 March 2016.
52. ^ Enersen, Ole Daniel (2016). "Whonamedit Dictionary of Medical Eponyms". *whonamedit.com*. Retrieved 11 March 2016.[*better source needed*]
53. ^ William B. Castle 1897–1990 A Biographical Memoir by James H. Jandl Copyright 1995 National Academies Press Washington D.C.[*full citation needed*]
54. ^ Nobel Prize archive. "The Nobel Prize in Physiology or Medicine 1934" (Nobelprize.org). Retrieved 2012-08-05.[*full citation needed*]
55. ^ John G. Sotos, *The Mary Lincoln Mind-Body Sourcebook: Including a Unifying Diagnosis to Explain Her Public Decay, Manifest Insanity, and Slow Death* (Mt. Vernon, VA: Mt. Vernon Book Systems, 2016) ISBN 978-0-9818193-8-9
56. ^ John G. Sotos, *What an Affliction* -- Mary Todd Lincoln's Fatal Pernicious Anemia. Perspectives in Biology and Medicine. 2015; 58: 419-443.
57. ^ Castelli, M. C.; Wong, D. F.; Friedman, K.; Riley, M. G. I. (2011). "Pharmacokinetics of Oral Cyanocobalamin Formulated with Sodium N-\8-(2-hydroxybenzoyl)amino]caprylate (SNAC): An Open-Label, Randomized, Single-Dose, Parallel-Group Study in Healthy Male Subjects". *Clinical Therapeutics*. **33** (7): 934–945. doi:10.1016/j.clinthera.2011.05.088. PMID 21722960.
58. ^ Fedosov, S. N.; Laursen, N. B.; Nexo, E.; Moestrup, S. K.; Petersen, T. E.; Jensen, E. O.; Berglund, L. (2003). "Human intrinsic factor expressed in the plant Arabidopsis thaliana". *European Journal of Biochemistry*. **270** (16): 3362–3367. doi:10.1046/j.1432-1033.2003.03716.x. PMID 12899693.
59. ^ Sharabi, A.; Cohen, E.; Sulkes, J.; Garty, M. (2003). "Replacement therapy for vitamin B12 deficiency: Comparison between the sublingual and oral route". *British Journal of Clinical Pharmacology*. **56** (6): 635–638. doi:10.1046/j.1365-2125.2003.01907.x. PMC 1884303. PMID 14616423.
60. ^ Slot WB, Merkus FW, Van Deventer SJ, Tytgat GN (August 1997). "Normalization of plasma vitamin B12 concentration by intranasal hydroxocobalamin in vitamin B12-deficient patients". *Gastroenterology*. **113** (2): 430–3. doi:10.1053/gast.1997.v113.pm9247460. PMID 9247460.
61. ^ Zeltman, Jon D. (2015-01-27). "Patent US20080233180 - Transdermal Patch and Method For Delivery Of Vitamin B12". *google.com*. Retrieved 11 March 2016. "Priority date, 2007-03-19."

62. ^ Madhaiyan, K.; Sridhar, R.; Sundarrajan, S.; Venugopal, J. R.; Ramakrishna, S. (2013). "Vitamin B12 Loaded Polycaprolactone Nanofibers: A Novel Transdermal Route for the Water Soluble Energy Supplement Delivery". *International Journal of Pharmaceutics*. **444** (1–2): 70–76. doi:10.1016/j.ijpharm.2013.01.040. PMID 23370432. [*non-primary source needed*]

## External links [edit]

- Vitamin B12 deficiency anemia at DMOZ

| v · t · e · | Diseases of red blood cells (D50–69,74, 280–287) | | |
|---|---|---|---|
| ↑ | **Polycythemia** | Polycythemia vera · | |
| ↓ | **Anemia** | **Nutritional** | Micro-: Iron-deficiency anemia (Plummer–Vinson syndrome · · Macro-: Megaloblastic anemia (Pernicious anemia · · |
| | | **Hemolytic (mostly normo-)** | **Hereditary**: *enzymopathy:* G6PD · *glycolysis* (PK · TI · HK · · *hemoglobinopathy:* Thalassemia (alpha · beta · delta · · Sickle-cell disease/trait · HPFH · *membrane:* Hereditary spherocytosis (Minkowski–Chauffard syndrome · · Hereditary elliptocytosis (Southeast Asian ovalocytosis · · Hereditary stomatocytosis · |
| | | | **Acquired**: Autoimmune (WAHA · CAD · PCH · · *membrane* (PNH · · MAHA · TM (HUS · · Drug-induced autoimmune · Drug-induced nonautoimmune · Hemolytic disease of the newborn · |
| | | **Aplastic (mostly normo-)** | Hereditary: Fanconi anemia · Diamond–Blackfan anemia · Acquired: PRCA · Sideroblastic anemia · Myelophthisic · |
| | | **Blood tests** | *MCV* (Normocytic · Microcytic · Macrocytic · · *MCHC* (Normochromic · Hypochromic · · |
| | **Other** | Methemoglobinemia · Sulfhemoglobinemia · Reticulocytopenia · | |

| v · t · e · | Hypersensitivity and autoimmune diseases (279.5–6) | | |
|---|---|---|---|
| **Type I / allergy / atopy (IgE)** | **Foreign** | Atopic eczema · Allergic urticaria · Allergic rhinitis (Hay fever) · Allergic asthma · Anaphylaxis · Food allergy (common allergies include: Milk · Egg · Peanut · Tree nut · Seafood · Soy · Wheat · · Penicillin allergy · | |
| | **Autoimmune** | Eosinophilic esophagitis · | |
| **Type II / ADCC (IgM · IgG · ·** | **Foreign** | Hemolytic disease of the newborn · | |
| | **Autoimmune** | **Cytotoxic** | Autoimmune hemolytic anemia · Immune thrombocytopenic purpura · Bullous pemphigoid · Pemphigus vulgaris · Rheumatic fever · Goodpasture's syndrome · Guillain–Barré syndrome · |

| | | | |
|---|---|---|---|
| | | **"Type V"/receptor** | Graves' disease · Myasthenia gravis · Pernicious anemia · |
| **Type III (Immune complex)** | **Foreign** | | Henoch–Schönlein purpura · Hypersensitivity vasculitis · Reactive arthritis · Farmer's lung · Post-streptococcal glomerulonephritis · Serum sickness · Arthus reaction · |
| | **Autoimmune** | | Systemic lupus erythematosus · Subacute bacterial endocarditis · Rheumatoid arthritis · |
| **Type IV/cell-mediated (T cells)** | **Foreign** | | Allergic contact dermatitis · Mantoux test · |
| | **Autoimmune** | | Diabetes mellitus type 1 · Hashimoto's thyroiditis · Multiple sclerosis · Coeliac disease · Giant-cell arteritis · Postorgasmic illness syndrome · Reactive arthritis · |
| | **GVHD** | | Transfusion-associated graft versus host disease · |
| **Unknown/ multiple** | **Foreign** | | Hypersensitivity pneumonitis (Allergic bronchopulmonary aspergillosis · · Transplant rejection · Latex allergy (I+IV) · |
| | **Autoimmune** | | Sjögren's syndrome · Autoimmune hepatitis · Autoimmune polyendocrine syndrome (APS1 · APS2 · · Autoimmune adrenalitis · Systemic autoimmune disease · |

Categories: Hematopathology | Nutritional anemias

# Ulcerative colitis

From Wikipedia, the free encyclopedia

**Ulcerative colitis** (**UC**) is a long-term condition that results in inflammation and ulcers of the colon and rectum.[1][2] The primary symptom of active disease is abdominal pain and diarrhea, mixed with blood. Weight loss, fever, and anemia may also occur. Often symptoms come on slowly and can range from mild to severe. Symptoms typically occur intermittently with periods of no symptoms between flares.[1] Complications may include megacolon, inflammation of the eye, joints, or liver, and colon cancer.[1][3]

The cause of UC is unknown.[1] Theories involve immune system dysfunction, genetics, changes in the normal gut bacteria, and environmental factors.[1][4] Rates tend to be higher in the developed world with some proposing this to be the result of less exposure to intestinal infections, or a Western diet and lifestyle.[2][5] The removal of the appendix at an early age may be protective.[5] Diagnosis is typically by colonoscopy with tissue biopsies. It is a kind of inflammatory bowel disease (IBD) along with Crohn's disease and microscopic colitis.[1]

Dietary changes may improve symptoms. A number of medications are used to treat symptoms and bring about and maintain remission. These include aminosalicylates such as sulfasalazine, steroids, immunosuppressants such as azathioprine, and biological therapy. Removal of the colon by surgery may be necessary if the disease is severe, does not respond to treatment, or if complications such as colon cancer develop.[1] Removal of the colon and rectum can cure the disease.[1][5]

The first description of ulcerative colitis occurred around the 1850s.[5] Each year it newly occurs in 1 to 20 people per 100,000 and 5 to 500 per 100,000 individuals are affected.[2][5] The disease is more common in North America and Europe.[5] Often it begins between 15 and 30 years of age or among those over 60.[1] Males and females appear to be affected equally.[2] It has also become more common since the 1950s.[2][5] Together, ulcerative colitis and Crohn's disease affect approximately 500,000 to 2 million people in the United States.[6] With appropriate treatment the risk of death appears the same as that of the general population.[3]

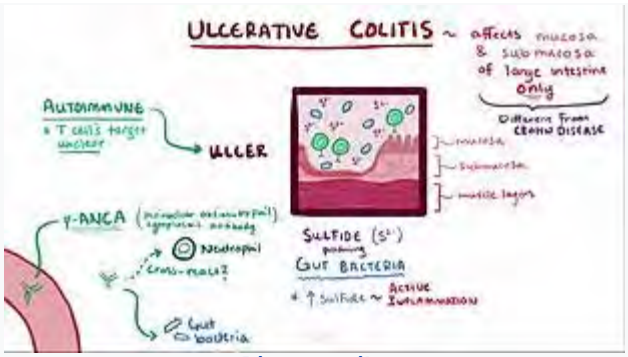
## Variants

Endoscopic image of a colon affected by ulcerative colitis. The internal surface of the colon is blotchy and broken in places.

| Classification and external resources | |
|---|---|
| **Specialty** | gastroenterology |
| **ICD-10** | K51 |
| **ICD-9-CM** | 556 |
| **OMIM** | 191390 |
| **DiseasesDB** | 13495 |
| **MedlinePlus** | 000250 |
| **eMedicine** | med/2336 |
| **Patient UK** | Ulcerative colitis |
| **MeSH** | D003093 |

[edit on Wikidata]

Contents




Play media

Video explanation

# Signs and symptoms [edit]

## Gastrointestinal [edit]

**Signs and symptoms**

| | Crohn's disease | Ulcerative colitis |
|---|---|---|
| Defecation | Often porridge-like,[7] sometimes steatorrhea | Often mucus-like and with blood[7] |
| Tenesmus | Less common[7] | More common[7] |
| Fever | Common[7] | Indicates severe disease[7] |
| Fistulae | Common[8] | Seldom |
| Weight loss | Often | More seldom |

The clinical presentation[9] of ulcerative colitis depends on the extent of the disease process. Patients usually present with diarrhea mixed with blood and mucus, of gradual onset that persists for an extended period (weeks). They may also have weight loss and blood on rectal examination. The inflammation caused by the disease along with the chronic blood from the GI tract leads to increased rates of anemia. The disease may be accompanied by different degrees of abdominal pain, from mild discomfort to painful bowel movements or painful abdominal cramping with bowel movements.

Ulcerative colitis is associated with a general inflammatory process that affects many parts of the body. Sometimes these associated extra-intestinal symptoms are the initial signs of the disease, such as painful arthritic knees in a teenager and may be seen in adults also. The presence of the disease may not be confirmed immediately, however, until the onset of intestinal manifestations.

## Extent of involvement [edit]

Ulcerative colitis is normally continuous from the rectum up the colon. The disease is classified by the extent of involvement, depending on how far up the colon the disease extends:

- *Distal colitis*, potentially treatable with enemas:[10]
  - *Proctitis*: Involvement limited to the rectum.
  - *Proctosigmoiditis*: Involvement of the rectosigmoid colon, the portion of the colon adjacent to the rectum.
  - *Left-sided colitis*: Involvement of the descending colon, which runs along the patient's left side, up to the splenic flexure and the beginning of the transverse colon.
- *Extensive colitis*, inflammation extending beyond the reach of enemas:
  - *Pancolitis*: Involvement of the entire colon, extending from the rectum to the cecum, beyond which the small intestine begins.

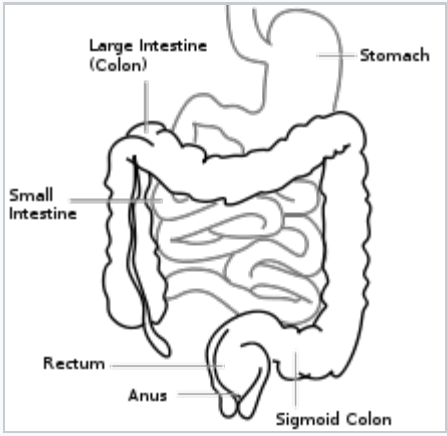


Diagram of the human intestine

## Severity of disease [edit]

In addition to the extent of involvement, people may also be characterized by the severity of their disease.[10]

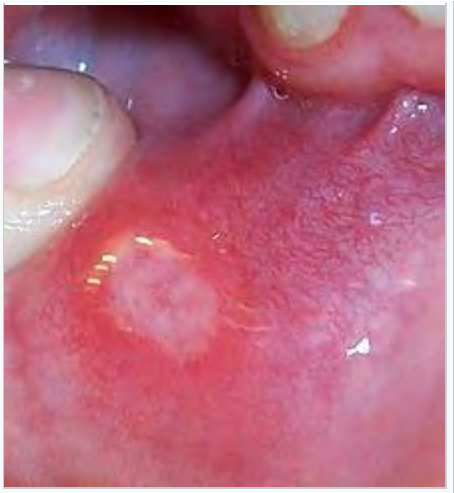

Colonic pseudopolyps of a patient with intractable ulcerative colitis. Colectomy specimen.

- *Mild disease* correlates with fewer than four stools daily, with or without blood, no systemic signs of toxicity, and a normal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). There may be mild abdominal pain or cramping. Patients may believe they are constipated when in fact they are experiencing tenesmus, which is a constant feeling of the need to empty the bowel accompanied by involuntary straining efforts, pain, and cramping with little or no fecal output. Rectal pain is uncommon.
- *Moderate disease* correlates with more than four stools daily, but with minimal signs of toxicity. Patients may display anemia (not requiring transfusions), moderate abdominal pain, and low grade fever, 38 to 39 °C (100 to 102 °F).
- *Severe disease*, correlates with more than six bloody stools a day or observable massive and significant bloody bowel movement, and evidence of toxicity as demonstrated by fever, tachycardia, anemia or an elevated ESR or CRP.
- *Fulminant disease* correlates with more than ten bowel movements daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement and colonic dilation (expansion). Patients in this category may have inflammation extending beyond just the mucosal layer, causing impaired colonic motility and leading to toxic megacolon. If the serous membrane is involved, a colonic perforation may ensue. Unless treated, the fulminant disease will soon lead to death.

## Extraintestinal features [edit]

As ulcerative colitis is believed to have a systemic (i.e., autoimmune) origin, patients may present with comorbidities leading to symptoms and complications outside the colon. The frequency of such extraintestinal manifestations has been reported as anywhere between 6 and 47 percent.[11] These include the following:

- Aphthous ulcer of the mouth
- Ophthalmic
  - Iritis or uveitis, which is inflammation of the eye's iris
  - Episcleritis
- Musculoskeletal:
  - Seronegative arthritis, which can be a large-joint oligoarthritis (affecting one or two joints), or may affect many small joints of



Patients with ulcerative colitis can occasionally have aphthous ulcers involving the tongue, lips, palate and pharynx

the hands and feet
    - Ankylosing spondylitis, arthritis of the spine
    - Sacroiliitis, arthritis of the lower spine
- Cutaneous (related to the skin):
    - Erythema nodosum, which is a panniculitis, or inflammation of subcutaneous tissue involving the lower extremities
    - Pyoderma gangrenosum, which is a painful ulcerating lesion involving the skin
- Deep venous thrombosis and pulmonary embolism
- Autoimmune hemolytic anemia
- Clubbing, a deformity of the ends of the fingers.
- Primary sclerosing cholangitis, a distinct disease that causes inflammation of the bile ducts

## Causes [edit]

There are no direct known causes for ulcerative colitis, but there are many possible factors such as genetics and stress.

### Genetic factors [edit]

A genetic component to the etiology of ulcerative colitis can be hypothesized based on the following:[12]

- Aggregation of ulcerative colitis in families.
- Identical twin concordance rate of 10% and dizygotic twin concordance rate of 3%[13]
- Ethnic differences in incidence
- Genetic markers and linkages

There are 12 regions of the genome that may be linked to ulcerative colitis, including, in the order of their discovery, chromosomes 16, 12, 6, 14, 5, 19, 1, and 3,[14] but none of these loci have been consistently shown to be at fault, suggesting that the disorder arises from the combination of multiple genes. For example, chromosome band 1p36 is one such region thought to be linked to inflammatory bowel disease.[15]

Some of the putative regions encode transporter proteins such as OCTN1 and OCTN2. Other potential regions involve cell scaffolding proteins such as the MAGUK family. There may even be human leukocyte antigen associations at work. In fact, this linkage on chromosome 6 may be the most convincing and consistent of the genetic candidates.[14]

Multiple autoimmune disorders have been recorded with the neurovisceral and cutaneous genetic porphyrias including ulcerative colitis, Crohn's disease, celiac disease, dermatitis herpetiformis, diabetes, systemic and discoid lupus, rheumatoid arthritis, ankylosing spondylitis, scleroderma, Sjogren's disease and scleritis. Physicians should be on high alert for porphyrias in families with autoimmune disorders and care must be taken with potential porphyrinogenic drugs, including sulfasalazine.

## Environmental factors [edit]

Many hypotheses have been raised for environmental contributants to the pathogenesis of ulcerative colitis. They include the following:

- Diet: as the colon is exposed to many dietary substances which may encourage inflammation, dietary factors have been hypothesized to play a role in the pathogenesis of both ulcerative colitis and Crohn's disease. There have been few studies to investigate such an association, one study showed no association of refined sugar on the prevalence of ulcerative colitis.[16] High intake of unsaturated fat and vitamin B6 may enhance the risk of developing ulcerative colitis.[17] Other identified dietary factors that may influence the development and/or relapse of the disease include meat protein and alcoholic beverages.[18][19] Specifically, sulfur has been investigated as being involved in the etiology of ulcerative colitis, but this is controversial.[20] Sulfur restricted diets have been investigated in patients with UC and animal models of the disease. The theory of sulfur as an etiological factor is related to the gut microbiota and mucosal sulfide detoxification in addition to the diet.[21][22][23]
- Breastfeeding: There have been conflicting reports of the protection of breastfeeding in the development of inflammatory bowel disease. One Italian study showed a potential protective effect.[24]
- One study of isotretinoin found a small increased in the rate of ulcerative colitis.[25]

## Autoimmune disease [edit]

Ulcerative colitis is an autoimmune disease characterized by T-cells infiltrating the colon.[26] In contrast to Crohn's disease, which can affect areas of the gastrointestinal tract outside of the colon, ulcerative colitis usually involves the rectum and is confined to the colon, with occasional involvement of the ileum. This so-called "backwash ileitis" can occur in 10–20% of patients with pancolitis and is believed to be of little clinical significance.[27] Ulcerative colitis can also be associated with comorbidities that produce symptoms in many areas of the body outside the digestive system. Surgical removal of the large intestine often cures the disease.[10]

## Alternative theories [edit]

Levels of sulfate-reducing bacteria tend to be higher in persons with ulcerative colitis. This could mean that there are higher levels of hydrogen sulfide in the intestine. An alternative theory suggests that the symptoms of the disease may be caused by toxic effects of the hydrogen sulfide on the cells lining the intestine.[30]

**Risk factors**

| | Crohn's disease | Ulcerative colitis |
|---|---|---|
| Smoking | Higher risk for smokers | Lower risk for smokers[28] |
| Age | Usual onset between 15 and 30 years[29] | Peak incidence between 15 and 25 years |

# Pathophysiology [edit]

An increased amount of colonic sulfate-reducing bacteria has been observed in some patients with ulcerative colitis, resulting in higher concentrations of the toxic gas hydrogen sulfide. Human colonic mucosa is maintained by the colonic epithelial barrier and immune cells in the lamina propria (see intestinal mucosal barrier). N-butyrate, a short-chain fatty acid, gets oxidized through the beta oxidation pathway into carbon dioxide and ketone bodies. It has been shown that N-butyrate helps supply nutrients to this epithelial barrier. Studies have proposed that hydrogen sulfide plays a role in impairing this beta-oxidation pathway by interrupting the short chain acetyl-CoA dehydrogenase, an enzyme within the

**Pathophysiology**

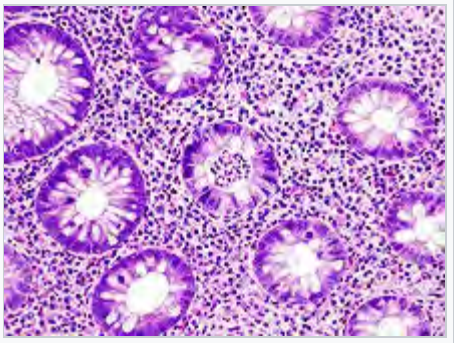
| | Crohn's disease | Ulcerative colitis |
|---|---|---|
| Cytokine response | Associated with $T_h17$[31] | Vaguely associated with $T_h2$ |

pathway. Furthermore, it has been suggested that the protective benefit of smoking in ulcerative colitis is due to the hydrogen cyanide from cigarette smoke reacting with hydrogen sulfide to produce the non-toxic isothiocyanate, thereby inhibiting sulfides from interrupting the pathway.[32] An unrelated study suggested that the sulfur contained in red meats and alcohol may lead to an increased risk of relapse for patients in remission.[30]

Ulcerative colitis patients typically present with rectal bleeding, diarrhea, tenesmus (urgent desire to evacuate the bowels but with the passage of little stool), and lower abdominal pain. The severity of disease at clinical presentation is important in determining the appropriate therapy. Patients with mildly active disease will have fewer than 4 bowel movements daily and no signs of toxicity. Individuals with moderate-severity UC have more frequent bowel movements with bleeding. Approximately 70% of patients with ulcerative colitis will have moderately active disease at presentation. Patients with severely active disease will have signs of toxicity with fever, tachycardia, and anemia. Patients with fulminant or toxic colitis or toxic megacolon often have more than 10 bowel movements in a day, continuous bleeding, abdominal distention and tenderness, and radiologic evidence of edema and, in some cases, bowel dilation. These people most often require immediate colectomy because 10% have perforated colon at the time of surgery.

## Diagnosis [edit]

The initial diagnostic workup for ulcerative colitis includes the following:[10][33]



H&E stain of a colonic biopsy showing a crypt abscess, a classic finding in ulcerative colitis

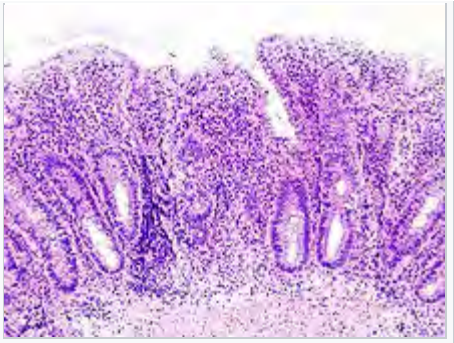
- A complete blood count is done to check for anemia; thrombocytosis, a high platelet count, is occasionally seen
- Electrolyte studies and renal function tests are done, as chronic diarrhea may be associated with hypokalemia, hypomagnesemia and pre-renal failure.
- Liver function tests are performed to screen for bile duct involvement: primary sclerosing cholangitis.
- X-ray
- Urinalysis
- Stool culture, to rule out parasites and infectious causes.
- Erythrocyte sedimentation rate can be measured, with an elevated sedimentation rate indicating that an inflammatory process is present.
- C-reactive protein can be measured, with an elevated level being another indication of inflammation.
- sigmoidoscopy a type of endoscopy which can detect the presence of ulcers in the large intestine after a trial of an enema.

Although ulcerative colitis is a disease of unknown causation, inquiry should be made as to unusual factors believed to trigger the disease.[10] Factors may include: recent cessation of tobacco smoking; recent administration of large doses of iron or vitamin B6; hydrogen peroxide in enemas or other procedures.[*citation needed*]

The simple clinical colitis activity index was created in 1998 and is used to assess the severity of symptoms.[34][35]

### Endoscopic [edit]

The best test for diagnosis of ulcerative colitis remains endoscopy. Full colonoscopy to the cecum and entry into the terminal ileum is attempted only if the diagnosis of UC is unclear. Otherwise, a flexible sigmoidoscopy is sufficient to support the diagnosis. The physician may elect to limit the extent of the exam if severe colitis is encountered to minimize the risk of perforation of the colon. Endoscopic findings in ulcerative colitis include the following:



Biopsy sample (H&E stain) that demonstrates marked lymphocytic infiltration (blue/purple) of the intestinal mucosa and architectural distortion of the crypts.

- Loss of the vascular appearance of the colon
- Erythema (or redness of the mucosa) and friability of the mucosa
- Superficial ulceration, which may be confluent, and
- Pseudopolyps.

Ulcerative colitis is usually continuous from the rectum, with the rectum almost universally being involved. There is rarely perianal disease, but cases have been reported. The degree of involvement endoscopically ranges from proctitis or inflammation of the rectum, to left sided colitis, to pancolitis, which is inflammation involving the ascending colon.

## Histologic [edit]

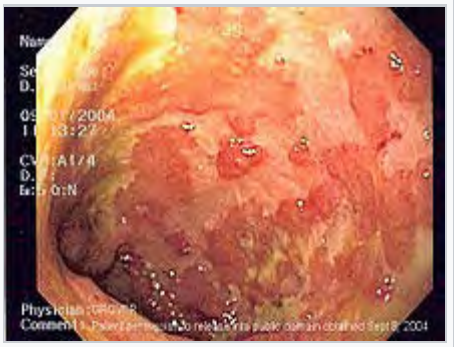
Biopsies of the mucosa are taken to definitively diagnose UC and differentiate it from Crohn's disease, which is managed differently clinically. Microbiological samples are typically taken at the time of endoscopy. The pathology in ulcerative colitis typically involves distortion of crypt architecture, inflammation of crypts (cryptitis), frank crypt abscesses, and hemorrhage or inflammatory cells in the lamina propria. In cases where the clinical picture is unclear, the histomorphologic analysis often plays a pivotal role in determining the diagnosis and thus the management. By contrast, a biopsy analysis may be indeterminate, and thus the clinical progression of the disease must inform its treatment.

## Differential diagnosis [edit]

The following conditions may present in a similar manner as ulcerative colitis, and should be excluded:

- Crohn's disease
- Infectious colitis, which is typically detected on stool cultures
  - Pseudomembranous colitis, or *Clostridium difficile*-associated colitis, bacterial upsets often seen following administration of antibiotics
- Ischemic colitis, inadequate blood supply to the intestine, which typically affects the elderly
- Radiation colitis in patients with previous pelvic radiotherapy
- Chemical colitis resulting from the introduction of harsh chemicals into the colon from an enema or other procedure.

The most common disease that mimics the symptoms of ulcerative colitis is Crohn's disease, as both are inflammatory bowel diseases that can affect the colon with similar symptoms. It is important to differentiate these diseases since the course of the diseases and treatments may be different. In some cases, however, it may not be possible to tell the difference, in which case the disease is classified as indeterminate colitis.



Endoscopic image of ulcerative colitis affecting the left side of the colon. The image shows confluent superficial ulceration and loss of mucosal architecture. Crohn's disease may be similar in appearance, a fact that can make diagnosing UC a challenge.

**Diagnostic findings**

| | Crohn's disease | Ulcerative colitis |
|---|---|---|
| Terminal ileum involvement | Commonly | Seldom |
| Colon involvement | Usually | Always |

| | | |
|---|---|---|
| Rectum involvement | Seldom | Usually[28] |
| Involvement around the anus | Common[8] | Seldom |
| Bile duct involvement | No increase in rate of primary sclerosing cholangitis | Higher rate[36] |
| Distribution of disease | Patchy areas of inflammation (skip lesions) | Continuous area of inflammation[28] |
| Endoscopy | Deep geographic and serpiginous (snake-like) ulcers | Continuous ulcer |
| Depth of inflammation | May be transmural, deep into tissues[8][14] | Shallow, mucosal |
| Stenosis | Common | Seldom |
| Granulomas on biopsy | May have non-necrotizing non-peri-intestinal crypt granulomas[8][37][38] | Non-peri-intestinal crypt granulomas not seen[28] |

## Management [edit]

*Main article: Management of ulcerative colitis*

Standard treatment for ulcerative colitis depends on the extent of involvement and disease severity. The goal is to induce remission initially with medications, followed by the administration of maintenance medications to prevent a relapse of the disease. The concept of induction of remission and maintenance of remission is very important. The medications used to induce and maintain a remission somewhat overlap, but the treatments are different. Physicians first direct treatment to inducing a remission which involves relief of symptoms and mucosal healing of the lining of the colon and then longer term treatment to maintain the remission and prevent complications. Acute severe ulcerative colitis requires hospitalisation, exclusion of infections, and corticosteroids.[39]

### Medication [edit]

Ulcerative colitis can be treated with a number of medications, including 5-ASA drugs such as sulfasalazine and mesalazine. Corticosteroids such as prednisone can also be used due to their immunosuppressing and short-term healing properties, but because their risks outweigh their benefits, they are not used long-term in treatment. Immunosuppressive medications such as azathioprine and biological agents such as infliximab and adalimumab are given only if people cannot achieve remission with 5-ASA and corticosteroids. This is because of their possible risk factors, including but not limited to increased risk of cancers in teenagers and adults,[40] tuberculosis, and new or worsening heart failure (these side effects are rare). A formulation of budesonide was approved by the FDA for treatment of active ulcerative colitis in January 2013.[41] The evidence on methotrexate does not show a benefit in producing remission in people with ulcerative colitis.[42] Off-label use of drugs such as ciclosporin and tacrolimus has shown some benefits.[43][44] Fexofenadine, an antihistamine drug used in treatment of allergies, has shown promise in a combination therapy in some studies.[45][46] Opportunely, low gastrointestinal absorption (or high absorbed drug gastrointestinal secretion) of fexofenadine results in higher concentration at the site of inflammation. Thus, the drug may locally decrease histamine secretion by involved gastrointestinal mast cells and alleviate the inflammation.

### Aminosalicylates [edit]

Sulfasalazine has been a major agent in the therapy of mild to moderate ulcerative colitis for over 50 years. In 1977, Mastan S. Kalsi *et al.* determined that 5-aminosalicylic acid (5-ASA and mesalazine) was the therapeutically active component in sulfasalazine.[47] Since then, many 5-ASA compounds have been developed with the aim of maintaining efficacy but reducing the common side effects associated with the sulfapyridine moiety in sulfasalazine.[48]

## Biologics [edit]

Biologic treatments such as the TNF inhibitors infliximab, adalimumab, and golimumab are commonly used to treat people with UC who are no longer responding to corticosteroids. Tofacitinib, vedolizumab, and etrolizumab can also produce good clinical remission and response rates in UC.[4] Usually, these medications are only used if other options have been exhausted (i.e., the person has received and not responded favorably to high-dose corticosteroids and immunomodulators such as azathioprine and mesalazine).

Unlike aminosalicylates, biologics can cause serious side effects such as an increased risk of developing extra-intestinal cancers,[40] heart failure; and weakening of the immune system, resulting in a decreased ability of the immune system to clear infections and reactivation of latent infections such as tuberculosis. For this reason, patients on these treatments are closely monitored and are often given tests for hepatitis and tuberculosis at least once a year.

## Nicotine [edit]

Unlike Crohn's disease, ulcerative colitis has a lesser prevalence in smokers than non-smokers.[49][50] Studies using a transdermal nicotine patch have shown clinical and histological improvement.[51]

In one double-blind, placebo-controlled study conducted in the United Kingdom, 48.6% of patients who used the nicotine patch, in conjunction with their standard treatment, showed complete resolution of symptoms. Another randomized, double-blind, placebo-controlled, single-center clinical trial conducted in the United States showed that 39% of patients who used the patch showed significant improvement, versus 9% of those given a placebo.[52] Use of a transdermal nicotine patch without the addition of other standard treatments such as mesalazine has relapse occurrence rates similar to standard treatment without the use of nicotine.

## Iron supplementation [edit]

The gradual loss of blood from the gastrointestinal tract, as well as chronic inflammation, often leads to anemia, and professional guidelines suggest routinely monitoring for this with blood tests repeated every three months in active disease and annually in quiescent disease.[53] Adequate disease control usually improves anemia of chronic disease, but iron deficiency anemia should be treated with iron supplements. The form in which treatment is administered depends both on the severity of the anemia and on the guidelines that are followed. Some advise that parenteral iron be used first because patients respond to it more quickly, it is associated with fewer gastrointestinal side effects, and it is not associated with compliance issues.[54] Others require oral iron to be used first, as patients eventually respond and many will tolerate the side effects.[53][55] All guidelines advise that parenteral iron should be administered in cases of severe anemia (a hemoglobin level less than 10).

## Treatments in development [edit]

This section **may be too technical for most readers to understand**. Please help improve this section to make it understandable to non-experts, without removing the technical details. The talk page may contain suggestions. *(May 2013) (Learn how and when to remove this template message)*

Inflammation of the colon is a characteristic symptom of ulcerative colitis, and a new series of drugs in

development looks to disrupt the inflammation process by selectively targeting an ion channel. A crucial step involved in the inflammation signaling cascade involves an intermediate conductance calcium activated potassium channel (IK channel) known as KCa3.1;[56][*non-primary source needed*] a protein coded for in the human gene KCNN4.[57] Ongoing research seeks to prevent T-cell activation and inflammation by inhibiting the KCa3.1 channel, selectively.[58][*non-primary source needed*] Since there is an upregulation of IK channel activity during T cell activation,[56][*non-primary source needed*] inhibition of the KCa3.1 is able to disrupt the production of Th1 cytokines IL-2 and TNF- . Production of these cytokines decreases because inhibition of KCa3.1 reduces the efflux of $K^+$, which in turn diminishes the influx of $Ca^{2+}$. By lowering elevated intracellular $Ca^{2+}$ in patients with ulcerative colitis, these novel drug candidates can inhibit the signaling cascade involved in the inflammation process[58][*non-primary source needed*] and help relieve many of the symptoms associated with ulcerative colitis.

Preclinical study results in 2012 indicated that these selective inhibitors decreased colon inflammation in mice and rats cloned with the human KCa3.1 protein as effectively as the standard inflammatory bowel disease treatment of sulfasalazine. However, these novel selective IK channel blockers are significantly more potent and theoretically would be able to be taken at a much more manageable dosage.[58][*non-primary source needed*]

Benzothiazinone, NS6180, is a novel class KCa3.1 channel inhibitor in development. Through a number of in vitro experiments, NS6180 was qualified for KCa3.1 channel inhibition. In vivo experiment of DNBS (2,4 - dinitrobenzene sulfonic acid) induced rat colitis, a frequently used animal model for inflammatory bowel disease, showed comparable efficacy and greater potency than sulfasalazine.[58][*non-primary source needed*]

## Surgery [edit]

Unlike in Crohn's disease, the gastrointestinal aspects of ulcerative colitis can generally be cured by surgical removal of the large intestine, though extraintestinal symptoms may persist. This procedure is necessary in the event of: exsanguinating hemorrhage, frank perforation, or documented or strongly suspected carcinoma. Surgery is also indicated for patients with severe colitis or toxic megacolon. Patients with symptoms that are disabling and do not respond to drugs may wish to consider whether surgery would improve the quality of life.

**Management**

| | Crohn's disease | Ulcerative colitis |
|---|---|---|
| Mesalazine | Less useful[59] | More useful[59] |
| Antibiotics | Effective in long-term[60] | Generally not useful[61] |
| Surgery | Often returns following removal of affected part | Usually cured by removal of colon |

Ulcerative colitis affects many parts of the body outside the intestinal tract. In rare cases, the extra-intestinal manifestations of the disease may require removal of the colon.[10]

Another surgical option for ulcerative colitis that is affecting most of the large bowel is called the ileo-anal pouch procedure. This is a two- to three-step procedure in which the large bowel is removed, except for the rectal stump and anus, and a temporary ileostomy is made. The next part of the surgery can be done in one or two steps and is usually done at six- to twelve-month intervals from each prior surgery.

In the next step of the surgery, an internal pouch is made of the patient's own small bowel, and this pouch is then hooked back up internally to the rectal stump so that the patient can once again have a reasonably functioning bowel system, all internal. The temporary ileostomy can be reversed at this time so that the patient is internalized for bowel functions, or, in another step to the procedure, the pouch, and rectal stump anastamosis can be left inside the patient to heal for some time while the patient still uses the ileostomy for bowel function. Then, on a subsequent surgery, the ileostomy is reversed and the patient has internalized bowel function again.

## Leukocyte apheresis [edit]

A type of leukocyte apheresis, known as granulocyte and monocyte adsorptive apheresis, still requires [62]

large-scale trials to determine whether or not it is effective. Results from small trials have been tentatively positive.[63]

## Bacterial recolonization [edit]

- In a number of randomized clinical trials, probiotics have demonstrated the potential to be helpful in the treatment of ulcerative colitis. Specific types of probiotics such as Escherichia coli Nissle have been shown to induce remission in some patients for up to a year.[64] Another type of probiotic that is said to have a similar effect is *Lactobacillus acidophilus*.[*citation needed*] The probiotics are said to work by calming some of the ongoing inflammation that causes the disease, which in turn allows the body to mobilize dendritic cells, otherwise known as messenger immune cells. These cells then are able to produce other T-cells that further aid in restoring balance in the intestines by rebalancing systematic inflammation.[65]
- Fecal bacteriotherapy involves the infusion of human probiotics through fecal enemas. Ulcerative colitis typically requires a more prolonged bacteriotherapy treatment than *Clostridium difficile* infection to be successful, possibly due to the time needed to heal the ulcerated epithelium. The response of ulcerative colitis is potentially very favorable with one study reporting 67.7% of sufferers experiencing complete remission.[66] It suggests that the cause of ulcerative colitis may be a previous infection by a still unknown pathogen. This initial infection resolves itself naturally, but somehow causes an imbalance in the colonic bacterial flora, leading to a cycle of inflammation which can be broken by "recolonizing" the colon with bacteria from a healthy bowel. There have been several reported cases of patients who have remained in remission for up to 13 years.[67]

## Alternative medicine [edit]

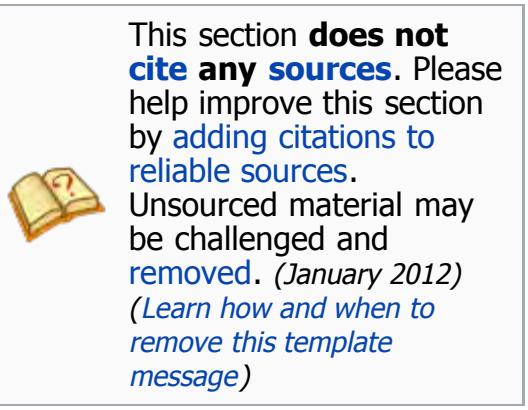
About 21% of inflammatory bowel disease patients use alternative treatments.[68] A variety of dietary treatments show promise, but they require further research before they can be recommended.[69]

- Melatonin may be beneficial according to *in vitro* research, animal studies, and a preliminary human study.[70]
- Dietary fiber, meaning indigestible plant matter, has been recommended for decades in the maintenance of bowel function. Of peculiar note is fiber from brassica, which seems to contain soluble constituents capable of reversing ulcers along the entire human digestive tract before it is cooked.[71]
- Fish oil, and eicosapentaenoic acid (EPA) derived from fish oil, inhibits leukotriene activity, the latter which may be a key factor of inflammation. As an IBD therapy, there are no conclusive studies in support and no recommended dosage. But dosages of EPA between 180 and 1500 mg/day are recommended for other conditions, most commonly cardiac.[72] Fish oil also contains vitamin D, of which the many people with IBD are deficient.[73]
- Short chain fatty acid (butyrate) enema. The epithelial cells in the colon uses butyrate from the contents of the intestine as an energy source. The amount of butyrate available decreases toward the rectum. Inadequate butyrate levels in the lower intestine have been suggested as a contributing factor for the disease. This might be addressed through butyrate enemas.[74] The results however are not conclusive.[*citation needed*]
- Herbal medications are used by patients with ulcerative colitis. Compounds that contain sulfhydryl may have an effect in ulcerative colitis (under a similar hypothesis that the sulfa moiety of sulfasalazine may have activity in addition to the active 5-ASA component).[75] One randomized control trial evaluated the over-the-counter medication *S*-methylmethionine and found a significant decreased rate of relapse when the medication was used in conjunction with oral sulfasalazine.[76]
- Helminthic therapy is the use of intestinal parasitic nematodes to treat ulcerative colitis, and is based on the premises of the hygiene hypothesis. Studies have shown that helminths ameliorate and are more effective than daily corticosteroids at blocking chemically induced colitis in mice,[77][78] and a trial of intentional helminth infection of rhesus monkeys with idiopathic chronic diarrhea (a condition similar to ulcerative colitis in humans) resulted in remission of symptoms in 4 out of 5 of the animals treated.[79] A randomised controlled trial of Trichuris suis ova in humans found the therapy to be safe and

effective,[80] and further human trials are ongoing.
- Curcumin (tumeric) therapy, in conjunction with taking the medications mesalamine or sulfasalazine, may be effective and safe for maintaining remission in people with quiescent ulcerative colitis. The effect of curcumin therapy alone on quiescent ulcerative colitis is unknown.[81]

# Prognosis [edit]

## Progression or remission [edit]




Patients with ulcerative colitis usually have an intermittent course, with periods of disease inactivity alternating with "flares" of disease. Patients with proctitis or left-sided colitis usually have a more benign course: only 15% progress proximally with their disease, and up to 20% can have sustained remission in the absence of any therapy. Patients with more extensive disease are less likely to sustain remission, but the rate of remission is independent of the severity of the disease.

**Complications**

| | | Crohn's disease | Ulcerative colitis |
|---|---|---|---|
| Nutrient deficiency | | Higher risk | |
| Colon cancer risk | | Slight | Considerable |
| Prevalence of **extraintestinal complications**[82] | | | |
| Iritis/uveitis | Females | 2.2% | 3.2% |
| | Males | 1.3% | 0.9% |
| Primary sclerosing cholangitis | Females | 0.3% | 1% |
| | Males | 0.4% | 3% |
| Ankylosing spondylitis | Females | 0.7% | 0.8% |
| | Males | 2.7% | 1.5% |
| Pyoderma gangrenosum | Females | 1.2% | 0.8% |
| | Males | 1.3% | 0.7% |
| Erythema nodosum | Females | 1.9% | 2% |
| | Males | 0.6% | 0.7% |

## Colorectal cancer [edit]

There is a significantly increased risk of colorectal cancer in patients with ulcerative colitis after ten years if involvement is beyond the splenic flexure. Those with only proctitis or rectosigmoiditis usually have no increased risk.[10] It is recommended that patients have screening colonoscopies with random biopsies to look for dysplasia after eight years of disease activity, at one to two year intervals.[83]

## Primary sclerosing cholangitis [edit]

Ulcerative colitis has a significant association with primary sclerosing cholangitis (PSC), a progressive inflammatory disorder of small and large bile ducts. As many as 5% of patients with ulcerative colitis may progress to develop primary sclerosing cholangitis.[84]

## Mortality [edit]

Research has not revealed any difference in overall risk of dying in patients with Ulcerative colitis from that of the background population. The cause-of-death distribution may be different from that of the background population.[85] It is thought that the disease primarily affects quality of life, and not lifespan.

## Other long-term features [edit]

Changes that can be seen in chronic ulcerative colitis include granularity, loss of the vascular pattern of the mucosa, loss of haustra, effacement of the ileocecal valve, mucosal bridging, strictures and pseudopolyps.[86]

## Epidemiology [edit]

The number of new cases per year of ulcerative colitis in North America is 10–12 per 100,000 per year. It begins most commonly between the ages of 15 and 25. The number of people affected is 1–3 per 1000.[87] Another frequent age of onset is the 6th decade of life.

The geographic distribution of ulcerative colitis and Crohn's disease is similar worldwide,[88] with highest incidences in the United States, Canada, the United Kingdom, and Scandinavia. Higher incidences are seen in northern locations compared to southern locations in Europe[89] and the United States.[90]

As with Crohn's disease, the prevalence of ulcerative colitis is greater among Ashkenazi Jews and decreases progressively in other persons of Jewish descent, non-Jewish Caucasians, Africans, Hispanics, and Asians.[27] Appendectomy prior to age 20 for appendicitis[91] and current tobacco use[92] are protective against development of ulcerative colitis (although former tobacco use is associated with a higher risk of developing ulcerative colitis.[92])

## Research [edit]

Helminthic therapy using the whipworm *Trichuris suis* has been shown in a randomized control trial from Iowa to show benefit in patients with ulcerative colitis.[93] The therapy tests the hygiene hypothesis which argues that the absence of helminths in the colons of patients in the developed world may lead to inflammation. Both helminthic therapy and fecal bacteriotherapy induce a characteristic Th2 white cell response in the diseased areas, which was unexpected given that ulcerative colitis was thought to involve Th2 overproduction.[94]

Alicaforsen is a first generation antisense oligodeoxynucleotide designed to bind specifically to the human ICAM-1 messenger RNA through Watson-Crick base pair interactions in order to subdue expression of ICAM-1.[95] ICAM-1 propagates an inflammatory response promoting the extravasation and activation of leukocytes (white blood cells) into inflamed tissue.[95] Increased expression of ICAM-1 has been observed within the inflamed intestinal mucosa of ulcerative colitis sufferers, where ICAM-1 over production correlated with disease activity.[96] This suggests that ICAM-1 is a potential therapeutic target in the treatment of ulcerative colitis.[97]

Gram positive bacteria present in the lumen could be associated with extending the time of relapse for ulcerative colitis.[98]

## Notable cases [edit]

*Main article: List of people diagnosed with ulcerative colitis*

## References [edit]


1. ^ *a b c d e f g h i* "Ulcerative Colitis". *NIDDK*. September 2014. Retrieved 3 August 2016.
2. ^ *a b c d e* Ford, AC; Moayyedi, P; Hanauer, SB (5 February 2013). "Ulcerative colitis.". *BMJ (Clinical research ed.)*. **346**: f432. doi:10.1136/bmj.f432. PMID 23386404.
3. ^ *a b* Wanderås, Magnus Hofrenning; Moum, Bjørn A; Høivik, Marte Lie; Hovde, Øistein (2016-05-06). "Predictive factors for a severe clinical course in ulcerative colitis: Results from population-based studies". *World Journal of Gastrointestinal Pharmacology and Therapeutics*. **7** (2): 235–241. doi:10.4292/wjgpt.v7.i2.235. ISSN 2150-5349. PMC 4848246. PMID 27158539.

4. ^ a b Akiho, Hirotada; Yokoyama, Azusa; Abe, Shuichi; Nakazono, Yuichi; Murakami, Masatoshi; Otsuka, Yoshihiro; Fukawa, Kyoko; Esaki, Mitsuru; Niina, Yusuke (2015-11-15). "Promising biological therapies for ulcerative colitis: A review of the literature". *World Journal of Gastrointestinal Pathophysiology*. **6** (4): 219–227. doi:10.4291/wjgp.v6.i4.219. ISSN 2150-5330. PMC 4644886. PMID 26600980.
5. ^ a b c d e f g Danese, S; Fiocchi, C (3 November 2011). "Ulcerative colitis.". *The New England Journal of Medicine*. **365** (18): 1713–25. doi:10.1056/NEJMra1102942. PMID 22047562.
6. ^ Tamparo, Carol (2011). *Fifth Edition: Diseases of the Human Body*. Philadelphia, PA: F. A. Davis Company. p. 409. ISBN 978-0-8036-2505-1.
7. ^ a b c d e f internetmedicin.se > Inflammatorisk tarmsjukdom, kronisk, IBD By Robert Löfberg. Retrieved Oct 2010 Translate.
8. ^ a b c d Hanauer SB, Sandborn W (2001-03-01). "Management of Crohn's disease in adults" (PDF). *American Journal of Gastroenterology*. **96** (3): 635–43. doi:10.1111/j.1572-0241.2001.03671.x. PMID 11280528. Retrieved 2009-11-07.
9. ^ Hanauer SB (1996). "Inflammatory bowel disease". *The New England Journal of Medicine*. **334** (13): 841–8. doi:10.1056/NEJM199603283341307. PMID 8596552.
10. ^ a b c d e f g Kornbluth A, Sachar DB (2004). "Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee". *The American Journal of Gastroenterology*. **99** (7): 1371–85. doi:10.1111/j.1572-0241.2004.40036.x. PMID 15233681.
11. ^ Langan RC, Gotsch PB, Krafczyk MA, Skillinge DD (November 2007). "Ulcerative colitis: diagnosis and treatment" (PDF). *American Family Physician*. **76** (9): 1323–30. PMID 18019875.
12. ^ Orholm M, Binder V, Sørensen TI, Rasmussen LP, Kyvik KO (2000). "Concordance of inflammatory bowel disease among Danish twins. Results of a nationwide study". *Scandinavian Journal of Gastroenterology*. **35** (10): 1075–81. doi:10.1080/003655200451207. PMID 11099061.
13. ^ Tysk C, Lindberg E, Järnerot G, Flodérus-Myrhed B (1988). "Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking". *Gut*. **29** (7): 990–996. doi:10.1136/gut.29.7.990. PMC 1433769. PMID 3396969.
14. ^ a b c Baumgart DC, Sandborn WJ (May 2007). "Inflammatory bowel disease: clinical aspects and established and evolving therapies.". *The Lancet*. **369** (9573): 1641–57. doi:10.1016/S0140-6736(07)60751-X. PMID 17499606. Retrieved 2009-11-04.
15. ^ Cho JH, Nicolae DL, Ramos R, Fields CT, Rabenau K, Corradino S, Brant SR, Espinosa R, LeBeau M, Hanauer SB, Bodzin J, Bonen DK (2000). "Linkage and linkage disequilibrium in chromosome band 1p36 in American Chaldeans with inflammatory bowel disease" (PDF). *Human Molecular Genetics*. **9** (9): 1425–32. doi:10.1093/hmg/9.9.1425. PMID 10814724.
16. ^ Järnerot G, Järnmark I, Nilsson K (1983). "Consumption of refined sugar by patients with Crohn's disease, ulcerative colitis, or irritable bowel syndrome". *Scandinavian Journal of Gastroenterology*. **18** (8): 999–1002. doi:10.3109/00365528309181832. PMID 6673083.
17. ^ Geerling BJ, Dagnelie PC, Badart-Smook A, Russel MG, Stockbrügger RW, Brummer RJ (April 2000). "Diet as a risk factor for the development of ulcerative colitis". *The American Journal of Gastroenterology*. **95** (4): 1008–13. doi:10.1111/j.1572-0241.2000.01942.x. PMID 10763951.
18. ^ Jowett SL, Seal CJ, Pearce MS, Phillips E, Gregory W, Barton JR, Welfare MR (October 2004). "Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study". *Gut*. **53** (10): 1479–84. doi:10.1136/gut.2003.024828. PMC 1774231. PMID 15361498.
19. ^ Andersen V, Olsen A, Carbonnel F, Tjønneland A, Vogel U (March 2012). "Diet and risk of inflammatory bowel disease". *Digestive and Liver Disease*. **44** (3): 185–94. doi:10.1016/j.dld.2011.10.001. PMID 22055893.
20. ^ Tilg H, Kaser A (1 October 2004). "Diet and relapsing ulcerative colitis: take off the meat?". *Gut*. **53** (10): 1399–1401. doi:10.1136/gut.2003.035287. PMC 1774255. PMID 15361484.
21. ^ Moore J, Babidge W, Millard S, Roediger W (January 1998). "Colonic luminal hydrogen sulfide is not elevated in ulcerative colitis". *Digestive Diseases and Sciences*. **43** (1): 162–5. doi:10.1023/A:1018848709769. PMID 9508519.
22. ^ Jørgensen J, Mortensen PB (August 2001). "Hydrogen sulfide and colonic epithelial metabolism: implications for ulcerative colitis". *Digestive Diseases and Sciences*. **46** (8): 1722–32. doi:10.1023/A:1010661706385. PMID 11508674.
23. ^ Picton R, Eggo MC, Langman MJ, Singh S (February 2007). "Impaired detoxication of hydrogen sulfide in ulcerative colitis?". *Digestive Diseases and Sciences*. **52** (2): 373–8. doi:10.1007/s10620-006-9529-y. PMID 17216575.
24. ^ Corrao G, Tragnone A, Caprilli R, Trallori G, Papi C, Andreoli A, Di Paolo M, Riegler G, Rigo GP, Ferraù O, Mansi C, Ingrosso M, Valpiani D (1998). "Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study. Cooperative Investigators of the Italian Group for the Study

of the Colon and the Rectum (GISC)" (PDF). *International Journal of Epidemiology*. **27** (3): 397–404. doi:10.1093/ije/27.3.397. PMID 9698126.
25. ^ Wolverton, SE; Harper, JC (April 2013). "Important controversies associated with isotretinoin therapy for acne.". *American Journal of Clinical Dermatology*. **14** (2): 71–6. doi:10.1007/s40257-013-0014-z. PMID 23559397.
26. ^ Ko IK, Kim BG, Awadallah A, Mikulan J, Lin P, Letterio JJ, Dennis JE (2010). "Targeting improves MSC treatment of inflammatory bowel disease". *Mol. Ther*. **18** (7): 1365–72. doi:10.1038/mt.2010.54. PMC 2911249. PMID 20389289.
27. ^ *a b* Fauci *et al. Harrison's Internal Medicine*, 17th ed. New York: McGraw-Hill Medical, 2008. ISBN 978-0-07-159991-7
28. ^ *a b c d* Kornbluth A, Sachar DB (July 2004). "Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee" (PDF). *American Journal of Gastroenterology*. **99** (7): 1371–85. doi:10.1111/j.1572-0241.2004.40036.x. PMID 15233681. Archived (PDF) from the original on April 6, 2008. Retrieved 2009-11-07.
29. ^ Crohn's Disease Overview
30. ^ *a b* Roediger WE, Moore J, Babidge W (1997). "Colonic sulfide in pathogenesis and treatment of ulcerative colitis" (PDF). *Digestive Diseases and Sciences*. **42** (8): 1571–9. doi:10.1023/A:1018851723920. PMID 9286219.
31. ^ Elson CO, Cong Y, Weaver CT, Schoeb TR, McClanahan TK, Fick RB, Kastelein RA (2007). "Monoclonal anti-interleukin 23 reverses active colitis in a T cell-mediated model in mice". *Gastroenterology*. **132** (7): 2359–70. doi:10.1053/j.gastro.2007.03.104. PMID 17570211.
32. ^ Levine J, Ellis CJ, Furne JK, Springfield J, Levitt, MD (1998). "Fecal Hydrogen Sulfide Production in Ulcerative Colitis". *The American Journal of Gastroenterology*. **98** (8): 83–87.
33. ^ *Ulcerative colitis* at eMedicine
34. ^ Walmsley, R S; Ayres, R C S; Pounder, R E; Allan, R N (1998). "A simple clinical colitis activity index". *Gut*. **43** (1): 29–32. doi:10.1136/gut.43.1.29. ISSN 0017-5749.
35. ^ Mardini, Houssam E.; Grigorian, Alla Y. (2014). "Probiotic Mix VSL#3 Is Effective Adjunctive Therapy for Mild to Moderately Active Ulcerative Colitis". *Inflammatory Bowel Diseases*. **20** (9): 1562–1567. doi:10.1097/MIB.0000000000000084. ISSN 1078-0998. PMID 24918321.
36. ^ Broomé U, Bergquist A (February 2006). "Primary sclerosing cholangitis, inflammatory bowel disease, and colon cancer". *Seminars in Liver Disease*. **26** (1): 31–41. doi:10.1055/s-2006-933561. PMID 16496231.
37. ^ Shepherd NA (August 2002). "Granulomas in the diagnosis of intestinal Crohn's disease: a myth exploded?". *Histopathology*. **41** (2): 166–8. doi:10.1046/j.1365-2559.2002.01441.x. PMID 12147095.
38. ^ Mahadeva U, Martin JP, Patel NK, Price AB (July 2002). "Granulomatous ulcerative colitis: a re-appraisal of the mucosal granuloma in the distinction of Crohn's disease from ulcerative colitis". *Histopathology*. **41** (1): 50–5. doi:10.1046/j.1365-2559.2002.01416.x. PMID 12121237.
39. ^ Chen, J (Jul 2016). "Review article: acute severe ulcerative colitis - evidence-based consensus statements.". *Alimentary Pharmacology and Therapeutics*. **44** (2): 127–44. doi:10.1111/apt.13670. PMID 27226344.
40. ^ *a b* Axelrad, JE; Lichtiger, S; Yajnik, V (28 May 2016). "Inflammatory bowel disease and cancer: The role of inflammation, immunosuppression, and cancer treatment.". *World journal of gastroenterology* (Review). **22** (20): 4794–801. doi:10.3748/wjg.v22.i20.4794. PMC 4873872. PMID 27239106.
41. ^ "Uceris Approved for Active Ulcerative Colitis". empr.com. 2013-01-16. Retrieved 2013-01-16.
42. ^ Chande, N; Wang, Y; MacDonald, JK; McDonald, JW (27 August 2014). "Methotrexate for induction of remission in ulcerative colitis". *The Cochrane Database of Systematic Reviews*. **8** (8): CD006618. doi:10.1002/14651858.CD006618.pub3. PMID 25162749.
43. ^ Krishnamoorthy, R., K. R. Abrams, N. Guthrie, S. Samuel, and T. Thomas. "PWE-237 Ciclosporin in acute severe ulcerative colitis: a meta-analysis". *Gut* 61, no. Suppl 2 (2012): A394-A394.
44. ^ Ogata Haruhiko; Kato Jun; Hirai Fumihito; Hida Nobuyuki; Matsui Toshiyuki; Matsumoto Takayuki; Koyanagi Katsuyoshi; Hibi Toshifumi (2012). "Double blind, placebo controlled trial of oral tacrolimus (FK506) in the management of hospitalized patients with steroid refractory ulcerative colitis". *Inflammatory Bowel Diseases*. **18** (5): 803–808. doi:10.1002/ibd.21853. PMID 21887732.
45. ^ Raithel, M; Winterkamp, S; Weidenhiller, M; Müller, S; Hahn, EG (2007). "Combination therapy using fexofenadine, disodium cromoglycate, and a hypoallergenic amino acid-based formula induced remission in a patient with steroid-dependent, chronically active ulcerative colitis". *International Journal of Colorectal Disease*. **22** (7): 833–839. doi:10.1007/s00384-006-0120-y. PMID 16944185.
46. ^ Dhaneshwar, S; Gautam, H (August 2012). "Exploring novel colon-targeting antihistaminic prodrug for colitis". *Journal of Physiology and Pharmacology*. **63** (4): 327–337. PMID 23070081.
47. ^ "Ulcerative Colitis Treatment". *Ahealthgroup.com*. Retrieved 30 August 2014.
48. ^ S. Kane (2006). "Asacol - A Review Focusing on Ulcerative Colitis" (PDF).

49. ^ Calkins BM (1989). "A meta-analysis of the role of smoking in inflammatory bowel disease". *Digestive Diseases and Sciences*. **34** (12): 1841–54. doi:10.1007/BF01536701. PMID 2598752.
50. ^ Lakatos PL, Szamosi T, Lakatos L (2007). "Smoking in inflammatory bowel diseases: good, bad or ugly?". *World Journal of Gastroenterology*. **13** (46): 6134–9. doi:10.3748/wjg.13.6134. PMC 4171221. PMID 18069751.
51. ^ Guslandi M (October 1999). "Nicotine treatment for ulcerative colitis". *British Journal of Clinical Pharmacology*. **48** (4): 481–4. doi:10.1046/j.1365-2125.1999.00039.x. PMC 2014383. PMID 10583016.
52. ^ Sandborn WJ, Tremaine WJ, Offord KP, Lawson GM, Petersen BT, Batts KP, Croghan IT, Dale LC, Schroeder DR, Hurt RD (March 1997). "Transdermal nicotine for mildly to moderately active ulcerative colitis. A randomized, double-blind, placebo-controlled trial". *Annals of Internal Medicine*. **126** (5): 364–71. doi:10.7326/0003-4819-126-5-199703010-00004. PMID 9054280.
53. ^ *a b* Goddard, A. F.; James, M. W.; McIntyre, A. S.; Scott, B. B.; British Society of Gastroenterology (2011). "Guidelines for the management of iron deficiency anaemia". *Gut*. **60** (10): 1309–1316. doi:10.1136/gut.2010.228874. PMID 21561874.
54. ^ Inflamm Bowel Dis 2007;13:1545–1553
55. ^ Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L, Lees C, Ho GT, Satsangi J, Bloom S (May 2011). "Guidelines for the management of inflammatory bowel disease in adults". *Gut*. **60** (5): 571–607. doi:10.1136/gut.2010.224154. PMID 21464096.
56. ^ *a b* Ghanshani S.; Wulff H.; Miller M. J.; Rohm H.; Neben A.; Gutman G. A.; Chandy K. G. (2000). "Up-regulation of the IKCa1 potassium channel during T-cell activation Molecular mechanism and functional consequences". *Journal of Biological Chemistry*. **275** (47): 37137–37149. doi:10.1074/jbc.m003941200. PMID 10961988.
57. ^ Wei AD, Gutman GA, Aldrich R, et al. (2006). "International Union of Pharmacology. LII. Nomenclature and molecular relationships of calcium-activated potassium channels". *Pharmacological Reviews*. **57** (4): 463–72. doi:10.1124/pr.57.4.9. PMID 16382103.
58. ^ *a b c d* Strøbæk D.; Brown D. T.; Jenkins D. P.; Chen Y. J.; Coleman N.; Ando Y.; Christophersen P. (2013). "NS6180, a new KCa3. 1 channel inhibitor prevents T cell activation and inflammation in a rat model of inflammatory bowel disease". *British Journal of Pharmacology*. **168** (2): 432–444. doi:10.1111/j.1476-5381.2012.02143.x. PMC 3572569. PMID 22891655.
59. ^ *a b* Pages 152–156 (Section: Inflammatory bowel disease (IBD)) in: Elizabeth D Agabegi; Agabegi, Steven S. (2008). *Step-Up to Medicine (Step-Up Series)*. Hagerstwon, MD: Lippincott Williams & Wilkins. ISBN 0-7817-7153-6.
60. ^ Feller M, Huwiler K, Schoepfer A, Shang A, Furrer H, Egger M (2010). "Long-term antibiotic treatment for Crohn's disease: systematic review and meta-analysis of placebo-controlled trials". *Clin. Infect. Dis.* **50** (4): 473–80. doi:10.1086/649923. PMID 20067425.
61. ^ Section "Antibiotics and Ulcerative Colitis" in: Prantera C, Scribano ML (2009). "Antibiotics and probiotics in inflammatory bowel disease: why, when, and how". *Curr. Opin. Gastroenterol.* **25** (4): 329–33. doi:10.1097/MOG.0b013e32832b20bf. PMID 19444096.
62. ^ Abreu, MT; Plevy, S; Sands, BE; Weinstein, R (2007). "Selective leukocyte apheresis for the treatment of inflammatory bowel disease". *Journal of Clinical Gastroenterology*. **41** (10): 874–88. doi:10.1097/MCG.0b013e3180479435. PMID 18090155.
63. ^ Vernia, P; D'Ovidio, V; Meo, D (October 2010). "Leukocytapheresis in the treatment of inflammatory bowel disease: Current position and perspectives". *Transfusion and Apheresis Science*. **43** (2): 227–9. doi:10.1016/j.transci.2010.07.023. PMID 20817610.
64. ^ Fedorak Richard (2010). "Probiotics in the Management of Ulcerative Colitis". *Gastroenterology & Hepatology*. **6** (11): 688–90. PMC 3033537. PMID 21437015.
65. ^ Northwestern University (2011). "New Probiotics Combats Inflammatory Bowel Disease". *Science Daily*.
66. ^ Borody TJ, Brandt LJ, Paramsothy S (January 2014). "Therapeutic faecal microbiota transplantation: current status and future developments". *Current Opinion in Gastroenterology*. **30** (1): 97–105. doi:10.1097/MOG.0000000000000027. PMC 3868025. PMID 24257037.
67. ^ Borody TJ, Warren EF, Leis S, Surace R, Ashman O (2003). "Treatment of ulcerative colitis using fecal bacteriotherapy" (PDF). *Journal of Clinical Gastroenterology*. **37** (1): 42–7. doi:10.1097/00004836-200307000-00012. PMID 12811208.
68. ^ Bensoussan M, Jovenin N, Garcia B, Vandromme L, Jolly D, Bouché O, Thiéfin G, Cadiot G (January 2006). "Complementary and alternative medicine use by patients with inflammatory bowel disease: results from a postal survey" (PDF). *Gastroentérologie Clinique et Biologique*. **30** (1): 14–23. doi:10.1016/S0399-8320(06)73072-X. PMID 16514377.
69. ^ Shah S (2007). "Dietary factors in the modulation of inflammatory bowel disease activity". *Medscape General Medicine*. **9** (1): 60. PMC 1925010. PMID 17435660.
70. ^ Terry PD, Villinger F, Bubenik GA, Sitaraman SV (January 2009). "Melatonin and ulcerative colitis: evidence, biological mechanisms, and future research". *Inflammatory Bowel Diseases*. **15** (1): 134–40.

doi:10.1002/ibd.20527. PMID 18626968.
71. ^ Akhtar MS, Munir M (November 1989). "Evaluation of the gastric anti-ulcerogenic effects of Solanum nigrum, Brassica oleracea and Ocimum basilicum in rats". *Journal of Ethnopharmacology*. **27** (1–2): 163–76. doi:10.1016/0378-8741(89)90088-3. PMID 2515396. "Brassica oleracea (leaf) powder did not affect the ulcer index significantly but its aqueous extract lowered the index and increased hexosamine levels, suggesting gastric mucosal protection."
72. ^ "Fish oil". MedlinePlus.
73. ^ Del Pinto R, Pietropaoli D, Chandar AK, Ferri C, Cominelli F (April 2015). "Association Between Inflammatory Bowel Disease and Vitamin D Deficiency: A Systematic Review and Meta-analysis". *Inflammatory Bowel Diseases*. **21** (11): 2708–17. doi:10.1097/MIB.0000000000000546. PMC 4615394. PMID 26348447.
74. ^ Scheppach W, Sommer H, Kirchner T, Paganelli GM, Bartram P, Christl S, Richter F, Dusel G, Kasper H (July 1992). "Effect of butyrate enemas on the colonic mucosa in distal ulcerative colitis". *Gastroenterology*. **103** (1): 51–6. PMID 1612357.
75. ^ Brzezinski A, Rankin GB, Seidner DL, Lashner BA (1995). "Use of old and new oral 5-aminosalicylic acid formulations in inflammatory bowel disease". *Cleveland Clinic Journal of Medicine*. **62** (5): 317–23. doi:10.3949/ccjm.62.5.317. PMID 7586488.
76. ^ Salim AS (1992). "Role of sulphydryl-containing agents in the management of recurrent attacks of ulcerative colitis. A new approach". *Pharmacology*. **45** (6): 307–18. doi:10.1159/000139016. PMID 1362613.
77. ^ Khan WI, Blennerhasset PA, Varghese AK, Chowdhury SK, Omsted P, Deng Y, Collins SM (2002). "Intestinal nematode infection ameliorates experimental colitis in mice". *Infection and Immunity*. **70** (11): 5931–7. doi:10.1128/iai.70.11.5931-5937.2002. PMC 130294. PMID 12379667.
78. ^ Melon A, Wang A, Phan V, McKay DM (2010). "Infection with Hymenolepis diminuta is more effective than daily corticosteroids in blocking chemically induced colitis in mice". *Journal of Biomedicine and Biotechnology*. **2010**: 384523. doi:10.1155/2010/384523. PMC 2789531. PMID 20011066.
79. ^ Broadhurst MJ, Ardeshir A, Kanwar B, Mirpuri J, Gundra UM, Leung JM, Wiens KE, Vujkovic-Cvijin I, Kim CC, Yarovinsky F, Lerche NW, McCune JM, Loke P (2012). "Therapeutic helminth infection of macaques with idiopathic chronic diarrhea alters the inflammatory signature and mucosal microbiota of the colon". *PLoS Pathogens*. **8** (11): e1003000. doi:10.1371/journal.ppat.1003000. PMC 3499566. PMID 23166490.
80. ^ Summers RW, Elliott DE, Urban JF, Thompson RA, Weinstock JV (2005). "Trichuris suis therapy for active ulcerative colitis: A randomized controlled trial". *Gastroenterology*. **128** (4): 825–832. doi:10.1053/j.gastro.2005.01.005. PMID 15825065.
81. ^ Kumar, Sushil; Ahuja, Vineet; Sankar, Mari Jeeva; Kumar, Atul; Moss, Alan C. (2012-10-17). "Curcumin for maintenance of remission in ulcerative colitis". *The Cochrane Database of Systematic Reviews*. **10**: CD008424. doi:10.1002/14651858.CD008424.pub2. ISSN 1469-493X. PMC 4001731. PMID 23076948.
82. ^ Greenstein AJ, Janowitz HD, Sachar DB (September 1976). "The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients". *Medicine (Baltimore)*. **55** (5): 401–12. doi:10.1097/00005792-197609000-00004. PMID 957999.
83. ^ Leighton JA, Shen B, Baron TH, Adler DG, Davila R, Egan JV, Faigel DO, Gan SI, Hirota WK, Lichtenstein D, Qureshi WA, Rajan E, Zuckerman MJ, VanGuilder T, Fanelli RD (2006). "ASGE guideline: endoscopy in the diagnosis and treatment of inflammatory bowel disease". *Gastrointestinal Endoscopy*. **63** (4): 558–65. doi:10.1016/j.gie.2006.02.005. PMID 16564852.
84. ^ Olsson R, Danielsson A, Järnerot G, Lindström E, Lööf L, Rolny P, Rydén BO, Tysk C, Wallerstedt S (1991). "Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis". *Gastroenterology*. **100** (5 Pt 1): 1319–23. PMID 2013375.
85. ^ Jess T, Gamborg M, Munkholm P, Sørensen TI (March 2007). "Overall and cause-specific mortality in ulcerative colitis: meta-analysis of population-based inception cohort studies". *The American Journal of Gastroenterology*. **102** (3): 609–17. doi:10.1111/j.1572-0241.2006.01000.x. PMID 17156150.
86. ^ Page 481 in: *Colonic diseases*. By Timothy R. Koch. 2003. ISBN 978-0-89603-961-2
87. ^ Büsch, K.; Ludvigsson, J. F.; Ekström-Smedby, K.; Ekbom, A.; Askling, J.; Neovius, M. (2014-01-01). "Nationwide prevalence of inflammatory bowel disease in Sweden: a population-based register study". *Alimentary Pharmacology & Therapeutics*. **39** (1): 57–68. doi:10.1111/apt.12528. ISSN 1365-2036. PMID 24127738.
88. ^ Podolsky DK (2002). "Inflammatory bowel disease". *The New England Journal of Medicine*. **347** (6): 417–29. doi:10.1056/NEJMra020831. PMID 12167685.
89. ^ Shivananda S, Lennard-Jones J, Logan R, Fear N, Price A, Carpenter L, van Blankenstein M (1996). "Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD)" (PDF). *Gut*. **39** (5): 690–7. doi:10.1136/gut.39.5.690. PMC 1383393. PMID 9014768.
90. ^ Sonnenberg A, McCarty DJ, Jacobsen SJ (January 1991). "Geographic variation of inflammatory bowel disease within the United States". *Gastroenterology*. **100** (1): 143–9. PMID 1983816.

91. ^ Andersson RE, Olaison G, Tysk C, Ekbom A (March 2001). "Appendectomy and protection against ulcerative colitis". *The New England Journal of Medicine*. **344** (11): 808–14. doi:10.1056/NEJM200103153441104. PMID 11248156.
92. ^ [a] [b] Boyko EJ, Koepsell TD, Perera DR, Inui TS (March 1987). "Risk of ulcerative colitis among former and current cigarette smokers". *The New England Journal of Medicine*. **316** (12): 707–10. doi:10.1056/NEJM198703193161202. PMID 3821808.
93. ^ Summers RW, Elliott DE, Urban JF, Thompson RA, Weinstock JV (April 2005). "Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial" (PDF). *Gastroenterology*. **128** (4): 825–32. doi:10.1053/j.gastro.2005.01.005. PMID 15825065. Retrieved 22 December 2012.
94. ^ Summers RW, Elliott DE, Urban JF, Thompson RA, Weinstock JV (2005). "Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial". *Gastroenterology*. **128** (4): 825–32. doi:10.1053/j.gastro.2005.01.005. PMID 15825065.
95. ^ [a] [b] Bennett CF, Condon TC, Grimm S, Chan H, Chiang MY (1994). "Inhibition of endothelial cell-leukocyte adhesion molecule expression with antisense oligonucleotides". *The Journal of Immunology*. **152** (1): 3530–40.
96. ^ Jones SC, Banks RE, Haidar A, Gearing AJ, Hemingway IK, Ibbotson SH, Dixon MF, Axon AT (1995). "Adhesion molecules in inflammatory bowel disease". *Gut*. **36** (5): 724–30. doi:10.1136/gut.36.5.724. PMC 1382677. PMID 7541009.
97. ^ van Deventer SJ, Wedel MK, Baker BF, Xia S, Chuang E, Miner PB (2006). "A Phase II dose ranging, double-blind, placebo-controlled study of alicaforsen enema in subjects with acute exacerbation of mild to moderate left-sided ulcerative colitis". *Alimentary Pharmacology & Therapeutics*. **23** (10): 1415–25. doi:10.1111/j.1365-2036.2006.02910.x. PMID 16669956.
98. ^ Ghouri, Yezaz A; Richards, David M; Rahimi, Erik F; Krill, Joseph T; Jelinek, Katherine A; DuPont, Andrew W (9 December 2014). "Systematic review of randomized controlled trials of probiotics, prebiotics, and synbiotics in inflammatory bowel disease". *Clin Exp Gastroenterol*. **7**: 473–487. doi:10.2147/CEG.S27530. PMC 4266241. PMID 25525379.


## External links [edit]

- Ulcerative colitis at DMOZ
- MedlinePlus ulcerative colitis page
- Ulcerative colitis information page at Crohn's & Colitis Foundation of America
- Torpy JM, Lynm C, Golub RM (2012). "JAMA patient page. Ulcerative colitis" (PDF). *JAMA*. **307** (1): 104. doi:10.1001/jama.2011.1889. PMID 22215172.

| v · t · e | **Diseases of the digestive system (primarily K20–K93, 530–579)** | |
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| **Accessory** | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · Acute liver failure · · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |
| | **Gallbladder** | Cholecystitis · Gallstones/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · Gallstones/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
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| **Abdominopelvic** | **Hernia** | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
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| **Main** | Crohn's Disease Activity Index · Treatment (Biological therapy · Crohn's disease · · |
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|---|---|
| **Complications** | Malabsorption · Proctitis · Protein losing enteropathy · Pyoderma gangrenosum · Sacroiliitis · Short bowel syndrome · Small bowel obstruction · Stenosis · |
| **History** | Giovanni Battista Morgagni · Burrill Bernard Crohn · |
| **Organizations** | Crohn's and Colitis Foundation of America · Digestive Disorders Foundation · National Society for Colitis and Crohn's Disease · Crohn's and Colitis Canada · |
| **People** | List of people diagnosed with Crohn's disease · List of people diagnosed with ulcerative colitis · Deaths from Crohn's disease · |
| **Authority control** | NDL: 00564684 · |

Categories: Colitis | Diarrhea | Abdominal pain | Autoimmune diseases | Conditions diagnosed by stool test | Inflammations | Noninfective enteritis and colitis | Cytomegalovirus-associated diseases | Steroid-responsive inflammatory conditions




# Volvulus



From Wikipedia, the free encyclopedia



It has been suggested that *Sigmoid colon volvulus* be merged into this article (Discuss) *Proposed since November 2016.*

## Variants

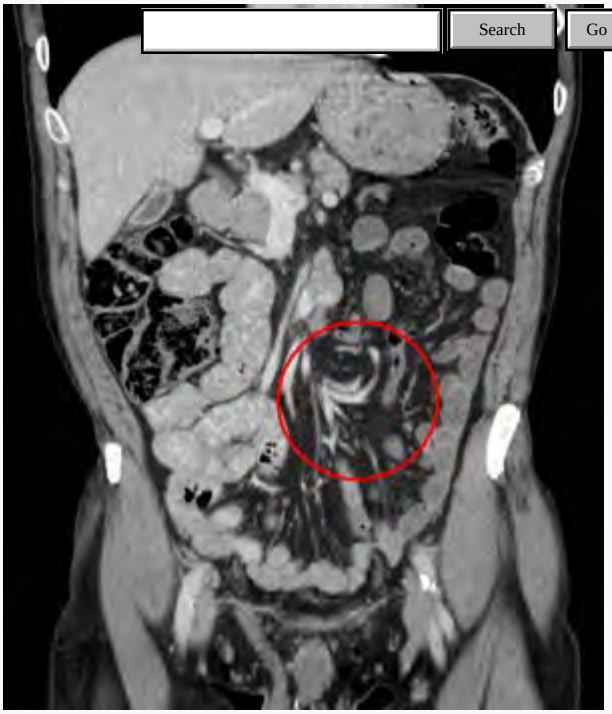
A **volvulus** is when a loop of intestine twists around itself and the mesentery that supports it, resulting in a bowel obstruction.[1] Symptoms include abdominal pain, abdominal bloating, vomiting, constipation, and bloody stool.[1][2] Onset of symptoms may be rapid or more gradual.[2] The mesentery may become so tightly twisted that blood flow to part of the intestine is cut off, resulting in ischemic bowel.[1] In this situation there may be fever or significant pain when the abdomen is touched.[2]

Risk factors include a birth defect known as intestinal malrotation, an enlarged colon, Hirschsprung disease, pregnancy, and abdominal adhesions.[1] Long term constipation and a high fiber diet may also increase the risk.[3] The most commonly affected part of the intestines in adults is the sigmoid colon with the cecum being second most affected.[1] In children the small intestine is more often involved.[4] The stomach can also be affected.[5] Diagnosis is typically with medical imaging such as plain X-rays, a GI series, or CT scan.[1]

Initial treatment for sigmoid volvulus may occasionally occur via sigmoidoscopy or with a barium enema. Due to the high risk of recurrence, a bowel resection within the next two days is generally recommended.[3] If the bowel is severely twisted or the blood supply is cut off, immediate surgery is required.[1] In a cecal volvulus, often part of the bowel needs to be surgically removed.[3] If the cecum is still healthy, it may occasionally be returned to a normal position and sutured in place.[1][3]

Cases of volvulus were described in ancient Egypt as early as 1550 BC. It occurs most frequently in Africa, the Middle East, and India.[3] Rates of volvulus in the United States are about 2-3 per 100,000 people per year.[6][2] Sigmoid and cecal volvulus typically occurs between the ages of 30 and 70.[1][7] Outcomes are related to whether or not the bowel tissue has died.[1] The term volvulus is from the Latin "volvere"; which means "to roll".[3]

**Volvulus**




Coronal CT of the abdomen, demonstrating a volvulus as indicated by twisting of the bowel stock

| Classification and external resources | |
|---|---|
| **Specialty** | General surgery |
| **ICD-10** | K56.2 |
| **ICD-9-CM** | 537.3, 560.2 |
| **DiseasesDB** | 13996 |
| **eMedicine** | ped/2415 |
| **MeSH** | D045822 |

[edit on Wikidata]

Contents [edit links]



## Signs and symptoms [edit]

Regardless of cause, volvulus causes symptoms by two mechanisms:[*citation needed*]

- Bowel obstruction manifested as abdominal distension and bilious vomiting.
- Ischemia (loss of blood flow) to the affected portion of intestine.

Depending on the location of the volvulus, symptoms may vary. For example, in patients with a cecal volvulus, the predominant symptoms may be those of a small bowel obstruction (nausea, vomiting and lack of stool or flatus), because the obstructing point is close to the ileocecal valve and small intestine. In patients with a sigmoid volvulus, although abdominal pain may be present, symptoms of constipation may be more prominent.

Volvulus causes severe pain and progressive injury to the intestinal wall, with accumulation of gas and fluid in the portion of the bowel obstructed.[8] Ultimately, this can result in necrosis of the affected intestinal wall, acidosis, and death. This is known as a closed loop obstruction because there exists an isolated ("closed") loop of bowel. Acute volvulus often requires immediate surgical intervention to untwist the affected segment of bowel and possibly resect any unsalvageable portion.[8]

Volvulus occurs most frequently in middle-aged and elderly men.[8] Volvulus can also arise as a rare complication in persons with redundant colon, a normal anatomic variation resulting in extra colonic loops.[9]

Sigmoid volvulus is the most-common form of volvulus of the gastrointestinal tract.[10] and is responsible for 8% of all intestinal obstructions.[*citation needed*] Sigmoid volvulus is particularly common in elderly persons and constipated patients. Patients experience abdominal pain, distension, and absolute constipation.

Cecal volvulus is slightly less common than sigmoid volvulus and is associated with symptoms of abdominal pain and small bowel obstruction.

Volvulus can also occur in patients with Duchenne muscular dystrophy due to the smooth muscle dysfunction.[*citation needed*]

## Causes [edit]

This section **does not cite any sources**. Please help improve this section by adding citations to reliable sources. Unsourced material may be challenged and removed. *(April 2012) (Learn how and when to remove this template message)*

Midgut volvulus occurs in people (usually babies) that are predisposed because of congenital intestinal malrotation. Segmental volvulus occurs in people of any age, usually with a predisposition because of abnormal intestinal contents (e.g. meconium ileus) or adhesions. Volvulus of the cecum, transverse colon,

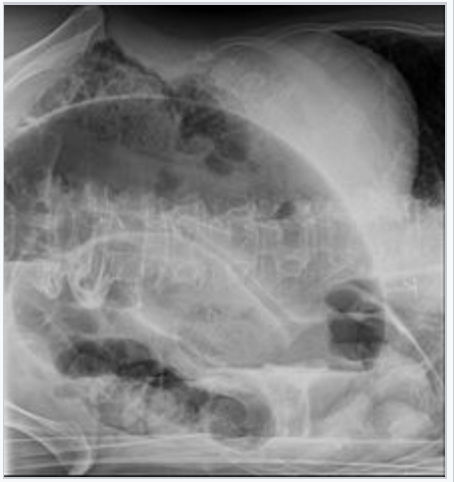
or sigmoid colon occurs, usually in adults, with only minor predisposing factors such as redundant (excess, inadequately supported) intestinal tissue and constipation.

### Types [edit]

- volvulus neonatorum
- volvulus of the small intestine
- volvulus of the caecum (cecum), also cecal volvulus
- sigmoid colon volvulus (sigmoid volvulus)
- volvulus of the transverse colon
- volvulus of the splenic flexure, the rarest
- gastric volvulus
- ileosigmoid knotting

## Diagnosis [edit]

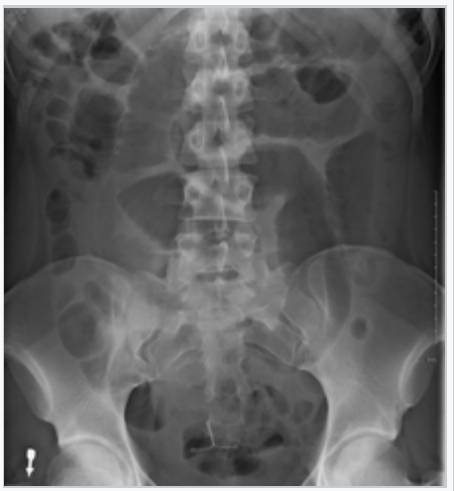
After taking a thorough history, the diagnosis of colonic volvulus is usually easily included in the differential diagnosis. Abdominal plain x-rays are commonly confirmatory for a volvulus, especially if a "bent inner tube" sign or a "coffee bean" sign are seen. These refer to the shape of the air filled closed loop of colon which forms the volvulus. Should the diagnosis be in doubt, a barium enema may be used to demonstrate a "bird's beak" at the point where the segment of proximal bowel and distal bowel rotate to form the volvulus. This area shows an acute and sharp tapering and looks like a bird's beak. If a perforation is suspected, barium should not be used due to its potentially lethal effects when distributed throughout the free infraperitoneal cavity. Gastrografin, which is safer, can be substituted for barium.



Coffee bean sign in a patient with sigmoid volvulus

The differential diagnosis includes the much more common constricting or obstructing carcinoma. In approximately 80 percent of colonic obstructions, an invasive carcinoma is found to be the cause of the obstruction. This is usually easily diagnosed with endoscopic biopsies.

Diverticulitis is a common condition with different presentations. Although diverticulitis may be the source of a colonic obstruction, it more commonly causes an ileus, which appears to be a colonic obstruction.[11] Endoscopic means can be used to secure a diagnosis although this may cause a perforation of the inflamed diverticular area. CT scanning is the more common method to diagnose diverticulitis. The scan will show mesenteric stranding in the involved segment of edematous colon which is usually in the sigmoid region. Micro perforations with free air may be seen.



An x-ray of a person with a small bowel volvulus.

Ulcerative colitis or Crohn's disease may cause colonic obstruction. The obstruction may be acute or chronic after years of uncontrolled disease leads to the formation of strictures and fistulas . The medical history is helpful in that most cases of inflammatory bowel disease are well known to both patient and doctor.

Other rare syndromes, including Ogilvie's syndrome, chronic constipation and impaction may cause a pseudo obstruction.[12]

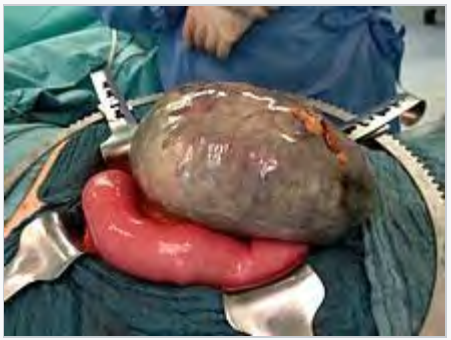
- Abdominal x-ray – tire-like shadow arising from right iliac fossa and passing to left
- Upper GI series

## Treatment [edit]

### Sigmoid volvulus [edit]

Treatment for sigmoid volvulus may include sigmoidoscopy. If the mucosa of the sigmoid looks normal and pink, place a rectal tube for decompression, correct any fluid, electrolyte, cardiac, renal or pulmonary abnormalities and then take the person to the operating room for repair. If surgery is not performed, there is a high rate of recurrence.[*citation needed*]

For people with signs of sepsis or an abdominal catastrophe, immediate surgery and resection is advised.



Volvulus with gangrene of the sigmoid

### Cecal volvulus [edit]

In a cecal volvulus, the cecum may be returned to a normal position and sutured in place, a procedure known as cecopexy.[1]

### Other [edit]

Laparotomy for other forms of volvulus, especially anal volvulus.

## Complications [edit]

- Strangulation
- Gangrene
- Perforation
- Faecal peritonitis
- Recurrent volvulus

## References [edit]


1. ^ *a b c d e f g h i j* "Anatomic Problems of the Lower GI Tract". *NIDDK*. July 2013. Retrieved 3 August 2016.
2. ^ *a b c d e* Marx, John; Walls, Ron; Hockberger, Robert (2013). "95". *Rosen's Emergency Medicine - Concepts and Clinical Practice*. Elsevier Health Sciences. ISBN 1455749877.
3. ^ *a b c d e f* Gingold, D; Murrell, Z (December 2012). "Management of colonic volvulus.". *Clinics in colon and rectal surgery*. **25** (4): 236–44. doi:10.1055/s-0032-1329535. PMC 3577612. PMID 24294126.
4. ^ Wilkins, Lippincott Williams & (2009). *Professional Guide to Diseases*. Lippincott Williams & Wilkins. p. 283. ISBN 9780781778992.
5. ^ Feldman, Mark; Friedman, Lawrence S.; Brandt, Lawrence J. (2010). *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management, Expert Consult Premium Edition - Enhanced Online Features* (9 ed.). Elsevier Health Sciences. p. 384. ISBN 1437727670.
6. ^ Gordon, Philip H.; Nivatvongs, Santhat (2007). *Principles and Practice of Surgery for the Colon, Rectum, and Anus, Third Edition*. CRC Press. p. 971. ISBN 9781420017991.
7. ^ Beck, David; Beck, David E. (2012). "23". *Handbook of Colorectal Surgery: Third Edition*. JP Medical Ltd. ISBN 9781907816208.
8. ^ *a b c* Wedding, Mary Ellen; Gylys, Barbara A. (2004). *Medical Terminology Systems: A Body Systems Approach (Medical Terminology (W/CD & CD-ROM) (Davis))*. Philadelphia, Pa: F. A. Davis Company. ISBN 0-8036-1249-4.
9. ^ Mayo Clinic Staff (2006-10-13). "Redundant colon: A health concern?". *Ask a Digestive System Specialist*. MayoClinic.com. Archived from the original on 2007-09-29. Retrieved 2007-06-11.
10. ^ Turan M, Sen M, Karadayi K, et al. (January 2004). "Our sigmoid colon volvulus experience and benefits of colonoscope in detortion process". *Rev Esp Enferm Dig*. **96** (1): 32–5. doi:10.4321/s1130-01082004000100005. PMID 14971995.
11. ^ Hoffman, Gary H. (2007-08-16). "Diverticulosis/Diverticulitis - For Physicians". *Time To Call The Surgeon?*. Los Angeles Colon and Rectal Surgical Associates. LAcolon.com. Retrieved 2012-07-07.

12. ^ Hoffman, Gary H. (2009-10-27). "What is Constipation?". *What Can Be Done About Constipation*. Los Angeles Colon and Rectal Surgical Associates. LAcolon.com. Retrieved 2012-07-06.

## External links [edit]

- CT of an abdomen with sigmoid volvulus

Wikimedia Commons has media related to *Volvulus*.

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# Book:Infectious disease

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Categories: Wikipedia books (community books)

# African trypanosomiasis

From Wikipedia, the free encyclopedia

*For other uses, see Sleeping sickness (disambiguation).*
*For "Sleepy sickness", see Encephalitis lethargica.*

**African trypanosomiasis**, also known as **sleeping sickness**,[1] is a parasitic disease of humans and other animals. It is caused by protozoa of the species *Trypanosoma brucei*. There are two types that infect humans, *Trypanosoma brucei gambiense* (T.b.g) and *Trypanosoma brucei rhodesiense* (T.b.r.).[1] T.b.g causes over 98% of reported cases.[1] Both are usually transmitted by the bite of an infected tsetse fly and are most common in rural areas.[1]

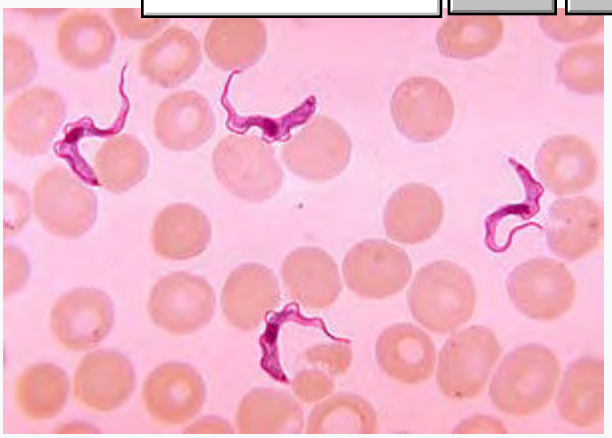
Initially, in the first stage of the disease, there are fevers, headaches, itchiness, and joint pains.[1] This begins one to three weeks after the bite. Weeks to months later the second stage begins with confusion, poor coordination, numbness and trouble sleeping. Diagnosis is via finding the parasite in a blood smear or in the fluid of a lymph node. A lumbar puncture is often needed to tell the difference between first and second stage disease.[3]

Prevention of severe disease involves screening the population at risk with blood tests for T.b.g.[1] Treatment is easier when the disease is detected early and before neurological symptoms occur.[1] Treatment of the first stage is with the medications pentamidine or suramin.[1] Treatment of the second stage involves: eflornithine or a combination of nifurtimox and eflornithine for T.b.g.[3] While melarsoprol works for both stages, it is typically only used for T.b.r., due to serious side effects.[1] Without treatment it typically results in death.[1]

The disease occurs regularly in some regions of sub-Saharan Africa with the population at risk being about 70 million in 36 countries.[4] As of 2010 it caused around 9,000 deaths per year, down from 34,000 in 1990.[5] An estimated 30,000 people are currently infected with 7,000 new infections in 2012.[1] More than 80% of these cases are in the Democratic Republic of the Congo.[1] Three major outbreaks have occurred in recent history: one from 1896 to 1906 primarily in Uganda and the Congo Basin and two in 1920 and 1970 in several African countries.[1] Other animals, such as cows, may carry the disease and become infected in which case it is known as Nagana.[1]

**African trypanosomiasis**

**Synonyms** African sleeping sickness



Trypanosoma forms in a blood smear

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | B56 |
| **ICD-9-CM** | 086.5 |
| **DiseasesDB** | 29277 13400 |
| **MedlinePlus** | 001362 |
| **eMedicine** | med/2140 |
| **Patient UK** | African trypanosomiasis |
| **MeSH** | D014353 |

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Contents
1 Signs and symptoms

## Signs and symptoms [edit]

African trypanosomiasis symptoms occur in two stages. The first stage, known as the hemolymphatic phase, is characterized by fever, headaches, joint pains, and itching. Fever is intermittent, with attacks lasting from a day to a week, separated by intervals of a few days to a month or longer. Invasion of the circulatory and lymphatic systems by the parasites is associated with severe swelling of lymph nodes, often to tremendous sizes. Winterbottom's sign, the tell-tale swollen lymph nodes along the back of the neck, may appear.[6]

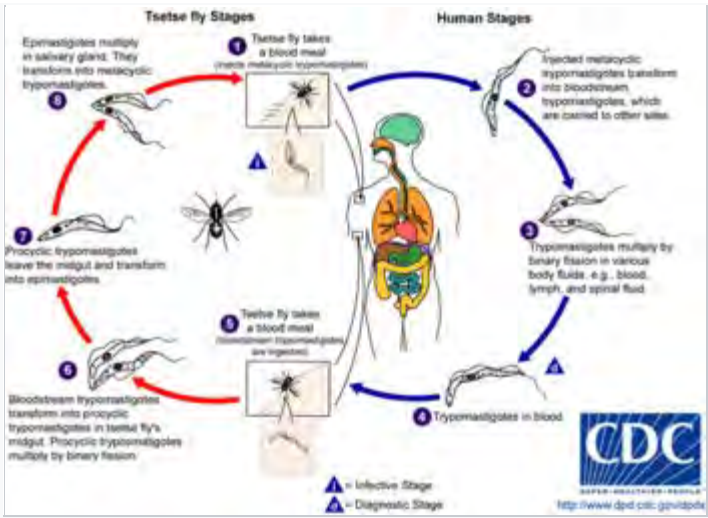
Occasionally, a chancre (red sore) will develop at the location of the tsetse fly bite. If left untreated, the disease overcomes the host's defenses and can cause more extensive damage, broadening symptoms to include anemia, endocrine, cardiac, and kidney dysfunctions. The second, neurological phase, begins when the parasite invades the central nervous system by passing through the blood–brain barrier. Disruption of the sleep cycle is a leading symptom of this stage and is the one that gave the disease the name 'sleeping sickness.' Infected individuals experience a disorganized and fragmented 24-hour rhythm of the sleep-wake cycle, resulting in daytime sleep episodes and nighttime periods of wakefulness.[6]

Other neurological symptoms include confusion, tremor, general muscle weakness, hemiparesis and paralysis of a limb. Parkinson-like movements might arise due to non-specific movement disorders and speech disorders. Individuals may also exhibit psychiatric symptoms such as irritability, psychotic reactions, aggressive behaviour, or apathy which can sometimes dominate the clinical diagnosis.[7] Without treatment, the disease is invariably fatal, with progressive mental deterioration leading to coma, systemic organ failure, and death. An untreated infection with *T. b. rhodesiense* will cause death within months[8] whereas an untreated infection with *T. b. gambiense* will cause death after several years.[9] Damage caused in the neurological phase is irreversible.[10]

## Cause [edit]

### *Trypanosoma brucei* [edit]

There are two subspecies of the parasite that are responsible for starting the disease in humans. *Trypanosoma brucei gambiense* causes the diseases in west and central Africa, whereas *Trypanosoma brucei rhodesiense* has a limited geographical range and is responsible for causing the disease in east and



The life cycle of the *Trypanosoma brucei* parasites.

southern Africa. In addition, a third subspecies of the parasite known as *Trypanosoma brucei brucei* is responsible for affecting animals but not humans.[7]

Humans are the main reservoir for *T. b. gambiense* but this species can also be found in pigs and other animals. Wild game animals and cattle are the main reservoir of *T. b. rhodesiense*. These parasites primarily infect individuals in sub-Saharan Africa because that is where the vector (tsetse fly) is located. The two human forms of the disease also vary greatly in intensity. *T. b. gambiense* causes a chronic condition that can remain in a passive phase for months or years before symptoms emerge and the infection can last about 3 years before death occurs.[7]

*T. b. rhodesiense* is the acute form of the disease and death can occur within months since the symptoms emerge within weeks and it is more virulent and faster developing than *T. b. gambiense*. Furthermore, trypanosomes are surrounded by a coat that is composed of variant surface glycoproteins (VSG). These proteins act to protect the parasite from any lytic factors that are present in human plasma. The host's immune system recognizes the glycoproteins present on the coat of the parasite leading to the production of different antibodies (IgM and IgG).[7]

These antibodies will then act to destroy the parasites that circulate around the blood. However, from the several parasites present in the plasma, a small number of them will experience changes in their surface coats resulting in the formation of new VSGs. Thus, the antibodies produced by the immune system will no longer recognize the parasite leading to proliferation until new antibodies are created to combat the novel VSGs. Eventually the immune system will no longer be able to fight off the parasite due to the constant changes in VSGs and infection will arise.[7]

## Vector [edit]

The tsetse fly (genus *Glossina*) is a large, brown, biting fly that serves as both a host and vector for the trypanosome parasites. While taking blood from a mammalian host, an infected tsetse fly injects metacyclic trypomastigotes into skin tissue. From the bite, parasites first enter the lymphatic system and then pass into the bloodstream. Inside the mammalian host, they transform into bloodstream trypomastigotes, and are carried to other sites throughout the body, reach other body fluids (e.g., lymph, spinal fluid), and continue to replicate by binary fission.

The entire life cycle of African trypanosomes is represented by extracellular stages. A tsetse fly becomes infected with bloodstream trypomastigotes when taking a blood meal on an infected mammalian host. In the fly's midgut, the parasites transform into procyclic trypomastigotes, multiply by binary fission, leave the midgut, and transform into epimastigotes. The epimastigotes reach the fly's salivary glands and continue multiplication by binary fission.

The entire life cycle of the fly takes about three weeks. In addition to the bite of the tsetse fly, the disease can be transmitted by:

- Mother-to-child infection: the trypanosome can sometimes cross the placenta and infect the fetus.[11]
- Laboratories: accidental infections, for example, through the handling of blood of an infected person and organ transplantation, although this is uncommon.
- Blood transfusion
- Sexual contact (This may be possible)[12]

Horse-flies (Tabanidae) and stable flies (Muscidae) possibly play a role in transmission of nagana (the animal form of sleeping sickness) and the human disease form.[13]

## Mechanism [edit]

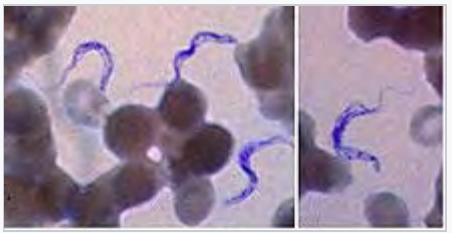
Tryptophol is a chemical compound that induces sleep in humans. It is produced by the trypanosomal parasite in sleeping sickness.[14]

## Diagnosis [edit]

The gold standard for diagnosis is identification of trypanosomes in a patient sample by microscopic examination. Patient samples that can be used for diagnosis include chancre fluid, lymph node aspirates, blood, bone marrow, and, during the neurological stage, cerebrospinal fluid. Detection of trypanosome-specific antibodies can be used for diagnosis, but the sensitivity and specificity of these methods are too variable to be used alone for clinical diagnosis. Further, seroconversion occurs after the onset of clinical symptoms during a *T. b. rhodesiense* infection, so is of limited diagnostic use.[*citation needed*]

Trypanosomes can be detected from patient samples using two different preparations. A wet preparation can be used to look for the motile trypanosomes. Alternatively, a fixed (dried) smear can be stained using Giemsa's or Field's technique and examined under a microscope. Often, the parasite is in relatively low abundance in the sample, so techniques to concentrate the parasites can be used prior to microscopic examination. For blood samples, these include centrifugation followed by examination of the buffy coat; mini anion-exchange/centrifugation; and the quantitative buffy coat (QBC) technique. For other samples, such as spinal fluid, concentration techniques include centrifugation followed by examination of the sediment.[*citation needed*]

Three serological tests are also available for detection of the parasite: the micro-CATT, wb-CATT, and wb-LATEX. The first uses dried blood, while the other two use whole blood samples. A 2002 study found the wb-CATT to be the most efficient for diagnosis, while the wb-LATEX is a better exam for situations where greater sensitivity is required.[15]



Two areas from a blood smear from a patient with African trypanosomiasis, thin blood smear stained with Giemsa: Typical trypomastigote stages (the only stages found in patients), with a posterior kinetoplast, a centrally located nucleus, an undulating membrane, and an anterior flagellum. The two *Trypanosoma brucei* subspecies that cause human trypanosomiasis, *T. b. gambiense* and *T. b. rhodesiense*, are indistinguishable morphologically. The trypanosomes' length range is 14 to 33 μm, Source: CDC

## Prevention [edit]

*See also: Tsetse fly § Control techniques*

Currently there are few medically related prevention options for African Trypanosomiasis (i.e. no vaccine exists for immunity). Although the risk of infection from a tsetse fly bite is minor (estimated at less than 0.1%), the use of insect repellants, wearing long-sleeved clothing, avoiding tsetse-dense areas, implementing bush clearance methods and wild game culling are the best options to avoid infection available for local residents of affected areas.[16]

At the 25th ISCTRC (International Scientific Council for Trypanosomiasis Research and Control) in Mombasa, Kenya, in October 1999, the idea of an African-wide initiative to control tsetse and trypanosomiasis populations was discussed. During the 36th summit of the Organization for African Unity in Lome, Togo, in July 2000, a resolution was passed to form the Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC). The campaign works to eradicate the tsetse vector population levels and subsequently the protozoan disease, by use of insecticide-impregnated targets, fly traps, insecticide-treated cattle, ultra-low dose aerial/ground spraying (SAT) of tsetse resting sites and the sterile insect technique (SIT).[17] The

use of SIT in Zanzibar proved effective in eliminating the entire population of tsetse flies but was expensive and is relatively impractical to use in many of the endemic countries afflicted with African trypanosomiasis.[16]

Regular active surveillance, involving detection and prompt treatment of new infections, and tsetse fly control is the backbone of the strategy used to control sleeping sickness. Systematic screening of at-risk communities is the best approach, because case-by-case screening is not practical in endemic regions. Systematic screening may be in the form of mobile clinics or fixed screening centres where teams travel daily to areas of high infection rates. Such screening efforts are important because early symptoms are not evident or serious enough to warrant patients with gambiense disease to seek medical attention, particularly in very remote areas. Also, diagnosis of the disease is difficult and health workers may not associate such general symptoms with trypanosomiasis. Systematic screening allows early-stage disease to be detected and treated before the disease progresses, and removes the potential human reservoir.[18] A single case of sexual transmission of West African sleeping sickness has been reported.[12]

# Treatment [edit]

## First stage [edit]

The current treatment for first-stage disease is intravenous or intramuscular pentamidine for *T. b. gambiense* or intravenous suramin for *T. b. rhodesiense*.[1]

## Second stage [edit]

For *T. b. gambiense* the combination of nifurtimox and eflornithine (NECT) or eflornithine alone appear to be more effective and result in fewer side effects.[19] These treatments may replace melarsoprol when available[19] with the combination being first line.[3] NECT has the benefit of requiring less injections of eflornithine.[19]

Intravenous melarsoprol was previously the standard treatment for second-stage (neurological phase) disease and is effective for both types.[3] Melarsoprol is the only treatment for second stage *T. b. rhodesiense*; however, it causes death in 5% of people who take it.[3] Resistance to melarsoprol can occur.[3]

# Epidemiology [edit]

As of 2010 it caused around 9,000 deaths, down from 34,000 in 1990.[5] As of 2000, the disability-adjusted life-years (9 to 10 years) lost due to sleeping sickness are 2.0 million.[21] Over 60 million people living in some 250 locations are at risk of contracting the disease, and under 10,000 new cases were reported in 2009.[22]

The disease has been recorded as occurring in 37 countries, all in sub-Saharan Africa. It occurs regularly in southeast Uganda and western Kenya, and killed more than 48,000 Africans in 2008.[10] The population at risk being about 69 million with one third of this number being at a 'very high' to 'moderate' risk and the remaining two thirds at a 'low' to 'very low' risk.[4]


Deaths per 100,000 population due to African trypanosomiasis by country in 2002.[20]

# Prognosis [edit]

If untreated, *T. b. gambiense* almost always results in death, with only a few individuals shown in a long-term 15 year follow-up to have survived after refusing treatment. *T. b. rhodesiense*, being a more acute and severe form of the disease, is consistently fatal if not treated.[3] Disease progression greatly varies depending on disease form. For individuals which are infected by *T. b. gambiense*, which accounts for 98% of all of the reported cases, a person can be infected for months or even years without signs or symptoms until the advanced disease stage, where it is too late to be treated successfully. For individuals affected by *T. b. rhodesiense*, which accounts for 2% of all reported cases, symptoms appear within weeks or months of the infection. Disease progression is rapid and invades the central nervous system, causing death within a short amount of time.[23]

## History [edit]

The condition has been present in Africa for thousands of years.[24] Because of a lack of travel between indigenous people, sleeping sickness in humans had been limited to isolated pockets. This changed once Arab slave traders entered central Africa from the east, following the Congo River, bringing parasites along. Gambian sleeping sickness travelled up the Congo River, then further eastwards.[25]

An Arab writer of the 14th century left the following description in the case of a sultan of the Malli [*sic*] Kingdom: "His end was to be overtaken by the sleeping sickness (*illat an-nawm*) which is a disease that frequently befalls the inhabitants of these countries especially their chieftains. Sleep overtakes one of them in such a manner that it is hardly possible to awake him."[25]

British naval surgeon John Atkins described the disease on his return from West Africa in 1734:

> "The Sleepy Distemper (common among the Negroes) gives no other previous Notice, than a want of Appetite 2 or 3 days before; their sleeps are sound, and Sense and Feeling very little; for pulling, drubbing or whipping will scarce stir up Sense and Power enough to move; and the Moment you cease beating the smart is forgot, and down they fall again into a state of Insensibility, drivling constantly from the Mouth as in deep salivation; breathe slowly, but not unequally nor snort. Young people are more subject to it than the old; and the Judgement generally pronounced is Death, the Prognostik seldom failing. If now and then one of them recovers, he certainly loses the little Reason he had, and turns Ideot..."[25]

In 1903, David Bruce recognized the tsetse fly as the arthropod vector.

In 1901, a devastating epidemic erupted in Uganda, killing more than 250,000 people,[26] including about two-thirds of the population in the affected lakeshore areas. According to *The Cambridge History of Africa*, "It has been estimated that up to half the people died of sleeping-sickness and smallpox in the lands on either bank of the lower river Congo."[27]

The causative agent and vector were identified in 1903 by David Bruce, and the differentiation between the subspecies of the protozoa made in 1910. Bruce had earlier shown that *T. brucei* was the cause of a similar disease in horses and cattle that was transmitted by the tse-tse fly (*Glossina morsitans*).[25]

The first effective treatment, atoxyl, an arsenic-based drug developed by Paul Ehrlich and Kiyoshi Shiga, was introduced in 1910, but blindness was a serious side effect.

Collecting Tsetse flies with the British led *Sleeping Sickness Commission*, Uganda and Nyasaland, 1908-1913.

Suramin was first synthesized by Oskar Dressel and Richard Kothe in 1916 for Bayer. It was introduced in 1920 to treat the first stage of the disease. By 1922, Suramin was generally combined with tryparsamide (another pentavalent organoarsenic drug), the first drug to enter the nervous system and be useful in the treatment of the second stage of the gambiense form. Tryparsamide was announced in the *Journal of Experimental Medicine* in 1919 and tested in the Belgian Congo by Louise Pearce of the Rockefeller Institute in 1920. It was used during the grand epidemic in West and Central Africa on millions of people and was the mainstay of therapy until the 1960s.[28] American medical missionary Arthur Lewis Piper was active in using tryparsamide to treat sleeping sickness in the Belgian Congo in 1925.[29]

Pentamidine, a highly effective drug for the first stage of the disease, has been used since 1939. During the 1950s, it was widely used as a prophylactic agent in western Africa, leading to a sharp decline in infection rates. At the time, eradication of the disease was thought to be at hand.[*citation needed*]

The organoarsenical melarsoprol (Arsobal) developed in the 1940s is effective for patients with second-stage sleeping sickness. However, 3–10% of those injected have reactive encephalopathy (convulsions, progressive coma, or psychotic reactions), and 10–70% of such cases result in death; it can cause brain damage in those who survive the encephalopathy. However, due to its effectiveness, melarsoprol is still used today. Resistance to melarsoprol is increasing, and combination therapy with nifurtimox is currently under research.[*citation needed*]

Eflornithine (difluoromethylornithine or DFMO), the most modern treatment, was developed in the 1970s by Albert Sjoerdsma and underwent clinical trials in the 1980s. The drug was approved by the United States Food and Drug Administration in 1990.[30] Aventis, the company responsible for its manufacture, halted production in 1999. In 2001, Aventis, in association with Médecins Sans Frontières and the World Health Organization, signed a long-term agreement to manufacture and donate the drug.[*citation needed*]

In addition to sleeping sickness, previous names have included negro lethargy, maladie du sommeil (Fr), Schlafkrankheit (Gr), African lethargy,[31] and Congo trypanosomiasis.[31][32]

## Research [edit]

The genome of the parasite has been sequenced and several proteins have been identified as potential targets for drug treatment. Analysis of the genome also revealed the reason why generating a vaccine for this disease has been so difficult. *T. brucei* has over 800 genes that make proteins the parasite "mixes and matches" to evade immune system detection.[33]

Using a genetically modified form of a bacterium that occurs naturally in the gut of the vectors is being studied as a method of controlling the disease.[34]

Recent findings indicate the parasite is unable to survive in the bloodstream without its flagellum. This insight gives researchers a new angle with which to attack the parasite.[35]

Trypanosomiasis vaccines are undergoing research.

Additionally, the Drugs for Neglected Disease Initiative has contributed to the African sleeping sickness research effort by developing a compound called fexinidazole. This project was originally started in April 2007 and is currently in a pivotal study in clinical phase II/III.36 The goal is to have the drug succeed and be proven effective again stage one and stage two HAT caused by *T. b. gambiense*, as well HAT caused by *T. b. rhodesiense*.[36]

### Funding [edit]

For current funding statistics, human African trypanosomiasis is grouped with kinetoplastid infections. Kinetoplastids refer to a group of flagellate protozoa.[37] Kinetoplastid infections include African sleeping sickness, Chagas' disease, and Leishmaniasis. All together, these three diseases accounted for 4.4 million disability adjusted life years (DALYs) and an additional 70,075 recorded deaths yearly.[37] For kinetoplastid infections, the total global research and development funding was approximately $136.3 million in 2012.

Each of the three diseases, African sleeping sickness, Chagas' disease, and Leishmaniasis each received approximately a third of the funding, which was about $36.8 million US dollars, $38.7 million US dollars, and $31.7 million US dollars, respectively.[37]

For sleeping sickness, funding was split into basic research, drug discovery, vaccines, and diagnostics. The greatest amount of funding was directed towards basic research of the disease; approximately $21.6 million US dollars were directed towards that effort. As for therapeutic development, approximately $10.9 billion were invested.[37]

The top funder for kinetoplastid infection research and development are public sources. About 62% of the funding comes from high-income countries while 9% comes from low- and middle-income countries. High-income countries public funding is largest contributors to the neglected disease research effort. However, in recent years, funding from high-income countries has been steadily decreasing; in 2007, high-income countries provided 67.5% of the total funding whereas, in 2012, high-income countries public funds only provided 60% of the total funding for kinetoplastid infections. This downwards trend leaves a gap for other funders, such as philanthropic foundations and private pharmaceutical companies to fill.[37]

Much of the progress that has been made in African sleeping sickness and neglected disease research as a whole is a result of the other non-public funders. One of these major sources of funding has come from foundations, which have increasingly become more committed to neglected disease drug discovery in the 21st century. In 2012, philanthropic sources provided 15.9% of the total funding.[37] The Bill and Melinda Gates Foundation has been a leader in providing funding for neglected disease drug development. They have provided $444.1 million US dollars towards neglected disease research in 2012. To date, they have donated over $1.02 billion US dollars towards the neglected disease discovery efforts.[38]

For kinetoplastid infections specifically, they have donated an average of $28.15 million US dollars annually between the years 2007 to 2011.[37] They have labeled human African trypanosomiasis a high-opportunity target meaning it is a disease that presents the greatest opportunity for control, elimination, and eradication, through the development on new drugs, vaccines, public-health programs, and diagnostics. They are the second highest funding source for neglected diseases, immediately behind the US National Institutes of Health.[37] At a time where public funding is decreasing and government grants for scientific research are harder to obtain, the philanthropic world has stepped in to push the research forward.

Another important component of increased interest and funding has come from industry. In 2012, they contributed 13.1% total to the kinetoplastid research and development effort, and have additionally played an important role by contributing to public-private partnerships (PPP) as well as product-development partnerships (PDP).[37] A public-private partnership is an arrangement between one or more public entities and one or more private entities that exists to achieve a specific health outcome or to produce a health product. The partnership can exist in numerous ways; they may share and exchange funds, property, equipment, human resources, and intellectual property. These public-private partnerships and product-development partnerships have been established to address challenges in pharmaceutical industry, especially related to neglected disease research. These partnerships can help increase the scale of the effort towards therapeutic development by using different knowledge, skills, and expertise from different sources. These types of partnerships have been shown to be more effective than industry or public groups working independently.[39]

## Other animals [edit]

*Trypanosoma* of both the *rhodesiense* and *gambiense* types can affect other animals such as cattle and wild animals.[1] In animals it is known as nagana (animal African trypanosomiasis)

## References [edit]


1. ^ *a b c d e f g h i j k l m n o p* WHO Media centre (March 2014). "Fact sheet N°259: Trypanosomiasis, Human African (sleeping sickness)". *World Health*

19. ^ *a b c* Lutje, V; Seixas, J; Kennedy, A (28 June 2013). "Chemotherapy for second-stage human

*Organization*. Retrieved 25 April 2014.
2. ^ MedlinePlus Encyclopedia *Sleeping sickness*
3. ^ a b c d e f g Kennedy, PG (Feb 2013). "Clinical features, diagnosis, and treatment of human African trypanosomiasis (sleeping sickness).". *Lancet neurology*. **12** (2): 186–94. doi:10.1016/S1474-4422(12)70296-X. PMID 23260189.
4. ^ a b Simarro PP, Cecchi G, Franco JR, et al. (2012). "Estimating and mapping the population at risk of sleeping sickness". *PLoS Negl Trop Dis*. **6** (10): e1859. doi:10.1371/journal.pntd.0001859. PMC 3493382. PMID 23145192.
5. ^ a b Lozano, R (15 December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
6. ^ a b GB Lundkvist; K Kristensson; M Bentivoglio (August 2004). "Why trypanosomes cause sleeping sickness". *Physiology*. **19** (4): 198–206. doi:10.1152/physiol.00006.2004. PMID 15304634.
7. ^ a b c d e Brun R, Blum J, Chappuis F, Burri C (January 2010). "Human African trypanosomiasis". *Lancet*. **375** (9709): 148–59. doi:10.1016/S0140-6736(09)60829-1. PMID 19833383.
8. ^ "East African Trypanosomiasis FAQs". *Parasites — African Trypanosomiasis (also known as Sleeping Sickness)*. Centers for Disease Control and Prevention. 29 August 2012.
9. ^ "West African Trypanosomiasis FAQs". *Parasites – African Trypanosomiasis (also known as Sleeping Sickness)*. Centers for Disease Control and Prevention. 29 August 2012.
10. ^ a b "Uganda: Sleeping Sickness Reaching Alarming Levels". *New Vision*. 11 May 2008.
11. ^ Olowe SA (1975). "A case of congenital trypanosomiasis in Lagos". *Trans. R. Soc. Trop. Med. Hyg*. **69** (1): 57–9. doi:10.1016/0035-9203(75)90011-5. PMID 1170654.
12. ^ a b Rocha G, Martins A, Gama G, Brandão F, Atouguia J (January 2004). "Possible cases of sexual and congenital transmission of sleeping sickness". *Lancet*. **363** (9404): 247. doi:10.1016/S0140-6736(03)15345-7. PMID 14738812.
13. ^ Cherenet T, Sani RA, Panandam JM, Nadzr S, Speybroeck N, van den Bossche P (December 2004). "Seasonal prevalence of bovine trypanosomosis in a tsetse-infested zone and a tsetse-free zone of the Amhara Region, north-west Ethiopia". *Onderstepoort J. Vet. Res*. **71** (4): 307–12. doi:10.4102/ojvr.v71i4.250. PMID 15732457.
14. ^ Cornford, E M; Bocash, W D; Braun, L D; Crane, P D; Oldendorf, W H; MacInnis, A J (1979). "Rapid distribution of tryptophol (3-indole ethanol) to the brain and other tissues". *Journal of Clinical Investigation*. **63** (6): 1241–8.
African trypanosomiasis.". *The Cochrane database of systematic reviews*. **6**: CD006201. doi:10.1002/14651858.CD006201.pub3. PMID 23807762.
20. ^ WHO mortality and health data and statistics, accessed 10 February 2009.
21. ^ World Health Organization (Geneva) (2000). "World Health Report 2000: Health Systems Improving Performance".
22. ^ WHO Expert Committee on Control and Surveillance of African trypanosomiasis (Geneva) (1998). "WHO Technical Report Series,No.881".
23. ^ "Trypanosomiasis, human African (sleeping sickness)". World Health Organization. March 2014.
24. ^ Steverding, D (12 February 2008). "The history of African trypanosomiasis.". *Parasites & vectors*. **1** (1): 3. doi:10.1186/1756-3305-1-3. PMC 2270819. PMID 18275594.
25. ^ a b c d Strong, Richard P (1944). *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases* (Seventh ed.). York, PA: The Blakiston company. p. 165.
26. ^ Fèvre EM, Coleman PG, Welburn SC, Maudlin I (April 2004). "Reanalyzing the 1900–1920 sleeping sickness epidemic in Uganda". *Emerging Infect. Dis*. **10** (4): 567–73. doi:10.3201/eid1004.020626. PMID 15200843.
27. ^ Fage, John D. (5 September 1985). *The Cambridge History of Africa: From the earliest times to c. 500 BC*. Cambridge University Press. p. 748. ISBN 978-0-521-22803-9.
28. ^ Steverding, Dietmar (2010). "The development of drugs for treatment of sleeping sickness: a historical review". *Parasites & Vectors*. **3** (1): 15. doi:10.1186/1756-3305-3-15. PMC 2848007. PMID 20219092. Retrieved 14 October 2014.
29. ^ Klingman, Jack (1994). "Arthur Lewis Piper, M.D.: A Medical Missionary in the Belgian Congo". *Journal of Community Health*. **19** (2). Periodicals Archive Online accessed 15 October 2013.
30. ^ Urban Hellgren; Orjan Ericsson; Yakoub AdenAbdi; Lars L Gustafsson. *Handbook of Drugs for Tropical Parasitic Infections*. p. 60. ISBN 9780203211519.
31. ^ a b Robinson, Victor, ed. (1939). "African Lethargy, Sleeping Sickness, or Congo trypanosomiasis; Trypanosoma gambiense". *The Modern Home Physician, A New Encyclopedia of Medical Knowledge*. WM. H. Wise & Company (New York)., pp. 20–21.
32. ^ Strong, Richard P (1944). *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases* (Seventh ed.). York, PA: The Blakiston company. p. 164.
33. ^ Berriman M; Ghedin E; Hertz-Fowler C; et al. (2005). "The genome of the African trypanosome *Trypanosoma brucei*". *Science*. **309** (5733): 416–22. Bibcode:2005Sci...309..416B. doi:10.1126/science.1112642. PMID 16020726.
34. ^ Doudoumis V, Alam U, Aksoy E, et al. (March

doi:10.1172/JCI109419. PMC 372073. PMID 447842.
15. ^ Truc P; Lejon V; Magnus E; et al. (2002). "Evaluation of the micro-CATT, CATT/Trypanosoma brucei gambiense, and LATEX/T b gambiense methods for serodiagnosis and surveillance of human African trypanosomiasis in West and Central Africa". *Bull. World Health Organ.* **80** (11): 882–6. PMC 2567684. PMID 12481210. Retrieved 16 March 2009.
16. ^ *a b* Brun R, Blum J, Chappuis F, Burri C (January 2010). "Human African trypanosomiasis". *Lancet*. **375** (9709): 148–59. doi:10.1016/S0140-6736(09)60829-1. PMID 19833383. "See pp. 154–5"
17. ^ Schofield CJ, Kabayo JP (2008). "Trypanosomiasis vector control in Africa and Latin America". *Parasit Vectors*. **1** (1): 24. doi:10.1186/1756-3305-1-24. PMC 2526077. PMID 18673535.
18. ^ "Strategic Direction for African Trypanosomiasis Research". *Special Programme for Research and Training in Tropical Diseases*. Archived from the
2013). "Tsetse-Wolbachia symbiosis: comes of age and has great potential for pest and disease control". *J. Invertebr. Pathol.* **112** (Suppl): S94–103. doi:10.1016/j.jip.2012.05.010. PMC 3772542. PMID 22835476.
35. ^ "African Sleeping Sickness Breakthrough". Archived from the original on 13 May 2006. Retrieved 7 April 2006.
36. ^ "Fexinidazole". Drugs for Neglected Disease Initiative. October 2013.
37. ^ *a b c d e f g h i* Moran, M.; Guzman, J.; Chapman, N.; Abela-Oversteengen, L.; Howard, R.; Farrell, P.; Luxford, J. "Neglected Disease Research and Development: The Public Divide." (PDF). Global Funding of Innovation for Neglected Disease. Retrieved 30 October 2016.
38. ^ "Strategy Overview". *Neglected Infectious Diseases*. Bill and Melinda Gates Foundation. 2013.
39. ^ "Background Paper 8: 8.1 Public-Private Partnerships and Innovation" (PDF). *Priority Medicines for Europe and the World Update Report*. World Health Organization. 2013.

## External links [edit]

- "Sleeping sickness". Médecins Sans Frontières.
- Links to pictures of Sleeping Sickness (Hardin MD/ University of Iowa) archived 2006-02-19.
- Hale Carpenter, G.D. (1920). *A Naturalist on Lake Victoria, with an Account of Sleeping Sickness and the Tse-tse Fly*. Unwin. OCLC 2649363.

| v · t · e | **Infectious diseases – Parasitic disease: protozoan infection: Excavata (A06–A07, B55–B57, 007, 085–086)** | | |
|---|---|---|---|
| **Discicristata** | **Trypanosomatida** | **Trypanosomiasis** | *T. brucei* (**African trypanosomiasis** · · *T. cruzi* (Chagas disease · · |
| | | **Leishmaniasis** | *Leishmania major* / *L. mexicana* / *L. aethiopica* / *L. tropica* (Cutaneous leishmaniasis · · *L. braziliensis* (Mucocutaneous leishmaniasis · · *L. donovani* / *infantum* (Visceral leishmaniasis · · |
| | **Schizopyrenida** | | *Naegleria fowleri* (Primary amoebic meningoencephalitis · · |
| **Trichozoa** | **Diplomonadida** | | *Giardia lamblia* (Giardiasis) · |
| | **Trichomonadida** | | *Trichomonas vaginalis* (Trichomoniasis · · *Dientamoeba fragilis* (Dientamoebiasis · · |

| v · t · e | **Psychophysiology: Sleep and sleep disorders (F51 and G47 / 307.4 and 327)** | |
|---|---|---|
| **Sleep stages** | Rapid eye movement (REM) (Non-rapid eye movement · · Slow-wave · | |
| **Brain waves** | Alpha wave · Beta wave · Delta wave · Gamma wave · K-complex · Mu rhythm · Sensorimotor rhythm · Sleep spindle · Theta wave · | |
| | **Dyssomnia** | Hypersomnia · Insomnia · Kleine–Levin syndrome · Narcolepsy · Sleep apnea (Central hypoventilation syndrome · Obesity hypoventilation syndrome · · |

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| **Sleep disorders** | | Sleep state misperception · |
| | **Circadian rhythm disorder** | Advanced sleep phase disorder · Delayed sleep phase disorder · Irregular sleep–wake rhythm · Jet lag · Non-24-hour sleep–wake disorder · Shift work sleep disorder · |
| | **Parasomnia** | Catathrenia · Night terror · Rapid eye movement sleep behavior disorder · Sleepwalking · Somniloquy · |
| | **Other** | Bruxism · Night eating syndrome · Nocturia · Nocturnal myoclonus · |
| **Benign phenomena** | | Dream · Exploding head syndrome · False awakening · Hypnagogia / Sleep onset · Hypnic jerk · Lucid dream · Nightmare · Nocturnal clitoral tumescence · Nocturnal emission · Nocturnal penile tumescence · Sleep paralysis · Somnolence · Vivid dream · |
| **Related topics** | | Bed (Bunk bed · Daybed · Four-poster bed · Futon · Hammock · Mattress · Sleeping bag · · Bed bug · Bedding · Bedroom · Bedtime · Bedtime story · Bedtime toy · Biphasic and polyphasic sleep · Chronotype · Dream journal · Excessive daytime sleepiness · Hypnopompic state · Lullaby · Microsleep · Nap · Nightwear · Polysomnography · Power nap · Second wind · Siesta · Sleep and creativity · Sleep and learning · Sleep debt · Sleep deprivation · Sleep diary · Sleep hygiene · Sleep induction · Sleep inertia · Sleep medicine · "**Sleeping sickness**"[1] · Sleeping while on duty · Sleepover · Snoring · Somnology · |

[1] Not a sleep disorder. ·

| v · t · e · | **Diseases of poverty** |
|---|---|
| **Diseases of poverty** | AIDS · Malaria · Tuberculosis · Measles · Pneumonia · Diarrheal diseases · |
| **Neglected diseases** | Cholera · Chagas disease · **African sleeping sickness** · Schistosomiasis · Dracunculiasis · River blindness · Leishmaniasis · Trachoma · |
| **Miscellaneous** | Malnutrition · Priority review voucher · |

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| **Authority control** | NDL: 00571566 · |

Categories: Health in Africa | Sleep disorders | Protozoal diseases | Tropical diseases | Neglected diseases | Insect-borne diseases | Parasitic diseases




# Ascariasis

From Wikipedia, the free encyclopedia

*This article is about the infection. For the organism, see Ascaris.*

**Ascariasis** is a disease caused by the parasitic roundworm *Ascaris lumbricoides*.[1] Infections have no symptoms in more than 85% of cases, especially if the number of worms is small.[1] Symptoms increase with the number of worms present and may include shortness of breath and fever in the beginning of the disease.[1] These may be followed by symptoms of abdominal swelling, abdominal pain, and diarrhea.[1] Children are most commonly affected, and in this age group the infection may also cause poor weight gain, malnutrition, and learning problems.[1][2][3]

Infection occurs by eating food or drink contaminated with *Ascaris* eggs from feces.[2] The eggs hatch in the intestines, burrow through the gut wall, and migrate to the lungs via the blood.[2] There they break into the alveoli and pass up the trachea, where they are coughed up and swallowed.[2] The larvae then pass through the stomach for a second time into the intestine, where they become adult worms.[2] Ascariasis is classified as a neglected tropical disease as it is a type of soil-transmitted helminthiasis. These diseases are in turn part of a group of diseases called helminthiases.[4]

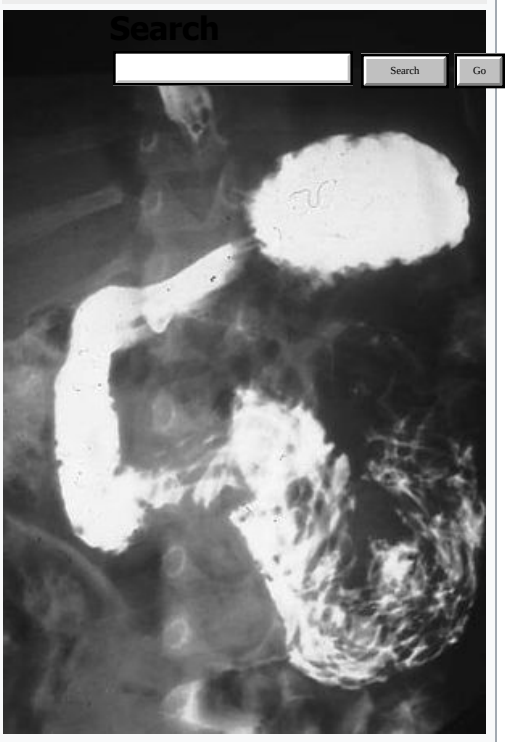
Prevention is by improved sanitation, which includes improving access to toilets and proper disposal of feces.[1][5] Handwashing with soap appears protective.[6] In areas where more than 20% of the population is affected, treating everyone at regular intervals is recommended.[1] Reoccurring infections are common.[2][7] There is no vaccine.[2] Treatments recommended by the World Health Organization are the medications albendazole, mebendazole, levamisole, or pyrantel pamoate.[2] Other effective agents include tribendimidine and nitazoxanide.[2]

About 0.8 to 1.2 billion people globally have ascariasis, with the most heavily affected populations being in sub-Saharan Africa, Latin America, and Asia.[1][8][9] This makes ascariasis the most common form of soil-transmitted helminthiasis.[8] As of 2010 it caused about 2,700 deaths a year, down from 3,400 in 1990.[10] Another type of *Ascaris* infects pigs.[1]

Contents



Ascariasis



High number of ascaris worms – visible as black tangled mass – are filling the duodenum, the first portion of the bowel after the stomach, of this South African patient (X-ray image with barium as contrast medium)

| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | B77 |
| **ICD-9-CM** | 127.0 |
| **OMIM** | 604291 |
| **DiseasesDB** | 934 |
| **MedlinePlus** | 000628 |
| **eMedicine** | article/212510 |
| **MeSH** | D001196 |

[edit on Wikidata]

## Signs and symptoms [edit]

*Further information: Helminthiasis § Signs and symptoms*

Most people who are infected with only a small number of worms have no symptoms. It is common to find that most people are infected by a small number of worms, while a small number of people are heavily infected, something that is characteristic of many worm infections.[1][11] Clinical features depend on the affected body site.

### Migrating larvae [edit]

As larval stages travel through the body, they may cause visceral damage, peritonitis and inflammation, enlargement of the liver or spleen, and an inflammation of the lungs. Pulmonary manifestations take place during larval migration and may present as Loeffler's syndrome, a transient respiratory illness associated with blood eosinophilia and pulmonary infiltrates with radiographic shadowing.[12]

### Intestinal blockage [edit]

The worms can occasionally cause intestinal blockage when large numbers get tangled into a bolus or they may migrate from the small intestine, which may require surgery. More than 796 *A. lumbricoides* worms weighing up to 550 g [19 ounces] were recovered at autopsy from a 2-year-old South African girl. The worms had caused torsion and gangrene of the ileum, which was interpreted as the cause of death.[14]

Piece of intestine, blocked by worms, surgically removed from a 3-year-old boy in South Africa.[13]

### Bowel obstruction [edit]

Bowel obstruction may occur in up to 0.2 per 1000 per year.[1] A worm may block the ampulla of Vater, or go into the main pancreatic duct, resulting in acute pancreatitis with raised serum levels of amylase and lipase. Occasionally, a worm can travel through the biliary tree and even into the gallbladder, causing acute cholangitis or acute cholecystitis.

### Allergies [edit]

Ascariasis may result in allergies to shrimp and dustmites due to the shared antigen, tropomyosin; this has not been confirmed in the laboratory.[15][16]

### Malnutrition [edit]

The worms in the intestine may cause malabsorption and anorexia which contribute to malnutrition.[17] The malabsorption may be due to a loss of brush border enzymes, erosion and flattening of the villi, and inflammation of the lamina propria.[18]

### Others [edit]

*Ascaris* have an aversion to some general anesthetics and may exit the body, sometimes through the mouth, when an infected individual is put under general anesthesia.[19]

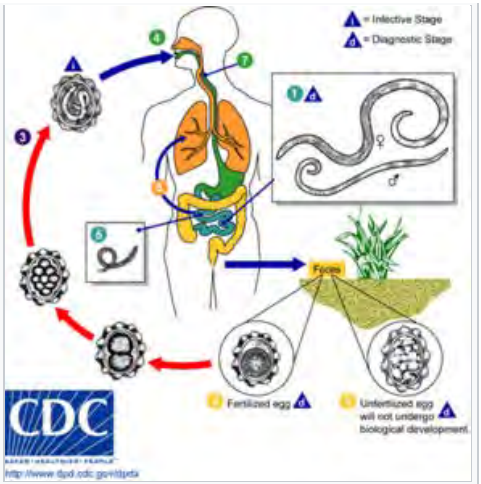
## Cause [edit]

### Transmission [edit]

The source of infection is from objects which have been contaminated with fecal matter containing eggs.[2] Ingestion of infective eggs from soil contaminated with human feces or contaminated vegetables and water is the primary route of infection. Infectious eggs may occur on other objects such as hands, money and furniture.[2] Transmission from human to human by direct contact is impossible.[20]

Transmission comes through municipal recycling of wastewater into crop fields. This is quite common in emerging industrial economies and poses serious risks for local crop sales and exports of contaminated vegetables. A 1986 outbreak of ascariasis in Italy was traced to irresponsible wastewater recycling used to grow Balkan vegetable exports.[21]

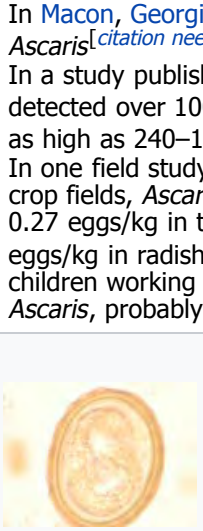
The number of ova (eggs) in sewage or in crops that were irrigated with raw or




Ascaris life cycle: Adult worms (1) live in the lumen of the small intestine. A female may produce approximately 200,000 eggs per day, which are passed with the feces (2). Unfertilized eggs may be ingested but are not infective. Fertile eggs embryonate and become infective after 18 days to several weeks (3), depending on the environmental conditions (optimum: moist, warm, shaded soil). After infective eggs are swallowed (4), the larvae hatch (5), invade the intestinal mucosa and are carried via the portal, then systemic circulation and/or lymphatics to the lungs . The larvae mature further in the lungs (6) (10 to 14 days), penetrate the alveolar walls, ascend the bronchial tree to the throat, and are swallowed (7). Upon reaching the small intestine, they develop into adult worms (8). Between 2 and 3 months are required from ingestion of the infective eggs to oviposition by the adult female. Adult worms can live 1 to 2 years.

partially treated sewage, is a measure of the degree of ascariasis incidence. For example:

- A 1978 study showed about 75% of all sewage sludge samples sampled in United States urban catchments contained *Ascaris* ova, with rates as high as 5 to 100 eggs per litre[*citation needed*].
- In Frankfort, Indiana, 87.5% of the sludge samples were positive with *Ascaris*, *Toxocara*, *Trichuris*, and hookworm[*citation needed*].
- In Macon, Georgia, one of the 13 soil samples tested positive for *Ascaris*[*citation needed*].
- In a study published in 1992, municipal wastewater in Riyadh, Saudi Arabia detected over 100 eggs per litre of wastewater[22] and in Czechoslovakia was as high as 240–1050 eggs per litre.[23]
- In one field study in Marrakech, Morocco, where raw sewage is used to fertilize crop fields, *Ascaris* eggs were detected at the rate of 0.18 eggs/kg in potatoes, 0.27 eggs/kg in turnip, 4.63 eggs/kg in mint, 0.7 eggs/kg in carrots, and 1.64 eggs/kg in radish.[24] A similar study in the same area showed that 73% of children working on these farms were infected with helminths, particularly *Ascaris*, probably as a result of exposure to the raw sewage.



The larva of Ascaris lumbricoides developing in the egg

Ascaris lumbricoides adult worms (with measuring tape for scale)

Ascaris lumbricoides adult worms

Ascaris egg, incubation process: The Ascaris egg incubation process consists in placing the egg in a controlled environment, at 26°C during 28 days, in acidic conditions. This process allows for evaluation of an egg

to determine if it is viable or not, by watching the bipartition of the nucleus, and the growth of the larva.

### Lifecycle [edit]

The first appearance of eggs in stools is 60–70 days. In larval ascariasis, symptoms occur 4–16 days after infection. The final symptoms are gastrointestinal discomfort, colic and vomiting, fever, and observation of live worms in stools. Some patients may have pulmonary symptoms or neurological disorders during migration of the larvae. There are generally few or no symptoms. A bolus of worms may obstruct the intestine; migrating larvae may cause pneumonitis and eosinophilia. Adult worms have a lifespan of 1–2 years which means that individuals may be infected all their lives as worms die and new worms are acquired.[11]

Eggs can survive potentially for 15 years and a single worm may produce 200 thousand eggs a day.[2] They maintain their position by swimming against the intestinal flow.[25]

## Diagnosis [edit]

Most diagnoses are made by identifying the appearance of the worm or eggs in feces. Due to the large quantity of eggs laid, physicians can diagnose using only one or two fecal smears.[*citation needed*]

The diagnosis is usually incidental when the host passes a worm in the stool or vomit. The eggs can be seen in a smear of fresh feces examined on a glass slide under a microscope and there are various techniques to concentrate them first or increase their visibility, such as the ether sedimentation method or the Kato technique. The eggs have a characteristic shape: they are oval with a thick, mamillated shell (covered with rounded mounds or lumps), measuring 35-50 micrometer in diameter and 40-70 in length. During pulmonary disease, larvae may be found in fluids aspirated from the lungs. White blood cells counts may demonstrate peripheral eosinophilia; this is common in many parasitic infections and is not specific to ascariasis. On X-ray, 15–35 cm long filling defects, sometimes with whirled appearance (bolus of worms).

## Mechanism [edit]

*Ascaris* takes most of its nutrients from the partially digested host food in the intestine. There is some evidence that it can secrete anti-enzymes, presumably to protect itself from digestion by the hosts' enzymes. Children are often more severely affected.[1]

## Prevention [edit]

Prevention is by improved access to sanitation which includes the use of properly functioning and clean toilets by all community members as one important aspect.[1] Handwashing with soap may be protective; however, there is no evidence it affects the severity of disease.[6] Eliminating the use of untreated human faeces as fertilizer is also important.

In areas where more than 20% of the population is affected treating everyone is recommended.[1] This has a cost of about 2 to 3 cents per person per treatment.[1] This is known as mass drug administration and is often carried out among school-age children.[26] For this purpose, broad-spectrum benzimidazoles such as mebendazole and albendazole are the drugs of choice recommended by WHO.[27]

## Treatment [edit]

*Further information: Helminthiasis § Treatment*

### Medications [edit]

Medications that are used to kill roundworms are called ascaricides. Those recommended by the World Health Organization for ascariasis are: albendazole, mebendazole, levamisole and pyrantel pamoate.[2] Other effective agents include tribendimidine and nitazoxanide.[2] Pyrantel pamoate may induce intestinal obstruction in a heavy worm load. Albendazole is contraindicated during pregnancy and children under two years of age. Thiabendazole may cause migration of the worm into the esophagus, so it is usually combined with piperazine.

Piperazine is a flaccid paralyzing agent that blocks the response of Ascaris muscle to acetylcholine, which immobilizes the worm. It prevents migration when treatment is accomplished with weak drugs such as thiabendazole. If used by itself, it causes the worm to be passed out in the feces and may be used when worms have caused blockage of the intestine or the biliary duct.

Corticosteroids can treat some of the symptoms, such as inflammation.

## Surgical intervention [edit]

In some cases with severe infestation the worms may cause bowel obstruction, requiring emergency surgery.[28] The bowel obstruction may be due to all the worms or twisting of the bowel.[28] During the surgery the worms may be manually removed.[28]

## Alternative medicine [edit]

- Hexylresorcinol effective in single dose[29]
- Santonin, more toxic than hexylresorcinol[29]
- Oil of chenopodium, more toxic than hexylresorcinol[29]

Santonin is often only partly effective.[30]

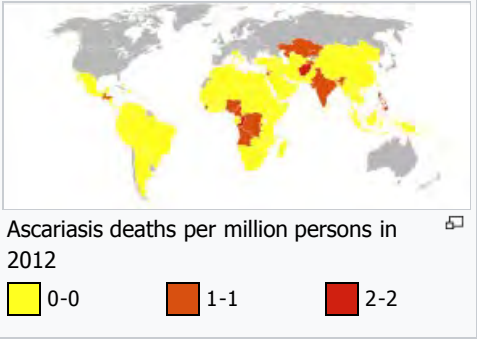
# Prognosis [edit]

It is rare for the infections to be life-threatening.[1]

# Epidemiology [edit]

## Regions [edit]

Ascariasis is common in Africa and in Southeast Asia. It also occurs in the United States including Gulf Coast.[*citation needed*]

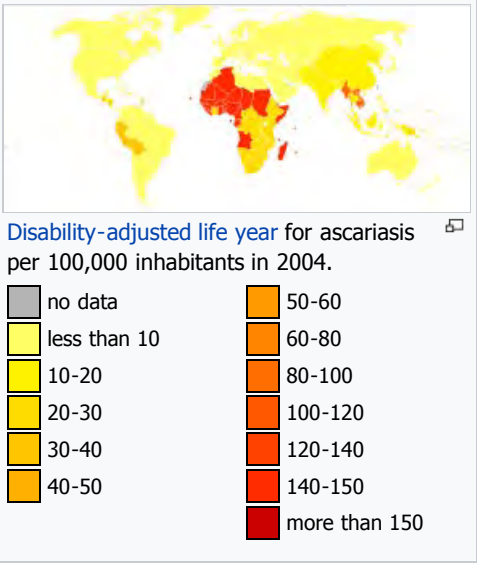



## Infection estimates [edit]

Roughly 0.8-1.3 billion individuals are infected with this intestinal worm, primarily in Africa and Asia.[1][2][9] About 120 to 220 million of these cases are symptomatic.[1] One study indicated that the prevalence of ascariasis in the United States at about 4 million (2%).[*citation needed*]

## Deaths [edit]

As of 2010 Ascariasis caused about 2,700 directly attributable deaths, down from 3,400 in 1990.[10] The indirectly attributable deaths due to the malnutrition link may be much higher.




# Research [edit]

There are two animal models, the mouse and pig, used in studying *Ascaris* infection.[31][32]

# Other animals [edit]

Infections in pigs leads to poor weight gain and thus financial losses for the farmer.[1] In pigs the infection is due to *Ascaris suum*.[1] In horses and other equines, the equine roundworm is *Parascaris equorum* and the parasites are colloquially called Ascarids. A problem for young animals more than for mature ones, clinical signs include unthriftiness, potbelly, rough hair coat, and slow growth.[33]

# References [edit]


1. ^ *a b c d e f g h i j k l m n o p q r s t* Dold, C; Holland, CV (Jul 2011). "Ascaris and ascariasis.". *Microbes and infection / Institut Pasteur*. **13** (7): 632–7. doi:10.1016/j.micinf.2010.09.012. PMID 20934531.
2. ^ *a b c d e f g h i j k l m n o* Hagel, I; Giusti, T (Oct 2010). "Ascaris lumbricoides: an overview of therapeutic targets.". *Infectious disorders drug targets*. **10** (5): 349–67. doi:10.2174/1871526107931808 76. PMID 20701574.
18. ^ Stephenson, L.S. (1987). The Impact of Helminth Infections on Human Nutrition. London: Taylor & Francis.
19. ^ Wu ML, Jones VA (January 2000). "*Ascaris lumbricoides*". *Arch. Pathol. Lab. Med.* **124** (1): 174–5. doi:10.1043/0003-9985(2000)124<0174:AL>2.0.CO;2 (inactive 2016-04-29). PMID 10629158.
20. ^ "*Ascaris* Infection Fact Sheet".
21. ^ Pawlowski, ZS; Schultzberg K (1986). "Ascariasis and sewage in Europe". In Block JC. *Epidemiological Studies of Risks*

3. ^ "Soil-transmitted helminth infections Fact sheet N°366". *World Health Organization*. June 2013.
4. ^ "Neglected Tropical Diseases". *cdc.gov*. June 6, 2011. Retrieved 28 November 2014.
5. ^ Ziegelbauer, K; Speich, B; Mäusezahl, D; Bos, R; Keiser, J; Utzinger, J (Jan 2012). "Effect of sanitation on soil-transmitted helminth infection: systematic review and meta-analysis.". *PLOS Medicine*. **9** (1): e1001162. doi:10.1371/journal.pmed.1001162. PMC 3265535. PMID 22291577.
6. ^ *a b* Fung, IC; Cairncross, S (Mar 2009). "Ascariasis and handwashing.". *Transactions of the Royal Society of Tropical Medicine and Hygiene*. **103** (3): 215–22. doi:10.1016/j.trstmh.2008.08.003. PMID 18789465.
7. ^ Jia, TW; Melville, S; Utzinger, J; King, CH; Zhou, XN (2012). "Soil-transmitted helminth reinfection after drug treatment: a systematic review and meta-analysis.". *PLoS neglected tropical diseases*. **6** (5): e1621. doi:10.1371/journal.pntd.0001621. PMC 3348161. PMID 22590656.
8. ^ *a b* Keiser, J; Utzinger, J (2010). "The drugs we have and the drugs we need against major helminth infections". *Advances in parasitology*. Advances in Parasitology. **73**: 197–230. doi:10.1016/s0065-308x(10)73008-6. ISBN 978-0-12-381514-9. PMID 20627144.
9. ^ *a b* Fenwick, A (Mar 2012). "The global burden of neglected tropical diseases.". *Public health*. **126** (3): 233–6. doi:10.1016/j.puhe.2011.11.015. PMID 22325616.
10. ^ *a b* Lozano, R (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
11. ^ *a b* Anderson, R.M. & May, R.M. (1991). Infectious diseases of humans. Dynamics and control. Oxford: Oxford Scientific Publications
12. ^ Torok E. Oxford Handbook Infect Dis and Microbiol, 2009
13. ^ Fincham, J., Dhansay, A. (2006). Worms in SA's children – MRC Policy Brief. Nutritional Intervention Research Unit of the South African Medical Research Council, South Africa
14. ^ Baird JK, Mistrey M, Pimsler M, Connor DH (March 1986). "Fatal human ascariasis following secondary massive infection". *Am. J. Trop. Med. Hyg*. **35** (2): 314–8. PMID 3953945.
15. ^ Berman, Jules J. (2012), *Taxonomic Guide to Infectious Diseases: Understanding the Biologic Classes of Pathogenic Organisms*, Academic Press, p. 151, ISBN 978-0-12-415895-5
16. ^ Rollinson, D.; Hay, S.I. (2011), *Advances in Parasitology, Volume 66*, Academic Press, p. 165, ISBN 978-0-08-087900-0
17. ^ Hall A.; Hewitt G.; Tuffrey V. (2008). "A review and meta-analysis of the impact of intestinal worms on child growth and nutrition". *Maternal and Child Nutrition*. **4** (Suppl 1): 118–236. doi:10.1111/j.1740-8709.2007.00127.x. PMID 18289159.

*Associated With the Agricultural Use of Sewage Sludge: Knowledge and Needs (EUR)*. Elsevier Science Pub Co. pp. 83–93. ISBN 1-85166-035-6.

22. ^ Bolbol AS (1992). "Risk of contamination of human and agricultural environment with parasites through reuse of treated municipal wastewater in Riyadh, Saudi Arabia". *J Hyg Epidemiol Microbiol Immunol*. **36** (4): 330–7. PMID 1300348.
23. ^ Horák P (1992). "Helminth eggs in the sludge from three sewage treatment plants in Czechoslovakia". *Folia Parasitol*. **39** (2): 153–7. PMID 1644362.
24. ^ Habbari K, Tifnouti A, Bitton G, Mandil A (September 1999). "Helminthic infections associated with the use of raw wastewater for agricultural purposes in Beni Mellal, Morocco". *East. Mediterr. Health J*. **5** (5): 912–21. PMID 10983530.
25. ^ Crompton, D.W. and Pawlowski, Z. (1985). Life history and development of *Ascaris lumbricoides* and the persistence of human ascariasis. In: Ascariasis and its public health significance. Eds Crompton, D.W. Nesheim, M.C. and Pawlowski, Z.S. London: Taylor & Francis
26. ^ Mascarini-Serra L (2011). "Prevention of soil-transmitted helminth infection". *Journal of Global Infectious Diseases*. **3** (2): 175–182. doi:10.4103/0974-777X.81696. PMC 3125032. PMID 21731306.
27. ^ WHO (2006). *Preventive Chemotherapy in Human Helminthiasis : Coordinated Use of Anthelminthic Drugs in Control Interventions : a Manual for Health Professionals and Programme Managers* (PDF). WHO Press, World Health Organization, Geneva, Switzerland. pp. 1–61. ISBN 9241547103.
28. ^ *a b c* Hefny, AF; Saadeldin, YA; Abu-Zidan, FM (May 2009). "Management algorithm for intestinal obstruction due to ascariasis: a case report and review of the literature.". *Ulusal travma ve acil cerrahi dergisi = Turkish journal of trauma & emergency surgery : TJTES*. **15** (3): 301–5. PMID 19562557.
29. ^ *a b c* Holt, Jr Emmett L, McIntosh Rustin: Holt's Diseases of Infancy and Childhood: A Textbook for the Use of Students and Practitioners. Appleton and Co, New York,11th edition
30. ^ Ravina, Enrique (2011). *The evolution of drug discovery : from traditional medicines to modern drugs* (1. Aufl. ed.). Weinheim: Wiley-VCH. p. 91. ISBN 978-3-527-32669-3.
31. ^ Howes HL (June 1971). "Anthelmintic studies with pyrantel. II. Prophylactic activity in a mouse-ascaris suum test model". *J. Parasitol*. The Journal of Parasitology, Vol. 57, No. 3. **57** (3): 487–93. doi:10.2307/3277899. JSTOR 3277899. PMID 5090955.
32. ^ Lichtensteiger CA, DiPietro JA, Paul AJ, Neumann EJ, Thompson L (April 1999). "Persistent activity of doramectin and ivermectin against *Ascaris suum* in experimentally infected pigs". *Vet. Parasitol*. **82** (3): 235–41. doi:10.1016/S0304-4017(99)00018-7. PMID 10348103.
33. ^ "Parasites:Ascarids". *eXtension*. September 27, 2011. Retrieved 9 November 2014.


## External links [edit]

- Image (warning, very graphic):Image 1
- CDC *DPDx Parasitology Diagnostic Web Site*
- Ascariasis: Radiology[*permanent dead link*] and color pathology pictures[*permanent dead link*] from MedPix
- Discussion of Ascaris on the "This week in Parasitism" Podcast

| v · t · e · | **Infectious diseases · Parasitic disease: helminthiases (B65–B83 · 120–129 · ·** | | |
|---|---|---|---|
| | **Fluke/trematode (Trematode infection)** | **Blood fluke** | *Schistosoma mansoni/japonicum/mekongi/haematobium* (Schistosomiasis · · *Trichobilharzia regenti* (Swimmer's itch · · |
| | | **Liver fluke** | *Clonorchis sinensis* (Clonorchiasis · · *Dicrocoelium dendriticum/Dicrocoelium hospes* (Dicrocoeliasis · · *Fasciola hepatica/gigantica* (Fasciolosis · · *Opisthorchis viverrini/Opisthorchis felineus* (Opisthorchiasis · · |
| | | **Lung fluke** | *Paragonimus westermani/Paragonimus kellicotti* (Paragonimiasis · · |

| | | | | | |
|---|---|---|---|---|---|
| **Flatworm/ platyhelminth** | | **Intestinal fluke** | | | *Fasciolopsis buski* (Fasciolopsiasis · · *Metagonimus yokagawai* (Metagonimiasis · · *Heterophyes heterophyes* (Heterophyiasis · · |
| | **Cestoda (Tapeworm infection)** | **Cyclophyllidea** | | | *Echinococcus granulosus*/*Echinococcus multilocularis* (Echinococcosis · · *Taenia saginata*/*Taenia asiatica*/*Taenia solium (pork)* (Taeniasis/Cysticercosis · · *Hymenolepis nana*/*Hymenolepis diminuta* (Hymenolepiasis · · |
| | | **Pseudophyllidea** | | | *Diphyllobothrium latum* (Diphyllobothriasis · · *Spirometra erinaceieuropaei* (Sparganosis · · *Diphyllobothrium mansonoides* (Sparganosis · · |
| **Roundworm/ nematode (Nematode infection)** | **Secernentea** | **Spiruria** | **Camallanida** | | *Dracunculus medinensis* (Dracunculiasis · · |
| | | | **Spirurida** | **Filarioidea (Filariasis)** | *Onchocerca volvulus* (Onchocerciasis · · *Loa loa* (Loa loa filariasis · · *Mansonella* (Mansonelliasis · · *Dirofilaria repens* (Dirofilariasis · · *Wuchereria bancrofti*/*Brugia malayi*/*Brugia timori* (*Lymphatic filariasis* · · |
| | | | | **Thelazioidea** | *Gnathostoma spinigerum*/*Gnathostoma hispidum* (Gnathostomiasis · · *Thelazia* (Thelaziasis · · |
| | | | | **Spiruroidea** | *Gongylonema* · |
| | | **Strongylida (hookworm)** | | | Hookworm infection · *Ancylostoma duodenale*/*Ancylostoma braziliense* (Ancylostomiasis · Cutaneous larva migrans · · *Necator americanus* (Necatoriasis · · *Angiostrongylus cantonensis* (Angiostrongyliasis · · *Metastrongylus* (Metastrongylosis · · |
| | | **Ascaridida** | | | *Ascaris lumbricoides* (**Ascariasis** · · *Anisakis* (Anisakiasis · · *Toxocara canis*/*Toxocara cati* (Visceral larva migrans/Toxocariasis · · *Baylisascaris* · *Dioctophyme renale* (Dioctophymosis · · *Parascaris equorum* · |
| | | **Rhabditida** | | | *Strongyloides stercoralis* (Strongyloidiasis · · *Trichostrongylus spp.* (Trichostrongyliasis · · *Halicephalobus gingivalis* · |
| | | **Oxyurida** | | | *Enterobius vermicularis* (Enterobiasis · Pinworm · · |
| | **Adenophorea** | *Trichinella spiralis* (Trichinosis · · *Trichuris trichiura* (Trichuriasis * Whipworm) · *Capillaria philippinensis* (Intestinal capillariasis · · *Capillaria hepatica* · | | | |

**Biology portal** **Medicine portal**

Categories: Helminthiases | Foodborne illnesses | Ascaridida | Neglected diseases | Conditions diagnosed by stool test

# Buruli ulcer

From Wikipedia, the free encyclopedia

**Buruli ulcer** (also known as the **Bairnsdale ulcer**, **Searls ulcer**, or **Daintree ulcer**[1][2][3]) is an infectious disease caused by *Mycobacterium ulcerans*.[4] The early stage of the infection is characterised by a painless nodule or area of swelling.[4] This nodule can turn into an ulcer.[4] The ulcer may be larger inside than at the surface of the skin,[5] and can be surrounded by swelling.[5] As the disease worsens, bone can be infected.[4] Buruli ulcers most commonly affect the arms or legs.[4] Fever is uncommon.[4]

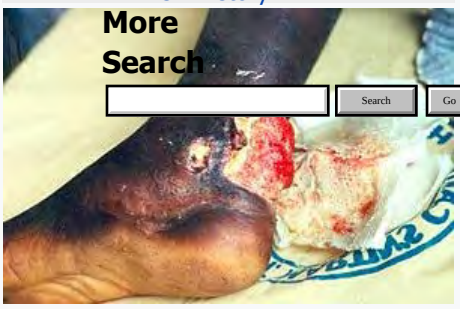
*M. ulcerans* releases a toxin known as mycolactone, which decreases immune system function and results in tissue death.[4] Bacteria from the same family also cause tuberculosis and leprosy (*M. tuberculosis* and *M. leprae*, respectively).[4] How the disease is spread is not known.[4] Sources of water may be involved in the spread.[5] As of 2013 there is no effective vaccine.[4][6]

If people are treated early, antibiotics for eight weeks are effective in 80%.[4] The treatment often includes the medications rifampicin and streptomycin.[4] Clarithromycin or moxifloxacin are sometimes used instead of streptomycin.[4] Other treatments may include cutting out the ulcer.[4][7] After the infection heals, the area typically has a scar.[6]

Buruli ulcers occurs most commonly in rural sub-Saharan Africa especially Cote d'Ivoire, but can also occur in Asia, the Western Pacific and the Americas.[4] Cases have occurred in more than 32 countries.[5] About five to six thousand cases occur every year.[4] The disease also occurs in a number of animals other than humans.[4] Albert Ruskin Cook was the first to describe buruli ulcers in 1897.[5]

Contents


Buruli ulcer



Buruli ulcer on the ankle of a person from Ghana.

| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | A31.1 (ILDS A31.120) |
| **ICD-9-CM** | 031.1 |
| **DiseasesDB** | 8568 |
| **Patient UK** | Buruli ulcer |
| **MeSH** | D054312 |

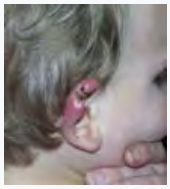
[edit on Wikidata]

## Signs and symptoms [edit]

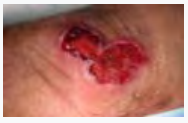
The infection in most instances presents as a painless lump just under the skin. In southern Australia, the presentation is more often as a pimple in the skin (dermis) rather than under it. The infection is mostly in the limbs, most often in exposed areas, but not on the hands or feet. In children, all areas may be involved, including the face or abdomen. A more severe form of infection produces diffuse swelling of a limb, which, unlike the papule or nodule, can be painful and accompanied by fever. Infection may frequently follow physical trauma, often minor trauma such as a small scratch.

A typical Buruli ulcer on the left hand of a 17-year-old boy in

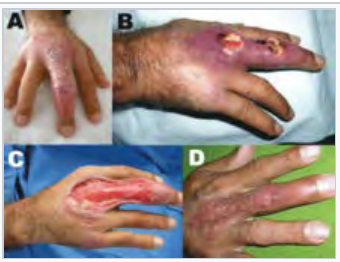
Healed Buruli ulcer lesions in a Ghanaian woman



Ear of an 18-month-old child with culture- and PCR-confirmed



Buruli ulcer in a long-term traveler to Senegal




Buruli ulcer on the hand of a person from Peru. A) nonulcerative edematous lesion on the right middle finger as first seen B) ulcerated lesions on the right middle finger about 4 weeks later C) extensive debridement, 5.5 weeks after first seen D) cured

Buruli ulcer

lesion 5 months after first seen, 1 month after autologous skin graft

## Cause [edit]

The disease is caused by *Mycobacterium ulcerans*.[4] It often occurs in close proximity to water bodies, but no specific activities that bring people into contact with water have been identified (i.e. fetching of water, fishing, washing, bathing, etc.). The mode of transmission of Buruli ulcer is not entirely known. Recent evidence suggests insects may be involved in the transmission of the infection.[8] These insects are aquatic bugs belonging to the genus Naucoris (family Naucoridae) and Diplonychus (family Belostomatidae). Trauma is probably the most frequent means by which *M. ulcerans* is introduced into the skin from surface contamination.[9] The initial trauma can be as slight as a hypodermic needle puncture or as severe as gunshot or exploding land mine wounds.[10] Other studies have suggested aerosol spread but these are not proven.[11] In Australia, animals such as koalas and possums are naturally infected.[12][13] Epidemiological evidence has not clearly supported person-to-person transmission. However, Muelder & Nourou found that 10 out of 28 patients had relatives who had also had the disease, and cautioned against the dismissal of person-to-person transmission.[14] Given the number of patients who shed large numbers of bacilli from their wounds and live in very close contact with relatives, more cases should have been observed. The cases reported by Muelder & Nourou could perhaps have been exposed to a common source of infection, and there might also be genetic component to sensitivity to the disease.

After considering the various suspected agents, Portaels *et al.* proposed the hypothesis that human beings, as well as domestic and wild animals, could be contaminated or infected by biting insects such as water bugs.[15] Aquatic bugs are cosmopolite insects found throughout temperate and tropical regions especially rich in freshwater. They represent about 10% of all species of Hemiptera associated with water and belong to two series of the suborder Heteroptera: the Nepomorpha, which include four superfamilies whose members spend most of their time under water, and the Naucoridae, which include a single family, the Naucoridae, whose members are commonly termed creeping water bugs.

Whether found in temperate countries like France or tropical ones like Ivory Coast, aquatic bugs exhibit the same way of life, preying, according to their size, on mollusks, snails, young fish, and the adults and larvae of other insects that they capture with their raptorial front legs and bite with their rostrum. These insects can inflict painful bites on humans as well. In the Ivory Coast, where Buruli ulcer is endemic, the water bugs are present in swamps and rivers, where human activities such as farming, fishing, and bathing take place. Present findings[16] describing the experimental transmission of *M. ulcerans* from water bugs to mice are in good agreement with the possibility of this mode of transmission to humans by bites.

Also in strong support of this hypothesis was the localization of *M. ulcerans* within the salivary glands of Naucoridae.[16] Local physiological conditions of this niche appear to fit the survival and the replication needs of *M. ulcerans* but not those of other mycobacteria. Surprisingly, infiltration of the salivary glands of Naucoridae by *M. ulcerans* does not seem to be accompanied by any tissue damage similar to the ulcerative skin lesions developed by bitten individuals and mediated by the cytotoxic activity of the mycolactone[17] and other toxins produced by *M. ulcerans*.[18] The inactivation of the latter toxins could be the result of salivary enzymatic activities, which remain to be determined.

Mycobacterium ulcerans was first cultivated and characterized from the environment in 2008.[19]

## Pathology [edit]

The disease is primarily an infection of subcutaneous fat, resulting in a focus of necrotic (dead) fat containing myriads of the mycobacteria in characteristic spherules formed within the dead fat cells. Skin ulceration is a secondary event.

*M. ulcerans* releases a lipid toxin, mycolactone, which functions as an immune suppressant, necrotising agent and activator of cellular death.[20][21]

Healing may occur spontaneously but more often the disease is slowly progressive with further ulceration, granulation, scarring, and contractures. Satellite infection may occur with other nodules developing and infection may occur into bone. Although seldom fatal, the disease results in considerable morbidity and deformity.

Th1-mediated immune responses are protective against *M. ulcerans* infection, whereas Th2-mediated responses are not.

## Diagnosis [edit]

The diagnosis of Buruli ulcer is usually based on the characteristic appearance of the ulcer in an endemic area. If there is any doubt about the diagnosis, then PCR using the IS2404 target is helpful, but this is not specific for *M. ulcerans*. The Ziehl-Neelsen stain is only 40–80% sensitive, and culture is 20–60% sensitive. Simultaneous use of multiple methods may be necessary to make the diagnosis.[22]

## Prevention [edit]

There is no specific vaccine for *Myocobacterium ulcerans*.[6] The Bacillus Calmette-Guérin vaccine may offer temporary protection.[4]

## Treatment [edit]

If treated early antibiotics for eight weeks are effective in 80% of people.[4] This often includes the medications rifampicin and streptomycin.[4] Clarithromycin or moxifloxacin are sometimes used instead of streptomycin.[4]

Treatment may also include cutting out the ulcer.[7] This may be a minor operation and very successful if undertaken early. Advanced disease may require prolonged treatment with extensive skin grafting. Surgical practice can be dangerous in the developing countries where the disease is common.

## Epidemiology [edit]

The infection occurs in well-defined areas throughout the world, mostly tropical areas — in several areas in Australia, in Uganda, in several countries in West Africa, in Central and South America, in southeast Asia and New Guinea. It is steadily rising as a serious disease, especially in West Africa and underdeveloped countries, where it is the third leading cause of mycobacterial infection in healthy people, after tuberculosis and leprosy.

The disease is more likely to occur where there have been environmental changes such as the development of water storages, sand mining, and irrigation.

Buruli ulcer is currently endemic in Benin, Côte d'Ivoire, Ghana, Guinea, Liberia, Nigeria, Sierra Leone and Togo.[23] In Ghana, 1999 data indicated that the prevalence rate of the disease in the Ga West District was 87.7 per 100,000, higher than the estimated national prevalence rate at 20.7 per 100,000 generally, and 150.8 per 100,000 in the most disease-endemic districts.[24]

Map with number of reported cases of Buruli ulcer in 2009.

## Geographical distribution [edit]

Buruli ulcer has been reported from at least 32 countries around the world, mostly in tropical areas:

- West Africa: Benin, Burkina Faso, Côte d'Ivoire, Ghana, Liberia, Nigeria, Togo, Guinea, Sierra Leone.
- Other African Countries: Angola, Cameroon, Congo, Democratic Republic of Congo, Equatorial Guinea, Gabon, Sudan, Uganda.
- Western Pacific: Australia, Papua New Guinea, Kiribati.
- Americas: French Guyana, Mexico, Peru, Surinam.
- Asia: China, Malaysia, Japan.

In several of these countries, the disease is not considered to be a public health problem, hence the current distribution and the number of cases are not known. Possible reasons include:

- the distribution of the disease is often localized in certain parts of endemic countries;
- Buruli ulcer is not a notifiable disease
- In most places where the disease occurs, patients receive care from private sources such as voluntary mission hospitals and traditional healers. Hence the existence of the disease may not come to the attention of the ministries of health.

It most commonly occurs in Africa: Congo and Cameroon in Central Africa, Côte d'Ivoire, Ghana and Benin in West Africa. Some Southeast Asian countries (Papua New Guinea) and Australia have major foci, and there have been a few patients reported from South America (French Guyana and Surinam) and Mexico. Focal outbreaks have followed flooding, human migrations,[25] and man-made topographic modifications such as dams and resorts. Deforestation and increased basic agricultural activities may significantly contribute to the recent marked increases in the incidence of *M. ulcerans* infections, especially in West Africa, where the disease is rapidly emerging.

## Race, age and sex [edit]

Buruli ulcer commonly affects poor people in remote rural areas with limited access to health care. The disease can affect all age groups, although children under the age of 15 years (range 2–14 years) are predominantly affected. There are no sex differences in the distribution of cases among children. Among adults, some studies have reported higher rates among women than males (Debacker *et al.* accepted for publication). No racial or socio-economic group is exempt from the disease. Most ulcers occur on the extremities; lesions on the lower extremities are almost twice as common as those on the upper extremities. Ulcers on the head and trunk accounted for less than 8% of cases in one large series.[26]

# History [edit]

James Augustus Grant, in his book *A Walk across Africa* (1864), describes how his leg became grossly swollen and stiff with later a copious discharge. This was almost certainly the severe edematous form of the disease, and is the first known description of the infection[*citation needed*]. Buruli ulcer disease was identified in 1897 by Sir Albert Cook, a British physician, at Mengo Hospital in Kampala, Uganda. A detailed description of the disease was written in 1948 by Professor Peter MacCallum and his colleagues, who were treating patients from the Bairnsdale district, near Melbourne, Australia. They were the first to identify *Mycobacterium ulcerans* as the pathogen causing it. The disease was so named after Buruli County in Uganda (now called Nakasongola District), because of the many cases that occurred there in the 1960s.[27] The incidence of the disease has recently been rising in tropical Africa.

In March 2008, researchers announced the first isolation of *M. ulcerans* from the environment.[19] This suggested that the disease might be transmitted via contact with the environment rather than person to person.[19] The entire genome of *M. ulcerans* has been sequenced.[*citation needed*]

## Other names [edit]

Other names include Bairnsdale ulcer, Searls ulcer, Daintree ulcer,[1][2][3] Kumusi ulcer,[28] and mycoburuli ulcers.[29] Searls was one of the first physician who first described it.[30]

# See also [edit]

- Neglected diseases

# References [edit]


1. ^ [a] [b] James, William D.; Berger, Timothy G.; et al. (2006). *Andrews' Diseases of the Skin: clinical Dermatology*. Saunders Elsevier. p. 340. ISBN 0-7216-2921-0.
2. ^ [a] [b] Rapini, Ronald P.; Bolognia, Jean L.; Jorizzo, Joseph L. (2007).
17. ^ George, K. M.; L. Pascopella; D. M. Welty & P. L. C. Small (2000). "A *Mycobacterium ulcerans* toxin, mycolactone, causes apoptosis in Guinea

**68** (9): 4623–8. doi:10.1128/AEM.68.9.4623-4628.2002. PMC 124085. PMID 12200321.

*Dermatology: 2-Volume Set*. St. Louis: Mosby. Chapter 74. ISBN 1-4160-2999-0.

3. ^ *a b* Lavender CJ, Senanayake SN, Fyfe JA, et al. (January 2007). "First case of *Mycobacterium ulcerans* disease (Bairnsdale or Buruli ulcer) acquired in New South Wales". *Med. J. Aust*. **186** (2): 62–3. PMID 17223764.
4. ^ *a b c d e f g h i j k l m n o p q r s t u v* "Buruli ulcer (*Mycobacterium ulcerans* infection) Fact sheet N°199". *World Health Organization*. June 2013. Retrieved 23 February 2014.
5. ^ *a b c d e* Nakanaga, K; Yotsu, RR; Hoshino, Y; Suzuki, K; Makino, M; Ishii, N (2013). "Buruli ulcer and mycolactone-producing mycobacteria.". *Japanese journal of infectious diseases*. **66** (2): 83–8. doi:10.7883/yoken.66.83. PMID 23514902.
6. ^ *a b c* Einarsdottir T, Huygen K (November 2011). "Buruli ulcer". *Hum Vaccin*. **7** (11): 1198–203. doi:10.4161/hv.7.11.17751. PMID 22048117.
7. ^ *a b* Sizaire V, Nackers F, Comte E, Portaels F (2006). "*Mycobacterium ulcerans* infection: control, diagnosis, and treatment". *Lancet Infect Dis*. **6** (5): 288–296. doi:10.1016/S1473-3099(06)70464-9. PMID 16631549.
8. ^ Portaels, F.; Elsen, P.; Guimaraes-Peres, A.; Fonteyne, P.A.; Meyers, W.M. (1999). "Insects in the transmission of *Mycobacterium ulcerans* infection". *Lancet*. **353** (9157): 986. doi:10.1016/S0140-6736(98)05177-0. PMID 10459918.
9. ^ Stienstra, Y.; van der Graaf, T.A.; te Meerman, G.J.; The, T.H.; de Leij, L.F.; van der Werf, T.S. (2001). "Susceptibility to development of *Mycobacterium ulcerans* disease: review of possible risk factors". *Trop Med Int Health*. **6** (7): 554–562. doi:10.1046/j.1365-3156.2001.00746.x. PMID 11469950.
10. ^ Meyers, W.M.; Shelly, W.M.; Connor, D.H.; Meyers, E.K. (1974). "Human *Mycobacterium ulcerans* infections developing at sites of trauma to skin". *Am J Trop Med Hyg*. **23** (5): 919–923. PMID 4451232.
11. ^ Veitch MG, Johnson PD, Flood PE, Leslie DE, Street AC, Hayman JA (December 1997). "A large localized outbreak of Mycobacterium ulcerans infection on a temperate southern Australian island". *Epidemiol. Infect*. **119** (3): 313–8. doi:10.1017/S0950268897008273. PMC 2809003. PMID 9440434.
12. ^ Mitchell PJ, Jerrett IV, Slee KJ (1984). "Skin ulcers caused by *Mycobacterium ulcerans* in koalas near Bairnsdale, Australia". *Pathology*. **16** (3): 256–260. doi:10.3109/00313028409068533. PMID 6514393.
13. ^ Flood P, Street A, O'Brien P, Hayman J (February 1994). "*Mycobacterium ulcerans* infection on Phillip Island, Victoria". *Med. J. Aust*. **160** (3): 160. PMID 8295586.
14. ^ Muelder, K.; A. Nourou (1990). "Buruli ulcer in Benin.". *Lancet*. **336** (8723): 1109–1111. doi:10.1016/0140-6736(90)92581-2. PMID 1977990.
15. ^ Portaels F, Chemlal K, Elsen P, et al. (April 2001). "Mycobacterium ulcerans in wild animals". *Rev. - Off. Int. Epizoot*. **20** (1): 252–64. PMID 11288515.
16. ^ *a b* Marsollier, L.; R. Robert; J. Aubry; J. P. Saint André; H. Kouakou; P. Legras; A. L. Manceau; C. Mahaza & B. Carbonnelle (2002). "Aquatic insects as a vector for *Mycobacterium ulcerans*". *Appl Environ Microbiol*. pig ulcers and tissue culture cells". *Infect Immun*. **68**: 877–883. doi:10.1128/IAI.68.2.877-883.2000. PMC 97217. PMID 10639458.
18. ^ Dobos, K.M.; Small, P.L.; Deslauriers, M.; Quinn, F.D.; King, C.H. (2001). "*Mycobacterium ulcerans* cytotoxicity in an adipose cell". *Infect Immun*. **69** (11): 7182–6. doi:10.1128/IAI.69.11.7182-7186.2001. PMC 100123. PMID 11598099.
19. ^ *a b c* Portaels F, Meyers WM, Ablordey A, Castro AG, Chemlal K, de Rijk P, Elsen P, Fissette K, Fraga AG, Lee R, Mahrous E, Small PL, Stragier P, Torrado E, Van Aerde A, Silva MT, Pedrosa J (2008). "First Cultivation and Characterization of *Mycobacterium ulcerans* from the Environment". *PLoS Negl Trop Dis*. **2** (3): e178. doi:10.1371/journal.pntd.0000178. PMC 2268003. PMID 18365032. Lay summary – *EurekAlert!* (2008-03-25).
20. ^ van der Werf TS, Stinear T, Stienstra Y, van der Graaf WT, Small PL (September 2003). "Mycolactones and *Mycobacterium ulcerans* disease". *Lancet*. **362** (9389): 1062–4. doi:10.1016/S0140-6736(03)14417-0. PMID 14522538.
21. ^ Adusumilli S, Mve-Obiang A, Sparer T, Meyers W, Hayman J, Small PL (September 2005). "*Mycobacterium ulcerans* toxic macrolide, mycolactone modulates the host immune response and cellular location of M. ulcerans in vitro and in vivo". *Cell. Microbiol*. **7** (9): 1295–304. doi:10.1111/j.1462-5822.2005.00557.x. PMID 16098217.
22. ^ Herbinger K-H; Adjei O; Awua Boateng N-Y; et al. (2009). "Comparative study of the sensitivity of different diagnostic methods for the laboratory diagnosis of Buruli ulcer disease". *Clin Infect Dis*. **48** (8): 1055–64. doi:10.1086/597398. PMID 19275499.
23. ^ WHO, (2000) Buruli ulcer: Mycobacterium ulcerans infection. Geneva
24. ^ Amofah G, Bonsu F, Tetteh C, et al. (February 2002). "Buruli ulcer in Ghana: results of a national case search". *Emerging Infect. Dis*. **8** (2): 167–70. doi:10.3201/eid0802.010119. PMC 2732443. PMID 11897068.
25. ^ Uganda Buruli Group (1971). "Epidemiology of Mycobacterium ulcerans infection (Buruli ulcer) at Kinyara, Uganda". *Trans R Soc Trop Med Hyg*. **65** (6): 763–775. doi:10.1016/0035-9203(71)90090-3. PMID 5157438.
26. ^ Marston, B.J.; Diallo, M.O.; Horsburgh jr., C.R.; Diomande, I.; Saki, M.Z.; Kanga, J.M.; Patrice, G.; Lipman, H.B.; Ostroff, S.M.; Good, R.C. (1995). "Emergence of Buruli Ulcer disease in the Daloa region of Côte d'Ivoire". *Am J Trop Med Hyg*. **52** (3): 219–224. PMID 7694962.
27. ^ "Buruli ulcer disease -Mycobacterium ulcerans infection". *Health Topics A TO Z*. Retrieved 2010-12-24.
28. ^ Rudolf, Zdenek Hubálek, Ivo (2011). *Microbial zoonoses and sapronoses*. Dordrecht: Springer. p. 258. ISBN 9789048196579.
29. ^ *Tropical diseases : a practical guide for medical practitioners and students*. Contributions from Michael Hole, Takudzwa Shumba & B.J. Swanner. Oxford: Oxford University Press. 2014. p. 167. ISBN 9780199997909. `|first1=` missing `|last1=` in Authors list (help)
30. ^ *Medical Journal of Australia*. **2** (14-26): 926. 1966 https://books.google.ca/books?id=5UBRAQAAIAAJ&q=%22Searls+ulcer%22&dq=%22Searls+ulcer%22&hl=en&sa=X&ei=HE3tVMbIBsPooATR-oEQ&ved=0CDcQ6AEwBQ. Missing or empty `|title=` (help)

## Further reading [edit]

- Merritt, R. W.; Walker, E. D.; Small, P. L. C.; Wallace, J. R.; Johnson, P. D. R.; Benbow, M. E.; Boakye, D. A. (2010). Phillips, Richard O, ed. "Ecology and Transmission of Buruli Ulcer Disease: A Systematic Review". *PLoS Neglected Tropical Diseases*. **4** (12): e911. doi:10.1371/journal.pntd.0000911. PMC 3001905. PMID 21179505.

## External links [edit]

- World Health Organization buruli ulcer page
- "*Mycobacterium ulcerans*". *NCBI Taxonomy Browser*. 1809.

| v · t · e · | **Gram-positive bacterial infection: Actinobacteria (primarily A00–A79, 001–041, 080–109)** | | |
|---|---|---|---|
| **Actinomycineae** | **Actinomycetaceae** | *Actinomyces israelii* (Actinomycosis · Cutaneous actinomycosis · · *Tropheryma whipplei* (Whipple's disease · · *Arcanobacterium haemolyticum* (Arcanobacterium haemolyticum infection · · *Actinomyces gerencseriae* · | |
| | **Propionibacteriaceae** | *Propionibacterium acnes* · | |
| | | *M. tuberculosis*/ | Tuberculosis: Ghon focus/Ghon's complex · Pott disease · *brain* (Meningitis · Rich focus · · Tuberculous lymphadenitis (Tuberculous cervical lymphadenitis · · *cutaneous* (Scrofuloderma · Erythema induratum · Lupus vulgaris · Prosector's wart · Tuberculosis cutis orificialis · Tuberculous cellulitis · Tuberculous gumma · · |

| | | | |
|---|---|---|---|
| **Corynebacterineae** | **Mycobacteriaceae** | *M. bovis* | Lichen scrofulosorum · Tuberculid (Papulonecrotic tuberculid · · Primary inoculation tuberculosis · Miliary · Tuberculous pericarditis · Urogenital tuberculosis · Multi-drug-resistant tuberculosis · Extensively drug-resistant tuberculosis · |
| | | *M. leprae* | Leprosy: Tuberculoid leprosy · Borderline tuberculoid leprosy · Borderline leprosy · Borderline lepromatous leprosy · Lepromatous leprosy · Histoid leprosy · |
| | | **Nontuberculous** | **R1:** *M. kansasii* · *M. marinum* (Aquarium granuloma · · |
| | | | **R2:** *M. gordonae* · |
| | | | **R3:** *M. avium* complex/*Mycobacterium avium*/*Mycobacterium intracellulare*/MAP (MAI infection · · *M. ulcerans* (**Buruli ulcer** · · *M. haemophilum* · |
| | | | **R4/RG:** *M. fortuitum* · *M. chelonae* · *M. abscessus* · |
| | **Nocardiaceae** | *Nocardia asteroides*/*Nocardia brasiliensis* (Nocardiosis · · *Rhodococcus equi* · | |
| | **Corynebacteriaceae** | *Corynebacterium diphtheriae* (Diphtheria · · *Corynebacterium minutissimum* (Erythrasma · · *Corynebacterium jeikeium* (Group JK corynebacterium sepsis · · | |
| **Bifidobacteriaceae** | *Gardnerella vaginalis* · | | |

Categories: Bacterial diseases | Neglected diseases | Mycobacterium-related cutaneous conditions

# Chagas disease



From Wikipedia, the free encyclopedia

**Chagas disease**, also known as **American trypanosomiasis**, is a tropical parasitic disease caused by the protozoan *Trypanosoma cruzi*.[1] It is spread mostly by insects known as Triatominae or kissing bugs.[1] The symptoms change over the course of the infection. In the early stage, symptoms are typically either not present or mild, and may include fever, swollen lymph nodes, headaches, or local swelling at the site of the bite.[1] After 8–12 weeks, individuals enter the chronic phase of disease and in 60–70% it never produces further symptoms.[2][3] The other 30 to 40% of people develop further symptoms 10 to 30 years after the initial infection,[3] including enlargement of the ventricles of the heart in 20 to 30%, leading to heart failure.[1] An enlarged esophagus or an enlarged colon may also occur in 10% of people.[1]

*T. cruzi* is commonly spread to humans and other mammals by the blood-sucking "kissing bugs" of the subfamily Triatominae.[4] These insects are known by a number of local names, including: *vinchuca* in Argentina, Bolivia, Chile and Paraguay, *barbeiro* (the barber) in Brazil, *pito* in Colombia, *chinche* in Central America, and *chipo* in Venezuela.[5] The disease may also be spread through blood transfusion, organ transplantation, eating food contaminated with the parasites, and by vertical transmission (from a mother to her fetus).[1] Diagnosis of early disease is by finding the parasite in the blood using a microscope.[3] Chronic disease is diagnosed by finding antibodies for *T. cruzi* in the blood.[3]

Prevention mostly involves eliminating kissing bugs and avoiding their bites.[1] Other preventative efforts include screening blood used for transfusions.[1] A vaccine has not been developed as of 2013.[1] Early infections are treatable with the medication benznidazole or nifurtimox.[1] Medication nearly always results in a cure if given early, but becomes less effective the longer a person has had Chagas disease.[1] When used in chronic disease, medication may delay or prevent the development of end-stage symptoms.[1] Benznidazole and nifurtimox cause temporary side effects in up to 40% of people[1] including skin disorders, brain toxicity, and digestive system irritation.[2][6][7]

It is estimated that 7 to 8 million people, mostly in Mexico, Central America and South America, have Chagas disease as of 2013.[1] In 2006, Chagas was estimated to result in 12,500 deaths per year.[2] Most people with the disease are poor,[2] and most people with the disease do not realize they are infected.[8]

## Variants

## Chagas disease

Photomicrograph of Giemsa-stained *Trypanosoma cruzi*

**Pronunciation** /ˈtʃɑːgəs/, Portuguese pronunciation: [ˈʃaˌgəs]

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | B57 |
| **ICD-9-CM** | 086 |
| **DiseasesDB** | 13415 |
| **MedlinePlus** | 001372 |
| **eMedicine** | med/327 |
| **Patient UK** | Chagas disease |
| **MeSH** | D014355 |

[edit on Wikidata]

Large-scale population movements have increased the areas where Chagas disease is found and these include many European countries and the United States.[1] These areas have also seen an increase in the years up to 2014.[9] The disease was first described in 1909 by Carlos Chagas after whom it is named.[1] It affects more than 150 other animals.[2]

**Contents**



## Signs and symptoms [edit]

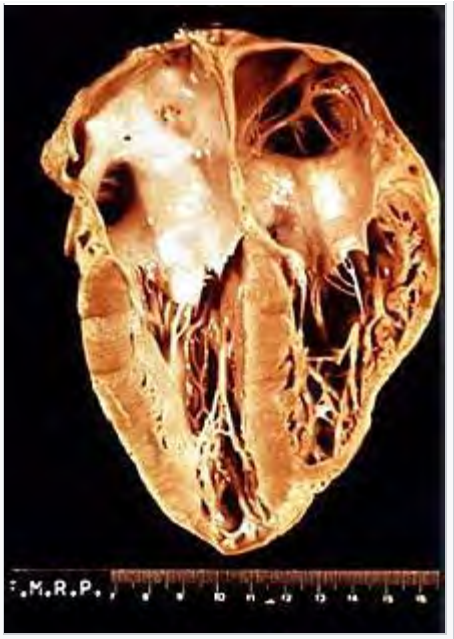
The human disease occurs in two stages: an acute stage, which occurs shortly after an initial infection, and a chronic stage that develops over many years.

The acute phase lasts for the first few weeks or months of infection. It usually occurs unnoticed because it is symptom-free or exhibits only mild symptoms that are not unique to Chagas disease. These can include fever, fatigue, body aches, muscle pain, headache, rash, loss of appetite, diarrhea, nausea, and vomiting. The signs on physical examination can include mild enlargement of the liver or spleen, swollen glands, and local swelling (a chagoma) where the parasite entered the body.[10]

The most recognized marker of acute Chagas disease is called Romaña's sign, which includes swelling of the eyelids on the side of the face near the bite wound or where the bug feces were deposited or accidentally rubbed into the eye. Rarely, young children, or adults may die from the acute disease due to severe inflammation/infection of the heart muscle (myocarditis) or brain (meningoencephalitis).[10] The acute phase also can be severe in people with weakened immune systems.[4]

If symptoms develop during the acute phase, they usually resolve spontaneously within three to eight weeks in approximately 90% of individuals.[2][6] Although the symptoms resolve, even with treatment the infection persists and enters a chronic phase. Of individuals with chronic Chagas disease, 60–80% will never develop symptoms (called *indeterminate* chronic Chagas disease), while the remaining 20–40% will develop life-threatening heart and/or digestive disorders during their lifetime (called *determinate* chronic Chagas disease). In 10% of individuals, the disease progresses directly from the acute form to a symptomatic clinical form of chronic Chagas disease.[2][6]

An acute Chagas disease infection with swelling of the right eye (Romaña's sign).



Large scale anatomy of a heart that has been damaged by chronic Chagas disease – see also: Chagas heart, radiology

The symptomatic (determinate) chronic stage affects the nervous system, digestive system and heart. About two-thirds of people with chronic symptoms have cardiac damage, including dilated cardiomyopathy, which causes heart rhythm abnormalities and may result in sudden death. About one-third of patients go on to develop digestive system damage, resulting in dilation of the digestive tract (megacolon and megaesophagus), accompanied by severe weight loss. Swallowing difficulties (secondary achalasia) may be the first symptom of digestive disturbances and may lead to malnutrition.[11]

20% to 50% of individuals with intestinal involvement also exhibit cardiac involvement.[11] Up to 10% of chronically infected individuals develop neuritis that results in altered tendon reflexes and sensory impairment. Isolated cases exhibit central nervous system involvement, including dementia, confusion, chronic encephalopathy and sensory and motor deficits.[12]

The clinical manifestations of Chagas disease are due to cell death in the target tissues that occurs during the infective cycle, by sequentially inducing an inflammatory response, cellular lesions, and fibrosis. For example, intracellular amastigotes destroy the intramural neurons of the autonomic nervous system in the intestine and heart, leading to megaintestine and heart aneurysms, respectively. If left untreated, Chagas disease can be fatal, in most cases due to heart muscle damage.[11]

## Transmission [edit]

*Rhodnius prolixus* is the principal vector in Colombia, Venezuela, Guatemala, Honduras, and some parts of Nicaragua and El Salvador.

In Chagas-endemic areas, the main mode of transmission is through an insect vector called a triatomine bug.[4] A triatomine becomes infected with *T. cruzi* by feeding on the blood of an infected person or animal. During the day, triatomines hide in crevices in the walls and roofs.[4]

The bugs emerge at night, when the inhabitants are sleeping. Because they tend to feed on people's faces, triatomine bugs are also known as "kissing bugs". After they bite and ingest blood, they defecate on the person. Triatomines pass *T. cruzi* parasites (called trypomastigotes) in feces left near the site of the bite wound.[4]

Scratching the site of the bite causes the trypomastigotes to enter the host through the wound, or through intact mucous membranes, such as the conjunctiva. Once inside the host, the trypomastigotes invade cells, where they differentiate into intracellular amastigotes. The amastigotes multiply by binary fission and differentiate into trypomastigotes, which are then released into the bloodstream. This cycle is repeated in each newly infected cell. Replication resumes only when the parasites enter another cell or are ingested by another vector.[4] (See also: Life cycle and transmission of *T. cruzi*)

Dense vegetation (such as that of tropical rainforests) and urban habitats are not ideal for the establishment of the human transmission cycle. However, in regions where the sylvatic habitat and its fauna are thinned by economic exploitation and human habitation, such as in newly deforested areas, piassava palm culture areas, and some parts of the Amazon region, a human transmission cycle may develop as the insects search for new food sources.[13]

*T. cruzi* can also be transmitted through blood transfusions. With the exception of blood derivatives (such as fractionated antibodies), all blood components are infective. The parasite remains viable at 4 °C for at least 18 days or up to 250 days when kept at room temperature. It is unclear whether *T. cruzi* can be transmitted through frozen-thawed blood components.[14]

Other modes of transmission include organ transplantation, through breast milk,[15] and by accidental laboratory exposure. Chagas disease can also be spread congenitally (from a pregnant woman to her baby) through the placenta, and accounts for approximately 13% of stillborn deaths in parts of Brazil.[16]

Oral transmission is an unusual route of infection, but has been described. In 1991, farm workers in the state of Paraíba, Brazil, were infected by eating contaminated food; transmission has also occurred via contaminated açaí palm fruit juice and garapa.[17][18][19][20][21] A 2007 outbreak in 103 Venezuelan school children was attributed to contaminated guava juice.[22]

Chagas disease is a growing problem in Europe, because the majority of cases with chronic infection are asymptomatic and because of migration from Latin America.[23]

## Diagnosis [edit]

The presence of *T. cruzi* is diagnostic of Chagas disease. It can be detected by microscopic examination of fresh anticoagulated blood, or its buffy coat, for motile parasites; or by preparation of thin and thick blood smears stained with Giemsa, for direct visualization of parasites. Microscopically, *T. cruzi* can be confused with *Trypanosoma rangeli*, which is not known to be pathogenic in humans. Isolation of *T. cruzi* can occur by inoculation into mice, by culture in specialized media (for example, NNN, LIT); and by xenodiagnosis,[24] where uninfected Reduviidae bugs are fed on the patient's blood, and their gut contents examined for parasites.[11]

Various immunoassays for *T. cruzi* are available and can be used to distinguish among strains (zymodemes of *T.cruzi* with divergent pathogenicities). These tests include: detecting complement fixation, indirect hemagglutination, indirect fluorescence assays, radioimmunoassays, and ELISA. Alternatively, diagnosis and strain identification can be made using polymerase chain reaction (PCR).[11]

## Prevention [edit]

There is currently no vaccine against Chagas disease.[25] Prevention is generally focused on decreasing the numbers of the insect that spreads it (*Triatoma*) and decreasing their contact with humans. This is done by using sprays and paints containing insecticides (synthetic pyrethroids), and improving housing and sanitary conditions in rural areas.[26] For urban dwellers, spending vacations and camping out in the wilderness or sleeping at hostels or mud houses in endemic areas can be dangerous; a mosquito net is recommended. Some measures of vector control include:

- A yeast trap can be used for monitoring infestations of certain species of triatomine bugs (*Triatoma sordida*, *Triatoma brasiliensis*, *Triatoma pseudomaculata*, and *Panstrongylus megistus*).[27]
- Promising results were gained with the treatment of vector habitats with the fungus *Beauveria bassiana*.[28]
- Targeting the symbionts of Triatominae through paratransgenesis can be done.[29]

A number of potential vaccines are currently being tested. Vaccination with *Trypanosoma rangeli* has produced positive results in animal models.[30] More recently, the potential of DNA vaccines for

Awareness and prevention

immunotherapy of acute and chronic Chagas disease is being tested by several research groups.[31]

campaign poster in Cayenne, French Guiana, 2008

Blood transfusion was formerly the second-most common mode of transmission for Chagas disease, but the development and implementation of blood bank screening tests has dramatically reduced this risk in the 21st century. Blood donations in all endemic Latin American countries undergo Chagas screening, and testing is expanding in countries, such as France, Spain and the United States, that have significant or growing populations of immigrants from endemic areas.[32][33] In Spain, donors are evaluated with a questionnaire to identify individuals at risk of Chagas exposure for screening tests.[33]

The US FDA has approved two Chagas tests, including one approved in April 2010, and has published guidelines that recommend testing of all donated blood and tissue products.[33][34] While these tests are not required in US, an estimated 75–90% of the blood supply is currently tested for Chagas, including all units collected by the American Red Cross, which accounts for 40% of the U.S. blood supply.[34][35] The Chagas Biovigilance Network reports current incidents of Chagas-positive blood products in the United States, as reported by labs using the screening test approved by the FDA in 2007.[36]

## Management [edit]

There are two approaches to treating Chagas disease: antiparasitic treatment, to kill the parasite; and symptomatic treatment, to manage the symptoms and signs of the infection. Management uniquely involves addressing selective incremental failure of the parasympathetic nervous system. Autonomic disease imparted by Chagas may eventually result in megaesophagus, megacolon and accelerated dilated cardiomyopathy. The mechanisms that explain why Chagas targets the parasympathetic autonomic nervous system and spares the sympathetic autonomic nervous system remain poorly understood.

### Medication [edit]

Antiparasitic treatment is most effective early in the course of infection, but is not limited to cases in the acute phase. Drugs of choice include azole or nitro derivatives, such as benznidazole[37] or nifurtimox. Both agents are limited in their capacity to completely eliminate *T. cruzi* from the body (parasitologic cure), especially in chronically infected patients, and resistance to these drugs has been reported.[38]

Studies suggest antiparasitic treatment leads to parasitological cure in more than 90% of infants but only about 60–85% of adults treated in the first year of acute phase Chagas disease. Children aged six to 12 years with chronic disease have a cure rate of about 60% with benznidazole. While the rate of cure declines the longer an adult has been infected with Chagas, treatment with benznidazole has been shown to slow the onset of heart disease in adults with chronic Chagas infections.[2][11]

Treatment of chronic infection in women prior to or during pregnancy does not appear to reduce the probability the disease will be passed on to the infant. Likewise, it is unclear whether prophylactic treatment of chronic infection is beneficial in persons who will undergo immunosuppression (for example, organ transplant recipients) or in persons who are already immunosuppressed (for example, those with HIV infection).[11]

### Complications [edit]

In the chronic stage, treatment involves managing the clinical manifestations of the disease. For example, pacemakers and medications for irregular heartbeats, such as the anti-arrhythmia drug amiodarone, may be life saving for some patients with chronic cardiac disease,[39] while surgery may be required for megaintestine. The disease cannot be cured in this phase, however. Chronic heart disease caused by Chagas disease is now a common reason for heart transplantation surgery. Until recently, however, Chagas disease was considered a contraindication for the procedure, since the heart damage could recur as the parasite was expected to seize the opportunity provided by the immunosuppression that follows surgery.[40]

# Epidemiology [edit]

Chagas disease affects 8 to 10 million people living in endemic Latin American countries, with an additional 300,000–400,000 living in nonendemic countries, including Spain and the United States. An estimated 41,200 new cases occur annually in endemic countries, and 14,400 infants are born with congenital Chagas disease annually.[2][11] in 2010 it resulted in approximately 10,300 deaths up from 9,300 in 1990.[41]

Chagas disease in Latin America (endemic zones).

The disease is present in 18 countries on the American continents, ranging from the southern United States to northern Argentina.[4] Chagas exists in two different ecological zones. In the Southern Cone region, the main vector lives in and around human homes. In Central America and Mexico, the main vector species lives both inside dwellings and in uninhabited areas. In both zones, Chagas occurs almost exclusively in rural areas, where triatomines breed and feed on the more than 150 species from 24 families of domestic and wild mammals, as well as humans, that are the natural reservoirs of *T. cruzi*.[42]

Although Triatominae bugs feed on them, birds appear to be immune to infection and therefore are not considered to be a *T. cruzi* reservoir. Even when colonies of insects are eradicated from a house and surrounding domestic animal shelters, they can re-emerge from plants or animals that are part of the ancient, sylvatic (referring to wild animals) infection cycle. This is especially likely in zones with mixed open savannah, with clumps of trees interspersed by human habitation.[43]

The primary wildlife reservoirs for *Trypanosoma cruzi* in the United States include opossums, raccoons, armadillos, squirrels, woodrats, and mice.[44] Opossums are particularly important as reservoirs, because the parasite can complete its life cycle in the anal glands of this animal without having to re-enter the insect vector.[44] Recorded prevalence of the disease in opossums in the U.S. ranges from 8.3%[44] to 37.5%.[45]

Studies on raccoons in the Southeast have yielded infection rates ranging from 47%[46] to as low as 15.5%.[44] Armadillo prevalence studies have been described in Louisiana, and range from a low of 1.1%[45] to 28.8%.[47] Additionally, small rodents, including squirrels, mice, and rats, are important in the sylvatic transmission cycle because of their importance as bloodmeal sources for the insect vectors. A Texas study revealed 17.3% percent *T. cruzi* prevalence in 75 specimens representing four separate small rodent species.[48]

Chronic Chagas disease remains a major health problem in many Latin American countries, despite the effectiveness of hygienic and preventive measures, such as eliminating the transmitting insects. However, several landmarks have been achieved in the fight against it in Latin America, including a reduction by 72% of the incidence of human infection in children and young adults in the countries of the Southern Cone Initiative, and at least three countries (Uruguay, in 1997, and Chile, in 1999, and Brazil in 2006) have been certified free of vectorial and transfusional transmission.[11][49][50] In Argentina, vectorial transmission has been interrupted in 13 of the 19 endemic provinces,[49] and major progress toward this goal has also been made in both Paraguay and Bolivia.

Screening of donated blood, blood components, and solid organ donors, as well as donors of cells, tissues,

and cell and tissue products for *T. cruzi* is mandated in all Chagas-endemic countries and has been implemented.[51] Approximately 300,000 infected people live in the United States, which is likely the result of immigration from Latin American countries,[52] and there have been 23 cases acquired from kissing bugs in the United States reported between 1955 and 2014.[53] With increased population movements, the possibility of transmission by blood transfusion became more substantial in the United States. Transfusion blood and tissue products are now actively screened in the U.S., thus addressing and minimizing this risk.[54]

## History [edit]

*Further information: Carlos Chagas § Discovery of Chagas disease*

Carlos Chagas, in his laboratory at the Instituto Oswaldo Cruz.

The disease was named after the Brazilian physician and epidemiologist Carlos Chagas, who first described it in 1909.[55][56][57][58] The disease was not seen as a major public health problem in humans until the 1960s (the outbreak of Chagas disease in Brazil in the 1920s went widely ignored[59]). Dr Chagas discovered that the intestines of Triatomidae (now Reduviidae: Triatominae) harbored a flagellate protozoan, a new species of the *Trypanosoma* genus, and was able to demonstrate experimentally that it could be transmitted to marmoset monkeys that were bitten by the infected bug. Later studies showed squirrel monkeys were also vulnerable to infection.[60]

Chagas named the pathogenic parasite as *Trypanosoma cruzi*[55] and later that year as *Schizotrypanum cruzi*,[57] both honoring Oswaldo Cruz, the noted Brazilian physician and epidemiologist who successfully fought epidemics of yellow fever, smallpox, and bubonic plague in Rio de Janeiro and other cities in the beginning of the 20th century. Chagas was also the first to unknowingly discover and illustrate the parasitic fungal genus *Pneumocystis*, later infamously linked to PCP (*Pneumocystis* pneumonia in AIDS victims).[56] Confusion between the two pathogens' life-cycles led him to briefly recognize his genus *Schizotrypanum*, but following the description of *Pneumocystis* by others as an independent genus, Chagas returned to the use of the name *Trypanosoma cruzi*.

In Argentina, the disease is known as *mal de Chagas-Mazza*, in honor of Salvador Mazza, the Argentine physician who in 1926 began investigating the disease and over the years became the principal researcher of this disease in the country.[61] Mazza produced the first scientific confirmation of the existence of *Trypanosoma cruzi* in Argentina in 1927, eventually leading to support from local and European medical schools and Argentine government policy makers.[62]

It has been hypothesized that Charles Darwin might have suffered from Chagas disease as a result of a bite of the so-called great black bug of the Pampas (*vinchuca*) (see Charles Darwin's illness). The episode was reported by Darwin in his diaries of the Voyage of the Beagle as occurring in March 1835 to the east of the Andes near Mendoza. Darwin was young and generally in good health, though six months previously he had been ill for a month near Valparaiso, but in 1837, almost a year after he returned to England, he began to suffer intermittently from a strange group of symptoms, becoming incapacitated for much of the rest of his life. Attempts to test Darwin's remains at Westminster Abbey by using modern PCR techniques were met with a refusal by the Abbey's curator.[63]

## Research [edit]

Several experimental treatments have shown promise in animal models. These include inhibitors of oxidosqualene cyclase and squalene synthase,[64][65] cysteine protease inhibitors,[64][66] dermaseptins collected from frogs in the genus *Phyllomedusa* (*P. oreades* and *P. distincta*),[67] the sesquiterpene lactone [68]

dehydroleucodine (DhL), which affects the growth of cultured epimastigote-phase *Trypanosoma cruzi*, inhibitors of purine uptake,[64] and inhibitors of enzymes involved in trypanothione metabolism.[69] Hopefully, new drug targets may be revealed following the sequencing of the *T. cruzi* genome.[70]

Chagas disease has a serious economic impact on the United States and the world. The cost of treatment in the United States alone, where the disease is not indigenous, is estimated to be $900 million annually, which includes hospitalization and medical devices such as pacemakers. The global cost is estimated at $7 billion.[71]

Megazol in a study seems more active against Chagas than benznidazole but has not been studied in humans.[72] A Chagas vaccine (TcVac3) has been found to be effective in mice with plans for studies in dogs. It is hoped that it will be commercially available by 2018.[73]

## See also [edit]

- Drugs for Neglected Diseases Initiative
- Chagas: Time to Treat campaign
- Association for the Promotion of Independent Disease Control in Developing Countries

## References [edit]


1. ^ *a b c d e f g h i j k l m n o p* "Chagas disease (American trypanosomiasis) Fact sheet N°340". *World Health Organization*. March 2013. Retrieved 23 February 2014.
2. ^ *a b c d e f g h i* Rassi A, Rassi A, Marin-Neto JA (April 2010). "Chagas disease". *Lancet*. **375** (9723): 1388–402. doi:10.1016/S0140-6736(10)60061-X. PMID 20399979.
3. ^ *a b c d* Rassi A Jr, Rassi A, Marcondes de Rezende J (June 2012). "American trypanosomiasis (Chagas disease)". *Infectious disease clinics of North America*. **26** (2): 275–91. doi:10.1016/j.idc.2012.03.002. PMID 22632639.
4. ^ *a b c d e f g* "DPDx – Trypanosomiasis, American. Fact Sheet". Centers for Disease Control (CDC). Retrieved 12 May 2010.
5. ^ Maudlin I, Holmes PH, Miles MA, eds. (2004). *The Trypanosomiases*. Wallingford: CAB International. p. 184. ISBN 9780851990347.
6. ^ *a b c* Bern C, Montgomery SP, Herwaldt BL, et al. (November 2007). "Evaluation and treatment of chagas disease in the United States: a systematic review". *JAMA*. **298** (18): 2171–81. doi:10.1001/jama.298.18.2171. PMID 18000201.
7. ^ Rassi A, Dias JC, Marin-Neto JA, Rassi A (April 2009). "Challenges and opportunities for primary, secondary, and tertiary prevention of Chagas' disease". *Heart*. **95** (7): 524–34. doi:10.1136/hrt.2008.159624. PMID 19131444.
8. ^ Capinera JL, ed. (2008). *Encyclopedia of entomology* (2nd ed.). Dordrecht: Springer. p. 824. ISBN 9781402062421.
9. ^ Bonney, Kevin M. (2014). "Chagas disease in the 21st Century: a public health success or an emerging threat?". *Parasite*. **21**: 11. doi:10.1051/parasite/2014012. ISSN 1776-1042. PMC 3952655. PMID 24626257.
10. ^ *a b* Guimarães FN, da Silva NN, Clausell DT, de Mello AL, Rapone T, Snell T, Rodrigues N (1968). "Um surto epidêmico de doença de Chagas de provável transmissão digestiva, ocorrido em Teutonia (Estrêla – Rio Grande Do Sul)". *Hospital (Rio J)* (in Portuguese). **73** (6): 1767–804. PMID 4976999.
11. ^ *a b c d e f g h i* Louis V Kirchhoff (17 December 2010). "Chagas Disease (American Trypanosomiasis)". eMedicine. Retrieved 12 May 2010.
12. ^ Córdova E, Maiolo E, Corti M, Orduña T (April 2010). "Neurological manifestations of Chagas' disease". *Neurol. Res*. **32** (3): 238–44. doi:10.1179/016164110X12644252260637. PMID 20406601.
13. ^ Teixeira AR, Monteiro PS, Rebelo JM (2001). "Emerging Chagas disease: trophic network and cycle of transmission of Trypanosoma cruzi from palm trees in the Amazon". *Emerging Infect Dis*. **7** (1): 100–12. doi:10.3201/eid0701.010115. PMC 2631687. PMID 11266300.
14. ^ Wendel S (January 2010). "Transfusion transmitted Chagas disease: Is it really under control?". *Acta Trop*. **115** (1–2): 28–34. doi:10.1016/j.actatropica.2009.12.006. PMID 20044970. Retrieved 13 May 2010.
15. ^ Santos Ferreira C, Amato Neto V, Gakiya E, Bezerra RC, Alarcón RS (2003). "Microwave treatment of human milk to prevent transmission of Chagas disease". *Revista do Instituto de Medicina Tropical de São Paulo*. **45** (1): 41–2.

doi:10.1590/S0036-46652003000100008. PMID 12751321.
16. ^ Hudson L, Turner MJ (November 1984). "Immunological consequences of infection and vaccination in South American trypanosomiasis [and discussion]". *Philosophical Transactions of the Royal Society B*. **307** (1131): 51–61. Bibcode:1984RSPTB.307...51H. doi:10.1098/rstb.1984.0108. JSTOR 2990154. PMID 6151688. Retrieved 22 February 2007 through JSTOR.
17. ^ Benchimol-Barbosa PR (2006). "The oral transmission of Chagas' disease: an acute form of infection responsible for regional outbreaks.". *Int J Cardiol*. **112** (1): 132–3. doi:10.1016/j.ijcard.2005.11.087. PMID 16600406.
18. ^ Benchimol-Barbosa PR (2010). "Trends on acute Chagas' disease transmitted by oral route in Brazil: steady increase in new cases and a concealed residual fluctuation.". *Int J Cardiol*. **145** (3): 494–6. doi:10.1016/j.ijcard.2009.08.030. PMID 19762096.
19. ^ "Chagas' disease (American trypanosomiasis) in southern Brazil" (PDF). *CDR Weekly*. United Kingdom Health Protection Agency. **15** (13). April 2005. Retrieved 26 November 2007.
20. ^ Shikanai-Yasuda MA, Marcondes CB, Guedes LA (1991). "Possible oral transmission of acute Chagas' disease in Brazil". *Rev Inst Med Trop São Paulo*. **33** (5): 351–7. doi:10.1590/S0036-46651991000500003. PMID 1844961.
21. ^ da Silva Valente SA, de Costa Valente V, Neto HF (1999). "Considerations on the epidemiology and transmission of Chagas disease in the Brazilian Amazon". *Mem Inst Oswaldo Cruz*. 94 Suppl 1: 395–8. doi:10.1590/s0074-02761999000700077. PMID 10677763.
22. ^ Alarcón de Noya B, Díaz-Bello Z, Colmenares C, et al. (2010). "Large urban outbreak of orally acquired acute Chagas disease at a school in Caracas, Venezuela". *J Infect Dis*. **201** (9): 1308–15. doi:10.1086/651608. PMID 20307205.
23. ^ Roca C, Pinazo MJ, López-Chejade P, Bayó J, Posada E, López-Solana J, Gállego M, Portús M, Gascón J, Chagas-Clot Research Group (2011). Da Costa Santiago H, ed. "Chagas Disease among the Latin American Adult Population Attending in a Primary Care Center in Barcelona, Spain". *PLoS Negl Trop Dis*. **5** (4): e1135. doi:10.1371/journal.pntd.0001135. PMC 3082512. PMID 21572511.
24. ^ Brumpt E (1914). "Le xénodiagnostic. Application au diagnostic de quelques infections parasitaires et en particulier à la trypanosomose de Chagas" (PDF). *Bull Soc Pathol Exot*. **7** (10): 706–10. Archived from the original (PDF) on 26 November 2008.
25. ^ "A killer that preys on the poor: Chagas disease" (pdf). *Médecins Sans Frontières: Activity Report 2003/2004*. Retrieved 29 August 2008.
26. ^ Eduardo N. Zerba (1999). "Susceptibility and resistance to insecticides of Chagas disease vectors" (PDF). *Medicina (Buenos Aires)*. **59** (Suppl 2): 41–6.
27. ^ Pires HH, Lazzari CR, Diotaiuti L, Lorenzo MG (June 2000). "Performance of yeast-baited traps with *Triatoma sordida*, *Triatoma brasiliensis*, *Triatoma pseudomaculata*, and *Panstrongylus megistus* in laboratory assays". *Rev Panam Salud Publica*. **7** (6): 384–8. doi:10.1590/S1020-49892000000600005. PMID 10949899.
28. ^ Luz C, Rocha LF, Nery GV, Magalhães BP, Tigano MS (March 2004). "Activity of oil-formulated *Beauveria bassiana* against *Triatoma sordida* in peridomestic areas in Central Brazil". *Mem Inst Oswaldo Cruz*. **99** (2): 211–8. doi:10.1590/S0074-02762004000200017. PMID 15250478.
29. ^ Beard CB, Cordon-Rosales C, Durvasula RV (2002). "Bacterial symbionts of the Triatominae and their potential use in control of Chagas disease transmission". *Annu Rev Entomol*. **47**: 123–41. doi:10.1146/annurev.ento.47.091201.145144. PMID 11729071.
30. ^ Basso B, Moretti E, Fretes R (June 2008). "Vaccination with epimastigotes of different strains of *Trypanosoma rangeli* protects mice against *Trypanosoma cruzi* infection". *Mem Inst Oswaldo Cruz*. **103** (4): 370–4. doi:10.1590/S0074-02762008000400010. PMID 18660992.
31. ^ Dumonteil E, Escobedo-Ortegon J, Reyes-Rodriguez N, Arjona-Torres A, Ramirez-Sierra M (2004). "Immunotherapy of *Trypanosoma cruzi* Infection with DNA Vaccines in Mice". *Infect Immun*. **72** (1): 46–53. doi:10.1128/IAI.72.1.46-53.2004. PMC 343959. PMID 14688079.
32. ^ Castro E (February 2009). "Chagas' disease: lessons from routine donation testing". *Transfus Med*. **19** (1): 16–23. doi:10.1111/j.1365-3148.2009.00915.x. PMID 19302451. Retrieved 12 May 2010.
33. ^ *a b c* Gascon J, Bern C, Pinazo MJ (July 2009). "Chagas disease in Spain, the United States and other non-endemic countries". *Acta Trop*. **115** (1–2): 22–7. doi:10.1016/j.actatropica.2009.07.019. PMID 19646412. Retrieved 12 May 2010.
34. ^ *a b* "FDA Approves Chagas Disease Screening Test for Blood, Tissue and Organ Donors". Retrieved 12 May 2010.
35. ^ "Infectious Disease Testing". *American Red Cross*. Retrieved 12 May 2010.
36. ^ "Chagas' Biovigilance Network". Retrieved 12 May 2010.
37. ^ Garcia S, Ramos CO, Senra JF (April 2005). "Treatment with Benznidazole during the Chronic Phase of Experimental Chagas' Disease Decreases Cardiac Alterations". *Antimicrob Agents Chemother*. **49** (4): 1521–8. doi:10.1128/AAC.49.4.1521-1528.2005. PMC 1068607. PMID 15793134.

38. ^ Buckner FS, Wilson AJ, White TC, Van Voorhis WC (December 1998). "Induction of Resistance to Azole Drugs in *Trypanosoma cruzi*". *Antimicrob Agents Chemother*. **42** (12): 3245–50. PMC 106029. PMID 9835521.
39. ^ Dubner S, Schapachnik E, Riera AR, Valero E (2008). "Chagas disease: state-of-the-art of diagnosis and management". *Cardiol J*. **15** (6): 493–504. PMID 19039752.
40. ^ Bocchi EA, Bellotti G, Mocelin AO (June 1996). "Heart transplantation for chronic Chagas' heart disease". *Ann Thorac Surg*. **61** (6): 1727–33. doi:10.1016/0003-4975(96)00141-5. PMID 8651775.
41. ^ Lozano R (15 December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
42. ^ Morel CM, Lazdins J (October 2003). "Chagas disease". *Nat Rev Microbiol*. **1** (1): 14–5. doi:10.1038/nrmicro735. PMID 15040175.
43. ^ Pinto-Dias JC (1992). "Epidemiology of Chagas disease". In Wendel S, Brener Z, Camargo ME, Rassi A. *Chagas Disease – American Trypanosomiasis: its impact on transfusion and clinical medicine*. ISBT Brazil '92. XXII Congress of the International Society of Blood Transfusion. XX Brazilian Congress of Hematology. Extraordinary Congress of the Brazilian College of Hematology. São Paulo: Editorial ISBT Brazil. OCLC 69892472. Retrieved 11 September 2008.
44. ^ *a b c d* Karsten V, Davis C, Kuhn R (June 1992). "*Trypanosoma cruzi* in wild raccoons and opossums in North Carolina". *J Parasitol*. **78** (3): 547–9. doi:10.2307/3283667. JSTOR 3283667. PMID 1597808.
45. ^ *a b* Barr SC, Brown CC, Dennis VA, Klei TR (August 1991). "The lesions and prevalence of *Trypanosoma cruzi* in opossums and armadillos from southern Louisiana". *J Parasitol*. **77** (4): 624–7. doi:10.2307/3283170. JSTOR 3283170. PMID 1907654.
46. ^ Yabsley MJ, Noblet GP (1 January 2002). "Seroprevalence of *Trypanosoma cruzi* in raccoons from South Carolina and Georgia". *J Wildl Dis*. **38** (1): 75–83. doi:10.7589/0090-3558-38.1.75. PMID 11838232.
47. ^ Yaeger RG (March 1988). "The prevalence of *Trypanosoma cruzi* infection in armadillos collected at a site near New Orleans, Louisiana". *Am J Trop Med Hyg*. **38** (2): 323–6. PMID 3128127.
48. ^ Burkholder JE, Allison TC, Kelly VP (April 1980). "*Trypanosoma cruzi* (Chagas) (Protozoa: Kinetoplastida) in invertebrate, reservoir, and human hosts of the lower Rio Grande valley of Texas". *J Parasitol*. **66** (2): 305–11. doi:10.2307/3280824. JSTOR 3280824. PMID 6771371.
49. ^ *a b* "The Southern Cone Initiative: an update". *Special Programme for Research and Training in Tropical Diseases (TDR)* (Press release). WHO. 2004. Archived from the original on 22 September 2009. Retrieved 29 August 2008.
50. ^ Massad E (September 2008). "The elimination of Chagas' disease from Brazil". *Epidemiol Infect*. **136** (9): 1153–64. doi:10.1017/S0950268807009879. PMC 2870925. PMID 18053273.
51. ^ Castro E (February 2009). "Chagas' disease: lessons from routine donation testing". *Transfus Med*. **19** (1): 16–23. doi:10.1111/j.1365-3148.2009.00915.x. PMID 19302451. Retrieved 13 May 2010.
52. ^ "Medical Encyclopedia: Chagas disease". National Institutes of Health. Retrieved 11 September 2008.
53. ^ Montgomery SP, Starr MC, Cantey PT, Edwards MS, Meymandi SK (May 2014). "Neglected Parasitic Infections in the United States: Chagas Disease". *Am J Trop Med Hyg*. **90** (5): 814–818. doi:10.4269/ajtmh.13-0726.
54. ^ Kirchhoff LV (August 1993). "American trypanosomiasis (Chagas' disease) – a tropical disease now in the United States". *N Engl J Med*. **329** (9): 639–44. doi:10.1056/NEJM199308263290909. PMID 8341339.
55. ^ *a b* Chagas C (1909). "Neue Trypanosomen". *Vorläufige Mitteilung Arch Schiff Tropenhyg*. **13**: 120–2.
56. ^ *a b* Redhead SA, Cushion MT, Frenkel JK, Stringer JR (2006). "*Pneumocystis* and *Trypanosoma cruzi*: nomenclature and typifications". *J Eukaryot Microbiol*. **53** (1): 2–11. doi:10.1111/j.1550-7408.2005.00072.x. PMID 16441572.
57. ^ *a b* Chagas C (1909). "Nova tripanozomiase humana: Estudos sobre a morfolojia e o ciclo evolutivo do Schizotrypanum cruzi n. gen., n. sp., ajente etiolojico de nova entidade morbida do homem [New human trypanosomiasis. Studies about the morphology and life-cycle of *Schizotripanum cruzi*, etiological agent of a new morbid entity of man]". *Mem Inst Oswaldo Cruz*. **1** (2): 159–218. doi:10.1590/S0074-02761909000200008. ISSN 0074-0276. (in Portuguese with German full translation as "Ueber eine neue Trypanosomiasis des Menschen.")
58. ^ Kropf SP, Sá MR (July 2009). "The discovery of *Trypanosoma cruzi* and Chagas disease (1908–1909): tropical medicine in Brazil". *Hist Cienc Saude Manguinhos*. **16** (Suppl 1): 13–34. doi:10.1590/s0104-59702009000500002. PMID 20027916.
59. ^ Coutinho M (June 1999). "Review of *Historical Aspects of American Trypanosomiasis (Chagas' Disease)* by Matthias Perleth". *Isis*. **90** (2): 397. doi:10.1086/384393. JSTOR 237120.
60. ^ Hulsebos LH, Choromanski L, Kuhn RE (1989). "The effect of interleukin-2 on parasitemia and myocarditis in experimental Chagas' disease". *J Protozool*. **36** (3): 293–8. doi:10.1111/j.1550-7408.1989.tb05366.x. PMID 2499678.

61. ^ "Enfermedad de Chagas – Mazza" (in Spanish). Asociación Lucha Contra el Mal de Chagas. Archived from the original on 16 September 2011. Retrieved 15 September 2011.
62. ^ "Historia de la enfermedad de Chagas" (in Spanish). Archived from the original on 4 December 2009.
63. ^ Adler D (1989). "Darwin's Illness". *Isr J Med Sci*. **25** (4): 218–21. PMID 2496051.
64. ^ *a b c* Scientific Working Group on Chagas Disease [April 2005] (July 2007). Guhl F, Lazdins-Helds JK (eds.): *Reporte del grupo de trabajo científico sobre la enfermedad de Chagas* Archived 17 December 2008 at the Wayback Machine. (in Spanish). Geneva: WHO. Retrieved on 29 August 2008. summary in English
65. ^ Urbina JA, Concepcion JL, Rangel S, Visbal G, Lira R (2002). "Squalene synthase as a chemotherapeutic target in *Trypanosoma cruzi* and *Leishmania mexicana*". *Mol Biochem Parasitol*. **125** (1–2): 35–45. doi:10.1016/S0166-6851(02)00206-2. PMID 12467972.
66. ^ Engel JC, Doyle PS, Hsieh I, McKerrow JH (August 1998). "Cysteine Protease Inhibitors Cure an Experimental *Trypanosoma cruzi* Infection". *J Exp Med*. **188** (4): 725–34. doi:10.1084/jem.188.4.725. PMC 2213346. PMID 9705954.
67. ^ Brand GD, Leite JR, Silva LP (December 2002). "Dermaseptins from *Phyllomedusa oreades* and *Phyllomedusa distincta*. Anti-*Trypanosoma cruzi* activity without cytotoxicity to mammalian cells". *J Biol Chem*. **277** (51): 49332–40. doi:10.1074/jbc.M209289200. PMID 12379643.
68. ^ Brengio SD, Belmonte SA, Guerreiro E, Giordano OS, Pietrobon EO, Sosa MA (April 2000). "The sesquiterpene lactone dehydroleucodine (DhL) affects the growth of cultured epimastigotes of *Trypanosoma cruzi*". *J Parasitol*. **86** (2): 407–12. doi:10.1645/0022-3395(2000)086[0407:TSLDDA]2.0.CO;2. ISSN 0022-3395. PMID 10780563.
69. ^ Fairlamb AH, Cerami A (1992). "Metabolism and functions of trypanothione in the Kinetoplastida". *Annu Rev Microbiol*. **46**: 695–729. doi:10.1146/annurev.mi.46.100192.003403. PMID 1444271.
70. ^ El-Sayed NM, Myler PJ, Bartholomeu DC (July 2005). "The genome sequence of *Trypanosoma cruzi*, etiologic agent of Chagas disease". *Science*. **309** (5733): 409–15. Bibcode:2005Sci...309..409E. doi:10.1126/science.1112631. PMID 16020725.
71. ^ Bruce Y Lee; Kristina M Bacon; Maria Elena Bottazzi; Peter J Hotez (April 2013). "Global economic burden of Chagas disease: a computational simulation model". *The Lancet infectious diseases*. **13** (4): 342–348. doi:10.1016/S1473-3099(13)70002-1.
72. ^ "Activation of Benznidazole by Trypanosomal Type I Nitroreductases Results in Glyoxal Formation". *Antimicrob. Agents Chemother*. **56** (1): 115–123. 2012. doi:10.1128/AAC.05135-11.
73. ^ "Potential Chagas vaccine candidate shows unprecedented efficacy". ScienceDaily. March 26, 2013. Retrieved 12 January 2015.


## Further reading [edit]


- "Blood donor screening for Chagas disease — (United States, 2006–2007)". *Morbidity and Mortality Weekly Report*. **56** (7): 141–43. 23 February 2007. PMID 17318113.
- Franco-Paredes C, Von A, Hidron A, et al. (2007). "Chagas disease: an impediment in achieving the Millennium Development Goals in Latin America". *BMC International Health and Human Rights*. **7**: 7. doi:10.1186/1472-698X-7-7. PMC 2034380. PMID 17725836.
- Hotez PJ, Dumonteil E, Woc-Colburn L, et al. (29 May 2012). "Chagas disease: 'The new HIV/AIDS of the Americas'". *PLoS Neglected Tropical Diseases*. **6** (5): e1498. doi:10.1371/journal.pntd.0001498. PMC 3362306. PMID 22666504. An editorial.
- "International symposium to commemorate the 90th anniversary of the discovery of Chagas disease (Rio de Janeiro, April 11–16, 1999)". *Memorias do Instituto Oswaldo Cruz*. **94** (Suppl. I). 1999. A special issue of the *Memórias do Instituto Oswaldo Cruz*, covering all aspects of Chagas Disease
- Miles MW, Tyler KM (2003). *American trypanosomiasis*. Boston: Kluwer Academic. ISBN 978-1-4020-7323-6. OCLC 50685296.


## External links [edit]

- Chagas disease at DMOZ
- Chagas information at the U.S. Centers for Disease Control
- Chagas information from the Drugs for Neglected Diseases initiative
- Norma Andrews's seminar: *Trypanosoma cruzi* and Chagas Disease
- UNHCO site on Chagas Disease

Wikimedia Commons has media related to *Chagas disease*.

- Chagas Disease information for travellers from IAMAT (International Association for Medical Assistance to Travellers)
- Boodman, Eric (August 10, 2016). "In the dark of night, a hunt for a deadly bug in the name of science". STAT. Retrieved August 12, 2016.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# Common cold

From Wikipedia, the free encyclopedia

*For other uses, see Cold (disambiguation).*

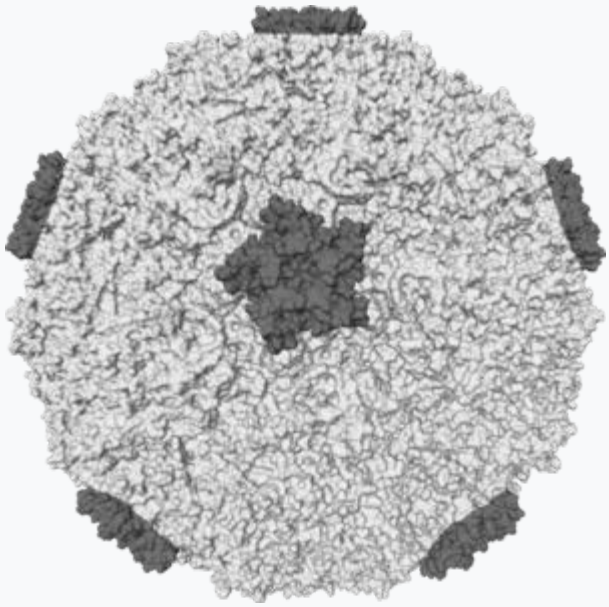
**Common cold**, also known simply as a **cold**, is a viral infectious disease of the upper respiratory tract that primarily affects the nose.[2] The throat, sinuses, and voice box may also be affected.[3] Signs and symptoms may begin less than two days following exposure.[3] They include coughing, sore throat, runny nose, sneezing, headache, and fever.[4][5] People usually recover in seven to ten days.[4] Some symptoms may last up to three weeks.[6] In those with other health problems, pneumonia may occasionally develop.[4]

Well over 200 virus strains are implicated in the cause of the common cold, the rhinoviruses are the most common.[7] They spread through the air during close contact with infected people and indirectly through contact with objects in the environment followed by transfer to the mouth or nose.[4] Risk factors include going to daycare, not sleeping well, and psychological stress.[3] Symptoms are mostly due to the body's immune response to the infection rather than to tissue destruction by the viruses themselves.[8] People with influenza often show similar symptoms as people with a cold, though symptoms are usually more severe in the former.[3]

There is no vaccine for the common cold. The primary methods of prevention are hand washing; not touching the eyes, nose or mouth with unwashed hands; and staying away from other sick people.[4] Some evidence supports the use of face masks.[9] No cure for the common cold exists, but the symptoms can be treated.[4] Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen may help with pain.[10] Antibiotics should not be used.[11] Evidence does not support a benefit from cough medicines.[3]

The common cold is the most frequent infectious disease in humans.[12] The average adult gets two to four colds a year, while the average child may get six to eight.[13] They occur more commonly during the winter.[4] These infections have been with humanity since ancient times.[14]

Contents

| Common cold | |
|---|---|
| **Synonyms** | acute viral nasopharyngitis, nasopharyngitis, viral rhinitis, rhinopharyngitis, acute coryza, head cold[1] |
| |  |
| | A representation of the molecular surface of one variant of human rhinovirus. |
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| **MeSH** | D003139 |

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# Signs and symptoms

The typical symptoms of a cold include a cough, a runny nose, nasal congestion and a sore throat, sometimes accompanied by muscle ache, fatigue, headache, and loss of appetite.[15] A sore throat is present in about 40% of the cases and a cough in about 50%,[2] while muscle ache occurs in about half.[5] In adults, a fever is generally not present but it is common in infants and young children.[5] The cough is usually mild compared to that accompanying influenza.[5] While a cough and a fever indicate a higher likelihood of influenza in adults, a great deal of similarity exists between these two conditions.[16] A number of the viruses that cause the common cold may also result in asymptomatic infections.[17][18]

The color of the sputum or nasal secretion may vary from clear to yellow to green and does not indicate the class of agent causing the infection.[19]

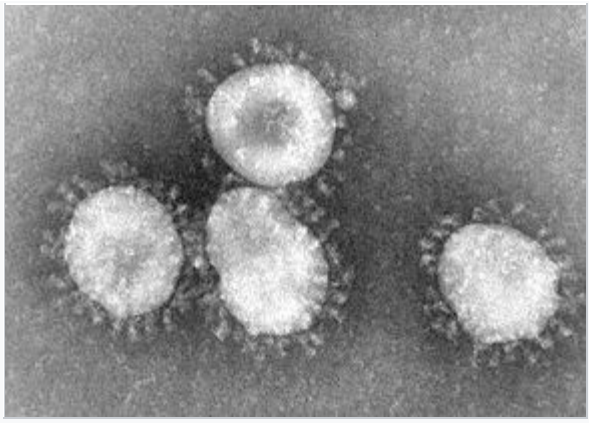
## Progression

A cold usually begins with fatigue, a feeling of being chilled, sneezing, and a headache, followed in a couple of days by a runny nose and cough.[15] Symptoms may begin within sixteen hours of exposure[20] and typically peak two to four days after onset.[5][21] They usually resolve in seven to ten days, but some can last for up to three weeks.[6] The average duration of cough is eighteen days[22] and in some cases people develop a post-viral cough which can linger after the infection is gone.[23] In children, the cough lasts for more than ten days in 35%–40% of the cases and continues for more than 25 days in 10%.[24]

# Cause

## Viruses

The common cold is a viral infection of the upper respiratory tract. The most commonly implicated virus is a rhinovirus (30%–80%), a type of picornavirus with 99 known



Coronaviruses are a group of viruses known for causing the common cold. They have a halo or crown-like (corona) appearance when viewed under an electron microscope.

serotypes.[25][26] Other commonly implicated viruses include human coronavirus (≈15%),[27][28] influenza viruses (10%–15%),[29] adenoviruses (5%),[29] human respiratory syncytial virus, enteroviruses other than rhinoviruses, human parainfluenza viruses, and metapneumovirus.[30] Frequently more than one virus is present.[31] In total over 200 different viral types are associated with colds.[5]

## Transmission

The common cold virus is typically transmitted via airborne droplets (aerosols), direct contact with infected nasal secretions, or fomites (contaminated objects).[2][32] Which of these routes is of primary importance has not been determined; however, hand-to-hand and hand-to-surface-to-hand contact seems of more importance than transmission via aerosols.[33] The viruses may survive for prolonged periods in the environment (over 18 hours for rhinoviruses) and can be picked up by people's hands and subsequently carried to their eyes or nose where infection occurs.[32] Transmission is common in daycare and at school due to the proximity of many children with little immunity and frequently poor hygiene.[34] These infections are then brought home to other members of the family.[34] There is no evidence that recirculated air during commercial flight is a method of transmission.[32] People sitting in close proximity appear to be at greater risk of infection.[33]

Rhinovirus-caused colds are most infectious during the first three days of symptoms; they are much less infectious afterwards.[35]

## Weather

The traditional theory is that a cold can be "caught" by prolonged exposure to cold weather such as rain or winter conditions, which is how the disease got its name.[36] Some of the viruses that cause the common colds are seasonal, occurring more frequently during cold or wet weather.[37] The reason for the seasonality has not been conclusively determined.[38] Possible explanations may include cold temperature-induced changes in the respiratory system,[39] decreased immune response,[40] and low humidity causing an increase in viral transmission rates, perhaps due to dry air allowing small viral droplets to disperse farther and stay in the air longer.[41]

The apparent seasonality may also be due to social factors, such as people spending more time indoors, near infected people,[39] and specifically children at school.[34][38] There is some controversy over the role of low body temperature as a risk factor for the common cold; the majority of the evidence suggests that it may result in greater susceptibility to infection.[40]

## Other

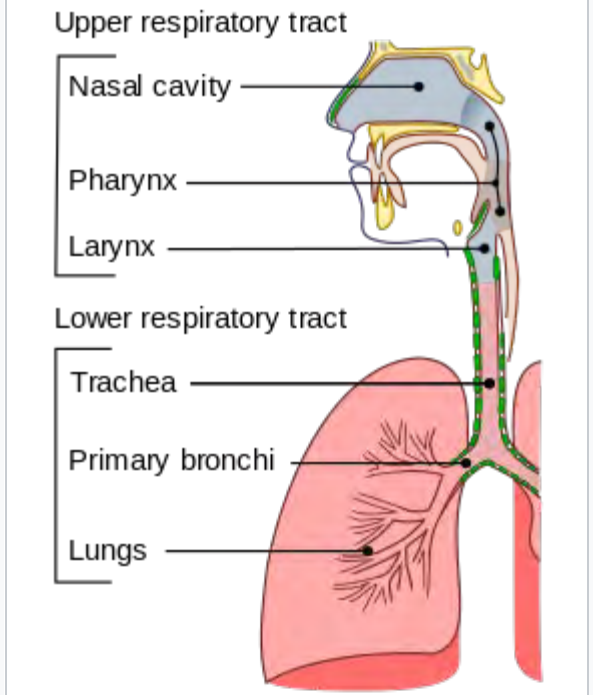
Herd immunity, generated from previous exposure to cold viruses, plays an important role in limiting viral spread, as seen with younger populations that have greater rates of respiratory infections.[42] Poor immune function is a risk factor for disease.[42][43] Insufficient sleep and malnutrition have been associated with a greater risk of developing infection following rhinovirus exposure; this is believed to be due to their effects on immune function.[44][45] Breast feeding decreases the risk of acute otitis media and lower respiratory tract infections among other diseases,[46] and it is recommended that breast feeding be continued when an infant has a cold.[47] In the developed world breast feeding may not be protective against the common cold

in and of itself.[48]

## Pathophysiology



The symptoms of the common cold are believed to be primarily related to the immune response to the virus.[8] The mechanism of this immune response is virus specific. For example, the rhinovirus is typically acquired by direct contact; it binds to human ICAM-1 receptors through unknown mechanisms to trigger the release of inflammatory mediators.[8] These inflammatory mediators then produce the symptoms.[8] It does not generally cause damage to the nasal epithelium.[5] The respiratory syncytial virus (RSV), on the other hand, is contracted by direct contact and airborne droplets. It then replicates in the nose and throat before frequently spreading to the lower respiratory tract.[49] RSV does cause epithelium damage.[49] Human parainfluenza virus typically results in inflammation of the nose, throat, and bronchi.[50] In young children when it affects the trachea it may produce the symptoms of croup due to the small size of their airways.[50]




The common cold is a disease of the upper respiratory tract.

## Diagnosis

The distinction between viral upper respiratory tract infections is loosely based on the location of symptoms with the common cold affecting primarily the nose, pharyngitis the throat, and bronchitis the lungs.[2] However, there can be significant overlap and multiple areas can be affected.[2] The common cold is frequently defined as nasal inflammation with varying amount of throat inflammation.[51] Self-diagnosis is frequent.[5] Isolation of the viral agent involved is rarely performed,[51] and it is generally not possible to identify the virus type through symptoms.[5]

## Prevention

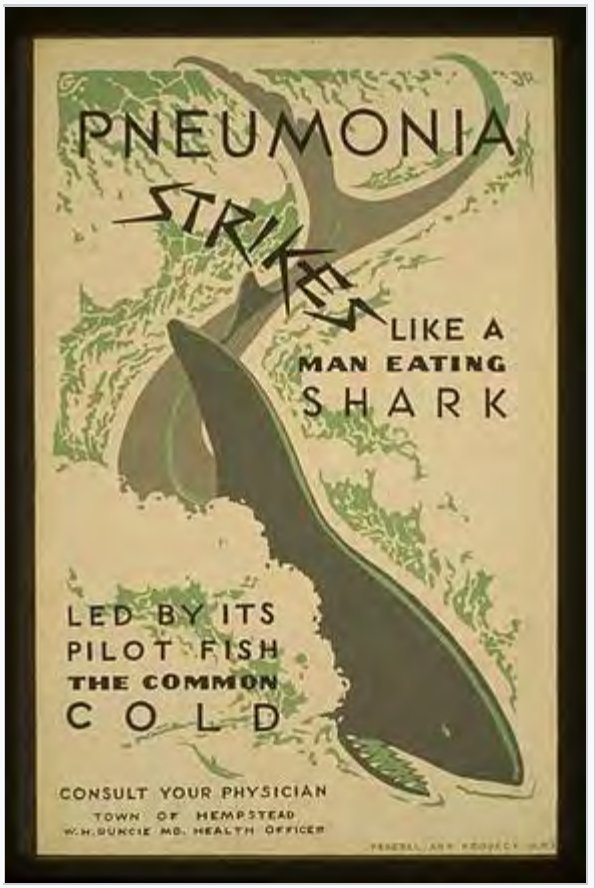
The only useful ways to reduce the spread of cold viruses are physical measures[9] such as hand washing and face masks; in the healthcare environment, gowns and disposable gloves are also used.[9] Isolation or quarantine is not used as the disease is so widespread and symptoms are non-specific. Vaccination has proved difficult as there are many viruses involved and they mutate rapidly.[9] Creation of a broadly effective vaccine is, thus, highly improbable.[52]

Regular hand washing appears to be effective in reducing the transmission of cold viruses, especially among children.[53] Whether the addition of antivirals or antibacterials to normal hand washing provides greater benefit is unknown.[53] Wearing face masks when around people who are infected may be beneficial; however, there is insufficient evidence for maintaining a greater social distance.[53]

Zinc supplements may help to reduce the prevalence of colds.[54] Routine vitamin C supplements do not reduce the risk or severity of the common cold, though they may reduce its duration.[55] Gargling with water was found useful in one small trial.[56]

# Management

No medications or herbal remedies have been conclusively demonstrated to shorten the duration of infection.[57] Treatment thus comprises symptomatic relief.[13] Getting plenty of rest, drinking fluids to maintain hydration, and gargling with warm salt water are reasonable conservative measures.[30] Much of the benefit from treatment is, however, attributed to the placebo effect.[58]




Poster from 1937 encouraging citizens to "consult your physician" for treatment of the common cold

## Symptomatic

Treatments that help with symptoms include simple pain medication and medications for fevers such as ibuprofen[59][*needs update*] and acetaminophen/paracetamol.[60] There is not good evidence for cough medicines.[61][*needs update*][62] Cough medicine are not recommended for use in children due to a lack of evidence supporting effectiveness and the potential for harm.[63][64] In 2009, Canada restricted the use of over-the-counter cough and cold medication in children six years and under due to concerns regarding risks and unproven benefits.[63] The misuse of dextromethorphan (an over-the-counter cough medicine) has led to its ban in a number of countries.[65]

In adults short term use of nasal decongestants may have a small benefit.[66] Antihistamines may improve symptoms in the first day or two; however, there is no longer-term benefit and they have adverse effects such as drowsiness.[67] Other decongestants such as pseudoephedrine appear effective in adults.[68][69] Ipratropium nasal spray may reduce the symptoms of a runny nose but has little effect on stuffiness.[70][*needs update*] The safety and effectiveness of nasal decongestant use in children is unclear.[69]

Due to lack of studies, it is not known whether increased fluid intake improves symptoms or shortens respiratory illness,[71] and there is a similar lack of data for the use of heated humidified air.[72] One study has found chest vapor rub to provide some relief of nocturnal cough, congestion, and sleep difficulty.[73]

## Antibiotics and antivirals

Antibiotics have no effect against viral infections or against the viruses that cause the common cold.[74] Due to their side effects, antibiotics cause overall harm but are still frequently prescribed.[74][75] Some of the reasons that antibiotics are so commonly prescribed include people's expectations for them, physicians' desire to help, and the difficulty in excluding complications that may be amenable to antibiotics.[76] There are no effective antiviral drugs for the common cold even though some preliminary research has shown benefits.[13][77]

## Alternative medicine

While there are many alternative treatments used for the common cold, there is insufficient scientific evidence to support the use of most.[13] As of 2014 there is insufficient evidence to recommend for or against honey.[78] As of 2015 there is tentative evidence to support nasal irrigation.[79] Zinc has been used

to treat symptoms, with studies suggesting that zinc, if taken within 24 hours of the onset of symptoms, reduces the duration and severity of the common cold in otherwise healthy people.[54] Due to wide differences between the studies, further research may be needed to determine how and when zinc may be effective.[80] Whereas zinc lozenges may produce side effects, there is only a weak rationale for physicians to recommend zinc for the treatment of the common cold.[81] Some zinc remedies directly applied to the inside of the nose have led to the loss of the sense of smell.[82]

Vitamin C's effect on the common cold, while extensively researched, is disappointing, except in limited circumstances: specifically, individuals exercising vigorously in cold environments.[55][83] There is no firm evidence that Echinacea products provide any meaningful benefit in treating or preventing colds.[84] It is unknown if garlic is effective.[85] A single trial of vitamin D did not find benefit.[86]

## Prognosis

The common cold is generally mild and self-limiting with most symptoms generally improving in a week.[2] Half of cases go away in 10 days and 90% in 15 days.[87] Severe complications, if they occur, are usually in the very old, the very young, or those who are immunosuppressed.[12] Secondary bacterial infections may occur resulting in sinusitis, pharyngitis, or an ear infection.[88] It is estimated that sinusitis occurs in 8% and ear infection in 30% of cases.[89]

## Epidemiology

The common cold is the most common human disease[12] and affects people all over the globe.[34] Adults typically have two to five infections annually,[2][5] and children may have six to ten colds a year (and up to twelve colds a year for school children).[13] Rates of symptomatic infections increase in the elderly due to declining immunity.[42]

Native Americans and Inuit are more likely to be infected with colds and develop complications such as otitis media than Caucasians.[29] This may be explained by issues such as poverty and overcrowding rather than by ethnicity.[29]

## History

While the cause of the common cold has only been identified since the 1950s, the disease has been with humanity since ancient times.[14] Its symptoms and treatment are described in the Egyptian Ebers papyrus, the oldest existing medical text, written before the 16th century BCE.[91] The name "cold" came into use in the 16th century, due to the similarity between its symptoms and those of exposure to cold weather.[92]

In the United Kingdom, the Common Cold Unit was set up by the Medical Research Council in 1946 and it was where the rhinovirus was discovered in 1956.[93] In the 1970s, the CCU demonstrated that treatment with interferon during the incubation phase of rhinovirus infection protects somewhat against the disease,[94] but no practical treatment could be developed. The unit was closed in 1989, two years after it completed research of zinc gluconate lozenges in the prophylaxis and treatment of rhinovirus colds, the only [95]


A British poster from World War II describing the cost of the common cold[90]

successful treatment in the history of the unit.

## Society and culture

The economic impact of the common cold is not well understood in much of the world.[89] In the United States, the common cold leads to 75–100 million physician visits annually at a conservative cost estimate of $7.7 billion per year. Americans spend $2.9 billion on over-the-counter drugs and another $400 million on prescription medicines for symptom relief.[96] More than one-third of people who saw a doctor received an antibiotic prescription, which has implications for antibiotic resistance.[96] An estimated 22–189 million school days are missed annually due to a cold. As a result, parents missed 126 million workdays to stay home to care for their children. When added to the 150 million workdays missed by employees suffering from a cold, the total economic impact of cold-related work loss exceeds $20 billion per year.[30][96] This accounts for 40% of time lost from work in the United States.[97]

## Research directions

Antivirals have been tested for effectiveness in the common cold; as of 2009, none had been both found effective and licensed for use.[77] There are ongoing trials of the anti-viral drug pleconaril which shows promise against picornaviruses as well as trials of BTA-798.[98] The oral form of pleconaril had safety issues and an aerosol form is being studied.[98] DRACO, a broad-spectrum antiviral therapy, has shown preliminary effectiveness in treating rhinovirus, as well as other infectious viruses.[99]

The genomes for all known human rhinovirus strains have been sequenced.[100]

## References

1. ^ John, Pramod R. John (2008). *Textbook of Oral Medicine*. Jaypee Brothers Publishers. p. 336. ISBN 9788180615627.
2. ^ *a b c d e f g* Arroll, B (March 2011). "Common cold". *Clinical evidence*. **2011** (3): 1510. PMC 3275147. PMID 21406124. "Common colds are defined as upper respiratory tract infections that affect the predominantly nasal part of the respiratory mucosa"

3. ^ a b c d e Allan, GM; Arroll, B (18 February 2014). "Prevention and treatment of the common cold: making sense of the evidence.". *CMAJ : Canadian Medical Association*. **186** (3): 190–9. doi:10.1503/cmaj.121442. PMC 3928210. PMID 24468694.
4. ^ a b c d e f g "Common Colds: Protect Yourself and Others". *CDC*. 6 October 2015. Retrieved 4 February 2016.
5. ^ a b c d e f g h i j Eccles R (November 2005). "Understanding the symptoms of the common cold and influenza". *Lancet Infect Dis*. **5** (11): 718–25. doi:10.1016/S1473-3099(05)70270-X. PMID 16253889.
6. ^ a b Heikkinen T, Järvinen A (January 2003). "The common cold". *Lancet*. **361** (9351): 51–9. doi:10.1016/S0140-6736(03)12162-9. PMID 12517470.
7. ^ "Common Cold and Runny Nose" (17 April 2015). *CDC*. Retrieved 4 February 2016.
8. ^ a b c d Eccles p. 112
9. ^ a b c d Eccles p. 209
10. ^ Kim, SY; Chang, YJ; Cho, HM; Hwang, YW; Moon, YS (21 September 2015). "Non-steroidal anti-inflammatory drugs for the common cold.". *The Cochrane database of systematic reviews*. **9**: CD006362. doi:10.1002/14651858.CD006362.pub4. PMID 26387658.
11. ^ Harris, AM; Hicks, LA; Qaseem, A; High Value Care Task Force of the American College of Physicians and for the Centers for Disease Control and, Prevention (19 January 2016). "Appropriate Antibiotic Use for Acute Respiratory Tract Infection in Adults: Advice for High-Value Care From the American College of Physicians and the Centers for Disease Control and Prevention.". *Annals of Internal Medicine*. **164**: 425. doi:10.7326/M15-1840. PMID 26785402.
12. ^ a b c Eccles p. 1
13. ^ a b c d e Simasek M, Blandino DA (2007). "Treatment of the common cold". *American Family Physician*. **75** (4): 515–20. PMID 17323712.
14. ^ a b Eccles, Ronald; Weber, Olaf (2009). *Common cold*. Basel: Birkhäuser. p. 3. ISBN 978-3-7643-9894-1.
15. ^ a b Eccles p. 24
16. ^ Eccles p. 26
17. ^ Eccles p. 129
18. ^ Eccles p. 50
19. ^ Eccles p. 30
20. ^ Richard A. Helms, ed. (2006). *Textbook of therapeutics: drug and disease management* (8. ed.). Philadelphia, Pa. [u.a.]: Lippincott Williams & Wilkins. p. 1882. ISBN 9780781757348.
21. ^ al.], edited by Helga Rübsamen-Waigmann ... [et (2003). *Viral Infections and Treatment.* Hoboken: Informa Healthcare. p. 111. ISBN 9780824756413.
22. ^ Ebell, M. H.; Lundgren, J.; Youngpairoj, S. (Jan–Feb 2013). "How long does a cough last? Comparing patients' expectations with data from a systematic review of the literature.". *Annals of Family Medicine*. **11** (1): 5–13. doi:10.1370/afm.1430. PMC 3596033. PMID 23319500.
23. ^ Dicpinigaitis PV (May 2011). "Cough: an unmet clinical need". *Br. J. Pharmacol*. **163** (1): 116–24. doi:10.1111/j.1476-5381.2010.01198.x. PMC 3085873. PMID 21198555.
24. ^ Goldsobel AB, Chipps BE (March 2010). "Cough in the pediatric population". *J. Pediatr*. **156** (3): 352–358.e1. doi:10.1016/j.jpeds.2009.12.004. PMID 20176183.
25. ^ Palmenberg AC, Spiro D, Kuzmickas R, Wang S, Djikeng A, Rathe JA, Fraser-Liggett CM, Liggett SB (2009). "Sequencing and Analyses of All Known Human Rhinovirus Genomes Reveals Structure and Evolution". *Science*. **324** (5923): 55–9. doi:10.1126/science.1165557. PMC 3923423. PMID 19213880.
26. ^ Eccles p. 77
27. ^ Pelczar (2010). *Microbiology: Application Based Approach*. p. 656. ISBN 978-0-07-015147-5.
28. ^ medicine, s cecil. *Goldman* (24th ed.). Philadelphia: Elsevier Saunders. p. 2103. ISBN 978-1-4377-2788-3.
29. ^ a b c d Michael Rajnik; Robert W Tolan (13 Sep 2013). "Rhinovirus Infection". Medscape Reference. Retrieved 19 March 2013.
30. ^ a b c "Common Cold". National Institute of Allergy and Infectious Diseases. 27 November 2006. Retrieved 11 June 2007.
31. ^ Eccles p. 107
32. ^ a b c Eccles, Ronald; Weber, Olaf (2009). *Common cold* (Online-Ausg. ed.). Basel: Birkhäuser. p. 197. ISBN 978-3-7643-9894-1.
33. ^ a b Eccles pp. 211, 215
34. ^ a b c d al.], edited by Arie J. Zuckerman ... [et (2007). *Principles and practice of clinical virology* (6th ed.). Hoboken, N.J.: Wiley. p. 496. ISBN 978-0-470-51799-4.

35. ^ Gwaltney JM Jr; Halstead SB. "Contagiousness of the common cold". Invited letter in "Questions and answers". *Journal of the American Medical Association*. **278** (3): 256–257. 16 July 1997. doi:10.1001/jama.1997.03550030096050. Retrieved 16 September 2011.
36. ^ Zuger, Abigail (4 March 2003). "'You'll Catch Your Death!' An Old Wives' Tale? Well..". *The New York Times*.
37. ^ Eccles p. 79
38. ^ a b "Common cold – Background information". National Institute for Health and Clinical Excellence. Retrieved 19 March 2013.
39. ^ a b Eccles p. 80
40. ^ a b Mourtzoukou EG, Falagas ME (September 2007). "Exposure to cold and respiratory tract infections". *The International Journal of Tuberculosis and Lung Disease*. **11** (9): 938–43. PMID 17705968.
41. ^ Eccles p. 157
42. ^ a b c Eccles p. 78
43. ^ Eccles p. 166
44. ^ Cohen S, Doyle WJ, Alper CM, Janicki-Deverts D, Turner RB (January 2009). "Sleep habits and susceptibility to the common cold". *Arch. Intern. Med*. **169** (1): 62–7. doi:10.1001/archinternmed.2008.505. PMC 2629403. PMID 19139325.
45. ^ Eccles pp. 160–165
46. ^ McNiel, ME; Labbok, MH; Abrahams, SW (July 2010). "What are the risks associated with formula feeding? A re-analysis and review.". *Breastfeeding Review*. **18** (2): 25–32. PMID 20879657.
47. ^ Lawrence, Ruth A. Lawrence, Robert M. (2010-09-30). *Breastfeeding a guide for the medical profession* (7th ed.). Maryland Heights, Mo.: Mosby/Elsevier. p. 478. ISBN 9781437735901.
48. ^ Williams, [edited by] Kenrad E. Nelson, Carolyn F. Masters (2007). *Infectious disease epidemiology : theory and practice* (2nd ed.). Sudbury, Mass.: Jones and Bartlett Publishers. p. 724. ISBN 9780763728793.
49. ^ a b Eccles p. 116
50. ^ a b Eccles p. 122
51. ^ a b Eccles pp. 51–52
52. ^ Lawrence DM (May 2009). "Gene studies shed light on rhinovirus diversity". *Lancet Infect Dis*. **9** (5): 278. doi:10.1016/S1473-3099(09)70123-9.
53. ^ a b c Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Nair S, Jones MA, Thorning S, Conly JM (July 2011). Jefferson T, ed. "Physical interventions to interrupt or reduce the spread of respiratory viruses". *Cochrane Database of Systematic Reviews* (7): CD006207. doi:10.1002/14651858.CD006207.pub4. PMID 21735402.
54. ^ a b Singh M, Das RR (February 2011). Singh M, ed. "Zinc for the common cold". *Cochrane Database of Systematic Reviews* (2): CD001364. doi:10.1002/14651858.CD001364.pub3. PMID 21328251.
55. ^ a b Hemilä, H; Chalker, E (31 January 2013). "Vitamin C for preventing and treating the common cold.". *The Cochrane database of systematic reviews*. **1**: CD000980. doi:10.1002/14651858.CD000980.pub4. PMID 23440782.
56. ^ Satomura, K; Kitamura, T; Kawamura, T; Shimbo, T; Watanabe, M; Kamei, M; Takano, Y; Tamakoshi, A; Great Cold, Investigators-I (November 2005). "Prevention of upper respiratory tract infections by gargling: a randomized trial.". *American journal of preventive medicine*. **29** (4): 302–7. doi:10.1016/j.amepre.2005.06.013. PMID 16242593.
57. ^ "Common Cold: Treatments and Drugs". Mayo Clinic. Retrieved 9 January 2010.
58. ^ Eccles p. 261
59. ^ Kim, SY; Chang, YJ; Cho, HM; Hwang, YW; Moon, YS (4 June 2013). "Non-steroidal anti-inflammatory drugs for the common cold.". *The Cochrane database of systematic reviews*. **6**: CD006362. doi:10.1002/14651858.CD006362.pub3. PMID 23733384.
60. ^ Eccles R (2006). "Efficacy and safety of over-the-counter analgesics in the treatment of common cold and flu". *Journal of Clinical Pharmacy and Therapeutics*. **31** (4): 309–319. doi:10.1111/j.1365-2710.2006.00754.x. PMID 16882099.
61. ^ Smith, SM; Schroeder, K; Fahey, T (15 August 2012). "Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings.". *The Cochrane database of systematic reviews*. **8**: CD001831. doi:10.1002/14651858.CD001831.pub4. PMID 22895922.
62. ^ Smith, SM; Schroeder, K; Fahey, T (24 November 2014). "Over-the-counter (OTC) medications for acute cough in children and adults in community settings.". *The Cochrane database of systematic reviews*. **11**: CD001831. doi:10.1002/14651858.CD001831.pub5. PMID 25420096.
63. ^ a b Shefrin AE, Goldman RD (November 2009). "Use of over-the-counter cough and cold medications in

children" (PDF). *Can Fam Physician*. **55** (11): 1081–3. PMC 2776795. PMID 19910592.
64. ^ Vassilev ZP, Kabadi S, Villa R (March 2010). "Safety and efficacy of over-the-counter cough and cold medicines for use in children". *Expert opinion on drug safety*. **9** (2): 233–42. doi:10.1517/14740330903496410. PMID 20001764.
65. ^ Eccles p. 246
66. ^ Deckx, L; De Sutter, AI; Guo, L; Mir, NA; van Driel, ML (17 October 2016). "Nasal decongestants in monotherapy for the common cold.". *The Cochrane database of systematic reviews*. **10**: CD009612. doi:10.1002/14651858.CD009612.pub2. PMID 27748955.
67. ^ De Sutter, AI; Saraswat, A; van Driel, ML (29 November 2015). "Antihistamines for the common cold.". *The Cochrane database of systematic reviews*. **11**: CD009345. doi:10.1002/14651858.CD009345.pub2. PMID 26615034.
68. ^ Taverner D, Latte GJ (2007). Latte, G. Jenny, ed. "Nasal decongestants for the common cold". *Cochrane Database Syst Rev* (1): CD001953. doi:10.1002/14651858.CD001953.pub3. PMID 17253470.
69. ^ *a b* Deckx, Laura; De Sutter, An Im; Guo, Linda; Mir, Nabiel A.; van Driel, Mieke L. (17 October 2016). "Nasal decongestants in monotherapy for the common cold". *The Cochrane Database of Systematic Reviews*. **10**: CD009612. doi:10.1002/14651858.CD009612.pub2. PMID 27748955.
70. ^ Albalawi ZH, Othman SS, Alfaleh K (July 2011). Albalawi ZH, ed. "Intranasal ipratropium bromide for the common cold". *Cochrane Database of Systematic Reviews* (7): CD008231. doi:10.1002/14651858.CD008231.pub2. PMID 21735425.
71. ^ Guppy MP, Mickan SM, Del Mar CB, Thorning S, Rack A (February 2011). Guppy MP, ed. "Advising patients to increase fluid intake for treating acute respiratory infections". *Cochrane Database of Systematic Reviews* (2): CD004419. doi:10.1002/14651858.CD004419.pub3. PMID 21328268.
72. ^ Singh, M; Singh, M (4 June 2013). "Heated, humidified air for the common cold.". *The Cochrane database of systematic reviews*. **6**: CD001728. doi:10.1002/14651858.CD001728.pub5. PMID 23733382.
73. ^ Paul IM, Beiler JS, King TS, Clapp ER, Vallati J, Berlin CM (December 2010). "Vapor rub, petrolatum, and no treatment for children with nocturnal cough and cold symptoms". *Pediatrics*. **126** (6): 1092–9. doi:10.1542/peds.2010-1601. PMC 3600823. PMID 21059712.
74. ^ *a b* Kenealy, T; Arroll, B (4 June 2013). "Antibiotics for the common cold and acute purulent rhinitis.". *The Cochrane database of systematic reviews*. **6**: CD000247. doi:10.1002/14651858.CD000247.pub3. PMID 23733381.
75. ^ Eccles p. 238
76. ^ Eccles p. 234
77. ^ *a b* Eccles p. 218
78. ^ Oduwole, O; Meremikwu, MM; Oyo-Ita, A; Udoh, EE (23 December 2014). "Honey for acute cough in children.". *The Cochrane database of systematic reviews*. **12**: CD007094. doi:10.1002/14651858.CD007094.pub4. PMID 25536086.
79. ^ King, D; Mitchell, B; Williams, CP; Spurling, GK (20 April 2015). "Saline nasal irrigation for acute upper respiratory tract infections.". *The Cochrane database of systematic reviews*. **4**: CD006821. doi:10.1002/14651858.CD006821.pub3. PMID 25892369.
80. ^ "Zinc for the common cold — Health News — NHS Choices". *nhs.uk*. 2012. Retrieved 24 February 2012. "In this review, there was a high level of heterogeneity between the studies that were pooled to determine the effect of zinc on the duration of cold symptoms. This may suggest that it was inappropriate to pool them. It certainly makes this particular finding less conclusive."
81. ^ Science, M.; Johnstone, J.; Roth, D. E.; Guyatt, G.; Loeb, M. (10 July 2012). "Zinc for the treatment of the common cold: a systematic review and meta-analysis of randomized controlled trials". *Canadian Medical Association Journal*. **184** (10): E551–E561. doi:10.1503/cmaj.111990. PMC 3394849. PMID 22566526.
82. ^ "Loss of Sense of Smell with Intranasal Cold Remedies Containing Zinc". 2009.
83. ^ Heiner KA, Hart AM, Martin LG, Rubio-Wallace S (2009). "Examining the evidence for the use of vitamin C in the prophylaxis and treatment of the common cold". *Journal of the American Academy of Nurse Practitioners*. **21** (5): 295–300. doi:10.1111/j.1745-7599.2009.00409.x. PMID 19432914.
84. ^ Karsch-Völk M, Barrett B, Kiefer D, Bauer R, Ardjomand-Woelkart K, Linde K (2014). "Echinacea for preventing and treating the common cold". *Cochrane Database Syst Rev* (Systematic review). **2**: CD000530. doi:10.1002/14651858.CD000530.pub3. PMC 4068831. PMID 24554461.
85. ^ Lissiman E, Bhasale AL, Cohen M (2014). Lissiman E, ed. "Garlic for the common cold". *Cochrane Database Syst Rev*. **11**: CD006206. doi:10.1002/14651858.CD006206.pub4. PMID 25386977.
86. ^ Murdoch, David R. (3 October 2012). "Effect of Vitamin $D_3$ Supplementation on Upper Respiratory Tract Infections in Healthy Adults: The VIDARIS Randomized Controlled Trial</subtitle>". *JAMA: The Journal of the American Medical Association*. **308** (13): 1333. doi:10.1001/jama.2012.12505.

87. ^ Thompson, M; Vodicka, TA; Blair, PS; Buckley, DI; Heneghan, C; Hay, AD; TARGET Programme, Team (11 Dec 2013). "Duration of symptoms of respiratory tract infections in children: systematic review." *BMJ (Clinical research ed.)*. **347**: f7027. doi:10.1136/bmj.f7027. PMC 3898587. PMID 24335668.
88. ^ Eccles p. 76
89. ^ *a b* Eccles p. 90
90. ^ "The Cost of the Common Cold and Influenza". *Imperial War Museum: Posters of Conflict*. vads.
91. ^ Eccles p. 6
92. ^ "Cold". Online Etymology Dictionary. Retrieved 12 January 2008.
93. ^ Eccles p. 20
94. ^ Tyrrell DA (1987). "Interferons and their clinical value". *Rev. Infect. Dis.* **9** (2): 243–9. doi:10.1093/clinids/9.2.243. PMID 2438740.
95. ^ Al-Nakib W; Higgins, P.G.; Barrow, I.; Batstone, G.; Tyrrell, D.A.J. (December 1987). "Prophylaxis and treatment of rhinovirus colds with zinc gluconate lozenges". *J Antimicrob Chemother*. **20** (6): 893–901. doi:10.1093/jac/20.6.893. PMID 3440773.
96. ^ *a b c* Fendrick AM, Monto AS, Nightengale B, Sarnes M (2003). "The economic burden of non-influenza-related viral respiratory tract infection in the United States". *Arch. Intern. Med.* **163** (4): 487–94. doi:10.1001/archinte.163.4.487. PMID 12588210.
97. ^ Kirkpatrick GL (December 1996). "The common cold". *Prim. Care*. **23** (4): 657–75. doi:10.1016/S0095-4543(05)70355-9. PMID 8890137.
98. ^ *a b* Eccles p. 226
99. ^ Rider TH, Zook CE, Boettcher TL, Wick ST, Pancoast JS, Zusman BD (2011). Sambhara S, ed. "Broad-spectrum antiviral therapeutics". *PLoS ONE*. **6** (7): e22572. doi:10.1371/journal.pone.0022572. PMC 3144912. PMID 21818340.
100. ^ Val Willingham (12 February 2009). "Genetic map of cold virus a step toward cure, scientists say". CNN. Retrieved 28 April 2009.


## Notes


- Ronald Eccles, Olaf Weber (eds) (2009). *Common cold*. Basel: Birkhäuser. ISBN 978-3-7643-9894-1.


# External links

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*Medicine portal*
*Viruses portal*

| v · t · e · | **Infectious diseases – viral systemic diseases (A80–B34, 042–079)** | |
|---|---|---|
| **Oncovirus** | **DNA virus:** *HBV* (Hepatocellular carcinoma · · *HPV* (Cervical cancer · Anal cancer · Penile cancer · Vulvar cancer · Vaginal cancer · Oropharyngeal cancer · · *KSHV* (Kaposi's sarcoma · · *EBV* (Nasopharynx cancer · Burkitt's lymphoma · Hodgkin's lymphoma · Follicular dendritic cell sarcoma · Extranodal NK/T-cell lymphoma, nasal type · · *MCPyV* (Merkel-cell carcinoma · · **RNA virus:** *HCV* (Hepatocellular carcinoma · Splenic marginal zone lymphoma · · *HTLV-I* (Adult T-cell leukemia/lymphoma · · | |
| **Immune disorders** | *HIV* (AIDS · · | |
| **Central** | **Encephalitis/ meningitis** | **DNA virus:** *JCV* (Progressive multifocal leukoencephalopathy · · **RNA virus:** *MeV* (Subacute sclerosing panencephalitis · · *LCV* (Lymphocytic choriomeningitis · · Arbovirus encephalitis · *Orthomyxoviridae (probable)* (Encephalitis lethargica · · *RV* (Rabies · · Chandipura virus · Herpesviral meningitis · |

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|---|---|---|
| **nervous system** | | Ramsay Hunt syndrome type 2 · |
| | **Myelitis** | *Poliovirus* (Poliomyelitis · Post-polio syndrome · · *HTLV-I* (Tropical spastic paraparesis · · |
| | **Eye** | *Cytomegalovirus* (Cytomegalovirus retinitis · · *HSV* (Herpes of the eye · · |
| **Cardiovascular** | *CBV* (Pericarditis · Myocarditis · · | |
| **Respiratory system/ acute viral nasopharyngitis/ viral pneumonia** | **DNA virus** | *Epstein–Barr virus* (EBV infection/Infectious mononucleosis · · *Cytomegalovirus* · |
| | **RNA virus** | IV: *SARS coronavirus* (Severe acute respiratory syndrome · · V: *Orthomyxoviridae: Influenzavirus A/B/C* (Influenza/Avian influenza · · V, *Paramyxoviridae: Human parainfluenza viruses* (Parainfluenza · · *RSV* · *hMPV* · |
| **Human digestive system** | **Pharynx/Esophagus** | *MuV* (Mumps · · *Cytomegalovirus* (Cytomegalovirus esophagitis · · |
| | **Gastroenteritis/ diarrhea** | **DNA virus:** *Adenovirus* (Adenovirus infection · · **RNA virus:** *Rotavirus* · *Norovirus* · *Astrovirus* · *Coronavirus* · |
| | **Hepatitis** | **DNA virus:** *HBV* (B) · **RNA virus:** *CBV* · *HAV* (A) · *HCV* (C) · *HDV* (D) · *HEV* (E) · *HGV* (G) · |
| | **Pancreatitis** | *CBV* · |
| **Urogenital** | *BK virus* · *MuV* (Mumps · · | |

| V · T · E · | **Diseases of the respiratory system (J, 460–519)** | |
|---|---|---|
| **Upper RT (including URTIs, common cold)** | **Head** | *sinuses*: Sinusitis · *nose*: Rhinitis (Vasomotor rhinitis · Atrophic rhinitis · Hay fever · · Nasal polyp · Rhinorrhea · *nasal septum* (Nasal septum deviation · Nasal septum perforation · Nasal septal hematoma · · *tonsil*: Tonsillitis · Adenoid hypertrophy · Peritonsillar abscess · |
| | **Neck** | *pharynx*: Pharyngitis (Strep throat · · Laryngopharyngeal reflux (LPR) · Retropharyngeal abscess · *larynx*: Croup · Laryngomalacia · Laryngeal cyst · Laryngitis · Laryngopharyngeal reflux (LPR) · Laryngospasm · *vocal folds*: Laryngopharyngeal reflux (LPR) · Vocal fold nodule · Vocal cord paresis · Vocal cord dysfunction · *epiglottis*: Epiglottitis · *trachea*: Tracheitis · Tracheal stenosis · |
| | **Bronchial/ obstructive** | *acute*: Acute bronchitis · *chronic*: COPD (Chronic bronchitis · Acute exacerbations of chronic bronchitis · Acute exacerbation of COPD · Emphysema) · Asthma (Status asthmaticus · Aspirin-induced · |

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|---|---|---|---|---|
| **Lower RT/lung disease (including LRTIs)** | | Exercise-induced · · Bronchiectasis · *unspecified*: Bronchitis · Bronchiolitis (Bronchiolitis obliterans · · Diffuse panbronchiolitis · | | |
| | **Interstitial/restrictive (fibrosis)** | **External agents/occupational lung disease** | | Pneumoconiosis (Asbestosis · Baritosis · Bauxite fibrosis · Berylliosis · Caplan's syndrome · Chalicosis · Coalworker's pneumoconiosis · Siderosis · Silicosis · Talcosis · Byssinosis · · Hypersensitivity pneumonitis (Bagassosis · Bird fancier's lung · Farmer's lung · Lycoperdonosis · · |
| | | **Other** | | ARDS · Pulmonary edema · Löffler's syndrome/Eosinophilic pneumonia · Respiratory hypersensitivity (Allergic bronchopulmonary aspergillosis · · Hamman-Rich syndrome · Idiopathic pulmonary fibrosis · Sarcoidosis · |
| | **Obstructive or restrictive** | **Pneumonia/pneumonitis** | **By pathogen** | Viral · Bacterial (Pneumococcal · Klebsiella) · · Atypical bacterial (Mycoplasma · Legionnaires' disease · Chlamydiae · · Fungal (Pneumocystis · · Parasitic · *noninfectious* (Chemical/Mendelson's syndrome · Aspiration/Lipid · · |
| | | | **By vector/route** | Community-acquired · Healthcare-associated · Hospital-acquired · |
| | | | **By distribution** | Broncho- · Lobar · |
| | | | **IIP** | UIP · DIP · BOOP-COP · NSIP · RB · |
| | | **Other** | | Atelectasis · *circulatory* (Pulmonary hypertension · Pulmonary embolism · · Lung abscess · |
| **Pleural cavity/mediastinum** | **Pleural disease** | | | Pleuritis/pleurisy · Pneumothorax/Hemopneumothorax · **Pleural effusion:** Hemothorax · Hydrothorax · Chylothorax · Empyema/pyothorax · Malignant · Fibrothorax · |
| | **Mediastinal disease** | | | Mediastinitis · Mediastinal emphysema · |
| **Other/general** | | | | Respiratory failure · Influenza · SARS · Idiopathic pulmonary haemosiderosis · Pulmonary alveolar proteinosis · |

v · t · e · **Common cold**

| | |
|---|---|
| **Viruses** | Adenovirus · Coronavirus · Enterovirus · Human metapneumovirus · Human parainfluenza viruses · Human respiratory syncytial virus · Orthomyxoviruses (Influenza A virus · Influenza B virus · Influenza C virus · · Rhinovirus · |
| **Symptoms** | Cough · Fatigue · Fever · Headache · Loss of appetite · Malaise · Muscle aches · Nasal congestion · Rhinorrhea · Sneezing · Sore throat · Weakness · |
| **Complications** | Acute bronchitis · Bronchiolitis · Croup · Otitis media · Pharyngitis · Pneumonia · Sinusitis · Strep throat · |
| **Drugs** | Antiviral drugs · Pleconaril *(experimental)* · |
| **Authority control** | GND: 4136665-7 · NDL: 00564849 · |

Categories: Acute upper respiratory infections | Inflammations | Animal viral diseases | Enterovirus-associated diseases

# Cysticercosis

From Wikipedia, the free encyclopedia



*This article is about the infection. For the organism, see Taenia solium.*

**Cysticercosis** is a tissue infection caused by the young form of the pork tapeworm.[1][2] People may have few or no symptoms for years.[3][4] In some cases, particularly in Asia, solid lumps of between one and two centimetres may develop under the skin.[2] After months or years these lumps can become painful and swollen and then resolve.[3][4] A specific form called neurocysticercosis, which affects the brain, can cause neurological symptoms. In developing countries this is one of the most common causes of seizures.[4]

Cysticercosis is usually acquired by eating food or drinking water that has tapeworm eggs in it. Among foods, uncooked vegetables are the major source.[2] The tapeworm eggs are present in the feces of a person infected with the adult worms, a condition known as taeniasis.[4][5] Taeniasis, in the strict sense, is a different disease and is due to eating cysts in poorly cooked pork.[2] People who live with someone with the tapeworm have a greater risk of getting cysticercosis.[5] The diagnosis can be made by aspiration of a cyst.[4] Taking pictures of the brain with computer tomography (CT) or magnetic resonance imaging (MRI) are most useful for the diagnosis of disease in the brain. An increased number of a type of white blood cell, called eosinophils, in the cerebral spinal fluid and blood is also an indicator.[4]

Infection can be effectively prevented by personal hygiene and sanitation: this includes cooking pork well, proper toilets and sanitary practices, and improved access to clean water. Treating those with taeniasis is important to prevent spread.[2] Treating the disease when it does not involve the nervous system may not be required.[4] Treatment of those with neurocysticercosis may be with the medications praziquantel or albendazole. These may be required for long periods of time.[2] Steroids, for anti-inflammation during treatment, and anti-seizure medications may also be required. Surgery is sometimes done to remove the cysts.[2]

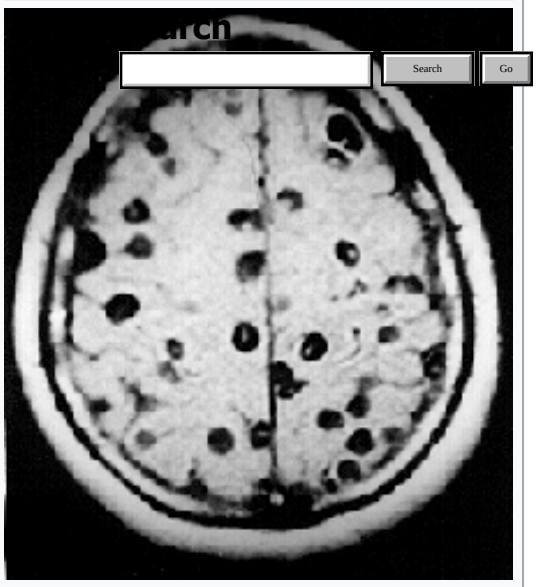
The pork tapeworm is particularly common in Asia, Sub-Saharan Africa, and Latin America.[4] In some areas it is believed that up to 25% of people are affected.[4] In the developed world it is very uncommon.[6] Worldwide as of 2010 it caused about 1,200 deaths, up from 700 in 1990.[7] Cysticercosis also affects pigs and cows but rarely causes symptoms as most do not live long enough.[2] The disease has occurred in humans throughout history.[6] It is one of the neglected tropical diseases.[8]

Contents



## Variants

## More Cysticercosis




Magnetic resonance image in a person with neurocysticercosis showing many cysts within the brain.

| Classification and external resources | |
|---|---|
| **Specialty** | infectious disease |
| **ICD-10** | B69 |
| **ICD-9-CM** | 123.1 |
| **DiseasesDB** | 3341 |
| **MedlinePlus** | 000627 |
| **eMedicine** | emerg/119 med/494 ped/537 |
| **MeSH** | D003551 |

[edit on Wikidata]

## Signs and symptoms [edit]

### Muscles [edit]

Cysticerci can develop in any voluntary muscles in humans. Invasion of muscle by cysticerci can cause myositis, with fever, eosinophilia, and muscular pseudohypertrophy, which initiates with muscle swelling and later progress to atrophy and fibrosis. In most cases, it is asymptomatic since the cysticerci die and become calcified.[9]

### Nervous system [edit]

The term neurocysticercosis is generally accepted to refer to cysts in the parenchyma of the brain. It presents with seizures and, less commonly, headaches.[10] Cysticerca in brain parenchyma are usually 5–20 mm in diameter. In subarachnoid space and fissures, lesions may be as large as 6 cm in diameter and lobulated. They may be numerous and life-threatening.[11]

Cysts located within the ventricles of the brain can block the outflow of cerebrospinal fluid and present with symptoms of increased intracranial pressure.[12]

Racemose neurocysticercosis refers to cysts in the subarachnoid space. These can occasionally grow into large lobulated masses causing pressure on surrounding structures.[13]

Neurocysticercosis involving the spinal cord, most commonly presenting as back pain and radiculopathy.[14]

### Eyes [edit]

In some cases, cysticerci may be found in the globe, extraocular muscles, and under the conjunctiva (*subconjunctiva*). Depending on the location, they may cause visual difficulties that fluctuate with eye position, retinal edema, hemorrhage, a decreased vision or even a visual loss.[9]

### Skin [edit]

Subcutaneous cysts are in the form of firm, mobile nodules, occurring mainly on the trunk and extremities.[15] Subcutaneous nodules are sometimes painful.

## Cause [edit]

The cause of human cysticercosis is the egg form of *Taenia solium* (often abbreviated as *T. solium* and also called pork tapeworm), which is transmitted through the oral-fecal route. Eggs are accidentally ingested from contaminated water or vegetables. The eggs enter the intestine where they develop into larvae. The larvae enter bloodstream and invade host tissues, where they further develop into larvae called cysticerci. The cysticercus larva completes development in about 2 months. It is semitransparent, opalescent white, and elongate oval in shape and may reach a length of 0.6 to 1.8 cm.[9]

## Diagnosis [edit]

The traditional method of demonstrating either tapeworm eggs or proglottids in stool samples diagnoses only taeniasis, carriage of the tapeworm stage of the life cycle.[5] Only a small minority of patients with cysticercosis will harbor a tapeworm, rendering stool studies ineffective for diagnosis.[16] Ophthalmic cysticercosis can be diagnosed by visualizing parasite in eye by fundoscopy.

Life cycle of *Taenia solium*

In cases of human cysticercosis, diagnosis is a sensitive problem and requires biopsy of the infected tissue or sophisticated instruments.[17] *Taenia solium* eggs and proglottids found in feces, ELISA, or polyacrylamide gel electrophoresis diagnose only taeniasis and not cysticercosis. Radiological tests, such as X-ray, CT scans which demonstrate "ring-enhancing brain lesions", and MRIs, can also be used to detect diseases. X-rays are used to identify calcified larvae in the subcutaneous and muscle tissues, and CT scans and MRIs are used to find lesions in the brain.[18][19]

### Serological [edit]

Antibodies to cysticerci can be demonstrated in serum by EITB (Enzyme Linked Immunotransfer Blot) assay and in CSF by ELISA. An immunoblot assay using lentil-lectin (agglutinin from Lens culinaris) is highly sensitive and specific. However, Individuals with intracranial lesions and calcifications may be seronegative. In the CDC's immunoblot assay, cysticercosis-specific antibodies can react with structural glycoprotein antigens from the larval cysts of *Taenia solium*.[5] However, this is mainly a research tool not widely available in clinical practice and nearly unobtainable in resource limited settings.

### Neurocysticercosis [edit]

The diagnosis of neurocysticercosis is mainly clinical, based on a compatible presentation of symptoms and findings of imaging studies.

### Imaging [edit]

Neuroimaging with CT or MRI is the most useful method of diagnosis. CT scan shows both calcified and uncalcified cysts, as well as distinguishing active and inactive cysts. Cystic lesions can show ring enhancement and focal enhancing lesions. Some cystic lesions, especially the ones in ventricles and subarachnoid space may not be visible on CT scan, since the cyst fluid is isodense with cerebrospinal fluid (CSF). Thus diagnosis of extraparenchymal cysts usually relies on signs like hydrocephalus or enhanced basilar meninges. In such cases CT scan with intraventricular contrast or MRI can be used. MRI is more sensitive in detection of intraventricular cysts.[20][21]

### CSF [edit]

CSF findings include pleocytosis, elevated protein levels and depressed glucose levels; but these may not be always present.

## Prevention [edit]

Cysticercosis is considered as "tools-ready disease" according to WHO.[22] International Task Force for Disease Eradication in 1992 reported that cysticercosis is potentially eradicable.[23] It is feasible because there are no animal reservoirs besides humans and pigs. The only source of *Taenia solium* infection for pigs is from humans, a definite host. Theoretically, breaking the life cycle seems easy by doing intervention strategies from various stages in the life cycle.[24]

For example,

1. Massive chemotherapy of infected individuals, improving sanitation, and educating people are all major ways to discontinue the cycle, in which eggs from human feces are transmitted to other humans and/or pigs.
2. Cooking of pork or freezing it and inspecting meat are effective means to cease the life cycle
3. The management of pigs by treating them or vaccinating them is another possibility to intervene
4. The separation of pigs from human faeces by confining them in enclosed piggeries. In Western European countries post World War 2 the pig industry developed rapidly and most pigs were housed.[*citation needed*] This was the main reason for pig cysticercosis largely being eliminated from the region. This of course is not a quick answer to the problem in developing countries.

## Pigs [edit]

The intervention strategies to eradicate cysticercosis includes surveillance of pigs in foci of transmission and massive chemotherapy treatment of humans.[23] In reality, control of *T. solium* by a single intervention, for instance, by treating only human population will not work because the existing infected pigs can still carry on the cycle. The proposed strategy for eradication is to do multilateral intervention by treating both human and porcine populations.[25] It is feasible because treatment pigs with oxfendazole have been shown to be effective and once treated, they are protected from further infections for at least 3 months.[26]

## Limitations [edit]

Even with the concurrent treatment of humans and pigs, complete elimination is hard to achieve. In one study conducted in 12 villages in Peru, both humans and porcine were treated with praziquantel and oxfendazole, with the coverage of more than 75% in humans and 90% in pigs[27] The result shows a decreased in prevalence and incidence in the intervention area; however the effect did not completely eliminate *T. solium*. The possible reason includes the incomplete coverage and re-infection.[28] Even though *T. solium* could be eliminated through mass treatment of human and porcine population, it is not sustainable.[25] Moreover, both tapeworm carriers of humans and pigs tend to spread the disease from endemic to non-endemic areas resulting in periodic outbreaks of cysticercosis or outbreaks in new areas.[29][30]

## Vaccines [edit]

Given the fact that pigs are part of a life cycle, vaccination of pigs is another feasible intervention to eliminate cysticercosis. Research studies have been focusing on vaccine against cestode parasites, since many immune cell types are found to be capable of destroying cysticercus.[31] Many vaccine candidates are extracted from antigens of different cestodes such as *Taenia solium*, *T. crassiceps*, *T. saginata*, *T. ovis* and target oncospheres and/or cysticerci. In 1983, Molinari et al. reported the first vaccine candidate against porcine cysticercosis using antigen from cysticercus cellulosae drawn out from naturally infected.[32] Recently, vaccines extracted from genetically engineered 45W-4B antigens have been successfully tested to pigs in an experimental condition.[33] This type of vaccine can protect against cysticercosis in both Chinese and Mexican type of *T. solium*. However, it has not been tested in endemic field conditions, which is important because the realistic condition in the field differ greatly from experimental condition, and this can result in a great difference in the chances of infection and immune reaction.[31]

Even though vaccines have been successfully generated, the feasibility of its production and usage in rural free ranging pigs still remains a challenge. If a vaccine is to be injected, the burden of work and the cost of vaccine administration to pigs will remain high and unrealistic.[31] The incentives of using vaccines by pig owners will decrease if the vaccine administration to pigs takes time by injecting every single pig in their livestock. A hypothetical oral vaccine is proposed to be more effective in this case as it can be easily delivered to the pigs by food.[31]

## S3PVAC vaccine [edit]

The vaccine constituted by 3 peptide synthetically produced (S3Pvac) has proven its efficacy in natural conditions of transmission.[34] The S3PVAC vaccine so far, can be considered as the best vaccine candidate to be used in endemic areas such as Mexico (20). S3Pvac consists of three protective peptides: KETc12, KETc1 and GK1, whose sequences belong to native antigens that are present in the different developmental stages of *T. solium* and other cestode parasites.[31][35]

Non-infected pigs from rural villages in Mexico were vaccinated with S3Pvac and the vaccine reduced 98% the number of cysticerci and 50% the number of prevalence.[34][36] The diagnostic method involves necropsy and tongue inspection of pigs. The natural challenge conditions used in the study proved the efficacy of the S3Pvac vaccine in transmission control of *T. solium* in Mexico.[31] The S3Pvac vaccine is owned by the National Autonomous University of Mexico and the method of high scale production of the vaccine has already been developed.[31] The validation of the vaccine in agreement with the Secretary of Animal Health in Mexico is currently in the process of completion.[37] It is also hoped that the vaccine will be well-accepted by pig owners because they also lose their income if pigs are infected cysticercosis.[37] Vaccination of pigs against cysticercosis, if succeeded, can potentially have a great impact on transmission control since there is no chance of re-infection once pigs receive vaccination.

## Other [edit]

Cysticercosis can also be prevented by routine inspection of meat and condemnation of measly meat by the local government.[38] However, in areas where food is scarce, cyst-infected meat might be considered as wasted since pork can provide high quality protein.[39] At times, infected pigs are consumed within the locality or sold at low prices to traffickers who take the uninspected pigs at urban areas for sale.[40]

Due to these limitations, cysticercosis has not been eliminated in any endemic areas.

# Management [edit]

## Neurocysticercosis [edit]

Asymptomatic cysts, such as those discovered incidentally on neuroimaging done for another reason, may never lead to symptomatic disease and in many cases do not require therapy. Calcified cysts have already died and involuted. Further antiparasitic therapy will be of no benefit.

Neurocysticercosis may present as hydrocephalus and acute onset seizures, thus the immediate therapy is emergent reduction of intracranial pressure and anticonvulsant medications. Once the seizures have been brought under control, antihelminthic treatments may be undertaken. The decision to treat with antiparasitic therapy is complex and based on the stage and number of cysts present, their location, and the persons specific symptoms.[41]

Adult *Taenia solium* are easily treated with niclosamide, and is most commonly used in taeniasis. However cysticercosis is a complex disease and requires careful medication. Praziquantel (PZQ) is the drug of choice. In neurocysticercosis praziquantel is widely used.[42] Albendazole appears to be more effective and a safe drug for neurocysticercosis.[43][44] In complicated situation a combination of praziquantel, albendazole and steroid (such as corticosteroids to reduces the inflammation) is recommended.[45] In the brain the cysts can be usually found on the surface. Most cases of brain cysts are found by accident, during diagnosis for other ailments. Surgical removals are the only option of complete removal even if treated successfully with medications.[18]

Antiparasitic treatment should be given in combination with corticosteroids and anticonvulsants to reduce inflammation surrounding the cysts and lower the risk of seizures. When corticosteroids are given in combination with praziquantel, cimetidine is also given, as corticosteroids decrease action of praziquantel by enhancing its first pass metabolism. Albendazole is generally preferable over praziquantel due to its lower cost and fewer drug interactions.[43]

Surgical intervention is much more likely to be needed in cases of intraventricular, racemose, or spinal neurocysticercosis. Treatments includes direct excision of ventricular cysts, shunting procedures, and removal of cysts via endoscopy.

## Eyes [edit]

In eye disease, surgical removal is necessary for cysts within the eye itself as treating intraocular lesions with anthelmintics will elicit an inflammatory reaction causing irreversible damage to structural components. Cysts outside the globe can be treated with anthelmintics and steroids. Treatment recommendations for subcutaneous cysticercosis includes surgery, praziquantel and albendazole.[15]

## Skin [edit]

In general, subcutaneous disease does not need specific therapy. Painful or bothersome cysts can be surgically removed.

# Epidemiology [edit]

## Regions [edit]

*Taenia solium* is found worldwide, but is more common where pork is part of the diet. Cysticercosis is most prevalent where humans live in close contact with pigs. Therefore, high prevalences are reported in Mexico, Latin America, West Africa, Russia, India, Pakistan, North-East China, and Southeast Asia.[46] In Europe it is most widespread among Slavic people.[18][47]

The frequency has decreased in developed countries owing to stricter meat inspection, better hygiene and better sanitation of facilities.

## Infection estimates [edit]

In Latin America, an estimated 75 million persons live in endemic areas and 400,000 people have symptomatic disease.[48] Some studies suggest that the prevalence of cysticercosis in Mexico is between 3.1 and 3.9 percent. Other studies have found the seroprevalence in areas of Guatemala, Bolivia, and Peru as high as 20 percent in humans, and 37 percent in pigs.[49] In Ethiopia, Kenya and the Democratic Republic of Congo around 10% of the population is infected, in Madagascar 16%. The distribution of cysticercosis coincides with the distribution of *T. solium*.[50] Cysticercosis is the most common cause of symptomatic epilepsy worldwide.[51]

Prevalence rates in the United States have shown immigrants from Mexico, Central and South America, and Southeast Asia account for most of the domestic cases of cysticercosis.[52]

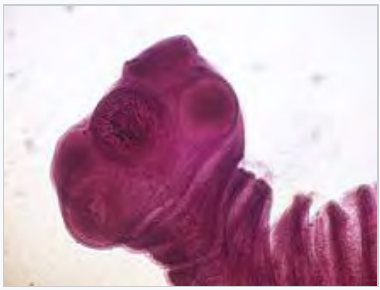
In 1990 and 1991, four unrelated members of an Orthodox Jewish community in New York City developed recurrent seizures and brain lesions, which were found to have been caused by *T. solium*. All of the families had housekeepers from Latin American countries and were suspected to be source of the infections.[53][54]

## Deaths [edit]

Worldwide as of 2010 it caused about 1,200 deaths, up from 700 in 1990.[7]

In US during 1990–2002, 221 cysticercosis deaths were identified. Mortality rates were highest for Latinos and men. The mean age at death was 40.5 years (range 2–88). Most patients, 84.6%, were foreign born, and 62% had emigrated from Mexico. The 33 US-born persons who died of cysticercosis represented 15% of all cysticercosis-related deaths. The cysticercosis mortality rate was highest in California, which accounted for 60% of all cysticercosis deaths.[55]

## History [edit]



Scolex (head) of *Taenia solium*

The earliest reference to tapeworms were found in the works of ancient Egyptians that date back to almost 2000 BC.[56] The description of measled pork in the *History of Animals* written by Aristotle (384–322 BC) showed that the infection of pork with tapeworm was known to ancient Greeks at that time.[56] It was also known to Jewish[57] and later to early Muslim physicians and has been proposed as one of the reasons for pork being forbidden by Jewish and Islamic dietary laws.[58] Recent examination of evolutionary histories of hosts and parasites and DNA evidence show that over 10,000 years ago, ancestors of modern humans in Africa became exposed to tapeworm when they scavenged for food or preyed on antelopes and bovids, and later passed the infection on to domestic animals such as pigs.[59]

Cysticercosis was described by Johannes Udalric Rumler in 1555; however, the connection between tapeworms and cysticercosis had not been recognized at that time.[60] Around 1850, Friedrich Küchenmeister fed pork containing cysticerci of *T. solium* to humans awaiting execution in a prison, and after they had been executed, he recovered the developing and adult tapeworms in their intestines.[56][60] By the middle of the 19th century, it was established that cysticercosis was caused by the ingestion of the eggs of *T. solium*.[61]

## Society and culture [edit]

- The first patient on the television show *House* (in the pilot episode) had cysticercosis.
- In the crossover of the series *Grey's Anatomy* (season 5, episode 15) and *Private Practice* (season 2), Archer Montgomery, brother of *Addison Forbes Montgomery*, suffered from neurocysticercosis. He was cured via the surgical removal of the cysts by his former brother-in-law Derek Shepherd.

## References [edit]


1. ^ Roberts, Larry S.; Janovy Jr., John (2009). *Gerald D. Schmidt & Larry S. Roberts' Foundations of Parasitology* (8th ed.). Boston: McGraw-Hill Higher Education. pp. 348–351. ISBN 978-0-07-302827-9.
2. ^ *a b c d e f g* "Taeniasis/Cysticercosis Fact sheet N°376". *World Health Organization*. February 2013. Retrieved 18 March 2014.
3. ^ *a b* García HH, Evans CA, Nash TE, et al. (October 2002). "Current consensus guidelines for treatment of neurocysticercosis". *Clin. Microbiol. Rev*. **15** (4): 747–56. doi:10.1128/CMR.15.4.747-756.2002. PMC 126865. PMID 12364377.
4. ^ *a b c d e f g h i* García HH, Gonzalez AE, Evans CA, Gilman RH (August 2003). "*Taenia solium* cysticercosis". *Lancet*. **362** (9383): 547–56. doi:10.1016/S0140-6736(03)14117-7. PMC 3103219. PMID 12932389.
5. ^ *a b c d* "CDC - Cysticercosis".
6. ^ *a b* Bobes RJ, Fragoso G, Fleury A, et al. (April 2014). "Evolution, molecular epidemiology and perspectives on the research of taeniid parasites with special emphasis on *Taenia solium*". *Infect. Genet. Evol*. **23**: 150–60. doi:10.1016/j.meegid.2014.02.005. PMID 24560729.
7. ^ *a b* Lozano R, Naghavi M, Foreman K, et al. (December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0.
31. ^ *a b c d e f g* Sciutto E, Fragoso G, de Aluja AS, Hernández M, Rosas G, Larralde C (2008). "Vaccines against cysticercosis". *Curr Top Med Chem*. **8** (5): 415–23. doi:10.2174/156802608783790839. PMID 18393905.
32. ^ Molinari JL, Meza R, Suárez B, Palacios S, Tato P, Retana A (June 1983). "*Taenia solium*: immunity in hogs to the Cysticercus". *Exp. Parasitol*. **55** (3): 340–57. doi:10.1016/0014-4894(83)90031-0. PMID 6852171.
33. ^ Luo X, Zheng Y, Hou J, Zhang S, Cai X (February 2009). "Protection against Asiatic *Taenia solium* induced by a recombinant 45W-4B protein". *Clin. Vaccine Immunol*. **16** (2): 230–2. doi:10.1128/CVI.00367-08. PMC 2643551. PMID 19091992.
34. ^ *a b* Huerta M, De Aluja AS, Fragoso G, Toledo A, Villalobos N, Hernandez M, Gevorkian G, Acero G, Diaz A, et al. (2001). "Synthetic peptide vaccine against *Taenia solium* pig cysticercosis: successful vaccination in a controlled field trial in rural Mexico". *Vaccine*. **20** (1–2): 262–6. doi:10.1016/S0264-410X(01)00249-3. PMID 11567772.
35. ^ http://www-lab.biomedicas.unam.mx/cistimex/s1.html#capitulo6
36. ^ Sciutto E, Morales J, Martinez JJ, Toledo A, Villalobos MN, Cruz-Revilla C, Meneses G, Hernandez M, Diaz A, et al. (2007). "Further evaluation of the synthetic peptide vaccine S3Pvac against *Taenia solium* cysticercosis in pigs in an endemic town of Indonesia, 1991–95". *Trans. R. Soc. Trop. Med. Hyg*. **94** (1): 46–50. doi:10.1016/s0035-9203(00)90433-4. PMID 10748897.

PMID 23245604.
8. ^ "Neglected Tropical Diseases". *cdc.gov*. June 6, 2011. Retrieved 28 November 2014.
9. ^ [a] [b] [c] Markell, E.K.; John, D.T.; Krotoski, W.A. (1999). *Markell and Voge's medical parasitology* (8th ed.). Saunders. ISBN 978-0-7216-7634-0.
10. ^ Kerstein AH, Massey AD (2010). "Neurocysticercosis". *Kansas Journal of Medicine*. **3** (4): 52–4.
11. ^ Fleury, A; Dessein, A; Preux, PM; Dumas, M; Tapia, G; Larralde, C; Sciutto, E (July 2004). "Symptomatic human neurocysticercosis--age, sex and exposure factors relating with disease heterogeneity.". *Journal of neurology*. **251** (7): 830–7. doi:10.1007/s00415-004-0437-9. PMID 15258785.
12. ^ Suri A, Goel RK, Ahmad FU, Vellimana AK, Sharma BS, Mahapatra AK (January 2008). "Transventricular, transaqueductal scope-in-scope endoscopic excision of fourth ventricular neurocysticercosis: a series of 13 cases and a review". *J Neurosurg Pediatr*. **1** (1): 35–9. doi:10.3171/PED-08/01/035. PMID 18352801.
13. ^ Hauptman JS, Hinrichs C, Mele C, Lee HJ (April 2005). "Radiologic manifestations of intraventricular and subarachnoid racemose neurocysticercosis". *Emerg Radiol*. **11** (3): 153–7. doi:10.1007/s10140-004-0383-y. PMID 16028320.
14. ^ Jang JW, Lee JK, Lee JH, Seo BR, Kim SH (Mar 2010). "Recurrent primary spinal subarachnoid neurocysticercosis.". *Spine*. **35** (5): E172–5. doi:10.1097/BRS.0b013e3181b9d8b6. PMID 20118838.
15. ^ [a] [b] Wortman PD (August 1991). "Subcutaneous cysticercosis". *J. Am. Acad. Dermatol*. **25** (2 Pt 2): 409–14. doi:10.1016/0190-9622(91)70217-p. PMID 1894783.
16. ^ HH Garcia; R Araoz; RH Gilman; J Valdez; AE Gonzalez; C Gavidia; ML Bravo; VC Tsang (1998). "Increased prevalence of cysticercosis and taeniasis among professional fried pork vendors and the general population of a village in the Peruvian highlands. Cysticercosis Working Group in Peru". *Am. J. Trop. Med. Hyg*. **59** (6): 902–905. PMID 9886197.
17. ^ Richards F, Jr; Schantz, PM (1991). "Laboratory diagnosis of cysticercosis.". *Clinics in Laboratory Medicine*. **11** (4): 1011–28. PMID 1802519.
18. ^ [a] [b] [c] Gutierrez, Yezid (2000). "26. Cysticercosis, Coenurosis, Sparganosis and proliferating Cestode larvae". *Diagnostic Pathology of Parasitic Infections with Clinical Correlations* (2nd ed.). Oxford University Press. pp. 635–652. ISBN 978-0-19-512143-8.
19. ^ Webbe, G. (1994). "Human cysticercosis: Parasitology, pathology, clinical manifestations and available treatment". *Pharmacology & Therapeutics*. **64** (1): 175–200. doi:10.1016/0163-7258(94)90038-8. PMID 7846114.
20. ^ Robbani, I; Razdan, S; Pandita, KK (2004). "Diagnosis of intraventricular cysticercosis by magnetic resonance imaging: improved detection with three-dimensional spoiled gradient recalled echo sequences.\". *Australasian Radiology*. **48** (2): 237–9. doi:10.1111/j.1440-1673.2004.01279.x. PMID 15230764.
21. ^ Lucato, L.T.; Guedes, M.S.; Sato, J.R.; Bacheschi, L.A.; Machado, L.R.; Leite, C.C. (1 September 2007). "The Role of Conventional MR Imaging Sequences in the Evaluation of Neurocysticercosis: Impact on Characterization of the Scolex and Lesion Burden". *American Journal of Neuroradiology*. **28** (8): 1501–1504. doi:10.3174/ajnr.A0623.
22. ^ "Global Plan to Combat Neglected Tropical Diseases 2008–2015" (PDF). World Health Organization. 2007. Box 1. Selected neglected tropical diseases and zoonoses to be addressed within the Global Plan. p. 2.
23. ^ [a] [b] "Update: International Task Force for Disease Eradication, 1992". *MMWR Morb. Mortal. Wkly. Rep*. **41** (37): 691, 697–8. September 1992. PMID 1518501.
24. ^ Schantz, P. "Eradication of *T. solium* Cysticercosis" International Conference on Emerging Infectious Diseases 2002. CDC.ftp://ftp.cdc.gov/pub/infectious_diseases/iceid/2002/pdf/schantz.pdf
Mexico". *Parasitology*. **134** (Pt 1): 129–33. doi:10.1017/S0031182006001132. PMID 16948875.
37. ^ [a] [b] E-mail interview with Edda Sciutto. Feb 26 2009.
38. ^ http://www.cwgesa.org/CWGESA%20Action%20Plan/CWGESA%20Action%20Plan.aspx
39. ^ CWGESA. 5th General Assembly of the Cysticercosis Working Group in Eastern and Southern Africa. 2007. CIRADhttp://pigtrop.cirad.fr/sp/recursos/publications/procedimier
40. ^ Morales J, Martínez JJ, Garcia-Castella J, et al. (March 2006). "*Taenia solium*: the complex interactions, of biological, social, geographical and commercial factors, involved in the transmission dynamics of pig cysticercosis in highly endemic areas". *Ann Trop Med Parasitol*. **100** (2): 123–35. doi:10.1179/136485906x86275. PMID 16492360.
41. ^ White AC (May 2009). "New developments in the management of neurocysticercosis". *J. Infect. Dis*. **199** (9): 1261–2. doi:10.1086/597758. PMID 19358667.
42. ^ Pawlowski ZS (2006). "Role of chemotherapy of taeniasis in prevention of neurocysticercosis". *Parasitol. Int*. **55** (Suppl): S105–9. doi:10.1016/j.parint.2005.11.017. PMID 16356763.
43. ^ [a] [b] Matthaiou DK, Panos G, Adamidi ES, Falagas ME (2008). Carabin H, ed. "Albendazole versus Praziquantel in the Treatment of Neurocysticercosis: A Meta-analysis of Comparative Trials". *PLOS Neglected Tropical Diseases*. **2** (3): e194. doi:10.1371/journal.pntd.0000194. PMC 2265431. PMID 18335068.
44. ^ Garcia HH; Pretell EJ; Gilman RH; Martinez SM; Moulton LH; Del Brutto OH; Herrera G; Evans CA; Gonzalez AE; Cysticercosis Working Group in Peru (2004). "A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis". *N Engl J Med*. **350** (3): 249–258. doi:10.1056/NEJMoa031294. PMID 14724304.
45. ^ "Taeniasis/Cysticercosis". World Health Organization. Retrieved 6 February 2014.
46. ^ Reeder, P.E.S. Palmer, M.M. (2001). *Imaging of Tropical Diseases : With Epidemiological, Pathological, and Clinical Correlation* (2 (revised) ed.). Heidelberg, Germany: Springer-Verlag. pp. 641–642. ISBN 978-3-540-56028-9.
47. ^ Hansen, NJ; Hagelskjaer, LH; Christensen, T (1992). "Neurocysticercosis: a short review and presentation of a Scandinavian case.". *Scandinavian Journal of Infectious Diseases*. **24** (3): 255–62. doi:10.3109/00365549209061330. PMID 1509231.
48. ^ Bern C, Garcia HH, Evans C, et al. (November 1999). "Magnitude of the disease burden from neurocysticercosis in a developing country". *Clin. Infect. Dis*. **29** (5): 1203–9. doi:10.1086/313470. PMC 2913118. PMID 10524964.
49. ^ Yeh J, Sheffield JS (April 2008). "Cysticercosis: A Zebra in the Neighborhood". *Virtual Mentor*. **10** (4): 220–3. doi:10.1001/virtualmentor.2008.10.4.cprl1-0804.
50. ^ "Taeniasis/Cysticercosis". *Zoonoses*. World Health Organization.
51. ^ "Relationship between epilepsy and tropical diseases. Commission on Tropical Diseases of the International League Against Epilepsy". *Epilepsia*. **35** (1): 89–93. 1994. doi:10.1111/j.1528-1157.1994.tb02916.x. PMID 8112262.
52. ^ Flisser A. (May 1988). "Neurocysticercosis in Mexico". *Parasitology Today*. **4** (5): 131–137. doi:10.1016/0169-4758(88)90187-1. PMID 15463066.
53. ^ Dworkin, Mark S. (2010). *Outbreak Investigations Around the World: Case Studies in Infectious Disease*. Jones and Bartlett Publishers. pp. 192–196. ISBN 978-0-7637-5143-2. Retrieved August 9, 2011.
54. ^ Schantz, Peter M.; Moore, Anne C.; et al. (September 3, 1992). "Neurocysticercosis in an Orthodox Jewish Community in New York City". *New England Journal of Medicine*. **327** (10): 692–695. doi:10.1056/NEJM199209033271004.
55. ^ Sorvillo FJ, DeGiorgio C, Waterman SH (February 2007).

25. ^ [a] [b] Gonzalez AE, García HH, Gilman RH, Tsang VC (June 2003). "Control of *Taenia solium*". *Acta Trop.* **87** (1): 103–9. doi:10.1016/S0001-706X(03)00025-1. PMID 12781384.
26. ^ Gonzalez AE, Gavidia C, Falcon N, et al. (July 2001). "Protection of pigs with cysticercosis from further infections after treatment with oxfendazole". *Am. J. Trop. Med. Hyg.* **65** (1): 15–8. PMID 11504400.
27. ^ Garcia, H.H., 2002. "Effectiveness of an interventional control program for human and porcine *Taenia solium* cysticercosis in field conditions." In: International Health. Johns Hopkins University, Baltimore, p. 250.
28. ^ Gilman, R.H.; Garcia, H.H.; Gonzalez, A.E.; Dunleavy, M.; Verastegui, M. (1999). "Short cuts to development: methods to control the transmission of cysticercosis in developing countries". In García, H.H.; Martínez, M. Taenia solium *taeniasis/cysticercosis*. Lima: Editorial Universo. pp. 313–326. ISBN 9972910202.
29. ^ Margono SS, Subahar R, Hamid A, et al. (2001). "Cysticercosis in Indonesia: epidemiological aspects". *Southeast Asian J. Trop. Med. Public Health.* **32** (Suppl 2): 79–84. PMID 12041608.
30. ^ Wandra T, Subahar R, Simanjuntak GM, et al. (2000). "Resurgence of cases of epileptic seizures and burns associated with cysticercosis in Assologaima, Jayawijaya, Irian Jaya, "Deaths from cysticercosis, United States" . *Emerging Infect. Dis.* **13** (2): 230–5. doi:10.3201/eid1302.060527. PMC 2725874. PMID 17479884.
56. ^ [a] [b] [c] Wadia, N.H.; Singh, G. (2002). "*Taenia Solium*: A Historical Note". In Singh, G.; Prabhakar, S. Taenia Solium *Cysticercosis: From Basic to Clinical Science*. CABI Publishing. pp. 157–168. ISBN 0851996280.
57. ^ Ancient Hebrew Medicine<http://www.healthguidance.org/entry/6309/1/Ancient-Hebrew-Medicine.html>
58. ^ del Brutto, O.H.; Sotelo, J.; Román, G.C. (1998). *Neurocysticercosis*. Taylor and Francis. p. 3. ISBN 90-265-1513-8.
59. ^ Becker H (May 2001). "Out of Africa: The Origins of the Tapeworms". *Agricultural Research Magazine*. US Department of Agriculture. **49** (5).
60. ^ [a] [b] Cox FE (October 2002). "History of human parasitology". *Clin. Microbiol. Rev.* **15** (4): 595–612. doi:10.1128/CMR.15.4.595-612.2002. PMC 126866. PMID 12364371.
61. ^ Küchenmeister, F. The Cysticercus cellulosus transformed within the organism of man into *Taenia solium*. Lancet 1861 i:39.

- "*Taenia solium*". *NCBI Taxonomy Browser*. 6204.


| v · t · e · | **Infectious diseases · Parasitic disease: helminthiases (B65–B83 · 120–129 · ·** | | | |
|---|---|---|---|---|
| **Flatworm/ platyhelminth** | **Fluke/trematode (Trematode infection)** | **Blood fluke** | *Schistosoma mansoni/japonicum/mekongi/haematobium* (Schistosomiasis · · *Trichobilharzia regenti* (Swimmer's itch · · | |
| | | **Liver fluke** | *Clonorchis sinensis* (Clonorchiasis · · *Dicrocoelium dendriticum/Dicrocoelium hospes* (Dicrocoeliasis · · *Fasciola hepatica/gigantica* (Fasciolosis · · *Opisthorchis viverrini/ Opisthorchis felineus* (Opisthorchiasis · · | |
| | | **Lung fluke** | *Paragonimus westermani/Paragonimus kellicotti* (Paragonimiasis · · | |
| | | **Intestinal fluke** | *Fasciolopsis buski* (Fasciolopsiasis · · *Metagonimus yokagawai* (Metagonimiasis · · *Heterophyes heterophyes* (Heterophyiasis · · | |
| | **Cestoda (Tapeworm infection)** | **Cyclophyllidea** | *Echinococcus granulosus/Echinococcus multilocularis* (Echinococcosis · · *Taenia saginata/Taenia asiatica/Taenia solium (pork)* (Taeniasis/**Cysticercosis** · · *Hymenolepis nana/Hymenolepis diminuta* (Hymenolepiasis · · | |
| | | **Pseudophyllidea** | *Diphyllobothrium latum* (Diphyllobothriasis · · *Spirometra erinaceieuropaei* (Sparganosis · · *Diphyllobothrium mansonoides* (Sparganosis · · | |
| **Roundworm/ nematode (Nematode infection)** | **Secernentea** | **Spiruria** | **Camallanida** | *Dracunculus medinensis* (Dracunculiasis · · |
| | | | **Spirurida** | **Filarioidea (Filariasis)** | *Onchocerca volvulus* (Onchocerciasis · · *Loa loa* (Loa loa filariasis · · *Mansonella* (Mansonelliasis · · *Dirofilaria repens* (Dirofilariasis · · *Wuchereria bancrofti/ Brugia malayi/ Brugia timori* (*Lymphatic filariasis* · · |
| | | | | **Thelazioidea** | *Gnathostoma spinigerum/ Gnathostoma hispidum* (Gnathostomiasis · · *Thelazia* (Thelaziasis · · |
| | | | | **Spiruroidea** | *Gongylonema* · |
| | | **Strongylida (hookworm)** | Hookworm infection · *Ancylostoma duodenale/Ancylostoma braziliense* (Ancylostomiasis · Cutaneous larva migrans · · *Necator americanus* (Necatoriasis · · *Angiostrongylus cantonensis* (Angiostrongyliasis · · *Metastrongylus* (Metastrongylosis · · | |
| | | | *Ascaris lumbricoides* (Ascariasis · · *Anisakis* (Anisakiasis · · | |

| | | | |
|---|---|---|---|
| | | **Ascaridida** | *Toxocara canis*/*Toxocara cati* (Visceral larva migrans/Toxocariasis · · *Baylisascaris* · *Dioctophyme renale* (Dioctophymosis · · *Parascaris equorum* · |
| | | **Rhabditida** | *Strongyloides stercoralis* (Strongyloidiasis · · *Trichostrongylus spp.* (Trichostrongyliasis · · *Halicephalobus gingivalis* · |
| | | **Oxyurida** | *Enterobius vermicularis* (Enterobiasis · Pinworm · · |
| | **Adenophorea** | | *Trichinella spiralis* (Trichinosis · · *Trichuris trichiura* (Trichuriasis * Whipworm) · *Capillaria philippinensis* (Intestinal capillariasis · · *Capillaria hepatica* · |

Categories: Helminthiases | Parasitic diseases associated with beef and pork consumption | Zoonoses




# Dracunculiasis

From Wikipedia, the free encyclopedia
(Redirected from Dracunculiasis)



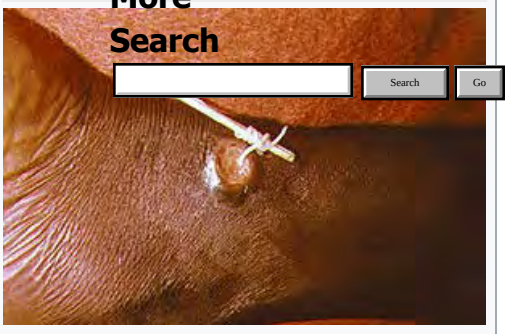
**Dracunculiasis**, also called **Guinea-worm disease** (**GWD**), is an infection by the Guinea worm. A person becomes infected when they drink water that contains water fleas infected with guinea worm larvae.[1] Initially there are no symptoms.[2] About one year later, the person develops a painful burning feeling as the female worm forms a blister in the skin, usually on the lower limb.[1] The worm then comes out of the skin over the course of a few weeks.[3] During this time, it may be difficult to walk or work.[2] It is very uncommon for the disease to cause death.[1]

In humans, the only known cause is *Dracunculus medinensis*.[2] The worm is about one to two millimeters wide, and an adult female is 60 to 100 centimeters long (males are much shorter at 12–29 mm or 0.47–1.14 in).[1][2] Outside of humans, the young form can survive up to three weeks,[4] during which they must be eaten by water fleas to continue to develop.[1] The larva inside water fleas may survive up to four months.[4] Thus, in order for the disease to remain in an area, it must occur each year in humans.[5] A diagnosis of the disease can usually be made based on the signs and symptoms of the disease.[6]

Prevention is by early diagnosis of the disease followed by keeping the person from putting the wound in drinking water to decrease spread of the parasite. Other efforts include improving access to clean water and otherwise filtering water if it is not clean.[1] Filtering through a cloth is often enough.[3] Contaminated drinking water may be treated with a chemical called temefos to kill the larva. There is no medication or vaccine against the disease.[1] The worm may be slowly removed over a few weeks by rolling it over a stick. The ulcers formed by the emerging worm may get infected by bacteria. Pain may continue for months after the worm has been removed.[2]

In 2015 there were 22 reported cases of the disease[7] and in the first half of 2016 there were 7 confirmed cases.[8] This is down from an estimated 3.5 million cases in 1986.[2] It only exists in 4 countries in Africa, down from 20 countries in the 1980s.[1][7] It will likely be the first parasitic disease to be globally eradicated.[9] Guinea worm disease has been known since ancient times.[2] It is mentioned in the Egyptian medical Ebers Papyrus, dating from 1550 BC.[10] The name dracunculiasis is derived from the Latin "affliction with little dragons",[11] while the name "guinea worm" appeared after Europeans saw the disease on the Guinea coast of West Africa in the 17th century.[10] Other *Dracunculus* species are known to infect various mammals, but do not appear to infect humans.[12][13] Dracunculiasis is classified as a neglected tropical disease.[14] Because dogs may also become infected,[15] the eradication program is monitoring and treating dogs as well.[16]

**Dracunculiasis**



Using a matchstick to wind up and remove a guinea worm from the leg of a human

| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | B72 |
| **ICD-9-CM** | 125.7 |
| **DiseasesDB** | 3945 |
| **eMedicine** | ped/616 |
| **Patient UK** | Dracunculiasis |
| **MeSH** | D004320 |
| **Orphanet** | 231 |

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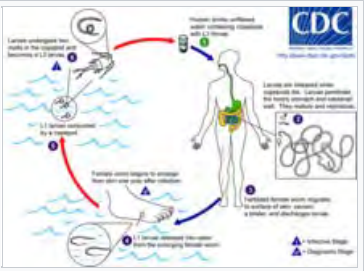
## Signs and symptoms [edit]

Dracunculiasis is diagnosed by seeing the worms emerging from the lesions on the legs of infected individuals and by microscopic examinations of the larvae.[17]

As the worm moves downwards, usually to the lower leg, through the subcutaneous tissues, it leads to intense pain localized to its path of travel. The painful, burning sensation experienced by infected people has led to the disease being called "the fiery serpent". Other symptoms include fever, nausea, and vomiting.[18] Female worms cause allergic reactions during blister formation as they migrate to the skin, causing an intense burning pain. Such allergic reactions produce rashes, nausea, diarrhea, dizziness, and localized edema. When the blister bursts, allergic reactions subside, but skin ulcers form, through which the worm can protrude. Only when the worm is removed is healing complete. Death of adult worms in joints can lead to arthritis and paralysis in the spinal cord.[19]

## Cause [edit]

Dracunculiasis is caused by drinking water contaminated by water fleas that host the *D. medinensis* larvae.[18] Dracunculiasis has a history of being very common in some of the world's poorest areas, particularly those with limited or no access to clean water.[20] In these areas, stagnant water sources may still host copepods, which can carry the larvae of the guinea worm.



Life cycle of *Dracunculus medinensis*

Humans and dogs are the only known animals that guinea worms infect.[2][15] Other species in the Dracunculus genus affect other mammals.

After ingestion, the copepods die and are digested, thus releasing the stage 3 larvae, which then penetrate the host's stomach or intestinal wall, and then enter into the abdominal cavity and retroperitoneal space. After maturation, which takes approximately three months, mating takes place; the male worm dies after mating and is absorbed by the host's body.

Approximately one year after mating, the fertilized females migrate in the subcutaneous tissues adjacent to long bones or joints of the extremities.[10] They then move towards the surface, resulting in blisters on the skin, generally on the distal lower extremity (foot). Within 72 hours, the blister ruptures, exposing one end of the emergent worm. The blister causes a very painful burning sensation as the worm emerges, and the sufferer will often immerse the affected limb in water to relieve the burning sensation. When a blister or open sore is submerged in water, the adult female releases hundreds of thousands of stage 1 guinea worm larvae, thereby contaminating the water.

During the next few days, the female worm can release more larvae whenever it comes in contact with water, as it extends its posterior end through the hole in the host's skin. These larvae are eaten by copepods, and after two weeks (and two molts), the stage 3 larvae become infectious and, if not filtered from drinking water, will cause the cycle to repeat. Infected copepods can live in the water for up to 4 months.

The male guinea worm is typically much smaller (12–29 mm or 0.47–1.14 in) than the female, which, as an adult, can grow to 60–100 cm (2–3 ft) long and be as thick as a spaghetti noodle.[10][20]

Infection does not create immunity, so people can repeatedly experience Dracunculiasis throughout their lives.[20]

In drier areas just south of the Sahara desert, cases of the disease often emerge during the rainy season, which for many agricultural communities is also the planting or harvesting season. Elsewhere, the emerging worms are more prevalent during the dry season, when ponds and lakes are smaller and copepods are thus more concentrated in them. Guinea worm disease outbreaks can cause serious disruption to local food supplies and school attendance.[20]

The infection can be acquired by eating a fish paratenic host, but this is rare. No reservoir hosts are known; that is, each generation of worms must pass through a human – or possibly a dog.[19][21]

## Prevention [edit]

Guinea worm disease can be transmitted only by drinking contaminated water, and can be completely prevented through two relatively simple measures:[18]

1. Prevent people from drinking contaminated water containing the Cyclops copepod (water flea), which can be seen in clear water as swimming white specks.
   - Drink water drawn only from sources free from contamination.
   - Filter all drinking water, using a fine-mesh cloth filter like nylon, to remove the guinea worm-containing crustaceans. Regular cotton cloth folded over a few times is an effective filter.
   - Filter the water through ceramic or sand filters.
   - Boil the water.
   - Develop new sources of drinking water without the parasites, or repair dysfunctional water sources.
   - Treat water sources with larvicides to kill the water fleas.[22]
2. Prevent people with emerging Guinea worms from entering water sources used for drinking.

Community-level case detection and containment is key. For this, staff must go door to door looking for cases, and the population must be willing to help and not hide their cases.
- Immerse emerging worms in buckets of water to reduce the number of larvae in those worms, and then discard that water on dry ground.
- Discourage all members of the community from setting foot in the drinking water source.
- Guard local water sources to prevent people with emerging worms from entering.

## Treatment [edit]

There is no vaccine or medicine to treat or prevent Guinea worm disease.[18] Once a Guinea worm begins emerging, the first step is to do a controlled submersion of the affected area in a bucket of water. This causes the worm to discharge many of its larvae, making it less infectious. The water is then discarded on the ground far away from any water source. Submersion results in subjective relief of the burning sensation and makes subsequent extraction of the worm easier. To extract the worm, a person must wrap the live worm around a piece of gauze or a stick. The process can be long, taking anywhere from hours to a week. Gently massaging the area around the blister can help loosen the worm.[9] This is nearly the same treatment that is noted in the famous ancient Egyptian medical text, the Ebers papyrus from 1550 BC.[10] Some people have said that extracting a Guinea worm feels like the afflicted area is on fire.[23][24] However, if the infection is identified before an ulcer forms, the worm can also be surgically removed by a trained doctor in a medical facility.[20]

Although Guinea worm disease is usually not fatal, the wound where the worm emerges could develop a secondary bacterial infection such as tetanus, which may be life-threatening—a concern in endemic areas where there is typically limited or no access to health care.[25] Analgesics can be used to help reduce swelling and pain and antibiotic ointments can help prevent secondary infections at the wound site.[20] At least in the Northern region of Ghana, the Guinea worm team found that antibiotic ointment on the wound site caused the wound to heal too well and too quickly making it more difficult to extract the worm and more likely that pulling would break the worm. The local team preferred to use something called "Tamale oil" (after the regional capital) which lubricated the worm and aided its extraction.

It is of great importance not to break the worm when pulling it out. Broken worms have a tendency to putrefy or petrify. Putrefaction leads to the skin sloughing off around the worm. Petrification is a problem if the worm is in a joint or wrapped around a vein or other important area.

Use of metronidazole or thiabendazole may make extraction easier, but also may lead to migration to other parts of the body.[26]

## Epidemiology [edit]

In 1986, there were an estimated 3.5 million cases of Guinea worm in 20 endemic nations in Asia and Africa.[9] Ghana alone reported 180,000 cases in 1989. The number of cases has since been reduced by more than 99.999% to 22 in 2015[27] — in the four remaining endemic nations of Africa: South Sudan, Chad, Mali and Ethiopia. This is the lowest number of cases since the eradication campaign began. As of 2010, however, the WHO predicted it will be "a few years yet" before eradication is achieved, on the basis that it took 6–12 years for the countries that have so far eliminated Guinea worm transmission to do so after reporting a similar number of cases to that reported in southern Sudan (now South Sudan) in 2009.[28]

The World Health Organization is the international body that certifies whether a disease has been eliminated from a country or eradicated from the world.[29] Former U.S. President Jimmy Carter's not-for-profit organization, the Carter Center, also reports the status of the Guinea worm eradication program by country.[30]

### Certified free [edit]

Endemic countries must report to the International Commission for the Certification of Dracunculiasis Eradication and document the absence of indigenous cases of Guinea worm disease for at least three consecutive years to be certified as Guinea worm-free by the World Health Organization.[31]

The results of this certification scheme have been remarkable: by 2007, Benin, Burkina Faso, Chad, Côte d'Ivoire, Kenya, Mauritania, Togo, and Uganda had stopped transmission, and Cameroon, Central African Republic, India, Pakistan, Senegal, Yemen were WHO certified.[32] Nigeria was certified as having ended transmission in 2013, followed by Ghana in 2015.[33]

### Endemic [edit]

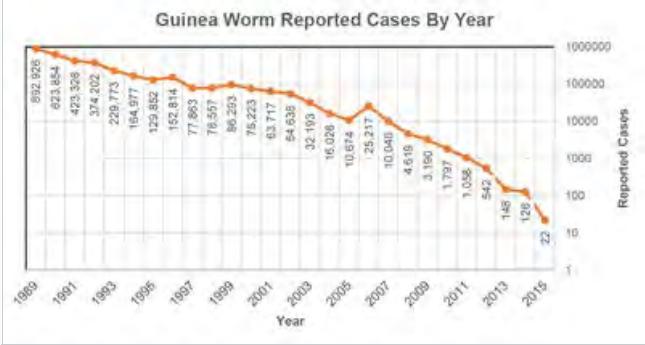
With the current eradication campaign the areas that dracunculiasis are found are shrinking. In the early 1980s, the disease was endemic in Pakistan, Yemen and 17 countries in Africa with a total of 3.5 million cases per year. In 1985, 3.5 million cases were still reported annually, but by 2008, the number had dropped to 5,000.[34] This number further dropped to 1058 in 2011. At the end of 2013, South Sudan, Mali, Ethiopia and Chad still had endemic transmissions. For many years the major focus was South Sudan (independent after 2011, formerly the southern region of Sudan), which reported 76% of all cases in 2013. Now all 4 countries with endemic cases look close to eliminating the disease.[27]

| Date | South Sudan | Mali | Ethiopia | Chad | Total |
|---|---|---|---|---|---|
| | | | | | |

| |  |  |  |  | |
|---|---|---|---|---|---|
| 2011 | 1,028[35] | 12[35] | 8[35] | 10[35] | **1058** |
| 2012 | 521[35] | 7[35] | 4[35] | 10[35] | **542** |
| 2013 | 113[35] | 11[35] | 7[35] | 14[35] | **148** (including 3 exported to Sudan) |
| 2014 | 70[35] | 40[35] | 3[35] | 13[35] | **126** |
| 2015 | 5[35] | 5[35] | 3[35] | 9[35] | **22** |
| 2016 - up to 31 October | 5[35] | 0[35] | 3[35] | 11[35] | **19** (provisional) |

## Eradication program [edit]

In 1984, the WHO asked the United States Centers for Disease Control and Prevention (CDC) to spearhead the effort to eradicate dracunculiasis, an effort that was further supported by the Carter Center, former U.S. President Jimmy Carter's not-for-profit organization.[34] In 1986, Carter and the Carter Center began leading the global campaign, in conjunction with CDC, UNICEF, and WHO.[37] At that time the disease was endemic in Pakistan, Yemen and 17 countries in Africa, which reported a total of 3.5 million cases per year.



Logarithmic scale of reported human cases of guinea worm by year, 1989–2015 (2015 data is provisional). Data from Guinea Worm Eradication Program.[36]

Since humans are the principal host for Guinea worm, and there is no evidence that *D. medinensis* has ever been reintroduced to humans in any formerly endemic country as the result of non-human infections, the disease can be controlled by identifying all cases and modifying human behavior to prevent it from recurring.[9][38] Once all human cases are eliminated, the disease cycle will be broken, resulting in its eradication.[9]

The eradication of Guinea worm disease has faced several challenges:

- Inadequate security in some endemic countries
- Lack of political will from the leaders of some of the countries in which the disease is endemic
- The need for change in behavior in the absence of a magic bullet treatment like a vaccine or medication
- Inadequate funding at certain times[11]

Carter made a personal visit to a Guinea-worm endemic village in 1988. He said, "Encountering those victims first-hand, particularly the teenagers and small children, propelled me and Rosalynn [his wife] to step up the Carter Center's efforts to eradicate Guinea worm disease."[39]

In 1991, the World Health Assembly (WHA) agreed that Guinea worm disease should be eradicated.[25] At this time there were 400,000 cases reported each year. The Carter Center has continued to lead the eradication efforts, primarily through its Guinea Worm Eradication Program.[40]

In the 1980s, Carter persuaded President Zia al-Haq of Pakistan to accept the proposal of the eradication program, and by 1993, Pakistan was free of the disease. Key to the effort was, according to Carter, the work of "village volunteers" who educated people about the need to filter drinking water.[34] Other countries followed, and by 2004, the worm was eradicated in Asia.

In December 2008, The Carter Center announced new financial support totaling $55 million from the Bill & Melinda Gates Foundation and the United Kingdom Department for International Development.[41] The funds will help address the higher cost of identifying and reporting the last cases of Guinea worm disease. Since the worm has a one-year incubation period, there is a very high cost of maintaining a broad and sensitive monitoring system and providing a rapid response when necessary.[41]

One of the most significant challenges facing Guinea worm eradication has been the civil war in southern Sudan, which was largely inaccessible to health workers due to violence.[11][42] To address some of the humanitarian needs in southern Sudan, in 1995, the longest ceasefire in the history of the war, and the longest humanitarian cease-fire in history,[43] was achieved through negotiations by Jimmy Carter.[11][42] Commonly called the "Guinea worm cease-fire," both warring parties agreed to halt hostilities for nearly six months to allow public health officials to begin Guinea worm eradication programming, among other interventions.[42][44]

Public health officials cite the formal end of the war in 2005 as a turning point in Guinea worm eradication because it has allowed health care workers greater access to southern Sudan's endemic areas.[45] In 2006, there was an increase from 5,569 cases in 2005 to 15,539 cases, as a result of better reporting from areas that were no longer war-torn. The Southern Sudan Guinea Worm Eradication Program (SSGWEP) has deployed over 28,000 village volunteers, supervisors and other health staff to work on the program full-time. The SSGWEP was able to slash the number of cases reported in 2006 by 63% to 5,815 cases in

2007. Since 2011, at the time that South Sudan became independent, its northern neighbor Sudan had reported no endemic cases of dracunculiasis .[46]

Sporadic insecurity or widespread civil conflict could at any time ignite, thwarting eradication efforts.[46] The remaining endemic communities in South Sudan are remote, poor and devoid of infrastructure, presenting significant hurdles for effective delivery of interventions against disease. Moreover, residents in these communities are nomadic, moving seasonally with cattle in pursuit of water and pasture, making it very difficult to know where and when transmission occurred. The peak transmission season coincides with the rainy season, hampering travel by public health workers.[47]

One remaining area in West Africa outside of Ghana remains challenging to ending Guinea worm: northern Mali, where Tuareg rebels have made some affected areas unsafe for health workers. Four of Mali's regions—(Kayes, Koulikoro, Ségou, and Sikasso)—have eliminated dracunculiasis, while the disease is still endemic in the country's other four regions (Gao, Kidal, Mopti, and Timbuktu). Late detection of two outbreaks, due to inadequate surveillance resulted in a meager 36% containment rate in Mali in 2007.[46] The years 2008 and 2009 were more successful, however, with containment rates of 85% and 73% respectively.[48] The civil war prevented accurate information from being gathered in northern Mali in 2012.

From June 2006 to March 2008, there had been no cases reported in Ethiopia.[49]

Before 2010, Chad had not reported any indigenous cases of guinea worm in over 10 years.[50]

In Ghana, after a decade of frustration and stagnation, in 2006 a decisive turnaround was achieved. Multiple changes can be attributed to the improved containment and lower incidence of dracunculiasis: better supervision and accountability, active oversight of infected people daily by paid staff, and an intensified public awareness campaign. After Jimmy Carter's visit to Ghana in August 2006, the government of Ghana declared Guinea worm disease to be a public health emergency. The overall rate of contained cases has increased in Ghana from 60% in 2005, to 75% in 2006, 84% in 2007, 85% in 2008, 93% in 2009, and 100% in 2010.[46][48][50]

On 30 January 2012 the WHO meeting at the Royal College of Physicians in London launched the most ambitious and largest coalition health project ever, known as *London Declaration on Neglected Tropical Diseases* which aims to end/control dracunculiasis by 2020, among other neglected tropical disease.[51] This project is supported of all major pharmaceutical companies, the Bill & Melinda Gates Foundation, the governments of the United States, United Kingdom DFID and United Arab Emirates and the World Bank.[52]

In 2015 22 cases of dracunculiasis were reported: 9 in Chad, 3 in Ethiopia, 5 in Mali and 5 in South Sudan. This is an 83% reduction from 2014. The proportion of people contained (i.e. treated and isolated from drinking water sources early enough to remove the risk they can contaminate the water source) is 36%, compared to 73% in 2014. That means 14 cases have not been contained in 2015, compared to 34 cases in 2014. 9 of these 14 cases not contained were in Chad.[53]

A significant change from 2014 is the increased effort being used to identify and treat infected dogs—mainly in Chad where the vast majority of cases of dogs hosting the worm have been found, but also significantly in Ethiopia. In 2015, 483 infected dogs were identified and treated in Chad — more than 20 times the number reported in humans worldwide. This is more than 4 times larger than the number treated in 2014 (114 dogs). A major factor in this increase is probably the financial reward started in January for reporting an infected dog. 68% of dogs treated were also contained, compared to 40% in 2014. Dogs are believed to be the major source of the parasite infecting humans in Chad. 15 dogs outside Chad have also been identified and treated, as well 5 cats and 1 baboon. The August Carter Center report predicts that Chad may be the last country that eliminates dracunculiasis, and reports on further ongoing research into the relationship between the parasite and dogs there, and some different treatments for dogs. It also predicts that the large increase in monitoring, treating and containing dogs this year will not affect the number of human cases for many months due to the 1 year incubation period of the disease.[35][53][54]

In August 2015, when discussing his diagnosis of melanoma metastasized to his brain, Jimmy Carter stated that he hopes the last Guinea worm dies before he does.[55]

In 2016 11 cases have been reported up to 31 July - 5 in Chad, 4 in South Sudan and 2 in Ethiopia - compared to 8 cases last year in the same period - 6 in Chad, 1 in South Sudan and 1 in Ethiopia. Insecurity around Juba in South Sudan has caused the evacuation of all expatriate Guinea Worm Eradication Program (GWEP) staff. Members of the local staff have been given the option of continuing to work if possible. It is unclear what impact this is having. Mali has not reported any new cases in 7 months. The efforts against infected dogs continue to increase in Chad, with 498 dogs being identified and treated up to 31 May, compared to 196 cases in the same period the previous year. The level of containment of infected dogs before they become a risk of spreading the parasite has improved to 81% compared to 67% last year.[56]

## Society and culture [edit]

The pain caused by the worm's emergence—which typically occurs during planting and harvesting seasons—prevents many people from working or attending school for as long as three months. In heavily burdened agricultural villages fewer people are able to tend their fields or livestock, resulting in food shortages and lower earnings.[9][45] A study in southeastern Nigeria, for example, found that rice farmers in a small area lost US$20 million in just one year due to outbreaks of Guinea worm disease.[9]

## History [edit]

Dracunculiasis has been a recognized disease for thousands of years:

- Guinea worm has been found in calcified Egyptian mummies.[9]
- An Old Testament description of "fiery serpents" may have been referring to Guinea worm: "And the Lord sent fiery serpents among the people, and they bit the people; and much people of Israel died." (Numbers 21:4–9).[10]
- The 2nd century BC, Greek writer Agatharchides, described this affliction as being endemic amongst certain nomads in what is now Sudan and along the Red Sea.[10]
- The unusually high incidence of dracunculiasis in the city of Medina led to it being included in part of the disease's scientific name "medinensis." A similar high incidence along the Guinea coast of West Africa gave the disease its more commonly used name.[10] Guinea worm is no longer endemic in either location.

The Russian scientist Alexei Pavlovich Fedchenko (1844–1873) during the 1860s while living in Samarkand was provided with a number of specimens of the worm by a local doctor which he kept in water. While examining the worms Fedchenko noted the presence of water fleas with embryos of the guinea worm within them.

In modern times, the first to describe dracunculiasis and its pathogenesis was the Bulgarian physician Hristo Stambolski, during his exile in Yemen (1877–1878).[57] His theory was that the cause was infected water which people were drinking.

### Etymology [edit]

Dracunculiasis once plagued a wide band of tropical countries in Africa and Asia. Its Latin name, *Dracunculus medinensis* ("little dragon from Medina"), derives from its one-time high incidence in the city of Medina, and its common name, Guinea worm, is due to a similar past high incidence along the Guinea coast of West Africa; both of these locations are now free of Guinea worm.[58] In the 18th century, Swedish naturalist Carl Linnaeus identified *D. medinensis* in merchants who traded along the Gulf of Guinea (West African Coast), hence the name Guinea worm.

## Other animals [edit]

A very similar or possibly the same worm has been found in dogs.[15] It is unclear if dog and human infections are related.[59] It is possible that dogs may be able to spread the disease to people, that a third organism may be able to spread it to both dogs and people, or that this may be a different type of *Dracunculus*.[59]

## References [edit]


1. ^ a b c d e f g h "Dracunculiasis (guinea-worm disease) Fact sheet N°359 (Revised)". *World Health Organization*. March 2014. Retrieved 18 March 2014.
2. ^ a b c d e f g h Greenaway, C (Feb 17, 2004). "Dracunculiasis (guinea worm disease)." *CMAJ : Canadian Medical Association*. **170** (4): 495–500. PMC 332717. PMID 14970098.
3. ^ a b Cairncross, S; Tayeh, A; Korkor, AS (Jun 2012). "Why is dracunculiasis eradication taking so long?". *Trends in parasitology*. **28** (6): 225–30. doi:10.1016/j.pt.2012.03.003. PMID 22520367.
4. ^ a b Junghanss, Jeremy Farrar, Peter J. Hotez, Thomas (2013). *Manson's tropical diseases.* (23rd ed.). Oxford: Elsevier/Saunders. p. e62. ISBN 9780702053061.
5. ^ "Parasites – Dracunculiasis (also known as Guinea Worm Disease) Eradication Program". *CDC*. November 22, 2013. Retrieved 19 March 2014.
6. ^ Cook, Gordon (2009). *Manson's tropical diseases.* (22nd ed.). [Edinburgh]: Saunders. p. 1506. ISBN 9781416044703.
7. ^ a b "Guinea Worm Cases Left in the World". Carter Center. Jan 12, 2015. Retrieved 14 March 2015.
8. ^ "The Last Days of Guinea Worm". *Oregon Public Broadcasting*. Retrieved 6 June 2016.
9. ^ a b c d e f g h "Guinea Worm Eradication Program". Carter Center. Retrieved 2011-03-01.
10. ^ a b c d e f g h Tropical Medicine Central Resource. "Dracunculiasis". Uniformed Services University of the Health Sciences. Retrieved 2008-07-15.
11. ^ a b c d Barry M (June 2007). "The tail end of guinea worm — global eradication without a drug or a vaccine". *N. Engl. J. Med.* **356** (25): 2561–4. doi:10.1056/NEJMp078089. PMID 17582064.
12. ^ Junghanss, Jeremy Farrar, Peter J. Hotez, Thomas (2013). *Manson's tropical diseases.* (23rd ed.). Oxford: Elsevier/Saunders. p. 763. ISBN 9780702053061.
13. ^ "North American Guinea Worm". Michigan Department of Natural Resources. Retrieved 10 December 2015.
14. 731–5. PMID 11411827.
15. ^ The Carter Center. "Activities by Country—Guinea Worm Eradication Program". *The Carter Center*. Retrieved 2010-03-16.
16. ^ "WHO certifies Ghana free of dracunculiasis". *World Health Organization*. Retrieved 2016-01-07.
17. ^ a b c Drisdelle R. *Parasites. Tales of Humanity's Most Unwelcome Guests*. Univ. of California Publ., 2010. p. 197. ISBN 978-0-520-25938-6.
18. ^ a b c d e f g h i j k l m n o p q r s t u v w x y "Guinea Worm Disease: Case Countdown". Carter Center.
19. ^ ""Number of Reported Cases of Guinea Worm Disease by Year: 1989–2015*"" (PDF). Guinea Worm Eradication Program. 2016-01-06. Retrieved 2016-01-10.
20. ^ "International Task Force for Disease Eradication—Original Members (1989–1992)." Carter Center. Retrieved 2008-07-17.
21. ^ BIMI, L.; A. R. FREEMAN; M. L. EBERHARD; E. RUIZ-TIBEN; N. J. PIENIAZEK (10 May 2005). "Differentiating Dracunculus medinensis from D. insignis, by the sequence analysis of the 18S rRNA gene" (PDF). *Annals of Tropical Medicine and Parasitology*. **99** (5): 511–517. doi:10.1179/136485905x51355. PMID 16004710. Retrieved 18 May 2012.
22. ^ Carter, Jimmy; Lodge, Michelle (2008-03-31). "A Village Woman's Legacy." (PDF). *TIME*. Retrieved 2008-07-15.
23. ^ "2006 Gates Award for Global Health: The Carter Center". Carter Center. 2006. Retrieved 2010-03-08.
24. ^ a b "Guinea Worm Cases Hit All-Time Low: Carter Center, WHO, Gates Foundation, and U.K. Government Commit $55 Million Toward Ultimate Eradication Goal". Carter Center. Retrieved 2008-12-08.
25. ^ a b c "Sudan". Carter Center. Retrieved 2008-07-15.
26. ^ "The Guinea worm, and the havoc it wreaks, has nearly been wiped out". *The Economist*. 3 February 2016. Retrieved 4 February 2016.
27. ^ Hopkins, Donald R.; Withers, P. Craig, Jr. (2002). "Sudan's

14. ^ "Neglected Tropical Diseases". *cdc.gov*. June 6, 2011. Retrieved 28 November 2014.
15. ^ *a b c* Centers for Disease Control and, Prevention (25 October 2013). "Progress toward global eradication of dracunculiasis—January 2012 – June 2013.". *MMWR. Morbidity and mortality weekly report*. **62** (42): 829–33. PMID 24153313.
16. ^ WHO Collaborating Center for Research, Training and Eradication of Dracunculiasis, CDC (March 25, 2016). "Guinea Worm Wrap-Up #239" (PDF). Carter Center. Retrieved 2 April 2016.
17. ^ Z. Harrat; R. Halimi (2009). "La dracunculose d'importation : quatre cas confirmés dans le sud algérien" [Imported dracunculiasis: four cases confirmed in the south of Algeria] (PDF). *Bulletin de la Société de pathologie exotique* (in French). **102** (2): 119–122. doi:10.3185/pathexo3352. PMID 19583036.
18. ^ *a b c d* "Dracunculiasis". World Health Organization. Retrieved 2010-07-12.
19. ^ *a b* G. D. Schmidt; L S. Roberts (2009). Larry S. Roberts; John Janovy, Jr., eds. *Foundations of Parasitology* (8th ed.). McGraw-Hill. pp. 480–484. ISBN 978-0-07-128458-5.
20. ^ *a b c d e f* "Fact Sheet:Dracunculiasis—Guinea Worm Disease". CDC. 2008-07-15. Retrieved 2010-07-12.
21. ^ http://www.cartercenter.org/resources/pdfs/news/health_publications/guinea_worm/wrap-up/233.pdf
22. ^ Hopkins, D.; Richards Jr, F.; Ruiz-Tiben, E.; Emerson, P.; Withers Jr, P. (2008). "Dracunculiasis, onchocerciasis, schistosomiasis, and trachoma". *Annals of the New York Academy of Sciences*. **1136**: 45–52. Bibcode:2008NYASA1136...45H. doi:10.1196/annals.1425.015. PMID 17954680.
23. ^ "World moves closer to eradicating ancient worm disease". World Health Organization. 2007-03-27. Retrieved 2008-07-15.
24. ^ McNeil, DG (2006-03-26). "Dose of Tenacity Wears Down a Horrific Disease". *New York Times*. Retrieved 2008-07-15.
25. ^ *a b* Centers for Disease Control and Prevention (CDC) (December 1993). "Recommendations of the International Task Force for Disease Eradication". *MMWR Recomm Rep*. **42** (RR–16): 1–38. PMID 8145708.
26. ^ *Dracunculiasis: Treatment & Medication~treatment* at eMedicine
27. ^ *a b* http://www.cartercenter.org/resources/pdfs/news/health_publications/guinea_worm/wrap-up/226.pdf
28. ^ WHO (7 May 2010). "Dracunculiasis eradication – global surveillance summary, 2009" (PDF). *Wkly Epidemiol Rec*. World Health Organization. **85** (19): 166–175.
29. ^ "WHO certifies seven more countries as free of guinea-worm disease". World Health Organization. Retrieved 2010-05-14.
30. ^ "Activities by Country—Guinea Worm Eradication Program". Carter Center. Retrieved 2010-03-16.
31. ^ CDC (2000-10-11). "Progress Toward Global Dracunculiasis Eradication, June 2000". *MMWR Morb. Mortal. Wkly. Rep*. **49**: war and eradication of dracunculiasis". *Lancet*. **360**: s21–2. doi:10.1016/S0140-6736(02)11806-X.
45. ^ *a b* Hopkins DR; Ruiz-Tiben E; Downs P; Withers PC Jr.; Maguire JH (2005-10-01). "Dracunculiasis Eradication: The Final Inch". *American Journal of Tropical Medicine and Hygiene*. **73** (4): 669–675. PMID 16222007.
46. ^ *a b c d* Hopkins DR, Ruiz-Tiben E, Downs P, Withers PC, Roy S (October 2008). "Dracunculiasis eradication: neglected no longer". *Am. J. Trop. Med. Hyg.* **79** (4): 474–9. PMID 18840732.
47. ^ WHO (2 May 2008). "Dracunculiasis eradication" (PDF). *Wkly Epidemiol Rec*. World Health Organization. **83** (18): 159–167. PMID 18453066.
48. ^ *a b* WHO Collaborating Center for Research, Training and Eradication of Dracunculiasis (March 12, 2010). "GUINEA WORM WRAP-UP #195" (PDF). Centers for Disease Control and Prevention (CDC)."Guinea worm wrap-up 195, 12 March 2010" (PDF). Carter Center. Retrieved 2010-03-16.
49. ^ Centers for Disease Control and Prevention (CDC) (October 2008). "Update: progress toward global eradication of dracunculiasis, January 2007 – June 2008". *MMWR Morb. Mortal. Wkly. Rep*. **57** (43): 1173–6. PMID 18971919.
50. ^ *a b* WHO Collaborating Center for Research, Training and Eradication of Dracunculiasis (January 7, 2011). "GUINEA WORM WRAP-UP #202" (PDF). Centers for Disease Control and Prevention (CDC).
51. ^ Uniting to Combat Neglected Tropical Diseases (30 January 2012). "London Declaration on Neglected Tropical Diseases" (PDF). *Uniting to Combat NTDs*. Retrieved 2013-05-06.
52. ^ WHO (3 February 2012). "WHO roadmap inspires unprecedented support to defeat neglected tropical diseases". *World Health Organization*. Retrieved 2013-05-06.
53. ^ *a b* http://www.cartercenter.org/resources/pdfs/news/health_publications/guinea_worm/wrap-up/238.pdf
54. ^ http://www.cartercenter.org/resources/pdfs/news/health_publications/guinea_worm/wrap-up/235.pdf
55. ^ VOX (20 August 2015). "President Jimmy Carter's Amazing Last Wish". Retrieved 2015-08-20.
56. ^ http://www.cartercenter.org/resources/pdfs/news/health_publications/guinea_worm/wrap-up/242.pdf
57. ^ Христо Стамболски: Автобиография, дневници и мспомени. (Autobiography of Hristo Stambolski. Sofia : Dŭržavna pečatnica, 1927–1931)
58. ^ "Guinea Worm Infection (Dracunculiasis)". *The Imaging of Tropical Diseases*. International Society of Radiology. 2008. Retrieved December 2, 2009.
59. ^ *a b* Eberhard, ML; Ruiz-Tiben, E; Hopkins, DR; Farrell, C; Toe, F; Weiss, A; Withers PC, Jr; Jenks, MH; Thiele, EA; Cotton, JA; Hance, Z; Holroyd, N; Cama, VA; Tahir, MA; Mounda, T (January 2014). "The peculiar epidemiology of dracunculiasis in Chad.". *The American journal of tropical medicine and hygiene*. **90** (1): 61–70. doi:10.4269/ajtmh.13-0554. PMID 24277785.


## External links [edit]

- "Guinea Worm Disease Eradication Program". Carter Center.
- Nicholas D. Kristof from the New York Times follows a young Sudanese boy with a Guinea Worm parasite infection who is quarantined for treatment as part of the Carter program
- Tropical Medicine Central Resource: "Guinea Worm Infection (Dracunculiasis)"
- World Health Organization on Dracunculiasis

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| | | **Pseudophyllidea** | *Diphyllobothrium latum* (Diphyllobothriasis · · *Spirometra erinaceieuropaei* (Sparganosis · · *Diphyllobothrium mansonoides* (Sparganosis · · | | |
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| | | | | **Thelazioidea** | *Gnathostoma spinigerum/ Gnathostoma hispidum* (Gnathostomiasis · · *Thelazia* (Thelaziasis · · |
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# Ebola virus disease

From Wikipedia, the free encyclopedia

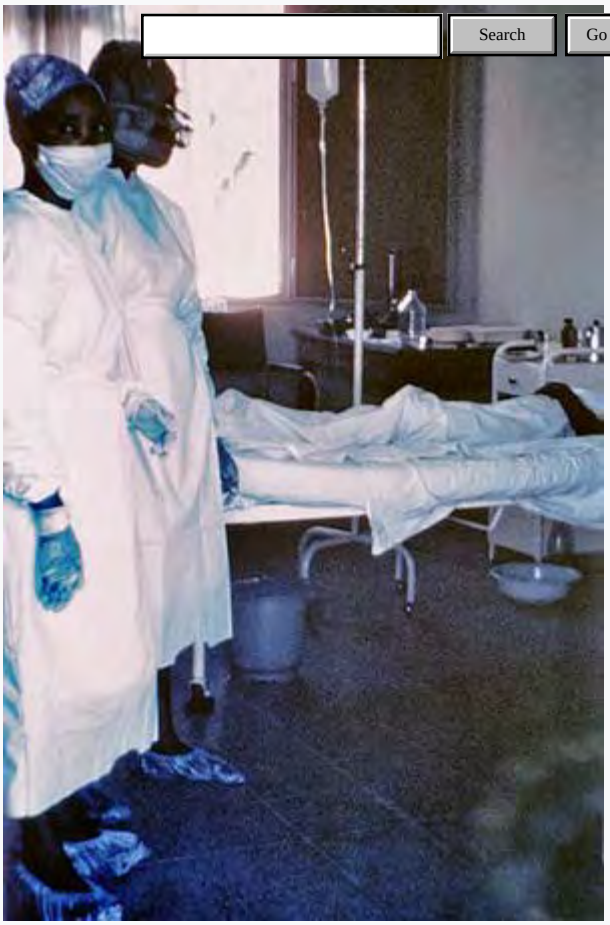
*"Ebola" redirects here. For other uses, see Ebola (disambiguation).*

**Ebola virus disease** (**EVD**), also known as **Ebola hemorrhagic fever** (**EHF**) or simply **Ebola**, is a viral hemorrhagic fever of humans and other primates caused by ebolaviruses. Signs and symptoms typically start between two days and three weeks after contracting the virus with a fever, sore throat, muscular pain, and headaches. Then, vomiting, diarrhea and rash usually follow, along with decreased function of the liver and kidneys. At this time some people begin to bleed both internally and externally.[1] The disease has a high risk of death, killing between 25 and 90 percent of those infected, with an average of about 50 percent.[1] This is often due to low blood pressure from fluid loss, and typically follows six to sixteen days after symptoms appear.[2]

The virus spreads by direct contact with body fluids, such as blood, of an infected human or other animals.[1] This may also occur through contact with an item recently contaminated with bodily fluids.[1] Spread of the disease through the air between primates, including humans, has not been documented in either laboratory or natural conditions.[3] Semen or breast milk of a person after recovery from EVD may carry the virus for several weeks to months.[1][4][5] Fruit bats are believed to be the normal carrier in nature, able to spread the virus without being affected by it. Other diseases such as malaria, cholera, typhoid fever, meningitis and other viral hemorrhagic fevers may resemble EVD. Blood samples are tested for viral RNA, viral antibodies or for the virus itself to confirm the diagnosis.[1]

Control of outbreaks requires coordinated medical services, alongside a certain level of community engagement. The medical services include rapid detection of cases of disease, contact tracing of those who have come into contact with infected individuals, quick access to laboratory services, proper healthcare for those who are infected, and proper disposal of the dead through cremation or burial.[1][6] Samples of body fluids and tissues from people with the disease should be handled with special caution. Prevention includes limiting the spread of disease from infected animals to humans. This may be done by handling potentially infected bushmeat only while wearing protective clothing and by thoroughly cooking it before eating it. It also includes wearing

Ebola virus disease



Two nurses standing near Mayinga N'Seka, a nurse with Ebola virus disease in the 1976 outbreak in Zaire. N'Seka died a few days later.

| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | A98.4 |
| **ICD-9-CM** | 078.89 |
| **DiseasesDB** | 18043 |
| **MedlinePlus** | 001339 |

proper protective clothing and washing hands when around a person with the disease. No specific treatment or vaccine for the virus is available, although a number of potential treatments are being studied. Supportive efforts, however, improve outcomes. This includes either oral rehydration therapy (drinking slightly sweetened and salty water) or giving intravenous fluids as well as treating symptoms.[1]

| | |
|---|---|
| **eMedicine** | med/626 |
| **MeSH** | D019142 |

[edit on Wikidata]

The disease was first identified in 1976 in two simultaneous outbreaks, one in Nzara, and the other in Yambuku, a village near the Ebola River from which the disease takes its name.[7] EVD outbreaks occur intermittently in tropical regions of sub-Saharan Africa.[1] Between 1976 and 2013, the World Health Organization reports a total of 24 outbreaks involving 1,716 cases.[1][8] The largest outbreak to date was the epidemic in West Africa, which occurred from December 2013 to January 2016 with 28,616 cases and 11,310 deaths.[9][10][11] It was declared no longer an emergency on 29 March 2016.[12]



**Contents**

# Signs and symptoms

## Onset

Signs and symptoms of Ebola[13]

The length of time between exposure to the virus and the development of symptoms (incubation period) is between 2 and 21 days,[1][13] and usually between 4 and 10 days.[14] However, recent estimates based on mathematical models predict that around 5% of cases may take greater than 21 days to develop.[15]

Symptoms usually begin with a sudden influenza-like stage characterized by feeling tired, fever, weakness, decreased appetite, muscular pain, joint pain, headache, and sore throat.[1][14][16][17] The fever is usually higher than 38.3 °C (101 °F).[18] This is often followed by vomiting, diarrhea and abdominal pain.[17] Next, shortness of breath and chest pain may occur, along with swelling, headaches and confusion.[17] In about half of the cases, the skin may develop a maculopapular rash, a flat red area covered with small bumps, 5 to 7 days after symptoms begin.[14][18]

## Bleeding

In some cases, internal and external bleeding may occur.[1] This typically begins five to seven days after the first symptoms.[19] All infected people show some decreased blood clotting.[18] Bleeding from mucous membranes or from sites of needle punctures has been reported in 40–50 percent of cases.[20] This may cause vomiting blood, coughing up of blood, or blood in stool.[21] Bleeding into the skin may create petechiae, purpura, ecchymoses or hematomas (especially around needle injection sites).[22] Bleeding into the whites of the eyes may also occur. Heavy bleeding is uncommon; if it occurs, it is usually located within the gastrointestinal tract.[18][23]

## Recovery and death

Recovery may begin between 7 and 14 days after first symptoms.[17] Death, if it occurs, follows typically 6 to 16 days from first symptoms and is often due to low blood pressure from fluid loss.[2] In general, bleeding often indicates a worse outcome, and blood loss may result in death.[16] People are often in a coma near the end of life.[17]

Those who survive often have ongoing muscular and joint pain, liver inflammation, decreased hearing, and may have continued feelings of tiredness, continued weakness, decreased appetite, and difficulty returning to pre-illness weight.[17][24] Problems with vision may develop.[25]

Additionally, they develop antibodies against Ebola that last at least 10 years, but it is unclear if they are immune to repeated infections.[26]

# Cause

EVD in humans is caused by four of five viruses of the genus *Ebolavirus*. The four are Bundibugyo virus (BDBV), Sudan virus (SUDV), Taï Forest virus (TAFV) and one simply called Ebola virus (EBOV, formerly Zaire Ebola virus).[27] EBOV, species *Zaire ebolavirus*, is the most dangerous of the known EVD-causing viruses, and is responsible for the largest number of outbreaks.[28] The fifth virus, Reston virus (RESTV), is not thought to cause disease in humans, but has caused disease in other primates.[29][30] All five viruses

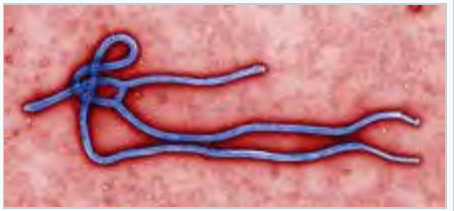
are closely related to marburgviruses.[27]



## Virology

*Main articles:* Ebolavirus *(taxonomic group)* and *Ebola virus (specific virus)*

Ebolaviruses contain single-stranded, non-infectious RNA genomes.[31] *Ebolavirus* genomes contain seven genes including 3'-UTR-*NP-VP35-VP40-GP-VP30-VP24-L*-5'-UTR.[22][32] The genomes of the five different ebolaviruses (BDBV, EBOV, RESTV, SUDV and TAFV) differ in sequence and the number and location of gene overlaps. As with all filoviruses, ebolavirus virions are filamentous particles that may appear in the shape of a shepherd's crook, of a "U" or of a "6," and they may be coiled, toroid or branched.[32][33] In general, ebolavirions are 80 nanometers (nm) in width and may be as long as 14,000 nm.[34]

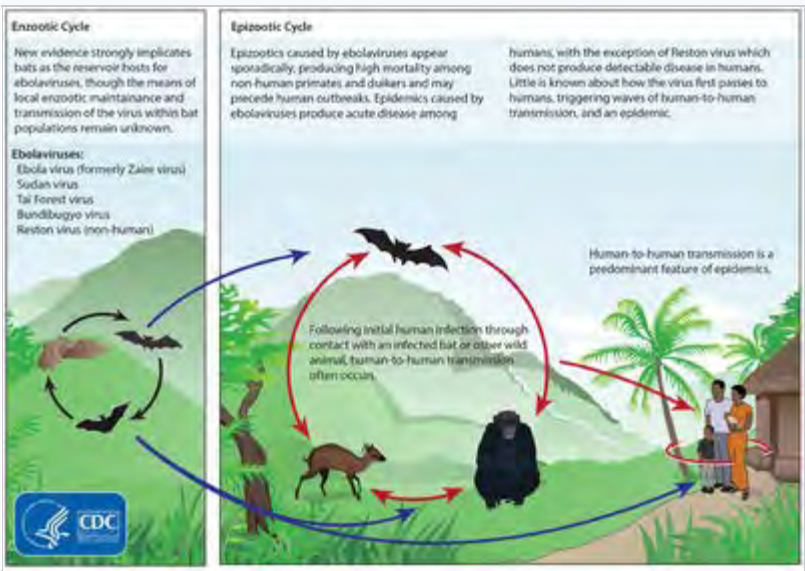


Electron micrograph of an Ebola virus virion

Their life cycle is thought to begin with a virion attaching to specific cell-surface receptors such as C-type lectins, DC-SIGN, or integrins, which is followed by fusion of the viral envelope with cellular membranes.[35] The virions taken up by the cell then travel to acidic endosomes and lysosomes where the viral envelope glycoprotein GP is cleaved.[35] This processing appears to allow the virus to bind to cellular proteins enabling it to fuse with internal cellular membranes and release the viral nucleocapsid.[35] The *Ebolavirus* structural glycoprotein (known as GP1,2) is responsible for the virus' ability to bind to and infect targeted cells.[36] The viral RNA polymerase, encoded by the *L* gene, partially uncoats the nucleocapsid and transcribes the genes into positive-strand mRNAs, which are then translated into structural and nonstructural proteins. The most abundant protein produced is the nucleoprotein, whose concentration in the host cell determines when L switches from gene transcription to genome replication. Replication of the viral genome results in full-length, positive-strand antigenomes that are, in turn, transcribed into genome copies of negative-strand virus progeny.[37] Newly synthesized structural proteins and genomes self-assemble and accumulate near the inside of the cell membrane. Virions bud off from the cell, gaining their envelopes from the cellular membrane from which they bud. The mature progeny particles then infect other cells to repeat the cycle. The genetics of the Ebola virus are difficult to study because of EBOV's virulent characteristics.[38]

## Transmission

It is believed that between people, Ebola disease spreads only by direct contact with the blood or other body fluids of a person who has developed symptoms of the disease.[39][40][41] Body fluids that may contain Ebola viruses include saliva, mucus, vomit, feces, sweat, tears, breast milk, urine and semen.[4][26] The WHO states that only people who are very sick are able to spread Ebola disease in saliva, and whole virus has not been reported to be transmitted through sweat. Most people spread the virus through blood, feces and vomit.[42] Entry points for the virus include the nose, mouth, eyes, open wounds, cuts and abrasions.[26] Ebola may be spread through large droplets; however, this is believed to occur only when a person is very sick.[43] This contamination can happen if a person is splashed with droplets.[43] Contact with surfaces or objects contaminated by the virus,




Life cycles of the *Ebolavirus*

particularly needles and syringes, may also transmit the infection.[44][45] The virus is able to survive on objects for a few hours in a dried state, and can survive for a few days within body fluids outside of a person.[26][46]

The Ebola virus may be able to persist for more than 3 months in the semen after recovery, which could lead to infections via sexual intercourse.[4][47][48] Virus persistence in semen for over a year has been recorded in a national screening programme.[49] Ebola may also occur in the breast milk of women after recovery, and it is not known when it is safe to breastfeed again.[5] The virus was also found in the eye of one patient in 2014, two months after it was cleared from his blood.[50] Otherwise, people who have recovered are not infectious.[44]

The potential for widespread infections in countries with medical systems capable of observing correct medical isolation procedures is considered low.[51] Usually when someone has symptoms of the disease, they are unable to travel without assistance.[52]

Dead bodies remain infectious; thus, people handling human remains in practices such as traditional burial rituals or more modern processes such as embalming are at risk.[51] 69% of the cases of Ebola infections in Guinea during the 2014 outbreak are believed to have been contracted via unprotected (or unsuitably protected) contact with infected corpses during certain Guinean burial rituals.[53][54]

Health-care workers treating people with Ebola are at greatest risk of infection.[44] The risk increases when they do not have appropriate protective clothing such as masks, gowns, gloves and eye protection; do not wear it properly; or handle contaminated clothing incorrectly.[44] This risk is particularly common in parts of Africa where the disease mostly occurs and health systems function poorly.[55] There has been transmission in hospitals in some African countries that reuse hypodermic needles.[56][57] Some health-care centers caring for people with the disease do not have running water.[58] In the United States the spread to two medical workers treating infected patients prompted criticism of inadequate training and procedures.[59]

Human-to-human transmission of EBOV through the air has not been reported to occur during EVD outbreaks,[3] and airborne transmission has only been demonstrated in very strict laboratory conditions, and then only from pigs to primates, but not from primates to primates.[39][45] Spread of EBOV by water, or food other than bushmeat, has not been observed.[44][45] No spread by mosquitos or other insects has been reported.[44] Other possible methods of transmission are being studied.[46]

The apparent lack of airborne transmission among humans is believed to be due to low levels of the virus in the lungs and other parts of the respiratory system of primates, insufficient to cause new infections.[60] A number of studies examining airborne transmission broadly concluded that transmission from pigs to primates could happen without direct contact because, unlike humans and primates, pigs with EVD get very high ebolavirus concentrations in their lungs, and not their bloodstream.[61] Therefore, pigs with EVD can spread the disease through droplets in the air or on the ground when they sneeze or cough.[62] By contrast, humans and other primates accumulate the virus throughout their body and specifically in their blood, but not very much in their lungs.[62] It is believed that this is the reason researchers have observed pig to primate transmission without physical contact, but no evidence has been found of primates being infected without actual contact, even in experiments where infected and uninfected primates shared the same air.[61][62]

## Initial case

Although it is not entirely clear how Ebola initially spreads from animals to humans, the spread is believed to involve direct contact with an infected wild animal or fruit bat.[44] Besides bats, other wild animals sometimes infected with EBOV include several monkey species, chimpanzees, gorillas, baboons and duikers.[66]

Animals may become infected when they eat fruit partially eaten by bats [67]

Bushmeat being prepared for cooking in Ghana. In Africa, wild animals including fruit bats are hunted for food and are referred to as bushmeat.[63][64] In equatorial Africa, human consumption of bushmeat has been linked to animal-to-human transmission of diseases, including Ebola.[65]

carrying the virus. Fruit production, animal behavior and other factors may trigger outbreaks among animal populations.[67]

Evidence indicates that both domestic dogs and pigs can also be infected with EBOV.[68] Dogs do not appear to develop symptoms when they carry the virus, and pigs appear to be able to transmit the virus to at least some primates.[68] Although some dogs in an area in which a human outbreak occurred had antibodies to EBOV, it is unclear whether they played a role in spreading the disease to people.[68]

### Reservoir

The natural reservoir for Ebola has yet to be confirmed; however, bats are considered to be the most likely candidate species.[45] Three types of fruit bats (*Hypsignathus monstrosus*, *Epomops franqueti* and *Myonycteris torquata*) were found to possibly carry the virus without getting sick.[69] As of 2013, whether other animals are involved in its spread is not known.[68] Plants, arthropods and birds have also been considered possible viral reservoirs.[1]

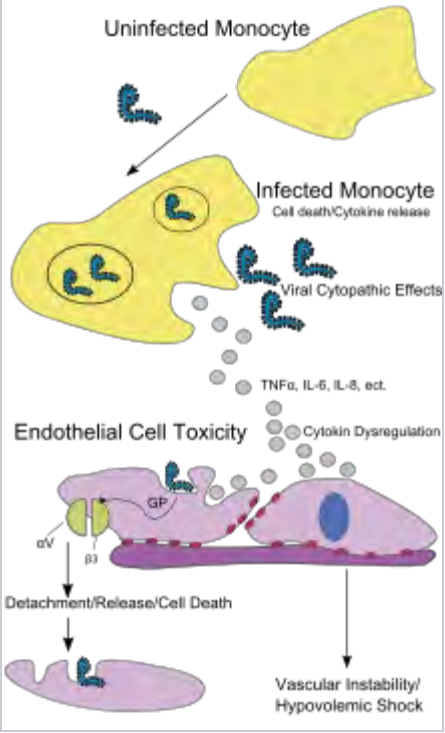
Bats were known to roost in the cotton factory in which the first cases of the 1976 and 1979 outbreaks were observed, and they have also been implicated in Marburg virus infections in 1975 and 1980.[70] Of 24 plant and 19 vertebrate species experimentally inoculated with EBOV, only bats became infected.[71] The bats displayed no clinical signs of disease, which is considered evidence that these bats are a reservoir species of EBOV. In a 2002–2003 survey of 1,030 animals including 679 bats from Gabon and the Republic of the Congo, 13 fruit bats were found to contain EBOV RNA.[72] Antibodies against Zaire and Reston viruses have been found in fruit bats in Bangladesh, suggesting that these bats are also potential hosts of the virus and that the filoviruses are present in Asia.[73]

Between 1976 and 1998, in 30,000 mammals, birds, reptiles, amphibians and arthropods sampled from regions of EBOV outbreaks, no Ebola virus was detected apart from some genetic traces found in six rodents (belonging to the species *Mus setulosus* and *Praomys*) and one shrew (*Sylvisorex ollula*) collected from the Central African Republic.[70][74] However, further research efforts have not confirmed rodents as a reservoir.[75] Traces of EBOV were detected in the carcasses of gorillas and chimpanzees during outbreaks in 2001 and 2003, which later became the source of human infections. However, the high rates of death in these species resulting from EBOV infection make it unlikely that these species represent a natural reservoir for the virus.[70]

## Pathophysiology

Similar to other filoviruses, EBOV replicates very efficiently in many cells, producing large amounts of virus in monocytes, macrophages, dendritic cells and other cells including liver cells, fibroblasts, and adrenal gland cells.[76] Viral replication triggers the release of high levels of inflammatory chemical signals and leads to a septic state.[24]

EBOV is thought to infect humans through contact with mucous membranes or through skin breaks.[39] Once infected, endothelial cells (cells lining the inside of blood vessels), liver cells, and several types of immune cells such as macrophages, monocytes, and dendritic cells are



Pathogenesis schematic

the main targets of infection.[39] Following infection with the virus, the immune cells carry the virus to nearby lymph nodes where further reproduction of the virus takes place.[39] From there, the virus can enter the bloodstream and lymphatic system and spread throughout the body.[39] Macrophages are the first cells infected with the virus, and this infection results in programmed cell death.[34] Other types of white blood cells, such as lymphocytes, also undergo programmed cell death leading to an abnormally low concentration of lymphocytes in the blood.[39] This contributes to the weakened immune response seen in those infected with EBOV.[39]

Endothelial cells may be infected within 3 days after exposure to the virus.[34] The breakdown of endothelial cells leading to blood vessel injury can be attributed to EBOV glycoproteins. This damage occurs due to the synthesis of Ebola virus glycoprotein (GP), which reduces the availability of specific integrins responsible for cell adhesion to the intercellular structure and causes liver damage, leading to improper clotting. The widespread bleeding that occurs in affected people causes swelling and shock due to loss of blood volume.[77] The dysfunction in bleeding and clotting commonly seen in EVD has been attributed to increased activation of the extrinsic pathway of the coagulation cascade due to excessive tissue factor production by macrophages and monocytes.[14]

After infection, a secreted glycoprotein, small soluble glycoprotein (sGP or GP) is synthesized. EBOV replication overwhelms protein synthesis of infected cells and the host immune defenses. The GP forms a trimeric complex, which tethers the virus to the endothelial cells. The sGP forms a dimeric protein that interferes with the signaling of neutrophils, another type of white blood cell, which enables the virus to evade the immune system by inhibiting early steps of neutrophil activation. The presence of viral particles and the cell damage resulting from viruses budding out of the cell causes the release of chemical signals (such as TNF-α, IL-6 and IL-8), which are molecular signals for fever and inflammation.[*citation needed*]

## Immune system evasion

Filoviral infection also interferes with proper functioning of the innate immune system.[35][37] EBOV proteins blunt the human immune system's response to viral infections by interfering with the cells' ability to produce and respond to interferon proteins such as interferon-alpha, interferon-beta, and interferon gamma.[36][78]

The VP24 and VP35 structural proteins of EBOV play a key role in this interference. When a cell is infected with EBOV, receptors located in the cell's cytosol (such as RIG-I and MDA5) or outside of the cytosol (such as Toll-like receptor 3 (TLR3), TLR7, TLR8 and TLR9), recognize infectious molecules associated with the virus.[36] On TLR activation, proteins including interferon regulatory factor 3 and interferon regulatory factor 7 trigger a signaling cascade that leads to the expression of type 1 interferons.[36] The type 1 interferons are then released and bind to the IFNAR1 and IFNAR2 receptors expressed on the surface of a neighboring cell.[36] Once interferon has bound to its receptors on the neighboring cell, the signaling proteins STAT1 and STAT2 are activated and move to the cell's nucleus.[36] This triggers the expression of interferon-stimulated genes, which code for proteins with antiviral properties.[36] EBOV's V24 protein blocks the production of these antiviral proteins by preventing the STAT1 signaling protein in the neighboring cell from entering the nucleus.[36] The VP35 protein directly inhibits the production of interferon-beta.[78] By

inhibiting these immune responses, EBOV may quickly spread throughout the body.[34]

# Diagnosis

When EVD is suspected in a person, his or her travel and work history, along with an exposure to wildlife, are important factors to consider with respect to further diagnostic efforts.

## Laboratory testing

Possible non-specific laboratory indicators of EVD include a low platelet count; an initially decreased white blood cell count followed by an increased white blood cell count; elevated levels of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST); and abnormalities in blood clotting often consistent with disseminated intravascular coagulation (DIC) such as a prolonged prothrombin time, partial thromboplastin time, and bleeding time.[79] Filovirions, such as EBOV, may be identified by their unique filamentous shapes in cell cultures examined with electron microscopy, but this method cannot distinguish the various filoviruses.[80]

The specific diagnosis of EVD is confirmed by isolating the virus, detecting its RNA or proteins, or detecting antibodies against the virus in a person's blood. Isolating the virus by cell culture, detecting the viral RNA by polymerase chain reaction (PCR)[14] and detecting proteins by enzyme-linked immunosorbent assay (ELISA) are methods best used in the early stages of the disease and also for detecting the virus in human remains. Detecting antibodies against the virus is most reliable in the later stages of the disease and in those who recover.[81] IgM antibodies are detectable two days after symptom onset and IgG antibodies can be detected 6 to 18 days after symptom onset.[14] During an outbreak, isolation of the virus via cell culture methods is often not feasible. In field or mobile hospitals, the most common and sensitive diagnostic methods are real-time PCR and ELISA.[82] In 2014, with new mobile testing facilities deployed in parts of Liberia, test results were obtained 3–5 hours after sample submission.[83] In 2015 a rapid antigen test which gives results in 15 minutes was approved for use by WHO. It is able to confirm Ebola in 92% of those affected and rule it out in 85% of those not affected.[84]

## Differential diagnosis

Early symptoms of EVD may be similar to those of other diseases common in Africa, including malaria and dengue fever.[16] The symptoms are also similar to those of other viral hemorrhagic fevers such as Marburg virus disease.[85]

The complete differential diagnosis is extensive and requires consideration of many other infectious diseases such as typhoid fever, shigellosis, rickettsial diseases, cholera, sepsis, borreliosis, EHEC enteritis, leptospirosis, scrub typhus, plague, Q fever, candidiasis, histoplasmosis, trypanosomiasis, visceral leishmaniasis, measles, and viral hepatitis among others.[86]

Non-infectious diseases that may result in symptoms similar to those of EVD include acute promyelocytic leukemia, hemolytic uremic syndrome, snake envenomation, clotting factor deficiencies/platelet disorders, thrombotic thrombocytopenic purpura, hereditary hemorrhagic telangiectasia, Kawasaki disease, and warfarin poisoning.[82][87][88][89]

# Prevention

*Main article: Prevention of viral hemorrhagic fever*

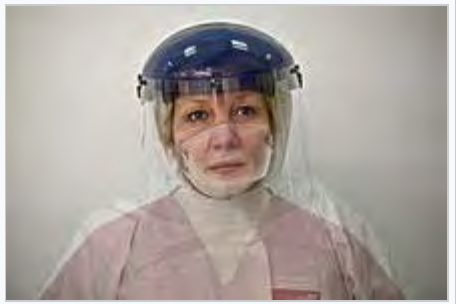
## Infection control

People who care for those infected with Ebola should wear protective clothing including masks, gloves, gowns and [90]

VHF isolation precautions poster

goggles. The US Centers for Disease Control (CDC) recommend that the protective gear leaves no skin exposed.[91] These measures are also recommended for those who may handle objects contaminated by an infected person's body fluids.[92] In 2014, the CDC began recommending that medical personnel receive training on the proper suit-up and removal of personal protective equipment (PPE); in addition, a designated person, appropriately trained in biosafety, should be watching each step of these procedures to ensure they are done correctly.[91] In Sierra Leone, the typical training period for the use of such safety equipment lasts approximately 12 days.[93]

The infected person should be in barrier-isolation from other people.[90] All equipment, medical waste, patient waste and surfaces that may have come into contact with body fluids need to be disinfected.[92] During the 2014 outbreak, kits were put together to help families treat Ebola disease in their homes, which include protective clothing as well as chlorine powder and other cleaning supplies.[94] Education of those who provide care in these techniques, and the provision of such barrier-separation supplies has been a priority of Doctors Without Borders.[95]


British woman wearing protective gear

Ebolaviruses can be eliminated with heat (heating for 30 to 60 minutes at 60 °C or boiling for 5 minutes). To disinfect surfaces, some lipid solvents such as some alcohol-based products, detergents, sodium hypochlorite (bleach) or calcium hypochlorite (bleaching powder), and other suitable disinfectants may be used at appropriate concentrations.[66][96] Education of the general public about the risk factors for Ebola infection and of the protective measures individuals may take to prevent infection is recommended by the World Health Organization.[1] These measures include avoiding direct contact with infected people and regular hand washing using soap and water.[97]

Bushmeat, an important source of protein in the diet of some Africans, should be handled and prepared with appropriate protective clothing and thoroughly cooked before consumption.[1] Some research suggests that an outbreak of Ebola disease in the wild animals used for consumption may result in a corresponding human outbreak. Since 2003, such animal outbreaks have been monitored to predict and prevent Ebola outbreaks in humans.[98]

If a person with Ebola disease dies, direct contact with the body should be avoided.[90] Certain burial rituals, which may have included making various direct contacts with a dead body, require reformulation such that they consistently maintain a proper protective barrier between the dead body and the living.[99][100][101] Social anthropologists may help find alternatives to traditional rules for burials.[102]

Transportation crews are instructed to follow a certain isolation procedure, should anyone exhibit symptoms resembling EVD.[103] As of August 2014, the WHO does not consider travel bans to be useful in decreasing spread of the disease.[52] In October 2014, the CDC defined four risk levels used to determine the level of 21-day monitoring for symptoms and restrictions on public activities.[104] In the United States, the CDC recommends that restrictions on public activity, including travel restrictions, are not required for the

following defined risk levels:[104]

- having been in a country with widespread Ebola disease transmission and having no known exposure (low risk); or having been in that country more than 21 days ago (no risk)
- encounter with a person showing symptoms; but not within 3 feet of the person with Ebola without wearing PPE; and no direct contact of body fluids
- having had brief skin contact with a person showing symptoms of Ebola disease when the person was believed to be not very contagious (low risk)
- in countries without widespread Ebola disease transmission: direct contact with a person showing symptoms of the disease while wearing PPE (low risk)
- contact with a person with Ebola disease before the person was showing symptoms (no risk).

The CDC recommends monitoring for the symptoms of Ebola disease for those both at "low risk" and at higher risk.[104]

In laboratories where diagnostic testing is carried out, biosafety level 4-equivalent containment is required.[105] Laboratory researchers must be properly trained in BSL-4 practices and wear proper PPE.[105]

## Putting on protective equipment


Play media

Introduction


Play media

Trained observer


Play media

Removing own clothing


Play media

Examining equipment


Play media

Hand cleaning


Play media

Boot covers


Play media

Inner gloves


Play media

Coverall


Play media

N95 respirator


Play media

Surgical hood


Play media

Outer apron


Play media

Outer gloves


Play media

Face shield


Play media

Verification

## Isolation

Isolation refers to separating those who are sick from those who are not. Quarantine refers to separating those who may have been exposed to a disease until they either show signs of the disease or are no longer at risk.[106] Quarantine, also known as enforced isolation, is usually effective in decreasing spread.[107][108] Governments often quarantine areas where the disease is occurring or individuals who may transmit the disease outside of an initial area.[109] In the United States, the law allows quarantine of those infected with ebolaviruses.[110]

## Contact tracing

Contact tracing is considered important to contain an outbreak. It involves finding everyone who had close contact with infected individuals and watching for signs of illness for 21 days. If any of these contacts comes down with the disease, they should be isolated, tested and treated. Then the process is repeated by tracing the contacts' contacts.[111][112]

# Management

No specific treatment is currently approved.[113] The Food and Drug Administration (FDA) advises people to be careful of advertisements making unverified or fraudulent claims of benefits supposedly gained from various anti-Ebola products.[114][115]

## Standard support

Treatment is primarily supportive in nature.[116] Early supportive care with rehydration and symptomatic treatment improves survival.[1] Rehydration may be via the oral or by intravenous route.[116] These measures may include management of pain, nausea, fever and anxiety.[116] The World Health Organization recommends avoiding the use of aspirin or ibuprofen for pain due to the bleeding risk associated with use of these medications.[117]

Blood products such as packed red blood cells, platelets or fresh frozen plasma may also be used.[116] Other regulators of coagulation have also been tried including heparin in an effort to prevent disseminated intravascular coagulation and clotting factors to decrease bleeding.[116] Antimalarial medications and antibiotics are often used before the diagnosis is confirmed,[116] though there is no evidence to suggest such treatment helps. A number of experimental treatments are being studied.


A hospital isolation ward in Gulu, Uganda, during the October 2000 outbreak

If hospital care is not possible, the World Health Organization has guidelines for care at home that have been relatively successful. In such situations, recommendations include using towels soaked in bleach solutions when moving infected people or bodies and applying bleach on stains. It is also recommended that the caregivers wash hands with bleach solutions and cover their mouth and nose with a cloth.[118]

### Intensive care

Intensive care is often used in the developed world.[22] This may include maintaining blood volume and electrolytes (salts) balance as well as treating any bacterial infections that may develop.[22] Dialysis may be needed for kidney failure, and extracorporeal membrane oxygenation may be used for lung dysfunction.[22]

## Prognosis

EVD has a high risk of death in those infected which varies between 25 percent and 90 percent of those infected.[1][119] As of September 2014, the average risk of death among those infected is 50 percent.[1] The highest risk of death was 90 percent in the 2002–2003 Republic of the Congo outbreak.[120]

Death, if it occurs, follows typically six to sixteen days after symptoms appear and is often due to low blood pressure from fluid loss.[2] Early supportive care to prevent dehydration may reduce the risk of death.[121]

If an infected person survives, recovery may be quick and complete. Prolonged cases are often complicated by the occurrence of long-term problems, such as inflammation of the testicles, joint pains, muscular pain, skin peeling, or hair loss.[14] Eye symptoms, such as light sensitivity, excess tearing, and vision loss have been described.[122]

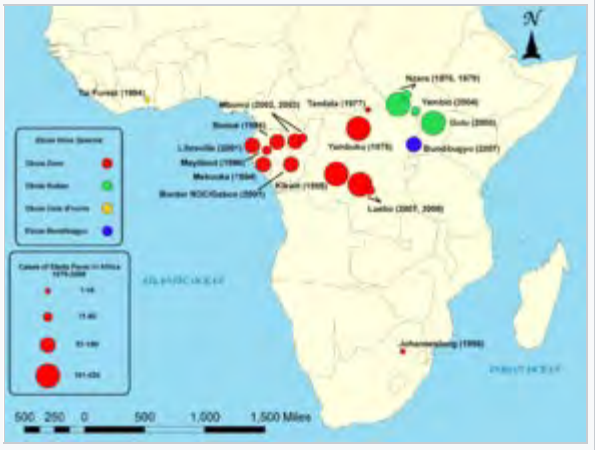
Ebola can stay in some body parts like the eyes,[123] breasts, and testicles after infection.[4][124] Sexual transmission after recovery has been suggested.[125][126] If sexual transmission occurs following recovery it is believed to be a rare event.[127] One case of a condition similar to meningitis has been reported many months after recovery as of Oct. 2015.[128]

A study of 44 survivors of the Ebola virus in Sierra Leone reported musculoskeletal pain in 70%, headache in 48% and eye problems in 14%.[129]

## Epidemiology

*For more about specific outbreaks, see List of Ebola outbreaks.*

The disease typically occurs in outbreaks in tropical regions of Sub-Saharan Africa.[1] From 1976 (when it was first identified) through 2013, the World Health Organization reported 1,716 confirmed cases.[1][8] The largest outbreak to date was the Ebola virus epidemic in West Africa, which had caused a large number of deaths in Guinea, Sierra Leone, and Liberia.[10][11]

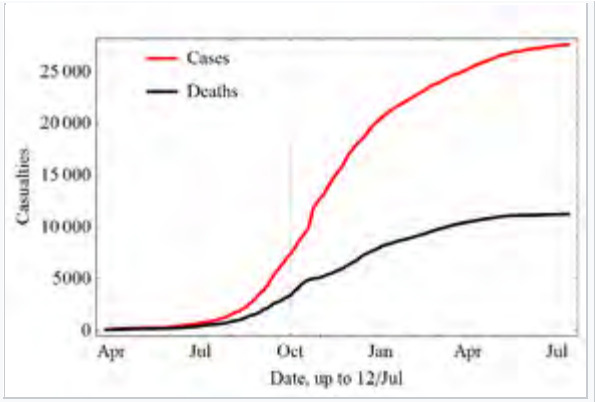


Cases of Ebola fever in Africa from 1979 to 2008

### 2013—2016 West African outbreak

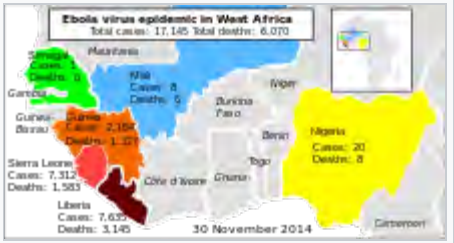
*Main article: West African Ebola virus epidemic*

In March 2014, the World Health Organization (WHO) reported a major Ebola outbreak in Guinea, a western African nation.[130] Researchers traced the outbreak to a one-year-old child who died December 2013.[131][132] The disease then rapidly spread to the neighboring countries of Liberia and Sierra Leone. It is the largest Ebola outbreak ever




Cases and deaths from April 2014 to July 2015 during the 2013–2015 outbreak

documented, and the first recorded in the region.[130] On 8 August 2014, the WHO declared the epidemic to be an international public health emergency. Urging the world to offer aid to the affected regions, the Director-General said, "Countries affected to date simply do not have the capacity to manage an outbreak of this size and complexity on their own. I urge the international community to provide this support on the most urgent basis possible."[133] By mid-August 2014, Doctors Without Borders reported the situation in Liberia's capital Monrovia as "catastrophic" and "deteriorating daily". They reported that fears of Ebola among staff members and patients had shut down much of the city's health system, leaving many people without treatment for other conditions.[134] In a 26 September statement, the WHO said, "The Ebola epidemic ravaging parts of West Africa is the most severe acute public health emergency seen in modern times. Never before in recorded history has a biosafety level four pathogen infected so many people so quickly, over such a broad geographical area, for so long."[135]




2014 Ebola virus epidemic in West Africa

Intense contact tracing and strict isolation techniques largely prevented further spread of the disease in the countries that had imported cases; this disease is still ongoing in Guinea. As of 8 May 2016, 28,616 suspected cases and 11,310 deaths have been reported;[9][136] however, the WHO has said that these numbers may be underestimated.[137] Because they work closely with the body fluids of infected patients, healthcare workers have been especially vulnerable to catching the disease; in August 2014, the WHO reported that ten percent of the dead have been healthcare workers.[138]

Checking for symptoms of Ebola in Sierra Leone, November 2014

In September 2014, it was estimated that the countries' capacity for treating Ebola patients was insufficient by the equivalent of 2,122 beds; by December there were a sufficient number of beds to treat and isolate all reported Ebola cases, although the uneven distribution of cases was resulting in serious shortfalls in some areas.[139] On 28 January 2015, the WHO reported that for the first time since the week ending 29 June 2014, there had been fewer than 100 new confirmed cases reported in a week in the three most-affected countries. The response to the epidemic then moved to a second phase, as the focus shifted from slowing transmission to ending the epidemic.[140] On 8 April 2015, the WHO reported a total of only 30 confirmed cases, the lowest weekly total since the third week of May 2014.[141]

On 29 December 2015, 42 days after the last person tested negative for a second time, Guinea was declared free of Ebola transmission.[142] At that time, a 90-day period of heightened surveillance was announced by that agency. "This is the first time that all three countries – Guinea, Liberia and Sierra Leone – have stopped the original chains of transmission ...", the organization stated in a news release.[143] A new case was detected in Sierra Leone on 14 January 2016.[144] However, the outbreak was declared no longer an emergency on 29 March 2016.[12]

## 2014 Ebola spread outside West Africa

*Main articles: Ebola virus cases in the United States, Ebola virus disease in Spain, and Ebola virus disease in the United Kingdom*

As of 15 October 2014, there have been 17 cases of Ebola treated outside Africa, four of whom have died.[145]

In early October, Teresa Romero, a 44-year-old Spanish nurse, contracted Ebola after caring for a priest who had been repatriated from West Africa. This was the first transmission of the virus to occur outside Africa.[146] On 20 October, it was announced that Teresa Romero had tested negative for the Ebola virus, suggesting that she may have recovered from Ebola infection.[147]

On 19 September, Eric Duncan flew from his native Liberia to Texas; 5 days later he began showing symptoms and visited a hospital but was sent home. His condition worsened and he returned to the hospital on 28 September, where he died on 8 October.[148] Health officials confirmed a diagnosis of Ebola on 30 September—the first case in the United States.[59] On 12 October, the CDC confirmed that a nurse in Texas, Nina Pham, who had treated Duncan was found to be positive for the Ebola virus, the first known case of the disease to be contracted in the United States.[149] On 15 October, a second Texas health-care worker who had treated Duncan was confirmed to have the virus.[150] Both of these people have since recovered.[151]

On 23 October, a doctor in New York City, who returned to the United States from Guinea after working with Doctors Without Borders, tested positive for Ebola. His case is unrelated to the Texas cases.[152] The person has recovered and was discharged from Bellevue Hospital Center on 11 November.[151] On 24 December 2014, a laboratory in Atlanta, Georgia reported that a technician had been exposed to Ebola.[153]

On 29 December 2014, Pauline Cafferkey, a British nurse who had just returned to Glasgow from Sierra Leone was diagnosed with Ebola at Glasgow's Gartnavel General Hospital.[154] After initial treatment in Glasgow, she was transferred by air to RAF Northolt, then to the specialist high-level isolation unit at the Royal Free Hospital in London for longer-term treatment.[155]

## 1995 to 2014

The second major outbreak occurred in Zaire (now the Democratic Republic of the Congo) in 1995, affecting 315 and killing 254.[1]

In 2000, Uganda had an outbreak affecting 425 and killing 224; in this case, the Sudan virus was found to be the Ebola species responsible for the outbreak.[1]

In 2003 there was an outbreak in the Republic of the Congo that affected 143 and killed 128, a death rate of 90 percent, the highest death rate of a genus *Ebolavirus* outbreak to date.[156]

In 2004 a Russian scientist died from Ebola after sticking herself with an infected needle.[157]

Between April and August 2007, a fever epidemic[158] in a four-village region[159] of the Democratic Republic of the Congo was confirmed in September to have cases of Ebola.[160] Many people who attended the recent funeral of a local village chief died.[159] The 2007 outbreak eventually affected 264 individuals and resulted in the deaths of 187.[1]

On 30 November 2007, the Uganda Ministry of Health confirmed an outbreak of Ebola in the Bundibugyo District in Western Uganda. After confirmation of samples tested by the United States National Reference Laboratories and the Centers for Disease Control, the World Health Organization confirmed the presence of a new species of genus *Ebolavirus*, which was tentatively named Bundibugyo.[161] The WHO reported 149 cases of this new strain and 37 of those led to deaths.[1]

The WHO confirmed two small outbreaks in Uganda in 2012. The first outbreak affected 7 people and resulted in the death of 4 and the second affected 24, resulting in the death of 17. The Sudan variant was responsible for both outbreaks.[1]

On 17 August 2012, the Ministry of Health of the Democratic Republic of the Congo reported an outbreak of the Ebola-Bundibugyo variant[162] in the eastern region.[163][164] Other than its discovery in 2007, this was

the only time that this variant has been identified as responsible for an outbreak. The WHO revealed that the virus had sickened 57 people and claimed 29 lives. The probable cause of the outbreak was tainted bush meat hunted by local villagers around the towns of Isiro and Viadana.[1][165]

In 2014, an outbreak of Ebola virus disease occurred in the Democratic Republic of the Congo (DRC). Genome-sequencing has shown that this outbreak was not related to the 2014–15 West Africa Ebola virus outbreak, but was the same EBOV species, the Zaire species.[166] It began in August 2014 and was declared over in November of that year with a total of 66 cases and 49 deaths.[167] This is the 7th outbreak in the DRC, three of which occurred during the period when the country was known as Zaire.[168]

## 1976

### Sudan outbreak

CDC worker incinerates medical waste from Ebola patients in Zaire in 1976.

The first known outbreak of EVD was identified only after the fact, occurring between June and November 1976 in Nzara, South Sudan,[27][169] (then part of Sudan) and was caused by Sudan virus (SUDV). The Sudan outbreak infected 284 people and killed 151. The first identifiable case in Sudan occurred on 27 June in a storekeeper in a cotton factory in Nzara, who was hospitalized on 30 June and died on 6 July.[22][170] Although the WHO medical staff involved in the Sudan outbreak were aware that they were dealing with a heretofore unknown disease, the actual "positive identification" process and the naming of the virus did not occur until some months later in the Democratic Republic of the Congo.[170]

### Zaire outbreak

*See also: Yambuku § Ebola outbreak*

On 26 August 1976, a second outbreak of EVD began in Yambuku, a small rural village in Mongala District in northern Zaire (now known as the Democratic Republic of the Congo).[171][172] This outbreak was caused by EBOV, formerly designated *Zaire ebolavirus*, which is a different member of the genus *Ebolavirus* than in the first Sudan outbreak. The first person infected with the disease was village school headmaster Mabalo Lokela, who began displaying symptoms on 26 August 1976.[173] Lokela had returned from a trip to Northern Zaire near the Central African Republic border, having visited the Ebola River between 12 and 22 August. He was originally believed to have malaria and was given quinine. However, his symptoms continued to worsen, and he was admitted to Yambuku Mission Hospital on 5 September. Lokela died on 8 September 14 days after he began displaying symptoms.[174][175]

Soon after Lokela's death, others who had been in contact with him also died, and people in the village of Yambuku began to panic. This led the country's Minister of Health along with Zaire President Mobutu Sese Seko to declare the entire region, including Yambuku and the country's capital, Kinshasa, a quarantine zone. No one was permitted to enter or leave the area, with roads, waterways, and airfields placed under martial law. Schools, businesses and social organizations were closed.[176] Researchers from the CDC, including Peter Piot, co-discoverer of Ebola, later arrived to assess the effects of the outbreak, observing that "the whole region was in panic."[177][178][179] Piot concluded that the Belgian nuns had inadvertently started the epidemic by giving unnecessary vitamin injections to pregnant women, without sterilizing the syringes and needles. The outbreak lasted 26 days, with the quarantine lasting 2 weeks. Among the reasons that researchers speculated caused the disease to disappear, were the precautions taken by locals, the quarantine of the area, and discontinuing the injections.[176]

During this outbreak, Dr. Ngoy Mushola recorded the first clinical description of EVD in Yambuku, where he

wrote the following in his daily log: "The illness is characterized with a high temperature of about 39 °C (102 °F), hematemesis, diarrhea with blood, retrosternal abdominal pain, prostration with 'heavy' articulations, and rapid evolution death after a mean of 3 days."[180]

The virus responsible for the initial outbreak, first thought to be Marburg virus, was later identified as a new type of virus related to marburgviruses. Virus strain samples isolated from both outbreaks were named as the "Ebola virus" after the Ebola River, located near the originally identified viral outbreak site in Zaire.[22] Reports conflict about who initially coined the name: either Karl Johnson of the American CDC team[181] or Belgian researchers.[182] Subsequently, a number of other cases were reported, almost all centered on the Yambuku mission hospital or having close contact with another case.[173] 318 cases and 280 deaths (an 88 percent fatality rate) occurred in Zaire.[183] Although it was assumed that the two outbreaks were connected, scientists later realized that they were caused by two distinct ebolaviruses, SUDV and EBOV.[172] The Zaire outbreak was contained with the help of the World Health Organization and transport from the Congolese air force, by quarantining villagers, sterilizing medical equipment, and providing protective clothing.

# Society and culture

*See also: Cultural effects of the Ebola crisis*

## Weaponization

*Ebolavirus* is classified as a biosafety level 4 agent, as well as a Category A bioterrorism agent by the Centers for Disease Control and Prevention.[76][184] It has the potential to be weaponized for use in biological warfare,[185][186] and was investigated by Biopreparat for such use, but might be difficult to prepare as a weapon of mass destruction because the virus becomes ineffective quickly in open air.[187] Fake emails pretending to be Ebola information from the WHO or the Mexican Government have in 2014 been misused to spread computer malware.[188] The BBC reported in 2015 that, "North Korean state media has suggested the disease was created by the US military as a biological weapon."[189]

## Literature

Richard Preston's 1995 best-selling book, *The Hot Zone*, dramatized the Ebola outbreak in Reston, Virginia.[190]

William Close's 1995 *Ebola: A Documentary Novel of Its First Explosion* and 2002 *Ebola: Through the Eyes of the People* focused on individuals' reactions to the 1976 Ebola outbreak in Zaire.[191]

Tom Clancy's 1996 novel, *Executive Orders*, involves a Middle Eastern terrorist attack on the United States using an airborne form of a deadly Ebola virus strain named "Ebola Mayinga" (see Mayinga N'Seka).[192][193]

As the Ebola virus epidemic in West Africa developed in 2014, a number of popular self-published and well-reviewed books containing sensational and misleading information about the disease appeared in electronic and printed formats. The authors of some such books admitted that they lacked medical credentials and were not technically qualified to give medical advice. The World Health Organization and the United Nations stated that such misinformation had contributed to the spread of the disease.[194]

# Other animals

## Wild animals

Ebola has a high mortality among primates.[113] Frequent outbreaks of Ebola may have resulted in the deaths of 5,000 gorillas.[195] Outbreaks of Ebola may have been responsible for an 88 percent decline in

tracking indices of observed chimpanzee populations in 420 square kilometer Lossi Sanctuary between 2002 and 2003.[196] Transmission among chimpanzees through meat consumption constitutes a significant risk factor, whereas contact between the animals, such as touching dead bodies and grooming, is not.[197]

Recovered carcasses from gorillas contain multiple Ebola virus strains, which suggest multiple introductions of the virus. Bodies decompose quickly and carcasses are not infectious after 3 to 4 days. Contact between gorilla groups is rare, suggesting transmission among gorilla groups is unlikely, and that outbreaks result from transmission between viral reservoir and animal populations.[196]

### Domestic animals

In 2012 it was demonstrated that the virus can travel without contact from pigs to nonhuman primates, although the same study failed to achieve transmission in that manner between primates.[68][198]

Dogs may become infected with EBOV but not develop symptoms. Dogs in some parts of Africa scavenge for food, and they sometimes eat EBOV-infected animals and also the corpses of humans. A 2005 survey of dogs during an EBOV outbreak found that although they remain asymptomatic, about 32 percent of dogs closest to an outbreak showed a seroprevalence for EBOV versus 9 percent of those farther away.[199] The authors concluded that there were "potential implications for preventing and controlling human outbreaks."

### Reston virus

*For more about the outbreak in Virginia, US, see Reston virus.*

In late 1989, Hazelton Research Products' Reston Quarantine Unit in Reston, Virginia, suffered an outbreak of fatal illness amongst certain lab monkeys. This lab outbreak was initially diagnosed as simian hemorrhagic fever virus (SHFV) and occurred amongst a shipment of crab-eating macaque monkeys imported from the Philippines. Hazelton's veterinary pathologist sent tissue samples from dead animals to the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick, Maryland, where an ELISA test indicated the antibodies present in the tissue were a response to Ebola virus and not SHFV.[200] An electron microscopist from USAMRIID discovered filoviruses similar in appearance to Ebola in the tissue samples sent from Hazelton Research Products' Reston Quarantine Unit.[201]

A US Army team headquartered at USAMRIID euthanized the surviving monkeys, and brought all the monkeys to Ft. Detrick for study by the Army's veterinary pathologists and virologists, and eventual disposal under safe conditions.[200] Blood samples were taken from 178 animal handlers during the incident.[202] Of those, six animal handlers eventually seroconverted, including one who had cut himself with a bloody scalpel.[77][203] Despite its status as a Level 4 organism and its apparent pathogenicity in monkeys, when the handlers did not become ill, the CDC concluded that the virus had a very low pathogenicity to humans.[203][204]

The Philippines and the United States had no previous cases of Ebola infection, and upon further isolation, researchers concluded it was another strain of Ebola, or a new filovirus of Asian origin, which they named *Reston ebolavirus* (RESTV) after the location of the incident.[200] Reston virus (RESTV) can be transmitted to pigs.[68] Since the initial outbreak it has since been found in nonhuman primates in Pennsylvania, Texas, and Italy,[205] where the virus had infected pigs.[206] According to the WHO, routine cleaning and disinfection of pig (or monkey) farms with sodium hypochlorite or detergents should be effective in inactivating the *Reston ebolavirus*. Pigs that have been infected with RESTV tend to show symptoms of the disease.

## Research

### Treatments

*Main article: Ebola virus disease treatment research*

As of July 2015, there is no medication which has been proven to be safe and effective in treating Ebola. By the time the Ebola virus epidemic in West Africa began in 2013, there were at least nine different candidate treatments. Several trials were conducted in late 2014 and early 2015, but some were abandoned due to lack of efficacy or lack of people to study.[*citation needed*]

Researchers looking at slides of cultures of cells that make monoclonal antibodies. These are grown in a lab and the researchers are analyzing the products to select the most promising.

## Vaccines

*Main article: Ebola vaccine*

Many Ebola vaccine candidates had been developed in the decade prior to 2014,[207] but as of November 2014, none had been approved for use in humans in the United States.[208][209][210] In December 2016, Ebola virus disease was found to be 70–100% prevented by rVSV-ZEBOV vaccine, making it the first proven vaccine against the disease.[211][212][213]

## Diagnostic tests

One issue which hinders control of Ebola is that diagnostic tests which are currently available require specialized equipment and highly trained personnel. Since there are few suitable testing centers in West Africa, this leads to delay in diagnosis. In December 2014, a conference in Geneva will aim to work out which diagnostic tools could be to identify Ebola reliably and more quickly. The meeting, convened by the WHO and the non-profit Foundation for Innovative New Diagnostics, seeks to identify tests that can be used by untrained staff, do not require electricity or can run on batteries or solar power and use reagents that can withstand temperatures of 40 °C.[214]

On 29 November 2014, a new 15-minute Ebola test was reported that if successful, "not only gives patients a better chance of survival, but it prevents transmission of the virus to other people." The new equipment, about the size of a laptop and solar-powered, allows testing to be done in remote areas. The equipment is currently being tested in Guinea.[215]

On 29 December 2014, the FDA approved LightMix (R) Ebola Zaire rRT-PCR Test on patients with symptoms of Ebola. The report indicates it could help health care authorities around the world.[216]

# See also

- List of human disease case fatality rates

# References

### Notes


1. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z aa* "Ebola virus disease Fact sheet No. 103". *World Health Organization*. September 2014.
2. ^ *a b c* Ruzek, edited by Sunit K. Singh, Daniel (2014). *Viral hemorrhagic fevers*. Boca Raton: CRC Press, Taylor & Francis Group. p. 444. ISBN 9781439884294.
3. ^ *a b* "2014 Ebola Virus Disease (EVD) outbreak in West Africa". WHO. 21 April 2014. Retrieved 3 August 2014.
4. ^ *a b c d* "Preliminary study finds that Ebola virus fragments can persist in the semen of some survivors for at least nine months". CDC. 14 October 2015.
5. ^ *a b* "Recommendations for Breastfeeding/Infant Feeding in the Context of Ebola". *cdc.gov*. 19 September 2014. Retrieved 26 October 2014.
6. ^ "Guidance for Safe Handling of Human Remains of Ebola Patients in U. S. Hospitals and Mortuaries". Retrieved 10 October 2014.
7. ^ "Ebola virus disease, Fact sheet N°103, Updated September 2014". World Health Organization. September

2014. Retrieved 15 December 2014.
8. ^ a b "Ebola Viral Disease Outbreak — West Africa, 2014". *CDC*. 27 June 2014. Retrieved 26 June 2014.
9. ^ a b "Ebola data and statistics". World Health Organisation. Retrieved 9 June 2016.
10. ^ a b "CDC urges all US residents to avoid nonessential travel to Liberia, Guinea and Sierra Leone because of an unprecedented outbreak of Ebola.". *CDC*. 31 July 2014. Retrieved 2 August 2014.
11. ^ a b "2014 Ebola Outbreak in West Africa". *CDC*. 4 August 2014. Retrieved 5 August 2014.
12. ^ a b "Statement on the 9th meeting of the IHR Emergency Committee regarding the Ebola outbreak in West Africa". *WHO*. 29 March 2016. Retrieved 30 March 2016.
13. ^ a b "Ebola Hemorrhagic Fever Signs and Symptoms". *CDC*. 28 January 2014. Retrieved 2 August 2014.
14. ^ a b c d e f g Goeijenbier M, van Kampen JJ, Reusken CB, Koopmans MP, van Gorp EC (November 2014). "Ebola virus disease: a review on epidemiology, symptoms, treatment and pathogenesis". *Neth J Med*. **72** (9): 442–8. PMID 25387613.
15. ^ Charles N. Haas (14 October 2014). "On the Quarantine Period for Ebola Virus". *PLOS Currents Outbreaks*. doi:10.1371/currents.outbreaks.2ab4b76ba7263ff0f084766e43abbd89.
16. ^ a b c Gatherer D (August 2014). "The 2014 Ebola virus disease outbreak in West Africa". *J Gen Virol*. **95** (Pt 8): 1619–1624. doi:10.1099/vir.0.067199-0. PMID 24795448.
17. ^ a b c d e f Magill, Alan (2013). *Hunter's tropical medicine and emerging infectious diseases.* (9th ed.). New York: Saunders. p. 332. ISBN 9781416043904.
18. ^ a b c d Hoenen T, Groseth A, Falzarano D, Feldmann H (May 2006). "Ebola virus: unravelling pathogenesis to combat a deadly disease". *Trends in Molecular Medicine*. **12** (5): 206–215. doi:10.1016/j.molmed.2006.03.006. PMID 16616875.
19. ^ Simpson DIH (1977). "Marburg and Ebola virus infections: a guide for their diagnosis, management, and control" (PDF). *WHO Offset Publication No. 36*. p. 10f.
20. ^ "Ebola Virus, Clinical Presentation". Medscape. Retrieved 30 July 2012.
21. ^ "Appendix A: Disease-Specific Chapters" (PDF). *Chapter: Hemorrhagic fevers caused by: i) Ebola virus and ii) Marburg virus and iii) Other viral causes including bunyaviruses, arenaviruses, and flaviviruses*. Ministry of Health and Long-Term Care. Retrieved 9 October 2014.
22. ^ a b c d e f g Feldmann H, Geisbert TW (March 2011). "Ebola haemorrhagic fever". *Lancet*. **377** (9768): 849–62. doi:10.1016/S0140-6736(10)60667-8. PMC 3406178. PMID 21084112.
23. ^ Fisher-Hoch SP, Platt GS, Neild GH, Southee T, Baskerville A, Raymond RT, Lloyd G, Simpson DI (November 1985). "Pathophysiology of shock and hemorrhage in a fulminating viral infection (Ebola)". *J. Infect. Dis.* **152** (5): 887–894. doi:10.1093/infdis/152.5.887. PMID 4045253.
24. ^ a b Tosh PK, Sampathkumar P (December 2014). "What Clinicians Should Know About the 2014 Ebola Outbreak". *Mayo Clin Proc*. **89** (12): 1710–17. doi:10.1016/j.mayocp.2014.10.010. PMID 25467644.
25. ^ "An emergency within an emergency: caring for Ebola survivors". *World Health Organization*. 7 August 2015. Retrieved 12 August 2015.
26. ^ a b c d "Q&A on Transmission, Ebola". *CDC*. September 2014. Retrieved 3 October 2014.
27. ^ a b c Hoenen T, Groseth A, Feldmann H (July 2012). "Current Ebola vaccines". *Expert Opin Biol Ther*. **12** (7): 859–72. doi:10.1517/14712598.2012.685152. PMC 3422127. PMID 22559078.
28. ^ Kuhn JH, Becker S, Ebihara H, Geisbert TW, Johnson KM, Kawaoka Y, Lipkin WI, Negredo AI, Netesov SV, Nichol ST, Palacios G, Peters CJ, Tenorio A, Volchkov VE, Jahrling PB (December 2010). "Proposal for a revised taxonomy of the family Filoviridae: Classification, names of taxa and viruses, and virus abbreviations". *Archives of Virology*. **155** (12): 2083–103. doi:10.1007/s00705-010-0814-x. PMC 3074192. PMID 21046175.
29. ^ Spickler, Anna. "Ebolavirus and Marburgvirus Infections" (PDF).
30. ^ "About Ebola Virus Disease". *CDC*. Retrieved 18 October 2014.
31. ^ Pringle, C. R. (2005). "Order Mononegavirales". In Fauquet, C. M.; Mayo, M. A.; Maniloff, J.; Desselberger, U.; Ball, L. A. *Virus Taxonomy – Eighth Report of the International Committee on Taxonomy of Viruses*. San Diego, US: Elsevier/Academic Press. pp. 609–614. ISBN 0-12-370200-3.
32. ^ a b Stahelin RV (June 2014). "Membrane binding and bending in Ebola VP40 assembly and egress". *Front Microbiol*. **2014** (5): 300. doi:10.3389/fmicb.2014.00300. PMC 4061899. PMID 24995005.
33. ^ Ascenzi P, Bocedi A, Heptonstall J, Capobianchi MR, Di Caro A, Mastrangelo E, Bolognesi M, Ippolito G (June 2008). "Ebolavirus and Marburgvirus: insight the Filoviridae family". *Mol Aspects Med*. **29** (3): 151–85. doi:10.1016/j.mam.2007.09.005. PMID 18063023.
34. ^ a b c d Chippaux JP (October 2014). "Outbreaks of Ebola virus disease in Africa: the beginnings of a tragic saga". *J Venom Anim Toxins Incl Trop Dis*. **20** (1): 44. doi:10.1186/1678-9199-20-44. PMC 4197285.

PMID 25320574.
35. ^ a b c d Misasi J, Sullivan NJ (October 2014). "Camouflage and Misdirection: The Full-On Assault of Ebola Virus Disease". *Cell*. **159** (3): 477–86. doi:10.1016/j.cell.2014.10.006. PMID 25417101.
36. ^ a b c d e f g h Kühl A, Pöhlmann S (September 2012). "How Ebola virus counters the interferon system". *Zoonoses Public Health*. **59** (Supplement 2): 116–31. doi:10.1111/j.1863-2378.2012.01454.x. PMID 22958256.
37. ^ a b Olejnik J, Ryabchikova E, Corley RB, Mühlberger E (August 2011). "Intracellular events and cell fate in filovirus infection". *Viruses*. **3** (8): 1501–31. doi:10.3390/v3081501. PMC 3172725. PMID 21927676.
38. ^ Feldmann, H.; Geisbert, T. W.; Jahrling, P. B.; Klenk, H.-D.; Netesov, S. V.; Peters, C. J.; Sanchez, A.; Swanepoel, R.; Volchkov, V. E. (2005). "Family Filoviridae". In Fauquet, C. M.; Mayo, M. A.; Maniloff, J.; Desselberger, U.; Ball, L. A. *Virus Taxonomy – Eighth Report of the International Committee on Taxonomy of Viruses*. San Diego, US: Elsevier/Academic Press. pp. 645–653. ISBN 0-12-370200-3.
39. ^ a b c d e f g h Funk DJ, Kumar A (November 2014). "Ebola virus disease: an update for anesthesiologists and intensivists". *Can J Anaesth*. **62** (1): 80–91. doi:10.1007/s12630-014-0257-z. PMID 25373801.
40. ^ "Ebola (Ebola Virus Disease) Transmission". *CDC*. 5 November 2014. Retrieved 7 November 2014.
41. ^ Drazen JM, Kanapathipillai R, Campion EW, Rubin EJ, Hammer SM, Morrissey S, Baden LR (November 2014). "Ebola and quarantine". *N Engl J Med*. **371** (21): 2029–30. doi:10.1056/NEJMe1413139. PMID 25347231.
42. ^ Donald G. McNeil Jr. (3 October 2014). "Ask Well: How Does Ebola Spread? How Long Can the Virus Survive?". *The New York Times*. Retrieved 24 October 2014.
43. ^ a b "How Ebola Is Spread" (PDF). Centers for Disease Control and Prevention (CDC). 1 November 2014.
44. ^ a b c d e f g "Transmission". *CDC*. 17 October 2014. Retrieved 18 October 2014.
45. ^ a b c d Chowell G, Nishiura H (October 2014). "Transmission dynamics and control of Ebola virus disease (EVD): a review". *BMC Med*. **12** (1): 196. doi:10.1186/s12916-014-0196-0. PMC 4207625. PMID 25300956.
46. ^ a b Osterholm, MT; Moore, KA; Kelley, NS; Brosseau, LM; Wong, G; Murphy, FA; Peters, CJ; LeDuc, JW; Russell, PK; Van Herp, M; Kapetshi, J; Muyembe, JJ; Ilunga, BK; Strong, JE; Grolla, A; Wolz, A; Kargbo, B; Kargbo, DK; Formenty, P; Sanders, DA; Kobinger, GP (19 February 2015). "Transmission of Ebola viruses: what we know and what we do not know.". *mBio*. **6** (2): e00137. doi:10.1128/mBio.00137-15. PMID 25698835.
47. ^ "Sexual transmission of the Ebola Virus : evidence and knowledge gaps". *who.int*. 4 April 2015. Retrieved 16 April 2015.
48. ^ Wu, Brian (2 May 2015). "Ebola Can Be Transmitted Through Sex". *Science Times*. Retrieved 3 May 2015.
49. ^ Moses J Soka, Mary J Choi, April Baller, Stephen White, Emerson Rogers, Lawrence J Purpura et al. (2016). "Prevention of sexual transmission of Ebola in Liberia through a national semen testing and counselling programme for survivors: an analysis of Ebola virus RNA results and behavioural data". *Lancet Global Health*. **4**: e736–e743. doi:10.1016/S2214-109X(16)30175-9.
50. ^ Varkey, JB; Shantha, JG; Crozier, I; Kraft, CS; Lyon, GM; Mehta, AK; Kumar, G; Smith, JR; Kainulainen, MH; Whitmer, S; Ströher, U; Uyeki, TM; Ribner, BS; Yeh, S (7 May 2015). "Persistence of Ebola Virus in Ocular Fluid during Convalescence.". *The New England Journal of Medicine*. **372**: 2423–7. doi:10.1056/NEJMoa1500306. PMID 25950269.
51. ^ a b "CDC Telebriefing on Ebola outbreak in West Africa". *CDC*. 28 July 2014. Retrieved 3 August 2014.
52. ^ a b "Air travel is low-risk for Ebola transmission". *WHO*. 14 August 2014.
53. ^ Chan M (September 2014). "Ebola virus disease in West Africa—no early end to the outbreak". *N Engl J Med*. **371** (13): 1183–5. doi:10.1056/NEJMp1409859. PMID 25140856.
54. ^ "Sierra Leone: a traditional healer and a funeral". *World Health Organization*. Retrieved 6 October 2014.
55. ^ Tiaji Salaam-Blyther (26 August 2014). "The 2014 Ebola Outbreak: International and U.S. Responses" (PDF). Retrieved 9 September 2014.
56. ^ Lashley, Felissa R.; Durham, Jerry D., eds. (2007). *Emerging infectious diseases trends and issues* (2nd ed.). New York: Springer. p. 141. ISBN 9780826103505.
57. ^ Alan J. Magill, G. Thomas Strickland, James H. Maguire, Edward T Ryan, Tom Solomon, eds. (2013). *Hunter's tropical medicine and emerging infectious disease* (9th ed.). London, New York: Elsevier. pp. 170–172. OCLC 822525408.
58. ^ "Questions and Answers on Ebola | Ebola Hemorrhagic Fever | CDC". *CDC*.
59. ^ a b "Ebola in Texas: Second Health Care Worker Tests Positive". 15 October 2014.
60. ^ Irving WL (August 1995). "Ebola virus transmission". *International Journal of Experimental Pathology*. **76** (4): 225–6. PMC 1997188. PMID 7547434.
61. ^ a b "Transmission of Ebola virus". *virology.ws*. 27 September 2014. Retrieved 22 January 2016.
62. ^ a b c Weingartl, HM; Embury-Hyatt, C; Nfon, C; Leung, A; Smith, G; Kobinger, G (2012). "Transmission of Ebola virus from pigs to non-human primates.". *Scientific Reports*. **2**: 811. doi:10.1038/srep00811. PMC 3498927.

PMID 23155478.
63. ^ "Risk of Exposure". *CDC*. 12 October 2014. Retrieved 18 October 2014.
64. ^ "FAO warns of fruit bat risk in West African Ebola epidemic". *fao.org*. 21 July 2014. Retrieved 22 October 2014.
65. ^ Williams E. "African monkey meat that could be behind the next HIV". *Health News – Health & Families*. The Independent. "25 people in Bakaklion, Cameroon killed due to eating of ape"
66. ^ *a b* "Ebolavirus – Pathogen Safety Data Sheets". Public Health Agency of Canada. Retrieved 22 August 2014.
67. ^ *a b* Gonzalez JP, Pourrut X, Leroy E (2007). "Wildlife and Emerging Zoonotic Diseases: The Biology, Circumstances and Consequences of Cross-Species Transmission". *Current Topics in Microbiology and Immunology*. Ebolavirus and other filoviruses. **315**: 363–387. doi:10.1007/978-3-540-70962-6_15. ISBN 978-3-540-70961-9. PMID 17848072.
68. ^ *a b c d e f* Weingartl HM, Nfon C, Kobinger G (May 2013). "Review of Ebola virus infections in domestic animals". *Dev Biol (Basel)*. **135**: 211–8. doi:10.1159/000178495. PMID 23689899.
69. ^ Laupland KB, Valiquette L (May 2014). "Ebola virus disease". *Can J Infect Dis Med Microbiol*. **25** (3): 128–9. PMC 4173971. PMID 25285105.
70. ^ *a b c* Pourrut X, Kumulungui B, Wittmann T, Moussavou G, Délicat A, Yaba P, Nkoghe D, Gonzalez JP, Leroy EM (June 2005). "The natural history of Ebola virus in Africa". *Microbes Infect*. **7** (7–8): 1005–14. doi:10.1016/j.micinf.2005.04.006. PMID 16002313.
71. ^ Swanepoel R, Leman PA, Burt FJ, Zachariades NA, Braack LE, Ksiazek TG, Rollin PE, Zaki SR, Peters CJ (October 1996). "Experimental inoculation of plants and animals with Ebola virus". *Emerging Infectious Diseases*. **2** (4): 321–325. doi:10.3201/eid0204.960407. ISSN 1080-6040. PMC 2639914. PMID 8969248.
72. ^ Leroy EM, Kumulungui B, Pourrut X, Rouquet P, Hassanin A, Yaba P, Délicat A, Paweska JT, Gonzalez JP, Swanepoel R (December 2005). "Fruit bats as reservoirs of Ebola virus". *Nature*. **438** (7068): 575–576. Bibcode:2005Natur.438..575L. doi:10.1038/438575a. PMID 16319873.
73. ^ Olival KJ, Islam A, Yu M, Anthony SJ, Epstein JH, Khan SA, Khan SU, Crameri G, Wang LF, Lipkin WI, Luby SP, Daszak P (February 2013). "Ebola virus antibodies in fruit bats, Bangladesh". *Emerging Infect Dis*. **19** (2): 270–3. doi:10.3201/eid1902.120524. PMC 3559038. PMID 23343532.
74. ^ Morvan JM, Deubel V, Gounon P, Nakouné E, Barrière P, Murri S, Perpète O, Selekon B, Coudrier D, Gautier-Hion A, Colyn M, Volehkov V (December 1999). "Identification of Ebola virus sequences present as RNA or DNA in organs of terrestrial small mammals of the Central African Republic". *Microbes and Infection*. **1** (14): 1193–1201. doi:10.1016/S1286-4579(99)00242-7. PMID 10580275.
75. ^ Groseth A, Feldmann H, Strong JE (September 2007). "The ecology of Ebola virus". *Trends Microbiol*. **15** (9): 408–16. doi:10.1016/j.tim.2007.08.001. PMID 17698361.
76. ^ *a b* Ansari AA (September 2014). "Clinical features and pathobiology of Ebolavirus infection". *J Autoimmun*. **55**: 1–9. doi:10.1016/j.jaut.2014.09.001. PMID 25260583.
77. ^ *a b* Smith, Tara (2005). *Ebola (Deadly Diseases and Epidemics)*. Chelsea House Publications. ISBN 0-7910-8505-8.
78. ^ *a b* Ramanan P, Shabman RS, Brown CS, Amarasinghe GK, Basler CF, Leung DW (September 2011). "Filoviral immune evasion mechanisms". *Viruses*. **3** (9): 1634–49. doi:10.3390/v3091634. PMC 3187693. PMID 21994800.
79. ^ Kortepeter MG, Bausch DG, Bray M (November 2011). "Basic clinical and laboratory features of filoviral hemorrhagic fever". *J Infect Dis*. **204** (Supplement 3): S810–6. doi:10.1093/infdis/jir299. PMID 21987756.
80. ^ Geisbert TW, Jahrling PB (December 1995). "Differentiation of filoviruses by electron microscopy". *Virus Res*. **39** (2–3): 129–50. doi:10.1016/0168-1702(95)00080-1. PMID 8837880.
81. ^ "Ebola Hemorrhagic Fever Diagnosis". *CDC*. 28 January 2014. Retrieved 3 August 2014.
82. ^ *a b* Grolla A, Lucht A, Dick D, Strong JE, Feldmann H (September 2005). "Laboratory diagnosis of Ebola and Marburg hemorrhagic fever". *Bull Soc Pathol Exot*. **98** (3): 205–9. PMID 16267962.
83. ^ "Liberia: New Ebola mobile lab speeds up diagnosis and improves care,". *WHO.int*. W.H.O. October 2014. Retrieved 26 October 2014.
84. ^ "First Antigen Rapid Test for Ebola through Emergency Assessment and Eligible for Procurement". *who.int*. Retrieved 20 February 2015.
85. ^ Longo, DL; Kasper, DL; Jameson, JL; Fauci, AS; Hauser, SL; Loscalzo, J, eds. (2012). "Chapter 197". *Harrison's Principles of Internal Medicine* (18th ed.). McGraw-Hill. ISBN 0-07-174889-X.
86. ^ "Viral Hemorrhagic Fever". *San Francisco Department of Public Health*. Communicable Disease Control and Prevention. Archived from the original on 20 April 2013. Retrieved 17 August 2014.
87. ^ Gear JH (May–June 1989). "Clinical aspects of African viral hemorrhagic fevers". *Rev Infect Dis*. **11** (Supplement 4): S777–82. doi:10.1093/clinids/11.supplement_4.s777. PMID 2665013.
88. ^ Gear JH, Ryan J, Rossouw E (February 1978). "A consideration of the diagnosis of dangerous infectious fevers in South Africa". *South African medical [Suid-Afrikaanse tydskrif vir geneeskunde]*. **53** (7): 235–237. PMID 565951.

89. ^ Bogomolov BP (1998). "Differential diagnosis of infectious diseases with hemorrhagic syndrome". *Terapevticheskii arkhiv*. **70** (4): 63–68. PMID 9612907.
90. ^ *a b c* "Ebola Hemorrhagic Fever Prevention". *CDC*. 31 July 2014. Retrieved 2 August 2014.
91. ^ *a b* "Guidance on Personal Protective Equipment To Be Used by Healthcare Workers During Management of Patients with Ebola Virus Disease in U.S. Hospitals, Including Procedures for Putting On (Donning) and Removing (Doffing)". *cdc.gov*. 20 October 2014. Retrieved 22 October 2014.
92. ^ *a b* C. J. Peters (December 1998). *Infection Control for Viral Haemorrhagic Fevers in the African Health Care Setting* (PDF). Centers for Disease Control and Prevention.
93. ^ Ebola medics 'better trained in Sierra Leone than Spain' The Telegraph, by Fiona Govan, 11 October 2014
94. ^ This Is How Ebola Patients Are Equipping Their Homes Time magazine, by Alexandra Sifferlin, 9 October 2014
95. ^ Nossiter and Kanter (10 October 2014). "Doctors Without Borders Evolves as It Forms the Vanguard in Ebola Fight". *The New York Times*. Retrieved 12 October 2014.
96. ^ "Infection Prevention and Control Guidance for Care of Patients with Suspected or Confirmed Filovirus Haemorrhagic Fever in Health-care Settings with Focus on Ebola" (PDF). *Infection Prevention and Control Guidance for Care of Patients with Suspected or Confirmed Filovirus Haemorrhagic Fever in Health-care Settings with Focus on Ebola*. WHO. August 2014. Retrieved 21 August 2014.
97. ^ "Ebola – 5 tips to avoid the deadly disease". Plan International. 6 September 2014.
98. ^ Rouquet P, Froment JM, Bermejo M, Kilbourn A, Karesh W, Reed P, Kumulungui B, Yaba P, Délicat A, Rollin PE, Leroy EM (February 2005). "Wild animal mortality monitoring and human Ebola outbreaks, Gabon and Republic of Congo, 2001–2003" (Free full text). *Emerging Infectious Diseases*. **11** (2): 283–290. doi:10.3201/eid1102.040533. ISSN 1080-6040. PMC 3320460. PMID 15752448.
99. ^ Centers for Disease Control and Prevention and World Health Organization (1998). *Infection Control for Viral Haemorrhagic Fevers in the African Health Care Setting* (PDF). Atlanta, Georgia, US: Centers for Disease Control and Prevention. Retrieved 8 February 2013.
100. ^ "Section 7: Use Safe Burial Practices" (PDF). *Information resources on Ebola virus disease*. World Health Organization. 1 June 2014.
101. ^ Blaine Harden (24 December 2000). "Ebola's Shadow". *The New York Times*. Retrieved 12 October 2014.
102. ^ Faye SL (September 2014). "How anthropologists help medics fight Ebola in Guinea". SciDev.Net. Retrieved 3 October 2014.
103. ^ "West Africa – Ebola virus disease Update: Travel and transport". *International travel and health*. World Health Organization.
104. ^ *a b c* "Monitoring Symptoms and Controlling Movement to Stop Spread of Ebola". cdc.gov. 27 October 2014.
105. ^ *a b* "Ebola: Control and Prevention". OSHA. Retrieved 9 November 2014.
106. ^ "About Quarantine and Isolation". *cdc.gov*. 28 August 2014. Retrieved 26 October 2014.
107. ^ Sompayrac, Lauren (2002). *How pathogenic viruses work* (3. print. ed.). Boston: Jones and Bartlett Publishers. p. 87. ISBN 9780763720827.
108. ^ Alazard-Dany N, Ottmann Terrangle M, Volchkov V (April 2006). "[Ebola and Marburg viruses: the humans strike back]". *Med Sci (Paris)* (in French). **22** (4): 405–10. doi:10.1051/medsci/2006224405. PMID 16597410.
109. ^ "Ebola virus disease update – west Africa". *who.int*. 19 August 2014. Retrieved 26 October 2014.
110. ^ Schultz, edited by Kristi Koenig, Carl (2009). *Koenig and Schultz's disaster medicine : comprehensive principles and practices*. Cambridge: Cambridge University Press. p. 209. ISBN 9780521873673.
111. ^ "Ebola 2014 — New Challenges, New Global Response and Responsibility". *NEJM*. New England Journal of Medicine. Retrieved 15 September 2014.
112. ^ "What is Contact Tracing?" (PDF). *CDC*. Centers for Disease Control. Retrieved 15 September 2014.
113. ^ *a b* Choi JH, Croyle MA (December 2013). "Emerging targets and novel approaches to Ebola virus prophylaxis and treatment". *BioDrugs*. **27** (6): 565–83. doi:10.1007/s40259-013-0046-1. PMC 3833964. PMID 23813435.
114. ^ "FDA warns consumers about fraudulent Ebola treatment products". Retrieved 20 August 2014.
115. ^ "Inspections, Compliance, Enforcement, and Criminal Investigations". *FDA*. Retrieved 9 October 2014.
116. ^ *a b c d e f* Clark DV, Jahrling PB, Lawler JV (September 2012). "Clinical management of filovirus-infected patients". *Viruses*. **4** (9): 1668–86. doi:10.3390/v4091668. PMC 3499825. PMID 23170178.
117. ^ "Ebola messages for the general public". *World Health Organization*. Retrieved 26 October 2014.
118. ^ "Annex 18. Transmission risk reduction of filoviruses in home-care settings" (PDF). *Ebola and Marburg virus disease epidemics: preparedness, alert, control, and evaluation Interim manual version 1.2 CHAPTER 7 ANNEXES*. Retrieved 26 October 2014.
119. ^ C.M. Fauquet (2005). *Virus taxonomy classification and nomenclature of viruses; 8th report of the International Committee on Taxonomy of Viruses*. Oxford: Elsevier/Academic Press. p. 648. ISBN 9780080575483.
120. ^ "More or Less behind the stats Ebola". *www.bbc.co.uk*. BBC World Service. Retrieved 8 October 2014.

121. ^ "Who, What, Why: How many people infected with ebola die?". *BBC News*. 9 August 2014.
122. ^ Wiwanitkit, S; Wiwanitkit, V (2015). "Ocular problem in Ebola virus infection: A short review.". *Saudi Journal of Ophthalmology*. **29** (3): 225–6. doi:10.1016/j.sjopt.2015.02.006. PMID 26155084.
123. ^ Varkey, Jay B.; Shantha, Jessica G.; Crozier, Ian; Kraft, Colleen S.; Lyon, G. Marshall; Mehta, Aneesh K.; Kumar, Gokul; Smith, Justine R.; Kainulainen, Markus H.; Whitmer, Shannon; Ströher, Ute; Uyeki, Timothy M.; Ribner, Bruce S.; Yeh, Steven (2015). "Persistence of Ebola Virus in Ocular Fluid during Convalescence". *New England Journal of Medicine*. **372** (25): 2423–2427. doi:10.1056/NEJMoa1500306. ISSN 0028-4793. PMID 25950269.
124. ^ Mackay, Ian M; Arden, Katherine E (2015). "Ebola virus in the semen of convalescent men". *The Lancet Infectious Diseases*. **15** (2): 149–150. doi:10.1016/S1473-3099(14)71033-3. ISSN 1473-3099.
125. ^ Rogstad, KE; Tunbridge, A (February 2015). "Ebola virus as a sexually transmitted infection.". *Current opinion in infectious diseases*. **28** (1): 83–5. doi:10.1097/qco.0000000000000135. PMID 25501666.
126. ^ Christie, A; Davies-Wayne, GJ; Cordier-Lasalle, T; Blackley, DJ; Laney, AS; Williams, DE; Shinde, SA; Badio, M; Lo, T; Mate, SE; Ladner, JT; Wiley, MR; Kugelman, JR; Palacios, G; Holbrook, MR; Janosko, KB; de Wit, E; van Doremalen, N; Munster, VJ; Pettitt, J; Schoepp, RJ; Verhenne, L; Evlampidou, I; Kollie, KK; Sieh, SB; Gasasira, A; Bolay, F; Kateh, FN; Nyenswah, TG; De Cock, KM; Centers for Disease Control and Prevention, (CDC) (8 May 2015). "Possible sexual transmission of Ebola virus - Liberia, 2015.". *MMWR. Morbidity and mortality weekly report*. **64** (17): 479–81. PMID 25950255.
127. ^ Sprecher, A (14 October 2015). "Handle Survivors with Care.". *The New England Journal of Medicine*: 151014140056007. doi:10.1056/NEJMe1512928. PMID 26465064.
128. ^ "Neuro complications cited in UK nurse's Ebola case". Retrieved 19 October 2015.
129. ^ Scottr, Janet et. al (April 2016). "Post-Ebola Syndrome, Sierra Leone". *Emerg Infect Dis*. **22** (4): 641–646. doi:10.3201/eid2204.151302. PMC 4806950. PMID 26983037.
130. ^ *a b* "Guidelines for Evaluation of US Patients Suspected of Having Ebola Virus Disease". *CDC*. 1 August 2014. Retrieved 5 August 2014.
131. ^ Baize S, Pannetier D, Oestereich L, Rieger T, Koivogui L, Magassouba N, Soropogui B, Sow MS, Keïta S, De Clerck H, Tiffany A, Dominguez G, Loua M, Traoré A, Kolié M, Malano ER, Heleze E, Bocquin A, Mély S, Raoul H, Caro V, Cadar D, Gabriel M, Pahlmann M, Tappe D, Schmidt-Chanasit J, Impouma B, Diallo AK, Formenty P, Van Herp M, Günther S (October 2014). "Emergence of Zaire Ebola Virus Disease in Guinea". *New England Journal of Medicine*. **371** (15): 1418–25. doi:10.1056/NEJMoa1404505. PMID 24738640.
132. ^ "The first cases of this Ebola outbreak traced by WHO" (png). *who.int*. WHO. 2014.
133. ^ "WHO raises global alarm over Ebola outbreak". *CBS*. Retrieved 2 August 2014.
134. ^ "In Liberia's Ebola-Stricken Villages, Residents Face 'Stark' Choices". *n Liberia's Ebola-Stricken Villages, Residents Face 'Stark' Choices*. Common Dreams. 18 August 2014. Retrieved 20 August 2014.
135. ^ Media centre (26 September 2014). "Experimental therapies: growing interest in the use of whole blood or plasma from recovered Ebola patients (convalescent therapies)". World Health Organization. Retrieved 28 September 2014.
136. ^ "2014 Ebola Outbreak in West Africa – Case Counts". *2014 Ebola Outbreak in West Africa*. CDC (Centers for Disease Control and Prevention). 2014.
137. ^ "Ebola Response Roadmap Situation Report" (PDF). World Health Organization. 1 October 2014.
138. ^ "Unprecedented number of medical staff infected with Ebola". *WHO*. 25 August 2014. Retrieved 29 August 2014.
139. ^ "Ebola response roadmap - Situation report" (PDF). World Health Organization. 10 December 2014. Retrieved 11 December 2014.
140. ^ "Ebola Situation Report - 28 January 2015". *Ebola*. WHO. 28 January 2015. Retrieved 5 February 2015.
141. ^ "Ebola Situation Report" (PDF). WHO. 8 April 2015. Retrieved 14 April 2015.
142. ^ Thomson Reuters (29 December 2015). "Ebola gone from Guinea". *CBC News - Health*. CBC/Radio Canada. Retrieved 30 December 2015.
143. ^ no by-line.-->. "UN declares end to Ebola virus transmission in Guinea; first time all three host countries free". *UN News Center*. United Nations. Retrieved 30 December 2015.
144. ^ "New Ebola case in Sierra Leone. WHO continues to stress risk of more flare-ups". *WHO*. 15 January 2016. Retrieved 25 January 2016.
145. ^ "How Many Ebola Patients Have Been Treated Outside of Africa?".
146. ^ "Second US Ebola diagnosis 'deeply concerning', admits CDC chief". Archived from the original on 14 October 2014.archive-url=https://web.archive.org/web/20141014175544/http://www.msn.com/en-us/news/us/second-us-ebola-diagnosis-deeply-concerning-admits-cdc-chief/ar-BB8UFz0%7Carchive-date=14 October 2013
147. ^ "Ebola crisis: Tests show Spanish nurse Teresa Romero no longer has the virus". ABC News. 20 October 2014.
148. ^ "Thomas Eric Duncan: First Ebola death in U.S.".
149. ^ Fernandez, Manny (12 October 2014). "Texas Health Worker Tests Positive for Ebola". *New York Times*.

Retrieved 12 October 2014.
150. ^ "Ebola in Texas: Second Health Care Worker Tests Positive".
151. ^ a b "Cases of Ebola Diagnosed in the United States".
152. ^ Sanchez, Ray; Prokupecz, Shimon (23 October 2014). "N.Y. doctor positive for Ebola had no symptoms until Thursday, officials say". CNN. Retrieved 23 October 2014.
153. ^ "CDC reports potential Ebola exposure in Atlanta lab". *washingtonpost.com*. Retrieved 25 December 2014.
154. ^ "Ebola case confirmed in Glasgow hospital". *BBC News*. 29 December 2014.
155. ^ "Ebola nurse Pauline Cafferkey transferred to London unit". BBC News. 30 December 2014.
156. ^ Formenty P, Libama F, Epelboin A, Allarangar Y, Leroy E, Moudzeo H, Tarangonia P, Molamou A, Lenzi M, Ait-Ikhlef K, Hewlett B, Roth C, Grein T (2003). "[Outbreak of Ebola hemorrhagic fever in the Republic of the Congo, 2003: a new strategy?]". *Med Trop (Mars)* (in French). **63** (3): 291–5. PMID 14579469.
157. ^ "Russian Scientist Dies in Ebola Accident at Former Weapons Lab". *The New York Times*. Retrieved 12 October 2014.
158. ^ "Ebola outbreak in Congo". *CBC.ca*. CBC/Radio-Canada. 12 September 2007.
159. ^ a b "Mystery DR Congo fever kills 100". *BBC News*. 31 August 2007.
160. ^ "Ebola Outbreak Confirmed in Congo". *NewScientist.com*. 11 September 2007.
161. ^ "Uganda: Deadly Ebola Outbreak Confirmed – UN". *UN News Service*. 30 November 2007. Retrieved 25 February 2008.
162. ^ "DRC Confirms Ebola Outbreak". Voanews.com. Retrieved 15 April 2013.
163. ^ "WHO | Ebola outbreak in Democratic Republic of Congo". Who.int. 17 August 2012. Retrieved 15 April 2013.
164. ^ "WHO | Ebola outbreak in Democratic Republic of Congo – update". Who.int. 21 August 2012. Retrieved 15 April 2013.
165. ^ Castillo M (2012). "Ebola virus claims 31 lives in Democratic Republic of the Congo". United States: CBS News. Retrieved 14 September 2012.
166. ^ "Virological Analysis: no link between Ebola outbreaks in west Africa and Democratic Republic of Congo". World Health Organization. 2 September 2014.
167. ^ "Congo declares its Ebola outbreak over". reuters. 15 November 2014. Retrieved 15 November 2014.
168. ^ "Democratic Republic of the Congo: The country that knows how to beat Ebola". World Health Organization. December 2014. Retrieved 26 February 2015.
169. ^ Peterson AT, Bauer JT, Mills JN (2004). "Ecologic and Geographic Distribution of Filovirus Disease". *Emerging Infectious Diseases*. **10** (1): 40–47. doi:10.3201/eid1001.030125. PMC 3322747. PMID 15078595.
170. ^ a b "Ebola haemorrhagic fever in Sudan, 1976" (PDF).
171. ^ Hewlett, Barry; Hewlett, Bonnie (2007). *Ebola, Culture and Politics: The Anthropology of an Emerging Disease*. Cengage Learning. p. 103. ISBN 1111797315. Retrieved 31 July 2014.
172. ^ a b Feldmann H, Jones S, Klenk HD, Schnittler HJ (August 2003). "Ebola virus: from discovery to vaccine". *Nature Reviews. Immunology*. **3** (8): 677–85. doi:10.1038/nri1154. PMID 12974482.
173. ^ a b "Ebola haemorrhagic fever in Zaire, 1976" (PDF). *Bull. World Health Organ*. **56** (2): 271–93. 1978. PMC 2395567. PMID 307456.
174. ^ Centers for Disease Control Prevention (CDC) (1995). "Outbreak of Ebola Viral Hemorrhagic Fever – Zaire, 1995". *Morbidity and Mortality Weekly Report*. **44** (19): 381–2. PMID 7739512.
175. ^ Elezra M. "Ebola: The Truth Behind The Outbreak (Video) I". *Mabalo Lokela Archives – Political Mol*.
176. ^ a b Stimola A (2011). *Ebola* (1st ed.). New York: Rosen Pub. pp. 31, 52. ISBN 978-1435894334.
177. ^ Piot P, Marshall R (2012). *No time to lose: a life in pursuit of deadly viruses* (1st ed.). New York: W.W. Norton & Co. pp. 30, 90. ISBN 978-0393063165.
178. ^ Peter Piot (11 August 2014). "Part one: A virologist's tale of Africa's first encounter with Ebola". *ScienceInsider*.Free access
179. ^ Peter Piot (13 August 2014). "Part two: A virologist's tale of Africa's first encounter with Ebola". *ScienceInsider*.Free access
180. ^ Bardi, Jason Socrates. "Death Called a River". *The Scripps Research Institute*. Retrieved 9 October 2014.
181. ^ Preston, Richard (20 July 1995). *The Hot Zone*. Anchor Books (Random House). p. 117. "Karl Johnson named it Ebola"
182. ^ Bredow, Rafaela von; Hackenbroch, Veronika (4 October 2014). "'In 1976 I Discovered Ebola – Now I Fear an Unimaginable Tragedy'". *The Observer*. Guardian Media Group.
183. ^ King JW (2 April 2008). "Ebola Virus". *eMedicine*. WebMD. Retrieved 6 October 2008.
184. ^ MacNeil A, Rollin PE (June 2012). "Ebola and Marburg hemorrhagic fevers: neglected tropical diseases?". *PLoS Negl Trop Dis*. **6** (6): e1546. doi:10.1371/journal.pntd.0001546. PMC 3385614. PMID 22761967.
185. ^ Borio L, Inglesby T, Peters CJ, Schmaljohn AL, Hughes JM, Jahrling PB, Ksiazek T, Johnson KM, Meyerhoff A,

O'Toole T, Ascher MS, Bartlett J, Breman JG, Eitzen EM, Hamburg M, Hauer J, Henderson DA, Johnson RT, Kwik G, Layton M, Lillibridge S, Nabel GJ, Osterholm MT, Perl TM, Russell P, Tonat K (May 2002). "Hemorrhagic fever viruses as biological weapons: medical and public health management". *Journal of the American Medical Association*. **287** (18): 2391–405. doi:10.1001/jama.287.18.2391. PMID 11988060.

186. ^ Salvaggio MR, Baddley JW (July 2004). "Other viral bioweapons: Ebola and Marburg hemorrhagic fever". *Dermatologic clinics*. **22** (3): 291–302, vi. doi:10.1016/j.det.2004.03.003. PMID 15207310.
187. ^ Zubray, Geoffrey (2013). *Agents of Bioterrorism: Pathogens and Their Weaponization*. New York, NY, USA: Columbia University Press. pp. 73–74. ISBN 9780231518130.
188. ^ "Malicious Ebola-Themed Emails Are on the Rise". *NYTimes.com*. N.Y.Times. 24 October 2014. Retrieved 26 October 2014.
189. ^ "North Korea bans foreigners from Pyongyang marathon over Ebola". *BBC News*. BBC News. 23 February 2015. Retrieved 23 February 2015.
190. ^ (1) Preston, Richard (1995). *The Hot Zone, A Terrifying True Story*. Anchor Books. ISBN 0-385-47956-5. OCLC 32052009.
(2) "Best Sellers: June 4, 1995". *The New York Times Book Review*. New York: The New York Times. 4 June 1995. Retrieved 10 September 2014.
(3) "About The Hot Zone". Random House. Retrieved 10 September 2014.archive-url=https://web.archive.org/web/20141006105554/http://www.randomhouse.com/features/richardpreston/bookshelf/hz.html%7Carchive-date=6 October 2014
191. ^ (1) Close, William T. (1995). *Ebola: A Documentary Novel of Its First Explosion*. New York: Ivy Books. ISBN 0804114323. OCLC 32753758.
(2) Grove, Ryan (2 June 2006). "More about the people than the virus". *Review of Close, William T.,* Ebola: A Documentary Novel of Its First Explosion. Amazon.com. Retrieved 17 September 2014.
(3) Close, William T. (2002). *Ebola: Through the Eyes of the People*. Marbleton, Wyoming: Meadowlark Springs Productions. ISBN 0970337116. OCLC 49193962.
(4) Pink, Brenda (24 June 2008). "A fascinating perspective". *Review of Close, William T.,* Ebola: Through the Eyes of the People. Amazon.com. Retrieved 17 September 2014.
192. ^ Clancy, Tom (1996). *Executive Orders*. New York: Putnam. ISBN 0399142185. OCLC 34878804.
193. ^ Stone, Oliver (2 September 1996). "Who's That in the Oval Office?". *Books News & Reviews*. The New York Times Company. Archived from the original on 10 April 2009. Retrieved 10 September 2014.
194. ^ Dewey, Caitlin (2 October 2014). "Popular on Amazon: Wildly misleading self-published books about Ebola, by random people without medical degrees". The Washington Post. Retrieved 27 October 2014.
195. ^ *Ebola 'kills over 5,000 gorillas'*. BBC. 8 December 2006. Retrieved 31 May 2009.
196. ^ [a] [b] Leroy EM, Rouquet P, Formenty P, Souquière S, Kilbourne A, Froment JM, Bermejo M, Smit S, Karesh W, Swanepoel R, Zaki SR, Rollin PE (January 2004). "Multiple Ebola virus transmission events and rapid decline of central African wildlife". *Science*. **303** (5656): 387–390. Bibcode:2004Sci...303..387L. doi:10.1126/science.1092528. PMID 14726594.
197. ^ Formenty P, Boesch C, Wyers M, Steiner C, Donati F, Dind F, Walker F, Le Guenno B (February 1999). "Ebola virus outbreak among wild chimpanzees living in a rain forest of Côte d'Ivoire". *The Journal of Infectious Diseases*. 179. Suppl 1 (s1): S120–S126. doi:10.1086/514296. PMID 9988175.
198. ^ Weingartl HM, Embury-Hyatt C, Nfon C, Leung A, Smith G, Kobinger G (November 2012). "Transmission of Ebola virus from pigs to non-human primates". *Sci Rep*. **2**: 811. doi:10.1038/srep00811. PMC 3498927. PMID 23155478.
199. ^ Allela L, Boury O, Pouillot R, Délicat A, Yaba P, Kumulungui B, Rouquet P, Gonzalez JP, Leroy EM (March 2005). "Ebola virus antibody prevalence in dogs and human risk". *Emerging Infect. Dis.* **11** (3): 385–90. doi:10.3201/eid1103.040981. PMC 3298261. PMID 15757552.
200. ^ [a] [b] [c] Preston, Richard (1994). *The Hot Zone*. New York: Random House. p. 300. ISBN 978-0679437840.
201. ^ McCormick & Fisher-Hoch 1999, pp. 277–279
202. ^ Waterman, Tara (1999). *Ebola Reston Outbreaks*. Stanford University. Retrieved 2 August 2008.
203. ^ [a] [b] McCormick & Fisher-Hoch 1999, pp. 298–299
204. ^ McCormick & Fisher-Hoch 1999, p. 300
205. ^ "Outbreaks Chronology: Ebola Virus Disease". *cdc.gov*. Retrieved 26 October 2014.
206. ^ McNeil Jr, Donald G. (24 January 2009). "Pig-to-Human Ebola Case Suspected in Philippines". New York Times. Retrieved 26 January 2009.
207. ^ Richardson JS, Dekker JD, Croyle MA, Kobinger GP (June 2010). "Recent advances in *Ebolavirus* vaccine development". *Human Vaccines (open access)*. **6** (6): 439–49. doi:10.4161/hv.6.6.11097. PMID 20671437.
208. ^ "Statement on the WHO Consultation on potential Ebola therapies and vaccines". *WHO*. 5 September 2014. Retrieved 1 October 2014.

209. ^ "2014 Ebola Outbreak in West Africa". Retrieved 1 October 2014.
210. ^ Alison P. Galvani with three others (21 August 2014). "Ebola Vaccination: If Not Now, When?". *Annals of Internal Medicine*. **161** (10): 749–50. doi:10.7326/M14-1904. PMC 4316820. PMID 25141813.
211. ^ Geisbert, Thomas W (December 2016). "First Ebola virus vaccine to protect human beings?". *The Lancet*. doi:10.1016/S0140-6736(16)32618-6.
212. ^ Henao-Restrepo,Ana Maria; et al. (22 December 2016). "Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)". *The Lancet*. doi:10.1016/S0140-6736(16)32621-6. Retrieved 27 December 2016.
213. ^ Berlinger, Joshua (22 December 2016). "Ebola vaccine gives 100% protection, study finds". *CNN*. Retrieved 27 December 2016.
214. ^ "Ebola Experts Seek to Expand Testing". Scientific American. Retrieved 11 December 2014.
215. ^ "Ebola outbreak: New 15-minute test offers hope for thousands". *The Independent*. Retrieved 1 December 2014.
216. ^ Marta Falconi (29 December 2014). "Roche Secures Emergency Approval by U.S. Regulators for Ebola Test". *WSJ*. Retrieved 29 December 2014.


- *The article uses public domain text from the CDC as cited.*

### Bibliography


- Center For Disease Control; Francois Wilson (2014). *CDC Guidance on Ebola Virus (EVD): 2014 Edition*. International Publications Media Group. ISBN 978-1-63267-011-3.
- *Ebola Virus: New Insights for the Healthcare Professional: 2011 Edition: ScholarlyPaper*. Scholarly Editions. 2012. ISBN 978-1-4649-1493-5.
- Klenk, Hans-Dieter (January 1999). *Marburg and Ebola Viruses (Current Topics in Microbiology and Immunology)*. Berlin: Springer-Verlag Telos. ISBN 978-3-540-64729-4.
- Klenk, Hans-Dieter; Feldmann, Heinz (2004). *Ebola and Marburg viruses: molecular and cellular biology* (Limited preview). Wymondham, Norfolk, UK: Horizon Bioscience. ISBN 978-0-9545232-3-7.
- Kuhn, Jens H. (2008). *Filoviruses: A Compendium of 40 Years of Epidemiological, Clinical, and Laboratory Studies. Archives of Virology Supplement, vol. 20* (Limited preview). Vienna: SpringerWienNewYork. ISBN 978-3-211-20670-6.
- McCormick, Joseph; Fisher-Hoch, Susan (June 1999) [1996]. *Level 4: Virus Hunters of the CDC* (Limited preview). Horvitz, Leslie Alan (Updated [3rd] ed.). Barnes & Noble. ISBN 978-0-7607-1208-5.
- Pattyn, S. R. (1978). *Ebola Virus Haemorrhagic Fever* (Full free text) (1st ed.). Amsterdam: Elsevier/North-Holland Biomedical Press. ISBN 0-444-80060-3.
- Ryabchikova, Elena I.; Price, Barbara B. (2004). *Ebola and Marburg Viruses: A View of Infection Using Electron Microscopy*. Columbus, Ohio: Battelle Press. ISBN 978-1-57477-131-2.


## External links

- Ebola virus disease at DMOZ
- CDC: Ebola hemorrhagic fever – Centers for Disease Control and Prevention, Special Pathogens Branch
- WHO: Ebola haemorrhagic fever – World Health Organization, Global Alert and Response
- [1] – World Health Organization, Fact Sheet 103 Ebola Virus Disease, Updated September 2013
- [2] WHO Ebola videos
- [3] *Scientific American* articles related to Ebola – note these are general reading articles, they are not scientific peer-reviewed research articles.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Quotations from Wikiquote
Learning resources from Wikiversity
Data from Wikidata

v · t · e **Family *Filoviridae* (Ebola virus disease, Marburg virus disease)**

| | | |
|---|---|---|
| *Ebolavirus* | **Species** | *Bundibugyo ebolavirus* (BDBV) · *Reston ebolavirus* (RESTV) · *Sudan ebolavirus* (SUDV) · *Taï Forest ebolavirus* (TAFV) · *Zaire ebolavirus* (EBOV) · |
| | **Outbreaks** | List of Ebola outbreaks · 1976 Sudan outbreak · 1976 Zaire outbreak · 2013–2016 West African Ebola virus epidemic (Timeline · Responses · United Nations Ebola Response Fund · Operation United Assistance · in Guinea · in Liberia · in Mali · in Sierra Leone · in Spain · in the United States · in the United Kingdom · Ouse to Ouse Tock · Womey Massacre · · 2014 DR Congo outbreak · |
| | **Drug candidates** | BCX4430 · Brincidofovir · DZNep · Favipiravir · FGI-103 · FGI-104 · FGI-106 · JK-05 · Lamivudine · Triazavirin · ZMapp · Vaccines (cAd3-ZEBOV · rVSV-ZEBOV · · |
| | **Failed drug candidates** | TKM-Ebola · |
| | **Notable people** | William Close · Peter Piot · Notable patients (Ameyo Adadevoh · Kent Brantly · Pauline Cafferkey · Thomas Eric Duncan · Sheik Umar Khan · Matthew Lukwiya · Patrick Sawyer · · |
| | **In popular culture** | *The Hot Zone* (1995 book) · *Outbreak* (1995 film) · *Ebola Syndrome* (1996 film) · *Executive Orders* (1996 novel) · *93 Days* (2016 film) · |
| | **Miscellaneous** | **Ebola virus disease** · Ebola River · |
| *Marburgvirus* | **Species** | *Marburg marburgvirus* (MARV · RAVV · · |
| | **Drug candidates** | BCX4430 · FGI-103 · FGI-106 · |
| | **In popular culture** | *The Hot Zone* (1995 book) · |
| | **Miscellaneous** | Marburg virus disease · Marburg · |
| **"Cuevavirus"** (proposed inclusion) | **Species** | "Lloviu cuevavirus" (LLOV) · |
| Commons · Wikispecies · | | |

| | | | |
|---|---|---|---|
| v · t · e · | **Zoonotic viral diseases (A80–B34, 042–079)** | | |
| | **Mosquito-borne** | *Bunyaviridae* | Arbovirus encephalitides: La Crosse encephalitis (LACV · · Batai virus (BATV) · Bwamba Fever (BWAV) · California encephalitis (CEV · · Jamestown Canyon virus · Tete virus · Tahyna virus (TAHV) · Viral hemorrhagic fevers: Rift Valley fever (RVFV · · Bunyamwera fever (BUNV) · Ngari virus (NRIV) · |
| | | *Flaviviridae* | Arbovirus encephalitides: Japanese encephalitis (JEV · · Australian encephalitis (MVEV · KUNV · · Saint Louis encephalitis (SLEV · · West Nile fever (WNV · · Viral hemorrhagic fevers: Dengue fever (DENV-1-4 · · Yellow fever (YFV · · Zika fever (Zika virus · · |
| | | | Arbovirus encephalitides: |

| | | | |
|---|---|---|---|
| **Arthropod-borne** | | *Togaviridae* | Eastern equine encephalomyelitis (EEEV · · Western equine encephalomyelitis (WEEV · · Venezuelan equine encephalomyelitis (VEEV · · Chikungunya (CHIKV · · O'Nyong-nyong fever (ONNV · · Ross River fever (RRV · · Semliki Forest virus · Sindbis fever · |
| | | *Reoviridae* | Banna virus encephalitis · |
| | **Tick-borne** | *Bunyaviridae* | Viral hemorrhagic fevers: Crimean–Congo hemorrhagic fever (CCHFV · · Heartland virus · Bhanja virus · Sandfly fever Naples virus · Lone Star virus · Tete virus · |
| | | *Flaviviridae* | Arbovirus encephalitides: Tick-borne encephalitis (TBEV · · Powassan encephalitis (POWV · · Viral hemorrhagic fevers: Omsk hemorrhagic fever (OHFV · · Kyasanur forest disease (KFDV · AHFV · · Langat virus (LGTV) · |
| | | *Reoviridae* | Colorado tick fever (CTFV · · Kemerovo tickborne viral fever · |
| | **Sandfly-borne** | *Bunyaviridae* | Adria virus (ADRV) · Pappataci fever (Toscana virus · · Sandfly fever Naples virus · Oropouche fever (Oropouche virus · · SFTS virus · |
| | | *Rhabdoviridae* | Chandipura virus · |
| **Mammal-borne** | **Rodent-borne** | *Arenaviridae* | Viral hemorrhagic fevers: Lassa fever (LASV · · Venezuelan hemorrhagic fever (GTOV · · Argentine hemorrhagic fever (JUNV · · Brazilian hemorrhagic fever (SABV · · Bolivian hemorrhagic fever (MACV · · LUJV · CHPV · |
| | | *Bunyaviridae* | Hemorrhagic fever with renal syndrome (DOBV · HTNV · PUUV · SEOV · AMRV · · Hantavirus pulmonary syndrome (ANDV · SNV · · |
| | **Bat-borne** | *Filoviridae* | Viral hemorrhagic fevers: **Ebola virus disease** · BDBV · EBOV · SUDV · TAFV · Marburg virus disease · MARV · RAVV · |
| | | *Rhabdoviridae* | Rabies (ABLV · MOKV · DUVV · LBV · · CHPV · |
| | | *Paramyxoviridae* | Henipavirus encephalitis (HeV · NiV · · |
| | *Primate-borne* | *Herpesviridae* | Herpes B virus · |
| | | *Retroviridae* | Simian foamy virus · HTLV-1 · HTLV-2 · |
| | | *Poxviridae* | Tanapox · Yaba monkey tumor virus · |
| | **Multiple vectors** | *Rhabdoviridae* | Rabies (RABV · · Mokola virus · |
| | | *Poxviridae* | Monkeypox · |

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Categories: Ebola | Zoonoses | Tropical diseases | Animal viral diseases | Animal virology | Arthropod-borne viral fevers and viral haemorrhagic fevers | Bat-borne viruses | Biological weapons | Health in Africa | Hemorrhagic fevers | Human diseases and disorders | Sexually transmitted diseases and infections | Virus-related cutaneous conditions | Wikipedia pages referenced by the press

# Hepatitis A

From Wikipedia, the free encyclopedia

**Hepatitis A** (formerly known as **infectious hepatitis**) is an infectious disease of the liver caused by the hepatitis A virus (HAV).[1] Many cases have few or no symptoms, especially in the young.[2] The time between infection and symptoms, in those who develop them, is between two and six weeks.[3] When symptoms occur, they typically last eight weeks and may include nausea, vomiting, diarrhea, jaundice, fever, and abdominal pain.[2] Around 10–15% of people experience a recurrence of symptoms during the six months after the initial infection.[2] Acute liver failure may rarely occur, with this being more common in the elderly.[2]

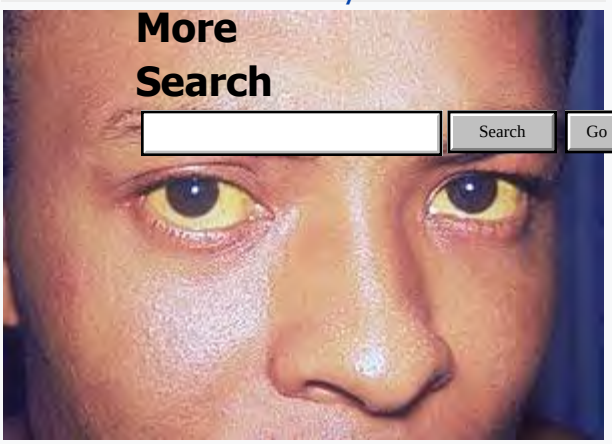
It is usually spread by eating food or drinking water contaminated with infected feces.[2] Shellfish which have not been sufficiently cooked are a relatively common source.[4] It may also be spread through close contact with an infectious person.[2] While children often do not have symptoms when infected, they are still able to infect others.[2] After a single infection, a person is immune for the rest of his or her life.[5] Diagnosis requires blood testing, as the symptoms are similar to those of a number of other diseases.[2] It is one of five known hepatitis viruses: A, B, C, D, and E.

The hepatitis A vaccine is effective for prevention.[2][6] Some countries recommend it routinely for children and those at higher risk who have not previously been vaccinated.[2][7] It appears to be effective for life.[2] Other preventive measures include hand washing and properly cooking food.[2] No specific treatment is available, with rest and medications for nausea or diarrhea recommended on an as-needed basis.[2] Infections usually resolve completely and without ongoing liver disease.[2] Treatment of acute liver failure, if it occurs, is with liver transplantation.[2]

Globally, around 1.4 million symptomatic cases occur each year[2] and about 102 million infections (symptomatic and asymptomatic).[8] It is more common in regions of the world with poor sanitation and not enough safe water.[7] In the developing world about 90% of children have been infected by age 10 and thus are immune by adulthood.[7] It often occurs in outbreaks in moderately developed countries where children are not exposed when young and vaccination is not widespread.[7] Acute hepatitis A resulted in 102,000 deaths in 2010.[9] World Hepatitis Day occurs each year on July 28 to bring awareness to viral hepatitis.[7]

## Variants

## Hepatitis A



A case of jaundice caused by hepatitis A

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Infectious disease, gastroenterology |
| **ICD-10** | B15 |
| **ICD-9-CM** | 070.0, 070.1 |
| **DiseasesDB** | 5757 |
| **MedlinePlus** | 000278 |
| **eMedicine** | med/991 ped/977 |
| **Patient UK** | Hepatitis A |
| **MeSH** | D006506 |

[edit on Wikidata]

## Signs and symptoms [edit]

Early symptoms of hepatitis A infection can be mistaken for influenza, but some sufferers, especially children, exhibit no symptoms at all. Symptoms typically appear 2 to 6 weeks (the incubation period) after the initial infection.[10] 90% of children do not have symptoms. The time between infection and symptoms, in those who develop them, is between two and six weeks with an average of 28 days.[3]

The risk for symptomatic infection is directly related to age, with more than 80% of adults having symptoms compatible with acute viral hepatitis and the majority of children having either asymptomatic or unrecognized infections.[11]

Symptoms usually last less than 2 months, although some people can be ill for as long as 6 months:[12]

- Fatigue
- Fever
- Nausea
- Appetite loss
- Jaundice, a yellowing of the skin or the whites of the eyes owing to hyperbilirubinemia
- Bile is removed from the bloodstream and excreted in the urine, giving it a dark amber colour
- Diarrhea
- Light, or clay-coloured faeces (acholic faeces)
- Abdominal discomfort[13]

## Virology [edit]

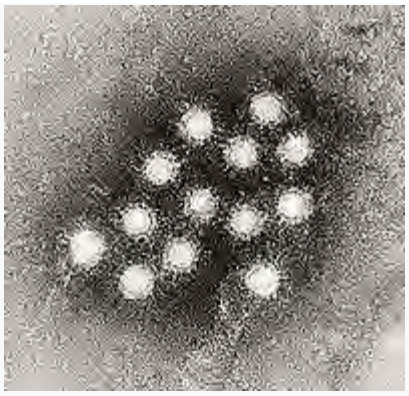
### Taxonomy [edit]

*Hepatovirus A* is a species of virus in the order *Picornavirales* in the family *Picornaviridae* and is the type species of the genus *Hepatovirus*. Humans and vertebrates serve as natural hosts.[14][15]

At least 13 additional species of the genus *Hepatovirus* have now been identified.[16] These species infect bats, rodents, hedgehogs and shrews. Phylogenetic analysis suggests a rodent origin for Hepatitis A.

A species of hepatovirus (Phopivirus) has been isolated from a seal.[17] This species shared a common ancestor with hepatitis A virus about 1800

**Hepatitis A**



Electron micrograph of hepatitis A virions

**Virus classification**

Group: Group IV ((+)ssRNA)

Order: *Picornavirales*

Family: *Picornaviridae*

Genus: *Hepatovirus*

Species: *Hepatovirus A*

**Synonyms**

- *Hepatitis A virus*



years ago.

Another hepatovirus - Marmota Himalayana hepatovirus - has been isolated from the woodchuck *Marmota himalayana*.[18] This species appears to have had a common ancestor with the primate species ~1000 years ago.

## Genotypes [edit]

One serotype and seven different genetic groups (four humans and three simians) have been described.[19] The human genotypes are numbered I-III. Six subtypes have been described (IA, IB, IIA, IIB, IIIA, IIIB). The simian genotypes have been numbered IV-VI. A single isolate of genotype VII isolated from a human has also been described.[20] Genotype III has been isolated from both humans and owl monkeys. Most human isolates are of genotype I.[21] Of the type I isolates subtype IA accounts for the majority.

The mutation rate in the genome has been estimated to be 1.73–9.76 x $10^{-4}$ nucleotide substitution per site per year.[22][23] The human strains appear to have diverged from the simian about 3600 years ago.[23] The mean age of genotypes III and IIIA strains has been estimated to be 592 and 202 years, respectively.[23]

## Structure [edit]

Hepatovirus A is a picornavirus; it is nonenveloped and contains a single-stranded RNA packaged in a protein shell.[19] There is only one serotype of the virus, but multiple genotypes exist.[24] Codon use within the genome is biased and unusually distinct from its host. It also has a poor internal ribosome entry site.[25] In the region that codes for the HAV capsid, highly conserved clusters of rare codons restrict antigenic variability.[14][26]

| Genus | Structure | Symmetry | Capsid | Genomic arrangement | Genomic segmentation |
|---|---|---|---|---|---|
| Hepatovirus | Icosahedral | Pseudo T=3 | Nonenveloped | Linear | Monopartite |

## Life cycle [edit]

Humans and vertebrates serve as the natural hosts. Transmission routes are fecal-oral and blood.[14]

Following ingestion, HAV enters the bloodstream through the epithelium of the oropharynx or intestine.[27] The blood carries the virus to its target, the liver, where it multiplies within hepatocytes and Kupffer cells (liver macrophages). Viral replication is cytoplasmic. Entry into the host cell is achieved by attachment of the virus to host receptors, which mediates endocytosis. Replication follows the positive-stranded RNA virus replication model. Positive-stranded RNA virus transcription is the method of transcription. Translation takes place by viral initiation. The virus exits the host cell by lysis and viroporins. Virions are secreted into the bile

and released in stool. HAV is excreted in large quantities about 11 days prior to the appearance of symptoms or anti-HAV IgM antibodies in the blood. The incubation period is 15–50 days and mortality is less than 0.5%.

Within the liver hepatocytes, the RNA genome is released from the protein coat and is translated by the cell's own ribosomes. Unlike other picornaviruses, this virus requires an intact eukaryote initiating factor 4G (eIF4G) for the initiation of translation.[28] The requirement for this factor results in an inability to shut down host protein synthesis, unlike other picornaviruses. The virus must then inefficiently compete for the cellular translational machinery which may explain its poor growth in cell culture. Presumably for this reason, the virus has strategically adopted a naturally highly deoptimized codon usage with respect to that of its cellular host. Precisely how this strategy works is not quite clear yet.

No apparent virus-mediated cytotoxicity occurs, presumably because of the virus' own requirement for an intact eIF4G and liver pathology is likely immune-mediated.

| Genus | Host details | Tissue tropism | Entry details | Release details | Replication site | Assembly site | Transmission |
|---|---|---|---|---|---|---|---|
| Hepatovirus | Humans; vertebrates | Liver | Cell receptor endocytosis | Lysis | Cytoplasm | Cytoplasm | Oral-fecal; blood |

## Transmission [edit]

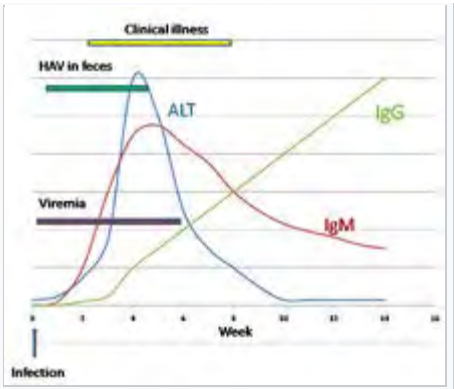
The virus spreads by the fecal–oral route, and infections often occur in conditions of poor sanitation and overcrowding. Hepatitis A can be transmitted by the parenteral route, but very rarely by blood and blood products. Food-borne outbreaks are not uncommon,[29] and ingestion of shellfish cultivated in polluted water is associated with a high risk of infection.[30] About 40% of all acute viral hepatitis is caused by HAV.[27] Infected individuals are infectious prior to onset of symptoms, roughly 10 days following infection. The virus is resistant to detergent, acid (pH 1), solvents (e.g., ether, chloroform), drying, and temperatures up to 60 °C. It can survive for months in fresh and salt water. Common-source (e.g., water, restaurant) outbreaks are typical. Infection is common in children in developing countries, reaching 100% incidence, but following infection, lifelong immunity results. HAV can be inactivated by chlorine treatment (drinking water), formalin (0.35%, 37 °C, 72 hours), peracetic acid (2%, 4 hours), beta-propiolactone (0.25%, 1 hour), and UV radiation (2 μW/cm$^2$/min).

In developing countries, and in regions with poor hygiene standards, the rates of infection with this virus are high[31] and the illness is usually contracted in early childhood. As incomes rise and access to clean water increases, the incidence of HAV decreases.[32] In developed countries, though, the infection is contracted primarily by susceptible young adults, most of whom are infected with the virus during trips to countries with a high incidence of the disease[3] or through contact with infectious persons.

Humans are the only natural reservoir of the virus. There are no known insect or other animal vectors that can transmit the virus. A chronic HAV state has not been reported.[33]

# Diagnosis [edit]

Although HAV is excreted in the feces towards the end of the incubation period, specific diagnosis is made by the detection of HAV-specific IgM antibodies in the blood.[34] IgM antibody is only present in the blood following an acute hepatitis A infection. It is detectable from one to two weeks after the initial infection and persists for up to 14 weeks. The presence of IgG antibodies in the blood means the acute stage of the illness is past and the person is immune to further infection. IgG antibodies to HAV are also found in the blood following vaccination, and tests for immunity to the virus are based on the detection of this antibody.[34]



Serum IgG, IgM and ALT following hepatovirus A infection

During the acute stage of the infection, the liver enzyme alanine transferase (ALT) is present in the blood at levels much higher than is normal. The enzyme comes from the liver cells damaged by the virus.[35]

Hepatovirus A is present in the blood (viremia) and feces of infected people up to two weeks before clinical illness develops.[35]

## Prevention [edit]

*For information about the vaccine, its properties, and its application, see Hepatitis A vaccine.*

Hepatitis A can be prevented by vaccination, good hygiene, and sanitation.[1][36]

The two types of vaccines are one containing inactivated hepatitis A virus, and another containing a live but attenuated virus.[37] Both provide active immunity against a future infection. The vaccine protects against HAV in more than 95% of cases for longer than 25 years.[38] In the US, the vaccine was first used in 1996 for children in high-risk areas, and in 1999 it was spread to areas with elevating levels of infection.[39]

The vaccine is given by injection. An initial dose provides protection starting two to four weeks after vaccination; the second booster dose, given six to 12 months later, provides protection for over 20 years.[39]

### Vaccination programmes [edit]

The vaccine was introduced in 1992 and was initially recommended for persons at high risk. Since then, Bahrain and Israel have embarked on eradication programmes.[40] Australia, China, Belarus, Italy, Spain, and the United States have started similar programmes. The incidence of hepatitis A where widespread vaccination has been practised has decreased dramatically. In China and the United States, the incidence of hepatitis A has decreased by 90% since 1990.[41][42]

In the United States, vaccination of children is recommended at 1 and 2 years of age.[2] It is also recommended in those who have not been previously immunized and who have been exposed or are likely to be exposed due to travel.[2]

## Treatment [edit]

There is no specific treatment for hepatitis A. Recovery from symptoms following infection may be slow and may take several weeks or months. Therapy is aimed at maintaining comfort and adequate nutritional balance, including replacement of fluids that are lost from vomiting and diarrhoea.[13]

## Prognosis [edit]

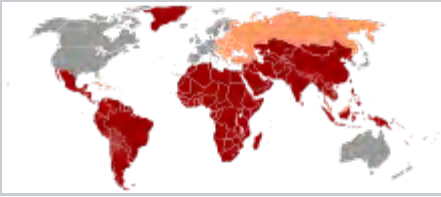
In the United States in 1991, the mortality rate for hepatitis A was four deaths per 1000 cases for the general population, but a higher at 17.5 per 1000 in those aged 50 and over. The risk of death from acute

liver failure following HAV infection increases with age and when the person has underlying chronic liver disease.

Young children who are infected with hepatitis A typically have a milder form of the disease, usually lasting from 1–3 weeks, whereas adults tend to experience a much more severe form of the disease.[29]

# Epidemiology [edit]

Globally, symptomatic HAV infections are believed to occur in around 1.4 million people a year.[2] About 102 million infections (asymptomatic and symptomatic) occurred all together in 2013.[8] In 2010, acute hepatitis A resulted in 102,000 deaths, which is slightly up from 99,000 in 1990.[9] Developed countries have low circulating levels of hepatovirus A while developing countries have higher levels of circulation.[43] Most adolescents and adults in developing countries have already had the disease, thus are immune.[43] Adults in midlevel countries may be at risk of disease with the potential of being exposed.[43]



Hepatitis A distribution 2005

## Countries [edit]

Over 30,000 cases of hepatitis A were reported to the CDC in the US in 1997, but the number has since dropped to less than 2,000 cases reported per year.[44]

The most widespread hepatitis A outbreak in the 2003 United States hepatitis outbreak afflicted at least 640 people (killing four) in northeastern Ohio and southwestern Pennsylvania in late 2003. The outbreak was blamed on tainted green onions at a restaurant in Monaca, Pennsylvania.[45][46] In 1988, more than 300,000 people in Shanghai, China, were infected with HAV after eating clams (*Anadara subcrenata*) from a contaminated river.[27] In June 2013, frozen berries sold by US retailer Costco and purchased by around 240,000 people were the subject of a recall, after at least 158 people were infected with HAV, 69 of whom were hospitalized.[47][48] In April 2016, frozen berries sold by Costco were once again the subject of a recall, after at least 13 people in Canada were infected with HAV, three of whom were hospitalized.[49] In Australia in February 2015, a recall of frozen berries was issued after at least 19 people contracted the illness following their consumption of the product.[50]

# References [edit]


1. ^ *a b* Ryan KJ, Ray CG (editors) (2004). *Sherris Medical Microbiology* (4th ed.). McGraw Hill. pp. 541–4. ISBN 0-8385-8529-9.
2. ^ *a b c d e f g h i j k l m n o p q r s* Matheny, SC; Kingery, JE (1 December 2012). "Hepatitis A.". *Am Fam Physician*. **86** (11): 1027–34; quiz 1010–2. PMID 23198670.
3. ^ *a b c* Connor BA (2005). "Hepatitis A vaccine in the last-minute traveler". *Am. J. Med.* **118** (Suppl 10A): 58S–62S. doi:10.1016/j.amjmed.2005.07.018. PMID 16271543.
4. ^ Bellou, M.; Kokkinos, P.; Vantarakis, A. (March 2013). "Shellfish-borne viral outbreaks: a systematic review.". *Food Environ Virol*. **5** (1): 13–23. doi:10.1007/s12560-012-9097-6. PMID 23412719.
5. ^ *The Encyclopedia of Hepatitis and Other Liver Diseases*. Infobase. 2006. p. 105. ISBN 9780816069903.
6. ^ Irving, GJ.; Holden, J.; Yang, R.; Pope, D. (2012). "Hepatitis A immunisation in persons not previously exposed to hepatitis A.". *Cochrane Database Syst Rev*. **7**: CD009051. doi:10.1002/14651858.CD009051.pub2. PMID 22786522.
7. ^ *a b c d e* "Hepatitis A Fact sheet N°328". *World Health Organization*. July 2013. Retrieved 20 February 2014.
8. ^ *a b* Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
   *a b*

9. ^ Lozano, R (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.(subscription required) **Cite error: Invalid `<ref>` tag; name "Loz2012" defined multiple times with different content (see the help page).**
10. ^ "Hepatitis A Symptoms". eMedicineHealth. 2007-05-17. Retrieved 2007-05-18.
11. ^ Ciocca M. (2000). "Clinical course and consequences of hepatitis A infection". *Vaccine*. **18**: 71–4. doi:10.1016/S0264-410X(99)00470-3. PMID 10683554.
12. ^ "Hepatitis A Information for the Public". Center for Disease Control. 2009-09-17. Retrieved 2011-01-08.
13. ^ *a b* http://www.who.int/mediacentre/factsheets/fs328/en/
14. ^ *a b c* "Viral Zone". ExPASy. Retrieved 15 June 2015.
15. ^ ICTV. "Virus Taxonomy: 2014 Release". Retrieved 15 June 2015.
16. ^ Drexler JF, Corman VM, Lukashev AN, van den Brand JM, Gmyl AP, Brünink S, Rasche A, Seggewiss N, Feng H, Leijten LM, Vallo P, Kuiken T, Dotzauer A, Ulrich RG, Lemon SM, Drosten C. "Hepatovirus Ecology Consortium. Evolutionary origins of hepatitis A virus in small mammals". *Proc Natl Acad Sci U S A*. **112** (49): 15190–15195. doi:10.1073/pnas.1516992112.
17. ^ Anthony SJ, St Leger JA, Liang E, Hicks AL, Sanchez-Leon MD, Jain K, Lefkowitch JH, Navarrete-Macias I, Knowles N, Goldstein T, Pugliares K, Ip HS, Rowles T, Lipkin WI (2015). "Discovery of a novel hepatovirus (Phopivirus of seals) related to human hepatitis A virus". *MBio*. **6** (4): e01180–15. doi:10.1128/mBio.01180-15.
18. ^ Yu JM, Li LL, Zhang CY, Lu S, Ao YY, Gao HC, Xie ZP, Xie GC, Sun XM, Pang LL, Xu JG, Lipkin WI, Duan ZJ (2016). "A novel hepatovirus identified in wild woodchuck *Marmota himalayana*". *Sci Rep*. **6**: 22361. doi:10.1038/srep22361.
19. ^ *a b* Cristina J, Costa-Mattioli M (August 2007). "Genetic variability and molecular evolution of hepatitis A virus". *Virus Res*. **127** (2): 151–7. doi:10.1016/j.virusres.2007.01.005. PMID 17328982.
20. ^ Ching KZ, Nakano T, Chapman LE, Demby A, Robertson BH (January 2002). "Genetic characterization of wild-type genotype VII hepatitis A virus". *J. Gen. Virol*. **83** (Pt 1): 53–60. PMID 11752700.
21. ^ de Paula VS, Baptista ML, Lampe E, Niel C, Gaspar AM (January 2002). "Characterization of hepatitis A virus isolates from subgenotypes IA and IB in Rio de Janeiro, Brazil". *J. Med. Virol*. **66** (1): 22–7. doi:10.1002/jmv.2106. PMID 11748654.
22. ^ Moratorio G, Costa-Mattioli M, Piovani R, Romero H, Musto H, Cristina J (November 2007). "Bayesian coalescent inference of hepatitis A virus populations: evolutionary rates and patterns". *J. Gen. Virol*. **88** (Pt 11): 3039–42. doi:10.1099/vir.0.83038-0. PMID 17947528.
23. ^ *a b c* Kulkarni MA, Walimbe AM, Cherian S, Arankalle VA (December 2009). "Full length genomes of genotype IIIA Hepatitis A Virus strains (1995–2008) from India and estimates of the evolutionary rates and ages". *Infect. Genet. Evol*. **9** (6): 1287–94. doi:10.1016/j.meegid.2009.08.009. PMID 19723592.
24. ^ Costa-Mattioli M, Di Napoli A, Ferré V, Billaudel S, Perez-Bercoff R, Cristina J (December 2003). "Genetic variability of hepatitis A virus". *J. Gen. Virol*. **84** (Pt 12): 3191–201. doi:10.1099/vir.0.19532-0. PMID 14645901.
25. ^ Whetter LE, Day SP, Elroy-Stein O, Brown EA, Lemon SM (August 1994). "Low efficiency of the 5' nontranslated region of hepatitis A virus RNA in directing cap-independent translation in permissive monkey kidney cells". *J. Virol*. **68** (8): 5253–63. PMC 236470. PMID 8035522.
26. ^ Aragonès L, Bosch A, Pintó RM (February 2008). "Hepatitis A virus mutant spectra under the selective pressure of monoclonal antibodies: codon usage constraints limit capsid variability". *J. Virol*. **82** (4): 1688–700. doi:10.1128/JVI.01842-07. PMC 2258700. PMID 18057242.
27. ^ *a b c* Murray, P.R., Rosenthal, K.S. & Pfaller, M.A. (2005). Medical Microbiology 5th ed., Elsevier Mosby.
28. ^ Aragonès L, Guix S, Ribes E, Bosch A, Pintó RM (March 2010). Andino, Raul, ed. "Fine-tuning translation kinetics selection as the driving force of codon usage bias in the hepatitis A virus capsid". *PLoS Pathog*. **6** (3): e1000797. doi:10.1371/journal.ppat.1000797. PMC 2832697. PMID 20221432.
29. ^ *a b* Brundage SC, Fitzpatrick AN (2006). "Hepatitis A". *Am Fam Physician*. **73** (12): 2162–8. PMID 16848078.
30. ^ Lees D (2000). "Viruses and bivalve shellfish". *Int. J. Food Microbiol*. **59** (1–2): 81–116. doi:10.1016/S0168-1605(00)00248-8. PMID 10946842.
31. ^ Steffen R (October 2005). "Changing travel-related global epidemiology of hepatitis A". *Am. J. Med*. **118** (Suppl 10A): 46S–49S. doi:10.1016/j.amjmed.2005.07.016. PMID 16271541.
32. ^ Jacobsen KH, Koopman JS (2005). "The effects of socioeconomic development on worldwide hepatitis A virus seroprevalence patterns". *Int J Epidemiol*. **34** (3): 600–9. doi:10.1093/ije/dyi062. PMID 15831565.
33. ^ "Hepatitis A." Centers for Disease Control and Prevention. Centers for Disease Control and Prevention, 2015. Web. 25 Oct. 2016.


*a b*

34. ^ Stapleton JT (1995). "Host immune response to hepatitis A virus". *J. Infect. Dis.* **171** (Suppl 1): S9–14. doi:10.1093/infdis/171.Supplement_1.S9. PMID 7876654.
35. ^ [a] [b] Musana KA, Yale SH, Abdulkarim AS (2004). "Tests of Liver Injury". *Clin Med Res*. **2** (2): 129–31. doi:10.3121/cmr.2.2.129. PMC 1069083. PMID 15931347.
36. ^ "Hepatitis A — Prevention". *NHS Choices*. National Health Service (England). 21 March 2012.
37. ^ Irving GJ, Holden J, Yang R, Pope D (2012). Irving, Greg J, ed. "Hepatitis A immunisation in persons not previously exposed to hepatitis A". *Cochrane Database Syst Rev*. **7**: CD009051. doi:10.1002/14651858.CD009051.pub2. PMID 22786522.
38. ^ Nothdurft HD (July 2008). "Hepatitis A vaccines". *Expert Rev Vaccines*. **7** (5): 535–45. doi:10.1586/14760584.7.5.535. PMID 18564009.
39. ^ [a] [b] "Hepatitis A Vaccine: What you need to know" (PDF). *Vaccine Information Statement*. CDC. 2006-03-21. Retrieved 2007-03-12.
40. ^ André FE (2006). "Universal mass vaccination against hepatitis A". *Curr Top Microbiol Immunol*. **304**: 95–114. PMID 16989266.
41. ^ Cui F, Hadler SC, Zheng H, Wang F, Zhenhua W, Yuansheng H, Gong X, Chen Y, Liang X, et al. (2009). "Hepatitis A surveillance and vaccine use in China from 1990 through 2007". *J Epidemiol*. **19** (4): 189–195. doi:10.2188/jea.JE20080087. PMID 19561383.
42. ^ Daniels D, Grytdal S, Wasley A (May 2009). "Surveillance for acute viral hepatitis — United States, 2007" (PDF). *MMWR Surveill Summ*. **58** (3): 1–27. PMID 19478727.
43. ^ [a] [b] [c] Jacobsen, KH; Wiersma, ST (24 September 2010). "Hepatitis A virus seroprevalence by age and world region, 1990 and 2005". *Vaccine*. **28** (41): 6653–7. doi:10.1016/j.vaccine.2010.08.037. PMID 20723630.
44. ^ "Hepatitis A Information for Health Professionals — Statistics and Surveillance". Centers for Disease Control and Prevention. Retrieved 28 January 2014.
45. ^ Centers for Disease Control and Prevention (CDC) (November 2003). "Hepatitis A outbreak associated with green onions at a restaurant—Monaca, Pennsylvania, 2003" (PDF). *MMWR Morb. Mortal. Wkly. Rep.* **52** (47): 1155–7. PMID 14647018.
46. ^ Wheeler C, Vogt TM, Armstrong GL, et al. (September 2005). "An outbreak of hepatitis A associated with green onions". *N. Engl. J. Med.* **353** (9): 890–7. doi:10.1056/NEJMoa050855. PMID 16135833.
47. ^ Weise, Elizabeth (18 June 2013). "118 sickened in hepatitis A outbreak linked to berries". *USA Today*.
48. ^ "Outbreak Cases". *Viral Hepatitis*. Centers for Disease Control and Prevention. 28 October 2013.
49. ^ "Recalled Costco frozen berries linked to 13 cases of Hepatitis A". *The Canadian Press*. 19 April 2016.
50. ^ "Frozen berries Heptitus A scare". *ABC News Australia*. 17 February 2015.


## External links [edit]

- Hepatitis A at DMOZ
- CDC's hepatitis A links
- Virus Pathogen Database and Analysis Resource (ViPR): Picornaviridae
- "*Human hepatitis A virus*". *NCBI Taxonomy Browser*. 208726.

| v · t · e | **Infectious diseases – viral systemic diseases (A80–B34, 042–079)** | |
|---|---|---|
| **Oncovirus** | **DNA virus:** *HBV* (Hepatocellular carcinoma · · *HPV* (Cervical cancer · Anal cancer · Penile cancer · Vulvar cancer · Vaginal cancer · Oropharyngeal cancer · · *KSHV* (Kaposi's sarcoma · · *EBV* (Nasopharynx cancer · Burkitt's lymphoma · Hodgkin's lymphoma · Follicular dendritic cell sarcoma · Extranodal NK/T-cell lymphoma, nasal type · · *MCPyV* (Merkel-cell carcinoma · · **RNA virus:** *HCV* (Hepatocellular carcinoma · Splenic marginal zone lymphoma · · *HTLV-I* (Adult T-cell leukemia/lymphoma · · | |
| **Immune disorders** | *HIV* (AIDS · · | |
| | **Encephalitis/** | **DNA virus:** *JCV* (Progressive multifocal leukoencephalopathy · · **RNA virus:** *MeV* (Subacute sclerosing panencephalitis · · *LCV* (Lymphocytic choriomeningitis · · Arbovirus encephalitis · |

| | | |
|---|---|---|
| **Central nervous system** | **meningitis** | *Orthomyxoviridae (probable)* (Encephalitis lethargica · · *RV* (Rabies · · Chandipura virus · Herpesviral meningitis · Ramsay Hunt syndrome type 2 · |
| | **Myelitis** | *Poliovirus* (Poliomyelitis · Post-polio syndrome · · *HTLV-I* (Tropical spastic paraparesis · · |
| | **Eye** | *Cytomegalovirus* (Cytomegalovirus retinitis · · *HSV* (Herpes of the eye · · |
| **Cardiovascular** | *CBV* (Pericarditis · Myocarditis · · | |
| **Respiratory system/ acute viral nasopharyngitis/ viral pneumonia** | **DNA virus** | *Epstein–Barr virus* (EBV infection/Infectious mononucleosis · · *Cytomegalovirus* · |
| | **RNA virus** | IV: *SARS coronavirus* (Severe acute respiratory syndrome · · V: *Orthomyxoviridae: Influenzavirus A/B/C* (Influenza/Avian influenza · · V, *Paramyxoviridae: Human parainfluenza viruses* (Parainfluenza · · *RSV* · *hMPV* · |
| **Human digestive system** | **Pharynx/Esophagus** | *MuV* (Mumps · · *Cytomegalovirus* (Cytomegalovirus esophagitis · · |
| | **Gastroenteritis/ diarrhea** | **DNA virus:** *Adenovirus* (Adenovirus infection · · **RNA virus:** *Rotavirus* · *Norovirus* · *Astrovirus* · *Coronavirus* · |
| | **Hepatitis** | **DNA virus:** *HBV* (B) · **RNA virus:** *CBV* · *HAV* (**A**) · *HCV* (C) · *HDV* (D) · *HEV* (E) · *HGV* (G) · |
| | **Pancreatitis** | *CBV* · |
| **Urogenital** | *BK virus* · *MuV* (Mumps · · | |

| v · t · e · **Food safety** | |
|---|---|
| **Adulterants, food contaminants** | 3-MCPD · Aldicarb · Cyanide · Formaldehyde · Lead poisoning · Melamine · Mercury in fish · Sudan I · |
| **Flavorings** | Monosodium glutamate (MSG) · Salt · Sugar (High fructose corn syrup · · |
| **Microorganisms** | Botulism · *Campylobacter jejuni* · *Clostridium perfringens* · *Escherichia coli* O104:H4 · *Escherichia coli* O157:H7 · **Hepatitis A** · Hepatitis E · Listeria · Norovirus · Rotavirus · *Salmonella* · |
| **Parasitic infections through food** | Anisakiasis · Amoebiasis/Amoebic dysentery · Cryptosporidiosis · Cyclosporiasis · Diphyllobothriasis · Enterobiasis · Fascioliasis · Fasciolopsiasis · Giardiasis · Gnathostomiasis · Paragonimiasis · Toxoplasmosis · Trichinosis · Trichuriasis · |
| **Pesticides** | Chlorpyrifos · DDT · Lindane · Malathion · Methamidophos · |
| **Preservatives** | Benzoic acid · Ethylenediaminetetraacetic acid (EDTA) · Sodium benzoate · |
| **Sugar substitutes** | Acesulfame potassium · Aspartame · Saccharin · Sodium cyclamate · Sorbitol · Sucralose · |

| | |
|---|---|
| **Toxins, poisons, environment pollution** | Aflatoxin · Arsenic contamination of groundwater · Benzene in soft drinks · Bisphenol A · Mycotoxins · Shellfish poisoning · dioxin · Dieldrin · Nonylphenol · Diethylstilbestrol · |
| **Food contamination incidents** | Devon colic · 1858 Bradford sweets poisoning · 1989 Chilean grape scare · 1993 Jack in the Box *E. coli* outbreak · 1996 Odwalla E. coli outbreak · 1999 Sun Orchard salmonellosis outbreak · 2005 Indonesia food scare · 2006 North American *E. coli* O157:H7 outbreaks · 2007 Vietnam food scare · 2008 Canada listeriosis outbreak · 2008 Chinese milk scandal · 2008 Irish pork crisis · 2008 United States salmonellosis outbreak · 2011 Germany *E. coli* O104:H4 outbreak · 2011 Taiwan food scandal · 2011 United States listeriosis outbreak · Food safety incidents in China · Foodborne illness (outbreaks · death toll · United States · · ICA meat repackaging controversy · Minamata disease · StarLink corn recall · Toxic oil syndrome · 2013 meat adulteration scandal · 2013 aflatoxin contamination · 2013 Taiwan food scandal · 2014 Taiwan food scandal · 2015 United States *E. coli* outbreak · |
| **Regulation, standards, watchdogs** | Acceptable daily intake · E number · Food labeling regulations · Food libel laws · International Food Safety Network · ISO 22000 · Quality Assurance International · |
| **Institutions** | International Food Safety Network · List of food safety organisations · Institute for Food Safety and Health · Ministry of Food and Drug Safety · Centre for Food Safety · European Food Safety Authority · |

Categories: Hepatitis A

# Hepatitis B



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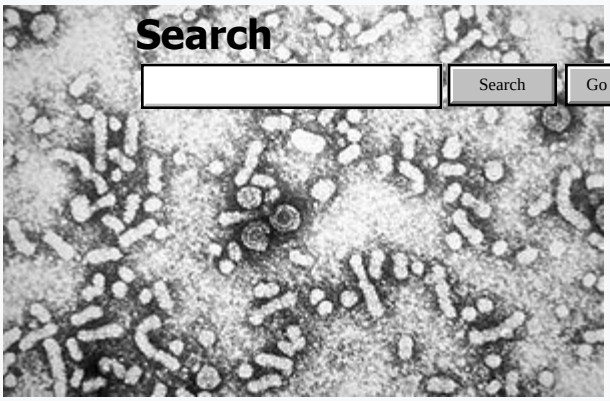
## Variants

## Hepatitis B



Electron micrograph of hepatitis B virus

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Infectious disease, gastroenterology |
| **ICD-10** | B16, B18.0–B18.1 |
| **ICD-9-CM** | 070.2–070.3 |
| **OMIM** | 610424 |
| **DiseasesDB** | 5765 |
| **MedlinePlus** | 000279 |
| **eMedicine** | med/992 ped/978 |
| **Patient UK** | Hepatitis B |
| **MeSH** | D006509 |

[edit on Wikidata]

**Hepatitis B** is an infectious disease caused by the hepatitis B virus (HBV) which affects the liver. It can cause both acute and chronic infections. Many people have no symptoms during the initial infection. Some develop a rapid onset of sickness with vomiting, yellowish skin, tiredness, dark urine and abdominal pain.[1] Often these symptoms last a few weeks and rarely does the initial infection result in death.[1][2] It may take 30 to 180 days for symptoms to begin.[1] In those who get infected around the time of birth 90% develop chronic hepatitis B while less than 10% of those infected after the age of five do.[3] Most of those with chronic disease have no symptoms; however, cirrhosis and liver cancer may eventually develop.[4] These complications result in the death of 15 to 25% of those with chronic disease.[1]

The virus is transmitted by exposure to infectious blood or body fluids. Infection around the time of birth or from contact with other people's blood during childhood is the most frequent method by which hepatitis B is acquired in areas where the disease is common. In areas where the disease is rare, intravenous drug use and sexual intercourse are the most frequent routes of infection.[1] Other risk factors include working in healthcare, blood transfusions, dialysis, living with an infected person, travel in countries where the infection rate is high, and living in an institution.[1][3] Tattooing and acupuncture led to a significant number of cases in the 1980s; however, this has become less common with improved sterility.[5] The hepatitis B viruses cannot be spread by holding hands, sharing eating utensils, kissing, hugging, coughing, sneezing, or breastfeeding.[3] The infection can be diagnosed 30 to 60 days after exposure. Diagnosis is typically by testing the blood for parts of the virus and for antibodies against the virus.[1] It is one of five known hepatitis viruses: A, B, C, D, and E.

The infection has been preventable by vaccination since 1982.[1][6] Vaccination is recommended by the World Health Organization in the first day of life if possible. Two or three more doses are required at a later time for full effect. This vaccine works about 95% of the time.[1] About 180 countries gave the vaccine as part of national programs as of 2006.[7] It is also recommended that all blood be tested for hepatitis B before transfusion and condoms be used to prevent infection. During an initial infection, care is based on the symptoms that a person has. In those who develop chronic disease, antiviral medication such as tenofovir or interferon may be useful; however, these drugs are expensive. Liver transplantation is [1]

sometimes used for cirrhosis.

About a third of the world population has been infected at one point in their lives, including 240 million to 350 million who have chronic infections.[1][8] Another 129 million new infections occurred in 2013.[9] Over 750,000 people die of hepatitis B each year.[1] About 300,000 of these are due to liver cancer.[10] The disease is now only common in East Asia and sub-Saharan Africa where between 5 and 10% of adults are chronically infected. Rates in Europe and North America are less than 1%.[1] It was originally known as "serum hepatitis".[11] Research is looking to create foods that contain HBV vaccine.[12] The disease may affect other great apes as well.[13]

**Contents**





## Signs and symptoms [edit]

Acute infection with hepatitis B virus is associated with acute viral hepatitis, an illness that begins with general ill health, loss of appetite, nausea, vomiting, body aches, mild fever, and dark urine, and then progresses to development of jaundice. It has been noted that itchy skin has been an indication as a possible symptom of all hepatitis virus types. The illness lasts for a few weeks and then gradually improves in most affected people. A few people may have a more severe form of liver disease known as (fulminant hepatic failure) and may die as a result. The infection may be entirely asymptomatic and may go unrecognized.[14]

Chronic infection with hepatitis B virus either may be asymptomatic or may be associated with a chronic inflammation of the liver (chronic hepatitis), leading to cirrhosis over a period of several years. This type of infection dramatically increases the incidence of hepatocellular carcinoma (HCC; liver cancer). Across Europe, hepatitis B and C cause approximately 50% of hepatocellular carcinomas.[15][16] Chronic carriers are encouraged to avoid consuming alcohol as it increases their risk for cirrhosis and liver cancer. Hepatitis B virus has been linked to the development of membranous glomerulonephritis (MGN).[17]

Symptoms outside of the liver are present in 1–10% of HBV-infected people and include serum-sickness–like syndrome, acute necrotizing vasculitis (polyarteritis nodosa), membranous glomerulonephritis, and papular acrodermatitis of childhood (Gianotti–Crosti syndrome).[18][19] The serum-sickness–like syndrome occurs in the setting of acute hepatitis B, often preceding the onset of jaundice.[20] The clinical features are fever, skin rash, and polyarteritis. The symptoms often subside shortly after the onset of jaundice but can persist throughout the duration of acute hepatitis B.[21] About 30–50% of people with acute necrotizing vasculitis (polyarteritis nodosa) are HBV carriers.[22] HBV-associated nephropathy has been described in adults but is more common in children.[23][24] Membranous glomerulonephritis is the most common

form.[20] Other immune-mediated hematological disorders, such as essential mixed cryoglobulinemia and aplastic anemia.[21]

# Cause [edit]

## Transmission [edit]

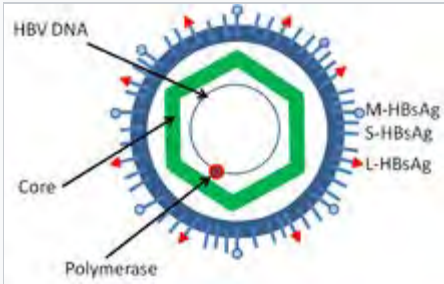
Transmission of hepatitis B virus results from exposure to infectious blood or body fluids containing blood. It is 50 to 100 times more infectious than HIV.[25] Possible forms of transmission include sexual contact,[26] blood transfusions and transfusion with other human blood products,[27] re-use of contaminated needles and syringes,[28] and vertical transmission from mother to child (MTCT) during childbirth. Without intervention, a mother who is positive for HBsAg has a 20% risk of passing the infection to her offspring at the time of birth. This risk is as high as 90% if the mother is also positive for HBeAg. HBV can be transmitted between family members within households, possibly by contact of nonintact skin or mucous membrane with secretions or saliva containing HBV.[29] However, at least 30% of reported hepatitis B among adults cannot be associated with an identifiable risk factor.[30] Breastfeeding after proper immunoprophylaxis does not appear to contribute to mother-to-child-transmission (MTCT) of HBV.[31] The virus may be detected within 30 to 60 days after infection and can persist and develop into chronic hepatitis B. The incubation period of the hepatitis B virus is 75 days on average but can vary from 30 to 180 days.[32]

## Virology [edit]

*Main article: Hepatitis B virus*

## Structure [edit]

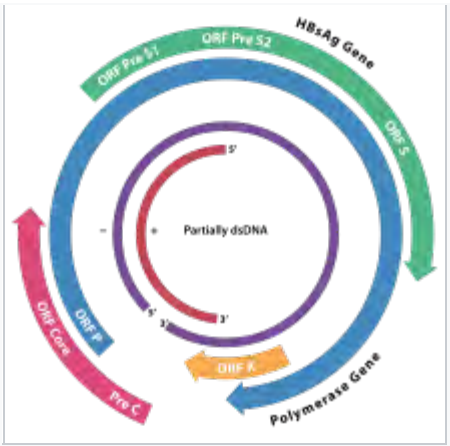
Hepatitis B virus (HBV) is a member of the hepadnavirus family.[33] The virus particle (virion) consists of an outer lipid envelope and an icosahedral nucleocapsid core composed of protein. These virions are 30–42 nm in diameter. The nucleocapsid encloses the viral DNA and a DNA polymerase that has reverse transcriptase activity.[34] The outer envelope contains embedded proteins that are involved in viral binding of, and entry into, susceptible cells. The virus is one of the smallest enveloped animal viruses, and the 42 nm virions, which are capable of infecting liver cells known as hepatocytes, are referred to as "Dane particles".[35] In addition to the Dane particles, filamentous and spherical bodies lacking a core can be found in the serum of infected individuals. These particles are not infectious and are composed of the lipid and protein that forms part of the surface of the virion, which is called the surface antigens (HBsAg), and is produced in excess during the life cycle of the virus.[36]



The structure of hepatitis B virus

## Genome [edit]

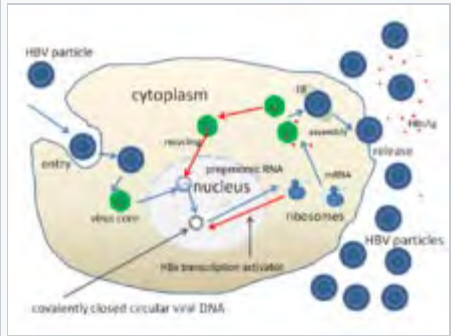
The genome of HBV is made of circular DNA, but it is unusual because the DNA is not fully double-stranded. One end of the full length strand is linked to the viral DNA polymerase. The genome is 3020–3320 nucleotides long (for the full-length strand) and 1700–2800 nucleotides long (for the short length-strand).[37] The negative-sense (non-coding) is complementary to the viral mRNA. The viral DNA is found in the nucleus soon after infection of the cell. The partially double-stranded DNA is rendered fully double-stranded by completion of the (+) sense strand and removal of a protein molecule from the (−) sense strand and




The genome organisation of HBV. The genes overlap.

a short sequence of RNA from the (+) sense strand. Non-coding bases are removed from the ends of the (−) sense strand and the ends are rejoined. There are four known genes encoded by the genome, called C, X, P, and S. The core protein is coded for by gene C (HBcAg), and its start codon is preceded by an upstream in-frame AUG start codon from which the pre-core protein is produced. HBeAg is produced by proteolytic processing of the pre-core protein. In some rare strains of the virus known as Hepatitis B virus precore mutants, no HBeAg is present.[38] The DNA polymerase is encoded by gene P. Gene S is the gene that codes for the surface antigen (HBsAg). The HBsAg gene is one long open reading frame but contains three in frame "start" (ATG) codons that divide the gene into three sections, pre-S1, pre-S2, and S. Because of the multiple start codons, polypeptides of three different sizes called large (the order from surface to the inside: pre-S1, pre-S2, and S ), middle (pre-S2, S), and small (S) [39] are produced.[40] The function of the protein coded for by gene X is not fully understood but it is associated with the development of liver cancer. It stimulates genes that promote cell growth and inactivates growth regulating molecules.[41]

## Pathogenesis [edit]




Hepatitis B virus replication

The life cycle of hepatitis B virus is complex. Hepatitis B is one of a few known pararetroviruses: non-retroviruses that still use reverse transcription in their replication process. The virus gains entry into the cell by binding to NTCP [42] on the surface and being endocytosed. Because the virus multiplies via RNA made by a host enzyme, the viral genomic DNA has to be transferred to the cell nucleus by host proteins called chaperones. The partially double-stranded viral DNA is then made fully double stranded by a viral polymerase and transformed into covalently closed circular DNA (cccDNA). This cccDNA serves as a template for transcription of four viral mRNAs by host RNA polymerase. The largest mRNA, (which is longer than the viral genome), is used to make the new copies of the genome and to make the capsid core protein and the viral DNA polymerase. These four viral transcripts undergo additional processing and go on to form progeny virions that are released from the cell or returned to the nucleus and re-cycled to produce even more copies.[40][43] The long mRNA is then transported back to the cytoplasm where the virion P protein (the DNA polymerase) synthesizes DNA via its reverse transcriptase activity.

## Serotypes and genotypes [edit]

The virus is divided into four major serotypes (adr, adw, ayr, ayw) based on antigenic epitopes presented on its envelope proteins, and into eight major genotypes (A–H). The genotypes have a distinct geographical distribution and are used in tracing the evolution and transmission of the virus. Differences between genotypes affect the disease severity, course and likelihood of complications, and response to treatment and possibly vaccination.[44][45] There are two other genotypes I and J but they are not universally accepted as of 2015[46]

Genotypes differ by at least 8% of their sequence and were first reported in 1988 when six were initially described (A–F).[47] Two further types have since been described (G and H).[48] Most genotypes are now

divided into subgenotypes with distinct properties.[49]

## Mechanisms [edit]

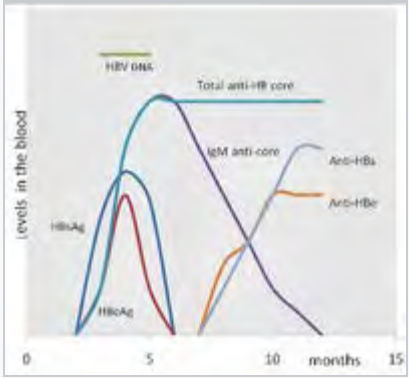
Hepatitis B virus primarily interferes with the functions of the liver by replicating in hepatocytes. A functional receptor is NTCP.[42] There is evidence that the receptor in the closely related duck hepatitis B virus is carboxypeptidase D.[50][51] The virions bind to the host cell via the preS domain of the viral surface antigen and are subsequently internalized by endocytosis. HBV-preS-specific receptors are expressed primarily on hepatocytes; however, viral DNA and proteins have also been detected in extrahepatic sites, suggesting that cellular receptors for HBV may also exist on extrahepatic cells.[52]

During HBV infection, the host immune response causes both hepatocellular damage and viral clearance. Although the innate immune response does not play a significant role in these processes, the adaptive immune response, in particular virus-specific cytotoxic T lymphocytes(CTLs), contributes to most of the liver injury associated with HBV infection. CTLs eliminate HBV infection by killing infected cells and producing antiviral cytokines, which are then used to purge HBV from viable hepatocytes.[53] Although liver damage is initiated and mediated by the CTLs, antigen-nonspecific inflammatory cells can worsen CTL-induced immunopathology, and platelets activated at the site of infection may facilitate the accumulation of CTLs in the liver.[54]

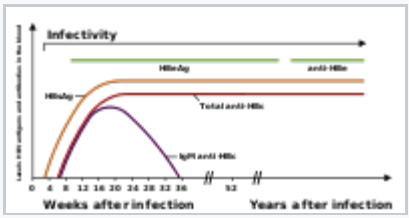
## Diagnosis [edit]

The tests, called assays, for detection of hepatitis B virus infection involve serum or blood tests that detect either viral antigens (proteins produced by the virus) or antibodies produced by the host. Interpretation of these assays is complex.[55]

The hepatitis B surface antigen (HBsAg) is most frequently used to screen for the presence of this infection. It is the first detectable viral antigen to appear during infection. However, early in an infection, this antigen may not be present and it may be undetectable later in the infection as it is being cleared by the host. The infectious virion contains an inner "core particle" enclosing viral genome. The icosahedral core particle is made of 180 or 240 copies of the core protein, alternatively known as hepatitis B core antigen, or HBcAg. During this 'window' in which the host remains infected but is successfully clearing the virus, IgM antibodies specific to the hepatitis B core antigen (*anti-HBc IgM*) may be the only serological evidence of disease. Therefore, most hepatitis B diagnostic panels contain HBsAg and total anti-HBc (both IgM and IgG).[56]



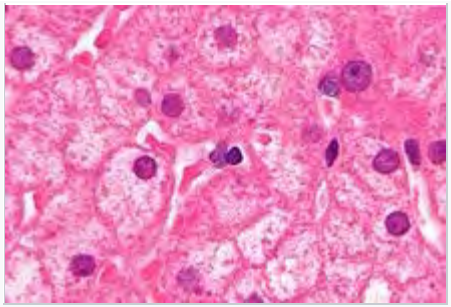
Hepatitis B viral antigens and antibodies detectable in the blood following acute infection



Hepatitis B viral antigens and antibodies detectable in the blood of a chronically infected person

Shortly after the appearance of the HBsAg, another antigen called hepatitis B e antigen (HBeAg) will appear. Traditionally, the presence of HBeAg in a host's serum is associated with much higher rates of viral replication and enhanced infectivity; however, variants of the hepatitis B virus do not produce the 'e' antigen, so this rule does not always hold true.[57] During the natural course of an infection, the HBeAg may be cleared, and antibodies to the 'e' antigen (*anti-HBe*) will arise immediately afterwards. This conversion is usually associated with a dramatic decline in viral replication.

If the host is able to clear the infection, eventually the HBsAg will become undetectable and will be followed by IgG antibodies to the hepatitis B surface antigen and core antigen (*anti-HBs* and *anti HBc IgG*).[33] The time between the removal of the HBsAg and the appearance of anti-HBs



Ground glass hepatocytes as seen in a chronic hepatitis B liver biopsy. H&E stain

is called the window period. A person negative for HBsAg but positive for anti-HBs either has cleared an infection or has been vaccinated previously.

Individuals who remain HBsAg positive for at least six months are considered to be hepatitis B carriers.[58] Carriers of the virus may have chronic hepatitis B, which would be reflected by elevated serum alanine aminotransferase (ALT) levels and inflammation of the liver, if they are in the immune clearance phase of chronic infection. Carriers who have seroconverted to HBeAg negative status, in particular those who acquired the infection as adults, have very little viral multiplication and hence may be at little risk of long-term complications or of transmitting infection to others.[59]

PCR tests have been developed to detect and measure the amount of HBV DNA, called the viral load, in clinical specimens. These tests are used to assess a person's infection status and to monitor treatment.[60] Individuals with high viral loads, characteristically have ground glass hepatocytes on biopsy.

# Prevention [edit]

*Main article: Hepatitis B vaccine*

Vaccines for the prevention of hepatitis B have been routinely recommended for infants since 1991 in the United States.[61] Most vaccines are given in three doses over a course of months. A protective response to the vaccine is defined as an anti-HBs antibody concentration of at least 10 mIU/ml in the recipient's serum. The vaccine is more effective in children and 95 percent of those vaccinated have protective levels of antibody. This drops to around 90% at 40 years of age and to around 75 percent in those over 60 years. The protection afforded by vaccination is long lasting even after antibody levels fall below 10 mIU/ml. Vaccination at birth is recommended for all infants of HBV infected mothers.[62] A combination of hepatitis B immune globulin and an accelerated course of HBV vaccine prevents HBV transmission around the time of birth in 86% to 99% of cases.[63]

All those with a risk of exposure to body fluids such as blood should be vaccinated, if not already.[61] Testing to verify effective immunization is recommended and further doses of vaccine are given to those who are not sufficiently immunized.[61]

In assisted reproductive technology, sperm washing is not necessary for males with hepatitis B to prevent transmission, unless the female partner has not been effectively vaccinated.[64] In females with hepatitis B, the risk of transmission from mother to child with IVF is no different from the risk in spontaneous conception.[64]

Those at high risk of infection should be tested as there is effective treatment for those who have the disease.[65] Groups that screening is recommended for include those who have not been vaccinated and one of the following: people from areas of the world where hepatitis B occurs in more than 2%, those with HIV, intravenous drug users, men who have sex with men, and those who live with someone with hepatitis B.[65]

## Duration of vaccination [edit]

In 10- to 22-year follow-up studies there were no cases of hepatitis B among those with a normal immune system who were vaccinated. Only rare chronic infections have been documented.[66]

# Treatment [edit]

This section needs to be **updated**. Please update this article to reflect recent events or newly available information. *(June 2016)*

Acute hepatitis B infection does not usually require treatment and most adults clear the infection spontaneously.[67][68] Early antiviral treatment may be required in fewer than 1% of people, whose infection takes a very aggressive course (fulminant hepatitis) or who are immunocompromised. On the other hand, treatment of chronic infection may be necessary to reduce the risk of cirrhosis and liver cancer. Chronically infected individuals with persistently elevated serum alanine aminotransferase, a marker of liver damage, and HBV DNA levels are candidates for therapy.[69] Treatment lasts from six months to a year, depending on medication and genotype.[70]

Although none of the available drugs can clear the infection, they can stop the virus from replicating, thus minimizing liver damage. As of 2008, there are seven medications licensed for the treatment of hepatitis B infection in the United States. These include antiviral drugs lamivudine (Epivir), adefovir (Hepsera), tenofovir (Viread), telbivudine (Tyzeka) and entecavir (Baraclude), and the two immune system modulators interferon alpha-2a and PEGylated interferon alpha-2a (Pegasys). The World Health Organization recommended a combination of tenofovir and entecavir as first-line agents.[71] Those with current cirrhosis are in most need of treatment.[71]

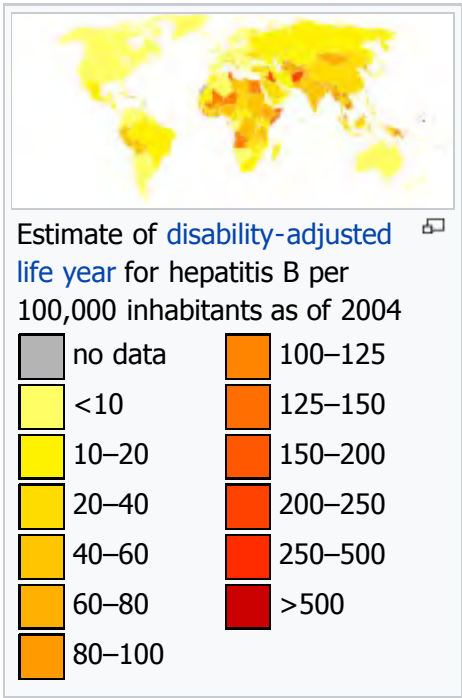
The use of interferon, which requires injections daily or thrice weekly, has been supplanted by long-acting PEGylated interferon, which is injected only once weekly.[72] However, some individuals are much more likely to respond than others, and this might be because of the genotype of the infecting virus or the person's heredity. The treatment reduces viral replication in the liver, thereby reducing the viral load (the amount of virus particles as measured in the blood).[73] Response to treatment differs between the genotypes. Interferon treatment may produce an e antigen seroconversion rate of 37% in genotype A but only a 6% seroconversion in type D. Genotype B has similar seroconversion rates to type A while type C seroconverts only in 15% of cases. Sustained e antigen loss after treatment is ~45% in types A and B but only 25–30% in types C and D.[74]

## Prognosis [edit]

Hepatitis B virus infection may be either acute (self-limiting) or chronic (long-standing). Persons with self-limiting infection clear the infection spontaneously within weeks to months.

Children are less likely than adults to clear the infection. More than 95% of people who become infected as adults or older children will stage a full recovery and develop protective immunity to the virus. However, this drops to 30% for younger children, and only 5% of newborns that acquire the infection from their mother at birth will clear the infection.[75] This population has a 40% lifetime risk of death from cirrhosis or hepatocellular carcinoma.[72] Of those infected between the age of one to six, 70% will clear the infection.[76]

Hepatitis D (HDV) can occur only with a concomitant hepatitis B infection, because HDV uses the HBV surface antigen to form a capsid.[77] Co-infection with hepatitis D increases the risk of liver cirrhosis and liver cancer.[78] Polyarteritis nodosa is more common in people with hepatitis B infection.




### Cirrhosis [edit]

A number of different tests are available to determine the degree of cirrhosis present. Transient elastography (FibroScan) is the test of [71]

choice, but it is expensive. Aspartate aminotransferase to platelet ratio index may be used when cost is an issue.[71]

### Reactivation [edit]

Hepatitis B virus DNA persists in the body after infection, and in some people the disease recurs.[79] Although rare, reactivation is seen most often following alcohol or drug use,[80] or in people with impaired immunity.[81] HBV goes through cycles of replication and non-replication. Approximately 50% of overt carriers experience acute reactivation. Males with baseline ALT of 200 UL/L are three times more likely to develop a reactivation than people with lower levels. Although reactivation can occur spontaneously,[82] people who undergo chemotherapy have a higher risk.[83] Immunosuppressive drugs favor increased HBV replication while inhibiting cytotoxic T cell function in the liver.[84] The risk of reactivation varies depending on the serological profile; those with detectable HBsAg in their blood are at the greatest risk, but those with only antibodies to the core antigen are also at risk. The presence of antibodies to the surface antigen, which are considered to be a marker of immunity, does not preclude reactivation.[83] Treatment with prophylactic antiviral drugs can prevent the serious morbidity associated with HBV disease reactivation.[83]

## Epidemiology [edit]

In 2004, an estimated 350 million individuals were infected worldwide. National and regional prevalences range from over 10% in Asia to under 0.5% in the United States and Northern Europe.

Prevalence of hepatitis B virus as of 2005

Routes of infection include vertical transmission (such as through childbirth), early life horizontal transmission (bites, lesions, and sanitary habits), and adult horizontal transmission (sexual contact, intravenous drug use).[85]

The primary method of transmission reflects the prevalence of chronic HBV infection in a given area. In low prevalence areas such as the continental United States and Western Europe, injection drug abuse and unprotected sex are the primary methods, although other factors may also be important.[86] In moderate prevalence areas, which include Eastern Europe, Russia, and Japan, where 2–7% of the population is chronically infected, the disease is predominantly spread among children. In high-prevalence areas such as China and South East Asia, transmission during childbirth is most common, although in other areas of high endemicity such as Africa, transmission during childhood is a significant factor.[87] The prevalence of chronic HBV infection in areas of high endemicity is at least 8% with 10–15% prevalence in Africa/Far East.[88] As of 2010, China has 120 million infected people, followed by India and Indonesia with 40 million and 12 million, respectively. According to World Health Organization (WHO), an estimated 600,000 people die every year related to the infection.[89]

In the United States about 19,000 new cases occurred in 2011 down nearly 90% from 1990.[61]

## History [edit]

The earliest record of an epidemic caused by hepatitis B virus was made by Lurman in 1885.[90] An outbreak of smallpox occurred in Bremen in 1883 and 1,289 shipyard employees were vaccinated with lymph from other people. After several weeks, and up to eight months later, 191 of the vaccinated workers became ill with jaundice and were diagnosed as suffering from serum hepatitis. Other employees who had been inoculated with different batches of lymph remained healthy. Lurman's paper, now regarded as a classical example of an epidemiological study, proved that contaminated lymph was the source of the outbreak. Later, numerous similar outbreaks were reported following the introduction, in 1909, of hypodermic needles that were used, and, more importantly, reused, for administering Salvarsan for the treatment of syphilis. The virus was not discovered until 1966 when Baruch Blumberg, then working at the

National Institutes of Health (NIH), discovered the Australia antigen (later known to be hepatitis B surface antigen, or HBsAg) in the blood of Australian aboriginal people.[91] Although a virus had been suspected since the research published by Frederick MacCallum in 1947,[92] David Dane and others discovered the virus particle in 1970 by electron microscopy.[93] By the early 1980s the genome of the virus had been sequenced,[94] and the first vaccines were being tested.[95]

## Society and culture [edit]

World Hepatitis Day, observed July 28, aims to raise global awareness of hepatitis B and hepatitis C and encourage prevention, diagnosis, and treatment. It has been led by the World Hepatitis Alliance since 2007 and in May 2010, it got global endorsement from the World Health Organization.[96]

## See also [edit]

- Infectious causes of cancer
- Oncovirus

Medicine portal
Viruses portal

## References [edit]


1. ^ *a b c d e f g h i j k l m* "Hepatitis B Fact sheet N°204". *who.int*. July 2014. Retrieved 4 November 2014.
2. ^ Raphael Rubin; David S. Strayer (2008). *Rubin's Pathology : clinicopathologic foundations of medicine ; [includes access to online text, cases, images, and audio review questions!]* (5. ed.). Philadelphia [u.a.]: Wolters Kluwer/Lippincott Williams & Wilkins. p. 638. ISBN 9780781795166.
3. ^ *a b c* "Hepatitis B FAQs for the Public — Transmission". U.S. Centers for Disease Control and Prevention (CDC). Retrieved 2011-11-29.
4. ^ Chang MH (June 2007). "Hepatitis B virus infection". *Semin Fetal Neonatal Med*. **12** (3): 160–167. doi:10.1016/j.siny.2007.01.013. PMID 17336170.
5. ^ Thomas HC (2013). *Viral Hepatitis* (4th ed.). Hoboken: Wiley. p. 83. ISBN 9781118637302.
6. ^ Pungpapong S, Kim WR, Poterucha JJ (2007). "Natural History of Hepatitis B Virus Infection: an Update for Clinicians". *Mayo Clinic Proceedings*. **82** (8): 967–975. doi:10.4065/82.8.967. PMID 17673066.
7. ^ Williams R (2006). "Global challenges in liver disease". *Hepatology (Baltimore, Md.)*. **44** (3): 521–526. doi:10.1002/hep.21347. PMID 16941687.
8. ^ Schilsky ML (2013). "Hepatitis B "360" ". *Transplantation Proceedings*. **45** (3): 982–985. doi:10.1016/j.transproceed.2013.02.099. PMID 23622604.
9. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013." *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/S0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
10. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013." *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
11. ^ Barker LF, Shulman NR, Murray R, Hirschman RJ, Ratner F, Diefenbach WC, Geller HM (1996). "Transmission of serum hepatitis. 1970". *Journal of the American Medical Association*. **276** (10): 841–844. doi:10.1001/jama.276.10.841. PMID 8769597.
12. ^ Thomas, Bruce (2002). *Production of Therapeutic Proteins in Plants*. p. 4. ISBN 9781601072542. Retrieved 25 November 2014.
13. ^ Plotkin, [edited by] Stanley A.; Orenstein,, Walter A.; Offit, Paul A. (2013). *Vaccines* (6th ed.). [Edinburgh]: Elsevier/Saunders. p. 208. ISBN 9781455700905.
14. ^ Terrault N, Roche B, Samuel D (July 2005). "Management of the hepatitis B virus in the liver transplantation setting: a European and an American perspective". *Liver Transpl*. **11** (7): 716–32. doi:10.1002/lt.20492. PMID 15973718.
15. ^ El-Serag HB, Rudolph KL (June 2007). "Hepatocellular carcinoma: epidemiology and molecular carcinogenesis". *Gastroenterology*. **132** (7): 2557–76. doi:10.1053/j.gastro.2007.04.061. PMID 17570226.

16. ^ El-Serag HB (22 September 2011). "Hepatocellular carcinoma". *New England Journal of Medicine*. **365** (12): 1118–27. doi:10.1056/NEJMra1001683. PMID 21992124.
17. ^ Gan SI, Devlin SM, Scott-Douglas NW, Burak KW (October 2005). "Lamivudine for the treatment of membranous glomerulopathy secondary to chronic hepatitis B infection". *Canadian journal of gastroenterology = Journal canadien de gastroenterologie*. **19** (10): 625–9. PMID 16247526.
18. ^ Dienstag JL (February 1981). "Hepatitis B as an immune complex disease". *Seminars in Liver Disease*. **1** (1): 45–57. doi:10.1055/s-2008-1063929. PMID 6126007.
19. ^ Trepo C, Guillevin L (May 2001). "Polyarteritis nodosa and extrahepatic manifestations of HBV infection: the case against autoimmune intervention in pathogenesis". *Journal of Autoimmunity*. **16** (3): 269–74. doi:10.1006/jaut.2000.0502. PMID 11334492.
20. ^ Alpert E, Isselbacher KJ, Schur PH (July 1971). "The pathogenesis of arthritis associated with viral hepatitis. Complement-component studies". *The New England Journal of Medicine*. **285** (4): 185–9. doi:10.1056/NEJM197107222850401. PMID 4996611.
21. ^ [a] [b] [c] Liang TJ (May 2009). "Hepatitis B: the virus and disease". *Hepatology (Baltimore, Md.)*. **49** (5 Suppl): S13–21. doi:10.1002/hep.22881. PMC 2809016. PMID 19399811.
22. ^ Gocke DJ, Hsu K, Morgan C, Bombardieri S, Lockshin M, Christian CL (December 1970). "Association between polyarteritis and Australia antigen". *Lancet*. **2** (7684): 1149–53. doi:10.1016/S0140-6736(70)90339-9. PMID 4098431.
23. ^ Lai KN, Li PK, Lui SF, Au TC, Tam JS, Tong KL, Lai FM (May 1991). "Membranous nephropathy related to hepatitis B virus in adults". *The New England Journal of Medicine*. **324** (21): 1457–63. doi:10.1056/NEJM199105233242103. PMID 2023605.
24. ^ Takekoshi Y, Tanaka M, Shida N, Satake Y, Saheki Y, Matsumoto S (November 1978). "Strong association between membranous nephropathy and hepatitis-B surface antigenaemia in Japanese children". *Lancet*. **2** (8099): 1065–8. doi:10.1016/S0140-6736(78)91801-9. PMID 82085.
25. ^ "Hepatitis B FAQs for the Public". Centers for Disease Control and Prevention. Retrieved 2015-08-24.
26. ^ Fairley CK, Read TR (February 2012). "Vaccination against sexually transmitted infections". *Current Opinion in Infectious Diseases*. **25** (1): 66–72. doi:10.1097/QCO.0b013e32834e9aeb. PMID 22143117.
27. ^ Buddeberg F, Schimmer BB, Spahn DR (September 2008). "Transfusion-transmissible infections and transfusion-related immunomodulation". *Best Practice & Research. Clinical Anaesthesiology*. **22** (3): 503–17. doi:10.1016/j.bpa.2008.05.003. PMID 18831300.
28. ^ Hughes RA (March 2000). "Drug injectors and the cleaning of needles and syringes". *European Addiction Research*. **6** (1): 20–30. doi:10.1159/000019005. PMID 10729739.
29. ^ "Hepatitis B – the facts: IDEAS –Victorian Government Health Information, Australia". State of Victoria. 2009-07-28. Retrieved 2009-09-19.
30. ^ Shapiro CN (May 1993). "Epidemiology of hepatitis B". *Pediatr. Infect. Dis. J.* **12** (5): 433–437. doi:10.1097/00006454-199305000-00036. PMID 8392167.
31. ^ Shi Z, Yang Y, Wang H, Ma L, Schreiber A, Li X, Sun W, Zhao X, Yang X, Zhang L, Lu W, Teng J, An Y (2011). "Breastfeeding of Newborns by Mothers Carrying Hepatitis B Virus: A Meta-analysis and Systematic Review". *Archives of Pediatrics and Adolescent Medicine*. **165** (9): 837–846. doi:10.1001/archpediatrics.2011.72. PMID 21536948.
32. ^ WHO | Hepatitis B
33. ^ [a] [b] Zuckerman AJ (1996). "Hepatitis Viruses". In Baron S; et al. *Baron's Medical Microbiology* (4th ed.). University of Texas Medical Branch. ISBN 0-9631172-1-1.
34. ^ Locarnini S (2004). "Molecular Virology of Hepatitis B Virus". *Seminars in Liver Disease*. **24**: 3–10. doi:10.1055/s-2004-828672. PMID 15192795.
35. ^ Harrison T (2009). *Desk Encyclopedia of General Virology*. Boston: Academic Press. p. 455. ISBN 0-12-375146-2.
36. ^ Howard CR (1986). "The Biology of Hepadnaviruses". *Journal of General Virology*. **67** (7): 1215–1235. doi:10.1099/0022-1317-67-7-1215. PMID 3014045.
37. ^ Kay A, Zoulim F (2007). "Hepatitis B virus genetic variability and evolution". *Virus research*. **127** (2): 164–176. doi:10.1016/j.virusres.2007.02.021. PMID 17383765.
38. ^ Buti M, Rodriguez-Frias F, Jardi R, Esteban R (December 2005). "Hepatitis B virus genome variability and disease progression: the impact of pre-core mutants and HBV genotypes". *Journal of Clinical Virology*. 34 Suppl 1: S79–82. doi:10.1016/s1386-6532(05)80015-0. PMID 16461229.
39. ^ Glebe, Dieter; Urban, Stephan (2007-01-07). "Viral and cellular determinants involved in hepadnaviral entry". *World Journal of Gastroenterology : WJG*. **13** (1): 22–38. doi:10.3748/wjg.v13.i1.22. ISSN 1007-9327. PMC 4065874. PMID 17206752.
40. ^ [a] [b] Beck J, Nassal M (January 2007). "Hepatitis B virus replication". *World J. Gastroenterol*. **13** (1): 48–64. doi:10.3748/wjg.v13.i1.48. PMC 4065876. PMID 17206754.

41. ^ Li W, Miao X, Qi Z, Zeng W, Liang J, Liang Z (2010). "Hepatitis B virus X protein upregulates HSP90alpha expression via activation of c-Myc in human hepatocarcinoma cell line, HepG2". *Virol. J.* **7**: 45. doi:10.1186/1743-422X-7-45. PMC 2841080. PMID 20170530.
42. ^ [a] [b] Yan H, Zhong G, Xu G, He W, Jing Z, Gao Z, Huang Y, Qi Y, Peng B, Wang H, Fu L, Song M, Chen P, Gao W, Ren B, Sun Y, Cai T, Feng X, Sui J, Li W (2012). "Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus". *ELife*. **1**: e00049. doi:10.7554/eLife.00049. PMC 3485615. PMID 23150796.
43. ^ Bruss V (January 2007). "Hepatitis B virus morphogenesis". *World J. Gastroenterol*. **13** (1): 65–73. PMC 4065877. PMID 17206755.
44. ^ Kramvis A, Kew M, François G (March 2005). "Hepatitis B virus genotypes". *Vaccine*. **23** (19): 2409–23. doi:10.1016/j.vaccine.2004.10.045. PMID 15752827.
45. ^ Magnius LO, Norder H (1995). "Subtypes, genotypes and molecular epidemiology of the hepatitis B virus as reflected by sequence variability of the S-gene". *Intervirology*. **38** (1–2): 24–34. PMID 8666521.
46. ^ Araujo, NM (December 2015). "Hepatitis B virus intergenotypic recombinants worldwide: An overview.". *Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases*. **36**: 500–10. doi:10.1016/j.meegid.2015.08.024. PMID 26299884.
47. ^ Norder H, Couroucé AM, Magnius LO (1994). "Complete genomes, phylogenic relatedness and structural proteins of six strains of the hepatitis B virus, four of which represent two new genotypes". *Virology*. **198** (2): 489–503. doi:10.1006/viro.1994.1060. PMID 8291231.
48. ^ Shibayama T, Masuda G, Ajisawa A, Hiruma K, Tsuda F, Nishizawa T, Takahashi M, Okamoto H (May 2005). "Characterization of seven genotypes (A to E, G and H) of hepatitis B virus recovered from Japanese patients infected with human immunodeficiency virus type 1". *Journal of Medical Virology*. **76** (1): 24–32. doi:10.1002/jmv.20319. PMID 15779062.
49. ^ Schaefer S (January 2007). "Hepatitis B virus taxonomy and hepatitis B virus genotypes". *World Journal of Gastroenterology : WJG*. **13** (1): 14–21. doi:10.3748/wjg.v13.i1.14. PMC 4065870. PMID 17206751.
50. ^ Tong S, Li J, Wands JR (1999). "Carboxypeptidase D is an avian hepatitis B virus receptor" (PDF). *Journal of Virology*. **73** (10): 8696–8702. PMC 112890. PMID 10482623.
51. ^ Glebe D, Urban S (January 2007). "Viral and cellular determinants involved in hepadnaviral entry". *World J. Gastroenterol*. **13** (1): 22–38. doi:10.3748/wjg.v13.i1.22. PMC 4065874. PMID 17206752.
52. ^ Coffin CS, Mulrooney-Cousins PM, van Marle G, Roberts JP, Michalak TI, Terrault NA (April 2011). "Hepatitis B virus (HBV) quasispecies in hepatic and extrahepatic viral reservoirs in liver transplant recipients on prophylactic therapy". *Liver Transpl*. **17** (8): 955–62. doi:10.1002/lt.22312. PMID 21462295.
53. ^ Iannacone M, Sitia G, Ruggeri ZM, Guidotti LG (2007). "HBV pathogenesis in animal models: Recent advances on the role of platelets". *Journal of Hepatology*. **46** (4): 719–726. doi:10.1016/j.jhep.2007.01.007. PMC 1892635. PMID 17316876.
54. ^ Iannacone M, Sitia G, Isogawa M, Marchese P, Castro MG, Lowenstein PR, Chisari FV, Ruggeri ZM, Guidotti LG (November 2005). "Platelets mediate cytotoxic T lymphocyte-induced liver damage". *Nat. Med*. **11** (11): 1167–9. doi:10.1038/nm1317. PMC 2908083. PMID 16258538.
55. ^ Bonino F, Chiaberge E, Maran E, Piantino P (1987). "Serological markers of HBV infectivity". *Ann. Ist. Super. Sanita*. **24** (2): 217–23. PMID 3331068.
56. ^ Karayiannis P, Thomas HC (2009). Mahy BWJ, van Regenmortel MHV, eds. *Desk Encyclopedia of Human and Medical Virology*. Boston: Academic Press. p. 110. ISBN 0-12-375147-0.
57. ^ Liaw YF, Brunetto MR, Hadziyannis S (2010). "The natural history of chronic HBV infection and geographical differences". *Antiviral Therapy*. **15**: 25–33. doi:10.3851/IMP1621. PMID 21041901.
58. ^ Lok AS, McMahon BJ (February 2007). "Chronic hepatitis B". *Hepatology*. **45** (2): 507–39. doi:10.1002/hep.21513. PMID 17256718.
59. ^ Chu CM, Liaw YF (November 2007). "Predictive factors for reactivation of hepatitis B following hepatitis B e antigen seroconversion in chronic hepatitis B". *Gastroenterology*. **133** (5): 1458–65. doi:10.1053/j.gastro.2007.08.039. PMID 17935720.
60. ^ Zoulim F (November 2006). "New nucleic acid diagnostic tests in viral hepatitis". *Semin. Liver Dis*. **26** (4): 309–317. doi:10.1055/s-2006-951602. PMID 17051445.
61. ^ [a] [b] [c] [d] Schillie S, Murphy TV, Sawyer M, Ly K, Hughes E, Jiles R, de Perio MA, Reilly M, Byrd K, Ward JW (20 December 2013). "CDC Guidance for Evaluating Health-Care Personnel for Hepatitis B Virus Protection and for Administering Postexposure Management". *MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control*. **62** (RR-10): 1–19. PMID 24352112.
62. ^ Aspinall EJ, Hawkins G, Fraser A, Hutchinson SJ, Goldberg D (December 2011). "Hepatitis B prevention, diagnosis, treatment and care: a review". *Occupational Medicine*. **61** (8): 531–40. doi:10.1093/occmed/kqr136. PMID 22114089.

63. ^ Wong, F; Pai, R; Van Schalkwyk, J; Yoshida, EM (2014). "Hepatitis B in pregnancy: a concise review of neonatal vertical transmission and antiviral prophylaxis.". *Annals of Hepatology*. **13** (2): 187–95. PMID 24552860.
64. ^ [a] [b] Lutgens SP, Nelissen EC, van Loo IH, Koek GH, Derhaag JG, Dunselman GA (22 July 2009). "To do or not to do: IVF and ICSI in chronic hepatitis B virus carriers". *Human Reproduction*. **24** (11): 2676–8. doi:10.1093/humrep/dep258. PMID 19625309.
65. ^ [a] [b] LeFevre ML (May 27, 2014). "Screening for Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults: U.S. Preventive Services Task Force Recommendation Statement". *Annals of Internal Medicine*. **161** (1): 58–66. doi:10.7326/M14-1018. PMID 24863637.
66. ^ Shepard CW, Simard EP, Finelli L, Fiore AE, Bell BP (2006). "Hepatitis B virus infection: epidemiology and vaccination.". *Epidemiologic reviews*. **28**: 112–25. doi:10.1093/epirev/mxj009. PMID 16754644.
67. ^ Hollinger FB, Lau DT (December 2006). "Hepatitis B: the pathway to recovery through treatment". *Gastroenterology Clinics of North America*. **35** (4): 895–931. doi:10.1016/j.gtc.2006.10.002. PMID 17129820.(registration required)
68. ^ HBV FAQs for Health Professionals | Division of Viral Hepatitis | CDC
69. ^ Lai CL, Yuen MF (July 2007). "The natural history and treatment of chronic hepatitis B: a critical evaluation of standard treatment criteria and end points". *Annals of Internal Medicine*. **147** (1): 58–61. doi:10.7326/0003-4819-147-1-200707030-00010. PMID 17606962.
70. ^ Alberti A, Caporaso N (January 2011). "HBV therapy: guidelines and open issues". *Digestive and Liver Disease*. **43** (Suppl 1): S57–63. doi:10.1016/S1590-8658(10)60693-7. PMID 21195373.
71. ^ [a] [b] [c] [d] *GUIDELINES FOR THE PREVENTION, CARE AND TREATMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION* (PDF). World Health Organization. Mar 2015. ISBN 978924154905 9.
72. ^ [a] [b] Dienstag JL (2008). "Hepatitis B Virus Infection". *New England Journal of Medicine*. **359** (14): 1486–1500. doi:10.1056/NEJMra0801644. PMID 18832247.
73. ^ Pramoolsinsup C (February 2002). "Management of viral hepatitis B". *Journal of Gastroenterology and Hepatology*. **17** (Suppl): S125–45. doi:10.1046/j.1440-1746.17.s1.3.x. PMID 12000599.(subscription required)
74. ^ Cao GW (December 2009). "Clinical relevance and public health significance of hepatitis B virus genomic variations". *World Journal of Gastroenterology : WJG*. **15** (46): 5761–9. doi:10.3748/wjg.15.5761. PMC 2791267. PMID 19998495.
75. ^ Bell SJ, Nguyen T (2009). "The management of hepatitis B". *Aust Prescr*. **32** (4): 99–104. doi:10.18773/austprescr.2009.048.
76. ^ Kerkar N (2005). "Hepatitis B in children: complexities in management". *Pediatric transplantation*. **9** (5): 685–691. doi:10.1111/j.1399-3046.2005.00393.x. PMID 16176431.
77. ^ Taylor JM (2006). "Hepatitis delta virus". *Virology*. **344** (1): 71–76. doi:10.1016/j.virol.2005.09.033. PMID 16364738.
78. ^ Oliveri F, Brunetto MR, Actis GC, Bonino F (November 1991). "Pathobiology of chronic hepatitis virus infection and hepatocellular carcinoma (HCC)". *Ital J Gastroenterol*. **23** (8): 498–502. PMID 1661197.
79. ^ Vierling JM (November 2007). "The immunology of hepatitis B". *Clin Liver Dis*. **11** (4): 727–759, vii–759. doi:10.1016/j.cld.2007.08.001. PMID 17981227.
80. ^ Villa E, Fattovich G, Mauro A, Pasino M (January 2011). "Natural history of chronic HBV infection: special emphasis on the prognostic implications of the inactive carrier state versus chronic hepatitis". *Digestive and Liver Disease*. **43** (Suppl 1): S8–14. doi:10.1016/S1590-8658(10)60686-X. PMID 21195374.
81. ^ Katz LH, Fraser A, Gafter-Gvili A, Leibovici L, Tur-Kaspa R (February 2008). "Lamivudine prevents reactivation of hepatitis B and reduces mortality in immunosuppressed patients: systematic review and meta-analysis". *J. Viral Hepat*. **15** (2): 89–102. doi:10.1111/j.1365-2893.2007.00902.x. PMID 18184191.
82. ^ Roche B, Samuel D (January 2011). "The difficulties of managing severe hepatitis B virus reactivation". *Liver International : Official Journal of the International Association for the Study of the Liver*. **31** (Suppl 1): 104–10. doi:10.1111/j.1478-3231.2010.02396.x. PMID 21205146.
83. ^ [a] [b] [c] Mastroianni CM, Lichtner M, Citton R, Del Borgo C, Rago A, Martini H, Cimino G, Vullo V (September 2011). "Current trends in management of hepatitis B virus reactivation in the biologic therapy era". *World Journal of Gastroenterology : WJG*. **17** (34): 3881–7. doi:10.3748/wjg.v17.i34.3881. PMC 3198017. PMID 22025876.
84. ^ Bonacini, Maurizio, MD. "Hepatitis B Reactivation". University of Southern California Department of Surgery. Archived from the original on 27 November 2008. Retrieved 2009-01-24.
85. ^ Custer B, Sullivan SD, Hazlet TK, Iloeje U, Veenstra DL, Kowdley KV (Nov–Dec 2004). "Global epidemiology of hepatitis B virus". *Journal of Clinical Gastroenterology*. **38** (10 Suppl 3): S158–68. doi:10.1097/00004836-200411003-00008. PMID 15602165.
86. ^ Redd JT, Baumbach J, Kohn W, Nainan O, Khristova M, Williams I (May 2007). "Patient-to-patient transmission of hepatitis B virus associated with oral surgery". *J. Infect. Dis*. **195** (9): 1311–4. doi:10.1086/513435. PMID 17397000.

87. ^ Alter MJ (2003). "Epidemiology and prevention of hepatitis B". *Seminars in liver disease*. **23** (1): 39–46. doi:10.1055/s-2003-37583. PMID 12616449.
88. ^ Komas NP, Vickos U, Hübschen JM, Béré A, Manirakiza A, Muller CP, Le Faou A (1 January 2013). "Cross-sectional study of hepatitis B virus infection in rural communities, Central African Republic". *BMC Infectious Diseases*. **13**: 286. doi:10.1186/1471-2334-13-286. PMC 3694350. PMID 23800310.
89. ^ "Healthcare stumbling in RI's Hepatitis fight". *The Jakarta Post*. 2011-01-13.
90. ^ Lurman A (1885). "Eine icterus epidemic". *Berl Klin Woschenschr* (in German). **22**: 20–3.
91. ^ Alter HJ, Blumberg BS (March 1966). "Further studies on a "new" human isoprecipitin system (Australia antigen)". *Blood*. **27** (3): 297–309. PMID 5930797.
92. ^ MacCallum FO (1947). "Homologous serum hepatitis". *Lancet*. **2**: 691–692. doi:10.1016/S0140-6736(47)90722-8.
93. ^ Dane DS, Cameron CH, Briggs M (April 1970). "Virus-like particles in serum of patients with Australia-antigen-associated hepatitis". *Lancet*. **1** (7649): 695–8. doi:10.1016/S0140-6736(70)90926-8. PMID 4190997.
94. ^ Galibert F, Mandart E, Fitoussi F, Tiollais P, Charnay P (October 1979). "Nucleotide sequence of the hepatitis B virus genome (subtype ayw) cloned in E. coli". *Nature*. **281** (5733): 646–50. Bibcode:1979Natur.281..646G. doi:10.1038/281646a0. PMID 399327.
95. ^ "Hepatitis B vaccine". *Lancet*. **2** (8206): 1229–1230. December 1980. doi:10.1016/S0140-6736(80)92484-8. PMID 6108398.
96. ^ "Viral hepatitis" (PDF).


## External links [edit]

- Hepatitis B at DMOZ
- *GUIDELINES FOR THE PREVENTION, CARE AND TREATMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION* (PDF). World Health Organization. Mar 2015. ISBN 978924154905 9.
- "*Hepatitis B virus*". *NCBI Taxonomy Browser*. 10407.

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| v · t · e · | **Sexually transmitted infection (STI) (primarily A50–A64, 090–099)** |
|---|---|
| **Bacterial** | Chancroid (*Haemophilus ducreyi*) · Chlamydia/Lymphogranuloma venereum (*Chlamydia trachomatis*) · Donovanosis or Granuloma Inguinale (*Klebsiella granulomatis*) · Gonorrhea (*Neisseria gonorrhoeae*) · Mycoplasma hominis infection (*Mycoplasma hominis*) · Syphilis (*Treponema pallidum*) · Ureaplasma infection (*Ureaplasma urealyticum*) · |
| **Protozoal** | Trichomoniasis (*Trichomonas vaginalis*) · |
| **Parasitic** | Crab louse/crabs · Scabies · |
| **Viral** | AIDS (*HIV-1/HIV-2*) · Cervical cancer, vulvar cancer & Genital warts (condyloma), Penile cancer, Anal cancer (*Human papillomavirus (HPV)*) · **Hepatitis B** (*Hepatitis B virus*) · Herpes simplex (*HSV1/HSV2*) · Molluscum contagiosum (*MCV*) · |
| **General inflammation** | *female*: Cervicitis · Pelvic inflammatory disease (PID) · *male*: Epididymitis · Prostatitis · *either*: Proctitis · Urethritis/Non-gonococcal urethritis (NGU) · |

| v · t · e · | **Infectious diseases – viral systemic diseases (A80–B34, 042–079)** |
|---|---|
| **Oncovirus** | **DNA virus:** *HBV* (Hepatocellular carcinoma · · *HPV* (Cervical cancer · Anal cancer · Penile cancer · Vulvar cancer · Vaginal cancer · Oropharyngeal cancer · · *KSHV* (Kaposi's sarcoma · · *EBV* (Nasopharynx cancer · Burkitt's lymphoma · Hodgkin's lymphoma · Follicular dendritic cell sarcoma · Extranodal NK/T-cell lymphoma, nasal type · · *MCPyV* (Merkel-cell carcinoma · · **RNA virus:** *HCV* (Hepatocellular carcinoma · Splenic marginal zone lymphoma · · |

| | | |
|---|---|---|
| | *HTLV-I* (Adult T-cell leukemia/lymphoma | |
| **Immune disorders** | *HIV* (AIDS | |
| **Central nervous system** | **Encephalitis/ meningitis** | **DNA virus:** *JCV* (Progressive multifocal leukoencephalopathy<br>**RNA virus:** *MeV* (Subacute sclerosing panencephalitis *LCV* (Lymphocytic choriomeningitis Arbovirus encephalitis *Orthomyxoviridae (probable)* (Encephalitis lethargica *RV* (Rabies Chandipura virus Herpesviral meningitis Ramsay Hunt syndrome type 2 |
| | **Myelitis** | *Poliovirus* (Poliomyelitis Post-polio syndrome *HTLV-I* (Tropical spastic paraparesis |
| | **Eye** | *Cytomegalovirus* (Cytomegalovirus retinitis *HSV* (Herpes of the eye |
| **Cardiovascular** | *CBV* (Pericarditis Myocarditis | |
| **Respiratory system/ acute viral nasopharyngitis/ viral pneumonia** | **DNA virus** | *Epstein–Barr virus* (EBV infection/Infectious mononucleosis *Cytomegalovirus* |
| | **RNA virus** | IV: *SARS coronavirus* (Severe acute respiratory syndrome<br>V: *Orthomyxoviridae: Influenzavirus A/B/C* (Influenza/Avian influenza<br>V, *Paramyxoviridae: Human parainfluenza viruses* (Parainfluenza *RSV* *hMPV* |
| **Human digestive system** | **Pharynx/Esophagus** | *MuV* (Mumps *Cytomegalovirus* (Cytomegalovirus esophagitis |
| | **Gastroenteritis/ diarrhea** | **DNA virus:** *Adenovirus* (Adenovirus infection<br>**RNA virus:** *Rotavirus* *Norovirus* *Astrovirus* *Coronavirus* |
| | **Hepatitis** | **DNA virus:** *HBV* (**B**)<br>**RNA virus:** *CBV* *HAV* (A) *HCV* (C) *HDV* (D) *HEV* (E) *HGV* (G) |
| | **Pancreatitis** | *CBV* |
| **Urogenital** | *BK virus* *MuV* (Mumps | |

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|---|---|
| **Authority control** | NDL: 00986940 |

Categories: Hepatitis B | Sexually transmitted diseases and infections | Virus-related cutaneous conditions | Infectious causes of cancer | Viral diseases

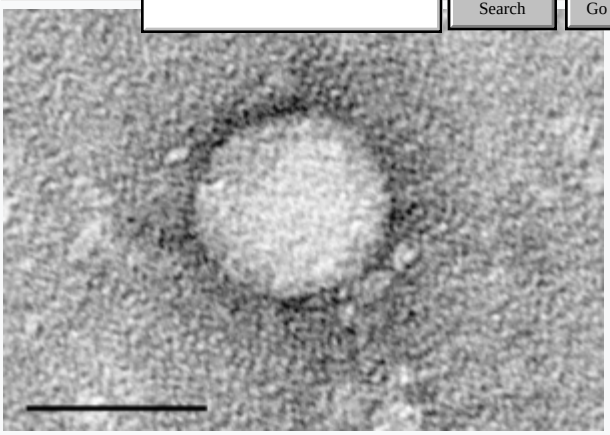
# Hepatitis C

From Wikipedia, the free encyclopedia

**Hepatitis C** is an infectious disease caused by the hepatitis C virus (HCV) that primarily affects the liver.[1] During the initial infection people often have mild or no symptoms. Occasionally a fever, dark urine, abdominal pain, and yellow tinged skin occurs. The virus persists in the liver in about 75% to 85% of those initially infected. Early on chronic infection typically has no symptoms. Over many years however, it often leads to liver disease and occasionally cirrhosis.[2] In some cases, those with cirrhosis will develop complications such as liver failure, liver cancer, or esophageal and gastric varices.[1]

HCV is spread primarily by blood-to-blood contact associated with intravenous drug use, poorly sterilized medical equipment, needlestick injuries in healthcare, and transfusions.[2][3] Using blood screening, the risk from a transfusion is less than one per two million.[2] It may also be spread from an infected mother to her baby during birth.[2] It is not spread by superficial contact.[4] It is one of five known hepatitis viruses: A, B, C, D, and E.[5] Diagnosis is by blood testing to look for either antibodies to the virus or its RNA. Testing is recommended in all people who are at risk.[2]

There is no vaccine against hepatitis C.[2][6] Prevention includes harm reduction efforts among people who use intravenous drugs and testing donated blood.[4] Chronic infection can be cured about 90% of the time with treatments that include the medications sofosbuvir or simeprevir.[2][4] Previous to this a combination of peginterferon and ribavirin was used which had a cure rate around 50% and greater side effects. Getting access to the newer treatments however can be expensive.[4] Those who develop cirrhosis or liver cancer may require a liver transplant. Hepatitis C is the leading reason for liver transplantation, though the virus usually recurs after transplantation.[7]



Electron micrograph of hepatitis C virus from cell culture (scale = 50 nanometers)

| Classification and external resources | |
|---|---|
| **Specialty** | Gastroenterology, infectious disease |
| **ICD-10** | B17.1, B18.2 |
| **ICD-9-CM** | 070.70,070.4, 070.5 |
| **OMIM** | 609532 |
| **DiseasesDB** | 5783 |
| **MedlinePlus** | 000284 |
| **eMedicine** | med/993 ped/979 |
| **Patient UK** | Hepatitis C |
| **MeSH** | D006526 |

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An estimated 130–200 million people worldwide are infected with hepatitis C.[4][8][9] In 2013 about 11 million new cases occurred.[10] It occurs most commonly in Africa and Central and East Asia.[4] About 343,000 deaths due to liver cancer and 358,000 deaths due to cirrhosis occurred in 2013 due to hepatitis C.[11] The existence of hepatitis C – originally identifiable only as a type of non-A non-B hepatitis – was

suggested in the 1970s and proven in 1989.[12] Hepatitis C infects only humans and chimpanzees.[13]





# Signs and symptoms

## Acute infection

Hepatitis C infection causes acute symptoms in 15% of cases.[14] Symptoms are generally mild and vague, including a decreased appetite, fatigue, nausea, muscle or joint pains, and weight loss[15] and rarely does acute liver failure result.[16] Most cases of acute infection are not associated with jaundice.[17] The infection resolves spontaneously in 10–50% of cases, which occurs more frequently in individuals who are young and female.[17]

## Chronic infection

About 80% of those exposed to the virus develop a chronic infection.[18] This is defined as the presence of detectable viral replication for at least six months. Most experience minimal or no symptoms during the initial few decades of the infection.[19] Chronic hepatitis C can be associated with fatigue[20] and mild cognitive problems.[21] Chronic infection after several years may cause cirrhosis or liver cancer.[7] The liver

enzymes are normal in 7–53%.[22] Late relapses after apparent cure have been reported, but these can be difficult to distinguish from reinfection.[22]

Fatty changes to the liver occur in about half of those infected and are usually present before cirrhosis develops.[23][24] Usually (80% of the time) this change affects less than a third of the liver.[23] Worldwide hepatitis C is the cause of 27% of cirrhosis cases and 25% of hepatocellular carcinoma.[25] About 10–30% of those infected develop cirrhosis over 30 years.[7][15] Cirrhosis is more common in those also infected with hepatitis B, schistosoma, or HIV, in alcoholics and in those of male gender.[15] In those with hepatitis C, excess alcohol increases the risk of developing cirrhosis 100-fold.[26] Those who develop cirrhosis have a 20-fold greater risk of hepatocellular carcinoma. This transformation occurs at a rate of 1–3% per year.[7][15] Being infected with hepatitis B in addition to hepatitis C increases this risk further.[27]

Liver cirrhosis may lead to portal hypertension, ascites (accumulation of fluid in the abdomen), easy bruising or bleeding, varices (enlarged veins, especially in the stomach and esophagus), jaundice, and a syndrome of cognitive impairment known as hepatic encephalopathy.[28] Ascites occurs at some stage in more than half of those who have a chronic infection.[29]

## Extrahepatic complications

The most common problem due to hepatitis C but not involving the liver is mixed cryoglobulinemia (usually the type II form) — an inflammation of small and medium-sized blood vessels.[30][31] Hepatitis C is also associated with the autoimmune disorder Sjögren's syndrome, a low platelet count, lichen planus, porphyria cutanea tarda, necrolytic acral erythema, insulin resistance, diabetes mellitus, diabetic nephropathy, autoimmune thyroiditis, and B-cell lymphoproliferative disorders.[32][33] 20–30% of people infected have rheumatoid factor — a type of antibody.[34] Possible associations include Hyde's prurigo nodularis[35] and membranoproliferative glomerulonephritis.[20] Cardiomyopathy with associated abnormal heart rhythms has also been reported.[36] A variety of central nervous system disorders has been reported.[37] Chronic infection seems to be associated with an increased risk of pancreatic cancer.[6][38]

## Occult infection

Persons who have been infected with hepatitis C may appear to clear the virus but remain infected.[39] The virus is not detectable with conventional testing but can be found with ultra-sensitive tests.[40] The original method of detection was by demonstrating the viral genome within liver biopsies, but newer methods include an antibody test for the virus' core protein and the detection of the viral genome after first concentrating the viral particles by ultracentrifugation.[41] A form of infection with persistently moderately elevated serum liver enzymes but without antibodies to hepatitis C has also been reported.[42] This form is known as cryptogenic occult infection.

Several clinical pictures have been associated with this type of infection.[43] It may be found in people with anti-hepatitis-C antibodies but with normal serum levels of liver enzymes; in antibody-negative people with ongoing elevated liver enzymes of unknown cause; in healthy populations without evidence of liver disease; and in groups at risk for HCV infection including those on hemodialysis or family members of people with occult HCV. The clinical relevance of this form of infection is under investigation.[44] The consequences of occult infection appear to be less severe than with chronic infection but can vary from minimal to hepatocellular carcinoma.[41]

The rate of occult infection in those apparently cured is controversial but appears to be low.[22] 40% of those with hepatitis but with both negative hepatitis C serology and the absence of detectable viral genome in the serum have hepatitis C virus in the liver on biopsy.[45] How commonly this occurs in children is unknown.[46]

# Virology

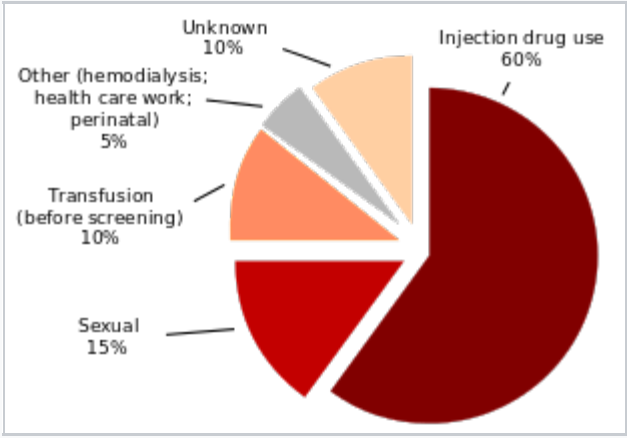
*Main article: Hepatitis C virus*

The hepatitis C virus (HCV) is a small, enveloped, single-stranded, positive-sense RNA virus.[7] It is a member of the *Hepacivirus* genus in the family *Flaviviridae*.[20] There are seven major genotypes of HCV, which are known as genotypes one to seven.[47] The genotypes are divided into several subtypes with the number of subtypes depending on the genotype. In the United States, about 70% of cases are caused by genotype 1, 20% by genotype 2 and about 1% by each of the other genotypes.[15] Genotype 1 is also the most common in South America and Europe.[7]

The half life of the virus particles in the serum is around 3 hours and may be as short as 45 minutes.[48][49] In an infected person, about $10^{12}$ virus particles are produced each day.[48] In addition to replicating in the liver the virus can multiply in lymphocytes.[50]

# Transmission

The primary route of transmission in the developed world is intravenous drug use (IDU), while in the developing world the main methods are blood transfusions and unsafe medical procedures.[3] The cause of transmission remains unknown in 20% of cases;[51] however, many of these are believed to be accounted for by IDU.[17]



Hepatitis C infection in the United States by source

## Drug use

Intravenous drug use (IDU) is a major risk factor for hepatitis C in many parts of the world.[52] Of 77 countries reviewed, 25 (including the United States) were found to have prevalences of hepatitis C in the intravenous drug user population of between 60% and 80%.[18][52] Twelve countries had rates greater than 80%.[18] It is believed that ten million intravenous drug users are infected with hepatitis C; China (1.6 million), the United States (1.5 million), and Russia (1.3 million) have the highest absolute totals.[18] Occurrence of hepatitis C among prison inmates in the United States is 10 to 20 times that of the occurrence observed in the general population; this has been attributed to high-risk behavior in prisons such as IDU and tattooing with nonsterile equipment.[53][54] Shared intranasal drug use may also be a risk factor.[55]

## Healthcare exposure

Blood transfusion, transfusion of blood products, or organ transplants without HCV screening carry significant risks of infection.[15] The United States instituted universal screening in 1992[56] and Canada instituted universal screening in 1990.[57] This decreased the risk from one in 200 units[56] to between one in 10,000 to one in 10,000,000 per unit of blood.[17][51] This low risk remains as there is a period of about 11–70 days between the potential blood donor's acquiring hepatitis C and the blood's testing positive depending on the method.[51] Some countries do not screen for hepatitis C due to the cost.[25]

Those who have experienced a needle stick injury from someone who was HCV positive have about a 1.8% chance of subsequently contracting the disease themselves.[15] The risk is greater if the needle in question is hollow and the puncture wound is deep.[25] There is a risk from mucosal exposures to blood, but this risk is low, and there is no risk if blood exposure occurs on intact skin.[25]

Hospital equipment has also been documented as a method of transmission of hepatitis C, including reuse of needles and syringes; multiple-use medication vials; infusion bags; and improperly sterilized surgical equipment, among others.[25] Limitations in the implementation and enforcement of stringent standard

precautions in public and private medical and dental facilities are known to be the primary cause of the spread of HCV in Egypt, the country with highest rate of infection in the world.[58]

### Sexual intercourse

Whether hepatitis C can be transmitted through sexual activity is controversial.[59] While there is an association between high-risk sexual activity and hepatitis C, and multiple sexual partners are a risk factor for hepatitis C, there is no conclusive evidence that hepatitis C can be transmitted by sexual activity, since people who report transmission with sex as their only risk factor may actually have used drugs but denied it.[15] The majority of evidence supports there being no risk for heterosexual couples with only one sexual partner.[59] Sexual practices that involve higher levels of trauma to the anogenital mucosa, such as anal penetrative sex, or that occur when there is a concurrent sexually transmitted infection, including HIV or genital ulceration, do present a risk.[59] The United States Department of Veterans Affairs recommends condom use to prevent hepatitis C transmission in those with multiple partners, but not those in relationships that involve only a single partner.[60]

### Body modification

Tattooing is associated with two to threefold increased risk of hepatitis C.[61] This can be due to either improperly sterilized equipment or contamination of the dyes being used.[61] Tattoos or piercings performed either before the mid-1980s, "underground," or nonprofessionally are of particular concern, since sterile techniques in such settings may be lacking. The risk also appears to be greater for larger tattoos.[61] It is estimated that nearly half of prison inmates share unsterilized tattooing equipment.[61] It is rare for tattoos in a licensed facility to be directly associated with HCV infection.[62]

### Shared personal items

Personal-care items such as razors, toothbrushes, and manicuring or pedicuring equipment can be contaminated with blood. Sharing such items can potentially lead to exposure to HCV.[63][64] Appropriate caution should be taken regarding any medical condition that results in bleeding, such as cuts and sores.[64] HCV is not spread through casual contact, such as hugging, kissing, or sharing eating or cooking utensils.[64] Neither is it transmitted through food or water.[65]

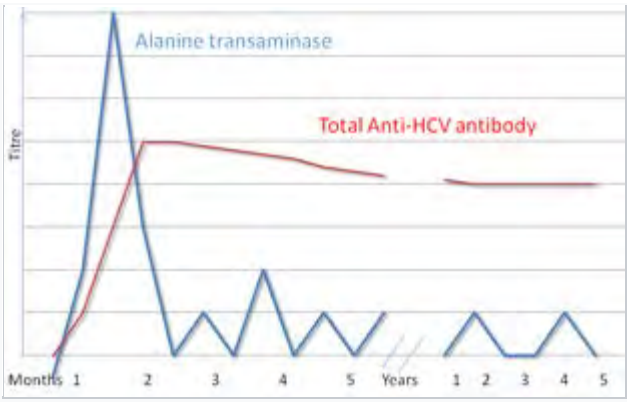
### Mother-to-child transmission

Mother-to-child transmission of hepatitis C occurs in less than 10% of pregnancies.[66] There are no measures that alter this risk.[66] It is not clear when transmission occurs during pregnancy, but it may occur both during gestation and at delivery.[51] A long labor is associated with a greater risk of transmission.[25] There is no evidence that breast-feeding spreads HCV; however, to be cautious, an infected mother is advised to avoid breastfeeding if her nipples are cracked and bleeding,[67] or if her viral loads are high.[51]

## Diagnosis

There are a number of diagnostic tests for hepatitis C, including HCV antibody enzyme immunoassay or ELISA, recombinant immunoblot assay, and quantitative HCV RNA polymerase chain reaction (PCR).[15] HCV RNA can be detected by PCR typically one to two weeks after infection, while antibodies can take substantially longer to form and thus be detected.[28]

Chronic hepatitis C is defined as infection with the



Serologic profile of Hepatitis C infection

hepatitis C virus persisting for more than six months based on the presence of its RNA.[19] Chronic infections are typically asymptomatic during the first few decades,[19] and thus are most commonly discovered following the investigation of elevated liver enzyme levels or during a routine screening of high-risk individuals. Testing is not able to distinguish between acute and chronic infections.[25] Diagnosis in the infant is difficult as maternal antibodies may persist for up to 18 months.[46]

## Serology

Hepatitis C testing typically begins with blood testing to detect the presence of antibodies to the HCV, using an enzyme immunoassay.[15] If this test is positive, a confirmatory test is then performed to verify the immunoassay and to determine the viral load.[15] A recombinant immunoblot assay is used to verify the immunoassay and the viral load is determined by an HCV RNA polymerase chain reaction.[15] If there is no RNA and the immunoblot is positive, it means that the person tested had a previous infection but cleared it either with treatment or spontaneously; if the immunoblot is negative, it means that the immunoassay was wrong.[15] It takes about 6–8 weeks following infection before the immunoassay will test positive.[20] A number of tests are available as point of care testing which means that results are available within 30 minutes.[68]

Liver enzymes are variable during the initial part of the infection[19] and on average begin to rise at seven weeks after infection.[20] The elevation of liver enzymes does not closely follow disease severity.[20]

## Biopsy

Liver biopsies are used to determine the degree of liver damage present; however, there are risks from the procedure.[7] The typical changes seen are lymphocytes within the parenchyma, lymphoid follicles in portal triad, and changes to the bile ducts.[7] There are a number of blood tests available that try to determine the degree of hepatic fibrosis and alleviate the need for biopsy.[7]

## Screening

It is believed that only 5–50% of those infected in the United States and Canada are aware of their status.[61] Testing is recommended for those at high risk, which includes injection drug users, those who have received blood transfusions before 1992,[69] those who have been in jail, those on long term hemodialysis,[70] and those with tattoos.[61] Screening is also recommended in those with elevated liver enzymes, as this is frequently the only sign of chronic hepatitis.[71] Routine screening is not currently recommended in the United States.[15] In 2012, the U.S. Centers for Disease Control and Prevention (CDC) added a recommendation for a single screening test for those born between 1945 and 1965.[72]

# Prevention

*See also: Hepatitis C vaccine*

[73]

As of 2016, no approved vaccine protects against contracting hepatitis C. However, there are a number of vaccines under development and some have shown encouraging results.[73]

A combination of harm reduction strategies, such as the provision of new needles and syringes and treatment of substance use, decreases the risk of hepatitis C in intravenous drug users by about 75%.[74] The screening of blood donors is important at a national level, as is adhering to universal precautions within healthcare facilities.[20] In countries where there is an insufficient supply of sterile syringes, medications should be given orally rather than via injection (when possible).[25]

# Treatment

HCV induces chronic infection in 50–80% of infected persons. Approximately 40–80% of these clear with treatment.[75][76] In rare cases, infection can clear without treatment.[17] Those with chronic hepatitis C are advised to avoid alcohol and medications toxic to the liver,[15] and to be vaccinated for hepatitis A and hepatitis B.[15] Ultrasound surveillance for hepatocellular carcinoma is recommended in those with accompanying cirrhosis.[15]

## Medications

Treatment with antiviral medication is recommended in all people with proven chronic hepatitis C who are not at high risk of dying from other causes.[77] People with the highest complication risk should be treated first, with the risk of complications based on the degree of liver scarring.[77] The initial recommended treatment depends on the type of hepatitis C virus with which a person is infected.[77]

- HCV genotype 1a: 12 weeks of ledipasvir and sofosbuvir OR 12 to 24 weeks of paritaprevir, ombitasvir, dasabuvir, and ribavirin[6][77]
- HCV genotype 1b: 12 weeks of ledipasvir and sofosbuvir OR 12 weeks of paritaprevir, ombitasvir, and dasabuvir[77]
- HCV genotype 2: 12 to 16 weeks of sofosbuvir and ribavirin[77]
- HCV genotype 3: 12 weeks of sofosbuvir, ribavirin, and pegylated interferon[77]
- HCV genotype 4: 12 weeks of ledipasvir and sofosbuvir OR paritaprevir, ritonavir, ombitasvir, and ribavirin, OR 24 weeks of sofosbuvir and ribavirin[77]
- HCV genotype 5 or 6: sofosbuvir and ledipasvir[77]

Sofosbuvir with ribavirin and interferon appears to be around 90% effective in those with genotype 1, 4, 5, or 6 disease.[78] Sofosbuvir with just ribavirin appears to be 70 to 95% effective in type 2 and 3 disease but has a higher rate of adverse effects.[78][79] Treatments that contain ledipasvir and sofosbuvir for genotype 1 has success rates of around 93 to 99% but is very expensive.[80] In genotype 6 infection, pegylated interferon and ribavirin is effective in 60 to 90% of cases.[81] There is some tentative data for simeprevir use in type 6 disease as well.[81]

Prior to 2011, treatments consisted of a combination of pegylated interferon alpha and ribavirin for a period of 24 or 48 weeks, depending on HCV genotype.[15] This produces cure rates of between 70 and 80% for genotype 2 and 3, respectively, and 45 to 70% for genotypes 1 and 4.[79] Adverse effects with these treatments were common, with half of people getting flu like symptoms and a third experiencing emotional problems.[15] Treatment during the first six months is more effective than once hepatitis C has become chronic.[28]

## Surgery

Cirrhosis due to hepatitis C is a common reason for liver transplantation[28] though the virus usually (80–90% of cases) recurs afterwards.[7][82] Infection of the graft leads to 10–30% of people developing cirrhosis within five years.[83] Treatment with pegylated interferon and ribavirin post transplant decreases

the risk of recurrence to 70%.[84]

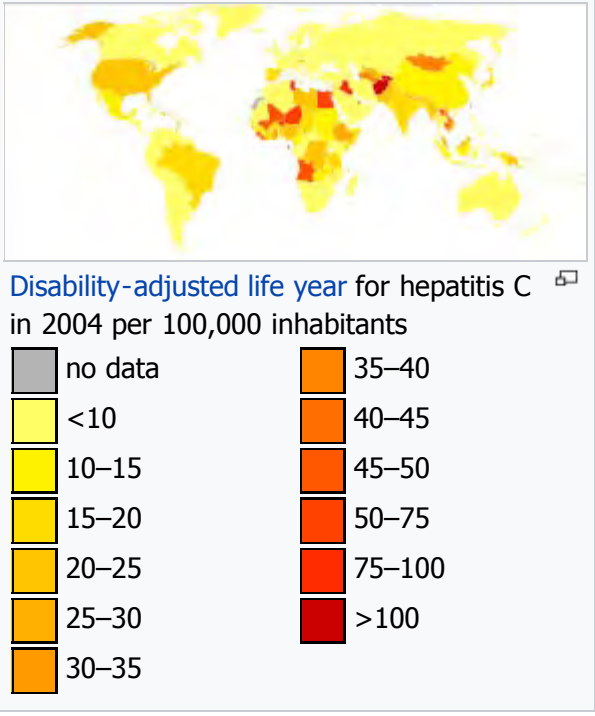
### Alternative medicine

Several alternative therapies are claimed by their proponents to be helpful for hepatitis C including milk thistle, ginseng, and colloidal silver.[85] However, no alternative therapy has been shown to improve outcomes in hepatitis C, and no evidence exists that alternative therapies have any effect on the virus at all.[85][86][87]

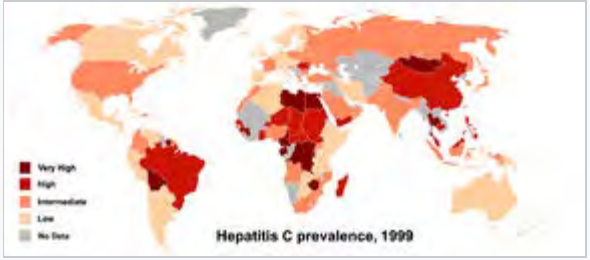
## Prognosis

The responses to treatment is measured by *sustained viral response* (SVR), defined as the absence of detectable RNA of the hepatitis C virus in blood serum for at least 24 weeks after discontinuing the treatment,[88] and rapid virological response (RVR) defined as undetectable levels achieved within four weeks of treatment. Successful treatment decreases the future risk of hepatocellular carcinoma by 75%.[89]

Prior to 2012 sustained response occurs in about 40–50% in people with HCV genotype 1 given 48 weeks of treatment.[7] A sustained response is seen in 70–80% of people with HCV genotypes 2 and 3 with 24 weeks of treatment.[7] A sustained response occurs about 65% in those with genotype 4 after 48 weeks of treatment. The evidence for treatment in genotype 6 disease is sparse and what evidence there is supports 48 weeks of treatment at the same doses used for genotype 1 disease.[90]




## Epidemiology



Prevalence of hepatitis C worldwide in 1999

It is estimated that 150–200 million people, or ~3% of the world's population, are living with chronic hepatitis C.[8][9][91] About 3–4 million people are infected per year, and more than 350,000 people die yearly from hepatitis C-related diseases.[91] During 2010 it is estimated that 16,000 people died from acute infections while 196,000 deaths occurred from liver cancer secondary to the infection.[92] Rates have increased substantially in the 20th century due to a combination of intravenous drug abuse and reused but poorly sterilized medical equipment.[25]

Rates are high (>3.5% population infected) in Central and East Asia, North Africa and the Middle East, they are intermediate (1.5%-3.5%) in South and Southeast Asia, sub-Saharan Africa, Andean, Central and Southern Latin America, Caribbean, Oceania, Australasia and Central, Eastern and Western Europe; and they are low (<1.5%) in Asia-Pacific, Tropical Latin America and North America.[9]

Among those chronically infected, the risk of cirrhosis after 20 years varies between studies but has been estimated at ~10–15% for men and ~1–5% for women. The reason for this difference is not known. Once cirrhosis is established, the rate of developing hepatocellular carcinoma is ~1–4% per year.[93] Rates of new infections have decreased in the Western world since the 1990s due to improved screening of blood

before transfusion.[28]

In the United States, about 2% of people have chronic hepatitis C.[15] In 2014, an estimated 30,500 new acute hepatitis C cases occurred (0.7 per 100,000 population), an increase from 2010–2012.[94] The number of deaths from hepatitis C has increased to 15,800 in 2008[95] having overtaken HIV/AIDS as a cause of death in the USA in 2007.[96] In 2014 it was the single greatest cause of infectious death in the United States.[97] This mortality rate is expected to increase, as those infected by transfusion before HCV testing become apparent.[98] In Europe the percentage of people with chronic infections has been estimated to be between 0.13 and 3.26%.[99]

In England about 160,000 people are chronically infected.[100] Between 2006 and 2011 28,000 about 3%, received treatment.[100]

The total number of people with this infection is higher in some countries in Africa and Asia.[101] Countries with particularly high rates of infection include Egypt (22%), Pakistan (4.8%) and China (3.2%).[91] It is believed that the high prevalence in Egypt is linked to a now-discontinued mass-treatment campaign for schistosomiasis, using improperly sterilized glass syringes.[25]

## History

In the mid-1970s, Harvey J. Alter, Chief of the Infectious Disease Section in the Department of Transfusion Medicine at the National Institutes of Health, and his research team demonstrated how most post-transfusion hepatitis cases were not due to hepatitis A or B viruses. Despite this discovery, international research efforts to identify the virus, initially called *non-A, non-B hepatitis* (NANBH), failed for the next decade. In 1987, Michael Houghton, Qui-Lim Choo, and George Kuo at Chiron Corporation, collaborating with Daniel W. Bradley at the Centers for Disease Control and Prevention, used a novel molecular cloning approach to identify the unknown organism and develop a diagnostic test.[102] In 1988, Alter confirmed the virus by verifying its presence in a panel of NANBH specimens. In April 1989, the discovery of HCV was published in two articles in the journal *Science*.[103][104] The discovery led to significant improvements in diagnosis and improved antiviral treatment.[6][102] In 2000, Drs. Alter and Houghton were honored with the Lasker Award for Clinical Medical Research for "pioneering work leading to the discovery of the virus that causes hepatitis C and the development of screening methods that reduced the risk of blood transfusion-associated hepatitis in the U.S. from 30% in 1970 to virtually zero in 2000."[105]

Chiron filed for several patents on the virus and its diagnosis.[106] A competing patent application by the CDC was dropped in 1990 after Chiron paid $1.9 million to the CDC and $337,500 to Bradley. In 1994, Bradley sued Chiron, seeking to invalidate the patent, have himself included as a coinventor, and receive damages and royalty income. He dropped the suit in 1998 after losing before an appeals court.[107]

## Society and culture

*See also: List of people with hepatitis C*

World Hepatitis Day, held on July 28, is coordinated by the World Hepatitis Alliance.[108] The economic costs of hepatitis C are significant both to the individual and to society. In the United States the average lifetime cost of the disease was estimated at 33,407 USD in 2003[109] with the cost of a liver transplant as of 2011 costing approximately 200,000 USD.[110] In Canada the cost of a course of antiviral treatment is as high as 30,000 CAD in 2003,[111] while the United States costs are between 9,200 and 17,600 in 1998 USD.[109] In many areas of the world, people are unable to afford treatment with antivirals as they either lack insurance coverage or the insurance they have will not pay for antivirals.[112] In the English National Health Service treatment rates for hepatitis C are higher among wealthier groups per 2010–2012 data.[100] Spanish anaesthetist Juan Maeso infected 275 patients between 1988 and 1997 as he used the same

needles to give both himself and the patients opioids.[113] For this he was jailed.[114]

# Research

As of 2011, there are about one hundred medications in development for hepatitis C.[110] These include vaccines to treat hepatitis, immunomodulators, and cyclophilin inhibitors, among others.[115] These potential new treatments have come about due to a better understanding of the hepatitis C virus.[116]

The combination of sofosbuvir and velpatasvir in one trial (reported in 2015) resulted in cure rates of 99%.[117]

## Animal models

One barrier to finding treatments for hepatitis C is the lack of a suitable animal model. Despite moderate success, current research highlights the need for pre-clinical testing in mammalian systems such as mouse, particularly for the development of vaccines in poorer communities. Currently, chimpanzees remain the available living system to study, yet their use has ethical concerns and regulatory restrictions. While scientists have made use of human cell culture systems such as hepatocytes, questions have been raised about their accuracy in reflecting the body's response to infection.[118]

One aspect of hepatitis research is to reproduce infections in mammalian models. A strategy is to introduce liver tissues from humans into mice, a technique known as xenotransplantation. This is done by generating chimeric mice, and exposing the mice HCV infection. This engineering process is known to create humanized mice, and provide opportunities to study hepatitis C within the 3D architectural design of the liver and evaluating antiviral compounds.[118] Alternatively, generating inbred mice with susceptibility to HCV would simplify the process of studying mouse models.

# Special populations

## Children and pregnancy

*Main article: HCV in children and pregnancy*

Compared with adults, infection in children is much less well understood. Worldwide the prevalence of hepatitis C virus infection in pregnant women and children has been estimated to 1–8% and 0.05–5% respectively.[119] The vertical transmission rate has been estimated to be 3–5% and there is a high rate of spontaneous clearance (25–50%) in the children. Higher rates have been reported for both vertical transmission (18%, 6–36% and 41%).[120][121] and prevalence in children (15%).[122]

In developed countries transmission around the time of birth is now the leading cause of HCV infection. In the absence of virus in the mother's blood transmission seems to be rare.[121] Factors associated with an increased rate of infection include membrane rupture of longer than 6 hours before delivery and procedures exposing the infant to maternal blood.[123] Cesarean sections are not recommended. Breastfeeding is considered safe if the nipples are not damaged. Infection around the time of birth in one child does not increase the risk in a subsequent pregnancy. All genotypes appear to have the same risk of transmission.

HCV infection is frequently found in children who have previously been presumed to have non-A, non-B hepatitis and cryptogenic liver disease.[124] The presentation in childhood may be asymptomatic or with elevated liver function tests.[125] While infection is commonly asymptomatic both cirrhosis with liver failure and hepatocellular carcinoma may occur in childhood.

## Immunosuppressed

*See also: Hepatitis C and HIV coinfection*

The rate of hepatitis C in immunosuppressed people is higher than the normal population. This is particularly true in those with human immunodeficiency virus infection, recipients of organ transplants and those with hypogammaglobulinemia.[126] Infection in these people is associated with an unusually rapid progression to cirrhosis.

# References


1. ^ a b Ryan KJ, Ray CG, eds. (2004). *Sherris Medical Microbiology* (4th ed.). McGraw Hill. pp. 551–2. ISBN 0-8385-8529-9.
2. ^ a b c d e f g "Hepatitis C FAQs for Health Professionals". *CDC*. January 8, 2016. Retrieved 4 February 2016.
3. ^ a b Maheshwari, A; Thuluvath, PJ (February 2010). "Management of acute hepatitis C". *Clinics in liver disease*. **14** (1): 169–76; x. doi:10.1016/j.cld.2009.11.007. PMID 20123448.
4. ^ a b c d e f "Hepatitis C Fact sheet N°164". *WHO*. July 2015. Retrieved 4 February 2016.
5. ^ "Viral Hepatitis: A through E and Beyond". *National Institute of Diabetes and Digestive and Kidney Diseases*. April 2012. Retrieved 4 February 2016.
6. ^ a b c d Webster, Daniel P; Klenerman, Paul; Dusheiko, Geoffrey M (2015). "Hepatitis C". *The Lancet*. **385** (9973): 1124–1135. doi:10.1016/S0140-6736(14)62401-6. ISSN 0140-6736. PMC 4878852. PMID 25687730.
7. ^ a b c d e f g h i j k l Rosen, HR (2011-06-23). "Clinical practice. Chronic hepatitis C infection". *The New England Journal of Medicine*. **364** (25): 2429–38. doi:10.1056/NEJMcp1006613. PMID 21696309.
8. ^ a b Gravitz L. (2011). "A smouldering public-health crisis". *Nature*. **474** (7350): S2–4. doi:10.1038/474S2a. PMID 21666731.
9. ^ a b c Mohd Hanafiah, K; Groeger, J; Flaxman, AD; Wiersma, ST (April 2013). "Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence.". *Hepatology (Baltimore, Md.)*. **57** (4): 1333–42. doi:10.1002/hep.26141. PMID 23172780.
10. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
11. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
12. ^ Houghton M (November 2009). "The long and winding road leading to the identification of the hepatitis C virus". *Journal of Hepatology*. **51** (5): 939–48. doi:10.1016/j.jhep.2009.08.004. PMID 19781804.
13. ^ Shors, Teri (2011-11-08). *Understanding viruses* (2nd ed.). Burlington, MA: Jones & Bartlett Learning. p. 535. ISBN 978-0-7637-8553-6.
14. ^ Maheshwari, A; Ray S; Thuluvath PJ (2008-07-26). "Acute hepatitis C". *Lancet*. **372** (9635): 321–32. doi:10.1016/S0140-6736(08)61116-2. PMID 18657711.
15. ^ a b c d e f g h i j k l m n o p q r s t Wilkins, T; Malcolm JK; Raina D; Schade RR (2010-06-01). "Hepatitis C: diagnosis and treatment" (PDF). *American family physician*. **81** (11): 1351–7. PMID 20521755.
16. ^ Bailey, Caitlin (Nov 2010). "Hepatic Failure: An Evidence-Based Approach In The Emergency Department". *Emergency Medicine Practice*. **12** (4).
17. ^ a b c d e *Chronic Hepatitis C Virus Advances in Treatment, Promise for the Future*. Springer Verlag. 2011. p. 4. ISBN 978-1-4614-1191-8.
18. ^ a b c d Nelson, PK; Mathers BM; Cowie B; Hagan H; Des Jarlais D; Horyniak D; Degenhardt L (2011-08-13). "Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews". *Lancet*. **378** (9791): 571–83. doi:10.1016/S0140-6736(11)61097-0. PMC 3285467. PMID 21802134.
19. ^ a b c d *Chronic Hepatitis C Virus Advances in Treatment, Promise for the Future*. Springer Verlag. 2011. pp. 103–104. ISBN 978-1-4614-1191-8.
20. ^ a b c d e f g Ray, Stuart C.; Thomas, David L. (2009). "Chapter 154: Hepatitis C". In Mandell, Gerald L.; Bennett, John E.; Dolin, Raphael. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* (7th ed.). Philadelphia, PA: Churchill Livingstone. ISBN 978-0-443-06839-3.
21. ^ Forton, DM; Allsop, JM; Cox, IJ; Hamilton, G; Wesnes, K; Thomas, HC; Taylor-Robinson, SD (October 2005). "A review of cognitive impairment and cerebral metabolite abnormalities in patients with hepatitis C infection.". *AIDS*

*(London, England)*. **19** (Suppl 3): S53–63. doi:10.1097/01.aids.0000192071.72948.77. PMID 16251829.

22. ^ [a] [b] [c] Nicot, F (2004). "Chapter 19. Liver biopsy in modern medicine.". *Occult hepatitis C virus infection: Where are we now?*. ISBN 978-953-307-883-0.
23. ^ [a] [b] El-Zayadi, AR (2008-07-14). "Hepatic steatosis: a benign disease or a silent killer.". *World journal of gastroenterology : WJG*. **14** (26): 4120–6. doi:10.3748/wjg.14.4120. PMID 18636654.
24. ^ Paradis, V; Bedossa, P (December 2008). "Definition and natural history of metabolic steatosis: histology and cellular aspects.". *Diabetes & metabolism*. **34** (6 Pt 2): 638–42. doi:10.1016/S1262-3636(08)74598-1. PMID 19195624.
25. ^ [a] [b] [c] [d] [e] [f] [g] [h] [i] [j] Alter, MJ (2007-05-07). "Epidemiology of hepatitis C virus infection" (PDF). *World journal of gastroenterology : WJG*. **13** (17): 2436–41. doi:10.3748/wjg.v13.i17.2436. PMID 17552026.
26. ^ Mueller, S; Millonig G; Seitz HK (2009-07-28). "Alcoholic liver disease and hepatitis C: a frequently underestimated combination" (PDF). *World journal of gastroenterology : WJG*. **15** (28): 3462–71. doi:10.3748/wjg.15.3462. PMC 2715970. PMID 19630099.
27. ^ Fattovich, G; Stroffolini, T; Zagni, I; Donato, F (November 2004). "Hepatocellular carcinoma in cirrhosis: incidence and risk factors.". *Gastroenterology*. **127** (5 Suppl 1): S35–50. doi:10.1053/j.gastro.2004.09.014. PMID 15508101.
28. ^ [a] [b] [c] [d] [e] Ozaras, R; Tahan, V (April 2009). "Acute hepatitis C: prevention and treatment". *Expert review of anti-infective therapy*. **7** (3): 351–61. doi:10.1586/eri.09.8. PMID 19344247.
29. ^ Zaltron, S; Spinetti, A; Biasi, L; Baiguera, C; Castelli, F (2012). "Chronic HCV infection: epidemiological and clinical relevance.". *BMC infectious diseases*. 12 Suppl 2: S2. doi:10.1186/1471-2334-12-S2-S2. PMID 23173556.
30. ^ Dammacco F, Sansonno D (September 12, 2013). "Review Article: Therapy for Hepatitis C Virus–Related Cryoglobulinemic Vasculitis". *N Engl J Med*. **369** (11): 1035–1045. doi:10.1056/NEJMra1208642. PMID 24024840.
31. ^ Iannuzzella, F; Vaglio, A; Garini, G (May 2010). "Management of hepatitis C virus-related mixed cryoglobulinemia". *Am. J. Med*. **123** (5): 400–8. doi:10.1016/j.amjmed.2009.09.038. PMID 20399313.
32. ^ Zignego, AL; Ferri, C; Pileri, SA; et al. (January 2007). "Extrahepatic manifestations of Hepatitis C Virus infection: a general overview and guidelines for a clinical approach". *Digestive and Liver Disease*. **39** (1): 2–17. doi:10.1016/j.dld.2006.06.008. PMID 16884964.
33. ^ Ko, HM; Hernandez-Prera, JC; Zhu, H; Dikman, SH; Sidhu, HK; Ward, SC; Thung, SN (2012). "Morphologic features of extrahepatic manifestations of hepatitis C virus infection.". *Clinical & developmental immunology*. **2012**: 740138. doi:10.1155/2012/740138. PMID 22919404.
34. ^ Dammacco, F; Sansonno, D; Piccoli, C; Racanelli, V; D'Amore, FP; Lauletta, G (2000). "The lymphoid system in hepatitis C virus infection: autoimmunity, mixed cryoglobulinemia, and Overt B-cell malignancy.". *Seminars in liver disease*. **20** (2): 143–57. doi:10.1055/s-2000-9613. PMID 10946420.
35. ^ Lee, MR; Shumack, S (November 2005). "Prurigo nodularis: a review". *The Australasian journal of dermatology*. **46** (4): 211–18; quiz 219–20. doi:10.1111/j.1440-0960.2005.00187.x. PMID 16197418.
36. ^ Matsumori, A (2006). "Role of hepatitis C virus in cardiomyopathies.". *Ernst Schering Research Foundation workshop* (55): 99–120. PMID 16329660.
37. ^ Monaco, S; Ferrari, S; Gajofatto, A; Zanusso, G; Mariotto, S (2012). "HCV-related nervous system disorders.". *Clinical & developmental immunology*. **2012**: 236148. doi:10.1155/2012/236148. PMID 22899946.
38. ^ Xu, JH; Fu, JJ; Wang, XL; Zhu, JY; Ye, XH; Chen, SD (2013-07-14). "Hepatitis B or C viral infection and risk of pancreatic cancer: A meta-analysis of observational studies.". *World journal of gastroenterology : WJG*. **19** (26): 4234–41. doi:10.3748/wjg.v19.i26.4234. PMID 23864789.
39. ^ Sugden, PB; Cameron, B; Bull, R; White, PA; Lloyd, AR (September 2012). "Occult infection with hepatitis C virus: friend or foe?". *Immunology and cell biology*. **90** (8): 763–73. doi:10.1038/icb.2012.20. PMID 22546735.
40. ^ Carreño, V (2006-11-21). "Occult hepatitis C virus infection: a new form of hepatitis C.". *World journal of gastroenterology : WJG*. **12** (43): 6922–5. PMID 17109511.
41. ^ [a] [b] Carreño García, V; Nebreda, JB; Aguilar, IC; Quiroga Estévez, JA (March 2011). "[Occult hepatitis C virus infection].". *Enfermedades infecciosas y microbiologia clinica*. 29 Suppl 3: 14–9. doi:10.1016/S0213-005X(11)70022-2. PMID 21458706.
42. ^ Pham, TN; Coffin, CS; Michalak, TI (April 2010). "Occult hepatitis C virus infection: what does it mean?". *Liver international : official journal of the International Association for the Study of the Liver*. **30** (4): 502–11. doi:10.1111/j.1478-3231.2009.02193.x. PMID 20070513.
43. ^ Carreño, V; Bartolomé, J; Castillo, I; Quiroga, JA (2012-06-21). "New perspectives in occult hepatitis C virus infection.". *World journal of gastroenterology : WJG*. **18** (23): 2887–94. doi:10.3748/wjg.v18.i23.2887. PMID 22736911.
44. ^ Carreño, V; Bartolomé, J; Castillo, I; Quiroga, JA (May–June 2008). "Occult hepatitis B virus and hepatitis C virus infections.". *Reviews in medical virology*. **18** (3): 139–57. doi:10.1002/rmv.569. PMID 18265423.

45. ^ Scott, JD; Gretch, DR (2007-02-21). "Molecular diagnostics of hepatitis C virus infection: a systematic review.". *JAMA: The Journal of the American Medical Association*. **297** (7): 724–32. doi:10.1001/jama.297.7.724. PMID 17312292.
46. ^ a b Robinson, JL (July 4, 2008). "Vertical transmission of the hepatitis C virus: Current knowledge and issues". *Paediatr Child Health*. **13** (6): 529–534. PMC 2532905. PMID 19436425.
47. ^ Nakano, T; Lau, GM; Lau, GM; et al. (December 2011). "An updated analysis of hepatitis C virus genotypes and subtypes based on the complete coding region". *Liver Int*. **32** (2): 339–45. doi:10.1111/j.1478-3231.2011.02684.x. PMID 22142261.
48. ^ a b Lerat, H; Hollinger, FB (2004-01-01). "Hepatitis C virus (HCV) occult infection or occult HCV RNA detection?". *The Journal of Infectious Diseases*. **189** (1): 3–6. doi:10.1086/380203. PMID 14702146.
49. ^ Pockros, Paul (2011). *Novel and Combination Therapies for Hepatitis C Virus, An Issue of Clinics in Liver Disease,*. p. 47. ISBN 978-1-4557-7198-1.
50. ^ Zignego, AL; Giannini, C; Gragnani, L; Piluso, A; Fognani, E (2012-08-03). "Hepatitis C virus infection in the immunocompromised host: a complex scenario with variable clinical impact.". *Journal of translational medicine*. **10** (1): 158. doi:10.1186/1479-5876-10-158. PMID 22863056.
51. ^ a b c d e Pondé, RA (February 2011). "Hidden hazards of HCV transmission". *Medical microbiology and immunology*. **200** (1): 7–11. doi:10.1007/s00430-010-0159-9. PMID 20461405.
52. ^ a b Xia, X; Luo J; Bai J; Yu R (October 2008). "Epidemiology of HCV infection among injection drug users in China: systematic review and meta-analysis". *Public health*. **122** (10): 990–1003. doi:10.1016/j.puhe.2008.01.014. PMID 18486955.
53. ^ Imperial, JC (June 2010). "Chronic hepatitis C in the state prison system: insights into the problems and possible solutions". *Expert review of gastroenterology & hepatology*. **4** (3): 355–64. doi:10.1586/egh.10.26. PMID 20528122.
54. ^ Vescio, MF; Longo B; Babudieri S; Starnini G; Carbonara S; Rezza G; Monarca R (April 2008). "Correlates of hepatitis C virus seropositivity in prison inmates: a meta-analysis". *Journal of epidemiology and community health*. **62** (4): 305–13. doi:10.1136/jech.2006.051599. PMID 18339822.
55. ^ Moyer, VA; U.S. Preventive Services Task, Force (3 September 2013). "Screening for hepatitis C virus infection in adults: U.S. Preventive Services Task Force recommendation statement.". *Annals of Internal Medicine*. **159** (5): 349–57. doi:10.7326/0003-4819-159-5-201309030-00672. PMID 23798026.
56. ^ a b Marx, John (2010). *Rosen's emergency medicine: concepts and clinical practice 7th edition*. Philadelphia, PA: Mosby/Elsevier. p. 1154. ISBN 978-0-323-05472-0.
57. ^ Day RA, Paul P, Williams B, et al. (November 2009). *Brunner & Suddarth's textbook of Canadian medical-surgical nursing* (Canadian 2nd ed.). Philadelphia, PA: Lippincott Williams & Wilkins. p. 1237. ISBN 978-0-7817-9989-8.
58. ^ "Highest Rates of Hepatitis C Virus Transmission Found in Egypt". Al Bawaaba. 2010-08-09. Retrieved 2010-08-27.
59. ^ a b c Tohme RA, Holmberg SD (June 2010). "Is sexual contact a major mode of hepatitis C virus transmission?". *Hepatology*. **52** (4): 1497–505. doi:10.1002/hep.23808. PMID 20635398.
60. ^ "Hepatitis C Group Education Class". United States Department of Veteran Affairs.
61. ^ a b c d e f Jafari, S; Copes R; Baharlou S; Etminan M; Buxton J (November 2010). "Tattooing and the risk of transmission of hepatitis C: a systematic review and meta-analysis" (PDF). *International Journal of Infectious Diseases*. **14** (11): e928–40. doi:10.1016/j.ijid.2010.03.019. PMID 20678951.
62. ^ "Hepatitis C" (PDF). Centers for Disease Control and Prevention (CDC). Retrieved 2 January 2012.
63. ^ Lock G, Dirscherl M, Obermeier F, et al. (September 2006). "Hepatitis C — contamination of toothbrushes: myth or reality?". *J. Viral Hepat*. **13** (9): 571–3. doi:10.1111/j.1365-2893.2006.00735.x. PMID 16907842.
64. ^ a b c "Hepatitis C FAQs for Health Professionals". Centers for Disease Control and Prevention (CDC). Retrieved 2 January 2012.
65. ^ Wong T, Lee SS (February 2006). "Hepatitis C: a review for primary care physicians". *CMAJ*. **174** (5): 649–59. doi:10.1503/cmaj.1030034. PMC 1389829. PMID 16505462.
66. ^ a b Lam, NC; Gotsch, PB; Langan, RC (2010-11-15). "Caring for pregnant women and newborns with hepatitis B or C" (PDF). *American family physician*. **82** (10): 1225–9. PMID 21121533.
67. ^ Mast EE (2004). "Mother-to-infant hepatitis C virus transmission and breastfeeding". *Advances in Experimental Medicine and Biology*. **554**: 211–6. doi:10.1007/978-1-4757-4242-8_18. PMID 15384578.
68. ^ Shivkumar, S; Peeling, R; Jafari, Y; Joseph, L; Pant Pai, N (2012-10-16). "Accuracy of Rapid and Point-of-Care Screening Tests for Hepatitis C: A Systematic Review and Meta-analysis.". *Annals of Internal Medicine*. **157** (8): 558–66. doi:10.7326/0003-4819-157-8-201210160-00006. PMID 23070489.
69. ^ Moyer, VA (on behalf of the U.S. Preventive Services Task Force) (2013-06-25). "Screening for Hepatitis C Virus Infection in Adults: U.S. Preventive Services Task Force Recommendation Statement.". *Annals of Internal Medicine*.

**159** (5): 349–57. doi:10.7326/0003-4819-159-5-201309030-00672. PMID 23798026.
70. ^ Moyer, VA (U.S. Preventive Services Task Force) (2013-09-03). "Screening for hepatitis C virus infection in adults: U.S. Preventive Services Task Force recommendation statement.". *Annals of Internal Medicine*. **159** (5): 349–57. doi:10.7326/0003-4819-159-5-201309030-00672. PMID 23798026.
71. ^ Senadhi, V (July 2011). "A paradigm shift in the outpatient approach to liver function tests". *Southern Medical Journal*. **104** (7): 521–5. doi:10.1097/SMJ.0b013e31821e8ff5. PMID 21886053.
72. ^ Smith BD, Morgan RL, Beckett GA, et al. (August 2012). "Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965". *MMWR Recomm Rep*. **61** (RR-4): 1–32. PMID 22895429.
73. ^ *a b* Abdelwahab, KS; Ahmed Said, ZN (14 January 2016). "Status of hepatitis C virus vaccination: Recent update.". *World journal of gastroenterology*. **22** (2): 862–73. doi:10.3748/wjg.v22.i2.862. PMC 4716084. PMID 26811632.
74. ^ Hagan, H; Pouget, ER; Des Jarlais, DC (2011-07-01). "A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs". *The Journal of Infectious Diseases*. **204** (1): 74–83. doi:10.1093/infdis/jir196. PMC 3105033. PMID 21628661.
75. ^ Torresi, J; Johnson D; Wedemeyer H (June 2011). "Progress in the development of preventive and therapeutic vaccines for hepatitis C virus" (PDF). *Journal of hepatology*. **54** (6): 1273–85. doi:10.1016/j.jhep.2010.09.040. PMID 21236312.
76. ^ Ilyas, JA; Vierling, JM (August 2011). "An overview of emerging therapies for the treatment of chronic hepatitis C". *Clinics in liver disease*. **15** (3): 515–36. doi:10.1016/j.cld.2011.05.002. PMID 21867934.
77. ^ *a b c d e f g h i* AASLD/IDSA HCV Guidance, Panel (September 2015). "Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus.". *Hepatology (Baltimore, Md.)*. **62** (3): 932–54. doi:10.1002/hep.27950. PMID 26111063.
78. ^ *a b* De Clercq, E (Nov 15, 2013). "Dancing with chemical formulae of antivirals: A panoramic view (Part 2).". *Biochemical Pharmacology*. **86** (10): 1397–410. doi:10.1016/j.bcp.2013.09.010. PMID 24070654.
79. ^ *a b* Liang, TJ; Ghany, MG (May 16, 2013). "Current and future therapies for hepatitis C virus infection.". *The New England Journal of Medicine*. **368** (20): 1907–17. doi:10.1056/NEJMra1213651. PMID 23675659.
80. ^ Hoofnagle, JH; Sherker, AH (Apr 17, 2014). "Therapy for hepatitis C--the costs of success.". *The New England Journal of Medicine*. **370** (16): 1552–3. doi:10.1056/nejme1401508. PMID 24725236.
81. ^ *a b* Bunchorntavakul, C; Chavalitdhamrong, D; Tanwandee, T (Sep 27, 2013). "Hepatitis C genotype 6: A concise review and response-guided therapy proposal.". *World journal of hepatology*. **5** (9): 496–504. doi:10.4254/wjh.v5.i9.496. PMID 24073301.
82. ^ Sanders, Mick (2011). *Mosby's Paramedic Textbook*. Jones & Bartlett Publishers. p. 839. ISBN 978-0-323-07275-5.
83. ^ Ciria R, Pleguezuelo M, Khorsandi SE, et al. (May 2013). "Strategies to reduce hepatitis C virus recurrence after liver transplantation". *World J Hepatol*. **5** (5): 237–50. doi:10.4254/wjh.v5.i5.237. PMC 3664282. PMID 23717735.
84. ^ Coilly A, Roche B, Samuel D (February 2013). "Current management and perspectives for HCV recurrence after liver transplantation". *Liver Int*. 33 Suppl 1: 56–62. doi:10.1111/liv.12062. PMID 23286847.
85. ^ *a b* Hepatitis C and CAM: What the Science Says. National Center for Complementary and Alternative Medicine (NCCAM). March 2011. (Retrieved 7 March 2011)
86. ^ Liu, J; Manheimer E; Tsutani K; Gluud C (March 2003). "Medicinal herbs for hepatitis C virus infection: a Cochrane hepatobiliary systematic review of randomized trials". *The American journal of gastroenterology*. **98** (3): 538–44. doi:10.1111/j.1572-0241.2003.07298.x. PMID 12650784.
87. ^ Rambaldi, A; Jacobs, BP; Gluud, C (17 October 2007). "Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases.". *The Cochrane database of systematic reviews* (4): CD003620. doi:10.1002/14651858.CD003620.pub3. PMID 17943794.
88. ^ Helms, Richard A.; Quan, David J., eds. (2006). *Textbook of Therapeutics: Drug and Disease Management* (8. ed.). Philadelphia, Pa. [u.a.]: Lippincott Williams & Wilkins. p. 1340. ISBN 0-7817-5734-7. Retrieved 7 November 2014.
89. ^ Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y (March 2013). "Eradication of Hepatitis C Virus Infection and the Development of Hepatocellular Carcinoma: A Meta-analysis of Observational Studies". *Annals of Internal Medicine*. **158** (5 Pt 1): 329–37. doi:10.7326/0003-4819-158-5-201303050-00005. PMID 23460056.
90. ^ Fung J, Lai CL, Hung I, et al. (September 2008). "Chronic hepatitis C virus genotype 6 infection: response to pegylated interferon and ribavirin". *The Journal of Infectious Diseases*. **198** (6): 808–12. doi:10.1086/591252. PMID 18657036.
91. ^ *a b c* "Hepatitis C". World Health Organization (WHO). June 2011. Retrieved 2011-07-13.

92. ^ Lozano, R (2012-12-15). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
93. ^ Yu ML; Chuang WL (March 2009). "Treatment of chronic hepatitis C in Asia: when East meets West". *J. Gastroenterol. Hepatol*. **24** (3): 336–45. doi:10.1111/j.1440-1746.2009.05789.x. PMID 19335784.
94. ^ "U.S. 2014 Surveillance Data for Viral Hepatitis, Statistics & Surveillance, Division of Viral Hepatitis". CDC. Retrieved 2016-08-04.
95. ^ Table 4.5. "Number and rate of deaths with hepatitis C listed as a cause of death, by demographic characteristic and year — United States, 2004–2008". *Viral Hepatitis on the CDC web site*. Centers for Disease Control and Prevention, Atlanta, GA. Retrieved 28 July 2013.
96. ^ "Hepatitis Death Rate Creeps past AIDS". *New York Times*. 27 February 2012. Retrieved 28 July 2013.
97. ^ "Hepatitis C Kills More Americans than Any Other Infectious Disease". Centers for Disease Control and Prevention. May 4, 2016. Retrieved 3 August 2016.
98. ^ Blatt, L. M.; Tong, M. (2004). Colacino, J. M.; Heinz, B. A., eds. *Hepatitis prevention and treatment*. Basel: Birkhäuser. p. 32. ISBN 978-3-7643-5956-0.
99. ^ Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F (March 2013). "The burden of liver disease in Europe: a review of available epidemiological data". *J. Hepatol*. **58** (3): 593–608. doi:10.1016/j.jhep.2012.12.005. PMID 23419824.
100. ^ *a b c* "Commissioning supplement: Health inequalities tell a tale of data neglect". Health Service Journal. 19 March 2015. Retrieved 30 April 2015.
101. ^ Holmberg, Scott. Brunette, Gary W.; Kozarsky, Phyllis E.; Magill, Alan J.; Shlim, David R.; Whatley, Amanda D., eds. *CDC Health Information for International Travel 2012*. New York: Oxford University Press. p. 231. ISBN 978-0-19-976901-8.
102. ^ *a b* Boyer, JL (2001). *Liver cirrhosis and its development: proceedings of the Falk Symposium 115*. Springer. pp. 344. ISBN 978-0-7923-8760-2.
103. ^ Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M (April 1989). "Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome". *Science*. **244** (4902): 359–62. doi:10.1126/science.2523562. PMID 2523562.
104. ^ Kuo G, Choo QL, Alter HJ, et al. (April 1989). "An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis". *Science*. **244** (4902): 362–4. doi:10.1126/science.2496467. PMID 2496467.
105. ^ 2000 Winners Albert Lasker Award for Clinical Medical Research at the Wayback Machine (archived February 25, 2008). Retrieved 20 February 2008.
106. ^ EP patent 0318216, Houghton, M; Choo, Q-L & Kuo, G, "NANBV diagnostics", issued 1989-05-31, assigned to Chiron
107. ^ Wilken. "United States Court of Appeals for the Federal Circuit". United States Court of Appeals for the Federal Circuit. Archived from the original on 19 November 2009. Retrieved 11 January 2012.
108. ^ Eurosurveillance editorial team (2011-07-28). "World Hepatitis Day 2011" (PDF). *Eurosurveillance*. **16** (30). PMID 21813077.
109. ^ *a b* Wong, JB (2006). "Hepatitis C: cost of illness and considerations for the economic evaluation of antiviral therapies". *PharmacoEconomics*. **24** (7): 661–72. doi:10.2165/00019053-200624070-00005. PMID 16802842.
110. ^ *a b* El Khoury, AC; Klimack, WK; Wallace, C; Razavi, H (1 December 2011). "Economic burden of hepatitis C-associated diseases in the United States". *Journal of Viral Hepatitis*. **19** (3): 153–60. doi:10.1111/j.1365-2893.2011.01563.x. PMID 22329369.
111. ^ "Hepatitis C Prevention, Support and Research ProgramHealth Canada". Public Health Agency of Canada. Nov 2003. Archived from the original on 22 March 2011. Retrieved 10 January 2012.
112. ^ Thomas, Howard; Lemon, Stanley; Zuckerman, Arie, eds. (2008). *Viral Hepatitis* (3rd ed.). Oxford: John Wiley & Sons. p. 532. ISBN 978-1-4051-4388-2.
113. ^ "Spanish Anesthetist Infected Patients". *The Washington Post*. 15 May 2007. Retrieved 13 July 2016.
114. ^ "Spanish Hep C anaesthetist jailed". *BBC*. 15 May 2007. Retrieved 13 July 2016.
115. ^ Ahn, J; Flamm, SL (August 2011). "Hepatitis C therapy: other players in the game". *Clinics in liver disease*. **15** (3): 641–56. doi:10.1016/j.cld.2011.05.008. PMID 21867942.
116. ^ Vermehren, J; Sarrazin, C (February 2011). "New HCV therapies on the horizon". *Clinical Microbiology and Infection*. **17** (2): 122–34. doi:10.1111/j.1469-0691.2010.03430.x. PMID 21087349.
117. ^ Feld, Jordan J.; Jacobson, Ira M.; Hézode, Christophe; Asselah, Tarik; Ruane, Peter J.; Gruener, Norbert; Abergel, Armand; Mangia, Alessandra; Lai, Ching-Lung; Chan, Henry L.Y.; Mazzotta, Francesco; Moreno, Christophe; Yoshida, Eric; Shafran, Stephen D.; Towner, William J.; Tran, Tram T.; McNally, John; Osinusi, Anu; Svarovskaia, Evguenia; Zhu, Yanni; Brainard, Diana M.; McHutchison, John G.; Agarwal, Kosh; Zeuzem, Stefan (16 November 2015). "Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection". *New England Journal of Medicine*:

151117120417004. doi:10.1056/NEJMoa1512610.
118. ^ a b Sandmann, L; Ploss, A (2013-01-05). "Barriers of hepatitis C virus interspecies transmission.". *Virology*. **435** (1): 70–80. doi:10.1016/j.virol.2012.09.044. PMID 23217617.
119. ^ Arshad M, El-Kamary SS, Jhaveri R (April 2011). "Hepatitis C virus infection during pregnancy and the newborn period—are they opportunities for treatment?". *J. Viral Hepat.* **18** (4): 229–36. doi:10.1111/j.1365-2893.2010.01413.x. PMID 21392169.
120. ^ Hunt CM, Carson KL, Sharara AI (May 1997). "Hepatitis C in pregnancy". *Obstet Gynecol*. **89** (5 Pt 2): 883–90. PMID 9166361.
121. ^ a b Thomas SL, Newell ML, Peckham CS, Ades AE, Hall AJ (February 1998). "A review of hepatitis C virus (HCV) vertical transmission: risks of transmission to infants born to mothers with and without HCV viraemia or human immunodeficiency virus infection". *Int J Epidemiol*. **27** (1): 108–17. doi:10.1093/ije/27.1.108. PMID 9563703.
122. ^ Fischler B (June 2007). "Hepatitis C virus infection". *Semin Fetal Neonatal Med*. **12** (3): 168–73. doi:10.1016/j.siny.2007.01.008. PMID 17320495.
123. ^ Indolfi G, Resti M (May 2009). "Perinatal transmission of hepatitis C virus infection". *J. Med. Virol*. **81** (5): 836–43. doi:10.1002/jmv.21437. PMID 19319981.
124. ^ González-Peralta RP (November 1997). "Hepatitis C virus infection in pediatric patients". *Clin Liver Dis*. **1** (3): 691–705, ix. doi:10.1016/s1089-3261(05)70329-9. PMID 15560066.
125. ^ Suskind DL, Rosenthal P (February 2004). "Chronic viral hepatitis". *Adolesc Med Clin*. **15** (1): 145–58, x–xi. doi:10.1016/S154733680300010X. PMID 15272262.
126. ^ Einav S, Koziel MJ (June 2002). "Immunopathogenesis of hepatitis C virus in the immunosuppressed host". *Transpl Infect Dis*. **4** (2): 85–92. doi:10.1034/j.1399-3062.2002.t01-2-02001.x. PMID 12220245.

## Further reading


- *Guidelines for the screening, care and treatment of persons with hepatitis C infection* (PDF). World Health Organization. April 2014. ISBN 978 92 4 154875 5.
- Infectious Disease Society of America. "Recommendations for Testing, Managing, and Treating Hepatitis C". Retrieved 26 June 2015.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|---|---|---|
| **Central nervous system** | **Encephalitis/ meningitis** | (Lymphocytic choriomeningitis · · Arbovirus encephalitis · *Orthomyxoviridae (probable)* (Encephalitis lethargica · · *RV* (Rabies · · Chandipura virus · Herpesviral meningitis · Ramsay Hunt syndrome type 2 · |
| | **Myelitis** | *Poliovirus* (Poliomyelitis · Post-polio syndrome · · *HTLV-I* (Tropical spastic paraparesis · · |
| | **Eye** | *Cytomegalovirus* (Cytomegalovirus retinitis · · *HSV* (Herpes of the eye · · |
| **Cardiovascular** | *CBV* (Pericarditis · Myocarditis · · | |
| **Respiratory system/ acute viral nasopharyngitis/ viral pneumonia** | **DNA virus** | *Epstein–Barr virus* (EBV infection/Infectious mononucleosis · · *Cytomegalovirus* · |
| | **RNA virus** | IV: *SARS coronavirus* (Severe acute respiratory syndrome · · V: *Orthomyxoviridae: Influenzavirus A/B/C* (Influenza/Avian influenza · · V, *Paramyxoviridae: Human parainfluenza viruses* (Parainfluenza · · *RSV* · *hMPV* · |
| **Human digestive system** | **Pharynx/Esophagus** | *MuV* (Mumps · · *Cytomegalovirus* (Cytomegalovirus esophagitis · · |
| | **Gastroenteritis/ diarrhea** | **DNA virus:** *Adenovirus* (Adenovirus infection · · **RNA virus:** *Rotavirus* · *Norovirus* · *Astrovirus* · *Coronavirus* · |
| | **Hepatitis** | **DNA virus:** *HBV* (B) · **RNA virus:** *CBV* · *HAV* (A) · *HCV* (**C**) · *HDV* (D) · *HEV* (E) · *HGV* (G) · |
| | **Pancreatitis** | *CBV* · |
| **Urogenital** | *BK virus* · *MuV* (Mumps · · | |

| v · t · e · | **Diseases of the digestive system (primarily K20–K93, 530–579)** | |
|---|---|---|
| **Upper GI tract** | **Esophagus** | Esophagitis (Candidal · Eosinophilic · Herpetiform · · *Rupture* (Boerhaave syndrome · Mallory-Weiss syndrome · · UES (Zenker's diverticulum · · LES (Barrett's esophagus · · Esophageal motility disorder (Nutcracker esophagus · Achalasia · Diffuse esophageal spasm · Gastroesophageal reflux disease (GERD) · · Laryngopharyngeal reflux (LPR) · Esophageal stricture · Megaesophagus · |
| | **Stomach** | Gastritis (Atrophic · Ménétrier's disease · Gastroenteritis · · Peptic (gastric) ulcer (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
| | **Small intestine (Duodenum/Jejunum/Ileum)** | Enteritis (Duodenitis · Jejunitis · Ileitis · · Peptic (duodenal) ulcer (Curling's ulcer · · Malabsorption: Coeliac · Tropical sprue · Blind loop syndrome · Small bowel bacterial overgrowth syndrome · Whipple's · Short bowel syndrome · Steatorrhea · Milroy disease · Bile acid malabsorption · |

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| **Lower GI tract: Intestinal/ Enteropathy** | **Large intestine (Appendix/Colon)** | Appendicitis · Colitis (Pseudomembranous · Ulcerative · Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (IBS · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
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| **Accessory** | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · Acute liver failure · · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |
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| | **Pancreatic** | Pancreatitis (Acute · Chronic · Hereditary · Pancreatic abscess · · Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |
| **Abdominopelvic** | **Hernia** | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
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Categories: Hepatitis C | Healthcare-associated infections | Infectious causes of cancer | Viral diseases


# HIV/AIDS

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*This article is about the disease. For the virus, see HIV.*
*"AIDS" redirects here. For other uses, see AIDS (disambiguation).*

**Human immunodeficiency virus infection and acquired immune deficiency syndrome** (**HIV/AIDS**) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV).[5][6][7] Following initial infection, a person may not notice any symptoms or may experience a brief period of influenza-like illness.[8] Typically, this is followed by a prolonged period with no symptoms.[9] As the infection progresses, it interferes more with the immune system, increasing the risk of common infections like tuberculosis, as well as other opportunistic infections, and tumors that rarely affect people who have working immune systems.[8] These late symptoms of infection are referred to as AIDS.[9] This stage is often also associated with weight loss.[9]

HIV is spread primarily by unprotected sex (including anal and oral sex), contaminated blood transfusions, hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding.[10] Some bodily fluids, such as saliva and tears, do not transmit HIV.[11] Methods of prevention include safe sex, needle exchange programs, treating those who are infected, and male circumcision.[8] Disease in a baby can often be prevented by giving both the mother and child antiretroviral medication.[8] There is no cure or vaccine; however, antiretroviral treatment can slow the course of the disease and may lead to a near-normal life expectancy.[9][12] Treatment is recommended as soon as the diagnosis is made.[13] Without treatment, the average survival time after infection is 11 years.[14]

In 2015 about 36.7 million people were living with HIV and it resulted in 1.1 million deaths.[8] Most of those infected live in sub-Saharan Africa.[8] Between its discovery and 2014 AIDS has caused an estimated 39 million deaths worldwide.[15] HIV/AIDS is considered a pandemic—a disease outbreak which is present over a large area and is actively spreading.[16] HIV is believed to have originated in west-central Africa during the late 19th or early 20th century.[17] AIDS was first recognized by the United States Centers for Disease Control and Prevention (CDC) in 1981 and its

| HIV/AIDS | |
|---|---|
| **Synonyms** | HIV disease, HIV infection[1][2][3] |

The red ribbon is a symbol for solidarity with HIV-positive people and those living with AIDS.[4]

| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | B20 – B24 |
| **ICD-9-CM** | 042-044 |
| **OMIM** | 609423 |
| **DiseasesDB** | 5938 |
| **MedlinePlus** | 000594 |
| **eMedicine** | emerg/253 |
| **Patient UK** | HIV/AIDS |
| **MeSH** | D000163 |

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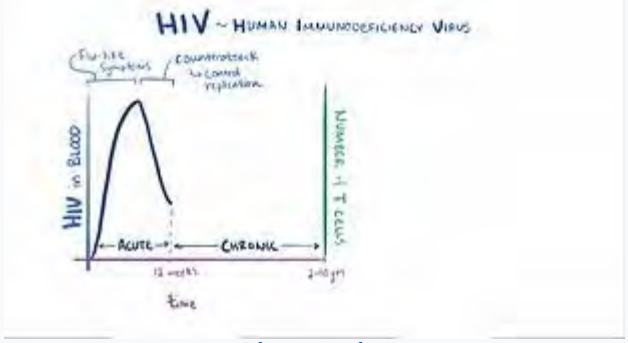
cause—HIV infection—was identified in the early part of the decade.[18]

HIV/AIDS has had a great impact on society, both as an illness and as a source of discrimination.[19] The disease also has large economic impacts.[19] There are many misconceptions about HIV/AIDS such as the belief that it can be transmitted by casual non-sexual contact.[20] The disease has become subject to many controversies involving religion including the Catholic Church's decision not to support condom use as prevention.[21] It has attracted international medical and political attention as well as large-scale funding since it was identified in the 1980s.[22]

**Contents**





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Video explanation

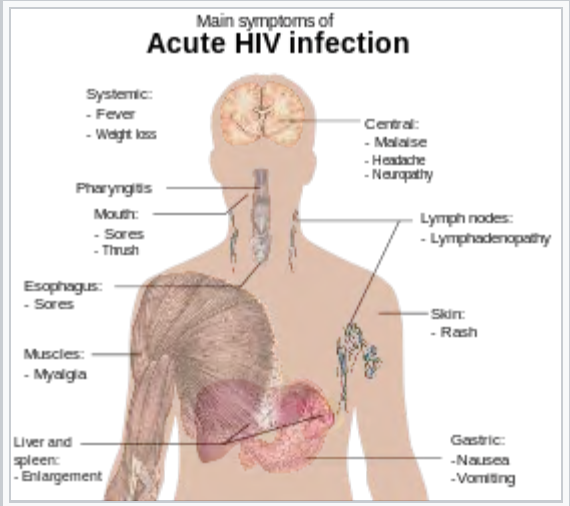
# Signs and symptoms

*Main article: Signs and symptoms of HIV/AIDS*

There are three main stages of HIV infection: acute infection, clinical latency and AIDS.[1]

## Acute infection

The initial period following the contraction of HIV is called acute HIV, primary HIV or acute retroviral syndrome.[2][23] Many individuals develop an influenza-like illness or a mononucleosis-like illness 2–4 weeks post exposure while others have no significant symptoms.[24][25] Symptoms occur in 40–90% of cases and most commonly include fever, large tender lymph nodes, throat inflammation, a rash, headache, and/or sores of the mouth and genitals.[23][25] The rash, which occurs in 20–50% of cases, presents itself on the trunk and is maculopapular, classically.[26] Some people also develop opportunistic infections at this stage.[23] Gastrointestinal symptoms such as nausea, vomiting or diarrhea may occur, as may neurological symptoms of peripheral neuropathy or Guillain–Barré syndrome.[25] The duration of the symptoms varies, but is usually one or two weeks.[25]



Main symptoms of acute HIV infection

Due to their nonspecific character, these symptoms are not often recognized as signs of HIV infection. Even cases that do get seen by a family doctor or a hospital are often misdiagnosed as one of the many common infectious diseases with overlapping symptoms. Thus, it is recommended that HIV be considered in people presenting an unexplained fever who may have risk factors for the infection.[25]

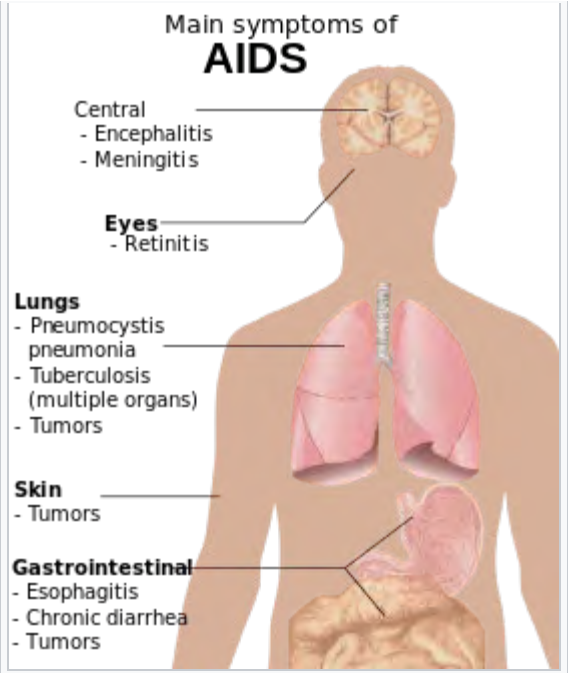
## Clinical latency

The initial symptoms are followed by a stage called clinical latency, asymptomatic HIV, or chronic HIV.[1] Without treatment, this second stage of the natural history of HIV infection can last from about three years[27] to over 20 years[28] (on average, about eight years).[29] While typically there are few or no symptoms at first, near the end of this stage many people experience fever, weight loss, gastrointestinal problems and muscle pains.[1] Between 50 and 70% of people also develop persistent generalized lymphadenopathy, characterized by unexplained, non-painful enlargement of more than one group of lymph nodes (other than in the groin) for over three to six months.[2]

Although most HIV-1 infected individuals have a detectable viral load and in the absence of treatment will eventually progress to AIDS, a small proportion (about 5%) retain high levels of $CD4^+$ T cells (T helper cells) without antiretroviral therapy for more than 5 years.[25][30] These individuals are classified as HIV controllers or long-term nonprogressors (LTNP).[30] Another group consists of those who maintain a low or undetectable viral load without anti-retroviral treatment, known as "elite controllers" or "elite suppressors". They represent approximately 1 in 300 infected persons.[31]

## Acquired immunodeficiency syndrome

Acquired immunodeficiency syndrome (AIDS) is defined in terms of either a $CD4^+$ T cell count below 200 cells per μL or the occurrence of specific diseases in association with an HIV infection.[25] In the absence of specific treatment, around half of people infected with HIV develop AIDS within ten years.[25] The most common initial conditions that alert to the presence of AIDS are pneumocystis pneumonia (40%), cachexia in the form of HIV wasting syndrome (20%), and esophageal candidiasis.[25] Other common signs include recurring respiratory tract infections.[25]



Main symptoms of AIDS.

Opportunistic infections may be caused by bacteria, viruses, fungi, and parasites that are normally controlled by the immune system.[32] Which infections occur depends partly on what organisms are common in the person's environment.[25] These infections may affect nearly every organ system.[33]

People with AIDS have an increased risk of developing various viral-induced cancers, including Kaposi's sarcoma, Burkitt's lymphoma, primary central nervous system lymphoma, and cervical cancer.[26] Kaposi's sarcoma is the most common cancer occurring in 10 to 20% of people with HIV.[34] The second most common cancer is lymphoma, which is the cause of death of nearly 16% of people with AIDS and is the initial sign of AIDS in 3 to 4%.[34] Both these cancers are associated with human herpesvirus 8.[34] Cervical cancer occurs more frequently in those with AIDS because of its association with human papillomavirus (HPV).[34] Conjunctival cancer (of the layer that lines the inner part of eyelids and the white part of the eye) is also more common in those with HIV.[35]

Additionally, people with AIDS frequently have systemic symptoms such as prolonged fevers, sweats (particularly at night), swollen lymph nodes, chills, weakness, and unintended weight loss.[36] Diarrhea is another common symptom, present in about 90% of people with AIDS.[37] They can also be affected by diverse psychiatric and neurological symptoms independent of opportunistic infections and cancers.[38]

# Transmission

HIV is transmitted by three main routes: sexual contact, significant exposure to infected body fluids or tissues, and from mother to child during pregnancy, delivery, or breastfeeding (known as vertical transmission).[10] There is no risk of acquiring HIV if exposed to feces, nasal secretions, saliva, sputum, sweat, tears, urine, or vomit unless these are contaminated with blood.[46] It is possible to be co-infected by more than one strain of HIV—a condition known as HIV superinfection.[47]

**Average per act risk of getting HIV by exposure route to an infected source**

| Exposure route | Chance of infection |
|---|---|
| **Blood transfusion** | 90%[39] |
| **Childbirth (to child)** | 25%[40] |
| **Needle-sharing injection drug use** | 0.67%[39] |
| **Percutaneous needle stick** | 0.30%[41] |
| **Receptive anal intercourse*** | 0.04–3.0%[42] |
| **Insertive anal intercourse*** | 0.03%[43] |
| **Receptive penile-vaginal intercourse*** | 0.05–0.30%[42][44] |
| **Insertive penile-vaginal intercourse*** | 0.01–0.38%[42][44] |
| **Receptive oral intercourse*§** | 0–0.04%[42] |
| **Insertive oral intercourse*§** | 0–0.005%[45] |

## Sexual

The most frequent mode of transmission of HIV is through sexual contact with an infected person.[10] The majority of all transmissions worldwide occur through heterosexual contacts

*** assuming no condom use**
**§ source refers to oral intercourse performed on a man**

(i.e. sexual contacts between people of the opposite sex);[10] however, the pattern of transmission varies significantly among countries. As of 2014, most HIV transmission in the United States occurred among men who had sex with men, with this population accounting for 67% of new cases and 83% of new cases among males over 12 years old.[48] About 15% of gay and bisexual men have HIV while 28 percent of transgender women test positive.[49][48]

With regard to unprotected heterosexual contacts, estimates of the risk of HIV transmission per sexual act appear to be four to ten times higher in low-income countries than in high-income countries.[50] In low-income countries, the risk of female-to-male transmission is estimated as 0.38% per act, and of male-to-female transmission as 0.30% per act; the equivalent estimates for high-income countries are 0.04% per act for female-to-male transmission, and 0.08% per act for male-to-female transmission.[50] The risk of transmission from anal intercourse is especially high, estimated as 1.4–1.7% per act in both heterosexual and homosexual contacts.[50][51] While the risk of transmission from oral sex is relatively low, it is still present.[52] The risk from receiving oral sex has been described as "nearly nil";[53] however, a few cases have been reported.[54] The per-act risk is estimated at 0–0.04% for receptive oral intercourse.[55] In settings involving prostitution in low income countries, risk of female-to-male transmission has been estimated as 2.4% per act and male-to-female transmission as 0.05% per act.[50]

Risk of transmission increases in the presence of many sexually transmitted infections[56] and genital ulcers.[50] Genital ulcers appear to increase the risk approximately fivefold.[50] Other sexually transmitted infections, such as gonorrhea, chlamydia, trichomoniasis, and bacterial vaginosis, are associated with somewhat smaller increases in risk of transmission.[55]

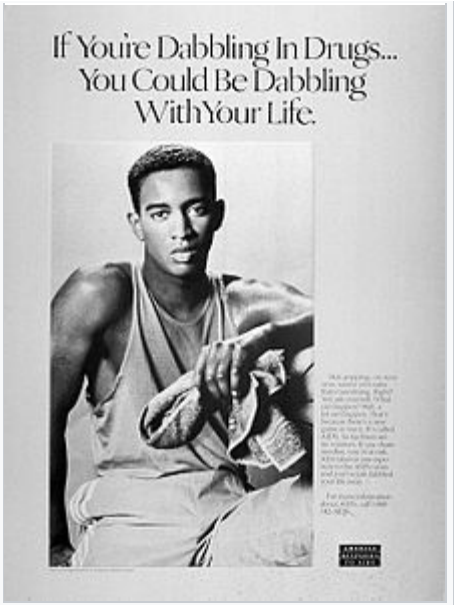
The viral load of an infected person is an important risk factor in both sexual and mother-to-child transmission.[57] During the first 2.5 months of an HIV infection a person's infectiousness is twelve times higher due to this high viral load.[55] If the person is in the late stages of infection, rates of transmission are approximately eightfold greater.[50]

Commercial sex workers (including those in pornography) have an increased rate of HIV.[58][59] Rough sex can be a factor associated with an increased risk of transmission.[60] Sexual assault is also believed to carry an increased risk of HIV transmission as condoms are rarely worn, physical trauma to the vagina or rectum is likely, and there may be a greater risk of concurrent sexually transmitted infections.[61]

## Body fluids

The second most frequent mode of HIV transmission is via blood and blood products.[10] Blood-borne transmission can be through needle-sharing during intravenous drug use, needle stick injury, transfusion of contaminated blood or blood product, or medical injections with unsterilized equipment. The risk from sharing a needle during drug injection is between 0.63 and 2.4% per act, with an average of 0.8%.[62] The risk of acquiring HIV from a needle stick from an HIV-infected person is estimated as 0.3% (about 1 in 333) per act and the risk following mucous membrane exposure to infected blood as 0.09% (about 1 in 1000) per act.[46] In the United States intravenous drug users made up 12% of all new cases of HIV in 2009,[63] and in some areas more than 80% of people who inject drugs are HIV positive.[10]

HIV is transmitted in about 93% of blood transfusions using infected blood.[62] In developed countries the risk of acquiring HIV from a blood transfusion is extremely low (less than one in half a million) where improved donor selection and HIV screening is performed;[10] for




CDC poster from 1989 highlighting the threat of AIDS associated with drug use

example, in the UK the risk is reported at one in five million[64] and in the United States it was one in 1.5 million in 2008.[65] In low income countries, only half of transfusions may be appropriately screened (as of 2008),[66] and it is estimated that up to 15% of HIV infections in these areas come from transfusion of infected blood and blood products, representing between 5% and 10% of global infections.[10][67] Although rare because of screening, it is possible to acquire HIV from organ and tissue transplantation.[68]

Unsafe medical injections play a significant role in HIV spread in sub-Saharan Africa. In 2007, between 12 and 17% of infections in this region were attributed to medical syringe use.[69] The World Health Organization estimates the risk of transmission as a result of a medical injection in Africa at 1.2%.[69] Significant risks are also associated with invasive procedures, assisted delivery, and dental care in this area of the world.[69]

People giving or receiving tattoos, piercings, and scarification are theoretically at risk of infection but no confirmed cases have been documented.[70] It is not possible for mosquitoes or other insects to transmit HIV.[71]

### Mother-to-child

*Main articles: HIV and pregnancy and HIV and breastfeeding*

HIV can be transmitted from mother to child during pregnancy, during delivery, or through breast milk resulting in infection in the baby.[72][73] This is the third most common way in which HIV is transmitted globally.[10] In the absence of treatment, the risk of transmission before or during birth is around 20% and in those who also breastfeed 35%.[72] As of 2008, vertical transmission accounted for about 90% of cases of HIV in children.[72] With appropriate treatment the risk of mother-to-child infection can be reduced to about 1%.[72] Preventive treatment involves the mother taking antiretrovirals during pregnancy and delivery, an elective caesarean section, avoiding breastfeeding, and administering antiretroviral drugs to the newborn.[74] Antiretrovirals when taken by either the mother or the infant decrease the risk of transmission in those who do breastfeed.[75] Many of these measures are however not available in the developing world.[74] If blood contaminates food during pre-chewing it may pose a risk of transmission.[70]

## Virology

*Main article: HIV*

HIV is the cause of the spectrum of disease known as HIV/AIDS. HIV is

a retrovirus that primarily infects components of the human immune system such as CD4+ T cells, macrophages and dendritic cells. It directly and indirectly destroys CD4+ T cells.[76]

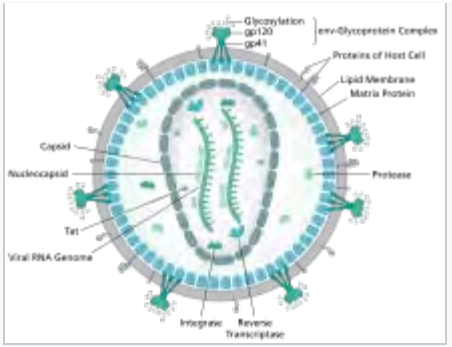
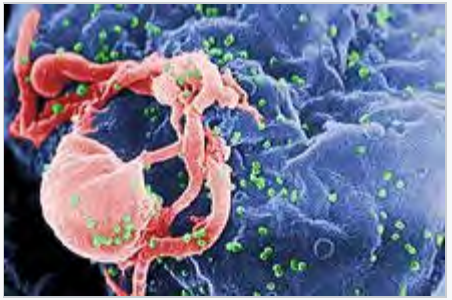


Diagram of a HIV virion structure

HIV is a member of the genus *Lentivirus*,[77] part of the family *Retroviridae*.[78] Lentiviruses share many morphological and biological characteristics. Many species of mammals are infected by lentiviruses, which are characteristically responsible for long-duration illnesses with a long incubation period.[79] Lentiviruses are transmitted as single-stranded, positive-sense, enveloped RNA viruses. Upon entry into the target cell, the viral RNA genome is converted (reverse transcribed) into double-stranded DNA by a virally encoded reverse transcriptase that is transported along with the viral genome in the virus particle. The resulting viral DNA is then imported into the cell nucleus and integrated into the cellular DNA by a virally encoded integrase and host co-factors.[80] Once integrated, the virus may become latent, allowing the virus and its host cell to avoid detection by the immune system.[81] Alternatively, the virus may be transcribed, producing new RNA genomes and viral proteins that are packaged and released from the cell as new virus particles that begin the replication cycle anew.[82]


Scanning electron micrograph of HIV-1, colored green, budding from a cultured lymphocyte.

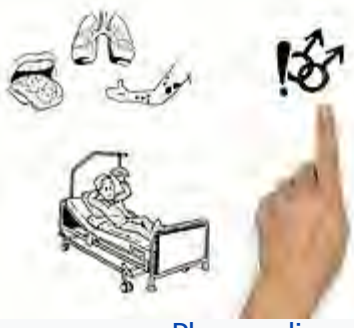
HIV is now known to spread between CD4+ T cells by two parallel routes: cell-free spread and cell-to-cell spread, i.e. it employs hybrid spreading mechanisms.[83] In the cell-free spread, virus particles bud from an infected T cell, enter the blood/extracellular fluid and then infect another T cell following a chance encounter.[83] HIV can also disseminate by direct transmission from one cell to another by a process of cell-to-cell spread.[84][85] The hybrid spreading mechanisms of HIV contribute to the virus's ongoing replication against antiretroviral therapies.[83][86]

Two types of HIV have been characterized: HIV-1 and HIV-2. HIV-1 is the virus that was originally discovered (and initially referred to also as LAV or HTLV-III). It is more virulent, more infective,[87] and is the cause of the majority of HIV infections globally. The lower infectivity of HIV-2 as compared with HIV-1 implies that fewer people exposed to HIV-2 will be infected per exposure. Because of its relatively poor capacity for transmission, HIV-2 is largely confined to West Africa.[88]

# Pathophysiology

*Main article: Pathophysiology of HIV/AIDS*

After the virus enters the body there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood.[89] This response is accompanied by a marked drop in the number of circulating CD4+ T cells. The acute viremia is almost invariably associated with activation of CD8+ T cells, which kill HIV-infected cells, and subsequently with antibody production, or seroconversion. The CD8+ T cell response is thought to be important in controlling virus levels, which peak and then decline, as the CD4+ T cell counts recover. A good CD8+ T cell response has been linked to slower disease progression and a better prognosis, though it does not eliminate the virus.[90]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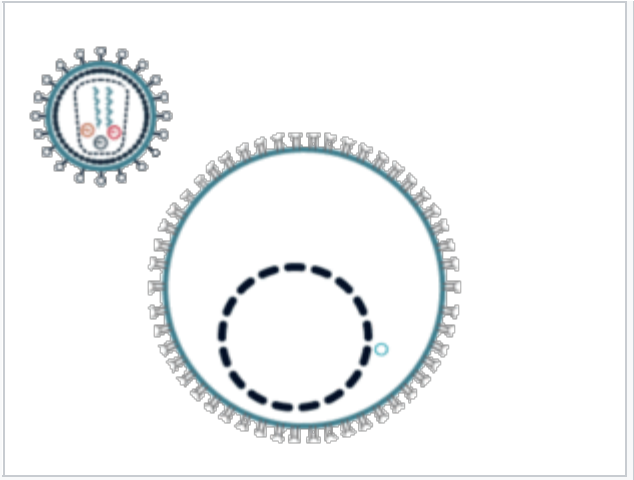
HIV/AIDS explained in a simple way

Ultimately, HIV causes AIDS by depleting CD4+ T cells. This weakens the immune system and allows opportunistic infections. T cells are essential to the immune response and without them, the body cannot fight infections or kill cancerous cells. The mechanism of CD4+ T cell depletion differs in the acute and chronic phases.[91] During the acute phase, HIV-induced cell lysis and killing of infected cells by cytotoxic T cells accounts for CD4+ T cell depletion, although apoptosis may also be a factor. During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in CD4+ T cell numbers.[92]



HIV replication cycle

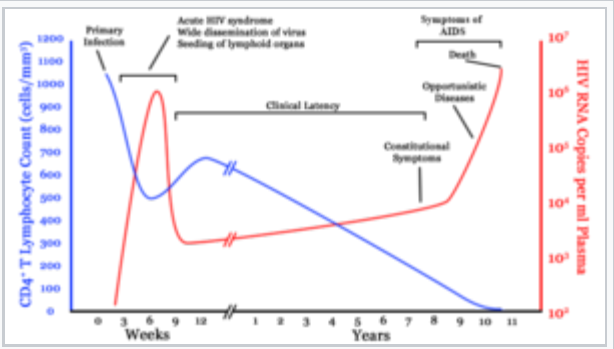
Although the symptoms of immune deficiency characteristic of AIDS do not appear for years after a person is infected, the bulk of CD4+ T cell loss occurs during the first weeks of infection, especially in the intestinal mucosa, which harbors the majority of the lymphocytes found in the body.[93] The reason for the preferential loss of mucosal CD4+ T cells is that the majority of mucosal CD4+ T cells express the CCR5 protein which HIV uses as a co-receptor to gain access to the cells, whereas only a small fraction of CD4+ T cells in the bloodstream do so.[94] A specific genetic change that alters the CCR5 protein when present in both chromosomes very effectively prevents HIV-1 infection.[95]

HIV seeks out and destroys CCR5 expressing CD4+ T cells during acute infection.[96] A vigorous immune response eventually controls the infection and initiates the clinically latent phase. CD4+ T cells in mucosal tissues remain particularly affected.[96] Continuous HIV replication causes a state of generalized immune activation persisting throughout the chronic phase.[97] Immune activation, which is reflected by the increased activation state of immune cells and release of pro-inflammatory cytokines, results from the activity of several HIV gene products and the immune response to ongoing HIV replication. It is also linked to the breakdown of the immune surveillance system of the gastrointestinal mucosal barrier caused by the depletion of mucosal CD4+ T cells during the acute phase of disease.[98]

# Diagnosis

*Main article: Diagnosis of HIV/AIDS*

HIV/AIDS is diagnosed via laboratory testing and then staged based on the presence of certain signs or symptoms.[23] HIV screening is recommended by the United States Preventive Services Task Force for all people 15 years to 65 years of age including all pregnant women.[99] Additionally, testing is recommended for those at high risk, which includes anyone diagnosed with a sexually transmitted illness.[26] In many areas of the world, a third of HIV carriers only discover they are infected at an advanced stage of the disease when AIDS or severe immunodeficiency has become apparent.[26]




A generalized graph of the relationship between HIV copies (viral load) and CD4+ T cell counts over the average course of untreated HIV infection.

CD4+ T Lymphocyte count (cells/mm³)

HIV RNA copies per mL of plasma

## HIV testing

Most people infected with HIV develop specific antibodies (i.e. seroconvert) within three to twelve weeks of the initial infection.[25] Diagnosis of primary HIV before seroconversion is done by measuring HIV-RNA or p24 antigen.[25] Positive results obtained by antibody or PCR testing are confirmed

either by a different antibody or by PCR.[23]

Antibody tests in children younger than 18 months are typically inaccurate due to the continued presence of maternal antibodies.[100] Thus HIV infection can only be diagnosed by PCR testing for HIV RNA or DNA, or via testing for the p24 antigen.[23] Much of the world lacks access to reliable PCR testing and many places simply wait until either symptoms develop or the child is old enough for accurate antibody testing.[100] In sub-Saharan Africa as of 2007–2009 between 30 and 70% of the population were aware of their HIV status.[101] In 2009, between 3.6 and 42% of men and women in Sub-Saharan countries were tested[101] which represented a significant increase compared to previous years.[101]

## Classifications

Two main clinical staging systems are used to classify HIV and HIV-related disease for surveillance purposes: the WHO disease staging system for HIV infection and disease,[23] and the CDC classification system for HIV infection.[102] The CDC's classification system is more frequently adopted in developed countries. Since the WHO's staging system does not require laboratory tests, it is suited to the resource-restricted conditions encountered in developing countries, where it can also be used to help guide clinical management. Despite their differences, the two systems allow comparison for statistical purposes.[2][23][102]

The World Health Organization first proposed a definition for AIDS in 1986.[23] Since then, the WHO classification has been updated and expanded several times, with the most recent version being published in 2007.[23] The WHO system uses the following categories:

- Primary HIV infection: May be either asymptomatic or associated with acute retroviral syndrome.[23]
- Stage I: HIV infection is asymptomatic with a $CD4^+$ T cell count (also known as CD4 count) greater than 500 per microlitre (μl or cubic mm) of blood.[23] May include generalized lymph node enlargement.[23]
- Stage II: Mild symptoms which may include minor mucocutaneous manifestations and recurrent upper respiratory tract infections. A CD4 count of less than 500/μl.[23]
- Stage III: Advanced symptoms which may include unexplained chronic diarrhea for longer than a month, severe bacterial infections including tuberculosis of the lung, and a CD4 count of less than 350/μl.[23]
- Stage IV or AIDS: severe symptoms which include toxoplasmosis of the brain, candidiasis of the esophagus, trachea, bronchi or lungs and Kaposi's sarcoma. A CD4 count of less than 200/μl.[23]

The United States Center for Disease Control and Prevention also created a classification system for HIV, and updated it in 2008 and 2014.[102][103] This system classifies HIV infections based on CD4 count and clinical symptoms, and describes the infection in five groups.[103] In those greater than six years of age it is:[103]

- Stage 0: the time between a negative or indeterminate HIV test followed less than 180 days by a positive test
- Stage 1: CD4 count ≥ 500 cells/μl and no AIDS defining conditions
- Stage 2: CD4 count 200 to 500 cells/μl and no AIDS defining conditions
- Stage 3: CD4 count ≤ 200 cells/μl or AIDS defining conditions
- Unknown: if insufficient information is available to make any of the above classifications

For surveillance purposes, the AIDS diagnosis still stands even if, after treatment, the $CD4^+$ T cell count rises to above 200 per μL of blood or other AIDS-defining illnesses are cured.[2]

# Prevention

*Main article: Prevention of HIV/AIDS*

## Sexual contact

AIDS Clinic, McLeod Ganj, Himachal Pradesh, India, 2010

Consistent condom use reduces the risk of HIV transmission by approximately 80% over the long term.[104] When condoms are used consistently by a couple in which one person is infected, the rate of HIV infection is less than 1% per year.[105] There is some evidence to suggest that female condoms may provide an equivalent level of protection.[106] Application of a vaginal gel containing tenofovir (a reverse transcriptase inhibitor) immediately before sex seems to reduce infection rates by approximately 40% among African women.[107] By contrast, use of the spermicide nonoxynol-9 may increase the risk of transmission due to its tendency to cause vaginal and rectal irritation.[108]

Circumcision in Sub-Saharan Africa "reduces the acquisition of HIV by heterosexual men by between 38% and 66% over 24 months".[109] Due to these studies, both the World Health Organization and UNAIDS recommended male circumcision as a method of preventing female-to-male HIV transmission in 2007 in areas with a high rates of HIV.[110] However, whether it protects against male-to-female transmission is disputed,[111][112] and whether it is of benefit in developed countries and among men who have sex with men is undetermined.[113][114][115] The International Antiviral Society, however, does recommend for all sexually active heterosexual males and that it be discussed as an option with men who have sex with men.[116] Some experts fear that a lower perception of vulnerability among circumcised men may cause more sexual risk-taking behavior, thus negating its preventive effects.[117]

Programs encouraging sexual abstinence do not appear to affect subsequent HIV risk.[118] Evidence of any benefit from peer education is equally poor.[119] Comprehensive sexual education provided at school may decrease high risk behavior.[120] A substantial minority of young people continues to engage in high-risk practices despite knowing about HIV/AIDS, underestimating their own risk of becoming infected with HIV.[121] Voluntary counseling and testing people for HIV does not affect risky behavior in those who test negative but does increase condom use in those who test positive.[122] It is not known whether treating other sexually transmitted infections is effective in preventing HIV.[56]

## Pre-exposure

Antiretroviral treatment among people with HIV whose CD4 count ≤ 550 cells/μL is a very effective way to prevent HIV infection of their partner (a strategy known as treatment as prevention, or TASP).[123] TASP is associated with a 10 to 20 fold reduction in transmission risk.[123][124] Pre-exposure prophylaxis (PrEP) with a daily dose of the medications tenofovir, with or without emtricitabine, is effective in a number of groups including men who have sex with men, couples where one is HIV positive, and young heterosexuals in Africa.[107] It may also be effective in intravenous drug users with a study finding a decrease in risk of 0.7 to 0.4 per 100 person years.[125]

Universal precautions within the health care environment are believed to be effective in decreasing the risk of HIV.[126] Intravenous drug use is an important risk factor and harm reduction strategies such as needle-exchange programs and opioid substitution therapy appear effective in decreasing this risk.[127][128]

## Post-exposure

A course of antiretrovirals administered within 48 to 72 hours after exposure to HIV-positive blood or genital secretions is referred to as post-exposure prophylaxis (PEP).[129] The use of the single agent zidovudine reduces the risk of a HIV infection five-fold following a needle-stick injury.[129] As of 2013, the prevention regimen recommended in the United States consists of three medications—tenofovir,

emtricitabine and raltegravir—as this may reduce the risk further.[130]

PEP treatment is recommended after a sexual assault when the perpetrator is known to be HIV positive, but is controversial when their HIV status is unknown.[131] The duration of treatment is usually four weeks[132] and is frequently associated with adverse effects—where zidovudine is used, about 70% of cases result in adverse effects such as nausea (24%), fatigue (22%), emotional distress (13%) and headaches (9%).[46]

### Mother-to-child

*Main article: HIV and pregnancy*

Programs to prevent the vertical transmission of HIV (from mothers to children) can reduce rates of transmission by 92–99%.[72][127] This primarily involves the use of a combination of antiviral medications during pregnancy and after birth in the infant and potentially includes bottle feeding rather than breastfeeding.[72][133] If replacement feeding is acceptable, feasible, affordable, sustainable, and safe, mothers should avoid breastfeeding their infants; however exclusive breastfeeding is recommended during the first months of life if this is not the case.[134] If exclusive breastfeeding is carried out, the provision of extended antiretroviral prophylaxis to the infant decreases the risk of transmission.[135] In 2015, Cuba became the first country in the world to eradicate mother-to-child transmission of HIV.[136]

### Vaccination

*Main article: HIV vaccine*

Currently, there is no licensed vaccine for HIV or AIDS.[12] The most effective vaccine trial to date, RV 144, was published in 2009 and found a partial reduction in the risk of transmission of roughly 30%, stimulating some hope in the research community of developing a truly effective vaccine.[137] Further trials of the RV 144 vaccine are ongoing.[138][139]

## Treatment

*Main article: Management of HIV/AIDS*

There is currently no cure or effective HIV vaccine. Treatment consists of highly active antiretroviral therapy (HAART) which slows progression of the disease.[140] As of 2010 more than 6.6 million people were taking them in low and middle income countries.[141] Treatment also includes preventive and active treatment of opportunistic infections.

### Antiviral therapy

*Stribild* – a common once-daily

Current HAART options are combinations (or "cocktails") consisting of at least three medications belonging to at least two types, or "classes," of antiretroviral agents.[142] Initially treatment is typically a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside analog reverse transcriptase inhibitors (NRTIs).[143] Typical NRTIs include: zidovudine (AZT) or tenofovir (TDF) and lamivudine (3TC) or emtricitabine (FTC).[143] Combinations of agents which include protease inhibitors (PI) are used if the above regimen loses effectiveness.[142]

The World Health Organization and United States recommends antiretrovirals in people of all ages including pregnant women as soon as the diagnosis is made regardless of CD4 count.[13][116][144] Once treatment is begun it is recommended that it is continued without breaks or "holidays".[26] Many people are diagnosed only after treatment

ART regime consisting of elvitegravir, emtricitabine, tenofovir and the booster cobicistat

ideally should have begun.[26] The desired outcome of treatment is a long term plasma HIV-RNA count below 50 copies/mL.[26] Levels to determine if treatment is effective are initially recommended after four weeks and once levels fall below 50 copies/mL checks every three to six months are typically adequate.[26] Inadequate control is deemed to be greater than 400 copies/mL.[26] Based on these criteria treatment is effective in more than 95% of people during the first year.[26]

Benefits of treatment include a decreased risk of progression to AIDS and a decreased risk of death.[145] In the developing world treatment also improves physical and mental health.[146] With treatment there is a 70% reduced risk of acquiring tuberculosis.[142] Additional benefits include a decreased risk of transmission of the disease to sexual partners and a decrease in mother-to-child transmission.[142] The effectiveness of treatment depends to a large part on compliance.[26] Reasons for non-adherence include poor access to medical care,[147] inadequate social supports, mental illness and drug abuse.[148] The complexity of treatment regimens (due to pill numbers and dosing frequency) and adverse effects may reduce adherence.[149] Even though cost is an important issue with some medications,[150] 47% of those who needed them were taking them in low and middle income countries as of 2010[141] and the rate of adherence is similar in low-income and high-income countries.[151]

Specific adverse events are related to the antiretroviral agent taken.[152] Some relatively common adverse events include: lipodystrophy syndrome, dyslipidemia, and diabetes mellitus, especially with protease inhibitors.[2] Other common symptoms include diarrhea,[152][153] and an increased risk of cardiovascular disease.[154] Newer recommended treatments are associated with fewer adverse effects.[26] Certain medications may be associated with birth defects and therefore may be unsuitable for women hoping to have children.[26]

Treatment recommendations for children are somewhat different from those for adults. The World Health Organization recommends treating all children less than 5 years of age; children above 5 are treated like adults.[155] The United States guidelines recommend treating all children less than 12 months of age and all those with HIV RNA counts greater than 100,000 copies/mL between one year and five years of age.[156]

## Opportunistic infections

Measures to prevent opportunistic infections are effective in many people with HIV/AIDS. In addition to improving current disease, treatment with antiretrovirals reduces the risk of developing additional opportunistic infections.[152] Adults and adolescents who are living with HIV (even on anti-retroviral therapy) with no evidence of active tuberculosis in settings with high tuberculosis burden should receive isoniazid preventive therapy (IPT), the tuberculin skin test can be used to help decide if IPT is needed.[157] Vaccination against hepatitis A and B is advised for all people at risk of HIV before they become infected; however it may also be given after infection.[158] Trimethoprim/sulfamethoxazole prophylaxis between four and six weeks of age and ceasing breastfeeding in infants born to HIV positive mothers is recommended in resource limited settings.[159] It is also recommended to prevent PCP when a person's CD4 count is below 200 cells/uL and in those who have or have previously had PCP.[160] People with substantial immunosuppression are also advised to receive prophylactic therapy for toxoplasmosis and Cryptococcus meningitis.[161] Appropriate preventive measures have reduced the rate of these infections by 50% between 1992 and 1997.[162] Influenza vaccination and pneumococcal polysaccharide vaccine are often recommended in people with HIV/AIDS with some evidence of benefit.[163][164]

## Diet

*Main article: Nutrition and HIV/AIDS*

The World Health Organization (WHO) has issued recommendations regarding nutrient requirements in [165]

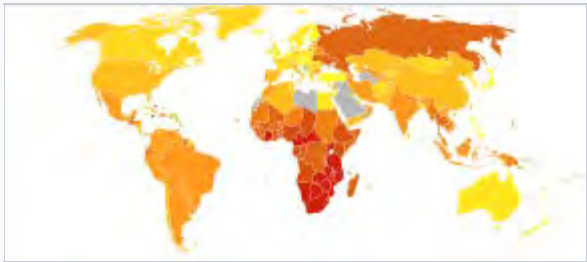
HIV/AIDS. A generally healthy diet is promoted. Some evidence has shown a benefit from micronutrient supplements.[166] Evidence for supplementation with selenium is mixed with some tentative evidence of benefit.[167] There is some evidence that vitamin A supplementation in children reduces mortality and improves growth.[166] In Africa in nutritionally compromised pregnant and lactating women a multivitamin supplementation has improved outcomes for both mothers and children.[166] Dietary intake of micronutrients at RDA levels by HIV-infected adults is recommended by the WHO; higher intake of vitamin A, zinc, and iron can produce adverse effects in HIV positive adults, and is not recommended unless there is documented deficiency.[165][168][169][170]

### Alternative medicine

In the US, approximately 60% of people with HIV use various forms of complementary or alternative medicine,[171] even though the effectiveness of most of these therapies has not been established.[172] There is not enough evidence to support the use of herbal medicines.[173] There is insufficient evidence to recommend or support the use of medical cannabis to try to increase appetite or weight gain.[174]

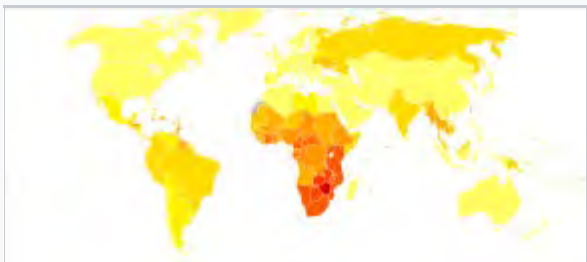
## Prognosis

HIV/AIDS has become a chronic rather than an acutely fatal disease in many areas of the world.[175] Prognosis varies between people, and both the CD4 count and viral load are useful for predicted outcomes.[25] Without treatment, average survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV subtype.[14] After the diagnosis of AIDS, if treatment is not available, survival ranges between 6 and 19 months.[176][177] HAART and appropriate prevention of opportunistic infections reduces the death rate by 80%, and raises the life expectancy for a newly diagnosed young adult to 20–50 years.[175][178][179] This is between two thirds[178] and nearly that of the general population.[26][180] If treatment is started late in the infection, prognosis is not as good:[26] for example, if treatment is begun following the diagnosis of AIDS, life expectancy is ~10–40 years.[26][175] Half of infants born with HIV die before two years of age without treatment.[159]



Deaths due to HIV/AIDS per million persons in 2012

| | | |
|---|---|---|
| 0 | 35–61 | 459-1,402 |
| 1–4 | 62–134 | 1,403-5,828 |
| 5–12 | 135–215 | |
| 13–34 | 216–458 | |



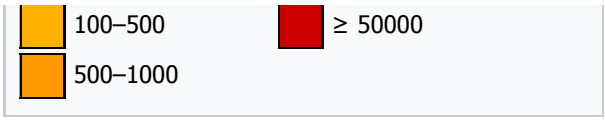
Disability-adjusted life year for HIV and AIDS per 100,000 inhabitants as of 2004.

| | |
|---|---|
| no data | 1000–2500 |
| ≤ 10 | 2500–5000 |
| 10–25 | 5000–7500 |
| 25–50 | 7500-10000 |
| 50–100 | 10000-50000 |

The primary causes of death from HIV/AIDS are opportunistic infections and cancer, both of which are frequently the result of the progressive failure of the immune system.[162][181] Risk of cancer appears to increase once the CD4 count is below 500/μL.[26] The rate of clinical disease progression varies widely between individuals and has been shown to be affected by a number of factors such as a person's susceptibility and immune function;[182] their access to health care, the presence of co-infections;[176][183] and the particular strain (or strains) of the virus involved.[184][185]

Tuberculosis co-infection is one of the leading causes of sickness and death in those with HIV/AIDS being present in a third of all HIV-infected people and causing 25% of HIV-related deaths.[186] HIV is also one of the most important risk factors for tuberculosis.[187] Hepatitis C is another very common co-infection where each disease increases the

progression of the other.[188] The two most common cancers associated with HIV/AIDS are Kaposi's sarcoma and AIDS-related non-Hodgkin's lymphoma.[181]

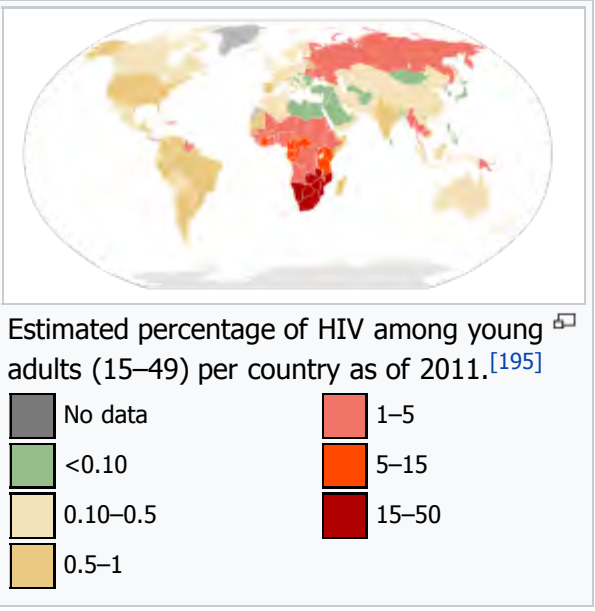



Even with anti-retroviral treatment, over the long term HIV-infected people may experience neurocognitive disorders,[189] osteoporosis,[190] neuropathy,[191] cancers,[192][193] nephropathy,[194] and cardiovascular disease.[153] Some conditions like lipodystrophy may be caused both by HIV and its treatment.[153]

# Epidemiology

*Main article: Epidemiology of HIV/AIDS*

HIV/AIDS is a global pandemic.[196] As of 2014, approximately 37 million people have HIV worldwide with the number of new infections that year being about 2 million.[197] This is down from 3.1 million new infections in 2001.[198] Of these 37 million more than half are women and 2.6 million are less than 15 years old.[197][199] It resulted in about 1.2 million deaths in 2014,[197] down from a peak of 2.2 million in 2005.[141][198]



Estimated percentage of HIV among young adults (15–49) per country as of 2011.[195]

Sub-Saharan Africa is the region most affected. In 2010, an estimated 68% (22.9 million) of all HIV cases and 66% of all deaths (1.2 million) occurred in this region.[200] This means that about 5% of the adult population is infected[201] and it is believed to be the cause of 10% of all deaths in children.[202] Here in contrast to other regions women compose nearly 60% of cases.[200] South Africa has the largest population of people with HIV of any country in the world at 5.9 million.[200] Life expectancy has fallen in the worst-affected countries due to HIV/AIDS; for example, in 2006 it was estimated that it had dropped from 65 to 35 years in Botswana.[16] Mother-to-child transmission, as of 2013, in Botswana and South Africa has decreased to less than 5% with improvement in many other African nations due to improved access to antiretroviral therapy.[203]

South & South East Asia is the second most affected; in 2010 this region contained an estimated 4 million cases or 12% of all people living with HIV resulting in approximately 250,000 deaths.[201] Approximately 2.4 million of these cases are in India.[200]

In 2008 in the United States approximately 1.2 million people were living with HIV, resulting in about 17,500 deaths. The US Centers for Disease Control and Prevention estimated that in 2008 20% of infected Americans were unaware of their infection.[204] As of 2016 about 675,000 people have died HIV/AIDS in the USA since the beginning of the HIV epidemic.[49] In the United Kingdom as of 2009 there were approximately 86,500 cases which resulted in 516 deaths.[205] In Canada as of 2008 there were about 65,000 cases causing 53 deaths.[206] Between the first recognition of AIDS in 1981 and 2009 it has led to nearly 30 million deaths.[207] Prevalence is lowest in Middle East and North Africa at 0.1% or less, East Asia at 0.1% and Western and Central Europe at 0.2%.[201] The worst affected European countries, in 2009 and 2012 estimates, are Russia, Ukraine, Latvia, Moldova, Portugal and Belarus, in decreasing order of prevalence.[208]

# History

*Main article: History of HIV/AIDS*

## Discovery

AIDS was first clinically observed in 1981 in the United States.[34] The initial cases were a cluster of injecting drug users and homosexual men with no known cause of impaired immunity who showed symptoms of *Pneumocystis carinii* pneumonia (PCP), a rare opportunistic infection that was known to occur in people with very compromised immune systems.[209] Soon thereafter, an unexpected number of homosexual men developed a previously rare skin cancer called Kaposi's sarcoma (KS).[210][211] Many more cases of PCP and KS emerged, alerting U.S. Centers for Disease Control and Prevention (CDC) and a CDC task force was formed to monitor the outbreak.[212]

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MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Epidemiologic Notes and Reports

**Kaposi's Sarcoma and *Pneumocystis* Pneumonia Among Homosexual Men — New York City and California**

TABLE 1. Presenting complaints in 20 patients with Kaposi's sarcoma

| Presenting complaint | Number (percentage) of patients |
|---|---|
| Skin lesion(s) only | 10 (50%) |
| Skin lesions plus lymphadenopathy | 4 (20%) |
| Oral mucosal lesion only | 1 (5%) |
| Inguinal adenopathy plus perirectal abscess | 1 (5%) |
| Weight loss and fever | 2 (10%) |
| Weight loss, fever, and pneumonia (one due to *Pneumocystis carinii*) | 2 (10%) |

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES / PUBLIC HEALTH SERVICE

The *Morbidity and Mortality Weekly Report* reported in 1981 on what was later to be called "AIDS".

In the early days, the CDC did not have an official name for the disease, often referring to it by way of the diseases that were associated with it, for example, lymphadenopathy, the disease after which the discoverers of HIV originally named the virus.[213][214] They also used *Kaposi's sarcoma and opportunistic infections*, the name by which a task force had been set up in 1981.[215] At one point, the CDC coined the phrase "the 4H disease", since the syndrome seemed to affect heroin users, homosexuals, hemophiliacs, and Haitians.[216][217] In the general press, the term "GRID", which stood for gay-related immune deficiency, had been coined.[218] However, after determining that AIDS was not isolated to the gay community,[215] it was realized that the term GRID was misleading and the term AIDS was introduced at a meeting in July 1982.[219] By September 1982 the CDC started referring to the disease as AIDS.[220]

In 1983, two separate research groups led by Robert Gallo and Luc Montagnier declared that a novel retrovirus may have been infecting people with AIDS, and published their findings in the same issue of the journal *Science*.[221][222] Gallo claimed that a virus his group had isolated from a person with AIDS was strikingly similar in shape to other human T-lymphotropic viruses (HTLVs) his group had been the first to isolate. Gallo's group called their newly isolated virus HTLV-III. At the same time, Montagnier's group isolated a virus from a person presenting with swelling of the lymph nodes of the neck and physical weakness, two characteristic symptoms of AIDS. Contradicting the report from Gallo's group, Montagnier and his colleagues showed that core proteins of this virus were immunologically different from those of HTLV-I. Montagnier's group named their isolated virus lymphadenopathy-associated virus (LAV).[212] As these two viruses turned out to be the same, in 1986, LAV and HTLV-III were renamed HIV.[223]

## Origins

Both HIV-1 and HIV-2 are believed to have originated in non-human primates in West-central Africa and were transferred to humans in the early 20th century.[17] HIV-1 appears to have originated in southern Cameroon through the evolution of SIV(cpz), a simian immunodeficiency virus (SIV) that infects wild chimpanzees (HIV-1 descends from the SIVcpz endemic in the chimpanzee subspecies *Pan troglodytes troglodytes*).[224][225] The closest relative of HIV-2 is SIV(smm), a virus of the sooty mangabey (*Cercocebus atys atys*), an Old World monkey living in coastal West Africa (from southern Senegal to western Côte d'Ivoire).[88] New World monkeys such as the owl monkey are resistant to HIV-1 infection, possibly because of a genomic fusion of two viral

Left to right: the African green monkey source of SIV, the sooty mangabey source of HIV-2 and the chimpanzee source of HIV-1

resistance genes.[226] HIV-1 is thought to have jumped the species barrier on at least three separate occasions, giving rise to the three groups of the virus, M, N, and O.[227]

There is evidence that humans who participate in bushmeat activities, either as hunters or as bushmeat vendors, commonly acquire SIV.[228] However, SIV is a weak virus which is typically suppressed by the human immune system within weeks of infection. It is thought that several transmissions of the virus from individual to individual in quick succession are necessary to allow it enough time to mutate into HIV.[229] Furthermore, due to its relatively low person-to-person transmission rate, SIV can only spread throughout the population in the presence of one or more high-risk transmission channels, which are thought to have been absent in Africa before the 20th century.

Specific proposed high-risk transmission channels, allowing the virus to adapt to humans and spread throughout the society, depend on the proposed timing of the animal-to-human crossing. Genetic studies of the virus suggest that the most recent common ancestor of the HIV-1 M group dates back to circa 1910.[230] Proponents of this dating link the HIV epidemic with the emergence of colonialism and growth of large colonial African cities, leading to social changes, including a higher degree of sexual promiscuity, the spread of prostitution, and the accompanying high frequency of genital ulcer diseases (such as syphilis) in nascent colonial cities.[231] While transmission rates of HIV during vaginal intercourse are low under regular circumstances, they are increased many fold if one of the partners suffers from a sexually transmitted infection causing genital ulcers. Early 1900s colonial cities were notable due to their high prevalence of prostitution and genital ulcers, to the degree that, as of 1928, as many as 45% of female residents of eastern Kinshasa were thought to have been prostitutes, and, as of 1933, around 15% of all residents of the same city had syphilis.[231]

An alternative view holds that unsafe medical practices in Africa after World War II, such as unsterile reuse of single use syringes during mass vaccination, antibiotic and anti-malaria treatment campaigns, were the initial vector that allowed the virus to adapt to humans and spread.[229][232][233]

The earliest well-documented case of HIV in a human dates back to 1959 in the Congo.[234] The earliest retrospectively described case of AIDS is believed to have been in Norway beginning in 1966.[235] In July 1960, in the wake its independence, the United Nations recruited Francophone experts and technicians from all over the world to assist in filling administrative gaps left by Belgium, who did not leave behind an African elite to run the country. By 1962, Haitians made up the second largest group of well-educated experts (out of the 48 national groups recruited), that totaled around 4500 in the country.[236][237] Dr. Jacques Pépin, a Quebecer author of *The Origins of AIDS*, stipulates that Haiti was one of HIV's entry points to the United States and that one of them may have carried HIV back across the Atlantic in the 1960s.[237] Although, the virus may have been present in the United States as early as 1966,[238] the vast majority of infections occurring outside sub-Saharan Africa (including the U.S.) can be traced back to a single unknown individual who became infected with HIV in Haiti and then brought the infection to the United States some time around 1969.[239] The epidemic then rapidly spread among high-risk groups (initially, sexually promiscuous men who have sex with men). By 1978, the prevalence of HIV-1 among homosexual male residents of New York City and San Francisco was estimated at 5%, suggesting that several thousand individuals in the country had been infected.[239]

# Society and culture

## Stigma

*Main article: Discrimination against people with HIV/AIDS*

AIDS stigma exists around the world in a variety of ways, including ostracism, rejection, discrimination and avoidance of HIV infected people; compulsory HIV testing without prior consent or protection of confidentiality; violence against HIV infected individuals or people who are perceived to be infected with HIV;

Ryan White became a poster child for HIV after being expelled from school because he was infected.[240]

and the quarantine of HIV infected individuals.[19] Stigma-related violence or the fear of violence prevents many people from seeking HIV testing, returning for their results, or securing treatment, possibly turning what could be a manageable chronic illness into a death sentence and perpetuating the spread of HIV.[241]

AIDS stigma has been further divided into the following three categories:

- *Instrumental AIDS stigma*—a reflection of the fear and apprehension that are likely to be associated with any deadly and transmissible illness.[242]
- *Symbolic AIDS stigma*—the use of HIV/AIDS to express attitudes toward the social groups or lifestyles perceived to be associated with the disease.[242]
- *Courtesy AIDS stigma*—stigmatization of people connected to the issue of HIV/AIDS or HIV-positive people.[243]

Often, AIDS stigma is expressed in conjunction with one or more other stigmas, particularly those associated with homosexuality, bisexuality, promiscuity, prostitution, and intravenous drug use.[244]

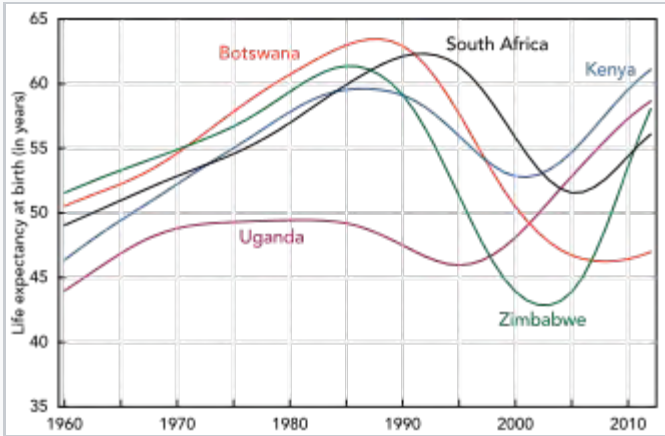
In many developed countries, there is an association between AIDS and homosexuality or bisexuality, and this association is correlated with higher levels of sexual prejudice, such as anti-homosexual/bisexual attitudes.[245] There is also a perceived association between AIDS and all male-male sexual behavior, including sex between uninfected men.[242] However, the dominant mode of spread worldwide for HIV remains heterosexual transmission.[246]

In 2003, as part of an overall reform of marriage and population legislation, it became legal for people with AIDS to marry in China.[247]

## Economic impact

*Main articles: Economic impact of HIV/AIDS and Cost of HIV treatment*

HIV/AIDS affects the economics of both individuals and countries.[202] The gross domestic product of the most affected countries has decreased due to the lack of human capital.[202][248] Without proper nutrition, health care and medicine, large numbers of people die from AIDS-related complications. They will not only be unable to work, but will also require significant medical care. It is estimated that as of 2007 there were 12 million AIDS orphans.[202] Many are cared for by elderly grandparents.[249]




Changes in life expectancy in some African countries, 1960–2012

Returning to work after beginning treatment for HIV/AIDS is difficult, and affected people often work less than the average worker. Unemployment in people with HIV/AIDS also is associated with suicidal ideation, memory problems, and social isolation; employment increases self-esteem, sense of dignity, confidence, and quality of life. A 2015 Cochrane review found low-quality evidence that antiretroviral treatment helps people with HIV/AIDS work more, and increases the chance that a person with HIV/AIDS will be employed.[250]

By affecting mainly young adults, AIDS reduces the taxable population, in turn reducing the resources

available for public expenditures such as education and health services not related to AIDS resulting in increasing pressure for the state's finances and slower growth of the economy. This causes a slower growth of the tax base, an effect that is reinforced if there are growing expenditures on treating the sick, training (to replace sick workers), sick pay and caring for AIDS orphans. This is especially true if the sharp increase in adult mortality shifts the responsibility and blame from the family to the government in caring for these orphans.[249]

At the household level, AIDS causes both loss of income and increased spending on healthcare. A study in Côte d'Ivoire showed that households having a person with HIV/AIDS spent twice as much on medical expenses as other households. This additional expenditure also leaves less income to spend on education and other personal or family investment.[251]

## Religion and AIDS

*Main article: Religion and HIV/AIDS*

The topic of religion and AIDS has become highly controversial in the past twenty years, primarily because some religious authorities have publicly declared their opposition to the use of condoms.[252][253] The religious approach to prevent the spread of AIDS according to a report by American health expert Matthew Hanley titled *The Catholic Church and the Global AIDS Crisis* argues that cultural changes are needed including a re-emphasis on fidelity within marriage and sexual abstinence outside of it.[253]

Some religious organizations have claimed that prayer can cure HIV/AIDS. In 2011, the BBC reported that some churches in London were claiming that prayer would cure AIDS, and the Hackney-based Centre for the Study of Sexual Health and HIV reported that several people stopped taking their medication, sometimes on the direct advice of their pastor, leading to a number of deaths.[254] The Synagogue Church Of All Nations advertise an "anointing water" to promote God's healing, although the group deny advising people to stop taking medication.[254]

## Media portrayal

*Main article: Media portrayal of HIV/AIDS*

One of the first high-profile cases of AIDS was the American Rock Hudson, a gay actor who had been married and divorced earlier in life, who died on October 2, 1985 having announced that he was suffering from the virus on July 25 that year. He had been diagnosed during 1984.[255] A notable British casualty of AIDS that year was Nicholas Eden, a gay politician and son of the late prime minister Anthony Eden.[256] On November 24, 1991, the virus claimed the life of British rock star Freddie Mercury, lead singer of the band Queen, who died from an AIDS-related illness having only revealed the diagnosis on the previous day.[257] However, he had been diagnosed as HIV positive in 1987.[258] One of the first high-profile heterosexual cases of the virus was Arthur Ashe, the American tennis player. He was diagnosed as HIV positive on August 31, 1988, having contracted the virus from blood transfusions during heart surgery earlier in the 1980s. Further tests within 24 hours of the initial diagnosis revealed that Ashe had AIDS, but he did not tell the public about his diagnosis until April 1992.[259] He died as a result on February 6, 1993 at age 49.[260]

Therese Frare's photograph of gay activist David Kirby, as he lay dying from AIDS while surrounded by family, was taken in April 1990. *LIFE magazine* said the photo became the one image "most powerfully identified with the HIV/AIDS epidemic." The photo was displayed in *LIFE magazine*, was the winner of the World Press Photo, and acquired worldwide notoriety after being used in a United Colors of Benetton advertising campaign in 1992.[261] In 1996, Johnson Aziga, a Ugandan-born Canadian was diagnosed with HIV, but subsequently had unprotected sex with 11 women without disclosing his diagnosis. By 2003 seven had contracted HIV, and two died from complications related to AIDS.[262][263] Aziga was convicted of first-degree murder and is liable to a life sentence.[264]

## Criminal transmission

*Main article: Criminal transmission of HIV*

Criminal transmission of HIV is the intentional or reckless infection of a person with the human immunodeficiency virus (HIV). Some countries or jurisdictions, including some areas of the United States, have laws that criminalize HIV transmission or exposure.[265] Others may charge the accused under laws enacted before the HIV pandemic.

### Misconceptions

*Main articles: Misconceptions about HIV/AIDS and Discredited HIV/AIDS origins theories*

There are many misconceptions about HIV and AIDS. Three of the most common are that AIDS can spread through casual contact, that sexual intercourse with a virgin will cure AIDS,[266][267][268] and that HIV can infect only gay men and drug users. In 2014, some among the British public wrongly thought one could get HIV from kissing (16%), sharing a glass (5%), spitting (16%), a public toilet seat (4%), and coughing or sneezing (5%).[269] Other misconceptions are that any act of anal intercourse between two uninfected gay men can lead to HIV infection, and that open discussion of HIV and homosexuality in schools will lead to increased rates of AIDS.[270][271]

A small group of individuals continue to dispute the connection between HIV and AIDS,[272] the existence of HIV itself, or the validity of HIV testing and treatment methods.[273][274] These claims, known as AIDS denialism, have been examined and rejected by the scientific community.[275] However, they have had a significant political impact, particularly in South Africa, where the government's official embrace of AIDS denialism (1999–2005) was responsible for its ineffective response to that country's AIDS epidemic, and has been blamed for hundreds of thousands of avoidable deaths and HIV infections.[276][277][278]

Several discredited conspiracy theories have held that HIV was created by scientists, either inadvertently or deliberately. Operation INFEKTION was a worldwide Soviet active measures operation to spread the claim that the United States had created HIV/AIDS. Surveys show that a significant number of people believed – and continue to believe – in such claims.[279]

## Research

*Main article: HIV/AIDS research*

HIV/AIDS research includes all medical research which attempts to prevent, treat, or cure HIV/AIDS along with fundamental research about the nature of HIV as an infectious agent and AIDS as the disease caused by HIV.

Many governments and research institutions participate in HIV/AIDS research. This research includes behavioral health interventions such as sex education, and drug development, such as research into microbicides for sexually transmitted diseases, HIV vaccines, and antiretroviral drugs. Other medical research areas include the topics of pre-exposure prophylaxis, post-exposure prophylaxis, and circumcision and HIV.

## References


1. ^ *a b c d* "Stages of HIV". *U.S. Department of Health & Human Services*. Dec 2010. Retrieved June 13, 2012.
2. ^ *a b c d e f* Mandell, Bennett, and Dolan (2010). Chapter 121.
3. ^ "HIV Classification: CDC and WHO Staging Systems". *Guide for HIV/AIDS Clinical Care*. AIDS Education and Training Center Program. Retrieved November 21, 2015.
4. ^ "World AIDS Day". World Health Organization. Retrieved June 16, 2015.
5. ^ Sepkowitz KA (June 2001). "AIDS—the first 20 years". *N. Engl. J. Med.* **344** (23): 1764–72. doi:10.1056/NEJM200106073442306. PMID 11396444.
6. ^ editors, Alexander Krämer, Mirjam Kretzschmar, Klaus Krickeberg, (2010). *Modern infectious disease epidemiology concepts, methods, mathematical models, and public health* (Online-Ausg. ed.). New York: Springer. p. 88. ISBN 9780387938356.

7. ^ Wilhelm Kirch (2008). *Encyclopedia of public health*. New York: Springer. pp. 676–677. ISBN 9781402056130.
8. ^ a b c d e f "HIV/AIDS Fact sheet N°360". *WHO*. November 2015. Retrieved 11 February 2016.
9. ^ a b c d "About HIV/AIDS". *CDC*. December 6, 2015. Retrieved 11 February 2016.
10. ^ a b c d e f g h i Markowitz, edited by William N. Rom ; associate editor, Steven B. (2007). *Environmental and occupational medicine* (4th ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins. p. 745. ISBN 978-0-7817-6299-1.
11. ^ "HIV and Its Transmission". Centers for Disease Control and Prevention. 2003. Archived from the original on February 4, 2005. Retrieved May 23, 2006.
12. ^ a b UNAIDS (May 18, 2012). "The quest for an HIV vaccine".
13. ^ a b *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV.* (PDF). WHO. 2015. p. 13. ISBN 9789241509565.
14. ^ a b UNAIDS, WHO (December 2007). "2007 AIDS epidemic update" (PDF). Retrieved March 12, 2008.
15. ^ "Basic Statistics". *CDC*. November 3, 2015. Retrieved 11 February 2016.
16. ^ a b Kallings LO (2008). "The first postmodern pandemic: 25 years of HIV/AIDS". *Journal of Internal Medicine*. **263** (3): 218–43. doi:10.1111/j.1365-2796.2007.01910.x. PMID 18205765.(subscription required)
17. ^ a b Sharp, PM; Hahn, BH (September 2011). "Origins of HIV and the AIDS Pandemic". *Cold Spring Harbor perspectives in medicine*. **1** (1): a006841. doi:10.1101/cshperspect.a006841. PMC 3234451. PMID 22229120.
18. ^ Gallo RC (2006). "A reflection on HIV/AIDS research after 25 years". *Retrovirology*. **3** (1): 72. doi:10.1186/1742-4690-3-72. PMC 1629027. PMID 17054781.
19. ^ a b c "The impact of AIDS on people and societies" (PDF). *2006 Report on the global AIDS epidemic*. UNAIDS. 2006. ISBN 92-9173-479-9. Retrieved June 14, 2006.
20. ^ "Myth Busters". Retrieved 14 February 2016.
21. ^ McCullom, Rob (26 Feb 2013). "An African Pope Won't Change the Vatican's Views on Condoms and AIDS previousnext An African Pope Won't Change the Vatican's Views on Condoms and AIDS". *The Atlantic*. Retrieved 14 February 2016.
22. ^ Harden, Victoria Angela (2012). *AIDS at 30: A History*. Potomac Books Inc. p. 324. ISBN 1-59797-294-0.
23. ^ a b c d e f g h i j k l m n o p *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children.* (PDF). Geneva: World Health Organization. 2007. pp. 6–16. ISBN 978-92-4-159562-9.
24. ^ *Diseases and disorders.* Tarrytown, NY: Marshall Cavendish. 2008. p. 25. ISBN 978-0-7614-7771-6.
25. ^ a b c d e f g h i j k l m n Mandell, Bennett, and Dolan (2010). Chapter 118.
26. ^ a b c d e f g h i j k l m n o p q Vogel, M; Schwarze-Zander, C; Wasmuth, JC; Spengler, U; Sauerbruch, T; Rockstroh, JK (July 2010). "The treatment of patients with HIV". *Deutsches Ärzteblatt international*. **107** (28–29): 507–15; quiz 516. doi:10.3238/arztebl.2010.0507. PMC 2915483. PMID 20703338.
27. ^ Evian, Clive (2006). *Primary HIV/AIDS care: a practical guide for primary health care personnel in a clinical and supportive setting* (Updated 4th ed.). Houghton [South Africa]: Jacana. p. 29. ISBN 978-1-77009-198-6.
28. ^ Charles B. Hicks, MD (2001). Jacques W. A. J. Reeders & Philip Charles Goodman, ed. *Radiology of AIDS*. Berlin [u.a.]: Springer. p. 19. ISBN 978-3-540-66510-6.
29. ^ Elliott, Tom (2012). *Lecture Notes: Medical Microbiology and Infection*. John Wiley & Sons. p. 273. ISBN 978-1-118-37226-5.
30. ^ a b Blankson, JN (March 2010). "Control of HIV-1 replication in elite suppressors". *Discovery medicine*. **9** (46): 261–6. PMID 20350494.
31. ^ Walker, BD (Aug–Sep 2007). "Elite control of HIV Infection: implications for vaccines and treatment". *Topics in HIV medicine : a publication of the International AIDS Society, USA*. **15** (4): 134–6. PMID 17720999.
32. ^ Holmes CB, Losina E, Walensky RP, Yazdanpanah Y, Freedberg KA (2003). "Review of human immunodeficiency virus type 1-related opportunistic infections in sub-Saharan Africa". *Clin. Infect. Dis.* **36** (5): 656–662. doi:10.1086/367655. PMID 12594648.
33. ^ Chu, C; Selwyn, PA (February 15, 2011). "Complications of HIV infection: a systems-based approach". *American family physician*. **83** (4): 395–406. PMID 21322514.
34. ^ a b c d e Mandell, Bennett, and Dolan (2010). Chapter 169.
35. ^ Mittal, R; Rath, S; Vemuganti, GK (Jul 2013). "Ocular surface squamous neoplasia – Review of etio-pathogenesis and an update on clinico-pathological diagnosis.". *Saudi Journal of Ophthalmology*. **27** (3): 177–86. doi:10.1016/j.sjopt.2013.07.002. PMID 24227983.
36. ^ "AIDS". *MedlinePlus*. A.D.A.M. Retrieved June 14, 2012.
37. ^ Sestak K (July 2005). "Chronic diarrhea and AIDS: insights into studies with non-human primates". *Curr. HIV Res.* **3** (3): 199–205. doi:10.2174/1570162054368084. PMID 16022653.

38. ^ Murray ED, Buttner N, Price BH (2012). "Depression and Psychosis in Neurological Practice". In Bradley WG, Daroff RB, Fenichel GM, Jankovic J. *Bradley's Neurology in Clinical Practice: Expert Consult – Online and Print, 6e (Bradley, Neurology in Clinical Practice e-dition 2v Set)*. **1** (6th ed.). Philadelphia, PA: Elsevier/Saunders. p. 101. ISBN 1-4377-0434-4.
39. ^ [a] [b] Smith DK, Grohskopf LA, Black RJ, Auerbach JD, Veronese F, Struble KA, Cheever L, Johnson M, Paxton LA, Onorato IM, Greenberg AE (21 January 2005). "Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of Health and Human Services.". *MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control*. **54** (RR-2): 1–20. PMID 15660015.
40. ^ Coovadia H (2004). "Antiretroviral agents—how best to protect infants from HIV and save their mothers from AIDS". *N. Engl. J. Med*. **351** (3): 289–292. doi:10.1056/NEJMe048128. PMID 15247337.
41. ^ Kripke C (1 August 2007). "Antiretroviral prophylaxis for occupational exposure to HIV.". *American family physician*. **76** (3): 375–6. PMID 17708137.
42. ^ [a] [b] [c] [d] Dosekun O, Fox J (July 2010). "An overview of the relative risks of different sexual behaviours on HIV transmission.". *Current opinion in HIV and AIDS*. **5** (4): 291–7. doi:10.1097/COH.0b013e32833a88a3. PMID 20543603.
43. ^ Cunha, Burke (2012). *Antibiotic Essentials 2012* (11 ed.). Jones & Bartlett Publishers. p. 303. ISBN 9781449693831.
44. ^ [a] [b] Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, Alary M (February 2009). "Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies.". *The Lancet infectious diseases*. **9** (2): 118–29. doi:10.1016/S1473-3099(09)70021-0. PMID 19179227.
45. ^ Baggaley RF, White RG, Boily MC (December 2008). "Systematic review of orogenital HIV-1 transmission probabilities.". *International Journal of Epidemiology*. **37** (6): 1255–65. doi:10.1093/ije/dyn151. PMC 2638872. PMID 18664564.
46. ^ [a] [b] [c] Kripke, C (August 1, 2007). "Antiretroviral prophylaxis for occupational exposure to HIV". *American family physician*. **76** (3): 375–6. PMID 17708137.
47. ^ van der Kuyl, AC; Cornelissen, M (September 24, 2007). "Identifying HIV-1 dual infections". *Retrovirology*. **4**: 67. doi:10.1186/1742-4690-4-67. PMC 2045676. PMID 17892568.
48. ^ [a] [b] "HIV Among Gay and Bisexual Men" (PDF). Retrieved 1 January 2017.
49. ^ [a] [b] "Today's HIV/AIDS Epidemic Factsheet" (PDF). *Centers for Disease Control and Prevention*. U.S. government. Retrieved 31 December 2016.
50. ^ [a] [b] [c] [d] [e] [f] [g] Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, Alary M (February 2009). "Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies". *The Lancet Infectious Diseases*. **9** (2): 118–129. doi:10.1016/S1473-3099(09)70021-0. PMID 19179227.
51. ^ Beyrer, C; Baral, SD; van Griensven, F; Goodreau, SM; Chariyalertsak, S; Wirtz, AL; Brookmeyer, R (Jul 28, 2012). "Global epidemiology of HIV infection in men who have sex with men". *Lancet*. **380** (9839): 367–77. doi:10.1016/S0140-6736(12)60821-6. PMID 22819660.
52. ^ Yu, M; Vajdy, M (August 2010). "Mucosal HIV transmission and vaccination strategies through oral compared with vaginal and rectal routes". *Expert opinion on biological therapy*. **10** (8): 1181–95. doi:10.1517/14712598.2010.496776. PMC 2904634. PMID 20624114.
53. ^ Stürchler, Dieter A. (2006). *Exposure a guide to sources of infections*. Washington, DC: ASM Press. p. 544. ISBN 978-1-55581-376-5.
54. ^ al.], edited by Richard Pattman (2010). *Oxford handbook of genitourinary medicine, HIV, and sexual health* (2nd ed.). Oxford: Oxford University Press. p. 95. ISBN 978-0-19-957166-6.
55. ^ [a] [b] [c] Dosekun, O; Fox, J (July 2010). "An overview of the relative risks of different sexual behaviours on HIV transmission". *Current Opinion in HIV and AIDS*. **5** (4): 291–7. doi:10.1097/COH.0b013e32833a88a3. PMID 20543603.
56. ^ [a] [b] Ng, BE; Butler, LM; Horvath, T; Rutherford, GW (March 16, 2011). Butler, Lisa M, ed. "Population-based biomedical sexually transmitted infection control interventions for reducing HIV infection". *Cochrane database of systematic reviews (Online)* (3): CD001220. doi:10.1002/14651858.CD001220.pub3. PMID 21412869.
57. ^ Anderson, J (February 2012). "Women and HIV: motherhood and more". *Current Opinion in Infectious Diseases*. **25** (1): 58–65. doi:10.1097/QCO.0b013e32834ef514. PMID 22156896.
58. ^ Kerrigan, Deanna (2012). *The Global HIV Epidemics among Sex Workers*. World Bank Publications. p. 1. ISBN 978-0-8213-9775-6.
59. ^ Aral, Sevgi (2013). *The New Public Health and STD/HIV Prevention: Personal, Public and Health Systems Approaches*. Springer. p. 120. ISBN 978-1-4614-4526-5.
60. ^ Klimas, N; Koneru, AO; Fletcher, MA (June 2008). "Overview of HIV". *Psychosomatic Medicine*. **70** (5): 523–30.

doi:10.1097/PSY.0b013e31817ae69f. PMID 18541903.
61. ^ Draughon, JE; Sheridan, DJ (2012). "Nonoccupational post exposure prophylaxis following sexual assault in industrialized low-HIV-prevalence countries: a review". *Psychology, health & medicine*. **17** (2): 235–54. doi:10.1080/13548506.2011.579984. PMID 22372741.
62. ^ *a b* Baggaley, RF; Boily, MC; White, RG; Alary, M (April 4, 2006). "Risk of HIV-1 transmission for parenteral exposure and blood transfusion: a systematic review and meta-analysis". *AIDS (London, England)*. **20** (6): 805–12. doi:10.1097/01.aids.0000218543.46963.6d. PMID 16549963.
63. ^ "HIV in the United States: An Overview". *Center for Disease Control and Prevention*. March 2012.
64. ^ "Will I need a blood transfusion?" (PDF). *NHS patient information*. National Health Services. 2011. Retrieved August 29, 2012.
65. ^ Centers for Disease Control and Prevention, (CDC) (October 22, 2010). "HIV transmission through transfusion --- Missouri and Colorado, 2008.". *MMWR. Morbidity and mortality weekly report*. **59** (41): 1335–9. PMID 20966896.
66. ^ UNAIDS 2011 pg. 60–70
67. ^ "Blood safety ... for too few". WHO. 2001. Archived from the original on January 17, 2005.
68. ^ Simonds, RJ (November 1993). "HIV transmission by organ and tissue transplantation". *AIDS*. 7 Suppl 2: S35–8. doi:10.1097/00002030-199311002-00008. PMID 8161444.
69. ^ *a b c* Reid, SR (August 28, 2009). "Injection drug use, unsafe medical injections, and HIV in Africa: a systematic review". *Harm reduction journal*. **6**: 24. doi:10.1186/1477-7517-6-24. PMC 2741434. PMID 19715601.
70. ^ *a b* "Basic Information about HIV and AIDS". *Center for Disease Control and Prevention*. April 2012.
71. ^ Crans, Wayne J. (June 1, 2010). "Why Mosquitoes Cannot Transmit AIDS". *rci.rutgers.edu*. Rutgers University. New Jersey Agricultural Experiment Station Publication No. H-40101-01-93. Archived from the original on March 29, 2014. Retrieved March 29, 2014.
72. ^ *a b c d e f* Coutsoudis, A; Kwaan, L; Thomson, M (October 2010). "Prevention of vertical transmission of HIV-1 in resource-limited settings". *Expert review of anti-infective therapy*. **8** (10): 1163–75. doi:10.1586/eri.10.94. PMID 20954881.
73. ^ "Fluids of transmission". *AIDS.gov*. United States Department of Health and Human Services. November 1, 2011. Retrieved September 14, 2012.
74. ^ *a b* Thorne, C; Newell, ML (June 2007). "HIV". *Seminars in fetal & neonatal medicine*. **12** (3): 174–81. doi:10.1016/j.siny.2007.01.009. PMID 17321814.
75. ^ White, AB; Mirjahangir, JF; Horvath, H; Anglemyer, A; Read, JS (Oct 4, 2014). "Antiretroviral interventions for preventing breast milk transmission of HIV.". *The Cochrane database of systematic reviews*. **10**: CD011323. doi:10.1002/14651858.CD011323. PMID 25280769.
76. ^ Alimonti JB, Ball TB, Fowke KR (2003). "Mechanisms of CD4+ T lymphocyte cell death in human immunodeficiency virus infection and AIDS". *J. Gen. Virol*. **84** (7): 1649–1661. doi:10.1099/vir.0.19110-0. PMID 12810858.
77. ^ International Committee on Taxonomy of Viruses (2002). "61.0.6. Lentivirus". National Institutes of Health. Archived from the original on April 18, 2006. Retrieved June 25, 2012.
78. ^ International Committee on Taxonomy of Viruses (2002). "61. Retroviridae". National Institutes of Health. Archived from the original on December 17, 2001. Retrieved June 25, 2012.
79. ^ Lévy, J. A. (1993). "HIV pathogenesis and long-term survival". *AIDS*. **7** (11): 1401–10. doi:10.1097/00002030-199311000-00001. PMID 8280406.
80. ^ Smith, Johanna A.; Daniel, René (Division of Infectious Diseases, Center for Human Virology, Thomas Jefferson University, Philadelphia) (2006). "Following the path of the virus: the exploitation of host DNA repair mechanisms by retroviruses". *ACS Chem Biol*. **1** (4): 217–26. doi:10.1021/cb600131q. PMID 17163676.
81. ^ Martínez, edited by Miguel Angel (2010). *RNA interference and viruses : current innovations and future trends*. Norfolk: Caister Academic Press. p. 73. ISBN 978-1-904455-56-1.
82. ^ Gerald B. Pier, ed. (2004). *Immunology, infection, and immunity*. Washington, D.C.: ASM Press. p. 550. ISBN 978-1-55581-246-1.
83. ^ *a b c* Zhang C, Zhou S, Groppelli E, Pellegrino P, Williams I, Borrow P, Chain BM, Jolly C (2015). "Hybrid Spreading Mechanisms and T Cell Activation Shape the Dynamics of HIV-1 Infection". *PLOS Computational Biology*. **11** (4): e1004179. doi:10.1371/journal.pcbi.1004179. PMC 4383537. PMID 25837979.
84. ^ Jolly C, Kashefi K, Hollinshead M, Sattentau QJ (2004). "HIV-1 cell to cell transfer across an Env-induced, actin-dependent synapse". *Journal of Experimental Medicine*. **199** (2): 283–293. doi:10.1084/jem.20030648. PMC 2211771. PMID 14734528.
85. ^ Sattentau Q (2008). "Avoiding the void: cell-to-cell spread of human viruses". *Nature Reviews Microbiology*. **6** (11): 815–826. doi:10.1038/nrmicro1972. PMID 18923409.
86. ^ Sigal A, Kim JT, Balazs AB, Dekel E, Mayo A, Milo R, Baltimore D (2011). "Cell-to-cell spread of HIV permits ongoing replication despite antiretroviral therapy". *Nature*. **477** (7362): 95–98. doi:10.1038/nature10347.

PMID 21849975.
87. ^ Gilbert, PB; et al. (February 28, 2003). "Comparison of HIV-1 and HIV-2 infectivity from a prospective cohort study in Senegal". *Statistics in Medicine*. **22** (4): 573–593. doi:10.1002/sim.1342. PMID 12590415.
88. ^ [a] [b] Reeves, J. D.; Doms, R. W (2002). "Human Immunodeficiency Virus Type 2". *J. Gen. Virol*. **83** (Pt 6): 1253–65. doi:10.1099/0022-1317-83-6-1253. PMID 12029140.
89. ^ Piatak, M., Jr, Saag, M. S., Yang, L. C., Clark, S. J., Kappes, J. C., Luk, K. C., Hahn, B. H., Shaw, G. M. and Lifson, J.D. (1993). "High levels of HIV-1 in plasma during all stages of infection determined by competitive PCR". *Science*. **259** (5102): 1749–1754. Bibcode:1993Sci...259.1749P. doi:10.1126/science.8096089. PMID 8096089.
90. ^ Pantaleo G, Demarest JF, Schacker T, Vaccarezza M, Cohen OJ, Daucher M, Graziosi C, Schnittman SS, Quinn TC, Shaw GM, Perrin L, Tambussi G, Lazzarin A, Sekaly RP, Soudeyns H, Corey L, Fauci AS (1997). "The qualitative nature of the primary immune response to HIV infection is a prognosticator of disease progression independent of the initial level of plasma viremia". *Proc Natl Acad Sci U S A*. **94** (1): 254–258. Bibcode:1997PNAS...94..254P. doi:10.1073/pnas.94.1.254. PMC 19306. PMID 8990195.
91. ^ Hel Z, McGhee JR, Mestecky J (June 2006). "HIV infection: first battle decides the war". *Trends Immunol*. **27** (6): 274–81. doi:10.1016/j.it.2006.04.007. PMID 16679064.
92. ^ Pillay, Deenan; Genetti, Anna Maria; Weiss, Robin A. (2007). "Human Immunodeficiency Viruses". In Zuckerman, Arie J.; et al. *Principles and practice of clinical virology* (6th ed.). Hoboken, N.J.: Wiley. p. 905. ISBN 978-0-470-51799-4.
93. ^ Mehandru S, Poles MA, Tenner-Racz K, Horowitz A, Hurley A, Hogan C, Boden D, Racz P, Markowitz M (September 2004). "Primary HIV-1 infection is associated with preferential depletion of $CD4^+$ T cells from effector sites in the gastrointestinal tract". *J. Exp. Med*. **200** (6): 761–70. doi:10.1084/jem.20041196. PMC 2211967. PMID 15365095.
94. ^ Brenchley JM, Schacker TW, Ruff LE, Price DA, Taylor JH, Beilman GJ, Nguyen PL, Khoruts A, Larson M, Haase AT, Douek DC (September 2004). "$CD4^+$ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract". *J. Exp. Med*. **200** (6): 749–59. doi:10.1084/jem.20040874. PMC 2211962. PMID 15365096.
95. ^ Olson, WC; Jacobson, JM (March 2009). "CCR5 monoclonal antibodies for HIV-1 therapy.". *Current opinion in HIV and AIDS*. **4** (2): 104–11. doi:10.1097/COH.0b013e3283224015. PMID 19339948.
96. ^ [a] [b] editor, Julio Aliberti, (2011). *Control of Innate and Adaptive Immune Responses During Infectious Diseases*. New York, NY: Springer Verlag. p. 145. ISBN 978-1-4614-0483-5.
97. ^ Appay V, Sauce D (January 2008). "Immune activation and inflammation in HIV-1 infection: causes and consequences". *J. Pathol*. **214** (2): 231–41. doi:10.1002/path.2276. PMID 18161758.
98. ^ Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, Kazzaz Z, Bornstein E, Lambotte O, Altmann D, Blazar BR, Rodriguez B, Teixeira-Johnson L, Landay A, Martin JN, Hecht FM, Picker LJ, Lederman MM, Deeks SG, Douek DC (December 2006). "Microbial translocation is a cause of systemic immune activation in chronic HIV infection". *Nat. Med*. **12** (12): 1365–71. doi:10.1038/nm1511. PMID 17115046.
99. ^ Moyer,, Virginia A. (April 2013). "Screening for HIV: U.S. Preventive Services Task Force Recommendation Statement". *Annals of Internal Medicine*. doi:10.7326/0003-4819-159-1-201307020-00645.
100. ^ [a] [b] Kellerman, S; Essajee, S (Jul 20, 2010). "HIV testing for children in resource-limited settings: what are we waiting for?". *PLOS Medicine*. **7** (7): e1000285. doi:10.1371/journal.pmed.1000285. PMC 2907270. PMID 20652012.
101. ^ [a] [b] [c] UNAIDS 2011 pg. 70–80
102. ^ [a] [b] [c] Schneider, E; Whitmore, S; Glynn, KM; Dominguez, K; Mitsch, A; McKenna, MT; Centers for Disease Control and Prevention, (CDC) (December 5, 2008). "Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008". *MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control*. **57** (RR–10): 1–12. PMID 19052530.
103. ^ [a] [b] [c] Centers for Disease Control and Prevention, (CDC) (April 11, 2014). "Revised surveillance case definition for HIV infection—United States, 2014.". *MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control*. **63** (RR-03): 1–10. PMID 24717910.
104. ^ Crosby, R; Bounse, S (March 2012). "Condom effectiveness: where are we now?". *Sexual health*. **9** (1): 10–7. doi:10.1071/SH11036. PMID 22348628.
105. ^ "Condom Facts and Figures". WHO. August 2003. Retrieved January 17, 2006.
106. ^ Gallo, MF; Kilbourne-Brook, M; Coffey, PS (March 2012). "A review of the effectiveness and acceptability of the female condom for dual protection". *Sexual health*. **9** (1): 18–26. doi:10.1071/SH11037. PMID 22348629.
107. ^ [a] [b] Celum, C; Baeten, JM (February 2012). "Tenofovir-based pre-exposure prophylaxis for HIV prevention: evolving evidence". *Current Opinion in Infectious Diseases*. **25** (1): 51–7. doi:10.1097/QCO.0b013e32834ef5ef.

PMC 3266126. PMID 22156901.
108. ^ Baptista, M; Ramalho-Santos, J (November 1, 2009). "Spermicides, microbicides and antiviral agents: recent advances in the development of novel multi-functional compounds". *Mini reviews in medicinal chemistry*. **9** (13): 1556–67. doi:10.2174/138955709790361548. PMID 20205637.
109. ^ Siegfried, N; Muller, M; Deeks, JJ; Volmink, J (April 15, 2009). Siegfried, Nandi, ed. "Male circumcision for prevention of heterosexual acquisition of HIV in men". *Cochrane database of systematic reviews (Online)* (2): CD003362. doi:10.1002/14651858.CD003362.pub2. PMID 19370585.
110. ^ "WHO and UNAIDS announce recommendations from expert consultation on male circumcision for HIV prevention". World Health Organization. Mar 28, 2007.
111. ^ Larke, N (May 27, 2010). "Male circumcision, HIV and sexually transmitted infections: a review". *British journal of nursing (Mark Allen Publishing)*. **19** (10): 629–34. doi:10.12968/bjon.2010.19.10.48201. PMID 20622758.
112. ^ Eaton, L; Kalichman, SC (November 2009). "Behavioral aspects of male circumcision for the prevention of HIV infection". *Current HIV/AIDS reports*. **6** (4): 187–93. doi:10.1007/s11904-009-0025-9. PMC 3557929. PMID 19849961.(subscription required)
113. ^ Kim, HH; Li, PS; Goldstein, M (November 2010). "Male circumcision: Africa and beyond?". *Current Opinion in Urology*. **20** (6): 515–9. doi:10.1097/MOU.0b013e32833f1b21. PMID 20844437.
114. ^ Templeton, DJ; Millett, GA; Grulich, AE (February 2010). "Male circumcision to reduce the risk of HIV and sexually transmitted infections among men who have sex with men". *Current Opinion in Infectious Diseases*. **23** (1): 45–52. doi:10.1097/QCO.0b013e328334e54d. PMID 19935420.
115. ^ Wiysonge, Charles Shey; Kongnyuy, Eugene J; Shey, Muki; Muula, Adamson S; Navti, Osric B; Akl, Elie A; Lo, Ying-Ru (June 15, 2011). Wiysonge, Charles Shey, ed. "Male circumcision for prevention of homosexual acquisition of HIV in men". *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd (6): CD007496. doi:10.1002/14651858.CD007496.pub2. PMID 21678366.
116. ^ *a b* Marrazzo, JM; del Rio, C; Holtgrave, DR; Cohen, MS; Kalichman, SC; Mayer, KH; Montaner, JS; Wheeler, DP; Grant, RM; Grinsztejn, B; Kumarasamy, N; Shoptaw, S; Walensky, RP; Dabis, F; Sugarman, J; Benson, CA; International Antiviral Society-USA, Panel (Jul 23–30, 2014). "HIV prevention in clinical care settings: 2014 recommendations of the International Antiviral Society-USA Panel.". *JAMA: The Journal of the American Medical Association*. **312** (4): 390–409. doi:10.1001/jama.2014.7999. PMID 25038358.
117. ^ Eaton LA, Kalichman S (December 2007). "Risk compensation in HIV prevention: implications for vaccines, microbicides, and other biomedical HIV prevention technologies". *Curr HIV/AIDS Rep*. **4** (4): 165–72. doi:10.1007/s11904-007-0024-7. PMC 2937204. PMID 18366947.
118. ^ Underhill K, Operario D, Montgomery P (2008). Operario, Don, ed. "Abstinence-only programs for HIV infection prevention in high-income countries". *Cochrane Database of Systematic Reviews* (4): CD005421. doi:10.1002/14651858.CD005421.pub2. PMID 17943855.
119. ^ Tolli, MV (May 28, 2012). "Effectiveness of peer education interventions for HIV prevention, adolescent pregnancy prevention and sexual health promotion for young people: a systematic review of European studies". *Health education research*. **27** (5): 904–13. doi:10.1093/her/cys055. PMID 22641791.
120. ^ Ljubojević, S; Lipozenčić, J (2010). "Sexually transmitted infections and adolescence". *Acta Dermatovenerologica Croatica*. **18** (4): 305–10. PMID 21251451.
121. ^ Patel VL, Yoskowitz NA, Kaufman DR, Shortliffe EH (2008). "Discerning patterns of human immunodeficiency virus risk in healthy young adults". *Am J Med*. **121** (4): 758–764. doi:10.1016/j.amjmed.2008.04.022. PMC 2597652. PMID 18724961.
122. ^ Fonner, VA; Denison, J; Kennedy, CE; O'Reilly, K; Sweat, M (Sep 12, 2012). "Voluntary counseling and testing (VCT) for changing HIV-related risk behavior in developing countries.". *The Cochrane database of systematic reviews*. **9**: CD001224. doi:10.1002/14651858.CD001224.pub4. PMID 22972050.
123. ^ *a b* Anglemyer, A; Rutherford, GW; Horvath, T; Baggaley, RC; Egger, M; Siegfried, N (April 30, 2013). "Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples.". *The Cochrane database of systematic reviews*. **4**: CD009153. doi:10.1002/14651858.CD009153.pub3. PMID 23633367.
124. ^ Chou R, Selph S, Dana T, et al. (November 2012). "Screening for HIV: systematic review to update the 2005 U.S. Preventive Services Task Force recommendation". *Annals of Internal Medicine*. **157** (10): 706–18. doi:10.7326/0003-4819-157-10-201211200-00007. PMID 23165662.
125. ^ Choopanya, Kachit; Martin, Michael; Suntharasamai, Pravan; Sangkum, Udomsak; Mock, Philip A; Leethochawalit, Manoj; Chiamwongpaet, Sithisat; Kitisin, Praphan; Natrujirote, Pitinan; Kittimunkong, Somyot; Chuachoowong, Rutt; Gvetadze, Roman J; McNicholl, Janet M; Paxton, Lynn A; Curlin, Marcel E; Hendrix, Craig W; Vanichseni, Suphak (June 1, 2013). "Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial". *The Lancet*. **381** (9883): 2083–2090. doi:10.1016/S0140-6736(13)61127-7. PMID 23769234.
126. ^ Centers for Disease Control (CDC) (August 1987). "Recommendations for prevention of HIV transmission in

health-care settings" . *MMWR*. **36** (Suppl 2): 1S–18S. PMID 3112554 .

127. ^ [a] [b] Kurth, AE; Celum, C; Baeten, JM; Vermund, SH; Wasserheit, JN (March 2011). "Combination HIV prevention: significance, challenges, and opportunities". *Current HIV/AIDS reports*. **8** (1): 62–72. doi:10.1007/s11904-010-0063-3. PMC 3036787. PMID 20941553.
128. ^ MacArthur, G. J.; Minozzi, S.; Martin, N.; Vickerman, P.; Deren, S.; Bruneau, J.; Degenhardt, L.; Hickman, M. (October 4, 2012). "Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis". *BMJ*. **345** (oct03 3): e5945–e5945. doi:10.1136/bmj.e5945.
129. ^ [a] [b] [No authors listed] (April 2012). "HIV exposure through contact with body fluids". *Prescrire Int*. **21** (126): 100–1, 103–5. PMID 22515138.
130. ^ Kuhar DT, Henderson DK, Struble KA, et al. (September 2013). "Updated US Public Health Service Guidelines for the Management of Occupational Exposures to Human Immunodeficiency Virus and Recommendations for Postexposure Prophylaxis". *Infect Control Hosp Epidemiol*. **34** (9): 875–92. doi:10.1086/672271. PMID 23917901.
131. ^ Linden, JA (September 1, 2011). "Clinical practice. Care of the adult patient after sexual assault". *The New England Journal of Medicine*. **365** (9): 834–41. doi:10.1056/NEJMcp1102869. PMID 21879901.
132. ^ Young, TN; Arens, FJ; Kennedy, GE; Laurie, JW; Rutherford, G (January 24, 2007). Young, Taryn, ed. "Antiretroviral post-exposure prophylaxis (PEP) for occupational HIV exposure". *Cochrane database of systematic reviews (Online)* (1): CD002835. doi:10.1002/14651858.CD002835.pub3. PMID 17253483.
133. ^ Siegfried, N; van der Merwe, L; Brocklehurst, P; Sint, TT (July 6, 2011). Siegfried, Nandi, ed. "Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection". *Cochrane database of systematic reviews (Online)* (7): CD003510. doi:10.1002/14651858.CD003510.pub3. PMID 21735394.
134. ^ "WHO HIV and Infant Feeding Technical Consultation Held on behalf of the Inter-agency Task Team (IATT) on Prevention of HIV – Infections in Pregnant Women, Mothers and their Infants – Consensus statement" (PDF). October 25–27, 2006. Archived (PDF) from the original on April 9, 2008. Retrieved March 12, 2008.
135. ^ Horvath, T; Madi, BC; Iuppa, IM; Kennedy, GE; Rutherford, G; Read, JS (January 21, 2009). Horvath, Tara, ed. "Interventions for preventing late postnatal mother-to-child transmission of HIV". *Cochrane database of systematic reviews (Online)* (1): CD006734. doi:10.1002/14651858.CD006734.pub2. PMID 19160297.
136. ^ "WHO validates elimination of mother-to-child transmission of HIV and syphilis in Cuba". WHO. June 30, 2015. Retrieved August 30, 2015.
137. ^ Reynell, L; Trkola, A (March 2, 2012). "HIV vaccines: an attainable goal?". *Swiss Medical Weekly*. **142**: w13535. doi:10.4414/smw.2012.13535. PMID 22389197.
138. ^ U.S. Army Office of the Surgeon General (March 21, 2011). "HIV Vaccine Trial in Thai Adults". *ClinicalTrials.gov*. Retrieved June 28, 2011.
139. ^ U.S. Army Office of the Surgeon General (June 2, 2010). "Follow up of Thai Adult Volunteers With Breakthrough HIV Infection After Participation in a Preventive HIV Vaccine Trial". *ClinicalTrials.gov*.
140. ^ May, MT; Ingle, SM (December 2011). "Life expectancy of HIV-positive adults: a review". *Sexual health*. **8** (4): 526–33. doi:10.1071/SH11046. PMID 22127039.
141. ^ [a] [b] [c] UNAIDS 2011 pg. 1–10
142. ^ [a] [b] [c] [d] *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach* (PDF). World Health Organization. 2010. pp. 19–20. ISBN 978-92-4-159976-4.
143. ^ [a] [b] *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (PDF). World Health Organization. 2013. pp. 28–30. ISBN 978-92-4-150572-7.
144. ^ "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents" (pdf). *Department of Health and Human Services*. February 12, 2013. p. i. Retrieved January 3, 2014.
145. ^ When To Start, Consortium; Sterne, JA; May, M; Costagliola, D; de Wolf, F; Phillips, AN; Harris, R; Funk, MJ; Geskus, RB; Gill, J; Dabis, F; Miró, JM; Justice, AC; Ledergerber, B; Fätkenheuer, G; Hogg, RS; Monforte, AD; Saag, M; Smith, C; Staszewski, S; Egger, M; Cole, SR (April 18, 2009). "Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies". *Lancet*. **373** (9672): 1352–63. doi:10.1016/S0140-6736(09)60612-7. PMC 2670965. PMID 19361855.
146. ^ Beard, J; Feeley, F; Rosen, S (November 2009). "Economic and quality of life outcomes of antiretroviral therapy for HIV/AIDS in developing countries: a systematic literature review". *AIDS Care*. **21** (11): 1343–56. doi:10.1080/09540120902889926. PMID 20024710.
147. ^ Orrell, C (November 2005). "Antiretroviral adherence in a resource-poor setting". *Current HIV/AIDS reports*. **2** (4): 171–6. doi:10.1007/s11904-005-0012-8. PMID 16343374.
148. ^ Malta, M; Strathdee, SA; Magnanini, MM; Bastos, FI (August 2008). "Adherence to antiretroviral therapy for human immunodeficiency virus/acquired immune deficiency syndrome among drug users: a systematic review". *Addiction (Abingdon, England)*. **103** (8): 1242–57. doi:10.1111/j.1360-0443.2008.02269.x. PMID 18855813.
149. ^ Nachega, JB; Marconi, VC; van Zyl, GU; Gardner, EM; Preiser, W; Hong, SY; Mills, EJ; Gross, R (April 2011). "HIV

treatment adherence, drug resistance, virologic failure: evolving concepts". *Infectious disorders drug targets*. **11** (2): 167–74. doi:10.2174/187152611795589663. PMID 21406048.

150. ^ Orsi, F; d'almeida, C (May 2010). "Soaring antiretroviral prices, TRIPS and TRIPS flexibilities: a burning issue for antiretroviral treatment scale-up in developing countries". *Current Opinion in HIV and AIDS*. **5** (3): 237–41. doi:10.1097/COH.0b013e32833860ba. PMID 20539080.
151. ^ Nachega, JB; Mills, EJ; Schechter, M (January 2010). "Antiretroviral therapy adherence and retention in care in middle-income and low-income countries: current status of knowledge and research priorities". *Current Opinion in HIV and AIDS*. **5** (1): 70–7. doi:10.1097/COH.0b013e328333ad61. PMID 20046150.
152. ^ *a b c* Montessori, V., Press, N., Harris, M., Akagi, L., Montaner, J. S. (2004). "Adverse effects of antiretroviral therapy for HIV infection". *CMAJ*. **170** (2): 229–238. PMC 315530. PMID 14734438.
153. ^ *a b c* Burgoyne RW, Tan DH (March 2008). "Prolongation and quality of life for HIV-infected adults treated with highly active antiretroviral therapy (HAART): a balancing act". *J. Antimicrob. Chemother*. **61** (3): 469–73. doi:10.1093/jac/dkm499. PMID 18174196.
154. ^ Barbaro, G; Barbarini, G (December 2011). "Human immunodeficiency virus & cardiovascular risk". *The Indian journal of medical research*. **134** (6): 898–903. doi:10.4103/0971-5916.92634. PMC 3284097. PMID 22310821.
155. ^ "Summary of recommendations on when to start ART in children" (PDF). *Consolidated ARV guidelines, June 2013*. June 2013.
156. ^ "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection" (PDF). *Department of Health and Human Services, February 2014*. March 2014.
157. ^ "Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings" (PDF). *Department of HIV/AIDS, World Health Organization 2011*. 2011.
158. ^ Laurence J (2006). "Hepatitis A and B virus immunization in HIV-infected persons". *AIDS Reader*. **16** (1): 15–17. PMID 16433468.
159. ^ *a b* UNAIDS 2011 pg. 150–160
160. ^ Huang, L; Cattamanchi, A; Davis, JL; den Boon, S; Kovacs, J; Meshnick, S; Miller, RF; Walzer, PD; Worodria, W; Masur, H; International HIV-associated Opportunistic Pneumonias (IHOP), Study; Lung HIV, Study (June 2011). "HIV-associated Pneumocystis pneumonia". *Proceedings of the American Thoracic Society*. **8** (3): 294–300. doi:10.1513/pats.201009-062WR. PMC 3132788. PMID 21653531.
161. ^ "Treating opportunistic infections among HIV-infected adults and adolescents. Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America.". Department of Health and Human Services. February 2, 2007.
162. ^ *a b* Smith, Blaine T., ed. (2008). *Concepts in immunology and immunotherapeutics* (4th ed.). Bethesda, Md.: American Society of Health-System Pharmacists. p. 143. ISBN 978-1-58528-127-5.
163. ^ Beck, CR; McKenzie, BC; Hashim, AB; Harris, RC; Zanuzdana, A; Agboado, G; Orton, E; Béchard-Evans, L; Morgan, G; Stevenson, C; Weston, R; Mukaigawara, M; Enstone, J; Augustine, G; Butt, M; Kim, S; Puleston, R; Dabke, G; Howard, R; O'Boyle, J; O'Brien, M; Ahyow, L; Denness, H; Farmer, S; Figureroa, J; Fisher, P; Greaves, F; Haroon, M; Haroon, S; Hird, C; Isba, R; Ishola, DA; Kerac, M; Parish, V; Roberts, J; Rosser, J; Theaker, S; Wallace, D; Wigglesworth, N; Lingard, L; Vinogradova, Y; Horiuchi, H; Peñalver, J; Nguyen-Van-Tam, JS (September 2013). "Influenza vaccination for immunocompromised patients: summary of a systematic review and meta-analysis.". *Influenza and other respiratory viruses*. 7 Suppl 2: 72–5. doi:10.1111/irv.12084. PMID 24034488.
164. ^ Lee, KY; Tsai, MS; Kuo, KC; Tsai, JC; Sun, HY; Cheng, AC; Chang, SY; Lee, CH; Hung, CC (2014). "Pneumococcal vaccination among HIV-infected adult patients in the era of combination antiretroviral therapy.". *Human vaccines & immunotherapeutics*. **10** (12): 3700–10. doi:10.4161/hv.32247. PMC 4514044. PMID 25483681.
165. ^ *a b* World Health Organization (May 2003). *Nutrient requirements for people living with HIV/AIDS: Report of a technical consultation* (PDF). Geneva. Archived (PDF) from the original on March 25, 2009. Retrieved March 31, 2009.
166. ^ *a b c* Irlam, JH; Visser, MM; Rollins, NN; Siegfried, N (December 8, 2010). Irlam, James H, ed. "Micronutrient supplementation in children and adults with HIV infection". *Cochrane database of systematic reviews (Online)* (12): CD003650. doi:10.1002/14651858.CD003650.pub3. PMID 21154354.
167. ^ Stone, CA; Kawai, K; Kupka, R; Fawzi, WW (November 2010). "Role of selenium in HIV infection". *Nutrition Reviews*. **68** (11): 671–81. doi:10.1111/j.1753-4887.2010.00337.x. PMC 3066516. PMID 20961297.
168. ^ Forrester, JE; Sztam, KA (December 2011). "Micronutrients in HIV/AIDS: is there evidence to change the WHO 2003 recommendations?". *The American Journal of Clinical Nutrition*. **94** (6): 1683S–1689S. doi:10.3945/ajcn.111.011999. PMC 3226021. PMID 22089440.
169. ^ Nunnari G, Coco C, Pinzone MR, Pavone P, Berretta M, Di Rosa M, Schnell M, Calabrese G, Cacopardo B (2012). "The role of micronutrients in the diet of HIV-1-infected individuals". *Front Biosci (Elite Ed)*. **4**: 2442–56. PMID 22652651.

170. ^ Zeng L, Zhang L (2011). "Efficacy and safety of zinc supplementation for adults, children and pregnant women with HIV infection: systematic review". *Trop. Med. Int. Health*. **16** (12): 1474–82. doi:10.1111/j.1365-3156.2011.02871.x. PMID 21895892.
171. ^ Littlewood RA, Vanable PA (September 2008). "Complementary and alternative medicine use among HIV-positive people: research synthesis and implications for HIV care". *AIDS Care*. **20** (8): 1002–18. doi:10.1080/09540120701767216. PMC 2570227. PMID 18608078.
172. ^ Mills E, Wu P, Ernst E (June 2005). "Complementary therapies for the treatment of HIV: in search of the evidence". *Int J STD AIDS*. **16** (6): 395–403. doi:10.1258/0956462054093962. PMID 15969772.
173. ^ Liu JP, Manheimer E, Yang M (2005). Liu, Jian Ping, ed. "Herbal medicines for treating HIV infection and AIDS". *Cochrane Database Syst Rev* (3): CD003937. doi:10.1002/14651858.CD003937.pub2. PMID 16034917.
174. ^ Lutge EE, Gray A, Siegfried N (2013). "The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS". *Cochrane Database Syst Rev*. **4** (4): CD005175. doi:10.1002/14651858.CD005175.pub3. PMID 23633327.
175. ^ *a b c* Knoll B, Lassmann B, Temesgen Z (2007). "Current status of HIV infection: a review for non-HIV-treating physicians". *Int J Dermatol*. **46** (12): 1219–28. doi:10.1111/j.1365-4632.2007.03520.x. PMID 18173512.
176. ^ *a b* Morgan D, Mahe C, Mayanja B, Okongo JM, Lubega R, Whitworth JA (2002). "HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries?". *AIDS*. **16** (4): 597–632. doi:10.1097/00002030-200203080-00011. PMID 11873003.
177. ^ Zwahlen M, Egger M (2006). "Progression and mortality of untreated HIV-positive individuals living in resource-limited settings: update of literature review and evidence synthesis" (PDF). UNAIDS Obligation HQ/05/422204. Archived (PDF) from the original on April 9, 2008. Retrieved March 19, 2008.
178. ^ *a b* Antiretroviral Therapy Cohort Collaboration (2008). "Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies". *Lancet*. **372** (9635): 293–9. doi:10.1016/S0140-6736(08)61113-7. PMC 3130543. PMID 18657708.
179. ^ Schackman BR, Gebo KA, Walensky RP, Losina E, Muccio T, Sax PE, Weinstein MC, Seage GR 3rd, Moore RD, Freedberg KA. (2006). "The lifetime cost of current HIV care in the United States". *Med Care*. **44** (11): 990–997. doi:10.1097/01.mlr.0000228021.89490.2a. PMID 17063130.
180. ^ van Sighem, AI; Gras, LA; Reiss, P; Brinkman, K; de Wolf, F; ATHENA national observational cohort, study (June 19, 2010). "Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals". *AIDS (London, England)*. **24** (10): 1527–35. doi:10.1097/QAD.0b013e32833a3946. PMID 20467289.
181. ^ *a b* Cheung, MC; Pantanowitz, L; Dezube, BJ (Jun–Jul 2005). "AIDS-related malignancies: emerging challenges in the era of highly active antiretroviral therapy". *The oncologist*. **10** (6): 412–26. doi:10.1634/theoncologist.10-6-412. PMID 15967835.
182. ^ Tang J, Kaslow RA (2003). "The impact of host genetics on HIV infection and disease progression in the era of highly active antiretroviral therapy". *AIDS*. **17** (Suppl 4): S51–S60. doi:10.1097/00002030-200317004-00006. PMID 15080180.
183. ^ Lawn SD (2004). "AIDS in Africa: the impact of co-infections on the pathogenesis of HIV-1 infection". *J. Infect. Dis*. **48** (1): 1–12. doi:10.1016/j.jinf.2003.09.001. PMID 14667787.
184. ^ Campbell GR, Pasquier E, Watkins J, et al. (2004). "The glutamine-rich region of the HIV-1 Tat protein is involved in T-cell apoptosis". *J. Biol. Chem*. **279** (46): 48197–48204. doi:10.1074/jbc.M406195200. PMID 15331610.
185. ^ Campbell GR, Watkins JD, Esquieu D, Pasquier E, Loret EP, Spector SA (2005). "The C terminus of HIV-1 Tat modulates the extent of CD178-mediated apoptosis of T cells". *J. Biol. Chem*. **280** (46): 38376–39382. doi:10.1074/jbc.M506630200. PMID 16155003.
186. ^ "Tuberculosis". *Fact sheet 104*. World Health Organization. March 2012. Retrieved August 29, 2012.
187. ^ World Health Organization (2011). "Global tuberculosis control 2011" (PDF). ISBN 978-92-4-156438-0. Retrieved August 29, 2012.
188. ^ Pennsylvania, Editors, Raphael Rubin, M.D., Professor of Pathology, David S. Strayer, M.D., Ph.D., Professor of Pathology, Department of Pathology and Cell Biology, Jefferson Medical College of Thomas Jefferson University Philadelphia, Pennsylvania ; Founder and Consulting Editor, Emanuel Rubin, M.D., Gonzalo Aponte Distinguished Professor of Pathology, Chairman Emeritus of the Department of Pathology and Cell Biology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, (2011). *Rubin's pathology : clinicopathologic foundations of medicine* (Sixth ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 154. ISBN 978-1-60547-968-2.
189. ^ Woods, S.; Moore, D.; Weber, E.; Grant, I. (2009). "Cognitive neuropsychology of HIV-associated neurocognitive disorders". *Neuropsychology review*. **19** (2): 152–168. doi:10.1007/s11065-009-9102-5. PMC 2690857. PMID 19462243.
190. ^ Brown, T.; Qaqish, R. (2006). "Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-

analytic review". *AIDS (London, England)*. **20** (17): 2165–2174. doi:10.1097/QAD.0b013e32801022eb. PMID 17086056.
191. ^ Nicholas, P.K.; Kemppainen, J.K.; Canaval, G.E.; et al. (February 2007). "Symptom management and self-care for peripheral neuropathy in HIV/AIDS". *AIDS Care*. **19** (2): 179–89. doi:10.1080/09540120600971083. PMID 17364396.
192. ^ Boshoff C, Weiss R (2002). "AIDS-related malignancies". *Nature Reviews Cancer*. **2** (5): 373–382. doi:10.1038/nrc797. PMID 12044013.
193. ^ Yarchoan R, Tosato G, Little RF (2005). "Therapy insight: AIDS-related malignancies – the influence of antiviral therapy on pathogenesis and management". *Nat. Clin. Pract. Oncol.* **2** (8): 406–415. doi:10.1038/ncponc0253. PMID 16130937.
194. ^ Post, F. .; Holt, S. . (2009). "Recent developments in HIV and the kidney". *Current opinion in infectious diseases*. **22** (1): 43–48. doi:10.1097/QCO.0b013e328320ffec. PMID 19106702.
195. ^ "AIDSinfo". *UNAIDS*. Retrieved March 4, 2013.
196. ^ Cohen, MS; Hellmann, N; Levy, JA; DeCock, K; Lange, J (April 2008). "The spread, treatment, and prevention of HIV-1: evolution of a global pandemic". *The Journal of Clinical Investigation*. **118** (4): 1244–54. doi:10.1172/JCI34706. PMC 2276790. PMID 18382737.
197. ^ *a b c* "Fact sheet 2015" (PDF). *UNAIDS*. Retrieved 1 February 2016.
198. ^ *a b* "UNAIDS reports a 52% reduction in new HIV infections among children and a combined 33% reduction among adults and children since 2001". *UNAIDS*. Retrieved October 7, 2013.
199. ^ "Statistics: Women and HIV/AIDS". *amfAR*. July 2015. Retrieved 1 February 2016.
200. ^ *a b c d* UNAIDS 2011 pg. 20–30
201. ^ *a b c* UNAIDS 2011 pg. 40–50
202. ^ *a b c d* Mandell, Bennett, and Dolan (2010). Chapter 117.
203. ^ New HIV infections among children have been reduced by 50% or more in seven countries in sub-Saharan Africa, UN AIDS, Geneva, June 25, 2013.
204. ^ Centers for Disease Control and Prevention, (CDC) (June 3, 2011). "HIV surveillance—United States, 1981–2008". *MMWR. Morbidity and mortality weekly report*. **60** (21): 689–93. PMID 21637182.
205. ^ Health Protection Agency (2010). *HIV in the United Kingdom: 2010 Report*.
206. ^ Surveillance; riques, Risk Assessment Division = Le VIH et le sida au Canada: rapport de surveillance en date du 31 décembre 2009 / Division de la surveillance et de l'évaluation des (2010). *HIV and AIDS in Canada : surveillance report to December 31, 2009* (PDF). Ottawa: Public Health Agency of Canada, Centre for Communicable Diseases and Infection Control, Surveillance and Risk Assessment Division. ISBN 978-1-100-52141-1.
207. ^ "Global Report Fact Sheet" (PDF). *UNAIDS*. 2010.
208. ^ "COUNTRY COMPARISON :: HIV/AIDS – ADULT PREVALENCE RATE". *CIA World Factbook*. Retrieved November 6, 2014.
209. ^ Gottlieb MS (2006). "Pneumocystis pneumonia—Los Angeles. 1981". *Am J Public Health*. **96** (6): 980–1; discussion 982–3. doi:10.2105/AJPH.96.6.980. PMC 1470612. PMID 16714472. Archived from the original on April 22, 2009. Retrieved March 31, 2009.
210. ^ Friedman-Kien AE (October 1981). "Disseminated Kaposi's sarcoma syndrome in young homosexual men". *J. Am. Acad. Dermatol.* **5** (4): 468–71. doi:10.1016/S0190-9622(81)80010-2. PMID 7287964.
211. ^ Hymes KB, Cheung T, Greene JB, et al. (September 1981). "Kaposi's sarcoma in homosexual men-a report of eight cases". *Lancet*. **2** (8247): 598–600. doi:10.1016/S0140-6736(81)92740-9. PMID 6116083.
212. ^ *a b* Basavapathruni, A; Anderson, KS (December 2007). "Reverse transcription of the HIV-1 pandemic". *The FASEB Journal*. **21** (14): 3795–3808. doi:10.1096/fj.07-8697rev. PMID 17639073.
213. ^ Centers for Disease Control (CDC) (1982). "Persistent, generalized lymphadenopathy among homosexual males". *MMWR Morb Mortal Wkly Rep*. **31** (19): 249–251. PMID 6808340. Retrieved August 31, 2011.
214. ^ Barré-Sinoussi, F.; Chermann, J.C.; Rey, F.; et al. (1983). "Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS)". *Science*. **220** (4599): 868–871. Bibcode:1983Sci...220..868B. doi:10.1126/science.6189183. PMID 6189183.
215. ^ *a b* Centers for Disease Control (CDC) (1982). "Opportunistic infections and Kaposi's sarcoma among Haitians in the United States". *MMWR Morb Mortal Wkly Rep*. **31** (26): 353–354; 360–361. PMID 6811853. Retrieved August 31, 2011.
216. ^ Gilman, Sander L., ed. (1987). "AIDS and Syphilis: The Iconography of Disease". Retrieved April 25, 2015.
217. ^ "Making Headway Under Hellacious Circumstances" (PDF). American Association for the Advancement of Science. July 28, 2006. Retrieved June 23, 2008.
218. ^ Altman LK (May 11, 1982). "New homosexual disorder worries health officials". *The New York Times*. Retrieved August 31, 2011.

219. ^ Kher U (July 27, 1982). "A Name for the Plague". *Time*. Archived from the original on March 7, 2008. Retrieved March 10, 2008.
220. ^ Centers for Disease Control (CDC) (1982). "Update on acquired immune deficiency syndrome (AIDS)—United States". *MMWR Morb Mortal Wkly Rep*. **31** (37): 507–508; 513–514. PMID 6815471.
221. ^ RC Gallo; PS Sarin; EP Gelmann; M Robert-Guroff; E Richardson; VS Kalyanaraman; D Mann; GD Sidhu; RE Stahl; S Zolla-Pazner; J Leibowitch; M Popovic (1983). "Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS)". *Science*. **220** (4599): 865–867. Bibcode:1983Sci...220..865G. doi:10.1126/science.6601823. PMID 6601823.
222. ^ Barre-Sinoussi, F.; Chermann, J.; Rey, F.; Nugeyre, M.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Vézinet-Brun, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. (1983). "Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS)". *Science*. **220** (4599): 868–871. Bibcode:1983Sci...220..868B. doi:10.1126/science.6189183. PMID 6189183.
223. ^ Aldrich, ed. by Robert; Wotherspoon, Garry (2001). *Who's who in gay and lesbian history.* London: Routledge. p. 154. ISBN 978-0-415-22974-6.
224. ^ Gao, F.; Bailes, E.; Robertson, D.L.; et al. (February 1999). "Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes". *Nature*. **397** (6718): 436–41. Bibcode:1999Natur.397..436G. doi:10.1038/17130. PMID 9989410.
225. ^ Keele, B. F., van Heuverswyn, F., Li, Y. Y., Bailes, E., Takehisa, J., Santiago, M. L., Bibollet-Ruche, F., Chen, Y., Wain, L. V., Liegois, F., Loul, S., Mpoudi Ngole, E., Bienvenue, Y., Delaporte, E., Brookfield, J. F. Y., Sharp, P. M., Shaw, G. M., Peeters, M., and Hahn, B. H. (July 28, 2006). "Chimpanzee Reservoirs of Pandemic and Nonpandemic HIV-1". *Science*. **313** (5786): 523–6. Bibcode:2006Sci...313..523K. doi:10.1126/science.1126531. PMC 2442710. PMID 16728595.
226. ^ Goodier, J.; Kazazian, H. (2008). "Retrotransposons Revisited: The Restraint and Rehabilitation of Parasites". *Cell*. **135** (1): 23–35. doi:10.1016/j.cell.2008.09.022. PMID 18854152.(subscription required)
227. ^ Sharp, P. M.; Bailes, E.; Chaudhuri, R. R.; Rodenburg, C. M.; Santiago, M. O.; Hahn, B. H. (2001). "The origins of acquired immune deficiency syndrome viruses: where and when?" (PDF). *Philosophical Transactions of the Royal Society B*. **356** (1410): 867–76. doi:10.1098/rstb.2001.0863. PMC 1088480. PMID 11405934.
228. ^ Kalish, M.; Wolfe, N.D.; Ndongmo, C.D.; McNicholl. J.; Robbins, K.E.; et al. (2005). "Central African hunters exposed to simian immunodeficiency virus". *Emerg Infect Dis*. **11** (12): 1928–30. doi:10.3201/eid1112.050394. PMC 3367631. PMID 16485481.
229. ^ *a b* Marx PA, Alcabes PG, Drucker E (2001). "Serial human passage of simian immunodeficiency virus by unsterile injections and the emergence of epidemic human immunodeficiency virus in Africa" (PDF). *Philosophical Transactions of the Royal Society B*. **356** (1410): 911–20. doi:10.1098/rstb.2001.0867. PMC 1088484. PMID 11405938.
230. ^ Worobey, Michael; Gemmel, Marlea; Teuwen, Dirk E.; Haselkorn, Tamara; Kunstman, Kevin; Bunce, Michael; Muyembe, Jean-Jacques; Kabongo, Jean-Marie M.; Kalengayi, Raphaël M.; Van Marck, Eric; Gilbert, M. Thomas P.; Wolinsky, Steven M. (2008). "Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960" (PDF). *Nature*. **455** (7213): 661–4. Bibcode:2008Natur.455..661W. doi:10.1038/nature07390. PMC 3682493. PMID 18833279. (subscription required)
231. ^ *a b* Sousa, João Dinis de; Müller, Viktor; Lemey, Philippe; Vandamme, Anne-Mieke; Vandamme, Anne-Mieke (2010). Martin, Darren P., ed. "High GUD Incidence in the Early 20th Century Created a Particularly Permissive Time Window for the Origin and Initial Spread of Epidemic HIV Strains". *PLoS ONE*. **5** (4): e9936. doi:10.1371/journal.pone.0009936. PMC 2848574. PMID 20376191.
232. ^ Chitnis, Amit; Rawls, Diana; Moore, Jim (2000). "Origin of HIV Type 1 in Colonial French Equatorial Africa?". *AIDS Research and Human Retroviruses*. **16** (1): 5–8. doi:10.1089/088922200309548. PMID 10628811.(subscription required)
233. ^ Donald G. McNeil, Jr. (September 16, 2010). "Precursor to H.I.V. Was in Monkeys for Millennia". *New York Times*. Retrieved September 17, 2010. "Dr. Marx believes that the crucial event was the introduction into Africa of millions of inexpensive, mass-produced syringes in the 1950s. ... suspect that the growth of colonial cities is to blame. Before 1910, no Central African town had more than 10,000 people. But urban migration rose, increasing sexual contacts and leading to red-light districts."
234. ^ Zhu, T., Korber, B. T., Nahmias, A. J., Hooper, E., Sharp, P. M. and Ho, D. D. (1998). "An African HIV-1 Sequence from 1959 and Implications for the Origin of the epidemic". *Nature*. **391** (6667): 594–7. Bibcode:1998Natur.391..594Z. doi:10.1038/35400. PMID 9468138.
235. ^ Lederberg, editor-in-chief Joshua (2000). *Encyclopedia of Microbiology, (4 Volume Set).* (2nd ed.). Burlington: Elsevier. p. 106. ISBN 9780080548487. Retrieved 9 June 2016.
236. ^ Jackson, Regine O., ed. (2011). "Geographies of the Haitian Diaspora". Routledge. p. 12. ISBN 9780415887083. Retrieved 13 March 2016.
*a b*

237. ^ Pépin, Jacques (2011). "The Origin of Aids". Cambridge University Press. p. 188. ISBN 9780521186377. Retrieved 13 March 2016.
238. ^ Kolata, Gina (October 28, 1987). "Boy's 1969 Death Suggests AIDS Invaded U.S. Several Times". The New York Times. Retrieved February 11, 2009.
239. ^ *a b* Gilbert, M. Thomas P.; Rambaut, Andrew; Wlasiuk, Gabriela; Spira, Thomas J.; Pitchenik, Arthur E.; Worobey, Michael (November 20, 2007). "The emergence of HIV/AIDS in the Americas and beyond" (PDF). *PNAS*. **104** (47): 18566–18570. Bibcode:2007PNAS..10418566G. doi:10.1073/pnas.0705329104. PMC 2141817. PMID 17978186.
240. ^ "Ryan White, an American AIDS Victim". *Encyclopædia Britannica*. November 7, 2013. Retrieved July 16, 2015.
241. ^ Ogden J, Nyblade L (2005). "Common at its core: HIV-related stigma across contexts" (PDF). International Center for Research on Women. Retrieved February 15, 2007.
242. ^ *a b c* Herek GM, Capitanio JP (1999). "AIDS Stigma and sexual prejudice" (PDF). *American Behavioral Scientist*. **42** (7): 1130–1147. doi:10.1177/0002764299042007006. Retrieved March 27, 2006.
243. ^ Snyder M, Omoto AM, Crain AL (1999). "Punished for their good deeds: stigmatization for AIDS volunteers". *American Behavioral Scientist*. **42** (7): 1175–1192. doi:10.1177/0002764299042007009.
244. ^ Sharma, A.K. (2012). *Population and society*. New Delhi: Concept Pub. Co. p. 242. ISBN 978-81-8069-818-7.
245. ^ Herek, GM; Capitanio, JP; Widaman, KF (March 2002). "HIV-related stigma and knowledge in the United States: prevalence and trends, 1991–1999". *American Journal of Public Health*. **92** (3): 371–7. doi:10.2105/AJPH.92.3.371. PMC 1447082. PMID 11867313.
246. ^ De Cock, KM; Jaffe, HW; Curran, JW (June 19, 2012). "The evolving epidemiology of HIV/AIDS". *AIDS (London, England)*. **26** (10): 1205–13. doi:10.1097/QAD.0b013e328354622a. PMID 22706007.
247. ^ Richard Spencer (August 21, 2003). "China relaxes laws on love and marriage". *The Telegraph*. Retrieved October 24, 2013.
248. ^ Bell C, Devarajan S, Gersbach H (2003). "The long-run economic costs of AIDS: theory and an application to South Africa" (PDF). World Bank Policy Research Working Paper No. 3152. Retrieved April 28, 2008.
249. ^ *a b* Greener R (2002). "AIDS and macroeconomic impact". In S, Forsyth. *State of The Art: AIDS and Economics* (PDF). IAEN. pp. 49–55.
250. ^ Robinson, Rachel; Okpo, Emmanuel; Mngoma, Nomusa (2015). "Interventions for improving employment outcomes for workers with HIV". *The Cochrane Database of Systematic Reviews*. **5**: CD010090. doi:10.1002/14651858.CD010090.pub2. ISSN 1469-493X. PMID 26022149.
251. ^ Over M (1992). "The macroeconomic impact of AIDS in Sub-Saharan Africa, Population and Human Resources Department" (PDF). The World Bank. Archived (PDF) from the original on May 27, 2008. Retrieved May 3, 2008.
252. ^ "AIDS Stigma". *News-medical.net*. Retrieved November 1, 2011.
253. ^ *a b* "Thirty years after AIDS discovery, appreciation growing for Catholic approach". *Catholicnewsagency.com*. June 5, 2011. Retrieved November 1, 2011.
254. ^ *a b* "Church HIV prayer cure claims 'cause three deaths'". BBC News. October 18, 2011. Retrieved October 18, 2011.
255. ^ "Rock Hudson announces he has AIDS – History.com This Day in History – 7/25/1985". *History.com*. Retrieved November 1, 2011.
256. ^ Coleman, Brian (June 25, 2007). "Thatcher the gay icon". *New Statesman*. Retrieved November 1, 2011.
257. ^ "November 24, 1991: Giant of rock dies". *BBC On This Day*. BBC News. November 24, 1991. Archived from the original on October 21, 2011. Retrieved November 1, 2011.
258. ^ "Freddie Mercury". *Nndb.com*. Retrieved November 1, 2011.
259. ^ Bliss, Dominic. "Frozen In Time: Arthur Ashe". *iTENNISstore.com*. Retrieved June 25, 2012.
260. ^ "Tributes to Arthur Ashe". *The Independent*. London. February 8, 1993. Retrieved July 24, 2012.
261. ^ Cosgrove, Ben. "Behind the Picture: The Photo That Changed the Face of AIDS". *LIFE magazine*. Retrieved August 16, 2012.
262. ^ "Aziga found guilty of first-degree murder". CTV.ca News. Retrieved April 9, 2013.
263. ^ "HIV killer ruled dangerous offender". CBC News. Retrieved April 9, 2013.
264. ^ "A fraudster, not a murderer". National Post. Retrieved April 9, 2013.
265. ^ "HIV-Specific Criminal Laws". *cdc.gov*. June 30, 2014. Retrieved November 22, 2014.
266. ^ "'Virgin cure': Three women killed to 'cure' Aids". *International Herald Tribune*. February 28, 2013. Retrieved September 14, 2013.
267. ^ Jenny, Carole (2010). *Child Abuse and Neglect: Diagnosis, Treatment and Evidence – Expert Consult*. Elsevier Health Sciences. p. 187. ISBN 978-1-4377-3621-2.
268. ^ Klot, Jennifer; Monica Kathina Juma (2011). *HIV/AIDS, Gender, Human Security and Violence in Southern Africa*. Pretoria: Africa Institute of South Africa. p. 47. ISBN 0-7983-0253-4.

269. ^ "HIV Public Knowledge and Attitudes 2014" (pdf). *National AIDS Trust*. Nov 2014. p. 9. Retrieved February 12, 2015.
270. ^ Blechner MJ (1997). *Hope and mortality: psychodynamic approaches to AIDS and HIV*. Hillsdale, NJ: Analytic Press. ISBN 0-88163-223-6.
271. ^ Kirby DB, Laris BA, Rolleri LA (March 2007). "Sex and HIV education programs: their impact on sexual behaviors of young people throughout the world". *J Adolesc Health*. **40** (3): 206–17. doi:10.1016/j.jadohealth.2006.11.143. PMID 17321420.
272. ^ Duesberg, P. H. (1988). "HIV is not the cause of AIDS". *Science*. **241** (4865): 514, 517. Bibcode:1988Sci...241..514D. doi:10.1126/science.3399880. PMID 3399880.Cohen, J. (1994). "The Controversy over HIV and AIDS" (PDF). *Science*. **266** (5191): 1642–1649. Bibcode:1994Sci...266.1642C. doi:10.1126/science.7992043. PMID 7992043. Retrieved March 31, 2009.
273. ^ Kalichman, Seth (2009). *Denying AIDS: Conspiracy Theories, Pseudoscience, and Human Tragedy*. New York: Copernicus Books (Springer Science+Business Media). ISBN 978-0-387-79475-4.
274. ^ Smith TC, Novella SP (August 2007). "HIV Denial in the Internet Era". *PLoS Med*. **4** (8): e256. doi:10.1371/journal.pmed.0040256. PMC 1949841. PMID 17713982. Retrieved November 7, 2009.
275. ^ Various (January 14, 2010). "Resources and Links, HIV-AIDS Connection". National Institute of Allergy and Infectious Diseases. Retrieved February 22, 2009.
276. ^ Watson J (2006). "Scientists, activists sue South Africa's AIDS 'denialists'". *Nat. Med*. **12** (1): 6. doi:10.1038/nm0106-6a. PMID 16397537.
277. ^ Baleta A (2003). "S Africa's AIDS activists accuse government of murder". *Lancet*. **361** (9363): 1105. doi:10.1016/S0140-6736(03)12909-1. PMID 12672319.
278. ^ Cohen J (2000). "South Africa's new enemy". *Science*. **288** (5474): 2168–70. doi:10.1126/science.288.5474.2168. PMID 10896606.
279. ^ Boghardt, Thomas (2009). "Operation INFEKTION Soviet Bloc Intelligence and Its AIDS Disinformation Campaign". Central Intelligence Agency.


## Further reading


- Mandell, Gerald L.; Bennett, John E.; Dolin, Raphael, eds. (2010). *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases* (7th ed.). Philadelphia, PA: Churchill Livingstone/Elsevier. ISBN 978-0-443-06839-3.
- Joint United Nations Programme on HIV/AIDS (UNAIDS) (2011). *Global HIV/AIDS Response, Epidemic update and health sector progress towards universal access* (PDF). Joint United Nations Programme on HIV/AIDS.


## External links

- HIV/AIDS at DMOZ.
- UNAIDS – Joint United Nations Program on HIV/AIDS.
- AIDSinfo – Information on HIV/AIDS treatment, prevention, and research, U.S. Department of Health and Human Services.

*Medicine portal*
*Viruses portal*

Wikimedia Commons has media related to *AIDS*.

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| **Conditions** | Signs and symptoms · AIDS-defining clinical condition · Diffuse infiltrative lymphocytosis syndrome · Lipodystrophy · Nephropathy · Neurocognitive disorders · Pruritus · Superinfection · Tuberculosis co-infection · HIV Drug Resistance Database · Innate resistance to HIV · |
| **History** | History · Epidemiology (Multiple sex partners · · Timeline · AIDS Museum · |
| **Social** | AIDS orphan · Catholic Church and HIV/AIDS · Circumcision and HIV · Criminal transmission · Discrimination against people · Economic impact · HIV-affected community · HIV/AIDS denialism · Safe sex · Sex education · List of HIV-positive people · People With AIDS Self-Empowerment Movement · |
| **Culture** | International AIDS Conference · International AIDS Society · Joint United Nations Programme on HIV/AIDS (UNAIDS) · President's Emergency Plan for AIDS Relief (PEPFAR) · Treatment Action Campaign · World AIDS Day · Media portrayal of HIV/AIDS · Misconceptions about HIV/AIDS · Discredited HIV/AIDS origins theories · |
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| List of countries by HIV/AIDS adult prevalence rate · List of HIV/AIDS cases and deaths registered by region · | |

| | | |
|---|---|---|
| v · t · e · | **Infectious diseases – viral systemic diseases (A80–B34, 042–079)** | |
| **Oncovirus** | | **DNA virus:** *HBV* (Hepatocellular carcinoma · · *HPV* (Cervical cancer · Anal cancer · Penile cancer · Vulvar cancer · Vaginal cancer · Oropharyngeal cancer · · *KSHV* (Kaposi's sarcoma · · *EBV* (Nasopharynx cancer · Burkitt's lymphoma · Hodgkin's lymphoma · Follicular dendritic cell sarcoma · Extranodal NK/T-cell lymphoma, nasal type · · *MCPyV* (Merkel-cell carcinoma · · **RNA virus:** *HCV* (Hepatocellular carcinoma · Splenic marginal zone lymphoma · · *HTLV-I* (Adult T-cell leukemia/lymphoma · · |
| **Immune disorders** | | *HIV* (**AIDS** · · |
| | **Encephalitis/** | **DNA virus:** *JCV* (Progressive multifocal leukoencephalopathy · · **RNA virus:** *MeV* (Subacute sclerosing panencephalitis · · *LCV* (Lymphocytic choriomeningitis · · Arbovirus encephalitis · |

| | | |
|---|---|---|
| **Central nervous system** | **meningitis** | *Orthomyxoviridae (probable)* (Encephalitis lethargica · · *RV* (Rabies · · Chandipura virus · Herpesviral meningitis · Ramsay Hunt syndrome type 2 · |
| | **Myelitis** | *Poliovirus* (Poliomyelitis · Post-polio syndrome · · *HTLV-I* (Tropical spastic paraparesis · · |
| | **Eye** | *Cytomegalovirus* (Cytomegalovirus retinitis · · *HSV* (Herpes of the eye · · |
| **Cardiovascular** | *CBV* (Pericarditis · Myocarditis · · | |
| **Respiratory system/ acute viral nasopharyngitis/ viral pneumonia** | **DNA virus** | *Epstein–Barr virus* (EBV infection/Infectious mononucleosis · · *Cytomegalovirus* · |
| | **RNA virus** | IV: *SARS coronavirus* (Severe acute respiratory syndrome · · V: *Orthomyxoviridae: Influenzavirus A/B/C* (Influenza/Avian influenza · · V, *Paramyxoviridae: Human parainfluenza viruses* (Parainfluenza · · *RSV* · *hMPV* · |
| **Human digestive system** | **Pharynx/Esophagus** | *MuV* (Mumps · · *Cytomegalovirus* (Cytomegalovirus esophagitis · · |
| | **Gastroenteritis/ diarrhea** | **DNA virus:** *Adenovirus* (Adenovirus infection · · **RNA virus:** *Rotavirus* · *Norovirus* · *Astrovirus* · *Coronavirus* · |
| | **Hepatitis** | **DNA virus:** *HBV* (B) · **RNA virus:** *CBV* · *HAV* (A) · *HCV* (C) · *HDV* (D) · *HEV* (E) · *HGV* (G) · |
| | **Pancreatitis** | *CBV* · |
| **Urogenital** | *BK virus* · *MuV* (Mumps · · | |

| v · t · e · | **Sexually transmitted infection (STI) (primarily A50–A64, 090–099)** |
|---|---|
| **Bacterial** | Chancroid (*Haemophilus ducreyi*) · Chlamydia/Lymphogranuloma venereum (*Chlamydia trachomatis*) · Donovanosis or Granuloma Inguinale (*Klebsiella granulomatis*) · Gonorrhea (*Neisseria gonorrhoeae*) · Mycoplasma hominis infection (*Mycoplasma hominis*) · Syphilis (*Treponema pallidum*) · Ureaplasma infection (*Ureaplasma urealyticum*) · |
| **Protozoal** | Trichomoniasis (*Trichomonas vaginalis*) · |
| **Parasitic** | Crab louse/crabs · Scabies · |
| **Viral** | **AIDS** (*HIV-1/HIV-2*) · Cervical cancer, vulvar cancer & Genital warts (condyloma), Penile cancer, Anal cancer (*Human papillomavirus (HPV)*) · Hepatitis B (*Hepatitis B virus*) · Herpes simplex (*HSV1/HSV2*) · Molluscum contagiosum (*MCV*) · |
| **General inflammation** | *female*: Cervicitis · Pelvic inflammatory disease (PID) · *male*: Epididymitis · Prostatitis · *either*: Proctitis · Urethritis/Non-gonococcal urethritis (NGU) · |

| | |
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# Leprosy



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*For the Biblical term and its varied meanings, see Tzaraath. For other uses, see Leprosy (disambiguation).*

**Leprosy**, also known as **Hansen's disease** (**HD**), is a long-term infection by the bacteria *Mycobacterium leprae* or *Mycobacterium lepromatosis*.[2][3] Initially, infections are without symptoms and typically remain this way for 5 to 20 years.[2] Symptoms that develop include granulomas of the nerves, respiratory tract, skin, and eyes.[2] This may result in a lack of ability to feel pain and thus loss of parts of extremities due to repeated injuries or infection due to unnoticed wounds.[4] Weakness and poor eyesight may also be present.[4]

Leprosy is spread between people. This is thought to occur through a cough or contact with fluid from the nose of an infected person.[5] Leprosy occurs more commonly among those living in poverty.[1] Contrary to popular belief, it is not highly contagious.[4] The two main types of disease are based on the number of bacteria present: paucibacillary and multibacillary.[4] The two types are differentiated by the number of poorly pigmented, numb skin patches present, with paucibacillary having five or fewer and multibacillary having more than five.[4] The diagnosis is confirmed by finding acid-fast bacilli in a biopsy of the skin or by detecting the DNA using polymerase chain reaction.[4]

Leprosy is curable with a treatment known as multidrug therapy.[2] Treatment for paucibacillary leprosy is with the medications dapsone and rifampicin for six months.[4] Treatment for multibacillary leprosy consists of rifampicin, dapsone, and clofazimine for 12 months.[4] A number of other antibiotics may also be used.[4] These treatments are provided free of charge by the World Health Organization.[2] Globally in 2012, the number of chronic cases of leprosy was 189,000, down from some 5.2 million in the 1980s.[2][6][7] The number of new cases was 230,000.[2] Most new cases occur in 16 countries, with India accounting for more than half.[2][4] In the past 20 years, 16 million people worldwide have been cured of leprosy.[2] About 200 cases are reported per year in the United States.[8]

Leprosy has affected humanity for thousands of years.[4] The disease takes its name from the Latin word *lepra*, which means "scaly", while the term "Hansen's disease" is named after the physician Gerhard Armauer Hansen.[4] Separating people by placing them in leper colonies still occurs in places such as India,[9] China,[10] and Africa.[11] However, most colonies have closed since leprosy is not very contagious.[11] Social stigma has been associated with leprosy for much of history, which continues to be a barrier to self-reporting and early treatment.[2] Some consider the word "leper" offensive, preferring the phrase "person affected with leprosy".[12] World Leprosy Day was started in 1954 to draw awareness to those affected by leprosy.[13]

A 24 year old man with Leprosy (1886)

**Pronunciation** /ˈlɛprəsi/[1]

| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | A30 |
| **ICD-9-CM** | 030 |
| **OMIM** | 246300 |
| **DiseasesDB** | 8478 |
| **MedlinePlus** | 001347 |
| **eMedicine** | med/1281 derm/223 neuro/187 |
| **Patient UK** | Leprosy |
| **MeSH** | D007918 |

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Contents

## Signs and symptoms [edit]

Leprosy is primarily a granulomatous disease of the peripheral nerves and mucosa of the upper respiratory tract; skin lesions (light or dark patches) are the primary external sign.[14] If untreated, leprosy can progress and cause permanent damage to the skin, nerves, limbs, and eyes. Contrary to folklore, leprosy does not cause body parts to fall off, although they can become numb or diseased as a result of secondary infections; these occur as a result of the body's defenses being compromised by the primary disease.[15][16] Secondary infections, in turn, can result in tissue loss, causing fingers and toes to become shortened and deformed, as cartilage is absorbed into the body.[15][16][17]

Hands deformed by leprosy

Leprosy in Tahiti, *circa* 1895

A 26-year-old woman with leprous lesions

A 13-year-old boy with severe leprosy

## Cause [edit]

### *M. leprae* [edit]

*Main article: Mycobacterium leprae*

*M. leprae*, one of the causative agents of leprosy: As an acid-fast bacterium, *M. leprae* appears red when a Ziehl-Neelsen stain is used.

*M. leprae* and *M. lepromatosis* are the causative agents of leprosy. *M. lepromatosis* is a relatively newly identified mycobacterium isolated from a fatal case of diffuse lepromatous leprosy in 2008.[3][14]

An intracellular, acid-fast bacterium, *M. leprae* is aerobic and rod-shaped, and is surrounded by the waxy cell membrane coating characteristic of the *Mycobacterium* genus.[18]

Due to extensive loss of genes necessary for independent growth, *M. leprae* and *M. lepromatosis* are obligate intracellular pathogens, and unculturable in the laboratory, a factor that leads to difficulty in definitively identifying the organism under a strict interpretation of Koch's postulates.[3][19] The use of nonculture-based techniques such as molecular genetics has allowed for alternative establishment of causation.

While the causative organisms have to date been impossible to culture *in vitro*, it has been possible to grow them in animals such as mice and armadillos.

Naturally occurring infection also has been reported in nonhuman primates, including the African chimpanzee, sooty mangabey, and cynomolgus macaque, as well as in armadillos and red squirrels.[20]

Red squirrels (*Sciurus vulgaris*) - a threatened species - in England were found to have leprosy in November 2016.[21] There have been no squirrel cases spread to a human for hundreds of years, though.[22]

### Risk factors [edit]

The greatest risk factor for developing leprosy is contact with another case of leprosy. Contacts of people with leprosy are five to eight times more likely to develop leprosy than members of the general population.[23] Other risk factors are poorly understood. However, conditions that reduce immune function, such as malnutrition, other illnesses, or host genetic differences, may increase the risk of developing leprosy.[23] Despite this, infection with HIV does not appear to increase the risk of developing leprosy.[24]

### Transmission [edit]

Transmission of leprosy occurs during close contact with those who are infected.[25] Transmission is proposed to be by nasal droplets,[7][25] but many questions remain about its mode of transmission and epidemiology.[26]

Leprosy is not known to be either sexually transmitted or highly infectious. People are no longer infectious after as little as two weeks of treatment.[27]

Leprosy may also be transmitted to humans by armadillos[28]

Two exit routes of *M. leprae* from the human body often described are the skin and the nasal mucosa, although their relative importance is not clear. Lepromatous cases show large numbers of organisms deep in the dermis, but whether they reach the skin surface in sufficient numbers is doubtful.[29]

The skin and the upper respiratory tract are most likely entry route. While older research dealt with the skin route, recent research has increasingly favored the respiratory route. Experimental transmission of leprosy through aerosols containing *M. leprae* in immunosuppressed mice was accomplished, suggesting a similar possibility in humans.[30]

### Genetics [edit]

Several genes have been associated with a susceptibility to leprosy. Often, the immune system is able to eliminate leprosy during the early infection stage before severe symptoms develop.[31] A defect in cell-mediated immunity may cause susceptibility to leprosy. The region of DNA responsible for this variability is also involved in Parkinson's disease, giving rise to current speculation that the two disorders may be linked in some way at the biochemical level.[32] Some evidence indicates not all people who are infected with *M. leprae* develop leprosy, and genetic factors have long been thought to play a role, due to the observation of clustering of leprosy around certain families, and the failure to understand why certain individuals develop lepromatous leprosy while others develop other types of leprosy.[33]

| Name | Locus | OMIM | Gene |
|---|---|---|---|
| LPRS1 | 10p13 | 609888 | |
| LPRS2 | 6q25 | 607572 | *PARK2*, *PACRG* |
| LPRS3 | 4q32 | 246300 | *TLR2* |
| LPRS4 | 6p21.3 | 610988 | *LTA* |
| LPRS5 | 4p14 | 613223 | *TLR1* |
| LPRS6 | 13q14.11 | 613407 | |

## Pathophysiology [edit]

How the infection produces the symptoms of the disease is not known.[7]

## Diagnosis [edit]

According to the World Health Organization, diagnosis in areas where people are frequently infected is based on one of these main signs:

- Skin lesion consistent with leprosy and with definite sensory loss
- Positive skin smears

Skin lesions can be single or multiple, and usually hypopigmented, although occasionally reddish or copper-colored. The lesions may be macules (flat), papules (raised), or nodular. The sensory loss at the skin lesion is important because this feature can help differentiate it from other causes of skin lesions such as tinea versicolor. Thickened nerves are associated with leprosy and can be accompanied by loss of sensation or muscle weakness. However, without the characteristic skin lesion and sensory loss, muscle weakness is not considered a reliable sign of leprosy.

In some cases, acid-fast leprosy bacilli in skin smears are considered diagnostic; however, the diagnosis is clinical.[34]

Diagnosis in areas where the disease is uncommon, such as the United States, is often delayed because healthcare providers are unaware of leprosy and its symptoms. Early diagnosis and treatment prevent nerve involvement, the hallmark of leprosy, and the disability it causes.[35]

Many kinds of leprosy are known, but some symptoms are common to them, including runny nose, dry scalp, eye problems, skin lesions, muscle weakness, reddish skin, smooth, shiny, diffuse thickening of facial skin, ear, and hand, loss of sensation in fingers and toes, thickening of peripheral nerves, and flat nose due to destruction of nasal cartilage. Also, phonation and resonation of sound occur during speech. Often, atrophy of the testes with resulting impotency occurs.

### Classification [edit]

Several different approaches for classifying leprosy exist, but parallels exist.

- The World Health Organization system distinguishes "paucibacillary" and "multibacillary" based upon the proliferation of bacteria.[36]("pauci-" refers to a low quantity.)
- The SHAY scale provides five gradations.[37][38]
- The ICD-10, though developed by the WHO, uses Ridley-Jopling and not the WHO system. It also adds an indeterminate ("I") entry.[29]
- In MeSH, three groupings are used.

| WHO | Ridley-Jopling | ICD-10 | MeSH | Description | Lepromin test |
|---|---|---|---|---|---|
| Paucibacillary | tuberculoid ("TT"), borderline tuberculoid ("BT") | A30.1, A30.2 | Tuberculoid | It is characterized by one or more hypopigmented skin macules and patches where skin sensations are lost because of damaged peripheral nerves that have been attacked by the human host's immune cells. | Positive |
| Multibacillary | midborderline or borderline ("BB") | A30.3 | Borderline | Borderline leprosy is of intermediate severity and is the most common form. Skin lesions resemble tuberculoid leprosy, but are more numerous and irregular; large patches may affect a whole limb, and peripheral nerve involvement with weakness and loss of sensation is common. This type is unstable and may become more like lepromatous leprosy or may undergo a reversal reaction, becoming more like the tuberculoid form. | |
| Multibacillary | borderline lepromatous ("BL"), and lepromatous ("LL") | A30.4, A30.5 | Lepromatous | It is associated with symmetric skin lesions, nodules, plaques, thickened dermis, and frequent involvement of the nasal mucosa resulting in nasal congestion and nose bleeds, but, typically, detectable nerve damage is late. | Negative |

A difference in immune response to the tuberculoid and lepromatous forms is seen.[39]

Leprosy may also be divided into:[40]:344–346

- Early and indeterminate leprosy
- Tuberculoid leprosy
- Borderline tuberculoid leprosy

- Borderline leprosy
- Borderline lepromatous leprosy
- Lepromatous leprosy
- Histoid leprosy
- Diffuse leprosy of Lucio and Latapí

This disease may also occur with only neural involvement, without skin lesions.[25][41][42][43][44][45]

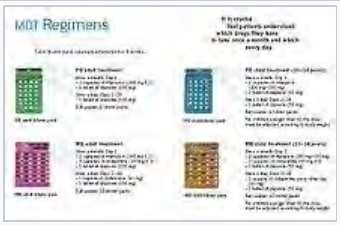
## Prevention [edit]

Early detection of the disease is important, since physical and neurological damage may be irreversible even if cured. Medications can decrease the risk of those living with people with leprosy from acquiring the disease and likely those with whom people with leprosy come into contact outside the home.[46] However, concerns are known of resistance, cost, and disclosure of a person's infection status when doing follow-up of contacts. Therefore, the WHO recommends that people who live in the same household be examined for leprosy and be treated only if symptoms are present.[46]

The Bacillus Calmette–Guérin (BCG) vaccine offers a variable amount of protection against leprosy in addition to tuberculosis.[47] It appears to be 26 to 41% effective (based on controlled trials) and about 60% effective based on observational studies with two doses possibly working better than one.[48][49] Development of a more effective vaccine is ongoing.[46][50][51][52]

## Treatment [edit]

A number of leprostatic agents are available for treatment. For paucibacillary (PB or tuberculoid) cases, treatment with daily dapsone and monthly rifampicin for six months is recommended.[4] While for multibacillary (MB or lepromatous) cases, treatment with daily dapsone and clofazimine along with monthly rifampicin for 12 months is recommended.[4]



MDT antileprosy drugs: standard regimens

Multidrug therapy (MDT) remains highly effective, and people are no longer infectious after the first monthly dose.[25] It is safe and easy to use under field conditions due to its presentation in calendar blister packs.[25] Relapse rates remain low, and no resistance to the combined drugs is seen.[25]

## Epidemiology [edit]

*Main article: Epidemiology of leprosy*

In 2012, the number of cases of leprosy was about 180,000.[6] In 2011, the approximate number of new leprosy cases diagnosed was 220,000.[6]


World distribution of leprosy, 2003

As of 2013, 14 countries contain 95% of the globally reported leprosy cases.[54] Of these, India has the greatest number of cases (59%), followed by Brazil (14%) and Indonesia (8%).[54] Although the number of cases worldwide continues to fall, pockets of high prevalence remain in certain areas such as Brazil, South Asia (India, Nepal, Bhutan), some parts of Africa (Tanzania, Madagascar, Mozambique), and the western Pacific.

The number of cases of leprosy was in the tens of millions in the 1960s, a series of national (the International Federation of Anti-Leprosy Associations) and international (the WHO's "Global Strategy for Reducing Disease Burden Due to Leprosy") initiatives have reduced the total number and the number of new cases of the disease.[7][55] In 1995, two to three million people were estimated to be permanently disabled because of leprosy.[56]


Disability-adjusted life year for leprosy per 100,000 inhabitants in 2004[53]

| | |
|---|---|
| no data | 9–10.5 |
| <1.5 | 10.5–12 |
| 1.5–3 | 12–13.5 |
| 3–4.5 | 13.5–15 |
| 4.5–6 | 15–20 |
| 6–7.5 | >20 |
| 7.5–9 | |

### Disease burden [edit]

Although the number of new leprosy cases occurring each year is important as a measure of transmission, it is difficult to measure due to leprosy's long incubation period, delays in diagnosis after onset of the disease, and the lack of laboratory tools to detect it in the very early stages. Instead, the registered prevalence is used. Registered prevalence is a useful proxy indicator of the disease burden, as it reflects the number of active leprosy cases diagnosed with the disease and receiving treatment with MDT at a given point in time. The prevalence rate is defined as the number of cases registered for MDT treatment among the population in which the cases have occurred, again at a given point in time.[57]

New case detection is another indicator of the disease that is usually reported by countries on an annual basis. It includes cases diagnosed with the onset of disease in the year in question (true incidence) and a large proportion of cases with onset in previous years (termed a backlog prevalence of undetected cases).

Endemic countries also report the number of new cases with established disabilities at the time of detection, as an indicator of the backlog prevalence. Determination of the time of onset of the disease is, in general, unreliable, is very labor-intensive, and is seldom done in recording these statistics.

## History [edit]

*Main article: History of leprosy*

Using comparative genomics, in 2005, geneticists traced the origins and worldwide distribution of leprosy from East Africa or the Near East along human migration routes. They found four strains of *M. leprae* with specific regional locations. Strain 1 occurs predominantly in Asia, the Pacific region, and East Africa; strain 4, in West Africa and the Caribbean; strain 3 in Europe, North Africa, and the Americas; and strain 2 only in Ethiopia, Malawi, Nepal/north India, and New Caledonia.

On the basis of this, they offer a map of the dissemination of leprosy in the world. This confirms the spread of the disease along the migration, colonisation, and slave trade routes taken from East Africa to India, West Africa to the New World, and from Africa into Europe and vice versa.[58]

The oldest skeletal evidence for the disease was found in the human remains from the archaeological sites of Balathal and Harappa, in India and Pakistan, respectively.[59][60]

Although retrospectively identifying descriptions of leprosy-like symptoms is difficult, what appears to be leprosy was discussed by Hippocrates in 460 BC. In 1846, Francis Adams produced *The Seven Books of Paulus Aegineta* which included a commentary on all medical and surgical knowledge and descriptions and remedies to do with leprosy from the Romans, Greeks, and Arabs.[61]

Interpretations of the presence of leprosy have been made on the basis of descriptions in ancient Indian (Atharva Verda and Kausika Sutra), Greek, and Middle Eastern documentary sources that describe skin afflictions.[62]


G. H. A. Hansen, discoverer of *M. leprae*

Skeletal remains from the second millennium BC, discovered in 2009, represent the oldest documented evidence for leprosy. Located at Balathal, in Rajasthan, northwest India, the discoverers suggest that if the disease did migrate from Africa to India, during the third millennium BC "at a time when there was substantial interaction among the Indus Civilization, Mesopotamia, and Egypt, there needs to be additional skeletal and molecular evidence of leprosy in India and Africa so as to confirm the African origin of the disease."[63] A proven human case was verified by DNA taken from the shrouded remains of a man discovered in a tomb next to the Old City of Jerusalem dated by radiocarbon methods to 1–50 AD.[64]

The causative agent of leprosy, *M. leprae*, was discovered by G. H. Armauer Hansen in Norway in 1873, making it the first bacterium to be identified as causing disease in humans.[65] The first effective treatment (promin) became available in the 1940s.[66] In the 1950s, dapsone was introduced. The search for further effective antileprosy drugs led to the use of clofazimine and rifampicin in the 1960s and 1970s.[67] Later, Indian scientist Shantaram Yawalkar and his colleagues formulated a combined therapy using rifampicin and dapsone, intended to mitigate bacterial resistance.[68] MDT combining all three drugs was first recommended by the WHO] in 1981. These three antileprosy drugs are still used in the standard MDT regimens.

Leprosy was once believed to be highly contagious and was treated with mercury—all of which applied to syphilis, which was first described in 1530. Many early cases thought to be leprosy could actually have been syphilis.[69] Resistance has developed to initial treatment. Until the introduction of MDT in the early 1980s, the disease could not be diagnosed and treated successfully within the community.[70]

Japan still has sanatoriums (although Japan's sanatoriums no longer have active leprosy cases, nor are survivors held in them by law).[71]

The importance of the nasal mucosa in the transmission of *M leprae* was recognized as early as 1898 by Schäffer, in particular, that of the ulcerated mucosa.[72]

## Society and culture [edit]

### India [edit]

India was one of the first countries to have acted against leprosy. India enacted the Leprosy Act of 1898 which institutionalized those affected and segregated them by gender to prevent reproduction. The Act was difficult to enforce but was repealed in 1983 only after MDT therapy became widely available. In 1983, the National Leprosy Elimination Programme, previously the National Leprosy Control Programme, changed its methods from surveillance to the treatment of people with leprosy. India still accounts for over half of the global disease burden.[73]


Two lepers denied entrance to town, 14th century

### Treatment cost [edit]

Between 1995 and 1999, the WHO, with the aid of the Nippon Foundation, supplied all endemic countries with free MDT in blister packs, channeled through ministries of health. This free provision was extended in 2000 and again in 2005, 2010 and 2015 with donations by the MDT manufacturer Novartis through the WHO. In the latest agreement signed between the company and the WHO in October 2015, the provision of free MDT by the WHO to all endemic countries will run until the end of 2020. At the national level, nongovernment organizations affiliated with the national program will continue to be provided with an appropriate free supply of this WHO-supplied MDT by the government.

### Historical texts [edit]

Written accounts of leprosy date back thousands of years. Various skin diseases translated as leprosy appear in the ancient Indian text, the *Atharava Veda*, as early as 2000 BC. Another Indian text, the *Laws of Manu* (1500 BC), prohibited contact with those infected with the disease and made marriage to a person infected with leprosy punishable.[74]

Many English translations of the Bible translate *tzaraath* as "leprosy," a confusion that derives from the use of the koine cognate "Λέπρα" (which can mean any disease causing scaly skin) in the Septuagint. Ancient sources such as the Talmud (Sifra 63) make clear that *tzaraath* refers to various types of lesions or stains associated with ritual impurity and occurring on cloth, leather, or houses, as well as skin. It may sometimes be a symptom of the disease described in this article but has many other causes, as well. The New Testament describes instances of Jesus healing people with leprosy (Luke 5:10), although the precise relationship between this, *tzaraath*, and Hansen's disease is not established.

The biblical perception that people with leprosy were unclean may be connected to a passage from Leviticus 13: 44-46. Judeo-Christian belief held that leprosy was a moral disease, and early Christians believed that those affected by leprosy were being punished by God for sinful

behavior. Moral associations have persisted throughout history. Pope Gregory the Great (540-604) and Isidor of Seville (560-636) considered people with the disease to be heretics.[75]

## Middle Ages [edit]


Medieval leper bell

It is believed that a rise in leprosy in Europe occurred in the Middle Ages based on the increased number of hospitals created to treat leprosy patients in the 12th and 13th centuries.[76][77][78] France alone had nearly 2,000 leprosariums during this period.

The social perception in medieval communities was generally one of fear, and those people infected with the disease were thought to be unclean, untrustworthy, and morally corrupt.[75] People with leprosy were also often required to wear clothing that identified them as such or carry a bell announcing their presence. Segregation from mainstream society was common. The third Lateran Council of 1179 and a 1346 edict by King Edward expelled lepers from city limits. Because of the moral stigma of the disease, methods of treatment were both physical and spiritual, and leprosariums were established under the purview of the church.[75][79]

## Nineteenth century [edit]

### Norway [edit]

Norway was the location of a progressive stance on leprosy tracking and treatment and played an influential role in European understanding of the disease. In 1832, Dr. JJ Hjort conducted the first leprosy survey, thus establishing a basis for epidemiological surveys. Subsequent surveys resulted in the establishment of a national leprosy registry to study the causes of leprosy and for tracking of the rate of infection.

Early leprosy research throughout Europe was conducted by Norwegian scientists, Daniel Cornelius Danielssen and C.W. Boeck. Their work resulted in the establishment of the National Leprosy Research and Treatment Center. Danielssen and Boeck believed the cause of leprosy transmission was hereditary. This stance was influential in advocating for the isolation of those infected by gender to prevent reproduction.[80]

## Colonialism and imperialism [edit]


Father Damien on his deathbed in 1889

Though leprosy in Europe was again on the decline by the 1860s, Western countries embraced isolation treatment out of fear of the spread of disease from developing countries, minimal understanding of bacteriology, lack of diagnostic ability or knowledge of how contagious the disease was, and missionary activity.[81] Growing imperialism and pressures of the industrial revolution resulted in a Western presence in countries where leprosy was endemic, namely the British presence in India. Isolation treatment methods were observed by Surgeon-Mayor Henry Vandyke Carter of the British Colony in India while visiting Norway, and these methods were applied in India with the financial and logistical assistance of religious missionaries. Colonial and religious influence and associated stigma continued to be a major factor in the treatment and public perception of leprosy in endemic developing countries until the mid-twentieth century.[81]

## Stigma [edit]

*See also: Leprosy stigma*

Despite effective treatment and education efforts, leprosy stigma continues to be problematic in endemic developing countries. Leprosy is most prevalent amongst impoverished or marginalized populations where social stigma is likely to be compounded by other social inequities. Fears of ostracism, loss of employment, or expulsion from family and society may contribute to a delayed diagnosis and treatment.

Folk models of belief, lack of education, and religious connotations of the disease continue to influence social perceptions of those afflicted in many parts of the world. In Brazil, for example, folklore holds that leprosy is transmitted by dogs, it is a disease associated with sexual promiscuity, and is sometimes thought to be punishment for sins or moral transgressions.[82] Socioeconomic factors also have a direct impact. Lower-class domestic workers who are often employed by those in a higher socioeconomic class may find their employment in jeopardy as physical manifestations of the disease become apparent. Skin discoloration and darker pigmentation resulting from the disease also has social repercussions.

In extreme cases in northern India, leprosy is equated with an "untouchable" status that "often persists long after (individuals with leprosy) have been cured of the disease, creating lifelong prospects of divorce, eviction, loss of employment, and ostracism from family and social networks."[83]

## Programs and treatment [edit]

The WHO states that diagnosis and treatment with MDT are easy and effective, and a 45% decline in disease burden has occurred since MDT has become more widely available. The organization emphasizes the importance of fully integrating leprosy treatment into public health services, effective diagnosis and treatment, and access to information.[84]

In some instances in India, community-based rehabilitation is embraced by local governments and NGOs alike. Often, the identity cultivated by a community environment is preferable to reintegration, and models of self-management and collective agency independent of NGOs and government support have been desirable and successful.[85]

## Notable cases [edit]

- Saint Damien DeVeuster, a Roman Catholic priest from Belgium, himself eventually contracting leprosy, ministered to lepers who had been placed under a government-sanctioned medical quarantine on the island of Moloka'i in the Kingdom of Hawai'i.[86]
- Baldwin IV of Jerusalem was a Christian king of Latin Jerusalem afflicted with leprosy. Baldwin, and the effects of his disease, were portrayed in the film *Kingdom of Heaven*.[87]

- King Henry IV of England (reigned 1399 to 1413) possibly had leprosy.[88]
- Vietnamese poet Hàn Mặc Tử[89]
- Ōtani Yoshitsugu, a Japanese *daimyō*[90]
- Forough Farrokhzad made a 22-minute documentary about a leprosy colony in Iran in 1962 called *The House Is Black*. The film humanizes the people affected and opens by saying that "there is no shortage of ugliness in the world, but by closing our eyes on ugliness, we will intensify it."

## Other animals [edit]

Wild nine-banded armadillos (*Dayspus novemcinctus*) in south central United States often carry Mycobacterium leprae.[91] This is believed to be because armadillos have such a low body temperature. Leprosy lesions appear mainly in cooler body regions such as the skin and mucous membranes of the upper respiratory tract. Because of armadillo's armor, skin lesions are hard to see.[92] Abrasions around the eyes, nose and feet are the most common signs. Infected armadillos make up a large reservoir of *M. leprae* and may be a source of infection for some humans in the United States or other locations in the armadillos' home range. In armadillo leprosy, lesions did not persist at the site of entry in animals, *M. leprae* multiplied in macrophages at the site of inoculation and lymph nodes.[93]

## References [edit]


1. ^ "Definition of leprosy". The Free Dictionary. Retrieved 2015-01-25.
2. ^ *a b c d e f g h i j* "Leprosy Fact sheet N°101". *World Health Organization*. Jan 2014.
3. ^ *a b c* "New Leprosy Bacterium: Scientists Use Genetic Fingerprint To Nail 'Killing Organism'". *ScienceDaily*. 2008-11-28. Retrieved 2010-01-31.
4. ^ *a b c d e f g h i j k l m n o* Suzuki K, Akama T, Kawashima A, Yoshihara A, Yotsu RR, Ishii N (February 2012). "Current status of leprosy: epidemiology, basic science and clinical perspectives.". *The Journal of dermatology*. **39** (2): 121–9. doi:10.1111/j.1346-8138.2011.01370.x. PMID 21973237.
5. ^ "Hansen's Disease (Leprosy) Transmission". *cdc.gov*. April 29, 2013. Retrieved 28 February 2015.
6. ^ *a b c* "Global leprosy situation, 2012". *Wkly. Epidemiol. Rec.* **87** (34): 317–28. August 2012. PMID 22919737.
7. ^ *a b c d* Rodrigues LC; Lockwood DNj (June 2011). "Leprosy now: epidemiology, progress, challenges, and research gaps.". *The Lancet infectious diseases*. **11** (6): 464–70. doi:10.1016/S1473-3099(11)70006-8. PMID 21616456.
8. ^ "Hansen's Disease Data & Statistics". *Health Resources and Services Administration*. Retrieved 12 January 2015.
9. ^ Walsh F (2007-03-31). "The hidden suffering of India's lepers". BBC News.
10. ^ Lyn TE (2006-09-13). "Ignorance breeds leper colonies in China". Independat News & Media. Retrieved 2010-01-31.
11. ^ *a b* Byrne, Joseph P. (2008). *Encyclopedia of pestilence, pandemics, and plagues*. Westport, Conn.[u.a.]: Greenwood Press. p. 351. ISBN 978-0-313-34102-1.
12. ^ editors, Enrico Nunzi, Cesare Massone, (2012). *Leprosy a practical guide*. Milan: Springer. p. 326. ISBN 978-88-470-2376-5.
13. ^ McMenamin, Dorothy (2011). *Leprosy and stigma in the South Pacific : a region-by-region history with first person accounts*. Jefferson, N.C.: McFarland. p. 17. ISBN 978-0-7864-6323-7.
14. ^ *a b* Ryan, Kenneth J.; Ray, C. George, eds. (2004). *Sherris Medical Microbiology* (4th ed.). McGraw Hill. pp. 451–3. ISBN 0-8385-8529-9. OCLC 61405904.
15. ^ *a b* "Lifting the stigma of leprosy: a new vaccine offers hope against an ancient disease". *Time*. **119** (19): 87. May 1982. PMID 10255067.
16. ^ *a b* Kulkarni GS (2008). *Textbook of Orthopedics and Trauma* (2 ed.). Jaypee Brothers Publishers. p. 779. ISBN 978-81-8448-242-3.
17. ^ "Q and A about leprosy". American Leprosy Missions. Retrieved 2011-01-22. "Do fingers and toes fall off when someone gets leprosy? No. The bacillus attacks nerve endings and destroys the body's ability to feel pain and injury. Without feeling pain, people injure themselves on fire, thorns, rocks, even hot coffee cups. Injuries become infected and result in tissue loss. Fingers and toes become shortened and deformed as the cartilage is absorbed into the body."
18. ^ McMurray DN (1996). "Mycobacteria and Nocardia". In Baron S; et al. *Baron's Medical Microbiology* (4th ed.). Univ of Texas Medical Branch. ISBN 0-9631172-1-1. OCLC 33838234.
19. ^ Bhattacharya S, Vijayalakshmi N, Parija SC (1 October 2002). "Uncultivable bacteria: Implications and recent trends towards identification". *Indian journal of medical microbiology*. **20** (4): 174–7. PMID 17657065.
20. ^ Meredith, Anna; Del Pozo, Jorge; Smith, Sionagh; Milne, Elspeth; Stevenson, Karen; McLuckie, Joyce (September 2014). "Leprosy in red squirrels in Scotland". *Veterinary Record*. **175** (11): 285–286. 1172–83. doi:10.4161/hv.7.11.16848. PMC 3323495. PMID 22048122.
48. ^ Setia MS, Steinmaus C, Ho CS, Rutherford GW; Steinmaus; Ho; Rutherford (March 2006). "The role of BCG in prevention of leprosy: a meta-analysis". *Lancet Infect Dis.* **6** (3): 162–70. doi:10.1016/S1473-3099(06)70412-1. PMID 16500597.
49. ^ Merle CS, Cunha SS, Rodrigues LC; Cunha; Rodrigues (2010). "BCG vaccination and leprosy protection: Review of current evidence and status of BCG in leprosy control". *Expert Review of Vaccines*. **9** (2): 209–222. doi:10.1586/ERV.09.161. PMID 20109030.
50. ^ "Leprosy Vaccine". American Leprosy Missions. Retrieved October 20, 2015.
51. ^ "Trial set for world's first leprosy vaccine". The Guardian. June 6, 2014. Retrieved October 20, 2015.
52. ^ "China's Mars plans, leprosy vaccine and self-driving taxis". Nature. 2016-08-31. Retrieved 2016-09-03.
53. ^ "Mortality and Burden of Disease Estimates for WHO Member States in 2002" (xls). *World Health Organization*. 2002.
54. ^ *a b* "Global Leprosy Update, 2013: Reducing Disease Burden" (PDF). *Weekly Epidemiological Record*. World Health Organization. **36** (89): 389–400. 5 September 2014. Retrieved 26 February 2016.
55. ^ "About ILEP". ILEP. Retrieved 2014-08-25.
56. ^ WHO (1995). "Leprosy disabilities: magnitude of the problem". *Weekly Epidemiological Record*. **70** (38): 269–75. PMID 7577430.
57. ^ World Health Organization. (1985). "Epidemiology of leprosy in relation to control. Report of a WHO Study Group". *World Health Organ Tech Rep Ser*. Geneva: World Health Organization. **716**: 1–60. ISBN 92-4-120716-7. OCLC 12095109. PMID 3925646.
58. ^ Monot, Marc; Honoré, Nadine; Garnier, Thierry; Araoz, Romul; Coppée, Jean-Yves; Lacroix, Céline; Sow, Samba; Spencer, John S.; Truman, Richard W.; Williams, Diana L.; Gelber, Robert; Virmond, Marcos; Flageul, Béatrice; Cho, Sang-Nae; Ji, Baohong; Paniz-Mondolfi, Alberto; Convit, Jacinto; Young, Saroj; Fine, Paul E.; Rasolofo, Voahangy; Brennan, Patrick J.; Cole, Stewart T. (13 May 2005). "On the Origin of Leprosy". *Science*. **308** (5724): 1040–1042. doi:10.1126/science/1109759. PMID 15894530.
59. ^ Robbins, G; Mushrif, V.; Misra, V.N.; Mohanty, R.K.; Shinde, V.S.; Gray, K.M.; Schug, M.D. (May 2009). "Ancient skeletal evidence for Leprosy in India (2000 B.C.)". *PLoS ONE*. e5669 (5): e5669. doi:10.1371/journal.pone.0005669. PMC 2682583. PMID 19479078.
60. ^ Robbins Schug, G; Blevins, K. Elaine; Cox, Brett; Gray, Kelsey; Mushrif-Tripathy, Veena (December 2013). "Infection, Disease, and Biosocial Process at the End of the Indus Civilization". *PLoS ONE*. 0084814 (12): e84814. doi:10.1371/journal.pone.0084814.
61. ^ Francis Adams, *The Seven Books of Paulus Aegineta: Translated from the Greek with Commentary Embracing a Complete View of the Knowledge Possessed by the Greeks, Romans and Arabians on all Subjects Connected with Medicine and Surgery*, 3 vols. (London: Sydenham Society, 1678
62. ^ Roman: Celsus, Pliny, Serenus Samonicus, Scribonius Largus, Caelius Aurelianus, Themison, Octavius Horatianus, Marcellus the Emperic; Greek: Aretaeus, Plutarch, Galen, Oribasius, Aetius, Actuarius, Nonnus, Psellus, Leo, Myrepsus; Arabic: Scrapion, Avenzoar, Albucasis, the Haly Abbas translated by Stephanus Antiochensis, Alsharavius, Rhases, and Guido de Cauliaco
63. ^ Robbins, Gwen; Tripathy, V. Mushrif; Misra, V. N.; Mohanty, R. K.; Shinde, V. S.; Gray, Kelsey M.; Schug, Malcolm D. (May 27, 2009).

doi:10.1136/vr.g5680. PMID 25234460.
21. ^ *Red squirrels in the British Isles are infected with leprosy bacilli*, Dr. Andrej Benjak, Prof Anna Meredith and others, *Science*, 11 November 2016.Retrieved 11 November 2016.
22. ^ *Leprosy revealed in red squirrels across the British Isles*, Damian Carrington, 11 November 2016.Retrieved 11 November 2016.
23. ^ [a] [b] Schreuder, P.A.M.; Noto, S.; Richardus J.H. (January 2016). "Epidemiologic trends of leprosy for the 21st century". *Clinics in Dermatology*. **34** (1): 24–31. doi:10.1016/j.clindermatol.2015.11.001. PMID 26773620.
24. ^ Lockwood DN, Lambert SM (January 2011). "Human immunodeficiency virus and leprosy: an update.". *Dermatologic clinics*. **29** (1): 125–8. doi:10.1016/j.det.2010.08.016. PMID 21095536.
25. ^ [a] [b] [c] [d] [e] [f] "Leprosy". *WHO*. 2009-08-01. Retrieved 2010-01-31.
26. ^ Brosch, Roland; Stinear, Timothy P. (11 November 2016). "Leprosy in red squirrels". *Science*. **354** (6313): 702–703. doi:10.1126/science.aal0145. Retrieved 2016-11-11.
27. ^ "Functional Haplotypes That Produce Normal Ficolin-2 Levels Protect against Clinical Leprosy". Oxford Journals. Retrieved March 8, 2014.
28. ^ Truman RW, Singh P, Sharma R, Busso P, Rougemont J, Paniz-Mondolfi A, Kapopoulou A, Brisse S, Scollard DM, Gillis TP, Cole ST (April 2011). "Probable Zoonotic Leprosy in the Southern United States". *The New England Journal of Medicine*. Massachusetts Medical Society. **364** (17): 1626–1633. doi:10.1056/NEJMoa1010536. PMC 3138484. PMID 21524213.
29. ^ [a] [b] "What Is Leprosy?" THE MEDICAL NEWS | from News-Medical.Net – Latest Medical News and Research from Around the World. Web. 20 Nov. 2010. [1].
30. ^ Rees RJ, McDougall AC; McDougall (1977). "Airborne infection with Mycobacterium leprae in mice". *J Med Microbiol*. **10** (1): 63–8. doi:10.1099/00222615-10-1-63. PMID 320339.
31. ^ Cook, Gordon C. (2009). *Manson's tropical diseases.* (22nd ed.). [Edinburgh]: Saunders. p. 1056. ISBN 978-1-4160-4470-3.
32. ^ Buschman E, Skamene E (Jun 2004). "Linkage of leprosy susceptibility to Parkinson's disease genes" (PDF). *International journal of leprosy and other mycobacterial diseases*. **72** (2): 169–70. doi:10.1489/1544-581X(2004)072<0169:LOLSTP>2.0.CO;2. ISSN 0148-916X. PMID 15301585. Retrieved January 31, 2011.
33. ^ Alcaïs A, Mira M, Casanova JL, Schurr E, Abel L (2005). "Genetic dissection of immunity in leprosy". *Curr. Opin. Immunol*. **17** (1): 44–8. doi:10.1016/j.coi.2004.11.006. PMID 15653309.
34. ^ "Diagnosis of Leprosy." WHO. from http://www.who.int/lep/diagnosis/en/ accessed on 14 July 2014.
35. ^ U.S. Department of Health and Human Services, Health Resources and Services Administration. (n.d.). National Hansen's disease (leprosy) program Retrieved from http://www.hrsa.gov/hansens/
36. ^ Smith DS (2008-08-19). "Leprosy: Overview". *eMedicine Infectious Diseases*. Retrieved 2010-02-01.
37. ^ Singh N, Manucha V, Bhattacharya SN, Arora VK, Bhatia A; Manucha; Bhattacharya; Arora; Bhatia (June 2004). "Pitfalls in the cytological classification of borderline leprosy in the Ridley-Jopling scale". *Diagn. Cytopathol*. **30** (6): 386–8. doi:10.1002/dc.20012. PMID 15176024.
38. ^ Ridley DS, Jopling WH; Jopling (1966). "Classification of leprosy according to immunity. A five-group system". *Int. J. Lepr. Other Mycobact. Dis.* **34** (3): 255–73. PMID 5950347.
39. ^ Modlin RL (June 1994). "Th1-Th2 paradigm: insights from leprosy". *J. Invest. Dermatol*. **102** (6): 828–32. doi:10.1111/1523-1747.ep12381958. PMID 8006444.
40. ^ James, William D.; Berger, Timothy G.; et al. (2006). *Andrews' Diseases of the Skin: clinical Dermatology*. Saunders Elsevier. ISBN 0-7216-2921-0.
41. ^ Jardim MR, Antunes SL, Santos AR, Nascimento OJ, Nery JA, Sales AM, Illarramendi X, Duppre N, Chimelli L, Sampaio EP, Sarno EP; Antunes; Santos; et al. (July 2003). "Criteria for diagnosis of pure neural leprosy". *J. Neurol*. **250** (7): 806–9. doi:10.1007/s00415-003-1081-5. PMID 12883921.
42. ^ Mendiratta V, Khan A, Jain A; Khan; Jain (2006). "Primary neuritic leprosy: a reappraisal at a tertiary care hospital". *Indian J Lepr*. **78** (3): 261–7. PMID 17120509.
43. ^ Ishida Y, Pecorini L, Guglielmelli E; Pecorini l; Guglielmelli e (July 2000). "Three cases of pure neuritic (PN) leprosy at detection in which skin lesions became visible during their course". *Nihon Hansenbyo Gakkai Zasshi*. **69** (2): 101–6. doi:10.5025/hansen.69.101. PMID 10979277.
44. ^ Mishra B, Mukherjee A, Girdhar A, Husain S, Malaviya GN, Girdhar BK; Mukherjee; Girdhar; Husain; Malaviya; Girdhar (1995). "Neuritic leprosy: further progression and significance". *Acta Leprol*. **9** (4): 187–94. PMID 8711979.
45. ^ Talwar S, Jha PK, Tiwari VD; Jha; Tiwari (September 1992). "Neuritic leprosy: epidemiology and therapeutic responsiveness". *Lepr Rev*. **63** (3): "Ancient Skeletal Evidence for Leprosy in India (2000 B.C.)". *PLoS ONE*. **4** (5): e5669. doi:10.1371/journal.pone.0005669. PMC 2682583. PMID 19479078.
64. ^ "DNA of Jesus-Era Shrouded Man in Jerusalem Reveals Earliest Case of Leprosy". *ScienceDaily*. 2009-12-16. Retrieved 2010-01-31.
65. ^ Irgens LM (2002). "The discovery of the leprosy bacillus". *Tidsskr nor Laegeforen*. **122** (7): 708–9. PMID 11998735.
66. ^ Andrew Baum; et al. (1997). *Cambridge handbook of psychology, health and medicine*. Cambridge, Angleterre: Cambridge University Press. p. 521. ISBN 978-0-521-43686-1.
67. ^ Rees RJ, Pearson JM, Waters MF; Pearson; Waters (1970). "Experimental and Clinical Studies on Rifampicin in Treatment of Leprosy". *Br Med J*. **688** (1): 89–92. doi:10.1136/bmj.1.5688.89. PMC 1699176. PMID 4903972.
68. ^ Yawalkar SJ, McDougall AC, Languillon J, Ghosh S, Hajra SK, Opromolla DV, Tonello CJ; McDougall; Languillon; Ghosh; Hajra; Opromolla; Tonello (1982). "Once-monthly rifampicin plus daily dapsone in initial treatment of lepromatous leprosy". *Lancet*. **8283** (1): 1199–1202. doi:10.1016/S0140-6736(82)92334-0. PMID 6122970.
69. ^ Syphilis through history Encyclopædia Britannica
70. ^ "Communicable Diseases Department, Leprosy FAQ". World Health Organization. 2006-05-25. Retrieved 2010-01-31.
71. ^ Japan repealed its "Leprosy Prevention Laws" in 1996, but former patients still reside in sanatoriums. "Koizumi apologises for leper colonies". BBC News. May 25, 2001. and Former Hansen's disease patients still struggling with prejudice *Japan Times* June 7, 2007.
72. ^ *Arch Dermato Syphilis* 1898; 44:159–174
73. ^ Gussow, Zachary (1989). *Leprosy, Racism, and Public Health*. Boulder, Colorado: Westview Press. ISBN 978-0-8133-0674-2.
74. ^ Jacob, Jesse; Franco-Paredes, Carlos (2008). "The stigmatization of leprosy in India and its impact on future approaches to elimination and control". *PLoS Neglected Tropical Diseases*. **2**: e113. doi:10.1371/journal.pntd.0000113.
75. ^ [a] [b] [c] Covey, Herbert C. (2001). "People with leprosy (Hansen's disease) during the Middle Ages" (PDF). *Social Science Journal*. **38** (2): 315–321. doi:10.1016/S0362-3319(01)00116-1. Retrieved June 25, 2016.
76. ^ Le Goff, Jacques (1990). *The Medieval world*. London: Collins & Brown. ISBN 1-85585-081-8.
77. ^ Clay, Rotha (1909). *The Mediaeval Hospitals of England*. Cornell University Library. ISBN 1-112-20443-1.
78. ^ Rubin, Stanley (1974). *Medieval English medicine*. New York: Barnes & Noble Books: Newton Abbot: David & Charles. ISBN 0-06-496016-1.
79. ^ Moore, R. I. (2007). *The Formation of a Persecuting Society*. Oxford: Blackwell. ISBN 1-4051-2964-6.
80. ^ Alter, Andrea (2010). *Genetic susceptibility to leprosy*. McGill University (Canada): ProQuest Dissertations Publishing. ISBN 978-0-494-72613-6.
81. ^ [a] [b] Gussow, Zachary (1989). *Leprosy, Racism, and Public Health*. Boulder, Colorado: Westview Press. ISBN 978-0-8133-0674-2.
82. ^ White, Cassandra (2005). "Explaining a Complex Disease Process: Talking to Patients about Hansen's Disease (Leprosy) in Brazil". *Medical Anthropology Quarterly*. ISSN 0745-5194.
83. ^ Barret, Ronald (June 2005). "Self-Mortification and the Stigma of Leprosy in Northern India". *Medical Anthropology Quarterly*. ISSN 1548-1387.
84. ^ "World Health Organization".
85. ^ Staples, James (2014). "Communities of the afflicted: constituting leprosy through place in South India.". *Medical Anthropology: Cross-Cultural Studies in Health and Illness*. **33**: 6–20. doi:10.1080/01459740.2012.714021.
86. ^ Tayman, John (2007). *The Colony: The Harrowing True Story of the Exiles of Molokai*. New York: Simon and Schuster. ISBN 978-0-7432-3301-9.
87. ^ Hamilton, Bernard (2000). *The leper king and his heirs: Baldwin IV and the Crusader Kingdom of Jerusalem*. Cambridge, UK: Cambridge University Press. ISBN 0-521-64187-X.
88. ^ Webber, Roger (2015). *Disease Selection: The Way Disease Changed the World*. CABI. p. 8. ISBN 978-1-78064-682-4.
89. ^ Cung giu Nguyên (1955). "Contemporary Vietnamese Writing". *Books Abroad*. University of Oklahoma. **29** (1): 19–25. doi:10.2307/40093803. JSTOR 40093803.
90. ^ Bryant A (1995). *Sekigahara 1600: The Final Struggle for Power (Campaign Series, 40)*. Osprey Publishing (UK). ISBN 1-85532-395-8. Retrieved 2010-02-28.
91. ^ Truman, Richard (2005). "Leprosy in wild armadillos". *Lepr Rev*. **76**: 198–208.
92. ^ Sharma, Rahul; Lahiri, Ramanuj; Scollard, David M.; Pena, Maria; Williams, Diana L.; Adams, Linda B.; Figarola, John; Truman, Richard W. (2013-01-01). "The armadillo: a model for the neuropathy of leprosy and

263–8. PMID 1406021.
46. ^ a b c Rodrigues LC, Lockwood DNj; Lockwood (June 2011). "Leprosy now: epidemiology, progress, challenges, and research gaps". *Lancet Infect Dis.* **11** (6): 464–70. doi:10.1016/S1473-3099(11)70006-8. PMID 21616456.
47. ^ Duthie MS, Gillis TP, Reed SG; Gillis; Reed (November 2011). "Advances and hurdles on the way toward a leprosy vaccine". *Hum Vaccin.* **7** (11): potentially other neurodegenerative diseases". *Disease Models & Mechanisms*. **6** (1): 19–24. doi:10.1242/dmm.010215. ISSN 1754-8403. PMC 3529335. PMID 23223615.
93. ^ Job, C. K.; Drain, V.; Truman, R.; Deming, A. T.; Sanchez, R. M.; Hastings, R. C. (2016-06-01). "The pathogenesis of leprosy in the nine-banded armadillo and the significance of IgM antibodies to PGL-1". *Indian Journal of Leprosy*. **64** (2): 137–151. ISSN 0254-9395. PMID 1607712.

## External links [edit]

- Leprosy at DMOZ
- Links and resources Links to information about leprosy selected by the World Health Organization

Wikimedia Commons has media related to *Leprosy*.

| v • t • e • | **Diseases of the skin and appendages by morphology** | | | | |
|---|---|---|---|---|---|
| **Growths** | **Epidermal** | wart • callus • seborrheic keratosis • acrochordon • molluscum contagiosum • actinic keratosis • squamous-cell carcinoma • basal-cell carcinoma • Merkel-cell carcinoma • nevus sebaceous • trichoepithelioma • | | | |
| | **Pigmented** | Freckles • lentigo • melasma • nevus • melanoma • | | | |
| | **Dermal and subcutaneous** | epidermal inclusion cyst • hemangioma • dermatofibroma (benign fibrous histiocytoma) • keloid • lipoma • neurofibroma • xanthoma • Kaposi's sarcoma • infantile digital fibromatosis • granular cell tumor • leiomyoma • lymphangioma circumscriptum • myxoid cyst • | | | |
| **Rashes** | **With epidermal involvement** | **Eczematous** | contact dermatitis • atopic dermatitis • seborrheic dermatitis • stasis dermatitis • lichen simplex chronicus • Darier's disease • glucagonoma syndrome • langerhans cell histiocytosis • lichen sclerosus • pemphigus foliaceus • Wiskott–Aldrich syndrome • Zinc deficiency • | | |
| | | **Scaling** | psoriasis • tinea (corporis • cruris • pedis • manuum • faciei) • pityriasis rosea • secondary syphilis • mycosis fungoides • systemic lupus erythematosus • pityriasis rubra pilaris • parapsoriasis • ichthyosis • | | |
| | | **Blistering** | herpes simplex • herpes zoster • varicella • bullous impetigo • acute contact dermatitis • pemphigus vulgaris • bullous pemphigoid • dermatitis herpetiformis • porphyria cutanea tarda • epidermolysis bullosa simplex • | | |
| | | **Papular** | scabies • insect bite reactions • lichen planus • miliaria • keratosis pilaris • lichen spinulosus • transient acantholytic dermatosis • lichen nitidus • pityriasis lichenoides et varioliformis acuta • | | |
| | | **Pustular** | acne vulgaris • acne rosacea • folliculitis • impetigo • candidiasis • gonococcemia • dermatophyte • coccidioidomycosis • subcorneal pustular dermatosis • | | |
| | | **Hypopigmented** | tinea versicolor • vitiligo • pityriasis alba • postinflammatory hyperpigmentation • tuberous sclerosis • idiopathic guttate hypomelanosis • **leprosy** • hypopigmented mycosis fungoides • | | |
| | **Without epidermal involvement** | **Red** | **Blanchable Erythema** | **Generalized** | drug eruptions • viral exanthems • toxic erythema • systemic lupus erythematosus • |
| | | | | **Localized** | cellulitis • abscess • boil • erythema nodosum • carcinoid syndrome • fixed drug eruption • |
| | | | | **Specialized** | urticaria • erythema (multiforme • migrans • gyratum repens • annulare centrifugum • ab igne) • |
| | | | **Nonblanchable Purpura** | **Macular** | thrombocytopenic purpura • actinic/solar purpura • |
| | | | | **Papular** | disseminated intravascular coagulation • vasculitis • |
| | | **Indurated** | scleroderma/morphea • granuloma annulare • lichen sclerosis et atrophicus • necrobiosis lipoidica • | | |
| **Miscellaneous disorders** | **Ulcers** | | | | |
| | **Hair** | telogen effluvium • androgenic alopecia • trichotillomania • alopecia areata • systemic lupus erythematosus • tinea capitis • loose anagen syndrome • lichen planopilaris • folliculitis decalvans • acne keloidalis nuchae • | | | |
| | **Nail** | onychomycosis • psoriasis • paronychia • ingrown nail • | | | |
| | **Mucous membrane** | Aphthous stomatitis • oral candidiasis • lichen planus • leukoplakia • pemphigus vulgaris • mucous membrane pemphigoid • cicatricial pemphigoid • herpesvirus • coxsackievirus • syphilis • systemic histoplasmosis • squamous-cell carcinoma • | | | |

| v • t • e • | **Gram-positive bacterial infection: Actinobacteria (primarily A00–A79, 001–041, 080–109)** | | |
|---|---|---|---|
| **Actinomycineae** | **Actinomycetaceae** | *Actinomyces israelii* (Actinomycosis • Cutaneous actinomycosis • • *Tropheryma whipplei* (Whipple's disease • • *Arcanobacterium haemolyticum* (Arcanobacterium haemolyticum infection • • *Actinomyces gerencseriae* • | |
| | **Propionibacteriaceae** | *Propionibacterium acnes* • | |
| | | | Tuberculosis: Ghon focus/Ghon's complex • Pott disease • *brain* (Meningitis • Rich focus • • Tuberculous lymphadenitis (Tuberculous cervical lymphadenitis • • *cutaneous* (Scrofuloderma • Erythema induratum • Lupus vulgaris • Prosector's wart • |

| | | | |
|---|---|---|---|
| **Corynebacterineae** | **Mycobacteriaceae** | *M. tuberculosis*/ *M. bovis* | Tuberculosis cutis orificialis · Tuberculous cellulitis · Tuberculous gumma · · Lichen scrofulosorum · Tuberculid (Papulonecrotic tuberculid · · Primary inoculation tuberculosis · Miliary · Tuberculous pericarditis · Urogenital tuberculosis · Multi-drug-resistant tuberculosis · Extensively drug-resistant tuberculosis · |
| | | *M. leprae* | **Leprosy**: Tuberculoid leprosy · Borderline tuberculoid leprosy · Borderline leprosy · Borderline lepromatous leprosy · Lepromatous leprosy · Histoid leprosy · |
| | | **Nontuberculous** | **R1:** *M. kansasii* · *M. marinum* (Aquarium granuloma · · |
| | | | **R2:** *M. gordonae* · |
| | | | **R3:** *M. avium* complex/*Mycobacterium avium*/*Mycobacterium intracellulare*/MAP (MAI infection · · *M. ulcerans* (Buruli ulcer · · *M. haemophilum* · |
| | | | **R4/RG:** *M. fortuitum* · *M. chelonae* · *M. abscessus* · |
| | **Nocardiaceae** | *Nocardia asteroides*/*Nocardia brasiliensis* (Nocardiosis · · *Rhodococcus equi* · | |
| | **Corynebacteriaceae** | *Corynebacterium diphtheriae* (Diphtheria · · *Corynebacterium minutissimum* (Erythrasma · · *Corynebacterium jeikeium* (Group JK corynebacterium sepsis · · | |
| **Bifidobacteriaceae** | *Gardnerella vaginalis* · | | |
| **Authority control** | GND: 4035392-8 · NDL: 00569249 · | | |

Categories: Bacterial diseases | Leprosy

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# Lyme disease



From Wikipedia, the free encyclopedia

*Not to be confused with photodermatitis, also known as "lime disease".*

**Lyme disease**, also known as **Lyme borreliosis**, is an infectious disease caused by bacteria of the *Borrelia* type.[1] The most common sign of infection is an expanding area of redness, known as erythema migrans, that begins at the site of a tick bite about a week after it has occurred. The rash is typically neither itchy nor painful. Approximately 25–50% of infected people do not develop a rash. Other early symptoms may include fever, headache and feeling tired. If untreated, symptoms may include loss of the ability to move one or both sides of the face, joint pains, severe headaches with neck stiffness, or heart palpitations, among others. Months to years later, repeated episodes of joint pain and swelling may occur. Occasionally, people develop shooting pains or tingling in their arms and legs. Despite appropriate treatment, about 10 to 20% of people develop joint pains, memory problems, and feel tired for at least six months.[2][3]

Lyme disease is transmitted to humans by the bite of infected ticks of the *Ixodes* genus.[4] Usually, the tick must be attached for 36 to 48 hours before the bacteria can spread.[5] In North America, *Borrelia burgdorferi sensu stricto* and *Borrelia mayonii* are the cause.[1][6] In Europe and Asia, the bacteria *Borrelia afzelii* and *Borrelia garinii* are also causes of the disease.[1] The disease does not appear to be transmissible between people, by other animals, or through food.[5] Diagnosis is based upon a combination of symptoms, history of tick exposure, and possibly testing for specific antibodies in the blood.[7][8] Blood tests are often negative in the early stages of the disease.[1] Testing of individual ticks is not typically useful.[9]

Prevention includes efforts to prevent tick bites such as by wearing long pants and using DEET.[1] Using pesticides to reduce tick numbers may also be effective.[1] Ticks can be removed using tweezers.[10] If the removed tick was full of blood, a single dose of doxycycline may be used to prevent development of infection, but is not generally recommended since development of infection is rare.[1] If an infection develops, a number of antibiotics are effective, including doxycycline, amoxicillin, and cefuroxime.[1] Treatment is usually for two or three weeks.[1] Some people develop a

## Variants

## More

## Lyme disease

An adult deer tick

### Classification and external resources

| | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | A69.2 |
| **ICD-9-CM** | 088.81 |
| **DiseasesDB** | 1531 |
| **MedlinePlus** | 001319 |
| **eMedicine** | 330178<br>965922<br>786767 |
| **Patient UK** | Lyme disease |
| **MeSH** | D008193 |

[edit on Wikidata]

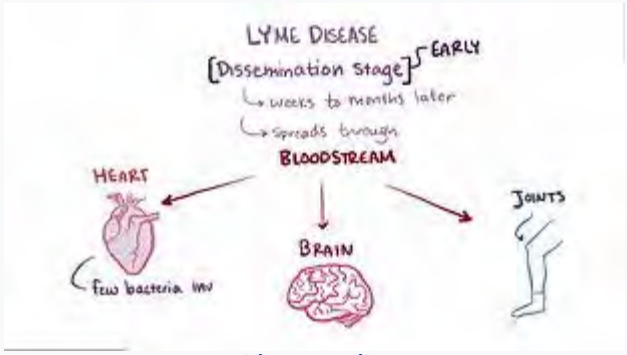
fever and muscle and joint pains from treatment which may last for one or two days.[1] In those who develop persistent symptoms, long-term antibiotic therapy has not been found to be useful.[1][11]

Lyme disease is the most common disease spread by ticks in the Northern Hemisphere.[12] It is estimated to affect 300,000 people a year in the United States and 65,000 people a year in Europe.[1][13] Infections are most common in the spring and early summer.[1] Lyme disease was diagnosed as a separate condition for the first time in 1975 in Old Lyme, Connecticut. It was originally mistaken for juvenile rheumatoid arthritis.[14] The bacterium involved was first described in 1981 by Willy Burgdorfer.[15] Chronic symptoms are well described and are known as post-treatment Lyme disease syndrome, although it is often called chronic Lyme disease.[11] Some healthcare providers claim that it is due to ongoing infection; however, this is not believed to be true.[16] A previous vaccine is no longer available. Research is ongoing to develop new vaccines.[1]



**Contents**






Play media

Video explanation

## Signs and symptoms



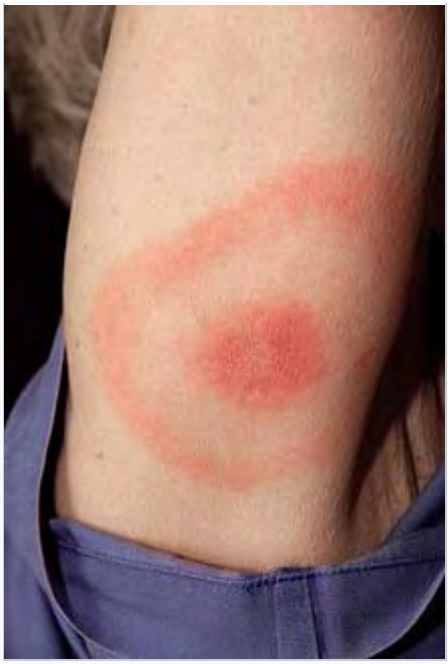
Lyme disease can affect multiple body systems and produce a broad range of symptoms. Not all patients with Lyme disease have all symptoms, and many of the symptoms are not specific to Lyme disease, but can occur with other diseases, as well. The incubation period from

infection to the onset of symptoms is usually one to two weeks, but can be much shorter (days), or much longer (months to years).[18]

Symptoms most often occur from May to September, because the nymphal stage of the tick is responsible for most cases.[18] Asymptomatic infection exists, but occurs in less than 7% of infected individuals in the United States.[19] Asymptomatic infection may be much more common among those infected in Europe.[20]

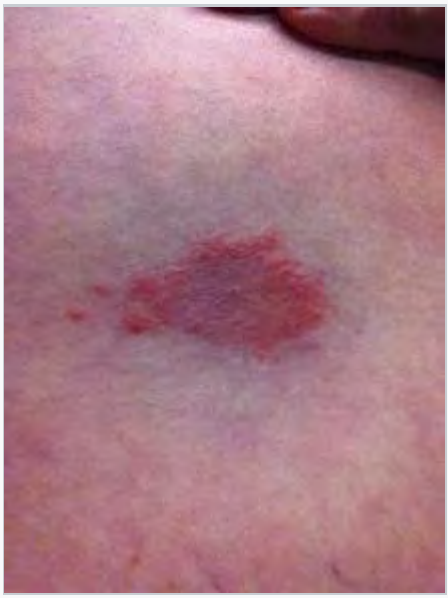
## Early localized infection

Early localized infection can occur when the infection has not yet spread throughout the body. Only the site where the infection has first come into contact with the skin is affected. The classic sign of early local infection with Lyme disease is a circular, outwardly expanding rash called erythema chronicum migrans (EM), which occurs at the site of the tick bite three to 32 days after the tick bite.[1] The rash is red, and may be warm, but is generally painless. Classically, the innermost portion remains dark red and becomes indurated (is thicker and firmer), the outer edge remains red, and the portion in between clears, giving the appearance of a bull's eye. However, partial clearing is uncommon, and the bull's-eye pattern more often involves central redness.[1]



This "classic" bull's-eye rash is also called erythema migrans. A rash caused by Lyme does not always look like this and approximately 25% of those infected with Lyme disease may have no rash.[2][17]

The EM rash associated with early infection is found in about 70-80% of people infected.[2] It can have a range of appearances including the classic target bull's-eye lesion and nontarget appearing lesions. The 20-30% without the EM and the nontarget lesions can often cause misidentification of Lyme disease.[21] Affected individuals can also experience flu-like symptoms, such as headache, muscle soreness, fever, and malaise.[22] Lyme disease can progress to later stages even in people who do not develop a rash.[20][23]



Raised, red borders around indurated central portion

## Early disseminated infection

Within days to weeks after the onset of local infection, the *Borrelia* bacteria may begin to spread through the bloodstream. EM may develop at sites across the body that bear no relation to the original tick bite.[24] Another skin condition, apparently absent in North American patients, but found in Europe, is borrelial lymphocytoma, a purplish lump that develops on the ear lobe, nipple, or scrotum.[25] Various acute neurological problems, termed neuroborreliosis, appear in 10–15% of untreated patients.[22][26] These include facial palsy, which is the loss of muscle tone on one or both sides of the face, as well as meningitis, which involves severe headaches, neck stiffness, and sensitivity to light. Inflammation of the spinal cord's nerve roots can cause shooting pains that may interfere with sleep, as well as abnormal skin sensations. Mild encephalitis may lead to memory loss, sleep disturbances, or mood changes. In addition, some case reports have described altered mental status as the only symptom seen in a few cases of early neuroborreliosis.[27] The disease may adversely impact the heart's electrical conduction system and can cause abnormal heart rhythms such as atrioventricular block.[28]

## Late disseminated infection

After several months, untreated or inadequately treated patients may go on to develop severe and chronic symptoms that affect many parts of the body, including the brain, nerves, eyes, joints, and heart. Many disabling symptoms can occur, including permanent impairment of motor or sensory function of the lower extremities in extreme cases.[20] The associated nerve pain radiating out from the spine is termed Bannwarth syndrome,[29] named after Alfred Bannwarth.

The late disseminated stage is where the infection has fully spread throughout the body. Chronic neurologic symptoms occur in up to 5% of untreated patients.[22] A polyneuropathy that involves shooting pains, numbness, and tingling in the hands or feet may develop. A neurologic syndrome called Lyme encephalopathy is associated with subtle cognitive difficulties, insomnia, a general sense of feeling unwell, and changes in personality.[30] Other problems, however, such as depression and fibromyalgia, are no more common in people with Lyme disease than in the general population.[31][32]

Chronic encephalomyelitis, which may be progressive, can involve cognitive impairment, brain fog, migraines, balance issues, weakness in the legs, awkward gait, facial palsy, bladder problems, vertigo, and back pain. In rare cases, untreated Lyme disease may cause frank psychosis, which has been misdiagnosed as schizophrenia or bipolar disorder. Panic attacks and anxiety can occur; also, delusional behavior may be seen, including somatoform delusions, sometimes accompanied by a depersonalization or derealization syndrome, where the patients begin to feel detached from themselves or from reality.[33][34]

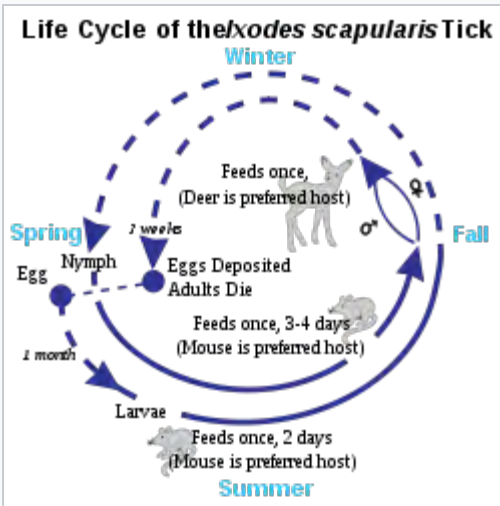
Lyme arthritis usually affects the knees.[35] In a minority of patients, arthritis can occur in other joints, including the ankles, elbows, wrists, hips, and shoulders. Pain is often mild or moderate, usually with swelling at the involved joint. Baker's cysts may form and rupture. In some cases, joint erosion occurs.

*Acrodermatitis chronica atrophicans* (ACA) is a chronic skin disorder observed primarily in Europe among the elderly.[25] ACA begins as a reddish-blue patch of discolored skin, often on the backs of the hands or feet. The lesion slowly atrophies over several weeks or months, with the skin becoming first thin and wrinkled and then, if untreated, completely dry and hairless.[36]

# Cause

*Main article: Lyme disease microbiology*

Lyme disease is caused by spirochetal bacteria from the genus *Borrelia*. Spirochetes are surrounded by peptidoglycan and flagella, along with an outer membrane similar to other Gram-negative bacteria. Because of their double-membrane envelope, *Borrelia* bacteria are often mistakenly described as Gram negative despite the considerable differences in their envelope components from Gram-negative bacteria.[37] The Lyme-related *Borrelia* species are collectively known as *Borrelia burgdorferi sensu lato*, and show a great deal of genetic diversity.



Deer tick life cycle

*B. burgdorferi sensu lato* is made up of 21 closely related species, but only three clearly cause Lyme disease: *B. burgdorferi sensu stricto* (predominant in North America, but also present in Europe), *B. afzelii*, and *B. garinii* (both predominant in Eurasia).[38][39] Some studies have also proposed *B. bissettii* and *B. valaisiana* may sometimes infect humans, but these species do not seem to be important causes of disease.[40][41]

*Further information: Weather and climate effects on Lyme disease exposure*

## Transmission

Lyme disease is classified as a zoonosis, as it is transmitted to humans

*Borrelia* bacteria, the causative agent of Lyme disease, magnified

from a natural reservoir among small mammals and birds by ticks that feed on both sets of hosts.[42] Hard-bodied ticks of the genus *Ixodes* are the main vectors of Lyme disease (also the vector for *Babesia*).[43] Most infections are caused by ticks in the nymphal stage, because they are very small and thus may feed for long periods of time undetected.[42] Larval ticks are very rarely infected.[44] Although deer are the preferred hosts of the adult stage of deer ticks, and tick populations are much lower in the absence of deer, ticks generally do not acquire Lyme disease spirochetes from deer. Rather, deer ticks acquire *Borrelia* microbes from infected small mammals and occasionally birds, including the white-footed mouse, *Peromyscus leucopus*.[45]

Within the tick midgut, the *Borrelia*'s outer surface protein A (OspA) binds to the tick receptor for OspA, known as TROSPA. When the tick feeds, the *Borrelia* downregulates OspA and upregulates OspC, another surface protein. After the bacteria migrate from the midgut to the salivary glands, OspC binds to Salp15, a tick salivary protein that appears to have immunosuppressive effects that enhance infection.[46] Successful infection of the mammalian host depends on bacterial expression of OspC.[47]

*Ixodes scapularis*, the primary vector of Lyme disease in eastern North America

Tick bites often go unnoticed because of the small size of the tick in its nymphal stage, as well as tick secretions that prevent the host from feeling any itch or pain from the bite. However, transmission is quite rare, with only about 1% of recognized tick bites resulting in Lyme disease.

In Europe, the vector is *Ixodes ricinus*, which is also called the sheep tick or castor bean tick.[48] In China, *Ixodes persulcatus* (the taiga tick) is probably the most important vector.[49] In North America, the black-legged tick or deer tick (*Ixodes scapularis*) is the main vector on the East Coast.[44]

The lone star tick (*Amblyomma americanum*), which is found throughout the Southeastern United States as far west as Texas, is unlikely to transmit the Lyme disease spirochetes,[50] though it may be implicated in a related syndrome called southern tick-associated rash illness, which resembles a mild form of Lyme disease.[51]

Tick *ixodes ricinus*, developmental stages

On the West Coast of the United States, the main vector is the western black-legged tick (*Ixodes pacificus*).[52] The tendency of this tick species to feed predominantly on host species such as lizards that are resistant to *Borrelia* infection appears to diminish transmission of Lyme disease in the West.[53][54]

Transmission across the placenta during pregnancy has not been demonstrated, and no consistent pattern of teratogenicity or specific "congenital Lyme borreliosis" has been identified. As with a number of other spirochetal diseases, adverse pregnancy outcomes are possible with untreated infection; prompt treatment with antibiotics reduces or eliminates this risk.[55][56]

While Lyme spirochetes have been found in insects, as well as ticks,[57] reports of actual infectious transmission appear to be rare.[58] Lyme spirochete DNA has been found in semen[59] and breast milk,[60] but transmission has not been known to take place through sexual contact.[61] According to the CDC, live

spirochetes have not been found in breast milk, urine, or semen.[62] However, more recent studies published in 2014, suggest a link might exist.[63]

### Tick-borne coinfections

Ticks that transmit *B. burgdorferi* to humans can also carry and transmit several other parasites, such as *Theileria microti* and *Anaplasma phagocytophilum*, which cause the diseases babesiosis and human granulocytic anaplasmosis (HGA), respectively.[64] Among early Lyme disease patients, depending on their location, 2–12% will also have HGA and 2–40% will have babesiosis.[65] Ticks in certain regions, including the lands along the eastern Baltic Sea, also transmit tick-borne encephalitis.[66]

Coinfections complicate Lyme symptoms, especially diagnosis and treatment. It is possible for a tick to carry and transmit one of the coinfections and not *Borrelia*, making diagnosis difficult and often elusive. The Centers for Disease Control and Prevention studied 100 ticks in rural New Jersey, and found 55% of the ticks were infected with at least one of the pathogens.[67]

## Pathophysiology

*B. burgdorferi* can spread throughout the body during the course of the disease, and has been found in the skin, heart, joints, peripheral nervous system, and central nervous system.[47][68] Many of the signs and symptoms of Lyme disease are a consequence of the immune response to the spirochete in those tissues.[22]

*B. burgdorferi* is injected into the skin by the bite of an infected *Ixodes* tick. Tick saliva, which accompanies the spirochete into the skin during the feeding process, contains substances that disrupt the immune response at the site of the bite.[69] This provides a protective environment where the spirochete can establish infection. The spirochetes multiply and migrate outward within the dermis. The host inflammatory response to the bacteria in the skin causes the characteristic circular EM lesion.[47] Neutrophils, however, which are necessary to eliminate the spirochetes from the skin, fail to appear in the developing EM lesion. This allows the bacteria to survive and eventually spread throughout the body.[70]

Days to weeks following the tick bite, the spirochetes spread via the bloodstream to joints, heart, nervous system, and distant skin sites, where their presence gives rise to the variety of symptoms of the disseminated disease. The spread of *B. burgdorferi* is aided by the attachment of the host protease plasmin to the surface of the spirochete.[71]

If untreated, the bacteria may persist in the body for months or even years, despite the production of *B. burgdorferi* antibodies by the immune system.[72] The spirochetes may avoid the immune response by decreasing expression of surface proteins that are targeted by antibodies, antigenic variation of the VlsE surface protein, inactivating key immune components such as complement, and hiding in the extracellular matrix, which may interfere with the function of immune factors.[73][74]

In the brain, *B. burgdorferi* may induce astrocytes to undergo astrogliosis (proliferation followed by apoptosis), which may contribute to neurodysfunction.[75] The spirochetes may also induce host cells to secrete quinolinic acid, which stimulates the NMDA receptor on nerve cells, which may account for the fatigue and malaise observed with Lyme encephalopathy.[76] In addition, diffuse white matter pathology during Lyme encephalopathy may disrupt gray matter connections, and could account for deficits in attention, memory, visuospatial ability, complex cognition, and emotional status. White matter disease may have a greater potential for recovery than gray matter disease, perhaps because the neuronal loss is less common. Resolution of MRI white matter hyperintensities after antibiotic treatment has been observed.[77]

Tryptophan, a precursor to serotonin, appears to be reduced within the central nervous system in a number of infectious diseases that affect the brain, including Lyme.[78] Researchers are investigating if this neurohormone secretion is the cause of neuropsychiatric disorders developing in some patients with borreliosis.[79]

## Immunological studies

Exposure to the *Borrelia* bacterium during Lyme disease possibly causes a long-lived and damaging inflammatory response,[80] a form of pathogen-induced autoimmune disease.[81] The production of this reaction might be due to a form of molecular mimicry, where *Borrelia* avoids being killed by the immune system by resembling normal parts of the body's tissues.[82][83]

Chronic symptoms from an autoimmune reaction could explain why some symptoms persist even after the spirochetes have been eliminated from the body. This hypothesis may explain why chronic arthritis persists after antibiotic therapy, similar to rheumatic fever, but its wider application is controversial.[84][85]

# Diagnosis

Lyme disease is diagnosed clinically based on symptoms, objective physical findings (such as EM, facial palsy, or arthritis), or a history of possible exposure to infected ticks, as well as serological blood tests. The EM rash is not always a bull's eye, i.e., it can be solid red. When making a diagnosis of Lyme disease, health care providers should consider other diseases that may cause similar illnesses. Not all individuals infected with Lyme disease develop the characteristic bull's-eye rash, and many may not recall a tick bite.[86]

Because of the difficulty in culturing *Borrelia* bacteria in the laboratory, diagnosis of Lyme disease is typically based on the clinical exam findings and a history of exposure to endemic Lyme areas.[43] The EM rash, which does not occur in all cases, is considered sufficient to establish a diagnosis of Lyme disease even when serologic blood tests are negative.[87][88] Serological testing can be used to support a clinically suspected case, but is not diagnostic by itself.[43]

Diagnosis of late-stage Lyme disease is often complicated by a multifaceted appearance and nonspecific symptoms, prompting one reviewer to call Lyme the new "great imitator".[89] Lyme disease may be misdiagnosed as multiple sclerosis, rheumatoid arthritis, fibromyalgia, chronic fatigue syndrome, lupus, Crohn's disease, HIV, or other autoimmune and neurodegenerative diseases. As all people with later-stage infection will have a positive antibody test, simple blood tests can exclude Lyme disease as a possible cause of a person's symptoms.[90]

## Laboratory testing

Several forms of laboratory testing for Lyme disease are available, some of which have not been adequately validated. The most widely used tests are serologies, which measure levels of specific antibodies in a patient's blood. These tests may be negative in early infection as the body may not have produced a significant quantity of antibodies, but they are considered a reliable aid in the diagnosis of later stages of Lyme disease.[91] Serologic tests for Lyme disease are of limited use in people lacking objective signs of Lyme disease because of false positive results and cost.[92]

The serological laboratory tests most widely available and employed are the Western blot and ELISA. A two-tiered protocol is recommended by the Centers for Disease Control and Prevention: the sensitive ELISA test is performed first, and if it is positive or equivocal, then the more specific Western blot is run.[93] The reliability of testing in diagnosis remains controversial.[43] Studies show the Western blot IgM has a specificity of 94–96% for people with clinical symptoms of early Lyme disease.[94][95] The initial ELISA test has a sensitivity of about 70%, and in two-tiered testing, the overall sensitivity is only 64%, although this rises to 100% in the subset of people with disseminated symptoms, such as arthritis.[96]

Erroneous test results have been widely reported in both early and late stages of the disease, and can be caused by several factors, including antibody cross-reactions from other infections, including Epstein–Barr virus and cytomegalovirus,[97] as well as herpes simplex virus.[98] The overall rate of false positives is low, only about 1 to 3%, in comparison to a false-negative rate of up to 36% in the early stages of infection using two-tiered testing.[96]

Polymerase chain reaction (PCR) tests for Lyme disease have also been developed to detect the genetic material (DNA) of the Lyme disease spirochete. PCR tests are susceptible to false positive results from poor laboratory technique.[99] Even when properly performed, PCR often shows false negative results with blood and cerebrospinal fluid specimens.[100] Hence, PCR is not widely performed for diagnosis of Lyme disease, but it may have a role in the diagnosis of Lyme arthritis because it is a highly sensitive way of detecting *ospA* DNA in synovial fluid.[101]

Culture or PCR are the current means for detecting the presence of the organism, as serologic studies only test for antibodies of *Borrelia*. OspA antigens, shedded by live Borrelia bacteria into urine, are a promising technique being studied.[102] The use of nanotrap particles for their detection is being looked at and the OspA has been linked to active symptoms of Lyme.[103][104] High titers of either immunoglobulin G (IgG) or immunoglobulin M (IgM) antibodies to *Borrelia* antigens indicate disease, but lower titers can be misleading, because the IgM antibodies may remain after the initial infection, and IgG antibodies may remain for years.[105]

Western blot, ELISA, and PCR can be performed by either blood test via venipuncture or cerebrospinal fluid (CSF) via lumbar puncture. Though lumbar puncture is more definitive of diagnosis, antigen capture in the CSF is much more elusive; reportedly, CSF yields positive results in only 10–30% of affected individuals cultured. The diagnosis of neurologic infection by *Borrelia* should not be excluded solely on the basis of normal routine CSF or negative CSF antibody analyses.[106]

New techniques for clinical testing of *Borrelia* infection have been developed, such as LTT-MELISA,[107] although the results of studies are contradictory. The first peer reviewed study assessing the diagnostic sensitivity and specificity of the test was presented in 2012 and demonstrated potential for LTT to become a supportive diagnostic tool.[108] In 2014, research of LTT-MELISA concluded that it is "sensible" to include the LTT test in the diagnostic protocol for putative European-acquired Lyme borreliosis infections.[109] Other diagnostic techniques, such as focus floating microscopy, are under investigation.[110] New research indicates chemokine CXCL13 may also be a possible marker for neuroborreliosis.[111]

Some laboratories offer Lyme disease testing using assays whose accuracy and clinical usefulness have not been adequately established. These tests include urine antigen tests, PCR tests on urine, immunofluorescent staining for cell-wall-deficient forms of *B. burgdorferi*, and lymphocyte transformation tests. The CDC does not recommend these tests, and stated their use is "of great concern and is strongly discouraged".[100]

### Imaging

Neuroimaging is controversial in whether it provides specific patterns unique to neuroborreliosis, but may aid in differential diagnosis and in understanding the pathophysiology of the disease.[112] Though controversial, some evidence shows certain neuroimaging tests can provide data that are helpful in the diagnosis of a patient. Magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) are two of the tests that can identify abnormalities in the brain of a patient affected with this disease. Neuroimaging findings in an MRI include lesions in the periventricular white matter, as well as enlarged ventricles and cortical atrophy. The findings are considered somewhat unexceptional because the lesions have been found to be reversible following antibiotic treatment. Images produced using SPECT show numerous areas where an insufficient amount of blood is being delivered the cortex and subcortical white matter. However, SPECT images are known to be nonspecific because they show a heterogeneous pattern in the imaging. The abnormalities seen in the SPECT images are very similar to those seen in people with cerebral vacuities and Creutzfeldt–Jakob disease, which makes them questionable.[113]

## Prevention

Protective clothing includes a hat, long-sleeved shirt, and long pants tucked into socks or boots. Light-colored clothing makes the tick more easily visible before it attaches itself. People should use special care in

handling and allowing outdoor pets inside homes because they can bring ticks into the house. People who work in areas with woods, bushes, leaf litter, and tall grass are at risk of becoming infected with Lyme at work. Employers can reduce the risk for employees by providing education on Lyme transmission and infection risks, and about how to check themselves for ticks on the groin, armpits, and hair. Work clothing used in risky areas should be washed in hot water and dried in a hot dryer to kill any ticks.[114]

Permethrin sprayed on clothing kills ticks on contact, and is sold for this purpose. According to the CDC, only DEET is effective at repelling ticks.[115]

## Management of host animals

Lyme and other deer tick-borne diseases can sometimes be reduced by greatly reducing the deer population on which the adult ticks depend for feeding and reproduction. Lyme disease cases fell following deer eradication on an island, Monhegan, Maine[116] and following deer control in Mumford Cove, Connecticut.[117] It is worth noting that eliminating deer may lead to a temporary increase in tick density.[118]

For example, in the U.S., reducing the deer population to levels of 8 to 10 per square mile (from the current levels of 60 or more deer per square mile in the areas of the country with the highest Lyme disease rates), may reduce tick numbers and reduce the spread of Lyme and other tick-borne diseases.[119] However, such a drastic reduction may be very difficult to implement in many areas, and low to moderate densities of deer or other large mammal hosts may continue to feed sufficient adult ticks to maintain larval densities at high levels. Routine veterinary control of ticks of domestic animals, including livestock, by use of acaricides can contribute to reducing exposure of humans to ticks.

Action can be taken to avoid getting bitten by ticks by using insect repellants, for example, those that contain DEET. DEET-containing repellants are thought to be moderately effective in the prevention of tick bites.[120]

In Europe known reservoirs of *Borrelia burgdorferi* were 9 small mammals, 7 medium-sized mammals and 16 species of birds (including passerines, sea-birds and pheasants).[121] These animals seem to transmit spirochetes to ticks and thus participate in the natural circulation of B. burgdorferi in Europe. The house mouse is also suspected as well as other species of small rodents, particularly in Eastern Europe and Russia.[121]
"The reservoir species that contain the most pathogens are the European roe deer *Capreolus capreolus*;[122] "*it does not appear to serve as a major reservoir of B. burgdorferi*" thought Jaenson & al. (1992)[123] (incompetent host for *B. burgdorferi* and TBE virus) but it is important for feeding the ticks,[124] as red deer and wild boars (*Sus scrofa*),[125] in which one *Rickettsia* and three *Borrelia* species were identified",[122] with high risks of coinfection in roe deer.[126] Nevertheless, in the 2000s, in roe deer in Europe " *two species of Rickettsia and two species of Borrelia were identified*".[125]

## Vaccination

A recombinant vaccine against Lyme disease, based on the outer surface protein A (ospA) of *B. burgdorferi*, was developed by SmithKline Beecham. In clinical trials involving more than 10,000 people, the vaccine, called LYMErix, was found to confer protective immunity to *Borrelia* in 76% of adults and 100% of children with only mild or moderate and transient adverse effects.[127] LYMErix was approved on the basis of these trials by the Food and Drug Administration (FDA) on December 21, 1998.

Following approval of the vaccine, its entry in clinical practice was slow for a variety of reasons, including its cost, which was often not reimbursed by insurance companies.[128] Subsequently, hundreds of vaccine recipients reported they had developed autoimmune side effects. Supported by some patient advocacy groups, a number of class-action lawsuits were filed against GlaxoSmithKline, alleging the vaccine had caused these health problems. These claims were investigated by the FDA and the Centers for Disease Control, which found no connection between the vaccine and the autoimmune complaints.[129]

Despite the lack of evidence that the complaints were caused by the vaccine, sales plummeted and LYMErix

was withdrawn from the U.S. market by GlaxoSmithKline in February 2002,[130] in the setting of negative media coverage and fears of vaccine side effects.[129][131] The fate of LYMErix was described in the medical literature as a "cautionary tale";[131] an editorial in *Nature* cited the withdrawal of LYMErix as an instance in which "unfounded public fears place pressures on vaccine developers that go beyond reasonable safety considerations."[132] The original developer of the OspA vaccine at the Max Planck Institute told *Nature*: "This just shows how irrational the world can be... There was no scientific justification for the first OspA vaccine LYMErix being pulled."[129]

New vaccines are being researched using outer surface protein C (OspC) and glycolipoprotein as methods of immunization.[133][134] Vaccines have been formulated and approved for prevention of Lyme disease in dogs. Currently, three Lyme disease vaccines are available. LymeVax, formulated by Fort Dodge Laboratories, contains intact dead spirochetes which expose the host to the organism. Galaxy Lyme, Intervet-Schering-Plough's vaccine, targets proteins OspC and OspA. The OspC antibodies kill any of the bacteria that have not been killed by the OspA antibodies. Canine Recombinant Lyme, formulated by Merial, generates antibodies against the OspA protein so a tick feeding on a vaccinated dog draws in blood full of anti-OspA antibodies, which kill the spirochetes in the tick's gut before they are transmitted to the dog.[135]

### Tick removal

Removal of a tick using tweezers

Attached ticks should be removed promptly, as removal within 36 hours can reduce transmission rates.[136] Folk remedies for tick removal tend to be ineffective, offer no advantages in preventing the transfer of disease, and may increase the risks of transmission or infection.[137] The best method is simply to pull the tick out with tweezers as close to the skin as possible, without twisting, and avoiding crushing the body of the tick or removing the head from the tick's body.[138] The risk of infection increases with the time the tick is attached, and if a tick is attached for fewer than 24 hours, infection is unlikely. However, since these ticks are very small, especially in the nymph stage, prompt detection is quite difficult.[136] The Australian Society of Clinical Immunology recommends against using tweezers to remove ticks but rather to kill the tick first by using a product to rapidly freeze the tick to prevent it from injecting more allergen-containing saliva. In a tick allergic person, the tick should be killed and removed in a safe place (e.g. an emergency department of a hospital).[139]

### Preventive antibiotics

The risk of infectious transmission increases with the duration of tick attachment.[140] It requires between 36 and 48 hours of attachment for the bacteria that causes Lyme to travel from within the tick into its saliva.[140] If a deer tick that is sufficiently likely to be carrying *Borrelia* is found attached to a person and removed, and if the tick has been attached for 36 hours or is engorged, a single dose of doxycycline administered within the 72 hours after removal may reduce the risk of Lyme disease. It is not generally recommended for all people bitten, as development of infection is rare: about 50 bitten people would have to be treated this way to prevent one case of erythema migrans (i.e. the typical rash found in about 70-80% of people infected).[1][140]

## Treatment

Antibiotics are the primary treatment.[1][140] The specific approach to their use is dependent on the individual affected and the stage of the disease.[140] For most people with early localized infection, oral administration of doxycycline is widely recommended as the first choice, as it is effective against not only *Borrelia* bacteria but also a variety of other illnesses carried by ticks.[140] Doxycycline is contraindicated in children younger than eight years of age and women who are pregnant or breastfeeding;[140] alternatives

to doxycycline are amoxicillin, cefuroxime axetil, and azithromycin.[140] Individuals with early disseminated or late infection may have symptomatic cardiac disease, refractory Lyme arthritis, or neurologic symptoms like meningitis or encephalitis.[140] Intravenous administration of ceftriaxone is recommended as the first choice in these cases;[140] cefotaxime and doxycycline are available as alternatives.[140]

These treatment regimens last from one to four weeks.[140] If joint swelling persists or returns, a second round of antibiotics may be considered.[140] Outside of that, a prolonged antibiotic regimen lasting more than 28 days is not recommended as no clinical evidence shows it to be effective.[140][141] IgM and IgG antibody levels may be elevated for years even after successful treatment with antibiotics.[140] As antibody levels are not indicative of treatment success, testing for them is not recommended.[140]

# Prognosis

For early cases, prompt[*specify*] treatment is usually curative.[142] However, the severity and treatment of Lyme disease may be complicated due to late diagnosis, failure of antibiotic treatment, and simultaneous infection with other tick-borne diseases (coinfections), including ehrlichiosis, babesiosis, and immune suppression[*citation needed*] in the patient.

A meta-analysis published in 2005 found some patients with Lyme disease have fatigue, joint or muscle pain, and neurocognitive symptoms persisting for years, despite antibiotic treatment.[143] Patients with late stage Lyme disease have been shown to experience a level of physical disability equivalent to that seen in congestive heart failure.[144]

In dogs, a serious long-term prognosis may result in glomerular disease,[145] which is a category of kidney damage that may cause chronic kidney disease.[135] Dogs may also experience chronic joint disease if the disease is left untreated. However, the majority of cases of Lyme disease in dogs result in a complete recovery with, and sometimes without, treatment with antibiotics.[146][*verification needed*] In rare cases, Lyme disease can be fatal to both humans and dogs.[147]

# Epidemiology

Lyme disease occurs regularly in Northern Hemisphere temperate regions.[148]

Countries with reported Lyme disease cases.

## Africa

In northern Africa, *B. burgdorferi sensu lato* has been identified in Morocco, Algeria, Egypt and Tunisia.[149][150][151]

Lyme disease in sub-Saharan Africa is presently unknown, but evidence indicates it may occur in humans in this region. The abundance of hosts and tick vectors would favor the establishment of Lyme infection in Africa.[152] In East Africa, two cases of Lyme disease have been reported in Kenya.[153]

## Asia

*B. burgdorferi sensu lato*-infested ticks are being found more frequently in Japan, as well as in northwest China, Nepal, Thailand and far eastern Russia.[154][155] *Borrelia* has also been isolated in Mongolia.[156]

## Europe

In Europe, Lyme disease is caused by infection with one or more pathogenic European genospecies of the spirochaete *B. burgdorferi sensu lato*, mainly transmitted by the tick *Ixodes ricinus*.[157] Cases of *B. burgdorferi sensu lato*-infected ticks are found predominantly in central Europe, particularly in Slovenia and Austria, but have been isolated in almost every country on the continent.[158] Incidence in southern Europe, such as Italy and Portugal, is much lower.[159]

## United Kingdom

In the United Kingdom the number of laboratory confirmed cases of Lyme disease has been rising steadily since voluntary reporting was introduced in 1986[160] when 68 cases were recorded in the UK and Republic of Ireland combined.[161] In the UK there were 23 confirmed cases in 1988 and 19 in 1990,[162] but 973 in 2009[160] and 953 in 2010.[163] Provisional figures for the first 3 quarters of 2011 show a 26% increase on the same period in 2010.[164]

It is thought, however, that the actual number of cases is significantly higher than suggested by the above figures, with the UK's Health Protection Agency estimating that there are between 2,000 and 3,000 cases per year,[163] (with an average of around 15% of the infections acquired overseas[160]), while Dr Darrel Ho-Yen, Director of the Scottish Toxoplasma Reference Laboratory and National Lyme Disease Testing Service, believes that the number of confirmed cases should be multiplied by 10 "to take account of wrongly diagnosed cases, tests giving false results, sufferers who weren't tested, people who are infected but not showing symptoms, failures to notify and infected individuals who don't consult a doctor."[165][166]

Despite Lyme disease (Borrelia burgdorferi infection) being a notifiable disease in Scotland[167] since January 1990[168] which should therefore be reported on the basis of clinical suspicion, it is believed that many GPs are unaware of the requirement.[169] Mandatory reporting, limited to laboratory test results only, was introduced throughout the UK in October 2010, under the Health Protection (Notification) Regulations 2010.[160]

Although there is a greater incidence of Lyme disease in the New Forest, Salisbury Plain, Exmoor, the South Downs, parts of Wiltshire and Berkshire, Thetford Forest[170] and the West coast and islands of Scotland[171] infected ticks are widespread, and can even be found in the parks of London.[162][172] A 1989 report found that 25% of forestry workers in the New Forest were seropositive, as were between 2% and 4-5% of the general local population of the area.[173][174]

Tests on pet dogs, carried out throughout the country in 2009 indicated that around 2.5% of ticks in the UK may be infected, considerably higher than previously thought.[175][176] It is thought that global warming may lead to an increase in tick activity in the future, as well as an increase in the amount of time that people spend in public parks, thus increasing the risk of infection.[177]

## North America

Many studies in North America have examined ecological and environmental correlates of Lyme disease prevalence. A 2005 study using climate suitability modelling of *I. scapularis* projected that climate change would cause an overall 213% increase in suitable vector habitat by the year 2080, with northward expansions in Canada, increased suitability in the central U.S., and decreased suitable habitat and vector retraction in the southern U.S.[178] A 2008 review of published studies concluded that the presence of forests or forested areas was the only variable that consistently elevated the risk of Lyme disease whereas other environmental variables showed little or no concordance between studies.[179] The authors argued that the factors influencing tick density and human risk between sites are still poorly understood, and that future studies should be conducted over longer time periods, become more standardized across regions, and incorporate existing knowledge of regional Lyme disease ecology.[179]

## Canada

Owing to changing climate, the range of ticks able to carry Lyme disease has expanded from a limited area

of Ontario to include areas of southern Quebec, Manitoba, northern Ontario, southern New Brunswick, southwest Nova Scotia and limited parts of Saskatchewan and Alberta, as well as British Columbia. Cases have been reported as far east as the island of Newfoundland.[180][181][182] A model-based prediction by Leighton *et al.* (2012) suggests that the range of the *I. scapularis* tick will expand into Canada by 46 km/year over the next decade, with warming climatic temperatures as the main driver of increased speed of spread.[183]

## Mexico

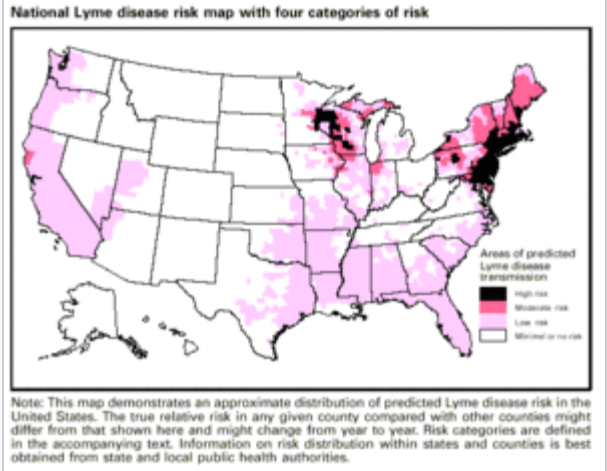
A 2007 study suggests *Borrelia burgdorferi* infections are endemic to Mexico, from four cases reported between 1999 and 2000.[184]

## United States

Each year, approximately 30,000 new cases are reported to the CDC however, this number is likely underestimated. The CDC is currently conducting research on evaluation and diagnostics of the disease and preliminary results suggest the number of new cases to be around 300,000.[185][186]

Lyme disease is the most common tick-borne disease in North America and Europe, and one of the fastest-growing infectious diseases in the United States. Of cases reported to the United States CDC, the ratio of Lyme disease infection is 7.9 cases for every 100,000 persons. In the ten states where Lyme disease is most common, the average was 31.6 cases for every 100,000 persons for the year 2005.[187][188][189]

Although Lyme disease has been reported in all states[185][190] about 99% of all reported cases are confined to just five geographic areas (New England, Mid-Atlantic, East-North Central, South Atlantic, and West North-Central).[191] New 2011 CDC Lyme case definition guidelines are used to determine confirmed CDC surveillance cases.[192]




CDC map showing the risk of Lyme disease in the United States, particularly its concentration in the Northeast Megalopolis and western Wisconsin.

Effective January 2008, the CDC gives equal weight to laboratory evidence from 1) a positive culture for *B. burgdorferi*; 2) two-tier testing (ELISA screening and Western blot confirming); or 3) single-tier IgG (old infection) Western blot.[193] Previously, the CDC only included laboratory evidence based on (1) and (2) in their surveillance case definition. The case definition now includes the use of Western blot without prior ELISA screen.[193]

The number of reported cases of the disease has been increasing, as are endemic regions in North America. For example, *B. burgdorferi sensu lato* was previously thought to be hindered in its ability to be maintained in an enzootic cycle in California, because it was assumed the large lizard population would dilute the prevalence of *B. burgdorferi* in local tick populations; this has since been brought into question, as some evidence has suggested lizards can become infected.[194]

Except for one study in Europe,[195] much of the data implicating lizards is based on DNA detection of the spirochete and has not demonstrated lizards are able to infect ticks feeding upon them.[194][196][197][198] As some experiments suggest lizards are refractory to infection with *Borrelia*, it appears likely their involvement in the enzootic cycle is more complex and species-specific.[54]

While *B. burgdorferi* is most associated with ticks hosted by white-tailed deer and white-footed mice, *Borrelia afzelii* is most frequently detected in rodent-feeding vector ticks, and *Borrelia garinii* and *Borrelia valaisiana* appear to be associated with birds. Both rodents and birds are competent reservoir hosts for *B. burgdorferi sensu stricto*. The resistance of a genospecies of Lyme disease spirochetes to the bacteriolytic activities of the alternative complement pathway of various host species may determine its reservoir host [*citation needed*]

association.

Several similar but apparently distinct conditions may exist, caused by various species or subspecies of *Borrelia* in North America. A regionally restricted condition that may be related to *Borrelia* infection is southern tick-associated rash illness (STARI), also known as Masters' disease. *Amblyomma americanum*, known commonly as the lone-star tick, is recognized as the primary vector for STARI. In some parts of the geographical distribution of STARI, Lyme disease is quite rare (e.g., Arkansas), so patients in these regions experiencing Lyme-like symptoms—especially if they follow a bite from a lone-star tick—should consider STARI as a possibility. It is generally a milder condition than Lyme and typically responds well to antibiotic treatment.[*citation needed*]

In recent years there have been 5 to 10 cases a year of a disease similar to Lyme occurring in Montana. It occurs primarily in pockets along the Yellowstone River in central Montana. People have developed a red bull's-eye rash around a tick bite followed by weeks of fatigue and a fever.[190]

Lyme disease prevalence is comparable among males and females. A wide range of age groups is affected, though the number of cases is highest among 10- to 19-year-olds. For unknown reasons, Lyme disease is seven times more common among Asians.[199]

### South America

In South America, tick-borne disease recognition and occurrence is rising. In Brazil, a Lyme-like disease known as Baggio–Yoshinari syndrome was identified, caused by microorganisms that do not belong to the *B. burgdorferi sensu lato* complex and transmitted by ticks of the *Amblyomma* and *Rhipicephalus* genera.[200] The first reported case of BYS in Brazil was made in 1992 in Cotia, São Paulo.[201] *B. burgdorferi sensu stricto* antigens in patients have been identified in Colombia and Bolivia.[*citation needed*]

## History

The evolutionary history of *Borrelia burgdorferi* genetics has been the subject of recent studies. One study has found that prior to the reforestation that accompanied post-colonial farm abandonment in New England and the wholesale migration into the mid-west that occurred during the early 19th century, Lyme disease was present for thousands of years in America and had spread along with its tick hosts from the Northeast to the Midwest.[202]

John Josselyn, who visited New England in 1638 and again from 1663–1670, wrote "there be infinite numbers of tikes hanging upon the bushes in summer time that will cleave to man's garments and creep into his breeches eating themselves in a short time into the very flesh of a man. I have seen the stockins of those that have gone through the woods covered with them."[203]

This is also confirmed by the writings of Peter Kalm, a Swedish botanist who was sent to America by Linnaeus, and who found the forests of New York "abound" with ticks when he visited in 1749. When Kalm's journey was retraced 100 years later, the forests were gone and the Lyme bacterium had probably become isolated to a few pockets along the northeast coast, Wisconsin, and Minnesota.[204]

Perhaps the first detailed description of what is now known as Lyme disease appeared in the writings of Reverend Dr. John Walker after a visit to the Island of Jura (Deer Island) off the west coast of Scotland in 1764.[205] He gives a good description both of the symptoms of Lyme disease (with "exquisite pain [in] the interior parts of the limbs") and of the tick vector itself, which he describes as a "worm" with a body which is "of a reddish colour and of a compressed shape with a row of feet on each side" that "penetrates the skin". Many people from this area of Great Britain emigrated to North America between 1717 and the end of the 18th century.

The examination of preserved museum specimens has found *Borrelia* DNA in an infected *Ixodes ricinus* tick from Germany that dates back to 1884, and from an infected mouse from Cape Cod that died in 1894.[204] The 2010 autopsy of Ötzi the Iceman, a 5,300-year-old mummy, revealed the presence of the DNA sequence of *Borrelia burgdorferi* making him the earliest known human with Lyme disease.[206]

The early European studies of what is now known as Lyme disease described its skin manifestations. The first study dates to 1883 in Breslau, Germany (now Wrocław, Poland), where physician Alfred Buchwald described a man who had suffered for 16 years with a degenerative skin disorder now known as acrodermatitis chronica atrophicans.[207]

At a 1909 research conference, Swedish dermatologist Arvid Afzelius presented a study about an expanding, ring-like lesion he had observed in an older woman following the bite of a sheep tick. He named the lesion *erythema migrans*.[207] The skin condition now known as borrelial lymphocytoma was first described in 1911.[208]

Neurological problems following tick bites were recognized starting in the 1920s. French physicians Garin and Bujadoux described a farmer with a painful sensory radiculitis accompanied by mild meningitis following a tick bite. A large, ring-shaped rash was also noted, although the doctors did not relate it to the meningoradiculitis. In 1930, the Swedish dermatologist Sven Hellerström was the first to propose EM and neurological symptoms following a tick bite were related.[209] In the 1940s, German neurologist Alfred Bannwarth described several cases of chronic lymphocytic meningitis and polyradiculoneuritis, some of which were accompanied by erythematous skin lesions.

Carl Lennhoff, who worked at the Karolinska Institute in Sweden, believed many skin conditions were caused by spirochetes. In 1948, he used a special stain to microscopically observe what he believed were spirochetes in various types of skin lesions, including EM.[210] Although his conclusions were later shown to be erroneous, interest in the study of spirochetes was sparked. In 1949, Nils Thyresson, who also worked at the Karolinska Institute, was the first to treat ACA with penicillin.[211] In the 1950s, the relationship among tick bite, lymphocytoma, EM and Bannwarth's syndrome was recognized throughout Europe leading to the widespread use of penicillin for treatment in Europe.[212][213]

In 1970, a dermatologist in Wisconsin named Rudolph Scrimenti recognized an EM lesion in a patient after recalling a paper by Hellerström that had been reprinted in an American science journal in 1950. This was the first documented case of EM in the United States. Based on the European literature, he treated the patient with penicillin.[214]

The full syndrome now known as Lyme disease was not recognized until a cluster of cases originally thought to be juvenile rheumatoid arthritis was identified in three towns in southeastern Connecticut in 1975, including the towns Lyme and Old Lyme, which gave the disease its popular name.[215] This was investigated by physicians David Snydman and Allen Steere of the Epidemic Intelligence Service, and by others from Yale University, including Dr. Stephen Malawista, who is credited as a co-discover of the disease.[216] The recognition that the patients in the United States had EM led to the recognition that "Lyme arthritis" was one manifestation of the same tick-borne condition known in Europe.[217]

Before 1976, the elements of *B. burgdorferi sensu lato* infection were called or known as tick-borne meningopolyneuritis, Garin-Bujadoux syndrome, Bannwarth syndrome, Afzelius' disease,[218] Montauk Knee or sheep tick fever. Since 1976 the disease is most often referred to as Lyme disease,[219][220] Lyme borreliosis or simply borreliosis.[*citation needed*]

In 1980, Steere, *et al.*, began to test antibiotic regimens in adult patients with Lyme disease.[221] In the same year, New York State Health Dept. epidemiologist Jorge Benach provided Willy Burgdorfer, a researcher at the Rocky Mountain Biological Laboratory, with collections of *I. dammini* [*scapularis*] from Shelter Island, NY, a known Lyme-endemic area as part of an ongoing investigation of Rocky Mountain spotted fever. In examining the ticks for rickettsiae, Burgdorfer noticed "poorly stained, rather long, irregularly coiled spirochetes." Further examination revealed spirochetes in 60% of the ticks. Burgdorfer credited his familiarity with the European literature for his realization that the spirochetes might be the "long-sought cause of ECM and Lyme disease." Benach supplied him with more ticks from Shelter Island and sera from patients diagnosed with Lyme disease. University of Texas Health Science Center researcher Alan Barbour "offered his expertise to culture and immunochemically characterize the organism." Burgdorfer subsequently confirmed his discovery by isolating, from patients with Lyme disease, spirochetes identical to those found in ticks.[222] In June 1982, he published his findings in Science, and the spirochete was named *Borrelia burgdorferi* in his honor.[223]

After the identification of *B. burgdorferi* as the causative agent of Lyme disease, antibiotics were selected for testing, guided by *in vitro* antibiotic sensitivities, including tetracycline antibiotics, amoxicillin, cefuroxime axetil, intravenous and intramuscular penicillin and intravenous ceftriaxone.[224][225] The mechanism of tick transmission was also the subject of much discussion. *B. burgdorferi* spirochetes were identified in tick saliva in 1987, confirming the hypothesis that transmission occurred via tick salivary glands.[226]

Jonathan Edlow, Professor of Medicine at Harvard Medical School, quotes the late Ed Masters (discoverer of STARI, a Lyme-like illness) in his book *Bull's-Eye*, on the history of Lyme disease. Edlow writes:

> Masters points out that the "track record" of the "conventional wisdom" regarding Lyme disease is not very good: "First off, they said it was a new disease, which it wasn't. Then it was thought to be viral, but it isn't. Then it was thought that sero-negativity didn't exist, which it does. They thought it was easily treated with short courses of antibiotics, which sometimes it isn't. Then it was only the *Ixodes dammini* tick, which we now know is not even a separate valid tick species. If you look throughout the history, almost every time a major dogmatic statement has been made about what we 'know' about this disease, it was subsequently proven wrong or underwent major modifications."[227]

# Society and culture

Urbanization and other anthropogenic factors can be implicated in the spread of Lyme disease to humans. In many areas, expansion of suburban neighborhoods has led to gradual deforestation of surrounding wooded areas and increased border contact between humans and tick-dense areas. Human expansion has also resulted in a reduction of predators that hunt deer as well as mice, chipmunks and other small rodents —the primary reservoirs for Lyme disease. As a consequence of increased human contact with host and vector, the likelihood of transmission of the disease has greatly increased.[228][229] Researchers are investigating possible links between global warming and the spread of vector-borne diseases, including Lyme disease.[230]

## Controversy

*Main article: Lyme disease controversy*

The term "chronic Lyme disease" is controversial and not recognized in the medical literature,[231] and most medical authorities advise against long-term antibiotic treatment for Lyme disease.[92][232][233] Studies have shown that most people diagnosed with "chronic Lyme disease" either have no objective evidence of previous or current infection with *B. burgdorferi* or are people who should be classified as having post-treatment Lyme disease syndrome (PTLDS), which is defined as continuing or relapsing non-specific symptoms (such as fatigue, musculoskeletal pain, and cognitive complaints) in a person previously treated for Lyme disease.[234]

## Notable cases

Singer Avril Lavigne was diagnosed in December 2014 with Lyme disease.[235] In September 2015, billionaire John Caudwell discussed his family's experience with Lyme.[236] *The Punk Singer*, a 2013 documentary film by Sini Anderson, portrays feminist singer Kathleen Hanna's experience with late-stage Lyme disease.[237] Professional basketball player and WNBA MVP Elena Delle Donne has discussed her experience with Lyme.[238]

# Other animals

Prevention of Lyme disease is an important step in keeping dogs safe in endemic areas. Prevention education and a number of preventative measures are available. First, for dog owners who live near or who

often frequent tick-infested areas, routine vaccinations of their dogs is an important step.[239]

Another crucial preventive measure is the use of persistent acaricides, such as topical repellents or pesticides that contain triazapentadienes (Amitraz), phenylpyrazoles (Fipronil), or permethrin (pyrethroids).[240] These acaricides target primarily the adult stages of Lyme-carrying ticks and reduce the number of reproductively active ticks in the environment.[239] Formulations of these ingredients are available in a variety of topical forms, including spot-ons, sprays, powders, impregnated collars, solutions, and shampoos.[240]

Examination of a dog for ticks after being in a tick-infested area is an important precautionary measure to take in the prevention of Lyme disease. Key spots to examine include the head, neck, and ears.[241]

## Research

The National Institutes of Health have supported research into bacterial persistence.[242]

## References


1. ^ *a b c d e f g h i j k l m n o p q r* Shapiro, ED (1 May 2014). "Clinical practice. Lyme disease." (PDF). *The New England Journal of Medicine*. **370** (18): 1724–31. doi:10.1056/NEJMcp1314325. PMID 24785207.
2. ^ *a b c* "Signs and Symptoms of Lyme Disease". *cdc.gov*. January 11, 2013. Archived from the original on Jan 16, 2013. Retrieved 2 March 2015.
3. ^ Aucott JN (2015). "Posttreatment Lyme disease syndrome". *Infectious Disease Clinics of North America*. **29** (2): 309–23. doi:10.1016/j.idc.2015.02.012. PMID 25999226.
4. ^ Johnson RC (1996). "Borrelia". In Baron S et al. *Baron's Medical Microbiology* (4th ed.). Univ of Texas Medical Branch. ISBN 0-9631172-1-1. PMID 21413339.
5. ^ *a b* "Lyme disease transmission". *cdc.gov*. January 11, 2013. Retrieved 2 March 2015.
6. ^ Pritt, BS; Mead, PS; Johnson, DK; Neitzel, DF; Respicio Kingry, LB; Davis, JP; Schiffman, E; Sloan, LM; Schriefer, ME; Replogle, AJ; Paskewitz, SM; Ray, JA; Bjork, J; Steward, CR; Deedon, A; Lee, X; Kingry, LC; Miller, TK; Feist, MA; Theel, ES; Patel, R; Irish, CL; Petersen, JM (5 February 2016). "Identification of a novel pathogenic Borrelia species causing Lyme borreliosis with unusually high spirochaetaemia: a descriptive study.". *The Lancet. Infectious diseases*. doi:10.1016/S1473-3099(15)00464-8. PMID 26856777.
7. ^ "Lyme Disease Diagnosis and Testing". *cdc.gov*. January 10, 2013. Retrieved 2 March 2015.
8. ^ "Two-step Laboratory Testing Process". *cdc.gov*. November 15, 2011. Retrieved 2 March 2015.
9. ^ "Testing of Ticks". *cdc.gov*. June 4, 2013. Retrieved 2 March 2015.
10. ^ "Tick Removal". *cdc.gov*. June 23, 2014. Retrieved 2 March 2015.
11. ^ *a b* "Post-Treatment Lyme Disease Syndrome". *cdc.gov*. August 11, 2014. Retrieved 2 March 2015.
12. ^ *Regional Disease Vector Ecology Profile: Central Europe*. DIANE Publishing. April 2001. p. 136. ISBN 9781428911437.
13. ^ Berger, Stephen (2014). *Lyme disease: Global Status 2014 Edition*. GIDEON Informatics Inc. p. 7. ISBN 9781498803434.
14. ^ Williams, Carolyn (2007). *Infectious disease epidemiology : theory and practice* (2nd ed.). Sudbury, Mass.: Jones and Bartlett Publishers. p. 447. ISBN 9780763728793.
15. ^ "Willy Burgdorfer - obituary". *Daily Telegraph*. 1 December 2014. Retrieved 1 December 2014.
16. ^ Lantos PM (June 2015). "Chronic Lyme disease". *Infectious disease clinics of North America*. **29** (2): 325–40. doi:10.1016/j.idc.2015.02.006. PMC 4477530. PMID 25999227.
17. ^ Arthritis and Lyme Disease, WebMD Rheumatoid Arthritis Health Center, reviewed by David Zelman, MD on Oct. 1, 2012.
18. ^ *a b* *Lyme disease* at eMedicine
19. ^ Steere AC, Sikand VK, Schoen RT, Nowakowski J (August 2003). "Asymptomatic infection with Borrelia burgdorferi". *Clin. Infect. Dis.* **37** (4): 528–32. doi:10.1086/376914. PMID 12905137. (primary source)
20. ^ *a b c* Biesiada G, Czepiel J, Leśniak MR, Garlicki A, Mach T (Dec 20, 2012). "Lyme disease: review". *Arch Med Sci*. **8** (6): 978–82. doi:10.5114/aoms.2012.30948. PMC 3542482. PMID 23319969.
21. ^ Aucott JN, Crowder LA, Yedlin V, Kortte KB (2012). "Bull's-Eye and nontarget skin lesions of Lyme disease: an internet survey of identification of *erythema migrans*". *Dermatol Res Pract*. **2012**: 451727.

doi:10.1155/2012/451727. PMC 3485866. PMID 23133445. (primary source)
22. ^ a b c d Auwaerter PG, Aucott J, Dumler JS (January 2004). "Lyme borreliosis (Lyme disease): molecular and cellular pathobiology and prospects for prevention, diagnosis and treatment". *Expert Rev Mol Med*. **6** (2): 1–22. doi:10.1017/S1462399404007276. PMID 14987414.
23. ^ Steere AC, Dhar A, Hernandez J, et al. (January 2003). "Systemic symptoms without *erythema migrans* as the presenting picture of early Lyme disease". *Am. J. Med*. **114** (1): 58–62. doi:10.1016/S0002-9343(02)01440-7. PMID 12543291. (primary source)
24. ^ Dandache P, Nadelman RB (June 2008). "*Erythema migrans*". *Infect. Dis. Clin. North Am*. **22** (2): 235–60, vi. doi:10.1016/j.idc.2007.12.012. PMID 18452799.
25. ^ a b Stanek G, Strle F (June 2008). "Lyme disease: European perspective". *Infect. Dis. Clin. North Am*. **22** (2): 327–39, vii. doi:10.1016/j.idc.2008.01.001. PMID 18452805.
26. ^ Halperin JJ (June 2008). "Nervous system Lyme disease". *Infect. Dis. Clin. North Am*. **22** (2): 261–74, vi. doi:10.1016/j.idc.2007.12.009. PMID 18452800.
27. ^ Chabria SB, Lawrason J (2007). "Altered mental status, an unusual manifestation of early disseminated Lyme disease: A case report". *Journal of Medical Case Reports*. **1**: 62. doi:10.1186/1752-1947-1-62. PMC 1973078. PMID 17688693.
28. ^ Stanek G, Wormser GP, Gray J, Strle F (February 2012). "Lyme borreliosis". *Lancet*. **379** (9814): 461–73. doi:10.1016/S0140-6736(11)60103-7. PMID 21903253.
29. ^ Nau R, Christen HJ, Eiffert H (January 2009). "Lyme disease--current state of knowledge". *Dtsch Arztebl Int*. **106** (5): 72–81; quiz 82, I. doi:10.3238/arztebl.2009.0072. PMC 2695290. PMID 19562015.
30. ^ Bratton RL, Whiteside JW, Hovan MJ, Engle RL, Edwards FD (May 2008). "Diagnosis and treatment of Lyme disease". *Mayo Clinic Proceedings*. **83** (5): 566–71. doi:10.4065/83.5.566. PMID 18452688.
31. ^ Shadick NA, Phillips CB, Sangha O, et al. (December 1999). "Musculoskeletal and neurologic outcomes in patients with previously treated Lyme disease". *Annals of Internal Medicine*. **131** (12): 919–26. doi:10.7326/0003-4819-131-12-199912210-00003. PMID 10610642.
32. ^ Seltzer EG, Gerber MA, Cartter ML, Freudigman K, Shapiro ED (February 2000). "Long-term outcomes of persons with Lyme disease". *JAMA*. **283** (5): 609–16. doi:10.1001/jama.283.5.609. PMID 10665700.
33. ^ Fallon BA, Nields JA (November 1994). "Lyme disease: a neuropsychiatric illness". *Am J Psychiatry*. **151** (11): 1571–83. doi:10.1176/ajp.151.11.1571. PMID 7943444.
34. ^ Hess A, Buchmann J, Zettl UK, et al. (March 1999). "Borrelia burgdorferi central nervous system infection presenting as an organic schizophrenialike disorder". *Biol. Psychiatry*. **45** (6): 795. doi:10.1016/S0006-3223(98)00277-7. PMID 10188012.
35. ^ Puius YA, Kalish RA (June 2008). "Lyme arthritis: pathogenesis, clinical presentation, and management". *Infect. Dis. Clin. North Am*. **22** (2): 289–300, vi–vii. doi:10.1016/j.idc.2007.12.014. PMID 18452802.
36. ^ Mullegger RR (2004). "Dermatological manifestations of Lyme borreliosis". *Eur J Dermatol*. **14** (5): 296–309. PMID 15358567.
37. ^ Samuels DS; Radolf, JD, eds. (2010). "Chapter 6, Structure, Function and Biogenesis of the *Borrelia* Cell Envelope". *Borrelia: Molecular Biology, Host Interaction and Pathogenesis*. Caister Academic Press. ISBN 978-1-904455-58-5.
38. ^ Cutler SJ, Ruzic-Sabljic E, Potkonjak A (2016). "Emerging borreliae - Expanding beyond Lyme borreliosis". *Molecular and Cellular Probes*. doi:10.1016/j.mcp.2016.08.003. PMID 27523487.
39. ^ Stanek G, Reiter M (2011). "The expanding Lyme Borrelia complex - clinical significance of genomic species". *Clin Microbiol Infect*. **17** (4): 487–93. doi:10.1111/j.1469-0691.2011.03492.x. PMID 21414082.
40. ^ Schneider BS, Schriefer ME, Dietrich G, Dolan MC, Morshed MG, Zeidner NS (October 2008). "Borrelia bissettii isolates induce pathology in a murine model of disease". *Vector-Borne and Zoonotic Diseases*. **8** (5): 623–33. doi:10.1089/vbz.2007.0251. PMID 18454594.
41. ^ Rudenko N, Golovchenko M, Mokrácek A, et al. (October 2008). "Detection of Borrelia bissettii in cardiac valve tissue of a patient with endocarditis and aortic valve stenosis in the Czech Republic". *J. Clin. Microbiol*. **46** (10): 3540–3. doi:10.1128/JCM.01032-08. PMC 2566110. PMID 18650352.
42. ^ a b Tilly K, Rosa PA, Stewart PE (June 2008). "Biology of infection with Borrelia burgdorferi". *Infect. Dis. Clin. North Am*. **22** (2): 217–34, v. doi:10.1016/j.idc.2007.12.013. PMC 2440571. PMID 18452798.
43. ^ a b c d Ryan KJ; Ray CG, eds. (2004). *Sherris Medical Microbiology* (4th ed.). McGraw Hill. pp. 434–37. ISBN 0-8385-8529-9.
44. ^ a b Lo Re V, Occi JL, MacGregor RR (April 2004). "Identifying the vector of Lyme disease". *Am Fam Physician*. **69** (8): 1935–37. PMID 15117014.
45. ^ "Westport Weston Health District". 2004. Retrieved 2013-09-26.
46. ^ Hovius JW, van Dam AP, Fikrig E (September 2007). "Tick-host-pathogen interactions in Lyme borreliosis".

*Trends Parasitol*. **23** (9): 434–8. doi:10.1016/j.pt.2007.07.001 . PMID 17656156 .

47. ^ [a] [b] [c] Steere AC, Coburn J, Glickstein L (April 2004). "The emergence of Lyme disease". *J. Clin. Invest*. **113** (8): 1093–101. doi:10.1172/JCI21681. PMC 385417. PMID 15085185.
48. ^ de Mik EL, van Pelt W, Docters-van Leeuwen BD, van der Veen A, Schellekens JF, Borgdorff MW (April 1997). "The geographical distribution of tick bites and *erythema migrans* in general practice in The Netherlands". *Int J Epidemiol*. **26** (2): 451–7. doi:10.1093/ije/26.2.451. PMID 9169184.
49. ^ Sun Y, Xu R (2003). "Ability of Ixodes persulcatus, Haemaphysalis concinna and Dermacentor silvarum ticks to acquire and transstadially transmit Borrelia garinii". *Exp. Appl. Acarol*. **31** (1-2): 151–60. doi:10.1023/B:APPA.0000005119.30172.43. PMID 14756409.
50. ^ Ledin KE, Zeidner NS, Ribeiro JM, et al. (March 2005). "Borreliacidal activity of saliva of the tick Amblyomma americanum". *Med. Vet. Entomol*. **19** (1): 90–5. doi:10.1111/j.0269-283X.2005.00546.x. PMID 15752182.
51. ^ Masters EJ, Grigery CN, Masters RW (June 2008). "STARI, or Masters disease: Lone Star tick-vectored Lyme-like illness". *Infect. Dis. Clin. North Am*. **22** (2): 361–76, viii. doi:10.1016/j.idc.2007.12.010. PMID 18452807.
52. ^ Clark K (November 2004). "Borrelia species in host-seeking ticks and small mammals in northern Florida". *J. Clin. Microbiol*. **42** (11): 5076–86. doi:10.1128/JCM.42.11.5076-5086.2004. PMC 525154. PMID 15528699.
53. ^ Eisen L, Eisen RJ, Lane RS (December 2004). "The roles of birds, lizards, and rodents as hosts for the western black-legged tick Ixodes pacificus". *J. Vector Ecol*. **29** (2): 295–308. PMID 15709249.
54. ^ [a] [b] Lane RS, Mun J, Eisen L, Eisen RJ (August 2006). "Refractoriness of the western fence lizard (Sceloporus occidentalis) to the Lyme disease group spirochete Borrelia bissettii". *J. Parasitol*. **92** (4): 691–96. doi:10.1645/GE-738R1.1. PMID 16995383.
55. ^ Walsh CA, Mayer EW, Baxi LV; Mayer; Baxi (January 2007). "Lyme disease in pregnancy: case report and review of the literature". *Obstet Gynecol Surv*. **62** (1): 41–50. doi:10.1097/01.ogx.0000251024.43400.9a. PMID 17176487.
56. ^ Lakos A, Solymosi N (June 2010). "Maternal Lyme borreliosis and pregnancy outcome". *Int. J. Infect. Dis*. **14** (6): e494–98. doi:10.1016/j.ijid.2009.07.019. PMID 19926325.
57. ^ Magnarelli LA, Anderson JF (August 1988). "Ticks and biting insects infected with the etiologic agent of Lyme disease, Borrelia burgdorferi". *J. Clin. Microbiol*. **26** (8): 1482–6. PMC 266646. PMID 3170711.
58. ^ Luger SW (June 1990). "Lyme disease transmitted by a biting fly". *N. Engl. J. Med*. **322** (24): 1752. doi:10.1056/NEJM199006143222415. PMID 2342543.
59. ^ Bach G (2001). "Recovery of Lyme spirochetes by PCR in semen samples of previously diagnosed Lyme disease patients". *14th International Scientific Conference on Lyme Disease*.
60. ^ Schmidt BL, Aberer E, Stockenhuber C, Klade H, Breier F, Luger A (March 1995). "Detection of Borrelia burgdorferi DNA by polymerase chain reaction in the urine and breast milk of patients with Lyme borreliosis". *Diagn. Microbiol. Infect. Dis*. **21** (3): 121–28. doi:10.1016/0732-8893(95)00027-8. PMID 7648832.
61. ^ Steere AC (2003-02-01). "Lyme Disease: Questions and Answers" (PDF). Massachusetts General Hospital / Harvard Medical School. Archived from the original (PDF) on 2008-03-07. Retrieved 2009-04-01.
62. ^ "CDC Lyme FAQ". *CDC Lyme FAQ*. Centers for Disease Control.
63. ^ Marianne Middelveen; Jennie Burke; Augustin Franco; Yean Wang; Peter Mayne; Eva Sapi; Cheryl Bandoski; Hilary Schlinger; Raphael Stricker (January 2014). "Lyme Disease May Be Sexually Transmitted". *The Journal of Investigative Medicine*. **62**: 280–281. Retrieved January 26, 2014.
64. ^ Swanson SJ, Neitzel D, Reed KD, Belongia EA (October 2006). "Coinfections acquired from ixodes ticks". *Clin. Microbiol. Rev*. **19** (4): 708–27. doi:10.1128/CMR.00011-06. PMC 1592693. PMID 17041141.
65. ^ Wormser GP (June 2006). "Clinical practice. Early Lyme disease". *N. Engl. J. Med*. **354** (26): 2794–801. doi:10.1056/NEJMcp061181. PMID 16807416.
66. ^ Lindgren E, Gustafson R (July 2001). "Tick-borne encephalitis in Sweden and climate change". *Lancet*. **358** (9275): 16–8. doi:10.1016/S0140-6736(00)05250-8. PMID 11454371.
67. ^ Varde S, Beckley J, Schwartz I (1998). "Prevalence of tick-borne pathogens in Ixodes scapularis in a rural New Jersey County". *Emerging Infect. Dis*. **4** (1): 97–99. doi:10.3201/eid0401.980113. PMC 2627663. PMID 9452402.
68. ^ Pachner AR, Steiner I (June 2007). "Lyme neuroborreliosis: infection, immunity, and inflammation". *Lancet Neurol*. **6** (6): 544–52. doi:10.1016/S1474-4422(07)70128-X. PMID 17509489.
69. ^ Fikrig E, Narasimhan S (April 2006). "Borrelia burgdorferi--traveling incognito?". *Microbes Infect*. **8** (5): 1390–9. doi:10.1016/j.micinf.2005.12.022. PMID 16698304.
70. ^ Xu Q, Seemanapalli SV, Reif KE, Brown CR, Liang FT (April 2007). "Increasing the recruitment of neutrophils to the site of infection dramatically attenuates Borrelia burgdorferi infectivity". *Journal of Immunology*. **178** (8): 5109–15. doi:10.4049/jimmunol.178.8.5109. PMID 17404293.
71. ^ Coleman JL, Gebbia JA, Piesman J, Degen JL, Bugge TH, Benach JL (June 1997). "Plasminogen is required for efficient dissemination of B. burgdorferi in ticks and for enhancement of spirochetemia in mice". *Cell*. **89** (7): 1111–

9. doi:10.1016/S0092-8674(00)80298-6. PMID 9215633.
72. ^ Steere AC (July 2001). "Lyme disease". *N. Engl. J. Med.* **345** (2): 115–25. doi:10.1056/NEJM200107123450207. PMID 11450660.
73. ^ Rupprecht TA, Koedel U, Fingerle V, Pfister HW (2008). "The pathogenesis of lyme neuroborreliosis: from infection to inflammation". *Mol. Med.* **14** (3-4): 205–12. doi:10.2119/2007-00091.Rupprecht (inactive 2015-01-01). PMC 2148032. PMID 18097481.
74. ^ Cabello FC, Godfrey HP, Newman SA (August 2007). "Hidden in plain sight: Borrelia burgdorferi and the extracellular matrix". *Trends Microbiol.* **15** (8): 350–54. doi:10.1016/j.tim.2007.06.003. PMID 17600717.
75. ^ Ramesh G, Alvarez AL, Roberts ED, et al. (September 2003). "Pathogenesis of Lyme neuroborreliosis: Borrelia burgdorferi lipoproteins induce both proliferation and apoptosis in rhesus monkey astrocytes". *Eur. Journal of Immunology*. **33** (9): 2539–50. doi:10.1002/eji.200323872. PMID 12938230.
76. ^ Halperin JJ, Heyes MP (January 1992). "Neuroactive kynurenines in Lyme borreliosis". *Neurology*. **42** (1): 43–50. doi:10.1212/WNL.42.1.43. PMID 1531156.
77. ^ Fallon BA, Keilp J, Prohovnik I, Heertum RV, Mann JJ (2003). "Regional cerebral blood flow and cognitive deficits in chronic lyme disease". *J Neuropsychiatry Clin Neurosci*. **15** (3): 326–32. doi:10.1176/appi.neuropsych.15.3.326. PMID 12928508.
78. ^ Gasse T; Murr C; Meyersbach P; et al. (1994). "Neopterin production and tryptophan degradation in acute Lyme neuroborreliosis versus late Lyme encephalopathy". *European Journal of Clinical Chemistry and Clinical Biochemistry*. **32** (9): 685–689. doi:10.1515/cclm.1994.32.9.685. PMID 7865624.
79. ^ Zajkowska J, Grygorczuk S, Kondrusik M, Pancewicz S, Hermanowska-Szpakowicz T; Grygorczuk; Kondrusik; Pancewicz; Hermanowska-Szpakowicz (2006). "[New aspects of pathogenesis of Lyme borreliosis]". *Przegl Epidemiol* (in Polish). **60** (Suppl 1): 167–70. PMID 16909797.
80. ^ Ercolini AM, Miller SD (January 2009). "The role of infections in autoimmune disease". *Clin. Exp. Immunol*. **155** (1): 1–15. doi:10.1111/j.1365-2249.2008.03834.x. PMC 2665673. PMID 19076824.
81. ^ Singh SK, Girschick HJ (July 2004). "Lyme borreliosis: from infection to autoimmunity". *Clin. Microbiol. Infect*. **10** (7): 598–614. doi:10.1111/j.1469-0691.2004.00895.x. PMID 15214872.
82. ^ Oldstone MB (October 1998). "Molecular mimicry and immune-mediated diseases" (PDF). *FASEB J.* **12** (13): 1255–65. PMID 9761770.
83. ^ Raveche ES; Schutzer SE; Fernandes H; et al. (February 2005). "Evidence of Borrelia autoimmunity-induced component of Lyme carditis and arthritis". *J. Clin. Microbiol*. **43** (2): 850–56. doi:10.1128/JCM.43.2.850-856.2005. PMC 548028. PMID 15695691.
84. ^ Weinstein A, Britchkov M; Britchkov (July 2002). "Lyme arthritis and post-Lyme disease syndrome". *Current Opinion in Rheumatology*. **14** (4): 383–87. doi:10.1097/00002281-200207000-00008. PMID 12118171.
85. ^ Bolz DD, Weis JJ (August 2004). "Molecular mimicry to Borrelia burgdorferi: pathway to autoimmunity?". *Autoimmunity*. **37** (5): 387–92. doi:10.1080/08916930410001713098. PMID 15621562.
86. ^ Wormser G, Masters E, Nowakowski J, et al. (2005). "Prospective clinical evaluation of patients from missouri and New York with *erythema migrans*-like skin lesions". *Clin Infect Dis*. **41** (7): 958–65. doi:10.1086/432935. PMID 16142659.
87. ^ Brown SL, Hansen SL, Langone JJ (July 1999). "Role of serology in the diagnosis of Lyme disease". *JAMA*. **282** (1): 62–66. doi:10.1001/jama.282.1.62. PMID 10404913.
88. ^ Hofmann H (1996). "Lyme borreliosis--problems of serological diagnosis". *Infection*. **24** (6): 470–72. doi:10.1007/BF01713052. PMID 9007597.
89. ^ Pachner AR (1989). "Neurologic manifestations of Lyme disease, the new "great imitator" ". *Rev. Infect. Dis*. 11 Suppl 6: S1482–1486. doi:10.1093/clinids/11.Supplement_6.S1482. PMID 2682960.
90. ^ Branda, JA; Linskey, K; Kim, YA; Steere, AC; Ferraro, MJ (Sep 2011). "Two-tiered antibody testing for Lyme disease with use of 2 enzyme immunoassays, a whole-cell sonicate enzyme immunoassay followed by a VlsE C6 peptide enzyme immunoassay.". *Clinical Infectious Diseases*. **53** (6): 541–7. doi:10.1093/cid/cir464. PMID 21865190.
91. ^ "Lyme disease diagnosis". Centers for Disease Control and Prevention (CDC). October 7, 2008. Retrieved July 6, 2009.
92. ^ *a b* Wormser GP; Dattwyler RJ; Shapiro ED; et al. (November 2006). "The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America" (PDF). *Clin. Infect. Dis.* **43** (9): 1089–1134. doi:10.1086/508667. PMID 17029130.
93. ^ Wilske B (2005). "Epidemiology and diagnosis of Lyme borreliosis". *Annals of Medicine*. **37** (8): 568–79. doi:10.1080/07853890500431934. PMID 16338759.
94. ^ Engstrom SM, Shoop E, Johnson RC (February 1995). "Immunoblot interpretation criteria for serodiagnosis of early Lyme disease". *J. Clin. Microbiol.* **33** (2): 419–27. PMC 227960. PMID 7714202.

95. ^ Sivak SL, Aguero-Rosenfeld ME, Nowakowski J, Nadelman RB, Wormser GP; Aguero-Rosenfeld; Nowakowski; Nadelman; Wormser (October 1996). "Accuracy of IgM immunoblotting to confirm the clinical diagnosis of early Lyme disease". *Arch. Intern. Med.* **156** (18): 2105–09. doi:10.1001/archinte.156.18.2105. PMID 8862103.
96. ^ [a] [b] Steere AC, McHugh G, Damle N, Sikand VK; McHugh; Damle; Sikand (July 2008). "Prospective study of serologic tests for lyme disease". *Clin. Infect. Dis.* **47** (2): 188–95. doi:10.1086/589242. PMID 18532885.
97. ^ Goossens HA, Nohlmans MK, van den Bogaard AE (1999). "Epstein–Barr virus and cytomegalovirus infections cause false-positive results in IgM two-test protocol for early Lyme borreliosis". *Infection*. **27** (3): 231. doi:10.1007/BF02561539. PMID 10378140.
98. ^ Strasfeld L, Romanzi L, Seder RH, Berardi VP; Romanzi; Seder; Berardi (December 2005). "False-positive serological test results for Lyme disease in a patient with acute herpes simplex virus type 2 infection". *Clin. Infect. Dis.* **41** (12): 1826–27. doi:10.1086/498319. PMID 16288417.
99. ^ Molloy PJ, Persing DH, Berardi VP (August 2001). "False-positive results of PCR testing for Lyme disease". *Clin. Infect. Dis.* **33** (3): 412–13. doi:10.1086/321911. PMID 11438915.
100. ^ [a] [b] Aguero-Rosenfeld ME, Wang G, Schwartz I, Wormser GP (July 2005). "Diagnosis of lyme borreliosis". *Clin. Microbiol. Rev.* **18** (3): 484–509. doi:10.1128/CMR.18.3.484-509.2005. PMC 1195970. PMID 16020686.
101. ^ Nocton JJ, Dressler F, Rutledge BJ, Rys PN, Persing DH, Steere AC (January 1994). "Detection of Borrelia burgdorferi DNA by polymerase chain reaction in synovial fluid from patients with Lyme arthritis". *N. Engl. J. Med.* **330** (4): 229–34. doi:10.1056/NEJM199401273300401. PMID 8272083.
102. ^ Hyde, F. W.; Johnson, R. C.; White, T. J.; Shelburne, C. E. (1989-01-01). "Detection of antigens in urine of mice and humans infected with Borrelia burgdorferi, etiologic agent of Lyme disease". *Journal of Clinical Microbiology*. **27** (1): 58–61. ISSN 0095-1137. PMC 267232. PMID 2913036.
103. ^ Shafagati, Nazly; Patanarut, Alexis; Luchini, Alessandra; Lundberg, Lindsay; Bailey, Charles; Petricoin, Emanuel; Liotta, Lance; Narayanan, Aarthi; Lepene, Benjamin (2014-07-01). "The use of Nanotrap particles for biodefense and emerging infectious disease diagnostics". *Pathogens and Disease*. **71** (2): 164–176. doi:10.1111/2049-632X.12136. ISSN 2049-632X. PMID 24449537.
104. ^ Shafagati, N; Patanarut, A; Luchini, A; Lundberg, L; Bailey, C; Petricoin E, 3rd; Liotta, L; Narayanan, A; Lepene, B; Kehn-Hall, K (July 2014). "The use of Nanotrap particles for biodefense and emerging infectious disease diagnostics.". *Pathogens and disease*. **71** (2): 164–76. doi:10.1111/2049-632x.12136. PMID 24449537.
105. ^ Burdash N, Fernandes J (June 1991). "Lyme borreliosis: detecting the great imitator". *J Am Osteopath Assoc.* **91** (6): 573–74, 577–8. PMID 1874654.
106. ^ Coyle PK, Schutzer SE, Deng Z, et al. (November 1995). "Detection of Borrelia burgdorferi-specific antigen in antibody-negative cerebrospinal fluid in neurologic Lyme disease". *Neurology*. **45** (11): 2010–15. doi:10.1212/WNL.45.11.2010. PMID 7501150.
107. ^ Valentine-Thon E, Ilsemann K, Sandkamp M; Ilsemann; Sandkamp (January 2007). "A novel lymphocyte transformation test (LTT-MELISA) for Lyme borreliosis". *Diagn. Microbiol. Infect. Dis.* **57** (1): 27–34. doi:10.1016/j.diagmicrobio.2006.06.008. PMID 16876371.
108. ^ von Baehr V, Doebis C, Volk HD, von Baehr R (October 2012). "The lymphocyte transformation test for borrelia detects active lyme borreliosis and verifies effective antibiotic treatment.". *Open Neurol J.* **6** (2): 104–12. doi:10.2174/1874205X01206010104. PMID 23091571.
109. ^ Monro JA (December 2014). "Diagnostic use of the lymphocyte transformation test-memory lymphocyte immunostimulation assay in confirming active Lyme borreliosis in clinically and serologically ambiguous cases". *Int J Clin Exp Med 2014*. **7** (12): 5890–5892. PMID 25664127.
110. ^ Eisendle K, Grabner T, Zelger B (February 2007). "Focus floating microscopy: 'gold standard' for cutaneous borreliosis?". *Am. J. Clin. Pathol.* **127** (2): 213–22. doi:10.1309/3369XXFPEQUNEP5C. PMID 17210530.
111. ^ Cadavid D (November 2006). "The mammalian host response to borrelia infection". *Wien. Klin. Wochenschr.* **118** (21-22): 653–58. doi:10.1007/s00508-006-0692-0. PMID 17160603.
112. ^ Hildenbrand P, Craven DE, Jones R, Nemeskal P (June 2009). "Lyme neuroborreliosis: manifestations of a rapidly emerging zoonosis". *AJNR Am J Neuroradiol*. **30** (6): 1079–87. doi:10.3174/ajnr.A1579. PMID 19346313.
113. ^ Westervelt, Holly; McCaffrey, Robert (September 2002). "Neuropsychological Functioning in Chronic Lyme Disease". *Neuropsychological Review*. **12** (3): 153–177. doi:10.1023/A:1020381913563.
114. ^ "CDC - Lyme Disease - NIOSH Workplace Safety and Health Topic". *www.cdc.gov*. Retrieved 2015-11-03.
115. ^ Centers for Disease Control and Prevention. "Avoid bug bites". Retrieved 15 March 2016.
116. ^ Rand PW, Lubelczyk C, Holman MS, Lacombe EH, Smith RP (July 2004). "Abundance of Ixodes scapularis (Acari: Ixodidae) after the complete removal of deer from an isolated offshore island, endemic for Lyme Disease". *J. Med. Entomol.* **41** (4): 779–84. doi:10.1603/0022-2585-41.4.779. PMID 15311475.
117. ^ "Figure 2: Changes in deer density and cases of Lyme disease in Mumford Cove, Connecticut, 1996–2004 (CT DEP data)". *Managing Urban Deer in Connecticut* (PDF) (2nd ed.). Connecticut Department of Environmental Protection - Wildlife Division. June 2007. p. 4.

118. ^ Perkins SE, Cattadori IM, Tagliapietra V, Rizzoli AP, Hudson PJ (August 2006). "Localized deer absence leads to tick amplification". *Ecology*. **87** (8): 1981–86. doi:10.1890/0012-9658(2006)87[1981:LDALTT]2.0.CO;2. PMID 16937637.
119. ^ Stafford, Kirby C. (2004). *Tick Management Handbook* (PDF). Connecticut Agricultural Experiment Station and Connecticut Department of Public Health. p. 46. Retrieved 2007-08-21.
120. ^ Staub D, Debrunner M, Amsler L, Steffen R (2002). "Effectiveness of a repellent containing DEET and EBAAP for preventing tick bites". *Wilderness Environ Med*. **13** (1): 12–20. doi:10.1580/1080-6032(2002)013[0012:EOARCD]2.0.CO;2. PMID 11929056.
121. ^ *a b* Gern L.; Estrada-Pena A.; Frandsen F.; Gray J. S.; Jaenson T. G. T.; Jongejan F.; Nuttall P. A. (1998). "European reservoir hosts of Borrelia burgdorferi sensu lato". *Zentralblatt für Bakteriologie*. **287** (3): 196–204. doi:10.1016/S0934-8840(98)80121-7.
122. ^ *a b* Wodecka, B., Rymaszewska, A., & Skotarczak, B. (2013), *Host and pathogen DNA identification in blood meals of nymphal Ixodes ricinus ticks from forest parks and rural forests of Poland*. *Experimental and Applied Acarology*, 1-13
123. ^ Jaenson T.G; TÄLleklint L (1992). "Incompetence of roe deer as reservoirs of the Lyme borreliosis spirochete". *Journal of medical entomology*. **29** (5): 813–817. doi:10.1093/jmedent/29.5.813.
124. ^ TÄLleklint L.; Jaenson T. G. (1994). "Transmission of Borrelia burgdorferi sl from mammal reservoirs to the primary vector of Lyme borreliosis, Ixodes ricinus (Acari: Ixodidae), in Sweden". *Journal of Medical Entomology*. **31** (6): 880–886. doi:10.1093/jmedent/31.6.880.
125. ^ *a b* Wodecka B, Rymaszewska A, Skotarczak B (Apr 2014). "Host and pathogen DNA identification in blood meals of nymphal Ixodes ricinus ticks from forest parks and rural forests of Poland". *Exp Appl Acarol*. **62** (4): 543–55. doi:10.1007/s10493-013-9763-x.
126. ^ Overzier E, Pfister K, Herb I, Mahling M, Böck G, Silaghi C (Jun 2013). "Detection of tick-borne pathogens in roe deer (Capreolus capreolus), in questing ticks (Ixodes ricinus), and in ticks infesting roe deer in southern Germany". *Ticks Tick Borne Dis*. **4** (4): 320–8. doi:10.1016/j.ttbdis.2013.01.004. PMID 23571115.
127. ^ Poland GA, Jacobson RM (March 2001). "The prevention of Lyme disease with vaccine". *Vaccine*. **19** (17-19): 2303–08. doi:10.1016/S0264-410X(00)00520-X. PMID 11257352.
128. ^ Rowe, Claudia (June 13, 1999). "Lukewarm Response To New Lyme Vaccine". *The New York Times*. Retrieved July 11, 2008.
129. ^ *a b c* Abbott A (February 2006). "Lyme disease: uphill struggle". *Nature*. **439** (7076): 524–25. doi:10.1038/439524a. PMID 16452949.
130. ^ "Sole Lyme Vaccine Is Pulled Off Market". *The New York Times*. February 28, 2002. Retrieved July 11, 2008.
131. ^ *a b* Nigrovic LE, Thompson KM (January 2007). "The Lyme vaccine: a cautionary tale". *Epidemiol. Infect*. **135** (1): 1–8. doi:10.1017/S0950268806007096. PMC 2870557. PMID 16893489.
132. ^ "When a vaccine is safe". *Nature*. **439** (7076): 509. February 2006. Bibcode:2006Natur.439Q.509. doi:10.1038/439509a. PMID 16452935.
133. ^ Earnhart CG, Marconi RT (2007). "An octavalent lyme disease vaccine induces antibodies that recognize all incorporated OspC type-specific sequences". *Hum Vaccin*. **3** (6): 281–89. doi:10.4161/hv.4661. PMID 17921702.
134. ^ Pozsgay V, Kubler-Kielb J (February 2007). "Synthesis of an experimental glycolipoprotein vaccine against Lyme disease". *Carbohydr. Res*. **342** (3-4): 621–26. doi:10.1016/j.carres.2006.11.014. PMC 2709212. PMID 17182019.
135. ^ *a b* Brooks, DVM, Wendy C. "Lyme Disease". Veterinary Information Network. Retrieved 10 February 2012.
136. ^ *a b* Piesman J, Dolan MC (May 2002). "Protection against lyme disease spirochete transmission provided by prompt removal of nymphal Ixodes scapularis (Acari: Ixodidae)". *J. Med. Entomol*. **39** (3): 509–12. doi:10.1603/0022-2585-39.3.509. PMID 12061448.
137. ^ http://www.tickbitepreventionweek.org/tick-removal.html
138. ^ Zeller JL, Burke AE, Glass RM (June 2007). "JAMA patient page. Lyme disease". *JAMA*. **297** (23): 2664. doi:10.1001/jama.297.23.2664. PMID 17579234.
139. ^ "Tick Allergy". 2014. Retrieved 30 April 2015.
140. ^ *a b c d e f g h i j k l m n o p* Wright WF, Riedel DJ, Talwani R, Gilliam BL; Riedel; Talwani; Gilliam (June 2012). "Diagnosis and management of Lyme disease". *Am Fam Physician*. **85** (11): 1086–93. PMID 22962880.
141. ^ Berende A, ter Hofstede HJ, Vos FJ, van Middendorp H, Vogelaar ML, Tromp M, van den Hoogen FH, Donders AR, Evers AW, Kullberg BJ (2016). "Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease". *The New England Journal of Medicine*. **374** (13): 1209–20. doi:10.1056/NEJMoa1505425. PMID 27028911.
142. ^ Krause PJ, Foley DT, Burke GS, Christianson D, Closter L, Spielman A (December 2006). "Reinfection and relapse

in early Lyme disease". *Am. J. Trop. Med. Hyg*. **75** (6): 1090–94. PMID 17172372.
143. ^ Cairns V, Godwin J (December 2005). "Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms". *Int J Epidemiol*. **34** (6): 1340–45. doi:10.1093/ije/dyi129. PMID 16040645.
144. ^ Klempner MS, Hu LT, Evans J, et al. (July 2001). "Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease". *N. Engl. J. Med*. **345** (2): 85–92. doi:10.1056/NEJM200107123450202. PMID 11450676.
145. ^ "Glomerular Disease". The Merck Veterinary Manual. Retrieved 11 Feb 2012.
146. ^ Staubinger, PhD, R. "Lyme Disease". Sirius Dog. Retrieved 10 Feb 2012.[*unreliable source?*]
147. ^ Fatal cases of Lyme disease reported in the medical literature include:
    - Kirsch M, Ruben FL, Steere AC, Duray PH, Norden CW, Winkelstein A (May 1988). "Fatal adult respiratory distress syndrome in a patient with Lyme disease". *JAMA*. **259** (18): 2737–39. doi:10.1001/jama.1988.03720180063034. PMID 3357244.
    - Oksi J, Kalimo H, Marttila RJ, et al. (December 1996). "Inflammatory brain changes in Lyme borreliosis. A report on three patients and review of literature". *Brain*. **119** (Pt 6): 2143–54. doi:10.1093/brain/119.6.2143. PMID 9010017.
    - Waniek C, Prohovnik I, Kaufman MA, Dwork AJ (1995). "Rapidly progressive frontal-type dementia associated with Lyme disease". *J Neuropsychiatry Clin Neurosci*. **7** (3): 345–47. PMID 7580195.
    - Cary NR, Fox B, Wright DJ, Cutler SJ, Shapiro LM, Grace AA (February 1990). "Fatal Lyme carditis and endodermal heterotopia of the atrioventricular node". *Postgrad Med J*. **66** (772): 134–36. doi:10.1136/pgmj.66.772.134. PMC 2429516. PMID 2349186.
148. ^ Higgins R (August 2004). "Emerging or re-emerging bacterial zoonotic diseases: bartonellosis, leptospirosis, Lyme borreliosis, plague". *Rev. - Off. Int. Epizoot*. **23** (2): 569–81. PMID 15702720.
149. ^ Bouattour A, Ghorbel A, Chabchoub A, Postic D (2004). "Situation de la borreuose de lyme au maghreb" [Lyme borreliosis situation in North Africa]. *Arch Inst Pasteur Tunis* (in French). **81** (1-4): 13–20. PMID 16929760.
150. ^ Dsouli N, Younsi-Kabachii H, Postic D, Nouira S, Gern L, Bouattour A (July 2006). "Reservoir role of lizard Psammodromus algirus in transmission cycle of Borrelia burgdorferi sensu lato (Spirochaetaceae) in Tunisia". *J. Med. Entomol*. **43** (4): 737–42. doi:10.1603/0022-2585(2006)43[737:RROLPA]2.0.CO;2. PMID 16892633.
151. ^ Helmy N (August 2000). "Seasonal abundance of Ornithodoros (O.) savignyi and prevalence of infection with Borrelia spirochetes in Egypt". *J Egypt Soc Parasitol*. **30** (2): 607–19. PMID 10946521.
152. ^ Fivaz BH, Petney TN (September 1989). "Lyme disease--a new disease in southern Africa?". *J S Afr Vet Assoc*. **60** (3): 155–58. PMID 2699499.
153. ^ Jowi JO, Gathua SN (May 2005). "Lyme disease: report of two cases". *East Afr Med J*. **82** (5): 267–69. doi:10.4314/eamj.v82i5.9318. PMID 16119758.
154. ^ Li M, Masuzawa T, Takada N, et al. (July 1998). "Lyme disease Borrelia species in northeastern China resemble those isolated from far eastern Russia and Japan". *Appl. Environ. Microbiol*. **64** (7): 2705–09. PMC 106449. PMID 9647853.
155. ^ Masuzawa T (December 2004). "Terrestrial distribution of the Lyme borreliosis agent Borrelia burgdorferi sensu lato in East Asia". *Jpn. J. Infect. Dis*. **57** (6): 229–35. PMID 15623946.
156. ^ Walder, Gernot; Lkhamsuren, Erdenechimeg; Shagdar, Abmed; et al. (2006). "Serological evidence for tick-borne encephalitis, borreliosis, and human granulocytic anaplasmosis in Mongolia". *International Journal of Medical Microbiology*. **296**: 69–75. doi:10.1016/j.ijmm.2006.01.031. ISSN 1438-4221. PMID 16524782.
157. ^ Rizzoli A, Hauffe H, Carpi G, Vourc HG, Neteler M, Rosa R (2011). "Lyme borreliosis in Europe". *Euro Surveill*. **16** (27). PMID 21794218.
158. ^ Smith R, Takkinen J (2006). "Lyme borreliosis: Europe-wide coordinated surveillance and action needed?". *Euro Surveill*. **11** (6): E060622.1. PMID 16819127.
159. ^ Lopes de Carvalho I, Núncio MS (2006). "Laboratory diagnosis of Lyme borreliosis at the Portuguese National Institute of Health (1990–2004)". *Euro Surveill*. **11** (10): 257–60. PMID 17130658.
160. ^ *a b c d* "Epidemiology of Lyme borreliosis in the UK". HPA. Retrieved 2012-12-15.
161. ^ Muhlemann MF, Wright DJ (January 1987). "Emerging pattern of Lyme disease in the United Kingdom and Irish Republic". *Lancet*. **1** (8527): 260–62. doi:10.1016/S0140-6736(87)90074-2. PMID 2880076.
162. ^ *a b* Lyme Disease Hansard 1991-11-11
163. ^ *a b* "Tick Lyme disease off your holiday list" (Press release). Health Protection Agency. 14 April 2011. Retrieved March 29, 2013.
164. ^ "Concern about rise in Lyme disease cases". Lyme Disease Action. 2011-12-15. Retrieved 2012-12-15.
165. ^ Cassidy, Frank (14 March 2011). "Tayside revealed as a Lyme disease hotspot as cases soar". *Press and Journal*.
166. ^ "Lyme disease: A clear and present danger". RCN. 2009-04-28. Retrieved 2012-12-15.
167. ^ "Guidance on Part 2 - Notifiable Diseases, Notifiable Organisms and Health Risk States". Scotland.gov.uk. 2012-

09-10. Retrieved 2012-12-15.
168. ^ Lyme Disease Hansard, 1997-02-03
169. ^ Tick-Borne Disease, Risk and Realit BADA-UK, Wendy Fox, 2010
170. ^ "Lyme borreliosis epidemiology and surveillance: May 2013". HPA. Retrieved 2015-11-24.
171. ^ "Zoonoses report UK 2009" (PDF). DEFRA. 24 January 2011.
172. ^ Overview Tick Bite Prevention Week
173. ^ Haywood GA, O'Connell S, Gray HH (July 1993). "Lyme carditis: a United Kingdom perspective". *Br Heart J*. **70** (1): 15–16. doi:10.1136/hrt.70.1.15. PMC 1025222. PMID 8037992.
174. ^ Guy EC, Bateman DE, Martyn CN, Heckels JE, Lawton NF (March 1989). "Lyme disease: prevalence and clinical importance of Borrelia burgdorferi specific IgG in forestry workers". *Lancet*. **1** (8636): 484–86. doi:10.1016/S0140-6736(89)91377-9. PMID 2563850.
175. ^ Smith FD, Ballantyne R, Morgan ER, Wall R; Ballantyne; Morgan; Wall (March 2012). "Estimating Lyme disease risk using pet dogs as sentinels". *Comp. Immunol. Microbiol. Infect. Dis*. **35** (2): 163–67. doi:10.1016/j.cimid.2011.12.009. PMID 22257866. Lay summary – *Bristol University* (25 January 2012).
176. ^ "Lyme disease risk from dogs 'higher than thought'". BBC News Online. 24 January 2012.
177. ^ The London climate change adaptation strategy - Draft report Greater London Authority, August 2008
178. ^ John S. Brownstein; Theodore R. Holford; Durland Fish (2005). "Effect of Climate Change on Lyme Disease Risk in North America". *Ecohealth*. **2** (1): 38–46. doi:10.1007/s10393-004-0139-x. PMC 2582486. PMID 19008966.
179. ^ *a b* Killilea, Mary E.; Swei, Andrea; Lane, Robert S.; Briggs, Cheryl J.; Ostfeld, Richard S. (2008). "Spatial Dynamics of Lyme Disease: A Review" (PDF). *EcoHealth*. **5** (2): 167–195. doi:10.1007/s10393-008-0171-3. PMID 18787920.
180. ^ BC Ministry of Agriculture. "Ticks and Humans in British Columbia". Agf.gov.bc.ca. Retrieved 2012-12-15.
181. ^ "Lyme Disease Fact Sheet". Phac-aspc.gc.ca. 2012-07-04. Retrieved 2012-12-15.
182. ^ Ogden NH, Lindsay LR, Morshed M, Sockett PN, Artsob H (June 2009). "The emergence of Lyme disease in Canada". *CMAJ*. **180** (12): 1221–24. doi:10.1503/cmaj.080148. PMC 2691438. PMID 19506281.
183. ^ Leighton, Patrick A; Koffi, Jules K; Pelcat, Yann; Lindsay, L Robbin; Ogden, Nicholas H (2012). "Predicting the speed of tick invasion: An empirical model of range expansion for the Lyme disease vector Ixodes scapularis in Canada". *Journal of Applied Ecology*. **49** (2): 457–64. doi:10.1111/j.1365-2664.2012.02112.x.
184. ^ Gordillo-Pérez, Guadalupe; Torres, Javier; Solórzano-Santos, Fortino; de Martino, Sylvie; Lipsker, Dan; Velázquez, Edmundo; Ramon, Guillermo; Onofre, Muñoz; Jaulhac, Benoit (Oct 2007), "Borrelia burgdorferi Infection and Cutaneous Lyme Disease, Mexico", *Emerg Infect Dis [serial on the Internet]*, **13** (10): 1556–1558, doi:10.3201/eid1310.060630
185. ^ *a b* "Reported cases of Lyme disease by state or locality, 2005-2014†". *cdc.gov*.
186. ^ "How many people get Lyme disease?". *cdc.gov*.
187. ^ CDC (January 4, 2012). "Reported Lyme disease cases by state, 2000-2010". Centers for Disease Control and Prevention (CDC). Retrieved April 29, 2012.
188. ^ "Lyme disease--United States, 2003–2005". *MMWR Morb. Mortal. Wkly. Rep*. **56** (23): 573–76. June 2007. PMID 17568368.
189. ^ Bacon RM, Kugeler KJ, Mead PS (October 2008). "Surveillance for Lyme disease--United States, 1992–2006". *MMWR Surveill Summ*. **57** (10): 1–9. PMID 18830214.
190. ^ *a b* Robbins, Jim (May 20, 2003). "Montana Lab Tries to Identify Tick-Borne Disease". *The New York Times*.
191. ^ "Lyme Disease Data". Centers for Disease Control and Prevention (CDC).
192. ^ "Lyme disease (Borrelia burgdorferi) 2011 case definition". U.S. Centers for Disease Control and Prevention.
193. ^ *a b* "Lyme disease (Borrelia burgdorferi) 2008 case definition". U.S. Centers for Disease Control and Prevention.
194. ^ *a b* Swanson KI, Norris DE (2007). "Detection of Borrelia burgdorferi DNA in lizards from Southern Maryland". *Vector-Borne and Zoonotic Diseases*. **7** (1): 42–49. doi:10.1089/vbz.2006.0548. PMID 17417956.
195. ^ Richter D, Matuschka FR (July 2006). "Perpetuation of the Lyme disease spirochete Borrelia lusitaniae by lizards". *Appl. Environ. Microbiol*. **72** (7): 4627–32. doi:10.1128/AEM.00285-06. PMC 1489336. PMID 16820453.
196. ^ Giery ST, Ostfeld RS (June 2007). "The role of lizards in the ecology of Lyme disease in two endemic zones of the northeastern United States". *J. Parasitol*. **93** (3): 511–17. doi:10.1645/GE-1053R1.1. PMID 17626342.
197. ^ Amore G, Tomassone L, Grego E, et al. (March 2007). "Borrelia lusitaniae in immature Ixodes ricinus (Acari: Ixodidae) feeding on common wall lizards in Tuscany, central Italy". *J. Med. Entomol*. **44** (2): 303–07. doi:10.1603/0022-2585(2007)44[303:BLIIIR]2.0.CO;2. PMID 17427701.
198. ^ Majláthová V, Majláth I, Derdáková M, Víchová B, Pet'ko B (December 2006). "Borrelia lusitaniae and green lizards (Lacerta viridis), Karst Region, Slovakia". *Emerging Infect. Dis*. **12** (12): 1895–901. doi:10.3201/eid1212.060784. PMC 3291370. PMID 17326941.

199. ^ Lyme disease fact sheet Analysis of CDC data on VoxHealth. Retrieved on 2013-30-1
200. ^ Mantovani E, Costa IP, Gauditano G, Bonoldi VL, Higuchi ML, Yoshinari NH (April 2007). "Description of Lyme disease-like syndrome in Brazil. Is it a new tick borne disease or Lyme disease variation?". *Braz. J. Med. Biol. Res.* **40** (4): 443–56. doi:10.1590/S0100-879X2006005000082. PMID 17401487.
201. ^ Yoshinari NH, Oyafuso LK, Monteiro FG, et al. (1993). "Doença de Lyme: Relato de um caso observado no Brasil" [Lyme disease. Report of a case observed in Brazil]. *Rev Hosp Clin Fac Med Sao Paulo* (in Portuguese). **48** (4): 170–74. PMID 8284588.
202. ^ Hoen AG, Margos G, Bent SJ, et al. (September 2009). "Phylogeography of Borrelia burgdorferi in the eastern United States reflects multiple independent Lyme disease emergence events". *Proc. Natl. Acad. Sci. U.S.A.* **106** (35): 15013–18. Bibcode:2009PNAS..10615013H. doi:10.1073/pnas.0903810106. JSTOR 40484546. PMC 2727481. PMID 19706476. Lay summary – *YaleNews* (August 10, 2009).
203. ^ Josselyn, John (1670). *An Account of Two Voyages to New-England Made during the Years 1638, 1663*.page 92
204. ^ *a b* Drymon, MM (2008). *Disguised as the devil: how Lyme disease created witches and changed history*. pp. 51–52. ISBN 978-0-615-20061-3.
205. ^ Summerton N (1995). "Lyme disease in the eighteenth century". *BMJ.* **311** (7018): 1478. doi:10.1136/bmj.311.7018.1478.
206. ^ Hall, Stephen S (November 2011). "Iceman Autopsy". *National Geographic*. Retrieved October 17, 2011.
207. ^ *a b* Marcus, Karl (1910). "Verhandlungen der dermatologischen Gesellschaft zu Stockholm". *Archiv für Dermatologie und Syphilis*. **101** (2–3): 403–06. doi:10.1007/BF01832773.
208. ^ Burckhardt JL (1911). "Zur Frage der Follikel- und Keimzentrenbildung in der Haut". *Frankfurter Zeitschrift für Pathologie* (in German). **6**: 352–59.
209. ^ Hellerström S (1930). "*Erythema chronicum migrans Afzelii*". *Acta Dermato-Venereologica* (in German). **11**: 315–21.
210. ^ Lenhoff C (1948). "Spirochetes in aetiologically obscure diseases". *Acta Derm. Venereol*. **28**: 295–324.
211. ^ Thyresson N (1949). "The penicillin treatment of acrodermatitis atrophicans chronica (Herxheimer)". *Acta Derm. Venereol*. **29** (6): 572–621. PMID 18140373.
212. ^ Bianchi GE (1950). "Die Penicillinbehandlung der Lymphozytome" [Penicillin therapy of lymphocytoma]. *Dermatologica* (in German). **100** (4-6): 270–73. doi:10.1159/000257185. PMID 15421023.
213. ^ Paschoud JM (1954). "Lymphocytom nach Zeckenbiss" [Lymphocytoma after tick bite]. *Dermatologica* (in German). **108** (4-6): 435–37. PMID 13190934.
214. ^ Scrimenti RJ (July 1970). "*Erythema chronicum migrans".* Arch Dermatol*. 102 (1): 104–05. doi:10.1001/archderm.102.1.104. PMID 5497158.*
215. ^ Borchers AT, Keen CL, Huntley AC, Gershwin ME (February 2015). "Lyme disease: a rigorous review of diagnostic criteria and treatment". *Journal of autoimmunity*. **57**: 82–115. doi:10.1016/j.jaut.2014.09.004. PMID 25451629.
216. ^ Weir, William (2013-09-19). "Lyme Disease Pioneer Stephen Malawista Dies". *Hartford Courant*. Retrieved 2013-10-14.
217. ^ Sternbach G, Dibble CL (1996). "Willy Burgdorfer: Lyme disease". *J Emerg Med*. **14** (5): 631–34. doi:10.1016/S0736-4679(96)00143-6. PMID 8933327.
218. ^ Bolognia JL; Jorizzo JL; Rapini RP (2007). *Dermatology* (2nd ed.). St. Louis: Mosby. ISBN 978-1-4160-2999-1.[*page needed*]
219. ^ Mast WE, Burrows WM (November 1976). "*Erythema chronicum migrans* and 'lyme arthritis'". *JAMA*. **236** (21): 2392. doi:10.1001/jama.236.21.2392d. PMID 989847.
220. ^ Steere AC; Malawista SE; Snydman DR; et al. (1977). "Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three connecticut communities". *Arthritis Rheum*. **20** (1): 7–17. doi:10.1002/art.1780200102. PMID 836338.
221. ^ Steere AC, Hutchinson GJ, Rahn DW, et al. (July 1983). "Treatment of the early manifestations of Lyme disease". *Annals of Internal Medicine*. **99** (1): 22–26. doi:10.7326/0003-4819-99-1-22. PMID 6407378.
222. ^ Burgdorfer W (1984). "Discovery of the Lyme disease spirochete and its relation to tick vectors". *Yale J Biol Med*. **57** (4): 515–20. PMC 2590008. PMID 6516454.
223. ^ Burgdorfer W, Barbour AG, Hayes SF, Benach JL, Grunwaldt E, Davis JP (June 1982). "Lyme disease-a tick-borne spirochetosis?". *Science*. **216** (4552): 1317–19. Bibcode:1982Sci...216.1317B. doi:10.1126/science.7043737. PMID 7043737.
224. ^ Luft BJ, Volkman DJ, Halperin JJ, Dattwyler RJ (1988). "New chemotherapeutic approaches in the treatment of Lyme borreliosis". *Annals of the New York Academy of Sciences*. **539**: 352–61. Bibcode:1988NYASA.539..352L. doi:10.1111/j.1749-6632.1988.tb31869.x. PMID 3056203.
225. ^ Dattwyler RJ, Volkman DJ, Conaty SM, Platkin SP, Luft BJ (December 1990). "Amoxycillin plus probenecid versus doxycycline for treatment of *erythema migrans borreliosis*". *Lancet*. **336** (8728): 1404–06. doi:10.1016/0140-

6736(90)93103-V. PMID 1978873.
226. ^ Ribeiro JM, Mather TN, Piesman J, Spielman A (March 1987). "Dissemination and salivary delivery of Lyme disease spirochetes in vector ticks (Acari: Ixodidae)". *J. Med. Entomol*. **24** (2): 201–05. PMID 3585913.
227. ^ Edlow, Jonathan A (2003). *Bull's-eye: unraveling the medical mystery of Lyme disease*. Yale University Press. ISBN 0-300-09867-7. page 191.
228. ^ LoGiudice K, Ostfeld RS, Schmidt KA, Keesing F (January 2003). "The ecology of infectious disease: effects of host diversity and community composition on Lyme disease risk". *Proc. Natl. Acad. Sci. U.S.A*. **100** (2): 567–71. Bibcode:2003PNAS..100..567L. doi:10.1073/pnas.0233733100. PMC 141036. PMID 12525705.
229. ^ Patz JA, Daszak P, Tabor GM, et al. (July 2004). "Unhealthy landscapes: Policy recommendations on land use change and infectious disease emergence". *Environ. Health Perspect*. **112** (10): 1092–98. doi:10.1289/ehp.6877. PMC 1247383. PMID 15238283.
230. ^ Khasnis AA, Nettleman MD (2005). "Global warming and infectious disease". *Arch. Med. Res*. **36** (6): 689–96. doi:10.1016/j.arcmed.2005.03.041. PMID 16216650.
231. ^ Feder, HM; Johnson, BJB; O'Connell, S; et al. (October 2007). "A Critical Appraisal of "Chronic Lyme Disease" ". *The New England Journal of Medicine*. **357** (14): 1422–30. doi:10.1056/NEJMra072023. PMID 17914043.
232. ^ Halperin JJ, Shapiro ED, Logigian E, et al. (July 2007). "Practice parameter: treatment of nervous system Lyme disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology". *Neurology*. **69** (1): 91–102. doi:10.1212/01.wnl.0000265517.66976.28. PMID 17522387.
233. ^ " "Chronic Lyme Disease" Fact Sheet". National Institute of Allergy and Infectious Diseases. April 17, 2009.
234. ^ Marques, Adriana (June 2008). "Chronic Lyme Disease: An appraisal". *Infect Dis Clin North Am*. **22** (2): 341–60. doi:10.1016/j.idc.2007.12.011. PMC 2430045. PMID 18452806.
235. ^ http://www.people.com/article/avril-lavigne-lyme-disease-bedridden
236. ^ Sophie Jamieson (22 Sep 2015). "Phones4U billionaire John Caudwell 'devastated' after whole family diagnosed with Lyme disease". *Daily Telegraph*. Retrieved 8 February 2016.
237. ^ Anderson, Sini (Director) (2013). *The Punk Singer* (Documentary film).
238. ^ Steve Ginsburg for Reuters. Sep 15, 2015 Lyme disease never far from thoughts of WNBA star Delle Donne
239. ^ *a b* Little SE, Heise SR, Blagburn BL, Callister SM, Mead PS (April 2010). "Lyme borreliosis in dogs and humans in the USA". *Trends Parasitol*. **26** (4): 213–18. doi:10.1016/j.pt.2010.01.006. PMID 20207198.
240. ^ *a b* Krupka I, Straubinger RK (November 2010). "Lyme borreliosis in dogs and cats: background, diagnosis, treatment and prevention of infections with Borrelia burgdorferi sensu stricto". *Vet. Clin. North Am. Small Anim. Pract*. **40** (6): 1103–19. doi:10.1016/j.cvsm.2010.07.011. PMID 20933139.
241. ^ Hahn, Jeffrey. "Ticks and Their Control". Regents of the University of Minnesota.
242. ^ "Chronic Lyme Disease". National Institute of Allergy and Infectious Diseases. Archived from the original on 2012. Retrieved 15 October 2013.

# Further reading

- Jonathan A. Edlow (2004). *Bull's Eye: Unraveling the Medical Mystery of Lyme Disease* (2nd ed.). Yale University Press. ISBN 0300103700.
- Richard Ostfeld (2012). *Lyme Disease: The Ecology of a Complex System*. New York: Oxford University Press. ISBN 0199928479.
- Pamela Weintraub (2008). *Cure Unknown: Inside the Lyme Disease Epidemic*. St. Martin's Press. ISBN 9780312378127.

# External links

- Lyme disease organizations at DMOZ
- CDC - Lyme Disease - NIOSH Workplace Safety and Health Topic: from the Centers for Disease Control and Prevention (CDC)
- Lyme Disease *The Merck Manual*
- Lyme Disease Tests - Lab Tests Online
- Tick-borne Diseases Passive Surveillance Public Database - Laboratory of Medical Zoology at the University of Massachusetts, Amherst
- Lyme Disease Map Project

Wikimedia Commons has media related to *Borreliosis*.

| v · t · e · | Tick-borne diseases and mite-borne diseases | |
|---|---|---|
| **Bacterial infection (all G-)** | **Rickettsiales** | Rocky Mountain spotted fever · Ehrlichiosis (Human granulocytic, Human monocytic) · Boutonneuse fever · |
| | **Spirochaete** | **Lyme disease** · Relapsing fever · Baggio–Yoshinari syndrome · |
| | **Thiotrichales** | Tularemia · |
| **Viral infection** | | Colorado tick fever · Tick-borne encephalitis · Crimean-Congo hemorrhagic fever · Omsk hemorrhagic fever · Kyasanur forest disease · Powassan encephalitis · Heartland virus · Kemerovo tickborne viral fever · Bhanja virus · |
| **Protozoan infection** | | Babesiosis · |
| **Neurotoxin** | | Tick paralysis · |
| **General** | | Tick infestation · |
| **Vectors** | **Ticks** | *Ixodes*: *Ixodes scapularis* · *Ixodes cornuatus* · *Ixodes holocyclus* · *Ixodes pacificus* · *Ixodes ricinus* · *Dermacentor*: *Dermacentor variabilis* · *Dermacentor andersoni* · *Amblyomma*: *Amblyomma americanum* · *Amblyomma cajennense* · *Amblyomma triguttatum* · *Ornithodoros*: *Ornithodoros moubata* · *Ornithodoros hermsi* · *Ornithodoros gurneyi* · other: *Rhipicephalus sanguineus* · |
| | **Mites** | *Leptotrombidium deliense* · *Liponyssoides sanguineus* · |

| v · t · e · | Infectious diseases · Bacterial diseases: BV4 non-proteobacterial G- (primarily A00–A79, 001–041, 080–109) · | | |
|---|---|---|---|
| **Spirochaete** | **Spirochaetaceae** | **Treponema** | *Treponema pallidum* (Syphilis/bejel · Yaws · · *Treponema carateum* (Pinta) · *Treponema denticola* · |
| | | **Borrelia** | *Borrelia burgdorferi*/*Borrelia afzelii* (**Lyme disease** · Erythema chronicum migrans · Neuroborreliosis · · *Borrelia recurrentis* (Louse borne relapsing fever) · *Borrelia hermsii*/*Borrelia duttoni*/*Borrelia parkeri* (Tick borne relapsing fever) · |
| | **Leptospiraceae** | **Leptospira** | *Leptospira interrogans* (Leptospirosis) · |
| | **Spirillaceae** | **Spirillum** | *Spirillum minus* (Rat-bite fever/Sodoku) · |
| **Chlamydiaceae** | **Chlamydophila** | | *Chlamydophila psittaci* (Psittacosis) · *Chlamydophila pneumoniae* · |
| | **Chlamydia** | | *Chlamydia trachomatis* (Chlamydia · Lymphogranuloma venereum · Trachoma · · |
| **Bacteroidetes** | | | *Bacteroides fragilis* · *Tannerella forsythia* · *Capnocytophaga canimorsus* · *Porphyromonas gingivalis* · *Prevotella intermedia* · |
| **Fusobacteria** | | | *Fusobacterium necrophorum* (Lemierre's syndrome) · *Fusobacterium nucleatum* · *Fusobacterium polymorphum* · *Streptobacillus moniliformis* (Rat-bite fever/Haverhill fever) · |

| v · t · e · | Arthritis in children |
|---|---|

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|---|---|---|
| **Inflammatory** | **Idiopathic** | Juvenile idiopathic arthritis · |
| | **Inflammatory disease** | Inflammatory bowel disease · Sarcoidosis · Cystic fibrosis · Autoimmune hepatitis · |
| | **Hematological malignancy** | Acute lymphoblastic leukemia · Lymphoma · |
| | **Malignancy** | Neuroblastoma · |
| | **Reactive** | post-streptococcal · Rheumatic fever · postenteric, post-viral · |
| | **Infection** | Septic arthritis · Osteomyelitis · Tuberculosis · Lyme arthritis · |
| **Mechanical** | Osgood–Schlatter disease · | |
| **Tumours of cartilage bone or muscle** | **Benign** | Osteoid osteoma · Pigmented villonodular synovitis · Hemangioma · |
| | **Malignant** | Synovial sarcoma · Rhabdomyosarcoma · Ewing's sarcoma · |
| **Central Nervous System** | Idiopathic pain syndromes · **Local:** Complex regional pain syndrome/Reflex sympathetic dystrophy · **Generalized:** Fibromyalgia · | |

Categories: Bacterial diseases | Bacterium-related cutaneous conditions | Lyme disease | Medical controversies | Neurodegenerative disorders | Tick-borne diseases




# Malaria



From Wikipedia, the free encyclopedia

**Malaria** is a mosquito-borne infectious disease affecting humans and other animals caused by parasitic protozoans (a group of single-celled microorganisms) belonging to the *Plasmodium* type.[1] Malaria causes symptoms that typically include fever, fatigue, vomiting, and headaches. In severe cases it can cause yellow skin, seizures, coma, or death.[2] Symptoms usually begin ten to fifteen days after being bitten. If not properly treated, people may have recurrences of the disease months later.[1] In those who have recently survived an infection, reinfection usually causes milder symptoms. This partial resistance disappears over months to years if the person has no continuing exposure to malaria.[2]

The disease is most commonly transmitted by an infected female *Anopheles* mosquito. The mosquito bite introduces the parasites from the mosquito's saliva into a person's blood.[1] The parasites travel to the liver where they mature and reproduce. Five species of *Plasmodium* can infect and be spread by humans.[2] Most deaths are caused by *P. falciparum* because *P. vivax*, *P. ovale*, and *P. malariae* generally cause a milder form of malaria.[1][2] The species *P. knowlesi* rarely causes disease in humans.[1] Malaria is typically diagnosed by the microscopic examination of blood using blood films, or with antigen-based rapid diagnostic tests.[2] Methods that use the polymerase chain reaction to detect the parasite's DNA have been developed, but are not widely used in areas where malaria is common due to their cost and complexity.[3]

The risk of disease can be reduced by preventing mosquito bites through the use of mosquito nets and insect repellents, or with mosquito control measures such as spraying insecticides and draining standing water.[2] Several medications are available to prevent malaria in travellers to areas where the disease is common. Occasional doses of the combination medication sulfadoxine/pyrimethamine are recommended in infants and after the first trimester of pregnancy in areas with high rates of malaria. Despite a need, no effective vaccine exists, although efforts to develop one are ongoing.[1] The recommended treatment for malaria is a combination of antimalarial medications that includes an artemisinin.[1][2] The second medication may be either mefloquine, lumefantrine, or sulfadoxine/pyrimethamine.[4] Quinine along with doxycycline may be used if an artemisinin is not available.[4] It is recommended that in areas where the disease is common, malaria is confirmed if possible before treatment is started due to concerns of increasing drug resistance. Resistance

## Variants


A *Plasmodium* from the saliva of a female mosquito moving across a mosquito cell

| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | B50-B54 |
| **ICD-9-CM** | 084 |
| **OMIM** | 248310 |
| **DiseasesDB** | 7728 |
| **MedlinePlus** | 000621 |
| **eMedicine** | med/1385 emerg/305 ped/1357 |
| **Patient UK** | Malaria |
| **MeSH** | *C03.752.250.552* |
| **Orphanet** | 673 |

[edit on Wikidata]

among the parasites has developed to several antimalarial medications; for example, chloroquine-resistant *P. falciparum* has spread to most malarial areas, and resistance to artemisinin has become a problem in some parts of Southeast Asia.[1]

The disease is widespread in the tropical and subtropical regions that exist in a broad band around the equator.[2] This includes much of Sub-Saharan Africa, Asia, and Latin America. In 2015, there were 214 million cases of malaria worldwide resulting in an estimated 438,000 deaths, 90% of which occurred in Africa.[5] Rates of disease have decreased from 2000 to 2015 by 37%,[5] but increased from 2014 during which there were 198 million cases.[6] Malaria is commonly associated with poverty and has a major negative effect on economic development.[7][8] In Africa, it is estimated to result in losses of US$12 billion a year due to increased healthcare costs, lost ability to work, and negative effects on tourism.[9]

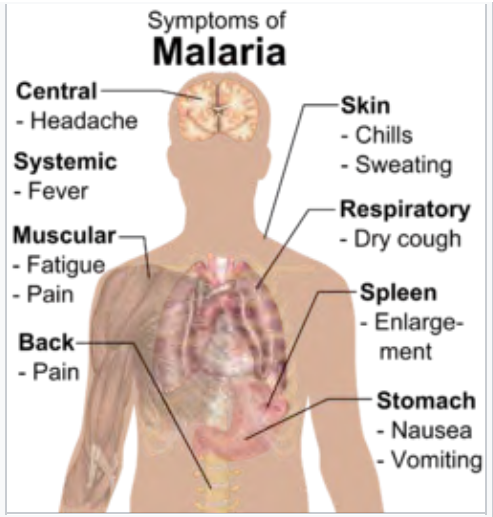


**Contents**



# Signs and symptoms

The signs and symptoms of malaria typically begin 8–25 days following infection,[10] however, symptoms may occur later in those who have taken antimalarial medications as prevention.[3] Initial manifestations of the disease—common to all malaria species—are similar to flu-like symptoms,[11] and can resemble other conditions such as sepsis, gastroenteritis, and viral diseases.[3] The presentation may include headache, fever, shivering, joint pain, vomiting, hemolytic anemia, jaundice, hemoglobin in the urine, retinal damage, and convulsions.[12]



Main symptoms of malaria[10]

The classic symptom of malaria is paroxysm—a cyclical occurrence of sudden coldness followed by shivering and then fever and sweating, occurring every two days (tertian fever) in *P. vivax* and *P. ovale* infections, and every three days (quartan fever) for *P. malariae*. *P. falciparum* infection can cause recurrent fever every 36–48 hours, or a less pronounced and almost continuous fever.[13]

Severe malaria is usually caused by *P. falciparum* (often referred to as falciparum malaria). Symptoms of falciparum malaria arise 9–30 days after infection.[11] Individuals with cerebral malaria frequently exhibit neurological symptoms, including abnormal posturing, nystagmus, conjugate gaze palsy (failure of the eyes to turn together in the same direction), opisthotonus, seizures, or coma.[11]

## Complications

Malaria has several serious complications. Among these is the development of respiratory distress, which occurs in up to 25% of adults and 40% of children with severe *P. falciparum* malaria. Possible causes include respiratory compensation of metabolic acidosis, noncardiogenic pulmonary oedema, concomitant pneumonia, and severe anaemia. Although rare in young children with severe malaria, acute respiratory distress syndrome occurs in 5–25% of adults and up to 29% of pregnant women.[14] Coinfection of HIV with malaria increases mortality.[15] Renal failure is a feature of blackwater fever, where hemoglobin from lysed red blood cells leaks into the urine.[11]

Infection with *P. falciparum* may result in cerebral malaria, a form of severe malaria that involves encephalopathy. It is associated with retinal whitening, which may be a useful clinical sign in distinguishing malaria from other causes of fever.[16] Enlarged spleen, enlarged liver or both of these, severe headache, low blood sugar, and hemoglobin in the urine with renal failure may occur.[11] Complications may include spontaneous bleeding, coagulopathy, and shock.[17]

Malaria in pregnant women is an important cause of stillbirths, infant mortality, abortion and low birth weight,[18] particularly in *P. falciparum* infection, but also with *P. vivax*.[19]

## Cause

*Main article: Plasmodium*

Malaria parasites belong to the genus *Plasmodium* (phylum Apicomplexa). In humans, malaria is caused by *P. falciparum*, *P. malariae*, *P. ovale*, *P. vivax* and *P. knowlesi*.[20][21] Among those infected, *P. falciparum* is the most common species identified (~75%) followed by *P. vivax* (~20%).[3] Although *P. falciparum* traditionally accounts for the majority of deaths,[22] recent evidence suggests that *P. vivax* malaria is associated with potentially life-threatening conditions about as often as with a diagnosis of *P. falciparum* infection.[23] *P. vivax* proportionally is more common outside Africa.[24] There have been documented human infections with several species of *Plasmodium* from higher apes; however, except for *P. knowlesi*—a zoonotic species that causes malaria in macaques[21]—these are mostly of limited public health importance.[25]

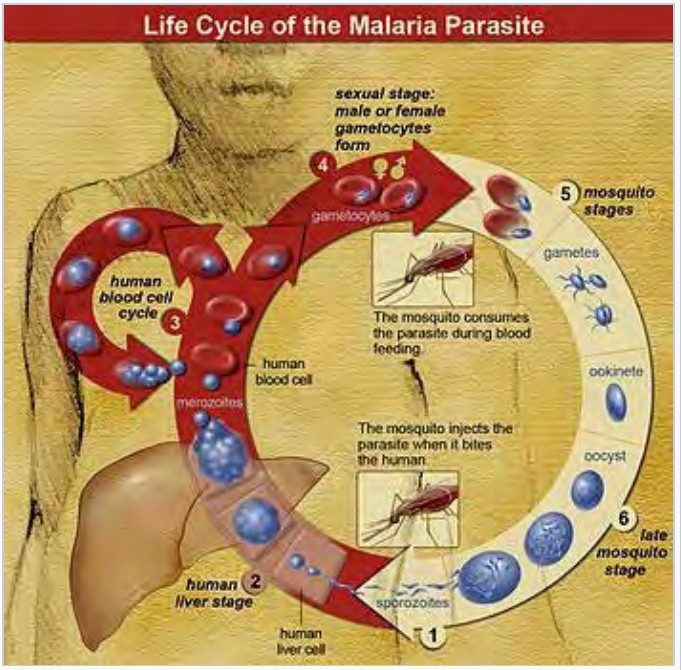
Global warming is likely to affect malaria transmission, but the severity and geographic distribution of such effects is uncertain.[26][27]

## Life cycle

In the life cycle of *Plasmodium*, a female *Anopheles* mosquito (the definitive host) transmits a motile infective form (called the sporozoite) to a vertebrate host such as a human (the secondary host), thus acting as a transmission vector. A sporozoite travels through the blood vessels to liver cells (hepatocytes), where it reproduces asexually (tissue schizogony), producing thousands of merozoites. These infect new red blood cells and initiate a series of asexual multiplication cycles (blood schizogony) that produce 8 to 24 new infective merozoites, at which point the cells burst and the infective cycle begins anew.[28]

Other merozoites develop into immature gametocytes, which are the precursors of male and female gametes. When a fertilized mosquito bites an infected person, gametocytes are taken up with the blood and mature in the mosquito gut. The male and female gametocytes fuse and form an ookinete—a fertilized, motile zygote. Ookinetes develop into new sporozoites that migrate to the insect's salivary glands, ready to infect a new vertebrate host. The sporozoites are injected into the skin, in the saliva, when the mosquito takes a subsequent blood meal.[29]

Only female mosquitoes feed on blood; male mosquitoes feed on plant nectar and do not transmit the disease. The females of the *Anopheles* genus of mosquito prefer to feed at night. They usually start searching for a meal at dusk and will continue throughout the night until taking a meal.[30] Malaria parasites can also be transmitted by blood transfusions, although this is rare.[31]




The life cycle of malaria parasites. A mosquito causes an infection by a bite. First, sporozoites enter the bloodstream, and migrate to the liver. They infect liver cells, where they multiply into merozoites, rupture the liver cells, and return to the bloodstream. The merozoites infect red blood cells, where they develop into ring forms, trophozoites and schizonts that in turn produce further merozoites. Sexual forms are also produced, which, if taken up by a mosquito, will infect the insect and continue the life cycle.

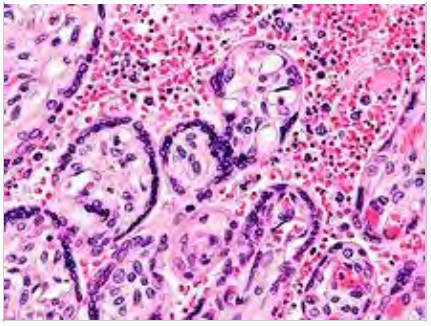
## Recurrent malaria

Symptoms of malaria can recur after varying symptom-free periods. Depending upon the cause, recurrence can be classified as either recrudescence, relapse, or reinfection. Recrudescence is when symptoms return after a symptom-free period. It is caused by parasites surviving in the blood as a result of inadequate or ineffective treatment.[32] Relapse is when symptoms reappear after the parasites have been eliminated from blood but persist as dormant hypnozoites in liver cells. Relapse commonly occurs between 8–24 weeks and is commonly seen with *P. vivax* and *P. ovale* infections.[3] *P. vivax* malaria cases in temperate areas often involve overwintering by hypnozoites, with relapses beginning the year after the mosquito bite.[33] Reinfection means the parasite that caused the past infection was eliminated from the body but a new parasite was introduced. Reinfection cannot readily be distinguished from recrudescence, although recurrence of infection within two weeks of treatment for the initial infection is typically attributed to treatment failure.[34] People may develop some immunity when exposed to frequent infections.[35]

# Pathophysiology

*Further information:* Plasmodium falciparum *biology*

Malaria infection develops via two phases: one that involves the liver (exoerythrocytic phase), and one that involves red blood cells, or erythrocytes (erythrocytic phase). When an infected mosquito pierces a person's skin to take a blood meal, sporozoites in the mosquito's saliva enter the bloodstream and migrate to the liver where they infect hepatocytes, multiplying asexually and asymptomatically for a period of 8–30 days.[36]



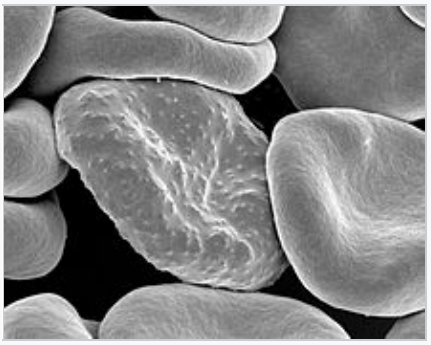
Micrograph of a placenta from a stillbirth due to maternal malaria. H&E stain. Red blood cells are anuclear; blue/black staining in bright red structures (red blood cells) indicate foreign nuclei from the parasites.

After a potential dormant period in the liver, these organisms differentiate to yield thousands of merozoites, which, following rupture of their host cells, escape into the blood and infect red blood cells to begin the erythrocytic stage of the life cycle.[36] The parasite escapes from the liver undetected by wrapping itself in the cell membrane of the infected host liver cell.[37]

Within the red blood cells, the parasites multiply further, again asexually, periodically breaking out of their host cells to invade fresh red blood cells. Several such amplification cycles occur. Thus, classical descriptions of waves of fever arise from simultaneous waves of merozoites escaping and infecting red blood cells.[36]

Some *P. vivax* sporozoites do not immediately develop into exoerythrocytic-phase merozoites, but instead, produce hypnozoites that remain dormant for periods ranging from several months (7–10 months is typical) to several years. After a period of dormancy, they reactivate and produce merozoites. Hypnozoites are responsible for long incubation and late relapses in *P. vivax* infections,[33] although their existence in *P. ovale* is uncertain.[38]

The parasite is relatively protected from attack by the body's immune system because for most of its human life cycle it resides within the liver and blood cells and is relatively invisible to immune surveillance. However, circulating infected blood cells are destroyed in the spleen. To avoid this fate, the *P. falciparum* parasite displays adhesive proteins on the surface of the infected blood cells, causing the blood cells to stick to the walls of small blood vessels, thereby sequestering the parasite from passage through the general circulation and the spleen.[39] The blockage of the microvasculature causes symptoms such as in placental malaria.[40] Sequestered red blood cells can breach the blood–brain barrier and cause cerebral malaria.[41]



Electron micrograph of a *Plasmodium falciparum*-infected red blood cell (center), illustrating adhesion protein "knobs"

## Genetic resistance

*Main article: Human genetic resistance to malaria*

According to a 2005 review, due to the high levels of mortality and morbidity caused by malaria—especially the *P. falciparum* species—it has placed the greatest selective pressure on the human genome in recent history. Several genetic factors provide some resistance to it including sickle cell trait, thalassaemia traits, glucose-6-phosphate dehydrogenase deficiency, and the absence of Duffy antigens on red blood cells.[42][43]

The impact of sickle cell trait on malaria immunity illustrates some evolutionary trade-offs that have occurred because of endemic malaria. Sickle cell trait causes a change in the hemoglobin molecule in the blood. Normally, red blood cells have a very flexible, biconcave shape that allows them to move through narrow capillaries; however, when the modified hemoglobin S molecules are exposed to low amounts of oxygen, or crowd together due to dehydration, they can stick together forming strands that cause the cell to sickle or distort into a curved shape. In these strands the molecule is not as effective in taking or releasing oxygen, and the cell is not flexible enough to circulate freely. In the early stages of malaria, the parasite can cause infected red cells to sickle, and so they are removed from circulation sooner. This reduces the frequency with which malaria parasites complete their life cycle in the cell. Individuals who are homozygous (with two copies of the abnormal hemoglobin beta allele) have sickle-cell anaemia, while those who are heterozygous (with one abnormal allele and one normal allele) experience resistance to malaria without severe anemia. Although the shorter life expectancy for those with the homozygous condition would tend to disfavor the trait's survival, the trait is preserved in malaria-prone regions because of the benefits provided by the heterozygous form.[43][44]

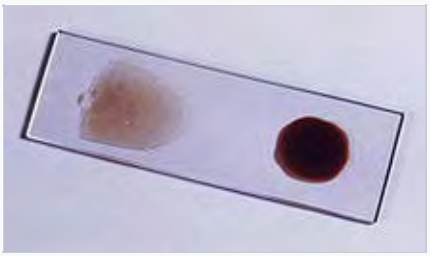
## Liver dysfunction

Liver dysfunction as a result of malaria is uncommon and usually only occurs in those with another liver condition such as viral hepatitis or chronic liver disease. The syndrome is sometimes called *malarial hepatitis*.[45] While it has been considered a rare occurrence, malarial hepatopathy has seen an increase, particularly in Southeast Asia and India. Liver compromise in people with malaria correlates with a greater likelihood of complications and death.[45]

# Diagnosis

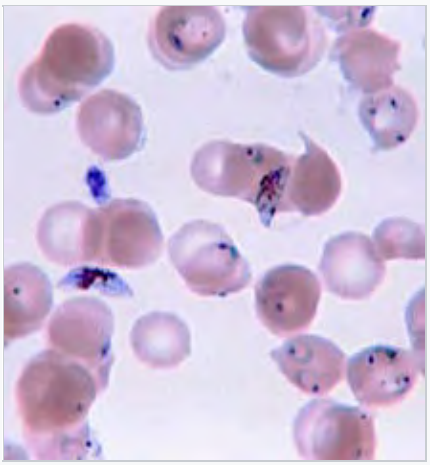
*Main article: Diagnosis of malaria*

Owing to the non-specific nature of the presentation of symptoms, diagnosis of malaria in non-endemic areas requires a high degree of suspicion, which might be elicited by any of the following: recent travel history, enlarged spleen, fever, low number of platelets in the blood, and higher-than-normal levels of bilirubin in the blood combined with a normal level of white blood cells.[3]



The blood film is the gold standard for malaria diagnosis.

Malaria is usually confirmed by the microscopic examination of blood films or by antigen-based rapid diagnostic tests (RDT).[46][47] In some areas, RDTs need to be able to distinguish whether the malaria symptoms are caused by Plasmodium falciparum or by other species of parasites since treatment strategies could differ for non-falciparum infections.[48] Microscopy is the most commonly used method to detect the malarial parasite—about 165 million blood films were examined for malaria in 2010.[49] Despite its widespread usage, diagnosis by microscopy suffers from two main drawbacks: many settings (especially rural) are not equipped to perform the test, and the accuracy of the results depends on both the skill of the person examining the blood film and the levels of the parasite in the blood. The sensitivity of blood films ranges from 75–90% in optimum conditions, to as low as 50%. Commercially available RDTs are often more accurate than blood films at predicting the presence of malaria parasites, but they are widely variable in diagnostic sensitivity and specificity depending on manufacturer, and are unable to tell how many parasites are present.[49]



Ring-forms and gametocytes of *Plasmodium falciparum* in human blood

In regions where laboratory tests are readily available, malaria should be suspected, and tested for, in any unwell person who has been in an area where malaria is endemic. In areas that cannot afford laboratory diagnostic tests, it has become common to use only a history of fever as the indication to treat for malaria—thus the common teaching "fever equals malaria unless proven otherwise". A drawback of this practice is overdiagnosis of malaria and mismanagement of non-malarial fever, which wastes limited resources, erodes confidence in the health care system, and contributes to drug resistance.[50] Although polymerase chain reaction-based tests have been developed, they are not widely used in areas where malaria is common as of 2012, due to their complexity.[3]

## Classification

Malaria is classified into either "severe" or "uncomplicated" by the World Health Organization (WHO).[3] It is deemed severe when *any* of the following criteria are present, otherwise it is considered uncomplicated.[51]

- Decreased consciousness
- Significant weakness such that the person is unable to walk
- Inability to feed
- Two or more convulsions
- Low blood pressure (less than 70 mmHg in adults and 50 mmHg in children)
- Breathing problems
- Circulatory shock
- Kidney failure or hemoglobin in the urine

Bleeding problems, or hemoglobin less than 50 g/L (5 g/dL)
- Pulmonary oedema
- Blood glucose less than 2.2 mmol/L (40 mg/dL)
- Acidosis or lactate levels of greater than 5 mmol/L
- A parasite level in the blood of greater than 100,000 per microlitre (μL) in low-intensity transmission areas, or 250,000 per μL in high-intensity transmission areas

Cerebral malaria is defined as a severe *P. falciparum*-malaria presenting with neurological symptoms, including coma (with a Glasgow coma scale less than 11, or a Blantyre coma scale greater than 3), or with a coma that lasts longer than 30 minutes after a seizure.[52]

Various types of malaria have been called by the names below:[53]

| Name | Pathogen | Notes |
|---|---|---|
| algid malaria | *Plasmodium falciparum* | severe malaria affecting the cardiovascular system and causing chills and circulatory shock |
| bilious malaria | *Plasmodium falciparum* | severe malaria affecting the liver and causing vomiting and jaundice |
| cerebral malaria | *Plasmodium falciparum* | severe malaria affecting the cerebrum |
| congenital malaria | various plasmodia | plasmodium introduced from the mother via the fetal circulation |
| falciparum malaria, *Plasmodium falciparum* malaria, pernicious malaria | *Plasmodium falciparum* | |
| ovale malaria, *Plasmodium ovale* malaria | *Plasmodium ovale* | |
| quartan malaria, malariae malaria, *Plasmodium malariae* malaria | *Plasmodium malariae* | paroxysms every fourth day (quartan), counting the day of occurrence as the first day |
| quotidian malaria | *Plasmodium falciparum*, *Plasmodium vivax* | paroxysms daily (quotidian) |
| tertian malaria | *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium vivax* | paroxysms every third day (tertian), counting the day of occurrence as the first |
| transfusion malaria | various plasmodia | plasmodium introduced by blood transfusion, needle sharing, or needlestick injury |
| vivax malaria, *Plasmodium vivax* malaria | *Plasmodium vivax* | |

# Prevention

Methods used to prevent malaria include medications, mosquito elimination and the prevention of bites. There is no vaccine for malaria. The presence of malaria in an area requires a combination of high human population density, high anopheles mosquito population density and high rates of transmission from humans to mosquitoes and from mosquitoes to humans. If any of these is lowered sufficiently, the parasite will eventually disappear from that area, as happened in North America, Europe and parts of the Middle East. However, unless the parasite is eliminated from the whole world, it could become re-established if conditions revert to a combination that favors the parasite's reproduction. Furthermore, the cost per person of eliminating anopheles mosquitoes rises with decreasing population density, making it

An *Anopheles stephensi*

economically unfeasible in some areas.[54]

Prevention of malaria may be more cost-effective than treatment of the disease in the long run, but the initial costs required are out of reach of many of the world's poorest people. There is a wide difference in the costs of control (i.e. maintenance of low endemicity) and elimination programs between countries. For example, in China—whose government in 2010 announced a strategy to pursue malaria elimination in the Chinese provinces—the required investment is a small proportion of public expenditure on health. In contrast, a similar program in Tanzania would cost an estimated one-fifth of the public health budget.[55]

mosquito shortly after obtaining blood from a human (the droplet of blood is expelled as a surplus). This mosquito is a vector of malaria, and mosquito control is an effective way of reducing its incidence.

In areas where malaria is common, children under five years old often have anemia which is sometimes due to malaria. Giving children with anemia in these areas preventive antimalarial medication improves red blood cell levels slightly but did not affect the risk of death or need for hospitalization.[56]

## Mosquito control

*Further information: Mosquito control*

Man spraying kerosene oil in standing water, Panama Canal Zone 1912

Vector control refers to methods used to decrease malaria by reducing the levels of transmission by mosquitoes. For individual protection, the most effective insect repellents are based on DEET or picaridin.[57] Insecticide-treated mosquito nets (ITNs) and indoor residual spraying (IRS) have been shown to be highly effective in preventing malaria among children in areas where malaria is common.[58][59] Prompt treatment of confirmed cases with artemisinin-based combination therapies (ACTs) may also reduce transmission.[60]

Mosquito nets help keep mosquitoes away from people and reduce infection rates and transmission of malaria. Nets are not a perfect barrier and are often treated with an insecticide designed to kill the mosquito before it has time to find a way past the net. Insecticide-treated nets are estimated to be twice as effective as untreated nets and offer greater than 70% protection compared with no net.[61] Between 2000 and 2008, the use of ITNs saved the lives of an estimated 250,000 infants in Sub-Saharan Africa.[62] About 13% of households in Sub-Saharan countries owned ITNs in 2007[63] and 31% of African households were estimated to own at least one ITN in 2008. In 2000, 1.7 million (1.8%) African children living in areas of the world where malaria is common were protected by an ITN. That number increased to 20.3 million (18.5%) African children using ITNs in 2007, leaving 89.6 million children unprotected[64] and to 68% African children using mosquito nets in 2015.[65] Most nets are impregnated with pyrethroids, a class of insecticides with low toxicity. They are most effective when used from dusk to dawn.[66] It is recommended to hang a large "bed net" above the center of a bed and either tuck the edges under the mattress or make sure it is large enough such that it touches the ground.[67]

Walls where indoor residual spraying of DDT has been applied. The mosquitoes remain on the wall until they fall down dead on the floor.

Indoor residual spraying is the spraying of insecticides on the walls inside a home. After feeding, many mosquitoes rest on a nearby surface while digesting the bloodmeal, so if the walls of houses have been coated with insecticides, the resting mosquitoes can be killed before they can bite another [68]


A mosquito net in use.

person and transfer the malaria parasite. As of 2006, the World Health Organization recommends 12 insecticides in IRS operations, including DDT and the pyrethroids cyfluthrin and deltamethrin.[69] This public health use of small amounts of DDT is permitted under the Stockholm Convention, which prohibits its agricultural use.[70] One problem with all forms of IRS is insecticide resistance. Mosquitoes affected by IRS tend to rest and live indoors, and due to the irritation caused by spraying, their descendants tend to rest and live outdoors, meaning that they are less affected by the IRS.[71]

There are a number of other methods to reduce mosquito bites and slow the spread of malaria. Efforts to decrease mosquito larva by decreasing the availability of open water in which they develop or by adding substances to decrease their development is effective in some locations.[72] Electronic mosquito repellent devices which make very high-frequency sounds that are supposed to keep female mosquitoes away, do not have supporting evidence.[73]

## Other methods

Community participation and health education strategies promoting awareness of malaria and the importance of control measures have been successfully used to reduce the incidence of malaria in some areas of the developing world.[74] Recognizing the disease in the early stages can stop the disease from becoming fatal. Education can also inform people to cover over areas of stagnant, still water, such as water tanks that are ideal breeding grounds for the parasite and mosquito, thus cutting down the risk of the transmission between people. This is generally used in urban areas where there are large centers of population in a confined space and transmission would be most likely in these areas.[75] Intermittent preventive therapy is another intervention that has been used successfully to control malaria in pregnant women and infants,[76] and in preschool children where transmission is seasonal.[77]

## Medications

*Main article: Malaria prophylaxis*

There are a number of drugs that can help prevent or interrupt malaria in travelers to places where infection is common. Many of these drugs are also used in treatment. Chloroquine may be used where chloroquine-resistant parasites are not common.[78] In places where *Plasmodium* is resistant to one or more medications, three medications—mefloquine (*Lariam*), doxycycline (available generically), or the combination of atovaquone and proguanil hydrochloride (*Malarone*)—are frequently used when prophylaxis is needed.[78] Doxycycline and the atovaquone plus proguanil combination are the best tolerated; mefloquine is associated with death, suicide, and neurological and psychiatric symptoms.[78]

The protective effect does not begin immediately, and people visiting areas where malaria exists usually start taking the drugs one to two weeks before arriving and continue taking them for four weeks after leaving (except for atovaquone/proguanil, which only needs to be started two days before and continued for seven days afterward).[79] The use of preventative drugs is often not practical for those who live in areas where malaria exists, and their use is usually only in pregnant women and short-term visitors. This is due to the cost of the drugs, side effects from long-term use, and the difficulty in obtaining anti-malarial drugs outside of wealthy nations.[80] During pregnancy, medication to prevent malaria has been found to improve the weight of the baby

at birth and decrease the risk of anemia in the mother.[81] The use of preventative drugs where malaria-bearing mosquitoes are present may encourage the development of partial resistance.[82]

# Treatment

Malaria is treated with antimalarial medications; the ones used depends on the type and severity of the disease. While medications against fever are commonly used, their effects on outcomes are not clear.[83]

Simple or uncomplicated malaria may be treated with oral medications. The most effective treatment for *P. falciparum* infection is the use of artemisinins in combination with other antimalarials (known as artemisinin-combination therapy, or ACT), which decreases resistance to any single drug component.[84] These additional antimalarials include: amodiaquine, lumefantrine, mefloquine or sulfadoxine/pyrimethamine.[85] Another recommended combination is dihydroartemisinin and piperaquine.[86][87] ACT is about 90% effective when used to treat uncomplicated malaria.[62] To treat malaria during pregnancy, the WHO recommends the use of quinine plus clindamycin early in the pregnancy (1st trimester), and ACT in later stages (2nd and 3rd trimesters).[88] In the 2000s (decade), malaria with partial resistance to artemisins emerged in Southeast Asia.[89][90] Infection with *P. vivax*, *P. ovale* or *P. malariae* usually do not require hospitalization. Treatment of *P. vivax* requires both treatment of blood stages (with chloroquine or ACT) and clearance of liver forms with primaquine.[91] Treatment with tafenoquine prevents relapses after confirmed *P. vivax* malaria.[92]

An advertisement for quinine as a malaria treatment from 1927.

Severe and complicated malaria are almost always caused by infection with *P. falciparum*. The other species usually cause only febrile disease.[93] Severe and complicated malaria are medical emergencies since mortality rates are high (10% to 50%).[94] Cerebral malaria is the form of severe and complicated malaria with the worst neurological symptoms.[95] Recommended treatment for severe malaria is the intravenous use of antimalarial drugs. For severe malaria, parenteral artesunate was superior to quinine in both children and adults.[96] In another systematic review, artemisinin derivatives (artemether and arteether) were as efficacious as quinine in the treatment of cerebral malaria in children.[97] Treatment of severe malaria involves supportive measures that are best done in a critical care unit. This includes the management of high fevers and the seizures that may result from it. It also includes monitoring for poor breathing effort, low blood sugar, and low blood potassium.[22]

## Resistance

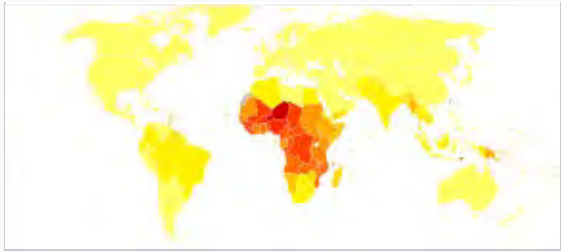
Drug resistance poses a growing problem in 21st-century malaria treatment.[98] Resistance is now common against all classes of antimalarial drugs apart from artemisinins. Treatment of resistant strains became increasingly dependent on this class of drugs. The cost of artemisinins limits their use in the developing world.[99] Malaria strains found on the Cambodia–Thailand border are resistant to combination therapies that include artemisinins, and may, therefore, be untreatable.[100] Exposure of the parasite population to artemisinin monotherapies in subtherapeutic doses for over 30 years and the availability of substandard artemisinins likely drove the selection of the resistant phenotype.[101] Resistance to artemisinin has been detected in Cambodia, Myanmar, Thailand, and Vietnam,[102] and there has been emerging resistance in Laos.[103][104]

# Prognosis

When properly treated, people with malaria can usually expect a complete recovery.[105] However, severe malaria can progress extremely rapidly and cause death within hours or days.[106] In the

most severe cases of the disease, fatality rates can reach 20%, even with intensive care and treatment.[3] Over the longer term, developmental impairments have been documented in children who have suffered episodes of severe malaria.[107] Chronic infection without severe disease can occur in an immune-deficiency syndrome associated with a decreased responsiveness to *Salmonella* bacteria and the Epstein–Barr virus.[108]

During childhood, malaria causes anemia during a period of rapid brain development, and also direct brain damage resulting from cerebral malaria.[107] Some survivors of cerebral malaria have an increased risk of neurological and cognitive deficits, behavioural disorders, and epilepsy.[109] Malaria prophylaxis was shown to improve cognitive function and school performance in clinical trials when compared to placebo groups.[107]



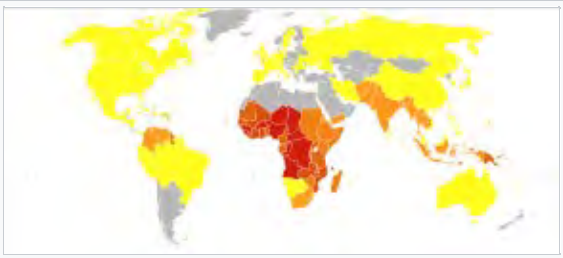
Disability-adjusted life year for malaria per 100,000 inhabitants in 2004

| | |
|---|---|
| no data | 1500–2000 |
| <10 | 2000–2500 |
| 0–100 | 2500–2750 |
| 100–500 | 2750–3000 |
| 500–1000 | 3000–3250 |
| 1000–1500 | 3250–3500 |
| | ≥3500 |

## Epidemiology

Distribution of malaria in the world:[110]

- Elevated occurrence of chloroquine- or multi-resistant malaria
- Occurrence of chloroquine-resistant malaria
- No *Plasmodium falciparum* or chloroquine-resistance
- No malaria



Deaths due to malaria per million persons in 2012

| | | |
|---|---|---|
| 0–0 | 55–325 | 950–1,358 |
| 1–2 | 326–679 | |
| 3–54 | 680–949 | |

The WHO estimates that in 2015 there were 214 million new cases of malaria resulting in 438,000 deaths.[111] Others have estimated the number of cases at between 350 and 550 million for falciparum malaria[112] The majority of cases (65%) occur in children under 15 years old.[113] About 125 million pregnant women are at risk of infection each year; in Sub-Saharan Africa, maternal malaria is associated with up to 200,000 estimated infant deaths yearly.[18] There are about 10,000 malaria cases per year in Western Europe, and 1300–1500 in the United States.[14] About 900 people died from the disease in Europe between 1993 and 2003.[57] Both the global incidence of disease and resulting mortality have declined in recent years. According to the WHO and UNICEF, deaths attributable to malaria in 2015 were reduced by 60%[65] from a 2000 estimate of 985,000, largely due to the widespread use of insecticide-treated nets and artemisinin-based combination therapies.[62] In 2012, there were 207 million cases of malaria. That year, the disease is estimated to have killed between 473,000 and 789,000 people, many of whom were children in Africa.[1] Efforts at decreasing the disease in Africa since the turn of millennium have been partially effective, with rates of the disease dropping by an estimated forty percent on the continent.[114]

Malaria is presently endemic in a broad band around the equator, in areas of the Americas, many parts of Asia, and much of Africa; in Sub-Saharan Africa, 85–90% of malaria fatalities occur.[115] An estimate for 2009 reported that countries with the highest death rate per 100,000 of population were Ivory Coast (86.15), Angola (56.93) and Burkina Faso (50.66).[116] A 2010 estimate indicated the deadliest countries per population were Burkina Faso, Mozambique and Mali.[113] The Malaria Atlas Project aims to map global endemic levels of malaria, providing a means with which to determine the global spatial limits of the disease and to assess disease burden.[117][118] This effort led to the publication of a map of *P. falciparum* endemicity in 2010.[119] As of 2010, about 100 countries have endemic malaria.[120][121] Every

year, 125 million international travellers visit these countries, and more than 30,000 contract the disease.[57]

The geographic distribution of malaria within large regions is complex, and malaria-afflicted and malaria-free areas are often found close to each other.[122] Malaria is prevalent in tropical and subtropical regions because of rainfall, consistent high temperatures and high humidity, along with stagnant waters in which mosquito larvae readily mature, providing them with the environment they need for continuous breeding.[123] In drier areas, outbreaks of malaria have been predicted with reasonable accuracy by mapping rainfall.[124] Malaria is more common in rural areas than in cities. For example, several cities in the Greater Mekong Subregion of Southeast Asia are essentially malaria-free, but the disease is prevalent in many rural regions, including along international borders and forest fringes.[125] In contrast, malaria in Africa is present in both rural and urban areas, though the risk is lower in the larger cities.[126]

## History

*Main articles: History of malaria and Mosquito-malaria theory*

Although the parasite responsible for *P. falciparum* malaria has been in existence for 50,000–100,000 years, the population size of the parasite did not increase until about 10,000 years ago, concurrently with advances in agriculture[127] and the development of human settlements. Close relatives of the human malaria parasites remain common in chimpanzees. Some evidence suggests that the *P. falciparum* malaria may have originated in gorillas.[128]

Ancient malaria oocysts preserved in Dominican amber

References to the unique periodic fevers of malaria are found throughout recorded history.[129] Hippocrates described periodic fevers, labelling them tertian, quartan, subtertian and quotidian.[130] The Roman Columella associated the disease with insects from swamps.[130] Malaria may have contributed to the decline of the Roman Empire,[131] and was so pervasive in Rome that it was known as the "Roman fever".[132] Several regions in ancient Rome were considered at-risk for the disease because of the favourable conditions present for malaria vectors. This included areas such as southern Italy, the island of Sardinia, the Pontine Marshes, the lower regions of coastal Etruria and the city of Rome along the Tiber River. The presence of stagnant water in these places was preferred by mosquitoes for breeding grounds. Irrigated gardens, swamp-like grounds, runoff from agriculture, and drainage problems from road construction led to the increase of standing water.[133]

British doctor Ronald Ross received the Nobel Prize for

The term malaria originates from Medieval Italian: *mala aria*—"bad air"; the disease was formerly called *ague* or *marsh fever* due to its association with swamps and marshland.[134] The term first appeared in the English literature about 1829.[130] Malaria was once common in most of Europe and North America,[135] where it is no longer endemic,[136] though imported cases do occur.[137]

Scientific studies on malaria made their first significant advance in 1880, when Charles Louis Alphonse Laveran—a French army doctor working in the military hospital of Constantine in Algeria—observed parasites inside the red blood cells of infected people for the first time. He, therefore, proposed that malaria is caused by this organism, the first time a protist was identified as causing disease.[138] For this and later discoveries, he was awarded the 1907 Nobel Prize for Physiology or Medicine. A year later, Carlos Finlay, a Cuban doctor treating people with yellow fever in Havana, provided strong evidence that mosquitoes were transmitting disease to and from humans.[139] This work followed earlier suggestions by Josiah C. Nott,[140] and work by Sir Patrick Manson, the "father of tropical medicine", on the transmission of filariasis.[141]

In April 1894, a Scottish physician Sir Ronald Ross visited Sir Patrick Manson at his house on Queen Anne Street, London. This visit was the start of four

Physiology or Medicine in 1902 for his work on malaria.

Chinese traditional Chinese medicine researcher Tu Youyou received the Nobel Prize for Physiology or Medicine in 2015 for her work on antimalarial drug artemisin.

years of collaboration and fervent research that culminated in 1898 when Ross, who was working in the Presidency General Hospital in Calcutta, proved the complete life-cycle of the malaria parasite in mosquitoes. He thus proved that the mosquito was the vector for malaria in humans by showing that certain mosquito species transmit malaria to birds. He isolated malaria parasites from the salivary glands of mosquitoes that had fed on infected birds.[142] For this work, Ross received the 1902 Nobel Prize in Medicine. After resigning from the Indian Medical Service, Ross worked at the newly established Liverpool School of Tropical Medicine and directed malaria-control efforts in Egypt, Panama, Greece and Mauritius.[143] The findings of Finlay and Ross were later confirmed by a medical board headed by Walter Reed in 1900. Its recommendations were implemented by William C. Gorgas in the health measures undertaken during construction of the Panama Canal. This public-health work saved the lives of thousands of workers and helped develop the methods used in future public-health campaigns against the disease.[144]

*Artemisia annua*, source of the antimalarial drug artemisin

The first effective treatment for malaria came from the bark of cinchona tree, which contains quinine. This tree grows on the slopes of the Andes, mainly in Peru. The indigenous peoples of Peru made a tincture of cinchona to control fever. Its effectiveness against malaria was found and the Jesuits introduced the treatment to Europe around 1640; by 1677, it was included in the London Pharmacopoeia as an antimalarial treatment.[145] It was not until 1820 that the active ingredient, quinine, was extracted from the bark, isolated and named by the French chemists Pierre Joseph Pelletier and Joseph Bienaimé Caventou.[146][147]

Quinine became the predominant malarial medication until the 1920s when other medications began to be developed. In the 1940s, chloroquine replaced quinine as the treatment of both uncomplicated and severe malaria until resistance supervened, first in Southeast Asia and South America in the 1950s and then globally in the 1980s.[148]

The medicinal value of Artemisia annua has been used by Chinese herbalists in traditional Chinese medicines for 2,000 years. In 1596, Li Shizhen recommended tea made from qinghao specifically to treat malaria symptoms in his "Compendium of Materia Medica". Artemisinins, discovered by Chinese scientist Tu Youyou and colleagues in the 1970s from the plant *Artemisia annua*, became the recommended treatment for *P. falciparum* malaria, administered in combination with other antimalarials as well as in severe disease.[149] Tu says she was influenced by a traditional Chinese herbal medicine source, *The Handbook of Prescriptions for Emergency Treatments*, written in 340 by Ge Hong[150] For her work on malaria, Tu Youyou received the 2015 Nobel Prize in Physiology or Medicine[151]

*Plasmodium vivax* was used between 1917 and the 1940s for malariotherapy—deliberate injection of malaria parasites to induce a fever to combat certain diseases such as tertiary syphilis. In 1927, the inventor of this technique, Julius Wagner-Jauregg, received the Nobel Prize in Physiology or Medicine for his discoveries. The technique was dangerous, killing about 15% of patients, so it is no longer in use.[152]

The first pesticide used for indoor residual spraying was DDT.[153] Although it was initially used exclusively to combat malaria, its use quickly spread to agriculture. In time, pest control, rather than disease control, came to dominate DDT use, and this large-scale agricultural use led to the evolution of resistant mosquitoes in many regions. The DDT resistance shown by *Anopheles* mosquitoes can be compared to antibiotic resistance shown by bacteria. During the 1960s, awareness of the negative consequences of its indiscriminate use increased, ultimately leading to bans on agricultural applications of DDT in many countries in the 1970s.[70] Before DDT, malaria

U.S. Marines with malaria in a rough field hospital on Guadalcanal, October 1942

was successfully eliminated or controlled in tropical areas like Brazil and Egypt by removing or poisoning the breeding grounds of the mosquitoes or the aquatic habitats of the larva stages, for example by applying the highly toxic arsenic compound Paris Green to places with standing water.[154]

Malaria vaccines have been an elusive goal of research. The first promising studies demonstrating the potential for a malaria vaccine were performed in 1967 by immunizing mice with live, radiation-attenuated sporozoites, which provided significant protection to the mice upon subsequent injection with normal, viable sporozoites. Since the 1970s, there has been a considerable effort to develop similar vaccination strategies for humans.[155] The first vaccine, called RTS,S, was approved by European regulators in 2015.[156]

# Society and culture

*See also: World Malaria Day*

## Economic impact

Malaria clinic in Tanzania

Malaria is not just a disease commonly associated with poverty: some evidence suggests that it is also a cause of poverty and a major hindrance to economic development.[7][8] Although tropical regions are most affected, malaria's furthest influence reaches into some temperate zones that have extreme seasonal changes. The disease has been associated with major negative economic effects on regions where it is widespread. During the late 19th and early 20th centuries, it was a major factor in the slow economic development of the American southern states.[157]

A comparison of average per capita GDP in 1995, adjusted for parity of purchasing power, between countries with malaria and countries without malaria gives a fivefold difference ($1,526 USD versus $8,268 USD). In the period 1965 to 1990, countries where malaria was common had an average per capita GDP that increased only 0.4% per year, compared to 2.4% per year in other countries.[158]

Poverty can increase the risk of malaria since those in poverty do not have the financial capacities to prevent or treat the disease. In its entirety, the economic impact of malaria has been estimated to cost Africa US$12 billion every year. The economic impact includes costs of health care, working days lost due to sickness, days lost in education, decreased productivity due to brain damage from cerebral malaria, and loss of investment and tourism.[9] The disease has a heavy burden in some countries, where it may be responsible for 30–50% of hospital admissions, up to 50% of outpatient visits, and up to 40% of public health spending.[159]

Cerebral malaria is one of the leading causes of neurological disabilities in African children.[109] Studies comparing cognitive functions before and after treatment for severe malarial illness continued to show significantly impaired school performance and cognitive abilities even after recovery.[107] Consequently, severe and cerebral malaria have far-reaching socioeconomic consequences that extend beyond the immediate effects of the disease.[160]

## Counterfeit and substandard drugs

Child with malaria in Ethiopia

Sophisticated counterfeits have been found in several Asian countries such as Cambodia,[161] China,[162] Indonesia, Laos, Thailand, and Vietnam, and are an important cause of avoidable death in those countries.[163] The WHO said that studies indicate that up to 40% of artesunate-based malaria medications are counterfeit, especially in the Greater Mekong region and have established a rapid alert system to enable information about counterfeit drugs to be rapidly reported to the relevant authorities in participating countries.[164] There is no reliable way for doctors or lay people to detect counterfeit drugs without help from a laboratory. Companies are attempting to combat the persistence of counterfeit drugs by using new technology to provide security from source to distribution.[165]

Another clinical and public health concern is the proliferation of substandard antimalarial medicines resulting from inappropriate concentration of ingredients, contamination with other drugs or toxic impurities, poor quality ingredients, poor stability and inadequate packaging.[166] A 2012 study demonstrated that roughly one-third of antimalarial medications in Southeast Asia and Sub-Saharan Africa failed chemical analysis, packaging analysis, or were falsified.[167]

## War

World War II poster

Throughout history, the contraction of malaria has played a prominent role in the fates of government rulers, nation-states, military personnel, and military actions.[168] In 1910, Nobel Prize in Medicine-winner Ronald Ross (himself a malaria survivor), published a book titled *The Prevention of Malaria* that included a chapter titled "The Prevention of Malaria in War." The chapter's author, Colonel C. H. Melville, Professor of Hygiene at Royal Army Medical College in London, addressed the prominent role that malaria has historically played during wars: "The history of malaria in war might almost be taken to be the history of war itself, certainly the history of war in the Christian era. ... It is probably the case that many of the so-called camp fevers, and probably also a considerable proportion of the camp dysentery, of the wars of the sixteenth, seventeenth and eighteenth centuries were malarial in origin."[169]

Malaria was the most important health hazard encountered by U.S. troops in the South Pacific during World War II, where about 500,000 men were infected.[170] According to Joseph Patrick Byrne, "Sixty thousand American soldiers died of malaria during the African and South Pacific campaigns."[171]

Significant financial investments have been made to procure existing and create new anti-malarial agents. During World War I and World War II, inconsistent supplies of the natural anti-malaria drugs cinchona bark and quinine prompted substantial funding into research and development of other drugs and vaccines. American military organizations conducting such research initiatives include the Navy Medical Research Center, Walter Reed Army Institute of Research, and the U.S. Army Medical Research Institute of Infectious Diseases of the US Armed Forces.[172]

Additionally, initiatives have been founded such as Malaria Control in War Areas (MCWA), established in 1942, and its successor, the Communicable Disease Center (now known as the Centers for Disease Control and Prevention, or CDC) established in 1946. According to the CDC, MCWA "was established to control malaria around military training bases in the southern United States and its territories, where malaria was still problematic".[173]

## Eradication efforts

Several notable attempts are being made to eliminate the parasite from sections of the world, or to eradicate it worldwide. In 2006, the organization Malaria No More set a public goal of eliminating malaria from Africa by 2015, and the organization plans to dissolve if that goal is accomplished.[174] Several malaria vaccines are in clinical trials, which are intended to provide protection for children in endemic areas and reduce the speed of transmission of the disease. As of 2012, The Global Fund to Fight AIDS, Tuberculosis and Malaria has distributed 230 million insecticide-treated nets intended to stop

Members of the Malaria Commission of the League of Nations collecting larvae on the Danube delta, 1929

mosquito-borne transmission of malaria.[175] The U.S.-based Clinton Foundation has worked to manage demand and stabilize prices in the artemisinin market.[176] Other efforts, such as the Malaria Atlas Project, focus on analysing climate and weather information required to accurately predict the spread of malaria based on the availability of habitat of malaria-carrying parasites.[117] The Malaria Policy Advisory Committee (MPAC) of the World Health Organization (WHO) was formed in 2012, "to provide strategic advice and technical input to WHO on all aspects of malaria control and elimination".[177] In November 2013, WHO and the malaria vaccine funders group set a goal to develop vaccines designed to interrupt malaria transmission with the long-term goal of malaria eradication.[178]

Malaria has been successfully eliminated or greatly reduced in certain areas. Malaria was once common in the United States and southern Europe, but vector control programs, in conjunction with the monitoring and treatment of infected humans, eliminated it from those regions. Several factors contributed, such as the draining of wetland breeding grounds for agriculture and other changes in water management practices, and advances in sanitation, including greater use of glass windows and screens in dwellings.[179] Malaria was eliminated from most parts of the USA in the early 20th century by such methods, and the use of the pesticide DDT and other means eliminated it from the remaining pockets in the South in the 1950s as part of the National Malaria Eradication Program.[180] Bill Gates has said that he thinks global eradication is possible by 2040.[181]

# Research

The Malaria Eradication Research Agenda (malERA) initiative was a consultative process to identify which areas of research and development (R&D) needed to be addressed for the worldwide eradication of malaria.[182][183]

## Vaccine

*See also: Malaria vaccine*

A vaccine against malaria called RTS,S, was approved by European regulators in 2015.[156] It is undergoing pilot trials in select countries in 2016.

Immunity (or, more accurately, tolerance) to *P. falciparum* malaria does occur naturally, but only in response to years of repeated infection.[35] An individual can be protected from a *P. falciparum* infection if they receive about a thousand bites from mosquitoes that carry a version of the parasite rendered non-infective by a dose of X-ray irradiation.[184] The highly polymorphic nature of many *P. falciparum* proteins results in significant challenges to vaccine design. Vaccine candidates that target antigens on gametes, zygotes, or ookinetes in the mosquito midgut aim to block the transmission of malaria. These transmission-blocking vaccines induce antibodies in the human blood; when a mosquito takes a blood meal from a protected individual, these antibodies prevent the parasite from completing its development in the mosquito.[185] Other vaccine candidates, targeting the blood-stage of the parasite's life cycle, have been inadequate on their own.[186] For example, SPf66 was tested extensively in areas where the disease is common in the 1990s, but trials showed it to be insufficiently effective.[187]

## Medications

Malaria parasites contain apicoplasts, organelles usually found in plants, complete with their own genomes. These apicoplasts are thought to have originated through the endosymbiosis of algae and play a crucial role in various aspects of parasite metabolism, such as fatty acid biosynthesis. Over 400 proteins have been found to be produced by apicoplasts and these are now being investigated as possible targets for novel anti-malarial

drugs.[188]

With the onset of drug-resistant *Plasmodium* parasites, new strategies are being developed to combat the widespread disease. One such approach lies in the introduction of synthetic pyridoxal-amino acid adducts, which are taken up by the parasite and ultimately interfere with its ability to create several essential B vitamins.[189][190] Antimalarial drugs using synthetic metal-based complexes are attracting research interest.[191][192]

- (+)-SJ733: Part of a wider class of experimental drugs called spiroindolone. It inhibits the ATP4 protein of infected red blood cells that cause the cells to shrink and become rigid like the aging cells. This triggers the immune system to eliminate the infected cells from the system as demonstrated in a mouse model. As of 2014, a Phase 1 clinical trial to assess the safety profile in human is planned by the Howard Hughes Medical Institute.[193]
- NITD246 and NITD609: Also belonged to the class of spiroindolone and target the ATP4 protein.[193]

### Other

A non-chemical vector control strategy involves genetic manipulation of malaria mosquitoes. Advances in genetic engineering technologies make it possible to introduce foreign DNA into the mosquito genome and either decrease the lifespan of the mosquito, or make it more resistant to the malaria parasite. Sterile insect technique is a genetic control method whereby large numbers of sterile male mosquitoes are reared and released. Mating with wild females reduces the wild population in the subsequent generation; repeated releases eventually eliminate the target population.[61]

Genomics is central to malaria research. With the sequencing of *P. falciparum*, one of its vectors *Anopheles gambiae*, and the human genome, the genetics of all three organisms in the malaria lifecycle can be studied.[194] Another new application of genetic technology is the ability to produce genetically modified mosquitoes that do not transmit malaria, potentially allowing biological control of malaria transmission.[195]

In one study, a genetically-modified strain of *Anopheles stephensi* was created that no longer supported malaria transmission, and this resistance was passed down to mosquito offspring.[196]

Gene drive is a technique for changing wild populations, for instance to combat insects so they cannot transmit diseases (in particular mosquitoes in the cases of malaria and zika).[197]

## Other animals

Nearly 200 parasitic *Plasmodium* species have been identified that infect birds, reptiles, and other mammals,[198] and about 30 species naturally infect non-human primates.[199] Some malaria parasites that affect non-human primates (NHP) serve as model organisms for human malarial parasites, such as *P. coatneyi* (a model for *P. falciparum*) and *P. cynomolgi* (*P. vivax*). Diagnostic techniques used to detect parasites in NHP are similar to those employed for humans.[200] Malaria parasites that infect rodents are widely used as models in research, such as *P. berghei*.[201] Avian malaria primarily affects species of the order Passeriformes, and poses a substantial threat to birds of Hawaii, the Galapagos, and other archipelagoes. The parasite *P. relictum* is known to play a role in limiting the distribution and abundance of endemic Hawaiian birds. Global warming is expected to increase the prevalence and global distribution of avian malaria, as elevated temperatures provide optimal conditions for parasite reproduction.[202]

## References


1. ^ *a b c d e f g h i* "Malaria Fact sheet N°94". *WHO*. March 2014. Retrieved 28 August 2014.
2. ^ *a b c d e f g h* Caraballo H (2014). "Emergency department management of mosquito-borne illness: Malaria, dengue, and west nile virus". *Emergency Medicine Practice*. **16** (5).
3. ^ *a b c d e f g h i* Nadjm B, Behrens RH (2012). "Malaria: An update for physicians". *Infectious Disease Clinics of North America*. **26** (2): 243–59. doi:10.1016/j.idc.2012.03.010. PMID 22632637.
4. ^ *a b* Organization, World Health (2010). *Guidelines for the treatment of malaria* (2nd ed.). Geneva: World Health Organization. p. ix. ISBN 9789241547925.
   *a b*

5. ^ "Malaria Fact sheet N°94". WHO. Retrieved 2 February 2016.
6. ^ WHO (2014). *World Malaria Report 2014*. Geneva, Switzerland: World Health Organization. pp. 32–42. ISBN 978-92-4156483-0.
7. ^ a b Gollin D, Zimmermann C (August 2007). Malaria: Disease Impacts and Long-Run Income Differences (PDF) (Report). Institute for the Study of Labor.
8. ^ a b Worrall E, Basu S, Hanson K (2005). "Is malaria a disease of poverty? A review of the literature". *Tropical Health and Medicine*. **10** (10): 1047–59. doi:10.1111/j.1365-3156.2005.01476.x. PMID 16185240.
9. ^ a b Greenwood BM, Bojang K, Whitty CJ, Targett GA (2005). "Malaria". *Lancet*. **365** (9469): 1487–98. doi:10.1016/S0140-6736(05)66420-3. PMID 15850634.
10. ^ a b Fairhurst RM, Wellems TE (2010). "Chapter 275. *Plasmodium* species (malaria)". In Mandell GL, Bennett JE, Dolin R. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. **2** (7th ed.). Philadelphia, Pennsylvania: Churchill Livingstone/Elsevier. pp. 3437–62. ISBN 978-0-443-06839-3.
11. ^ a b c d e Bartoloni A, Zammarchi L (2012). "Clinical aspects of uncomplicated and severe malaria". *Mediterranean Journal of Hematology and Infectious Diseases*. **4** (1): e2012026. doi:10.4084/MJHID.2012.026. PMC 3375727. PMID 22708041.
12. ^ Beare NA, Taylor TE, Harding SP, Lewallen S, Molyneux ME (2006). "Malarial retinopathy: A newly established diagnostic sign in severe malaria". *American Journal of Tropical Medicine and Hygiene*. **75** (5): 790–7. PMC 2367432. PMID 17123967.
13. ^ Ferri FF (2009). "Chapter 332. Protozoal infections". *Ferri's Color Atlas and Text of Clinical Medicine*. Elsevier Health Sciences. p. 1159. ISBN 978-1-4160-4919-7.
14. ^ a b Taylor WR, Hanson J, Turner GD, White NJ, Dondorp AM (2012). "Respiratory manifestations of malaria". *Chest*. **142** (2): 492–505. doi:10.1378/chest.11-2655. PMID 22871759.
15. ^ Korenromp E, Williams B, de Vlas S, Gouws E, Gilks C, Ghys P, Nahlen B (2005). "Malaria attributable to the HIV-1 epidemic, sub-Saharan Africa". *Emerging Infectious Diseases*. **11** (9): 1410–9. doi:10.3201/eid1109.050337. PMC 3310631. PMID 16229771.
16. ^ Beare NA, Lewallen S, Taylor TE, Molyneux ME (2011). "Redefining cerebral malaria by including malaria retinopathy". *Future Microbiology*. **6** (3): 349–55. doi:10.2217/fmb.11.3. PMC 3139111. PMID 21449844.
17. ^ Davidson's Principles and Practice of Medicine/21st/351
18. ^ a b Hartman TK, Rogerson SJ, Fischer PR (2010). "The impact of maternal malaria on newborns". *Annals of Tropical Paediatrics*. **30** (4): 271–82. doi:10.1179/146532810X12858955921032. PMID 21118620.
19. ^ Rijken MJ, McGready R, Boel ME, Poespoprodjo R, Singh N, Syafruddin D, Rogerson S, Nosten F (2012). "Malaria in pregnancy in the Asia-Pacific region". *Lancet Infectious Diseases*. **12** (1): 75–88. doi:10.1016/S1473-3099(11)70315-2. PMID 22192132.
20. ^ Mueller I, Zimmerman PA, Reeder JC (2007). "*Plasmodium malariae* and *Plasmodium ovale*—the "bashful" malaria parasites". *Trends in Parasitology*. **23** (6): 278–83. doi:10.1016/j.pt.2007.04.009. PMC 3728836. PMID 17459775.
21. ^ a b Collins WE (2012). "*Plasmodium knowlesi*: A malaria parasite of monkeys and humans". *Annual Review of Entomology*. **57**: 107–21. doi:10.1146/annurev-ento-121510-133540. PMID 22149265.
22. ^ a b Sarkar PK, Ahluwalia G, Vijayan VK, Talwar A (2009). "Critical care aspects of malaria". *Journal of Intensive Care Medicine*. **25** (2): 93–103. doi:10.1177/0885066609356052. PMID 20018606.
23. ^ Baird JK (2013). "Evidence and implications of mortality associated with acute *Plasmodium vivax* malaria". *Clinical Microbiology Reviews*. **26** (1): 36–57. doi:10.1128/CMR.00074-12. PMC 3553673. PMID 23297258.
24. ^ Arnott A, Barry AE, Reeder JC (2012). "Understanding the population genetics of *Plasmodium vivax* is essential for malaria control and elimination". *Malaria Journal*. **11**: 14. doi:10.1186/1475-2875-11-14. PMC 3298510. PMID 22233585.
25. ^ Collins WE, Barnwell JW (2009). "*Plasmodium knowlesi:* finally being recognized". *Journal of Infectious Diseases*. **199** (8): 1107–8. doi:10.1086/597415. PMID 19284287.
26. ^ Parham PE, Christiansen-Jucht C, Pople D, Michael E (2011). "Understanding and modelling the impact of climate change on infectious diseases". In Blanco J, Kheradmand H. *Climate Change – Socioeconomic Effects*. pp. 43–66. ISBN 978-9533074115.
27. ^ "Climate Change And Infectious Diseases" (PDF). *Climate Change and Human Health—Risk and Responses*. World Health Organization.
28. ^ Schlagenhauf-Lawlor 2008, pp. 70–1
29. ^ Cowman AF, Berry D, Baum J (2012). "The cellular and molecular basis for malaria parasite invasion of the human red blood cell". *Journal of Cell Biology*. **198** (6): 961–71. doi:10.1083/jcb.201206112. PMC 3444787. PMID 22986493.
30. ^ Arrow KJ, Panosian C, Gelband H (2004). *Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance*. National Academies Press. p. 141. ISBN 978-0-309-09218-0.
31. ^ Owusu-Ofori AK, Parry C, Bates I (2010). "Transfusion-transmitted malaria in countries where malaria is endemic: A review of the literature from sub-Saharan Africa". *Clinical Infectious Diseases*. **51** (10): 1192–8. doi:10.1086/656806.

PMID 20929356. 
32. ^ WHO 2010, p. vi
33. ^ a b White NJ (2011). "Determinants of relapse periodicity in *Plasmodium vivax* malaria". *Malaria Journal*. **10**: 297. doi:10.1186/1475-2875-10-297. PMC 3228849. PMID 21989376. 
34. ^ WHO 2010, p. 17
35. ^ a b Tran TM, Samal B, Kirkness E, Crompton PD (2012). "Systems immunology of human malaria". *Trends in Parasitology*. **28** (6): 248–57. doi:10.1016/j.pt.2012.03.006. PMC 3361535. PMID 22592005.
36. ^ a b c Bledsoe GH (2005). "Malaria primer for clinicians in the United States". *Southern Medical Journal*. **98** (12): 1197–204; quiz 1205, 1230. doi:10.1097/01.smj.0000189904.50838.eb. PMID 16440920.
37. ^ Vaughan AM, Aly AS, Kappe SH (2008). "Malaria parasite pre-erythrocytic stage infection: Gliding and hiding". *Cell Host & Microbe*. **4** (3): 209–18. doi:10.1016/j.chom.2008.08.010. PMC 2610487. PMID 18779047. 
38. ^ Richter J, Franken G, Mehlhorn H, Labisch A, Häussinger D (2010). "What is the evidence for the existence of *Plasmodium ovale* hypnozoites?". *Parasitology Research*. **107** (6): 1285–90. doi:10.1007/s00436-010-2071-z. PMID 20922429.
39. ^ Tilley L, Dixon MW, Kirk K (2011). "The *Plasmodium falciparum*-infected red blood cell". *International Journal of Biochemistry and Cell Biology*. **43** (6): 839–42. doi:10.1016/j.biocel.2011.03.012. PMID 21458590.
40. ^ Mens PF; Bojtor EC; Schallig HDFH (2012). "Molecular interactions in the placenta during malaria infection". *European Journal of Obstetrics & Gynecology and Reproductive Biology*. **152** (2): 126–32. doi:10.1016/j.ejogrb.2010.05.013. PMID 20933151.
41. ^ Rénia L, Wu Howland S, Claser C, Charlotte Gruner A, Suwanarusk R, Hui Teo T, Russell B, Ng LF (2012). "Cerebral malaria: mysteries at the blood-brain barrier". *Virulence*. **3** (2): 193–201. doi:10.4161/viru.19013. PMC 3396698. PMID 22460644. 
42. ^ Kwiatkowski DP (2005). "How malaria has affected the human genome and what human genetics can teach us about malaria". *American Journal of Human Genetics*. **77** (2): 171–92. doi:10.1086/432519. PMC 1224522. PMID 16001361. 
43. ^ a b Hedrick PW (2011). "Population genetics of malaria resistance in humans". *Heredity*. **107** (4): 283–304. doi:10.1038/hdy.2011.16. PMC 3182497. PMID 21427751. 
44. ^ Weatherall DJ (2008). "Genetic variation and susceptibility to infection: The red cell and malaria". *British Journal of Haematology*. **141** (3): 276–86. doi:10.1111/j.1365-2141.2008.07085.x. PMID 18410566.
45. ^ a b Bhalla A, Suri V, Singh V (2006). "Malarial hepatopathy". *Journal of Postgraduate Medicine*. **52** (4): 315–20. PMID 17102560. 
46. ^ Abba K, Deeks JJ, Olliaro P, Naing CM, Jackson SM, Takwoingi Y, Donegan S, Garner P (2011). Abba K, ed. "Rapid diagnostic tests for diagnosing uncomplicated *P. falciparum* malaria in endemic countries". *Cochrane Database of Systematic Reviews* (7): CD008122. doi:10.1002/14651858.CD008122.pub2. PMID 21735422.
47. ^ Kattenberg JH, Ochodo EA, Boer KR, Schallig HD, Mens PF, Leeflang MM (2011). "Systematic review and meta-analysis: Rapid diagnostic tests versus placental histology, microscopy and PCR for malaria in pregnant women". *Malaria Journal*. **10**: 321. doi:10.1186/1475-2875-10-321. PMC 3228868. PMID 22035448. 
48. ^ Abba, Katharine; Kirkham, Amanda J; Olliaro, Piero L; Deeks, Jonathan J; Donegan, Sarah; Garner, Paul; Takwoingi, Yemisi (18 December 2014). "Rapid diagnostic tests for diagnosing uncomplicated non-falciparum or Plasmodium vivax malaria in endemic countries". *Cochrane Database of Systematic Reviews*. **12**: CD011431. doi:10.1002/14651858.cd011431. PMC 4453861. PMID 25519857.
49. ^ a b Wilson ML (2012). "Malaria rapid diagnostic tests". *Clinical Infectious Diseases*. **54** (11): 1637–41. doi:10.1093/cid/cis228. PMID 22550113.
50. ^ Perkins MD, Bell DR (2008). "Working without a blindfold: The critical role of diagnostics in malaria control". *Malaria Journal*. **1** (Suppl 1): S5. doi:10.1186/1475-2875-7-S1-S5. PMC 2604880. PMID 19091039. 
51. ^ WHO 2010, p. 35
52. ^ WHO 2010, p. v
53. ^ Elsevier, *Dorland's Illustrated Medical Dictionary*, Elsevier.
54. ^ World Health Organization (1958). "Malaria". *The First Ten Years of the World Health Organization* (PDF). World Health Organization. pp. 172–87.
55. ^ Sabot O, Cohen JM, Hsiang MS, Kahn JG, Basu S, Tang L, Zheng B, Gao Q, Zou L, Tatarsky A, Aboobakar S, Usas J, Barrett S, Cohen JL, Jamison DT, Feachem RG (2010). "Costs and financial feasibility of malaria elimination". *Lancet*. **376** (9752): 1604–15. doi:10.1016/S0140-6736(10)61355-4. PMC 3044845. PMID 21035839.
56. ^ Athuman, M; Kabanywanyi, AM; Rohwer, AC (13 January 2015). "Intermittent preventive antimalarial treatment for children with anaemia.". *The Cochrane database of systematic reviews*. **1**: CD010767. doi:10.1002/14651858.CD010767.pub2. PMID 25582096.
57. ^ a b c Kajfasz P (2009). "Malaria prevention". *International Maritime Health*. **60** (1–2): 67–70. PMID 20205131. 
58. ^ Lengeler C (2004). Lengeler, Christian, ed. "Insecticide-treated bed nets and curtains for preventing malaria". *Cochrane Database of Systematic Reviews* (2): CD000363. doi:10.1002/14651858.CD000363.pub2. PMID 15106149.

59. ^ Tanser FC, Lengeler C, Sharp BL (2010). Lengeler C, ed. "Indoor residual spraying for preventing malaria". *Cochrane Database of Systematic Reviews* (4): CD006657. doi:10.1002/14651858.CD006657.pub2. PMID 20393950.
60. ^ Palmer, J. "WHO gives indoor use of DDT a clean bill of health for controlling malaria". WHO.
61. ^ a b Raghavendra K, Barik TK, Reddy BP, Sharma P, Dash AP (2011). "Malaria vector control: From past to future". *Parasitology Research*. **108** (4): 757–79. doi:10.1007/s00436-010-2232-0. PMID 21229263.
62. ^ a b c Howitt P, Darzi A, Yang GZ, Ashrafian H, Atun R, Barlow J, Blakemore A, Bull AM, Car J, Conteh L, Cooke GS, Ford N, Gregson SA, Kerr K, King D, Kulendran M, Malkin RA, Majeed A, Matlin S, Merrifield R, Penfold HA, Reid SD, Smith PC, Stevens MM, Templeton MR, Vincent C, Wilson E (2012). "Technologies for global health". *The Lancet*. **380** (9840): 507–35. doi:10.1016/S0140-6736(12)61127-1. PMID 22857974.
63. ^ Miller JM, Korenromp EL, Nahlen BL, W Steketee R (2007). "Estimating the number of insecticide-treated nets required by African households to reach continent-wide malaria coverage targets". *Journal of the American Medical Association*. **297** (20): 2241–50. doi:10.1001/jama.297.20.2241. PMID 17519414.
64. ^ Noor AM, Mutheu JJ, Tatem AJ, Hay SI, Snow RW (2009). "Insecticide-treated net coverage in Africa: Mapping progress in 2000–07". *Lancet*. **373** (9657): 58–67. doi:10.1016/S0140-6736(08)61596-2. PMC 2652031. PMID 19019422.
65. ^ a b "Achieving the malaria MDG target: reversing the incidence of malaria 2000–2015." (PDF). *UNICEF*. WHO. September 2015. ISBN 978924150944 2. Retrieved 26 December 2015.
66. ^ Schlagenhauf-Lawlor 2008, pp. 215
67. ^ *Instructions for treatment and use of insecticide-treated mosquito nets* (pdf). World Health Organization. 2002. p. 34.
68. ^ Enayati A, Hemingway J (2010). "Malaria management: Past, present, and future". *Annual Review of Entomology*. **55**: 569–91. doi:10.1146/annurev-ento-112408-085423. PMID 19754246.
69. ^ Indoor Residual Spraying: Use of Indoor Residual Spraying for Scaling Up Global Malaria Control and Elimination. WHO Position Statement (PDF) (Report). World Health Organization. 2006.
70. ^ a b van den Berg H (2009). "Global status of DDT and its alternatives for use in vector control to prevent disease". *Environmental Health Perspectives*. **117** (11): 1656–63. doi:10.1289/ehp.0900785. PMC 2801202. PMID 20049114.
71. ^ Pates H, Curtis C (2005). "Mosquito behaviour and vector control". *Annual Review of Entomology*. **50**: 53–70. doi:10.1146/annurev.ento.50.071803.130439. PMID 15355233.
72. ^ Tusting LS, Thwing J, Sinclair D, Fillinger U, Gimnig J, Bonner KE, Bottomley C, Lindsay SW (2013). "Mosquito larval source management for controlling malaria". *Cochrane Database of Systematic Reviews*. **8**: CD008923. doi:10.1002/14651858.CD008923.pub2. PMID 23986463.
73. ^ Enayati AA, Hemingway J, Garner P (2007). Enayati A, ed. "Electronic mosquito repellents for preventing mosquito bites and malaria infection" (PDF). *Cochrane Database of Systematic Reviews* (2): CD005434. doi:10.1002/14651858.CD005434.pub2. PMID 17443590.
74. ^ Lalloo DG, Olukoya P, Olliaro P (2006). "Malaria in adolescence: Burden of disease, consequences, and opportunities for intervention". *Lancet Infectious Diseases*. **6** (12): 780–93. doi:10.1016/S1473-3099(06)70655-7. PMID 17123898.
75. ^ Mehlhorn H, ed. (2008). "Disease Control, Methods". *Encyclopedia of Parasitology* (3rd ed.). Springer. pp. 362–6. ISBN 978-3-540-48997-9.
76. ^ Bardají A, Bassat Q, Alonso PL, Menéndez C (2012). "Intermittent preventive treatment of malaria in pregnant women and infants: making best use of the available evidence". *Expert Opinion on Pharmacotherapy*. **13** (12): 1719–36. doi:10.1517/14656566.2012.703651. PMID 22775553.
77. ^ Meremikwu MM, Donegan S, Sinclair D, Esu E, Oringanje C (2012). Meremikwu MM, ed. "Intermittent preventive treatment for malaria in children living in areas with seasonal transmission". *Cochrane Database of Systematic Reviews*. **2** (2): CD003756. doi:10.1002/14651858.CD003756.pub4. PMID 22336792.
78. ^ a b c Jacquerioz FA, Croft AM (2009). Jacquerioz FA, ed. "Drugs for preventing malaria in travellers". *Cochrane Database of Systematic Reviews* (4): CD006491. doi:10.1002/14651858.CD006491.pub2. PMID 19821371.
79. ^ Freedman DO (2008). "Clinical practice. Malaria prevention in short-term travelers". *New England Journal of Medicine*. **359** (6): 603–12. doi:10.1056/NEJMcp0803572. PMID 18687641.
80. ^ Fernando SD, Rodrigo C, Rajapakse S (2011). "Chemoprophylaxis in malaria: Drugs, evidence of efficacy and costs". *Asian Pacific Journal of Tropical Medicine*. **4** (4): 330–6. doi:10.1016/S1995-7645(11)60098-9. PMID 21771482.
81. ^ Radeva-Petrova, D; Kayentao, K; Ter Kuile, FO; Sinclair, D; Garner, P (10 October 2014). "Drugs for preventing malaria in pregnant women in endemic areas: any drug regimen versus placebo or no treatment.". *The Cochrane database of systematic reviews*. **10**: CD000169. doi:10.1002/14651858.CD000169.pub3. PMID 25300703.
82. ^ Turschner S, Efferth T (2009). "Drug resistance in *Plasmodium*: Natural products in the fight against malaria". *Mini Reviews in Medicinal Chemistry*. **9** (2): 206–14. doi:10.2174/138955709787316074. PMID 19200025.
83. ^ Meremikwu MM, Odigwe CC, Akudo Nwagbara B, Udoh EE (2012). Meremikwu MM, ed. "Antipyretic measures for treating fever in malaria". *Cochrane Database of Systematic Reviews*. **9**: CD002151. doi:10.1002/14651858.CD002151.pub2. PMID 22972057.
84. ^ Kokwaro G (2009). "Ongoing challenges in the management of malaria". *Malaria Journal*. **8** (Suppl 1): S2. doi:10.1186/1475-2875-8-S1-S2. PMC 2760237. PMID 19818169.
85. ^ WHO 2010, pp. 75–86
86. ^ WHO 2010, p. 21

87. ^ Keating GM (2012). "Dihydroartemisinin/piperaquine: A review of its use in the treatment of uncomplicated *Plasmodium falciparum* malaria". *Drugs*. **72** (7): 937–61. doi:10.2165/11203910-000000000-00000. PMID 22515619.
88. ^ Manyando C, Kayentao K, D'Alessandro U, Okafor HU, Juma E, Hamed K (2011). "A systematic review of the safety and efficacy of artemether-lumefantrine against uncomplicated *Plasmodium falciparum* malaria during pregnancy". *Malaria Journal*. **11**: 141. doi:10.1186/1475-2875-11-141. PMC 3405476. PMID 22548983.
89. ^ O'Brien C, Henrich PP, Passi N, Fidock DA (2011). "Recent clinical and molecular insights into emerging artemisinin resistance in *Plasmodium falciparum*". *Current Opinion in Infectious Diseases*. **24** (6): 570–7. doi:10.1097/QCO.0b013e32834cd3ed. PMC 3268008. PMID 22001944.
90. ^ Fairhurst RM, Nayyar GM, Breman JG, Hallett R, Vennerstrom JL, Duong S, Ringwald P, Wellems TE, Plowe CV, Dondorp AM (2012). "Artemisinin-resistant malaria: research challenges, opportunities, and public health implications". *American Journal of Tropical Medicine and Hygiene*. **87** (2): 231–41. doi:10.4269/ajtmh.2012.12-0025. PMC 3414557. PMID 22855752.
91. ^ Waters NC, Edstein MD (2012). "8-Aminoquinolines: Primaquine and tafenoquine". In Staines HM, Krishna S. *Treatment and Prevention of Malaria: Antimalarial Drug Chemistry, Action and Use*. Springer. pp. 69–93. ISBN 978-3-0346-0479-6.
92. ^ Rajapakse, Senaka; Rodrigo, Chaturaka; Fernando, Sumadhya Deepika (29 April 2015). "Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria". *Cochrane Database of Systematic Reviews*. **4**: CD010458. doi:10.1002/14651858.cd010458.pub2. PMC 4468925. PMID 25921416.
93. ^ Kochar, DK; Saxena, V; Singh, N; Kochar, SK; Kumar, SV; Das, A (January 2005). "Plasmodium vivax malaria.". *Emerging Infectious Diseases*. **11** (1): 132–4. doi:10.3201/eid1101.040519. PMC 3294370. PMID 15705338.
94. ^ Pasvol, G (2005). "The treatment of complicated and severe malaria.". *British medical bulletin*. 75-76: 29–47. doi:10.1093/bmb/ldh059. PMID 16495509.
95. ^ Idro, R; Marsh, K; John, CC; Newton, CR (October 2010). "Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome.". *Pediatric research*. **68** (4): 267–74. doi:10.1203/pdr.0b013e3181eee738. PMC 3056312. PMID 20606600.
96. ^ Sinclair D, Donegan S, Isba R, Lalloo DG (2012). Sinclair D, ed. "Artesunate versus quinine for treating severe malaria". *Cochrane Database of Systematic Reviews*. **6**: CD005967. doi:10.1002/14651858.CD005967.pub4. PMID 22696354.
97. ^ Kyu, Hmwe Hmwe; Fernández, Eduardo (2009). "Artemisinin derivatives versus quinine for cerebral malaria in African children: a systematic review". *Bulletin of the World Health Organization*. **87**: 896–904. doi:10.2471/BLT.08.060327.
98. ^ Sinha, Shweta; Medhi, Bikash; Sehgal, Rakesh (2014). "Challenges of drug-resistant malaria". *Parasite*. **21**: 61. doi:10.1051/parasite/2014059. ISSN 1776-1042. PMID 25402734.
99. ^ White NJ (2008). "Qinghaosu (artemisinin): The price of success". *Science*. **320** (5874): 330–4. doi:10.1126/science.1155165. PMID 18420924.
100. ^ Wongsrichanalai C, Meshnick SR (2008). "Declining artesunate-mefloquine efficacy against falciparum malaria on the Cambodia–Thailand border". *Emerging Infectious Diseases*. **14** (5): 716–9. doi:10.3201/eid1405.071601. PMC 2600243. PMID 18439351.
101. ^ Dondorp AM, Yeung S, White L, Nguon C, Day NP, Socheat D, von Seidlein L (2010). "Artemisinin resistance: Current status and scenarios for containment". *Nature Reviews Microbiology*. **8** (4): 272–80. doi:10.1038/nrmicro2331. PMID 20208550.
102. ^ World Health Organization (2013). "Q&A on artemisinin resistance". *WHO malaria publications*.
103. ^ Briggs, Helen (30 July 2014) Call for 'radical action' on drug-resistant malaria BBC News, health, Retrieved 30 July 2013
104. ^ Ashley EA, Dhorda M, Fairhurst RM, Amaratunga C, Lim P, et al. (2014). "Spread of artemisinin resistance in *Plasmodium falciparum* malaria". *New England Journal of Medicine*. **371** (5): 411–23. doi:10.1056/NEJMoa1314981. PMC 4143591. PMID 25075834.
105. ^ "Frequently Asked Questions (FAQs): If I get malaria, will I have it for the rest of my life?". US Centers for Disease Control and Prevention. February 8, 2010. Retrieved 2012-05-14.
106. ^ Trampuz A, Jereb M, Muzlovic I, Prabhu R (2003). "Clinical review: Severe malaria". *Critical Care*. **7** (4): 315–23. doi:10.1186/cc2183. PMC 270697. PMID 12930555.
107. ^ *a b c d* Fernando SD, Rodrigo C, Rajapakse S (2010). "The 'hidden' burden of malaria: Cognitive impairment following infection". *Malaria Journal*. **9**: 366. doi:10.1186/1475-2875-9-366. PMC 3018393. PMID 21171998.
108. ^ Riley EM, Stewart VA (2013). "Immune mechanisms in malaria: New insights in vaccine development". *Nature Medicine*. **19** (2): 168–78. doi:10.1038/nm.3083. PMID 23389617.
109. ^ *a b* Idro R, Marsh K, John CC, Newton CR (2010). "Cerebral malaria: Mechanisms of brain injury and strategies for improved neuro-cognitive outcome". *Pediatric Research*. **68** (4): 267–74. doi:10.1203/PDR.0b013e3181eee738. PMC 3056312. PMID 20606600.
110. ^ "Malaria". US Centers for Disease Control and Prevention. April 15, 2010. Retrieved 2012-05-02.
111. ^ *World Malaria Report 2015*. World Health Organization. December 2015. ISBN 978-92-4-156515-8.
112. ^ Olupot-Olupot P, Maitland, K (2013). "Management of severe malaria: Results from recent trials". *Advances in Experimental Medicine and Biology*. Advances in Experimental Medicine and Biology. **764**: 241–50. doi:10.1007/978-1-4614-4726-9_20. ISBN 978-1-4614-4725-2. PMID 23654072.

113. ^ [a] [b] Murray CJ, Rosenfeld LC, Lim SS, Andrews KG, Foreman KJ, Haring D, Fullman N, Naghavi M, Lozano R, Lopez AD (2012). "Global malaria mortality between 1980 and 2010: A systematic analysis". *Lancet*. **379** (9814): 413–31. doi:10.1016/S0140-6736(12)60034-8. PMID 22305225.
114. ^ Bhatt, S.; J. Weiss, D.; Cameron, E.; Bisanzio, D.; Mappin, B.; Dalrymple, U.; Battle, K.E.; Moyes, C.L.; Henry, A.; Eckhoff, P.A.; Wenger, E.A.; Briët, O.; Penny, M.A.; Smith, T.A.; Bennett, A.; Yukich, J.; Eisele, T.P.; Griffin, J.T.; A. Fergus, C.; Lynch, M.; Lindgren, F.; Cohen, J.M.; Murray, C.L.J.; Smith, D.L.; Hay, S.I.; Cibulskis, R.E.; Gething, P.W. (16 September 2015). "The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015". *Nature*. **526** (7572): 207–211. doi:10.1038/nature15535. PMID 26375008.
115. ^ Layne SP. "Principles of Infectious Disease Epidemiology" (PDF). *EPI 220*. UCLA Department of Epidemiology. Retrieved 2007-06-15.[*dead link*]
116. ^ Provost C (April 25, 2011). "World Malaria Day: Which countries are the hardest hit? Get the full data". *The Guardian*. Retrieved 2012-05-03.
117. ^ [a] [b] Guerra CA, Hay SI, Lucioparedes LS, Gikandi PW, Tatem AJ, Noor AM, Snow RW (2007). "Assembling a global database of malaria parasite prevalence for the Malaria Atlas Project". *Malaria Journal*. **6** (1): 17. doi:10.1186/1475-2875-6-17. PMC 1805762. PMID 17306022.
118. ^ Hay SI, Okiro EA, Gething PW, Patil AP, Tatem AJ, Guerra CA, Snow RW (2010). Mueller I, ed. "Estimating the global clinical burden of *Plasmodium falciparum* malaria in 2007". *PLoS Medicine*. **7** (6): e1000290. doi:10.1371/journal.pmed.1000290. PMC 2885984. PMID 20563310.
119. ^ Gething PW, Patil AP, Smith DL, Guerra CA, Elyazar IR, Johnston GL, Tatem AJ, Hay SI (2011). "A new world malaria map: *Plasmodium falciparum* endemicity in 2010". *Malaria Journal*. **10** (1): 378. doi:10.1186/1475-2875-10-378. PMC 3274487. PMID 22185615.
120. ^ World Malaria Report 2012 (PDF) (Report). World Health Organization.
121. ^ Feachem RG, Phillips AA, Hwang J, Cotter C, Wielgosz B, Greenwood BM, Sabot O, Rodriguez MH, Abeyasinghe RR, Ghebreyesus TA, Snow RW (2010). "Shrinking the malaria map: progress and prospects". *Lancet*. **376** (9752): 1566–78. doi:10.1016/S0140-6736(10)61270-6. PMC 3044848. PMID 21035842.
122. ^ Greenwood B, Mutabingwa T (2002). "Malaria in 2002". *Nature*. **415** (6872): 670–2. doi:10.1038/415670a. PMID 11832954.
123. ^ Jamieson A, Toovey S, Maurel M (2006). *Malaria: A Traveller's Guide*. Struik. p. 30. ISBN 978-1-77007-353-1.
124. ^ Abeku TA (2007). "Response to malaria epidemics in Africa". *Emerging Infectious Diseases*. **14** (5): 681–6. doi:10.3201/eid1305.061333. PMC 2738452. PMID 17553244.
125. ^ Cui L, Yan G, Sattabongkot J, Cao Y, Chen B, Chen X, Fan Q, Fang Q, Jongwutiwes S, Parker D, Sirichaisinthop J, Kyaw MP, Su XZ, Yang H, Yang Z, Wang B, Xu J, Zheng B, Zhong D, Zhou G (2012). "Malaria in the Greater Mekong Subregion: Heterogeneity and complexity". *Acta Tropica*. **121** (3): 227–39. doi:10.1016/j.actatropica.2011.02.016. PMC 3132579. PMID 21382335.
126. ^ Machault V, Vignolles C, Borchi F, Vounatsou P, Pages F, Briolant S, Lacaux JP, Rogier C (2011). "The use of remotely sensed environmental data in the study of malaria" (PDF). *Geospatial Health*. **5** (2): 151–68. doi:10.4081/gh.2011.167. PMID 21590665.
127. ^ Harper K, Armelagos G (2011). "The changing disease-scape in the third epidemiological transition". *International Journal of Environmental Research and Public Health*. **7** (2): 675–97. doi:10.3390/ijerph7020675. PMC 2872288. PMID 20616997.
128. ^ Prugnolle F, Durand P, Ollomo B, Duval L, Ariey F, Arnathau C, Gonzalez JP, Leroy E, Renaud F (2011). Manchester M, ed. "A fresh look at the origin of *Plasmodium falciparum*, the most malignant malaria agent". *PLoS Pathogens*. **7** (2): e1001283. doi:10.1371/journal.ppat.1001283. PMC 3044689. PMID 21383971.
129. ^ Cox F (2002). "History of human parasitology". *Clinical Microbiology Reviews*. **15** (4): 595–612. doi:10.1128/CMR.15.4.595-612.2002. PMC 126866. PMID 12364371.
130. ^ [a] [b] [c] Strong, Richard P (1944). *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases* (Seventh ed.). York, PA: The Blakiston Company. p. 3.
131. ^ "DNA clues to malaria in ancient Rome". *BBC News*. February 20, 2001., in reference to Sallares R, Gomzi S (2001). "Biomolecular archaeology of malaria". *Ancient Biomolecules*. **3** (3): 195–213. OCLC 538284457.
132. ^ Sallares R (2002). *Malaria and Rome: A History of Malaria in Ancient Italy*. Oxford University Press. doi:10.1093/acprof:oso/9780199248506.001.0001. ISBN 978-0-19-924850-6.
133. ^ Hays JN (2005). *Epidemics and Pandemics: Their Impacts on Human History*. Santa Barbara, California: ABC-CLIO. p. 11. ISBN 978-1-85109-658-9.
134. ^ Reiter, P (1999). "From Shakespeare to Defoe: malaria in England in the Little Ice Age.". *Emerging Infectious Diseases*. **6** (1): 1–11. doi:10.3201/eid0601.000101. PMC 2627969. PMID 10653562.
135. ^ Lindemann M (1999). *Medicine and Society in Early Modern Europe*. Cambridge University Press. p. 62. ISBN 978-0-521-42354-0.
136. ^ Gratz NG; World Health Organization (2006). *The Vector- and Rodent-borne Diseases of Europe and North America: Their Distribution and Public Health Burden*. Cambridge University Press. p. 33. ISBN 978-0-521-85447-4.
137. ^ Webb Jr JLA (2009). *Humanity's Burden: A Global History of Malaria*. Cambridge University Press. ISBN 978-0-521-

67012-8.
138. ^ "The Nobel Prize in Physiology or Medicine 1907: Alphonse Laveran". The Nobel Foundation. Retrieved 2012-05-14.
139. ^ Tan SY, Sung H (2008). "Carlos Juan Finlay (1833–1915): Of mosquitoes and yellow fever" (PDF). *Singapore Medical Journal*. **49** (5): 370–1. PMID 18465043.
140. ^ Chernin E (1983). "Josiah Clark Nott, insects, and yellow fever". *Bulletin of the New York Academy of Medicine*. **59** (9): 790–802. PMC 1911699. PMID 6140039.
141. ^ Chernin E (1977). "Patrick Manson (1844–1922) and the transmission of filariasis". *American Journal of Tropical Medicine and Hygiene*. **26** (5 Pt 2 Suppl): 1065–70. PMID 20786.
142. ^ "The Nobel Prize in Physiology or Medicine 1902: Ronald Ross". The Nobel Foundation. Retrieved 2012-05-14.
143. ^ "Ross and the Discovery that Mosquitoes Transmit Malaria Parasites". *CDC Malaria website*. Archived from the original on 2007-06-02. Retrieved 2012-06-14.
144. ^ Simmons JS (1979). *Malaria in Panama*. Ayer Publishing. ISBN 978-0-405-10628-6.
145. ^ Kaufman TS, Rúveda EA (2005). "The quest for quinine: Those who won the battles and those who won the war". *Angewandte Chemie International Edition in English*. **44** (6): 854–85. doi:10.1002/anie.200400663. PMID 15669029.
146. ^ Pelletier PJ, Caventou JB (1820). "Des recherches chimiques sur les Quinquinas" [Chemical research on quinquinas]. *Annales de Chimie et de Physique* (in French). **15**: 337–65.
147. ^ Kyle R, Shampe M (1974). "Discoverers of quinine". *Journal of the American Medical Association*. **229** (4): 462. doi:10.1001/jama.229.4.462. PMID 4600403.
148. ^ Achan J, Talisuna AO, Erhart A, Yeka A, Tibenderana JK, Baliraine FN, Rosenthal PJ, D'Alessandro U (2011). "Quinine, an old anti-malarial drug in a modern world: Role in the treatment of malaria". *Malaria Journal*. **10** (1): 144. doi:10.1186/1475-2875-10-144. PMC 3121651. PMID 21609473.
149. ^ Hsu E (2006). "Reflections on the 'discovery' of the antimalarial *qinghao*". *British Journal of Clinical Pharmacology*. **61** (3): 666–70. doi:10.1111/j.1365-2125.2006.02673.x. PMC 1885105. PMID 16722826.
150. ^ Hao, C. (29 September 2011). "Lasker Award Rekindles Debate Over Artemisinin's Discovery". *News: ScienceInsider*. Science/AAAS.
151. ^ "Nobel Prize announcement" (PDF). *NobelPrize.org*. Retrieved 5 October 2015.
152. ^ Vogel V (2013). "Malaria as a lifesaving therapy". *Science*. **342** (6159): 684–7. doi:10.1126/science.342.6159.684.
153. ^ "Eradication of Malaria in the United States (1947–1951)". US Centers for Disease Control and Prevention. February 8, 2010. Retrieved 2012-05-02.
154. ^ Killeen G, Fillinger U, Kiche I, Gouagna L, Knols B (2002). "Eradication of *Anopheles gambiae* from Brazil: Lessons for malaria control in Africa?". *Lancet Infectious Diseases*. **2** (10): 618–27. doi:10.1016/S1473-3099(02)00397-3. PMID 12383612.
155. ^ Vanderberg JP (2009). "Reflections on early malaria vaccine studies, the first successful human malaria vaccination, and beyond". *Vaccine*. **27** (1): 2–9. doi:10.1016/j.vaccine.2008.10.028. PMC 2637529. PMID 18973784.
156. ^ *a b* Walsh, Fergus (24 July 2015). "Malaria vaccine gets 'green light'". *BBC News Online*.
157. ^ Humphreys M (2001). *Malaria: Poverty, Race, and Public Health in the United States*. Johns Hopkins University Press. p. 256. ISBN 0-8018-6637-5.
158. ^ Sachs J, Malaney P (2002). "The economic and social burden of malaria". *Nature*. **415** (6872): 680–5. doi:10.1038/415680a. PMID 11832956.
159. ^ Roll Back Malaria WHO partnership (2003). "Economic costs of malaria" (PDF). WHO.
160. ^ Ricci F (2012). "Social implications of malaria and their relationships with poverty". *Mediterranean Journal of Hematology and Infectious Diseases*. **4** (1): e2012048. doi:10.4084/MJHID.2012.048. PMC 3435125. PMID 22973492.
161. ^ Lon CT, Tsuyuoka R, Phanouvong S, Nivanna N, Socheat D, Sokhan C, Blum N, Christophel EM, Smine A (2006). "Counterfeit and substandard antimalarial drugs in Cambodia". *Transactions of the Royal Society of Tropical Medicine and Hygiene*. **100** (11): 1019–24. doi:10.1016/j.trstmh.2006.01.003. PMID 16765399.
162. ^ Newton PN, Fernández FM, Plançon A, Mildenhall DC, Green MD, Ziyong L, Christophel EM, Phanouvong S, Howells S, McIntosh E, Laurin P, Blum N, Hampton CY, Faure K, Nyadong L, Soong CW, Santoso B, Zhiguang W, Newton J, Palmer K (2008). "A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia". *PLoS Medicine*. **5** (2): e32. doi:10.1371/journal.pmed.0050032. PMC 2235893. PMID 18271620.
163. ^ Newton PN, Green MD, Fernández FM, Day NP, White NJ (2006). "Counterfeit anti-infective drugs". *Lancet Infectious Diseases*. **6** (9): 602–13. doi:10.1016/S1473-3099(06)70581-3. PMID 16931411.
164. ^ Parry J (2005). "WHO combats counterfeit malaria drugs in Asia". *British Medical Journal*. **330** (7499): 1044. doi:10.1136/bmj.330.7499.1044-d. PMC 557259. PMID 15879383.
165. ^ Gautam CS, Utreja A, Singal GL (2009). "Spurious and counterfeit drugs: A growing industry in the developing world". *Postgraduate Medical Journal*. **85** (1003): 251–6. doi:10.1136/pgmj.2008.073213. PMID 19520877.
166. ^ Caudron JM, Ford N, Henkens M, Macé, Kidle-Monroe R, Pinel J (2008). "Substandard medicines in resource-poor settings: A problem that can no longer be ignored". *Tropical Medicine & International Health*. **13** (8): 1062–72. doi:10.1111/j.1365-3156.2008.02106.x. PMID 18631318.
167. ^ Nayyar GM, Breman JG, Newton PN, Herrington J (2012). "Poor-quality antimalarial drugs in southeast Asia and sub-

Saharan Africa". *Lancet Infectious Diseases*. **12** (6): 488–96. doi:10.1016/S1473-3099(12)70064-6 . PMID 22632187 .
168. ^ Russell PF (January 6, 2009). "Communicable diseases Malaria". *Medical Department of the United States Army in World War II*. U.S. Army Medical Department. Office of Medical History. Retrieved 2012-09-24.
169. ^ Melville CH (1910). "The prevention of malaria in war". In Ross R. *The Prevention of Malaria*. New York, New York: E.P. Dutton. p. 577.
170. ^ Bray RS (2004). *Armies of Pestilence: The Effects of Pandemics on History*. James Clarke. p. 102. ISBN 978-0-227-17240-7.
171. ^ Byrne JP (2008). *Encyclopedia of Pestilence, Pandemics, and Plagues: A-M*. ABC-CLIO. p. 383. ISBN 978-0-313-34102-1.
172. ^ Kakkilaya BS (April 14, 2006). "History of Malaria During Wars". Malariasite.com. Retrieved 2012-05-03.
173. ^ "History | CDC Malaria". US Centers for Disease Control and Prevention. February 8, 2010. Retrieved 2012-05-15.
174. ^ Strom S (April 1, 2011). "Mission Accomplished, Nonprofits Go Out of Business". *The New York Times*. nytimes.com. OCLC 292231852. Retrieved 2012-05-09.
175. ^ "Fighting AIDS, Tuberculosis and Malaria". The Global Fund. Retrieved 2012-05-09.
176. ^ Schoofs M (July 17, 2008). "Clinton foundation sets up malaria-drug price plan". Wall Street Journal. Retrieved 2012-05-14.
177. ^ "Executive summary and key points" (PDF). *World Malaria Report 2013*. World Health Organization. Retrieved 13 February 2014.
178. ^ "World Malaria Report 2013" (PDF). World Health Organization. Retrieved 13 February 2014.
179. ^ Meade MS, Emch M (2010). *Medical Geography* (3rd ed.). Guilford Press. pp. 120–3. ISBN 978-1-60623-016-9.
180. ^ Williams LL (1963). "Malaria eradication in the United States". *American Journal of Public Health and the Nation's Health*. **53** (1): 17–21. doi:10.2105/AJPH.53.1.17. PMC 1253858. PMID 14000898.
181. ^ Radwick, Danielle (October 5, 2016). "Can Malaria Be Eradicated?". Council on Foreign Relations.
182. ^ Hall, B. Fenton; Fauci, Anthony S. (2009-12-01). "Malaria Control, Elimination, and Eradication: The Role of the Evolving Biomedical Research Agenda". *Journal of Infectious Diseases*. **200** (11): 1639–43. doi:10.1086/646611. PMID 19877843.
183. ^ "WHO | A research agenda for malaria eradication". *www.who.int*. Retrieved 2016-03-07.
184. ^ Hill AVS (2011). "Vaccines against malaria". *Philosophical Transactions of the Royal Society B*. **366** (1579): 2806–14. doi:10.1098/rstb.2011.0091. PMC 3146776. PMID 21893544.
185. ^ Crompton PD, Pierce SK, Miller LH (2010). "Advances and challenges in malaria vaccine development". *Journal of Clinical Investigation*. **120** (12): 4168–78. doi:10.1172/JCI44423. PMC 2994342. PMID 21123952.
186. ^ Graves P, Gelband H (2006). Graves PM, ed. "Vaccines for preventing malaria (blood-stage)". *Cochrane Database of Systematic Reviews* (4): CD006199. doi:10.1002/14651858.CD006199. PMID 17054281.
187. ^ Graves P, Gelband H (2006). Graves PM, ed. "Vaccines for preventing malaria (SPf66)". *Cochrane Database of Systematic Reviews* (2): CD005966. doi:10.1002/14651858.CD005966. PMID 16625647.
188. ^ Kalanon M, McFadden GI (2010). "Malaria, *Plasmodium falciparum* and its apicoplast". *Biochemical Society Transactions*. **38** (3): 775–82. doi:10.1042/BST0380775. PMID 20491664.
189. ^ Müller IB, Hyde JE, Wrenger C (2010). "Vitamin B metabolism in *Plasmodium falciparum* as a source of drug targets". *Trends in Parasitology*. **26** (1): 35–43. doi:10.1016/j.pt.2009.10.006. PMID 19939733.
190. ^ Du Q, Wang H, Xie J (2011). "Thiamin (vitamin B1) biosynthesis and regulation: A rich source of antimicrobial drug targets?". *International Journal of Biological Sciences*. **7** (1): 41–52. doi:10.7150/ijbs.7.41. PMC 3020362. PMID 21234302.
191. ^ Biot C, Castro W, Botté CY, Navarro M (2012). "The therapeutic potential of metal-based antimalarial agents: Implications for the mechanism of action". *Dalton Transactions*. **41** (21): 6335–49. doi:10.1039/C2DT12247B. PMID 22362072.
192. ^ Roux C, Biot C (2012). "Ferrocene-based antimalarials". *Future Medicinal Chemistry*. **4** (6): 783–97. doi:10.4155/fmc.12.26. PMID 22530641.
193. ^ *a b* Carroll John (8 December 2014). "New malaria drug unleashes an immune system assault on infected cells". fiercebiotechresearch.com. Retrieved 16 December 2014.
194. ^ Aultman KS, Gottlieb M, Giovanni MY, Fauci AS (2002). "*Anopheles gambiae* genome: completing the malaria triad". *Science*. **298** (5591): 13. doi:10.1126/science.298.5591.13. PMID 12364752.
195. ^ Ito J, Ghosh A, Moreira LA, Wimmer EA, Jacobs-Lorena M (2002). "Transgenic anopheline mosquitoes impaired in transmission of a malaria parasite". *Nature*. **417** (6887): 452–5. doi:10.1038/417452a. PMID 12024215.
196. ^ Gantz, Valentino M.; Jasinskiene, Nijole; Tatarenkova, Olga; Fazekas, Aniko; Macias, Vanessa M.; Bier, Ethan; James, Anthony A. (23 November 2015). "Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito". *Proceedings of the National Academy of Sciences*: 201521077. doi:10.1073/pnas.1521077112. PMID 26598698. Retrieved 24 November 2015.
197. ^ Flam, Faye (4 February 2016). "Fighting Zika Virus With Genetic Engineering". *Bloomberg*.
198. ^ Rich SM, Ayala FJ (2006). "Evolutionary origins of human malaria parasites". In Dronamraju KR, Arese P. *Malaria: Genetic and Evolutionary Aspects*. New York, New York: Springer. pp. 125–46. ISBN 978-0-387-28294-7.

199. ^ Baird JK. (2009). "Malaria zoonoses". *Travel Medicine and Infectious Disease*. **7** (5): 269–77. doi:10.1016/j.tmaid.2009.06.004. PMID 19747661.
200. ^ Ameri M (2010). "Laboratory diagnosis of malaria in nonhuman primates". *Veterinary Clinical Pathology*. **39** (1): 5–19. doi:10.1111/j.1939-165X.2010.00217.x. PMID 20456124.
201. ^ Mlambo G, Kumar N (2008). "Transgenic rodent *Plasmodium berghei* parasites as tools for assessment of functional immunogenicity and optimization of human malaria vaccines". *Eukaryotic Cell*. **7** (11): 1875–9. doi:10.1128/EC.00242-08. PMC 2583535. PMID 18806208.
202. ^ Lapointe DA, Atkinson CT, Samuel MD (2012). "Ecology and conservation biology of avian malaria". *Annals of the New York Academy of Sciences*. **1249**: 211–26. doi:10.1111/j.1749-6632.2011.06431.x. PMID 22320256.


### Cited literature


- WHO (2010). Guidelines for the Treatment of Malaria (PDF) (Report) (2nd ed.). World Health Organization. ISBN 978-9-2415-4792-5.
- Schlagenhauf-Lawlor P (2008). *Travelers' Malaria*. PMPH-USA. ISBN 978-1-55009-336-0.


## Further reading


- Bynum WF, Overy C (1998). *The Beast in the Mosquito: The Correspondence of Ronald Ross and Patrick Manson*. Wellcome Institute Series in The History of Medicine. Rodopi. ISBN 978-90-420-0721-5.
- *Guidelines for the treatment of malaria* (3rd ed.). World Health Organization. 2015. ISBN 9789241549127.


## External links

- Malaria at DMOZ
- WHO site on malaria
- UNHCO site on malaria
- Global Malaria Action Plan (2008)
- Doctors Without Borders/Médecins Sans Frontières – *Malaria* information pages
- WHO/TDR Malaria Database via the Wayback Machine
- Anti-malaria and sustainable development
- Worldwide Antimalarial Resistance Network (WWARN)



| v · t · e · | **Malaria** |
|---|---|
| **Biology** | **Malaria** (Cerebral · Blackwater fever · Pregnancy-associated · · Plasmodium (biology · life cycle · *vivax* · *falciparum* · *ovale* · *malariae* · · Anopheles mosquito · Lifecycle (Schizont · Merozoite · Hypnozoite · Gametocyte · · |
| **Control and prevention** | Public health (DDT · Mosquito net · Malaria prophylaxis · Mosquito control · Sterile insect technique · · Genetic resistance (Duffy antigen · Sickle cell anaemia · Thalassemia · G6PDH deficiency · · Malaria vaccine (RTS,S · · |
| **Diagnosis and treatment** | Diagnosis of malaria (Malaria culture · Blood film · Malaria antigen detection tests · · Antimalarials (Artemisinin · Mefloquine · Proguanil · · |
| **Society and malaria** | Diseases of poverty · Millennium Development Goals · History of malaria (Timeline · Roman fever · National Malaria Eradication Program · · World Malaria Day · Epidemiology (Malaria and the Caribbean · Malaria Atlas Project · · |

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| **Organisations** | Roll Back Malaria Partnership · Malaria Consortium · Against Malaria Foundation · Bill and Melinda Gates Foundation · Imagine No Malaria · Malaria No More · Africa Fighting Malaria · African Malaria Network Trust · South African Malaria Initiative · African Leaders Malaria Alliance · Amazon Malaria Initiative · The Global Fund to Fight AIDS, Tuberculosis and Malaria · Medicines for Malaria Venture · |

| v · t · e · **Diseases of poverty** | |
|---|---|
| **Diseases of poverty** | AIDS · **Malaria** · Tuberculosis · Measles · Pneumonia · Diarrheal diseases · |
| **Neglected diseases** | Cholera · Chagas disease · African sleeping sickness · Schistosomiasis · Dracunculiasis · River blindness · Leishmaniasis · Trachoma · |
| **Miscellaneous** | Malnutrition · Priority review voucher · |

| v · t · e · **Protozoan infection: Chromalveolate and Archaeplastida (A07, B50–B54,B58, 007, 084)** | | | | |
|---|---|---|---|---|
| **Chromalveolate** | **Alveolate** | **Apicomplexa** | **Conoidasida/ Coccidia** | Coccidia: *Cryptosporidium hominis*/*Cryptosporidium parvum* (Cryptosporidiosis · · *Cystoisospora belli* (Isosporiasis · · *Cyclospora cayetanensis* (Cyclosporiasis · · *Toxoplasma gondii* (Toxoplasmosis · · |
| | | | **Aconoidasida** | *Plasmodium falciparum*/*vivax*/*ovale*/*malariae* (**Malaria** · Blackwater fever · · *Babesia* (Babesiosis · · |
| | | **Ciliophora** | *Balantidium coli* (Balantidiasis · · | |
| | **Heterokont** | *Blastocystis* (Blastocystosis · · *Pythium insidiosum* (Pythiosis · · | | |
| **Archaeplastida** | Algaemia: *Prototheca wickerhamii* (Protothecosis · · | | | |

| **Authority control** | GND: 4037197-9 · NDL: 00567482 · |
|---|---|

Categories: Malaria | Plasmodium | Insect-borne diseases | Protozoal diseases | Tropical diseases

# Meningitis



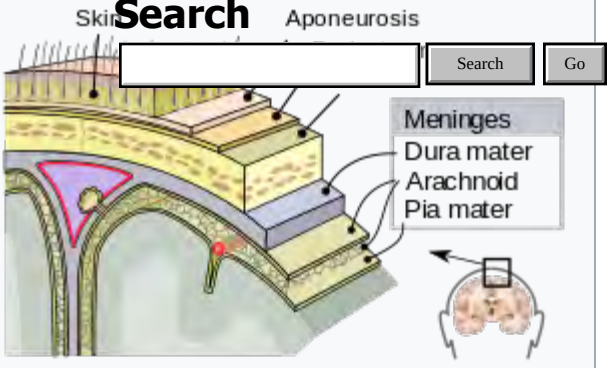
From Wikipedia, the free encyclopedia

**Meningitis** is an acute inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges.[1] The most common symptoms are fever, headache and neck stiffness. Other symptoms include confusion or altered consciousness, vomiting, and an inability to tolerate light or loud noises. Young children often exhibit only nonspecific symptoms, such as irritability, drowsiness, or poor feeding.[2] If a rash is present, it may indicate a particular cause of meningitis; for instance, meningitis caused by meningococcal bacteria may be accompanied by a characteristic rash.[1][3]

The inflammation may be caused by infection with viruses, bacteria, or other microorganisms, and less commonly by certain drugs.[4] Meningitis can be life-threatening because of the inflammation's proximity to the brain and spinal cord; therefore, the condition is classified as a medical emergency.[1][5] A lumbar puncture diagnoses or excludes meningitis.[2] A needle is inserted into the spinal canal to collect a sample of cerebrospinal fluid (CSF), that envelops the brain and spinal cord. The CSF is examined in a medical laboratory.[5]

Some forms of meningitis are preventable by immunization with the meningococcal, mumps, pneumococcal, and Hib vaccines.[1] Giving antibiotics to people with significant exposure to certain types of meningitis may also be useful.[2] The first treatment in acute meningitis consists of promptly giving antibiotics and sometimes antiviral drugs.[2][6] Corticosteroids can also be used to prevent complications from excessive inflammation.[3][5] Meningitis can lead to serious long-term consequences such as deafness, epilepsy, hydrocephalus, or cognitive deficits, especially if not treated quickly.[1][3]

## Variants




Meninges of the central nervous system: dura mater, arachnoid mater, and pia mater.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Infectious disease, neurology |
| **ICD-10** | G00–G03 |
| **ICD-9-CM** | 320–322 |
| **DiseasesDB** | 22543 |
| **MedlinePlus** | 000680 |
| **eMedicine** | med/2613 emerg/309 emerg/390 |
| **Patient UK** | Meningitis |
| **MeSH** | D008581 |

[edit on Wikidata]

In 2013 meningitis occurred in about 16 million people worldwide.[7] This resulted in 303,000 deaths – down from 464,000 deaths in 1990.[8] With appropriate treatment the risk of death in bacterial meningitis is less than 15%.[2] Outbreaks of bacterial meningitis occur between December and June each year in an area of sub-Saharan Africa known as the meningitis belt.[9] Smaller outbreaks may also occur in other areas of the world.[9] The word meningitis is from Greek μῆνιγξ *méninx*, "membrane" and the medical suffix *-itis*, "inflammation".[10][11]

Contents





# Signs and symptoms [edit]

## Clinical features [edit]

Neck stiffness, Texas meningitis epidemic of 1911–12

In adults, the most common symptom of meningitis is a severe headache, occurring in almost 90% of cases of bacterial meningitis, followed by nuchal rigidity (the inability to flex the neck forward passively due to increased neck muscle tone and stiffness).[12] The classic triad of diagnostic signs consists of nuchal rigidity, sudden high fever, and altered mental status; however, all three features are present in only 44–46% of bacterial meningitis cases.[12][13] If none of the three signs are present, acute meningitis is extremely unlikely.[13] Other signs commonly associated with meningitis include photophobia (intolerance to bright light) and phonophobia (intolerance to loud noises). Small children often do not exhibit the aforementioned symptoms, and may only be irritable and look unwell.[1] The fontanelle (the soft spot on the top of a baby's head) can bulge in infants aged up to 6 months. Other features that distinguish meningitis from less severe illnesses in young children are leg pain, cold extremities, and an abnormal skin color.[14][15]

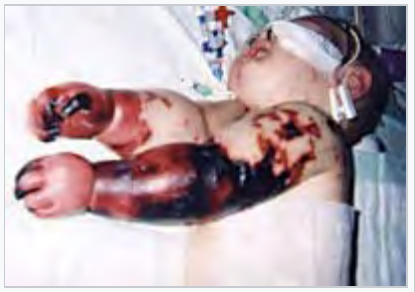
Nuchal rigidity occurs in 70% of bacterial meningitis in adults.[13] Other signs of meningism include the presence of positive Kernig's sign or Brudziński sign. Kernig's sign is assessed with the person lying supine, with the hip and knee flexed to 90 degrees. In a person with a positive Kernig's sign, pain limits passive extension of the knee. A positive Brudzinski's sign occurs when flexion of the neck causes involuntary flexion of the knee and hip. Although Kernig's sign and Brudzinski's sign are both commonly used to screen for meningitis, the sensitivity of these tests is limited.[13][16] They do, however, have very good specificity

for meningitis: the signs rarely occur in other diseases.[13] Another test, known as the "jolt accentuation maneuver" helps determine whether meningitis is present in those reporting fever and headache. A person is asked to rapidly rotate the head horizontally; if this does not make the headache worse, meningitis is unlikely.[13]

Meningitis caused by the bacterium *Neisseria meningitidis* (known as "meningococcal meningitis") can be differentiated from meningitis with other causes by a rapidly spreading petechial rash, which may precede other symptoms.[14] The rash consists of numerous small, irregular purple or red spots ("petechiae") on the trunk, lower extremities, mucous membranes, conjuctiva, and (occasionally) the palms of the hands or soles of the feet. The rash is typically non-blanching; the redness does not disappear when pressed with a finger or a glass tumbler. Although this rash is not necessarily present in meningococcal meningitis, it is relatively specific for the disease; it does, however, occasionally occur in meningitis due to other bacteria.[1] Other clues on the cause of meningitis may be the skin signs of hand, foot and mouth disease and genital herpes, both of which are associated with various forms of viral meningitis.[17]

## Early complications [edit]

Additional problems may occur in the early stage of the illness. These may require specific treatment, and sometimes indicate severe illness or worse prognosis. The infection may trigger sepsis, a systemic inflammatory response syndrome of falling blood pressure, fast heart rate, high or abnormally low temperature, and rapid breathing. Very low blood pressure may occur at an early stage, especially but not exclusively in meningococcal meningitis; this may lead to insufficient blood supply to other organs.[1] Disseminated intravascular coagulation, the excessive activation of blood clotting, may obstruct blood flow to organs and paradoxically increase the bleeding risk. Gangrene of limbs can occur in meningococcal disease.[1] Severe meningococcal and pneumococcal infections may result in hemorrhaging of the adrenal glands, leading to Waterhouse-Friderichsen syndrome, which is often fatal.[18]



Charlotte Cleverley-Bisman developed severe meningococcal meningitis as a young child; in her case, the petechial rash progressed to gangrene and required amputation of all limbs. She survived the disease and became a poster child for a meningitis vaccination campaign in New Zealand.

The brain tissue may swell, pressure inside the skull may increase and the swollen brain may herniate through the skull base. This may be noticed by a decreasing level of consciousness, loss of the pupillary light reflex, and abnormal posturing.[3] The inflammation of the brain tissue may also obstruct the normal flow of CSF around the brain (hydrocephalus).[3] Seizures may occur for various reasons; in children, seizures are common in the early stages of meningitis (in 30% of cases) and do not necessarily indicate an underlying cause.[5] Seizures may result from increased pressure and from areas of inflammation in the brain tissue.[3] Focal seizures (seizures that involve one limb or part of the body), persistent seizures, late-onset seizures and those that are difficult to control with medication indicate a poorer long-term outcome.[1]

Inflammation of the meninges may lead to abnormalities of the cranial nerves, a group of nerves arising from the brain stem that supply the head and neck area and which control, among other functions, eye movement, facial muscles, and hearing.[1][13] Visual symptoms and hearing loss may persist after an episode of meningitis.[1] Inflammation of the brain (encephalitis) or its blood vessels (cerebral vasculitis), as well as the formation of blood clots in the veins (cerebral venous thrombosis), may all lead to weakness, loss of sensation, or abnormal movement or function of the part of the body supplied by the affected area of the brain.[1][3]

## Causes [edit]

Meningitis is typically caused by an infection with microorganisms. Most infections are due to viruses,[13]

with bacteria, fungi, and protozoa being the next most common causes.[4] It may also result from various non-infectious causes.[4] The term *aseptic meningitis* refers to cases of meningitis in which no bacterial infection can be demonstrated. This type of meningitis is usually caused by viruses but it may be due to bacterial infection that has already been partially treated, when bacteria disappear from the meninges, or pathogens infect a space adjacent to the meninges (e.g. sinusitis). Endocarditis (an infection of the heart valves which spreads small clusters of bacteria through the bloodstream) may cause aseptic meningitis. Aseptic meningitis may also result from infection with spirochetes, a type of bacteria that includes *Treponema pallidum* (the cause of syphilis) and *Borrelia burgdorferi* (known for causing Lyme disease). Meningitis may be encountered in cerebral malaria (malaria infecting the brain) or amoebic meningitis, meningitis due to infection with amoebae such as *Naegleria fowleri*, contracted from freshwater sources.[4]

## Bacterial [edit]

*See also: Neonatal infection*

The types of bacteria that cause bacterial meningitis vary according to the infected individual's age group.

- In premature babies and newborns up to three months old, common causes are *group B streptococci* (subtypes III which normally inhabit the vagina and are mainly a cause during the first week of life) and bacteria that normally inhabit the digestive tract such as *Escherichia coli* (carrying the K1 antigen). *Listeria monocytogenes* (serotype IVb) is transmitted by the mother before birth and may cause meningitis in the newborn.[19]
- Older children are more commonly affected by *Neisseria meningitidis* (meningococcus) and *Streptococcus pneumoniae* (serotypes 6, 9, 14, 18 and 23) and those under five by *Haemophilus influenzae* type B (in countries that do not offer vaccination).[1][5]
- In adults, *Neisseria meningitidis* and *Streptococcus pneumoniae* together cause 80% of bacterial meningitis cases. Risk of infection with *Listeria monocytogenes* is increased in persons over 50 years old.[3][5] The introduction of pneumococcal vaccine has lowered rates of pneumococcal meningitis in both children and adults.[20]

Recent skull trauma potentially allows nasal cavity bacteria to enter the meningeal space. Similarly, devices in the brain and meninges, such as cerebral shunts, extraventricular drains or Ommaya reservoirs, carry an increased risk of meningitis. In these cases, the persons are more likely to be infected with Staphylococci, Pseudomonas, and other Gram-negative bacteria.[5] These pathogens are also associated with meningitis in people with an impaired immune system.[1] An infection in the head and neck area, such as otitis media or mastoiditis, can lead to meningitis in a small proportion of people.[5] Recipients of cochlear implants for hearing loss are more at risk for pneumococcal meningitis.[21]

Tuberculous meningitis, which is meningitis caused by *Mycobacterium tuberculosis*, is more common in people from countries in which tuberculosis is endemic, but is also encountered in persons with immune problems, such as AIDS.[22]

Recurrent bacterial meningitis may be caused by persisting anatomical defects, either congenital or acquired, or by disorders of the immune system.[23] Anatomical defects allow continuity between the external environment and the nervous system. The most common cause of recurrent meningitis is a skull fracture,[23] particularly fractures that affect the base of the skull or extend towards the sinuses and petrous pyramids.[23] Approximately 59% of recurrent meningitis cases are due to such anatomical abnormalities, 36% are due to immune deficiencies (such as complement deficiency, which predisposes especially to recurrent meningococcal meningitis), and 5% are due to ongoing infections in areas adjacent to the meninges.[23]

## Viral [edit]

Viruses that cause meningitis include enteroviruses, herpes simplex virus (generally type 2, which produces most genital sores; less commonly type 1), varicella zoster virus (known for causing chickenpox and shingles), mumps virus, HIV, and LCMV.[17] Mollaret's meningitis is a chronic recurrent form of herpes [24]

meningitis; it is thought to be caused by herpes simplex virus type 2.

### Fungal [edit]

There are a number of risk factors for fungal meningitis, including the use of immunosuppressants (such as after organ transplantation), HIV/AIDS,[25] and the loss of immunity associated with aging.[26] It is uncommon in those with a normal immune system[27] but has occurred with medication contamination.[28] Symptom onset is typically more gradual, with headaches and fever being present for at least a couple of weeks before diagnosis.[26] The most common fungal meningitis is cryptococcal meningitis due to *Cryptococcus neoformans*.[29] In Africa, cryptococcal meningitis is now the most common cause of meningitis in multiple studies,[30][31] and it accounts for 20–25% of AIDS-related deaths in Africa.[32] Other less common fungal pathogens which can cause meningitis include: *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Candida* species.[26]

### Parasitic [edit]

A parasitic cause is often assumed when there is a predominance of eosinophils (a type of white blood cell) in the CSF. The most common parasites implicated are *Angiostrongylus cantonensis*, *Gnathostoma spinigerum*, *Schistosoma*, as well as the conditions cysticercosis, toxocariasis, baylisascariasis, paragonimiasis, and a number of rarer infections and noninfective conditions.[33]

### Non-infectious [edit]

Meningitis may occur as the result of several non-infectious causes: spread of cancer to the meninges (*malignant or neoplastic meningitis*)[34] and certain drugs (mainly non-steroidal anti-inflammatory drugs, antibiotics and intravenous immunoglobulins).[35] It may also be caused by several inflammatory conditions, such as sarcoidosis (which is then called neurosarcoidosis), connective tissue disorders such as systemic lupus erythematosus, and certain forms of vasculitis (inflammatory conditions of the blood vessel wall), such as Behçet's disease.[4] Epidermoid cysts and dermoid cysts may cause meningitis by releasing irritant matter into the subarachnoid space.[4][23] Rarely, migraine may cause meningitis, but this diagnosis is usually only made when other causes have been eliminated.[4]

## Mechanism [edit]

The meninges comprise three membranes that, together with the cerebrospinal fluid, enclose and protect the brain and spinal cord (the central nervous system). The pia mater is a very delicate impermeable membrane that firmly adheres to the surface of the brain, following all the minor contours. The arachnoid mater (so named because of its spider-web-like appearance) is a loosely fitting sac on top of the pia mater. The subarachnoid space separates the arachnoid and pia mater membranes and is filled with cerebrospinal fluid. The outermost membrane, the dura mater, is a thick durable membrane, which is attached to both the arachnoid membrane and the skull.

In bacterial meningitis, bacteria reach the meninges by one of two main routes: through the bloodstream or through direct contact between the meninges and either the nasal cavity or the skin. In most cases, meningitis follows invasion of the bloodstream by organisms that live upon mucous surfaces such as the nasal cavity. This is often in turn preceded by viral infections, which break down the normal barrier provided by the mucous surfaces. Once bacteria have entered the bloodstream, they enter the subarachnoid space in places where the blood–brain barrier is vulnerable—such as the choroid plexus. Meningitis occurs in 25% of newborns with bloodstream infections due to group B streptococci; this phenomenon is less common in adults.[1] Direct contamination of the cerebrospinal fluid may arise from indwelling devices, skull fractures, or infections of the nasopharynx or the nasal sinuses that have formed a tract with the subarachnoid space (see above); occasionally, congenital defects of the dura mater can be identified.[1]

The large-scale inflammation that occurs in the subarachnoid space during meningitis is not a direct result

of bacterial infection but can rather largely be attributed to the response of the immune system to the entry of bacteria into the central nervous system. When components of the bacterial cell membrane are identified by the immune cells of the brain (astrocytes and microglia), they respond by releasing large amounts of cytokines, hormone-like mediators that recruit other immune cells and stimulate other tissues to participate in an immune response. The blood–brain barrier becomes more permeable, leading to "vasogenic" cerebral edema (swelling of the brain due to fluid leakage from blood vessels). Large numbers of white blood cells enter the CSF, causing inflammation of the meninges and leading to "interstitial" edema (swelling due to fluid between the cells). In addition, the walls of the blood vessels themselves become inflamed (cerebral vasculitis), which leads to decreased blood flow and a third type of edema, "cytotoxic" edema. The three forms of cerebral edema all lead to increased intracranial pressure; together with the lowered blood pressure often encountered in acute infection, this means that it is harder for blood to enter the brain, consequently brain cells are deprived of oxygen and undergo apoptosis (programmed cell death).[1]

It is recognized that administration of antibiotics may initially worsen the process outlined above, by increasing the amount of bacterial cell membrane products released through the destruction of bacteria. Particular treatments, such as the use of corticosteroids, are aimed at dampening the immune system's response to this phenomenon.[1][3]

# Diagnosis [edit]

## Blood tests and imaging [edit]

In someone suspected of having meningitis, blood tests are performed for markers of inflammation (e.g. C-reactive protein, complete blood count), as well as blood cultures.[5][37]

**CSF findings in different forms of meningitis**[36]

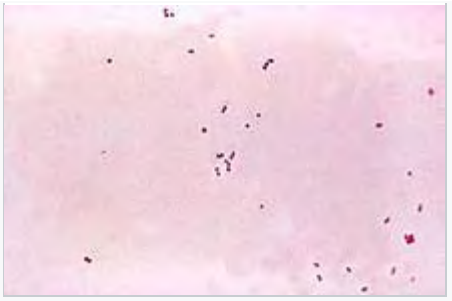
| Type of meningitis | Glucose | Protein | Cells |
|---|---|---|---|
| **Acute bacterial** | low | high | PMNs, often > 300/mm³ |
| **Acute viral** | normal | normal or high | mononuclear, < 300/mm³ |
| **Tuberculous** | low | high | mononuclear and PMNs, < 300/mm³ |
| **Fungal** | low | high | < 300/mm³ |
| **Malignant** | low | high | usually mononuclear |

The most important test in identifying or ruling out meningitis is analysis of the cerebrospinal fluid through lumbar puncture (LP, spinal tap).[38] However, lumbar puncture is contraindicated if there is a mass in the brain (tumor or abscess) or the intracranial pressure (ICP) is elevated, as it may lead to brain herniation. If someone is at risk for either a mass or raised ICP (recent head injury, a known immune system problem, localizing neurological signs, or evidence on examination of a raised ICP), a CT or MRI scan is recommended prior to the lumbar puncture.[5][37][39] This applies in 45% of all adult cases.[3] If a CT or MRI is required before LP, or if LP proves difficult, professional guidelines suggest that antibiotics should be administered first to prevent delay in treatment,[5] especially if this may be longer than 30 minutes.[37][39] Often, CT or MRI scans are performed at a later stage to assess for complications of meningitis.[1]

In severe forms of meningitis, monitoring of blood electrolytes may be important; for example, hyponatremia is common in bacterial meningitis, due to a combination of factors, including dehydration, the inappropriate secretion of the antidiuretic hormone (SIADH), or overly aggressive intravenous fluid administration.[3][40]

## Lumbar puncture [edit]

A lumbar puncture is done by positioning the person, usually lying on the side, applying local anesthetic, and inserting a needle into the dural sac (a sac around the spinal cord) to collect cerebrospinal fluid (CSF). When this has been achieved, the "opening pressure" of the CSF is measured using a manometer. The pressure is normally between 6 and 18 cm water ($cmH_2O$);[38] in bacterial meningitis the pressure is usually



Gram stain of meningococci from a culture showing Gram negative (pink) bacteria, often in pairs

elevated.[5][37] In cryptococcal meningitis, intracranial pressure is markedly elevated.[41] The initial appearance of the fluid may prove an indication of the nature of the infection: cloudy CSF indicates higher levels of protein, white and red blood cells and/or bacteria, and therefore may suggest bacterial meningitis.[5]

The CSF sample is examined for presence and types of white blood cells, red blood cells, protein content and glucose level.[5] Gram staining of the sample may demonstrate bacteria in bacterial meningitis, but absence of bacteria does not exclude bacterial meningitis as they are only seen in 60% of cases; this figure is reduced by a further 20% if antibiotics were administered before the sample was taken. Gram staining is also less reliable in particular infections such as listeriosis. Microbiological culture of the sample is more sensitive (it identifies the organism in 70–85% of cases) but results can take up to 48 hours to become available.[5] The type of white blood cell predominantly present (see table) indicates whether meningitis is bacterial (usually neutrophil-predominant) or viral (usually lymphocyte-predominant),[5] although at the beginning of the disease this is not always a reliable indicator. Less commonly, eosinophils predominate, suggesting parasitic or fungal etiology, among others.[33]

The concentration of glucose in CSF is normally above 40% of that in blood. In bacterial meningitis it is typically lower; the CSF glucose level is therefore divided by the blood glucose (CSF glucose to serum glucose ratio). A ratio ≤0.4 is indicative of bacterial meningitis;[38] in the newborn, glucose levels in CSF are normally higher, and a ratio below 0.6 (60%) is therefore considered abnormal.[5] High levels of lactate in CSF indicate a higher likelihood of bacterial meningitis, as does a higher white blood cell count.[38] If lactate levels are less than 35 mg/dl and the person has not previously received antibiotics then this may rule out bacterial meningitis.[42]

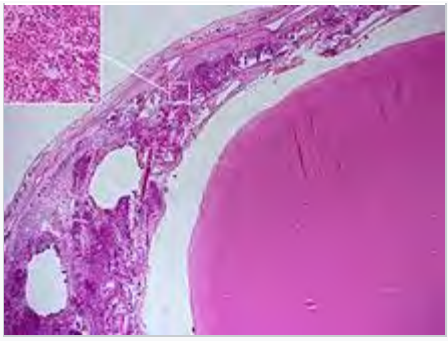
Various other specialized tests may be used to distinguish between different types of meningitis. A latex agglutination test may be positive in meningitis caused by *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Escherichia coli* and *group B streptococci*; its routine use is not encouraged as it rarely leads to changes in treatment, but it may be used if other tests are not diagnostic. Similarly, the limulus lysate test may be positive in meningitis caused by Gram-negative bacteria, but it is of limited use unless other tests have been unhelpful.[5] Polymerase chain reaction (PCR) is a technique used to amplify small traces of bacterial DNA in order to detect the presence of bacterial or viral DNA in cerebrospinal fluid; it is a highly sensitive and specific test since only trace amounts of the infecting agent's DNA is required. It may identify bacteria in bacterial meningitis and may assist in distinguishing the various causes of viral meningitis (enterovirus, herpes simplex virus 2 and mumps in those not vaccinated for this).[17] Serology (identification of antibodies to viruses) may be useful in viral meningitis.[17] If tuberculous meningitis is suspected, the sample is processed for Ziehl-Neelsen stain, which has a low sensitivity, and tuberculosis culture, which takes a long time to process; PCR is being used increasingly.[22] Diagnosis of cryptococcal meningitis can be made at low cost using an India ink stain of the CSF; however, testing for cryptococcal antigen in blood or CSF is more sensitive, particularly in people with AIDS.[43][44]

A diagnostic and therapeutic difficulty is "partially treated meningitis", where there are meningitis symptoms after receiving antibiotics (such as for presumptive sinusitis). When this happens, CSF findings may resemble those of viral meningitis, but antibiotic treatment may need to be continued until there is definitive positive evidence of a viral cause (e.g. a positive enterovirus PCR).[17]

## Postmortem [edit]

Meningitis can be diagnosed after death has occurred. The findings from

a post mortem are usually a widespread inflammation of the pia mater and arachnoid layers of the meninges. Neutrophil granulocytes tend to have migrated to the cerebrospinal fluid and the base of the brain, along with cranial nerves and the spinal cord, may be surrounded with pus – as may the meningeal vessels.[45]



Histopathology of bacterial meningitis: autopsy case of a person with pneumococcal meningitis showing inflammatory infiltrates of the pia mater consisting of neutrophil granulocytes (inset, higher magnification).

## Prevention [edit]

For some causes of meningitis, protection can be provided in the long term through vaccination, or in the short term with antibiotics. Some behavioral measures may also be effective.

### Behavioral [edit]

Bacterial and viral meningitis are contagious, but neither is as contagious as the common cold or flu.[46] Both can be transmitted through droplets of respiratory secretions during close contact such as kissing, sneezing or coughing on someone, but cannot be spread by only breathing the air where a person with meningitis has been.[46] Viral meningitis is typically caused by enteroviruses, and is most commonly spread through fecal contamination.[46] The risk of infection can be decreased by changing the behavior that led to transmission.

### Vaccination [edit]

Since the 1980s, many countries have included immunization against *Haemophilus influenzae* type B in their routine childhood vaccination schemes. This has practically eliminated this pathogen as a cause of meningitis in young children in those countries. In the countries in which the disease burden is highest, however, the vaccine is still too expensive.[47][48] Similarly, immunization against mumps has led to a sharp fall in the number of cases of mumps meningitis, which prior to vaccination occurred in 15% of all cases of mumps.[17]

Meningococcus vaccines exist against groups A, B, C, W135 and Y.[49][50][51] In countries where the vaccine for meningococcus group C was introduced, cases caused by this pathogen have decreased substantially.[47] A quadrivalent vaccine now exists, which combines four vaccines with the exception of B; immunization with this ACW135Y vaccine is now a visa requirement for taking part in Hajj.[52] Development of a vaccine against group B meningococci has proved much more difficult, as its surface proteins (which would normally be used to make a vaccine) only elicit a weak response from the immune system, or cross-react with normal human proteins.[47][49] Still, some countries (New Zealand, Cuba, Norway and Chile) have developed vaccines against local strains of group B meningococci; some have shown good results and are used in local immunization schedules.[49] Two new vaccines, both approved in 2014, are effective against a wider range of group B meningococci strains.[50][51] In Africa, until recently, the approach for prevention and control of meningococcal epidemics was based on early detection of the disease and emergency reactive mass vaccination of the at-risk population with bivalent A/C or trivalent A/C/W135 polysaccharide vaccines,[53] though the introduction of MenAfriVac (meningococcus group A vaccine) has demonstrated effectiveness in young people and has been described as a model for product development partnerships in resource-limited settings.[54][55]

Routine vaccination against *Streptococcus pneumoniae* with the pneumococcal conjugate vaccine (PCV), which is active against seven common serotypes of this pathogen, significantly reduces the incidence of pneumococcal meningitis.[47][56] The pneumococcal polysaccharide vaccine, which covers 23 strains, is only administered to certain groups (e.g. those who have had a splenectomy, the surgical removal of the spleen); it does not elicit a significant immune response in all recipients, e.g. small children.[56] Childhood vaccination with Bacillus Calmette-Guérin has been reported to significantly reduce the rate of tuberculous meningitis, but its waning effectiveness in adulthood has prompted a search for a better vaccine.[47]

### Antibiotics [edit]

Short-term antibiotic prophylaxis is another method of prevention, particularly of meningococcal meningitis. In cases of meningococcal meningitis, preventative treatment in close contacts with antibiotics (e.g. rifampicin, ciprofloxacin or ceftriaxone) can reduce their risk of contracting the condition, but does not protect against future infections.[37][57] Resistance to rifampicin has been noted to increase after use, which has caused some to recommend considering other agents.[57] While antibiotics are frequently used in an attempt to prevent meningitis in those with a basilar skull fracture there is not enough evidence to determine whether this is beneficial or harmful.[58] This applies to those with or without a CSF leak.[58]

## Management [edit]

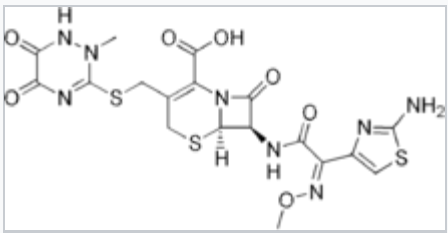
Meningitis is potentially life-threatening and has a high mortality rate if untreated;[5] delay in treatment has been associated with a poorer outcome.[3] Thus, treatment with wide-spectrum antibiotics should not be delayed while confirmatory tests are being conducted.[39] If meningococcal disease is suspected in primary care, guidelines recommend that benzylpenicillin be administered before transfer to hospital.[14] Intravenous fluids should be administered if hypotension (low blood pressure) or shock are present.[39] In children routine intravenous fluids for two days may improve outcomes in those who arrive at hospital after being sick for some time.[59] Given that meningitis can cause a number of early severe complications, regular medical review is recommended to identify these complications early[39] and to admit the person to an intensive care unit if deemed necessary.[3]

Mechanical ventilation may be needed if the level of consciousness is very low, or if there is evidence of respiratory failure. If there are signs of raised intracranial pressure, measures to monitor the pressure may be taken; this would allow the optimization of the cerebral perfusion pressure and various treatments to decrease the intracranial pressure with medication (e.g. mannitol).[3] Seizures are treated with anticonvulsants.[3] Hydrocephalus (obstructed flow of CSF) may require insertion of a temporary or long-term drainage device, such as a cerebral shunt.[3]

### Bacterial meningitis [edit]

#### Antibiotics [edit]

Empiric antibiotics (treatment without exact diagnosis) should be started immediately, even before the results of the lumbar puncture and CSF analysis are known. The choice of initial treatment depends largely on the kind of bacteria that cause meningitis in a particular place and population. For instance, in the United Kingdom empirical treatment consists of a third-generation cefalosporin such as cefotaxime or ceftriaxone.[37][39] In the USA, where resistance to cefalosporins is increasingly found in streptococci, addition of vancomycin to the initial treatment is recommended.[3][5][37] Chloramphenicol, either alone or in combination with ampicillin, however, appears to work equally well.[60]



Structural formula of ceftriaxone, one of the third-generation cefalosporin antibiotics recommended for the initial treatment of bacterial meningitis.

Empirical therapy may be chosen on the basis of the person's age, whether the infection was preceded by a head injury, whether the person has undergone recent neurosurgery and whether or not a cerebral shunt is present.[5] In young children and those over 50 years of age, as well as those who are immunocompromised, the addition of ampicillin is recommended to cover *Listeria monocytogenes*.[5][37] Once the Gram stain results become available, and the broad type of bacterial cause is known, it may be possible to change the antibiotics to those likely to deal with the presumed group of pathogens.[5] The results of the CSF culture generally take longer to become available

(24–48 hours). Once they do, empiric therapy may be switched to specific antibiotic therapy targeted to the specific causative organism and its sensitivities to antibiotics.[5] For an antibiotic to be effective in meningitis it must not only be active against the pathogenic bacterium but also reach the meninges in adequate quantities; some antibiotics have inadequate penetrance and therefore have little use in meningitis. Most of the antibiotics used in meningitis have not been tested directly on people with meningitis in clinical trials. Rather, the relevant knowledge has mostly derived from laboratory studies in rabbits.[5] Tuberculous meningitis requires prolonged treatment with antibiotics. While tuberculosis of the lungs is typically treated for six months, those with tuberculous meningitis are typically treated for a year or longer.[22]

### Steroids [edit]

Additional treatment with corticosteroids (usually dexamethasone) has shown some benefits, such as a reduction of hearing loss, and better short term neurological outcomes[61] in adolescents and adults from high-income countries with low rates of HIV.[62] Some research has found reduced rates of death[62] while other research has not.[61] They also appear to be beneficial in those with tuberculosis meningitis, at least in those who are HIV negative.[63]

Professional guidelines therefore recommend the commencement of dexamethasone or a similar corticosteroid just before the first dose of antibiotics is given, and continued for four days.[37][39] Given that most of the benefit of the treatment is confined to those with pneumococcal meningitis, some guidelines suggest that dexamethasone be discontinued if another cause for meningitis is identified.[5][37] The likely mechanism is suppression of overactive inflammation.[64]

Additional treatment with corticosteroids have a different role in children than in adults. Though the benefit of corticosteroids has been demonstrated in adults as well as in children from high-income countries, their use in children from low-income countries is not supported by the evidence; the reason for this discrepancy is not clear.[61] Even in high-income countries, the benefit of corticosteroids is only seen when they are given prior to the first dose of antibiotics, and is greatest in cases of *H. influenzae* meningitis,[5][65] the incidence of which has decreased dramatically since the introduction of the Hib vaccine. Thus, corticosteroids are recommended in the treatment of pediatric meningitis if the cause is *H. influenzae*, and only if given prior to the first dose of antibiotics; other uses are controversial.[5]

### Viral meningitis [edit]

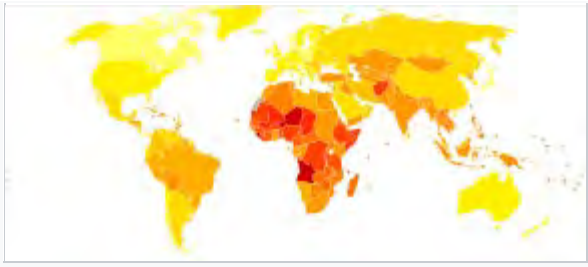
Viral meningitis typically only requires supportive therapy; most viruses responsible for causing meningitis are not amenable to specific treatment. Viral meningitis tends to run a more benign course than bacterial meningitis. Herpes simplex virus and varicella zoster virus may respond to treatment with antiviral drugs such as aciclovir, but there are no clinical trials that have specifically addressed whether this treatment is effective.[17] Mild cases of viral meningitis can be treated at home with conservative measures such as fluid, bedrest, and analgesics.[66]

### Fungal meningitis [edit]

Fungal meningitis, such as cryptococcal meningitis, is treated with long courses of high dose antifungals, such as amphotericin B and flucytosine.[43][67] Raised intracranial pressure is common in fungal meningitis, and frequent (ideally daily) lumbar punctures to relieve the pressure are recommended,[43] or alternatively a lumbar drain.[41]

## Prognosis [edit]

Untreated, bacterial meningitis is almost always fatal. Viral meningitis, in contrast, tends to resolve spontaneously and is rarely fatal. With treatment, mortality (risk of death) from



Disability-adjusted life year for meningitis per 100,000 inhabitants in 2004.[68]

| | |
|---|---|
| no data | 200-300 |
| <10 | 300-400 |
| 10-25 | 400-500 |
| 25-50 | 500-750 |
| 50-75 | 750–1000 |
| 75-100 | >1000 |
| 100-200 | |

bacterial meningitis depends on the age of the person and the underlying cause. Of newborns, 20–30% may die from an episode of bacterial meningitis. This risk is much lower in older children, whose mortality is about 2%, but rises again to about 19–37% in adults.[1][3] Risk of death is predicted by various factors apart from age, such as the pathogen and the time it takes for the pathogen to be cleared from the cerebrospinal fluid,[1] the severity of the generalized illness, a decreased level of consciousness or an abnormally low count of white blood cells in the CSF.[3] Meningitis caused by *H. influenzae* and meningococci has a better prognosis than cases caused by group B streptococci, coliforms and *S. pneumonia*.[1] In adults, too, meningococcal meningitis has a lower mortality (3–7%) than pneumococcal disease.[3]

In children there are several potential disabilities which may result from damage to the nervous system, including sensorineural hearing loss, epilepsy, learning and behavioral difficulties, as well as decreased intelligence.[1] These occur in about 15% of survivors.[1] Some of the hearing loss may be reversible.[69] In adults, 66% of all cases emerge without disability. The main problems are deafness (in 14%) and cognitive impairment (in 10%).[3]

Tuberculous meningitis in children continues to be associated with a significant risk of death even with treatment (19%), and a significant proportion of the surviving children have ongoing neurological problems. Just over a third of all cases survives with no problems.[70]

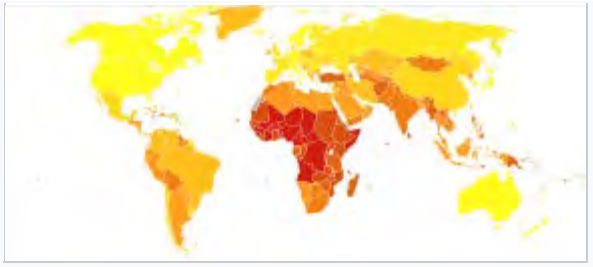
## Epidemiology [edit]

Demography of meningococcal meningitis.

- meningitis belt
- epidemic zones
- sporadic cases only

Although meningitis is a notifiable disease in many countries, the exact incidence rate is unknown.[17] In 2013 meningitis resulted in 303,000 deaths – down from 464,000 deaths in 1990.[8] In 2010 it was estimated that meningitis resulted in 420,000 deaths,[71] excluding cryptococcal meningitis.[72]

Bacterial meningitis occurs in about 3 people per 100,000 annually in Western countries. Population-wide studies have shown that viral meningitis is more common, at 10.9 per 100,000, and occurs more often in the summer. In Brazil, the rate of bacterial meningitis is higher, at 45.8 per 100,000 annually.[13] Sub-Saharan Africa has been plagued by large epidemics of meningococcal meningitis for over a century,[73] leading to it being labeled the "meningitis belt". Epidemics typically occur in the dry season (December to June), and an epidemic wave can last two to three years, dying out during the intervening rainy seasons.[74] Attack rates of 100–800 cases per 100,000 are encountered in this area,[75] which is poorly served by medical care. These cases are predominantly caused by meningococci.[13] The largest epidemic ever recorded in history swept across the entire region in 1996–1997, causing over 250,000 cases and 25,000 deaths.[76]



Deaths from meningitis per million persons in 2012

| | | |
|---|---|---|
| 0-2 | 7-9 | 32-61 |
| 3-3 | 10-20 | 62-153 |
| 4-6 | 21-31 | 154-308 |
| | | 309-734 |

Meningococcal disease occurs in epidemics in areas where many people live together for the first time, such as army barracks during mobilization, college campuses[1] and the annual Hajj pilgrimage.[52] Although the pattern of epidemic cycles in Africa is not well understood, several factors have been associated with the development of epidemics in the meningitis belt. They include: medical conditions (immunological susceptibility of the population), demographic conditions (travel and large population displacements), socioeconomic conditions (overcrowding and poor living conditions), climatic conditions (drought and dust storms), and concurrent infections (acute respiratory infections).[75]

There are significant differences in the local distribution of causes for bacterial meningitis. For instance, while *N. meningitides* groups B and C cause most disease episodes in Europe, group A is found in Asia and continues to predominate in Africa, where it causes most of the major epidemics in the meningitis belt, accounting for about 80% to 85% of documented meningococcal meningitis cases.[75]

## History [edit]

Some suggest that Hippocrates may have realized the existence of meningitis,[13] and it seems that meningism was known to pre-Renaissance physicians such as Avicenna.[77] The description of tuberculous meningitis, then called "dropsy in the brain", is often attributed to Edinburgh physician Sir Robert Whytt in a posthumous report that appeared in 1768, although the link with tuberculosis and its pathogen was not made until the next century.[77][78]

It appears that epidemic meningitis is a relatively recent phenomenon.[79] The first recorded major outbreak occurred in Geneva in 1805.[79][80] Several other epidemics in Europe and the United States were described shortly afterward, and the first report of an epidemic in Africa appeared in 1840. African epidemics became much more common in the 20th century, starting with a major epidemic sweeping Nigeria and Ghana in 1905–1908.[79]

The first report of bacterial infection underlying meningitis was by the Austrian bacteriologist Anton Weichselbaum, who in 1887 described the *meningococcus*.[81] Mortality from meningitis was very high (over 90%) in early reports. In 1906, antiserum was produced in horses; this was developed further by the American scientist Simon Flexner and markedly decreased mortality from meningococcal disease.[82][83] In 1944, penicillin was first reported to be effective in meningitis.[84] The introduction in the late 20th century of *Haemophilus* vaccines led to a marked fall in cases of meningitis associated with this pathogen,[48] and in 2002, evidence emerged that treatment with steroids could improve the prognosis of bacterial meningitis.[61][64][83] World Meningitis Day is celebrated on the 24th of April each year.

## References [edit]


1. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z* Sáez-Llorens X, McCracken GH (June 2003). "Bacterial meningitis in children". *Lancet*. **361** (9375): 2139–48. doi:10.1016/S0140-6736(03)13693-8. PMID 12826449.
2. ^ *a b c d e* "Bacterial Meningitis". *CDC*. April 1, 2014. Retrieved 5 March 2016.
3. ^ *a b c d e f g h i j k l m n o p q r s t u* van de Beek D, de Gans J, Tunkel AR, Wijdicks EF (January 2006).

"Community-acquired bacterial meningitis in adults". *The New England Journal of Medicine*. **354** (1): 44–53. doi:10.1056/NEJMra052116. PMID 16394301.

4. ^ *a b c d e f g* Ginsberg L (March 2004). "Difficult and recurrent meningitis" (PDF). *Journal of Neurology, Neurosurgery, and Psychiatry*. 75 Suppl 1 (90001): i16–21. doi:10.1136/jnnp.2003.034272. PMC 1765649. PMID 14978146.
5. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab* Tunkel AR; Hartman BJ; Kaplan SL; et al. (November 2004). "Practice guidelines for the management of bacterial meningitis" (PDF). *Clinical Infectious Diseases*. **39** (9): 1267–84. doi:10.1086/425368. PMID 15494903.
6. ^ "Viral Meningitis". *CDC*. November 26, 2014. Retrieved 5 March 2016.
7. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
8. ^ *a b* GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
9. ^ *a b* "Meningococcal meningitis Fact sheet N°141". *WHO*. November 2015. Retrieved 5 March 2016.
10. ^ *Mosby's pocket dictionary of medicine, nursing & health professions* (6th ed.). St. Louis, Mo.: Mosby/Elsevier. 2010. p. traumatic meningitis. ISBN 9780323066044.
11. ^ Liddell HG, Scott R (1940). "μήνιγξ". *A Greek-English Lexicon*. Oxford: Clarendon Press.
12. ^ *a b* van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M (October 2004). "Clinical features and prognostic factors in adults with bacterial meningitis". *The New England Journal of Medicine*. **351** (18): 1849–59. doi:10.1056/NEJMoa040845. PMID 15509818.
13. ^ *a b c d e f g h i j k* Attia J, Hatala R, Cook DJ, Wong JG (July 1999). "The rational clinical examination. Does this adult patient have acute meningitis?". *Journal of the American Medical Association*. **282** (2): 175–81. doi:10.1001/jama.282.2.175. PMID 10411200.
14. ^ *a b c* Theilen U, Wilson L, Wilson G, Beattie JO, Qureshi S, Simpson D (June 2008). "Management of invasive meningococcal disease in children and young people: Summary of SIGN guidelines". *BMJ (Clinical research ed.)*. **336** (7657): 1367–70. doi:10.1136/bmj.a129. PMC 2427067. PMID 18556318.
15. ^ *Management of invasive meningococcal disease in children and young people* (PDF). Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN). May 2008. ISBN 978-1-905813-31-5.
16. ^ Thomas KE, Hasbun R, Jekel J, Quagliarello VJ (July 2002). "The diagnostic accuracy of Kernig's sign, Brudzinski neck sign, and nuchal rigidity in adults with suspected meningitis" (PDF). *Clinical Infectious Diseases*. **35** (1): 46–52. doi:10.1086/340979. PMID 12060874.
17. ^ *a b c d e f g h* Logan SA, MacMahon E (January 2008). "Viral meningitis". *BMJ (Clinical research ed.)*. **336** (7634): 36–40. doi:10.1136/bmj.39409.673657.AE. PMC 2174764. PMID 18174598.
18. ^ Varon J, Chen K, Sternbach GL (1998). "Rupert Waterhouse and Carl Friderichsen: adrenal apoplexy". *J Emerg Med*. **16** (4): 643–7. doi:10.1016/S0736-4679(98)00061-4. PMID 9696186.
19. ^ "Listeria (Listeriosis)". Centers for Disease Control and Prevention. 22 October 2015. Retrieved 2015-12-23.
20. ^ Hsu HE; Shutt KA; Moore MR; et al. (2009). "Effect of pneumococcal conjugate vaccine on pneumococcal meningitis". *N Engl J Med*. **360** (3): 244–256. doi:10.1056/NEJMoa0800836. PMID 19144940.
21. ^ Wei BP, Robins-Browne RM, Shepherd RK, Clark GM, O'Leary SJ (January 2008). "Can we prevent cochlear implant recipients from developing pneumococcal meningitis?" (PDF). *Clin. Infect. Dis.* **46** (1): e1–7. doi:10.1086/524083. PMID 18171202.
22. ^ *a b c* Thwaites G, Chau TT, Mai NT, Drobniewski F, McAdam K, Farrar J (March 2000). "Tuberculous meningitis" (PDF). *Journal of Neurology, Neurosurgery, and Psychiatry*. **68** (3): 289–99. doi:10.1136/jnnp.68.3.289. PMC 1736815. PMID 10675209.
23. ^ *a b c d e* Tebruegge M, Curtis N (July 2008). "Epidemiology, etiology, pathogenesis, and diagnosis of recurrent bacterial meningitis". *Clinical Microbiology Reviews*. **21** (3): 519–37. doi:10.1128/CMR.00009-08. PMC 2493086. PMID 18625686.
24. ^ Shalabi, M.; Whitley, R. J. (1 November 2006). "Recurrent Benign Lymphocytic Meningitis". *Clinical Infectious Diseases*. **43** (9): 1194–1197. doi:10.1086/508281. PMID 17029141.
25. ^ Raman Sharma R (2010). "Fungal infections of the nervous system: current perspective and controversies in management". *International journal of surgery (London, England)*. **8** (8): 591–601. doi:10.1016/j.ijsu.2010.07.293. PMID 20673817.

*a b c*

26. ^ Sirven JI, Malamut BL (2008). *Clinical neurology of the older adult* (2nd ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 439. ISBN 978-0-7817-6947-1.
27. ^ Honda H, Warren DK (September 2009). "Central nervous system infections: meningitis and brain abscess". *Infectious disease clinics of North America*. **23** (3): 609–23. doi:10.1016/j.idc.2009.04.009. PMID 19665086.
28. ^ Kauffman CA, Pappas PG, Patterson TF (19 October 2012). "Fungal infections associated with contaminated methyprednisolone injections—preliminary report". *New England Journal of Medicine*. Online first (26): 2495–500. doi:10.1056/NEJMra1212617. PMID 23083312.
29. ^ Kauffman CA, Pappas PG, Sobel JD, Dismukes WE (1 January 2011). *Essentials of clinical mycology* (2nd ed.). New York: Springer. p. 77. ISBN 978-1-4419-6639-1.
30. ^ Durski, Kara N.; Kuntz, Karen M.; Yasukawa, Kosuke; Virnig, Beth A.; Meya, David B.; Boulware, David R. (Jul 1, 2013). "Cost-Effective Diagnostic Checklists for Meningitis in Resource-Limited Settings". *JAIDS Journal of Acquired Immune Deficiency Syndromes*. **63** (3): e101–e108. doi:10.1097/QAI.0b013e31828e1e56. PMID 23466647.
31. ^ Kauffman CA, Pappas PG, Sobel JD, Dismukes WE (1 January 2011). *Essentials of clinical mycology* (2nd ed.). New York: Springer. p. 31. ISBN 978-1-4419-6639-1.
32. ^ Park, Benjamin J; Park BJ; Wannemuehler KA; Marston BJ; Govender N; Pappas PG; Chiller TM. (1 February 2009). "Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS". *AIDS*. **23** (4): 525–530. doi:10.1097/QAD.0b013e328322ffac. PMID 19182676.
33. ^ *a b* Graeff-Teixeira C, da Silva AC, Yoshimura K (Apr 2009). "Update on eosinophilic meningoencephalitis and its clinical relevance" (PDF). *Clinical Microbiology Reviews*. **22** (2): 322–48. doi:10.1128/CMR.00044-08. PMC 2668237. PMID 19366917.
34. ^ Gleissner B, Chamberlain MC (May 2006). "Neoplastic meningitis". *Lancet Neurol*. **5** (5): 443–52. doi:10.1016/S1474-4422(06)70443-4. PMID 16632315.
35. ^ Moris G, Garcia-Monco JC (June 1999). "The Challenge of Drug-Induced Aseptic Meningitis" (PDF). *Archives of Internal Medicine*. **159** (11): 1185–94. doi:10.1001/archinte.159.11.1185. PMID 10371226.
36. ^ Provan, Drew; Andrew Krentz (2005). *Oxford Handbook of Clinical and Laboratory Investigation*. Oxford: Oxford University Press. ISBN 0-19-856663-8.
37. ^ *a b c d e f g h i j* Chaudhuri A; Martinez–Martin P; Martin PM; et al. (July 2008). "EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults". *European Journal of Neurolology*. **15** (7): 649–59. doi:10.1111/j.1468-1331.2008.02193.x. PMID 18582342.
38. ^ *a b c d* Straus SE, Thorpe KE, Holroyd-Leduc J (October 2006). "How do I perform a lumbar puncture and analyze the results to diagnose bacterial meningitis?". *Journal of the American Medical Association*. **296** (16): 2012–22. doi:10.1001/jama.296.16.2012. PMID 17062865.
39. ^ *a b c d e f g* Heyderman RS, Lambert HP, O'Sullivan I, Stuart JM, Taylor BL, Wall RA (February 2003). "Early management of suspected bacterial meningitis and meningococcal septicaemia in adults" (PDF). *The Journal of infection*. **46** (2): 75–7. doi:10.1053/jinf.2002.1110. PMID 12634067. – formal guideline at British Infection Society; UK Meningitis Research Trust (December 2004). "Early management of suspected meningitis and meningococcal septicaemia in immunocompetent adults". British Infection Society Guidelines. Retrieved 19 October 2008.
40. ^ Maconochie IK, Bhaumik S (2014). Maconochie, Ian K, ed. "Fluid therapy for acute bacterial meningitis". *Cochrane Database of Systematic Reviews*. **5** (5): CD004786. doi:10.1002/14651858.CD004786.pub4. PMID 24793545. CD004786.
41. ^ *a b* Perfect JR, Dismukes WE, Dromer F, et al. (2010). "Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america". *Clinical Infectious Diseases*. **50** (3): 291–322. doi:10.1086/649858. PMID 20047480.
42. ^ Sakushima, K; Hayashino, Y; Kawaguchi, T; Jackson, JL; Fukuhara, S (April 2011). "Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: a meta-analysis". *The Journal of infection*. **62** (4): 255–62. doi:10.1016/j.jinf.2011.02.010. PMID 21382412.
43. ^ *a b c* Bicanic T, Harrison TS (2004). "Cryptococcal meningitis" (PDF). *British Medical Bulletin*. **72** (1): 99–118. doi:10.1093/bmb/ldh043. PMID 15838017.
44. ^ Sloan D, Dlamini S, Paul N, Dedicoat M (2008). Sloan D, ed. "Treatment of acute cryptococcal meningitis in HIV infected adults, with an emphasis on resource-limited settings". *Cochrane Database of Systematic Reviews* (4): CD005647. doi:10.1002/14651858.CD005647.pub2. PMID 18843697. CD005647.
45. ^ Warrell DA, Farrar JJ, Crook DW (2003). "24.14.1 Bacterial meningitis". *Oxford Textbook of Medicine Volume 3* (Fourth ed.). Oxford University Press. pp. 1115–29. ISBN 0-19-852787-X.
46. ^ *a b c* "CDC – Meningitis: Transmission". Centers for Disease Control and Prevention (CDC). 6 August 2009. Retrieved 18 June 2011.
    *a b c d e*

47. ^ Segal S, Pollard AJ (2004). "Vaccines against bacterial meningitis" (PDF). *British Medical Bulletin*. **72** (1): 65–81. doi:10.1093/bmb/ldh041. PMID 15802609.
48. ^ [a] [b] Peltola H (April 2000). "Worldwide Haemophilus influenzae type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates" (PDF). *Clinical Microbiology Reviews*. **13** (2): 302–17. doi:10.1128/CMR.13.2.302-317.2000. PMC 100154. PMID 10756001.
49. ^ [a] [b] [c] Harrison LH (January 2006). "Prospects for vaccine prevention of meningococcal infection" (PDF). *Clinical Microbiology Reviews*. **19** (1): 142–64. doi:10.1128/CMR.19.1.142-164.2006. PMC 1360272. PMID 16418528.
50. ^ [a] [b] Man, Diana. "A new MenB (meningococcal B) vaccine". Meningitis Research Foundation. Retrieved 23 November 2014.
51. ^ [a] [b] FDA News Release (29 October 2014). "First vaccine approved by FDA to prevent serogroup B Meningococcal disease". FDA.
52. ^ [a] [b] Wilder-Smith A (October 2007). "Meningococcal vaccine in travelers". *Current Opinion in Infectious Diseases*. **20** (5): 454–60. doi:10.1097/QCO.0b013e3282a64700. PMID 17762777.
53. ^ WHO (September 2000). "Detecting meningococcal meningitis epidemics in highly-endemic African countries" (PDF). *Weekly Epidemiological Record*. **75** (38): 306–9. PMID 11045076.
54. ^ Bishai, DM; Champion, C; Steele, ME; Thompson, L (June 2011). "Product development partnerships hit their stride: lessons from developing a meningitis vaccine for Africa". *Health affairs (Project Hope)*. **30** (6): 1058–64. doi:10.1377/hlthaff.2011.0295. PMID 21653957.
55. ^ Marc LaForce, F; Ravenscroft, N; Djingarey, M; Viviani, S (24 June 2009). "Epidemic meningitis due to Group A Neisseria meningitidis in the African meningitis belt: a persistent problem with an imminent solution". *Vaccine*. 27 Suppl 2: B13–9. doi:10.1016/j.vaccine.2009.04.062. PMID 19477559.
56. ^ [a] [b] Weisfelt M, de Gans J, van der Poll T, van de Beek D (April 2006). "Pneumococcal meningitis in adults: new approaches to management and prevention". *Lancet Neurol*. **5** (4): 332–42. doi:10.1016/S1474-4422(06)70409-4. PMID 16545750.
57. ^ [a] [b] Zalmanovici Trestioreanu, A; Fraser, A; Gafter-Gvili, A; Paul, M; Leibovici, L (25 October 2013). "Antibiotics for preventing meningococcal infections.". *The Cochrane database of systematic reviews*. **10**: CD004785. doi:10.1002/14651858.CD004785.pub5. PMID 24163051.
58. ^ [a] [b] Ratilal, BO; Costa, J; Pappamikail, L; Sampaio, C (28 April 2015). "Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures.". *The Cochrane database of systematic reviews*. **4**: CD004884. doi:10.1002/14651858.CD004884.pub4. PMID 25918919.
59. ^ Maconochie, IK; Bhaumik, S (May 5, 2014). "Fluid therapy for acute bacterial meningitis.". *The Cochrane database of systematic reviews*. **5**: CD004786. doi:10.1002/14651858.CD004786.pub4. PMID 24793545.
60. ^ Prasad, K; Kumar, A; Gupta, PK; Singhal, T (17 October 2007). Prasad, Kameshwar, ed. "Third generation cephalosporins versus conventional antibiotics for treating acute bacterial meningitis". *Cochrane database of systematic reviews (Online)* (4): CD001832. doi:10.1002/14651858.CD001832.pub3. PMID 17943757.
61. ^ [a] [b] [c] [d] Brouwer, MC; McIntyre, P; Prasad, K; van de Beek, D (September 2015). "Corticosteroids for acute bacterial meningitis". *Cochrane Database of Systematic Reviews* (9): CD004405. doi:10.1002/14651858.CD004405.pub5. PMID 26362566.
62. ^ [a] [b] Assiri AM, Alasmari FA, Zimmerman VA, Baddour LM, Erwin PJ, Tleyjeh IM (May 2009). "Corticosteroid administration and outcome of adolescents and adults with acute bacterial meningitis: a meta-analysis". *Mayo Clin. Proc.* **84** (5): 403–9. doi:10.4065/84.5.403. PMC 2676122. PMID 19411436.
63. ^ Prasad, K; Singh, MB (23 January 2008). Prasad, Kameshwar, ed. "Corticosteroids for managing tuberculous meningitis". *Cochrane database of systematic reviews (Online)* (1): CD002244. doi:10.1002/14651858.CD002244.pub3. PMID 18254003.
64. ^ [a] [b] de Gans J, van de Beek D (November 2002). "Dexamethasone in adults with bacterial meningitis". *The New England Journal of Medicine*. **347** (20): 1549–56. doi:10.1056/NEJMoa021334. PMID 12432041.
65. ^ McIntyre PB; Berkey CS; King SM; et al. (September 1997). "Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988". *Journal of the American Medical Association*. **278** (11): 925–31. doi:10.1001/jama.1997.03550110063038. PMID 9302246.
66. ^ "Meningitis and Encephalitis Fact Sheet". National Institute of Neurological Disorders and Stroke (NINDS). 11 December 2007. Retrieved 27 April 2009.
67. ^ Gottfredsson M, Perfect JR (2000). "Fungal meningitis". *Seminars in Neurology*. **20** (3): 307–22. doi:10.1055/s-2000-9394. PMID 11051295.
68. ^ "Mortality and Burden of Disease Estimates for WHO Member States in 2002" (xls). World Health Organization (WHO). 2002.
69. ^ Richardson MP, Reid A, Tarlow MJ, Rudd PT (February 1997). "Hearing loss during bacterial meningitis" (PDF).

*Archives of Disease in Childhood*. **76** (2): 134–38. doi:10.1136/adc.76.2.134. PMC 1717058. PMID 9068303.

70. ^ Chiang, SS; Khan, FA; Milstein, MB; Tolman, AW; Benedetti, A; Starke, JR; Becerra, MC. "Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis". *The Lancet Infectious Diseases*. **14** (10): 947–957. doi:10.1016/S1473-3099(14)70852-7.
71. ^ Lozano, R; Naghavi, M; Foreman, K; Lim, S; Shibuya, K; Aboyans, V; Abraham, J; Adair, T; et al. (15 December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
72. ^ Park, BJ; Wannemuehler, KA; Marston, BJ; Govender, N; Pappas, PG; Chiller, TM (Feb 20, 2009). "Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS.". *AIDS (London, England)*. **23** (4): 525–30. doi:10.1097/QAD.0b013e328322ffac. PMID 19182676.
73. ^ Lapeyssonnie L (1963). "Cerebrospinal meningitis in Africa". *Bulletin of the World Health Organization*. **28** (Suppl): SUPPL:1–114. PMC 2554630. PMID 14259333.
74. ^ Greenwood B (1999). "Manson Lecture. Meningococcal meningitis in Africa". *Trans. R. Soc. Trop. Med. Hyg*. **93** (4): 341–53. doi:10.1016/S0035-9203(99)90106-2. PMID 10674069.
75. ^ *a b c* World Health Organization (1998). *Control of epidemic meningococcal disease, practical guidelines, 2nd edition, WHO/EMC/BA/98* (PDF). **3**. pp. 1–83.
76. ^ WHO (2003). "Detecting meningococcal meningitis epidemics in highly-endemic African countries" (PDF). *Weekly Epidemiological Record*. **78** (33): 294–6. PMID 14509123.
77. ^ *a b* Arthur Earl Walker; Edward R. Laws; George B. Udvarhelyi (1998). "Infections and inflammatory involvement of the CNS". *The Genesis of Neuroscience*. Thieme. pp. 219–21. ISBN 1-879284-62-6.
78. ^ Whytt R (1768). *Observations on the Dropsy in the Brain*. Edinburgh: J. Balfour.
79. ^ *a b c* Greenwood B (June 2006). "100 years of epidemic meningitis in West Africa – has anything changed?". *Tropical Medicine & International health: TM & IH*. **11** (6): 773–80. doi:10.1111/j.1365-3156.2006.01639.x. PMID 16771997.
80. ^ Vieusseux G (1806). "Mémoire sur le Maladie qui a regne à Génève au printemps de 1805". *Journal de Médecine, de Chirurgie et de Pharmacologie (Bruxelles)* (in French). **11**: 50–53.
81. ^ Weichselbaum A (1887). "Ueber die Aetiologie der akuten Meningitis cerebro-spinalis". *Fortschrift der Medizin* (in German). **5**: 573–583.
82. ^ Flexner S (1913). "The results of the serum treatment in thirteen hundred cases of epidemic meningitis" (PDF). *J Exp Med*. **17** (5): 553–76. doi:10.1084/jem.17.5.553. PMC 2125091. PMID 19867668.
83. ^ *a b* Swartz MN (October 2004). "Bacterial meningitis—a view of the past 90 years". *The New England Journal of Medicine*. **351** (18): 1826–28. doi:10.1056/NEJMp048246. PMID 15509815.
84. ^ Rosenberg DH, Arling PA (1944). "Penicillin in the treatment of meningitis". *Journal of the American Medical Association*. **125** (15): 1011–17. doi:10.1001/jama.1944.02850330009002. reproduced in Rosenberg DH, Arling PA (April 1984). "Penicillin in the treatment of meningitis". *Journal of the American Medical Association*. **251** (14): 1870–6. doi:10.1001/jama.251.14.1870. PMID 6366279.

## External links [edit]

- Meningitis at DMOZ
- Meningitis Centers for Disease Control and Prevention (CDC)

*Medicine portal*

*Viruses portal*

Wikimedia Commons has media related to *Meningitis*.

| v · t · e | **Meningitis and other diseases of meninges (G00–G03, 320–322)** |
|---|---|
| **Meningitis** | Arachnoiditis · Bacterial (Tuberculous · Haemophilus · Pneumococcal · · Viral (Herpesviral · · Fungal (Cryptococcal · · Aseptic (Drug-induced · · |
| **Other** | Meningoencephalitis · |

| v · t · e · | Inflammation | | |
|---|---|---|---|
| **Acute** | **Plasma derived mediators** | Bradykinin · *complement* (C3 · C5a · MAC · · *coagulation* (Factor XII · Plasmin · Thrombin · · | |
| | **Cell derived mediators** | *preformed:* | Lysosome granules · *biogenic amines* (Histamine · Serotonin · · |
| | | *synthesized on demand:* | *cytokines* (IFN-γ · IL-8 · TNF-α · IL-1 · · *eicosanoids* (Leukotriene B4 · Prostaglandins · · Nitric oxide · Kinins · |
| **Chronic** | Macrophage · Epithelioid cell · Giant cell · Granuloma · | | |
| **Processes** | **Traditional:** | Rubor · Calor · Tumor · Dolor · Functio laesa · | |
| | **Modern:** | Acute-phase reaction/Fever · Vasodilation · Increased vascular permeability · Exudate · Leukocyte extravasation · Chemotaxis · | |
| **Specific locations** | **Nervous** | *CNS* (Encephalitis · Myelitis · · **Meningitis** (Arachnoiditis · · *PNS* (Neuritis · · *eye* (Dacryoadenitis · Scleritis · Episcleritis · Keratitis · chorioretinitis · Retinitis · Chorioretinitis · Blepharitis · Conjunctivitis · Uveitis · · *ear* (Otitis · Labyrinthitis · Mastoiditis · · | |
| | **Cardiovascular** | Carditis (Endocarditis · Myocarditis · Pericarditis · · Vasculitis (Arteritis · Phlebitis · Capillaritis · · | |
| | **Respiratory** | *upper* (Sinusitis · Rhinitis · Pharyngitis · Laryngitis · · *lower* (Tracheitis · Bronchitis · Bronchiolitis · Pneumonitis · Pleuritis · · Mediastinitis · | |
| | **Digestive** | *mouth* | Stomatitis · Gingivitis · Gingivostomatitis · Glossitis · Tonsillitis · Sialadenitis/Parotitis · Cheilitis · Pulpitis · Gnathitis · |
| | | *tract* | Esophagitis · Gastritis · Gastroenteritis · Enteritis · Colitis · Enterocolitis · Duodenitis · Ileitis · Caecitis · Appendicitis · Proctitis · |
| | | *accessory* | Hepatitis · Ascending cholangitis · Cholecystitis · Pancreatitis · Peritonitis · |
| | **Integumentary** | Dermatitis (Folliculitis · · Cellulitis · Hidradenitis · | |
| | **Musculoskeletal** | Arthritis · Dermatomyositis · *soft tissue* (Myositis · Synovitis/Tenosynovitis · Bursitis · Enthesitis · Fasciitis · Capsulitis · Epicondylitis · Tendinitis · Panniculitis · · Osteochondritis: Osteitis/Osteomyelitis (Spondylitis · Periostitis · · Chondritis · | |
| | **Urinary** | Nephritis (Glomerulonephritis · Pyelonephritis · · Ureteritis · Cystitis · Urethritis · | |
| | **Reproductive** | *female:* | Oophoritis · Salpingitis · Endometritis · Parametritis · Cervicitis · Vaginitis · Vulvitis · Mastitis · |
| | | *male:* | Orchitis · Epididymitis · Prostatitis · Seminal vesiculitis · Balanitis · Posthitis · |

| | | | |
|---|---|---|---|
| | | | Balanoposthitis · |
| | | *pregnancy/newborn:* | Chorioamnionitis · Funisitis · Omphalitis · |
| | **Endocrine** | | Insulitis · Hypophysitis · Thyroiditis · Parathyroiditis · Adrenalitis · |
| | **Lymphatic** | | Lymphangitis · Lymphadenitis · |
| **Authority control** | NDL: 00568667 · | | |

Categories: Disorders causing seizures | Medical emergencies | Meningitis | Acute pain




# Rabies

From Wikipedia, the free encyclopedia

*"Rabid" redirects here. For the 1977 film, see Rabid (film). For the punk rock band, see Rabid (band). For other uses, see Rabies (disambiguation).*

**Rabies** is a viral disease that causes inflammation of the brain in humans and other mammals.[1] Early symptoms can include fever and tingling at the site of exposure.[1] These symptoms are followed by one or more of the following symptoms: violent movements, uncontrolled excitement, fear of water, an inability to move parts of the body, confusion, and loss of consciousness.[1] Once symptoms appear, the result is nearly always death.[1] The time period between contracting the disease and the start of symptoms is usually one to three months; however, this time period can vary from less than one week to more than one year.[1] The time is dependent on the distance the virus must travel to reach the central nervous system.[2]

Rabies is caused by *lyssaviruses*, including rabies virus and Australian bat lyssavirus.[3] Rabies is spread when an infected animal scratches or bites another animal or human.[1] Saliva from an infected animal can also transmit rabies if the saliva comes into contact with the eyes, mouth, or nose.[1] Globally, dogs are the most common animal involved.[1] More than 99% of rabies cases in countries where dogs commonly have the disease are caused by dog bites.[4] In the Americas, bat bites are the most common source of rabies infections in humans, and less than 5% of cases are from dogs.[1][4] Rodents are very rarely infected with rabies.[4] The rabies virus travels to the brain by following the peripheral nerves. The disease can only be diagnosed after the start of symptoms.[1]

Animal control and vaccination programs have decreased the risk of rabies from dogs in a number of regions of the world.[1] Immunizing people before they are exposed is recommended for those who are at high risk. The high-risk group includes people who work with bats or who spend prolonged periods in areas of the world where rabies is common.[1] In people who have been exposed to rabies, the rabies vaccine and sometimes rabies immunoglobulin are effective in preventing the disease if the person receives the treatment before the start of rabies symptoms.[1] Washing bites and scratches for 15 minutes with soap and water, povidone iodine, or detergent may reduce the number of viral




A dog with rabies in the paralytic (post-furious) stage

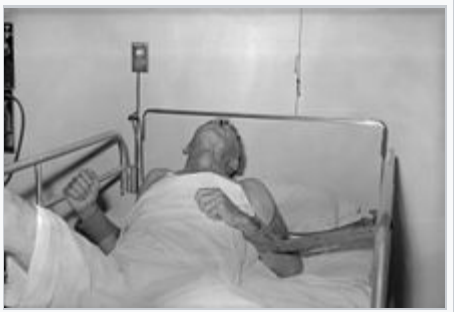
| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | A82 |
| **DiseasesDB** | 11148 |
| **MedlinePlus** | 001334 |
| **eMedicine** | med/1374 eerg/493 ped/1974 |
| **Patient UK** | Rabies |
| **MeSH** | D011818 |
| **Orphanet** | 770 |

particles and may be somewhat effective at preventing transmission.[1][5] Only five people have survived a rabies infection after showing symptoms, and this was with extensive treatment known as the Milwaukee protocol.[6][7]

Rabies causes about 24,000 to 60,000 deaths worldwide per year.[8][9] More than 95% of human deaths caused by rabies occur in Africa and Asia.[1] Rabies is present in more than 150 countries and on all continents but Antarctica.[1] More than 3 billion people live in regions of the world where rabies occurs.[1] A number of countries, including Australia, Canada, Japan, and the United States, and Western Europe, do not have rabies among dogs.[10][11] Many small island nations do not have rabies at all.[12]



## Signs and symptoms [edit]



A person with rabies, 1959

The period between infection and the first symptoms (incubation period) is typically 1–3 months in humans.[8] Incubation periods as short as four days and longer than six years have been documented, depending on the location and severity of the contaminated wound and the amount of virus introduced.[8] Initial signs and symptoms of rabies are often nonspecific such as fever and headache.[8] As rabies progresses and causes inflammation of the brain and/or meninges, signs and symptoms can include slight or partial paralysis, anxiety, insomnia, confusion, agitation, abnormal behavior, paranoia, terror, and hallucinations, progressing to delirium, and coma.[2][8] The person may also have hydrophobia.[1]

Death usually occurs 2 to 10 days after first symptoms. Survival is rare once symptoms have presented,[8] even with the administration of proper and intensive care.[13] Jeanna Giese, who in 2004 was the first patient treated with the Milwaukee protocol,[14] became the first person ever recorded to have survived rabies without receiving successful post-exposure prophylaxis. An intention-to-treat analysis has since found this protocol has a survival rate of about 8%.[15]

### Hydrophobia [edit]

Hydrophobia ("fear of water") is the historic name for rabies.[16] It refers to a set of symptoms in the later stages of an infection in which the person has difficulty swallowing, shows panic when presented with liquids to drink, and cannot quench his or her thirst. Any mammal infected with the virus may demonstrate hydrophobia.[17]

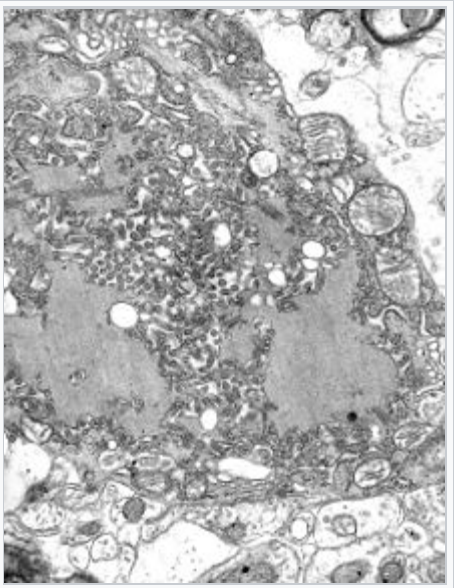
A rabid dog

Saliva production is greatly increased, and attempts to drink, or even the intention or suggestion of drinking, may cause excruciatingly painful spasms of the muscles in the throat and larynx. This can be attributed to the fact that the virus multiplies and assimilates in the salivary glands of the infected animal for the purpose of further transmission through biting. The ability to transmit the virus would decrease significantly if the infected individual could swallow saliva and water.[18]

Hydrophobia is commonly associated with furious rabies, which affects 80% of rabies-infected people. The remaining 20% may experience a paralytic form of rabies that is marked by muscle weakness, loss of sensation, and paralysis; this form of rabies does not usually cause fear of water.[17]

## Cause [edit]

Rabies is caused by a number of *lyssaviruses* including: rabies virus and Australian bat lyssavirus.[3]



TEM micrograph with numerous rabies virions (small, dark grey, rodlike particles) and Negri bodies (the larger pathognomonic cellular inclusions of rabies infection)

The rabies virus is the type species of the *Lyssavirus* genus, in the family *Rhabdoviridae*, order *Mononegavirales*. Lyssavirions have helical symmetry, with a length of about 180 nm and a cross-section of about 75 nm.[19] These virions are enveloped and have a single-stranded RNA genome with negative sense. The genetic information is packed as a ribonucleoprotein complex in which RNA is tightly bound by the viral nucleoprotein. The RNA genome of the virus encodes five genes whose order is highly conserved: nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and the viral RNA polymerase (L).[20]

Once within a muscle or nerve cell, the virus undergoes replication. The trimeric spikes on the exterior of the membrane of the virus interact with a specific cell receptor, the most likely one being the acetylcholine receptor. The cellular membrane pinches in a procession known as pinocytosis and allows entry of the virus into the cell by way of an endosome. The virus then uses the acidic environment, which is necessary, of that endosome and binds to its membrane simultaneously, releasing its five proteins and single strand RNA into the cytoplasm.[21]

The L protein then transcribes five mRNA strands and a positive strand of RNA all from the original negative strand RNA using free nucleotides in the cytoplasm. These five mRNA strands are then translated into their corresponding proteins (P, L, N, G and M proteins) at free ribosomes in the cytoplasm. Some proteins require post-translative modifications. For example, the G protein travels through the rough endoplasmic reticulum, where it undergoes further folding, and is then transported to the Golgi apparatus, where a sugar group is added to it (glycosylation).[21]

Where there are enough proteins, the viral polymerase will begin to synthesize new negative strands of RNA from the template of the positive strand RNA. These negative strands will then form complexes with the N, P, L and M proteins and then travel to the inner membrane of the cell, where a G protein has embedded itself in the membrane. The G protein then coils around the N-P-L-M complex of proteins taking some of the host cell membrane with it, which will form the new outer envelope of the virus particle. The virus then buds from the cell.[21]

From the point of entry, the virus is neurotropic, traveling quickly along the neural pathways into the central nervous system. The virus usually first infects muscle cells close to the site of infection, where they are able to replicate without being 'noticed' by the host's immune system. Once enough virus has been replicated, they begin to bind to acetylcholine receptors (p75NR) at the neuromuscular junction.[22] The virus then travels through the nerve cell axon via retrograde transport, as its P protein interacts with dynein, a protein present in the cytoplasm of nerve cells. Once the virus reaches the cell body it travels rapidly to the Central Nervous System (CNS), replicating in motor neurons and eventually reaching the brain.[2] After the brain is infected, the virus travels centrifugally to the peripheral and autonomic nervous systems, eventually migrating to the salivary glands, where it is ready to be transmitted to the next host.[23]:317

## Transmission [edit]

*Main article: Rabies transmission*

All warm-blooded species, including humans, may become infected with the rabies virus and develop symptoms. Birds were first artificially infected with rabies in 1884; however, infected birds are largely if not wholly asymptomatic, and recover.[24] Other bird species have been known to develop rabies antibodies, a sign of infection, after feeding on rabies-infected mammals.[25][26]

The virus has also adapted to grow in cells of poikilothermic ("cold-blooded") vertebrates.[27][28] Most animals can be infected by the virus and can transmit the disease to humans. Infected bats,[29][30] monkeys, raccoons, foxes, skunks, cattle, wolves, coyotes, dogs, mongooses (normally yellow mongoose)[31] and cats present the greatest risk to humans.

Rabies may also spread through exposure to infected bears, domestic farm animals, groundhogs, weasels, and other wild carnivorans. Lagomorphs, such as hares and rabbits, and small rodents such as chipmunks, gerbils, guinea pigs, hamsters, mice, rats, and squirrels, are almost never found to be infected with rabies and are not known to transmit rabies to humans.[32] Bites from mice, rats, or squirrels rarely require rabies prevention because these rodents are typically killed by any encounter with a larger, rabid animal, and would, therefore, not be carriers.[33] The Virginia opossum is resistant but not immune to rabies.[34]

The virus is usually present in the nerves and saliva of a symptomatic rabid animal.[35][36] The route of infection is usually, but not always, by a bite. In many cases, the infected animal is exceptionally aggressive, may attack without provocation, and exhibits otherwise uncharacteristic behavior.[37] This is an example of a viral pathogen modifying the behavior of its host to facilitate its transmission to other hosts.

Transmission between humans is extremely rare. A few cases have been recorded through transplant surgery.[38] The only well-documented cases of rabies caused by human-to-human transmission occurred among eight recipients of transplanted corneas and among three recipients of solid organs.[39] In addition to transmission from cornea and organ transplants, bite and non-bite exposures inflicted by infected humans could theoretically transmit rabies, but no such cases have been documented, since infected humans are usually hospitalized and necessary precautions taken. Casual contact, such as touching a person with rabies or contact with non-infectious fluid or tissue (urine, blood, feces) does not constitute an exposure and does not require post-exposure prophylaxis. Additionally, as the virus is present in sperm or vaginal secretions, spread through sex may be possible.[40]

After a typical human infection by bite, the virus enters the peripheral nervous system. It then travels along the afferent nerves toward the central nervous system.[41] During this phase, the virus cannot be easily detected within the host, and vaccination may still confer cell-mediated immunity to prevent symptomatic rabies. When the virus reaches the brain, it rapidly causes encephalitis, the prodromal phase, which is the beginning of the symptoms. Once the patient becomes symptomatic, treatment is almost never effective and mortality is over 99%. Rabies may also inflame the spinal cord, producing transverse myelitis.[42][43]

## Diagnosis [edit]

Rabies can be difficult to diagnose, because, in the early stages, it is easily confused with other diseases or

with aggressiveness.[44] The reference method for diagnosing rabies is the fluorescent antibody test (FAT), an immunohistochemistry procedure, which is recommended by the World Health Organization (WHO).[45] The FAT relies on the ability of a detector molecule (usually fluorescein isothiocyanate) coupled with a rabies-specific antibody, forming a conjugate, to bind to and allow the visualisation of rabies antigen using fluorescent microscopy techniques. Microscopic analysis of samples is the only direct method that allows for the identification of rabies virus-specific antigen in a short time and at a reduced cost, irrespective of geographical origin and status of the host. It has to be regarded as the first step in diagnostic procedures for all laboratories. Autolysed samples can, however, reduce the sensitivity and specificity of the FAT.[46] The RT PCR assays proved to be a sensitive and specific tool for routine diagnostic purposes,[47] particularly in decomposed samples[48] or archival specimens.[49] The diagnosis can be reliably made from brain samples taken after death. The diagnosis can also be made from saliva, urine, and cerebrospinal fluid samples, but this is not as sensitive and reliable as brain samples.[46] Cerebral inclusion bodies called Negri bodies are 100% diagnostic for rabies infection but are found in only about 80% of cases.[19] If possible, the animal from which the bite was received should also be examined for rabies.[50]

Some light microscopy techniques may also be used to diagnose rabies at a tenth of the cost of traditional fluorescence microscopy techniques, allowing identification of the disease in less-developed countries.[51]

### Differential diagnosis [edit]

The differential diagnosis in a case of suspected human rabies may initially include any cause of encephalitis, in particular infection with viruses such as herpesviruses, enteroviruses, and arboviruses such as West Nile virus. The most important viruses to rule out are herpes simplex virus type one, varicella zoster virus, and (less commonly) enteroviruses, including coxsackieviruses, echoviruses, polioviruses, and human enteroviruses 68 to 71.[52]

New causes of viral encephalitis are also possible, as was evidenced by the 1999 outbreak in Malaysia of 300 cases of encephalitis with a mortality rate of 40% caused by Nipah virus, a newly recognized paramyxovirus.[53] Likewise, well-known viruses may be introduced into new locales, as is illustrated by the outbreak of encephalitis due to West Nile virus in the eastern United States.[54] Epidemiologic factors, such as season, geographic location, and the patient's age, travel history, and possible exposure to bites, rodents, and ticks, may help direct the diagnosis.

## Prevention [edit]

Almost all human cases of rabies were fatal until a vaccine was developed in 1885 by Louis Pasteur and Émile Roux. Their original vaccine was harvested from infected rabbits, from which the virus in the nerve tissue was weakened by allowing it to dry for five to ten days.[55] Similar nerve tissue-derived vaccines are still used in some countries, as they are much cheaper than modern cell culture vaccines.[56]

The human diploid cell rabies vaccine was started in 1967. Less expensive purified chicken embryo cell vaccine and purified vero cell rabies vaccine are now available.[50] A recombinant vaccine called V-RG has been used in Belgium, France, Germany, and the United States to prevent outbreaks of rabies in undomesticated animals.[57] Immunization before exposure has been used in both human and nonhuman populations, where, as in many jurisdictions, domesticated animals are required to be vaccinated.[58]

The number of recorded human deaths from rabies in the United States has dropped from 100 or more annually in the early 20th century to one or two per year due to widespread vaccination of domestic dogs and cats and the development of human vaccines and immunoglobulin treatments. Most deaths now result from bat bites, which may go unnoticed by the victim and hence untreated.[59]

The Missouri Department of Health and Senior Services Communicable Disease Surveillance 2007 Annual Report states the following can help reduce the risk of contracting rabies:[60]

- Vaccinating dogs, cats, and ferrets against rabies
- Keeping pets under supervision

- Not handling wild animals or strays
- Contacting an animal control officer upon observing a wild animal or a stray, especially if the animal is acting strangely
- If bitten by an animal, washing the wound with soap and water for 10 to 15 minutes and contacting a healthcare provider to determine if post-exposure prophylaxis is required

September 28 is World Rabies Day, which promotes the information, prevention, and elimination of the disease.[61]

## Treatment [edit]

Treatment after exposure can prevent the disease if administered promptly, generally within 10 days of infection.[19] Thoroughly washing the wound as soon as possible with soap and water for approximately five minutes is effective in reducing the number of viral particles.[62] Povidone-iodine or alcohol is then recommended to reduce the virus further.[63]

In the US, the Centers for Disease Control and Prevention recommends people receive one dose of human rabies immunoglobulin (HRIG) and four doses of rabies vaccine over a 14-day period.[64] The immunoglobulin dose should not exceed 20 units per kilogram body weight. HRIG is expensive and constitutes most of the cost of post exposure treatment, ranging as high as several thousand dollars.[65] As much as possible of this dose should be injected around the bites, with the remainder being given by deep intramuscular injection at a site distant from the vaccination site.[21]

The first dose of rabies vaccine is given as soon as possible after exposure, with additional doses on days three, seven and 14 after the first. Patients who have previously received pre-exposure vaccination do not receive the immunoglobulin, only the postexposure vaccinations on days 0 and 3.[66]

The pain and side effects of modern cell-based vaccines are similar to flu shots. The old nerve-tissue-based vaccinations that require multiple painful injections into the abdomen with a large needle are inexpensive, but are being phased out and replaced by affordable World Health Organization intradermal-vaccination regimens.[50]

Intramuscular vaccination should be given into the deltoid, not the gluteal area, which has been associated with vaccination failure due to injection into fat rather than muscle. In infants, the lateral thigh is recommended.[67]

Awakening to find a bat in the room, or finding a bat in the room of a previously unattended child or mentally disabled or intoxicated person, is regarded as an indication for post-exposure prophylaxis (PEP). The recommendation for the precautionary use of PEP in occult bat encounters where no contact is recognized has been questioned in the medical literature, based on a cost–benefit analysis.[68] However, a 2002 study has supported the protocol of precautionary administering of PEP where a child or mentally compromised individual has been alone with a bat, especially in sleep areas, where a bite or exposure may occur without the victim being aware.[69] Begun with little or no delay, PEP is 100% effective against rabies.[14] In the case in which there has been a significant delay in administering PEP, the treatment should be administered regardless, as it may still be effective.[21]

### Induced coma [edit]

*See also: Milwaukee protocol*

In 2004, American teenager Jeanna Giese survived an infection of rabies unvaccinated. She was placed into an induced coma upon onset of symptoms and given ketamine, midazolam, ribavirin, and amantadine. Her doctors administered treatment based on the hypothesis that detrimental effects of rabies were caused by temporary dysfunctions in the brain and could be avoided by inducing a temporary partial halt in brain function that would protect the brain from damage while giving the immune system time to defeat the virus. After 31 days of isolation and 76 days of hospitalization, Giese was released from the hospital.[70] She survived with all higher level brain functions, but an inability to walk and balance.[71] On a podcast of

NPR's *Radiolab*, Giese recounted: "I had to learn how to stand and then to walk, turn around, move my toes. I was really, after rabies, a new born baby who couldn't do anything. I had to relearn that all...mentally I knew how to do stuff but my body wouldn't cooperate with what I wanted it to do. It definitely took a toll on me psychologically. You know I'm still recovering. I'm not completely back. Stuff like balance, and I can't run normally."[72]

Giese's treatment regimen became known as the Milwaukee protocol, which has since undergone revision with the second version omitting the use of ribavirin. Two of 25 patients survived when treated under the first protocol. A further 10 patients have been treated under the revised protocol, with a further two survivors.[15]

On June 12, 2011, Precious Reynolds, an eight-year-old girl from Humboldt County, California, became the third reported person in the United States to have recovered from rabies without receiving PEP.[73]

## Prognosis [edit]

In unvaccinated humans, rabies is almost always fatal after neurological symptoms have developed.[74]

Vaccination after exposure, PEP, is highly successful in preventing the disease if administered promptly, in general within 6 days of infection. Begun with little or no delay, PEP is 100% effective against rabies.[14] In the case of significant delay in administering PEP, the treatment still has a chance of success.[21]

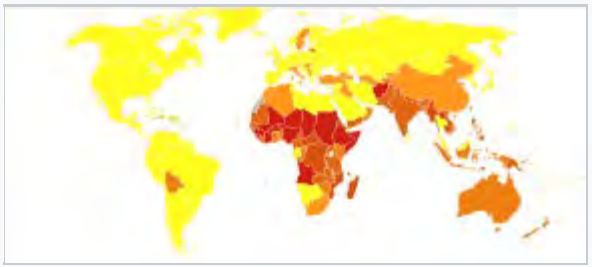
Five of the first 43 patients (12%) treated with the Milwaukee protocol survived, and those receiving treatment survived longer than those not receiving the treatment.[75]

## Epidemiology [edit]

*Main article: Prevalence of rabies*

In 2010, an estimated 26,000 people died from rabies, down from 54,000 in 1990.[76] The majority of the deaths occurred in Asia and Africa.[74] India has the highest rate of human rabies in the world, primarily because of stray dogs,[77] whose number has greatly increased since a 2001 law forbade the killing of dogs.[78] Effective control and treatment of rabies in India is also hindered by a form of mass hysteria known as puppy pregnancy syndrome (PPS). Dog bite victims with PPS (both male and female) become convinced that puppies are growing inside them, and often seek help from faith healers rather than from conventional medical services. In cases where the bite was from a rabid dog, this decision can prove fatal. Dr. Nitai Kishore Marik, former district medical officer of West Midnapur, states "I have seen scores of cases of rabies that reached our hospitals very late because of the intervention of faith healers. We could not save those lives."[79] An estimated 20,000 people die every year from rabies in India — more than a third of the global toll.[78] As of 2015, China had the second-highest number of cases (approximately 6,000), followed by the Democratic Republic of the Congo (5,600).[80]

The rabies virus survives in widespread, varied, rural animal reservoirs. Despite Australia's official rabies-free status,[81] Australian bat lyssavirus (ABLV), discovered in 1996, is a strain of rabies prevalent in native bat populations. There have been three human cases of ABLV in Australia, all of them fatal.



Deaths from rabies per million persons in 2012


Rabies-free countries (in green) as of 2013. always rabies-free

rabies eliminated before 1990
rabies eliminated in or after 1990
year of rabies elimination unknown

In Asia and in parts of the Americas and Africa, dogs remain the principal host. Mandatory vaccination of animals is less effective in rural areas. Especially in developing countries, pets may not be privately kept and their destruction may be unacceptable. Oral vaccines can be safely distributed in baits, a practice that has successfully reduced rabies in rural areas of Canada, France, and the United States. In Montréal, Quebec, Canada, baits are successfully used on raccoons in the Mont-Royal Park area. Vaccination campaigns may be expensive, and cost-benefit analysis suggests baits may be a cost-effective method of control.[82] In Ontario, a dramatic drop in rabies was recorded when an aerial bait-vaccination campaign was launched.[83]

Rabies is common among wild animals in the US. Bats, raccoons, skunks and foxes account for almost all reported cases (98% in 2009). Rabid bats are found in all 48 contiguous states. Other reservoirs are more limited geographically; for example, the raccoon rabies virus variant is only found in a relatively narrow band along the East Coast. Due to a high public awareness of the virus, efforts at vaccination of domestic animals and curtailment of feral populations, and availability of postexposure prophylaxis, incidents of rabies in humans are very rare. A total of 49 cases of the disease was reported in the country between 1995 and 2011; of these, 11 are thought to have been acquired abroad. Almost all domestically acquired cases are attributed to bat bites.[84]

In Switzerland, the disease has been virtually eliminated after scientists placed chicken heads laced with live attenuated vaccine in the Swiss Alps.[83] The foxes of Switzerland, proven to be the main source of rabies in the country, ate the chicken heads and immunized themselves.[83]

Italy, after being declared rabies-free from 1997 to 2008, has witnessed a reemergence of the disease in wild animals in the Triveneto regions (Trentino-Alto Adige/Südtirol, Veneto and Friuli-Venezia Giulia), due to the spreading of an epidemic in the Balkans that hit Austria too. An extensive wild animals vaccination campaign eliminated the virus from Italy again, and it regained the rabies-free country status in 2013, the last reported case of rabies being reported in a red fox in early 2011.[85][86]

## History [edit]

Rabies has been known since around 2000 B.C.[87] The first written record of rabies is in the Mesopotamian Codex of Eshnunna (circa 1930 BC), which dictates that the owner of a dog showing symptoms of rabies should take preventive measure against bites. If another person were bitten by a rabid dog and later died, the owner was heavily fined.[88]


A woodcut from the Middle Ages showing a rabid dog.

Ineffective folk remedies abounded in the medical literature of the ancient world. The physician Scribonius Largus prescribed a poultice of cloth and hyena skin; Antaeus recommended a preparation made from the skull of a hanged man.[89]

Rabies appears to have originated in the Old World, the first epizootic in the New World occurring in Boston in 1768.[90] It spread from there, over the next few years, to various other states, as well as to the French West Indies, eventually becoming common all across North America.

Rabies was considered a scourge for its prevalence in the 19th century. In France and Belgium, where Saint Hubert was venerated, the "St Hubert's Key" was heated and applied to cauterize the wound. By an application of magical thinking, dogs were branded with the key in hopes of protecting them from rabies. The fear of rabies was almost irrational, due to the insignificant number of vectors (mostly rabid dogs) and the absence of any efficacious treatment. It was not uncommon for


François Boissier de Sauvages de Lacroix, *Della natura e causa della rabbia* (*Dissertation sur la nature et la cause de la Rage*), 1777

a person bitten by a dog but merely suspected of being rabid, to commit suicide or to be killed by others.[91] This gave Louis Pasteur ample opportunity to test postexposure treatments from 1885.[8] In ancient times, the attachment of the tongue (the lingual frenulum, a mucous membrane) was cut and removed as this is where rabies was thought to originate. This practice ceased with the discovery of the actual cause of rabies.[23]

In modern times, the fear of rabies has not diminished, and the disease and its symptoms, particularly agitation has served as an inspiration for several works of zombie or similarly-themed fiction, often portraying rabies as having mutated into a stronger virus which fills humans with murderous rage or uncurable illness, bringing about a devastating, widespread pandemic.[92]

## Etymology [edit]

The term is derived from the Latin *rabies*, "madness".[93] This, in turn, may be related to the Sanskrit *rabhas*, "to do violence".[*citation needed*][94] The Greeks derived the word *lyssa*, from *lud* or "violent"; this root is used in the genus name of the rabies virus, *Lyssavirus*.[91]

# Other animals [edit]

*Main article: Rabies in animals*

Rabies is infectious to mammals; three stages of central nervous system infection are recognized. The first stage is a one- to three-day period characterized by behavioral changes and is known as the prodromal stage. The second is the excitative stage, which lasts three to four days. This stage is often known as "furious rabies" for the tendency of the affected animal to be hyper-reactive to external stimuli and bite at anything near. The third is the paralytic stage and is caused by damage to motor neurons. Incoordination is seen, owing to rear limb paralysis, and drooling and difficulty swallowing is caused by paralysis of facial and throat muscles. Death is usually caused by respiratory arrest.[95]

# Research [edit]

Rabies has the advantage over other pseudotyping methods for gene delivery in that the cell-targeting (tissue tropism) is more specific for difficult-to-reach sites, such as the central nervous system without invasive delivery methods, as well as being capable of retrograde tracing (i.e., going against the flow of information at synapses) in neuronal circuits.[96]

Evidence indicates artificially increasing the permeability of the blood–brain barrier, which normally does not allow most immune cells across, promotes viral clearance.[97][98]

# See also [edit]

- Global Alliance for Rabies Control
- Neglected tropical diseases
- Rabies in popular culture
- World Rabies Day

Viruses portal

# References [edit]


1. ^ a b c d e f g h i j k l m n o p q r "Rabies Fact Sheet N°99". *World Health Organization*. July 2013. Retrieved 28 February 2014.
2. ^ a b c Cotran RS, Kumar V, Fausto N (2005). *Robbins and Cotran Pathologic Basis of Disease* (7th ed.). Elsevier/Saunders. p. 1375. ISBN 0-7216-0187-1.
3. ^ a b "Rabies, Australian bat lyssavirus and other lyssaviruses". *The Department of Health*. Dec 2013. Retrieved 1 March 2014.
4. ^ a b c Tintinalli, Judith E. (2010). *Emergency Medicine: A Comprehensive Study Guide (Emergency Medicine (Tintinalli))*. McGraw-Hill. pp. Chapter 152. ISBN 0-07-148480-9.
5. ^ William H. Wunner (2010). *Rabies: Scientific Basis of the Disease and Its Management*. Academic Press. p. 556. ISBN 9780080550091.
6. ^ Hemachudha T, Ugolini G, Wacharapluesadee S, Sungkarat W, Shuangshoti S, Laothamatas J (May 2013). "Human rabies: neuropathogenesis, diagnosis, and management.". *Lancet neurology*. **12** (5): 498–513. doi:10.1016/s1474-4422(13)70038-3. PMID 23602163.
7. ^ "UC Davis Children's Hospital patient becomes third person in U.S. to survive rabies". UC Davis Medical Center. Retrieved 3 May 2012.
8. ^ a b c d e f g Giesen, A; Gniel, D; Malerczyk, C (March 2015). "30 Years of rabies vaccination with Rabipur: a summary of clinical data and global experience". *Expert Review of Vaccines* (Review). **14** (3): 351–67. doi:10.1586/14760584.2015.1011134. PMID 25683583.
9. ^ GBD 2013 Mortality and Causes of Death, Collaborators (10 January 2015). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **385** (9963): 117–71. doi:10.1016/s0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
10. ^ *WHO Expert Consultation on Rabies : second report.* (PDF) (2 ed.). Geneva: WHO. 2013. p. 3. ISBN 9789241209823.
11. ^ "Penang on rabies alert". The Star. September 17, 2015. Retrieved 19 September 2015.
12. ^ "Rabies-Free Countries and Political Units". *CDC*. Retrieved 1 March 2014.
13. ^ Rupprecht CE, Willoughby R, Slate D (2006). "Current and future trends in the prevention, treatment and control of rabies". *Expert Review of Anti-infective Therapy*. **4** (6): 1021–38. doi:10.1586/14787210.4.6.1021. PMID 17181418.
14. ^ a b c Jordan Lite (2008-10-08). "Medical Mystery: Only One Person Has Survived Rabies without Vaccine—But How?". *Scientific American*. Retrieved 2010-01-30.
15. ^ a b Willoughby RE (2009). "Are we getting closer to the treatment of rabies?: medical benchmarks". *Future Virology*. MedScape. **4** (6): 563–70. doi:10.2217/fvl.09.52.
16. ^ Smallman-Raynor, Andrew Cliff, Peter Haggett, Matthew (2004). *World atlas of epidemic diseases*. London: Arnold. p. 51. ISBN 9780340761717.
17. ^ a b "Symptoms of rabies". *NHS.uk*. June 12, 2012. Retrieved 3 September 2014.
18. ^ "Rabies". *AnimalsWeCare.com*.
19. ^ a b c Drew WL (2004). "Chapter 41: Rabies". In Ryan KJ, Ray CG (editors). *Sherris Medical Microbiology* (4th ed.). McGraw Hill. pp. 597–600. ISBN 0-8385-8529-9.
20. ^ Finke S, Conzelmann KK (August 2005). "Replication strategies of rabies virus". *Virus Res*. **111** (2): 120–31. doi:10.1016/j.virusres.2005.04.004. PMID 15885837.
21. ^ a b c d e f "Rabies Post-Exposure Prophylaxis". Centers for Disease Control and Prevention (CDC). 2009-12-23. Retrieved 2010-01-30.
22. ^ Gluska, Shani & Zahavi, Eitan Erez & Chein, Michael & Gradus, Tal & Bauer, Anja & Finke, Stefan & Perlson, Eran (August 28, 2014). "Rabies Virus Hijacks and Accelerates the p75NTR Retrograde Axonal Transport Machinery". *PLOS Pathogens*. doi:10.1371/journal.ppat.1004348.
23. ^ a b Baer, George (1991). *The Natural History of Rabies*. CRC Press. ISBN 9780849367601. Retrieved 31 October 2011.

24. ^ Shannon LM, Poulton JL, Emmons RW, Woodie JD, Fowler ME (April 1988). "Serological survey for rabies antibodies in raptors from California". *J. Wildl. Dis.* **24** (2): 264–7. doi:10.7589/0090-3558-24.2.264. PMID 3286906.
25. ^ Gough PM, Jorgenson RD (1976). "Rabies antibodies in sera of wild birds". *Journal of Wildlife Diseases*. **12** (3): 392–5. doi:10.7589/0090-3558-12.3.392. PMID 16498885.
26. ^ Jorgenson RD, Gough PM (July 1976). "Experimental rabies in a great horned owl". *J. Wildl. Dis.* **12** (3): 444–7. doi:10.7589/0090-3558-12.3.444.
27. ^ Wong, Derek. "Rabies". Wong's Virology. Retrieved 19 Mar 2009.
28. ^ Campbell, James B.; Charlton, K.M. (1988). *Developments in Veterinary Virology: Rabies*. Springer. p. 48. ISBN 0-89838-390-0.
29. ^ Pawan JL (1959). "The transmission of paralytic rabies in Trinidad by the vampire bat (*Desmodus rotundus murinus* Wagner)". *Caribbean Medical Journal*. **21**: 110–36. PMID 13858519.
30. ^ Pawan JL (1959). "Rabies in the vampire bat of Trinidad, with special reference to the clinical course and the latency of infection". *Caribbean Medical Journal*. **21**: 137–56. PMID 14431118.
31. ^ Taylor PJ (December 1993). "A systematic and population genetic approach to the rabies problem in the yellow mongoose (Cynictis penicillata)". *The Onderstepoort Journal of Veterinary Research*. **60** (4): 379–87. PMID 7777324.
32. ^ "Rabies. Other Wild Animals: Terrestrial carnivores: raccoons, skunks and foxes.". Centers for Disease Control and Prevention(CDC). Retrieved 2010-12-23.
33. ^ Anderson, Janet & Frey, Rebecca (2006). "Rabies". *Gale Encyclopedia of Medicine* (3rd ed.).
34. ^ McRuer DL, Jones KD (May 2009). "Behavioral and nutritional aspects of the Virginian opossum (Didelphis virginiana)". *The Veterinary Clinics of North America. Exotic Animal Practice*. **12** (2): 217–36, viii. doi:10.1016/j.cvex.2009.01.007. PMID 19341950.
35. ^ *The Merck Manual* (11th ed.). 1983. p. 183.
36. ^ *The Merck manual of Medical Information* (Second Home ed.). 2003. p. 484.
37. ^ Turton, Jenny (2000). "Rabies: a killer disease". National Department of Agriculture.
38. ^ Srinivasan A, Burton EC, Kuehnert MJ, Rupprecht C, Sutker WL, Ksiazek TG, Paddock CD, Guarner J, Shieh WJ, Goldsmith C, Hanlon CA, Zoretic J, Fischbach B, Niezgoda M, El-Feky WH, Orciari L, Sanchez EQ, Likos A, Klintmalm GB, Cardo D, LeDuc J, Chamberland ME, Jernigan DB, Zaki SR (March 2005). "Transmission of rabies virus from an organ donor to four transplant recipients" (PDF). *N Engl J Med*. **352** (11): 1103–11. doi:10.1056/NEJMoa043018. PMID 15784663.
39. ^ "Exposure to the Virus".
40. ^ RabiesAlliance.org
41. ^ Jackson, Alan C.; Wunner, William H. (2002). *Rabies*. Academic Press. p. 290. ISBN 978-0-12-379077-4.
42. ^ Lynn DJ, Newton HB, Rae-Grant AD (2012). *The 5-Minute Neurology Consult*. Lippincott Williams & Wilkins. pp. 414–. ISBN 978-1-4511-0012-9.
43. ^ Davis, Larry Ernest & King, Molly K. & Schultz, Jessica L. (June 15, 2005). *Fundamentals of neurologic disease*. Demos Medical Publishing. p. 73. ISBN 978-1-888799-84-2.
44. ^ Cynthia M.; Kahn, BA, eds. (2010). *The Merck Veterinary Manual* (10th ed.). Kendallville, Indiana: Courier Kendallville, Inc. p. 1193. ISBN 0-911910-93-X.
45. ^ Dean, D.J.; Abelseth, M.K. (1973). "Ch. 6: The fluorescent antibody test". In Kaplan, M.M.; Koprowski, H. *Laboratory techniques in rabies*. Monograph series. **23** (3rd ed.). World Health Organization. p. 73.
46. ^ *a b* Fooks AR, Johnson N, Freuling CM, Wakeley PR, Banyard AC, McElhinney LM, Marston DA, Dastjerdi A, Wright E, Weiss RA, Müller T (2009). "Emerging technologies for the detection of rabies virus: challenges and hopes in the 21st century". *PLoS Neglected Tropical Diseases*. **3** (9): e530. doi:10.1371/journal.pntd.0000530. PMC 2745658. PMID 19787037.
47. ^ Tordo, N; Bourhy, H; Sacramento, D (1994). "Ch. 10: PCR technology for lyssavirus diagnosis". In Clewley, J.P. *The Polymerase Chain Reaction (PCR) for Human Viral Diagnosis*. CRC Press. pp. 125–145. ISBN 978-0-8493-4833-4.
48. ^ David D, Yakobson B, Rotenberg D, Dveres N, Davidson I, Stram Y (2002). "Rabies virus detection by RT-PCR in decomposed naturally infected brains". *Veterinary Microbiology*. **87** (2): 111–8. doi:10.1016/s0378-1135(02)00041-x. PMID 12034539.
49. ^ Biswal M, Ratho R, Mishra B (September 2007). "Usefulness of reverse transcriptase-polymerase chain reaction for detection of rabies RNA in archival samples". *Japanese Journal of Infectious Diseases*. **60** (5): 298–9. PMID 17881871.
50. ^ *a b c* Ly S, Buchy P, Heng NY, Ong S, Chhor N, Bourhy H, Vong S (2009). Carabin H, ed. "Rabies situation in Cambodia" (PDF). *PLoS Neglected Tropical Diseases*. **3** (9): e511. doi:10.1371/journal.pntd.0000511. PMC 2731168. PMID 19907631. e511.

51. ^ Dürr S, Naïssengar S, Mindekem R, Diguimbye C, Niezgoda M, Kuzmin I, Rupprecht CE, Zinsstag J (2008). Cleaveland S, ed. "Rabies diagnosis for developing countries" (PDF). *PLoS Neglected Tropical Diseases*. **2** (3): e206. doi:10.1371/journal.pntd.0000206. PMC 2268742. PMID 18365035. e206.
52. ^ "Rabies: Differential Diagnoses & Workup". *eMedicine Infectious Diseases*. 2008-10-03. Retrieved 2010-01-30.
53. ^ Taylor DH, Straw BE, Zimmerman JL, D'Allaire S (2006). *Diseases of swine*. Oxford: Blackwell. pp. 463–5. ISBN 0-8138-1703-X. Retrieved 2010-01-30.
54. ^ Minagar, Alireza; J. Steven Alexander (2005). *Inflammatory Disorders Of The Nervous System: Pathogenesis, Immunology, and Clinical Management*. Humana Press. ISBN 1-58829-424-2.
55. ^ Geison GL (April 1978). "Pasteur's work on rabies: Reexamining the ethical issues". *Hastings Center Report*. **8** (2): 26–33. doi:10.2307/3560403. JSTOR 3560403. PMID 348641.
56. ^ Srivastava AK, Sardana V, Prasad K, Behari M (March 2004). "Diagnostic dilemma in flaccid paralysis following anti-rabies vaccine". *Neurol India*. **52** (1): 132–3. PMID 15069272.
57. ^ Reece JF, Chawla SK (2006). "Control of rabies in Jaipur, India, by the sterilisation and vaccination of neighbourhood dogs". *Vet Rec*. **159** (12): 379–83. doi:10.1136/vr.159.12.379. PMID 16980523.
58. ^ "Compendium of Animal Rabies Prevention and Control" (PDF). National Association of State Public Health Veterinarians. 2007-12-31. Retrieved 2010-01-03.
59. ^ "Rabies in the U.S.". Centers for Disease Control and Prevention (CDC). April 22, 2011. Retrieved December 31, 2011.
60. ^ 2007 Annual Report (PDF) (Report). Bureau of Communicable Disease Control and Prevention. 2007.
61. ^ "World Rabies Day". World Health Organization (WHO).
62. ^ "Rabies & Australian bat lyssavirus information sheet". Health.vic.gov.au. Retrieved 2012-01-30.
63. ^ National Center for Disease Control (2014). "National Guidelines on Rabies Prophylaxis" (pdf). Retrieved 5 September 2014.
64. ^ "Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies". Centers for Disease Control and Prevention (CDC).
65. ^ "Cost of Rabies Prevention".
66. ^ Park's textbook of Community medicine,22nd edition,2013,p 254
67. ^ "Rabies". *www.who.int*. World Health Organization. Retrieved 1 February 2015.
68. ^ De Serres G, Skowronski DM, Mimault P, Ouakki M, Maranda-Aubut R, Duval B (2009). "Bats in the bedroom, bats in the belfry: Reanalysis of the rationale for rabies post-exposure prophylaxis". *Clin Infect Dis*. **48** (11): 1493–9. doi:10.1086/598998. PMID 19400689.
69. ^ Despond O, Tucci M, Decaluwe H, Grégoire MC, S Teitelbaum J, Turgeon N (March 2002). "Rabies in a nine-year-old child: The myth of the bite". *Can J Infect Dis*. **13** (2): 121–5. PMC 2094861. PMID 18159381.
70. ^ Willoughby RE, Tieves KS, Hoffman GM, Ghanayem NS, Amlie-Lefond CM, Schwabe MJ, Chusid MJ, Rupprecht CE (June 2005). "Survival after treatment of rabies with induction of coma" (PDF). *New England Journal of Medicine*. **352** (24): 2508–14. doi:10.1056/NEJMoa050382. PMID 15958806.
71. ^ Hu WT, Willoughby RE, Dhonau H, Mack KJ (August 2007). "Long-term follow-up after treatment of rabies by induction of coma" (PDF). *New England Journal of Medicine*. **357** (9): 945–6. doi:10.1056/NEJMc062479. PMID 17761604.
72. ^ "Rodney Versus Death". Radiolab. 13 August 2013.
73. ^ "UC Davis Children's Hospital patient becomes third person in US to survive rabies". *Health News*. 2011-06-12. Retrieved 2011-06-12.
74. ^ *a b* "Rabies". World Health Organization (WHO). September 2011. Retrieved 31 December 2011.
75. ^ "Rabies Registry". Medical College of Wisconsin. 2005. Retrieved 29 December 2009.
76. ^ Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R et al. (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
77. ^ Dugan, Emily (2008-04-30). "Dead as a dodo? Why scientists fear for the future of the Asian vulture". *The Independent*. London. Retrieved 2008-10-11. "India now has the highest rate of human rabies in the world."
78. ^ *a b* Harris, Gardiner (6 August 2012). "Where Streets Are Thronged With Strays Baring Fangs". *New York Times*. Retrieved 6 August 2012.
79. ^ Medicine challenges Indian superstition | Asia | DW.DE | 31.12.2012
80. ^ Hampson, Katie; Coudeville, Laurent; Lembo, Tiziana; Sambo, Maganga; Kieffer, Alexia; Attlan, Michaël; Barrat, Jacques; Blanton, Jesse D.; Briggs, Deborah J.; Cleaveland, Sarah; Costa, Peter; Freuling, Conrad M.; Hiby, Elly; Knopf, Lea; Leanes, Fernando; Meslin, François-Xavier; Metlin, Artem; Miranda, Mary Elizabeth; Müller, Thomas; Nel, Louis H.; Recuenco, Sergio; Rupprecht, Charles E.; Schumacher, Carolin; Taylor, Louise; Vigilato, Marco Antonio Natal; Zinsstag, Jakob; Dushoff, Jonathan (2015). "Estimating the Global Burden of Endemic Canine Rabies". *PLOS*

*Neglected Tropical Diseases*. **9** (4): e0003709. doi:10.1371/journal.pntd.0003709. PMC 4400070. PMID 25881058.
81. ^ "Essential rabies maps". World Health Organization (WHO).
82. ^ Meltzer MI (October–December 1996). "Assessing the costs and benefits of an oral vaccine for raccoon rabies: a possible model". *Emerg Infect Dis*. **2** (4): 343–9. doi:10.3201/eid0204.960411. PMC 2639934. PMID 8969251.
83. ^ [a] [b] [c] Grambo, Rebecca L (1995). *The World of the Fox*. Vancouver: Greystone Books. pp. 94–5. ISBN 0-87156-377-0.
84. ^ "Rabies Surveillance Data in the United States". Centers for Disease Control and Prevention.
85. ^ http://www.izsvenezie.com/rabies-in-africa-the-resolab-network/
86. ^ http://www.quotidianosanita.it/governo-e-parlamento/articolo.php?articolo_id=13650
87. ^ Adamson PB (1977). "The spread of rabies into Europe and the probable origin of this disease in antiquity". *The Journal of the Royal Asiatic Society of Great Britain and Ireland*. **2** (2): 140–4. doi:10.1017/S0035869X00133829. JSTOR 25210880. PMID 11632333.
88. ^ Dunlop, Robert H; Williams, David J (1996). *Veterinary Medicine: An Illustrated History*. Mosby. ISBN 0-8016-3209-9.
89. ^ Barrett, Alan D.T.; Stanberry, Lawrence R. (2009). *Vaccines for Biodefense and Emerging and Neglected Diseases*. Academic Press. p. 612. ISBN 9780080919027. Retrieved 2016-01-08.
90. ^ The Natural History of Rabies
The first major epizootic in North America was reported in 1768, continuing until 1771 when foxes and dogs carried the disease to swine and domestic animals. The malady was so unusual that it was reported as a new disease
91. ^ [a] [b] Rotivel, Yolande. "Introduction". Federation of American Scientists. Retrieved 2009-04-25.
92. ^ Than, Ker. " "Zombie Virus" Possible via Rabies-Flu Hybrid?". *National Geographic*. National Geographic. Retrieved 13 September 2015.
93. ^ Simpson DP (1979). *Cassell's Latin Dictionary* (5 ed.). London: Cassell. p. 883. ISBN 0-304-52257-0.
94. ^ Dalfardi, Behnam; Esnaashary, Mohammad Hosein; Yarmohammadi, Hassan (2014-02-17). "Rabies in medieval Persian literature – the Canon of Avicenna (980–1037 AD)". *Infectious Diseases of Poverty*. **3**: 7. doi:10.1186/2049-9957-3-7. ISSN 2049-9957. PMC 3933285. PMID 24533686.
95. ^ Ettinger, Stephen J; Feldman, Edward C (1995). *Textbook of Veterinary Internal Medicine* (4th ed.). W.B. Saunders Company. ISBN 0-7216-6795-3.
96. ^ Carpentier DC, Vevis K, Trabalza A, Georgiadis C, Ellison SM, Asfahani RI, Mazarakis ND (8 September 2011). "Enhanced pseudotyping efficiency of HIV-1 lentiviral vectors by a rabies/vesicular stomatitis virus chimeric envelope glycoprotein". *Gene Therapy*. **19** (7): 761–74. doi:10.1038/gt.2011.124. PMID 21900965.
97. ^ Roy A, Hooper DC (2007). "Lethal silver-haired bat rabies virus infection can be prevented by opening the blood–brain barrier". *J. Virol*. **81** (15): 7993–8. doi:10.1128/JVI.00710-07. PMC 1951307. PMID 17507463.
98. ^ Roy A, Phares TW, Koprowski H, Hooper DC (2007). "Failure to open the blood–brain barrier and deliver immune effectors to central nervous system tissues leads to the lethal outcome of silver-haired bat rabies virus infection". *J. Virol*. **81** (3): 1110–8. doi:10.1128/JVI.01964-06. PMC 1797506. PMID 17108029.

## Further reading [edit]

- George M. Baer, ed. (1991). *The Natural History of Rabies* (2 ed.). CRC Press. ISBN 978-0849367601.
- Jackson, Alan C.; William H. Wunner (2007). *Rabies, Second Edition: Scientific Basis of the Disease and Its Management*. London, UK: Academic Press. ISBN 978-0123693662.
- Murphy, Monica; Bill Wasik (26 July 2012). "Undead: The Rabies Virus Remains a Medical Mystery". *Wired*. Retrieved 12 August 2012.
- "Rabies". Centers for Disease Control and Prevention. 2 August 2012. Retrieved 12 August 2012.
- Wasik, Bill; Monica Murphy (2012). *Rabid: A Cultural History of the World's Most Diabolical Virus*. Viking. ISBN 978-0670023738.
- George M. Baer (2 December 2012). *THE NATURAL HISTORY OF RABIES*. Elsevier. p. 335. ISBN 978-0-323-13970-0.
- "Latent Rabies". *N Engl J Med*. **324**: 1890–1891. June 27, 1991. doi:10.1056/NEJM199106273242611.

## External links [edit]

- Rabies at DMOZ

- Virus Pathogen Database and Analysis Resource (ViPR): Rhabdoviridae
- World Rabies Day
- OIE's Rabies Portal
- Aerophobia and Hydrophobia in Rabies Videos
- "*Rabies virus*". *NCBI Taxonomy Browser*. 11292.

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| v · t · e · | **Infectious diseases – viral systemic diseases (A80–B34, 042–079)** | | |
|---|---|---|---|
| **Oncovirus** | | | **DNA virus:** *HBV* (Hepatocellular carcinoma · · *HPV* (Cervical cancer · Anal cancer · Penile cancer · Vulvar cancer · Vaginal cancer · Oropharyngeal cancer · · *KSHV* (Kaposi's sarcoma · · *EBV* (Nasopharynx cancer · Burkitt's lymphoma · Hodgkin's lymphoma · Follicular dendritic cell sarcoma · Extranodal NK/T-cell lymphoma, nasal type · · *MCPyV* (Merkel-cell carcinoma · ·<br>**RNA virus:** *HCV* (Hepatocellular carcinoma · Splenic marginal zone lymphoma · · *HTLV-I* (Adult T-cell leukemia/lymphoma · · |
| **Immune disorders** | | | *HIV* (AIDS · · |
| **Central nervous system** | **Encephalitis/ meningitis** | | **DNA virus:** *JCV* (Progressive multifocal leukoencephalopathy · ·<br>**RNA virus:** *MeV* (Subacute sclerosing panencephalitis · · *LCV* (Lymphocytic choriomeningitis · · Arbovirus encephalitis · *Orthomyxoviridae (probable)* (Encephalitis lethargica · · *RV* (**Rabies** · · Chandipura virus · Herpesviral meningitis · Ramsay Hunt syndrome type 2 · |
| | **Myelitis** | | *Poliovirus* (Poliomyelitis · Post-polio syndrome · · *HTLV-I* (Tropical spastic paraparesis · · |
| | **Eye** | | *Cytomegalovirus* (Cytomegalovirus retinitis · · *HSV* (Herpes of the eye · · |
| **Cardiovascular** | | | *CBV* (Pericarditis · Myocarditis · · |
| **Respiratory system/ acute viral nasopharyngitis/ viral pneumonia** | **DNA virus** | | *Epstein–Barr virus* (EBV infection/Infectious mononucleosis · · *Cytomegalovirus* · |
| | **RNA virus** | | IV: *SARS coronavirus* (Severe acute respiratory syndrome · ·<br>V: *Orthomyxoviridae: Influenzavirus A/B/C* (Influenza/Avian influenza · ·<br>V, *Paramyxoviridae: Human parainfluenza viruses* (Parainfluenza · · *RSV* · *hMPV* · |
| **Human digestive system** | **Pharynx/Esophagus** | | *MuV* (Mumps · · *Cytomegalovirus* (Cytomegalovirus esophagitis · · |
| | **Gastroenteritis/ diarrhea** | | **DNA virus:** *Adenovirus* (Adenovirus infection · ·<br>**RNA virus:** *Rotavirus* · *Norovirus* · *Astrovirus* · *Coronavirus* · |
| | **Hepatitis** | | **DNA virus:** *HBV* (B) ·<br>**RNA virus:** *CBV* · *HAV* (A) · *HCV* (C) · *HDV* (D) · *HEV* (E) · *HGV* (G) · |
| | **Pancreatitis** | | *CBV* · |

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|---|---|---|---|
| | **Urogenital** | | *BK virus* · *MuV* (Mumps · · |

| v · t · e · | **Zoonotic viral diseases (A80–B34, 042–079)** | | |
|---|---|---|---|
| **Arthropod-borne** | **Mosquito-borne** | *Bunyaviridae* | Arbovirus encephalitides: La Crosse encephalitis (LACV · · Batai virus (BATV) · Bwamba Fever (BWAV) · California encephalitis (CEV · · Jamestown Canyon virus · Tete virus · Tahyna virus (TAHV) · Viral hemorrhagic fevers: Rift Valley fever (RVFV · · Bunyamwera fever (BUNV) · Ngari virus (NRIV) · |
| | | *Flaviviridae* | Arbovirus encephalitides: Japanese encephalitis (JEV · · Australian encephalitis (MVEV · KUNV · · Saint Louis encephalitis (SLEV · · West Nile fever (WNV · · Viral hemorrhagic fevers: Dengue fever (DENV-1-4 · · Yellow fever (YFV · · Zika fever (Zika virus · · |
| | | *Togaviridae* | Arbovirus encephalitides: Eastern equine encephalomyelitis (EEEV · · Western equine encephalomyelitis (WEEV · · Venezuelan equine encephalomyelitis (VEEV · · Chikungunya (CHIKV · · O'Nyong-nyong fever (ONNV · · Ross River fever (RRV · · Semliki Forest virus · Sindbis fever · |
| | | *Reoviridae* | Banna virus encephalitis · |
| | **Tick-borne** | *Bunyaviridae* | Viral hemorrhagic fevers: Crimean–Congo hemorrhagic fever (CCHFV · · Heartland virus · Bhanja virus · Sandfly fever Naples virus · Lone Star virus · Tete virus · |
| | | *Flaviviridae* | Arbovirus encephalitides: Tick-borne encephalitis (TBEV · · Powassan encephalitis (POWV · · Viral hemorrhagic fevers: Omsk hemorrhagic fever (OHFV · · Kyasanur forest disease (KFDV · AHFV · · Langat virus (LGTV) · |
| | | *Reoviridae* | Colorado tick fever (CTFV · · Kemerovo tickborne viral fever · |
| | **Sandfly-borne** | *Bunyaviridae* | Adria virus (ADRV) · Pappataci fever (Toscana virus · · Sandfly fever Naples virus · Oropouche fever (Oropouche virus · · SFTS virus · |
| | | *Rhabdoviridae* | Chandipura virus · |
| | **Rodent-borne** | *Arenaviridae* | Viral hemorrhagic fevers: Lassa fever (LASV · · Venezuelan hemorrhagic fever (GTOV · · Argentine hemorrhagic fever (JUNV · · Brazilian hemorrhagic fever (SABV · · Bolivian hemorrhagic fever (MACV · · LUJV · CHPV · |
| | | | Hemorrhagic fever with renal syndrome (DOBV · HTNV · |

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| **Mammal-borne** | | *Bunyaviridae* | PUUV · SEOV · AMRV · · Hantavirus pulmonary syndrome (ANDV · SNV · · |
| | **Bat-borne** | *Filoviridae* | Viral hemorrhagic fevers: Ebola virus disease · BDBV · EBOV · SUDV · TAFV · Marburg virus disease · MARV · RAVV · |
| | | *Rhabdoviridae* | **Rabies** (ABLV · MOKV · DUVV · LBV · · CHPV · |
| | | *Paramyxoviridae* | Henipavirus encephalitis (HeV · NiV · · |
| | *Primate-borne* | *Herpesviridae* | Herpes B virus · |
| | | *Retroviridae* | Simian foamy virus · HTLV-1 · HTLV-2 · |
| | | *Poxviridae* | Tanapox · Yaba monkey tumor virus · |
| | **Multiple vectors** | *Rhabdoviridae* | **Rabies** (RABV · · Mokola virus · |
| | | *Poxviridae* | Monkeypox · |

| v · t · e · | **Domestic cats** |
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| **Felinology** | Cats in ancient Egypt · Cats and Islam · Anatomy · Genetics · Dwarf cat · Kitten · Odd-eyed cat · Squitten · Coat genetics: Bicolor cat · Black cat · Calico cat · Deaf white cat · Tabby cat · Tortoiseshell cat · |
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| **Registries** | American Cat Fanciers Association · Associazione Nazionale Felina Italiana · Canadian Cat Association · Cat Aficionado Association · Cat Fanciers' Association · Emirates Feline Federation · Fédération Internationale Féline · Governing Council of the Cat Fancy · Southern Africa Cat Council · The International Cat Association · |
| **Breeds (full list) (experimental breeds)** | **Fully domestic:** Abyssinian · American Curl · American Shorthair · Balinese · Brazilian Shorthair · British Shorthair · Birman · Bombay · Burmese · California Spangled · Chartreux · Chinese Li Hua · Colorpoint Shorthair · Cornish Rex · Cymric · Devon Rex · Donskoy · Egyptian Mau · European Shorthair · Exotic Shorthair · German Rex · Himalayan · Japanese Bobtail · Javanese · Khao Manee · Korat · Kurilian Bobtail · Maine Coon · Manx · Munchkin · Norwegian Forest · Ocicat · Oriental Shorthair · Persian · Peterbald · Pixie-bob · Raas · Ragdoll · Ragamuffin · Russian Blue · Scottish Fold · Selkirk Rex · Siamese · Siberian · Singapura · Snowshoe · Somali · Sphynx · Thai · Traditional Persian · Tonkinese · Toyger · Turkish Angora · Turkish Van · **Hybrid:** Bengal · Chausie · Highlander · Savannah · Serengeti · |

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| **Landraces** | Aegean · Cyprus · Domestic long-haired · Domestic short-haired · Kellas · Sokoke · Van · |

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| **Work** | Assistance dog · Attack dog · Detection dog · Guard dog · Guide dog · Hearing dog · Herding dog · Hunting dog · Livestock guardian dog · Pet dog · Police dog · Search and rescue dog · Service dog · Sled dog · Therapy dog · War dog · Working Group (dogs) · |
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Categories: Cat diseases | Dog diseases | Wildlife diseases | Neurological disorders | Rabies | Rodent-carried diseases | Viral encephalitis | Viral infections of the central nervous system | Zoonoses

# Syphilis



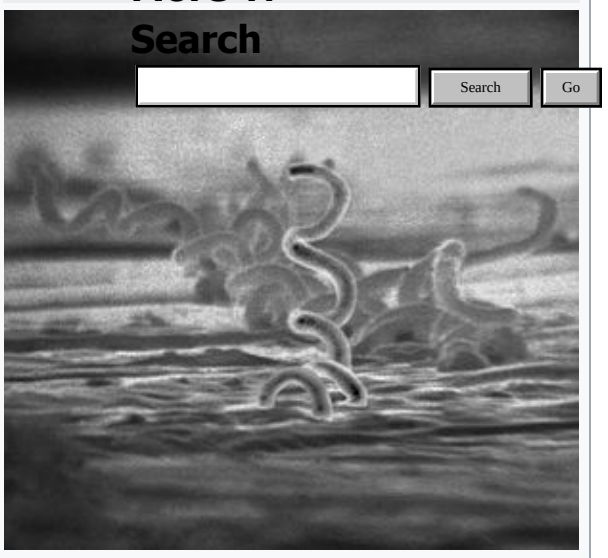
From Wikipedia, the free encyclopedia

**Syphilis** is a sexually transmitted infection caused by the bacterium *Treponema pallidum* subspecies *pallidum*.[1] The signs and symptoms of syphilis vary depending in which of the four stages it presents (primary, secondary, latent, and tertiary). The primary stage classically presents with a single chancre (a firm, painless, non-itchy skin ulceration) but there may be multiple sores. In secondary syphilis a diffuse rash occurs, which frequently involves the palms of the hands and soles of the feet. There may also be sores in the mouth or vagina. In latent syphilis, which can last for years, there are little to no symptoms.[2] In tertiary syphilis there are gummas (soft non-cancerous growths), neurological, or heart symptoms.[3] Syphilis has been known as "the great imitator" as it may cause symptoms similar to many other diseases.[2][3]

Syphilis is most commonly spread through sexual activity.[2] It may also be transmitted from mother to baby during pregnancy or at birth, resulting in congenital syphilis.[2][4] Other human diseases caused by related *Treponema pallidum* subspecies include yaws (subspecies *pertenue*), pinta (subspecies *carateum*), and bejel (subspecies *endemicum*).[3] Diagnosis is usually made by using blood tests; the bacteria can also be detected using dark field microscopy. The Center for Disease Control recommends all pregnant women be tested.[2]

The risk of syphilis can be decreased by latex condom use, or not having sex.[2] Syphilis can be effectively treated with antibiotics. The preferred antibiotic for most cases is benzathine penicillin G injected into a muscle. In those who have a severe penicillin allergy, doxycycline or tetracycline may be used. In those with neurosyphilis, intravenous penicillin G potassium or ceftriaxone is recommended. During treatment people may develop fever, headache, and muscle pains, a reaction known as Jarisch-Herxheimer.[1]

In 2012, about 0.5% of adults were infected with syphilis with 6 million new cases.[5] During 2010, it caused about 113,000 deaths, down from 202,000 in 1990.[6] After decreasing dramatically with the availability of penicillin in the 1940s, rates of infection have increased since the turn of the millennium in many countries, often in combination with human immunodeficiency virus (HIV).[3][7] This is believed to be partly due to increased promiscuity, prostitution, decreasing use of condoms, and unsafe sexual practices among men who have sex with men.[8][9][10] In 2015, Cuba became the first country in the world to eliminate mother-to-child transmission of syphilis.[11]



Electron micrograph of *Treponema pallidum*

| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | A50-A53 |
| **ICD-9-CM** | 090-097 |
| **DiseasesDB** | 29054 |
| **MedlinePlus** | 000861 |
| **eMedicine** | med/2224 emerg/563 derm/413 |
| **Patient UK** | Syphilis |
| **MeSH** | D013587 |

[edit on Wikidata]



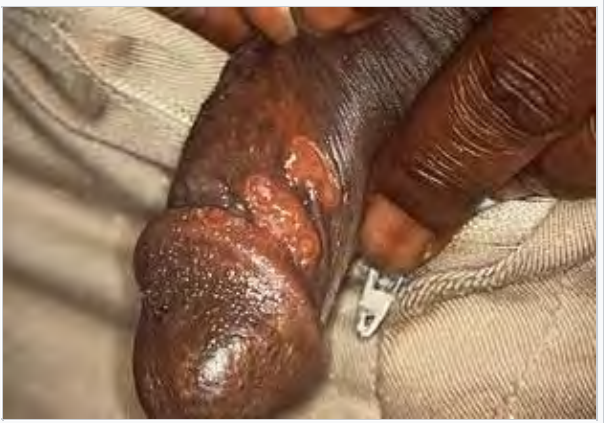
Contents

# Signs and symptoms

Syphilis can present in one of four different stages: primary, secondary, latent, and tertiary,[3] and may also occur congenitally.[12] It was referred to as "the great imitator" by Sir William Osler due to its varied presentations.[3][13]

## Primary

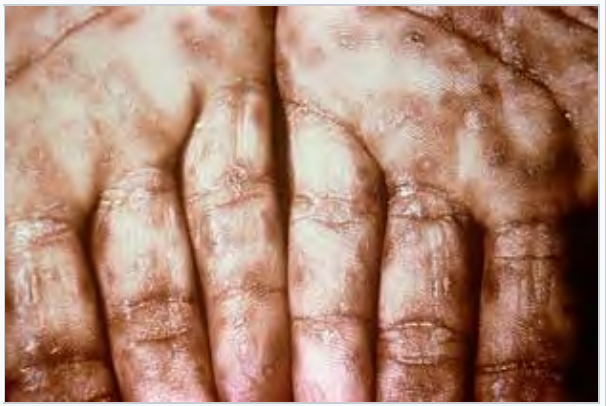
Primary syphilis is typically acquired by direct sexual contact with the infectious lesions of another person.[14] Approximately 3 to 90 days after the initial exposure (average 21 days) a skin lesion, called a chancre, appears at the point of contact. This is classically (40% of the time) a single, firm, painless, non-itchy skin ulceration with a clean base and sharp borders 0.3–3.0 cm in size.[3] The lesion may take on almost any form. In the classic form, it evolves from a macule to a papule and finally to an erosion or ulcer.[15] Occasionally, multiple lesions may be present (~40%),[3] with multiple lesions more common when coinfected with HIV. Lesions may be painful or tender (30%), and they may occur in places other than the genitals (2–7%). The most common location in women is the cervix (44%), the penis in heterosexual men (99%), and anally and rectally relatively commonly in men who have sex with men (34%).[15] Lymph node enlargement frequently (80%) occurs around the area of infection,[3] occurring seven to 10 days after chancre formation.[15] The lesion may persist for three to six weeks without treatment.[3]



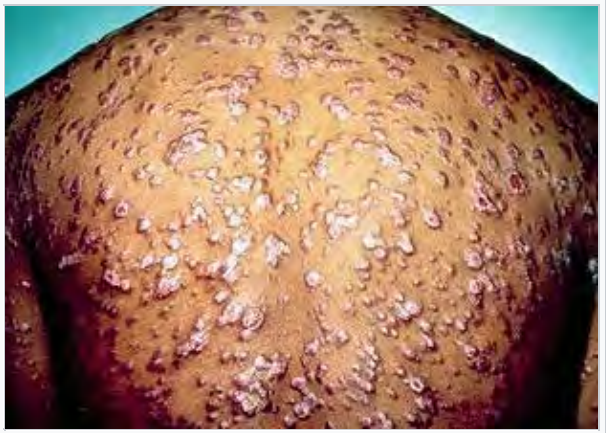
Primary chancre of syphilis at the site of infection on the penis

## Secondary

Secondary syphilis occurs approximately four to ten weeks after the primary infection.[3] While secondary disease is known for the many different ways it can manifest, symptoms most commonly involve the skin, mucous membranes, and lymph nodes.[16] There may be a symmetrical, reddish-pink, non-itchy rash on the trunk and extremities, including the palms and soles.[3][17] The rash may become maculopapular or pustular. It may form flat, broad, whitish, wart-like lesions known as condyloma latum on mucous membranes. All of these lesions harbor bacteria and are infectious. Other symptoms may include fever, sore throat, malaise, weight loss, hair loss, and headache.[3] Rare manifestations include liver inflammation, kidney disease, joint inflammation, periostitis, inflammation of the optic nerve, uveitis, and interstitial keratitis.[3][18] The acute symptoms usually resolve after three to six weeks;[18] about 25% of people may present with a recurrence of secondary symptoms. Many people who present with secondary syphilis (40–85% of women, 20–65% of men) do not report previously having had the classic chancre of primary syphilis.[16]



Typical presentation of secondary syphilis with a rash on the palms of the hands



Reddish papules and nodules over much of the body due to secondary syphilis

## Latent

Latent syphilis is defined as having serologic proof of infection without symptoms of disease.[14] It is further described as either early (less than 1 year after secondary syphilis) or late (more than 1 year after secondary syphilis) in the United States.[18] The United Kingdom uses a cut-off of two years for early and late latent syphilis.[15] Early latent syphilis may have a relapse of symptoms. Late latent syphilis is asymptomatic, and not as contagious as early latent syphilis.[18]

## Tertiary

Tertiary syphilis may occur approximately 3 to 15 years after the initial infection, and may be divided into three different forms: gummatous syphilis (15%), late neurosyphilis (6.5%), and cardiovascular syphilis (10%).[3][18] Without treatment, a third of infected people develop tertiary disease.[18] People with tertiary syphilis are not infectious.[3]

Gummatous syphilis or late benign syphilis usually occurs 1 to 46 years after the initial infection, with an average of 15 years. This stage is characterized by the formation of chronic gummas, which are soft, tumor-like balls of inflammation which may vary considerably in size. They typically affect the skin, bone, and liver, but can occur anywhere.[3]

Neurosyphilis refers to an infection involving the central nervous system. It may occur early, being either asymptomatic or in the form of syphilitic meningitis, or late as meningovascular syphilis, general paresis, or tabes dorsalis, which is associated with poor balance and lightning pains in the lower extremities. Late neurosyphilis typically occurs 4 to 25 years after the initial infection. Meningovascular syphilis typically presents with apathy and seizure, and general paresis with dementia and tabes dorsalis.[3] Also, there may be Argyll Robertson pupils, which are bilateral small pupils that constrict when the person focuses on near objects but do not constrict when exposed to bright light.

Person with tertiary (gummatous) syphilis. Bust in Musée de l'Homme, Paris.

Cardiovascular syphilis usually occurs 10–30 years after the initial infection. The most common complication is syphilitic aortitis, which may result in aneurysm formation.[3]

### Congenital

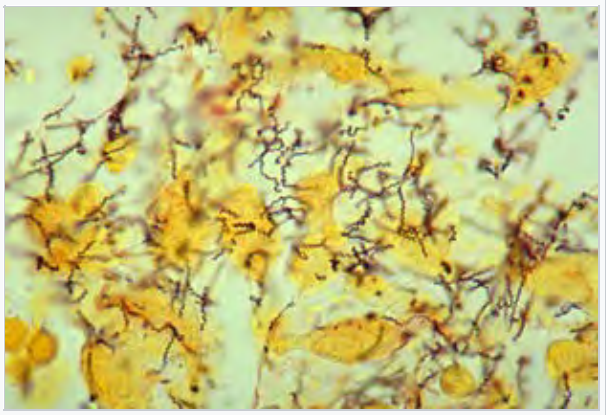
Congenital syphilis is that which is transmitted during pregnancy or during birth. Two-thirds of syphilitic infants are born without symptoms. Common symptoms that develop over the first couple of years of life include enlargement of the liver and spleen (70%), rash (70%), fever (40%), neurosyphilis (20%), and lung inflammation (20%). If untreated, late congenital syphilis may occur in 40%, including saddle nose deformation, Higoumenakis sign, saber shin, or Clutton's joints among others.[4]

## Cause

### Bacteriology

*Main article: Treponema pallidum*

*Treponema pallidum* subspecies *pallidum* is a spiral-shaped, Gram-negative, highly mobile bacterium.[7][15] Three other human diseases are caused by related *Treponema pallidum* subspecies, including yaws (subspecies *pertenue*), pinta (subspecies *carateum*) and bejel (subspecies *endemicum*).[3] Unlike subtype *pallidum*, they do not cause neurological disease.[4] Humans are the only known natural reservoir for subspecies *pallidum*.[12] It is unable to survive without a host for more than a few days. This is due to its small genome (1.14 MDa) failing to encode the metabolic pathways necessary to make most of its macronutrients. It has a slow doubling time of greater than 30 hours.[15]



Histopathology of *Treponema pallidum* spirochetes using a modified Steiner silver stain

### Transmission

Syphilis is transmitted primarily by sexual contact or during pregnancy from a mother to her fetus; the spirochete is able to pass through intact mucous membranes or compromised skin.[3][12] It is thus transmissible by kissing near a lesion, as well as oral, vaginal, and anal sex.[3] Approximately 30% to 60% of those exposed to primary or secondary syphilis will get the disease.[18] Its infectivity is exemplified by the fact that an individual inoculated with only 57 organisms has a 50% chance of being infected.[15] Most (60%) of new cases in the United States occur in men who have sex with men. Syphilis can be transmitted by blood products, but the risk is low due to blood testing in many countries. The risk of transmission from sharing needles appears limited.[3]

It is not generally possible to contract syphilis through toilet seats, daily activities, hot tubs, or sharing eating utensils or clothing.[19] This is mainly because the bacteria die very quickly outside of the body, making transmission by objects extremely difficult.[20]

## Diagnosis

Syphilis is difficult to diagnose clinically early in its presentation.[15] Confirmation is either via blood tests or direct visual inspection using microscopy. Blood tests are more commonly used, as they are easier to perform.[3] Diagnostic tests are unable to distinguish between the stages of the disease.[21]

### Blood tests


This poster acknowledges the social stigma of syphilis, while urging those who possibly have the disease to be tested (circa 1936).

Blood tests are divided into nontreponemal and treponemal tests.[15]

Nontreponemal tests are used initially, and include venereal disease research laboratory (VDRL) and rapid plasma reagin (RPR) tests. False positives on the nontreponemal tests can occur with some viral infections, such as varicella (chickenpox) and measles. False positives can also occur with lymphoma, tuberculosis, malaria, endocarditis, connective tissue disease, and pregnancy.[14]

Because of the possibility of false positives with nontreponemal tests, confirmation is required with a treponemal test, such as treponemal pallidum particle agglutination (TPHA) or fluorescent treponemal antibody absorption test (FTA-Abs).[3] Treponemal antibody tests usually become positive two to five weeks after the initial infection.[15] Neurosyphilis is diagnosed by finding high numbers of leukocytes (predominately lymphocytes) and high protein levels in the cerebrospinal fluid in the setting of a known syphilis infection.[3][14]

### Direct testing

Dark ground microscopy of serous fluid from a chancre may be used to make an immediate diagnosis. Hospitals do not always have equipment or experienced staff members, and testing must be done within 10 minutes of acquiring the sample. Sensitivity has been reported to be nearly 80%; therefore the test can only be used to confirm a diagnosis, but not to rule one out. Two other tests can be carried out on a sample from the chancre: direct fluorescent antibody testing and nucleic acid amplification tests. Direct fluorescent testing uses antibodies tagged with fluorescein, which attach to specific syphilis proteins, while nucleic acid amplification uses techniques, such as the polymerase chain reaction, to detect the presence of specific syphilis genes. These tests are not as time-sensitive, as they do not require living bacteria to make the diagnosis.[15]

## Prevention

### Vaccine

As of 2010, there is no vaccine effective for prevention.[12] Several vaccines based on treponemal proteins reduce lesion development in an animal model, and research is ongoing.[22]

### Sex

Condom use reduces the likelihood of transmission during sex, but does not completely eliminate the risk.[23] The Centers for Disease Control and Prevention states, "Correct and consistent use of latex condoms can reduce the risk of syphilis only when the infected area or site of potential exposure is protected. However, a syphilis sore outside of the area covered by a latex condom can still allow transmission, so caution should be exercised even when using a condom."[24]

Abstinence from intimate physical contact with an infected person is effective at reducing the transmission of syphilis. The CDC states, "The surest way to avoid transmission of sexually transmitted diseases, including syphilis, is to abstain from sexual contact or to be in a long-term mutually monogamous relationship with a partner who has been tested and is known to be uninfected."[24]

### Congenital disease

Congenital syphilis in the newborn can be prevented by screening mothers during early pregnancy and treating those who are infected.[25] The United States Preventive Services Task Force (USPSTF) strongly recommends universal screening of all pregnant women,[26] while the World Health Organization recommends all women be tested at their first antenatal visit and again in the third trimester. If they are positive, they recommend their partners also be treated.[27] Congenital syphilis is still common in the developing world, as many women do not receive antenatal care at all, and the antenatal care others receive does not include screening, and it still occasionally occurs in the developed world, as those most likely to acquire syphilis (through drug use, etc.) are least likely to receive care during pregnancy.[25] Several measures to increase access to testing appear effective at reducing rates of congenital syphilis in low- to middle-income countries.[27] Point-of-care testing to detect syphilis appeared to be good although more research is needed to assess its effectiveness and into improving outcomes in mothers and babies.[28]

### Screening

The CDC recommends that sexually active men who have sex with men be tested at least yearly.[29] The USPSTF also recommends screening among those at high risk.[30]

Syphilis is a notifiable disease in many countries, including Canada[31] the European Union,[32] and the United States.[33] This means health care providers are required to notify public health authorities, which will then ideally provide partner notification to the person's partners.[34] Physicians may also encourage patients to send their partners to seek care.[35] Several strategies have been found to improve follow-up for STI testing including email and text messaging as reminders of appointments.[36]

## Treatment

### Early infections

The first-choice treatment for uncomplicated syphilis remains a single dose of intramuscular benzathine penicillin G.[37] Doxycycline and tetracycline are alternative choices for those allergic to penicillin; due to the risk of birth defects these are not recommended for pregnant women.[37] Resistance to macrolides, rifampin, and clindamycin is often present.[12] Ceftriaxone, a third-generation cephalosporin antibiotic, may be as effective as penicillin-based treatment.[3] It is recommended that a treated person avoid sex until the sores are healed.[19]

### Late infections

For neurosyphilis, due to the poor penetration of penicillin G into the central nervous system, those affected are recommended to be given large doses of intravenous penicillin for a minimum of 10 days.[3][12] If a person is allergic, ceftriaxone may be used or penicillin desensitization attempted. Other late presentations may be treated with once-weekly intramuscular penicillin G for three weeks. If allergic, as in the case of early disease, doxycycline or tetracycline may be used, albeit for a longer duration. Treatment at this stage limits further progression but has only slight effect on damage which has already occurred.[3]

### Jarisch-Herxheimer reaction

One of the potential side effects of treatment is the Jarisch-Herxheimer reaction. It frequently starts within one hour and lasts for 24 hours, with symptoms of fever, muscle pains, headache, and a fast heart rate.[3] It is caused by cytokines released by the immune system in response to lipoproteins released from rupturing syphilis bacteria.[38]

### Pregnancy

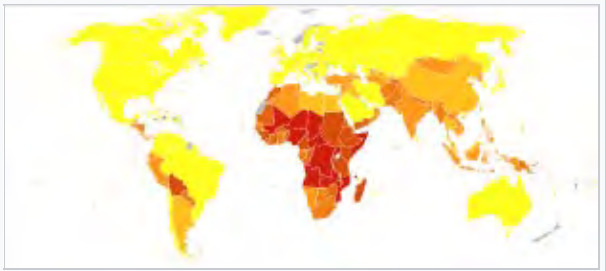
Penicillin is an effective treatment for syphilis in pregnancy[39] but there is no agreement on which dose or way of giving it is most effective.[40] More research is needed into how much antibiotic to give and when to give

it.[40]

# Epidemiology

*Main article: Epidemiology of syphilis*

In 2012 about 0.5% of adults were infected with syphilis with 6 million new cases.[5] In 1999 it is believed to have infected 12 million additional people, with greater than 90% of cases in the developing world.[12] It affects between 700,000 and 1.6 million pregnancies a year, resulting in spontaneous abortions, stillbirths, and congenital syphilis.[4] During 2010 it caused about 113,000 deaths down from 202,000 in 1990.[6] In sub-Saharan Africa, syphilis contributes to approximately 20% of perinatal deaths.[4] Rates are proportionally higher among intravenous drug users, those who are infected with HIV, and men who have sex with men.[8][9][10] In the United States, rates of syphilis as of 2007 were six times greater in men than women; they were nearly equal in 1997.[42] African Americans accounted for almost half of all cases in 2010.[43] As of 2014, syphilis infections continue to increase in the United States.[44]



Syphilis deaths per million persons in 2012

| | |
|---|---|
| 0–0 | 11–19 |
| 1–1 | 20–28 |
| 2–3 | 29–57 |
| 4–10 | 58–138 |

Syphilis was very common in Europe during the 18th and 19th centuries.[7] Flaubert found it universal among nineteenth-century Egyptian prostitutes.[45] In the developed world during the early 20th century, infections declined rapidly with the widespread use of antibiotics, until the 1980s and 1990s.[7] Since 2000, rates of syphilis have been increasing in the USA, Canada, the UK, Australia and Europe, primarily among men who have sex with men.[12] Rates of syphilis among American women have remained stable during this time, and rates among UK women have increased, but at a rate less than that of men.[46] Increased rates among heterosexuals have occurred in China and Russia since the 1990s.[12] This has been attributed to unsafe sexual practices, such as sexual promiscuity, prostitution, and decreasing use of barrier protection.[12][46][47]

Age-standardized disability adjusted life years from syphilis per 100,000 inhabitants in 2004[41]

| | |
|---|---|
| no data | 210–245 |
| <35 | 245–280 |
| 35–70 | 280–315 |
| 70–105 | 315–350 |
| 105–140 | 350–500 |
| 140–175 | >500 |
| 175–210 | |

Untreated, it has a mortality of 8% to 58%, with a greater death rate in males.[3] The symptoms of syphilis have become less severe over the 19th and 20th centuries, in part due to widespread availability of effective treatment and partly due to virulence of the spirochaete.[16] With early treatment, few complications result.[15] Syphilis increases the risk of HIV transmission by two to five times, and coinfection is common (30–60% in some urban centers).[3][12] In 2015 Cuba became the first country in the world to eradicate mother to child transmission of syphilis.[11]

# History

*Main article: History of syphilis*

The exact origin of syphilis is disputed.[3] Syphilis was definitely present in the Americas before European contact,[49] and it may have been carried from the Americas to Europe by the returning crewmen from Christopher Columbus's voyage to the Americas; or it may have existed in Europe previously, but

Portrait of Gerard de Lairesse by Rembrandt van Rijn, *circa* 1665–67, oil on canvas - De Lairesse, himself a painter and art theorist, had congenital syphilis that deformed his face and eventually blinded him.[48]

went unrecognized until shortly after Columbus returned.These are referred to as the *Columbian* and *pre-Columbian* hypotheses, respectively.[21]

The Columbian hypothesis is best supported by the available evidence.[50][51] The first written records of an outbreak of syphilis in Europe occurred in 1494 or 1495 in Naples, Italy, during a French invasion (Italian War of 1494–98).[7][21] As it was claimed to have been spread by French troops, it was initially known as the "French disease" by the people of Naples.[52] In 1530, the pastoral name "syphilis" (the name of a character) was first used by the Italian physician and poet Girolamo Fracastoro as the title of his Latin poem in dactylic hexameter describing the ravages of the disease in Italy.[53][54] It was also known historically as the "Great Pox".[55][56]

The causative organism, *Treponema pallidum*, was first identified by Fritz Schaudinn and Erich Hoffmann in 1905.[7] The first effective treatment for syphilis was Salvarsan, developed in 1910 by Paul Ehrlich. In 1943, trials of penicillin confirmed its effectiveness.[7][55] Before the discovery and use of antibiotics in the mid-twentieth century, mercury and isolation were commonly used, with treatments often worse than the disease.[55]

Many famous historical figures, including Franz Schubert, Arthur Schopenhauer, Édouard Manet,[7] Charles Baudelaire,[57] and Guy de Maupassant are believed to have had the disease.[58] Friedrich Nietzsche was long believed to have gone mad as a result of tertiary syphilis, but that diagnosis has recently come into question.[59]

## Arts and literature

*See also: List of syphilis cases*

An early medical illustration of people with syphilis, Vienna, 1498

The earliest known depiction of an individual with syphilis is Albrecht Dürer's *Syphilitic Man*, a woodcut believed to represent a Landsknecht, a Northern European mercenary.[60] The myth of the *femme fatale* or "poison women" of the 19th century is believed to be partly derived from the devastation of syphilis, with classic examples in literature including John Keats' *La Belle Dame sans Merci*.[61][62]

The artist Jan van der Straet painted a scene of a wealthy man receiving treatment for syphilis with the tropical wood guaiacum sometime around 1580.[63] The title of the work is "Preparation and Use of Guayaco for Treating Syphilis". That the artist chose to include this image in a series of works celebrating the New World indicates how important a treatment, however ineffective, for syphilis was to the European elite at that time. The richly colored and detailed work depicts four servants preparing the concoction while a physician looks on, hiding something behind his back while the hapless patient drinks.[64]

## Tuskegee and Guatemala studies

*See also: Tuskegee syphilis experiment and Guatemala syphilis experiment*

One of the most infamous United States cases of questionable medical ethics in the 20th century was the Tuskegee syphilis study.[65] The study took place in Tuskegee, Alabama, and was supported by the U.S. Public Health Service (PHS) in partnership with the Tuskegee Institute.[66] The study began in 1932, when syphilis was a widespread problem and there was no safe and effective treatment.[13] The study was designed to measure the progression

of untreated syphilis. By 1947, penicillin had been shown to be an effective cure for early syphilis and was becoming widely used to treat the disease.[66] Its use in later syphilis was still unclear.[13] Study directors continued the study and did not offer the participants treatment with penicillin.[66] This is debated, and some have found that penicillin was given to many of the subjects.[13]

A Work Projects Administration poster about syphilis circa 1940.

In the 1960s, Peter Buxtun sent a letter to the CDC, who controlled the study, expressing concern about the ethics of letting hundreds of black men die of a disease that could be cured. The CDC asserted that it needed to continue the study until all of the men had died. In 1972, Buxton went to the mainstream press, causing a public outcry. As a result, the program was terminated, a lawsuit brought those affected nine million dollars, and Congress created a commission empowered to write regulations to deter such abuses from occurring in the future.[66]

On 16 May 1997, thanks to the efforts of the Tuskegee Syphilis Study Legacy Committee formed in 1994, survivors of the study were invited to the White House to be present when President Bill Clinton apologized on behalf of the United States government for the study.[67]

Syphilis experiments were also carried out in Guatemala from 1946 to 1948. They were United States-sponsored human experiments, conducted during the government of Juan José Arévalo with the cooperation of some Guatemalan health ministries and officials. Doctors infected soldiers, prisoners, and mental patients with syphilis and other sexually transmitted diseases, without the informed consent of the subjects, and then treated them with antibiotics. In October 2010, the U.S. formally apologized to Guatemala for conducting these experiments.[68]

# References


1. ^ a b "Syphilis". *CDC*. June 4, 2015. Retrieved 3 February 2016.
2. ^ a b c d e f "Syphilis - CDC Fact Sheet (Detailed)". *CDC*. November 2, 2015. Retrieved 3 February 2016.
3. ^ a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af ag Kent ME, Romanelli F (February 2008). "Reexamining syphilis: an update on epidemiology, clinical manifestations, and management". *Annals of Pharmacotherapy*. **42** (2): 226–36. doi:10.1345/aph.1K086. PMID 18212261.
4. ^ a b c d e Woods CR (June 2009). "Congenital syphilis-persisting pestilence". *Pediatr. Infect. Dis. J.* **28** (6): 536–7. doi:10.1097/INF.0b013e3181ac8a69. PMID 19483520.
5. ^ a b Newman, L; Rowley, J; Vander Hoorn, S; Wijesooriya, NS; Unemo, M; Low, N; Stevens, G; Gottlieb, S; Kiarie, J; Temmerman, M (2015). "Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting.". *PLOS ONE*. **10** (12): e0143304. doi:10.1371/journal.pone.0143304. PMC 4672879. PMID 26646541.
6. ^ a b Lozano, R (15 December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
7. ^ a b c d e f g h Franzen, C (December 2008). "Syphilis in composers and musicians--Mozart, Beethoven, Paganini, Schubert, Schumann, Smetana". *European Journal of Clinical Microbiology & Infectious Diseases*. **27** (12): 1151–7. doi:10.1007/s10096-008-0571-x. PMID 18592279.
8. ^ a b Coffin, L. S.; Newberry, A.; Hagan, H.; Cleland, C. M.; Des Jarlais, D. C.; Perlman, D. C. (January 2010). "Syphilis in Drug Users in Low and Middle Income Countries". *The International journal on drug policy*. **21** (1): 20–7. doi:10.1016/j.drugpo.2009.02.008. PMC 2790553. PMID 19361976.
9. ^ a b Gao, L; Zhang, L; Jin, Q (September 2009). "Meta-analysis: prevalence of HIV infection and syphilis among MSM in China". *Sexually transmitted infections*. **85** (5): 354–8. doi:10.1136/sti.2008.034702. PMID 19351623.
10. ^ a b Karp, G; Schlaeffer, F; Jotkowitz, A; Riesenberg, K (January 2009). "Syphilis and HIV co-infection". *European journal of internal medicine*. **20** (1): 9–13. doi:10.1016/j.ejim.2008.04.002. PMID 19237085.
11. ^ a b "WHO validates elimination of mother-to-child transmission of HIV and syphilis in Cuba". WHO. 30 June 2015.

Retrieved 30 August 2015.
12. ^ a b c d e f g h i j k Stamm, LV (February 2010). "Global challenge of antibiotic-resistant Treponema pallidum.". *Antimicrobial Agents and Chemotherapy*. **54** (2): 583–9. doi:10.1128/aac.01095-09. PMC 2812177. PMID 19805553.
13. ^ a b c d White, RM (13 March 2000). "Unraveling the Tuskegee Study of Untreated Syphilis". *Archives of Internal Medicine*. **160** (5): 585–98. doi:10.1001/archinte.160.5.585. PMID 10724044.
14. ^ a b c d Committee on Infectious Diseases (2006). Larry K. Pickering, ed. *Red book 2006 Report of the Committee on Infectious Diseases* (27th ed.). Elk Grove Village, IL: American Academy of Pediatrics. pp. 631–44. ISBN 978-1-58110-207-9.
15. ^ a b c d e f g h i j k l Eccleston, K; Collins, L; Higgins, SP (March 2008). "Primary syphilis". *International journal of STD & AIDS*. **19** (3): 145–51. doi:10.1258/ijsa.2007.007258. PMID 18397550.
16. ^ a b c Mullooly, C; Higgins, SP (August 2010). "Secondary syphilis: the classical triad of skin rash, mucosal ulceration and lymphadenopathy". *International journal of STD & AIDS*. **21** (8): 537–45. doi:10.1258/ijsa.2010.010243. PMID 20975084.
17. ^ Dylewski J, Duong M (2 January 2007). "The rash of secondary syphilis". *Canadian Medical Association Journal*. **176** (1): 33–5. doi:10.1503/cmaj.060665. PMC 1764588. PMID 17200385.
18. ^ a b c d e f g Bhatti MT (2007). "Optic neuropathy from viruses and spirochetes". *Int Ophthalmol Clin*. **47** (4): 37–66, ix. doi:10.1097/IIO.0b013e318157202d. PMID 18049280.
19. ^ a b "Syphilis & MSM (Men Who Have Sex With Men) - CDC Fact Sheet". Centers for Disease Control and Prevention (CDC). 16 September 2010. Retrieved 18 October 2014.
20. ^ G. W. Csonka (1990). *Sexually transmitted diseases: a textbook of genitourinary medicine*. Baillière Tindall. p. 232. ISBN 978-0-7020-1258-7.
21. ^ a b c Farhi, D; Dupin, N (September–October 2010). "Origins of syphilis and management in the immunocompetent patient: facts and controversies". *Clinics in Dermatology*. **28** (5): 533–8. doi:10.1016/j.clindermatol.2010.03.011. PMID 20797514.
22. ^ Cameron, CE; Lukehart, SA (20 March 2014). "Current status of syphilis vaccine development: need, challenges, prospects.". *Vaccine*. **32** (14): 1602–9. doi:10.1016/j.vaccine.2013.09.053. PMC 3951677. PMID 24135571.
23. ^ Koss CA, Dunne EF, Warner L (July 2009). "A systematic review of epidemiologic studies assessing condom use and risk of syphilis". *Sex Transm Dis*. **36** (7): 401–5. doi:10.1097/OLQ.0b013e3181a396eb. PMID 19455075.
24. ^ a b "Syphilis - CDC Fact Sheet". Centers for Disease Control and Prevention (CDC). 16 September 2010. Retrieved 30 May 2007.
25. ^ a b Schmid, G (June 2004). "Economic and programmatic aspects of congenital syphilis prevention". *Bulletin of the World Health Organization*. **82** (6): 402–9. PMC 2622861. PMID 15356931.
26. ^ U.S. Preventive Services Task, Force (19 May 2009). "Screening for syphilis infection in pregnancy: U.S. Preventive Services Task Force reaffirmation recommendation statement". *Annals of Internal Medicine*. **150** (10): 705–9. doi:10.7326/0003-4819-150-10-200905190-00008. PMID 19451577.
27. ^ a b Hawkes, S; Matin, N; Broutet, N; Low, N (15 June 2011). "Effectiveness of interventions to improve screening for syphilis in pregnancy: a systematic review and meta-analysis". *The Lancet infectious diseases*. **11** (9): 684–91. doi:10.1016/S1473-3099(11)70104-9. PMID 21683653.
28. ^ Shahrook, S; Mori, R; Ochirbat, T; Gomi, H (29 October 2014). "Strategies of testing for syphilis during pregnancy.". *The Cochrane database of systematic reviews*. **10**: CD010385. doi:10.1002/14651858.CD010385.pub2. PMID 25352226.
29. ^ "Trends in Sexually Transmitted Diseases in the United States: 2009 National Data for Gonorrhea, Chlamydia and Syphilis". Centers for Disease Control and Prevention. 22 November 2010. Retrieved 3 August 2011.
30. ^ Bibbins-Domingo, Kirsten; Grossman, David C.; Curry, Susan J.; Davidson, Karina W.; Epling, John W.; García, Francisco A. R.; Gillman, Matthew W.; Harper, Diane M.; Kemper, Alex R.; Krist, Alex H.; Kurth, Ann E.; Landefeld, C. Seth; Mangione, Carol M.; Phillips, William R.; Phipps, Maureen G.; Pignone, Michael P. (7 June 2016). "Screening for Syphilis Infection in Nonpregnant Adults and Adolescents". *JAMA*. **315** (21): 2321. doi:10.1001/jama.2016.5824.
31. ^ "National Notifiable Diseases". Public Health Agency of Canada. 5 April 2005. Retrieved 2 August 2011.
32. ^ Viñals-Iglesias, H; Chimenos-Küstner, E (1 September 2009). "The reappearance of a forgotten disease in the oral cavity: syphilis". *Medicina oral, patologia oral y cirugia bucal*. **14** (9): e416–20. PMID 19415060.
33. ^ "Table 6.5. Infectious Diseases Designated as Notifiable at the National Level-United States, 2009 [a]". *Red Book*. Retrieved 2 August 2011.
34. ^ *Brunner & Suddarth's textbook of medical-surgical nursing.* (12th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. 2010. p. 2144. ISBN 978-0-7817-8589-1.
35. ^ Hogben, M (1 April 2007). "Partner notification for sexually transmitted diseases". *Clinical Infectious Diseases*. 44 Suppl 3: S160–74. doi:10.1086/511429. PMID 17342669.
36. ^ Desai, Monica; Woodhall, Sarah C; Nardone, Anthony; Burns, Fiona; Mercey, Danielle; Gilson, Richard (2015). "Active recall to increase HIV and STI testing: a systematic review". *Sexually Transmitted Infections*: sextrans–2014–051930. doi:10.1136/sextrans-2014-051930. ISSN 1368-4973.

37. ^ [a] [b] Center for Disease Control and Prevention (CDC). "Syphilis-CDC fact sheet". *CDC*. Retrieved 1 March 2015.
38. ^ Radolf, JD; Lukehart SA (editors) (2006). *Pathogenic* Treponema*: Molecular and Cellular Biology*. Caister Academic Press. ISBN 1-904455-10-7.
39. ^ Alexander, JM; Sheffield, JS; Sanchez, PJ; Mayfield, J; Wendel GD, Jr (January 1999). "Efficacy of treatment for syphilis in pregnancy.". *Obstetrics and gynecology*. **93** (1): 5–8. doi:10.1016/s0029-7844(98)00338-x. PMID 9916946.
40. ^ [a] [b] Walker, GJ (2001). "Antibiotics for syphilis diagnosed during pregnancy.". *The Cochrane database of systematic reviews* (3): CD001143. doi:10.1002/14651858.CD001143. PMID 11686978.
41. ^ "Disease and injury country estimates". World Health Organization (WHO). 2004. Retrieved 11 November 2009.
42. ^ "Trends in Reportable Sexually Transmitted Diseases in the United States, 2007". Centers for Disease Control and Prevention (CDC). 13 January 2009. Retrieved 2 August 2011.
43. ^ "STD Trends in the United States: 2010 National Data for Gonorrhea, Chlamydia, and Syphilis". Centers for Disease Control and Prevention (CDC). 22 November 2010. Retrieved 20 November 2011.
44. ^ Clement, Meredith E.; Okeke, N. Lance; Hicks, Charles B. (2014). "Treatment of Syphilis". *JAMA*. **312** (18): 1905. doi:10.1001/jama.2014.13259. ISSN 0098-7484.
45. ^ Francis Steegmuller (1979). *Flaubert in Egypt, A Sensibility on Tour*. ISBN 9780897330183.
46. ^ [a] [b] Kent, ME; Romanelli, F (February 2008). "Reexamining syphilis: an update on epidemiology, clinical manifestations, and management". *Annals of Pharmacotherapy*. **42** (2): 226–36. doi:10.1345/aph.1K086. PMID 18212261.
47. ^ Ficarra, G; Carlos, R (September 2009). "Syphilis: The Renaissance of an Old Disease with Oral Implications". *Head and neck pathology*. **3** (3): 195–206. doi:10.1007/s12105-009-0127-0. PMC 2811633. PMID 20596972.
48. ^ *The Metropolitan Museum of Art Bulletin*, Summer 2007, pp. 55–56.
49. ^ Armelagos, George J. (2012), "The Science behind Pre-Columbian Evidence of Syphilis in Europe: Research by Documentary", *Evol. Anthropol.*, **21** (2): 50–7, doi:10.1002/evan.20340, PMC 3413456, PMID 22499439
50. ^ Rothschild, BM (15 May 2005). "History of syphilis". *Clinical Infectious Diseases*. **40** (10): 1454–63. doi:10.1086/429626. PMID 15844068.
51. ^ Harper, KN; Zuckerman, MK; Harper, ML; Kingston, JD; Armelagos, GJ (2011). "The origin and antiquity of syphilis revisited: an appraisal of Old World pre-Columbian evidence for treponemal infection". *American Journal of Physical Anthropology*. 146 Suppl 53: 99–133. doi:10.1002/ajpa.21613. PMID 22101689.
52. ^ Winters, Adam (2006). *Syphilis*. New York: Rosen Pub. Group. p. 17. ISBN 9781404209060.
53. ^ Dormandy, Thomas (2006). *The worst of evils: man's fight against pain: a history* (Uncorrected page proof. ed.). New Haven: Yale University Press. p. 99. ISBN 978-0300113228.
54. ^ Anthony Grafton (March 1995). "Drugs and Diseases: New World Biology and Old World Learning". *New Worlds, Ancient Texts The Power of Tradition and the Shock of Discovery*. Harvard University Press. pp. 159–194. ISBN 9780674618763.
55. ^ [a] [b] [c] Dayan, L; Ooi, C (October 2005). "Syphilis treatment: old and new". *Expert opinion on pharmacotherapy*. **6** (13): 2271–80. doi:10.1517/14656566.6.13.2271. PMID 16218887.
56. ^ Knell, RJ (7 May 2004). "Syphilis in renaissance Europe: rapid evolution of an introduced sexually transmitted disease?" (PDF). *Proceedings. Biological sciences/ the Royal Society*. 271 Suppl 4 (Suppl 4): S174–6. doi:10.1098/rsbl.2003.0131. PMC 1810019. PMID 15252975.
57. ^ Hayden, Deborah (2008). *Pox: Genius, Madness, And The Mysteries Of Syphilis*. Basic Books. p. 113. ISBN 0786724137.
58. ^ Halioua, Bruno (30 June 2003). "Comment la syphilis emporta Maupassant | La Revue du Praticien". *www.larevuedupraticien.fr*. Retrieved 29 November 2016.
59. ^ Bernd, Magnus. "Nietzsche, Friedrich". *Encyclopædia Britannica*. Retrieved May 19, 2012.
60. ^ Eisler, CT (Winter 2009). "Who is Dürer's "Syphilitic Man"?". *Perspectives in biology and medicine*. **52** (1): 48–60. doi:10.1353/pbm.0.0065. PMID 19168944.
61. ^ Hughes, Robert (2007). *Things I didn't know: a memoir* (1st Vintage Book ed.). New York: Vintage. p. 346. ISBN 978-0-307-38598-7.
62. ^ Wilson, [ed]: Joanne Entwistle, Elizabeth (2005). *Body dressing* ([Online-Ausg.] ed.). Oxford: Berg Publishers. p. 205. ISBN 978-1-85973-444-5.
63. ^ Reid, Basil A. (2009). *Myths and realities of Caribbean history* ([Online-Ausg.] ed.). Tuscaloosa: University of Alabama Press. p. 113. ISBN 978-0-8173-5534-0.
64. ^ "Preparation and Use of Guayaco for Treating Syphilis". Jan van der Straet. Retrieved 6 August 2007.
65. ^ Katz RV, Kegeles SS, Kressin NR, et al. (November 2006). "The Tuskegee Legacy Project: Willingness of Minorities to Participate in Biomedical Research". *J Health Care Poor Underserved*. **17** (4): 698–715. doi:10.1353/hpu.2006.0126. PMC 1780164. PMID 17242525.
66. ^ [a] [b] [c] [d] "U.S. Public Health Service Syphilis Study at Tuskegee". Centers for Disease Control and Prevention. 15 June 2011. Retrieved 7 July 2010.
67. ^ "Bad Blood: The Tuskegee Syphilis Study: President Bill Clinton's Apology". University of Virginia Health Sciences Library. Retrieved 2 December 2014.
68. ^ "U.S. apologizes for newly revealed syphilis experiments done in Guatemala". *The Washington Post*. 1 October 2010. Retrieved 1 October 2010. "The United States revealed on Friday that the government conducted medical experiments in

the 1940s in which doctors infected soldiers, prisoners and mental patients in Guatemala with syphilis and other sexually transmitted diseases."

## Further reading


- Bliss, Katherine Elaine. "The Science of Redemption: Syphilis, Sexual Promiscuity, and Reformism in Revolutionary Mexico City" *Hispanic American Historical Review* 79:1 1999, pp. 1–40.
- Parascandola, John. *Sex, Sin, and Science: A History of Syphilis in America* (Praeger, 2008) 195 pp. ISBN 978-0-275-99430-3 excerpt and text search
- Shmaefsky, Brian, Hilary Babcock and David L. Heymann. *Syphilis* (Deadly Diseases & Epidemics) (2009)
- Stein, Claudia. *Negotiating the French Pox in Early Modern Germany* (2009)


## External links

- "Syphilis - CDC Fact Sheet" Centers for Disease Control and Prevention (CDC)
- UCSF HIV InSite Knowledge Base Chapter: Syphilis and HIV



| v · t · e · | Diseases of the skin and appendages by morphology | | |
|---|---|---|---|
| **Growths** | **Epidermal** | | wart · callus · seborrheic keratosis · acrochordon · molluscum contagiosum · actinic keratosis · squamous-cell carcinoma · basal-cell carcinoma · Merkel-cell carcinoma · nevus sebaceous · trichoepithelioma · |
| | **Pigmented** | | Freckles · lentigo · melasma · nevus · melanoma · |
| | **Dermal and subcutaneous** | | epidermal inclusion cyst · hemangioma · dermatofibroma (benign fibrous histiocytoma) · keloid · lipoma · neurofibroma · xanthoma · Kaposi's sarcoma · infantile digital fibromatosis · granular cell tumor · leiomyoma · lymphangioma circumscriptum · myxoid cyst · |
| | | **Eczematous** | contact dermatitis · atopic dermatitis · seborrheic dermatitis · stasis dermatitis · lichen simplex chronicus · Darier's disease · glucagonoma syndrome · langerhans cell histiocytosis · lichen sclerosus · pemphigus foliaceus · Wiskott–Aldrich syndrome · Zinc deficiency · |
| | | **Scaling** | psoriasis · tinea (corporis · cruris · pedis · manuum · faciei) · pityriasis rosea · **secondary syphilis** · mycosis fungoides · systemic lupus erythematosus · pityriasis rubra pilaris · parapsoriasis · ichthyosis · |
| | | | herpes simplex · herpes zoster · varicella · bullous impetigo · |

| | | | | | |
|---|---|---|---|---|---|
| **Rashes** | **With epidermal involvement** | **Blistering** | | | acute contact dermatitis · pemphigus vulgaris · bullous pemphigoid · dermatitis herpetiformis · porphyria cutanea tarda · epidermolysis bullosa simplex · |
| | | **Papular** | | | scabies · insect bite reactions · lichen planus · miliaria · keratosis pilaris · lichen spinulosus · transient acantholytic dermatosis · lichen nitidus · pityriasis lichenoides et varioliformis acuta · |
| | | **Pustular** | | | acne vulgaris · acne rosacea · folliculitis · impetigo · candidiasis · gonococcemia · dermatophyte · coccidioidomycosis · subcorneal pustular dermatosis · |
| | | **Hypopigmented** | | | tinea versicolor · vitiligo · pityriasis alba · postinflammatory hyperpigmentation · tuberous sclerosis · idiopathic guttate hypomelanosis · leprosy · hypopigmented mycosis fungoides · |
| | **Without epidermal involvement** | **Red** | **Blanchable Erythema** | **Generalized** | drug eruptions · viral exanthems · toxic erythema · systemic lupus erythematosus · |
| | | | | **Localized** | cellulitis · abscess · boil · erythema nodosum · carcinoid syndrome · fixed drug eruption · |
| | | | | **Specialized** | urticaria · erythema (multiforme · migrans · gyratum repens · annulare centrifugum · ab igne) · |
| | | | **Nonblanchable Purpura** | **Macular** | thrombocytopenic purpura · actinic/solar purpura · |
| | | | | **Papular** | disseminated intravascular coagulation · vasculitis · |
| | | **Indurated** | | | scleroderma/morphea · granuloma annulare · lichen sclerosis et atrophicus · necrobiosis lipoidica · |
| **Miscellaneous disorders** | **Ulcers** | | | | |
| | **Hair** | telogen effluvium · androgenic alopecia · trichotillomania · alopecia areata · systemic lupus erythematosus · tinea capitis · loose anagen syndrome · lichen planopilaris · folliculitis decalvans · acne keloidalis nuchae · | | | |
| | **Nail** | onychomycosis · psoriasis · paronychia · ingrown nail · | | | |
| | **Mucous membrane** | Aphthous stomatitis · oral candidiasis · lichen planus · leukoplakia · pemphigus vulgaris · mucous membrane pemphigoid · cicatricial pemphigoid · herpesvirus · coxsackievirus · **syphilis** · systemic histoplasmosis · squamous-cell carcinoma · | | | |

| v · t · e · | **Sexually transmitted infection (STI) (primarily A50–A64, 090–099)** |
|---|---|
| **Bacterial** | Chancroid (*Haemophilus ducreyi*) · Chlamydia/Lymphogranuloma venereum (*Chlamydia trachomatis*) · Donovanosis or Granuloma Inguinale (*Klebsiella granulomatis*) · Gonorrhea (*Neisseria gonorrhoeae*) · Mycoplasma hominis infection (*Mycoplasma hominis*) · **Syphilis** (*Treponema pallidum*) · Ureaplasma infection (*Ureaplasma urealyticum*) · |
| **Protozoal** | Trichomoniasis (*Trichomonas vaginalis*) · |

| | |
|---|---|
| **Parasitic** | Crab louse/crabs · Scabies · |
| **Viral** | AIDS (*HIV-1/HIV-2*) · Cervical cancer, vulvar cancer & Genital warts (condyloma), Penile cancer, Anal cancer (*Human papillomavirus (HPV)*) · Hepatitis B (*Hepatitis B virus*) · Herpes simplex (*HSV1/HSV2*) · Molluscum contagiosum (*MCV*) · |
| **General inflammation** | *female*: Cervicitis · Pelvic inflammatory disease (PID) ·<br>*male*: Epididymitis · Prostatitis ·<br>*either*: Proctitis · Urethritis/Non-gonococcal urethritis (NGU) · |

| v · t · e · | **Infectious diseases · Bacterial diseases: BV4 non-proteobacterial G- (primarily A00–A79, 001–041, 080–109)** · | | |
|---|---|---|---|
| **Spirochaete** | **Spirochaetaceae** | **Treponema** | *Treponema pallidum* (**Syphilis**/bejel · Yaws · · *Treponema carateum* (Pinta) · *Treponema denticola* · |
| | | **Borrelia** | *Borrelia burgdorferi*/*Borrelia afzelii* (Lyme disease · Erythema chronicum migrans · Neuroborreliosis · · *Borrelia recurrentis* (Louse borne relapsing fever) · *Borrelia hermsii*/*Borrelia duttoni*/*Borrelia parkeri* (Tick borne relapsing fever) · |
| | **Leptospiraceae** | **Leptospira** | *Leptospira interrogans* (Leptospirosis) · |
| | **Spirillaceae** | **Spirillum** | *Spirillum minus* (Rat-bite fever/Sodoku) · |
| **Chlamydiaceae** | **Chlamydophila** | | *Chlamydophila psittaci* (Psittacosis) · *Chlamydophila pneumoniae* · |
| | **Chlamydia** | | *Chlamydia trachomatis* (Chlamydia · Lymphogranuloma venereum · Trachoma · · |
| **Bacteroidetes** | | | *Bacteroides fragilis* · *Tannerella forsythia* · *Capnocytophaga canimorsus* · *Porphyromonas gingivalis* · *Prevotella intermedia* · |
| **Fusobacteria** | | | *Fusobacterium necrophorum* (Lemierre's syndrome) · *Fusobacterium nucleatum* · *Fusobacterium polymorphum* · *Streptobacillus moniliformis* (Rat-bite fever/Haverhill fever) · |

| v · t · e · | **Vertically transmitted infections (P35–P39, 771)** |
|---|---|
| **Gestational** | Viruses (Congenital rubella syndrome · Congenital cytomegalovirus infection · Neonatal herpes simplex · Hepatitis B · Congenital varicella syndrome · HIV · Fifth disease · · Bacteria (Congenital syphilis · · Other (Toxoplasmosis · · transplacental · TORCH complex · |
| **During birth** | transcervical · Candidiasis · Gonorrhea · Listeriosis · |
| **Late pregnancy** | Listeriosis · Congenital cytomegalovirus infection · |
| **By breastfeeding** | Breastfeeding · Tuberculosis · HIV · |
| **Authority control** | NDL: 00560462 · |

Categories: Bacterial diseases | Bacterium-related cutaneous conditions | Infections with a predominantly sexual mode of transmission | Infectious diseases | Sexually transmitted diseases and infections | Spirochaetes | Syphilis


# Tuberculosis

From Wikipedia, the free encyclopedia

**Tuberculosis** (**TB**) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* (MTB).[1] Tuberculosis generally affects the lungs, but can also affect other parts of the body. Most infections do not have symptoms; in which case it is known as latent tuberculosis. About 10% of latent infections progress to active disease which, if left untreated, kills about half of those infected. The classic symptoms of active TB are a chronic cough with blood-containing sputum, fever, night sweats, and weight loss.[1] The historical term "**consumption**" came about due to the weight loss.[2] Infection of other organs can cause a wide range of symptoms.[3]

Tuberculosis is spread through the air when people who have active TB in their lungs cough, spit, speak, or sneeze.[1][4] People with latent TB do not spread the disease. Active infection occurs more often in people with HIV/AIDS and in those who smoke.[1] Diagnosis of active TB is based on chest X-rays, as well as microscopic examination and culture of body fluids. Diagnosis of latent TB relies on the tuberculin skin test (TST) or blood tests.[5]

Prevention of TB involves screening those at high risk, early detection and treatment of cases, and vaccination with the bacillus Calmette-Guérin vaccine.[6][7][8] Those at high risk include household, workplace, and social contacts of people with active TB.[8] Treatment requires the use of multiple antibiotics over a long period of time.[1] Antibiotic resistance is a growing problem with increasing rates of multiple drug-resistant tuberculosis (MDR-TB).[1]

One-third of the world's population is thought to be infected with TB.[1] New infections occur in about 1% of the population each year.[9] In 2014, there were 9.6 million cases of active TB which resulted in 1.5 million deaths. More than 95% of deaths occurred in developing countries. The number of new cases each year has decreased since 2000.[1] About 80% of people in many Asian and African countries test positive while 5–10% of people in the United States population tests positive by the tuberculin test.[10] Tuberculosis has been present in humans since ancient times.[11]

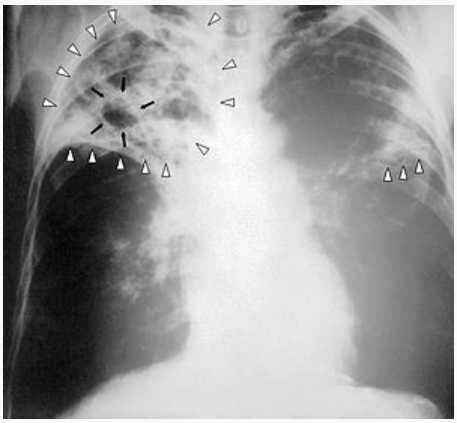
Contents





## Tuberculosis

**Synonyms** phthisis, phthisis pulmonalis, consumption

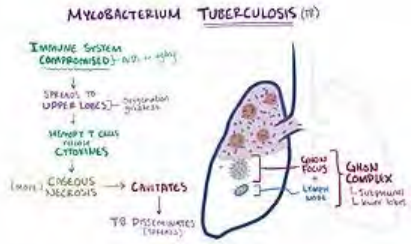


Chest X-ray of a person with advanced tuberculosis: Infection in both lungs is marked by white arrow-heads, and the formation of a cavity is marked by black arrows.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Infectious disease, pulmonology |
| **ICD-10** | A15–A19 |
| **ICD-9-CM** | 010–018 |
| **OMIM** | 607948 |
| **DiseasesDB** | 8515 |
| **MedlinePlus** | 000077 *000624* |
| **eMedicine** | med/2324 emerg/618 radio/411 |
| **Patient UK** | Tuberculosis |
| **MeSH** | D014376 |
| **Orphanet** | 3389 |

[edit on Wikidata]




Play media

Video explanation

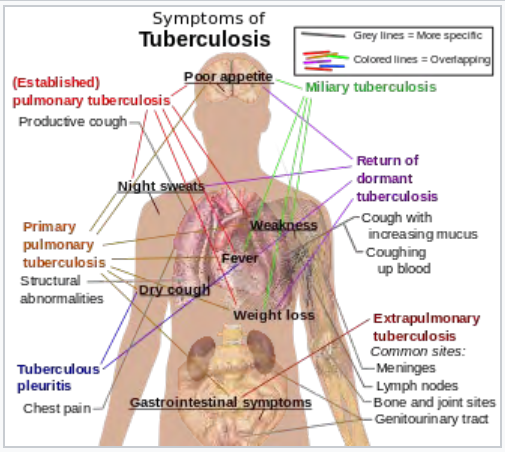
## Signs and symptoms

Tuberculosis may infect any part of the body, but most commonly occurs in the lungs (known as pulmonary tuberculosis).[3] Extrapulmonary TB occurs when tuberculosis develops outside of the lungs, although extrapulmonary TB may coexist with pulmonary TB.[3]

General signs and symptoms include fever, chills, night sweats, loss of appetite, weight loss, and fatigue.[3] Significant nail clubbing may also occur.[13]

### Pulmonary

If a tuberculosis infection does become active, it most commonly involves the lungs (in about 90% of cases).[11][14] Symptoms may include chest pain and a prolonged cough producing sputum. About 25% of people may not have any symptoms (i.e. they remain "asymptomatic").[11] Occasionally, people may cough up blood in small amounts, and in very rare cases, the infection may erode into the pulmonary artery or a Rasmussen's aneurysm, resulting in massive bleeding.[3][15] Tuberculosis may become a chronic illness and cause extensive scarring in the upper lobes of the lungs. The upper lung lobes are more frequently affected by tuberculosis than the lower ones.[3] The reason for this difference is not clear.[10] It may be due to either better air flow,[10] or poor lymph drainage within the upper lungs.[3]



The main symptoms of variants and stages of tuberculosis are given,[12] with many symptoms overlapping with other variants, while others are more (but not entirely) specific for certain variants. Multiple variants may be present simultaneously.

### Extrapulmonary

In 15–20% of active cases, the infection spreads outside the lungs, causing other kinds of TB.[16] These are collectively denoted as "extrapulmonary tuberculosis".[17] Extrapulmonary TB occurs more commonly in immunosuppressed persons and young children. In those with HIV, this occurs in more than 50% of cases.[17] Notable extrapulmonary infection sites include the pleura (in tuberculous pleurisy), the central nervous system (in tuberculous meningitis), the lymphatic system (in scrofula of the neck), the genitourinary system (in urogenital tuberculosis), and the bones and joints (in Pott disease of the spine), among others.

Spread to lymph nodes is the most common.[18] An ulcer originating from nearby infected lymph nodes may occur and is painless, slowly enlarging and has an appearance of "wash leather".[19]

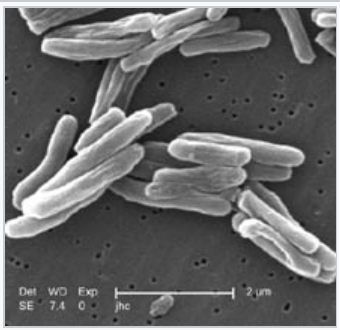
When it spreads to the bones, it is known as "osseous tuberculosis",[20] a form of osteomyelitis.[10] A potentially more serious, widespread form of TB is called "disseminated tuberculosis", also known as miliary tuberculosis.[3] Miliary TB currently makes up about 10% of extrapulmonary cases.[21]

## Causes

### Mycobacteria

*Main article: Mycobacterium tuberculosis*

The main cause of TB is *Mycobacterium tuberculosis* (MTB), a small, aerobic, nonmotile bacillus.[3] The high lipid content of this pathogen accounts for many of its unique clinical characteristics.[22] It divides every 16 to 20 hours, which is an extremely slow rate compared with other bacteria, which usually divide in less than an hour.[23] Mycobacteria have an outer membrane lipid bilayer.[24] If a Gram stain is performed, MTB either stains very weakly "Gram-positive" or does not retain dye as a result of the high lipid and mycolic acid content of its cell wall.[25] MTB can withstand weak disinfectants and survive in a dry state for weeks. In nature, the bacterium can grow only within the cells of a host organism, but *M. tuberculosis* can be cultured in the laboratory.[26]



Scanning electron micrograph of *M. tuberculosis*

Using histological stains on expectorated samples from phlegm (also called "sputum"), scientists can identify MTB under a microscope. Since MTB retains certain stains even after being treated with acidic solution, it is classified as an acid-fast bacillus.[10][25] The most common acid-fast staining techniques are the Ziehl–Neelsen stain[27] and the Kinyoun stain, which dye acid-fast bacilli a bright red that stands out against a blue background.[28] Auramine-rhodamine staining[29] and fluorescence microscopy[30] are also used.

The *M. tuberculosis* complex (MTBC) includes four other TB-causing mycobacteria: *M. bovis*, *M. africanum*, *M. canetti*, and *M. microti*.[31] *M. africanum* is not widespread, but it is a significant cause of tuberculosis in parts of Africa.[32][33] *M. bovis* was once a common cause of tuberculosis, but the introduction of pasteurized milk has almost completely eliminated this as a public health problem in developed countries.[10][34] *M. canetti* is rare and seems to be limited to the Horn of Africa, although a few cases have been seen in African emigrants.[35][36] *M. microti* is also rare and is seen almost only in immunodeficient people, although its prevalence may be significantly underestimated.[37]

Other known pathogenic mycobacteria include *M. leprae*, *M. avium*, and *M. kansasii*. The latter two species are classified as "nontuberculous mycobacteria" (NTM). NTM cause neither TB nor leprosy, but they do cause pulmonary diseases that resemble TB.[38]

### Risk factors

*Main article: Risk factors for tuberculosis*

A number of factors make people more susceptible to TB infections. The most important risk factor globally is HIV; 13% of all people with TB

are infected by the virus.[39] This is a particular problem in sub-Saharan Africa, where rates of HIV are high.[40][41] Of people without HIV who are infected with tuberculosis, about 5–10% develop active disease during their lifetimes;[13] in contrast, 30% of those coinfected with HIV develop the active disease.[13]

Tuberculosis is closely linked to both overcrowding and malnutrition, making it one of the principal diseases of poverty.[11] Those at high risk thus include: people who inject illicit drugs, inhabitants and employees of locales where vulnerable people gather (e.g. prisons and homeless shelters), medically underprivileged and resource-poor communities, high-risk ethnic minorities, children in close contact with high-risk category patients, and health-care providers serving these patients.[42]

Chronic lung disease is another significant risk factor. Silicosis increases the risk about 30-fold.[43] Those who smoke cigarettes have nearly twice the risk of TB compared to nonsmokers.[44]

Other disease states can also increase the risk of developing tuberculosis. These include alcoholism[11] and diabetes mellitus (three-fold increase).[45]

Certain medications, such as corticosteroids and infliximab (an anti-αTNF monoclonal antibody), are becoming increasingly important risk factors, especially in the developed world.[11]

Genetic susceptibility also exists,[46] for which the overall importance remains undefined.[11]

# Mechanism

## Transmission

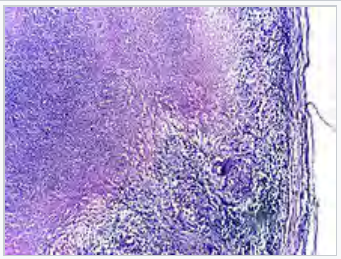
When people with active pulmonary TB cough, sneeze, speak, sing, or spit, they expel infectious aerosol droplets 0.5 to 5.0 μm in diameter. A single sneeze can release up to 40,000 droplets.[47] Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very small (the inhalation of fewer than 10 bacteria may cause an infection).[48]

People with prolonged, frequent, or close contact with people with TB are at particularly high risk of becoming infected, with an estimated 22% infection rate.[49] A person with active but untreated tuberculosis may infect 10–15 (or more) other people per year.[50] Transmission should occur from only people with active TB – those with latent infection are not thought to be contagious.[10] The probability of transmission from one person to another depends upon several factors, including the number of infectious droplets expelled by the carrier, the effectiveness of ventilation, the duration of exposure, the virulence of the *M. tuberculosis* strain, the level of immunity in the uninfected person, and others.[51] The cascade of person-to-person spread can be circumvented by segregating those with active ("overt") TB and putting them on anti-TB drug regimens. After about two weeks of effective treatment, subjects with nonresistant active infections generally do not remain contagious to others.[49] If someone does become infected, it typically takes three to four weeks before the newly infected person becomes infectious enough to transmit the disease to others.[52]

Public health campaigns in the 1920s tried to halt the spread of TB.

## Pathogenesis

About 90% of those infected with *M. tuberculosis* have asymptomatic, latent TB infections (sometimes called LTBI),[53] with only a 10% lifetime chance that the latent infection will progress to overt, active tuberculous disease.[54] In those with HIV, the risk of developing active TB increases to nearly 10% a year.[54] If effective treatment is not given, the death rate for active TB cases is up to 66%.[50]


Microscopy of tuberculous epididymitis. H&E stain

TB infection begins when the mycobacteria reach the pulmonary alveoli, where they invade and replicate within endosomes of alveolar macrophages.[10][55] Macrophages identify the bacterium as foreign and attempt to eliminate it by phagocytosis. During this process, the bacterium is enveloped by the macrophage and stored temporarily in a membrane-bound vesicle called a phagosome. The phagosome then combines with a lysosome to create a phagolysosome. In the phagolysosome, the cell attempts to use reactive oxygen species and acid to kill the bacterium. However, *M. tuberculosis* has a thick, waxy mycolic acid capsule that protects it from these toxic substances. *M. tuberculosis* is able to reproduce inside the macrophage and will eventually kill the immune cell.

The primary site of infection in the lungs, known as the "Ghon focus", is generally located in either the upper part of the lower lobe, or the lower part of the upper lobe.[10] Tuberculosis of the lungs may also occur via infection from the blood stream. This is known as a Simon focus and is typically found in the top of the lung.[56] This hematogenous transmission can also spread infection to more distant sites, such as peripheral lymph nodes, the kidneys, the brain, and the bones.[10][57] All parts of the body can be affected by the disease, though for unknown reasons it rarely affects the heart, skeletal muscles, pancreas, or thyroid.[58]

Tuberculosis is classified as one of the granulomatous inflammatory diseases. Macrophages, T lymphocytes, B lymphocytes, and fibroblasts aggregate to form granulomas, with lymphocytes surrounding the infected macrophages. When other macrophages attack the infected macrophage, they fuse together to form a giant multinucleated cell in the alveolar lumen. The granuloma may prevent dissemination of the mycobacteria and provide a local environment for interaction of cells of the immune system.[60] However, more recent evidence suggests that the bacteria use the granulomas to avoid destruction by the host's immune system. Macrophages and dendritic cells in the granulomas are unable to present antigen to lymphocytes; thus the immune response is suppressed.[61] Bacteria inside the granuloma can become dormant, resulting in latent infection. Another feature of the granulomas is the development of abnormal cell death (necrosis) in the

Robert Carswell's illustration of tubercle[59]

center of tubercles. To the naked eye, this has the texture of soft, white cheese and is termed caseous necrosis.[60]

If TB bacteria gain entry to the blood stream from an area of damaged tissue, they can spread throughout the body and set up many foci of infection, all appearing as tiny, white tubercles in the tissues.[62] This severe form of TB disease, most common in young children and those with HIV, is called miliary tuberculosis.[63] People with this disseminated TB have a high fatality rate even with treatment (about 30%).[21][64]

In many people, the infection waxes and wanes. Tissue destruction and necrosis are often balanced by healing and fibrosis.[60] Affected tissue is replaced by scarring and cavities filled with caseous necrotic material. During active disease, some of these cavities are joined to the air passages bronchi and this material can be coughed up. It contains living bacteria, so can spread the infection. Treatment with appropriate antibiotics kills bacteria and allows healing to take place. Upon cure, affected areas are eventually replaced by scar tissue.[60]

## Diagnosis

*Main article: Tuberculosis diagnosis*

### Active tuberculosis

*M. tuberculosis* (stained red) in sputum

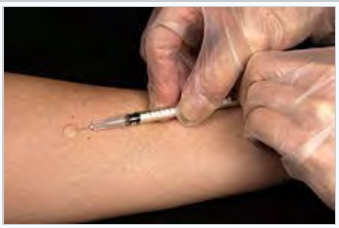
Diagnosing active tuberculosis based only on signs and symptoms is difficult,[65] as is diagnosing the disease in those who are immunosuppressed.[66] A diagnosis of TB should, however, be considered in those with signs of lung disease or constitutional symptoms lasting longer than two weeks.[66] A chest X-ray and multiple sputum cultures for acid-fast bacilli are typically part of the initial evaluation.[66] Interferon-γ release assays and tuberculin skin tests are of little use in the developing world.[67][68] IGRA have similar limitations in those with HIV.[68][69]

A definitive diagnosis of TB is made by identifying *M. tuberculosis* in a clinical sample (e.g., sputum, pus, or a tissue biopsy). However, the difficult culture process for this slow-growing organism can take two to six weeks for blood or sputum culture.[70] Thus, treatment is often begun before cultures are confirmed.[71]

Nucleic acid amplification tests and adenosine deaminase testing may allow rapid diagnosis of TB.[65] These tests, however, are not routinely recommended, as they rarely alter how a person is treated.[71] Blood tests to detect antibodies are not specific or sensitive, so they are not recommended.[72]

### Latent tuberculosis

*Main article: Latent tuberculosis*



Mantoux tuberculin skin test

The Mantoux tuberculin skin test is often used to screen people at high risk for TB.[66] Those who have been previously immunized may have a false-positive test result.[73] The test may be falsely negative in those with sarcoidosis, Hodgkin's lymphoma, malnutrition, and most notably, active tuberculosis.[10] Interferon gamma release assays (IGRAs), on a blood sample, are recommended in those who are positive to the Mantoux test.[71] These are not affected by immunization or most environmental mycobacteria, so they generate fewer false-positive results.[74] However, they are affected by *M. szulgai*, *M. marinum*, and *M. kansasii*.[75] IGRAs may increase sensitivity when used in addition to the skin test, but may be less sensitive than the skin test when used alone.[76]

## Prevention

Tuberculosis prevention and control efforts rely primarily on the vaccination of infants and the detection and appropriate treatment of active cases.[11] The World Health Organization has achieved some success with improved treatment regimens, and a small decrease in case numbers.[11] The US Preventive Services Task Force (USPSTF) recommends screening people who are at high risk for latent tuberculosis with either tuberculin skin tests or interferon-gamma release assays.[77]

### Vaccines

*Main articles: Tuberculosis vaccines and BCG vaccine*

The only available vaccine as of 2011 is Bacillus Calmette-Guérin (BCG).[78] In children it decreases the risk of getting the infection by 20% and the risk of infection turning into disease by nearly 60%.[79]

[11]

It is the most widely used vaccine worldwide, with more than 90% of all children being vaccinated. The immunity it induces decreases after about ten years.[11] As tuberculosis is uncommon in most of Canada, the United Kingdom, and the United States, BCG is administered to only those people at high risk.[80][81][82] Part of the reasoning against the use of the vaccine is that it makes the tuberculin skin test falsely positive, reducing the test's use in screening.[82] A number of new vaccines are currently in development.[11]

### Public health

The World Health Organization declared TB a "global health emergency" in 1993,[11] and in 2006, the Stop TB Partnership developed a Global Plan to Stop Tuberculosis that aimed to save 14 million lives between its launch and 2015.[83] A number of targets they set were not achieved by 2015, mostly due to the increase in HIV-associated tuberculosis and the emergence of multiple drug-resistant tuberculosis.[11] A tuberculosis classification system developed by the American Thoracic Society is used primarily in public health programs.[84]

## Management

*Main article: Tuberculosis management*

Treatment of TB uses antibiotics to kill the bacteria. Effective TB treatment is difficult, due to the unusual structure and chemical composition of the mycobacterial cell wall, which hinders the entry of drugs and makes many antibiotics ineffective.[85] The two antibiotics most commonly used are isoniazid and rifampicin, and treatments can be prolonged, taking several months.[51] Latent TB treatment usually employs a single antibiotic,[86] while active TB disease is best treated with combinations of several antibiotics to reduce the risk of the bacteria developing antibiotic resistance.[11] People with latent infections are also treated to prevent them from progressing to active TB disease later in life.[86] Directly observed therapy, i.e., having a health care provider watch the person take their medications, is recommended by the WHO in an effort to reduce the number of people not appropriately taking antibiotics.[87] The evidence to support this practice over people simply taking their medications independently is poor.[88][*needs update*] Methods to remind people of the importance of treatment do, however, appear effective.[89][*needs update*]

### New onset

The recommended treatment of new-onset pulmonary tuberculosis, as of 2010, is six months of a combination of antibiotics containing rifampicin, isoniazid, pyrazinamide, and ethambutol for the first two months, and only rifampicin and isoniazid for the last four months.[11] Where resistance to isoniazid is high, ethambutol may be added for the last four months as an alternative.[11]

### Recurrent disease

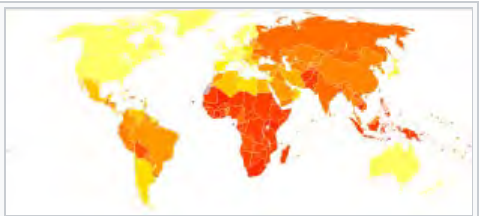
If tuberculosis recurs, testing to determine to which antibiotics it is sensitive is important before determining treatment.[11] If multiple drug-resistant TB is detected, treatment with at least four effective antibiotics for 18 to 24 months is recommended.[11]

### Medication resistance

Primary resistance occurs when a person becomes infected with a resistant strain of TB. A person with fully susceptible MTB may develop secondary (acquired) resistance during therapy because of inadequate treatment, not taking the prescribed regimen appropriately (lack of compliance), or using low-quality medication.[90] Drug-resistant TB is a serious public health issue in many developing countries, as its treatment is longer and requires more expensive drugs. MDR-TB is defined as resistance to the two most effective first-line TB drugs: rifampicin and isoniazid. Extensively drug-resistant TB is also resistant to three or more of the six classes of second-line drugs.[91] Totally drug-resistant TB is resistant to all currently used drugs.[92] It was first observed in 2003 in Italy,[93] but not widely reported until 2012,[92][94] and has also been found in Iran and India.[95][96] Bedaquiline is tentatively supported for use in multiple drug-resistant TB.[97]

XDR-TB is a term sometimes used to define *extensively resistant* TB, and constitutes one in ten cases of MDR-TB. Cases of XDR TB have been identified in more than 90% of countries.[95]

## Prognosis



Age-standardized disability-adjusted life years caused by tuberculosis per 100,000 inhabitants in 2004.[98]

| | |
|---|---|
| no data | 250–500 |
| ≤10 | 500–750 |
| 10–25 | 750–1000 |
| 25–50 | 1000–2000 |
| 50–75 | 2000–3000 |
| 75–100 | ≥ 3000 |

Progression from TB infection to overt TB disease occurs when the bacilli overcome the immune system defenses and begin to multiply. In primary TB disease (some 1–5% of cases), this occurs soon after the initial infection.[10] However, in the majority of cases, a latent infection occurs with no obvious symptoms.[10] These dormant bacilli produce active tuberculosis in 5–10% of these latent cases, often many years after infection.[13]

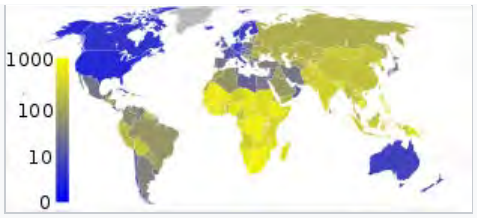
The risk of reactivation increases with immunosuppression, such as that caused by infection with HIV. In people coinfected with *M. tuberculosis* and HIV, the risk of reactivation increases to 10% per year.[10] Studies using DNA fingerprinting of *M. tuberculosis* strains have shown reinfection contributes more substantially to recurrent TB than previously thought,[99] with estimates that it might account for more than 50% of reactivated cases in areas where TB is common.[100] The chance of death from a case of tuberculosis is about 4% as of 2008, down from 8% in 1995.[11]

## Epidemiology

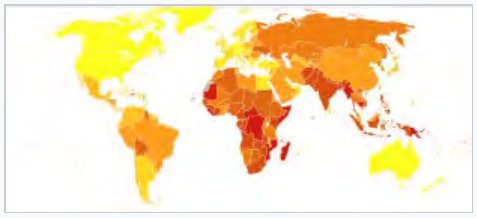
*Main article: Epidemiology of tuberculosis*

Roughly one-third of the world's population has

100–250




In 2007, the number of cases of TB per 100,000 people was highest in sub-Saharan Africa, and was also relatively high in Asia.[101]



Tuberculosis deaths per million persons in 2012

0-3
4-7
8-16
17-26
27-45
46-83
84-137
138-215
216-443
444-1,359

been infected with *M. tuberculosis*,[50] with new infections occurring in about 1% of the population each year.[9] However, most infections with *M. tuberculosis* do not cause TB disease,[102] and 90–95% of infections remain asymptomatic.[53] In 2012, an estimated 8.6 million chronic cases were active.[103] In 2010, 8.8 million new cases of TB were diagnosed, and 1.20–1.45 million deaths occurred, most of these occurring in developing countries.[39][104] Of these 1.45 million deaths, about 0.35 million occur in those also infected with HIV.[105]

Tuberculosis is the second-most common cause of death from infectious disease (after those due to HIV/AIDS).[3] The total number of tuberculosis cases has been decreasing since 2005, while new cases have decreased since 2002.[39] China has achieved particularly dramatic progress, with about an 80% reduction in its TB mortality rate between 1990 and 2010.[105] The number of new cases has declined by 17% between 2004–2014.[95] Tuberculosis is more common in developing countries; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5–10% of the US population test positive.[10] Hopes of totally controlling the disease have been dramatically dampened because of a number of factors, including the difficulty of developing an effective vaccine, the expensive and time-consuming diagnostic process, the necessity of many months of treatment, the increase in HIV-associated tuberculosis, and the emergence of drug-resistant cases in the 1980s.[11]

In 2007, the country with the highest estimated incidence rate of TB was Swaziland, with 1,200 cases per 100,000 people. India had the largest total incidence, with an estimated 2.0 million new cases.[106] In developed countries, tuberculosis is less common and is found mainly in urban areas. Rates per 100,000 people in different areas of the world were: globally 178, Africa 332, the Americas 36, Eastern Mediterranean 173, Europe 63, Southeast Asia 278, and Western Pacific 139 in 2010.[105] In Canada and Australia, tuberculosis is many times more common among the aboriginal peoples, especially in remote areas.[107][108] In the United States Native Americans have a fivefold greater mortality from TB,[109] and racial and ethnic minorities accounted for 84% of all reported TB cases.[110]

The rates of TB varies with age. In Africa, it primarily affects adolescents and young adults.[111] However, in countries where incidence rates have declined dramatically (such as the United States), TB is mainly a disease of older people and the immunocompromised (risk factors are listed above).[10][112] Worldwide, 22 "high-burden" states or countries together experience 80% of cases as well as 83% of deaths.[95]

## History

*Main articles: History of tuberculosis and Timeline of tuberculosis*

Tuberculosis has been present in humans since antiquity.[11] The earliest unambiguous detection of *M. tuberculosis* involves evidence of the disease in the remains of bison in Wyoming dated to around 17,000 years ago.[113] However, whether tuberculosis originated in bovines, then was transferred to humans, or whether it diverged from a common ancestor, is currently unclear.[114] A comparison of the genes of *M. tuberculosis* complex (MTBC) in humans to MTBC in animals suggests humans did not acquire MTBC from animals during animal domestication, as was previously believed. Both strains of the tuberculosis bacteria share a common ancestor, which could have infected humans even before the Neolithic Revolution.[115]

Egyptian mummy in the British Museum – tubercular decay has been found in the spine

Skeletal remains show prehistoric humans (4000 BC) had TB, and researchers have found tubercular decay in the spines of Egyptian mummies dating from 3000–2400 BC.[116] Genetic studies suggest TB was present in the Americas from about 100 AD.[117]

Before the Industrial Revolution, folklore often associated tuberculosis with vampires. When one member of a family died from it, the other infected members would lose their health slowly. People believed this was caused by the original person with TB draining the life from the other family members.[118]

Although the pulmonary form associated with tubercles was established as a pathology by Dr Richard Morton in 1689,[119][120] due to the variety of its symptoms, TB was not identified as a single disease until the 1820s. It was not named "tuberculosis" until 1839, by J. L. Schönlein.[121]

During 1838–1845, Dr. John Croghan, the owner of Mammoth Cave, brought a number of people with tuberculosis into the cave in the hope of curing the disease with the constant temperature and purity of the cave air; they died within a year.[122] Hermann Brehmer opened the first TB sanatorium in 1859 in Görbersdorf (now Sokołowsko), Silesia.[123]

The bacillus causing tuberculosis, *M. tuberculosis*, was identified and described on 24 March 1882 by Robert Koch. He received the Nobel Prize in physiology or medicine in 1905 for this discovery.[124] Koch did not believe the bovine (cattle) and human tuberculosis diseases were similar, which delayed the recognition of infected milk as a source of infection. Later, the risk of transmission from this source was dramatically reduced by the invention of the pasteurization process. Koch announced a glycerine extract of the tubercle bacilli as a "remedy" for tuberculosis in 1890, calling it "tuberculin". While it was not effective, it was later successfully adapted as a screening test for the presence of pre-symptomatic tuberculosis.[125] The World Tuberculosis Day was established on 24 March for this reason.

Albert Calmette and Camille Guérin achieved the first genuine success in immunization against tuberculosis in 1906, using attenuated bovine-strain tuberculosis. It was called bacille Calmette–Guérin (BCG). The BCG vaccine was first used on humans in 1921 in France,[126] but received widespread acceptance in the US, Great Britain, and Germany

Dr. Robert Koch discovered the tuberculosis bacillus.

only after World War II.[127]

Tuberculosis caused the most widespread public concern in the 19th and early 20th centuries as an endemic disease of the urban poor. In 1815, one in four deaths in England was due to "consumption". By 1918, one in six deaths in France was still caused by TB. After TB was determined to be contagious, in the 1880s, it was put on a notifiable disease list in Britain; campaigns were started to stop people from spitting in public places, and the infected poor were "encouraged" to enter sanatoria that resembled prisons (the sanatoria for the middle and upper classes offered excellent care and constant medical attention).[123] Whatever the (purported) benefits of the "fresh air" and labor in the sanatoria, even under the best conditions, 50% of those who entered died within five years (*circa* 1916).[123]

In Europe, rates of tuberculosis began to rise in the early 1600s to a peak level in the 1800s, when it caused nearly 25% of all deaths.[128] By the 1950s, mortality had decreased nearly 90%.[129] Improvements in public health began significantly reducing rates of tuberculosis even before the arrival of streptomycin and other antibiotics, although the disease remained a significant threat to public health such that when the Medical Research Council was formed in Britain in 1913, its initial focus was tuberculosis research.[130]

In 1946, the development of the antibiotic streptomycin made effective treatment and cure of TB a reality. Prior to the introduction of this drug, the only treatment (except sanatoria) was surgical intervention, including the "pneumothorax technique", which involved collapsing an infected lung to "rest" it and allow tuberculous lesions to heal.[131]

Because of the emergence of MDR-TB, surgery has been re-introduced as an option within the generally accepted standard of care in treating TB infections. Current surgical interventions involve removal of pathological chest cavities ("bullae") in the lungs to reduce the number of bacteria and to increase the exposure of the remaining bacteria to drugs in the bloodstream, thereby simultaneously reducing the total bacterial load and increasing the effectiveness of systemic antibiotic therapy.[132]

Hopes of completely eliminating TB (*cf.* smallpox) from the population were dashed after the rise of drug-resistant strains in the 1980s. The subsequent resurgence of tuberculosis resulted in the declaration of a global health emergency by the World Health Organization in 1993.[133]

# Society and culture

## Names

*Phthisis* (Φθισις) is a Greek word for consumption, an old term for pulmonary tuberculosis;[2] around 460 BC, Hippocrates described phthisis as a disease of dry seasons.[134] The abbreviation "TB" is short for *tubercle bacillus*.

"Consumption" was the most common nineteenth century English word for the disease. The Latin root "con" meaning "completely" is linked to "sumere" meaning "to take up from under."[135] In The Life and Death of Mr. Badman by John Bunyan, the author calls consumption "the captain of all these men of death."[136]

## Public health efforts

The World Health Organization, Bill and Melinda Gates Foundation, and US government are subsidizing a fast-acting diagnostic tuberculosis test for use in low- and middle-income countries.[137][138][139] In addition to being fast-acting, the test can determine if there is resistance to the antibiotic rifampicin which may indicate multi-drug resistant tuberculosis and is accurate in those who are also infected with HIV.[137][140] Many resource-poor places as of 2011 have access to only sputum microscopy.[141]

India had the highest total number of TB cases worldwide in 2010, in part due to poor disease management within the private and public health care sector.[142] Programs such as the Revised National Tuberculosis Control Program are working to reduce TB levels amongst people receiving public health care.[143][144]

A 2014 the EIU-healthcare report that the need to address apathy and urging for increased funding. The report cites among others Lucica Ditui "[TB] is like an orphan. It has been neglected even in countries with a high burden and often forgotten by donors and those investing in health interventions."[95]

Slow progress has led to frustration, expressed by the executive director of the Global Fund to Fight AIDS, Tuberculosis and Malaria – Mark Dybul: "we have the tools to end TB as a pandemic and public health threat on the planet, but we are not doing it."[95] Several international organizations are pushing for more transparency in treatment, and more countries are implementing mandatory reporting of cases to the government, although adherence is often sketchy. Commercial treatment providers may at times overprescribe second-line drugs as well as supplementary treatment, promoting demands for further regulations.[95] The government of Brazil provides universal TB-care, which reduces this problem.[95] Conversely, falling rates of TB-infection may not relate to the number of programs directed at reducing infection rates but may be tied to increased level of education, income, and health of the population.[95] Costs of the disease, as calculated by the World Bank in 2009 may exceed 150 billion USD per year in "high burden" countries.[95] Lack of progress eradicating the disease may also be due to lack of patient follow-up – as among the 250M rural migrants in China.[95]

### Stigma

Slow progress in preventing the disease may in part be due to stigma associated with TB.[95] Stigma may be due to the fear of transmission from affected individuals. This stigma may additionally arise due to links between TB and poverty, and in Africa, AIDS.[95] Such stigmatization may be both real and perceived, for example; in Ghana individuals with TB are banned from attending public gatherings.[145]

Stigma towards TB may result in delays in seeking treatment,[95] lower treatment compliance, and family members keeping cause of death secret[145] – allowing the disease to spread further.[95] At odds is Russia, where stigma was associated with increased treatment compliance.[145] TB stigma also affects socially marginalized individuals to a greater degree and varies between regions.[145]

One way to decrease stigma may be through the promotion of "TB clubs", where those infected may share experiences and offer support, or through counseling.[145] Some studies have shown TB education programs to be effective in decreasing stigma, and may thus be effective in increasing treatment adherence.[145] Despite this, studies on the relationship between reduced stigma and mortality are lacking as of 2010, and similar efforts to decrease stigma surrounding AIDS have been minimally effective.[145] Some have claimed the stigma to be worse than the disease, and healthcare providers may unintentionally reinforce stigma, as those with TB are often perceived as difficult or otherwise undesirable.[95] A greater understanding of the social and cultural dimensions of tuberculosis may also help with stigma reduction.[146]

## Research

The BCG vaccine has limitations, and research to develop new TB vaccines is ongoing.[147] A number of potential candidates are currently in phase I and II clinical trials.[147] Two main approaches are being used to attempt to improve the efficacy of available vaccines. One approach involves adding a subunit vaccine to BCG, while the other strategy is attempting to create new and better live vaccines.[147] MVA85A, an example of a subunit vaccine, currently in trials in South Africa, is based on a genetically modified vaccinia virus.[148] Vaccines are hoped to play a significant role in treatment of both latent and active disease.[149]

To encourage further discovery, researchers and policymakers are promoting new economic models of vaccine development, including prizes, tax incentives, and advance market commitments.[150][151] A number of groups, including the Stop TB Partnership,[152] the South African Tuberculosis Vaccine Initiative, and the Aeras Global TB Vaccine Foundation, are involved with research.[153] Among these, the Aeras Global TB Vaccine Foundation received a gift of more than $280 million (US) from the Bill and Melinda Gates Foundation to develop and license an improved vaccine against tuberculosis for use in high burden countries.[154][155]

A number of medications are being studied for multi drug resistant tuberculosis including: bedaquiline and delamanid.[156] Bedaquiline received U.S. Food and Drug Administration (FDA) approval in late 2012.[157] The safety and effectiveness of these new agents are still uncertain, because they are based on the results of a relatively small studies.[156][158] However, existing data suggest that patients taking bedaquiline in addition to standard TB therapy are five times more likely to die than those without the new drug,[159] which has resulted in medical journal articles raising health policy questions about why the FDA approved the drug and whether financial ties to the company making bedaquiline influenced physicians' support for its use [158][160]

## Other animals

Mycobacteria infect many different animals, including birds,[161] rodents,[162] and reptiles.[163] The subspecies *Mycobacterium tuberculosis*, though, is rarely present in wild animals.[164] An effort to eradicate bovine tuberculosis caused by *Mycobacterium bovis* from the cattle and deer herds of New Zealand has been relatively successful.[165] Efforts in Great Britain have been less successful.[166][167]

As of 2015, tuberculosis appears to be widespread among captive elephants in the US. It is believed that the animals originally acquired the disease from humans, a process called reverse zoonosis. Because the disease can spread through the air to infect both humans and other animals, it is a public health concern affecting circuses and zoos.[168][169]

## References


1. ^ a b c d e f g h "Tuberculosis Fact sheet N°104". *WHO*. October 2015. Retrieved 11 February 2016.
2. ^ a b *The Chambers Dictionary.* New Delhi: Allied Chambers India Ltd. 1998. p. 352. ISBN 978-81-86062-25-8.
3. ^ a b c d e f g h i j Dolin, [edited by] Gerald L. Mandell, John E. Bennett, Raphael (2010). *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* (7th ed.). Philadelphia, PA: Churchill Livingstone/Elsevier. pp. Chapter 250. ISBN 978-0-443-06839-3.
4. ^ "Basic TB Facts". *CDC*. March 13, 2012. Retrieved 11 February 2016.
5. ^ Konstantinos A (2010). "Testing for tuberculosis". *Australian Prescriber*. **33** (1): 12–18.
6. ^ Hawn, TR; Day, TA; Scriba, TJ; Hatherill, M; Hanekom, WA; Evans, TG; Churchyard, GJ; Kublin, JG; Bekker, LG; Self, SG (December 2014). "Tuberculosis vaccines and prevention of infection." *Microbiology and molecular biology reviews: MMBR*. **78** (4): 650–71. doi:10.1128/MMBR.00021-14. PMC 4248657. PMID 25428938.
7. ^ Harris, Randall E. (2013). *Epidemiology of chronic disease: global perspectives*. Burlington, MA: Jones & Bartlett Learning. p. 682. ISBN 9780763780470.
8. ^ a b Organization, World Health (2008). *Implementing the WHO Stop TB Strategy: a handbook for national TB control programmes*. Geneva:
81. ^ "BCG Vaccine Usage in Canada – Current and Historical". *Public Health Agency of Canada*. September 2010. Retrieved 30 December 2011.
82. ^ a b Teo, SS; Shingadia, DV (June 2006). "Does BCG have a role in tuberculosis control and prevention in the United Kingdom?". *Archives of Disease in Childhood*. **91** (6): 529–31. doi:10.1136/adc.2005.085043. PMC 2082765. PMID 16714729.
83. ^ "The Global Plan to Stop TB". World Health Organization. 2011. Retrieved 13 June 2011.
84. ^ Warrell, ed. by D. J. Weatherall ... [4. + 5. ed.] ed. by David A. (2005). *Sections 1 – 10.* (4. ed., paperback. ed.). Oxford [u.a.]: Oxford Univ. Press. p. 560. ISBN 978-0-19-857014-1.
85. ^ Brennan PJ, Nikaido H (1995). "The envelope of mycobacteria". *Annu. Rev. Biochem.* **64**: 29–63. doi:10.1146/annurev.bi.64.070195.000333. PMID 7574484.
86. ^ a b Menzies, D; Al Jahdali, H; Al Otaibi, B (March 2011). "Recent developments in treatment of latent tuberculosis infection". *The Indian journal of medical research*. **133** (3): 257–66. PMC 3103149. PMID 21441678.
87. ^ Arch G.; III Mainous (2010). *Management of Antimicrobials in Infectious Diseases: Impact of Antibiotic Resistance*. Totowa, N.J.: Humana Press. p. 69. ISBN 1-60327-238-0.
88. ^ Volmink J, Garner P (2007). Volmink, Jimmy, ed. "Directly observed

World Health Organization. p. 179. ISBN 9789241546676.
9. ^ a b "Tuberculosis". *World Health Organization*. 2002.
10. ^ a b c d e f g h i j k l m n o p Kumar V, Abbas AK, Fausto N, Mitchell RN (2007). *Robbins Basic Pathology* (8th ed.). Saunders Elsevier. pp. 516–522. ISBN 978-1-4160-2973-1.
11. ^ a b c d e f g h i j k l m n o p q r s t u v Lawn, SD; Zumla, AI (2 July 2011). "Tuberculosis". *Lancet*. **378** (9785): 57–72. doi:10.1016/S0140-6736(10)62173-3. PMID 21420161.
12. ^ Schiffman G (15 January 2009). "Tuberculosis Symptoms". eMedicineHealth.
13. ^ a b c d Gibson, Peter G. (ed.); Abramson, Michael (ed.); Wood-Baker, Richard (ed.); Volmink, Jimmy (ed.); Hensley, Michael (ed.); Costabel, Ulrich (ed.) (2005). *Evidence-Based Respiratory Medicine* (1st ed.). BMJ Books. p. 321. ISBN 978-0-7279-1605-1.
14. ^ Behera, D. (2010). *Textbook of Pulmonary Medicine* (2nd ed.). New Delhi: Jaypee Brothers Medical Publishers. p. 457. ISBN 978-81-8448-749-7.
15. ^ Halezeroğlu, S; Okur, E (March 2014). "Thoracic surgery for haemoptysis in the context of tuberculosis: what is the best management approach?". *Journal of Thoracic Disease*. **6** (3): 182–5. doi:10.3978/j.issn.2072-1439.2013.12.25. PMID 24624281.
16. ^ Jindal, editor-in-chief SK (2011). *Textbook of Pulmonary and Critical Care Medicine*. New Delhi: Jaypee Brothers Medical Publishers. p. 549. ISBN 978-93-5025-073-0.
17. ^ a b Golden MP, Vikram HR (2005). "Extrapulmonary tuberculosis: an overview". *American Family Physician*. **72** (9): 1761–8. PMID 16300038.
18. ^ Rockwood, RR (August 2007). "Extrapulmonary TB: what you need to know.". *The Nurse practitioner*. **32** (8): 44–9. PMID 17667766.
19. ^ Burkitt, H. George (2007). *Essential Surgery: Problems, Diagnosis & Management 4th ed*. p. 34. ISBN 9780443103452.
20. ^ Kabra, [edited by] Vimlesh Seth, S.K. (2006). *Essentials of tuberculosis in children* (3rd ed.). New Delhi: Jaypee Bros. Medical Publishers. p. 249. ISBN 978-81-8061-709-6.
21. ^ a b Ghosh, editors-in-chief, Thomas M. Habermann, Amit K. (2008). *Mayo Clinic internal medicine: concise textbook*. Rochester, MN: Mayo Clinic Scientific Press. p. 789. ISBN 978-1-4200-6749-1.
22. ^ Southwick F (10 December 2007). "Chapter 4: Pulmonary Infections". *Infectious Diseases: A Clinical Short Course, 2nd ed*. McGraw-Hill Medical Publishing Division. pp. 104, 313–4. ISBN 0-07-147722-5.
23. ^ Jindal, editor-in-chief SK (2011). *Textbook of Pulmonary and Critical Care Medicine*. New Delhi: Jaypee Brothers Medical Publishers. p. 525. ISBN 978-93-5025-073-0.
24. ^ Niederweis M, Danilchanka O, Huff J, Hoffmann C, Engelhardt H (March 2010). "Mycobacterial outer membranes: in search of proteins". *Trends in Microbiology*. **18** (3): 109–16. doi:10.1016/j.tim.2009.12.005. PMC 2931330. PMID 20060722.
25. ^ a b Madison B (2001). "Application of stains in clinical microbiology". *Biotechnic & Histochemistry*. **76** (3): 119–25. doi:10.1080/714028138. PMID 11475314.
26. ^ Parish T.; Stoker N. (1999). "Mycobacteria: bugs and bugbears (two steps forward and one step back)". *Molecular Biotechnology*. **13** (3): 191–200. doi:10.1385/MB:13:3:191. PMID 10934532.
27. ^ *Medical Laboratory Science: Theory and Practice*. New Delhi: Tata McGraw-Hill. 2000. p. 473. ISBN 0-07-463223-X.
28. ^ "Acid-Fast Stain Protocols". 21 August 2013. Retrieved 26 March 2016.
29. ^ Kommareddi S.; Abramowsky C.; Swinehart G.; Hrabak L. (1984). "Nontuberculous mycobacterial infections: comparison of the fluorescent auramine-O and Ziehl-Neelsen techniques in tissue diagnosis". *Human Pathology*. **15** (11): 1085–1089. doi:10.1016/S0046-8177(84)80253-1. PMID 6208117.
30. ^ van Lettow, Monique; Whalen, Christopher (2008). *Nutrition and health in developing countries* (2nd ed.). Totowa, N.J. (Richard D. Semba and Martin W. Bloem, eds.): Humana Press. p. 291. ISBN 978-1-934115-24-4.
31. ^ van Soolingen D., et al. (1997). "A novel pathogenic taxon of the Mycobacterium tuberculosis complex, Canetti: characterization of an exceptional isolate from Africa". *International Journal of Systematic Bacteriology*. **47** (4): 1236–45. doi:10.1099/00207713-47-4-1236. PMID 9336935.
32. ^ Niemann S., et al. (2002). "Mycobacterium africanum Subtype II Is Associated with Two Distinct Genotypes and Is a Major Cause of Human Tuberculosis in Kampala, Uganda". *Journal of Clinical Microbiology*. **40** (9): 3398–405. doi:10.1128/JCM.40.9.3398-3405.2002. PMC 130701. PMID 12202584.
33. ^ Niobe-Eyangoh S.N., et al. (2003). "Genetic Biodiversity of Mycobacterium tuberculosis Complex Strains from Patients with Pulmonary Tuberculosis in Cameroon". *Journal of Clinical Microbiology*. **41** (6): 2547–53. doi:10.1128/JCM.41.6.2547-2553.2003. PMC 156567 .
therapy for treating tuberculosis". *Cochrane Database Syst Rev* (4): CD003343. doi:10.1002/14651858.CD003343.pub3. PMID 17943789.
89. ^ Liu, Q; Abba, K; Alejandria, MM; Balanag, VM; Berba, RP; Lansang, MA (8 October 2008). Liu, Qin, ed. "Reminder systems and late patient tracers in the diagnosis and management of tuberculosis". *Cochrane database of systematic reviews (Online)* (4): CD006594. doi:10.1002/14651858.CD006594.pub2. PMID 18843723.
90. ^ O'Brien R (1994). "Drug-resistant tuberculosis: etiology, management and prevention". *Semin Respir Infect*. **9** (2): 104–12. PMID 7973169.
91. ^ Centers for Disease Control and Prevention (CDC) (2006). "Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000–2004". *MMWR Morb Mortal Wkly Rep*. **55** (11): 301–5. PMID 16557213.
92. ^ a b Maryn McKenna (12 January 2012). "Totally Resistant TB: Earliest Cases in Italy". Wired. Retrieved 12 January 2012.
93. ^ Migliori, G.B.; De Iaco, G.; Besozzi, G.; Centis, R.; Cirillo, D.M. (May 17, 2007). "First tuberculosis cases in Italy resistant to all tested drugs". *Euro surveillance: bulletin Européen sur les maladies transmissibles (European communicable disease bulletin)*. **12** (5): E070517.1. PMID 17868596.
94. ^ "Totally Drug-Resistant TB: a WHO consultation on the diagnostic definition and treatment options" (PDF). *who.int*. World Health Organization. Retrieved 25 March 2016.
95. ^ a b c d e f g h i j k l m n o p Paul Kielstra (30 June 2014). Zoe Tabary, ed. "Ancient enemy, modern imperative – A time for greater action against tuberculosis". *Economist Insights*. The Economist Group. Retrieved 1 August 2014.
96. ^ Velayati, A.A.; Masjedi, M.R.; Farnia, P.; Tabarsi, P.; Ghanavi, J.; Ziazarifi, A.H.; Hoffner, S.E. (August 2009). "Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran". *Chest*. **136** (2): 420–425. doi:10.1378/chest.08-2427. PMID 19349380.
97. ^ "Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis".
98. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2004. Retrieved 11 November 2009.
99. ^ Lambert M, et al. (2003). "Recurrence in tuberculosis: relapse or reinfection?". *Lancet Infect Dis*. **3** (5): 282–7. doi:10.1016/S1473-3099(03)00607-8. PMID 12726976.
100. ^ Wang, JY; Lee, LN; Lai, HC; Hsu, HL; Liaw, YS; Hsueh, PR; Yang, PC (15 July 2007). "Prediction of the tuberculosis reinfection proportion from the local incidence". *The Journal of Infectious Diseases*. **196** (2): 281–8. doi:10.1086/518898. PMID 17570116.
101. ^ World Health Organization (2009). "The Stop TB Strategy, case reports, treatment outcomes and estimates of TB burden". *Global tuberculosis control: epidemiology, strategy, financing*. pp. 187–300. ISBN 978-92-4-156380-2. Retrieved 14 November 2009.
102. ^ "Fact Sheets: The Difference Between Latent TB Infection and Active TB Disease". Centers for Disease Control. 20 June 2011. Retrieved 26 July 2011.
103. ^ "Global tuberculosis report 2013". *World Health Organization*. 2013.
104. ^ Lozano, R (15 December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
105. ^ a b c "Global Tuberculosis Control 2011" (PDF). *World Health Organization*. Retrieved 15 April 2012.
106. ^ World Health Organization (2009). "Epidemiology" (PDF). *Global tuberculosis control: epidemiology, strategy, financing*. pp. 6–33. ISBN 978-92-4-156380-2.
107. ^ FitzGerald, JM; Wang, L; Elwood, RK (8 February 2000). "Tuberculosis: 13. Control of the disease among aboriginal people in Canada". *Canadian Medical Association Journal*. **162** (3): 351–5. PMC 1231016. PMID 10693593.
108. ^ Quah, Stella R.; Carrin, Guy; Buse, Kent; Kristian Heggenhougen (2009). *Health Systems Policy, Finance, and Organization*. Boston: Academic Press. p. 424. ISBN 0-12-375087-3.
109. ^ Anne-Emanuelle Birn (2009). *Textbook of International Health: Global Health in a Dynamic World*. p. 261. ISBN 9780199885213.
110. ^ Centers for Disease Control and Prevention. "CDC Surveillance Slides 2012 – TB".
111. ^ World Health Organization. "Global Tuberculosis Control Report, 2006 – Annex 1 Profiles of high-burden countries" (PDF). Retrieved 13 October 2006.
112. ^ Centers for Disease Control and Prevention (12 September 2006). "2005 Surveillance Slide Set". Retrieved 13 October 2006.
113. ^ Rothschild BM, Martin LD, Lev G, et al. (August 2001). "Mycobacterium

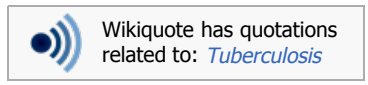
PMID 12791879.
34. ^ Thoen C, Lobue P, de Kantor I (2006). "The importance of *Mycobacterium bovis* as a zoonosis". *Veterinary Microbiology*. **112** (2–4): 339–45. doi:10.1016/j.vetmic.2005.11.047. PMID 16387455.
35. ^ Acton, Q. Ashton (2011). *Mycobacterium Infections: New Insights for the Healthcare Professional*. ScholarlyEditions. p. 1968. ISBN 978-1-4649-0122-5.
36. ^ Pfyffer, GE; Auckenthaler, R; van Embden, JD; van Soolingen, D (Oct–Dec 1998). "Mycobacterium canettii, the smooth variant of M. tuberculosis, isolated from a Swiss patient exposed in Africa". *Emerging Infectious Diseases*. **4** (4): 631–4. doi:10.3201/eid0404.980414. PMC 2640258. PMID 9866740.
37. ^ Panteix, G; Gutierrez, MC; Boschiroli, ML; Rouviere, M; Plaidy, A; Pressac, D; Porcheret, H; Chyderiotis, G; Ponsada, M; Van Oortegem, K; Salloum, S; Cabuzel, S; Bañuls, AL; Van de Perre, P; Godreuil, S (August 2010). "Pulmonary tuberculosis due to Mycobacterium microti: a study of six recent cases in France". *Journal of Medical Microbiology*. **59** (Pt 8): 984–9. doi:10.1099/jmm.0.019372-0. PMID 20488936.
38. ^ American Thoracic Society (1997). "Diagnosis and treatment of disease caused by nontuberculous mycobacteria. This official statement of the American Thoracic Society was approved by the Board of Directors, March 1997. Medical Section of the American Lung Association". *American Journal of Respiratory and Critical Care Medicine*. **156** (2 Pt 2): S1–25. doi:10.1164/ajrccm.156.2.atsstatement. PMID 9279284.
39. ^ [a] [b] [c] World Health Organization (2011). "The sixteenth global report on tuberculosis" (PDF).
40. ^ World Health Organization. "Global tuberculosis control–surveillance, planning, financing WHO Report 2006". Retrieved 13 October 2006.
41. ^ Chaisson, RE; Martinson, NA (13 March 2008). "Tuberculosis in Africa—combating an HIV-driven crisis". *The New England Journal of Medicine*. **358** (11): 1089–92. doi:10.1056/NEJMp0800809. PMID 18337598.
42. ^ Griffith D, Kerr C (1996). "Tuberculosis: disease of the past, disease of the present". *Journal of Perianesthesia Nursing*. **11** (4): 240–5. doi:10.1016/S1089-9472(96)80023-2. PMID 8964016.
43. ^ ATS/CDC Statement Committee on Latent Tuberculosis Infection (June 2000). "Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society". *MMWR. Recommendations and Reports*. **49** (RR–6): 1–51. PMID 10881762.
44. ^ van Zyl Smit, RN; Pai, M; Yew, WW; Leung, CC; Zumla, A; Bateman, ED; Dheda, K (January 2010). "Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD". *European Respiratory Journal*. **35** (1): 27–33. doi:10.1183/09031936.00072909. PMID 20044459. "These analyses indicate that smokers are almost twice as likely to be infected with TB and to progress to active disease (RR of about 1.5 for latent TB infection (LTBI) and RR of 2.0 for TB disease). Smokers are also twice as likely to die from TB (RR of about 2.0 for TB mortality), but data are difficult to interpret because of heterogeneity in the results across studies."
45. ^ Restrepo, BI (15 August 2007). "Convergence of the tuberculosis and diabetes epidemics: renewal of old acquaintances". *Clinical Infectious Diseases*. **45** (4): 436–8. doi:10.1086/519939. PMC 2900315. PMID 17638190.
46. ^ Möller, M; Hoal, EG (March 2010). "Current findings, challenges and novel approaches in human genetic susceptibility to tuberculosis". *Tuberculosis*. **90** (2): 71–83. doi:10.1016/j.tube.2010.02.002. PMID 20206579.
47. ^ Cole E, Cook C (1998). "Characterization of infectious aerosols in health care facilities: an aid to effective engineering controls and preventive strategies". *Am J Infect Control*. **26** (4): 453–64. doi:10.1016/S0196-6553(98)70046-X. PMID 9721404.
48. ^ Nicas M, Nazaroff WW, Hubbard A (2005). "Toward understanding the risk of secondary airborne infection: emission of respirable pathogens". *J Occup Environ Hyg*. **2** (3): 143–54. doi:10.1080/15459620590918466. PMID 15764538.
49. ^ [a] [b] Ahmed N, Hasnain S (2011). "Molecular epidemiology of tuberculosis in India: Moving forward with a systems biology approach". *Tuberculosis*. **91** (5): 407–3. doi:10.1016/j.tube.2011.03.006. PMID 21514230.
50. ^ [a] [b] [c] "Tuberculosis Fact sheet N°104". World Health Organization. November 2010. Retrieved 26 July 2011.
51. ^ [a] [b] "Core Curriculum on Tuberculosis: What the Clinician Should Know" (PDF) (5th ed.). Centers for Disease Control and Prevention (CDC), Division of Tuberculosis Elimination. 2011. p. 24.
52. ^ "Causes of Tuberculosis". Mayo Clinic. 21 December 2006. Retrieved 19 October 2007.
53. ^ [a] [b] Skolnik, Richard (2011). *Global health 101* (2nd ed.). Burlington, MA: Jones & Bartlett Learning. p. 253. ISBN 978-0-7637-9751-5.
54. ^ [a] [b] editors, Arch G. Mainous III, Claire Pomeroy, (2009). *Management* tuberculosis complex DNA from an extinct bison dated 17,000 years before the present". *Clin. Infect. Dis.* **33** (3): 305–11. doi:10.1086/321886. PMID 11438894.
114. ^ Pearce-Duvet J (2006). "The origin of human pathogens: evaluating the role of agriculture and domestic animals in the evolution of human disease". *Biol Rev Camb Philos Soc*. **81** (3): 369–82. doi:10.1017/S1464793106007020. PMID 16672105.
115. ^ Comas, I; Gagneux, S (October 2009). Manchester, Marianne, ed. "The past and future of tuberculosis research". *PLoS Pathogens*. **5** (10): e1000600. doi:10.1371/journal.ppat.1000600. PMC 2745564. PMID 19855821.
116. ^ Zink A, Sola C, Reischl U, Grabner W, Rastogi N, Wolf H, Nerlich A (2003). "Characterization of Mycobacterium tuberculosis Complex DNAs from Egyptian Mummies by Spoligotyping". *J Clin Microbiol*. **41** (1): 359–67. doi:10.1128/JCM.41.1.359-367.2003. PMC 149558. PMID 12517873.
117. ^ Konomi N, Lebwohl E, Mowbray K, Tattersall I, Zhang D (2002). "Detection of Mycobacterial DNA in Andean Mummies". *J Clin Microbiol*. **40** (12): 4738–40. doi:10.1128/JCM.40.12.4738-4740.2002. PMC 154635. PMID 12454182.
118. ^ Sledzik, Paul S.; Nicholas Bellantoni (June 1994). "Bioarcheological and biocultural evidence for the New England vampire folk belief" (PDF). *American Journal of Physical Anthropology*. **94** (2): 269–274. doi:10.1002/ajpa.1330940210. PMID 8085617.
119. ^ *Léon Charles Albert Calmette* at Who Named It?
120. ^ Trail RR (April 1970). "Richard Morton (1637–1698)". *Med Hist*. **14** (2): 166–74. doi:10.1017/S0025727300015350. PMC 1034037. PMID 4914685.
121. ^ *Zur Pathogenie der Impetigines. Auszug aus einer brieflichen Mitteilung an den Herausgeber*. [Müller's] *Archiv für Anatomie, Physiologie und wissenschaftliche Medicin*. 1839, page 82.
122. ^ Kentucky: Mammoth Cave long on history. *CNN*. 27 February 2004. Accessed 8 October 2006.
123. ^ [a] [b] [c] McCarthy OR (August 2001). "The key to the sanatoria". *J R Soc Med*. **94** (8): 413–7. PMC 1281640. PMID 11461990.
124. ^ Nobel Foundation. The Nobel Prize in Physiology or Medicine 1905. Accessed 7 October 2006.
125. ^ Waddington K (January 2004). "To stamp out "So Terrible a Malady": bovine tuberculosis and tuberculin testing in Britain, 1890–1939". *Med Hist*. **48** (1): 29–48. doi:10.1017/S0025727300007043. PMC 546294. PMID 14968644.
126. ^ Bonah C (2005). "The 'experimental stable' of the BCG vaccine: safety, efficacy, proof, and standards, 1921–1933". *Stud Hist Philos Biol Biomed Sci*. **36** (4): 696–721. doi:10.1016/j.shpsc.2005.09.003. PMID 16337557.
127. ^ Comstock G (1994). "The International Tuberculosis Campaign: a pioneering venture in mass vaccination and research". *Clin Infect Dis*. **19** (3): 528–40. doi:10.1093/clinids/19.3.528. PMID 7811874.
128. ^ Bloom, editor, Barry R. (1994). *Tuberculosis: pathogenesis, protection, and control*. Washington, D.C.: ASM Press. ISBN 978-1-55581-072-6.
129. ^ Persson, Sheryl (2010). *Smallpox, Syphilis and Salvation: Medical Breakthroughs That Changed the World*. ReadHowYouWant.com. p. 141. ISBN 978-1-4587-6712-7.
130. ^ editor, Caroline Hannaway, (2008). *Biomedicine in the twentieth century: practices, policies, and politics*. Amsterdam: IOS Press. p. 233. ISBN 978-1-58603-832-8.
131. ^ Shields, Thomas (2009). *General thoracic surgery* (7th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 792. ISBN 978-0-7817-7982-1.
132. ^ Lalloo UG, Naidoo R, Ambaram A (May 2006). "Recent advances in the medical and surgical treatment of multi-drug resistant tuberculosis". *Curr Opin Pulm Med*. **12** (3): 179–85. doi:10.1097/01.mcp.0000219266.27439.52. PMID 16582672.
133. ^ "Frequently asked questions about TB and HIV". *World Health Organization*. Retrieved 15 April 2012.
134. ^ "Hippocrates 3.16 Classics, MIT". Archived from the original on 11 February 2005. Retrieved 15 December 2015.
135. ^ Caldwell, Mark (1988). *The Last Crusade*. New York: Macmillan. p. 21. ISBN 0689118104.
136. ^ Bunyan, John. "The Life and Death of Mr. Badman". *Google Books*. Google. Retrieved 28 September 2016.
137. ^ [a] [b] "Public-Private Partnership Announces Immediate 40 Percent Cost Reduction for Rapid TB Test" (pdf). *World Health Organization*. 6 August 2012.
138. ^ Lawn, SD; Nicol, MP (September 2011). "Xpert® MTB/RIF assay: development, evaluation and implementation of a new rapid molecular diagnostic for tuberculosis and rifampicin resistance". *Future microbiology*. **6** (9): 1067–82. doi:10.2217/fmb.11.84. PMC 3252681 .

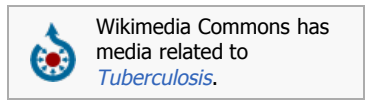
*of antimicrobials in infectious diseases: impact of antibiotic resistance* (2nd rev. ed.). Totowa, N.J.: Humana Press. p. 74. ISBN 978-1-60327-238-4.
55. ^ Houben E, Nguyen L, Pieters J (2006). "Interaction of pathogenic mycobacteria with the host immune system". *Curr Opin Microbiol*. **9** (1): 76–85. doi:10.1016/j.mib.2005.12.014. PMID 16406837.
56. ^ Khan (2011). *Essence Of Paediatrics*. Elsevier India. p. 401. ISBN 978-81-312-2804-3.
57. ^ Herrmann J, Lagrange P (2005). "Dendritic cells and *Mycobacterium tuberculosis*: which is the Trojan horse?". *Pathol Biol (Paris)*. **53** (1): 35–40. doi:10.1016/j.patbio.2004.01.004. PMID 15620608.
58. ^ Agarwal R, Malhotra P, Awasthi A, Kakkar N, Gupta D (2005). "Tuberculous dilated cardiomyopathy: an under-recognized entity?". *BMC Infect Dis*. **5** (1): 29. doi:10.1186/1471-2334-5-29. PMC 1090580. PMID 15857515.
59. ^ John Mason Good; Samuel Cooper; Augustus Sidney Doane (1835). *The Study of Medicine*. Harper. p. 32.
60. ^ *a b c d* Grosset J (2003). "Mycobacterium tuberculosis in the Extracellular Compartment: an Underestimated Adversary". *Antimicrob Agents Chemother*. **47** (3): 833–6. doi:10.1128/AAC.47.3.833-836.2003. PMC 149338. PMID 12604509.
61. ^ Bozzano F (2014). "Immunology of tuberculosis". *Mediterr J Hematol Infect Dis*. **6** (1): e2014027. doi:10.4084/MJHID.2014.027. PMC 4010607. PMID 24804000.
62. ^ Crowley, Leonard V. (2010). *An introduction to human disease: pathology and pathophysiology correlations* (8th ed.). Sudbury, Mass.: Jones and Bartlett. p. 374. ISBN 978-0-7637-6591-0.
63. ^ Anthony, Harries (2005). *TB/HIV a Clinical Manual.* (2nd ed.). Geneva: World Health Organization. p. 75. ISBN 978-92-4-154634-8.
64. ^ Jacob, JT; Mehta, AK; Leonard, MK (January 2009). "Acute forms of tuberculosis in adults". *The American Journal of Medicine*. **122** (1): 12–7. doi:10.1016/j.amjmed.2008.09.018. PMID 19114163.
65. ^ *a b* Bento, J; Silva, AS; Rodrigues, F; Duarte, R (Jan–Feb 2011). "[Diagnostic tools in tuberculosis]". *Acta Médica Portuguesa*. **24** (1): 145–54. PMID 21672452.
66. ^ *a b c d* Escalante, P (2 June 2009). "In the clinic. Tuberculosis". *Annals of Internal Medicine*. **150** (11): ITC61–614; quiz ITV616. doi:10.7326/0003-4819-150-11-200906020-01006. PMID 19487708.
67. ^ Metcalfe, JZ; Everett, CK; Steingart, KR; Cattamanchi, A; Huang, L; Hopewell, PC; Pai, M (15 November 2011). "Interferon-γ release assays for active pulmonary tuberculosis diagnosis in adults in low- and middle-income countries: systematic review and meta-analysis". *The Journal of Infectious Diseases*. 204 Suppl 4 (suppl_4): S1120–9. doi:10.1093/infdis/jir410. PMC 3192542. PMID 21996694.
68. ^ *a b* Sester, M; Sotgiu, G; Lange, C; Giehl, C; Girardi, E; Migliori, GB; Bossink, A; Dheda, K; Diel, R; Dominguez, J; Lipman, M; Nemeth, J; Ravn, P; Winkler, S; Huitric, E; Sandgren, A; Manissero, D (January 2011). "Interferon-γ release assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis". *The European Respiratory Journal*. **37** (1): 100–11. doi:10.1183/09031936.00114810. PMID 20847080.
69. ^ Chen, J; Zhang, R; Wang, J; Liu, L; Zheng, Y; Shen, Y; Qi, T; Lu, H (2011). Vermund, Sten H, ed. "Interferon-gamma release assays for the diagnosis of active tuberculosis in HIV-infected patients: a systematic review and meta-analysis". *PLoS ONE*. **6** (11): e26827. doi:10.1371/journal.pone.0026827. PMC 3206065. PMID 22069472.
70. ^ Diseases, Special Programme for Research & Training in Tropical (2006). *Diagnostics for tuberculosis: global demand and market potential.* Geneva: World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases. p. 36. ISBN 978-92-4-156330-7.
71. ^ *a b c* National Institute for Health and Clinical Excellence. *Clinical guideline 117: Tuberculosis*. London, 2011.
72. ^ Steingart, KR; Flores, LL; Dendukuri, N; Schiller, I; Laal, S; Ramsay, A; Hopewell, PC; Pai, M (August 2011). Evans, Carlton, ed. "Commercial serological tests for the diagnosis of active pulmonary and extrapulmonary tuberculosis: an updated systematic review and meta-analysis". *PLOS Medicine*. **8** (8): e1001062. doi:10.1371/journal.pmed.1001062. PMC 3153457. PMID 21857806.
73. ^ Rothel J, Andersen P (2005). "Diagnosis of latent *Mycobacterium tuberculosis* infection: is the demise of the Mantoux test imminent?". *Expert Rev Anti Infect Ther*. **3** (6): 981–93. doi:10.1586/14787210.3.6.981. PMID 16307510.
74. ^ Pai M, Zwerling A, Menzies D (2008). "Systematic Review: T-Cell–based Assays for the Diagnosis of Latent Tuberculosis Infection: An Update". *Ann. Intern. Med*. **149** (3): 1–9. doi:10.7326/0003-4819-149-3-200808050-00241. PMC 2951987. PMID 18593687.
PMID 21958145.
139. ^ "WHO says Cepheid rapid test will transform TB care". *Reuters*. 8 December 2010.
140. ^ STOPTB (5 April 2013). "The Stop TB Partnership, which operates through a secretariat hosted by the World Health Organization (WHO) in Geneva, Switzerland." (pdf).
141. ^ Lienhardt, C; Espinal, M; Pai, M; Maher, D; Raviglione, MC (November 2011). "What research is needed to stop TB? Introducing the TB Research Movement". *PLOS Medicine*. **8** (11): e1001135. doi:10.1371/journal.pmed.1001135. PMC 3226454. PMID 22140369.
142. ^ Mishra, G (2013). "Tuberculosis Prescription Practices In Private And Public Sector In India". *NJIRM*. **4** (2): 71–78.
143. ^ Anurag Bhargava; Lancelot Pinto; Madhukar Pai (2011). "Mismanagement of tuberculosis in India: Causes, consequences, and the way forward". *Hypothesis*. **9** (1): e7. doi:10.5779/hypothesis.v9i1.214.
144. ^ Amdekar, Y (July 2009). "Changes in the management of tuberculosis". *Indian journal of pediatrics*. **76** (7): 739–42. doi:10.1007/s12098-009-0164-4. PMID 19693453.
145. ^ *a b c d e f g* Courtwright, A; Turner, AN (Jul–Aug 2010). "Tuberculosis and stigmatization: pathways and interventions". *Public Health Reports*. 125 Suppl 4: 34–42. PMID 20626191.
146. ^ Mason, PH; Roy, A; Spillane, J; Singh, P (22 May 2015). "SOCIAL, HISTORICAL AND CULTURAL DIMENSIONS OF TUBERCULOSIS.". *Journal of biosocial science*: 1–27. doi:10.1017/S0021932015000115. PMID 25997539.
147. ^ *a b c* Martín Montañés, C.; Gicquel, B. (March 2011). "New tuberculosis vaccines". *Enfermedades infecciosas y microbiologia clinica*. 29 Suppl 1: 57–62. doi:10.1016/S0213-005X(11)70019-2. PMID 21420568.
148. ^ Ibanga H.; Brookes R.; Hill P.; Owiafe P.; Fletcher H.; Lienhardt C.; Hill A.; Adegbola R.; McShane H. (2006). "Early clinical trials with a new tuberculosis vaccine, MVA85A, in tuberculosis-endemic countries: issues in study design". *Lancet Infectious Diseases*. **6** (8): 522–8. doi:10.1016/S1473-3099(06)70552-7. PMID 16870530.
149. ^ Kaufmann S.H. (2010). "Future vaccination strategies against tuberculosis: Thinking outside the box". *Immunity*. **33** (4): 567–77. doi:10.1016/j.immuni.2010.09.015. PMID 21029966.
150. ^ Webber D.; Kremer M. (2001). "Stimulating Industrial R&D for Neglected Infectious Diseases: Economic Perspectives" (PDF). *Bulletin of the World Health Organization*. **79** (8): 693–801.
151. ^ Barder O.; Kremer M.; Williams H. (2006). "Advance Market Commitments: A Policy to Stimulate Investment in Vaccines for Neglected Diseases". *The Economists' Voice*. **3** (3). doi:10.2202/1553-3832.1144.
152. ^ Economic, Department of; Affairs, Social (2009). *Achieving the global public health agenda: dialogues at the Economic and Social Council*. New York: United Nations. p. 103. ISBN 978-92-1-104596-3.
153. ^ Jong, [edited by] Jane N. Zuckerman, Elaine C. (2010). *Travelers' vaccines* (2nd ed.). Shelton, CT: People's Medical Publishing House. p. 319. ISBN 978-1-60795-045-5.
154. ^ Bill and Melinda Gates Foundation Announcement (12 February 2004). "Gates Foundation Commits $82.9 Million to Develop New Tuberculosis Vaccines".
155. ^ Nightingale, Katherine (19 September 2007). "Gates foundation gives US$280 million to fight TB".
156. ^ *a b* Zumla, A; Hafner, R; Lienhardt, C; Hoelscher, M; Nunn, A (1 March 2012). "Advancing the development of tuberculosis therapy". *Nature reviews. Drug discovery*. **11** (3): 171–2. doi:10.1038/nrd3694. PMID 22378254.
157. ^ "J&J Sirturo Wins FDA Approval to Treat Drug-Resistant TB". *Bloombeg*. 31 December 2012. Retrieved 1 January 2013.
158. ^ *a b* Avorn, J (April 2013). "Approval of a tuberculosis drug based on a paradoxical surrogate measure". *JAMA*. **309** (13): 1349–1350. doi:10.1001/jama.2013.623. PMID 23430122.
159. ^ US Food and Drug Administration. "Briefing Package: NDA 204–384: Sirturo" (PDF).
160. ^ Zuckerman, Diana; Jennifer Yttri (January 2013). "Antibiotics: When science and wishful thinking collide". *Health Affairs*.
161. ^ Shivaprasad, H.L.; Palmieri, C. (January 2012). "Pathology of mycobacteriosis in birds". *The Veterinary Clinics of North America. Exotic Animal Practice*. **15** (1): 41–55, v–vi. doi:10.1016/j.cvex.2011.11.004. PMID 22244112.
162. ^ Reavill, D.R.; Schmidt, R.E. (January 2012). "Mycobacterial lesions in fish, amphibians, reptiles, rodents, lagomorphs, and ferrets with reference to animal models". *The Veterinary Clinics of North America. Exotic Animal Practice*. **15** (1): 25–40, v. doi:10.1016/j.cvex.2011.10.001. PMID 22244111.

75. ^ Jindal, editor-in-chief SK (2011). *Textbook of Pulmonary and Critical Care Medicine*. New Delhi: Jaypee Brothers Medical Publishers. p. 544. ISBN 978-93-5025-073-0.
76. ^ Amicosante, M; Ciccozzi, M; Markova, R (April 2010). "Rational use of immunodiagnostic tools for tuberculosis infection: guidelines and cost effectiveness studies". *The new microbiologica*. **33** (2): 93–107. PMID 20518271.
77. ^ Bibbins-Domingo, Kirsten; Grossman, David C.; Curry, Susan J.; Bauman, Linda; Davidson, Karina W.; Epling, John W.; García, Francisco A.R.; Herzstein, Jessica; Kemper, Alex R.; Krist, Alex H.; Kurth, Ann E.; Landefeld, C. Seth; Mangione, Carol M.; Phillips, William R.; Phipps, Maureen G.; Pignone, Michael P. (6 September 2016). "Screening for Latent Tuberculosis Infection in Adults". *JAMA*. **316** (9): 962. doi:10.1001/jama.2016.11046.
78. ^ McShane, H (12 October 2011). "Tuberculosis vaccines: beyond bacille Calmette–Guérin". *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*. **366** (1579): 2782–9. doi:10.1098/rstb.2011.0097. PMC 3146779. PMID 21893541.
79. ^ Roy, A; Eisenhut, M; Harris, RJ; Rodrigues, LC; Sridhar, S; Habermann, S; Snell, L; Mangtani, P; Adetifa, I; Lalvani, A; Abubakar, I (Aug 5, 2014). "Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis.". *BMJ (Clinical research ed.)*. **349**: g4643. doi:10.1136/bmj.g4643. PMC 4122754. PMID 25097193.
80. ^ "Vaccine and Immunizations: TB Vaccine (BCG)". Centers for Disease Control and Prevention. 2011. Retrieved 26 July 2011.
163. ^ Mitchell, M.A. (January 2012). "Mycobacterial infections in reptiles". *The Veterinary Clinics of North America. Exotic Animal Practice*. **15** (1): 101–11, vii. doi:10.1016/j.cvex.2011.10.002. PMID 22244116.
164. ^ Wobeser, Gary A. (2006). *Essentials of disease in wild animals* (1st ed.). Ames, Iowa [u.a.]: Blackwell Publishing. p. 170. ISBN 978-0-8138-0589-4.
165. ^ Ryan, T.J.; Livingstone, P.G.; Ramsey, D.S.; de Lisle, G.W.; Nugent, G.; Collins, D.M.; Buddle, B.M. (25 February 2006). "Advances in understanding disease epidemiology and implications for control and eradication of tuberculosis in livestock: the experience from New Zealand". *Veterinary Microbiology*. **112** (2–4): 211–9. doi:10.1016/j.vetmic.2005.11.025. PMID 16330161.
166. ^ White, P.C.; Böhm, M.; Marion, G.; Hutchings, M.R. (September 2008). "Control of bovine tuberculosis in British livestock: there is no 'silver bullet'". *Trends in Microbiology*. **16** (9): 420–7. doi:10.1016/j.tim.2008.06.005. PMID 18706814.
167. ^ Ward, A.I.; Judge, J.; Delahay, R.J. (1 January 2010). "Farm husbandry and badger behaviour: opportunities to manage badger to cattle transmission of Mycobacterium bovis?". *Preventive veterinary medicine*. **93** (1): 2–10. doi:10.1016/j.prevetmed.2009.09.014. PMID 19846226.
168. ^ Holt, Nathalia (24 March 2015). "The Infected Elephant in the Room". *Slate*. Retrieved 2016-04-05.
169. ^ Mikota, Susan K. "A Brief History of TB in Elephants" (PDF). *APHIS*. US Department of Agriculture. Retrieved 2016-04-05.


## External links

- Tuberculosis at DMOZ
- "Tuberculosis (TB)". Centers for Disease Control.
- "Tuberculosis (TB)". UK Health Protection Agency.




| v · t · e · | **Gram-positive bacterial infection: Actinobacteria (primarily A00–A79, 001–041, 080–109)** | | |
|---|---|---|---|
| **Actinomycineae** | **Actinomycetaceae** | | *Actinomyces israelii* (Actinomycosis · Cutaneous actinomycosis · · *Tropheryma whipplei* (Whipple's disease · · *Arcanobacterium haemolyticum* (Arcanobacterium haemolyticum infection · · *Actinomyces gerencseriae* · |
| | **Propionibacteriaceae** | | *Propionibacterium acnes* · |
| **Corynebacterineae** | **Mycobacteriaceae** | *M. tuberculosis*/ *M. bovis* | **Tuberculosis**: Ghon focus/Ghon's complex · Pott disease · *brain* (Meningitis · Rich focus · · Tuberculous lymphadenitis (Tuberculous cervical lymphadenitis · · *cutaneous* (Scrofuloderma · Erythema induratum · Lupus vulgaris · Prosector's wart · Tuberculosis cutis orificialis · Tuberculous cellulitis · Tuberculous gumma · · Lichen scrofulosorum · Tuberculid (Papulonecrotic tuberculid · · Primary inoculation tuberculosis · Miliary · Tuberculous pericarditis · Urogenital tuberculosis · Multi-drug-resistant tuberculosis · Extensively drug-resistant tuberculosis · |
| | | *M. leprae* | Leprosy: Tuberculoid leprosy · Borderline tuberculoid leprosy · Borderline leprosy · Borderline lepromatous leprosy · Lepromatous leprosy · Histoid leprosy · |
| | | **Nontuberculous** | **R1:** *M. kansasii* · *M. marinum* (Aquarium granuloma · · |
| | | | **R2:** *M. gordonae* · |
| | | | **R3:** *M. avium* complex/*Mycobacterium avium*/*Mycobacterium intracellulare*/MAP (MAI infection · · *M. ulcerans* (Buruli ulcer · · *M. haemophilum* · |
| | | | **R4/RG:** *M. fortuitum* · *M. chelonae* · *M. abscessus* · |
| | **Nocardiaceae** | | *Nocardia asteroides*/*Nocardia brasiliensis* (Nocardiosis · · *Rhodococcus equi* · |
| | **Corynebacteriaceae** | | *Corynebacterium diphtheriae* (Diphtheria · · *Corynebacterium minutissimum* (Erythrasma · · *Corynebacterium jeikeium* (Group JK corynebacterium sepsis · · |
| **Bifidobacteriaceae** | *Gardnerella vaginalis* · | | |

| v · t · e · | **Tuberculosis** |
|---|---|
| **Treatment/vaccines** | ATC code J04 · Isoniazid · 4-Aminosalicylic acid · Ethambutol · Capreomycin · Cycloserine · Rifampicin · Thioacetazone · Streptomycin · Bedaquiline · RBCG30 · Pyrazinamide · MVA85A · Rifater · |
| | Manuel de Abreu · Hermann Brehmer · Albert Calmette · Christopher Dye · Marcos Espinal · Friedrich Franz Friedmann · Max Gerson |

| | |
|---|---|
| **History of tuberculosis** | • Philip D'Arcy Hart • F. R. G. Heaf • George M. Heath • Robert Koch • Charles Mantoux • Richard Morton • Mario Raviglione • Carl Rüedi • Lucius Rüedi • Madonna Swan • Edward Livingston Trudeau • |
| **Conditions/symptoms/signs** | Caseous necrosis • Ghon focus/Ghon's complex • Giant multinucleated cell • Pott disease • Canga's bead symptom • Prosector's wart • Latent tuberculosis • Paronychia • Lupus vulgaris • Tuberculous lymphadenitis • Tuberculous meningitis • Miliary tuberculosis • |
| **Mycobacterium species** | Mycobacterium tuberculosis • Mycobacterium africanum • Mycobacterium bovis • Mycobacterium bovis BCG • Mycobacterium caprae • |
| **Type by resistance** | Multi-drug-resistant tuberculosis • Extensively drug-resistant tuberculosis • Totally drug-resistant tuberculosis • |
| **Tuberculosis diagnosis** | Ziehl–Neelsen stain • Auramine phenol stain • Culture on Löwenstein–Jensen medium and/or MGIT • Chest photofluorography • Tuberculin (Heaf test • Mantoux test • Tine test • • Interferon gamma release assay (QuantiFERON • T-SPOT.TB • • Microscopic Observation Drug Susceptibility assay • |
| **Organizations** | Adirondack Cottage Sanitarium • Campaign for Access to Essential Medicines • Center for Infectious Disease Research • Cure Cottages of Saranac Lake • Glen Lake Children's Camp • Glen Lake Sanatorium • Glenn Dale Hospital • The Global Fund to Fight AIDS, Tuberculosis and Malaria • Global Plan to Stop Tuberculosis • International Congress on Tuberculosis • Millennium Foundation • Mycobacterium Tuberculosis Structural Genomics Consortium • National Jewish Health • Phipps Institute for the Study, Treatment and Prevention of Tuberculosis • Stop TB Partnership • TB Alliance • Unitaid • |
| **Other** | 2007 tuberculosis scare • 72F fusion protein vaccine • Baumgarten-Tangl law • CFP-10 • ESAT-6 • Iowa Cow War • List of tuberculosis cases • Plombage • Preventorium • Sanatorium • Sunshine Way • Tuberculosis classification • Tuberculosis in China • Tuberculosis in popular culture • Tuberculosis radiology • Tygerberg score • World Tuberculosis Day • |

| v • t • e • | **Diseases of poverty** |
|---|---|
| **Diseases of poverty** | AIDS • Malaria • **Tuberculosis** • Measles • Pneumonia • Diarrheal diseases • |
| **Neglected diseases** | Cholera • Chagas disease • African sleeping sickness • Schistosomiasis • Dracunculiasis • River blindness • Leishmaniasis • Trachoma • |
| **Miscellaneous** | Malnutrition • Priority review voucher • |

| v • t • e • **Arthritis in children** | | |
|---|---|---|
| **Inflammatory** | **Idiopathic** | Juvenile idiopathic arthritis • |
| | **Inflammatory disease** | Inflammatory bowel disease • Sarcoidosis • Cystic fibrosis • Autoimmune hepatitis • |
| | **Hematological malignancy** | Acute lymphoblastic leukemia • Lymphoma • |
| | **Malignancy** | Neuroblastoma • |
| | **Reactive** | post-streptococcal • Rheumatic fever • postenteric, post-viral • |
| | **Infection** | Septic arthritis • Osteomyelitis • **Tuberculosis** • Lyme arthritis • |
| **Mechanical** | Osgood–Schlatter disease • | |
| **Tumours of cartilage bone or muscle** | **Benign** | Osteoid osteoma • Pigmented villonodular synovitis • Hemangioma • |
| | **Malignant** | Synovial sarcoma • Rhabdomyosarcoma • Ewing's sarcoma • |
| **Central Nervous System** | Idiopathic pain syndromes • **Local:** Complex regional pain syndrome/Reflex sympathetic dystrophy • **Generalized:** Fibromyalgia • | |

| | |
|---|---|
| **Authority control** | GND: 4130621-1 • NDL: 00565484 • |

Categories: Tuberculosis | Health in Africa | Mycobacterium-related cutaneous conditions | Healthcare-associated infections | Infectious causes of cancer

# Yellow fever

From Wikipedia, the free encyclopedia

*For other uses of "yellow fever", see Yellow fever (disambiguation).*
*"American Plague" redirects here. For the rock band, see The American Plague.*
*"Yellow plague" redirects here. For the Yellow Plague of Rhos in medieval Wales, see Maelgwn Gwynedd.*

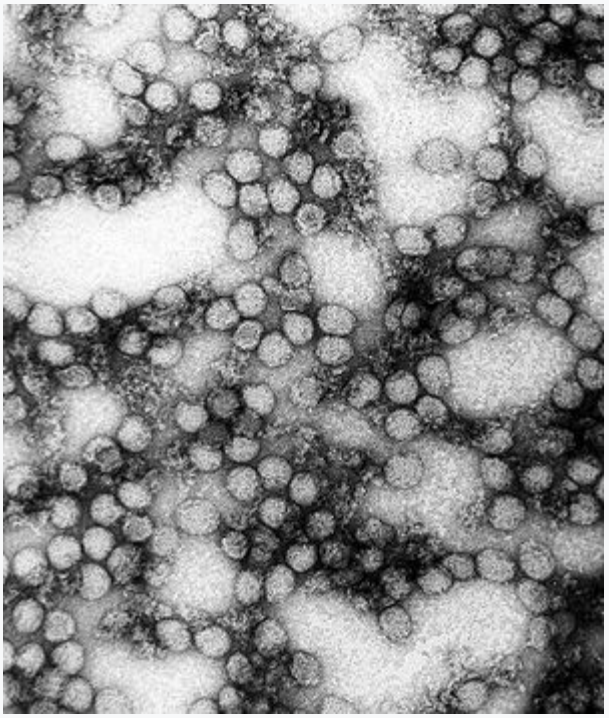
**Yellow fever** is an acute viral disease.[3] In most cases, symptoms include fever, chills, loss of appetite, nausea, muscle pains particularly in the back, and headaches.[3] Symptoms typically improve within five days.[3] In some people within a day of improving, the fever comes back, abdominal pain occurs, and liver damage begins causing yellow skin.[5] If this occurs, the risk of bleeding and kidney problems is also increased.[3]

The disease is caused by the yellow fever virus and is spread by the bite of an infected female mosquito.[3] It infects only humans, other primates, and several species of mosquitoes.[3] In cities, it is spread primarily by mosquitoes of the *Aedes aegypti* type.[3] The virus is an RNA virus of the genus *Flavivirus*.[4] The disease may be difficult to tell apart from other illnesses, especially in the early stages.[3] To confirm a suspected case, blood sample testing with polymerase chain reaction is required.[5]

A safe and effective vaccine against yellow fever exists and some countries require vaccinations for travelers.[3] Other efforts to prevent infection include reducing the population of the transmitting mosquito.[3] In areas where yellow fever is common and vaccination is uncommon, early diagnosis of cases and immunization of large parts of the population is important to prevent outbreaks.[3] Once infected, management is symptomatic with no specific measures effective against the virus.[3] The second and more severe phase results in death in up to half of people without treatment.[3][6]

Yellow fever causes 200,000 infections and 30,000 deaths every year[3] with nearly 90% of these occurring in Africa.[5] Nearly a billion people live in an area of the world where the disease is common.[3] It is common in tropical areas of South America and Africa, but not in Asia.[3][7] Since the 1980s, the number of cases of yellow fever has been increasing.[3][8] This is believed to be due to fewer people being immune, more people living in cities, people moving frequently, and

**Synonyms** yellow jack, yellow plague,[1] bronze john[2]



A TEM micrograph of the yellow fever virus (234,000X magnification)

| Classification and external resources | |
|---|---|
| **Specialty** | Infectious disease |
| **ICD-10** | A95 |
| **ICD-9-CM** | 060 |
| **DiseasesDB** | 14203 |
| **MedlinePlus** | 001365 |
| **eMedicine** | med/2432 emerg/645 |
| **MeSH** | D015004 |

changing climate.[3] The disease originated in Africa, from where it spread to South America through the slave trade in the 17th century.[1] Since the 17th century, several major outbreaks of the disease have occurred in the Americas, Africa, and Europe.[1] In the 18th and 19th centuries, yellow fever was seen as one of the most dangerous infectious diseases.[1] In 1927 yellow fever virus became the first human virus to be isolated.[4][9]



**Contents**



## Signs and symptoms [edit]

Yellow fever begins after an incubation period of three to six days.[10] Most cases only cause a mild infection with fever, headache, chills, back pain, fatigue, loss of appetite, muscle pain, nausea, and vomiting.[11] In these cases, the infection lasts only three to four days.

In 15 percent of cases, however, people enter a second, toxic phase of the disease with recurring fever, this time accompanied by jaundice due to liver damage, as well as abdominal pain.[12] Bleeding in the mouth, the eyes, and the gastrointestinal tract will cause vomit containing blood, hence the Spanish name for yellow fever, *vomito negro* ("black vomit").[13] There may also be kidney failure, hiccups, and delirium.[14][15]

The toxic phase is fatal in about 20 to 50 percent of cases, making the overall fatality rate for the disease about 3.0 to 7.5 percent.[16][17] However, the fatality rate of those with the toxic phase of the disease may exceed 50%.[18]

Surviving the infection provides lifelong immunity,[19] and normally there is no permanent organ damage.[20]

## Cause [edit]

Yellow fever is caused by the yellow fever virus, a 40- to 50-nm-wide enveloped RNA virus, the type species and namesake of the family Flaviviridae.[4] It was the first illness shown to be transmissible by filtered human serum and transmitted by mosquitoes, by Walter Reed around

| *Yellow fever virus* |
| --- |
| **Virus classification** |

| | |
|---|---|
| Group: | Group IV ((+)ssRNA) |
| Order: | *Unassigned* |
| Family: | *Flaviviridae* |
| Genus: | *Flavivirus* |
| Species: | *Yellow fever virus* |

1900.[21] The positive-sense, single-stranded RNA is around 11,000 nucleotides long and has a single open reading frame encoding a polyprotein. Host proteases cut this polyprotein into three structural (C, prM, E) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5); the enumeration corresponds to the arrangement of the protein coding genes in the genome.[22] Minimal yellow fever virus (YFV) 3'UTR region is required for stalling of the host 5'-3' exonuclease XRN1. The UTR contains PKS3 pseudoknot structure which serves as a molecular signal to stall the exonuclease and is the only viral requirement for subgenomic flavivirus RNA (sfRNA) production. The sfRNAs are a result of incomplete degradation of the viral genome by the exonuclease and are important for viral pathogenicity.[23] Yellow fever belongs to the group of hemorrhagic fevers.

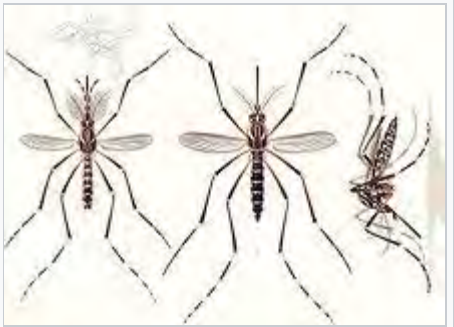
The viruses infect, amongst others, monocytes, macrophages, and dendritic cells. They attach to the cell surface via specific receptors and are taken up by an endosomal vesicle. Inside the endosome, the decreased pH induces the fusion of the endosomal membrane with the virus envelope. The capsid enters the cytosol, decays, and releases the genome. Receptor binding, as well as membrane fusion, are catalyzed by the protein E, which changes its conformation at low pH, causing a rearrangement of the 90 homodimers to 60 homotrimers.[22]

After entering the host cell, the viral genome is replicated in the rough endoplasmic reticulum (ER) and in the so-called vesicle packets. At first, an immature form of the virus particle is produced inside the ER, whose M-protein is not yet cleaved to its mature form and is therefore denoted as prM (precursor M) and forms a complex with protein E. The immature particles are processed in the Golgi apparatus by the host protein furin, which cleaves prM to M. This releases E from the complex which can now take its place in the mature, infectious virion.[22]

## Transmission [edit]

Yellow fever virus is mainly transmitted through the bite of the yellow fever mosquito *Aedes aegypti*, but other mostly Aedes mosquitoes such as the tiger mosquito (*Aedes albopictus*) can also serve as a vector for this virus. Like other arboviruses which are transmitted by mosquitoes, the yellow fever virus is taken up by a female mosquito when it ingests the blood of an infected human or other primate. Viruses reach the stomach of the mosquito, and if the virus concentration is high enough, the virions can infect epithelial cells and replicate there. From there, they reach the haemocoel (the blood system of mosquitoes) and from there the salivary glands. When the mosquito next sucks blood, it injects its saliva into the wound, and the virus reaches the bloodstream of the bitten person. Transovarial and transstadial transmission of the yellow fever virus within *A. aegypti*, that is, the transmission from a female mosquito to her eggs and then larvae, are indicated. This infection of vectors without a previous blood meal seems to play a role in single, sudden breakouts of the disease.[24]

*Aedes aegypti* feeding



Adults of the yellow fever mosquito *A. aegypti*: The male is on the left, females are on the right. Only the female mosquito bites humans to transmit the

Three epidemiologically different infectious cycles occur,[8] in which the virus is transmitted from mosquitoes to humans or other primates.[25] In the "urban cycle", only the yellow fever mosquito *A. aegypti* is involved. It is well adapted to urban areas and can also transmit other diseases, including Zika fever, dengue fever and chikungunya. The urban cycle is responsible for the major outbreaks of yellow fever that occur in Africa. Except in an outbreak in 1999 in Bolivia, this urban cycle no longer exists in South America.

Besides the urban cycle, both in Africa and South America, a sylvatic cycle (forest cycle or jungle cycle) is present, where *Aedes africanus* (in

disease.

Africa) or mosquitoes of the genus *Haemagogus* and *Sabethes* (in South America) serve as vectors. In the jungle, the mosquitoes infect mainly non-human primates; the disease is mostly asymptomatic in African primates. In South America, the sylvatic cycle is currently the only way humans can become infected, which explains the low incidence of yellow fever cases on the continent. People who become infected in the jungle can carry the virus to urban areas, where *A. aegypti* acts as a vector. Because of this sylvatic cycle, the yellow fever cannot be eradicated.[8]

In Africa, a third infectious cycle known as "savannah cycle" or intermediate cycle, occurs between the jungle and urban cycles. Different mosquitoes of the genus *Aedes* are involved. In recent years, this has been the most common form of transmission of yellow fever in Africa.[26]

There is concern about yellow fever spreading to southeast Asia, where its vector *Aedes aegypti* already occurs.[27]

## Pathogenesis [edit]

After transmission from a mosquito, the viruses replicate in the lymph nodes and infect dendritic cells in particular. From there, they reach the liver and infect hepatocytes (probably indirectly via Kupffer cells), which leads to eosinophilic degradation of these cells and to the release of cytokines. Apoptotic masses known as Councilman bodies appear in the cytoplasm of hepatocytes.[28][29]

Fatality may occur when cytokine storm, shock, and multiple organ failure follow.[16]

## Diagnosis [edit]

Yellow fever is most frequently a clinical diagnosis, made on the basis of symptoms and the diseased person's whereabouts prior to becoming ill. Mild courses of the disease can only be confirmed virologically. Since mild courses of yellow fever can also contribute significantly to regional outbreaks, every suspected case of yellow fever (involving symptoms of fever, pain, nausea and vomiting six to 10 days after leaving the affected area) is treated seriously.

If yellow fever is suspected, the virus cannot be confirmed until six to 10 days after the illness. A direct confirmation can be obtained by reverse transcription polymerase chain reaction where the genome of the virus is amplified.[5] Another direct approach is the isolation of the virus and its growth in cell culture using blood plasma; this can take one to four weeks.

Serologically, an enzyme linked immunosorbent assay during the acute phase of the disease using specific IgM against yellow fever or an increase in specific IgG-titer (compared to an earlier sample) can confirm yellow fever. Together with clinical symptoms, the detection of IgM or a fourfold increase in IgG-titer is considered sufficient indication for yellow fever. Since these tests can cross-react with other flaviviruses, like dengue virus, these indirect methods cannot conclusively prove yellow fever infection.

Liver biopsy can verify inflammation and necrosis of hepatocytes and detect viral antigens. Because of the bleeding tendency of yellow fever patients, a biopsy is only advisable *post mortem* to confirm the cause of death.

In a differential diagnosis, infections with yellow fever must be distinguished from other feverish illnesses like malaria. Other viral hemorrhagic fevers, such as Ebola virus, Lassa virus, Marburg virus, and Junin virus, must be excluded as cause.

## Prevention [edit]

Personal prevention of yellow fever includes vaccination, as well as avoidance of mosquito bites in areas where yellow fever is endemic. Institutional measures for prevention of yellow fever include vaccination programmes and measures of controlling mosquitoes. Programmes for distribution of mosquito nets for use in homes are providing reductions in cases of both malaria and yellow fever. Usage of EPA-registered insect

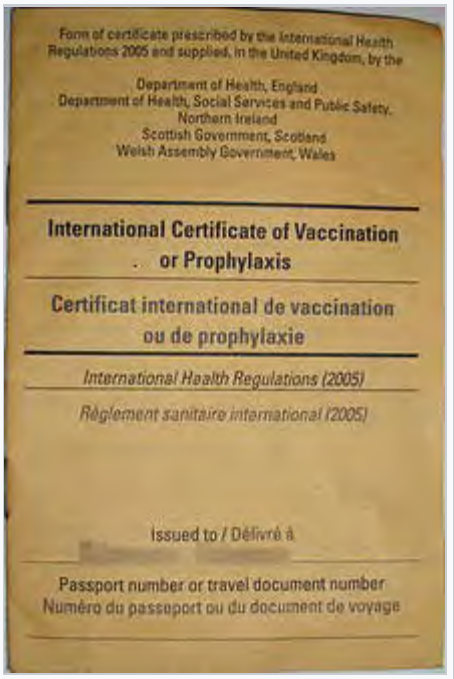
repellent is recommended when outdoors. A short duration of time is enough exposure for a potential mosquito bite. Long sleeved clothing, long pants, and socks are useful for prevention. The awareness of peak mosquito exposure is from dusk to dawn.The application of larvicides to water storage containers can help eliminate potential mosquito breeding sites. Adult mosquitos can be killed through insecticide spray usage, which decreases the transmission of yellow fever. [30]

- Use insect repellent when outdoors such as those containing DEET, picaridin, IR3535, or oil of lemon eucalyptus on exposed skin.
- Wear proper clothing to reduce mosquito bites. When weather permits, wear long-sleeves, long pants and socks when outdoors. Mosquitoes may bite through thin clothing, so spraying clothes with repellent containing permethrin or another EPA-registered repellent will give extra protection. Clothing pre-treated with permethrin is commercially available. Mosquito repellents containing permethrin are not approved for application directly to skin.
- The peak biting times for many mosquito species is dusk to dawn. However,& ;*Aedes aegypti*, one of the mosquitoes that transmits yellow fever virus, feeds during the daytime. Staying in accommodations with screened or air-conditioned rooms, particularly during peak biting times, will also reduce risk of mosquito bites.

## Vaccination [edit]

*Main article: Yellow fever vaccine*

Vaccination is recommended for those traveling to affected areas, because non-native people tend to suffer more severe illness when infected. Protection begins by the 10th day after vaccine administration in 95% of people,[31] and lasts for at least 10 years. About 81% of people are still immune after 30 years. The attenuated live vaccine stem 17D was developed in 1937 by Max Theiler.[31] The World Health Organization (WHO) recommends routine vaccinations for people living in affected areas between the ninth and 12th month after birth.[5] Up to one in four people experience fever, aches, and local soreness and redness at the site of injection.[32]


Form of certificate prescribed by the International Health Regulations 2005 and supplied, in the United Kingdom, by the

Department of Health, England
Department of Health, Social Services and Public Safety, Northern Ireland
Scottish Government, Scotland
Welsh Assembly Government, Wales

International Certificate of Vaccination or Prophylaxis

Certificat international de vaccination ou de prophylaxie

International Health Regulations (2005)

Règlement sanitaire international (2005)

Issued to / Délivré à

Passport number or travel document number
Numéro du passeport ou du document de voyage

The cover of a certificate that confirms the holder has been vaccinated against yellow fever

In rare cases (less than one in 200,000 to 300,000[31]), the vaccination can cause yellow fever vaccine–associated viscerotropic disease, which is fatal in 60% of cases. It is probably due to the genetic morphology of the immune system. Another possible side effect is an infection of the nervous system, which occurs in one in 200,000 to 300,000 cases, causing yellow fever vaccine-associated neurotropic disease, which can lead to meningoencephalitis and is fatal in less than 5%[31] of cases.[5][16]

In 2009, the largest mass vaccination against yellow fever began in West Africa, specifically Benin, Liberia, and Sierra Leone.[33][34] When it is completed in 2015, more than 12 million people will have been vaccinated against the disease.[33] According to the WHO, the mass vaccination cannot eliminate yellow fever because of the vast number of infected mosquitoes in urban areas of the target countries, but it will significantly reduce the number of people infected.[33] The WHO plans to continue the vaccination campaign in another five African countries — the Central African Republic, Ghana, Guinea, Ivory Coast, and Nigeria — and stated that about 160 million people in the continent could be at risk unless the organization acquires additional funding to support widespread vaccinations.[35]

In 2013, the WHO stated, "a single dose of vaccination is sufficient to confer life-long immunity against yellow fever disease."[36]

## Compulsory vaccination [edit]

Some countries in Asia are theoretically in danger of yellow fever epidemics (mosquitoes with the capability to transmit yellow fever and susceptible monkeys are present), although the disease does not yet occur there. To prevent introduction of the virus, some countries demand previous vaccination of foreign visitors if they have passed through yellow fever areas. Vaccination has to be proven in a vaccination certificate which is valid 10 days after the vaccination and lasts for 10 years. Although the WHO on 17 May 2013 advised that subsequent booster vaccinations are unnecessary, an older (than 10 years) certificate may not be acceptable at all border posts in all affected countries. A list of the countries that require yellow fever vaccination is published by the WHO.[37] If the vaccination cannot be conducted for some reasons, dispensation may be possible. In this case, an exemption certificate issued by a WHO-approved vaccination center is required. Although 32 of 44 countries where yellow fever occurs endemically do have vaccination programmes, in many of these countries, less than 50% of their population is vaccinated.[5]

## Vector control [edit]


Information campaign for prevention of dengue and yellow fever in Paraguay

Control of the yellow fever mosquito *A. aegypti* is of major importance, especially because the same mosquito can also transmit dengue fever and chikungunya disease. *A. aegypti* breeds preferentially in water, for example in installations by inhabitants of areas with precarious drinking water supply, or in domestic waste; especially tires, cans, and plastic bottles. These conditions are common in urban areas in developing countries.

Two main strategies are employed to reduce mosquito populations. One approach is to kill the developing larvae. Measures are taken to reduce the water accumulations in which the larva develops. Larvicides are used, as well as larvae-eating fish and copepods, which reduce the number of larvae. For many years, copepods of the genus *Mesocyclops* have been used in Vietnam for preventing dengue fever. It eradicated the mosquito vector in several areas. Similar efforts may be effective against yellow fever. Pyriproxyfen is recommended as a chemical larvicide, mainly because it is safe for humans and effective even in small doses.[5]

The second strategy is to reduce populations of the adult yellow fever mosquito. Lethal ovitraps can reduce *Aedes* populations, but with a decreased amount of pesticide because it targets the mosquitoes directly. Curtains and lids of water tanks can be sprayed with insecticides, but application inside houses is not recommended by the WHO. Insecticide-treated mosquito nets are effective, just as they are against the *Anopheles* mosquito that carries malaria.[5]

# Treatment [edit]

As for other flavivirus infections, no cure is known for yellow fever. Hospitalization is advisable and intensive care may be necessary because of rapid deterioration in some cases. Different methods for acute treatment of the disease have been shown to not be very successful; passive immunisation after emergence of symptoms is probably without effect. Ribavirin and other antiviral drugs, as well as treatment with interferons, do not have a positive effect in patients.[16] A symptomatic treatment includes rehydration and pain relief with drugs such as paracetamol (acetaminophen in the United States). Acetylsalicylic acid (aspirin) should not be given because of its anticoagulant effect, which can be devastating in the case of internal bleeding that can occur with yellow fever.

# Epidemiology [edit]

Yellow fever is common in tropical and subtropical areas of South America and Africa. Worldwide, about 600 million people live in endemic areas. The WHO estimates 200,000 cases of disease and 30,000 deaths a year occur; the number of officially reported cases is far lower.

## Africa [edit]

An estimated 90% of the infections occur on the African continent.[5] In 2008, the largest number of recorded cases were in Togo.

In March 2016, the Chinese government confirmed the first imported case in a 32-year-old man who had been in Angola, the site of an ongoing outbreak of yellow fever.[38] On 28 March 2016, ProMED-mail issued a warning that the yellow fever outbreak in Angola might spread further and that countries where dengue and the mosquito vector of dengue and yellow fever are present are at risk of a potential outbreak of yellow fever.[39] Authorities are warning that a spread to Asia could be serious since vaccine stockpiles are insufficient.[40]

Endemic range of yellow fever in Africa (2009)

Phylogenetic analysis identified seven genotypes of yellow fever viruses, and they are assumed to be differently adapted to humans and to the vector *A. aegypti*. Five genotypes (Angola, Central/East Africa, East Africa, West Africa I, and West Africa II) occur only in Africa. West Africa genotype I is found in Nigeria and the surrounding areas.[41] This appears to be especially virulent or infectious, as this type is often associated with major outbreaks. The three genotypes in East and Central Africa occur in areas where outbreaks are rare. Two recent outbreaks in Kenya (1992–1993) and Sudan (2003 and 2005) involved the East African genotype, which had remained unknown until these outbreaks occurred.[42]

## South America [edit]

In South America, two genotypes have been identified (South American genotypes I and II).[8] Based on phylogenetic analysis these two genotypes appear to have originated in West Africa[43] and were first introduced into Brazil.[44] The date of introduction into South America appears to be 1822 (95% confidence interval 1701 to 1911).[44] The historical record shows an outbreak of yellow fever occurred in Recife, Brazil, between 1685 and 1690. The disease seems to have disappeared, with the next outbreak occurring in 1849. It was likely introduced with the importation of slaves through the slave trade from Africa. Genotype I has been divided into five subclades, A through E.[45]


Endemic range of yellow fever in South America (2009)

## Asia [edit]

Though the main vector (*A. aegypti*) also occurs in tropical and subtropical regions of Asia, the Pacific and Australia, yellow fever does not occur in these parts of the globe. Proposed explanations include the idea that the strains of the mosquito in the East are less able to transmit the yellow fever virus, that immunity is present in the populations because of other diseases caused by related viruses (for example, dengue), and that the disease was never introduced because the shipping trade was insufficient, but none are considered satisfactory.[46][47] Another proposal is the absence of a slave trade to Asia on the scale of that to the Americas.[48] The trans-Atlantic slave trade was probably the means of introduction into the Western hemisphere from Africa.[49]

# History [edit]

*Main articles: History of yellow fever and Yellow fever epidemic of 1793*

Carlos Finlay

Walter Reed

The evolutionary origins of yellow fever most likely lie in Africa, with transmission of the disease from non-human primates to humans.[50][51] The virus is thought to have originated in East or Central Africa and spread from there to West Africa. As it was endemic in Africa, the natives had developed some immunity to it. When an outbreak of yellow fever would occur in an African village where colonists resided, most Europeans died, while the native population usually suffered nonlethal symptoms resembling influenza.[52] This phenomenon, in which certain populations develop immunity to yellow fever due to prolonged exposure in their childhood, is known as acquired immunity.[53] The virus, as well as the vector *A. aegypti,* were probably transferred to North and South America with the importation of slaves from Africa, part of the Columbian Exchange following European exploration and colonization.

The first definitive outbreak of yellow fever in the New World was in 1647 on the island of Barbados.[54] An outbreak was recorded by Spanish colonists in 1648 in the Yucatán Peninsula, where the indigenous Mayan people called the illness *xekik* ("blood vomit"). In 1685, Brazil suffered its first epidemic, in Recife. The first mention of the disease by the name "yellow fever" occurred in 1744.[55] McNeill argues that the environmental and ecological disruption caused by the introduction of sugar plantations created the conditions for mosquito and viral reproduction, and subsequent outbreaks of yellow fever.[56] Deforestation reduced insectivorous bird populations and other creatures that fed on mosquitoes and their eggs.

Although yellow fever is most prevalent in tropical-like climates, the northern United States were not exempted from the fever. The first outbreak in English-speaking North America occurred in New York in 1668, and a serious one afflicted Philadelphia in 1793.[57] English colonists in Philadelphia and the French in the Mississippi River Valley recorded major outbreaks in 1669, as well as those occurring later in the 18th and 19th centuries.

Sugar curing house, 1762. Sugar pots and jars on sugar plantations served as breeding place for larvae of *A. aegypti*, the vector of yellow fever.

The southern city of New Orleans was plagued with major epidemics during the 19th century, most notably in 1833 and 1853. At least 25 major outbreaks took place in the Americas during the 18th and 19th centuries, including particularly serious ones in Cartagena in 1741, Cuba in 1762 and 1900, Santo Domingo in 1803, and Memphis in 1878.[58] There has been considerable debate over whether the number of deaths caused by disease in the Haitian Revolution of the 1780s was exaggerated.[59]

Major outbreaks have also occurred in southern Europe. Gibraltar lost many to outbreaks in 1804, in 1814, and again in 1828.[60] Barcelona suffered the loss of several thousand citizens during an outbreak in 1821. Urban epidemics continued in the United States until 1905, with the last outbreak affecting New Orleans.[61]

In Colonial times and during the Napoleonic Wars, the West Indies were known as a particularly dangerous posting for soldiers due to the presence of yellow fever. The mortality rate in British garrisons in Jamaica was seven times that of garrisons in Canada, mostly because of yellow fever and other tropical disease like malaria.[62] Both English and French forces posted there were seriously affected by the "yellow jack." Wanting to regain control of the lucrative sugar trade in Saint-Domingue(Hispaniola), and with an eye on regaining France's New World empire, Napoleon sent an army under the command of his brother-in-law to Saint-Domingue to seize control after a slave revolt. The historian J. R. McNeill asserts that yellow fever accounted for about 35,000 to 45,000 casualties of these forces during the fighting.[63] Only one-third of

the French troops survived for withdrawal and return to France. Napoleon gave up on the island, and in 1804 Haiti proclaimed its independence as the second republic in the Western Hemisphere.

The yellow fever epidemic of 1793 in Philadelphia, which was then the capital of the United States, resulted in the deaths of several thousand people, more than 9% of the population. The national government fled the city, including President George Washington.[64] Additional yellow fever epidemics struck Philadelphia, Baltimore, and New York in the 18th and 19th centuries, and traveled along steamboat routes from New Orleans. They caused some 100,000–150,000 deaths in total.[65]

Yellow Fever Epidemic of 1878 can still be found in New Orleans' cemeteries.

In 1853, Cloutierville, Louisiana, had a late summer outbreak of yellow fever that quickly killed 68 of the 91 inhabitants. A local doctor concluded that some unspecified infectious agent had arrived in a package from New Orleans.[66][67] In 1858, St. Matthew's German Evangelical Lutheran Church in Charleston, South Carolina, suffered 308 yellow fever deaths, reducing the congregation by half.[68] A ship carrying persons infected with the virus arrived in Hampton Roads in southeastern Virginia in June 1855.[69] The disease spread quickly through the community, eventually killing over 3,000 people, mostly residents of Norfolk and Portsmouth. In 1873, Shreveport, Louisiana, lost almost a quarter of its population to yellow fever. In 1878, about 20,000 people died in a widespread epidemic in the Mississippi River Valley.[70] That year, Memphis had an unusually large amount of rain, which led to an increase in the mosquito population. The result was a huge epidemic of yellow fever.[71] The steamship *John D. Porter* took people fleeing Memphis northward in hopes of escaping the disease, but passengers were not allowed to disembark due to concerns of spreading yellow fever. The ship roamed the Mississippi River for the next two months before unloading her passengers.[72] The last major U.S. outbreak was in 1905 in New Orleans.[8][73]

Ezekiel Stone Wiggins, known as the Ottawa Prophet, proposed that the cause of a yellow fever epidemic in Jacksonville, Florida, in 1888, was astronomical.

> The planets were in the same line as the sun and earth and this produced, besides Cyclones, Earthquakes, etc., a denser atmosphere holding more carbon and creating microbes. Mars had an uncommonly dense atmosphere, but its inhabitants were probably protected from the fever by their newly discovered canals, which were perhaps made to absorb carbon and prevent the disease.[74]

In 1848 Josiah C. Nott suggested that yellow fever was spread by insects such as moths or mosquitoes, basing his ideas on the pattern of transmission of the disease.[75] Carlos Finlay, a Cuban doctor and scientist, proposed in 1881 that yellow fever might be transmitted by mosquitoes rather than direct human contact.[76][77] Since the losses from yellow fever in the Spanish–American War in the 1890s were extremely high, Army doctors began research experiments with a team led by Walter Reed, composed of doctors James Carroll, Aristides Agramonte, and Jesse William Lazear. They successfully proved Finlay's "mosquito hypothesis". Yellow fever was the first virus shown to be transmitted by mosquitoes. The physician William Gorgas applied these insights and eradicated yellow fever from Havana. He also campaigned against yellow fever during the construction of the Panama Canal, after a previous effort on the part of the French failed (in part due to mortality from the high incidence of yellow fever and malaria, which killed many workers).[8]

Yellow fever in Buenos Aires, 1871

Although Dr. Reed has received much of the credit in United States history books for "beating" yellow fever, he had fully credited Dr. Finlay with the discovery of the yellow fever vector, and how it might be controlled. Reed

often cited Finlay's papers in his own articles, and also gave him credit for the discovery in his personal correspondence.[78] The acceptance of Finlay's work was one of the most important and far-reaching effects of the Walter Reed Commission of 1900.[79] Applying methods first suggested by Finlay, the United States government and Army eradicated yellow fever in Cuba and later in Panama, allowing completion of the Panama Canal. While Reed built on the research of Carlos Finlay, historian François Delaporte notes that yellow fever research was a contentious issue. Scientists, including Finlay and Reed, became successful by building on the work of less prominent scientists, without always giving them the credit they were due.[80] Reed's research was essential in the fight against yellow fever. He should also receive full credit for his use of the first type of medical consent form during his experiments in Cuba, an attempt to ensure that participants knew they were taking a risk by being part of testing.[81]


Max Theiler

During 1920–23, the Rockefeller Foundation's International Health Board (IHB) undertook an expensive and successful yellow fever eradication campaign in Mexico. The IHB gained the respect of Mexico's federal government because of the success. The eradication of yellow fever strengthened the relationship between the US and Mexico, which had not been very good in the past. The eradication of yellow fever was also a major step toward better global health.[82]

In 1927, scientists isolated the yellow fever virus in West Africa.[83] Following this, two vaccines were developed in the 1930s. The vaccine 17D was developed by the South African microbiologist Max Theiler at the Rockefeller Institute in New York City. This vaccine was widely used by the U.S. Army during World War II.[54] Following the work of Ernest Goodpasture, Theiler used chicken eggs to culture the virus and won a Nobel Prize in 1951 for this achievement. A French team developed the French neurotropic vaccine (FNV), which was extracted from mouse brain tissue. Since this vaccine was associated with a higher incidence of encephalitis, FNV was not recommended after 1961. 17D is still in use and more than 400 million doses have been distributed. Little research has been done to develop new vaccines. Some researchers worry that the 60-year-old technology for vaccine production may be too slow to stop a major new yellow fever epidemic. Newer vaccines, based on vero cells, are in development and should replace 17D at some point.[5]

Using vector control and strict vaccination programs, the urban cycle of yellow fever was nearly eradicated from South America. Since 1943, only a single urban outbreak in Santa Cruz de la Sierra, Bolivia, has occurred. But, since the 1980s, the number of yellow fever cases has been increasing again, and *A. aegypti* has returned to the urban centers of South America. This is partly due to limitations on available insecticides, as well as habitat dislocations caused by climate change. It is also because the vector control program was abandoned. Although no new urban cycle has yet been established, scientists believe this could happen again at any point. An outbreak in Paraguay in 2008 was thought to be urban in nature, but this ultimately proved not to be the case.[5]

In Africa, virus eradication programs have mostly relied upon vaccination. These programs have largely been unsuccessful because they were unable to break the sylvatic cycle involving wild primates. With few countries establishing regular vaccination programs, measures to fight yellow fever have been neglected, making the future spread of the virus more likely.[5]

## Research [edit]

In the hamster model of yellow fever, early administration of the antiviral ribavirin is an effective early treatment of many pathological features of the disease.[84] Ribavirin treatment during the first five days after virus infection improved survival rates, reduced tissue damage in the liver and spleen, prevented hepatocellular steatosis, and normalised levels of alanine aminotransferase, a liver damage marker. The mechanism of action of ribavirin in reducing liver pathology in yellow fever virus infection may be similar to its activity in treatment of hepatitis C, a related virus.[84] Because ribavirin had failed to improve survival in a virulent rhesus model of yellow fever infection, it had been previously discounted as a possible

therapy.[85] Infection was reduced in mosquitoes with the wMel strain of Wolbachia.[86]

In the past, yellow fever has been researched by several countries as a potential biological weapon.[87]

## References [edit]


1. ^ a b c d Oldstone, Michael (2009). *Viruses, Plagues, and History: Past, Present and Future*. Oxford University Press. pp. 102–4. ISBN 9780199758494.
2. ^ Bazin, Hervé (2011). *Vaccination : a history from Lady Montagu to genetic engineering*. Montrouge: J. Libbey Eurotext. p. 407. ISBN 9782742007752.
3. ^ a b c d e f g h i j k l m n o p q r s "Yellow fever Fact sheet N°100". *World Health Organization*. May 2013. Retrieved 23 February 2014.
4. ^ a b c Lindenbach, B. D.; et al. (2007). "Flaviviridae: The Viruses and Their Replication". In Knipe, D. M.; P. M. Howley. *Fields Virology* (5th ed.). Philadelphia, PA: Lippincott Williams & Wilkins. p. 1101. ISBN 0-7817606-0-7.
5. ^ a b c d e f g h i j k l Tolle MA (April 2009). "Mosquito-borne diseases". *Curr Probl Pediatr Adolesc Health Care*. **39** (4): 97–140. doi:10.1016/j.cppeds.2009.01.001. PMID 19327647.
6. ^ "Frequently Asked Questions About Yellow Fever". *CDC*. August 21, 2015. Retrieved 18 March 2016.
7. ^ "CDC Yellow Fever". Retrieved 2012-12-12.
8. ^ a b c d e f Barrett AD, Higgs S (2007). "Yellow fever: a disease that has yet to be conquered". *Annu. Rev. Entomol.* **52**: 209–29. doi:10.1146/annurev.ento.52.110405.091454. PMID 16913829.
9. ^ Sfakianos, Jeffrey; Hecht, Alan (2009). Babcock, Hilary, ed. *West Nile virus*. Foreword by David Heymann (2nd ed.). New York: Chelsea House. p. 17. ISBN 9781604132540.
10. ^ "CDC: Yellow fever—Symptoms and treatment". Retrieved 2010-11-10.
11. ^ "Yellow fever". WHO. Retrieved 2009-08-13.
12. ^ *Control of Communicable Diseases Manual* (20th ed.). Amer Public Health Assn. ISBN 978-0875530185.
13. ^ Chastel C (August 2003). "[Centenary of the discovery of yellow fever virus and its transmission by a mosquito (Cuba 1900–1901)]". *Bull Soc Pathol Exot* (in French). **96** (3): 250–6. PMID 14582304.
14. ^ Dr. Irwin Sherman "Twelve Diseases that Changed Our World". P. 144. ASM Press. 2007. ISBN 978-1-55581-466-3. OCLC 141178241.
15. ^ Franklin, Jon; Sutherland, John. "Guinea Pig Doctors: The Drama of Medical Research Through Self-Experimentation" by Jon Franklin (Author), John Sutherland (Author) Publisher: William Morrow & Co (March 1984) ISBN 068-8-02666-4
16. ^ a b c d Monath TP (April 2008). "Treatment of yellow fever". *Antiviral Res.* **78** (1): 116–24. doi:10.1016/j.antiviral.2007.10.009. PMID 18061688.
17. ^ "Yellow fever, Complications," Mayo Clinic, 2014-08-20. Retrieved 2016-07-25.
18. ^ Tomori O (2004). "Yellow fever: the recurring plague". *Crit Rev Clin Lab Sci*. **41** (4): 391–427. doi:10.1080/10408360490497474. PMID 15487593.
19. ^ Modrow, S.; et al. (2002). *Molekulare Virologie – Eine Einführung für Biologen und Mediziner* (2nd ed.). Spektrum Akademischer Verlag. p. 182. ISBN 3-8274-1086-X.
20. ^ Rogers DJ, Wilson AJ, Hay SI, Graham AJ (2006). "The global distribution of yellow fever and dengue". *Adv. Parasitol.* **62**: 181–220. doi:10.1016/S0065-308X(05)62006-4. PMC 3164798. PMID 16647971.
21. ^ Staples JE, Monath TP (Aug 27, 2008). "Yellow fever: 100 years of discovery". *JAMA: The Journal of the American Medical Association*. **300** (8): 960–2. doi:10.1001/jama.300.8.960. PMID 18728272.
22. ^ a b c Sampath A, Padmanabhan R (January 2009). "Molecular targets for flavivirus drug discovery". *Antiviral Research*. **81** (1): 6–15. doi:10.1016/j.antiviral.2008.08.004. PMC 2647018. PMID 18796313.
23. ^ Silva, Patricia A. G. C. (2010). "An RNA Pseudoknot Is Required for Production of Yellow Fever Virus Subgenomic RNA by the Host Nuclease XRN1". *Journal of Virology*. **84**: 11395–11406. doi:10.1128/jvi.01047-10. PMC 2953177. PMID 20739539.
24. ^ Fontenille D, Diallo M, Mondo M, Ndiaye M, Thonnon J (1997). "First evidence of natural vertical transmission of yellow fever virus in *Aedes aegypti*, its epidemic vector". *Transactions of the Royal Society of Tropical Medicine and Hygiene*. **91** (5): 533–5. doi:10.1016/S0035-9203(97)90013-4. PMID 9463659.
25. ^ "Infectious Diseases Related to Travel". *Yellow Book*. Centers for Disease Control and Prevention. Retrieved 20 March 2016.
26. ^ "Yellow fever fact sheet". *WHO—Yellow fever*. Retrieved 2006-04-18.
27. ^ "Ebola outbreak Alert and response operations Diseases Biorisk reduction Yellow fever : a current threat". *WHO*. Retrieved 4 August 2016.

28. ^ Ryan, K. J.; C. G. Ray., eds. (2004). *Sherris Medical Microbiology* (4th ed.). McGraw Hill. ISBN 0-8385-8529-9.
29. ^ Quaresma JA, Barros VL, Pagliari C, Fernandes ER, Guedes F, Takakura CF, Andrade HF, Vasconcelos PF, Duarte MI (2006). "Revisiting the liver in human yellow fever: virus-induced apoptosis in hepatocytes associated with TGF-beta, TNF-alpha and NK cells activity". *Virology*. **345** (1): 22–30. doi:10.1016/j.virol.2005.09.058. PMID 16278000.
30. ^ "Prevention | Yellow Fever | CDC". *www.cdc.gov*. Retrieved 2016-10-26.
31. ^ *a b c d* Barrett AD, Teuwen DE (June 2009). "Yellow fever vaccine – how does it work and why do rare cases of serious adverse events take place?". *Current Opinion in Immunology*. **21** (3): 308–13. doi:10.1016/j.coi.2009.05.018. PMID 19520559.
32. ^ Yellow Fever Vaccine Information Statement. Centers for Disease Control and Prevention. March 30, 2011.
33. ^ *a b c* "Twelve million West Africans get yellow fever vaccines". BBC News. 23 November 2009. Retrieved 23 November 2009.
34. ^ "West Africa: 12m to be vaccinated for yellow fever". Times Live. 22 November 2009. Archived from the original on November 24, 2009. Retrieved 20 August 2014.
35. ^ Nebehay, S. (17 November 2009). "Mass vaccinations to fight yellow fever in Africa". Reuters. Retrieved 24 November 2009.
36. ^ WHO | Yellow fever vaccination booster not needed. Who.int (2013-05-17). Retrieved on 2014-05-12.
37. ^ "Country list: Yellow fever vaccination requirements and recommendations; malaria situation; and other vaccination requirements" (PDF). WHO. 2013. p. 32. Retrieved 2015-04-12.
38. ^ "Yellow fever - China: ex Angola, 1st case in Asia". *ProMED-mail*. International Society for Infectious Diseases. Retrieved 17 March 2016.
39. ^ "Yellow fever - countries with dengue: alert 2016-03-28 20:39:56 Archive Number: Archive Number: 20160328.4123983". *ProMED-mail*. International Society for Infectious Diseases. Retrieved 29 March 2016.
40. ^ "Yellow fever - countries with dengue: alert 2016-03-28 20:39:56 Archive Number: Archive Number: 20160328.4123983". *ProMED-mail*. International Society for Infectious Diseases. Retrieved 29 March 2016.
41. ^ Mutebi JP, Barrett AD (2002). "The epidemiology of yellow fever in Africa". *Microbes Infect*. **4** (14): 1459–1468. doi:10.1016/S1286-4579(02)00028-X. PMID 12475636.
42. ^ Ellis BR, Barrett AD (2008). "The enigma of yellow fever in East Africa". *Rev Med Virol*. **18** (5): 331–346. doi:10.1002/rmv.584. PMID 18615782.
43. ^ Mutebi JP, Rijnbrand RC, Wang H, Ryman KD, Wang E, Fulop LD, Titball R, Barrett AD (2004). "Genetic relationships and evolution of genotypes of yellow fever virus and other members of the yellow fever virus group within the *Flavivirus* genus based on the 3' noncoding region". *J Virol*. **78** (18): 9652–9665. doi:10.1128/JVI.78.18.9652-9665.2004. PMC 515011. PMID 15331698.
44. ^ *a b* Auguste AJ, Lemey P, Pybus OG, Suchard MA, Salas RA, Adesiyun AA, Barrett AD, Tesh RB, Weaver SC, Carrington CV (2010). "Yellow fever virus maintenance in Trinidad and its dispersal throughout the Americas". *J Virol*. **84** (19): 9967–9977. doi:10.1128/JVI.00588-10. PMC 2937779. PMID 20631128.
45. ^ de Souza RP, Foster PG, Sallum MA, Coimbra TL, Maeda AY, Silveira VR, Moreno ES, da Silva FG, Rocco IM, Ferreira IB, Suzuki A, Oshiro FM, Petrella SM, Pereira LE, Katz G, Tengan CH, Siciliano MM, Dos Santos CL (2010). "Detection of a new yellow fever virus lineage within the South American genotype I in Brazil". *J Med Virol*. **82** (1): 175–185. doi:10.1002/jmv.21606. PMID 19950229.
46. ^ Vainio J.; F. Cutts, eds. (1998). *Yellow Fever*. WHO Division of Emerging and other Communicable Diseases Surveillance and Control.
47. ^ Monath, T. P. (1989). "The absence of yellow fever in Asia: hypotheses. A cause for concern?". *Virus Inf Exch Newslett*: 106–7.
48. ^ Cathey JT, Marr JS (2014). "Yellow fever, Asia and the East African slave trade". *Trans R Soc Trop Med Hyg*. **108** (5): 252–7. doi:10.1093/trstmh/tru043. PMID 24743951.
49. ^ Bryant JE, Holmes EC, Barrett AD (2007). "Out of Africa: a molecular perspective on the introduction of yellow fever virus into the Americas". *PLoS Pathog*. **3** (5): e75. doi:10.1371/journal.ppat.0030075. PMC 1868956. PMID 17511518.
50. ^ Gould EA, de Lamballerie X, Zanotto PM, Holmes EC (2003). "Origins, evolution, coadaptations within the genus Flavivirus". *Advances in Virus Research*. **59**: 277–314. doi:10.1016/S0065-3527(03)59008-X. ISBN 9780120398591. PMID 14696332.
51. ^ Bryant, JE; Holmes, EC; Barrett, AD (18 May 2007). "Out of Africa: a molecular perspective on the introduction of yellow fever virus into the Americas.". *PLOS Pathogens*. **3** (5): e75. doi:10.1371/journal.ppat.0030075. PMC 1868956. PMID 17511518.
52. ^ Oldstone, M. (1998). *Viruses, Plagues, and History,* New York: Oxford University Press.
53. ^ McNeill, J. R. (2010). *Mosquito Empires: Ecology and war in the greater Caribbean, 1620–1914*. NY: Cambridge University Press. pp. 44–45.

54. ^ [a] [b] McNeill, J. R. (1 April 2004). "Yellow Jack and Geopolitics: Environment, Epidemics, and the Struggles for Empire in the American Tropics, 1650–1825". *OAH Magazine of History*. **18** (3): 9–13. doi:10.1093/maghis/18.3.9.
55. ^ The earliest mention of "yellow fever" appears in a manuscript of 1744 by Dr. John Mitchell of Virginia; copies of the manuscript were sent to Mr. Cadwallader Colden, a physician in New York, and to Dr. Benjamin Rush of Philadelphia; the manuscript was eventually printed (in large part) in 1805 and reprinted in 1814. See:
    - (John Mitchell) (1805) (Mitchell's account of the Yellow Fever in Virginia in 1741–2), *The Philadelphia Medical Museum,* 1 (1) : 1–20.
    - (John Mitchell) (1814) "Account of the Yellow fever which prevailed in Virginia in the years 1737, 1741, and 1742, in a letter to the late Cadwallader Colden, Esq. of New York, from the late John Mitchell, M.D.F.R.S. of Virginia," *American Medical and Philosophical Register* … , **4** : 181–215. The term "yellow fever" appears on p. 186. On p. 188, Mitchell mentions "… the distemper was what is generally called the yellow fever in America." However, on pages 191–192, he states "… I shall consider the cause of the yellowness which is so remarkable in this distemper, as to have given it the name of the Yellow Fever."

    It should be noted, however, that Dr. Mitchell misdiagnosed the disease that he observed and treated, and that the disease was probably Weil's disease or hepatitis. See: Jarcho S (1957). "John Mitchell, Benjamin Rush, and yellow fever". *Bull Hist Med*. **31** (2): 132–6. PMID 13426674.
56. ^ McNeill, John (2010). *Mosquito Empires: Ecology and War in the Greater Caribbean, 1620-1914*. New York, NY: Cambridge University Press. ISBN 978-0-511-67268-2.
57. ^ Miller, Jacquelyn C (2005). "The Wages of Blackness: African American Workers and the Meanings of Race during Philadelphia's 1793 Yellow Fever Epidemic". *The Pennsylvania Magazine of History and Biography*. **129** (2): 163–194.
58. ^ John S. Marr, and John T. Cathey. "The 1802 Saint-Domingue yellow fever epidemic and the Louisiana Purchase." *Journal of Public Health Management and Practice* 19#.1 (2013): 77-82. online
59. ^ Philippe R. Girard (2011). *The Slaves Who Defeated Napoleon: Toussaint Louverture and the Haitian War of Independence, 1801-1804*. University of Alabama Press. pp. 179–80.
60. ^ "Gibraltar's 1804 Yellow Fever Scourge: The Search for Scapegoats". *Oxford Journals—Journal of the History of Medicine and Allied Sciences*. Retrieved 2013-04-05.
61. ^ John Pierce & Jim Writer (2005). *Yellow Jack: How Yellow Fever ravaged America and Walter Reed Discovered Its Deadly Secrets*. Hoboken: John Wiley & Sons. p. 3.
62. ^ McNeill, JR (2002). "Yellow fever and geopolitics: environment, epidemics, and the struggles for empire in the American tropics, 1650-1900.". *History now (Christchurch, N.Z.)*. **8** (2): 10–6. PMID 20690235.
63. ^ McNeill, J.R. (2010). *Moaquito Empires: Ecology and war in the greater Caribbean, 1620–1914*. Cambridge University Press. p. 259.
64. ^ "Yellow Fever Attacks Philadelphia, 1793". *EyeWitness to History*. Retrieved 2009-08-14.
65. ^ Patterson KD (1992). "Yellow fever epidemics and mortality in the United States, 1693–1905". *Social science & medicine (1982)*. **34** (8): 855–865. doi:10.1016/0277-9536(92)90255-O. PMID 1604377.
66. ^ The Transactions of the American Medical Association, Volume IX, TK and PG Collins, 1856, page 704, "Yellow Fever at the Village of Cloutierville, La, in the Years 1853 and 1854" by Samuel O. Scruggs, M.D.
67. ^ New Orleans Genesis June 1970, page 261-262, "Cloutierville Yellow Fever Deaths, 1853"
68. ^ St. Matthew's Evangelical Lutheran Church: 125 Years of Christian Service, 1967.
69. ^ Mauer HB. "Mosquito control ends fatal plague of yellow fever". etext.lib.virginia.edu. Retrieved 2007-06-11. (undated newspaper clipping).
70. ^ Crosby, Molly Caldwell (2006). *The American Plague*. New York: Berkley Publishing Group. p. 75.
71. ^ "Yellow Fever — the plague of Memphis". HistoricMemphis.com. Retrieved August 20, 2014.
72. ^ Barnes, E. (2005). *Diseases and Human Evolution*. Albuquerque: University of New Mexico. ISBN 0-8263-3065-7.
73. ^ "The Tennessee Encyclopedia of History and Culture:Yellow Fever Epidemics". Tennessee Historical Society. Retrieved June 20, 2013.
74. ^ John W. Cowart, "Yellow Jack in Jacksonville, Yellow Fever visited Duval County, Florida, in 1888", Historical Text Archive
75. ^ Josiah C. Nott (1848) "Yellow Fever contrasted with Bilious Fever - Reasons for believing it a disease sui generis - Its mode of Propagation - Remote Cause - Probable insect or animalcular origin" "The New Orleans Medical and Surgical Journal," "4" : 563-601.
76. ^ Carlos Juan Finlay (presented: August 14, 1881 ; published: 1882) "El mosquito hipoteticamente considerado como agente de trasmision de la fiebre amarilla" (The mosquito hypothetically considered as an agent in the transmission of yellow fever) *Anales de la Real Academia de Ciencias Médicas, Físicas y Naturales de la Habana*, **18** : 147–169. Available on-line in English at:
    - Charles Finlay, with Rudolph Matas, translator (1881) "The mosquito hypothetically considered as an agent in the transmission of yellow fever poison," *New Orleans Medical and Surgical Journal,* **9** : 601–616.

- Delta Omega.org
77. ^ Chaves-Carballo E (2005). "Carlos Finlay and yellow fever: triumph over adversity". *Mil Med*. **170** (10): 881–5. doi:10.7205/milmed.170.10.881. PMID 16435764.
78. ^ Pierce, J.R.; Writer, J. (2005). *Yellow Jack: How Yellow Fever Ravaged America and Walter Reed Discovered Its Deadly Secrets*. Wiley. ISBN 0-471-47261-1.
79. ^ "Phillip S. Hench Walter Reed Yellow Fever Collection". *UVA Health Sciences: Historical Collections*. Retrieved 2006-05-06.
80. ^ Delaporte, Francois (1991). *The History of Yellow Fever: An Essay on the Birth of Tropical Medicine*. Cambridge: MIT Press. pp. 89–90.
81. ^ Crosby, Molly Caldwell (2006). *The American Plague:*. New York: Berkley Publishing Group. p. 177.
82. ^ Birn AE, Solórzano A (1999). "Public health policy paradoxes: science and politics in the Rockefeller Foundation's hookworm campaign in Mexico in the 1920s". *Soc Sci Med*. **49** (9): 1197–213. doi:10.1016/s0277-9536(99)00160-4. PMID 10501641.
83. ^ L. Bigon (2014), "Transnational Networks of Administrating Disease and Urban Planning in West Africa: The Inter-Colonial Conference on Yellow Fever, Dakar, 1928" GeoJournal, 79 (1):103-111.
84. ^ *a b* Sbrana E, Xiao SY, Guzman H, Ye M, Travassos da Rosa AP, Tesh RB (2004). "Efficacy of post-exposure treatment of yellow fever with ribavirin in a hamster model of the disease". *Am J Trop Med Hyg*. **71** (3): 306–12. PMID 15381811.
85. ^ Huggins JW (1989). "Prospects for treatment of viral hemorrhagic fevers with ribavirin, a broad-spectrum antiviral drug". *Rev Infect Dis*. **11** (Suppl 4): S750–61. doi:10.1093/clinids/11.Supplement_4.S750. PMID 2546248.
86. ^ http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0001892 Impact of Wolbachia on Infection with Chikungunya and Yellow Fever Viruses in the Mosquito Vector Aedes aegypti
87. ^ Endicott, S.L.; Hageman, E. (1998). *The United States and Biological Warfare: Secrets from the Early Cold War and Korea*. Indiana University Press. ISBN 0-253-33472-1.


## Further reading [edit]


- Crosby, M. (2006). *The American Plague: The Untold Story of Yellow Fever, the Epidemic that Shaped Our History*. New York: The Berkley Publishing Group. ISBN 0-425-21202-5.
- Espinosa, M. (2009). *Epidemic Invasions: Yellow Fever and the Limits of Cuban Independence, 1878–1930*. Chicago: University of Chicago Press. ISBN 978-0-226-21811-3.
- Murphy, J. (2003). *An American Plague: The True and Terrifying Story of the Yellow Fever Epidemic of 1793*. New York: Clarion Books. ISBN 0-395-77608-2.
- Nuwer, D. S. (2009). *Plague Among the Magnolias: The 1878 Yellow Fever Epidemic in Mississippi*. University of Alabama Press. ISBN 978-0-8173-1653-2.


## External links [edit]

- Yellow fever at DMOZ
- Finlay CJ (2012). "The Mosquito Hypothetically Considered as the Transmitting Agent of Yellow Fever". *MEDICC Review*. **14** (1): 56–9.
- "Philip S. Hench Walter Reed Yellow Fever Collection." Claude Moore Health Sciences Library, University of Virginia
- "Yellow Fever and the Reed Commission." Claude Moore Health Sciences Library, University of Virginia
- "*Yellow fever virus*". *NCBI Taxonomy Browser*. 11089.

*Medicine portal*

*Viruses portal*

Wikivoyage has a travel guide for *Yellow fever*.

| v · t · e | **Zoonotic viral diseases (A80–B34, 042–079)** | | |
|---|---|---|---|
| | | *Bunyaviridae* | Arbovirus encephalitides: La Crosse encephalitis (LACV · · Batai virus (BATV) · Bwamba Fever (BWAV) · California encephalitis (CEV · · Jamestown Canyon virus · Tete virus · Tahyna virus (TAHV) · Viral hemorrhagic fevers: Rift Valley fever (RVFV · · Bunyamwera fever (BUNV) · Ngari virus (NRIV) · |

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|---|---|---|---|
| **Arthropod-borne** | **Mosquito-borne** | *Flaviviridae* | Arbovirus encephalitides: Japanese encephalitis (JEV · · Australian encephalitis (MVEV · KUNV · · Saint Louis encephalitis (SLEV · · West Nile fever (WNV · · Viral hemorrhagic fevers: Dengue fever (DENV-1-4 · · **Yellow fever** (YFV · · Zika fever (Zika virus · · |
| | | *Togaviridae* | Arbovirus encephalitides: Eastern equine encephalomyelitis (EEEV · · Western equine encephalomyelitis (WEEV · · Venezuelan equine encephalomyelitis (VEEV · · Chikungunya (CHIKV · · O'Nyong-nyong fever (ONNV · · Ross River fever (RRV · · Semliki Forest virus · Sindbis fever · |
| | | *Reoviridae* | Banna virus encephalitis · |
| | **Tick-borne** | *Bunyaviridae* | Viral hemorrhagic fevers: Crimean–Congo hemorrhagic fever (CCHFV · · Heartland virus · Bhanja virus · Sandfly fever Naples virus · Lone Star virus · Tete virus · |
| | | *Flaviviridae* | Arbovirus encephalitides: Tick-borne encephalitis (TBEV · · Powassan encephalitis (POWV · · Viral hemorrhagic fevers: Omsk hemorrhagic fever (OHFV · · Kyasanur forest disease (KFDV · AHFV · · Langat virus (LGTV) · |
| | | *Reoviridae* | Colorado tick fever (CTFV · · Kemerovo tickborne viral fever · |
| | **Sandfly-borne** | *Bunyaviridae* | Adria virus (ADRV) · Pappataci fever (Toscana virus · · Sandfly fever Naples virus · Oropouche fever (Oropouche virus · · SFTS virus · |
| | | *Rhabdoviridae* | Chandipura virus · |
| **Mammal-borne** | **Rodent-borne** | *Arenaviridae* | Viral hemorrhagic fevers: Lassa fever (LASV · · Venezuelan hemorrhagic fever (GTOV · · Argentine hemorrhagic fever (JUNV · · Brazilian hemorrhagic fever (SABV · · Bolivian hemorrhagic fever (MACV · · LUJV · CHPV · |
| | | *Bunyaviridae* | Hemorrhagic fever with renal syndrome (DOBV · HTNV · PUUV · SEOV · AMRV · · Hantavirus pulmonary syndrome (ANDV · SNV · · |
| | **Bat-borne** | *Filoviridae* | Viral hemorrhagic fevers: Ebola virus disease · BDBV · EBOV · SUDV · TAFV · Marburg virus disease · MARV · RAVV · |
| | | *Rhabdoviridae* | Rabies (ABLV · MOKV · DUVV · LBV · · CHPV · |
| | | *Paramyxoviridae* | Henipavirus encephalitis (HeV · NiV · · |

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|---|---|---|---|
| | *Primate-borne* | *Herpesviridae* | Herpes B virus · |
| | | *Retroviridae* | Simian foamy virus · HTLV-1 · HTLV-2 · |
| | | *Poxviridae* | Tanapox · Yaba monkey tumor virus · |
| | **Multiple vectors** | *Rhabdoviridae* | Rabies (RABV · · Mokola virus · |
| | | *Poxviridae* | Monkeypox · |
| **Authority control** | GND: 4276496-8 · NDL: 00568824 · | | |

Categories: Yellow fever | Biological weapons | Epidemics

# Zika fever

From Wikipedia, the free encyclopedia

*"Zika" redirects here. For other uses, see Zika (disambiguation).*

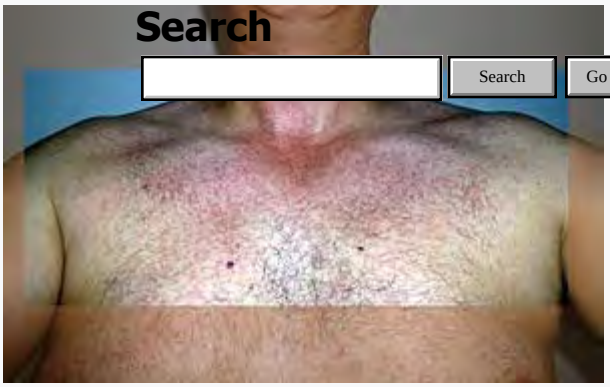
**Zika fever** (also known as **Zika virus disease** and simply **Zika**) is an infectious disease caused by the Zika virus.[1] Most cases have no symptoms, but when present they are usually mild and can resemble dengue fever.[1][2] Symptoms may include fever, red eyes, joint pain, headache, and a maculopapular rash.[1][3][4] Symptoms generally last less than seven days.[3] It has not caused any reported deaths during the initial infection.[2] Mother-to-child transmission during pregnancy can cause microcephaly and other brain malformations in some babies.[5][6] Infections in adults have been linked to Guillain–Barré syndrome (GBS).[2]

Zika fever is mainly spread via the bite of mosquitoes of the *Aedes* type.[3] It can also be sexually transmitted and potentially spread by blood transfusions.[3][7] Infections in pregnant women can spread to the baby.[5][6][8] Diagnosis is by testing the blood, urine, or saliva for the presence of Zika virus RNA when the person is sick.[1][3]

Prevention involves decreasing mosquito bites in areas where the disease occurs and proper use of condoms.[3][7] Efforts to prevent bites include the use of insect repellent, covering much of the body with clothing, mosquito nets, and getting rid of standing water where mosquitoes reproduce.[1] There is no effective vaccine.[3] Health officials recommended that women in areas affected by the 2015–16 Zika outbreak consider putting off pregnancy and that pregnant women not travel to these areas.[3][9] While there is no specific treatment, paracetamol (acetaminophen) may help with the symptoms.[3] Admission to hospital is rarely necessary.[2]

The virus that causes the disease was first isolated in Africa in 1947.[10] The first documented outbreak among people occurred in 2007 in the Federated States of Micronesia.[3] As of January 2016, the disease was occurring in twenty regions of the Americas.[3] It is also known to occur in Africa, Asia, and the Pacific.[1] Due to an outbreak which started in Brazil in 2015, the World Health Organization declared it a Public Health Emergency of International Concern in February 2016.[11]

**Zika fever**



Rash during Zika fever infection

| | |
|---|---|
| **Pronunciation** | Zika /ˈziːkə/ |
| **Classification and external resources** | |
| **Specialty** | Infectious disease |
| **ICD-10** | U06 |
| **ICD-9-CM** | 066.3 |
| **DiseasesDB** | 36480 |
| **MedlinePlus** | 007666 |
| **MeSH** | D000071243 |

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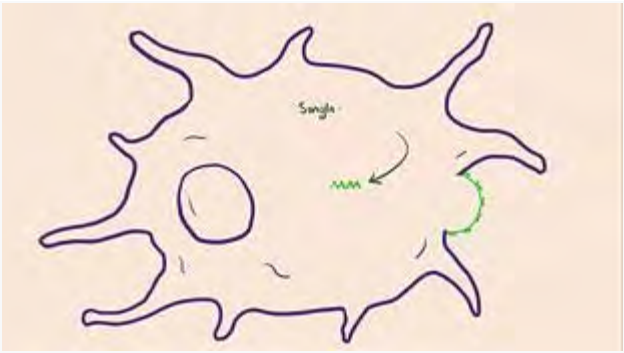
Contents

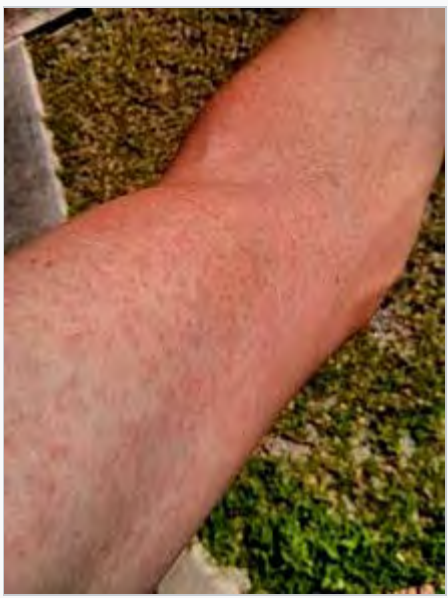


Play media

Video explanation of Zika virus and Zika fever

## Signs and symptoms [edit]

Most people who are infected have no or few symptoms.[12] Otherwise the most common signs and symptoms of Zika fever are fever, rash, conjunctivitis (red eyes), muscle and joint pain, and headache, which are similar to signs and symptoms of dengue and chikungunya fever.[13] The time from a mosquito bite to developing symptoms is not yet known, but is probably a few days to a week.[14] The disease lasts for several days to a week and is usually mild enough that people do not have to go to a hospital.[1][15]



Rash on an arm due to Zika fever

Due to being in the same family as dengue, there has been concern that it could cause similar bleeding disorders. However that has only been documented in one case, with blood seen in semen, also known as hematospermia.[16]

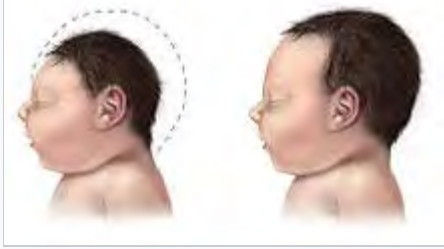
### Guillain–Barré syndrome [edit]

Zika virus infections have been strongly associated with GBS, which is a rapid onset of muscle weakness caused by the immune system damaging the peripheral nervous system, and which can progress to paralysis.[17] While both GBS and Zika infection can simultaneously occur in the same individual, it is difficult to definitively identify Zika virus as the cause of GBS.[18] Several countries affected by Zika outbreaks have reported increases in the rate of new cases of GBS. During the 2013–2014 outbreak in French Polynesia there were 42 reported cases of GBS over a 3-month period, compared to between 3 and

10 annually prior to the outbreak.[19]

### Pregnancy [edit]

The disease spreads from mother to child in the womb and can cause multiple problems, most notably microcephaly, in the baby. The full range of birth defects caused by infection during pregnancy is not known, but they appear to be common, with large scale abnormalities seen in up to 42% of live births.[20][21] The most common observed associations have been abnormalities with brain and eye development such as microcephaly and chorioretinal scarring.[22] Less commonly there have been systemic abnormalities such as hydrops fetalis, where there is abnormal accumulation of fluid in the fetus.[23][24] These abnormalities can lead to intellectual problems, seizures, vision problems, hearing problems, problems feeding and slow development.[25]


Microcephaly

Whether the stage of pregnancy at which the mother becomes infected affects the risk to the fetus is not well understood, nor is whether other risk factors affect outcomes.[5][6][8] One group has estimated the risk of a baby developing microcephaly at about 1% when the mother is infected during the first trimester, with the risk of developing microcephaly is uncertain beyond the first trimester.[26] Affected babies might appear normal but actually have brain abnormalities; infection in newborns could also lead to brain damage.[27]

## Cause [edit]

### Reservoir [edit]

Zika virus is a mosquito-borne flavivirus closely related to the dengue virus. While mosquitoes are the vector, the reservoir species remains unknown, though serological evidence has been found in West African monkeys and rodents.[28][29]

### Transmission [edit]

Transmission is via the bite of mosquitoes from the *Aedes* genus, primarily *Aedes aegypti* in tropical regions. It has also been isolated from *Ae. africanus*, *Ae. apicoargenteus*, *Ae. luteocephalus*,[30] *Ae. Albopictus*,[31][32] *Ae. vittatus* and *Ae. furcifer*.[28] During the 2007 outbreak on Yap Island in the South Pacific, *Aedes hensilli* was the vector, while *Aedes polynesiensis* spread the virus in French Polynesia in 2013.[33]

Zika virus can also spread by sexual transmission from infected men to their partners.[34][35][36] Zika virus has been isolated from semen samples, with one person having 100,000 times more virus in semen than blood or urine, two weeks after being infected.[37] It is unclear why levels in semen can be higher than other body fluids, and it is also unclear how long infectious virus can remain in semen. There have also been cases of men with no symptoms of Zika virus infection transmitting the disease.[38] The CDC has recommended that all men who have travelled to affected areas should wait at least 6 months before trying to attempt conception, regardless of if they were ill.[39] To date there have been no reported sexual transmissions from women to their sexual partners.[36] Oral, anal or vaginal sex can spread the disease.[40][41]

Cases of vertical perinatal transmission have been reported.[42] The CDC recommends that women with Zika fever should wait at least 8 weeks after they start having symptoms of disease before attempting to conceive.[43] There have been no reported cases of transmission from breastfeeding, but infectious virus has been found in breast milk.[44]

Like other flaviviruses it could potentially be transmitted by blood transfusion and several affected countries have developed strategies to screen blood donors.[15][45] The U.S. FDA has recommended universal screening of blood products for Zika.[46] The virus is detected in 3% of asymptomatic blood donors in French Polynesia.[47]

## Pathophysiology [edit]

While the pathophysiology of Zika-induced microcephaly is not yet fully known, it is reported to involve infection of the primary neural stem cells of the fetal brain, known as neural progenitor cells.[48][24] The main roles of brain stem cells are to proliferate until the correct number is achieved, and then to produce neurons through the process of neurogenesis.[49] Zika proteins NS4A and NS4B have also been shown to directly suppress neurogensis.[24] Infection of brain stem cells can cause cell death, which reduces the production of future neurons and leads to a smaller brain.[48] Zika also appears to have an equal tropism for cells of the developing eye, leading to high rates of eye abnormalities as well.[24]

## Diagnosis [edit]

It is difficult to diagnose Zika virus infection based on clinical signs and symptoms alone due to overlaps with other arboviruses that are endemic to similar areas.[15][50] The US Centers for Disease Control and Prevention (CDC) advises that "based on the typical clinical features, the differential diagnosis for Zika virus infection is broad. In addition to dengue, other considerations include leptospirosis, malaria, rickettsia, group A streptococcus, rubella, measles, and parvovirus, enterovirus, adenovirus, and alphavirus infections (e.g., chikungunya, Mayaro, Ross River, Barmah Forest, O'nyong'nyong, and Sindbis viruses)."[51]

In small case series, routine chemistry and complete blood counts have been normal in most patients. A few have been reported to have mild leukopenia, thrombocytopenia, and elevated liver transaminases.[52]

Zika virus can be identified by reverse transcriptase PCR (RT-PCR) in acutely ill patients. However, the period of viremia can be short[2] and the World Health Organization (WHO) recommends RT-PCR testing be done on serum collected within 1 to 3 days of symptom onset or on saliva samples collected during the first 3 to 5 days.[33] When evaluating paired samples, Zika virus was detected more frequently in saliva than serum.[52] Urine samples can be collected and tested up to 14 days after the onset of symptoms, as the virus has been seen to survive longer in the urine than either saliva or serum.[53] The longest period of detectable virus has been 11 days and Zika virus does not appear to establish latency.[28]

Later on, serology for the detection of specific IgM and IgG antibodies to Zika virus can be used. IgM antibodies can be detectable within 3 days of the onset of illness.[28] Serological cross-reactions with closely related flaviviruses such as dengue and West Nile virus as well as vaccines to flaviviruses are possible.[2][54][55] Commercial assays for Zika antibodies are now available but have not yet been FDA approved.[50][56]

### Screening in pregnancy [edit]

The CDC recommends screening some pregnant women even if they do not have symptoms of infection. Pregnant women who have traveled to affected areas should be tested between two and twelve weeks after their return from travel.[57] Due to the difficulties with ordering and interpreting tests for Zika virus, the CDC also recommends that healthcare providers contact their local health department for assistance.[57] For women living in affected areas, the CDC has recommended testing at the first prenatal visit with a doctor as well as in the mid-second trimester, though this may be adjusted based on local resources and the local burden of Zika virus.[57] Additional testing should be done if there are any signs of Zika virus disease. Women with positive test results for Zika virus infection should have their fetus monitored by ultrasound every three to four weeks to monitor fetal anatomy and growth.[57]

### Infant testing [edit]

For infants with suspected congenital Zika virus disease, the CDC recommends testing with both serologic and molecular assays such as RT-PCR, IgM ELISA and plaque reduction neutralization test (PRNT).[58] RT-PCR of the infants serum and urine should be performed in the first two days of life.[58] Newborns with a mother who was potentially exposed and who have positive blood tests, microcephaly or intracranial calcifications should have further testing including a thorough physical investigation for neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly, and rash or other skin lesions.[58] Other recommended tests are cranial ultrasound, hearing evaluation,[59] and eye examination.[58] Testing should be done for any abnormalities encountered as well as for other congenital infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus infection, lymphocytic choriomeningitis virus infection, and herpes simplex virus.[58] Some tests should be repeated up to 6 months later as there can be delayed effects, particularly with hearing.[58]

## Prevention [edit]

The virus is spread by mosquitoes, making mosquito avoidance an important element to disease control. The CDC recommends that individuals:[60]

- Cover exposed skin by wearing long-sleeved shirts and long pants treated with permethrin.[61]
- Use an insect repellent containing DEET,[62] picaridin, oil of lemon eucalyptus (OLE), or IR3535
- Always follow product directions and reapply as directed
- If you are also using sunscreen, apply sunscreen first, let it dry, then apply insect repellent
- Follow package directions when applying repellent on children. Avoid applying repellent to their hands, eyes, or mouth
- Stay and sleep in screened-in or air-conditioned rooms
- Use a bed net if the area where you are sleeping is exposed to the outdoors
- Cover cribs, strollers and carriers with mosquito netting for babies under 2 months old.

The CDC also recommends strategies for controlling mosquitoes such as eliminating standing water, repairing septic tanks and using screens on doors and windows.[63][64] Spraying insecticide is used to kill flying mosquitoes and larvicide can be used in water containers.[1]

Because Zika virus can be sexually transmitted, men who have gone to an area where Zika fever is occurring should be counseled to either abstain from sex or use condoms for 6 months after travel if their partner is pregnant or could potentially become pregnant.[15][34][43] Breastfeeding is still recommended by the WHO, even by women who have had Zika fever. There have been no recorded cases of Zika transmission to infants through breastfeeding, though the replicative virus has been detected in breast milk.[44][65]

When returning from travel, with or without symptoms, it is suggested that prevention of mosquito bites continue for 3 weeks in order reduce the risk of virus transmission to uninfected mosquitos.[60]

### CDC travel alert [edit]

Because of the "growing evidence of a link between Zika and microcephaly", in January 2016, the CDC issued a travel alert advising pregnant women to consider postponing travel to countries and territories with ongoing local transmission of Zika virus.[66] Later, the advice was updated to caution pregnant women to avoid these areas entirely if possible and, if travel is unavoidable, to protect themselves from mosquito bites.[67] Male partners of pregnant women and couples contemplating pregnancy who must travel to areas where Zika is active are advised to use condoms or abstain from sex entirely.[67] The agency also suggested that women thinking about becoming pregnant should consult with their physicians before traveling.[66][68]

As of September 2016, the CDC travel advisories include:[69]

- Cape Verde
- Many parts of the Caribbean: Anguilla, Antigua and Barbuda, Aruba, The Bahamas, Barbados, Bonaire, British Virgin Islands, Cayman Islands, Cuba, Curaçao, Dominica, Dominican Republic, Grenada, Guadeloupe, Haiti, Jamaica, Martinique, Puerto Rico, Saba, Saint Saint Barthélemy, Saint Lucia, Saint Martin, Saint Vincent and the Grenadines, Sint Eustatius, Sint Maarten, Trinidad and Tobago, and the U.S. Virgin Islands
- Central America: Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama
- Mexico
- Most of South America: Argentina, Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Peru, Suriname, and Venezuela
- Several Pacific Islands: American Samoa, Fiji, Marshall Islands, Micronesia, New Caledonia, Papua New Guinea, Samoa, and Tonga
- In Asia: Singapore, Malaysia, Brunei

### WHO response [edit]

Both the regional Pan American Health Organization (PAHO) as well as the WHO have issued statements of concern about the widespread public health impact of the Zika virus and its links to GBS and microcephaly.[70][71] The WHO Director-General, Margaret Chan, issued a statement in February 2016 "declaring that the recent cluster of microcephaly cases and other neurological disorders reported in Brazil, following a similar cluster in French Polynesia in 2014, constitutes a Public Health Emergency of International Concern."[11] The declaration allowed the WHO to coordinate international response to the virus as well as gave its guidance the force of international law under the International Health Regulations.[72][73] The declaration was ended in November 2016.[74]

### Vaccine [edit]

As of 2016 there was no available vaccine. Development was a priority of the US National Institutes of Health (NIH), but officials stated that development of a vaccine could take years.[2][15][50][75] To speed new drug development regulatory strategies were proposed by the WHO and NIH.[76][77] Animal and early human studies were underway as of September 2016.[78][79]

### Mosquito control [edit]

Disease control in the affected countries currently centres around mosquito control. Several approaches are available for the management of *Aedes aegypti* mosquito populations, including the destruction of larval breeding sites (the aquatic pools in which eggs are laid and larvae hatch prior to mosquito development into flying adults); and, insecticides targeting either the larval stages, adult mosquitoes or both. Additionally, a whole host of novel technologies are under current development for mosquito control and the World Health Organization has recently lent its support for the accelerated development of modern methods for mosquito control such as the use of *Wolbachia* bacteria to render mosquitoes resistant to the virus, and, the release of sterilized male mosquitoes that breed with wild female mosquitoes to give rise to non-viable offspring (offspring that do not survive to the biting, adult stage).[80]

Oxitec's genetically modified OX513A mosquito was approved by Brazil's National Biosecurity Technical Commission (CTNBio) in April 2014[81] and it was being used to try to combat mosquitoes carrying the Zika virus in the town of Piracicaba, São Paulo in 2016.[82]

## Treatment [edit]

There is currently no specific treatment for Zika virus infection. Care is supportive with treatment of pain, fever, and itching.[33] Some authorities have recommended against using aspirin and other NSAIDs as these have been associated with hemorrhagic syndrome when used for other flaviviruses.[2][15] Additionally, aspirin use is generally avoided in children when possible due to the risk of Reye syndrome.[83]

Zika virus had been relatively little studied until the major outbreak in 2015, and no specific antiviral treatments are available as yet.[15] Advice to pregnant women is to avoid any risk of infection so far as possible, as once infected there is little that can be done beyond supportive treatment.[84]

## Outcomes [edit]

Most of the time, Zika fever resolves on its own in 2 to 7 days, but rarely, some people develop Guillain–Barré syndrome.[2][85] The fetus of a pregnant woman who has Zika fever may die or be born with congenital central nervous system malformations, like microcephaly.[2]

## Epidemiology [edit]

Countries with active Zika virus transmission as of September 2016. From http://www.cdc.gov/zika/geo/active-countries.html

In April 1947, as part of studies sponsored by the Rockefeller Foundation into yellow fever, 6 caged rhesus monkeys were placed in the canopy of the Zika Forest of Uganda.[86] On April 18 one of the monkeys (no. 776) developed a fever and blood samples revealed the first known case of Zika fever.[28][86] Population surveys at the time in Uganda found a 6.1% prevalence.[42] The first human cases were reported in Nigeria in 1954.[87] A few outbreaks have been reported in tropical Africa and in some areas in Southeast Asia.[88] There have been no documented cases of Zika virus in the Indian subcontinent. Surveys have found antibodies to Zika in healthy people in India which could indicate past exposure, though it could also be due to cross-reaction with other flaviviruses.[89]

By using phylogenetic analysis of Asian strains, it was estimated that Zika virus had moved to Southeast Asia by 1945.[42] In 1977–1978, Zika virus infection was described as a cause of fever in Indonesia.[90] Before 2007, there were only 13 reported natural infections with Zika virus, all with a mild, self-limited febrile illness.[28][91]

### Yap Islands [edit]

*Main article: 2007 Yap Islands Zika virus outbreak*

The first major outbreak, with 185 confirmed cases, was reported in 2007 in the Yap Islands of the Federated States of Micronesia.[92] A total of 108 cases were confirmed by PCR or serology and 72 additional cases were suspected. The most common symptoms were rash, fever, arthralgia, and conjunctivitis, and no deaths were reported. The mosquito *Aedes hensilli*, which was the predominant species identified in Yap during the outbreak, was probably the main vector of transmission. While the way of introduction of the virus on Yap Island remains uncertain, it is likely to have happened through introduction of infected mosquitoes or a human infected with a strain related to those in Southeast Asia.[42][92] This was also the first time Zika fever had been reported outside Africa and Asia.[4] Before the Yap Island outbreak, only 14 human cases had ever been reported.[93]

### Oceania [edit]

*Main article: 2013–2014 Zika virus outbreaks in Oceania*

In 2013–2014, several outbreaks of Zika were reported in French Polynesia, New Caledonia, Easter Island and the Cook Islands. The source of the virus was thought to be an independent introduction of the virus from Southeast Asia, unrelated to the Yap Islands outbreak.[42]

### Americas [edit]

*Further information: 2015–16 Zika virus epidemic*

Genetic analyses of Zika virus strains suggest that Zika first entered the Americas between May and December 2013.[94] It was first detected in the Western Hemisphere in February 2014, and rapidly spread throughout South and Central America, reaching Mexico in November 2015.[15][42][95] In 2016 it established local transmission in Florida and Texas.[96][97] The first death in the United States due to Zika occurred in February 2016.[98]

Areas of active Zika Virus transmission, April 2016

In May 2015, Brazil officially reported its first 16 cases of the illness.[99] According to the Brazilian Health Ministry, as of November 2015 there was no official count of the number of people infected with the virus in Brazil, since the disease is not subject to compulsory notification. Even so, cases were reported in 14 states of the country. Mosquito-borne Zika virus is suspected to be the cause of 2,400 possible cases of microcephaly and 29 infant deaths in Brazil in 2015 (of the 2400 or so notified cases in 2015, 2165 were under investigation in December 2015, 134 were confirmed and 102 were ruled out for microcephaly).[100]

The Brazilian Health Ministry has reported at least 2,400 suspected cases of microcephaly in the country in 2015 as of 12 December, and 29 fatalities.[100][101][102][103] Before the Zika outbreak, only an average of 150 to 200 cases per year were reported in Brazil.[104] In the state of Pernambuco the reported rates of microcephaly in 2015 are 77 times higher than in the previous 5 years.[104] A model using data from a Zika outbreak in French Polynesia estimated the risk of microcephaly in children born to mothers who acquired Zika virus in the first trimester to be 1%.[105]

On 24 January 2016, the WHO warned that the virus is likely to spread to nearly all countries of the Americas, since its vector, the mosquito *Aedes aegypti*, is found in all countries in the region, except for Canada and continental Chile.[106][107] The mosquito and dengue fever have been detected in Chile's Easter Island, some 3,500 km (2,200 mi) away from its closest point in mainland Chile, since 2002.[108]

In February 2016, WHO declared the outbreak a Public Health Emergency of International Concern as evidence grew that Zika is a cause of birth defects and neurological problems.[15][109][110][111] In April 2016, WHO stated there is a scientific consensus, based on preliminary evidence, that Zika is a cause of microcephaly in infants and Guillain–Barré syndrome in adults.[8] Studies of this and prior outbreaks have found Zika infection during pregnancy to be associated with early pregnancy loss and other pregnancy problems.[112][113]

### Asia [edit]

In 2016 imported or locally transmitted Zika was reported in all the countries of Asia except Brunei, Hong Kong, Myanmar and Nepal.[114] Serological surveys have indicated that Zika virus is endemic in most areas of Asia, though at a low level.[114] While there was a sharp rise in the amount of cases of Zika detected in Singapore after the 2016 Summer Olympics in Brazil, genetic analysis revealed that the strains were more closely related to strains from Thailand than from those causing the epidemic in the Americas.[115][116][117]

## History [edit]

### Microcephaly and other infant disorders [edit]

Following the initial Zika outbreak in Northeastern Brazil, physicians observed a very large surge of reports of infants born with microcephaly, with 20 times the number of expected cases.[118][119] Many of these

cases have since been confirmed, leading WHO officials to project that approximately 2,500 infants will be found to have born in Brazil with Zika-related microcephaly.[120][121] On 10 March 2016, a research group from the Faculty of Medicine, University of Ljubljana (Slovenia), led by young researcher Jernej Mlakar, M.D., published an article in The New England Journal of Medicine, connecting the Zika virus to microcephaly.[122]

Proving that Zika causes these effects is difficult and complex for several reasons.[123][124] For example, the effects on an infant might not be seen until months after the mother's initial infection, long after the time when Zika is easily detected in the body.[123] In addition, research is also needed to determine the mechanism by which Zika produces these effects.[125]

Since the initial outbreak, studies that use several different methods found evidence of a link, leading public health officials to conclude that it appears increasingly likely the virus is linked to microcephaly and miscarriage.[125][126] On 1 February 2016, the World Health Organization declared recently reported clusters of microcephaly and other neurological disorders a Public Health Emergency of International Concern (PHEIC).[127] On 8 March 2016, the WHO Committee reconfirmed that the association between Zika and neurological disorders is of global concern.[125]

The Zika virus was first linked with newborn microcephaly during the Brazil Zika virus outbreak. In 2015, there were 2,782 suspected cases of microcephaly compared with 147 in 2014 and 167 in 2013.[118] Confirmation of many of the recent cases is pending,[128] and it is difficult to estimate how many cases went unreported before the recent awareness of the risk of virus infections.[129]


Brazilian President Dilma Rousseff in a videoconference about the Zika virus at the National Center for Disaster Management.

In March 2016, researchers published a prospective cohort study that found profound impacts in 29 percent of infants of mothers infected with Zika, some of whom were infected late in pregnancy.[20] This study did not suffer from some of the difficulties of studying Zika: the study followed women who presented to a Rio de Janeiro clinic with fever and rash within the last five days. The women were then tested for Zika using PCR, then the progress of the pregnancies were followed using ultrasound.[20][130]

In November 2015, the Zika virus was isolated in a newborn baby from the northeastern state of Ceará, Brazil, with microcephaly and other congenital disorders. *The Lancet* medical journal reported in January 2016 that the Brazilian Ministry of Health had confirmed 134 cases of microcephaly "believed to be associated with Zika virus infection" with an additional 2,165 cases in 549 counties in 20 states remaining under investigation.[15][131] An analysis of 574 cases of microcephaly in Brazil during 2015 and the first week of 2016, reported in March 2016, found an association with maternal illness involving rash and fever during the first trimester of pregnancy.[132] During this period, 12 Brazilian states reported increases of at least 3 standard deviations (SDs) in cases of microcephaly compared with 2000–14, with the northeastern states of Bahia, Paraíba and Pernambuco reporting increases of more than 20 SDs.[132]

In January 2016, a baby in Oahu, Hawaii, was born with microcephaly, the first case in the United States of brain damage linked to the virus. The baby and mother tested positive for a past Zika virus infection. The mother, who had probably acquired the virus while traveling in Brazil in May 2015 during the early stages of her pregnancy, had reported her bout of Zika. She recovered before relocating to Hawaii. Her pregnancy had progressed normally, and the baby's condition was not known until birth.[133]

In March 2016, first solid evidence was reported on how the virus affects the development of the brain. It appears to preferentially kill developing brain cells.[134] The first cases of birth defects linked to Zika in Colombia[135] and in Panama were reported in March 2016.[136]

Ocular disorders in newborns have also been linked to Zika virus infection.[137] In one study in Pernambuco state in Brazil, about 40 percent of babies with Zika-related microcephaly also had scarring of the retina [138]

with spots, or pigment alteration.

On 20 February 2016, Brazilian scientists announced that they had successfully sequenced the Zika virus genome, and expressed hope that this would help in both developing a vaccine and in determining the nature of any link to birth defects.[139]

In February 2016, rumors that microcephaly is caused by the use of the larvicide pyriproxyfen in drinking water were refuted by scientists.[140][141][142] "It's important to state that some localities that do not use pyriproxyfen also had reported cases of microcephaly", read a Brazilian government statement.[143] The Brazilian government also refuted conspiracy theories that chickenpox and rubella vaccinations or genetically modified mosquitoes were causing increases in microcephaly.[142]

Researchers also suspected that Zika virus could be transmitted by a pregnant woman to her babies ("vertical transmission"). This remained unproven until February 2016, when a paper by Calvet et al. was published, showing not only was the Zika virus genome found in the amniotic fluid but also IgM antibodies against the virus.[144] This means that not only can the virus cross the placental barrier, but also the antibodies produced by the mother can reach the fetus, which suggests that vertical transmission is plausible in these cases. One other study published in March 2016 by Mlakar and colleagues analyzed autopsy tissues from a fetus with microcephaly that was probably related to Zika virus; researchers found ZIKV in the brain tissue and suggested that the brain injuries were probably associated with the virus, which also shed a light on the vertical transmission theory.[122]

### Guillain–Barré syndrome [edit]

A high rate of the autoimmune disease Guillain–Barré syndrome (GBS), noted in the French Polynesia outbreak, has also been found in the outbreak that began in Brazil.[131] Laboratory analysis found Zika infections in some patients with GBS in Brazil, El Salvador, Suriname and Venezuela,[145] and the WHO declared on 22 March 2016 that Zika appeared to be "implicated" in GBS infection and that if the pattern was confirmed it would represent a global public health crisis.[146]

## Research [edit]

Some experimental methods of prevention include breeding and releasing mosquitoes that have been genetically modified to prevent them from transmitting pathogens, or have been infected with the *Wolbachia* bacterium, believed to inhibit the spread of viruses.[15][147] A strain of *Wolbachia* helped to reduce the vector competence of the Zika virus in infected *Aedes aegypti* released in Medellin, Colombia.[148] Gene drive is a technique for changing wild populations, for instance to combat insects so they cannot transmit diseases (in particular mosquitoes in the cases of malaria and Zika).[149] Another method which been researched aims to render male mosquitoes infertile by nuclear radiation in the hope to reduce populations; this is done with a cobalt-60 gamma cell irradiator.[150] In 2016 the World Health Organisation encouraged field trials of transgenic male *Aedes aegypti* mosquitoes developed by Oxitec to try to halt the spread of the Zika virus.[151]

## References [edit]


1. ^ *a b c d e f g h* "Zika virus". World Health Organization. January 2016. Retrieved 3 February 2016.
2. ^ *a b c d e f g h i j* "Factsheet for health professionals". *Zika virus infection*. European Centre for Disease Prevention and Control. Retrieved 22 December 2015.
3. ^ *a b c d e f g h i j k* Chen, Lin H.; Hamer, Davidson H. (2016). "Zika Virus: Rapid Spread in the Western Hemisphere". *Annals of Internal Medicine*. **164**: 613. doi:10.7326/M16-0150. ISSN 0003-4819. PMID 26832396.
4. ^ *a b* Musso, D.; Nilles, E.J.; Cao-Lormeau, V.-M. (2014). "Rapid spread of emerging Zika virus in the Pacific area". *Clinical Microbiology and Infection*. **20** (10): O595–6. doi:10.1111/1469-0691.12707. PMID 24909208.
5. ^ *a b c* Rasmussen, Sonja A.; Jamieson, Denise J.; Honein, Margaret A.; Petersen, Lyle R. (2016). "Zika Virus and

Birth Defects — Reviewing the Evidence for Causality". *New England Journal of Medicine*. **374**: 1981–1987. doi:10.1056/NEJMsr1604338. ISSN 0028-4793. PMID 27074377.

6. ^ [a] [b] [c] "CDC Concludes Zika Causes Microcephaly and Other Birth Defects". *CDC*. 13 April 2016. Retrieved 14 April 2016.
7. ^ [a] [b] Oster, Alexandra M.; Russell, Kate; Stryker, Jo Ellen; Friedman, Allison; Kachur, Rachel E.; Petersen, Emily E.; Jamieson, Denise J.; Cohn, Amanda C.; Brooks, John T. (1 April 2016). "Update: Interim Guidance for Prevention of Sexual Transmission of Zika Virus — United States, 2016". *MMWR. Morbidity and Mortality Weekly Report*. **65** (12): 323–325. doi:10.15585/mmwr.mm6512e3. PMID 27032078.
8. ^ [a] [b] [c] "Zika Virus Microcephaly And Guillain–Barré Syndrome Situation Report" (PDF). World Health Organization. 7 April 2016. Retrieved 8 April 2016.
9. ^ "Brazil warns against pregnancy due to spreading virus". *CNN*. 24 December 2015. Retrieved 24 December 2015.
10. ^ Olson, Ken E.; Haddow, Andrew D.; Schuh, Amy J.; et al. (2012). "Genetic Characterization of Zika Virus Strains: Geographic Expansion of the Asian Lineage". *PLoS Neglected Tropical Diseases*. **6** (2): e1477. doi:10.1371/journal.pntd.0001477. ISSN 1935-2735. PMC 3289602. PMID 22389730.
11. ^ [a] [b] "WHO Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain–Barré syndrome". *Media Centre*. World Health Organization. 1 February 2016. Retrieved 3 February 2016.
12. ^ "Symptoms, Diagnosis, & Treatment of Zika Virus". *Zika Virus Home*. Centers for Disease Control and Prevention. Retrieved 29 April 2016.
13. ^ Heang, Vireak; Yasuda, Chadwick Y.; Sovann, Ly; et al. (2012). "Zika Virus Infection, Cambodia, 2010". *Emerging Infectious Diseases*. **18** (2): 349–351. doi:10.3201/eid1802.111224. ISSN 1080-6040. PMC 3310457. PMID 22305269.
14. ^ "Signs and Symptoms". *Zika virus home*. Centers for Disease Control and Prevention. Retrieved 30 January 2016.
15. ^ [a] [b] [c] [d] [e] [f] [g] [h] [i] [j] [k] Sikka, Veronica; Chattu, Vijay Kumar; Popli, Raaj K.; et al. (11 February 2016). "The emergence of zika virus as a global health security threat: A review and a consensus statement of the INDUSEM Joint working Group (JWG)". *Journal of Global Infectious Diseases*. **8** (1): 3–15. doi:10.4103/0974-777X.176140. ISSN 0974-8245. PMC 4785754. PMID 27013839.
16. ^ Foy, Brian D.; Kobylinski, K.C.; Foy, J.L.C.; et al. (2011). "Probable Non–Vector-borne Transmission of Zika Virus, Colorado, USA". *Emerging Infectious Diseases*. **17** (5): 880–882. doi:10.3201/eid1705.101939. ISSN 1080-6040. PMC 3321795. PMID 21529401.
17. ^ Frontera, Jennifer A.; Silva, Ivan R.F. da (2016-10-05). "Zika Getting on Your Nerves? The Association with the Guillain–Barré Syndrome". *New England Journal of Medicine*. **375** (16): 1581–1582. doi:10.1056/nejme1611840.
18. ^ "Guillain–Barré syndrome Q & A". Centers for Disease Control and Prevention. 8 February 2016. Retrieved 10 March 2016.
19. ^ Cao-Lormeau, Van-Mai; Blake, Alexandre; Mons, Sandrine; et al. (2016). "Guillain–Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study". *The Lancet*. **387**: 1531–1539. doi:10.1016/S0140-6736(16)00562-6. ISSN 0140-6736.
20. ^ [a] [b] [c] Brasil, Patrícia; Pereira, Jr., Jose P.; Raja Gabaglia, Claudia; et al. (4 March 2016). "Zika Virus Infection in Pregnant Women in Rio de Janeiro – Preliminary Report". *New England Journal of Medicine*. doi:10.1056/NEJMoa1602412. ISSN 0028-4793.
21. ^ Brasil, Patrícia; Pereira, José P.; Moreira, M. Elisabeth; Nogueira, Rita M. Ribeiro; Damasceno, Luana; Wakimoto, Mayumi; Rabello, Renata S.; Valderramos, Stephanie G.; Halai, Umme-Aiman (2016-03-04). "Zika Virus Infection in Pregnant Women in Rio de Janeiro". *New England Journal of Medicine*. **375** (24): 2321–2334. doi:10.1056/nejmoa1602412.
22. ^ de Paula Freitas B; de Oliveira Dias J; Prazeres J; et al. (9 February 2016). "Ocular findings in infants with microcephaly associated with presumed zika virus congenital infection in salvador, brazil". *JAMA Ophthalmology*. doi:10.1001/jamaophthalmol.2016.0267. ISSN 2168-6165.
23. ^ Sarno, Manoel; Sacramento, Gielson A.; Khouri, Ricardo; Rosário, Mateus S. do; Costa, Federico; Archanjo, Gracinda; Santos, Luciane A.; Jr, Nivison Nery; Vasilakis, Nikos (25 February 2016). "Zika Virus Infection and Stillbirths: A Case of Hydrops Fetalis, Hydranencephaly and Fetal Demise". *PLOS Negl Trop Dis*. **10** (2): e0004517. doi:10.1371/journal.pntd.0004517. ISSN 1935-2735. PMC 4767410. PMID 26914330.
24. ^ [a] [b] [c] [d] Li, Hongda; Saucedo-Cuevas, Laura; Shresta, Sujan; Gleeson, Joseph G. "The Neurobiology of Zika Virus". *Neuron*. **92** (5): 949–958. doi:10.1016/j.neuron.2016.11.031.
25. ^ Boeuf, Phillipe; Drummer, Heidi E.; Richards, Jack S.; Scoullar, Michelle J. L.; Beeson, James G. (2016-01-01).

"The global threat of Zika virus to pregnancy: epidemiology, clinical perspectives, mechanisms, and impact" . *BMC Medicine*. **14**: 112. doi:10.1186/s12916-016-0660-0. ISSN 1741-7015. PMC 4973112. PMID 27487767.

26. ^ "Risk estimates for microcephaly related to Zika virus infection - from French Polynesia to Bahia, Brazil". May 2, 2016. doi:10.1101/051060.
27. ^ http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30902-3/abstract Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation
28. ^ *a b c d e f* Hayes, Edward B. (2009). "Zika Virus Outside Africa". *Emerging Infectious Diseases*. **15** (9): 1347–50. doi:10.3201/eid1509.090442. PMC 2819875. PMID 19788800.
29. ^ Brack, Manfred (6 December 2012). *Agents Transmissible from Simians to Man*. Springer Science & Business Media. ISBN 978-3-642-71911-0.
30. ^ "*Aedes luteocephala*". *Medically Important Mosquitoes*. Walter Reed Biosystematics Unit. Retrieved 1 February 2016.
31. ^ Grard, G; Caron, M; Mombo, I M; Nkoghe, D; Ondo, S M; Jiolle, D; Fontenille, D; Paupy, C; Leroy, E M (2014). "Zika Virus in Gabon (Central Africa) – 2007: A New Threat from Aedes albopictus ?". *PLOS Negl Trop Dis*. **8** (2): e2681. doi:10.1371/journal.pntd.0002681. ISSN 1935-2735. PMC 3916288. PMID 24516683.
32. ^ Wong, PJ; Li, M I; Chong, C; Ng, L; Tan, C (2013). "Aedes ( Stegomyia ) albopictus (Skuse): A Potential Vector of Zika Virus in Singapore". *PLOS Negl Trop Dis*. **7** (8): e2348. doi:10.1371/journal.pntd.0002348. ISSN 1935-2735. PMC 3731215. PMID 23936579.
33. ^ *a b c* "Zika virus". Retrieved 24 December 2015.
34. ^ *a b* Oster, Alexandra M.; Brooks, John T.; Stryker, Jo Ellen; et al. (2016). "Interim Guidelines for Prevention of Sexual Transmission of Zika Virus — United States, 2016". *MMWR. Morbidity and Mortality Weekly Report*. **65** (5): 120–121. doi:10.15585/mmwr.mm6505e1. ISSN 0149-2195. PMID 26866485.
35. ^ "CDC encourages following guidance to prevent sexual transmission of Zika virus". *CDC Newsroom Releases*. Centers for Disease Control and Prevention. 23 February 2016.
36. ^ *a b* Hills, Susan L.; Russell, Kate; Hennessey, Morgan; et al. (2016). "Transmission of Zika Virus Through Sexual Contact with Travelers to Areas of Ongoing Transmission — Continental United States, 2016". *MMWR. Morbidity and Mortality Weekly Report*. **65** (8). doi:10.15585/mmwr.mm6508e2er. ISSN 0149-2195.
37. ^ Mansuy, Jean Michel; Dutertre, Marine; Mengelle, Catherine; et al. (2016). "Zika virus: high infectious viral load in semen, a new sexually transmitted pathogen?". *The Lancet Infectious Diseases*. **16**: 405. doi:10.1016/S1473-3099(16)00138-9. ISSN 1473-3099.
38. ^ Brooks, Richard B.; Carlos, Maria Paz; Myers, Robert A.; White, Mary Grace; Bobo-Lenoci, Tanya; Aplan, Debra; Blythe, David; Feldman, Katherine A. (2016-01-01). "Likely Sexual Transmission of Zika Virus from a Man with No Symptoms of Infection — Maryland, 2016". *MMWR. Morbidity and Mortality Weekly Report*. **65** (34): 915–916. doi:10.15585/mmwr.mm6534e2. ISSN 0149-2195.
39. ^ Petersen, Emily E.; Meaney-Delman, Dana; Neblett-Fanfair, Robyn; Havers, Fiona; Oduyebo, Titilope; Hills, Susan L.; Rabe, Ingrid B.; Lambert, Amy; Abercrombie, Julia (2016-01-01). "Update: Interim Guidance for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus for Persons with Possible Zika Virus Exposure — United States, September 2016". *MMWR. Morbidity and Mortality Weekly Report*. **65** (39): 1077–1081. doi:10.15585/mmwr.mm6539e1. ISSN 0149-2195.
40. ^ http://www.nytimes.com/2016/04/15/health/zika-virus-can-be-transmitted-through-anal-sex-cdc-says.html Zika Virus Can Be Transmitted Through Anal Sex, C.D.C. Says
41. ^ D'Ortenzio, Eric; Matheron, Sophie; de Lamballerie, Xavier; Hubert, Bruno; Piorkowski, Géraldine; Maquart, Marianne; Descamps, Diane; Damond, Florence; Yazdanpanah, Yazdan (2016-06-02). "Evidence of Sexual Transmission of Zika Virus". *New England Journal of Medicine*. **374** (22): 2195–2198. doi:10.1056/NEJMc1604449. ISSN 0028-4793. PMID 27074370.
42. ^ *a b c d e f* Gatherer, Derek; Kohl, Alain (18 December 2015). "Zika virus: a previously slow pandemic spreads rapidly through the Americas". *Journal of General Virology*. **97** (2): 269–273. doi:10.1099/jgv.0.000381. PMID 26684466.
43. ^ *a b* Petersen, Emily E.; Polen, Kara N.D.; Meaney-Delman, Dana; et al. (2016). "Update: Interim Guidance for Health Care Providers Caring for Women of Reproductive Age with Possible Zika Virus Exposure — United States, 2016". *MMWR. Morbidity and Mortality Weekly Report*. **65** (12): 315–322. doi:10.15585/mmwr.mm6512e2. ISSN 0149-2195.
44. ^ *a b* Dupont-Rouzeyrol, Myrielle; Biron, Antoine; O'Connor, Olivia; et al. "Infectious Zika viral particles in breastmilk". *The Lancet*. **387**: 1051. doi:10.1016/s0140-6736(16)00624-3.
45. ^ Franchini, M.; Velati, C. (2016). "Blood safety and zoonotic emerging pathogens: now it's the turn of Zika virus!". *Blood Transfusion* (14): 93–94. doi:10.2450/2015.0187-15. PMID 26674809.
46. ^ "FDA advises testing for Zika virus in all donated blood and blood components in the US". August 26, 2016.

47. ^ Guillaume, Theiry (27 April 2016). "Zika virus-associated Guillain–Barré syndrome: a warning for critical care physicians". *Intensive Care Medicine*: 1–2.
48. ^ *a b* Nayak, Shriddha; Lei, Jun; Pekosz, Andrew; Klein, Sabra; Burd, Irina (2016-09-09). "Pathogenesis and Molecular Mechanisms of Zika Virus". *Seminars in Reproductive Medicine*. **34**: 266–272. doi:10.1055/s-0036-1592071. ISSN 1526-8004.
49. ^ Rakic, P (October 2009). "Evolution of the neocortex: a perspective from developmental biology.". *Nature reviews. Neuroscience*. **10** (10): 724–35. doi:10.1038/nrn2719. PMC 2913577. PMID 19763105.
50. ^ *a b c* Fauci, Anthony S.; Morens, David M. (18 February 2016). "Zika Virus in the Americas – Yet Another Arbovirus Threat". *New England Journal of Medicine*. **374**: 601–604. doi:10.1056/NEJMp1600297. PMID 26761185.
51. ^ "Clinical Evaluation & Disease". *For Health Care Providers*. Centers for Disease Control and Prevention. Retrieved 24 December 2015.
52. ^ *a b* Waggoner, Jesse J.; Pinsky, Benjamin A. (17 February 2016). "Zika Virus: Diagnostics for an Emerging Pandemic Threat". *Journal of Clinical Microbiology*. **54**: JCM.00279–16. doi:10.1128/JCM.00279-16. ISSN 0095-1137. PMID 26888897.
53. ^ "Interim Guidance for Zika Virus Testing of Urine - United States, 2016.". *MMWR. Morbidity and mortality weekly report*. **65** (18): 474. 13 May 2016. doi:10.15585/mmwr.mm6518e1. PMID 27171368.
54. ^ Faye, Oumar; Faye, Ousmane; Dupressoir, Anne; et al. (2008). "One-step RT-PCR for detection of Zika virus". *Journal of Clinical Virology*. **43** (1): 96–101. doi:10.1016/j.jcv.2008.05.005. ISSN 1386-6532. PMID 18674965.
55. ^ Lanciotti, Robert S.; Kosoy, Olga L.; Laven, Janeen J.; et al. (2008). "Genetic and Serologic Properties of Zika Virus Associated with an Epidemic, Yap State, Micronesia, 2007". *Emerging Infectious Diseases*. **14** (8): 1232–1239. doi:10.3201/eid1408.080287. ISSN 1080-6040.
56. ^ "Revised diagnostic testing for Zika, chikungunya, and dengue viruses in US Public Health Laboratories" (PDF). *Division of Vector-Borne Diseases*. Centers for Disease Control and Prevention. 7 February 2016. Retrieved 15 March 2016.
57. ^ *a b c d* Oduyebo, Titilope; Petersen, Emily E.; Rasmussen, Sonja A.; et al. (2016). "Update: Interim Guidelines for Health Care Providers Caring for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure — United States, 2016". *MMWR. Morbidity and Mortality Weekly Report*. **65** (05): 1–6. doi:10.15585/mmwr.mm6505e2er. ISSN 0149-2195.
58. ^ *a b c d e f* Russell, Kate; Oliver, Sara E.; Lewis, Lillianne; Barfield, Wanda D.; Cragan, Janet; Meaney-Delman, Dana; Staples, J. Erin; Fischer, Marc; Peacock, Georgina (2016-01-01). "Update: Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection — United States, August 2016". *MMWR. Morbidity and Mortality Weekly Report*. **65** (33): 870–878. doi:10.15585/mmwr.mm6533e2. ISSN 0149-2195.
59. ^ "Hearing Loss Observed in 6% of Infants with Zika and Microcephaly". *NEJM Journal Watch*. **2016**. 2016-08-31. doi:10.1056/nejm-jw.FW111979. ISSN 0896-7210.
60. ^ *a b* "Avoid bug bites". *Travelers' Health*. Centers for Disease Control and Prevention. Retrieved 15 March 2016.
61. ^ https://www.cdc.gov/zika/prevention/prevent-mosquito-bites.html Permethrin-treated clothing will protect you after multiple washings
62. ^ http://www.nytimes.com/2016/04/05/health/zika-virus-deet-pregant-women-safety.html DEET Seen as Safe for Pregnant Women to Avoid Zika Despite Few Studies
63. ^ "Surveillance and Control of *Aedes aegypti* and *Aedes albopictus* in the United States". *Chikungunya Virus Home: Resources*. Centers for Disease Control and Prevention. 10 March 2016.
64. ^ "Help Control Mosquitoes that Spread Dengue, Chikungunya, and Zika Viruses" (PDF). *Chikungunya Virus Home: Fact Sheets and Posters*. Centers for Disease Control and Prevention. August 2015.
65. ^ "Breastfeeding in the context of Zika virus" (PDF). *Institutional Repository for Information Sharing*. World Health Organization. 25 February 2016. Retrieved 28 February 2016.
66. ^ *a b* Lowes, R. (15 January 2016). "CDC Issues Zika Travel Alert". *Medscape Medical News*. Retrieved 16 January 2016.
67. ^ *a b* "How to Protect Yourself". Centers for Disease Control and Prevention. 4 March 2016. Retrieved 16 March 2016.
68. ^ "CDC issues interim travel guidance related to Zika virus for 14 Countries and Territories in Central and South America and the Caribbean". *CDC Newsroom Releases*. Centers for Disease Control and Prevention. 15 January 2016.
69. ^ "Zika Travel Information | Travelers' Health | CDC". *wwwnc.cdc.gov*. Retrieved 2016-09-02.
70. ^ "Neurological syndrome, congenital malformations, and Zika virus infection – Epidemiological Update". *Epidemiological Alerts and Updates CHA.01.04b Epidemic Alert and Response*. Pan American Health Organization. 17 January 2016.

71. ^ "WHO Declares Zika a Public Health Emergency". *NBC News*. Retrieved 8 February 2016.
72. ^ Tavernise, Sabrina; McNeil, Jr., Donald G. (1 February 2016). "Zika Virus a Global Health Emergency, W.H.O. Says". *The New York Times*. ISSN 0362-4331. Retrieved 8 February 2016.
73. ^ "IHR Procedures concerning public health emergencies of international concern (PHEIC)". World Health Organization. Retrieved 8 February 2016.
74. ^ CNN, Debra Goldschmidt. "WHO ends Zika public health emergency". *CNN*. Retrieved 2016-12-24.
75. ^ Sifferlin, Alexandra (21 January 2016). "U.S. Launches 'Full-court Press' for a Zika Vaccine". *Time*. Retrieved 23 January 2016.
76. ^ J., Thomas, Stephen; Maïna, L'Azou,; D.T., Barrett, Alan; A.C., Jackson, Nicholas (2016-09-28). "Fast-Track Zika Vaccine Development — Is It Possible?". *New England Journal of Medicine*. **375**: 1212–1216. doi:10.1056/nejmp1609300.
77. ^ D., Marston, Hilary; Nicole, Lurie,; L., Borio, Luciana; S., Fauci, Anthony (2016-09-28). "Considerations for Developing a Zika Virus Vaccine". *New England Journal of Medicine*. **375**: 1209–1212. doi:10.1056/nejmp1607762.
78. ^ Barzon, Luisa; Trevisan, Marta; Sinigaglia, Alessandro; Lavezzo, Enrico; Palù, Giorgio (2016-09-01). "Zika virus: from pathogenesis to disease control". *FEMS Microbiology Letters*. **363** (18): fnw202. doi:10.1093/femsle/fnw202. ISSN 1574-6968. PMID 27549304.
79. ^ Morrison, Chris (2016-08-01). "DNA vaccines against Zika virus speed into clinical trials". *Nature Reviews Drug Discovery*. **15** (8): 521–522. doi:10.1038/nrd.2016.159. ISSN 1474-1776.
80. ^ Yakob, Laith; Walker, Thomas (March 2016). "Zika virus outbreak in the Americas: the need for novel mosquito control methods". *The Lancet Global Health*. **4** (3): e148–e149. doi:10.1016/S2214-109X(16)00048-6.
81. ^ Tracy Thompson: *Oxitec's solution for controlling the dengue mosquito is approved by CTNBio.* Oxitech, 11 April 2014
82. ^ Pollack, Andrew (30 January 2016). "New Weapon to Fight Zika: The Mosquito". New York Times. Retrieved 16 March 2016.
83. ^ Fulginiti, Vincent A.; Brunell, Philip A.; Cherry, James D.; et al. (June 1982). "Aspirin and Reye Syndrome". *Pediatrics*. **69** (6): 810–812. ISSN 1098-4275. PMID 7079050. Retrieved 11 March 2016.
84. ^ Petersen, Emily E.; Staples, J. Erin; Meaney-Delman, Dana; et al. (2016). "Interim Guidelines for Pregnant Women During a Zika Virus Outbreak — United States, 2016". *Morbidity and Mortality Weekly Report*. **65** (2): 30–33. doi:10.15585/mmwr.mm6502e1. ISSN 0149-2195. PMID 26796813.
85. ^ CDC Zika Virus: Health Effects & Risks Page last reviewed: August 9, 2016; Page last updated: August 9, 2016
86. ^ *a b* Musso, Didier; Gubler, Duane J. (2016-07-01). "Zika Virus". *Clinical Microbiology Reviews*. **29** (3): 487–524. doi:10.1128/CMR.00072-15. ISSN 0893-8512. PMC 4861986. PMID 27029595.
87. ^ MacNamara, F.N. (1954). "Zika virus : A report on three cases of human infection during an epidemic of jaundice in Nigeria". *Transactions of the Royal Society of Tropical Medicine and Hygiene*. **48** (2): 139–145. doi:10.1016/0035-9203(54)90006-1. ISSN 0035-9203. PMID 13157159.
88. ^ Simpson, D.I.H. (1964). "Zika virus infection in man". *Transactions of the Royal Society of Tropical Medicine and Hygiene*. **58** (4): 339–348. doi:10.1016/0035-9203(64)90201-9. ISSN 0035-9203.
89. ^ Smithburn, K. C.; Kerr, J. A.; Gatne, P. B. (1 April 1954). "Neutralizing antibodies against certain viruses in the sera of residents of India". *Journal of Immunology (Baltimore, Md.: 1950)*. **72** (4): 248–257. PMID 13163397.
90. ^ Olson, J. G.; Ksiazek, T. G. (1 January 1981). "Zika virus, a cause of fever in Central Java, Indonesia". *Transactions of the Royal Society of Tropical Medicine and Hygiene*. **75** (3): 389–393. doi:10.1016/0035-9203(81)90100-0. PMID 6275577.
91. ^ Baden, Lindsey R.; Petersen, Lyle R.; Jamieson, Denise J.; Powers, Ann M.; Honein, Margaret A. (30 March 2016). "Zika Virus". *New England Journal of Medicine*. **374** (16): 1552–1563. doi:10.1056/nejmra1602113. PMID 27028561.
92. ^ *a b* Duffy, M.R.; Chen, T.H.; Hancock, W.T.; et al. (2009). "Zika Virus Outbreak on Yap Island, Federated States of Micronesia". *New England Journal of Medicine*. **360** (24): 2536–43. doi:10.1056/NEJMoa0805715. PMID 19516034.
93. ^ Faye, Oumar; Freire, Caio C. M.; Iamarino, Atila; et al. (9 January 2014). "Molecular Evolution of Zika Virus during Its Emergence in the 20th Century". *PLoS Neglected Tropical Diseases*. **8** (1): e2636. doi:10.1371/journal.pntd.0002636. PMC 3888466. PMID 24421913.
94. ^ Faria, Nuno Rodrigues; Azevedo, Raimunda do Socorro da Silva; Kraemer, Moritz U.G.; Souza, Renato; Cunha, Mariana Sequetin; Hill, Sarah C.; Thézé, Julien; Bonsall, Michael B.; Bowden, Thomas A. (2016-04-15). "Zika virus in the Americas: Early epidemiological and genetic findings". *Science*. **352** (6283): 345–349. doi:10.1126/science.aaf5036. ISSN 0036-8075. PMC 4918795. PMID 27013429.
95. ^ Dyer, Owen (23 December 2015). "Zika virus spreads across Americas as concerns mount over birth defects". *BMJ*. **351**: h6983. doi:10.1136/bmj.h6983. PMID 26698165.

96. ^ Jr, Donald G. Mcneil; Fernandez, Manny (2016-11-28). "Local Transmission of Zika Virus Is Reported in Texas". *The New York Times*. ISSN 0362-4331. Retrieved 2016-12-09.
97. ^ Likos, Anna; Griffin, Isabel; Bingham, Andrea M.; Stanek, Danielle; Fischer, Marc; White, Stephen; Hamilton, Janet; Eisenstein, Leah; Atrubin, David (2016-01-01). "Local Mosquito-Borne Transmission of Zika Virus — Miami-Dade and Broward Counties, Florida, June–August 2016". *MMWR. Morbidity and Mortality Weekly Report*. **65** (38): 1032–1038. doi:10.15585/mmwr.mm6538e1. ISSN 0149-2195.
98. ^ "First Zika virus-related death reported in U.S. in Puerto Rico". *Washington Post*. Retrieved 29 April 2016.
99. ^ "Ministério da Saúde confirma 8 casos de zika vírus no RN e 8 na BA" [Ministry of Health confirms 8 cases of zika virus in infants and 8 in BA]. *Ben Estar* (in Portuguese). 14 May 2015.
100. ^ *a b* "Monitoramento dos casos de microcefalias no Brasil" [Monitoring cases of microcephaly in Brazil] (PDF) (in Portuguese). Centro de Operações de Emergências em Saúde Pública sobre Microcefalias. 12 December 2015. Retrieved 24 December 2015.
101. ^ "Governo confirma relação entre zika vírus e epidemia de microcefalia" [Government confirms relationship between zika virus and epidemic microcephaly]. *BBC Brasil* (in Portuguese). 28 November 2015. Retrieved 10 March 2016.
102. ^ Blount, Jeb (28 November 2015). "Brazil confirms zica virus link to fetal brain-damage outbreak". *Reuters*. Retrieved 4 February 2016.
103. ^ "País registra 1.248 casos de microcefalia e sete mortes; maioria em PE" [The country has recorded 1,248 cases of microcephaly and seven deaths; most are in PE]. *UOL Notícias* (in Portuguese). 30 November 2015. Retrieved 4 February 2016.
104. ^ *a b* "Rapid risk assessment: Zika virus epidemic in the Americas: potential association with microcephaly and Guillain–Barré syndrome" (PDF). European Centre for Disease Prevention and Control. 10 December 2015. Retrieved 11 February 2016.
105. ^ Cauchemez, Simon; Besnard, Marianne; Bompard, Priscillia; Dub, Timothée; Guillemette-Artur, Prisca; Eyrolle-Guignot, Dominique; Salje, Henrik; Kerkhove, Maria D Van; Abadie, Véronique (2016). "Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study". *The Lancet*. **387** (10033): 2125–2132. doi:10.1016/s0140-6736(16)00651-6.
106. ^ "Zika Virus likely to spread throughout the Americas, says WHO". *The Guardian*. 25 January 2016.
107. ^ "PAHO Statement on Zika Virus Transmission and Prevention". Pan American Health Organization.
108. ^ Collao, X.; Prado, L.; González, C.; et al. (February 2015). "Detection of flavivirus in mosquitoes (Diptera: Culicidae) from Easter Island-Chile". *Revista Chilena de Infectología* (in Spanish). **32** (1): 113–6. doi:10.4067/S0716-10182015000200021. PMID 25860055.
109. ^ "WHO Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain–Barré syndrome". World Health Organization. 1 February 2016. Retrieved 2 February 2016.
110. ^ Roberts, Michelle (1 February 2016). "Zika-linked condition: WHO declares global emergency". *BBC News Online*. Retrieved 1 February 2016.
111. ^ Pearson, Michael (2 February 2016). "Zika virus sparks 'public health emergency'". *CNN*. Retrieved 2 February 2016.
112. ^ "Zika Fever". Centers for Disease Control and Prevention. 1 February 2016. Retrieved 1 February 2016.
113. ^ Rosen, Meghan (22 January 2016). "Rapid spread of Zika virus in the Americas raises alarm". *Science News*. Society for Science and the Public. **189** (4): 16. Retrieved 16 February 2016.
114. ^ *a b* Duong, Veasna; Dussart, Philippe; Buchy, Philippe. "Zika virus in Asia". *International Journal of Infectious Diseases*. **54**: 121–128. doi:10.1016/j.ijid.2016.11.420.
115. ^ de Bernardi Schneider, Adriano; Malone, Robert W.; Guo, Jun-Tao; Homan, Jane; Linchangco, Gregorio; Witter, Zachary L.; Vinesett, Dylan; Damodaran, Lambodhar; Janies, Daniel A. (2016-12-01). "Molecular evolution of Zika virus as it crossed the Pacific to the Americas". *Cladistics*: n/a–n/a. doi:10.1111/cla.12178. ISSN 1096-0031.
116. ^ Maurer-Stroh, Sebastian; Mak, Tze-Minn; Ng, Yi-Kai; Phuah, Shiau-Pheng; Huber, Roland G; Marzinek, Jan K; Holdbrook, Daniel A; Lee, Raphael TC; Cui, Lin. "South-east Asian Zika virus strain linked to cluster of cases in Singapore, August 2016". *Eurosurveillance*. **21** (38). doi:10.2807/1560-7917.es.2016.21.38.30347.
117. ^ Fisher, Dale; Cutter, Jeffery (2016-01-01). "The inevitable colonisation of Singapore by Zika virus". *BMC Medicine*. **14**: 188. doi:10.1186/s12916-016-0737-9. ISSN 1741-7015. PMC 5116805. PMID 27866470.
118. ^ *a b* Romero, Simon (30 December 2015). "Alarm Spreads in Brazil Over a Virus and a Surge in Malformed Infants". *The New York Times*. Retrieved 24 January 2016.
119. ^ Romero, Simon; McNeil, Donald G., Jr. (21 January 2016). "Zika Virus May be Linked to Surge in Rare Syndrome in Brazil". *The New York Times*. Retrieved 13 March 2016.
120. ^ Sun, Lena H. (22 March 2016). "Zika: More than 2,500 babies born with microcephaly in Brazil, WHO predicts". *Washington Post*. Retrieved 23 March 2016.
121. ^ Tavernise, Sabrina (22 March 2016). "Birth Defects Tied to Zika in Panama". *New York Times*. Retrieved

23 March 2016.
122. ^ a b Mlakar, Jernej; Korva, Misa; Tul, Nataša; et al. (10 March 2016). "Zika Virus Associated with Microcephaly". *New England Journal of Medicine*. **374** (10): 951–958. doi:10.1056/NEJMoa1600651. ISSN 0028-4793. PMID 26862926.
123. ^ a b Fine Maron, Dina (28 January 2016). "Zika–Microcephaly Link: Public health officials are not yet ready to say the connection is causal". *Scientific American*. Retrieved 13 March 2016.
124. ^ McNeil Jr., Donald G. (19 February 2016). "Proof of Zika's Role in Birth Defects Still Months Away, W.H.O. Says". *New York Times*. Retrieved 13 March 2016.
125. ^ a b c "WHO statement on the 2nd meeting of IHR Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations". *World Health Organization*. 8 March 2016. Retrieved 13 March 2016.
126. ^ McNeil, Donald G., Jr.; Saint Louis, Catherine (4 March 2016). "Two Studies Strengthen Links Between the Zika Virus and Serious Birth Defects". *New York Times*. Retrieved 13 March 2016.
127. ^ Heymann, David L; Hodgson, Abraham; Sall, Amadou Alpha; et al. (20 February 2016). "Zika virus and microcephaly: why is this situation a PHEIC?". *The Lancet*. **387** (10020): 719–721. doi:10.1016/S0140-6736(16)00320-2.
128. ^ "Brazil may have fewer Zika-related microcephaly cases than previously reported".
129. ^ "Brazil's Pre-Zika Microcephaly Cases".
130. ^ McNeil, Donald G. Jr.; Saint Louis, Catherine (4 March 2016). "Two Studies Strengthen Links Between the Zika Virus and Serious Birth Defects". *New York Times*. Retrieved 23 March 2016.
131. ^ a b Triunfol, Marcia (2016). "A new mosquito-borne threat to pregnant women in Brazil". *The Lancet Infectious Diseases*. **16** (2): 156–157. doi:10.1016/S1473-3099(15)00548-4. ISSN 1473-3099. PMID 26723756.
132. ^ a b Kleber de Oliveira, Wanderson; Cortez-Escalante, Juan; De Oliveira, Wanessa Tenório Gonçalves Holanda; et al. (2016). "Increase in Reported Prevalence of Microcephaly in Infants Born to Women Living in Areas with Confirmed Zika Virus Transmission During the First Trimester of Pregnancy – Brazil, 2015". *MMWR. Morbidity and Mortality Weekly Report*. **65** (9): 242–247. doi:10.15585/mmwr.mm6509e2. ISSN 0149-2195. PMID 26963593.
133. ^ McNeil Jr., Donald G. (16 January 2016). "Hawaii Baby With Brain Damage Is First U.S. Case Tied to Zika Virus". *The New York Times*.
134. ^ Vogel, Gretchen (4 March 2016). "Zika virus kills developing brain cells". *Science*.
135. ^ Butler, Declan (4 March 2016). "First Zika-linked birth defects detected in Colombia". *Nature*. **531** (7593): 153. doi:10.1038/nature.2016.19502. ISSN 0028-0836. PMID 26961637.
136. ^ "Zika: Panama has 'first microcephaly case outside Brazil'". *BBC News Latin America*. BBC. 19 March 2016. Retrieved 20 March 2016.
137. ^ Ventura, Camila V; et al. (January 2016). "Zika virus in Brazil and macular atrophy in a child with microcephaly" (PDF). *The Lancet*. **387** (10015): 228. doi:10.1016/S0140-6736(16)00006-4.
138. ^ "Zika virus: Americas, Asia". *ProMED-mail*. International Society for Infectious Diseases. 28 January 2016. Retrieved 8 February 2016.
139. ^ Martinez, Michael (20 February 2016). "Zika virus: Brazilian scientists decipher its genome, agency says". *CNN*.
140. ^ Szabo, Liz (16 February 2016). "Scientists debunk theory linking pesticide, not Zika, to birth defects". *USA Today*.
141. ^ "Report says Monsanto-linked pesticide is to blame for microcephaly outbreak – not Zika". *Science Alert*. Australia. 16 February 2016. "But let's be clear – there is no scientific evidence to support that link."
142. ^ a b Jacobs, Andrew (16 February 2016). "Conspiracy Theories About Zika Spread Along With the Virus". *The New York Times*. Retrieved 16 February 2016.
143. ^ Bowater, Donna (15 February 2016). "Zika virus: Brazil dismisses link between larvicide and microcephaly". *Daily Telegraph*.
144. ^ Calvet, Guilherme; Aguiar, Renato S; Melo, Adriana S O; et al. (February 2016). "Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study". *The Lancet Infectious Diseases*. doi:10.1016/S1473-3099(16)00095-5. ISSN 1473-3099.
145. ^ "Zika situation report" (PDF). World Health Organisation. 17 March 2016. Retrieved 23 March 2016.
146. ^ Bosley, Sarah (22 March 2016). "WHO: Zika virus 'implicated' in large numbers of brain-damaged babies". *The Guardian*. Retrieved 23 March 2016.
147. ^ Gale, Jason (4 February 2016). "The Best Weapon for Fighting Zika? More Mosquitoes". *Bloomberg*.
148. ^ http://www.nature.com/articles/srep28792 The wMel strain of Wolbachia Reduces Transmission of Zika virus by Aedes aegypti
149. ^ Flam, Faye (4 February 2016). "Fighting Zika Virus With Genetic Engineering". *Bloomberg*.

150. ^ Viegas, Luciana (23 February 2016). "IAEA Helps Brazil Step up the Fight Against 'Zika' Mosquitoes". *International Atomic Energy Agency*.
151. ^ Kelland, Kate (18 March 2016). "WHO backs trials of genetically modified mosquitoes to fight Zika". The Globe and Mail. Retrieved 19 March 2016.

| v · t · e · | **Zoonotic viral diseases (A80–B34, 042–079)** | | |
|---|---|---|---|
| **Arthropod-borne** | **Mosquito-borne** | *Bunyaviridae* | Arbovirus encephalitides: La Crosse encephalitis (LACV · · Batai virus (BATV) · Bwamba Fever (BWAV) · California encephalitis (CEV · · Jamestown Canyon virus · Tete virus · Tahyna virus (TAHV) · Viral hemorrhagic fevers: Rift Valley fever (RVFV · · Bunyamwera fever (BUNV) · Ngari virus (NRIV) · |
| | | *Flaviviridae* | Arbovirus encephalitides: Japanese encephalitis (JEV · · Australian encephalitis (MVEV · KUNV · · Saint Louis encephalitis (SLEV · · West Nile fever (WNV · · Viral hemorrhagic fevers: Dengue fever (DENV-1-4 · · Yellow fever (YFV · · **Zika fever** (Zika virus · · |
| | | *Togaviridae* | Arbovirus encephalitides: Eastern equine encephalomyelitis (EEEV · · Western equine encephalomyelitis (WEEV · · Venezuelan equine encephalomyelitis (VEEV · · Chikungunya (CHIKV · · O'Nyong-nyong fever (ONNV · · Ross River fever (RRV · · Semliki Forest virus · Sindbis fever · |
| | | *Reoviridae* | Banna virus encephalitis · |
| | **Tick-borne** | *Bunyaviridae* | Viral hemorrhagic fevers: Crimean–Congo hemorrhagic fever (CCHFV · · Heartland virus · Bhanja virus · Sandfly fever Naples virus · Lone Star virus · Tete virus · |
| | | *Flaviviridae* | Arbovirus encephalitides: Tick-borne encephalitis (TBEV · · Powassan encephalitis (POWV · · Viral hemorrhagic fevers: Omsk hemorrhagic fever (OHFV · · Kyasanur forest disease (KFDV · AHFV · · Langat virus (LGTV) · |
| | | *Reoviridae* | Colorado tick fever (CTFV · · Kemerovo tickborne viral fever · |
| | **Sandfly-borne** | *Bunyaviridae* | Adria virus (ADRV) · Pappataci fever (Toscana virus · · Sandfly fever Naples virus · Oropouche fever (Oropouche virus · · SFTS virus · |
| | | *Rhabdoviridae* | Chandipura virus · |
| | | *Arenaviridae* | Viral hemorrhagic fevers: Lassa fever (LASV · · Venezuelan hemorrhagic fever (GTOV · · Argentine hemorrhagic fever (JUNV · · |

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| **Mammal-borne** | **Rodent-borne** | | Brazilian hemorrhagic fever (SABV · · Bolivian hemorrhagic fever (MACV · · LUJV · CHPV · |
| | | *Bunyaviridae* | Hemorrhagic fever with renal syndrome (DOBV · HTNV · PUUV · SEOV · AMRV · · Hantavirus pulmonary syndrome (ANDV · SNV · · |
| | **Bat-borne** | *Filoviridae* | Viral hemorrhagic fevers: Ebola virus disease · BDBV · EBOV · SUDV · TAFV · Marburg virus disease · MARV · RAVV · |
| | | *Rhabdoviridae* | Rabies (ABLV · MOKV · DUVV · LBV · · CHPV · |
| | | *Paramyxoviridae* | Henipavirus encephalitis (HeV · NiV · · |
| | *Primate-borne* | *Herpesviridae* | Herpes B virus · |
| | | *Retroviridae* | Simian foamy virus · HTLV-1 · HTLV-2 · |
| | | *Poxviridae* | Tanapox · Yaba monkey tumor virus · |
| | **Multiple vectors** | *Rhabdoviridae* | Rabies (RABV · · Mokola virus · |
| | | *Poxviridae* | Monkeypox · |

Categories: Animal viral diseases | Zika virus




# Book:Medications

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# Birth control



From Wikipedia, the free encyclopedia

*For other uses, see Birth control (disambiguation).*

**Birth control**, also known as **contraception** and **fertility control**, is a method or device used to prevent pregnancy.[1] Birth control has been used since ancient times, but effective and safe methods of birth control only became available in the 20th century.[2] Planning, making available, and using birth control is called family planning.[3][4] Some cultures limit or discourage access to birth control because they consider it to be morally, religiously, or politically undesirable.[2]

The most effective methods of birth control are sterilization by means of vasectomy in males and tubal ligation in females, intrauterine devices (IUDs), and implantable birth control. This is followed by a number of hormone based methods including oral pills, patches, vaginal rings, and injections. Less effective methods include physical barriers such as condoms, diaphragms and birth control sponges and fertility awareness methods. The least effective methods are spermicides and withdrawal by the male before ejaculation. Sterilization, while highly effective, is not usually reversible; all other methods are reversible, most immediately upon stopping them.[5] Safe sex practices, such as with the use of male or female condoms, can also help prevent sexually transmitted infections.[6] Other methods of birth control do not protect against sexually transmitted diseases.[7] Emergency birth control can prevent pregnancy if taken within the 72 to 120 hours after unprotected sex.[8][9] Some argue not having sex as a form of birth control, but abstinence-only sex education may increase teenage pregnancies if offered without birth control education, due to non-compliance.[10][11]

A package of birth control pills

MeSH D003267

[edit on Wikidata]

In teenagers, pregnancies are at greater risk of poor outcomes. Comprehensive sex education and access to birth control decreases the rate of unwanted pregnancies in this age group.[12][13] While all forms of birth control can generally be used by young people,[14] long-acting reversible birth control such as implants, IUDs, or vaginal rings are more successful in reducing rates of teenage pregnancy.[13] After the delivery of a child, a woman who is not exclusively breastfeeding may become pregnant again after as few as four to six weeks. Some methods of birth control can be started immediately following the birth, while others require a delay of up to six months. In women who are breastfeeding, progestin-only methods are preferred over combined oral birth control pills. In women who have reached menopause, it is recommended that birth control be continued for one year after the last period.[14]

About 222 million women who want to avoid pregnancy in developing countries are not using a modern birth control method.[15][16] Birth control use in developing countries has decreased the number of deaths during or around the time of pregnancy by 40% (about 270,000 deaths prevented in 2008) and could prevent 70% if the full demand for birth control were met.[17][18] By lengthening the time between pregnancies, birth control can improve adult women's delivery outcomes and the survival of their children.[17] In the developing world women's earnings, assets, weight, and their children's schooling and health all improve with greater access to birth control.[19] Birth control increases economic growth because of fewer dependent children, more women participating in the workforce, and less use of scarce resources.[19][20]

Contents

## Methods [edit]

*See also: Comparison of birth control methods*

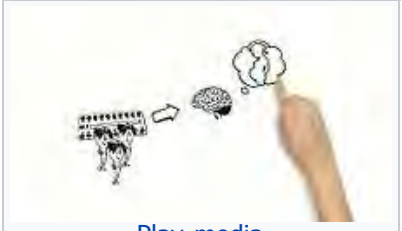
Birth control methods include barrier methods, hormonal birth control, intrauterine devices (IUDs), sterilization, and behavioral methods. They are used before or during sex while emergency contraceptives are effective for up to a few days after sex. Effectiveness is generally expressed as the percentage of women who become pregnant using a given method during the first year,[25] and sometimes as a lifetime failure rate among methods with high effectiveness, such as tubal ligation.[26] The most effective methods are those that are long acting and do not require ongoing health care visits.[27] Surgical sterilization, implantable hormones, and intrauterine devices all have first-year failure rates of less than 1%.[21] Hormonal contraceptive pills, patches or vaginal rings, and the lactational amenorrhea method (LAM), if used strictly, can also have first-year (or for LAM, first-6-month) failure rates of less than 1%.[27] With typical use first-year failure rates are considerably high, at 9%, due to incorrect usage.[21] Other methods such as condoms, diaphragms, and spermicides have higher first-year failure rates even with perfect usage.[27] The American Academy of Pediatrics recommends long acting reversible birth control as first line for young people.[28]

**Chance of pregnancy during first year of use**[21][22]

| Method | Typical use | Perfect use |
|---|---|---|
| No birth control | 85% | 85% |
| Combination pill | 9% | 0.3% |
| Progestin-only pill | 13% | 1.1% |
| Sterilization (female) | 0.5% | 0.5% |
| Sterilization (male) | 0.15% | 0.1% |
| Condom (female) | 21% | 5% |
| Condom (male) | 18% | 2% |
| Copper IUD | 0.8% | 0.6% |
| Hormonal IUD | 0.2% | 0.2% |
| Patch | 9% | 0.3% |
| Vaginal ring | 9% | 0.3% |
| Depo-Provera | 6% | 0.2% |
| Implant | 0.05% | 0.05% |
| Diaphragm and spermicide | 12% | 6% |
| Fertility awareness | 24% | 0.4–5% |
| Withdrawal | 22% | 4% |
| Lactational amenorrhea method (6 months failure rate) | 0-7.5%[23] | <2%[24] |

While all methods of birth control have some potential adverse effects, the risk is less than that of pregnancy.[27] After stopping or removing many methods of birth control, including oral contraceptives, IUDs, implants and injections, the rate of pregnancy during the subsequent year is the same as for those who used no birth control.[29]

In those with specific health problems, certain forms of birth control may require further investigations.[30] For women who are otherwise healthy, many methods of birth control should not require a medical exam—including birth control pills, injectable or implantable birth control, and condoms.[31] Specifically, a pelvic



Play media

exam, breast exam, or blood test before starting birth control pills do not appear to affect outcomes and, therefore, are not required.[32][33] In 2009, the World Health Organization (WHO) published a detailed list of medical eligibility criteria for each type of birth control.[30]

Contraception – How to prevent unwanted pregnancy

## Hormonal [edit]

Hormonal contraception is available in a number of different forms, including oral pills, implants under the skin, injections, patches, IUDs and a vaginal ring. They are currently available only for women, although hormonal contraceptives for men have and are being clinically tested.[34] There are two types of oral birth control pills, the combined oral contraceptive pills (which contain both estrogen and a progestogen) and the progestogen-only pills (sometimes called minipills).[35] If either is taken during pregnancy, they do not increase the risk of miscarriage nor cause birth defects.[33] Both types of birth control pills prevent fertilization mainly by inhibiting ovulation and thickening cervical mucous.[36][37] Their effectiveness depends on the user remembering to take the pills.[33] They may also change the lining of the uterus and thus decrease implantation.[37]

Combined hormonal contraceptives are associated with a slightly increased risk of venous and arterial blood clots.[38] Venous clots, on average, increase from 2.8 to 9.8 per 10,000 women years[39] which is still less than that associated with pregnancy.[38] Due to this risk, they are not recommended in women over 35 years of age who continue to smoke.[40] Due to the increased risk they are included in decision tools such as the DASH score and PERC rule used to predict the risk of blood clots.[41]

The effect on sexual desire is varied, with increase or decrease in some but with no effect in most.[42] Combined oral contraceptives reduce the risk of ovarian cancer and endometrial cancer and do not change the risk of breast cancer.[43][44] They often reduce menstrual bleeding and painful menstruation cramps.[33] The lower doses of estrogen released from the vaginal ring may reduce the risk of breast tenderness, nausea, and headache associated with higher dose estrogen products.[43]

Progestin-only pills, injections and intrauterine devices are not associated with an increased risk of blood clots and may be used by women with previous blood clots in their veins.[38][45] In those with a history of arterial blood clots, non-hormonal birth control or a progestin-only method other than the injectable version should be used.[38] Progestin-only pills may improve menstrual symptoms and can be used by breastfeeding women as they do not affect milk production. Irregular bleeding may occur with progestin-only methods, with some users reporting no periods.[46] The progestins drospirenone and desogestrel minimize the androgenic side effects but increase the risks of blood clots and are thus not first line.[47] The perfect use first-year failure rate of the injectable progestin, Depo-Provera, is 0.2%; the typical use first failure rate is 6%.[21]

Three varieties of birth control pills in calendar oriented packaging

Birth control pills

A transdermal contraceptive patch

A NuvaRing vaginal ring

## Barrier [edit]

Barrier contraceptives are devices that attempt to prevent pregnancy by physically preventing sperm from entering the uterus.[48] They include male condoms, female condoms, cervical caps, diaphragms, and contraceptive sponges with spermicide.[48]

Globally, condoms are the most common method of birth control.[49] Male condoms are put on a man's erect penis and physically block ejaculated sperm from entering the body of a sexual partner.[50] Modern condoms are most often made from latex, but some are made from other materials such as polyurethane, or lamb's intestine.[50] Female condoms are also available, most often made of nitrile, latex or polyurethane.[51] Male condoms have the advantage of being inexpensive, easy to use, and have few adverse effects.[52] Making condoms available to teenagers does not [53]

appear to affect the age of onset of sexual activity or its frequency. In Japan about 80% of couples who are using birth control use condoms, while in Germany this number is about 25%,[54] and in the United States it is 18%.[55]

Male condoms and the diaphragm with spermicide have typical use first-year failure rates of 18% and 12%, respectively.[21] With perfect use condoms are more effective with a 2% first-year failure rate versus a 6% first-year rate with the diaphragm.[21] Condoms have the additional benefit of helping to prevent the spread of some sexually transmitted infections such as HIV/AIDS.[5]

Contraceptive sponges combine a barrier with a spermicide.[27] Like diaphragms, they are inserted vaginally before intercourse and must be placed over the cervix to be effective.[27] Typical failure rates during the first year depend on whether or not a woman has previously given birth, being 24% in those who have and 12% in those who have not.[21] The sponge can be inserted up to 24 hours before intercourse and must be left in place for at least six hours afterward.[27] Allergic reactions[56] and more severe adverse effects such as toxic shock syndrome have been reported.[57]

A rolled up male condom.

An unrolled male latex condom

A polyurethane female condom

A diaphragm vaginal-cervical barrier, in its case with a quarter U.S. coin.

A contraceptive sponge set inside its open package.

## Intrauterine devices [edit]

The current intrauterine devices (IUD) are small devices, often 'T'-shaped, often containing either copper or levonorgestrel, which are inserted into the uterus. They are one form of long-acting reversible contraception which are the most effective types of reversible birth control.[58] Failure rates with the copper IUD is about 0.8% while the levonorgestrel IUD has a failure rates of 0.2% in the first year of use.[59] Among types of birth control, they along with birth control implants result in the greatest satisfaction among users.[60] As of 2007, IUDs are the most widely used form of reversible contraception, with more than 180 million users worldwide.[61]

Copper T shaped IUD with removal strings

Evidence supports effectiveness and safety in adolescents[60] and those who have and have not previously had children.[62] IUDs do not affect breastfeeding and can be inserted immediately after delivery.[63] They may also be used immediately after an abortion.[64] Once removed, even after long term use, fertility returns to normal immediately.[65]

While copper IUDs may increase menstrual bleeding and result in more painful cramps[66] hormonal IUDs may reduce menstrual bleeding or stop menstruation altogether.[63] Cramping can be treated with NSAIDs.[67] Other potential complications include expulsion (2–5%) and rarely perforation of the uterus (less than 0.7%).[63][67] A previous model of the intrauterine device (the Dalkon shield) was associated with an increased risk of pelvic inflammatory disease, however the risk is not affected with current models in those without sexually transmitted infections around the time of insertion.[68]

## Sterilization [edit]

Surgical sterilization is available in the form of tubal ligation for women and vasectomy for men.[2] There are no significant long-term side effects, and tubal ligation decreases the risk of ovarian cancer.[2] Short term complications are twenty times less likely from a vasectomy than a tubal ligation.[2][69] After a vasectomy, there may be swelling and pain of the scrotum which usually resolves in a week or two.[70] With tubal ligation, complications occur in 1 to 2 percent of procedures with serious complications usually due to the anesthesia.[71] Neither method offers protection from sexually transmitted infections.[2]

This decision may cause regret in some men and women. Of women aged over 30 who have undergone tubal

ligation, about 5% regret their decision, as compared with 20% of women aged under 30.[2] By contrast, less than 5% of men are likely to regret sterilization. Men more likely to regret sterilization are younger, have young or no children, or have an unstable marriage.[72] In a survey of biological parents, 9% stated they would not have had children if they were able to do it over again.[73]

Although sterilization is considered a permanent procedure,[74] it is possible to attempt a tubal reversal to reconnect the fallopian tubes or a vasectomy reversal to reconnect the vasa deferentia. In women the desire for a reversal is often associated with a change in spouse.[74] Pregnancy success rates after tubal reversal are between 31 and 88 percent, with complications including an increased risk of ectopic pregnancy.[74] The number of males who request reversal is between 2 and 6 percent.[75] Rates of success in fathering another child after reversal are between 38 and 84 percent; with success being lower the longer the time period between the original procedure and the reversal.[75] Sperm extraction followed by in vitro fertilization may also be an option in men.[76]

## Behavioral [edit]

Behavioral methods involve regulating the timing or method of intercourse to prevent introduction of sperm into the female reproductive tract, either altogether or when an egg may be present.[77] If used perfectly the first-year failure rate may be around 3.4%, however if used poorly first-year failure rates may approach 85%.[78]

## Fertility awareness [edit]

Fertility awareness methods involve determining the most fertile days of the menstrual cycle and avoiding unprotected intercourse.[77] Techniques for determining fertility include monitoring basal body temperature, cervical secretions, or the day of the cycle.[77] They have typical first-year failure rates of 24%; perfect use first-year failure rates depend on which method is used and range from 0.4% to 5%.[21] The evidence on which these estimates are based, however, is poor as the majority of people in trials stop their use early.[77] Globally, they are used by about 3.6% of couples.[79] If based on both basal body temperature and another primary sign, the method is referred to as symptothermal. Overall first-year failure rates of <2% to 20% have been reported in clinical studies of the symptothermal method.[80][81]

A CycleBeads, used for estimating fertility based on days since last menstruation

## Withdrawal [edit]

The withdrawal method (also known as coitus interruptus) is the practice of ending intercourse ("pulling out") before ejaculation.[82] The main risk of the withdrawal method is that the man may not perform the maneuver correctly or in a timely manner.[82] First-year failure rates vary from 4% with perfect usage to 22% with typical usage.[21] It is not considered birth control by some medical professionals.[27]

There is little data regarding the sperm content of pre-ejaculatory fluid.[83] While some tentative research did not find sperm,[83] one trial found sperm present in 10 out of 27 volunteers.[84] The withdrawal method is used as birth control by about 3% of couples.[79]

## Abstinence [edit]

Though some groups advocate total sexual abstinence, by which they mean the avoidance of all sexual activity, in the context of birth control the term usually means abstinence from vaginal intercourse.[85][86] Abstinence is 100% effective in preventing pregnancy; however, not everyone who intends to be abstinent refrains from all sexual activity, and in many populations there is a significant risk of pregnancy from nonconsensual sex.[87][88]

Abstinence-only sex education does not reduce teenage pregnancy.[7][89] Teen pregnancy rates are higher in students given abstinence-only education, as compared with comprehensive sex education.[89][90] Some authorities recommend that those using abstinence as a primary method have backup method(s) available (such as condoms or emergency contraceptive pills).[91] Deliberate non-penetrative sex without vaginal sex or deliberate oral sex without vaginal sex are also sometimes considered birth control.[92] While this generally avoids pregnancy, pregnancy can still occur with intercrural sex and other forms of penis-near-vagina sex (genital rubbing, and the penis exiting from anal intercourse) where sperm can be deposited near the entrance to the vagina and can travel along the vagina's lubricating fluids.[93][94]

## Lactation [edit]

The lactational amenorrhea method involves the use of a woman's natural postpartum infertility which occurs after delivery and may be extended by breastfeeding.[95] This usually requires the presence of no periods, exclusively breastfeeding the infant, and a child younger than six months.[24] The World Health Organization states that if breastfeeding is the infant's only source of nutrition, the failure rate is 2% in the six months following delivery.[96] Six uncontrolled studies of lactational amenorrhea method users found failure rates at 6 months postpartum between 0% and 7.5%.[97] Failure rates increase to 4–7% at one year and 13% at two years.[98] Feeding formula, pumping instead of nursing, the use of a pacifier, and feeding solids all increase its failure rate.[99] In those who are exclusively breastfeeding, about 10% begin having periods before three months and 20% before six months.[98] In those who are not breastfeeding, fertility may return four weeks after delivery.[98]

### Emergency [edit]


A split dose of two emergency contraceptive pills

Emergency contraceptive methods are medications (sometimes misleadingly referred to as "morning-after pills")[100] or devices used after unprotected sexual intercourse with the hope of preventing pregnancy.[8] They work primarily by preventing ovulation or fertilization.[2][101] They are unlikely to affect implantation, but this has not been completely exclude.[101] A number of options exist, including high dose birth control pills, levonorgestrel, mifepristone, ulipristal and IUDs.[102] Levonorgestrel pills, when used within 3 days, decrease the chance of pregnancy after a single episode of unprotected sex or condom failure by 70% (resulting in a pregnancy rate of 2.2%).[8] Ulipristal, when used within 5 days, decreases the chance of pregnancy by about 85% (pregnancy rate 1.4%) and might be a little more effective than levonorgestrel.[8][102][103] Mifepristone is also more effective than levonorgestrel while copper IUDs are the most effective method.[102] IUDs can be inserted up to five days after intercourse and prevent about 99% of pregnancies after an episode of unprotected sex (pregnancy rate of 0.1 to 0.2%).[2][104] This makes them the most effective form of emergency contraceptive.[105] In those who are overweight or obese levonorgestrel is less effective and an IUD or ulipristal is recommended.[106]

Providing emergency contraceptive pills to women in advance does not affect rates of sexually transmitted infections, condom use, pregnancy rates, or sexual risk-taking behavior.[107][108] All methods have minimal side effects.[102]

### Dual protection [edit]

Dual protection is the use of methods that prevent both sexually transmitted infections and pregnancy.[109] This can be with condoms either alone or along with another birth control method or by the avoidance of penetrative sex.[110][111] If pregnancy is a high concern using two methods at the same time is reasonable,[110] and two forms of birth control is recommended in those taking the anti-acne drug isotretinoin, due to the high risk of birth defects if taken during pregnancy.[112]

## Effects [edit]

### Health [edit]

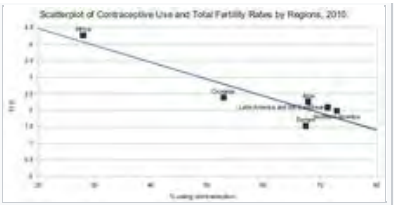
*See also: Maternal health*


Maternal mortality rate as of 2010.[113]

Contraceptive use in developing countries is estimated to have decreased the number of maternal deaths by 40% (about 270,000 deaths prevented in 2008) and could prevent 70% of deaths if the full demand for birth control were met.[17][18] These benefits are achieved by reducing the number of unplanned pregnancies that subsequently result in unsafe abortions and by preventing pregnancies in those at high risk.[17]

Birth control also improves child survival in the developing world by lengthening the time between pregnancies.[17] In this population, outcomes are worse when a mother gets pregnant within eighteen months of a previous delivery.[17][114] Delaying another pregnancy after a miscarriage however does not appear to alter risk and women are advised to attempt pregnancy in this situation whenever they are ready.[114]

Teenage pregnancies, especially among younger teens, are at greater risk of adverse outcomes including early birth, low birth weight, and death of the

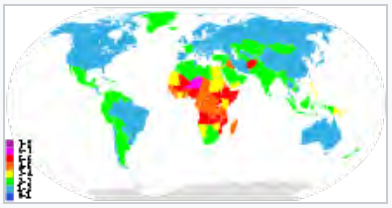


Contraceptive use and total fertility rate by region.

infant.[12] In the United States 82% of pregnancies in those between 15 and 19 are unplanned.[67] Comprehensive sex education and access to birth control are effective in decreasing pregnancy rates in this age group.[115]

## Finances [edit]

*See also: Family economics and Cost of raising a child*



Countries by fertility rate as of 2015

| | |
|---|---|
| 7–8 Children | 3–4 Children |
| 6–7 Children | 2–3 Children |
| 5–6 Children | 1–2 Children |
| 4–5 Children | 0–1 Children |

In the developing world, birth control increases economic growth due to there being fewer dependent children and thus more women participating in the workforce.[19] Women's earnings, assets, body mass index, and their children's schooling and body mass index all improve with greater access to birth control.[19] Family planning via the use of modern birth control is one of the most cost-effective health interventions.[116] For every dollar spent, the United Nations estimates that two to six dollars are saved.[16] These cost savings are related to preventing unplanned pregnancies and decreasing the spread of sexually transmitted illnesses.[116] While all methods are beneficial financially, the use of copper IUDs resulted in the greatest savings.[116]

The total medical cost for a pregnancy, delivery and care of a newborn in the United States is on average $21,000 for a vaginal delivery and $31,000 for a Caesarean section as of 2012.[117] In most other countries the cost is less than half.[117] For a child born in 2011, an average US family will spend $235,000 over 17 years to raise them.[118]

# Prevalence [edit]

*Main article: Prevalence of birth control*

Percentage of women using modern birth control as of 2010

| | | |
|---|---|---|
| 6% | 42% | 78% |
| 12% | 48% | 84% |
| 18% | 54% | 86% |
| 24% | 60% | No data |
| 30% | 66% | |
| 36% | 72% | |

Globally, as of 2009, approximately 60% of those who are married and able to have children use birth control.[119] How frequently different methods are used varies widely between countries.[119] The most common method in the developed world is condoms and oral contraceptives, while in Africa it is oral contraceptives and in Latin America and Asia it is sterilization.[119] In the developing world overall, 35% of birth control is via female sterilization, 30% is via IUDs, 12% is via oral contraceptives, 11% is via condoms, and 4% is via male sterilization.[119]

While less used in the developed countries than the developing world, the number of women using IUDs as of 2007 was more than 180 million.[61] Avoiding sex when fertile is used by about 3.6% of women of childbearing age, with usage as high as 20% in areas of South America.[120] As of 2005, 12% of couples are using a male form of birth control (either condoms or a vasectomy) with higher rates in the developed world.[121] Usage of male forms of birth control has decreased between 1985 and 2009.[119] Contraceptive use among women in Sub-Saharan Africa has risen from about 5% in 1991 to about 30% in 2006.[122]

As of 2012, 57% of women of childbearing age want to avoid pregnancy (867 of 1520 million).[123] About 222 million women however were not able to access birth control, 53 million of whom were in sub-Saharan Africa and 97 million of whom were in Asia.[123] This results in 54 million unplanned pregnancies and nearly 80,000 maternal deaths a year.[119] Part of the reason that many women are without birth control is that many countries limit access due to religious or political reasons,[2] while another contributor is poverty.[124] Due to restrictive abortion laws in Sub-Saharan Africa, many women turn to unlicensed abortion providers for unintended pregnancy, resulting in about 2–4% obtaining unsafe abortions each year.[124]

# History [edit]

*Main article: History of birth control*

## Early history [edit]

The Egyptian Ebers Papyrus from 1550 BCE and the Kahun Papyrus from 1850 BCE have within them some of the earliest documented descriptions of birth control: the use of honey, acacia leaves and lint to be placed in the vagina to block sperm.[125][126] It is believed that in Ancient Greece silphium was used as birth control which, due to its effectiveness and thus desirability, was harvested into extinction.[127]

Ancient silver coin from Cyrene depicting a stalk of silphium

In medieval Europe, any effort to halt pregnancy was deemed immoral by the Catholic Church,[125] although it is believed that women of the time still used a number of birth control measures, such as coitus interruptus and inserting lily root and rue into the vagina.[128] Women in the Middle Ages were also encouraged to tie weasel testicles around their thighs during sex to prevent pregnancy.[129] The oldest condoms discovered to date were recovered in the ruins of Dudley Castle in England, and are dated back to 1640.[129] They were made of animal gut, and were most likely used to prevent the spread of sexually transmitted diseases during the English Civil War.[129] Casanova, living in 18th century Italy, described the use of a lambskin covering to prevent pregnancy; however, condoms only became widely available in the 20th century.[125]

## Birth control movement [edit]


"And the villain still pursues her", a satirical Victorian era postcard

The birth control movement developed during the 19th and early 20th centuries.[130] The Malthusian League, based on the ideas of Thomas Malthus, was established in 1877 in the United Kingdom to educate the public about the importance of family planning and to advocate for getting rid of penalties for promoting birth control.[131] It was founded during the "Knowlton trial" of Annie Besant and Charles Bradlaugh, who were prosecuted for publishing on various methods of birth control.[132]

In the United States, Margaret Sanger and Otto Bobsein popularized the phrase "birth control" in 1914.[133][134] Sanger was mainly active in the United States but had gained an international reputation by the 1930s. At the time, under the Comstock Law, distribution of birth control information was illegal. She jumped bail in 1914 after her arrest for distributing birth control information and left the United States for the United Kingdom to return in 1915.[135] Sanger established a short-lived birth-control clinic based in the Brownville section of Brooklyn, New York [136] in 1916, which was shut down after eleven days and resulted in her arrest.[137] The publicity surrounding the arrest, trial, and appeal sparked birth control activism across the United States.[138]

The first permanent birth-control clinic was established in Britain in 1921 by Marie Stopes working with the Malthusian League.[139] The clinic, run by midwives and supported by visiting doctors,[140] offered women's birth-control advice and taught them the use of a cervical cap. Her clinic made contraception acceptable during the 1920s by presenting it in scientific terms. In 1921, Sanger founded the American Birth Control League, which later became the Planned Parenthood Federation of America.[141] In 1924 the Society for the Provision of Birth Control Clinics was founded to campaign for municipal clinics; this led to the opening of a second clinic in Greengate, Salford in 1926.[142] Throughout the 1920s, Stopes and other feminist pioneers, including Dora Russell and Stella Browne, played a major role in breaking down taboos about sex. In April 1930 the Birth Control Conference assembled 700 delegates and was successful in bringing birth control and abortion into the political sphere – three months later, the Ministry of Health, in the United Kingdom, allowed local authorities to give birth-control advice in welfare centres.[143]

In 1936 the U.S. court ruled in U.S. v. One Package that medically prescribing contraception to save a persons life or well being was not illegal under the Comstock Law; following this decision, the American Medical Association Committee on Contraception revoked its 1936 statement condemning birth control. A national survey in 1937 showed 71 percent of the adult population supported the use of contraception. By 1938 347 birth control clinics were running in the United States despite their advertisement still being illegal. First Lady Eleanor Roosevelt publicly supported birth control and family planning.[144] In 1966, President Lyndon B. Johnson started endorsing public funding for family planning services, and the Federal Government began subsidizing birth control services for low-income families.[145] The Affordable Care Act, passed into law on March 23, 2010 under President Barack Obama, requires all plans in the Health Insurance Marketplace to cover contraceptive methods. These include barrier methods, hormonal methods, implanted devices, emergency contraceptives, and sterilization procedures.[146]

## Modern methods [edit]

In 1909, Richard Richter developed the first intrauterine device made from silkworm gut, which was further developed and marketed in Germany by Ernst Gräfenberg in the late 1920s.[147] In 1951, a chemist, named Carl Djerassi from Mexico City made the hormones in progesterone pill using Mexican yams.[148] Djerassi had chemically created the pill but was not equipped to distribute them to patients. Meanwhile, Gregory Pincus and John Rock with help from the Planned Parenthood Federation of America developed the first birth control pills in the 1950s, such as mestranol/noretynodrel, which became publicly available in the 1960s through the Food and Drug Administration under the name *Enovid*.[141][149] Medical abortion became an alternative to surgical abortion with the availability of prostaglandin analogs in the 1970s and mifepristone in the 1980s.[150]

# Society and culture [edit]

## Legal positions [edit]

*Further information: Timeline of reproductive rights legislation*

Human rights agreements require most governments to provide family planning and contraceptive information and services. These include the requirement to create a national plan for family planning services, remove laws that limit access to family planning, ensure that a wide variety of safe and effective birth control methods are available including emergency contraceptives, make sure there are appropriately trained healthcare providers and facilities at an affordable price, and create a process to review the programs implemented. If governments fail to do the above it may put them in breach of binding international treaty obligations.[151]

In America, Griswold v. Connecticut overturned a state law prohibiting dissemination of contraception information based on a constitutional right to privacy for marital relationships. In 1971, Eisenstadt v. Baird extended this right to privacy to single people.[152]

In 2010, the United Nations launched the *Every Woman Every Child* movement to assess the progress toward meeting women's contraceptive needs. The initiative has set a goal of increasing the number of users of modern birth control by 120 million women in the world's 69 poorest countries by the year 2020. Additionally, they aim to eradicate discrimination against girls and young women who seek contraceptives.[153] The American Congress of Obstetricians and Gynecologists (ACOG) recommended in 2014 that oral birth control pills should be over the counter medications.[154]

Since at least the 1870s, American religious, medical, legislative, and legal commentators have debated contraception laws. Ana Garner and Angela Michel have found that in these discussions men often attach reproductive rights to moral and political matters, as part of an ongoing attempt to regulate human bodies. In press coverage between 1873-2013 they found a divide between institutional ideology and real-life experiences of women.[155]

## Religious views [edit]

*Main article: Religion and birth control*

Religions vary widely in their views of the ethics of birth control.[156] The Roman Catholic Church officially only accepts natural family planning,[157] although large numbers of Catholics in developed countries accept and use modern methods of birth control.[158][159][160] Among Protestants there is a wide range of views from supporting none to allowing all methods of birth control.[161] Views in Judaism range from the stricter Orthodox sect to the more relaxed Reform sect.[162] Hindus may use both natural and artificial contraceptives.[163] A common Buddhist view is that preventing conception is acceptable, while intervening after conception has occurred is not.[164] In Islam, contraceptives are allowed if they do not threaten health, although their use is discouraged by some.[165]

## World Contraception Day [edit]

September 26 is World Contraception Day, devoted to raising awareness and improving education about sexual and reproductive health, with a vision of *a world where every pregnancy is wanted.*[166] It is supported by a group of governments and international NGOs, including the Office of Population Affairs, the Asian Pacific Council on Contraception, Centro Latinamericano Salud y Mujer, the European Society of Contraception and Reproductive Health, the German Foundation for World Population, the International Federation of Pediatric and Adolescent Gynecology, International Planned Parenthood Federation, the Marie Stopes International, Population Services International, the Population Council, the United States Agency for International Development (USAID), and Women Deliver.[166]

## Misconceptions [edit]

There are a number of common misconceptions regarding sex and pregnancy.[167] Douching after sexual intercourse [168]

is not an effective form of birth control. Additionally, it is associated with a number of health problems and thus is not recommended.[169] Women can become pregnant the first time they have sexual intercourse[170] and in any sexual position.[171] It is possible, although not very likely, to become pregnant during menstruation.[172]

## Research directions [edit]

### Females [edit]

Improvements of existing birth control methods are needed, as around half of those who get pregnant unintentionally are using birth control at the time.[27] A number of alterations of existing contraceptive methods are being studied, including a better female condom, an improved diaphragm, a patch containing only progestin, and a vaginal ring containing long-acting progesterone.[173] This vaginal ring appears to be effective for three or four months and is currently available in some areas of the world.[173] For women who rarely have sex, the taking of the hormonal birth control levonorgestrel around the time of sex looks promising.[174]

A number of methods to perform sterilization via the cervix are being studied. One involves putting quinacrine in the uterus which causes scarring and infertility. While the procedure is inexpensive and does not require surgical skills, there are concerns regarding long-term side effects.[175] Another substance, polidocanol, which functions in the same manner is being looked at.[173] A device called Essure, which expands when placed in the fallopian tubes and blocks them, was approved in the United States in 2002.[175]

### Males [edit]

*Main article: Male contraceptive*

Methods of male birth control include condoms, vasectomies and withdrawal.[176][177] Between 25 and 75% of males who are sexually active would use hormonal birth control if it was available for them.[121][176] A number of hormonal and non-hormonal methods are in trials,[121] and there is some research looking at the possibility of contraceptive vaccines.[178]

A reversible surgical method under investigation is reversible inhibition of sperm under guidance (RISUG) which consists of injecting a polymer gel, styrene maleic anhydride in dimethyl sulfoxide, into the vas deferens. An injection with sodium bicarbonate washes out the substance and restores fertility. Another is an intravas device which involves putting a urethane plug into the vas deferens to block it. A combination of an androgen and a progestin seems promising, as do selective androgen receptor modulators.[121] Ultrasound and methods to heat the testicles have undergone preliminary studies.[179]

## Other animals [edit]

Neutering or spaying, which involves removing some of the reproductive organs, is often carried out as a method of birth control in household pets. Many animal shelters require these procedures as part of adoption agreements.[180] In large animals the surgery is known as castration.[181]

Birth control is also being considered as an alternative to hunting as a means of controlling overpopulation in wild animals.[182] Contraceptive vaccines have been found to be effective in a number of different animal populations.[183][184] Kenyan goat herders fix a skirt, called and olor, to male goats to prevent them from impregnating female goats.[185]

## References [edit]


1. ^ "Definition of Birth control". *MedicineNet*. Retrieved August 9, 2012.
2. ^ *a b c d e f g h i j* Hanson, S.J.; Burke, Anne E. (December 21, 2010). "Fertility control: contraception, sterilization, and abortion". In Hurt, K. Joseph; Guile, Matthew W.; Bienstock, Jessica L.; Fox, Harold E.; Wallach, Edward E. *The Johns Hopkins manual of gynecology and obstetrics* (4th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. pp. 382–395. ISBN 978-1-60547-433-5.
3. ^ *Oxford English Dictionary*. Oxford University Press. June 2012.
4. ^ World Health Organization (WHO). "Family planning". *Health topics*. World Health Organization (WHO). Retrieved March 28, 2016.
5. ^ *a b* World Health Organization Department of Reproductive Health and Research (2011). *Family planning: A global handbook for providers: Evidence-based guidance developed through worldwide collaboration* (PDF) (Rev. and Updated ed.). Geneva, Switzerland: WHO and Center for Communication Programs. ISBN 978-0-9788563-7-3.

6. ^ Taliaferro, L. A.; Sieving, R.; Brady, S. S.; Bearinger, L. H. (2011). "We have the evidence to enhance adolescent sexual and reproductive health--do we have the will?". *Adolescent medicine: state of the art reviews*. **22** (3): 521–543, xii. PMID 22423463.
7. ^ a b Chin, H. B.; Sipe, T. A.; Elder, R.; Mercer, S. L.; Chattopadhyay, S. K.; Jacob, V.; Wethington, H. R.; Kirby, D.; Elliston, D. B. (2012). "The Effectiveness of Group-Based Comprehensive Risk-Reduction and Abstinence Education Interventions to Prevent or Reduce the Risk of Adolescent Pregnancy, Human Immunodeficiency Virus, and Sexually Transmitted Infections". *American Journal of Preventive Medicine*. **42** (3): 272–294. doi:10.1016/j.amepre.2011.11.006. PMID 22341164.
8. ^ a b c d Gizzo, S; Fanelli, T; Di Gangi, S; Saccardi, C; Patrelli, TS; Zambon, A; Omar, A; D'Antona, D; Nardelli, GB (October 2012). "Nowadays which emergency contraception? Comparison between past and present: latest news in terms of clinical efficacy, side effects and contraindications.". *Gynecological Endocrinology*. **28** (10): 758–63. doi:10.3109/09513590.2012.662546. PMID 22390259.
9. ^ *Selected practice recommendations for contraceptive use.* (2 ed.). Geneva: World Health Organization. 2004. p. 13. ISBN 9789241562843.
10. ^ DiCenso A, Guyatt G, Willan A, Griffith L (June 2002). "Interventions to reduce unintended pregnancies among adolescents: systematic review of randomised controlled trials". *BMJ*. **324** (7351): 1426. doi:10.1136/bmj.324.7351.1426. PMC 115855. PMID 12065267.
11. ^ Duffy, K.; Lynch, D. A.; Santinelli, J. (2008). "Government Support for Abstinence-Only-Until-Marriage Education". *Clinical Pharmacology & Therapeutics*. **84** (6): 746–748. doi:10.1038/clpt.2008.188. PMID 18923389.
12. ^ a b Black, A. Y.; Fleming, N. A.; Rome, E. S. (2012). "Pregnancy in adolescents". *Adolescent medicine: state of the art reviews*. **23** (1): 123–138, xi. PMID 22764559.
13. ^ a b Rowan, S. P.; Someshwar, J.; Murray, P. (2012). "Contraception for primary care providers". *Adolescent medicine: state of the art reviews*. **23** (1): 95–110, x–xi. PMID 22764557.
14. ^ a b World Health Organization Department of Reproductive Health and Research (2011). *Family planning: A global handbook for providers: Evidence-based guidance developed through worldwide collaboration* (PDF) (Rev. and Updated ed.). Geneva, Switzerland: WHO and Center for Communication Programs. pp. 260–300. ISBN 978-0-9788563-7-3.
15. ^ "Costs and Benefits of Contraceptive Services: Estimates for 2012" (PDF). *United Nations Population Fund*. June 2012. p. 1.
16. ^ a b Carr, B.; Gates, M. F.; Mitchell, A.; Shah, R. (2012). "Giving women the power to plan their families". *The Lancet*. **380** (9837): 80–82. doi:10.1016/S0140-6736(12)60905-2. PMID 22784540.
17. ^ a b c d e f Cleland, J; Conde-Agudelo, A; Peterson, H; Ross, J; Tsui, A (Jul 14, 2012). "Contraception and health.". *Lancet*. **380** (9837): 149–56. doi:10.1016/S0140-6736(12)60609-6. PMID 22784533.
18. ^ a b Ahmed, S.; Li, Q.; Liu, L.; Tsui, A. O. (2012). "Maternal deaths averted by contraceptive use: An analysis of 172 countries". *The Lancet*. **380** (9837): 111–125. doi:10.1016/S0140-6736(12)60478-4. PMID 22784531.
19. ^ a b c d Canning, D.; Schultz, T. P. (2012). "The economic consequences of reproductive health and family planning". *The Lancet*. **380** (9837): 165–171. doi:10.1016/S0140-6736(12)60827-7. PMID 22784535.
20. ^ Van Braeckel, D.; Temmerman, M.; Roelens, K.; Degomme, O. (2012). "Slowing population growth for wellbeing and development". *The Lancet*. **380** (9837): 84–85. doi:10.1016/S0140-6736(12)60902-7. PMID 22784542.
21. ^ a b c d e f g h i Trussell, James (May 2011). "Contraceptive failure in the United States". *Contraception*. **83** (5): 397–404. doi:10.1016/j.contraception.2011.01.021. PMC 3638209. PMID 21477680.
Trussell, James (November 1, 2011). "Contraceptive efficacy". In Hatcher, Robert A.; Trussell, James; Nelson, Anita L.; Cates, Willard Jr.; Kowal, Deborah; Policar, Michael S. *Contraceptive technology* (20th revised ed.). New York: Ardent Media. pp. 779–863. ISBN 978-1-59708-004-0. ISSN 0091-9721. OCLC 781956734.
22. ^ Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention (CDC) (June 21, 2013). "U.S. Selected practice recommendations for contraceptive use, 2013: adapted from the World Health Organization Selected practice recommendations for contraceptive use, 2nd edition". *MMWR Recommendations and Reports*. **62** (5): 1–60. PMID 23784109.
23. ^ Van der Wijden, C; Kleijnen, J; Van den Berk, T (2003). "Lactational amenorrhea for family planning". *Cochrane Database of Systematic Reviews* (4): CD001329. doi:10.1002/14651858.CD001329. PMID 14583931.
24. ^ a b Blenning, CE; Paladine, H (Dec 15, 2005). "An approach to the postpartum office visit.". *American family physician*. **72** (12): 2491–6. PMID 16370405.
25. ^ Brown, Gordon Edlin, Eric Golanty, Kelli McCormack (2000). *Essentials for health and wellness* (2nd ed.). Sudbury, Mass.: Jones and Bartlett. p. 161. ISBN 978-0-7637-0909-9.
26. ^ Edmonds, edited by D. Keith (2012). *Dewhurst's textbook of obstetrics & gynaecology* (8th ed.). Chichester, West Sussex: Wiley-Blackwell. p. 508. ISBN 978-0-470-65457-6.
27. ^ a b c d e f g h i Cunningham, F. Gary; Stuart, Gretchen S. (April 12, 2012). "Contraception and sterilization". In Hoffman, Barbara; Schorge, John O.; Schaffer, Joseph I.; Halvorson, Lisa M.; Bradshaw, Karen D.; Cunningham, F. Gary. *Williams gynecology* (2nd ed.). New York: McGraw-Hill Medical. pp. 132–169. ISBN 978-0-07-171672-7.
28. ^ "Contraception for Adolescents". *Pediatrics*. **134**: e1244–e1256. September 29, 2014. doi:10.1542/peds.2014-2299.
29. ^ Mansour, D; Gemzell-Danielsson, K; Inki, P; Jensen, JT (November 2011). "Fertility after discontinuation of contraception: a comprehensive review of the literature". *Contraception*. **84** (5): 465–77. doi:10.1016/j.contraception.2011.04.002. PMID 22018120.
30. ^ a b Organization, World Health (2009). *Medical eligibility criteria for contraceptive use* (PDF) (4th ed.). Geneva: Reproductive Health and Research, World Health Organization. pp. 1–10. ISBN 9789241563888.
31. ^ Department of Reproductive Health and Research, Family and Community (2004). *Selected practice recommendations for contraceptive use.* (PDF) (2 ed.). Geneva: World Health Organization. p. Chapter 31. ISBN 9241562846.
32. ^ Tepper, NK; Curtis, KM; Steenland, MW; Marchbanks, PA (May 2013). "Physical examination prior to initiating hormonal

contraception: a systematic review.". *Contraception*. **87** (5): 650–4. doi:10.1016/j.contraception.2012.08.010 . PMID 23121820.

33. ^ *a b c d* World Health Organization Department of Reproductive Health and Research (2011). *Family planning: A global handbook for providers: Evidence-based guidance developed through worldwide collaboration* (PDF) (Rev. and Updated ed.). Geneva, Switzerland: WHO and Center for Communication Programs. pp. 1–10. ISBN 978-0-9788563-7-3.
34. ^ Mackenzie, James (December 6, 2013). "The male pill? Bring it on". *The Guardian*. Retrieved May 20, 2014.
35. ^ Ammer, Christine (2009). "oral contraceptive". *The encyclopedia of women's health* (6th ed.). New York: Facts On File. pp. 312–315. ISBN 978-0-8160-7407-5.
36. ^ Nelson, Anita L.; Cwiak, Carrie (2011). "Combined oral contraceptives (COCs)". In Hatcher, Robert A.; Trussell, James; Nelson, Anita L.; Cates, Willard Jr.; Kowal, Deborah; Policar, Michael S. *Contraceptive technology* (20th revised ed.). New York: Ardent Media. pp. 249–341. ISBN 978-1-59708-004-0. ISSN 0091-9721. OCLC 781956734. pp. 257–258:
37. ^ *a b* Barbara L. Hoffman (2011). "5 Second-Tier Contraceptive Methods—Very Effective". *Williams gynecology* (2nd ed.). New York: McGraw-Hill Medical. ISBN 0-07-171672-6.
38. ^ *a b c d* Brito, MB; Nobre, F; Vieira, CS (April 2011). "Hormonal contraception and cardiovascular system". *Arquivos brasileiros de cardiologia*. **96** (4): e81–9. doi:10.1590/S0066-782X2011005000022. PMID 21359483.
39. ^ Stegeman, BH; de Bastos, M; Rosendaal, FR; van Hylckama Vlieg, A; Helmerhorst, FM; Stijnen, T; Dekkers, OM (Sep 12, 2013). "Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis". *BMJ (Clinical research ed.)*. **347**: f5298. doi:10.1136/bmj.f5298. PMC 3771677. PMID 24030561.
40. ^ Kurver, Miranda J.; van der Wijden, Carla L.; Burgers, Jako (October 4, 2012). "Samenvatting van de NHG-standaard 'Anticonceptie' [Summary of the Dutch College of General Practitioners' practice guideline 'Contraception']". *Nederlands Tijdschrift voor Geneeskunde* (in Dutch). **156** (41): A5083. PMID 23062257.
41. ^ Tosetto, A; et al. (2012). "Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH)". *J Thromb Haemost*. **10** (6): 1019-25. doi:10.1111/j.1538-7836.2012.04735.x.
42. ^ Burrows, LJ; Basha, M; Goldstein, AT (September 2012). "The effects of hormonal contraceptives on female sexuality: a review.". *The journal of sexual medicine*. **9** (9): 2213–23. doi:10.1111/j.1743-6109.2012.02848.x. PMID 22788250.
43. ^ *a b* Shulman, LP (October 2011). "The state of hormonal contraception today: benefits and risks of hormonal contraceptives: combined estrogen and progestin contraceptives.". *American Journal of Obstetrics and Gynecology*. **205** (4 Suppl): S9–13. doi:10.1016/j.ajog.2011.06.057. PMID 21961825.
44. ^ Havrilesky, LJ; Moorman, PG; Lowery, WJ; Gierisch, JM; Coeytaux, RR; Urrutia, RP; Dinan, M; McBroom, AJ; Hasselblad, V; Sanders, GD; Myers, ER (July 2013). "Oral Contraceptive Pills as Primary Prevention for Ovarian Cancer: A Systematic Review and Meta-analysis". *Obstetrics and gynecology*. **122** (1): 139–147. doi:10.1097/AOG.0b013e318291c235. PMID 23743450.
45. ^ Mantha, S.; Karp, R.; Raghavan, V.; Terrin, N.; Bauer, K. A.; Zwicker, J. I. (August 7, 2012). "Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis". *BMJ*. **345** (aug07 2): e4944–e4944. doi:10.1136/bmj.e4944. PMC 3413580. PMID 22872710.
46. ^ Burke, AE (October 2011). "The state of hormonal contraception today: benefits and risks of hormonal contraceptives: progestin-only contraceptives.". *American Journal of Obstetrics and Gynecology*. **205** (4 Suppl): S14–7. doi:10.1016/j.ajog.2011.04.033. PMID 21961819.
47. ^ Rott, H (August 2012). "Thrombotic risks of oral contraceptives.". *Current Opinion in Obstetrics and Gynecology*. **24** (4): 235–40. doi:10.1097/GCO.0b013e328355871d. PMID 22729096.
48. ^ *a b* Neinstein, Lawrence (2008). *Adolescent health care : a practical guide* (5th ed.). Philadelphia: Lippincott Williams & Wilkins. p. 624. ISBN 978-0-7817-9256-1.
49. ^ Chaudhuri (2007). *Practice Of Fertility Control: A Comprehensive Manual* (7th ed.). Elsevier India. p. 88. ISBN 9788131211502.
50. ^ *a b* Hamilton, Richard (2012). *Pharmacology for nursing care* (8th ed.). St. Louis, Mo.: Elsevier/Saunders. p. 799. ISBN 978-1-4377-3582-6.
51. ^ *Facts for life* (4th ed.). New York: United Nations Children's Fund. 2010. p. 141. ISBN 9789280644661.
52. ^ Pray, Walter Steven (2005). *Nonprescription product therapeutics* (2nd ed.). Philadelphia: Lippincott Williams & Wilkins. p. 414. ISBN 978-0-7817-3498-1.
53. ^ "Condom Use by Adolescents". *Pediatrics*. **132** (5): 973–981. October 28, 2013. doi:10.1542/peds.2013-2821.
54. ^ Eberhard, Nieschlag, (2010). *Andrology Male Reproductive Health and Dysfunction* (3rd ed.). [S.l.]: Springer-Verlag Berlin Heidelberg. p. 563. ISBN 978-3-540-78355-8.
55. ^ Barbieri, Jerome F. (2009). *Yen and Jaffe's reproductive endocrinology : physiology, pathophysiology, and clinical management* (6th ed.). Philadelphia, PA: Saunders/Elsevier. p. 873. ISBN 978-1-4160-4907-4.
56. ^ Kuyoh, MA; Toroitich-Ruto, C; Grimes, DA; Schulz, KF; Gallo, MF (January 2003). "Sponge versus diaphragm for contraception: a Cochrane review.". *Contraception*. **67** (1): 15–8. doi:10.1016/s0010-7824(02)00434-1. PMID 12521652.
57. ^ Organization, World Health (2009). *Medical eligibility criteria for contraceptive use* (4th ed.). Geneva: Reproductive Health and Research, World Health Organization. p. 88. ISBN 9789241563888.
58. ^ Winner, B; Peipert, JF; Zhao, Q; Buckel, C; Madden, T; Allsworth, JE; Secura, GM. (2012). "Effectiveness of Long-Acting Reversible Contraception". *New England Journal of Medicine*. **366** (21): 1998–2007. doi:10.1056/NEJMoa1110855. PMID 22621627.
59. ^ Hurt, K. Joseph; et al., eds. (March 28, 2012). *The Johns Hopkins manual of gynecology and obstetrics*. Department of Gynecology and Obstetrics, The Johns Hopkins University School of Medicine, Baltimore Maryland (4th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 232. ISBN 978-1-60547-433-5.
60. ^ *a b* Committee on Adolescent Health Care Long-Acting Reversible Contraception Working Group, The American College of Obstetricians and, Gynecologists (October 2012). "Committee opinion no. 539: adolescents and long-acting reversible contraception: implants and intrauterine devices.". *Obstetrics and gynecology*. **120** (4): 983–8.

doi:10.1097/AOG.0b013e3182723b7d . PMID 22996129 .
61. ^ a b Darney, Leon Speroff, Philip D. (2010). *A clinical guide for contraception* (5th ed.). Philadelphia, Pa.: Lippincott Williams & Wilkins. pp. 242–243. ISBN 978-1-60831-610-6.
62. ^ Black, K; Lotke, P; Buhling, KJ; Zite, NB; Intrauterine contraception for Nulliparous women: Translating Research into Action (INTRA), group (October 2012). "A review of barriers and myths preventing the more widespread use of intrauterine contraception in nulliparous women.". *The European Journal of Contraception & Reproductive Health Care*. **17** (5): 340–50. doi:10.3109/13625187.2012.700744. PMID 22834648.
63. ^ a b c Gabbe, Steven (2012). *Obstetrics: Normal and Problem Pregnancies*. Elsevier Health Sciences. p. 527. ISBN 978-1-4557-3395-8.
64. ^ Steenland, MW; Tepper, NK; Curtis, KM; Kapp, N (November 2011). "Intrauterine contraceptive insertion postabortion: a systematic review.". *Contraception*. **84** (5): 447–64. doi:10.1016/j.contraception.2011.03.007. PMID 22018119.
65. ^ Hurd, [edited by] Tommaso Falcone, William W. (2007). *Clinical reproductive medicine and surgery*. Philadelphia: Mosby. p. 409. ISBN 978-0-323-03309-1.
66. ^ Grimes, D.A. (2007). ""Intrauterine Devices (IUDs)" In:Hatcher, RA; Nelson, TJ; Guest, F; Kowal, D". *Contraceptive Technology 19th ed*. New York: Ardent Media.
67. ^ a b c Marnach, ML; Long, ME; Casey, PM (March 2013). "Current issues in contraception.". *Mayo Clinic proceedings. Mayo Clinic*. **88** (3): 295–9. doi:10.1016/j.mayocp.2013.01.007. PMID 23489454.
68. ^ "Popularity Disparity: Attitudes About the IUD in Europe and the United States". Guttmacher Policy Review. 2007. Retrieved April 27, 2010.
69. ^ Adams CE, Wald M (August 2009). "Risks and complications of vasectomy". *Urol. Clin. North Am*. **36** (3): 331–6. doi:10.1016/j.ucl.2009.05.009. PMID 19643235.
70. ^ Hillard, Paula Adams (2008). *The 5-minute obstetrics and gynecology consult*. Hagerstwon, MD: Lippincott Williams & Wilkins. p. 265. ISBN 0-7817-6942-6.
71. ^ Hillard, Paula Adams (2008). *The 5-minute obstetrics and gynecology consult*. Hagerstwon, MD: Lippincott Williams & Wilkins. p. 549. ISBN 0-7817-6942-6.
72. ^ Hatcher, Robert (2008). *Contraceptive technology* (19th ed.). New York, N.Y.: Ardent Media. p. 390. ISBN 978-1-59708-001-9.
73. ^ Moore, David S. (2010). *The basic practice of statistics* (5th ed.). New York: Freeman. p. 25. ISBN 978-1-4292-2426-0.
74. ^ a b c Deffieux, X; Morin Surroca, M; Faivre, E; Pages, F; Fernandez, H; Gervaise, A (May 2011). "Tubal anastomosis after tubal sterilization: a review.". *Archives of gynecology and obstetrics*. **283** (5): 1149–58. doi:10.1007/s00404-011-1858-1. PMID 21331539.
75. ^ a b Shridharani, A; Sandlow, JI (November 2010). "Vasectomy reversal versus IVF with sperm retrieval: which is better?". *Current Opinion in Urology*. **20** (6): 503–9. doi:10.1097/MOU.0b013e32833f1b35. PMID 20852426.
76. ^ Nagler, HM; Jung, H (August 2009). "Factors predicting successful microsurgical vasectomy reversal.". *The Urologic clinics of North America*. **36** (3): 383–90. doi:10.1016/j.ucl.2009.05.010. PMID 19643240.
77. ^ a b c d Grimes, DA; Gallo, MF; Grigorieva, V; Nanda, K; Schulz, KF (Oct 18, 2004). "Fertility awareness-based methods for contraception.". *Cochrane Database of Systematic Reviews* (4): CD004860. doi:10.1002/14651858.CD004860.pub2. PMID 15495128.
78. ^ Lawrence, Ruth (2010). *Breastfeeding : a guide for the medical professional.* (7th ed.). Philadelphia, Pa.: Saunders. p. 673. ISBN 978-1-4377-0788-5.
79. ^ a b Freundl, G; Sivin, I; Batár, I (April 2010). "State-of-the-art of non-hormonal methods of contraception: IV. Natural family planning.". *The European Journal of Contraception & Reproductive Health Care*. **15** (2): 113–23. doi:10.3109/13625180903545302. PMID 20141492.
80. ^ Jennings, Victoria H.; Burke, Anne E. (November 1, 2011). "Fertility awareness-based methods". In Hatcher, Robert A.; Trussell, James; Nelson, Anita L.; Cates, Willard Jr.; Kowal, Deborah; Policar, Michael S. *Contraceptive technology* (20th revised ed.). New York: Ardent Media. pp. 417–434. ISBN 978-1-59708-004-0. ISSN 0091-9721. OCLC 781956734.
81. ^ Frank-Herrmann, Petra; Heil, Jörg; Gnoth, Christian; Toledo, Estefania; Baur, Siegfried; Pyper, Cecilia; Jenetzky, Ekkehart; Strowitzki, Thomas; Freundl, Günter (May 2007). "The effectiveness of a fertility awareness based method to avoid pregnancy in relation to a couple's sexual behaviour during the fertile time: a prospective longitudinal study". *Human Reproduction*. **22** (5): 1310–1319. doi:10.1093/humrep/dem003. PMID 17314078.
82. ^ a b Organization, World Health (2009). *Medical eligibility criteria for contraceptive use* (PDF) (4th ed.). Geneva: Reproductive Health and Research, World Health Organization. pp. 91–100. ISBN 9789241563888.
83. ^ a b Jones, RK; Fennell, J; Higgins, JA; Blanchard, K (June 2009). "Better than nothing or savvy risk-reduction practice? The importance of withdrawal.". *Contraception*. **79** (6): 407–10. doi:10.1016/j.contraception.2008.12.008. PMID 19442773.
84. ^ Killick, SR; Leary, C; Trussell, J; Guthrie, KA (March 2011). "Sperm content of pre-ejaculatory fluid.". *Human fertility (Cambridge, England)*. **14** (1): 48–52. doi:10.3109/14647273.2010.520798. PMC 3564677. PMID 21155689.
85. ^ "Abstinence". *Planned Parenthood*. 2009. Retrieved September 9, 2009.
86. ^ Murthy, Amitasrigowri S; Harwood, Bryna (2007). *Contraception Update* (2nd ed.). New York: Springer. pp. Abstract. doi:10.1007/978-0-387-32328-2_12. ISBN 978-0-387-32327-5.
87. ^ Fortenberry, J. Dennis (2005). "The limits of abstinence-only in preventing sexually transmitted infections". *Journal of Adolescent Health*. **36** (4): 269–70. doi:10.1016/j.jadohealth.2005.02.001. PMID 15780781., which cites:
Brückner, Hannah; Bearman, Peter (2005). "After the promise: The STD consequences of adolescent virginity pledges". *Journal of Adolescent Health*. **36** (4): 271–8. doi:10.1016/j.jadohealth.2005.01.005. PMID 15780782.
88. ^ Kim Best (2005). "Nonconsensual Sex Undermines Sexual Health". *Network*. **23** (4).
89. ^ a b Ott, MA; Santelli, JS (October 2007). "Abstinence and abstinence-only education". *Current Opinion in Obstetrics and Gynecology*. **19** (5): 446–52. doi:10.1097/GCO.0b013e3282efdc0b. PMID 17885460.

90. ^ Duffy, K; Lynch, DA; Santelli, J (December 2008). "Government support for abstinence-only-until-marriage education.". *Clinical pharmacology and therapeutics*. **84** (6): 746–8. doi:10.1038/clpt.2008.188. PMID 18923389.
91. ^ Kowal D (2007). "Abstinence and the Range of Sexual Expression". In Hatcher, Robert A.; et al. *Contraceptive Technology* (19th rev. ed.). New York: Ardent Media. pp. 81–86. ISBN 0-9664902-0-7.
92. ^ Feldmann, J.; Middleman, A. B. (2002). "Adolescent sexuality and sexual behavior". *Current Opinion in Obstetrics and Gynecology*. **14** (5): 489–493. doi:10.1097/00001703-200210000-00008. PMID 12401976.
93. ^ Thomas, R. Murray (2009). *Sex and the American teenager seeing through the myths and confronting the issues*. Lanham, Md.: Rowman & Littlefield Education. p. 81. ISBN 978-1-60709-018-2.
94. ^ Edlin, Gordon (2012). *Health & Wellness.* Jones & Bartlett Learning. p. 213. ISBN 978-1-4496-3647-0.
95. ^ Blackburn, Susan Tucker (2007). *Maternal, fetal, & neonatal physiology : a clinical perspective* (3rd ed.). St. Louis, Mo.: Saunders Elsevier. p. 157. ISBN 978-1-4160-2944-1.
96. ^ "WHO 10 facts on breastfeeding". *World Health Organization*. April 2005.
97. ^ Van der Wijden, Carla; Brown, Julie; Kleijnen, Jos (October 8, 2008). "Lactational amenorrhea for family planning". *Cochrane Database of Systematic Reviews* (4): CD001329. doi:10.1002/14651858.CD001329. PMID 14583931.
98. ^ [a] [b] [c] Fritz, Marc (2012). *Clinical Gynecologic Endocrinology and Infertility*. pp. 1007–1008. ISBN 978-1-4511-4847-3.
99. ^ Swisher, Judith Lauwers, Anna. *Counseling the nursing mother a lactation consultant's guide* (5th ed.). Sudbury, MA: Jones & Bartlett Learning. pp. 465–466. ISBN 978-1-4496-1948-0.
100. ^ Office of Population Research; Association of Reproductive Health Professionals (July 31, 2013). "What is the difference between emergency contraception, the 'morning after pill', and the 'day after pill'?". Princeton: Princeton University. Retrieved September 7, 2013.
101. ^ [a] [b] Leung, Vivian W. Y; Levine, Marc; Soon, Judith A (February 2010). "Mechanisms of Action of Hormonal Emergency Contraceptives". *Pharmacotherapy*. **30** (2): 158–168. doi:10.1592/phco.30.2.158. PMID 20099990. "The evidence strongly supports disruption of ovulation as a mechanism of action. The data suggest that emergency contraceptives are unlikely to act by interfering with implantation"
102. ^ [a] [b] [c] [d] Cheng, L; Che, Y; Gülmezoglu, AM (Aug 15, 2012). "Interventions for emergency contraception.". *Cochrane Database of Systematic Reviews*. **8**: CD001324. doi:10.1002/14651858.CD001324.pub4. PMID 22895920.
103. ^ Richardson, AR; Maltz, FN (January 2012). "Ulipristal acetate: review of the efficacy and safety of a newly approved agent for emergency contraception.". *Clinical therapeutics*. **34** (1): 24–36. doi:10.1016/j.clinthera.2011.11.012. PMID 22154199.
104. ^ "Update on Emergency Contraception". Association of Reproductive Health Professionals. March 2011. Retrieved May 20, 2013.
105. ^ Cleland K, Zhu H, Goldstruck N, Cheng L, Trussel T (2012). "The efficacy of intrauterine devices for emergency contraception: a systematic review of 35 years of experience". *Human Reproduction*. **27** (7): 1994–2000. doi:10.1093/humrep/des140. PMID 22570193.
106. ^ Glasier, A; Cameron, ST; Blithe, D; Scherrer, B; Mathe, H; Levy, D; Gainer, E; Ulmann, A (Oct 2011). "Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel.". *Contraception*. **84** (4): 363–7. doi:10.1016/j.contraception.2011.02.009. PMID 21920190.
107. ^ Kripke C (September 2007). "Advance provision for emergency oral contraception". *Am Fam Physician*. **76** (5): 654. PMID 17894132.
108. ^ Shrader SP, Hall LN, Ragucci KR, Rafie S (September 2011). "Updates in hormonal emergency contraception". *Pharmacotherapy*. **31** (9): 887–95. doi:10.1592/phco.31.9.887. PMID 21923590.
109. ^ "Dual protection against unwanted pregnancy and HIV / STDs". *Sex Health Exch* (3): 8. 1998. PMID 12294688.
110. ^ [a] [b] Cates, W.; Steiner, M. J. (2002). "Dual Protection Against Unintended Pregnancy and Sexually Transmitted Infections: What Is the Best Contraceptive Approach?". *Sexually Transmitted Diseases*. **29** (3): 168–174. doi:10.1097/00007435-200203000-00007. PMID 11875378.
111. ^ "Statement on Dual Protection against Unwanted Pregnancy and Sexually Transmitted Infections, including HIV". International Planned Parenthood Federation. May 2000.
112. ^ Gupta, Ramesh C. (February 25, 2011). *Reproductive and Developmental Toxicology*. Academic Press. p. 105. ISBN 978-0-12-382032-7.
113. ^ Country Comparison: Maternal Mortality Rate in The CIA World Factbook
114. ^ [a] [b] Sholapurkar, SL (February 2010). "Is there an ideal interpregnancy interval after a live birth, miscarriage or other adverse pregnancy outcomes?". *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology*. **30** (2): 107–10. doi:10.3109/01443610903470288. PMID 20143964.
115. ^ Lavin, C; Cox, JE (August 2012). "Teen pregnancy prevention: current perspectives.". *Current Opinion in Pediatrics*. **24** (4): 462–9. doi:10.1097/MOP.0b013e3283555bee. PMID 22790099.
116. ^ [a] [b] [c] Tsui AO, McDonald-Mosley R, Burke AE (April 2010). "Family planning and the burden of unintended pregnancies". *Epidemiol Rev*. **32** (1): 152–74. doi:10.1093/epirev/mxq012. PMC 3115338. PMID 20570955.
117. ^ [a] [b] Rosenthal, Elisabeth (June 30, 2013). "American Way of Birth, Costliest in the World". *New York Times*.
118. ^ "Expenditures on Children by Families, 2011". United States Department of Agriculture, Center for Nutrition Policy and Promotion.
119. ^ [a] [b] [c] [d] [e] [f] Darroch, JE (March 2013). "Trends in contraceptive use.". *Contraception*. **87** (3): 259–63. doi:10.1016/j.contraception.2012.08.029. PMID 23040137.
120. ^ Darney, Leon Speroff, Philip D. (2010). *A clinical guide for contraception* (5th ed.). Philadelphia, Pa.: Lippincott Williams & Wilkins. p. 315. ISBN 1-60831-610-6.
121. ^ [a] [b] [c] [d] Naz, RK; Rowan, S (June 2009). "Update on male contraception.". *Current Opinion in Obstetrics and Gynecology*. **21** (3): 265–9. doi:10.1097/gco.0b013e328329247d. PMID 19469045.
122. ^ Cleland, JG; Ndugwa, RP; Zulu, EM (Feb 1, 2011). "Family planning in sub-Saharan Africa: progress or stagnation?".

*Bulletin of the World Health Organization*. **89** (2): 137–43. doi:10.2471/BLT.10.077925. PMC 3040375. PMID 21346925.

123. ^ [a] [b] Darroch, JE; Singh, S (May 18, 2013). "Trends in contraceptive need and use in developing countries in 2003, 2008, and 2012: an analysis of national surveys.". *Lancet*. **381** (9879): 1756–1762. doi:10.1016/S0140-6736(13)60597-8. PMID 23683642.
124. ^ [a] [b] Rasch, V (July 2011). "Unsafe abortion and postabortion care -an overview.". *Acta Obstetricia et Gynecologica Scandinavica*. **90** (7): 692–700. doi:10.1111/j.1600-0412.2011.01165.x. PMID 21542813.
125. ^ [a] [b] [c] Cuomo, Amy (2010). "Birth control". In O'Reilly, Andrea. *Encyclopedia of motherhood*. Thousand Oaks, Calif.: Sage Publications. pp. 121–126. ISBN 978-1-4129-6846-1.
126. ^ Lipsey, Richard G.; Carlaw, Kenneth; Bekar, Clifford (2005). "Historical Record on the Control of Family Size". *Economic Transformations: General Purpose Technologies and Long-Term Economic Growth*. Oxford University Press. pp. 335–40. ISBN 978-0-19-928564-8.
127. ^ unspecified (2001). "Herbal contraceptives and abortifacients". In Bullough, Vern L. *Encyclopedia of birth control*. Santa Barbara, Calif.: ABC-CLIO. pp. 125–128. ISBN 978-1-57607-181-6.
128. ^ McTavish, Lianne (2007). "Contraception and birth control". In Robin, Diana. *Encyclopedia of women in the Renaissance : Italy, France, and England*. Santa Barbara, Calif.: ABC-CLIO. pp. 91–92. ISBN 978-1-85109-772-2.
129. ^ [a] [b] [c] "A History of Birth Control Methods" (PDF). *Planned Parenthood Report*. January 2012.
130. ^ Hartmann, B (1997). "Population control I: Birth of an ideology.". *International Journal of Health Services*. **27** (3): 523–40. doi:10.2190/bl3n-xajx-0yqb-vqbx. PMID 9285280.
131. ^ Simms, Madeleine (January 27, 1977). "Review: A History of the Malthusian League 1877–1927". *New Scientist*.
132. ^ d'Arcy, F (Nov 1977). "The Malthusian League and the resistance to birth control propaganda in late Victorian Britain.". *Population studies*. **31** (3): 429–48. doi:10.2307/2173367. PMID 11630505.
133. ^ Wilkinson Meyer, Jimmy Elaine (2004). *Any friend of the movement: networking for birth control, 1920–1940*. Ohio State University Press. p. 184. ISBN 978-0-8142-0954-7.
134. ^ Galvin, Rachel (1998). "Margaret Sanger's "Deeds of Terrible Virtue" ". *National Endowment for the Humanities*.
135. ^ Karen Pastorello (2013). *The Progressives: Activism and Reform in American Society, 1893–1917*. John Wiley & Sons. p. 65. ISBN 978-1-118-65112-4.
136. ^ Zorea, Aharon (2012). *Birth Control*. Santa Barbara, California: Greenwood. p. 43. ISBN 978-0-313-36254-5.
137. ^ Baker, Jean H. (2012). *Margaret Sanger : a life of passion* (First pbk. ed.). pp. 115–117. ISBN 978-1-4299-6897-3.
138. ^ McCann, Carole Ruth (2010). "Women as Leaders in the Contraceptive Movement". In Karen O'Connor. *Gender and Women's Leadership: A Reference Handbook*. SAGE. p. 751. OCLC 568741234.
139. ^ Hall, Ruth (1977). *Passionate Crusader*. Harcourt, Brace, Jovanovich. p. 186.
140. ^ Marie Carmichael Stopes (1925). *The First Five Thousand*. London: John Bale, Sons & Danielsson. p. 9. OCLC 12690936.
141. ^ [a] [b] "Family Planning Timeline". *Congressional Digest*. 2015.
142. ^ Herbert, Michael (September 5, 2012). "Salford's birth control pioneers". The Guardian. Retrieved May 28, 2015.
143. ^ Hall, Lesley (2011). *The life and times of Stella Browne : feminist and free spirit*. London: I. B. Tauris. p. 173. ISBN 978-1-84885-583-0.
144. ^ Alesha Doan (2007). *Opposition and Intimidation: The Abortion Wars and Strategies of Political Harassment*. University of Michigan Press. pp. 53–54. ISBN 978-0-472-06975-0.
145. ^ "History of Birth Control in the United States". *Congressional Digest*. 2012.
146. ^ "Birth control benefits and reproductive health care options in the Health Insurance Marketplace". *HealthCare.gov*. Retrieved February 17, 2016.
147. ^ Fritz, Marc A.; Speroff, Leon (2011). "Intrauterine contraception". *Clinical gynecologic endocrinology and infertility* (8th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. pp. 1095–1098. ISBN 978-0-7817-7968-5.
148. ^ "American Experience | The Pill | Timeline". *www.pbs.org*. Retrieved 2016-10-20.
149. ^ Poston, Dudley (2010). *Population and Society: An Introduction to Demography*. Cambridge University Press. p. 98. ISBN 978-1-139-48938-6.
150. ^ Kulier, Regina; Kapp, Nathalie; Gülmezoglu, A. Metin; Hofmeyr, G. Justus; Cheng, Linan; Campana, Aldo (November 9, 2011). "Medical methods for first trimester abortion". *Cochrane Database of Systematic Reviews* (11): CD002855. doi:10.1002/14651858.CD002855.pub4. PMID 22071804.
151. ^ Cottingham J.; Germain A.; Hunt P. (2012). "Use of human rights to meet the unmet need for family planning". *The Lancet*. **380** (9837): 172–180. doi:10.1016/S0140-6736(12)60732-6. PMID 22784536.
152. ^ Alesha Doan (2007). *Opposition and Intimidation: The Abortion Wars and Strategies of Political Harassment*. University of Michigan Press. pp. 62–63. ISBN 978-0-472-06975-0.
153. ^ Susheela Singh; Jacqueline E. Darroch (June 2012). "Adding It Up: Costs and Benefits of Contraceptive Services Estimates for 2012" (PDF). *Guttmacher Institute and United Nations Population Fund (UNFPA), 201*.
154. ^ ACOG (September 9, 2014). "ACOG Statement on OTC Access to Contraception". Archived from the original on September 10, 2014. Retrieved September 11, 2014.
155. ^ Garner, A. C.; Michel, A. R. (4 November 2016). " "The Birth Control Divide": U.S. Press Coverage of Contraception, 1873-2013". *Journalism & Communication Monographs*. **18** (4): 180–234. doi:10.1177/1522637916672457.
156. ^ Srikanthan, A; Reid, RL (February 2008). "Religious and cultural influences on contraception". *Journal of obstetrics and gynaecology Canada – Journal d'obstetrique et gynecologie du Canada (JOGC)*. **30** (2): 129–37. PMID 18254994.
157. ^ Pope Paul VI (July 25, 1968). "Humanae Vitae: Encyclical of Pope Paul VI on the Regulation of Birth". Vatican. Archived from the original on March 19, 2011. Retrieved October 1, 2006.
158. ^ Rosemary Radford Ruether (2006). "Women in North American Catholicism". In Rosemary Skinner Keller. *Encyclopedia of women and religion in North America*. Bloomington, Ind. [u.a.]: Indiana Univ. Press. p. 132. ISBN 978-0-253-34686-5.
159. ^ Bob Digby; et al. (2001). Bob Digby, ed. *Heinemann 16-19 Geography: Global Challenges Student Book 2nd Edition*.

Heinemann. p. 158. ISBN 978-0-435-35249-3.
160. ^ Rengel, Marian (2000). *Encyclopedia of birth control*. Phoenix, Ariz: Oryx Press. p. 202. ISBN 978-1-57356-255-3.
161. ^ Bennett, Jana Marguerite (2008). *Water is thicker than blood : an Augustinian theology of marriage and singleness*. Oxford: Oxford University Press. p. 178. ISBN 978-0-19-531543-1.
162. ^ Feldman, David M. (1998). *Birth Control in Jewish Law*. Lanham, MD: Jason Aronson. ISBN 0-7657-6058-4.
163. ^ "Hindu Beliefs and Practices Affecting Health Care". University of Virginia Health System. Retrieved October 6, 2006.[*dead link*]
164. ^ "More Questions & Answers on Buddhism: Birth Control and Abortion". Alan Khoo. Retrieved June 14, 2008.
165. ^ Khalid Farooq Akbar. "Family Planning and Islam: A Review". *Hamdard Islamicus*. **XVII** (3).
166. ^ *a b* "World Contraception Day". Archived from the original on August 18, 2014.
167. ^ Hutcherson, Hilda (2002). *What your mother never told you about s.e.x* (1st Perigee ed.). New York: Perigee Book. p. 201. ISBN 978-0-399-52853-8.
168. ^ Rengel, Marian (2000). *Encyclopedia of birth control*. Phoenix, Ariz: Oryx Press. p. 65. ISBN 978-1-57356-255-3.
169. ^ Cottrell, BH (Mar–Apr 2010). "An updated review of evidence to discourage douching.". *MCN. The American journal of maternal child nursing*. **35** (2): 102–7; quiz 108–9. doi:10.1097/NMC.0b013e3181cae9da. PMID 20215951.
170. ^ Alexander, William (2013). *New Dimensions In Women's Health – Book Alone* (6th ed.). Jones & Bartlett Publishers. p. 105. ISBN 978-1-4496-8375-7.
171. ^ Sharkey, Harriet (2013). *Need to Know Fertility and Conception and Pregnancy*. HarperCollins. p. 17. ISBN 978-0-00-751686-5.
172. ^ Strange, Mary (2011). *Encyclopedia of women in today's world*. Thousand Oaks, Calif.: Sage Reference. p. 928. ISBN 978-1-4129-7685-5.
173. ^ *a b c* Jensen, JT (October 2011). "The future of contraception: innovations in contraceptive agents: tomorrow's hormonal contraceptive agents and their clinical implications.". *American Journal of Obstetrics and Gynecology*. **205** (4 Suppl): S21–5. doi:10.1016/j.ajog.2011.06.055. PMID 21961821.
174. ^ Halpern, V; Raymond, EG; Lopez, LM (Sep 26, 2014). "Repeated use of pre- and postcoital hormonal contraception for prevention of pregnancy.". *The Cochrane database of systematic reviews*. **9**: CD007595. doi:10.1002/14651858.CD007595.pub3. PMID 25259677.
175. ^ *a b* Castaño, PM; Adekunle, L (March 2010). "Transcervical sterilization.". *Seminars in reproductive medicine*. **28** (2): 103–9. doi:10.1055/s-0030-1248134. PMID 20352559.
176. ^ *a b* Glasier, A (November 2010). "Acceptability of contraception for men: a review.". *Contraception*. **82** (5): 453–6. doi:10.1016/j.contraception.2010.03.016. PMID 20933119.
177. ^ Kogan, P; Wald, M (Feb 2014). "Male contraception: history and development.". *The Urologic clinics of North America*. **41** (1): 145–61. doi:10.1016/j.ucl.2013.08.012. PMID 24286773.
178. ^ Naz, RK (July 2011). "Antisperm contraceptive vaccines: where we are and where we are going?". *American journal of reproductive immunology (New York, N.Y. : 1989)*. **66** (1): 5–12. doi:10.1111/j.1600-0897.2011.01000.x. PMID 21481057.
179. ^ Ojeda, edited by William J. Kovacs, Sergio R. (2011). *Textbook of endocrine physiology* (6th ed.). Oxford: Oxford University Press. p. 262. ISBN 978-0-19-974412-1.
180. ^ Millar, Lila (2011). *Infectious Disease Management in Animal Shelters*. John Wiley & Sons. ISBN 978-1-119-94945-9.
181. ^ Ackerman, [edited by] Lowell (2007). *Blackwell's five-minute veterinary practice management consult* (1st ed.). Ames, Iowa: Blackwell Pub. p. 80. ISBN 978-0-7817-5984-7.
182. ^ Boyle, Rebecca (March 3, 2009). "Birth control for animals: a scientific approach to limiting the wildlife population explosion". *Popular Science*. New York: PopSci.com.
183. ^ Kirkpatrick, JF; Lyda, RO; Frank, KM (July 2011). "Contraceptive vaccines for wildlife: a review.". *American journal of reproductive immunology (New York, N.Y. : 1989)*. **66** (1): 40–50. doi:10.1111/j.1600-0897.2011.01003.x. PMID 21501279.
184. ^ Levy, JK (July 2011). "Contraceptive vaccines for the humane control of community cat populations.". *American journal of reproductive immunology (New York, N.Y. : 1989)*. **66** (1): 63–70. doi:10.1111/j.1600-0897.2011.01005.x. PMID 21501281.
185. ^ "Goat 'condoms' save Kenyan herds". BBC News. 2008-10-06. Retrieved 2008-10-06.

## Further reading [edit]

- Speroff, Leon; Darney, Philip D. (November 22, 2010). *A clinical guide for contraception* (5th ed.). Philadelphia, Pa.: Lippincott Williams & Wilkins. ISBN 978-1-60831-610-6.
- Stubblefield, Phillip G.; Roncari, Danielle M. (December 12, 2011). "Family Planning", pp. 211 – 269, in Berek, Jonathan S. (ed.) *Berek & Novak's Gynecology, 15th ed.* Philadelphia: Lippincott Williams & Wilkins, ISBN 978-1-4511-1433-1.
- Jensen, Jeffrey T.; Mishell, Daniel R. Jr. (March 19, 2012). "Family Planning: Contraception, Sterilization, and Pregnancy Termination", pp. 215 – 272, in Lentz, Gretchen M.; Lobo, Rogerio A.; Gershenson, David M.; Katz, Vern L. (eds.) *Comprehensive Gynecology, 6th ed.* Philadelphia: Mosby Elsevier, ISBN 978-0-323-06986-1.
- Gavin, L; Moskosky, S; Carter, M; Curtis, K; Glass, E (Apr 25, 2014). Godfrey, E; Marcell, A; Mautone-Smith, N; Pazol, K; Tepper, N; Zapata, L; Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion,, CDC. "Providing Quality Family Planning Services: Recommendations of CDC and the U.S. Office of Population Affairs". *MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control*. **63** (RR-04): 1–54. PMID 24759690.

## External links [edit]

- Birth control at DMOZ
- World Health Organization Department of Reproductive Health and Research and Johns Hopkins Bloomberg School of Public Health (2011). *Family planning: A global handbook for providers: Evidence-based guidance developed through worldwide collaboration* (PDF) (Rev. and Updated ed.). Geneva, Switzerland: WHO and Center for Communication Programs. ISBN 978-0-9788563-7-3.
- Curtis, Kathryn M.; Jatlaoui, Tara C.; Tepper, Naomi K.; Zapata, Lauren B.; Horton, Leah G.; Jamieson, Denise J.; Whiteman, Maura K. (29 July 2016). "U.S. Selected Practice Recommendations for Contraceptive Use, 2016". *MMWR. Recommendations and Reports*. **65** (4): 1–66. doi:10.15585/mmwr.rr6504a1.
- "Birth Control Comparison Chart". Cedar River Clinics.
- Bulk procurement of birth control by the World Health Organization
- Example of hormonal contraceptives as risk factor for blood clots: DASH Score for VTE



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| **Education** | Genetic counseling • Pre-conception counseling • Sex education • |
| **Planning** | Assisted reproductive technology • **Birth control** • Childfree/Childlessness • Parenting (Adoption • Childbirth • Foster care • • Reproductive life plan • Safe sex • |
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| **Pregnancy** | Abortion • Maternal health • Obstetrics • Options counseling • Pregnancy from rape • Pregnant patients' rights • Prenatal care • Teenage pregnancy • Preteen pregnancy • Unintended pregnancy • |
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| **Disorder** | Disorders of sex development • Infertility • Reproductive system disease • Sexual dysfunction • Sexually transmitted infection (Clinic • • |
| **By country** | China • India • Iran • Ireland • Pakistan • Philippines • Singapore • United Kingdom (Teen • • United States (Teen pregnancy • Birth control • • |
| **History** | Birth control movement in the United States • History of condoms • Social hygiene movement • Timeline of reproductive rights legislation • |
| **Policy** | One-child policy • Two-child policy • Financial (Baby bonus • Bachelor tax • Birth credit • Child benefit • Tax on childlessness • • |

| v • t • e | **Birth control methods (G02B, G03A)** | |
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| **Barrier and / or spermicidal** | Cervical cap • Condom • Contraceptive sponge • Diaphragm • Female condom • Spermicide • | |
| **Hormonal (formulations)** | **Combined** | Contraceptive patch • Extended cycle • Injectable • NuvaRing • Oral / 'the pill' • |
| | **Progestogen-only** | LARC (Depo-Provera • Implanon/Nexplanon • Norplant/Jadelle) • Progestogen-only pill • Progesterone vaginal ring • |

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| **Post-intercourse** | Emergency contraception (pills or copper IUD) (Ulipristal acetate · Yuzpe regimen) · |
| **Intrauterine device** | IUD with copper (Paragard · · IUD with progestogen (Mirena) · |
| **Abortion** | Medical (RU-486/abortion pill) · Surgical · |
| **Sterilization** | **Female**: Essure · Tubal ligation<br>**Male**: Vasectomy · |
| **Experimental** | Reversible inhibition of sperm under guidance (Vasalgel) · |

| v · t · e · | **Human impact on the environment** | |
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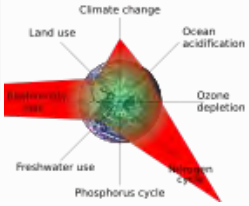
| **Causes** | Agriculture (fishing · irrigation · meat production · palm oil · · Energy industry (biodiesel · coal · electricity generation · nuclear power · oil shale · petroleum · reservoirs · wind power · · Manufacturing (cleaning agents · concrete · nanotechnology · paint · paper · pesticides · pharmaceuticals and personal care · · Transport (aviation · roads · shipping · · Other (land use · mining · genetic pollution · human overpopulation · overexploitation · particulates · pollution · war · · |  |
| **Effects** | Biodiversity threats · Climate change · Deforestation · Desertification · Ecocide · Erosion · Coral reefs · Freshwater cycle · Global warming · Habitat destruction · Holocene extinction · Nitrogen cycle · Land degradation · Land surface effects on climate · Phosphorus cycle · Ocean acidification · Ozone depletion · Runaway climate change · | |
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**Authority control** LCCN: sh85031589 · GND: 4070794-5 ·

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Categories: Women's health | Birth control | Demography | Medical technology | Midwifery


# Carbamazepine

From Wikipedia, the free encyclopedia
(Redirected from Carbamazepine)



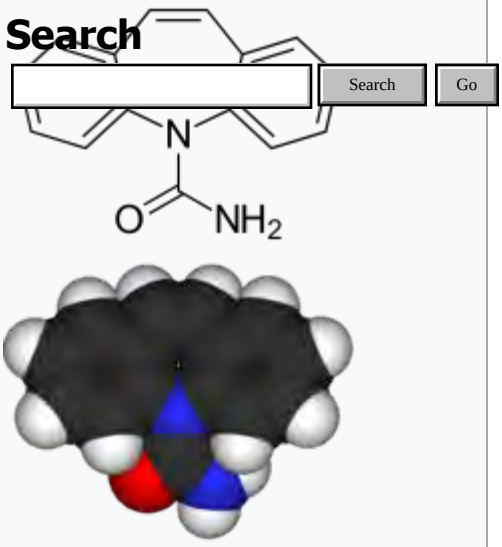
**Carbamazepine** (**CBZ**), sold under the tradename **Tegretol** among others, is a medication used primarily in the treatment of epilepsy and neuropathic pain.[2] It is not effective for absence seizures or myoclonic seizures. It is used in schizophrenia along with other medications and as a second line agent in bipolar disorder.[2] Carbamazepine appears to work as well as phenytoin and valproate.[3][4]

Common side effects include nausea and drowsiness. Serious side effects may include skin rashes, decreased bone marrow function, suicidal thoughts, or confusion. It should not be used in those with a history of bone marrow problems. Use during pregnancy may cause harm to the baby; however stopping it in pregnant women with seizures is not recommended. Its use during breastfeeding is not recommended. Care should be taken in those with either kidney or liver problems.[2]

Carbamazepine was discovered in 1953 by Swiss chemist Walter Schindler.[5] It was first marketed in 1962.[6] It is available as a generic medication and is not very expensive.[7] It is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system.[8] The wholesale cost in the developing world is between 0.01 and 0.07 USD per dose as of 2014.[9]

Contents






| Clinical data | |
|---|---|
| **Trade names** | Tegretol |
| **AHFS/Drugs.com** | Monograph |
| **MedlinePlus** | a682237 |
| **License data** | US DailyMed: 8d409411-aa9f-4f3a-a52c-fbcb0c3ec053 |
| **Pregnancy category** | AU: D<br>US: D (Evidence of risk) |
| **Routes of administration** | Oral |
| **ATC code** | N03AF01 (WHO) |
| **Legal status** | |
| **Legal status** | AU: S4 (Prescription only)<br>CA: -only<br>UK: POM (Prescription only)<br>US: -only |
| **Pharmacokinetic data** | |
| **Bioavailability** | ~100%[1] |

## Medical uses [edit]

Carbamazepine is typically used for the treatment of seizure

disorders and neuropathic pain.[2] It is used off-label as a second-line treatment for bipolar disorder and in combination with an antipsychotic in some cases of schizophrenia when treatment with a conventional antipsychotic alone has failed.[2][10] It is not effective for absence seizures or myoclonic seizures.[2]

In the United States, the FDA-approved medical uses are epilepsy (including partial seizures, generalized tonic-clonic seizures and mixed seizures), trigeminal neuralgia, and manic and mixed episodes of bipolar I disorder.[11]

As of 2014 a controlled release formulation was available for which there is tentative evidence showing fewer side effects and unclear evidence with regard to whether there is a difference in efficacy.[12]



## Adverse effects [edit]

In the US, the label for carbamazepine contains warnings concerning:

- effects on the body's production of red blood cells, white blood cells, and platelets: rarely, there are major effects of aplastic anemia and agranulocytosis reported and more commonly, there are minor changes such as decreased white blood cell or platelet counts, that do not progress to more serious problems.[1]
- increased risks of suicide[1]
- increased risks of hyponatraemia and SIADH[1][13]
- risk of seizures, if the person stops taking the drug abruptly[1]
- risks to the fetus in women who are pregnant, specifically congenital malformations like spina bifida, and developmental disorders.[1][14]

Common adverse effects may include drowsiness, dizziness, headaches and migraines, motor coordination impairment, nausea, vomiting, and/or constipation. Alcohol use while taking carbamazepine may lead to enhanced depression of the central nervous system.[1] Less common side effects may include increased risk of seizures in people with mixed seizure disorders,[15] abnormal heart rhythms, blurry or double vision.[1] Also, rare case reports of an auditory side effect have been made, whereby patients perceive sounds about a semitone lower than previously; this unusual side effect is usually not noticed by most people, and disappears after the person stops taking carbamazepine.[16]

## Interactions [edit]

Carbamazepine has a potential for drug interactions; caution should be used in combining other medicines with it, including other antiepileptics and mood stabilizers.[11] Lower levels of carbamazepine are seen when administrated with phenobarbital, phenytoin, or primidone, which can

| | |
|---|---|
| **Protein binding** | 70-80%[1] |
| **Metabolism** | Hepatic—by CYP3A4, to active epoxide form (carbamazepine-10,11 epoxide)[1] |
| **Biological half-life** | 36 hours (single dose), 16-24 hours (repeated dosing)[1] |
| **Excretion** | Urine (72%), feces (28%)[1] |

**Identifiers**

**IUPAC name**

5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide

| | |
|---|---|
| **CAS Number** | 298-46-4 ✓ 85756-57-6 |
| **PubChem** (CID) | 2554 |
| **IUPHAR/BPS** | 5339 |
| **DrugBank** | DB00564 ✓ |
| **ChemSpider** | 2457 ✓ |
| **UNII** | 33CM23913M ✓ |
| **KEGG** | D00252 ✓ |
| **ChEBI** | CHEBI:3387 ✓ |
| **ChEMBL** | CHEMBL108 ✓ |
| **ECHA InfoCard** | 100.005.512 |

**Chemical and physical data**

| | |
|---|---|
| **Formula** | $C_{15}H_{12}N_2O$ |
| **Molar mass** | 236.269 g/mol |
| **3D model (Jmol)** | Interactive image |

**SMILES**

c1ccc2c(c1)C=Cc3ccccc3N2C(=O)N

**InChI**

InChI=1S/C15H12N2O/c16-15(18)17-13-7-3-1-5-11(13)9-10-12-6-2-4-8-14(12)17/h1-10H,(H2,16,18) ✓

Key:FFGPTBGBLSHEPO-UHFFFAOYSA-N ✓

(verify)

Tegretol 200-mg CR (made in NZ)

result in breakthrough seizure activity. Carbamazepine, as a CYP450 inducer, may increase clearance of many drugs, decreasing their concentration in the blood to subtherapeutic levels and reducing their desired effects.[17] Drugs that are more rapidly metabolized with carbamazepine include warfarin, lamotrigine, phenytoin, theophylline, and valproic acid.[11] Drugs that decrease the metabolism of carbamazepine or otherwise increase its levels include erythromycin,[18] cimetidine, propoxyphene, and calcium channel blockers.[11] Carbamazepine also increases the metabolism of the hormones in birth control pills and can reduce their effectiveness, potentially leading to unexpected pregnancies.[11] As a drug that induces cytochrome P450 enzymes, it accelerates elimination of many benzodiazepines and decreases their action.[19]

Valproic acid and valnoctamide both inhibit microsomal epoxide hydrolase (MEH), the enzyme responsible for the breakdown of carbamazepine-10,11 epoxide into inactive metabolites.[20] By inhibiting MEH, valproic acid and valnoctamide cause a build-up of the active metabolite, prolonging the effects of carbamazepine and delaying its excretion.

Grapefruit juice raises the bioavailability of carbamazepine by inhibiting CYP3A4 enzymes in the gut wall and in the liver.[1] Carbamazepine increases the processing of methadone resulting in lower blood levels.[21]

### Pharmacogenetics [edit]

Dangerous and potentially fatal skin reactions, including Stevens–Johnson syndrome and toxic epidermal necrolysis, caused by carbamazepine therapy are significantly more common in patients with a particular human leukocyte antigen allele, HLA-B*1502.[22] Odds ratios for the development of Stevens-Johnson syndrome or toxic epidermal necrolysis in patients who carry the allele can be in the double, triple or even quadruple digits, depending on the population studied.[23][24] HLA-B*1502 occurs almost exclusively in patients with ancestry across broad areas of Asia, but has a very low or absent frequency in European, Japanese, Korean and African populations.[22][25] However, the HLA-A*31:01 allele has been shown to be a strong predictor of both mild and severe adverse reactions to carbamazepine among Japanese and Europeans.[24]

## Pharmacokinetics [edit]

Carbamazepine is relatively slowly but well absorbed after oral administration. Its plasma half-life is about 30 hours when it is given as single dose, but it is a strong inducer of hepatic enzymes and the plasma half-life shortens to about 15 hours when it is given repeatedly.[*medical citation needed*]

## Mechanism of action [edit]

The mechanism of action of carbamazepine and its derivatives is relatively well understood. Carbamazepine is a use-dependant blocker of voltage-gated sodium channels. It is ionised within intracellular fluid, and is then able to bind to activated voltage-gated sodium channels, preventing repetitive and sustained firing of an action potential.This leaves the affected cells less excitable until the drug dissociates. Carbamazepine is

also a GABA receptor agonist, as it has also been shown to potentiate GABA receptors made up of alpha1, beta2, and gamma2 subunits.[26] This mechanism may contribute to its efficacy in neuropathic pain and bipolar disorder. Laboratory research has further demonstrated that carbamazepine is a serotonin releasing agent and possibly even a serotonin reuptake inhibitor.[27][28][29]

## History [edit]

Carbamazepine was discovered by chemist Walter Schindler at J.R. Geigy AG (now part of Novartis) in Basel, Switzerland, in 1953.[30][31] It was first marketed as a drug to treat epilepsy in Switzerland in 1963 under the brand name "Tegretol"; its use for trigeminal neuralgia (formerly known as tic douloureux) was introduced at the same time.[30] It has been used as an anticonvulsant and antiepileptic in the UK since 1965, and has been approved in the US since 1968.[2]

In 1971, Drs. Takezaki and Hanaoka first used carbamazepine to control mania in patients refractory to antipsychotics (lithium was not available in Japan at that time). Dr. Okuma, working independently, did the same thing with success. As they were also epileptologists, they had some familiarity with the antiaggression effects of this drug. Carbamazepine was studied for bipolar disorder throughout the 1970s.[32]

## Environmental fate [edit]

*Main article: Environmental impact of pharmaceuticals and personal care products*

Carbamazepine has been detected in wastewater effluent.[33]:224 Field and laboratory studies have been conducted to understand the accumulation of carbamazepine in food plants grown in soil treated with sludge, which vary with respect to the concentrations of carbamazepine present in sludge and in the concentrations of sludge in the soil; taking into account only studies that used concentrations normally found, a 2014 review found that "the accumulation of carbamazepine into plants grown in soil amended with biosolids poses a *de minimis* risk to human health according to the approach."[33]:227

## Brand names [edit]

Carbamazepine is available worldwide under many brand names.[34]

## See also [edit]

- Imipramine
- Oxcarbazepine
- Toll-like receptor 4 investigating agonist (proinflammatory) property

## References [edit]


1. ^ *a b c d e f g h i j k l m* "Carbamazepine Drug Label".
2. ^ *a b c d e f g* "Carbamazepine". *The American Society of Health-System Pharmacists*. Retrieved Mar 2015. Check date values in: `|access-date=` (help)
3. ^ Nolan, SJ; Marson, AG; Weston, J; Tudur Smith, C (28 April 2016). "Phenytoin versus valproate monotherapy for partial onset seizures and generalised onset tonic-clonic seizures: an individual participant data review". *The Cochrane database of*

benzodiazepines". In Raymon LP, Mozayani A. *Handbook of Drug Interactions: a Clinical and Forensic Guide*. Humana. pp. 3–88. ISBN 1-58829-211-8.

20. ^ Gonzalez, Frank J.; Robert H. Tukey (2006). "Drug Metabolism". In Laurence Brunton; John Lazo; Keith Parker. *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (11th ed.). New York: McGraw-Hill. p. 79. ISBN 978-0-07-142280-2.
21. ^ Schlatter, J; Madras, JL; Saulnier, JL; Poujade, F (4 September 1999). "Interactions médicamenteuses

*systematic reviews*. **4**: CD001769. doi:10.1002/14651858.CD001769.pub3. PMID 27123830.
4. ^ Nolan, SJ; Marson, AG; Weston, J; Tudur Smith, C (14 August 2015). "Carbamazepine versus phenytoin monotherapy for epilepsy: an individual participant data review". *The Cochrane database of systematic reviews* (8): CD001911. doi:10.1002/14651858.CD001911.pub2. PMID 26275105.
5. ^ Smith, Howard S. (2009). *Current therapy in pain*. Philadelphia: Saunders/Elsevier. p. 460. ISBN 9781416048367.
6. ^ Moshé, Solomon (2009). *The treatment of epilepsy* (3 ed.). Chichester, UK: Wiley-Blackwell. p. xxix. ISBN 9781444316674.
7. ^ *Principles and practice of stereotactic radiosurgery*. New York: Springer. 2008. p. 536. ISBN 9780387710709.
8. ^ "WHO Model List of Essential Medicines" (PDF). *World Health Organization*. October 2013. Retrieved 22 April 2014.
9. ^ "Carbamazepine". *International Drug Price Indicator Guide*. Retrieved 2 December 2015.
10. ^ Ceron-Litvoc D, Soares BG, Geddes J, Litvoc J, de Lima MS (January 2009). "Comparison of carbamazepine and lithium in treatment of bipolar disorder: a systematic review of randomized controlled trials". *Hum Psychopharmacol*. **24** (1): 19–28. doi:10.1002/hup.990. PMID 19053079.
11. ^ *a b c d e* Lexi-Comp (February 2009). "Carbamazepine". *The Merck Manual Professional*. Archived from the original on 2010-11-18. Retrieved on May 3, 2009.
12. ^ Powell, G; Saunders, M; Rigby, A; Marson, AG (3 December 2014). "Immediate-release versus controlled-release carbamazepine in the treatment of epilepsy". *The Cochrane database of systematic reviews*. **12**: CD007124. doi:10.1002/14651858.CD007124.pub4. PMID 25470302.
13. ^ Gandelman, MS (March 1994). "Review of carbamazepine-induced hyponatremia". *Progress in neuro-psychopharmacology & biological psychiatry*. **18** (2): 211–33. doi:10.1016/0278-5846(94)90055-8. PMID 8208974.
14. ^ Jentink, J; Dolk, H; Loane, MA; Morris, JK; Wellesley, D; Garne, E; de Jong-van den Berg, L; EUROCAT Antiepileptic Study Working Group (2010-12-02). "Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study". *BMJ*. **341**: c6581. doi:10.1136/bmj.c6581. PMC 2996546. PMID 21127116.
15. ^ Lige Liu; Thomas Zheng; Margaret J. Morris; Charlott Wallengren; Alison L. Clarke; Christopher A. Reid; Steven Petrou; Terence J. O'Brien (2006). "The Mechanism of Carbamazepine Aggravation of Absence Seizures". *JPET*. **319** (2): 790–798.
avec la méthadone" [Drug interactions with methadone]. *Presse medicale* (in French). **28** (25): 1381–4. PMID 10506872.
22. ^ *a b* "Carbamazepine Drug Label". *http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7a1e523a-b377-43dc-b231-7591c4c888ea*. External link in |website= (help);
23. ^ Kaniwa, N; Saito, Y (June 2013). "Pharmacogenomics of severe cutaneous adverse reactions and drug-induced liver injury". *Journal of human genetics*. **58** (6): 317–26. doi:10.1038/jhg.2013.37. PMID 23635947.
24. ^ *a b* Amstutz, U; Shear, NH; Rieder, MJ; Hwang, S; Fung, V; Nakamura, H; Connolly, MB; Ito, S; Carleton, BC; CPNDS clinical recommendation, group (April 2014). "Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions". *Epilepsia*. **55** (4): 496–506. doi:10.1111/epi.12564. PMID 24597466.
25. ^ Leckband, SG; Kelsoe, JR; Dunnenberger, HM; George AL, Jr; Tran, E; Berger, R; Müller, DJ; Whirl-Carrillo, M; Caudle, KE; Pirmohamed, M; Clinical Pharmacogenetics Implementation, Consortium (September 2013). "Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and carbamazepine dosing". *Clinical pharmacology and therapeutics*. **94** (3): 324–8. doi:10.1038/clpt.2013.103. PMID 23695185.
26. ^ Granger P.; et al. (1995). "Modulation of the gamma-aminobutyric acid type A receptor by the antiepileptic drugs carbamazepine and phenytoin". *Mol. Pharmacol*. **47**: 1189–1196.
27. ^ Dailey, JW; Reith, ME; Steidley, KR; Milbrandt, JC; Jobe, PC (1998). "Carbamazepine-induced release of serotonin from rat hippocampus in vitro". *Epilepsia*. **39**: 1054–63. doi:10.1111/j.1528-1157.1998.tb01290.x. PMID 9776325.
28. ^ Dailey, JW; Reith, ME; Yan, QS; Li, MY; Jobe, PC (11 June 1997). "Carbamazepine increases extracellular serotonin concentration: lack of antagonism by tetrodotoxin or zero Ca2+". *European Journal of Pharmacology*. **328**: 153–62. doi:10.1016/s0014-2999(97)83041-5. PMID 9218697.
29. ^ Kawata, Yuko; Okada, Motohiro; Murakami, Takuya; Kamata, Akihisa; Zhu, Gang; Kaneko, Sunao (2001). "Pharmacological discrimination between effects of carbamazepine on hippocampal basal evoked serotonin release". *British Journal of Pharmacology*. **133** (4): 557–567. doi:10.1038/sj.bjp.0704104. PMC 1572811. PMID 11399673.
30. ^ *a b* D.F. Scott. "Carbamazepine". Chapter 8 in The History of Epileptic Therapy: An Account of How Medication was Developed. History of Medicine Series. CRC Press, 1993 ISBN 9781850703914
31. ^ Schindler W, Häfliger F (1954). "Über Derivate des

doi:10.1124/jpet.106.104968. PMID 16895979.
16. ^ "Carbamazepine-induced transient auditory pitch-perception deficit.". *Pediatr Neurol*. **35**: 131–4. Aug 2006. doi:10.1016/j.pediatrneurol.2006.01.011. PMID 16876011.
17. ^ "eMedicine - Toxicity, Carbamazepine". Archived from the original on 2008-08-04.
18. ^ Stafstrom CE, Nohria V, Loganbill H, Nahouraii R, Boustany RM, DeLong GR (January 1995). "Erythromycin-induced carbamazepine toxicity: a continuing problem". *Arch Pediatr Adolesc Med*. **149** (1): 99–101. doi:10.1001/archpedi.1995.02170130101025. PMID 7827672. Archived from the original on 2010-11-18.
19. ^ Moody D (2004). "Drug interactions with Iminodibenzyls". *Helvetica Chimica Acta*. **37** (2): 472–83. doi:10.1002/hlca.19540370211.
32. ^ Okuma T, Kishimoto A (February 1998). "A history of investigation on the mood stabilizing effect of carbamazepine in Japan". *Psychiatry Clin. Neurosci*. **52** (1): 3–12. doi:10.1111/j.1440-1819.1998.tb00966.x. PMID 9682927.
33. ^ *a b* Prosser RS, Sibley PK2. Human health risk assessment of pharmaceuticals and personal care products in plant tissue due to biosolids and manure amendments, and wastewater irrigation. Environ Int. 2014 Dec 5;75C:223-233. doi: 10.1016/j.envint.2014.11.020. PMID 25486094
34. ^ drugs.com drugs.com international listings for carbamazepine Page accessed June 3, 2015

## External links [edit]

- Carbamazepine overview from PsychEducation.org
- Extensive review of the effects of carbamazepine in pregnancy and breastfeeding

Wikimedia Commons has media related to *Carbamazepine*.

| v · t · e · | Anticonvulsants (N03) | |
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| **GABAergics** | **GABA$_A$R PAMs** | **Barbiturates:** Barbexaclone · Metharbital · Methylphenobarbital · Pentobarbital · Phenobarbital# · Primidone; **Carbamates**: Felbamate; **Benzodiazepines**: Clobazam · Clonazepam · Clorazepate · Diazepam# · Lorazepam# · Midazolam · Nimetazepam · Nitrazepam · Temazepam; **Others:** Bromide (potassium bromide, sodium bromide) · Paraldehyde · Stiripentol · |
| | **GABA-T inhibitors** | **Fatty acids:** Valproate · Valpromide · Valproate pivoxil; **Others:** Ethanolamine-*O*-sulfate · Vigabatrin · |
| | **Others** | **GABAR agonists**: Progabide; **GAT-1 inhibitors:** Tiagabine · |
| **Channelergics** | **Sodium blockers** | **Hydantoins:** Ethotoin · Fosphenytoin · Mephenytoin · Phenytoin#; **Ureides:** Acetylpheneturide · Chlorphenacemide · Phenacemide‡ · Pheneturide; **Fatty acids:** Valproate · Valpromide · Valproate pivoxil; **Carboxamides:** **Carbamazepine**# · Eslicarbazepine acetate · Oxcarbazepine; **Others:** Lacosamide · Lamotrigine · Rufinamide · Topiramate · Zonisamide · |
| | **Calcium blockers** | **Oxazolidinediones:** Ethadione · Paramethadione · Trimethadione; **Succinimides**: Ethosuximide# · Mesuximide · Phensuximide; **Gabapentinoids:** Gabapentin · Pregabalin; **Others:** Lamotrigine · Topiramate · Zonisamide · |
| | **Potassium openers** | Retigabine · |
| **Others** | **CA inhibitors** | **Sulfonamides:** Acetazolamide · Ethoxzolamide · Sultiame · Topiramate · Zonisamide · |
| | **Others** | Beclamide · Brivaracetam · Levetiracetam · Perampanel · |

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WHO-EM · Withdrawn from market · Clinical trials: ( Phase III · Never to phase III · ·

| v · t · e · | Mood stabilizers |
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| **Anticonvulsants** | **Carbamazepine** · Lamotrigine · Oxcarbazepine · Sodium valproate · Valnoctamide · Valproate pivoxil · Valproate semisodium · Valproic acid · Valpromide · |
| **Atypical antipsychotics** | Aripiprazole · Cariprazine · Clozapine · Lurasidone · Olanzapine (+fluoxetine) · Paliperidone · Quetiapine · Risperidone · Ziprasidone · |
| **Others** | Ketamine · Lithium (lithium acetate, lithium carbonate, lithium chloride, lithium citrate, lithium hydroxide) · Omega-3 fatty acids · |

| v · t · e · | Neuropathic pain and fibromyalgia pharmacotherapies |
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| **Monoaminergics** | SNRIs (e.g., duloxetine, milnacipran) · TCAs (e.g., amitriptyline, nortriptyline, dosulepin) · Tapentadol · Tramadol · |
| **Ion channel blockers** | Anticonvulsants (e.g., gabapentin, pregabalin, **carbamazepine**, oxcarbazepine, lacosamide, lamotrigine) · Local anesthetics (e.g., lidocaine) · Mexiletine · TCAs (e.g., amitriptyline, nortriptyline, desipramine) · Ziconotide · |
| **Others** | Alpha lipoic acid · Benfotiamine · Botulinum toxin A · Bupropion · Cannabinoids (e.g., cannabis, dronabinol, nabilone) · NMDAR antagonists (e.g., ketamine, dextromethorphan, methadone) · Opioids (e.g., hydrocodone, morphine, oxycodone, methadone, buprenorphine, tramadol, tapentadol) · Sodium oxybate (GHB) · |

| v · t · e · | Ion channel modulators | |
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| **Calcium ($Ca^{2+}$)** | **Blockers** | **L-type-selective:** *Dihydropyridines:* Amlodipine · Aranidipine · Azelnidipine · Barnidipine · Clevidipine · Cronidipine · Darodipine · Dexniguldipine · Elgodipine · Elnadipine · Felodipine · Flordipine · Furnidipine · Iganidipine · Isradipine · Lacidipine · Lemildipine · Lercanidipine · Levamlodipine · Levniguldipine · Manidipine · Mepirodipine · Mesudipine · Nicardipine · Nifedipine · Niguldipine · Niludipine · Nilvadipine · Nimodipine · Nisoldipine · Nitrendipine · Olradipine · Oxodipine · Palonidipine · Pranidipine · Ryodipine (riodipine) · Sagandipine · Sornidipine · Teludipine · Tiamdipine · Trombodipine · Vatanidipine<br>*Diltiazem derivatives:* Clentiazem · Diltiazem · Iprotiazem · Nictiazem · Siratiazem<br>*Phenylalkylamines:* Anipamil · Dagapamil · Devapamil · Dexverapamil · Emopamil · Etripamil · Falipamil · Gallopamil · Levemopamil · Nexopamil · Norverapamil · Ronipamil · Tiapamil · Verapamil<br>*Others:* AH-1058 · Brinazarone · Budiodarone · Celivarone · Cyproheptadine · Dronedarone · Fantofarone · SR-33805 ·<br>**N-type-selective:** ω-Conotoxins · ω-Conotoxin GVIA · Caroverine · Huwentoxin XVI · Leconotide (ω-conotoxin CVID) · PD-173212 · Ralfinamide · Safinamide · Z160 · Ziconotide (ω-conotoxin MVIIA) ·<br>**P-type-selective:** ω-Agatoxin IVA · ω-Agatoxin IVB ·<br>**R-type-selective:** SNX-482 ·<br>**T-type-selective:** ABT-639 · ML-218 · Niflumic acid · NNC 55-0396 · ProTx I · Z944 · Zonisamide ·<br>**Non-selective:** ω-Agatoxin TK · ω-Conotoxin MVIIC · Benidipine · Bepridil · Cilnidipine · Cinnarizine · Dotarizine · Efonidipine · Flunarizine · Lamotrigine · |

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| | | Levetiracetam · Lomerizine · Loperamide · Mibefradil · NP078585 · Ruthenium red · TROX-1 ·<br>**$\alpha_2\delta$ subunit-selective (gabapentinoids):** 4-Methylpregabalin · Arbaclofen · Arbaclofen placarbil · Atagabalin · Baclofen · Gabapentin · Gabapentin enacarbil · Imagabalin · Mirogabalin · PD-200,347 · PD-217,014 · PD-299,685 · Phenibut · Pregabalin ·<br>**Others/unsorted:** Bencyclane · Berbamine · Bevantolol · Canadine · Carboxyamidotriazole · Cycleanine · Dauricine · Dimeditiapramine · Diproteverine · Enpiperate · Eperisone · Elpetrigine · Ethadione · Ethosuximide · Fasudil · Fendiline · Fostedil · JTV-519 · Lidoflazine · Magnesium · Manoalide · Mesuximide · Monatepil · Naftopidil · Ochratoxin A · Osthol · Otilonium bromide · Paramethadione · Phensuximide · Pinaverium · Prenylamine · Rhynchophylline · Sesamodil · Silperisone · Sipatrigine · Terodiline · Tetrahydropalmatine · Tetrandrine · Tolperisone · Trimethadione · Valperinol · |
| | **Openers** | **L-type-selective:** Bay K8644 · |
| **Potassium ($K^+$)** | **Blockers** | 3,4-Diaminopyridine (amifampridine) · 4-Aminopyridine (fampridine/dalfampridine) · Adekalant · Almokalant · Amiodarone · Azimilide · Bretylium · Bunaftine · Charybdotoxin · Clamikalant · Conotoxins · Dalazatide · Dendrotoxin · Dofetilide · Dronedarone · E-4031 · Hanatoxin · HgeTx1 · HsTx1 · Ibutilide · Inakalant · Kaliotoxin · Linopirdine · Lolitrem B · Maurotoxin · Nifekalant · Notoxin · Paxilline · Pinokalant · ShK-186 · Sotalol · Tedisamil · Terikalant · Tetraethylammonium · Vernakalant ·<br>**GIRK blockers:** Barium · Caramiphen · Cloperastine · Clozapine · Dextromethorphan · Ethosuximide · Ifenprodil · Tertiapin · Tipepidine ·<br>**hERG blockers:** Ajmaline · Amiodarone · AmmTX3 · Astemizole · Azaspiracid · AZD1305 · Azimilide · Bedaquiline · BeKm-1 · BmTx3 · BRL-32872 · Chlorpromazine · Cisapride · Clarithromycin · Darifenacin · Dextropropoxyphene · Diallyl trisulfide · Domperidone · E-4031 · Ergtoxins · Erythromycin · Gigactonine · Haloperidol · Ketoconazole · Norpropoxyphene · Orphenadrine · Pimozide · PNU-282,987 · Promethazine · Ranolazine · Roxithromycin · Sertindole · Solifenacin · Tamulotoxin · Terodiline · Terfenadine · Thioridazine · Tolterodine · Vanoxerine · Vernakalant ·<br>**$K_{ATP}$ blockers:** Acetohexamide · Carbutamide · Chlorpropamide · Glibenclamide (glyburide) · Glibornuride · Glicaramide · Gliclazide · Glimepiride · Glipizide · Gliquidone · Glisoxepide · Glyclopyramide · Glycyclamide · Metahexamide · Mitiglinide · Nateglinide · Repaglinide · Tolazamide · Tolbutamide · |
| | **Openers** | **$K_{ATP}$ openers:** Aprikalim · Bimakalim · Cromakalim · Emakalim · Levcromakalim · Mazokalim · Rilmakalim · Sarakalim ·<br>**Others:** Diazoxide · Flupirtine · Minoxidil · ML-297 · Naminidil · Nicorandil · Pinacidil · Retigabine · Rottlerin · |
| | | **VGSC blockers:** *Antianginals:* Ranolazine<br>*Antiarrhythmics (class I):* Ajmaline · Aprindine · Disopyramide · Dronedarone · Encainide · Flecainide · Lidocaine · Lorajmine · Lorcainide · Mexiletine · Moricizine · Pilsicainide · Prajmaline · Procainamide · Propafenone · Quinidine · Sparteine · Tocainide<br>*Anticonvulsants:* Acetylpheneturide · **Carbamazepine** · Cenobamate · |

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| **Sodium ($Na^+$)** | **Blockers** | Chlorphenacemide · Elpetrigine · Eslicarbazepine acetate · Ethotoin · Fosphenytoin · Lacosamide · Licarbazepine · Mephenytoin · Oxcarbazepine · Oxitriptyline · Phenacemide · Pheneturide · Phenytoin · Rufinamide · Sipatrigine · Topiramate · Sodium valproate · Valnoctamide · Valproate pivoxil · Valproate semisodium · Valproic acid · Valpromide · Zonisamide<br>*Diuretics:* Amiloride · Benzamil · Triamterene<br>*Local anesthetics:* *p*FBT · Amylocaine · Articaine · Benzocaine · Bupivacaine (Levobupivacaine, Ropivacaine) · Butacaine · Butamben · Chloroprocaine · Cinchocaine · Cocaine · Cyclomethycaine · Dimethocaine · Diphenhydramine · Etidocaine · Hexylcaine · Iontocaine · Lidocaine · Mepivacaine · Meprylcaine · Metabutoxycaine · Orthocaine · Piperocaine · Prilocaine · Procaine · Propoxycaine · Proxymetacaine · Risocaine · Tetracaine · Trimecaine<br>*Analgesics:* AZD-3161 · DSP-2230 · Funapide · GDC-0276 · NKTR-171 · PF-04531083 · PF-05089771 · Ralfinamide · Raxatrigine · RG7893 (GDC-0287)<br>*Toxins:* Conotoxins · Neosaxitoxin · Saxitoxin · Tetrodotoxin<br>*Others:* Buprenorphine · Evenamide · Menthol · Safinamide · Tricyclic antidepressants · |
| | **Openers** | **VGSC openers:** Atracotoxins (Robustoxin, Versutoxin) · Ciguatoxins · **ENaC openers:** Solnatide · |
| **Chloride ($Cl^-$)** | **Blockers** | Bumetanide · DIDS · Flufenamic acid · Furosemide · Glibenclamide · Lonidamine · Meclofenamic acid · Mefenamic acid · Mepacrine · Niflumic acid · Piretanide · Talniflumate · Tolfenamic acid · Trifluoperazine · |
| | **Openers** | **CFTR openers:** 1,7-Phenanthroline · 1,10-Phenanthroline · 4,7-Phenanthroline · 7,8-Benzoquinoline · Phenanthridine · |

| v · t · e · | **$GABA_A$ receptor positive allosteric modulators** |
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| **Alcohols** | Brometone · Butanol · Chloralodol · Chlorobutanol (cloretone) · Ethanol (drinking alcohol) · Ethchlorvynol · Isobutanol · Isopropanol · Menthol · Methanol · Methylpentynol · Pentanol · Petrichloral · Propanol · *tert*-Butanol (2M2P) · *tert*-Pentanol (2M2B) · Tribromoethanol · Trichloroethanol · Triclofos · Trifluoroethanol · |
| **Barbiturates** | (-)-DMBB · Allobarbital · Alphenal · Amobarbital · Aprobarbital · Barbexaclone · Barbital · Benzobarbital · Benzylbutylbarbiturate · Brallobarbital · Brophebarbital · Butabarbital/Secbutabarbital · Butalbital · Buthalital · Butobarbital · Butallylonal · Carbubarb · CP-1414S · Crotylbarbital · Cyclobarbital · Cyclopentobarbital · Difebarbamate · Enallylpropymal · Ethallobarbital · Eterobarb · Febarbamate · Heptabarb · Heptobarbital · Hexethal · Hexobarbital · Metharbital · Methitural · Methohexital · Methylphenobarbital · Narcobarbital · Nealbarbital · Pentobarbital · Phenallymal · Phenobarbital · Phetharbital · Primidone · Probarbital · Propallylonal · Propylbarbital · Proxibarbital · Reposal · Secobarbital · Sigmodal · Spirobarbital · Talbutal · Tetrabamate · Tetrabarbital · Thialbarbital · Thiamylal · Thiobarbital · Thiobutabarbital · Thiopental · Thiotetrabarbital · Valofane · Vinbarbital · Vinylbital · |
| | 2-Oxoquazepam · 3-Hydroxyphenazepam · Adinazolam · Alprazolam · Arfendazam · Avizafone · Bentazepam · Bretazenil · Bromazepam · Brotizolam · Camazepam · Carburazepam · Chlordiazepoxide · Ciclotizolam · Cinazepam · Cinolazepam · Clazolam · Climazolam · Clobazam · Clonazepam · Clonazolam · Clorazepate · Clotiazepam · Cloxazolam · Cyprazepam |

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| **Benzodiazepines** | • Delorazepam • Demoxepam • Diazepam • Diclazepam • Doxefazepam • Elfazepam • Estazolam • Ethyl carfluzepate • Ethyl dirazepate • Ethyl loflazepate • Etizolam • EVT-201 • FG-8205 • Fletazepam • Flubromazepam • Flubromazolam • Fludiazepam • Flunitrazepam • Flurazepam • Flutazolam • Flutemazepam • Flutoprazepam • Fosazepam • Gidazepam • Halazepam • Haloxazolam • Iclazepam • Imidazenil • Irazepine • Ketazolam • Lofendazam • Lopirazepam • Loprazolam • Lorazepam • Lormetazepam • Meclonazepam • Medazepam • Menitrazepam • Metaclazepam • Mexazolam • Midazolam • Motrazepam • N-Desalkylflurazepam • Nifoxipam • Nimetazepam • Nitrazepam • Nitrazepate • Nitrazolam • Nordazepam • Nortetrazepam • Oxazepam • Oxazolam • Phenazepam • Pinazepam • Pivoxazepam • Prazepam • Premazepam • Proflazepam • Pyrazolam • QH-II-66 • Quazepam • Reclazepam • Remimazolam • Rilmazafone • Ripazepam • Ro48-6791 • Ro48-8684 • SH-053-R-CH3-2′F • Sulazepam • Temazepam • Tetrazepam • Tolufazepam • Triazolam • Triflubazam • Triflunordazepam (Ro5-2904) • Tuclazepam • Uldazepam • Zapizolam • Zolazepam • Zomebazam • |
| **Carbamates** | Carisbamate • Carisoprodol • Clocental • Cyclarbamate • Difebarbamate • Emylcamate • Ethinamate • Febarbamate • Felbamate • Hexapropymate • Lorbamate • Mebutamate • Meprobamate • Nisobamate • Pentabamate • Phenprobamate • Procymate • Styramate • Tetrabamate • Tybamate • |
| **Flavonoids** | 6-Methylapigenin • Ampelopsin (dihydromyricetin) • Apigenin • Baicalein • Baicalin • Catechin • EGC • EGCG • Hispidulin • Linarin • Luteolin • Rc-OMe • Skullcap constituents (e.g., baicalin) • Wogonin • |
| **Imidazoles** | Etomidate • Metomidate • Propoxate • |
| **Kava constituents** | 10-Methoxyyangonin • 11-Methoxyyangonin • 11-Hydroxyyangonin • Desmethoxyyangonin • 11-Methoxy-12-hydroxydehydrokavain • 7,8-Dihydroyangonin • Kavain • 5-Hydroxykavain • 5,6-Dihydroyangonin • 7,8-Dihydrokavain • 5,6,7,8-Tetrahydroyangonin • 5,6-Dehydromethysticin • Methysticin • 7,8-Dihydromethysticin • Yangonin • |
| **Monoureides** | Acecarbromal • Apronal (apronalide) • Bromisoval • Carbromal • Capuride • Ectylurea • |
| **Neuroactive steroids** | Acebrochol • Allopregnanolone (SAGE-547) • Alfadolone • Alfaxalone • Anabolic steroids • 3α-Androstanediol • Androstenol • Androsterone • Cholesterol • DHDOC • 3α-DHP • 5α-DHP • 5β-DHP • DHT • Etiocholanolone • Ganaxolone • Hydroxydione • Minaxolone • Org 20599 • Org 21465 • P1-185 • Pregnanolone (eltanolone) • Progesterone • Renanolone • SAGE-105 • SAGE-217 • SAGE-324 • SAGE-516 • SAGE-689 • SAGE-872 • Testosterone • THDOC • |
| **Nonbenzodiazepines** | **β-Carbolines**: Abecarnil • Gedocarnil • Harmane • SL-651,498 • ZK-93423; **Cyclopyrrolones**: Eszopiclone • Pagoclone • Pazinaclone • Suproclone • Suriclone • Zopiclone; **Imidazopyridines**: Alpidem • DS-1 • Necopidem • Saripidem • Zolpidem; **Pyrazolopyrimidines**: Divaplon • Fasiplon • Indiplon • Lorediplon • Ocinaplon • Panadiplon • Taniplon • Zaleplon; **Others**: Adipiplon • CGS-8216 • CGS-9896 • CGS-13767 • CGS-20625 • CL-218,872 • CP-615,003 • CTP-354 • ELB-139 • GBLD-345 • JM-1232 • L-838,417 • Lirequinil (Ro41-3696) • NS-2664 • NS-2710 • NS-11394 • Pipequaline • ROD-188 • RWJ-51204 • SB-205,384 • SX-3228 • TGSC01AA • TP-003 • TPA-023 • TP-13 • U-89843A • U-90042 • Viqualine • Y-23684 • |
| **Phenols** | Fospropofol • Propofol • Thymol • |
| **Piperidinediones** | Glutethimide • Methyprylon • Piperidione • Pyrithyldione • |

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| **Pyrazolopyridines** | Cartazolate · Etazolate · ICI-190,622 · Tracazolate · |
| **Quinazolinones** | Afloqualone · Cloroqualone · Diproqualone · Etaqualone · Mebroqualone · Mecloqualone · Methaqualone · Methylmethaqualone · Nitromethaqualone · SL-164 · |
| **Volatiles/gases** | Acetone · Acetophenone · Acetylglycinamide chloral hydrate · Aliflurane · Benzene · Butane · Butylene · Centalun · Chloral · Chloral betaine · Chloral hydrate · Chloroform · Cryofluorane · Desflurane · Dichloralphenazone · Dichloromethane · Diethyl ether · Enflurane · Ethyl chloride · Ethylene · Fluroxene · Gasoline · Halopropane · Halothane · Isoflurane · Kerosine · Methoxyflurane · Methoxypropane · Nitric oxide · Nitrogen · Nitrous oxide · Norflurane · Paraldehyde · Propane · Propylene · Roflurane · Sevoflurane · Synthane · Teflurane · Toluene · Trichloroethane (methyl chloroform) · Trichloroethylene · Vinyl ether · |
| **Others/unsorted** | 3-Hydroxybutanal · α-EMTBL · AA-29504 · Avermectins (e.g., ivermectin) · Bromide compounds (e.g., lithium bromide, potassium bromide, sodium bromide) · **Carbamazepine** · Chloralose · Chlormezanone · Clomethiazole · DEABL · Dihydroergolines (e.g., dihydroergocryptine, dihydroergosine, dihydroergotamine, ergoloid (dihydroergotoxine)) · DS2 · Efavirenz · Etazepine · Etifoxine · Fenamates (e.g., flufenamic acid, mefenamic acid, niflumic acid, tolfenamic acid) · Fluoxetine · Flupirtine · Hopantenic acid · Lanthanum · Lavender oil · Lignans (e.g., 4-O-methylhonokiol, honokiol, magnolol, obovatol) · Loreclezole · Menthyl isovalerate (validolum) · Monastrol · Niacin · Nicotinamide (niacinamide) · Org 25,435 · Phenytoin · Propanidid · Retigabine (ezogabine) · Safranal · Seproxetine · Stiripentol · Sulfonylalkanes (e.g., sulfonmethane (sulfonal), tetronal, trional) · Terpenoids (e.g., borneol) · Topiramate · Valerian constituents (e.g., isovaleric acid, isovaleramide, valerenic acid, valerenol) · **Unsorted benzodiazepine site PAMs:** MRK-409 (MK-0343) · TCS-1105 · TCS-1205 · |
| *See also: GABAergics* | |

v · t · e · **Nuclear receptor modulators**

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| **CAR** | **Agonists** | | 6,7-Dimethylesculetin · Amiodarone · Artemisinin · Benfuracarb · **Carbamazepine** · Carvedilol · Chlorpromazine · Chrysin · CITCO · Clotrimazole · Cyclophosphamide · Cypermethrin · DHEA · Efavirenz · Ellagic acid · Griseofulvin · Methoxychlor · Mifepristone · Nefazodone · Nevirapine · Nicardipine · Octicizer · Permethrin · Phenobarbital · Phenytoin · Pregnanedione (5β-dihydroprogesterone) · Reserpine · TCPOBOP · Telmisartan · Tolnaftate · Troglitazone · Valproic acid · |
| | **Antagonists** | | 3,17β-Estradiol · 3α-Androstanol · 3α-Androstenol · 3β-Androstanol · 17-Androstanol · AITC · Ethinylestradiol · Meclizine · Nigramide J · Okadaic acid · PK-11195 · S-07662 · T-0901317 · |
| **ERR** | **ERRα** | **Agonists** | 6,3′,4′-Trihydroxyflavone · Biochanin A · Cholesterol · Daidzein · Genistein · |
| | | **Antagonists** | Diethylstilbestrol · XCT-790 · |
| | **ERRβ** | **Agonists** | DY-131 (GSK-9089) · GSK-4716 (GW-4716) · |
| | | **Antagonists** | 4-Hydroxytamoxifen (afimoxifene) · Diethylstilbestrol · |
| | **ERRγ** | **Agonists** | Bisphenol A · DY-131 (GSK-9089) · GSK-4716 (GW-4716) · |
| | | **Antagonists** | 4-Hydroxytamoxifen (afimoxifene) · Diethylstilbestrol · |
| **FXR** | **Agonists** | | Bile acids · Cafestol · Chenodeoxycholic acid · Fexaramine · GW-4064 · Obeticholic acid · |

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| | **Antagonists** | | Guggulsterone · |
| **LXR** | **Agonists** | | 22R-Hydroxycholesterol · 24S-Hydroxycholesterol · 27-Hydroxycholesterol · Cholestenoic acid · DMHCA · GW-3965 · Hypocholamide · T-0901317 · |
| | **Antagonists** | | Efavirenz · |
| **PPAR** | **PPARα** | **Agonists** | 15-HETE · 15-HpETE · Aleglitazar · Aluminium clofibrate · Arachidonic acid · Bezafibrate · Clofibrate · CP-775146 · Daidzein · DHEA · Elafibranor · Etomoxir · Fenofibrate · Genistein · Gemfibrozil · GW-7647 · Leukotriene $B_4$ · LG-101506 · LG-100754 · Lobeglitazone · Muraglitazar · Oleylethanolamide · Palmitoylethanolamide · Pemafibrate · Perfluorononanoic acid · Perfluorooctanoic acid · Pioglitazone · Saroglitazar · Sodelglitazar · Tesaglitazar · Tetradecylthioacetic acid · Troglitazone · WY-14643 · |
| | | **Antagonists** | GW-6471 · MK-886 · |
| | **PPARδ** | **Agonists** | 15-HETE · 15-HpETE · Arachidonic acid · Bezafibrate · Daidzein · Elafibranor · Fonadelpar · Genistein · GW-0742 · GW-501516 · L-165,041 · LG-101506 · MBX-8025 · Sodelglitazar · Tetradecylthioacetic acid · |
| | | **Antagonists** | FH-535 · GSK-0660 · GSK-3787 · |
| | **PPARγ** | **Agonists** | 5-Oxo-ETE · 5-Oxo-15-hydroxy-ETE · 15-Deoxy-$\Delta^{12,14}$-prostaglandin $J_2$ · 15-HETE · 15-HpETE · Aleglitazar · Arachidonic acid · Balaglitazone · Berberine · Bezafibrate · Cevoglitazar · Ciglitazone · Daidzein · Darglitazone · Edaglitazone · Efatutazone · Englitazone · Etalocib · Farglitazar · Genistein · GW-1929 · Ibuprofen · Imiglitazar · Indeglitazar · LG-100268 · LG-100754 · LG-101506 · Lobeglitazone · Muraglitazar (muroglitazar) · nTZDpa · Naveglitazar · Netoglitazone · Oxeglitazar · Peliglitazar · Pemaglitazar · Perfluorononanoic acid · Pioglitazone · Prostaglandin $J_2$ · Ragaglitazar · Reglitazar · Rivoglitazone · Rosiglitazone · RS5444 · Saroglitazar · Sipoglitazar · Sodelglitazar · Telmisartan · Tesaglitazar · Troglitazone · |
| | | **SPPARMs** | BADGE · EPI-001 · INT-131 · MK-0533 · S26948 · |
| | | **Antagonists** | FH-535 · GW-9662 · SR-202 · T-0070907 · |
| | | **Unknown** | SR-1664 · |
| | **Unselective** | **Agonists** | Ciprofibrate · Clinofibrate · Clofibride · Englitazone · Etofibrate · Farglitazar · Netoglitazone · Ronifibrate · Rivoglitazone · Simfibrate · |
| | **Unsorted** | **Agonists** | Seladelpar · |
| | | | 17α-Hydroxypregnenolone · 17α-Hydroxyprogesterone · $\Delta^4$-Androstenedione · $\Delta^5$-Androstenediol · $\Delta^5$-Androstenedione · AA-861 · Allopregnanediol · Allopregnanedione (5α-dihydroprogesterone) · Allopregnanolone · Alpha-Lipoic acid · Ambrisentan · AMI-193 · Amlodipine besylate · Antimycotics · Artemisinin · Aurothioglucose · Bile acids · Bithionol · Bosentan · Bumecaine · Cafestol · Cephaloridine · Cephradine · Chlorpromazine · Ciglitazone · Clindamycin · Clofenvinfos · Chloroxine · Clotrimazole · Colforsin · Corticosterone · Cyclophosphamide · Cyproterone acetate · Demecolcine · Dexamethasone · DHEA · DHEA-S · Dibunate sodium · Diclazuril · Dicloxacillin · Dimercaprol · Dinaline · Docetaxel · Docusate calcium · Dodecylbenzenesulfonic acid · Dronabinol · Droxidopa · Eburnamonine · Ecopipam · Enzacamene · Epothilone B · Erythromycin · |

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| **PXR** | **Agonists** | Famprofazone · Febantel · Felodipine · Fenbendazole · Fentanyl · Flucloxacillin · Fluorometholone · Griseofulvin · Guggulsterone · Haloprogin · Hetacillin potassium · Hyperforin · *Hypericum perforatum* (St John's wort) · Indinavir sulfate · Lasalocid sodium · Levothyroxine · Linolenic acid · LOE-908 · Loratadine · Lovastatin · Meclizine · Methacycline · Methylprednisolone · Metyrapone · Mevastatin · Mifepristone · Nafcillin · Nicardipine · Nicotine · Nifedipine · Nilvadipine · Nisoldipine · Norelgestromin · Omeprazole · Orlistat · Oxatomide · Paclitaxel · Phenobarbital · Piperine · Plicamycin · Prednisolone · Pregnanediol · Pregnanedione (5β-dihydroprogesterone) · Pregnanolone · Pregnenolone · Pregnenolone 16α-carbonitrile · Proadifen · Progesterone · Quingestrone · Reserpine · Reverse triiodothyronine · Rifampicin · Rifaximin · Rimexolone · Riodipine · Ritonavir · Simvastatin · Sirolimus · Spironolactone · Spiroxatrine · SR-12813 · Suberoylanilide · Sulfisoxazole · Suramin · Tacrolimus · Tenylidone · Terconazole · Testosterone isocaproate · Tetracycline · Thiamylal sodium · Thiothixene · Thonzonium bromide · Tianeptine · Troglitazone · Troleandomycin · Tropanyl 3,5-dimethulbenzoate · Zafirlukast · Zearalanol · |
| | **Antagonists** | Ketoconazole · Sesamin · |
| **RAR** | **Agonists** | 9CDHRA · 9-*cis*-Retinoic acid (alitretinoin) · AC-261066 · AC-55649 · Acitretin · Adapalene · all-*trans*-Retinoic acid (tretinoin) · AM-580 · BMS-493 · BMS-753 · BMS-961 · CD-1530 · CD-2314 · CD-437 · Ch-55 · EC 23 · Etretinate · Fenretinide · Isotretinoin · Palovarotene · Retinoic acid · Retinol (vitamin A) · Tamibarotene · Tazarotene · Tazarotenic acid · TTNPB · |
| | **Antagonists** | BMS-195614 · BMS-493 · CD-2665 · ER-50891 · LE-135 · MM-11253 · |
| | **Others** | *Retinoic acid metabolism inhibitors:* Liarozole · |
| **RXR** | **Agonists** | 9CDHRA · 9-*cis*-Retinoic acid (alitretinoin) · all-*trans*-Retinoic acid (tretinoin) · Bexarotene · CD 3254 · Docosahexaenoic acid · Fluorobexarotene · Isotretinoin · LG-100268 · LG-101506 · LG-100754 · Retinoic acid · Retinol (vitamin A) · SR-11237 · |
| | **Antagonists** | HX-531 · HX-630 · LG-100754 · PA-452 · UVI-3003 · |
| **SHR** | **AR** | See here instead. |
| | **ER** | See here instead. |
| | **PR** | See here instead. |
| | **GR** | See here instead. |
| | **MR** | See here instead. |
| | **VDR** | **Agonists** — 7-Dehydrocholesterol · 22-Oxacalcitriol · 25-Hydroxyergocalciferol · Alfacalcidol · Calcifediol · Calciferol · Calcipotriol · Calcitriol · Cholecalciferol (vitamin $D_3$) · Dihydrotachysterol · Doxercalciferol · EB-1089 · Eldecalcitol · Ercalcidiol · Ercalcitriol · Ergocalciferol (vitamin $D_2$) · Lithocholic acid · Paricalcitol · Tacalcitol · |
| **TR** | **Agonists** | Dextrothyroxine · DITPA · Eprotirome (KB-2115) · KB-2611 · KB-130015 · Levothyroxine · Liothyronine · MB-07811 · MGL-3196 (VIA-3196) · Sobetirome (GC-1, GRX-431) · Thyroxine · Tiratricol · Triiodothyronine · VK-0214 · VK-2809 · ZYT1 · |
| | **Others** | *Carrier proteins:* Albumin · Thyroxine-binding globulin · Transthyretin · |

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| v · t · e · | **Tricyclics** |
| **Classes** | Acridine · Anthracene · Dibenzazepine · Dibenzocycloheptene · Dibenzodiazepine · Dibenzothiazepine · Dibenzothiepin · Dibenzoxazepine · Dibenzoxepin · Phenothiazine · |

| | |
|---|---|
| | Pyridazinobenzoxazine · Pyridinobenzodiazepine · Thioxanthene · |
| **Antidepressants** (**TCAs** and **TeCAs**) | 7-OH-Amoxapine · Amezepine · Amineptine · Amitriptyline · Amitriptylinoxide · Amoxapine · Aptazapine · Azepindole · Azipramine · Batelapine · Butriptyline · Cianopramine · Ciclazindol · Ciclopramine · Cidoxepin · Clomipramine · Cotriptyline · Cyanodothiepin · Demexiptiline · Depramine/Balipramine · Desipramine · Dibenzepin · Dimetacrine · Dosulepin/Dothiepin · Doxepin · Enprazepine · Esmirtazapine · Fantridone · Fluotracen · Hepzidine · Homopipramol · Imipramine · Imipraminoxide · Intriptyline · Iprindole · Ketipramine · Litracen · Lofepramine · Losindole · Loxapine · Maprotiline · Mariptiline · Mazindol · Melitracen · Metapramine · Mezepine · Mianserin · Mirtazapine · Monometacrine · Naranol · Nitroxazepine · Nortriptyline · Noxiptiline · Octriptyline · Opipramol · Oxaprotiline · Pipofezine · Pirandamine · Propizepine · Protriptyline · Quinupramine · Setiptiline/Teciptiline · Spiroxepin · Tandamine · Tampramine · Tianeptine · Tienopramine · Trimipramine · |
| **Antihistamines** | Azatadine · Clobenzepam · Cyproheptadine · Dacemazine · Deptropine · Desloratadine · Epinastine · Etymemazine · Fenethazine · Hydroxyethylpromethazine · Isopromethazine · Isothipendyl · Ketotifen · Latrepirdine · Loratadine · Mebhydrolin · Mequitazine · Methdilazine · Olopatadine · Oxomemazine · Phenindamine · Pimethixene · Promethazine · Propiomazine · Rupatadine · Thiazinamium · |
| **Antipsychotics** | Acetophenazine · Alimemazine · Amoxapine · Asenapine · Butaclamol · Butaperazine · Carfenazine (carphenazine) · Carpipramine · Chlorpromazine · Chlorprothixene · Ciclindole · Citatepine · Clocapramine · Clomacran · Clorotepine · Clotiapine · Clozapine · Cyanothepin · Doclothepin · Docloxythepin · Erizepine · Flucindole · Flumezapine · Fluotracen · Flupentixol · Fluphenazine · Gevotroline · Homopipramol · Isofloxythepin · Levomepromazine/Methotrimeprazine · Loxapine · Maroxepin · Meperathiepin · Mesoridazine · Metiapine · Metitepine · Metoxepin · Mosapramine · Naranol · Octomethothepin · Olanzapine · Oxyclothepin · Oxyprothepin · Pentiapine · Peradithiepin · Perathiepin · Perazine · Perphenazine · Periciazine · Pinoxepin · Piperacetazine · Pipotiazine · Piquindone · Prochlorperazine · Promazine · Prothipendyl · Quetiapine · Savoxepin/Cipazoxapine · Sulforidazine · Tenilapine · Thiethylperazine · Thiopropazate · Thioridazine · Thiothixene · Tilozepine · Traboxopine · Trifluoperazine · Triflupromazine · Trifluthepin · Zotepine · Zuclopenthixol · |
| **Anticonvulsants** | **Carbamazepine** · Dizocilpine · Eslicarbazepine · Eslicarbazepine acetate · Etazepine · Licarbazepine · Oxcarbazepine · Oxitriptyline · Rispenzepine · |
| **Others** | Adosopine · Aminopromazine · Atiprosin · Beloxepin · Carvedilol · Cidoxepin · Cyclobenzaprine · Damotepine · Darenzepine · Elanzepine · Methylene blue · Monatepil · Nuvenzepine · Oxetorone · Perlapine · P7C3 · Pinadoline · Pirenzepine · Pirolate · Pitrazepin · Pizotifen · Profenamine · Serazapine · Siltenzepine · Telenzepine · Tipindole · Tropatepine · Zolenzepine · |

Categories: Anticonvulsants | Mood stabilizers | Prodrugs | Ureas | World Health Organization essential medicines | Dibenzazepines | GABAA receptor positive allosteric modulators | Antidiuretics


# Cefalexin

From Wikipedia, the free encyclopedia

(Redirected from Cephalexin)

**Cefalexin**, also spelled **cephalexin**, is an antibiotic that can treat a number of bacterial infections. It kills gram-positive and some gram-negative bacteria by disrupting the growth of the bacterial cell wall. Cefalexin is a beta-lactam antibiotic within the class of first-generation cephalosporins.[3] It works similarly to other agents within this class, including intravenous cefazolin, but can be taken by mouth.[4]

Cefalexin can treat certain bacterial infections, including those of the middle ear, bone and joint, skin, and urinary tract. It may also be used for certain types of pneumonia, strep throat, and to prevent bacterial endocarditis. Cefalexin is not effective against infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus*, or *Pseudomonas*. Like other antibiotics, cefalexin cannot treat viral infections, such as the flu, common cold or acute bronchitis. Cefalexin can be used in those who have mild or moderate allergies to penicillin. However, it is not recommended in those with severe penicillin allergies.[3]

Common side effects include stomach upset and diarrhea.[3] An allergic reaction and infection with *Clostridium difficile*, a type of diarrhea, is also possible.[3] To date, no evidence of harm to the baby has been found when used during pregnancy[3][5] or breast feeding.[6] It can be used in children and those over 65 years of age. Those with kidney problems may require a decrease in dose.[3]

In 2012, cefalexin was one of the top 100 most prescribed medications in the United States.[7] In Canada, it was the 5th most common antibiotic used in 2013.[8] In Australia, it is one of the top 15 most prescribed medications.[9] Cefalexin was developed in 1967.[10] It was first marketed in 1969 and 1970 under the names **Keflex** and **Ceporex**, among others.[1][11] Generic drug versions are available under several other trade names and are inexpensive.[3][12] Cefalexin is on the World Health Organization's List of Essential Medicines, the most important medications needed in a health system.[13]

**Contents**



## Medical uses [edit]

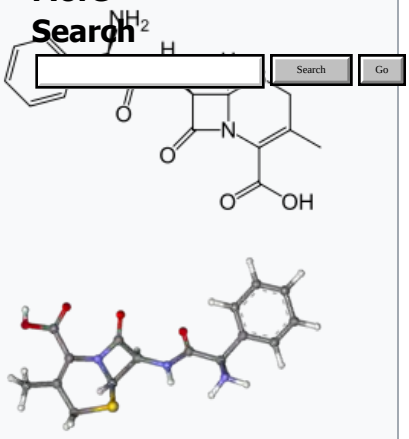
A course of cefalexin capsules, commonly prescribed for infections

Cefalexin can treat a number of bacterial infections including: otitis media, streptococcal pharyngitis, bone and joint infections, pneumonia, cellulitis, and urinary tract infections.[3] It may be used to prevent bacterial endocarditis.[3] It can also be used for the prevention of recurrent urinary-tract infections.[14]

Cefalexin does not treat methicillin-resistant *Staphylococcus aureus* infections.[14]

Cefalexin is a useful alternative to penicillins in patients with penicillin intolerance. For example, penicillin is the treatment of choice for respiratory tract infections caused by *Streptococcus*, but cefalexin may be used as an alternative in penicillin-intolerant patients.[15] Caution must be exercised when administering cephalosporin antibiotics to penicillin-sensitive patients, because cross sensitivity with beta-lactam antibiotics has been documented in up to 10% of patients with a documented penicillin allergy.[16]

**Cefalexin**



| Clinical data | |
|---|---|
| **Pronunciation** | /ˌsɛfəˈlɛksɪn/ |
| **Trade names** | Keflex, Cepol, Ceporex, others[1] |
| **AHFS / Drugs.com** | Monograph |
| **MedlinePlus** | a682733 |
| **License data** | US FDA: Keflex |
| **Pregnancy category** | AU: A<br>US: B (No risk in non-human studies) |
| **Routes of administration** | Oral |
| **ATC code** | J01DB01 (WHO)<br>QJ51DB01 (WHO) |
| **Legal status** | |
| **Legal status** | AU: S4 (Prescription only)<br>UK: POM (Prescription only)<br>US: -only |
| **Pharmacokinetic data** | |
| **Bioavailability** | Well absorbed |
| **Protein binding** | 15% |
| **Metabolism** | 80% excreted unchanged in urine within 6 hours of administration |
| **Biological half-life** | For an adult with normal renal function, the serum half-life is 0.5–1.2 hours[2] |
| **Excretion** | Renal |
| **Identifiers** | |
| **IUPAC name** | (7R)-3-Methyl-7- (α- D -phenylglycylamino) -3-cephem-4-c |

## Pregnancy and breastfeeding [edit]

It is pregnancy category B in the United States and category A in Australia, meaning that no evidence of harm has been found after being taken by many pregnant women.[3][5] Use during breast feeding is generally safe.[6]

## Adverse effects [edit]

The most common adverse effects of cefalexin, like other oral cephalosporins, are gastrointestinal (stomach area) disturbances and hypersensitivity reactions. Gastrointestinal disturbances include nausea, vomiting, and diarrhea, diarrhea being most common.[17] Hypersensitivity reactions include skin rashes, urticaria, fever, and anaphylaxis.[18] Pseudomembranous colitis and *Clostridium difficile* have been reported with use of cefalexin.[18]

Signs and symptoms of an allergic reaction include rash, itching, swelling, trouble breathing, or red, blistered, swollen, or peeling skin. Overall, cefalexin allergy occurs in less than 0.1% of patients, but it is seen in 1% to 10% of patients with a penicillin allergy.[19]

## Interactions [edit]

Like other β-lactam antibiotics, renal excretion of cefalexin is delayed by probenecid.[20] Alcohol consumption does not have a negative interaction with cefalexin,[21] but reduces the rate at which it is absorbed.[22] Cefalexin also interacts with metformin, an antidiabetic drug,[18] and this can lead to higher concentrations of metformin in the body.[18][23]

## Mechanism of action [edit]

Cefalexin is a beta-lactam antibiotic of the cephalosporin family.[24] It is bactericidal and acts by inhibiting synthesis of the peptidoglycan layer of the bacterial cell wall.[25] As cefalexin closely resembles d-alanyl-d-alanine, an amino acid ending on the peptidoglycan layer of the cell wall, it is able to irreversibly bind to the active site of PBP, which is essential for the synthesis of the cell wall.[25] It is most active against gram-positive cocci, and has moderate activity against some gram-negative bacilli.[26] However, some bacterial cells have the enzyme β-lactamase, which hydrolyzes the beta-lactam ring, rendering the drug inactive. This contributes to antibacterial resistance towards cephalexin.[27]

arboxylic acid monohydrate

| | |
|---|---|
| **CAS Number** | 15686-71-2 ✓ |
| **PubChem** (CID) | 2666 |
| **IUPHAR/BPS** | 4832 |
| **DrugBank** | DB00567 ✓ |
| **ChemSpider** | 25541 ✓ |
| **UNII** | 5SFF1W6677 ✓ |
| **KEGG** | D00263 ✓ |
| **ChEBI** | CHEBI:3534 ✓ |
| **ChEMBL** | CHEMBL1727 ✓ |
| **ECHA InfoCard** | 100.036.142 |

**Chemical and physical data**

| | |
|---|---|
| **Formula** | $C_{16}H_{17}N_3O_4S$ |
| **Molar mass** | 347.39 g/mol |
| **3D model (Jmol)** | Interactive image |
| **Melting point** | 326.8 °C (620.2 °F) |

**SMILES**

O=C2N1/C(=C(\CS[C@@H]1[C@@H]2NC(=O)[C@@H](c3ccccc3)N)C)C(=O)O

**InChI**

InChI=1S/C16H17N3O4S/c1-8-7-24-15-11(14(21)19(15)12(8)16(22)23)18-13(20)10(17)9-5-3-2-4-6-9/h2-6,10-11,15H,7,17H2,1H3,(H,18,20)(H,22,23)/t10-,11-,15-/m1/s1 ✓

Key:ZAIPMKNFIOOWCQ-UEKVPHQBSA-N ✓

(verify)

## Society and culture [edit]

Cefalexin is on the World Health Organization's List of Essential Medicines, the most important medications needed in a health system.[13] The World Health Organization classifies cephalexin as a highly important antimicrobial in their list of Critically Important Antimicrobials for Human Medicine.[28]

### Names [edit]

Cefalexin is the INN and BAN while cephalexin is the USAN and AAN.

Common brand names for cefalexin include Keflex, Cepol, Ceporexine, Ceporex, Cefadal, Derantel, Mecilex, Medoxine, Sporibest (Bionova), Xahl, and Tokiolexin.[29]

## References [edit]


1. ^ a b McPherson, Edwin M. (2007). *Pharmaceutical Manufacturing Encyclopedia.* (3rd ed.). Burlington: Elsevier. p. 915. ISBN 9780815518563.
2. ^ McEvoy, G.K. (ed.). American Hospital Formulary Service — Drug Information 95. Bethesda, MD: American Society of Hospital Pharmacists, Inc., 1995 (Plus Supplements 1995)., p. 166
3. ^ a b c d e f g h i j "Cephalexin". The American Society of Health-System Pharmacists. Retrieved Apr 21, 2014.
4. ^ Brunton, Laurence L. (2011). "53, Penicillins, Cephalosporins, and Other β-Lactam Antibiotics". *Goodman & Gilman's pharmacological basis of therapeutics.* (12th ed.). New York: McGraw-Hill. ISBN 978-0071624428.
5. ^ a b "Prescribing medicines in pregnancy database". *Australian Government*. 3 March 2014. Retrieved 22 April 2014.
6. ^ a b Wendy Jones (2013). *Breastfeeding and Medication*. Routledge. p. 227. ISBN 9781136178153.
7. ^ Bartholow, Michael. "Top 200 Drugs of 2012". *Pharmacy Times*. Retrieved 22 April 2014.
8. ^ "Human Antimicrobial Drug Use Report 2012/2013" (PDF). Public
14. ^ a b "Lexicomp: Cefalexin". (subscription required (help)).
15. ^ "Lexicomp: Antibacterials". (subscription required (help)).
16. ^ "FDA Cephalexin drug label" (PDF). Retrieved 18 April 2014.
17. ^ "Cephalexin Side Effects". *Drugs.com*. Retrieved 9 February 2015.
18. ^ a b c d "Cefalexin". *Lexicomp*. Retrieved 18 April 2014. (subscription required (help)).
19. ^ Haberfeld, H, ed. (2009). *Austria-Codex* (in German) (2009/2010 ed.). Vienna: Österreichischer Apothekerverlag. ISBN 3-85200-196-X.
20. ^ "Cefalexin". *Lexicomp*. Retrieved 17 April 2014. (subscription required (help)).
21. ^ "Cefalexin (Cefalexin 250mg capsules)". *NHS Choices*.
22. ^ Barrio Lera JP, Alvarez AI, Prieto JG (Jun 1991). "Effects of ethanol on the pharmacokinetics of cephalexin and cefadroxil in the rat". *Journal of Pharmaceutical Sciences*. **80** (6): 511–6. doi:10.1002/jps.2600800602. PMID 1941538.
23. ^ Jayasagar G, Krishna Kumar M, Chandrasekhar K, Madhusudan Rao C, Madhusudan Rao Y (2002). "Effect of cephalexin on the pharmacokinetics of metformin in healthy human volunteers". *Drug Metabolism and Drug Interactions*. **19** (1): 41–8. doi:10.1515/dmdi.2002.19.1.41. PMID 12222753.

Health Agency of Canada (PHAC). November 2014. Retrieved February 24, 2015.
9. ^ *Australia's Health 2012: The Thirteenth Biennial Health Report of the Australian Institute of Health and Welfare*. Australian Institute of Health and Welfare. 2012. p. 408. ISBN 9781742493053.
10. ^ Hey, Edmund, ed. (2007). *Neonatal formulary 5 drug use in pregnancy and the first year of life* (5th ed.). Blackwell. p. 67. ISBN 9780470750353.
11. ^ Ravina, Enrique (2011). *The evolution of drug discovery : from traditional medicines to modern drugs* (1. Aufl. ed.). Weinheim: Wiley-VCH. p. 267. ISBN 9783527326693.
12. ^ Hanlon, Geoffrey; Hodges, Norman (2012). *Essential Microbiology for Pharmacy and Pharmaceutical Science*. Hoboken: Wiley. p. 140. ISBN 9781118432433.
13. ^ [a] [b] "WHO Model List of EssentialMedicines" (PDF). *World Health Organization*. October 2013. p. 6. Retrieved 22 April 2014.
24. ^ Bothara SS, Kadam KR, Mahadik KG (2006). "Antibiotics". *Principles of Medicinal Chemistry*. **1** (14th ed.). Pune: Nirali Prakashan. p. 81. ISBN 8185790043.
25. ^ [a] [b] Fisher JF, Meroueh SO, Mobashery S (Feb 2005). "Bacterial resistance to beta-lactam antibiotics: compelling opportunism, compelling opportunity". *Chemical Reviews*. **105** (2): 395–424. doi:10.1021/cr030102i. PMID 15700950.
26. ^ "Cefalexin". *Lexicomp*. Retrieved 17 April 2014. (subscription required (help)).
27. ^ Drawz SM, Bonomo RA (Jan 2010). "Three decades of beta-lactamase inhibitors". *Clinical Microbiology Reviews*. **23** (1): 160–201. doi:10.1128/CMR.00037-09. PMC 2806661. PMID 20065329.
28. ^ "Critically Important Medicines for Human Medicine, 3rd Revision 2011" (PDF). World Health Organization. Retrieved 24 February 2015.
29. ^ "SciFinder". *scifinder.cas.org*. Retrieved 2016-02-20. (subscription

## External links [edit]

- U.S. National Library of Medicine: Drug Information Portal — Cephalexin

| v • t • e | **Antibacterials: cell envelope antibiotics (J01C-J01D)** | | | |
|---|---|---|---|---|
| **Intracellular** | Inhibit peptidoglycan subunit synthesis and transport: NAM synthesis inhibition (Fosfomycin) • DADAL/AR inhibitors (Cycloserine) • bactoprenol inhibitors (Bacitracin) • | | | |
| **Glycopeptide** | Inhibit PG chain elongation: Vancomycin# (Oritavancin • Telavancin) • Teicoplanin (Dalbavancin) • Ramoplanin • | | | |
| **β-lactams/ (inhibit PBP cross-links)** | **Penicillins (Penams)** | **Narrow spectrum** | **β-lactamase sensitive (1st generation)** | Benzylpenicillin (G)# • Benzathine benzylpenicillin# • Procaine benzylpenicillin# • Phenoxymethylpenicillin (V)# • Propicillin‡ • Pheneticillin‡ • Azidocillin‡ • Clometocillin‡ • Penamecillin‡ • |
| | | | **β-lactamase resistant (2nd generation)** | Cloxacillin# (Dicloxacillin • Flucloxacillin) • Oxacillin • Nafcillin • Methicillin‡ • |
| | | **Extended spectrum** | **Aminopenicillins (3rd generation)** | Amoxicillin# • Ampicillin# (Pivampicillin • Hetacillin‡ • Bacampicillin‡ • Metampicillin‡ • Talampicillin‡) • Epicillin‡ • |
| | | | **Carboxypenicillins (4th generation)** | Ticarcillin • Carbenicillin‡ / Carindacillin‡ • Temocillin‡ • |
| | | | **Ureidopenicillins (4th generation)** | Piperacillin • Azlocillin‡ • Mezlocillin‡ • |
| | | | **Other** | Mecillinam‡ (Pivmecillinam‡) • Sulbenicillin‡ • |
| | **Penems** | Faropenem‡ • Ritipenem§ • | | |
| | **Carbapenems** | Ertapenem • Antipseudomonal (Doripenem • Imipenem • Meropenem) • Biapenem‡ • Panipenem‡ • | | |
| | **Cephalosporins/Cephamycins (Cephems)** | **1st generation (PEcK)** | | Cefazolin# • **Cefalexin** # • Cefadroxil • Cefapirin • Cefazedone‡ • Cefazaflur‡ • Cefradine‡ • Cefroxadine‡ • Ceftezole‡ • Cefaloglycin‡ • Cefacetrile‡ • Cefalonium‡ • Cefaloridine‡ • Cefalotin‡ • Cefatrizine‡ • |
| | | **2nd generation (HEN)** | | Cefaclor • Cefotetan • Cephamycin (Cefoxitin • Cefprozil • Cefuroxime • Cefuroxime axetil • Cefamandole‡ • Cefminox‡ • Cefonicid‡ • Ceforanide‡ • Cefotiam‡ • Cefbuperazone‡ • Cefuzonam‡ • Cefmetazole)‡ • Carbacephem‡ (Loracarbef‡) • |
| | | **3rd generation** | | Cefixime# • Ceftriaxone# • Antipseudomonal (Ceftazidime# • Cefoperazone) • Cefdinir • Cefcapene • Cefdaloxime • Ceftizoxime • Cefmenoxime • Cefotaxime • Cefpiramide • Cefpodoxime • Ceftibuten • Cefditoren • Cefetamet‡ • Cefodizime‡ • Cefpimizole‡ • Cefsulodin‡ • Cefteram‡ • Ceftiolene‡ • Oxacephem (Flomoxef‡ • Latamoxef‡) • |

| | | | |
|---|---|---|---|
| | | **4th generation (Pseudomonas)** | Cefepime · Cefozopran‡ · Cefpirome‡ · Cefquinome‡ · |
| | | **5th generation** | Ceftaroline fosamil · Ceftolozane · Ceftobiprole · |
| | | **Veterinary** | Ceftiofur · Cefquinome · Cefovecin · |
| | **Monobactams** | | Aztreonam · Tigemonam‡ · Carumonam‡ · Nocardicin A‡ · |
| | **β-lactamase inhibitors** | | Penam (Sulbactam · Tazobactam) · Clavam (Clavulanic acid) · Avibactam · |
| | **Combinations** | | Amoxicillin/clavulanic acid# · Imipenem/cilastatin# · Ampicillin/flucloxacillin · Ampicillin/sulbactam (Sultamicillin) · Ceftazidime/avibactam · Piperacillin/tazobactam · Ceftolozane/tazobactam · |
| **Other** | | | polymyxins/detergent (Colistin · Polymyxin B · · depolarizing (Daptomycin · · Hydrolyze NAM-NAG (lysozyme · · Tyrothricin (Gramicidin · Tyrocidine · · Isoniazid · Teixobactin · |

#WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · ·

Categories: 1967 introductions | Cephalosporin antibiotics | Eli Lilly and Company | Enantiopure drugs | World Health Organization essential medicines

# Cholera vaccine

From Wikipedia, the free encyclopedia

**Cholera vaccines** are vaccines that are effective at preventing cholera.[1] They are about 85% effective during the first six months and 50–60% effective during the first year.[1][2][3] The effectiveness decreases to less than 50% after two years. When a significant portion of the population is immunized benefits from herd immunity may occur among those not immunized. The World Health Organization recommends their use in combination with other measures among those at high risk. Two doses or three doses of the oral form are typically recommended.[1] An injectable form is available in some, but not all, areas of the world.[1][2]

Both of the available types of oral vaccine are generally safe. Mild abdominal pain or diarrhea may occur. They are safe in pregnancy and in those with poor immune function. They are licensed for use in more than 60 countries. In countries where the disease is common, the vaccine appears to be cost effective.[1]

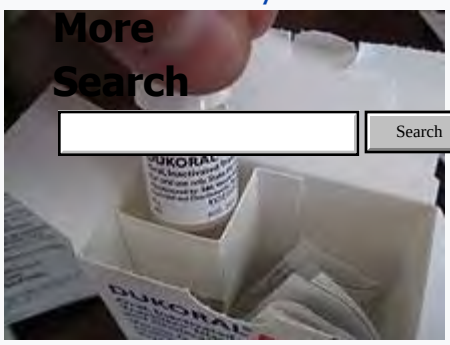
The first vaccines used against cholera were developed in the late 1800s. They were the first widely used vaccine that was made in a laboratory.[4] Oral vaccines were first introduced in the 1990s.[1] It is on the World Health Organization's List of Essential Medicines, the most important medication needed in a basic health system.[5] The cost to immunize against cholera is between 0.1 and 4.0 USD.[6]

Contents


## Medical use [edit]

Oral cholera vaccines are increasingly used as an additional tool to control cholera outbreaks in combination with the traditional interventions to improve safe water supply, sanitation, handwashing and other means to improve hygiene. Since licensure of Dukoral and Shanchol, over a million doses of these vaccines have been deployed in various mass oral cholera campaigns around the world.[7] In addition, Vietnam incorporates oral cholera vaccination in its public health programme and over 9 million doses have been administered through targeted mass vaccination or immunization of school-aged children in cholera endemic regions.

**Cholera vaccine**




| Vaccine description | |
|---|---|
| **Target disease** | Cholera |
| **Type** | Killed/Inactivated |
| **Clinical data** | |
| **Trade names** | Dukoral, Vaxchora, other |
| **AHFS/Drugs.com** | Micromedex Detailed Consumer Information |
| **Pregnancy category** | US: C (Risk not ruled out) |
| **ATC code** | J07AE01 (WHO) J07AE02 (WHO) |
| **Identifiers** | |
| **ChemSpider** | none |

(what is this?) (verify)

The cholera vaccine is largely used by backpackers and persons visiting locations where there is a high risk of cholera infection. However, since it does not provide 100% immunity from the disease, food hygiene precautions should also be taken into consideration when visiting an area where there is a high risk of becoming infected with cholera. Although the protection observed has been described as "moderate", herd immunity can multiply the effectiveness of vaccination. Dukoral has been licensed for children 2 years of age and older, Shanchol for children 1 year of age and older. The administration of the vaccine to adults confers additional indirect protection (herd immunity) to children.

The World Health Organization (WHO) recommends both preventive and reactive use of the vaccine, making the following key statements:[8]

> WHO recommends that current available cholera vaccines be used as complements to traditional control and preventive measures in areas where the disease is endemic and should be considered in areas at risk for outbreaks. Vaccination should not disrupt the provision of other high priority health interventions to control or prevent cholera outbreaks.... Reactive vaccination might be considered in view of limiting the extent of large prolonged outbreaks, provided the local infrastructure allows it, and an in-depth analysis of past cholera data and identification of a defined target area have been performed.

The WHO as of late 2013 established a revolving stockpile of 2 million OCV doses.[9] The supply is increasing to 6 million as a South Korean companies has gone into production (2016), the old production not being able to handle WHO demand in Haiti and Sudan for 2015, nor prior years. GAVI Alliance donated $115 million to help pay for expansions.[10][11]

## Oral [edit]

Oral vaccines provide protection in 52% of cases the first year following vaccination and in 62% of cases the second year.[3] There are two variants of the oral vaccine currently in use: WC-rBS and BivWC. WC-rBS (marketed as "Dukoral") is a monovalent inactivated vaccine containing killed whole cells of *V. cholerae* O1 plus additional recombinant cholera toxin B subunit. BivWC (marketed as "Shanchol" and "mORCVAX") is a bivalent inactivated vaccine containing killed whole cells of *V. cholerae* O1 and *V. cholerae* O139. mORCVAX is only available in Vietnam.

Dukoral: vial of inactivated vaccine with packet of sodium bicarbonate buffer.

Bacterial strains of both Inaba and Ogawa serotypes and of El Tor and Classical biotypes are included in the vaccine. Dukoral is taken orally with bicarbonate buffer, which protects the antigens from the gastric acid. The vaccine acts by inducing antibodies against both the bacterial components and CTB. The antibacterial intestinal antibodies prevent the bacteria from attaching to the intestinal wall, thereby impeding colonisation of V. cholerae O1. The anti-toxin intestinal antibodies prevent the cholera toxin from binding to the intestinal mucosal surface, thereby preventing the toxin-mediated diarrhoeal symptoms.[12]

## Injectable [edit]

Although rarely in use, the injected cholera vaccines are effective for people living where cholera is common. They offer some degree of protection for up to two years after a single shot, and for three to four years with annual booster. They reduce the risk of death from cholera by 50% in the first year after vaccination.[2]

# Side effects [edit]

Both of the available types of oral vaccine are generally safe. Mild abdominal pain or diarrhea may occur.

They are safe in pregnancy and in those with poor immune function. They are licensed for use in more than 60 countries. In countries where the disease is common, the vaccine appears to be cost effective.[1]

## Society and culture [edit]

The first vaccines used against cholera were developed in the late 19th century. They were the first widely used vaccine that was made in a laboratory.[4] There were several pioneers in the development of the vaccine. In 1884, Catalan physician Jaume Ferran i Clua developed a live vaccine he had isolated from cholera patients in Marseilles, and used it that on over 30,000 individuals in Valencia during that year's epidemic. Waldemar Haffkine then developed a vaccine with less severe side effects, testing it on more than 40,000 people in the Calcutta area from 1893 to 1896. Finally, in 1896, Wilhelm Kolle introduced a heat-killed vaccine that was significantly easier to prepare than Haffkine's, using it on a large scale in Japan in 1902.[13]

Oral vaccines were first introduced in the 1990s.[1] It is on the World Health Organization's List of Essential Medicines, the most important medication needed in a basic health system.[5] The cost to immunize against cholera is between 0.1 and 4.0 USD.[14]

In 2016 the US Food and Drug Administration approved Vaxchora to prevent cholera for travelers. Vaxchora is the only FDA-approved vaccine for the prevention of cholera.[15]

## References [edit]


1. ^ *a b c d e f g h* "Cholera vaccines: WHO position paper." (PDF). *Weekly epidemiological record*. **13** (85): 117–128. Mar 26, 2010. PMID 20349546.
2. ^ *a b c* Graves PM, Deeks JJ, Demicheli V, Jefferson T (2010). "Vaccines for preventing cholera: killed whole cell or other subunit vaccines (injected)". *Cochrane Database Syst Rev* (8): CD000974. doi:10.1002/14651858.CD000974.pub2. PMID 20687062.
3. ^ *a b* Sinclair D, Abba K, Zaman K, Qadri F, Graves PM (2011). "Oral vaccines for preventing cholera". *Cochrane Database Syst Rev* (3): CD008603. doi:10.1002/14651858.CD008603.pub2. PMID 21412922.
4. ^ *a b* Stanberry, Lawrence R. (2009). *Vaccines for biodefense and emerging and neglected diseases* (1 ed.). Amsterdam: Academic. p. 870. ISBN 9780080919027.
5. ^ *a b* "WHO Model List of EssentialMedicines" (PDF). *World Health Organization*. October 2013. Retrieved 22 April 2014.
6. ^ Martin, S; Lopez, AL; Bellos, A; Deen, J; Ali, M; Alberti, K; Anh, DD; Costa, A; Grais, RF; Legros, D; Luquero, FJ; Ghai, MB; Perea, W; Sack, DA (1 December 2014). "Post-licensure deployment of oral cholera vaccines: a systematic review.". *Bulletin of the World Health Organization*. **92** (12): 881–93. doi:10.2471/blt.14.139949. PMID 25552772.
7. ^ Harris, JB; LaRocque, RC; Qadri, F; Ryan, ET; Calderwood, SB (Jun 30, 2012). "Cholera.". *Lancet*. **379** (9835): 2466–76. doi:10.1016/s0140-6736(12)60436-x. PMID 22748592.
8. ^ *Oral cholera vaccines in mass immunization campaigns: guidance for planning and use* (PDF). World Health Organization. 2010. ISBN 9789241500432.
9. ^ "Oral cholera vaccine stockpile". World Health Organization. Retrieved 18 December 2013.
10. ^ http://www.nbcnews.com/health/health-news/world-health-organization-doubles-cholera-vaccine-supply-n492796
11. ^ "GAVI Board Approves Support to Expand Oral Cholera Vaccine Stockpile". The Task Force on Global Health. Retrieved 18 December 2013.
12. ^ "Dukoral Canadian Product Monograph Part III: Consumer Information" (PDF). Retrieved 8 May 2013.
13. ^ Artenstein, Andrew W. (2009). *Vaccines: A Biography* (1 ed.). New York City: Springer Science & Business Media. p. 89-92. ISBN 9780080919027.
14. ^ Martin, S; Lopez, AL; Bellos, A; Deen, J; Ali, M; Alberti, K; Anh, DD; Costa, A; Grais, RF; Legros, D; Luquero, FJ; Ghai, MB; Perea, W; Sack, DA (1 December 2014). "Post-licensure deployment of oral cholera vaccines: a systematic review.". *Bulletin of the World Health Organization*. **92** (12): 881–93. doi:10.2471/blt.14.139949. PMID 25552772.
15. ^ "FDA approves vaccine to prevent cholera for travelers". US Food and Drug Administration. 10 June 2016.


v · t · e · **Artificial induction of immunity / Immunization: Vaccines, Vaccination,**

| Infection, Inoculation (J07) | | |
|---|---|---|
| **Development** | Adjuvants · List of vaccine ingredients · Mathematical modelling · Timeline · Trials · | |
| **Classes** | Conjugate vaccine · DNA vaccination · Inactivated vaccine · Live vector vaccine (Attenuated vaccine · Heterologous vaccine · · Subunit/component / Peptide / Virus-like particle · Toxoid · | |
| **Administration** | Global: (GAVI Alliance · Policy · Schedule · Vaccine injury · · USA: (ACIP · Vaccine court · Vaccines for Children Program · VAERS · VSD · · | |
| **Vaccines** | **Bacterial** | Anthrax · Brucellosis · **Cholera**# · Diphtheria# · Hib# · Leptospirosis · Lyme disease‡ · Meningococcus# (MeNZB · NmVac4-A/C/Y/W-135 · · Pertussis# · Plague · Pneumococcal# (PCV · PPSV · · Q fever · Tetanus# · Tuberculosis (BCG# · · Typhoid# (Ty21a · ViCPS · · Typhus · combination: DTwP/DTaP · |
| | **Viral** | Adenovirus · Flu# (H1N1 (Pandemrix) · LAIV · · Hantavirus · Hepatitis A# · Hepatitis B# · Hepatitis E · HPV (Cervarix · Gardasil · · Japanese encephalitis# · Measles# · Mumps# (Mumpsvax · · Polio# (Sabin · Salk · · Rabies# · Rotavirus# · Rubella# · Smallpox (Dryvax · · Tick-borne encephalitis · Varicella zoster (chicken pox# · shingles (live) · · Yellow fever# · combination: (MMR · MMRV · · research: (Chikungunya · Cytomegalovirus · Dengue · Ebola · Epstein–Barr virus · Hepatitis C · HIV · · |
| | **Protozoan** | research: (Malaria · Trypanosomiasis · · |
| | **Helminthiasis** | research: (Hookworm · Schistosomiasis · · |
| | **Other** | Androvax (androstenedione albumin) · Cancer vaccines (ALVAC-CEA · Hepatitis B# · HPV (Cervarix · Gardasil · · · NicVAX · Ovandrotone albumin (Fecundin) · TA-CD · TA-NIC · |
| **Controversy** | General · MMR · NCVIA · Pox party · Thiomersal · Andrew Wakefield · *Cedillo v. Secretary of Health and Human Services* · Alternative vaccination schedule · | |
| **Related** | Epidemiology · Eradication of infectious diseases · Every Child by Two · List of vaccine topics · | |
| #WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · · | | |

Categories: Vaccines | World Health Organization essential medicines (vaccines)

# Cocaine





From Wikipedia, the free encyclopedia

*For other uses, see Cocaine (disambiguation).*

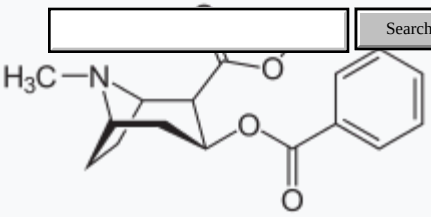
**Cocaine**, also known as **coke**, is a strong stimulant mostly used as a recreational drug.[9] It is commonly snorted, inhaled, or injected into the veins. Mental effects may include loss of contact with reality, an intense feeling of happiness, or agitation. Physical symptoms may include a fast heart rate, sweating, and large pupils.[8] High doses can result in very high blood pressure or body temperature.[10] Effects begin within seconds to minutes of use and last between five and ninety minutes.[8] Cocaine has a small number of accepted medical uses such as numbing and decreasing bleeding during nasal surgery.[11]

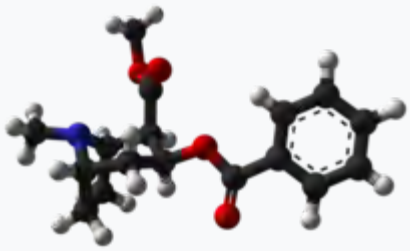
Cocaine is addictive due to its effect on the reward pathway in the brain. After a short period of use, there is a high risk that dependence will occur.[9] Its use also increases the risk of stroke, myocardial infarction, lung problems in those who smoke it, blood infections, and sudden cardiac death.[9][12] Cocaine sold on the street is commonly mixed with local anesthetics, cornstarch, quinine, or sugar which can result in additional toxicity.[13] Following repeated doses a person may have decreased ability to feel pleasure and be very physically tired.[9]

Cocaine acts by inhibiting the reuptake of serotonin, norepinephrine, and dopamine. This results in greater concentrations of these three neurotransmitters in the brain.[9] It can easily cross the blood–brain barrier and may lead to the breakdown of the barrier.[14][15] Cocaine is made from the leaves of the *coca* plant which are mostly grown in South America.[8] In 2013, 419 kilograms were produced legally.[16] It is estimated that the illegal market for cocaine is 100 to 500 billion USD each year. With further processing crack cocaine can be produced from cocaine.[9]

After cannabis, cocaine is the most frequently used illegal drug globally.[17] Between 14 and 21 million people use the drug each year. Use is highest in North America followed by Europe and South America. Between one and three percent of people in the developed world have used cocaine at some point in their life.[9] In 2013 cocaine use directly resulted in 4,300 deaths, up from 2,400 in 1990.[18] The leaves of the *coca*

## Variants





| Clinical data | |
|---|---|
| **Trade names** | Psicaine, Delcaine, Ensan Cocaine |
| **AHFS / Drugs.com** | Micromedex Detailed Consumer Information |
| **Pregnancy category** | US: C (Risk not ruled out) |
| **Dependence liability** | Physical: none[1]<br>Psychological: High[2] |
| **Addiction liability** | High[3] |
| **Routes of administration** | Topical, oral, insufflation, intravenous |
| **Drug class** | CNS stimulant<br>Local anesthetic |
| **ATC code** | N01BC01 (WHO)<br>R02AD03 (WHO),<br>S01HA01 (WHO),<br>S02DA02 (WHO) |

plant have been used by Peruvians since ancient times.[13] Cocaine was first isolated from the leaves in 1860.[9] Since 1961 the international Single Convention on Narcotic Drugs has required countries to make recreational use of cocaine a crime.[10]

**Contents**



## Uses

This article **needs more medical references for verification or relies too heavily on primary sources**. Please review the contents of the article and add the appropriate references if you can. Unsourced or poorly sourced material may be challenged

| Legal status | |
|---|---|
| **Legal status** | AU: S8 (Controlled)<br>CA: Schedule I<br>DE: Anlage III (Prescription only)<br>NZ: Class A<br>UK: Class A<br>US: Schedule II<br>UN: Narcotic Schedules I and III |
| **Pharmacokinetic data** | |
| **Bioavailability** | By mouth: 33%[4]<br>insufflated: 60[5]–80%[6]<br>nasal spray: 25[7]–43%[4] |
| **Metabolism** | liver CYP3A4 |
| **Onset of action** | seconds to minutes[8] |
| **Biological half-life** | 1 hour |
| **Duration of action** | 5 to 90 minutes[8] |
| **Excretion** | Kidney |
| **Identifiers** | |
| **IUPAC name** | Methyl (1*R*,2*R*,3*S*,5*S*)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate |
| **Synonyms** | Benzoylmethylecgonine, coke |
| **CAS Number** | 50-36-2 ✓<br>53-21-4 |
| **PubChem** (CID) | 446220 |
| **IUPHAR/BPS** | 2286 |
| **DrugBank** | DB00907 ✓ |
| **ChemSpider** | 10194104 ✓ |
| **UNII** | I5Y540LHVR ✓ |
| **KEGG** | D00110 ✓ |
| **ChEBI** | CHEBI:27958 ✓ |
| **ChEMBL** | CHEMBL370805 ✓ |
| **PDB ligand ID** | COC (PDBe, RCSB PDB) |
| **ECHA InfoCard** | 100.000.030 |
| **Chemical and physical data** | |
| **Formula** | $C_{17}H_{21}NO_4$ |

and removed. *(May 2016)*

| | |
|---|---|
| **Molar mass** | 303.353 g/mol |
| **3D model (Jmol)** | Interactive image |
| **Melting point** | 98 °C (208 °F) |
| **Boiling point** | 187 °C (369 °F) |
| **Solubility in water** | ~1.8 mg/mL (20 °C) |

**SMILES**

CN1[C@H]2CC[C@@H]1[C@@H](C(OC)=O)[C@@H](OC(C3=CC=CC=C3)=O)C2

**InChI**

InChI=1S/C17H21NO4/c1-18-12-8-9-13(18)15(17(20)21-2)14(10-12)22-16(19)11-6-4-3-5-7-11/h3-7,12-15H,8-10H2,1-2H3/t12-,13+,14-,15+/m0/s1 ✓

Key:ZPUCINDJVBIVPJ-LJISPDSOSA-N ✓

*See also: data page*

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## Medical

Topical cocaine can be used as a local numbing agent to help with painful procedures in the mouth or nose.[20] TAC is one such formulation used for pediatrics.

Cocaine was historically useful as a topical anesthetic in eye and nasal surgery, although it is now predominantly used for nasal and lacrimal duct surgery. The major disadvantages of this use are cocaine's intense vasoconstrictor activity and the potential for cardiovascular toxicity. Cocaine has since been largely replaced in Western medicine by synthetic local anesthetics such as benzocaine, proparacaine, lidocaine, and tetracaine, though it remains available for use if specified. If vasoconstriction is desired for a procedure (as it reduces bleeding), the anesthetic is combined with a vasoconstrictor such as phenylephrine or epinephrine. In Australia it is currently[*when?*] prescribed for use as a local anesthetic for conditions such as mouth and lung ulcers.[*citation needed*] Some ENT specialists occasionally use cocaine within the practice when performing procedures such as nasal cauterization. In this scenario dissolved cocaine is soaked into a ball of cotton wool, which is placed in the nostril for the 10–15 minutes immediately before the procedure, thus performing the dual role of both numbing the area to be cauterized, and vasoconstriction. Even when used this way, some of the used cocaine may be absorbed through oral or nasal mucosa and give systemic effects.[*citation needed*] An alternative method of administration for ENT surgery is mixed with adrenaline and sodium bicarbonate, as Moffett's Solution.

## Recreational

Cocaine is a powerful nervous system stimulant.[21] Its effects can last from fifteen or thirty minutes to an hour. The duration of cocaine's effects depends on the amount taken and the route of administration.[22] Cocaine can be in the form of fine white powder, bitter to the taste. When inhaled or injected, it causes a numbing effect. Crack cocaine is a smokeable form of cocaine made into small "rocks" by processing cocaine with sodium bicarbonate (baking soda) and water.[*citation needed*]

Cocaine increases alertness, feelings of well-being and euphoria, energy and motor activity, feelings of competence and sexuality. Cocaine's stimulant effects are similar to that of amphetamine, however, these effects tend to be much shorter lasting and more prominent.[*citation needed*]

## Oral

Many users rub the powder along the gum line, or onto a cigarette filter which is then smoked, which numbs the gums and teeth – hence the colloquial names of "numbies", "gummers", or "cocoa puffs" for this type of administration. This is mostly done with the small amounts of cocaine remaining on a surface after insufflation (snorting). Another oral method is to wrap up some cocaine in rolling paper and swallow (parachute) it. This is sometimes called a "snow bomb."[*citation needed*]

A spoon containing baking soda, cocaine, and a small amount of water. Used in a "poor-man's" crack-cocaine production

### Coca leaf

Coca leaves are typically mixed with an alkaline substance (such as lime) and chewed into a wad that is retained in the mouth between gum and cheek (much in the same as chewing tobacco is chewed) and sucked of its juices. The juices are absorbed slowly by the mucous membrane of the inner cheek and by the gastrointestinal tract when

swallowed. Alternatively, coca leaves can be infused in liquid and consumed like tea. Ingesting coca leaves generally is an inefficient means of administering cocaine. Advocates of the consumption of the coca leaf state that coca leaf consumption should not be criminalized as it is not actual cocaine, and consequently it is not properly the illicit drug.[*citation needed*]

Because cocaine is hydrolyzed and rendered inactive in the acidic stomach, it is not readily absorbed when ingested alone. Only when mixed with a highly alkaline substance (such as lime) can it be absorbed into the bloodstream through the stomach. The efficiency of absorption of orally administered cocaine is limited by two additional factors. First, the drug is partly catabolized by the liver. Second, capillaries in the mouth and esophagus constrict after contact with the drug, reducing the surface area over which the drug can be absorbed. Nevertheless, cocaine metabolites can be detected in the urine of subjects that have sipped even one cup of coca leaf infusion. Therefore, this is an actual additional form of administration of cocaine, albeit an inefficient one.[*citation needed*]

Orally administered cocaine takes approximately 30 minutes to enter the bloodstream. Typically, only a third of an oral dose is absorbed, although absorption has been shown to reach 60% in controlled settings. Given the slow rate of absorption, maximum physiological and psychotropic effects are attained approximately 60 minutes after cocaine is administered by ingestion. While the onset of these effects is slow, the effects are sustained for approximately 60 minutes after their peak is attained.[*citation needed*]

Contrary to popular belief, both ingestion and insufflation result in approximately the same proportion of the drug being absorbed: 30 to 60%. Compared to ingestion, the faster absorption of insufflated cocaine results in quicker attainment of maximum drug effects. Snorting cocaine produces maximum physiological effects within 40 minutes and maximum psychotropic effects within 20 minutes, however, a more realistic activation period is closer to 5 to 10 minutes, which is similar to ingestion of cocaine. Physiological and psychotropic effects from nasally insufflated cocaine are sustained for approximately 40–60 minutes after the peak effects are attained.[23]

Coca tea, an infusion of coca leaves, is also a traditional method of consumption. The tea has often been recommended for travelers in the Andes to prevent altitude sickness.[24] However, its actual effectiveness has never been systematically studied.[24] This method of consumption has been practised for many centuries by the indigenous tribes of South America. One specific purpose of ancient coca leaf consumption was to increase energy and reduce fatigue in messengers who made multi-day quests to other settlements.[*citation needed*]

In 1986 an article in the *Journal of the American Medical Association* revealed that U.S. health food stores were selling dried coca leaves to be prepared as an infusion as "Health Inca Tea."[25] While the packaging claimed it had been "decocainized," no such process had actually taken place. The article stated that drinking two cups of the tea per day gave a mild stimulation, increased heart rate, and mood elevation, and the tea was essentially harmless. Despite this, the DEA seized several shipments in Hawaii, Chicago, Georgia, and several locations on the East Coast of the United States, and the product was removed from the shelves.

## Insufflation

Nasal insufflation (known colloquially as "snorting," "sniffing," or "blowing") is a common method of ingestion of recreational powdered cocaine.[26] The drug coats and is absorbed through the mucous membranes lining the nasal passages. When insufflating cocaine, absorption through the nasal membranes is approximately 30–60%, with higher doses leading to increased absorption efficiency. Any material not directly absorbed through the mucous membranes is collected in mucus and swallowed (this "drip" is considered pleasant by some and unpleasant by others). In a study[27] of cocaine users, the average time taken to reach peak subjective effects was 14.6 minutes. Any damage to the inside of the nose is because cocaine highly constricts blood vessels – and therefore blood and oxygen/nutrient flow – to that area.

Lines of cocaine prepared for insufflation

Nosebleeds after cocaine insufflation are due to irritation and damage of mucus membranes by foreign particles and adulterants and not the cocaine itself;[*citation needed*] as a vasoconstrictor, cocaine acts to reduce bleeding.

Rolled up banknotes, hollowed-out pens, cut straws, pointed ends of keys, specialized spoons, long fingernails, and (clean) tampon applicators are often used to insufflate cocaine. Such devices are often called "tooters" by users. The cocaine typically is poured onto a flat, hard surface (such as a mirror, CD case or book) and divided into "bumps", "lines" or "rails", and then insufflated.[28] The amount of cocaine in a line varies widely from person to person and occasion to occasion (the purity of the cocaine is also a factor), but one line is generally considered to be a single dose and is typically 35 mg (a "bump") to 100 mg (a "rail")[*dubious – discuss*]. As tolerance builds rapidly in the short-term (hours), many lines are often snorted to produce greater effects.[*citation needed*]

A 2001 study reported that the sharing of straws used to "snort" cocaine can spread blood diseases such as hepatitis C.[29]

## Injection

Drug injection provides the highest blood levels of drug in the shortest amount of time. Subjective effects not commonly shared with other methods of administration include a ringing in the ears moments after injection (usually when in excess of 120 milligrams) lasting 2 to 5 minutes including tinnitus and audio distortion. This is colloquially referred to as a "bell ringer". In a study of cocaine users, the average time taken to reach peak subjective effects was 3.1 minutes.[27] The euphoria passes quickly. Aside from the toxic effects of cocaine, there is also danger of circulatory emboli from the insoluble substances that may be used to cut the drug. As with all injected illicit substances, there is a risk of the user contracting blood-borne infections if sterile injecting equipment is not available or used. Additionally, because cocaine is a vasoconstrictor, and usage often entails multiple injections within several hours or less, subsequent injections are progressively more difficult to administer, which in turn may lead to more injection attempts and more consequences from improperly performed injection.[*citation needed*]

An injected mixture of cocaine and heroin, known as "speedball" is a particularly dangerous combination, as the converse effects of the drugs actually complement each other, but may also mask the symptoms of an overdose. It has been responsible for numerous deaths, including celebrities such as John Belushi, Chris Farley, Mitch Hedberg, River Phoenix, Layne Staley and Philip Seymour Hoffman.

Experimentally, cocaine injections can be delivered to animals such as fruit flies to study the mechanisms of cocaine addiction.[30]

## Inhalation

*See also: Crack cocaine*

Inhalation or smoking is one of the several means cocaine is administered. Cocaine is smoked by inhaling the vapor by sublimating solid cocaine by heating.[31] In a 2000 Brookhaven National Laboratory medical department study, based on self reports of 32 abusers who participated in the study,"peak high" was found [27]

at mean of 1.4min +/- 0.5 minutes. Pyrolysis products of cocaine that occur only when heated/smoked have been shown to change the effect profile, *i.e.* anhydroecgonine methyl ester when co-administered with cocaine increases the dopamine in CPu and NAc brain regions, and has $M_1$- and $M_3$- receptor affinity.[32]

Smoking freebase or crack cocaine is most often accomplished using a pipe made from a small glass tube, often taken from "love roses," small glass tubes with a paper rose that are promoted as romantic gifts.[33] These are sometimes called "stems", "horns", "blasters" and "straight shooters". A small piece of clean heavy copper or occasionally stainless steel scouring pad – often called a "brillo" (actual Brillo Pads contain soap, and are not used) or "chore" (named for Chore Boy brand copper scouring pads) – serves as a reduction base and flow modulator in which the "rock" can be melted and boiled to vapor. Crack smokers also sometimes smoke through a soda can with small holes in the bottom.[*citation needed*]

Crack is smoked by placing it at the end of the pipe; a flame held close to it produces vapor, which is then inhaled by the smoker. The effects, felt almost immediately after smoking, are very intense and do not last long – usually 5 to 15 minutes.[*citation needed*]

When smoked, cocaine is sometimes combined with other drugs, such as cannabis, often rolled into a joint or blunt. Powdered cocaine is also sometimes smoked, though heat destroys much of the chemical; smokers often sprinkle it on cannabis.[*citation needed*]

The language referring to paraphernalia and practices of smoking cocaine vary, as do the packaging methods in the street level sale.[*citation needed*]

### Suppository

Little research has been focused on the suppository (anal or vaginal insertion) method of administration, also known as "plugging". This method of administration is commonly administered using an oral syringe. Cocaine can be dissolved in water and withdrawn into an oral syringe which may then be lubricated and inserted into the anus or vagina before the plunger is pushed. Anecdotal evidence of its effects is infrequently discussed, possibly due to social taboos in many cultures. The rectum and the vaginal canal is where the majority of the drug would be taken up through the membranes lining its walls.[*citation needed*]

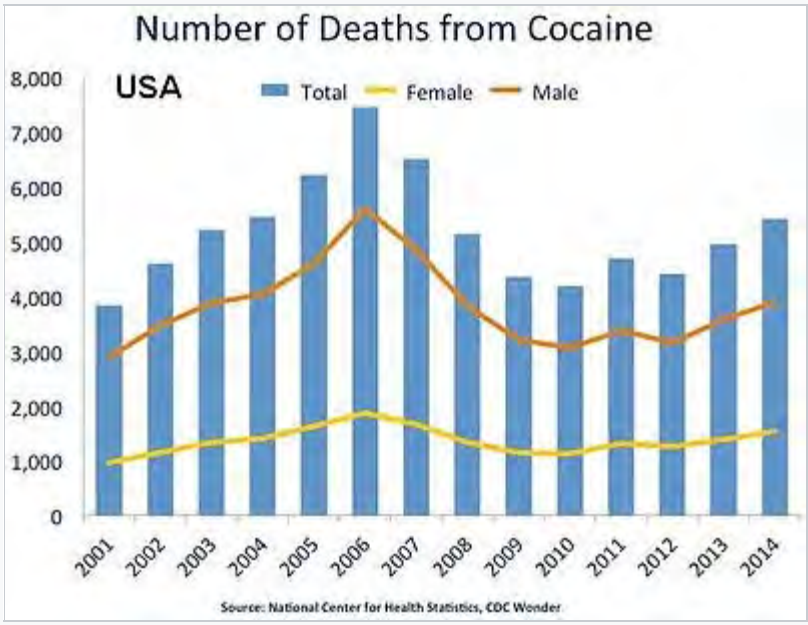
## Adverse effects

### Acute

*Main article: Cocaine intoxication*

With excessive or prolonged use, the drug can cause itching, fast heart rate, hallucinations, and paranoid delusions.[36] Overdoses cause hyperthermia and a marked elevation of blood pressure, which can be life-threatening,[36] arrhythmias,[37] and death.[37]

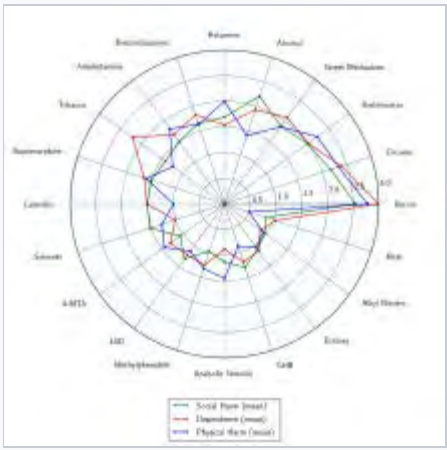
Anxiety, paranoia, and restlessness can also occur, especially during the comedown. With excessive dosage, tremors, convulsions and increased body temperature are observed.[21] Severe cardiac adverse events, particularly sudden cardiac death, become a serious risk at high doses due to cocaine's blocking effect on cardiac sodium channels.[37]




Timeline of number of yearly U.S. overdose deaths involving cocaine.[34]

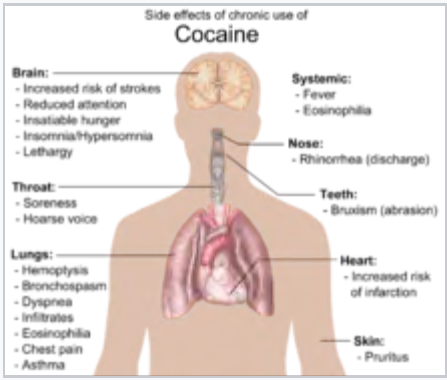
### Chronic

Chronic cocaine intake causes strong imbalances of transmitter levels in order to compensate extremes. Thus, receptors disappear from the cell surface or reappear on it, resulting more or less in an "off" or "working mode" respectively, or they change their susceptibility for binding partners (ligands) – mechanisms called downregulation and upregulation. However, studies suggest cocaine abusers do not show normal age-related loss of striatal dopamine transporter (DAT) sites, suggesting cocaine has neuroprotective properties for dopamine neurons.[38] Possible side effects include insatiable hunger, aches, insomnia/oversleeping, lethargy, and persistent runny nose. Depression with suicidal ideation may develop in very heavy users. Finally, a loss of vesicular monoamine transporters, neurofilament proteins, and other morphological changes appear to indicate a long term damage of dopamine neurons. All these effects contribute a rise in tolerance thus requiring a larger dosage to achieve the same effect. [39] The lack of normal amounts of serotonin and dopamine in the brain is the cause of the dysphoria and depression felt after the initial high. Physical withdrawal is not dangerous. Physiological changes caused by cocaine withdrawal include vivid and unpleasant dreams, insomnia or hypersomnia, increased appetite and psychomotor retardation or agitation.[39]



Addiction experts in psychiatry, chemistry, pharmacology, forensic science, epidemiology, and the police and legal services engaged in delphic analysis regarding 20 popular recreational drugs. Cocaine was ranked the 2nd in dependence and physical harm and 3rd in social harm.[35]

Physical side effects from chronic smoking of cocaine include coughing up blood, bronchospasm, itching, fever, diffuse alveolar infiltrates without effusions, pulmonary and systemic eosinophilia, chest pain, lung trauma, sore throat, asthma, hoarse voice, dyspnea (shortness of breath), and an aching, flu-like syndrome. Cocaine constricts blood vessels, dilates pupils, and increases body temperature, heart rate, and blood pressure. It can also cause headaches and gastrointestinal complications such as abdominal pain and nausea. A common but untrue belief is that the smoking of cocaine chemically breaks down tooth enamel and causes tooth decay. However, cocaine does often cause involuntary tooth grinding, known as bruxism, which can deteriorate tooth enamel and lead to gingivitis.[40] Additionally, stimulants like cocaine, methamphetamine, and even caffeine cause dehydration and dry mouth. Since saliva is an important mechanism in maintaining one's oral pH level, chronic stimulant abusers who do not hydrate sufficiently may experience demineralization of their teeth due to the pH of the tooth surface dropping too low (below 5.5).




Side effects of chronic cocaine use

Chronic intranasal usage can degrade the cartilage separating the nostrils (the septum nasi), leading eventually to its complete disappearance. Due to the absorption of the cocaine from cocaine hydrochloride, the remaining hydrochloride forms a dilute hydrochloric acid.[41]

Cocaine may also greatly increase this risk of developing rare autoimmune or connective tissue diseases such as lupus, Goodpasture syndrome, vasculitis, glomerulonephritis, Stevens–Johnson syndrome, and other diseases.[42][43][44][45] It can also cause a wide array of kidney diseases and kidney failure.[46][47]

Cocaine misuse doubles both the risks of hemorrhagic and ischemic strokes,[48] as well as increases the risk of other infarctions, such as myocardial infarction.[49]

## Addiction

Cocaine hydrochloride

Cocaine addiction occurs through accumbal ΔFosB overexpression, which arises through transcriptional regulation and epigenetic remodeling of the nucleus accumbens.

## Dependence and withdrawal

Cocaine dependence is a form of psychological dependence that develops from regular cocaine use and produces a withdrawal state with emotional-motivational deficits upon cessation of cocaine use.

# Pharmacology

## Pharmacodynamics

The pharmacodynamics of cocaine involve the complex relationships of neurotransmitters (inhibiting monoamine uptake in rats with ratios of about: serotonin:dopamine = 2:3, serotonin:norepinephrine = 2:5[50]) The most extensively studied effect of cocaine on the central nervous system is the blockade of the dopamine transporter protein. Dopamine transmitter released during neural signaling is normally recycled via the transporter; i.e., the transporter binds the transmitter and pumps it out of the synaptic cleft back into the presynaptic neuron, where it is taken up into storage vesicles. Cocaine binds tightly at the dopamine transporter forming a complex that blocks the transporter's function. The dopamine transporter can no longer perform its reuptake function, and thus dopamine accumulates in the synaptic cleft.

Cocaine's affects certain serotonin (5-HT) receptors; in particular, it has been shown to antagonize the 5-HT3 receptor, which is a ligand-gated ion channel. The overabundance of 5-HT3 receptors in cocaine conditioned rats display this trait, however the exact effect of 5-HT3 in this process is unclear.[51] The 5-HT2 receptor (particularly the subtypes 5-HT2AR, 5-HT2BR and 5-HT2CR) are involved in the locomotor-activating effects of cocaine.[52]

Cocaine has been demonstrated to bind as to directly stabilize the DAT transporter on the open outward-facing conformation. Further, cocaine binds in such a way as to inhibit a hydrogen bond innate to DAT. Cocaine's binding properties are such that it attaches so this hydrogen bond will not form and is blocked from formation due to the tightly locked orientation of the cocaine molecule. Research studies have suggested that the affinity for the transporter is not what is involved in habituation of the substance so much as the conformation and binding properties to where and how on the transporter the molecule binds.[53]

Sigma receptors are affected by cocaine, as cocaine functions as a sigma ligand agonist.[54] Further specific receptors it has been demonstrated to function on are NMDA and the D1 dopamine receptor.[55]

Cocaine also blocks sodium channels, thereby interfering with the propagation of action potentials;[37] thus, like lignocaine and novocaine, it acts as a local anesthetic. It also functions on the binding sites to the dopamine and serotonin sodium dependent transport area as targets as separate mechanisms from its

reuptake of those transporters; unique to its local anesthetic value which makes it in a class of functionality different from both its own derived phenyltropanes analogues which have that removed. In addition to this cocaine has some target binding to the site of the Kappa-opioid receptor as well.[56] Cocaine also causes vasoconstriction, thus reducing bleeding during minor surgical procedures. The locomotor enhancing properties of cocaine may be attributable to its enhancement of dopaminergic transmission from the substantia nigra. Recent research points to an important role of circadian mechanisms[57] and clock genes[58] in behavioral actions of cocaine.

Cocaine can often cause reduced food intake, many chronic users lose their appetite and can experience severe malnutrition and significant weight loss. Cocaine effects, further, are shown to be potentiated for the user when used in conjunction with new surroundings and stimuli, and otherwise novel environs.[59]

### Pharmacokinetics

Cocaine is extensively metabolized, primarily in the liver, with only about 1% excreted unchanged in the urine. The metabolism is dominated by hydrolytic ester cleavage, so the eliminated metabolites consist mostly of benzoylecgonine (BE), the major metabolite, and other significant metabolites in lesser amounts such as ecgonine methyl ester (EME) and ecgonine. Further minor metabolites of cocaine include norcocaine, p-hydroxycocaine, m-hydroxycocaine, p-hydroxybenzoylecgonine (pOHBE), and m-hydroxybenzoylecgonine.[60] If consumed with alcohol, cocaine combines with alcohol in the liver to form cocaethylene. Studies have suggested cocaethylene is both more euphoric, and has a higher cardiovascular toxicity than cocaine by itself.[61][62][63]

Depending on liver and kidney function, cocaine metabolites are detectable in urine. Benzoylecgonine can be detected in urine within four hours after cocaine intake and remains detectable in concentrations greater than 150 ng/mL typically for up to eight days after cocaine is used. Detection of accumulation of cocaine metabolites in hair is possible in regular users until the sections of hair grown during use are cut or fall out.

## Chemistry

### Appearance

Cocaine in its purest form is a white, pearly product. Cocaine appearing in powder form is a salt, typically cocaine hydrochloride. Street cocaine is often adulterated or "cut" with talc, lactose, sucrose, glucose, mannitol, inositol, caffeine, procaine, phencyclidine, phenytoin, lignocaine, strychnine, amphetamine, or heroin.[64]

The color of "crack" cocaine depends upon several factors including the origin of the cocaine used, the method of preparation – with ammonia or baking soda – and the presence of impurities, but will generally range from white to a yellowish cream to a light brown. Its texture will also depend on the adulterants, origin and processing of the powdered cocaine, and the method of converting the base. It ranges from a crumbly texture, sometimes extremely oily, to a hard, almost crystalline nature.

A pile of cocaine hydrochloride

### Forms

#### Salt

Cocaine - a tropane alkaloid - is a weakly alkaline compound, and can therefore combine with acidic compounds to form various salts. The hydrochloride (HCl) salt of cocaine is by far the most commonly encountered, although the sulfate ($-SO_4$) and the nitrate ($-NO_3$) are

A piece of compressed cocaine powder

occasionally seen. Different salts dissolve to a greater or lesser extent in various solvents – the hydrochloride salt is polar in character and is quite soluble in water.

## Base

*Main article: Freebase (chemistry)*

As the name implies, "freebase" is the base form of cocaine, as opposed to the salt form. It is practically insoluble in water whereas hydrochloride salt is water-soluble.

Smoking freebase cocaine has the additional effect of releasing methylecgonidine into the user's system due to the pyrolysis of the substance (a side effect which insufflating or injecting powder cocaine does not create). Some research suggests that smoking freebase cocaine can be even more cardiotoxic than other routes of administration[65] because of methylecgonidine's effects on lung tissue[66] and liver tissue.[67]

Pure cocaine is prepared by neutralizing its compounding salt with an alkaline solution which will precipitate to non-polar basic cocaine. It is further refined through aqueous-solvent liquid-liquid extraction.

## Crack cocaine

*Main article: Crack cocaine*

A woman smoking crack cocaine

Crack is a lower purity form of free-base cocaine that is usually produced by neutralization of cocaine hydrochloride with a solution of baking soda (sodium bicarbonate, $NaHCO_3$) and water, producing a very hard/brittle, off-white-to-brown colored, amorphous material that contains sodium carbonate, entrapped water, and other by-products as the main impurities.

The "freebase" and "crack" forms of cocaine are usually administered by vaporization of the powdered substance into smoke, which is then inhaled.[68]

The origin of the name "crack" comes from the "crackling" sound (and hence the onomatopoeic moniker "crack") that is produced when the cocaine and its impurities (i.e. water, sodium bicarbonate) are heated past the point of vaporization.[69]

"Rocks" of crack cocaine

Pure cocaine base/crack can be smoked because it vaporizes smoothly, with little or no decomposition at 98 °C (208 °F),[70] which is below the boiling point of water.

In contrast, cocaine hydrochloride does not vaporize until heated to a much higher temperature (about 197 °C), and considerable decomposition/burning occurs at these high temperatures. This effectively destroys some of the cocaine and yields a sharp, acrid, and foul-tasting smoke.

Smoking or vaporizing cocaine and inhaling it into the lungs produces an almost immediate "high" that can be very powerful (and addicting) quite rapidly – this initial crescendo of stimulation is known as a "rush". While the stimulating effects may last for hours, the euphoric sensation is very brief, prompting the user to smoke more immediately.

## Coca leaf infusions

This article **needs additional citations for verification**. Please help improve this article by adding citations to reliable sources. Unsourced material may be challenged and removed. *(April 2014) (Learn how and when to remove this template message)*

Coca herbal infusion (also referred to as coca tea) is used in coca-leaf producing countries much as any herbal medicinal infusion would elsewhere in the world. The free and legal commercialization of dried coca leaves under the form of filtration bags to be used as "coca tea" has been actively promoted by the governments of Peru and Bolivia for many years as a drink having medicinal powers. Visitors to the city of Cuzco in Peru, and La Paz in Bolivia are greeted with the offering of coca leaf infusions (prepared in teapots with whole coca leaves) purportedly to help the newly arrived traveler overcome the malaise of high altitude sickness. The effects of drinking coca tea are a mild stimulation and mood lift. It does not produce any significant numbing of the mouth nor does it give a rush like snorting cocaine. In order to prevent the demonization of this product, its promoters publicize the unproven concept that much of the effect of the ingestion of coca leaf infusion would come from the secondary alkaloids, as being not only quantitatively different from pure cocaine but also qualitatively different.

It has been promoted as an adjuvant for the treatment of cocaine dependence. In one controversial study, coca leaf infusion was used—in addition to counseling—to treat 23 addicted coca-paste smokers in Lima, Peru. Relapses fell from an average of four times per month before treatment with coca tea to one during the treatment. The duration of abstinence increased from an average of 32 days prior to treatment to 217 days during treatment. These results suggest that the administration of coca leaf infusion plus counseling would be an effective method for preventing relapse during treatment for cocaine addiction. Importantly, these results also suggest strongly that the primary pharmacologically active metabolite in coca leaf infusions is actually cocaine and not the secondary alkaloids.[*improper synthesis?*]

The cocaine metabolite benzoylecgonine can be detected in the urine of people a few hours after drinking one cup of coca leaf infusion.[71]

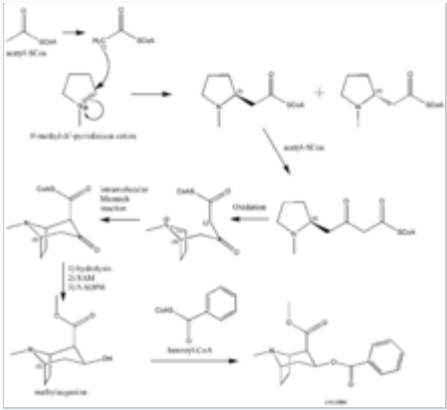
## Biosynthesis

*Main article: Biosynthesis of cocaine*

The first synthesis and elucidation of the cocaine molecule was by Richard Willstätter in 1898.[72] Willstätter's synthesis derived cocaine from tropinone. Since then, Robert Robinson and Edward Leete have made significant contributions to the mechanism of the synthesis. (-$NO_3$)

Biosynthesis of *N*-methyl-pyrrolinium cation

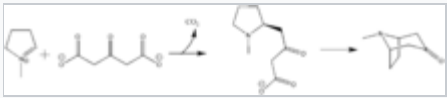
The additional carbon atoms required for the synthesis of cocaine are derived from acetyl-CoA, by addition of two acetyl-CoA units to the *N*-methyl-$\Delta^1$-pyrrolinium cation.[73] The first addition is a Mannich-like reaction with the enolate anion from acetyl-CoA acting as a nucleophile towards the pyrrolinium cation. The second addition occurs through a Claisen condensation. This produces a racemic mixture of the 2-substituted pyrrolidine, with the retention of the thioester from the Claisen condensation. In formation of tropinone from racemic ethyl [2,3-$^{13}C_2$]$_4$(Nmethyl-2-pyrrolidinyl)-3-oxobutanoate there is no preference for either stereoisomer.[74] In the biosynthesis of cocaine, however, only the (S)-enantiomer can cyclize to form the tropane ring system of cocaine. The stereoselectivity of this reaction was further investigated through study of prochiral methylene hydrogen discrimination.[75] This is due to the extra chiral center at C-2.[76] This process occurs through an oxidation, which regenerates the pyrrolinium cation and formation of an enolate anion, and an intramolecular Mannich reaction. The tropane ring



Biosynthesis of cocaine

system undergoes hydrolysis, SAM-dependent methylation, and reduction via NADPH for the formation of methylecgonine. The benzoyl moiety required for the formation of the cocaine diester is synthesized from phenylalanine via cinnamic acid.[77] Benzoyl-CoA then combines the two units to form cocaine.

## *N*-methyl-pyrrolinium cation



Robinson biosynthesis of tropane

The biosynthesis begins with L-Glutamine, which is derived to L-ornithine in plants. The major contribution of L-ornithine and L-arginine as a precursor to the tropane ring was confirmed by Edward Leete.[78] Ornithine then undergoes a pyridoxal phosphate-dependent decarboxylation to form putrescine. In animals, however, the urea cycle derives putrescine from ornithine. L-ornithine is converted to L-arginine,[79] which is then decarboxylated via PLP to form agmatine. Hydrolysis of the imine derives *N*-carbamoylputrescine followed with hydrolysis of the urea to form putrescine. The separate pathways of converting ornithine to putrescine in plants and animals have converged. A SAM-dependent *N*-methylation of putrescine gives the *N*-methylputrescine product, which then undergoes oxidative deamination by the action of diamine oxidase to yield the aminoaldehyde. Schiff base formation confirms the biosynthesis of the *N*-methyl-$\Delta^1$-pyrrolinium cation.

Reduction of tropinone

## Robert Robinson's acetonedicarboxylate

The biosynthesis of the tropane alkaloid, however, is still uncertain. Hemscheidt proposes that Robinson's acetonedicarboxylate emerges as a potential intermediate for this reaction.[80] Condensation of *N*-methylpyrrolinium and acetonedicarboxylate would generate the oxobutyrate. Decarboxylation leads to tropane alkaloid formation.

## Reduction of tropinone

The reduction of tropinone is mediated by NADPH-dependent reductase enzymes, which have been characterized in multiple plant species.[81] These plant species all contain two types of the reductase enzymes, tropinone reductase I and tropinone reductase II. TRI produces tropine and TRII produces pseudotropine. Due to differing kinetic and pH/activity characteristics of the enzymes and by the 25-fold higher activity of TRI over TRII, the majority of the tropinone reduction is from TRI to form tropine.[82]

# Detection in body fluids

Cocaine and its major metabolites may be quantified in blood, plasma, or urine to monitor for abuse, confirm a diagnosis of poisoning, or assist in the forensic investigation of a traffic or other criminal violation or a sudden death. Most commercial cocaine immunoassay screening tests cross-react appreciably with the major cocaine metabolites, but chromatographic techniques can easily distinguish and separately measure each of these substances. When interpreting the results of a test, it is important to consider the cocaine usage history of the individual, since a chronic user can develop tolerance to doses that would incapacitate a cocaine-naive individual, and the chronic user often has high baseline values of the metabolites in his system. Cautious interpretation of testing results may allow a distinction between passive or active usage,

and between smoking versus other routes of administration.[83] In 2011, researchers at John Jay College of Criminal Justice reported that dietary zinc supplements can mask the presence of cocaine and other drugs in urine. Similar claims have been made in web forums on that topic.[84]

# Usage

According to a 2007 United Nations report, Spain is the country with the highest rate of cocaine usage (3.0% of adults in the previous year).[86] Other countries where the usage rate meets or exceeds 1.5% are the United States (2.8%), England and Wales (2.4%), Canada (2.3%), Italy (2.1%), Bolivia (1.9%), Chile (1.8%), and Scotland (1.5%).[86]

**Global estimates of illegal drug users in 2014 (in millions of users)**[85]

| Substance | Best estimate | Low estimate | High estimate |
|---|---|---|---|
| Amphetamine-type stimulants | 35.65 | 15.34 | 55.90 |
| Cannabis | 182.50 | 127.54 | 233.65 |
| **Cocaine** | 18.26 | 14.88 | 22.08 |
| Ecstasy | 19.40 | 9.89 | 29.01 |
| Opiates | 17.44 | 13.74 | 21.59 |
| Opioids | 33.12 | 28.57 | 38.52 |

## Europe

Cocaine is the second most popular illegal recreational drug in Europe (behind cannabis). Since the mid-1990s, overall cocaine usage in Europe has been on the rise, but usage rates and attitudes tend to vary between countries. European countries with the highest usage rates are the United Kingdom, Spain, Italy, and the Republic of Ireland.

Approximately 12 million Europeans (3.6%) have used cocaine at least once, 4 million (1.2%) in the last year, and 2 million in the last month (0.5%).

About 3.5 million or 87.5% of those who have used the drug in the last year[*when?*] are young adults (15–34 years old). Usage is particularly prevalent among this demographic: 4% to 7% of males have used cocaine in the last year in Spain, Denmark, Republic of Ireland, Italy, and the United Kingdom. The ratio of male to female users is approximately 3.8:1, but this statistic varies from 1:1 to 13:1 depending on country.[87]

In 2014 London had the highest amount of cocaine in their sewage out of 50 European cities.[88]

## United States

*Main article: Cocaine in the United States*

Cocaine is the second most popular illegal recreational drug in the United States (behind cannabis)[89] and the U.S. is the world's largest consumer of cocaine.[90] Cocaine is commonly used in middle to upper-class communities and is known as a "rich man's drug". It is also popular amongst college students, as a party drug. A study throughout the entire United States has reported that around 48 percent of people who graduated high school in 1979 have used Cocaine recreationally during some point in their lifetime, compared to approximately 20 percent of students who graduated between the years of 1980 and 1995.[91] Its users span over different ages, races, and professions. In the 1970s and 1980s, the drug became particularly popular in the disco culture as cocaine usage was very common and popular in many discos such as Studio 54.

# History

## Discovery

For over a thousand years South American indigenous peoples have chewed the leaves of *Erythroxylon coca*, a plant that contains vital

Coca leaf in Bolivia

nutrients as well as numerous alkaloids, including cocaine. The coca leaf was, and still is, chewed almost universally by some indigenous communities. The remains of coca leaves have been found with ancient Peruvian mummies, and pottery from the time period depicts humans with bulged cheeks, indicating the presence of something on which they are chewing.[92] There is also evidence that these cultures used a mixture of coca leaves and saliva as an anesthetic for the performance of trepanation.[93]

When the Spanish arrived in South America, most at first ignored aboriginal claims that the leaf gave them strength and energy, and declared the practice of chewing it the work of the Devil.[*citation needed*] But after discovering that these claims were true, they legalized and taxed the leaf, taking 10% off the value of each crop.[94] In 1569, Nicolás Monardes described the indigenous peoples' practice of chewing a mixture of tobacco and coca leaves to induce "great contentment":[95]

> When they wished to make themselves drunk and out of judgment they chewed a mixture of tobacco and coca leaves which make them go as they were out of their wittes.

In 1609, Padre Blas Valera wrote:

> Coca protects the body from many ailments, and our doctors use it in powdered form to reduce the swelling of wounds, to strengthen broken bones, to expel cold from the body or prevent it from entering, and to cure rotten wounds or sores that are full of maggots. And if it does so much for outward ailments, will not its singular virtue have even greater effect in the entrails of those who eat it?[*citation needed*]

## Isolation and naming

Although the stimulant and hunger-suppressant properties of coca had been known for many centuries, the isolation of the cocaine alkaloid was not achieved until 1855. Various European scientists had attempted to isolate cocaine, but none had been successful for two reasons: the knowledge of chemistry required was insufficient at the time,[*citation needed*] and contemporary conditions of sea-shipping from South America could degrade the cocaine in the plant samples available to European chemists.[*citation needed*]

The cocaine alkaloid was first isolated by the German chemist Friedrich Gaedcke in 1855. Gaedcke named the alkaloid "erythroxyline", and published a description in the journal *Archiv der Pharmazie*.[96]

In 1856, Friedrich Wöhler asked Dr. Carl Scherzer, a scientist aboard the *Novara* (an Austrian frigate sent by Emperor Franz Joseph to circle the globe), to bring him a large amount of coca leaves from South America. In 1859, the ship finished its travels and Wöhler received a trunk full of coca. Wöhler passed on the leaves to Albert Niemann, a Ph.D. student at the University of Göttingen in Germany, who then developed an improved purification process.[97]

Niemann described every step he took to isolate cocaine in his dissertation titled *Über eine neue organische Base in den Cocablättern* (*On a New Organic Base in the Coca Leaves*), which was published in 1860—it earned him his Ph.D. and is now in the British Library. He wrote of the alkaloid's "colourless transparent prisms" and said that "Its solutions have an alkaline reaction, a bitter taste, promote the flow of saliva and leave a peculiar numbness, followed by a sense of cold when applied to the tongue." Niemann named the alkaloid "cocaine" from "coca" (from Quechua "cuca") + suffix "ine".[97][98] Because of its use as a local anesthetic, a suffix "-caine" was later extracted and used to form names of synthetic local anesthetics.

The first synthesis and elucidation of the structure of the cocaine molecule was by Richard Willstätter in 1898.[72] It was the first biomimetic synthesis of an organic structure recorded in academic chemical

literature.[99][100] The synthesis started from tropinone, a related natural product and took five steps. The name comes from "coca" and the alkaloid suffix "-ine", forming "cocaine".

## Medicalization

With the discovery of this new alkaloid, Western medicine was quick to exploit the possible uses of this plant.

In 1879, Vassili von Anrep, of the University of Würzburg, devised an experiment to demonstrate the analgesic properties of the newly discovered alkaloid. He prepared two separate jars, one containing a cocaine-salt solution, with the other containing merely salt water. He then submerged a frog's legs into the two jars, one leg in the treatment and one in the control solution, and proceeded to stimulate the legs in several different ways. The leg that had been immersed in the cocaine solution reacted very differently from the leg that had been immersed in salt water.[101]

Karl Koller (a close associate of Sigmund Freud, who would write about cocaine later) experimented with cocaine for ophthalmic usage. In an infamous experiment in 1884, he experimented upon himself by applying a cocaine solution to his own eye and then pricking it with pins. His findings were presented to the Heidelberg Ophthalmological Society. Also in 1884, Jellinek demonstrated the effects of cocaine as a respiratory system anesthetic. In 1885, William Halsted demonstrated nerve-block anesthesia,[102] and James Leonard Corning demonstrated peridural anesthesia.[103] 1898 saw Heinrich Quincke use cocaine for spinal anesthesia.

Today, cocaine has a very limited medical use.


"Cocaine toothache drops", 1885 advertisement of cocaine for dental pain in children


Advertisement in the January 1896 issue of *McClure's Magazine* for Burnett's Cocaine "for the hair".

## Popularization

In 1859, an Italian doctor, Paolo Mantegazza, returned from Peru, where he had witnessed first-hand the use of coca by the local indigenous peoples. He proceeded to experiment on himself and upon his return to Milan he wrote a paper in which he described the effects. In this paper he declared coca and cocaine (at the time they were assumed to be the same) as being useful medicinally, in the treatment of "a furred tongue in the morning, flatulence, and whitening of the teeth."

A chemist named Angelo Mariani who read Mantegazza's paper became immediately intrigued with coca and its economic potential. In 1863, Mariani started marketing a wine called Vin Mariani, which had been treated with coca leaves, to become cocawine. The ethanol in wine acted as a solvent and extracted the cocaine from the coca leaves, altering the drink's effect. It contained 6 mg cocaine per ounce of wine, but Vin Mariani which was to be exported contained 7.2 mg per ounce, to compete with the higher cocaine content of similar drinks in the United States. A "pinch of coca leaves" was included in John Styth Pemberton's original 1886 recipe for Coca-Cola, though the company began using decocainized leaves in 1906 when the Pure Food and Drug Act was passed.

In 1879 cocaine began to be used to treat morphine addiction. Cocaine was introduced into clinical use as a local anesthetic in Germany in 1884, about the same time as Sigmund Freud published his work *Über Coca*, in which he wrote that cocaine causes:[*citation needed*]


Pope Leo XIII purportedly carried a hip flask of the coca-treated Vin Mariani with him, and awarded a Vatican gold medal to Angelo Mariani.[104]

> Exhilaration and lasting euphoria, which in no way differs from the normal euphoria of the healthy person. You perceive an increase of self-control and possess more vitality and capacity for work. In other words, you are simply normal, and it is soon hard to believe you are under the influence of any drug. Long intensive physical work is performed without any fatigue. This result is enjoyed without any of the unpleasant after-effects that follow exhilaration brought about by alcoholic beverages. No craving for the further use of cocaine appears after the first, or even after repeated taking of the drug.

In 1885 the U.S. manufacturer Parke-Davis sold cocaine in various forms, including cigarettes, powder, and even a cocaine mixture that could be injected directly into the user's veins with the included needle. The company promised that its cocaine products would "supply the place of food, make the coward brave, the silent eloquent and render the sufferer insensitive to pain."

By the late Victorian era, cocaine use had appeared as a vice in literature. For example, it was injected by Arthur Conan Doyle's fictional Sherlock Holmes, generally to offset the boredom he felt when he was not working on a case.

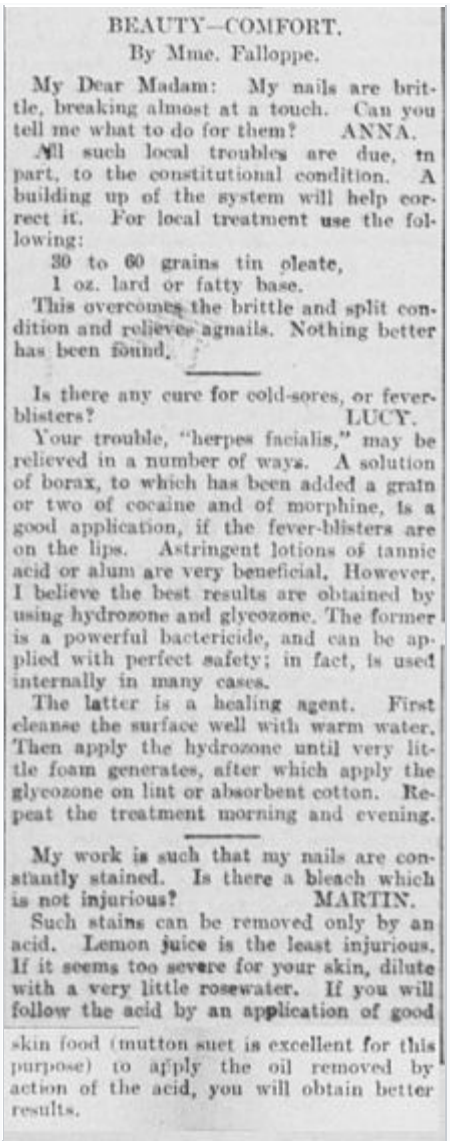
In early 20th-century Memphis, Tennessee, cocaine was sold in neighborhood drugstores on Beale Street, costing five or ten cents for a small boxful. Stevedores along the Mississippi River used the drug as a stimulant, and white employers encouraged its use by black laborers.[105]

In 1909, Ernest Shackleton took "Forced March" brand cocaine tablets to Antarctica, as did Captain Scott a year later on his ill-fated journey to the South Pole.[106]

During the mid-1940s, amidst WWII, cocaine was considered for inclusion as an ingredient of a future generation of 'pep pills' for the German military code named D-IX.[107]

## Modern usage

In many countries, cocaine is a popular recreational drug. In the United States, the development of "crack" cocaine introduced the substance to a generally poorer inner-city market. Use of the powder form has stayed relatively constant, experiencing a new height of use



BEAUTY—COMFORT.
By Mme. Falloppe.

My Dear Madam: My nails are brittle, breaking almost at a touch. Can you tell me what to do for them? ANNA.

All such local troubles are due, in part, to the constitutional condition. A building up of the system will help correct it. For local treatment use the following:

30 to 60 grains tin oleate,
1 oz. lard or fatty base.

This overcomes the brittle and split condition and relieves agnails. Nothing better has been found.

Is there any cure for cold-sores, or fever-blisters? LUCY.

Your trouble, "herpes facialis," may be relieved in a number of ways. A solution of borax, to which has been added a grain or two of cocaine and of morphine, is a good application, if the fever-blisters are on the lips. Astringent lotions of tannic acid or alum are very beneficial. However, I believe the best results are obtained by using hydrozone and glycozone. The former is a powerful bactericide, and can be applied with perfect safety; in fact, is used internally in many cases.

The latter is a healing agent. First cleanse the surface well with warm water. Then apply the hydrozone until very little foam generates, after which apply the glycozone on lint or absorbent cotton. Repeat the treatment morning and evening.

My work is such that my nails are constantly stained. Is there a bleach which is not injurious? MARTIN.

Such stains can be removed only by an acid. Lemon juice is the least injurious. If it seems too severe for your skin, dilute with a very little rosewater. If you will follow the acid by an application of good skin food (mutton suet is excellent for this purpose) to apply the oil removed by action of the acid, you will obtain better results.

In this 1904 advice column from *the Tacoma Times*, "Madame Falloppe" recommended that cold sores be treated with a solution of borax, cocaine, and morphine.



Women purchase cocaine capsules in Berlin, 1924

during the late 1990s and early 2000s in the U.S., and has become much more popular in the last few years in the UK.[*citation needed*][*when?*]

Cocaine use is prevalent across all socioeconomic strata, including age, demographics, economic, social, political, religious, and livelihood.[*citation needed*]

The estimated U.S. cocaine market exceeded US$70 billion in street value for the year 2005, exceeding revenues by corporations such as Starbucks.[108][109] There is a tremendous demand for cocaine in the U.S. market, particularly among those who are making incomes affording luxury spending, such as single adults and professionals with discretionary income. Cocaine's status as a club drug shows its immense popularity among the "party crowd".


D.C. Mayor Marion Barry captured on a surveillance camera smoking crack cocaine during a sting operation by the FBI and D.C. Police.

In 1995 the World Health Organization (WHO) and the United Nations Interregional Crime and Justice Research Institute (UNICRI) announced in a press release the publication of the results of the largest global study on cocaine use ever undertaken. However, a decision by an American representative in the World Health Assembly banned the publication of the study, because it seemed to make a case for the positive uses of cocaine. An excerpt of the report strongly conflicted with accepted paradigms, for example "that occasional cocaine use does not typically lead to severe or even minor physical or social problems." In the sixth meeting of the B committee, the US representative threatened that "If World Health Organization activities relating to drugs failed to reinforce proven drug control approaches, funds for the relevant programs should be curtailed". This led to the decision to discontinue publication. A part of the study was recuperated and published in 2010, including profiles of cocaine use in 20 countries,

but are unavailable as of 2015.[110]

In October 2010 it was reported that the use of cocaine in Australia has doubled since monitoring began in 2003.[111]

A problem with illegal cocaine use, especially in the higher volumes used to combat fatigue (rather than increase euphoria) by long-term users, is the risk of ill effects or damage caused by the compounds used in adulteration. Cutting or "stepping on" the drug is commonplace, using compounds which simulate ingestion effects, such as Novocain (procaine) producing temporary anesthaesia, as many users believe a strong numbing effect is the result of strong and/or pure cocaine, ephedrine or similar stimulants that are to produce an increased heart rate. The normal adulterants for profit are inactive sugars, usually mannitol, creatine or glucose, so introducing active adulterants gives the illusion of purity and to 'stretch' or make it so a dealer can sell more product than without the adulterants.[*citation needed*] The adulterant of sugars allows the dealer to sell the product for a higher price because of the illusion of purity and allows to sell more of the product at that higher price, enabling dealers to significantly increase revenue with little additional cost for the adulterants. A 2007 study by the European Monitoring Centre for Drugs and Drug Addiction showed that the purity levels for street purchased cocaine was often under 5% and on average under 50% pure.[112]

# Society and culture

## Legal status

*Main article: Legal status of cocaine*

The production, distribution, and sale of cocaine products is restricted (and illegal in most contexts) in most countries as regulated by the Single Convention on Narcotic Drugs, and the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances. In the United States the manufacture, importation, possession, and distribution of cocaine are additionally regulated by the 1970 Controlled Substances Act.

Some countries, such as Peru and Bolivia permit the cultivation of coca leaf for traditional consumption by the local indigenous population, but nevertheless, prohibit the production, sale, and consumption of cocaine.[113] The provisions as to how much a coca farmer can yield annually is protected by laws such as the Bolivian Cato accord.[114] In addition, some parts of Europe and Australia allow processed cocaine for medicinal uses only.

## Australia

Cocaine is a Schedule 8 prohibited substance in Australia under the Poisons Standard (July 2016).[115] A schedule 8 substance is a controlled Drug – Substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.[115]

In Western Australia under the Misuse of Drugs Act 1981 4.0g of cocaine is the amount of prohibited drugs determining a court of trial, 2.0g is the amount of cocaine required for the presumption of intention to sell or supply and 28.0g is the amount of cocaine required for purposes of drug trafficking [116]

## United States

*See also: Cocaine in the United States*

The US federal government instituted a national labeling requirement for cocaine and cocaine-containing products through the Food and Drug Act of 1906.[117] The next important federal regulation was the Harrison Narcotics Tax Act of 1914. While this act is often seen as the start of prohibition, the act itself was not actually a prohibition on cocaine, but instead set up a regulatory and licensing regime.[118] The Harrison Act did not recognize addiction as a treatable condition and therefore the therapeutic use of cocaine, heroin

or morphine to such individuals was outlawed – leading the Journal of American Medicine to remark, "[the addict] is denied the medical care he urgently needs, open, above-board sources from which he formerly obtained his drug supply are closed to him, and he is driven to the underworld where he can get his drug, but of course, surreptitiously and in violation of the law."[119] The Harrison Act left manufacturers of cocaine untouched so long as they met certain purity and labeling standards.[120] Despite that cocaine was typically illegal to sell and legal outlets were rarer, the quantities of legal cocaine produced declined very little.[120] Legal cocaine quantities did not decrease until the Jones-Miller Act of 1922 put serious restrictions on cocaine manufactures.[120]

## Interdiction

In 2004, according to the United Nations, 589 tonnes of cocaine were seized globally by law enforcement authorities. Colombia seized 188 t, the United States 166 t, Europe 79 t, Peru 14 t, Bolivia 9 t, and the rest of the world 133 t.[121]

## Economics

Because of the drug's potential for addiction and overdose, cocaine is generally treated as a 'hard drug', with severe penalties for possession and trafficking. Demand remains high, and consequently, black market cocaine is quite expensive. Unprocessed cocaine, such as coca leaves, are occasionally purchased and sold, but this is exceedingly rare as it is much easier and more profitable to conceal and smuggle it in powdered form. The scale of the market is immense: 770 tonnes times $100 per gram retail = up to $77 billion.[*citation needed*]

## Production

Until 2012, Colombia was the world's leading producer of cocaine.[122][123] Three-quarters of the world's annual yield of cocaine has been produced in Colombia, both from cocaine base imported from Peru (primarily the Huallaga Valley) and Bolivia, and from locally grown coca. There was a 28% increase from the amount of potentially harvestable coca plants which were grown in Colombia in 1998. This, combined with crop reductions in Bolivia and Peru, made Colombia the nation with the largest area of coca under cultivation after the mid-1990s. Coca is grown for traditional purposes by indigenous communities, a use which is still present and is permitted by Colombian laws only makes up a small fragment of total coca production, most of which is used for the illegal drug trade.[*citation needed*]

An interview with a coca farmer published in 2003 described a mode of production by acid-base extraction that has changed little since 1905. Roughly 625 pounds (283 kg) of leaves were harvested per hectare, six times per year. The leaves were dried for half a day, then chopped into small pieces with a strimmer and sprinkled with a small amount of powdered cement (replacing sodium carbonate from former times). Several hundred pounds of this mixture were soaked in 50 US gallons (190 L) of gasoline for a day, then the gasoline was removed and the leaves were pressed for remaining liquid, after which they could be discarded. Then battery acid (weak sulfuric acid) was used, one bucket per 55 lb (25 kg) of leaves, to create a phase separation in which the cocaine free base in the gasoline was acidified and extracted into a few buckets of "murky-looking smelly liquid". Once powdered caustic soda was added to this, the cocaine precipitated and could be removed by filtration through a cloth. The resulting material, when dried, was termed *pasta* and sold by the farmer. The 3750 pound yearly harvest of leaves from a hectare produced 6 lb (2.5 kg) of *pasta*, approximately 40–60% cocaine. Repeated recrystallization from solvents, producing *pasta lavada* and eventually crystalline cocaine were performed at specialized laboratories after the sale.[124]

Attempts to eradicate coca fields through the use of defoliants have devastated part of the farming economy in some coca growing regions of Colombia, and strains appear to have been developed that are more resistant or immune to their use. Whether these strains are natural mutations or the product of human tampering is unclear. These strains have also shown to be more potent than those previously grown, increasing profits for the drug cartels responsible for the exporting of cocaine. Although production fell temporarily, coca crops rebounded in numerous smaller fields in Colombia, rather than the larger
[*citation needed*]

plantations.

The cultivation of coca has become an attractive economic decision for many growers due to the combination of several factors, including the lack of other employment alternatives, the lower profitability of alternative crops in official crop substitution programs, the eradication-related damages to non-drug farms, the spread of new strains of the coca plant due to persistent worldwide demand.[*citation needed*]

**Estimated Andean region coca cultivation and potential pure cocaine production**[125]

| | 2000 | 2001 | 2002 | 2003 | 2004 |
|---|---|---|---|---|---|
| Net cultivation $km^2$ (sq mi) | 1,875 (724) | 2,218 (856) | 2,007.5 (775.1) | 1,663 (642) | 1,662 (642) |
| Potential pure cocaine production (tonnes) | 770 | 925 | 830 | 680 | 645 |

The latest estimate provided by the U.S. authorities on the annual production of cocaine in Colombia refers to 290 metric tons. As of the end of 2011, the seizure operations of Colombian cocaine carried out in different countries have totaled 351.8 metric tons of cocaine, i.e. 121.3% of Colombia's annual production according to the U.S. Department of State's estimates. [126][127]

## Synthesis

Synthetic cocaine would be highly desirable to the illegal drug industry as it would eliminate the high visibility and low reliability of offshore sources and international smuggling, replacing them with clandestine domestic laboratories, as are common for illicit methamphetamine. However, natural cocaine remains the lowest cost and highest quality supply of cocaine. Actual full synthesis of cocaine is rarely done. Formation of inactive enantiomers (cocaine has 4 chiral centres – *1R*, *2R*, *3S*, and *5S* – hence a total potential of 16 possible enantiomers and diastereoisomers) plus synthetic by-products limits the yield and purity.[*citation needed*] Names like "synthetic cocaine" and "new cocaine" have been misapplied to phencyclidine (PCP) and various designer drugs.[*citation needed*]

## Trafficking and distribution

Organized criminal gangs operating on a large scale dominate the cocaine trade. Most cocaine is grown and processed in South America, particularly in Colombia, Bolivia, Peru, and smuggled into the United States and Europe, the United States being the world's largest consumer of cocaine,[90] where it is sold at huge markups; usually in the US at $80–120 for 1 gram, and $250–300 for 3.5 grams (⅛ of an ounce, or an "eight ball").[*citation needed*]

Cocaine smuggled in a charango, 2008

### Caribbean and Mexican routes

As of 2005, cocaine shipments from South America transported through Mexico or Central America were generally moved over land or by air to staging sites in northern Mexico. The cocaine is then broken down into smaller loads for smuggling across the U.S.–Mexico border. The primary cocaine importation points in the United States have been in Arizona, southern California, southern Florida, and Texas. Typically, land vehicles are driven across the U.S.–Mexico border. Sixty-five percent of cocaine enters the United States through Mexico, and the vast majority of the rest enters through Florida.[128][*page needed*] As of 2015, the Sinaloa Cartel is the most active drug cartel involved in smuggling illicit drugs like cocaine into the United States and trafficking them throughout the United States.[129]

Cocaine traffickers from Colombia and Mexico have established a labyrinth of smuggling routes throughout the Caribbean, the Bahama Island chain, and South Florida. They often hire traffickers from Mexico or the Dominican Republic to transport the drug using a variety of smuggling techniques to U.S. markets. These include airdrops of 500 to 700 kg (1,100 to 1,500 lb) in the Bahama Islands or off the coast of Puerto Rico,

mid-ocean boat-to-boat transfers of 500 to 2,000 kg (1,100 to 4,400 lb), and the commercial shipment of tonnes of cocaine through the port of Miami.[*citation needed*]

### Chilean route

Another route of cocaine traffic goes through Chile, which is primarily used for cocaine produced in Bolivia since the nearest seaports lie in northern Chile. The arid Bolivia–Chile border is easily crossed by 4×4 vehicles that then head to the seaports of Iquique and Antofagasta. While the price of cocaine is higher in Chile than in Peru and Bolivia, the final destination is usually Europe, especially Spain where drug dealing networks exist among South American immigrants.[*citation needed*]

### Techniques

Cocaine is also carried in small, concealed, kilogram quantities across the border by couriers known as "mules" (or "mulas"), who cross a border either legally, for example, through a port or airport, or illegally elsewhere. The drugs may be strapped to the waist or legs or hidden in bags, or hidden in the body. If the mule gets through without being caught, the gangs will reap most of the profits. If he or she is caught, however, gangs will sever all links and the mule will usually stand trial for trafficking alone.[*citation needed*]

Bulk cargo ships are also used to smuggle cocaine to staging sites in the western Caribbean–Gulf of Mexico area. These vessels are typically 150–250-foot (50–80 m) coastal freighters that carry an average cocaine load of approximately 2.5 tonnes. Commercial fishing vessels are also used for smuggling operations. In areas with a high volume of recreational traffic, smugglers use the same types of vessels, such as go-fast boats, as those used by the local populations.[*citation needed*]

Sophisticated drug subs are the latest tool drug runners are using to bring cocaine north from Colombia, it was reported on 20 March 2008. Although the vessels were once viewed as a quirky sideshow in the drug war, they are becoming faster, more seaworthy, and capable of carrying bigger loads of drugs than earlier models, according to those charged with catching them.[130]

## Sales to consumers

Cocaine adulterated with fruit flavoring

Cocaine is readily available in all major countries' metropolitan areas. According to the *Summer 1998 Pulse Check*, published by the U.S. Office of National Drug Control Policy, cocaine use had stabilized across the country, with a few increases reported in San Diego, Bridgeport, Miami, and Boston. In the West, cocaine usage was lower, which was thought to be due to a switch to methamphetamine among some users; methamphetamine is cheaper, three and a half times more powerful, and lasts 12–24 times longer with each dose.[131][132] Nevertheless, the number of cocaine users remain high, with a large concentration among urban youth.

In addition to the amounts previously mentioned, cocaine can be sold in "bill sizes": As of 2007 for example, $10 might purchase a "dime bag", a very small amount (0.1–0.15 g) of cocaine. Twenty dollars might purchase 0.15–0.3 g. However, in lower Texas, it is sold cheaper due to it being easier to receive: a dime for $10 is 0.4 g, a 20 is 0.8–1.0 g and an 8-ball (3.5 g) is sold for $60 to $80, depending on the quality and dealer.[*citation needed*] These amounts and prices are very popular among young people because they are inexpensive and easily concealed on one's body. Quality and price can vary dramatically depending on supply and demand, and on geographic region.[133]

In 2008, the European Monitoring Centre for Drugs and Drug Addiction reports that the typical retail price of cocaine varied between €50 and €75 per gram in most European countries, although Cyprus, Romania, Sweden and Turkey reported much higher values.[134]

## Consumption

World annual cocaine consumption, as of 2000, stood at around 600 tonnes, with the United States

consuming around 300 t, 50% of the total, Europe about 150 t, 25% of the total, and the rest of the world the remaining 150 t or 25%.[135]

The 2010 UN World Drug Report concluded that "it appears that the North American cocaine market has declined in value from US$47 billion in 1998 to US$38 billion in 2008. Between 2006 and 2008, the value of the market remained basically stable."[136]

## Research

In 2005, researchers proposed the use of cocaine in conjunction with phenylephrine administered in the form of an eye drop as a diagnostic test for Parkinson's disease.[137]

## See also


- Black cocaine
- Cocaine- and amphetamine-regulated transcript
- Coca alkaloids
- Cocaine dependence
- Coca eradication
- Cocaine Anonymous
- Cocaine paste
- Crack epidemic
- Crack lung
- Legal status of cocaine
- List of cocaine analogues
- Pre-Columbian trans-oceanic evidence for cocaine in ancient Egypt
- Prenatal cocaine exposure
- Route 36, cocaine bar in Bolivia
- TA-CD
- Ypadu

## References


1. ^ Malenka RC, Nestler EJ, Hyman SE (2009). "Chapter 15: Reinforcement and Addictive Disorders". In Sydor A, Brown RY. *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience* (2nd ed.). New York: McGraw-Hill Medical. p. 367. ISBN 9780071481274. "While physical dependence and withdrawal occur with some drugs of abuse (opiates, ethanol), these phenomena are not useful in the diagnosis of addiction because they do not occur with other drugs of abuse (cocaine, amphetamine) and can occur with many drugs that are not abused (propranolol, clonidine)."
2. ^ Hamid Ghodse (2010). *Ghodse's Drugs and Addictive Behaviour: A Guide to Treatment* (4 ed.). Cambridge University Press. p. 91. ISBN 9781139485678.
3. ^ *Introduction to Pharmacology Third Edition*. Abingdon: CRC Press. 2007. pp. 222–223. ISBN 9781420047424.
4. ^ *a b* Fattinger K, Benowitz NL, Jones RT, Verotta D (2000). "Nasal mucosal versus gastrointestinal absorption of nasally administered cocaine". *Eur. J. Clin. Pharmacol*. **56** (4): 305–10. doi:10.1007/s002280000147. PMID 10954344.
5. ^ Barnett G, Hawks R, Resnick R (1981). "Cocaine pharmacokinetics in humans". *J Ethnopharmacol*. **3** (2–3): 353–66. doi:10.1016/0378-8741(81)90063-5. PMID 7242115.
6. ^ Jeffcoat AR, Perez-Reyes M, Hill JM, Sadler BM, Cook CE (1989). "Cocaine disposition in humans after intravenous injection, nasal insufflation (snorting), or smoking". *Drug Metab. Dispos*. **17** (2): 153–9. PMID 2565204.
7. ^ Wilkinson P, Van Dyke C, Jatlow P, Barash P, Byck R (1980). "Intranasal and oral cocaine kinetics". *Clin. Pharmacol. Ther*. **27** (3): 386–94. doi:10.1038/clpt.1980.52. PMID 7357795.
8. ^ *a b c d e* Zimmerman, JL (October 2012). "Cocaine intoxication.". *Critical care clinics*. **28** (4): 517–26. doi:10.1016/j.ccc.2012.07.003. PMID 22998988.
9. ^ *a b c d e f g h* Pomara, C; Cassano, T; D'Errico, S; Bello, S; Romano, AD; Riezzo, I; Serviddio, G (2012). "Data

available on the extent of cocaine use and dependence: biochemistry, pharmacologic effects and global burden of disease of cocaine abusers.". *Current medicinal chemistry*. **19** (33): 5647–57. doi:10.2174/092986712803988811. PMID 22856655.

10. ^ Connors, NJ; Hoffman, RS (November 2013). "Experimental treatments for cocaine toxicity: a difficult transition to the bedside.". *The Journal of Pharmacology and Experimental Therapeutics*. **347** (2): 251–7. doi:10.1124/jpet.113.206383. PMID 23978563.
11. ^ Harper, SJ; Jones, NS (October 2006). "Cocaine: what role does it have in current ENT practice? A review of the current literature.". *The Journal of laryngology and otology*. **120** (10): 808–11. doi:10.1017/s0022215106001459. PMID 16848922.
12. ^ Sordo, L; Indave, BI; Barrio, G; Degenhardt, L; de la Fuente, L; Bravo, MJ (1 September 2014). "Cocaine use and risk of stroke: a systematic review.". *Drug and Alcohol Dependence*. **142**: 1–13. doi:10.1016/j.drugalcdep.2014.06.041. PMID 25066468.
13. ^ [a] [b] Goldstein, RA; DesLauriers, C; Burda, AM (January 2009). "Cocaine: history, social implications, and toxicity—a review.". *Disease-a-month : DM*. **55** (1): 6–38. doi:10.1016/j.disamonth.2008.10.002. PMID 19081448.
14. ^ Sharma, HS; Muresanu, D; Sharma, A; Patnaik, R (2009). "Cocaine-induced breakdown of the blood–brain barrier and neurotoxicity". *International Review of Neurobiology*. International Review of Neurobiology. **88**: 297–334. doi:10.1016/S0074-7742(09)88011-2. ISBN 978-0-12-374504-0. PMID 19897082.
15. ^ Karch, Steven B. (2009). *Karch's pathology of drug abuse* (4 ed.). Boca Raton: CRC Press. p. 70. ISBN 9780849378812.
16. ^ *Narcotic Drugs 2014* (pdf). INTERNATIONAL NARCOTICS CONTROL BOARD. 2015. p. 21. ISBN 9789210481571.
17. ^ Karila, L; Zarmdini, R; Petit, A; Lafaye, G; Lowenstein, W; Reynaud, M (January 2014). "[Cocaine addiction: current data for the clinician].". *Presse medicale (Paris, France : 1983)*. **43** (1): 9–17. doi:10.1016/j.lpm.2013.01.069. PMID 23727012.
18. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385**: 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
19. ^ Room, R; Reuter, P (7 January 2012). "How well do international drug conventions protect public health?". *Lancet*. **379** (9810): 84–91. doi:10.1016/s0140-6736(11)61423-2. PMID 22225673.
20. ^ "cocaine (Topical route)". *drugs.com*. Retrieved 14 January 2015.
21. ^ [a] [b] World Health Organization (2004). *Neuroscience of psychoactive substance use and dependence*. p. 89. ISBN 9789241562355.
22. ^ World Health Organization (2007). *International medical guide for ships*. p. 242. ISBN 9789241547208.
23. ^ Barnett, G; Hawks, R; Resnick, R (1981). "Cocaine pharmacokinetics in humans". *Journal of Ethnopharmacology*. **3** (2–3): 353–66. doi:10.1016/0378-8741(81)90063-5. PMID 7242115.; Jones, supra note 19; Wilkinson *et al.*, Van Dyke *et al.*
24. ^ [a] [b] Luks, Andrew M. (2010). "Wilderness Medical Society Consensus Guidelines for the Prevention and Treatment of Acute Altitude Illness" (PDF). *Wilderness*. Wilderness & Environmental Medicine. **21** (2): 146–155. doi:10.1016/j.wem.2010.03.002. (mirror: [1])
25. ^ Siegel RK, Elsohly MA, Plowman T, Rury PM, Jones RT (3 January 1986). "Cocaine in herbal tea". *Journal of the American Medical Association*. **255** (1): 40. doi:10.1001/jama.255.1.40. PMID 3940302.
26. ^ "DrugFacts: Cocaine". National Institute on Drug Abuse. April 2013. Retrieved 11 July 2015.
27. ^ [a] [b] [c] Nora D. Volkow; et al. (2000). "Effects of route of administration on cocaine induced dopamine transporter blockade in the human brain". *Life Sciences*. **67** (12): 1507–1515. doi:10.1016/S0024-3205(00)00731-1. PMID 10983846.
28. ^ "Cocaine terminology".
29. ^ Bonkovsky HL, Mehta S (2001). "Hepatitis C: a review and update". *J. Am. Acad. Dermatol*. **44** (2): 159–82. doi:10.1067/mjd.2001.109311. PMID 11174373.
30. ^ Dimitrijevic N, Dzitoyeva S, Manev H (2004). "An automated assay of the behavioral effects of cocaine injections in adult Drosophila". *J Neurosci Methods*. **137** (2): 181–184. doi:10.1016/j.jneumeth.2004.02.023. PMID 15262059.
31. ^ "Appendix B: Production of Cocaine Hydrochloride and Cocaine Base". US Justice Dep.
32. ^ Garcia, Raphael Caio Tamborelli; Torres, Larissa Helena; Balestrin, Natália Trigo; Andrioli, Tatiana Costa; Flório, Jorge Camilo; de Oliveira, Carolina Dizioli Rodrigues; da Costa, José Luiz; Yonamine, Mauricio; Sandoval, Maria Regina Lopes; Camarini, Rosana; Marcourakis, Tania (2016). "Anhydroecgonine methyl ester, a cocaine pyrolysis product, may contribute to cocaine behavioral sensitization". *Toxicology*. doi:10.1016/j.tox.2016.04.009. ISSN 0300-483X.

33. ^ Margaret Reist (16 January 2005). "A rose by another name: crack pipe". *Lincoln Journal Star*. Retrieved 21 August 2009.
34. ^ Overdose Death Rates. By National Institute on Drug Abuse (NIDA).
35. ^ Nutt, D.; King, L. A.; Saulsbury, W.; Blakemore, C. (2007). "Development of a rational scale to assess the harm of drugs of potential misuse". *The Lancet*. **369** (9566): 1047–1053. doi:10.1016/S0140-6736(07)60464-4. PMID 17382831.
36. ^ *a b* Zhao, Wei (2008). *Mechanisms Mediating Sex Differences in the Effects of Cocaine*. ProQuest. p. 3. ISBN 0-549-99458-0. Retrieved 25 September 2012.
37. ^ *a b c d* O'Leary, ME; Hancox, JC (May 2010). "Role of voltage-gated sodium, potassium and calcium channels in the development of cocaine-associated cardiac arrhythmias". *British Journal of Clinical Pharmacology*. **69** (5): 427–42. doi:10.1111/j.1365-2125.2010.03629.x. PMC 2856043. PMID 20573078.
38. ^ Hugo D'haenen; Johan A. den Boer; P. Willner, eds. (2002). *Biological Psychiatry*. **2** (2 ed.). Wiley. p. 528. ISBN 978-0-471-49198-9.
39. ^ *a b* Lowinson, Joyce, H; Ruiz, Pedro; Millman, Robert B. (2004). *Substance abuse: a comprehensive textbook* (4th ed.). Lippincott Williams & Wilkins. p. 204. ISBN 978-0-7817-3474-5. Retrieved 5 January 2014.
40. ^ Baigent, Michael (2003). "Physical complications of substance abuse: what the psychiatrist needs to know". *Curr Opin Psychiatry*. **16** (3): 291–296. doi:10.1097/00001504-200305000-00004.
41. ^ Pagliaro, Louis; Ann Marie Pagliaro (2004). *Pagliaros' Comprehensive Guide to Drugs and Substances of Abuse*. Washington, D.C.: American Pharmacists Association. ISBN 978-1-58212-066-9.
42. ^ "More bad news for cocaine users: Drug can triple risk of aneurysm". *Scienceblog.com*. 1999. Retrieved 10 July 2007.
43. ^ Trozak D, Gould W (1984). "Cocaine abuse and connective tissue disease". *J Am Acad Dermatol*. **10** (3): 525. doi:10.1016/S0190-9622(84)80112-7. PMID 6725666.
44. ^ Ramón Peces; Navascués, RA; Baltar, J; Seco, M; Alvarez, J (1999). "Antiglomerular Basement Membrane Antibody-Mediated Glomerulonephritis after Intranasal Cocaine Use". *Nephron*. **81** (4): 434–438. doi:10.1159/000045328. PMID 10095180.
45. ^ Moore PM, Richardson B (1998). "Neurology of the vasculitides and connective tissue diseases". *J. Neurol. Neurosurg. Psychiatr*. **65** (1): 10–22. doi:10.1136/jnnp.65.1.10. PMC 2170162. PMID 9667555.
46. ^ Jared A. Jaffe; Kimmel, PL (2006). "Chronic Nephropathies of Cocaine and Heroin Abuse: A Critical Review". *Clinical Journal of the American Society of Nephrology*. American Society of Nephrology. **1** (4): 655–67. doi:10.2215/CJN.00300106. PMID 17699270.
47. ^ Fokko J. van der Woude (2000). "Cocaine use and kidney damage". *Nephrology Dialysis Transplantation*. Oxford University Press. **15** (3): 299–301. doi:10.1093/ndt/15.3.299. PMID 10692510.
48. ^ Susan Jeffrey; Charles Vega (17 April 2008) [16 April 2007]. "Stimulant Abuse May Increase Stroke Among Young Adults". Retrieved 6 February 2011. (registration required (help)).
49. ^ Vasica G, Tennant CC (2002). "Cocaine use and cardiovascular complications". *Med. J. Aust*. **177** (5): 260–2. PMID 12197823.
50. ^ Rothman, Richard B.; et al. (2001). "Amphetamine-Type Central Nervous System Stimulants Release Norepinepehrine more Potently than they Release Dopamine and Serotonin". *Synapse*. **39** (1): 32–41. doi:10.1002/1098-2396(20010101)39:1<32::AID-SYN5>3.0.CO;2-3. PMID 11071707. (Table V. on page 37)
51. ^ Carta M, Allan AM, Partridge LD, Valenzuela CF (2003). "Cocaine inhibits 5-HT3 receptor function in neurons from transgenic mice overexpressing the receptor". *Eur. J. Pharmacol*. **459** (2–3): 167–9. doi:10.1016/S0014-2999(02)02867-4. PMID 12524142.
52. ^ Filip M, Bubar MJ, Cunningham KA (2004). "Contribution of serotonin (5-hydroxytryptamine; 5-HT) 5-HT2 receptor subtypes to the hyperlocomotor effects of cocaine: acute and chronic pharmacological analyses". *J. Pharmacol. Exp. Ther*. **310** (3): 1246–54. doi:10.1124/jpet.104.068841. PMID 15131246.
53. ^ Beuming, Thijs; et al. (2008). "The binding sites for cocaine and dopamine in the dopamine transporter overlap". *Nature Neuroscience*. **11** (7): 780–9. doi:10.1038/nn.2146. PMC 2692229. PMID 18568020.
54. ^ "Sigma Receptors Play Role In Cocaine-induced Suppression Of Immune System". Sciencedaily.com. 6 May 2003. Retrieved 9 March 2010.
55. ^ Lluch J, Rodríguez-Arias M, Aguilar MA, Miñarro J (2005). "Role of dopamine and glutamate receptors in cocaine-induced social effects in isolated and grouped male OF1 mice". *Pharmacol. Biochem. Behav*. **82** (3): 478–87. doi:10.1016/j.pbb.2005.10.003. PMID 16313950.
56. ^ "Drugbank website "drug card", "(DB00907)" for Cocaine: Giving ten targets of the molecule in vivo, including dopamine/serotonin sodium channel affinity & K-opioid affinity". Drugbank.ca. Retrieved 9 March 2010.
57. ^ Uz T, Akhisaroglu M, Ahmed R, Manev H (2003). "The pineal gland is critical for circadian Period 1 expression in the striatum and for circadian cocaine sensitization in mice". *Neuropsychopharmacology*. **28** (12): 2117–2123. doi:10.1038/sj.npp.1300254. PMID 12865893.

58. ^ McClung C, Sidiropoulou K, Vitaterna M, Takahashi J, White F, Cooper D, Nestler E (2005). "Regulation of dopaminergic transmission and cocaine reward by the Clock gene". *Proc Natl Acad Sci USA*. **102** (26): 9377–81. doi:10.1073/pnas.0503584102. PMC 1166621. PMID 15967985.
59. ^ Carey RJ, Damianopoulos EN, Shanahan AB (2008). "Cocaine effects on behavioral responding to a novel object placed in a familiar environment". *Pharmacol. Biochem. Behav*. **88** (3): 265–71. doi:10.1016/j.pbb.2007.08.010. PMID 17897705.
60. ^ Kolbrich EA, Barnes AJ, Gorelick DA, Boyd SJ, Cone EJ, Huestis MA (2006). "Major and minor metabolites of cocaine in human plasma following controlled subcutaneous cocaine administration". *J Anal Toxicol*. **30** (8): 501–10. doi:10.1093/jat/30.8.501. PMID 17132243.
61. ^ Wilson LD, Jeromin J, Garvey L, Dorbandt A (2001). "Cocaine, ethanol, and cocaethylene cardiotoxity in an animal model of cocaine and ethanol abuse". *Acad Emerg Med*. **8** (3): 211–22. doi:10.1111/j.1553-2712.2001.tb01296.x. PMID 11229942.
62. ^ Pan WJ, Hedaya MA (1999). "Cocaine and alcohol interactions in the rat: effect of cocaine and alcohol pretreatments on cocaine pharmacokinetics and pharmacodynamics". *J Pharm Sci*. **88** (12): 1266–74. doi:10.1021/js990184j. PMID 10585221.
63. ^ Hayase T, Yamamoto Y, Yamamoto K (1999). "Role of cocaethylene in toxic symptoms due to repeated subcutaneous cocaine administration modified by oral doses of ethanol". *J Toxicol Sci*. **24** (3): 227–35. doi:10.2131/jts.24.3_227. PMID 10478337.
64. ^ VV Pillay (2013), *Modern Medical Toxicology* (4th ed.), Jaypee, pp. 553–554, ISBN 978-93-5025-965-8
65. ^ Scheidweiler, K. B.; Plessinger, MA; Shojaie, J; Wood, RW; Kwong, TC (15 October 2003). "Pharmacokinetics and Pharmacodynamics of Methylecgonidine, a Crack Cocaine Pyrolyzate". *Journal of Pharmacology and Experimental Therapeutics*. **307** (3): 1179–87. doi:10.1124/jpet.103.055434. PMID 14561847.
66. ^ Yang Y, Ke Q, Cai J, Xiao YF, Morgan JP (2001). "Evidence for cocaine and methylecgonidine stimulation of M2 muscarinic receptors in cultured human embryonic lung cells". *Br. J. Pharmacol*. **132** (2): 451–60. doi:10.1038/sj.bjp.0703819. PMC 1572570. PMID 11159694.
67. ^ Fandiño AS, Toennes SW, Kauert GF (2002). "Studies on hydrolytic and oxidative metabolic pathways of anhydroecgonine methyl ester (methylecgonidine) using microsomal preparations from rat organs". *Chem. Res. Toxicol*. **15** (12): 1543–8. doi:10.1021/tx0255828. PMID 12482236.
68. ^ "Substances – Cocaine". The Steinhardt School of Culture, Education, and Human Development. Retrieved 1 August 2009.
69. ^ George, Nelson (1998). *Hip Hop America*. Viking Penguin. p. 40.
70. ^ Ries, Richard K.; Miller, Sharon C.; Fiellin, David A. (2009). *Principles of addiction medicine*. Lippincott Williams & Wilkins. p. 137. ISBN 0-7817-7477-2. Retrieved 5 January 2014.
71. ^ "Coca tea or mate de coca – the holy coca leaf infusion". *inkanat.com*. Retrieved 17 December 2015.
72. ^ *a b* Humphrey AJ, O'Hagan D (2001). "Tropane alkaloid biosynthesis. A century old problem unresolved". *Nat Prod Rep*. **18** (5): 494–502. doi:10.1039/b001713m. PMID 11699882.
73. ^ Dewick, P. M. (2009). *Medicinal Natural Products*. Chicester: Wiley-Blackwell. ISBN 978-0-470-74276-1.
74. ^ R. J. Robins; T. W. Abraham; A. J. Parr; J. Eagles; N. J. Walton (1997). "The Biosynthesis of Tropane Alkaloids in Datura stramonium: The Identity of the Intermediates between *N*-Methylpyrrolinium Salt and Tropinone". *J. Am. Chem. Soc*. **119** (45): 10929–10934. doi:10.1021/ja964461p.
75. ^ Hoye TR, Bjorklund JA, Koltun DO, Renner MK (2000). "*N*-methylputrescine oxidation during cocaine biosynthesis: study of prochiral methylene hydrogen discrimination using the remote isotope method". *Org. Lett*. **2** (1): 3–5. doi:10.1021/ol990940s. PMID 10814231.
76. ^ E. Leete; J. A. Bjorklund; M. M. Couladis; S. H. Kim (1991). "Late intermediates in the biosynthesis of cocaine: 4-(1-methyl-2-pyrrolidinyl)-3-oxobutanoate and methyl ecgonine". *J. Am. Chem. Soc*. **113** (24): 9286–9292. doi:10.1021/ja00024a039.
77. ^ E. Leete; J. A. Bjorklund; S. H. Kim (1988). "The biosynthesis of the benzoyl moiety of cocaine". *Phytochemistry*. **27** (8): 2553–2556. doi:10.1016/0031-9422(88)87026-2.
78. ^ Leete E, Marion L, Sspenser ID (1954). "Biogenesis of hyoscyamine". *Nature*. **174** (4431): 650–1. doi:10.1038/174650a0. PMID 13203600.
79. ^ Robins RJ, Waltons NJ, Hamill JD, Parr AJ, Rhodes MJ (1991). "Strategies for the genetic manipulation of alkaloid-producing pathways in plants". *Planta Med*. **57** (7 Suppl): S27–35. doi:10.1055/s-2006-960226. PMID 17226220.
80. ^ T. Hemscheidt; Vederas, John C. (2000). Leeper, Finian J.; Vederas, John C., eds. "Tropane and Related Alkaloids". *Top. Curr. Chem*. Topics in Current Chemistry. **209**: 175. doi:10.1007/3-540-48146-X. ISBN 978-3-540-66573-1.
81. ^ A. Portsteffen; B. Draeger; A. Nahrstedt (1992). "Two tropinone reducing enzymes from Datura stramonium transformed root cultures". *Phytochemistry*. **31** (4): 1135–1138. doi:10.1016/0031-9422(92)80247-C.

82. ^ Boswell HD, Dräger B, McLauchlan WR (1999). "Specificities of the enzymes of *N*-alkyltropane biosynthesis in Brugmansia and Datura". *Phytochemistry*. **52** (5): 871–8. doi:10.1016/S0031-9422(99)00293-9. PMID 10626376.
83. ^ R. Baselt, *Disposition of Toxic Drugs and Chemicals in Man*, 9th edition, Biomedical Publications, Seal Beach, CA, 2011, pp. 390–394.
84. ^ Venkatratnam, Abhishek; Nathan H. Lents (July 2011). "Zinc Reduces the Detection of Cocaine, Methamphetamine, and THC by ELISA Urine Testing". *Journal of Analytical Toxicology*. **35** (6): 333–340. doi:10.1093/anatox/35.6.333. PMID 21740689.
85. ^ "Statistical tables". *World Drug Report 2016* (pdf). Vienna, Austria: United Nations Office on Drugs and Crime. 2016. ISBN 9789210578622. Retrieved 1 August 2016.
86. ^ [a] [b] *World Drug Report 2007* (PDF). New York: United Nations. 2007. p. 243. Retrieved 31 December 2013.
87. ^ *The State of the Drugs Problem in Europe 2008* (PDF). Luxembourg: European Monitoring Centre for Drugs and Drug Addiction. 2008. pp. 58–62. Retrieved 31 December 2013.
88. ^ Dominic Casciani (4 June 2015). "Cocaine in sewage: London tops league table". *BBC news*. Retrieved 4 June 2015.
89. ^ "Cocaine & Crack". Erowid.org. Archived from the original on 6 October 2007. Retrieved 10 July 2007.
90. ^ [a] [b] "Field Listing – Illicit drugs (by country)". Cia.gov. Retrieved 15 January 2011.
91. ^ http://connect.mcgraw-hill.com/connect/hmEBook.do?setTab=sectionTabs Johnson et al., 2012. Hoeksema, Susan Nolen. "Sign In." McGraw-Hill Connect. N.p., n.d. Web. 16 April 2014.
92. ^ Altman AJ, Albert DM, Fournier GA (1985). "Cocaine's use in ophthalmology: our 100-year heritage". *Surv Ophthalmol*. **29** (4): 300–6. doi:10.1016/0039-6257(85)90153-5. PMID 3885453.
93. ^ Gay GR, Inaba DS, Sheppard CW, Newmeyer JA (1975). "Cocaine: history, epidemiology, human pharmacology, and treatment. a perspective on a new debut for an old girl". *Clin. Toxicol*. **8** (2): 149–78. doi:10.3109/15563657508988061. PMID 1097168.
94. ^ "Drug that spans the ages: The history of cocaine". London: The Independent (UK). 2006. Archived from the original on 28 February 2010. Retrieved 30 April 2010.
95. ^ Monardes, Nicholas (1925). *Joyfull Newes out of the Newe Founde Worlde*. J. Frampton. New York, NY: Alfred Knopf.
96. ^ Gaedcke, F. (1855). "Ueber das Erythroxylin, dargestellt aus den Blättern des in Südamerika cultivirten Strauches Erythroxylon Coca". *Archiv der Pharmazie*. **132** (2): 141–150. doi:10.1002/ardp.18551320208.
97. ^ [a] [b] Albert Niemann (1860). "Ueber eine neue organische Base in den Cocablättern". *Archiv der Pharmazie*. **153** (2): 129–256. doi:10.1002/ardp.18601530202.
98. ^ Harper, Douglas. "Cocaine". *Online Etymology Dictionary*.
99. ^ Satendra Singh et al Chemistry, Design, and Structure-Activity Relationship of Cocaine Antagonists." *Chem. Rev* 2000; 100. 925-1024. PubMed; Chemical Reviews (Impact Factor: 45.66). 04/2000; 100(3):925-1024 American Chemical Society; 2000 ISSN 0009-2665 ChemInform; May, 16th 2000, Volume 31, Issue 20, doi:10.1002/chin.200020238. Mirror hotlink. ←Page #970 (46th page of article) 1st ¶. ninth & tenth lines.
100. ^ Willstatter, R. Leibigs Am. Chem. 1903, 326, 23. (b) Robinson, R. J. Chem. Soc. 1917, 111, 762. (c) Schopf, C.; Lehman, G. Liebigs Am. 1935, 518, 1.
101. ^ Yentis SM, Vlassakov KV (1999). "Vassily von Anrep, forgotten pioneer of regional anesthesia". *Anesthesiology*. **90** (3): 890–5. doi:10.1097/00000542-199903000-00033. PMID 10078692.
102. ^ Halsted W (1885). "Practical comments on the use and abuse of cocaine". *New York Medical Journal*. **42**: 294–295.
103. ^ Corning JL (1885). "An experimental study". *New York Medical Journal*. **42**: 483.
104. ^ "Experience Vin Mariani today | Grupo Mariani S.A". Cocanaturally.com. Retrieved 15 January 2011.
105. ^ Barlow, William. *"Looking Up At Down": The Emergence of Blues Culture*. Temple University Press (1989), p. 207. ISBN 978-0-87722-583-6.
106. ^ Streatfeild, Dominic (2003). *Cocaine: An Unauthorized Biography*. Picador. ISBN 978-0-312-42226-4.
107. ^ "Jeevan Vasagar: cocaine-based "wonder drug" tested on concentration camp inmates". Amphetamines.com. 19 November 2002. Retrieved 15 January 2011.
108. ^ "Apple Sanity – Fetish – Blow: War on Drugs VS. Cocaine". Applesanity.com. 17 June 2008. Archived from the original on 17 June 2008. Retrieved 13 November 2011.
109. ^ "Cocaine Market". Havocscope.com. Archived from the original on 11 November 2012. Retrieved 9 March 2010.
110. ^ WHO/UNICRI (4 February 2010). "The WHO Cocaine Project". Transnational Institute. Retrieved 8 June 2012.
111. ^ "Cocaine use doubles in a decade". Sydney Morning Herald. 15 October 2010. Retrieved 19 October 2010.
112. ^ EMCDDA (2007). "EMCDDA Retail Cocaine Purity Study". Retrieved 31 December 2013.
113. ^ Franklin, Jonathan (2009-08-18). "The world's first cocaine bar". *The Guardian*. ISSN 0261-3077. Retrieved

2016-12-23.
114. ^ http://ain-bolivia.org/wp-content/uploads/The-Cato-Accord-Bolivias-Humane-and-Effective-Approach-to-Controlling-Coca-Cultivation.pdf
115. ^ *a b* Poisons Standard July 2016 Comlaw.gov.au
116. ^ Misuse of Drugs Act 1981 (2015) Slp.wa.gov.au
117. ^ (Gootenberg 1999, p. 37)
118. ^ (Madge 2001, p. 106)
119. ^ (Madge 2001, p. 107)
120. ^ *a b c* (Gootenberg 1999, p. 40)
121. ^ "Cocaine: Seizures, 1998–2003". *World Drug Report 2006* (PDF). **2**. New York: United Nations. 2006.
122. ^ Colombia. CIA World Factbook
123. ^ Peru Overtakes Colombia as Top Cocaine Producer. NBC News (31 July 2012)
124. ^ Streatfeild, Dominic (2003). *Cocaine: An Unauthorized Biography*. Macmillan. ISBN 978-0-312-42226-4. Retrieved 5 January 2014.
125. ^ NDIC (2006). "National Drug Threat Assessment 2006".
126. ^ "Cocaine Seized Worldwide Highest Ever in 2011". Flare Network (Flarenetwork.org). 18 January 2012. Retrieved 5 January 2014.
127. ^ "Colombia". State.gov. Retrieved 26 March 2013.
128. ^ Jacobson, Robert (2005). *Illegal Drugs: America's Anguish*. Farmington Hills, MI: Thomson Gale. ISBN 1-4144-0419-0.
129. ^ "2015 National Drug Threat Assessment Summary" (PDF). *Drug Enforcement Administration*. United States Department of Justice: Drug Enforcement Administration. October 2015. pp. 1–2. Retrieved 10 April 2016. "Mexican TCOs pose the greatest criminal drug threat to the United States; no other group is currently positioned to challenge them. These Mexican poly-drug organizations traffic heroin, methamphetamine, cocaine, and marijuana throughout the United States, using established transportation routes and distribution networks. …While all of these Mexican TCOs transport wholesale quantities of illicit drugs into the United States, the Sinaloa Cartel appears to be the most active supplier. The Sinaloa Cartel leverages its expansive resources and dominance in Mexico to facilitate the smuggling and transportation of drugs throughout the United States."
130. ^ "Coast Guard hunts drug-running semi-subs". CNN. 20 March 2008. Retrieved 20 March 2008.
131. ^ "Meth Info". Methproject.org. Archived from the original on 27 March 2010.
132. ^ "Drugs of Abuse". *City of Denison Iowa*. Retrieved 13 November 2011.
133. ^ "Drugs: Pricing Power". *The Economist*. 28 June 2007. "Prices: USA around $110/g, Israel/Germany/Britain around $46/g, Colombia $2/g, New Zealand recordbreaking $714.30/g."
134. ^ European Monitoring Centre for Drugs and Drug Addiction (2008). *Annual report: the state of the drugs problem in Europe* (PDF). Luxembourg: Office for Official Publications of the European Communities. p. 59. ISBN 978-92-9168-324-6. Retrieved 31 December 2013.
135. ^ *The Cocaine Threat: A Hemispheric Perspective* (PDF). United States Department of Defense. Archived from the original (PDF) on 11 September 2008.
136. ^ United Nations (June 2010). *World Drug Report 2010*. United Nations Publications. p. 77. ISBN 978-92-1-148256-0.
137. ^ Sawada, H.; et al. (23 February 2005). "Cocaine and Phenylephrine Eye Drop Test for Parkinson Disease". *JAMA the Journal of the American Medical Association*. Journal of the American Medical Association. **293** (8): 932–4. doi:10.1001/jama.293.8.932-c. PMID 15728162.

# Bibliography

- Gootenberg, Paul, ed. (1999). *Cocaine: Global Histories*. London: Routledge. ISBN 0-203-02646-2.
- Madge, Tim (2001). *White Mischief: A Cultural History of Cocaine*. *Madge*. Edinburgh: Mainstream Publishing Company. ISBN 978-1-84018-405-1.
- Spillane, Joseph F. (2000). *Cocaine: From Medical Marvel to Modern Menace in the United States, 1884–1920*. Baltimore and London: The Johns Hopkins University Press. ISBN 0-8018-6230-2.

# Further reading

- Feiling, Tom (2009). *The Candy Machine: How Cocaine Took Over the World*. London: Penguin. ISBN 978-0-14-103446-1.

# External links

- "A look at the Evidence for Cocaine in Mummies". Archived from the original on 22 August 2013. Retrieved 2010-04-18.
- EMCDDA drugs profile: Cocaine (2007)
- Erowid – Cocaine Information — A collection of data about cocaine including dose, effects, chemistry, legal status, images and more.
- Slang Dictionary for Cocaine.
- Cocaine content of plants
- Cocaine – The History and the Risks at h2g2
- Cocaine Frequently Asked Questions
- U.S. National Library of Medicine: Drug Information Portal – Cocaine
- Cocaine Market Data and Value-Havocscope Black Markets at the Wayback Machine (archived 23 March 2011) Data on cocaine trafficking worldwide.

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| v · t · e · | **Recreational drug use** | | |
|---|---|---|---|
| **Major recreational drugs** | **Depressants** | | Barbiturates · Benzodiazepines · Carbamates · Ethanol (Alcoholic drinks · · Gabapentinoids · GHB · Intoxicative inhalants (contact cement · gasoline · nail polish remover · · Kava · Nonbenzodiazepines · Quinazolinones · |
| | **Opioids** | | Buprenorphine (Suboxone · Subutex · · Codeine · Desomorphine (Krokodil · · Dextropropoxyphene (Darvocet · Darvon · · Fentanyl · Diamorphine (Heroin · · Hydrocodone · Hydromorphone (Dilaudid · · Methadone · Mitragyna speciosa (Kratom · · Morphine (Opium · · Oxycodone (/paracetamol · · |
| | **Stimulants** | | Amphetamine · Arecoline (Areca · · Betel · Caffeine (Coffee · Energy drinks · Tea · · Cathinone (Khat · · **Cocaine** (Coca · Crack · · Ephedrine (Ephedra · · MDPV · Mephedrone · Methamphetamine · Methylone · Methylphenidate · Nicotine (Tobacco · · Theobromine (Cocoa · · |
| | **Entactogens** | | MDA · MDMA (Ecstasy · · 2C-* series · alpha-Methyltryptamine · 6-APB (Benzofury · · |
| | **Hallucinogens** | **Psychedelics** | Bufotenin (Psychoactive toads · Vilca · Yopo · · DMT (Ayahuasca · · LSA · LSD-25 · Mescaline (Peruvian Torch · Peyote · San Pedro · · Psilocybin / Psilocin (Psilocybin mushrooms · · |
| | | **Dissociatives** | DXM · Glaucine · Inhalants (Nitrous oxide · alkyl nitrites · poppers · amyl nitrite · · Ketamine · MXE · Muscimol (Amanita muscaria · · PCP · Salvinorin A (Salvia divinorum · · |
| | | **Deliriants** | Atropine and Scopolamine (Atropa belladonna · Datura · Hyoscyamus niger · Mandragora officinarum · · Dimenhydrinate · Diphenhydramine · |
| | | **Cannabinoids** | JWH-018 · THC (Cannabis · Hashish · Hash oil · · |
| | | **Oneirogens** | Calea zacatechichi · Silene capensis · |
| | **Cannabis culture** | | 420 · Cannabis cultivation · Cannabis smoking · Legal history of cannabis in the United States · Legality of cannabis · Marijuana Policy Project · Medical cannabis · NORML · |

| | | |
|---|---|---|
| **Drug culture** | | Religious and spiritual use of cannabis · Stoner film · |
| | **Coffee culture** | Coffee break · Coffeehouse · Latte art · Tea house · |
| | **Drinking culture** | Bartending · Beer culture · Beer festival · Binge drinking · Drinking games · Drinking song · Happy hour · Hip flask · Nightclub · Pub crawl · |
| | **Psychedelia** | Art · Drug · Era · Experience · Literature · Music · Therapy · |
| | **Smoking culture** | Cigarette card · Fashion cigarettes · Cloud-chasing · Loosie · Smokeasy · Smoking fetishism · Tobacco smoking · |
| | **Other** | Club drug · Counterculture of the 1960s · Dance party · Drug paraphernalia · Drug tourism · Entheogen · Hippie · Party and play · Poly drug use · Rave · Self-medication · Sex and drugs · Whoonga · |
| **Drug production and trade** | **Drug production** | Coca production in Colombia · Drug precursors · Opium production in Afghanistan · Rolling meth lab · |
| | **Drug trade** | Illegal drug trade in Colombia · |
| **Issues with drug use** | | Abuse · Date rape drug · Effects of cannabis · Addiction · Dependence (Prevention · Opioid replacement therapy · Rehabilitation · Responsible use · · Drug-related crime · Fetal alcohol spectrum disorder · Illegal drug trade · Long-term effects of cannabis · Neurotoxicity · Overdose · Passive smoking (of tobacco or other substances · · |
| **Legality of drug use** | **International** | 1961 Narcotic Drugs · 1971 Psychotropic Substances · 1988 Drug Trafficking · Council of the European Union decisions on designer drugs · |
| | **State level** | Drug policy (Decriminalization · Prohibition · Supply reduction · · Policy reform (Demand reduction · Drug Policy Alliance · Harm reduction · Law Enforcement Against Prohibition · Liberalization (Latin America · · Students for Sensible Drug Policy · Transform Drug Policy Foundation · · |
| | **Drug policy by country** | Australia · Canada · Germany · India · Netherlands · Portugal · Slovakia · Soviet Union · Sweden · Switzerland · United States (Just Say No · Office of National Drug Control Policy · School district drug policies · California · Colorado · Maryland · Virginia · · |
| | **Other** | Arguments for and against drug prohibition · Capital punishment for drug trafficking · Designer drug · Drug court · Drug harmfulness · Drug possession · Drug test · Mexican Drug War · Philippine Drug War · Narc · Politics of drug abuse · War on Drugs · Zero tolerance · |
| **Lists of countries by...** | | Alcohol legality (Alcohol consumption · · Anabolic steroid legality · Cannabis legality (Annual use · Lifetime use · · Cigarette consumption · Cocaine legality (Cocaine use · · Methamphetamine legality · Opiates use · Psilocybin mushrooms legality · Salvia legality · |

v · t · e · **Euphoriants**

μ-Opioid receptor agonists (opioids) (e.g., morphine, heroin, hydrocodone, oxycodone, opium, kratom) · $\alpha_2\delta$ subunit-containing voltage-dependent calcium channels blockers (gabapentinoids) (e.g., gabapentin, pregabalin, phenibut) · AMPA receptor antagonists (e.g., perampanel) · $CB_1$ receptor agonists (cannabinoids) (e.g., THC, cannabis) · Dopamine receptor agonists (e.g., levodopa) · Dopamine releasing agents (e.g., amphetamine, methamphetamine, MDMA, mephedrone) · Dopamine reuptake inhibitors (e.g., **cocaine**, methylphenidate) · $GABA_A$ receptor positive allosteric modulators (e.g., barbiturates, benzodiazepines, carbamates, ethanol (drinking alcohol), inhalants,

nonbenzodiazepines, quinazolinones) · GHB (sodium oxybate) and analogues · Glucocorticoids (corticosteroids) (e.g., dexamethasone, prednisone) · nACh receptor agonists (e.g., nicotine, tobacco, arecoline, areca nut) · Nitric oxide prodrugs (e.g., alkyl nitrites (poppers)) · NMDA receptor antagonists (e.g., DXM, ketamine, methoxetamine, nitrous oxide, phencyclidine, inhalants) · Orexin receptor antagonists (e.g., suvorexant) ·

*See also: Recreational drug use*

| v · t · e · | **Stimulants (category)** |
|---|---|
| **Adamantanes** | Adaphenoxate · Adapromine · Amantadine · Bromantane · Chlodantane · Gludantane · Memantine · Rimantadine · |
| **Adenosine antagonists** | 8-Chlorotheophylline · 8-Cyclopentyltheophylline · 8-Phenyltheophylline · Aminophylline · Caffeine · CGS-15943 · Dimethazan · Paraxanthine · SCH-58261 · Theobromine · Theophylline · |
| **Alkylamines** | Cyclopentamine · Cypenamine · Cyprodenate · Heptaminol · Isometheptene · Levopropylhexedrine · Methylhexaneamine · Octodrine · Propylhexedrine · Tuaminoheptane · |
| **Ampakines** | CX-516 · CX-546 · CX-614 · CX-691 · CX-717 · IDRA-21 · LY-404,187 · LY-503,430 · Nooglutyl · Org 26576 · PEPA · S-18986 · Sunifiram · Unifiram · |
| **Arylcyclohexylamines** | Benocyclidine · Dieticyclidine · Esketamine · Eticyclidine · Gacyclidine · Ketamine · Phencyclamine · Phencyclidine · Rolicyclidine · Tenocyclidine · Tiletamine · |
| **Benzazepines** | 6-Br-APB · SKF-77434 · SKF-81297 · SKF-82958 · |
| **Cholinergics** | A-84,543 · A-366,833 · ABT-202 · ABT-418 · AR-R17779 · Altinicline · Anabasine · Arecoline · Bradanicline · Cotinine · Cytisine · Dianicline · Epibatidine · Epiboxidine · GTS-21 · Ispronicline · Nicotine · PHA-543,613 · PNU-120,596 · PNU-282,987 · Pozanicline · Rivanicline · Sazetidine A · SIB-1553A · SSR-180,711 · TC-1698 · TC-1827 · TC-2216 · Tebanicline · UB-165 · Varenicline · WAY-317,538 · |
| **Convulsants** | Anatoxin-a · Bicuculline · DMCM · Flurothyl · Gabazine · Pentetrazol · Picrotoxin · Strychnine · Thujone · |
| **Eugeroics** | Adrafinil · Armodafinil · CRL-40,940 · CRL-40,941 · Fluorenol · JZ-IV-10 · Modafinil · |
| **Oxazolines** | 4-Methylaminorex · Aminorex · Clominorex · Cyclazodone · Fenozolone · Fluminorex · Pemoline · Thozalinone · |
| | 1-(4-Methylphenyl)-2-aminobutane · 1-Phenyl-2-(piperidin-1-yl)pentan-3-one · 1-Methylamino-1-(3,4-methylenedioxyphenyl)propane · 2-Fuoroamphetamine · 2-Fuoromethamphetamine · 2-OH-PEA · 2-Phenyl-3-aminobutane · 2-Phenyl-3-methylaminobutane · 2,3-MDA · 3-Fuoroamphetamine · 3-Fluoroethamphetamine · 3-Fluoromethcathinone · 3-Methoxyamphetamine · 3-Methylamphetamine · 3,4-DMMC · 4-BMC · 4-CMC · 4-Ethylamphetamine · 4-Fluoroamphetamine · 4-Fluoromethamphetamine · 4-MA · 4-Methylbuphedrone · 4-Methylcathinone · 4-MMA · 4-Methylpentedrone · 4-MTA · 6-FNE · AL-1095 · Alfetamine · a-Ethylphenethylamine · Amfecloral · Amfepentorex · Amfepramone · Amidephrine · 2-Amino-1,2-dihydronaphthalene · 2-Aminoindane · 5-(2-Aminopropyl)indole · 2-Aminotetralin · Acridorex · Amphetamine (Dextroamphetamine, Levoamphetamine) · Amphetaminil · Arbutamine · β-Methylphenethylamine · β-Phenylmethamphetamine · Benfluorex · Benzedrone · Benzphetamine · BDB · BOH · 3-Benzhydrylmorpholine · BPAP · Buphedrone · Bupropion · Butylone · Camfetamine · Cathine · Cathinone · |

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| **Phenethylamines** | Chlorphentermine · Cilobamine · Cinnamedrine · Clenbuterol · Clobenzorex · Cloforex · Clortermine · Cypenamine · D-Deprenyl · Denopamine · Dimethoxyamphetamine · Dimethylamphetamine · Dimethylcathinone · Dobutamine · DOPA (Dextrodopa, Levodopa) · Dopamine · Dopexamine · Droxidopa · EBDB · Ephedrine · Epinephrine · Epinine · Etafedrine · Ethcathinone · Ethylnorepinephrine · Ethylone · Etilamfetamine · Etilefrine · Famprofazone · Fencamfamine · Fencamine · Fenethylline · Fenfluramine (Dexfenfluramine, Levofenfluramine) · Fenproporex · Feprosidnine · Flephedrone · Fludorex · Formetorex · Furfenorex · Gepefrine · Hexapradol · Hexedrone · HMMA · Hordenine · 4-Hydroxyamphetamine · 5-Iodo-2-aminoindane · Ibopamine · IMP · Indanylamphetamine · Iofetamine · Isoetarine · Isoethcathinone · Isoprenaline · L-Deprenyl (Selegiline) · Lefetamine · Lisdexamfetamine · Lophophine · MBDB · MDA · MDBU · MDEA · MDMA · MDMPEA · MDOH · MDPR · MDPEA · Mefenorex · Mephedrone · Mephentermine · Metanephrine · Metaraminol · Mesocarb · Methamphetamine (Dextromethamphetamine, Levomethamphetamine) · Methoxamine · Methoxyphenamine · MMA · Methcathinone · Methedrone · Methoxyphenamine · Methylenedioxycathinone · Methylone · Mexedrone · MMDA · MMDMA · MMMA · Morforex · N,alpha-Diethylphenylethylamine · N-Benzyl-1-phenethylamine · N-Ethylbuphedrone · N-Ethylhexedrone · N,N-Dimethylphenethylamine · Naphthylamphetamine · Nisoxetine · Norepinephrine · Norfenefrine · Norfenfluramine · Normetanephrine · L-Norpseudoephedrine · Octopamine (drug) · Orciprenaline · Ortetamine · Oxifentorex · Oxilofrine · PBA · PCA · PCMA · PHA · Pentorex · Pentedrone · Pentylone · Phenatine · Phenpromethamine · Phentermine · Phenylalanine · Phenylephrine · Phenylpropanolamine · Pholedrine · PIA · PMA · PMEA · PMMA · PPAP · Phthalimidopropiophenone · Prenylamine · Propylamphetamine · Pseudoephedrine · Ropinirole · Salbutamol (Levosalbutamol) · Sibutramine · Synephrine · Theodrenaline · Tiflorex · Tranylcypromine · Tyramine · Tyrosine · Xylopropamine · Zylofuramine · |
| **Phenylmorpholines** | 3-Fluorophenmetrazine · Fenbutrazate · Fenmetramide · G-130 · Manifaxine · Morazone · Morforex · Oxaflozane · PD-128,907 · Phendimetrazine · Phenmetrazine · 2-Phenyl-3,6-dimethylmorpholine · Pseudophenmetrazine · Radafaxine · |
| **Piperazines** | 2C-B-BZP · 3C-PEP · BZP · CM156 · DBL-583 · GBR-12783 · GBR-12935 · GBR-13069 · GBR-13098 · GBR-13119 · MeOPP · MBZP · Vanoxerine · |
| **Piperidines** | 1-Benzyl-4-(2-(diphenylmethoxy)ethyl)piperidine · 1-(3,4-Dichlorophenyl)-1-(piperidin-2-yl)butane · 2-Benzylpiperidine · 2-Methyl-3-phenylpiperidine · 3-Chloromethylphenidate · 3,4-Dichloromethylphenidate · 4-Benzylpiperidine · 4-Fluoromethylphenidate · 4-Methylmethylphenidate · Desoxypipradrol · Difemetorex · Diphenylpyraline · Ethylnaphthidate · Ethylphenidate · Methylnaphthidate · Isopropylphenidate · Methylphenidate (Dexmethylphenidate) · N-Methyl-3β-propyl-4β-(4-chlorophenyl)piperidine · Nocaine · Phacetoperane · Pipradrol · Propylphenidate · SCH-5472 · |
| **Pyrrolidines** | 2-Diphenylmethylpyrrolidine · 5-DBFPV · α-PPP · α-PBP · α-PHP · α-PVP · α-PVT · Diphenylprolinol · DMPVP · FPOP · FPVP · MDPPP · MDPBP · MPBP · MPHP · MPPP · MOPVP · MOPPP · Indapyrophenidone · MDPV · Naphyrone · PEP · Picilorex · Prolintane · Pyrovalerone · |
| **Racetams** | Oxiracetam · Phenylpiracetam · Phenylpiracetam hydrazide · |
| | 3-CPMT · 3'-Chloro-3a-(diphenylmethoxy)tropane · 4-fluorotropacocaine · 4'-Fluorococaine |

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| **Tropanes** | · AHN-1055 · Altropane (IACFT) · Brasofensine · CFT (WIN 35,428) · β-CIT (RTI-55) · Cocaethylene · **Cocaine** · Dichloropane (RTI-111) · Difluoropine · FE-β-CPPIT · FP-β-CPPIT · Ioflupane ($^{123}$I) · Norcocaine · PIT · PTT · RTI-31 · RTI-32 · RTI-51 · RTI-105 · RTI-112 · RTI-113 · RTI-117 · RTI-120 · RTI-121 (IPCIT) · RTI-126 · RTI-150 · RTI-154 · RTI-171 · RTI-177 · RTI-183 · RTI-193 · RTI-194 · RTI-199 · RTI-202 · RTI-204 · RTI-229 · RTI-241 · RTI-336 · RTI-354 · RTI-371 · RTI-386 · Salicylmethylecgonine · Tesofensine · Troparil (β-CPT, WIN 35,065-2) · Tropoxane · WF-23 · WF-33 · WF-60 · |
| **Tryptamines** | 4-HO-αMT · 4-Methyl-αET · 4-Methyl-αMT · 5-Chloro-αMT · 5-Fluoro-αMT · 5-MeO-αET · 5-MeO-αMT · 5-MeO-DIPT · 6-Fluoro-αMT · 7-Methyl-αET · αET · αMT · |
| **Others** | 2-MDP · 2-Phenylcyclohexylamine · 3,3-Diphenylcyclobutanamine · Amfonelic acid · Amineptine · Amiphenazole · Atipamezole · Atomoxetine · Bemegride · Benzydamine · BTQ · BTS 74,398 · Centanafadine · Ciclazindol · Clofenciclan · Cropropamide · Crotetamide · D-161 · Diclofensine · Dimethocaine · Efaroxan · Etamivan · Fenisorex · Fenpentadiol · Gamfexine · Gilutensin · GSK1360707F · GYKI-52895 · Hexacyclonate · Idazoxan · Indanorex · Indatraline · JNJ-7925476 · Lazabemide · Leptacline · Lomevactone · LR-5182 · Mazindol · Meclofenoxate · Medifoxamine · Mefexamide · Methamnetamine · Methastyridone · Methiopropamine · Naphthylaminopropane · Nefopam · Nikethamide · Nomifensine · O-2172 · Oxaprotiline · PNU-99,194 · PRC200-SS · Rasagiline · Rauwolscine · Rubidium chloride · Setazindol · Tametraline · Tandamine · Thiopropamine · Thiothinone · Trazium · UH-232 · Yohimbine · |
| *ATC code: N06B* | |

| v · t · e · | **Local anesthetics (primarily sodium channel blockers) (N01B)** | |
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| **Esters by acid** | **Aminobenzoic** | Benzocaine · Butacaine · Butamben · Chloroprocaine · Dimethocaine · Lucaine · Meprylcaine · Metabutethamine · Metabutoxycaine · Nitracaine · Orthocaine · Propoxycaine · Procaine (Novocaine) · Proxymetacaine · Risocaine · Tetracaine · |
| | **Benzoic** | Amylocaine · **Cocaine** · Cyclomethycaine · α-Eucaine · β-Eucaine · Hexylcaine · Isobucaine · Piperocaine · |
| | **ArCO2- (not para-amino or Ph)** | Amoproxan (3,4,5-Trimethoxybenzoyl) · 3-(p-Fluorobenzoyloxy)tropane · |
| **Amides** | | Articaine · Bupivacaine[#] / Levobupivacaine / Ropivacaine · Butanilicaine · Carticaine · Dibucaine · Etidocaine · Lidocaine[#] · Mepivacaine · Prilocaine · Trimecaine · |
| **Combinations** | | Lidocaine / prilocaine · Anesthetic / vasoconstrictor · TAC · Iontocaine · |
| [#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III · · | | |

| v · t · e · | **Ancient anaesthesia** |
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| **Plants / animals** | *Aconitum* (aconite) · *Atropa belladonna* (belladonna) · Cannabis (medical use · · Castoreum · Coca · *Conium* (hemlock) · *Datura inoxia* (thorn-apple) · *Datura metel* (devil's trumpet) · *Hyoscyamus niger* (henbane) · Lactucarium · *Mandragora officinarum* (mandrake) · Opium · *Saussurea* (saw-wort) · Willow · |
| **People** | Abulcasis · Avenzoar · Avicenna · Celsus · Dioscorides · Galen · Hippocrates · Rhazes · |

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| | Sabuncuoğlu · Sushrutha · Theophrastus · Zhang · |
| **Compounds** | Aconitine · Atropine · **Cocaine** · Coniine · Hyoscine · Δ9-THC · Hyoscyamine · Morphine · Salicylate · |

| v · t · e · | **Ion channel modulators** | |
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| **Calcium ($Ca^{2+}$)** | **Blockers** | **L-type-selective:** *Dihydropyridines:* Amlodipine · Aranidipine · Azelnidipine · Barnidipine · Clevidipine · Cronidipine · Darodipine · Dexniguldipine · Elgodipine · Elnadipine · Felodipine · Flordipine · Furnidipine · Iganidipine · Isradipine · Lacidipine · Lemildipine · Lercanidipine · Levamlodipine · Levniguldipine · Manidipine · Mepirodipine · Mesudipine · Nicardipine · Nifedipine · Niguldipine · Niludipine · Nilvadipine · Nimodipine · Nisoldipine · Nitrendipine · Olradipine · Oxodipine · Palonidipine · Pranidipine · Ryodipine (riodipine) · Sagandipine · Sornidipine · Teludipine · Tiamdipine · Trombodipine · Vatanidipine<br>*Diltiazem derivatives:* Clentiazem · Diltiazem · Iprotiazem · Nictiazem · Siratiazem<br>*Phenylalkylamines:* Anipamil · Dagapamil · Devapamil · Dexverapamil · Emopamil · Etripamil · Falipamil · Gallopamil · Levemopamil · Nexopamil · Norverapamil · Ronipamil · Tiapamil · Verapamil<br>*Others:* AH-1058 · Brinazarone · Budiodarone · Celivarone · Cyproheptadine · Dronedarone · Fantofarone · SR-33805 ·<br>**N-type-selective:** ω-Conotoxins · ω-Conotoxin GVIA · Caroverine · Huwentoxin XVI · Leconotide (ω-conotoxin CVID) · PD-173212 · Ralfinamide · Safinamide · Z160 · Ziconotide (ω-conotoxin MVIIA) ·<br>**P-type-selective:** ω-Agatoxin IVA · ω-Agatoxin IVB ·<br>**R-type-selective:** SNX-482 ·<br>**T-type-selective:** ABT-639 · ML-218 · Niflumic acid · NNC 55-0396 · ProTx I · Z944 · Zonisamide ·<br>**Non-selective:** ω-Agatoxin TK · ω-Conotoxin MVIIC · Benidipine · Bepridil · Cilnidipine · Cinnarizine · Dotarizine · Efonidipine · Flunarizine · Lamotrigine · Levetiracetam · Lomerizine · Loperamide · Mibefradil · NP078585 · Ruthenium red · TROX-1 ·<br>**$\alpha_2\delta$ subunit-selective (gabapentinoids):** 4-Methylpregabalin · Arbaclofen · Arbaclofen placarbil · Atagabalin · Baclofen · Gabapentin · Gabapentin enacarbil · Imagabalin · Mirogabalin · PD-200,347 · PD-217,014 · PD-299,685 · Phenibut · Pregabalin ·<br>**Others/unsorted:** Bencyclane · Berbamine · Bevantolol · Canadine · Carboxyamidotriazole · Cycleanine · Dauricine · Dimeditiapramine · Diproteverine · Enpiperate · Eperisone · Elpetrigine · Ethadione · Ethosuximide · Fasudil · Fendiline · Fostedil · JTV-519 · Lidoflazine · Magnesium · Manoalide · Mesuximide · Monatepil · Naftopidil · Ochratoxin A · Osthol · Otilonium bromide · Paramethadione · Phensuximide · Pinaverium · Prenylamine · Rhynchophylline · Sesamodil · Silperisone · Sipatrigine · Terodiline · Tetrahydropalmatine · Tetrandrine · Tolperisone · Trimethadione · Valperinol · |
| | **Openers** | **L-type-selective:** Bay K8644 · |
| | | 3,4-Diaminopyridine (amifampridine) · 4-Aminopyridine (fampridine/dalfampridine) · Adekalant · Almokalant · Amiodarone · Azimilide · Bretylium · Bunaftine · |

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| **Potassium ($K^+$)** | **Blockers** | Charybdotoxin · Clamikalant · Conotoxins · Dalazatide · Dendrotoxin · Dofetilide · Dronedarone · E-4031 · Hanatoxin · HgeTx1 · HsTx1 · Ibutilide · Inakalant · Kaliotoxin · Linopirdine · Lolitrem B · Maurotoxin · Nifekalant · Notoxin · Paxilline · Pinokalant · ShK-186 · Sotalol · Tedisamil · Terikalant · Tetraethylammonium · Vernakalant ·<br>**GIRK blockers:** Barium · Caramiphen · Cloperastine · Clozapine · Dextromethorphan · Ethosuximide · Ifenprodil · Tertiapin · Tipepidine ·<br>**hERG blockers:** Ajmaline · Amiodarone · AmmTX3 · Astemizole · Azaspiracid · AZD1305 · Azimilide · Bedaquiline · BeKm-1 · BmTx3 · BRL-32872 · Chlorpromazine · Cisapride · Clarithromycin · Darifenacin · Dextropropoxyphene · Diallyl trisulfide · Domperidone · E-4031 · Ergtoxins · Erythromycin · Gigactonine · Haloperidol · Ketoconazole · Norpropoxyphene · Orphenadrine · Pimozide · PNU-282,987 · Promethazine · Ranolazine · Roxithromycin · Sertindole · Solifenacin · Tamulotoxin · Terodiline · Terfenadine · Thioridazine · Tolterodine · Vanoxerine · Vernakalant ·<br>**$K_{ATP}$ blockers:** Acetohexamide · Carbutamide · Chlorpropamide · Glibenclamide (glyburide) · Glibornuride · Glicaramide · Gliclazide · Glimepiride · Glipizide · Gliquidone · Glisoxepide · Glyclopyramide · Glycyclamide · Metahexamide · Mitiglinide · Nateglinide · Repaglinide · Tolazamide · Tolbutamide · |
| | **Openers** | **$K_{ATP}$ openers:** Aprikalim · Bimakalim · Cromakalim · Emakalim · Levcromakalim · Mazokalim · Rilmakalim · Sarakalim ·<br>**Others:** Diazoxide · Flupirtine · Minoxidil · ML-297 · Naminidil · Nicorandil · Pinacidil · Retigabine · Rottlerin · |
| **Sodium ($Na^+$)** | **Blockers** | **VGSC blockers:** *Antianginals:* Ranolazine<br>*Antiarrhythmics (class I):* Ajmaline · Aprindine · Disopyramide · Dronedarone · Encainide · Flecainide · Lidocaine · Lorajmine · Lorcainide · Mexiletine · Moricizine · Pilsicainide · Prajmaline · Procainamide · Propafenone · Quinidine · Sparteine · Tocainide<br>*Anticonvulsants:* Acetylpheneturide · Carbamazepine · Cenobamate · Chlorphenacemide · Elpetrigine · Eslicarbazepine acetate · Ethotoin · Fosphenytoin · Lacosamide · Licarbazepine · Mephenytoin · Oxcarbazepine · Oxitriptyline · Phenacemide · Pheneturide · Phenytoin · Rufinamide · Sipatrigine · Topiramate · Sodium valproate · Valnoctamide · Valproate pivoxil · Valproate semisodium · Valproic acid · Valpromide · Zonisamide<br>*Diuretics:* Amiloride · Benzamil · Triamterene<br>*Local anesthetics:* *p*FBT · Amylocaine · Articaine · Benzocaine · Bupivacaine (Levobupivacaine, Ropivacaine) · Butacaine · Butamben · Chloroprocaine · Cinchocaine · **Cocaine** · Cyclomethycaine · Dimethocaine · Diphenhydramine · Etidocaine · Hexylcaine · Iontocaine · Lidocaine · Mepivacaine · Meprylcaine · Metabutoxycaine · Orthocaine · Piperocaine · Prilocaine · Procaine · Propoxycaine · Proxymetacaine · Risocaine · Tetracaine · Trimecaine<br>*Analgesics:* AZD-3161 · DSP-2230 · Funapide · GDC-0276 · NKTR-171 · PF-04531083 · PF-05089771 · Ralfinamide · Raxatrigine · RG7893 (GDC-0287)<br>*Toxins:* Conotoxins · Neosaxitoxin · Saxitoxin · Tetrodotoxin<br>*Others:* Buprenorphine · Evenamide · Menthol · Safinamide · Tricyclic antidepressants · |

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| | **Openers** | **VGSC openers:** Atracotoxins (Robustoxin, Versutoxin) · Ciguatoxins · **ENaC openers:** Solnatide · |
| **Chloride ($Cl^-$)** | **Blockers** | Bumetanide · DIDS · Flufenamic acid · Furosemide · Glibenclamide · Lonidamine · Meclofenamic acid · Mefenamic acid · Mepacrine · Niflumic acid · Piretanide · Talniflumate · Tolfenamic acid · Trifluoperazine · |
| | **Openers** | **CFTR openers:** 1,7-Phenanthroline · 1,10-Phenanthroline · 4,7-Phenanthroline · 7,8-Benzoquinoline · Phenanthridine · |

| v · t · e · | **Adrenergic receptor modulators** |
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| | *Agonists*: 6-FNE · Amidephrine · Anisodine · Buspirone · Cirazoline · Corbadrine · Dexisometheptene · Dipivefrine · Dopamine · Droxidopa (L-DOPS) · Ephedrine · Epinephrine · Etilefrine · Etilevodopa · Ethylnorepinephrine · Indanidine · Isometheptene · L-DOPA (levodopa) · L-Phenylalanine · L-Tyrosine · Melevodopa · Metaraminol · Methoxamine · Methyldopa · Midodrine · Naphazoline · Norepinephrine · Octopamine (drug) · Oxymetazoline · Phenylephrine · Phenylpropanolamine · Pseudoephedrine · Synephrine · Tetryzoline · Tiamenidine · XP21279 · Xylometazoline · |
| **$\alpha_1$** | *Antagonists*: Abanoquil · Adimolol · Ajmalicine · Alfuzosin · Amosulalol · Anisodamine · Arotinolol · Atiprosin · Atypical antipsychotics (e.g., clozapine, olanzapine, quetiapine, risperidone) · Benoxathian · Buflomedil · Bunazosin · Carvedilol · Corynanthine · Dapiprazole · Domesticine · Doxazosin · Ergolines (e.g., ergotamine, dihydroergotamine, lisuride, terguride) · Etoperidone · Eugenodilol · Fenspiride · Hydroxyzine · Indoramin · Ketanserin · L-765,314 · Labetalol · mCPP · Mepiprazole · Metazosin · Monatepil · Moxisylyte · Naftopidil · Nantenine · Nefazodone · Neldazosin · Niaprazine · Nicergoline · Niguldipine · Pardoprunox · Pelanserin · Phendioxan · Phenoxybenzamine · Phentolamine · Piperoxan · Prazosin · Quinazosin · Ritanserin · Silodosin · Spiperone · Talipexole · Tamsulosin · Terazosin · Tiodazosin · Tolazoline · Trazodone · Tetracyclic antidepressants (e.g., amoxapine, maprotiline, mianserin) · Tricyclic antidepressants (e.g., amitriptyline, clomipramine, doxepin, imipramine, trimipramine) · Trimazosin · Typical antipsychotics (e.g., chlorpromazine, fluphenazine, loxapine, thioridazine) · Urapidil · WB-4101 · Zolertine · |
| **$\alpha_2$** | *Agonists*: (R)-3-Nitrobiphenyline · 4-NEMD · 6-FNE · Amitraz · Apraclonidine · Brimonidine · Cannabivarin · Clonidine · Corbadrine · Detomidine · Dexmedetomidine · Dihydroergotamine · Dipivefrine · Dopamine · Droxidopa (L-DOPS) · Etilevodopa · Ephedrine · Ergotamine · Epinephrine · Etilefrine · Ethylnorepinephrine · Guanabenz · Guanfacine · Guanoxabenz · L-DOPA (levodopa) · L-Phenylalanine · L-Tyrosine · Lofexidine · Medetomidine · Melevodopa · Methyldopa · Mivazerol · Naphazoline · Norepinephrine · Oxymetazoline · Phenylpropanolamine · Piperoxan · Pseudoephedrine · Rilmenidine · Romifidine · Talipexole · Tetrahydrozoline · Tiamenidine · Tizanidine · Tolonidine · Urapidil · XP21279 · Xylazine · Xylometazoline · |
| | *Antagonists*: 1-PP · Adimolol · Aptazapine · Atipamezole · Atypical antipsychotics (e.g., asenapine, clozapine, lurasidone, paliperidone, quetiapine, risperidone, zotepine) · Azapirones (e.g., buspirone, tandospirone) · BRL-44408 · Buflomedil · Cirazoline · Efaroxan · Esmirtazapine · Fenmetozole · Fluparoxan · Idazoxan · mCPP · Mianserin · Mirtazapine · NAN-190 · Olanzapine · Pardoprunox · Phentolamine · Phenoxybenzamine · Piperoxan · Piribedil · Rauwolscine · Rotigotine · SB-269970 · Setiptiline · Spiroxatrine · Sunepitron · Tolazoline · Typical antipsychotics (e.g., chlorpromazine, fluphenazine, loxapine, thioridazine) · Yohimbine · |
| | *Agonists*: Abediterol · Alifedrine · Amibegron · Arbutamine · Arformoterol · Arotinolol · BAAM · Bambuterol · Befunolol · Bitolterol · Broxaterol · Buphenine · Carbuterol · Carmoterol · Cimaterol · Clenbuterol · Corbadrine · Denopamine · Dipivefrine · Dobutamine · Dopamine · Dopexamine · Droxidopa (L-DOPS) · Ephedrine · Epinephrine · Etafedrine · Etilefrine · Etilevodopa · Ethylnorepinephrine · Fenoterol · Formoterol · Hexoprenaline · Higenamine · Indacaterol · Isoetarine · Isoprenaline · Isoxsuprine · L-DOPA (levodopa) · L-Phenylalanine · L-Tyrosine · Levosalbutamol · Mabuterol · Melevodopa · Methoxyphenamine · Methyldopa · Mirabegron · Norepinephrine · |

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|---|---|
| | Orciprenaline • Oxyfedrine • PF-610355 • Phenylpropanolamine • Pirbuterol • Prenalterol • Ractopamine • Procaterol • Pseudoephedrine • Reproterol • Rimiterol • Ritodrine • Salbutamol • Salmeterol • Solabegron • Terbutaline • Tretoquinol • Tulobuterol • Vilanterol • Xamoterol • XP21279 • Zilpaterol • Zinterol • |
| **β** | *Antagonists*: Acebutolol • Adaprolol • Adimolol • Afurolol • Alprenolol • Alprenoxime • Amosulalol • Ancarolol • Arnolol • Arotinolol • Atenolol • Befunolol • Betaxolol • Bevantolol • Bisoprolol • Bopindolol • Bornaprolol • Brefonalol • Bucindolol • Bucumolol • Bufetolol • Bufuralol • Bunitrolol • Bunolol • Bupranolol • Butaxamine • Butidrine • Butofilolol • Capsinolol • Carazolol • Carpindolol • Carteolol • Carvedilol • Celiprolol • Cetamolol • Cicloprolol • Cinamolol • Cloranolol • Cyanopindolol • Dalbraminol • Dexpropranolol • Diacetolol • Dichloroisoprenaline • Dihydroalprenolol • Dilevalol • Diprafenone • Draquinolol • Ecastolol • Epanolol • Ericolol • Ersentilide • Esatenolol • Esprolol • Eugenodilol • Exaprolol • Falintolol • Flestolol • Flusoxolol • Hydroxycarteolol • Hydroxytertatolol • ICI-118,551 • Idropranolol • Indenolol • Indopanolol • Iodocyanopindolol • Iprocrolol • Isoxaprolol • Isamoltane • Labetalol • Landiolol • Levobetaxolol • Levobunolol • Levomoprolol • Medroxalol • Mepindolol • Metipranolol • Metoprolol • Moprolol • Nadolol • Nadoxolol • Nebivolol • Nifenalol • Nipradilol • Oxprenolol • Pacrinolol • Pafenolol • Pamatolol • Pargolol • Penbutolol • Pindolol • Practolol • Primidolol • Procinolol • Pronethalol • Propafenone • Propranolol • Ridazolol • Ronactolol • Soquinolol • Sotalol • Spirendolol • SR 59230A • Sulfinalol • Talinolol • Tazolol • Tertatolol • Tienoxolol • Tilisolol • Timolol • Tiprenolol • Tolamolol • Toliprolol • Xibenolol • Xipranolol • |

*See also: Dopaminergics • Melatonergics • Serotonergics • Monoamine reuptake and release modulators • Monoamine metabolism modulators • Monoamine neurotoxins •*

v • t • e • **Sigma receptor modulators**

| | |
|---|---|
| **Agonists** | 3-MeO-PCE • 3-MeO-PCP • 3-PPP • 4-MeO-PCP • 4-IBP • 4-PPBP • Afobazole • Alazocine • Amantadine • Amitriptyline • Arketamine • BD-1008 • BD1031 • BD1052 • Berberine • Buprenorphine • Captodiame • Citalopram • Clorgiline • **Cocaine** • Cutamesine • Cyclazocine • DHEA • DHEA-S • Desipramine • Dextrallorphan • Dextromethorphan • Dextrorphan • Dimemorfan • DMT • Donepezil • DTG • Escitalopram • Fluoxetine • Fluvoxamine • Heroin • Ibogaine • Igmesine • Imipramine • JO-1784 • Ketamine • L-687,384 • Lamotrigine • Lu 28-179 • MDMA • Memantine • Metaphit • Methamphetamine • Methoxetamine • Methylphenidate • Morphine • Naluzotan • Noscapine • OPC-14523 • Opipramol • PB-28 • PD-144,415 • Pentazocine • Pentoxyverine • Phencyclidine • PRE-084 • Pregnenolone • Pregnenolone sulfate • Quetiapine • RTI-55 • SA-4503 • Siramesine • Tapentadol • Tenocyclidine • Tramadol • UMB23 • UMB82 • Venlafaxine • |
| **Antagonists** | AC927 • AHD1 • AZ66 • BD1008 • BD1047 • BD1060 • BD1063 • BD1067 • BMY-14802 • CM156 • E-5842 • Haloperidol • Lamotrigine • LR132 • LR172 • MIN-101 • MS-377 • Naloxone • Naltrexone • NE-100 • Panamesine • PD-144418 • Progesterone • Quingestrone • Rimcazole • S1RA (E-52862) • Sertraline • SM-21 • SR-31742A • UMB100 • UMB101 • UMB103 • UMB116 • YZ-011 • YZ-069 • YZ-185 • |
| **Unknown / unsorted** | 4C-T-2 • 5-MeO-DiPT • 18-MC • β-Endopsychosin • Chlorpromazine • Clemastine • Clocapramine • Cloperastine • D-Deprenyl • DiPT • DPT • Gevotroline • Nepinalone • Selegiline • TMA; *Allosteric modulators:* SKF-83959 • |

**Authority control** GND: 4128249-8 • NDL: 00575600 •

Categories: Cocaine | Tropane alkaloids found in Erythroxylum coca | Alkaloids found in Erythroxylum | Anorectics | Benzoates | Cardiac stimulants | Euphoriants | Local anesthetics | Otologicals | Serotonin-norepinephrine-dopamine reuptake inhibitors | Sigma agonists | Stimulants | Sympathomimetic amines | Teratogens | Vasoconstrictors | German inventions | Carboxylate esters | Methyl esters | Glycine receptor agonists | Secondary metabolites


# Dapsone

From Wikipedia, the free encyclopedia

**Dapsone**, also known as **diaminodiphenyl sulfone** (**DDS**),[1] is an antibiotic commonly used in combination with rifampicin and clofazimine for the treatment of leprosy.[2] It is a second-line medication for the treatment and prevention of pneumocystis pneumonia and for the prevention of toxoplasmosis in those who have poor immune function.[2] Additionally, it has been used for acne, dermatitis herpetiformis, and various other skin conditions.[3] Dapsone is available both topically and by mouth.[4]

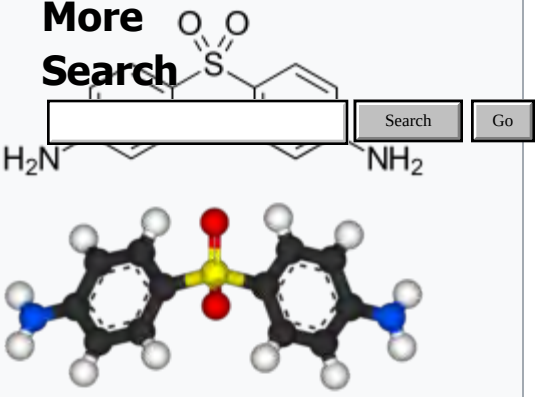
Severe side effects may include: a decrease in blood cells, red blood cell breakdown especially in those with glucose-6-phosphate dehydrogenase deficiency (G-6-PD), or hypersensitivity.[2] Common side effects include nausea and loss of appetite.[4] Other side effects include liver inflammation and a number of types of skin rashes.[2] While it is not entirely clear the safety of use during pregnancy some physicians recommend that it be continued in those with leprosy.[2] It is of the sulfone class.[2]

Dapsone was first studied as an antibiotic in 1937.[3] Its use for leprosy began in 1945.[3] It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[5] The oral form is available as a generic drug and not very expensive.[2][6]

Contents



## Dapsone



| Clinical data | |
|---|---|
| **Trade names** | Aczone |
| **AHFS/Drugs.com** | Monograph |
| **MedlinePlus** | a682128 |
| **Pregnancy category** | AU: B2<br>US: C (Risk not ruled out) |
| **Routes of administration** | Oral, Topical |
| **ATC code** | D10AX05 (WHO)<br>J04BA02 (WHO) |
| **Legal status** | |
| **Legal status** | -only (U.S.), POM (UK) |
| **Pharmacokinetic data** | |
| **Bioavailability** | 70 to 80% |
| **Protein binding** | 70 to 90% |
| **Metabolism** | Hepatic (mostly CYP2E1-mediated) |
| **Biological half-life** | 20 to 30 hours |
| **Excretion** | Renal |
| **Identifiers** | |
| **IUPAC name** | |

4-[(4-aminobenzene)sulfonyl]aniline

| | |
|---|---|
| **CAS Number** | 80-08-0 ✓ |
| **PubChem** (CID) | 2955 |
| **DrugBank** | DB00250 ✓ |
| **ChemSpider** | 2849 ✓ |
| **UNII** | 8W5C518302 ✓ |
| **KEGG** | D00592 ✓ |
| **ChEBI** | CHEBI:4325 ✓ |
| **ChEMBL** | CHEMBL1043 ✓ |
| **ECHA InfoCard** | 100.001.136 |
| **Chemical and physical data** | |
| **Formula** | $C_{12}H_{12}N_2O_2S$ |
| **Molar mass** | 248.302 g/mol |
| **3D model (Jmol)** | Interactive image |
| **Melting point** | 175 to 176 °C (347 to 349 °F) |
| **SMILES** | O=S(=O)(c1ccc(N)cc1)c2ccc(N)cc2 |
| **InChI** | InChI=1S/C12H12N2O2S/c13-9-1-5-11(6-2-9)17(15,16)12-7-3-10(14)4-8-12/h1-8H,13-14H2 ✓ Key:MQJKPEGWNLWLTK-UHFFFAOYSA-N ✓ |
| | (verify) |

# Medical uses [edit]

## Infections [edit]

Dapsone is commonly used in combination with rifampicin and clofazimine for the treatment of leprosy.[2] It is also used to both treat and prevent pneumocystis pneumonia (PCP).[2][7] It is also used for toxoplasmosis in people unable to tolerate trimethoprim with sulfamethoxazole.[7]

Dapsone by mouth was one of the first medications used to treat moderate to severe acne vulgaris, and is still occasionally prescribed for the treatment of severe cases.[8][9] A topical form of dapsone is also effective with potentially less side effects.[10]

It is unclear if the combination with pyrimethamine is useful in the prevention of malaria.[11]

## Other [edit]

Dermatitis herpetiformis, often in combination with a gluten-free diet.[2]

Dapsone may be used to treat brown recluse spider bites that become necrotic.[12]

Dapsone is the recommended treatment for erythema elevatum diutinum, as a review found that using oral dapsone alone was effective in 80% of early cases of the disease. However, dapsone can potentially cause severe side effects, meaning that sometimes steroids or other antibiotics should be used instead, although these alternative treatments are much less effective.[13]

An August 2015 review notes that dapsone is reported to be effective against generalized granuloma annulare.[14]

# Adverse effects [edit]

The dapsone hypersensitivity syndrome develops in 0.5–3.6% of persons treated with the drug, and is associated with a mortality of 9.9%.[15]

## Blood [edit]

The most prominent side-effects of this drug are dose-related hemolysis (which may lead to hemolytic anemia) and methemoglobinemia.[16] About 20% of patients treated with dapsone suffer hemolysis[17] and the side-effect is more common and severe in those with glucose-6-phosphate dehydrogenase deficiency, leading to the dapsone-containing antimalarial combination Lapdap being withdrawn from clinical use.[18][19] A case of hemolysis in a neonate from dapsone in breast milk has been reported.[20] Agranulocytosis occurs rarely when dapsone is used alone but more frequently in combination regimens for malaria prophylaxis.[21] Abnormalities in white blood cell formation, including aplastic anemia, are rare, yet are the cause of the majority of deaths attributable to dapsone therapy.[22][23][24]

## Liver [edit]

Toxic hepatitis and cholestatic jaundice have been reported by the manufacturer. Jaundice may also occur as part of the dapsone reaction or dapsone syndrome (see below). Dapsone is metabolized by the Cytochrome P450 system, specifically isozymes CYP2D6, CYP2B6, CYP3A4, and CYP2C19.[25] Dapsone metabolites produced by the cytochrome P450 2C19 isozyme are associated with the methemoglobinemia side effect of the drug.

### Skin [edit]

When used topically, dapsone can cause mild skin irritation, redness, dry skin, burning and itching. When used together with benzoyl peroxide products, temporary yellow or orange skin discolorations can occur.[26][27]

### Other adverse effects [edit]

Other adverse effects include nausea, headache, and rash (which are common), and insomnia, psychosis, and peripheral neuropathy. Effects on the lung occur rarely and may be serious, though are generally reversible.[28]

### Dapsone reaction [edit]

Hypersensitivity reactions occur in some patients. This reaction may be more frequent in patients receiving multiple-drug therapy.[29][30][31]

The reaction always involves a rash and may also include fever, jaundice, and eosinophilia.[32][33][34][35][36] In general, these symptoms will occur within the first six weeks of therapy or not at all, and may be ameliorated by corticosteroid therapy.[7]

## Mechanism of action [edit]

As an antibacterial, dapsone inhibits bacterial synthesis of dihydrofolic acid, via competition with para-aminobenzoate for the active site of dihydropteroate synthase.[37] Though structurally distinct from dapsone, the sulfonamide group of antibacterial drugs also work in this way.

As an anti-inflammatory, dapsone inhibits the enzyme myeloperoxidase. As part of the respiratory burst that neutrophils use to kill bacteria, myeloperoxidase converts hydrogen peroxide ($H_2O_2$) into hypochlorous acid (HOCl). HOCl is the most potent oxidant generated by neutrophils, and can cause significant tissue damage during inflammation. Dapsone arrests myeloperoxidase in an inactive intermediate form, reversibly inhibiting the enzyme. This prevents accumulation of hypochlorous acid, and reduces tissue damage during inflammation.[38][39][40][41][42] Myeloperoxidase inhibition has also been suggested as a neuron-sparing mechanism for reducing inflammation in neurodegenerative diseases such as Alzheimer's disease and stroke.[43]

When used for the treatment of skin conditions in which bacteria do not have a role, the mechanism or action of dapsone is not well understood. Dapsone has anti-inflammatory and immunomodulatory effects,[44] which are thought to come from the drug's blockade of myeloperoxidase. This is thought to be its mechanism of action in treating dermatitis herpetiformis.[45]

Dapsone is an odorless white to creamy-white crystalline powder with a slightly bitter taste.

## Specific considerations [edit]

Certain patients are at higher risks of adverse effects when using dapsone. Some specific issues that should be considered are:[7]

- Related to the blood (a full blood count should be obtained prior to initiating therapy):

- Porphyria
- Anemia
- Cardiac disease
- Pulmonary disease
- HIV infection
- G6PD deficiency

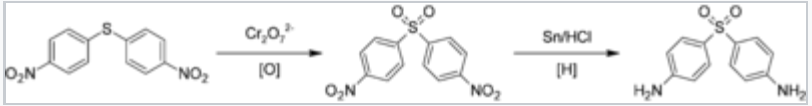
- Related to the liver (obtain liver function tests before starting therapy):
  - Liver impairment
- Related to allergy:
  - Sulfonamide allergy is associated with dapsone allergy

HbA1c may be an unreliable measure of glycemic control in people with diabetes mellitus taking dapsone due to increased red cell turnover.

# History [edit]

## Discovery [edit]

In the early 20th century, the German chemist Paul Ehrlich was developing theories of selective toxicity based largely on the ability of certain dyes to kill microbes. Gerhard Domagk, who would later win a Nobel Prize for his efforts, made a major breakthrough in 1932 with the discovery of the antibacterial prontosil red (sulfonamidochrysoidine). Further investigation into the involved chemicals opened the way to sulfa drug and sulfone therapy, first with the discovery of sulfanilamide, the active agent of prontosil, by Daniel Bovet and his team at Pasteur Institute (1935),[46] then with of dapsone independently by Ernest Fourneau[47] in France and Gladwin Buttle[48] in United-Kingdom.[49]




First synthesis of Dapsone from 4,4'-Thiodianiline
Fromm & Wittman, 1908

## Proposed use in antimalarial drugs [edit]

The spread of drug-resistant malaria in Africa has encouraged the development of new, low-cost antimalarial drugs. *Plasmodium falciparum*, one of the *Plasmodium* species that causes malaria, has developed resistance both to chloroquine and sulfadoxine/pyrimethamine, two of the most common treatments for malaria. Artemisinin, another antimalarial drug, had been developed in the 1980s but was too expensive for large-scale use. This led GlaxoSmithKline to develop Lapdap, a combination drug consisting of chlorproguanil and dapsone. Lapdap was licensed in the United Kingdom starting in October 2003.[19]

One advantage of Lapdap had was that chlorproguanil and dapsone are both low-cost drugs. Another was that by virtue of being of a combination drug, it was less likely to cause drug resistance. However, because dapsone causes hemolytic anemia in patients with G6PD deficiency, and because G6PD deficiency affects 10-25% of the population of sub-Saharan Africa, it was discovered that Lapdap is not safe for use in Africa. It was available in many African countries for four years before GlaxoSmithKline took it off the market in February 2008.[19]

## Dapsone gel [edit]

Dapsone had been reported in a few cases to effectively treat acne, but the risk of hemolytic anemia kept it from being widely used for this purpose. For many years scientists attempted to develop a topical formulation of dapsone that would be as effective against acne as oral dapsone, but without the hemolysis

side effect. This was difficult to accomplish because dapsone is highly insoluble in aqueous solvents. In the early 2000s QLT USA developed Aczone, a 5% dapsone gel that was shown to be effective against acne without causing clinically significant declines in hemoglobin levels, even in subjects with G6PD deficiency.[50] In February 2016, the FDA approved a 7.5% dapsone gel. This higher strength has the advantage of a once-daily application, versus twice-daily application of the 5% formulation.[51]

## References [edit]


1. ^ Thomas L. Lemke (2008). *Foye's Principles of Medicinal Chemistry*. Lippincott Williams & Wilkins. p. 1142. ISBN 9780781768795.
2. ^ *a b c d e f g h i j* "Dapsone". The American Society of Health-System Pharmacists. Retrieved Jan 12, 2015.
3. ^ *a b c* Zhu, YI; Stiller, MJ; et al. (2001). "Dapsone and sulfones in dermatology: overview and update". *Journal of the American Academy of Dermatology*. **45** (3): 420–34. doi:10.1067/mjd.2001.114733. PMID 11511841.
4. ^ *a b* Joel E. Gallant (2008). *Johns Hopkins HIV Guide 2012*. Jones & Bartlett Publishers. p. 193. ISBN 9781449619794.
5. ^ "WHO Model List of EssentialMedicines" (PDF). *World Health Organization*. October 2013. Retrieved 22 April 2014.
6. ^ Greenwood, David (2008). *Antimicrobial Drugs: Chronicle of a Twentieth Century Medical Triumph*. Oxford University Press. p. 197. ISBN 9780199534845.
7. ^ *a b c d* Rossi S, ed. (2006). *Australian Medicines Handbook*. Adelaide. ISBN 0-9757919-2-3.
8. ^ Ross, CM (1961). "The treatment of acne vulgaris with dapsone". *Br J Dermatol*. **73** (10): 367–70. doi:10.1111/j.1365-2133.1961.tb14398.x. PMID 14494150.
9. ^ "Dapsone and Acne Vulgaris". ScienceOfAcne.com. 2012-10-10. Retrieved 2012-08-17.
10. ^ Pickert, A; Raimer, S (June 2009). "An evaluation of dapsone gel 5% in the treatment of acne vulgaris". *Expert opinion on pharmacotherapy*. **10** (9): 1515–21. doi:10.1517/14656560903002097. PMID 19505219.
11. ^ Croft, AM (29 November 2007). "Malaria: prevention in travellers.". *Clinical evidence*. **2007**. PMC 2943798. PMID 19450348.
12. ^ Forks, TP (2000). "Brown recluse spider bites.". *J Am Board Fam Pract*. **13** (6): 415–23. doi:10.3122/15572625-13-6-415. PMID 11117338.
13. ^ Momen, S.E.; Jorizzo, J.; Al-Niaimi, F. (December 2014). "Erythema elevatum diutinum: a review of presentation and treatment". *Journal of the European Academy of Dermatology and Venereology*. John Wiley & Sons. **28** (12): 1594–1602. doi:10.1111/jdv.12566.
14. ^ Lukács, J.; Schliemann, S.; Elsner, P. (August PharmacistAnswers.
28. ^ Jaffuel D, Lebel B, Hillaire-Buys D, Pene J, Godard P, Michel FB, Blayac JP, Bousquet J, Demolyi P (1998). "Eosinophilic pneumonia induced by dapsone". *BMJ*. **317** (7152): 181. doi:10.1136/bmj.317.7152.181. PMC 28611. PMID 9665900.
29. ^ Richardus JH, Smith TC (1989). "Increased incidence in leprosy of hypersensitivity reactions to dapsone after introduction of multidrug therapy". *Lepr Rev*. **60** (4): 267–73. PMID 2491425.
30. ^ Kumar RH, Kumar MV, Thappa DM (1998). "Dapsone syndrome—a five year retrospective analysis". *Indian J Lepr*. **70** (3): 271–6. PMID 9801899.
31. ^ Rao PN, Lakshmi TS (2001). "Increase in the incidence of dapsone hypersensitivity syndrome—an appraisal". *Lepr Rev*. **72** (1): 57–62. PMID 11355519.
32. ^ Joseph MS (1985). "Hypersensitivity reaction to dapsone. Four case reports". *Lepr Rev*. **56** (4): 315–20. PMID 4079634.
33. ^ Jamrozik K (1986). "Dapsone syndrome occurring in two brothers". *Lepr Rev*. **57** (1): 57–62. PMID 3702581.
34. ^ Hortaleza AR, Salta-Ramos NG, Barcelona-Tan J, Abad-Venida L (1995). "Dapsone syndrome in a Filipino man". *Lepr Rev*. **66** (4): 307–13. PMID 8637384.
35. ^ Tomecki KJ, Catalano CJ (1981). "Dapsone hypersensitivity. The sulfone syndrome revisited". *Arch Dermatol*. **117** (1): 38–9. doi:10.1001/archderm.1981.01650010044023. PMID 6450569.
36. ^ Kromann NP, Vilhelmsen R, Stahl D (1982). "The dapsone syndrome". *Arch Dermatol*. **118** (7): 531–2. doi:10.1001/archderm.1982.01650190085028. PMID 7092282.
37. ^ "Mechanisms of Action of Dapsone in Dermatological Diseases". *Dapsone: Clinical Uses in Various Cutaneous Diseases*. Medscape Today. Archived from the original on May 17, 2011.
38. ^ Bozeman PM, Learn DB, Thomas EL (1990). "Assay of the human leukocyte enzymes myeloperoxidase and eosinophil peroxidase". *J. Immunol. Methods*. **126** (1): 125–33. doi:10.1016/0022-1759(90)90020-v. PMID 2154520.
39. ^ Bozeman PM, Learn DB, Thomas EL (1992). "Inhibition of the human leukocyte enzymes myeloperoxidase and eosinophil peroxidase by

2015). "Treatment of generalized granuloma annulare – a systematic review". *Journal of the European Academy of Dermatology and Venereology*. John Wiley & Sons. **29** (8): 1467–1480. doi:10.1111/jdv.12976.
15. ^ Zhang FR, Liu, H; Irwanto, A et al. (October 2013). "HLA-B*13:01 and the dapsone hypersensitivity syndrome.". *N Engl J Med*. **369** (17): 1620–8. doi:10.1056/NEJMoa1213096. PMID 24152261.
16. ^ Jopling WH (1983). "Side-effects of antileprosy drugs in common use". *Lepr Rev*. **54** (4): 261–70. PMID 6199637.
17. ^ Puavilai S, Chutha S, Polnikorn N, et al. (July 1984). "Incidence of anemia in leprosy patients treated with dapsone". *J Med Assoc Thai*. **67** (7): 404–7. PMID 6512448.
18. ^ "Antimalarial chlorproguanil-dapsone (LapDap™) withdrawn following demonstration of post-treatment haemolytic anaemia in G6PD deficient patients in a Phase III trial of chlorproguanil-dapsone-artesunate (Dacart™) versus artemether-lumefantrine (Coartem®) and confirmation of findings in a comparative trial of LapDap™ versus Dacart (PDF). World Health Organization. 4 March 2008. QSM/MC/IEA.1.
19. ^ *a b c* Luzzatto L (August 2010). "The rise and fall of the antimalarial Lapdap: a lesson in pharmacogenetics". *Lancet*. **376** (9742): 739–41. doi:10.1016/S0140-6736(10)60396-0. PMID 20599264.
20. ^ Sanders SW, Zone JJ, Foltz RL, Tolman KG, Rollins DE (April 1982). "Hemolytic anemia induced by dapsone transmitted through breast milk.". *Ann Intern Med*. **96** (4): 465–6. doi:10.7326/0003-4819-96-4-465. PMID 7065565.
21. ^ Firkin FC, Mariani AF (1977). "Agranulocytosis due to dapsone". *Med. J. Aust*. **2** (8): 247–51. PMID 909500.
22. ^ Foucauld J, Uphouse W, Berenberg J (1985). "Dapsone and aplastic anemia". *Ann. Intern. Med*. **102** (1): 139. doi:10.7326/0003-4819-102-1-139_2. PMID 3966740.
23. ^ Meyerson MA, Cohen PR (1994). "Dapsone-induced aplastic anemia in a woman with bullous systemic lupus erythematosus". *Mayo Clin. Proc*. **69** (12): 1159–62. doi:10.1016/s0025-6196(12)65768-1. PMID 7967777.
24. ^ Björkman A, Phillips-Howard PA (1991). "Adverse reactions to sulfa drugs: implications for malaria chemotherapy". *Bull. World Health Organ*. **69** (3): 297–304. PMC 2393107. PMID 1893504.
25. ^ Ganesan, S; Sahu, R; Walker, LA; Tekwani, BL (April 2010). "Cytochrome P450-dependent toxicity of dapsone in human erythrocytes". *J Appl Toxicol*. **30** (3): 271–5. doi:10.1002/jat.1493. PMID 19998329.
26. ^ Aczone(Dapsone) Package insert. Irvine CA: Allergan Inc; September 2008
dapsone". *Biochem. Pharmacol*. **44** (3): 553–63. doi:10.1016/0006-2952(92)90449-s. PMID 1324677.
40. ^ Stendahl O, Molin L, Lindroth M (1983). "Granulocyte-mediated release of histamine from mast cells. Effect of myeloperoxidase and its inhibition by antiinflammatory sulfone compounds". *Int. Arch. Allergy Appl. Immunol*. **70** (3): 277–84. doi:10.1159/000233335. PMID 6186607.
41. ^ Kettle AJ, Gedye CA, Winterbourn CC (1993). "Superoxide is an antagonist of antiinflammatory drugs that inhibit hypochlorous acid production by myeloperoxidase". *Biochem. Pharmacol*. **45** (10): 2003–10. doi:10.1016/0006-2952(93)90010-t. PMID 8390258.
42. ^ Kettle AJ, Winterbourn CC (1991). "Mechanism of inhibition of myeloperoxidase by anti-inflammatory drugs". *Biochem. Pharmacol*. **41** (10): 1485–92. doi:10.1016/0006-2952(91)90565-m. PMID 1850278.
43. ^ Diaz-Ruiz A, Zavala C, Montes S, et al. (November 2008). "Antioxidant, antiinflammatory and antiapoptotic effects of dapsone in a model of brain ischemia/reperfusion in rats". *J. Neurosci. Res*. **86** (15): 3410–9. doi:10.1002/jnr.21775. PMID 18615706.
44. ^ Begon E, Chosidow O, Wolkenstein P (December 2004). "[Disulone]". *Ann Dermatol Venereol* (in French). **131** (12): 1062–73. doi:10.1016/S0151-9638(04)93842-2. PMID 15692440.
45. ^ Uetrecht JP (1995). "Myeloperoxidase as a generator of drug free radicals". *Biochem. Soc. Symp*. **61**: 163–70. PMID 8660393.
46. ^ Tréfouël, J. et T.; Nitti, F.; Bovet, D. (23 November 1935). "Activité du p.aminophénylsulfamide sur l'infection streptococcique expérimentale de la souris et du lapin". *Comptes rendus des séances de la Société de biologie et de ses filiales* (in French). **120**: 756.
47. ^ Fourneau, E.; Tréfouël, Th. et J.; Nitti, F.; Bovet, D. (1937). "Action antistreptococcique des dérivés sulfurés organiques". *Comptes rendus de l'Académie des sciences* (in French). **204**: 1763.
48. ^ Buttle, G.A.H.; Stephenson, D.; Smith, S.; Dewing, T.; Foster, G.E. (June 1937). "Treatment of streptococcal infections in mice with 4:4'diamino-dipheni-sulphone". *Lancet*. **229** (5936): 1331–4. doi:10.1016/S0140-6736(00)75868-5.
49. ^ "Leprosy | 14 History of dapsone and dyes". Archived from the original on 2009-02-12. Retrieved 2009-02-24. (1937)
50. ^ Stotland, Mira; Shalita, Alan R.; Kissling, Robert F. (April 2009). "Dapsone 5% Gel: A Review of its Efficacy and Safety in the Treatment of Acne Vulgaris". *American Journal of Clinical Dermatology*. John Wiley & Sons. **10** (4): 1594–1602. doi:10.2165/00128071-200910040-00002.
51. ^ "Aczone (dapsone) 7.5% Gel Prescribing Information" (PDF). Allergan. February 2016.

27. ^ "Dapsone (Aczone)". *Medications For Acne*. Retrieved 23 June 2016.

## External links [edit]

- MedlinePlus Drug Information
- U.S. National Library of Medicine: Drug Information Portal - Dapsone

| v · t · e · **Antimycobacterials, including tuberculosis treatment and leprostatic agents (J04)** | | |
|---|---|---|
| **Nucleic acid inhibitor** | **Rifamycins/ RNA polymerase inhibitor** | Rifampicin# · Rifabutin · Rifapentine · Rifalazil§ · |
| | **Antifolates/ DSI** | **Dapsone**# · Acedapsone · Aldesulfone sodium · |
| | **ASA** | *4-Aminosalicylic acid*# (Calcium aminosalicylate · Sodium aminosalicylate) · |
| **Protein synthesis inhibitor** | **Aminoglycosides** | Amikacin# · Capreomycin# · Kanamycin# · Streptomycin# · |
| | **Oxazolidone** | Linezolid · |
| **Cell envelope antibiotic** | **Peptidoglycan layer** | Alanine analogue: Cycloserine# · |
| | **Arabinogalactan layer** | Ethylenediamine/arabinosyltransferase inhibitor: Ethambutol# · SQ109† · |
| | **Mycolic acid layer** | Hydrazides/mycolic acid synth. inhibition: Isoniazid# · Thiocarbamides: Ethionamide# · Prothionamide · Thiocarlide · |
| **Other/unknown** | *Phenazine* (Clofazimine)# · *Pyrazine* (Pyrazinamide#, Morinamide) · *Isoxazole* (Terizidone) · Bedaquiline · *Metronidazole* (*delamanid*) · | |
| **Combinations** | Rifampicin/isoniazid/pyrazinamide · | |
| #WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · · | | |

| v · t · e · **Antibacterials: nucleic acid inhibitors (J01E, J01M)** | | | |
|---|---|---|---|
| **Antifolates (inhibits purine metabolism, thereby inhibiting DNA and RNA synthesis)** | **DHFR inhibitor** | 2,4-Diaminopyrimidine (Trimethoprim# · Brodimoprim · Tetroxoprim · Iclaprim† · · | |
| | **Sulfonamides (DHPS inhibitor)** | **Short-acting** | Sulfaisodimidine · Sulfamethizole · Sulfadimidine · Sulfapyridine · Sulfafurazole · Sulfanilamide (Prontosil · · Sulfathiazole · Sulfathiourea · |
| | | **Intermediate-acting** | Sulfamethoxazole · Sulfadiazine# · Sulfamoxole · |
| | | **Long-acting** | Sulfadimethoxine · Sulfadoxine · Sulfalene · Sulfametomidine · Sulfametoxydiazine · Sulfamethoxypyridazine · Sulfaperin · Sulfamerazine · Sulfaphenazole · |

| | | | |
|---|---|---|---|
| | | | Sulfamazone · |
| | | **Other/ungrouped** | Sulfacetamide · Sulfadicramide · Sulfametrole · |
| | **Combinations** | | Trimethoprim/sulfamethoxazole[#] · |
| **Topoisomerase inhibitors/ quinolones/ (inhibits DNA replication)** | **1st g.** | | Cinoxacin[‡] · Flumequine[‡] · Nalidixic acid[‡] · Oxolinic acid[‡] · Pipemidic acid[‡] · Piromidic acid[‡] · Rosoxacin[‡] · |
| | **Fluoro-quinolones** | **2nd g.** | Ciprofloxacin[#] · Ofloxacin · Enoxacin[‡] · Fleroxacin[‡] · Lomefloxacin[‡] · Nadifloxacin[‡] · Norfloxacin[‡] · Pefloxacin[‡] · Rufloxacin[‡] · |
| | | **3rd g.** | Levofloxacin · Balofloxacin[‡] · Grepafloxacin[‡] · Pazufloxacin[‡] · Sparfloxacin[‡] · Temafloxacin[‡] · Tosufloxacin[‡] · |
| | | **4th g.** | Besifloxacin · Gatifloxacin · Finafloxacin · Gemifloxacin · Moxifloxacin · Clinafloxacin[†] · Garenoxacin[‡] · Prulifloxacin[‡] · Sitafloxacin[‡] · Trovafloxacin[‡]/Alatrofloxacin[‡] · |
| | | **Vet.** | Danofloxacin · Difloxacin · Enrofloxacin · Ibafloxacin · Marbofloxacin · Orbifloxacin · Pradofloxacin · Sarafloxacin · |
| | **Newer non-fluorinated** | | Nemonoxacin · |
| | **Related (DG)** | | Aminocoumarins: Novobiocin · |
| **Anaerobic DNA inhibitors** | **Nitro- imidazole derivatives** | | Metronidazole[#] · Tinidazole · Ornidazole · |
| | **Nitrofuran derivatives** | | Nitrofurantoin[#] · Furazolidone[‡] · Nifurtoinol · |
| **RNA synthesis** | **Rifamycins/ RNA polymerase** | | Rifampicin[#] · Rifabutin · Rifapentine · Rifaximin · Rifalazil[§] · |

[#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III · ·

| v · t · e · | **Acne-treating agents (D10)** |
|---|---|
| **Antibacterial** | Azelaic acid · Benzoyl peroxide[#] · 8-Hydroxyquinoline · Blue light therapy · Tea tree oil · |
| **Keratolytic** | Glycolic acid · Salicylic acid[#] · Sulfur · Benzoyl peroxide[#] · |
| **Anti-inflammatory** | Nicotinamide · Ibuprofen # · Aspirin # · Red light therapy · |
| **Antibiotics** | Clindamycin · **Dapsone** · Erythromycin · Sulfacetamide · Tetracyclines (Lymecycline · Minocycline · Doxycycline) · |
| **Hormonal** | Antiandrogens (Bicalutamide · Cyproterone acetate · Drospirenone · Flutamide · Spironolactone) · · Estrogens (Estradiol · Ethinylestradiol · · |
| **Retinoids** | Adapalene · Isotretinoin · Motretinide · Tazarotene · Tretinoin · |
| **Other** | Benzamycin · Epristeride · Mesulfen · Pelretin · Stridex · Tioxolone · |
| **Combinations** | Adapalene/benzoyl peroxide · Benzoyl peroxide/clindamycin · Clindamycin/tretinoin · Erythromycin/isotretinoin · Sulfacetamide/sulfur · |

· [#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III · ·

Categories: Anilines | Sulfones | Dihydropteroate synthetase inhibitors | Antibiotics | Anti-acne preparations | Leprosy | World Health Organization essential medicines




# Diazepam

From Wikipedia, the free encyclopedia

**Diazepam**, first marketed as **Valium**, is a medication of the benzodiazepine family that typically produces a calming effect. It is commonly used to treat a range of conditions including anxiety, alcohol withdrawal syndrome, benzodiazepine withdrawal syndrome, muscle spasms, seizures, trouble sleeping, and restless legs syndrome.[3] It may also be used to cause memory loss during certain medical procedures.[4][5] It can be taken by mouth, inserted into the rectum, injected into muscle, or injected into a vein.[5] When given into a vein, effects begin in one to five minutes and last up to an hour.[5] By mouth, effects may take 40 minutes to begin.[6]

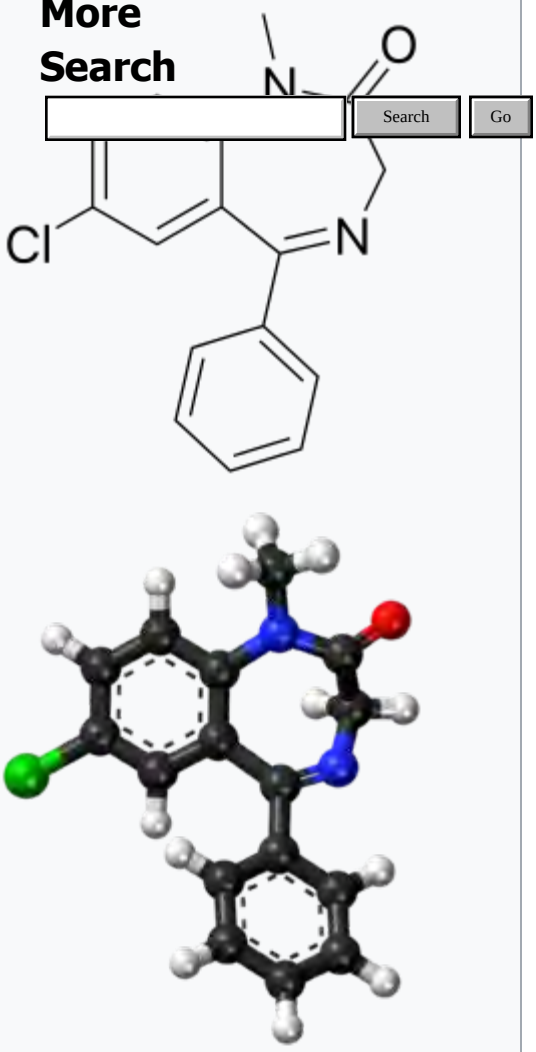
Common side effects include sleepiness and trouble with coordination.[5] Serious side effects are rare.[3] They include suicide, decreased breathing, and an increased risk of seizures if used too frequently in those with epilepsy.[3][5] Occasionally excitement or agitation may occur.[7][8] Long term use can result in tolerance, dependence, and withdrawal symptoms on dose reduction. Abrupt stopping after long-term use can be potentially dangerous.[3] After stopping, cognitive problems may persist for six months or longer.[7] It is not recommended during pregnancy or breastfeeding.[5] Its mechanism of action is by increasing the effect of the neurotransmitter *gamma*-Aminobutyric acid (GABA).[7]

Diazepam was first synthesized by Leo Sternbach, and was first manufactured by Hoffmann-La Roche. It has been one of the most frequently prescribed medications in the world since its launch in 1963. In the United States it was the highest selling medication between 1968 and 1982, selling more than two billion tablets in 1978 alone. In 1985 the patent ended, and there are now more than 500 brands available on the market.[3] Diazepam is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[9] The wholesale cost in the developing world is about 0.01 USD per dose as of 2014.[10] In the United States it is about 0.40 USD per dose.[5]

Contents



**Diazepam**




| Clinical data | |
|---|---|
| **Pronunciation** | /daɪˈæzɨpæm/ |
| **Trade names** | Valium and many others |
| **AHFS / Drugs.com** | Monograph |
| **MedlinePlus** | a682047 |
| **License data** | US FDA: Diazepam |
| **Pregnancy category** | AU: C<br>US: D (Evidence of risk) |

## Medical uses [edit]

Diazepam is mainly used to treat anxiety, insomnia, panic attacks and symptoms of acute alcohol withdrawal. It is also used as a premedication for inducing sedation, anxiolysis, or amnesia before certain medical procedures (e.g., endoscopy).[11][12] Diazepam is the drug of choice for treating benzodiazepine dependence with its long half-life allowing easier dose reduction. Benzodiazepines have a relatively low toxicity in overdose.[7]

Diazepam has a number of uses including:

- Treatment of anxiety, panic attacks, and states of agitation[11]
- Treatment of neurovegetative symptoms associated with vertigo[13]
- Treatment of the symptoms of alcohol, opiate, and benzodiazepine withdrawal[11][14]
- Short-term treatment of insomnia[11]
- Treatment of tetanus, together with other measures of intensive treatment[15]
- Adjunctive treatment of spastic muscular paresis (paraplegia/tetraplegia) caused by cerebral or spinal cord conditions such as stroke, multiple sclerosis, or spinal cord injury (long-term treatment is coupled with other rehabilitative measures)[16]
- Palliative treatment of stiff person syndrome[17]
- Pre- or postoperative sedation, anxiolysis and/or amnesia (e.g., before endoscopic or surgical procedures)[16]
- Treatment of complications with a hallucinogen crisis and stimulant overdoses and psychosis, such as LSD, cocaine, or methamphetamine[18]

| | |
|---|---|
| **Dependence liability** | Moderate |
| **Addiction liability** | Moderate[1][2] |
| **Routes of administration** | Oral, IM, IV, suppository |
| **ATC code** | N05BA01 (WHO) |
| **Legal status** | |
| **Legal status** | AU: S4 (Prescription only)<br>CA: Schedule IV<br>DE: Anlage III (Prescription only)<br>NZ: Class C<br>UK: Class C<br>US: Schedule IV<br>UN: Psychotropic Schedule IV (Prescription only) |
| **Pharmacokinetic data** | |
| **Bioavailability** | 93–100% |
| **Metabolism** | Hepatic—CYP2B6 (minor route) to desmethyldiazepam, CYP2C19 (major route) to inactive metabolites, CYP3A4 (major route) to desmethyldiazepam |
| **Biological half-life** | 20–100 hours (36–200 hours for main active metabolite desmethyldiazepam) |
| **Excretion** | Renal |
| **Identifiers** | |
| **IUPAC name** | 7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-one |
| **CAS Number** | 439-14-5 ✓ |
| **PubChem** (CID) | 3016 |
| **IUPHAR/BPS** | 3364 |
| **DrugBank** | DB00829 ✗ |
| **ChemSpider** | 2908 ✓ |
| **UNII** | Q3JTX2Q7TU ✓ |
| **KEGG** | D00293 ✓ |
| **ChEBI** | CHEBI:49575 ✓ |

- Preventative treatment of oxygen toxicity during hyperbaric oxygen therapy[19]

Dosages should be determined on an individual basis, depending on the condition being treated, severity of symptoms, patient body weight, and any other conditions the person may have.[18]

## Seizures [edit]

Intravenous diazepam or lorazepam are first-line treatments for status epilepticus.[7][20] However, lorazepam has advantages over diazepam, including a higher rate of terminating seizures and a more prolonged anticonvulsant effect.[21][*needs update*] Diazepam is rarely used for the long-term treatment of epilepsy because tolerance to its anticonvulsant effects usually develops within six to 12 months of treatment, effectively rendering it useless for that purpose.[18][22]

The anticonvulsant effects of diazepam can help in the treatment of seizures due to a drug overdose or chemical toxicity as a result of exposure to sarin, VX, or soman (or other organophosphate poisons), lindane, chloroquine, physostigmine, or pyrethroids.[18][23]

It is sometimes used intermittently for the prevention of febrile seizures that may occur in children under five years of age.[7] This use, however, is not typically recommended as the benefits are small and side effects are common.[24] Long-term use of diazepam for the management of epilepsy is not recommended; however, a subgroup of individuals with treatment-resistant epilepsy benefit from long-term benzodiazepines, and for such individuals, clorazepate has been recommended due to its slower onset of tolerance to the anticonvulsant effects.[7]

| | |
|---|---|
| **ChEMBL** | CHEMBL12 ✓ |
| **ECHA InfoCard** | 100.006.476 |
| **Chemical and physical data** | |
| **Formula** | $C_{16}H_{13}ClN_2O$ |
| **Molar mass** | 284.7 g/mol |
| **3D model (Jmol)** | Interactive image |

**SMILES**
CN1C2=C(C(C3=CC=CC=C3)=NCC1=O)C=C(Cl)C=C2

**InChI**
InChI=1S/C16H13ClN2O/c1-19-14-8-7-12(17)9-13(14)16(18-10-15(19)20)11-5-3-2-4-6-11/h2-9H,10H2,1H3 ✓
Key:AAOVKJBEBIDNHE-UHFFFAOYSA-N ✓

✗✓ (what is this?) (verify)

Diazepam tablets (2, 5, and 10 mg)

## Other [edit]

Diazepam is used for the emergency treatment of eclampsia, when IV magnesium sulfate and blood-pressure control measures have failed.[25][26] Benzodiazepines do not have any pain-relieving properties themselves, and are generally recommended to avoid in individuals with pain.[27] However, benzodiazepines such as diazepam can be used for their muscle-relaxant properties to alleviate pain caused by muscle spasms and various dystonias, including blepharospasm.[28][29] Tolerance often develops to the muscle relaxant effects of benzodiazepines such as diazepam.[30] Baclofen[31] or tizanidine is sometimes used as an alternative to diazepam.

## Availability [edit]

Diazepam is marketed in over 500 brands throughout the world.[32] It is supplied in oral, injectable, inhalation, and rectal forms.[18][33][34]

The United States military employs a specialized diazepam preparation known as Convulsive Antidote, Nerve Agent (CANA), which contains diazepam. One CANA kit is typically issued to service members, along with three Mark I NAAK kits, when operating in circumstances where chemical weapons in the form of nerve agents are considered a potential hazard. Both of these kits deliver drugs using autoinjectors. They are intended for use in "buddy aid" or "self aid" administration of the drugs in the field prior to decontamination and delivery of the patient to definitive medical care.[35]

# Contraindications [edit]

Use of diazepam should be avoided, when possible, in individuals with:[36]

- Ataxia
- Severe hypoventilation
- Acute narrow-angle glaucoma
- Severe hepatic deficiencies (hepatitis and liver cirrhosis decrease elimination by a factor of two)
- Severe renal deficiencies (for example, patients on dialysis)
- Liver disorders
- Severe sleep apnea
- Severe depression, particularly when accompanied by suicidal tendencies
- Psychosis
- Pregnancy or breast feeding
- Caution required in elderly or debilitated patients
- Coma or shock
- Abrupt discontinuation of therapy
- Acute intoxication with alcohol, narcotics, or other psychoactive substances (with the exception of some hallucinogens and/or stimulants, where it is occasionally used as a treatment for overdose)
- History of alcohol or drug dependence
- Myasthenia gravis, an autoimmune disorder causing marked fatiguability
- Hypersensitivity or allergy to any drug in the benzodiazepine class

## Caution [edit]

- Benzodiazepine abuse and misuse should be checked if used in the alcohol- or drug-dependent people or those with comorbid psychiatric disorders.[37]
- Pediatric patients
  - Less than 18 years of age, this treatment is usually not indicated, except for treatment of epilepsy, and pre- or postoperative treatment. The smallest possible effective dose should be used for this group of patients.[38]
  - Under 6 months of age, safety and effectiveness have not been established; diazepam should not be given to those in this age group.[17][38]
- Elderly and very ill patients can possibly suffer apnea or cardiac arrest. Concomitant use of other central nervous system depressants increases this risk. The smallest possible effective dose should be used for this group of people.[38][39] The elderly metabolise benzodiazepines much more slowly than younger adults, and are also more sensitive to the effects of benzodiazepines, even at similar blood plasma levels. Doses of diazepam are recommended to be about half of those given to younger people, and treatment limited to a maximum of two weeks. Long-acting benzodiazepines such as diazepam are not recommended for the elderly.[7] Diazepam can also be dangerous in geriatric patients owing to a significant increased risk of falls.[40]
- Intravenous or intramuscular injections in hypotensive people or those in shock should be administered carefully and vital signs should be monitored.[39]
- Benzodiazepines such as diazepam are lipophilic and rapidly penetrate membranes, so rapidly cross over into the placenta with significant uptake of the drug. Use of benzodiazepines including diazepam in late pregnancy, especially high doses, can result in floppy infant syndrome.[41] Diazepam when taken late in pregnancy, during the third trimester, causes a definite risk of a severe benzodiazepine withdrawal syndrome in the neonate with symptoms including hypotonia, and reluctance to suck, to apnoeic spells, cyanosis, and impaired metabolic responses to cold stress. Floppy infant syndrome and sedation in the newborn may also occur. Symptoms of floppy infant syndrome and the neonatal benzodiazepine withdrawal syndrome have been reported to persist from hours to months after birth.[42]

# Adverse effects [edit]

Adverse effects of benzodiazepines such as diazepam include anterograde amnesia and confusion (especially pronounced in higher doses) and sedation. The elderly are more prone to adverse effects of diazepam, such as confusion, amnesia, ataxia, and hangover effects, as well as falls. Long-term use of benzodiazepines such as diazepam is associated with drug tolerance, benzodiazepine dependence, and benzodiazepine withdrawal syndrome.[7] Like other benzodiazepines, diazepam can impair short-term memory and learning of new information. While benzodiazepine drugs such as diazepam can cause anterograde amnesia, they do not cause retrograde amnesia; information learned before using benzodiazepines is not impaired. Tolerance to the cognitive-impairing effects of benzodiazepines does not tend to develop with long-term use, and the elderly are more sensitive to them.[43] Additionally, after cessation of benzodiazepines, cognitive deficits may persist for at least six months; it is unclear whether these impairments take longer than six months to abate or if they are permanent. Benzodiazepines may also cause or worsen depression.[7] Infusions or repeated intravenous injections of diazepam when managing seizures, for example, may lead to drug toxicity, including respiratory depression, sedation and hypotension. Drug tolerance may also develop to infusions of diazepam if it is given for longer than 24 hours.[7] Adverse effects such as sedation, benzodiazepine dependence, and abuse potential limit the use of benzodiazepines.[44]

Diazepam has a range of side effects common to most benzodiazepines, including:

- Suppression of REM sleep
- Impaired motor function
  - Impaired coordination
  - Impaired balance
  - Dizziness
- Depression[45]
- Reflex tachycardia[46]

Less commonly, paradoxical side effects can occur, including nervousness, irritability, excitement, worsening of seizures, insomnia, muscle cramps, changes in libido, and in some cases, rage and violence. These adverse reactions are more likely to occur in children, the elderly, and individuals with a history of drug or alcohol abuse and or aggression.[7][47][48][49] Diazepam may increase, in some people, the propensity toward self-harming behaviours and, in extreme cases, may provoke suicidal tendencies or acts.[50] Very rarely dystonia can occur.[51]

Diazepam may impair the ability to drive vehicles or operate machinery. The impairment is worsened by consumption of alcohol, because both act as central nervous system depressants.[17]

During the course of therapy, tolerance to the sedative effects usually develops, but not to the anxiolytic and myorelaxant effects.[52]

Patients with severe attacks of apnea during sleep may suffer respiratory depression (hypoventilation), leading to respiratory arrest and death.

Diazepam in doses of 5 mg or more causes significant deterioration in alertness performance combined with increased feelings of sleepiness.[53]

## Tolerance and dependence [edit]

Diazepam, as with other benzodiazepine drugs, can cause tolerance, physical dependence, substance use disorder, and benzodiazepine withdrawal syndrome. Withdrawal from diazepam or other benzodiazepines often leads to withdrawal symptoms similar to those seen during barbiturate or alcohol withdrawal. The higher the dose and the longer the drug is taken, the greater the risk of experiencing unpleasant withdrawal symptoms.

Withdrawal symptoms can occur from standard dosages and also after short-term use, and can range from insomnia and anxiety to more serious symptoms, including seizures and psychosis. Withdrawal symptoms can sometimes resemble pre-existing conditions and be misdiagnosed. Diazepam may produce less intense withdrawal symptoms due to its long elimination half-life.

Benzodiazepine treatment should be discontinued as soon as possible by a slow and gradual dose reduction regimen.[7][54] Tolerance develops to the therapeutic effects of benzodiazepines; for example tolerance occurs to the anticonvulsant effects and as a result benzodiazepines are not generally recommended for the long-term management of epilepsy. Dose increases may overcome the effects of tolerance, but tolerance may then develop to the higher dose and adverse effects may increase. The mechanism of tolerance to benzodiazepines includes uncoupling of receptor sites, alterations in gene expression, down-regulation of receptor sites, and desensitisation of receptor sites to the effect of GABA. About one-third of individuals who take benzodiazepines for longer than four weeks become dependent and experience withdrawal syndrome on cessation.[7]

Differences in rates of withdrawal (50–100%) vary depending on the patient sample. For example, a random sample of long-term benzodiazepine users typically finds around 50% experience few or no withdrawal symptoms, with the other 50% experiencing notable withdrawal symptoms. Certain select patient groups show a higher rate of notable withdrawal symptoms, up to 100%.[55]

Rebound anxiety, more severe than baseline anxiety, is also a common withdrawal symptom when discontinuing diazepam or other benzodiazepines.[56] Diazepam is therefore only recommended for short-term therapy at the lowest possible dose owing to risks of severe withdrawal problems from low doses even after gradual reduction.[57] The risk of pharmacological dependence on diazepam is significant, and patients experience symptoms of benzodiazepine withdrawal syndrome if it is taken for six weeks or longer.[58] In humans, tolerance to the anticonvulsant effects of diazepam occurs frequently.[59]

### Dependence [edit]

Improper or excessive use of diazepam can lead to dependence.[60] At a particularly high risk for diazepam misuse, abuse or dependence are:

- People with a history of alcohol or drug abuse or dependence[17][61] Diazepam increases craving for alcohol in problem alcohol consumers. Diazepam also increases the volume of alcohol consumed by problem drinkers.[62]
- People with severe personality disorders, such as borderline personality disorder[63]

Patients from the aforementioned groups should be monitored very closely during therapy for signs of abuse and development of dependence. Therapy should be discontinued if any of these signs are noted, although if dependence has developed, therapy must still be discontinued gradually to avoid severe withdrawal symptoms. Long-term therapy in these people is not recommended.[17][61]

People suspected of being dependent on benzodiazepine drugs should be very gradually tapered off the drug. Withdrawals can be life-threatening, particularly when excessive doses have been taken for extended periods of time. Equal prudence should be used whether dependence has occurred in therapeutic or recreational contexts.

## Overdose [edit]

*Main article: Benzodiazepine overdose*

An individual who has consumed too much diazepam typically displays one or more of these symptoms in a period of approximately four hours immediately following a suspected overdose:[17][64]

- Drowsiness
- Mental confusion
- Hypotension
- Impaired motor functions
  - Impaired reflexes
  - Impaired coordination
  - Impaired balance
  - Dizziness

- Coma

Although not usually fatal when taken alone, a diazepam overdose is considered a medical emergency and generally requires the immediate attention of medical personnel. The antidote for an overdose of diazepam (or any other benzodiazepine) is flumazenil (Anexate). This drug is only used in cases with severe respiratory depression or cardiovascular complications. Because flumazenil is a short-acting drug, and the effects of diazepam can last for days, several doses of flumazenil may be necessary. Artificial respiration and stabilization of cardiovascular functions may also be necessary. Though not routinely indicated, activated charcoal can be used for decontamination of the stomach following a diazepam overdose. Emesis is contraindicated. Dialysis is minimally effective. Hypotension may be treated with levarterenol or metaraminol.[17][18][64][65]

The oral $LD_{50}$ (lethal dose in 50% of the population) of diazepam is 720 mg/kg in mice and 1240 mg/kg in rats.[17] D. J. Greenblatt and colleagues reported in 1978 on two patients who had taken 500 and 2000 mg of diazepam, respectively, went into moderately deep comas, and were discharged within 48 hours without having experienced any important complications, in spite of having high concentrations of diazepam and its metabolites desmethyldiazepam, oxazepam, and temazepam, according to samples taken in the hospital and as follow-up.[66]

Overdoses of diazepam with alcohol, opiates and/or other depressants may be fatal.[65][67]

## Interactions [edit]

If diazepam is administered concomitantly with other drugs, attention should be paid to the possible pharmacological interactions. Particular care should be taken with drugs that potentiate the effects of diazepam, such as barbiturates, phenothiazines, opioids, and antidepressants.[17]

Diazepam does not increase or decrease hepatic enzyme activity, and does not alter the metabolism of other compounds. No evidence would suggest diazepam alters its own metabolism with chronic administration.[18]

Agents with an effect on hepatic cytochrome P450 pathways or conjugation can alter the rate of diazepam metabolism. These interactions would be expected to be most significant with long-term diazepam therapy, and their clinical significance is variable.[18]

- Diazepam increases the central depressive effects of alcohol, other hypnotics/sedatives (e.g., barbiturates), other muscle relaxants, certain antidepressants, sedative antihistamines, opioids, and antipsychotics, as well as anticonvulsants such as phenobarbital, phenytoin, and carbamazepine. The euphoriant effects of opioids may be increased, leading to increased risk of psychological dependence.[7][38][68]
- Cimetidine, omeprazole, oxcarbazepine, ticlopidine, topiramate, ketoconazole, itraconazole, disulfiram, fluvoxamine, isoniazid, erythromycin, probenecid, propranolol, imipramine, ciprofloxacin, fluoxetine, and valproic acid prolong the action of diazepam by inhibiting its elimination.[7][18][33]
- Alcohol in combination with diazepam may cause a synergistic enhancement of the hypotensive properties of benzodiazepines and alcohol.[69]
- Oral contraceptives significantly decrease the elimination of desmethyldiazepam, a major metabolite of diazepam.[38][70]
- Rifampin, phenytoin, carbamazepine, and phenobarbital increase the metabolism of diazepam, thus decreasing drug levels and effects.[18] Dexamethasone and St John's wort also increase the metabolism of diazepam.[7]
- Diazepam increases the serum levels of phenobarbital.[71]
- Nefazodone can cause increased blood levels of benzodiazepines.[38]
- Cisapride may enhance the absorption, and therefore the sedative activity, of diazepam.[72]
- Small doses of theophylline may inhibit the action of diazepam.[73]
- Diazepam may block the action of levodopa (used in the treatment of Parkinson's disease).[68]
[18]

- Diazepam may alter digoxin serum concentrations.
- Other drugs that may have interactions with diazepam include antipsychotics (e.g. chlorpromazine), MAO inhibitors, and ranitidine.[38]
- Because it acts on the GABA receptor, the herb valerian may produce an adverse effect.[74]
- Foods that acidify the urine can lead to faster absorption and elimination of diazepam, reducing drug levels and activity.[68]
- Foods that alkalinize the urine can lead to slower absorption and elimination of diazepam, increasing drug levels and activity.[18]
- Reports conflict as to whether food in general has any effects on the absorption and activity of orally administered diazepam.[68]

# Pharmacology [edit]

Diazepam is a long-acting "classical" benzodiazepine. Other classical benzodiazepines include chlordiazepoxide, clonazepam, lorazepam, oxazepam, nitrazepam, temazepam, flurazepam, bromazepam, and clorazepate.[75] Diazepam has anticonvulsant properties.[76] Diazepam has no effect on GABA levels and no effect on glutamate decarboxylase activity, but has a slight effect on gamma-aminobutyric acid transaminase activity. It differs from some other anticonvulsive drugs with which it was compared.[77] Benzodiazepines act via micromolar benzodiazepine binding sites as Ca2+ channel blockers and significantly inhibit depolarization-sensitive Calcium uptake in rat nerve cell preparations.[78]

5 mg Valium Roche packaging Australia

Diazepam inhibits acetylcholine release in mouse hippocampal synaptosomes. This has been found by measuring sodium-dependent high-affinity choline uptake in mouse brain cells *in vitro*, after pretreatment of the mice with diazepam *in vivo*. This may play a role in explaining diazepam's anticonvulsant properties.[79]

Diazepam binds with high affinity to glial cells in animal cell cultures.[80] Diazepam at high doses has been found to decrease histamine turnover in mouse brain via diazepam's action at the benzodiazepine-GABA receptor complex.[81] Diazepam also decreases prolactin release in rats.[82]

## Mechanism of action [edit]

*See also: Benzodiazepine*

Benzodiazepines are positive allosteric modulators of the GABA type A receptors (GABAA). The GABAA receptors are ligand-gated chloride-selective ion channels that are activated by GABA, the major inhibitory neurotransmitter in the brain. Binding of benzodiazepines to this receptor complex promotes binding of GABA, which in turn increases the total conduction of chloride ions across the neuronal cell membrane. This increased chloride ion influx hyperpolarizes the neuron's membrane potential. As a result, the difference between resting potential and threshold potential is increased and firing is less likely.

The GABAA receptor is a heteromer composed of five subunits, the most common ones being two αs, two βs, and one γ (α2β2γ). For each subunit, many subtypes exist (α1–6, β1–3, and γ1–3). GABAA receptors containing the α1 subunit mediate the sedative, the anterograde amnesic, and partly the anticonvulsive effects of diazepam. GABAA receptors containing α2 mediate the anxiolytic actions and to a large degree the myorelaxant effects. GABAA receptors containing α3 and α5 also contribute to benzodiazepines myorelaxant actions, whereas GABAA receptors comprising the α5 subunit were shown to modulate the temporal and spatial memory effects of benzodiazepines.[83] Diazepam is not the only drug to target these GABAA receptors. Drugs like Flumazenil also bind to GABAA to induce their effects. [84]

Diazepam appears to act on areas of the limbic system, thalamus, and hypothalamus, inducing anxiolytic effects. Benzodiazepine drugs including diazepam increase the inhibitory processes in the cerebral [85]

cortex.

The anticonvulsant properties of diazepam and other benzodiazepines may be in part or entirely due to binding to voltage-dependent sodium channels rather than benzodiazepine receptors. Sustained repetitive firing seems limited by benzodiazepines' effect of slowing recovery of sodium channels from inactivation.[86]

The muscle relaxant properties of diazepam are produced via inhibition of polysynaptic pathways in the spinal cord.[87]

### Pharmacokinetics [edit]

Diazepam can be administered orally, intravenously (must be diluted, as it is painful and damaging to veins), intramuscularly (IM), or as a suppository.[18]

When administered orally, it is rapidly absorbed and has a fast onset of action. The onset of action is one to five minutes for IV administration and 15–30 minutes for IM administration. The duration of diazepam's peak pharmacological effects is 15 minutes to one hour for both routes of administration.[46] The bioavailability after oral administration is 100%, and 90% after rectal administration. Peak plasma levels occur between 30 and 90 minutes after oral administration and between 30 and 60 minutes after intramuscular administration; after rectal administration, peak plasma levels occur after 10 to 45 minutes. Diazepam is highly protein-bound, with 96 to 99% of the absorbed drug being protein-bound. The distribution half-life of diazepam is two to 13 minutes.[7]

When diazepam is administered IM, absorption is slow, erratic, and incomplete.[11]

Diazepam is highly lipid-soluble, and is widely distributed throughout the body after administration. It easily crosses both the blood–brain barrier and the placenta, and is excreted into breast milk. After absorption, diazepam is redistributed into muscle and adipose tissue. Continual daily doses of diazepam quickly build to a high concentration in the body (mainly in adipose tissue), far in excess of the actual dose for any given day.[7][18]

Diazepam is stored preferentially in some organs, including the heart. Absorption by any administered route and the risk of accumulation is significantly increased in the neonate, and withdrawal of diazepam during pregnancy and breast feeding is clinically justified.[88]

Diazepam undergoes oxidative metabolism by demethylation (CYP 2C9, 2C19, 2B6, 3A4, and 3A5), hydroxylation (CYP 3A4 and 2C19) and glucuronidation in the liver as part of the cytochrome P450 enzyme system. It has several pharmacologically active metabolites. The main active metabolite of diazepam is desmethyldiazepam (also known as nordazepam or nordiazepam). Its other active metabolites include the minor active metabolites temazepam and oxazepam. These metabolites are conjugated with glucuronide, and are excreted primarily in the urine. Because of these active metabolites, the serum values of diazepam alone are not useful in predicting the effects of the drug. Diazepam has a biphasic half-life of about one to three days, and two to seven days for the active metabolite desmethyldiazepam.[7] Most of the drug is metabolised; very little diazepam is excreted unchanged.[18] The elimination half-life of diazepam and also the active metabolite desmethyldiazepam increases significantly in the elderly, which may result in prolonged action, as well as accumulation of the drug during repeated administration.[89]

## Physical and chemical properties [edit]

Diazepam occurs as solid white or yellow crystals with a melting point of 131.5 to 134.5 °C. It is odorless, and has a slightly bitter taste. The British Pharmacopoeia lists it as being very slightly soluble in water, soluble in alcohol, and freely soluble in chloroform. The United States Pharmacopoeia lists diazepam as soluble 1 in 16 ethyl alcohol, 1 in 2 of chloroform, 1 in 39 ether, and practically insoluble in water. The pH of diazepam is neutral (i.e., pH = 7). Due to additives such as benzoic acid/benzoate in the injectable form. (Plumb's, 6th edition page 372) Diazepam has a shelf life of five years for oral tablets and three years for IV/IM solutions.[18] Diazepam should be stored at room temperature (15–30 °C). The solution for parenteral injection should be protected from light and kept from freezing. The oral forms should be stored [33]

in air-tight containers and protected from light.

Diazepam can absorb into plastics, so liquid preparations should not be kept in plastic bottles or syringes, etc. As such, it can leach into the plastic bags and tubing used for intravenous infusions. Absorption appears to depend on several factors, such as temperature, concentration, flow rates, and tube length. Diazepam should not be administered if a precipitate has formed and does not dissolve.[33]

### Detection in body fluids [edit]

Diazepam may be quantified in blood or plasma to confirm a diagnosis of poisoning in hospitalized patients, provide evidence in an impaired driving arrest, or to assist in a medicolegal death investigation. Blood or plasma diazepam concentrations are usually in a range of 0.1–1.0 mg/l in persons receiving the drug therapeutically, 1–5 mg/l in those arrested for impaired driving, and 2–20 mg/l in victims of acute overdose. Most commercial immunoassays for the benzodiazepine class of drugs cross-react with diazepam, but confirmation and quantitation are usually performed using chromatographic techniques.[90][91][92]

## History [edit]

Diazepam was the second benzodiazepine invented by Dr. Leo Sternbach of Hoffmann-La Roche at the company's Nutley, New Jersey, facility[93] following chlordiazepoxide (Librium), which was approved for use in 1960. Released in 1963 as an improved version of Librium, diazepam became incredibly popular, helping Roche to become a pharmaceutical industry giant. It is 2.5 times more potent than its predecessor, which it quickly surpassed in terms of sales. After this initial success, other pharmaceutical companies began to introduce other benzodiazepine derivatives.[94]

The benzodiazepines gained popularity among medical professionals as an improvement over barbiturates, which have a comparatively narrow therapeutic index, and are far more sedative at therapeutic doses. The benzodiazepines are also far less dangerous; death rarely results from diazepam overdose, except in cases where it is consumed with large amounts of other depressants (such as alcohol or opioids).[65] Benzodiazepine drugs such as diazepam initially had widespread public support, but with time the view changed to one of growing criticism and calls for restrictions on their prescription.[95]

Diazepam was the top-selling pharmaceutical in the United States from 1969 to 1982, with peak sales in 1978 of 2.3 billion tablets.[94] Diazepam, along with oxazepam, nitrazepam and temazepam, represents 82% of the benzodiazepine market in Australia.[96] While psychiatrists continue to prescribe diazepam for the short-term relief of anxiety, neurology has taken the lead in prescribing diazepam for the palliative treatment of certain types of epilepsy and spastic activity, for example, forms of paresis. It is also the first line of defense for a rare disorder called stiff-person syndrome.[16]

## Society and culture [edit]

### Recreational use [edit]

*See also: Benzodiazepine drug misuse*

Diazepam is a drug of potential abuse and can cause drug dependence. Urgent action by national governments has been recommended to improve prescribing patterns of benzodiazepines such as diazepam.[97][98] A single dose of diazepam modulates the dopamine system in similar ways to how morphine and alcohol modulate the dopaminergic pathways.[99] Between 50 and 64% of rats will self-administer diazepam.[100] Diazepam has been shown to be able to substitute for the behavioural effects of barbiturates in a primate study.[101] Diazepam has been found as an adulterant in heroin.[102]

Diazepam drug misuse can occur either through recreational misuse where the drug is taken to achieve a high or when the drug is continued long term against medical advice.[103]

Sometimes, it is used by stimulant users to "come down" and sleep and to help control the urge to binge.[104]

A large-scale study in the US, conducted by SAMHSA, using data from 2011, determined benzodiazepines were present in 28.7% of emergency department visits involving nonmedical use of pharmaceuticals. In this regard, benzodiazepines are second only to opiates, the study found in 39.2% of visits. About 29.3% of drug-related suicide attempts involve benzodiazepines, making them the most frequently represented class in drug-related suicide attempts. Males abuse benzodiazepines as commonly as females.[105]

Benzodiazepines, including diazepam, nitrazepam, and flunitrazepam, account for the largest volume of forged drug prescriptions in Sweden, a total of 52% of drug forgeries being for benzodiazepines.[106]

Diazepam was detected in 26% of cases of people suspected of driving under the influence of drugs in Sweden, and its active metabolite nordazepam was detected in 28% of cases. Other benzodiazepines and zolpidem and zopiclone also were found in high numbers. Many drivers had blood levels far exceeding the therapeutic dose range, suggesting a high degree of abuse potential for benzodiazepines and zolpidem and zopiclone.[90] In Northern Ireland in cases where drugs were detected in samples from impaired drivers who were not impaired by alcohol, benzodiazepines were found in 87% of cases. Diazepam was the most commonly detected benzodiazepine.[107]

### Legal status [edit]

Diazepam is regulated in most countries as a prescription drug:

- International: diazepam is a Schedule IV controlled drug under the Convention on Psychotropic Substances.[108]
- UK: classified as a controlled drug, listed under Schedule IV, Part I (CD Benz POM) of the Misuse of Drugs Regulations 2001, allowing possession with a valid prescription. The Misuse of Drugs Act 1971 makes it illegal to possess the drug without a prescription, and for such purposes it is classified as a Class C drug.[109]
- Germany: classified as a prescription drug, or in high dosage as a restricted drug (*Betäubungsmittelgesetz, Anhang III*).[110]
- Australia: Diazepam is Schedule 4 substance under the Poisons Standard (October 2015).[111] A schedule 4 drug is outlined in the Poisons Act 1964 as, "Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription." [111]
- US: Diazepam is controlled as a Schedule IV substance under the Controlled Substances Act of 1970

### Judicial executions [edit]

The states of California and Florida offer diazepam to condemned inmates as a pre-execution sedative as part of their lethal injection program, although the state of California has not executed a prisoner since 2006.[112][113]

## Veterinary uses [edit]

Diazepam is used as a short-term sedative and anxiolytic for cats and dogs,[114] sometimes used as an appetite stimulant.[114][115] It can also be used to stop seizures in dogs and cats.[116][117]

## References [edit]


1. ^ *Clinical Addiction Psychiatry*. Cambridge University Press. 2010. p. 156. ISBN 9781139491693.
2. ^ Ries, Richard K. (2009). *Principles of addiction medicine.* (4 ed.). Philadelphia: Wolters

KI (2005). "Predictors of benzodiazepine discontinuation in subjects manifesting complicated dependence". *Substance Use & Misuse*. **40** (4): 499–510. doi:10.1081/JA-200052433.

Kluwer/Lippincott Williams & Wilkins. p. 106. ISBN 9780781774772.
3. ^ a b c d e Calcaterra, NE; Barrow, JC (16 April 2014). "Classics in chemical neuroscience: diazepam (valium).". *ACS Chemical Neuroscience*. **5** (4): 253–60. doi:10.1021/cn5000056. PMID 24552479.
4. ^ "Diazepam". *PubChem*. National Institute of Health: National Library of Medicine. 2006. Retrieved 2006-03-11.
5. ^ a b c d e f g "Diazepam". The American Society of Health-System Pharmacists. Retrieved Jun 5,15. Check date values in: |access-date= (help)
6. ^ Ogle, guest editors, Harry Dym, Orrett E. (2012). *Oral surgery for the general dentist*. Philadelphia: Saunders. p. 8. ISBN 9781455710324.
7. ^ a b c d e f g h i j k l m n o p q r s t Riss J, Cloyd J, Gates J, Collins S (August 2008). "Benzodiazepines in epilepsy: pharmacology and pharmacokinetics". *Acta Neurologica Scandinavica*. **118** (2): 69–86. doi:10.1111/j.1600-0404.2008.01004.x. PMID 18384456.
8. ^ Perkin, Ronald M. (2008). *Pediatric hospital medicine : textbook of inpatient management* (2nd ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 862. ISBN 9780781770323.
9. ^ "WHO Model List of Essential Medicines" (PDF). World Health Organization. March 2005. Retrieved 2006-03-12.
10. ^ "Diazepam". *International Drug Price Indicator Guide*. Retrieved 2 December 2015.
11. ^ a b c d e "Drug Bank – Diazepam". Archived from the original on December 24, 2006.
12. ^ Bråthen G, Ben-Menachem E, Brodtkorb E, Galvin R, Garcia-Monco JC, Halasz P, Hillbom M, Leone MA, Young AB (August 2005). "EFNS guideline on the diagnosis and management of alcohol-related seizures: report of an EFNS task force". *European Journal of Neurology*. **12** (8): 575–81. doi:10.1111/j.1468-1331.2005.01247.x. PMID 16053464.
13. ^ Cesarani A, Alpini D, Monti B, Raponi G (March 2004). "The treatment of acute vertigo". *Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 25 Suppl 1: S26–30. doi:10.1007/s10072-004-0213-8. PMID 15045617.
14. ^ Lader M, Tylee A, Donoghue J (2009). "Withdrawing benzodiazepines in primary care". *CNS Drugs*. **23** (1): 19–34. doi:10.2165/0023210-200923010-00002. PMID 19062773.
15. ^ Okoromah CN, Lesi FE (2004). Okoromah, Christy AN, ed. "Diazepam for treating tetanus". *The Cochrane Database of Systematic Reviews* (1): CD003954. doi:10.1002/14651858.CD003954.pub2. PMID 14974046.
16. ^ a b c "Diazepam: indications". *Rxlist.com*. RxList PMID 15830732.
64. ^ a b "Diazepam: overdose". *Rxlist.com*. RxList Inc. January 24, 2005. Retrieved 2006-03-10.
65. ^ a b c Barondes SH (2003). *Better Than Prozac*. New York: Oxford University Press. pp. 47–59. ISBN 0-19-515130-5.
66. ^ Greenblatt DJ, Woo E, Allen MD, Orsulak PJ, Shader RI (October 1978). "Rapid recovery from massive diazepam overdose". *JAMA: The Journal of the American Medical Association*. **240** (17): 1872–4. doi:10.1001/jama.240.17.1872. PMID 357765.
67. ^ Lai SH, Yao YJ, Lo DS (October 2006). "A survey of buprenorphine related deaths in Singapore". *Forensic Science International*. **162** (1–3): 80–6. doi:10.1016/j.forsciint.2006.03.037. PMID 16879940.
68. ^ a b c d Holt, Gary A. (1998). *Food and Drug Interactions: A Guide for Consumers*. Chicago: Precept Press. pp. 90–91. ISBN 0-944496-59-8.
69. ^ Zácková P, Květina J, Němec J, Němcová J (December 1982). "Cardiovascular effects of diazepam and nitrazepam in combination with ethanol". *Die Pharmazie*. **37** (12): 853–6. PMID 7163374.
70. ^ Back DJ, Orme ML (June 1990). "Pharmacokinetic drug interactions with oral contraceptives". *Clinical Pharmacokinetics*. **18** (6): 472–84. doi:10.2165/00003088-199018060-00004. PMID 2191822.
71. ^ Bendarzewska-Nawrocka B, Pietruszewska E, Stepień L, Bidziński J, Bacia T (January–February 1980). "[Relationship between blood serum luminal and diphenylhydantoin level and the results of treatment and other clinical data in drug-resistant epilepsy]". *Neurologia I Neurochirurgia Polska*. **14** (1): 39–45. PMID 7374896.
72. ^ Bateman DN (1986). "The action of cisapride on gastric emptying and the pharmacodynamics and pharmacokinetics of oral diazepam". *European Journal of Clinical Pharmacology*. **30** (2): 205–8. doi:10.1007/BF00614304. PMID 3709647.
73. ^ Mattila MJ, Nuotto E (1983). "Caffeine and theophylline counteract diazepam effects in man". *Medical Biology*. **61** (6): 337–43. PMID 6374311.
74. ^ "Possible Interactions with: Valerian". *University of Maryland Medical Center*. May 13, 2013. Retrieved December 12, 2014.
75. ^ Braestrup C, Squires RF (1 April 1978). "Pharmacological characterization of benzodiazepine receptors in the brain". *European Journal of Pharmacology*. **48** (3): 263–70. doi:10.1016/0014-2999(78)90085-7. PMID 639854.
76. ^ Chweh AY, Swinyard EA, Wolf HH, Kupferberg HJ (February 25, 1985). "Effect of GABA agonists on the neurotoxicity and anticonvulsant activity of benzodiazepines". *Life Sciences*. **36** (8): 737–44. doi:10.1016/0024-3205(85)90193-6. PMID 2983169.
77. ^ Battistin L, Varotto M, Berlese G, Roman G

Inc. January 24, 2005. Retrieved 2006-03-11.
17. ^ a b c d e f g h i Thomson Healthcare (Micromedex) (March 2000). "Diazepam". *Prescription Drug Information*. Drugs.com. Retrieved 2006-03-11.
18. ^ a b c d e f g h i j k l m n o p Pere Munne (1998). M. Ruse, ed. "Diazepam". *Inchem.org*. Inchem.org. Retrieved 2006-03-11.
19. ^ Kindwall, Eric P.; Whelan, Harry T. (1999). *Hyperbaric Medicine Practice* (2nd ed.). Best Publishing Company. ISBN 0-941332-78-0.
20. ^ Walker M (September 2005). "Status epilepticus: an evidence based guide". *BMJ (Clinical Research Ed.)*. **331** (7518): 673–7. doi:10.1136/bmj.331.7518.673. PMC 1226249. PMID 16179702.
21. ^ Prasad K, Al-Roomi K, Krishnan PR, Sequeira R (2005). "Anticonvulsant therapy for status epilepticus". *The Cochrane Database of Systematic Reviews* (4): CD003723. doi:10.1002/14651858.CD003723.pub2. PMID 16235337.
22. ^ Isojärvi JI, Tokola RA (December 1998). "Benzodiazepines in the treatment of epilepsy in people with intellectual disability". *Journal of Intellectual Disability Research : JIDR*. 42 Suppl 1: 80–92. PMID 10030438.
23. ^ Bajgar J (2004). "Organophosphates/nerve agent poisoning: mechanism of action, diagnosis, prophylaxis, and treatment". *Advances in Clinical Chemistry*. Advances in Clinical Chemistry. **38**: 151–216. doi:10.1016/S0065-2423(04)38006-6. ISBN 978-0-12-010338-6. PMID 15521192.
24. ^ Offringa, M; Newton, R (18 April 2012). "Prophylactic drug management for febrile seizures in children.". *The Cochrane database of systematic reviews*. **4**: CD003031. doi:10.1002/14651858.CD003031.pub2. PMID 22513908.
25. ^ Kaplan PW (November 2004). "Neurologic aspects of eclampsia". *Neurologic Clinics*. **22** (4): 841–61. doi:10.1016/j.ncl.2004.07.005. PMID 15474770.
26. ^ Duley L (February 2005). "Evidence and practice: the magnesium sulphate story". *Best Practice & Research. Clinical Obstetrics & Gynaecology*. **19** (1): 57–74. doi:10.1016/j.bpobgyn.2004.10.010. PMID 15749066.
27. ^ Zeilhofer HU, Witschi R, Hösl K (May 2009). "Subtype-selective GABAA receptor mimetics—novel antihyperalgesic agents?". *Journal of Molecular Medicine (Berlin, Germany)*. **87** (5): 465–9. doi:10.1007/s00109-009-0454-3. PMID 19259638.
28. ^ Mezaki T, Hayashi A, Nakase H, Hasegawa K (September 2005). "[Therapy of dystonia in Japan]". *Rinshō Shinkeigaku = Clinical Neurology* (in Japanese). **45** (9): 634–42. PMID 16248394.
29. ^ Kachi T (December 2001). "[Medical treatment of dystonia]". *Rinshō Shinkeigaku = Clinical Neurology* (in Japanese). **41** (12): 1181–2. PMID 12235832.
(February 1984). "Effects of some anticonvulsant drugs on brain GABA level and GAD and GABA-T activities". *Neurochemical Research*. **9** (2): 225–31. doi:10.1007/BF00964170. PMID 6429560.
78. ^ Taft WC, DeLorenzo RJ (May 1984). "Micromolar-affinity benzodiazepine receptors regulate voltage-sensitive calcium channels in nerve terminal preparations" (PDF). *Proceedings of the National Academy of Sciences of the United States of America* (PDF). **81** (10): 3118–22. doi:10.1073/pnas.81.10.3118. PMC 345232. PMID 6328498.
79. ^ Miller JA, Richter JA (January 1985). "Effects of anticonvulsants in vivo on high affinity choline uptake in vitro in mouse hippocampal synaptosomes". *British Journal of Pharmacology*. **84** (1): 19–25. doi:10.1111/j.1476-5381.1985.tb17368.x. PMC 1987204. PMID 3978310.
80. ^ Gallager DW, Mallorga P, Oertel W, Henneberry R, Tallman J (February 1981). "[3H]Diazepam binding in mammalian central nervous system: a pharmacological characterization". *The Journal of Neuroscience*. **1** (2): 218–25. PMID 6267221.
81. ^ Oishi R, Nishibori M, Itoh Y, Saeki K (May 27, 1986). "Diazepam-induced decrease in histamine turnover in mouse brain". *European Journal of Pharmacology*. **124** (3): 337–42. doi:10.1016/0014-2999(86)90236-0. PMID 3089825.
82. ^ Grandison L (1982). "Suppression of prolactin secretion by benzodiazepines in vivo". *Neuroendocrinology*. **34** (5): 369–73. doi:10.1159/000123330. PMID 6979001.
83. ^ Tan, Kelly R.; Rudolph, Uwe; Lüscher, Christian (2011). "Hooked on benzodiazepines: $GABA_A$ receptor subtypes and addiction" (PDF). *University of Geneva*. Retrieved December 12, 2014.
84. ^ Whirl-Carrillo, M; McDonagh, EM; Hebert, JM; Gong, L; Sangkuhl, K; Thorn, CF; Altman, RB; Klein, TE (2012). "Pharmacogenomics Knowledge for Personalized Medicine". *Clinical Pharmacology & Therapeutics*. **92** (4): 414–417. doi:10.1038/clpt.2012.96. PMC 3660037. PMID 22992668.
85. ^ Zakusov VV, Ostrovskaya RU, Kozhechkin SN, Markovich VV, Molodavkin GM, Voronina TA (October 1977). "Further evidence for GABA-ergic mechanisms in the action of benzodiazepines". *Archives Internationales de Pharmacodynamie et de Thérapie*. **229** (2): 313–26. PMID 23084.
86. ^ McLean MJ, Macdonald RL (February 1988). "Benzodiazepines, but not beta carbolines, limit high frequency repetitive firing of action potentials of spinal cord neurons in cell culture". *The Journal of Pharmacology and Experimental Therapeutics*. **244** (2): 789–95. PMID 2450203.
87. ^ Date SK, Hemavathi KG, Gulati OD (November 1984). "Investigation of the muscle relaxant activity of nitrazepam". *Archives Internationales de Pharmacodynamie et de Thérapie*. **272** (1): 129–39.

30. ^ Ashton H (2005). "The diagnosis and management of benzodiazepine dependence" (PDF). *Current Opinion in Psychiatry*. **18** (3): 249–55. doi:10.1097/01.yco.0000165594.60434.84. PMID 16639148.
31. ^ Mañon-Espaillat R, Mandel S (1999). "Diagnostic algorithms for neuromuscular diseases". *Clinics in Podiatric Medicine and Surgery*. **16** (1): 67–79. PMID 9929772.
32. ^ "International AED Database". ILAE. Retrieved 2009-09-16.
33. ^ *a b c d* Mikota, Susan K.; Plumb, Donald C. (2005). "Diazepam". *The Elephant Formulary*. Elephant Care International.
34. ^ "Delivery of diazepam through an inhalation route". *US Patent 6,805,853*. PharmCast.com. October 19, 2004. Retrieved December 12, 2014.
35. ^ U.S. Army Medical Research Institute of Chemical Defense, *Medical Management of Chemical Casualties Handbook*, Third Edition (June 2000), Aberdeen Proving Ground, MD, pp. 118–126.
36. ^ Epocrates. "Diazepam Contraindications and Cautions". US: Epocrates Online. Retrieved 16 December 2008.
37. ^ Authier N, Balayssac D, Sautereau M, Zangarelli A, Courty P, Somogyi AA, Vennat B, Llorca PM, Eschalier A (November 2009). "Benzodiazepine dependence: focus on withdrawal syndrome". *Annales Pharmaceutiques Françaises*. **67** (6): 408–13. doi:10.1016/j.pharma.2009.07.001. PMID 19900604.
38. ^ *a b c d e f g* "Diazepam". *PDRHealth.com*. PDRHealth.com. 2006. Archived from the original on 2006-01-17. Retrieved 2006-03-10.
39. ^ *a b* "Diazepam: precautions". *Rxlist.com*. RxList Inc. January 24, 2005. Retrieved 2006-03-10.
40. ^ Shats V, Kozacov S (June 1995). "[Falls in the geriatric department: responsibility of the care-giver and the hospital]". *Harefuah* (in Hebrew). **128** (11): 690–3, 743. PMID 7557666.
41. ^ Kanto JH (May 1982). "Use of benzodiazepines during pregnancy, labour and lactation, with particular reference to pharmacokinetic considerations". *Drugs*. **23** (5): 354–80. doi:10.2165/00003495-198223050-00002. PMID 6124415.
42. ^ McElhatton PR (1994). "The effects of benzodiazepine use during pregnancy and lactation". *Reproductive Toxicology (Elmsford, N.Y.)*. **8** (6): 461–75. doi:10.1016/0890-6238(94)90029-9. PMID 7881198.
43. ^ Yudofsky SC, Hales RE (1 December 2007). *The American Psychiatric Publishing Textbook of Neuropsychiatry and Behavioral Neurosciences, Fifth Edition (American Psychiatric Press Textbook of Neuropsychiatry)*. US: American Psychiatric Publishing, Inc. pp. 583–584. ISBN 978-1-58562-239-9.
44. ^ Whiting PJ (February 2006). "GABA-A receptors: a PMID 6517646.
88. ^ Olive G, Dreux C (January 1977). "Pharmacologic bases of use of benzodiazepines in peréinatal medicine". *Archives Françaises De Pédiatrie*. **34** (1): 74–89. PMID 851373.
89. ^ Vozeh S (November 21, 1981). "[Pharmacokinetic of benzodiazepines in old age]". *Schweizerische Medizinische Wochenschrift*. **111** (47): 1789–93. PMID 6118950.
90. ^ *a b* Jones AW, Holmgren A, Kugelberg FC (April 2007). "Concentrations of scheduled prescription drugs in blood of impaired drivers: considerations for interpreting the results". *Therapeutic Drug Monitoring*. **29** (2): 248–60. doi:10.1097/FTD.0b013e31803d3c04. PMID 17417081.
91. ^ Fraser AD, Bryan W (1991). "Evaluation of the Abbott ADx and TDx serum benzodiazepine immunoassays for analysis of alprazolam". *Journal of Analytical Toxicology*. **15** (2): 63–5. doi:10.1093/jat/15.2.63. PMID 1675703.
92. ^ Baselt R (2011). *Disposition of Toxic Drugs and Chemicals in Man* (9th ed.). Seal Beach, CA: Biomedical Publications. pp. 471–473. ISBN 978-0-9626523-8-7.
93. ^ Pollack, Andrew (June 26, 2012). "Roche to Shut Former U.S. Headquarters". *New York Times*. Retrieved January 10, 2014.
94. ^ *a b* Sample I (October 3, 2005). "Leo Sternbach's Obituary". The Guardian (Guardian Unlimited). Retrieved 2006-03-10.
95. ^ Marshall KP, Georgievskava Z, Georgievsky I (June 2009). "Social reactions to Valium and Prozac: a cultural lag perspective of drug diffusion and adoption". *Research in Social & Administrative Pharmacy : RSAP*. **5** (2): 94–107. doi:10.1016/j.sapharm.2008.06.005. PMID 19524858.
96. ^ Mant A, Whicker SD, McManus P, Birkett DJ, Edmonds D, Dumbrell D (December 1993). "Benzodiazepine utilisation in Australia: report from a new pharmacoepidemiological database". *Australian Journal of Public Health*. **17** (4): 345–9. doi:10.1111/j.1753-6405.1993.tb00167.x. PMID 7911332.
97. ^ Atack JR (May 2005). "The benzodiazepine binding site of GABA(A) receptors as a target for the development of novel anxiolytics". *Expert Opinion on Investigational Drugs*. **14** (5): 601–18. doi:10.1517/13543784.14.5.601. PMID 15926867.
98. ^ Dièye AM, Sylla M, Ndiaye A, Ndiaye M, Sy GY, Faye B (June 2006). "Benzodiazepines prescription in Dakar: a study about prescribing habits and knowledge in general practitioners, neurologists and psychiatrists". *Fundamental & Clinical Pharmacology*. **20** (3): 235–8. doi:10.1111/j.1472-8206.2006.00400.x. PMID 16671957.
99. ^ "New Evidence on Addiction To Medicines

viable target for novel anxiolytics?". *Current Opinion in Pharmacology*. **6** (1): 24–9. doi:10.1016/j.coph.2005.08.005. PMID 16359919.

45. ^ Kay DW, Fahy T, Garside RF (December 1970). "A seven-month double-blind trial of amitriptyline and diazepam in ECT-treated depressed patients". *The British Journal of Psychiatry*. **117** (541): 667–71. doi:10.1192/bjp.117.541.667. PMID 4923720.
46. ^ *a b* Langsam, Yedidyah. "DIAZEPAM (VALIUM AND OTHERS)". Brooklyn College (Eilat.sci.Brooklyn.CUNY.edu). Retrieved 2006-03-23.
47. ^ Marrosu F, Marrosu G, Rachel MG, Biggio G (1987). "Paradoxical reactions elicited by diazepam in children with classic autism". *Functional Neurology*. **2** (3): 355–61. PMID 2826308.
48. ^ "Diazepam: Side Effects". *RxList.com*. Retrieved September 26, 2006.
49. ^ Michel L, Lang JP (2003). "[Benzodiazepines and forensic aspects]". *L'Encéphale* (in French). **29** (6): 479–85. PMID 15029082.
50. ^ Berman ME, Jones GD, McCloskey MS (February 2005). "The effects of diazepam on human self-aggressive behavior". *Psychopharmacology*. **178** (1): 100–6. doi:10.1007/s00213-004-1966-8. PMID 15316710.
51. ^ Pérez Trullen JM, Modrego Pardo PJ, Vázquez André M, López Lozano JJ (1992). "Bromazepam-induced dystonia". *Biomedicine & Pharmacotherapy = Biomédecine & Pharmacothérapie*. **46** (8): 375–6. doi:10.1016/0753-3322(92)90306-R. PMID 1292648.
52. ^ Hriscu A, Gherase F, Năstasă V, Hriscu E (October–December 2002). "[An experimental study of tolerance to benzodiazepines]". . **106** (4): 806–811. PMID 14974234.
53. ^ Kozená L, Frantik E, Horváth M (May 1995). "Vigilance impairment after a single dose of benzodiazepines". *Psychopharmacology*. **119** (1): 39–45. doi:10.1007/BF02246052. PMID 7675948.
54. ^ MacKinnon GL, Parker WA (1982). "Benzodiazepine withdrawal syndrome: a literature review and evaluation". *The American Journal of Drug and Alcohol Abuse*. **9** (1): 19–33. doi:10.3109/00952998209002608. PMID 6133446.
55. ^ Onyett SR (April 1989). "The benzodiazepine withdrawal syndrome and its management". *The Journal of the Royal College of General Practitioners*. **39** (321): 160–3. PMC 1711840. PMID 2576073.
56. ^ Chouinard G, Labonte A, Fontaine R, Annable L (1983). "New concepts in benzodiazepine therapy: rebound anxiety and new indications for the more potent benzodiazepines". *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. **7** (4–6): 669–73. doi:10.1016/0278-5846(83)90043-X.

Diazepam Has Effect on Nerve Cells in the Brain Reward System". Medical News Today. August 2008. Retrieved September 25, 2008.

100. ^ Yoshimura K, Horiuchi M, Inoue Y, Yamamoto K (January 1984). "[Pharmacological studies on drug dependence. (III): Intravenous self-administration of some CNS-affecting drugs and a new sleep-inducer, 1H-1, 2, 4-triazolyl benzophenone derivative (450191-S), in rats]". *Nihon Yakurigaku Zasshi. Folia Pharmacologica Japonica*. **83** (1): 39–67. doi:10.1254/fpj.83.39. PMID 6538866.
101. ^ Woolverton WL, Nader MA (December 1995). "Effects of several benzodiazepines, alone and in combination with flumazenil, in rhesus monkeys trained to discriminate pentobarbital from saline". *Psychopharmacology*. **122** (3): 230–6. doi:10.1007/BF02246544. PMID 8748392.
102. ^ "Report of the International Narcotics Control Board for 1996" (PDF). *United Nations*. International Narcotics Control Board. 1996. p. 27. Retrieved December 12, 2014. "Phenobarbital was identified as the psychotropic substance most frequently used as an adulterant in seized heroin; it was followed by diazepam and flunitrazepam."
103. ^ Griffiths RR, Johnson MW (2005). "Relative abuse liability of hypnotic drugs: a conceptual framework and algorithm for differentiating among compounds". *The Journal of Clinical Psychiatry*. 66 Suppl 9: 31–41. PMID 16336040.
104. ^ Overclocker. "Methamphetamine and Benzodiazepines: Methamphetamine & Benzodiazepines". *Erowid Experience Vaults*. Retrieved September 26, 2006.
105. ^ U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration (2011). "Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits". Substance Abuse and Mental Health Services Administration. Archived from the original on 31 March 2008. Retrieved 20 April 2014.
106. ^ Bergman U, Dahl-Puustinen ML (1989). "Use of prescription forgeries in a drug abuse surveillance network". *European Journal of Clinical Pharmacology*. **36** (6): 621–3. doi:10.1007/BF00637747. PMID 2776820.
107. ^ Cosbey SH (December 1986). "Drugs and the impaired driver in Northern Ireland: an analytical survey". *Forensic Science International*. **32** (4): 245–58. doi:10.1016/0379-0738(86)90201-X. PMID 3804143.
108. ^ International Narcotics Control Board (2003). "List of psychotropic substances under international control" (PDF). *Green list*. Retrieved 2014-12-12.
109. ^ "List of Controlled Drugs".
110. ^ "Anlage III (zu § 1 Abs. 1) verkehrsfähige und verschreibungsfähige Betäubungsmittel". *Betäubungsmittelgesetz*. 2001. Retrieved 2010-01-05.
*a b*

PMID 6141609.
57. ^ Lader M (December 1987). "Long-term anxiolytic therapy: the issue of drug withdrawal". *The Journal of Clinical Psychiatry*. **48**: 12–6. PMID 2891684.
58. ^ Murphy SM, Owen R, Tyrer P (1989). "Comparative assessment of efficacy and withdrawal symptoms after 6 and 12 weeks' treatment with diazepam or buspirone". *The British Journal of Psychiatry*. **154** (4): 529–34. doi:10.1192/bjp.154.4.529. PMID 2686797.
59. ^ Loiseau P (1983). "[Benzodiazepines in the treatment of epilepsy]". *L'Encéphale*. **9** (4 Suppl 2): 287B–292B. PMID 6373234.
60. ^ "Treating Anxiety – Avoiding Dependence on Xanax, Klonopin, Valium, and Other Antianxiety Drugs". *johnshopkinshealthalerts.com*. Johnshopkinshealthalerts.com. 2005. Retrieved 2007-12-23.
61. ^ *a b* "Diazepam: abuse and dependence". *Rxlist.com*. RxList Inc. January 24, 2005. Retrieved 2006-03-10.
62. ^ Poulos CX, Zack M (November 2004). "Low-dose diazepam primes motivation for alcohol and alcohol-related semantic networks in problem drinkers". *Behavioural Pharmacology*. **15** (7): 503–12. doi:10.1097/00008877-200411000-00006. PMID 15472572.
63. ^ Vorma H, Naukkarinen HH, Sarna SJ, Kuoppasalmi
111. ^ Poisons Standard October 2015 https://www.comlaw.gov.au/Details/F2015L01534
112. ^ San Quentin State Prison Operational Procedure 0–770, Execution By Lethal Injection (pp. 44 & 92). Accessed January 10, 2014.
113. ^ "Execution by lethal injection procedures" (PDF). Florida Department of Corrections. 9 September 2013. Retrieved 25 August 2014.
114. ^ *a b* "Drugs Affecting Appetite (Monogastric)". The Merck Veterinary Manual. Retrieved 2014-01-04.
115. ^ Rahminiwati M, Nishimura M (April 1999). "Effects of delta 9-tetrahydrocannabinol and diazepam on feeding behavior in mice". *The Journal of Veterinary Medical Science / the Japanese Society of Veterinary Science*. **61** (4): 351–5. doi:10.1292/jvms.61.351. PMID 10342284.
116. ^ Linda Shell (March 2012). "Anticonvulsants Used to Stop Ongoing Seizure Activity". Retrieved 10 January 2014. "Dogs and Cats:
A variety of drugs can be used to stop seizures in dogs and cats.
Benzodiazepines:
Diazepam is the most common benzodiazepine used in dogs and cats to reduce motor activity and permit placement of an IV catheter."
117. ^ Hines, Ron DVM PhD (2006-01-14). "Epilepsy in Your Dog Or Cat". Second Chance Sanctuary Pet Health Center. Retrieved May 18, 2006.

## External links [edit]

- Roche Pharmaceuticals (AUS) – Valium Product Information
- US National Library of Medicine: Drug Information Portal – Diazepam
- Flash animation about how bromazepam works (mechanism of action)
- "Medication of the Month" at Albany Medical Center at the Wayback Machine (archived June 28, 2006)

Wikimedia Commons has media related to *Diazepam*.

| v · t · e · | **Anticonvulsants (N03)** | |
|---|---|---|
| **GABAergics** | **GABA$_A$R PAMs** | **Barbiturates:** Barbexaclone · Metharbital · Methylphenobarbital · Pentobarbital · Phenobarbital# · Primidone; **Carbamates**: Felbamate; **Benzodiazepines**: Clobazam · Clonazepam · Clorazepate · **Diazepam**# · Lorazepam# · Midazolam · Nimetazepam · Nitrazepam · Temazepam; **Others:** Bromide (potassium bromide, sodium bromide) · Paraldehyde · Stiripentol · |
| | **GABA-T inhibitors** | **Fatty acids:** Valproate · Valpromide · Valproate pivoxil; **Others:** Ethanolamine-*O*-sulfate · Vigabatrin · |
| | **Others** | **GABAR agonists**: Progabide; **GAT-1 inhibitors:** Tiagabine · |
| | **Sodium blockers** | **Hydantoins:** Ethotoin · Fosphenytoin · Mephenytoin · Phenytoin#; **Ureides:** Acetylpheneturide · Chlorphenacemide · Phenacemide‡ · Pheneturide; **Fatty acids:** Valproate · Valpromide · Valproate pivoxil; |

#

| | | |
|---|---|---|
| **Channelergics** | | **Carboxamides:** Carbamazepine · Eslicarbazepine acetate · Oxcarbazepine; **Others:** Lacosamide · Lamotrigine · Rufinamide · Topiramate · Zonisamide · |
| | **Calcium blockers** | **Oxazolidinediones:** Ethadione · Paramethadione · Trimethadione; **Succinimides**: Ethosuximide[#] · Mesuximide · Phensuximide; **Gabapentinoids:** Gabapentin · Pregabalin; **Others:** Lamotrigine · Topiramate · Zonisamide · |
| | **Potassium openers** | Retigabine · |
| **Others** | **CA inhibitors** | **Sulfonamides:** Acetazolamide · Ethoxzolamide · Sultiame · Topiramate · Zonisamide · |
| | **Others** | Beclamide · Brivaracetam · Levetiracetam · Perampanel · |

[#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III · ·

| v · t · e · | **Antidotes (V03AB)** | |
|---|---|---|
| **Nervous system** | **Nerve agent / Organophosphate poisoning** | Atropine[#] · Biperiden · **Diazepam**[#] · Oximes (Obidoxime · Pralidoxime · · *see also:* Cholinesterase · |
| | **Barbiturate overdose** | Bemegride · Ethamivan · |
| | **Benzodiazepine overdose** | Cyprodenate · Flumazenil · |
| | **GHB overdose** | Physostigmine · SCH-50911 · |
| | **Opioid overdose** | Diprenorphine · Doxapram · Nalmefene · Nalorphine · Naloxone[#] · Naltrexone · |
| | **Reversal of neuromuscular blockade** | Sugammadex · |
| **Circulatory system** | **Beta blocker** | Glucagon · |
| | **Digoxin toxicity** | Digoxin Immune Fab · |
| | **Heparin** | Protamine[#] · |
| **Other** | **Arsenic poisoning** | Dimercaprol[#] · Succimer · |
| | **Cyanide poisoning** | 4-Dimethylaminophenol · Hydroxocobalamin · *nitrite* (Amyl nitrite · Sodium nitrite[#] · · Sodium thiosulfate[#] · |
| | **Hydrofluoric acid** | Calcium gluconate[#] · |
| | **Methanol / Ethylene glycol poisoning** | Primary alcohols: Ethanol · Fomepizole · |
| | **Paracetamol toxicity (Acetaminophen)** | Acetylcysteine[#] · Glutathione · Methionine[#] · |
| | **Toxic metals (cadmium · lead · mercury · thallium) ·** | Dimercaprol[#] · Edetates · Prussian blue[#] · |

| | | |
|---|---|---|
| | **Other** | *iodine-131* (Potassium iodide · · Methylthioninium chloride[#] · *oxidizing agent* (Potassium permanganate · · Prednisolone/promethazine · |
| **Emetic** | Copper sulfate · Ipecacuanha (Syrup of ipecac · · | |

[#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III · ·

| v · t · e · | **Anxiolytics (N05B)** |
|---|---|
| **5-HT$_{1A}$ agonists** | Buspirone · Tandospirone · |
| **GABA$_A$R PAMs** | **Benzodiazepines:** · Adinazolam · Alprazolam · Bromazepam · Camazepam · Chlordiazepoxide · Clobazam · Clonazepam · Clorazepate · Clotiazepam · Cloxazolam · **Diazepam**[#] · Ethyl loflazepate · Etizolam · Fludiazepam · Halazepam · Ketazolam · Lorazepam[#] · Medazepam · Nordazepam · Oxazepam · Pinazepam · Prazepam · **Others:** Alpidem[‡] · Barbiturates · Carbamates · Chlormezanone[‡] · Ethanol · Etifoxine; *Herbs:* · Kava · Skullcap · Valerian · |
| **α$_2$δ VDCC blockers** | Gabapentin · Gabapentin enacarbil · Phenibut · Pregabalin · |
| **Antidepressants** | SSRIs · SNRIs · SARIs · TCAs · TeCAs · MAOIs; *Others:* Agomelatine · Bupropion · Vilazodone · Vortioxetine · |
| **Sympatholytics** | Beta blockers (e.g., propranolol) · Clonidine · Dexmedetomidine · Guanfacine · Prazosin · |
| **Others** | Benzoctamine · Cannabidiol · Cycloserine · Fabomotizole · Hydroxyzine · Kanna · Lavender · Lorpiprazole · Mebicar · Mepiprazole · Nicotine · Opipramol · Oxaflozane[‡] · Phenaglycodol · Phenibut · Picamilon · Selank · Tiagabine · Tofisopam · Validolum · |

| v · t · e · | **Benzodiazepines** |
|---|---|
| **1,4-Benzodiazepines** | 2-Oxoquazepam · 3-Hydroxyphenazepam · Bromazepam · Camazepam · Carburazepam · Chlordiazepoxide · Cinazepam · Cinolazepam · Clonazepam · Clorazepate · Cyprazepam · Delorazepam · Demoxepam · Desmethylflunitrazepam · Devazepide* · **Diazepam** · Diclazepam · Doxefazepam · Elfazepam · Ethyl carfluzepate · Ethyl dirazepate · Ethyl loflazepate · Flubromazepam · Fletazepam · Fludiazepam · Flunitrazepam · Flurazepam · Flutemazepam · Flutoprazepam · Fosazepam · Gidazepam · Halazepam · Iclazepam · Irazepine · Kenazepine · Ketazolam · Lorazepam · Lormetazepam · Lufuradom* · Meclonazepam · Medazepam · Menitrazepam · Metaclazepam · Motrazepam · *N*-Desalkylflurazepam · Nifoxipam · Nimetazepam · Nitrazepam · Nitrazepate · Nordazepam · Nortetrazepam · Oxazepam · Phenazepam · Pinazepam · Pivoxazepam · Prazepam · Proflazepam · Quazepam · QH-II-66 · Reclazepam · RO4491533* · Ro5-4864* · Sulazepam · Temazepam · Tetrazepam · Tifluadom* · Tolufazepam · Triflunordazepam · Tuclazepam · Uldazepam · |
| **1,5-Benzodiazepines** | Arfendazam · Clobazam · CP-1414S · Lofendazam · Triflubazam · |
| **2,3-Benzodiazepines*** | Girisopam · GYKI-52466 · GYKI-52895 · Nerisopam · Talampanel · Tofisopam · |
| **Triazolobenzodiazepines** | Adinazolam · Alprazolam · Clonazolam · Estazolam · Flubromazolam · Nitrazolam · Pyrazolam · Triazolam · |

| | |
|---|---|
| **Imidazobenzodiazepines** | Bretazenil · Climazolam · EVT-201 · FG-8205 · Flumazenil · Imidazenil · $^{123}$I-Iomazenil · L-655,708 · Loprazolam · Midazolam · PWZ-029 · Remimazolam · Ro15-4513 · Ro48-6791 · Ro48-8684 · Ro4938581 · Sarmazenil · SH-053-R-CH3-2′F · |
| **Oxazolobenzodiazepines** | Cloxazolam · Flutazolam · Haloxazolam · Mexazolam · Oxazolam · |
| **Thienodiazepines** | Bentazepam · Clotiazepam · |
| **Thienotriazolodiazepines** | Brotizolam · Ciclotizolam · Deschloroetizolam · Etizolam · Israpafant* · JQ1* · Metizolam · |
| **Thienobenzodiazepines*** | Olanzapine · Telenzepine · |
| **Pyridodiazepines** | Lopirazepam · |
| **Pyridotriazolodiazepines** | Zapizolam · |
| **Pyrazolodiazepines** | Razobazam* · Ripazepam · Zolazepam · Zomebazam · Zometapine* · |
| **Pyrrolodiazepines** | Premazepam · |
| **Tetrahydroisoquinobenzodiazepines** | Clazolam · |
| **Pyrrolobenzodiazepines*** | Anthramycin · |
| **Benzodiazepine prodrugs** | Avizafone · Rilmazafone · |

* atypical activity profile (not $GABA_A$ receptor ligands)

| v · t · e · | **$GABA_A$ receptor positive allosteric modulators** |
|---|---|
| **Alcohols** | Brometone · Butanol · Chloralodol · Chlorobutanol (cloretone) · Ethanol (drinking alcohol) · Ethchlorvynol · Isobutanol · Isopropanol · Menthol · Methanol · Methylpentynol · Pentanol · Petrichloral · Propanol · *tert*-Butanol (2M2P) · *tert*-Pentanol (2M2B) · Tribromoethanol · Trichloroethanol · Triclofos · Trifluoroethanol · |
| **Barbiturates** | (-)-DMBB · Allobarbital · Alphenal · Amobarbital · Aprobarbital · Barbexaclone · Barbital · Benzobarbital · Benzylbutylbarbiturate · Brallobarbital · Brophebarbital · Butabarbital/Secbutabarbital · Butalbital · Buthalital · Butobarbital · Butallylonal · Carbubarb · CP-1414S · Crotylbarbital · Cyclobarbital · Cyclopentobarbital · Difebarbamate · Enallylpropymal · Ethallobarbital · Eterobarb · Febarbamate · Heptabarb · Heptobarbital · Hexethal · Hexobarbital · Metharbital · Methitural · Methohexital · Methylphenobarbital · Narcobarbital · Nealbarbital · Pentobarbital · Phenallymal · Phenobarbital · Phetharbital · Primidone · Probarbital · Propallylonal · Propylbarbital · Proxibarbital · Reposal · Secobarbital · Sigmodal · Spirobarbital · Talbutal · Tetrabamate · Tetrabarbital · Thialbarbital · Thiamylal · Thiobarbital · Thiobutabarbital · Thiopental · Thiotetrabarbital · Valofane · Vinbarbital · Vinylbital · |
| | 2-Oxoquazepam · 3-Hydroxyphenazepam · Adinazolam · Alprazolam · Arfendazam · Avizafone · Bentazepam · Bretazenil · Bromazepam · Brotizolam · Camazepam · Carburazepam · Chlordiazepoxide · Ciclotizolam · Cinazepam · Cinolazepam · Clazolam · Climazolam · Clobazam · Clonazepam · Clonazolam · Clorazepate · Clotiazepam · Cloxazolam · Cyprazepam · Delorazepam · Demoxepam · **Diazepam** · Diclazepam · Doxefazepam · Elfazepam · Estazolam · Ethyl carfluzepate · Ethyl dirazepate · Ethyl loflazepate · Etizolam · EVT-201 · FG-8205 · Fletazepam · Flubromazepam · Flubromazolam · Fludiazepam · Flunitrazepam · Flurazepam · Flutazolam · Flutemazepam · Flutoprazepam · Fosazepam · Gidazepam · |

| | |
|---|---|
| **Benzodiazepines** | Halazepam • Haloxazolam • Iclazepam • Imidazenil • Irazepine • Ketazolam • Lofendazam • Lopirazepam • Loprazolam • Lorazepam • Lormetazepam • Meclonazepam • Medazepam • Menitrazepam • Metaclazepam • Mexazolam • Midazolam • Motrazepam • N-Desalkylflurazepam • Nifoxipam • Nimetazepam • Nitrazepam • Nitrazepate • Nitrazolam • Nordazepam • Nortetrazepam • Oxazepam • Oxazolam • Phenazepam • Pinazepam • Pivoxazepam • Prazepam • Premazepam • Proflazepam • Pyrazolam • QH-II-66 • Quazepam • Reclazepam • Remimazolam • Rilmazafone • Ripazepam • Ro48-6791 • Ro48-8684 • SH-053-R-CH3-2′F • Sulazepam • Temazepam • Tetrazepam • Tolufazepam • Triazolam • Triflubazam • Triflunordazepam (Ro5-2904) • Tuclazepam • Uldazepam • Zapizolam • Zolazepam • Zomebazam • |
| **Carbamates** | Carisbamate • Carisoprodol • Clocental • Cyclarbamate • Difebarbamate • Emylcamate • Ethinamate • Febarbamate • Felbamate • Hexapropymate • Lorbamate • Mebutamate • Meprobamate • Nisobamate • Pentabamate • Phenprobamate • Procymate • Styramate • Tetrabamate • Tybamate • |
| **Flavonoids** | 6-Methylapigenin • Ampelopsin (dihydromyricetin) • Apigenin • Baicalein • Baicalin • Catechin • EGC • EGCG • Hispidulin • Linarin • Luteolin • Rc-OMe • Skullcap constituents (e.g., baicalin) • Wogonin • |
| **Imidazoles** | Etomidate • Metomidate • Propoxate • |
| **Kava constituents** | 10-Methoxyyangonin • 11-Methoxyyangonin • 11-Hydroxyyangonin • Desmethoxyyangonin • 11-Methoxy-12-hydroxydehydrokavain • 7,8-Dihydroyangonin • Kavain • 5-Hydroxykavain • 5,6-Dihydroyangonin • 7,8-Dihydrokavain • 5,6,7,8-Tetrahydroyangonin • 5,6-Dehydromethysticin • Methysticin • 7,8-Dihydromethysticin • Yangonin • |
| **Monoureides** | Acecarbromal • Apronal (apronalide) • Bromisoval • Carbromal • Capuride • Ectylurea • |
| **Neuroactive steroids** | Acebrochol • Allopregnanolone (SAGE-547) • Alfadolone • Alfaxalone • Anabolic steroids • 3α-Androstanediol • Androstenol • Androsterone • Cholesterol • DHDOC • 3α-DHP • 5α-DHP • 5β-DHP • DHT • Etiocholanolone • Ganaxolone • Hydroxydione • Minaxolone • Org 20599 • Org 21465 • P1-185 • Pregnanolone (eltanolone) • Progesterone • Renanolone • SAGE-105 • SAGE-217 • SAGE-324 • SAGE-516 • SAGE-689 • SAGE-872 • Testosterone • THDOC • |
| **Nonbenzodiazepines** | **β-Carbolines**: Abecarnil • Gedocarnil • Harmane • SL-651,498 • ZK-93423; **Cyclopyrrolones**: Eszopiclone • Pagoclone • Pazinaclone • Suproclone • Suriclone • Zopiclone; **Imidazopyridines**: Alpidem • DS-1 • Necopidem • Saripidem • Zolpidem; **Pyrazolopyrimidines**: Divaplon • Fasiplon • Indiplon • Lorediplon • Ocinaplon • Panadiplon • Taniplon • Zaleplon; **Others**: Adipiplon • CGS-8216 • CGS-9896 • CGS-13767 • CGS-20625 • CL-218,872 • CP-615,003 • CTP-354 • ELB-139 • GBLD-345 • JM-1232 • L-838,417 • Lirequinil (Ro41-3696) • NS-2664 • NS-2710 • NS-11394 • Pipequaline • ROD-188 • RWJ-51204 • SB-205,384 • SX-3228 • TGSC01AA • TP-003 • TPA-023 • TP-13 • U-89843A • U-90042 • Viqualine • Y-23684 • |
| **Phenols** | Fospropofol • Propofol • Thymol • |
| **Piperidinediones** | Glutethimide • Methyprylon • Piperidione • Pyrithyldione • |
| **Pyrazolopyridines** | Cartazolate • Etazolate • ICI-190,622 • Tracazolate • |
| **Quinazolinones** | Afloqualone • Cloroqualone • Diproqualone • Etaqualone • Mebroqualone • Mecloqualone • Methaqualone • Methylmethaqualone • Nitromethaqualone • SL-164 • |
| | Acetone • Acetophenone • Acetylglycinamide chloral hydrate • Aliflurane • Benzene • Butane • |

| | |
|---|---|
| **Volatiles/gases** | Butylene · Centalun · Chloral · Chloral betaine · Chloral hydrate · Chloroform · Cryofluorane · Desflurane · Dichloralphenazone · Dichloromethane · Diethyl ether · Enflurane · Ethyl chloride · Ethylene · Fluroxene · Gasoline · Halopropane · Halothane · Isoflurane · Kerosine · Methoxyflurane · Methoxypropane · Nitric oxide · Nitrogen · Nitrous oxide · Norflurane · Paraldehyde · Propane · Propylene · Roflurane · Sevoflurane · Synthane · Teflurane · Toluene · Trichloroethane (methyl chloroform) · Trichloroethylene · Vinyl ether · |
| **Others/unsorted** | 3-Hydroxybutanal · α-EMTBL · AA-29504 · Avermectins (e.g., ivermectin) · Bromide compounds (e.g., lithium bromide, potassium bromide, sodium bromide) · Carbamazepine · Chloralose · Chlormezanone · Clomethiazole · DEABL · Dihydroergolines (e.g., dihydroergocryptine, dihydroergosine, dihydroergotamine, ergoloid (dihydroergotoxine)) · DS2 · Efavirenz · Etazepine · Etifoxine · Fenamates (e.g., flufenamic acid, mefenamic acid, niflumic acid, tolfenamic acid) · Fluoxetine · Flupirtine · Hopantenic acid · Lanthanum · Lavender oil · Lignans (e.g., 4-O-methylhonokiol, honokiol, magnolol, obovatol) · Loreclezole · Menthyl isovalerate (validolum) · Monastrol · Niacin · Nicotinamide (niacinamide) · Org 25,435 · Phenytoin · Propanidid · Retigabine (ezogabine) · Safranal · Seproxetine · Stiripentol · Sulfonylalkanes (e.g., sulfonmethane (sulfonal), tetronal, trional) · Terpenoids (e.g., borneol) · Topiramate · Valerian constituents (e.g., isovaleric acid, isovaleramide, valerenic acid, valerenol) · **Unsorted benzodiazepine site PAMs:** MRK-409 (MK-0343) · TCS-1105 · TCS-1205 · |
| *See also: GABAergics* | |

| v · t · e · | **Glycinergics** |
|---|---|
| **Receptor (ligands)** | **GlyR** |
| | **Agonists:** β-Alanine · β-ABA (BABA) · β-AIBA · Caesium · D-Alanine · D-Serine · GABA · Glycine · Hypotaurine · Ivermectin · L-Alanine · L-Proline · L-Serine · L-Threonine · MDL-27531 · Milacemide · Picolinic acid · Propofol · Quisqualamine · Sarcosine · Taurine · |
| | **PAMs:** Alcohols (e.g., brometone, chlorobutanol (chloretone), ethanol, *tert*-butanol (2M2P), tribromoethanol, trichloroethanol, trifluoroethanol) · Alkylbenzene sulfonate · Anandamide · Barbiturates (e.g., pentobarbital, sodium thiopental) · Chlormethiazole · D12-116 · Dihydropyridines (e.g., nicardipine) · Etomidate · Ginseng constituents (e.g., ginsenosides (e.g., ginsenoside-Rf)) · Glutamic acid (glutamate) · Ivermectin · Ketamine · Neuroactive steroids (e.g., alfaxolone, pregnenolone (eltanolone), pregnenolone acetate, minaxolone, Org 20599) · Nitrous oxide · Penicillin G · Propofol · Tamoxifen · Tetrahydrocannabinol · Triclofos · Tropeines (e.g., atropine, bemesetron, cocaine, LY-278584, tropisetron, zatosetron) · Volatiles/gases (e.g., chloral hydrate, chloroform, desflurane, diethyl ether (ether), enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, toluene, trichloroethane (methyl chloroform), trichloroethylene) · Xenon · Zinc · |
| | **Antagonists:** 2-Aminostrychnine · 2-Nitrostrychnine · 4-Phenyl-4-formyl-N-methylpiperidine · αEMBTL · Bicuculline · Brucine · Cacotheline · Caffeine · Colchicine · Colubrine · Cyanotriphenylborate · Dendrobine · Diaboline · Endocannabinoids (e.g., 2-AG, anandamide (AEA)) · Gaboxadol (THIP) · Gelsemine · iso-THAZ · Isobutyric acid · Isonipecotic acid · Isostrychnine · Laudanosine · N-Methylbicuculline · N-Methylstrychnine · N,N-Dimethylmuscimol · Nipecotic acid · Pitrazepin · Pseudostrychnine · Quinolines (e.g., 4-hydroxyquinoline, 4-hydroxyquinoline-3-carboxylic acid, 5,7-CIQA, 7-CIQ, 7-TFQ, 7-TFQA) · RU-5135 · Sinomenine · Strychnine · Thiocolchicoside · Tutin · |
| | **NAMs:** Amiloride · Benzodiazepines (e.g., bromazepam, clonazepam, **diazepam**, |

| | | |
|---|---|---|
| | | flunitrazepam, flurazepam) · Corymine · Cyanotriphenylborate · Daidzein · Dihydropyridines (e.g., nicardipine, nifedipine, nitrendipine) · Furosemide · Genistein · Ginkgo constituents (e.g., bilobalide, ginkgolides (e.g., ginkgolide A, ginkgolide B, ginkgolide C, ginkgolide J, ginkgolide M)) · Imipramine · NBQX · Neuroactive steroids (e.g., 3α-androsterone sulfate, 3β-androsterone sulfate, deoxycorticosterone, DHEA sulfate, pregnenolone sulfate, progesterone) · Opioids (e.g., codeine, dextromethorphan, dextrorphan, levomethadone, levorphanol, morphine, oripavine, pethidine, thebaine) · Picrotoxin (i.e., picrotin and picrotoxinin) · PMBA · Riluzole · Tropeines (e.g., bemesetron, LY-278584, tropisetron, zatosetron) · Verapamil · Zinc · |
| **Transporter (blockers)** | **GlyT1** | ACPPB · ALX-1393 · ALX-5407 (NFPS) · AMG-747 · ASP2535 · Bitopertin (RG1678/RO4917838) · CP-802079 · Ethanol · Glycyldodecylamide · GSK1018921 · LY-2365109 · Org 24598 · Org 25935 (SCH-900435) · PF-02545920 · PF-03463275 · PF-04958242 · Sarcosine · SSR-103,800 · SSR-504,734 · |
| | **GlyT2** | Amoxapine · Ethanol · NAGly · Org 25543 · |
| **Others** | **Precursors:** 3-PG · GHB · L-Serine · L-Theonine · **Cofactors:** Vitamin $B_6$ · | |
| *See also: GABAergics • GHBergics • Glutamatergics* | | |

| | |
|---|---|
| **Authority control** | LCCN: sh88005436 · GND: 4149530-5 · |

Categories: Benzodiazepines | Chloroarenes | Depressogenics | GABAA receptor positive allosteric modulators | Glycine receptor antagonists | Hoffmann-La Roche | Lactams | TSPO ligands | World Health Organization essential medicines | Chemical substances for emergency medicine

# Hydrochlorothiazide

From Wikipedia, the free encyclopedia

**Hydrochlorothiazide** (abbreviated **HCTZ**, **HCT**, or **HZT**), is a diuretic medication often used to treat high blood pressure and swelling due to fluid build up.[2] Other uses include diabetes insipidus, renal tubular acidosis, and to decrease the risk of kidney stones in those with high calcium level in the urine.[2] For high blood pressure it is often recommended as a first line treatment.[2][3] HCTZ is taken by mouth and may be combined with other blood pressure medications as a single pill to increase the effectiveness.[2]

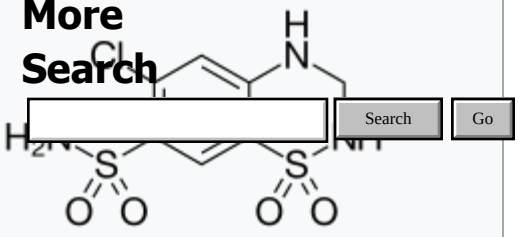
Potential side effects include poor kidney function, electrolyte imbalances especially low blood potassium and less commonly low blood sodium, gout, high blood sugar, and feeling faint initially upon standing up.[2] While allergies to HCTZ are reported to occur more often in those with allergies to sulfa drugs this association is not well supported.[2] It may be used during pregnancy but is not a first line medication in this group.[2]

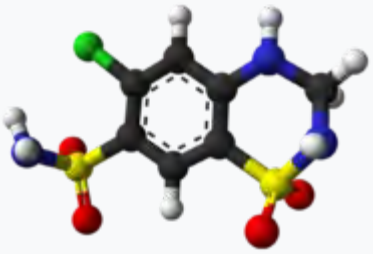
It is in the thiazide medication class and acts by decreasing the kidneys' ability to retain water.[2] This initially reduces blood volume, decreasing blood return to the heart and thus cardiac output.[4] Long term, however, it is believed to lower peripheral vascular resistance.[4]

Two companies, Merck and Ciba, state they discovered the medication which became commercially available in 1959.[5] It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[6] In 2008 it was the second most commonly used blood pressure medication in the United States.[4] It is available as a generic drug[2] and is relatively affordable.[7]

Contents


**Hydrochlorothiazide**





| Clinical data | |
|---|---|
| **Trade names** | Apo-hydro, others |
| **AHFS/Drugs.com** | Monograph |
| **MedlinePlus** | a682571 |
| **Pregnancy category** | B (D if used to treat pregnancy-induced hypertension) |
| **Routes of administration** | Oral (capsules, tablets, oral solution) |
| **ATC code** | C03AA03 (WHO) |
| **Legal status** | |
| **Legal status** | (Prescription only) |
| **Pharmacokinetic data** | |
| **Bioavailability** | Variable (~70% on average) |
| **Metabolism** | Not significant[1] |
| **Biological half-life** | 5.6–14.8 h |
| **Excretion** | Primarily kidney (>95% as unchanged drug) |

## Medical uses [edit]

Hydrochlorothiazide is frequently used for the treatment of hypertension, congestive heart failure, symptomatic edema, *diabetes insipidus*, renal tubular acidosis.[2] It is also used for the prevention of kidney stones in those who have high levels of calcium in their urine.[2]

Most of the research supporting the use of thiazide diuretics in hypertension was done using chlorthalidone, a different medication in the same class. Some more recent studies have suggested that chlorthalidone might be the more effective thiazide diuretic.[8]

It is also sometimes used for treatment of hypoparathyroidism,[9] hypercalciuria, Dent's disease, and Ménière's disease. For *diabetes insipidus*, the effect of thiazide diuretics is presumably mediated by a hypovolemia-induced increase in proximal sodium and water reabsorption, thereby diminishing water delivery to the ADH-sensitive sites in the collecting tubules and increasing the urine osmolality.

Thiazides are also used in the treatment of osteoporosis. Thiazides decrease mineral bone loss by promoting calcium retention in the kidney, and by directly stimulating osteoblast differentiation and bone mineral formation.[10]

It may be given together with other antihypertensive agents in fixed-dose combination preparations, such as in losartan/hydrochlorothiazide (see below).

| Identifiers | |
|---|---|
| **IUPAC name** | 6-chloro-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide |
| **CAS Number** | 58-93-5 ✓ |
| **PubChem** (CID) | 3639 |
| **IUPHAR/BPS** | 4836 |
| **DrugBank** | DB00999 ✓ |
| **ChemSpider** | 3513 ✓ |
| **UNII** | 0J48LPH2TH ✓ |
| **KEGG** | D00340 ✓ |
| **ChEBI** | CHEBI:5778 ✗ |
| **ChEMBL** | CHEMBL435 ✓ |
| **ECHA InfoCard** | 100.000.367 |
| **Chemical and physical data** | |
| **Formula** | $C_7H_8ClN_3O_4S_2$ |
| **Molar mass** | 297.74 g/mol |
| **3D model (Jmol)** | Interactive image |
| **SMILES** | O=S(=O)(N)c1c(Cl)cc2c(c1)S(=O)(=O)NCN2 |
| **InChI** | InChI=1S/C7H8ClN3O4S2/c8-4-1-5-7(2-6(4)16(9,12)13)17(14,15)11-3-10-5/h1-2,10-11H,3H2,(H2,9,12,13) ✓ Key:JZUFKLXOESDKRF-UHFFFAOYSA-N ✓ |
| ✗✓ (what is this?) (verify) | |

## Adverse effects [edit]

- Hypokalemia, or low blood levels of potassium are an occasional side effect. It can be usually prevented by potassium supplements or by combining hydrochlorothiazide with a potassium-sparing diuretic
- Other disturbances in the levels of serum electrolytes including hypomagnesemia (low magnesium), hyponatremia (low sodium), and hypercalcemia (high calcium)
- Hyperuricemia, high levels of uric acid in the blood
- Hyperglycemia, high blood sugar
- Hyperlipidemia, high cholesterol and triglycerides
- Headache
- Nausea/vomiting
- Photosensitivity
- Weight gain
- Gout
- Pancreatitis

These side effects increase with the dose of the medication and are most common at doses of greater than 25 mg per day.

Package inserts, based on case reports and observational studies, have reported that an allergy to a sulfa drug predisposes the patient to cross sensitivity to a thiazide diuretic. A 2005 review of the literature did not find support for this cross-sensitivity.[11]

# Mechanism of action [edit]

Hydrochlorothiazide belongs to thiazide class of diuretics. It reduces blood volume by acting on the kidneys to reduce sodium ($Na^+$) reabsorption in the distal convoluted tubule. The major site of action in the nephron appears on an electroneutral NaCl co-transporter by competing for the chloride site on the transporter. By impairing $Na^+$ transport in the distal convoluted tubule, hydrochlorothiazide induces a natriuresis and concomitant water loss. Thiazides increase the reabsorption of calcium in this segment in a manner unrelated to sodium transport.[12] Additionally, by other mechanisms, HCTZ is believed to lower peripheral vascular resistance.[13]

# Society and culture [edit]

## Trade names [edit]

Hydrochlorothiazide is available as a generic drug under a large number of brand names, including Apo-Hydro, Aquazide, BPZide, Dichlotride, Esidrex, Hydrochlorot, Hydrodiuril, HydroSaluric, Hypothiazid, Microzide, Oretic and many others.

To reduce pill burden and in order to reduce side effects, hydrochlorothiazide is often used in fixed-dose combinations with many other classes of antihypertensive drugs such as:

- ACE inhibitors — e.g. Prinzide or Zestoretic (with lisinopril), Co-Renitec (with enalapril), Capozide (with captopril), Accuretic (with quinapril), Monopril HCT (with fosinopril), Lotensin HCT (with benazepril), etc.
- Angiotensin receptor blockers — e.g. Hyzaar (with losartan), Co-Diovan or Diovan HCT (with valsartan), Teveten Plus (with eprosartan), Avalide or CoAprovel (with irbesartan), Atacand HCT or Atacand Plus (with candesartan), etc.
- Beta blockers — e.g. Ziac or Lodoz (with bisoprolol), Nebilet Plus or Nebilet HCT (with nebivolol), Dutoprol or Lopressor HCT (with metoprolol), etc.
- Direct renin inhibitors — e.g. Co-Rasilez or Tekturna HCT (with aliskiren)
- Potassium sparing diuretics: Dyazide and Maxzide triamterene[14]

Co-Diovan (valsartan and HCTZ)


Two generic benazepril HCl 20 mg and HCTZ 25 mg oral tablets

## Sport [edit]

Hydrochlorothiazide was detected in the urine of the Russian cyclist Alexandr Kolobnev during the 2011 Tour de France.[15] Kolobnev was the only cyclist to leave the 2011 race in connection with adverse findings at a doping control.[16] While hydrochlorothiazide is not itself a performance-enhancing drug, it may be used to mask the use of performance-enhancing drugs, and is classed by the World Anti-Doping Agency as a "specified substance". Kolobnev was subsequently cleared of all charges of intentional doping.[17][18]

# References [edit]

1. ^ Beermann B, Groschinsky-Grind M, Rosén A (1976). "Absorption, metabolism, and excretion of hydrochlorothiazide". *Clin Pharmacol Ther*. **19** (5 (Pt 1)): 531–7.
2. ^ *a b c d e f g h i j k* "Hydrochlorothiazide". The
10. ^ Dvorak MM, De Joussineau C, Carter DH, et al. (2007). "Thiazide diuretics directly induce osteoblast differentiation and mineralized nodule formation by targeting a NaCl cotransporter in bone". *J. Am. Soc. Nephrol*. **18** (9): 2509–16.

American Society of Health-System Pharmacists. Retrieved 2016-11-30.
3. ^ Wright, JM; Musini, VM (8 July 2009). "First-line drugs for hypertension.". *The Cochrane database of systematic reviews* (3): CD001841. doi:10.1002/14651858.CD001841.pub2. PMID 19588327.
4. ^ *a b c* Duarte JD, Cooper-DeHoff RM (June 2010). "Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics". *Expert Rev Cardiovasc Ther*. **8** (6): 793–802. doi:10.1586/erc.10.27. PMC 2904515. PMID 20528637.
5. ^ Ravina, Enrique (2011). *The evolution of drug discovery: from traditional medicines to modern drugs* (1 ed.). Weinheim: Wiley-VCH. p. 74. ISBN 9783527326693.
6. ^ "WHO Model List of EssentialMedicines" (PDF). *World Health Organization*. October 2013. Retrieved 22 April 2014.
7. ^ "Best drugs to treat high blood pressure The least expensive medications may be the best for many people". November 2014. Retrieved 10 January 2015.
8. ^ Messerli, Franz; Makani,Harikrishna; Benjo,Alexandre; Romero,Jorge; Alviar,Carlos; Bangalore,Sripal (2011). "Antihypertensive Efficacy of Hydrochlorothiazide as Evaluated by Ambulatory Blood Pressure Monitoring: A Meta-Analysis of Randomized Trials". *J.Am.Coll.Cardiol*. **57** (5): 590–600. doi:10.1016/j.jacc.2010.07.053.
9. ^ Mitchell, Deborah. "Long-Term Follow-Up of Patients with Hypoparathyroidism". *J Clin Endocrin Metab*. Endocrine Society. Retrieved 19 June 2013. doi:10.1681/ASN.2007030348. PMC 2216427. PMID 17656470.
11. ^ Johnson, KK; Green, DL; Rife, JP; Limon, L (February 2005). "Sulfonamide cross-reactivity: fact or fiction?". *The Annals of pharmacotherapy*. **39** (2): 290–301. doi:10.1345/aph.1E350. PMID 15644481.
12. ^ Uniformed Services University Pharmacology Note Set #3 2010, Lectures #39 & #40, Eric Marks
13. ^ Duarte, JD; Cooper-Dehoff, RM (2010). "Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics". *Expert review of cardiovascular therapy*. **8** (6): 793–802. doi:10.1586/erc.10.27. PMC 2904515. PMID 20528637. NIHMSID: NIHMS215063
14. ^ "Triamterene and Hydrochlorothiazide". MedlinePlus. U.S. National Library of Medicine. National Institutes of Health. September 1, 2008.
15. ^ "Tour de France: Alexandr Kolobnev positive for banned diuretic". Velonation. 2011-07-11. Archived from the original on 2011-07-12. Retrieved 2011-07-12.
16. ^ "Kolobnev denies knowledge of doping product, says not fired by Katusha". Velonation. 2011-07-12. Archived from the original on 2011-07-12. Retrieved 2011-07-12.
17. ^ "Press release: Adverse Analytical Finding for Kolobnev". Union Cycliste Internationale. 2011-07-11. Archived from the original on 2011-07-12. Retrieved 2011-07-12.
18. ^ "Kolobnev Tour de France's first doping case". *Cycling News*. Bath, UK: Future Publishing Limited. 2011-07-11. Archived from the original on 2011-07-12. Retrieved 2011-07-12.

## External links [edit]

- NIH medlineplus druginfo
- U.S. National Library of Medicine: Drug Information Portal - Hydrochlorothiazide

| v · t · e · | Antihypertensives: diuretics (C03) | |
|---|---|---|
| Sulfonamides (and etacrynic acid) | CA inhibitors (at PT) | Acetazolamide · |
| | Loop (Na-K-Cl at AL) | Furosemide# · Bumetanide · Etacrynic acid · Etozolin · Muzolimine · Ozolinone · Piretanide · Tienilic acid · Torasemide · |
| | Thiazides (Na-Cl at DCT, Calcium-sparing) | Altizide · Bendroflumethiazide · Chlorothiazide · Cyclopenthiazide · Cyclothiazide · Epitizide · **Hydrochlorothiazide#** · Hydroflumethiazide · Mebutizide · Methyclothiazide · Polythiazide · Trichlormethiazide · |

| | | |
|---|---|---|
| | **Thiazide-likes (primarily DCT)** | Quinethazone · Clopamide · Chlortalidone · Mefruside · Clofenamide · Metolazone · Meticrane · Xipamide · Indapamide · Clorexolone · Fenquizone · |
| **Potassium-sparing (at CD)** | **ESC blockers** | Amiloride[#] · Triamterene · Benzamil · |
| | **Aldosterone antagonists** | *Spirolactones:* Spironolactone[#] · Eplerenone · Potassium canrenoate · Canrenone · *Non-steroidal:* Finerenone · |
| **Osmotic diuretics (PT, DL)** | | Mannitol[#] · Glycerol · Urea · |
| **Vasopressin receptor inhibitors (DCT and CD)** | | *Vaptans:* Conivaptan · Mozavaptan · Satavaptan · Tolvaptan · *Others:* Demeclocycline · Lithium carbonate · |
| **Other** | | Ethanol, Isopropanol, 2M2B · *mercurial diuretics* (Chlormerodrin, Mersalyl, Meralluride) · Theobromine · Cicletanine · |

[#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III · ·

v · t · e · **Symporter inhibitors**

| | |
|---|---|
| **$Na^+$-$Cl^-$** | **Thiazides:** Bendroflumethiazide · Chlorothiazide · Cyclopenthiazide · Cyclothiazide · **Hydrochlorothiazide** · Hydroflumethiazide · Methyclothiazide · Polythiazide · Trichlormethiazide; **Others:** Chlortalidone (chlorthalidone) · Metolazone · |
| **$Na^+$-$K^+$-$Cl^-$** | Bumetanide · Furosemide · |

v · t · e · **Glutamatergics**

| | |
|---|---|
| **AMPA** | **Agonists:** *Glutamate/active site agonists:* 5-Fluorowillardiine · Acromelic acid (acromelate) · AMPA · BOAA · Domoic acid · Glutamate · Ibotenic acid · Proline · Quisqualic acid · Willardiine; *Positive allosteric modulators:* Aniracetam · Cyclothiazide · CX-516 · CX-546 · CX-614 · Farampator (CX-691, Org 24448) · CX-717 · CX-1739 · CX-1942 · Diazoxide · **Hydrochlorothiazide (HCTZ)** · IDRA-21 · LY-392,098 · LY-404,187 · LY-451,646 · LY-503,430 · Mibampator (LY-451,395) · Org 26576 · Oxiracetam · PEPA · PF-04958242 · Piracetam · Pramiracetam · S-18986 · Sunifiram · Unifiram · **Antagonists:** ACEA-1011 · ATPO · Becampanel · Caroverine · CNQX · Dasolampanel · DNQX · Fanapanel (MPQX) · GAMS · GYKI-52466 · Kynurenic acid · Kynurenine · Licostinel (ACEA-1021) · NBQX · PNQX · Selurampanel · Tezampanel · Theanine · Topiramate · YM90K · Zonampanel; *Negative allosteric modulators:* Barbiturates (e.g., pentobarbital, sodium thiopental) · Cyclopropane · Enflurane · Ethanol · Evans blue · GYKI-53,655 · Halothane · Irampanel · Isoflurane · Perampanel · Pregnenolone sulfate · Talampanel · |
| | **Agonists:** *Glutamate/active site agonists:* AMAA · Aspartate · Glutamate · Homocysteic acid (L-HCA) · Homoquinolinic acid · Ibotenic acid · NMDA · Proline · Quinolinic acid · Tetrazolylglycine · Theanine; *Glycine site agonists:* β-Fluoro-D-alanine · ACBD · ACC (ACPC) · ACPD · AK-51 · Apimostinel (NRX-1074) · B6B21 · CCG · D-Alanine · D-Cycloserine · D-Serine · DHPG · Dimethylglycine · Glycine · HA-966 · L-687,414 · L-Alanine · L-Serine · Milacemide · Neboglamine (nebostinel) · Rapastinel (GLYX-13) · Sarcosine; *Polyamine site agonists:* Spermidine · Spermine; *Other positive allosteric modulators:* 24S-Hydroxycholesterol · DHEA · DHEA sulfate · Pregnenolone sulfate · |

| | | |
|---|---|---|
| **Receptor (ligands)** | **NMDA** | SAGE-718 ·<br>**Antagonists:** *Competitive antagonists:* AP5 (APV) · AP7 · CGP-37849 · CGP-39551 · CGP-39653 · CGP-40116 · CGS-19755 · CPP · LY-233,053 · LY-235,959 · LY-274,614 · MDL-100,453 · Midafotel (d-CPPene) · NPC-12,626 · NPC-17,742 · PBPD · PEAQX · Perzinfotel · PPDA · SDZ-220581 · Selfotel; *Noncompetitive antagonists:* ARR-15,896 · Caroverine · Dexanabinol · FPL-12495 · FR-115,427 · Hodgkinsine · Magnesium · MDL-27,266 · NPS-1506 · Psychotridine · Zinc; *Uncompetitive pore blockers:* 2-MDP · 3-HO-PCP · 3-MeO-PCE · 3-MeO-PCMo · 3-MeO-PCP · 4-MeO-PCP · 8A-PDHQ · 18-MC · α-Endopsychosin · Alaproclate · Amantadine · Aptiganel · Arketamine · ARL-12,495 · ARL-15,896-AR · ARL-16,247 · Budipine · Conaridine · Delucemine · Dexoxadrol · Dextrallorphan · Dieticyclidine · Diphenidine · Dizocilpine · Ephenidine · Esketamine · Etoxadrol · Eticyclidine · Fluorolintane · Gacyclidine · Ibogaine · Ibogamine · Indantadol · Ketamine · Ketobemidone · Lanicemine · Loperamide · Memantine · Methadone (Levomethadone) · Methorphan (Dextromethorphan · Levomethorphan) · Methoxetamine · Methoxphenidine · Milnacipran · Morphanol (Dextrorphan · Levorphanol) · NEFA · Neramexane · Nitromemantine · Nitrous oxide · Noribogaine · Norketamine · Orphenadrine · PCPr · Pethidine (meperidine) · Phencyclamine · Phencyclidine · Propoxyphene · Remacemide · Rhynchophylline · Rimantadine · Rolicyclidine · Sabeluzole · Tabernanthine · Tenocyclidine · Tiletamine · Tramadol · Xenon; *Glycine site antagonists:* 4-Cl-KYN (AV-101) · 5,7-DCKA · 7-CKA · ACC · ACEA-1011 · ACEA-1328 · AV-101 · Carisoprodol · CGP-39653 · CNQX · DNQX · Felbamate · Gavestinel · GV-196,771 · Kynurenic acid · Kynurenine · L-689,560 · L-701,324 · Licostinel (ACEA-1021) · LU-73,068 · MDL-105,519 · Meprobamate · MRZ 2/576 · PNQX · ZD-9379; *NR2B subunit antagonists:* Besonprodil · CERC-301 (MK-0657) · CO-101,244 (PD-174,494) · Eliprodil · Haloperidol · Ifenprodil · Isoxsuprine · Nylidrin · Ro8-4304 · Ro25-6981 · Traxoprodil; *Polyamine site antagonists:* Arcaine · Co 101676 · Diaminopropane · Diethylenetriamine · Huperzine A · Putrescine · Ro 25-6981; *Unclassified/unsorted antagonists:* Bumetanide · Chloroform · Cyclopropane · D-αAA · Diethyl ether · Enflurane · Ethanol · Flufenamic acid · Flupirtine · Furosemide · Halothane · Isoflurane · Metaphit · Methoxyflurane · Niflumic acid · Pentamidine isethionate · Piretanide · Toluene · Transcrocetin (saffron) · Trichloroethane · Trichloroethanol · Trichloroethylene · Xylene · |
| | **Kainate** | **Agonists:** *Glutamate/active site agonists:* 5-Bromowillardiine · 5-Iodowillardiine · Acromelic acid (acromelate) · AMPA · ATPA · Domoic acid · Glutamate · Ibotenic acid · Kainic acid · LY-339,434 · Proline · Quisqualic acid · SYM-2081; *Positive allosteric modulators:* Cyclothiazide · Diazoxide · Enflurane · Halothane · Isoflurane ·<br>**Antagonists:** ACEA-1011 · CNQX · Dasolampanel · DNQX · GAMS · Kynurenic acid · Licostinel (ACEA-1021) · LY-382,884 · NBQX · NS102 · Selurampanel · Tezampanel · Theanine · Topiramate · UBP-302; *Negative allosteric modulators:* Barbiturates (e.g., pentobarbital, sodium thiopental) · Enflurane · Ethanol · Evans blue · NS-3763 · Pregnenolone sulfate · |
| | **$mGlu_1$** | **Agonists:** ACPD · DHPG · Glutamate · Ibotenic acid · Quisqualic acid · Ro01-6128 · Ro67-4853 · Ro67-7476 · VU-71 ·<br>**Antagonists:** BAY 36-7620 · CPCCOEt · Cyclothiazide · LY-367,385 · LY-456,236 · MCPG · NPS-2390 · |
| | | **Agonists:** BINA · CBiPES · DCG-IV · Eglumegad · Glutamate · Ibotenic acid · LY-379,268 |

| | | |
|---|---|---|
| | **$mGlu_2$** | • LY-404,039 (pomaglumetad) • LY-487,379 • LY-566,332 • MGS-0028 • Pomaglumetad methionil (LY-2140023) • Talaglumetad; *Positive allosteric modulators:* JNJ-40411813 (ADX-71149) • **Antagonists:** APICA • CECXG • EGLU • HYDIA • LY-307,452 • LY-341,495 • MCPG • MGS-0039 • PCCG-4; *Negative allosteric modulators:* Decoglurant • RO4491533 • |
| | **$mGlu_3$** | **Agonists:** CBiPES • DCG-IV • Eglumegad • Glutamate • Ibotenic acid • LY-379,268 • LY-404,039 (pomaglumetad) • LY-487,379 • MGS-0028 • Pomaglumetad methionil (LY-2140023) • Talaglumetad • **Antagonists:** APICA • CECXG • EGLU • HYDIA • LY-307,452 • LY-341,495 • MCPG • MGS-0039; *Negative allosteric modulators:* Decoglurant • RO4491533 • |
| | **$mGlu_4$** | **Agonists:** Glutamate • L-AP4 • PHCCC • VU-001,171 • VU-0155,041; *Positive allosteric modulators:* MPEP • **Antagonists:** CPPG • MAP4 • MPPG • MSOP • MTPG • UBP-1112 • |
| | **$mGlu_5$** | **Agonists:** ACPD • ADX-47273 • CDPPB • CHPG • DFB • DHPG • Glutamate • Ibotenic acid • Quisqualic acid • VU-1545 • **Antagonists:** CTEP • DMeOB • LY-344,545 • Mavoglurant • MCPG • NPS-2390 • Remeglurant • SIB-1757 • SIB-1893; *Negative allosteric modulators:* Basimglurant • Dipraglurant • Fenobam • GRN-529 • MPEP • MTEP • Raseglurant • |
| | **$mGlu_6$** | **Agonists:** Glutamate • L-AP4 • **Antagonists:** CPPG • MAP4 • MPPG • MSOP • MTPG • UBP-1112 • |
| | **$mGlu_7$** | **Agonists:** AMN082 • Glutamate • L-AP4 • **Antagonists:** CPPG • MAP4 • MMPIP • MPPG • MSOP • MTPG • UBP-1112 • |
| | **$mGlu_8$** | **Agonists:** DCPG • Glutamate • L-AP4 • **Antagonists:** CPPG • MAP4 • MPPG • MSOP • MTPG • UBP-1112 • |
| **Transporter (blockers)** | **EAATs** | Amphetamine • Aspartic acid (aspartate) • *cis*-ACBD • DHKA • Glutamic acid (glutamate) • HIP-A • HIP-B • Kainic acid • L-(-)-*threo*-3-Hydroxyaspartic acid • L-αAA • L-CCG-III ((2S,3S,4R)-CCG) • L-Serine-O-sulphate (SOS) • L-*trans*-2,4-PDC • MPDC • SYM-2081 • TBOA • TFB-TBOA • Theanine • *threo*-3-Methylglutamic acid • UCPH-101 • WAY-213,613 • |
| | **vGluTs** | 4-Methylene-L-glutamate • 6-(4'-Phenylstyryl)-QDC • 6-Biphenyl-4-yl-QDC • 7-CKA • Acid red 114 • Amido black 10B (naphthol blue black) • Bafilomycin A1 • Benzopurpurin 4B • Bumetamide • Chicago sky blue 6B • Aspartic acid (aspartate) • DIDS • Direct blue 71 • Erythro-4-methyl-L-glutamic acid • Evans blue • Furosemide • Glutamic acid (glutamate) • Kynurenic acid • Nigericin • NPPB (N144) • Ponceau SS • Reactive blue 2 • Rose bengal • SITS • *trans*-ACDP • Trypan blue • Valinomycin • Xanthurenic acid • |
| **Enzyme (inhibitors)** | **GAH** | BPTES • CB-839 • DON • |
| | **AST** | 2-Amino-3-butenoic acid • AAOA • AMB • β-DL-Methylene-aspartate • Hydrazinosuccinate • |
| | **ALT** | β-Chloro-L-alanine • L-Cycloserine • Propargylglycine • |
| | **GDH** | AAOA • Bithionol • Chloroquine • EGCG • GTP • GW5074 • Hexachlorophene • Hydroxylamine • Palmitoyl-CoA • Pyridoxal phosphate • |
| | **GS** | 2-Aminoadipic acid • JFD01307SC • Methionine sulfoximine • Phosphinothricin (glufosinate) • |
| | **GAD** | 3-Mercaptopropionic acid • AAOA • L-Allylglycine • Semicarbazide • |

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| **Others** | **Precursors:** GHB · L-Glutamine ·<br>**Cofactors:** α-Ketoglutaric acid · Iron · Sulfur · Vitamin $B_2$ · Vitamin $B_3$ ·<br>**Prodrugs:** Aceglutamide (to L-glutamine) ·<br>**Others:** Acamprosate · Cysteine · Cytidine · Cytisine · Glutathione · Glutathione disulfide · Minocycline · N-Acetylcysteine · Riluzole · S-Nitrosoglutathione · Tianeptine · |
| *See also: GABAergics • GHBergics • Glycinergics* | |

Categories: AMPA receptor agonists | Antihypertensive agents | Benzothiadiazines | Carbonic anhydrase inhibitors | Diuretics | IARC Group 2B carcinogens | Sulfonamides | Thiazides | World Health Organization essential medicines | World Anti-Doping Agency prohibited substances




# Ibuprofen

From Wikipedia, the free encyclopedia



**Ibuprofen** is a medication in the nonsteroidal anti-inflammatory drug (NSAID) class that is used for treating pain, fever, and inflammation.[4] This includes painful menstrual periods, migraines, and rheumatoid arthritis.[4] About 60% of people improve with any given NSAID, and it is recommended that if one does not work then another should be tried.[5] It may also be used to close a patent ductus arteriosus in a premature baby. It can be used by mouth or intravenously. It typically begins working within an hour.[4]

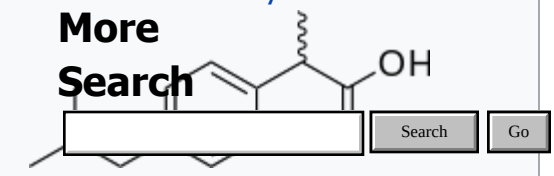
Common side effects include heartburn and a rash.[4] Compared to other NSAIDs it may have fewer side effects such as gastrointestinal bleeding.[5] It increases the risk of heart failure, kidney failure, and liver failure.[4] At low doses, it does not appear to increase the risk of myocardial infarction, however, at higher doses it may. Ibuprofen can also result in worsened asthma.[5] While it is unclear if it is safe in early pregnancy,[4] it appears to be harmful in later pregnancy and therefore is not recommended.[6] Like other NSAIDs, it works by inhibiting the making of prostaglandins by decreasing the activity of the enzyme cyclooxygenase.[4] Ibuprofen might be a weaker anti-inflammatory than other NSAIDs.[5]

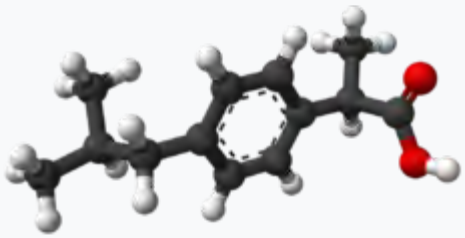
Ibuprofen was discovered in 1961 by Stewart Adams and marketed as **Brufen**.[7] It is available under a number of trade names, including **Advil** and **Motrin**.[4][8] It was first marketed in 1969 in the United Kingdom and in the United States in 1974.[4][7] It is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system.[9] It is available as a generic medication.[4] The wholesale cost in the developing world is between 0.01 and 0.04 USD per dose.[10] In the United States it costs about 0.05 USD per dose.[4]

Contents



## Ibuprofen



| Clinical data | |
|---|---|
| **Pronunciation** | /ˈaɪbjuːproʊfɛn/, /aɪbjuːˈproʊfən/, *EYE-bew-PROH-fən* |
| **Trade names** | Advil, Motrin, Nurofen, others |
| **AHFS/Drugs.com** | Monograph |
| **MedlinePlus** | a682159 |
| **License data** | US FDA: Ibuprofen |
| **Pregnancy category** | AU: C<br>US: C (Risk not ruled out)<br>D (US) at ≥30 weeks of gestation, due to the potential for premature closure of the *ductus arteriosus* |
| **Routes of administration** | by mouth, rectal, topical, and intravenous |
| **ATC code** | C01EB16 (WHO)<br>G02CC01 (WHO)<br>M01AE01 (WHO)<br>M02AA13 (WHO) |

## Medical uses [edit]

Ibuprofen is used primarily to treat fever (including postimmunisation fever), mild to moderate pain (including pain relief after surgery), painful menstruation, osteoarthritis, dental pain, headaches, and pain from kidney stones. About 60% of people respond to any NSAID; those who do not respond well to a particular one may respond to another.[11]

It is used for inflammatory diseases such as juvenile idiopathic arthritis and rheumatoid arthritis.[12][13] It is also used for pericarditis and patent ductus arteriosus.[14]

### Ibuprofen lysine [edit]

In some countries, ibuprofen lysine (the lysine salt of ibuprofen, sometimes called "ibuprofen lysinate") is licensed for treatment of the same conditions as ibuprofen; the lysine salt is used because it is more water-soluble.[15] In 2006, ibuprofen lysine was approved in the US by the Food and Drug Administration (FDA) for closure of *patent ductus arteriosus* in premature infants weighing between 500 and 1,500 grams (1 and 3 lb), who are no more than 32 weeks gestational age when usual medical management (such as fluid restriction, diuretics, and respiratory support) is not effective.[16]

## Adverse effects [edit]

Adverse effects include nausea, dyspepsia, diarrhea, constipation, gastrointestinal ulceration/bleeding, headache, dizziness, rash, salt and fluid retention, and hypertension.[13][17]

Infrequent adverse effects include esophageal ulceration, heart failure, hyperkalemia, renal impairment, confusion, and bronchospasm.[13] Ibuprofen can exacerbate asthma, sometimes fatally.[18]

Ibuprofen may be quantified in blood, plasma, or serum to demonstrate the presence of the drug in a person having experienced an anaphylactic reaction, confirm a diagnosis of poisoning in hospitalized patients, or assist in a medicolegal death investigation. A monograph relating ibuprofen plasma concentration, time since ingestion, and risk of developing

| | |
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| | R02AX02 (WHO ) |
| **Legal status** | |
| **Legal status** | AU: Pharmacy Only (S2) to Prescription Only (S4)<br>CA: OTC<br>UK: General sales list (GSL, OTC)<br>US: OTC/$R_x$-only |
| **Pharmacokinetic data** | |
| **Bioavailability** | 87–100% (oral), 87% (rectal)[1] |
| **Protein binding** | 98%[1] |
| **Metabolism** | Hepatic (CYP2C9)[1] |
| **Onset of action** | 30 min[2] |
| **Biological half-life** | 1.3–3 h[1] |
| **Excretion** | Urine (95%)[1][3] |
| **Identifiers** | |
| **IUPAC name** | (*RS*)-2-(4-(2-Methylpropyl)phenyl)propanoic acid |
| **Synonyms** | isobutylphenylpropionic acid |
| **CAS Number** | 15687-27-1 ✓ |
| **PubChem** (CID) | 3672 |
| **IUPHAR/BPS** | 2713 |
| **DrugBank** | DB01050 ✓ |
| **ChemSpider** | 3544 ✓ |
| **UNII** | WK2XYI10QM ✓ |
| **KEGG** | D00126 ✓ |
| **ChEBI** | CHEBI:5855 ✓ |
| **ChEMBL** | CHEMBL521 ✓ |
| **PDB ligand ID** | IBP (PDBe, RCSB PDB) |
| **ECHA InfoCard** | 100.036.152 |
| **Chemical and physical data** | |
| **Formula** | $C_{13}H_{18}O_2$ |
| **Molar mass** | 206.29 g/mol |
| **3D model (Jmol)** | Interactive image |
| **Chirality** | Racemic mixture |
| **Density** | 1.03 g/ml g/$cm^3$ |
| **Melting point** | 75 to 78 °C (167 to 172 °F) |

renal toxicity in overdose patients has been published.[19]

## Cardiovascular risk [edit]

Along with several other NSAIDs, chronic ibuprofen use has been found correlated with risk of hypertension[20] and myocardial infarction (heart attack),[21] particularly among those chronically using high doses. In older hypertensive patients treated with hydrochlorothiazide, ibuprofen at a high daily dose was found to significantly increase systolic blood pressure.[22] On 9 July 2015, the US FDA toughened warnings of increased heart attack and stroke risk associated with ibuprofen and related NSAIDs; the NSAID aspirin is not included in this warning.[23]

**Boiling point** 157 °C (315 °F)

**SMILES**

CC(C)Cc1ccc(cc1)C(C)C(=O)O

**InChI**

InChI=1S/C13H18O2/c1-9(2)8-11-4-6-12(7-5-11)10(3)13(14)15/h4-7,9-10H,8H2,1-3H3,(H,14,15) ✓

Key:HEFNNWSXXWATRW-UHFFFAOYSA-N ✓

(verify)

200-mg ibuprofen tablets

## Skin [edit]

Along with other NSAIDs, ibuprofen has been associated with the onset of bullous pemphigoid or pemphigoid-like blistering.[24] As with other NSAIDs, ibuprofen has been reported to be a photosensitising agent,[25] but it is considered a weak photosensitising agent compared to other members of the 2-arylpropionic acid class. Like other NSAIDs, ibuprofen is an extremely rare cause of the autoimmune disease Stevens–Johnson syndrome (SJS).[26][27] Ibuprofen is also an extremely rare cause of Lyell's Syndrome (toxic epidermal necrolysis).[28]

## Interactions [edit]

Drinking alcohol when taking ibuprofen may increase the risk of stomach bleeding.[29]

According to the US Food and Drug Administration, "ibuprofen can interfere with the antiplatelet effect of low-dose aspirin, potentially rendering aspirin less effective when used for cardioprotection and stroke prevention." Allowing sufficient time between doses of ibuprofen and immediate-release (IR) aspirin can avoid this problem. The recommended elapsed time between a dose of ibuprofen and a dose of aspirin depends on which is taken first. It would be 30 minutes or more for ibuprofen taken after IR aspirin, and 8 hours or more for ibuprofen taken before IR aspirin. However, this timing cannot be recommended for enteric-coated aspirin. But, if ibuprofen is taken only occasionally without the recommended timing, the reduction of the cardioprotection and stroke prevention of a daily aspirin regimen is minimal.[30]

## Overdose [edit]

Ibuprofen overdose has become common since it was licensed for OTC use. Many overdose experiences are reported in the medical literature, although the frequency of life-threatening complications from ibuprofen overdose is low.[31] Human response in cases of overdose ranges from absence of symptoms to fatal outcome despite intensive-care treatment. Most symptoms are an excess of the pharmacological action of ibuprofen, and include abdominal pain, nausea, vomiting, drowsiness, dizziness, headache, tinnitus, and nystagmus. Rarely, more severe symptoms, such as gastrointestinal bleeding, seizures, metabolic acidosis, hyperkalaemia, hypotension, bradycardia, tachycardia, atrial fibrillation, coma, hepatic dysfunction, acute renal failure, cyanosis, respiratory depression, and cardiac arrest have been reported.[32] The severity of symptoms varies with the ingested dose and the time elapsed; however, individual sensitivity also plays an important role. Generally, the symptoms observed with an overdose of ibuprofen are similar to the symptoms caused by overdoses of other NSAIDs.

Correlation between severity of symptoms and measured ibuprofen plasma levels is weak. Toxic effects are unlikely at doses below 100 mg/kg, but can be severe above 400 mg/kg (around 150 tablets of 200 mg units for an average man);[33] however, large doses do not indicate the clinical course is likely to be lethal.[34] A precise lethal dose is difficult to determine, as it may vary with age, weight, and concomitant conditions of the individual person.

Therapy is largely symptomatic. In cases presenting early, gastric decontamination is recommended. This is achieved using activated charcoal; charcoal adsorbs the drug before it can enter the systemic circulation. Gastric lavage is now rarely used, but can be considered if the amount ingested is potentially life-threatening, and it can be performed within 60 minutes of ingestion. Emesis is not recommended.[35] The majority of ibuprofen ingestions produce only mild effects and the management of overdose is straightforward. Standard measures to maintain normal urine output should be instituted and renal function monitored.[33] Since ibuprofen has acidic properties and is also excreted in the urine, forced alkaline diuresis is theoretically beneficial. However, because ibuprofen is highly protein-bound in the blood, renal excretion of unchanged drug is minimal. Forced alkaline diuresis is, therefore, of limited benefit.[36] Symptomatic therapy for hypotension, gastrointestinal bleeding, acidosis, and renal toxicity may be indicated. On occasion, close monitoring in an intensive-care unit for several days is necessary. A patient who survives the acute intoxication usually experiences no late sequelae.

### Miscarriage [edit]

A study of pregnant woman suggests those taking any type or amount of NSAIDs (including ibuprofen, diclofenac and naproxen) were 2.4 times more likely to miscarry than those not taking the drugs.[37] However, an Israeli study found no increased risk of miscarriage in the group of mothers using NSAIDs.[38]

## Mechanism of action [edit]

Nonsteroidal anti-inflammatory drugs such as ibuprofen work by inhibiting the cyclooxygenase (COX) enzymes, which convert arachidonic acid to prostaglandin $H_2$ ($PGH_2$). $PGH_2$, in turn, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation, and fever) and to thromboxane $A_2$ (which stimulates platelet aggregation, leading to the formation of blood clots).

Like aspirin and indometacin, ibuprofen is a nonselective COX inhibitor, in that it inhibits two isoforms of cyclooxygenase, COX-1 and COX-2. The analgesic, antipyretic, and anti-inflammatory activity of NSAIDs appears to operate mainly through inhibition of COX-2, which decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever, and swelling. Antipyretic effects may be due to action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation. Inhibition of COX-1 instead would be responsible for unwanted effects on the gastrointestinal tract.[39] However, the role of the individual COX isoforms in the analgesic, anti-inflammatory, and gastric damage effects of NSAIDs is uncertain and different compounds cause different degrees of analgesia and gastric damage.[40]

Ibuprofen is administered as a racemic mixture. The R-enantiomer undergoes extensive interconversion to the S-enantiomer *in vivo*. The S-enantiomer is believed to be the more pharmacologically active enantiomer.[41] The R-enantiomer is converted through a series of three main enzymes. These enzymes include acyl-CoA-synthetase, which converts the R-enantiomer to (-)-R-ibuprofen I-CoA; 2-arylpropionyl-CoA epimerase, which converts (-)-R-ibuprofen I-CoA to (+)-S-Ibuprofen I-CoA; and hydrolase, which converts (+)-S-ibuprofen I-CoA to the S-enantiomer.[28] In addition to the conversion of ibuprofen to the S-enantiomer, the body can metabolize ibuprofen to several other compounds, including numerous hydroxyl, carboxyl and glucuronyl metabolites. Virtually all of these have no pharmacological effects.[28]

## Chemistry [edit]

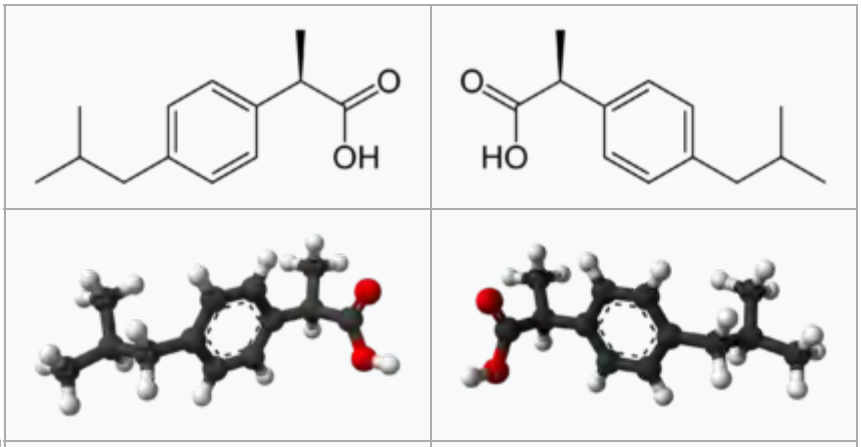
It is practically insoluble in water, but very soluble in most organic solvents (ethanol, methanol, acetone and dichloromethane).[42]

The original synthesis of ibuprofen by the Boots Group started with the compound 2-methylpropylbenzene. The synthesis took six steps. A modern, greener technique for the synthesis involves only three steps.[43]

### Stereochemistry [edit]

It is an optically active compound with both *S* and *R*-isomers, of which the *S* (dextrorotatory) isomer is the more biologically active; this isomer has also been isolated and used medically (see dexibuprofen for details).[42]

Ibuprofen is produced industrially as a racemate. The compound, like other 2-arylpropionate derivatives (including ketoprofen, flurbiprofen, naproxen, etc.), does contain a chiral center in the α-position of the propionate moiety. So two enantiomers of ibuprofen occur, with the potential for different biological effects and metabolism for each enantiomer. Indeed, the (*S*)-(+)-ibuprofen (dexibuprofen) was found to be the active form both *in vitro* and *in vivo*.




(*R*)-ibuprofen | (*S*)-ibuprofen

An isomerase (alpha-methylacyl-CoA racemase) converts (*R*)-ibuprofen to the active (*S*)-enantiomer.[44][45][46]

## History [edit]

Ibuprofen was derived from propionic acid by the research arm of Boots Group during the 1960s.[47] Its discovery was the result of research during the 1950s and 1960s to find a safer alternative to aspirin.[7][48] It was discovered by a team led by Stewart Adams and the patent application was filed in 1961.[7] Adams initially tested the drug as treatment for his hangover.[49] The drug was launched as a treatment for rheumatoid arthritis in the United Kingdom in 1969, and in the United States in 1974. Later, in 1983 and 1984, it became the first NSAID (other than aspirin) to be available over the counter (OTC) in these two countries.[7][48] Dr. Adams was subsequently awarded an OBE in 1987. Boots was awarded the Queen's Award for Technical Achievement for the development of the drug in 1987.[7]

## Marketing [edit]

*See also: Ibuprofen brand names*

Ibuprofen was made available under prescription in the United Kingdom in 1969, and in the United States in 1974.[50] In the years since, the good tolerability profile, along with extensive experience in the population, as well as in so-called phase-IV trials (postapproval studies), have resulted in the availability of ibuprofen OTC in pharmacies worldwide, as well as in supermarkets and other general retailers.[*citation needed*] Ibuprofen is its INN, BAN, AAN and USAN approved name. Advil is manufactured by Pfizer and has been on the market since 1984.


A bottle of generic ibuprofen

### North America [edit]

Ibuprofen is commonly available in the United States up to the FDA's 1984 dose limit OTC, rarely used higher by prescription.[51] In 2009, the first injectable formulation of ibuprofen was approved in the United States, under the trade name Caldolor.[52][53]

## Research [edit]

Ibuprofen is sometimes used for the treatment of acne because of its anti-inflammatory properties, and has been sold in Japan in topical form for adult acne.[54][55] As with other NSAIDs, ibuprofen may be useful in the treatment of severe orthostatic hypotension (low blood pressure when standing up).[56] In some studies, ibuprofen showed superior results compared with a placebo in the prevention of Alzheimer's disease, when given in low doses over a long time.[57][58]

Ibuprofen has been associated with a lower risk of Parkinson's disease, and may delay or prevent it. Aspirin, other NSAIDs, and paracetamol (acetaminophen) had no effect on the risk for Parkinson's.[59] In March 2011, researchers at Harvard Medical School announced in *Neurology* that ibuprofen had a neuroprotective effect against the risk of developing Parkinson's disease.[60][61][62] People regularly consuming ibuprofen were reported to have a 38% lower risk of developing Parkinson's disease, but no such effect was found for other pain relievers, such as aspirin and paracetamol. Use of ibuprofen to lower the risk of Parkinson's disease in the general population would not be problem-free, given the possibility of adverse effects on the urinary and digestive systems.[63]

## References [edit]


1. ^ *a b c d e* Davies, NM (February 1998). "Clinical pharmacokinetics of ibuprofen. The first 30 years.". *Clinical Pharmacokinetics*. **34** (2): 101–54. doi:10.2165/00003088-199834020-00002. PMID 9515184.
2. ^ "ibuprofen". Retrieved 31 January 2015.
3. ^ "PRODUCT INFORMATION BRUFEN® TABLETS AND SYRUP" (PDF). *TGA eBusiness Services*. Abbott Australasia Pty Ltd. 31 July 2012. Retrieved 8 May 2014.
4. ^ *a b c d e f g h i j k* "Ibuprofen". The American Society of Health-System Pharmacists. Retrieved 2016-10-12.
5. ^ *a b c d* *Bnf : march 2014-september 2014.* (2014 ed.). London: British Medical Assn. 2014. pp. 686–688. ISBN 0857110861.
6. ^ "Ibuprofen Pregnancy and Breastfeeding Warnings". *Drugs.com*. Retrieved 22 May 2016.
7. ^ *a b c d e f* Halford, GM; Lordkipanidzé, M; Watson, SP (2012). "50th anniversary of the discovery of ibuprofen: an interview with Dr Stewart Adams.". *Platelets*. **23** (6): 415–22. doi:10.3109/09537104.2011.632032. PMID 22098129.
8. ^ "Chemistry in your cupboard | Nurofen".
9. ^ *WHO Model List of Essential Medicines* (PDF) (16th ed.). World Health Organization. March 2009. Retrieved 28 March 2011.
10. ^ "Ibuprofen". Retrieved 12 January 2016.
11. ^ "10.1.1 Non-steroidal anti-inflammatory drugs". *: British National Formulary*. Retrieved 13 April 2016.
12. ^ Joint Formulary Committee (2013). *British National Formulary (BNF)* (65 ed.). London, UK: Pharmaceutical Press. pp. 665, 671. ISBN 978-0-85711-084-8.
13. ^ *a b c* Rossi, S, ed. (2013). *Australian Medicines Handbook* (2013 ed.). Adelaide: The Australian Medicines Handbook Unit Trust. ISBN 978-0-9805790-9-3.
14. ^ "Ibuprofen". *The American Society of Health-System Pharmacists*. Retrieved 3 April 2011.
15. ^ Beaver, WT (2003). "Review of the analgesic efficacy of ibuprofen". *Int J Clin Pract Suppl*: 13–7. PMID 12723741.
16. ^ Fanos, V; Antonucci, R; Zaffanello, M (2010). "Ibuprofen and acute kidney injury in the newborn". *Turk. J. Pediatr*. **52**: 231–8. PMID 20718179.
17. ^ Castellsague, Dr Jordi; Riera-Guardia, Nuria; Calingaert, Brian; Varas-Lorenzo, Cristina; Fourrier-Reglat, Annie; Nicotra, Federica; Sturkenboom, Miriam; Perez-Gutthann, Susana; Project, Safety of Non-Steroidal Anti-Inflammatory Drugs (SOS) (2012-12-13). "Individual NSAIDs and Upper Gastrointestinal Complications". *Drug Safety*. **35** (12): 1127–1146. doi:10.1007/BF03261999. ISSN 0114-5916. PMC 3714137. PMID 23137151.
18. ^ Ayres, JG; Fleming, D; Whittington, R (9 May 1987). "Asthma death due to ibuprofen". *Lancet*. **1** (8541): 1082. doi:10.1016/S0140-6736(87)90499-5. PMID 2883408.
19. ^ Baselt, R (2008). *Disposition of Toxic Drugs and Chemicals in Man* (8th ed.). Foster City, USA: Biomedical Publications. pp. 758–761.
20. ^ Forman, JP; Stampfer, MJ; Curhan, GC (September 2005). "Non-narcotic analgesic dose and risk of incident hypertension in US women.". *Hypertension*. **46** (3): 500–7. doi:10.1161/01.HYP.0000177437.07240.70. PMID 16103274.
21. ^ Hippisley-Cox, J; Coupland, C (11 June 2005). "Risk of myocardial infarction in patients taking cyclo-oxygenase-2

inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis.". *British Medical Journal*. **330** (7504): 1366. doi:10.1136/bmj.330.7504.1366. PMC 558288. PMID 15947398.
22. ^ Gurwitz, JH; Everitt, DE; Monane, M; Glynn, RJ; Choodnovskiy, I; Beaudet, MP; Avorn, J (March 1996). "The impact of ibuprofen on the efficacy of antihypertensive treatment with hydrochlorothiazide in elderly persons.". *The Journals of Gerontology. Series A, Biological Sciences and Medical sciences*. **51** (2): M74–9. doi:10.1093/gerona/51A.2.M74. PMID 8612107.
23. ^ Staff (9 July 2015). "FDA Strengthens Warning of Heart Attack and Stroke Risk for Non-Steroidal Anti-Inflammatory Drugs". *FDA*. Retrieved 9 July 2015.
24. ^ Chan, LS (12 June 2014). Hall, R; Vinson, RP; Nunley, JR; Gelfand, JM; Elston, DM, eds. "Bullous Pemphigoid Clinical Presentation". *Medscape Reference*. United States: WebMD.
25. ^ Bergner, T; Przybilla, B (January 1992). "Photosensitization caused by ibuprofen.". *Journal of the American Academy of Dermatology*. **26** (1): 114–6. doi:10.1016/0190-9622(92)70018-b. PMID 1531054.
26. ^ Raksha, MP; Marfatia, YS (2008). "Clinical study of cutaneous drug eruptions in 200 patients". *Indian J Dermatol Venereol Leprol*. **74** (1): 80. doi:10.4103/0378-6323.38431. PMID 18193504.
27. ^ Ward, KE; Archambault, R; Mersfelder, TL (1 February 2010). "Severe adverse skin reactions to nonsteroidal antiinflammatory drugs: A review of the literature.". *American Journal of Health-System Pharmacy*. **67** (3): 206–13. doi:10.2146/ajhp080603. PMID 20101062.
28. ^ [a] [b] [c] Rainsford, K.D. (2012). *Ibuprofen: Pharmacology, Therapeutics and Side Effects*. London: Springer.
29. ^ "Ibuprofen". Drugs.com.
30. ^ "Information for Healthcare Professionals: Concomitant Use of Ibuprofen and Aspirin". U.S. Food and Drug Administration. September 2006. Retrieved 22 November 2010.
31. ^ McElwee, NE; Veltri, JC; Bradford, DC; Rollins, DE (June 1990). "A prospective, population-based study of acute ibuprofen overdose: complications are rare and routine serum levels not warranted.". *Annals of Emergency Medicine*. **19** (6): 657–62. doi:10.1016/S0196-0644(05)82471-0. PMID 2188537.
32. ^ Vale, JA; Meredith, TJ (January 1986). "Acute poisoning due to non-steroidal anti-inflammatory drugs. Clinical features and management.". *Medical Toxicology*. **1** (1): 12–31. PMID 3537613.
33. ^ [a] [b] Volans, G; Hartley, V; McCrea, S; Monaghan, J (March–April 2003). "Non-opioid analgesic poisoning.". *Clinical Medicine*. **3** (2): 119–23. doi:10.7861/clinmedicine.3-2-119. PMID 12737366.
34. ^ Seifert, SA; Bronstein, AC; McGuire, T (2000). "Massive ibuprofen ingestion with survival.". *Journal of Toxicology. Clinical Toxicology*. **38** (1): 55–7. doi:10.1081/clt-100100917. PMID 10696926.
35. ^ "Position paper: Ipecac syrup.". *Journal of Toxicology. Clinical Toxicology*. **42** (2): 133–143. 2004. doi:10.1081/CLT-120037421. PMID 15214617.
36. ^ Hall, AH; Smolinske, SC; Conrad, FL; Wruk, KM; Kulig, KW; Dwelle, TL; Rumack, BH (November 1986). "Ibuprofen overdose: 126 cases.". *Annals of Emergency Medicine*. **15** (11): 1308–13. doi:10.1016/S0196-0644(86)80617-5. PMID 3777588.
37. ^ Verma, P; Clark, CA; Spitzer, KA; Laskin, CA; Ray, J; Koren, G (July 2012). "Use of non-aspirin NSAIDs during pregnancy may increase the risk of spontaneous abortion.". *Evidence-Based Nursing*. **15** (3): 76–7. doi:10.1136/ebnurs-2011-100439. PMID 22411163.
38. ^ Daniel, S; Koren, G; Lunenfeld, E; Bilenko, N; Ratzon, R; Levy, A (March 2014). "Fetal exposure to nonsteroidal anti-inflammatory drugs and spontaneous abortions.". *Canadian Medical Association Journal*. **186** (5): E177–82. doi:10.1503/cmaj.130605. PMC 3956584. PMID 24491470.
39. ^ Rao, P; Knaus, EE (20 September 2008). "Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond.". *Journal of Pharmacy & Pharmaceutical Sciences*. **11** (2): 81s–110s. PMID 19203472.
40. ^ Kakuta, H; Zheng, X; Oda, H; Harada, S; Sugimoto, Y; Sasaki, K; Tai, A (24 April 2008). "Cyclooxygenase-1-selective inhibitors are attractive candidates for analgesics that do not cause gastric damage. design and in vitro/in vivo evaluation of a benzamide-type cyclooxygenase-1 selective inhibitor.". *Journal of Medicinal Chemistry*. **51** (8): 2400–11. doi:10.1021/jm701191z. PMID 18363350.
41. ^ "Ibuprofen: Pharmacology: Mechanism of Action. Updated on September 16, 2013". *DrugBank, Open Data Drug & Drug Target Database*. Retrieved 24 July 2014.
42. ^ [a] [b] Brayfield, A, ed. (14 January 2014). "Ibuprofen". *Martindale: The Complete Drug Reference*. London, UK: Pharmaceutical Press. Retrieved 26 June 2014.
43. ^ "The Synthesis of Ibuprofen". Royal Society of Chemistry. Retrieved 14 November 2016.
44. ^ Tracy, TS; Hall, SD (March–April 1992). "Metabolic inversion of (R)-ibuprofen. Epimerization and hydrolysis of ibuprofenyl-coenzyme A.". *Drug metabolism and disposition: the biological fate of chemicals*. **20** (2): 322–7. PMID 1352228.
45. ^ Chen, CS; Shieh, WR; Lu, PH; Harriman, S; Chen, CY (12 July 1991). "Metabolic stereoisomeric inversion of ibuprofen in mammals.". *Biochimica et Biophysica Acta*. **1078** (3): 411–7. doi:10.1016/0167-4838(91)90164-U.

PMID 1859831.
46. ^ Reichel, C; Brugger, R; Bang, H; Geisslinger, G; Brune, K (April 1997). "Molecular cloning and expression of a 2-arylpropionyl-coenzyme A epimerase: a key enzyme in the inversion metabolism of ibuprofen.". *Molecular Pharmacology*. **51** (4): 576–82. PMID 9106621.
47. ^ Adams, SS (April 1992). "The propionic acids: a personal perspective.". *Journal of Clinical Pharmacology*. **32** (4): 317–23. doi:10.1002/j.1552-4604.1992.tb03842.x. PMID 1569234.
48. ^ *a b* Rainsford, KD (April 2003). "Discovery, mechanisms of action and safety of ibuprofen.". *International Journal of Clinical Practice. Supplement* (135): 3–8. PMID 12723739.
49. ^ Lambert, Victoria (8 October 2007). "Dr Stewart Adams: 'I tested ibuprofen on my hangover'". *The Daily Telegraph*. UK. Retrieved 23 October 2015.
50. ^ "Written submission to the NDAC meeting on risks of NSAIDs presented by the International Ibuprofen Foundation". International Ibuprofen Foundation. August 2002. Retrieved 20 March 2014.
51. ^ "Ibuprofen". U.S. Food and Drug Administration (FDA).
52. ^ "Drug Approval Package: Caldolor (Ibuprofen) NDA #022348". U.S. Food and Drug Administration (FDA). 11 March 2010.
53. ^ "FDA Approves Injectable Form of Ibuprofen" (Press release). U.S. Food and Drug Administration (FDA). 11 June 2009.
54. ^ Wong, RC; Kang, S; Heezen, JL; Voorhees, JJ; Ellis, CN (December 1984). "Oral ibuprofen and tetracycline for the treatment of acne vulgaris.". *Journal of the American Academy of Dermatology*. **11** (6): 1076–81. doi:10.1016/S0190-9622(84)80192-9. PMID 6239884.
55. ^ "In Japan, an OTC ibuprofen ointment (Fukidia) for alleviating adult acne has been launched". *Inpharma*. Adis. **1** (1530): 18. 25 March 2006. doi:10.2165/00128413-200615300-00043. ISSN 1173-8324.
56. ^ Zawada ET, Jr (May 1982). "Renal consequences of nonsteroidal antiinflammatory drugs.". *Postgraduate Medicine*. **71** (5): 223–30. PMID 7041104.
57. ^ Townsend, KP; Praticò, D (October 2005). "Novel therapeutic opportunities for Alzheimer's disease: focus on nonsteroidal anti-inflammatory drugs.". *FASEB Journal*. **19** (12): 1592–601. doi:10.1096/fj.04-3620rev. PMID 16195368.
58. ^ Vlad, SC; Miller, DR; Kowall, NW; Felson, DT (6 May 2008). "Protective effects of NSAIDs on the development of Alzheimer disease.". *Neurology*. **70** (19): 1672–7. doi:10.1212/01.wnl.0000311269.57716.63. PMC 2758242. PMID 18458226.
59. ^ Chen, H; Jacobs, E; Schwarzschild, MA; McCullough, ML; Calle, EE; Thun, MJ; Ascherio, A (December 2005). "Nonsteroidal antiinflammatory drug use and the risk for Parkinson's disease.". *Annals of Neurology*. **58** (6): 963–7. doi:10.1002/ana.20682. PMID 16240369.
60. ^ Bower, JH; Ritz, B (8 March 2011). "Is the answer for Parkinson disease already in the medicine cabinet?: Unfortunately not.". *Neurology*. **76** (10): 854–5. doi:10.1212/WNL.0b013e31820f2e7a. PMID 21368280.
61. ^ Gao, X; Chen, H; Schwarzschild, MA; Ascherio, A (8 March 2011). "Use of ibuprofen and risk of Parkinson disease.". *Neurology*. **76** (10): 863–9. doi:10.1212/WNL.0b013e31820f2d79. PMC 3059148. PMID 21368281.
62. ^ McSharry, C (May 2011). "Parkinson disease: Could over-the-counter treatment protect against Parkinson disease?". *Nature Reviews. Neurology*. **7** (5): 244. doi:10.1038/nrneurol.2011.49. PMID 21555992.
63. ^ Gleason, JM; Slezak, JM; Jung, H; Reynolds, K; Van den Eeden, SK; Haque, R; Quinn, VP; Loo, RK; Jacobsen, SJ (April 2011). "Regular nonsteroidal anti-inflammatory drug use and erectile dysfunction". *The Journal of Urology*. **185** (4): 1388–93. doi:10.1016/j.juro.2010.11.092. PMID 21334642.

## External links [edit]

- U.S. National Library of Medicine: MedlinePlus Drug Information: Ibuprofen
- University of Bristol chemistry department page on Ibuprofen
- U.S. National Library of Medicine: Drug Information Portal – Ibuprofen

Wikimedia Commons has media related to *Ibuprofen*.

| v · t · e | **Non-steroidal anti-inflammatory drugs (NSAIDs) (primarily M01A and M02A, also N02BA)** |
|---|---|
| **Pyrazolones /** | Aminophenazone · Ampyrone · Azapropazone · Clofezone · Difenamizole · Famprofazone · Feprazone · Kebuzone · Metamizole · Mofebutazone · Morazone · Nifenazone · |

| | |
|---|---|
| **Pyrazolidines** | Oxyphenbutazone · Phenazone · **Phenylbutazone** · Propyphenazone · Sulfinpyrazone · Suxibuzone‡ · |
| **Salicylates** | **Aspirin (acetylsalicylic acid)**# · Aloxiprin · Benorylate · Carbasalate calcium · Diflunisal · Dipyrocetyl · Ethenzamide · Guacetisal · Magnesium salicylate · Methyl salicylate · Salsalate · Salicin · Salicylamide · Salicylic acid (salicylate) · Sodium salicylate · |
| **Acetic acid derivatives and related substances** | Aceclofenac · Acemetacin · Alclofenac · Amfenac · Bendazac · Bromfenac · Bumadizone · Bufexamac · **Diclofenac** · Difenpiramide · Etodolac · Felbinac · Fenclozic acid · Fentiazac · Indomethacin · Indomethacin farnesil · Isoxepac · Ketorolac · Lonazolac · Oxametacin · Prodolic acid · Proglumetacin · Sulindac · Tiopinac · Tolmetin · Zomepirac† · |
| **Oxicams** | Ampiroxicam · Droxicam · Isoxicam · Lornoxicam · Meloxicam · **Piroxicam** · Tenoxicam · |
| **Propionic acid derivatives (profens)** | Alminoprofen · Benoxaprofen† · Carprofen‡ · Dexibuprofen · Dexketoprofen · Fenbufen · Fenoprofen · Flunoxaprofen · Flurbiprofen · **Ibuprofen**# · Ibuproxam · Indoprofen† · Ketoprofen · Loxoprofen · Miroprofen · **Naproxen** · Oxaprozin · Pirprofen · Suprofen · Tarenflurbil · Tepoxalin‡ · Tiaprofenic acid · Vedaprofen‡ · *COX-inhibiting nitric oxide donator*: Naproxcinod · |
| ***N*-Arylanthranilic acids (fenamates)** | Azapropazone · Clonixin · Etofenamate · Flufenamic acid · Flunixin · Meclofenamic acid · **Mefenamic acid** · Morniflumate · Niflumic acid · Tolfenamic acid · Flutiazin · |
| **Coxibs** | Apricoxib · **Celecoxib** · Cimicoxib‡ · Deracoxib‡ · Etoricoxib · Firocoxib‡ · Lumiracoxib† · Mavacoxib‡ · Parecoxib · Robenacoxib‡ · Rofecoxib† · Valdecoxib† · |
| **Other** | Aminopropionitrile · Benzydamine · Chondroitin sulfate · Diacerein · Fluproquazone · Glucosamine · Glycosaminoglycan · Hyperforin · Nabumetone · Nimesulide · Oxaceprol · Proquazone · Superoxide dismutase/Orgotein · Tenidap · |

Items listed in **bold** indicate initially developed compounds of specific groups. #WHO-EM †Withdrawn drugs. ‡Veterinary use medications.

| v · t · e · | **Topical products for joint and muscular pain (M02)** | |
|---|---|---|
| **Anti-inflammatory preparations, non-steroids** | **Pyrazolidines** | Clofezone · Mofebutazone · Oxyphenbutazone · Phenylbutazone · |
| | **Acetic acid derivatives** | Diclofenac · Fentiazac · Tolmetin · |
| | **Other** | Bendazac · Benzydamine · Bufexamac · Etofenamate · Felbinac · Feprazone · Flurbiprofen · **Ibuprofen** · Indometacin · Ketoprofen · Meclofenamic acid · Naproxen · Nifenazone · Niflumic acid · Piketoprofen · Piroxicam · Suxibuzone · |
| **Capsaicin derivatives** | Zucapsaicin · | |
| **Other** | Dimethyl sulfoxide · Idrocilamide · Tolazoline · | |

| v · t · e · | **Analgesics (N02A, N02B)** | |
|---|---|---|
| | **Opiates/opium** | Codeine# (+paracetamol, +aspirin) · Morphine# (+naltrexone) · Opium · Laudanum · Paregoric · |
| | | Acetyldihydrocodeine · Benzylmorphine · Buprenorphine (+naloxone) · |

| | | |
|---|---|---|
| **Opioids** | **Semisynthetic** | Desomorphine · Diamorphine (heroin) · Dihydrocodeine (+paracetamol) · Dihydromorphine · Ethylmorphine · Hydrocodone (+paracetamol, +ibuprofen, +aspirin) · Hydromorphinol · Hydromorphone · Nicocodeine · Nicodicodeine · Nicomorphine · Oxycodone (+paracetamol, +aspirin, +ibuprofen, +naloxone, +naltrexone) · Oxymorphone · Thebacon · |
| | **Synthetic** | Alphaprodine · Anileridine · Butorphanol · Dextromoramide · Dextropropoxyphene · Dezocine · Fentanyl (+fluanisone) · Ketobemidone · Levorphanol · Meptazinol · Methadone · Nalbuphine · Pentazocine · Pethidine · Phenadoxone · Phenazocine · Piminodine · Piritramide · Propiram · Tapentadol · Tilidine · Tramadol · |
| **Paracetamol-type** | | Acetanilide‡ · Bucetin‡ · Butacetin‡ · Paracetamol (acetaminophen)# · Parapropamol‡ · Phenacetin‡ · Propacetamol‡ · |
| **NSAIDs** | **Propionates** | Fenoprofen · Flurbiprofen · **Ibuprofen**# · Ketoprofen · Naproxen · Oxaprozin · |
| | **Oxicams** | Meloxicam · Piroxicam · |
| | **Acetates** | Diclofenac · Indometacin · Ketorolac · Nabumetone · Sulindac · Tolmetin · |
| | **COX-2 inhibitors** | Celecoxib · Etoricoxib · Lumiracoxib · Parecoxib · Rofecoxib ‡ · Valdecoxib ‡ · |
| | **Fenamates** | Meclofenamic acid · Mefenamic acid · |
| | **Salicylates** | Aspirin (acetylsalicylic acid)# (+paracetamol/caffeine) · Benorylate · Diflunisal · Ethenzamide · Magnesium salicylate · Salicin · Salicylamide · Salsalate · Wintergreen (methyl salicylate) · |
| | **Pyrazolones** | Aminophenazone‡ · Ampyrone · Metamizole (dipyrone) · Nifenazone · Phenazone · Propyphenazone · |
| | **Others** | Glafenine · |
| **Cannabinoids** | | Cannabidiol · Cannabis · Nabilone · Nabiximols · Tetrahydrocannabinol (dronabinol) · |
| **Ion channel modulators** | **Calcium blockers** | Gabapentin · Gabapentin enacarbil · Pregabalin · Ziconotide · |
| | **Sodium blockers** | Carbamazepine · Lacosamide · Local anesthetics (e.g., cocaine, lidocaine) · Mexiletine · Nefopam · Tricyclic antidepressants (e.g., amitriptyline#) · *$Na_v1.7/1.8$-selective:* DSP-2230§ · Funapide§ · PF-05089771§ · Raxatrigine§ · |
| | **Potassium openers** | Flupirtine · |
| **Myorelaxants** | | Carisoprodol · Chlorzoxazone · Cyclobenzaprine · Mephenoxalone · Methocarbamol · Orphenadrine · |
| **Others** | | Camphor · Capsaicin · Clonidine · Ketamine · Menthol · Methoxyflurane · Nefopam · Proglumide · Tricyclic antidepressants (e.g., amitriptyline#) · |

· #WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · ·

| | |
|---|---|
| v · t · e · | **Acne-treating agents (D10)** |
| **Antibacterial** | Azelaic acid · Benzoyl peroxide# · 8-Hydroxyquinoline · Blue light therapy · Tea tree oil · |

| | |
|---|---|
| **Keratolytic** | Glycolic acid · Salicylic acid[#] · Sulfur · Benzoyl peroxide[#] · |
| **Anti-inflammatory** | Nicotinamide · **Ibuprofen** # · Aspirin # · Red light therapy · |
| **Antibiotics** | Clindamycin · Dapsone · Erythromycin · Sulfacetamide · Tetracyclines (Lymecycline · Minocycline · Doxycycline) · |
| **Hormonal** | Antiandrogens (Bicalutamide · Cyproterone acetate · Drospirenone · Flutamide · Spironolactone) · · Estrogens (Estradiol · Ethinylestradiol · · |
| **Retinoids** | Adapalene · Isotretinoin · Motretinide · Tazarotene · Tretinoin · |
| **Other** | Benzamycin · Epristeride · Mesulfen · Pelretin · Stridex · Tioxolone · |
| **Combinations** | Adapalene/benzoyl peroxide · Benzoyl peroxide/clindamycin · Clindamycin/tretinoin · Erythromycin/isotretinoin · Sulfacetamide/sulfur · |

· [#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III · ·

| v · t · e · **Prolactin inhibitors and anti-inflammatory products for vaginal administration (G02CB–G02CC)** | |
|---|---|
| **Prolactin inhibitors** | Bromocriptine · Lisuride · Cabergoline · Quinagolide · Metergoline · Terguride · |
| **Anti-inflammatory products for vaginal administration** | **Ibuprofen** · Naproxen · Benzydamine · Flunoxaprofen · |

| v · t · e · **Prostanoid signaling modulators** | | | |
|---|---|---|---|
| **Receptor (ligands)** | **DP ($D_2$)** | **$DP_1$** | **Agonists:** Prostaglandin $D_2$ · Treprostinil · **Antagonists:** Asapiprant · Laropiprant · Vidupiprant · |
| | | **$DP_2$** | **Agonists:** Indometacin · Prostaglandin $D_2$ · **Antagonists:** ADC-3680 · AZD-1981 · Bay U3405 · Fevipiprant · MK-1029 · MK-7246 · OC-459 · OC000459 · QAV-680 · Ramatroban · Setipiprant · TM30089 · Vidupiprant · |
| | **EP ($E_2$)** | **$EP_1$** | **Agonists:** Beraprost · Enprostil · Iloprost (ciloprost) · Latanoprost · Lubiprostone · Misoprostol · Prostaglandin $E_1$ (alprostadil) · Prostaglandin $E_2$ (dinoprostone) · Sulprostone · **Antagonists:** AH-6809 · ONO-8130 · SC-19220 · SC-51089 · SC-51322 · |
| | | **$EP_2$** | **Agonists:** Butaprost · Misoprostol · Prostaglandin $E_1$ (alprostadil) · Prostaglandin $E_2$ (dinoprostone) · Treprostinil · **Antagonists:** AH-6809 · PF-04418948 · TG 4-155 · |
| | | **$EP_3$** | **Agonists:** Beraprost · Carbacyclin · Cicaprost · Enprostil · Iloprost (ciloprost) · Isocarbacyclin · Latanoprost · Misoprostol · Prostaglandin $D_2$ · Prostaglandin $E_1$ (alprostadil) · Prostaglandin $E_2$ (dinoprostone) · Remiprostol · Sulprostone · **Antagonists:** L-798106 · |
| | | **$EP_4$** | **Agonists:** Lubiprostone · Misoprostol · Prostaglandin $E_1$ (alprostadil) · Prostaglandin $E_2$ (dinoprostone) · TCS-2510 · **Antagonists:** GW-627368 · L-161982 · ONO-AE3-208 · |
| | | **Unsorted** | **Agonists:** 16,16-Dimethyl Prostaglandin $E_2$ · Aganepag · Carboprost · Evatanepag · Gemeprost · Nocloprost · Omidenepag · |

| | | |
|---|---|---|
| | | Prostaglandin $F_{2\alpha}$ (dinoprost) · Simenepag · Taprenepag · |
| | **FP ($F_{2\alpha}$)** | **Agonists:** Alfaprostol · Bimatoprost · Carboprost · Cloprostenol · Enprostil · Fluprostenol · Latanoprost · Prostaglandin $D_2$ · Prostaglandin $F_{2\alpha}$ (dinoprost) · Sulotroban · Tafluprost · Travoprost · Unoprostone · |
| | **IP ($I_2$)** | **Agonists:** ACT-333679 · AFP-07 · Beraprost · BMY-45778 · Carbacyclin · Cicaprost · Iloprost (ciloprost) · Isocarbacyclin · MRE-269 · NS-304 · Prostacyclin (prostaglandin $I_2$, epoprostenol) · Prostaglandin $E_1$ (alprostadil) · Ralinepag · Selexipag · Taprostene · TRA-418 · Treprostinil · **Antagonists:** RO1138452 · |
| | **TP ($TX_{A2}$)** | **Agonists:** Carbocyclic thromboxane $A_2$ · I-BOP · Thromboxane $A_2$ · U-46619 · Vapiprost · **Antagonists:** 12-HETE · 13-APA · AA-2414 · Argatroban · Bay U3405 · BMS-180,291 · Daltroban · Domitroban · EP-045 · GR-32191 · ICI-185282 · ICI-192605 · Ifetroban · Imitrodast · L-655240 · L-670596 · Linotroban · Mipitroban · ONO-3708 · ONO-11120 · Picotamide · Pinane thromboxane $A_2$ · Ramatroban · Ridogrel · S-145 · Samixogrel · Seratrodast · SQ-28,668 · SQ-29,548 · Sulotroban · Terbogrel · Terutroban · TRA-418 · |
| | **Unsorted** | Arbaprostil · Ataprost · Ciprostene · Clinprost · Cobiprostone · Delprostenate · Deprostil · Dimoxaprost · Doxaprost · Ecraprost · Eganoprost · Enisoprost · Eptaloprost · Esuberaprost · Etiproston · Fenprostalene · Flunoprost · Froxiprost · Lanproston · Limaprost · Luprostiol · Meteneprost · Mexiprostil · Naxaprostene · Nileprost · Nocloprost · Ornoprostil · Oxoprostol · Penprostene · Pimilprost · Piriprost · Posaraprost · Prostalene · Rioprostil · Rivenprost · Rosaprostol · Spiriprostil · Tiaprost · Tilsuprost · Tiprostanide · Trimoprostil · Viprostol · |
| **Enzyme** (**inhibitors**) | **COX (PTGS)** | Aceclofenac · Acemetacin · Acetanilide · Alclofenac · Alminoprofen · Aloxiprin · AM404 · Amfenac · Ampiroxicam · Anitrazafen · Antrafenine · Apricoxib · Aspirin (acetylsalicylic acid) · Azapropazone · Bendazac · Benorilate (benorylate) · Benoxaprofen · Bromfenac · Bucetin · Bucloxic acid (blucloxate) · Bufexamac · Bumadizone · Butibufen · Carbasalate calcium · Carprofen · Celecoxib · Cimicoxib · Cinmetacin · Clobuzarit · Clometacin · Clonixeril · Clonixin · Curcumin · Deracoxib · Dexibuprofen · Dexindoprofen · Dexketoprofen · Diclofenac · Difenpiramide · Diflunisal · Dipyrocetyl · Droxicam · DuP-697 · Enolicam · Ethenzamide · Etodolac · Etofenamate · Etoricoxib · Felbinac · Fenbufen · Fenclofenac · Fenoprofen · Fentiazac · Firocoxib · FK-3311 · Floctafenic acid (floctafenate) · Floctafenine · Flosulide · Flufenamic acid (flufenamate) · Flumizole · Flunixin · Flunoxaprofen · Fluproquazone · Flurbiprofen · FR-122047 · Glafenine · Glimepiride · Glucametacin · Guacetisal · Hyperforin · **Ibuprofen** · Ibuproxam · Indometacin farnesil · Indometacin (indomethacin) · Indoprofen · Isoxicam · Itazigrel · Ketoprofen · Ketorolac · L-655240 · L-670596 · Licofelone · Lonazolac · Lornoxicam · Loxoprofen · Lumiracoxib · Magnesium salicylate · Mavacoxib · Meclofenamic acid (meclofenamate) · Mefenamic acid (mefenamate) · Meloxicam · Menatetrenone (vitamin $K_2$) · Mesalazine (5-aminosalicylic acid) · Methyl salicylate · Miroprofen · Mofezolac · Morniflumate · Nabumetone · Naproxcinod · Naproxen · NCX-466 · NCX-4040 · Niflumic acid (niflumate) · Nimesulide · NS-398 · Oxametacin · Oxaprozin · Oxindanac · Pamicogrel · Paracetamol (acetaminophen) · Parapropamol · Parecoxib · Phenacetin · Piroxicam · Pirprofen · Polmacoxib · Pranoprofen · Proglumetacin · Propacetamol · Resveratrol · Robenacoxib · Rofecoxib |

| | | |
|---|---|---|
| | | · Romazarit · Rutecarpine · Salacetamide · Salicin · Salicylamide · Salicylic acid (salicylate) · Salsalate · Satigrel · SC-236 · SC-560 · SC-58125 · Sodium salicylate · Sulindac · Sulindac sulfide · Suprofen · Talinflumic acid (talinflumate) · Tarenflurbil · Tenidap · Tenoxicam · Tepoxalin · Tiaprofenic acid (tiaprofenate) · Tiflamizole · Tilmacoxib · Timegadine · Tolfenamic acid (tolfenamate) · Tolmetin · Trifenagrel · Triflusal · Tropesin · Valdecoxib · Vedaprofen · Zidometacin · Zomepirac · |
| | **$PGD_2$ synthase** | Retinoids · Selenium (selenium tetrachloride, sodium selenite, selenium disulfide) · |
| | **PGE synthase** | HQL-79 |
| | **PGF synthase** | Bimatoprost |
| | **$PGI_2$ synthase** | Tranylcypromine |
| | **TXA synthase** | Camonagrel · Dazmegrel · Dazoxiben · Furegrelate · Isbogrel · Midazogrel · Nafagrel · Nicogrelate · Ozagrel · Picotamide · Pirmagrel · Ridogrel · Rolafagrel · Samixogrel · Terbogrel · U63557A · |
| **Others** | | **Precursors:** Linoleic acid · γ-Linolenic acid (gamolenic acid) · Dihomo-γ-linolenic acid · Diacylglycerol · Arachidonic acid · Prostaglandin $G_2$ · Prostaglandin $H_2$ · |
| | | *See also: Leukotrienergics* |

| v · t · e · | **Nuclear receptor modulators** | | |
|---|---|---|---|
| **CAR** | **Agonists** | | 6,7-Dimethylesculetin · Amiodarone · Artemisinin · Benfuracarb · Carbamazepine · Carvedilol · Chlorpromazine · Chrysin · CITCO · Clotrimazole · Cyclophosphamide · Cypermethrin · DHEA · Efavirenz · Ellagic acid · Griseofulvin · Methoxychlor · Mifepristone · Nefazodone · Nevirapine · Nicardipine · Octicizer · Permethrin · Phenobarbital · Phenytoin · Pregnanedione (5β-dihydroprogesterone) · Reserpine · TCPOBOP · Telmisartan · Tolnaftate · Troglitazone · Valproic acid · |
| | **Antagonists** | | 3,17β-Estradiol · 3α-Androstanol · 3α-Androstenol · 3β-Androstanol · 17-Androstanol · AITC · Ethinylestradiol · Meclizine · Nigramide J · Okadaic acid · PK-11195 · S-07662 · T-0901317 · |
| **ERR** | **ERRα** | **Agonists** | 6,3′,4′-Trihydroxyflavone · Biochanin A · Cholesterol · Daidzein · Genistein · |
| | | **Antagonists** | Diethylstilbestrol · XCT-790 · |
| | **ERRβ** | **Agonists** | DY-131 (GSK-9089) · GSK-4716 (GW-4716) · |
| | | **Antagonists** | 4-Hydroxytamoxifen (afimoxifene) · Diethylstilbestrol · |
| | **ERRγ** | **Agonists** | Bisphenol A · DY-131 (GSK-9089) · GSK-4716 (GW-4716) · |
| | | **Antagonists** | 4-Hydroxytamoxifen (afimoxifene) · Diethylstilbestrol · |
| **FXR** | **Agonists** | | Bile acids · Cafestol · Chenodeoxycholic acid · Fexaramine · GW-4064 · Obeticholic acid · |
| | **Antagonists** | | Guggulsterone · |
| **LXR** | **Agonists** | | 22R-Hydroxycholesterol · 24S-Hydroxycholesterol · 27-Hydroxycholesterol · Cholestenoic acid · DMHCA · GW-3965 · Hypocholamide · T-0901317 · |
| | **Antagonists** | | Efavirenz · |
| | | | 15-HETE · 15-HpETE · Aleglitazar · Aluminium clofibrate · Arachidonic acid · |

| | | | |
|---|---|---|---|
| **PPAR** | **PPARα** | **Agonists** | Bezafibrate · Clofibrate · CP-775146 · Daidzein · DHEA · Elafibranor · Etomoxir · Fenofibrate · Genistein · Gemfibrozil · GW-7647 · Leukotriene $B_4$ · LG-101506 · LG-100754 · Lobeglitazone · Muraglitazar · Oleylethanolamide · Palmitoylethanolamide · Pemafibrate · Perfluorononanoic acid · Perfluorooctanoic acid · Pioglitazone · Saroglitazar · Sodelglitazar · Tesaglitazar · Tetradecylthioacetic acid · Troglitazone · WY-14643 · |
| | | **Antagonists** | GW-6471 · MK-886 · |
| | **PPARδ** | **Agonists** | 15-HETE · 15-HpETE · Arachidonic acid · Bezafibrate · Daidzein · Elafibranor · Fonadelpar · Genistein · GW-0742 · GW-501516 · L-165,041 · LG-101506 · MBX-8025 · Sodelglitazar · Tetradecylthioacetic acid · |
| | | **Antagonists** | FH-535 · GSK-0660 · GSK-3787 · |
| | **PPARγ** | **Agonists** | 5-Oxo-ETE · 5-Oxo-15-hydroxy-ETE · 15-Deoxy-$\Delta^{12,14}$-prostaglandin $J_2$ · 15-HETE · 15-HpETE · Aleglitazar · Arachidonic acid · Balaglitazone · Berberine · Bezafibrate · Cevoglitazar · Ciglitazone · Daidzein · Darglitazone · Edaglitazone · Efatutazone · Englitazone · Etalocib · Farglitazar · Genistein · GW-1929 · **Ibuprofen** · Imiglitazar · Indeglitazar · LG-100268 · LG-100754 · LG-101506 · Lobeglitazone · Muraglitazar (muroglitazar) · nTZDpa · Naveglitazar · Netoglitazone · Oxeglitazar · Peliglitazar · Pemaglitazar · Perfluorononanoic acid · Pioglitazone · Prostaglandin $J_2$ · Ragaglitazar · Reglitazar · Rivoglitazone · Rosiglitazone · RS5444 · Saroglitazar · Sipoglitazar · Sodelglitazar · Telmisartan · Tesaglitazar · Troglitazone · |
| | | **SPPARMs** | BADGE · EPI-001 · INT-131 · MK-0533 · S26948 · |
| | | **Antagonists** | FH-535 · GW-9662 · SR-202 · T-0070907 · |
| | | **Unknown** | SR-1664 · |
| | **Unselective** | **Agonists** | Ciprofibrate · Clinofibrate · Clofibride · Englitazone · Etofibrate · Farglitazar · Netoglitazone · Ronifibrate · Rivoglitazone · Simfibrate · |
| | **Unsorted** | **Agonists** | Seladelpar · |
| **PXR** | **Agonists** | 17α-Hydroxypregnenolone · 17α-Hydroxyprogesterone · $\Delta^4$-Androstenedione · $\Delta^5$-Androstenediol · $\Delta^5$-Androstenedione · AA-861 · Allopregnanediol · Allopregnanedione (5α-dihydroprogesterone) · Allopregnanolone · Alpha-Lipoic acid · Ambrisentan · AMI-193 · Amlodipine besylate · Antimycotics · Artemisinin · Aurothioglucose · Bile acids · Bithionol · Bosentan · Bumecaine · Cafestol · Cephaloridine · Cephradine · Chlorpromazine · Ciglitazone · Clindamycin · Clofenvinfos · Chloroxine · Clotrimazole · Colforsin · Corticosterone · Cyclophosphamide · Cyproterone acetate · Demecolcine · Dexamethasone · DHEA · DHEA-S · Dibunate sodium · Diclazuril · Dicloxacillin · Dimercaprol · Dinaline · Docetaxel · Docusate calcium · Dodecylbenzenesulfonic acid · Dronabinol · Droxidopa · Eburnamonine · Ecopipam · Enzacamene · Epothilone B · Erythromycin · Famprofazone · Febantel · Felodipine · Fenbendazole · Fentanyl · Flucloxacillin · Fluorometholone · Griseofulvin · Guggulsterone · Haloprogin · Hetacillin potassium · Hyperforin · *Hypericum perforatum* (St John's wort) · Indinavir sulfate · Lasalocid sodium · Levothyroxine · Linolenic acid · LOE-908 · Loratadine · Lovastatin · Meclizine · Methacycline · Methylprednisolone · Metyrapone · Mevastatin · Mifepristone · Nafcillin · Nicardipine · |

| | | |
|---|---|---|
| | | Nicotine · Nifedipine · Nilvadipine · Nisoldipine · Norelgestromin · Omeprazole · Orlistat · Oxatomide · Paclitaxel · Phenobarbital · Piperine · Plicamycin · Prednisolone · Pregnanediol · Pregnanedione (5β-dihydroprogesterone) · Pregnanolone · Pregnenolone · Pregnenolone 16α-carbonitrile · Proadifen · Progesterone · Quingestrone · Reserpine · Reverse triiodothyronine · Rifampicin · Rifaximin · Rimexolone · Riodipine · Ritonavir · Simvastatin · Sirolimus · Spironolactone · Spiroxatrine · SR-12813 · Suberoylanilide · Sulfisoxazole · Suramin · Tacrolimus · Tenylidone · Terconazole · Testosterone isocaproate · Tetracycline · Thiamylal sodium · Thiothixene · Thonzonium bromide · Tianeptine · Troglitazone · Troleandomycin · Tropanyl 3,5-dimethulbenzoate · Zafirlukast · Zearalanol · |
| | **Antagonists** | Ketoconazole · Sesamin · |
| **RAR** | **Agonists** | 9CDHRA · 9-*cis*-Retinoic acid (alitretinoin) · AC-261066 · AC-55649 · Acitretin · Adapalene · all-*trans*-Retinoic acid (tretinoin) · AM-580 · BMS-493 · BMS-753 · BMS-961 · CD-1530 · CD-2314 · CD-437 · Ch-55 · EC 23 · Etretinate · Fenretinide · Isotretinoin · Palovarotene · Retinoic acid · Retinol (vitamin A) · Tamibarotene · Tazarotene · Tazarotenic acid · TTNPB · |
| | **Antagonists** | BMS-195614 · BMS-493 · CD-2665 · ER-50891 · LE-135 · MM-11253 · |
| | **Others** | *Retinoic acid metabolism inhibitors:* Liarozole · |
| **RXR** | **Agonists** | 9CDHRA · 9-*cis*-Retinoic acid (alitretinoin) · all-*trans*-Retinoic acid (tretinoin) · Bexarotene · CD 3254 · Docosahexaenoic acid · Fluorobexarotene · Isotretinoin · LG-100268 · LG-101506 · LG-100754 · Retinoic acid · Retinol (vitamin A) · SR-11237 · |
| | **Antagonists** | HX-531 · HX-630 · LG-100754 · PA-452 · UVI-3003 · |
| **SHR** | **AR** | See here instead. |
| | **ER** | See here instead. |
| | **PR** | See here instead. |
| | **GR** | See here instead. |
| | **MR** | See here instead. |
| | **VDR** | **Agonists** — 7-Dehydrocholesterol · 22-Oxacalcitriol · 25-Hydroxyergocalciferol · Alfacalcidol · Calcifediol · Calciferol · Calcipotriol · Calcitriol · Cholecalciferol (vitamin $D_3$) · Dihydrotachysterol · Doxercalciferol · EB-1089 · Eldecalcitol · Ercalcidiol · Ercalcitriol · Ergocalciferol (vitamin $D_2$) · Lithocholic acid · Paricalcitol · Tacalcitol · |
| **TR** | **Agonists** | Dextrothyroxine · DITPA · Eprotirome (KB-2115) · KB-2611 · KB-130015 · Levothyroxine · Liothyronine · MB-07811 · MGL-3196 (VIA-3196) · Sobetirome (GC-1, GRX-431) · Thyroxine · Tiratricol · Triiodothyronine · VK-0214 · VK-2809 · ZYT1 · |
| | **Others** | *Carrier proteins:* Albumin · Thyroxine-binding globulin · Transthyretin · |
| **Authority control** | LCCN: sh97005926 · GND: 4123405-4 · | |

Categories: Nonsteroidal anti-inflammatory drugs | Propionic acids | World Health Organization essential medicines | Pfizer products | British inventions


# Influenza vaccine

From Wikipedia, the free encyclopedia

**Influenza vaccines**, also known as **flu shots** or **jabs**, are vaccines that protect against influenza.[2] A new version of the vaccine is developed twice a year as the influenza virus rapidly changes.[2] While their effectiveness varies from year to year, most provide moderate to high protection against influenza.[2][3] They decrease the number of missed days of work by a half day on average.[4] Vaccinating children may protect those around them.[2] The effectiveness in those under 2 years old and over 65 years old is unknown due to the low quality of the research.[5][6][7]

The Centers for Disease Control and Prevention recommends nearly all people over the age of 6 months get the vaccine yearly.[8] The World Health Organization also recommends yearly vaccination, especially in those at high risk.[2] These groups include pregnant women, children between six months and five years of age, those with other health problems, Native Americans, and those who work in healthcare.[1][2]

The vaccines are generally safe. In children, fever occurs in 5 to 10%, as may muscle pains or feeling tired. In certain years, the vaccine causes Guillain–Barré syndrome in older people in about one per million doses. It should not be given to those with severe allergies to eggs or to previous versions of the vaccine. The vaccines come in both inactive and weakened viral forms. The inactive version should be used for those who are pregnant. They come in forms that are injected into a muscle, sprayed into the nose, or injected into the middle layer of the skin.[2]

Vaccination against influenza began in the 1930s with large scale availability in the United States beginning in 1945.[9][10] It is on the World Health Organization's List of Essential Medicines, the most important medications recommended for a basic health system.[11] The wholesale price in the developing world is about $5.25 USD per dose as of 2014.[12] In the United States, it costs less than $25 USD.[13]

## Variants

U.S. Navy crew member having an influenza vaccination

| Influenza vaccine | |
|---|---|
| **Vaccine description** | |
| **Target disease** | influenza virus |
| **Type** | ? |
| **Clinical data** | |
| **Trade names** | Fluarix, Fluzone, other |
| **AHFS/Drugs.com** | Monograph |
| **Pregnancy category** | US: C[1] |
| **Routes of administration** | IM, intranasal, intradermal |
| **ATC code** | J07BB01 (WHO) |
| **Legal status** | |
| **Legal status** | US: -only |
| **Identifiers** | |
| **ChemSpider** | none |

Contents

## Medical uses [edit]

The Centers for Disease Control and Prevention, recommend the flu vaccine as the best way to protect people against the flu and prevent its spread. The flu vaccine can also reduce the severity of the flu if a person contracts a flu strain that the vaccine did not contain.[14] It takes about two weeks following vaccination for protective antibodies to form.[15]

A 2012 meta-analysis found that flu vaccination was effective 67 percent of the time; the populations that benefited the most were HIV-positive adults ages 18 to 55 (76 percent), healthy adults ages 18 to 46 (approximately 70 percent), and healthy children ages 6 to 24 months (66 percent).[16]

### Effectiveness [edit]

A vaccine is assessed by its *efficacy*; the extent to which it reduces risk of disease under controlled conditions, and its *effectiveness*, the observed reduction in risk after the vaccine is put into use.[17] In the case of influenza, effectiveness is expected to be lower than the efficacy because it is measured using the rates of influenza-like illness, which is not always caused by influenza.[4] Influenza vaccines generally show high efficacy, as measured by the antibody production in animal models or vaccinated people.[18] However, studies on the effectiveness of flu vaccines in the real world are difficult; vaccines may be imperfectly matched, virus prevalence varies widely between years, and influenza is often confused with other influenza-like illnesses.[19] However, in most years (16 of the 19 years before 2007), the flu vaccine strains have been a good match for the circulating strains,[20] and even a mismatched vaccine can often provide

cross-protection.[21]

Trials of both live and inactivated influenza vaccines against seasonal influenza have been summarized in several 2012 meta-analyses. Studies on live vaccines have very limited data, but these preparations may be more effective than inactivated vaccines.[22] The meta-analyses examined the efficacy and effectiveness of inactivated vaccines against seasonal influenza in adults,[4] children,[23] and the elderly.[24][25]

## Children [edit]

The CDC recommend that everyone except children under the age of six months should receive the seasonal influenza vaccine.[8] Vaccination campaigns usually focus special attention on people who are at high risk of serious complications if they catch the flu, such as pregnant women, children over six months, the elderly, and people living with chronic illness or those with weakened immune systems, as well as those to whom they are exposed, such as health care workers.[8][26]

As the death rate is also high among infants who catch influenza, the household contacts and caregivers of infants should be vaccinated to reduce the risk of passing an influenza infection to the infant.[26]

In children, vaccines again showed high efficacy, but low effectiveness in preventing "flu-like illness".[23] In children under the age of two, the data are extremely limited, but vaccination appeared to confer no measurable benefit.[23]

## Adults [edit]

In unvaccinated adults, 16% get symptoms similar to the flu, while about 10% of vaccinated adults do.[4] Vaccination decreased confirmed cases of influenza from about 2.4% to 1.1%.[4] No effect on hospitalization was found.[4]

In working adults a review by the Cochrane Collaboration found that vaccination resulted in a modest decrease in both influenza symptoms and working days lost, without affecting transmission or influenza-related complications.[4] In healthy working adults, influenza vaccines can provide moderate protection against virologically confirmed influenza, though such protection is greatly reduced or absent in some seasons.[5]

In health care workers, a 2006 review found a net benefit.[27] Of the eighteen studies in this review, only two also assessed the relationship of patient mortality relative to staff influenza vaccine uptake; both found that higher rates of health care worker vaccination correlated with reduced patient deaths.[27] A 2014 review found benefits to patients when health care workers were immunized, as supported by moderate evidence[28] based in part on the observed reduction in all-cause deaths in patients whose health care workers were given immunization compared with comparison patients in which the health care workers were not offered vaccine.[29]

## Elderly [edit]

Evidence for an effect in adults over 65 years old is unclear.[30] Systematic reviews examining both randomized controlled and case control studies found a lack of high-quality evidence.[5][31] Reviews of case control studies found effects against laboratory-confirmed influenza, pneumonia, and death among the community-dwelling elderly.[32][33]

The group most vulnerable to non-pandemic flu, the elderly, benefits least from the vaccine. There are multiple reasons behind this steep decline in vaccine efficacy, the most common of which are the declining immunological function and frailty associated with advanced age.[34] In a non-pandemic year, a person in the United States aged 50–64 is nearly ten times more likely to die an influenza-associated death than a younger person, and a person over age 65 is over ten times more likely to die an influenza-associated death than the 50–64 age group.[35]

[36]

There is a new high-dose flu vaccine specifically formulated to provide a stronger immune response. Available evidence indicates that vaccinating the elderly with the high-dose vaccine leads to a stronger immune response against influenza than the regular-dose vaccine.[37]

Vaccinating health care workers who work with elderly people is recommended in many countries, with the goal of reducing influenza outbreaks in this vulnerable population.[38][39][40] While there is no conclusive evidence from randomized clinical trials that vaccinating health care workers helps protect the elderly people from influenza, there is tentative evidence of benefit.[41]

### Pregnancy [edit]

As well as protecting mother and child from the effects of an influenza infection, the immunization of pregnant women tends to increase their chances of experiencing a successful full-term pregnancy.[42]

The trivalent inactivated influenza vaccine is protective in pregnant women infected with HIV.[43]

## Safety [edit]

*See also: Vaccine controversies*

While side effects of the flu vaccine may occur, they are usually minor and the safety of flu vaccines is high. The flu vaccine can cause serious side effects, including an allergic reaction, but this is rare. Furthermore, the common side effects and risks of inoculation are mild and temporary when compared to the risks and severe health effects of the annual influenza epidemic's well-documented toll of illness, hospitalization, and death.[44]

Flu vaccination may lead to side effects such as runny nose and sore throat, which can last for up to several days. Egg allergy may also be a concern, since flu vaccines are typically made using eggs;[45][46] however, research into egg-allergy and influenza vaccination[47] has led some advisory groups to recommend vaccine for those with mild allergies and monitored vaccination for those with severe.[48] A large study of nearly 800 children in the UK with egg allergy, including over 250 with previous anaphylactic reactions, had zero systemic allergic reactions when given the live attenuated flu vaccine.[49][50] On January 17, 2013, the U.S. FDA approved Flublok, a faster-turnaround influenza vaccine which is the first grown in insect cells instead of eggs. Since eggs are not used in its production, it avoids any problem with egg allergies.[51]

Although Guillain–Barré syndrome had been feared as a complication of vaccination, the CDC states that most studies on modern influenza vaccines have seen no link with Guillain–Barré.[52][53] Infection with influenza virus itself increases both the risk of death (up to 1 in 10,000) and increases the risk of developing Guillain–Barré syndrome to a far higher level than the highest level of suspected vaccine involvement (approximately 10 times higher by 2009 estimates).[54][55]

Although one review gives an incidence of about one case of Guillain–Barré per million vaccinations,[56] a large study in China, reported in *The New England Journal of Medicine* covering close to 100 million doses of vaccine against the 2009 H1N1 "swine" flu found only eleven cases of Guillain–Barré syndrome, (0.1 per million doses) total incidence in persons vaccinated, actually lower than the normal rate of the disease in China, and no other notable side effects; "The risk-benefit ratio, which is what vaccines and everything in medicine is about, is overwhelmingly in favor of vaccination."[57][58] Several studies have identified an increased incidence of narcolepsy among recipients of the pandemic H1N1 influenza ASO3-adjuvanted vaccine,[59] efforts to identify a mechanism for this suggest that narcolepsy is autoimmune, and that the ASO3-adjuvanted H1N1 vaccine may mimic hypocretin, serving as a trigger.[60]

Some injection-based flu vaccines intended for adults in the United States contain thiomersal (also known as thimerosal), a mercury-based preservative. Despite some controversy in the media,[61] the World Health Organization's Global Advisory Committee on Vaccine Safety has concluded that there is no evidence of toxicity from thiomersal in vaccines and no reason on grounds of safety to change to more-expensive [62]

single-dose administration.

## Injection versus nasal spray [edit]

Flu vaccines are available either as

- a trivalent or quadrivalent injection (TIV or QIV), which contains the inactivated form of the virus.
- a nasal spray of live attenuated influenza vaccine (LAIV, Q/LAIV), which contains the attenuated or weakened form of the virus.

TIV induces protection after injection (typically intramuscular, though subcutaneous and intradermal routes can also be protective)[63] based on an immune response to the antigens present on the inactivated virus, while cold-adapted LAIV works by establishing infection in the nasal passages.[64]

## Recommendations [edit]

Various public health organizations, including the World Health Organization, have recommended that yearly influenza vaccination be routinely offered, particularly to people at risk of complications of influenza and those individuals who live with or care for high-risk individuals, including:

- the elderly (UK recommendation is those aged 65 or above)
- people with chronic lung diseases (asthma, COPD, etc.)
- people with chronic heart diseases (congenital heart disease, chronic heart failure, ischaemic heart disease)
- people with chronic liver diseases (including cirrhosis)
- people with chronic kidney diseases (such as the nephrotic syndrome)
- people who are immunosuppressed (those with HIV or who are receiving drugs to suppress the immune system such as chemotherapy and long-term steroids) and their household contacts
- people who live together in large numbers in an environment where influenza can spread rapidly, such as prisons, nursing homes, schools, and dormitories.[65]
- healthcare workers (both to prevent sickness and to prevent spread to patients)[66][67]
- pregnant women. However, a 2009 review concluded that there was insufficient evidence to recommend routine use of trivalent influenza vaccine during the first trimester of pregnancy.[68] Influenza vaccination during flu season is part of recommendations for influenza vaccination of pregnant women in the United States.[69]

Both types of flu vaccines are contraindicated for those with severe allergies to egg proteins and people with a history of Guillain–Barré syndrome.[70]

### World Health Organization [edit]

As of 2012, the UN World Health Organization recommends annual vaccinations:

> Annual vaccination (or re-vaccination, if the vaccine strains are identical) is recommended, particularly for high-risk groups.

High risk groups include, in order of priority:[71]

1. nursing-home residents (the elderly or disabled)
2. people with chronic medical conditions
3. elderly individuals
4. other groups such as pregnant women, health care workers, those with essential functions in society, as well as children from 6 to 24 months.

### Canada [edit]

In 2008, the National Advisory Committee on Immunization, the group that advises the Public Health

Agency of Canada, recommended that everyone aged 2 to 64 years be encouraged to receive annual influenza vaccination, and that children between the age of six and 24 months, and their household contacts, should be considered a high priority for the flu vaccine.[72] The NACI also recommends the flu vaccine for:[73]

- People at high risk of influenza-related complications or hospitalization, including the morbidly obese, healthy pregnant women, children 6 to 59 months, the elderly, aboriginals, and people suffering from one of an itemized list of chronic health conditions
- People capable of transmitting influenza to those at high risk, including household contacts and healthcare workers
- People who provide essential community services
- Certain poultry workers

## Europe [edit]

The European Center for Disease Prevention and Control recommends vaccinating the elderly as a priority, with a secondary priority people with chronic medical conditions and healthcare workers.[74]

The influenza vaccination strategy is generally that of protecting vulnerable people, rather than limiting influenza circulation or totally eliminating human influenza sickness. This is in contrast with the high herd immunity strategies for other Infectious diseases such as polio and measles.[75] This is also due in part to the financial and logistics burden associated with the need of an annual injection.[76]

## United States [edit]

In the United States routine influenza vaccination is recommended for all persons aged ≥ 6 months.[77][78][79]

According to the CDC, the live attenuated virus (which comes in the form of the nasal spray in the US) should be avoided by:

- Children younger than 2 years
- Adults 50 years and older
- People with a history of severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine
- People with asthma
- Children or adolescents on long-term aspirin treatment.
- Children and adults who have chronic pulmonary, cardiovascular (except isolated hypertension), renal, hepatic, neurologic/neuromuscular, hematologic, or metabolic disorders
- Children and adults who have immunosuppression (including immunosuppression caused by medications or by HIV)
- Pregnant women[80]

A young woman shows off her flu shot after receiving vaccine at a local drug store.

Within its blanket recommendation for general vaccination in the United States, the Centers for Disease Control and Prevention (CDC), which began recommending the influenza vaccine to health care workers in 1981, emphasizes to clinicians the special urgency of vaccination for members of certain vulnerable groups, and their caregivers:

Vaccination is especially important for people at higher risk of serious influenza complications or people who live with or care for people at higher risk for serious complications.[81] In 2009, a new high-dose formulation of the standard influenza vaccine was approved. The Fluzone High Dose is specifically for people 65 and older; the difference is that it has four times the antigen dose of the standard Fluzone.[82]

The U.S. government requires hospitals to report worker vaccination

rates. Some U.S. states and hundreds of U.S. hospitals require health-care workers to either get vaccinations or wear masks during flu season. These requirements occasionally engender union lawsuits on narrow collective bargaining grounds, but proponents note that courts have generally endorsed forced vaccination laws affecting the general population during disease outbreaks.[83]

Vaccination against influenza is especially important for members of high-risk groups who would be likely to have complications from influenza, for example pregnant women[77][84] and children and teenagers from six months to 18 years of age;[85]

- In raising the upper age limit to 18 years, the aim is to reduce both the time children and parents lose from visits to pediatricians and missing school and the need for antibiotics for complications[86]
- An added benefit expected from the vaccination of children is a reduction in the number of influenza cases among parents and other household members, and of possible spread to the general community.[86]

In USA : The CDC has indicated that live attenuated influenza vaccine (LAIV), also called the nasal spray vaccine, is not recommended for the 2016-2017 flu season, in the United States.[87]

Furthermore, health care personnel who care for severely immunocompromised persons should receive injections (TIV or QIV) rather than LAIV.[88]

## Uptake [edit]

### At risk groups [edit]

Uptake of flu vaccination, both seasonally and during pandemics, is often low.[89] Systematic reviews of pandemic flu vaccination uptake have identified several personal factors that may influence uptake, including gender (higher uptake in men), ethnicity (higher in people from ethnic minorities) and having a chronic illness.[90][91] Beliefs in the safety and effectiveness of the vaccine are also important.[89]

### Healthcare workers [edit]

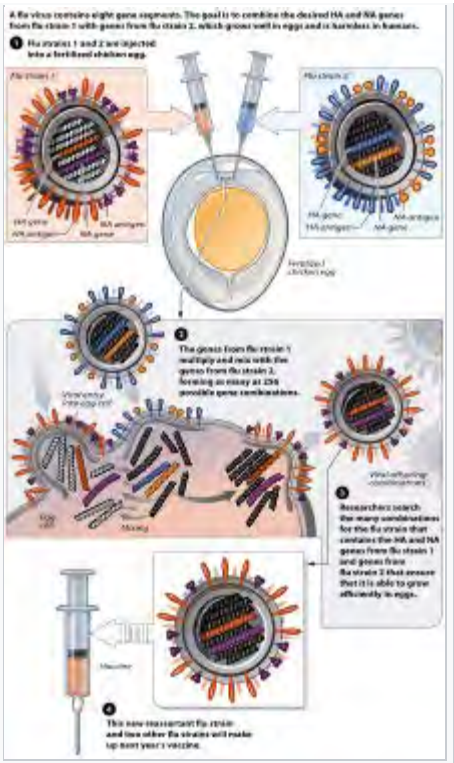
Frontline healthcare workers are often recommended to get seasonal and any pandemic flu vaccination. For example, in the UK, all healthcare workers involved in patient care are recommended to receive the seasonal flu vaccine and were also recommended to receive the swine flu vaccine during the 2009 pandemic. However, uptake is often low.[67] During the 2009 pandemic, low uptake by healthcare workers was seen in countries including the UK,[67] Italy,[92] Greece,[93] and Hong Kong.[94]

In a 2010 survey of United States healthcare workers, 63.5% reported that they received the flu vaccine during the 2010–11 season, an increase from 61.9% reported the previous season. US Health professionals with direct patient contact had higher vaccination uptake, such as physicians and dentists (84.2%) and nurse practitioners (82.6%).[95][96][97]

The main reason to vaccinate healthcare workers is to prevent staff from spreading flu to their patients and to reduce staff absence at a time of high service demand, but the reasons healthcare workers state for their decisions to accept vaccination or not may more often be to do with perceived personal benefits.[67]

## Manufacturing [edit]

Flu vaccine is usually grown by vaccine manufacturers in fertilized chicken eggs.[98][99] In the Northern hemisphere, the manufacturing process begins following the announcement (typically in February) of the WHO recommended strains for the winter flu season.[98][100] Three strains (representing an H1N1, an H3N2, and a B strain) of flu are



Schematic of influenza vaccine creation

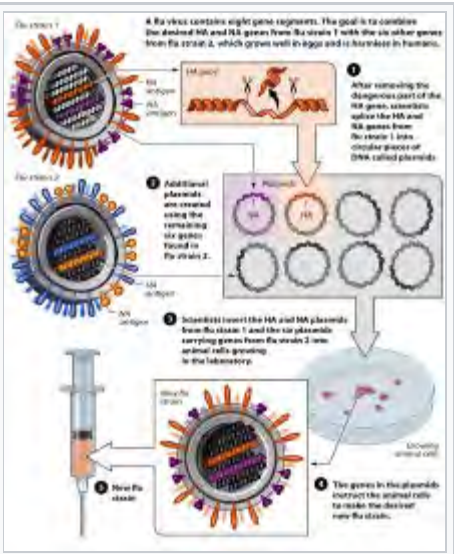
selected and chicken eggs inoculated separately, these monovalent harvests are then combined to make the trivalent vaccine.[101]

As of November 2007, both the conventional injection and the nasal spray are manufactured using chicken eggs.[99] The European Union has also approved Optaflu, a vaccine produced by Novartis using vats of animal cells.[99] This technique is expected to be more scalable and avoid problems with eggs, such as allergic reactions and incompatibility with strains that affect avians like chickens.[99] Research continues into the idea of a "universal" influenza vaccine that would not require tailoring to a particular strain, but would be effective against a broad variety of influenza viruses. However, no vaccine candidates had been announced by Nov 2007.[99]

A DNA-based vaccination, which is hoped to be even faster to manufacture, is as of 2011 in clinical trials, determining safety and efficacy.[102]

On November 20, 2012, Novartis received FDA approval for the first cell-culture vaccine.[103][104][105]

In a 2007 report, the global capacity of approximately 826 million seasonal influenza vaccine doses (inactivated and live) was double the production of 413 million doses. In an aggressive scenario of producing pandemic influenza vaccines by 2013, only 2.8 billion courses could be produced in a six-month time frame. If all high- and upper-middle-income countries sought vaccines for their entire populations in a pandemic, nearly 2 billion courses would be required. If China pursued this goal as well, more than 3 billion courses would be required to serve these populations.[106] Vaccine research and development is ongoing to identify novel vaccine approaches that could produce much greater quantities of vaccine at a price that is affordable to the global population.



Avian flu vaccine development by reverse genetics technique

Methods of vaccine generation that bypass the need for eggs include the construction of influenza virus-like particles (VLP). VLP resemble viruses, but there is no need for inactivation, as they do not include viral coding elements, but merely present antigens in a similar manner to a virion. Some methods of producing VLP include cultures of Spodoptera frugiperda Sf9 insect cells and plant-based vaccine production (e.g., production in *Nicotiana benthamiana*). There is evidence that some VLPs elicit antibodies that recognize a broader panel of antigenically distinct viral isolates compared to other vaccines in the hemagglutination-inhibition assay (HIA).[107]

Influenza vaccines are produced in pathogen-free eggs that are 11 to 12 days old.[108] The top of the egg is disinfected by wiping it with alcohol and then the egg is candled to identify a non-veinous area in the allantoic cavity where a small hole is poked to serve as a pressure release.[109] A second hole is made at the top of the egg, where the influenza virus is injected in the allantoic cavity, past the chorioallantoic membrane. The two holes are then sealed with melted paraffin and the inoculated eggs are incubated for 48 hours at 37 degrees Celsius.[108] During incubation time, the virus replicates and newly replicated viruses are released into the allantoic fluid [110]

After the 48 hour incubation period, the top of the egg is cracked and the 10 milliliters of allantoic fluid is removed, from which about 15 micrograms of the flu vaccine can be obtained. At this point, the viruses have been weakened or killed and the viral antigen is purified and placed inside vials, syringes, or nasal sprayers.[110] Done on a large scale, this method is used to produce the flu vaccine for the human population.

## Annual reformulation [edit]

*Further information: Historical annual reformulations of the influenza vaccine*
*See also: 2009 flu pandemic vaccine*

Each year, three strains are chosen for selection in that year's flu vaccination by the WHO Global Influenza Surveillance Network. The chosen strains are the H1N1, H3N2, and Type-B strains thought most likely to cause significant human suffering in the coming season. Starting with the 2012–2013 Northern Hemisphere influenza season (coincident with the approval of quadrivalent influenza vaccines), the WHO has also recommended a 2nd B-strain for use in quadrivalent vaccines. The World Health Organization coordinates the contents of the vaccine each year to contain the most likely strains of the virus to attack the next year.

> "The WHO Global Influenza Surveillance Network was established in 1952. The network comprises 4 WHO Collaborating Centres (WHO CCs) and 112 institutions in 83 countries, which are recognized by WHO as WHO National Influenza Centres (NICs). These NICs collect specimens in their country, perform primary virus isolation and preliminary antigenic characterization. They ship newly isolated strains to WHO CCs for high level antigenic and genetic analysis, the result of which forms the basis for WHO recommendations on the composition of influenza vaccine for the Northern and Southern Hemisphere each year."[111]

The Global Influenza Surveillance Network's selection of viruses for the vaccine manufacturing process is based on its best estimate of which strains will predominate the next year, amounting in the end to well-informed but fallible guesswork.[112]

Formal WHO recommendations were first issued in 1973. Beginning in 1999 there have been two recommendations per year: one for the northern hemisphere (N) and the other for the southern hemisphere (S).[113]

Historical annual reformulations of the influenza vaccine are listed in a separate article. Recent WHO seasonal influenza vaccine composition recommendations:

## 2016–2017 Northern Hemisphere influenza season [edit]

The composition of trivalent virus vaccines for use in the 2016–2017 Northern Hemisphere influenza season recommended by the World Health Organization on February 25, 2016 was:

- an A/California/7/2009 (H1N1)pdm09-like virus†
- an A/Hong Kong/4801/2014 (H3N2)-like virus
- a B/Brisbane/60/2008-like virus

The WHO recommends that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Phuket/3073/2013-like virus.[114]

## 2016 Southern Hemisphere influenza season [edit]

The composition of virus vaccines for use in the 2016 Southern Hemisphere influenza season recommended by the World Health Organisation on September 24, 2015 was:

- an A/California/7/2009 (H1N1)pdm09-like virus†
- an A/Hong Kong/4801/2014 (H3N2)-like virus
- a B/Brisbane/60/2008-like virus

WHO recommended that quadrivalent vaccines containing two influenza B viruses should contain the above three viruses and a B/Phuket/3073/2013-like virus.[115]

†Strain A(H1N1)pdm09 is a newer name for the strain used in the 2009 flu pandemic vaccine.[116]

### 2017 Southern Hemisphere influenza season [edit]

The composition of virus vaccines for use in the 20167Southern Hemisphere influenza season recommended by the World Health Organisation on September 29, 2016 was:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus†
- an A/Hong Kong/4801/2014 (H3N2)-like virus
- a B/Brisbane/60/2008-like virus

WHO recommended that quadrivalent vaccines containing two influenza B viruses should contain the above three viruses and a B/Phuket/3073/2013-like virus.[117]

†Strain A(H1N1)pdm09 is a newer name for the strain used in the 2009 flu pandemic vaccine.[116]

## History [edit]

*See also: Timeline of vaccines*

Vaccines are used in both humans and nonhumans. Human vaccine is meant unless specifically identified as a veterinary, poultry or livestock vaccine.

### Origins and development [edit]

In the worldwide Spanish flu pandemic of 1918, "Physicians tried everything they knew, everything they had ever heard of, from the ancient art of bleeding patients, to administering oxygen, to developing new vaccines and sera (chiefly against what we now call *Hemophilus influenzae*—a name derived from the fact that it was originally considered the etiological agent—and several types of pneumococci). Only one therapeutic measure, transfusing blood from recovered patients to new victims, showed any hint of success."[118]

In 1931, viral growth in embryonated hens' eggs was reported by Ernest William Goodpasture and colleagues at Vanderbilt University. The work was extended to growth of influenza virus by several workers, including Thomas Francis, Jonas Salk, Wilson Smith and Macfarlane Burnet, leading to the first experimental influenza vaccines.[119] In the 1940s, the US military developed the first approved inactivated vaccines for influenza, which were used in the Second World War.[120] Hen's eggs continued to be used to produce virus used in influenza vaccines, but manufacturers made improvements in the purity of the virus by developing improved processes to remove egg proteins and to reduce systemic reactivity of the vaccine.[121] Recently, the US FDA has approved influenza vaccines made by growing virus in cell cultures[122] and influenza vaccines made from recombinant proteins[123] have been approved, with plant-based influenza vaccines being tested in clinical trials.[124]

### Acceptance [edit]

According to the CDC: "Influenza vaccination is the primary method for preventing influenza and its severe complications. [...] Vaccination is associated with reductions in influenza-related respiratory illness and physician visits among all age groups, hospitalization and death among persons at high risk, otitis media among children, and work absenteeism among adults. Although influenza vaccination levels increased substantially during the 1990s, further improvements in vaccine coverage levels are needed".[125]

The egg-based technology (still in use as of 2005) for producing influenza vaccine was created in the 1950s.[126] In the U.S. swine flu scare of 1976, President Gerald Ford was confronted with a potential swine flu pandemic. The vaccination program was rushed, yet plagued by delays and public relations problems. Meanwhile, maximum military containment efforts succeeded unexpectedly in confining the new strain to the single army base where it had originated. On that base a number of soldiers fell severely ill, but only one died. The program was canceled, after about 24% of the population had received

vaccinations. An excess in deaths of twenty-five over normal annual levels as well as 400 excess hospitalizations, both from Guillain–Barré syndrome, were estimated to have occurred from the vaccination program itself, illustrating that vaccine itself is not free of risks. The result has been cited to stoke lingering doubts about vaccination.[127] In the end, however, even the maligned 1976 vaccine may have saved lives. A 2010 study found a significantly enhanced immune response against the 2009 pandemic H1N1 in study participants who had received vaccination against the swine flu in 1976.[128]

# Society and culture [edit]

## Evaluation of evidence [edit]

Tom Jefferson, who has led Cochrane Collaboration reviews of flu vaccines, has called clinical evidence concerning flu vaccines "rubbish" and has therefore declared them to be ineffective; he has called for placebo-controlled randomized clinical trials. His views on clinical trials are considered unethical by mainstream medicine and his views on the efficacy of vaccines are rejected by medical institutions including the CDC and the National Institutes of Health, and by key figures in the field like Anthony Fauci.[129]

Michael Osterholm who has led the Center for Infectious Disease Research and Policy 2012 review on flu vaccines recommends getting the vaccine but criticizes its promotion "We have overpromoted and overhyped this vaccine...it does not protect as promoted. It's all a sales job: it's all public relations".[130]

## Cost-effectiveness [edit]

The cost-effectiveness of seasonal influenza vaccination has been widely evaluated for different groups and in different settings.[131] In the elderly (aged over 65 years) the majority of published studies have found that vaccination is cost saving, with the cost savings associated with influenza vaccination (e.g. prevented health care visits) outweighing the cost of vaccination.[132] In older adults (aged 50–64 years), several published studies have found that influenza vaccination is likely to be cost-effective, however the results of these studies were often found to be dependent on key assumptions used in the economic evaluations.[133] The uncertainty in influenza cost-effectiveness models can partially be explained by the complexities involved in estimating the disease burden,[134] as well as the seasonal variability in the circulating strains and the match of the vaccine.[135][136] In healthy working adults (aged 18–49 years), a 2012 review found that vaccination was generally not cost-saving, with the suitability for funding being dependent on the willingness to pay to obtain the associated health benefits.[137] In children, the majority of studies have found that influenza vaccination was cost-effective, however many of the studies included (indirect) productivity gains, which may not be given the same weight in all settings.[138] Several studies have attempted to predict the cost-effectiveness of interventions (including prepandemic vaccination) to help protect against a future pandemic, however estimating the cost-effectiveness has been complicated by uncertainty as to the severity of a potential future pandemic and the efficacy of measures against it.[139]

# Research [edit]

Influenza research includes molecular virology, molecular evolution, pathogenesis, host immune responses, genomics, and epidemiology. These help in developing influenza countermeasures such as vaccines, therapies and diagnostic tools. Improved influenza countermeasures require basic research on how viruses enter cells, replicate, mutate, evolve into new strains and induce an immune response. The Influenza Genome Sequencing Project is creating a library of influenza sequences[140] that will help us understand what makes one strain more lethal than another, what genetic determinants most affect immunogenicity, and how the virus evolves over time. Solutions to limitations in current[*when?*] vaccine methods are being researched.

A different approach is where Internet content is used to estimate the impact of an influenza vaccination campaign. More specifically, researchers have used data from Twitter and Bing, and proposed a statistical

framework which, after a series of operations, maps this information to estimates of the percentage of influenza-like illness in areas, where vaccinations have been performed. Their impact estimates were in accordance with estimations from Public Health England.[141]

### Rapid response to pandemic flu [edit]

The rapid development, production, and distribution of pandemic influenza vaccines could potentially save millions of lives during an influenza pandemic. Due to the short time frame between identification of a pandemic strain and need for vaccination, researchers are looking at novel technologies for vaccine production that could provide better "real-time" access and be produced more affordably, thereby increasing access for people living in low- and moderate-income countries, where an influenza pandemic may likely originate, such as live attenuated (egg-based or cell-based) technology and recombinant technologies (proteins and virus-like particles).[142] As of July 2009, more than 70 known clinical trials have been completed or are ongoing for pandemic influenza vaccines.[143] In September 2009, the US Food and Drug Administration approved four vaccines against the 2009 H1N1 influenza virus (the 2009 pandemic strain), and expected the initial vaccine lots to be available within the following month.[144]

### Quadrivalent vaccines for seasonal flu [edit]

A quadrivalent flu vaccine administered by nasal mist was approved by the U.S. Food and Drug Administration (FDA) in March 2012.[145][146] Fluarix Quadrivalent was approved by the FDA in December 2012.[147]

### Universal flu vaccines [edit]

A "universal vaccine" that would not have to be designed and made for each flu season in each hemisphere would be useful, in order to stabilize the supply and to ensure against error in the design or escape of the circulating strains by mutation. Such a vaccine has been the subject of research for decades.[148]

One promising approach is using broadly neutralizing antibodies that unlike the vaccine used today, which provoke the body to generate an immune response, instead provide a component of the immune response itself. The first neutralizing antibodies were identified in 1993 via experimentation; with time researchers understood that the flu neutralizing antibodies were binding to the stalk of the Hemagglutinin protein; later researchers identified antibodies that could bind to the head of those proteins. Later yet, researchers identified the highly conserved M2 proton channel as a potential target for broadly neutralizing antibodies.[148][149]

The challenges for researchers have been identifying single antibodies that could neutralize many subtypes of the virus, so that they could be useful in any season, and that target conserved domains that are resistant to antigenic drift.[148]

Another approach has been taking the conserved domains identified from these projects, and delivering groups of these antigens to provoke an immune response; various approaches with different antigens, presented different ways (as fusion proteins, mounted on virus-like particles, on non-pathogenic viruses, as DNA, and others), are under development.[149][150][151]

Efforts have also been undertaken to develop universal vaccines that specifically activate a T-cell response, based on clinical data showing that people with a strong, early T-cell response have better outcomes when infected with influenza and because T-cells respond to conserved epitopes. The challenge for developers is that these epitopes are on internal protein domains that are only mildly immunogenic.[149]

Along with the rest of the vaccine field, people working on universal vaccines have been experimenting with vaccine adjuvants to improve the ability of their vaccines to create a sufficiently powerful and enduring immune response.[149][152]

## Veterinary use [edit]

*See also: Influenza A virus and Influenza § Infection in other animals*

"Vaccination in the veterinary world pursues four goals: (i) protection from clinical disease, (ii) protection from infection with virulent virus, (iii) protection from virus excretion, and (iv) serological differentiation of infected from vaccinated animals (so-called DIVA principle). In the field of influenza vaccination, neither commercially available nor experimentally tested vaccines have been shown so far to fulfill all of these requirements."[153]

## Horses [edit]

Horses with horse flu can run a fever, have a dry hacking cough, have a runny nose, and become depressed and reluctant to eat or drink for several days but usually recover in two to three weeks. "Vaccination schedules generally require a primary course of 2 doses, 3–6 weeks apart, followed by boosters at 6–12 month intervals. It is generally recognized that in many cases such schedules may not maintain protective levels of antibody and more frequent administration is advised in high-risk situations."[154]

It is a common requirement at shows in the United Kingdom that horses be vaccinated against equine flu and a vaccination card must be produced; the International Federation for Equestrian Sports (FEI) requires vaccination every six months.[155][156]

## Poultry [edit]

Poultry vaccines for bird flu are made inexpensively and are not filtered and purified like human vaccines to remove bits of bacteria or other viruses. They usually contain whole virus, not just hemagglutinin as in most human flu vaccines. Purification to standards needed for humans is far more expensive than the original creation of the unpurified vaccine from eggs. There is no market for veterinary vaccines that are that expensive. Another difference between human and poultry vaccines is that poultry vaccines are adjuvated with mineral oil, which induces a strong immune reaction but can cause inflammation and abscesses. "Chicken vaccinators who have accidentally jabbed themselves have developed painful swollen fingers or even lost thumbs, doctors said. Effectiveness may also be limited. Chicken vaccines are often only vaguely similar to circulating flu strains — some contain an H5N2 strain isolated in Mexico years ago. 'With a chicken, if you use a vaccine that's only 85 percent related, you'll get protection,' Dr. Cardona said. 'In humans, you can get a single point mutation, and a vaccine that's 99.99 percent related won't protect you.' And they are weaker [than human vaccines]. 'Chickens are smaller and you only need to protect them for six weeks, because that's how long they live till you eat them,' said Dr. John J. Treanor, a vaccine expert at the University of Rochester. Human seasonal flu vaccines contain about 45 micrograms of antigen, while an experimental A(H5N1) vaccine contains 180. Chicken vaccines may contain less than 1 microgram. 'You have to be careful about extrapolating data from poultry to humans,' warned Dr. David E. Swayne, director of the agriculture department's Southeast Poultry Research Laboratory. 'Birds are more closely related to dinosaurs.'"[157]

Researchers, led by Nicholas Savill of the University of Edinburgh in Scotland, used mathematical models to simulate the spread of H5N1 and concluded that "at least 95 percent of birds need to be protected to prevent the virus spreading silently. In practice, it is difficult to protect more than 90 percent of a flock; protection levels achieved by a vaccine are usually much lower than this."[158] The Food and Agriculture Organization of the United Nations has issued recommendations on the prevention and control of avian influenza in poultry, including the use of vaccination.[159]

A filtered and purified Influenza A vaccine for humans is being developed[*when?*] and many countries have recommended it be stockpiled so if an Avian influenza pandemic starts jumping to humans, the vaccine can quickly be administered to avoid loss of life. Avian influenza is sometimes called avian flu, and commonly bird flu.[160]

## Pigs [edit]

Swine influenza vaccines are extensively used in pig farming in Europe and North America. Most swine flu vaccines include an H1N1 and an H3N2 strain.

Swine influenza has been recognized as a major problem since the outbreak in 1976. Evolution of the virus has resulted in inconsistent responses to traditional vaccines. Standard commercial swine flu vaccines are effective in controlling the problem when the virus strains match enough to have significant cross-protection. Customised (autogenous) vaccines made from the specific viruses isolated, are made and used in the more difficult cases.[161] The vaccine manufacturer Novartis claims that the H3N2 strain (first identified in 1998) has brought major losses to pig farmers. Abortion storms are a common sign and sows stop eating for a few days and run a high fever. The mortality rate can be as high as 15%.[162]

### Dogs [edit]

In 2004, influenza A virus subtype H3N8 was discovered to cause canine influenza. Because of the lack of previous exposure to this virus, dogs have no natural immunity to this virus. However, a vaccine is now available.[163]

## References [edit]


1. ^ *a b* "Influenza Virus Vaccine Inactivated". The American Society of Health-System Pharmacists. Retrieved Jan 8, 2015.
2. ^ *a b c d e f g* "Vaccines against influenza WHO position paper – November 2012." (PDF). *Wkly Epidemiol Rec*. **87** (46): 461–76. Nov 23, 2012. PMID 23210147.
3. ^ Manzoli L, Ioannidis JP, Flacco ME, De Vito C, Villari P (July 2012). "Effectiveness and harms of seasonal and pandemic influenza vaccines in children, adults and elderly: a critical review and re-analysis of 15 meta-analyses". *Hum Vaccin Immunother*. **8** (7): 851–62. doi:10.4161/hv.19917. PMC 3495721. PMID 22777099.
4. ^ *a b c d e f g* Jefferson, T; Di Pietrantonj, C; Rivetti, A; Bawazeer, GA; Al-Ansary, LA; Ferroni, E (13 March 2014). "Vaccines for preventing influenza in healthy adults.". *The Cochrane database of systematic reviews*. **3**: CD001269. doi:10.1002/14651858.CD001269.pub5. PMID 24623315.
5. ^ *a b c* Osterholm, MT; Kelley, NS; Sommer, A; Belongia, EA (Jan 2012). "Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis.". *The Lancet. Infectious diseases*. **12** (1): 36–44. doi:10.1016/S1473-3099(11)70295-X. PMID 22032844.
6. ^ Jefferson, T; Di Pietrantonj, C; Al-Ansary, LA; Ferroni, E; Thorning, S; Thomas, RE (Feb 17, 2010). "Vaccines for preventing influenza in the elderly". *The Cochrane database of systematic reviews* (2): CD004876. doi:10.1002/14651858.CD004876.pub3. PMID 20166072.
7. ^ Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E (2012). "Vaccines for preventing influenza in healthy children". *Cochrane Database Syst Rev*. **8**: CD004879. doi:10.1002/14651858.CD004879.pub4. PMID 22895945.
8. ^ *a b c* "Who Should Get Vaccinated Against Influenza". U.S. Centers for Disease Control and Prevention. 2015-11-04. Retrieved 2015-12-08.
9. ^ Compans, Richard W. (2009). *Vaccines for pandemic influenza*. Dordrecht: Springer. p. 49. ISBN 9783540921653.
10. ^ *Vaccine Analysis: Strategies, Principles, and Control*. Springer. 2014. p. 61. ISBN 9783662450246.
11. ^ "19th WHO Model List of Essential Medicines (April 2015)" (PDF). WHO. April 2015. Retrieved May 10, 2015.
12. ^ "Vaccine, influenza". *International Drug Price Indicator Guide*. Retrieved 6 December 2015.
13. ^ Hamilton, Richart (2015). *Tarascon Pocket Pharmacopoeia 2015 Deluxe Lab-Coat Edition*. Jones & Bartlett Learning. p. 314. ISBN 9781284057560.
14. ^ Center for Disease Control and Prevention. "Key Facts About Seasonal Flu Vaccine". Retrieved 7 February 2013.
15. ^ "Key Facts About Seasonal Flu Vaccine"
16. ^ Osterholm, MT; Kelley, NS; Sommer, A; Belongia, EA (January 2012). "Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis.". *The Lancet. Infectious diseases*. **12** (1): 36–44. doi:10.1016/s1473-3099(11)70295-x. PMID 22032844.
17. ^ Fedson DS (1998). "Measuring protection: efficacy versus effectiveness". *Dev Biol Stand*. **95**: 195–201. PMID 9855432.
18. ^ Stephenson, I.; Zambon, M. C.; Rudin, A.; Colegate, A.; Podda, A.; Bugarini, R.; Del Giudice, G.; Minutello, A.; et al. (May 2006). "Phase I Evaluation of Intranasal Trivalent Inactivated Influenza Vaccine with Nontoxigenic Escherichia coli Enterotoxin and Novel Biovector as Mucosal Adjuvants, Using Adult Volunteers". *J Virol*. **80** (10): 4962–70. doi:10.1128/JVI.80.10.4962-4970.2006. PMC 1472052. PMID 16641287.

19. ^ Jefferson, T. (October 2006). "Influenza vaccination: policy versus evidence". *BMJ*. **333** (7574): 912–5. doi:10.1136/bmj.38995.531701.80. PMC 1626345. PMID 17068038.
20. ^ CDC – Influenza (Flu) | Q & A: 2007–08 Flu Season
21. ^ CDC - Key Facts About Seasonal Flu Vaccine
22. ^ Treanor, J.; Kotloff, K.; Betts, R.; Belshe, R.; Newman, F.; Iacuzio, D.; Wittes, J.; Bryant, M. (December 1999). "Evaluation of trivalent, live, cold-adapted (CAIV-T) and inactivated (TIV) influenza vaccines in prevention of virus infection and illness following challenge of adults with wild-type influenza A (H1N1), A (H3N2), and B viruses". *Vaccine*. **18** (9–10): 899–906. doi:10.1016/S0264-410X(99)00334-5. PMID 10580204.
23. ^ [a] [b] [c] Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E (2012). "Vaccines for preventing influenza in healthy children". *Cochrane Database Syst Rev*. **8**: CD004879. doi:10.1002/14651858.CD004879.pub4. PMID 22895945.
24. ^ Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE (2010). "Vaccines for preventing influenza in the elderly". *Cochrane Database Syst Rev* (2): CD004876. doi:10.1002/14651858.CD004876.pub3. PMID 20166072.
25. ^ Jefferson T, Rivetti D, Rivetti A, Rudin M, Di Pietrantonj C, Demicheli V (2005). "Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review". *Lancet*. **366** (9492): 1165–74. doi:10.1016/S0140-6736(05)67339-4. PMID 16198765.
26. ^ [a] [b] "Influenza (Seasonal)". World Health Organization. November 2016.
27. ^ [a] [b] Burls, A; Jordan, R; Barton, P; Olowokure, B; Wake, B; Albon, E; Hawker, J (8 May 2006). "Vaccinating healthcare workers against influenza to protect the vulnerable--is it a good use of healthcare resources? A systematic review of the evidence and an economic evaluation.". *Vaccine*. **24** (19): 4212–21. doi:10.1016/j.vaccine.2005.12.043. PMID 16546308.
28. ^ Ahmed F, Lindley MC, Allred N, Weinbaum CM, Grohskopf L (2014). "Effect of influenza vaccination of healthcare personnel on morbidity and mortality among patients: systematic review and grading of evidence". *Clin Infect Dis*. **58** (1): 50–57. doi:10.1093/cid/cit580. PMID 24046301.
29. ^ Griffin MR (2014). "Editorial Commentary: Influenza Vaccination of Healthcare Workers: Making the Grade for Action". *Clinical Infectious Diseases*. **58** (1): 58–60. doi:10.1093/cid/cit590.
30. ^ Simonsen L, Viboud C, Taylor RJ, Miller MA, Jackson L (October 2009). "Influenza vaccination and mortality benefits: new insights, new opportunities". *Vaccine*. **27** (45): 6300–4. doi:10.1016/j.vaccine.2009.07.008. PMID 19840664.
31. ^ Jefferson, T; Di Pietrantonj, C; Al-Ansary, LA; Ferroni, E; Thorning, S; Thomas, RE (17 February 2010). "Vaccines for preventing influenza in the elderly.". *The Cochrane database of systematic reviews* (2): CD004876. doi:10.1002/14651858.CD004876.pub3. PMID 20166072.
32. ^ Darvishian, M; Bijlsma, MJ; Hak, E; van den Heuvel, ER (December 2014). "Effectiveness of seasonal influenza vaccine in community-dwelling elderly people: a meta-analysis of test-negative design case-control studies.". *The Lancet. Infectious diseases*. **14** (12): 1228–39. doi:10.1016/S1473-3099(14)70960-0. PMID 25455990.
33. ^ Nichol, K.L.; Nordin, J.D.; Nelson, D.B.; Mullooly, J.D.; Hak, E. (2007). "Effectiveness of Influenza Vaccine in the community-dwelling elderly". *The New England Journal of Medicine*. **357** (14): 1373–1381. doi:10.1056/NEJMoa070844. PMID 17914038.
34. ^ Simonsen, L.; Taylor, R.J.; Viboud, C.; Miller, M.A.; Jackson, L.A. (2007). "Mortality benefits of influenza vaccination in elderly people: An ongoing controversy". *The Lancet Infectious Diseases*. **7** (10): 658–666. doi:10.1016/S1473-3099(07)70236-0. PMID 17897608.
35. ^ Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, Fukuda K (2003). "Mortality associated with influenza and respiratory syncytial virus in the United States". *The Journal of the American Medical Association*. **289** (2): 179–186. doi:10.1001/jama.289.2.179. PMID 12517228.
36. ^ "High Dose Flu Vaccine for the Elderly « Science-Based Medicine". Sciencebasedmedicine.org. Retrieved October 17, 2013.
37. ^ "CDC – Seasonal Influenza (Flu) – Q & A: Fluzone High-Dose Seasonal Influenza Vaccine". Cdc.gov. August 13, 2013. Retrieved October 17, 2013.
38. ^ Haverkate, M.; D'Ancona, F.; Giambi, C.; Johansen, K.; Lopalco, P. L.; Cozza, V.; Appelgren, E.; VENICE project gatekeepers and contact points (2012-05-31). "Mandatory and recommended vaccination in the EU, Iceland and Norway: results of the VENICE 2010 survey on the ways of implementing national vaccination programmes". *Euro Surveillance: Bulletin Europeen Sur Les Maladies Transmissibles = European Communicable Disease Bulletin*. **17** (22). ISSN 1560-7917. PMID 22687916.
39. ^ Field, Robert I. (2016-11-26). "Mandatory Vaccination of Health Care Workers". *Pharmacy and Therapeutics*. **34** (11): 615–618. ISSN 1052-1372. PMC 2810172. PMID 20140133.
40. ^ Kassianos, George (2015-01-21). "Willingness of European healthcare workers to undergo vaccination against seasonal influenza: current situation and suggestions for improvement". *Drugs in Context*. **4**: 1–9.

doi:10.7573/dic.212268. ISSN 1745-1981. PMC 4316812. PMID 25657810.
41. ^ Thomas, Roger E.; Jefferson, Tom; Lasserson, Toby J. (2016-06-02). "Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions". *The Cochrane Database of Systematic Reviews* (6): CD005187. doi:10.1002/14651858.CD005187.pub5. ISSN 1469-493X. PMID 27251461.
42. ^ Fell, Deshayne B.; Sprague, Ann E.; Liu, Ning; Yasseen, Abdool S.; Wen, Shi-Wu; Smith, Graeme; Walker, Mark C. (June 2012). "H1N1 Influenza Vaccination During Pregnancy and Fetal and Neonatal Outcomes". *American Journal of Public Health*. **102** (6): e33–e40. doi:10.2105/AJPH.2011.300606.
43. ^ Madhi, Shabir A.; Cutland, Clare L.; Kuwanda, Locadiah; Weinberg, Adriana; Hugo, Andrea; Jones, Stephanie; Adrian, Peter V.; van Niekerk, Nadia; Treurnicht, Florette; Ortiz, Justin R.; Venter, Marietjie; Violari, Avy; Neuzil, Kathleen M.; Simões, Eric A.F.; Klugman, Keith P.; Nunes, Marta C. (2014). "Influenza Vaccination of Pregnant Women and Protection of Their Infants". *New England Journal of Medicine*. **371** (10): 918–931. doi:10.1056/NEJMoa1401480. ISSN 0028-4793.
44. ^ "Key Facts About Seasonal Flu Vaccine". *cdc.gov*. Center for Disease Control. Retrieved 26 September 2014.
45. ^ CDC – Inactivated Influenza Vaccine 2007–2008 – What You Need To Know
46. ^ Flu – LAIV
47. ^ Gagnon, R; Primeau MN; Des Roches A; Lemire C; Kagan R; Carr S; Ouakki M; Benoît M; De Serres G (August 2010). "Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine.". *The Journal of Allergy and Clinical Immunology*. **126** (2): 317–323. doi:10.1016/j.jaci.2010.05.037. PMID 20579720.
48. ^ National Advisory Committee on Immunization (August 2012). "Statement on Seasonal Influenza Vaccine for 2012–2013" (PDF). *Canadian Communicable Disease Report*. **38**. Retrieved 18 July 2013.
49. ^ Turner, Paul J.; Southern, Jo; Andrews, Nick J.; Miller, Elizabeth; Erlewyn-Lajeunesse, Michel (2015-12-08). "Safety of live attenuated influenza vaccine in young people with egg allergy: multicentre prospective cohort study". *BMJ*. **351**: h6291. doi:10.1136/bmj.h6291. ISSN 1756-1833. PMC 4673102. PMID 26645895.
50. ^ Greenhawt, Matthew (2015-12-09). "Live attenuated influenza vaccine for children with egg allergy". *BMJ*. **351**: h6656. doi:10.1136/bmj.h6656. ISSN 1756-1833. PMID 26657778.
51. ^ Andrew Pollack, "Rapidly Produced Flu Vaccine Wins F.D.A. Approval", *The New York Times*, January 16, 2013
52. ^ Haber P, Sejvar J, Mikaeloff Y, DeStefano F (2009). "Vaccines and Guillain–Barré syndrome". *Drug Safety*. **32** (4): 309–23. doi:10.2165/00002018-200932040-00005. PMID 19388722.
53. ^ Kaplan JE, Katona P, Hurwitz ES, Schonberger LB (August 1982). "Guillain–Barré syndrome in the United States, 1979–1980 and 1980–1981. Lack of an association with influenza vaccination". *JAMA*. **248** (6): 698–700. doi:10.1001/jama.248.6.698. PMID 7097920.
54. ^ Stowe J, Andrews N, Wise L, Miller E (February 2009). "Investigation of the temporal association of Guillain–Barré syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database". *Am. J. Epidemiol.* **169** (3): 382–8. doi:10.1093/aje/kwn310. PMID 19033158.
55. ^ Sivadon-Tardy V; Orlikowski, David; Porcher, Raphaël; Sharshar, Tarek; Durand, Marie Christine; Enouf, Vincent; Rozenberg, Flore; Caudie, Christiane; Annane, Djillali; Van Der Werf, Sylvie; Lebon, Pierre; Raphaël, Jean Claude; Gaillard, Jean Louis; Gault, Elyanne (January 2009). "Guillain–Barré syndrome and influenza virus infection". *Clin. Infect. Dis.* **48** (1): 48–56. doi:10.1086/594124. PMID 19025491.
56. ^ Vellozzi C, Burwen DR, Dobardzic A, Ball R, Walton K, Haber P (March 2009). "Safety of trivalent inactivated influenza vaccines in adults: Background for pandemic influenza vaccine safety monitoring". *Vaccine*. **27** (15): 2114–2120. doi:10.1016/j.vaccine.2009.01.125. PMID 19356614.
57. ^ Steven Reinberg (February 2, 2011). "Last Year's H1N1 Flu Vaccine Was Safe, Study Finds". *U.S. News & World Report*.
58. ^ Sivadon-Tardy V, Orlikowski D, Porcher R, et al. (January 2009). "Guillain–Barré syndrome and influenza virus infection". *Clinical Infectious Diseases*. **48** (1): 48–56. doi:10.1086/594124. PMID 19025491.
59. ^ *TECHNICAL REPORT: Narcolepsy in association with pandemic influenza vaccination* (PDF). Stockholm, Sweden: European Centre for Disease Prevention and Contro. 2012. ISBN 978-92-9193-388-4.
60. ^ Yong, Ed (18 December 2013). "Narcolepsy confirmed as autoimmune disease". *Nature*. doi:10.1038/nature.2013.14413.
61. ^ Offit PA (September 2007). "Thimerosal and vaccines—a cautionary tale". *N Engl J Med* (PDF). **357** (13): 1278–9. doi:10.1056/NEJMp078187. PMID 17898096.
62. ^ Global Advisory Committee on Vaccine Safety (2006-07-14). "Thiomersal and vaccines". World Health Organization. Retrieved 2007-11-20.
63. ^ Plotkin & Mortimer (1988). *Vaccines*. Philadelphia: W.B. Saunders Company. ISBN 0-7216-1946-0.
64. ^ *Product Monograph: Flumist*, Astrazeneca Canada Inc., 2011
65. ^ "Prevention and Control of Seasonal Influenza with Vaccines Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009" (PDF). *Morbidity and Mortality Weekly Report*. Centers for Disease Control.

**58** (RR-8): 31. 2009. "Students or other persons in institutional settings (e.g., those who reside in dormitories or correctional facilities) should be encouraged to receive vaccine to minimize morbidity and the disruption of routine activities during influenza epidemics"

66. ^ To, K.W.; Lai, A.; Lee, K.C.K.; Koh, D.; Lee, S.S. (October 2016). "Increasing the coverage of influenza vaccination in healthcare workers: review of challenges and solutions". *Journal of Hospital Infection*. **94** (2): 133–142. doi:10.1016/j.jhin.2016.07.003. PMID 27546456.
67. ^ *a b c d* Rubin GJ, Potts HWW, Michie S (2011). Likely uptake of swine and seasonal flu vaccines among healthcare workers. A cross-sectional analysis of UK telephone survey data. Vaccine, 29(13), 2421-8. doi:10.1016/j.vaccine.2011.01.035 http://www.sciencedirect.com/science/article/pii/S0264410X11000740
68. ^ Skowronski DM, De Serres G (2009). "Is routine influenza immunization warranted in early pregnancy?". *Vaccine*. **27** (35): 4754–70. doi:10.1016/j.vaccine.2009.03.079. PMID 19515466.
69. ^ Health Care Guideline: Routine Prenatal Care. Fourteenth Edition. By the Institute for Clinical Systems Improvement. July 2010.
70. ^ CDC
71. ^ "WHO | World Health Organization". Who.int. Retrieved 2014-07-24.
72. ^ "U.S. panel recommends all kids get the flu shot". CTV. February 27, 2008. "In Canada, the National Advisory Committee on Immunization (NACI), the group that advises the Public Health Agency of Canada, currently says that children between the age of six and 24 months should be considered a high priority for the flu vaccine."
73. ^ "Statement on Seasonal Influenza Vaccine for 2013–2014 – CCDR Vol.39 ACS-4 – Public Health Agency of Canada". Phac-aspc.gc.ca. 2013-11-14. Retrieved 2014-07-24.
74. ^ "Influenza vaccination". *ecdc.europa.eu*. Retrieved 24 December 2016.
75. ^ "ECDC Reviews - New WHO recommendations on seasonal influenza...". *ecdc.europa.eu*. Retrieved 25 December 2016.
76. ^ "ECDC GUIDANCE: Priority risk groups for influenza vaccination (p. 7-8)" (PDF). European Centre for Disease Prevention and Control. Retrieved 25 December 2016.
77. ^ *a b* Fiore, AE; Uyeki; Broder, K; Finelli, L; Euler, GL; Singleton, JA; Iskander, JK; Wortley, PM; et al. (August 2010). "Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010" (PDF). *MMWR Recomm Rep*. **59** (RR–8): 1–62. PMID 20689501.
78. ^ "Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) – United States, 2012–13 influenza season" (PDF). *MMWR Morb. Mortal. Wkly. Rep.* **61** (32): 613–8. August 2012. ISSN 0149-2195. PMID 22895385.
79. ^ "Children, the Flu, and the Flu Vaccine"
80. ^ "Who Should Get Vaccinated Against Influenza". Centers for Disease Control. Retrieved 14 January 2014.
81. ^ CDC – Influenza (Flu) | Vaccination: Summary for Clinicians
82. ^ Couch, Robert B.; Patricia Winokur; Rebecca Brady; Robert Belshe; Wilbur H. Chen; Thomas R. Cate; Bryndis Sigurdardottir; Amy Hoeper; Irene L. Graham; Robert Edelman; Fenhua He; Diane Nino; Jose Capellan; Frederick L. Ruben (1 November 2007). "Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects". *Vaccine*. **25** (44): 7656–7663. doi:10.1016/j.vaccine.2007.08.042.
83. ^ Tanner, Lindsey (2013-01-13). "Hospitals crack down on workers who refuse flu shots". NBC News. Retrieved 2014-07-24.
84. ^ Centers for Disease Control and Prevention (CDC) (December 2010). "Seasonal influenza and 2009 H1N1 influenza vaccination coverage among pregnant women – 10 states, 2009–10 influenza season" (PDF). *MMWR Morb Mortal Wkly Rep*. **59** (47): 1541–5. PMID 21124293. "Because pregnant women are at increased risk for severe disease associated with influenza infection, the American College of Obstetricians and Gynecologists and the Advisory Committee on Immunization Practices have recommended seasonal influenza vaccination for women while pregnant, regardless of trimester (1,2). In 2009, a novel strain of influenza A (H1N1) virus was identified (3), and pregnant women also were found at greater risk for influenza-related complications from this new virus (4). As a result, during the 2009–10 influenza season, two separate influenza vaccines were recommended to pregnant women: inactivated trivalent 2009–10 seasonal vaccine and influenza A (H1N1) 2009 monovalent vaccine (2,5)"
85. ^ Fiore, AE; Shay, DK; Broder, K; Iskander, JK; Uyeki, TM; Mootrey, G; Bresee, JS; Cox, NJ; Centers for Disease Control and Prevention (2009). "Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009" (PDF). *MMWR Recomm Rep*. **58** (RR–8): 1–52. PMID 19644442. "Annual vaccination of all children aged 6 months – 18 years should begin as soon as the 2009–10 influenza vaccine is available. Annual vaccination of all children aged 6 months – 4 years (59 months) and older children with conditions that place them at increased risk for complications from influenza should continue to be a primary focus of vaccination efforts as providers and programs transition to routinely vaccinating all children."
86. ^ *a b* Altman, Lawrence K. (February 28, 2008). "Panel Advises Flu Shots for Children Up to Age 18". *The New York Times*.

87. ^ "CDC Press Releases". *CDC*. Retrieved 2016-11-26.
88. ^ "Immunization Schedules". *CDC*. Center for Disease Control and Prevention. Retrieved 4 November 2014.
89. ^ *a b* Han YKJ, Michie S, Potts HWW, Rubin GJ (2016). Predictors of influenza vaccine uptake during the 2009/10 influenza A H1N1v ('swine flu') pandemic: Results from five national surveys in the United Kingdom. Preventive Medicine. doi:10.1016/j.ypmed.2015.12.018 http://www.sciencedirect.com/science/article/pii/S0091743515003916
90. ^ A. Bish, L. Yardley, A. Nicoll, S. Michie. Factors associated with uptake of vaccination against pandemic influenza: a systematic review. Vaccine, 29 (2011), pp. 6472–6484
91. ^ S. Brien, J.C. Kwong. The determinants of 2009 pandemic A/H1N1 influenza vaccination: a systematic review. Vaccine, 30 (2011), pp. 1255–1264
92. ^ La Torre, D. Di Thiene, C. Cadeddu, W. Ricciardi, A. Boccia, Behaviours regarding preventive measures against pandemic H1N1 influenza among Italian healthcare workers, October 2009, Eurosurveillance, Vol. 14, 2009
93. ^ G. Rachiotis, V.A. Mouchtouri, J. Kremastinou, K. Gourgoulianis, C. Hadjichristodoulou, Low acceptance of vaccination against the 2009 pandemic influenza A(H1N1) among healthcare workers in Greece, Eurosurveillance, Vol. 5, Iss. 6, 2010
94. ^ S.Y. Chor, K.L. Ngai, W.B. Goggins, M.C.S. Wong, S.Y.S. Wong, N. Lee, Willingness of Hong Kong healthcare workers to accept pre-pandemic influenza vaccination at different WHO alert levels: two questionnaire surveys, BMJ, Vol. 339, 2009, b3398
95. ^ Coverage in healthcare workers
96. ^ "Influenza Vaccination Coverage Among Health-Care Personnel – United States, 2010–11 Influenza Season". *Morbidity and Mortality Weekly Report (MMWR)*
97. ^ "Influenza vaccination coverage among health-care personnel: 2011–12 influenza season, United States" (PDF). *MMWR Morb. Mortal. Wkly. Rep.* **61** (38): 753–7. September 2012. ISSN 0149-2195. PMID 23013720.
98. ^ *a b* how it's made
99. ^ *a b c d e* New and Old Ways to Make Flu Vaccines, November 8, 2007, National Public Radio.
100. ^ WHO:Influenza vaccine viruses and reagents
101. ^ "Recommendations for the production and control of influenza vaccine (inactivated)" (PDF). World Health Organization. Retrieved 27 May 2013.
102. ^ "Priming with DNA vaccine makes avian flu vaccine work better (NIH News)". October 3, 2011.
103. ^ "Novartis receives FDA approval for Flucelvax, the first cell-culture vaccine in US to help protect against seasonal influenza" (Press release). Novartis. November 20, 2012.
104. ^ "FDA approves first seasonal influenza vaccine manufactured using cell culture technology"
105. ^ "November 20, 2012 Approval Letter- Flucelvax"
106. ^ PATH, Oliver Wyman. Influenza Vaccine Strategies for Broad Global Access. 2007. http://www.path.org/files/VAC_infl_publ_rpt_10-07.pdf
107. ^ Bright, R. A.; Carter, D. M.; Daniluk, S.; Toapanta, F. R.; Ahmad, A.; Gavrilov, V.; Massare, M.; Pushko, P.; et al. (May 2007). "Influenza virus-like particles elicit broader immune responses than whole virion inactivated influenza virus or recombinant hemagglutinin". *Vaccine*. **25** (19): 3871–8. doi:10.1016/j.vaccine.2007.01.106. PMID 17337102.
108. ^ *a b* Racaniello, Vincent (Dec 2009). "Influenza virus growth in eggs". Virology Blog.
109. ^ Izzat, Fakhrul (Apr 2012). "Viral Cultivation in Chicken Embryo". Youtube.
110. ^ *a b* "How Influenza (Flu) Vaccines Are Made". Centers for Disease Control and Prevention. May 2014.
111. ^ WHO article *Global influenza surveillance*[*verification needed*]
112. ^ Brown, David (2008-02-18). "Keeping ahead of flu comes down to guessing game". *Knoxville News Sentinel*. The Washington Post. Archived from the original on 2009-01-11. Retrieved 2015-12-22.
113. ^ WHO Report on Global Surveillance of Epidemic-prone Infectious Diseases (pdf)
114. ^ WHO | Recommended composition of influenza virus vaccines for use in the 2016–2017 northern hemisphere influenza season
115. ^ WHO | Recommended composition of influenza virus vaccines for use in the 2016 southern hemisphere influenza season.
116. ^ *a b* Update on Influenza A (H1N1) 2009 Monovalent Vaccines, 9 October 2009 Accessed 9 February 2015
117. ^ WHO | Recommended composition of influenza virus vaccines for use in the 2017 southern hemisphere influenza season.
118. ^ The Threat of Pandemic Influenza: Are We Ready? Workshop Summary (2005) (free online book) page 62
119. ^ Plotkin, S.L. and Plotkin, S.A. "A short history of vaccination." *In: Vaccines*, Stanley A. Plotkin, Walter A. Orenstein, Paul A. Offit, eds. Elsevier Health Sciences, 2008, pp. 6–7.
120. ^ Artenstein, A.W. "Influenza" *In: Vaccines: A Biography* Andrew W. Artenstein, ed. pp. 191–205.
121. ^ Hampson AW (2008). "Vaccines for Pandemic Influenza. The History of our Current Vaccines, their Limitations and

the Requirements to Deal with a Pandemic Threat". *Ann Acad Med Singap*. **37**: 510–7.
122. ^ USFDA FDA approves first seasonal influenza vaccine manufactured using cell culture technology. November 20, 2012.
123. ^ USFDA FDA approves new seasonal influenza vaccine made using novel technology. Jan. 16, 2013.
124. ^ Landry, Nathalie; Ward, Brian J.; Trépanier, Sonia; Montomoli, Emanuele; Dargis, Michèle; Lapini, Giulia; Vézina, Louis-P. (2010-12-22). "Preclinical and Clinical Development of Plant-Made Virus-Like Particle Vaccine against Avian H5N1 Influenza". *PLOS ONE*. **5** (12): e15559. Bibcode:2010PLoSO...515559L. doi:10.1371/journal.pone.0015559. PMC 3008737. PMID 21203523. Retrieved 14 May 2013.
125. ^ CDC report *Prevention and Control of Influenza* published April 12, 2002.
126. ^ Osterholm, Michael T. (2005). "Preparing for the Next Pandemic". *New England Journal of Medicine*. **352** (18): 1839–42. doi:10.1056/NEJMp058068. PMID 15872196.
127. ^ The Sky is Falling: An Analysis of the Swine Flu Affair of 1976
128. ^ McCullers JA, Van De Velde LA, Allison KJ, Branum KC, Webby RJ, Flynn PM (June 2010). "Vaccinees against the 1976 "swine flu" have enhanced neutralization responses to the 2009 novel H1N1 influenza virus". *Clin. Infect. Dis.* **50** (11): 1487–92. doi:10.1086/652441. PMC 2946351. PMID 20415539.
129. ^ Brownlee, Shannon (1 November 2009). "Does the Vaccine Matter?". *The Atlantic*. Retrieved 8 December 2014.
130. ^ Rabin, Roni Caryn. "Reassessing Flu Shots as the Season Draws Near". New York Times. Retrieved 30 December 2016.
131. ^ Jit, Mark; Newall, Anthony T.; Beutels, Philippe (1 April 2013). "Key issues for estimating the impact and cost-effectiveness of seasonal influenza vaccination strategies". *Human vaccines & immunotherapeutics*. **9** (4): 834–840. doi:10.4161/hv.23637. PMC 3903903. PMID 23357859.
132. ^ Postma, M.J; Baltussen, R.P.M.; Palache, A.M; Wilschut, J.C. (2006). "Further evidence for favorable cost-effectiveness of elderly influenza vaccination". *Expert Review of Pharmacoeconomics and Outcomes Research*. **6** (2): 215–27. doi:10.1586/14737167.6.2.215. PMID 20528557.
133. ^ Newall, AT; Kelly, H; Harsley, S; Scuffham, PA (2009). "Cost Effectiveness of Influenza Vaccination in Older Adults". *PharmacoEconomics*. **27** (6): 439–50. doi:10.2165/00019053-200927060-00001. PMID 19640008.
134. ^ Newall, AT; Viboud, C; Wood, JG (2009). "Influenza-attributable mortality in Australians aged more than 50 years: A comparison of different modelling approaches". *Epidemiology and Infection*. **138** (6): 836–42. doi:10.1017/S095026880999118X. PMID 19941685.
135. ^ Newall, Anthony T.; Dehollain, Juan Pablo; Creighton, Prudence; Beutels, Philippe; Wood, James G. (4 May 2013). "Understanding the Cost-Effectiveness of Influenza Vaccination in Children: Methodological Choices and Seasonal Variability". *PharmacoEconomics*. **31** (8): 693–702. doi:10.1007/s40273-013-0060-7.
136. ^ Newall, A.T.; Scuffham, P.A (2011). "Uncertainty and variability in influenza cost-effectiveness models". *Australian and New Zealand Journal of Public Health*. **35** (6): 576; author reply 576–7. doi:10.1111/j.1753-6405.2011.00788.x. PMID 22151168.
137. ^ Gatwood, J; Meltzer, MI; Messonnier, M; Ortega-Sanchez, IR; Balkrishnan, R; Prosser, LA (2012). "Seasonal Influenza Vaccination of Healthy Working-Age Adults". *Drugs*. **72** (1): 35–48. doi:10.2165/11597310-000000000-00000. PMID 22191794.
138. ^ Newall, Anthony T.; Jit, Mark; Beutels, Philippe (August 1, 2012). "Economic Evaluations of Childhood Influenza Vaccination". *PharmacoEconomics*. **30** (8): 647–660. doi:10.2165/11599130-000000000-00000.
139. ^ Newall, A.T.; Wood, J.G.; Oudin, N.; MacIntyre, C.R. (2010). "Cost-effectiveness of pharmaceutical-based pandemic influenza mitigation strategies". *Emerging Infectious Diseases*. **16** (2): 224–230. doi:10.3201/eid1602.090571.
140. ^ "Influenza Genome Sequencing Project – Overview". National Institutes of Health – National Institute of Allergy and Infectious Diseases. Retrieved 27 May 2013.
141. ^ Lampos, Vasileios; Yom-Tov, Elad; Pebody, Richard; Cox, Ingemar J. (2 July 2015). "Assessing the impact of a health intervention via user-generated Internet content". *Data Mining and Knowledge Discovery*. **29**: 1434–1457. doi:10.1007/s10618-015-0427-9.
142. ^ World Health Organization. Acyte Respiratory Infections: Influenza. 2009. http://www.who.int/vaccine_research/diseases/ari/en/index1.html
143. ^ World Health Organization. Tables on the Clinical trials of pandemic influenza prototype vaccines. July 2009. http://www.who.int/vaccine_research/immunogenicity/immunogenicity_table.xls
144. ^ US Food & Drug Administration. FDA Approves Vaccines for 2009 H1N1 Influenza Virus Approval Provides Important Tool to Fight Pandemic. September 15, 2009. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm182399.htm
145. ^ "First Quadrivalent Vaccine Against Seasonal Flu Wins FDA Approval"
146. ^ "FDA approves first quadrivalent vaccine to prevent seasonal influenza"
147. ^ "December 14, 2012 Approval Letter- Fluarix Quadrivalent"
*a b c*

148. ^ Cho A, Wrammert J (2016). "Implications of broadly neutralizing antibodies in the development of a universal influenza vaccine". *Curr Opin Virol*. **17**: 110–5. doi:10.1016/j.coviro.2016.03.002. PMID 27031684.
149. ^ *a b c d* Soema PC, Kompier R, Amorij JP, Kersten GF (2015). "Current and next generation influenza vaccines: Formulation and production strategies". *Eur J Pharm Biopharm*. **94**: 251–63. doi:10.1016/j.ejpb.2015.05.023. PMID 26047796.
150. ^ Deng L, Cho KJ, Fiers W, Saelens X (2015). "M2e-Based Universal Influenza A Vaccines". *Vaccines (Basel)*. **3**: 105–36. doi:10.3390/vaccines3010105. PMC 4494237. PMID 26344949.
151. ^ Gottlieb T, Ben-Yedidia T (2014). "Epitope-based approaches to a universal influenza vaccine". *J. Autoimmun*. **54**: 15–20. doi:10.1016/j.jaut.2014.07.005. PMID 25172355.
152. ^ Toussi DN, Massari P Immune Adjuvant Effect of Molecularly-defined Toll-Like Receptor Ligands. Vaccines (Basel). 2014 Apr 25;2(2):323-53. PMID 26344622 PMC 4494261/
153. ^ Influenza Report (online book) chapter *Avian Influenza* by Timm C. Harder and Ortrud Werner
154. ^ equiflunet_vaccines
155. ^ UAE Equestrian & Racing Federation
156. ^ FEI guidelines
157. ^ McNeil, Donald G. Jr. (May 2, 2006). "Turning to Chickens in Fight With Bird Flu". *The New York Times*.
158. ^ SciDev.Net article *Bird flu warning over partial protection of flocks* published August 16, 2006
159. ^ FAO Recommendations on the Prevention, Control and Eradication of Highly Pathogenic Avian Influenza (HPAI) in Asia http://www.fao.org/docs/eims/upload/246982/aj126e00.pdf
160. ^ Yen, Hui-Ling; Joseph Sriyal Malik Peiris (21 June 2012). "Virology: Bird flu in mammals". *Nature*. **486** (7403): 332–333. Bibcode:2012Natur.486..332Y. doi:10.1038/nature11192. PMID 22722190. Retrieved 27 May 2013.
161. ^ National Hog Farmer article *Swine Flu Virus Turns Endemic* published September 15, 2007
162. ^ livestock.novartis.com Custom Vaccines: Swine
163. ^ Karaca K, Dubovi E, Siger L, Robles A, Audonnet J, Jiansheng Y, Nordgren R, Minke J; Dubovi; Siger; Robles; Audonnet; Jiansheng; Nordgren; Minke (2007). "Evaluation of the ability of canarypox-vectored equine influenza virus vaccines to induce humoral immune responses against canine influenza viruses in dogs". *Am. J. Vet. Res*. **68** (2): 208–12. doi:10.2460/ajvr.68.2.208. PMID 17269888.


## External links [edit]

- PATH's Vaccine Resource Library influenza resources
- CDC Inactivated Influenza Vaccine Information Statement
- Vaccines and Preventable Diseases – Seasonal Influenza (Flu) Vaccination
- Misconceptions about Seasonal Influenza and Influenza Vaccines

| v · t · e · | **Influenza** | |
|---|---|---|
| **General topics** | Research · **Vaccine** · Treatment · Genome sequencing · Reassortment · Superinfection · Flu season · | |
| **Viruses** | Orthomyxoviridae · Influenza A · Influenza B · Influenza C · | |
| **Influenza A virus subtypes** | H1N1 · H1N2 · H2N2 · H2N3 · H3N1 · H3N2 · H3N8 · H5N1 · H5N2 · H5N3 · H5N6 · H5N8 · H5N9 · H6N1 · H7N1 · H7N2 · H7N3 · H7N4 · H7N7 · H7N9 · H9N2 · H10N7 · | |
| **H1N1** | Pandemics | 1918 ("Spanish flu") · 2009 ("swine flu") · |
| | Science | 2009 A/H1N1 · |
| **H5N1** | Outbreaks | Croatia (2005) · India (2006) · UK (2007) · West Bengal (2008) · |
| | Science | Genetic structure · Transmission and infection · Global spread · Vaccine (clinical trials · · Human mortality · Social impact · Pandemic preparation · |
| **Treatments** | Antiviral drugs | Adamantane derivatives (Amantadine · Rimantadine · · Neuraminidase inhibitor (Oseltamivir · Laninamivir · Peramivir · Zanamivir · · Peramivir (experimental) · Umifenovir · |

| | | |
|---|---|---|
| | **Vaccines** | Live attenuated influenza vaccine · Fluzone · Pandemrix · |
| **Pandemics and epidemics** | Pandemics | "Russian flu" (1889–1890) · "Spanish flu" (1918) · "Asian flu" · "Hong Kong flu" (1968) · 2009 · |
| | Epidemics | "Russian flu" (1977–1978) · "Fujian flu" (H3N2) · |
| **Non-human** | Mammals | Canine · Feline · Equine (2007 Australian outbreak · · Swine · |
| | Non-mammals | Avian · Fujian (H5N1) · |
| **Complications** | | Acute bronchitis · Bronchiolitis · Croup · Otitis media · Pharyngitis · Pneumonia · Sinusitis · Strep throat · |
| **Related topics** | | Influenza-like illness · |

| v · t · e · | **Artificial induction of immunity / Immunization: Vaccines, Vaccination, Infection, Inoculation (J07)** | |
|---|---|---|
| **Development** | | Adjuvants · List of vaccine ingredients · Mathematical modelling · Timeline · Trials · |
| **Classes** | | Conjugate vaccine · DNA vaccination · Inactivated vaccine · Live vector vaccine (Attenuated vaccine · Heterologous vaccine · · Subunit/component / Peptide / Virus-like particle · Toxoid · |
| **Administration** | | Global: (GAVI Alliance · Policy · Schedule · Vaccine injury · · USA: (ACIP · Vaccine court · Vaccines for Children Program · VAERS · VSD · · |
| **Vaccines** | **Bacterial** | Anthrax · Brucellosis · Cholera# · Diphtheria# · Hib# · Leptospirosis · Lyme disease‡ · Meningococcus# (MeNZB · NmVac4-A/C/Y/W-135 · · Pertussis# · Plague · Pneumococcal# (PCV · PPSV · · Q fever · Tetanus# · Tuberculosis (BCG# · · Typhoid# (Ty21a · ViCPS · · Typhus · combination: DTwP/DTaP · |
| | **Viral** | Adenovirus · **Flu**# (H1N1 (Pandemrix) · LAIV · · Hantavirus · Hepatitis A# · Hepatitis B# · Hepatitis E · HPV (Cervarix · Gardasil · · Japanese encephalitis# · Measles# · Mumps# (Mumpsvax · · Polio# (Sabin · Salk · · Rabies# · Rotavirus# · Rubella# · Smallpox (Dryvax · · Tick-borne encephalitis · Varicella zoster (chicken pox# · shingles (live) · · Yellow fever# · combination: (MMR · MMRV · · research: (Chikungunya · Cytomegalovirus · Dengue · Ebola · Epstein–Barr virus · Hepatitis C · HIV · · |
| | **Protozoan** | research: (Malaria · Trypanosomiasis · · |
| | **Helminthiasis** | research: (Hookworm · Schistosomiasis · · |
| | **Other** | Androvax (androstenedione albumin) · Cancer vaccines (ALVAC-CEA · Hepatitis B# · HPV (Cervarix · Gardasil · · · NicVAX · Ovandrotone albumin (Fecundin) · TA-CD · TA-NIC · |
| **Controversy** | | General · MMR · NCVIA · Pox party · Thiomersal · Andrew Wakefield · *Cedillo v. Secretary of Health and Human Services* · Alternative vaccination schedule · |
| **Related** | | Epidemiology · Eradication of infectious diseases · Every Child by Two · List of vaccine topics · |

#WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · ·

Categories: Influenza vaccines | Influenza | Vaccines | World Health Organization essential medicines (vaccines)


# Ipratropium bromide

From Wikipedia, the free encyclopedia

**Ipratropium bromide**, sold under the trade name **Atrovent** among others, is a medication which opens up the medium and large airways in the lungs.[1] It is used to treat the symptoms of chronic obstructive pulmonary disease and asthma. It is used by inhaler or nebulizer. Onset of action is typically within 15 to 30 minutes and lasts for three to five hours.[1]

Common side effects include dry mouth, cough, and inflammation of the airways. Potentially serious side effects include urinary retention, worsening spasms of the airways, and a severe allergic reaction.[1] It appears to be safe in pregnancy and breastfeeding.[1][2] Ipratropium is an anticholinergic and muscarinic antagonist which works by causing smooth muscles to relax.[1]

Ipratropium bromide was developed in Germany in 1976.[3] It was approved for medical use in the United States in 1986.[1] It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[4] Ipratropium is available as a generic medication.[1] The wholesale price in the developing world is about 6.60 USD for a 200 dose inhaler.[5] In the United States, a month worth of medication costs 100 to 200 USD.[6]

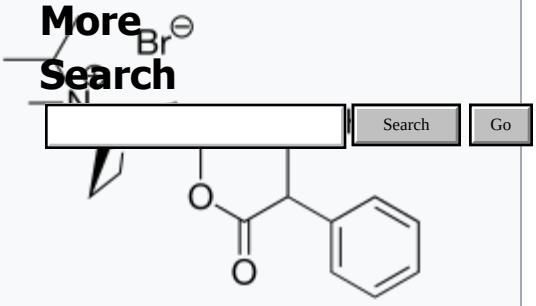
Contents


## Medical uses [edit]

Ipratropium is administered by inhalation for the treatment of chronic obstructive pulmonary disease (COPD). For that purpose, it is supplied in a canister for use in an inhaler or in single dose vials for use in a nebulizer.[7]

It is also used to treat and prevent minor and moderate bronchial asthma, especially asthma that is accompanied by

**Ipratropium bromide**



| Clinical data | |
|---|---|
| **Trade names** | Atrovent, Apovent, Ipraxa, Rinatec, other |
| **AHFS/Drugs.com** | Monograph |
| **Pregnancy category** | US: B (No risk in non-human studies) |
| **Routes of administration** | Inhalation |
| **ATC code** | R01AX03 (WHO) R03BB01 (WHO) |
| **Legal status** | |
| **Legal status** | UK: POM (Prescription only) US: -only |
| **Pharmacokinetic data** | |
| **Protein binding** | 0 to 9% *in vitro* |
| **Metabolism** | Hepatic |
| **Biological half-life** | 2 hours |
| **Identifiers** | |
| **IUPAC name** | [8-methyl-8-(1-methylethyl)- 8-azoniabicyclo[3.2.1] oct-3-yl ] 3-hydroxy-2-phenyl-propanoate |
| **CAS Number** | 22254-24-6 60205-81-4 (cation) |
| **PubChem** (CID) | 657308 |

cardiovascular system diseases.[*citation needed*]

It is also combined with salbutamol (albuterol — USAN) under the trade names Combivent (metered-dose inhaler or MDI) and Duoneb (nebulizer) for the management of COPD and asthma, and with fenoterol (trade names Duovent and Berodual N) for the management of asthma.

Ipratropium as a nasal solution sprayed into the nostrils can reduce rhinorrhea but will not help nasal congestion.[8]

Combination with beta-adrenergic agonists, increases the dilating effect on the bronchi.

| | |
|---|---|
| **IUPHAR/BPS** | 325 |
| **DrugBank** | DB00332 |
| **ChemSpider** | 10481997 |
| **UNII** | GR88G0I6UL ✓ |
| **ChEMBL** | CHEMBL1464005 ✗ |
| **ECHA InfoCard** | 100.040.779 |
| **Chemical and physical data** | |
| **Formula** | $C_{20}H_{30}BrNO_3$ |
| **Molar mass** | 412.37 g/mol |
| **3D model (Jmol)** | Interactive image |

**SMILES**

CC(C)[N+]1([C@@H]2CC[C@H]1C[C@H](C2)OC(=O)C(CO)C3=CC=CC=C3)C.[Br-]

**InChI**

InChI=1S/C20H30NO3.BrH/c1-14(2)21(3)16-9-10-17(21)12-18(11-16)24-20(23)19(13-22)15-7-5-4-6-8-15;/h4-8,14,16-19,22H,9-13H2,1-3H3;1H/q+1;/p-1/t16-,17+,18+,19?,21?;

Key:LHLMOSXCXGLMMN-WDTICOSOSA-M

✗✓ (what is this?) (verify)

## Contraindications [edit]

The main contraindication for inhaled ipratropium is hypersensitivity to atropine and related substances. For oral administration, contraindications are similar to other anticholinergics; they include narrow angle glaucoma and obstructions in the gastrointestinal tract and urinary system.[9][10]

### Peanut allergy [edit]

Previously atrovent inhalers used chlorofluorocarbon (CFC) as a propellant and contained soy lecithin in the propellant ingredients. In 2008 all CFC inhalers were phased out and hydrofluoroalkane (HFA) inhalers replaced them. Allergy to peanuts was noted for the inhaler as a contraindication but now is not. It has never been a contraindication when administered as a nebulized solution.[11]

## Side effects [edit]

If ipratropium is inhaled, side effects resembling those of other anticholinergics are minimal. However, dry mouth and sedation have been reported. Also, effects such as skin flushing, tachycardia, acute angle-closure glaucoma, nausea, palpitations and headache have been observed. Inhaled ipratropium does not decrease mucociliary clearance.[10] The inhalation itself can cause headache and irritation of the throat in a few percent of patients.[9]

Urinary retention has been reported in patients receiving doses by nebulizer. As a result, caution may be warranted, especially by men with prostatic hypertrophy.[12]

## Interactions [edit]

Interactions with other anticholinergics like tricyclic antidepressants, antiparkinson drugs and quinidine, which theoretically increase side effects, are clinically irrelevant when ipratropium is administered as an inhalant.[9][10]

## Pharmacology [edit]

Ipratropium exhibits broncholytic action by reducing cholinergic influence on the bronchial musculature. It blocks muscarinic acetylcholine receptors, without specificity for subtypes, and therefore promotes the degradation of cyclic guanosine monophosphate (cGMP), resulting in a decreased intracellular concentration of cGMP.[13] Most likely due to actions of cGMP on intracellular calcium, this results in decreased

contractility of smooth muscle in the lung, inhibiting bronchoconstriction and mucus secretion. It is a nonselective muscarinic antagonist,[9] and does not diffuse into the blood, which prevents systemic side effects. Ipratropium is a derivative of atropine[14] but is a quaternary amine and therefore does not cross the blood–brain barrier, which prevents central side effects (anticholinergic syndrome). Ipratropium is not considered a short-acting bronchodilator and should never be used in place of salbutamol (albuterol) as a rescue medication.

## References [edit]


1. ^ *a b c d e f g* "Ipratropium Bromide". The American Society of Health-System Pharmacists. Retrieved Dec 2, 2015.
2. ^ Yaffe, Gerald G. Briggs, Roger K. Freeman, Sumner J. (2011). *Drugs in pregnancy and lactation : a reference guide to fetal and neonatal risk* (9th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 763. ISBN 9781608317080.
3. ^ Ravina, Enrique (2011). *The evolution of drug discovery : from traditional medicines to modern drugs* (1. Aufl. ed.). Weinheim: Wiley-VCH. p. 144. ISBN 9783527326693.
4. ^ "WHO Model List of EssentialMedicines" (PDF). *World Health Organization*. October 2013. Retrieved 22 April 2014.
5. ^ "Ipratropium Bromide". *International Drug Price Indicator Guide*. Retrieved 5 December 2015.
6. ^ Hamilton, Richart (2015). *Tarascon Pocket Pharmacopoeia 2015 Deluxe Lab-Coat Edition*. Jones & Bartlett Learning. p. 455. ISBN 9781284057560.
7. ^ Ipratropium Oral Inhalation *PubMed Health* Retrieved May 28, 2012
8. ^ Atrovent Nasal Spray *Drugs.com* Retrieved May 28, 2012
9. ^ *a b c d* Haberfeld, H, ed. (2009). *Austria-Codex* (in German) (2009/2010 ed.). Vienna: Österreichischer Apothekerverlag. ISBN 3-85200-196-X.
10. ^ *a b c* Dinnendahl, V; Fricke, U, eds. (2010). *Arzneistoff-Profile* (in German). **2** (23 ed.). Eschborn, Germany: Govi Pharmazeutischer Verlag. ISBN 978-3-7741-9846-3.
11. ^ Ipratropium Soybean and Nuts Allergy *EMSMedRx* Retrieved April 6, 2013
12. ^ Afonso, A. S. M.; Verhamme, K. M. C.; Stricker, B. H. C.; Sturkenboom, M. C. J. M.; Brusselle, G. G. O. (2011). "Inhaled anticholinergic drugs and risk of acute urinary retention". *BJU International*. **107** (8): 1265–1272. doi:10.1111/j.1464-410X.2010.09600.x. PMID 20880196.
13. ^ Ipratropium *Drugs.com*
14. ^ Yamatake Y, Sasagawa S, Yanaura S, Okamiya Y (1977). "[Antiallergic asthma effect of ipratropium bromide (Sch 1000) in dogs (author's transl)]". *Nippon Yakurigaku Zasshi* (in Japanese). **73** (7): 785–91. doi:10.1254/fpj.73.785. PMID 145994.


| V · T · E · | **Decongestants and other nasal preparations (R01)** | |
|---|---|---|
| **Topical** | **Sympathomimetics, plain** | Cyclopentamine · Ephedrine · Epinephrine · Fenoxazoline · Levomethamphetamine · Metizoline · Naphazoline · Oxymetazoline · Phenylephrine · Propylhexedrine · Tetryzoline · Tramazoline · Tuaminoheptane · Tymazoline · Xylometazoline · |
| | **Antiallergic agents, excluding corticosteroids** | Spaglumic acid · *histamine antagonists* (Levocabastine · Antazoline · Thonzylamine) · *mast cell stabilizer (some are also antihistamines)* (Cromoglicic acid · Nedocromil · Azelastine · Olopatadine · Lodoxamide) · |
| | **Corticosteroids** | Beclometasone dipropionate · Betamethasone · Budesonide · Ciclesonide · Dexamethasone · Flunisolide · Fluticasone · Mometasone furoate · Prednisolone · Tixocortol · Triamcinolone · |
| | **Other nasal preparations** | Cafaminol · Calcium hexamine thiocyanate · Eucalyptus oil · Framycetin · Hexamidine · Hyaluronan · **Ipratropium bromide** · Mupirocin · Retinol · Ritiometan · |

| | | |
|---|---|---|
| | | Saline water · |
| **Systemic use: Sympathomimetics** | Phenylephrine · Phenylpropanolamine · Phenylpropylamine · Pseudoephedrine (+loratadine) · | |

| v · t · e · | **Drugs for obstructive airway diseases: asthma/COPD (R03)** | |
|---|---|---|
| **Adrenergics, inhalants** | **Short-acting $\beta_2$ agonists** | Bitolterol · Carbuterol · Fenoterol · Isoetarine · Pirbuterol · Procaterol · Reproterol · Rimiterol · Salbutamol (albuterol)# /Levosalbutamol (levalbuterol) · Terbutaline · Tulobuterol · |
| | **Long-acting $\beta_2$ agonists** | Bambuterol · Clenbuterol · Formoterol/Arformoterol · Salmeterol · Salmefamol · |
| | **Ultra-long-acting $\beta_2$ agonists** | Abediterol · Carmoterol · Indacaterol · Olodaterol · Vilanterol · |
| | **Other** | Epinephrine# · Hexoprenaline · Isoprenaline (isoproterenol) · Orciprenaline (metaproterenol) · |
| **Glucocorticoids** | Beclometasone# · Betamethasone · Budesonide · Ciclesonide · Flunisolide · Fluticasone · Mometasone · Triamcinolone · | |
| **Anticholinergics/ muscarinic antagonist** | Aclidinium bromide · Glycopyrronium bromide · **Ipratropium bromide**# · Oxitropium bromide · Tiotropium bromide · Umeclidinium bromide · | |
| **Mast cell stabilizers** | Cromoglicate · Nedocromil · | |
| **Xanthines** | Acefylline · Ambuphylline · Bamifylline · Doxofylline · Enprofylline · Etamiphylline · Proxyphylline · Theophylline/Aminophylline/Choline theophyllinate · | |
| **Eicosanoid inhibition** | **Leukotriene antagonists** | Montelukast · Pranlukast · Zafirlukast · |
| | **Arachidonate 5-lipoxygenase inhibitors** | Zileuton · |
| | **Thromboxane receptor antagonists** | Ramatroban · Seratrodast · |
| | **Non-xanthine PDE4 inhibitors** | Ibudilast · Roflumilast · |
| **Others/unknown** | Amlexanox · Eprozinol · Fenspiride · Omalizumab · | |
| **Combination products** | Aclidinium/formoterol · Beclometasone/formoterol · Budesonide/formoterol · Fluticasone furoate/vilanterol · Fluticasone propionate/salmeterol · Indacaterol/glycopyrronium bromide · Ipratropium bromide/salbutamol · Mometasone/formoterol · Umeclidinium bromide/vilanterol · | |

#WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · ·

| v · t · e · | **Cholinergics** |
|---|---|
| | **Receptor ligands** |
| | **Muscarinic agonists:** 77-LH-28-1 · AC-42 · AC-260,584 · Aceclidine · Acetylcholine · AF30 · AF150(S) · AF267B · AFDX-384 · Alvameline · AQRA-741 · Arecoline · Bethanechol · Butyrylcholine · Carbachol · CDD-0034 · CDD-0078 · CDD-0097 · CDD-0098 · CDD-0102 · Cevimeline · Choline · cis-Dioxolane · Ethoxysebacylcholine · Itameline · LY-593,039 · L-689,660 · LY-2,033,298 · McNA343 · Methacholine · Milameline · Muscarine · NGX-267 · Ocvimeline · Oxotremorine · PD-151,832 · Pilocarpine · RS86 · Sabcomeline · SDZ 210-086 · Sebacylcholine · Suberyldicholine · Talsaclidine · Tazomeline · Thiopilocarpine · |

| | |
|---|---|
| **mACh** | Vedaclidine · VU-0029767 · VU-0090157 · VU-0152099 · VU-0152100 · VU-0238429 · WAY-132,983 · Xanomeline · YM-796 ·<br>**Muscarinic antagonists:** 3-Quinuclidinyl benzilate · 4-DAMP · Aclidinium bromide · Anisodamine · Anisodine · Antihistamines (first-generation) (e.g., brompheniramine, chlorphenamine, cyproheptadine, dimenhydrinate, diphenhydramine, doxylamine, mepyramine (pyrilamine), phenindamine, pheniramine, promethazine, tripelennamine, triprolidine) · Atropine · Atropine methonitrate · Atypical antipsychotics (e.g., clozapine, olanzapine, quetiapine, zotepine) · Benactyzine · Benzatropine (benztropine) · Benzilylcholine mustard · Benzydamine · BIBN 99 · Biperiden · Bornaprine · CAR-226,086 · CAR-301,060 · CAR-302,196 · CAR-302,282 · CAR-302,368 · CAR-302,537 · CAR-302,668 · Caramiphen · Cloperastine · CS-27349 · Cyclobenzaprine · Cyclopentolate · Darifenacin · DAU-5884 · Dimethindene · Dexetimide · DIBD · Dicyclomine (dicycloverine) · Ditran · EA-3167 · EA-3443 · EA-3580 · EA-3834 · Etanautine · Etybenzatropine (ethybenztropine) · Flavoxate · Himbacine · HL-031,120 · **Ipratropium bromide** · J-104,129 · Hyoscyamine · Mamba toxin 3 · Mamba toxin 7 · Mazaticol · Mebeverine · Methoctramine · Metixene · N-Ethyl-3-piperidyl benzilate · N-Methyl-3-piperidyl benzilate · Orphenadrine · Otenzepad · Oxybutynin · PBID · PD-102,807 · PD-0298029 · Phenglutarimide · Phenyltoloxamine · Pipenzolate bromide · Pirenzepine · Piroheptine · Procyclidine · Profenamine · Revefenacin · RU-47,213 · SCH-57,790 · SCH-72,788 · SCH-217,443 · Scopolamine (hyoscine) · Sofpironium bromide · Solifenacin · Telenzepine · Tetracyclic antidepressants (e.g., amoxapine, maprotiline, mianserin, mirtazapine) · Timepidium bromide · Tiotropium bromide · Tolterodine · Tricyclic antidepressants (e.g., amitriptyline, butriptyline, clomipramine, desipramine, dosulepin (dothiepin), doxepin, imipramine, lofepramine, nortriptyline, protriptyline, trimipramine) · Trihexyphenidyl · Tripitamine · Tropacine · Tropatepine · Tropicamide · Typical antipsychotics (e.g., chlorpromazine, loxapine, thioridazine) · WIN-2299 · Xanomeline · Zamifenacin · |
| **nACh** | **Nicotinic agonists:** 5-HIAA · A-84,543 · A-366,833 · A-582,941 · A-867,744 · ABT-202 · ABT-418 · ABT-560 · ABT-894 · Acetylcholine · Altinicline · Anabasine · Anatoxin-a · AR-R17779 · Butinoline · Butyrylcholine · Carbachol · Choline · Cotinine · Cytisine · Decamethonium · Desformylflustrabromine · Dianicline · Dimethylphenylpiperazinium · Epibatidine · Epiboxidine · Ethanol · Ethoxysebacylcholine · EVP-4473 · EVP-6124 · Galantamine · GTS-21 · Ispronicline · Ivermectin · Levamisole · Lobeline · MEM-63,908 (RG-3487) · Morantel · Nicotine (tobacco) · NS-1738 · PHA-543,613 · PHA-709,829 · PNU-120,596 · PNU-282,987 · Pozanicline · Rivanicline · RJR-2429 · Sazetidine A · SB-206553 · Sebacylcholine · SIB-1508Y · SIB-1553A · SSR-180,711 · Suberyldicholine · Suxamethonium (succinylcholine) · TC-1698 · TC-1734 · TC-1827 · TC-2216 · TC-5214 · TC-5619 · TC-6683 · Tebanicline · Tropisetron · UB-165 · Varenicline · WAY-317,538 · XY-4083 ·<br>**Nicotinic antagonists:** 18-MAC · 18-MC · α-Neurotoxins (e.g., α-bungarotoxin, α-cobratoxin, α-conotoxin, many others) · ABT-126 · Alcuronium · Allopregnanolone · Amantadine · Anatruxonium · AQW051 · Atracurium · Barbiturates (e.g., pentobarbital, sodium thiopental) · Bungarotoxins (e.g., α-bungarotoxin, κ-bungarotoxin) · Bupropion · Chandonium · Chlorisondamine · Cisatracurium · Coclaurine · Coronaridine · Cyclopropane · Dacuronium · Decamethonium · Dehydronorketamine · Desflurane · Dextromethorphan · Dextropropoxyphene · Dextrorphan · Diadonium · DHβE · Dihydrochandonium · Dimethyltubocurarine (metocurine) · Dipyrandium · Dizocilpine (MK-801) · Doxacurium · Encenicline · Enflurane · Esketamine · Fazadinium · Gallamine · Halothane · Hexafluronium · Hexamethonium (benzohexonium) · Hydroxybupropion · Hydroxynorketamine · Ibogaine · Isoflurane · Ketamine · Kynurenic acid · Laudexium (laudolissin) · Levacetylmethadol · Levomethadone · Malouetine · ME-18-MC · Mecamylamine · Memantine · Methadone · Methorphan (racemethorphan) · Methyllycaconitine · Metocurine · Mivacurium · Morphanol (racemorphan) · Neramexane · Nitrous oxide · Norketamine · Pancuronium bromide · Pempidine · Pentamine · Pentolinium · Phencyclidine · Pipecuronium · Progesterone · Promegestone · Radafaxine · Rapacuronium · Reboxetine · Rocuronium · Sevoflurane · Surugatoxin · Thiocolchicoside · Toxiferine · Tramadol · Trimetaphan camsilate (trimethaphan camsylate) · |

| | |
|---|---|
| | Tropeinium · Tubocurarine · Vanoxerine · Vecuronium · Xenon · |
| **Transporter ligands** | |
| **CHT** | **Inhibitors:** Hemicholinium-3 (hemicholine) · Triethylcholine · **Enhancers:** Coluracetam · |
| **VAChT** | **Inhibitors:** Vesamicol · |
| **Enzyme modulators** | |
| **ChAT** | **Inhibitors:** 1-(-Benzoylethyl)pyridinium · 2-(α-Naphthoyl)ethyltrimethylammonium · 3-Chloro-4-stillbazole · 4-(1-Naphthylvinyl)pyridine · Acetylseco hemicholinium-3 · Acryloylcholine · AF64A · B115 · BETA · CM-54,903 · N,N-Dimethylaminoethylacrylate · N,N-Dimethylaminoethylchloroacetate · |
| **AChE** | **Inhibitors:** *Reversible:* Carbamates: Aldicarb · Bendiocarb · Bufencarb · Caffeine · Carbaryl · Carbendazim · Carbetamide · Carbofuran · Chlorbufam · Chloropropham · Ethienocarb · Ethiofencarb · Fenobucarb · Fenoxycarb · Formetanate · Furadan · Itopride · Ladostigil · Methiocarb · Methomyl · Miotine · Oxamyl · Phenmedipham · Pinmicarb · Pirimicarb · Propamocarb · Propham · Propoxur; Stigmines: Distigmine bromide · Eptastigmine · Ganstigmine · Neostigmine · Phenserine · Physostigmine · Pyridostigmine bromide · Quilostigmine · Rivastigmine · Terestigmine; Others: Acotiamide · Ambenonium · Donepezil · Caffeine · Edrophonium · Galantamine · Huperzine A · Ipidacrine · Minaprine · Tacrine · Zanapezil · *Irreversible:* Organophosphates: Acephate · Azinphos-methyl · Bensulide · Cadusafos · Chlorethoxyfos · Chlorfenvinphos · Chlorpyrifos · Chlorpyrifos-methyl · Coumaphos · Cyclosarin · Demeton · Demeton-S-methyl · Diazinon · Dichlorvos · Dicrotophos · Diisopropyl fluorophosphate · Diisopropylphosphate · Dimethoate · Dioxathion · Disulfoton · EA-3148 · Echothiophate · Ethion · Ethoprop · Fenamiphos · Fenitrothion · Fenthion · Fosthiazate · GV · Isofluorophate · Isoxathion · Malaoxon · Malathion · Methamidophos · Methidathion · Metrifonate · Mevinphos · Monocrotophos · Naled · Novichok agent · Omethoate · Oxydemeton-methyl · Paraoxon · Parathion · Parathion-methyl · Phorate · Phosalone · Phosmet · Phoxim · Pirimiphos-methyl · Sarin · Soman · Tabun · Tebupirimfos · Temefos · Terbufos · Tetrachlorvinphos · Tribufos · Trichlorfon · VE · VG · VM · VR · VX; Others: Demecarium · Fasciculins (green mamba toxins) (1, 2, 3, 4) · Onchidal (*Onchidella binneyi*) · **Reactivators:** Asoxime · Obidoxime · Pralidoxime · |
| **BChE** | **Inhibitors:** Cymserine · Many of the AChE inhibitors listed above · |
| **Release modulators** | |
| **Inhibitors** | **SNAP-25 inactivators:** Botulinum toxin (A, C, E) · **VAMP inactivators:** Botulinum toxin (B, D, F, G) · **Others:** Bungarotoxins (β-bungarotoxin, γ-bungarotoxin) · |
| **Enhancers** | **LPHN agonists:** α-Latrotoxin · **Others:** Atracotoxin (e.g., robustoxin, versutoxin) · Crotoxin · |
| **Others** | |
| **Precursors / prodrugs** | Adafenoxate · Choline (lecithin) · Citicoline · Cyprodenate · Dimethylethanolamine · Glycerophosphocholine · Meclofenoxate (centrophenoxine) · Phosphatidylcholine · Phosphatidylethanolamine · Phosphorylcholine · Pirisudanol · |
| **Cofactors** | Acetic acid · Acetylcarnitine · Acetyl-coA · Vitamin $B_5$ · |

Categories: Alcohols | Bronchodilators | Muscarinic antagonists | Propionates | Quaternary ammonium compounds | Tropanes | World Health Organization essential medicines


# Ketamine

From Wikipedia, the free encyclopedia

*For the functional group referred to as ketimine, see imine.*

**Ketamine**, sold under the brand name **Ketalar** among others, is a medication mainly used for starting and maintaining anesthesia.[4] It induces a trance-like state while providing pain relief, sedation, and memory loss.[5] Other uses include for chronic pain and for sedation in intensive care.[6][7] Heart function, breathing, and airway reflexes generally remain functional.[5] Effects typically begin within five minutes when given by injection with the main effects lasting up to 25 minutes.[3][4]

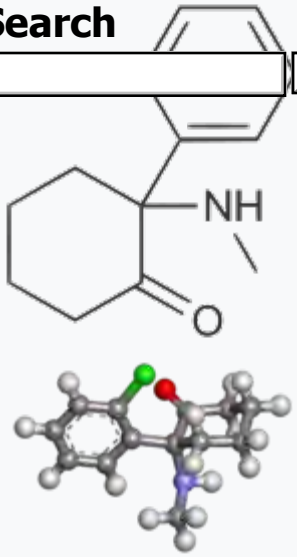
Common side effects include psychological reactions as the medication wears off.[8] These reactions may include agitation, confusion, or hallucinations.[4][8][9] Elevated blood pressure and muscle tremors are relatively common, while low blood pressure and a decrease in breathing are less so.[4][9] Spasms of the larynx may rarely occur.[4] Ketamine has been classified as an NMDA receptor antagonist; it also acts on opioid receptors and monoamine transporters among others.[10]

Ketamine was discovered in 1962.[3] It is on the World Health Organization's List of Essential Medicines, of the most important medications needed in a basic health system.[11] It is available as a generic medication.[4] The wholesale cost in the developing world is between 0.08 and 0.32 USD per dose.[12] Ketamine is also used as a recreational drug.[13]

Contents








| Clinical data | |
|---|---|
| **AHFS/Drugs.com** | Consumer Drug Information |
| **License data** | US FDA: Ketamine |
| **Pregnancy category** | AU: B3<br>US: C (Risk not ruled out) |
| **Addiction liability** | Low–moderate[1] |
| **Routes of administration** | IV, IM, insufflated, by mouth, intraossesous, intranasal, topical |
| **ATC code** | N01AX03 (WHO) |
| **Legal status** | |
| **Legal status** | AU: S8 (Controlled)<br>CA: Schedule I<br>UK: Class B<br>US: Schedule III<br>UN: Unscheduled |

## Uses [edit]

### Medical [edit]

#### Anesthesia [edit]

Uses as an anaesthetic:

- Anesthesia in children, as the sole anesthetic for minor procedures or as an induction agent followed by muscle relaxant and tracheal intubation
- Asthmatics or people with chronic obstructive airway disease
- As a sedative for physically painful procedures in emergency departments[5]
- Emergency surgery in field conditions in war zones
- To supplement spinal or epidural anesthesia/analgesia using low doses

Since it suppresses breathing much less than most other available anaesthetics,[14] ketamine is used in medicine as an anesthetic; however, due to the hallucinations it may cause, it is not typically used as a primary anesthetic, although it is the anaesthetic of choice when reliable ventilation equipment is not available.

Ketamine is frequently used in severely injured people and appears to be safe in this group.[15] A 2011 clinical practice guideline supports the use of ketamine as a dissociative sedative in emergency medicine.[5] It is the drug of choice for people in traumatic shock who are at risk of hypotension.[16] Low blood pressure is harmful in people with severe head injury[17] and ketamine is least likely to cause low blood pressure, often even able to prevent it.[18][19]

The effect of ketamine on the respiratory and circulatory systems is different from that of other anesthetics. When used at anesthetic doses, it will usually stimulate rather than depress the circulatory system.[20] It is sometimes possible to perform ketamine anesthesia without protective measures to the airways.[*citation needed*] Ketamine is considered relatively safe because protective airway reflexes are preserved.[21]

Ketamine is used as a bronchodilator in the treatment of severe [22] [22][23]

| Pharmacokinetic data | |
|---|---|
| **Metabolism** | Liver, primarily by CYP3A4[2] |
| **Onset of action** | < 5min (IM, IV), < 30min (by mouth)[3] |
| **Biological half-life** | 2.5–3 hours |
| **Duration of action** | less than one hour[3] |
| **Excretion** | Kidney (>90%) |

| Identifiers | |
|---|---|
| **IUPAC name** | (*RS*)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone |
| **CAS Number** | 6740-88-1 ✓ |
| **PubChem** (CID) | 3821 |
| **IUPHAR/BPS** | 4233 |
| **DrugBank** | DB01221 ✓ |
| **ChemSpider** | 3689 ✓ |
| **UNII** | 690G0D6V8H ✓ |
| **KEGG** | D08098 ✓ |
| **ChEBI** | CHEBI:6121 ✓ |
| **ChEMBL** | CHEMBL742 ✓ |
| **ECHA InfoCard** | 100.027.095 |

| Chemical and physical data | |
|---|---|
| **Formula** | $C_{13}H_{16}ClNO$ |
| **Molar mass** | 237.725 g/mol |
| **3D model (Jmol)** | Interactive image |
| **Chirality** | Racemic mixture |
| **Melting point** | 262 °C (504 °F) |

**SMILES**
CNC1(C2=CC=CC=C2Cl)CCCCC1=O

**InChI**
InChI=1S/C13H16ClNO/c1-15-13(9-5-4-8-12(13)16)10-6-2-3-7-11(10)14/h2-3,6-7,15H,4-5,8-9H2,1H3 ✓
Key:YQEZLKZALYSWHR-UHFFFAOYSA-N ✓

(verify)


1000mg/10ml vial of ketamine

asthma. However, evidence of clinical benefit is limited.

## Pain management [edit]

Ketamine may be used for postoperative pain management. Low doses of ketamine reduce morphine use and nausea and vomiting after surgery.[24] High quality evidence in acute pain is insufficient to determine if ketamine is useful in this situation.[25]

It may also be used as an intravenous analgesic with opiates to manage otherwise intractable pain, particularly if this pain is neuropathic. It has the added benefit of counteracting spinal sensitization or wind-up phenomena experienced with chronic pain. At these doses, the psychotropic side effects are less apparent and well managed with benzodiazepines.[26] Ketamine is an analgesic that is most effective when used alongside a low-dose opioid; because, while it does have analgesic effects by itself, the doses required for adequate pain relief when it is used as the sole analgesic agent are considerably higher and far more likely to produce disorienting side effects.[26] A review article in 2013 concluded, "despite limitations in the breadth and depth of data available, there is evidence that ketamine may be a viable option for treatment-refractory cancer pain".[27]

Low-dose ketamine is sometimes used in the treatment of complex regional pain syndrome (CRPS).[28] A 2013 systematic review found only low-quality evidence to support the use of ketamine for CRPS.[29]

## Depression [edit]

*See also: Rapid-acting antidepressant*

Ketamine has been tested in treatment-resistant bipolar disorder, major depressive disorder, and people in a suicidal crisis in emergency rooms.[30] Benefit is often of a short duration.[31] The quality of the evidence supporting benefit is generally low.[31]

The drug is given by a single intravenous infusion at doses less than those used in anesthesia, and preliminary data indicate it produces a rapid (within 2 hours) and relatively sustained (about 1–2 weeks long) reduction in symptoms in some people.[32] Initial studies have resulted in interest due to its rapid onset,[33] and because it appears to work by blocking NMDA receptors for glutamate, a different mechanism from most modern antidepressants that operate on other targets.[31][34]

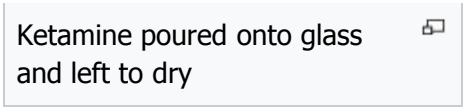
## Recreational [edit]

*Main article: Recreational use of ketamine*

Ketamine use as a recreational drug has been implicated in deaths globally, with more than 90 deaths in England and Wales in the years of 2005-2013.[35] They include accidental poisonings, drownings, traffic accidents, and suicides.[35] The majority of deaths were among young people.[36] This has led to increased regulation (e.g., upgrading ketamine from a Class C to a Class B banned substance in the U.K.).[37]

Unlike the other well-known dissociatives phencyclidine (PCP) and dextromethorphan (DXM), ketamine is very short-acting. It takes effect within about 10 minutes,[38] while its hallucinogenic effects last 60

minutes when insufflated or injected and up to two hours when ingested orally.[39]


Ketamine poured onto glass and left to dry

At anaesthetic doses, under-dosaged from a medical point of view, ketamine produces a dissociative state, characterised by a sense of detachment from one's physical body and the external world which is known as depersonalization and derealization.[40] At sufficiently high doses, users may experience what is called the "K-hole", a state of extreme dissociation with visual and auditory hallucinations.[41] John C. Lilly, Marcia Moore and D. M. Turner (amongst others) have written extensively about their own entheogenic use of, and psychonautic experiences with ketamine.[42] Both Moore and Turner died prematurely (due to hypothermia and drowning respectively) during presumed unsupervised ketamine use.[43]

## Side effects [edit]

Ketamine is generally safe for those critically ill, when administered by trained medical professionals.[44] Even in these cases, there are known side effects that include one or more of the following:[45]

- Cardiovascular: abnormal heart rhythms, slow heart rate or fast heart rate, high blood pressure or low blood pressure
- Central nervous system: Ketamine is traditionally avoided in people with or at risk of intracranial hypertension (ICP) due to concerns about ketamine causing increased intracranial pressure. It does not increase ICP more than opioids.[46]
- Dermatologic: Transient erythema, transient morbilliform rash
- Gastrointestinal: Anorexia, nausea, increased salivation, vomiting
- Local: Pain or exanthema of the injection site
- Neuromuscular and skeletal: Increased skeletal muscle tone (tonic-clonic movements)
- Ocular: Double vision, increased intraocular pressure, nystagmus, tunnel vision
- Respiratory: Airway obstruction, apnea, increased bronchial secretions, respiratory depression, laryngospasm
- Other: Anaphylaxis, dependence, emergence reaction

In 10-20% of patients at anesthetic doses experience adverse reactions that occur during emergence from anesthesia, reactions that can manifest as seriously as hallucinations and delirium.[8] These reactions may be less common in some patients subpopulations, and when administered intramuscularly, and can occur up to 24 hours postoperatively; the chance of this occurring can be reduced by minimizing stimulation to the patient during recovery and pretreating with a benzodiazepine, alongside a lower dose of ketamine.[8] Patients who experience severe reactions may require treatment with a small dose of a short- or ultrashort-acting barbiturate.[45]

Tonic-clonic movements are reported at higher anesthetic doses in greater than 10% of patients.[47]

### Neurological effects [edit]

In 1989, psychiatry professor John Olney reported ketamine caused irreversible changes in two small areas of the rat brain. However, the rat brain has significant differences in metabolism from the human brain, therefore such changes may not occur in humans.[48]

The first large-scale, longitudinal study of ketamine users found current frequent (averaging 20 days/month) ketamine users had increased depression and impaired memory by several measures, including verbal, short-term memory, and visual memory. Current infrequent (averaging 3.25 days/month) ketamine users and former ketamine users were not found to differ from controls in memory, attention, and psychological well-being tests. This suggests the infrequent use of ketamine does not cause cognitive deficits, and that any deficits that might occur may be reversible when ketamine use is discontinued. However, abstinent, frequent, and infrequent users all scored higher than controls on a test of delusional symptoms.[49]

Short-term exposure of cultures of GABAergic neurons to ketamine at high concentrations led to a significant loss of differentiated cells in one study, and noncell-death-inducing concentrations of ketamine (10 μg/ml) may still initiate long-term alterations of dendritic arbor in differentiated neurons. The same study also demonstrated chronic (>24 h) administration of ketamine at concentrations as low as 0.01 μg/ml can interfere with the maintenance of dendritic arbor architecture. These results raise the possibility that chronic exposure to low, subanesthetic concentrations of ketamine, while not affecting cell survival, could still impair neuronal maintenance and development.[50][51]

More recent studies of ketamine-induced neurotoxicity have focused on primates in an attempt to use a more accurate model than rodents. One such study administered daily ketamine doses consistent with typical recreational doses (1 mg/kg IV) to adolescent cynomolgus monkeys for varying periods of time.[52] Decreased locomotor activity and indicators of increased cell death in the prefrontal cortex were detected in monkeys given daily injections for six months, but not those given daily injections for one month.[52] A study conducted on rhesus monkeys found a 24-hour intravenous infusion of ketamine caused signs of brain damage in five-day-old but not 35-day-old animals.[53] Some neonatal experts do not recommend the use of ketamine as an anesthetic agent in human neonates because of the potential adverse effects it may have on the developing brain. These neurodegenerative changes in early development have been seen with other drugs that share the same mechanism of action of NMDA receptor antagonism as ketamine.[54]

The acute effects of ketamine cause cognitive impairment, including reductions in vigilance, verbal fluency, short-term memory, and executive function, as well as schizophrenia-like perceptual changes.[55]

## Urinary tract effects [edit]

A 2011 systematic review examined 110 reports of irritative urinary tract symptoms from ketamine recreational use.[56] Urinary tract symptoms have been collectively referred as "ketamine-induced ulcerative cystitis" or "ketamine-induced vesicopathy", and they include urge incontinence, decreased bladder compliance, decreased bladder volume, detrusor overactivity, and painful haematuria (blood in urine). Bilateral hydronephrosis and renal papillary necrosis have also been reported in some cases.[56][57] The pathogenesis of papillary necrosis has been investigated in mice, and mononuclear inflammatory infiltration in the renal papilla resulting from ketamine dependence has been suggested as a possible mechanism.[58]

The time of onset of lower urinary tract symptoms varies depending, in part, on the severity and chronicity of ketamine use; however, it is unclear whether the severity and chronicity of ketamine use corresponds linearly to the presentation of these symptoms. All reported cases where the user consumed greater than 5 g/day reported symptoms of the lower urinary tract.[56] Urinary tract symptoms appear to be most common in daily ketamine users who have used the drug recreationally for an extended period of time.[57] These symptoms have presented in only one case of medical use of ketamine. However, following dose reduction, the symptoms remitted.[57]

Management of these symptoms primarily involves ketamine cessation, for which compliance is low. Other treatments have been used, including antibiotics, NSAIDs, steroids, anticholinergics, and cystodistension.[56] Both hyaluronic acid instillation and combined pentosan polysulfate and ketamine cessation have been shown to provide relief in some patients, but in the latter case, it is unclear whether relief resulted from ketamine cessation, administration of pentosan polysulfate, or both. Further follow-up is required to fully assess the efficacy of these treatments.[56]

## Liver problems [edit]

In case reports of three patients treated with esketamine for relief of chronic pain, liver enzyme abnormalities occurred following repeat treatment with ketamine infusions, with the liver enzyme values returning below the upper reference limit of normal range on cessation of the drug. The result suggests liver enzymes must be monitored during such treatment.[59]

## Interactions [edit]

Other drugs which increase blood pressure may interact with ketamine in having an additive effect on blood pressure including: stimulants, SNRI antidepressants, and MAOIs. Increase blood pressure and heart rate, palpitations, and arrhythmias may be potential effects.

Ketamine may increase the effects of other sedatives in a dose dependent manner, including, but not limited to: alcohols,[60] benzodiazepines,[61] opioids,[62] quinazolinones, phenothiazines, anticholinergics and barbiturates.[63]

# Pharmacology [edit]

## Pharmacodynamics [edit]

Ketamine acts primarily as an antagonist of the NMDA receptor, and this action accounts for most of its effects.[10] However, the complete pharmacology of ketamine is more complex, and it is known to directly interact with a variety of other sites to varying degrees.[10]

A study conducted in mice found that ketamine's antidepressant activity is not caused by ketamine inhibiting NMDAR, but rather by sustained activation of a different glutamate receptor, the AMPA receptor, by a metabolite, (2R,6R)-hydroxynorketamine.[64][65]

Known actions of ketamine include:

- Non-competitive antagonist of the NMDA receptor (NMDAR)[10][66]
- Negative allosteric modulator of the nACh receptor[10]
- Weak agonist of the μ-opioid and κ-opioid receptors (10- and 20-fold less affinity relative to NMDAR, respectively),[10] and very weak agonist of the δ-opioid receptor[10]
- Agonist of the $D_2$ receptor[67]
- Weak mACh receptor antagonist (10- to 20-fold less affinity relative to NMDAR)[10]
- Inhibitor of the reuptake of serotonin, dopamine, and norepinephrine[10]
- Voltage-gated sodium channel and L-type calcium channel blocker,[10][68] and HCN1 cation channel blocker[69]
- Inhibitor of nitric oxide synthase[10][70]
- σ receptor 1 and 2 agonist (μM affinities).[10][70][71]
- Activation of AMPA receptors[72]

Ketamine appears to inhibit the NMDAR by binding both in the open channel and at an allosteric site.[73] The S(+) and R(-) stereoisomers bind with different affinities: $K_i$ = 3200 and 1100 nM, respectively.[74]

The significance of these additional mechanisms in the therapeutic effects of ketamine is poorly understood due to its relatively complex pharmacological profile.

## Effects in central nervous system [edit]

NMDAR antagonism is responsible for the anesthetic, amnesic, dissociative, and hallucinogenic effects of ketamine, although activation of κ-opioid receptors and possibly sigma and mACh receptors may also contribute to its hallucinogenic properties.[10] Dopamine reuptake inhibition is likely to underlie the euphoria the drug produces, although an additional involvement of μ-opioid receptor activation cannot be excluded.[10] The mechanisms of action for the possible antidepressant effects of ketamine at lower doses have yet to be elucidated.[75]

NMDAR antagonism results in analgesia by preventing central sensitization in dorsal horn neurons; in other words, ketamine's actions interfere with pain transmission in the spinal cord.[47] Inhibition of nitric oxide synthase lowers the production of nitric oxide – a neurotransmitter involved in pain perception, hence further contributing to analgesia.[76] The action of ketamine at sigma and μ-opioid receptors is relatively [10][77]

weak, and evidence is mixed as to whether the latter is of significance to its analgesic effects.

Ketamine also interacts with a host of other targets to cause analgesia. In particular, it blocks voltage-dependent calcium channels and sodium channels, attenuating hyperalgesia; it alters cholinergic neurotransmission, which is implicated in pain mechanisms; and it inhibits the reuptake of serotonin and norepinephrine, which are involved in descending antinociceptive pathways.[47][78]

### Effects in peripheral systems [edit]

Ketamine affects catecholaminergic transmission as noted above, producing measurable changes in peripheral organ systems, including the cardiovascular, gastrointestinal, and respiratory systems:[76]

- Cardiovascular: Ketamine inhibits the reuptake of catecholamines, stimulating the sympathetic nervous system, resulting in cardiovascular symptoms.
- Gastrointestinal: Serotonin reuptake inhibition is thought to underlie nausea and vomiting.[10]
- Respiratory: Catecholamine elevation and stimulation of $\beta_2$ adrenergic receptors probably causes bronchodilation, although other processes may also be involved. The exact mechanism is not fully understood.

### Pharmacokinetics [edit]

Ketamine is absorbable by intravenous, intramuscular, oral, and topical routes due to both its water and lipid solubilities.[76] When administered orally, it undergoes first-pass metabolism, where it is biotransformed in the liver by CYP3A4 (major), CYP2B6 (minor), and CYP2C9 (minor) isoenzymes into norketamine (through N-demethylation) and finally dehydronorketamine.[79] Intermediate in the biotransformation of norketamine into dehydronorketamine is the hydroxylation of norketamine into hydroxynorketamine by CYP2B6 and CYP2A6. Dehydronorketamine, followed by norketamine, is the most prevalent metabolite detected in urine.[80] As the major metabolite of ketamine, norketamine is one-third to one-fifth as potent anesthetically, and plasma levels of this metabolite are three times higher than ketamine following oral administration.[76][81] Bioavailability through the oral route reaches 17–20%; bioavailability through other routes are: 93% intramuscularly, 25–50% intranasally, 30% sublingually, and 30% rectally.[47][79] Peak plasma concentrations are reached within a minute intravenously, 5–15 min intramuscularly, and 30 min orally.[81] Ketamine's duration of action in a clinical setting is 30 min to 2 h intramuscularly and 4–6 h orally.[47]

Plasma concentrations of ketamine are increased by diazepam and other CYP3A4 inhibitors due to inhibition of conversion to norketamine.[47]

### Administration [edit]

In medical settings, ketamine is usually injected intravenously or intramuscularly.[82]

Ketamine can be started using the oral route, or people may be changed from a subcutaneous infusion once pain is controlled. Bioavailability of oral ketamine hydrochloride is around 20%

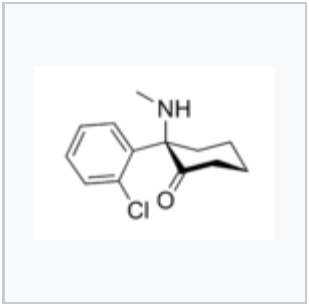
- Oral ketamine is easily broken down by bile acids, thus has a low bioavailability (about 20%). Often, lozenges or "gummies" for sublingual or buccal absorption prepared by a compounding pharmacy are used to combat this issue.
- Some specialists stop the subcutaneous infusion when the first dose of oral ketamine is given. Others gradually reduce the infusion dose as the oral dose is increased.[83]

## Chemistry [edit]

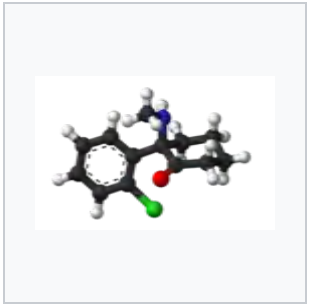
### Structure [edit]

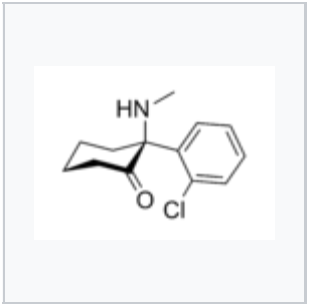
In chemical structure, ketamine is an arylcyclohexylamine derivative. Ketamine is a chiral compound. Most

pharmaceutical preparations of ketamine are racemic; however, some brands reportedly have (mostly undocumented) differences in their enantiomeric proportions. The more active enantiomer, esketamine (*S*-ketamine), is also available for medical use under the brand name Ketanest S,[84] while the less active enantiomer, arketamine (*R*-ketamine), has never been marketed as an enantiopure drug for clinical use.

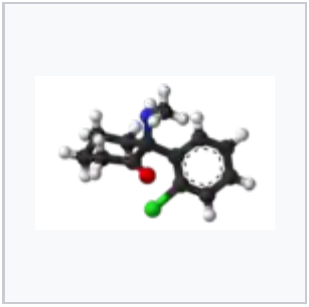


Skeletal formula of *(R)*-ketamine

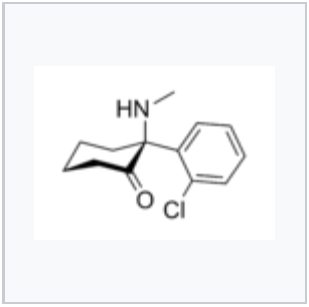

Ball-and-stick model of *(R)*-ketamine



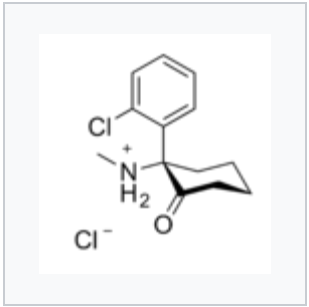
Skeletal formula of *(S)*-ketamine


Ball-and-stick model of *(S)*-ketamine

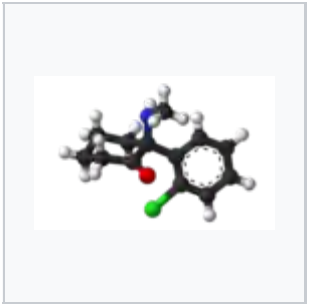
The optical rotation of a given enantiomer of ketamine can vary between its salts and free base form. The free base form of (*S*) ketamine exhibits dextrorotation and is therefore labelled (*S*) (+) ketamine. However, its hydrochloride salt shows levorotation and is thus labelled (*S*) (−) ketamine hydrochloride. The difference originates from the conformation of the cyclohexanone ring. In both the free base and the hydrochloride, the cyclohexanone ring adopts a chair conformation, but the orientation of the substituents varies. In the free base, the *o*-chlorophenyl group adopts an equatorial position and the methylamino group adopts an axial position.[85] In the hydrochloride salt, the positions are reversed, with the *o*-chlorophenyl group axial and the methylamino group equatorial.[86] Not all salts of ketamine show different optical rotation to the free base: (*S*)-ketamine (*R*,*R*)-tartrate is levorotatory, like (*S*) ketamine.[87]

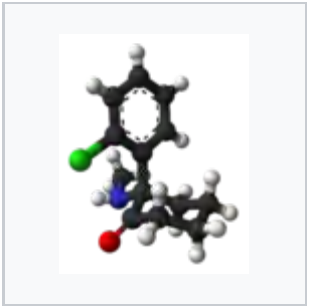


*(S)*-(−)-ketamine



*(S)*-(+)-ketamine hydrochloride


*(S)*-(−)-ketamine in the crystal structure of the free base


*(S)*-(+)-ketamine in the crystal structure of the hydrochloride

## History [edit]

### Medical use [edit]

Ketamine was first synthesized in 1962 by Calvin L. Stevens, a professor of Chemistry in Wayne State University and a Parke Davis consultant conducting research on alpha-hydroxyimine rearrangements.[88] After promising preclinical research in animals, ketamine was introduced to testing in human prisoners in 1964.[89][90] These investigations demonstrated ketamine's short duration of action and reduced behavioral toxicity made it a favorable choice over phencyclidine (PCP) as a dissociative anesthetic.[91] Following FDA approval in 1970, ketamine anesthesia was first given to American soldiers during the Vietnam War.[92]


Ketamine vials

## Nonmedical use [edit]

*Main article: Recreational use of ketamine*

See the foregoing discussion and citations regarding the increasing stringency of governmental regulation that has resulted from a number of deaths of youth and young adults by overdose, accident, and suicide in which nonmedical/recreational ketamine use is implicated (in the Recreational use section, above).

Nonmedical use of ketamine began on the West Coast of the United States in the early 1970s.[92] Early use was documented in underground literature such as *The Fabulous Furry Freak Brothers*. It was used in psychiatric and other academic research through the 1970s, culminating in 1978 with the publishing of psychonaut John Lilly's *The Scientist*, and Marcia Moore and Howard Alltounian's *Journeys into the Bright World*, which documented the unusual phenomenology of ketamine intoxication.[93] The incidence of nonmedical ketamine use increased through the end of the century, especially in the context of raves and other parties.[94] However, its emergence as a club drug differs from other club drugs (e.g. MDMA) due to its anesthetic properties (*e.g.*, slurred speech, immobilization) at higher doses;[95] in addition, there are reports of ketamine being sold as "ecstasy".[96] The use of ketamine as part of a "postclubbing experience" has also been documented.[97] Ketamine's rise in the dance culture was rapid in Hong Kong by the end of the 1990s.[95] Before becoming a federally controlled substance in the United States in 1999, ketamine was available as diverted pharmaceutical preparations and as a pure powder sold in bulk quantities from domestic chemical supply companies.[89] Much of the current ketamine diverted for nonmedical use originates in China and India.[89]

In addition to its ability to cause confusion and amnesia, ketamine can leave users vulnerable to date rape (i.e., because of the associated confusion and amnesia).[38][92]

# Society and culture [edit]

## Legal status [edit]

Ketamine is a "core" medicine in the World Health Organization's Essential Drugs List, a list of minimum medical needs for a basic healthcare system.[98]

The increase in illicit use prompted ketamine's placement in Schedule III of the United States Controlled Substance Act in August 1999.[99]

In the United Kingdom, it became labeled a Class C drug on 1 January 2006.[80][100] On 10 December 2013 the UK Advisory Council on the Misuse of Drugs (ACMD) recommended that the government reclassify ketamine to become a Class B drug,[101] and on 12 February 2014 the Home Office announced they would follow this advice "in light of the evidence of chronic harms associated with ketamine use, including chronic bladder and other urinary tract damage".[102][103]

The UK Minister of State for Crime Prevention, Norman Baker, responding to the ACMD's advice, said the issue of its rescheduling for medical and veterinary use would be addressed "separately to allow for a period of consultation."[102]

In Australia Ketamine is listed as a schedule 8 controlled drug under the Poisons Standard (October 2015).[104] A schedule 8 drug is outlined in the Poisons Act 1964 as "Substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence." [105]

In Canada, ketamine is classified as a Schedule I narcotic, since 2005.[106]

In Hong Kong, as of 2000, ketamine is regulated under Schedule 1 of Hong Kong Chapter 134 *Dangerous Drugs Ordinance*. It can only be used legally by health professionals, for university research purposes, or with a physician's prescription.[107][108] By 2002, ketamine was classified as class III in Taiwan; given the recent rise in prevalence in East Asia, however, rescheduling into class I or II is being considered.[80][109]

In December 2013, the government of India, in response to rising recreational use and the use of ketamine as a date rape drug, has added it to Schedule X of the Drug and Cosmetics Act requiring a special license for sale and maintenance of records of all sales for two years.[110][111]

Ketamine is legally marketed in many countries worldwide, under many brand names.[112]

## Research [edit]

### Treatment of addiction [edit]

Russian doctor Evgeny Krupitsky has claimed to have encouraging results by using ketamine as part of a treatment for alcohol addiction which combines psychedelic and aversive techniques.[113][114] Krupitsky and Kolp summarized their work to date in 2007.[115]

## Veterinary medicine [edit]

In veterinary anesthesia, ketamine is often used for its anesthetic and analgesic effects on cats, dogs, rabbits, rats, and other small animals. It is an important part of the "rodent cocktail", a mixture of drugs used for anesthetizing rodents.[116] Veterinarians often use ketamine with sedative drugs to produce balanced anesthesia and analgesia, and as a constant-rate infusion to help prevent pain wind-up. Ketamine is used to manage pain among large animals, though it has less effect on bovines.[*citation needed*] It is the primary intravenous anesthetic agent used in equine surgery, often in conjunction with detomidine and thiopental, or sometimes guaifenesin.

## See also [edit]

*Pharmacy and Pharmacology portal*

- 3-HO-PCP
- 3-MeO-PCE
- 3-MeO-PCP
- 4-MeO-PCP
- 4-Chlorokynurenine
- Apimostinel (NRX-1074)
- Dextromethorphan
- Dizocilpine (MK-801)
- Lanicemine
- Memantine
- Methoxetamine
- Nitrous oxide
- Rapastinel (GLYX-13)
- Tiletamine

## References [edit]


1. ^ Malenka RC, Nestler EJ, Hyman SE (2009). "Chapter 15: Reinforcement and Addictive Disorders". In Sydor A, Brown RY. *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience* (2nd ed.). New York: McGraw-Hill Medical. pp. 374–375. ISBN 9780071481274. "Phencyclidine (PCP or angel dust) and ketamine (also known as special K) are structurally related drugs... their reinforcing properties and risks related to compulsive abuse"
2. ^ Hijazi, Y; Boulieu, R (July 2002). "Contribution of CYP3A4, CYP2B6, and CYP2C9 isoforms to N-demethylation of ketamine in human liver microsomes". *Drug Metabolism and Disposition*. **30** (7): 853–8. doi:10.1124/dmd.30.7.853. PMID 12065445.
3. ^ *a b c d* "Ketamine - CESAR". *Center for substance abuse research*. University of Maryland. Retrieved 26 September 2014.

4. ^ a b c d e f "Ketamine Injection". *drugs.com*. Retrieved 1 December 2014.
5. ^ a b c d Green, SM; Roback, MG; Kennedy, RM; Krauss, B (2011). "Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation: 2011 Update". *Annals of Emergency Medicine*. **57** (5): 449–61. doi:10.1016/j.annemergmed.2010.11.030. PMID 21256625.
6. ^ Zgaia, AO; Irimie, A; Sandesc, D; Vlad, C; Lisencu, C; Rogobete, A; Achimas-Cadariu, P (2015). "The role of ketamine in the treatment of chronic cancer pain.". *Clujul medical (1957)*. **88** (4): 457–61. doi:10.15386/cjmed-500. PMC 4689236. PMID 26733743.
7. ^ Zapantis, A; Leung, S (September 2005). "Tolerance and withdrawal issues with sedation.". *Critical care nursing clinics of North America*. **17** (3): 211–23. doi:10.1016/j.ccell.2005.04.011. PMID 16115529.
8. ^ a b c d Strayer, RJ; Nelson, LS (2008). "Adverse events associated with ketamine for procedural sedation in adults". *American Journal of Emergency Medicine*. **26** (9): 985–1028. doi:10.1016/j.ajem.2007.12.005. PMID 19091264.
9. ^ a b "Ketamine Side Effects". *drugs.com*. Retrieved 1 December 2014.
10. ^ a b c d e f g h i j k l m n o p Kohrs, R; Durieux, ME (November 1998). "Ketamine: Teaching an old drug new tricks". *Anesthesia & Analgesia*. **87** (5): 1186–93. doi:10.1213/00000539-199811000-00039. PMID 9806706.
11. ^ "WHO Model List of EssentialMedicines" (PDF). *World Health Organization*. October 2013. Retrieved 22 April 2014.
12. ^ "Ketamine". Retrieved 12 January 2016.
13. ^ Morgan, Celia J. A.; Curran, H. Valerie (January 2012). "Ketamine use: a review". *Addiction*. **107** (1): 27–38. doi:10.1111/j.1360-0443.2011.03576.x. PMID 21777321. Retrieved 25 March 2016.
14. ^ Heshmati, F; Zeinali, MB; Noroozinia, H; Abbacivash, R; et al. (December 2003). "Use of ketamine in severe status asthmaticus in intensive care unit". *Iranian Journal of Allergy, Asthma, and Immunology*. **2** (4): 175–80. PMID 17301376.
15. ^ Cohen, L; Athaide, V; Wickham, ME; Doyle-Waters, MM; Rose, NG; Hohl, CM (Jul 16, 2014). "The Effect of Ketamine on Intracranial and Cerebral Perfusion Pressure and Health Outcomes: A Systematic Review.". *Annals of Emergency Medicine*. **65**: 43–51.e2. doi:10.1016/j.annemergmed.2014.06.018. PMID 25064742.
16. ^ Nickson, Chris (7 August 2013). "Intubation, Hypotension and Shock". *Life in the Fastlane* (blog). Critical Care Compendium. Retrieved 10 April 2014. [*unreliable medical source?*]
17. ^ Manley, G; Knudson, MM; Morabito, D; Damron, S; et al. (2001). "Hypotension, hypoxia, and head injury: Frequency, duration, and consequences". *Archives of Surgery*. **136** (10): 1118–23. doi:10.1001/archsurg.136.10.1118. PMID 11585502.
18. ^ Hemmingsen, C; Nielsen, JE (1991). "Intravenous ketamine for prevention of severe hypotension during spinal anaesthesia". *Acta Anaesthesiologica Scandinavica*. **35** (8): 755–7. doi:10.1111/j.1399-6576.1991.tb03385.x. PMID 1763596.
19. ^ Wong, DHW; Jenkins, LC (1975). "The cardiovascular effects of ketamine in hypotensive states" (PDF). *Canadian Anaesthetists' Society Journal*. **22** (3): 339–48. doi:10.1007/BF03004843. PMID 1139377.
20. ^ Adams, HA (December 1997). "S-(+)-ketamin kreislaufinteraktionen bei totaler intravenöser anästhesie und analgosedierung" [S-(+)-ketamine. Circulatory interactions during total intravenous anesthesia and analgesia-sedation]. *Der Anaesthesist* (in German). **46** (12): 1081–7. doi:10.1007/s001010050510. PMID 9451493.
21. ^ Wong, JJM; Lee, JH; Turner, DA; Rehder, KJ (2014). "A review of the use of adjunctive therapies in severe acute asthma exacerbation in critically ill children". *Expert Review of Respiratory Medicine*. **8** (4): 423–41. doi:10.1586/17476348.2014.915752. PMID 24993063.
22. ^ a b Goyal, S; Agrawal, A (May 2013). "Ketamine in status asthmaticus: A review". *Indian Journal of Critical Care Medicine*. **17** (3): 154–61. doi:10.4103/0972-5229.117048. PMC 3777369. PMID 24082612.
23. ^ Jat, KR; Chawla, D (November 2012). "Ketamine for management of acute exacerbations of asthma in children". Airways Group. *Cochrane Database of Systematic Reviews*. **11** (11): Art. No. CD009293. doi:10.1002/14651858.CD009293.pub2. PMID 23152273.
24. ^ Bell, RF; Dahl, JB; Moore, RA; Kalso, EA (25 January 2006). "Perioperative ketamine for acute postoperative pain". Pain, Palliative and Supportive Care Group. *Cochrane Database of Systematic Reviews* (1): CD004603. doi:10.1002/14651858.CD004603.pub2. PMID 16437490.
25. ^ Sin, B; Ternas, T; Motov, SM (March 2015). "The Use of Subdissociative-dose Ketamine for Acute Pain in the Emergency Department.". *Academic Emergency Medicine*. **22** (3): 251–7. doi:10.1111/acem.12604. PMID 25716117.
26. ^ a b Elia, N; Tramèr, MR (January 2005). "Ketamine and postoperative pain: A quantitative systematic review of randomised trials". *Pain*. **113** (1): 61–70. doi:10.1016/j.pain.2004.09.036. PMID 15621365.
27. ^ Bredlau, AL; Thakur, R; Korones, DN; Dworkin, RH (October 2013). "Ketamine for pain in adults and children with cancer: A systematic review and synthesis of the literature". *Pain Medicine*. **14** (10): 1505–17.

doi:10.1111/pme.12182. PMID 23915253.
28. ^ Correll, GE; Maleki, J; Gracely, EJ; Muir, JJ; Harbut, RE (September 2004). "Subanesthetic ketamine infusion therapy: A retrospective analysis of a novel therapeutic approach to complex regional pain syndrome". *Pain Medicine*. **5** (3): 263–75. doi:10.1111/j.1526-4637.2004.04043.x. PMID 15367304.
29. ^ O'Connell, NE; Wand, BM; McAuley, J; Marston, L; et al. (2013). "Interventions for treating pain and disability in adults with complex regional pain syndrome". Pain, Palliative and Supportive Care Group. *Cochrane Database of Systematic Reviews*. **4** (4): Art. No. CD009416. doi:10.1002/14651858.CD009416.pub2. PMID 23633371.
30. ^ Tondo, L; Vázquez, GH; Baldessarini, RJ (February 2014). "Options for pharmacological treatment of refractory bipolar depression.". *Current psychiatry reports*. **16** (2): 431. doi:10.1007/s11920-013-0431-y. PMID 24425269.
31. ^ *a b c* Caddy, C; Giaroli, G; White, TP; Shergill, SS; Tracy, DK (April 2014). "Ketamine as the prototype glutamatergic antidepressant: pharmacodynamic actions, and a systematic review and meta-analysis of efficacy.". *Therapeutic advances in psychopharmacology*. **4** (2): 75–99. doi:10.1177/2045125313507739. PMID 24688759.
32. ^ ECRI Institute, under contract to AHRQ. December 2013 AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report. Priority Area 05: Depression and Other Mental Health Disorders
33. ^ National Institute of Mental Health (7 August 2006). "Experimental Medication Kicks Depression in Hours Instead of Weeks". *NIH News* (Press release). National Institutes of Health; Dept. of Health and Human Services; United States. "National Institute of Mental Health director Thomas Insel said, "To my knowledge, this is the first report of any medication or other treatment that results in such a pronounced, rapid, prolonged response with a single dose. These were very treatment-resistant patients.""
34. ^ Naughton, M; Clarke, G; O'Leary, OF; Cryan, JF; Dinan, TG (Mar 2014). "A review of ketamine in affective disorders: current evidence of clinical efficacy, limitations of use and pre-clinical evidence on proposed mechanisms of action.". *Journal of Affective Disorders*. **156**: 24–35. doi:10.1016/j.jad.2013.11.014. PMID 24388038.
35. ^ *a b* See Max Daly, 2014, "The Sad Demise of Nancy Lee, One of Britain's Ketamine Casualties," at *Vice* (online), July 23, 2014, see [1], accessed 7 June 2015.
36. ^ The Crown, 2013, "Drug related deaths involving ketamine in England and Wales," a report of the Mortality team, Life Events and Population Sources Division, Office for National Statistics, the Crown (U.K.), see [2] and [3], accessed 7 June 2015.
37. ^ Hayley Dixon, 2014, "Ketamine death of public schoolgirl an 'act of stupidity which destroyed family'," at *The Telegraph* (online), February 12, 2014, see [4], accessed 7 June 2015.
38. ^ *a b* "Do you know... Ketamine". *Knowledge Exchange*. Toronto: Centre for Addiction and Mental Health. 2003. Archived from the original on 2014-04-07. Retrieved 27 July 2014.
39. ^ Giannini, AJ; Loiselle, RH; Giannini, MC; Price, WA (1985). "Phencyclidine and the dissociative". *Psychiatric Medicine*. **3** (3): 197–217. PMID 2893430.
40. ^ Giannini, AJ; Underwood, NA; Condon, M (November 2000). "Acute ketamine intoxication treated by haloperidol: A preliminary study". *American Journal of Therapeutics*. **7** (6): 389–91. doi:10.1097/00045391-200007060-00008. PMID 11304647.
41. ^ Giannini, AJ (1999). *Drug Abuse*. Los Angeles: Health Information Press. p. 104. ISBN 1885987110.
42. ^ References for recreational use in literature:
    - Lilly, John Cunningham (1997). *The Scientist: A Metaphysical Autobiography*. Berkeley, CA: Ronin. pp. 144–. ISBN 0914171720.
    - Kelly, Kit (2001). *The Little Book of Ketamine*. Ronin. pp. 23, 40–45, 46–51, ibid. ISBN 9781579511210.
    - Alltounian, Howard Sunny; Moore, Marcia (1978). *Journeys Into the Bright World*. Rockport, MA: Para Research. ISBN 9780914918127.
    - Palmer, Cynthia; Horowitz, Michael (2000). *Sisters of the Extreme: Women Writing on the Drug Experience*. Inner Traditions. pp. 254–8, ibid. ISBN 9780892817573.
    - Turner, D.M. (1994). *The Essential Psychedelic Guide*. San Francisco: Panther Press. ISBN 0964263610.
43. ^ Jansen, Karl (2001). *Ketamine: Dreams and Realities*. Multidisciplinary Association for Psychedelic Studies. pp. 50, 89. ISBN 0966001931.
44. ^ Cohen, L; Athaide, V; Wickham, ME; Doyle-Waters, MM; Rose, NG; Hohl, CM (January 2015). "The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review.". *Annals of Emergency Medicine*. **65** (1): 43–51.e2. doi:10.1016/j.annemergmed.2014.06.018. PMID 25064742.
45. ^ *a b* Merck Manual; Drug Information Provided by Lexi-Comp. Last full review/revision May 2014 Ketamine
46. ^ Wang, Xin; Ding, Xibing; Tong, Yao; Zong, Jiaying; Zhao, Xiang; Ren, Hao; Li, Quan (24 May 2014). "Ketamine does not increase intracranial pressure compared with opioids: meta-analysis of randomized controlled trials". *Journal of Anesthesia*. **28**: 7. doi:10.1007/s00540-014-1845-3.
47. ^ *a b c d e f* Quibell, R; Prommer, EE; Mihalyo, M; Twycross, R; et al. (March 2011). "Ketamine*". *Journal of Pain and Symptom Management* (Therapeutic Review). **41** (3): 640–9. doi:10.1016/j.jpainsymman.2011.01.001. PMID 21419322.

48. ^ Neurological effects of ketamine introduction references:
    - Olney, JW; Labruyere, J; Price, MT (June 1989). "Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs". *Science*. **244** (4910): 1360–2. doi:10.1126/science.2660263. PMID 2660263.
    - Anderson, Cliff (June 2003). "The Bad News Isn't In: A Look at Evidence for Specific Mechanisms of Dissociative-Induced Brain Damage and Cognitive Impairment". Erowid.[*unreliable medical source?*]
    - Tryba, M; Gehling, M (October 2002). "Clonidine - A potent analgesic adjuvant". *Current Opinion in Anaesthesiology*. **15** (5): 511–7. doi:10.1097/00001503-200210000-00007. PMID 17019247.
    - Dong, C; Anand, KJS (June 2013). "Developmental neurotoxicity of ketamine in pediatric clinical use". *Toxicology Letters*. **220** (1): 53–60. doi:10.1016/j.toxlet.2013.03.030. PMID 23566897.
49. ^ Morgan, CJA; Muetzelfeldt, L; Curran, HV (2009). "Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: A 1-year longitudinal study". *Addiction*. **105** (1): 121–33. doi:10.1111/j.1360-0443.2009.02761.x. PMID 19919593.
50. ^ Vutskits, L; Gascon, E; Potter, G; Tassonyi, E; et al. (May 2007). "Low concentrations of ketamine initiate dendritic atrophy of differentiated GABAergic neurons in culture". *Toxicology*. **234** (3): 216–26. doi:10.1016/j.tox.2007.03.004. PMID 17418473.
51. ^ Hargreaves, RJ; Hill, RG; Iversen, LL (1994). "Neuroprotective NMDA antagonists: the controversy over their potential for adverse effects on cortical neuronal morphology.". *Acta neurochirurgica. Supplementum*. **60**: 15–9. doi:10.1007/978-3-7091-9334-1_4. PMID 7976530.
52. ^ *a b* Sun, L; LI, Q; Li, Q; Zhang, Y; et al. (November 2012). "Chronic ketamine exposure induces permanent impairment of brain functions in adolescent cynomolgus monkeys". *Addiction Biology*. **19**: 185–94. doi:10.1111/adb.12004. PMID 23145560.
53. ^ Slikker, W; Zou, X; Hotchkiss, CE; Divine, RL; et al. (2007). "Ketamine-induced neuronal cell death in the perinatal rhesus monkey". *Toxicological Sciences*. **98** (1): 145–58. doi:10.1093/toxsci/kfm084. PMID 17426105.
54. ^ Patel, P; Sun, L (April 2009). "Update on neonatal anesthetic neurotoxicity: Insight into molecular mechanisms and relevance to humans". *Anesthesiology* (commentary). **110** (4): 703–8. doi:10.1097/ALN.0b013e31819c42a4. PMC 2737718. PMID 19276968.
55. ^ Krystal, JH; Karper, LP; Seibyl, JP; Freeman, GK; et al. (March 1994). "Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses". *Archives of General Psychiatry*. **51** (3): 199–214. doi:10.1001/archpsyc.1994.03950030035004. PMID 8122957.
56. ^ *a b c d e* Middela, S; Pearce, I (January 2011). "Ketamine-induced vesicopathy: A literature review". *International Journal of Clinical Practice*. **65** (1): 27–30. doi:10.1111/j.1742-1241.2010.02502.x. PMID 21155941.
57. ^ *a b c* Morgan, CJA; Curran, HV; Independent Scientific Committee on Drugs (ISCD) (January 2012). "Ketamine use: A review". *Addiction*. **107** (1): 27–38. doi:10.1111/j.1360-0443.2011.03576.x. PMID 21777321.
58. ^ Yeung, LY; Rudd, JA; Lam, WP; Mak, YT; et al. (December 2009). "Mice are prone to kidney pathology after prolonged ketamine addiction". *Toxicology Letters*. **191** (2–3): 275–8. doi:10.1016/j.toxlet.2009.09.006. PMID 19766175.
59. ^ Bell, RF (June 2012). "Ketamine for chronic noncancer pain: concerns regarding toxicity.". *Current opinion in supportive and palliative care*. **6** (2): 183–7. doi:10.1097/SPC.0b013e328352812c. PMID 22436323.
60. ^ Hui, TW; Short, TG; Hong, W; Suen, T; et al. (March 1995). "Additive interactions between propofol and ketamine when used for anesthesia induction in female patients". *Anesthesiology*. **82** (3): 641–8. doi:10.1097/00000542-199503000-00005. PMID 7879932.
61. ^ Hong, W; Short, TG; Hui, TW (December 1993). "Hypnotic and anesthetic interactions between ketamine and midazolam in female patients". *Anesthesiology*. **79** (6): 1227–32. doi:10.1097/00000542-199312000-00013. PMID 8267198.
62. ^ Akhavanakbari, G; Mohamadian, A; Entezariasl, M (April 2014). "Evaluation the effects of adding ketamine to morphine in intravenous patient-controlled analgesia after orthopedic surgery". *Perspectives in Clinical Research*. **5** (2): 85–7. doi:10.4103/2229-3485.128028. PMC 3980550. PMID 24741486.
63. ^ Eker, HE; Yalcin Cok, O; Aribogan, A; Arslan, G (October 2011). "Children on phenobarbital monotherapy requires more sedatives during MRI". *Pediatric Anesthesia*. **21** (10): 998–1002. doi:10.1111/j.1460-9592.2011.03606.x. PMID 21564387.
64. ^ Zanos, Panos; Moaddel, Ruin; Morris, Patrick J.; Georgiou, Polymnia; Fischell, Jonathan; Elmer, Greg I.; Alkondon, Manickavasagom; Yuan, Peixiong; Pribut, Heather J.; Singh, Nagendra S.; Dossou, Katina S. S.; Fang, Yuhong; Huang, Xi-Ping; Mayo, Cheryl L.; Wainer, Irving W.; Albuquerque, Edson X.; Thompson, Scott M.; Thomas, Craig J.; Zarate Jr, Carlos A.; Gould, Todd D. (2016). "NMDAR inhibition-independent antidepressant actions of ketamine metabolites". *Nature*. **533**: 481–486. doi:10.1038/nature17998. ISSN 0028-0836.
65. ^ Collins, Francis (2016-05-10). "Fighting Depression: Ketamine Metabolite May Offer Benefits Without the Risks".

*Director's Blog*. National Institutes of Health. Retrieved 2016-05-14.

66. ^ Harrison, NL; Simmonds, MA (February 1985). "Quantitative studies on some antagonists of N-methyl D-aspartate in slices of rat cerebral cortex". *British Journal of Pharmacology*. **84** (2): 381–91. doi:10.1111/j.1476-5381.1985.tb12922.x. PMC 1987274. PMID 2858237.
67. ^ Seeman, P; Guan, HC; Hirbec, H (August 2009). "Dopamine D2High receptors stimulated by phencyclidines, lysergic acid diethylamide, salvinorin A, and modafinil". *Synapse*. **63** (8): 698–704. doi:10.1002/syn.20647. PMID 19391150.
68. ^ Pharmaceutical Society of Australia; The Royal Australian College of General Practitioners; Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (2011). "2.1.1 IV General Anaesthetics". *Australian Medicines Handbook 2011* (12th ed.). Adelaide: Australian Medicines Handbook Pty Ltd. p. 13. ISBN 9780980579048.
69. ^ Chen, X; Shu, S; Bayliss, DA (2009). "HCN1 channel subunits are a molecular substrate for hypnotic actions of ketamine". *Journal of Neuroscience*. **29** (3): 600–9. doi:10.1523/JNEUROSCI.3481-08.2009. PMC 2744993. PMID 19158287.
70. ^ [a] [b] Narita, M; Yoshizawa, K; Aoki, K; Takagi, M; et al. (September 2001). "A putative sigma1 receptor antagonist NE-100 attenuates the discriminative stimulus effects of ketamine in rats". *Addiction Biology*. **6** (4): 373–6. doi:10.1080/13556210020077091. PMID 11900615.
71. ^ Robson MJ, Elliott M, Seminerio MJ, Matsumoto RR (22 April 2012). "Evaluation of sigma (σ) receptors in the antidepressant-like effects of ketamine in vitro and in vivo". *Journal of the European College of Neuropsychopharmacology*. **22**: 308–17. doi:10.1016/j.euroneuro.2011.08.002. PMID 21911285.
72. ^ "Ketamine Lifts Depression via a Byproduct of its Metabolism: NIH-funded team finds rapid-acting, non-addicting agent in mouse study".
73. ^ Orser, BA; Pennefather, PS; MacDonald, JF (1997). "Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors". *Anesthesiology*. **86** (4): 903–17. doi:10.1097/00000542-199704000-00021. PMID 9105235.
74. ^ Hirota, K; Lambert, DG (October 1996). "Ketamine: Its mechanism(s) of action and unusual clinical uses". *British Journal of Anaesthesia*. **77** (4): 441–4. doi:10.1093/bja/77.4.441. PMID 8942324.
75. ^ Browne, CA; Lucki, I (2013). "Antidepressant effects of ketamine: mechanisms underlying fast-acting novel antidepressants". *Frontiers in Pharmacology*. **4**: 161. doi:10.3389/fphar.2013.00161. PMC 3873522. PMID 24409146.
76. ^ [a] [b] [c] [d] Aroni, F; Iacovidou, N; Dontas, I; Pourzitaki, C; et al. (August 2009). "Pharmacological aspects and potential new clinical applications of ketamine: Reevaluation of an old drug". *Journal of Clinical Pharmacology*. **49** (8): 957–64. doi:10.1177/0091270009337941. PMID 19546251.
77. ^ Rowland, LM (July 2005). "Subanesthetic ketamine: How it alters physiology and behavior in humans". *Aviation, Space, and Environmental Medicine*. **76** (Suppl 7): C52–8. PMID 16018330.
78. ^ Meller, ST (December 1996). "Ketamine: Relief from chronic pain through actions at the NMDA receptor?". *Pain* (correspondence). **68** (2–3): 435–6. doi:10.1016/S0304-3959(96)03167-3. PMID 9121834.
79. ^ [a] [b] Sinner, B; Graf, BM (2008). "Ketamine". In Schüttler, J; Schwilden, H. *Modern Anesthetics*. Handbook of Experimental Pharmacology. **182**. pp. 313–33. ISBN 9783540728139. doi:10.1007/978-3-540-74806-9_15. PMID 18175098.
80. ^ [a] [b] [c] Li, JH; Vicknasingam, B; Cheung, YW; Zhou, W; et al. (2011). "To use or not to use: An update on licit and illicit ketamine use". *Substance Abuse and Rehabilitation*. **2** (1): 11–20. doi:10.2147/SAR.S15458. PMC 3846302. PMID 24474851.
81. ^ [a] [b] Haas, DA; Harper, DG (1992). "Ketamine: A review of its pharmacologic properties and use in ambulatory anesthesia". *Anesthesia Progress*. **39** (3): 61–8. PMC 2148758. PMID 1308374.
82. ^ Lankenau, SE; Sanders, B; Bloom, JJ; Hathazi, D; et al. (March 2007). "First injection of ketamine among young injection drug users (IDUs) in three U.S. cities". *Drug and Alcohol Dependence*. **87** (2–3): 183–93. doi:10.1016/j.drugalcdep.2006.08.015. PMC 1852477. PMID 16979848.
83. ^ "Ketamine in Palliative Care" (PDF). *Palliative Care Guidelines*. Edinburgh: NHS Lothian, NHS Scotland, Health and Social Care Directorates, Scotland. August 2013 [August 2010]. Archived (PDF) from the original on 2013-10-29.
84. ^ Krüger, AD (1998). "Current aspects of using ketamine in childhood". *Anaesthesiologie und Reanimation* (in German). **23** (3): 64–71. PMID 9707751.
85. ^ Chankvetadze, Bezhan; Burjanadze, Naira; Breitkreutz, Jörg; Bergander, Klaus; Bergenthal, Dieter; Kataeva, Olga; Fröhlich, Roland; Luftmann, Heinrich; Blaschke, Gottfried (2002). "Mechanistic study on the opposite migration order of the enantiomers of ketamine with α- and β-cyclodextrin in capillary electrophoresis". *J. Sep. Sci.* **25**: 1155–1166. doi:10.1002/1615-9314(20021101)25:15/17<1155::AID-JSSC1155>3.0.CO;2-M.
86. ^ Hakey, P.; Ouellette, W.; Zubieta, J.; Korter, T. (2008). "(*S*)-(+)-Ketamine hydrochloride". *Acta Crystallogr. E*. **64**:

o1487. doi:10.1107/S1600536808021053.
87. ^ Ratti-Mobery, Enrica; Groth, Per; Aasen, Arne Jørgen (1991). "The Absolute Configuration of Ketamine – A General Anaesthetic. The Crystal Structure of the (*R*,*R*)-Tartrate Salt of (−)-(*S*)-Ketamine". *Acta Chem. Scand.* **45**: 108–110. doi:10.3891/acta.chem.scand.45-0108.
88. ^ Clark, Michael R. (2011). *Chronic Pain and Addiction*. Basel, Zwitzerland: Karger AG. pp. 166–. ISBN 3805597258.
89. ^ *a b c* Morris, H; Wallach, J (July 2014). "From PCP to MXE: A comprehensive review of the non-medical use of dissociative drugs". *Drug Testing and Analysis*. **6** (7-8): 614–32. doi:10.1002/dta.1620. PMID 24678061.
90. ^ Domino, EF (September 2010). "Taming the ketamine tiger". *Anesthesiology*. **113** (3): 678–84. doi:10.1097/ALN.0b013e3181ed09a2. PMID 20693870.
91. ^ Corssen, G; Domino, EF (January–February 1966). "Dissociative anesthesia: Further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581". *Anesthesia & Analgesia*. **45** (1): 29–40. doi:10.1213/00000539-196601000-00007. PMID 5325977.
92. ^ *a b c* "Ketamine". Center for Substance Abuse Research (CESAR); University of Maryland, College Park. 29 October 2013. Archived from the original on 2013-11-12. Retrieved 27 July 2014.
93. ^ History of non-medical use in literature references:
    - Alltounian & Moore 1978
    - Palmer & Horowitz 2000
    - Kelly 2001
94. ^ Increased non-medical use references:
    - Awuonda, M (13 July 1996). "Swedes alarmed at ketamine misuse". *The Lancet*. **348** (9020): 122. doi:10.1016/S0140-6736(05)64628-4.
    - Curran, HV; Morgan, C (April 2000). "Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later". *Addiction*. **95** (4): 575–90. doi:10.1046/j.1360-0443.2000.9545759.x. PMID 10829333.
    - Gahlinger, PM (1 June 2004). "Club drugs: MDMA, gamma-hydroxybutyrate (GHB), Rohypnol, and ketamine". *American Family Physician*. **69** (11): 2619–26. PMID 15202696.
    - Jansen, KL (6 March 1993). "Non-medical use of ketamine". *BMJ*. **306** (6878): 601–2. doi:10.1136/bmj.306.6878.601. PMC 1676978. PMID 8461808.
    - Joe-Laider & Hunt 2008
95. ^ *a b* Joe-Laidler, K; Hunt, G (1 June 2008). "Sit down to float: The cultural meaning of ketamine use in Hong Kong". *Addiction Research & Theory*. **16** (3): 259–71. doi:10.1080/16066350801983673. PMC 2744071. PMID 19759834.
96. ^ Ketamine sold as "ecstasy" references:
    - Tanner-Smith, EE (July 2006). "Pharmacological content of tablets sold as "ecstasy": Results from an online testing service" (PDF). *Drug and Alcohol Dependence*. **83** (3): 247–54. doi:10.1016/j.drugalcdep.2005.11.016. PMID 16364567.
    - Copeland, J; Dillon, P (2005). "The health and psycho-social consequences of ketamine use". *International Journal of Drug Policy*. **16** (2): 122–31. doi:10.1016/j.drugpo.2004.12.003.
    - Measham, Fiona; Parker, Howard; Aldridge, Judith (2001). *Dancing on Drugs: Risk, Health and Hedonism in the British Club Scene*. London: Free Association Books. ISBN 9781853435126.[*verification needed*][*page needed*]
97. ^ Moore, K; Measham, F (2006). "Ketamine use: Minimising problems and maximising pleasure". *Drugs and Alcohol Today*. **6** (3): 29–32. doi:10.1108/17459265200600047.
98. ^ *WHO Model List of Essential Medicines* (PDF) (18th ed.). World Health Organization. October 2013 [April 2013]. p. 1 [p. 5 of pdf]. Retrieved 22 April 2014.
99. ^ Marshall, Donnie R.; (Deputy Administrator); Drug Enforcement Administration; Dept. of Justice (13 July 1999). "Schedules of Controlled Substances: Placement of Ketamine into Schedule III [21 CFR Part 1308. Final Rule 99-17803]" (PDF). Rules and Regulations. *Federal Register*. **64** (133): 37673–5.
100. ^ "Club 'horse' drug to be outlawed". *BBC News*. 28 December 2005. Archived from the original on 2009-09-03. Retrieved 7 May 2010.
101. ^ Advisory Council on the Misuse of Drugs (ACMD); Baker, Norman (10 December 2013), *Ketamine: A review of use and harm* (PDF) (Policy paper), Crown copyright; Open Government Licence, retrieved 22 January 2014.
102. ^ *a b* Baker, Norman; (Minister for Crime Prevention); Home Office; United Kingdom (12 February 2014), *Response to ACMD recommendation on ketamine* (PDF) (Correspondence to Les Iverson [chair of]; Advisory Council on the Misuse of Drugs), Crown copyright; Open Government Licence, retrieved 21 February 2014.
103. ^ Dixon, Hayley (12 February 2014). "Party drug ketamine to be upgraded to Class B". *The Daily Telegraph*. Retrieved 2 August 2014.
104. ^ Poisons Standard October 2015 https://www.comlaw.gov.au/Details/F2015L01534
105. ^ Poisons Act 1964

http://www.slp.wa.gov.au/pco/prod/FileStore.nsf/Documents/MRDocument:26063P/$FILE/Poisons%20Act%201964%20-%20%5B09-f0-04%5D.pdf?OpenElement
106. ^ Legal status of ketamine in Canada references:
   - "Statutes of Canada (S.C.)". *Justice Laws Website*. Government of Canada. 12 June 2014. |chapter= ignored (help)
   - "Order Amending Schedule I to the Controlled Drugs and Substances Act" (PDF). *Canada Gazette Part II*. **139** (19). 21 September 2005. p. 2130. Retrieved 2 August 2014.
   - "Status of ketamine under CDSA". Canadian Society of Customs Brokers. 2 May 2005. Retrieved 2 August 2014.
107. ^ "Government to tighten control on Ketamine", *info.gov.hk* (press release), Government of the Hong Kong Special Administrative, 22 November 2000, archived from the original on 2013-06-26, retrieved 2 August 2014
108. ^ Ho Wai-kin, Victor (2011). *Criminal Law in Hong Kong*. Kluwer Law International. p. 33. ISBN 9789041133069.
109. ^ Chang, Rich (4 December 2012). "Ketamine to be made a class-two drug: Official". *Taipei Times*. p. 3.
110. ^ "Ketamine drug brought under 'Schedule X' to curb abuse". *The Times of India*. 7 January 2014. Retrieved 2 August 2014.
111. ^ Deb Roy, Sumitra (30 December 2013). "Govt makes notorious 'date rape' drug ketamine harder to buy or sell". *The Times of India*. Archived from the original on 2013-12-30.
112. ^ Drugs.com International brands of ketamine Page accessed May 14, 2016
113. ^ Krupitsky, EM; Grineko, AYa; Berkaliev, TN; Paley, AI; et al. (1992). "The combination of psychedelic and aversive approaches in alcoholism treatment". *Alcoholism Treatment Quarterly*. **9** (1): 99–105. doi:10.1300/J020V09N01_09.
114. ^ Krupitsky, EM; Grinenko, AY (1997). "Ketamine psychedelic therapy (KPT): A review of the results of ten years of research". *Journal of Psychoactive Drugs*. **29** (2): 165–83. doi:10.1080/02791072.1997.10400185. PMID 9250944.
115. ^ Krupitsky, Evgeny; Kolp, Eli. "Ch. 6: Ketamine Psychedelic Psychotherapy". In Winkelman, Michael J.; Roberts, Thomas B. *Psychedelic Medicine: New Evidence for Hallucinogens as Treatments*. Vol. 2. Westport, CT: Praeger. ISBN 9780275990237.
116. ^ *STANDARD OPERATING PROCEDURE NO. 1 ANESTHESIA AND ANALGESIA IN RODENTS*, Washington College, 2012, pp. 1–2, retrieved 27 November 2015

## External links [edit]

- Ketamine on RxList
- DEA: Ketamine Fact Sheet

Wikimedia Commons has media related to *Ketamine*.

| v · t · e · | Recreational drug use | |
|---|---|---|
| **Major recreational drugs** | **Depressants** | Barbiturates · Benzodiazepines · Carbamates · Ethanol (Alcoholic drinks · · Gabapentinoids · GHB · Intoxicative inhalants (contact cement · gasoline · nail polish remover · · Kava · Nonbenzodiazepines · Quinazolinones · |
| | **Opioids** | Buprenorphine (Suboxone · Subutex · · Codeine · Desomorphine (Krokodil · · Dextropropoxyphene (Darvocet · Darvon · · Fentanyl · Diamorphine (Heroin · · Hydrocodone · Hydromorphone (Dilaudid · · Methadone · Mitragyna speciosa (Kratom · · Morphine (Opium · · Oxycodone (/paracetamol · · |
| | **Stimulants** | Amphetamine · Arecoline (Areca · · Betel · Caffeine (Coffee · Energy drinks · Tea · · Cathinone (Khat · · Cocaine (Coca · Crack · · Ephedrine (Ephedra · · MDPV · Mephedrone · Methamphetamine · Methylone · Methylphenidate · Nicotine (Tobacco · · Theobromine (Cocoa · · |
| | **Entactogens** | MDA · MDMA (Ecstasy · · 2C-* series · alpha-Methyltryptamine · 6-APB (Benzofury · · |
| | | Bufotenin (Psychoactive toads · Vilca · Yopo · · DMT |

| | | | |
|---|---|---|---|
| | **Hallucinogens** | **Psychedelics** | (Ayahuasca • • LSA • LSD-25 • Mescaline (Peruvian Torch • Peyote • San Pedro • • Psilocybin / Psilocin (Psilocybin mushrooms • • |
| | | **Dissociatives** | DXM • Glaucine • Inhalants (Nitrous oxide • alkyl nitrites • poppers • amyl nitrite • • **Ketamine** • MXE • Muscimol (Amanita muscaria • • PCP • Salvinorin A (Salvia divinorum • • |
| | | **Deliriants** | Atropine and Scopolamine (Atropa belladonna • Datura • Hyoscyamus niger • Mandragora officinarum • • Dimenhydrinate • Diphenhydramine • |
| | | **Cannabinoids** | JWH-018 • THC (Cannabis • Hashish • Hash oil • • |
| | | **Oneirogens** | Calea zacatechichi • Silene capensis • |
| **Drug culture** | **Cannabis culture** | | 420 • Cannabis cultivation • Cannabis smoking • Legal history of cannabis in the United States • Legality of cannabis • Marijuana Policy Project • Medical cannabis • NORML • Religious and spiritual use of cannabis • Stoner film • |
| | **Coffee culture** | | Coffee break • Coffeehouse • Latte art • Tea house • |
| | **Drinking culture** | | Bartending • Beer culture • Beer festival • Binge drinking • Drinking games • Drinking song • Happy hour • Hip flask • Nightclub • Pub crawl • |
| | **Psychedelia** | | Art • Drug • Era • Experience • Literature • Music • Therapy • |
| | **Smoking culture** | | Cigarette card • Fashion cigarettes • Cloud-chasing • Loosie • Smokeasy • Smoking fetishism • Tobacco smoking • |
| | **Other** | | Club drug • Counterculture of the 1960s • Dance party • Drug paraphernalia • Drug tourism • Entheogen • Hippie • Party and play • Poly drug use • Rave • Self-medication • Sex and drugs • Whoonga • |
| **Drug production and trade** | **Drug production** | | Coca production in Colombia • Drug precursors • Opium production in Afghanistan • Rolling meth lab • |
| | **Drug trade** | | Illegal drug trade in Colombia • |
| **Issues with drug use** | | | Abuse • Date rape drug • Effects of cannabis • Addiction • Dependence (Prevention • Opioid replacement therapy • Rehabilitation • Responsible use • • Drug-related crime • Fetal alcohol spectrum disorder • Illegal drug trade • Long-term effects of cannabis • Neurotoxicity • Overdose • Passive smoking (of tobacco or other substances • • |
| **Legality of drug use** | **International** | | 1961 Narcotic Drugs • 1971 Psychotropic Substances • 1988 Drug Trafficking • Council of the European Union decisions on designer drugs • |
| | **State level** | | Drug policy (Decriminalization • Prohibition • Supply reduction • • Policy reform (Demand reduction • Drug Policy Alliance • Harm reduction • Law Enforcement Against Prohibition • Liberalization (Latin America • • Students for Sensible Drug Policy • Transform Drug Policy Foundation • • |
| | **Drug policy by country** | | Australia • Canada • Germany • India • Netherlands • Portugal • Slovakia • Soviet Union • Sweden • Switzerland • United States (Just Say No • Office of National Drug Control Policy • School district drug policies • California • Colorado • Maryland • Virginia • • |
| | | | Arguments for and against drug prohibition • |

| | | |
|---|---|---|
| | **Other** | Capital punishment for drug trafficking · Designer drug · Drug court · Drug harmfulness · Drug possession · Drug test · Mexican Drug War · Philippine Drug War · Narc · Politics of drug abuse · War on Drugs · Zero tolerance · |
| **Lists of countries by...** | | Alcohol legality (Alcohol consumption · · Anabolic steroid legality · Cannabis legality (Annual use · Lifetime use · · Cigarette consumption · Cocaine legality (Cocaine use · · Methamphetamine legality · Opiates use · Psilocybin mushrooms legality · Salvia legality · |

| v · t · e · | **General anesthetics (N01A)** | |
|---|---|---|
| **Inhalational** | | Chloroethane (ethyl chloride)‡ · Chloroform‡ · Cyclopropane‡ · Desflurane · Diethyl ether‡ · Enflurane · Ethylene‡ · Fluroxene‡ · Halothane# · Isoflurane · Methoxyflurane · Methoxypropane‡ · Nitrous oxide# · Sevoflurane · Trichloroethylene‡ · Vinyl ether‡ · Xenon · |
| **Injection** | **Phenols** | Fospropofol · Propofol · |
| | **Opioids** | Morphine · Oxycodone · Anileridine‡ · Embutramide‡ · Fentanyl · Alfentanil · Phenoperidine · Remifentanil · Sufentanil · |
| | **Arylcyclohexylamines** | Esketamine · **Ketamine**# · Phencyclidine‡ · Tiletamine · |
| | **Others** | Alfadolone · Alfaxalone · Hydroxydione · Propanidid‡ · |

· #WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · ·

| v · t · e · | **Analgesics (N02A, N02B)** | |
|---|---|---|
| **Opioids** | **Opiates/opium** | Codeine# (+paracetamol, +aspirin) · Morphine# (+naltrexone) · Opium · Laudanum · Paregoric · |
| | **Semisynthetic** | Acetyldihydrocodeine · Benzylmorphine · Buprenorphine (+naloxone) · Desomorphine · Diamorphine (heroin) · Dihydrocodeine (+paracetamol) · Dihydromorphine · Ethylmorphine · Hydrocodone (+paracetamol, +ibuprofen, +aspirin) · Hydromorphinol · Hydromorphone · Nicocodeine · Nicodicodeine · Nicomorphine · Oxycodone (+paracetamol, +aspirin, +ibuprofen, +naloxone, +naltrexone) · Oxymorphone · Thebacon · |
| | **Synthetic** | Alphaprodine · Anileridine · Butorphanol · Dextromoramide · Dextropropoxyphene · Dezocine · Fentanyl (+fluanisone) · Ketobemidone · Levorphanol · Meptazinol · Methadone · Nalbuphine · Pentazocine · Pethidine · Phenadoxone · Phenazocine · Piminodine · Piritramide · Propiram · Tapentadol · Tilidine · Tramadol · |
| **Paracetamol-type** | | Acetanilide‡ · Bucetin‡ · Butacetin‡ · Paracetamol (acetaminophen)# · Parapropamol‡ · Phenacetin‡ · Propacetamol‡ · |
| **NSAIDs** | **Propionates** | Fenoprofen · Flurbiprofen · Ibuprofen# · Ketoprofen · Naproxen · Oxaprozin · |
| | **Oxicams** | Meloxicam · Piroxicam · |
| | **Acetates** | Diclofenac · Indometacin · Ketorolac · Nabumetone · Sulindac · Tolmetin · |
| | **COX-2 inhibitors** | Celecoxib · Etoricoxib · Lumiracoxib · Parecoxib · Rofecoxib ‡ · Valdecoxib ‡ · |
| | **Fenamates** | Meclofenamic acid · Mefenamic acid · |

| | | |
|---|---|---|
| | **Salicylates** | Aspirin (acetylsalicylic acid)[#] (+paracetamol/caffeine) · Benorylate · Diflunisal · Ethenzamide · Magnesium salicylate · Salicin · Salicylamide · Salsalate · Wintergreen (methyl salicylate) · |
| | **Pyrazolones** | Aminophenazone[‡] · Ampyrone · Metamizole (dipyrone) · Nifenazone · Phenazone · Propyphenazone · |
| | **Others** | Glafenine · |
| **Cannabinoids** | Cannabidiol · Cannabis · Nabilone · Nabiximols · Tetrahydrocannabinol (dronabinol) · | |
| **Ion channel modulators** | **Calcium blockers** | Gabapentin · Gabapentin enacarbil · Pregabalin · Ziconotide · |
| | **Sodium blockers** | Carbamazepine · Lacosamide · Local anesthetics (e.g., cocaine, lidocaine) · Mexiletine · Nefopam · Tricyclic antidepressants (e.g., amitriptyline[#]) · *$Na_v1.7/1.8$-selective:* DSP-2230[§] · Funapide[§] · PF-05089771[§] · Raxatrigine[§] · |
| | **Potassium openers** | Flupirtine · |
| **Myorelaxants** | Carisoprodol · Chlorzoxazone · Cyclobenzaprine · Mephenoxalone · Methocarbamol · Orphenadrine · | |
| **Others** | Camphor · Capsaicin · Clonidine · **Ketamine** · Menthol · Methoxyflurane · Nefopam · Proglumide · Tricyclic antidepressants (e.g., amitriptyline[#]) · | |

· [#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III · ·

| v · t · e · | **Antidepressants (N06A)** |
|---|---|
| **Specific reuptake inhibitors and/or receptor modulators** | |
| **SSRIs** | Citalopram · Escitalopram · Fluoxetine[#] · Fluvoxamine · Indalpine[‡] · Paroxetine · Sertraline · Zimelidine[‡] · |
| **SNRIs** | Desvenlafaxine · Duloxetine · Levomilnacipran · Milnacipran · Tofenacin · Venlafaxine · |
| **NRIs** | Atomoxetine · Reboxetine · Viloxazine · |
| **NDRIs** | Amineptine[‡] · Bupropion · Nomifensine[‡] · |
| **NaSSAs** | Mianserin · Mirtazapine · Setiptiline · |
| **SARIs** | Etoperidone · Nefazodone[‡] · Trazodone · |
| **SMSs** | Vilazodone · Vortioxetine · |
| **Others** | Agomelatine · Amisulpride · Amitriptyline/perphenazine · Buprenorphine · Bupropion · Etryptamine[‡] · Flupentixol/melitracen · Esketamine · **Ketamine** · Indeloxazine · Lurasidone · Medifoxamine[‡] · Metryptamine[‡] · Olanzapine/fluoxetine · Oxaflozane[‡] · Quetiapine · Tandospirone · Teniloxazine · Tianeptine · Tranylcypromine/trifluoperazine · |
| **Tricyclic and tetracyclic antidepressants** | |
| **TCAs** | Amineptine[‡] · Amitriptyline[#] · Amitriptylinoxide · Butriptyline[‡] · Clomipramine[#] · Demexiptiline[‡] · Desipramine · Dibenzepin · Dimetacrine[‡] · Dosulepin · Doxepin · Imipramine · Imipraminoxide[‡] · Iprindole[‡] · Lofepramine · Melitracen · Metapramine[‡] · Nitroxazepine · Nortriptyline · Noxiptiline · Opipramol · Pipofezine · Propizepine[‡] · Protriptyline · Quinupramine[‡] · Tianeptine · Trimipramine · |
| **TeCAs** | Amoxapine · Maprotiline · Mianserin · Mirtazapine · Setiptiline · |

| | |
|---|---|
| **Others** | Tiazesim · |

**Monoamine oxidase inhibitors**

| | |
|---|---|
| **Non-selective** | *Irreversible:* Benmoxin‡ · Iproclozide‡ · Iproniazid‡ · Isocarboxazid · Mebanazine‡ · Nialamide‡ · Octamoxin‡ · Phenelzine · Pheniprazine‡ · Phenoxypropazine‡ · Pivhydrazine‡ · Safrazine‡ · Tranylcypromine ·<br>*Reversible:* Caroxazone‡ · |
| **$MAO_A$-selective** | *Reversible:* Bifemelane · Eprobemide · Metralindole · Minaprine‡ · Moclobemide · Pirlindole · Tetrindole · Toloxatone · |
| **$MAO_B$-Selective** | *Irreversible:* Selegiline · |

**Adjunctive therapies**

Atypical antipsychotics (aripiprazole, lurasidone, olanzapine, quetiapine) · Buspirone · Lithium (lithium carbonate, lithium citrate) · Thyroid hormones (triiodothyronine ($T_3$), levothyroxine ($T_4$)) ·

**Miscellaneous**

Ademetionine (SAMe) · *Hypericum perforatum* (St. John's Wort) · Oxitriptan (5-HTP) · Tryptophan ·

#WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · ·

v · t · e ·

**Hallucinogens**

| | | |
|---|---|---|
| **Lysergamides** | | 1P-ETH-LAD · 1P-LSD · 2-Butyllysergamide · 3-Pentyllysergamide · AL-LAD · ALD-52 · BU-LAD · Diallyllysergamide · Dimethyllysergamide · Ergometrine · ETH-LAD · IP-LAD · LAE-32 · LPD-824 · LSA · LSD · LSD-Pip · LSH · LSM-775 · LSZ · Methylergometrine · Methylisopropyllysergamide · Methysergide · MLD-41 · PARGY-LAD · PRO-LAD · |
| **Phenethylamines** | **2C-*** | 2C-B · 2C-B-AN · 2C-C · 2C-CP · 2C-D · 2C-E · 2C-EF · 2C-F · 2C-G · 2C-I · 2C-iP · 2C-N · 2C-O · 2C-O-4 · 2C-P · 2C-T · 2C-T-2 · 2C-T-3 · 2C-T-4 · 2C-T-7 · 2C-T-8 · 2C-T-13 · 2C-T-15 · 2C-T-16 · 2C-T-17 · 2C-T-19 · 2C-T-21 · 2C-T-21.5 · 2C-T-22 · 2C-T-27 · 2C-T-28 · 2C-TFM · 2C-YN · TMA-2 · |
| | **HOT-*** | HOT-2 · HOT-7 · HOT-17 · |
| | **25*-NB* (excludes FLY)** | ***-NBF:** 25B-NBF · 25C-NBF · 25I-NBF<br>***-NBOH:** 25B-NBOH · 25C-NBOH · 25CN-NBOH · 25I-NBOH<br>***-NBMD:** 25B-NBMD · 25C-NBMD · 25I-NB34MD · 25I-NBMD<br>***-NBOMe:** 25B-NBOMe · 25C-NBOMe · 25CN-NBOMe · 25D-NBOMe · 25E-NBOMe · 25F-NBOMe · 25G-NBOMe · 25I-NBOMe · 25N-NBOMe · 25P-NBOMe · 25TFM-NBOMe · |
| | **Subst. mescaline** | 2-Bromomescaline · Allylescaline · Asymbescaline · Buscaline · Cyclopropylmescaline · Difluoromescaline · Difluoroescaline · Escaline · Fluoroproscaline · Isobuscaline · Isoproscaline · Mescaline · Metaescaline · Methallylescaline · Proscaline · Trifluoroescaline · Trifluoromescaline · |
| | **DO*** | (DOT) Aleph · DOB · DOC · DOEF · DOET · DOF · DOI · DOiPR · DOM · DON · DOPR · DOTFM · MEM · |
| | **3C-*** | 3C-AL · 3C-BZ · 3C-DFE · 3C-E · 3C-P · |

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| **Psychedelics** (**5-HT$_{2A}$ agonists**) | | **4C-*** | 4C-B · 4C-D · 4C-T-2 · |
| | | **FLY** | 2CBFly-NBOMe · 2C-B-DragonFLY · 2C-B-BUTTERFLY · 2C-B-FLY · Bromo-DragonFLY · DOB-FLY · TFMFly · |
| | | **MD*** | DMMDA · DMMDA-2 · Lophophine · MDA · MMDA · MMDA-2 · MMDA-3a · MMDMA · |
| | | **Others** | βk-2C-B · βk-2C-I · 2CB-Ind · 2CD-5EtO · 2CBCB-NBOMe · 2-TOM · 3-TE · 3-TM · 4-TE · 4-TM · 5-TOET · 5-TOM · BOB · BOD · DESOXY · DMBMPP · DMCPA · Fenfluramine · Ganesha · Jimscaline · Macromerine · MMA · NBOMe-mescaline · TCB-2 · Thioproscaline · TOMSO · TMA · |
| | **Piperazines** | | pFPP · TMFPP · mCPP · |
| | **Tryptamines** | **Sub. Trypt.** | 4,5-DHP-α-MT · 5-MeO-α-ET · 5-MeO-α-MT · α-ET · α-MT · |
| | | ***-DMT** | 4,5-DHP-DMT · 2,N,N-TMT · 4-AcO-DMT · 4-HO-5-MeO-DMT · 4,N,N-TMT · 4-Propionyloxy-DMT · 5,6-diBr-DMT · 5-AcO-DMT · 5-Bromo-DMT · 5-MeO-2,*N*,*N*-TMT · 5-MeO-4,*N*,*N*-TMT · 5-MeO-α,N,N-TMT · 5-MeO-DMT · 5-*N*,*N*-TMT · 7,N,N-TMT · α,N,N-TMT · (Bufotenin) 5-HO-DMT · DMT · Norbaeocystin · (Psilocin) 4-HO-DMT · (Psilocybin) 4-PO-DMT · |
| | | ***-DET** | (Ethacetin) 4-AcO-DET · (Ethocin) 4-HO-DET · 5-MeO-DET · (T-9) DET · (Ethocybin) 4-PO-DET · |
| | | ***-DPT** | (Depracetin) 4-AcO-DPT · (Deprocin) 4-HO-DPT · 5-MeO-DPT · (The Light) DPT · |
| | | ***-DiPT** | 1-Me-5-MeO-DiPT · (Ipracetin) 4-AcO-DiPT · (Iprocin) 4-HO-DiPT · (Foxy Methoxy) 5-MeO-DiPT · DiPT · |
| | | ***-DALT** | (Daltocin) 4-HO-DALT · (Daltacetin) 4-AcO-DALT · 5-MeO-DALT · DALT · |
| | | ***-MET** | (Metocin) 4-HO-MET · (Metocetin) 4-AcO-MET · 5-MeO-MET · MET · |
| | | ***-MiPT** | (Mipracetin) 4-AcO-MiPT · (Miprocin) 4-HO-MiPT · 5-Me-MiPT · (Moxy) 5-MeO-MiPT · MiPT · |
| | | **Subst. Ibogamine** | Ibogaine · Noribogaine · Voacangine · |
| | | **Others** | 4-HO-DBT · 4-HO-EPT · 4-HO-McPT · (Lucigenol) 4-HO-MPMI · (Meprocin) 4-HO-MPT · 5-MeO-EiPT · 5-MeO-MALT · 5-MeO-MPMI · Aeruginascin · Baeocystin · DBT · DCPT · EiPT · EPT · MPT · PiPT · |
| | **Others** | | 5-MeO-DiBF · AL-38022A · ALPHA · Dimemebfe · Efavirenz · Lorcaserin · M-ALPHA · RH-34<br>Also empathogens in general (e. g.: 5-APB, 5-MAPB, 6-APB and other substituted benzofurans, MDAI, MDMA). · |
| | **Arylcyclohexylamines** | | 2-Fluorodeschloroketamine · 3-HO-PCP · 3-MeO-PCE · 3-MeO-PCMo · 3-MeO-PCP · 4-MeO-PCP · Arketamine · Deschloroketamine · Dieticyclidine · Esketamine · Ethketamine · Eticyclidine · Gacyclidine · **Ketamine** · Methoxetamine · Methoxmetamine · Methoxyketamine · Norketamine · PCPr · |

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| **Dissociatives** (**NMDAR antagonists**) | | | PCP · Rolicyclidine · Tenocyclidine · Tiletamine · |
| | **Morphinans** | | Dextrallorphan · Dextromethorphan · Dextrorphan · Racemethorphan · Racemorphan · |
| | **Diarylethylamines** | | Diphenidine · Ephenidine · Fluorolintane · Methoxphenidine · |
| | **Others** | | 2-MDP · 8A-PDHQ · Aptiganel · Budipine · Delucemine · Dexoxadrol · Dizocilpine · Etoxadrol · Ibogaine · Midafotel · NEFA · Neramexane · Nitrous oxide · Noribogaine · Perzinfotel · Remacemide · Selfotel · Xenon · |
| **Deliriants** (**mAChR antagonists**) | | | Atropine · Benactyzine · Benzatropine · Benzydamine · Biperiden · BRN-1484501 · Brompheniramine · BZ · CAR-226,086 · CAR-301,060 · CAR-302,196 · CAR-302,282 · CAR-302,368 · CAR-302,537 · CAR-302,668 · Chloropyramine · Chlorphenamine · Clemastine · CS-27349 · Cyclizine · Cyproheptadine · Dicycloverine · Dimenhydrinate · Diphenhydramine · Ditran · Doxylamine · EA-3167 · EA-3443 · EA-3580 · EA-3834 · Elemicin · Flavoxate · Hyoscyamine · JB-318 · JB-336 · Meclozine · Mepyramine · Myristicin · Orphenadrine · Oxybutynin · Pheniramine · Phenyltoloxamine · Procyclidine · Promethazine · Scopolamine · Tolterodine · Trihexyphenidyl · Tripelennamine · Triprolidine · WIN-2299 · |
| **Others** | **Cannabinoids** (**$CB_1$ agonists**) | **Natural** | Cannabinol · THC (Dronabinol) · THCV · |
| | | **Synthetic** | 4-HTMPIPO · 5F-AB-FUPPYCA · 5F-AB-PINACA · 5F-ADB · 5F-ADB-PINACA · 5F-ADBICA · 5F-AMB · 5F-APINACA · 5F-CUMYL-PINACA · 5F-NNE1 · 5F-PB-22 · 5F-SDB-006 · A-796,260 · A-836,339 · AB-001 · AB-005 · AB-CHFUPYCA · AB-CHMINACA · AB-FUBINACA · AB-PINACA · ADAMANTYL-THPINACA · ADB-CHMINACA · ADB-FUBINACA · ADB-PINACA · ADBICA · ADSB-FUB-187 · AM-630 · AM-679 · AM-694 · AM-1220 · AM-1221 · AM-1235 · AM-1241 · AM-1248 · AM-2201 · AM-2232 · AM-2233 · AMB-FUBINACA · APICA · APINACA · APP-FUBINACA · CB-13 · CP 47,497 · CP 55,244 · CP 55,940 · CUMYL-PICA · CUMYL-PINACA · CUMYL-THPINACA · DMHP · EAM-2201 · FAB-144 · FDU-PB-22 · FUB-144 · FUB-APINACA · FUB-JWH-018 · FUB-PB-22 · FUBIMINA · HU-210 · HU-308 · JWH-007 · JWH-015 · JWH-018 · JWH-019 · JWH-030 · JWH-073 · JWH-081 · JWH-098 · JWH-116 · JWH-122 · JWH-149 · JWH-167 · JWH-182 · JWH-193 · JWH-198 · JWH-200 · JWH-203 · JWH-210 · JWH-250 · JWH-251 · JWH-398 · JWH-424 · JTE 7-31 · JTE-907 · Levonantradol · MDMB-CHMICA · MDMB-CHMINACA · MDMB-FUBINACA · MEPIRAPIM · MAM-2201 · MDA-19 · MN-18 · MN-25 · NESS-0327 · NESS-040C5 · Nabilone · Nabitan · NM-2201 · NNE1 · Org 28611 · Parahexyl · PTI-1 · PTI-2 · PX-1 · PX-2 · PX-3 · QUCHIC · QUPIC · RCS-4 · RCS-8 · SDB-005 · SDB-006 · STS-135 · THC-O-acetate · THC-O-phosphate · THJ-018 · THJ-2201 · UR-144 · WIN 55,212-2 · XLR-11 · |
| | **$D_2$ agonists** | | Apomorphine · Aporphine · Bromocriptine · Cabergoline · Lisuride · Memantine · Nuciferine · Pergolide · Phenethylamine · Piribedil · Pramipexole · Ropinirole · Rotigotine · Salvinorin A<br>Also indirect $D_2$ agonists, such as dopamine reuptake inhibitors (cocaine, methylphenidate), releasing agents (amphetamine, methamphetamine), and precursors (levodopa). · |

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| | **$GABA_A$ enhancers** | CI-966 · Eszopiclone · Ibotenic acid · Muscimol (*Amanita muscaria*) · Zaleplon · Zolpidem · Zopiclone · |
| | **Inhalants (Mixed MOA)** | Aliphatic hydrocarbons (Butane · Gasoline · Kerosene · Propane · · Aromatic hydrocarbons (Toluene · · Ethers (Diethyl ether · Enflurane · · Haloalkanes (Chlorofluorocarbons · Chloroform · · |
| | **κOR agonists** | 2-EMSB · 2-MMSB · Alazocine · Bremazocine · Butorphan · Butorphanol · Cyclazocine · Cyclorphan · Cyprenorphine · Diprenorphine · Enadoline · Herkinorin · Heroin · HZ-2 · Ibogaine · Ketazocine · Levallorphan · Levomethorphan · Levorphanol · LPK-26 · Metazocine · Morphine · Nalbuphine · Nalmefene · Nalorphine · Noribogaine · Oxilorphan · Pentazocine · Phenazocine · Proxorphan · Racemethorphan · Racemorphan · Salvinorin A · Spiradoline · Tifluadom · U-50488 · U-69,593 · Xorphanol · |
| | **Others** | Glaucine · Isoaminile · Noscapine · Pukateine · |

| v · t · e · | **Glutamatergics** | |
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| | **AMPA** | **Agonists:** *Glutamate/active site agonists:* 5-Fluorowillardiine · Acromelic acid (acromelate) · AMPA · BOAA · Domoic acid · Glutamate · Ibotenic acid · Proline · Quisqualic acid · Willardiine; *Positive allosteric modulators:* Aniracetam · Cyclothiazide · CX-516 · CX-546 · CX-614 · Farampator (CX-691, Org 24448) · CX-717 · CX-1739 · CX-1942 · Diazoxide · Hydrochlorothiazide (HCTZ) · IDRA-21 · LY-392,098 · LY-404,187 · LY-451,646 · LY-503,430 · Mibampator (LY-451,395) · Org 26576 · Oxiracetam · PEPA · PF-04958242 · Piracetam · Pramiracetam · S-18986 · Sunifiram · Unifiram · **Antagonists:** ACEA-1011 · ATPO · Becampanel · Caroverine · CNQX · Dasolampanel · DNQX · Fanapanel (MPQX) · GAMS · GYKI-52466 · Kynurenic acid · Kynurenine · Licostinel (ACEA-1021) · NBQX · PNQX · Selurampanel · Tezampanel · Theanine · Topiramate · YM90K · Zonampanel; *Negative allosteric modulators:* Barbiturates (e.g., pentobarbital, sodium thiopental) · Cyclopropane · Enflurane · Ethanol · Evans blue · GYKI-53,655 · Halothane · Irampanel · Isoflurane · Perampanel · Pregnenolone sulfate · Talampanel · |
| | | **Agonists:** *Glutamate/active site agonists:* AMAA · Aspartate · Glutamate · Homocysteic acid (L-HCA) · Homoquinolinic acid · Ibotenic acid · NMDA · Proline · Quinolinic acid · Tetrazolylglycine · Theanine; *Glycine site agonists:* β-Fluoro-D-alanine · ACBD · ACC (ACPC) · ACPD · AK-51 · Apimostinel (NRX-1074) · B6B21 · CCG · D-Alanine · D-Cycloserine · D-Serine · DHPG · Dimethylglycine · Glycine · HA-966 · L-687,414 · L-Alanine · L-Serine · Milacemide · Neboglamine (nebostinel) · Rapastinel (GLYX-13) · Sarcosine; *Polyamine site agonists:* Spermidine · Spermine; *Other positive allosteric modulators:* 24S-Hydroxycholesterol · DHEA · DHEA sulfate · Pregnenolone sulfate · SAGE-718 · **Antagonists:** *Competitive antagonists:* AP5 (APV) · AP7 · CGP-37849 · CGP-39551 · CGP-39653 · CGP-40116 · CGS-19755 · CPP · LY-233,053 · LY-235,959 · LY-274,614 · MDL-100,453 · Midafotel (d-CPPene) · NPC-12,626 · NPC-17,742 · PBPD · PEAQX · Perzinfotel · PPDA · SDZ-220581 · Selfotel; *Noncompetitive antagonists:* ARR-15,896 · Caroverine · Dexanabinol · FPL-12495 · FR-115,427 · Hodgkinsine · Magnesium · MDL-27,266 · NPS-1506 · Psychotridine · Zinc; *Uncompetitive pore blockers:* 2-MDP · 3-HO-PCP · 3-MeO-PCE · 3-MeO-PCMo · 3-MeO-PCP · 4-MeO-PCP · 8A-PDHQ · 18-MC · |

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| **Receptor (ligands)** | **NMDA** | α-Endopsychosin · Alaproclate · Amantadine · Aptiganel · Arketamine · ARL-12,495 · ARL-15,896-AR · ARL-16,247 · Budipine · Conaridine · Delucemine · Dexoxadrol · Dextrallorphan · Dieticyclidine · Diphenidine · Dizocilpine · Ephenidine · Esketamine · Etoxadrol · Eticyclidine · Fluorolintane · Gacyclidine · Ibogaine · Ibogamine · Indantadol · **Ketamine** · Ketobemidone · Lanicemine · Loperamide · Memantine · Methadone (Levomethadone) · Methorphan (Dextromethorphan · Levomethorphan) · Methoxetamine · Methoxphenidine · Milnacipran · Morphanol (Dextrorphan · Levorphanol) · NEFA · Neramexane · Nitromemantine · Nitrous oxide · Noribogaine · Norketamine · Orphenadrine · PCPr · Pethidine (meperidine) · Phencyclamine · Phencyclidine · Propoxyphene · Remacemide · Rhynchophylline · Rimantadine · Rolicyclidine · Sabeluzole · Tabernanthine · Tenocyclidine · Tiletamine · Tramadol · Xenon; *Glycine site antagonists:* 4-Cl-KYN (AV-101) · 5,7-DCKA · 7-CKA · ACC · ACEA-1011 · ACEA-1328 · AV-101 · Carisoprodol · CGP-39653 · CNQX · DNQX · Felbamate · Gavestinel · GV-196,771 · Kynurenic acid · Kynurenine · L-689,560 · L-701,324 · Licostinel (ACEA-1021) · LU-73,068 · MDL-105,519 · Meprobamate · MRZ 2/576 · PNQX · ZD-9379; *NR2B subunit antagonists:* Besonprodil · CERC-301 (MK-0657) · CO-101,244 (PD-174,494) · Eliprodil · Haloperidol · Ifenprodil · Isoxsuprine · Nylidrin · Ro8-4304 · Ro25-6981 · Traxoprodil; *Polyamine site antagonists:* Arcaine · Co 101676 · Diaminopropane · Diethylenetriamine · Huperzine A · Putrescine · Ro 25-6981; *Unclassified/unsorted antagonists:* Bumetanide · Chloroform · Cyclopropane · D-αAA · Diethyl ether · Enflurane · Ethanol · Flufenamic acid · Flupirtine · Furosemide · Halothane · Isoflurane · Metaphit · Methoxyflurane · Niflumic acid · Pentamidine isethionate · Piretanide · Toluene · Transcrocetin (saffron) · Trichloroethane · Trichloroethanol · Trichloroethylene · Xylene · |
| | **Kainate** | **Agonists:** *Glutamate/active site agonists:* 5-Bromowillardiine · 5-Iodowillardiine · Acromelic acid (acromelate) · AMPA · ATPA · Domoic acid · Glutamate · Ibotenic acid · Kainic acid · LY-339,434 · Proline · Quisqualic acid · SYM-2081; *Positive allosteric modulators:* Cyclothiazide · Diazoxide · Enflurane · Halothane · Isoflurane · **Antagonists:** ACEA-1011 · CNQX · Dasolampanel · DNQX · GAMS · Kynurenic acid · Licostinel (ACEA-1021) · LY-382,884 · NBQX · NS102 · Selurampanel · Tezampanel · Theanine · Topiramate · UBP-302; *Negative allosteric modulators:* Barbiturates (e.g., pentobarbital, sodium thiopental) · Enflurane · Ethanol · Evans blue · NS-3763 · Pregnenolone sulfate · |
| | **$mGlu_1$** | **Agonists:** ACPD · DHPG · Glutamate · Ibotenic acid · Quisqualic acid · Ro01-6128 · Ro67-4853 · Ro67-7476 · VU-71 · **Antagonists:** BAY 36-7620 · CPCCOEt · Cyclothiazide · LY-367,385 · LY-456,236 · MCPG · NPS-2390 · |
| | **$mGlu_2$** | **Agonists:** BINA · CBiPES · DCG-IV · Eglumegad · Glutamate · Ibotenic acid · LY-379,268 · LY-404,039 (pomaglumetad) · LY-487,379 · LY-566,332 · MGS-0028 · Pomaglumetad methionil (LY-2140023) · Talaglumetad; *Positive allosteric modulators:* JNJ-40411813 (ADX-71149) · **Antagonists:** APICA · CECXG · EGLU · HYDIA · LY-307,452 · LY-341,495 · MCPG · MGS-0039 · PCCG-4; *Negative allosteric modulators:* Decoglurant · RO4491533 · |
| | **$mGlu_3$** | **Agonists:** CBiPES · DCG-IV · Eglumegad · Glutamate · Ibotenic acid · LY-379,268 · LY-404,039 (pomaglumetad) · LY-487,379 · MGS-0028 · Pomaglumetad methionil (LY-2140023) · Talaglumetad · |

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| | | **Antagonists:** APICA · CECXG · EGLU · HYDIA · LY-307,452 · LY-341,495 · MCPG · MGS-0039; *Negative allosteric modulators:* Decoglurant · RO4491533 · |
| | **$mGlu_4$** | **Agonists:** Glutamate · L-AP4 · PHCCC · VU-001,171 · VU-0155,041; *Positive allosteric modulators:* MPEP · **Antagonists:** CPPG · MAP4 · MPPG · MSOP · MTPG · UBP-1112 · |
| | **$mGlu_5$** | **Agonists:** ACPD · ADX-47273 · CDPPB · CHPG · DFB · DHPG · Glutamate · Ibotenic acid · Quisqualic acid · VU-1545 · **Antagonists:** CTEP · DMeOB · LY-344,545 · Mavoglurant · MCPG · NPS-2390 · Remeglurant · SIB-1757 · SIB-1893; *Negative allosteric modulators:* Basimglurant · Dipraglurant · Fenobam · GRN-529 · MPEP · MTEP · Raseglurant · |
| | **$mGlu_6$** | **Agonists:** Glutamate · L-AP4 · **Antagonists:** CPPG · MAP4 · MPPG · MSOP · MTPG · UBP-1112 · |
| | **$mGlu_7$** | **Agonists:** AMN082 · Glutamate · L-AP4 · **Antagonists:** CPPG · MAP4 · MMPIP · MPPG · MSOP · MTPG · UBP-1112 · |
| | **$mGlu_8$** | **Agonists:** DCPG · Glutamate · L-AP4 · **Antagonists:** CPPG · MAP4 · MPPG · MSOP · MTPG · UBP-1112 · |
| **Transporter (blockers)** | **EAATs** | Amphetamine · Aspartic acid (aspartate) · *cis*-ACBD · DHKA · Glutamic acid (glutamate) · HIP-A · HIP-B · Kainic acid · L-(-)-*threo*-3-Hydroxyaspartic acid · L-αAA · L-CCG-III ((2S,3S,4R)-CCG) · L-Serine-O-sulphate (SOS) · L-*trans*-2,4-PDC · MPDC · SYM-2081 · TBOA · TFB-TBOA · Theanine · *threo*-3-Methylglutamic acid · UCPH-101 · WAY-213,613 · |
| | **vGluTs** | 4-Methylene-L-glutamate · 6-(4'-Phenylstyryl)-QDC · 6-Biphenyl-4-yl-QDC · 7-CKA · Acid red 114 · Amido black 10B (naphthol blue black) · Bafilomycin A1 · Benzopurpurin 4B · Bumetamide · Chicago sky blue 6B · Aspartic acid (aspartate) · DIDS · Direct blue 71 · Erythro-4-methyl-L-glutamic acid · Evans blue · Furosemide · Glutamic acid (glutamate) · Kynurenic acid · Nigericin · NPPB (N144) · Ponceau SS · Reactive blue 2 · Rose bengal · SITS · *trans*-ACDP · Trypan blue · Valinomycin · Xanthurenic acid · |
| **Enzyme (inhibitors)** | **GAH** | BPTES · CB-839 · DON · |
| | **AST** | 2-Amino-3-butenoic acid · AAOA · AMB · β-DL-Methylene-aspartate · Hydrazinosuccinate · |
| | **ALT** | β-Chloro-L-alanine · L-Cycloserine · Propargylglycine · |
| | **GDH** | AAOA · Bithionol · Chloroquine · EGCG · GTP · GW5074 · Hexachlorophene · Hydroxylamine · Palmitoyl-CoA · Pyridoxal phosphate · |
| | **GS** | 2-Aminoadipic acid · JFD01307SC · Methionine sulfoximine · Phosphinothricin (glufosinate) · |
| | **GAD** | 3-Mercaptopropionic acid · AAOA · L-Allylglycine · Semicarbazide · |
| **Others** | | **Precursors:** GHB · L-Glutamine · **Cofactors:** α-Ketoglutaric acid · Iron · Sulfur · Vitamin $B_2$ · Vitamin $B_3$ · **Prodrugs:** Aceglutamide (to L-glutamine) · **Others:** Acamprosate · Cysteine · Cytidine · Cytisine · Glutathione · Glutathione disulfide · Minocycline · N-Acetylcysteine · Riluzole · S-Nitrosoglutathione · Tianeptine · |

*See also: GABAergics • GHBergics • Glycinergics*

v · t · e · **Adrenergic receptor modulators**

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| $\alpha_1$ | *Agonists*: 6-FNE · Amidephrine · Anisodine · Buspirone · Cirazoline · Corbadrine · Dexisometheptene · Dipivefrine · Dopamine · Droxidopa (L-DOPS) · Ephedrine · Epinephrine · Etilefrine · Etilevodopa · Ethylnorepinephrine · Indanidine · Isometheptene · L-DOPA (levodopa) · L-Phenylalanine · L-Tyrosine · Melevodopa · Metaraminol · Methoxamine · Methyldopa · Midodrine · Naphazoline · Norepinephrine · Octopamine (drug) · Oxymetazoline · Phenylephrine · Phenylpropanolamine · Pseudoephedrine · Synephrine · Tetryzoline · Tiamenidine · XP21279 · Xylometazoline · |
| | *Antagonists*: Abanoquil · Adimolol · Ajmalicine · Alfuzosin · Amosulalol · Anisodamine · Arotinolol · Atiprosin · Atypical antipsychotics (e.g., clozapine, olanzapine, quetiapine, risperidone) · Benoxathian · Buflomedil · Bunazosin · Carvedilol · Corynanthine · Dapiprazole · Domesticine · Doxazosin · Ergolines (e.g., ergotamine, dihydroergotamine, lisuride, terguride) · Etoperidone · Eugenodilol · Fenspiride · Hydroxyzine · Indoramin · Ketanserin · L-765,314 · Labetalol · mCPP · Mepiprazole · Metazosin · Monatepil · Moxisylyte · Naftopidil · Nantenine · Nefazodone · Neldazosin · Niaprazine · Nicergoline · Niguldipine · Pardoprunox · Pelanserin · Phendioxan · Phenoxybenzamine · Phentolamine · Piperoxan · Prazosin · Quinazosin · Ritanserin · Silodosin · Spiperone · Talipexole · Tamsulosin · Terazosin · Tiodazosin · Tolazoline · Trazodone · Tetracyclic antidepressants (e.g., amoxapine, maprotiline, mianserin) · Tricyclic antidepressants (e.g., amitriptyline, clomipramine, doxepin, imipramine, trimipramine) · Trimazosin · Typical antipsychotics (e.g., chlorpromazine, fluphenazine, loxapine, thioridazine) · Urapidil · WB-4101 · Zolertine · |
| $\alpha_2$ | *Agonists*: (R)-3-Nitrobiphenyline · 4-NEMD · 6-FNE · Amitraz · Apraclonidine · Brimonidine · Cannabivarin · Clonidine · Corbadrine · Detomidine · Dexmedetomidine · Dihydroergotamine · Dipivefrine · Dopamine · Droxidopa (L-DOPS) · Etilevodopa · Ephedrine · Ergotamine · Epinephrine · Etilefrine · Ethylnorepinephrine · Guanabenz · Guanfacine · Guanoxabenz · L-DOPA (levodopa) · L-Phenylalanine · L-Tyrosine · Lofexidine · Medetomidine · Melevodopa · Methyldopa · Mivazerol · Naphazoline · Norepinephrine · Oxymetazoline · Phenylpropanolamine · Piperoxan · Pseudoephedrine · Rilmenidine · Romifidine · Talipexole · Tetrahydrozoline · Tiamenidine · Tizanidine · Tolonidine · Urapidil · XP21279 · Xylazine · Xylometazoline · |
| | *Antagonists*: 1-PP · Adimolol · Aptazapine · Atipamezole · Atypical antipsychotics (e.g., asenapine, clozapine, lurasidone, paliperidone, quetiapine, risperidone, zotepine) · Azapirones (e.g., buspirone, tandospirone) · BRL-44408 · Buflomedil · Cirazoline · Efaroxan · Esmirtazapine · Fenmetozole · Fluparoxan · Idazoxan · mCPP · Mianserin · Mirtazapine · NAN-190 · Olanzapine · Pardoprunox · Phentolamine · Phenoxybenzamine · Piperoxan · Piribedil · Rauwolscine · Rotigotine · SB-269970 · Setiptiline · Spiroxatrine · Sunepitron · Tolazoline · Typical antipsychotics (e.g., chlorpromazine, fluphenazine, loxapine, thioridazine) · Yohimbine · |
| β | *Agonists*: Abediterol · Alifedrine · Amibegron · Arbutamine · Arformoterol · Arotinolol · BAAM · Bambuterol · Befunolol · Bitolterol · Broxaterol · Buphenine · Carbuterol · Carmoterol · Cimaterol · Clenbuterol · Corbadrine · Denopamine · Dipivefrine · Dobutamine · Dopamine · Dopexamine · Droxidopa (L-DOPS) · Ephedrine · Epinephrine · Etafedrine · Etilefrine · Etilevodopa · Ethylnorepinephrine · Fenoterol · Formoterol · Hexoprenaline · Higenamine · Indacaterol · Isoetarine · Isoprenaline · Isoxsuprine · L-DOPA (levodopa) · L-Phenylalanine · L-Tyrosine · Levosalbutamol · Mabuterol · Melevodopa · Methoxyphenamine · Methyldopa · Mirabegron · Norepinephrine · Orciprenaline · Oxyfedrine · PF-610355 · Phenylpropanolamine · Pirbuterol · Prenalterol · Ractopamine · Procaterol · Pseudoephedrine · Reproterol · Rimiterol · Ritodrine · Salbutamol · Salmeterol · Solabegron · Terbutaline · Tretoquinol · Tulobuterol · Vilanterol · Xamoterol · XP21279 · Zilpaterol · Zinterol · |
| | *Antagonists*: Acebutolol · Adaprolol · Adimolol · Afurolol · Alprenolol · Alprenoxime · Amosulalol · Ancarolol · Arnolol · Arotinolol · Atenolol · Befunolol · Betaxolol · Bevantolol · Bisoprolol · Bopindolol · Bornaprolol · Brefonalol · Bucindolol · Bucumolol · Bufetolol · Bufuralol · Bunitrolol · Bunolol · Bupranolol · Butaxamine · Butidrine · Butofilolol · Capsinolol · Carazolol · Carpindolol · Carteolol · Carvedilol · Celiprolol · Cetamolol · Cicloprolol · Cinamolol · Cloranolol · Cyanopindolol · Dalbraminol · Dexpropranolol · Diacetolol · Dichloroisoprenaline · Dihydroalprenolol · Dilevalol · Diprafenone · Draquinolol · Ecastolol · Epanolol · Ericolol · Ersentilide · Esatenolol · |

Esprolol · Eugenodilol · Exaprolol · Falintolol · Flestolol · Flusoxolol · Hydroxycarteolol · Hydroxytertatolol · ICI-118,551 · Idropranolol · Indenolol · Indopanolol · Iodocyanopindolol · Iprocrolol · Isoxaprolol · Isamoltane · Labetalol · Landiolol · Levobetaxolol · Levobunolol · Levomoprolol · Medroxalol · Mepindolol · Metipranolol · Metoprolol · Moprolol · Nadolol · Nadoxolol · Nebivolol · Nifenalol · Nipradilol · Oxprenolol · Pacrinolol · Pafenolol · Pamatolol · Pargolol · Penbutolol · Pindolol · Practolol · Primidolol · Procinolol · Pronethalol · Propafenone · Propranolol · Ridazolol · Ronactolol · Soquinolol · Sotalol · Spirendolol · SR 59230A · Sulfinalol · Talinolol · Tazolol · Tertatolol · Tienoxolol · Tilisolol · Timolol · Tiprenolol · Tolamolol · Toliprolol · Xibenolol · Xipranolol ·

*See also:* *Dopaminergics* · *Melatonergics* · *Serotonergics* · *Monoamine reuptake and release modulators* · *Monoamine metabolism modulators* · *Monoamine neurotoxins* ·

**Authority control** LCCN: sh92004206 · GND: 4163657-0 ·

Categories: Antidepressants | Amines | Dissociative drugs | Euphoriants | General anesthetics | Ketones | Mood stabilizers | NMDA receptor antagonists | Glycine receptor agonists | Nicotinic antagonists | Muscarinic antagonists | Mu-opioid agonists | Kappa agonists | Delta-opioid agonists | Sigma agonists | Sodium channel blockers | Calcium channel blockers | Serotonin-norepinephrine-dopamine reuptake inhibitors | Chloroarenes | Sedatives | World Health Organization essential medicines

# Levofloxacin

From Wikipedia, the free encyclopedia

**Levofloxacin**, sold under the trade names **Levaquin** among others, is an antibiotic.[2] It is used to treat a number of bacterial infections including acute bacterial sinusitis, pneumonia, urinary tract infections, chronic prostatitis, and some types of gastroenteritis. Along with other antibiotics it may be used to treat tuberculosis, meningitis, or pelvic inflammatory disease. It is available by mouth or intravenously.[2]

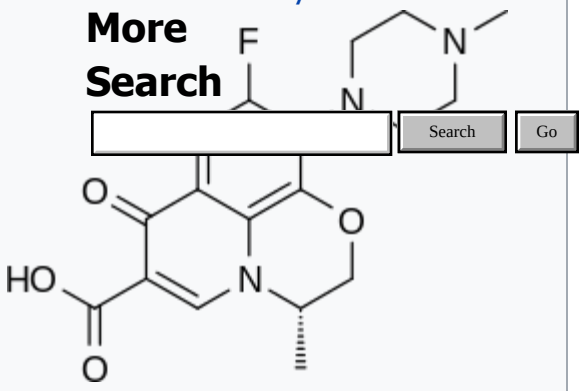
Common side effects include nausea, diarrhea, and trouble sleeping. Serious side effects may include tendon rupture, tendon inflammation, seizures, psychosis, and potentially permanent peripheral nerve damage. Tendon damage may appear months after treatment is completed. People may also sunburn more easiiy. In people with myasthenia gravis, muscle weakness and breathing problems may worsen.[2] The risk of use during pregnancy is low and it is probably okay during breastfeeding. Levofloxacin is a broad-spectrum antibiotic of the fluoroquinolone drug class.[3] It usually results in death of the bacteria.[2] It is the left sided isomer of the medication ofloxacin.[3]

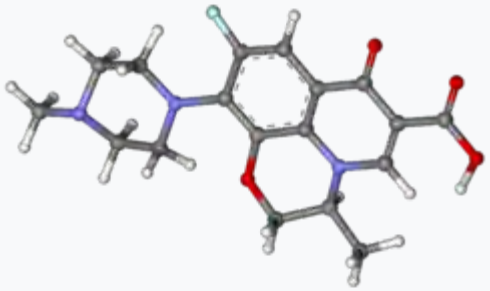
Levofloxacin was approved for medical use in the United States in 1996.[2] It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[4] It is available as a generic medication.[2] The wholesale cost in the developing world is about 0.44 to 0.95 USD per week of treatment.[5] In the United States a week of treatment cost about 50 to 100 USD.[6]

Contents



**Levofloxacin**





| Clinical data | |
|---|---|
| **Trade names** | Levaquin, Tavanic, Iquix, others |
| **AHFS/Drugs.com** | Monograph |
| **MedlinePlus** | a697040 |
| **License data** | US FDA: Levofloxacin |
| **Pregnancy category** | US: C (Risk not ruled out) |
| **Routes of administration** | By mouth, IV, eye drops |
| **ATC code** | J01MA12 (WHO) S01AE05 (WHO) |
| **Legal status** | |
| **Legal status** | (Prescription only) |
| **Pharmacokinetic data** | |
| **Bioavailability** | 99%[1] |

## Medical uses [edit]

Levofloxacin is used to treat infections including: respiratory tract infections, cellulitis, urinary tract infections, prostatitis, anthrax, endocarditis, meningitis, pelvic inflammatory disease, traveler's diarrhea, tuberculosis, and plague.[2][7]

As of 2016, the US Food and Drug Administration (FDA) recommended that "serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options."[8]

Levofloxacin is used for the treatment of pneumonia, urinary tract infections, and abdominal infections. As of 2007 the Infectious Disease Society of America (IDSA) and the American Thoracic Society recommended levofloxacin and other respiratory fluoroquinolines as first line treatment for community acquired pneumonia when co-morbidities such as heart, lung, or liver disease are present or when in-patient treatment is required.[9] Levofloxacin also plays an important role in recommended treatment regimens for ventilator-associated and healthcare-associated pneumonia.[10]

As of 2010 it was recommended by the IDSA as a first-line treatment option for catheter-associated urinary tract infections in adults.[11] In combination with metronidazole it is recommended as one of several first-line treatment options for adult patients with community-acquired intra-abdominal infections of mild-to-moderate severity.[12] The IDSA also recommends it in combination with rifampicin as a first-line treatment for prosthetic joint infections.[13] The American Urological Association recommends levofloxacin as a first-line treatment to prevent bacterial prostatitis when the prostate is biopsied.[14] and as of 20054 it was recommended to treat bacterial prostatitis by the NIH research network studying the condition.[15]

Levofloxacin and other fluoroquinolones have also been widely used for the treatment of uncomplicated community-acquired respiratory and urinary tract infections, indications for which major medical societies generally recommend the use of older, narrower spectrum drugs to avoid fluoroquinolone resistance development. Due to its widespread use, common pathogens such as *Escherichia coli* and *Klebsiella pneumoniae* have developed resistance. In many countries as of 2013, resistance rates among healthcare-associated infections with these pathogens exceeded 20%.[16][17]

## Pregnancy and breastfeeding [edit]

[7]

| | |
|---|---|
| **Protein binding** | 31%[1] |
| **Metabolism** | <5% desmethyl and N-oxide metabolites |
| **Biological half-life** | 6.9 hours[1] |
| **Excretion** | Renal, mostly unchanged (83%)[1] |

**Identifiers**

**IUPAC name**

(*S*)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-7*H*-pyrido[*1,2,3-de*]-1,4-benzoxazine-6-carboxylic acid

| | |
|---|---|
| **CAS Number** | 100986-85-4 ✓ |
| **PubChem** (CID) | 149096 |
| **DrugBank** | DB01137 ✓ |
| **ChemSpider** | 131410 ✓ |
| **UNII** | RIX4E89Y14 ✗ |
| **KEGG** | D08120 ✓ |
| **ChEMBL** | CHEMBL33 ✓ |
| **NIAID ChemDB** | 002307 |
| **ECHA InfoCard** | 100.115.581 |

**Chemical and physical data**

| | |
|---|---|
| **Formula** | $C_{18}H_{20}FN_3O_4$ |
| **Molar mass** | 361.368 g/mol |
| **3D model (Jmol)** | Interactive image |

**SMILES**

C[C@H]1COc2c3n1cc(c(=O)c3cc(c2N4CCN(CC4)C)F)C(=O)O

**InChI**

InChI=1S/C18H20FN3O4/c1-10-9-26-17-14-11(16(23)12(18(24)25)8-22(10)14)7-13(19)15(17)21-5-3-20(2)4-6-21/h7-8,10H,3-6,9H2,1-2H3,(H,24,25)/t10-/m0/s1 ✓

Key:GSDSWSVVBLHKDQ-JTQLQIEISA-N ✓

✗✓ (what is this?) (verify)

According to the FDA approved prescribing information, levofloxacin is pregnancy category C. This designation indicates that animal reproduction studies have shown adverse effects on the fetus and there are no adequate and well-controlled studies in humans, but the potential benefit to the mother may in some cases outweigh the risk to the fetus. Other fluoroquinolones have also been reported as being present in the mother's milk and are passed on to the nursing child.[18][19]

It is not known if levofloxacin is released in mother's milk, but other fluoroquinolones are.[7] Due to potential risks to the baby, levofloxacin is not recommended in nursing mothers.[7]

## Children [edit]

Levofloxacin is not approved in most countries for the treatment of children except in unique and life-threatening infections because it is associated with an elevated risk of musculoskeletal injury in this population, a property it shares with other fluoroquinolones.

In the United States levofloxacin is approved for the treatment of anthrax and plague in children over six months of age.[7]

Levofloxacin is recommended by the Pediatric Infectious Disease Society and the Infectious Disease Society of America as a first-line treatment for pediatric pneumonia caused by penicillin-resistant *Streptococcus pneumoniae*, and as a second-line agent for the treatment of penicillin-sensitive cases.[20]

In one study,[7][21] 1534 juvenile patients (age 6 months to 16 years) treated with levofloxacin as part of three efficacy trials were followed up to assess all musculoskeletal events occurring up to 12 months post-treatment. At 12 months follow-up the cumulative incidence of musculoskeletal adverse events was 3.4%, compared to 1.8% among 893 patients treated with other antibiotics. In the levafloxacin-treated group, approximately two-thirds of these musculoskeletal adverse events occurred in the first 60 days, 86% were mild, 17% were moderate, and all resolved without long-term sequelae.

## Spectrum of activity [edit]

Levofloxacin and later generation fluoroquinolones are collectively referred to as "respiratory quinolones" to distinguish them from earlier fluoroquinolones which exhibited modest activity toward the important respiratory pathogen *Streptococcus pneumoniae*.[22]

The drug exhibits enhanced activity against the important respiratory pathogen *Streptococcus pneumoniae* relative to earlier fluoroquinolone derivatives like ciprofloxacin. For this reason, it is considered a "respiratory fluoroquinolone" along with more recently developed fluoroquinolones such as moxifloxacin and gemifloxacin. It is less active than ciprofloxacin against Gram-negative bacteria, especially *Pseudomonas aeruginosa*, and lacks the anti-methicillin-resistant *Staphylococcus aureus* (MRSA) activity of moxifloxacin and gemifloxacin.[23][24][25][26] Levofloxacin has shown moderate activity against anaerobes, and is about twice as potent as ofloxacin against *Mycobacterium tuberculosis* and other mycobacteria, including *Mycobacterium avium* complex.[27]

Its spectrum of activity includes most strains of bacterial pathogens responsible for respiratory, urinary tract, gastrointestinal, and abdominal infections, including Gram negative (*Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*), Gram positive (methicillin-sensitive but not methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Streptococcus pyogenes*), and atypical bacterial pathogens (*Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*). Compared to earlier antibiotics of the fluoroquinoline class such as ciprofloxacin, levofloxacin exhibits greater activity towards Gram-positive bacteria[23] but lesser activity toward Gram-negative bacteria,[28] especially *Pseudomonas aeruginosa*.

## Availability [edit]

Levofloxacin is available in tablet form, injection, and oral solution.[7]

Levofloxacin and NaCl injection, specification is 100mL / 750mg

## Contraindications and drug interactions [edit]

Package inserts mention that levofloxacin is to be avoided in patients with a known hypersensitivity to levofloxacin or other quinolone drugs.[7][29]

Like all fluoroquinolines, levofloxacin is contraindicated in patients with epilepsy or other seizure disorders, and in patients who have a history of quinolone-associated tendon rupture.[7][29]

Levofloxacin may prolong the QT interval in some people, especially older ones, and levofloxacin should not be used for people with a family history of Long QT syndrome, or who have long QT, chronic low potassium,it should not be prescribed with other drugs that prolong the QT interval.[7]

Unlike ciprofloxacin, levofloxacin does not appear to deactivate the drug metabolizing enzyme CYP1A2. Therefore, drugs that use that enzyme, like theophylline, do not interact with levofloxacin. It is a weak inhibitor of CYP2C9,[30] suggesting potential to block the breakdown of warfarin and phenprocoumon. This can result in more action of drugs like warfarin, leading to more potential side effects, such as bleeding.[31]

The use of non-steroidal anti-inflammatory drugs (NSAIDs) in combination with high dose fluoroquinolone therapy may lead to seizures.[32]

When levofloxacin is taken with anti-acids containing magnesium hydroxide or aluminum hydroxide, the two combine to form insoluble salts that are difficult to absorb from the intestines. Peak serum concentrations of levofloxacin may be reduced by 90% or more, which can prevent the levofloxacin from working. Similar results have been reported when levofloxacin is taken with iron supplements and multi-vitamins containing zinc.[33][34]

A 2011 review examining musculoskeletal complications of fluoroquinolones proposed guidelines with respect to administration to athletes, that called for avoiding all use of fluoroquinolone antibiotics if possible, and if they are used: ensure there is informed consent about the musculoskeletal risks, and inform coaching staff; do not use any corticosteroids if fluoroquinolones are used; consider dietary supplements of magnesium and antioxidants during treatment; reduce training until the course of antibiotic is finished and then carefully increase back to normal; and monitor for six months after the course is finished, and stop all athletic activity if symptoms emerge.[35]

## Adverse effects [edit]

While typical drug side effects reactions are mild to moderate; sometimes serious adverse effects occur.

Prominent among these are side effects that became the subject of a black box warning by the FDA in 2016.[8] The FDA wrote: "An FDA safety review has shown that fluoroquinolones when used systemically (i.e. tablets, capsules, and injectable) are associated with disabling and potentially permanent serious side effects that can occur together. These side effects can involve the tendons, muscles, joints, nerves, and central nervous system."[8] Such injuries, including tendon rupture, has been observed up to 6 months after cessation of treatment; the elderly, transplant patients, and those with a current or historical corticosteroid use are at elevated risk.[36] A detailed overview of risk factors for fluoroquinolone-associated tendon rupture has been published; advanced age, concurrent treatment with corticosteroids, and higher doses of fluoroquinolone appear to be the most important risk factors.[37] The U.S. label for levofloxacin also contains a black box warning for the exacerbation of the symptoms of the neurological disease myasthenia gravis.[7][38]

Increasing age and concomitant corticosteroid use appears to increase the risk of musculoskeletal complications.[35]

A wide variety of other uncommon but serious adverse events have been associated with fluoroquinolone use, with varying degrees of evidence supporting causation. These include anaphylaxis, hepatotoxicity, central nervous system effects including seizures and psychiatric effects, prolongation of the QT interval, blood glucose disturbances, and photosensitivity, among others.[7][29] Levofloxacin may produce fewer of these rare serious adverse effects than other fluoroquinolones.[39]

There is some disagreement in the medical literature regarding whether and to what extent levofloxacin and other fluoroquinolones produce serious adverse effects more frequently than other broad spectrum antibacterial drugs.[40][41][42][43]

With regard to more usual side effects, in pooled results from 7537 patients exposed to levofloxcacin in 29 clinical trials, 4.3% discontinued treatment due to adverse drug reactions. The most common adverse reactions leading to discontinuation were gastrointestinal, including nausea, vomiting, and constipation. Overall, 7% of patients experienced nausea, 6% headache, 5% diarrhea, 4% insomnia, along with other adverse reactions experienced at lower rates.[7]

Administration of levofloxacin or other broad spectrum antibiotics is associated with *Clostridium difficile* associated diarrhea which may range in severity from mild diarrhea to fatal colitis. Fluoroquinoline administration may be associated with the acquisition and outgrowth of a particularly virulent *Clostridium* strain.[44]

## Overdose [edit]

Overdosing experiments in animals showed loss of body control and drooping, difficulty breathing, tremors, and convulsions. Doses in excess of 1500 mg/kg orally and 250 mg/kg IV produced significant mortality in rodents.[7]

In the event of an acute overdosage, authorities recommend unspecific standard procedures such as emptying the stomach, observing the patient and maintaining appropriate hydration. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.[7]

## Mechanism of action [edit]

Levofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. Like all quinolones, it functions by inhibiting the two type II topoisomerase enzymes, namely DNA gyrase and topoisomerase IV.[45] Topoisomerase IV is necessary to separate DNA that has been replicated (doubled) prior to bacterial cell division. With the DNA not being separated, the process is stopped, and the bacterium cannot divide. DNA gyrase, on the other hand, is responsible for supercoiling the DNA, so that it will fit in the newly formed cells. Both mechanisms amount to killing the bacterium. In this way, levofloxacin acts as a bactericide.[46]

As of 2011 the mechanism of action for the drug's musculoskeletal complications were not clear.[35]

## Chemical properties [edit]

Levofloxacin is the levo isomer of the racemate ofloxacin, another quinolone antimicrobial agent.[47] In layman terms, this means that levofloxacin is the 50% of ofloxacin that have been found to be effective against bacteria, while the other 50% have been removed. In chemical terms, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (−)-(*S*)-enantiomer of the racemic ofloxacin.[48][49]

The substance is used as the hemihydrate, which has the empirical formula $C_{18}H_{20}FN_3O_4 \cdot ½\ H_2O$ and a molecular mass of 370.38 g/mol. Levofloxacin is a light-yellowish-white to yellow-white crystal or crystalline

powder.[7]

## Pharmacokinetics [edit]

Levofloxacin is rapidly and essentially completely absorbed after oral administration, with a plasma concentration profile over time that is essentially identical to that obtained from intravenous administration of the same amount over 60 minutes. As such, the intravenous and oral formulations of levofloxacin are considered interchangeable.[7]

The drug undergoes widespread distribution into body tissues. Peak levels in skin are achieved 3 hours after administration and exceed those in plasma by a factor of 2. Similarly, lung tissue concentrations range from two-fold to five-fold higher than plasma concentrations in the 24 hours after a single dose.

The mean terminal plasma elimination half-life of levofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levofloxacin given orally or intravenously. Elimination occurs mainly via excretion of unmetabolized drug in the urine. Following oral administration, 87% of an administered dose was recovered in the urine as unchanged drug within 2 days. Less than 5% was recovered in the urine as the desmethyl and N-oxide metabolites, the only metabolites identified in humans.

## History [edit]

Levofloxacin is a second-generation fluoroquinolone, being one of the isomers of ofloxacin, which was a broader-spectrum analog of norfloxacin; both Ofloxacin and levofloxaxin were synthesized and developed by scientists at Daiichi Seiyaku.[50] The Daiichi scientists knew that ofloxacin was racemic, but tried unsuccessfully to separate the two isomers; in 1985 they succeeded in separately synthesizing the pure levo form and showed that it was less toxic and more potent than the other form.[51][52]

It was first approved for marketing in Japan in 1993 for oral administration, and Daiichi marketed it there under the brand name Cravit.[52] Daiichi, working with Johnson & Johnson as it had with ofloxacin, obtained FDA approval in 1996 under the brand name Levaquin[51] to treat bacterial sinusitus, bacterial exacerbations of bronchitis, community-acquired pneumonia, uncomplicated skin infections, complicated urinary tract infections, and acute pyelonephritis.[7]

Levofloxacin is marketed by Sanofi-Aventis under a license agreement signed with Daiichi in 1993 under the trade name "Tavanic".[53]

Levofloxacin had reached blockbuster status by this time; worldwide sales for J&J alone were US$1.6 billion in 2009.[53]

The term of the levofloxacin United States patent was extended by the U.S. Patent and Trademark Office 810 days under the provisions of the Hatch Waxman Amendment so that the patent would expire in 2010 instead of 2008.[51] This extension was challenged by generic drug manufacturer Lupin Pharmaceuticals, which did not challenge the validity of the patent, but only the validity of the patent extension, arguing that the patent did not cover a "product" and so Hatch-Waxman was not available for extensions.[51] The federal patent court ruled in favor of J&J and Daiichi, and generic versions of levofloxacin did not enter the U.S. market until 2009.[51][53]

## Society and culture [edit]

### Usage [edit]

The FDA estimated that in 2011 over 23 million outpatient prescriptions for fluoroquinolones, of which levofloxacin made up 28%, were filled in the United States.[54]

## Litigation [edit]

As of 2012, Johnson and Johnson was facing around 3400 state and federal lawsuits filed by people who claimed tendon damage from levofloxacin; about 1900 pending in a class action at the United States District Court in Minnesota[55] and about 1500 pending at a district court in New Jersey.[56][57]

In October 2012, J&J settled 845 cases in the Minnesota action, after Johnson and Johnson prevailed in three of the first four cases to go to trial. By May 2014, all but 363 cases had been settled or adjudicated.[57][58][59]

# References [edit]


1. ^ *a b c d* Zhanel GG, Fontaine S, Adam H, Schurek K, Mayer M, Noreddin AM, Gin AS, Rubinstein E, Hoban DJ (2006). "A Review of New Fluoroquinolones : Focus on their Use in Respiratory Tract Infections". *Treat Respir Med*. **5** (6): 437–65. PMID 17154673.
2. ^ *a b c d e f g* "Levofloxacin". The American Society of Health-System Pharmacists. Retrieved August 25, 2016.
3. ^ *a b* Yaffe, Gerald G. Briggs, Roger K. Freeman, Sumner J. (2011). *Drugs in pregnancy and lactation : a reference guide to fetal and neonatal risk* (9th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 828. ISBN 9781608317080.
4. ^ "WHO Model List of EssentialMedicines" (PDF). *World Health Organization*. October 2013. Retrieved 22 April 2014.
5. ^ "Levofloxacin". *International Drug Price Indicator Guide*. Retrieved August 25, 2016.
6. ^ Hamilton, Richart (2015). *Tarascon Pocket Pharmacopoeia 2015 Deluxe Lab-Coat Edition*. Jones & Bartlett Learning. p. 102. ISBN 9781284057560.
7. ^ *a b c d e f g h i j k l m n o p q r* "US Label" (PDF). 2016.
8. ^ *a b c* "FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur". US Department of Health and Human Services. US Food and Drug Administration. 25 August 2016.
9. ^ Mandell LA, Wunderink RG, Anzueto A, et al. (March 2007). "Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults". *Clin. Infect. Dis.* 44 Suppl 2: S27–72. doi:10.1086/511159. PMID 17278083.
10. ^ File TM (August 2010). "Recommendations for treatment of hospital-acquired and ventilator-associated pneumonia: review of recent international guidelines". *Clin. Infect. Dis.* 51 Suppl 1: S42–7. doi:10.1086/653048. PMID 20597671.
11. ^ Hooton TM, Bradley SF, Cardenas DD, et al. (March 2010). "Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America". *Clin. Infect. Dis.* **50** (5): 625–63. doi:10.1086/650482. PMID 20175247.
12. ^ Solomkin JS, Mazuski JE, Bradley JS, et al. (January 2010). "Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America". *Clin. Infect. Dis.* **50** (2): 133–64. doi:10.1086/649554. PMID 20034345.
13. ^ Osmon DR, Berbari EF, Berendt AR, et al. (January 2013). "Executive summary: diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America". *Clin. Infect. Dis.* **56** (1): 1–10. doi:10.1093/cid/cis966. PMID 23230301.
14. ^ American Urological Association. 2016 The Prevention and Treatment of the More Common Complications Related to Prostate Biopsy Update
15. ^ Schaeffer AJ (September 2004). "NIDDK-sponsored chronic prostatitis collaborative research network (CPCRN) 5-year data and treatment guidelines for bacterial prostatitis". *Int. J. Antimicrob. Agents*. 24 Suppl 1: S49–52. doi:10.1016/j.ijantimicag.2004.02.009. PMID 15364307.
16. ^ ECDC (2014). "Antimicrobial resistance surveillance in Europe 2014" (PDF).
17. ^ CDC. "Antibiotic Resistance Threats in the United States, 2013" (PDF).
18. ^ Shin HC, Kim JC, Chung MK (September 2003). "Fetal and maternal tissue distribution of the new fluoroquinolone DW-116 in pregnant rats". *Comp. Biochem. Physiol. C Toxicol. Pharmacol*. **136** (1): 95–102. doi:10.1016/j.cca.2003.08.004. PMID 14522602.
19. ^ Dan M, Weidekamm E, Sagiv R, Portmann R, Zakut H (February 1993). "Penetration of fleroxacin into breast milk and pharmacokinetics in lactating women". *Antimicrob. Agents Chemother*. **37** (2): 293–6. doi:10.1128/AAC.37.2.293. PMC 187655. PMID 8452360.
20. ^ Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, Kaplan SL, Mace SE, McCracken GH, Moore

MR, St Peter SD, Stockwell JA, Swanson JT (2011). "The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America". *Clin. Infect. Dis.* **53** (7): e25–76. doi:10.1093/cid/cir531. PMID 21880587.

21. ^ Noel GJ, Bradley JS, Kauffman RE (October 2007). "Comparative safety profile of levofloxacin in 2523 children with a focus on four specific musculoskeletal disorders". *Pediatr. Infect. Dis. J.* **26** (10): 879–91. doi:10.1097/INF.0b013e3180cbd382. PMID 17901792.
22. ^ Wispelwey B, Schafer KR (November 2010). "Fluoroquinolones in the management of community-acquired pneumonia in primary care". *Expert Rev Anti Infect Ther*. **8** (11): 1259–71. doi:10.1586/eri.10.110. PMID 21073291.
23. ^ *a b* Lafredo SC, Foleno BD, Fu KP (1993). "Induction of resistance of Streptococcus pneumoniae to quinolones in vitro". *Chemotherapy*. **39** (1): 36–9. doi:10.1159/000238971. PMID 8383031.
24. ^ Fu KP, Lafredo SC, Foleno B, et al. (April 1992). "In vitro and in vivo antibacterial activities of levofloxacin (l-ofloxacin), an optically active ofloxacin". *Antimicrob. Agents Chemother*. **36** (4): 860–6. doi:10.1128/aac.36.4.860. PMC 189464. PMID 1503449.
25. ^ Blondeau JM (May 1999). "A review of the comparative in-vitro activities of 12 antimicrobial agents, with a focus on five new respiratory quinolones'". *J. Antimicrob. Chemother*. 43 Suppl B (90002): 1–11. doi:10.1093/jac/43.suppl_2.1. PMID 10382869.
26. ^ Cormican MG, Jones RN (January 1997). "Antimicrobial activity and spectrum of LB20304, a novel fluoronaphthyridone". *Antimicrob. Agents Chemother*. **41** (1): 204–11. PMC 163688. PMID 8980783.
27. ^ John A. Bosso (1998). "New and Emerging Quinolone Antibiotics". *Journal of Infectious Disease Pharmacotherapy*. **2** (4): 61–76. doi:10.1300/J100v02n04_06. ISSN 1068-7777.
28. ^ Yamane N, Jones RN, Frei R, Hoban DJ, Pignatari AC, Marco F (April 1994). "Levofloxacin in vitro activity: results from an international comparative study with ofloxacin and ciprofloxacin". *J Chemother*. **6** (2): 83–91. PMID 8077990.
29. ^ *a b c* UK electronic Medicines Compendium (eMC) Levofloxacin 250mg and 500mg Tablets. Last revised in July 2013
30. ^ Zhang L, Wei MJ, Zhao CY, Qi HM (December 2008). "Determination of the inhibitory potential of 6 fluoroquinolones on CYP1A2 and CYP2C9 in human liver microsomes". *Acta Pharmacol. Sin*. **29** (12): 1507–14. doi:10.1111/j.1745-7254.2008.00908.x. PMID 19026171.
31. ^ Schelleman H, Bilker WB, Brensinger CM, Han X, Kimmel SE, Hennessy S (November 2008). "Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: interactions and the risk of hospitalization for gastrointestinal bleeding". *Clin. Pharmacol. Ther*. **84** (5): 581–8. doi:10.1038/clpt.2008.150. PMC 2574587. PMID 18685566.
32. ^ Domagala JM (April 1994). "Structure-activity and structure-side-effect relationships for the quinolone antibacterials". *J. Antimicrob. Chemother*. **33** (4): 685–706. doi:10.1093/jac/33.4.685. PMID 8056688.
33. ^ Rodvold KA, Piscitelli SC (August 1993). "New oral macrolide and fluoroquinolone antibiotics: an overview of pharmacokinetics, interactions, and safety". *Clin. Infect. Dis*. 17 Suppl 1: S192–9. doi:10.1093/clinids/17.supplement_1.s192. PMID 8399914.
34. ^ Tanaka M, Kurata T, Fujisawa C, et al. (October 1993). "Mechanistic study of inhibition of levofloxacin absorption by aluminum hydroxide". *Antimicrob. Agents Chemother*. **37** (10): 2173–8. doi:10.1128/aac.37.10.2173. PMC 192246. PMID 8257141.
35. ^ *a b c* Hall, MM; Finnoff, JT; Smith, J (February 2011). "Musculoskeletal complications of fluoroquinolones: guidelines and precautions for usage in the athletic population.". *PM & R : the journal of injury, function, and rehabilitation*. **3** (2): 132–42. doi:10.1016/j.pmrj.2010.10.003. PMID 21333952.
36. ^ Khaliq Y, Zhanel GG (June 2003). "Fluoroquinolone-associated tendinopathy: a critical review of the literature". *Clin. Infect. Dis*. **36** (11): 1404–10. doi:10.1086/375078. PMID 12766835.
37. ^ Kim GK (April 2010). "The Risk of Fluoroquinolone-induced Tendinopathy and Tendon Rupture: What Does The Clinician Need To Know?". *J Clin Aesthet Dermatol*. **3** (4): 49–54. PMC 2921747. PMID 20725547.
38. ^ Jones SC, Sorbello A, Boucher RM (October 2011). "Fluoroquinolone-associated myasthenia gravis exacerbation: evaluation of postmarketing reports from the US FDA adverse event reporting system and a literature review". *Drug Saf*. **34** (10): 839–47. doi:10.2165/11593110-000000000-00000. PMID 21879778.
39. ^ Carbon C (2001). "Comparison of side effects of levofloxacin versus other fluoroquinolones". *Chemotherapy*. 47 Suppl 3 (3): 9–14; discussion 44–8. doi:10.1159/000057839. PMID 11549784.
40. ^ Liu HH (May 2010). "Safety profile of the fluoroquinolones: focus on levofloxacin". *Drug Saf*. **33** (5): 353–69. doi:10.2165/11536360-000000000-00000. PMID 20397737.
41. ^ Karageorgopoulos DE, Giannopoulou KP, Grammatikos AP, Dimopoulos G, Falagas ME (March 2008). "Fluoroquinolones compared with beta-lactam antibiotics for the treatment of acute bacterial sinusitis: a meta-analysis of randomized controlled trials". *CMAJ*. **178** (7): 845–54. doi:10.1503/cmaj.071157. PMC 2267830.

PMID 18362380.
42. ^ Lipsky BA, Baker CA (February 1999). "Fluoroquinolone toxicity profiles: a review focusing on newer agents". *Clin. Infect. Dis.* **28** (2): 352–64. doi:10.1086/515104. PMID 10064255.
43. ^ Stahlmann R, Lode HM (July 2013). "Risks associated with the therapeutic use of fluoroquinolones". *Expert Opin Drug Saf.* **12** (4): 497–505. doi:10.1517/14740338.2013.796362. PMID 23651367.
44. ^ Vardakas KZ, Konstantelias AA, Loizidis G, Rafailidis PI, Falagas ME (November 2012). "Risk factors for development of Clostridium difficile infection due to BI/NAP1/027 strain: a meta-analysis". *Int. J. Infect. Dis.* **16** (11): e768–73. doi:10.1016/j.ijid.2012.07.010. PMID 22921930.
45. ^ Drlica K, Zhao X (1 September 1997). "DNA gyrase, topoisomerase IV, and the 4-quinolones". *Microbiol Mol Biol Rev.* **61** (3): 377–92. PMC 232616. PMID 9293187.
46. ^ Mutschler, Ernst; Schäfer-Korting, Monika (2001). *Arzneimittelwirkungen* (in German) (8 ed.). Stuttgart: Wissenschaftliche Verlagsgesellschaft. p. 814f. ISBN 3-8047-1763-2.
47. ^ "STATISTICAL REVIEW AND EVALUATION" (PDF). USA: FDA. 21 November 1996.
48. ^ Morrissey, I.; Hoshino, K.; Sato, K.; Yoshida, A.; Hayakawa, I.; Bures, MG.; Shen, LL. (August 1996). "Mechanism of differential activities of ofloxacin enantiomers" (PDF). *Antimicrob Agents Chemother.* **40** (8): 1775–84. PMC 163416. PMID 8843280.
49. ^ Kannappan, Valliappan; Mannemala, Sai Sandeep (7 June 2014). "Multiple Response Optimization of a HPLC Method for the Determination of Enantiomeric Purity of S-Ofloxacin". *Chromatographia.* **77** (17–18): 1203–1211. doi:10.1007/s10337-014-2699-4.
50. ^ Walter Sneader (31 October 2005). *Drug Discovery: A History*. John Wiley & Sons. p. 295. ISBN 978-0-470-01552-0.
51. ^ *a b c d e* Staff, Fish and Richardson. memorANDA, Q2, 2009 p. VIII. Cites US Patent 5,053,407
52. ^ *a b* S Atarashi from Daiichi. Research and Development of Quinolones in Daiichi Sankyo Co., Ltd. Page accessed August 25, 2016
53. ^ *a b c* Katie Taylor (October 2010). "Drug In Focus: Levofloxacin". *GenericsWeb*.
54. ^ "FDA Drug Safety Communication: FDA requires label changes to warn of risk for possibly permanent nerve damage from antibacterial fluoroquinolone drugs taken by mouth or by injection". US Department of Health and Human Services. US Food and Drug Administration. 16 January 2016.
55. ^ Judge John R. Tunheim. "Levaquin MDL". USA: US Courts. Retrieved 7 September 2009.
56. ^ Charles Toutant (6 July 2009). "Litigation Over Johnson & Johnson Antibiotic Levaquin Designated N.J. Mass Tort". New Jersey Law Journal.
57. ^ *a b* Margaret Cronin Fisk and Beth Hawkins for Bloomberg News. Nov 1, 2012 Johnson & Johnson Settles 845 Levaquin Lawsuits
58. ^ "Johnson & Johnson Settles 845 Levaquin Lawsuits - Businessweek".
59. ^ "Levaquin MDL | United States District Court - District of Minnesota, United States District Court - District of Minnesota".

## External links [edit]

- Levofloxacin at DMOZ
- U.S. National Library of Medicine: Drug Information Portal – Levofloxacin

| v · t · e · | Antibacterials: nucleic acid inhibitors (J01E, J01M) | | |
|---|---|---|---|
| Antifolates (inhibits | DHFR inhibitor | 2,4-Diaminopyrimidine (Trimethoprim# · Brodimoprim · Tetroxoprim · Iclaprim† · · | |
| | | Short-acting | Sulfaisodimidine · Sulfamethizole · Sulfadimidine · Sulfapyridine · Sulfafurazole · Sulfanilamide (Prontosil · · Sulfathiazole · Sulfathiourea · |
| | | Intermediate-acting | Sulfamethoxazole · Sulfadiazine# · Sulfamoxole · |

| | | | |
|---|---|---|---|
| **purine metabolism, thereby inhibiting DNA and RNA synthesis)** | **Sulfonamides (DHPS inhibitor)** | **Long-acting** | Sulfadimethoxine · Sulfadoxine · Sulfalene · Sulfametomidine · Sulfametoxydiazine · Sulfamethoxypyridazine · Sulfaperin · Sulfamerazine · Sulfaphenazole · Sulfamazone · |
| | | **Other/ungrouped** | Sulfacetamide · Sulfadicramide · Sulfametrole · |
| | **Combinations** | Trimethoprim/sulfamethoxazole[#] · | |
| **Topoisomerase inhibitors/ quinolones/ (inhibits DNA replication)** | **Fluoro-quinolones** | **1st g.** | Cinoxacin[‡] · Flumequine[‡] · Nalidixic acid[‡] · Oxolinic acid[‡] · Pipemidic acid[‡] · Piromidic acid[‡] · Rosoxacin[‡] · |
| | | **2nd g.** | Ciprofloxacin[#] · Ofloxacin · Enoxacin[‡] · Fleroxacin[‡] · Lomefloxacin[‡] · Nadifloxacin[‡] · Norfloxacin[‡] · Pefloxacin[‡] · Rufloxacin[‡] · |
| | | **3rd g.** | **Levofloxacin** · Balofloxacin[‡] · Grepafloxacin[‡] · Pazufloxacin[‡] · Sparfloxacin[‡] · Temafloxacin[‡] · Tosufloxacin[‡] · |
| | | **4th g.** | Besifloxacin · Gatifloxacin · Finafloxacin · Gemifloxacin · Moxifloxacin · Clinafloxacin[†] · Garenoxacin[‡] · Prulifloxacin[‡] · Sitafloxacin[‡] · Trovafloxacin[‡]/Alatrofloxacin[‡] · |
| | | **Vet.** | Danofloxacin · Difloxacin · Enrofloxacin · Ibafloxacin · Marbofloxacin · Orbifloxacin · Pradofloxacin · Sarafloxacin · |
| | **Newer non-fluorinated** | Nemonoxacin · | |
| | **Related (DG)** | Aminocoumarins: Novobiocin · | |
| **Anaerobic DNA inhibitors** | **Nitro- imidazole derivatives** | Metronidazole[#] · Tinidazole · Ornidazole · | |
| | **Nitrofuran derivatives** | Nitrofurantoin[#] · Furazolidone[‡] · Nifurtoinol · | |
| **RNA synthesis** | **Rifamycins/ RNA polymerase** | Rifampicin[#] · Rifabutin · Rifapentine · Rifaximin · Rifalazil[§] · | |

[#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III · ·

| v · t · e · **GABAergics** | | |
|---|---|---|
| | **Agonists** | (+)-Catechin · Bamaluzole · Barbiturates (e.g., phenobarbital) · BL-1020 · DAVA · Dihydromuscimol · GABA · Gabamide · GABOB · Gaboxadol (THIP) · Homotaurine (tramiprosate, 3-APS) · Ibotenic acid · iso-THAZ · iso-THIP · Isoguvacine · Isomuscimol · Isonipecotic acid · Kojic amine · Lignans (e.g., honokiol) · Monastrol · Muscimol · Neuroactive steroids (e.g., allopregnanolone) · Org 20599 · Phenibut · Picamilon · P4S · Progabide · Propofol · Quisqualamine · SL-75102 · TACA · TAMP · Terpenoids (e.g., borneol) · Thiomuscimol · Tolgabide · ZAPA · |

| | | | |
|---|---|---|---|
| **Receptor** (**ligands**) | **$GABA_A$** | **PAMs** | *(Abridged; see here for a full list)*: α-EMTBL · Alcohols (e.g., ethanol) · Anabolic steroids · Avermectins (e.g., ivermectin) · Barbiturates (e.g., phenobarbital) · Benzodiazepines (e.g., diazepam) · Bromide compounds (e.g., potassium bromide) · Carbamates (e.g., meprobamate) · Carbamazepine · Chloralose · Chlormezanone · Clomethiazole · Dihydroergolines (e.g., ergoloid (dihydroergotoxine)) · Etazepine · Etifoxine · Fenamates (e.g., mefenamic acid) · Flavonoids (e.g., apigenin, hispidulin) · Fluoxetine · Flupirtine · Imidazoles (e.g., etomidate) · Kava constituents (e.g., kavain) · Lanthanum · Loreclezole · Monastrol · Neuroactive steroids (e.g., allopregnanolone, cholesterol) · Niacin · Nicotinamide (niacinamide) · Nonbenzodiazepines (e.g., β-carbolines (e.g., abecarnil), cyclopyrrolones (e.g., zopiclone), imidazopyridines (e.g., zolpidem), pyrazolopyrimidines (e.g., zaleplon)) · Norfluoxetine · Petrichloral · Phenols (e.g., propofol) · Phenytoin · Piperidinediones (e.g., glutethimide) · Propanidid · Pyrazolopyridines (e.g., etazolate) · Quinazolinones (e.g., methaqualone) · Retigabine (ezogabine) · ROD-188 · Skullcap constituents (e.g., baicalin) · Stiripentol · Sulfonylalkanes (e.g., sulfonmethane (sulfonal)) · Topiramate · Valerian constituents (e.g., valerenic acid) · Volatiles/gases (e.g., chloral hydrate, chloroform, diethyl ether, paraldehyde, sevoflurane) · |
| | | **Antagonists** | Bicuculline · Coriamyrtin · Dihydrosecurinine · Gabazine (SR-95531) · Hydrastine · Hyenachin (mellitoxin) · PHP-501 · Pitrazepin · Securinine · Sinomenine · SR-42641 · SR-95103 · Thiocolchicoside · Tutin · |
| | | **NAMs** | 1,3M1B · 3M2B · 11-Ketoprogesterone · 17-Phenylandrostenol · α5IA (LS-193,268) · β-CCB · β-CCE · β-CCM · β-CCP · β-EMGBL · Anabolic steroids · Amiloride · Anisatin · β-Lactams (e.g., penicillins, cephalosporins, carbapenems) · Basmisanil · Bemegride · Bilobalide · CHEB · Cicutoxin · Cloflubicyne · Cyclothiazide · DHEA · DHEA-S · Dieldrin · (+)-DMBB · DMCM · DMPC · EBOB · Etbicyphat · FG-7142 (ZK-31906) · Fiproles (e.g., fipronil) · Flavonoids (e.g., amentoflavone, oroxylin A) · Flumazenil · Fluoroquinolones (e.g., ciprofloxacin) · Flurothyl · Furosemide · Iomazenil ($^{123}$I) · Isoallopregnanolone · Isopregnanolone (sepranolone) · L-655,708 · Laudanosine · Leptazol · Lindane · MaxiPost · Morphine · Morphine-3-glucuronide · MRK-016 · Naloxone · Naltrexone · Nicardipine · Non-steroidal antiandrogens (e.g., apalutamide, bicalutamide, enzalutamide, flutamide, nilutamide) · Oenanthotoxin · Pentetrazol (metrazol) · Phenylsilatrane · Picrotoxin (i.e., picrotin and picrotoxinin) · Pregnenolone sulfate · Propybicyphat · PWZ-029 · Radequinil · Ro 15-4513 · Ro 19-4603 · RO4882224 · RO4938581 · Sarmazenil · SCS · Suritozole · TB-21007 · TBOB · TBPS · TCS-1105 · Terbequinil · TETS · Thujone · U-93631 · Zinc · ZK-93426 · |
| | | **Agonists** | BL-1020 · CACA · CAMP · Homohypotaurine · GABA · GABOB · Ibotenic acid · Isoguvacine · Muscimol · $N^4$-Chloroacetylcytosine arabinoside · Picamilon · Progabide · TACA · |

| | | | |
|---|---|---|---|
| | $GABA_A$-ρ | | TAMP · Thiomuscimol · Tolgabide · |
| | | **PAMs** | Allopregnanolone · Alphaxolone · ATHDOC · Lanthanides · |
| | | **Antagonists** | (S)-2-MeGABA · (S)-4-ACPBPA · (S)-4-ACPCA · 2-MeTACA · 3-APMPA · 4-ACPAM · 4-GBA · *cis*-3-ACPBPA · CGP-36742 (SGS-742) · DAVA · Gabazine (SR-95531) · Gaboxadol (THIP) · I4AA · Isonipecotic acid · Loreclezole · P4MPA · P4S · SKF-97541 · SR-95318 · SR-95813 · TPMPA · *trans*-3-ACPBPA · ZAPA · |
| | | **NAMs** | 5α-Dihydroprogesterone · Bilobalide · Loreclezole · Picrotoxin (picrotin, picrotoxinin) · Pregnanolone · ROD-188 · THDOC · Zinc · |
| | $GABA_B$ | **Agonists** | 1,4-Butanediol · Aceburic acid · Arbaclofen · Arbaclofen placarbil · Baclofen · BL-1020 · GABA · Gabamide · GABOB · GBL · GHB · GHBAL · GHV · GVL · Isovaline · Lesogaberan · Phenibut · Picamilon · Progabide · Sodium oxybate · SKF-97,541 · SL 75102 · Tolgabide · Tolibut · |
| | | **Antagonists** | 2-Hydroxysaclofen · CGP-35348 · CGP-46381 · CGP-52432 · CGP-54626 · CGP-55845 · CGP-64213 · DAVA · Homotaurine (tramiprosate, 3-APS) · Phaclofen · Saclofen · SCH-50911 · SKF-97541 · |
| | | **NAMs** | Compound 14 · |
| | | **PAMs** | ADX-71441 · BHF-177 · BHFF · BSPP · CGP-7930 · CGP-13501 · GS-39783 · rac-BHFF · |
| **Transporter** (**blockers**) | **GAT** | | 4-Aminovaleric acid · β-Alanine · Arecaidine · CI-966 · DABA · Deramciclane (EGIS-3886, EGYT-3886) · EF-1502 · Gabaculine · Guvacine · Ibotenic acid · Muscimol · Nipecotic acid · NNC 05-2090 · NO-711 · Riluzole · SKF-89976A · SNAP-5114 · TACA · Tiagabine · |
| | **VIAAT** | | β-Alanine · Bafilomycin A1 · Chicago sky blue 6B · Evans blue · GABA · Glycine · N-Butyric acid · Nigericin · Nipecotic acid · Valinomycin · Vigabatrin · |
| **Enzyme** (**inhibitors**) | **GAD** | | 3-Mercaptopropionic acid · AAOA · L-Allylglycine · Semicarbazide · |
| | **GABA-T** | | 3-Hydrazinopropionic acid · γ-Acetylenic-GABA · AOAA · EOS · Gabaculine · Isoniazid · L-Cycloserine · Phenelzine · PEH · Rosmarinic acid (lemon balm) · Sodium valproate · Valnoctamide · Valproate pivoxil · Valproate semisodium (divalproex sodium) · Valproic acid · Valpromide · Vigabatrin · |
| **Others** | **Precursors** | | 1,4-Butanediol · GHB · GHBAL · Glutamate · Glutamine · |
| | **Analogues** | | Pregabalin · 4-Methylpregabalin · Atagabalin · Gabapentin · Gabapentin enacarbil · Imagabalin · Mirogabalin · PD-200,347 · PD-217,014 · PD-299,685 · Phenibut · |
| | **Others** | | Vitamin $B_6$ · *GABA-T activators:* 3-Methyl-GABA · |
| *See also: GHBergics • Glutamatergics • Glycinergics* | | | |

Categories: Enantiopure drugs | Fluoroquinolone antibiotics | Nitrogen heterocycles | Oxygen heterocycles | Piperazines | GABAA receptor negative allosteric modulators | World Health Organization essential medicines

This page was last modified on 10 December 2016, at 17:51.


# Measles vaccine

From Wikipedia, the free encyclopedia

**Measles vaccine** is a vaccine that is very effective at preventing measles.[1] After one dose 85% of children nine months of age and 95% over twelve months of age are immune.[2] Nearly all of those who do not develop immunity after a single dose develop it after a second dose. When rates of vaccination within a population are greater than 93% outbreaks of measles typically no longer occur; however, they may occur again if rates of vaccination decrease. The vaccine's effectiveness lasts many years. It is unclear if it becomes less effective over time. The vaccine may also protect against the disease if given within a couple of days of being exposed.[1]

The vaccine is generally safe including in those with HIV infections. Side effects are usually mild and short lived. This may include pain at the site of injection or mild fever. Anaphylaxis has been documented in about one per hundred thousand people. Rates of Guillain–Barré syndrome, autism and inflammatory bowel disease do not appear to be increased.[1]

The vaccine is available both by itself and in combination with other vaccines. This includes with the rubella vaccine and mumps vaccine to make the MMR vaccine,[1] first made available in 1971.[3] The addition of the varicella vaccine against chickenpox to these three in 2005 gave the MMRV vaccine.[4] The vaccine works equally well in all formulations. The World Health Organization recommends it be given at nine months of age in areas of the world where the disease is common. In areas where the disease is not common, giving it at twelve months is reasonable. It is a vaccine based on a live but weakened strain of measles. It comes as a dried powder which needs to be mixed with a specific liquid before being given either just under the skin or into a muscle. Verification that the vaccine was effective can be determined by blood tests.[1]

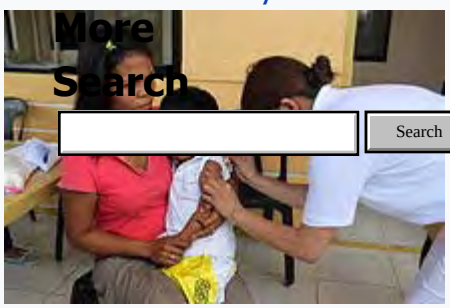
About 85% of children globally have received this vaccine as of 2013.[5] In 2008 at least 192 countries offered two doses.[1] It was first introduced in 1963.[2] It is on the WHO Model List of Essential Medicines, the most important medication needed in a basic health system.[6] The wholesale cost in the developing world is about 0.70 USD per dose as of 2014.[1][7]

Contents



## Variants

### Measles vaccine

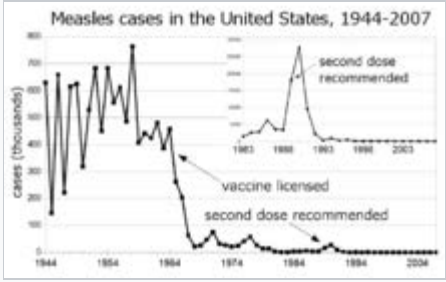


A child is given a measles vaccine.

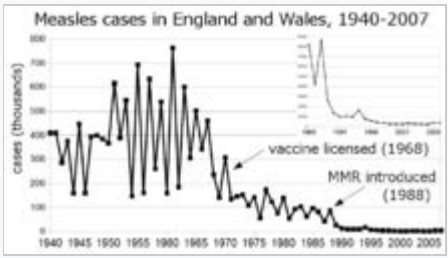
| Vaccine description | |
|---|---|
| **Target disease** | Measles |
| **Type** | Attenuated virus |
| **Clinical data** | |
| **MedlinePlus** | a601176 |
| **ATC code** | J07BD01 (WHO) |
| **Identifiers** | |
| **ChemSpider** | none |

(what is this?) (verify)

## Medical uses [edit]




Measles cases reported in the United States before and after introduction of the vaccine.




Measles cases reported in England and Wales.

Before the widespread use of the measles vaccine, its incidence was so high that infection with measles was felt to be "as inevitable as death and taxes."[8] In the United States, reported cases of measles fell from hundreds of thousands to tens of thousands per year following introduction of the vaccine in 1963 (see chart at right). Increasing uptake of the vaccine following outbreaks in 1971 and 1977 brought this down to thousands of cases per year in the 1980s. An outbreak of almost 30,000 cases in 1990 led to a renewed push for vaccination and the addition of a second vaccine to the recommended schedule. Fewer than 200 cases were reported each year from 1997 to 2013, and the disease was believed no longer endemic in the United States.[9][10][11] In 2014, 610 cases were reported.[12] Roughly 30 cases were diagnosed in January 2015, likely originating from exposure near Anaheim, California in late December 2014.

The benefit of measles vaccination in preventing illness, disability, and death has been well documented. The first 20 years of licensed measles vaccination in the U.S. prevented an estimated 52 million cases of the disease, 17,400 cases of mental retardation, and 5,200 deaths.[13] During 1999–2004, a strategy led by the World Health Organization and UNICEF led to improvements in measles vaccination coverage that averted an estimated 1.4 million measles deaths worldwide.[14] The vaccine for measles has led to the near-complete elimination of the disease in the United States and other developed countries.[15] It was introduced in 1963.[16] These impressive reductions in death and long-range after-effectiveness were initially achieved with a live virus version of the vaccine that itself caused side effects, although these are far fewer and less serious than the sickness and death caused by measles itself. While preventing many deaths and serious illnesses, the live virus version of the vaccine did cause side effects in a small percentage of recipients, ranging from rashes to, rarely, convulsions.[17]

Measles is common worldwide. Although it was declared eliminated from the U.S. in 2000, high rates of vaccination and excellent communication with those who refuse vaccination are needed to prevent outbreaks and sustain the elimination of measles in the U.S.[18] Of the 66 cases of measles reported in the U.S. in 2005, slightly over half were attributable to one unvaccinated individual who acquired measles during a visit to Romania.[19] This individual returned to a community with many unvaccinated children. The resulting outbreak infected 34 people, mostly children and virtually all unvaccinated; 9% were hospitalized, and the cost of containing the outbreak was estimated at $167,685. A major epidemic was averted due to high rates of vaccination in the surrounding communities.[18]

The live vaccine has non specific effects such as preventing respiratory infections that may be greater than those of measles prevention. These benefits were greater when used before a year of age. A high titre vaccine resulted in worse outcomes in girls and thus is no longer recommended by the world health organization.[20] As measles causes upper respiratory disease that leads to complications of pneumonia and bronchitis, measles vaccine is beneficial to reduce exacerbations of chronic obstructive pulmonary disease (COPD) and asthma.

### Schedule [edit]

The World Health Organization recommends two doses of vaccine for all children.[1] In countries with high

risk of disease the first dose should be given around nine months of age.[1] Otherwise in low risk countries it can be given at twelve months of age.[1] The second dose should be given at least one month after the first dose.[1] This is often done at age 15 to 18 months.[1]

The CDC recommends that children aged 6 to 12 months traveling outside the United States receive their first dose of MMR vaccine.[21] Otherwise the first dose is typically given between 12–18 months. A second dose is given by 7 years (on or before last day of year 6) or by Kindergarten entry.[22] Vaccine is administered in the outer aspect of the upper arm. In adults, it is give subcutaneously and a second dose 28 days apart is given. In adults greater than 50 years, only one dose is needed.

## Adverse effects [edit]

Adverse effects associated with the MMR vaccine include fever, injection site pain and, in rare cases, red or purple discolorations on the skin known as thrombocytopenic purpura, or seizures related to fever (febrile seizure).[23] Serious side effects are extremely rare.

There is no evidence of a link between the MMR vaccine and autism.[24][25][26][27] The MMR vaccine does not appear to cause subacute sclerosing panencephalitis.[28]

### Contraindications [edit]

- Pregnancy: MMR vaccine and its components should not be administered to pregnant women.[29]
- HIV-infected children may receive measles vaccines if their CD4+ lymphocyte count is greater than 15%.[30]

## History [edit]

As a fellow at Children's Hospital Boston, Dr. Thomas C. Peebles worked with Dr. John Franklin Enders. Dr. Enders became known as "The Father of Modern vaccines", and Enders shared the Nobel Prize in 1954 for his research on cultivating the polio virus that led to the development of a vaccination for the disease. Switching to study measles, Enders sent Peebles to Fay School in Massachusetts, where an outbreak of the disease was under way, and there Peebles was able to isolate the virus from some of the blood samples and throat swabs he had taken from the students. Even after Enders had taken him off the study team, Peebles was able to cultivate the virus and show that the disease could be passed on to monkeys inoculated with the material he had collected.[15] Enders was able to use the cultivated virus to develop a measles vaccine in 1963 based on the material isolated by Peebles.[31] In the late 1950s and early 1960s, nearly twice as many children died from measles as from polio.[32] The vaccine Enders developed was based on the Edmonston strain of attenuated live measles virus, which was named for the Fay student from whom Peebles had taken the culture that led to the virus's cultivation.[33]

The first ever trials of measles vaccine were undertaken by David Morley at the Wesley Guild Hospital in Ilesha, Nigeria[34] on his own children.

Dr. Maurice Hilleman at Merck & Co., a pioneer in the development of vaccinations, developed the MMR vaccine in 1971, which treats measles, mumps and rubella in a single shot followed by a booster.[17][35] One form is called "Attenuvax" with more than 40 peptide sequences.[36] The measles component of the MMR vaccine uses Attenuvax, which is grown in a chick embryo cell culture using the Enders' attenuated Edmonston strain. Merck decided not to resume production of attenuvax on October 21, 2009.[37]

## Types [edit]

Measles is seldom given as individual vaccine nowadays and is often given in combination with mumps and rubella. Two types of measles vaccines are currently available.

- Mumps Measles Rubella vaccine, live (MMR-II)
- Mumps Measles Rubella and varicella virus vaccine (Proquad)

Measles mumps rubella vaccine (MMR-II); MMR vaccine is a live attenuated viral vaccine used to induce immunity against measles, mumps and rubella.

## See also [edit]

- MMR vaccine
- Pulse vaccination strategy

## References [edit]


1. ^ *a b c d e f g h i j k l* "Measles vaccines: WHO position paper." (PDF). *Weekly epidemiological record*. **84** (35): 349–60. 28 August 2009. PMID 19714924.
2. ^ *a b* Control, Centers for Disease; Prevention (2014). *CDC health information for international travel 2014 the yellow book*. p. 250. ISBN 9780199948505.
3. ^ "Vaccine Timeline". Retrieved 10 February 2015.
4. ^ Mitchell, Deborah (2013). *The essential guide to children's vaccines*. New York: St. Martin's Press. p. 127. ISBN 9781466827509.
5. ^ "Measles Fact sheet N°286". *who.int*. November 2014. Retrieved 4 February 2015.
6. ^ "WHO Model List of EssentialMedicines" (PDF). *World Health Organization*. October 2013. Retrieved 22 April 2014.
7. ^ "Vaccine, Measles". *International Drug Price Indicator Guide*. Retrieved 6 December 2015.
8. ^ Babbott FL Jr; Gordon JE (1954). "Modern measles". *Am J Med Sci*. **228** (3): 334–61. PMID 13197385.
9. ^ Centers for Disease Control and Prevention Summary of notifable diseases—United States, 1993 Published October 21, 1994 for Morbidity and Mortality Weekly Report 1993; **42** (No. 53)
10. ^ Centers for Disease Control and Prevention Summary of notifable diseases—United States, 2007 Published July 9, 2009 for Morbidity and Mortality Weekly Report 2007; **56** (No. 53)
11. ^ Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Atkinson W, Wolfe S, Hamborsky J, McIntyre L, eds. 11th ed. Washington DC: Public Health Foundation, 2009
12. ^ [1]
13. ^ Bloch AB, Orenstein WA, Stetler HC, et al. (1985). "Health impact of measles vaccination in the United States". *Pediatrics*. **76** (4): 524–32. PMID 3931045.
14. ^ Centers for Disease Control and Prevention (CDC) (2006). "Progress in reducing global measles deaths, 1999–2004". *MMWR Morb Mortal Wkly Rep*. **55** (9): 247–9. PMID 16528234.
15. ^ *a b* Martin, Douglas. "Dr. Thomas C. Peebles, Who Identified Measles Virus, Dies at 89", *The New York Times*, August 4, 2010. Accessed August 4, 2010.
16. ^ Hayden GF (March 1979). "Measles vaccine failure. A survey of causes and means of prevention". *Clin Pediatr (Phila)*. **18** (3): 155–6, 161–3, 167. doi:10.1177/000992287901800308. PMID 371890.
17. ^ *a b* Collins, Huntly. "The Man Who Saved Your Life - Maurice R. Hilleman - Developer of Vaccines for Mumps and Pandemic Flu: Maurice Hilleman's Vaccines Prevent Millions of Deaths Every Year", copy of article from *The Philadelphia Inquirer*, August 30, 1999. Accessed August 4, 2010.
18. ^ *a b* Parker AA, Staggs W, Dayan GH, et al. (2006). "Implications of a 2005 measles outbreak in Indiana for sustained elimination of measles in the United States". *N Engl J Med*. **355** (5): 447–55. doi:10.1056/NEJMoa060775. PMID 16885548.
19. ^ Centers for Disease Control and Prevention (CDC) (2006). "Measles—United States, 2005". *MMWR Morb Mortal Wkly Rep*. **55** (50): 1348–51. PMID 17183226.
20. ^ Sankoh O, Welaga P, Debpuur C, Zandoh C, Gyaase S, Poma MA, Mutua MK, Hanifi SM, Martins C, Nebie E, Kagoné M, Emina JB, Aaby P (2014). "The non-specific effects of vaccines and other childhood interventions: the contribution of INDEPTH Health and Demographic Surveillance Systems". *Int J Epidemiol*. **43** (3): 645–53. doi:10.1093/ije/dyu101. PMC 4052142. PMID 24920644.
21. ^ "Measles and the Vaccine (Shot) to Prevent It". Centers for Disease Control. Retrieved 24 January 2015.
22. ^ Washington Stat Dept of Health
23. ^ Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C (2012). "Vaccines for measles, mumps and rubella in children". *Cochrane Database Syst Rev*. **2**: CD004407. doi:10.1002/14651858.CD004407.pub3. PMID 22336803.

24. ^ "Measles, mumps, and rubella (MMR) vaccine". Centers for Disease Control and Prevention. 2008-08-22. Archived from the original on 2008-10-08. Retrieved 2008-12-21.
25. ^ Immunization Safety Review: Vaccines and Autism. From the Institute of Medicine of the National Academy of Sciences. Report dated May 17, 2004; accessed June 13, 2007.
26. ^ MMR Fact Sheet, from the United Kingdom National Health Service. Accessed June 13, 2007.
27. ^ Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C (2012). "Vaccines for measles, mumps and rubella in children". *Cochrane Database Syst Rev*. **2**: CD004407. doi:10.1002/14651858.CD004407.pub3. PMID 22336803.
28. ^ http://www.cdc.gov/measles/about/complications.html "Complications of Measles."
29. ^ Guidelines for Vaccinating Pregnant Women
30. ^ Chart of Contraindications and Precautions to Commonly Used Vaccines
31. ^ Staff. "Work by Enders Brings Measles Vaccine License", *The Hartford Courant*, March 22, 1963. Accessed August 4, 2010. "A strain of measles virus isolated in 1954 by Dr. Thomas C. Peebles, instructor in pediatrics at Harvard, and Enders, formed the basis for the development of the present vaccine".
32. ^ Staff. "The Measles Vaccine", *The New York Times*, March 28, 1963. Accessed August 4, 2010.
33. ^ Hilleman, Maurice R. "Past, Present, and Future of Measles, Mumps, and Rubella Virus Vaccines", *Pediatrics (journal)*, Vol. 90 No. 1 July 1992, pp. 149-153. Accessed August 4, 2010.
34. ^ Pritchard, John (13 November 1997). "Obituary: Dr C. A. Pearson". *The Independent*. Retrieved 29 January 2014.
35. ^ Sullivan, Patricia (2005-04-13). "Maurice R. Hilleman Dies; Created Vaccines (washingtonpost.com)". *The Washington Post*. Retrieved 2009-07-21.
36. ^ Ovsyannikova IG, Johnson KL, Naylor S, Poland GA (February 2005). "Identification of HLA-DRB1-bound self-peptides following measles virus infection". *J. Immunol. Methods*. **297** (1-2): 153–67. doi:10.1016/j.jim.2004.12.020. PMID 15777939.
37. ^ Q & As about Monovalent M-M-R Vaccines



| v · t · e · | **Artificial induction of immunity / Immunization: Vaccines, Vaccination, Infection, Inoculation (J07)** | |
|---|---|---|
| **Development** | Adjuvants · List of vaccine ingredients · Mathematical modelling · Timeline · Trials · | |
| **Classes** | Conjugate vaccine · DNA vaccination · Inactivated vaccine · Live vector vaccine (Attenuated vaccine · Heterologous vaccine · · Subunit/component / Peptide / Virus-like particle · Toxoid · | |
| **Administration** | Global: (GAVI Alliance · Policy · Schedule · Vaccine injury · · USA: (ACIP · Vaccine court · Vaccines for Children Program · VAERS · VSD · · | |
| **Vaccines** | **Bacterial** | Anthrax · Brucellosis · Cholera# · Diphtheria# · Hib# · Leptospirosis · Lyme disease‡ · Meningococcus# (MeNZB · NmVac4-A/C/Y/W-135 · · Pertussis# · Plague · Pneumococcal# (PCV · PPSV · · Q fever · Tetanus# · Tuberculosis (BCG# · · Typhoid# (Ty21a · ViCPS · · Typhus · combination: DTwP/DTaP · |
| | **Viral** | Adenovirus · Flu# (H1N1 (Pandemrix) · LAIV · · Hantavirus · Hepatitis A# · Hepatitis B# · Hepatitis E · HPV (Cervarix · Gardasil · · Japanese encephalitis# · **Measles**# · Mumps# (Mumpsvax · · Polio# (Sabin · Salk · · Rabies# · Rotavirus# · Rubella# · Smallpox (Dryvax · · Tick-borne encephalitis · Varicella zoster (chicken pox# · shingles (live) · · Yellow fever# · combination: (MMR · MMRV · · research: (Chikungunya · Cytomegalovirus · Dengue · Ebola · Epstein–Barr virus · Hepatitis C · HIV · · |
| | **Protozoan** | research: (Malaria · Trypanosomiasis · · |
| | **Helminthiasis** | research: (Hookworm · Schistosomiasis · · |
| | **Other** | Androvax (androstenedione albumin) · Cancer vaccines (ALVAC-CEA · Hepatitis B# · HPV (Cervarix · Gardasil · · · NicVAX · Ovandrotone albumin (Fecundin) · TA-CD · TA-NIC · |
| | General · MMR · NCVIA · Pox party · Thiomersal · Andrew Wakefield · | |

| | |
|---|---|
| **Controversy** | *Cedillo v. Secretary of Health and Human Services* · Alternative vaccination schedule · |
| **Related** | Epidemiology · Eradication of infectious diseases · Every Child by Two · List of vaccine topics · |

[#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III · ·

Categories: Vaccines | Measles | Live vaccines | World Health Organization essential medicines (vaccines)




# Metoprolol

From Wikipedia, the free encyclopedia

**Metoprolol**, marketed under the tradename **Lopressor** among others, is a selective β1 receptor blocker medication.[3] It is used to treat high blood pressure, chest pain due to poor blood flow to the heart, and a number of conditions involving an abnormally fast heart rate. It is also used to prevent further heart problems after myocardial infarction and to prevent headaches in those with migraines.[3]

It comes in formulations that can be taken by mouth or given intravenously. The medication is often taken twice a day. There is an extended release formulation that is once per day. Metoprolol may be combined with hydrochlorothiazide in a single tablet.[3]

Common side effects include trouble sleeping, feeling tired, feeling faint, and abdominal discomfort.[3] Large doses may cause serious toxicity.[4][5] Risk in pregnancy has not been ruled out.[5][6] It appears to be safe in breastfeeding.[7] Greater care is required with use in those with liver problems or asthma.[3] If stopped this should be done slowly to decrease the risk of further health problems.[3]

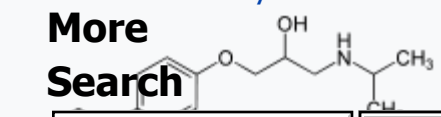
Metoprolol was first made in 1969.[8] It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[9] It is available as a generic drug.[3] In 2013, metoprolol was the 19th most prescribed medication in the United States.[10]

Contents



## Medical uses [edit]

**Metoprolol**



| Clinical data | |
|---|---|
| **Pronunciation** | /mɛˈtoʊproʊlɑːl/, /mɛtoʊˈproʊlɑːl/ |
| **Trade names** | Lopressor, Metolar XR |
| **AHFS/Drugs.com** | Monograph |
| **MedlinePlus** | a682864 |
| **License data** | US FDA: Metoprolol |
| **Pregnancy category** | AU: C<br>US: C (Risk not ruled out) |
| **Routes of administration** | By mouth, IV |
| **ATC code** | C07AB02 (WHO) |
| **Legal status** | |
| **Legal status** | (Prescription only) |
| **Pharmacokinetic data** | |
| **Bioavailability** | 50% (single dose)[1]<br>70% (repeated administration)[2] |
| **Protein binding** | 12% |
| **Metabolism** | Liver via CYP2D6, CYP3A4 |
| **Biological half-life** | 3–7 hours |
| **Excretion** | Kidney |
| **Identifiers** | |
| **IUPAC name** | (*RS*)-1-(Isopropylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol |
| **CAS Number** | 51384-51-1 ✓ |

Metoprolol is used for a number of conditions, including hypertension, angina, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, congestive heart failure, and prevention of migraine headaches.[11]

- Treatment of heart failure[12]
- Vasovagal syncope[13][14]
- Adjunct in treatment of hyperthyroidism[15]
- Long QT syndrome, especially for patients with asthma, as metoprolol's β1 selectivity tends to interfere less with asthma drugs, which are often β2-adrenergic receptor-agonist drugs[*citation needed*]
- Prevention of relapse into atrial fibrillation (controlled-release/extended-release form)[16]

Due to its selectivity in blocking the $beta_1$ receptors in the heart, metoprolol is also prescribed for off-label use in performance anxiety, social anxiety disorder, and other anxiety disorders.

| | |
|---|---|
| **PubChem** (CID) | 4171 |
| **IUPHAR/BPS** | 553 |
| **DrugBank** | DB00264 ✓ |
| **ChemSpider** | 4027 ✓ |
| **UNII** | GEB06NHM23 ✓ |
| **KEGG** | D02358 ✓ |
| **ChEBI** | CHEBI:6904 ✓ |
| **ChEMBL** | CHEMBL13 ✓ |
| **ECHA InfoCard** | 100.048.603 |
| **Chemical and physical data** | |
| **Formula** | $C_{15}H_{25}NO_3$ |
| **Molar mass** | 267.364 g/mol |
| **3D model (Jmol)** | Interactive image |
| **Chirality** | Racemic mixture |
| **Melting point** | 120 °C (248 °F) |
| **SMILES** | O(c1ccc(cc1)CCOC)CC(O)CNC(C)C |
| **InChI** | InChI=1S/C15H25NO3/c1-12(2)16-10-14(17)11-19-15-6-4-13(5-7-15)8-9-18-3/h4-7,12,14,16-17H,8-11H2,1-3H3 ✓ Key:IUBSYMUCCVWXPE-UHFFFAOYSA-N ✓ |
| | (verify) |

## Adverse effects [edit]

Side effects, especially with higher doses, include dizziness, drowsiness, fatigue, diarrhea, unusual dreams, ataxia, trouble sleeping, depression, and vision problems. It may also reduce blood flow to the hands and feet, causing them to feel numb and cold; smoking may worsen this effect.[17] Due to the high penetration across the blood-brain barrier, lipophilic beta blockers such as propranolol and metoprolol are more likely than other less lipophilic beta blockers to cause sleep disturbances such as insomnia and vivid dreams and nightmares.[18]

Serious side effects that are advised to be reported immediately include symptoms of bradycardia (resting heart rate slower than 60 beats per minute), persistent symptoms of dizziness, fainting and unusual fatigue, bluish discoloration of the fingers and toes, numbness/tingling/swelling of the hands or feet, sexual dysfunction, erectile dysfunction (impotence), hair loss, mental/mood changes, depression, trouble breathing, cough, dyslipidemia, and increased thirst. Taking it with alcohol might cause mild body rashes, so is not recommended.[17]

### Precautions [edit]

Metoprolol may worsen the symptoms of heart failure in some patients, who may experience chest pain or discomfort, dilated neck veins, extreme fatigue, irregular breathing, an irregular heartbeat, shortness of breath, swelling of the face, fingers, feet, or lower legs, weight gain, or wheezing.[19]

This medicine may cause changes in blood sugar levels or cover up signs of low blood sugar, such as a rapid pulse rate.[19] It also may cause some people to become less alert than they are normally, making it dangerous for them to drive or use machines.[19]

### Pregnancy and lactation [edit]

It is pregnancy category C in the United States, meaning that a risk for the fetus cannot be ruled out,[3] and category C in Australia, meaning that it may be suspected of causing harmful effects on the human fetus (but no malformations).[6]

## Overdose [edit]

Excessive doses of metoprolol can cause severe hypotension, bradycardia, metabolic acidosis, seizures, and cardiorespiratory arrest. Blood or plasma concentrations may be measured to confirm a diagnosis of overdose or poisoning in hospitalized patients or to assist in a medicolegal death investigation. Plasma levels are usually less than 200 µg/l during therapeutic administration, but can range from 1–20 mg/l in overdose victims.[20][21][22]

## Pharmacology [edit]

- beta-1 selective
- moderately lipophilic
- without intrinsic sympathomimetic activity
- with weak membrane stabilizing activity
- decreases heart rate, contractility, and cardiac output, therefore decreasing blood pressure

### Pharmacokinetics [edit]

Metoprolol has a short half-life of 3 to 7 hours, and therefore is taken at least twice daily or as a slow-release preparation.

It undergoes α-hydroxylation and O-demethylation as a substrate of the cytochrome liver enzymes CYP2D6[23][24] and a small percentage by CYP3A4, resulting in inactive metabolites.

## Chemistry [edit]

Metoprolol has a very low melting point; around 120 °C (248 °F) for the tartrate, and around 136 °C (277 °F) for the succinate. Because of this, metoprolol is always manufactured in a salt-based solution, as drugs with low melting points are difficult to work with in a manufacturing environment. The free base exists as a waxy white solid, and the tartrate salt is finer crystalline material.

The active substance metoprolol is employed either as metoprolol succinate or as metoprolol tartrate (where 100 mg metoprolol tartrate corresponds to 95 mg metoprolol succinate). The tartrate is an immediate-release formulation and the succinate is an extended-release formulation.[25]

## Society and culture [edit]

### Brand names [edit]

It is marketed under the brand name Lopressor by Novartis, and Toprol-XL (in the US); Selokeen (in the Netherlands); as Minax by Alphapharm and Metrol by Arrow Pharmaceuticals (in Australia), as Betaloc by AstraZeneca, as Bloxan by Krka (company) (in Slovenia), as Neobloc by Unipharm (in Israel), Presolol by Hemofarm (in Serbia), and Corvitol by Berlin-Chemie (in Germany). In India, this drug is available under the brand names Met-XL, Metolar, Starpress, and Restopress. A number of generic products are available, as well.

Toprol XL 50 mg

## References [edit]


1. ^ "Metolar 25/50 (metoprolol tartrate) tablet" (PDF). *FDA*. Retrieved 5 May 2015.
2. ^ Jasek, W, ed. (2007). *Austria-Codex* (in German) (62nd ed.). Vienna: Österreichischer Apothekerverlag. pp. 916–919. ISBN 978-3-85200-181-4.

3. ^ *a b c d e f g h i* "Metoprolol". The American Society of Health-System Pharmacists. Retrieved Apr 21, 2014.
4. ^ Pillay (2012). *Modern Medical Toxicology*. Jaypee Brothers Publishers. p. 303. ISBN 9789350259658.
5. ^ Marx, John A. Marx (2014). "Cardiovascular Drugs". *Rosen's emergency medicine : concepts and clinical practice* (8th ed.). Philadelphia, PA: Elsevier/Saunders. pp. Chapter 152. ISBN 1455706051.
6. ^ *a b* "Prescribing medicines in pregnancy database". *Australian Government*. 3 March 2014. Retrieved 22 April 2014.
7. ^ *Medical Toxicology*. Lippincott Williams & Wilkins. 2004. p. 684. ISBN 9780781728454.
8. ^ Carlsson, edited by Bo (1997). *Technological systems and industrial dynamics.* Dordrecht: Kluwer Academic. p. 106. ISBN 9780792399728.
9. ^ "WHO Model List of Essential Medicines" (PDF). *World Health Organization*. October 2013. Retrieved 22 April 2014.
10. ^ "Top 100 Drugs for 2013 by Units Sold". *Drugs.com*. February 2014. Retrieved 22 March 2015.
11. ^ "Metoprolol". *The American Society of Health-System Pharmacists*. Retrieved 3 April 2011.
12. ^ MERIT-HF Study Group (1999). "Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)". *Lancet*. **353** (9169): 2001–2007. doi:10.1016/S0140-6736(99)04440-2. PMID 10376614.
13. ^ Biffi, M.; Boriani, G.; Sabbatani, P.; Bronzetti, G.; Frabetti, L.; Zannoli, R.; Branzi, A.; Magnani, B. (Mar 1997). "Malignant vasovagal syncope: a randomised trial of metoprolol and clonidine.". *Heart*. **77** (3): 268–72. doi:10.1136/hrt.77.3.268. PMC 484696. PMID 9093048.
14. ^ Zhang Q, Jin H, Wang L, Chen J, Tang C, Du J (2008). "Randomized comparison of metoprolol versus conventional treatment in preventing recurrence of vasovagal syncope in children and adolescents". *Medical Science Monitor*. **14** (4): CR199–CR203. PMID 18376348.
15. ^ Geffner DL, Hershman JM (July 1992). "β-Adrenergic blockade for the treatment of hyperthyroidism". *The American Journal of Medicine*. **93** (1): 61–8. doi:10.1016/0002-9343(92)90681-Z. PMID 1352658.
16. ^ Kühlkamp, V; Schirdewan, A; Stangl, K; Homberg, M; Ploch, M; Beck, OA (2000). "Use of metoprolol CR/XL to maintain sinus rhythm after conversion from persistent atrial fibrillation". *J Am Coll Cardiol*. **36** (1): 139–146. doi:10.1016/S0735-1097(00)00693-8.
17. ^ *a b* "Metoprolol". Drugs.com.
18. ^ Cruickshank JM (2010). "Beta-blockers and heart failure". *Indian Heart Journal*. **62** (2): 101–110. PMID 21180298.
19. ^ *a b c* "Metoprolol (Oral Route) Precautions". *Drug Information*. Mayo Clinic.
20. ^ Page C, Hacket LP, Isbister GK (2009). "The use of high-dose insulin-glucose euglycemia in beta-blocker overdose: a case report". *Journal of Medical Toxicology*. **5** (3): 139–143. doi:10.1007/bf03161225. PMID 19655287.
21. ^ Albers S, Elshoff JP, Völker C, Richter A, Läer S (2005). "HPLC quantification of metoprolol with solid-phase extraction for the drug monitoring of pediatric patients". *Biomedical Chromatography*. **19** (3): 202–207. doi:10.1002/bmc.436. PMID 15484221.
22. ^ Baselt R (2008). *Disposition of Toxic Drugs and Chemicals in Man* (8th ed.). Foster City, CA: Biomedical Publications. pp. 1023–1025.
23. ^ Swaisland HC, Ranson M, Smith RP, Leadbetter J, Laight A, McKillop D, Wild MJ (2005). "Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol". *Clinical Pharmacokinetics*. **44** (10): 1067–1081. doi:10.2165/00003088-200544100-00005. PMID 16176119.
24. ^ Blake, CM.; Kharasch, ED.; Schwab, M.; Nagele, P. (Sep 2013). "A meta-analysis of CYP2D6 metabolizer phenotype and metoprolol pharmacokinetics.". *Clin Pharmacol Ther*. **94** (3): 394–9. doi:10.1038/clpt.2013.96. PMC 3818912. PMID 23665868.
25. ^ Cupp M (2009). "Alternatives for Metoprolol Succinate" (pdf). *Pharmacist's Letter / Prescriber's Letter*. **25** (250302). Retrieved 2012-07-06.


## External links [edit]

- U.S. National Library of Medicine: Drug Information Portal - Metoprolol

| v · t · e · | **Beta blockers (C07)** |
|---|---|
| **β, non-selective** | Alprenolol · Bopindolol · Bupranolol · Carteolol · Cloranolol · Mepindolol · Nadolol · Oxprenolol · Penbutolol · Pindolol/Iodopindolol · Propranolol · Sotalol · Tertatolol · Timolol · |

| | |
|---|---|
| **$\beta_1$-selective** | Acebutolol · Atenolol · Betaxolol · Bevantolol · Bisoprolol · Celiprolol · Epanolol · Esmolol · Landiolol · **Metoprolol** · Nebivolol · Practolol · S-Atenolol · Talinolol · |
| **$\beta_2$-selective** | Butaxamine · |
| **$\alpha_1$- + β-selective** | Arotinolol · Carvedilol · Labetalol · |

· #WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · ·

Categories: Alcohols | Beta blockers | Chemical substances for emergency medicine | Ethers | Phenol ethers | World Health Organization essential medicines




# Mifepristone



From Wikipedia, the free encyclopedia

*For the song RU486 by Stone Sour, see House of Gold & Bones – Part 1.*

**Mifepristone**, also known as **RU-486**, is a medication typically used with misoprostol to bring about an abortion.[1] This combination is more than 95% effective during the first 50 days of pregnancy. It is also effective in the second trimester of pregnancy.[2][3] Two weeks after use effectiveness should be verified. It is taken by mouth.[1]

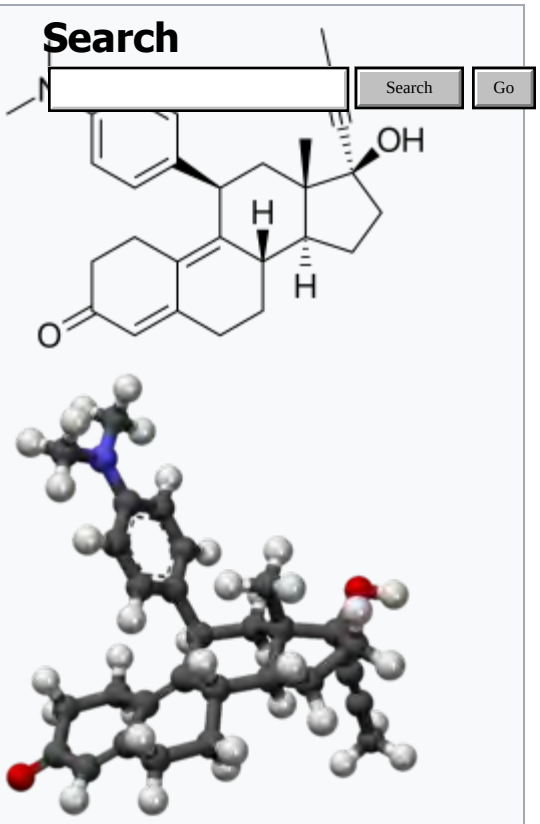
Common side effects include abdominal pain, feeling tired, and vaginal bleeding. Serious side effects may include heavy vaginal bleeding, bacterial infection, and a malformed baby if the pregnancy does not end. If used, appropriate follow up care needs to be available. Mifepristone works by blocking the effects of progesterone and causing contractions of the uterus.[1]

Mifepristone was developed in 1980 and came into use in France in 1987.[4] It became available in the United States in 2000.[2] It is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system.[5] Mifepristone was approved by Health Canada in July 2015 and is expected to become available in Canada in January 2017.[6][7][8] Cost and availability limits access in many parts of the developing world.[9][10] In the United States it costs more than US$200 (equivalent to $202.08 in 2016) a dose.[11]

Contents



**Mifepristone**




| Clinical data | |
|---|---|
| **Trade names** | Mifeprex |
| **AHFS/Drugs.com** | Monograph |
| **MedlinePlus** | a600042 |
| **Pregnancy category** | US: X (Contraindicated)<br>Used for terminating pregnancy |
| **Routes of administration** | By mouth |
| **ATC code** | G03XB01 (WHO) |
| **Legal status** | |
| **Legal status** | US: -only<br>(Prescription only) |

# Medical uses [edit]

## Abortion [edit]

Mifepristone followed by a prostaglandin analog (misoprostol or gemeprost) is used for medical abortion.[12][13]

A 2011 evidence-based clinical guideline by the Royal College of Obstetricians and Gynaecologists (RCOG) says medical abortion using mifepristone followed by the prostaglandin analog misoprostol is effective and appropriate at any gestational age.[14]

A 2012 technical and policy guidance book and a 2014 clinical practice handbook by the World Health Organization (WHO) recommend mifepristone followed by the prostaglandin analog misoprostol for first and second trimester medical abortions.[15][16]

2013 and 2014 practice bulletins by the American College of Obstetricians and Gynecologists (ACOG) recommend mifepristone followed by the prostaglandin analog misoprostol for first and second trimester medical abortions.[17][18]

Mifepristone alone results in abortion within two weeks of 54% to 92% of pregnancies.[19]

## Cushing's syndrome [edit]

Mifepristone is used for the medical treatment of high blood sugar (hyperglycemia) caused by high cortisol levels in the blood (hypercortisolism) in adults with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or cannot have surgery.[20][21]

## Emergency contraception [edit]

Mifepristone is used for emergency contraception.[22][23][24]

# Side effects [edit]

Nearly all women using the mifepristone/misoprostol regimen experienced abdominal pain, uterine cramping, and vaginal bleeding or spotting for an average of 9–16 days. Up to 8% of women experienced some type of bleeding for 30 days or more. Other less common side effects included nausea, vomiting, diarrhea, dizziness, fatigue, and fever.[25] Pelvic inflammatory disease is a very rare but serious complication.[26] Excessive bleeding and incomplete termination of a pregnancy require further intervention by a doctor (such as vacuum aspiration). Between 4.5 and 7.9% of women required surgical intervention in clinical trials.[25] Mifepristone

| Pharmacokinetic data | |
|---|---|
| **Bioavailability** | 69% |
| **Protein binding** | 98% |
| **Metabolism** | Liver |
| **Biological half-life** | 18 hours |
| **Excretion** | Fecal: 83%; Kidney: 9% |

| Identifiers | |
|---|---|
| **IUPAC name** | 11β-[*p*-(Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one |
| **CAS Number** | 84371-65-3 ✓ |
| **PubChem** (CID) | 55245 |
| **IUPHAR/BPS** | 2805 |
| **DrugBank** | DB00834 ✓ |
| **ChemSpider** | 49889 ✓ |
| **UNII** | 320T6RNW1F ✓ |
| **KEGG** | D00585 ✓ |
| **ChEBI** | CHEBI:50692 ✓ |
| **ChEMBL** | CHEMBL157 ✓ |
| **ECHA InfoCard** | 100.127.911 |

| Chemical and physical data | |
|---|---|
| **Formula** | $C_{29}H_{35}NO_2$ |
| **Molar mass** | 429.60 g/mol |
| **3D model (Jmol)** | Interactive image |
| **Density** | 1.189 g/cm$^3$ |
| **Melting point** | 194 °C (381 °F) |
| **Boiling point** | 629 °C (1,164 °F) |

**SMILES**
O=C5\C=C4/C(=C3/[C@@H](c1ccc(N(C)C)cc1)C[C@]2([C@@H](CC[C@]2(C#CC)O)[C@@H]3CC4)C)CC5

**InChI**
InChI=1S/C29H35NO2/c1-5-15-29(32)16-14-26-24-12-8-20-17-22(31)11-13-23(20)27(24)25(18-28(26,29)2)19-6-9-21(10-7-19)30(3)4/h6-7,9-10,17,24-26,32H,8,11-14,16,18H2,1-4H3/t24-,25+,26-,28-,29-/m0/s1 ✓
Key:VKHAHZOOUSRJNA-GCNJZUOMSA-N ✓

(verify)

is contraindicated in the presence of an intrauterine device, as well as with ectopic pregnancy, adrenal failure, hemorrhagic disorders, inherited porphyria, and anticoagulant or long-term corticosteroid therapy.[25]

The FDA prescribing information states no data are available on the safety and efficacy of mifepristone in women with chronic medical conditions, and "women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone."[25]

A postmarketing summary found, of about 1.52 million women who had received mifepristone until April 2011 in the United States, 14 were reported to have died after application. Eight of these cases were associated with sepsis; the other six had various causes such as drug abuse and suspected murder. Other incidents reported to the FDA included 612 nonlethal hospitalizations, 339 blood transfusions, 48 severe infections, and 2,207 (0.15%) adverse events altogether.[27]

### Cancer [edit]

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed. This is in accord with ICH guidelines, which do not require carcinogencity testing in nongenotoxic drugs intended for administration for less than six months.[28]

### Pregnancy [edit]

Under 49 days' gestational age, 60-80% of pregnancies will end with mifepristone alone; at any gestational age, 54-92% of pregnancies will end with mifepristone.[19][29] There is no evidence that the effects of mifepristone can be reversed.[19]

Exposure to a single large dose of mifepristone in newborn rats was not associated with any reproductive problems, although chronic low-dose exposure of newborn rats to mifepristone was associated with structural and functional reproductive abnormalities.[25]

Studies in mice, rats, and rabbits revealed teratogenicity for rabbits, but not rats or mice.[25] The rate of birth defects in human infants exposed *in utero* to mifepristone and misoprostol is very low,[30] and may be due to misoprostol alone.[31]

## Pharmacology [edit]

It is a synthetic, steroidal antiprogestogen ($IC_{50}$ = 0.025 nM for the PR), as well as an antiglucocorticoid ($IC_{50}$ = 2.2 nM for the GR) and antiandrogen ($IC_{50}$ = 10 nM for the AR) to a much lesser extent.[32] It is a 19-norsteroid with substitutions at positions C11 and C17 (17β-hydroxy-11β-(4-(dimethylamino)phenyl)-17α-(1-propynyl)estra-4,9-dien-3-one), which antagonizes cortisol action competitively at the receptor level.[33] Mifepristone is a low-efficacy partial agonist of the progesterone receptor. It is also a glucocorticoid receptor antagonist to a lesser extent.

In the presence of progesterone, mifepristone acts as a competitive progesterone receptor antagonist (in the absence of progesterone, mifepristone acts as a partial agonist). Mifepristone is a 19-nor steroid with a bulky *p*-(dimethylamino)phenyl substituent above the plane of the molecule at the 11β-position responsible for inducing or stabilizing an inactive receptor conformation and a hydrophobic 1-propynyl substituent below the plane of the molecule at the 17α-position that increases its progesterone receptor binding affinity.[34][35][36]

In addition to being an antiprogestogen, mifepristone is also an antiglucocorticoid and a weak antiandrogen. Mifepristone's relative binding affinity at the progesterone receptor is more than twice that of progesterone, its relative binding affinity at the glucocorticoid receptor is more than three times that of dexamethasone and more than ten times that of cortisol; its relative binding affinity at the androgen receptor is less than one-third that of testosterone. It does not bind to the estrogen receptor or the [37]

mineralocorticoid receptor.

Mifepristone as a regular contraceptive at 2 mg daily prevents ovulation (1 mg daily does not). A single preovulatory 10-mg dose of mifepristone delays ovulation by three to four days and is as effective an emergency contraceptive as a single 1.5-mg dose of the progestin levonorgestrel.[38]

In women, mifepristone at doses greater or equal to 1 mg/kg antagonizes the endometrial and myometrial effects of progesterone. In humans, an antiglucocorticoid effect of mifepristone is manifested at doses greater or equal to 4.5 mg/kg by a compensatory increase in ACTH and cortisol. In animals, a weak antiandrogenic effect is seen with prolonged administration of very high doses of 10 to 100 mg/kg.[39][40]

In medical abortion regimens, mifepristone blockade of progesterone receptors directly causes endometrial decidual degeneration, cervical softening and dilatation, release of endogenous prostaglandins, and an increase in the sensitivity of the myometrium to the contractile effects of prostaglandins. Mifepristone-induced decidual breakdown indirectly leads to trophoblast detachment, resulting in decreased syncytiotrophoblast production of hCG, which in turn causes decreased production of progesterone by the corpus luteum (pregnancy is dependent on progesterone production by the corpus luteum through the first nine weeks of gestation—until placental progesterone production has increased enough to take the place of corpus luteum progesterone production). When followed sequentially by a prostaglandin, mifepristone 200 mg is (100 mg may be, but 50 mg is not) as effective as 600 mg in producing a medical abortion.[34][36]

'Contragestion' is a term promoted by Étienne-Émile Baulieu in the context of his advocacy of mifepristone, defining it as inclusive of some hypothesized mechanisms of action of some contraceptives and those of mifepristone to induce abortion.[41] Baulieu's definition of a 'contragestive' included any birth control method that could possibly act after fertilization and before nine-weeks gestational age.[41]

## Usage [edit]

### United States [edit]

Medical abortions voluntarily reported by 33 U.S. states[42] to the CDC have increased as a percentage of total abortions every year since the approval of mifepristone: 1.0% in 2000, 2.9% in 2001, 5.2% in 2002, 7.9% in 2003, 9.3% in 2004, 9.9% in 2005, 10.6% in 2006, and 13.1% in 2007 (20.3% of those at less than 9 weeks gestation).[43] A Guttmacher Institute survey of abortion providers estimated that medical abortions accounted for 17% of all abortions and slightly over 25% of abortions before 9 weeks gestation in the United States in 2008 (94% of nonhospital medical abortions used mifepristone and misoprostol, 6% used methotrexate and misoprostol).[44] Medical abortions accounted for 32% of first trimester abortions at Planned Parenthood clinics in the United States in 2008.[45]

### Europe [edit]

In France, the percentage of medical abortions of all abortions continues to increase: 38% in 2003, 42% in 2004, 44% in 2005, 46% in 2006, 49% in 2007 (vs. 18% in 1996).[46] In England and Wales, 52% of early abortions (less than 9 weeks gestation) in 2009 were medical; the percentage of all abortions that are medical has increased every year for the past 14 years (from 5% in 1995 to 40% in 2009) and has more than doubled in the last five years.[47] In Scotland, 81.2% of early abortions in 2009 were medical (up from 55.8% in 1992 when medical abortion was introduced); the percentage of all abortions that are medical has increased every year for the past 17 years (from 16.4% in 1992 to 69.9% in 2009).[48] In Sweden, 85.6% of early abortions and 73.2% of abortions before the end of the 12th week of gestation in 2009 were medical; 68.2% of all abortions in 2009 were medical.[49] In Great Britain and Sweden, mifepristone is licensed for use with vaginal gemeprost or oral misoprostol. As of 2000, more than 620,000 women in Europe had had medical abortions using a mifepristone regimen.[50] In Denmark, mifepristone was used in between 3,000 and 4,000 of just over 15,000 abortions in 2005.[51]

## History [edit]

In April 1980, as part of a formal research project at the French pharmaceutical company Roussel-Uclaf for the development of glucocorticoid receptor antagonists, chemist Georges Teutsch synthesized mifepristone (RU-38486, the 38,486th compound synthesized by Roussel-Uclaf from 1949 to 1980; shortened to RU-486), which was discovered to also be a progesterone receptor antagonist.[52][53] In October 1981, endocrinologist Étienne-Émile Baulieu, a consultant to Roussel-Uclaf, arranged tests of its use for medical abortion in 11 women in Switzerland by gynecologist Walter Herrmann at the University of Geneva's Cantonal Hospital, with successful results announced on April 19, 1982.[52][54] On October 9, 1987, following worldwide clinical trials in 20,000 women of mifepristone with a prostaglandin analogue (initially sulprostone or gemeprost, later misoprostol) for medical abortion, Roussel-Uclaf sought approval in France for their use for medical abortion, with approval announced on September 23, 1988.[52][55]

On October 21, 1988, in response to antiabortion protests and concerns of majority (54.5%) owner Hoechst AG of Germany, Roussel-Uclaf's executives and board of directors voted 16 to 4 to stop distribution of mifepristone, which they announced on October 26, 1988.[52][56] Two days later, the French government ordered Roussel-Uclaf to distribute mifepristone in the interests of public health.[52][57] French Health Minister Claude Évin explained: "I could not permit the abortion debate to deprive women of a product that represents medical progress. From the moment Government approval for the drug was granted, RU-486 became the moral property of women, not just the property of a drug company."[52] Following use by 34,000 women in France from April 1988 to February 1990 of mifepristone distributed free of charge, Roussel-Uclaf began selling Mifegyne (mifepristone) to hospitals in France in February 1990 at a price (negotiated with the French government) of US$48 (equivalent to $87.99 in 2016) per 600-mg dose.[52]

Mifegyne was subsequently approved in Great Britain on July 1, 1991,[58] and in Sweden in September 1992,[59] but until his retirement in late April 1994, Hoechst AG chairman Wolfgang Hilger, a devout Roman Catholic, blocked any further expansion in availability.[52][60] On May 16, 1994, Roussel-Uclaf announced it was donating without remuneration all rights for medical uses of mifepristone in the United States to the Population Council,[61] which subsequently licensed mifepristone to Danco Laboratories, a new single-product company immune to antiabortion boycotts, which won FDA approval as Mifeprex on September 28, 2000.[62]

On April 8, 1997, after buying the remaining 43.5% of Roussel-Uclaf stock in early 1997,[63] Hoechst AG (US$30 (equivalent to $45.81 in 2016) billion annual revenue) announced the end of its manufacture and sale of Mifegyne (US$3.44 (equivalent to $5.25 in 2016) million annual revenue) and the transfer of all rights for medical uses of mifepristone outside of the United States to Exelgyn S.A., a new single-product company immune to antiabortion boycotts, whose CEO was former Roussel-Uclaf CEO Édouard Sakiz.[64] In 1999, Exelgyn won approval of Mifegyne in 11 additional countries, and in 28 more countries over the following decade.[65]

## Society and culture [edit]

Mifepristone is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system.[5] It is on the complementary list and is included with a special note "where permitted under national law and where culturally acceptable".[5]

### Legal status [edit]

### United States [edit]

Mifepristone was approved for abortion in the United States by the FDA in September 2000.[66] It is legal and available in all 50 states, Washington, D.C., Guam, and Puerto Rico.[67] It is a prescription drug, but it is not available to the public through pharmacies; its distribution is restricted to specially qualified licensed

physicians, sold by Danco Laboratories under the trade name Mifeprex.

Roussel Uclaf did not seek U.S. approval, so in the United States legal availability was not initially possible.[68] The United States banned importation of mifepristone for personal use in 1989, a decision supported by Roussel Uclaf. In 1994, Roussel Uclaf gave the U.S. drug rights to the Population Council in exchange for immunity from any product liability claims.[61][69] The Population Council sponsored clinical trials in the United States.[70] The drug went on approvable status from 1996. Production was intended to begin through the Danco Group in 1996, but they withdrew briefly in 1997 due to a corrupt business partner, delaying availability again.[71][72]

Mifepristone 200 mg tablets (Mifeprex) have a marketing authorization in the United States from the Food and Drug Administration (FDA) for early first trimester medical abortion when followed by the prostaglandin analog misoprostol through 70 days gestational age.[13][73][74]

Mifepristone 300 mg tablets (Korlym) have a marketing authorization in the United States from the FDA for the medical treatment of high blood sugar (hyperglycemia) caused by high cortisol levels in the blood (hypercortisolism) in adults with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or cannot have surgery.[20][21]

### Subsection H [edit]

Some drugs are approved by the FDA under subsection H, which has two subparts. The first sets forth ways to rush experimental drugs, such as aggressive HIV and cancer treatments, to market when speedy approval is deemed vital to the health of potential patients. The second part of subsection H applies to drugs that not only must meet restrictions for use due to safety requirements, but also are required to meet postmarketing surveillance to establish that the safety results shown in clinical trials are seconded by use in a much wider population. Mifepristone was approved under the second part of subsection H. The result is that women cannot pick the drug up at a pharmacy, but must now receive it directly from a doctor. Due to the possibility of adverse reactions such as excessive bleeding, which may require a blood transfusion, and incomplete abortion, which may require surgical intervention, the drug is only considered safe if a physician who is capable of administering a blood transfusion or a surgical abortion is available to the patient in the event of such emergencies.[75] The approval of mifepristone under subsection H included a black box warning.

## Europe [edit]

Outside the United States, it is marketed and distributed by Exelgyn Laboratories under the tradename Mifegyne. Mifepristone was approved for use in France in 1988 (initial marketing in 1989), the United Kingdom in 1991, Sweden in 1992, then Austria, Belgium, Denmark, Finland, Germany, Greece, Luxembourg, the Netherlands, Spain, and Switzerland in 1999.[76] In 2000, it was approved in Norway, Russia and Ukraine. Serbia and Montenegro approved it in 2001,[77] Belarus and Latvia in 2002, Estonia in 2003, Moldova in 2004, Albania and Hungary in 2005, Portugal in 2007, and Romania in 2008.[65] In Italy, clinical trials have been constrained by protocols requiring women be hospitalized for three days, but the drug was finally approved on July 30, 2009 (officialized later in the year), despite strong opposition from the Vatican. In Italy, the pill must be prescribed and used in a clinical structure and is not sold at chemists.[78] It was approved in Hungary in 2005, but as of 2005 had not been released on the market yet, and was the target of protests.[79] Mifepristone is not approved in Ireland, where abortion is illegal, or Poland, where abortion is highly restricted.[80]

Mifepristone 200 mg tablets (Mifegyne, Mifepristone Linepharma, Medabon) have marketing authorizations in the European Economic Area from the European Medicines Agency (EMA) for:[12][81][82]

- early first trimester medical abortion when followed by a prostaglandin analog (misoprostol or gemeprost) through 63 days gestational age
- second trimester medical abortion when followed by a prostaglandin analog
- cervical softening and dilation prior to first trimester surgical abortion
- induction of labor after fetal death in utero when prostaglandin analogs and oxytocin are contraindicated

## Other countries [edit]

Mifepristone was banned in Australia in 1996. In late 2005, a private member's bill was introduced to the Australian Senate to lift the ban and transfer the power of approval to the Therapeutic Goods Administration. The move caused much debate in the Australian media and amongst politicians. The bill passed the Senate on 10 February 2006, and mifepristone is now legal in Australia. It is provided regularly at several specialized abortion clinics per state.[83][84] Mifepristone 200 mg tablets have marketing authorizations in Australia from the Therapeutic Goods Administration (TPA) for early first trimester medical abortion when followed by the prostaglandin analog misoprostol through 63 days gestational age[85] and second trimester medical abortion when followed by a prostaglandin analog.[86]

In New Zealand, pro-choice doctors established an import company, Istar, and submitted a request for approval to MedSafe, the New Zealand pharmaceutical regulatory agency. After a court case brought by Right to Life New Zealand failed, use of mifepristone was permitted.[87]

The drug was approved in Israel in 1999.[88]

Clinical trials of mifepristone in China began in 1985. In October 1988, China became the first country in the world to approve mifepristone. Chinese organizations tried to purchase mifepristone from Roussel Uclaf, which refused to sell it to them, so in 1992 China began its own domestic production of mifepristone. In 2000, the cost of medical abortion with mifepristone was higher than surgical abortion and the percentage of medical abortions varied greatly, ranging from 30% to 70% in cities to being almost nonexistent in rural areas.[89][90] A report from the United States Embassy in Beijing in 2000 said mifepristone had been widely used in Chinese cities for about two years, and that according to press reports, a black market had developed with many women starting to buy it illegally (without a prescription) from private clinics and drugstores for about US$15 (equivalent to $20.86 in 2016), causing Chinese authorities to worry about medical complications from use without physician supervision.[91]

In 2001, mifepristone was approved in Taiwan.[92] Vietnam included mifepristone in the National Reproductive Health program in 2002.[93]

It is approved in only one sub-Saharan African country—South Africa, where it was approved in 2001.[94] It is also approved in one north African country—Tunisia, also in 2001.[95]

Mifepristone was approved for use in India in 2002, where medical abortion is referred to as "medical termination of pregnancy". It is only available under medical supervision, not by prescription, due to adverse reactions such as excessive bleeding, and criminal penalties are given for buying or selling it on the black market or over-the-counter at pharmacies.[96]

Medical abortion used to be available in Canada but on a limited basis using methotrexate and misoprostol. Clinical trials were done in 2000 in various Canadian cities comparing methotrexate to mifepristone, after approbation by the federal government. While both drugs had overall similar results, mifepristone was found to act faster.[97] Health Canada gave approval to mifepristone in July 2015.[98]

Mifepristone was registered for use in Azerbaijan, Georgia, and Uzbekistan in 2002, in Guyana and Moldova in 2004, in Mongolia in 2005, and in Armenia in 2007.[65][99]

Low dose mifepristone tablets (Bi Yun, Fu Nai Er, Hou Ding Nuo, Hua Dian, Si Mi An) for emergency contraception are available directly from a pharmacist without a prescription and with a prescription in China.[22][23][24]

Low dose mifepristone tablets for emergency contraception are available by prescription in Armenia (Gynepriston), Russia (Agesta, Gynepriston, Mifepristone 72, Negele), Ukraine (Gynepriston), and Vietnam (Mifestad 10, Ciel EC).[22][23][24]

## Controversy [edit]

*Main article: Abortion controversy*

Many pro-life groups in the United States actively campaigned against the approval of

mifepristone[100][101][102] and continue to actively campaign for its withdrawal.[103] They cite either ethical issues with abortion or safety concerns regarding the drug and the adverse reactions associated with it.[104] Religious and pro-life groups outside the United States have also protested mifepristone, especially in Germany[105] and Australia.[106][107]

## Research [edit]

The original target for the research group was the discovery and development of compounds with antiglucocorticoid properties.[108] These antiglucocorticoid properties are of great interest in the treatment of severe mood disorders and psychosis, although a review of published articles was inconclusive on their efficacy, and considered the use of these drugs in mood disorders at 'proof of concept' stage.[109]

Mifepristone showed no detectable anti-HIV activity in clinical trials.[35][38][110][111]

Mifepristone showed initial promise in psychotic major depression, a difficult-to-treat form of depression,[112] but a phase-III clinical trial was terminated early due to lack of efficacy.[113]

Use as a cervical ripening agent has also been described.[114]

## References [edit]


1. ^ a b c "Mifepristone". The American Society of Health-System Pharmacists. Retrieved December 19, 2015.
2. ^ a b Rexrode, edited by Marlene Goldman, Rebecca Troisi, Kathryn (2012). *Women and health* (2nd ed.). Oxford: Academic. p. 236. ISBN 9780123849793.
3. ^ Wildschut, H; Both, MI; Medema, S; Thomee, E; Wildhagen, MF; Kapp, N (19 January 2011). "Medical methods for mid-trimester termination of pregnancy.". *The Cochrane database of systematic reviews* (1): CD005216. doi:10.1002/14651858.CD005216.pub2. PMID 21249669.
4. ^ Corey, E.J. (2012). "Mifepristone". *Molecules and Medicine*. John Wiley & Sons. ISBN 9781118361733.
5. ^ a b c "19th WHO Model List of Essential Medicines (April 2015)" (PDF). WHO. April 2015. Retrieved May 10, 2015.
6. ^ Paperny, Anna Mehler (April 5, 2016). "Abortion pill: Canadian prescribers to get training for Mifegymiso this month". *Global News*. Retrieved 10 June 2016.
7. ^ Kirkey, Sharon (April 19, 2016). "Home abortion pill about to hit market in Canada, but has already garnered criticism". *National Post*. Retrieved June 26, 2016. "expected to become available in July [2016]."
8. ^ Szklarski, Cassandra (The Canadian Press) (November 28, 2016). "Canadian debut of abortion pill Mifegymiso delayed to January". *The Globe and Mail*. Retrieved December 9, 2016. "now expects to launch 'some time in January [2017]'."
9. ^ Hussein, edited by Julia; McCaw-Binns,, Affette; Webber, Roger (2012). *Maternal and perinatal health in developing countries*. Wallingford, Oxfordshire: CABI. p. 104. ISBN 9781845937461.
10. ^ Winikoff, B; Sheldon, W (September 2012). "Use of medicines changing the face of abortion.". *International perspectives on sexual and reproductive health*. **38** (3): 164–6. doi:10.1363/3816412. PMID 23018138.
11. ^ Hamilton, Richart (2015). *Tarascon Pocket Pharmacopoeia 2015 Deluxe Lab-Coat Edition*. Jones & Bartlett Learning. p. 368. ISBN 9781284057560.
12. ^ a b Exelgyn (March 25, 2015). "Mifegyne Summary of Product Characteristics (SPC)" (PDF). London: Medicines and Healthcare Products Regulatory Agency (MHRA). Retrieved 2016-04-04.
13. ^ a b U.S. Food and Drug Administration (March 30, 2016). "Mifeprex (mifepristone) Information". Silver Spring, Md.: U.S. Food and Drug Administration. Retrieved 2016-04-04.
14. ^ Royal College of Obstetricians and Gynaecologists (November 23, 2011). "The Care of Women Requesting Induced Abortion. Evidence-based Clinical Guideline No. 7, 3rd revised edition" (PDF). London: RCOG Press. pp. 68–75. Retrieved 2016-04-04.
15. ^ World Health Organization (June 21, 2012). *Safe abortion: technical and policy guidance for health systems, 2nd edition* (PDF). Geneva: WHO. pp. 113–116. ISBN 978-92-4-154843-4. Retrieved 2016-04-04.
16. ^ World Health Organization (January 10, 2014). *Clinical practice handbook for safe abortion* (PDF). Geneva: WHO. ISBN 978-92-4-154871-7. Retrieved 2016-04-04.
17. ^ American College of Obstetricians and Gynecologists (June 2013). "ACOG Practice Bulletin Number 135: Second-

Trimester Abortion" (PDF). *Obstetrics & Gynecology*. **121** (6): 1394–1406. doi:10.1097/01.AOG.0000431056.79334.cc. PMID 23812485. Retrieved 2016-04-04.
18. ^ American College of Obstetricians and Gynecologists (March 2014). "ACOG Practice Bulletin Number 143: Medical Management of First-Trimester Abortion" (PDF). *Obstetrics & Gynecology*. **123** (3): 676–692. doi:10.1097/01.AOG.0000444454.67279.7d. PMID 24553166. Retrieved 2016-04-04.
19. ^ *a b c* Grossman, D; White, K; Harris, L; Reeves, M; Blumenthal, PD; Winikoff, B; Grimes, DA (September 2015). "Continuing pregnancy after mifepristone and "reversal" of first-trimester medical abortion: a systematic review.". *Contraception*. **92** (3): 206–11. doi:10.1016/j.contraception.2015.06.001. PMID 26057457.
20. ^ *a b* Corcept Therapeutics (June 2013). "Korlym prescribing information" (PDF). Menlo Park, Calif.: Corcept Therapeutics. Retrieved 2016-04-04.
21. ^ *a b* Corcept Therapeutics (July 24, 2013). "Corcept Therapeutics announces partnership with Idis for global access to Korlym". Menlo Park, Calif.: Corcept Therapeutics. Retrieved 2016-04-04.
22. ^ *a b c* Trussell, James; Cleland, Kelly (February 13, 2013). "Dedicated emergency contraceptive pills worldwide" (PDF). Princeton: Office of Population Research, Princeton University. Retrieved 2016-04-04.
23. ^ *a b c* ICEC (2016). "EC pill types and countries of availability, by brand". New York: International Consortium for Emergency Contraception. Retrieved 2016-04-04.
24. ^ *a b c* Trussell, James; Raymond, Elizabeth G.; Cleland, Kelly (March 2016). "Emergency Contraception: A Last Chance to Prevent Unintended Pregnancylocation=Princeton" (PDF). Office of Population Research, Princeton University. Retrieved 2016-04-07.
25. ^ *a b c d e f* "Mifeprex label" (PDF). FDA. 2005-07-19. Archived from the original (PDF) on 2006-06-28. Retrieved 2006-08-22.
26. ^ Lawton BA, Rose SB, Shepherd J (April 2006). "Atypical presentation of serious pelvic inflammatory disease following mifepristone-induced medical abortion". *Contraception*. **73** (4): 431–2. doi:10.1016/j.contraception.2005.09.003. PMID 16531180.
27. ^ "Mifepristone U.S. Postmarketing Adverse Events Summary through 04/30/2011" (PDF). Retrieved 2011-11-14.
28. ^ "www.ich.org" (PDF).
29. ^ Paul, Maureen; Lichtenberg, Steve; Borgatta, Lynn; Grimes, David A.; Stubblefield, Phillip G.; Creinin, Mitchell D. (2011-08-24). *Management of Unintended and Abnormal Pregnancy: Comprehensive Abortion Care*. John Wiley & Sons. ISBN 9781444358476.
30. ^ Gary MM, Harrison DJ (February 2006). "Analysis of severe adverse events related to the use of mifepristone as an abortifacient". *Ann Pharmacother*. **40** (2): 191–7. doi:10.1345/aph.1G481. PMID 16380436.
31. ^ Orioli IM, Castilla EE (April 2000). "Epidemiological assessment of misoprostol teratogenicity". *BJOG*. **107** (4): 519–23. doi:10.1111/j.1471-0528.2000.tb13272.x. PMID 10759272.
32. ^ *Nuclear Receptors as Drug Targets: Design and Biological Evaluation of Small Molecule Modulators of Nuclear Receptor Action*. ProQuest. 2006. pp. 46–. ISBN 978-0-549-70288-7.
33. ^ Gallagher P, Young AH (March 2006). "Mifepristone (RU-486) treatment for depression and psychosis: a review of the therapeutic implications". *Neuropsychiatr Dis Treat*. **2** (1): 33–42. PMC 2671735. PMID 19412444.
34. ^ *a b* Loose, Davis S.; Stancel, George M. (2006). "Estrogens and Progestins". In in Brunton, Laurence L.; Lazo, John S.; Parker, Keith L. *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (11th ed.). New York: McGraw-Hill. pp. 1541–1571. ISBN 0-07-142280-3.
35. ^ *a b* Schimmer, Bernard P.; Parker, Keith L. (2006). "Adrenocorticotropic Hormone; Adrenocortical Steroids and Their Synthetic Analogs; Inhibitors of the Synthesis and Actions of Adrenocortical Hormones". In in Brunton, Laurence L.; Lazo, John S.; Parker, Keith L. *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (11th ed.). New York: McGraw-Hill. pp. 1587–1612. ISBN 0-07-142280-3.
36. ^ *a b* Fiala C, Gemzel-Danielsson K (July 2006). "Review of medical abortion using mifepristone in combination with a prostaglandin analogue". *Contraception*. **74** (1): 66–86. doi:10.1016/j.contraception.2006.03.018. PMID 16781264.
37. ^ Heikinheimo O, Kekkonen R, Lahteenmaki P (2003). "The pharmacokinetics of mifepristone in humans reveal insights into differential mechanisms of antiprogestin action". *Contraception*. **68** (6): 421–6. doi:10.1016/S0010-7824(03)00077-5. PMID 14698071.
38. ^ *a b* Chabbert-Buffet N, Meduri G, Bouchard P, Spitz IM (2005). "Selective progesterone receptor modulators and progesterone antagonists: mechanisms of action and clinical applications". *Hum Reprod Update*. **11** (3): 293–307. doi:10.1093/humupd/dmi002. PMID 15790602.
39. ^ Exelgyn Laboratories (February 2006). "Mifegyne UK Summary of Product Characteristics (SPC)". Retrieved 2007-03-09.
40. ^ Danco Laboratories (July 19, 2005). "Mifeprex U.S. prescribing information" (PDF). Archived from the original (PDF) on 2007-01-07. Retrieved 2007-03-09.

41. ^ [a] [b] Baulieu, Étienne-Émile (1985). "RU 486: An antiprogestin steroid with contragestive activity in women". In Baulieu, Étienne-Émile; Segal, Sheldon J. *The antiprogesin steroid RU 486 and human fertility control (Proceedings of a conference on the antiprogestational compound RU 486, held October 23–25, 1984, in Bellagio, Italy)*. New York: Plenum Press. pp. 1–25. ISBN 0-306-42103-8.
Baulieu, Étienne-Émile (1985). "Contragestion by antiprogestin: a new approach to human fertility control". *Abortion: medical progress and social implications (Symposium held at the Ciba Foundation, London, 27–29 November 1984)*. Ciba Foundation Symposium. **115**. London: Pitman. pp. 192–210. ISBN 0-272-79815-0. PMID 3849413.
Baulieu, Étienne-Émile (1989). "Contragestion with RU 486: a new approach to postovulatory fertility control (from Meet the experts — Antiprogestins, edited by Baulieu, É-É; Proceedings of a meeting held in Rio de Janeiro, Brazil, 27 October 1988)". *Acta Obstetricia et Gynecologica Scandinavica Supplement*. **149**: 5–8. ISSN 0300-8835. PMID 2694738.
Greenhouse, Steven (February 12, 1989). "A new pill, a fierce battle". *The New York Times Magazine*. p. SM22.
Palca J (September 1989). "The pill of choice?". *Science*. **245** (4924): 1319–23. doi:10.1126/science.2781280. JSTOR 1704254. PMID 2781280.
Baulieu EE (September 1989). "Contragestion and other clinical applications of RU 486, an antiprogesterone at the receptor". *Science*. **245** (4924): 1351–7. doi:10.1126/science.2781282. JSTOR 1704267. PMID 2781282.
Baulieu EE (October 1989). "The Albert Lasker Medical Awards. RU-486 as an antiprogesterone steroid. From receptor to contragestion and beyond". *JAMA*. **262** (13): 1808–1814. doi:10.1001/jama.262.13.1808. PMID 2674487.
Bonner, Staci (July 1991). "Drug of choice". *SPIN*. **7** (4): 55–56, 88. ISSN 0886-3032.
Baulieu, Étienne-Émile; Rosenblum, Mort (November 15, 1991). *The "abortion pill": RU-486: a woman's choice (translation of: 'Génération pilule)*. New York: Simon & Schuster. pp. 18, 26–28. ISBN 0-671-73816-X.
Beck, Joan (January 2, 1992). "RU-486 pill adds a new dimension to the abortion debate". *Chicago Tribune*. p. 25.
Chesler, Ellen (July 31, 1992). "RU-486: we need prudence, not politics". *The New York Times*. p. A27.
Baulieu, Étienne-Émile (April 13, 1993). "1993: RU 486—a decade on today and tomorrow". In Donaldson, Molla S.; Dorflinger, Laneta; Brown, Sarah S.; Benet, Leslie Z. *Clinical applications of mifepristone (RU 486) and other antiprogestins; assessing the science and recommending a research agenda; (Committee on Anti-progestins: Assessing the Science; Division of Health Promotion and Disease Prevention; Institute of Medicine)*. Washington, D.C.: National Academy Press. pp. 71–119. ISBN 0-309-04949-0.
Baulieu EE (June 1994). "RU486: a compound that gets itself talked about". *Hum. Reprod*. 9 Suppl 1: 1–6. doi:10.1093/humrep/9.suppl_1.1. PMID 7962455.
Baulieu, Étienne-Émile (1997). "Innovative procedures in family planning". In Johannisson, Elisabeth; Kovács, László; Resch, Bela A; Bruyniks, Nico P. *Assessment of research and service needs in reproductive health in Eastern Europe — concerns and commitments. Proceedings of a workshop organized by the ICRR and the WHO Collaborating Centre on Research in Human Reproduction in Szeged, Hungary, 25–27 October 1993*. New York: Parthenon Publishing. pp. 51–60. ISBN 1-85070-696-4.
. (2008). "contragestive". *The American Heritage medical dictionary*. Boston: Houghton Mifflin. p. 124. ISBN 978-0-618-94725-6.

> *adj.* Capable of preventing gestation, either by preventing implantation or by causing the uterine lining to shed after implantation. —*n.* A contragestive drug or agent.

Ammer, Christine (2009). "contragestive". *The encyclopedia of women's health* (6th ed.). New York: Facts On File. pp. 124–125. ISBN 978-0-8160-7407-5.

> Also *contragestant*, *abortion pill*. A substance called *mifepristone*, or *RU-486*, which was developed by Dr. Etienne Baulieu and the Roussel-Uclaf company. The contragestive blocks progesterone receptors in the endometrium (uterine lining), preventing its buildup by progesterone; hence the uterus cannot sustain a pregnancy. It does not prevent fertilization or implantation, so technically it is an ABORTIFACIENT rather than a contraceptive.

42. ^ excluding Alabama, California, Connecticut, Washington, D.C., Florida, Georgia, Hawaii, Illinois, Kentucky, Louisiana, Massachusetts, Maryland, Nebraska, Nevada, New Hampshire, Rhode Island, Tennessee, and Wisconsin
43. ^ Pazol, Karen; Zane, Suzanne B.; Parker, Wilda, Y.; Hall, Laura R.; Gamble, Sonya B.; Hamdan, Saeed; Berg, Cynthia; Cook, Douglas A.; Division of Reproductive Health (February 25, 2011). "Abortion surveillance — United States, 2007" (PDF). *MMWR Surveill Summ*. **60** (1): 1–44. PMID 21346710.
44. ^ Jones, Rachel K.; Kooistra, Kathryn (March 2011). "Abortion incidence and access to services in the United States, 2008" (PDF). *Perspect Sex Reprod Health*. **43** (1): 41–50. doi:10.1363/4304111. PMID 21388504.

Stein, Rob (January 11, 2011). "Decline in U.S. abortion rate stalls". *The Washington Post*. p. A3.
45. ^ Fjerstad, Mary; Trussell, James; Sivin, Irving; Lichtenberg, E. Steve; Cullins, Vanessa (July 9, 2009). "Rates of serious infection after changes in regimens for medical abortion" (PDF). *New England Journal of Medicine*. **361** (2): 145–151. doi:10.1056/NEJMoa0809146. PMC 3568698. PMID 19587339.
Allday, Erin (July 9, 2009). "Change cuts infections linked to abortion pill". *San Francisco Chronicle*. p. A1.
46. ^ Vilain, Annick (December 2009). "Voluntary terminations of pregnancies in 2007" (PDF). DREES, Ministry of Health. Archived from the original (PDF) on March 31, 2010. Retrieved 2010-06-09.
47. ^ Department of Health (May 25, 2010). "Abortion statistics, England and Wales: 2009". Department of Health (United Kingdom). Retrieved 2010-06-09.
48. ^ ISD Scotland (May 25, 2010). "Abortion Statistics, year ending December 2009". Information Services Division (ISD), NHS National Services Scotland. Retrieved 2010-06-09.
49. ^ National Board of Health and Welfare, Sweden (May 12, 2010). "Induced Abortions 2010" (PDF). National Board of Health and Welfare, Sweden. Retrieved 2010-06-09.
50. ^ "FDA Approves Mifepristone for the Termination of Early Pregnancy". FDA press release/U.S. Gov. 2000. Archived from the original on September 10, 2006. Retrieved 2009-04-27.
51. ^ "The abortion pill Mifegyne tested for adverse reactions". Danish Medicines Agency. July 27, 2005. Retrieved 2006-09-20. [*dead link*]
52. ^ *a b c d e f g h* Baulieu, Étienne-Émile; Rosenblum, Mort (1991). *The "abortion pill": RU-486, a woman's choice*. New York: Simon & Schuster. ISBN 0-671-73816-X.
Lader, Lawrence (1991). *RU 486: the pill that could end the abortion wars and why American women don't have it*. Reading: Addison-Wesley. ISBN 0-201-57069-6.
Villaran, Gilda (1998). "RU 486". In Schlegelmilch, Bodo B. *Marketing ethics: an international perspective*. London: Thomson Learning. pp. 155–190. ISBN 1-86152-191-X.
Ulmann, André (2000). "The development of mifepristone: a pharmaceutical drama in three acts". *J Am Med Womens Assoc*. **55** (3 Suppl): 117–20. PMID 10846319.
53. ^ Teutsch, Georges (November 24, 1989). "RU 486 development". *Science*. **246** (4933): 985. doi:10.1126/science.2587990. PMID 2587990.
Cherfas, J (November 24, 1989). "Dispute surfaces over paternity of RU 486". *Science*. **246** (4933): 994. doi:10.1126/science.2587988. PMID 2587988.
Philibert, D; Teutsch, G (February 9, 1990). "RU 486 development". *Science*. **246** (4943): 622. doi:10.1126/science.2300819. PMID 2300819.
Ulmann, A; Teutsch, G; Philibert, D (June 1990). "RU 486". *Scientific American*. Vol. 262 no. 6. pp. 42–8. doi:10.1038/scientificamerican0690-42. PMID 2343294.
Teutsch, G.; Deraedt, R.; Philibert, D. (1993). "Mifepristone". In Lednicer, Daniel. *Chronicles of drug discovery, Vol. 3*. Washington, DC: American Chemical Society. pp. 1–43. ISBN 0-8412-2523-0.
Teutsch, G; Philibert, D (June 1994). "History and perspectives of antiprogestins from the chemist's point of view". *Human Reprod*. **9** (Suppl 1): 12–31. doi:10.1093/humrep/9.suppl_1.12. PMID 7962457.
Sittig, Marshall, ed. (2007). "Mifepristone". *Pharmaceutical manufacturing encyclopedia* (3rd ed.). Norwich, NY: William Andrew Publishing. pp. 2307–2310. ISBN 1-60119-339-4.
US patent 4,386,085, Teutsch, Jean G.; Costerousse, Germain; Philibert, Daniel; Deraedt, Roger, "Novel steroids", issued 1983-05-31 assigned to Roussel Uclaf
54. ^ Eder, Richard (April 20, 1982). "Birth control: 4-day pill is promising in early test". *The New York Times*. p. C1.
Herrmann, Walter; Wyss, Rolf; Riondel, Anne; Philibert, Daniel; Teutsch, Georges; Sakiz, Edouard; Baulieu, Étienne-Émile (May 17, 1982). "The effects of an antiprogesterone steroid in women: interruption of the menstrual cycle and of early pregnancy". *C R Seances Acad Sci III*. **294** (18): 933–8. PMID 6814714.
55. ^ Kolata, Gina (September 24, 1988). "France and China allow sale of a drug for early abortion". *The New York Times*. p. A1.
56. ^ Greenhouse, Steven (October 27, 1988). "Drug maker stops all distribution of abortion pill". *The New York Times*. p. A1.
57. ^ Greenhouse, Steven (October 29, 1988). "France ordering company to sell its abortion drug". *The New York Times*. p. A1.
58. ^ Smith, W. (September 1991). "Great Britain second country to allow use of RU-486". *Plan Parent Eur*. **20** (2): 20. PMID 12284548.
59. ^ . (December 1992). "RU 486 licensed in Sweden". *IPPF Med Bull*. **26** (6): 6. PMID 12346922.
60. ^ Newman, Barry (February 22, 1993). "Drug dilemma: among those wary of abortion pill is maker's parent firm; Germany's Hoechst is facing pressure from Clinton to sell RU-486 in U.S.". *The Wall Street Journal*. p. A1.
"F.D.A. says company delays abortion pill". *The New York Times*. Associated Press. April 16, 1993. p. A14.
Jouzaitis, Carol (October 17, 1994). "Abortion pill battle surprises French firm". *Chicago Tribune*. p. 1 (Business).
61. ^ *a b* Seelye, Katharine Q. (May 17, 1994). "Accord opens way for abortion pill in U.S. in 2 years". *The New York*

*Times*. p. A1.
62. ^ Kolata, Gina (September 29, 2000). "U.S. approves abortion pill; drug offers more privacy and could reshape debate". *The New York Times*. p. A1.
63. ^ Moore, Stephen D.; Kamm, Thomas; Fleming, Charles (December 11, 1996). "Hoechst to seek rest of Roussel-Uclaf; expected $3.04 billion offer would add to the wave of drug-sector linkups". *The Wall Street Journal*. p. A3.
Marshall, Matt (December 11, 1996). "Hoechst offers to pay $3.6 billion for rest of Roussel". *The Wall Street Journal*. p. A8.
Bloomberg Business News (December 11, 1996). "Hoechst to buy rest of Roussel". *The New York Times*. p. D4.
64. ^ Bloomberg News (April 9, 1997). "Pill for abortion ends production". *The New York Times*. p. D2.
Jouzaitis, Carol (April 9, 1997). "Abortion pill maker bows to boycott heat; German firm gives up RU-486 patent; little impact likely in U.S.". *Chicago Tribune*. p. 4.
Lavin, Douglas (April 9, 1997). "Hoechst will stop making abortion pill". *The Wall Street Journal*. p. A3.
. (April 18, 1997). "Roussel-Uclaf to transfer RU 486 rights". *Reprod Freedom News*. **6** (7): 8. PMID 12292550.
Dorozynski, Alexander (April 19, 1997). "Boycott threat forces French company to abandon RU486". *BMJ*. **314** (7088): 1150. doi:10.1136/bmj.314.7088.1145m. PMC 2126515. PMID 9146386.
65. ^ *a b c* . (November 4, 2009). "List of mifepristone approval" (PDF). New York: Gynuity Health Projects.
. (November 4, 2009). "Map of mifepristone approval" (PDF). New York: Gynuity Health Projects. Retrieved 2010-06-11.
66. ^ "FDA approval letter for Mifepristone". FDA. September 28, 2000. Archived from the original on November 16, 2001. Retrieved 2006-09-16.
67. ^ "Medication Abortion in the United States: Mifepristone Fact Sheet" (PDF). Gynuity Health Projects. 2005. Archived from the original (PDF) on September 24, 2007.
68. ^ Klitsch M (November–December 1991). "Antiprogestins and the abortion controversy: a progress report". *Fam Plann Perspect*. **23** (6): 275–82. doi:10.2307/2135779. JSTOR 2135779. PMID 1786809.
69. ^ Nancy Gibbs (October 2, 2000). "The Pill Arrives". Cnn.com. Retrieved 2006-09-20.
70. ^ Tamar Lewin (January 30, 1995). "Clinical Trials Giving Glimpse of Abortion Pill". *The New York Times*. Retrieved 2006-09-20.
71. ^ Tamar Lewin (November 13, 1997). "Lawsuits' Settlement Brings New Hope for Abortion Pill". *The New York Times*. Retrieved 2006-09-16.
72. ^ Sharon Lerner (August 2000). "RU Pissed Off Yet?". *The Village Voice*. Retrieved 2006-09-16.
73. ^ Danco Laboratories (March 29, 2016). "Mifeprex prescribing information" (PDF). Silver Spring, Md.: U.S. Food and Drug Administration.
74. ^ American Congress of Obstetricians and Gynecologists (March 30, 2016). "ACOG Statement on Medication Abortion". Washington, D.C.: ACOG. Retrieved 2016-04-07.
75. ^ Woodcock, Janet (2006-05-12). "Testimony on RU-486". *Committee on Government Reform, House of Representatives*. FDA. Archived from the original on 2006-09-27. Retrieved 2006-08-19.
76. ^ Christin-Maitre, S., Bouchard, P., Spitz, I. M. (2000). "Medical termination of pregnancy". *New England Journal of Medicine*. **342** (13): 946–56. doi:10.1056/NEJM200003303421307. PMID 10738054.
77. ^ Stojnic J, et al. (2006). "Medicamentous abortion with mifepristone and misoprostol in Serbia and Montenegro". *Vojnosanitetski pregled. Military-medical and pharmaceutical review*. **63** (6): 558–63. doi:10.2298/VSP0606558S. PMID 16796021.
78. ^ "Abortion pill approved in Italy". BBC News. July 31, 2009. Retrieved 2009-07-31.
79. ^ "Abortion pill sparks bitter protest". The Budapest Times. September 19, 2005. Retrieved 2006-09-16.
80. ^ Peter S. Green (June 24, 2003). "A Rocky Landfall for a Dutch Abortion Boat". *The New York Times*. Retrieved 2006-09-16.
81. ^ Linepharma (November 7, 2014). "Mifepristone Linepharma Summary of Product Characteristics (SPC)" (PDF). London: Medicines and Healthcare Products Regulatory Agency (MHRA). Retrieved 2016-04-14.
82. ^ Sun Pharmaceuticals (March 4, 2015). "Medabon Summary of Product Characteristics (SPC)" (PDF). London: Medicines and Healthcare Products Regulatory Agency (MHRA). Retrieved 2016-04-04.
83. ^ "Marie Stopes International Australia – Medical Abortion". 2010. Archived from the original on November 22, 2010. Retrieved 2010-12-15.
84. ^ "Abortion pill – RU486 (mifepristone)". Better Health Channel Victoria. July 2010. Archived from the original on August 14, 2010. Retrieved 2010-12-15.
85. ^ MS Health (December 24, 2014). "Mifepristone Linepharma (MS-2 Step) 200 mg tablet product information". Symonston, Australian Capital Territory, Australia: Therapeutic Goods Administration. Retrieved 2016-04-04.
86. ^ MS Health (May 12, 2015). "Mifepristone Linepharma 200 mg tablet product information". Symonston, Australian Capital Territory, Australia: Therapeutic Goods Administration. Retrieved 2016-04-04.
87. ^ Sparrow MJ (2004). "A woman's choice". *Aust NZ J Obstet Gynaecol*. **44** (2): 88–92. doi:10.1111/j.1479-

828X.2004.00190.x . PMID 15089829 .
88. ^ Etienne-Emile Baulieu; Daniel S. Seidman; Selma Hajri (October 2001). "Mifepristone(RU-486) and voluntary termination of pregnancy: enigmatic variations or anecdotal religion-based attitudes?". Human Reproduction. Retrieved 2006-09-16.
89. ^ Ulmann A (2000). "The development of mifepristone: a pharmaceutical drama in three acts". *J Am Med Women's Assoc*. **55** (3 Suppl): 117–20. PMID 10846319.
90. ^ Wu S (2000). "Medical abortion in China". *J Am Med Women's Assoc*. **55** (3 Suppl): 197–9, 204. PMID 10846339.
91. ^ "Family planning in China: RU-486, abortion, and population trends". U.S. Embassy Beijing. 2000. Retrieved 2006-09-14.
92. ^ Tsai EM, Yang CH, Lee JN (2002). "Medical abortion with mifepristone and misoprostol: a clinical trial in Taiwanese women". *J Formos Med Assoc*. **101** (4): 277–82. PMID 12101864.
93. ^ Ganatra B, Bygdeman M, Nguyen DV, Vu ML, Phan BT (2004). "From research to reality: the challenges of introducing medical abortion into service delivery in Vietnam". *Reprod Health Matters*. **12** (24): 105–13. doi:10.1016/S0968-8080(04)24022-8. PMID 15938163.
94. ^ "Medical Abortion-Implications for Africa" (PDF). Ipas. 2003. Retrieved 2006-09-16.
95. ^ Hajri S (2004). "Medication abortion: the Tunisian experience". *Afr J Reprod Health*. **8** (1): 63–9. doi:10.2307/3583307. JSTOR 3583307. PMID 15487615.
96. ^ "Mifepristone can be sold only to approved MTP Centres: Rajasthan State HRC". Indian Express Health Care Management. 2000.
97. ^ ."Results of the Canadian trials of RU486, the 'Abortion Pill'[*permanent dead link*]." (n.d.). Retrieved 2006-12-08.
98. ^ "RU-486 abortion pill approved by Health Canada". Retrieved 2015-07-30.
99. ^ "Medication Abortion". Ibis. 2002. Retrieved 2006-09-19.
100. ^ Paige Comstock Cunningham; Leanne McCoy; Clarke D. Ferguson (February 28, 1995). "Citizen Petition to the U.S. Food and Drug Administration". Americans United for Life. Retrieved 2006-09-20.
101. ^ Margaret Talbot (July 11, 1999). "The Little White Bombshell". *The New York Times*. Retrieved 2006-09-20.
102. ^ "Abortion Foes To Boycott Drugs (Altace) Made By RU-486 Manufacturer". *The Virginia Pilot*. July 8, 1994. Retrieved 2006-09-15.
103. ^ Stan Guthrie (June 11, 2001). "Counteroffensive Launched on RU-486". *Christianity Today*. Retrieved 2006-09-20.
104. ^ Gina Kolata (September 24, 2003). "Death at 18 Spurs Debate Over a Pill For Abortion". *The New York Times*. Retrieved 2006-09-20.
105. ^ John L. Allen (February 12, 1999). "Abortion debates rock Germany: introduction of abortion pill exacerbates controversy". *National Catholic Reporter*. Retrieved 2006-09-14.
106. ^ "Catholic and Evangelical students join Muslims in RU-486 fight". *Catholic News*. February 9, 2006. Archived from the original on October 27, 2006. Retrieved 2006-09-18.
107. ^ "Death Toll Rises to 11 Women". Australians Against RU-486. 2006. Retrieved 2006-09-20.
108. ^ Hazra BG, Pore VS (2001). "Mifepristone (RU-486), the recently developed antiprogesterone drug and its analogues.". *J Indian Inst Sci*. **81**: 287–98.
109. ^ Peter Gallagher; Navdeep Malik; James Newham; Allan H Young; Nicol Ferrier; Paul Mackin (2008). "Antiglucocorticoid treatments for mood disorders.". *Cochrane Database Syst. Review*: CD005168. doi:10.1002/14651858.CD005168.pub2. PMID 18254070.
110. ^ Flexner C (December 2007). "HIV drug development: the next 25 years". *Nat Rev Drug Discov*. **6** (12): 959–66. doi:10.1038/nrd2336. PMID 17932493.
111. ^ Tang OS, Ho PC (2006). "Clinical applications of mifepristone". *Gynecol Endocrinol*. **22** (12): 655–9. doi:10.1080/09513590601005946. PMID 17162706.
112. ^ Belanoff JK, Flores BH, Kalezhan M, Sund B, Schatzberg AF (October 2001). "Rapid reversal of psychotic depression using mifepristone". *J Clin Psychopharmacol*. **21** (5): 516–21. doi:10.1097/00004714-200110000-00009. PMID 11593077.
113. ^ Damian Gard for Fierce Biotech. May 7, 2014. Corcept tanks as depression drug comes up short in Phase III Archived March 2, 2016, at the Wayback Machine.
114. ^ Clark K, Ji H, Feltovich H, Janowski J, Carroll C, Chien EK (May 2006). "Mifepristone-induced cervical ripening: structural, biomechanical, and molecular events". *Am. J. Obstet. Gynecol*. **194** (5): 1391–8. doi:10.1016/j.ajog.2005.11.026. PMID 16647925.

# External links [edit]

U.S. Food and Drug Administration Mifeprex (mifepristone) information
- Commonly asked questions about RU-486 from the education arm of the National Coalition of Abortion Providers
- Danco product web site – EarlyOptionPill.com
- Danco prescribing information
- Australians for RU-486 – established in February 2006 to lobby for passage of bill in Australia's Parliament to enable the availability of mifepristone

| v · t · e | **Progestogens and antiprogestogens** | |
|---|---|---|
| **Progestogens (and progestins)** | **Progesterone** | Progesterone · Quingestrone · |
| | **Retroprogesterone** | Dydrogesterone · Trengestone · |
| | **17α-Hydroxyprogesterone (and closely related)** | Acetomepregenol (mepregenol diacetate) · Algestone · Algestone acetophenide (dihydroxyprogesterone acetophenide) · Anagestone acetate · Chlormadinone acetate · Cyproterone acetate · Delmadinone acetate · Flugestone acetate (flurogestone acetate) · Flumedroxone acetate · Hydroxyprogesterone · Hydroxyprogesterone acetate · Hydroxyprogesterone caproate · Hydroxyprogesterone heptanoate · Medroxyprogesterone · Medroxyprogesterone acetate[#] · Megestrol acetate · Melengestrol acetate · Osaterone acetate · Pentagestrone acetate · *Other 17α-substitutions:* Haloprogesterone · Medrogestone · Proligestone · |
| | **19-Norprogesterone (including 17α-substituted)** | Demegestone · Gestonorone caproate (gestronol hexanoate) · Nomegestrol acetate · Norgestomet · Promegestone · Segesterone acetate (nestorone) · Trimegestone · |
| | **17α-Ethynyltestosterone** | Danazol · Dimethisterone · Ethisterone · |
| | **19-Nortestosterone (including 17α-substituted)** | *Estranes:* Etynodiol diacetate · Gestrinone · Lynestrenol · Norethisterone (norethindrone)[#] · Norethisterone acetate · Norethisterone enanthate · Noretynodrel · Norgestrienone · Quingestanol acetate · Tibolone · *Gonanes:* Desogestrel · Dienogest · Etonogestrel · Gestodene · Levonorgestrel[#] · Norelgestromin · Norgestimate · Norgestrel · *Others:* Allylestrenol · Altrenogest · Norgesterone · Normethandrone (methylestrenolone) · Norvinisterone · Oxendolone · |
| | **17α-Spirolactosteroid** | Canrenone · Drospirenone · Potassium canrenoate · Spironolactone · |
| | **Others** | Anabolic steroids (e.g., nandrolone esters, trenbolone esters, norethandrolone, normethandrone, propetandrol, others) · |
| **SPRMs** | Asoprisnil[†] · Telapristone[§] · Ulipristal acetate · | |
| **Antiprogestogens** | Aglepristone · **Mifepristone** · Valproic acid · | |

[#] WHO-EM · [‡] Withdrawn from market · Clinical trials: ([†] Phase III · [§] Never to phase III · ·

*See also:* *Androgens and antiandrogens* • *Estrogens and antiestrogens* • *Glucocorticoids and antiglucocorticoids* • *Mineralocorticoids and antimineralocorticoids* • *Gonadotropins and GnRH*

v · t · e · **Glucocorticoids and antiglucocorticoids (H02)**

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| **Glucocorticoids** | **Natural** | Cortisone · Cortodoxone (cortexolone, 11-deoxycortisol) · Desoxycortone (deoxycortone, cortexone, 11-deoxycorticosterone) · Hydrocortisone (cortisol)[#] (Hydrocortisone aceponate · Hydrocortisone buteprate · Hydrocortisone butyrate · · |
| | **Synthetic** | *Progesterone-type:* Flugestone acetate (flurogestone acetate) · Fluorometholone (Fluorometholone acetate · · Medrysone · Prebediolone acetate · Pregnenolone (Pregnenolone acetate · Pregnenolone succinate · · *Hydrocortisone-type:* Chloroprednisone · Cloprednol · Difluprednate · Fludrocortisone · Fluocinolone · Fluperolone (Fluperolone acetate · · Fluprednisolone · Loteprednol · Methylprednisolone (Methylprednisolone aceponate · Methylprednisolone acetate · Methylprednisolone suleptanate · · Prednicarbate · Prednisolone · Prednisone · Tixocortol (Tixocortol pivalate · · Triamcinolone · *Methasone-type (16-methylated):* Alclometasone · Beclometasone (Beclometasone dipropionate · · Betamethasone (Betamethasone dipropionate · · Clobetasol (Clobetasol propionate · · Clobetasone · Clocortolone · Cortivazol · Desoximetasone · Dexamethasone (Dexamethasone acefurate · Dexamethasone isonicotinate · · Diflorasone · Difluocortolone (Difluocortolone valerate · · Fluclorolone · Flumetasone · Fluocortin · Fluocortolone · Fluprednidene (Fluprednidene acetate · · Fluticasone (Fluticasone propionate · · Halometasone · Meprednisone · Mometasone · Paramethasone · Prednylidene · Rimexolone · Ulobetasol (halobetasol) · *Acetonides and related:* Amcinonide · Budesonide · Ciclesonide · Deflazacort · Desonide · Formocortal (fluoroformylone) · Fluclorolone acetonide (fluocloronide) · Fludroxycortide (flurandrenolone, flurandrenolide) · Flunisolide · Fluocinolone acetonide · Fluocinonide · Fluticasone furoate · Halcinonide · Mometasone furoate · Triamcinolone acetonide · Triamcinolone benetonide · Triamcinolone furetonide · Triamcinolone hexacetonide · |
| **Antiglucocorticoids** | | *SGRMs:* Dagrocorat[§] · Fosdagrocorat[§] · Mapracorat[†] · *Antagonists:* Ketoconazole · **Mifepristone** · |
| **Synthesis modifiers** | | Acetoxolone · Aminoglutethimide · Carbenoxolone · Enoxolone · Ketoconazole · Metyrapone · Mitotane · Trilostane · |

[#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III · ·

*See also:* *Androgens and antiandrogens* • *Estrogens and antiestrogens* • *Progestogens and antiprogestogens* • *Mineralocorticoids and antimineralocorticoids*

v · t · e · **Abortion**

| | |
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| **Main topics** | History of abortion · Methods of abortion · Abortion debate · Abortion law · |
| **Movements** | Abortion-rights movements · Anti-abortion movements · |

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| **Issues** | | Abortion and mental health · Beginning of human personhood · Beginning of pregnancy controversy · Abortion-breast cancer hypothesis · Anti-abortion violence · Birth control · Crisis pregnancy center · Ethical aspects of abortion · Eugenics · Fetal rights · Forced abortion · Genetics and abortion · Late-term abortion · Legalized abortion and crime effect · Libertarian perspectives on abortion · Limit of viability · Men's rights · Minors and abortion · One-child policy · Paternal rights and abortion · Philosophical aspects of the abortion debate · Prenatal development · Reproductive rights · Self-induced abortion · Sex-selective abortion · Sidewalk counseling · Societal attitudes towards abortion · Unsafe abortion · Women's rights · |
| **By country** | **Africa** | Algeria · Angola · Benin · Botswana · Burkina Faso · Namibia · Nigeria · South Africa · Uganda · Zimbabwe · |
| | **Americas** | Argentina · Belize · Bolivia · Brazil · Canada · Chile · Colombia · Costa Rica · Cuba · Dominican Republic · Ecuador · El Salvador · Guatemala · Guyana · Mexico · Nicaragua · Panama · Paraguay · Peru · Trinidad and Tobago · Suriname · United States · Uruguay · Venezuela · |
| | **Asia** | Afghanistan · Armenia · Azerbaijan · Bahrain · Bangladesh · Bhutan · Brunei · Cambodia · China · Cyprus · East Timor · India · Iran · Israel · Japan · Kazakhstan · Northern Cyprus · Philippines · Qatar · Russia · Saudi Arabia · Turkey · |
| | **Australasia** | Australia · Fiji · Kiribati · New Zealand · Papua New Guinea · Samoa · Solomon Islands · Tonga · Tuvalu · Vanuatu · |
| | **Europe** | Albania · Andorra · Armenia · Austria · Azerbaijan · Belarus · Belgium · Bosnia and Herzegovina · Bulgaria · Croatia · Cyprus · Czech Republic · Denmark · Estonia · Finland · France · Germany · Greece · Hungary · Iceland · Ireland · Italy · Kazakhstan · Latvia · Liechtenstein · Lithuania · Luxembourg · Macedonia · Malta · Moldova · Monaco · Montenegro · Netherlands · Northern Cyprus · Norway · Poland · Portugal · Romania · Russia · San Marino · Serbia · Slovakia · Slovenia · Spain · Sweden · Switzerland · Turkey · Ukraine · United Kingdom · |
| **Law** | | Case law · Constitutional law · History of abortion law · Laws by country · Buffer zones · Conscience clauses · Fetal heartbeat bills · Fetal protection · Informed consent · Late-term restrictions · Parental involvement · Spousal consent · |
| **Methods** | | Vacuum aspiration · Dilation and evacuation · Dilation and curettage · Intact D&X · Hysterotomy · Instillation · Menstrual extraction · Abortifacient drugs (**Mifepristone** · Misoprostol · Oxytocin · · Self-induced abortion · Unsafe abortion · |
| **Religion** | | Buddhism · Christianity (Catholicism · · Hinduism · Islam · Judaism · Scientology · |
| WikiSource · Wikimedia Commons · Wikiquote · Wiktionary · Wikiversity · | | |

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|---|---|---|
| v · t · e · | **Androgen receptor modulators** | |
| | | *Testosterone derivatives:* 4-Androstenediol · 4-Dehydroepiandrosterone (4-DHEA) · 4-Hydroxytestosterone · 5-Androstenedione · 11-Ketotestosterone · 11β-Hydroxyandrostenedione · Adrenosterone (11-ketoandrostenedione, 11-oxoandrostenedione) · Androstenediol (5-androstenediol) (Androstenediol 3β-acetate · Androstenediol 17β-acetate · Androstenediol diacetate · Androstenediol dipropionate · · Androstenedione (4-androstenedione) · Atamestane · Boldenone (Boldenone undecylenate · · Boldione (1,4-androstadienedione) · Clostebol |

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| | **Agonists** | (Clostebol acetate · Clostebol caproate · Clostebol propionate · · Cloxotestosterone (Cloxotestosterone acetate · · Dehydroandrosterone · DHEA (androstenolone, prasterone; 5-DHEA) (DHEA enanthate (prasterone enanthate) · DHEA sulfate · · Exemestane · Formestane · Plomestane · Quinbolone · Silandrone · Testosterone[#] (Testosterone acetate · Testosterone acetate butyrate · Testosterone acetate propionate · Testosterone benzoate · Testosterone butyrate · Testosterone buciclate · Testosterone capropate · Testosterone cyclohexylpropionate · Testosterone cypionate · Testosterone decanoate · Testosterone diacetate · Testosterone dipropionate · Testosterone enanthate · Testosterone enanthate benziloylhydrazone · Testosterone formate · Testosterone furoate · Testosterone hexahydrobenzoate · Testosterone hexahydrobenzylcarbonate · Testosterone hexyloxyphenylpropionate · Testosterone isobutyrate · Testosterone isocaproate · Testosterone isovalerate · Testosterone ketolaurate · Testosterone nicotinate · Testosterone palmitate · Testosterone phenylacetate · Testosterone phenylbutyrate · Testosterone phenylpropionate · Testosterone phosphate · Testosterone propionate · Testosterone stearate · Testosterone sulfate · Testosterone undecanoate · Testosterone valerate · ·<br>*Dihydrotestosterone derivatives:* 1-Androstenediol · 1-Androstenedione · 1-Androsterone (1-andro, 1-DHEA) · 1-Testosterone · 3α-Androstanediol · 5α-Androst-2-en-17-one · 7β-Hydroxyepiandrosterone · 11-Ketodihydrotestosterone · Androsterone · Bolazine (Bolazine capronate · · Dihydrotestosterone (androstanolone, stanolone) (Dihydrotestosterone acetate · Dihydrotestosterone benzoate · Dihydrotestosterone butyrate · Dihydrotestosterone enanthate · Dihydrotestosterone formate · Dihydrotestosterone propionate · Dihydrotestosterone valerate · · Drostanolone (Drostanolone propionate · · Epiandrosterone · Epitiostanol · Mepitiostane · Mesabolone · Mesterolone · Nisterime (Nisterime acetate · · Prostanozol · Stenbolone (Stenbolone acetate · · Testifenon (testiphenon, testiphenone) ·<br>*19-Nortestosterone derivatives:* 7α-Methyl-19-norandrostenedione (MENT dione, trestione) · 11β-Methyl-19-nortestosterone (11β-Methyl-19-nortestosterone dodecylcarbonate · · 19-Nor-5-androstenediol · 19-Nor-5-androstenedione · Bolandiol (Bolandiol dipropionate · · Bolandione (19-nor-4-androstenedione) · Bolmantalate (nandrolone adamantoate) · Dienedione · Dienolone · Dimethandrolone (Dimethandrolone buciclate · Dimethandrolone dodecylcarbonate · Dimethandrolone undecanoate · · LS-1727 (nandrolone 17β-*N*-(2-chloroethyl)-*N*-nitrosocarbamate) · Methoxydienone (methoxygonadiene) · Nandrolone (Nandrolone acetate · Nandrolone caproate · Nandrolone cypionate · Nandrolone cyclohexanecarboxylate · Nandrolone cyclohexylpropionate · Nandrolone cyclotate · Nandrolone decanoate · Nandrolone formate · Nandrolone furylpropionate · Nandrolone hexyloxyphenylpropionate · Nandrolone hydrogen succinate · Nandrolone laurate · Nandrolone phenylpropionate · Nandrolone propionate · Nandrolone sulfate · Nandrolone sulfate sodium · Nandrolone undecanoate · · Norclostebol (Norclostebol acetate · · |

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| **AR** | | Normethandrone (methylestrenolone, normethisterone) · Oxabolone (Oxabolone cipionate (oxabolone cypionate) · · Trenbolone (Trenbolone acetate · Trenbolone enanthate · Trenbolone hexahydrobenzylcarbonate · · Trestolone (MENT) (Trestolone acetate · ·<br>*Dihydrotestosterone and 19-nortestosterone derivatives:* 5α-Dihydronandrolone · 19-Norandrosterone ·<br>*17α-Alkylated testosterone derivatives:* · Bolasterone · Calusterone · Chlorodehydromethylandrostenediol (CDMA) · Chlorodehydromethyltestosterone (CDMT) · Chloromethylandrostenediol (CMA) · Enestebol · Ethyltestosterone · Fluoxymesterone · Formebolone · Hydroxystenozole · Metandienone (methandrostenolone) · Methandriol (methylandrostenediol) (Methandriol bisenanthoyl acetate · Methandriol diacetate · Methandriol dipropionate · Methandriol propionate · · Methylclostebol (chloromethyltestosterone) · Methyltestosterone (Methyltestosterone 3-hexyl ether · · Oxymesterone · Penmesterol · Tiomesterone ·<br>*17α-Alkylated dihydrotestosterone derivatives:* Androisoxazole · Desoxymethyltestosterone · Furazabol · Mebolazine (dimethazine) · Mestanolone · Metenolone (Metenolone acetate · Metenolone enanthate · · Methasterone · Methyl-1-testosterone · Methylepitiostanol · Methylstenbolone · Oxandrolone · Oxymetholone · Stanozolol ·<br>*17α-Alkylated 19-nortestosterone derivatives:* Bolenol · Dimethyltrienolone (7α-methylmetribolone, 7α,17α-dimethyltrenbolone) · Ethyldienolone · Ethylestrenol · Methyldienolone · Methylhydroxynandrolone (MOHN, MHN) · Metribolone · Mibolerone · Norboletone · Norethandrolone · Propetandrol · Tetrahydrogestrinone ·<br>*17α-Vinyltestosterone derivatives:* Norvinisterone (vinylnortestosterone) · Vinyltestosterone ·<br>*17α-Ethynyltestosterone derivatives:* $\Delta^4$-Tibolone · Danazol · Desogestrel · Ethisterone (ethynyltestosterone) · Etonogestrel · Etynodiol · Etynodiol diacetate · Gestodene · Gestrinone · Levonorgestrel · Levonorgestrel butanoate · Lynestrenol · Norethisterone (Norethisterone acetate · Norethisterone acetate oxime · Norethisterone enanthate · · Norgestrel · Norgestrienone · Quingestanol · Quingestanol acetate · Tibolone ·<br>*Progesterone derivatives:* Medroxyprogesterone acetate ·<br>*Others/unsorted:* Cl-4AS-1 · Drupanol · ZM-182345 · |
| | **Mixed (SARMs)** | *Non-steroidal:* 198RL26 · ACP-105 · AC-262,356 · Acetothiolutamide · Andarine (acetamidoxolutamide, androxolutamide, GTx-007, S-4) · BMS-564,929 · Enobosarm (ostarine, MK-2866, GTx-024, S-22) · FTBU-1 · GSK-4336A · GSK-8698 · LG-121071 (LGD-121071) · LGD-2226 · LGD-2941 (LGD-122941) · LGD-3303 · LGD-4033 · JNJ-26146900 · JNJ-28330835 · JNJ-37654032 · ORM-11984 · RAD140 · R-1 · R-2 · R-3 · S-1 · S-23 · S-40503 · S-101479 ·<br>*Steroidal:* MK-0773 · TFM-4AS-1 · YK-11 · |
| | | *Steroidal:* 9,11-Dehydrocortexolone 17α-butyrate (CB-03-04) · 11α-Hydroxyprogesterone · 15β-Hydroxycyproterone acetate · Abiraterone · Abiraterone acetate · Allyltestosterone · Benorterone · BOMT · Canrenoic acid · |

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| | **Antagonists** | Canrenone · Chlormadinone acetate · Clometerone · Cortexolone 17α-propionate (CB-03-01) · Cyproterone · Cyproterone acetate · Delanterone · Dienogest · Drospirenone · Edogestrone · Epitestosterone · Galeterone · Guggulsterone · Medrogestone · Megestrol acetate · Mespirenone · Metogest · Mexrenone · **Mifepristone** · Nomegestrol acetate · Nordinone · Osaterone · Osaterone acetate · Oxendolone · Potassium canrenoate · Prorenone · Rosterolone · SC-5233 (spirolactone) · Spironolactone · Spirorenone · Topterone · Trimethyltrienolone (R-2956) · Zanoterone · *Non-steroidal:* AA560 · Apalutamide · Atraric acid · AZD-3514 · Bakuchiol · BAY-1024767 · Bicalutamide · Bisphenols (e.g., BADGE, BFDGE, bisphenol A, bisphenol F, bisphenol S) · BMS-641,988 · Cimetidine · Cioteronel · Darolutamide · DDT (via metabolite p,p′-DDE) · Dieldrin · DIMP · Endosulfan · Enzalutamide · EPI-001 · EPI-506 · Fenarimol · Flutamide · Hydroxyflutamide · Inocoterone · Inocoterone acetate · Ketoconazole · Lavender oil · LG-105 · LG-120907 · Linuron · Methiocarb · N-Butylbenzenesulfonamide · N-Desmethylenzalutamide · Nilutamide · ONC1-13B · ORM-15341 · Pentomone · PF-998425 · Phenothrin · Prochloraz · Procymidone · RU-22930 · RU-58642 · RU-58841 · Seviteronel · Thalidomide · Topilutamide (fluridil) · Valproic acid · Vinclozolin · |
| **GPRC6A** | **Agonists** | Cations (incl. aluminum, calcium, gadolinium, magnesium, strontium) · Dehydroandrosterone · Dihydrotestosterone · Estradiol · L-α-Amino acids (incl. L-arginine, L-lysine, L-ornithine) · Osteocalcin · Testosterone · |

*See also: Estrogenics • Glucocorticoidics • Mineralocorticoidics • Progestogenics • Steroid hormone metabolism modulators • List of androgens/anabolic steroids*

v · t · e

## Glucocorticoid receptor modulators

| | | |
|---|---|---|
| | **Agonists** | *Corticosteroids:* 3α,5α-Tetrahydrocorticosterone · 5α-Dihydrocorticosterone · 11-Deoxycorticosterone (desoxycortone, cortexone) · 11-Deoxycortisol (cortodoxone, cortexolone)) · 17α-Hydroxyprogesterone · 21-Deoxycortisol · Acrocinonide · Alclometasone · Amcinafal · Amcinafide · Amcinonide · Amebucort · Amelometasone · Amicinonide · AZD5423 · Beclometasone · Beclometasone dipropionate · Betamethasone · Betamethasone acibutate · Betamethasone dipropionate · Budesonide · Butixocort · Chloroprednisone · Ciclesonide · Cicortonide · Ciprocinonide · Clobetasol · Clobetasol propionate · Clobetasone · Clocortolone · Cloprednol · Cloticasone · Cormetasone · Corticosterone · Cortifen (kortifen) · Cortisone · Cortisuzol · Cortivazol · Deflazacort · Deprodone · Descinolone · Desonide · Desoximetasone · Dexbudesonide · Dexamethasone · Dexamethasone acefurate · Dexamethasone cipecilate · Dexamethasone isonicotinate · Dichlorisone · Diflorasone · Difluocortolone · Difluocortolone valerate · Difluprednate · Domoprednate · Doxibetasol · Drocinonide · Etiprednol dicloacetate · Fluazacort · Fluclorolone · Fluclorolone (flucloronide) · Fludrocortisone · Fludroxycortide · Flumoxonide · Flumetasone · Flunisolide · Fluocinolone · Fluocinolone acetonide · Fluocinonide · Fluocortin · Fluocortolone · Fluorometholone · Fluperolone · Fluperolone acetate · Fluprednidene · Fluprednidene acetate · Fluprednisolone · Fluticasone · Fluticasone furoate · Fluticasone propionate · Formocortal · GSK-9027 · Halcinonide · Halocortolone · Halometasone · Halopredone · Hydrocortamate · Hydrocortisone (cortisol) · Hydrocortisone aceponate · Hydrocortisone buteprate · Hydrocortisone-17-butyrate · Hydrocortisone-21-butyrate · Icometasone enbutate · |

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| **GR** | | Isoflupredone · Isoprednidene · Itrocinonide · Locicortolone dicibate · Loteprednol · Mazipredone · Meclorisone · Medrysone · Meprednisone · Methylprednisolone · Methylprednisolone aceponate · Methylprednisolone acetate · Methylprednisolone suleptanate · Mometasone · Mometasone furoate · Naflocort · Nicocortonide · Nivacortol · Oxisopred · Paramethasone · Prebediolone · Prebediolone acetate · Prednazate · Prednazoline · Prednicarbate · Prednimustine · Prednisolamate · Prednisolone · Prednisolone steaglate · Prednisone · Prednylidene · Pregnenolone · Pregnenolone acetate · Pregnenolone succinate · Procinonide · Resocortol · Rimexolone · Rofleponide · RU-28362 · Timobesone · Tipredane · Tixocortol · Tixocortol pivalate · Tralonide · Triamcinolone · Triamcinolone acetonide · Triamcinolone benetonide · Triamcinolone furetonide · Triamcinolone hexacetonide · Triclonide · Ulobetasol (halobetasol) · Vamorolone · *Other steroids:* 15β-Hydroxycyproterone acetate · 17α-Hydroxyprogesterone · Chlormadinone acetate · Cyproterone · Cyproterone acetate · Delmadinone acetate · Flugestone · Flugestone acetate (flurogestone acetate) · Fluoxymesterone · Gestodene · Medrogestone · Medroxyprogesterone acetate · Megestrol acetate · Metribolone · Norgestomet · Osaterone acetate · Progesterone · Promegestone · Quingestrone · Segesterone acetate (nestorone) · Tetrahydrogestrinone · |
| | **Mixed (SEGRAs)** | Dagrocorat · Fosdagrocorat · Mapracorat · |
| | **Antagonists** | 7α-Hydroxy-DHEA · 17α-Methylprogesterone · Aglepristone · Asoprisnil · C108297 · C113176 · CORT-108297 · Cyproterone acetate · Formebolone · Guggulsterone · Ketoconazole · Lilopristone · LLY-2707 · Miconazole · **Mifepristone** · Onapristone · ORG-34116 · ORG-34517 (SCH-900636) · ORG-34850 · Pregnenolone 16α-carbonitrile · Telapristone · Tibolone · Toripristone · Ulipristal acetate · |

*See also: Androgenics • Estrogenics • Mineralocorticoidics • Progestogenics • Steroid hormone metabolism modulators*

| v · t · e · | **Progesterone receptor modulators** |
|---|---|
| | *Progesterone derivatives:* 5α-Dihydroprogesterone · 9α-Bromo-11-ketoprogesterone · 11-Dehydroprogesterone · 11-Deoxycorticosterone · 16α-Hydroxyprogesterone · 20α-Dihydroprogesterone · Dimepregnen · Diosgenin · P1-185 · Progesterone · Quingestrone · *Retroprogesterone derivatives:* Dydrogesterone · Retroprogesterone · Ro 6-3129 · Trengestone · *17α-Substituted progesterone derivatives:* 6α-Methyl-17α-bromoprogesterone · 15β-Hydroxycyproterone acetate · 17α-Hydroxyprogesterone (hydroxyprogesterone) · 17α-Methylprogesterone · Acetomepregenol (mepregenol diacetate) · Algestone · Algestone acetonide · Algestone acetophenide · Anagestone · Anagestone acetate · Butagest (buterol) · Chlormadinone · Chlormadinone acetate · Cismadinone · Cismadinone acetate · Clogestone · Clogestone acetate · Clomegestone · Clomegestone acetate · Cyproterone acetate · Delmadinone · Delmadinone acetate · Edogestrone · Flugestone · Flugestone acetate · Flumedroxone · Flumedroxone acetate · Gestaclone · Haloprogesterone · Hydromadinone · Hydromadinone acetate · Hydroxyprogesterone acetate · Hydroxyprogesterone caproate (hydroxyprogesterone hexanoate) · Hydroxyprogesterone heptanoate (hydroxyprogesterone enanthate) · |

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| **PR** | **Agonists** | Mecigestone (pentarane B) · Medrogestone · Medroxyprogesterone · Medroxyprogesterone acetate · Megestrol · Megestrol acetate · Melengestrol · Melengestrol acetate · Mometasone · Mometasone furoate · Osaterone · Osaterone acetate · Pentagestrone · Pentagestrone acetate · Pentarane A · Proligestone ·<br>*19-Norprogesterone derivatives:* 19-Norprogesterone · Amadinone · Amadinone acetate · Demegestone · Gestadienol · Gestonorone caproate (gestronol hexanoate) · Gestronol (gestonorone) · Nomegestrol · Nomegestrol acetate · Norgestomet · ORG-2058 · Oxogestone · Oxogestone phenpropionate · Promegestone · Segesterone · Segesterone acetate (nestorone) · Trimegestone ·<br>*Testosterone derivatives:* 6,6-Difluoronorethisterone · 6,6-Difluoronorethisterone acetate · 11β-Methyl-19-nortestosterone · 11β-Methyl-19-nortestosterone dodecylcarbonate · 19-Nor-5-androstenediol · 19-Nor-5-androstenedione · Allylestrenol · Altrenogest · Bolandiol · Bolandiol dipropionate · Bolandione · Chloroethynylnorgestrel · Cingestol · Danazol · Desogestrel · Dienedione · Dienogest · Dienolone · Dimethandrolone · Dimethandrolone buciclate · Dimethandrolone dodecylcarbonate · Dimethandrolone undecanoate · Dimethisterone · Dimethyltrienolone · Ethisterone · Ethyldienolone · Ethylestrenol (ethylnandrol) · Ethynerone · Etonogestrel · Etynodiol · Etynodiol diacetate · Gestodene · Gestrinone · Levonorgestrel · Levonorgestrel butanoate · Lynestrenol · Methyldienolone · Metribolone (R-1881) · Metynodiol · Metynodiol diacetate · Methoxydienone (methoxygonadiene) · Mibolerone · Nandrolone · Nandrolone esters (e.g., nandrolone decanoate, nandrolone phenylpropionate) · Norelgestromin · Norethisterone (norethindrone) · Norethisterone acetate · Norethisterone acetate oxime · Norethisterone enanthate · Noretynodrel · Norgesterone · Norgestimate · Norgestrel · Norgestrienone · Normethandrone (methylestrenolone, normethandrolone, normethisterone) · Norvinisterone · Oxendolone · Quingestanol · Quingestanol acetate · Tetrahydrogestrinone · Tibolone · Tigestol · Tosagestin · Trenbolone (trienolone) · Trestolone · Trestolone acetate ·<br>*Spirolactone derivatives:* Canrenoic acid · Canrenone · Drospirenone · Mespirenone · Potassium canrenoate · SC-5233 · SC-8109 · Spironolactone · Spirorenone ·<br>*Non-steroidal:* 3,8-Dihydrodiligustilide · Riligustilide · Tanaproget · ZM-182345 · |
| | **Mixed (SPRMs)** | Apigenin · Asoprisnil · Asoprisnil ecamate · Guggulsterone · Kaempferol · J1042 · LG-120838 · Naringenin · PRA-910 · Syringic acid · Telapristone ·<br>*Antagonistic:* **Mifepristone** · ORG-31710 · ORG-33628 · Ulipristal acetate · ZK-137316 · |
| | **Antagonists** | Aglepristone · LG-100127 · LG-100128 · Lilopristone · Lonaprisan · Onapristone · Toripristone · Valproic acid · Vilaprisan · Zanoterone · ZM-150271 · ZM-172406 · |
| **mPRs (PAQRs)** | **Agonists** | 5α-Dihydroprogesterone · 5β-Dihydroprogesterone · 11-Deoxycortisone (21-hydroxyprogesterone) · 11-Deoxycortisol (17α,21-dihydroxyprogesterone) · 17α-Hydroxyprogesterone · Allopregnanolone · **Mifepristone** · Pregnenolone · Progesterone · |
| | **Antagonists** | **Mifepristone** · |

*See also: Androgenics • Estrogenics • Glucocorticoidics • Mineralocorticoidics • Steroid hormone metabolism modulators*

| v • t • e • | Nuclear receptor modulators | | |
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| **CAR** | **Agonists** | | 6,7-Dimethylesculetin • Amiodarone • Artemisinin • Benfuracarb • Carbamazepine • Carvedilol • Chlorpromazine • Chrysin • CITCO • Clotrimazole • Cyclophosphamide • Cypermethrin • DHEA • Efavirenz • Ellagic acid • Griseofulvin • Methoxychlor • **Mifepristone** • Nefazodone • Nevirapine • Nicardipine • Octicizer • Permethrin • Phenobarbital • Phenytoin • Pregnanedione (5β-dihydroprogesterone) • Reserpine • TCPOBOP • Telmisartan • Tolnaftate • Troglitazone • Valproic acid • |
| | **Antagonists** | | 3,17β-Estradiol • 3α-Androstanol • 3α-Androstenol • 3β-Androstanol • 17-Androstanol • AITC • Ethinylestradiol • Meclizine • Nigramide J • Okadaic acid • PK-11195 • S-07662 • T-0901317 • |
| **ERR** | **ERRα** | **Agonists** | 6,3′,4′-Trihydroxyflavone • Biochanin A • Cholesterol • Daidzein • Genistein • |
| | | **Antagonists** | Diethylstilbestrol • XCT-790 • |
| | **ERRβ** | **Agonists** | DY-131 (GSK-9089) • GSK-4716 (GW-4716) • |
| | | **Antagonists** | 4-Hydroxytamoxifen (afimoxifene) • Diethylstilbestrol • |
| | **ERRγ** | **Agonists** | Bisphenol A • DY-131 (GSK-9089) • GSK-4716 (GW-4716) • |
| | | **Antagonists** | 4-Hydroxytamoxifen (afimoxifene) • Diethylstilbestrol • |
| **FXR** | **Agonists** | | Bile acids • Cafestol • Chenodeoxycholic acid • Fexaramine • GW-4064 • Obeticholic acid • |
| | **Antagonists** | | Guggulsterone • |
| **LXR** | **Agonists** | | 22R-Hydroxycholesterol • 24S-Hydroxycholesterol • 27-Hydroxycholesterol • Cholestenoic acid • DMHCA • GW-3965 • Hypocholamide • T-0901317 • |
| | **Antagonists** | | Efavirenz • |
| **PPAR** | **PPARα** | **Agonists** | 15-HETE • 15-HpETE • Aleglitazar • Aluminium clofibrate • Arachidonic acid • Bezafibrate • Clofibrate • CP-775146 • Daidzein • DHEA • Elafibranor • Etomoxir • Fenofibrate • Genistein • Gemfibrozil • GW-7647 • Leukotriene $B_4$ • LG-101506 • LG-100754 • Lobeglitazone • Muraglitazar • Oleylethanolamide • Palmitoylethanolamide • Pemafibrate • Perfluorononanoic acid • Perfluorooctanoic acid • Pioglitazone • Saroglitazar • Sodelglitazar • Tesaglitazar • Tetradecylthioacetic acid • Troglitazone • WY-14643 • |
| | | **Antagonists** | GW-6471 • MK-886 • |
| | **PPARδ** | **Agonists** | 15-HETE • 15-HpETE • Arachidonic acid • Bezafibrate • Daidzein • Elafibranor • Fonadelpar • Genistein • GW-0742 • GW-501516 • L-165,041 • LG-101506 • MBX-8025 • Sodelglitazar • Tetradecylthioacetic acid • |
| | | **Antagonists** | FH-535 • GSK-0660 • GSK-3787 • |
| | **PPARγ** | **Agonists** | 5-Oxo-ETE • 5-Oxo-15-hydroxy-ETE • 15-Deoxy-$\Delta^{12,14}$-prostaglandin $J_2$ • 15-HETE • 15-HpETE • Aleglitazar • Arachidonic acid • Balaglitazone • Berberine • Bezafibrate • Cevoglitazar • Ciglitazone • Daidzein • Darglitazone • Edaglitazone • Efatutazone • Englitazone • Etalocib • Farglitazar • Genistein • GW-1929 • Ibuprofen • Imiglitazar • Indeglitazar • LG-100268 • LG-100754 • LG-101506 • Lobeglitazone • Muraglitazar (muroglitazar) • nTZDpa • |

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| | **PPARγ** | | Naveglitazar · Netoglitazone · Oxeglitazar · Peliglitazar · Pemaglitazar · Perfluorononanoic acid · Pioglitazone · Prostaglandin $J_2$ · Ragaglitazar · Reglitazar · Rivoglitazone · Rosiglitazone · RS5444 · Saroglitazar · Sipoglitazar · Sodelglitazar · Telmisartan · Tesaglitazar · Troglitazone · |
| | | **SPPARMs** | BADGE · EPI-001 · INT-131 · MK-0533 · S26948 · |
| | | **Antagonists** | FH-535 · GW-9662 · SR-202 · T-0070907 · |
| | | **Unknown** | SR-1664 · |
| | **Unselective** | **Agonists** | Ciprofibrate · Clinofibrate · Clofibride · Englitazone · Etofibrate · Farglitazar · Netoglitazone · Ronifibrate · Rivoglitazone · Simfibrate · |
| | **Unsorted** | **Agonists** | Seladelpar · |
| **PXR** | **Agonists** | | 17α-Hydroxypregnenolone · 17α-Hydroxyprogesterone · $\Delta^4$-Androstenedione · $\Delta^5$-Androstenediol · $\Delta^5$-Androstenedione · AA-861 · Allopregnanediol · Allopregnanedione (5α-dihydroprogesterone) · Allopregnanolone · Alpha-Lipoic acid · Ambrisentan · AMI-193 · Amlodipine besylate · Antimycotics · Artemisinin · Aurothioglucose · Bile acids · Bithionol · Bosentan · Bumecaine · Cafestol · Cephaloridine · Cephradine · Chlorpromazine · Ciglitazone · Clindamycin · Clofenvinfos · Chloroxine · Clotrimazole · Colforsin · Corticosterone · Cyclophosphamide · Cyproterone acetate · Demecolcine · Dexamethasone · DHEA · DHEA-S · Dibunate sodium · Diclazuril · Dicloxacillin · Dimercaprol · Dinaline · Docetaxel · Docusate calcium · Dodecylbenzenesulfonic acid · Dronabinol · Droxidopa · Eburnamonine · Ecopipam · Enzacamene · Epothilone B · Erythromycin · Famprofazone · Febantel · Felodipine · Fenbendazole · Fentanyl · Flucloxacillin · Fluorometholone · Griseofulvin · Guggulsterone · Haloprogin · Hetacillin potassium · Hyperforin · *Hypericum perforatum* (St John's wort) · Indinavir sulfate · Lasalocid sodium · Levothyroxine · Linolenic acid · LOE-908 · Loratadine · Lovastatin · Meclizine · Methacycline · Methylprednisolone · Metyrapone · Mevastatin · **Mifepristone** · Nafcillin · Nicardipine · Nicotine · Nifedipine · Nilvadipine · Nisoldipine · Norelgestromin · Omeprazole · Orlistat · Oxatomide · Paclitaxel · Phenobarbital · Piperine · Plicamycin · Prednisolone · Pregnanediol · Pregnanedione (5β-dihydroprogesterone) · Pregnanolone · Pregnenolone · Pregnenolone 16α-carbonitrile · Proadifen · Progesterone · Quingestrone · Reserpine · Reverse triiodothyronine · Rifampicin · Rifaximin · Rimexolone · Riodipine · Ritonavir · Simvastatin · Sirolimus · Spironolactone · Spiroxatrine · SR-12813 · Suberoylanilide · Sulfisoxazole · Suramin · Tacrolimus · Tenylidone · Terconazole · Testosterone isocaproate · Tetracycline · Thiamylal sodium · Thiothixene · Thonzonium bromide · Tianeptine · Troglitazone · Troleandomycin · Tropanyl 3,5-dimethulbenzoate · Zafirlukast · Zearalanol · |
| | **Antagonists** | | Ketoconazole · Sesamin · |
| **RAR** | **Agonists** | | 9CDHRA · 9-*cis*-Retinoic acid (alitretinoin) · AC-261066 · AC-55649 · Acitretin · Adapalene · all-*trans*-Retinoic acid (tretinoin) · AM-580 · BMS-493 · BMS-753 · BMS-961 · CD-1530 · CD-2314 · CD-437 · Ch-55 · EC 23 · Etretinate · Fenretinide · Isotretinoin · Palovarotene · Retinoic acid · Retinol (vitamin A) · Tamibarotene · Tazarotene · Tazarotenic acid · TTNPB · |
| | **Antagonists** | | BMS-195614 · BMS-493 · CD-2665 · ER-50891 · LE-135 · MM-11253 · |
| | **Others** | | *Retinoic acid metabolism inhibitors:* Liarozole · |
| | **Agonists** | | 9CDHRA · 9-*cis*-Retinoic acid (alitretinoin) · all-*trans*-Retinoic acid (tretinoin) · Bexarotene · CD 3254 · Docosahexaenoic acid · Fluorobexarotene · Isotretinoin · LG-100268 · LG-101506 |

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| **RXR** | | · LG-100754 · Retinoic acid · Retinol (vitamin A) · SR-11237 · |
| | **Antagonists** | HX-531 · HX-630 · LG-100754 · PA-452 · UVI-3003 · |
| **SHR** | **AR** | See here instead. |
| | **ER** | See here instead. |
| | **PR** | See here instead. |
| | **GR** | See here instead. |
| | **MR** | See here instead. |
| | **VDR** | **Agonists** 7-Dehydrocholesterol · 22-Oxacalcitriol · 25-Hydroxyergocalciferol · Alfacalcidol · Calcifediol · Calciferol · Calcipotriol · Calcitriol · Cholecalciferol (vitamin $D_3$) · Dihydrotachysterol · Doxercalciferol · EB-1089 · Eldecalcitol · Ercalcidiol · Ercalcitriol · Ergocalciferol (vitamin $D_2$) · Lithocholic acid · Paricalcitol · Tacalcitol · |
| **TR** | **Agonists** | Dextrothyroxine · DITPA · Eprotirome (KB-2115) · KB-2611 · KB-130015 · Levothyroxine · Liothyronine · MB-07811 · MGL-3196 (VIA-3196) · Sobetirome (GC-1, GRX-431) · Thyroxine · Tiratricol · Triiodothyronine · VK-0214 · VK-2809 · ZYT1 · |
| | **Others** | *Carrier proteins:* Albumin · Thyroxine-binding globulin · Transthyretin · |

| v · t · e · **Serotonin receptor modulators** | |
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| **5-HT$_1$ receptors** · | |
| **5-HT$_{1A}$** | *Agonists:* 8-OH-DPAT · Adatanserin · Amphetamine · Antidepressants (e.g., etoperidone, nefazodone, trazodone, vilazodone, vortioxetine) · Atypical antipsychotics (e.g., aripiprazole, asenapine, clozapine, lurasidone, quetiapine, ziprasidone) · Azapirones (e.g., buspirone, eptapirone, gepirone, perospirone, tandospirone) · Bay R 1531 · Befiradol · BMY-14802 · Cannabidiol · Dimemebfe · Dopamine · Ebalzotan · Eltoprazine · Ergolines (e.g., bromocriptine, cabergoline, dihydroergotamine, ergotamine, lisuride, LSD, methylergometrine (methylergonovine), methysergide, pergolide) · F-11461 · F-12826 · F-13714 · F-14679 · F-15063 · F-15599 · Flesinoxan · Flibanserin · Flumexadol · Lesopitron · LY-293284 · LY-301317 · mCPP · MKC-242 · Naluzotan · NBUMP · Osemozotan · Oxaflozane · Pardoprunox · Piclozotan · Rauwolscine · Repinotan · Roxindole · RU-24969 · S-14506 · S-14671 · S-15535 · Sarizotan · Serotonin (5-HT) · SSR-181507 · Sunepitron · Tryptamines (e.g., 5-CT, 5-MeO-DMT, 5-MT, bufotenin, DMT, indorenate, N-Me-5-HT, psilocin, psilocybin) · TGBA01AD · U-92016A · Urapidil · Vilazodone · Xaliproden · Yohimbine · |
| | *Antagonists:* Atypical antipsychotics (e.g., iloperidone, risperidone, sertindole) · AV965 · Beta blockers (e.g., alprenolol, cyanopindolol, iodocyanopindolol, oxprenolol, pindobind, pindolol, propranolol, tertatolol) · BMY-7378 · CSP-2503 · Dotarizine · Ergolines (e.g., metergoline) · Flopropione · GR-46611 · Isamoltane · Lecozotan · Mefway · Metitepine (methiothepin) · MIN-117 (WF-516) · MPPF · NAN-190 · Robalzotan · S-15535 · SB-649915 · SDZ 216-525 · Spiperone · Spiramide · Spiroxatrine · UH-301 · WAY-100135 · WAY-100635 · Xylamidine · |
| | *Unknown/unsorted:* Ergolines (e.g., ergometrine (ergonovine)) · |
| **5-HT$_{1B}$** | *Agonists:* CGS-12066A · CP-93129 · CP-94253 · CP-122,288 · CP-135807 · Eltoprazine · Ergolines (e.g., bromocriptine, dihydroergotamine, ergotamine, methylergometrine (methylergonovine), methysergide, pergolide) · mCPP · RU-24969 · Serotonin (5-HT) · Triptans (e.g., avitriptan, donitriptan, eletriptan, sumatriptan, zolmitriptan) · TFMPP · Tryptamines (e.g., 5-BT, 5-CT, 5-MT, DMT) · Vortioxetine · |
| | *Antagonists:* AR-A000002 · Elzasonan · Ergolines (e.g., metergoline) · GR-127935 · Isamoltane · LY-393558 |

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| | · Metitepine (methiothepin) · SB-216641 · SB-224289 · SB-236057 · Yohimbine · |
| | *Unknown/unsorted:* Ergolines (e.g., cabergoline, ergometrine (ergonovine), lisuride) · |
| **5-HT$_{1D}$** | *Agonists:* CP-122,288 · CP-135807 · CP-286601 · Ergolines (e.g., bromocriptine, cabergoline, dihydroergotamine, ergotamine, LSD, methysergide) · GR-46611 · L-694247 · L-772405 · mCPP · PNU-109291 · PNU-142633 · Serotonin (5-HT) · TGBA01AD · Triptans (e.g., almotriptan, avitriptan, donitriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) · Tryptamines (e.g., 5-BT, 5-CT, 5-Et-DMT, 5-MT, 5-(nonyloxy)tryptamine, DMT) · |
| | *Antagonists:* Alniditan · BRL-15572 · Elzasonan · Ergolines (e.g., metergoline) · GR-127935 · Ketanserin · LY-310762 · LY-367642 · LY-393558 · LY-456219 · LY-456220 · Metitepine (methiothepin) · Mianserin · Ritanserin · Yohimbine · Ziprasidone · |
| | *Unknown/unsorted:* Ergolines (e.g., lisuride, lysergol, pergolide) · |
| **5-HT$_{1E}$** | *Agonists:* BRL-54443 · Ergolines (e.g., methysergide) · Serotonin (5-HT) · Triptans (e.g., eletriptan) · Tryptamines (e.g., tryptamine) · |
| | *Antagonists:* Metitepine (methiothepin) · |
| | *Unknown/unsorted:* Ergolines (e.g., ergometrine (ergonovine), lysergol, methylergometrine (methylergonovine) · |
| **5-HT$_{1F}$** | *Agonists:* BRL-54443 · CP-122,288 · Ergolines (e.g., bromocriptine, lysergol, methylergometrine (methylergonovine) methysergide) · Lasmiditan · LY-334370 · Serotonin (5-HT) · Triptans (e.g., eletriptan, naratriptan, sumatriptan) · Tryptamines (e.g., 5-MT) · |
| | *Antagonists:* Mianserin · Metitepine (methiothepin) · |
| **5-HT$_2$ receptors** · | |
| **5-HT$_{2A}$** | *Agonists:* 25H/NB series (e.g., 25I-NBF, 25I-NBMD, 25I-NBOH, 25I-NBOMe, 25B-NBOMe, 25C-NBOMe, 25TFM-NBOMe, 2CBCB-NBOMe, 25CN-NBOH, 2CBFly-NBOMe) · 2Cs (e.g., 2C-B, 2C-E, 2C-I, 2C-T-2, 2C-T-7, 2C-T-21) · 2C-B-FLY · 2CB-Ind · 5-Methoxytryptamines (5-MeO-DET, 5-MeO-DiPT, 5-MeO-DMT, 5-MeO-DPT, 5-MT) · α-Alkyltryptamines (e.g., 5-Cl-αMT, 5-Fl-αMT, 5-MeO-αET, 5-MeO-αMT, α-Me-5-HT, αET, αMT) · AL-34662 · AL-37350A · Bromo-DragonFLY · Dimemebfe · DMBMPP · DOx (e.g., DOB, DOC, DOI, DOM) · Efavirenz · Ergolines (e.g., 1P-LSD, ALD-52, bromocriptine, cabergoline, ergine (LSA), ergotamine, lisuride, LA-SS-Az, LSB, LSD, LSD-Pip, LSH, LSP, methylergometrine (methylergonovine), pergolide) · Flumexadol · Jimscaline · Lorcaserin · MDxx (e.g., MDA, MDMA, MDOH, MMDA) · O-4310 · Oxaflozane · PHA-57378 · PNU-22394 · PNU-181731 · RH-34 · Phenethylamines (e.g., lophophine, mescaline) · Piperazines (e.g., BZP, mCPP, quipazine, TFMPP) · Serotonin (5-HT) · TCB-2 · TFMFly · Tryptamines (e.g., 5-BT, 5-CT, bufotenin, DET, DiPT, DMT, DPT, psilocin, psilocybin, tryptamine) · |
| | *Antagonists:* 5-I-R91150 · 5-MeO-NBpBrT · AC-90179 · Adatanserin · Altanserin · AMDA · APD-215 · Atypical antipsychotics (e.g., amperozide, aripiprazole, asenapine, blonanserin, carpipramine, clocapramine, clorotepine, clozapine, fluperlapine, gevotroline, iloperidone, melperone, mosapramine, ocaperidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, zicronapine, ziprasidone, zotepine) · Cinanserin · CSP-2503 · Cyproheptadine · Deramciclane · Dotarizine · Eplivanserin · Ergolines (e.g., amesergide, LY-53857, LY-215840, mesulergine, metergoline, methysergide, sergolexole) · Etoperidone · Fananserin · Flibanserin · Glemanserin · Irindalone · Ketanserin · KML-010 · Lubazodone · LY-393558 · Medifoxamine · Mepiprazole · Metitepine (methiothepin) · MIN-101 · Naftidrofuryl · Nantenine · Nefazodone · Pelanserin · Phenoxybenzamine · Pimavanserin · Pirenperone · Pizotifen · Pruvanserin · Rauwolscine · Ritanserin · S-14671 · Sarpogrelate · Setoperone · Spiperone · Spiramide · SR-46349B · TGBA01AD · Teniloxazine · Temanogrel · Tetracyclic antidepressants (e.g., amoxapine, aptazapine, esmirtazapine, maprotiline, |

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| | mianserin, mirtazapine) · Trazodone · Tricyclic antidepressants (e.g., amitriptyline) · Typical antipsychotics (e.g., chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, pipamperone, prochlorperazine, thioridazine, thiothixene, trifluoperazine) · Volinanserin · Xylamidine · Yohimbine ·<br>*Unknown/unsorted:* Ergolines (e.g., dihydroergotamine, ergometrine (ergonovine), nicergoline) · MIN-117 (WF-516) · |
| **5-HT$_{2B}$** | *Agonists:* 4-Methylaminorex · Aminorex · Amphetamines (eg., chlorphentermine, cloforex, dexfenfluramine, fenfluramine, levofenfluramine, norfenfluramine) · BW-723C86 · DOx (e.g., DOB, DOC, DOI, DOM) · Ergolines (e.g., cabergoline, dihydroergocryptine, dihydroergotamine, ergotamine, methylergometrine (methylergonovine), methysergide, pergolide) · MDxx (e.g., MDA, MDMA, MDOH, MMDA) · Piperazines (e.g., mCPP) · PNU-22394 · Ro60-0175 · Serotonin (5-HT) · Tryptamines (e.g., 5-BT, 5-CT, 5-MT, α-Me-5-HT, bufotenin, DET, DiPT, DMT, DPT, psilocin, psilocybin, tryptamine) ·<br>*Antagonists:* Agomelatine · Asenapine · Cyproheptadine · EGIS-7625 · Ergolines (e.g., amesergide, bromocriptine, lisuride, LY-53857, LY-272015, mesulergine) · Ketanserin · LY-393558 · Metadoxine · Metitepine (methiothepin) · Pirenperone · Propranolol · PRX-08066 · Rauwolscine · Ritanserin · RS-127445 · Sarpogrelate · SB-200646 · SB-204741 · SB-206553 · SB-215505 · SB-221284 · SB-228357 · SDZ SER-082 · Tegaserod · Tetracyclic antidepressants (e.g., amoxapine, mianserin) · TIK-301 · Yohimbine ·<br>*Unknown/unsorted:* Ergolines (e.g., ergometrine (ergonovine)) · |
| **5-HT$_{2C}$** | *Agonists:* 2Cs (e.g., 2C-B, 2C-E, 2C-I, 2C-T-2, 2C-T-7, 2C-T-21) · 5-Methoxytryptamines (5-MeO-DET, 5-MeO-DiPT, 5-MeO-DMT, 5-MeO-DPT, 5-MT) · α-Alkyltryptamines (e.g., 5-Cl-αMT, 5-Fl-αMT, 5-MeO-αET, 5-MeO-αMT, α-Me-5-HT, αET, αMT) · A-372159 · AL-38022A · Alstonine · CP-809101 · Dimemebfe · DOx (e.g., DOB, DOC, DOI, DOM) · Ergolines (e.g., ALD-52, cabergoline, dihydroergotamine, ergine (LSA), ergotamine, lisuride, LA-SS-Az, LSB, LSD, LSD-Pip, LSH, LSP, pergolide) · Flumexadol · Lorcaserin · MDxx (e.g., MDA, MDMA, MDOH, MMDA) · MK-212 · Org 12962 · Org 37684 · Oxaflozane · PHA-57378 · Phenethylamines (e.g., lophophine, mescaline) · Piperazines (e.g., aripiprazole, BZP, mCPP, quipazine, TFMPP) · PNU-22394 · PNU-181731 · Ro60-0175 · Ro60-0213 · Serotonin (5-HT) · Tryptamines (e.g., 5-BT, 5-CT, bufotenin, DET, DiPT, DMT, DPT, psilocin, psilocybin, tryptamine) · Vabicaserin · WAY-629 · WAY-161503 · YM-348 ·<br>*Antagonists:* Adatanserin · Agomelatine · Atypical antipsychotics (e.g., asenapine, clorotepine, clozapine, fluperlapine, iloperidone, melperone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, zotepine) · Captodiame · CEPC · Cinanserin · Cyproheptadine · Deramciclane · Dotarizine · Eltoprazine · Ergolines (e.g., amesergide, bromocriptine, LY-53857, LY-215840, mesulergine, metergoline, methysergide, sergolexole) · Etoperidone · Fluoxetine · FR-260010 · Irindalone · Ketanserin · Ketotifen · Latrepirdine (dimebolin) · Medifoxamine · Metitepine (methiothepin) · Nefazodone · Pirenperone · Pizotifen · Propranolol · Ritanserin · RS-102221 · S-14671 · SB-200646 · SB-206553 · SB-221284 · SB-228357 · SB-242084 · SB-243213 · SDZ SER-082 · Tedatioxetine · Tetracyclic antidepressants (e.g., amoxapine, aptazapine, esmirtazapine, maprotiline, mianserin, mirtazapine) · TIK-301 · Trazodone · Tricyclic antidepressants (e.g., amitriptyline, nortriptyline) · Typical antipsychotics (e.g., chlorpromazine, loxapine, pimozide, pipamperone, thioridazine) · Xylamidine ·<br>*Unknown/unsorted:* Efavirenz · Ergolines (e.g., ergometrine (ergonovine), methylergometrine (methylergonovine)) · |
| **5-HT$_3$ – 5-HT$_7$ receptors** · | |
| | *Agonists:* Alcohols (e.g., butanol, ethanol, trichloroethanol) · m-CPBG · Phenylbiguanide · Piperazines (e.g., BZP, mCPP, quipazine) · RS-56812 · Serotonin (5-HT) · SR-57227 · SR-57227A · Tryptamines (e.g., 2-Me-5-HT, 5-CT, bufotenidine (5-HTQ)) · Volatiles/gases (e.g., halothane, isoflurane, toluene, |

| | |
|---|---|
| | trichloroethane) · YM-31636 · |
| **5-HT$_3$** | *Antagonists:* Alosetron · AS-8112 · Atypical antipsychotics (e.g., clozapine, olanzapine, quetiapine) · Azasetron · Batanopride · Bemesetron (MDL-72222) · Cilansetron · CSP-2503 · Dazopride · Dolasetron · Galanolactone · Granisetron · ICS-205930 · Lerisetron · Memantine · Ondansetron · Palonosetron · Ramosetron · Renzapride · Ricasetron · Tedatioxetine · Tetracyclic antidepressants (e.g., amoxapine, mianserin, mirtazapine) · Thujone · Tropanserin · Tropisetron · Typical antipsychotics (e.g., loxapine) · Volatiles/gases (e.g., nitrous oxide, sevoflurane, xenon) · Vortioxetine · Zacopride · Zatosetron · |
| | *Unknown/unsorted:* LY-53857 · Piperazines (e.g., naphthylpiperazine) · |
| **5-HT$_4$** | *Agonists:* 5-MT · BIMU8 · Capeserod · Cinitapride · Cisapride · CJ-033466 · Dazopride · Metoclopramide · Mosapride · Prucalopride · PRX-03140 · Renzapride · RS-67333 · RS-67506 · Serotonin (5-HT) · Tegaserod · Velusetrag · Zacopride · |
| | *Antagonists:* GR-113808 · GR-125487 · L-Lysine · Piboserod · RS-39604 · RS-67532 · SB-203186 · SB-204070 · |
| **5-HT$_{5A}$** | *Agonists:* Ergolines (e.g., 2-Br-LSD (BOL-148), ergotamine, LSD) · Serotonin (5-HT) · Tryptamines (e.g., 5-CT) · Valerenic Acid · |
| | *Antagonists:* Asenapine · Latrepirdine (dimebolin) · Metitepine (methiothepin) · Ritanserin · SB-699551 · *Unknown/unsorted:* Ergolines (e.g., metergoline, methysergide) · Piperazines (e.g., naphthylpiperazine) · |
| **5-HT$_6$** | *Agonists:* Ergolines (e.g., dihydroergocryptine, dihydroergotamine, ergotamine, lisuride, LSD, mesulergine, metergoline, methysergide) · Serotonin (5-HT) · Tryptamines (e.g., 2-Me-5-HT, 5-BT, 5-CT, 5-MT, Bufotenin, E-6801, E-6837, EMD-386088, EMDT, LY-586713, N-Me-5-HT, tryptamine) · WAY-181187 · WAY-208466 · |
| | *Antagonists:* ABT-354 · Atypical antipsychotics (e.g., aripiprazole, asenapine, clorotepine, clozapine, fluperlapine, iloperidone, olanzapine, tiospirone) · AVN-101 · AVN-211 · AVN-322 · AVN-397 · BGC20-760 · BVT-5182 · BVT-74316 · Cerlapirdine · EGIS-12233 · GW-742457 · Idalopirdine · Ketanserin · Latrepirdine (dimebolin) · Metitepine (methiothepin) · MS-245 · PRX-07034 · Ritanserin · Ro04-6790 · Ro 63-0563 · SB-258585 · SB-271046 · SB-357134 · SB-399885 · SB-742457 · Tetracyclic antidepressants (e.g., amoxapine, mianserin) · Tricyclic antidepressants (e.g., amitriptyline, clomipramine, doxepin, nortriptyline) · Typical antipsychotics (e.g., chlorpromazine, loxapine) · |
| | *Unknown/unsorted:* Ergolines (e.g., 2-Br-LSD (BOL-148), bromocriptine, lergotrile, pergolide) · Piperazines (e.g., naphthylpiperazine) · |
| **5-HT$_7$** | *Agonists:* 8-OH-DPAT · AS-19 · Bifeprunox · E-55888 · Ergolines (e.g., LSD) · LP-12 · LP-44 · RU-24969 · Sarizotan · Serotonin (5-HT) · Triptans (e.g., frovatriptan) · Tryptamines (e.g., 5-CT, 5-MT, bufotenin, N-Me-5-HT) · |
| | *Antagonists:* Atypical antipsychotics (e.g., amisulpride, aripiprazole, asenapine, clorotepine, clozapine, fluperlapine, olanzapine, risperidone, sertindole, tiospirone, ziprasidone, zotepine) · Butaclamol · DR-4485 · EGIS-12233 · Ergolines (e.g., 2-Br-LSD (BOL-148), amesergide, bromocriptine, cabergoline, dihydroergotamine, ergotamine, LY-53857, LY-215840, mesulergine, metergoline, methysergide, sergolexole) · JNJ-18038683 · Ketanserin · LY-215840 · Metitepine (methiothepin) · Ritanserin · SB-258719 · SB-258741 · SB-269970 · SB-656104 · SB-656104A · SB-691673 · SLV-313 · SLV-314 · Spiperone · SSR-181507 · Tetracyclic antidepressants (e.g., amoxapine, maprotiline, mianserin, mirtazapine) · Tricyclic antidepressants (e.g., amitriptyline, clomipramine, imipramine) · Typical antipsychotics (e.g., acetophenazine, chlorpromazine, chlorprothixene, fluphenazine, loxapine, pimozide) · Vortioxetine · |
| | *Unknown/unsorted:* Ergolines (e.g., lisuride, pergolide) · Piperazines (e.g., naphthylpiperazine) · |

*See also:* *Adrenergics* · *Dopaminergics* · *Melatonergics* · *Monoamine reuptake and release modulators* · *Monoamine metabolism modulators* · *Monoamine neurotoxins* ·

Categories: Abortifacients | Antiandrogens | Antiglucocorticoids | Antiprogestogens | CYP17A1 inhibitors | Methods of abortion | Alkynes | Anilines | Abortion | Estranes | Pregnane X receptor agonists | Serotonin reuptake inhibitors | World Health Organization essential medicines | French inventions




# Morphine







*"Morphia" redirects here. For other uses, see Morphia (disambiguation) and Morphine (disambiguation). Not to be confused with Morphinae, Morphea, or Morpholine.*

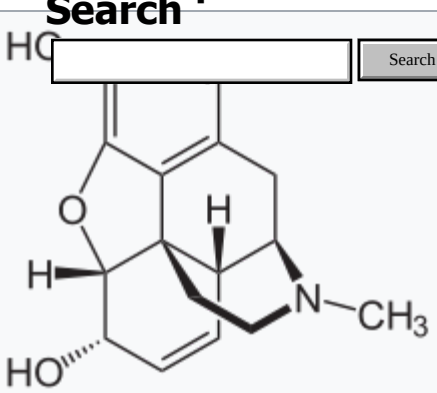
**Morphine** is a pain medication of the opiate type which is found naturally in a number of plants and animals.[5][7] It acts directly on the central nervous system (CNS) to decrease the feeling of pain. It can be taken for both acute pain and chronic pain. Morphine is frequently used for pain from myocardial infarction and during labour. It can be given by mouth, by injection into a muscle, by injecting under the skin, intravenously, into the space around the spinal cord, or rectally.[5] Maximum effect is around 20 min when given intravenously and 60 min when given by mouth while duration of effect is between three and seven hours.[5][6] Long-acting formulations also exist.[5]

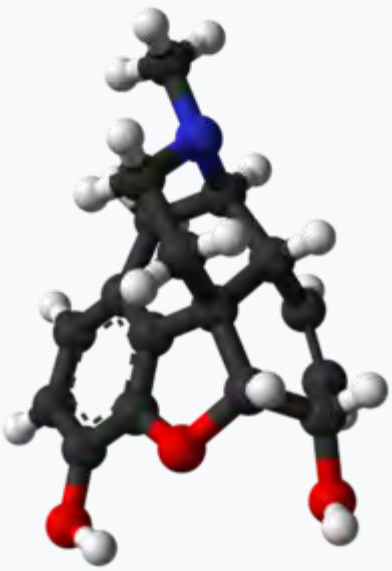
Potentially serious side effects include a decreased respiratory effort and low blood pressure. Morphine has a high potential for addiction and abuse. If the dose is reduced after long-term use, withdrawal may occur. Common side effects include drowsiness, vomiting, and constipation. Caution is advised when used during pregnancy or breast feeding, as morphine will affect the baby.[5]

Morphine was first isolated between 1803 and 1805 by Friedrich Sertürner.[8] This is generally believed to be the first isolation of an active ingredient from a plant.[9] Merck began marketing it commercially in 1827.[8] Morphine was more widely used after the invention of the hypodermic syringe in 1853–1855.[8][10] Sertürner originally named the substance *morphium* after the Greek god of dreams, Morpheus as it has a tendency to cause sleep.[10][11]

The primary source of morphine is isolation from poppy straw of the opium poppy.[12] In 2013, an estimated 523,000 kilograms of morphine were produced.[13] About 45,000 kilograms were used directly for pain, an increase over the last twenty years of four times.[13] Most use for this purpose was in the developed world.[13] About 70% of morphine is used to make other opioids such as hydromorphone, oxycodone and heroin.[13][14][15] It is a Schedule II drug in the United States, Class A in the United Kingdom,[16] and Schedule I in Canada.[17] It is on the WHO Model List of Essential Medicines, the most important medications needed in a basic

## Morphine



| Clinical data | |
|---|---|
| **Pronunciation** | /ˈmɔːrfiːn/ |
| **Trade names** | MScontin, Oramorph, Sevredol, and others[1] |
| **AHFS/Drugs.com** | Monograph |
| **Pregnancy category** | AU: C<br>US: C (Risk not ruled out) |
| **Dependence** | Physical: High |

health system.[18] Morphine is sold under many trade names.[1]





# Medical uses [edit]

## Pain [edit]

Morphine is used primarily to treat both acute and chronic severe pain. It is also used for pain due to myocardial infarction and for labor pains.[19] Its duration of analgesia is about three to seven hours.[5][6]

However, concerns exist that morphine may increase mortality in the setting of non ST elevation myocardial infarction.[20] Morphine has also traditionally been used in the treatment of acute pulmonary edema.[19] A 2006 review, though, found little evidence to support this practice.[21] A 2016 Cochrane review concluded that morphine is effective in relieving cancer pain. Side-effects of nausea and constipation are rarely severe enough to warrant stopping treatment.[22]

| | |
|---|---|
| **liability** | Psychological: Moderate |
| **Addiction liability** | High |
| **Routes of administration** | Inhalation (smoking), insufflation (snorting), oral (PO), rectal, subcutaneous (SC), intramuscular (IM), intravenous (IV), epidural, and intrathecal (IT) |
| **Drug class** | opiate |
| **ATC code** | N02AA01 (WHO) |
| **Legal status** | |
| **Legal status** | AU: S8 (Controlled)<br>CA: Schedule I<br>DE: Anlage III (Prescription only)<br>NZ: Class B<br>UK: Class A<br>US: Schedule II<br>UN: Narcotic Schedules I and III |
| **Pharmacokinetic data** | |
| **Bioavailability** | 20–40% (oral), 36–71% (rectally),[2] 100% (IV/IM) |
| **Protein binding** | 30–40% |
| **Metabolism** | Hepatic 90% |
| **Onset of action** | 5 min (IV), 15 min (IM),[3] 20 min (PO)[4] |
| **Biological half-life** | 2–3 h |
| **Duration of action** | 3 to 7 hours[5][6] |
| **Excretion** | Renal 90%, biliary 10% |
| **Identifiers** | |
| **IUPAC name** | (4R,4aR,7S,7aR,12bS)-3-methyl-2,3,4,4a,7,7a-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinoline-7,9-diol |
| **CAS Number** | 57-27-2 ✓<br>64-31-3 (neutral sulfate),<br>52-26-6 (hydrochloride) |
| **PubChem** (CID) | 5288826 |
| **IUPHAR/BPS** | 1627 |
| **DrugBank** | DB00295 ✓ |

## Shortness of breath [edit]

Immediate-release morphine is beneficial in reducing the symptom of shortness of breath due to both cancer and noncancer causes.[23][24] In the setting of breathlessness at rest or on minimal exertion from conditions such as advanced cancer or end-stage cardiorespiratory diseases, regular, low-dose sustained-release morphine significantly reduces breathlessness safely, with its benefits maintained over time.[25][26]

## Opioid use disorder [edit]

Morphine is also available as a slow-release formulation for opiate substitution therapy (OST) in Austria, Bulgaria, and Slovenia, for addicts who cannot tolerate either methadone or buprenorphine.[27]

# Contraindications [edit]

Relative contraindications to morphine include:

- respiratory depression when appropriate equipment is not available[5]
- Although it has previously been thought that morphine was contraindicated in acute pancreatitis, a review of the literature shows no evidence for this.[28]

| | |
|---|---|
| **ChemSpider** | 4450907 ✓ |
| **UNII** | 76I7G6D29C ✓ |
| **KEGG** | D08233 ✓ |
| **ChEBI** | CHEBI:17303 ✓ |
| **ChEMBL** | CHEMBL70 ✓ |
| **ECHA InfoCard** | 100.000.291 |
| **Chemical and physical data** | |
| **Formula** | $C_{17}H_{19}NO_3$ |
| **Molar mass** | 285.34 g/mol |
| **3D model (Jmol)** | Interactive image |
| **Solubility in water** | HCl & sulf.: 60 mg/mL (20 °C) |

**SMILES**
CN1CC[C@]23C4=C5C=CC(O)=C4O[C@H]2[C@@H](O)C=C[C@H]3[C@H]1C5

**InChI**
InChI=1S/C17H19NO3/c1-18-7-6-17-10-3-5-13(20)16(17)21-15-12(19)4-2-9(14(15)17)8-11(10)18/h2-5,10-11,13,16,19-20H,6-8H2,1H3/t10-,11+,13-,16-,17-/m0/s1 ✓
Key:BQJCRHHNABKAKU-KBQPJGBKSA-N ✓
(verify)

# Adverse effects [edit]

## Constipation [edit]

Like loperamide and other opioids, morphine acts on the myenteric plexus in the intestinal tract, reducing gut motility, causing constipation. The gastrointestinal effects of morphine are mediated primarily by μ-opioid receptors in the bowel. By inhibiting gastric emptying and reducing propulsive peristalsis of the intestine, morphine decreases the rate of intestinal transit. Reduction in gut secretion and increased intestinal fluid absorption also contribute to the constipating effect. Opioids also may act on the gut indirectly through tonic gut spasms after inhibition of nitric oxide generation.[30] This effect was shown in animals when a nitric oxide precursor, L-arginine, reversed morphine-induced changes in gut motility.[31]

## Hormone imbalance [edit]

*See also: Opioid § Hormone imbalance*

Clinical studies consistently conclude that morphine, like other opioids, often causes hypogonadism and hormone imbalances in chronic users of both sexes. This side effect is dose-dependent and occurs in both therapeutic and recreational users. Morphine can interfere with menstruation in women by suppressing levels of luteinizing hormone. Many studies suggest the majority (perhaps as

**Adverse effects of opioids**

**Common and short term**

- Itch[29]
- Nausea[29]
- Vomiting[29]
- Constipation[29]
- Drowsiness[29]
- dry mouth[29]

**Other**

- Opioid dependence
- Dizziness
- Decreased sex drive
- impaired sexual function
- Decreased testosterone levels
- Depression
- Immunodeficiency
- opioid-induced abnormal pain sensitivity
- Irregular menstruation
- Increased risk of falls
- Slowed breathing

much as 90%) of chronic opioid users have opioid-induced hypogonadism. This effect may cause the increased likelihood of osteoporosis and bone fracture observed in chronic morphine users. Studies suggest the effect is temporary. As of 2013, the effect of low-dose or acute use of morphine on the endocrine system is unclear.[32][33]

A localized reaction to intravenous morphine caused by histamine release in the veins

## Effects on human performance [edit]

Most reviews conclude that opioids produce minimal impairment of human performance on tests of sensory, motor, or attentional abilities. However, recent studies have been able to show some impairments caused by morphine, which is not surprising, given that morphine is a central nervous system depressant. Morphine has resulted in impaired functioning on critical flicker frequency (a measure of overall CNS arousal) and impaired performance on the Maddox wing test (a measure of deviation of the visual axes of the eyes). Few studies have investigated the effects of morphine on motor abilities; a high dose of morphine can impair finger tapping and the ability to maintain a low constant level of isometric force (i.e. fine motor control is impaired),[34] though no studies have shown a correlation between morphine and gross motor abilities.

In terms of cognitive abilities, one study has shown that morphine may have a negative impact on anterograde and retrograde memory,[35] but these effects are minimal and transient. Overall, it seems that acute doses of opioids in non-tolerant subjects produce minor effects in some sensory and motor abilities, and perhaps also in attention and cognition. It is likely that the effects of morphine will be more pronounced in opioid-naive subjects than chronic opioid users.

In chronic opioid users, such as those on Chronic Opioid Analgesic Therapy (COAT) for managing severe, chronic pain, behavioural testing has shown normal functioning on perception, cognition, coordination and behaviour in most cases. One recent study[36] analysed COAT patients to determine whether they were able to safely operate a motor vehicle. The findings from this study suggest that stable opioid use does not significantly impair abilities inherent in driving (this includes physical, cognitive and perceptual skills). COAT patients showed rapid completion of tasks that require speed of responding for successful performance (e.g., Rey Complex Figure Test) but made more errors than controls. COAT patients showed no deficits in visual-spatial perception and organization (as shown in the WAIS-R Block Design Test) but did show impaired immediate and short-term visual memory (as shown on the Rey Complex Figure Test – Recall). These patients showed no impairments in higher order cognitive abilities (i.e., planning). COAT patients appeared to have difficulty following instructions and showed a propensity toward impulsive behaviour, yet this did not reach statistical significance. It is important to note that this study reveals that COAT patients have no domain-specific deficits, which supports the notion that chronic opioid use has minor effects on psychomotor, cognitive, or neuropsychological functioning.

## Reinforcement disorders [edit]

### Addiction [edit]

Morphine is a highly addictive substance. In controlled studies comparing the physiological and subjective effects of heroin and morphine in individuals formerly addicted to opiates, subjects showed no preference for one drug over the other. Equipotent, injected doses had comparable action courses, with no difference in subjects' self-rated feelings of euphoria, ambition, nervousness, relaxation, drowsiness, or sleepiness.[37] Short-term addiction studies by the same researchers demonstrated that tolerance developed at a similar rate to both heroin and morphine. When compared to the opioids hydromorphone, fentanyl, oxycodone, and pethidine/meperidine, former addicts showed a strong preference for heroin and morphine, suggesting that heroin and morphine are particularly susceptible to abuse and addiction. Morphine

*Before the Morphine* by

Santiago Rusiñol

and heroin were also much more likely to produce euphoria and other positive subjective effects when compared to these other opioids.[37] The choice of heroin and morphine over other opioids by former drug addicts may also be because heroin (also known as morphine diacetate, diamorphine, or diacetyl morphine) is an ester of morphine and a morphine prodrug, essentially meaning they are identical drugs *in vivo*. Heroin is converted to morphine before binding to the opioid receptors in the brain and spinal cord, where morphine causes the subjective effects, which is what the addicted individuals are seeking.[38]

## Tolerance [edit]

Several hypotheses are given about how tolerance develops, including opioid receptor phosphorylation (which would change the receptor conformation), functional decoupling of receptors from G-proteins (leading to receptor desensitization),[39] μ-opioid receptor internalization or receptor down-regulation (reducing the number of available receptors for morphine to act on), and upregulation of the cAMP pathway (a counterregulatory mechanism to opioid effects) (For a review of these processes, see Koch and Hollt.[40]) CCK might mediate some counter-regulatory pathways responsible for opioid tolerance. CCK-antagonist drugs, specifically proglumide, have been shown to slow the development of tolerance to morphine.

## Dependence and withdrawal [edit]

*See also: Opioid dependence and Opioid withdrawal*

Cessation of dosing with morphine creates the prototypical opioid withdrawal syndrome, which, unlike that of barbiturates, benzodiazepines, alcohol, or sedative-hypnotics, is not fatal by itself in neurologically healthy patients without heart or lung problems.

Acute morphine withdrawal, along with that of any other opioid, proceeds through a number of stages. Other opioids differ in the intensity and length of each, and weak opioids and mixed agonist-antagonists may have acute withdrawal syndromes that do not reach the highest level. As commonly cited[*by whom?*], they are:

- **Stage I**, 6 to 14 hours after last dose: Drug craving, anxiety, irritability, perspiration, and mild to moderate dysphoria[*citation needed*]
- **Stage II**, 14 to 18 hours after last dose: Yawning, heavy perspiration, mild depression, lacrimation, crying, headaches, runny nose, dysphoria, also intensification of the above symptoms, "yen sleep" (a waking trance-like state) [*clarification needed*]
- **Stage III**, 16 to 24 hours after last dose: Rhinorrhea (runny nose) and increase in other of the above, dilated pupils, piloerection (goose bumps – a purported origin of the phrase, 'cold turkey,' but in fact the phrase originated outside of drug treatment),[41] muscle twitches, hot flashes, cold flashes, aching bones and muscles, loss of appetite, and the beginning of intestinal cramping[*citation needed*]
- **Stage IV**, 24 to 36 hours after last dose: Increase in all of the above including severe cramping and involuntary leg movements ("kicking the habit" also called restless leg syndrome), loose stool, insomnia, elevation of blood pressure, moderate elevation in body temperature, increase in frequency of breathing and tidal volume, tachycardia (elevated pulse), restlessness, nausea[*citation needed*]
- **Stage V**, 36 to 72 hours after last dose: Increase in the above, fetal position, vomiting, free and frequent liquid diarrhea, which sometimes can accelerate the time of passage of food from mouth to out of system, weight loss of 2 to 5 kg per 24 hours, increased white cell count, and other blood changes[*citation needed*]
- **Stage VI**, after completion of above: Recovery of appetite and normal bowel function, beginning of transition to postacute and chronic symptoms that are mainly psychological, but may also include increased sensitivity to pain, hypertension, colitis or other gastrointestinal afflictions related to motility, and problems with weight control in either direction[*citation needed*]

In advanced stages of withdrawal, ultrasonographic evidence of pancreatitis has been demonstrated in some patients and is presumably attributed to spasm of the pancreatic sphincter of Oddi.[42]

The withdrawal symptoms associated with morphine addiction are usually experienced shortly before the time of the next scheduled dose, sometimes within as early as a few hours (usually 6–12 hours) after the last administration. Early symptoms include watery eyes, insomnia, diarrhea, runny nose, yawning, dysphoria, sweating, and in some cases a strong drug craving. Severe headache, restlessness, irritability, loss of appetite, body aches, severe abdominal pain, nausea and vomiting, tremors, and even stronger and more intense drug craving appear as the syndrome progresses. Severe depression and vomiting are very common. During the acute withdrawal period, systolic and diastolic blood pressures increase, usually beyond premorphine levels, and heart rate increases,[43] which have potential to cause a heart attack, blood clot, or stroke.

Chills or cold flashes with goose bumps ("cold turkey") alternating with flushing (hot flashes), kicking movements of the legs ("kicking the habit"[38]) and excessive sweating are also characteristic symptoms.[44] Severe pains in the bones and muscles of the back and extremities occur, as do muscle spasms. At any point during this process, a suitable narcotic can be administered that will dramatically reverse the withdrawal symptoms. Major withdrawal symptoms peak between 48 and 96 hours after the last dose and subside after about 8 to 12 days. Sudden withdrawal by heavily dependent users who are in poor health is very rarely fatal. Morphine withdrawal is considered less dangerous than alcohol, barbiturate, or benzodiazepine withdrawal.[45][46]

The psychological dependence associated with morphine addiction is complex and protracted. Long after the physical need for morphine has passed, the addict will usually continue to think and talk about the use of morphine (or other drugs) and feel strange or overwhelmed coping with daily activities without being under the influence of morphine. Psychological withdrawal from morphine is usually a very long and painful process.[47][*unreliable medical source*] Addicts often suffer severe depression, anxiety, insomnia, mood swings, amnesia (forgetfulness), low self-esteem, confusion, paranoia, and other psychological disorders. Without intervention, the syndrome will run its course, and most of the overt physical symptoms will disappear within 7 to 10 days including psychological dependence. A high probability of relapse exists after morphine withdrawal when neither the physical environment nor the behavioral motivators that contributed to the abuse have been altered. Testimony to morphine's addictive and reinforcing nature is its relapse rate. Abusers of morphine (and heroin) have one of the highest relapse rates among all drug users, ranging up to 98% in the estimation of some medical experts.[48]

## Overdose [edit]

*See also: Opioid overdose*

A large overdose can cause asphyxia and death by respiratory depression if the person does not receive medical attention immediately.[49] Overdose treatment includes the administration of naloxone. The latter completely reverses morphine's effects, but may result in immediate onset of withdrawal in opiate-addicted subjects. Multiple doses may be needed.[49]

The minimum lethal dose is 200 mg, but in case of hypersensitivity, 60 mg can bring sudden death. In serious drug dependency (high tolerance), 2000–3000 mg per day can be tolerated.[50]

## Pharmacology [edit]

### Pharmacodynamics [edit]

*Main article: Opioid receptor*

This section's **factual accuracy may be compromised due to out-of-date information**. Please update this article to reflect recent events or newly available information. *(July 2014)*

Endogenous opioids include endorphins, enkephalins, dynorphins, and even morphine itself. Morphine

appears to mimic endorphins. Endorphins, a contraction of the term endogenous morphines, are responsible for analgesia (reducing pain), causing sleepiness, and feelings of pleasure. They can be released in response to pain, strenuous exercise, orgasm, or excitement.

Morphine is the prototype narcotic drug and is the standard against which all other opioids are tested. It interacts predominantly with the μ–δ-opioid (Mu-Delta) receptor heteromer.[51][52] The μ-binding sites are discretely distributed in the human brain, with high densities in the posterior amygdala, hypothalamus, thalamus, nucleus caudatus, putamen, and certain cortical areas. They are also found on the terminal axons of primary afferents within laminae I and II (substantia gelatinosa) of the spinal cord and in the spinal nucleus of the trigeminal nerve.[53]

Morphine is a phenanthrene opioid receptor agonist – its main effect is binding to and activating the μ-opioid receptors in the central nervous system. In clinical settings, morphine exerts its principal pharmacological effect on the central nervous system and gastrointestinal tract. Its primary actions of therapeutic value are analgesia and sedation. Activation of the μ-opioid receptors is associated with analgesia, sedation, euphoria, physical dependence, and respiratory depression. Morphine is a rapid-acting narcotic, and it is known to bind very strongly to the μ-opioid receptors, and for this reason, it often has a higher incidence of euphoria/dysphoria, respiratory depression, sedation, pruritus, tolerance, and physical and psychological dependence when compared to other opioids at equianalgesic doses. Morphine is also a κ-opioid and δ-opioid receptor agonist, κ-opioid's action is associated with spinal analgesia, miosis (pinpoint pupils) and psychotomimetic effects. δ-Opioid is thought to play a role in analgesia.[53] Although morphine does not bind to the σ-receptor, it has been shown that σ-agonists, such as (+)-pentazocine, inhibit morphine analgesia, and σ-antagonists enhance morphine analgesia,[54] suggesting downstream involvement of the σ-receptor in the actions of morphine.

The effects of morphine can be countered with opioid antagonists such as naloxone and naltrexone; the development of tolerance to morphine may be inhibited by NMDA antagonists such as ketamine or dextromethorphan.[55] The rotation of morphine with chemically dissimilar opioids in the long-term treatment of pain will slow down the growth of tolerance in the longer run, particularly agents known to have significantly incomplete cross-tolerance with morphine such as levorphanol, ketobemidone, piritramide, and methadone and its derivatives; all of these drugs also have NMDA antagonist properties. It is believed that the strong opioid with the most incomplete cross-tolerance with morphine is either methadone or dextromoramide.

## Gene expression [edit]

Studies have shown that morphine can alter the expression of a number of genes. A single injection of morphine has been shown to alter the expression of two major groups of genes, for proteins involved in mitochondrial respiration and for cytoskeleton-related proteins.[56]

## Effects on the immune system [edit]

Morphine has long been known to act on receptors expressed on cells of the central nervous system resulting in pain relief and analgesia. In the 1970s and '80s, evidence suggesting that opioid drug addicts show increased risk of infection (such as increased pneumonia, tuberculosis, and HIV/AIDS) led scientists to believe that morphine may also affect the immune system. This possibility increased interest in the effect of chronic morphine use on the immune system.

The first step of determining that morphine may affect the immune system was to establish that the opiate receptors known to be expressed on cells of the central nervous system are also expressed on cells of the immune system. One study successfully showed that dendritic cells, part of the innate immune system, display opiate receptors. Dendritic cells are responsible for producing cytokines, which are the tools for communication in the immune system. This same study showed that dendritic cells chronically treated with morphine during their differentiation produce more interleukin-12 (IL-12), a cytokine responsible for promoting the proliferation, growth, and differentiation of T-cells (another cell of the adaptive immune system) and less interleukin-10 (IL-10), a cytokine responsible for promoting a B-cell immune response (B cells produce antibodies to fight off infection).[57]

This regulation of cytokines appear to occur via the p38 MAPKs (mitogen-activated protein kinase)-dependent pathway. Usually, the p38 within the dendritic cell expresses TLR 4 (toll-like receptor 4), which is activated through the ligand LPS (lipopolysaccharide). This causes the p38 MAPK to be phosphorylated. This phosphorylation activates the p38 MAPK to begin producing IL-10 and IL-12. When the dendritic cells are chronically exposed to morphine during their differentiation process then treated with LPS, the production of cytokines is different. Once treated with morphine, the p38 MAPK does not produce IL-10, instead favoring production of IL-12. The exact mechanism through which the production of one cytokine is increased in favor over another is not known. Most likely, the morphine causes increased phosphorylation of the p38 MAPK. Transcriptional level interactions between IL-10 and IL-12 may further increase the production of IL-12 once IL-10 is not being produced. This increased production of IL-12 causes increased T-cell immune response.

Further studies on the effects of morphine on the immune system have shown that morphine influences the production of neutrophils and other cytokines. Since cytokines are produced as part of the immediate immunological response (inflammation), it has been suggested that they may also influence pain. In this way, cytokines may be a logical target for analgesic development. Recently, one study has used an animal model (hind-paw incision) to observe the effects of morphine administration on the acute immunological response. Following hind-paw incision, pain thresholds and cytokine production were measured. Normally, cytokine production in and around the wounded area increases in order to fight infection and control healing (and, possibly, to control pain), but pre-incisional morphine administration (0.1–10.0 mg/kg) reduced the number of cytokines found around the wound in a dose-dependent manner. The authors suggest that morphine administration in the acute post-injury period may reduce resistance to infection and may impair the healing of the wound.[58]

## Pharmacokinetics [edit]

## Absorption and metabolism [edit]

Morphine can be taken orally, sublingually, bucally, rectally, subcutaneously, intranasally, intravenously, intrathecally or epidurally and inhaled via a nebulizer. As a recreational drug, it is becoming more common to inhale ("Chasing the Dragon"), but, for medical purposes, intravenous (IV) injection is the most common method of administration. Morphine is subject to extensive first-pass metabolism (a large proportion is broken down in the liver), so, if taken orally, only 40–50% of the dose reaches the central nervous system. Resultant plasma levels after subcutaneous (SC), intramuscular (IM), and IV injection are all comparable. After IM or SC injections, morphine plasma levels peak in approximately 20 minutes, and, after oral administration, levels peak in approximately 30 minutes.[59] Morphine is metabolised primarily in the liver and approximately 87% of a dose of morphine is excreted in the urine within 72 hours of administration. Morphine is metabolized primarily into morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G)[60] via glucuronidation by phase II metabolism enzyme UDP-glucuronosyl transferase-2B7 (UGT2B7). About 60% of morphine is converted to M3G, and 6–10% is converted to M6G.[61] Not only does the metabolism occur in the liver but it may also take place in the brain and the kidneys. M3G does not undergo opioid receptor binding and has no analgesic effect. M6G binds to μ-receptors and is half as potent an analgesic as morphine in humans.[61] Morphine may also be metabolized into small amounts of normorphine, codeine, and hydromorphone. Metabolism rate is determined by gender, age, diet, genetic makeup, disease state (if any), and use of other medications. The elimination half-life of morphine is approximately 120 minutes, though there may be slight differences between men and women. Morphine can be stored in fat, and, thus, can be detectable even after death. Morphine can cross the blood–brain barrier, but, because of poor lipid solubility, protein binding, rapid conjugation with glucuronic acid and ionization, it does not cross easily. Diacetylmorphine, which is derived from morphine, crosses the blood–brain barrier more easily, making it more potent.[62]

## Extended-release [edit]

*Main article: Extended-release morphine*

There are extended-release formulations of orally administered morphine whose effect last longer, which [63] [63]

can be given once per day. Brand names for this formulation of morphine include Avinza, Kadian, MS Contin[63] and Dolcontin.[64] For constant pain, the relieving effect of extended-release morphine given once (for Kadian)[65] or twice (for MS Contin)[65] every 24 hours is roughly the same as multiple administrations of *immediate release* (or "regular") morphine.[66] Extended-release morphine can be administered together with "rescue doses" of immediate-release morphine as needed in case of breakthrough pain, each generally consisting of 5% to 15% of the 24-hour extended-release dosage.[66]

### Detection in body fluids [edit]

Morphine and its major metabolites, morphine-3-glucuronide and morphine-6-glucuronide, can be detected in blood, plasma, hair, and urine using an immunoassay. Chromatography can be used to test for each of these substances individually. Some testing procedures hydrolyze metabolic products into morphine before the immunoassay, which must be considered when comparing morphine levels in separately published results. Morphine can also be isolated from whole blood samples by solid phase extraction (SPE) and detected using liquid chromatography-mass spectrometry (LC-MS).

Ingestion of codeine or food containing poppy seeds can cause false positives.[67]

A 1999 review estimated that relatively low doses of heroin (which metabolizes immediately into morphine) are detectable by standard urine tests for 1-1.5 days after use.[68] A 2009 review determined that, when the analyte is morphine and the limit of detection is 1 ng/ml, a 20 mg intravenous (IV) dose of morphine is detectable for 12–24 hours. A limit of detection of 0.6 ng/ml had similar results.[69]

## Natural occurrence [edit]

*See also: Opium*

A freshly-scored opium poppy seedpod bleeding latex.

Morphine is the most abundant opiate found in opium, the dried latex extracted by shallowly scoring the unripe seedpods of the *Papaver somniferum* poppy. Morphine is generally 8–14% of the dry weight of opium,[70] although specially bred cultivars reach 26% or produce little morphine at all (under 1%, perhaps down to 0.04%). The latter varieties, including the 'Przemko' and 'Norman' cultivars of the opium poppy, are used to produce two other alkaloids, thebaine and oripavine, which are used in the manufacture of semi-synthetic and synthetic opioids like oxycodone and etorphine and some other types of drugs. *P. bracteatum* does not contain morphine or codeine, or other narcotic phenanthrene-type, alkaloids. This species is rather a source of thebaine.[71] Occurrence of morphine in other Papaverales and Papaveraceae, as well as in some species of hops and mulberry trees has not been confirmed. Morphine is produced most predominantly early in the life cycle of the plant. Past the optimum point for extraction, various processes in the plant produce codeine, thebaine, and in some cases negligible amounts of hydromorphone, dihydromorphine, dihydrocodeine, tetrahydro-thebaine, and hydrocodone (these compounds are rather synthesized from thebaine and oripavine).

In the brain of mammals, morphine is detectable in trace steady-state concentrations.[7] The human body also produces endorphins, which are chemically related endogenous opioid peptides that function as neuropeptides and have similar effects as morphine.[72]

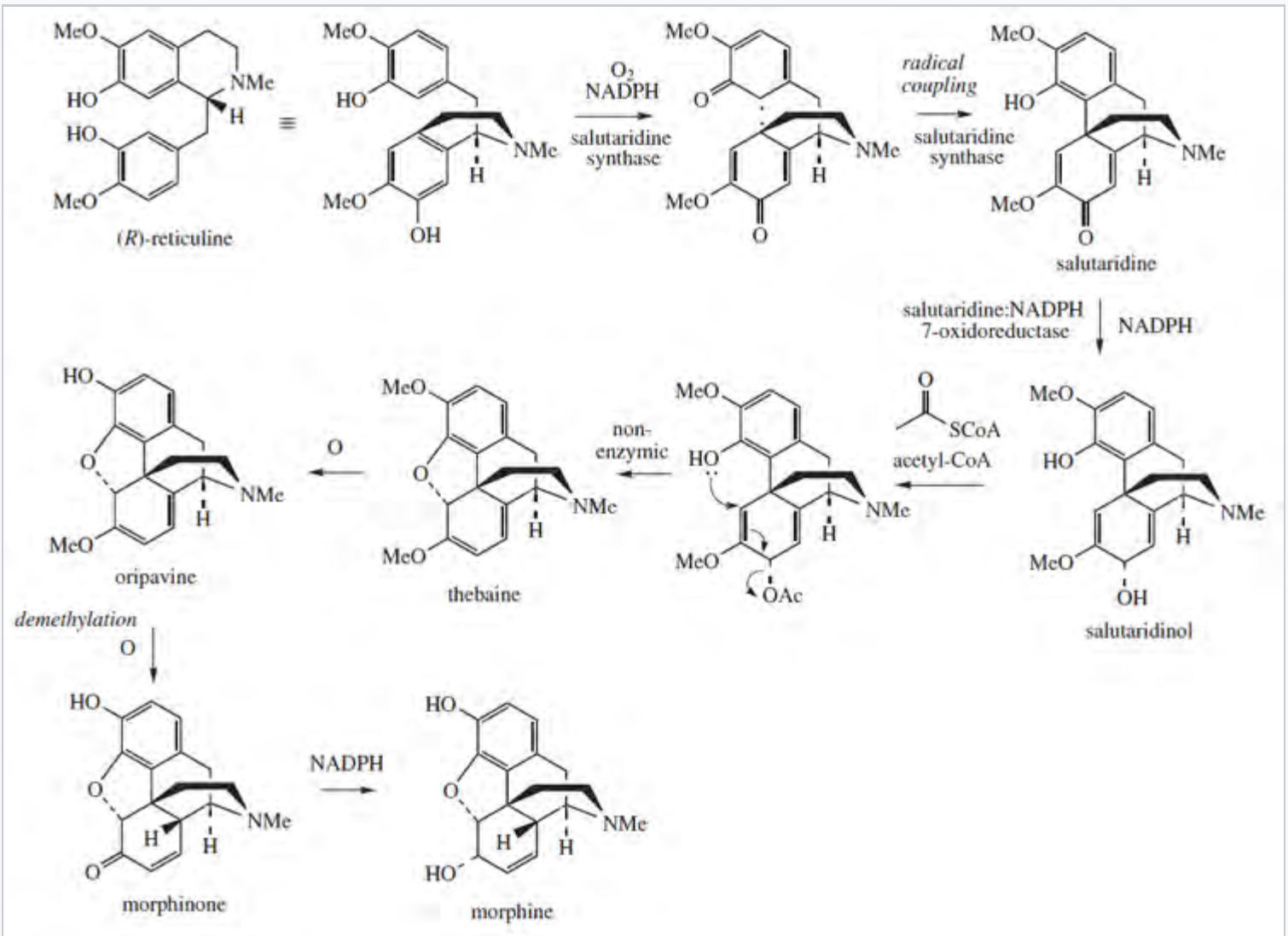
### Human biosynthesis [edit]

**This section needs expansion**. You can help by adding to it. *(October 2016)*

[7]

Morphine is an endogenous opioid in humans that can be synthesized and released by white blood cells. CYP2D6, a cytochrome P450 isoenzyme, catalyzes the biosynthesis of morphine from codeine and dopamine from tyramine along the biosynthetic pathway of morphine in humans.[7][73] The morphine biosynthetic pathway in humans occurs as follows:[7]
L-tyrosine → *para*-tyramine or L-DOPA → dopamine → (*S*)-norlaudanosoline → (*S*)-reticuline → 1,2-dehydroretinulinium → (*R*)-reticuline → salutaridine → salutaridinol → thebaine → neopinone → codeinone → codeine → morphine
(*S*)-Norlaudanosoline (also known as tetrahydropapaveroline) can also be synthesized from 3,4-dihydroxyphenylacetaldehyde (DOPAL), a metabolite of L-DOPA and dopamine.[7] Urinary concentrations of endogenous codeine and morphine have been found to significantly increase in individuals taking L-DOPA for the treatment of Parkinson's disease.[7]

## Biosynthesis in the opium poppy [edit]




Morphine biosynthesis in the opium poppy

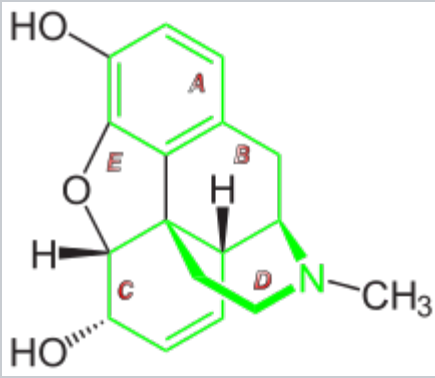
Morphine is biosynthesized in the opium poppy from the tetrahydroisoquinoline reticuline. It is converted into salutaridine, thebaine, and oripavine. The enzymes involved in this process are the salutaridine synthase, salutaridine:NADPH 7-oxidoreductase and the codeinone reductase.[74] Researchers are attempting to reproduce the biosynthetic pathway that produces morphine in genetically engineered yeast.[75] In June 2015 the *S*-reticuline could be produced from sugar and *R*-reticuline could be converted to morphine, but the intermediate reaction could not be performed.[76] In August 2015 the first complete synthesis of thebaine and hydrocodone in yeast were reported, but the process would need to be 100,000

times more productive to be suitable for commercial use.[77][78]

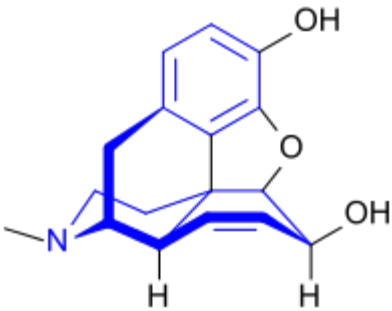
## Chemistry [edit]

Morphine is a benzylisoquinoline alkaloid with two additional ring closures. It has:

- A rigid pentacyclic structure consisting of a benzene ring (A), two partially unsaturated cyclohexane rings (B and C), a piperidine ring (D) and a tetrahydrofuran ring (E). Rings A, B and C are the phenanthrene ring system. This ring system has little conformational flexibility.
- Two hydroxyl functional groups: a C3-phenolic OH ($pK_a$ 9.9) and a C6-allylic OH,
- An ether linkage between C4 and C5,
- Unsaturation between C7 and C8,
- A basic, tertiary amine function at position 17,
- 5 centers of chirality (C5, C6, C9, C13 and C14) with morphine exhibiting a high degree of stereoselectivity of analgesic action.[79]



Chemical structure of morphine. The benzylisoquinoline backbone is shown in green.



Same structure with correct 3D configuration; backbone in blue.

Most of the licit morphine produced is used to make codeine by methylation. It is also a precursor for many drugs including heroin (3,6-diacetylmorphine), hydromorphone (dihydromorphinone), and oxymorphone (14-hydroxydihydromorphinone); many morphine derivatives can also be manufactured using thebaine or codeine as a starting material. Replacement of the *N*-methyl group of morphine with an *N*-phenylethyl group results in a product that is 18 times more powerful than morphine in its opiate agonist potency. Combining this modification with the replacement of the 6-hydroxyl with a 6-methylene group produces a compound some 1,443 times more potent than morphine, stronger than the Bentley compounds such as etorphine (M99, the Immobilon tranquilliser dart) by some measures.

The structure-activity relationship of morphine has been extensively studied. As a result of the extensive study and use of this molecule, more than 250 morphine derivatives (also counting codeine and related drugs) have been developed since the last quarter of the 19th century. These drugs range from 25% the analgesic strength of codeine (or slightly more than 2% of the strength of morphine) to several thousand times the strength of morphine, to powerful opioid antagonists, including naloxone (Narcan), naltrexone (Trexan), diprenorphine (M5050, the reversing agent for the Immobilon dart) and nalorphine (Nalline). Some opioid agonist-antagonists, partial agonists, and inverse agonists are also derived from morphine. The receptor-activation profile of the semi-synthetic morphine derivatives varies widely and some, like apomorphine are devoid of narcotic effects.

Morphine and most of its derivatives do not exhibit optical isomerism, although some more distant relatives like the morphinan series (levorphanol, dextorphan and the racemic parent chemical dromoran) do, and as noted above stereoselectivity in vivo is an important issue.

Morphine-derived agonist–antagonist drugs have also been developed. Elements of the morphine structure have been used to create completely synthetic drugs such as the morphinan family (levorphanol, dextromethorphan and others) and other groups that have many members with morphine-like qualities. The modification of morphine and the aforementioned synthetics has also given rise to non-narcotic drugs with other uses such as emetics, stimulants, antitussives, anticholinergics, muscle relaxants, local anaesthetics, general anaesthetics, and others.

Most semi-synthetic opioids, both of the morphine and codeine subgroups, are created by modifying one or more of the following:

- Halogenating or making other modifications at positions 1 or 2 on the morphine carbon skeleton.

- The methyl group that makes morphine into codeine can be removed or added back, or replaced with another functional group like ethyl and others to make codeine analogues of morphine-derived drugs and vice versa. Codeine analogues of morphine-based drugs often serve as prodrugs of the stronger drug, as in codeine and morphine, hydrocodone and hydromorphone, oxycodone and oxymorphone, nicocodeine and nicomorphine, dihydrocodeine and dihydromorphine, etc.
- Saturating, opening, or other changes to the bond between positions 7 and 8, as well as adding, removing, or modifying functional groups to these positions; saturating, reducing, eliminating, or otherwise modifying the 7–8 bond and attaching a functional group at 14 yields hydromorphinol; the oxidation of the hydroxyl group to a carbonyl and changing the 7–8 bond to single from double changes codeine into oxycodone.
- Attachment, removal or modification of functional groups to positions 3 or 6 (dihydrocodeine and related, hydrocodone, nicomorphine); in the case of moving the methyl functional group from position 3 to 6, codeine becomes heterocodeine, which is 72 times stronger, and therefore six times stronger than morphine
- Attachment of functional groups or other modification at position 14 (oxymorphone, oxycodone, naloxone)
- Modifications at positions 2, 4, 5 or 17, usually along with other changes to the molecule elsewhere on the morphine skeleton. Often this is done with drugs produced by catalytic reduction, hydrogenation, oxidation, or the like, producing strong derivatives of morphine and codeine.

| Structure and properties | |
|---|---|
| Molar mass[80] | 285.338 g/mol |
| Index of refraction, $n_D$ | ? |
| Acidity ($pK_a$)[80] | Step 1: 8.21 at 25 °C<br>Step 2: 9.85 at 20 °C |
| Solubility[80] | 0.15 g/L at 20 °C |
| Melting point[80] | 255 °C |
| Boiling point[80] | 190 °C sublimes |

Both morphine and its hydrated form, $C_{17}H_{19}NO_3H_2O$, are sparingly soluble in water. In five liters of water, only one gram of the hydrate will dissolve. For this reason, pharmaceutical companies produce sulfate and hydrochloride salts of the drug, both of which are over 300 times more water-soluble than their parent molecule. Whereas the pH of a saturated morphine hydrate solution is 8.5, the salts are acidic. Since they derive from a strong acid but weak base, they are both at about pH = 5; as a consequence, the morphine salts are mixed with small amounts of NaOH to make them suitable for injection.[81]

A number of salts of morphine are used, with the most common in current clinical use being the hydrochloride, sulfate, tartrate, and citrate; less commonly methobromide, hydrobromide, hydroiodide, lactate, chloride, and bitartrate and the others listed below. Morphine diacetate, which is another name for heroin, is a Schedule I controlled substance, so it is not used clinically in the United States; it is a sanctioned medication in the United Kingdom and in Canada and some countries in Continental Europe, its use being particularly common (nearly to the degree of the hydrochloride salt) in the United Kingdom. Morphine meconate is a major form of the alkaloid in the poppy, as is morphine pectinate, nitrate, sulphate, and some others. Like codeine, dihydrocodeine and other (especially older) opiates, morphine has been used as the salicylate salt by some suppliers and can be easily compounded, imparting the therapeutic advantage of both the opioid and the NSAID; multiple barbiturate salts of morphine were also used in the past, as was/is morphine valerate, the salt of the acid being the active principle of valerian. Calcium morphenate is the intermediate in various latex and poppy-straw methods of morphine production, more rarely sodium morphenate takes its place. Morphine ascorbate and other salts such as the tannate, citrate, and acetate, phosphate, valerate and others may be present in poppy tea depending on the method of preparation. Morphine valerate produced industrially was one ingredient of a medication available for both oral and parenteral administration popular many years ago in Europe and elsewhere called Trivalin (not to be confused with the current, unrelated herbal preparation of the same name), which also included the valerates of caffeine and cocaine, with a version containing codeine valerate as a fourth ingredient being distributed under the name Tetravalin.

Closely related to morphine are the opioids morphine-*N*-oxide (genomorphine), which is a pharmaceutical that is no longer in common use; and pseudomorphine, an alkaloid that exists in opium, form as degradation products of morphine.

The salts listed by the United States Drug Enforcement Administration for reporting purposes, in addition to a few others, are as follows:

**Select forms of morphine as 'morphiniums' or *N*-protonated cations of morphine, i.e. ionic salts & chemical form with freebase conversion ratios:**

| Salt or drug | CSA schedule | ACSCN | Free base conversion ratio |
|---|---|---|---|
| Morphine (base) | II | 9300 | 1 |
| Morphine citrate | II | 9300 | 0.81 |
| Morphine bitartrate | II | 9300 | 0.66 |
| Morphine stearate | II | 9300 | 0.51 |
| Morphine phthalate | II | 9300 | 0.89 |
| Morphine hydrobromide | II | 9300 | 0.78 |
| Morphine hydrobromide (2 $H_2O$) | II | 9300 | 0.71 |
| Morphine hydrochloride | II | 9300 | 0.89 |
| Morphine hydrochloride (3 $H_2O$) | II | 9300 | 0.76 |
| Morphine acetate | II | 9300 | 0.71 |
| Morphine hydriodide (2 $H_2O$) | II | 9300 | 0.64 |
| Morphine lactate | II | 9300 | 0.76 |
| Morphine monohydrate | II | 9300 | 0.94 |
| Morphine meconate (5 $H_2O$) | II | 9300 | 0.66 |
| Morphine mucate | II | 9300 | 0.57 |
| Morphine nitrate | II | 9300 | 0.82 |
| Morphine phosphate ( $^1/_2$ $H_2O$) | II | 9300 | 0.73 |
| Morphine phosphate (7 $H_2O$) | II | 9300 | 0.73 |
| Morphine salicylate | II | 9300 | |
| Morphine pectinate | II | 9300 | 0.778 |
| Morphine phenylpropionate | II | 9300 | 0.65 |
| Morphine methyliodide | II | 9300 | 0.67 |
| Morphine isobutyrate | II | 9300 | 0.76 |
| Morphine hypophosphite | II | 9300 | 0.81 |
| Morphine sulfate (5 $H_2O$) | II | 9300 | 0.75 |
| Morphine tannate | II | 9300 | |
| Morphine tartrate (3 $H_2O$) | II | 9300 | 0.74 |
| Morphine valerate | II | 9300 | 0.74 |
| Morphine diethylbarbiturate | II | 9300 | 0.619 |
| Morphine cyclopentylallylbarbiturate | II | 9300 | 0.561 |
| Morphine diacetate | I | 9200 | 0.74 |
| Morphine methylbromide | I | 9305 | 0.75 |
| Morphine methylsulfonate | I | 9306 | 0.75 |
| Morphine-N-oxide | I | 9307 | 1 |
| Morphine-N-oxide quinate | I | 9307 | 0.60 |

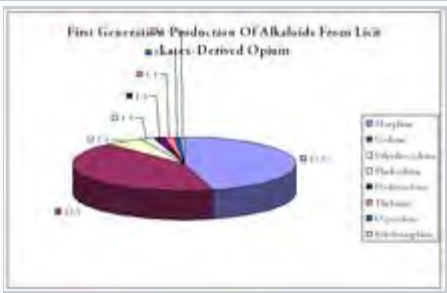
| | | | |
|---|---|---|---|
| Morphine dinicotinate HCl (Nicomorphine) | II | 9312 | 0.931 |
| Pseudomorphine | I | *not mentioned* | |

## Synthesis [edit]

*Main article: Morphine total synthesis*

The first morphine total synthesis, devised by Marshall D. Gates, Jr. in 1952, remains a widely used example of total synthesis.[82] Several other syntheses were reported, notably by the research groups of Rice,[83] Evans,[84] Fuchs,[85] Parker,[86] Overman,[87] Mulzer-Trauner,[88] White,[89] Taber,[90] Trost,[91] Fukuyama,[92] Guillou,[93] and Stork.[94] It is "highly unlikely" that a chemical synthesis will ever be able to compete with the cost of producing morphine from the opium poppy.[95]

## Production [edit]



First generation production of Alkaloids from licit latex-derived opium

In the opium poppy, the alkaloids are bound to meconic acid. The method is to extract from the crushed plant with diluted sulfuric acid, which is a stronger acid than meconic acid, but not so strong to react with alkaloid molecules. The extraction is performed in many steps (one amount of crushed plant is extracted at least six to ten times, so practically every alkaloid goes into the solution). From the solution obtained at the last extraction step, the alkaloids are precipitated by either ammonium hydroxide or sodium carbonate. The last step is purifying and separating morphine from other opium alkaloids. The somewhat similar Gregory process was developed in the United Kingdom during the Second World War, which begins with stewing the entire plant, in most cases save the roots and leaves, in plain or mildly acidified water, then proceeding through steps of concentration, extraction, and purification of alkaloids.[*citation needed*] Other methods of processing "poppy straw" (i.e., dried pods and stalks) use steam, one or more of several types of alcohol, or other organic solvents.

The poppy straw methods predominate in Continental Europe and the British Commonwealth, with the latex method in most common use in India. The latex method can involve either vertical or horizontal slicing of the unripe pods with a two-to five-bladed knife with a guard developed specifically for this purpose to the depth of a fraction of a millimetre and scoring of the pods can be done up to five times. An alternative latex method sometimes used in China in the past is to cut off the poppy heads, run a large needle through them, and collect the dried latex 24 to 48 hours later.[*citation needed*]

In India, opium harvested by licensed poppy farmers is dehydrated to uniform levels of hydration at government processing centers, and then sold to pharmaceutical companies that extract morphine from the opium. However, in Turkey and Tasmania, morphine is obtained by harvesting and processing the fully mature dry seed pods with attached stalks, called *poppy straw*. In Turkey, a water extraction process is used, while in Tasmania, a solvent extraction process is used.[*citation needed*]

Opium poppy contains at least 50 different alkaloids, but most of them are of very low concentration. Morphine is the principal alkaloid in raw opium and constitutes roughly 8–19% of opium by dry weight (depending on growing conditions).[62] Some purpose-developed strains of poppy now produce opium that is up to 26% morphine by weight.[*citation needed*] A rough rule of thumb to determine the morphine content of pulverised dried poppy straw is to divide the percentage expected for the strain or crop via the latex method by eight or an empirically determined factor, which is often in the range of 5 to 15.[*citation needed*] The Norman strain of *P. Somniferum*, also developed in Tasmania, produces down to 0.04% morphine but with much higher amounts of thebaine and oripavine, which can be used to synthesise semi-synthetic

opioids as well as other drugs like stimulants, emetics, opioid antagonists, anticholinergics, and smooth-muscle agents.[*citation needed*]

In the 1950s and 1960s, Hungary supplied nearly 60% of Europe's total medication-purpose morphine production. To this day, poppy farming is legal in Hungary, but poppy farms are limited by law to 2 acres (8,100 $m^2$). It is also legal to sell dried poppy in flower shops for use in floral arrangements.

It was announced in 1973 that a team at the National Institutes of Health in the United States had developed a method for total synthesis of morphine, codeine, and thebaine using coal tar as a starting material. A shortage in codeine-hydrocodone class cough suppressants (all of which can be made from morphine in one or more steps, as well as from codeine or thebaine) was the initial reason for the research.

Most morphine produced for pharmaceutical use around the world is actually converted into codeine as the concentration of the latter in both raw opium and poppy straw is much lower than that of morphine; in most countries, the usage of codeine (both as end-product and precursor) is at least equal or greater than that of morphine on a weight basis.

## Precursor to other opioids [edit]

### Pharmaceutical [edit]

Morphine is a precursor in the manufacture in a large number of opioids such as dihydromorphine, hydromorphone, hydrocodone, and oxycodone as well as codeine, which itself has a large family of semi-synthetic derivatives. Morphine is commonly treated with acetic anhydride and ignited to yield heroin.[96] Throughout Europe there is growing acceptance within the medical community of the use of slow release oral morphine as a substitution treatment alternative to methadone and buprenorphine for patients not able to tolerate the side-effects of buprenorphine and methadone. Slow-release oral morphine has been in widespread use for opiate maintenance therapy in Austria, Bulgaria, and Slovakia for many years and it is available on a small scale in many other countries including the UK. The long-acting nature of slow-release morphine mimics that of buprenorphine because the sustained blood levels are relatively flat so there is no "high" per se that a patient would feel but rather a sustained feeling of wellness and avoidance of withdrawal symptoms. For patients sensitive to the side-effects that in part may be a result of the unnatural pharmacological actions of buprenorphine and methadone, slow-release oral morphine formulations offer a promising future for use managing opiate addiction. The pharmacology of heroin and morphine is identical except the two acetyl groups increase the lipid solubility of the heroin molecule, causing heroin to cross the blood–brain barrier and enter the brain more rapidly in injection. Once in the brain, these acetyl groups are removed to yield morphine, which causes the subjective effects of heroin. Thus, heroin may be thought of as a more rapidly acting form of morphine.[97]

### Illicit [edit]

Illicit morphine is rarely produced from codeine found in over-the-counter cough and pain medicines. This demethylation reaction is often performed using pyridine and hydrochloric acid.[98]

Another source of illicit morphine comes from the extraction of morphine from extended-release morphine products, such as MS-Contin. Morphine can be extracted from these products with simple extraction techniques to yield a morphine solution that can be injected.[99] As an alternative, the tablets can be crushed and snorted, injected or swallowed, although this provides much less euphoria but retains some of the extended-release effect, and the extended-release property is why MS-Contin is used in some countries alongside methadone, dihydrocodeine, buprenorphine, dihydroetorphine, piritramide, levo-alpha-acetylmethadol (LAAM), and special 24-hour formulations of hydromorphone for maintenance and detoxification of those physically dependent on opioids.

Another means of using or misusing morphine is to use chemical reactions to turn it into heroin or another stronger opioid. Morphine can, using a technique reported in New Zealand (where the initial precursor is codeine) and elsewhere known as home-bake, be turned into what is usually a mixture of morphine, heroin, 3-monoacetylmorphine, 6-monoacetylmorphine, and codeine derivatives like acetylcodeine if the

process is using morphine made from demethylating codeine.

Since heroin is one of a series of 3,6 diesters of morphine, it is possible to convert morphine to nicomorphine (Vilan) using nicotinic anhydride, dipropanoylmorphine with propionic anhydride, dibutanoylmorphine and disalicyloylmorphine with the respective acid anhydrides. Glacial acetic acid can be used to obtain a mixture high in 6-monoacetylmorphine, niacin (vitamin $B_3$) in some form would be precursor to 6-nicotinylmorphine, salicylic acid may yield the salicyoyl analogue of 6-MAM, and so on.

The clandestine conversion of morphine to ketones of the hydromorphone class or other derivatives like dihydromorphine (Paramorfan), desomorphine (Permonid), metopon, etc. and codeine to hydrocodone (Dicodid), dihydrocodeine (Paracodin), etc. is more involved, time-consuming, requires lab equipment of various types, and usually requires expensive catalysts and large amounts of morphine at the outset and is less common but still has been discovered by authorities in various ways during the last 20 years or so. Dihydromorphine can be acetylated into another 3,6 morphine diester, namely diacetyldihydromorphine (Paralaudin), and hydrocodone into thebacon.

## History [edit]


Friedrich Sertürner

An opium-based elixir has been ascribed to alchemists of Byzantine times, but the specific formula was lost during the Ottoman conquest of Constantinople (Istanbul).[100] Around 1522, Paracelsus made reference to an opium-based elixir that he called *laudanum* from the Latin word *laudare*, meaning "to praise" He described it as a potent painkiller, but recommended that it be used sparingly. In the late eighteenth century, when the East India Company gained a direct interest in the opium trade through India, another opiate recipe called laudanum became very popular among physicians and their patients.

Morphine was discovered as the first active alkaloid extracted from the opium poppy plant in December 1804 in Paderborn, Germany, by Friedrich Sertürner.[9][101] In 1817 Sertürner reported experiments in which he administered morphine to himself, three young boys, three dogs, and a mouse; all four people almost died.[102] Sertürner originally named the substance *morphium* after the Greek god of dreams, Morpheus as it has a tendency to cause sleep.[10][103]

The drug was first marketed to the general public by Sertürner and Company in 1817 as an pain medication, and also as a treatment for opium and alcohol addiction. It was first used as a poison in 1822 when Dr. Edme Castaing of France was convicted of murdering a patient.[104] Commercial production began in Darmstadt, Germany in 1827 by the pharmacy that became the pharmaceutical company Merck, with morphine sales being a large part of their early growth.[*citation needed*] In the 1850s Alexander Wood reported that he had injected morphine into his wife as an experiment; his wife died from respiratory depression.[102]

Later it was found that morphine was more addictive than either alcohol or opium, and its extensive use during the American Civil War allegedly resulted in over 400,000[105] sufferers from the "soldier's disease" of morphine addiction.[106] This idea has been a subject of controversy, as there have been suggestions that such a disease was in fact a fabrication; the first documented use of the phrase "soldier's disease" was in 1915.[107][108]

Diacetylmorphine (better known as heroin) was synthesized from morphine in 1874 and brought to market by Bayer in 1898. Heroin is approximately 1.5 to 2 times more potent than morphine weight for weight. Due to the lipid solubility of diacetylmorphine, it can cross the blood–brain barrier faster than morphine, subsequently increasing the reinforcing component of addiction.[109] Using a variety of subjective and objective measures, one study estimated the relative potency of heroin to morphine administered intravenously to post-addicts to be 1.80–2.66 mg of morphine sulfate to 1 mg of diamorphine hydrochloride (heroin).[37]

An ampoule of morphine with integral needle for immediate use. Also known as a "syrette". From WWII. On display at the Army Medical Services Museum.


Advertisement for curing morphine addiction, ca. 1900[110]

Morphine became a controlled substance in the US under the Harrison Narcotics Tax Act of 1914, and possession without a prescription in the US is a criminal offense. Morphine was the most commonly abused narcotic analgesic in the world until heroin was synthesized and came into use. In general, until the synthesis of dihydromorphine (ca. 1900), the dihydromorphinone class of opioids (1920s), and oxycodone (1916) and similar drugs, there were no other drugs in the same efficacy range as opium, morphine, and heroin, with synthetics still several years away (pethidine was invented in Germany in 1937) and opioid agonists among the semi-synthetics were analogues and derivatives of codeine such as dihydrocodeine (Paracodin), ethylmorphine (Dionine), and benzylmorphine (Peronine). Even today, morphine is the most sought after prescription narcotic by heroin addicts when heroin is scarce, all other things being equal; local conditions and user preference may cause hydromorphone, oxymorphone, high-dose oxycodone, or methadone as well as dextromoramide in specific instances such as 1970s Australia, to top that particular list. The stop-gap drugs used by the largest absolute number of heroin addicts is probably codeine, with significant use also of dihydrocodeine, poppy straw derivatives like poppy pod and poppy seed tea, propoxyphene, and tramadol.

The structural formula of morphine was determined by 1925 by Robert Robinson. At least three methods of total synthesis of morphine from starting materials such as coal tar and petroleum distillates have been patented, the first of which was announced in 1952, by Dr. Marshall D. Gates, Jr. at the University of Rochester.[111] Still, the vast majority of morphine is derived from the opium poppy by either the traditional method of gathering latex from the scored, unripe pods of the poppy, or processes using poppy straw, the dried pods and stems of the plant, the most widespread of which was invented in Hungary in 1925 and announced in 1930 by the chemist János Kabay.

In 2003, there was discovery of endogenous morphine occurring naturally in the human body. Thirty years of speculation were made on this subject because there was a receptor that, it appeared, reacted only to morphine: the $\mu_3$-opioid receptor in human tissue.[112] Human cells that form in reaction to cancerous neuroblastoma cells have been found to contain trace amounts of endogenous morphine.[113]

## Society and culture [edit]

### Legal status [edit]

- In Australia, morphine is classified as a Schedule 8 drug under the variously titled State and Territory Poisons Acts.
- In Canada, morphine is classified as a Schedule I drug under the Controlled Drugs and Substances Act.
- In France, morphine is in the strictest schedule of controlled substances, based upon the December 1970 French controlled substances law.
- In Germany, morphine is a *verkehrsfähiges und verschreibungsfähiges Betäubungsmittel* listed under *Anlage III* (the equivalent of CSA Schedule II) of the Betäubungsmittelgesetz.[114]
  In Switzerland, morphine is similarly scheduled to Germany's legal classification of the drug.
- In Japan, morphine is classified as a narcotic under the Narcotics and Psychotropics Control Act (麻薬及び向精神薬取締法, *mayaku oyobi kōseishinyaku torishimarihō*).
- In the Netherlands, morphine is classified as a List 1 drug under the Opium Law.
- In the United Kingdom, morphine is listed as a Class A drug under the Misuse of Drugs Act 1971 and a Schedule 2 Controlled Drug under the Misuse of Drugs Regulations 2001.
- In the United States, morphine is classified as a Schedule II controlled substance under the Controlled

Substances Act with a main Administrative Controlled Substances Code Number (ACSCN) of ACSCN 9300. Morphine pharmaceuticals in the US are subject to annual manufacturing quotas; morphine production for use in extremely dilute formulations and its production as an intermediate, or chemical precursor, for conversion into other drugs is excluded from the US manufacturing quota.

- Internationally (UN), morphine is a Schedule I drug under the Single Convention on Narcotic Drugs.[115]

## Non-medical use [edit]

The euphoria, comprehensive alleviation of distress and therefore all aspects of suffering, promotion of sociability and empathy, "body high", and anxiolysis provided by narcotic drugs including the opioids can cause the use of high doses in the absence of pain for a protracted period, which can impart a morbid craving for the drug in the user. Being the prototype of the entire opioid class of drugs means that morphine has properties that may lend it to misuse. Morphine addiction is the model upon which the current perception of addiction is based.[*medical citation needed*]

Example of different morphine tablets

Animal and human studies and clinical experience back up the contention that morphine is one of the most euphoric of drugs on earth, and via all but the IV route heroin and morphine cannot be distinguished according to studies because heroin is a prodrug for the delivery of systemic morphine. Chemical changes to the morphine molecule yield other euphorigenics such as dihydromorphine, hydromorphone (Dilaudid, Hydal), and oxymorphone (Numorphan, Opana), as well as the latter three's methylated equivalents dihydrocodeine, hydrocodone, and oxycodone, respectively; in addition to heroin, there are dipropanoylmorphine, diacetyldihydromorphine, and other members of the 3,6 morphine diester category like nicomorphine and other similar semi-synthetic opiates like desomorphine, hydromorphinol, etc. used clinically in many countries of the world but in many cases also produced illicitly in rare instances.[*medical citation needed*]

In general, non-medical use of morphine entails taking more than prescribed or outside of medical supervision, injecting oral formulations, mixing it with unapproved potentiators such as alcohol, cocaine, and the like, or defeating the extended-release mechanism by chewing the tablets or turning into a powder for snorting or preparing injectables. The latter method can be as time-consuming and involved as traditional methods of smoking opium. This and the fact that the liver destroys a large percentage of the drug on the first pass impacts the demand side of the equation for clandestine re-sellers, as many customers are not needle users and may have been disappointed with ingesting the drug orally. As morphine is generally as hard or harder to divert than oxycodone in a lot of cases, morphine in any form is uncommon on the street, although ampoules and phials of morphine injection, pure pharmaceutical morphine powder, and soluble multi-purpose tablets are very popular where available.[*medical citation needed*]

Morphine is also available in a paste that is used in the production of heroin, which can be smoked by itself or turned to a soluble salt and injected; the same goes for the penultimate products of the Kompot (Polish Heroin) and black tar processes. Poppy straw as well as opium can yield morphine of purity levels ranging from poppy tea to near-pharmaceutical-grade morphine by itself or with all of the more than 50 other alkaloids. It also is the active narcotic ingredient in opium and all of its forms, derivatives, and analogues as well as forming from breakdown of heroin and otherwise present in many batches of illicit heroin as the result of incomplete acetylation.[*medical citation needed*]

## Slang terms [edit]

Informal names for morphine include: Cube Juice, Dope, Dreamer, Emsel, First Line, God's Drug, Hard Stuff, Hocus, Hows, Lydia, Lydic, M, Miss Emma, Mister Blue, Monkey, Morf, Morph, Morphide, Morphie, Morpho,

Mother, MS, Ms. Emma, Mud, New Jack Swing (if mixed with heroin), Sister, Tab, Unkie, Unkie White, and Stuff.[116]

MS Contin tablets are known as misties, and the 100 mg extended-release tablets as greys and blockbusters. The "speedball" can use morphine as the opioid component, which is combined with cocaine, amphetamines, methylphenidate, or similar drugs. "Blue Velvet" is a combination of morphine with the antihistamine tripelennamine (Pyrabenzamine, PBZ, Pelamine) taken by injection, or less commonly the mixture when swallowed or used as a retention enema; the name is also known to refer to a combination of tripelennamine and dihydrocodeine or codeine tablets or syrups taken by mouth. "Morphia" is an older official term for morphine also used as a slang term. "Driving Miss Emma" is intravenous administration of morphine. Multi-purpose tablets (readily soluble hypodermic tablets that can also be swallowed or dissolved under the tongue or betwixt the cheek and jaw) are known, as are some brands of hydromorphone, as Shake & Bake or Shake & Shoot.

Morphine can be smoked, especially diacetylmorphine (heroin), the most common method being the "Chasing The Dragon" method. To perform a relatively crude acetylation to turn the morphine into heroin and related drugs immediately prior to use is known as AAing (for Acetic Anhydride) or home-bake, and the output of the procedure also known as home-bake or, Blue Heroin (not to be confused with Blue Magic heroin, or the linctus known as Blue Morphine or Blue Morphone, or the Blue Velvet mixture described above).

## Trade names [edit]

Morphine is marketed under many different brand names in various parts of the world.[1]

## Access in developing countries [edit]

Although morphine is cheap, people in poorer countries often do not have access to it. According to a 2005 estimate by the International Narcotics Control Board, six countries (Australia, Canada, France, Germany, the United Kingdom, and the United States) consume 79% of the world's morphine. The less affluent countries, accounting for 80% of the world's population, consumed only about 6% of the global morphine supply. Some countries import virtually no morphine, and in others the drug is rarely available even for relieving severe pain while dying.

Experts in pain management attribute the under-distribution of morphine to an unwarranted fear of the drug's potential for addiction and abuse. While morphine is clearly addictive, Western doctors believe it is worthwhile to use the drug and then wean the patient off when the treatment is over.[117]

# References [edit]


1. ^ a b c drugs.com Drugs.com international listings for Morphine Page accessed 2 June 2015
2. ^ Jonsson T, Christensen CB, Jordening H, Frølund C (April 1988). "The bioavailability of rectally administered morphine". *Pharmacol. Toxicol.* **62** (4): 203–5. doi:10.1111/j.1600-0773.1988.tb01872.x. PMID 3387374.
3. ^ Whimster, Fiona (1997). *Cambridge textbook of accident and emergency medicine*. Cambridge: Cambridge University Press. p. 191. ISBN 978-0-521-43379-2.
4. ^ Liben, Stephen (2012). *Oxford textbook of palliative care for children* (2 ed.). Oxford: Oxford University Press. p. 240. ISBN 978-0-19-959510-5.
5. ^ a b c d e f g h "Morphine sulfate". The American Society of Health-System Pharmacists. Retrieved 1 June 2015.
6. ^ a b c Rockwood, Charles A. (2009). *Rockwood and Wilkins' fractures in children.* (7th ed.). Philadelphia, Pa.: Lippincott Williams & Wilkins. p. 54. ISBN 978-1-58255-784-7.
7. ^ a b c d e f g Stefano GB, Ptáček R, Kuželová H, Kream RM (2012). "Endogenous morphine: up-to-date review 2011" (PDF). *Folia Biol. (Praha).* **58** (2): 49–56. PMID 22578954. "Positive evolutionary pressure has apparently preserved the ability to synthesize chemically authentic morphine, albeit in homeopathic concentrations, throughout animal phyla."
8. ^ a b c Courtwright, David T. (2009). *Forces of habit drugs and the making of the modern world* (1 ed.). Cambridge, Mass.: Harvard University Press. pp. 36–37. ISBN 978-0-674-02990-3.

a b

9. ^ Luch A, ed. (2009). *Molecular, clinical and environmental toxicology* . Springer. p. 20. ISBN 3-7643-8335-6.
10. ^ [a b c] Clayton J. Mosher (2013). *Drugs and Drug Policy: The Control of Consciousness Alteration*. SAGE Publications. p. 123. ISBN 978-1-4833-2188-2.
11. ^ Fisher, Gary L. (2009). *Encyclopedia of substance abuse prevention, treatment, & recovery*. Los Angeles: SAGE. p. 564. ISBN 978-1-4522-6601-5.
12. ^ *Narcotic Drugs Estimated World Requirements for 2008, Statistics for 2006.* New York: United Nations Pubns. 2008. p. 77. ISBN 9789210481199.
13. ^ [a b c d] *Narcotic Drugs 2014* (pdf). INTERNATIONAL NARCOTICS CONTROL BOARD. 2015. pp. 21, 30. ISBN 9789210481571.
14. ^ [a b] Triggle, David J. (2006). *Morphine*. New York: Chelsea House Publishers. pp. 20–21. ISBN 978-1-4381-0211-5.
15. ^ Karch, Steven B. (2006). *Drug abuse handbook* (2nd ed.). Boca Raton: CRC/Taylor & Francis. pp. 7–8. ISBN 978-1-4200-0346-8.
16. ^ Macpherson, edited by Gordon (2002). *Black's medical dictionary* (40th ed.). London: A & C Black. p. 162. ISBN 978-0-7136-5442-4.
17. ^ *Davis's Canadian Drug Guide for Nurses*. F.A. Davis. 2014. p. 1409. ISBN 978-0-8036-4086-3.
18. ^ "WHO Model List of Essential Medicines" (PDF). *World Health Organization*. October 2013. Retrieved 22 April 2014.
19. ^ [a b] "Morphine Sulfate". The American Society of Health-System Pharmacists. Retrieved 3 April 2011.
20. ^ Meine TJ, Roe MT, Chen AY, Patel MR, Washam JB, Ohman EM, Peacock WF, Pollack CV, Gibler WB, Peterson ED (June 2005). "Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative". *Am. Heart J.* **149** (6): 1043–9. doi:10.1016/j.ahj.2005.02.010. PMID 15976786.
21. ^ Sosnowski MA. "BestBets: Does the application of opiates, during an attack of Acute Cardiogenic Pulmonary Oedma, reduce patients' mortality and morbidity?". *BestBets*. Best Evidence Topics. Retrieved 6 December 2008.
22. ^ Wiffen, Philip J; Wee, Bee; Moore, R Andrew (22 April 2016). "Oral morphine for cancer pain". *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd. **4**. doi:10.1002/14651858.cd003868.pub4. Retrieved 26 April 2016.
23. ^ Schrijvers D, van Fraeyenhove F (2010). "Emergencies in palliative care". *Cancer J.* **16** (5): 514–20. doi:10.1097/PPO.0b013e3181f28a8d. PMID 20890149.
24. ^ Naqvi F, Cervo F, Fields S (August 2009). "Evidence-based review of interventions to improve palliation of pain, dyspnea, depression". *Geriatrics*. **64** (8): 8–10, 12–4. PMID 20722311.
25. ^ Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, Gift AG, Harver A, Lareau SC, Mahler DA, Meek PM, O'Donnell DE (February 2012). "An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea". *Am. J. Respir. Crit. Care Med.* **185** (4): 435–52. doi:10.1164/rccm.201111-2042ST. PMID 22336677.
26. ^ Mahler DA, Selecky PA, Harrod CG, Benditt JO, Carrieri-Kohlman V, Curtis JR, Manning HL, Mularski RA, Varkey B, Campbell M, Carter ER, Chiong JR, Ely EW, Hansen-Flaschen J, O'Donnell DE, Waller A (March 2010). "American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease". *Chest*. **137** (3): 674–91. doi:10.1378/chest.09-1543. PMID 20202949.
27. ^ Mattick RP; Digiusto E; Doran C; O'Brien S; Kimber J; Henderson N; Breen B; Shearer J; Gates J; Shakeshaft A; NEPOD Trial Investigators (2004). *National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD): Report of Results and Recommendation* (PDF). *Monograph Series No. 52*. Australian Government. ISBN 0-642-82459-2.
28. ^ Thompson DR (April 2001). "Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis". *Am. J. Gastroenterol.* **96** (4): 1266–72. doi:10.1111/j.1572-0241.2001.03536.x. PMID 11316181.
29. ^ [a b c d e f] Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E (2006). "Opioids for chronic noncancer pain: A meta-analysis of effectiveness and side effects". *Canadian Medical Association Journal*. **174** (11): 1589–1594. doi:10.1503/cmaj.051528. PMC 1459894. PMID 16717269.
30. ^ Stefano GB, Zhu W, Cadet P, Bilfinger TV, Mantione K (March 2004). "Morphine enhances nitric oxide release in the mammalian gastrointestinal tract via the micro(3) opiate receptor subtype: a hormonal role for endogenous morphine". *J. Physiol. Pharmacol.* **55** (1 Pt 2): 279–88. PMID 15082884.
31. ^ Calignano A, Moncada S, Di Rosa M (December 1991). "Endogenous nitric oxide modulates morphine-induced constipation". *Biochem. Biophys. Res. Commun.* **181** (2): 889–93. doi:10.1016/0006-291X(91)91274-G. PMID 1755865.
32. ^ Brennan MJ (March 2013). "The effect of opioid therapy on endocrine function". *Am. J. Med.* **126** (3 Suppl 1): S12–8. doi:10.1016/j.amjmed.2012.12.001. PMID 23414717.

33. ^ Colameco S, Coren JS (January 2009). "Opioid-induced endocrinopathy". *J Am Osteopath Assoc*. **109** (1): 20–5. PMID 19193821.
34. ^ Kerr B, Hill H, Coda B, Calogero M, Chapman CR, Hunt E, Buffington V, Mackie A (November 1991). "Concentration-related effects of morphine on cognition and motor control in human subjects". *Neuropsychopharmacology*. **5** (3): 157–66. PMID 1755931.
35. ^ Friswell J, Phillips C, Holding J, Morgan CJ, Brandner B, Curran HV (2008). "Acute effects of opioids on memory functions of healthy men and women". *Psychopharmacology (Berl.)*. **198** (2): 243–50. doi:10.1007/s00213-008-1123-x. PMID 18379759.
36. ^ Galski T, Williams JB, Ehle HT (2000). "Effects of opioids on driving ability". *J Pain Symptom Manage*. **19** (3): 200–8. doi:10.1016/S0885-3924(99)00158-X. PMID 10760625.
37. ^ *a b c* Martin WR, Fraser HF (1961). "A comparative study of physiological and subjective effects of heroin and morphine administered intravenously in postaddicts". *J. Pharmacol. Exp. Ther*. **133**: 388–99. PMID 13767429.
38. ^ *a b* National Institute on Drug Abuse (NIDA) (April 2013). "Heroin". *DrugFacts*. U.S. National Institutes of Health.
39. ^ Roshanpour M, Ghasemi M, Riazi K, Rafiei-Tabatabaei N, Ghahremani MH, Dehpour AR (2009). "Tolerance to the anticonvulsant effect of morphine in mice: blockage by ultra-low dose naltrexone". *Epilepsy Res*. **83** (2–3): 261–4. doi:10.1016/j.eplepsyres.2008.10.011. PMID 19059761.
40. ^ Koch T, Höllt V (2008). "Role of receptor internalization in opioid tolerance and dependence". *Pharmacol. Ther*. **117** (2): 199–206. doi:10.1016/j.pharmthera.2007.10.003. PMID 18076994.
41. ^ http://www.merriam-webster.com/words-at-play/why-do-we-quit-cold-turkey
42. ^ [1]
43. ^ Chan R, Irvine R, White J (1999). "Cardiovascular changes during morphine administration and spontaneous withdrawal in the rat". *Eur. J. Pharmacol*. **368** (1): 25–33. doi:10.1016/S0014-2999(98)00984-4. PMID 10096766.
44. ^ "Morphine (and Heroin)". *Drugs and Human Performance Fact Sheets*. U.S. National Traffic Safety Administration.
45. ^ "Narcotics". *DEA Briefs & Background, Drugs and Drug Abuse, Drug Descriptions*. U.S. Drug Enforcement Administration. Archived from the original on 14 January 2012.
46. ^ Dalrymple T (2006). *Romancing Opiates: Pharmacological Lies and the Addiction Bureaucracy*. Encounter. p. 160. ISBN 978-1-59403-087-1.
47. ^ Anraku T, Ikegaya Y, Matsuki N, Nishiyama N (September 2001). "Withdrawal from chronic morphine administration causes prolonged enhancement of immobility in rat forced swimming test". *Psychopharmacology (Berl.)*. **157** (2): 217–20. doi:10.1007/s002130100793. PMID 11594449.
48. ^ O'Neil MJ (2006). *The Merck index : an encyclopedia of chemicals, drugs, and biological*. Whitehouse Station, N.J.: Merck. ISBN 0-911910-00-X.
49. ^ *a b* MedlinePlus – Morphine overdose Update Date: 2 March 2009. Updated by: John E. Duldner, Jr., MD
50. ^ Macchiarelli L, Arbarello Cave Bondi P. Di Luca NM, Feola T (2002). *Medicina Legale (compendio)* (II ed.). Italy, Turin: Minerva Medica Publications.
51. ^ Yekkirala AS, Kalyuzhny AE, Portoghese PS (2010). "Standard opioid agonists activate heteromeric opioid receptors: evidence for morphine and [d-Ala(2)-MePhe(4)-Glyol(5)]enkephalin as selective μ-δ agonists". *ACS Chem Neurosci*. **1** (2): 146–54. doi:10.1021/cn9000236. PMC 3398540. PMID 22816017.
52. ^ Yekkirala AS, Banks ML, Lunzer MM, Negus SS, Rice KC, Portoghese PS (2012). "Clinically employed opioid analgesics produce antinociception via μ-δ opioid receptor heteromers in Rhesus monkeys". *ACS Chem Neurosci*. **3** (9): 720–7. doi:10.1021/cn300049m. PMC 3447399. PMID 23019498.
53. ^ *a b* "MS-Contin (Morphine Sulfate Controlled-Release) Drug Information: Clinical Pharmacology". *Prescribing Information*. RxList.
54. ^ Chien CC, Pasternak GW (1995). "Sigma antagonists potentiate opioid analgesia in rats". *Neurosci. Lett*. **190** (2): 137–9. doi:10.1016/0304-3940(95)11504-P. PMID 7644123.
55. ^ Herman BH, Vocci F, Bridge P (1995). "The effects of NMDA receptor antagonists and nitric oxide synthase inhibitors on opioid tolerance and withdrawal. Medication development issues for opiate addiction". *Neuropsychopharmacology*. **13** (4): 269–93. doi:10.1016/0893-133X(95)00140-9. PMID 8747752.
56. ^ Loguinov A, Anderson L, Crosby G, Yukhananov R (2001). "Gene expression following acute morphine administration". *Physiol Genomics*. **6** (3): 169–81. PMID 11526201.
57. ^ Messmer D, Hatsukari I, Hitosugi N, Schmidt-Wolf IG, Singhal PC (2006). "Morphine reciprocally regulates IL-10 and IL-12 production by monocyte-derived human dendritic cells and enhances T cell activation". *Mol. Med*. **12** (11–12): 284–90. doi:10.2119/2006-00043.Messmer. PMC 1829197. PMID 17380193.
58. ^ Clark JD, Shi X, Li X, Qiao Y, Liang D, Angst MS, Yeomans DC (2007). "Morphine reduces local cytokine expression and neutrophil infiltration after incision". *Mol Pain*. **3**: 28. doi:10.1186/1744-8069-3-28. PMC 2096620.

PMID 17908329.
59. ^ Trescot AM, Datta S, Lee M, Hansen H (2008). "Opioid pharmacology". *Pain Physician*. **11** (2 Suppl): S133–53. PMID 18443637.
60. ^ Kilpatrick G.J.; Smith T.W. (2005). "Morphine-6-glucuronide: actions and mechanisms". *Med. Res. Rev*. **25** (5): 521–544. doi:10.1002/med.20035. PMID 15952175.
61. ^ *a b* van Dorp EL, Romberg R, Sarton E, Bovill JG, Dahan A (2006). "Morphine-6-glucuronide: morphine's successor for postoperative pain relief?". *Anesthesia and Analgesia*. **102** (6): 1789–1797. doi:10.1213/01.ane.0000217197.96784.c3. PMID 16717327.
62. ^ *a b* Jenkins AJ (2008) Pharmacokinetics of specific drugs. In Karch SB (*Ed*), *Pharmacokinetics and pharmacodynamics of abused drugs*. CRC Press: Boca Raton.
63. ^ *a b c* "Morphine, slow release (By mouth)". *University of Maryland Medical Center*.
64. ^ Pedersen, L; Fredheim, OMS (2015). "Opioids for Chronic Noncancer Pain: Still No Evidence for Superiority of Sustained-Release Opioids". *Clinical Pharmacology & Therapeutics*. **97** (2): 114–115. doi:10.1002/cpt.26. ISSN 0009-9236. Last reviewed on 18 November 2015
65. ^ *a b* "Dosing & Uses". *Medscape*. Retrieved 21 December 2015.
66. ^ *a b* "EndLink: An Internet-based End of Life Care Education Program – Morphine Dosing" (PDF). *Northwestern University*.
67. ^ Baselt RC (2008). *Disposition of Toxic Drugs and Chemicals in Man* (8th ed.). Foster City, CA: Biomedical Publications. pp. 1057–1062. ISBN 0-9626523-7-7.
68. ^ Vandevenne M, Vandenbussche H, Verstraete A (2000). "Detection time of drugs of abuse in urine". *Acta Clin Belg*. **55** (6): 323–33. PMID 11484423.
69. ^ Verstraete AG (April 2004). "Detection times of drugs of abuse in blood, urine, and oral fluid". *Ther Drug Monit*. **26** (2): 200–5. doi:10.1097/00007691-200404000-00020. PMID 15228165.
70. ^ Kapoor L (1995). *Opium Poppy: Botany, Chemistry, and Pharmacology*. United States: CRC Press. p. 164. ISBN 1-56024-923-4.
71. ^ Vincent PG, Bare CE, Gentner WA (December 1977). "Thebaine content of selections of Papaver bracteatum Lindl. at different ages". *J Pharm Sci*. **66** (12): 1716–9. doi:10.1002/jps.2600661215. PMID 925935.
72. ^ Stewart O (2000). *Functional Neuroscience*. New York: Springer. p. 116. ISBN 0-387-98543-3.
73. ^ Wang X, Li J, Dong G, Yue J (February 2014). "The endogenous substrates of brain CYP2D". *Eur. J. Pharmacol*. **724**: 211–218. doi:10.1016/j.ejphar.2013.12.025. PMID 24374199. "Additionally, CYP2D is involved in the synthesis of endogenous morphine from various precursors, including L-3,4-dihydroxyphenylalanine (L-DOPA), reticulin, tetrahydropapaveroline (THP), and tyramine (Kulkarni, 2001; Mantione et al., 2008; Zhu, 2008)."
74. ^ Novak B, Hudlicky T, Reed J, Mulzer J, Trauner D (March 2000). "Morphine Synthesis and Biosynthesis-An Update" (PDF). *Current Organic Chemistry*. **4** (3): 343–362. doi:10.2174/1385272003376292.
75. ^ Michael Le Page (18 May 2015). "Home-brew heroin: soon anyone will be able to make illegal drugs". New Scientist.
76. ^ Robert F. Service (25 June 2015). "Final step in sugar-to-morphine conversion deciphered". Science.
77. ^ Galanie S, Thodey K, Trenchard I, Filsinger Interrante M, Smolke C (August 2015). "Complete biosynthesis of opioids in yeast". *Science*. **349**: 1095–1100. doi:10.1126/science.aac9373. PMC 4924617. PMID 26272907.
78. ^ "Yeast-Based Opioid Production Completed". 13 August 2015. Retrieved 15 August 2015.
79. ^ DeRuiter J (Fall 2000). "Narcotic analgesics: morphine and "peripherally modified" morphine analogs" (PDF). *Principles of Drug Action 2*. Auburn University.
80. ^ *a b c d e* Lide DR, ed. (2004). *CRC handbook of chemistry and physics: a ready-reference book of chemical and physical data* (85 ed.). Boca Ratan Florida: CRC Press. ISBN 0-8493-0485-7.
81. ^ "Morphine". *LHA Science Page*. LaurenHill Academy.
82. ^ Gates M, Tschudi G (April 1956). "The Synthesis of Morphine". *Journal of the American Chemical Society*. **78** (7): 1380–1393. doi:10.1021/ja01588a033.
83. ^ Rice KC (July 1980). "Synthetic opium alkaloids and derivatives. A short total synthesis of (+/-)-dihydrothebainone, (+/-)-dihydrocodeinone, and (+/-)-nordihydrocodeinone as an approach to a practical synthesis of morphine, codeine, and congeners". *The Journal of Organic Chemistry*. **45** (15): 3135–3137. doi:10.1021/jo01303a045.
84. ^ Evans DA, Mitch CH (January 1982). "Studies directed towards the total synthesis of morphine alkaloids". *Tetrahedron Letters*. **23** (3): 285–288. doi:10.1016/S0040-4039(00)86810-0.
85. ^ Toth JE, Hamann PR, Fuchs PL (September 1988). "Studies culminating in the total synthesis of (dl)-morphine". *The Journal of Organic Chemistry*. **53** (20): 4694–4708. doi:10.1021/jo00255a008.
86. ^ Parker KA, Fokas D (November 1992). "Convergent synthesis of (+/-)-dihydroisocodeine in 11 steps by the tandem radical cyclization strategy. A formal total synthesis of (+/-)-morphine". *Journal of the American Chemical*

*Society*. **114** (24): 9688–9689. doi:10.1021/ja00050a075.
87. ^ Hong CY, Kado N, Overman LE (November 1993). "Asymmetric synthesis of either enantiomer of opium alkaloids and morphinans. Total synthesis of (−)- and (+)-dihydrocodeinone and (−)- and (+)-morphine". *Journal of the American Chemical Society*. **115** (23): 11028–11029. doi:10.1021/ja00076a086.
88. ^ Mulzer J, Dürner G, Trauner D (December 1996). "Formal Total Synthesis of(—)-Morphine by Cuprate Conjugate Addition". *Angewandte Chemie International Edition in English*. **35** (2324): 2830–2832. doi:10.1002/anie.199628301.
89. ^ White JD, Hrnciar P, Stappenbeck F (October 1999). "Asymmetric Total Synthesis of (+)-Codeine via Intramolecular Carbenoid Insertion". *The Journal of Organic Chemistry*. **64** (21): 7871–7884. doi:10.1021/jo990905z.
90. ^ Taber DF, Neubert TD, Rheingold AL (October 2002). "Synthesis of (−)-Morphine". *Journal of the American Chemical Society*. **124** (42): 12416–12417. doi:10.1021/ja027882h. PMID 12381175.
91. ^ Trost BM, Tang W (December 2002). "Enantioselective Synthesis of (−)-Codeine and (−)-Morphine". *Journal of the American Chemical Society*. **124** (49): 14542–14543. doi:10.1021/ja0283394. PMID 12465957.
92. ^ Uchida K, Yokoshima S, Kan T, Fukuyama T (November 2006). "Total Synthesis of (±)-Morphine". *Organic Letters*. **8** (23): 5311–5313. doi:10.1021/ol062112m. PMID 17078705.
93. ^ Varin M, Barré E, Iorga B, Guillou C (2008). "Diastereoselective Total Synthesis of (±)-Codeine". *Chemistry: A European Journal*. **14** (22): 6606–6608. doi:10.1002/chem.200800744.
94. ^ Stork G, Yamashita A, Adams J, Schulte GR, Chesworth R, Miyazaki Y, Farmer JJ (2009). "Regiospecific and Stereoselective Syntheses of (±) Morphine, Codeine, and Thebaine via a Highly Stereocontrolled Intramolecular 4 + 2 Cycloaddition Leading to a Phenanthrofuran System". *Journal of the American Chemical Society*. **131** (32): 11402–11406. doi:10.1021/ja9038505. PMID 19624126.
95. ^ Michael Freemantle (20 June 2005). "The Top Pharmaceuticals That Changed The World-Morphine". Chemical and Engineering News.
96. ^ Small LF, Lutz RE (1932). *Chemistry of the Opium Alkaloids*. Washington, D. C.: U. S. Government Printing Office. pp. 153–154. ASIN B000H4LBY8.
97. ^ Klous MG, Van den Brink W, Van Ree JM, Beijnen JH (December 2005). "Development of pharmaceutical heroin preparations for medical co-prescription to opioid dependent patients". *Drug Alcohol Depend*. **80** (3): 283–95. doi:10.1016/j.drugalcdep.2005.04.008. PMID 15916865.
98. ^ Rapoport H, Lovell CH, Tolbert BM (December 1951). "The Preparation of Morphine-N-methyl-$C^{14}$". *Journal of the American Chemical Society*. **73** (12): 5900–5900. doi:10.1021/ja01156a543.
99. ^ Crews JC, Denson DD (1990). "Recovery of morphine from a controlled-release preparation. A source of opioid abuse". *Cancer*. **66** (12): 2642–4. doi:10.1002/1097-0142(19901215)66:12<2642::AID-CNCR2820661229>3.0.CO;2-B. PMID 2249204.
100. ^ Ramoutsaki IA, Askitopoulou H, Konsolaki E (December 2002). "Pain relief and sedation in Roman Byzantine texts: *Mandragoras officinarum*, *Hyoscyamos niger* and *Atropa belladonna*". *International Congress Series*. **1242**: 43–50. doi:10.1016/S0531-5131(02)00699-4.
101. ^ Friedrich Sertürner (1805) (Untitled letter to the editor), *Journal der Pharmacie für Aerzte, Apotheker und Chemisten* (Journal of Pharmacy for Physicians, Apothecaries, and Chemists), **13** : 229–243 ; see especially "III. Säure im Opium" (acid in opium), pp. 234–235, and "I. Nachtrag zur Charakteristik der Säure im Opium" (Addendum on the characteristics of the acid in opium), pp. 236–241.
102. ^ *a b* Dahan, A; Aarts, L; Smith, TW (January 2010). "Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression.". *Anesthesiology*. **112** (1): 226–38. doi:10.1097/aln.0b013e3181c38c25. PMID 20010421.
103. ^ Sertürner coined the term *morphium* in: Sertuerner (1817) "Ueber das Morphium, eine neue salzfähige Grundlage, und die Mekonsäure, als Hauptbestandtheile des Opiums" (On morphine, a new salifiable [i.e., precipitable], fundamental substance, and meconic acid, as principal components of opium), *Annalen der Physik*, **55** : 56–89. It was Gay-Lussac, a French chemist and editor of *Annales de Chimie et de Physique*, who coined the word *morphine* in a French translation of Sertuener's original German article: Sertuener (1817) "Analyse de l'opium: De la morphine et de l'acide méconique, considérés comme parties essentielles de l'opium" (Analysis of opium: On morphine and on meconic acid, considered as essential constituents of opium), *Annales de Chimie et de Physique*, 2nd series, **5** : 21–42. From p. 22: *"… car il a pris pour cette substance, que j'appelle* morphine *(*morphium*), ce qui n'en était qu'une combinaison avec* l'acide de l'opium."( … for he [i.e., French chemist and pharmacist Charles Derosne (1780–1846)] took as that substance [i.e., the active ingredient in opium], which I call "morphine" (or *morphium*), what was only a compound of it with *acid of opium*.)
104. ^ *Annual Register*. J. Dodsley. 1824. p. 1. Retrieved 1 September 2015.
105. ^ Vassallo SA (July 2004). "Lewis H. Wright Memorial Lecture". *ASA New Letter*. **68** (7): 9–10.
106. ^ "Opiate Narcotics". *The Report of the Canadian Government Commission of Inquiry into the Non-Medical Use of Drugs*. Canadian Government Commission.

107. ^ Mandel J. "Mythical Roots of US Drug Policy – Soldier's Disease and Addicts in the Civil War".
108. ^ "Soldiers Disease A Historical Hoax?". iPromote Media Inc. 2006. Archived from the original on 27 September 2007.
109. ^ Winger G, Hursh SR, Casey KL, Woods JH (May 2002). "Relative reinforcing strength of three N-methyl-D-aspartate antagonists with different onsets of action". *J. Pharmacol. Exp. Ther.* **301** (2): 690–7. doi:10.1124/jpet.301.2.690. PMID 11961074.
110. ^ "Morphine Easy Home Cure". *Overland Monthly*. **35** (205): 14. 1900.
111. ^ Dickman S (3 October 2003). "Marshall D. Gates, Chemist to First Synthesize Morphine, Dies". *Press Release*. University of Rochester.
112. ^ Zhu W, Cadet P, Baggerman G, Mantione KJ, Stefano GB (2005). "Human white blood cells synthesize morphine: CYP2D6 modulation". *J. Immunol.* **175** (11): 7357–62. doi:10.4049/jimmunol.175.11.7357. PMID 16301642.
113. ^ Poeaknapo C, Schmidt J, Brandsch M, Dräger B, Zenk MH; Schmidt; Brandsch; Dräger; Zenk (2004). "Endogenous formation of morphine in human cells". *Proc. Natl. Acad. Sci. U.S.A.* **101** (39): 14091–6. Bibcode:2004PNAS..10114091P. doi:10.1073/pnas.0405430101. PMC 521124. PMID 15383669.
114. ^ Anlage III (zu § 1 Abs. 1) verkehrsfähige und verschreibungsfähige Betäubungsmittel
115. ^ "List of narcotic drugs under international control" (PDF). *Yellow List* (PDF) (50th ed.). Austria: International Narcotics Control Board: 5. March 2011.
116. ^ Miller, Richard Lawrence (1 January 2002). *The Encyclopedia of Addictive Drugs*. Greenwood Publishing Group. p. 306. ISBN 978-0-313-31807-8.
117. ^ Donald G. McNeil Jr. (10 September 2007). "Drugs Banned, Many of World's Poor Suffer in Pain". New York Times. Retrieved 11 September 2007.


## External links [edit]

- U.S. National Library of Medicine: Drug Information Portal – Morphine
- Morphine bound to proteins in the PDB
- Morphine and Heroin at *The Periodic Table of Videos* (University of Nottingham)
- Video: Intravenous morphine loading (Vimeo) (YouTube) – A short education video teaching health professionals the main points about intravenous loading of analgesics, in particular morphine.

Wikimedia Commons has media related to *Morphine*.

Wikinews has related news: *2005 Afghan opium harvest begins*

| v · t · e · **Opium components** | |
|---|---|
| **Alkaloids** | 16-Hydroxythebaine · Berberine · Canadine · Codamine · Coptisine · Coreximine · Cycloartenol · Cycloartenone · Cyclolaudenol · Dehydroreticuline · Dihydrosanguinarine · Glaucine · Isoboldine · Isocorypalmine · Laudanidine · Magnoflorine · Narceine · Narceinone · Norlaudanosoline · Norsanguinarine · Oripavine · Oxysanguinarine · Palaudine · Papaverrubine B (O-methyl-porphyroxine) · Papaverrubine C (epiporphyroxine) · Reticuline · Salutaridine (sinoacutine) · Sanguinarine · Scoulerine · Somniferine · Stepholidine · |
| **Morphine group (Phenanthrenes. Includes opioids)** | Codeine · **Morphine** · Narcotoline · Neopine · Perparin · Papaverrubine D (porphyroxine) · Pseudocodeine · Pseudomorphine · Thebaine · |
| **Isoquinolines** | Cotarnine · Eupaverine · Hydrocotarnine · Laudanosine · Laudanine · Noscapine (narcotine) · Papaverine · Papaveraldine · Xanthaline · |
| **Protopine group** | α-Allocryptopine · α-Fagarine · Corycavamine · Corycavine · Cryptopine · Protopine · |
| **Tetrahydroprotoberberine group** | Corydaline · Corybulbine · Isocorybulbine · Capaurine · |

| | |
|---|---|
| **Aporphine group** | Dicentrine · Glaucine · Corytuberine · Cularine · Corydine · Isocorydine · Bulbocapnine · |
| **Phtalide-isoquinolines** | Adulmine · Bicuculline · Bicucine · Corlumine · |
| **α-Naphthaphenanthridines** | Chelidonine · β-Homochelidonoine · Chelerythrine · Sanguinarine · |
| **Other components** | Meconic acid · |

| v · t · e · | **Analgesics (N02A, N02B)** | |
|---|---|---|
| **Opioids** | **Opiates/opium** | Codeine# (+paracetamol, +aspirin) · **Morphine**# (+naltrexone) · Opium · Laudanum · Paregoric · |
| | **Semisynthetic** | Acetyldihydrocodeine · Benzylmorphine · Buprenorphine (+naloxone) · Desomorphine · Diamorphine (heroin) · Dihydrocodeine (+paracetamol) · Dihydromorphine · Ethylmorphine · Hydrocodone (+paracetamol, +ibuprofen, +aspirin) · Hydromorphinol · Hydromorphone · Nicocodeine · Nicodicodeine · Nicomorphine · Oxycodone (+paracetamol, +aspirin, +ibuprofen, +naloxone, +naltrexone) · Oxymorphone · Thebacon · |
| | **Synthetic** | Alphaprodine · Anileridine · Butorphanol · Dextromoramide · Dextropropoxyphene · Dezocine · Fentanyl (+fluanisone) · Ketobemidone · Levorphanol · Meptazinol · Methadone · Nalbuphine · Pentazocine · Pethidine · Phenadoxone · Phenazocine · Piminodine · Piritramide · Propiram · Tapentadol · Tilidine · Tramadol · |
| **Paracetamol-type** | | Acetanilide‡ · Bucetin‡ · Butacetin‡ · Paracetamol (acetaminophen)# · Parapropamol‡ · Phenacetin‡ · Propacetamol‡ · |
| **NSAIDs** | **Propionates** | Fenoprofen · Flurbiprofen · Ibuprofen# · Ketoprofen · Naproxen · Oxaprozin · |
| | **Oxicams** | Meloxicam · Piroxicam · |
| | **Acetates** | Diclofenac · Indometacin · Ketorolac · Nabumetone · Sulindac · Tolmetin · |
| | **COX-2 inhibitors** | Celecoxib · Etoricoxib · Lumiracoxib · Parecoxib · Rofecoxib ‡ · Valdecoxib ‡ · |
| | **Fenamates** | Meclofenamic acid · Mefenamic acid · |
| | **Salicylates** | Aspirin (acetylsalicylic acid)# (+paracetamol/caffeine) · Benorylate · Diflunisal · Ethenzamide · Magnesium salicylate · Salicin · Salicylamide · Salsalate · Wintergreen (methyl salicylate) · |
| | **Pyrazolones** | Aminophenazone‡ · Ampyrone · Metamizole (dipyrone) · Nifenazone · Phenazone · Propyphenazone · |
| | **Others** | Glafenine · |
| **Cannabinoids** | | Cannabidiol · Cannabis · Nabilone · Nabiximols · Tetrahydrocannabinol (dronabinol) · |
| **Ion channel modulators** | **Calcium blockers** | Gabapentin · Gabapentin enacarbil · Pregabalin · Ziconotide · |
| | **Sodium blockers** | Carbamazepine · Lacosamide · Local anesthetics (e.g., cocaine, lidocaine) · Mexiletine · Nefopam · Tricyclic antidepressants (e.g., amitriptyline#) · *$Na_v1.7/1.8$-selective:* DSP-2230§ · Funapide§ · PF-05089771§ · |

| | | |
|---|---|---|
| | | Raxatrigine[§] · |
| | **Potassium openers** | Flupirtine · |
| **Myorelaxants** | | Carisoprodol · Chlorzoxazone · Cyclobenzaprine · Mephenoxalone · Methocarbamol · Orphenadrine · |
| **Others** | | Camphor · Capsaicin · Clonidine · Ketamine · Menthol · Methoxyflurane · Nefopam · Proglumide · Tricyclic antidepressants (e.g., amitriptyline[#]) · |

· [#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III · ·

v · t · e · **Euphoriants**

μ-Opioid receptor agonists (opioids) (e.g., **morphine**, heroin, hydrocodone, oxycodone, opium, kratom) · $\alpha_2\delta$ subunit-containing voltage-dependent calcium channels blockers (gabapentinoids) (e.g., gabapentin, pregabalin, phenibut) · AMPA receptor antagonists (e.g., perampanel) · $CB_1$ receptor agonists (cannabinoids) (e.g., THC, cannabis) · Dopamine receptor agonists (e.g., levodopa) · Dopamine releasing agents (e.g., amphetamine, methamphetamine, MDMA, mephedrone) · Dopamine reuptake inhibitors (e.g., cocaine, methylphenidate) · $GABA_A$ receptor positive allosteric modulators (e.g., barbiturates, benzodiazepines, carbamates, ethanol (drinking alcohol), inhalants, nonbenzodiazepines, quinazolinones) · GHB (sodium oxybate) and analogues · Glucocorticoids (corticosteroids) (e.g., dexamethasone, prednisone) · nACh receptor agonists (e.g., nicotine, tobacco, arecoline, areca nut) · Nitric oxide prodrugs (e.g., alkyl nitrites (poppers)) · NMDA receptor antagonists (e.g., DXM, ketamine, methoxetamine, nitrous oxide, phencyclidine, inhalants) · Orexin receptor antagonists (e.g., suvorexant) ·

*See also: Recreational drug use*

v · t · e · **Glycinergics**

| | | |
|---|---|---|
| **Receptor (ligands)** | **GlyR** | **Agonists:** β-Alanine · β-ABA (BABA) · β-AIBA · Caesium · D-Alanine · D-Serine · GABA · Glycine · Hypotaurine · Ivermectin · L-Alanine · L-Proline · L-Serine · L-Threonine · MDL-27531 · Milacemide · Picolinic acid · Propofol · Quisqualamine · Sarcosine · Taurine · |
| | | **PAMs:** Alcohols (e.g., brometone, chlorobutanol (chloretone), ethanol, *tert*-butanol (2M2P), tribromoethanol, trichloroethanol, trifluoroethanol) · Alkylbenzene sulfonate · Anandamide · Barbiturates (e.g., pentobarbital, sodium thiopental) · Chlormethiazole · D12-116 · Dihydropyridines (e.g., nicardipine) · Etomidate · Ginseng constituents (e.g., ginsenosides (e.g., ginsenoside-Rf)) · Glutamic acid (glutamate) · Ivermectin · Ketamine · Neuroactive steroids (e.g., alfaxolone, pregnenolone (eltanolone), pregnenolone acetate, minaxolone, Org 20599) · Nitrous oxide · Penicillin G · Propofol · Tamoxifen · Tetrahydrocannabinol · Triclofos · Tropeines (e.g., atropine, bemesetron, cocaine, LY-278584, tropisetron, zatosetron) · Volatiles/gases (e.g., chloral hydrate, chloroform, desflurane, diethyl ether (ether), enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, toluene, trichloroethane (methyl chloroform), trichloroethylene) · Xenon · Zinc · |
| | | **Antagonists:** 2-Aminostrychnine · 2-Nitrostrychnine · 4-Phenyl-4-formyl-N-methylpiperidine · αEMBTL · Bicuculline · Brucine · Cacotheline · Caffeine · Colchicine · Colubrine · Cyanotriphenylborate · Dendrobine · Diaboline · Endocannabinoids (e.g., 2-AG, anandamide (AEA)) · Gaboxadol (THIP) · Gelsemine · iso-THAZ · Isobutyric acid · Isonipecotic acid · Isostrychnine · Laudanosine · N-Methylbicuculline · N-Methylstrychnine · N,N-Dimethylmuscimol · Nipecotic acid · Pitrazepin · Pseudostrychnine · Quinolines (e.g., 4-hydroxyquinoline, 4-hydroxyquinoline-3-carboxylic acid, 5,7-CIQA, 7-CIQ, 7-TFQ, 7-TFQA) · RU-5135 · Sinomenine · Strychnine · Thiocolchicoside · Tutin · |
| | | **NAMs:** Amiloride · Benzodiazepines (e.g., bromazepam, clonazepam, diazepam, flunitrazepam, |

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|---|---|---|
| | | flurazepam) · Corymine · Cyanotriphenylborate · Daidzein · Dihydropyridines (e.g., nicardipine, nifedipine, nitrendipine) · Furosemide · Genistein · Ginkgo constituents (e.g., bilobalide, ginkgolides (e.g., ginkgolide A, ginkgolide B, ginkgolide C, ginkgolide J, ginkgolide M)) · Imipramine · NBQX · Neuroactive steroids (e.g., 3α-androsterone sulfate, 3β-androsterone sulfate, deoxycorticosterone, DHEA sulfate, pregnenolone sulfate, progesterone) · Opioids (e.g., codeine, dextromethorphan, dextrorphan, levomethadone, levorphanol, **morphine**, oripavine, pethidine, thebaine) · Picrotoxin (i.e., picrotin and picrotoxinin) · PMBA · Riluzole · Tropeines (e.g., bemesetron, LY-278584, tropisetron, zatosetron) · Verapamil · Zinc · |
| **Transporter (blockers)** | **GlyT1** | ACPPB · ALX-1393 · ALX-5407 (NFPS) · AMG-747 · ASP2535 · Bitopertin (RG1678/RO4917838) · CP-802079 · Ethanol · Glycyldodecylamide · GSK1018921 · LY-2365109 · Org 24598 · Org 25935 (SCH-900435) · PF-02545920 · PF-03463275 · PF-04958242 · Sarcosine · SSR-103,800 · SSR-504,734 · |
| | **GlyT2** | Amoxapine · Ethanol · NAGly · Org 25543 · |
| **Others** | **Precursors:** 3-PG · GHB · L-Serine · L-Theonine · **Cofactors:** Vitamin $B_6$ · | |

*See also: GABAergics • GHBergics • Glutamatergics*

| v · t · e · | **Opioid receptor modulators** |
|---|---|
| **MOR** | **Agonists** *(abridged; see here for a full list)*: 7-Acetoxymitragynine · 7-Hydroxymitragynine · ψ-Akuammigine · α-Chlornaltrexamine · α-Narcotine · Acetyldihydrocodeine · Acetylfentanyl · Acrylfentanyl · Adrenorphin (metorphamide) · AH-7921 · Akuammicine · Akuammidine · Alfentanil · Anileridine · Apparicine · β-Endorphin · BAM-12P · BAM-18P · BAM-22P · Benzhydrocodone · Benzylmorphine · Bezitramide · Biphalin · BU08070 · Buprenorphine · Butorphan · Butorphanol · Butyrfentanyl · BW-373U86 · Carfentanil · Casokefamide · Cebranopadol · Chloroxymorphamine · Codeine · DADLE · DAMGO (DAGO) · Dermorphin · Desomorphine · Dextromoramide · Dextropropoxyphene (propoxyphene) · Dezocine · Dimenoxadol · Dimethylaminopivalophenone · Eluxadoline · Diamorphine (heroin) · Dihydrocodeine · Dihydroetorphine · Dihydromorphine · Diphenoxylate · Dipipanone · Dynorphin A · Embutramide · Endomorphin-1 · Endomorphin-2 · Eseroline · Ethylmorphine · Etorphine · Fentanyl · Fluorophen · Frakefamide · Furanylfentanyl · Hemorphin-4 · Herkinorin · Hodgkinsine · Hydrocodone · Hydromorphinol · Hydromorphone · IBNtxA · Ketamine · Ketobemidone · Kratom · Laudanosine · Lefetamine · Leu-enkephalin · Levacetylmethadol · Levomethorphan · Levorphanol · Lexanopadol · Loperamide · Matrine · Meptazinol · Met-enkephalin (metenkefalin) · Methadone · Metkefamide · Metopon · Mitragynine · Mitragynine pseudoindoxyl · Morphiceptin · **Morphine** · Nalbuphine · Nalbuphine sebacate · NalBzOH · Nalmexone · Naltalimide · Neopine · Nicocodeine · Nicodicodeine · Nicomorphine · NKTR-181 · Norketamine · O-Desmethyltramadol · Octreotide · Oliceridine · OM-3-MNZ · Oripavine · Oxycodone · Oxymorphazone · Oxymorphonazine · Oxymorphone · Oxymorphone phenylhydrazone · OxyPNPH · *Papaver somniferum* (opium) · Pentazocine · Pericine · Pethidine (meperidine) · Phenazocine · Phencyclidine · Piminodine · Piritramide · PL-017 · Prodine · Propiram · PZM21 · Racemethorphan · Racemorphan · Remifentanil · Salsolinol · SC-17599 · Sinomenine · Sufentanil · Tapentadol · Tetrahydropapaveroline · TH-030418 · Thebaine · Thienorphine · Tianeptine · Tilidine · Tramadol · Trimebutine · TRIMU 5 · TRV734 · Tubotaiwine · U-47700 · Valorphin · Viminol · Xorphanol · **PAMs:** BMS-986121 · BMS-986122 · **Antagonists:** (3S,4S)-Picenadol · 2-(S)-N,N-(R)-Viminol · 4-Caffeoyl-1,5-quinide · 4′-Hydroxyflavanone · 4',7-Dihydroxyflavone · 6β-Naltrexol · 6β-Naltrexol-d4 · 18-MC · α-Gliadin · β-Chlornaltrexamine · |

| | |
|---|---|
| | β-Funaltrexamine · Akuammine · Alvimopan · AM-251 · Apigenin · AT-076 · Axelopran · Bevenopran · Catechin · Catechin gallate · Clocinnamox · CTAP · CTOP · Cyclofoxy · Cyprodime · Diacetylnalorphine · Diprenorphine · ECG · EGC · Epicatechin · Eptazocine · Gemazocine · Ginsenoside R · Hyperoside · Ibogaine · Levallorphan · Lobeline · LY-255582 · LY-2196044 · Methocinnamox · Methylnaltrexone · Methylsamidorphan chloride · Naldemedine · Nalmefene · Nalodeine (N-allylnorcodeine) · Nalorphine · Nalorphine dinicotinate · Naloxazone · Naloxegol · Naloxol · Naloxonazine · Naloxone · Naltrexazone · Naltrexonazine · Naltrexone · Naltrindole · Naringenin · Noribogaine · Oxilorphan · Pawhuskin A · Rimonabant · Quadazocine · Samidorphan · Taxifolin ·<br>**Unknown/unsorted:** Cannabidiol · Coronaridine · Cyproterone acetate · Dihydroakuuamine · Tabernanthine · Tetrahydrocannabinol · |
| **DOR** | **Agonists:** 6'-GNTI · 7-SIOM · ADL-5747 (PF-04856881) · ADL-5859 · Amoxapine · AR-M100390 (ARM390) · AZD2327 · β-Endorphin · BAM-18P · Biphalin · BU-48 · Butorphan · Butorphanol · BW-373U86 · Casokefamide · Cebranopadol · Codeine · Cyclazocine · DADLE · Deltorphin A · Deltorphin I · Deltorphin II · Desmethylclozapine · Dezocine · Diamorphine (heroin) · Dihydroetorphine · Dihydromorphine · DPDPE · DPI-221 · DPI-3290 · DSLET · Ethylketazocine · Etorphine · Fentanyl · FIT · Fluorophen · Hemorphin-4 · Hydrocodone · Hydromorphone · Ibogaine · Isomethadone · JNJ-20788560 · KNT-127 · Kratom · Laudanosine · Leu-enkephalin · Levomethorphan · Levorphanol · Lexanopadol · Lofentanil · Met-enkephalin (metenkefalin) · Metazocine · Metkefamide · Mitragynine · Mitragynine pseudoindoxyl · **Morphine** · N-Phenethyl-14-ethoxymetopon · Norbuprenorphine · NalBzOH · O-Desmethyltramadol · Oripavine · Oxycodone · Oxymorphone · Pethidine (meperidine) · Proglumide · Racemethorphan · Racemorphan · RWJ-394674 · Samidorphan · SB-235863 · SKF-10047 · SNC-80 · SNC-162 · TAN-67 (SB-205,607) · TH-030418 · Thebaine · Thiobromadol (C-8813) · Tianeptine · Tonazocine · Tramadol · TRV250 · Xorphanol · Zenazocine ·<br>**Antagonists:** 4',7-Dihydroxyflavone · 5'-NTII · 6β-Naltrexol · 6β-Naltrexol-d4 · α-Santolol · β-Chlornaltrexamine · Apigenin · AT-076 · Axelopran · Bevenopran · BNTX · Catechin · Catechin gallate · Clocinnamox · Diacetylnalorphine · Diprenorphine · ECG · EGC · Eluxadoline · Epicatechin · ICI-154129 · ICI-174864 · LY-255582 · LY-2196044 · Methylnaltrexone · Methylnaltrindole · N-Benzylnaltrindole · Nalmefene · Nalorphine · Naltrexone · Naltriben · Naltrindole · Naloxone · Naringenin · Noribogaine · Pawhuskin A · Quadazocine · SDM25N · SoRI-9409 · Taxifolin · Thienorphine ·<br>**Unknown/unsorted:** 18-MC · Cannabidiol · Coronaridine · Cyproterone acetate · Tabernanthine · Tetrahydrocannabinol · |
| **KOR** | **Agonists:** 6'-GNTI · 8-CAC · 18-MC · 14-Methoxymetopon · β-Chlornaltrexamine · β-Funaltrexamine · Adrenorphin (metorphamide) · Akuuamicine · Alazocine · Allomatrine · Asimadoline · BAM-12P · BAM-18P · BAM-22P · Big dynorphin · Bremazocine · BRL-52537 · Butorphan · Butorphanol · BW-373U86 · Cebranopadol · Ciprefadol · CR665 · Cyclazocine · Cyclorphan · Cyprenorphine · Diamorphine (heroin) · Diacetylnalorphine · Difelikefalin · Dihydroetorphine · Dihydromorphine · Diprenorphine · Dynorphin A · Dynorphin B (rimorphin) · Eluxadoline · Enadoline · Eptazocine · Erinacine E · Ethylketazocine · Etorphine · Fedotozine · Fentanyl · Gemazocine · GR-89696 · GR-103545 · Hemorphin-4 · Herkinorin · HS665 · Hydromorphone · HZ-2 · Ibogaine · ICI-199,441 · ICI-204,448 · Ketamine · Ketazocine · Laudanosine · Leumorphin (dynorphin B-29) · Levallorphan · Levomethorphan · Levorphanol · Lexanopadol · Lofentanil · LPK-26 · Lufuradom · Matrine · MB-1C-OH · Menthol · Metazocine · Metkefamide · Mianserin · Mirtazapine · **Morphine** · Moxazocine · MR-2034 · N-MPPP · Nalbuphine · Nalbuphine sebacate · NalBzOH · Nalfurafine · Nalmefene · Nalodeine (N-allylnorcodeine) · Nalorphine · Naltriben · Niravoline · Norbuprenorphine · Norbuprenorphine-3-glucuronide · Noribogaine · Norketamine · O-Desmethyltramadol · Oripavine · Oxilorphan · Oxycodone · Pentazocine · Pethidine (meperidine) · Phenazocine · Proxorphan · |

| | |
|---|---|
| | Racemethorphan · Racemorphan · RB-64 · Salvinorin A (salvia) · Salvinorin B ethoxymethyl ether · Salvinorin B methoxymethyl ether · Samidorphan · SKF-10047 · Spiradoline (U-62,066) · TH-030418 · Thienorphine · Tifluadom · Tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline) · U-50,488 · U-54,494A · U-69,593 · Xorphanol ·<br>**Antagonists:** 4′-Hydroxyflavanone · 4',7-Dihydroxyflavone · 5'-GNTI · 6'-GNTI · 6β-Naltrexol · 6β-Naltrexol-d4 · β-Chlornaltrexamine · Buprenorphine/samidorphan · Amentoflavone · ANTI · Apigenin · Arodyne · AT-076 · Axelopran · AZ-MTAB · Binaltorphimine · BU09059 · Buprenorphine · Catechin · Catechin gallate · CERC-501 (LY-2456302) · Clocinnamox · Cyclofoxy · Dezocine · DIPPA · EGC · ECG · Epicatechin · Hyperoside · JDTic · LY-255582 · LY-2196044 · LY-2444296 · LY-2459989 · LY-2795050 · MeJDTic · Methylnaltrexone · ML190 · ML350 · MR-2266 · N-Fluoropropyl-JDTic · Naloxone · Naltrexone · Naltrindole · Naringenin · Norbinaltorphimine · Noribogaine · Pawhuskin A · PF-4455242 · RB-64 · Quadazocine · Taxifolin · UPHIT · Zyklophin ·<br>**Unknown/unsorted:** Akuammicine · Akuammine · Coronaridine · Cyproterone acetate · Dihydroakuuamine · Ibogamine · Tabernanthine · |
| **NOP** | **Agonists:** (Arg14,Lys15)Nociceptin · ((pF)Phe$^4$)Nociceptin(1-13)$NH_2$ · (Phe$^1$Ψ($CH_2$-NH)Gly$^2$)Nociceptin(1-13)$NH_2$ · Ac-RYYRWK-$NH_2$ · Ac-RYYRIK-$NH_2$ · BU08070 · Buprenorphine · Cebranopadol · Dihydroetorphine · Etorphine · JNJ-19385899 · Levomethorphan · Levorphanol · Levorphanol · Lexanopadol · MCOPPB · MT-7716 · NNC 63-0532 · Nociceptin (orphanin FQ) · Nociceptin (1-11) · Nociceptin (1-13)$NH_2$ · Norbuprenorphine · Racemethorphan · Racemorphan · Ro64-6198 · Ro65-6570 · SCH-221510 · SCH-486757 · SR-8993 · SR-16435 · TH-030418 ·<br>**Antagonists:** (Nphe$^1$)Nociceptin(1-13)$NH_2$ · AT-076 · BAN-ORL-24 · J-113397 · JTC-801 · LY-2940094 · NalBzOH · Nociceptin (1-7) · Nocistatin · SB-612111 · SR-16430 · Thienorphine · Trap-101 · UFP-101 · |
| **Unsorted** | β-Casomorphins · Amidorphin · BAM-20P · Cytochrophin-4 · Deprolorphin · Gliadorphin (gluteomorphin) · Gluten exorphins · Hemorphins · Kava constituents · MEAGL · MEAP · NEM · Neoendorphins · Nepetalactone (catnip) · Peptide B · Peptide E · Peptide F · Peptide I · Rubiscolins · Soymorphins · |
| **Others** | **Enkephalinase inhibitors:** Amastatin · BL-2401 · Candoxatril · D -Phenylalanine · Dexecadotril (retorphan) · Ecadotril (sinorphan) · Kelatorphan · Racecadotril (acetorphan) · RB-101 · RB-120 · RB-3007 · Opiorphan · Selank · Semax · Spinorphin · Thiorphan · Tynorphin · Ubenimex (bestatin) ·<br>**Propeptides:** β-Lipotropin (proendorphin) · Prodynorphin · Proenkephalin · Pronociceptin · Proopiomelanocortin (POMC) ·<br>**Others:** Kyotorphin (met-enkephalin releaser/degradation stabilizer) · |
| *See also: Peptide receptor modulators* | |

| | |
|---|---|
| **Authority control** | LCCN: sh85087342 · GND: 4040284-8 · NDL: 01035412 · |

Categories: German inventions | Morphine | Ethers | Mu-opioid agonists | Kappa agonists | Natural opium alkaloids | Opiates | Phenols | World Health Organization essential medicines | Chemical substances for emergency medicine | Euphoriants | Alcohols | Morphinans | GABAA receptor negative allosteric modulators | Glycine receptor antagonists | Alkaloids | Secondary metabolites | Human metabolites | Biomolecules


# Nystatin

From Wikipedia, the free encyclopedia

**Nystatin**, sold under the brandname **Mycostatin** among others, is an antifungal medication.[1] It is used to treat *Candida* infections of the skin including diaper rash, thrush, esophageal candidiasis, and vaginal yeast infections. It may also be used to prevent candidiasis in those who are at high risk. Nystatin may be used by mouth, in the vagina, or applied to the skin.[1]

Common side effects when applied to the skin include burning, itching, and a rash. Common side effects when taken by mouth include vomiting and diarrhea. During pregnancy use in the vagina is safe while other formulations have not been studied in this group. It works by disrupting the cell membrane of the fungal cells.[1]

Nystatin was discovered in 1950 by Rachel Fuller Brown and Elizabeth Lee Hazen.[2] It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[3] It is available as a generic medication.[1] The wholesale price of the cream in the developing world is about 0.70 USD per 30 gram tube.[4] In the United States it is less than 25 USD for a course of treatment.[5] It is made from the bacterium, *Streptomyces noursei*.[2]

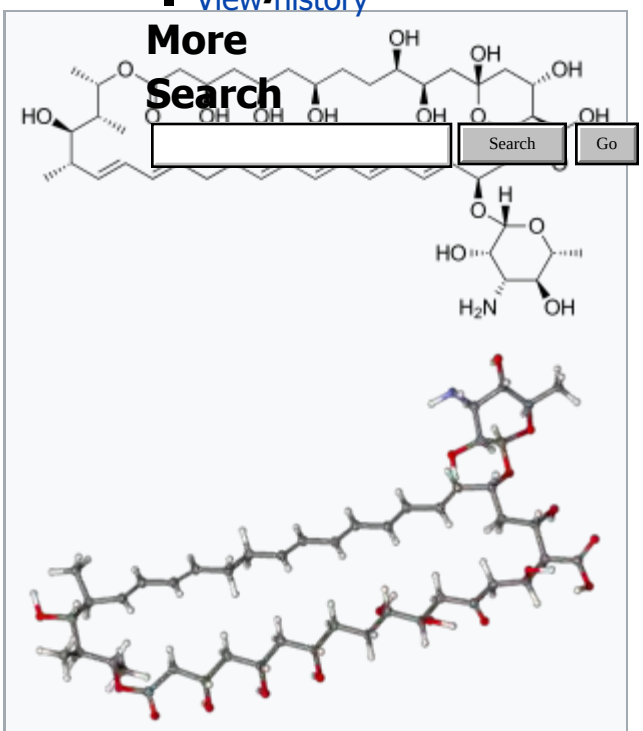
Contents



## Medical uses [edit]

Skin, vaginal, mouth, and esophageal *Candida* infections usually respond well to treatment with nystatin. It is available in many forms.

Oral nystatin is often used as a preventive treatment in people




| Clinical data | |
|---|---|
| **Trade names** | Mycostatin, Nystop, others[1] |
| **AHFS/Drugs.com** | Monograph |
| **MedlinePlus** | a682758 |
| **Pregnancy category** | A vaginal, C by mouth |
| **Routes of administration** | topical, vaginal, by mouth (but not absorbed orally) |
| **ATC code** | A07AA02 (WHO) D01AA01 (WHO) G01AA01 (WHO) |
| **Legal status** | |
| **Legal status** | (Prescription only) |
| **Pharmacokinetic data** | |

who are at risk for fungal infections, such as AIDS patients with a low CD4+ count and people receiving chemotherapy. It has been investigated for use in patients after liver transplantation, but fluconazole was found to be much more effective for preventing colonization, invasive infection, and death.[6]

It is also used in very low birth-weight (less than 1500 g or 3lb 5oz 0) infants to prevent invasive fungal infections, although fluconazole is the preferred treatment. It has been found to reduce the rate of invasive fungal infections and also reduce deaths when used in these babies.[7]

Liposomal nystatin is not commercially available, but investigational use has shown greater *in vitro* activity than colloidal formulations of amphotericin B, and demonstrated effectiveness against some amphotericin B-resistant forms of fungi.[8] It offers an intriguing possibility for difficult-to-treat systemic infections, such as invasive aspergillosis, or infections that demonstrate resistance to amphotericin B. *Cryptococcus* is also sensitive to nystatin. Additionally, liposomal nystatin appears to cause fewer cases of and less severe nephrotoxicity than observed with amphotericin B.[8]

In the UK, its license for treating neonatal oral thrush is restricted to those over the age of one month.[*citation needed*]

It is prescribed in 'units', with doses varying from 100,000 units (for oral infections) to 1 million (for intestinal ones). As it is not absorbed from the gut, it is fairly safe for oral use and does not have problems of drug interactions. On occasion, serum levels of the drug can be identified from oral, vaginal, or cutaneous administration, and lead to toxicity.



## Adverse effects [edit]

The oral suspension form produces a number of adverse effects including but not limited to:[9]

1. Diarrhea
2. Abdominal pain
3. Rarely, tachycardia, bronchospasm, facial swelling, muscle aches

Both the oral suspension and the topical form can cause:

1. Hypersensitivity reactions, including Stevens-Johnson syndrome in some cases [10]
2. Rash, itching, burning and acute generalized exanthematous pustulosis[11]

## Mechanism of action [edit]

Like amphotericin B and natamycin, nystatin binds to ergosterol, a major component of the fungal cell membrane. When present in sufficient concentrations, it forms pores in the membrane that lead to $K^+$ leakage, acidification, and death of the fungus.[12] Ergosterol is a sterol

| | |
|---|---|
| **Bioavailability** | 0% on oral ingestion |
| **Metabolism** | None (not extensively absorbed) |
| **Biological half-life** | Dependent upon GI transit time |
| **Excretion** | Fecal (100%) |

**Identifiers**

**IUPAC name**

(1*S*,3*R*,4*R*,7*R*,9*R*,11*R*,15*S*,16*R*,17*R*,18*S*,19*E*,21*E*, 25*E*,27*E*,29*E*,31*E*,33*R*,35*S*,36*R*,37*S*)-33-[(3-amino-3, 6-dideoxy-β-L-mannopyranosyl)oxy]-1, 3,4,7,9,11,17,37-octahydroxy-15, 16,18-trimethyl-13-oxo-14, 39-dioxabicyclo[33.3.1]nonatriaconta-19, 21,25,27,29,31-hexaene-36-carboxylic acid

| | |
|---|---|
| **CAS Number** | 1400-61-9 ✓ |
| **PubChem** (CID) | 14960 |
| **DrugBank** | DB00646 ✓ |
| **ChemSpider** | 23078586 ✗ |
| **UNII** | BDF1O1C72E ✓ |
| **KEGG** | D00202 ✓ |
| **ChEBI** | CHEBI:473992 ✓ |
| **ChEMBL** | CHEMBL229383 ✗ |
| **NIAID ChemDB** | 004993 |
| **ECHA InfoCard** | 100.014.317 |

**Chemical and physical data**

| | |
|---|---|
| **Formula** | $C_{47}H_{75}NO_{17}$ |
| **Molar mass** | 926.09 |
| **3D model (Jmol)** | Interactive image |

**SMILES**

CC1C=CC=CCCC=CC=CC=CC(CC2C(C(CC(O2)(CC(C(CCC(CC(CC(=O)OC(C(C1O)C)C)O)O)O)O)O)O)O)C(=O)OC3C(C(C(C(O3)C)O)N)O

**InChI**

InChI=1S/C47H75NO17/c1-27-17-15-13-11-9-7-5-6-8-10-12-14-16-18-34(64-46-44(58)41(48)43(57)30(4)63-46)24-38-40(45(59)60)37(54)26-47(61,65-38)25-36(53)35(52)20-19-31(49)21-32(50)22-33(51)23-39(55)62-29(3)28(2)42(27)56/h5-6,8,10-18,27-38,40-44,46,49-54,56-58,61H,7,9,19-26,48H2,1-4H3,(H,59,60)/b6-5+,10-8+,13-11+,14-12+,17-15+,18-16+/t27-,28-,29-,30+,31+,32+,33+,34-,35+,36+,37-,38-,40+,41-,42+,43+,44-,46-,47+/m0/s1 ✗

Key:VQOXZBDYSJBXMA-NQTDYLQESA-N ✗

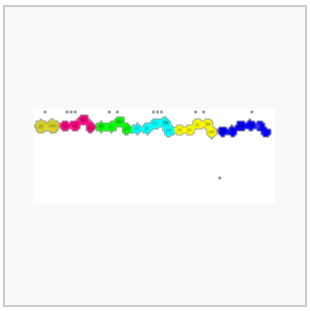
✗✓ (what is this?) (verify)

unique to fungi, so the drug does not have such catastrophic effects on animals or plants. However, many of the systemic/toxic effects of nystatin in humans are attributable to its binding to mammalian sterols, namely cholesterol. This is the effect that accounts for the nephrotoxicity observed when high serum levels of nystatin are achieved.

## Biosynthesis [edit]

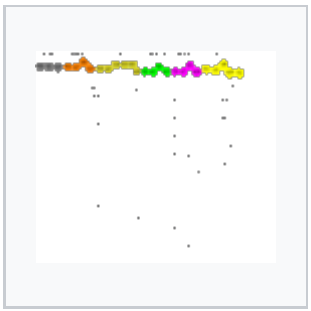
Nystatin $A_1$ (or referred to as nystatin) is biosynthesized by a bacterial strain, *Streptomyces noursei*.[13] The structure of this active compound is characterized as a polyene macrolide with a deoxysugar D-mycosamine, an aminoglycoside.[13] The genomic sequence of nystatin reveals the presence of the polyketide loading module (nysA), six polyketide synthases modules (nysB, nysC, nysI, nysJ, and nysK) and two thioesterase modules (nysK and nysE).[13] It is evident that the biosynthesis of the macrolide functionality follows the polyketide synthase I pathway.[14]

Following the biosynthesis of the macrolide, the compound undergoes post-synthetic modifications, which are aided by the following enzymes: GDP-mannose dehydratase (nysIII), P450 monooxygenase (nysL and nysN), aminotransferase (nysDII), and glycosyltransferase (nysDI).[13] The biosynthetic pathway is thought to proceed as shown to yield nystatin.

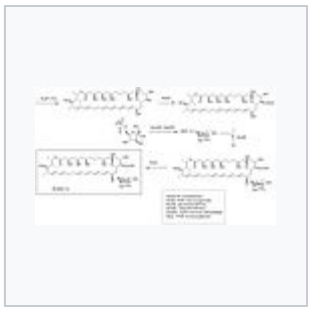


Loading to 5

Modules 6-12



Modules 13 -18



Completed molecule

## History [edit]

Like many other antifungals and antibiotics, nystatin is of bacterial origin. It was isolated from *Streptomyces noursei* in 1950 by Elizabeth Lee Hazen and Rachel Fuller Brown, who were doing research for the Division of Laboratories and Research of the New York State Department of Health. Hazen found a promising micro-organism in the soil of a friend's dairy farm. She named it *Streptomyces noursei*, after Jessie Nourse, the wife of the farm's owner.[15] Hazen and Brown named nystatin after the New York State Health Department in 1954.[16] The two discoverers patented the drug, and then donated the $13 million in profits to a foundation to fund similar research.[17][18]

Elizabeth Lee Hazen (left) and Rachel Fuller Brown in 1955.

## Other uses [edit]

It is also used in cellular biology as an inhibitor of the lipid raft-caveolae endocytosis pathway on mammalian cells, at concentrations around 3 µg/ml.

In certain cases, nystatin has been used to prevent the spread of mold on objects such as works of art. For example, it was applied to wood panel paintings damaged as a result of the Arno River Flood of 1966 in Florence, Italy.

*Penicillium*-infected tangerine: The spot absent of growth had nystatin applied to it before the fungus covered the fruit.

Nystatin is also used as a tool by scientists performing "perforated" patch-clamp electrophysiologic recordings of cells. When loaded in the recording pipette, it allows for measurement of electrical currents without washing out the intracellular contents, because it forms pores in the cell membrane that are permeable to only monovalent ions.[19]

## Formulations [edit]

- An oral suspension form is used for the prophylaxis or treatment of oropharyngeal thrush, a superficial candidal infection of the mouth and pharynx.
- A tablet form is preferred for candidal infections in the intestines.
- Nystatin is available as a topical cream and can be used for superficial candidal infections of the skin.
- Additionally, a liposomal formulation of nystatin was investigated in the 1980s and into the early 21st century. The liposomal form was intended to resolve problems arising from the poor solubility of the parent molecule and the associated systemic toxicity of the free drug.

Due to its toxicity profile when high levels in the serum are obtained, no injectable formulations of this drug are currently on the US market. However, injectable formulations have been investigated in the past.[8]

## Brand names [edit]

The original brandname was Fungicidin

- Nyamyc
- Pedi-Dri
- Pediaderm AF Complete
- Candistatin
- Nyaderm
- Bio-Statin
- PMS-Nystatin
- Nystan (oral tablets, topical ointment, and pessaries, formerly from Bristol-Myers Squibb)
- Infestat
- Nystalocal from Medinova AG
- Nystamont
- Nystop (topical powder, Paddock)
- Nystex
- Mykinac
- Nysert (vaginal suppositories, Procter & Gamble)
- Nystaform (topical cream, and ointment and cream combined with iodochlorhydroxyquine and hydrocortisone; formerly Bayer now Typharm Ltd)
- Nilstat (vaginal tablet, oral drops, Lederle)
- Korostatin (vaginal tablets, Holland Rantos)
- Mycostatin (vaginal tablets, topical powder, suspension Bristol-Myers Squibb)
- Mycolog-II (topical ointment, combined with triamcinolone; Apothecon)
- Mytrex (topical ointment, combined with triamcinolone)
- Mykacet (topical ointment, combined with triamcinolone)
- Myco-Triacet II (topical ointment, combined with triamcinolone)

Flagystatin II (cream, combined with metronidazole)
- Timodine (cream, combined with hydrocortisone and dimethicone)
- Nistatina (oral tablets, Antibiotice Iaşi)
- Nidoflor (cream, combined with neomycin sulfate and triamcinolone acetonide)
- Stamicin (oral tablets, Antibiotice Iaşi)
- Lystin
- Animax (veterinary topical ointment or cream; combined with neomycin sulfate, thiostrepton and triamcinolone acetonide)

## References [edit]


1. ^ *a b c d e* "Nystatin". American Society of Health-System Pharmacists. Retrieved 2016-01-27.
2. ^ *a b* Espinel-Ingroff, Ana Victoria (2013). *Medical Mycology in the United States a Historical Analysis (1894-1996)*. Dordrecht: Springer Netherlands. p. 62. ISBN 9789401703116.
3. ^ "WHO Model List of Essential Medicines" (PDF). *World Health Organization*. October 2013. Retrieved 22 April 2014.
4. ^ "Nystatin". *International Drug Price Indicator Guide*. Retrieved 2016-01-27.
5. ^ Hamilton, Richart (2015). *Tarascon Pocket Pharmacopoeia 2015 Deluxe Lab-Coat Edition*. Jones & Bartlett Learning. p. 180. ISBN 9781284057560.
6. ^ Gøtzsche PC, Johansen HK (2014). "Nystatin prophylaxis and treatment in severely immunodepressed patients". *Cochrane Database Syst Rev*. **9**: CD002033. doi:10.1002/14651858.CD002033.pub2. PMID 25188770.
7. ^ Pappas, PG; Kauffman CA; Andes D; et al. (2009). "Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America.". *Clin Infect Dis*. **48** (5): 503–35. doi:10.1086/596757. PMID 19191635.
8. ^ *a b c* Dismukes, WE; et al. *Clinical Mycology*. Oxford University Press. pp. 50–53.
9. ^ "Micromedex Detailed Drug Information". Retrieved Apr 1, 2014.
10. ^ "FDA approved package insert" (PDF).
11. ^ Rosenberger A, Tebbe B, Treudler R, Orfanos CE (1998). "[Acute generalized exanthematous pustulosis, induced by nystatin]". *Hautarzt* (in German). **49** (6): 492–5. PMID 9675578. Retrieved 2015-01-14.
12. ^ Hammond, S.M. (1977). "Biological activity of polyene antibiotics.". *Progress in medicinal chemistry*. **14** (105-179): 105–79. PMID 345355.
13. ^ *a b c d* Fjaervik E, Zotchev SB (2005). "Biosynthesis of the polyene macrolide antibiotic nystatin in *Streptomyces noursei*". *Appl. Microbiol. Biotechnol*. **67** (4): 436–443. doi:10.1007/s00253-004-1802-4. PMID 15700127.
14. ^ Dewick, Paul M. (2009). *Medicinal Natural Products: A Biosynthetic Approach (3rd ed.)*. UK: John Wiley & Sons Ltd. ISBN 0-471-97478-1.
15. ^ Ana Espinel-Ingroff, *Medical mycology in the United States: a historical analysis (1894-1996)*, Springer, 2003, p. 62.
16. ^ Kelly, K. (2010). *Medicine Becomes a Science: 1840-1999*. p. 71. ISBN 978-1-4381-2752-1.
17. ^ Sicherman, B.; Green, C.H. (1980). *Notable American Women: The Modern Period : a Biographical Dictionary*. Belknap Press of Harvard University Press. p. 327. ISBN 978-0-674-62733-8.
18. ^ Yount, L. (2007). *A to Z of Women in Science and Math*. p. 124. ISBN 978-1-4381-0795-0.
19. ^ Akaike N, Harata N (1994). "Nystatin perforated patch recording and its applications to analyses of intracellular mechanisms". *Jpn. J. Physiol*. **44** (5): 433–73. doi:10.2170/jjphysiol.44.433. PMID 7534361.[*dead link*]


| v · t · e | **Antidiarrheals, intestinal anti-inflammatory and anti-infective agents (A07)** |
|---|---|
| **Rehydration** | Oral rehydration therapy · |
| **Intestinal anti-infectives** | *Antibiotics* (Amphotericin B · Colistin · Fidaxomicin · Kanamycin · Natamycin · Neomycin · **Nystatin** · Paromomycin · Polymyxin B · Rifaximin · Streptomycin · Vancomycin · · *Sulfonamides* (Phthalylsulfathiazole · Succinylsulfathiazole · Sulfaguanidine · · *Nitrofuran* (Nifuroxazide · Nifurzide · · |

| | |
|---|---|
| | *Imidazole* (Miconazole · ·<br>*Arsenical* (Acetarsol · ·<br>*Oxyquinoline* (Broxyquinoline · · |
| **Intestinal adsorbents** | Charcoal · Bismuth · Pectin · Kaolin · Crospovidone · Attapulgite · Diosmectite · |
| **Antipropulsives (opioids)** | Opium tincture (laudanum) · Codeine · Morphine ·<br>Camphorated opium tincture (paregoric) ·<br>*crosses BBB:* Diphenoxylate (Diphenoxylate/atropine) · Difenoxin ·<br>*does not cross BBB:* Eluxadoline · Loperamide · |
| **Intestinal anti-inflammatory agents** | *corticosteroids acting locally* (Prednisolone · Hydrocortisone · Prednisone · Betamethasone · Tixocortol · Budesonide · Beclometasone · ·<br>*antiallergic agents, excluding corticosteroids* (Cromoglicic acid · ·<br>*aminosalicylic acid and similar agents* (Sulfasalazine · Mesalazine · Olsalazine · Balsalazide · · |
| **Antidiarrheal micro-organisms** | *Saccharomyces boulardii* · |
| **Other antidiarrheals** | Albumin tannate · Ceratonia · Crofelemer · Octreotide · Racecadotril · |

| v · t · e · | **Antifungals (D01 and J02)** | | | |
|---|---|---|---|---|
| **Wall/ membrane** | **Ergosterol inhibitors** | **Azoles (lanosterol 14 alpha-demethylase inhibitors)** | **Imidazoles** | Topical: bifonazole‡ · butoconazole · chlormidazole‡ · clotrimazole# · croconazole‡ · econazole · fenticonazole‡ · flutrimazole · isoconazole‡ · ketoconazole · luliconazole · miconazole# · neticonazole‡ · omoconazole‡ · oxiconazole · sertaconazole · sulconazole · tioconazole ·<br>Systemic: ketoconazole · |
| | | | | Topical: efinaconazole · fluconazole# · fosfluconazole · terconazole ·<br>Systemic: fluconazole# · |

| | | | | |
|---|---|---|---|---|
| | | | **Triazoles** | hexaconazole‡ · isavuconazole · itraconazole · posaconazole · voriconazole · Unknown: albaconazole‡ · ravuconazole† · |
| | | | **Thiazoles** | Topical: abafungin‡ · |
| | | **Polyene antimycotics (ergosterol binding)** | | Topical: hamycin‡ · natamycin · **nystatin**# Systemic: amphotericin B#, hamycin‡ · |
| | | **Squalene monooxygenase inhibitors** | **Allylamines** | Topical: naftifine · terbinafine Systemic: terbinafine · |
| | | | **Benzylamines** | Topical: butenafine · |
| | | **Others** | | Topical: amorolfine · |
| | **β-glucan synthase inhibitors** | echinocandins (anidulafungin · biafungin · caspofungin · cilofungin · micafungin) · | | |
| **Intracellular** | **Pyrimidine analogues/ thymidylate synthase inhibitors** | flucytosine# · | | |
| | **Mitotic inhibitors** | griseofulvin# · | | |
| | **Aminoacyl tRNA synthetase inhibitors** | tavaborole · | | |
| **Others** | bromochlorosalicylanilide · chlorophetanol · chlorphenesin · ciclopirox · crystal violet · dimazole · ethylparaben · haloprogin · polynoxylin · potassium iodide# · salicylic acid · selenium disulfide# · sodium thiosulfate# · sulbentine · taurolidine · ticlatone · tolciclate · tolnaftate · tribromometacresol · undecylenic acid · Whitfield's ointment# · citronella oil · lemon grass · lemon myrtle · orange oil · patchouli · tea tree oil · PCP: atovaquone · dapsone · pentamidine · | | | |

#WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · ·

| v · t · e · | **Gynecological anti-infectives and antiseptics (G01)** |
|---|---|
| **Antibiotics** | Candicidin · Chloramphenicol · Hachimycin · Oxytetracycline · Carfecillin · Mepartricin · Clindamycin · Pentamycin · |
| **Arsenic compounds** | Acetarsol · |
| **Quinoline derivatives** | Diiodohydroxyquinoline · Clioquinol · Chlorquinaldol · Dequalinium · Broxyquinoline · Oxyquinoline · |
| **Organic acids** | Lactic acid · Acetic acid · Ascorbic acid · |
| **Sulfonamides** | Sulfatolamide · |

| | | |
|---|---|---|
| **Antifungals** | **Imidazoles** | Metronidazole · Clotrimazole · Miconazole · Econazole · Ornidazole · Isoconazole · Tioconazole · Ketoconazole · Fenticonazole · Azanidazole · Propenidazole · Butoconazole · Omoconazole · Oxiconazole · Flutrimazole · |
| | **Triazoles** | Terconazole · |
| | **Polyenes** | **Nystatin** · Natamycin · Amphotericin B · |
| | **Other** | Ciclopirox · Methylrosaniline · |
| **Other** | | Clodantoin · Inosine · Policresulen · Nifuratel · Furazolidone · Povidone-iodine · Protiofate · *Lactobacillus fermentum* · Copper usnate · |

Categories: Antifungals | World Health Organization essential medicines | Polyketides




# Paracetamol

From Wikipedia, the free encyclopedia

**Paracetamol**, also known as **acetaminophen** or **APAP**, is a medication used to treat pain and fever.[10] It is typically used for mild to moderate pain.[10] There is poor evidence for fever relief in children.[11] It is often sold in combination with other ingredients such as in many cold medications.[10] In combination with opioid pain medication, paracetamol is used for more severe pain such as cancer pain and after surgery.[12] It is typically used either by mouth or rectally but is also available intravenously.[10][13] Effects last between two and four hours.[13]

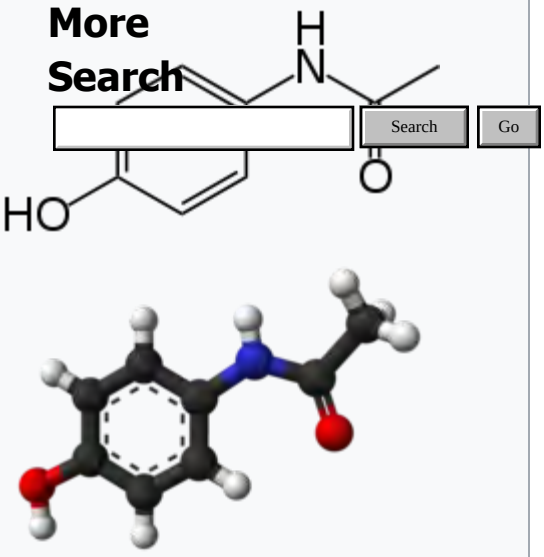
Paracetamol is generally safe at recommended doses.[14] Serious skin rashes may rarely occur, and too high a dose can result in liver failure.[10] It appears to be safe during pregnancy and when breastfeeding.[10] In those with liver disease, it may still be used, but lower doses should be taken.[15] Paracetamol is classified as a mild analgesic.[13] It does not have significant anti-inflammatory activity and how it works is not entirely clear.[16]

Paracetamol was discovered in 1877.[17] It is the most commonly used medication for pain and fever in both the United States and Europe.[18] It is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system.[19] Paracetamol is available as a generic medication with trade names including *Tylenol* and *Panadol* among others.[20] The wholesale price in the developing world is less than 0.01 USD per dose.[21] In the United States it costs about 0.04 USD per dose.[22]

Contents



**Paracetamol**




| Clinical data | |
|---|---|
| **Pronunciation** | Paracetamol: /ˌpærəˈsɛtəmɒl/<br>Acetaminophen: /əˌsiːtəˈmɪnəfɪn/ |
| **Trade names** | Tylenol, Panadol, others[1] |
| **AHFS/Drugs.com** | Monograph |
| **MedlinePlus** | a681004 |
| **License data** | US FDA: Acetaminophen |
| **Pregnancy category** | AU: A<br>US: C (Risk not ruled out)<br>Not tested but seems to be safe |
| **Routes of administration** | By mouth, through the cheek, rectal, intravenous (IV) |
| **ATC code** | N02BE01 (WHO) |
| **Legal status** | |
| **Legal status** | AU: Unscheduled |

| Pharmacokinetic data | |
|---|---|
| **Bioavailability** | 63–89%[2]:73 |
| **Protein binding** | 10–25%[3] |
| **Metabolism** | Predominantly in the liver[4] |
| **Metabolites** | APAP gluc, APAP sulfate, NAPQI, APAP-GSH, APAP-cys[5] |
| **Onset of action** | Pain relief onset by route:<br>By mouth – 37 minutes[6]<br>Buccal – 15 minutes[6]<br>Intravenous – 8 minutes[6] |
| **Biological half-life** | 1–4 hours[4] |
| **Excretion** | Urine (85–90%)[4] |

| Identifiers | |
|---|---|
| **IUPAC name** | *N*-(4-hydroxyphenyl)ethanamide<br>*N*-(4-hydroxyphenyl)acetamide |
| **CAS Number** | 103-90-2 ✓ |
| **PubChem** (CID) | 1983 |
| **IUPHAR/BPS** | 5239 |
| **DrugBank** | DB00316 ✓ |
| **ChemSpider** | 1906 ✓ |
| **UNII** | 362O9ITL9D ✓ |
| **KEGG** | D00217 ✓ |
| **ChEBI** | CHEBI:46195 ✓ |
| **ChEMBL** | CHEMBL112 ✓ |
| **PDB ligand ID** | TYL (PDBe, RCSB PDB) |
| **ECHA InfoCard** | 100.002.870 |

| Chemical and physical data | |
|---|---|
| **Formula** | $C_8H_9NO_2$ |
| **Molar mass** | 151.163 g/mol |
| **3D model (Jmol)** | Interactive image |
| **Density** | 1.263 g/cm$^3$ |
| **Melting point** | 169 °C (336 °F) [8][9] |
| **Boiling point** | 420 °C (788 °F) |
| **Solubility in** | 7.21 g/kg (0 °C)[7] |

# Medical uses [edit]

## Fever [edit]

Paracetamol is used for reducing fever in people of all ages.[23] The World Health Organization (WHO) recommends that paracetamol be used to treat fever in children only if their temperature is greater than 38.5 °C (101.3 °F).[24] The efficacy of paracetamol by itself in children with fevers has been questioned[25] and a meta-analysis showed that it is less effective than ibuprofen.[26]

## Pain [edit]

Paracetamol is used for the relief of mild to moderate pain. The use of the intravenous form for pain of sudden onset in people in the emergency department is supported by limited evidence.[27]

## Osteoarthritis [edit]

The American College of Rheumatology recommends paracetamol as one of several treatment options for people with arthritis pain of the hip, hand, or knee that does not improve with exercise and weight loss.[28] A 2015 review, however, found it provided only a small benefit in osteoarthritis.[29]

Paracetamol has relatively little anti-inflammatory activity, unlike other common analgesics such as the NSAIDs aspirin and ibuprofen, but ibuprofen and paracetamol have similar effects in the treatment of headache. Paracetamol can relieve pain in mild arthritis, but has no effect on the underlying inflammation, redness, and swelling of the joint.[30] It has analgesic properties comparable to those of aspirin, while its anti-inflammatory effects are weaker. It is better tolerated than aspirin due to concerns about bleeding with aspirin.

| | |
|---|---|
| **water** | 8.21 g/kg (5 °C)[7] |
| | 9.44 g/kg (10 °C)[7] |
| | 10.97 g/kg (15 °C)[7] |
| | 12.78 g/kg (20 °C)[7] |
| | ~14 mg/mL (20 °C) |

**SMILES**
CC(NC1=CC=C(O)C=C1)=O

**InChI**
InChI=1S/C8H9NO2/c1-6(10)9-7-2-4-8(11)5-3-7/h2-5,11H,1H3,(H,9,10) ✓
Key:RZVAJINKPMORJF-UHFFFAOYSA-N ✓
(verify)

## Low back pain [edit]

Based on a systematic review, paracetamol is recommended by the American College of Physicians and the American Pain Society as a first-line treatment for low back pain.[31][32] However, other systematic reviews concluded that evidence for its efficacy is lacking.[29][33]



## Headaches [edit]

A joint statement of the German, Austrian, and Swiss headache societies and the German Society of Neurology recommends the use of paracetamol in combination with caffeine as one of several first line therapies for treatment of tension or migraine headache.[34] In the treatment of acute migraine, it is superior to placebo, with 39% of people experiencing pain relief at 1 hour compared to 20% in the control group.[35]

## Postoperative pain [edit]

Paracetamol combined with NSAIDs may be more effective for treating postoperative pain than either paracetamol alone or NSAIDs alone.[36]

## Dental use [edit]

NSAIDs such as ibuprofen, naproxen, diclofenac are more effective than paracetamol for controlling dental pain or pain arising from dental procedures; combinations of NSAIDs and paracetamol are more effective than either alone.[37] Paracetamol is particularly useful when NSAIDs are contraindicated due to hypersensitivity or history of gastrointestinal ulceration or bleeding.[38] It can also be used in combination with NSAIDs when these are ineffective in controlling dental pain alone.[39] The Cochrane review of preoperative analgesics for additional pain relief in children and adolescents shows no evidence of benefit in taking paracetamol before dental treatment to help reduce pain after treatment for procedures under local anaesthetic, however the quality of evidence is low.[40]

## Other [edit]

The efficacy of paracetamol when used in combination with weak opioids (such as codeine) improved for approximately 50% of people but with increases in the number experiencing side effects.[41][42] Combination drugs of paracetamol and strong opioids like morphine improve analgesic effect.[43]

The combination of paracetamol with caffeine is superior to paracetamol alone for the treatment of common pain conditions including dental pain, postpartum pain, and headache.[44]

# Adverse effects [edit]

Healthy adults taking regular doses of up to 4,000 mg a day show little evidence of toxicity (although some researchers disagree). They are more likely to have abnormal liver function tests, but the significance of this is uncertain.[29]

## Liver damage [edit]

Acute overdoses of paracetamol can cause potentially fatal liver damage. In 2011 the US Food and Drug Administration launched a public education program to help consumers avoid overdose, warning: "Acetaminophen can cause serious liver damage if more than directed is used."[45][46][47] In a 2011 Safety

Warning the FDA immediately required manufacturers to update labels of all prescription combination acetaminophen products to warn of the potential risk for severe liver injury and required that such combinations contain no more than 325 mg of acetaminophen.[48][49] FDA has likewise requested prescribers to limit combination opioids to 325 mg of acetaminophen. Such overdoses are frequently related to high-dose recreational use of prescription opioids, as these opioids are most often combined with acetaminophen.[50] The overdose risk may be heightened by frequent consumption of alcohol.

Paracetamol toxicity is the foremost cause of acute liver failure in the Western world and accounts for most drug overdoses in the United States, the United Kingdom, Australia, and New Zealand.[51][52][53][54] According to the FDA, in the United States there were "56,000 emergency room visits, 26,000 hospitalizations, and 458 deaths per year related to acetaminophen-associated overdoses during the 1990s. Within these estimates, unintentional acetaminophen overdose accounted for nearly 25 percent of the emergency department visits, 10 percent of the hospitalizations, and 25 percent of the deaths."[55]

Paracetamol is metabolised by the liver and is hepatotoxic; side effects are multiplied when combined with alcoholic drinks, and are very likely in chronic alcoholics or patients with liver damage.[56][57] Some studies have suggested the possibility of a moderately increased risk of upper gastrointestinal complications such as stomach bleeding when high doses are taken chronically.[58] Kidney damage is seen in rare cases, most commonly in overdose.[59]

## Skin reactions [edit]

On August 2, 2013, the U.S. Food and Drug Administration (FDA) issued a new warning about paracetamol. It stated that the drug could cause rare and possibly fatal skin reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis. Prescription-strength products will be required to carry a warning label about skin reactions, and the FDA has urged manufacturers to do the same with over-the-counter products.[60]

## Asthma [edit]

There is an association between paracetamol use and asthma, but the evidence suggests that this likely reflects confounders[61] rather than a causal role.[62] A 2014 review found that among children the association disappeared when respiratory infections were taken into account.[63]

As of 2014, the American Academy of Pediatrics and the National Institute for Health and Care Excellence (NICE) continue to recommend paracetamol for pain and discomfort in children,[64][65][66][67][68][69] but some experts have recommended that paracetamol use by children with asthma or at risk for asthma should be avoided.[70][71]

## Other factors [edit]

In contrast to aspirin, paracetamol does not prevent blood from clotting (it is not an antiplatelet), and thus may be used in patients where failure of blood coagulation is a concern; and it does not cause gastric irritation.[72] However, paracetamol does not help reduce inflammation, while aspirin does.[73] Compared to ibuprofen—whose side effects may include diarrhea, vomiting and abdominal pain—paracetamol has fewer adverse gastrointestinal effects.[74] Unlike aspirin, paracetamol is generally considered safe for children, as it is not associated with a risk of Reye's syndrome in children with viral illnesses.[75] If taken recreationally with opioids, there is weak evidence suggesting that it may cause hearing loss.[76]

## Overdose [edit]

*Main article: Paracetamol toxicity*

Untreated paracetamol overdose results in a lengthy, painful illness. Signs and symptoms of paracetamol toxicity may initially be absent or non-specific symptoms. The first symptoms of overdose usually begin several hours after ingestion, with nausea, vomiting, sweating, and pain as acute liver failure starts.[77]

People who take overdoses of paracetamol do not fall asleep or lose consciousness, although most people who attempt suicide with paracetamol wrongly believe that they will be rendered unconscious by the drug.[78] The process of dying from an overdose takes from 3–5 days to 4–6 weeks.

Paracetamol hepatotoxicity is by far the most common cause of acute liver failure in both the United States and the United Kingdom.[54][79] Paracetamol overdose results in more calls to poison control centers in the US than overdose of any other pharmacological substance.[80] Toxicity of paracetamol is believed to be due to its quinone metabolite.[81]

Untreated overdose can lead to liver failure and death within days. Treatment is aimed at removing the paracetamol from the body and replacing glutathione.[81] Activated charcoal can be used to decrease absorption of paracetamol if the patient presents for treatment soon after the overdose. While the antidote, acetylcysteine (also called N-acetylcysteine or NAC), acts as a precursor for glutathione, helping the body regenerate enough to prevent or at least decrease the possible damage to the liver, a liver transplant is often required if damage to the liver becomes severe.[51][82] NAC was usually given following a treatment nomogram (one for patients with risk factors, and one for those without) but the use of the nomogram is no longer recommended as evidence to support the use of risk factors was poor and inconsistent, and many of the risk factors are imprecise and difficult to determine with sufficient certainty in clinical practice.[83] NAC also helps in neutralizing the imidoquinone metabolite of paracetamol.[81] Kidney failure is also a possible side effect.

Until 2004, tablets were available (brand-name in the UK Paradote) that combined paracetamol with an antidote (methionine) to protect the liver in case of an overdose. One theoretical, but rarely if ever used, option in the United States is to request a compounding pharmacy to make a similar drug mix for at-risk patients.

In June 2009, a U.S. Food and Drug Administration (FDA) advisory committee recommended that new restrictions be placed on paracetamol usage in the United States to help protect people from the potential toxic effects. The maximum dosage at any given time would be decreased from 1000 mg to 650 mg, while combinations of paracetamol and opioid analgesics would be prohibited. Committee members were particularly concerned by the fact that the present maximum dosages of paracetamol had been shown to produce alterations in hepatic function.[84]

In January 2011, the FDA asked manufacturers of prescription combination products containing paracetamol to limit the amount of paracetamol to no more than 325 mg per tablet or capsule and began requiring manufacturers to update the labels of all prescription combination paracetamol products to warn of the potential risk of severe liver damage.[85][86][87][88] Manufacturers had three years to limit the amount of paracetamol in their prescription drug products to 325 mg per dosage unit.[86][88] In November 2011, the Medicines and Healthcare products Regulatory Agency revised UK dosing of liquid paracetamol for children.[89]

## Pregnancy [edit]

Experimental studies in animals and cohort studies in humans indicate no detectable increase in congenital malformations associated with paracetamol use during pregnancy.[90] Additionally, paracetamol does not affect the closure of the fetal ductus arteriosus as NSAIDs can.[91]

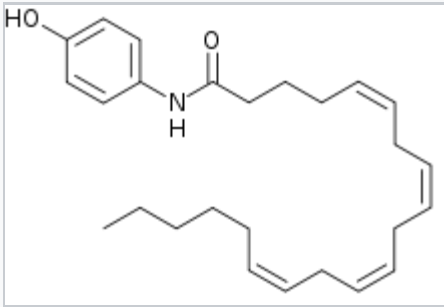
Paracetamol use by the mother during pregnancy is associated with an increased risk of childhood asthma.[92] It is also associated with an increase in ADHD but it is unclear whether the relationship is causal.[93] A 2015 review states that paracetamol remains a first-line recommended medication for pain and fever during pregnancy, despite these concerns.[94]

## Cancer [edit]

Some studies have found an association between paracetamol and a slight increase in kidney cancer,[95] but no effect on bladder cancer risk.[96]

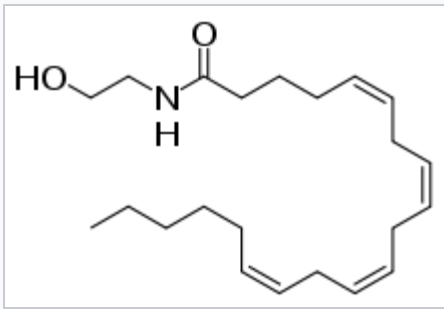
## Mechanism of action [edit]

To date, the mechanism of action of paracetamol is not completely understood. The main mechanism proposed is the inhibition of cyclooxygenase (COX), and recent findings suggest that it is highly selective for COX-2.[97] Because of its selectivity for COX-2, it does not significantly inhibit the production of the pro-clotting thromboxanes.[97] While it has analgesic and antipyretic properties comparable to those of aspirin or other NSAIDs, its peripheral anti-inflammatory activity is usually limited by several factors, one of which is the high level of peroxides present in inflammatory lesions.



AM404 – Metabolite of paracetamol

An article[98] in Nature Communications from researchers in London, UK and Lund, Sweden in November 2011 has found a hint to the analgesic mechanism of paracetamol, being that the metabolites of paracetamol (e.g., NAPQI), act on TRPA1-receptors in the spinal cord to suppress the signal transduction from the superficial layers of the dorsal horn, to alleviate pain.



Anandamide – Endogenous cannabinoid

This conclusion has been contested in a new hypothesis paper[99] on how paracetamol might act. The author concedes that NAPQI is the active metabolite but that this reactive compound should react not only with the thiol in TRPA1 but also with any other suitably available nucleophile that it happens to encounter. It is suggested that thiol groups in cysteine proteases, e.g. the proteases that take part in the processing of procytokines, such as those generating IL-1β and IL-6, might be the targets giving rise to overall analgesic effects.

The COX family of enzymes are responsible for the metabolism of arachidonic acid to prostaglandin $H_2$, an unstable molecule that is, in turn, converted to numerous other pro-inflammatory compounds. Classical anti-inflammatories such as the NSAIDs block this step. Only when appropriately oxidised is the COX enzyme highly active.[100][101] Paracetamol reduces the oxidised form of the COX enzyme, preventing it from forming pro-inflammatory chemicals.[102][103] This leads to a reduced amount of *prostaglandin E2* in the CNS, thus lowering the hypothalamic set-point in the thermoregulatory centre.

Aspirin is known to inhibit the cyclooxygenase (COX) family of enzymes and, because paracetamol's action is partially similar to aspirin's,[*clarification needed*] much research has focused on whether paracetamol also inhibits COX. It is now clear that paracetamol acts via at least two pathways.[102][104][105][106]

The exact mechanisms by which COX is inhibited in various circumstances are still a subject of discussion. Because of differences in the activity of paracetamol, aspirin, and other NSAIDs, it has been postulated that further COX variants may exist. One theory holds that paracetamol works by inhibiting the COX-3 isoform—a COX-1 splice variant—of the COX family of enzymes.[97] When expressed in dogs, this enzyme shares a strong similarity to the other COX enzymes, produces pro-inflammatory chemicals, and is selectively inhibited by paracetamol.[107] However, some research has suggested that, in humans and mice, the COX-3 enzyme is without inflammatory action and paracetamol's blockage of it is not significant in its functioning in humans.[97][105]

Another possibility is that paracetamol blocks cyclooxygenase (as in aspirin), but that, in an inflammatory environment where the concentration of peroxides is high, the high oxidation state of paracetamol prevents its actions. This idea would mean that paracetamol has no direct effect at the site of inflammation, but instead acts in the CNS where the environment is not oxidative, to reduce temperature, etc.[107]

Paracetamol also modulates the endogenous cannabinoid system.[108] Paracetamol is metabolised to AM404, a compound with several actions; what is most important is that it inhibits the reuptake of the endogenous cannabinoid/vanilloid anandamide by neurons. Anandamide reuptake lowers synaptic levels of

anandamide and results in more activation of the main pain receptor (nociceptor) of the body, the TRPV1 (older name: vanilloid receptor). By inhibiting anandamide reuptake, levels in the synapse remain high and are able to desensitise the TRPV1 receptor much like capsaicin. Furthermore, AM404 inhibits sodium channels, as do the anesthetics lidocaine and procaine.[109] Both of these actions by themselves have been shown to reduce pain, and are a possible mechanism for paracetamol. It has been demonstrated that when cannabinoid receptors are blocked with synthetic antagonists, paracetamol's analgesic effects are prevented, suggesting its pain-relieving action involves the endogenous cannabinoid system.[110] Spinal TRPA1 receptors have also been demonstrated to mediate antinociceptive effects of paracetamol and Δ9-tetrahydrocannabinol in mice.[111]

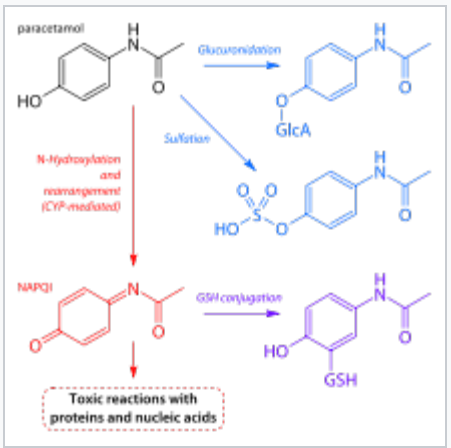
Increase of social behavior in mice dosed with paracetamol (which corresponds to a reduction of social rejection response in humans) does not appear to be due to cannabinoid receptor type 1 activity. It may result from serotonin receptor agonism.[112]

## Pharmacokinetics [edit]

After being taken by mouth it is rapidly absorbed by the GI tract (although absorption through the stomach is negligible);[113] its volume of distribution is roughly 50 L.[114] The concentration in serum after a typical dose of paracetamol usually peaks below 30 µg/ml, which equals 200 µmol/L.[115] After 4 hours the concentration is usually less than 10 µg/mL, which equals 66 µmol/L.[115]

Paracetamol is metabolised primarily in the liver, into toxic and non-toxic products. Three metabolic pathways are notable:[81]

- Glucuronidation (45-55%),[4] by UGT1A1 and UGT1A6;[96]
- Sulfation (sulfate conjugation) (20–30%)[4] by SULT1A1;[96]
- *N*-hydroxylation and dehydration, then glutathione conjugation, (less than 15%). The hepatic cytochrome P450 enzyme system metabolises paracetamol, forming a minor yet significant alkylating metabolite known as NAPQI (*N*-acetyl-*p*-benzoquinone imine) (also known as *N*-acetylimidoquinone).[81][116] NAPQI is then irreversibly conjugated with the sulfhydryl groups of glutathione.[116]



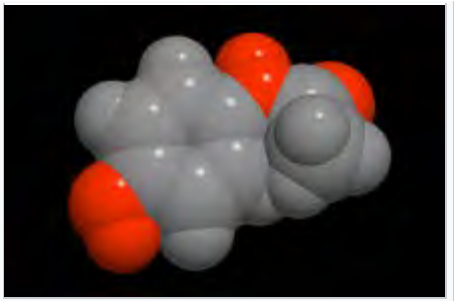

Main pathways of paracetamol metabolism *(click to enlarge)*. Pathways shown in blue and purple lead to non-toxic metabolites; the pathway in red leads to toxic NAPQI.

All three pathways yield final products that are inactive, non-toxic, and eventually excreted by the kidneys. In the third pathway, however, the intermediate product NAPQI is toxic. NAPQI is primarily responsible for the toxic effects of paracetamol; this constitutes an example of toxication.[117] Production of NAPQI is due primarily to two isoenzymes of cytochrome P450: CYP2E1[96] and CYP3A4.[117] At usual doses, NAPQI is quickly detoxified by conjugation with glutathione.[81][116]

## Chemistry [edit]

### Chemical properties [edit]

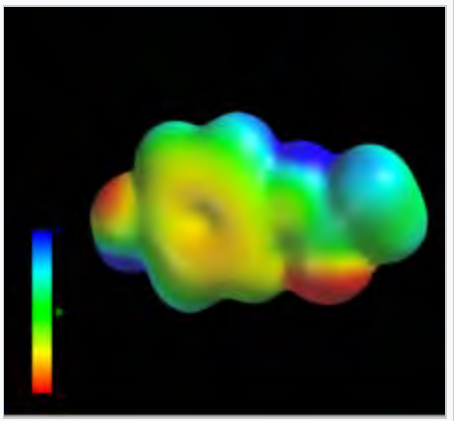
Paracetamol consists of a benzene ring core, substituted by one hydroxyl group and the nitrogen atom of an amide group in the *para* (1,4) pattern.[118] The amide group is acetamide (ethanamide). It is an extensively conjugated system, as the lone pair on the hydroxyl oxygen, the benzene pi cloud, the nitrogen lone pair, the p orbital on the carbonyl carbon, and the lone pair on the carbonyl oxygen are all conjugated. The presence of two activating groups also make the benzene ring highly reactive toward electrophilic aromatic substitution.



Paracetamol molecule polar surface area

As the substituents are *ortho, para*-directing and *para* with respect to each other, all positions on the ring are more or less equally activated. The conjugation also greatly reduces the basicity of the oxygens and the nitrogen, while making the hydroxyl acidic through delocalisation of charge developed on the phenoxide anion.

Paracetamol is part of the class of drugs known as "aniline analgesics"; it is the only such drug still in use today.[104] It is not considered an NSAID because it does not exhibit significant anti-inflammatory activity (it is a weak COX inhibitor).[119][120] This is despite the evidence that paracetamol and NSAIDs have some similar pharmacological activity.[121]

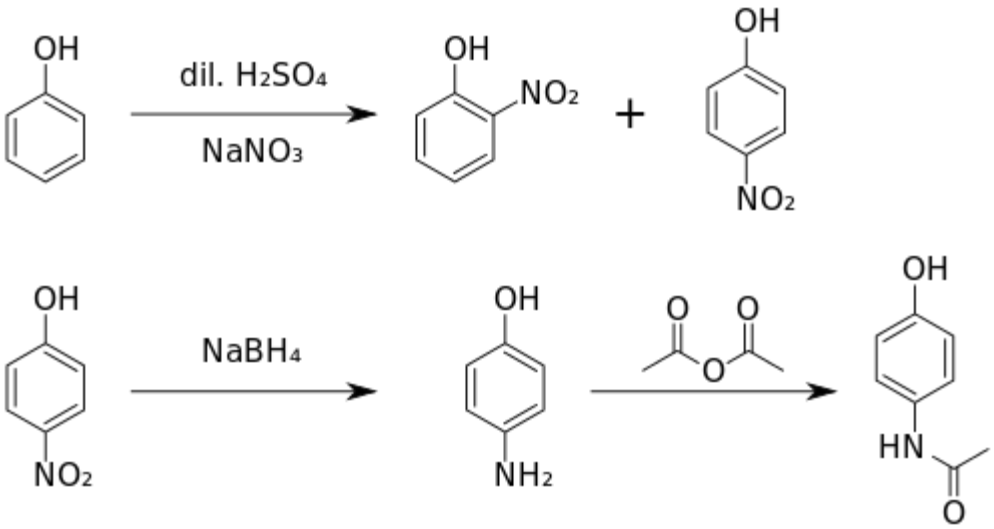


Paracetamol electron map electrostatic surface area[*citation needed*]

## Synthesis [edit]

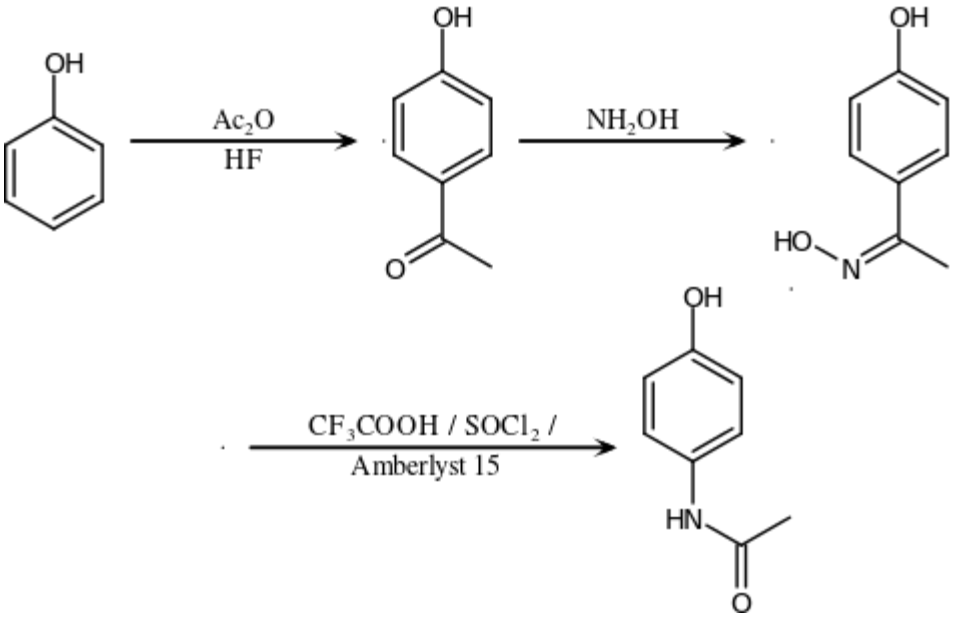
### Original (Boots) method [edit]

The original method for production involves the nitration of phenol with sodium nitrate gives a mixture of two isomers, from which the wanted 4-nitrophenol (bp 279 °C) can easily be separated by steam distillation. In this electrophilic aromatic substitution reaction, phenol's oxygen is strongly activating, thus the reaction requires only mild conditions as compared to nitration of benzene itself. The nitro group is then reduced to an amine, giving 4-aminophenol. Finally, the amine is acetylated with acetic anhydride.[122] Industrially direct hydrogenation is used, but in the laboratory scale sodium borohydride serves.[123][124]




### Green(er) synthesis [edit]

An alternative industrial synthesis developed by Hoechst–Celanese involves direct acylation of phenol with acetic anhydride catalyzed by HF, conversion of the ketone to a ketoxime with hydroxylamine, followed by the acid-catalyzed Beckmann rearrangement to give the amide.[124][125]




## Direct synthesis [edit]

More recently (2014) a "one-pot" synthesis from hydroquinone has been described before the Royal Society of Chemistry.[126][127] The process may be summarized as follows:

> Hydroquinone, ammonium acetate, and acetic acid were mixed in an argon atmosphere and heated slowly to 230 °C. The mixture was stirred at this temperature for 15 hours. After cooling the acetic acid was evaporated and the precipitate was filtered, washed with water and dried to give paracetamol as a white solid.

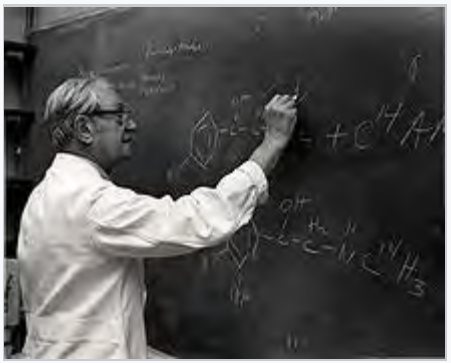
The authors go on to claim an 88% yield and 99% purity.

## Reactions [edit]

*4*-Aminophenol may be obtained by the amide hydrolysis of paracetamol. *4*-Aminophenol prepared this way, and related to the commercially available Metol, has been used as a developer in photography by hobbyists.[128] This reaction is also used to determine paracetamol in urine samples: After hydrolysis with hydrochloric acid, *4*-aminophenol reacts in ammonia solution with a phenol derivate, e.g. salicylic acid, to form an indophenol dye under oxidization by air.[129]

# History [edit]

Acetanilide was the first aniline derivative serendipitously found to possess analgesic as well as antipyretic properties, and was quickly introduced into medical practice under the name of Antifebrin by A. Cahn and P. Hepp in 1886.[130] But its unacceptable toxic effects, the most alarming being cyanosis due to methemoglobinemia, prompted the search for less toxic aniline derivatives.[104] Harmon Northrop Morse had already synthesised paracetamol at Johns Hopkins University via the reduction of *p*-nitrophenol with tin in glacial acetic acid in 1877,[131][132] but it was not until 1887 that clinical pharmacologist Joseph von Mering tried paracetamol on patients.[104] In 1893, von Mering published a paper reporting on the clinical results of paracetamol with phenacetin, another aniline derivative.[133] Von Mering claimed that, unlike phenacetin, paracetamol had a slight tendency to produce methemoglobinemia. Paracetamol was then quickly discarded in favor of phenacetin. The sales of phenacetin established Bayer as a leading



Julius Axelrod *(pictured)* and Bernard Brodie demonstrated that acetanilide and phenacetin are both metabolised to paracetamol,

which is a better tolerated analgesic.

pharmaceutical company.[134] Overshadowed in part by aspirin, introduced into medicine by Heinrich Dreser in 1899, phenacetin was popular for many decades, particularly in widely advertised over-the-counter "headache mixtures", usually containing phenacetin, an aminopyrine derivative of aspirin, caffeine, and sometimes a barbiturate.[104]

Paracetamol is the active metabolite of phenacetin and acetanilide, both once popular as analgesics and antipyretics in their own right.[114][135] However, unlike phenacetin, acetanilide and their combinations, paracetamol is not considered carcinogenic at therapeutic doses.[136]

Von Mering's claims remained essentially unchallenged for half a century, until two teams of researchers from the United States analyzed the metabolism of acetanilide and paracetamol.[134] In 1947 David Lester and Leon Greenberg found strong evidence that paracetamol was a major metabolite of acetanilide in human blood, and in a subsequent study they reported that large doses of paracetamol given to albino rats did not cause methemoglobinemia.[137] In three papers published in the September 1948 issue of the *Journal of Pharmacology and Experimental Therapeutics*, Bernard Brodie, Julius Axelrod and Frederick Flinn confirmed using more specific methods that paracetamol was the major metabolite of acetanilide in human blood, and established that it was just as efficacious an analgesic as its precursor.[138][139][140] They also suggested that methemoglobinemia is produced in humans mainly by another metabolite, phenylhydroxylamine. A follow-up paper by Brodie and Axelrod in 1949 established that phenacetin was also metabolised to paracetamol.[141] This led to a "rediscovery" of paracetamol.[104] It has been suggested that contamination of paracetamol with 4-aminophenol, the substance von Mering synthesised it from, may be the cause for his spurious findings.[134]

Paracetamol was first marketed in the United States in 1950 under the name Triagesic, a combination of paracetamol, aspirin, and caffeine.[132] Reports in 1951 of three users stricken with the blood disease agranulocytosis led to its removal from the marketplace, and it took several years until it became clear that the disease was unconnected.[132] Paracetamol was marketed in 1953 by Sterling-Winthrop Co. as Panadol, available only by prescription, and promoted as preferable to aspirin since it was safe for children and people with ulcers.[132][134][142] In 1955, paracetamol was marketed as Children's Tylenol Elixir by McNeil Laboratories.[143] In 1956, 500 mg tablets of paracetamol went on sale in the United Kingdom under the trade name Panadol, produced by Frederick Stearns & Co, a subsidiary of Sterling Drug Inc. In 1963, paracetamol was added to the *British Pharmacopoeia*, and has gained popularity since then as an analgesic agent with few side-effects and little interaction with other pharmaceutical agents.[132] Concerns about paracetamol's safety delayed its widespread acceptance until the 1970s, but in the 1980s paracetamol sales exceeded those of aspirin in many countries, including the United Kingdom. This was accompanied by the commercial demise of phenacetin, blamed as the cause of analgesic nephropathy and hematological toxicity.[104] In 1988 Sterling Winthrop was acquired by Eastman Kodak which sold the over the counter drug rights to SmithKline Beecham in 1994.[144]

Available without a prescription since 1959,[145] it has since become a common household drug.[146] Patents on paracetamol have long expired, and generic versions of the drug are widely available.[1][147]

## Society and culture [edit]

### Naming [edit]

Acetaminophen is the name generally used in the United States (USAN), Japan (JAN), Canada[148] Venezuela, Colombia.,[149] and Iran; paracetamol is used in international venues (INN, AAN, BAN).[148][149][150] In some contexts, such as on prescription bottles of painkillers that incorporate this medicine, it is simply abbreviated as APAP, for **a**cetyl-**p**ara-**a**mino**p**henol.

Both acetaminophen and paracetamol come from a chemical name for the compound: *para*-**acet**yl**aminophen**ol and *para*-**acet**yl**am**inophen**ol**.

## Available forms [edit]

*See also: Paracetamol brand names*

Paracetamol is available in a tablet, capsule, liquid suspension, suppository, intravenous, intramuscular and effervescent form. The common adult dose is 500 mg to 1000 mg. The recommended maximum daily dose for adults is 4000 mg. In recommended doses, paracetamol is generally safe for children and infants as well as for adults,[151] although rare cases of acute liver injury have been linked to amounts lower than 2500 mg per day.[152]

In some formulations, paracetamol is combined with the opioid codeine, sometimes referred to as co-codamol (BAN) and Panadeine in Australia. In the U.S., this combination is available only by prescription, while the lowest-strength preparation is over the counter in Canada, and in other countries other strengths may be available over the counter.[*citation needed*] Paracetamol is also combined with other opioids such as dihydrocodeine, referred to as co-dydramol (BAN), oxycodone or hydrocodone. Another very commonly used analgesic combination includes paracetamol in combination with propoxyphene napsylate. A combination of paracetamol, codeine, and the calmative doxylamine succinate is also available. The efficacy of paracetamol/codeine combinations has been questioned by recent research.[43]

Paracetamol is commonly used in multi-ingredient preparations for migraine headache, typically including butalbital and paracetamol with or without caffeine, and sometimes containing codeine.

Paracetamol is sometimes combined with phenylephrine hydrochloride.[153] Sometimes a third active ingredient, such as ascorbic acid,[153][154] caffeine,[155][156] chlorpheniramine maleate,[157] or guaifenesin[158][159][160] is added to this combination.

When marketed in combination with diphenhydramine hydrochloride, it is frequently given the label "PM" and is meant as a sleep aid. Diphenhydramine hydrochloride is known to have hypnotic effects and is non-habit forming. Unfortunately it has been implicated in the occasional development of restless leg syndrome.[161]

Tylenol 500 mg capsules


Panadol 500 mg tablets

For comparison: The pure drug is a white crystalline powder.

## Controversy [edit]

In September 2013, an episode of *This American Life* entitled "Use Only as Directed"[162] highlighted deaths from paracetamol overdose. This report was followed by two reports by ProPublica[163][164] alleging that the "FDA has long been aware of studies showing the risks of acetaminophen. So has the maker of Tylenol, McNeil Consumer Healthcare, a division of Johnson & Johnson" and "McNeil, the maker of Tylenol, ... has repeatedly opposed safety warnings, dosage restrictions and other measures meant to safeguard users of the drug."

A report prepared by an internal FDA working group describes a history of FDA initiatives designed to educate consumers about the risk of paracetamol overdose and notes that one challenge to the Agency has been "identifying the appropriate message about the relative safety of acetaminophen, especially compared to other OTC pain relievers (e.g., aspirin and other NSAIDs)". The report notes that "Chronic use of NSAIDs is also associated with significant morbidity and mortality. NSAID gastrointestinal risk is substantial, with deaths and hospitalization estimated in one publication as 3200 and 32,000 per year respectively. Possible cardiovascular toxicity with chronic NSAID use has been a major discussion recently", finally noting that "The goal of the educational efforts is not to decrease appropriate acetaminophen use or encourage substitution of NSAID use, but rather to educate consumers so that they can avoid unnecessary health risks."[165]

# Veterinary use [edit]

## Cats [edit]

Paracetamol is extremely toxic to cats, which lack the necessary glucuronyl transferase enzymes to break it down safely. Initial symptoms include vomiting, salivation, and discoloration of the tongue and gums.

Unlike an overdose in humans, liver damage is rarely the cause of death; instead, methemoglobin formation and the production of Heinz bodies in red blood cells inhibit oxygen transport by the blood, causing asphyxiation (methemoglobemia and hemolytic anemia).[166]

Treatment with N-acetylcysteine,[167] methylene blue or both is sometimes effective after the ingestion of small doses of paracetamol.

## Dogs [edit]

Although paracetamol is believed to have no significant anti-inflammatory activity, it has been reported as effective as aspirin in the treatment of musculoskeletal pain in dogs.[168]

A paracetamol-codeine product (trade name Pardale-V)[169] licensed for use in dogs is available on veterinary prescription in the UK.[169] It should be administered to dogs only on veterinary advice and with extreme caution.[169]

The main effect of toxicity in dogs is liver damage, and GI ulceration has been reported.[167][170][171][172] N-acetylcysteine treatment is efficacious in dogs when administered within 2 hours of paracetamol ingestion.[167][168]

## Snakes [edit]

Paracetamol is also lethal to snakes, and has been suggested as a chemical control program for the invasive brown tree snake (*Boiga irregularis*) in Guam.[173][174] Doses of 80 mg are inserted into dead mice scattered by helicopter.[175]

# References [edit]


1. ^ *a b* "International Listings for Paracetamol". Retrieved 11 January 2016.
2. ^ Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2010). Macintyre, PE; Schug, SA; Scott, DA; Visser, EJ; Walker, SM, eds. *Acute Pain Management: Scientific Evidence* (PDF) (3rd ed.). Melbourne, Australia: National Health and Medical Research Council. ISBN 9780977517459.[*dead link*]
3. ^ "Tylenol, Tylenol Infants' Drops (acetaminophen) dosing, indications, interactions, adverse effects, and more". *Medscape Reference*. WebMD. Retrieved 10 May 2014.
4. ^ *a b c d e* "Codapane Forte Paracetamol and codeine phosphate PRODUCT INFORMATION" (PDF). *TGA eBusiness Services*. Alphapharm Pty Limited. 29 April 2013. Retrieved 10 May 2014.
5. ^ "Acetaminophen Pathway (therapeutic doses), Pharmacokinetics". Retrieved 13 January 2016.
6. ^ *a b c* Pickering G, Macian N, Libert F, Cardot JM, Coissard S, Perovitch P, Maury M, Dubray C (September 2014). "Buccal acetaminophen provides fast analgesia: two randomized clinical trials in healthy volunteers". *Drug Des. Devel. Ther.* **8**: 1621–1627. doi:10.2147/DDDT.S63476. PMC 4189711. PMID 25302017. "bAPAP has a faster time of antinociception onset (15 minutes, P<0.01) and greater antinociception at 50 minutes (P<0.01, CT1) and 30 minutes (P<0.01, CT2) than ivAPAP and sAPAP. All routes are similar after 50 minutes. ... In postoperative conditions for acute pain of mild to moderate intensity, the quickest reported time to onset of analgesia with APAP is 8 minutes9 for the iv route and 37 minutes6 for the oral route."
7. ^ *a b c d e* Granberg RA, Rasmuson AC (1999). "Solubility of paracetamol in pure solvents". *Journal of Chemical & Engineering Data*. **44** (6): 1391–95. doi:10.1021/je990124v.
8. ^ Karthikeyan, M.; Glen, R. C.; Bender, A. (2005). "General Melting Point Prediction Based on a Diverse Compound

Data Set and Artificial Neural Networks". *Journal of Chemical Information and Modeling*. **45** (3): 581–590. doi:10.1021/ci0500132. PMID 15921448.
9. ^ "melting point data for paracetamol". Lxsrv7.oru.edu. Retrieved 19 March 2011.
10. ^ *a b c d e f* "Acetaminophen". The American Society of Health-System Pharmacists. Retrieved 16 September 2016.
11. ^ Meremikwu, M; Oyo-Ita, A (2002). "Paracetamol for treating fever in children". *The Cochrane database of systematic reviews* (2): CD003676. doi:10.1002/14651858.CD003676. PMID 12076499.
12. ^ Scottish Intercollegiate Guidelines Network (SIGN) (2008). "6.1 and 7.1.1". *Guideline 106: Control of pain in adults with cancer* (PDF). Scotland: National Health Service (NHS). ISBN 9781905813384.
13. ^ *a b c* Hochhauser, Daniel (2014). *Cancer and its Management*. John Wiley & Sons. p. 119. ISBN 9781118468715.
14. ^ Russell, FM; Shann, F; Curtis, N; Mulholland, K (2003). "Evidence on the use of paracetamol in febrile children". *Bulletin of the World Health Organization*. **81** (5): 367–72. PMC 2572451. PMID 12856055.
15. ^ Lewis, JH; Stine, JG (June 2013). "Review article: prescribing medications in patients with cirrhosis - a practical guide". *Alimentary pharmacology & therapeutics*. **37** (12): 1132–56. doi:10.1111/apt.12324. PMID 23638982.
16. ^ McKay, Gerard A.; Walters, Matthew R. (2013). "Non-Opioid Analgesics". *Lecture Notes Clinical Pharmacology and Therapeutics* (9th ed.). Hoboken: Wiley. ISBN 9781118344897.
17. ^ Mangus, Brent C.; Miller, Michael G. (2005). *Pharmacology application in athletic training*. Philadelphia, Pennsylvania: F.A. Davis. p. 39. ISBN 9780803620278.
18. ^ Aghababian, Richard V. (22 October 2010). *Essentials of emergency medicine*. Jones & Bartlett Publishers. p. 814. ISBN 978-1-4496-1846-9.
19. ^ "WHO Model list of essential medicines" (PDF). *World Health Organization*. October 2013. Retrieved 22 April 2014.
20. ^ Hamilton, Richard J. (2013). *Tarascon pocket pharmacopoeia : 2013 classic shirt-pocket edition* (27th ed.). Burlington, Massachusetts: Jones & Bartlett Learning. p. 12. ISBN 9781449665869.
21. ^ "Paracetamol". Retrieved 11 January 2016.
22. ^ "Acetaminophen prices, coupons and patient assistance programs". Retrieved 19 February 2016.
23. ^ "Acetaminophen". *The American Society of Health-System Pharmacists*. Retrieved 3 April 2011.
24. ^ "Baby paracetamol asthma concern". *BBC News*. September 19, 2008. Retrieved September 19, 2008.
25. ^ Meremikwu M, Oyo-Ita A (2002). "Paracetamol for treating fever in children". *Cochrane Database Syst Rev* (2): CD003676. doi:10.1002/14651858.CD003676. PMID 12076499.
26. ^ Perrott DA, Piira T, Goodenough B, Champion GD (2004). "Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever: a meta-analysis". *Arch Pediatr Adolesc Med*. **158** (6): 521–6. doi:10.1001/archpedi.158.6.521. PMID 15184213.
27. ^ Sin, B; Wai, M; Tatunchak, T; Motov, SM (29 January 2016). "The use of intravenous acetaminophen for acute pain in the emergency department.". *Academic Emergency Medicine*. **23**: 543–53. doi:10.1111/acem.12921. PMID 26824905.
28. ^ Hochberg MC, Altman RD, April KT, et al. (April 2012). "American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee". *Arthritis Care Res (Hoboken)*. **64** (4): 465–74. doi:10.1002/acr.21596. PMID 22563589.
29. ^ *a b c* Machado, GC; Maher, CG; Ferreira, PH; Pinheiro, MB; Lin, CW; Day, RO; McLachlan, AJ; Ferreira, ML (31 March 2015). "Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials.". *BMJ (Clinical research ed.)*. **350**: h1225. doi:10.1136/bmj.h1225. PMID 25828856.
30. ^ "Paracetamol". Arthritis Research UK. Retrieved October 16, 2013.
31. ^ "National Guideline Clearinghouse | Expert Commentaries: Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. *What's New? What's Different?"*.
32. ^ Chou R, Huffman LH (October 2007). "Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline". *Ann. Intern. Med*. **147** (7): 505–14. doi:10.7326/0003-4819-147-7-200710020-00008. PMID 17909211.
33. ^ Davies RA, Maher CG, Hancock MJ (November 2008). "A systematic review of paracetamol for non-specific low back pain". *Eur Spine J*. **17** (11): 1423–30. doi:10.1007/s00586-008-0783-x. PMC 2583194. PMID 18797937.
34. ^ Haag G, Diener HC, May A, et al. (April 2011). "Self-medication of migraine and tension-type headache: summary of the evidence-based recommendations of the Deutsche Migräne und Kopfschmerzgesellschaft (DMKG), the Deutsche Gesellschaft für Neurologie (DGN), the Österreichische Kopfschmerzgesellschaft (ÖKSG) and the Schweizerische Kopfwehgesellschaft (SKG)". *J Headache Pain*. **12** (2): 201–17. doi:10.1007/s10194-010-0266-

4. PMC 3075399. PMID 21181425.
35. ^ Derry S, Moore RA (2013). "Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults". *Cochrane Database Syst Rev*. **4**: CD008040. doi:10.1002/14651858.CD008040.pub3. PMID 23633349.
36. ^ Ong, CK; Seymour, RA; Lirk, P; Merry, AF (1 April 2010). "Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain.". *Anesthesia and Analgesia*. **110** (4): 1170–9. doi:10.1213/ANE.0b013e3181cf9281. PMID 20142348.
37. ^ Moore, RA; Derry, C (January 2013). "Efficacy of OTC analgesics.". *International journal of clinical practice. Supplement*. **67** (178): 21–5. doi:10.1111/ijcp.12054. PMID 23163544.
38. ^ "Relieving dental pain". American Dental Association. December 2016.
39. ^ Bailey, E; Worthington, H; Coulthard, P (April 2014). "Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth, a Cochrane systematic review.". *British dental journal*. **216** (8): 451–5. doi:10.1038/sj.bdj.2014.330. PMID 24762895.
40. ^ Ashley, PF; Parekh, S; Moles, DR; Anand, P; MacDonald, LC (8 August 2016). "Preoperative analgesics for additional pain relief in children and adolescents having dental treatment.". *The Cochrane database of systematic reviews* (8): CD008392. doi:10.1002/14651858.CD008392.pub3. PMID 27501304.
41. ^ Anton J M de Craen, Giuseppe Di Giulio, Angela J E M Lampe-Schoenmaeckers, Alphons G H Kessels, Jos Kleijnen (1996). "Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review". *BMJ*. **313** (7053): 321–324. doi:10.1136/bmj.313.7053.321.
42. ^ Laurence Toms; Sheena Derry; R Andrew Moore; Henry J McQuay (2009). "Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults". *Cochrane Database of Systematic Reviews* (1). doi:10.1002/14651858.CD001547.pub2.
43. ^ *a b* Murnion B (2010). "Combination analgesics in adults". *Australian Prescriber* (33): 113–5.
44. ^ Derry CJ, Derry S, Moore RA (2012). "Caffeine as an analgesic adjuvant for acute pain in adults". *Cochrane Database Syst Rev*. **3**: CD009281. doi:10.1002/14651858.CD009281.pub2. PMID 22419343.
45. ^ US FDA. Page Last Updated: January 16, 2014. Acetaminophen Information Page accessed February 23, 2014
46. ^ US FDA. Page updated August 6, 2013 Acetaminophen Toxicity[*dead link*] Page accessed February 23, 2014
47. ^ US FDA Page updated November 19, 2013 Using Acetaminophen and Nonsteroidal Anti-inflammatory Drugs Safely Page accessed February 23, 2014
48. ^ US FDA. January 13, 2011 FDA limits acetaminophen in prescription combination products; requires liver toxicity warnings Page accessed February 23, 2014
49. ^ Research, Center for Drug Evaluation and. "Drug Safety and Availability - FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure". *www.fda.gov*. Retrieved February 27, 2016.
50. ^ "FDA: Acetaminophen doses over 325 mg may lead to liver damage". Cnn.com. January 16, 2014. Retrieved 2014-02-18.
51. ^ *a b* Daly FF, Fountain JS, Murray L, Graudins A, Buckley NA (2008). "Guidelines for the management of paracetamol poisoning in Australia and New Zealand—explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres". *Med J Aust*. **188** (5): 296–301. PMID 18312195.
52. ^ Khashab M, Tector AJ, Kwo PY (2007). "Epidemiology of acute liver failure". *Curr Gastroenterol Rep*. **9** (1): 66–73. doi:10.1007/s11894-008-0023-x. PMID 17335680.
53. ^ Hawkins LC, Edwards JN, Dargan PI (2007). "Impact of restricting paracetamol pack sizes on paracetamol poisoning in the United Kingdom: a review of the literature". *Drug Saf*. **30** (6): 465–79. doi:10.2165/00002018-200730060-00002. PMID 17536874.
54. ^ *a b* Larson AM; Polson J; Fontana RJ; *et al.* (2005). "Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study". *Hepatology*. **42** (6): 1364–72. doi:10.1002/hep.20948. PMID 16317692.
55. ^ US FDA Date Posted Jan 14, 2011. Prescription Drug Products Containing Acetaminophen: Actions to Reduce Liver Injury from Unintentional Overdose Page accessed February 23, 2014
56. ^ Hughes, John (2008). *Pain Management: From Basics to Clinical Practice*. Elsevier Health Sciences. ISBN 9780443103360.
57. ^ Dukes, MNG; Jeffrey K Aronson (2000). *Meyler's Side Effects of Drugs, Vol XIV*. Elsevier. ISBN 9780444500939.
58. ^ García Rodríguez LA, Hernández-Díaz S (December 15, 2000). "The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents". *Arthritis Research & Therapy*. **3** (2): 98–101. doi:10.1186/ar146. PMC 128885. PMID 11178116.
59. ^ "Painkillers 'cause kidney damage'". *BBC News*. November 23, 2003. Retrieved March 27, 2010.
60. ^ "FDA Warns of Rare Acetaminophen Risk". August 1, 2013. Retrieved 12 April 2016.
61. ^ Henderson, AJ; Shaheen, SO (Mar 2013). "Acetaminophen and asthma.". *Paediatric Respiratory Reviews*. **14** (1):

9–15; quiz 16. doi:10.1016/j.prrv.2012.04.004. PMID 23347656.
62. ^ Heintze, K; Petersen, KU (Jun 2013). "The case of drug causation of childhood asthma: antibiotics and paracetamol.". *European journal of clinical pharmacology*. **69** (6): 1197–209. doi:10.1007/s00228-012-1463-7. PMC 3651816. PMID 23292157.
63. ^ Cheelo, M; Lodge, CJ; Dharmage, SC; Simpson, JA; Matheson, M; Heinrich, J; Lowe, AJ (26 November 2014). "Paracetamol exposure in pregnancy and early childhood and development of childhood asthma: a systematic review and meta-analysis.". *Archives of Disease in Childhood*. **100**: 81–9. doi:10.1136/archdischild-2012-303043. PMID 25429049.
64. ^ "Feverish illness in children: Assessment and initial management in children younger than 5 years". *NICE clinical guidelines*. UK National Institute for Health and Care Excellence. May 2013. Retrieved 25 February 2014.
65. ^ "Common over-the-counter medications". *Healthychildren.org*. American Academy of Pediatrics. July 10, 2013. Retrieved February 23, 2014.
66. ^ Heintze, K; Petersen, KU (Jun 2013). "The case of drug causation of childhood asthma: antibiotics and paracetamol". *European Journal of Clinical Pharmacology*. **69** (6): 1197–209. doi:10.1007/s00228-012-1463-7. PMC 3651816. PMID 23292157.
67. ^ "Link between Calpol and asthma 'not proven'". *NHS Choices*. UK National Health Service. September 16, 2013. Retrieved February 23, 2014.
68. ^ Section on Clinical Pharmacology and Therapeutics; Committee on Drugs; Sullivan, JE; Farrar, HC (Mar 2011). "Fever and antipyretic use in children". *Pediatrics*. American Academy of Pediatrics. **127** (3): 580–7. doi:10.1542/peds.2010-3852. PMID 21357332.
69. ^ CHMP Pharmacovigilance Working Party (February 24, 2011). Pharmacovigilance Working Party (PhVWP) February 2011 plenary meeting (PDF) (Report). European Medicines Agency & Heads of Medicines Agencies. pp. 6–7.
70. ^ Martinez-Gimeno, A; García-Marcos, Luis (Apr 2013). "The association between acetaminophen and asthma: should its pediatric use be banned?". *Expert Review of Respiratory Medicine*. **7** (2): 113–22. doi:10.1586/ers.13.8. PMID 23547988.
71. ^ McBride, JT (Dec 2011). "The association of acetaminophen and asthma prevalence and severity.". *Pediatrics*. **128** (6): 1181–5. doi:10.1542/peds.2011-1106. PMID 22065272.
72. ^ Sarg, Michael; Ann D Gross; Roberta Altman (2007). *The Cancer Dictionary*. Infobase Publishing. ISBN 9780816064113.
73. ^ Neuss,G (2007). *Chemistry: Course Companion*. Oxford University Press. ISBN 978-0-19-915146-2.
74. ^ Ebrahimi, Sedigheh; Soheil Ashkani Esfahani; Hamid Reza Ghaffarian; Mahsima Khoshneviszade (2010). "Comparison of efficacy and safety of acetaminophen and ibuprofen administration as single dose to reduce fever in children". *Iranian Journal of Pediatrics*. **20** (4): 500–501.[*dead link*]
75. ^ Lesko SM, Mitchell AA (1999). "The safety of acetaminophen and ibuprofen among children younger than two years old". *Pediatrics*. **104** (4): e39. doi:10.1542/peds.104.4.e39. PMID 10506264.
76. ^ Yorgason, JG; Luxford, W; Kalinec, F (Dec 2011). "In vitro and in vivo models of drug ototoxicity: studying the mechanisms of a clinical problem.". *Expert opinion on drug metabolism & toxicology*. **7** (12): 1521–34. doi:10.1517/17425255.2011.614231. PMID 21999330.
77. ^ Rumack B, Matthew H (1975). "Acetaminophen poisoning and toxicity". *Pediatrics*. **55** (6): 871–76. PMID 1134886.
78. ^ "Paracetamol". University of Oxford Centre for Suicide Research. 25 March 2013. Retrieved 20 April 2013.
79. ^ Ryder SD, Beckingham IJ (2001). "ABC of diseases of liver, pancreas, and biliary system. Other causes of parenchymal liver disease". *BMJ*. **322** (7281): 290–92. doi:10.1136/bmj.322.7281.290. PMC 1119531. PMID 11157536.
80. ^ Lee WM (2004). "Acetaminophen and the U. S. Acute Liver Failure Study Group: lowering the risks of hepatic failure". *Hepatology*. **40** (1): 6–9. doi:10.1002/hep.20293. PMID 15239078.
81. ^ *a b c d e f* Mehta, Sweety (August 25, 2012) Metabolism of Paracetamol (Acetaminophen), Acetanilide and Phenacetin. pharmaxchange.info
82. ^ "Highlights of Prescribing Information" (PDF). Acetadote. Retrieved 2014-02-10.
83. ^ "Paracetamol overdose: new guidance on treatment with intravenous acetylcysteine". *Drug Safety Update*. **6** (2): A1. September 2012.[*dead link*]
84. ^ "FDA May Restrict Acetaminophen". Webmd.com. 2009-07-01. Retrieved 2011-03-19.
85. ^ "FDA limits acetaminophen in prescription combination products; requires liver toxicity warnings" (Press release). U. S. Food and Drug Administration (FDA). January 13, 2011. Retrieved January 13, 2011.
86. ^ *a b* "FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure". U. S. Food and Drug Administration (FDA). January 13, 2011. Retrieved January 13, 2011.
87. ^ Matthew Perrone (January 13, 2011). "FDA orders lowering pain reliever in Vicodin". *The Boston Globe*.

Associated Press. Retrieved January 13, 2011.
88. ^ [a] [b] Gardiner Harris (January 13, 2011). "F. D. A. Plans New Limits on Prescription Painkillers". *The New York Times*. Retrieved January 13, 2011.
89. ^ "Liquid paracetamol for children: Revised UK dosing instructions have been introduced". Mhra.gov.uk. Retrieved 2014-02-18. [*dead link*]
90. ^ Scialli, AR; Ang, R; Breitmeyer, J; Royal, MA (Dec 2010). "A review of the literature on the effects of acetaminophen on pregnancy outcome" (PDF). *Reproductive Toxicology (Elmsford, N.Y.)*. **30** (4): 495–507. doi:10.1016/j.reprotox.2010.07.007. PMID 20659550.
91. ^ Rudolph, AM (Feb 23, 1981). "Effects of aspirin and acetaminophen in pregnancy and in the newborn". *Archives of Internal Medicine*. **141** (3): 358–63. doi:10.1001/archinte.141.3.358. PMID 7469626.
92. ^ Eyers, S; Weatherall, M; Jefferies, S; Beasley, R (Apr 2011). "Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis" (PDF). *Clinical and Experimental Allergy*. **41** (4): 482–9. doi:10.1111/j.1365-2222.2010.03691.x. PMID 21338428.
93. ^ Blaser, JA; Allan, GM (July 2014). "Acetaminophen in pregnancy and future risk of ADHD in offspring.". *Canadian Family Physician*. **60** (7): 642. PMID 25022638.
94. ^ de Fays, L; Van Malderen, K; De Smet, K; Sawchik, J; Verlinden, V; Hamdani, J; Dogné, JM; Dan, B (August 2015). "Use of paracetamol during pregnancy and child neurological development.". *Developmental medicine and child neurology*. **57** (8): 718–24. doi:10.1111/dmcn.12745. PMID 25851072.
95. ^ Choueiri, TK.; Je, Y.; Cho, E. (2014). "Analgesic use and the risk of kidney cancer: a meta-analysis of epidemiologic studies.". *International Journal of Cancer*. **134** (2): 384–396. doi:10.1002/ijc.28093. PMC 3815746. PMID 23400756.
96. ^ [a] [b] [c] [d] Fortuny, J.; Kogevinas, M.; Garcia-Closas, M.; Real, F. X.; Tardòn, A.; Garcia-Closas, R.; Serra, C.; Carrato, A.; Lloreta, J.; Rothman, N.; Villanueva, C.; Dosemeci, M.; Malats, N.; Silverman, D. (2006). "Use of Analgesics and Nonsteroidal Anti-inflammatory Drugs, Genetic Predisposition, and Bladder Cancer Risk in Spain". *Cancer Epidemiology, Biomarkers & Prevention*. **15** (9): 1696–1702. doi:10.1158/1055-9965.EPI-06-0038. PMID 16985032.
97. ^ [a] [b] [c] [d] Hinz, B.; Cheremina, O.; Brune, K. (2008). "Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man.". *The FASEB Journal*. **22** (2): 383–390. doi:10.1096/fj.07-8506com. PMID 17884974.
98. ^ Andersson DA, Gentry C, Alenmyr L, Killander D, Lewis SE, Andersson A, Bucher B, Galzi JL, Sterner O, Bevan S, Högestätt ED, Zygmunt PM (2011). "TRPA1 mediates spinal antinociception induced by acetaminophen and the cannabinoid Δ(9)-tetrahydrocannabiorcol". *Nat Commun*. **2**: 551. doi:10.1038/ncomms1559. PMID 22109525.
99. ^ Claesson, A. "On the mechanism of paracetamol's analgesic activity and a note on related NSAID pharmacology". *SlideShare*. Retrieved 1 March 2013.
100. ^ Ohki S, Ogino N, Yamamoto S, Hayaishi O (1979). "Prostaglandin hydroperoxidase, an integral part of prostaglandin endoperoxide synthetase from bovine vesicular gland microsomes". *J. Biol. Chem*. **254** (3): 829–36. PMID 104998.
101. ^ Harvison PJ, Egan RW, Gale PH, Nelson SD (1986). "Acetaminophen as a cosubstrate and inhibitor of prostaglandin H synthase". *Adv. Exp. Med. Biol*. Advances in Experimental Medicine and Biology. **197**: 739–47. doi:10.1007/978-1-4684-5134-4_68. ISBN 978-1-4684-5136-8. PMID 3094341.
102. ^ [a] [b] Aronoff DM, Oates JA, Boutaud O (2006). "New insights into the mechanism of action of acetaminophen: Its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases". *Clin. Pharmacol. Ther*. **79** (1): 9–19. doi:10.1016/j.clpt.2005.09.009. PMID 16413237.
103. ^ Roberts, L.J. II. & Marrow, J.D. "Analgesic-antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout" in, "Goodman & Gilman's The Pharmacological Basis of Therapeutics 10th Edition" by Hardman, J.G. & Limbird, L.E. Published by McGraw Hill, 2001, pp.687–731 ISBN 0071354697
104. ^ [a] [b] [c] [d] [e] [f] [g] Bertolini A, Ferrari A, Ottani A, Guerzoni S, Tacchi R, Leone S (2006). "Paracetamol: new vistas of an old drug". *CNS Drug Reviews*. **12** (3–4): 250–75. doi:10.1111/j.1527-3458.2006.00250.x. PMID 17227290.
105. ^ [a] [b] Kis B, Snipes JA, Busija DW (2005). "Acetaminophen and the cyclooxygenase-3 puzzle: sorting out facts, fictions, and uncertainties". *J. Pharmacol. Exp. Ther*. **315** (1): 1–7. doi:10.1124/jpet.105.085431. PMID 15879007.
106. ^ Graham GG, Scott KF (2005). "Mechanism of action of paracetamol". *American journal of therapeutics*. **12** (1): 46–55. doi:10.1097/00045391-200501000-00008. PMID 15662292.
107. ^ [a] [b] Chandrasekharan NV, Dai H, Roos KL, et al. (2002). "COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression". *Proc. Natl. Acad. Sci. U.S.A.* **99** (21): 13926–31. doi:10.1073/pnas.162468699. PMC 129799. PMID 12242329.
108. ^ Högestätt ED, Jönsson BA, Ermund A, et al. (2005). "Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous

system". *J. Biol. Chem*. **280** (36): 31405–12. doi:10.1074/jbc.M501489200. PMID 15987694.
109. ^ Köfalvi A (2008). "9. Alternative interacting sites and novel receptors for cannabinoid ligands". *Cannabinoids and the Brain*. Springer-Verlag. pp. 131–160. doi:10.1007/978-0-387-74349-3_9. ISBN 978-0-387-74348-6.
110. ^ Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A (2006). "The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors". *Eur. J. Pharmacol*. **531** (1–3): 280–1. doi:10.1016/j.ejphar.2005.12.015. PMID 16438952.
111. ^ Andersson, David A; Gentry, Clive; Alenmyr, Lisa; Killander, Dan; Lewis, Simon E; Andersson, Anders; Bucher, Bernard; Galzi, Jean-Luc; Sterner, Olov; Bevan, Stuart; Högestätt, Edward D; Zygmunt, Peter M (November 2011). "TRPA1 mediates spinal antinociception induced by acetaminophen and the cannabinoid Δ9-tetrahydrocannabiorcol". *Nature Communications*. **2** (2): 551. doi:10.1038/ncomms1559. PMID 22109525.
112. ^ Gould, G. G.; Seillier, A.; Weiss, G.; Giuffrida, A.; Burke, T. F.; Hensler, J. G.; Rock, C.; Tristan, A.; McMahon, L. R.; Salazar, A.; O'Connor, J. C.; Satsangi, N.; Satsangi, R. K.; Gu, T. T.; Treat, K.; Smolik, C.; Schultz, S. T. (2012). "Acetaminophen differentially enhances social behavior and cortical cannabinoid levels in inbred mice". *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. **38** (2): 260–269. doi:10.1016/j.pnpbp.2012.04.011. PMC 3389197. PMID 22542870.
113. ^ Prescott, LF (October 1980). "Kinetics and metabolism of paracetamol and phenacetin.". *British journal of clinical pharmacology*. 10 Suppl 2: 291S–298S. PMC 1430174. PMID 7002186.
114. ^ [a] [b] Graham, GG; Davies, MJ; Day, RO; Mohamudally, A; Scott, KF (June 2013). "The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings.". *Inflammopharmacology*. **21** (3): 201–32. doi:10.1007/s10787-013-0172-x. PMID 23719833.
115. ^ [a] [b] John Marx; Ron Walls; Robert Hockberger (2013). *Rosen's Emergency Medicine - Concepts and Clinical Practice*. Elsevier Health Sciences. ISBN 9781455749874.
116. ^ [a] [b] [c] Borne, Ronald F. "Nonsteroidal Anti-inflammatory Drugs" in *Principles of Medicinal Chemistry*, Fourth Edition. Eds. Foye, William O.; Lemke, Thomas L.; Williams, David A. Published by Williams & Wilkins, 1995. p. 544–545.
117. ^ [a] [b] Brayfield, A, ed. (15 January 2014). "Paracetamol". *Martindale: The Complete Drug Reference*. London, UK: Pharmaceutical Press. Retrieved 10 May 2014.
118. ^ Bales, JR; Nicholson JK; Sadler PJ (1985). "Two-dimensional proton nuclear magnetic resonance "maps" of acetaminophen metabolites in human urine". *Clinical Chemistry*. **31** (5): 757–762. PMID 3987005.
119. ^ Viswanathan, A. N.; Feskanich, D.; Schernhammer, E. S.; Hankinson, S. E. (2008). "Aspirin, NSAID, and Acetaminophen Use and the Risk of Endometrial Cancer". *Cancer Research*. **68** (7): 2507–13. doi:10.1158/0008-5472.CAN-07-6257. PMC 2857531. PMID 18381460.
120. ^ Altinoz, M. A.; Korkmaz, R. (2004). "NF-kappaB, macrophage migration inhibitory factor and cyclooxygenase-inhibitions as likely mechanisms behind the acetaminophen- and NSAID-prevention of the ovarian cancer". *Neoplasma*. **51** (4): 239–247. PMID 15254653.
121. ^ Byrant, Bronwen; Knights, Katleen; Salerno, Evelyn (2007). *Pharmacology for health professionals*. Elsevier. p. 270. ISBN 9780729537872.
122. ^ Ellis, Frank (2002). *Paracetamol: a curriculum resource*. Cambridge: Royal Society of Chemistry. ISBN 0-85404-375-6.
123. ^ Anthony S. Travis (2007). "Manufacture and uses of the anilines: A vast array of processes and products". In Zvi Rappoport. *The chemistry of Anilines Part 1*. Wiley. p. 764. ISBN 978-0-470-87171-3.
124. ^ [a] [b] Elmar Friderichs, Thomas Christoph, Helmut Buschmann (2005), "Analgesics and Antipyretics", *Ullmann's Encyclopedia of Industrial Chemistry*, Weinheim: Wiley-VCH, doi:10.1002/14356007.a02_269.pub2
125. ^ US patent 4524217, Kenneth G. Davenport & Charles B. Hilton, "Process for producing N-acyl-hydroxy aromatic amines", published 1985-06-18, assigned to Celanese Corporation
126. ^ Joncour, Roxan; Duguet, Nicolas; Métay, Estelle; Ferreira, Amadéo; Lemaire, Marc (2014). "Amidation of phenol derivatives: a direct synthesis of paracetamol (acetaminophen) from Hydroquinone". *Green Chem*. **16**: 2997–3002. doi:10.1039/C4GC00166D.
127. ^ Joncour, Roxan; Duguet, Nicolas; Métay, Estelle; Ferreira, Amadéo; Lemaire, Marc. "Supplementary Information Amidation of phenol derivatives: a direct synthesis of paracetamol (acetaminophen) from hydroquinone" (PDF).
128. ^ Henney, K; Dudley B (1939). *Handbook of Photography*. Whittlesey House. p. 324.
129. ^ Novotny PE, Elser RC (1984). "Indophenol method for acetaminophen in serum examined" (PDF). *Clin. Chem.* **30** (6): 884–6. PMID 6723045.
130. ^ Cahn, A; Hepp P (1886). "Das Antifebrin, ein neues Fiebermittel". *Centralbl. Klin. Med*. **7**: 561–64.
131. ^ Morse, H.N. (1878). "Ueber eine neue Darstellungsmethode der Acetylamidophenole" [On a new method of preparing acetylamidophenol]. *Berichte der deutschen chemischen Gesellschaft* (in German). **11** (1): 232–3. doi:10.1002/cber.18780110151.
132. ^ [a] [b] [c] [d] [e] Milton Silverman; Mia Lydecker; Philip Randolph Lee (1992). *Bad Medicine: The Prescription Drug*

*Industry in the Third World* . Stanford University Press. pp. 88–90. ISBN 0804716692.
133. ^ Von Mering, J (1893). "Beitrage zur Kenntniss der Antipyretica". *Ther Monatsch*. **7**: 577–587.
134. ^ *a b c d* Sneader, Walter (2005). *Drug Discovery: A History*. Hoboken, N.J.: Wiley. p. 439. ISBN 0471899801.
135. ^ Toussaint, K; Yang, XC; Zielinski, MA; Reigle, KL; Sacavage, SD; Nagar, S; Raffa, RB (December 2010). "What do we (not) know about how paracetamol (acetaminophen) works?" (PDF). *Journal of Clinical Pharmacy and Therapeutics*. **35** (6): 617–38. doi:10.1111/j.1365-2710.2009.01143.x. PMID 21054454.
136. ^ Bergman K, Müller L, Teigen SW (1996). "The genotoxicity and carcinogenicity of paracetamol: a regulatory (re)view". *Mutat Res*. **349** (2): 263–88. doi:10.1016/0027-5107(95)00185-9. PMID 8600357.
137. ^ Lester D, Greenberg LA, Carroll RP (1947). "The metabolic fate of acetanilid and other aniline derivatives: II. Major metabolites of acetanilid appearing in the blood". *J. Pharmacol. Exp. Ther*. **90** (1): 68–75. PMID 20241897.
138. ^ Brodie, BB; Axelrod J (1948). "The estimation of acetanilide and its metabolic products, aniline, *N*-acetyl *p*-aminophenol and *p*-aminophenol (free and total conjugated) in biological fluids and tissues". *J. Pharmacol. Exp. Ther*. **94** (1): 22–28. PMID 18885610.
139. ^ Brodie, BB; Axelrod J (1948). "The fate of acetanilide in man" (PDF). *J. Pharmacol. Exp. Ther*. **94** (1): 29–38. PMID 18885611.
140. ^ Flinn, Frederick B; Brodie BB (1948). "The effect on the pain threshold of *N*-acetyl *p*-aminophenol, a product derived in the body from acetanilide". *J. Pharmacol. Exp. Ther*. **94** (1): 76–77. PMID 18885618.
141. ^ Brodie BB, Axelrod J (1949). "The fate of acetophenetidin (phenacetin) in man and methods for the estimation of acetophenitidin and its metabolites in biological material". *J Pharmacol Exp Ther*. **94** (1): 58–67.
142. ^ Landau, Ralph; Achilladelis, Basil; Scriabine, Alexander (1999). *Pharmaceutical Innovation: Revolutionizing Human Health*. Chemical Heritage Foundation. pp. 248–249. ISBN 978-0-941901-21-5.
143. ^ Rapoport, Alan (15 December 1991). *Headache Relief*. Touchstone. p. 97. ISBN 978-0-671-74803-6.
144. ^ "SEC Info - Eastman Kodak Co - '8-K' for 6/30/94". Retrieved 3 March 2016.
145. ^ "Our Story". McNEIL-PPC, Inc. Retrieved March 8, 2014.
146. ^ "Medication and Drugs". *MedicineNet*. 1996–2010. Retrieved April 22, 2010.
147. ^ Thakkar, KB; Billa, G (Sep 2013). "The concept of: Generic drugs and patented drugs vs. brand name drugs and non-proprietary (generic) name drugs". *Front Pharmacol*. **4**: 113. doi:10.3389/fphar.2013.00113. PMID 24062686.
148. ^ *a b* Macintyre, Pamela; Rowbotham, David; Walker, Suellen (26 September 2008). *Clinical Pain Management Second Edition: Acute Pain*. CRC Press. p. 85. ISBN 978-0-340-94009-9.
149. ^ *a b* *International Nonproprietary Names (INN) for Pharmaceutical Substances: Lists 1-96 of Proposed INN and lists 1-57 of Recommended INN, cumulative list N°12*. World Health Organization. 2007. p. v. ISBN 9789240560253. Retrieved 20 January 2014.[*dead link*]
150. ^ "TGA Approved Terminology for Medicines, Section 1 – Chemical Substances" (PDF). Therapeutic Goods Administration, Department of Health and Ageing, Australian Government. July 1999: 97.
151. ^ "Acetaminophen." Physicians' Desk Reference, 63rd ed. Montvale, NJ: Thomson PDR; 2009: 1915–1916.
152. ^ "Acetaminophen Overdose and Liver Injury—Background and Options for Reducing Injury", *Charles Ganley, MD, Gerald Dal Pan, MD, Bob Rappaport, MD*, May 22, 2009, Retrieved July 8, 2010.
153. ^ *a b* Atkinson, Hartley C.; Stanescu, Ioana; Anderson, Brian J. (2014). "Increased Phenylephrine Plasma Levels with Administration of Acetaminophen". *New England Journal of Medicine*. **370** (12): 1171–1172. doi:10.1056/NEJMc1313942. ISSN 0028-4793. PMID 24645960.
154. ^ "Ascorbic acid/Phenylephrine/Paracetamol". *NHS Choices*. National Health Service. Retrieved March 25, 2014.
155. ^ "Phenylephrine/Caffeine/Paracetamol dual relief". *NHS Choices*. National Health Service. Retrieved March 25, 2014.
156. ^ "Beechams Decongestant Plus With Paracetamol". *NHS Choices*. National Health Service. Retrieved March 25, 2014.
157. ^ Senyuva, H.; Ozden, T. (2002). "Simultaneous High-Performance Liquid Chromatographic Determination of Paracetamol, Phenylephrine HCl, and Chlorpheniramine Maleate in Pharmaceutical Dosage Forms" (PDF). *Journal of Chromatographic Science*. **40** (2): 97–100. doi:10.1093/chromsci/40.2.97. ISSN 0021-9665. PMID 11881712.
158. ^ Janin, A.; Monnet, J. (2014). "Bioavailability of paracetamol, phenylephrine hydrochloride and guaifenesin in a fixed-combination syrup versus an oral reference product". *Journal of International Medical Research*. **42** (2): 347–359. doi:10.1177/0300060513503762. ISSN 0300-0605. PMID 24553480.
159. ^ "Paracetamol – phenylephrine hydrochloride – guaifenesin". *NPS MedicineWise*. National Prescribing Service (Australia). Retrieved March 25, 2014.
160. ^ "Phenylephrine/Guaifenesin/Paracetamol". *NHS Choices*. National Health Service. Archived from the original on September 12, 2013. Retrieved March 25, 2014.
161. ^ "Treating a Restless Legs Sydnrome (RLS)". Consumer Reports. 2011.

162. ^ "Use Only as Directed". *This American Life*. Episode 505. Chicago. 20 September 2013. Public Radio International. WBEZ. Retrieved 24 September 2013.
163. ^ Gerth, Jeff; T. Christian Miller (20 September 2013). "Use Only as Directed". ProPublica. Retrieved 24 September 2013.
164. ^ Miller, T. Christian; Jeff Gerth (20 September 2013). "Dose of Confusion". ProPublica. Retrieved 24 September 2013.
165. ^ "www.fda.gov" (PDF).
166. ^ Allen AL (2003). "The diagnosis of acetaminophen toxicosis in a cat". *Can Vet J*. **44** (6): 509–10. PMC 340185. PMID 12839249.
167. ^ *a b c* Richardson, JA (2000). "Management of acetaminophen and ibuprofen toxicoses in dogs and cats" (PDF). *J. Vet. Emerg. Crit. Care*. **10** (4): 285–91. doi:10.1111/j.1476-4431.2000.tb00013.x.[*dead link*]
168. ^ *a b* Maddison, Jill E.; Stephen W. Page; David Church (2002). *Small Animal Clinical Pharmacology*. Elsevier Health Sciences. pp. 260–1. ISBN 0702025739.
169. ^ *a b c* "Pardale-V Oral Tablets". *NOAH Compendium of Data Sheets for Animal Medicines*. The National Office of Animal Health (NOAH). 11 November 2010. Retrieved 20 January 2011.[*dead link*]
170. ^ Villar D, Buck WB, Gonzalez JM (1998). "Ibuprofen, aspirin and acetaminophen toxicosis and treatment in dogs and cats". *Vet Hum Toxicol*. **40** (3): 156–62. PMID 9610496.
171. ^ Meadows, Irina; Gwaltney-Brant, Sharon (2006). "The 10 Most Common Toxicoses in Dogs". *Veterinary Medicine*: 142–8.
172. ^ Dunayer, E (2004). "Ibuprofen toxicosis in dogs, cats, and ferrets". *Veterinary Medicine*: 580–6.
173. ^ Johnston J, Savarie P, Primus T, Eisemann J, Hurley J, Kohler D (2002). "Risk assessment of an acetaminophen baiting program for chemical control of brown tree snakes on Guam: evaluation of baits, snake residues, and potential primary and secondary hazards". *Environ Sci Technol*. **36** (17): 3827–33. doi:10.1021/es015873n. PMID 12322757.
174. ^ Brad Lendon (2010-09-07). "Tylenol-loaded mice dropped from air to control snakes". CNN. Retrieved 2010-09-07.
175. ^ Sabrina Richards (2012-05-01). "It's Raining Mice". The Scientist.


## External links [edit]

- Pharmacy and Pharmacology portal
- Paracetamol at Chemsynthesis
- Paracetamol International Chemical Safety Cards
- The Julius Axelrod Papers
- FDA: Safe Use of Over-the-Counter Pain Relievers/Fever Reducers
- FDA: Consumer Update "Acetaminophen and Liver Injury: Q and A for Consumers" (link)
- FDA: Consumer Update "Acetaminophen and Liver Injury: Q and A for Consumers" (PDF)
- U.S. National Library of Medicine: Drug Information Portal–Paracetamol
- Acetaminophen bound to proteins in the PDB

Wikimedia Commons has media related to *Paracetamol*.

| v · t · e | **Analgesics (N02A, N02B)** | |
|---|---|---|
| **Opioids** | **Opiates/opium** | Codeine# (+paracetamol, +aspirin) · Morphine# (+naltrexone) · Opium · Laudanum · Paregoric · |
| | **Semisynthetic** | Acetyldihydrocodeine · Benzylmorphine · Buprenorphine (+naloxone) · Desomorphine · Diamorphine (heroin) · Dihydrocodeine (+paracetamol) · Dihydromorphine · Ethylmorphine · Hydrocodone (+paracetamol, +ibuprofen, +aspirin) · Hydromorphinol · Hydromorphone · Nicocodeine · Nicodicodeine · Nicomorphine · Oxycodone (+paracetamol, +aspirin, +ibuprofen, +naloxone, +naltrexone) · Oxymorphone · Thebacon · |
| | | Alphaprodine · Anileridine · Butorphanol · Dextromoramide · Dextropropoxyphene · Dezocine · Fentanyl (+fluanisone) · Ketobemidone · |

| | | |
|---|---|---|
| | **Synthetic** | Levorphanol · Meptazinol · Methadone · Nalbuphine · Pentazocine · Pethidine · Phenadoxone · Phenazocine · Piminodine · Piritramide · Propiram · Tapentadol · Tilidine · Tramadol · |
| **Paracetamol-type** | | Acetanilide‡ · Bucetin‡ · Butacetin‡ · **Paracetamol (acetaminophen)**# · Parapropamol‡ · Phenacetin‡ · Propacetamol‡ · |
| **NSAIDs** | **Propionates** | Fenoprofen · Flurbiprofen · Ibuprofen# · Ketoprofen · Naproxen · Oxaprozin · |
| | **Oxicams** | Meloxicam · Piroxicam · |
| | **Acetates** | Diclofenac · Indometacin · Ketorolac · Nabumetone · Sulindac · Tolmetin · |
| | **COX-2 inhibitors** | Celecoxib · Etoricoxib · Lumiracoxib · Parecoxib · Rofecoxib ‡ · Valdecoxib ‡ · |
| | **Fenamates** | Meclofenamic acid · Mefenamic acid · |
| | **Salicylates** | Aspirin (acetylsalicylic acid)# (+paracetamol/caffeine) · Benorylate · Diflunisal · Ethenzamide · Magnesium salicylate · Salicin · Salicylamide · Salsalate · Wintergreen (methyl salicylate) · |
| | **Pyrazolones** | Aminophenazone‡ · Ampyrone · Metamizole (dipyrone) · Nifenazone · Phenazone · Propyphenazone · |
| | **Others** | Glafenine · |
| **Cannabinoids** | | Cannabidiol · Cannabis · Nabilone · Nabiximols · Tetrahydrocannabinol (dronabinol) · |
| **Ion channel modulators** | **Calcium blockers** | Gabapentin · Gabapentin enacarbil · Pregabalin · Ziconotide · |
| | **Sodium blockers** | Carbamazepine · Lacosamide · Local anesthetics (e.g., cocaine, lidocaine) · Mexiletine · Nefopam · Tricyclic antidepressants (e.g., amitriptyline#) · *$Na_V1.7/1.8$-selective:* DSP-2230§ · Funapide§ · PF-05089771§ · Raxatrigine§ · |
| | **Potassium openers** | Flupirtine · |
| **Myorelaxants** | | Carisoprodol · Chlorzoxazone · Cyclobenzaprine · Mephenoxalone · Methocarbamol · Orphenadrine · |
| **Others** | | Camphor · Capsaicin · Clonidine · Ketamine · Menthol · Methoxyflurane · Nefopam · Proglumide · Tricyclic antidepressants (e.g., amitriptyline#) · |

· #WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · ·

| v · t · e · | **Cannabinoidergics** | |
|---|---|---|
| | **$CB_1$** | **Agonists** *(abridged; see here for more)*: 2-AG · 2-AGE (noladin ether) · 11-Hydroxy-THC · α-Amyrin · β-Amyrin · AB-CHMINACA · AM-1172 · AM-1220 · AM-1221 · AM-1235 · AM-2201 · AM-2232 · Anandamide · Arvanil · AZ-11713908 · Cannabinol · CB-13 · CP 47,497 · CP 55,940 · Dimethylheptylpyran · DEA · ECG · EGCG · Epicatechin · Gallocatechol (gallocatechin) · Honokiol · HU-210 · JWH-007 · JWH-015 · JWH-018 · JWH-073 · Kavain · L-759,633 · Levonantradol · Menabitan · Nabilone · Nabitan · NADA · O-1812 · Oleamide · Pravadoline · Serinolamide A · THC (dronabinol) · UR-144 · WIN 55,212-2 · Yangonin · |

| | | |
|---|---|---|
| **Receptor (ligands)** | | **Antagonists:** AM-251 · AM-6545 · Cannabidiol · Cannabigerol · Drinabant · Falcarinol (carotatoxin) · Hemopressin · Ibipinabant · LY-320,135 · MK-9470 · NESS-0327 · O-2050 · Otenabant · PF-514273 · PipISB · Rimonabant · Rosonabant · Surinabant · Taranabant · THCV · TM-38837 · VCHSR · Virodhamine · **Antibodies:** Brizantin (Бризантин) · Dietressa (Диетресса) · **Unknown/unsorted:** MAFP · |
| | **$CB_2$** | **Agonists:** 2-AG · 2-AGE (noladin ether) · 3,3'-Diindolylmethane · 4-O-Methylhonokiol · α-Amyrin · β-Amyrin · A-796,260 · A-834,735 · A-836,339 · AM-1172 · AM-1221 · AM-1235 · AM-1241 · AM-2232 · Anandamide · AZ-11713908 · Cannabinol · Caryophyllene · CB-13 · CBS-0550 · CP-55,940 · GW-405,833 (L-768,242) · GW-842,166X · HU-308 · JTE 7-31 · JWH-007 · JWH-015 · JWH-018 · JWH-73 · JWH-133 · L-759,633 · L-759,656 · Magnolol · MDA-19 · Nabitan · NADA · PF-03550096 · S-444,823 · SER-601 · Serinolamide A · UR-144 · Tedalinab · THC (dronabinol) · THCV · Tetrahydromagnolol · Virodhamine · **Antagonists:** 4-O-Methylhonokiol · AM-630 · BML-190 · Cannabidiol · Honokiol · JTE-907 · SR-144,528 · WIN 54,461 · WIN 56,098 · |
| | **GPR18** | **Agonists:** Abnormal cannabidiol · ACPA · AM251 · Anandamide · Cannabidiol · NADGly · THC (dronabinol) · O-1602 · **Antagonists:** CID-85469571 · O-1918 · |
| | **GPR55** | **Agonists:** 2-AGE (noladin ether) · 2-ALPI · Abnormal cannabidiol · AM-251 · CID1011163 · CID1252842 · CID1792579 · CP 55,940 · GSK-494581A · Lysophosphatidylinositol · ML-184 · ML-185 · ML-186 · O-1602 · Oleoylethanolamide · Palmitoylethanolamide · THC (dronabinol) · **Antagonists:** Cannabidiol · CID-16020046 · ML-191 · ML-192 · ML-193 · O-1918 · PSB-SB-487 · PSB-SB-1202 · PSB-SB-1203 · Tetrahydromagnolol · |
| | **GPR119** | **Agonists:** 2-Oleoylglycerol · Anandamide · APD668 · AR-231,453 · AS-1269574 · MBX-2982 · N-Oleoyldopamine · Oleoylethanolamide · Olvanil · PSN-375,963 · PSN-632,408 · |
| **Transporter (modulators)** | **eCBTs** | **Inhibitors:** 5'-DMH-CBD · AM-404 · AM-1172 · Arachidonoyl serotonin · Arvanil · Cannabidiol · Guineensine · LY-2183240 · O-2093 · OMDM-2 · **Paracetamol (acetaminophen)** · SB-FI-26 · UCM-707 · URB-597 · VDM-11 · WOBE490 · WOBE491 · WOBE492 · |
| **Enzyme (modulators)** | **FAAH** | **Inhibitors:** 4-Nonylphenylboronic acid · $AACOCF_3$ · AM-404 · Arachidonoyl serotonin · BIA 10-2474 · Biochanin A · Genistein · IDFP · JNJ-1661010 · JNJ-42165279 · JZL-195 · Kaempferol · LY-2183240 · MAFP · Palmitoylisopropylamide · **Paracetamol (acetaminophen)** · PF-3845 · PF-04457845 · PF-750 · SA-47 · SA-57 · TAK 21d · TC-F 2 · UCM710 · URB-597 · **Activators:** PDP-EA · |
| | **MAGL** | **Inhibitors:** ABX-1431 · IDFP · JJKK 048 · JW 642 · JZL-184 · JZL-195 · JZP-361 · KML 29 · MAFP · MJN110 · NAM · Pristimerin · URB-602 · |
| | **ABHD6** | **Inhibitors:** JZP-169 · JZP-430 · KT182 · KT185 · KT195 · KT203 · LEI-106 · ML294 · ML295 · ML296 · UCM710 · WWL-70 · |
| | **ABHD12** | **Inhibitors:** Betulinic acid · Maslinic acid · MAFP · Oleanolic acid · Orlistat (tetrahydrolipstatin) · Ursolic acid · |

| | |
|---|---|
| **Others** | **Precursors:** Phosphatidylethanolamine · NAPE · Diacylglycerol ·<br>**Others:** 2-PG *(directly potentiates activity of 2-AG at $CB_1$ receptor)* · ARN-272 *(FAAH-like anandamide transporter inhibitor)* · |
| *See also: Cannabinoids (cannabinoids by structure)* · | |

| v · t · e · | **Prostanoid signaling modulators** | | |
|---|---|---|---|
| **Receptor (ligands)** | **DP ($D_2$)** | **$DP_1$** | **Agonists:** Prostaglandin $D_2$ · Treprostinil ·<br>**Antagonists:** Asapiprant · Laropiprant · Vidupiprant · |
| | | **$DP_2$** | **Agonists:** Indometacin · Prostaglandin $D_2$ ·<br>**Antagonists:** ADC-3680 · AZD-1981 · Bay U3405 · Fevipiprant · MK-1029 · MK-7246 · OC-459 · OC000459 · QAV-680 · Ramatroban · Setipiprant · TM30089 · Vidupiprant · |
| | **EP ($E_2$)** | **$EP_1$** | **Agonists:** Beraprost · Enprostil · Iloprost (ciloprost) · Latanoprost · Lubiprostone · Misoprostol · Prostaglandin $E_1$ (alprostadil) · Prostaglandin $E_2$ (dinoprostone) · Sulprostone ·<br>**Antagonists:** AH-6809 · ONO-8130 · SC-19220 · SC-51089 · SC-51322 · |
| | | **$EP_2$** | **Agonists:** Butaprost · Misoprostol · Prostaglandin $E_1$ (alprostadil) · Prostaglandin $E_2$ (dinoprostone) · Treprostinil ·<br>**Antagonists:** AH-6809 · PF-04418948 · TG 4-155 · |
| | | **$EP_3$** | **Agonists:** Beraprost · Carbacyclin · Cicaprost · Enprostil · Iloprost (ciloprost) · Isocarbacyclin · Latanoprost · Misoprostol · Prostaglandin $D_2$ · Prostaglandin $E_1$ (alprostadil) · Prostaglandin $E_2$ (dinoprostone) · Remiprostol · Sulprostone ·<br>**Antagonists:** L-798106 · |
| | | **$EP_4$** | **Agonists:** Lubiprostone · Misoprostol · Prostaglandin $E_1$ (alprostadil) · Prostaglandin $E_2$ (dinoprostone) · TCS-2510 ·<br>**Antagonists:** GW-627368 · L-161982 · ONO-AE3-208 · |
| | | **Unsorted** | **Agonists:** 16,16-Dimethyl Prostaglandin $E_2$ · Aganepag · Carboprost · Evatanepag · Gemeprost · Nocloprost · Omidenepag · Prostaglandin $F_{2\alpha}$ (dinoprost) · Simenepag · Taprenepag · |
| | **FP ($F_{2\alpha}$)** | | **Agonists:** Alfaprostol · Bimatoprost · Carboprost · Cloprostenol · Enprostil · Fluprostenol · Latanoprost · Prostaglandin $D_2$ · Prostaglandin $F_{2\alpha}$ (dinoprost) · Sulotroban · Tafluprost · Travoprost · Unoprostone · |
| | **IP ($I_2$)** | | **Agonists:** ACT-333679 · AFP-07 · Beraprost · BMY-45778 · Carbacyclin · Cicaprost · Iloprost (ciloprost) · Isocarbacyclin · MRE-269 · NS-304 · Prostacyclin (prostaglandin $I_2$, epoprostenol) · Prostaglandin $E_1$ (alprostadil) · Ralinepag · Selexipag · Taprostene · TRA-418 · Treprostinil ·<br>**Antagonists:** RO1138452 · |
| | **TP ($TX_{A2}$)** | | **Agonists:** Carbocyclic thromboxane $A_2$ · I-BOP · Thromboxane $A_2$ · U-46619 · Vapiprost ·<br>**Antagonists:** 12-HETE · 13-APA · AA-2414 · Argatroban · Bay U3405 · BMS-180,291 · Daltroban · Domitroban · EP-045 · GR-32191 · ICI-185282 · ICI-192605 · Ifetroban · Imitrodast · L-655240 · L-670596 · Linotroban · Mipitroban · ONO-3708 · ONO-11120 · Picotamide · Pinane thromboxane $A_2$ · Ramatroban · Ridogrel · S-145 · Samixogrel · |

| | | |
|---|---|---|
| | | Seratrodast · SQ-28,668 · SQ-29,548 · Sulotroban · Terbogrel · Terutroban · TRA-418 · |
| | **Unsorted** | Arbaprostil · Ataprost · Ciprostene · Clinprost · Cobiprostone · Delprostenate · Deprostil · Dimoxaprost · Doxaprost · Ecraprost · Eganoprost · Enisoprost · Eptaloprost · Esuberaprost · Etiproston · Fenprostalene · Flunoprost · Froxiprost · Lanproston · Limaprost · Luprostiol · Meteneprost · Mexiprostil · Naxaprostene · Nileprost · Nocloprost · Ornoprostil · Oxoprostol · Penprostene · Pimilprost · Piriprost · Posaraprost · Prostalene · Rioprostil · Rivenprost · Rosaprostol · Spiriprostil · Tiaprost · Tilsuprost · Tiprostanide · Trimoprostil · Viprostol · |
| **Enzyme (inhibitors)** | **COX (PTGS)** | Aceclofenac · Acemetacin · Acetanilide · Alclofenac · Alminoprofen · Aloxiprin · AM404 · Amfenac · Ampiroxicam · Anitrazafen · Antrafenine · Apricoxib · Aspirin (acetylsalicylic acid) · Azapropazone · Bendazac · Benorilate (benorylate) · Benoxaprofen · Bromfenac · Bucetin · Bucloxic acid (blucloxate) · Bufexamac · Bumadizone · Butibufen · Carbasalate calcium · Carprofen · Celecoxib · Cimicoxib · Cinmetacin · Clobuzarit · Clometacin · Clonixeril · Clonixin · Curcumin · Deracoxib · Dexibuprofen · Dexindoprofen · Dexketoprofen · Diclofenac · Difenpiramide · Diflunisal · Dipyrocetyl · Droxicam · DuP-697 · Enolicam · Ethenzamide · Etodolac · Etofenamate · Etoricoxib · Felbinac · Fenbufen · Fenclofenac · Fenoprofen · Fentiazac · Firocoxib · FK-3311 · Floctafenic acid (floctafenate) · Floctafenine · Flosulide · Flufenamic acid (flufenamate) · Flumizole · Flunixin · Flunoxaprofen · Fluproquazone · Flurbiprofen · FR-122047 · Glafenine · Glimepiride · Glucametacin · Guacetisal · Hyperforin · Ibuprofen · Ibuproxam · Indometacin farnesil · Indometacin (indomethacin) · Indoprofen · Isoxicam · Itazigrel · Ketoprofen · Ketorolac · L-655240 · L-670596 · Licofelone · Lonazolac · Lornoxicam · Loxoprofen · Lumiracoxib · Magnesium salicylate · Mavacoxib · Meclofenamic acid (meclofenamate) · Mefenamic acid (mefenamate) · Meloxicam · Menatetrenone (vitamin $K_2$) · Mesalazine (5-aminosalicylic acid) · Methyl salicylate · Miroprofen · Mofezolac · Morniflumate · Nabumetone · Naproxcinod · Naproxen · NCX-466 · NCX-4040 · Niflumic acid (niflumate) · Nimesulide · NS-398 · Oxametacin · Oxaprozin · Oxindanac · Pamicogrel · **Paracetamol (acetaminophen)** · Parapropamol · Parecoxib · Phenacetin · Piroxicam · Pirprofen · Polmacoxib · Pranoprofen · Proglumetacin · Propacetamol · Resveratrol · Robenacoxib · Rofecoxib · Romazarit · Rutecarpine · Salacetamide · Salicin · Salicylamide · Salicylic acid (salicylate) · Salsalate · Satigrel · SC-236 · SC-560 · SC-58125 · Sodium salicylate · Sulindac · Sulindac sulfide · Suprofen · Talinflumic acid (talinflumate) · Tarenflurbil · Tenidap · Tenoxicam · Tepoxalin · Tiaprofenic acid (tiaprofenate) · Tiflamizole · Tilmacoxib · Timegadine · Tolfenamic acid (tolfenamate) · Tolmetin · Trifenagrel · Triflusal · Tropesin · Valdecoxib · Vedaprofen · Zidometacin · Zomepirac · |
| | **$PGD_2$ synthase** | Retinoids · Selenium (selenium tetrachloride, sodium selenite, selenium disulfide) · |
| | **PGE synthase** | HQL-79 |
| | **PGF synthase** | Bimatoprost |
| | **$PGI_2$ synthase** | Tranylcypromine |
| | **TXA synthase** | Camonagrel · Dazmegrel · Dazoxiben · Furegrelate · Isbogrel · Midazogrel · Nafagrel · Nicogrelate · Ozagrel · Picotamide · Pirmagrel · Ridogrel · Rolafagrel · Samixogrel · |

| | |
|---|---|
| | Terbogrel · U63557A · |
| **Others** | **Precursors:** Linoleic acid · γ-Linolenic acid (gamolenic acid) · Dihomo-γ-linolenic acid · Diacylglycerol · Arachidonic acid · Prostaglandin $G_2$ · Prostaglandin $H_2$ · |
| *See also: Leukotrienergics* | |

Categories: Acetanilides | Analgesics | Antipyretics | Endocannabinoid reuptake inhibitors | Phenols | Drugs with unknown mechanisms of action | World Health Organization essential medicines




# Propofol



From Wikipedia, the free encyclopedia

*Not to be confused with Profadol, Propanol, or Propranolol.*

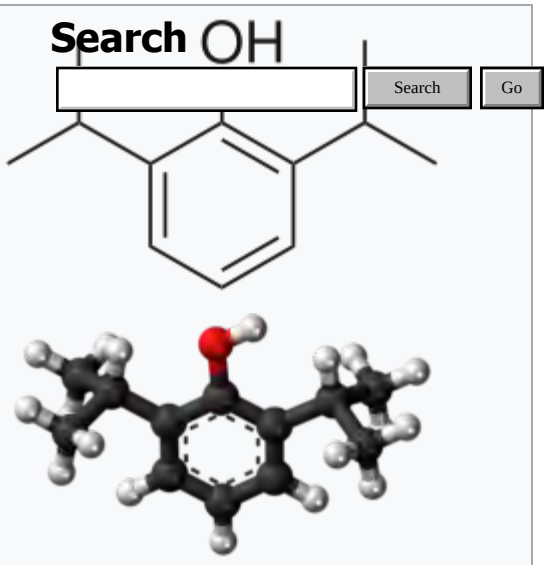
**Propofol**, marketed as **Diprivan** among others, is a short-acting medication that results in a decreased level of consciousness and lack of memory for events.[2] Its uses include the starting and maintenance of general anesthesia, sedation for mechanically ventilated adults, and procedural sedation. It is also used for status epilepticus if other medications have not worked. It is given intravenously. Maximum effect takes about two minutes to occur and it typically lasts five to ten minutes.[2]

Common side effects include an irregular heart rate, low blood pressure, burning sensation at the site of injection, and the stopping of breathing. Other serious side effects may include seizures, infections with improper use, addiction, and propofol infusion syndrome with long-term use. It appears to be safe for using during pregnancy but has not been well studied in this group. However, it is not recommended during cesarean section.[2] Propofol is not a pain medication, so opioids such as morphine may also be used.[3] Whether or not they are always needed is unclear.[4] Propofol is believed to work at least partly via the receptor for GABA.[2]

Propofol was discovered in 1977.[5] It is on the WHO Model List of Essential Medicines, the most important medications needed in a health system.[6] It is available as a generic medication.[2] The wholesale price in the developing world is between 0.61 and 8.50 USD per vial.[7] It has been referred to as **milk of amnesia** because of the milk-like appearance of the intravenous preparation.[8] Propofol is also used in veterinary medicine.[9]

## Contents






| Clinical data | |
|---|---|
| **AHFS / Drugs.com** | Monograph |
| **Pregnancy category** | AU: C<br>US: B (No risk in non-human studies) |
| **Dependence liability** | Physical: very low (seizures)<br>Psychological: no data |
| **Addiction liability** | Moderate[1] |
| **Routes of administration** | Intravenous |
| **ATC code** | N01AX10 (WHO) |
| **Legal status** | |
| **Legal status** | AU: S4 (Prescription only)<br>CA: -only<br>UK: POM (Prescription only)<br>US: -only (Prescription only) |

# Medical uses [edit]

## Anesthesia [edit]

Propofol is used for induction and maintenance (in some cases) of anesthesia, having largely replaced sodium thiopental.[3] It can also be administered as part of an anaesthesia maintenance technique called total intravenous anesthesia using either manually-programmed infusion pumps or computer-controlled infusion pumps in a process called target controlled infusion or TCI. Propofol is also used to sedate individuals who are receiving mechanical ventilation but are not undergoing surgery, such as patients in the intensive care unit. In critically ill patients, propofol has been found to be superior to lorazepam both in effectiveness and overall cost.[10]

Propofol is often used instead of sodium thiopental for starting anesthesia because recovery from propofol is more rapid and "clear."

## Procedural sedation [edit]

Propofol is also used for procedural sedation. Its use in these settings results in a faster recovery compared to midazolam.[11] It can also be combined with opioids or benzodiazepines.[12][13][14] Because of its fast induction and recovery time, propofol is also widely used for sedation of infants and children undergoing MRI.[15] It is also often used in combination with ketamine as the two together have lower rates of side effects.[16]

# Other uses [edit]

## Executions [edit]

The Missouri Supreme Court decided to allow the use of propofol to execute prisoners condemned to death. However, the first execution by administration of a lethal dose of propofol was halted on 11 October 2013 by governor Jay Nixon following threats from the European Union to limit the drug's export if it were used for that purpose.[17][18] The United Kingdom had already banned the export of medicines or veterinary medicines containing propofol to the United States.[19]

## Recreational use [edit]

| Pharmacokinetic data | |
|---|---|
| **Bioavailability** | NA |
| **Protein binding** | 95% to 99% |
| **Metabolism** | Liver glucuronidation |
| **Onset of action** | 15 to 30 sec[2] |
| **Biological half-life** | 30 to 60 min |
| **Duration of action** | 5 to 10 min[2] |
| **Excretion** | Liver |
| **Identifiers** | |
| **IUPAC name** | 2,6-Di(propan-2-yl)phenol |
| **CAS Number** | 2078-54-8 ✓ |
| **PubChem** (CID) | 4943 |
| **IUPHAR/BPS** | 5464 |
| **DrugBank** | DB00818 ✓ |
| **ChemSpider** | 4774 ✓ |
| **UNII** | YI7VU623SF ✓ |
| **KEGG** | D00549 ✓ |
| **ChEBI** | CHEBI:44915 ✓ |
| **ChEMBL** | CHEMBL526 ✓ |
| **ECHA InfoCard** | 100.016.551 |
| **Chemical and physical data** | |
| **Formula** | $C_{12}H_{18}O$ |
| **Molar mass** | 178.271 g/mol |
| **3D model (Jmol)** | Interactive image |
| **SMILES** | CC(C)c1cccc(c1O)C(C)C |
| **InChI** | InChI=1S/C12H18O/c1-8(2)10-6-5-7-11(9(3)4)12(10)13/h5-9,13H,1-4H3 ✓ Key:OLBCVFGFOZPWHH-UHFFFAOYSA-N ✓ |
| | (verify) |

Recreational use of the drug via self-administration has been reported[20][21] (including among medical professionals, see below), but is relatively rare due to its potency and the level of monitoring required for safe use.[*citation needed*] Critically, the steep dose-response curve of the drug makes potential misuse very dangerous without proper monitoring, and deaths from self-administration continue to be reported.[22][23]

The short-term effects sought via recreational use include mild euphoria, hallucinations, and disinhibition.[24][25] The euphoria caused by propofol has been reported to be unlike that caused by other sedation agents; as one anesthetist reported, "I... remember my first experience using [administering] propofol: a young woman... emerging from a MAC anesthesia looked at me as though I were a masked Brad Pitt and told me that she felt simply wonderful."[26]

Recreational use of the drug has been described among medical staff, such as anesthetists who have access to the drug,[27] and is reportedly more common among anesthetists on rotations with short rest periods (as rousing is to a well-rested state).[28] Long-term use has been reported to result in addiction.[27][29]

Attention to the risks of off-label use of propofol increased in August 2009 due to the Los Angeles County coroner's conclusion that music icon Michael Jackson died from a mixture of propofol and the benzodiazepine drugs lorazepam and diazepam on June 25, 2009, the propofol sometimes administered orally.[30][31][32][33] According to a 22 July 2009 search warrant affidavit unsealed by the district court of Harris County, Texas, Jackson's personal physician, Conrad Murray, administered 25 milligrams of propofol diluted with lidocaine shortly before Jackson's death.[31][32][34] Even so, as of 2016 propofol was not on a U.S Drug Enforcement Administration schedule.[28][35]

## Side effects [edit]

One of propofol's most frequent side effects is pain on injection, especially in smaller veins. This pain arises from activation of the pain receptor, TRPA1,[36] found on sensory nerves and can be mitigated by pretreatment with lidocaine.[37] Less pain is experienced when infused at a slower rate in a large vein (antecubital fossa). Patients show great variability in their response to propofol, at times showing profound sedation with small doses.

Additional side effects include low blood pressure related to vasodilation, transient apnea following induction doses, and cerebrovascular effects. Propofol has more pronounced hemodynamic effects relative to many intravenous anesthetic agents.[38] Reports of blood pressure drops of 30% or more are thought to be at least partially due to inhibition of sympathetic nerve activity.[39] This effect is related to dose and rate of propofol administration. It may also be potentiated by opioid analgesics.[40] Propofol can also cause decreased systemic vascular resistance, myocardial blood flow, and oxygen consumption, possibly through direct vasodilation.[41] There are also reports that it may cause green discolouration of the urine.[42]

As a respiratory depressant, propofol frequently produces apnea. The persistence of apnea can depend on factors such as premedication, dose administered, and rate of administration, and may sometimes persist for longer than 60 seconds.[43] Possibly as the result of depression of the central inspiratory drive, propofol may produce significant decreases in respiratory rate, minute volume, tidal volume, mean inspiratory flow rate, and functional residual capacity.[38]

Diminishing cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure are also characteristics of propofol administration.[44] In addition, propofol may decrease intraocular pressure by as much as 50% in patients with normal intraocular pressure.[45]

A more serious but rare side effect is dystonia.[46] Mild myoclonic movements are common, as with other intravenous hypnotic agents. Propofol appears to be safe for use in porphyria, and has not been known to trigger malignant hyperpyrexia.[*citation needed*]

Propofol is also reported to induce priapism in some individuals,[47][48] and has been observed to suppress REM sleep stage and to worsen the poor sleep quality in some patients.[49]

As with any other general anesthetic agent, propofol should be administered only where appropriately trained staff and facilities for monitoring are available, as well as proper airway management, a supply of supplemental oxygen, artificial ventilation, and cardiovascular resuscitation.[50]

### Propofol infusion syndrome [edit]

*Main article: Propofol infusion syndrome*

Another recently described rare, but serious, side effect is propofol infusion syndrome. This potentially lethal metabolic derangement has been reported in critically ill patients after a prolonged infusion of high-dose substance in combination with catecholamines and/or corticosteroids.[51]

### CBS genetic defects [edit]

People with this gene have trouble processing sulphites (one of the potential ingredients), and should discuss use of this drug with their specialist.

## Interactions [edit]

The respiratory effects of propofol are increased if given with other respiratory depressants, including benzodiazepines.[52]

## Mechanism of action [edit]

Propofol has been proposed to have several mechanisms of action,[53][54][55] both through potentiation of $GABA_A$ receptor activity, thereby slowing the channel-closing time,[56][57][58] and also acting as a sodium channel blocker.[59][60] Recent research has also suggested that the endocannabinoid system may contribute significantly to propofol's anesthetic action and to its unique properties.[61] EEG research upon those undergoing general anesthesia with propofol finds that it causes a prominent reduction in the brain's information integration capacity at gamma wave band frequencies.[62]

Researchers have identified the site where propofol binds to $GABA_A$ receptors in the brain, on the second transmembrane domain of the beta subunit of the GABA $_A$ receptor.[63]

## Pharmacokinetics [edit]

Propofol is highly protein-bound *in vivo* and is metabolised by conjugation in the liver.[64] The half-life of elimination of propofol has been estimated to be between 2 and 24 hours. However, its duration of clinical effect is much shorter, because propofol is rapidly distributed into peripheral tissues. When used for IV sedation, a single dose of propofol typically wears off within minutes. Propofol is versatile; the drug can be given for short or prolonged sedation, as well as for general anesthesia. Its use is not associated with nausea as is often seen with opioid medications. These characteristics of rapid onset and recovery along with its amnestic effects[65] have led to its widespread use for sedation and anesthesia.

## Chemistry [edit]

Propofol was originally developed in the UK by Imperial Chemical Industries as ICI 35868. Clinical trials followed in 1977, using a form solubilised in cremophor EL. However, due to anaphylactic reactions to cremophor, this formulation was withdrawn from the market and subsequently reformulated as an emulsion of a soya oil/propofol mixture in water. The emulsified formulation was relaunched in 1986 by ICI


A 20-ml ampoule of 1% propofol emulsion, as sold in Australia by Sandoz

(now AstraZeneca) under the brand name Diprivan. The currently available preparation is 1% propofol, 10% soybean oil, and 1.2% purified egg phospholipid as an emulsifier, with 2.25% glycerol as a tonicity-adjusting agent, and sodium hydroxide to adjust the pH. Diprivan contains EDTA, a common chelation agent, that also acts alone (bacteriostatically against some bacteria) and synergistically with some other antimicrobial agents. Newer generic formulations contain sodium metabisulfite or benzyl alcohol as antimicrobial agents. Propofol emulsion is a highly opaque white fluid due to the scattering of light from the tiny (about 150-nm) oil droplets it contains.

A water-soluble prodrug form, fospropofol, has recently been developed and tested with positive results. Fospropofol is rapidly broken down by the enzyme alkaline phosphatase to form propofol. Marketed as Lusedra, this new formulation may not produce the pain at injection site that often occurs with the traditional form of the drug. The US Food and Drug Administration approved the product in 2008.[66] However fospropofol is a Schedule IV controlled substance with the DEA ACSCN of 2138 in the United States unlike propofol.[67]

## Society and culture [edit]

### Supply issues [edit]

On 4 June 2010, Teva Pharmaceutical Industries Ltd., an Israel-based pharmaceutical firm and a major supplier of the drug, announced the firm would no longer manufacture it. This aggravates an already existing shortage, caused by manufacturing difficulties at Teva and Hospira. A Teva spokesperson attributed the halt to ongoing process difficulties, and a number of pending lawsuits related to the drug.[68] In Switzerland, various preparations of the drug are supplied by Fresenius-Kabi, a German company.

## Recent developments [edit]

By incorporation of an azobenzene unit, a photoswitchable version of propofol (AP2) was developed in 2012 that allows for optical control of $GABA_A$ receptors with light.[69] In 2013, a propofol binding site on mammalian $GABA_A$ receptors has been identified by photolabeling using a Diazirine derivative.[70] Additionally, it was shown that the hyaluronan polymer present in the synovia can be protected from free-radical synovia by propofol.[71]

Propofol is one of the chemicals used in the manufacture of Avasamibe (ACAT inhibitor).

## References [edit]


1. ^ Ruffle JK (November 2014). "Molecular neurobiology of addiction: what's all the (Δ)FosB about?". *Am J Drug Alcohol Abuse*. **40** (6): 428–437. doi:10.3109/00952990.2014.933840. PMID 25083822. "Propofol is a general anaesthetic, however its abuse for recreational

"Clinical pharmacology of propofol: an intravenous anesthetic agent [published erratum appears in DICP 1990 Jan; 24: 102]". *DICP*. **23**: 743–9.

42. ^ Jung SL, Hyun SJ, Byeong JP (2013). "Green discoloration of urine after propofol infusion". *Korean Journal of Anesthesiology*. **65** (2): 177–9.

purpose has been documented (120). Using control drugs implicated in both ΔFosB induction and addiction (ethanol and nicotine), similar ΔFosB expression was apparent when propofol was given to rats. Moreover, this cascade was shown to act via the dopamine D1 receptor in the NAc, suggesting that propofol has abuse potential (119)"

2. ^ a b c d e f g "Propofol". The American Society of Health-System Pharmacists. Retrieved Jan 2016. Check date values in: |access-date= (help)
3. ^ a b Miner, JR; Burton, JH (Aug 2007). "Clinical practice advisory: Emergency department procedural sedation with propofol". *Annals of Emergency Medicine*. **50** (2): 182–7. doi:10.1016/j.annemergmed.2006.12.017.
4. ^ Wakai, A; Blackburn, C; McCabe, A; Reece, E; O'Connor, G; Glasheen, J; Staunton, P; Cronin, J; Sampson, C; McCoy, SC; O'Sullivan, R; Cummins, F (29 July 2015). "The use of propofol for procedural sedation in emergency departments.". *The Cochrane database of systematic reviews*. **7**: CD007399. doi:10.1002/14651858.CD007399.pub2. PMID 26222247.
5. ^ *Miller's Anesthesia* (8 ed.). Elsevier Health Sciences. 2014. p. 920. ISBN 9780323280112.
6. ^ "WHO Model List of Essential Medicines" (PDF). *World Health Organization*. October 2013. p. 6. Retrieved 22 April 2014.
7. ^ "Propofol". *International Drug Price Indicator Guide*. Retrieved 23 January 2016.
8. ^ Euliano TY, Gravenstein JS (2004). "A brief pharmacology related to anesthesia". *Essential anesthesia: from science to practice*. Cambridge, UK: Cambridge University Press. p. 173. ISBN 0-521-53600-6. Retrieved 2 June 2009.
9. ^ "Anesthesia Medications". *Veterinary Dentistry for the Small Animal Technician*. Hoboken: Wiley. 2013. ISBN 9781118694800.
10. ^ Cox, CE.; Reed, SD.; Govert, JA.; Rodgers, JE.; Campbell-Bright, S.; Kress, JP.; Carson, SS. (March 2008). "Economic evaluation of propofol and lorazepam for critically ill patients undergoing mechanical ventilation.". *Crit Care Med*. **36** (3): 706–14. doi:10.1097/CCM.0B013E3181544248. PMC 2763279. PMID 18176312.
11. ^ McQuaid, KR.; Laine, L. (May 2008). "A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures.". *Gastrointest Endosc*. **67** (6): 910–23. doi:10.1016/j.gie.2007.12.046. PMID 18440381.
12. ^ Canadian National Forumulary 2010
13. ^ Appleton & Lange Nursing Drug Guide, 1999
14. ^ Numorphan® (oxymorphone) package insert (English), Endo 2009
15. ^ Machata, AM; Willschke, H; Kabon, B; Kettner, SC; Marhofer, P (August 2008). "Propofol-based sedation regimen for infants and children undergoing ambulatory magnetic resonance imaging.". *British journal of anaesthesia*. **101** (2): 239–43. doi:10.4097/kjae.2013.65.2.177. PMC 3766788. PMID 24024005.
43. ^ Langley, M; Heel, R (1988). "Propofol. A review of its pharmacodynamic and pharmacokinetic properties and use as an intravenous anaesthetic". *Drugs*. **35**: 334–72. doi:10.2165/00003495-198835040-00002.
44. ^ Bailey, J; Mora, C; Shafer, S (1996). "Pharmacokinetics of propofol in adult patients undergoing coronary revascularization". *Anesthesiology*. **84**: 1288–97. doi:10.1097/00000542-199606000-00003.
45. ^ Reilly, C; Nimmo, W (1987). "New intravenous anaesthetics and neuromuscular blocking drugs. A review of their properties and clinical use". *Drugs*. **34**: 115–9. doi:10.2165/00003495-198734010-00004.
46. ^ Schramm, BM; Orser, BA (2002). "Dystonic reaction to propofol attenuated by benztropine (Cogentin)". *Anesth Analg*. **94**: 1237–40. doi:10.1097/00000539-200205000-00034.
47. ^ Vesta, Kimi; Shaunta' Martina; Ellen Kozlowski (25 April 2009). "Propofol-Induced Priapism, a Case Confirmed with Rechallenge". *The Annals of Pharmacotherapy*. **40** (5): 980–982. doi:10.1345/aph.1G555. PMID 16638914.
48. ^ Fuentes, Ennio; Silvia Garcia; Manuel Garrido; Cristina Lorenzo; Jose Iglesias; Juan Sola (July 2009). "Successful treatment of propofol-induced priapism with distal glans to corporal cavernosal shunt". *Urology*. **74** (1): 113–115. doi:10.1016/j.urology.2008.12.066. PMID 19371930.
49. ^ Eumorfia Kondili; Christina Alexopoulou; Nectaria Xirouchaki; Dimitris Georgopoulos. "Effects of propofol on sleep quality in mechanically ventilated critically ill patients: a physiological study". *Intensive Care Medicine*. **38**: 1640–1646. doi:10.1007/s00134-012-2623-z. Retrieved 2 October 2012.
50. ^ "AstraZeneca - United States Home Page" (PDF). .astrazeneca-us.com. Retrieved 8 June 2013.
51. ^ Vasile B, Rasulo F, Candiani A, Latronico N (2003). "The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome". *Intensive Care Medicine*. **29** (9): 1417–25. doi:10.1007/s00134-003-1905-x. PMID 12904852.
52. ^ Doheny, Kathleen; Louise Chang; Hector Vila Jr (24 August 2009). "Propofol Linked to Michael Jackson's Death". WebMD. Retrieved 26 August 2009.
53. ^ Trapani G, Altomare C, Liso G, Sanna E, Biggio G (February 2000). "Propofol in anesthesia. Mechanism of action, structure-activity relationships, and drug delivery". *Curr. Med. Chem*. **7** (2): 249–71. doi:10.2174/0929867003375335. PMID 10637364.
54. ^ Kotani, Y; Shimazawa, M; Yoshimura, S; Iwama,

doi:10.1093/bja/aen153. PMID 18534971.
16. ^ Yan, JW; McLeod, SL; Iansavitchene, A (20 August 2015). "Ketamine-Propofol Versus Propofol Alone for Procedural Sedation in the Emergency Department: A Systematic Review and Meta-analysis.". *Academic Emergency Medicine*. **22**: 1003–13. doi:10.1111/acem.12737. PMID 26292077.
17. ^ Death Row Improvises, Lacking Lethal Mix, By RICK LYMAN, New York Times, 18 August 2013
18. ^ After EU threats, Missouri halts execution by Propofol injection Al Jazeera America October 12th 2013
19. ^ Article 4A of Export Control Order 2008 - provisions supplementing "the torture Regulation"
20. ^ Riezzo I, Centini F, Neri M, Rossi G, Spanoudaki E, Turillazzi E, Fineschi V (2009). "Brugada-like EKG pattern and myocardial effects in a chronic propofol abuser". *Clin Toxicol (Phila)*. **47** (4): 358–63. doi:10.1080/15563650902887842. PMID 19514884.
21. ^ Belluck, Pam (6 August 2009). "With High-Profile Death, Focus on High-Risk Drug". *New York Times*. Retrieved 7 August 2009.
22. ^ Iwersen-Bergmann S, Rösner P, Kühnau HC, Junge M, Schmoldt A (2001). "Death after excessive propofol abuse". *International Journal of Legal Medicine*. **114** (4–5): 248–51. doi:10.1007/s004149900129. PMID 11355404.
23. ^ Kranioti EF, Mavroforou A, Mylonakis P, Michalodimitrakis M (22 March 2007). "Lethal self-administration of propofol (Diprivan): A case report and review of the literature". *Forensic Science International*. **167** (1): 56–8. doi:10.1016/j.forsciint.2005.12.027. PMID 16431058.
24. ^ In Sweetman SC (Ed.). Martindale: The Complete Drug Reference 2005. 34th Edn London pp. 1305–7
25. ^ Baudoin Z. General anesthetics and anesthetic gases. In Dukes MNG and Aronson JK (Eds.). Meyler's Side Effects of Drugs 2000. 14th Edn Amsterdam pp. 330
26. ^ C.F. Ward, 2008, Propofol: Dancing with a "White Rabbit", CSA Bulletin, pp. 61-63, accessed 24 November 2014.
27. ^ [a] [b] Roussin A, Montastruc JL, Lapeyre-Mestre M (21 October 2007). "Pharmacological and clinical evidences on the potential for abuse and dependence of propofol: a review of the literature". *Fundamental and Clinical Pharmacology*. **21** (5): 459–66. doi:10.1111/j.1472-8206.2007.00497.x. PMID 17868199.
28. ^ [a] [b] Charatan F (2009). "Concerns mount over recreational use of propofol among US healthcare professionals". *BMJ*. **339**: b3673. doi:10.1136/bmj.b3673. PMID 19737827.
29. ^ Bonnet U, Harkener J, Scherbaum N (June 2008). "A case report of propofol dependence in a physician". *J Psychoactive Drugs*. **40** (2): 215–7. doi:10.1080/02791072.2008.10400634.
T; Hara, H (Summer 2008). "The experimental and clinical pharmacology of propofol, an anesthetic agent with neuroprotective properties". *CNS Neuroscience and Therapeutics*. **14** (2): 95–106. doi:10.1111/j.1527-3458.2008.00043.x. PMID 18482023.
55. ^ Vanlersberghe C, Camu F. Propofol. *Handbook of Experimental Pharmacology*. 2008;(182):227-52. doi:10.1007/978-3-540-74806-9_11 PMID 18175094
56. ^ Trapani G, Latrofa A, Franco M, Altomare C, Sanna E, Usala M, Biggio G, Liso G. "Propofol analogues. Synthesis, relationships between structure and affinity at $GABA_A$ receptor in rat brain, and differential electrophysiological profile at recombinant human GABAA receptors. *Journal of Medicinal Chemistry*. 21 May 1998;41(11):1846–54. doi:10.1021/jm970681h PMID 9599235
57. ^ Krasowski MD, Jenkins A, Flood P, Kung AY, Hopfinger AJ, Harrison NL (April 2001). "General anesthetic potencies of a series of propofol analogs correlate with potency for potentiation of gamma-aminobutyric acid (GABA) current at the GABA(A) receptor but not with lipid solubility". *J. Pharmacol. Exp. Ther.* **297** (1): 338–51. PMID 11259561.
58. ^ Krasowski MD, Hong X, Hopfinger AJ, Harrison NL. "4D-QSAR analysis of a set of propofol analogues: mapping binding sites for an anesthetic phenol on the GABA(A) receptor. *Journal of Medicinal Chemistry*. 18 July 2002;45(15):3210–21. doi:10.1021/jm010461a PMID 12109905
59. ^ Haeseler G, Leuwer M (March 2003). "High-affinity block of voltage-operated rat IIA neuronal sodium channels by 2,6 di-tert-butylphenol, a propofol analogue". *Eur J Anaesthesiol*. **20** (3): 220–4. doi:10.1017/s0265021503000371. PMID 12650493.
60. ^ Haeseler, G; Karst, M; Foadi, N; Gudehus, S; Roeder, A; Hecker, H; Dengler, R; Leuwer, M (Sep 2008). "High-affinity blockade of voltage-operated skeletal muscle and neuronal sodium channels by halogenated propofol analogues". *British Journal of Pharmacology*. **155** (2): 265–75. doi:10.1038/bjp.2008.255. PMC 2538694. PMID 18574460.
61. ^ Fowler CJ (February 2004). "Possible involvement of the endocannabinoid system in the actions of three clinically used drugs". *Trends Pharmacol. Sci.* **25** (2): 59–61. doi:10.1016/j.tips.2003.12.001.
62. ^ Lee, U; Mashour, GA; Kim, S; Noh, GJ; Choi, BM (2009). "Propofol induction reduces the capacity for neural information integration: implications for the mechanism of consciousness and general anesthesia". *Conscious Cogn*. **18** (1): 56–64. doi:10.1016/j.concog.2008.10.005. PMID 19054696.
63. ^ http://phys.org/news/2013-09-propofol-discovery-aid-anesthetics.html
64. ^ Favetta P, Degoute CS, Perdrix JP, Dufresne C, Boulieu R, Guitton J (2002). "Propofol metabolites in

PMID 18720673.
30. ^ Moore, Solomon (28 August 2009). "Jackson's Death Ruled a Homicide". *New York Times*.
31. ^ *a b* Surdin, Ashley (25 August 2009). "Coroner Attributes Michael Jackson's Death to Propofol". *The Washington Post*. Retrieved 22 May 2010.
32. ^ *a b* Itzkoff, Dave (24 August 2009). "Coroner's Findings in Jackson Death Revealed". *The New York Times*. Retrieved 22 May 2010.
33. ^ "Jackson's Death: How Dangerous Is Propofol?". *Time*. 25 August 2009. Retrieved 22 May 2010.
34. ^ "Michael Jackson search warrant". Scribd. Retrieved 2015-08-12.
35. ^ DEA may limit drug eyed in Jackson case *Associated Press*. 15 July 2009.
36. ^ "General anesthetics activate a nociceptive ion channel to enhance pain and inflammation". Pnas.org. Retrieved 8 June 2013.
37. ^ "Propofol Drug Information, Professional". m drugs.com. Retrieved 2 January 2007.
38. ^ *a b* Sebel, PS; Lowden, JD (1989). "Propofol: a new intravenous anesthetic". *Anesthesiology*. **71** (2): 260–77. doi:10.1097/00000542-198908000-00015.
39. ^ Robinson, B; Ebert, T; O'Brien, T; et al. "Mechanisms whereby propofol mediates peripheral vasodilation in humans (1997)". *Anesthesiology*. **86**: 64–72. doi:10.1097/00000542-199701000-00010.
40. ^ "New awakening in anaesthesia—at a price". *Lancet*. **8548**: 1469–70. 1987. doi:10.1016/s0140-6736(87)92214-8.
41. ^ Larijani, G; Gratz, I; Afshar, M; et al. (1989). man following propofol induction and maintenance". *British Journal of Anaesthesia*. **88** (5): 653–8. doi:10.1093/bja/88.5.653.
65. ^ Veselis RA, Reinsel RA, Feshchenko VA, Wroński M (October 1997). "The comparative amnestic effects of midazolam, propofol, thiopental, and fentanyl at equisedative concentrations". *Anesthesiology*. **87** (4): 749–64. doi:10.1097/00000542-199710000-00007. PMID 9357875.
66. ^ "Drugs@FDA: FDA Approved Drug Products". Accessdata.fda.gov. Retrieved 8 June 2013.
67. ^ http://www.deadiversion.usdoj.gov/schedules/orangebook/d_cs_drugcode.pdf pp. 3. accessed 23. January 2016
68. ^ "Teva won't make more of powerful sedative.".
69. ^ Stein M, et al. (September 2012). "Azo-Propofols: Photochromic Potentiators of GABAA Receptors". *Angewandte Chemie International Edition*. **51** (42): 15000–4. doi:10.1002/anie.201205475. PMID 22968919.
70. ^ Yip G, Z.-W Chen, Edge C J, Smith E H, Dickinson R, Hohenester, E, Townsend R R, Fuchs K, Sieghart W, Evers A S, Franks N P (September 2013). "A propofol binding site on mammalian GABAAreceptors identified by photolabeling". *Nature Chemical Biology*. **9** (11): 715–720. doi:10.1038/nchembio.1340.
71. ^ Kvam C, Granese D, Flaibani A, Pollesello P, Paoletti S (1993). "Hyaluronan can be protected from free-radical depolymerization by 2, 6-diisopropylphenol, a novel radical scavenger". *Biochem. Biophys. Res. Comm*. **193** (3): 927–33. doi:10.1006/bbrc.1993.1714. PMID 8391811.

## External links [edit]

- Diprivan web site run by AstraZeneca
- Detailed pharmaceutical information
- U.S. National Library of Medicine: Drug Information Portal – Propofol

Wikimedia Commons has media related to *Propofol*.

| v · t · e · | **General anesthetics (N01A)** | |
|---|---|---|
| **Inhalational** | Chloroethane (ethyl chloride)‡ · Chloroform‡ · Cyclopropane‡ · Desflurane · Diethyl ether‡ · Enflurane · Ethylene‡ · Fluroxene‡ · Halothane# · Isoflurane · Methoxyflurane · Methoxypropane‡ · Nitrous oxide# · Sevoflurane · Trichloroethylene‡ · Vinyl ether‡ · Xenon · | |
| **Injection** | **Phenols** | Fospropofol · **Propofol** · |
| | **Opioids** | Morphine · Oxycodone · Anileridine‡ · Embutramide‡ · Fentanyl · Alfentanil · Phenoperidine · Remifentanil · Sufentanil · |
| | **Arylcyclohexylamines** | Esketamine · Ketamine# · Phencyclidine‡ · Tiletamine · |
| | **Others** | Alfadolone · Alfaxalone · Hydroxydione · Propanidid‡ · |
| · #WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · · | | |

| v · t · e · | **Hypnotics/sedatives (N05C)** |
|---|---|

| | | |
|---|---|---|
| **$GABA_A$** | **Alcohols** | 2M2B · Chloralodol · Ethanol (Alcohol · · Ethchlorvynol · Methylpentynol · Trichloroethanol · |
| | **Barbiturates** | Allobarbital · Amobarbital · Aprobarbital · Barbital · Butabarbital · Butobarbital · Cyclobarbital · Ethallobarbital · Heptabarb · Hexobarbital · Mephobarbital · Methohexital · Narcobarbital · Pentobarbital · Phenallymal · Phenobarbital · Propylbarbital · Proxibarbal · Reposal · Secobarbital · Talbutal · Thiamylal · Thiopental · Thiotetrabarbital · Vinbarbital · Vinylbital · |
| | **Benzodiazepines** | Brotizolam · Cinolazepam · Climazolam · Doxefazepam · Estazolam · Flunitrazepam · Flurazepam · Flutoprazepam · Haloxazolam · Loprazolam · Lormetazepam · Midazolam · Nimetazepam · Nitrazepam · Phenazepam · Quazepam · Temazepam · Triazolam · |
| | **Carbamates** | Carisoprodol · Emylcamate · Ethinamate · Hexapropymate · Meprobamate · Methocarbamol · Phenprobamate · Procymate · Tybamate · |
| | **Imidazoles** | Etomidate · Metomidate · Propoxate · |
| | **Monoureides** | Acecarbromal · Apronal (apronalide) · Bromisoval · Capuride · Carbromal · Ectylurea · |
| | **Neuroactive steroids** | Acebrochol · Allopregnanolone · Alphadolone · Alphaxolone · Eltanolone · Hydroxydione · Minaxolone · Progesterone · |
| | **Nonbenzodiazepines** | Eszopiclone · Indiplon · Lirequinil · Necopidem · Pazinaclone · Saripidem · Suproclone · Suriclone · Zaleplon · Zolpidem · Zopiclone · |
| | **Piperidinediones** | Glutethimide · Methyprylon · Pyrithyldione · Piperidione · |
| | **Quinazolinones** | Afloqualone · Cloroqualone · Diproqualone · Etaqualone · Mebroqualone · Mecloqualone · Methaqualone · Methylmethaqualone · Nitromethaqualone · |
| | **Others** | Acetophenone · Acetylglycinamide chloral hydrate · Bromide compounds (Lithium bromide · Potassium bromide · Sodium bromide · · Centalun · Chloral betaine · Chloral hydrate · Chloralose · Clomethiazole · Dichloralphenazone · Gaboxadol · Kavalactones · Loreclezole · Paraldehyde · Petrichloral · Sulfonylalkanes (Sulfonmethane (sulfonal) · Tetronal · Trional · · Triclofos · Sesquiterpene (Isovaleramide · Isovaleric acid · Valerenic acid · · |
| **$GABA_B$** | | 1,4-Butanediol · Aceburic acid · Baclofen · GABOB · GHB (sodium oxybate) · GBL · GVL · Phenibut · Tolibut · |
| **$H_1$** | **Antihistamines** | Captodiame · Cyproheptadine · Diphenhydramine · Doxylamine · Hydroxyzine · Methapyrilene · Pheniramine · Promethazine · Propiomazine · |
| | **Antidepressants** | Tricyclic antidepressants (Amitriptyline · Doxepin · Trimipramine, etc. · · Tetracyclic antidepressants (Mianserin · Mirtazapine, etc. · · |
| | **Antipsychotics** | Typical antipsychotics (Chlorpromazine · Thioridazine, etc. · · Atypical antipsychotics (Olanzapine · Quetiapine · Risperidone, etc. · · |
| **$\alpha_2$-Adrenergic** | | Clonidine · Detomidine · Dexmedetomidine · Lofexidine · Medetomidine · Romifidine · Tizanidine · |

| | | |
|---|---|---|
| | | Xylazine · |
| **5-HT$_{2A}$** | **Antidepressants** | Trazodone · Tricyclic antidepressants (Amitriptyline · Doxepin · Trimipramine, etc. · · Tetracyclic antidepressants (Mianserin · Mirtazapine, etc. · · |
| | **Antipsychotics** | Typical antipsychotics (Chlorpromazine · Thioridazine, etc. · · Atypical antipsychotics (Olanzapine · Quetiapine · Risperidone, etc. · · |
| | **Others** | Niaprazine · |
| **Melatonin** | | Agomelatine · Melatonin · Ramelteon · Tasimelteon · |
| **Orexin** | | Almorexant · Filorexant · Suvorexant · |
| **Others** | | Cannabidiol (Cannabis · · Chlorophenylalkyldiols (Fenpentadiol · Metaglycodol · Phenaglycodol · · Diethylpropanediol · Evoxine · Fenadiazole · Gabapentinoids (Gabapentin · Gabapentin enacarbil · Phenibut · Pregabalin · · Guaifenesin-related muscle relaxants (Chlorphenesin · Mephenesin · Mephenoxalone · Metaxalone · Methocarbamol · · Passion flower · Scopolamine · Trazodone · UMB68 · Valnoctamide · |

| v · t · e · | **GABA$_A$ receptor positive allosteric modulators** |
|---|---|
| **Alcohols** | Brometone · Butanol · Chloralodol · Chlorobutanol (cloretone) · Ethanol (drinking alcohol) · Ethchlorvynol · Isobutanol · Isopropanol · Menthol · Methanol · Methylpentynol · Pentanol · Petrichloral · Propanol · *tert*-Butanol (2M2P) · *tert*-Pentanol (2M2B) · Tribromoethanol · Trichloroethanol · Triclofos · Trifluoroethanol · |
| **Barbiturates** | (-)-DMBB · Allobarbital · Alphenal · Amobarbital · Aprobarbital · Barbexaclone · Barbital · Benzobarbital · Benzylbutylbarbiturate · Brallobarbital · Brophebarbital · Butabarbital/Secbutabarbital · Butalbital · Buthalital · Butobarbital · Butallylonal · Carbubarb · CP-1414S · Crotylbarbital · Cyclobarbital · Cyclopentobarbital · Difebarbamate · Enallylpropymal · Ethallobarbital · Eterobarb · Febarbamate · Heptabarb · Heptobarbital · Hexethal · Hexobarbital · Metharbital · Methitural · Methohexital · Methylphenobarbital · Narcobarbital · Nealbarbital · Pentobarbital · Phenallymal · Phenobarbital · Phetharbital · Primidone · Probarbital · Propallylonal · Propylbarbital · Proxibarbital · Reposal · Secobarbital · Sigmodal · Spirobarbital · Talbutal · Tetrabamate · Tetrabarbital · Thialbarbital · Thiamylal · Thiobarbital · Thiobutabarbital · Thiopental · Thiotetrabarbital · Valofane · Vinbarbital · Vinylbital · |
| **Benzodiazepines** | 2-Oxoquazepam · 3-Hydroxyphenazepam · Adinazolam · Alprazolam · Arfendazam · Avizafone · Bentazepam · Bretazenil · Bromazepam · Brotizolam · Camazepam · Carburazepam · Chlordiazepoxide · Ciclotizolam · Cinazepam · Cinolazepam · Clazolam · Climazolam · Clobazam · Clonazepam · Clonazolam · Clorazepate · Clotiazepam · Cloxazolam · Cyprazepam · Delorazepam · Demoxepam · Diazepam · Diclazepam · Doxefazepam · Elfazepam · Estazolam · Ethyl carfluzepate · Ethyl dirazepate · Ethyl loflazepate · Etizolam · EVT-201 · FG-8205 · Fletazepam · Flubromazepam · Flubromazolam · Fludiazepam · Flunitrazepam · Flurazepam · Flutazolam · Flutemazepam · Flutoprazepam · Fosazepam · Gidazepam · Halazepam · Haloxazolam · Iclazepam · Imidazenil · Irazepine · Ketazolam · Lofendazam · Lopirazepam · Loprazolam · Lorazepam · Lormetazepam · Meclonazepam · Medazepam · Menitrazepam · Metaclazepam · Mexazolam · Midazolam · Motrazepam · N-Desalkylflurazepam · Nifoxipam · Nimetazepam · Nitrazepam · Nitrazepate · Nitrazolam · Nordazepam · Nortetrazepam · Oxazepam · Oxazolam · Phenazepam · Pinazepam · Pivoxazepam · Prazepam · Premazepam · Proflazepam · Pyrazolam · QH-II-66 · Quazepam · |

| | |
|---|---|
| | Reclazepam · Remimazolam · Rilmazafone · Ripazepam · Ro48-6791 · Ro48-8684 · SH-053-R-CH3-2′F · Sulazepam · Temazepam · Tetrazepam · Tolufazepam · Triazolam · Triflubazam · Triflunordazepam (Ro5-2904) · Tuclazepam · Uldazepam · Zapizolam · Zolazepam · Zomebazam · |
| **Carbamates** | Carisbamate · Carisoprodol · Clocental · Cyclarbamate · Difebarbamate · Emylcamate · Ethinamate · Febarbamate · Felbamate · Hexapropymate · Lorbamate · Mebutamate · Meprobamate · Nisobamate · Pentabamate · Phenprobamate · Procymate · Styramate · Tetrabamate · Tybamate · |
| **Flavonoids** | 6-Methylapigenin · Ampelopsin (dihydromyricetin) · Apigenin · Baicalein · Baicalin · Catechin · EGC · EGCG · Hispidulin · Linarin · Luteolin · Rc-OMe · Skullcap constituents (e.g., baicalin) · Wogonin · |
| **Imidazoles** | Etomidate · Metomidate · Propoxate · |
| **Kava constituents** | 10-Methoxyyangonin · 11-Methoxyyangonin · 11-Hydroxyyangonin · Desmethoxyyangonin · 11-Methoxy-12-hydroxydehydrokavain · 7,8-Dihydroyangonin · Kavain · 5-Hydroxykavain · 5,6-Dihydroyangonin · 7,8-Dihydrokavain · 5,6,7,8-Tetrahydroyangonin · 5,6-Dehydromethysticin · Methysticin · 7,8-Dihydromethysticin · Yangonin · |
| **Monoureides** | Acecarbromal · Apronal (apronalide) · Bromisoval · Carbromal · Capuride · Ectylurea · |
| **Neuroactive steroids** | Acebrochol · Allopregnanolone (SAGE-547) · Alfadolone · Alfaxalone · Anabolic steroids · 3α-Androstanediol · Androstenol · Androsterone · Cholesterol · DHDOC · 3α-DHP · 5α-DHP · 5β-DHP · DHT · Etiocholanolone · Ganaxolone · Hydroxydione · Minaxolone · Org 20599 · Org 21465 · P1-185 · Pregnanolone (eltanolone) · Progesterone · Renanolone · SAGE-105 · SAGE-217 · SAGE-324 · SAGE-516 · SAGE-689 · SAGE-872 · Testosterone · THDOC · |
| **Nonbenzodiazepines** | **β-Carbolines**: Abecarnil · Gedocarnil · Harmane · SL-651,498 · ZK-93423; **Cyclopyrrolones**: Eszopiclone · Pagoclone · Pazinaclone · Suproclone · Suriclone · Zopiclone; **Imidazopyridines**: Alpidem · DS-1 · Necopidem · Saripidem · Zolpidem; **Pyrazolopyrimidines**: Divaplon · Fasiplon · Indiplon · Lorediplon · Ocinaplon · Panadiplon · Taniplon · Zaleplon; **Others**: Adipiplon · CGS-8216 · CGS-9896 · CGS-13767 · CGS-20625 · CL-218,872 · CP-615,003 · CTP-354 · ELB-139 · GBLD-345 · JM-1232 · L-838,417 · Lirequinil (Ro41-3696) · NS-2664 · NS-2710 · NS-11394 · Pipequaline · ROD-188 · RWJ-51204 · SB-205,384 · SX-3228 · TGSC01AA · TP-003 · TPA-023 · TP-13 · U-89843A · U-90042 · Viqualine · Y-23684 · |
| **Phenols** | Fospropofol · **Propofol** · Thymol · |
| **Piperidinediones** | Glutethimide · Methyprylon · Piperidione · Pyrithyldione · |
| **Pyrazolopyridines** | Cartazolate · Etazolate · ICI-190,622 · Tracazolate · |
| **Quinazolinones** | Afloqualone · Cloroqualone · Diproqualone · Etaqualone · Mebroqualone · Mecloqualone · Methaqualone · Methylmethaqualone · Nitromethaqualone · SL-164 · |
| **Volatiles/gases** | Acetone · Acetophenone · Acetylglycinamide chloral hydrate · Aliflurane · Benzene · Butane · Butylene · Centalun · Chloral · Chloral betaine · Chloral hydrate · Chloroform · Cryofluorane · Desflurane · Dichloralphenazone · Dichloromethane · Diethyl ether · Enflurane · Ethyl chloride · Ethylene · Fluroxene · Gasoline · Halopropane · Halothane · Isoflurane · Kerosine · Methoxyflurane · Methoxypropane · Nitric oxide · Nitrogen · Nitrous oxide · Norflurane · Paraldehyde · Propane · Propylene · Roflurane · Sevoflurane · Synthane · Teflurane · Toluene · Trichloroethane (methyl chloroform) · Trichloroethylene · Vinyl ether · |

| | |
|---|---|
| **Others/unsorted** | 3-Hydroxybutanal · α-EMTBL · AA-29504 · Avermectins (e.g., ivermectin) · Bromide compounds (e.g., lithium bromide, potassium bromide, sodium bromide) · Carbamazepine · Chloralose · Chlormezanone · Clomethiazole · DEABL · Dihydroergolines (e.g., dihydroergocryptine, dihydroergosine, dihydroergotamine, ergoloid (dihydroergotoxine)) · DS2 · Efavirenz · Etazepine · Etifoxine · Fenamates (e.g., flufenamic acid, mefenamic acid, niflumic acid, tolfenamic acid) · Fluoxetine · Flupirtine · Hopantenic acid · Lanthanum · Lavender oil · Lignans (e.g., 4-O-methylhonokiol, honokiol, magnolol, obovatol) · Loreclezole · Menthyl isovalerate (validolum) · Monastrol · Niacin · Nicotinamide (niacinamide) · Org 25,435 · Phenytoin · Propanidid · Retigabine (ezogabine) · Safranal · Seproxetine · Stiripentol · Sulfonylalkanes (e.g., sulfonmethane (sulfonal), tetronal, trional) · Terpenoids (e.g., borneol) · Topiramate · Valerian constituents (e.g., isovaleric acid, isovaleramide, valerenic acid, valerenol) · **Unsorted benzodiazepine site PAMs:** MRK-409 (MK-0343) · TCS-1105 · TCS-1205 · |
| *See also: GABAergics* | |

| v · t · e · | **Glycinergics** |
|---|---|
| **Receptor (ligands)** | **GlyR** |
| | **Agonists:** β-Alanine · β-ABA (BABA) · β-AIBA · Caesium · D-Alanine · D-Serine · GABA · Glycine · Hypotaurine · Ivermectin · L-Alanine · L-Proline · L-Serine · L-Threonine · MDL-27531 · Milacemide · Picolinic acid · **Propofol** · Quisqualamine · Sarcosine · Taurine · |
| | **PAMs:** Alcohols (e.g., brometone, chlorobutanol (chloretone), ethanol, *tert*-butanol (2M2P), tribromoethanol, trichloroethanol, trifluoroethanol) · Alkylbenzene sulfonate · Anandamide · Barbiturates (e.g., pentobarbital, sodium thiopental) · Chlormethiazole · D12-116 · Dihydropyridines (e.g., nicardipine) · Etomidate · Ginseng constituents (e.g., ginsenosides (e.g., ginsenoside-Rf)) · Glutamic acid (glutamate) · Ivermectin · Ketamine · Neuroactive steroids (e.g., alfaxolone, pregnenolone (eltanolone), pregnenolone acetate, minaxolone, Org 20599) · Nitrous oxide · Penicillin G · **Propofol** · Tamoxifen · Tetrahydrocannabinol · Triclofos · Tropeines (e.g., atropine, bemesetron, cocaine, LY-278584, tropisetron, zatosetron) · Volatiles/gases (e.g., chloral hydrate, chloroform, desflurane, diethyl ether (ether), enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, toluene, trichloroethane (methyl chloroform), trichloroethylene) · Xenon · Zinc · |
| | **Antagonists:** 2-Aminostrychnine · 2-Nitrostrychnine · 4-Phenyl-4-formyl-N-methylpiperidine · αEMBTL · Bicuculline · Brucine · Cacotheline · Caffeine · Colchicine · Colubrine · Cyanotriphenylborate · Dendrobine · Diaboline · Endocannabinoids (e.g., 2-AG, anandamide (AEA)) · Gaboxadol (THIP) · Gelsemine · iso-THAZ · Isobutyric acid · Isonipecotic acid · Isostrychnine · Laudanosine · N-Methylbicuculline · N-Methylstrychnine · N,N-Dimethylmuscimol · Nipecotic acid · Pitrazepin · Pseudostrychnine · Quinolines (e.g., 4-hydroxyquinoline, 4-hydroxyquinoline-3-carboxylic acid, 5,7-CIQA, 7-CIQ, 7-TFQ, 7-TFQA) · RU-5135 · Sinomenine · Strychnine · Thiocolchicoside · Tutin · |
| | **NAMs:** Amiloride · Benzodiazepines (e.g., bromazepam, clonazepam, diazepam, flunitrazepam, flurazepam) · Corymine · Cyanotriphenylborate · Daidzein · Dihydropyridines (e.g., nicardipine, nifedipine, nitrendipine) · Furosemide · Genistein · Ginkgo constituents (e.g., bilobalide, ginkgolides (e.g., ginkgolide A, ginkgolide B, ginkgolide C, ginkgolide J, ginkgolide M)) · Imipramine · NBQX · Neuroactive steroids (e.g., 3α-androsterone sulfate, 3β-androsterone sulfate, deoxycorticosterone, DHEA sulfate, pregnenolone sulfate, progesterone) · Opioids (e.g., codeine, dextromethorphan, dextrorphan, levomethadone, |

| | | |
|---|---|---|
| | | levorphanol, morphine, oripavine, pethidine, thebaine) · Picrotoxin (i.e., picrotin and picrotoxinin) · PMBA · Riluzole · Tropeines (e.g., bemesetron, LY-278584, tropisetron, zatosetron) · Verapamil · Zinc · |
| **Transporter (blockers)** | **GlyT1** | ACPPB · ALX-1393 · ALX-5407 (NFPS) · AMG-747 · ASP2535 · Bitopertin (RG1678/RO4917838) · CP-802079 · Ethanol · Glycyldodecylamide · GSK1018921 · LY-2365109 · Org 24598 · Org 25935 (SCH-900435) · PF-02545920 · PF-03463275 · PF-04958242 · Sarcosine · SSR-103,800 · SSR-504,734 · |
| | **GlyT2** | Amoxapine · Ethanol · NAGly · Org 25543 · |
| **Others** | **Precursors:** 3-PG · GHB · L-Serine · L-Theonine · **Cofactors:** Vitamin $B_6$ · | |

*See also: GABAergics • GHBergics • Glutamatergics*

| V · T · E · | **AstraZeneca** |
|---|---|
| **Products** | Anastrozole · Atenolol · Bicalutamide · Brompheniramine · Budesonide · Disufenton sodium · Esomeprazole · FluMist · Fulvestrant · Gefitinib · Goserelin · Isosorbide mononitrate · Motavizumab · Omeprazole · Palivizumab · **Propofol** · Rosuvastatin · Tamoxifen · Ticagrelor · Vandetanib · Ximelagatran · Zafirlukast · Zolmitriptan · |
| **Predecessors and acquired companies** | Astra AB · Cambridge Antibody Technology · MedImmune · Zeneca · |
| **People** | Tom McKillop · Louis Schweitzer · |
| **Category · Commons ·** | |

Categories: AstraZeneca | Chemical substances for emergency medicine | General anesthetics | GABAA receptor positive allosteric modulators | GABAA receptor agonists | Glycine receptor agonists | Alkylphenols | World Health Organization essential medicines

# Salbutamol

From Wikipedia, the free encyclopedia

**Salbutamol**, also known as **albuterol** and marketed as **Ventolin** among other names,[1] is a medication that opens up the medium and large airways in the lungs.[3] It is used to treat asthma, exercise-induced bronchospasm, and chronic obstructive pulmonary disease (COPD).[3] It may also be used to treat high blood potassium levels.[4] It is usually used by inhaler or nebulizer but is also available as a pill and intravenous solution.[3][5] Onset of action of the inhaled version is typically within 15 minutes and lasts for two to six hours.[3]

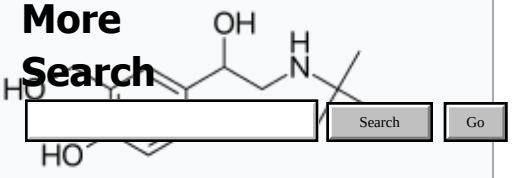
Common side effects include shakiness, headache, fast heart rate, dizziness, and feeling anxious. Serious side effects may include worsening bronchospasm, irregular heartbeat, and low blood potassium levels.[3] It can be used during pregnancy and breastfeeding, but safety is not entirely clear.[3][6] Salbutamol is a short-acting $\beta_2$ adrenergic receptor agonist which works by causing airway smooth muscles to relax.[3]

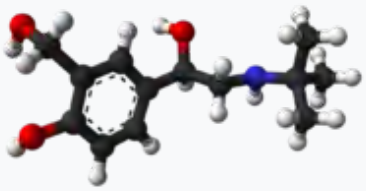
Salbutamol was first made in 1967 in Britain.[7] It was approved for medical use in the United States in 1982.[3] It is on the World Health Organization's List of Essential Medicines, the most important medication needed in a basic health system.[8] It is available as a generic medication.[3] The wholesale cost in the developing world of an inhaler which contains 200 doses is between $1.12 and $2.64 (USD) as of 2014.[9] In the United States it is between $25 and $50 for a typical month supply.[10]

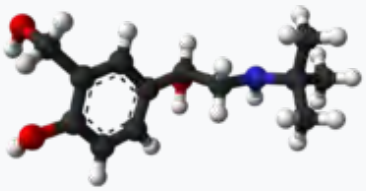
Contents



**Salbutamol**





Salbutamol (top),
(*R*)-(−)-salbutamol (center) and
(*S*)-(+)-salbutamol (bottom)

| Clinical data | |
|---|---|
| **Trade names** | Ventolin, Proventil, others[1] |
| **AHFS / Drugs.com** | Monograph |
| **License data** | US FDA: Albuterol |
| **Pregnancy category** | AU: A<br>US: C (Risk not ruled out) |
| **Routes of administration** | Oral, inhalational, IV |
| **ATC code** | R03AC02 (WHO)<br>R03CC02 (WHO) |
| **Legal status** | |
| **Legal status** | AU: S3 (Pharmacist only)<br>CA: F (prescription)[2]<br>UK: POM (Prescription only)<br>US: -only |

# Medical uses [edit]

Salbutamol is typically used to treat bronchospasm (due to any cause, allergen asthma or exercise-induced), as well as chronic obstructive pulmonary disease.[11]

As a $\beta_2$ agonist, salbutamol also finds use in obstetrics. Intravenous salbutamol can be used as a tocolytic to relax the uterine smooth muscle to delay premature labor. While preferred over agents such as atosiban and ritodrine, its role has largely been replaced by the calcium channel blocker nifedipine, which is more effective, better tolerated and orally administered.[12]

Salbutamol has been used to treat acute hyperkalemia, as it stimulates potassium flow into cells thus lowering the level in the blood.[4]

# Adverse effects [edit]

The most common side effects are fine tremor, anxiety, headache, muscle cramps, dry mouth, and palpitation.[13] Other symptoms may include tachycardia, arrhythmia, flushing, myocardial ischemia (rare), and disturbances of sleep and behaviour.[13] Rarely occurring, but of importance, are allergic reactions of paradoxical bronchospasm, urticaria, angioedema, hypotension, and collapse. High doses or prolonged use may cause hypokalaemia, which is of concern especially in patients with renal failure and those on certain diuretics and xanthine derivatives.[13]

# Chemistry [edit]

## Structure and activity [edit]

This drug is sold as a racemic mixture. The (*R*)-(−)-enantiomer (CIP nomenclature) is shown in the image at right (top), and is responsible for the pharmacologic activity; the (*S*)-(+)-enantiomer (bottom) blocks metabolic pathways associated with elimination of itself and of the pharmacologically active enantiomer (*R*).[14]

With regard to structure-activity relationships, the tertiary butyl group in salbutamol makes it more selective for $\beta_2$ receptors.[*citation needed*]

## Detection after dosing [edit]

Salbutamol may be quantified in blood or plasma; practical needs for this include to confirm a diagnosis of poisoning in hospitalized patients, or to aid in a forensic investigation.[*citation needed*] As well, urinary salbutamol concentrations are frequently measured in competitive sports programs, for which a level in excess of 1000 μg/L is considered to represent abuse.[*citation needed*]

The window of detection for urine testing is on the order of just 24 hours,

| Pharmacokinetic data | |
|---|---|
| **Metabolism** | Liver |
| **Onset of action** | <15 min (inhaled), <30 min (pill)[3] |
| **Biological half-life** | 3.8–6 hours |
| **Duration of action** | 2–6 hrs[3] |
| **Excretion** | Kidney |

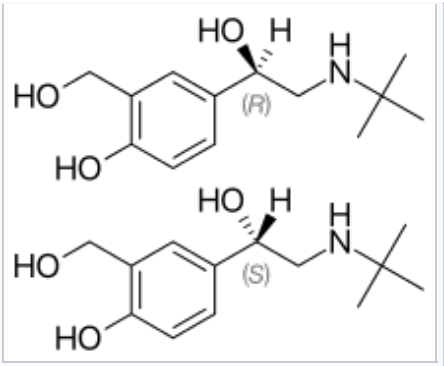
| Identifiers | |
|---|---|
| **IUPAC name** | (*RS*)-4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol |
| **CAS Number** | 18559-94-9 ✓ |
| **PubChem** (CID) | 2083 |
| **IUPHAR/BPS** | 558 |
| **DrugBank** | DB01001 ✗ |
| **ChemSpider** | 1999 ✓ |
| **UNII** | QF8SVZ843E ✓ |
| **KEGG** | D02147 ✓ |
| **ChEBI** | CHEBI:2549 ✗ |
| **ChEMBL** | CHEMBL714 ✓ |
| **ECHA InfoCard** | 100.038.552 |

| Chemical and physical data | |
|---|---|
| **Formula** | $C_{13}H_{21}NO_3$ |
| **Molar mass** | 239.311 g/mol |
| **3D model (Jmol)** | Interactive image |
| **Chirality** | Racemic mixture |

**SMILES**
OCc1cc(ccc1O)C(O)CNC(C)(C)C

**InChI**
InChI=1S/C13H21NO3/c1-13(2,3)14-7-12(17)9-4-5-11(16)10(6-9)8-15/h4-6,12,14-17H,7-8H2,1-3H3 ✓
Key:NDAUXUAQIAJITI-UHFFFAOYSA-N ✓

✗✓ (what is this?) (verify)



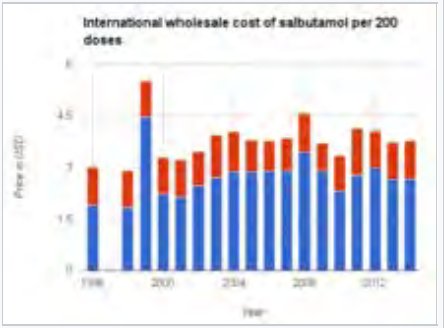

(*R*)-(−)-salbutamol (top) and (*S*)-(+)-salbutamol (bottom)

given the relatively short elimination half-life of the drug,[15][16][17] estimated at between 5 and 6 hours following oral administration of 4 mg.[18]

## Society and culture [edit]

### Cost [edit]

The wholesale cost of an inhaler which contains 200 doses is between $1.12 and $2.64 (USD) in the developing world as of 2014.[9] In the United Kingdom the wholesale price of an inhaler which contains 200 doses is GB£1.50 as of 2015.[19] In the United States a typical month supply is between $25 and $50.[10]



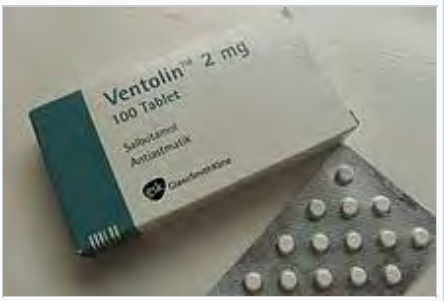

International wholesale price of 200 doses of salbutamol[9]

In some countries compliance with the Montreal Protocol, which requires the banning of the use of ozone-layer depleting CFCs, has caused the price of inhalers to increase as much as ten-fold, as generics have been forced off the market from 2009 to 2013 by new patents obtained by pharmaceutical companies for non-CFC delivery systems.[*citation needed*]

### Names [edit]

Salbutamol is the INN while albuterol is the USAN. The drug is usually manufactured and distributed as the sulfate salt (salbutamol sulfate).

It was first sold by Allen & Hanburys (UK) under the brand name Ventolin, and has been used for the treatment of asthma ever since.[20] The drug is marketed under many names worldwide.[1]




Ventolin 2 mg tablets made by GSK (Turkey)

### Doping [edit]

There is no compelling evidence that salbutamol and other $\beta_2$ agonists can increase performance in healthy athletes.[21] In spite of this, salbutamol required "a declaration of Use in accordance with the International Standard for Therapeutic Use Exemptions" under the 2010 WADA prohibited list. This requirement was relaxed when the 2011 list was published to permit the use of "salbutamol (maximum 1600 micrograms over 24 hours) and salmeterol when taken by inhalation in accordance with the manufacturers' recommended therapeutic regimen."[22][23]

According to two small and limited studies, performed on eight and 16 subjects, respectively, salbutamol increases performance on endurance exercise even for a person without asthma.[24][25][26]

Another study contradicts the above findings, however. The double blind, randomised test conducted on 12 non-asthmatic athletes concluded that salbutamol had a negligible effect on endurance performance. Nevertheless, the study also showed that the drug's bronchodilating effect may have improved respiratory adaptation at the beginning of exercise.[27]

Salbutamol has been shown to improve muscle weight in rats[28] and anecdotal reports hypothesise that it

might be an alternative to clenbuterol for purposes of fat burning and muscle gain, with multiple studies supporting this claim.[29][30][31][32][33] Abuse of the drug may be confirmed by detection of its presence in plasma or urine, typically exceeding 1000 µg/L.[15]

## History [edit]

Salbutamol was discovered in 1966 by a team led by David Jack at the Allen and Hanburys laboratory (a subsidiary of Glaxo) in Ware, Hertfordshire, England, and was launched as Ventolin in 1969.[34]

## Research [edit]

Salbutamol has also been tested in a trial aimed at treatment of spinal muscular atrophy; it is speculated to modulate the alternative splicing of the *SMN2* gene, increasing the amount of the SMN protein whose deficiency is regarded as a cause of the disease.[35][36]

It has been studied in subtypes of congenital myasthenic syndrome associated with mutations in *Dok-7*.[37]

## See also [edit]

- Levosalbutamol — the (*R*)-(−)-enantiomer
- Ipratropium/salbutamol
- Salmeterol
- Isoprenaline

## References [edit]


1. ^ a b c Drugs.com International brands of salbutamol Page accessed April 11, 2016
2. ^ Health Canada
3. ^ a b c d e f g h i j k "Albuterol". The American Society of Health-System Pharmacists. Retrieved Dec 2, 2015.
4. ^ a b Mahoney, BA; Smith, WA; Lo, DS; Tsoi, K; Tonelli, M; Clase, CM (18 April 2005). "Emergency interventions for hyperkalaemia.". *The Cochrane database of systematic reviews* (2): CD003235. doi:10.1002/14651858.CD003235.pub2. PMID 15846652.
5. ^ Starkey, ES; Mulla, H; Sammons, HM; Pandya, HC (September 2014). "Intravenous salbutamol for childhood asthma: evidence-based medicine?". *Archives of Disease in Childhood*. **99** (9): 873–7. doi:10.1136/archdischild-2013-304467. PMID 24938536.
6. ^ Yaffe, Sumner J. (2011). *Drugs in pregnancy and lactation : a reference guide to fetal and neonatal risk* (9th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 32. ISBN 9781608317080.
7. ^ Landau, Ralph (1999). *Pharmaceutical innovation : revolutionizing human health*. Philadelphia: Chemical Heritage Press. p. 226. ISBN 9780941901215.
8. ^ "WHO Model List of Essential Medicines" (PDF). *World Health Organization*. October 2013. Retrieved 22 April 2014.
9. ^ a b c "Salbutamol". *International Drug Price Indicator Guide*. Retrieved 5 December 2015.
10. ^ a b Hamilton, Richart (2015). *Tarascon Pocket Pharmacopoeia 2015 Deluxe Lab-Coat Edition*. Jones & Bartlett Learning. p. 448. ISBN 9781284057560.
11. ^ "Albuterol". *The American Society of Health-System Pharmacists*. Retrieved 3 April 2011.
12. ^ Rossi, S (2004). *Australian Medicines Handbook*. AMH. ISBN 0-9578521-4-2.
13. ^ a b c "3.1.1.1 Selective beta2 agonists – side effects". *British National Formulary* (57 ed.). London: BMJ Publishing Group Ltd and Royal Pharmaceutical Society Publishing. March 2008. ISBN 0-85369-778-7.
14. ^ Mehta, Akul. [The tertiary butyl group in salbutamol (or albuterol) makes it more selective for $\beta_2$ receptors. http://pharmaxchange.info/notes/medicinal_chemistry/adrenergics_cholinergics.html "Medicinal Chemistry of the Peripheral Nervous System – Adrenergics and Cholinergics their Biosynthesis, Metabolism, and Structure Activity Relationships"] Check |url= value (help). Retrieved 2010-10-20.
15. ^ a b Baselt, R. (2008). *Disposition of Toxic Drugs and Chemicals in Man* (8th ed.). Biomedical Publications. pp. 33–35. ISBN 0-9626523-6-9.

16. ^ Berges, Rosa; S; V; F; M; F; M; D (2000). "Discrimination of Prohibited Oral Use of Salbutamol from Authorized Inhaled Asthma Treatment". *Clinical Chemistry*. **46** (9): 1365–75. PMID 10973867.
17. ^ Schweizer, C; Saugy, M; Kamber, M (2004). "Doping test reveals high concentrations of salbutamol in a Swiss track and field athlete". *Clin. J. Sport Med.* **14** (5): 312–315. doi:10.1097/00042752-200409000-00018. PMID 15377972. |first4= missing |last4= in Authors list (help)
18. ^ "Albuterol Sulfate", *Rx List: The Internet Drug Index*, 6/12/2008, retrieved 2014-07-13 Check date values in: |date= (help)
19. ^ *BNF 69: March 2015 - September 2015* (69 ed.). Pharmaceutical Pr. March 31, 2015. p. 190. ISBN 9780857111562.
20. ^ "Ventolin remains a breath of fresh air for asthma sufferers, after 40 years" (PDF). *The Pharmaceutical Journal*. **279** (7473): 404–405. Archived from the original (PDF) on Oct 15, 2007.
21. ^ Davis, E; Loiacono, R; Summers, R J (2008). "The rush to adrenaline: drugs in sport acting on the β-adrenergic system". *British Journal of Pharmacology*. **154** (3): 584–97. doi:10.1038/bjp.2008.164. PMC 2439523. PMID 18500380.
22. ^ "THE 2010 PROHIBITED LIST INTERNATIONAL STANDARD" (PDF). WADA. Retrieved 2010-10-20.
23. ^ "THE 2011 PROHIBITED LIST INTERNATIONAL STANDARD" (PDF). WADA. Retrieved 2012-05-22.
24. ^ Collomp, K; Candau, R; Lasne, F; Labsy, Z; Préfaut, C; De Ceaurriz, J (2000). "Effects of short-term oral salbutamol administration on exercise endurance and metabolism". *Journal of applied physiology (Bethesda, Md.: 1985)*. **89** (2): 430–6. PMID 10926623.
25. ^ "Salbutamol: Ergogenic effects of salbutamol". Retrieved 2010-10-20.
26. ^ Van Baak, MA; De Hon, OM; Hartgens, F; Kuipers, H (2004). "Inhaled salbutamol and endurance cycling performance in non-asthmatic athletes". *International journal of sports medicine*. **25** (7): 533–8. doi:10.1055/s-2004-815716. PMID 15459835.
27. ^ Goubault, C; Perault, MC; Leleu, E; Bouquet, S; Legros, P; Vandel, B; Denjean, A (2001). "Effects of inhaled salbutamol in exercising non-asthmatic athletes". *Thorax*. **56** (9): 675–679. doi:10.1136/thorax.56.9.675. PMC 1746141. PMID 11514686.
28. ^ Carter WJ, Lynch ME (September 1994). "Comparison of the effects of salbutamol and clenbuterol on skeletal muscle mass and carcass composition in senescent rats". *Metab. Clin. Exp.* **43** (9): 1119–25. doi:10.1016/0026-0495(94)90054-X. PMID 7916118.
29. ^ Caruso, JF; Signorile, JF; Perry, AC; Leblanc, B; Williams, R; Clark, M; Bamman, MM (Nov 1995). "The effects of albuterol and isokinetic exercise on the quadriceps muscle group.". *Medicine and science in sports and exercise*. **27** (11): 1471–6. doi:10.1249/00005768-199511000-00002. PMID 8587482.
30. ^ Caruso, J. (20 January 2005). "Albuterol aids resistance exercise in reducing unloading-induced ankle extensor strength losses". *Journal of Applied Physiology*. **98** (5): 1705–1711. doi:10.1152/japplphysiol.01015.2004.
31. ^ Caruso, John F.; Hamill, John L.; De Garmo, Nicole (2005). "Oral Albuterol Dosing During the Latter Stages of a Resistance Exercise Program". *The Journal of Strength and Conditioning Research*. **19** (1): 102–7. doi:10.1519/R-14793.1. PMID 15705021.
32. ^ Caruso, JF; Hamill, JL; Yamauchi, M; Mercado, DR; Cook, TD; Keller, CP; Montgomery, AG; Elias, J (Jun 2004). "Albuterol helps resistance exercise attenuate unloading-induced knee extensor losses.". *Aviation, space, and environmental medicine*. **75** (6): 505–11. PMID 15198276.
33. ^ Caruso, JF; Hamill, JL; De Garmo, N (Feb 2005). "Oral albuterol dosing during the latter stages of a resistance exercise program.". *Journal of strength and conditioning research / National Strength & Conditioning Association*. **19** (1): 102–7. doi:10.1519/00124278-200502000-00018. PMID 15705021.
34. ^ "Sir David Jack, who has died aged 87, was the scientific brain behind the rise of the pharmaceuticals company Glaxo". Telegraph Newspaper. Nov 17, 2011.
35. ^ Van Meerbeke, J. P.; Sumner, C. J. (2011). "Progress and promise: The current status of spinal muscular atrophy therapeutics". *Discovery medicine*. **12** (65): 291–305. PMID 22031667.
36. ^ Lewelt, A.; Newcomb, T. M.; Swoboda, K. J. (2011). "New Therapeutic Approaches to Spinal Muscular Atrophy". *Current Neurology and Neuroscience Reports*. **12** (1): 42–53. doi:10.1007/s11910-011-0240-9. PMC 3260050. PMID 22134788.
37. ^ Liewluck, Teerin; Selcen, Duygu; Engel, Andrew G. (November 2011). "Beneficial effects of albuterol in congenital endplate acetylcholinesterase deficiency and Dok-7 myasthenia". *Muscle & Nerve*. **44** (5): 789–794. doi:10.1002/mus.22176. PMC 3196786. PMID 21952943.


## External links [edit]

- U.S. National Library of Medicine: Drug Information Portal – Albuterol
- Side Effects
- Salbutamol at *The Periodic Table of Videos*

| v · t · e · | **Adrenergic receptor modulators** |
|---|---|
| | *Agonists*: 6-FNE · Amidephrine · Anisodine · Buspirone · Cirazoline · Corbadrine · Dexisometheptene · Dipivefrine · Dopamine · Droxidopa (L-DOPS) · Ephedrine · Epinephrine · Etilefrine · Etilevodopa · Ethylnorepinephrine · Indanidine · Isometheptene · L-DOPA (levodopa) · L-Phenylalanine · L-Tyrosine · Melevodopa · Metaraminol · Methoxamine · Methyldopa · Midodrine · Naphazoline · Norepinephrine · Octopamine (drug) · Oxymetazoline · Phenylephrine · Phenylpropanolamine · Pseudoephedrine · Synephrine · Tetryzoline · Tiamenidine · XP21279 · Xylometazoline · |
| **$\alpha_1$** | *Antagonists*: Abanoquil · Adimolol · Ajmalicine · Alfuzosin · Amosulalol · Anisodamine · Arotinolol · Atiprosin · Atypical antipsychotics (e.g., clozapine, olanzapine, quetiapine, risperidone) · Benoxathian · Buflomedil · Bunazosin · Carvedilol · Corynanthine · Dapiprazole · Domesticine · Doxazosin · Ergolines (e.g., ergotamine, dihydroergotamine, lisuride, terguride) · Etoperidone · Eugenodilol · Fenspiride · Hydroxyzine · Indoramin · Ketanserin · L-765,314 · Labetalol · mCPP · Mepiprazole · Metazosin · Monatepil · Moxisylyte · Naftopidil · Nantenine · Nefazodone · Neldazosin · Niaprazine · Nicergoline · Niguldipine · Pardoprunox · Pelanserin · Phendioxan · Phenoxybenzamine · Phentolamine · Piperoxan · Prazosin · Quinazosin · Ritanserin · Silodosin · Spiperone · Talipexole · Tamsulosin · Terazosin · Tiodazosin · Tolazoline · Trazodone · Tetracyclic antidepressants (e.g., amoxapine, maprotiline, mianserin) · Tricyclic antidepressants (e.g., amitriptyline, clomipramine, doxepin, imipramine, trimipramine) · Trimazosin · Typical antipsychotics (e.g., chlorpromazine, fluphenazine, loxapine, thioridazine) · Urapidil · WB-4101 · Zolertine · |
| **$\alpha_2$** | *Agonists*: (R)-3-Nitrobiphenyline · 4-NEMD · 6-FNE · Amitraz · Apraclonidine · Brimonidine · Cannabivarin · Clonidine · Corbadrine · Detomidine · Dexmedetomidine · Dihydroergotamine · Dipivefrine · Dopamine · Droxidopa (L-DOPS) · Etilevodopa · Ephedrine · Ergotamine · Epinephrine · Etilefrine · Ethylnorepinephrine · Guanabenz · Guanfacine · Guanoxabenz · L-DOPA (levodopa) · L-Phenylalanine · L-Tyrosine · Lofexidine · Medetomidine · Melevodopa · Methyldopa · Mivazerol · Naphazoline · Norepinephrine · Oxymetazoline · Phenylpropanolamine · Piperoxan · Pseudoephedrine · Rilmenidine · Romifidine · Talipexole · Tetrahydrozoline · Tiamenidine · Tizanidine · Tolonidine · Urapidil · XP21279 · Xylazine · Xylometazoline · |
| | *Antagonists*: 1-PP · Adimolol · Aptazapine · Atipamezole · Atypical antipsychotics (e.g., asenapine, clozapine, lurasidone, paliperidone, quetiapine, risperidone, zotepine) · Azapirones (e.g., buspirone, tandospirone) · BRL-44408 · Buflomedil · Cirazoline · Efaroxan · Esmirtazapine · Fenmetozole · Fluparoxan · Idazoxan · mCPP · Mianserin · Mirtazapine · NAN-190 · Olanzapine · Pardoprunox · Phentolamine · Phenoxybenzamine · Piperoxan · Piribedil · Rauwolscine · Rotigotine · SB-269970 · Setiptiline · Spiroxatrine · Sunepitron · Tolazoline · Typical antipsychotics (e.g., chlorpromazine, fluphenazine, loxapine, thioridazine) · Yohimbine · |
| **β** | *Agonists*: Abediterol · Alifedrine · Amibegron · Arbutamine · Arformoterol · Arotinolol · BAAM · Bambuterol · Befunolol · Bitolterol · Broxaterol · Buphenine · Carbuterol · Carmoterol · Cimaterol · Clenbuterol · Corbadrine · Denopamine · Dipivefrine · Dobutamine · Dopamine · Dopexamine · Droxidopa (L-DOPS) · Ephedrine · Epinephrine · Etafedrine · Etilefrine · Etilevodopa · Ethylnorepinephrine · Fenoterol · Formoterol · Hexoprenaline · Higenamine · Indacaterol · Isoetarine · Isoprenaline · Isoxsuprine · L-DOPA (levodopa) · L-Phenylalanine · L-Tyrosine · Levosalbutamol · Mabuterol · Melevodopa · Methoxyphenamine · Methyldopa · Mirabegron · Norepinephrine · Orciprenaline · Oxyfedrine · PF-610355 · Phenylpropanolamine · Pirbuterol · Prenalterol · Ractopamine · Procaterol · Pseudoephedrine · Reproterol · Rimiterol · Ritodrine · **Salbutamol** · Salmeterol · Solabegron · Terbutaline · Tretoquinol · Tulobuterol · Vilanterol · Xamoterol · XP21279 · Zilpaterol · Zinterol · |
| | *Antagonists*: Acebutolol · Adaprolol · Adimolol · Afurolol · Alprenolol · Alprenoxime · Amosulalol · Ancarolol · Arnolol · Arotinolol · Atenolol · Befunolol · Betaxolol · Bevantolol · Bisoprolol · Bopindolol · Bornaprolol · Brefonalol · Bucindolol · Bucumolol · Bufetolol · Bufuralol · Bunitrolol · Bunolol · Bupranolol · Butaxamine · Butidrine · Butofilolol · Capsinolol · Carazolol · Carpindolol · Carteolol · Carvedilol · Celiprolol · Cetamolol · Cicloprolol · Cinamolol · Cloranolol · Cyanopindolol · Dalbraminol · Dexpropranolol · Diacetolol · Dichloroisoprenaline · Dihydroalprenolol · Dilevalol · Diprafenone · Draquinolol · Ecastolol · Epanolol · Ericolol · Ersentilide · Esatenolol · Esprolol · Eugenodilol · Exaprolol |

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| | · Falintolol · Flestolol · Flusoxolol · Hydroxycarteolol · Hydroxytertatolol · ICI-118,551 · Idropranolol · Indenolol · Indopanolol · Iodocyanopindolol · Iprocrolol · Isoxaprolol · Isamoltane · Labetalol · Landiolol · Levobetaxolol · Levobunolol · Levomoprolol · Medroxalol · Mepindolol · Metipranolol · Metoprolol · Moprolol · Nadolol · Nadoxolol · Nebivolol · Nifenalol · Nipradilol · Oxprenolol · Pacrinolol · Pafenolol · Pamatolol · Pargolol · Penbutolol · Pindolol · Practolol · Primidolol · Procinolol · Pronethalol · Propafenone · Propranolol · Ridazolol · Ronactolol · Soquinolol · Sotalol · Spirendolol · SR 59230A · Sulfinalol · Talinolol · Tazolol · Tertatolol · Tienoxolol · Tilisolol · Timolol · Tiprenolol · Tolamolol · Toliprolol · Xibenolol · Xipranolol · |

*See also: Dopaminergics · Melatonergics · Serotonergics · Monoamine reuptake and release modulators · Monoamine metabolism modulators · Monoamine neurotoxins ·*

| v · t · e · | **Drugs for obstructive airway diseases: asthma/COPD (R03)** | |
|---|---|---|
| **Adrenergics, inhalants** | **Short-acting $\beta_2$ agonists** | Bitolterol · Carbuterol · Fenoterol · Isoetarine · Pirbuterol · Procaterol · Reproterol · Rimiterol · **Salbutamol (albuterol)**[#]/Levosalbutamol (levalbuterol) · Terbutaline · Tulobuterol · |
| | **Long-acting $\beta_2$ agonists** | Bambuterol · Clenbuterol · Formoterol/Arformoterol · Salmeterol · Salmefamol · |
| | **Ultra-long-acting $\beta_2$ agonists** | Abediterol · Carmoterol · Indacaterol · Olodaterol · Vilanterol · |
| | **Other** | Epinephrine[#] · Hexoprenaline · Isoprenaline (isoproterenol) · Orciprenaline (metaproterenol) · |
| **Glucocorticoids** | | Beclometasone[#] · Betamethasone · Budesonide · Ciclesonide · Flunisolide · Fluticasone · Mometasone · Triamcinolone · |
| **Anticholinergics/ muscarinic antagonist** | | Aclidinium bromide · Glycopyrronium bromide · Ipratropium bromide[#] · Oxitropium bromide · Tiotropium bromide · Umeclidinium bromide · |
| **Mast cell stabilizers** | | Cromoglicate · Nedocromil · |
| **Xanthines** | | Acefylline · Ambuphylline · Bamifylline · Doxofylline · Enprofylline · Etamiphylline · Proxyphylline · Theophylline/Aminophylline/Choline theophyllinate · |
| **Eicosanoid inhibition** | **Leukotriene antagonists** | Montelukast · Pranlukast · Zafirlukast · |
| | **Arachidonate 5-lipoxygenase inhibitors** | Zileuton · |
| | **Thromboxane receptor antagonists** | Ramatroban · Seratrodast · |
| | **Non-xanthine PDE4 inhibitors** | Ibudilast · Roflumilast · |
| **Others/unknown** | | Amlexanox · Eprozinol · Fenspiride · Omalizumab · |
| **Combination products** | | Aclidinium/formoterol · Beclometasone/formoterol · Budesonide/formoterol · Fluticasone furoate/vilanterol · Fluticasone propionate/salmeterol · Indacaterol/glycopyrronium bromide · Ipratropium bromide/salbutamol · Mometasone/formoterol · Umeclidinium bromide/vilanterol · |

[#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III · ·

| v · t · e · | **Phenethylamines** |
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| | *Psychedelics:* 25B-NBOMe · 25C-NBOMe · 25D-NBOMe · 25I-NBOMe · 25N-NBOMe · 2C-B · 2C-B-AN · 2C-B-FLY · βk-2C-B · 2C-C · 2C-D · 2C-E · 2C-EF · 2C-F · 2C-G · 2C-I · 2C-N · |

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|---|---|
| **Phenethylamines** | 2C-P · 2C-SE · 2C-T · 2C-T-2 · 2C-T-4 · 2C-T-7 · 2C-T-8 · 2C-T-9 · 2C-T-13 · 2C-T-15 · 2C-T-16 · 2C-T-17 · 2C-T-21 · 2C-TFM · 2C-YN · Allylescaline · DESOXY · Escaline · Isoproscaline · Jimscaline · Macromerine · MEPEA · Mescaline · Metaescaline · Methallylescaline · Proscaline · Psi-2C-T-4 · TCB-2<br>*Stimulants:* Phenylethanolamine · Hordenine · Phenethylamine · α-Methylphenethylamine (amphetamine) · β-Methylphenethylamine · *m*-Methylphenethylamine · *N*-Methylphenethylamine · *o*-Methylphenethylamine · *p*-Methylphenethylamine ·<br>*Entactogens:* Lophophine · MDPEA · MDMPEA<br>*Others:* BOH · DMPEA · |
| **Amphetamines** | *Psychedelics:* 3C-BZ · 3C-E · 3C-P · Aleph · Beatrice · Bromo-DragonFLY · D-Deprenyl · DMA · DMCPA · DMMDA · DOB · DOC · DOEF · DOET · DOI · DOM · DON · DOPR · DOTFM · Ganesha · MMDA · MMDA-2 · Psi-DOM · TMA · TeMA<br>*Stimulants:* 2-FA · 2-FMA · 3-FA · 3-FMA · Acridorex · Alfetamine · Amfecloral · Amfepentorex · Amphetamine (Dextroamphetamine, Levoamphetamine) · Amphetaminil · Benfluorex · Benzphetamine · Cathine · Clobenzorex · Dimethylamphetamine · Ephedrine · Etilamfetamine · Fencamfamine · Fencamine · Fenethylline · Fenfluramine (Dexfenfluramine, Levofenfluramine) · Fenproporex · Flucetorex · Fludorex · Formetorex · Furfenorex · Gepefrine · 4-Hydroxyamphetamine · Iofetamine · Isopropylamphetamine · Lefetamine · Lisdexamfetamine · Mefenorex · Metaraminol · Methamphetamine (Dextromethamphetamine, Levomethamphetamine) · Methoxyphenamine · MMA · Morforex · Norfenfluramine · L -Norpseudoephedrine · N,alpha-Diethylphenylethylamine · Oxifentorex · Oxilofrine · Ortetamine · PBA · PCA · Phenpromethamine · PFA · PFMA · PIA · PMA · PMEA · PMMA · Phenylpropanolamine · Pholedrine · Prenylamine · Propylamphetamine · Pseudoephedrine · Sibutramine · Tiflorex · Tranylcypromine · Xylopropamine · Zylofuramine<br>*Entactogens:* 4-FA · 4-FMA · 4-MA · 4-MMA · 4-MTA · 5-APB · 5-APDB · 5-EAPB · 5-IT · 5-MAPB · 5-MAPDB · 6-APB · 6-APDB · 6-Chloro-MDMA · 6-EAPB · 6-IT · 6-MAPB · 6-MAPDB · EDA · IAP · 2,3-MDA · 3,4-MDA · MDEA · MDHMA · MDMA · MDOH · Methamnetamine · MMDMA · Naphthylaminopropane · TAP<br>*Others:* 3,4-DCA · Amiflamine · DFMDA · Selegiline (also D -Deprenyl) · |
| **Phentermines** | *Stimulants:* Chlorphentermine · Cloforex · Clortermine · Etolorex · Mephentermine · Pentorex · Phentermine<br>*Entactogens:* MDPH · MDMPH<br>*Others:* Cericlamine · |
| **Cathinones** | *Stimulants:* 3-FMC · 4-MC · 4-BMC · 4-CMC · 4-EMC · 4-FMC · 4-MEC · 4-MeMABP · 4-MPD · Amfepramone · Benzedrone · Brephedrone · Buphedrone · Bupropion · Cathinone · Dimethylcathinone · Ethcathinone · Eutylone · Hydroxybupropion · Methcathinone · Methedrone · NEB · Pentedrone · Pentylone · Radafaxine<br>*Entactogens:* 3,4-DMMC · 3-MMC · Butylone · Ethylone · Methylone · Methylenedioxycathinone · Mephedrone · |
| **Phenylisobutylamines** | *Entactogens:* 4-CAB · 4-MAB · Ariadne · BDB · Butylone · EBDB · Eutylone · MBDB<br>*Stimulants:* Phenylisobutylamine · |
| **Phenylalkylpyrrolidines** | *Stimulants:* α-PBP · α-PHP · α-PPP · α-PVP · MDPBP · MDPPP · MDPV · 4-MePBP · 4-MePHP · 4-MePPP · MOPPP · MOPVP · MPBP · MPHP · MPPP · Naphyrone · PEP · Prolintane · Pyrovalerone · |
| | 6-FNE · 6-OHDA · a-Me-DA · a-Me-TRA · Adrenochrome · Ciladopa · D -DOPA (Dextrodopa) · Dimetofrine · Dopamine · Epinephrine · Epinine · Etilefrine · Ethylnorepinephrine · |

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| **Catecholamines (and close relatives)** | Fenclonine · Ibopamine · Isoprenaline · Isoetarine · L -DOPA (Levodopa) · L -DOPS (Droxidopa) · L -Phenylalanine · L -Tyrosine · *m*-Tyramine · Metanephrine · Metaraminol · Metaterol · Metirosine · Methyldopa · N,N-Dimethyldopamine · Nordefrin (Levonordefrin) · Norepinephrine · Norfenefrine (*m*-Octopamine) · Normetanephrine · Orciprenaline · *p*-Octopamine · *p*-Tyramine · Phenylephrine · Synephrine · |
| **Miscellaneous** | AL-LAD · Amidephrine · Arbutamine · Cafedrine · Denopamine · Desvenlafaxine · Diphenidine · Dizocilpine · Dobutamine · Dopexamine · Ephenidine · Etafedrine · ETH-LAD · Famprofazone · Fluorolintane · Hexapradol · IP-LAD · Lysergic acid amide · Lysergic acid 2-butyl amide · Lysergic acid 2,4-dimethylazetidide · Lysergic acid diethylamide · Methoxamine · Methoxphenidine · MT-45 · PARGY-LAD · Phenibut · PRO-LAD · Pronethalol · **Salbutamol** (Levosalbutamol) · Theodrenaline · Thiamphenicol · UWA-101 · |

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| | **Former** | BC Powder · Geritol · Goody's Powder · Lucozade · Ribena · | |
| **People** | **Governance** | Chris Gent (chair) · Andrew Witty (CEO) · | |
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| **Litigation** | *Canada v. GlaxoSmithKline Inc.* · *Christopher v. SmithKline Beecham Corp.* · *GlaxoSmithKline Services Unlimited v Commission* · *United States v. Glaxo Group Ltd.* · *United States v. GlaxoSmithKline* · | | |
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# Book:Cancer

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# Brain tumor

From Wikipedia, the free encyclopedia

A **brain tumor** or **intracranial neoplasm** occurs when abnormal cells form within the brain.[1] There are two main types of tumors: malignant or cancerous tumors and benign tumors.[1] Cancerous tumors can be divided into primary tumors that start within the brain, and secondary tumors that have spread from somewhere else, known as brain metastasis tumors.[2] All types of brain tumors may produce symptoms that vary depending on the part of the brain involved.[1] These symptoms may include headaches, seizures, problem with vision, vomiting, and mental changes.[2][3][1] The headache is classically worse in the morning and goes away with vomiting.[1] More specific problems may include difficulty in walking, speaking, and with sensation.[2][4] As the disease progresses unconsciousness may occur.[4]

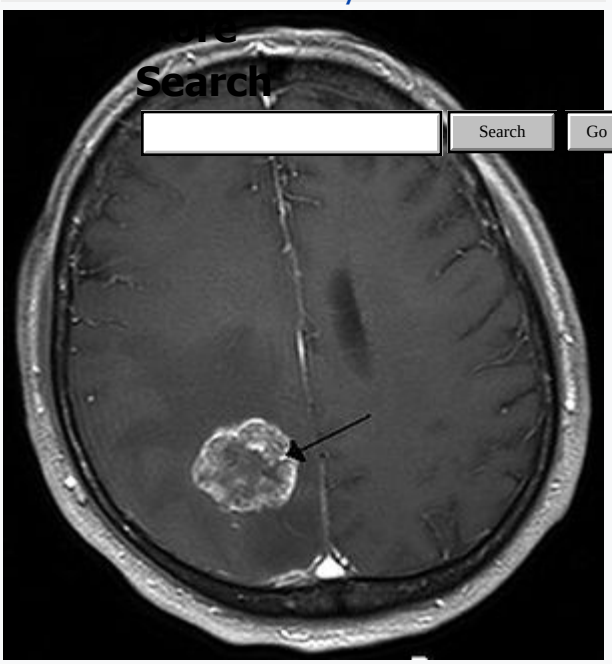
The cause of most brain tumors is unknown.[1] Uncommon risk factors include inherited neurofibromatosis, exposure to vinyl chloride, Epstein–Barr virus, and ionizing radiation.[1][2][4] The evidence for mobile phones is not clear.[1] The most common types of primary tumors in adults are meningiomas (usually benign), and astrocytomas such as glioblastomas.[2] In children, the most common type is a malignant medulloblastoma.[4] Diagnosis is usually by medical examination along with computed tomography or magnetic resonance imaging.[1] This is then often confirmed by a biopsy.[2] Based on the findings, the tumors are divided into different grades of severity.[2]

Treatment may include some combination of surgery, radiation therapy and chemotherapy.[2] Anticonvulsant medication may be needed if seizures occur.[2] Dexamethasone and furosemide may be used to decrease swelling around the tumor.[2] Some tumors grow gradually, requiring only monitoring and possibly needing no further intervention.[2] Treatments that use a person's immune system are being studied.[1] Outcome varies considerably depending on the type of tumor and how far it has spread at diagnosis.[4] Glioblastomas usually have poor outcomes while meningiomas usually have good outcomes.[4] The average five-year survival rate for brain cancer in the United States is 33%.[5]

Secondary or metastatic brain tumors are more common than primary brain tumors,[1] with about half of

## Variants

**Brain tumor**



Brain metastasis in the right cerebral hemisphere from lung cancer shown on magnetic resonance imaging.

| Classification and external resources | |
|---|---|
| **Specialty** | Neurosurgery, oncology |
| **ICD-10** | D71, D33, |
| **ICD-9-CM** | 191, 225.0 |
| **DiseasesDB** | 30781 |
| **MedlinePlus** | 007222 *000768* |
| **eMedicine** | emerg/334 |
| **MeSH** | D001932 |

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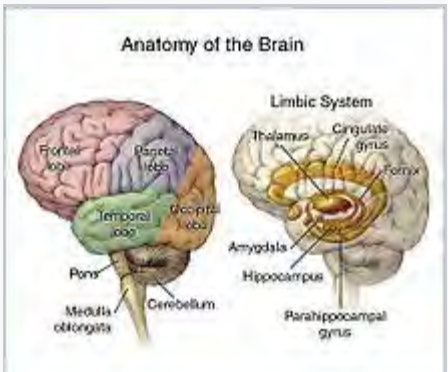
metastases coming from lung cancer.[1] Primary brain tumors occur in around 250,000 people a year globally, making up less than 2% of cancers.[4] In children younger than 15, brain tumors are second only to acute lymphoblastic leukemia as a cause of cancer.[6] In Australia the average economic cost of a case of brain cancer is $1.9 million, the greatest of any type of cancer.[7]





## Signs and symptoms [edit]

The signs and symptoms of brain tumors are broad. People with brain tumors will experience them no matter if the tumor is benign (not cancerous) or cancerous.[8] Primary and secondary brain tumors present with similar symptoms, with symptoms depend on the location, size, and rate of growth of the tumor.[9] For example, larger tumors in the frontal lobe can cause changes in the ability to think. However, a smaller tumor in an area such as Wernicke's area (small area responsible for language comprehension) can result in a greater loss of function.[10]



The main areas of the brain and limbic system.

Intracranial pressure is usually the first sign of a brain tumor and it can cause persistent headaches.[11][12] These headaches may not respond to headache remedies and they may be accompanied by vomiting.[11]

The brain is divided into 4 lobes and each lobe or area has its own function.[13][14] A tumor in any of these lobes may affect the area's

performance. The location of the tumor is often linked to the symptoms experienced but each person may experience something different.[15]

Frontal lobe tumors may contribute to poor reasoning, inappropriate social behavior, personality changes, poor planning, lower inhibition,[15] and decreased production of speech (Broca's area)

Temporal lobe: Tumors in this lobe may contribute to poor memory, loss of hearing,[14] difficulty in language comprehension (Wernicke's area)

Parietal lobe: Tumors here may result in poor interpretation of languages, decreased sense of touch and pain, and poor spatial and visual perception[16]

Occipital lobe: Damage to this lobe may result in poor or loss of vision[16]

Cerebellum: Tumors in this area may cause poor balance, muscle movement, and posture[16]

Brain stem: Tumors on this can affect blood pressure, swallowing, and heartbeat[14]

### Behavior changes [edit]

Despite the personality and behavior changes occur in people with brain tumors, little research on such changes has been done.[13] A person's personality may be altered due to the tumor damaging lobes of the brain. Since the frontal, temporal, and parietal lobes[9] control inhibition, emotions, mood, judgement, reasoning, and behavior, a primary or secondary tumor in that region can cause inappropriate social behavior,[12] temper tantrums,[12] laughing at things which merit no laughter,[12] and even psychological symptoms such as depression and anxiety.[15]

Personality changes can have damaging effects such as unemployment, unstable relationships, and a lack of control.[13]

## Cause [edit]

Epidemiological studies are required to determine risk factors.[17] Aside from exposure to vinyl chloride or ionizing radiation, there are no known environmental factors associated with brain tumors. Mutations and deletions of so-called tumor suppressor genes, such as P53, are thought to be the cause of some forms of brain tumor.[18] Inherited conditions, such as Von Hippel–Lindau disease, multiple endocrine neoplasia, and neurofibromatosis type 2 carry a high risk for the development of brain tumors.

Although studies have not shown any link between cell phone or mobile phone radiation and the occurrence of brain tumors,[19] the World Health Organization has classified mobile phone radiation on the IARC scale into Group 2B – possibly carcinogenic.[20] Discounting claims that current cell phone usage may cause brain cancer, modern, third-generation (3G) phones emit, on average, about 1% of the energy emitted by the GSM (2G) phones that were in use when epidemiological studies that observed a slight increase in the risk for glioma – a malignant type of brain cancer –among heavy users of wireless and cordless telephones were conducted.[4]

## Pathophysiology [edit]

### Meninges [edit]

Human brains are surrounded by a system of connective tissue membranes called meninges that separate the brain from the skull. This three-layered covering is composed of (from the outside in) the dura mater ("hard mother"), arachnoid mater ("spidery mother"), and pia mater ("tender mother"). The arachnoid and pia are physically connected and thus often considered as a single layer, the pia-

Brain cancer regions.

arachnoid. Between the arachnoid mater and the pia mater is the subarachnoid space which contains cerebrospinal fluid (CSF). This fluid circulates in the narrow spaces between cells and through the cavities in the brain called ventricles, to nourish, support, and protect the brain tissue. Blood vessels enter the central nervous system through the perivascular space above the pia mater. The cells in the blood vessel walls are joined tightly, forming the blood–brain barrier which protects the brain from toxins that might enter through the blood. Tumors of the meninges are meningiomas and are often benign.

### Brain matter [edit]

The brains of humans and other vertebrates are composed of very soft tissue and a gelatin-like texture. Living brain tissue has a pink tint in color on the outside (grey matter), and nearly complete white on the inside (white matter), with subtle variations in color. Three separate brain areas make up most of the brain's volume:

- telencephalon (cerebral hemispheres or cerebrum)
- mesencephalon (midbrain)
- cerebellum

These areas are composed of two broad classes of cells: neurons and glia. These two types are equally numerous in the brain as a whole, although glial cells outnumber neurons roughly 4 to 1 in the cerebral cortex. Glia come in several types, which perform a number of critical functions, including structural support, metabolic support, insulation, and guidance of development.

Primary tumors of the glial cells are called gliomas and often are malignant by the time they are diagnosed.

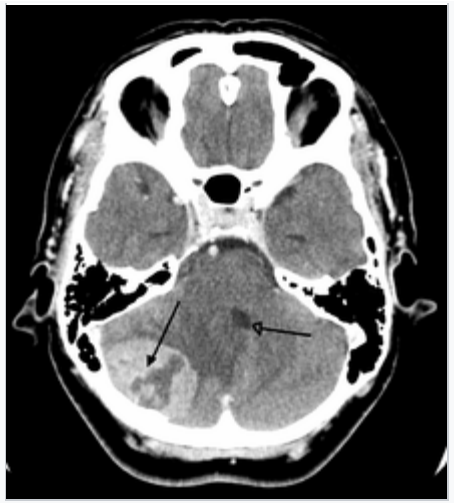
### Spinal cord and other tissues [edit]

The pons in the brainstem is a specific region that consists of myelinated axons much like the spinal cord. The thalamus and hypothalamus of the diencephalon also consist of neuron and glial cell tissue with the hypophysis (pituitary gland) and pineal gland (which is glandular tissue) attached at the bottom; tumors of the pituitary and pineal gland are often benign. The medulla oblongata is at the start of the spinal cord and is composed mainly of neuron tissue enveloped in Schwann cells and meninges tissue. The spinal cord is made up of bundles of these axons. Glial cells such as Schwann cells in the periphery or, within the cord itself, oligodendrocytes, wrap themselves around the axon, thus promoting faster transmission of electrical signals and also providing for general maintenance of the environment surrounding the cord, in part by shuttling different compounds around in response to injury or other stimulus.

## Diagnosis [edit]

Most of the brain is separated from the blood by the blood-brain barrier (BBB), which exerts a restrictive control as to which substances are allowed to pass. Therefore, many tracers that reach tumors in the body very easily would only reach brain tumors once there is a disruption of the BBB. Thus the disruption of the BBB, which can be detected by a MRI and CT, is regarded as the main diagnostic indicator for malignant gliomas, meningiomas, and brain metastases.[21]

Although there is no specific or singular clinical symptom or sign for any



A posterior fossa tumor leading to mass effect and midline shift

brain tumors, the presence of a combination of symptoms and the lack of corresponding clinical indications of infections or other causes can be an indicator to redirect diagnostic investigation towards the possibility of an intracranial neoplasm. Brain tumors have similar characteristics and obstacles when it comes to diagnosis and therapy with tumors located elsewhere in the body. However, they create specific issues that follow closely to the properties of the organ they are in.[21]

The diagnosis will often start by taking a medical history noting medical antecedents, and current symptoms. Clinical and laboratory investigations will serve to exclude infections as the cause of the symptoms. Examinations in this stage may include the eyes, otolaryngological (or ENT) and electrophysiological exams. The use of electroencephalography (EEG) often plays a role in the diagnosis of brain tumors.

Swelling, or obstruction of the passage of cerebrospinal fluid (CSF) from the brain may cause (early) signs of increased intracranial pressure which translates clinically into headaches, vomiting, or an altered state of consciousness, and in children changes to the diameter of the skull and bulging of the fontanelles. More complex symptoms such as endocrine dysfunctions should alarm doctors not to exclude brain tumors.

A bilateral temporal visual field defect (due to compression of the optic chiasm) or dilation of the pupil, and the occurrence of either slowly evolving or the sudden onset of focal neurologic symptoms, such as cognitive and behavioral impairment (including impaired judgment, memory loss, lack of recognition, spatial orientation disorders), personality or emotional changes, hemiparesis, hypoesthesia, aphasia, ataxia, visual field impairment, impaired sense of smell, impaired hearing, facial paralysis, double vision, or more severe symptoms such as tremors, paralysis on one side of the body hemiplegia, or (epileptic) seizures in a patient with a negative history for epilepsy, should raise the possibility of a brain tumor.

## Imaging [edit]

Medical imaging plays a central role in the diagnosis of brain tumors. Early imaging methods—invasive and sometimes dangerous— such as pneumoencephalography and cerebral angiography have been abandoned in favor of non-invasive, high-resolution techniques, especially magnetic resonance imaging (MRI) and computed tomography (CT) scans. Neoplasms will often show as differently colored masses (also referred to as processes) in CT or MRI results.

- Benign brain tumors often show up as hypodense (darker than brain tissue) mass lesions on CT scans. On MRI, they appear either hypodense or isointense (same intensity as brain tissue) on T1-weighted scans, or hyperintense (brighter than brain tissue) on T2-weighted MRI, although the appearance is variable.
- Contrast agent uptake, sometimes in characteristic patterns, can be demonstrated on either CT or MRI scans in most malignant primary and metastatic brain tumors.
- Pressure areas where the brain tissue has been compressed by a tumor also appear hyperintense on T2-weighted scans and might indicate the presence a diffuse neoplasm due to an unclear outline. Swelling around the tumor known as *peritumoral edema* can also show a similar result.

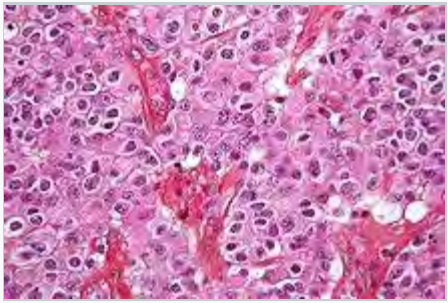
This is because these tumors disrupt the normal functioning of the BBB and lead to an increase in its permeability. However, it is not possible to diagnose high- versus low-grade gliomas based on enhancement pattern alone.

The definitive diagnosis of brain tumor can only be confirmed by histological examination of tumor tissue samples obtained either by means of brain biopsy or open surgery. The histological examination is essential

for determining the appropriate treatment and the correct prognosis. This examination, performed by a pathologist, typically has three stages: interoperative examination of fresh tissue, preliminary microscopic examination of prepared tissues, and follow-up examination of prepared tissues after immunohistochemical staining or genetic analysis.

## Pathology [edit]

Tumors have characteristics that allow determination of malignacy and how they will evolve, and determining these characteristics will allow the medical team to determine the management plan.



Micrograph of an oligodendroglioma, a type of brain cancer. Brain biopsy. H&E stain.

Anaplasia or dedifferentiation: loss of differentiation of cells and of their orientation to one another and blood vessels, a characteristic of anaplastic tumor tissue. Anaplastic cells have lost total control of their normal functions and many have deteriorated cell structures. Anaplastic cells often have abnormally high nuclear-to-cytoplasmic ratios, and many are multinucleated. Additionally, the nuclei of anaplastic cells are usually unnaturally shaped or oversized. Cells can become anaplastic in two ways: neoplastic tumor cells can dedifferentiate to become anaplasias (the dedifferentiation causes the cells to lose all of their normal structure/function), or cancer stem cells can increase in their capacity to multiply (i.e., uncontrollable growth due to failure of differentiation).

Atypia: an indication of abnormality of a cell (which may be indicative for malignancy). Significance of the abnormality is highly dependent on context.

Neoplasia: the (uncontrolled) division of cells. As such, neoplasia is not problematic but its consequences are: the uncontrolled division of cells means that the mass of a neoplasm increases in size, and in a confined space such as the intracranial cavity this quickly becomes problematic because the mass invades the space of the brain pushing it aside, leading to compression of the brain tissue and increased intracranial pressure and destruction of brain parenchyma. Increased intracranial pressure (ICP) may be attributable to the direct mass effect of the tumor, increased blood volume, or increased cerebrospinal fluid (CSF) volume, which may in turn have secondary symptoms.

Necrosis: the (premature) death of cells, caused by external factors such as infection, toxin or trauma. Necrotic cells send the wrong chemical signals which prevents phagocytes from disposing of the dead cells, leading to a buildup of dead tissue, cell debris and toxins at or near the site of the necrotic cells[22]

Arterial and venous hypoxia, or the deprivation of adequate oxygen supply to certain areas of the brain, occurs when a tumor makes use of nearby blood vessels for its supply of blood and the neoplasm enters into competition for nutrients with the surrounding brain tissue.

More generally a neoplasm may cause release of metabolic end products (e.g., free radicals, altered electrolytes, neurotransmitters), and release and recruitment of cellular mediators (e.g., cytokines) that disrupt normal parenchymal function.

## Classification [edit]

## Secondary brain tumors [edit]

Secondary tumors of the brain are metastatic and have invaded the brain from cancers originating in other organs. This means that a cancerous neoplasm has developed in another organ elsewhere in the body and that cancer cells have leaked from that primary tumor and then entered the lymphatic system and blood vessels. They then circulate through the bloodstream, and are deposited in the brain. There, these cells continue growing and dividing, becoming another invasive neoplasm of the primary cancer's tissue. Secondary tumors of the brain are very common in the terminal phases of patients with an incurable metastasized cancer; the most common types of cancers that bring about secondary tumors of the brain are lung cancer, breast cancer, malignant melanoma, kidney cancer, and colon cancer (in decreasing order

of frequency).

Secondary brain tumors are more common than primary ones; in the United States there are about 170,000 new cases every year. Secondary brain tumors are the most common cause of tumors in the intracranial cavity. The skull bone structure can also be subject to a neoplasm that by its very nature reduces the volume of the intracranial cavity, and can damage the brain.[23]

## By behavior [edit]

Brain tumors or intracranial neoplasms can be cancerous (malignant) or non-cancerous (benign). However, the definitions of malignant or benign neoplasms differs from those commonly used in other types of cancerous or non-cancerous neoplasms in the body. In cancers elsewhere in the body, three malignant properties differentiate benign tumors from malignant forms of cancer: benign tumors are self-limited and do not invade or metastasize. Characteristics of malignant tumors include:

- uncontrolled mitosis (growth by division beyond the normal limits)
- anaplasia: the cells in the neoplasm have an obviously different form (in size and shape). Anaplastic cells display marked pleomorphism. The cell nuclei are characteristically extremely hyperchromatic (darkly stained) and enlarged; the nucleus might have the same size as the cytoplasm of the cell (nuclear-cytoplasmic ratio may approach 1:1, instead of the normal 1:4 or 1:6 ratio). Giant cells – considerably larger than their neighbors – may form and possess either one enormous nucleus or several nuclei (syncytia). Anaplastic nuclei are variable and bizarre in size and shape.
- invasion or infiltration (medical literature uses these terms as synonymous equivalents. However, for clarity, the articles that follow adhere to a convention that they mean slightly different things; this convention is not followed outside these articles):
  - Invasion or invasiveness is the spatial expansion of the tumor through uncontrolled mitosis, in the sense that the neoplasm invades the space occupied by adjacent tissue, thereby pushing the other tissue aside and eventually compressing the tissue. Often these tumors are associated with clearly outlined tumors in imaging.
  - Infiltration is the behavior of the tumor either to grow (microscopic) tentacles that push into the surrounding tissue (often making the outline of the tumor undefined or diffuse) or to have tumor cells "seeded" into the tissue beyond the circumference of the tumorous mass; this does not mean that an infiltrative tumor does not take up space or does not compress the surrounding tissue as it grows, but an infiltrating neoplasm makes it difficult to say where the tumor ends and the healthy tissue starts.
- metastasis (spread to other locations in the body via lymph or blood).

Of the above malignant characteristics, some elements do not apply to primary neoplasms of the brain:

- Primary brain tumors rarely metastasize to other organs; some forms of primary brain tumors can metastasize but will not spread outside the intracranial cavity or the central spinal canal. Due to the BBB, cancerous cells of a primary neoplasm cannot enter the bloodstream and get carried to another location in the body. (Occasional isolated case reports suggest spread of certain brain tumors outside the central nervous system, e.g. bone metastasis of glioblastoma multiforme.[24])
- Primary brain tumors generally are invasive (i.e. they will expand spatially and intrude into the space occupied by other brain tissue and compress those brain tissues); however, some of the more malignant primary brain tumors will infiltrate the surrounding tissue.

Of numerous grading systems in use for the classification of tumor of the central nervous system, the World Health Organization (WHO) grading system is commonly used for astrocytoma. Established in 1993 in an effort to eliminate confusion regarding diagnoses, the WHO system established a four-tiered histologic grading guideline for astrocytomas that assigns a grade from 1 to 4, with 1 being the least aggressive and 4 being the most aggressive.

## Types [edit]

Tumors can be benign or malignant, can occur in different parts of the brain, and may be primary or secondary. A primary tumor is one that has started in the brain, as opposed to a metastatic tumor, which is something that has spread to the brain from another part of the body.[25] The incidence of metastatic

tumors are more prevalent than primary tumors by 4:1.[26] Tumors may or may not be symptomatic: some tumors are discovered because the patient has symptoms, others show up incidentally on an imaging scan, or at an autopsy.

The most common primary brain tumors are:[27]

- Gliomas (50.4%)
- Meningiomas (20.8%)
- Pituitary adenomas (15%)
- Nerve sheath tumors (8%)

These common tumors can also be organized according to tissue of origin as shown below:[28][*verification needed*]

| Tissue of origin | Children | Adults |
|---|---|---|
| Astrocytes | Pilocytic Astrocytoma (PCA) | Glioblastoma Multiforme (GBM) |
| Oligodendrocytes | | Oligodendroglioma |
| Ependyma | Ependymoma | |
| Neurons | Medulloblastoma | |
| Meninges | | Meningioma |

### Specific types [edit]

*Main article: WHO classification of the tumors of the central nervous system*

Anaplastic astrocytoma, Astrocytoma, Central neurocytoma, Choroid plexus carcinoma, Choroid plexus papilloma, Choroid plexus tumor, Dysembryoplastic neuroepithelial tumour, Ependymal tumor, Fibrillary astrocytoma, Giant-cell glioblastoma, Glioblastoma multiforme, Gliomatosis cerebri, Gliosarcoma, Hemangiopericytoma, Medulloblastoma, Medulloepithelioma, Meningeal carcinomatosis, Neuroblastoma, Neurocytoma, Oligoastrocytoma, Oligodendroglioma, Optic nerve sheath meningioma, Pediatric ependymoma, Pilocytic astrocytoma, Pinealoblastoma, Pineocytoma, Pleomorphic anaplastic neuroblastoma, Pleomorphic xanthoastrocytoma, Primary central nervous system lymphoma, Sphenoid wing meningioma, Subependymal giant cell astrocytoma, Subependymoma, Trilateral retinoblastoma.

## Treatment [edit]

When a brain tumor is diagnosed, a medical team will be formed to assess the treatment options presented by the leading surgeon to the patient and his/her family. Given the location of primary solid neoplasms of the brain in most cases a "do-nothing" option is usually not presented. Neurosurgeons take the time to observe the evolution of the neoplasm before proposing a management plan to the patient and his/her relatives. These various types of treatment are available depending on neoplasm type and location and may be combined to give the best chances of survival:

- Surgery: complete or partial resection of the tumor with the objective of removing as many tumor cells as possible.
- Radiotherapy: the most commonly used treatment for brain tumors; the tumor is irradiated with beta, x rays or gamma rays.
- Chemotherapy: is a treatment option for cancer, however it is not always used to treat brain tumors as the blood-brain barrier can prevent some drugs from reaching the cancerous cells.
- A variety of experimental therapies are available through clinical trials.

Survival rates in primary brain tumors depend on the type of tumor, age, functional status of the patient, the extent of surgical tumor removal and other factors specific to each case.[29]

## Surgery [edit]

The primary and most desired course of action described in medical literature is surgical removal (resection) via craniotomy. Minimally invasive techniques are becoming the dominant trend in neurosurgical oncology.[30] The prime remediating objective of surgery is to remove as many tumor cells as possible, with complete removal being the best outcome and cytoreduction ("debulking") of the tumor otherwise. In some cases access to the tumor is impossible and impedes or prohibits surgery.

Many meningiomas, with the exception of some tumors located at the skull base, can be successfully removed surgically. Most pituitary adenomas can be removed surgically, often using a minimally invasive approach through the nasal cavity and skull base (trans-nasal, trans-sphenoidal approach). Large pituitary adenomas require a craniotomy (opening of the skull) for their removal. Radiotherapy, including stereotactic approaches, is reserved for inoperable cases.

Several current research studies aim to improve the surgical removal of brain tumors by labeling tumor cells with 5-aminolevulinic acid that causes them to fluoresce.[31] Postoperative radiotherapy and chemotherapy are integral parts of the therapeutic standard for malignant tumors. Radiotherapy may also be administered in cases of "low-grade" gliomas, when a significant tumor burden reduction could not be achieved surgically.

Any person undergoing brain surgery may suffer from epileptic seizures. These can take the form of either absence seizures or tonic-clonic seizures. Medication can lessen and sometimes prevent these attacks.

Multiple metastatic tumors are generally treated with radiotherapy and chemotherapy rather than surgery and the prognosis in such cases is determined by the primary tumor, and is generally poor.

## Radiation therapy [edit]

The goal of radiation therapy is to kill tumor cells while leaving normal brain tissue unharmed. In standard external beam radiation therapy, multiple treatments of standard-dose "fractions" of radiation are applied to the brain. This process is repeated for a total of 10 to 30 treatments, depending on the type of tumor. This additional treatment provides some patients with improved outcomes and longer survival rates.

Radiosurgery is a treatment method that uses computerized calculations to focus radiation at the site of the tumor while minimizing the radiation dose to the surrounding brain. Radiosurgery may be an adjunct to other treatments, or it may represent the primary treatment technique for some tumors. Forms used include stereotactic radiosurgery, such as Gamma knife, Cyberknife or Novalis Tx radiosurgery.[32][*unreliable medical source?*]

Radiotherapy may be used following, or in some cases in place of, resection of the tumor. Forms of radiotherapy used for brain cancer include external beam radiation therapy, the most common, and brachytherapy and proton therapy, the last especially used for children.

Radiotherapy is the most common treatment for secondary brain tumors. The amount of radiotherapy depends on the size of the area of the brain affected by cancer. Conventional external beam "whole-brain radiotherapy treatment" (WBRT) or "whole-brain irradiation" may be suggested if there is a risk that other secondary tumors will develop in the future.[33] Stereotactic radiotherapy is usually recommended in cases involving fewer than three small secondary brain tumors.

People who receive stereotactic radiosurgery (SRS) and whole-brain radiation therapy (WBRT) for the treatment of metastatic brain tumors have more than twice the risk of developing learning and memory problems than those treated with SRS alone.[34][35]

## Chemotherapy [edit]

Patients undergoing chemotherapy are administered drugs designed to kill tumor cells. Although chemotherapy may improve overall survival in patients with the most malignant primary brain tumors, it does so in only about 20 percent of patients. Chemotherapy is often used in young children instead of radiation, as radiation may have negative effects on the developing brain. The decision to prescribe this treatment is based on a patient's overall health, type of tumor, and extent of the cancer. The toxicity and

many side effects of the drugs, and the uncertain outcome of chemotherapy in brain tumors puts this treatment further down the line of treatment options with surgery and radiation therapy preferred.

UCLA Neuro-Oncology publishes real-time survival data for patients with a diagnosis of glioblastoma multiforme. They are the only institution in the United States that displays how brain tumor patients are performing on current therapies. They also show a listing of chemotherapy agents used to treat high-grade glioma tumors.[36]

### Other [edit]

A shunt may be used to relieve symptoms caused by intracranial pressure, by reducing the build-up of fluid (hydrocephalus) caused by the blockage of the free flow of cerebrospinal fluid.[37]

## Prognosis [edit]

The prognosis of brain cancer depends on the type of cancer diagnosed. Medulloblastoma has a good prognosis with chemotherapy, radiotherapy, and surgical resection while glioblastoma multiforme has a median survival of only 12 months even with aggressive chemoradiotherapy and surgery. Brainstem gliomas have the poorest prognosis of any form of brain cancer, with most patients dying within one year, even with therapy that typically consists of radiation to the tumor along with corticosteroids. However, one type, focal brainstem gliomas in children, seems open to exceptional prognosis and long-term survival has frequently been reported.[38]

### Glioblastoma multiforme [edit]

*Main article: Glioblastoma multiforme*

Glioblastoma multiforme is the most aggressive (grade IV) and most common form of a malignant brain tumor. Even when aggressive multimodality therapy consisting of radiotherapy, chemotherapy, and surgical excision is used, median survival is only 12–17 months. Standard therapy for glioblastoma multiforme consists of maximal surgical resection of the tumor, followed by radiotherapy between two and four weeks after the surgical procedure to remove the cancer, then by chemotherapy. Most patients with glioblastoma take a corticosteroid, typically dexamethasone, during their illness to relieve symptoms. Experimental treatments include gamma knife radiosurgery,[39] boron neutron capture therapy and gene therapy.[40][41]

### Oligodendrogliomas [edit]

*Main article: Oligodendroglioma*

Oligodendrogliomas are incurable but slowly progressive malignant brain tumors. They can be treated with surgical resection, chemotherapy, radiotherapy or a combination. For some suspected low-grade (grade II) tumors, only a course of watchful waiting and symptomatic therapy is opted for. These tumors show a high frequency of co-deletions of the p and q arms of chromosome 1 and chromosome 19 respectively (1p19q co-deletion) and have been found to be especially chemosensitive with one report claiming them to be one of the most chemosensitive tumors.[42] A median survival of up to 16.7 years has been reported for grade II oligodendrogliomas.[43]

## Epidemiology [edit]

Figures for incidences of cancers of the brain show a significant difference between more- and less-developed countries (the less-developed countries have lower incidences of tumors of the brain),[44]— this could be explained by undiagnosed tumor-related deaths (patients in extreme poor situations do not get diagnosed, simply because they do not have access to the modern diagnostic facilities required to diagnose a brain tumor) and by deaths caused by other poverty-related causes that preempt a patient's life before tumors develop or tumors become life-threatening. Nevertheless, studies[*which?*] suggest that certain forms

of primary brain tumors are more prevalent among certain groups of the population.

The incidence of low-grade astrocytoma has not been shown to vary significantly with nationality. However, studies examining the incidence of malignant central nervous system (CNS) tumors have shown some variation with national origin. Since some high-grade lesions arise from low-grade tumors, these trends are worth mentioning. Specifically, the incidence of CNS tumors in the United States, Israel, and the Nordic countries is relatively high, while Japan and Asian countries have a lower incidence. These differences probably reflect some biological differences as well as differences in pathologic diagnosis and reporting.[45] Worldwide data on incidence of cancer can be found at the WHO (World Health Organisation) and is handled by the IARC (International Agency for Research on Cancer) located in France.[46]

### United States [edit]

For the United States in the year 2005, it was projected that there would be 43,800 new cases of brain tumors[47][48] which accounted for less than 1 percent of all cancers, 2.4 percent of all cancer deaths,[49] and 20–25 percent of pediatric cancers.[49][50] Ultimately, it is estimated there are 13,000 deaths per year in the United States alone as a result of brain tumors.[48]

### UK [edit]

Brain, other CNS or intracranial tumors are the ninth most common cancer in the UK (around 10,600 people were diagnosed in 2013), and it is the eighth most common cause of cancer death (around 5,200 people died in 2012).[51]

## Research [edit]

### Immunotherapy [edit]

Cancer immunotherapy is being actively studied. For malignant gliomas no therapy has been shown to improve life expectancy as of 2015.[52]

### Vesicular stomatitis virus [edit]

*See also: Oncolytic virus*

In 2000, researchers used the vesicular stomatitis virus, or VSV, to infect and kill cancer cells without affecting healthy cells.[53][54]

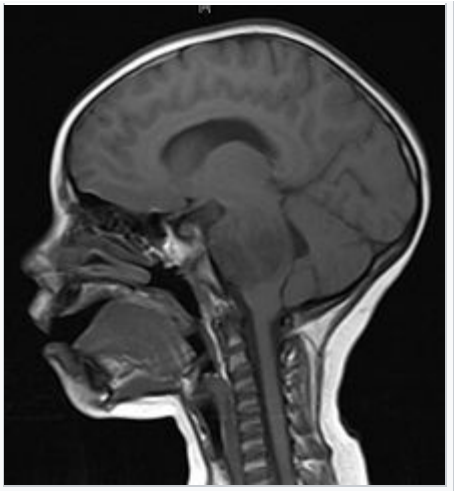
The initial discovery of the virus' oncolytic properties were limited to only a few types of cancer. Several independent studies have identified many more types susceptible to the virus, including glioblastoma multiforme cancer cells, which account for the majority of brain tumors.

In 2008, researchers artificially engineered strains of VSV that were less cytotoxic to normal cells. This advance allows administration of the virus without coadministration with interferon. Consequently, administration of the virus can be given intravenously or through the olfactory nerve. In the research, a human brain tumor was implanted into mice brains.

Research on virus treatment like this has been conducted for some years, but no other viruses have been shown to be as efficient or specific as the VSV mutant strains.

### Retroviral replicating vectors [edit]

Led by Prof. Nori Kasahara, researchers from USC, who are now at UCLA, reported in 2001 the first successful example of applying the use of retroviral replicating vectors towards transducing cell lines derived from solid tumors.[55] Building on this initial work, the researchers applied the technology to *in vivo* models of cancer and in 2005 reported



A brainstem glioma in four-year-old. MRI, sagittal, without contrast

a long-term survival benefit in an experimental brain tumor animal model.[56][*unreliable medical source?*] Subsequently, in preparation for human clinical trials, this technology was further developed by Tocagen (a pharmaceutical company primarily focused on brain cancer treatments) as a combination treatment (Toca 511 & Toca FC). This has been under investigation since 2010 in a Phase I/II clinical trial for the potential treatment of recurrent high-grade glioma including glioblastoma multiforme (GBM) and anaplastic astrocytoma. No results have yet been published.[57]

## Children [edit]

This section needs to be **updated**. Please update this article to reflect recent events or newly available information.
Last update: PMID 23436013 *(July 2014)*

In the USA, about 2,000 children and adolescents younger than 20 years of age are diagnosed with malignant brain tumors each year. Higher incidence rates were reported in 1985–1994 than in 1975–1983. There is some debate as to the reasons; one theory is that the trend is the result of improved diagnosis and reporting, since the jump occurred at the same time that MRIs became available widely, and there was no coincident jump in mortality. The central nervous system cancer survival rate in children is approximately 60%. The rate varies with the type of cancer and the age of onset: younger patients have higher mortality.[58]

In children under 2, about 70% of brain tumors are medulloblastomas, ependymomas, and low-grade gliomas. Less commonly, and seen usually in infants, are teratomas and atypical teratoid rhabdoid tumors.[59] Germ cell tumors, including teratomas, make up just 3% of pediatric primary brain tumors, but the worldwide incidence varies significantly.[60]

In the UK, 429 children aged 14 and under are diagnosed with a brain tumour on average each year, and 563 children and young people under the age of 19 are diagnosed.[61]

## See also [edit]

- Timeline of brain cancer
- List of notable brain tumor patients
- Pituitary adenomas ("pituitary tumours") are sometimes incorrectly referred to as a brain tumours.[62][63] This is perhaps because the pituitary gland is in the skull, however it is not part of the brain. Pituitary adenomas are rarely cancerous.

## References [edit]


1. ^ *a b c d e f g h i j k* "General Information About Adult Brain Tumors". *NCI*. 2014-04-14. Retrieved 8 June 2014.
2. ^ *a b c d e f g h i j k* "Adult Brain Tumors Treatment". *NCI*. 2014-02-28. Retrieved 8 June 2014.
33. ^ "Treating secondary brain tumours with WBRT". Cancer Research UK. Retrieved 5 June 2012.
34. ^ "Whole Brain Radiation increases risk of learning and memory problems in cancer patients with brain metastases". MD Anderson Cancer Center. Retrieved 5 June 2012.
35. ^ "Metastatic brain tumors". International

3. ^ Longo, Dan L (2012). "369 Seizures and Epilepsy". *Harrison's principles of internal medicine* (18th ed.). McGraw-Hill. p. 3258. ISBN 978-0-07-174887-2.
4. ^ *a b c d e f g h i* *World Cancer Report 2014.* World Health Organization. 2014. pp. Chapter 5.16. ISBN 9283204298.
5. ^ "SEER Stat Fact Sheets: Brain and Other Nervous System Cance". *NCI*. Retrieved 18 June 2014.
6. ^ *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 1.3. ISBN 9283204298.
7. ^ "Brain Tumour Facts 2011". *Brain Tumour Alliance Australia*. Archived from the original (PDF) on 20 Nov 2014. Retrieved 9 June 2014.
8. ^ "Brain Tumors". Retrieved 2016-08-02.
9. ^ *a b* "Mood Swings and Cognitive Changes | American Brain Tumor Association". *www.abta.org*. Retrieved 2016-08-03.
10. ^ "Coping With Personality & Behavioral Changes". *www.brainsciencefoundation.org*. Retrieved 2016-08-03.
11. ^ *a b* "Headaches | American Brain Tumor Association". *www.abta.org*. Retrieved 2016-08-03.
12. ^ *a b c d* Jones, Caleb. "Brain Tumor Symptoms | Miles for Hope | Brain Tumor Foundation". *milesforhope.org*. Retrieved 2016-08-03.
13. ^ *a b c* Gregg, N. (2014). " "Neurobehavioural Changes In Patients Following Brain Tumour: Patients And Relatives Perspective." ". *Supportive Care In Cancer*.
14. ^ *a b c* "Coping With Personality & Behavioral Changes". *www.brainsciencefoundation.org*. Retrieved 2016-07-27.
15. ^ *a b c* "Mood Swings and Cognitive Changes | American Brain Tumor Association". *www.abta.org*. Retrieved 2016-07-27.
16. ^ *a b c* "Anatomy of the Brain" (PDF).
17. ^ Krishnatreya, M; Kataki, AC; Sharma, JD; Bhattacharyya, M; Nandy, P; Hazarika, M (2014). "Brief descriptive epidemiology of primary malignant brain tumors from North-East India.". *Asian Pacific Journal of Cancer Prevention*. **15** (22): 9871–3. doi:10.7314/apjcp.2014.15.22.9871. PMID 25520120.
18. ^ Kleihues P, Ohgaki H, Eibl RH, Reichel MB, Mariani L, Gehring M, Petersen I, Höll T, von Deimling A, Wiestler OD, Schwab M (1994). "Type and frequency of p53 mutations in tumors of the nervous system and its coverings". *Molecular Neuro-oncology and Its Impact on the Clinical Management of Brain Tumors*. Recent results in cancer research. **135**. Springer. pp. 25–31. ISBN 3540573518.
19. ^ Frei P, Poulsen AH, Johansen C, Olsen JH, Steding-Jessen M, Schüz J (19 October 2011). "Use of mobile phones and risk of brain tumours: update of Danish cohort study.". *BMJ*. **343**: d6387. doi:10.1136/bmj.d6387. PMC 3197791.
RadioSurgery Association. Retrieved 5 June 2012.
36. ^ "How Our Patients Perform: Glioblastoma Multiforme". UCLA Neuro-Oncology Program. Retrieved 5 June 2012.
37. ^ Dalvi A. "Normal Pressure Hydrocephalus Causes, Symptoms, Treatment". *eMedicineHealth*. Emedicinehealth.com. Retrieved 17 February 2012.
38. ^ "Brain Stem Gliomas in Childhood". Childhoodbraintumor.org. Retrieved 17 February 2012.
39. ^ "GBM Guide – MGH Brain Tumor Center". Brain.mgh.harvard.edu. Retrieved 17 February 2012.
40. ^ Chien-Kuo Tai; Noriyuki Kasahara (1 January 2008). "Replication-competent retrovirus vectors for cancer gene therapy" (PDF). *Frontiers in Bioscience*. **13**: 3083–3095. doi:10.2741/2910. PMID 17981778.
41. ^ Murphy AM, Rabkin SD (Apr 2013). "Current status of gene therapy for brain tumors". *Transl. Res.* **161** (4): 339–54. doi:10.1016/j.trsl.2012.11.003. PMID 23246627.
42. ^ Ty AU, See SJ, Rao JP, Khoo JB, Wong MC (January 2006). "Oligodendroglial tumor chemotherapy using "decreased-dose-intensity" PCV: a Singapore experience". *Neurology*. **66** (2): 247–9. doi:10.1212/01.wnl.0000194211.68164.a0. PMID 16434664.
43. ^ "Neurology". Neurology. Retrieved 17 February 2012.
44. ^ Bondy ML, Scheurer ME, Malmer B, et al. (2008). "Brain Tumor Epidemiology: Consensus from the Brain Tumor Epidemiology Consortium (BTEC)". *Cancer*. **113** (7 Suppl): 1953–1968. doi:10.1002/cncr.23741.
45. ^ Jallo GI, Benardete EA (January 2010). "Low-Grade Astrocytoma".
46. ^ "CANCERMondial". International Agency for Research on Cancer. Retrieved 17 February 2012.
47. ^ "Central Brain Tumor Registry of the United States, Primary Brain Tumors in the United States, Statistical Report, 2005–2006" (PDF). Retrieved 23 July 2014.
48. ^ *a b* Greenlee RT, Murray T, Bolden S, Wingo PA (2000). "Cancer statistics, 2000". *CA Cancer J Clin*. **50** (1): 7–33. doi:10.3322/canjclin.50.1.7. PMID 10735013.
49. ^ *a b* "What are the key statistics about brain and spinal cord tumors?". American Cancer Society. May 1, 2012.
50. ^ Chamberlain MC, Kormanik PA (February 1998). "Practical guidelines for the treatment of malignant gliomas". *West. J. Med.* **168** (2): 114–20. PMC 1304839. PMID 9499745.
51. ^ "Brain, other CNS and intracranial tumours statistics". *Cancer Research UK*. Retrieved 27 October 2014.
52. ^ Bloch, O (2015). "Immunotherapy for malignant gliomas.". *Cancer Treatment and Research*. **163**:

PMID 22016439.
20. ^ "IARC classifies radiofrequency electromagnetic fields as possibly carcinogenic to humans" (PDF). *World Health Organization press release N° 208* (Press release). International Agency for Research on Cancer. 31 May 2011. Retrieved 2 June 2011.
21. ^ [a] [b] Herholz, Karl; Langen, Karl-Josef; Schiepers, Christiaan; Mountz, James M. (2012). "Brain Tumors". *Seminars in Nuclear Medicine*. **42** (6): 356–70. doi:10.1053/j.semnuclmed.2012.06.001. PMC 3925448. PMID 23026359.
22. ^ MedlinePlus Encyclopedia *Necrosis*
23. ^ MedlinePlus Encyclopedia *Metastatic brain tumor*
24. ^ Frappaz D, Mornex F, Saint-Pierre G, Ranchere-Vince D, Jouvet A, Chassagne-Clement C, Thiesse P, Mere P, Deruty R (1999). "Bone metastasis of glioblastoma multiforme confirmed by fine needle biopsy". *Acta Neurochirurgica*. **141** (5): 551–552. doi:10.1007/s007010050342. PMID 10392217.
25. ^ "What you need to know about brain tumors". National Cancer Institute. Retrieved 25 February 2012.
26. ^ Merrel RT (Dec 2012). "Brain tumors.". *Dis Mon*. **58** (12): 678–89. doi:10.1016/j.disamonth.2012.08.009. PMID 23149521.
27. ^ Park, Bong Jin; Kim, Han Kyu; Sade, Burak; Lee, Joung H. (2009). "Epidemiology". In Lee, Joung H. *Meningiomas: Diagnosis, Treatment, and Outcome*. Springer. p. 11. ISBN 978-1-84882-910-7.
28. ^ Sattar, Husain A. Pathoma.com
29. ^ Nicolato, Antonio; Gerosa, Massimo A.; Fina, Paolo; Iuzzolino, Paolo; Giorgiutti, Fabrizia; Bricolo, Albino (1995). "Prognostic factors in low-grade supratentorial astrocytomas: A uni-multivariate statistical analysis in 76 surgically treated adult patients". *Surgical Neurology*. **44** (3): 208–21; discussion 221–3. doi:10.1016/0090-3019(95)00184-0. PMID 8545771.
30. ^ Spetzler RF, Sanai N (2012). "The quiet revolution: Retractorless surgery for complex vascular and skull base lesions". *Journal of Neurosurgery*. **116** (2): 291–300. doi:10.3171/2011.8.JNS101896. PMID 21981642.
31. ^ Paul Brennan (4 August 2008). "Introduction to brain cancer". *cliniclog.com*. Retrieved 19 December 2011.
32. ^ "Radiosurgery treatment comparisons – Cyberknife, Gamma knife, Novalis Tx". Retrieved 22 July 2014.
143–58. doi:10.1007/978-3-319-12048-5_9. PMID 25468230.
53. ^ Auer R, Bell JC (January 2012). "Oncolytic viruses: smart therapeutics for smart cancers". *Future Oncology*. **8** (1): 1–4. doi:10.2217/fon.11.134. PMID 22149027.
54. ^ Garber K (1 March 2006). "China Approves World's First Oncolytic Virus Therapy For Cancer Treatment". *J Natl Cancer Inst*. **98** (5): 298–300. doi:10.1093/jnci/djj111. PMID 16507823.
55. ^ Logg CR, Tai CK, Logg A, Anderson WF, Kasahara N (20 May 2001). "A uniquely stable replication-competent retrovirus vector achieves efficient gene delivery in vitro and in solid tumors". *Human Gene Therapy*. **12** (8): 921–932. doi:10.1089/104303401750195881. PMID 11387057.
56. ^ Tai CK, Wang WJ, Chen TC, Kasahara N (November 2005). "Single-shot, multicycle suicide gene therapy by replication-competent retrovirus vectors achieves long-term survival benefit in experimental glioma". *Molecular Therapy*. **12** (5): 842–851. doi:10.1016/j.ymthe.2005.03.017. PMID 16257382.
57. ^ "A Study of a Retroviral Replicating Vector Administered to Subjects With Recurrent Malignant Glioma". Clinical Trials.gov. July 2014.
58. ^ Gurney JG, Smith MA, Bunin GR. "CNS and Miscellaneous Intracranial and Instraspinal Neoplasms" (PDF). *SEER Pediatric Monograph*. National Cancer Institute. pp. 51–57. Retrieved 4 December 2008. "In the US, approximately 2,200 children and adolescents younger than 20 years of age are diagnosed with malignant central nervous system tumors each year. More than 90 percent of primary CNS malignancies in children are located within the brain."
59. ^ Rood BR. "Infantile Brain Tumors". The Childhood Brain Tumor Foundation. Retrieved 23 July 2014.
60. ^ Echevarría ME, Fangusaro J, Goldman S (June 2008). "Pediatric central nervous system germ cell tumors: a review". *Oncologist*. **13** (6): 690–9. doi:10.1634/theoncologist.2008-0037. PMID 18586924.
61. ^ "About childhood brain tumours". Retrieved 16 June 2016.
62. ^ Tara Palmer-Tomkinson reveals brain tumour battle BBC News 19 November 2016
63. ^ UAE patient's brain tumour removed through nostrils Gulf News, 9 December 2016

## External links [edit]

- Brain and CNS cancers at DMOZ
- Brain tumour information from Cancer Research UK
- Neuro-Oncology: Cancer Management Guidelines
- MedPix Teaching File MR Scans of Primary Brain Lymphoma, etc.

Wikimedia Commons has media related to *Brain neoplasms*.

| v · t · e · | Nervous tissue tumors/NS neoplasm/Neuroectodermal tumor (ICD-O 9350–9589) (C70–C72, D32–D33, 191–192/225) | | | |
|---|---|---|---|---|
| **Endocrine** | *Sellar:* | Craniopharyngioma · Pituicytoma · | | |
| | *Other:* | Pinealoma · | | |
| **CNS** | **Neuroepithelial (brain tumors, spinal tumors)** | **Glioma** | **Astrocyte** | Astrocytoma (Pilocytic astrocytoma · Pleomorphic xanthoastrocytoma · Subependymal giant cell astrocytoma · Fibrillary astrocytoma · Anaplastic astrocytoma · Glioblastoma multiforme · · |
| | | | **Oligodendrocyte** | Oligodendroglioma · |
| | | | **Ependyma** | Ependymoma · Subependymoma · |
| | | | **Choroid plexus** | Choroid plexus tumor (Choroid plexus papilloma · Choroid plexus carcinoma · · |
| | | | **Multiple/unknown** | Oligoastrocytoma · Gliomatosis cerebri · Gliosarcoma · |
| | | **Mature neuron** | Ganglioneuroma: Ganglioglioma · Retinoblastoma · Neurocytoma · Dysembryoplastic neuroepithelial tumour · Lhermitte–Duclos disease · | |
| | | **PNET** | Neuroblastoma (Esthesioneuroblastoma · Ganglioneuroblastoma · · Medulloblastoma · Atypical teratoid rhabdoid tumor · | |
| | | **Primitive** | Medulloepithelioma · | |
| | **Meningiomas (Meninges)** | Meningioma · Hemangiopericytoma · | | |
| | **Hematopoietic** | Primary central nervous system lymphoma · | | |
| **PNS: NST** | *Cranial and paraspinal nerves:* Neurofibroma (Neurofibrosarcoma · Neurofibromatosis · · Neurilemmoma/Schwannoma (Acoustic neuroma · · Malignant peripheral nerve sheath tumor · | | | |

*Note: Not all brain tumors are of nervous tissue, and not all nervous tissue tumors are in the brain (see brain metastasis).*

| v · t · e · | Overview of tumors, cancer and oncology (C00–D48, 140–239) | |
|---|---|---|
| **Conditions** | **Benign tumors** | Hyperplasia · Cyst · Pseudocyst · Hamartoma · |
| | **Malignant progression** | Dysplasia · Carcinoma in situ · Cancer · Metastasis · Primary tumor · Sentinel lymph node · |
| | **Topography** | Head/Neck (Oral, Nasopharyngeal) · Digestive system · Respiratory system · Bone · Skin · Blood · Urogenital · Nervous system · Endocrine system · |
| | **Histology** | Carcinoma · Sarcoma · Blastoma · Papilloma · Adenoma · |
| | **Other** | Precancerous condition · Paraneoplastic syndrome · |
| **Staging/grading** | TNM · Ann Arbor · Prostate cancer staging · Gleason grading system · Dukes classification · | |

| | |
|---|---|
| **Carcinogenesis** | Cancer cell · Carcinogen · Tumor suppressor genes/oncogenes · Clonally transmissible cancer · Oncovirus · Cancer bacteria · |
| **Misc.** | Research · List of oncology-related terms · History · Cancer pain · Cancer and nausea · |
| **Authority control** | NDL: 00568723 · |

Categories: Disorders causing seizures | Brain tumor




# Breast cancer

From Wikipedia, the free encyclopedia

**Breast cancer** is cancer that develops from breast tissue.[1] Signs of breast cancer may include a lump in the breast, a change in breast shape, dimpling of the skin, fluid coming from the nipple, or a red scaly patch of skin.[2] In those with distant spread of the disease, there may be bone pain, swollen lymph nodes, shortness of breath, or yellow skin.[3]

Risk factors for developing breast cancer include being female, obesity, lack of physical exercise, drinking alcohol, hormone replacement therapy during menopause, ionizing radiation, early age at first menstruation, having children late or not at all, older age, and family history.[2][4] About 5–10% of cases are due to genes inherited from a person's parents, including BRCA1 and BRCA2 among others. Breast cancer most commonly develops in cells from the lining of milk ducts and the lobules that supply the ducts with milk. Cancers developing from the ducts are known as ductal carcinomas, while those developing from lobules are known as lobular carcinomas.[2] In addition, there are more than 18 other sub-types of breast cancer. Some cancers, such as ductal carcinoma in situ, develop from pre-invasive lesions.[4] The diagnosis of breast cancer is confirmed by taking a biopsy of the concerning lump. Once the diagnosis is made, further tests are done to determine if the cancer has spread beyond the breast and which treatments it may respond to.[2]

The balance of benefits versus harms of breast cancer screening is controversial. A 2013 Cochrane review stated that it is unclear if mammographic screening does more good or harm.[5] A 2009 review for the US Preventive Services Task Force found evidence of benefit in those 40 to 70 years of age,[6] and the organization recommends screening every two years in women 50 to 74 years old.[7] The medications tamoxifen or raloxifene may be used in an effort to prevent breast cancer in those who are at high risk of developing it.[4] Surgical removal of both breasts is another preventative measure in some high risk women.[4] In those who have been diagnosed with cancer, a number of treatments may be used, including surgery, radiation therapy, chemotherapy, hormonal therapy and targeted therapy.[2] Types of surgery vary from breast-conserving surgery to mastectomy.[8][9] Breast reconstruction may take place at the time of surgery or at a later date. In those in whom the cancer has spread to other parts of the body, treatments are mostly aimed at improving quality of life and comfort.[9]

Outcomes for breast cancer vary depending on the cancer type, extent of disease, and person's age.[9] Survival rates in the developed world are high,[10] with between 80% and 90% of those in England and the United States alive for at least 5 years.[11][12] In developing countries survival rates are poorer.[4] Worldwide, breast cancer is the leading type of cancer in women, accounting for 25% of all cases.[13] In 2012 it resulted in 1.68 million cases and 522,000 deaths.[13] It is more common in developed countries[4] and is more than 100 times more common in women than in men.[10][14]

**Breast cancer**

Mammograms showing a normal breast (left) and a breast with cancer (right, white arrows).

| Classification and external resources | |
|---|---|
| **Specialty** | Oncology |
| **ICD-10** | C50 |
| **ICD-9-CM** | 174-175,V10.3 |
| **ICD-O** | M8502/3 |
| **OMIM** | 114480 |
| **DiseasesDB** | 1598 |
| **MedlinePlus** | 000913 |
| **eMedicine** | med/2808 med/3287 radio/115 plastic/521 |
| **Patient UK** | Breast cancer |
| **MeSH** | D001943 |

[edit on Wikidata]

Contents





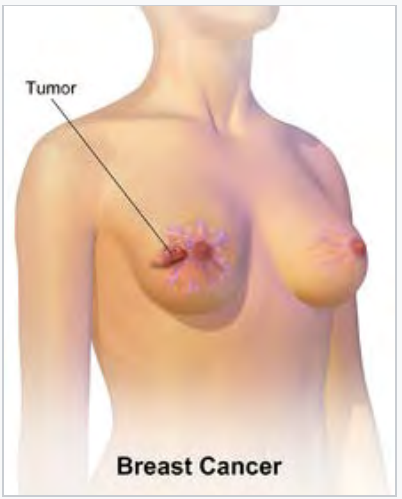
## Signs and symptoms [edit]

The first noticeable symptom of breast cancer is typically a lump that feels different from the rest of the breast tissue. More than 80% of breast cancer cases are discovered when the woman feels a lump.[15] The earliest breast cancers are detected by a mammogram.[16] Lumps found in lymph nodes located in the armpits[15] can also indicate breast cancer.

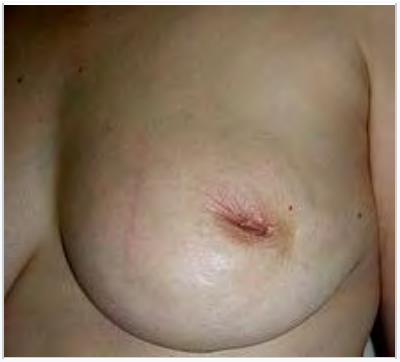
Indications of breast cancer other than a lump may include thickening different from the other breast tissue, one breast becoming larger or lower, a nipple changing position or shape or becoming inverted, skin puckering or dimpling, a rash on or around a nipple, discharge from nipple/s, constant pain in part of the breast or armpit, and swelling beneath the armpit or around the collarbone.[17] Pain ("mastodynia") is an unreliable tool in determining the presence or absence of breast cancer, but may be indicative of other breast health issues.[15][16][18]

Inflammatory breast cancer is a particular type of breast cancer which can pose a substantial diagnostic challenge. Symptoms may resemble a breast inflammation and may include itching, pain, swelling, nipple inversion, warmth and redness throughout the breast, as well as an orange-peel texture to the skin referred to as *peau d'orange*.[15] As inflammatory breast cancer does not present as a lump there can sometimes be a delay in diagnosis.

Another reported symptom complex of breast cancer is Paget's disease of the



Breast cancer



Breast cancer showing an inverted nipple, lump, and skin dimpling.

breast. This syndrome presents as skin changes resembling eczema, such as redness, discoloration, or mild flaking of the nipple skin. As Paget's disease of the breast advances, symptoms may include tingling, itching, increased sensitivity, burning, and pain. There may also be discharge from the nipple. Approximately half of women diagnosed with Paget's disease of the breast also have a lump in the breast.[19]

In rare cases, what initially appears as a fibroadenoma (hard, movable non-cancerous lump) could in fact be a phyllodes tumor. Phyllodes tumors are formed within the stroma (connective tissue) of the breast and contain glandular as well as stromal tissue. Phyllodes tumors are not staged in the usual sense; they are classified on the basis of their appearance under the microscope as benign, borderline, or malignant.[20]

Occasionally, breast cancer presents as metastatic disease—that is, cancer that has spread beyond the original organ. The symptoms caused by metastatic breast cancer will depend on the location of metastasis. Common sites of metastasis include bone, liver, lung and brain.[21] Unexplained weight loss can occasionally signal breast cancer, as can symptoms of fevers or chills. Bone or joint pains can sometimes be manifestations of metastatic breast cancer, as can jaundice or neurological symptoms. These symptoms are called *non-specific*, meaning they could be manifestations of many other illnesses.[22]

Most symptoms of breast disorders, including most lumps, do not turn out to represent underlying breast cancer. Fewer than 20% of lumps, for example, are cancerous,[23] and benign breast diseases such as mastitis and fibroadenoma of the breast are more common causes of breast disorder symptoms. Nevertheless, the appearance of a new symptom should be taken seriously by both patients and their doctors, because of the possibility of an underlying breast cancer at almost any age.[24]

## Risk factors [edit]

*Main article: Risk factors of breast cancer*

Risk factors can be divided into two categories:

- *modifiable* risk factors (things that people can change themselves, such as consumption of alcoholic beverages), and
- *fixed* risk factors (things that cannot be changed, such as age and biological sex).[25]

The primary risk factors for breast cancer are being female and older age.[26] Other potential risk factors include genetics,[27] lack of childbearing or lack of breastfeeding,[28] higher levels of certain hormones,[29][30] certain dietary patterns, and obesity. Recent studies have indicated that exposure to light pollution is a risk factor for the development of breast cancer.[31]

### Lifestyle [edit]

*See also: List of breast carcinogenic substances*

Smoking tobacco appears to increase the risk of breast cancer, with the greater the amount smoked and the earlier in life that smoking began, the higher the risk.[32] In those who are long-term smokers, the risk is increased 35% to 50%.[32] A lack of physical activity has been linked to about 10% of cases.[33] Sitting regularly for prolonged periods is associated with higher mortality from breast cancer. The risk is not negated by regular exercise, though it is lowered.[34]

There is an association between use of hormonal birth control and the development of premenopausal breast cancer,[25][35] but whether oral contraceptives use may actually cause premenopausal breast cancer is a matter of debate.[36] If there is indeed a link, the absolute effect is small.[36][37] Additionally, it is not clear if the association exists with newer hormonal birth controls.[37] In those with mutations in the breast cancer susceptibility genes *BRCA1* or *BRCA2*, or who have a family history of breast cancer, use of modern oral contraceptives does not appear to affect the risk of breast cancer.[38][39]

The association between breast feeding and breast cancer has not been clearly determined; some studies have found support for an association while others have not.[40] In the 1980s, the abortion–breast cancer hypothesis posited that induced abortion increased the risk of developing breast cancer.[41] This hypothesis was the subject of

extensive scientific inquiry, which concluded that neither miscarriages nor abortions are associated with a heightened risk for breast cancer.[42]

A number of dietary factors have been linked to the risk for breast cancer. Dietary factors which may increase risk include a high fat diet,[43] high alcohol intake,[44] and obesity-related high cholesterol levels.[45][46] Dietary iodine deficiency may also play a role.[47] Evidence for fiber is unclear. A 2015 review found that studies trying to link fiber intake with breast cancer produced mixed results.[48] In 2016 a tentative association between low fiber intake during adolescence and breast cancer was observed.[49]

Other risk factors include radiation[50] and shift-work.[51] A number of chemicals have also been linked, including polychlorinated biphenyls, polycyclic aromatic hydrocarbons, organic solvents[52] Although the radiation from mammography is a low dose, it is estimated that yearly screening from 40 to 80 years of age will cause approximately 225 cases of fatal breast cancer per million women screened.[53]

### Genetics [edit]

Some genetic susceptibility may play a minor role in most cases.[54] Overall, however, genetics is believed to be the primary cause of 5–10% of all cases.[55] Women whose mother was diagnosed before 50 have an increased risk of 1.7 and those whose mother was diagnosed at age 50 or after has an increased risk of 1.4.[56] In those with zero, one or two affected relatives, the risk of breast cancer before the age of 80 is 7.8%, 13.3%, and 21.1% with a subsequent mortality from the disease of 2.3%, 4.2%, and 7.6% respectively.[57] In those with a first degree relative with the disease the risk of breast cancer between the age of 40 and 50 is double that of the general population.[58]

In less than 5% of cases, genetics plays a more significant role by causing a hereditary breast–ovarian cancer syndrome.[54] This includes those who carry the *BRCA1* and *BRCA2* gene mutation.[54] These mutations account for up to 90% of the total genetic influence with a risk of breast cancer of 60–80% in those affected.[55] Other significant mutations include *p53* (Li–Fraumeni syndrome), *PTEN* (Cowden syndrome), and *STK11* (Peutz–Jeghers syndrome), *CHEK2*, *ATM*, *BRIP1*, and *PALB2*.[55] In 2012, researchers said that there are four genetically distinct types of the breast cancer and that in each type, hallmark genetic changes lead to many cancers.[59]

### Medical conditions [edit]

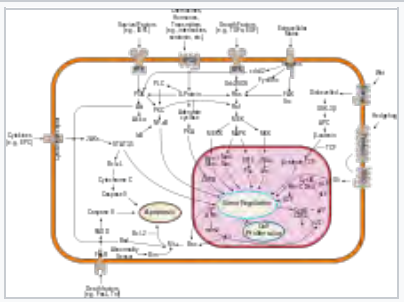
Breast changes like atypical ductal hyperplasia[60] and lobular carcinoma *in situ*,[61][62][63] found in benign breast conditions such as fibrocystic breast changes, are correlated with an increased breast cancer risk. Diabetes mellitus might also increase the risk of breast cancer.[64] Autoimmune diseases such as lupus erythematosus seem also to increase the risk for the acquisition of breast cancer.[65]

## Pathophysiology [edit]

*Main article: Carcinogenesis*

Breast cancer, like other cancers, occurs because of an interaction between an environmental (external) factor and a genetically susceptible host. Normal cells divide as many times as needed and stop. They attach to other cells and stay in place in tissues. Cells become cancerous when they lose their ability to stop dividing, to attach to other cells, to stay where they belong, and to die at the proper time.

Normal cells will commit cell suicide (programmed cell death) when they are no longer needed. Until then, they are protected from cell suicide by several protein clusters and pathways. One of the protective pathways is the PI3K/AKT pathway; another is the RAS/MEK/ERK pathway. Sometimes the genes along these protective pathways are mutated in a way that turns them permanently "on", rendering the cell incapable of committing suicide when it is no longer needed. This is one of the steps that causes cancer in combination with other mutations. Normally, the PTEN protein turns off the PI3K/AKT pathway when the cell is ready for programmed cell death. In some breast cancers, the gene for the PTEN protein is mutated, so the PI3K/AKT pathway is stuck in the "on" position, and the cancer cell does not commit suicide.[66]



Overview of signal transduction pathways involved in programmed cell death. Mutations leading to loss of this ability can lead to cancer formation.

Mutations that can lead to breast cancer have been experimentally linked to estrogen exposure.[67]

Abnormal growth factor signaling in the interaction between stromal cells and epithelial cells can facilitate malignant cell growth.[68][69] In breast adipose tissue, overexpression of leptin leads to increased cell proliferation and cancer.[70]

In the United States, 10 to 20 percent of people with breast cancer and people with ovarian cancer have a first- or second-degree relative with one of these diseases. The familial tendency to develop these cancers is called hereditary breast–ovarian cancer syndrome. The best known of these, the *BRCA* mutations, confer a lifetime risk of breast cancer of between 60 and 85 percent and a lifetime risk of ovarian cancer of between 15 and 40 percent. Some mutations associated with cancer, such as *p53*, *BRCA1* and *BRCA2*, occur in mechanisms to correct errors in DNA. These mutations are either inherited or acquired after birth. Presumably, they allow further mutations, which allow uncontrolled division, lack of attachment, and metastasis to distant organs.[50][71] However, there is strong evidence of residual risk variation that goes well beyond hereditary *BRCA* gene mutations between carrier families. This is caused by unobserved risk factors.[72] This implicates environmental and other causes as triggers for breast cancers. The inherited mutation in *BRCA1* or *BRCA2* genes can interfere with repair of DNA cross links and DNA double strand breaks (known functions of the encoded protein).[73] These carcinogens cause DNA damage such as DNA cross links and double strand breaks that often require repairs by pathways containing BRCA1 and BRCA2.[74][75] However, mutations in *BRCA* genes account for only 2 to 3 percent of all breast cancers.[76] Levin *et al.* say that cancer may not be inevitable for all carriers of *BRCA1* and *BRCA2* mutations.[77] About half of hereditary breast–ovarian cancer syndromes involve unknown genes.

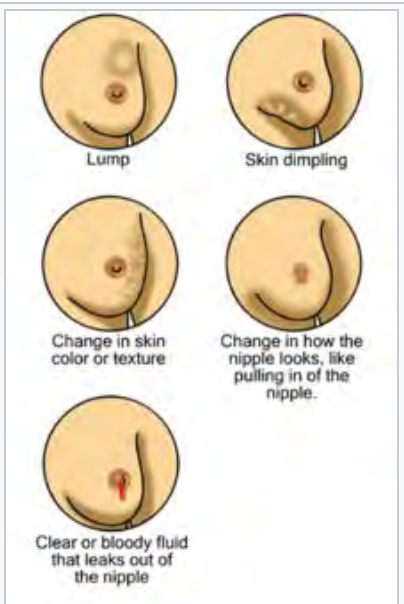
GATA-3 directly controls the expression of estrogen receptor (ER) and other genes associated with epithelial differentiation, and the loss of GATA-3 leads to loss of differentiation and poor prognosis due to cancer cell invasion and metastasis.[78]

## Diagnosis [edit]

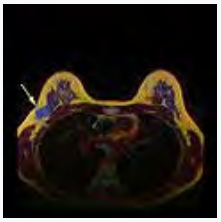
Most types of breast cancer are easy to diagnose by microscopic analysis of a sample—or biopsy—of the affected area of the breast. Also, there are types of breast cancer that require specialized lab exams.

The two most commonly used screening methods, physical examination of the breasts by a healthcare provider and mammography, can offer an approximate likelihood that a lump is cancer, and may also detect some other lesions, such as a simple cyst.[79] When these examinations are inconclusive, a healthcare provider can remove a sample of the fluid in the lump for microscopic analysis (a procedure known as fine needle aspiration, or fine needle aspiration and cytology—FNAC) to help establish the diagnosis. The needle aspiration may be performed in a healthcare provider's office or clinic using local anaesthetic if required.[*clarification needed*] A finding of clear fluid makes the lump highly unlikely to be cancerous, but bloody fluid may be sent off for inspection under a microscope for cancerous cells. Together, physical examination of the breasts, mammography, and FNAC can be used to diagnose breast cancer with a good degree of accuracy.

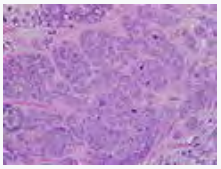
Other options for biopsy include a core biopsy or vacuum-assisted breast biopsy,[80] which are procedures in which a section of the breast lump is removed; or an excisional biopsy, in which the entire lump is removed. Very often the results of physical examination by a healthcare provider, mammography, and additional tests that may be performed in special circumstances (such as imaging by ultrasound or MRI) are sufficient to warrant excisional biopsy as the definitive diagnostic and primary treatment method.

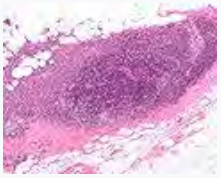


Early signs of possible breast cancer


MRI showing breast cancer


Excised human breast tissue,


High-grade invasive ductal carcinoma,


Micrograph showing a lymph node invaded

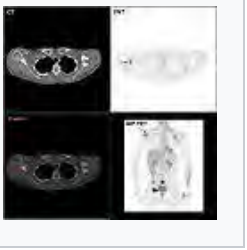

Neuropilin-2 expression in normal

showing an irregular, dense, white stellate area of cancer 2 cm in diameter, within yellow fatty tissue.

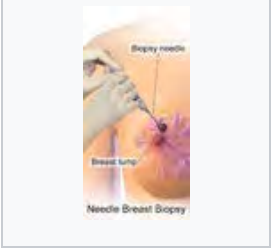
with minimal tubule formation, marked pleomorphism, and prominent mitoses, 40x field.

by ductal breast carcinoma, with an extension of the tumor beyond the lymph node.

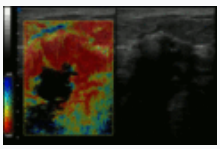
breast and breast carcinoma tissue.



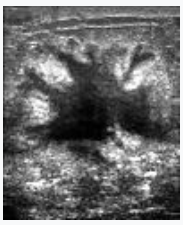
F-18 FDG PET/CT: A breast cancer metastasis to the right scapula




Needle breast biopsy.



Elastography shows stiff cancer tissue on ultrasound imaging.



Ultrasound image shows irregularly shaped mass of breast cancer.

Infiltrating (Invasive) breast carcinoma.

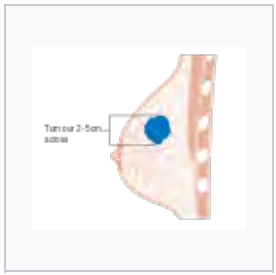
## Classification [edit]

*Main article: Breast cancer classification*

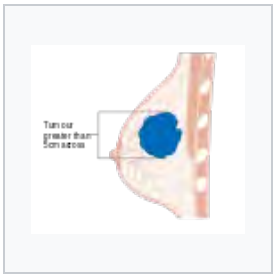
Breast cancers are classified by several grading systems. Each of these influences the prognosis and can affect treatment response. Description of a breast cancer optimally includes all of these factors.

- **Histopathology**. Breast cancer is usually classified primarily by its histological appearance. Most breast cancers are derived from the epithelium lining the ducts or lobules, and these cancers are classified as ductal or lobular carcinoma. *Carcinoma in situ* is growth of low-grade cancerous or precancerous cells within a particular tissue compartment such as the mammary duct without invasion of the surrounding tissue. In contrast, *invasive carcinoma* does not confine itself to the initial tissue compartment.[81]
- **Grade**. Grading compares the appearance of the breast cancer cells to the appearance of normal breast tissue. Normal cells in an organ like the breast become differentiated, meaning that they take on specific shapes and forms that reflect their function as part of that organ. Cancerous cells lose that differentiation. In cancer, the cells that would normally line up in an orderly way to make up the milk ducts become disorganized. Cell division becomes uncontrolled. Cell nuclei become less uniform. Pathologists describe cells as well differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade) as the cells progressively lose the features seen in normal breast cells. Poorly differentiated cancers (the ones whose tissue is least like normal breast tissue) have a worse prognosis.
- **Stage**. Breast cancer staging using the TNM system is based on the size of the tumor (**T**), whether or not the tumor has spread to the lymph nodes (**N**) in the armpits, and whether the tumor has metastasized (**M**) (i.e. spread to a more distant part of the body). Larger size, nodal spread, and metastasis have a larger stage number and a worse prognosis.
  The main stages are:
  - Stage 0 is a pre-cancerous or marker condition, either ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).
  - Stages 1–3 are within the breast or regional lymph nodes.
  - Stage 4 is 'metastatic' cancer that has a less favorable prognosis since it has spread beyond the breast and regional lymph nodes.

Stage T1 breast cancer



Stage T2 breast cancer



Stage T3 breast cancer

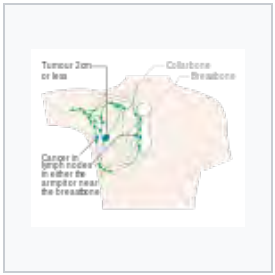
Where available, imaging studies may be employed as part of the staging process in select cases to look for signs of metastatic cancer. However, in cases of breast cancer with low risk for metastasis, the risks associated

with PET scans, CT scans, or bone scans outweigh the possible benefits, as these procedures expose the patient to a substantial amount of potentially dangerous ionizing radiation.[82][83]

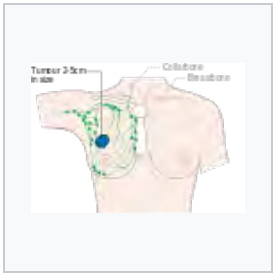
- **Receptor status**. Breast cancer cells have receptors on their surface and in their cytoplasm and nucleus. Chemical messengers such as hormones bind to receptors, and this causes changes in the cell. Breast cancer cells may or may not have three important receptors: estrogen receptor (ER), progesterone receptor (PR), and HER2.
  ER+ cancer cells (that is, cancer cells that have estrogen receptors) depend on estrogen for their growth, so they can be treated with drugs to block estrogen effects (e.g. tamoxifen), and generally have a better prognosis. Untreated, HER2+ breast cancers are generally more aggressive than HER2- breast cancers,[84][85] but HER2+ cancer cells respond to drugs such as the monoclonal antibody trastuzumab (in combination with conventional chemotherapy), and this has improved the prognosis significantly.[86] Cells that do not have any of these three receptor types (estrogen receptors, progesterone receptors, or HER2) are called triple-negative, although they frequently do express receptors for other hormones, such as androgen receptor and prolactin receptor.
- **DNA assays**. DNA testing of various types including DNA microarrays have compared normal cells to breast cancer cells. The specific changes in a particular breast cancer can be used to classify the cancer in several ways, and may assist in choosing the most effective treatment for that DNA type.

Stage 1A breast cancer

Stage 1B breast cancer



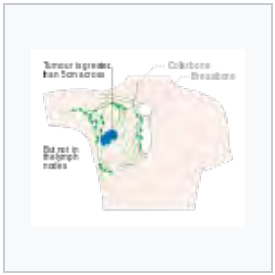
Stage 2A breast cancer



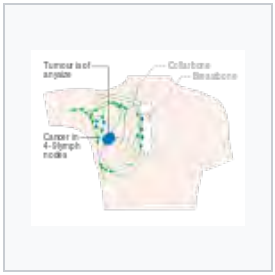
Stage 2A breast cancer

Stage 2B breast cancer

Stage 2B breast cancer

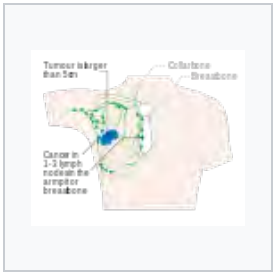


Stage 2B breast cancer



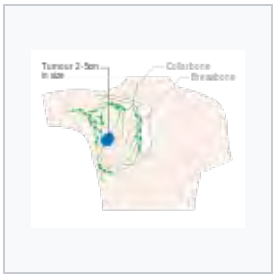
Stage 3A breast cancer

Stage 3A breast cancer

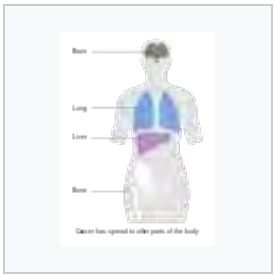


Stage 3A breast cancer

Stage 3B breast cancer



Stage 3B breast cancer



Stage 4 breast cancer

## Prevention [edit]

### Life-style [edit]

Women may reduce their risk of breast cancer by maintaining a healthy weight, drinking less alcohol, being physically active and breastfeeding their children.[87] These modifications might prevent 38% of breast cancers in the US, 42% in the UK, 28% in Brazil and 20% in China.[87] The benefits with moderate exercise such as brisk

walking are seen at all age groups including postmenopausal women.[87][88] High levels of physical activity reduce the risk of breast cancer by about 14%.[89] Strategies that encourage regular physical activity and reduce obesity could also have other benefits, such as reduced risks of cardiovascular disease and diabetes.[25]

High intake of citrus fruit has been associated with a 10% reduction in the risk of breast cancer.[90]

Marine omega-3 polyunsaturated fatty acids appear to reduce the risk.[91] High consumption of soy-based foods may reduce risk.[92]

### Pre-emptive surgery [edit]

Removal of both breasts before any cancer has been diagnosed or any suspicious lump or other lesion has appeared (a procedure known as prophylactic bilateral mastectomy) may be considered in people with BRCA1 and BRCA2 mutations, which are associated with a substantially heightened risk for an eventual diagnosis of breast cancer.[93][94] Evidence is not strong enough to support this procedure in anyone but those at the highest risk.[95] BRCA testing is recommended in those with a high family risk after genetic counseling. It is not recommended routinely.[96] This is because there are many forms of changes in *BRCA* genes, ranging from harmless polymorphisms to obviously dangerous frameshift mutations. The effect of most of the identifiable changes in the genes is uncertain. Testing in an average-risk person is particularly likely to return one of these indeterminate, useless results. It is unclear if removing the second breast in those who have breast cancer in one is beneficial.[95]

### Medications [edit]

The selective estrogen receptor modulators (such as tamoxifen) reduce the risk of breast cancer but increase the risk of thromboembolism and endometrial cancer.[97][97] There is no overall change in the risk of death.[97][98] They are thus not recommended for the prevention of breast cancer in women at average risk but may be offered for those at high risk.[99] The benefit of breast cancer reduction continues for at least five years after stopping a course of treatment with these medications.[100]

## Screening [edit]

*Main article: Breast cancer screening*

Breast cancer screening refers to testing otherwise-healthy women for breast cancer in an attempt to achieve an earlier diagnosis under the assumption that early detection will improve outcomes. A number of screening tests have been employed including clinical and self breast exams, mammography, genetic screening, ultrasound, and magnetic resonance imaging.

A mobile breast cancer screening unit in New Zealand

A clinical or self breast exam involves feeling the breast for lumps or other abnormalities. Clinical breast exams are performed by health care providers, while self-breast exams are performed by the person themselves.[101] Evidence does not support the effectiveness of either type of breast exam, as by the time a lump is large enough to be found it is likely to have been growing for several years and thus soon be large enough to be found without an exam.[102][103] Mammographic screening for breast cancer uses X-rays to examine the breast for any uncharacteristic masses or lumps. During a screening, the breast is compressed and a technician takes photos from multiple angles. A general mammogram takes photos of the entire breast, while a diagnostic mammogram focuses on a specific lump or area of concern.[104]

A number of national bodies recommend breast cancer screening. For the average woman, the U.S. Preventive Services Task Force recommends mammography every two years in women between the ages of 50 and 74,[7] the Council of Europe recommends mammography between 50 and 69 with most programs using a 2-year frequency,[105] and in Canada screening is recommended between the ages of 50 and 74 at a frequency of 2 to 3 years.[106] These task force reports point out that in addition to unnecessary surgery and anxiety, the risks of more frequent mammograms include a small but significant increase in breast cancer induced by radiation.[107]

The Cochrane collaboration (2013) states that the best quality evidence neither demonstrates a reduction in cancer specific, nor a reduction in all cause mortality from screening mammography.[5] When less rigorous trials are added to the analysis there is a reduction in mortality due to breast cancer of 0.05% (a decrease of 1 in 2000 deaths from breast cancer over 10 years or a relative decrease of 15% from breast cancer).[5] Screening over 10 years results in a 30% increase in rates of over-diagnosis and over-treatment (3 to 14 per 1000) and more than

half will have at least one falsely positive test.[5][108][109] This has resulted in the view that it is not clear whether mammography screening does more good or harm.[5] Cochrane states that, due to recent improvements in breast cancer treatment, and the risks of false positives from breast cancer screening leading to unnecessary treatment, "it therefore no longer seems beneficial to attend for breast cancer screening" at any age.[110] Whether MRI as a screening method has greater harms or benefits when compared to standard mammography is not known.[111]

# Management [edit]

*Main article: Breast cancer management*

The management of breast cancer depends on various factors, including the stage of the cancer and the age of the patient. Increasingly aggressive treatments are employed in accordance with the poorer the patient's prognosis and the higher the risk of recurrence of the cancer following treatment.

Breast cancer is usually treated with surgery, which may be followed by chemotherapy or radiation therapy, or both. A multidisciplinary approach is preferable.[112] Hormone receptor-positive cancers are often treated with hormone-blocking therapy over courses of several years. Monoclonal antibodies, or other immune-modulating treatments, may be administered in certain cases of metastatic and other advanced stages of breast cancer.

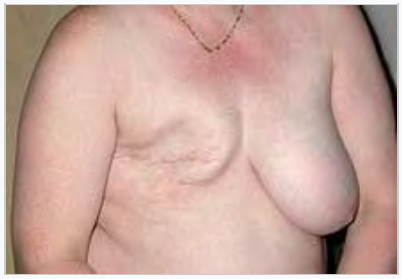
## Surgery [edit]

Surgery involves the physical removal of the tumor, typically along with some of the surrounding tissue. One or more lymph nodes may be biopsied during the surgery; increasingly the lymph node sampling is performed by a sentinel lymph node biopsy.

Standard surgeries include:

- Mastectomy: Removal of the whole breast.
- Quadrantectomy: Removal of one-quarter of the breast.
- Lumpectomy: Removal of a small part of the breast.

Once the tumor has been removed, if the patient desires, breast reconstruction surgery, a type of plastic surgery, may then be performed to improve the aesthetic appearance of the treated site. Alternatively, women use breast prostheses to simulate a breast under clothing, or choose a flat chest. Nipple prosthesis can be used at any time following the mastectomy.



Chest after right breast mastectomy

## Medication [edit]

Drugs used after and in addition to surgery are called adjuvant therapy. Chemotherapy or other types of therapy prior to surgery are called neoadjuvant therapy. Aspirin may reduce mortality from breast cancer.[113]

There are currently three main groups of medications used for adjuvant breast cancer treatment: hormone-blocking agents, chemotherapy, and monoclonal antibodies.

### Hormone blocking therapy

Some breast cancers require estrogen to continue growing. They can be identified by the presence of estrogen receptors (ER+) and progesterone receptors (PR+) on their surface (sometimes referred to together as hormone receptors). These ER+ cancers can be treated with drugs that either block the receptors, e.g. tamoxifen, or alternatively block the production of estrogen with an aromatase inhibitor, e.g. anastrozole[114] or letrozole. The use of tamoxifen is recommended for 10 years.[115] Letrozole is recommended for 5 years. Aromatase inhibitors are only suitable for women after menopause; however, in this group, they appear better than tamoxifen.[116] This is because the active aromatase in postmenopausal women is different from the prevalent form in premenopausal women, and therefore these agents are ineffective in inhibiting the predominant aromatase of premenopausal women.[117] Aromatase inhibitors should not be given to premenopausal women with intact ovarian function (unless they are also on treatment to stop their ovaries from working).[118]

### Chemotherapy

Chemotherapy is predominantly used for cases of breast cancer in stages 2–4, and is particularly beneficial in estrogen receptor-negative (ER-) disease. The chemotherapy medications are administered in combinations, usually for periods of 3–6 months. One of the most common regimens, known as "AC", combines cyclophosphamide with doxorubicin. Sometimes a taxane drug, such as docetaxel, is added, and the regime is

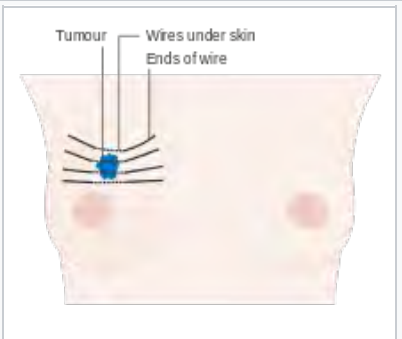
then known as "CAT". Another common treatment is cyclophosphamide, methotrexate, and fluorouracil (or "CMF"). Most chemotherapy medications work by destroying fast-growing and/or fast-replicating cancer cells, either by causing DNA damage upon replication or by other mechanisms. However, the medications also damage fast-growing normal cells, which may cause serious side effects. Damage to the heart muscle is the most dangerous complication of doxorubicin, for example.

### Monoclonal antibodies

Trastuzumab, a monoclonal antibody to HER2 (a cell receptor that is especially active in some breast cancer cells), has improved the 5-year disease free survival of stage 1–3 HER2-positive breast cancers to about 87% (overall survival 95%).[119] When stimulated by certain growth factors, HER2 causes cellular growth and division; in the absence of stimulation by the growth factor, the cell will normally stop growing. Between 25% and 30% of breast cancers overexpress the HER2 gene or its protein product,[120] and overexpression of HER2 in breast cancer is associated with increased disease recurrence and worse prognosis. When trastuzumab binds to the HER2 in breast cancer cells that overexpress the receptor, trastuzumab prevents growth factors from being able to bind to and stimulate the receptors, effectively blocking the growth of the cancer cells. Trastuzumab, however, is very expensive, and its use may cause serious side effects (approximately 2% of patients who receive it suffer significant heart damage).[121] Further, trastuzumab is only effective in patients with HER2 amplification/overexpression.

## Radiation [edit]

Radiotherapy is given after surgery to the region of the tumor bed and regional lymph nodes, to destroy microscopic tumor cells that may have escaped surgery. It may also have a beneficial effect on tumor microenvironment.[122][123] Radiation therapy can be delivered as external beam radiotherapy or as brachytherapy (internal radiotherapy). Conventionally radiotherapy is given *after* the operation for breast cancer. Radiation can also be given at the time of operation on the breast cancer. Radiation can reduce the risk of recurrence by 50–66% (1/2 – 2/3 reduction of risk) when delivered in the correct dose[124] and is considered essential when breast cancer is treated by removing only the lump (Lumpectomy or Wide local excision).



Internal radiotherapy for breast cancer


Breasts after double mastectomy followed by nipple-sparing reconstruction with implants

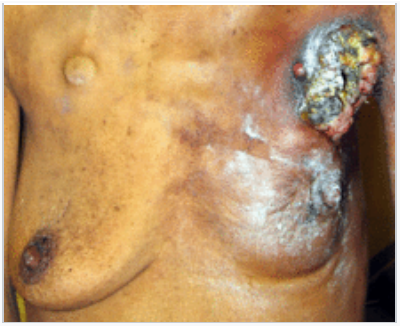
## Prognosis [edit]

Prognosis is usually given for the probability of progression-free survival (PFS) or disease-free survival (DFS). These predictions are based on experience with breast cancer patients with similar classification. A prognosis is an estimate, as patients with the same classification will survive a different amount of time, and classifications are not always precise. Survival is usually calculated as an average number of months (or years) that 50% of patients survive, or the percentage of patients that are alive after 1, 5, 15, and 20 years. Prognosis is important for treatment decisions because patients with a good prognosis are usually offered less invasive treatments, such as lumpectomy and radiation or hormone therapy, while patients with poor prognosis are usually offered more aggressive treatment, such as more extensive mastectomy and one or more chemotherapy drugs.

## Prognostic factors [edit]

Prognostic factors are reflected in the classification scheme for breast cancer including stage, (i.e., tumor size, location, whether disease has spread to lymph nodes and other parts of the body), grade, recurrence of the disease, and the age and health of the patient. The Nottingham Prognostic Index is a commonly used prognostic tool.

The stage of the breast cancer is the most important component of traditional classification methods of breast cancer, because it has a greater effect on the prognosis than the other considerations. Staging takes into consideration size, local involvement, lymph node status and whether metastatic disease is present. The higher the stage at diagnosis, the poorer the prognosis. The stage is raised by the invasiveness of disease to lymph nodes, chest wall, skin or beyond, and the aggressiveness of the cancer cells. The stage is lowered by the presence of cancer-free zones and close-to-normal cell behaviour



An example of an advanced recurrent breast cancer with an ulcerating axillary mass

(grading). Size is not a factor in staging unless the cancer is invasive. For example, Ductal Carcinoma In Situ (DCIS) involving the entire breast will still be stage zero and consequently an excellent prognosis with a 10-year disease free survival of about 98%.[125]

- Stage 1 cancers (and DCIS, LCIS) have an excellent prognosis and are generally treated with lumpectomy and sometimes radiation.[126] HER2+ cancers should be treated with the trastuzumab (Herceptin) regime.[127] Chemotherapy is uncommon for other types of stage 1 cancers.
- Stage 2 and 3 cancers with a progressively poorer prognosis and greater risk of recurrence are generally treated with surgery (lumpectomy or mastectomy with or without lymph node removal), chemotherapy (plus trastuzumab for HER2+ cancers) and sometimes radiation (particularly following large cancers, multiple positive nodes or lumpectomy).
- Stage 4, metastatic cancer, (i.e. spread to distant sites) has poor prognosis and is managed by various combination of all treatments from surgery, radiation, chemotherapy and targeted therapies. Ten-year survival rate is 5% without treatment and 10% with optimal treatment.[128]

The breast cancer grade is assessed by comparison of the breast cancer cells to normal breast cells. The closer to normal the cancer cells are, the slower their growth and the better the prognosis. If cells are not well differentiated, they will appear immature, will divide more rapidly, and will tend to spread. Well differentiated is given a grade of 1, moderate is grade 2, while poor or undifferentiated is given a higher grade of 3 or 4 (depending upon the scale used). The most widely used grading system is the Nottingham scheme;[129] details are provided in the discussion of breast cancer grade.

The presence of estrogen and progesterone receptors in the cancer cell is important in guiding treatment. Those who do not test positive for these specific receptors will not be able to respond to hormone therapy, and this can affect their chance of survival depending upon what treatment options remain, the exact type of cancer, and how advanced the disease is.

In addition to hormone receptors, there are other cell surface proteins that may affect prognosis and treatment. HER2 status directs the course of treatment. Patients whose cancer cells are positive for HER2 have a more aggressive disease and may be treated with the 'targeted therapy', trastuzumab (Herceptin), a monoclonal antibody that targets this protein and improves the prognosis significantly.

Younger women with an age of less than 40 years or women over 80 years tend to have a poorer prognosis than post-menopausal women due to several factors. Their breasts may change with their menstrual cycles, they may be nursing infants, and they may be unaware of changes in their breasts. Therefore, younger women are usually at a more advanced stage when diagnosed. There may also be biologic factors contributing to a higher risk of disease recurrence for younger women with breast cancer.[130][131]

High mammographic breast density, which is a marker of increased risk of developing breast cancer, may not mean an increased risk of death among breast cancer patients, according to a 2012 report of a study involving 9232 women by the National Cancer Institute (NCI).[132] On the other hand, more recent research has shown that women with extremely low mammographic densities (<10%) hold a significantly worse prognosis compared to women with other densities, irrespective of all possible confounding factors.[133]

Since breast cancer in males is usually detected at later stages, outcomes are typically worse.[134]

## Psychological aspects [edit]

The emotional impact of cancer diagnosis, symptoms, treatment, and related issues can be severe. Most larger hospitals are associated with cancer support groups which provide a supportive environment to help patients cope and gain perspective from cancer survivors.

Not all breast cancer patients experience their illness in the same manner. Factors such as age can have a significant impact on the way a patient copes with a breast cancer diagnosis. Premenopausal women with estrogen-receptor positive breast cancer must confront the issues of early menopause induced by many of the

chemotherapy regimens used to treat their breast cancer, especially those that use hormones to counteract ovarian function.[135]

On the other hand, a small 2007 study conducted by researchers at the College of Public Health of the University of Georgia suggested a need for greater attention to promoting functioning and psychological well-being among older cancer survivors, even when they may not have obvious cancer-related medical complications.[136] The study found that older breast cancer survivors showed multiple indications of decrements in their health-related quality of life, and lower psychosocial well-being than a comparison group. Survivors reported no more depressive symptoms or anxious mood than the comparison group, however, they did score lower on measures of positive psychosocial well-being and reported more depressed mood and days affected by fatigue. As the incidence of breast cancer in women over 50 rises and survival rates increase, breast cancer is increasingly becoming a geriatric issue that warrants both further research and the expansion of specialized cancer support services tailored for specific age groups.[136]

## Epidemiology [edit]

*Main article: Epidemiology of breast cancer*

Worldwide, breast cancer is the most common invasive cancer in women.[138] It affects about 12% of women worldwide.[138] (The most common form of cancer is non-invasive non-melanoma skin cancer; non-invasive cancers are generally easily cured, cause very few deaths, and are routinely excluded from cancer statistics.) Breast cancer comprises 22.9% of invasive cancers in women[139] and 16% of all female cancers.[140] In 2012, it comprised 25.2% of cancers diagnosed in women, making it the most common female cancer.[141]

Age-standardized death from breast cancer per 100,000 inhabitants in 2004.[137]

| | |
|---|---|
| no data | 12–14 |
| <2 | 14–16 |
| 2–4 | 16–18 |
| 4–6 | 18–20 |
| 6–8 | 20–22 |
| 8–10 | >22 |
| 10–12 | |

In 2008, breast cancer caused 458,503 deaths worldwide (13.7% of cancer deaths in women and 6.0% of all cancer deaths for men and women together).[139] Lung cancer, the second most common cause of cancer-related death in women, caused 12.8% of cancer deaths in women (18.2% of all cancer deaths for men and women together).[139]

The incidence of breast cancer varies greatly around the world: it is lowest in less-developed countries and greatest in the more-developed countries. In the twelve world regions, the annual age-standardized incidence rates per 100,000 women are as follows: in Eastern Asia, 18; South Central Asia, 22; sub-Saharan Africa, 22; South-Eastern Asia, 26; North Africa and Western Asia, 28; South and Central America, 42; Eastern Europe, 49; Southern Europe, 56; Northern Europe, 73; Oceania, 74; Western Europe, 78; and in North America, 90.[142]

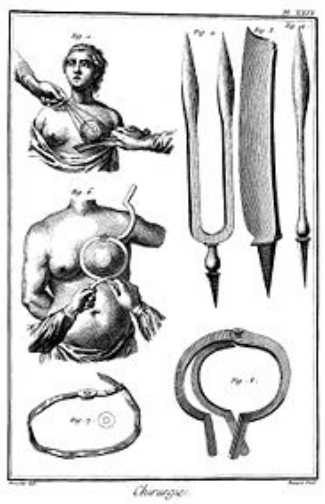
The number of cases worldwide has significantly increased since the 1970s, a phenomenon partly attributed to the modern lifestyles.[143][144] Breast cancer is strongly related to age with only 5% of all breast cancers occurring in women under 40 years old.[145] There were more than 41,000 newly diagnosed cases of breast cancer registered in England in 2011, around 80% of these cases were in women age 50 or older [146] Based on U.S. statistics in 2015 there were 2.8 million women affected by breast cancer.[138]

## History [edit]

It has been suggested that this section be split out into another article titled *History of breast cancer*. (Discuss) *(December 2015)*

Because of its visibility, breast cancer was the form of cancer most often described in ancient documents.[147] Because autopsies were rare, cancers of the internal organs were essentially invisible to ancient medicine. Breast cancer, however, could be felt through the skin, and in its advanced state often developed into fungating lesions: the tumor would become necrotic (die from the inside, causing the tumor to appear to break up) and ulcerate through the skin, weeping fetid, dark fluid.[147]

The oldest evidence of breast cancer was discovered in Egypt in 2015 and dates back to the Sixth Dynasty.[148] The study of a woman's remains from the



Breast cancer surgery in 18th century

necropolis of Qubbet el-Hawa showed the typical destructive damage due to metastatic spread.[148] The Edwin Smith Papyrus describes 8 cases of tumors or ulcers of the breast that were treated by cauterization. The writing says about the disease, "There is no treatment."[149] For centuries, physicians described similar cases in their practices, with the same conclusion. Ancient medicine, from the time of the Greeks through the 17th century, was based on humoralism, and thus believed that breast cancer was generally caused by imbalances in the fundamental fluids that controlled the body, especially an excess of black bile.[150] Alternatively, patients often saw it as divine punishment.[151] In the 18th century, a wide variety of medical explanations were proposed, including a lack of sexual activity, too much sexual activity, physical injuries to the breast, curdled breast milk, and various forms of lymphatic blockages, either internal or due to restrictive clothing.[150][152] In the 19th century, the Scottish surgeon John Rodman said that fear of cancer caused cancer, and that this anxiety, learned by example from the mother, accounted for breast cancer's tendency to run in families.[152]

Although breast cancer was known in ancient times, it was uncommon until the 19th century, when improvements in sanitation and control of deadly infectious diseases resulted in dramatic increases in lifespan. Previously, most women had died too young to have developed breast cancer.[152] Additionally, early and frequent childbearing and breastfeeding probably reduced the rate of breast cancer development in those women who did survive to middle age.[152]

Because ancient medicine believed that the cause was systemic, rather than local, and because surgery carried a high mortality rate, the preferred treatments tended to be pharmacological rather than surgical. Herbal and mineral preparations, especially involving the poison arsenic, were relatively common.

Mastectomy for breast cancer was performed at least as early as AD 548, when it was proposed by the court physician Aetios of Amida to Theodora.[147] It was not until doctors achieved greater understanding of the circulatory system in the 17th century that they could link breast cancer's spread to the lymph nodes in the armpit. The French surgeon Jean Louis Petit (1674–1750) and later the Scottish surgeon Benjamin Bell (1749–1806) were the first to remove the lymph nodes, breast tissue, and underlying chest muscle.[153]

Their successful work was carried on by William Stewart Halsted who started performing radical mastectomies in 1882, helped greatly by advances in general surgical technology, such as aseptic technique and anesthesia. The Halsted radical mastectomy often involved removing both breasts, associated lymph nodes, and the underlying chest muscles. This often led to long-term pain and disability, but was seen as necessary in order to prevent the cancer from recurring.[154] Before the advent of the Halsted radical mastectomy, 20-year survival rates were only 10%; Halsted's surgery raised that rate to 50%.[155] Extending Halsted's work, Jerome Urban promoted superradical mastectomies, taking even more tissue, until 1963, when the ten-year survival rates proved equal to the less-damaging radical mastectomy.[154]

Radical mastectomies remained the standard of care in America until the 1970s, but in Europe, breast-sparing procedures, often followed radiation therapy, were generally adopted in the 1950s.[154] One reason for this striking difference in approach may be the structure of the medical professions: European surgeons, descended from the barber surgeon, were held in less esteem than physicians; in America, the surgeon was the king of the medical profession.[154] Additionally, there were far more European women surgeons: Less than one percent of American surgical oncologists were female, but some European breast cancer wards boasted a medical staff that was half female.[154] American health insurance companies also paid surgeons more to perform radical mastectomies than they did to perform more intricate breast-sparing surgeries.[154]

Breast cancer staging systems were developed in the 1920s and 1930s.[154]

During the 1970s, a new understanding of metastasis led to perceiving cancer as a systemic illness as well as a localized one, and more sparing procedures were developed that proved equally effective. Modern chemotherapy developed after World War II.[156]

The French surgeon Bernard Peyrilhe (1737–1804) realized the first experimental transmission of cancer by injecting extracts of breast cancer into an animal.

Prominent women who died of breast cancer include Anne of Austria, the mother of Louis XIV of France; Mary Washington, mother of George, and Rachel Carson, the environmentalist.[157]

The first case-controlled study on breast cancer epidemiology was done by Janet Lane-Claypon, who published a comparative study in 1926 of 500 breast cancer cases and 500 control patients of the same background and lifestyle for the British Ministry of Health.[158]

In the 1980s and 1990s, thousands of women who had successfully completed standard treatment then demanded and received high-dose bone marrow transplants, thinking this would lead to better long-term survival. However, it proved completely ineffective, and 15–20% of women died because of the brutal treatment.[159]

The 1995 reports from the Nurses' Health Study and the 2002 conclusions of the Women's Health Initiative trial conclusively proved that hormone replacement therapy significantly increased the incidence of breast cancer.[159]

## Society and culture [edit]

*See also: Breast cancer awareness and List of people with breast cancer*

Before the 20th century, breast cancer was feared and discussed in hushed tones, as if it were shameful. As little could be safely done with primitive surgical techniques, women tended to suffer silently rather than seeking care. When surgery advanced, and long-term survival rates improved, women began raising awareness of the disease and the possibility of successful treatment. The "Women's Field Army", run by the American Society for the Control of Cancer (later the American Cancer Society) during the 1930s and 1940s was one of the first organized campaigns. In 1952, the first peer-to-peer support group, called "Reach to Recovery", began providing post-mastectomy, in-hospital visits from women who had survived breast cancer.[160]

The breast cancer movement of the 1980s and 1990s developed out of the larger feminist movements and women's health movement of the 20th century.[161] This series of political and educational campaigns, partly inspired by the politically and socially effective AIDS awareness campaigns, resulted in the widespread acceptance of second opinions before surgery, less invasive surgical procedures, support groups, and other advances in patient care.[162]

### Pink ribbon [edit]

*Main article: Pink ribbon*

A pink ribbon is the most prominent symbol of breast cancer awareness. Pink ribbons, which can be made inexpensively, are sometimes sold as fundraisers, much like poppies on Remembrance Day. They may be worn to honor those who have been diagnosed with breast cancer, or to identify products that the manufacturer would like to sell to consumers that are interested in breast cancer—usually white, middle-aged, middle-class and upper-class, educated women.[163]

The pink ribbon is a symbol to show support for breast cancer awareness

The pink ribbon is associated with individual generosity, faith in scientific progress, and a "can-do" attitude. It encourages consumers to focus on the emotionally appealing ultimate vision of a cure for breast cancer, rather than on the fraught path between current knowledge and any future cures.[164]

Wearing or displaying a pink ribbon has been criticized by the opponents of this practice as a kind of slacktivism, because it has no practical positive effect. It has also been criticized as hypocrisy, because some people wear the pink ribbon to show good will towards women with breast cancer, but then oppose these women's practical goals, like patient rights and anti-pollution legislation.[165][166] Critics say that the feel-good nature of pink ribbons and pink consumption distracts society from the lack of progress on preventing and curing breast cancer.[167] It is also criticized for reinforcing gender stereotypes and objectifying women and their breasts.[168] Breast Cancer Action launched the "Think Before You Pink" campaign, and said that businesses have co-opted the pink campaign to promote products that cause breast cancer, such as alcoholic beverages.[169]

### Breast cancer culture [edit]

This section **is written like a personal reflection or opinion essay that states a Wikipedia editor's personal feelings about a topic**. Please help improve it by rewriting it in an encyclopedic style. *(November 2015) (Learn how and when to remove this template message)*

Breast cancer culture, or pink ribbon culture, is the set of activities, attitudes, and values that surround and shape breast cancer in public. The dominant values are selflessness, cheerfulness, unity, and optimism. Appearing to have suffered bravely is the passport into the culture.

The woman with breast cancer is given a cultural template that constrains her emotional and social responses into a socially acceptable discourse: She is to use the emotional trauma of being diagnosed with breast cancer and the suffering of extended treatment to transform herself into a stronger, happier and more sensitive person who is grateful for the opportunity to become a better person. Breast cancer therapy becomes a rite of passage rather than a disease.[170] To fit into this mold, the woman with breast cancer needs to normalize and feminize her appearance, and minimize the disruption that her health issues cause anyone else. Anger, sadness, and negativity must be silenced.[170]

As with most cultural models, people who conform to the model are given social status, in this case as cancer survivors. Women who reject the model are shunned, punished and shamed.[170]

The culture is criticized for treating adult women like little girls, as evidenced by "baby" toys such as pink teddy bears given to adult women.[170]

The primary purposes or goals of breast cancer culture are to maintain breast cancer's dominance as the preëminent women's health issue, to promote the appearance that society is "doing something" effective about breast cancer, and to sustain and expand the social, political, and financial power of breast cancer activists.[171]

### Emphasis [edit]

Compared to other diseases or other cancers, breast cancer receives a proportionately greater share of resources and attention. In 2001 MP Ian Gibson, chairman of the House of Commons of the United Kingdom all party group on cancer stated "The treatment has been skewed by the lobbying, there is no doubt about that. Breast cancer sufferers get better treatment in terms of bed spaces, facilities and doctors and nurses."[172] Breast cancer also receives significantly more media coverage than other, equally prevalent cancers, with a study by Prostate Coalition showing 2.6 breast cancer stories for each one covering cancer of the prostate.[173] Ultimately there is a concern that favoring sufferers of breast cancer with disproportionate funding and research on their behalf may well be costing lives elsewhere.[172] Partly because of its relatively high prevalence and long-term survival rates, research is biased towards breast cancer. Some subjects, such as cancer-related fatigue, have been studied little except in women with breast cancer.

One result of breast cancer's high visibility is that statistical results can sometimes be misinterpreted, such as the claim that one in eight women will be diagnosed with breast cancer during their lives—a claim that depends on the unrealistic assumption that no woman will die of any other disease before the age of 95.[174] This obscures the reality, which is that about ten times as many women will die from heart disease or stroke than from breast cancer.[175]

The emphasis on breast cancer screening may be harming women by subjecting them to unnecessary radiation, biopsies, and surgery. One-third of diagnosed breast cancers might recede on their own.[176] Screening mammography efficiently finds non-life-threatening, asymptomatic breast cancers and pre-cancers, even while overlooking serious cancers. According to H. Gilbert Welch of the Dartmouth Institute for Health Policy and Clinical Practice, research on screening mammography has taken the "brain-dead approach that says the best test is the one that finds the most cancers" rather than the one that finds dangerous cancers.[176]

## Pregnancy [edit]

Breast cancers occur during pregnancy at the same rate as breast cancers in non-pregnant women of the same age. Breast cancer then becomes more common in the 5 or 10 years following pregnancy but then becomes less common than among the general population.[177] These cancers are known as postpartum breast cancer and have worse outcomes including an increased risk of distant spread of disease and mortality.[178] Other cancers found during or shortly after pregnancy appear at approximately the same rate as other cancers in women of a similar age.[179]

Diagnosing new cancer in a pregnant woman is difficult, in part because any symptoms are commonly assumed to be a normal discomfort associated with pregnancy.[179] As a result, cancer is typically discovered at a somewhat

later stage than average in many pregnant or recently pregnant women. Some imaging procedures, such as MRIs (magnetic resonance imaging), CT scans, ultrasounds, and mammograms with fetal shielding are considered safe during pregnancy; some others, such as PET scans are not.[179]

Treatment is generally the same as for non-pregnant women.[179] However, radiation is normally avoided during pregnancy, especially if the fetal dose might exceed 100 cGy. In some cases, some or all treatments are postponed until after birth if the cancer is diagnosed late in the pregnancy. Early deliveries to speed the start of treatment are not uncommon. Surgery is generally considered safe during pregnancy, but some other treatments, especially certain chemotherapy drugs given during the first trimester, increase the risk of birth defects and pregnancy loss (spontaneous abortions and stillbirths).[179] Elective abortions are not required and do not improve the likelihood of the mother surviving or being cured.[179]

Radiation treatments may interfere with the mother's ability to breastfeed her baby because it reduces the ability of that breast to produce milk and increases the risk of mastitis. Also, when chemotherapy is being given after birth, many of the drugs pass through breast milk to the baby, which could harm the baby.[179]

Regarding future pregnancy among breast cancer survivors, there is often fear of cancer recurrence.[180] On the other hand, many still regard pregnancy and parenthood to represent normalcy, happiness and life fulfillment.[180]

## Hormones [edit]

### Birth control [edit]

In breast cancer survivors, non-hormonal birth control methods should be used as first-line options. Progestogen-based methods such as depot medroxyprogesterone acetate, IUD with progestogen or progestogen only pills have a poorly investigated but possible increased risk of cancer recurrence, but may be used if positive effects outweigh this possible risk.[181]

### Menopausal hormone replacement [edit]

In breast cancer survivors, it is recommended to first consider non-hormonal options for menopausal effects, such as bisphosphonates or selective estrogen receptor modulators (SERMs) for osteoporosis, and vaginal estrogen for local symptoms. Observational studies of systemic hormone replacement therapy after breast cancer are generally reassuring. If hormone replacement is necessary after breast cancer, estrogen-only therapy or estrogen therapy with an intrauterine device with progestogen may be safer options than combined systemic therapy.[182]

## Research [edit]

It has been suggested that this section be split out into another article titled *Breast cancer research*. (Discuss) *(December 2015)*

Treatments are constantly evaluated in randomized, controlled trials, to evaluate and compare individual drugs, combinations of drugs, and surgical and radiation techniques. Investigations include new types of targeted therapy as well as cancer vaccines.

The latest research is reported annually at scientific meetings such as that of the American Society of Clinical Oncology, San Antonio Breast Cancer Symposium,[183] and the St. Gallen Oncology Conference in St. Gallen, Switzerland.[184] These studies are reviewed by professional societies and other organizations, and formulated into guidelines for specific treatment groups and risk category.

Fenretinide, a retinoid, is also being studied as a way to reduce the risk of breast cancer (retinoids are drugs related to vitamin A).[185][186]

### Cryoablation [edit]

As of 2014 cryoablation is being studied to see if it could be a substitute for a lumpectomy in small cancers.[187] There is tentative evidence in those with tumors less than 2 centimeters.[188] It may also be used in those in who surgery is not possible.[188] Another review states that cryoablation looks promising for early breast cancer of small size.[189]

### Breast cancer cell lines [edit]

*See also: List of breast cancer cell lines*

A considerable part of the current knowledge on breast carcinomas is based on in vivo and in vitro studies performed with cell lines derived from breast cancers. These provide an unlimited source of homogenous self-replicating material, free of contaminating stromal cells, and often easily cultured in simple standard media. The first breast cancer cell line described, BT-20, was established in 1958. Since then, and despite sustained work in this area, the number of permanent lines obtained has been strikingly low (about 100). Indeed, attempts to culture breast cancer cell lines from primary tumors have been largely unsuccessful. This poor efficiency was often due to technical difficulties associated with the extraction of viable tumor cells from their surrounding stroma. Most of the available breast cancer cell lines issued from metastatic tumors, mainly from pleural effusions. Effusions provided generally large numbers of dissociated, viable tumor cells with little or no contamination by fibroblasts and other tumor stroma cells. Many of the currently used BCC lines were established in the late 1970s. A very few of them, namely MCF-7, T-47D, and MDA-MB-231, account for more than two-thirds of all abstracts reporting studies on mentioned breast cancer cell lines, as concluded from a Medline-based survey.

### Molecular markers [edit]

### Transcription factors [edit]

NFAT transcription factors are implicated in breast cancer, more specifically in the process of cell motility at the basis of metastasis formation. Indeed, NFAT1 (NFATC2) and NFAT5 are pro-invasive and pro-migratory in breast carcinoma[190][191] and NFAT3 (NFATc4) is an inhibitor of cell motility.[192] NFAT1 regulates the expression of the TWEAKR and its ligand TWEAK with the Lipocalin 2 to increase breast cancer cell invasion[193] and NFAT3 inhibits Lipocalin 2 expression to blunt the cell invasion.[192]

### Metabolic markers [edit]

Clinically, the most useful metabolic markers in breast cancer are the estrogen and progesterone receptors that are used to predict response to hormone therapy. New or potentially new markers for breast cancer include BRCA1 and BRCA2[194] to identify patients at high risk of developing breast cancer, HER-2[195] and SCD1[196] for predicting response to therapeutic regimens, and urokinase plasminogen activator, PA1-1[197] and SCD1[198] for assessing prognosis.

## Other animals [edit]

- Mammary tumor for breast cancer in other animals
- Mouse models of breast cancer metastasis

## References [edit]


1. ^ "Breast Cancer". *NCI*. Retrieved 29 June 2014.
2. ^ *a b c d e* "Breast Cancer Treatment (PDQ®)". *NCI*. 23 May 2014. Retrieved 29 June 2014.
3. ^ Saunders, Christobel; Jassal, Sunil (2009). *Breast cancer* (1. ed.). Oxford: Oxford University Press. p. Chapter 13. ISBN 978-0-19-955869-8.
4. ^ *a b c d e f* *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 5.2. ISBN 92-832-0429-8.
5. ^ *a b c d e* Gøtzsche PC, Jørgensen KJ (4 June 2013). "Screening for breast cancer with mammography.". *The Cochrane database of systematic reviews*. **6**: CD001877. doi:10.1002/14651858.CD001877.pub5. PMID 23737396.
6. ^ Nelson, HD; Tyne, K; Naik, A; Bougatsos, C; Chan, B; Nygren, P; Humphrey, L (November 2009). "Screening for Breast Cancer: Systematic Evidence Review Update for the US Preventive Services Task Force [Internet].". PMID 20722173.
7. ^ *a b* Siu, Albert L. (12 January 2016). "Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement". *Annals of Internal Medicine*. doi:10.7326/M15-2886.
8. ^ American College of Surgeons (September 2013), "Five Things Physicians and Patients Should Question", *Choosing Wisely: an initiative of the ABIM Foundation*, American College of Surgeons, retrieved 2 January 2013
9. ^ *a b c* "Breast Cancer Treatment (PDQ®)". *NCI*. 26 June 2014. Retrieved 29 June 2014.
10. ^ *a b* "World Cancer Report" (PDF). International Agency for Research on Cancer. 2008. Retrieved 26 February 2011.
11. ^ "Cancer Survival in England: Patients Diagnosed 2007–2011 and Followed up to 2012" (PDF). *Office for National Statistics*. 29 October 2013. Retrieved 29 June 2014.
12. ^ "SEER Stat Fact Sheets: Breast Cancer". *NCI*. Retrieved 18 June 2014.
13. ^ *a b* *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 1.1. ISBN 92-832-0429-8.
14. ^ "Male Breast Cancer Treatment". National Cancer Institute. 2014. Retrieved 29 June 2014.
15. ^ *a b c d* Merck Manual of Diagnosis and Therapy (February 2003). "Breast Disorders: Breast Cancer". Retrieved

5 February 2008.
16. ^ [a] [b] American Cancer Society (2007). "Cancer Facts & Figures 2007" (PDF). Archived from the original (PDF) on 10 April 2007. Retrieved 26 April 2007.
17. ^ Watson M (2008). "Assessment of suspected cancer". *InnoAiT*. **1** (2): 94–107. doi:10.1093/innovait/inn001.
18. ^ eMedicine (23 August 2006). "Breast Cancer Evaluation". Retrieved 5 February 2008.
19. ^ National Cancer Institute (27 June 2005). "Paget's Disease of the Nipple: Questions and Answers". Retrieved 6 February 2008.
20. ^ answers.com. "Oncology Encyclopedia: Cystosarcoma Phyllodes". Retrieved 10 August 2010.
21. ^ Lacroix M (December 2006). "Significance, detection and markers of disseminated breast cancer cells". *Endocrine-Related Cancer*. Bioscientifica. **13** (4): 1033–67. doi:10.1677/ERC-06-0001. PMID 17158753.
22. ^ National Cancer Institute (1 September 2004). "Metastatic Cancer: Questions and Answers". Retrieved 6 February 2008.
23. ^ *Interpreting Signs and Symptoms*. Lippincott Williams & Wilkins. 2007. pp. 99–. ISBN 978-1-58255-668-0.
24. ^ Merck Manual of Diagnosis and Therapy (February 2003). "Breast Disorders: Overview of Breast Disorders". Retrieved 5 February 2008.
25. ^ [a] [b] [c] Hayes,, James; Ricahrdson, Ann; Frampton, Chris (15 November 2013). "Population attributable risks for modifiable lifestyle factors and breast cancer in New Zealand women". *IMJ*. **43** (11): 1198–1204. doi:10.1111/imj.12256. PMID 23910051.
26. ^ Reeder JG, Vogel VG (2008). "Breast cancer prevention.". *Cancer treatment and research*. **141**: 149–64. doi:10.1007/978-0-387-73161-2_10. PMID 18274088.
27. ^ "Am I at risk?". Breast Cancer Care. Retrieved 22 October 2013.
28. ^ Collaborative Group on Hormonal Factors in Breast Cancer (August 2002). "Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease.". *Lancet*. **360** (9328): 187–95. doi:10.1016/S0140-6736(02)09454-0. PMID 12133652.
29. ^ Yager JD, Davidson NE (2006). "Estrogen carcinogenesis in breast cancer". *New Engl J Med*. **354** (3): 270–82. doi:10.1056/NEJMra050776. PMID 16421368.
30. ^ Mazzucco A, Santoro E, DeSoto, M, Hong Lee J (February 2009). "Hormone Therapy and Menopause". National Research Center for Women & Families.
31. ^ Light Pollution as new risk factor for human Breast and Prostate Cancers- Haim,Abraham; Portnov, Biris P. ,2013,ISBN 978-94-007-6220-6
32. ^ [a] [b] Johnson KC, Miller AB, Collishaw NE, Palmer JR, Hammond SK, Salmon AG, Cantor KP, Miller MD, Boyd NF, Millar J, Turcotte F (Jan 2011). "Active smoking and secondhand smoke increase breast cancer risk: the report of the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk (2009).". *Tobacco control*. **20** (1): e2. doi:10.1136/tc.2010.035931. PMID 21148114.
33. ^ Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT (1 July 2012). "Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy". *The Lancet*. **380** (9838): 219–29. doi:10.1016/S0140-6736(12)61031-9. PMC 3645500. PMID 22818936.
34. ^ Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA (2015). "Sedentary Time and Its Association With Risk for Disease Incidence, Mortality, and Hospitalization in Adults: A Systematic Review and Meta-analysis". *Annals of Internal Medicine*. **162** (2): 123–32. doi:10.7326/M14-1651. PMID 25599350.
35. ^ Kahlenborn C, Modugno F, Potter DM, Severs WB (Oct 2006). "Oral contraceptive use as a risk factor for premenopausal breast cancer: a meta-analysis.". *Mayo Clinic proceedings. Mayo Clinic*. **81** (10): 1290–302. doi:10.4065/81.10.1290. PMID 17036554.
36. ^ [a] [b] Veljković M, Veljković S (Sep 2010). "[The risk of breast cervical, endometrial and ovarian cancer in oral contraceptive users].". *Medicinski pregled*. **63** (9–10): 657–61. doi:10.2298/mpns1010657v. PMID 21446095.
37. ^ [a] [b] Casey PM, Cerhan JR, Pruthi S (January 2008). "Oral contraceptive use and risk of breast cancer.". *Mayo Clinic proceedings. Mayo Clinic*. **83** (1): 86–90; quiz 90–1. doi:10.4065/83.1.86. PMID 18174010.
38. ^ Iodice S, Barile M, Rotmensz N, Feroce I, Bonanni B, Radice P, Bernard L, Maisonneuve P, Gandini S (August 2010). "Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis.". *European journal of cancer (Oxford, England : 1990)*. **46** (12): 2275–84. doi:10.1016/j.ejca.2010.04.018. PMID 20537530.
39. ^ Gaffield ME, Culwell KR, Ravi A (October 2009). "Oral contraceptives and family history of breast cancer.". *Contraception*. **80** (4): 372–80. doi:10.1016/j.contraception.2009.04.010. PMID 19751860.
40. ^ Yang L, Jacobsen KH (December 2008). "A systematic review of the association between breastfeeding and breast cancer.". *Journal of Women's Health*. **17** (10): 1635–45. doi:10.1089/jwh.2008.0917. PMID 19049358.
41. ^ Russo J, Russo IH (1980). "Susceptibility of the mammary gland to carcinogenesis. II. Pregnancy interruption as a risk factor in tumor incidence". *Am J Pathol*. **100** (2): 505–506. PMC 1903536. PMID 6773421. "In contrast, abortion is associated with increased risk of carcinomas of the breast. The explanation for these epidemiologic findings is not known, but the parallelism between the DMBA-induced rat mammary carcinoma model and the human situation is striking. ... Abortion would interrupt this process, leaving in the gland undifferentiated structures like those observed in the rat mammary gland, which could render the gland again susceptible to carcinogenesis."
42. ^ Beral V, Bull D, Doll R, Peto R, Reeves G (27 March 2004). "Breast cancer and abortion: collaborative reanalysis of data from 53 epidemiological studies, including 83?000 women with breast cancer from 16 countries.". *Lancet*. **363** (9414): 1007–16. doi:10.1016/S0140-6736(04)15835-2. PMID 15051280.
43. ^ Blackburn GL, Wang KA (September 2007). "Dietary fat reduction and breast cancer outcome: results from the Women's Intervention Nutrition Study (WINS).". *The American Journal of Clinical Nutrition*. **86** (3): s878–81. PMID 18265482.

44. ^ Boffetta P, Hashibe M, La Vecchia C, Zatonski W, Rehm J (August 2006). "The burden of cancer attributable to alcohol drinking". *International Journal of Cancer*. **119** (4): 884–7. doi:10.1002/ijc.21903. PMID 16557583.
45. ^ BBC report Weight link to breast cancer risk
46. ^ Kaiser J (29 November 2013). "Cancer. Cholesterol forges link between obesity and breast cancer.". *Science*. **342** (6162): 1028. doi:10.1126/science.342.6162.1028. PMID 24288308.
47. ^ Aceves C, Anguiano B, Delgado G (April 2005). "Is iodine a gatekeeper of the integrity of the mammary gland?". *Journal of Mammary Gland Biology and Neoplasia*. **10** (2): 189–96. doi:10.1007/s10911-005-5401-5. PMID 16025225.
48. ^ Mourouti, N; Kontogianni, MD; Papavagelis, C; Panagiotakos, DB (February 2015). "Diet and breast cancer: a systematic review.". *International journal of food sciences and nutrition*. **66** (1): 1–42. doi:10.3109/09637486.2014.950207. PMID 25198160.
49. ^ Aubrey, Allison (1 February 2016). "A Diet High In Fiber May Help Protect Against Breast Cancer". *NPR*. Retrieved 1 February 2016.
50. ^ *a b* American Cancer Society (2005). "Breast Cancer Facts & Figures 2005–2006" (PDF). Archived from the original (PDF) on 13 June 2007. Retrieved 26 April 2007.
51. ^ Wang XS, Armstrong ME, Cairns BJ, Key TJ, Travis RC (March 2011). "Shift work and chronic disease: the epidemiological evidence.". *Occupational Medicine*. **61** (2): 78–89. doi:10.1093/occmed/kqr001. PMC 3045028. PMID 21355031.
52. ^ Brody JG, Rudel RA, Michels KB, Moysich KB, Bernstein L, Attfield KR, Gray S (June 2007). "Environmental pollutants, diet, physical activity, body size, and breast cancer: where do we stand in research to identify opportunities for prevention?". *Cancer*. **109** (12 Suppl): 2627–34. doi:10.1002/cncr.22656. PMID 17503444.
53. ^ Hendrick RE (October 2010). "Radiation doses and cancer risks from breast imaging studies.". *Radiology*. **257** (1): 246–53. doi:10.1148/radiol.10100570. PMID 20736332.
54. ^ *a b c* Boris Pasche (2010). *Cancer Genetics (Cancer Treatment and Research)*. Berlin: Springer. pp. 19–20. ISBN 1-4419-6032-5.
55. ^ *a b c* Gage M, Wattendorf D, Henry LR (1 April 2012). "Translational advances regarding hereditary breast cancer syndromes". *Journal of surgical oncology*. **105** (5): 444–51. doi:10.1002/jso.21856. PMID 22441895.
56. ^ Colditz, Graham A.; Kaphingst, Kimberly A.; Hankinson, Susan E.; Rosner, Bernard (19 February 2012). "Family history and risk of breast cancer: nurses' health study". *Breast Cancer Research and Treatment*. **133** (3): 1097–1104. doi:10.1007/s10549-012-1985-9. ISSN 0167-6806. PMC 3387322. PMID 22350789.
57. ^ "Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease.". *Lancet*. **358** (9291): 1389–99. 27 October 2001. doi:10.1016/S0140-6736(01)06524-2. PMID 11705483.
58. ^ Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, Buist DS, Kerlikowske K, van Ravesteyn NT, Trentham-Dietz A, Mandelblatt JS, Miglioretti DL (1 May 2012). "Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis.". *Annals of Internal Medicine*. **156** (9): 635–48. doi:10.1059/0003-4819-156-9-201205010-00006. PMC 3561467. PMID 22547473.
59. ^ Kolata, Gina (23 September 2012). "Genetic Study Finds 4 Distinct Variations of Breast Cancer". *The New York Times*. Retrieved 23 September 2012.
60. ^ "Understanding Breast Changes – National Cancer Institute". Archived from the original on 27 May 2010.
61. ^ "Lobular carcinoma in situ: Marker for breast cancer risk". MayoClinic.com.
62. ^ "Breast Cancer Treatment". National Cancer Institute.
63. ^ Afonso N, Bouwman D (August 2008). "Lobular carcinoma in situ". *Eur. J. Cancer Prev*. **17** (4): 312–6. doi:10.1097/CEJ.0b013e3282f75e5d. PMID 18562954.
64. ^ Anothaisintawee T, Wiratkapun C, Lerdsitthichai P, Kasamesup V, Wongwaisayawan S, Srinakarin J, Hirunpat S, Woodtichartpreecha P, Boonlikit S, Teerawattananon Y, Thakkinstian A (2013). "Risk factors of breast cancer: a systematic review and meta-analysis". *Asian Pacific Journal of Public Health*. **25** (5): 368–387. doi:10.1177/1010539513488795. PMID 23709491.
65. ^ Böhm I (2011). "Breast cancer in lupus". *Breast*. **20** (3): 288–90. doi:10.1016/j.breast.2010.12.005. PMID 21237645.
66. ^ Adrian Lee; Carlos Arteaga (14 December 2009). "32nd Annual CTRC-AACR San Antonio Breast Cancer Symposium" (PDF). *Sunday Morning Year-End Review*. Archived from the original (PDF) on 13 August 2013.
67. ^ Cavalieri E, Chakravarti D, Guttenplan J, Hart E, Ingle J, Jankowiak R, Muti P, Rogan E, Russo J, Santen R, Sutter T (August 2006). "Catechol estrogen quinones as initiators of breast and other human cancers: implications for biomarkers of susceptibility and cancer prevention". *Biochimica et Biophysica Acta*. **1766** (1): 63–78. doi:10.1016/j.bbcan.2006.03.001. PMID 16675129.
68. ^ Haslam SZ, Woodward TL (June 2003). "Host microenvironment in breast cancer development: epithelial-cell-stromal-cell interactions and steroid hormone action in normal and cancerous mammary gland.". *Breast Cancer Res*. **5** (4): 208–15. doi:10.1186/bcr615. PMC 165024. PMID 12817994.
69. ^ Wiseman BS, Werb Z (May 2002). "Stromal effects on mammary gland development and breast cancer". *Science*. **296** (5570): 1046–9. doi:10.1126/science.1067431. PMC 2788989. PMID 12004111.
70. ^ Jardé T, Perrier S, Vasson MP, Caldefie-Chézet F (January 2011). "Molecular mechanisms of leptin and adiponectin in breast cancer". *Eur. J. Cancer*. **47** (1): 33–43. doi:10.1016/j.ejca.2010.09.005. PMID 20889333.
71. ^ Dunning AM, Healey CS, Pharoah PD, Teare MD, Ponder BA, Easton DF (October 1999). "A systematic review of genetic polymorphisms and breast cancer risk". *Cancer Epidemiology, Biomarkers & Prevention*. **8** (10): 843–54. PMID 10548311.
72. ^ Begg CB, Haile RW, Borg A, Malone KE, Concannon P, Thomas DC, Langholz B, Bernstein L, Olsen JH, Lynch CF, Anton-Culver H, Capanu M, Liang X, Hummer AJ, Sima C, Bernstein JL (January 2008). "Variation of breast cancer risk among

BRCA1/2 carriers". *JAMA*. **299** (2): 194–201. doi:10.1001/jama.2007.55-a. PMC 2714486. PMID 18182601.
73. ^ Patel KJ, Yu VP, Lee H, Corcoran A, Thistlethwaite FC, Evans MJ, Colledge WH, Friedman LS, Ponder BA, Venkitaraman AR (February 1998). "Involvement of Brca2 in DNA repair". *Mol. Cell*. **1** (3): 347–57. doi:10.1016/S1097-2765(00)80035-0. PMID 9660919.
74. ^ Marietta C, Thompson LH, Lamerdin JE, Brooks PJ (May 2009). "Acetaldehyde stimulates FANCD2 monoubiquitination, H2AX phosphorylation, and BRCA1 phosphorylation in human cells in vitro: implications for alcohol-related carcinogenesis". *Mutat. Res*. **664** (1–2): 77–83. doi:10.1016/j.mrfmmm.2009.03.011. PMC 2807731. PMID 19428384.
75. ^ Theruvathu JA, Jaruga P, Nath RG, Dizdaroglu M, Brooks PJ (2005). "Polyamines stimulate the formation of mutagenic 1,N2-propanodeoxyguanosine adducts from acetaldehyde". *Nucleic Acids Res*. **33** (11): 3513–20. doi:10.1093/nar/gki661. PMC 1156964. PMID 15972793.
76. ^ Wooster R, Weber BL (June 2003). "Breast and ovarian cancer". *N. Engl. J. Med*. **348** (23): 2339–47. doi:10.1056/NEJMra012284. PMID 12788999.
77. ^ Levin B, Lech D, Friedenson B (2012). "Evidence that BRCA1- or BRCA2-associated cancers are not inevitable". *Mol. Med*. **18**: 1327–37. doi:10.2119/molmed.2012.00280. PMC 3521784. PMID 22972572.
78. ^ Kouros-Mehr H, Kim JW, Bechis SK, Werb Z (Apr 2008). "GATA-3 and the regulation of the mammary luminal cell fate.". *Current opinion in cell biology*. **20** (2): 164–70. doi:10.1016/j.ceb.2008.02.003. PMC 2397451. PMID 18358709.
79. ^ Saslow D, Hannan J, Osuch J, Alciati MH, Baines C, Barton M, Bobo JK, Coleman C, Dolan M, Gaumer G, Kopans D, Kutner S, Lane DS, Lawson H, Meissner H, Moorman C, Pennypacker H, Pierce P, Sciandra E, Smith R, Coates R (2004). "Clinical breast examination: practical recommendations for optimizing performance and reporting". *CA: A Cancer Journal for Clinicians*. **54** (6): 327–344. doi:10.3322/canjclin.54.6.327. PMID 15537576.
80. ^ Yu YH, Liang C, Yuan XZ (2010). "Diagnostic value of vacuum-assisted breast biopsy for breast carcinoma: a meta-analysis and systematic review.". *Breast cancer research and treatment*. **120** (2): 469–79. doi:10.1007/s10549-010-0750-1. PMID 20130983.
81. ^ Merck Manual, Professional Edition, Ch. 253, Breast Cancer.
82. ^ American Society of Clinical Oncology, "Five Things Physicians and Patients Should Question" (PDF), *Choosing Wisely: an initiative of the ABIM Foundation*, American Society of Clinical Oncology, retrieved 14 August 2012
83. ^ Carlson RW, Allred DC, Anderson BO, Burstein HJ, Carter WB, Edge SB, Erban JK, Farrar WB, Goldstein LJ, Gradishar WJ, Hayes DF, Hudis CA, Jahanzeb M, Kiel K, Ljung BM, Marcom PK, Mayer IA, McCormick B, Nabell LM, Pierce LJ, Reed EC, Smith ML, Somlo G, Theriault RL, Topham NS, Ward JH, Winer EP, Wolff AC (2009). "Breast cancer. Clinical practice guidelines in oncology". *Journal of the National Comprehensive Cancer Network : JNCCN*. **7** (2): 122–192. PMID 19200416.
84. ^ Kumar, Vinay; Abul Abbas (2010). *Robbins and Cotran Pathologic Basis of Disease*. Philadelphia: Saunders, an imprint of Elsevier inc. p. 1090. ISBN 978-1-4160-3121-5.
85. ^ Sotiriou C, Pusztai L (February 2009). "Gene-expression signatures in breast cancer". *N. Engl. J. Med*. **360** (8): 790–800. doi:10.1056/NEJMra0801289. PMID 19228622.
86. ^ Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N (October 2005). "Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer". *N. Engl. J. Med*. **353** (16): 1673–84. doi:10.1056/NEJMoa052122. PMID 16236738.
87. ^ [a] [b] [c] American Institute for Cancer Research/ World Cancer Research Fund, Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective
88. ^ Eliassen AH, Hankinson SE, Rosner B, Holmes MD, Willett WC (October 2010). "Physical activity and risk of breast cancer among postmenopausal women". *Arch. Intern. Med*. **170** (19): 1758–64. doi:10.1001/archinternmed.2010.363. PMC 3142573. PMID 20975025.
89. ^ Kyu, Hmwe H; Bachman, Victoria F; Alexander, Lily T; Mumford, John Everett; Afshin, Ashkan; Estep, Kara; Veerman, J Lennert; Delwiche, Kristen; Iannarone, Marissa L; Moyer, Madeline L; Cercy, Kelly; Vos, Theo; Murray, Christopher J L; Forouzanfar, Mohammad H (9 August 2016). "Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013". *BMJ*: i3857. doi:10.1136/bmj.i3857.
90. ^ Song, Jung-Kook; Bae, Jong-Myon (2013-03-01). "Citrus fruit intake and breast cancer risk: a quantitative systematic review". *Journal of Breast Cancer*. **16** (1): 72–76. doi:10.4048/jbc.2013.16.1.72. ISSN 1738-6756. PMC 3625773. PMID 23593085.
91. ^ Zheng JS, Hu XJ, Zhao YM, Yang J, Li D (2013). "Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies". *BMJ*. **346**: f3706. doi:10.1136/bmj.f3706. PMID 23814120.
92. ^ Wu, AH; Yu, MC; Tseng, CC; Pike, MC (15 January 2008). "Epidemiology of soy exposures and breast cancer risk.". *British Journal of Cancer*. **98** (1): 9–14. doi:10.1038/sj.bjc.6604145. PMID 18182974.
93. ^ Hartmann LC, Schaid DJ, Woods JE, Crotty TP, Myers JL, Arnold PG, Petty PM, Sellers TA, Johnson JL, McDonnell SK, Frost MH, Jenkins RB (1999). "Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer". *N Engl J Med*. **340** (2): 77–84. doi:10.1056/NEJM199901143400201. PMID 9887158.
94. ^ Meijers-Heijboer H, van Geel B, van Putten WL, Henzen-Logmans SC, Seynaeve C, Menke-Pluymers MB, Bartels CC, Verhoog LC, van den Ouweland AM, Niermeijer MF, Brekelmans CT, Klijn JG (2001). "Breast cancer after prophylactic bilateral mastectomy in women with BRCA1 and BRCA2 mutations". *N Engl J Med*. **345** (3): 159–164. doi:10.1056/NEJM200107193450301. PMID 11463009.

95. ^ [a] [b] Lostumbo, L; Carbine, NE; Wallace, J (10 November 2010). "Prophylactic mastectomy for the prevention of breast cancer.". *The Cochrane database of systematic reviews* (11): CD002748. doi:10.1002/14651858.CD002748.pub3. PMID 21069671.
96. ^ "Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement". *Annals of Internal Medicine*. **160**: 271–281. 24 December 2013. doi:10.7326/M13-2747.
97. ^ [a] [b] [c] Nelson HD, Smith ME, Griffin JC, Fu R (16 April 2013). "Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force.". *Annals of Internal Medicine*. **158** (8): 604–14. doi:10.7326/0003-4819-158-8-201304160-00005. PMID 23588749.
98. ^ Cuzick J, Sestak I, Bonanni B, Costantino JP, Cummings S, DeCensi A, Dowsett M, Forbes JF, Ford L, LaCroix AZ, Mershon J, Mitlak BH, Powles T, Veronesi U, Vogel V, Wickerham DL (25 May 2013). "Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data.". *Lancet*. **381** (9880): 1827–34. doi:10.1016/S0140-6736(13)60140-3. PMID 23639488.
99. ^ Moyer VA (24 September 2013). "Medications for Risk Reduction of Primary Breast Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement.". *Annals of Internal Medicine*. doi:10.7326/0003-4819-159-10-201311190-00718. PMID 24061472.
100. ^ Cuzick J, Sestak I, Bonanni B, Costantino JP, Cummings S, DeCensi A, Dowsett M, Forbes JF, Ford L, LaCroix AZ, Mershon J, Mitlak BH, Powles T, Veronesi U, Vogel V, Wickerham DL (31 March 2013). "Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data". *The Lancet*. **381** (9880): 1827–34. doi:10.1016/S0140-6736(13)60140-3. PMID 23639488.
101. ^ "Screening". *Centers for Disease Control and Prevention*. Retrieved 17 November 2015.
102. ^ "Screening for Breast Cancer". *US Preventative Services Task Force*. December 2009. Retrieved 24 December 2012.
103. ^ Kösters JP, Gøtzsche PC (2003). "Cochrane Database of Systematic Reviews". *Cochrane Database Syst Rev* (2): CD003373. doi:10.1002/14651858.CD003373. PMID 12804462.
104. ^ "Breast Cancer and Mammograms". *WebMD*. Retrieved 24 December 2012.
105. ^ Biesheuvel C, Weigel S, Heindel W (2011). "Mammography Screening: Evidence, History and Current Practice in Germany and Other European Countries.". *Breast care (Basel, Switzerland)*. **6** (2): 104–109. doi:10.1159/000327493. PMID 21673820.
106. ^ Tonelli M, Connor Gorber S, Joffres M, Dickinson J, Singh H, Lewin G, Birtwhistle R, Fitzpatrick-Lewis D, Hodgson N, Ciliska D, Gauld M, Liu YY (22 November 2011). "Recommendations on screening for breast cancer in average-risk women aged 40–74 years.". *Canadian Medical Association Journal*. **183** (17): 1991–2001. doi:10.1503/cmaj.110334. PMC 3225421. PMID 22106103.
107. ^ "Breast Cancer: Screening". *United States Preventive Services Task Force*. Archived from the original on 16 June 2013.
108. ^ Welch HG, Passow HJ (30 December 2013). "Quantifying the Benefits and Harms of Screening Mammography.". *JAMA internal medicine*. **174** (3): 448–54. doi:10.1001/jamainternmed.2013.13635. PMID 24380095.
109. ^ Gøtzsche PC, Nielsen M (2011). "Screening for breast cancer with mammography". *Cochrane Database Syst Rev* (1): CD001877. doi:10.1002/14651858.CD001877.pub4. PMID 21249649.
110. ^ "Screening for breast cancer with mammography". Cochrane Nordic. 27 August 2015. Retrieved 15 October 2015.
111. ^ "Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement.". *Annals of Internal Medicine*. **151** (10): 716–26, W–236. 17 November 2009. doi:10.1059/0003-4819-151-10-200911170-00008. PMID 19920272.
112. ^ Saini KS, Taylor C, Ramirez AJ, Palmieri C, Gunnarsson U, Schmoll HJ, Dolci SM, Ghenne C, Metzger-Filho O, Skrzypski M, Paesmans M, Ameye L, Piccart-Gebhart MJ, de Azambuja E (August 2011). "Role of the multidisciplinary team in breast cancer management: results from a large international survey involving 39 countries". *Annals of Oncology*. **23** (4): 853–9. doi:10.1093/annonc/mdr352. PMID 21821551.
113. ^ Holmes MD, Chen WY, Li L, Hertzmark E, Spiegelman D, Hankinson SE (2010). "Aspirin Intake and Survival After Breast Cancer". *Journal of Clinical Oncology*. **28** (9): 1467–72. doi:10.1200/JCO.2009.22.7918. PMC 2849768. PMID 20159825.
114. ^ Ting Bao; Michelle A Rudek (2011). "The Clinical Pharmacology of Anastrozole". *European Oncology & Haematology*. **7** (2): 106–8.
115. ^ Burstein, HJ; Temin, S; Anderson, H; Buchholz, TA; Davidson, NE; Gelmon, KE; Giordano, SH; Hudis, CA; Rowden, D; Solky, AJ; Stearns, V; Winer, EP; Griggs, JJ (27 May 2014). "Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update.". *Journal of Clinical Oncology*. **32** (21): 2255–69. doi:10.1200/JCO.2013.54.2258. PMID 24868023.
116. ^ Early Breast Cancer Trialists' Collaborative Group (23 July 2015). "Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials". *The Lancet*. **386**: 1341–1352. doi:10.1016/S0140-6736(15)61074-1.
117. ^ Petit T, Dufour P, Tannock I (June 2011). "A critical evaluation of the role of aromatase inhibitors as adjuvant therapy for postmenopausal women with breast cancer". *Endocr. Relat. Cancer*. **18** (3): R79–89. doi:10.1530/ERC-10-0162. PMID 21502311.
118. ^ http://www.uptodate.com/contents/treatment-of-metastatic-breast-cancer-beyond-the-basics?source=search_result&search=letrozole&selectedTitle=4%7E6
119. ^ Jahanzeb M (August 2008). "Adjuvant trastuzumab therapy for HER2-positive breast cancer". *Clin. Breast Cancer*. **8** (4): 324–33. doi:10.3816/CBC.2008.n.037. PMID 18757259.
120. ^ "Entrez Gene: ERBB2 v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene

homolog (avian)". Retrieved 17 November 2015.
121. ^ "Herceptin (trastuzumab) Adjuvant HER2+ Breast Cancer Therapy Pivotal Studies and Efficacy Data". Herceptin.com. Retrieved 8 May 2010.
122. ^ Massarut S, Baldassare G, Belleti B, Reccanello S, D'Andrea S, Ezio C, Perin T, Roncadin M, Vaidya JS (2006). "Intraoperative radiotherapy impairs breast cancer cell motility induced by surgical wound fluid". *J Clin Oncol*. **24** (18S): 10611.
123. ^ Belletti B, Vaidya JS, D'Andrea S, Entschladen F, Roncadin M, Lovat F, Berton S, Perin T, Candiani E, Reccanello S, Veronesi A, Canzonieri V, Trovò MG, Zaenker KS, Colombatti A, Baldassarre G, Massarut S (March 2008). "Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding". *Clin. Cancer Res*. **14** (5): 1325–32. doi:10.1158/1078-0432.CCR-07-4453. PMID 18316551.
124. ^ "Radiation Therapy". *Breastcancer.org*. Retrieved 17 November 2015.
125. ^ "Breast Cancer: Breast Disorders: Merck Manual Professional". Merck.com. Retrieved 8 May 2010.
126. ^ "Surgery Choices for Women with Early Stage Breast Cancer" (PDF). National Cancer Institute and the National Research Center for Women & Families. August 2004. Archived from the original (PDF) on 13 August 2013.
127. ^ Gonzalez-Angulo AM, Litton JK, Broglio KR, Meric-Bernstam F, Rakkhit R, Cardoso F, Peintinger F, Hanrahan EO, Sahin A, Guray M, Larsimont D, Feoli F, Stranzl H, Buchholz TA, Valero V, Theriault R, Piccart-Gebhart M, Ravdin PM, Berry DA, Hortobagyi GN (December 2009). "High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller". *J. Clin. Oncol*. **27** (34): 5700–6. doi:10.1200/JCO.2009.23.2025. PMC 2792998. PMID 19884543. Lay summary – *ScienceDaily*.
128. ^ "Breast Cancer: Breast Disorders: Merck Manual Professional". Merck.com. Retrieved 14 November 2010.
129. ^ Elston CW, Ellis IO (November 1991). "Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up". *Histopathology*. **19** (5): 403–10. doi:10.1111/j.1365-2559.1991.tb00229.x. PMID 1757079.
130. ^ Peppercorn J (2009). "Breast Cancer in Women Under 40". *Oncology*. **23** (6).
131. ^ Brandt, Jasmine; Garne, Jens; Tengrup, Ingrid; Manjer, Jonas (2015). "Age at diagnosis in relation to survival following breast cancer: a cohort study". *World Journal of Surgical Oncology*. **13** (1): 33. doi:10.1186/s12957-014-0429-x. ISSN 1477-7819.
132. ^ Gierach GL, Ichikawa L, Kerlikowske K, Brinton LA, Farhat GN, Vacek PM, Weaver DL, Schairer C, Taplin SH, Sherman ME (August 2012). "Relationship between mammographic density and breast cancer death in the Breast Cancer Surveillance Consortium". *Journal of National Cancer Institute*. **104** (16): 1218–27. doi:10.1093/jnci/djs327. PMID 22911616.
133. ^ Amro Masarwah; Päivi Auvinen; Mazen Sudah; Suvi Rautiainen; Anna Sutela; Outi Pelkonen; Sanna Oikari; Veli-Matti Kosma; Ritva Vanninen; et al. (2015). "Very low mammographic breast density predicts poorer outcome in patients with invasive breast cancer". *European Radiology*. **25**: 1875–1882. doi:10.1007/s00330-015-3626-2. PMID 25735512.
134. ^ Klein, Judith. "Differences in male breast cancer stage, tumor size at diagnosis, and survival rate between metropolitan and nonmetropolitan regions". Proquest. Retrieved 7 December 2012.
135. ^ Pritchard KI (2009). "Ovarian Suppression/Ablation in Premenopausal ER-Positive Breast Cancer Patients". *Oncology*. **23** (1).
136. ^ *a b* Robb C, Haley WE, Balducci L, Extermann M, Perkins EA, Small BJ, Mortimer J (April 2007). "Impact of breast cancer survivorship on quality of life in older women". *Critical Reviews in Oncology/hematology*. **62** (1): 84–91. doi:10.1016/j.critrevonc.2006.11.003. PMID 17188505.
137. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved 11 November 2009.
138. ^ *a b c* McGuire, A; Brown, JA; Malone, C; McLaughlin, R; Kerin, MJ (22 May 2015). "Effects of age on the detection and management of breast cancer.". *Cancers*. **7** (2): 908–29. doi:10.3390/cancers7020815. PMID 26010605.
139. ^ *a b c* "World Cancer Report". International Agency for Research on Cancer. 2008. Retrieved 26 February 2011. (cancer statistics often exclude non-melanoma skin cancers such as basal-cell carcinoma, which are common but rarely fatal)
140. ^ "Breast cancer: prevention and control". *World Health Organization*. Archived from the original on 6 September 2015.
141. ^ *World Cancer Report 2014*. International Agency for Research on Cancer, World Health Organization. 2014. ISBN 978-92-832-0432-9.
142. ^ Stewart B. W. and Kleihues P. (Eds): World Cancer Report. IARCPress. Lyon 2003 Archived 20 October 2008 at the Wayback Machine.
143. ^ Laurance, Jeremy (29 September 2006). "Breast cancer cases rise 80% since Seventies". *The Independent*. London. Archived from the original on 25 April 2008. Retrieved 9 October 2006.
144. ^ "Breast Cancer: Statistics on Incidence, Survival, and Screening". Imaginis Corporation. 2006. Retrieved 9 October 2006.
145. ^ Breast Cancer: Breast Cancer in Young Women WebMD. Retrieved 9 September 2009
146. ^ Nearly 85% of women diagnosed with breast cancer now survive for 5 year or more Office for National Statistics, 2013
147. ^ *a b c* Olson, James Stuart (2002). *Bathsheba's breast: women, cancer & history*. Baltimore: The Johns Hopkins University Press. pp. 9–13. ISBN 0-8018-6936-6.
148. ^ *a b* "Oldest evidence of breast cancer found in Egyptian skeleton". Reuters. 24 March 2015. Retrieved 25 March 2015.
149. ^ "The History of Cancer". *American Cancer Society*. 25 March 2002. Retrieved 9 October 2006.
150. ^ *a b* Olson 2002, pp. 32–33
151. ^ Yalom, Marilyn (1997). *A history of the breast*. New York: Alfred A. Knopf. p. 234. ISBN 0-679-43459-3.
152. ^ *a b c d* Aronowitz, Robert A. (2007). *Unnatural history: breast cancer and American society*. Cambridge, UK: Cambridge University Press. pp. 22–24. ISBN 0-521-82249-1.
153. ^ "History of Breast Cancer". Random History. 27 February 2008. Retrieved 8 May 2010.

154. ^ a b c d e f g Olson 2002, pp. 102–6
155. ^ Olson 2002, p. 1
156. ^ Marc Lacroix (2011). *A Concise History of Breast Cancer*. USA: Nova Science Publishers. pp. 59–68. ISBN 978-1-61122-305-7.
157. ^ Olson 2002, pp. 26,28,229
158. ^ Alfredo Morabia (2004). *A History of Epidemiologic Methods and Concepts*. Boston: Birkhauser. pp. 301–302. ISBN 3-7643-6818-7. Retrieved 31 December 2007.
159. ^ a b Sulik, Gayle A. (2010). *Pink Ribbon Blues: How Breast Cancer Culture Undermines Women's Health*. USA: Oxford University Press. pp. 200–3. ISBN 0-19-974045-3. OCLC 535493589.
160. ^ Sulik 2010, pp. 37–38
161. ^ Sulik 2010, p. 4
162. ^ Bob Riter. "History of Breast Cancer Advocacy". Cancer Resource Center of the Finger Lakes. Retrieved 29 June 2013.
163. ^ Sulik 2010, pp. 27–72
164. ^ Sulik 2010, pp. 359–361
165. ^ Sulik 2010, pp. 366–8
166. ^ Landeman, Anne (11 June 2008). "Pinkwashing: Can Shopping Cure Breast Cancer?". Center for Media and Democracy.
167. ^ Sulik 2010, pp. 365–6
168. ^ Sulik 2010, pp. 372–4
169. ^ Breast cancer month overshadowed by 'pinkwashing' 9 October 2010, Angela Mulholland, CTV.ca News
170. ^ a b c d Ehrenreich, Barbara (November 2001). "Welcome to Cancerland". *Harper's Magazine*. Archived from the original on 20 November 2010.
171. ^ Sulik 2010, p. 57
172. ^ a b Browne, Anthony (7 October 2001). "Cancer bias puts breasts first". *The Guardian*. London.
173. ^ Arnst, Catherine (13 June 2007). "A Gender Gap in Cancer". *Bloomberg Businessweek*. ISSN 0007-7135.
174. ^ Olson 2002, pp. 199–200
175. ^ Ave, Melanie (10 October 2006). "Tampabay: All May Not Be in the Pink". *St. Petersburg Times*.
176. ^ a b Aschwanden, Christie (17 August 2009). "The Trouble with Mammograms". *The Los Angeles Times*.
177. ^ Azim HA, Jr; Santoro, L; Russell-Edu, W; Pentheroudakis, G; Pavlidis, N; Peccatori, FA (November 2012). "Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies.". *Cancer treatment reviews*. **38** (7): 834–42. doi:10.1016/j.ctrv.2012.06.004. PMID 22785217.
178. ^ Schedin, P (April 2006). "Pregnancy-associated breast cancer and metastasis.". *Nature reviews. Cancer*. **6** (4): 281–91. doi:10.1038/nrc1839. PMID 16557280.
179. ^ a b c d e f g Connie Henke Yarbro; Debra Wujcik; Barbara Holmes Gobel, eds. (2011). *Cancer nursing: principles and practice* (7 ed.). Jones & Bartlett Publishers. pp. 901–905. ISBN 978-1-4496-1829-2.
180. ^ a b Gonçalves V, Sehovic I, Quinn G (2013). "Childbearing attitudes and decisions of young breast cancer survivors: A systematic review". *Human Reproduction Update*. **20** (2): 279–92. doi:10.1093/humupd/dmt039. PMC 3922144. PMID 24077938.
181. ^ McNaught J, Reid RL, Provencher DM, et al. (July 2006). "Progesterone-only and non-hormonal contraception in the breast cancer survivor: Joint Review and Committee Opinion of the Society of Obstetricians and Gynaecologists of Canada and the Society of Gynecologic Oncologists of Canada". *J Obstet Gynaecol Can*. **28** (7): 616–39. PMID 16924781.
182. ^ Management of the menopause after breast cancer, from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists. College Statement C-Gyn 15. 1st Endorsed: February 2003. Current: November 2011. Review: November 2014
183. ^ San Antonio Breast Cancer Symposium Abstracts, newsletters, and other reports of the meeting. Archived 16 May 2010 at the Wayback Machine.
184. ^ Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ (August 2009). "Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009". *Annals of Oncology*. **20** (8): 1319–29. doi:10.1093/annonc/mdp322. PMC 2720818. PMID 19535820.
185. ^ "What's new in breast cancer research and treatment?". *Cancer*. Retrieved 17 November 2015.
186. ^ "Fenretinide (4-HPR): A Preventive Chance for Women at Genetic and Familial Risk?". *hindawi*. Retrieved 17 November 2015.
187. ^ Sabel, MS (July 2014). "Nonsurgical ablation of breast cancer: future options for small breast tumors.". *Surgical oncology clinics of North America*. **23** (3): 593–608. doi:10.1016/j.soc.2014.03.009. PMID 24882353.
188. ^ a b Roubidoux, MA; Yang, W; Stafford, RJ (March 2014). "Image-guided ablation in breast cancer treatment.". *Techniques in vascular and interventional radiology*. **17** (1): 49–54. doi:10.1053/j.tvir.2013.12.008. PMID 24636331.
189. ^ "Current Status of Imaging-Guided Percutaneous Ablation of Breast Cancer". *American Journal of Roentgenology*. **203** (2): 442–448. August 2014. doi:10.2214/AJR.13.11600.
190. ^ Jauliac S, López-Rodriguez C, Shaw LM, Brown LF, Rao A, Toker A (July 2002). "The role of NFAT transcription factors in integrin-mediated carcinoma invasion.". *Nature Cell Biology*. **4** (7): 540–4. doi:10.1038/ncb816. PMID 12080349.
191. ^ Yoeli-Lerner M, Yiu GK, Rabinovitz I, Erhardt P, Jauliac S, Toker A (23 November 2005). "Akt blocks breast cancer cell motility and invasion through the transcription factor NFAT.". *Molecular Cell*. **20** (4): 539–50. doi:10.1016/j.molcel.2005.10.033. PMID 16307918.
192. ^ a b Fougère M, Gaudineau B, Barbier J, Guaddachi F, Feugeas JP, Auboeuf D, Jauliac S (15 April 2010). "NFAT3 transcription factor inhibits breast cancer cell motility by targeting the Lipocalin 2 gene.". *Oncogene*. **29** (15): 2292–301.

doi:10.1038/onc.2009.499. PMID 20101218.
193. ^ Gaudineau B, Fougère M, Guaddachi F, Lemoine F, de la Grange P, Jauliac S (1 October 2012). "Lipocalin 2 (LCN2), the TNF-like receptor TWEAKR and its ligand TWEAK act downstream of NFAT1 to regulate breast cancer cell invasion.". *Journal of Cell Science*. **125** (19): 4475–4486. doi:10.1242/jcs.099879. PMID 22767506.
194. ^ Duffy MJ (2001). "Biochemical markers in breast cancer: which ones are clinically useful?". *Clin Biochem*. **34** (5): 347–52. doi:10.1016/s0009-9120(00)00201-0. PMID 11522269.
195. ^ Goldstein NS, Decker D, Severson D, Schell S, Vicini F, Margolis J, et al. (2007). "Molecular classification system identifies invasive breast carcinoma patients who are most likely and those who are least likely to achieve a complete pathologic response after neoadjuvant chemotherapy.". *Cancer*. **110** (8): 1687–96. doi:10.1002/cncr.22981. PMID 17722109.
196. ^ Mohammadzadeh F, Mosayebi G, Montazeri V, Darabi M, Fayezi S, Shaaker M, et al. (2014). "Fatty Acid Composition of Tissue Cultured Breast Carcinoma and the Effect of Stearoyl-CoA Desaturase 1 Inhibition.". *J Breast Cancer*. **17** (2): 136–42. doi:10.4048/jbc.2014.17.2.136. PMC 4090315. PMID 25013434.
197. ^ Ranson M, Andronicos NM (2003). "Plasminogen binding and cancer: promises and pitfalls.". *Front Biosci*. **8**: s294–304. doi:10.2741/1044. PMID 12700073.
198. ^ Holder AM, Gonzalez-Angulo AM, Chen H, Akcakanat A, Do KA, Fraser Symmans W, et al. (2013). "High stearoyl-CoA desaturase 1 expression is associated with shorter survival in breast cancer patients.". *Breast Cancer Res Treat*. **137** (1): 319–27. doi:10.1007/s10549-012-2354-4. PMC 3556743. PMID 23208590.

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**Breast cancer**
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The Wikibook *Sexual Health* has a page on the topic of: *Cancer#Breast Cancer*

**Biology portal** **Medicine portal**

| v · t · e · | **Breast cancer (C50/D24, 174–175/217)** | |
|---|---|---|
| **Fibroepithelial/stromal** | Phyllodes tumor · | |
| **Ductal, lobular, and medullary** | **Ductal** | Ductal carcinoma in situ (DCIS): Paget's disease of the breast · Comedocarcinoma · Invasive ductal carcinoma (IDC) · Intraductal papilloma · |
| | **Lobular** | Lobular carcinoma in situ (LCIS) · Invasive lobular carcinoma (ILC) · |
| | **Medullary** | Medullary carcinoma · |
| | **Other/ungrouped** | Inflammatory breast cancer · |
| **Precursor lesions** | Atypical ductal hyperplasia · | |
| **Classification** | Breast cancer classification · | |

| | |
|---|---|
| **Other** | Nipple adenoma · |
| **Related subjects** | **Main article** · Classification · Risk factors (Alcohol, Hereditary breast—ovarian cancer syndrome, BRCA mutation) · Screening · Treatment · Breast cancer awareness · Pink ribbon · National Breast Cancer Awareness Month · List of people with breast cancer · |
| **Authority control** | GND: 4008528-4 · NDL: 00568758 · |

Categories: Breast cancer | Hereditary cancers | Ribbon symbolism | Human female endocrine system




# Cancer



From Wikipedia, the free encyclopedia

*For other uses, see Cancer (disambiguation).*

**Cancer** is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body.[1][2] Not all tumors are cancerous; benign tumors do not spread to other parts of the body.[2] Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss and a change in bowel movements.[3] While these symptoms may indicate cancer, they may have other causes.[3] Over 100 cancers affect humans.[2]

Tobacco use is the cause of about 22% of cancer deaths.[1] Another 10% is due to obesity, poor diet, lack of physical activity and drinking alcohol.[1][4] Other factors include certain infections, exposure to ionizing radiation and environmental pollutants.[5] In the developing world nearly 20% of cancers are due to infections such as hepatitis B, hepatitis C and human papillomavirus (HPV).[1] These factors act, at least partly, by changing the genes of a cell.[6] Typically many genetic changes are required before cancer develops.[6] Approximately 5–10% of cancers are due to inherited genetic defects from a person's parents.[7] Cancer can be detected by certain signs and symptoms or screening tests.[1] It is then typically further investigated by medical imaging and confirmed by biopsy.[8]

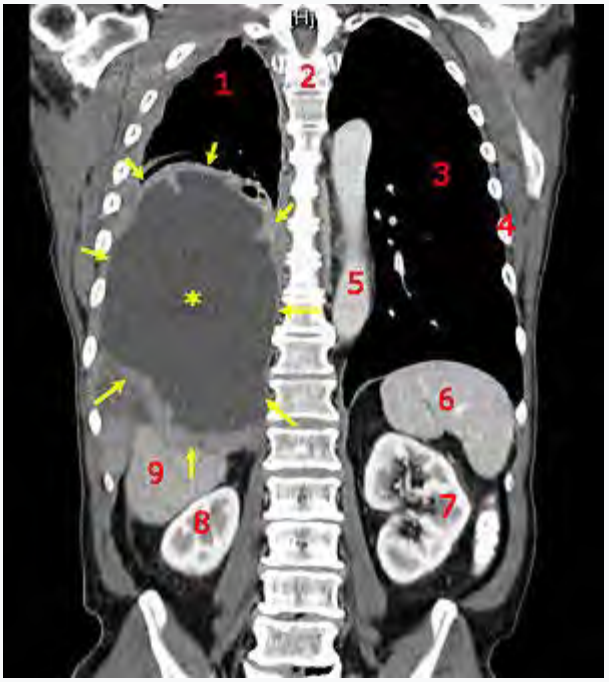
Many cancers can be prevented by not smoking, maintaining a healthy weight, not drinking too much alcohol, eating plenty of vegetables, fruits and whole grains, vaccination against certain infectious diseases, not eating too much processed and red meat, and avoiding too much sunlight exposure.[9][10] Early detection through screening is useful for cervical and colorectal cancer.[11] The benefits of screening in breast cancer are controversial.[11][12] Cancer is often treated with some combination of radiation therapy, surgery, chemotherapy, and targeted therapy.[1][13] Pain and symptom management are an important part of care. Palliative care is particularly important in people with advanced disease.[1] The chance of survival depends on the type of cancer and extent of disease at the start of treatment.[6] In children under 15 at diagnosis the five-year

## Variants



**Cancer**

**Synonyms** neoplasm




A coronal CT scan showing a malignant mesothelioma

Legend: → tumor ←, central pleural effusion, 1 & 3 lungs, 2 spine, 4 ribs, 5 aorta, 6 spleen, 7 & 8 kidneys, 9 liver.

**Pronunciation** /ˈkænsər/

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Oncology |
| **ICD-10** | C00—C97 |
| **ICD-9-CM** | 140—239 |
| **DiseasesDB** | 28843 |
| **MedlinePlus** | 001289 |

survival rate in the developed world is on average 80%.[14] For cancer in the United States the average five-year survival rate is 66%.[15]

| MeSH | D009369 |
|---|---|

[edit on Wikidata]

In 2012 about 14.1 million new cases of cancer occurred globally (not including skin cancer other than melanoma).[6] It caused about 8.2 million deaths or 14.6% of human deaths.[6][16] The most common types of cancer in males are lung cancer, prostate cancer, colorectal cancer and stomach cancer. In females, the most common types are breast cancer, colorectal cancer, lung cancer and cervical cancer.[6] If skin cancer other than melanoma were included in total new cancers each year it would account for around 40% of cases.[17][18] In children, acute lymphoblastic leukaemia and brain tumors are most common except in Africa where non-Hodgkin lymphoma occurs more often.[14] In 2012, about 165,000 children under 15 years of age were diagnosed with cancer. The risk of cancer increases significantly with age and many cancers occur more commonly in developed countries.[6] Rates are increasing as more people live to an old age and as lifestyle changes occur in the developing world.[19] The financial costs of cancer were estimated at $1.16 trillion US dollars per year as of 2010.[20]

**Contents**

# Definitions

Cancers are a large family of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body.[1][2] They form a subset of neoplasms. A neoplasm or tumor is a group of cells that have undergone unregulated growth and will often form a mass or lump, but may be distributed diffusely.[21][22]

All tumor cells show the six hallmarks of cancer. These characteristics are required to produce a malignant tumor. They include:[23]

- Cell growth and division absent the proper signals
- Continuous growth and division even given contrary signals
- Avoidance of programmed cell death
- Limitless number of cell divisions
- Promoting blood vessel construction
- Invasion of tissue and formation of metastases[24]

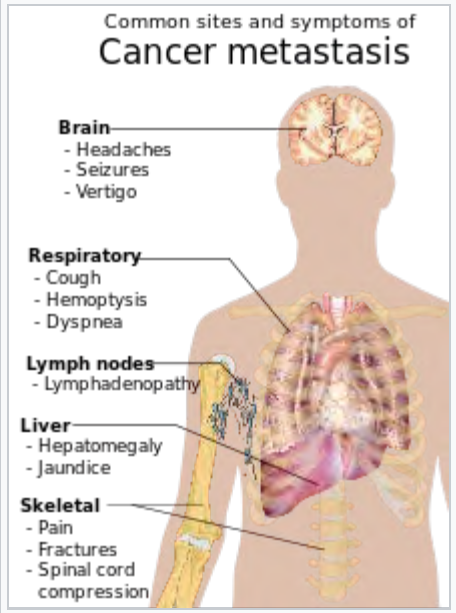
The progression from normal cells to cells that can form a detectable mass to outright cancer involves multiple steps known as malignant progression.[24][25]

# Signs and symptoms

*Main article: Cancer signs and symptoms*

When cancer begins, it produces no symptoms. Signs and symptoms appear as the mass grows or ulcerates. The findings that result depend on the cancer's type and location. Few symptoms are specific. Many frequently occur in individuals who have other conditions. Cancer is a "great imitator". Thus, it is common for people diagnosed with cancer to have been treated for other diseases, which were hypothesized to be causing their symptoms.[26]

People may become anxious or depressed post-diagnosis. The risk of suicide in people with cancer is approximately double.[27]




Symptoms of cancer metastasis depend on the location of the tumor.

## Local symptoms

Local symptoms may occur due to the mass of the tumor or its ulceration. For example, mass effects from lung cancer can block the bronchus resulting in cough or pneumonia; esophageal cancer can cause narrowing of the esophagus, making it difficult or painful to swallow; and colorectal cancer may lead to narrowing or blockages in the bowel, affecting bowel habits. Masses in breasts or testicles may produce observable lumps. Ulceration can cause bleeding that, if it occurs in the lung, will lead to coughing up blood, in the bowels to anemia or rectal bleeding, in the bladder to blood in the urine and in the uterus to vaginal bleeding. Although localized pain may occur in advanced cancer, the initial swelling is usually painless. Some cancers can cause a buildup of fluid within the chest or abdomen.[26]

## Systemic symptoms

General symptoms occur due to effects that are not related to direct or metastatic spread. These may include: unintentional weight loss, fever, excessive fatigue and changes to the skin.[28] Hodgkin disease, leukemias and cancers of the liver or kidney can cause a persistent fever.[26]

Some cancers may cause specific groups of systemic symptoms, termed paraneoplastic phenomena. Examples include the appearance of myasthenia gravis in thymoma and clubbing in lung cancer.[26]

## Metastasis

*Main article: Metastasis*

Cancer can spread from its original site by local spread, lymphatic spread to regional lymph nodes or by hematogenous spread via the blood to distant sites, known as metastasis. When cancer spreads by a hematogenous route, it usually spreads all over the body. However, cancer 'seeds' grow in certain selected site only ('soil') as hypothesized in the *soil and seed hypothesis* of cancer metastasis. The symptoms of metastatic cancers depend on the tumor location and can include enlarged lymph nodes (which can be felt or sometimes seen under the skin and are typically hard), enlarged liver or enlarged spleen, which can be felt in the abdomen, pain or fracture of affected bones and neurological symptoms.[26]

# Causes

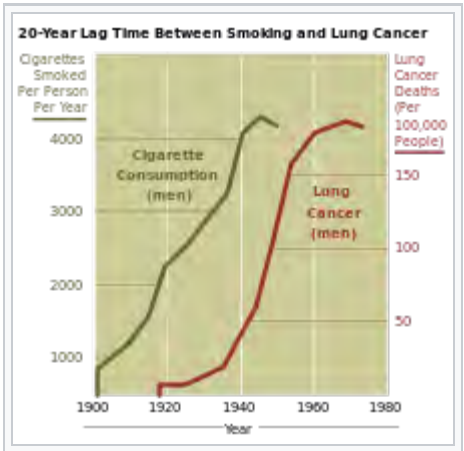
*Main article: Causes of cancer*

The majority of cancers, some 90–95% of cases, are due to environmental factors. The remaining 5–10% are due to inherited genetics.[5] *Environmental*, as used by cancer researchers, means any cause that is not inherited genetically, such as lifestyle, economic and behavioral factors and not merely pollution.[29] Common environmental factors that contribute to cancer death include tobacco (25–30%), diet and obesity (30–35%), infections (15–20%), radiation (both ionizing and non-ionizing, up to 10%), stress, lack of physical activity and environmental pollutants.[5]

It is not generally possible to prove what caused a particular cancer because the various causes do not have specific fingerprints. For example, if a person who uses tobacco heavily develops lung cancer, then it was probably caused by the tobacco use, but since everyone has a small chance of developing lung cancer as a result of air pollution or radiation, the cancer may have developed for one of those reasons. Excepting the rare transmissions that occur with pregnancies and occasional organ donors, cancer is generally not a transmissible disease.[30]

## Chemicals

*Further information: Alcohol and cancer and Smoking and cancer*

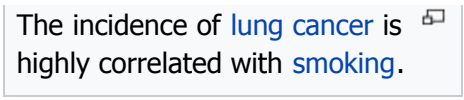



Exposure to particular substances have been linked to specific types of cancer. These substances are called *carcinogens*.

Tobacco smoke, for example, causes 90% of lung cancer.[31] It also causes cancer in the larynx, head, neck, stomach, bladder, kidney, esophagus and pancreas.[32] Tobacco smoke contains over fifty known carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons.[33]

Tobacco is responsible about one in five cancer deaths worldwide[33] and about one in three in the developed world[34] Lung cancer death rates in the United States have mirrored smoking patterns, with increases in smoking followed by dramatic increases in lung cancer death rates and, more recently, decreases in smoking rates since the

1950s followed by decreases in lung cancer death rates in men since 1990.[35][36]


The incidence of lung cancer is highly correlated with smoking.

In Western Europe, 10% of cancers in males and 3% of cancers in females are attributed to alcohol exposure, especially liver and digestive tract cancers.[37] Cancer from work-related substance exposures may cause between 2 and 20% of cases,[38] causing at least 200,000 deaths.[39] Cancers such as lung cancer and mesothelioma can come from inhaling tobacco smoke or asbestos fibers, or leukemia from exposure to benzene.[39]

## Diet and exercise

*Main article: Diet and cancer*

Diet, physical inactivity and obesity are related to up to 30–35% of cancer deaths.[5][40] In the United States excess body weight is associated with the development of many types of cancer and is a factor in 14–20% of cancer deaths.[40] A UK study including data on over 5 million people showed higher body mass index to be related to at least 10 types of cancer and responsible for around 12,000 cases each year in that country.[41] Physical inactivity is believed to contribute to cancer risk, not only through its effect on body weight but also through negative effects on the immune system and endocrine system.[40] More than half of the effect from diet is due to overnutrition (eating too much), rather than from eating too few vegetables or other healthful foods.

Some specific foods are linked to specific cancers. A high-salt diet is linked to gastric cancer.[42] Aflatoxin B1, a frequent food contaminant, causes liver cancer.[42] Betel nut chewing can cause oral cancer.[42] National differences in dietary practices may partly explain differences in cancer incidence. For example, gastric cancer is more common in Japan due to its high-salt diet[43] while colon cancer is more common in the United States. Immigrant cancer profiles develop mirror that of their new country, often within one generation.[44]

## Infection

*Main article: Infectious causes of cancer*

Worldwide approximately 18% of cancer deaths are related to infectious diseases.[5] This proportion ranges from a high of 25% in Africa to less than 10% in the developed world.[5] Viruses are the usual infectious agents that cause cancer but cancer bacteria and parasites may also play a role.

*Oncovirus*es (viruses that can cause cancer) include human papillomavirus (cervical cancer), Epstein–Barr virus (B-cell lymphoproliferative disease and nasopharyngeal carcinoma), Kaposi's sarcoma herpesvirus (Kaposi's sarcoma and primary effusion lymphomas), hepatitis B and hepatitis C viruses (hepatocellular carcinoma) and human T-cell leukemia virus-1 (T-cell leukemias). Bacterial infection may also increase the risk of cancer, as seen in *Helicobacter pylori*-induced gastric carcinoma.[45][46] Parasitic infections associated with cancer include *Schistosoma haematobium* (squamous cell carcinoma of the bladder) and the liver flukes, *Opisthorchis viverrini* and *Clonorchis sinensis* (cholangiocarcinoma).[47]

## Radiation

*Main article: Radiation-induced cancer*

Up to 10% of invasive cancers are related to radiation exposure, including both ionizing radiation and non-ionizing ultraviolet radiation.[5] Additionally, the majority of non-invasive cancers are non-melanoma skin cancers caused by non-ionizing ultraviolet radiation, mostly from sunlight. Sources of ionizing radiation include medical imaging and radon gas.

Ionizing radiation is not a particularly strong mutagen.[48] Residential exposure to radon gas, for example, has similar cancer risks as passive smoking.[48] Radiation is a more potent source of cancer when combined with other cancer-causing agents, such as radon plus tobacco smoke.[48] Radiation can cause cancer in

most parts of the body, in all animals and at any age. Children and adolescents are twice as likely to develop radiation-induced leukemia as adults; radiation exposure before birth has ten times the effect.[48]

Medical use of ionizing radiation is a small but growing source of radiation-induced cancers. Ionizing radiation may be used to treat other cancers, but this may, in some cases, induce a second form of cancer.[48] It is also used in some kinds of medical imaging.[49]

Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies.[50] Clear evidence establishes ultraviolet radiation, especially the non-ionizing medium wave UVB, as the cause of most non-melanoma skin cancers, which are the most common forms of cancer in the world.[50]

Non-ionizing radio frequency radiation from mobile phones, electric power transmission and other similar sources have been described as a possible carcinogen by the World Health Organization's International Agency for Research on Cancer.[51] However, studies have not found a consistent link between mobile phone radiation and cancer risk.[52]

## Heredity

*Main article: Cancer syndrome*

The vast majority of cancers are non-hereditary (sporadic). Hereditary cancers are primarily caused by an inherited genetic defect. Less than 0.3% of the population are carriers of a genetic mutation that has a large effect on cancer risk and these cause less than 3–10% of cancer.[53] Some of these syndromes include: certain inherited mutations in the genes *BRCA1* and *BRCA2* with a more than 75% risk of breast cancer and ovarian cancer,[53] and hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome), which is present in about 3% of people with colorectal cancer,[54] among others.

## Physical agents

Some substances cause cancer primarily through their physical, rather than chemical, effects.[55] A prominent example of this is prolonged exposure to asbestos, naturally occurring mineral fibers that are a major cause of mesothelioma (cancer of the serous membrane) usually the serous membrane surrounding the lungs.[55] Other substances in this category, including both naturally occurring and synthetic asbestos-like fibers, such as wollastonite, attapulgite, glass wool and rock wool, are believed to have similar effects.[55] Non-fibrous particulate materials that cause cancer include powdered metallic cobalt and nickel and crystalline silica (quartz, cristobalite and tridymite).[55] Usually, physical carcinogens must get inside the body (such as through inhalation) and require years of exposure to produce cancer.[55]

Physical trauma resulting in cancer is relatively rare.[56] Claims that breaking bones resulted in bone cancer, for example, have not been proven.[56] Similarly, physical trauma is not accepted as a cause for cervical cancer, breast cancer or brain cancer.[56] One accepted source is frequent, long-term application of hot objects to the body. It is possible that repeated burns on the same part of the body, such as those produced by kanger and kairo heaters (charcoal hand warmers), may produce skin cancer, especially if carcinogenic chemicals are also present.[56] Frequent consumption of scalding hot tea may produce esophageal cancer.[56] Generally, it is believed that cancer arises, or a pre-existing cancer is encouraged, during the process of healing, rather than directly by the trauma.[56] However, repeated injuries to the same tissues might promote excessive cell proliferation, which could then increase the odds of a cancerous mutation.

Chronic inflammation has been hypothesized to directly cause mutation.[56][57] Inflammation can contribute to proliferation, survival, angiogenesis and migration of cancer cells by influencing the tumor microenvironment.[58][59] Oncogenes build up an inflammatory pro-tumorigenic microenvironment.[60]

## Hormones

Some hormones play a role in the development of cancer by promoting cell proliferation.[61] Insulin-like growth factors and their binding proteins play a key role in cancer cell proliferation, differentiation and apoptosis, suggesting possible involvement in carcinogenesis.[62]

Hormones are important agents in sex-related cancers, such as cancer of the breast, endometrium, prostate, ovary and testis and also of thyroid cancer and bone cancer.[61] For example, the daughters of women who have breast cancer have significantly higher levels of estrogen and progesterone than the daughters of women without breast cancer. These higher hormone levels may explain their higher risk of breast cancer, even in the absence of a breast-cancer gene.[61] Similarly, men of African ancestry have significantly higher levels of testosterone than men of European ancestry and have a correspondingly higher level of prostate cancer.[61] Men of Asian ancestry, with the lowest levels of testosterone-activating androstanediol glucuronide, have the lowest levels of prostate cancer.[61]

Other factors are relevant: obese people have higher levels of some hormones associated with cancer and a higher rate of those cancers.[61] Women who take hormone replacement therapy have a higher risk of developing cancers associated with those hormones.[61] On the other hand, people who exercise far more than average have lower levels of these hormones and lower risk of cancer.[61] Osteosarcoma may be promoted by growth hormones.[61] Some treatments and prevention approaches leverage this cause by artificially reducing hormone levels and thus discouraging hormone-sensitive cancers.[61]

### Autoimmune diseases

There is an association between celiac disease and an increased risk of all cancers. People with untreated celiac disease have a higher risk, but this risk decreases with time after diagnosis and strict treatment, probably due to the adoption of a gluten-free diet, which seems to have a protective role against development of malignancy in people with celiac disease. However, the delay in diagnosis and initiation of a gluten-free diet seems to increase the risk of malignancies.[63] Rates of gastrointestinal cancers are increased in people with Crohn's disease and ulcerative colitis, due to chronic inflammation. Also, immunomodulators and biologic agents used to treat these diseases may promote developing extra-intestinal malignancies.[64]

## Pathophysiology

*Main article: Carcinogenesis*

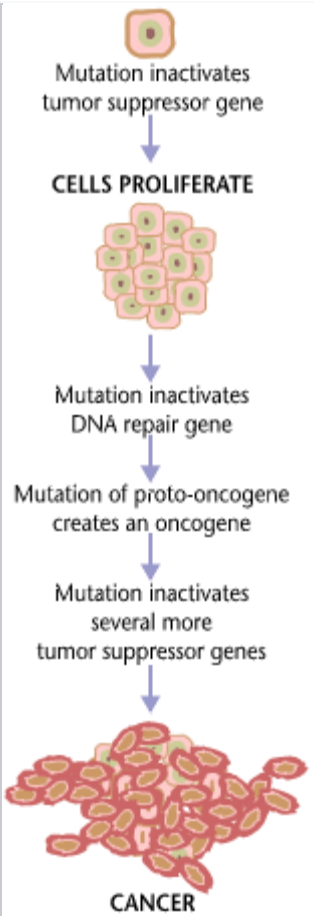
### Genetics

Cancer is fundamentally a disease of tissue growth regulation. In order for a normal cell to transform into a cancer cell, the genes that regulate cell growth and differentiation must be altered.[65]

The affected genes are divided into two broad categories. Oncogenes are genes that promote cell growth and reproduction. Tumor suppressor genes are genes that inhibit cell division and survival. Malignant transformation can occur through the formation of novel oncogenes, the inappropriate over-expression of normal oncogenes, or by the under-expression or disabling of tumor suppressor genes. Typically, changes in multiple genes are required to transform a normal cell into a cancer cell.[66]

Genetic changes can occur at different levels and by different mechanisms. The gain or loss of an entire chromosome can occur through errors in mitosis. More common are mutations, which are changes in the nucleotide sequence of genomic DNA.

Large-scale mutations involve the deletion or gain of a portion of a chromosome. Genomic amplification occurs when a cell gains copies (often 20 or more) of a




Cancers are caused by a series of mutations. Each mutation alters the behavior of the cell somewhat.

small chromosomal locus, usually containing one or more oncogenes and adjacent genetic material. Translocation occurs when two separate chromosomal regions become abnormally fused, often at a characteristic location. A well-known example of this is the Philadelphia chromosome, or translocation of chromosomes 9 and 22, which occurs in chronic myelogenous leukemia and results in production of the BCR-abl fusion protein, an oncogenic tyrosine kinase.

Small-scale mutations include point mutations, deletions, and insertions, which may occur in the promoter region of a gene and affect its expression, or may occur in the gene's coding sequence and alter the function or stability of its protein product. Disruption of a single gene may also result from integration of genomic material from a DNA virus or retrovirus, leading to the expression of *viral* oncogenes in the affected cell and its descendants.

Replication of the data contained within the DNA of living cells will probabilistically result in some errors (mutations). Complex error correction and prevention is built into the process and safeguards the cell against cancer. If a significant error occurs, the damaged cell can self-destruct through programmed cell death, termed apoptosis. If the error control processes fail, then the mutations will survive and be passed along to daughter cells.

Some environments make errors more likely to arise and propagate. Such environments can include the presence of disruptive substances called carcinogens, repeated physical injury, heat, ionising radiation or hypoxia.[67]

The errors that cause cancer are self-amplifying and compounding, for example:

- A mutation in the error-correcting machinery of a cell might cause that cell and its children to accumulate errors more rapidly.
- A further mutation in an oncogene might cause the cell to reproduce more rapidly and more frequently than its normal counterparts.
- A further mutation may cause loss of a tumor suppressor gene, disrupting the apoptosis signaling pathway and immortalizing the cell.
- A further mutation in the signaling machinery of the cell might send error-causing signals to nearby cells.

The transformation of a normal cell into cancer is akin to a chain reaction caused by initial errors, which compound into more severe errors, each progressively allowing the cell to escape more controls that limit normal tissue growth. This rebellion-like scenario is an undesirable survival of the fittest, where the driving forces of evolution work against the body's design and enforcement of order. Once cancer has begun to

develop, this ongoing process, termed *clonal evolution*, drives progression towards more invasive stages.[68] Clonal evolution leads to intra-tumour heterogeneity (cancer cells with heterogeneous mutations) that complicates designing effective treatment strategies.

Characteristic abilities developed by cancers are divided into categories, specifically evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, sustained angiogenesis, limitless replicative potential, metastasis, reprogramming of energy metabolism and evasion of immune destruction.[24][25]

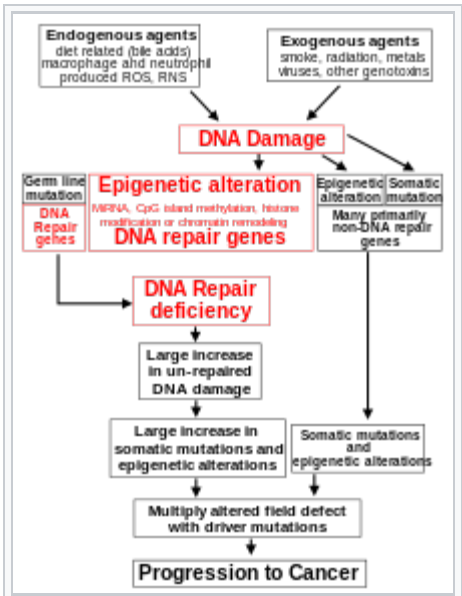
## Epigenetics

*Main article: Cancer epigenetics*

The classical view of cancer is a set of diseases that are driven by progressive genetic abnormalities that include mutations in tumor-suppressor genes and oncogenes and chromosomal abnormalities. Later epigenetic alterations' role was identified.[69]

Epigenetic alterations refer to functionally relevant modifications to the genome that do not change the nucleotide sequence. Examples of such modifications are changes in DNA methylation (hypermethylation and hypomethylation), histone modification[70] and changes in chromosomal architecture (caused by inappropriate expression of proteins such as HMGA2 or HMGA1).[71] Each of these alterations regulates gene expression without altering the underlying DNA sequence. These changes may remain through cell divisions, last for multiple generations and can be considered to be epimutations (equivalent to mutations).

Epigenetic alterations occur frequently in cancers. As an example, one study listed protein coding genes that were frequently altered in their methylation in association with colon cancer. These included 147 hypermethylated and 27 hypomethylated genes. Of the hypermethylated genes, 10 were hypermethylated in 100% of colon cancers and many others were hypermethylated in more than 50% of colon cancers.[72]




The central role of DNA damage and epigenetic defects in DNA repair genes in carcinogenesis

While epigenetic alterations are found in cancers, the epigenetic alterations in DNA repair genes, causing reduced expression of DNA repair proteins, may be of particular importance. Such alterations are thought to occur early in progression to cancer and to be a likely cause of the genetic instability characteristic of cancers.[73][74][75][76]

Reduced expression of DNA repair genes disrupts DNA repair. This is shown in the figure at the 4th level from the top. (In the figure, red wording indicates the central role of DNA damage and defects in DNA repair in progression to cancer.) When DNA repair is deficient DNA damage remains in cells at a higher than usual level (5th level) and cause increased frequencies of mutation and/or epimutation (6th level). Mutation rates increase substantially in cells defective in DNA mismatch repair[77][78] or in homologous recombinational repair (HRR).[79] Chromosomal rearrangements and aneuploidy also increase in HRR defective cells.[80]

Higher levels of DNA damage cause increased mutation (right side of figure) and increased epimutation. During repair of DNA double strand breaks, or repair of other DNA damage, incompletely cleared repair sites can cause epigenetic gene silencing.[81][82]

Deficient expression of DNA repair proteins due to an inherited mutation can increase cancer risks. Individuals with an inherited impairment in any of 34 DNA repair genes (see article DNA repair-deficiency disorder) have increased cancer risk, with some defects ensuring a 100% lifetime chance of cancer (e.g. p53 mutations).[83] Germ line DNA repair mutations are noted on the figure's left side. However, such germline mutations (which cause highly penetrant cancer syndromes) are the cause of only about 1 percent of cancers.[84]

In sporadic cancers, deficiencies in DNA repair are occasionally caused by a mutation in a DNA repair gene but are much more frequently caused by epigenetic alterations that reduce or silence expression of DNA repair genes. This is indicated in the figure at the 3rd level. Many studies of heavy metal-induced carcinogenesis show that such heavy metals cause a reduction in expression of DNA repair enzymes, some through epigenetic mechanisms. DNA repair inhibition is proposed to be a predominant mechanism in heavy metal-induced carcinogenicity. In addition, frequent epigenetic alterations of the DNA sequences code for small RNAs called microRNAs (or miRNAs). miRNAs do not code for proteins, but can "target" protein-coding genes and reduce their expression.

Cancers usually arise from an assemblage of mutations and epimutations that confer a selective advantage leading to clonal expansion (see Field defects in progression to cancer). Mutations, however, may not be as frequent in cancers as epigenetic alterations. An average cancer of the breast or colon can have about 60 to 70 protein-altering mutations, of which about three or four may be "driver" mutations and the remaining ones may be "passenger" mutations.[85]

### Metastasis

*Main article: Metastasis*

Metastasis is the spread of cancer to other locations in the body. The dispersed tumors are called metastatic tumors, while the original is called the primary tumor. Almost all cancers can metastasize.[86] Most cancer deaths are due to cancer that has metastasized.[87]

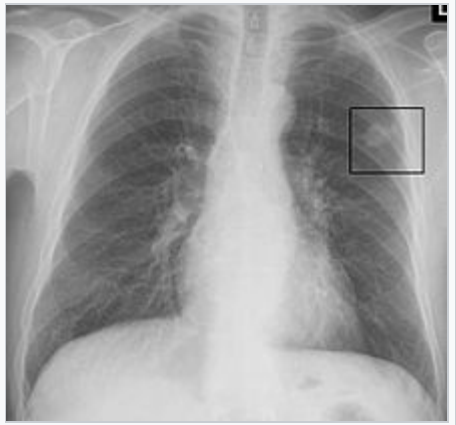
Metastasis is common in the late stages of cancer and it can occur via the blood or the lymphatic system or both. The typical steps in metastasis are local invasion, intravasation into the blood or lymph, circulation through the body, extravasation into the new tissue, proliferation and angiogenesis. Different types of cancers tend to metastasize to particular organs, but overall the most common places for metastases to occur are the lungs, liver, brain and the bones.[86]

## Diagnosis

Most cancers are initially recognized either because of the appearance of signs or symptoms or through screening. Neither of these leads to a definitive diagnosis, which requires the examination of a tissue sample by a pathologist. People with suspected cancer are investigated with medical tests. These commonly include blood tests, X-rays, CT scans and endoscopy.

The tissue diagnosis from the biopsy indicates the type of cell that is proliferating, its histological grade, genetic abnormalities and other features. Together, this information is useful to evaluate the prognosis and to choose the best treatment.

Cytogenetics and immunohistochemistry are other types of tissue tests. These tests provide information about molecular changes (such as mutations, fusion genes and numerical chromosome changes) and may thus also indicate the prognosis and best treatment.



Chest x-ray showing lung cancer in the left lung

## Classification

*Further information: List of cancer types and List of oncology-related terms*

Cancers are classified by the type of cell that the tumor cells resemble and is therefore presumed to be the origin of the tumor. These types include:

- Carcinoma: Cancers derived from epithelial cells. This group includes many of the most common cancers and include nearly all those in the breast, prostate, lung, pancreas and colon.
- Sarcoma: Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve), each of which

develops from cells originating in mesenchymal cells outside the bone marrow.
- Lymphoma and leukemia: These two classes arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively.[88]
- Germ cell tumor: Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).
- Blastoma: Cancers derived from immature "precursor" cells or embryonic tissue.

Cancers are usually named using *-carcinoma*, *-sarcoma* or *-blastoma* as a suffix, with the Latin or Greek word for the organ or tissue of origin as the root. For example, cancers of the liver parenchyma arising from malignant epithelial cells is called *hepatocarcinoma*, while a malignancy arising from primitive liver precursor cells is called a hepatoblastoma and a cancer arising from fat cells is called a *liposarcoma*. For some common cancers, the English organ name is used. For example, the most common type of breast cancer is called *ductal carcinoma of the breast*. Here, the adjective *ductal* refers to the appearance of cancer under the microscope, which suggests that it has originated in the milk ducts.

Benign tumors (which are not cancers) are named using *-oma* as a suffix with the organ name as the root. For example, a benign tumor of smooth muscle cells is called a *leiomyoma* (the common name of this frequently occurring benign tumor in the uterus is *fibroid*). Confusingly, some types of cancer use the *-noma* suffix, examples including melanoma and seminoma.

Some types of cancer are named for the size and shape of the cells under a microscope, such as giant cell carcinoma, spindle cell carcinoma and small-cell carcinoma.

An invasive ductal carcinoma of the breast (pale area at the center) surrounded by spikes of whitish scar tissue and yellow fatty tissue

An invasive colorectal carcinoma (top center) in a colectomy specimen

A squamous-cell carcinoma (the whitish tumor) near the bronchi in a lung specimen

A large invasive ductal carcinoma in a mastectomy specimen

# Prevention

*Main article: Cancer prevention*

Cancer prevention is defined as active measures to decrease cancer risk.[89] The vast majority of cancer cases are due to environmental risk factors. Many of these environmental factors are controllable lifestyle choices. Thus, cancer is generally preventable.[90] Between 70% and 90% of common cancers are due to environmental factors and therefore potentially preventable.[91]

Greater than 30% of cancer deaths could be prevented by avoiding risk factors including: tobacco, excess weight/obesity, insufficient diet, physical inactivity, alcohol, sexually transmitted infections and air pollution.[92] Not all environmental causes are controllable, such as naturally occurring background radiation and cancers caused through hereditary genetic disorders and thus are not preventable via personal behavior.

## Dietary

*Main article: Diet and cancer*

While many dietary recommendations have been proposed to reduce cancer risks, the evidence to support them is not definitive.[9][93] The primary dietary factors that increase risk are obesity and alcohol consumption. Diets low in fruits and vegetables and high in red meat have been implicated but reviews and meta-analyses do not come to a consistent conclusion.[94][95] A 2014 meta-analysis find no relationship between fruits and vegetables and cancer.[96] Coffee is associated with a reduced risk of liver cancer.[97] Studies have linked excess consumption of red or processed meat to an increased risk of breast cancer, colon cancer and pancreatic cancer, a phenomenon that could be due to the presence of carcinogens in meats cooked at high temperatures.[98][99] In 2015 the IARC reported that eating processed meat (e.g., bacon, ham, hot dogs, sausages) and, to a lesser degree, red meat was linked to some cancers.[100][101]

Dietary recommendations for cancer prevention typically include an emphasis on vegetables, fruit, whole grains and fish and an avoidance of processed and red meat (beef, pork, lamb), animal fats and refined carbohydrates.[9][93]

### Medication

Medications can be used to prevent cancer in a few circumstances.[102] In the general population, NSAIDs reduce the risk of colorectal cancer; however, due to cardiovascular and gastrointestinal side effects, they cause overall harm when used for prevention.[103] Aspirin has been found to reduce the risk of death from cancer by about 7%.[104] COX-2 inhibitors may decrease the rate of polyp formation in people with familial adenomatous polyposis; however, it is associated with the same adverse effects as NSAIDs.[105] Daily use of tamoxifen or raloxifene reduce the risk of breast cancer in high-risk women.[106] The benefit versus harm for 5-alpha-reductase inhibitor such as finasteride is not clear.[107]

Vitamins are not effective at preventing cancer,[108] although low blood levels of vitamin D are correlated with increased cancer risk.[109][110] People who have cancer are also at a high risk of developing vitamin D deficiency.[111] Whether this relationship is causal and vitamin D supplementation is protective is not determined.[112] Beta-carotene supplementation increases lung cancer rates in those who are high risk.[113] Folic acid supplementation is not effective in preventing colon cancer and may increase colon polyps.[114] It is unclear if selenium supplementation has an effect.[115]

### Vaccination

Vaccines have been developed that prevent infection by some carcinogenic viruses.[116] Human papillomavirus vaccine (Gardasil and Cervarix) decrease the risk of developing cervical cancer.[116] The hepatitis B vaccine prevents infection with hepatitis B virus and thus decreases the risk of liver cancer.[116] The administration of human papillomavirus and hepatitis B vaccinations is recommended when resources allow.[117]

## Screening

*Main article: Cancer screening*

Unlike diagnostic efforts prompted by symptoms and medical signs, cancer screening involves efforts to detect cancer after it has formed, but before any noticeable symptoms appear.[118] This may involve physical examination, blood or urine tests or medical imaging.[118]

Cancer screening is not available for many types of cancers. Even when tests are available, they may not be recommended for everyone. *Universal screening* or *mass screening* involves screening everyone.[119] *Selective screening* identifies people who are at higher risk, such as people with a family history.[119] Several factors are considered to determine whether the benefits of screening outweigh the risks and the costs of screening.[118] These factors include:

- Possible harms from the screening test: for example, X-ray images involve exposure to potentially harmful ionizing radiation
- The likelihood of the test correctly identifying cancer
- The likelihood that cancer is present: Screening is not normally useful for rare cancers.
- Possible harms from follow-up procedures
- Whether suitable treatment is available
- Whether early detection improves treatment outcomes
- Whether the cancer will ever need treatment
- Whether the test is acceptable to the people: If a screening test is too burdensome (for example, extremely painful), then people will refuse to participate.[119]
- Cost

### Recommendations

### U.S. Preventive Services Task Force

The U.S. Preventive Services Task Force (USPSTF) issues recommendations for various cancers:

- Strongly recommends cervical cancer screening in women who are sexually active and have a cervix at least until the age of 65.[120]
- Recommend that Americans be screened for colorectal cancer via fecal occult blood testing, sigmoidoscopy, or colonoscopy starting at age 50 until age 75.[121]
- Evidence is insufficient to recommend for or against screening for skin cancer,[122] oral cancer,[123] lung cancer,[124] or prostate cancer in men under 75.[125]
- Routine screening is not recommended for bladder cancer,[126] testicular cancer,[127] ovarian cancer,[128] pancreatic cancer,[129] or prostate cancer.[130]
- Recommends mammography for breast cancer screening every two years from ages 50–74. Do not recommend either breast self-examination or clinical breast examination.[131] (A 2011 Cochrane review came to slightly different conclusions with respect to breast cancer screening stating that routine mammography may do more harm than good.[132][*needs update*])

### Japan

Screens for gastric cancer using photofluorography due to the high incidence there.[19]

## Genetic testing

*See also: Cancer syndrome*

Genetic testing for

| Gene | Cancer types |
|---|---|
| BRCA1, BRCA2 | Breast, ovarian, pancreatic |
| HNPCC, MLH1, MSH2, MSH6, PMS1, PMS2 | Colon, uterine, small bowel, stomach, urinary tract |

individuals at high-risk of certain cancers is recommended by unofficial groups.[117][133] Carriers of these mutations may then undergo enhanced surveillance, chemoprevention, or preventative surgery to reduce their subsequent risk.[133]

# Management

*Main articles: Management of cancer and oncology*

Many treatment options for cancer exist. The primary ones include surgery, chemotherapy, radiation therapy, hormonal therapy, targeted therapy and palliative care. Which treatments are used depends on the

type, location and grade of the cancer as well as the patient's health and preferences. The treatment intent may or may not be curative.

## Chemotherapy

Chemotherapy is the treatment of cancer with one or more cytotoxic anti-neoplastic drugs (chemotherapeutic agents) as part of a standardized regimen. The term encompasses a variety of drugs, which are divided into broad categories such as alkylating agents and antimetabolites.[134] Traditional chemotherapeutic agents act by killing cells that divide rapidly, a critical property of most cancer cells.

Targeted therapy is a form of chemotherapy that targets specific molecular differences between cancer and normal cells. The first targeted therapies blocked the estrogen receptor molecule, inhibiting the growth of breast cancer. Another common example is the class of Bcr-Abl inhibitors, which are used to treat chronic myelogenous leukemia (CML).[135] Currently, targeted therapies exist for breast cancer, multiple myeloma, lymphoma, prostate cancer, melanoma and other cancers.[136]

The efficacy of chemotherapy depends on the type of cancer and the stage. In combination with surgery, chemotherapy has proven useful in cancer types including breast cancer, colorectal cancer, pancreatic cancer, osteogenic sarcoma, testicular cancer, ovarian cancer and certain lung cancers.[137] Chemotherapy is curative for some cancers, such as some leukemias,[138][139] ineffective in some brain tumors,[140] and needless in others, such as most non-melanoma skin cancers.[141] The effectiveness of chemotherapy is often limited by its toxicity to other tissues in the body. Even when chemotherapy does not provide a permanent cure, it may be useful to reduce symptoms such as pain or to reduce the size of an inoperable tumor in the hope that surgery will become possible in the future.

## Radiation

Radiation therapy involves the use of ionizing radiation in an attempt to either cure or improve symptoms. It works by damaging the DNA of cancerous tissue, killing it. To spare normal tissues (such as skin or organs, which radiation must pass through to treat the tumor), shaped radiation beams are aimed from multiple exposure angles to intersect at the tumor, providing a much larger dose there than in the surrounding, healthy tissue. As with chemotherapy, cancers vary in their response to radiation therapy.[142][143][144]

Radiation therapy is used in about half of cases. The radiation can be either from internal sources (brachytherapy) or external sources. The radiation is most commonly low energy x-rays for treating skin cancers, while higher energy x-rays are used for cancers within the body.[145] Radiation is typically used in addition to surgery and or chemotherapy. For certain types of cancer, such as early head and neck cancer, it may be used alone.[146] For painful bone metastasis, it has been found to be effective in about 70% of patients.[146]

## Surgery

Surgery is the primary method of treatment for most isolated, solid cancers and may play a role in palliation and prolongation of survival. It is typically an important part of definitive diagnosis and staging of tumors, as biopsies are usually required. In localized cancer, surgery typically attempts to remove the entire mass along with, in certain cases, the lymph nodes in the area. For some types of cancer this is sufficient to eliminate the cancer.[137]

## Palliative care

Palliative care refers to treatment that attempts to help the patient feel better and may be combined with an attempt to treat the cancer. Palliative care includes action to reduce physical, emotional, spiritual and psycho-social distress. Unlike treatment that is aimed at directly killing cancer cells, the primary goal of palliative care is to improve quality of life.

People at all stages of cancer treatment typically receive some kind of palliative care. In some cases,

medical specialty professional organizations recommend that patients and physicians respond to cancer only with palliative care.[147] This applies to patients who:[148]

1. display low performance status, implying limited ability to care for themselves[147]
2. received no benefit from prior evidence-based treatments[147]
3. are not eligible to participate in any appropriate clinical trial[147]
4. no strong evidence implies that treatment would be effective[147]

Palliative care may be confused with hospice and therefore only indicated when people approach end of life. Like hospice care, palliative care attempts to help the patient cope with their immediate needs and to increase comfort. Unlike hospice care, palliative care does not require people to stop treatment aimed at the cancer.

Multiple national medical guidelines recommend early palliative care for patients whose cancer has produced distressing symptoms or who need help coping with their illness. In patients first diagnosed with metastatic disease, palliative care may be immediately indicated. Palliative care is indicated for patients with a prognosis of less than 12 months of life even given aggressive treatment.[149][150][151]

### Immunotherapy

*Main article: Cancer immunotherapy*

A variety of therapies using immunotherapy, stimulating or helping the immune system to fight cancer, have come into use since 1997. Approaches include antibodies, checkpoint therapy and adoptive cell transfer.[152]

### Alternative medicine

Complementary and alternative cancer treatments are a diverse group of therapies, practices and products that are not part of conventional medicine.[153] "Complementary medicine" refers to methods and substances used along with conventional medicine, while "alternative medicine" refers to compounds used instead of conventional medicine.[154] Most complementary and alternative medicines for cancer have not been studied or tested using conventional techniques such as clinical trials. Some alternative treatments have been investigated and shown to be ineffective but still continue to be marketed and promoted. Cancer researcher Andrew J. Vickers stated, "The label 'unproven' is inappropriate for such therapies; it is time to assert that many alternative cancer therapies have been 'disproven'."[155]

## Prognosis

*See also: List of cancer mortality rates in the United States and Cancer survivor*

Survival rates vary by cancer type and by the stage at which it is diagnosed, ranging from majority survival to complete mortality five years after diagnosis. Once a cancer has metastasized, prognosis normally becomes much worse. About half of patients receiving treatment for invasive cancer (excluding carcinoma *in situ* and non-melanoma skin cancers) die from that cancer or its treatment.[19]

Survival is worse in the developing world,[19] partly because the types of cancer that are most common there are harder to treat than those associated with developed countries.[156]

Those who survive cancer develop a second primary cancer at about twice the rate of those never diagnosed.[157] The increased risk is believed to be primarily due to the same risk factors that produced the first cancer, partly due to treatment of the first cancer and to better compliance with screening.[157]

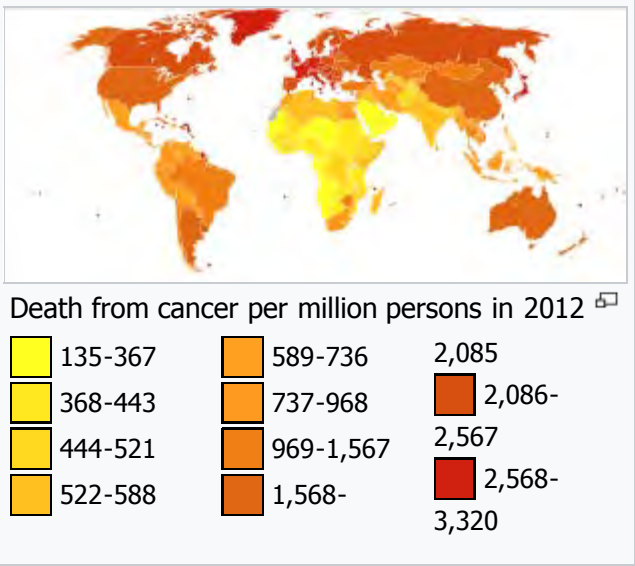
Predicting short- or long-term survival depends on many factors. The most important are the cancer type and the patient's age and overall health. Those who are frail with other health problems have lower survival rates than otherwise healthy people. Centenarians are unlikely to survive for five years even if treatment is successful. People who report a higher quality of life tend to survive longer.[158] People with lower quality

of life may be affected by depression and other complications and/or disease progression that both impairs quality and quantity of life. Additionally, patients with worse prognoses may be depressed or report poorer quality of life because they perceive that their condition is likely to be fatal.

Cancer patients have an increased risk of blood clots in veins. The use of heparin appears to improve survival and decrease the risk of blood clots.[159]

# Epidemiology

*Main article: Epidemiology of cancer*
*See also: List of countries by cancer rate*




In 2008, approximately 12.7 million cancers were diagnosed (excluding non-melanoma skin cancers and other non-invasive cancers)[19] and in 2010 nearly 7.98 million people died.[160] Cancers account for approximately 13% of deaths. The most common are lung cancer (1.4 million deaths), stomach cancer (740,000), liver cancer (700,000), colorectal cancer (610,000) and breast cancer (460,000).[161] This makes invasive cancer the leading cause of death in the developed world and the second leading in the developing world.[19] Over half of cases occur in the developing world.[19]

Deaths from cancer were 5.8 million in 1990.[160] Deaths have been increasing primarily due to longer lifespans and lifestyle changes in the developing world.[19] The most significant risk factor for developing cancer is age.[162] Although it is possible for cancer to strike at any age, most patients with invasive cancer are over 65.[162] According to cancer researcher Robert A. Weinberg, "If we lived long enough, sooner or later we all would get cancer."[163] Some of the association between aging and cancer is attributed to immunosenescence,[164] errors accumulated in DNA over a lifetime[165] and age-related changes in the endocrine system.[166] Aging's effect on cancer is complicated by factors such as DNA damage and inflammation promoting it and factors such as vascular aging and endocrine changes inhibiting it.[167]

Some slow-growing cancers are particularly common, but often are not fatal. Autopsy studies in Europe and Asia showed that up to 36% of people have undiagnosed and apparently harmless thyroid cancer at the time of their deaths and that 80% of men develop prostate cancer by age 80.[168][169] As these cancers do not cause the patient's death, identifying them would have represented overdiagnosis rather than useful medical care.

The three most common childhood cancers are leukemia (34%), brain tumors (23%) and lymphomas (12%).[170] In the United States cancer affects about 1 in 285 children.[171] Rates of childhood cancer increased by 0.6% per year between 1975 and 2002 in the United States[172] and by 1.1% per year between 1978 and 1997 in Europe.[170] Death from childhood cancer decreased by half since 1975 in the United States.[171]

# History

*Main article: History of cancer*

Cancer has existed for all of human history.[173] The earliest written record regarding cancer is from circa 1600 BC in the Egyptian Edwin Smith Papyrus and describes breast cancer.[173] Hippocrates (ca. 460 BC

Engraving with two views of a Dutch woman who had a tumor removed from her neck in 1689

– ca. 370 BC) described several kinds of cancer, referring to them with the Greek word καρκίνος *karkinos* (crab or crayfish).[173] This name comes from the appearance of the cut surface of a solid malignant tumor, with "the veins stretched on all sides as the animal the crab has its feet, whence it derives its name".[174] Galen stated that "cancer of the breast is so called because of the fancied resemblance to a crab given by the lateral prolongations of the tumor and the adjacent distended veins".[175]:738 Celsus (ca. 25 BC – 50 AD) translated *karkinos* into the Latin *cancer*, also meaning crab and recommended surgery as treatment.[173] Galen (2nd century AD) disagreed with the use of surgery and recommended purgatives instead.[173] These recommendations largely stood for 1000 years.[173]

In the 15th, 16th and 17th centuries, it became acceptable for doctors to dissect bodies to discover the cause of death.[176] The German professor Wilhelm Fabry believed that breast cancer was caused by a milk clot in a mammary duct. The Dutch professor Francois de la Boe Sylvius, a follower of Descartes, believed that all disease was the outcome of chemical processes and that acidic lymph fluid was the cause of cancer. His contemporary Nicolaes Tulp believed that cancer was a poison that slowly spreads and concluded that it was contagious.[177]

The physician John Hill described tobacco snuff as the cause of nose cancer in 1761.[176] This was followed by the report in 1775 by British surgeon Percivall Pott that chimney sweeps' carcinoma, a cancer of the scrotum, was a common disease among chimney sweeps.[178] With the widespread use of the microscope in the 18th century, it was discovered that the 'cancer poison' spread from the primary tumor through the lymph nodes to other sites ("metastasis"). This view of the disease was first formulated by the English surgeon Campbell De Morgan between 1871 and 1874.[179]

## Society and culture

Though many diseases (such as heart failure) may have a worse prognosis than most cases of cancer, cancer is the subject of widespread fear and taboos. The euphemism "after a long illness" is still commonly used (2012), reflecting an apparent stigma.[180] This deep belief that cancer is necessarily a difficult and usually deadly disease is reflected in the systems chosen by society to compile cancer statistics: the most common form of cancer—non-melanoma skin cancers, accounting for about one-third of cancer cases worldwide, but very few deaths[181][182]—are excluded from cancer statistics specifically because they are easily treated and almost always cured, often in a single, short, outpatient procedure.[183]

Cancer is regarded as a disease that must be "fought" to end the "civil insurrection"; a War on Cancer was declared in the US. Military metaphors are particularly common in descriptions of cancer's human effects and they emphasize both the state of the patient's health and the need to take immediate, decisive actions himself, rather than to delay, to ignore, or to rely entirely on others. The military metaphors also help rationalize radical, destructive treatments.[184][185]

In the 1970s, a relatively popular alternative cancer treatment in the US was a specialized form of talk therapy, based on the idea that cancer was caused by a bad attitude.[186] People with a "cancer personality"—depressed, repressed, self-loathing and afraid to express their emotions—were believed to have manifested cancer through subconscious desire. Some psychotherapists said that treatment to change the patient's outlook on life would cure the cancer.[186] Among other effects, this belief allowed society to blame the victim for having caused the cancer (by "wanting" it) or having prevented its cure (by not becoming a sufficiently happy, fearless and loving person).[187] It also increased patients' anxiety, as they incorrectly believed that natural emotions of sadness, anger or fear shorten their lives.[187] The idea was ridiculed by Susan Sontag, who published *Illness as Metaphor* while recovering from treatment for breast

cancer in 1978.[186] Although the original idea is now generally regarded as nonsense, the idea partly persists in a reduced form with a widespread, but incorrect, belief that deliberately cultivating a habit of positive thinking will increase survival.[187] This notion is particularly strong in breast cancer culture.[187]

One idea about why people with cancer are blamed or stigmatized, called the just-world hypothesis, is that blaming cancer on the patient's actions or attitudes allows the blamers to regain a sense of control. This is based upon the blamers' belief that the world is fundamentally just and so any dangerous illness, like cancer, must be a type of punishment for bad choices, because in a just world, bad things would not happen to good people.[188]

### Economic effect

In 2007, the overall costs of cancer in the US—including treatment and indirect mortality expenses (such as lost productivity in the workplace) — was estimated to be $226.8 billion. In 2009, 32% of Hispanics and 10% of children 17 years old or younger lacked health insurance; "uninsured patients and those from ethnic minorities are substantially more likely to be diagnosed with cancer at a later stage, when treatment can be more extensive and more costly."[189]

## Research

*Main article: Cancer research*

Because cancer is a class of diseases,[190][191] it is unlikely that there will ever be a single "cure for cancer" any more than there will be a single treatment for all infectious diseases.[192] Angiogenesis inhibitors were once incorrectly thought to have potential as a "silver bullet" treatment applicable to many types of cancer.[193] Angiogenesis inhibitors and other cancer therapeutics are used in combination to reduce cancer morbidity and mortality.[194]

University of Florida Cancer Hospital

Experimental cancer treatments are studied in clinical trials to compare the proposed treatment to the best existing treatment. Treatments that succeeded in one cancer type can be tested against other types.[195] Diagnostic tests are under development to better target the right therapies to the right patients, based on their individual biology.[196]

Cancer research focuses on the following issues:

- Agents (e.g. viruses) and events (e.g. mutations) that cause or facilitate genetic changes in cells destined to become cancer.
- The precise nature of the genetic damage and the genes that are affected by it.
- The consequences of those genetic changes on the biology of the cell, both in generating the defining properties of a cancer cell and in facilitating additional genetic events that lead to further progression of the cancer.

The improved understanding of molecular biology and cellular biology due to cancer research has led to new treatments for cancer since US President Richard Nixon declared the "War on Cancer" in 1971. Since then, the country has spent over $200 billion on cancer research, including resources from public and private sectors.[197] The cancer death rate (adjusting for size and age of the population) declined by five percent between 1950 and 2005.[198]

Competition for financial resources appears to have suppressed the creativity, cooperation, risk-taking and original thinking required to make fundamental discoveries, unduly favoring low-risk research into small incremental advancements over riskier, more innovative research. Other consequences of competition appear to be many studies with dramatic claims whose results cannot be replicated and perverse incentives that encourage grantee institutions to grow without making sufficient investments in their own faculty and facilities.[199][200][201][202]

## Pregnancy

Cancer affects approximately 1 in 1,000 pregnant women. The most common cancers found during pregnancy are the same as the most common cancers found in non-pregnant women during childbearing ages: breast cancer, cervical cancer, leukemia, lymphoma, melanoma, ovarian cancer and colorectal cancer.[203]

Diagnosing a new cancer in a pregnant woman is difficult, in part because any symptoms are commonly assumed to be a normal discomfort associated with pregnancy. As a result, cancer is typically discovered at a somewhat later stage than average. Some imaging procedures, such as MRIs (magnetic resonance imaging), CT scans, ultrasounds and mammograms with fetal shielding are considered safe during pregnancy; some others, such as PET scans, are not.[203]

Treatment is generally the same as for non-pregnant women. However, radiation and radioactive drugs are normally avoided during pregnancy, especially if the fetal dose might exceed 100 cGy. In some cases, some or all treatments are postponed until after birth if the cancer is diagnosed late in the pregnancy. Early deliveries are often used to advance the start of treatment. Surgery is generally safe, but pelvic surgeries during the first trimester may cause miscarriage. Some treatments, especially certain chemotherapy drugs given during the first trimester, increase the risk of birth defects and pregnancy loss (spontaneous abortions and stillbirths).[203]

Elective abortions are not required and, for the most common forms and stages of cancer, do not improve the mother's survival. In a few instances, such as advanced uterine cancer, the pregnancy cannot be continued and in others, the patient may end the pregnancy so that she can begin aggressive chemotherapy.[203]

Some treatments can interfere with the mother's ability to give birth vaginally or to breastfeed.[203] Cervical cancer may require birth by Caesarean section. Radiation to the breast reduces the ability of that breast to produce milk and increases the risk of mastitis. Also, when chemotherapy is given after birth, many of the drugs appear in breast milk, which could harm the baby.[203]

## Other animals

Veterinary oncology, concentrating mainly on cats and dogs, is a growing specialty in wealthy countries and the major forms of human treatment such as surgery and radiotherapy may be offered. The most common types of cancer differ, but the cancer burden seems at least as high in pets as in humans. Animals, typically rodents, are often used in cancer research and studies of natural cancers in larger animals may benefit research into human cancer.[204]

In non-humans, a few types of transmissible cancer have been described, wherein the cancer spreads between animals by transmission of the tumor cells themselves. This phenomenon is seen in dogs with Sticker's sarcoma, also known as canine transmissible venereal tumor.[205]

## Notes


1. ^ *a b c d e f g h* "Cancer Fact sheet N°297". *World Health Organization*. February 2014. Retrieved 10 June 2014.
2. ^ *a b c d* "Defining Cancer". *National Cancer Institute*. Retrieved 10 June 2014.
3. ^ *a b* "Cancer - Signs and symptoms". *NHS Choices*. Retrieved 10 June 2014.
4. ^ "Obesity and Cancer Risk". *National Cancer Institute*. January 3, 2012. Retrieved 4 July 2015.
5. ^ *a b c d e f g* Anand P, Kunnumakkara AB, Warlow CP, Meade TW (January 2011). "Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials". *Lancet*. **377** (9759): 31–41. doi:10.1016/S0140-6736(10)62110-1. PMID 21144578.
105. ^ Cooper K, Squires H, Carroll C, Papaioannou D, Booth A, Logan RF, Maguire C, Hind D, Tappenden P (June 2010). "Chemoprevention of colorectal cancer: systematic review and economic evaluation". *Health Technol Assess*. **14** (32): 1–206.

Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B, Aggarwal BB (September 2008). "Cancer is a preventable disease that requires major lifestyle changes". *Pharm. Res.* **25** (9): 2097–116. doi:10.1007/s11095-008-9661-9. PMC 2515569. PMID 18626751.

6. ^ *a b c d e f g* *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 1.1. ISBN 9283204298.
7. ^ "Heredity and Cancer". American Cancer Society. Retrieved July 22, 2013.
8. ^ "How is cancer diagnosed?". *American Cancer Society*. 2013-01-29. Retrieved 10 June 2014.
9. ^ *a b c* Kushi LH, Doyle C, McCullough M, et al. (2012). "American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity". *CA Cancer J Clin*. **62** (1): 30–67. doi:10.3322/caac.20140. PMID 22237782.
10. ^ Parkin, DM; Boyd, L; Walker, LC (6 December 2011). "16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010.". *British Journal of Cancer*. 105 Suppl 2: S77–81. doi:10.1038/bjc.2011.489. PMC 3252065. PMID 22158327.
11. ^ *a b* *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 4.7. ISBN 9283204298.
12. ^ Gøtzsche PC, Jørgensen KJ (4 Jun 2013). "Screening for breast cancer with mammography.". *The Cochrane database of systematic reviews*. **6**: CD001877. doi:10.1002/14651858.CD001877.pub5. PMID 23737396.
13. ^ "Targeted Cancer Therapies". *NCI*. 2014-04-25. Retrieved 11 June 2014.
14. ^ *a b* *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 1.3. ISBN 9283204298.
15. ^ "SEER Stat Fact Sheets: All Cancer Sites". *National Cancer Institute*. Retrieved 18 June 2014.
16. ^ "The top 10 causes of death Fact sheet N°310". *WHO*. May 2014. Retrieved 10 June 2014.
17. ^ Dubas, LE; Ingraffea, A (Feb 2013). "Nonmelanoma skin cancer.". *Facial plastic surgery clinics of North America*. **21** (1): 43–53. doi:10.1016/j.fsc.2012.10.003. PMID 23369588.
18. ^ Cakir, BÖ; Adamson, P; Cingi, C (Nov 2012). "Epidemiology and economic burden of nonmelanoma skin cancer.". *Facial plastic surgery clinics of North America*. **20** (4): 419–22. doi:10.1016/j.fsc.2012.07.004. PMID 23084294.
19. ^ *a b c d e f g h* Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (February 2011). "Global cancer statistics". *CA: A Cancer Journal for Clinicians*. **61** (2): 69–90. doi:10.3322/caac.20107. PMID 21296855.
20. ^ *World Cancer Report 2014*. World Health
doi:10.3310/hta14320. PMID 20594533.
106. ^ Thomsen A, Kolesar JM (December 2008). "Chemoprevention of breast cancer". *Am J Health Syst Pharm*. **65** (23): 2221–8. doi:10.2146/ajhp070663. PMID 19020189.
107. ^ Wilt TJ, MacDonald R, Hagerty K, Schellhammer P, Kramer BS (2008). Wilt TJ, ed. "Five-alpha-reductase Inhibitors for prostate cancer prevention". *Cochrane Database Syst Rev* (2): CD007091. doi:10.1002/14651858.CD007091. PMID 18425978.
108. ^ "Vitamins and minerals: not for cancer or cardiovascular prevention". *Prescrire Int*. **19** (108): 182. August 2010. PMID 20939459.
109. ^ Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, Willett WC (April 2006). "Prospective study of predictors of vitamin D status and cancer incidence and mortality in men". *J. Natl. Cancer Inst*. **98** (7): 451–9. doi:10.1093/jnci/djj101. PMID 16595781.
110. ^ "Vitamin D Has Role in Colon Cancer Prevention". Archived from the original on 4 December 2006. Retrieved 27 July 2007.
111. ^ Holick, MF (January 2013). "Vitamin D, sunlight and cancer connection.". *Anti-cancer agents in medicinal chemistry*. **13** (1): 70–82. doi:10.2174/187152013804487308. PMID 23094923.
112. ^ Schwartz GG, Blot WJ (April 2006). "Vitamin D status and cancer incidence and mortality: something new under the sun". *J. Natl. Cancer Inst*. **98** (7): 428–30. doi:10.1093/jnci/djj127. PMID 16595770.
113. ^ Fritz H, Kennedy D, Fergusson D, Fernandes R, Doucette S, Cooley K, Seely A, Sagar S, Wong R, Seely D (2011). Minna JD, ed. "Vitamin A and retinoid derivatives for lung cancer: a systematic review and meta analysis". *PLoS ONE*. **6** (6): e21107. Bibcode:2011PLoSO...6E1107F. doi:10.1371/journal.pone.0021107. PMC 3124481. PMID 21738614.
114. ^ Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, McKeown-Eyssen G, Summers RW, Rothstein RI, Burke CA, Snover DC, Church TR, Allen JI, Robertson DJ, Beck GJ, Bond JH, Byers T, Mandel JS, Mott LA, Pearson LH, Barry EL, Rees JR, Marcon N, Saibil F, Ueland PM, Greenberg ER (June 2007). "Folic acid for the prevention of colorectal adenomas: a randomized clinical trial". *JAMA*. **297** (21): 2351–9. doi:10.1001/jama.297.21.2351. PMID 17551129.
115. ^ Vinceti, M; Dennert, G; Crespi, CM; Zwahlen, M; Brinkman, M; Zeegers, MP; Horneber, M; D'Amico, R; Del Giovane, C (Mar 30, 2014). "Selenium for preventing cancer.". *The Cochrane database of systematic reviews*. **3**: CD005195. doi:10.1002/14651858.CD005195.pub3. PMID 24683040.
116. ^ *a b c* "Cancer Vaccine Fact Sheet". NCI. 8 June 2006. Retrieved 15 November 2008.

Organization. 2014. pp. Chapter 6.7. ISBN 9283204298.
21. ^ "Cancer Glossary". *cancer.org*. American Cancer Society. Retrieved September 11, 2013.
22. ^ "What is cancer?". *cancer.gov*. National Cancer Institute. Retrieved September 11, 2013.
23. ^ Hanahan, D; Weinberg, RA (7 January 2000). "The hallmarks of cancer.". *Cell*. **100** (1): 57–70. doi:10.1016/s0092-8674(00)81683-9. PMID 10647931.
24. ^ *a b c* Hanahan, Douglas; Weinberg, Robert A. (January 7, 2000). "The hallmarks of cancer". *Cell*. **100** (1): 57–70. doi:10.1016/S0092-8674(00)81683-9. PMID 10647931.
25. ^ *a b* Hanahan, Douglas; Weinberg, Robert A. (2011). "Hallmarks of Cancer: The Next Generation". *Cell*. **144** (5): 646–74. doi:10.1016/j.cell.2011.02.013. PMID 21376230.
26. ^ *a b c d e* Holland Chp. 1
27. ^ Anguiano L, Mayer DK, Piven ML, Rosenstein D (Jul–Aug 2012). "A literature review of suicide in cancer patients". *Cancer Nursing*. **35** (4): E14–26. doi:10.1097/NCC.0b013e31822fc76c. PMID 21946906.
28. ^ O'Dell, edited by Michael D. Stubblefield, Michael W. (2009). *Cancer rehabilitation principles and practice*. New York: Demos Medical. p. 983. ISBN 978-1-933864-33-4.
29. ^ Kravchenko J, Akushevich I, Manton KG (2009). *Cancer mortality and morbidity patterns in the U. S. population: an interdisciplinary approach*. Berlin: Springer. ISBN 0-387-78192-7. "The term *environment* refers not only to air, water, and soil but also to substances and conditions at home and at the workplace, including diet, smoking, alcohol, drugs, exposure to chemicals, sunlight, ionizing radiation, electromagnetic fields, infectious agents, etc. Lifestyle, economic and behavioral factors are all aspects of our environment."
30. ^ Tolar J, Neglia JP (June 2003). "Transplacental and other routes of cancer transmission between individuals". *J. Pediatr. Hematol. Oncol.* **25** (6): 430–4. doi:10.1097/00043426-200306000-00002. PMID 12794519.
31. ^ Biesalski HK, Bueno de Mesquita B, Chesson A, Chytil F, Grimble R, Hermus RJ, Köhrle J, Lotan R, Norpoth K, Pastorino U, Thurnham D (1998). "European Consensus Statement on Lung Cancer: risk factors and prevention. Lung Cancer Panel". *CA Cancer J Clin*. **48** (3): 167–76; discussion 164–6. doi:10.3322/canjclin.48.3.167. PMID 9594919.
32. ^ Kuper H, Boffetta P, Adami HO (September 2002). "Tobacco use and cancer causation: association by tumour type". *Journal of Internal Medicine*. **252** (3): 206–24. doi:10.1046/j.1365-2796.2002.01022.x. PMID 12270001.
33. ^ *a b* Kuper H, Adami HO, Boffetta P (June 2002). "Tobacco use, cancer causation and public health impact". *Journal of Internal Medicine*. **251** (6): 455–
117. ^ *a b* Lertkhachonsuk AA, Yip CH, Khuhaprema T, Chen DS, Plummer M, Jee SH, Toi M, Wilailak S (2013). "Cancer prevention in Asia: resource-stratified guidelines from the Asian Oncology Summit 2013". *Lancet Oncology*. **14** (12): e497–507. doi:10.1016/S1470-2045(13)70350-4. PMID 24176569.
118. ^ *a b c* "What Is Cancer Screening?". *National Cancer Institute*.
119. ^ *a b c* Wilson JMG, Jungner G. (1968) Principles and practice of screening for disease. Geneva: World Health Organization. Public Health Papers, #34.
120. ^ "Screening for Cervical Cancer". *U.S. Preventive Services Task Force*. 2003.
121. ^ "Screening for Colorectal Cancer". *U.S. Preventive Services Task Force*. 2008.
122. ^ "Screening for Skin Cancer". *U.S. Preventive Services Task Force*. 2009.
123. ^ "Screening for Oral Cancer". *U.S. Preventive Services Task Force*. 2004.
124. ^ "Lung Cancer Screening". *U.S. Preventive Services Task Force*. 2004.
125. ^ "Screening for Prostate Cancer". *U.S. Preventive Services Task Force*. 2008.
126. ^ "Screening for Bladder Cancer". *U.S. Preventive Services Task Force*. 2004.
127. ^ "Screening for Testicular Cancer". *U.S. Preventive Services Task Force*. 2004.
128. ^ "Screening for Ovarian Cancer". *U.S. Preventive Services Task Force*. 2004.
129. ^ "Screening for Pancreatic Cancer". *U.S. Preventive Services Task Force*. 2004.
130. ^ Chou, Roger; Croswell, Jennifer M.; Dana, Tracy; Bougatous, Christina; Blazina, Ian; Fu, Rongwei; Gleitsmann, Ken; Koenig, Helen C.; et al. (7 October 2011). "Screening for Prostate Cancer: A Review of the Evidence for the U.S. Preventive Services Task Force". United States Preventive Services Task Force. Retrieved 8 October 2011.
131. ^ "Screening for Breast Cancer". *U.S. Preventive Services Task Force*. 2009.
132. ^ Gøtzsche PC, Nielsen M (2011). Gøtzsche PC, ed. "Screening for breast cancer with mammography". *Cochrane Database Syst Rev* (1): CD001877. doi:10.1002/14651858.CD001877.pub4. PMID 21249649.
133. ^ *a b* Gulati AP, Domchek SM (Jan 2008). "The clinical management of BRCA1 and BRCA2 mutation carriers". *Current oncology reports*. **10** (1): 47–53. doi:10.1007/s11912-008-0008-9. PMID 18366960.
134. ^ Lind M.J., M.J. (2008). "Principles of cytotoxic chemotherapy". *Medicine*. **36** (1): 19–23. doi:10.1016/j.mpmed.2007.10.003.
135. ^ National Cancer Institute (Dec 2012). "Targeted Cancer Therapies". *www.cancer.gov*. Retrieved 9 March 2014.
136. ^ NCI: Targeted Therapy tutorials Archived 4

66. doi:10.1046/j.1365-2796.2002.00993.x. PMID 12028500.
34. ^ Sasco AJ, Secretan MB, Straif K (August 2004). "Tobacco smoking and cancer: a brief review of recent epidemiological evidence". *Lung Cancer*. 45 Suppl 2: S3–9. doi:10.1016/j.lungcan.2004.07.998. PMID 15552776.
35. ^ Thun MJ, Jemal A (October 2006). "How much of the decrease in cancer death rates in the United States is attributable to reductions in tobacco smoking?". *Tob Control*. **15** (5): 345–7. doi:10.1136/tc.2006.017749. PMC 2563648. PMID 16998161.
36. ^ Dubey S, Powell CA (May 2008). "Update in lung cancer 2007". *Am. J. Respir. Crit. Care Med*. **177** (9): 941–6. doi:10.1164/rccm.200801-107UP. PMC 2720127. PMID 18434333.
37. ^ Schütze M, Boeing H, Pischon T, Rehm J, Kehoe T, Gmel G, Olsen A, Tjønneland AM, Dahm CC, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Trichopoulou A, Benetou V, Zylis D, Kaaks R, Rohrmann S, Palli D, Berrino F, Tumino R, Vineis P, Rodríguez L, Agudo A, Sánchez MJ, Dorronsoro M, Chirlaque MD, Barricarte A, Peeters PH, van Gils CH, Khaw KT, Wareham N, Allen NE, Key TJ, Boffetta P, Slimani N, Jenab M, Romaguera D, Wark PA, Riboli E, Bergmann MM (2011). "Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study". *BMJ*. **342**: d1584. doi:10.1136/bmj.d1584. PMC 3072472. PMID 21474525.
38. ^ Irigaray P, Newby JA, Clapp R, Hardell L, Howard V, Montagnier L, Epstein S, Belpomme D (December 2007). "Lifestyle-related factors and environmental agents causing cancer: an overview". *Biomed. Pharmacother.* **61** (10): 640–58. doi:10.1016/j.biopha.2007.10.006. PMID 18055160.
39. ^ *a b* "WHO calls for prevention of cancer through healthy workplaces" (Press release). World Health Organization. 27 April 2007. Retrieved 13 October 2007.
40. ^ *a b c* Kushi LH, Byers T, Doyle C, Bandera EV, McCullough M, McTiernan A, Gansler T, Andrews KS, Thun MJ (2006). "American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity". *CA Cancer J Clin*. **56** (5): 254–81; quiz 313–4. doi:10.3322/canjclin.56.5.254. PMID 17005596.
41. ^ Bhaskaran, K (2014). "Body mass index and risk of 22 specific cancers". *Lancet*. **384** (9945): 755–765. doi:10.1016/S0140-6736(14)60892-8. PMID 25129328.
42. ^ *a b c* Park S, Bae J, Nam BH, Yoo KY (2008). "Aetiology of cancer in Asia" (PDF). *Asian Pac. J. Cancer Prev*. **9** (3): 371–80. PMID 18990005.
43. ^ Brenner H, Rothenbacher D, Arndt V (2009). October 2014 at the Wayback Machine.
137. ^ *a b* Holland Chp. 40
138. ^ Nastoupil, LJ; Rose, AC; Flowers, CR (May 2012). "Diffuse large B-cell lymphoma: current treatment approaches". *Oncology (Williston Park, N.Y.)*. **26** (5): 488–95. PMID 22730604.
139. ^ Freedman, A (October 2012). "Follicular lymphoma: 2012 update on diagnosis and management". *American journal of hematology*. **87** (10): 988–95. doi:10.1002/ajh.23313. PMID 23001911.
140. ^ Rampling, R; James, A; Papanastassiou, V (June 2004). "The present and future management of malignant brain tumours: surgery, radiotherapy, chemotherapy". *Journal of neurology, neurosurgery, and psychiatry*. 75 Suppl 2 (Suppl 2): ii24–30. doi:10.1136/jnnp.2004.040535. PMC 1765659. PMID 15146036.
141. ^ Madan, V; Lear, JT; Szeimies, RM (February 20, 2010). "Non-melanoma skin cancer". *Lancet*. **375** (9715): 673–85. doi:10.1016/S0140-6736(09)61196-X. PMID 20171403.
142. ^ CK Bomford, IH Kunkler, J Walter. Walter and Miller's Textbook of Radiation therapy (6th Ed), p311
143. ^ "Radiosensitivity"
144. ^ "Radiation therapy- what GPs need to know"
145. ^ Hill, R; Healy, B; Holloway, L; Kuncic, Z; Thwaites, D; Baldock, C (21 March 2014). "Advances in kilovoltage x-ray beam dosimetry.". *Physics in medicine and biology*. **59** (6): R183–231. doi:10.1088/0031-9155/59/6/r183. PMID 24584183.
146. ^ *a b* Holland Chp. 41
147. ^ *a b c d e* American Society of Clinical Oncology. "Five Things Physicians and Patients Should Question" (PDF). *Choosing Wisely: an initiative of the ABIM Foundation*. American Society of Clinical Oncology. Archived from the original (PDF) on 31 July 2012. Retrieved August 14, 2012
148. ^
    - The American Society of Clinical Oncology made this recommendation based on various cancers. See American Society of Clinical Oncology. "Five Things Physicians and Patients Should Question" (PDF). *Choosing Wisely: an initiative of the ABIM Foundation*. American Society of Clinical Oncology. Archived from the original (PDF) on 31 July 2012. Retrieved August 14, 2012
    - for lung cancer, see Azzoli, CG; Temin, S; Aliff, T; Baker, S; Brahmer, J; Johnson, DH; Laskin, JL; Masters, G; Milton, D; Nordquist, L; Pao, W; Pfister, DG; Piantadosi, S; Schiller, JH; Smith, R; Smith, TJ; Strawn, JR; Trent, D; Giaccone, G; American Society of Clinical Oncology (2011). "2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer". *Journal of Clinical Oncology*. **29** (28): 3825–31.

"Epidemiology of stomach cancer". *Methods Mol. Biol*. Methods in Molecular Biology. **472**: 467–77. doi:10.1007/978-1-60327-492-0_23. ISBN 978-1-60327-491-3. PMID 19107449.

44. ^ Buell P, Dunn JE (May 1965). "Cancer mortality among Japanese Issei and Nisei of California". *Cancer*. **18** (5): 656–64. doi:10.1002/1097-0142(196505)18:5<656::AID-CNCR2820180515>3.0.CO;2-3. PMID 14278899.
45. ^ Pagano JS, Blaser M, Buendia MA, Damania B, Khalili K, Raab-Traub N, Roizman B (December 2004). "Infectious agents and cancer: criteria for a causal relation". *Semin. Cancer Biol*. **14** (6): 453–71. doi:10.1016/j.semcancer.2004.06.009. PMID 15489139.
46. ^ Ljubojevic, Suzana; Skerlev, Mihael (2014). "HPV-associated diseases". *Clinics in Dermatology*. **32** (2): 227–234. doi:10.1016/j.clindermatol.2013.08.007. ISSN 0738-081X. PMID 24559558.
47. ^ Samaras V, Rafailidis PI, Mourtzoukou EG, Peppas G, Falagas ME (May 2010). "Chronic bacterial and parasitic infections and cancer: a review" (PDF). *J Infect Dev Ctries*. **4** (5): 267–81. doi:10.3855/jidc.819. PMID 20539059.
48. ^ *a b c d e* Little JB (2000). "Chapter 14: Ionizing Radiation". In Kufe DW, Pollock RE, Weichselbaum RR, Bast RC, Gansler TS, Holland JF, Frei E. *Cancer medicine* (6th ed.). Hamilton, Ont: B.C. Decker. ISBN 1-55009-113-1.
49. ^ Brenner DJ, Hall EJ (November 2007). "Computed tomography—an increasing source of radiation exposure". *N. Engl. J. Med*. **357** (22): 2277–84. doi:10.1056/NEJMra072149. PMID 18046031.
50. ^ *a b* Cleaver JE, Mitchell DL (2000). "15. Ultraviolet Radiation Carcinogenesis". In Bast RC, Kufe DW, Pollock RE, et al. *Holland-Frei Cancer Medicine* (5th ed.). Hamilton, Ontario: B.C. Decker. ISBN 1-55009-113-1. Retrieved 31 January 2011.
51. ^ "IARC classifies radiofrequency electromagnetic fields as possibly carcinogenic to humans" (PDF). *World Health Organization*.
52. ^ "Cell Phones and Cancer Risk - National Cancer Institute". Cancer.gov. 2013-05-08. Retrieved 2013-12-15.
53. ^ *a b* Roukos DH (April 2009). "Genome-wide association studies: how predictable is a person's cancer risk?". *Expert Rev Anticancer Ther*. **9** (4): 389–92. doi:10.1586/era.09.12. PMID 19374592.
54. ^ Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, Starling N (March 2010). "Colorectal cancer". *Lancet*. **375** (9719): 1030–47. doi:10.1016/S0140-6736(10)60353-4. PMID 20304247.
55. ^ *a b c d e* Maltoni CF, Holland JF (2000). "Chapter 16: Physical Carcinogens". In Bast RC, Kufe DW, Pollock RE, et al. *Holland-Frei Cancer Medicine* (5th ed.). Hamilton, Ontario: B.C. Decker. ISBN 1-55009-113-1. Retrieved 31 January 2011.

doi:10.1200/JCO.2010.34.2774. PMC 3675703. PMID 21900105. and Ettinger, DS; Akerley, W; Bepler, G; Blum, MG; Chang, A; Cheney, RT; Chirieac, LR; d'Amico, TA; Demmy, TL; Ganti, AK; Govindan, R; Grannis Jr, FW; Jahan, T; Jahanzeb, M; Johnson, DH; Kessinger, A; Komaki, R; Kong, FM; Kris, MG; Krug, LM; Le, QT; Lennes, IT; Martins, R; O'Malley, J; Osarogiagbon, RU; Otterson, GA; Patel, JD; Pisters, KM; Reckamp, K; Riely, GJ (2010). "Non-small cell lung cancer". *Journal of the National Comprehensive Cancer Network : JNCCN*. **8** (7): 740–801. PMID 20679538.

- for breast cancer, see Carlson, RW; Allred, DC; Anderson, BO; Burstein, HJ; Carter, WB; Edge, SB; Erban, JK; Farrar, WB; Goldstein, LJ; Gradishar, WJ; Hayes, DF; Hudis, CA; Jahanzeb, M; Kiel, K; Ljung, BM; Marcom, PK; Mayer, IA; McCormick, B; Nabell, LM; Pierce, LJ; Reed, EC; Smith, ML; Somlo, G; Theriault, RL; Topham, NS; Ward, JH; Winer, EP; Wolff, AC; NCCN Breast Cancer Clinical Practice Guidelines Panel (2009). "Breast cancer. Clinical practice guidelines in oncology". *Journal of the National Comprehensive Cancer Network : JNCCN*. **7** (2): 122–92. PMID 19200416.
- for colon cancer, see Engstrom, PF; Arnoletti, JP; Benson Ab, 3rd; Chen, YJ; Choti, MA; Cooper, HS; Covey, A; Dilawari, RA; Early, DS; Enzinger, PC; Fakih, MG; Fleshman Jr, J; Fuchs, C; Grem, JL; Kiel, K; Knol, JA; Leong, LA; Lin, E; Mulcahy, MF; Rao, S; Ryan, DP; Saltz, L; Shibata, D; Skibber, JM; Sofocleous, C; Thomas, J; Venook, AP; Willett, C; National Comprehensive Cancer Network (2009). "NCCN Clinical Practice Guidelines in Oncology: Colon cancer". *Journal of the National Comprehensive Cancer Network : JNCCN*. **7** (8): 778–831. PMID 19755046.
- for other general statements see Smith, Thomas J.; Hillner, Bruce E. (2011). "Bending the Cost Curve in Cancer Care". *New England Journal of Medicine*. **364** (21): 2060–5. doi:10.1056/NEJMsb1013826. PMID 21612477. and Peppercorn, J. M.; Smith, T. J.; Helft, P. R.; Debono, D. J.; Berry, S. R.; Wollins, D. S.; Hayes, D. M.; Von Roenn, J. H.; Schnipper, L. E.; American Society of Clinical Oncology (2011). "American Society of Clinical Oncology Statement: Toward Individualized Care for Patients with Advanced Cancer". *Journal of Clinical Oncology*. **29** (6): 755–60. doi:10.1200/JCO.2010.33.1744. PMID 21263086.

149. ^ "NCCN Guidelines".
150. ^ "Clinical Practice Guidelines for Quality Palliative Care" (PDF). The National Consensus Project for Quality Palliative Care (NCP).
151. ^ Levy MH, Back A, Bazargan S, Benedetti C, Billings JA, Block S, Bruera E, Carducci MA, Dy S, Eberle C,

56. ^ a b c d e f g Gaeta, John F (2000). "Chapter 17: Trauma and Inflammation". In Bast RC, Kufe DW, Pollock RE, et al. *Holland-Frei Cancer Medicine* (5th ed.). Hamilton, Ontario: B.C. Decker. ISBN 1-55009-113-1. Retrieved 27 January 2011.
57. ^ Colotta, F.; Allavena, P.; Sica, A.; Garlanda, C.; Mantovani, A. (2009). "Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability". *Carcinogenesis* (review). **30** (7): 1073–1081. doi:10.1093/carcin/bgp127. ISSN 0143-3334. PMID 19468060.
58. ^ Hendrik Ungefroren; Susanne Sebens; Daniel Seidl; Hendrik Lehnert; Ralf Haas (2011). "Interaction of tumor cells with the microenvironment". *Cell Communication and Signaling*. **9** (18): 18. doi:10.1186/1478-811X-9-18.
59. ^ Mantovani A (June 2010). "Molecular pathways linking inflammation and cancer". *Current Molecular Medicine* (review). **10** (4): 369–73. doi:10.2174/156652410791316968. PMID 20455855.
60. ^ Borrello, Maria Grazia; Degl'Innocenti, Debora; Pierotti, Marco A. (2008). "Inflammation and cancer: The oncogene-driven connection". *Cancer Letters* (review). **267** (2): 262–270. doi:10.1016/j.canlet.2008.03.060. ISSN 0304-3835. PMID 18502035.
61. ^ a b c d e f g h i j Henderson BE, Bernstein L, Ross RK (2000). "Chapter 13: Hormones and the Etiology of Cancer". In Bast RC, Kufe DW, Pollock RE, et al. *Holland-Frei Cancer Medicine* (5th ed.). Hamilton, Ontario: B.C. Decker. ISBN 1-55009-113-1. Retrieved 27 January 2011.
62. ^ Rowlands, Mari-Anne; Gunnell, David; Harris, Ross; Vatten, Lars J; Holly, Jeff MP; Martin, Richard M (May 15, 2009). "Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis". *Int J Cancer*. **124** (10): 2416–29. doi:10.1002/ijc.24202. PMC 2743036. PMID 19142965.
63. ^ Han Y, Chen W, Li P, Ye J (2015). "Association Between Coeliac Disease and Risk of Any Malignancy and Gastrointestinal Malignancy: A Meta-Analysis.". *Medicine (Baltimore)*. **94** (38): e1612. doi:10.1097/MD.0000000000001612. PMC 4635766. PMID 26402826.
64. ^ Axelrad, JE; Lichtiger, S; Yajnik, V (28 May 2016). "Inflammatory bowel disease and cancer: The role of inflammation, immunosuppression, and cancer treatment.". *World journal of gastroenterology*. **22** (20): 4794–801. doi:10.3748/wjg.v22.i20.4794. PMC 4873872. PMID 27239106.
65. ^ Croce CM (January 2008). "Oncogenes and cancer". *N. Engl. J. Med.* **358** (5): 502–11. doi:10.1056/NEJMra072367. PMID 18234754.
66. ^ Knudson AG (November 2001). "Two genetic hits (more or less) to cancer". *Nature Reviews Cancer*. **1** (2): 157–62. doi:10.1038/35101031.
Foley KM, Harris JD, Knight SJ, Milch R, Rhiner M, Slatkin NE, Spiegel D, Sutton L, Urba S, Von Roenn JH, Weinstein SM (September 2006). "Palliative care. Clinical practice guidelines in oncology". *Journal of the National Comprehensive Cancer Network: JNCCN*. National Comprehensive Cancer Network. **4** (8): 776–818. PMID 16948956.
152. ^ Waldmann, TA (March 2003). "Immunotherapy: past, present and future.". *Nature Medicine*. **9** (3): 269–77. doi:10.1038/nm0303-269. PMID 12612576.
153. ^ Cassileth BR, Deng G (2004). "Complementary and alternative therapies for cancer". *Oncologist*. **9** (1): 80–9. doi:10.1634/theoncologist.9-1-80. PMID 14755017.
154. ^ What Is CAM? National Center for Complementary and Alternative Medicine. retrieved 3 February 2008.
155. ^ Vickers A (2004). "Alternative cancer cures: 'unproven' or 'disproven'?". *CA Cancer J Clin*. **54** (2): 110–8. doi:10.3322/canjclin.54.2.110. PMID 15061600.
156. ^ *World Cancer Report 2014*. World Health Organization. 2014. p. 22. ISBN 9283204298.
157. ^ a b Rheingold, Susan; Neugut, Alfred; Meadows, Anna (2003). "156: Secondary Cancers: Incidence, Risk Factors, and Management". In Frei, Emil; Kufe, Donald W.; Holland, James F. *Holland-Frei Cancer Medicine* (6th ed.). Hamilton, Ont: BC Decker. p. 2399. ISBN 1-55009-213-8. Retrieved 5 November 2009.
158. ^ Montazeri A (December 2009). "Quality of life data as prognostic indicators of survival in cancer patients: an overview of the literature from 1982 to 2008". *Health Qual Life Outcomes*. **7**: 102. doi:10.1186/1477-7525-7-102. PMC 2805623. PMID 20030832.
159. ^ Akl, EA; Kahale, LA; Ballout, RA; Barba, M; Yosuico, VE; van Doormaal, FF; Middeldorp, S; Bryant, A; Schünemann, H (10 December 2014). "Parenteral anticoagulation in ambulatory patients with cancer.". *The Cochrane database of systematic reviews*. **12**: CD006652. doi:10.1002/14651858.CD006652.pub4. PMID 25491949.
160. ^ a b Lozano, R; Mohsen, N; Foreman, K; Lim, S; Shibuya, K; Aboyans, V; Abraham, J; Adair, T; Aggarwal, R; Ahn, SY; AlMazroa, MA; Alvarado, M; Anderson, HR; Anderson, LM; Andrews, KG; Atkinson, C; Baddour, LM; Barker-Collo, S; Bartels, DH; Bell, ML; Benjamin, EJ; Bennett, D; Bhalla, K; Bikbov, B; Bin Abdulhak, A; Birbeck, G; Blyth, F; Bolliger, I; Boufous, S; Bucello, C (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.

PMID 11905807 .
67. ^ Nelson DA, Tan TT, Rabson AB, Anderson D, Degenhardt K, White E (September 2004). "Hypoxia and defective apoptosis drive genomic instability and tumorigenesis". *Genes & Development*. **18** (17): 2095–107. doi:10.1101/gad.1204904. PMC 515288. PMID 15314031.
68. ^ Merlo LM, Pepper JW, Reid BJ, Maley CC (December 2006). "Cancer as an evolutionary and ecological process". *Nature Reviews Cancer*. **6** (12): 924–35. doi:10.1038/nrc2013. PMID 17109012.
69. ^ Baylin SB, Ohm JE (February 2006). "Epigenetic gene silencing in cancer - a mechanism for early oncogenic pathway addiction?". *Nature Reviews Cancer*. **6** (2): 107–16. doi:10.1038/nrc1799. PMID 16491070.
70. ^ Kanwal, R; Gupta, S (2012). "Epigenetic modifications in cancer". *Clinical Genetics*. **81** (4): 303–11. doi:10.1111/j.1399-0004.2011.01809.x. PMC 3590802. PMID 22082348.
71. ^ Baldassarre, G; Battista, S; Belletti, B; Thakur, S; Pentimalli, F; Trapasso, F; Fedele, M; Pierantoni, G; Croce, CM; Fusco, A (2003). "Negative regulation of BRCA1 gene expression by HMGA1 proteins accounts for the reduced BRCA1 protein levels in sporadic breast carcinoma". *Molecular and Cellular Biology*. **23** (7): 2225–38. doi:10.1128/MCB.23.7.2225-2238.2003. PMC 150734. PMID 12640109./
72. ^ Schnekenburger, M; Diederich, M (2012). "Epigenetics Offer New Horizons for Colorectal Cancer Prevention". *Current Colorectal Cancer Reports*. **8** (1): 66–81. doi:10.1007/s11888-011-0116-z. PMC 3277709. PMID 22389639.
73. ^ Jacinto FV, Esteller M (July 2007). "Mutator pathways unleashed by epigenetic silencing in human cancer". *Mutagenesis*. **22** (4): 247–53. doi:10.1093/mutage/gem009. PMID 17412712.
74. ^ Lahtz C, Pfeifer GP (February 2011). "Epigenetic changes of DNA repair genes in cancer". *J Mol Cell Biol*. **3** (1): 51–8. doi:10.1093/jmcb/mjq053. PMC 3030973. PMID 21278452.
75. ^ Bernstein C, Nfonsam V, Prasad AR, Bernstein H (March 2013). "Epigenetic field defects in progression to cancer". *World J Gastrointest Oncol*. **5** (3): 43–9. doi:10.4251/wjgo.v5.i3.43. PMC 3648662. PMID 23671730.
76. ^ Bernstein, Carol; Prasad, Anil R.; Nfonsam, Valentine; Bernstein, Harris (2013). "DNA Damage, DNA Repair and Cancer". In Clark Chen. *New Research Directions in DNA Repair*. InTech. doi:10.5772/53919. ISBN 978-953-51-1114-6.
77. ^ Narayanan, L; Fritzell, JA; Baker, SM; Liskay, RM; Glazer, PM (1997). "Elevated levels of mutation in multiple tissues of mice deficient in the DNA mismatch repair gene Pms2". *Proceedings of the National Academy of Sciences of the United States of America*. **94** (7): 3122–7. doi:10.1073/pnas.94.7.3122. PMC 20332. PMID 9096356.
161. ^ WHO (October 2010). "Cancer". World Health Organization. Retrieved 5 January 2011.
162. ^ *a b* Coleman, William B.; Rubinas, Tara C. (2009). "4". In Tsongalis, Gregory J.; Coleman, William L. *Molecular Pathology: The Molecular Basis of Human Disease*. Amsterdam: Elsevier Academic Press. p. 66. ISBN 0-12-374419-9.
163. ^ Johnson, George (28 December 2010). "Unearthing Prehistoric Tumors, and Debate". *The New York Times*.
164. ^ Pawelec G, Derhovanessian E, Larbi A (Aug 2010). "Immunosenescence and cancer". *Critical reviews in oncology/hematology*. **75** (2): 165–72. doi:10.1016/j.critrevonc.2010.06.012. PMID 20656212.
165. ^ Alberts, B, Johnson A, Lewis J, et al. (2002). "The Preventable Causes of Cancer". *Molecular biology of the cell* (4th ed.). New York: Garland Science. ISBN 0-8153-4072-9. "A certain irreducible background incidence of cancer is to be expected regardless of circumstances: mutations can never be absolutely avoided, because they are an inescapable consequence of fundamental limitations on the accuracy of DNA replication, as discussed in Chapter 5. If a human could live long enough, it is inevitable that at least one of his or her cells would eventually accumulate a set of mutations sufficient for cancer to develop."
166. ^ Anisimov VN, Sikora E, Pawelec G (Aug 2009). "Relationships between cancer and aging: a multilevel approach". *Biogerontology*. **10** (4): 323–38. doi:10.1007/s10522-008-9209-8. PMID 19156531.
167. ^ de Magalhaes JP (2013). "How ageing processes influence cancer". *Nature Reviews Cancer*. **13** (5): 357–65. doi:10.1038/nrc3497. PMID 23612461.
168. ^ Fraumeni, Joseph F.; Schottenfeld, David; Marshall, James M. (2006). *Cancer epidemiology and prevention*. Oxford [Oxfordshire]: Oxford University Press. p. 977. ISBN 0-19-514961-0.
169. ^ Bostwick, David G.; Eble, John N. (2007). *Urological Surgical Pathology*. St. Louis: Mosby. p. 468. ISBN 0-323-01970-6.
170. ^ *a b* Kaatsch P, Sikora E, Pawelec G (June 2010). "Epidemiology of childhood cancer". *Cancer treatment reviews*. **36** (4): 277–85. doi:10.1016/j.ctrv.2010.02.003. PMID 20231056.
171. ^ *a b* Ward, Elizabeth; DeSantis, Carol; Robbins, Anthony; Kohler, Betsy; Jemal, Ahmedin (January 2014). "Childhood and adolescent cancer statistics, 2014". *CA: A Cancer Journal for Clinicians*. **64**: 83–103. doi:10.3322/caac.21219. PMID 24488779.
172. ^ Ward EM, Thun MJ, Hannan LM, Jemal A (Sep 2006). "Interpreting cancer trends". *Annals of the New York Academy of Sciences*. **1076**: 29–53. Bibcode:2006NYASA1076...29W. doi:10.1196/annals.1371.048. PMID 17119192.
173. ^ *a b c d e f* Hajdu SI, Thun MJ, Hannan LM, Jemal A (March 2011). "A note from history: landmarks in

78. ^ Hegan, DC; Narayanan, L; Jirik, FR; Edelmann, W; Liskay, RM; Glazer, PM (2006). "Differing patterns of genetic instability in mice deficient in the mismatch repair genes Pms2, Mlh1, Msh2, Msh3 and Msh6". *Carcinogenesis*. **27** (12): 2402–8. doi:10.1093/carcin/bgl079. PMC 2612936. PMID 16728433.
79. ^ Tutt, AN; Van Oostrom, CT; Ross, GM; Van Steeg, H; Ashworth, A (2002). "Disruption of Brca2 increases the spontaneous mutation rate in vivo: Synergism with ionizing radiation". *EMBO Reports*. **3** (3): 255–60. doi:10.1093/embo-reports/kvf037. PMC 1084010. PMID 11850397.
80. ^ German, J (1969). "Bloom's syndrome. I. Genetical and clinical observations in the first twenty-seven patients". *American Journal of Human Genetics*. **21** (2): 196–227. PMC 1706430. PMID 5770175.
81. ^ O'Hagan, HM; Mohammad, HP; Baylin, SB (2008). Lee, Jeannie T, ed. "Double strand breaks can initiate gene silencing and SIRT1-dependent onset of DNA methylation in an exogenous promoter CpG island". *PLOS Genetics*. **4** (8): e1000155. doi:10.1371/journal.pgen.1000155. PMC 2491723. PMID 18704159.
82. ^ Cuozzo, C; Porcellini, A; Angrisano, T; Morano, A; Lee, B; Di Pardo, A; Messina, S; Iuliano, R; Fusco, A; Santillo, MR; Muller, MT; Chiariotti, L; Gottesman, ME; Avvedimento, EV (2007). "DNA damage, homology-directed repair, and DNA methylation". *PLOS Genetics*. **3** (7): e110. doi:10.1371/journal.pgen.0030110. PMC 1913100. PMID 17616978.
83. ^ Malkin, D (2011). "Li-fraumeni syndrome". *Genes & cancer*. **2** (4): 475–84. doi:10.1177/1947601911413466. PMC 3135649. PMID 21779515.
84. ^ Fearon, ER (1997). "Human cancer syndromes: Clues to the origin and nature of cancer". *Science*. **278** (5340): 1043–50. doi:10.1126/science.278.5340.1043. PMID 9353177.
85. ^ Vogelstein, B; Papadopoulos, N; Velculescu, VE; Zhou, S; Diaz Jr, LA; Kinzler, KW (2013). "Cancer genome landscapes". *Science*. **339** (6127): 1546–58. doi:10.1126/science.1235122. PMC 3749880. PMID 23539594.
86. ^ *a b* "Metastatic Cancer: Questions and Answers". National Cancer Institute. Retrieved 2008-08-28.
87. ^ "What is Metastasized Cancer?". *National Comprehensive Cancer Network*. Archived from the original on 7 July 2013. Retrieved 18 July 2013.
88. ^ Varricchio Claudette G. (2004). *A cancer source book for nurses*. Boston: Jones and Bartlett Publishers. p. 229. ISBN 0-7637-3276-1.
89. ^ "Cancer prevention: 7 steps to reduce your risk". Mayo Clinic. 27 September 2008. Retrieved 30 January 2010.
90. ^ Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M (2005). "Causes of cancer in the world: history of cancer, part 1". *Cancer*. **117** (5): 1097–102. doi:10.1002/cncr.25553. PMID 20960499.
174. ^ Paul of Aegina, 7th Century AD, quoted in Moss, Ralph W. (2004). "Galen on Cancer". CancerDecisions. Archived from the original on 16 July 2011. Referenced from Michael Shimkin, Contrary to Nature, Washington, D.C.: Superintendent of Document, DHEW Publication No. (NIH) 79-720, p. 35.
175. ^ Majno, Guido; Joris, Isabelle (August 12, 2004). *Cells, Tissues, and Disease : Principles of General Pathology: Principles of General Pathology*. Oxford University Press. ISBN 978-0-19-974892-1. Retrieved September 11, 2013.
176. ^ *a b* Hajdu SI, Thun MJ, Hannan LM, Jemal A (June 2011). "A note from history: landmarks in history of cancer, part 2". *Cancer*. **117** (12): 2811–20. doi:10.1002/cncr.25825. PMID 21656759.
177. ^ Yalom, Marilyn (1998). *A history of the breast* (1st Ballantine Books ed.). New York: Ballantine Books. ISBN 0-679-43459-3.
178. ^ Hajdu SI, Thun MJ, Hannan LM, Jemal A (July 2011). "A note from history: Landmarks in history of cancer, part 3". *Cancer*. **118** (4): 1155–68. doi:10.1002/cncr.26320. PMID 21751192.
179. ^ Grange JM, Stanford JL, Stanford CA (2002). "Campbell De Morgan's 'Observations on cancer', and their relevance today". *Journal of the Royal Society of Medicine*. **95** (6): 296–9. doi:10.1258/jrsm.95.6.296. PMC 1279913. PMID 12042378.
180. ^ Ehrenreich, Barbara (November 2001). "Welcome to Cancerland". *Harper's Magazine*. ISSN 0017-789X. Archived from the original on 6 July 2015.
181. ^ Rapini, Ronald P.; Bolognia, Jean L.; Jorizzo, Joseph L. (2007). *Dermatology: 2-Volume Set*. St. Louis: Mosby. ISBN 1-4160-2999-0.
182. ^ "Skin cancers". World Health Organization. Retrieved 19 January 2011.
183. ^ McCulley, Michelle; Greenwell, Pamela (2007). *Molecular therapeutics: 21st-century medicine*. London: J. Wiley. p. 207. ISBN 0-470-01916-6.
184. ^ Gwyn, Richard (1999). "10". In Cameron, Lynne; Low, Graham. *Researching and applying metaphor*. Cambridge, UK: Cambridge University Press. ISBN 0-521-64964-1.
185. ^ Sulik, Gayle (2010). *Pink Ribbon Blues: How Breast Cancer Culture Undermines Women's Health*. New York: Oxford University Press. pp. 78–89. ISBN 0-19-974045-3. OCLC 535493589.
186. ^ *a b c* Olson, James Stuart (2002). *Bathsheba's Breast: Women, Cancer and History*. Baltimore: The Johns Hopkins University Press. pp. 145–170. ISBN 0-8018-6936-6. OCLC 186453370.
187. ^ *a b c d* Ehrenreich, Barbara (2009). *Bright-sided: How the Relentless Promotion of Positive Thinking Has Undermined America*. New York: Metropolitan Books. pp. 15–44. ISBN 0-8050-8749-4.

comparative risk assessment of nine behavioural and environmental risk factors". *Lancet*. **366** (9499): 1784–93. doi:10.1016/S0140-6736(05)67725-2. PMID 16298215.

91. ^ Wu, S; Powers, S; Zhu, W; Hannun, YA (16 December 2015). "Substantial contribution of extrinsic risk factors to cancer development.". *Nature*. **529**: 43–7. doi:10.1038/nature16166. PMC 4836858. PMID 26675728.
92. ^ "Cancer". *World Health Organization*. Retrieved 9 January 2011.
93. ^ *a b* Wicki A, Hagmann J (September 2011). "Diet and cancer". *Swiss Medical Weekly*. **141**: w13250. doi:10.4414/smw.2011.13250. PMID 21904992.
94. ^ Cappellani A, Di Vita M, Zanghi A, Cavallaro A, Piccolo G, Veroux M, Berretta M, Malaguarnera M, Canzonieri V, Lo Menzo E (2012). "Diet, obesity and breast cancer: an update". *Front Biosci (Schol Ed)*. **4**: 90–108. PMID 22202045.
95. ^ Key TJ (January 2011). "Fruit and vegetables and cancer risk". *Br. J. Cancer*. **104** (1): 6–11. doi:10.1038/sj.bjc.6606032. PMC 3039795. PMID 21119663.
96. ^ Wang, X; Ouyang, Y; Liu, J; Zhu, M; Zhao, G; Bao, W; Hu, FB (29 July 2014). "Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies.". *BMJ (Clinical research ed.)*. **349**: g4490. doi:10.1136/bmj.g4490. PMC 4115152. PMID 25073782.
97. ^ Larsson SC, Wolk A (May 2007). "Coffee consumption and risk of liver cancer: a meta-analysis". *Gastroenterology*. **132** (5): 1740–5. doi:10.1053/j.gastro.2007.03.044. PMID 17484871.
98. ^ Zheng W, Lee SA (2009). "Well-done meat intake, heterocyclic amine exposure, and cancer risk". *Nutr Cancer*. **61** (4): 437–46. doi:10.1080/01635580802710741. PMC 2769029. PMID 19838915.
99. ^ Ferguson LR (February 2010). "Meat and cancer". *Meat Sci*. **84** (2): 308–13. doi:10.1016/j.meatsci.2009.06.032. PMID 20374790.
100. ^ Staff (October 26, 2015). "World Health Organization - IARC Monographs evaluate consumption of red meat and processed meat" (PDF). *International Agency for Research on Cancer*. Retrieved October 26, 2015.
101. ^ Hauser, Christine (October 26, 2015). "W.H.O. Report Links Some Cancers With Processed or Red Meat". *New York Times*. Retrieved October 26, 2015.
102. ^ Holland Chp.33
103. ^ Rostom A, Dubé C, Lewin G, Tsertsvadze A, Barrowman N, Code C, Sampson M, Moher D (March 2007). "Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of
188. ^ Huff, Charlotte (24 September 2013). "A Sick Stigma: Why are cancer patients blamed for their illness?". *Slate*.
189. ^ "Cancer Facts and Figures 2012". Journalist's Resource.org.
190. ^ "What Is Cancer?". National Cancer Institute. Retrieved 17 August 2009.
191. ^ "Cancer Fact Sheet". Agency for Toxic Substances & Disease Registry. 30 August 2002. Retrieved 17 August 2009.
192. ^ Wanjek, Christopher (16 September 2006). "Exciting New Cancer Treatments Emerge Amid Persistent Myths". Retrieved 17 August 2009.
193. ^ Hayden EC, Thun MJ, Hannan LM, Jemal A (April 2009). "Cutting off cancer's supply lines". *Nature*. **458** (7239): 686–687. doi:10.1038/458686b. PMID 19360048.
194. ^ Bagri, A; Kouros-Mehr, Hosein; Leong, KG; Plowman, GD (Mar 2010). "Use of anti-VEGF adjuvant therapy in cancer: challenges and rationale.". *Trends in molecular medicine*. **16** (3): 122–32. doi:10.1016/j.molmed.2010.01.004. PMID 20189876.
195. ^ Sleigh SH, Barton CL (2010). "Repurposing Strategies for Therapeutics". *Pharm Med*. **24** (3): 151–159. doi:10.2165/11536770-000000000-00000.
196. ^ Winther H, Jorgensen JT (2010). "Drug-Diagnostic Co-Development in Cancer". *Pharm Med*. **24** (6): 363–375. doi:10.2165/11586320-000000000-00000.
197. ^ Sharon Begley (16 September 2008). "Rethinking the War on Cancer". *Newsweek*. Archived from the original on 10 September 2008. Retrieved 8 September 2008.
198. ^ Kolata, Gina (23 April 2009). "Advances Elusive in the Drive to Cure Cancer". *The New York Times*. Retrieved 5 May 2009.
199. ^ Bruce Alberts, Marc W. Kirschner, Shirley Tilghman, and Harold Varmus, Rescuing US biomedical research from its systemic flaws, *Proceedings of the National Academy of Sciences of the United States of America*, vol. 111 no. 16, April 2014
200. ^ Kolata, Gina (April 23, 2009). "Advances Elusive in the Drive to Cure Cancer". *The New York Times*. Retrieved 2009-12-29.
201. ^ Kolata, Gina (June 27, 2009). "Grant System Leads Cancer Researchers to Play It Safe". *The New York Times*. Retrieved 2009-12-29.
202. ^ Kendall Powell, Young, talented and fed-up: scientists tell their stories, *Nature* 538, pp. 446–449 (27 October 2016), doi:10.1038/538446a
203. ^ *a b c d e f* Yarbro CH, Wujcik D, Holmes Gobel B (2011). *Cancer Nursing: Principles and Practice* (7 ed.). Jones & Bartlett Publishers. pp. 901–905. ISBN 978-1-4496-1829-2.
204. ^ Thamm, Douglas (March 2009). "How companion animals contribute to the fight against cancer in

colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force". *Annals of Internal Medicine*. **146** (5): 376–89. doi:10.7326/0003-4819-146-5-200703060-00010. PMID 17339623.
104. ^ Rothwell PM, Fowkes FG, Belch JF, Ogawa H, humans" (PDF). *Veterinaria Italiana*. **54** (1): 111–120. Retrieved 18 July 2014.
205. ^ Murgia C, Pritchard JK, Kim SY, Fassati A, Weiss RA (August 2006). "Clonal origin and evolution of a transmissible cancer". *Cell*. **126** (3): 477–87. doi:10.1016/j.cell.2006.05.051. PMC 2593932. PMID 16901782.

### References

- Holland, James F. (2009). *Holland-Frei cancer medicine.* (8th ed.). New York: McGraw-Hill Medical. ISBN 978-1-60795-014-1.

## Further reading

- Kleinsmith, Lewis J. (2006). *Principles of cancer biology*. Pearson Benjamin Cummings. ISBN 978-0-8053-4003-7.
- Mukherjee, Siddhartha (16 November 2010). *The Emperor of All Maladies: A Biography of Cancer*. Simon & Schuster. ISBN 978-1-4391-0795-9. Retrieved August 7, 2013.
- Pazdur, Richard; et al. (May 2009). *Cancer Management: A Multidisciplinary Approach*. Cmp United Business Media. ISBN 978-1-891483-62-2. (online at cancernetwork.com)
- Tannock, Ian (2005). *The basic science of oncology*. McGraw-Hill Professional. ISBN 978-0-07-138774-3.
- Manfred Schwab (2008). *Encyclopedia of Cancer (4 Volume Set)*. Berlin: Springer. ISBN 3-540-36847-7.

## External links

- Cancer at DMOZ

Wikimedia Commons has media related to *Cancer*.

Wikisource has the text of the 1911 *Encyclopædia Britannica* article *Cancer*.

| v · t · e | Overview of tumors, cancer and oncology (C00–D48, 140–239) | |
|---|---|---|
| Conditions | Benign tumors | Hyperplasia · Cyst · Pseudocyst · Hamartoma · |
| | Malignant progression | Dysplasia · Carcinoma in situ · **Cancer** · Metastasis · Primary tumor · Sentinel lymph node · |
| | Topography | Head/Neck (Oral, Nasopharyngeal) · Digestive system · Respiratory system · Bone · Skin · Blood · Urogenital · Nervous system · Endocrine system · |
| | Histology | Carcinoma · Sarcoma · Blastoma · Papilloma · Adenoma · |
| | Other | Precancerous condition · Paraneoplastic syndrome · |
| Staging/grading | | TNM · Ann Arbor · Prostate cancer staging · Gleason grading system · Dukes classification · |
| Carcinogenesis | | Cancer cell · Carcinogen · Tumor suppressor genes/oncogenes · Clonally transmissible cancer · Oncovirus · Cancer bacteria · |
| Misc. | | Research · List of oncology-related terms · History · Cancer pain · Cancer and nausea · |

| v · t · e | Cancer-causing materials and agents (carcinogens) |
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| **Cancer** · Cancer cells · | |
| **Prominent human carcinogens** | Acetaldehyde · Arsenic · Asbestos · Bacteria (Helicobacter Pylori · · Benzo[a]pyrene · Bisphenol A · 1,3-Butadiene · Diethylstilbestrol · Formaldehyde · Ionizing radiation (e.g., from isotopes of plutonium and radium) · Tobacco smoke · Ultraviolet light · Viruses (Epstein–Barr · Hepatitis B · Hepatitis C · Human papillomavirus · · |
| **IARC lists** | Group 1 · Group 2A · Group 2B · Group 3 · Caprolactam (Group 4) · |
| #WHO-EM · ‡Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III · · | |
| **Authority control** | LCCN: sh85019492 · GND: 4073781-0 · BNF: cb11931105q (data) · NDL: 00562220 · |

Categories: Cancer | Aging-associated diseases | Types of cancer | Occupational safety and health | Oncology | Pathology | Types of neoplasia | Cancer pathology




# Cervical cancer

From Wikipedia, the free encyclopedia

**Cervical cancer** is a cancer arising from the cervix.[1] It is due to the abnormal growth of cells that have the ability to invade or spread to other parts of the body.[2] Early on, typically no symptoms are seen. Later symptoms may include abnormal vaginal bleeding, pelvic pain, or pain during sexual intercourse.[1] While bleeding after sex may not be serious, it may also indicate the presence of cervical cancer.[3]

Human papillomavirus (HPV) infection appears to be involved in the development of more than 90% of cases;[4][5] most people who have had HPV infections, however, do not develop cervical cancer.[6][7] Other risk factors include smoking, a weak immune system, birth control pills, starting sex at a young age, and having many sexual partners, but these are less important.[1][8] Cervical cancer typically develops from precancerous changes over 10 to 20 years.[6] About 90% of cervical cancer cases are squamous cell carcinomas, 10% are adenocarcinoma, and a small number are other types.[8] Diagnosis is typically by cervical screening followed by a biopsy. Medical imaging is then done to determine whether or not the cancer has spread.[1]

HPV vaccines protect against between two and seven high-risk strains of this family of viruses and may prevent up to 90% of cervical cancers.[9][10][11] As a risk of cancer still exists, guidelines recommend continuing regular Pap smears.[10] Other methods of prevention include: having few or no sexual partners and the use of condoms.[12] Cervical cancer screening using the Pap smear or acetic acid can identify precancerous changes which when treated can prevent the development of cancer.[13] Treatment of cervical cancer may consist of some combination of surgery, chemotherapy, and radiotherapy.[1] Five year survival rates in the United States are 68%.[14] Outcomes, however, depend very much on how early the cancer is detected.[8]

Worldwide, cervical cancer is both the fourth-most common cause of cancer and the fourth-most common cause of death from cancer in women.[6] In 2012, an estimated 528,000 cases of cervical cancer occurred, with 266,000 deaths.[6] This is about 8% of the total cases and total deaths from cancer.[15] About 70% of cervical cancers occur in developing countries.[6] In low-income countries, it is the most common cause of cancer death.[13] In developed countries, the widespread use of cervical screening programs has dramatically reduced rates of cervical cancer.[16] In medical research, the most famous cell line known as HeLa was developed from cervical cancer cells of a woman named Henrietta Lacks.[17]

**Cervical cancer**

Location of cervical cancer and an example of normal and abnormal cells

| Classification and external resources | |
|---|---|
| **Specialty** | Oncology |
| **ICD-10** | C53 |
| **ICD-9-CM** | 180 |
| **OMIM** | 603956 |
| **DiseasesDB** | 2278 |
| **MedlinePlus** | 000893 |
| **eMedicine** | med/324 radio/140 |
| **MeSH** | D002583 |

[edit on Wikidata]

## Signs and symptoms [edit]

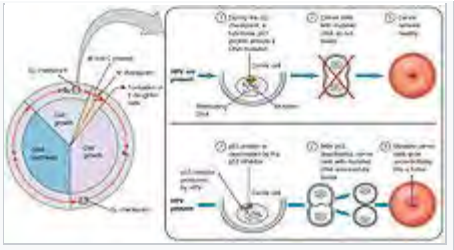
The early stages of cervical cancer may be completely free of symptoms.[4][16] Vaginal bleeding, contact bleeding (one most common form being bleeding after sexual intercourse), or (rarely) a vaginal mass may indicate the presence of malignancy. Also, moderate pain during sexual intercourse and vaginal discharge are symptoms of cervical cancer. In advanced disease, metastases may be present in the abdomen, lungs, or elsewhere.

Symptoms of advanced cervical cancer may include: loss of appetite, weight loss, fatigue, pelvic pain, back pain, leg pain, swollen legs, heavy vaginal bleeding, bone fractures, and/or (rarely) leakage of urine or feces from the vagina.[18] Bleeding after douching or after a pelvic exam is a common symptom of cervical cancer.[19]

## Causes [edit]

Infection with some types of HPV is the greatest risk factor for cervical cancer, followed by smoking.[20] HIV infection is also a risk factor.[20]

Not all of the causes of cervical cancer are known, however, and several other contributing factors have been implicated.[21]



In most cases, cells infected with the HPV virus heal on their own. In some cases, however, the virus continues to spread and becomes an invasive cancer.

## Human papillomavirus [edit]

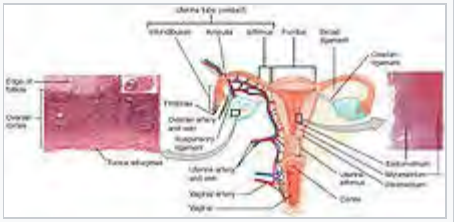
Human papillomavirus types 16 and 18 are the cause of 75% of cervical cancer cases globally, while 31 and 45 are the causes of another 10%.[22]

Women who have many sexual partners (or who have sex with men who have had many other partners) have a greater risk.[23][24]

Of the 150-200 types of HPV known,[25][26] 15 are classified as high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), three as probable high-risk (26, 53, and 66), and 12 as low-risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108).[27]

Genital warts, which are a form of benign tumor of epithelial cells, are also caused by various strains of HPV. However, these serotypes are usually not related to cervical cancer. It is common to have multiple strains at the same time, including those that can cause cervical cancer along with those that cause warts.

Infection with HPV is generally believed to be required for cervical cancer to occur.[28]



Cervix in relation to upper part of vagina and posterior portion of uterus., showing difference in covering epithelium of inner structures.

## Smoking [edit]

Cigarette smoking, both active and passive, increases the risk of cervical cancer. Among HPV-infected women, current and former smokers have roughly two to three times the incidence of invasive cancer. Passive smoking is also associated with increased risk, but to a lesser extent.[29]

Smoking has also been linked to the development of cervical cancer.[30][31][32] Smoking can increase the risk in women a few different ways, which can be by direct and indirect methods of inducing cervical cancer.[30][32][33] A direct way of contracting this cancer is a smoker has a higher chance of CIN3 occurring which has the potential of forming cervical cancer.[30] When CIN3 lesions lead to cancer, most of them have the assistance of the HPV virus, but that is not always the case, which is why it can be considered a direct link to cervical cancer.[33] Heavy smoking and long-term smoking seem to have more of a risk of getting the CIN3 lesions than lighter smoking or not smoking at all.[34] Although smoking has been linked to cervical cancer, it aids in the development of HPV which is the leading cause of this type of cancer.[32] Also, not only does it aid in the development of HPV, but also if the woman is already HPV-positive, she is at an even greater likelihood of contracting cervical cancer.[34]

## Oral contraceptives [edit]

Long-term use of oral contraceptives is associated with increased risk of cervical cancer. Women who have used oral contraceptives for 5 to 9 years have about three times the incidence of invasive cancer, and those who used them for 10 years or longer have about four times the risk.[29]

## Multiple pregnancies [edit]

Having many pregnancies is associated with an increased risk of cervical cancer. Among HPV-infected women, those who have had seven or more full-term pregnancies have around four times the risk of cancer compared with women with no pregnancies, and two to three times the risk of women who have had one [29]

or two full-term pregnancies.

## Diagnosis [edit]

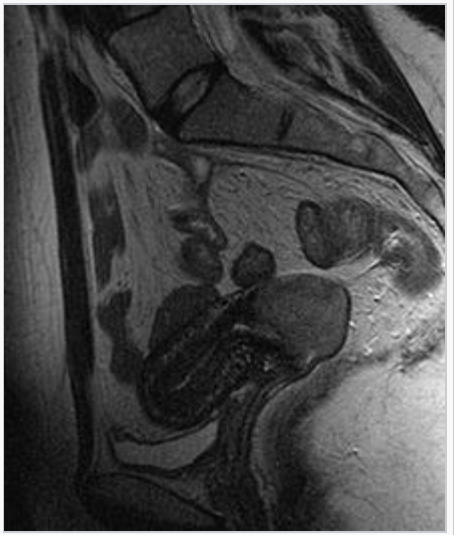
### Biopsy [edit]

The Pap smear can be used as a screening test, but is false negative in up to 50% of cases of cervical cancer.[35][36] Confirmation of the diagnosis of cervical cancer or precancer requires a biopsy of the cervix. This is often done through colposcopy, a magnified visual inspection of the cervix aided by using a dilute acetic acid (e.g. vinegar) solution to highlight abnormal cells on the surface of the cervix.[4] Medical devices used for biopsy of the cervix include punch forceps, SpiraBrush CX, SoftBiopsy, or Soft-ECC.

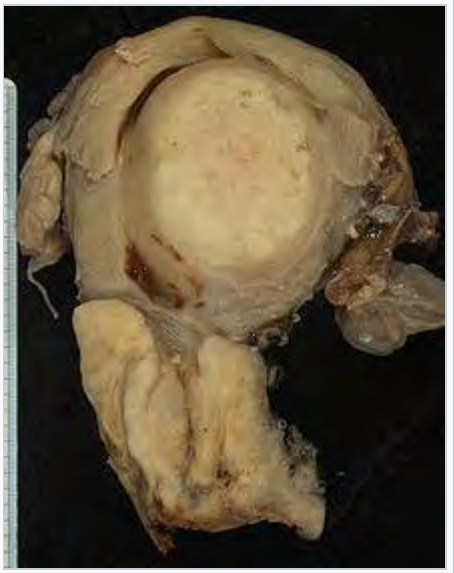
Colposcopic impression, the estimate of disease severity based on the visual inspection, forms part of the diagnosis.

Further diagnostic and treatment procedures are loop electrical excision procedure and conization, in which the inner lining of the cervix is removed to be examined pathologically. These are carried out if the biopsy confirms severe cervical intraepithelial neoplasia.

Often before the biopsy, the doctor asks for medical imaging to rule out other causes of woman's symptoms. Imaging modalities such as ultrasound, CT scan and MRI have been used to look for alternating disease, spread of tumor and effect on adjacent structures. Typically, they appear as heterogeneous mass in the cervix.[37]



Cervical cancer seen on a T2-weighted saggital MR image of the pelvis



This large squamous carcinoma (bottom of picture) has obliterated the cervix and invaded the lower uterine segment. The uterus also has a round leiomyoma up higher.

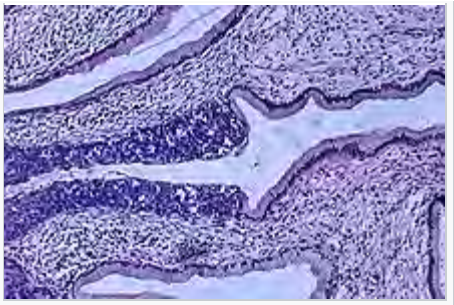
### Precancerous lesions [edit]

Cervical intraepithelial neoplasia, the potential precursor to cervical cancer, is often diagnosed on examination of cervical biopsies by a pathologist. For premalignant dysplastic changes, cervical intraepithelial neoplasia grading is used.

The naming and histologic classification of cervical carcinoma precursor lesions has changed many times over the 20th century. The World Health Organization classification[38][39] system was descriptive of the lesions, naming them mild, moderate, or severe dysplasia or carcinoma in situ (CIS). The term, cervical intraepithelial neoplasia (CIN) was developed to place emphasis on the spectrum of abnormality in these lesions, and to help standardise treatment.[39] It classifies mild dysplasia as CIN1, moderate dysplasia as CIN2, and severe dysplasia and CIS as CIN3. More recently, CIN2 and CIN3 have been combined into CIN2/3. These results are what a pathologist might report from a biopsy.

These should not be confused with the Bethesda system terms for Pap smear (cytopathology) results. Among the Bethesda results: Low-grade Squamous Intraepithelial Lesion (LSIL) and High-grade Squamous Intraepithelial Lesion (HSIL). An LSIL Pap may correspond to CIN1, and HSIL may correspond to CIN2 and CIN3,[39] however they are results of different tests, and the Pap smear results need not match the histologic findings.

### Cancer subtypes [edit]



Histopathologic image (H&E stain) of carcinoma *in situ* (also called CIN III), stage 0: The normal architecture of stratified squamous epithelium is replaced by irregular cells that extend throughout its full thickness. Normal columnar epithelium is also seen.

Histologic subtypes of invasive cervical carcinoma include the following:[40][41] Though squamous cell carcinoma is the cervical cancer with the most incidence, the incidence of adenocarcinoma of the cervix has been increasing in recent decades.[4]

- squamous cell carcinoma (about 80-85%[*citation needed*])
- adenocarcinoma (about 15% of cervical cancers in the UK[38])
- adenosquamous carcinoma
- small cell carcinoma
- neuroendocrine tumour
- glassy cell carcinoma
- villoglandular adenocarcinoma

Noncarcinoma malignancies which can rarely occur in the cervix include melanoma and lymphoma. The FIGO stage does not incorporate lymph node involvement in contrast to the TNM staging for most other cancers.

For cases treated surgically, information obtained from the pathologist can be used in assigning a separate pathologic stage, but is not to replace the original clinical stage.

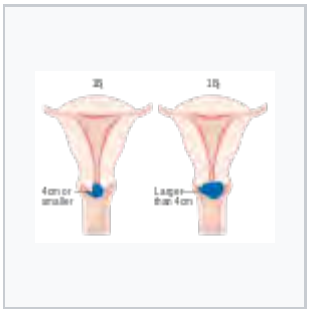
Cervical cancer with uterine leiomyoma

## Staging [edit]

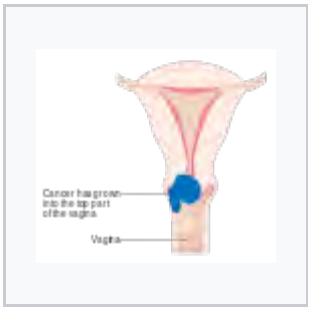
*Main article: Cervical cancer staging*

Cervical cancer is staged by the International Federation of Gynecology and Obstetrics (FIGO) staging system, which is based on clinical examination, rather than surgical findings. It allows only these diagnostic tests to be used in determining the stage: palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and X-ray examination of the lungs and skeleton, and cervical conization.

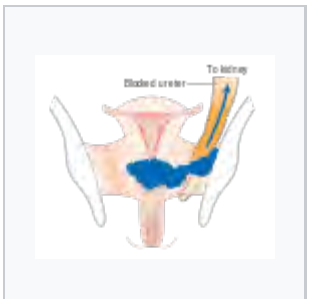
Stage 1A cervical cancer



Stage 1B cervical cancer



Stage 2A cervical cancer



| Stage 2B cervical cancer | Stage 3B cervical cancer | Stage 4A cervical cancer | Stage 4B cervical cancer |
|---|---|---|---|

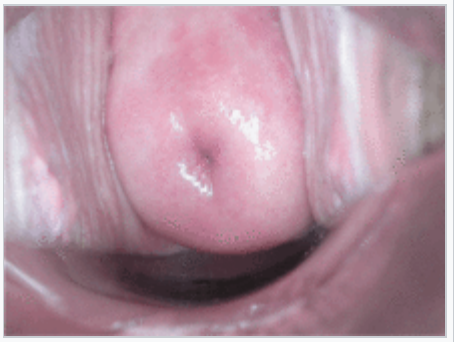
# Prevention [edit]

## Screening [edit]

*Main articles: Cervical screening and Pap test*

Cervical screening test vehicle in Taiwan

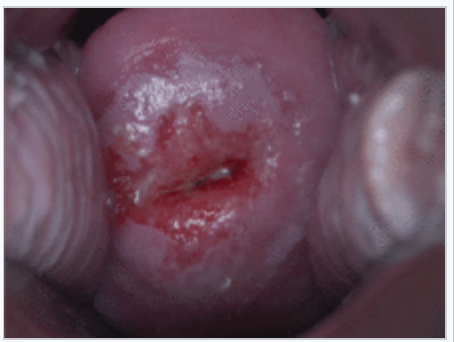
Checking the cervix by the Papanicolaou test, or Pap smear, for cervical cancer has been credited with dramatically reducing the number of cases of and mortality from cervical cancer in developed countries.[16] Pap smear screening every 3–5 years with appropriate follow-up can reduce cervical cancer incidence up to 80%.[42] Abnormal results may suggest the presence of precancerous changes, allowing examination and possible preventive treatment. The treatment of low-grade lesions may adversely affect subsequent fertility and pregnancy.[29] Personal invitations encouraging women to get screened are effective at increasing the likelihood they will do so. Educational materials also help increase the likelihood women will go for screening, but they are not as effective as invitations.[43]



Negative visual inspection with acetic acid of the cervix

According to the 2010 European guidelines, the age at which to start screening ranges between 20 and 30 years of age, "but preferentially not before age 25 or 30 years", and depends on burden of the disease in the population and the available resources.[44]

In the United States, screening is recommended to begin at age 21, regardless of age at which a woman began having sex or other risk factors.[45] Pap tests should be done every three years between the ages of 21 and 65.[45] In women over the age of 65, screening may be discontinued if no abnormal screening results were seen within the previous 10 years and no history of CIN 2 or higher exists.[45][46][47] HPV vaccination status does not change screening rates.[46] Screening can occur every 5 years between ages 30 and 65 when a combination of cervical cytology screening and HPV testing is used and this is preferred.[46] However, it is acceptable to screen this age group with a Pap smear alone every 3 years.[46] Screening is not beneficial before age 25 as the rate of disease is low. Screening is not beneficial in women older than 60 years if they have a history of negative results.[29]



Positive visual inspection with acetic acid of the cervix for CIN-1

Liquid-based cytology is another potential screening method.[48][49] Although it was probably intended to improve on the accuracy of the Pap test, its main advantage has been to reduce the number of inadequate smears from around 9% to around 1%.[50] This reduces the need to recall women for a further smear. The United States Preventive Services Task Force supports screening every 5 years in those who are between 30 and 65 years when cytology is used in combination with HPV testing.[51]

Pap smears have not been as effective in developing countries.[52] This is in part because many of these countries have an impoverished health care infrastructure, too few trained and skilled professionals to obtain and interepret Pap smears, uninformed women who get lost to follow-up, and a lengthy turn-around time to get results.[52] These realities have resulted in the investigation of

cervical screening approaches that use fewer resources and offer rapid results such as visual inspection with acetic acid or HPV DNA testing.[52]

### Barrier protection [edit]

Barrier protection and/or spermicidal gel use during sexual intercourse decreases cancer risk.[29] Condoms offer protection against cervical cancer.[53] Evidence on whether condoms protect against HPV infection is mixed, but they may protect against genital warts and the precursors to cervical cancer.[53] They also provide protection against other STIs, such as HIV and *Chlamydia*, which are associated with greater risks of developing cervical cancer.

Condoms may also be useful in treating potentially precancerous changes in the cervix. Exposure to semen appears to increase the risk of precancerous changes (CIN 3), and use of condoms helps to cause these changes to regress and helps clear HPV.[54] One study suggests that prostaglandin in semen may fuel the growth of cervical and uterine tumors and that affected women may benefit from the use of condoms.[55]

Abstinence also prevents HPV infection.[29]

### Vaccination [edit]

Two HPV vaccines (Gardasil and Cervarix) reduce the risk of cancerous or precancerous changes of the cervix and perineum by about 93% and 62%, respectively.[56] The vaccines are between 92% and 100% effective against HPV 16 and 18 up to at least 8 years.[29]

HPV vaccines are typically given to age 9 to 26 as the vaccine is only effective if given before infection occurs. The vaccines have been shown to be effective for at least 4[57] to 6[58] years, and they are believed to be effective for longer;[59] however, the duration of effectiveness and whether a booster will be needed is unknown. The high cost of this vaccine has been a cause for concern. Several countries have considered (or are considering) programs to fund HPV vaccination.

Since 2010, young women in Japan have been eligible to receive the cervical cancer vaccination for free.[60] In June 2013, the Japanese Ministry of Health, Labor and Welfare mandated that, before administering the vaccine, medical institutions must inform women that the Ministry does not recommend it.[60] However, the vaccine is still available at no cost to Japanese women who choose to accept the vaccination.[60]

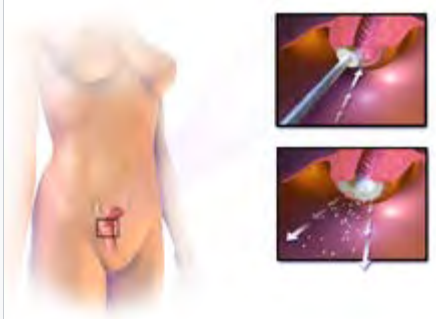
### Nutrition [edit]

Vitamin A is associated with a lower risk[61] as are vitamin B12, vitamin C, vitamin E, and beta-carotene.[62]

## Treatment [edit]

The treatment of cervical cancer varies worldwide, largely due to access to surgeons skilled in radical pelvic surgery, and the emergence of "fertility-sparing therapy" in developed nations. Because cervical cancers are radiosensitive, radiation may be used in all stages where surgical options do not exist. Surgical intervention may have better outcomes than radiological approaches.[63]

Microinvasive cancer (stage IA) may be treated by hysterectomy (removal of the whole uterus including part of the vagina).[*citation needed*] For stage IA2, the lymph nodes are removed, as well. Alternatives include local surgical procedures such as a loop electrical excision procedure or cone biopsy.[64] For 1A1 disease, a cone biopsy (cervical



Cervical cryotherapy

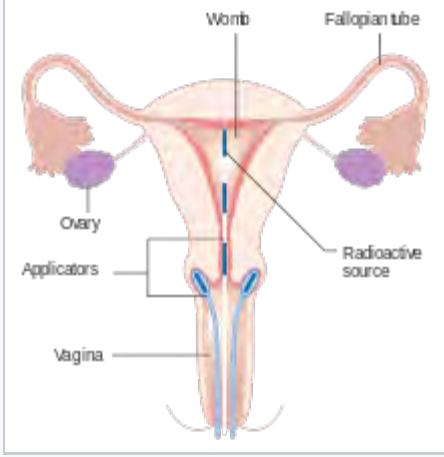
conization) is considered curative.

If a cone biopsy does not produce clear margins[65] (findings on biopsy showing that the tumor is surrounded by cancer free tissue, suggesting all of the tumor is removed), one more possible treatment option for women who want to preserve their fertility is a trachelectomy.[66] This attempts to surgically remove the cancer while preserving the ovaries and uterus, providing for a more conservative operation than a hysterectomy. It is a viable option for those in stage I cervical cancer which has not spread; however, it is not yet considered a standard of care,[67] as few doctors are skilled in this procedure. Even the most experienced surgeon cannot promise that a trachelectomy can be performed until after surgical microscopic examination, as the extent of the spread of cancer is unknown. If the surgeon is not able to microscopically confirm clear margins of cervical tissue once the woman is under general anesthesia in the operating room, a hysterectomy may still be needed. This can only be done during the same operation if the woman has given prior consent. Due to the possible risk of cancer spread to the lymph nodes in stage 1b cancers and some stage 1a cancers, the surgeon may also need to remove some lymph nodes from around the uterus for pathologic evaluation.

A radical trachelectomy can be performed abdominally[68] or vaginally[69] and opinions are conflicting as to which is better.[70] A radical abdominal trachelectomy with lymphadenectomy usually only requires a two- to three-day hospital stay, and most women recover very quickly (about six weeks). Complications are uncommon, although women who are able to conceive after surgery are susceptible to preterm labor and possible late miscarriage.[71] Wait at least one year is generally recommended before attempting to become pregnant after surgery.[72] Recurrence in the residual cervix is very rare if the cancer has been cleared with the trachelectomy.[67] Yet, women are recommended to practice vigilant prevention and follow-up care including Pap screenings/colposcopy, with biopsies of the remaining lower uterine segment as needed (every 3–4 months for at least 5 years) to monitor for any recurrence in addition to minimizing any new exposures to HPV through safe sex practices until one is actively trying to conceive.

Early stages (IB1 and IIA less than 4 cm) can be treated with radical hysterectomy with removal of the lymph nodes or radiation therapy. Radiation therapy is given as external beam radiotherapy to the pelvis and brachytherapy (internal radiation). Women treated with surgery who have high-risk features found on pathologic examination are given radiation therapy with or without chemotherapy to reduce the risk of relapse.

Larger early-stage tumors (IB2 and IIA more than 4 cm) may be treated with radiation therapy and cisplatin-based chemotherapy, hysterectomy (which then usually requires adjuvant radiation therapy), or cisplatin chemotherapy followed by hysterectomy. When cisplatin is present, it is thought to be the most active single agent in periodic diseases.[73] Such addition of platinum-based chemotherapy to chemoradiation seems not only to improve survival but also reduces risk of recurrence in women with early stage cervical cancer (IA2-IIA).[74]



Brachytherapy for cervical cancer

Advanced-stage tumors (IIB-IVA) are treated with radiation therapy and cisplatin-based chemotherapy. On June 15, 2006, the US Food and Drug Administration approved the use of a combination of two chemotherapy drugs, hycamtin and cisplatin, for women with late-stage (IVB) cervical cancer treatment.[75] Combination treatment has significant risk of neutropenia, anemia, and thrombocytopenia side effects.

For surgery to be curative, the entire cancer must be removed with no cancer found at the margins of the removed tissue on examination under a microscope.[76] This procedure is known as exenteration.[76]

Diagram showing the area removed with a posterior surgery

Diagram showing the area removed with a total operation

Diagram showing the area removed with an anterior operation

## Prognosis [edit]

Prognosis depends on the stage of the cancer. The chance of a survival rate around 100% is high for women with microscopic forms of cervical cancer.[77] With treatment, the five-year relative survival rate for the earliest stage of invasive cervical cancer is 92%, and the overall (all stages combined) five-year survival rate is about 72%. These statistics may be improved when applied to women newly diagnosed, bearing in mind that these outcomes may be partly based on the state of treatment five years ago when the women studied were first diagnosed.[78]

With treatment, 80 to 90% of women with stage I cancer and 60 to 75% of those with stage II cancer are alive 5 years after diagnosis. Survival rates decrease to 30 to 40% for women with stage III cancer and 15% or fewer of those with stage IV cancer 5 years after diagnosis.[79]

According to the International Federation of Gynecology and Obstetrics, survival improves when radiotherapy is combined with cisplatin-based chemotherapy.[80]

As the cancer metastasizes to other parts of the body, prognosis drops dramatically because treatment of local lesions is generally more effective than whole-body treatments such as chemotherapy.

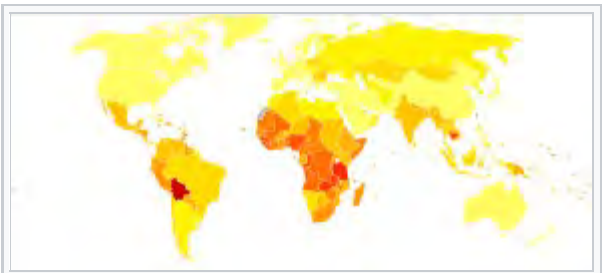
Interval evaluation of the woman after therapy is imperative. Recurrent cervical cancer detected at its earliest stages might be successfully treated with surgery, radiation, chemotherapy, or a combination of the three. About 35% of women with invasive cervical cancer have persistent or recurrent disease after treatment.[81]

Average years of potential life lost from cervical cancer are 25.3.[82] Around 4,600 women were projected to die in 2001 in the US of cervical cancer, and the annual incidence was 13,000 in 2002 in the US, as calculated by SEER. Thus, the ratio of deaths to incidence is about 35.4%.

Regular screening has meant that precancerous changes and early-stage cervical cancers have been detected and treated early. Figures suggest that cervical screening is saving 5,000 lives each year in the UK by preventing cervical cancer.[83] About 1,000 women per year die of cervical cancer in the UK. All of the Nordic countries have cervical cancer-screening programs in place.[84] Pap smear was integrated into clinical practice in the Nordic countries in the 1960s.[84]

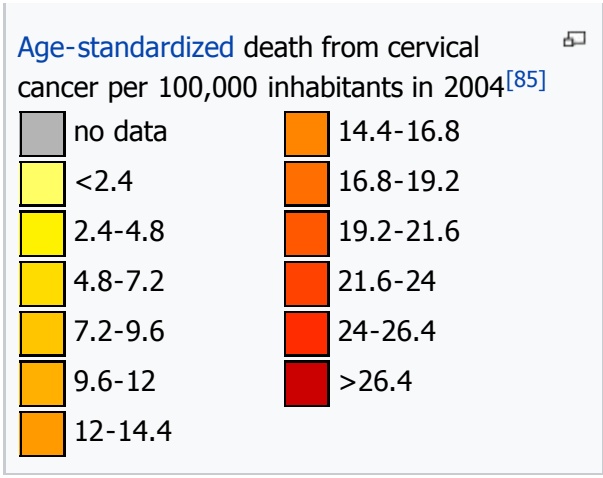
## Epidemiology [edit]

### Worldwide [edit]



Worldwide, cervical cancer is both the fourth-most common cause of cancer and deaths from cancer in women.[6] In 2012, 528,000 cases of cervical cancer were estimated to have occurred, with 266,000 deaths.[6] It is the second-most common cause of female-specific cancer after breast cancer,

accounting for around 8% of both total cancer cases and total cancer deaths in women.[15] About 80% of cervical cancers occur in developing countries.[86]




## United States [edit]

An estimated 12,900 new cervical cancers and 4,100 cervical cancer deaths will occur in the United States in 2015.[29] In the United States, it is the eight-most common cancer of women. The median age at diagnosis is 48. Hispanic women are significantly more likely to be diagnosed with cervical cancer than the general population.[87] In 1998, about 12,800 women were diagnosed in the US and about 4,800 died.[16] In 2014, an estimated 12,360 new cases were expected to be diagnosed, and about 4,020 were expected to die of cervical cancer.[87] Among cancers of the female reproductive tract it is less common than endometrial cancer and ovarian cancer. The rates of new cases in the United States was 7 per 100,000 women in 2004.[88] Cervical cancer deaths decreased by approximately 74% in the last 50 years, largely due to widespread Pap smear screening.[89] The annual direct medical cost of cervical cancer prevention and treatment prior to introduction of the HPV vaccine was estimated at $6 billion.[89]

## EU [edit]

In the European Union, about 34,000 new cases per year and over 16,000 deaths due to cervical cancer occurred in 2004.[42]

## UK [edit]

Cervical cancer is the 12th-most common cancer in women in the UK (around 3,100 women were diagnosed with the disease in 2011), and accounts for 1% of cancer deaths (around 920 died in 2012).[90] With a 42% reduction from 1988-1997, the NHS-implemented screening programme has been highly successful, screening the highest-risk age group (25–49 years) every 3 years, and those ages 50–64 every 5 years.

## Canada [edit]

In Canada, an estimated 1,300 women will have been diagnosed with cervical cancer in 2008 and 380 will have died.[91]

## Australia [edit]

Australia had 734 cases of cervical cancer (2005). The number of women diagnosed with cervical cancer has dropped on average by 4.5% each year since organised screening began in 1991 (1991–2005).[92] Regular twice-yearly Pap tests can reduce the incidence of cervical cancer up to 90% in Australia, and save 1,200 Australian women from dying from the disease each year.[93]

## India [edit]

In India, the number of people with cervical cancer is rising, but overall the age-adjusted rates are decreasing.[94] Usage of condoms in the female population has improved the survival of women with cancers of the cervix.[95]

# History [edit]

400 BCE - Hippocrates noted that cervical cancer was incurable
- 1925 - Hinselmann invented the colposcope
- 1928 - Papanicolaou developed the Papanicolaou technique
- 1941 - Papanicolaou and Traut: Pap smear screening began
- 1946 - Aylesbury spatula was developed to scrape the cervix, collecting the sample for the Pap smear
- 1951 - First successful in-vitro cell line, HeLa, derived from biopsy of cervical cancer of Henrietta Lacks
- 1976 - Harald zur Hausen and Gisam found HPV DNA in cervical cancer and genital warts; Hausen later won the Nobel Prize for his work[96]
- 1988 - Bethesda System for reporting Pap results was developed
- 2006 - First HPV vaccine was approved by the FDA

Epidemiologists working in the early 20th century noted that cervical cancer behaved like a sexually transmitted disease. In summary:

1. Cervical cancer was noted to be common in female sex workers.
2. It was rare in nuns, except for those who had been sexually active before entering the convent. (Rigoni in 1841)
3. It was more common in the second wives of men whose first wives had died from cervical cancer.
4. It was rare in Jewish women.[97]
5. In 1935, Syverton and Berry discovered a relationship between RPV (Rabbit Papillomavirus) and skin cancer in rabbits. (HPV is species-specific and therefore cannot be transmitted to rabbits)[*citation needed*]

These historical observations suggested that cervical cancer could be caused by a sexually transmitted agent. Initial research in the 1940s and 1950s attributed cervical cancer to smegma (e.g. Heins *et al.* 1958).[98] During the 1960s and 1970s it was suspected that infection with herpes simplex virus was the cause of the disease. In summary, HSV was seen as a likely cause because it is known to survive in the female reproductive tract, to be transmitted sexually in a way compatible with known risk factors, such as promiscuity and low socioeconomic status.[99] Herpes viruses were also implicated in other malignant diseases, including Burkitt's lymphoma, Nasopharyngeal carcinoma, Marek's disease and the Lucké renal adenocarcinoma. HSV was recovered from cervical tumour cells.

A description of human papillomavirus (HPV) by electron microscopy was given in 1949, and HPV-DNA was identified in 1963.[*citation needed*] It was not until the 1980s that HPV was identified in cervical cancer tissue.[100] It has since been demonstrated that HPV is implicated in virtually all cervical cancers.[101] Specific viral subtypes implicated are HPV 16, 18, 31, 45 and others.

In work that was initiated in the mid 1980s, the HPV vaccine was developed, in parallel, by researchers at Georgetown University Medical Center, the University of Rochester, the University of Queensland in Australia, and the U.S. National Cancer Institute.[102] In 2006, the U.S. Food and Drug Administration (FDA) approved the first preventive HPV vaccine, marketed by Merck & Co. under the trade name Gardasil.

## Society and culture [edit]

### Australia [edit]

In Australia, Aboriginal women are more than five times more likely to die from cervical cancer than non-Aboriginal women, suggesting that Aboriginal women are less likely to have regular Pap tests.[103] There are several factors that may limit indigenous women from engaging in regular cervical screening practices, including sensitivity in discussing the topic in Aboriginal communities, embarrassment, anxiety and fear about the procedure.[104] Difficulty in accessing screening services (for example, transport difficulties) and a lack of female GPs, trained pap smear providers and trained female Aboriginal Health Workers are also issues.[104]

The Australian Cervical Cancer Foundation (ACCF), founded in 2008, promotes 'women's health by eliminating cervical cancer and enabling treatment for women with cervical cancer and related health

issues, in Australia and in developing countries.'[105] Ian Frazer, one of the developers of the Gardasil cervical cancer vaccine, is the scientific advisor to ACCF.[106] Janette Howard, the wife of former Australian Prime Minister John Howard, was diagnosed with cervical cancer in 1996, and first spoke on her battle with the disease in 2006.[107]

### United States [edit]

A 2007 survey of 3,076 American women found only 40% had heard of HPV infection and less than half of those knew it causes cervical cancer.[108]

## Research [edit]

- Ludwig-McGill HPV Cohort, large longitudinal study of the natural history of human papillomavirus infection and cervical cancer risk

## References [edit]


1. ^ a b c d e "Cervical Cancer Treatment (PDQ®)". *NCI*. 2014-03-14. Retrieved 24 June 2014.
2. ^ "Defining Cancer". *National Cancer Institute*. Retrieved 10 June 2014.
3. ^ Tarney, CM; Han, J (2014). "Postcoital bleeding: a review on etiology, diagnosis, and management.". *Obstetrics and Gynecology International*. **2014**: 192087. doi:10.1155/2014/192087. PMID 25045355.
4. ^ a b c d Kumar V, Abbas AK, Fausto N, Mitchell RN (2007). *Robbins Basic Pathology* (8th ed.). Saunders Elsevier. pp. 718–721. ISBN 978-1-4160-2973-1.
5. ^ Kufe, Donald (2009). *Holland-Frei cancer medicine.* (8th ed.). New York: McGraw-Hill Medical. p. 1299. ISBN 9781607950141.
6. ^ a b c d e f g *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 5.12. ISBN 9283204298.
7. ^ Dunne, EF; Park, IU (Dec 2013). "HPV and HPV-associated diseases.". *Infectious Disease Clinics of North America*. **27** (4): 765–78. doi:10.1016/j.idc.2013.09.001. PMID 24275269.
8. ^ a b c "Cervical Cancer Treatment (PDQ®)". *National Cancer Institute*. 2014-03-14. Retrieved 25 June 2014.
9. ^ "FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV". *U.S. Food and Drug Administration*. 10 December 2014. Retrieved 8 March 2015.
10. ^ a b "Human Papillomavirus (HPV) Vaccines". *National Cancer Institute*. 2011-12-29. Retrieved 25 June 2014.
11. ^ Tran, NP; Hung, CF; Roden, R; Wu, TC (2014). "Control of HPV infection and related cancer through vaccination.". *Recent Results in Cancer Research*. **193**: 149–71. doi:10.1007/978-3-642-38965-8_9. PMID 24008298.
12. ^ "Cervical Cancer Prevention (PDQ®)". *National Cancer Institute*. 2014-02-27. Retrieved 25 June 2014.
13. ^ a b World Health Organization (February 2014). "Fact sheet No. 297: Cancer". Retrieved 2014-06-24.
14. ^ "SEER Stat Fact Sheets: Cervix Uteri Cancer". *NCI*. Retrieved 18 June 2014.
15. ^ a b *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 1.1. ISBN 9283204298.
16. ^ a b c d Canavan TP, Doshi NR (2000). "Cervical cancer". *Am Fam Physician*. **61** (5): 1369–76. PMID 10735343.
17. ^ Jr, Charles E. Carraher (2014). *Carraher's polymer chemistry* (Ninth ed.). Boca Raton: Taylor & Francis. p. 385. ISBN 9781466552036.
18. ^ Nanda, Rita (2006-06-09). "Cervical cancer". *MedlinePlus Medical Encyclopedia*. National Institutes of Health. Retrieved 2007-12-02.
19. ^ "Cervical Cancer Prevention and Early Detection". *Cancer*.
20. ^ a b Gadducci A, Barsotti C, Cosio S, Domenici L, Riccardo Genazzani A (2011). "Smoking habit, immune suppression, oral contraceptive use, and hormone replacement therapy use and cervical carcinogenesis: A review of the literature". *Gynecological Endocrinology*. **27** (8): 597–604. doi:10.3109/09513590.2011.558953. PMID 21438669.
21. ^ Stuart Campbell; Ash Monga (2006). *Gynaecology by Ten Teachers* (18 ed.). Hodder Education. ISBN 0-340-81662-7.
22. ^ Dillman, edited by Robert K. Oldham, Robert O. (2009). *Principles of cancer biotherapy* (5th ed.). Dordrecht: Springer. p. 149. ISBN 9789048122899.
23. ^ "What Causes Cancer of the Cervix?". American Cancer Society. 2006-11-30. Archived from the original on

2007-10-13. Retrieved 2007-12-02.
24. ^ Marrazzo JM, Koutsky LA, Kiviat NB, Kuypers JM, Stine K (2001). "Papanicolaou test screening and prevalence of genital human papillomavirus among women who have sex with women". *Am J Public Health*. **91** (6): 947–52. doi:10.2105/AJPH.91.6.947. PMC 1446473. PMID 11392939.
25. ^ "HPV Type-Detect". Medical Diagnostic Laboratories. 2007-10-30. Archived from the original on 2007-09-27. Retrieved 2007-12-02.
26. ^ Gottlieb, Nicole (2002-04-24). "A Primer on HPV". *Benchmarks*. National Cancer Institute. Retrieved 2007-12-02.
27. ^ Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, Snijders PJ, Meijer CJ (2003). "Epidemiologic classification of human papillomavirus types associated with cervical cancer". *N. Engl. J. Med.* **348** (6): 518–27. doi:10.1056/NEJMoa021641. PMID 12571259.
28. ^ Snijders PJ, Steenbergen RD, Heideman DA, Meijer CJ (2006). "HPV-mediated cervical carcinogenesis: concepts and clinical implications". *J. Pathol*. **208** (2): 152–64. doi:10.1002/path.1866. PMID 16362994.
29. ^ *a b c d e f g h i* National Institutes of Health, National Cancer Institute: PDQ® Cervical Cancer Prevention. Bethesda, MD: National Cancer Institute. Date last modified 12/17/2015. Accessed 05/20/2015.
30. ^ *a b c* Luhn P, Walker J, Schiffman M, Zuna RE, Dunn ST, Gold MA, Smith K, Mathews C, Allen RA, Zhang R, Wang S, Wentzensen N (2013). "The role of co-factors in the progression from human papillomavirus infection to cervical cancer". *Gynecologic Oncology*. **128** (2): 265–270. doi:10.1016/j.ygyno.2012.11.003. ISSN 0090-8258. PMID 23146688.
31. ^ Remschmidt C, Kaufmann AM, Hagemann I, Vartazarova E, Wichmann O, Deleré Y (2013). "Risk Factors for Cervical Human Papillomavirus Infection and High-Grade Intraepithelial Lesion in Women Aged 20 to 31 Years in Germany". *International Journal of Gynecological Cancer*. **23** (3): 519–526. doi:10.1097/IGC.0b013e318285a4b2. ISSN 1048-891X. PMID 23360813.
32. ^ *a b c* Gadducci A, Barsotti C, Cosio S, Domenici L, Riccardo Genazzani A (2011). "Smoking habit, immune suppression, oral contraceptive use, and hormone replacement therapy use and cervical carcinogenesis: a review of the literature". *Gynecological Endocrinology*. **27** (8): 597–604. doi:10.3109/09513590.2011.558953. ISSN 0951-3590. PMID 21438669.
33. ^ *a b* Agorastos T, Miliaras D, Lambropoulos AF, Chrisafi S, Kotsis A, Manthos A, Bontis J (2005). "Detection and typing of human papillomavirus DNA in uterine cervices with coexistent grade I and grade III intraepithelial neoplasia: biologic progression or independent lesions?". *European Journal of Obstetrics & Gynecology and Reproductive Biology*. **121** (1): 99–103. doi:10.1016/j.ejogrb.2004.11.024. ISSN 0301-2115. PMID 15949888.
34. ^ *a b* Jensen KE, Schmiedel S, Frederiksen K, Norrild B, Iftner T, Kjær SK (2012). "Risk for cervical intraepithelial neoplasia grade 3 or worse in relation to smoking among women with persistent human papillomavirus infection". *Cancer Epidemiology, Biomarkers & Prevention*. **21** (11): 1949–55. doi:10.1158/1055-9965.EPI-12-0663. PMC 3970163. PMID 23019238.
35. ^ Cecil Medicine: Expert Consult Premium Edition . ISBN 1437736084, 9781437736083. Page 1317.
36. ^ Berek and Hacker's Gynecologic Oncology. ISBN 0781795125, 9780781795128. Page 342
37. ^ H. K. Pannu; F. M. Corl; E. K. Fishman (September–October 2001). "CT evaluation of cervical cancer: spectrum of disease". *Radiographics*. **21** (5): 1155–1168. doi:10.1148/radiographics.21.5.g01se311155. PMID 11553823.
38. ^ *a b* "Cancer Research UK website". Retrieved 2009-01-03.
39. ^ *a b c* DeMay, M (2007). *Practical principles of cytopathology. Revised edition*. Chicago, IL: American Society for Clinical Pathology Press. ISBN 978-0-89189-549-7.
40. ^ Garcia A, Hamid O, El-Khoueiry A (2006-07-06). "Cervical Cancer". *eMedicine*. WebMD. Retrieved 2007-12-02.
41. ^ Dolinsky, Christopher (2006-07-17). "Cervical Cancer: The Basics". *OncoLink*. Abramson Cancer Center of the University of Pennsylvania. Retrieved 2007-12-02.
42. ^ *a b* Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, Wiener H, Herbert A, von Karsa L (2010). "European Guidelines for Quality Assurance in Cervical Cancer Screening. Second Edition—Summary Document". *Annals of Oncology*. **21** (3): 448–458. doi:10.1093/annonc/mdp471. PMC 2826099. PMID 20176693.
43. ^ Everett T, Bryant A, Griffin MF, Martin-Hirsch PP, Forbes CA, Jepson RG (2011). Everett T, ed. "Interventions targeted at women to encourage the uptake of cervical screening". *Cochrane Database Syst Rev* (5): CD002834. doi:10.1002/14651858.CD002834.pub2. PMID 21563135.
44. ^ Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, Wiener H, Herbert A, von Karsa L (Mar 2010). "European Guidelines for Quality Assurance in Cervical Cancer Screening. Second edition--summary document.". *Annals of Oncology*. **21** (3): 448–58. doi:10.1093/annonc/mdp471. PMC 2826099. PMID 20176693.
45. ^ *a b c* "Cervical Cancer Screening Guidelines for Average-Risk Women" (PDF). *cdc.gov*. Retrieved 8 November 2014.
46. ^ *a b c d* "ACOG Practice Bulletin Number 131: Screening for cervical cancer.". *Obstetrics and Gynecology*. **120** (5):

1222–38. Nov 2012. doi:10.1097/AOG.0b013e318277c92a. PMID 23090560.
47. ^ Karjane N, Chelmow D (June 2013). "New cervical cancer screening guidelines, again". *Obstetrics and Gynecology Clinics of North America*. **40** (2): 211–23. doi:10.1016/j.ogc.2013.03.001. PMID 23732026.
48. ^ Payne N, Chilcott J, McGoogan E (2000). "Liquid-based cytology in cervical screening: a rapid and systematic review". *Health Technology Assessment*. **4** (18): 1–73. PMID 10932023.
49. ^ Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N (May 2004). "Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis". *Health Technology Assessment*. **8** (20): iii, 1–78. doi:10.3310/hta8200. PMID 15147611.
50. ^ "Liquid Based Cytology (LBC): NHS Cervical Screening Programme". Retrieved 2010-10-01.
51. ^ Moyer VA (Jun 19, 2012). "Screening for cervical cancer: u.s. Preventive services task force recommendation statement". *Annals of Internal Medicine*. **156** (12): 880–91. doi:10.7326/0003-4819-156-12-201206190-00424. PMID 22711081.
52. ^ [a] [b] [c] World Health Organization (2014). *Comprehensive cervical cancer control. A guide to essential practice - Second edition*. ISBN 978-92-4-154895-3.
53. ^ [a] [b] Manhart LE, Koutsky LA (2002). "Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis". *Sex Transm Dis*. **29** (11): 725–35. doi:10.1097/00007435-200211000-00018. PMID 12438912.
54. ^ Hogewoning CJ, Bleeker MC, van den Brule AJ, Voorhorst FJ, Snijders PJ, Berkhof J, Westenend PJ, Meijer CJ (2003). "Condom use Promotes the Regression of Cervical Intraepithelial Neoplasia and Clearance of HPV: Randomized Clinical Trial". *International Journal of Cancer*. **107** (5): 811–816. doi:10.1002/ijc.11474. PMID 14566832.
55. ^ "Semen can worsen cervical cancer". Medical Research Council (UK). Retrieved 2007-12-02.
56. ^ Medeiros LR, Rosa DD, da Rosa MI, Bozzetti MC, Zanini RR (2009). "Efficacy of Human Papillomavirus Vaccines". *International Journal of Gynecological Cancer*. **19** (7): 1166–76. doi:10.1111/IGC.0b013e3181a3d100. PMID 19823051.
57. ^ "Human Papillomavirus (HPV) Vaccines: Q & A". *Fact Sheets: Risk Factors and Possible Causes*. National Cancer Institute (NCI). 2009-10-22. Retrieved 2009-11-11.
58. ^ Harper D, Gall S, Naud P, Quint W, Dubin G, Jenkins D, et al. (2008). "Sustained immunogenicity and high efficacy against HPV 16/18 related cervical neoplasia: Long-term follow up through 6.4 years in women vaccinated with Cervarix (GSK's HPV-16/18 AS04 candidate vaccine)". *Gynecol Oncol*. **109**: 158–159. doi:10.1016/j.ygyno.2008.02.017.
59. ^ "Committee opinion no. 467: human papillomavirus vaccination". *Obstet Gynecol*. **116** (3): 800–3. Sep 2010. doi:10.1097/AOG.0b013e3181f680c8. PMID 20733476.
60. ^ [a] [b] [c] The Asahi Shimbun (15 June 2013). "Health ministry withdraws recommendation for cervical cancer vaccine". The Asahi Shimbun.
61. ^ Zhang X, Dai B, Zhang B, Wang Z (2011). "Vitamin A and risk of cervical cancer: A meta-analysis". *Gynecologic Oncology*. **124** (2): 366–73. doi:10.1016/j.ygyno.2011.10.012. PMID 22005522.
62. ^ Myung SK, Ju W, Kim SC, Kim H (2011). "Vitamin or antioxidant intake (or serum level) and risk of cervical neoplasm: A meta-analysis". *BJOG*. **118** (11): 1285–91. doi:10.1111/j.1471-0528.2011.03032.x. PMID 21749626.
63. ^ Baalbergen, Astrid; Veenstra, Yerney; Stalpers, Lukas; Baalbergen, Astrid (2013). "Primary surgery versus primary radiotherapy with or without chemotherapy for early adenocarcinoma of the uterine cervix". *Reviews*. doi:10.1002/14651858.CD006248.pub3.
64. ^ Erstad, Shannon (2007-01-12). "Cone biopsy (conization) for abnormal cervical cell changes". WebMD. Retrieved 2007-12-02.
65. ^ Jones WB, Mercer GO, Lewis JL, Rubin SC, Hoskins WJ (1993). "Early invasive carcinoma of the cervix". *Gynecol. Oncol*. **51** (1): 26–32. doi:10.1006/gyno.1993.1241. PMID 8244170.
66. ^ Dolson, Laura (2001). "Trachelectomy". Retrieved 2007-12-02.
67. ^ [a] [b] Burnett AF (2006). "Radical trachelectomy with laparoscopic lymphadenectomy: review of oncologic and obstetrical outcomes". *Curr. Opin. Obstet. Gynecol*. **18** (1): 8–13. doi:10.1097/01.gco.0000192968.75190.dc. PMID 16493253.
68. ^ Cibula D, Ungár L, Svárovský J, Zivný J, Freitag P (2005). "[Abdominal radical trachelectomy--technique and experience]". *Ceska Gynekol* (in Czech). **70** (2): 117–22. PMID 15918265.
69. ^ Plante M, Renaud MC, Hoskins IA, Roy M (2005). "Vaginal radical trachelectomy: a valuable fertility-preserving option in the management of early-stage cervical cancer. A series of 50 pregnancies and review of the literature". *Gynecol. Oncol*. **98** (1): 3–10. doi:10.1016/j.ygyno.2005.04.014. PMID 15936061.
70. ^ Roy M, Plante M, Renaud MC, Têtu B (1996). "Vaginal radical hysterectomy versus abdominal radical hysterectomy in the treatment of early-stage cervical cancer". *Gynecol. Oncol*. **62** (3): 336–9.

doi:10.1006/gyno.1996.0245. PMID 8812529.
71. ^ Dargent D, Martin X, Sacchetoni A, Mathevet P (2000). "Laparoscopic vaginal radical trachelectomy: a treatment to preserve the fertility of cervical carcinoma patients". *Cancer*. **88** (8): 1877–82. doi:10.1002/(SICI)1097-0142(20000415)88:8<1877::AID-CNCR17>3.0.CO;2-W. PMID 10760765.
72. ^ Schlaerth JB, Spirtos NM, Schlaerth AC (2003). "Radical trachelectomy and pelvic lymphadenectomy with uterine preservation in the treatment of cervical cancer". *Am. J. Obstet. Gynecol.* **188** (1): 29–34. doi:10.1067/mob.2003.124. PMID 12548192.
73. ^ Waggoner, Steven E (2003). "Cervical Cancer". *The Lancet*. **361** (9376): 2217–25. doi:10.1016/S0140-6736(03)13778-6.
74. ^ Falcetta, FS; Medeiros, LR; Edelweiss, MI; Pohlmann, PR; Stein, AT; Rosa, DD (22 November 2016). "Adjuvant platinum-based chemotherapy for early stage cervical cancer.". *The Cochrane database of systematic reviews*. **11**: CD005342. doi:10.1002/14651858.CD005342.pub4. PMID 27873308.
75. ^ "FDA Approves First Drug Treatment for Late-Stage Cervical Cancer". U.S. Food and Drug Administration. 2006-06-15. Retrieved 2007-12-02.
76. ^ *a b* Sardain, H; Lavoue, V; Redpath, M; Bertheuil, N; Foucher, F; Levêque, J (August 2015). "Curative pelvic exenteration for recurrent cervical carcinoma in the era of concurrent chemotherapy and radiation therapy. A systematic review.". *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. **41** (8): 975–85. doi:10.1016/j.ejso.2015.03.235. PMID 25922209.
77. ^ "Cervical Cancer". Encyclopedia of Women's Health.
78. ^ "What Are the Key Statistics About Cervical Cancer?". American Cancer Society. 2006-08-04. Archived from the original on 2007-10-30. Retrieved 2007-12-02.
79. ^ "Cervical Cancer". *Cervical Cancer: Cancers of the Female Reproductive System: Merck Manual Home Edition*. Merck Manual Home Edition. Retrieved 2007-03-24.
80. ^ Committee on Practice Bulletins-Gynecology (2002). "ACOG practice bulletin. Diagnosis and treatment of cervical carcinomas, number 35, May 2002". *Obstetrics and gynecology*. **99** (5 Pt 1): 855–67. PMID 11978302.
81. ^ "Cervical Cancer". *Cervical Cancer: Pathology, Symptoms and Signs, Diagnosis, Prognosis and Treatment*. Armenian Health Network, Health.am.
82. ^ (SEER Cancer Statistics Review 1975-2000, National Cancer Institute (NCI)).
83. ^ "Cervical cancer statistics and prognosis". Cancer Research UK. Retrieved 2007-03-24.
84. ^ *a b* Nygård M (2011). "Screening for cervical cancer: When theory meets reality". *BMC Cancer*. **11**: 240. doi:10.1186/1471-2407-11-240. PMC 3146446. PMID 21668947.
85. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved Nov 11, 2009.
86. ^ Kent A (Winter 2010). "HPV Vaccination and Testing.". *Reviews in Obstetrics and Gynecology*. **3** (1): 33–4. PMC 2876324. PMID 20508781.
87. ^ *a b* Howlader (November 10, 2014). "SEER Stat Fact Sheets: Cervix Uteri". National Cancer Institute. Retrieved 7 February 2012.
88. ^ SEER cancer statistics
89. ^ *a b* Armstrong EP (April 2010). "Prophylaxis of Cervical Cancer and Related Cervical Disease: A Review of the Cost-Effectiveness of Vaccination Against Oncogenic HPV Types". *Journal of Managed Care Pharmacy*. **16** (3): 217–30. PMID 20331326.
90. ^ "Cervical cancer statistics". *Cancer Research UK*. Retrieved 27 October 2014.
91. ^ MacDonald N, Stanbrook MB, Hébert PC (September 2008). "Human papillomavirus vaccine risk and reality". *CMAJ* (in French). **179** (6): 503, 505. doi:10.1503/cmaj.081238. PMC 2527393. PMID 18762616.
92. ^ "Incidence and mortality rates".
93. ^ http://www.papscreen.org.au/
94. ^ National Cancer Registry Programme under Indian Council of Medical Research Reports
95. ^ Krishnatreya, M; Kataki, AC; Sharma, JD; Nandy, P; Gogoi, G (2015). "Association of educational levels with survival in Indian patients with cancer of the uterine cervix.". *Asian Pacific Journal of Cancer Prevention*. **16** (8): 3121–3. doi:10.7314/apjcp.2015.16.8.3121. PMID 25921107.
96. ^ zur Hausen, Harald (2002). "Papillomaviruses and cancer: from basic studies to clinical application". *Nature Reviews Cancer*. **2** (5): 342–350. doi:10.1038/nrc798. ISSN 1474-1768.
97. ^ Menczer, J (February 2003). "The low incidence of cervical cancer in Jewish women: has the puzzle finally been solved?". *The Israel Medical Association journal : IMAJ*. **5** (2): 120–3. PMID 12674663. Retrieved 28 November 2015.
98. ^ Heins HC, Dennis EJ, Pratthomas HR (1958). "The possible role of smegma in carcinoma of the cervix". *American Journal of Obstetrics & Gynecology*. **76** (4): 726–33. PMID 13583012.
99. ^ Alexander ER (1973). "Possible Etiologies of Cancer of the Cervix Other Than Herpesvirus". *Cancer Research*. **33**

(6): 1485–90. PMID 4352386.
100. ^ Dürst M, Gissmann L, Ikenberg H, zur Hausen H (1983). "A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions". *Proceedings of the National Academy of Sciences of the United States of America*. **80** (12): 3812–5. doi:10.1073/pnas.80.12.3812. PMC 394142. PMID 6304740..
101. ^ Lowy DR, Schiller JT (2006). "Prophylactic human papillomavirus vaccines". *J. Clin. Invest*. **116** (5): 1167–73. doi:10.1172/JCI28607. PMC 1451224. PMID 16670757.
102. ^ McNeil C (April 2006). "Who invented the VLP cervical cancer vaccines?". *J. Natl. Cancer Inst*. **98** (7): 433. doi:10.1093/jnci/djj144. PMID 16595773. PMID 16595773
103. ^ Cancer Institute NSW (2013). "Information about cervical screening for Aboriginal women". NSW Government. Archived from the original on 11 April 2013.
104. ^ *a b* Mary-Anne Romano (17 October 2011). "Aboriginal cervical cancer rates parallel health inequity". Science Network Western Australia. Archived from the original on 14 May 2013.
105. ^ Australian Cervical Cancer Foundation. "Vision and Mission". Australian Cervical Cancer Foundation. Archived from the original on 12 May 2013.
106. ^ Australian Cervical Cancer Foundation. "Our People". Australian Cervical Cancer Foundation. Archived from the original on 12 May 2013.
107. ^ Gillian Bradford (16 October 2006). "Janette Howard speaks on her battle with cervical cancer". Australian Broadcasting Corporation. Archived from the original on 13 November 2012.
108. ^ Tiro JA, Meissner HI, Kobrin S, Chollette V (2007). "What do women in the U.S. know about human papillomavirus and cervical cancer?". *Cancer Epidemiol. Biomarkers Prev*. **16** (2): 288–94. doi:10.1158/1055-9965.EPI-06-0756. PMID 17267388.

## Further reading [edit]

- Arbyn, M.; Castellsague, X.; de Sanjose, S.; Bruni, L.; Saraiya, M.; Bray, F.; Ferlay, J. (6 April 2011). "Worldwide burden of cervical cancer in 2008". *Annals of Oncology*. **22** (12): 2675–2686. doi:10.1093/annonc/mdr015. PMID 21471563.
- Chuang, L. T.; Temin, S.; Camacho, R.; Duenas-Gonzalez, A.; Feldman, S.; Gultekin, M.; Gupta, V.; Horton, S.; Jacob, G.; Kidd, E. A.; Lishimpi, K.; Nakisige, C.; Nam, J.-H.; Ngan, H. Y. S.; Small, W.; Thomas, G.; Berek, J. S. (25 May 2016). "Management and Care of Women With Invasive Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Clinical Practice Guideline". *Journal of Global Oncology*. doi:10.1200/JGO.2016.003954.
- Peto J, Gilham C, Fletcher O, Matthews FE (2004). "The cervical cancer epidemic that screening has prevented in the UK". *Lancet*. **364** (9430): 249–56. doi:10.1016/S0140-6736(04)16674-9. PMID 15262102.
- Pimenta, Jeanne M; Galindo, Claudia; Jenkins, David; Taylor, Sylvia M (21 November 2013). "Estimate of the global burden of cervical adenocarcinoma and potential impact of prophylactic human papillomavirus vaccination". *BMC Cancer*. **13** (1). doi:10.1186/1471-2407-13-553.

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# Colorectal cancer

From Wikipedia, the free encyclopedia

(Redirected from Colon cancer)

**Colorectal cancer** (**CRC**), also known as **bowel cancer**, is the development of cancer from the colon or rectum (parts of the large intestine).[1] It is due to the abnormal growth of cells that have the ability to invade or spread to other parts of the body.[2] Signs and symptoms may include blood in the stool, a change in bowel movements, weight loss, and feeling tired all the time.[3]

Most colorectal cancers are due to old age and lifestyle factors with only a small number of cases due to underlying genetic disorders.[4][5] Some risk factors include diet, obesity, smoking, and lack of physical activity.[4][5] Dietary factors that increase the risk include red and processed meat as well as alcohol.[4] Another risk factor is inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis.[4] Some of the inherited genetic disorders that can cause colorectal cancer include familial adenomatous polyposis and hereditary non-polyposis colon cancer; however, these represent less than 5% of cases.[4][5] It typically starts as a benign tumor, often in the form of a polyp, which over time becomes cancerous.[4]

Bowel cancer may be diagnosed by obtaining a sample of the colon during a sigmoidoscopy or colonoscopy.[3] This is then followed by medical imaging to determine if the disease has spread.[1] Screening is effective for preventing and decreasing deaths from colorectal cancer.[6] Screening is recommended starting from the age of 50 to 75.[6] During colonoscopy, small polyps may be removed if found. If a large polyp or tumor is found, a biopsy may be performed to check if it is cancerous. Aspirin and other non-steroidal anti-inflammatory drugs decrease the risk.[4][7] Their general use is not recommended for this purpose, however, due to side effects.[8]

Treatments used for colorectal cancer may include some combination of surgery, radiation therapy, chemotherapy and targeted therapy.[1] Cancers that are confined within the wall of the colon may be curable with surgery while cancer that has spread widely are usually not curable, with management being directed towards improving quality of life and symptoms.[1] Five year survival rates in the United States are around 65%.[9] This, however, depends on how advanced the cancer is, whether or not all the cancer can be removed with surgery, and the person's overall health.[3] Globally, colorectal cancer is the third most common type of cancer making up about 10% of all cases.[10] In 2012, there were 1.4 million new cases and 694,000 deaths from the disease.[10] It is more common in developed countries, where more than 65% of cases are found.[4] It is less common in women than men.[4]

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**Colorectal cancer**

**Synonyms** colon cancer, rectal cancer, bowel cancer

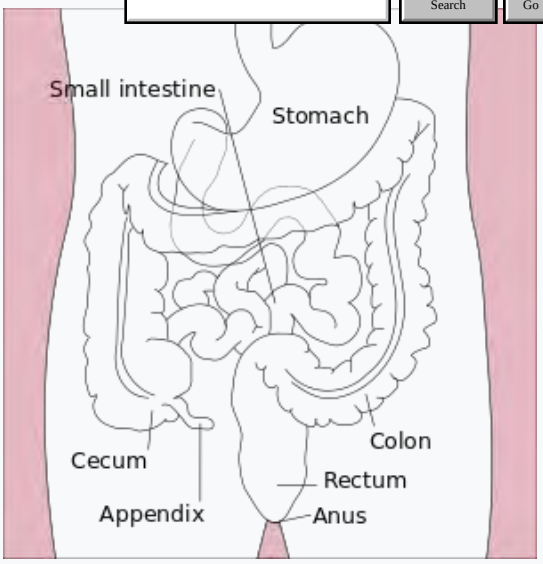


Diagram of the lower gastrointestinal tract

| Classification and external resources | |
|---|---|
| **Specialty** | Oncology |
| **ICD-10** | C18-C20/C21 |
| **ICD-9-CM** | 153.0-154.1 |
| **ICD-O** | M8140/3 (95% of cases) |
| **OMIM** | 114500 |
| **DiseasesDB** | 2975 |
| **MedlinePlus** | 000262 |
| **eMedicine** | med/413 med/1994 ped/3037 |
| **Patient UK** | Colorectal cancer |

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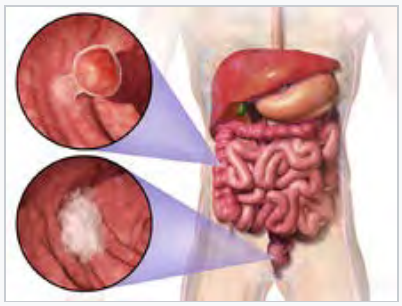
## Signs and symptoms [edit]

The signs and symptoms of colorectal cancer depend on the location of the tumor in the bowel, and whether it has spread elsewhere in the body (metastasis). The classic warning signs include: worsening constipation, blood in the stool, decrease in stool caliber (thickness), loss of appetite, loss of weight, and nausea or vomiting in someone over 50 years old.[11] While rectal bleeding or anemia are high-risk features in those over the age of 50,[12] other commonly described symptoms including weight loss and change in bowel habit are typically only concerning if associated with bleeding.[12][13]



Location and appearance of two example colorectal tumors

## Cause [edit]

Greater than 75–95% of colon cancer occurs in people with little or no genetic risk.[14][15] Risk factors include older age, male gender,[15] high intake of fat, alcohol, red meat, processed meats, obesity, smoking, and a lack of physical exercise.[14][16] Approximately 10% of cases are linked to insufficient activity.[17] The risk for alcohol appears to increase at greater than one drink per day.[18] Drinking 5 glasses of water a day is linked to a decrease in the risk of colorectal cancer and adenomatous polyps.[19]

### Inflammatory bowel disease [edit]

People with inflammatory bowel disease (ulcerative colitis and Crohn's disease) are at increased risk of colon cancer.[20] The risk increases the longer a person has the disease,[21] and the worse the severity of inflammation.[22] In these high risk groups, both prevention with aspirin and regular colonoscopies are recommended.[21] People with inflammatory bowel disease account for less than 2% of colon cancer cases yearly.[22] In those with Crohn's disease 2% get colorectal cancer after 10 years, 8% after 20 years, and 18% after 30 years.[22] In those with ulcerative colitis approximately 16% develop either a cancer precursor or cancer of the colon over 30 years.[22]

## Genetics [edit]

Those with a family history in two or more first-degree relatives (such as a parent or sibling) have a two to threefold greater risk of disease and this group accounts for about 20% of all cases. A number of genetic syndromes are also associated with higher rates of colorectal cancer. The most common of these is hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) which is present in about 3% of people with colorectal cancer.[15] Other syndromes that are strongly associated with colorectal cancer include Gardner syndrome,[23] and familial adenomatous polyposis (FAP). For people with these syndromes, cancer almost always occurs and makes up 1% of the cancer cases.[24] A total proctocolectomy may be recommended for people with FAP as a preventative measure due to the high risk of malignancy. Colectomy, removal of the colon, may not suffice as a preventative measure because of the high risk of rectal cancer if the rectum remains.[25]

Most deaths due to colon cancer are associated with metastatic disease. A gene that appears to contribute to the potential for metastatic disease, metastasis associated in colon cancer 1 (*MACC1*), has been isolated.[26] It is a transcriptional factor that influences the expression of hepatocyte growth factor. This gene is associated with the proliferation, invasion and scattering of colon cancer cells in cell culture, and tumor growth and metastasis in mice. MACC1 may be a potential target for cancer intervention, but this possibility needs to be confirmed with clinical studies.[27]

Epigenetic factors, such as abnormal DNA methylation of tumor suppressor promoters play a role in the development of colorectal cancer.[28]

# Pathogenesis [edit]

Colorectal cancer is a disease originating from the epithelial cells lining the colon or rectum of the gastrointestinal tract, most frequently as a result of mutations in the Wnt signaling pathway that increase signaling activity. The mutations can be inherited or acquired, and most probably occur in the intestinal crypt stem cell.[29][30][31] The most commonly mutated gene in all colorectal cancer is the *APC* gene, which produces the APC protein. The APC protein prevents the accumulation of β-catenin protein. Without APC, β-catenin accumulates to high levels and translocates (moves) into the nucleus, binds to DNA, and activates the transcription of proto-oncogenes. These genes are normally important for stem cell renewal and differentiation, but when inappropriately expressed at high levels, they can cause cancer. While APC is mutated in most colon cancers, some cancers have increased β-catenin because of mutations in β-catenin (CTNNB1) that block its own breakdown, or have mutations in other genes with function similar to APC such as AXIN1, AXIN2, TCF7L2, or NKD1.[32]

Beyond the defects in the Wnt signaling pathway, other mutations must occur for the cell to become cancerous. The p53 protein, produced by the *TP53* gene, normally monitors cell division and kills cells if they have Wnt pathway defects. Eventually, a cell line acquires a mutation in the *TP53* gene and transforms the tissue from a benign epithelial tumor into an invasive epithelial cell cancer. Sometimes the gene encoding p53 is not mutated, but another protective protein named BAX is mutated instead.[32]

Other proteins responsible for programmed cell death that are commonly deactivated in colorectal cancers are TGF-β and DCC (Deleted in Colorectal Cancer). TGF-β has a deactivating mutation in at least half of colorectal cancers. Sometimes TGF-β is not deactivated, but a downstream protein named SMAD is deactivated.[32] DCC commonly has a deleted segment of a chromosome in colorectal cancer.[33]

Some genes are oncogenes: they are overexpressed in colorectal cancer. For example, genes encoding the proteins KRAS, RAF, and PI3K, which normally stimulate the cell to divide in response to growth factors, can acquire mutations that result in over-activation of cell proliferation. The chronological order of mutations is sometimes important. If a previous APC mutation occurred, a primary KRAS mutation often progresses to cancer rather than a self-limiting hyperplastic or borderline lesion.[34] PTEN, a tumor suppressor, normally inhibits PI3K, but can sometimes become mutated and deactivated.[32]

Comprehensive, genome-scale analysis has revealed that colorectal carcinomas can be categorized into hypermutated and non-hypermutated tumor types.[35] In addition to the oncogenic and inactivating mutations described for the genes above, non-hypermutated samples also contain mutated CTNNB1, FAM123B, SOX9, ATM, and ARID1A. Progressing through a distinct set of genetic events, hypermutated tumors display mutated forms of ACVR2A, TGFBR2, MSH3, MSH6, SLC9A9, TCF7L2, and BRAF. The common theme among these genes, across both tumor types, is their involvement in WNT and TGF-β signaling pathways, which results in increased activity of MYC, a central player in colorectal cancer.[35]

## Field defects [edit]

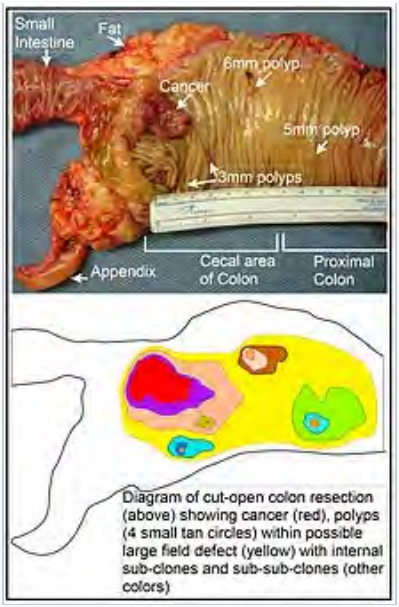
The term "field cancerization" was first used in 1953 to describe an area or

"field" of epithelium that has been preconditioned (by what were largely unknown processes at the time) to predispose it towards development of cancer.[36] Since then, the terms "field cancerization", "field carcinogenesis", "field defect", and "field effect" have been used to describe pre-malignant or pre-neoplastic tissue in which new cancers are likely to arise.[37]

Field defects are important in progression to colon cancer.[38][39][40]

However, in most cancer research, as pointed out by Rubin[41] "The vast majority of studies in cancer research has been done on well-defined tumors *in vivo*, or on discrete neoplastic foci *in vitro*. Yet there is evidence that more than 80% of the somatic mutations found in mutator phenotype human colorectal tumors occur before the onset of terminal clonal expansion."[42] Similarly, Vogelstein et al.[43] pointed out that more than half of somatic mutations identified in tumors occurred in a pre-neoplastic phase (in a field defect), during growth of apparently normal cells. Likewise, epigenetic alterations present in tumors may have occurred in pre-neoplastic field defects.

An expanded view of field effect has been termed "etiologic field effect", which encompasses not only molecular and pathologic changes in pre-neoplastic cells but also influences of exogenous environmental factors and molecular changes in the local microenvironment on neoplastic evolution from tumor initiation to death.[44]




Longitudinally opened freshly resected colon segment showing a cancer and four polyps. Plus a schematic diagram indicating a likely field defect (a region of tissue that precedes and predisposes to the development of cancer) in this colon segment. The diagram indicates sub-clones and sub-sub-clones that were precursors to the tumors.

## Epigenetics [edit]

Epigenetic alterations are much more frequent in colon cancer than genetic (mutational) alterations. As described by Vogelstein et al.,[43] an average cancer of the colon has only 1 or 2 oncogene mutations and 1 to 5 tumor suppressor mutations (together designated "driver mutations"), with about 60 further "passenger" mutations. The oncogenes and tumor suppressor genes are well studied and are described above under Pathogenesis.

However, by comparison, epigenetic alterations in colon cancers are frequent and affect hundreds of genes. For instance, there are types of small RNAs called microRNAs that are about 22 nucleotides long. These microRNAs (or miRNAs) do not code for proteins, but they can target protein coding genes and reduce their expression. Expression of these miRNAs can be epigenetically altered. As one example, the epigenetic alteration consisting of CpG island methylation of the DNA sequence encoding miR-137 reduces its expression. This is a frequent early epigenetic event in colorectal carcinogenesis, occurring in 81% of colon cancers and in 14% of the normal appearing colonic mucosa adjacent to the cancers. The altered adjacent tissues associated with these cancers are called field defects. Silencing of miR-137 can affect expression of about 500 genes, the targets of this miRNA.[45]

Changes in the level of miR-137 expression result in changed mRNA expression of the target genes by 2 to 20-fold and corresponding, though often smaller, changes in expression of the protein products of the genes. Other microRNAs, with likely comparable numbers of target genes, are even more frequently epigenetically altered in colonic field defects and in the colon cancers that arise from them. These include miR-124a, miR-34b/c and miR-342 which are silenced by CpG island methylation of their encoding DNA sequences in primary tumors at rates of 99%, 93% and 86%, respectively, and in the adjacent normal appearing mucosa at rates of 59%, 26% and 56%, respectively.[46][47]

In addition to epigenetic alteration of expression of miRNAs, other common types of epigenetic alterations in cancers that change gene expression levels include direct hypermethylation or hypomethylation of CpG islands of protein-encoding genes and alterations in histones and chromosomal architecture that influence gene expression.[48][49] As an example, 147 hypermethylations and 27 hypomethylations of protein coding genes were frequently associated with colorectal cancers. Of the hypermethylated genes, 10 were hypermethylated in 100% of colon cancers, and many others were hypermethylated in more than 50% of colon cancers.[50] In addition, 11 hypermethylations and 96 hypomethylations of miRNAs were also associated with colorectal cancers.[50]

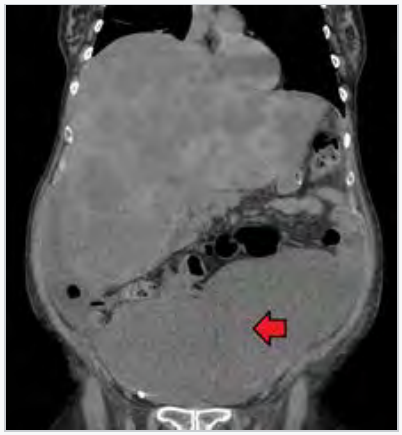
Recent evidence indicates that early epigenetic reductions of DNA repair enzyme expression likely lead to the genomic and epigenomic instability characteristic of cancer.[38][51][52][53]

As summarized in the articles Carcinogenesis and Neoplasm, for sporadic cancers in general, a deficiency in DNA repair is occasionally due to a mutation in a DNA repair gene, but is much more frequently due to epigenetic alterations that reduce or silence expression of DNA repair genes.

# Diagnosis [edit]

Colorectal cancer diagnosis is performed by sampling of areas of the colon suspicious for possible tumor development, typically during colonoscopy or sigmoidoscopy, depending on the location of the lesion. Disease extent is usually determined by a CT scan of the chest, abdomen and pelvis. Other potential imaging tests such as PET and MRI may be used in certain cases. Colon cancer staging is done next, based on the TNM system which considers how much the initial tumor has spread, if and where lymph nodes are involved and the extent of metastatis.[15]

The microscopic cellular characteristics of the tumor are usually reported from the analysis of tissue taken from a biopsy or surgery. A pathology report usually contains a description of cell type and grade. The most common colon cancer cell type is adenocarcinoma (98% of cases).[54] Other, rarer types include lymphoma and squamous cell carcinoma.



Colon cancer with extensive metastases to the liver

## Macroscopy [edit]

Cancers on the right side of the large intestine (ascending colon and cecum) tend to be exophytic, that is, the tumor grows outwards from one location in the bowel wall. This very rarely causes obstruction of feces, and presents with symptoms such as anemia. Left-sided tumors tend to be circumferential, and can obstruct the bowel lumen, much like a napkin ring, and results in thinner caliber stools.

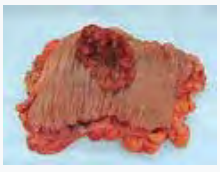
## Microscopy [edit]

Adenocarcinoma is a malignant epithelial tumor, originating from superficial glandular epithelial cells lining the colon and rectum. It invades the wall, infiltrating the muscularis mucosae layer, the submucosa, and then the muscularis propria. Tumor cells describe irregular tubular structures, harboring pluristratification, multiple lumens, reduced stroma ("back to back" aspect). Sometimes, tumor cells are discohesive and secrete mucus, which invades the interstitium producing large pools of mucus/colloid (optically "empty" spaces). This occurs in *mucinous (colloid)* adenocarcinoma, in which cells are poorly differentiated. If the mucus remains inside the tumor cell, it pushes the nucleus at the periphery. This occurs in "signet-ring cell." Depending on glandular architecture, cellular pleomorphism, and mucosecretion of the predominant pattern, adenocarcinoma may present three degrees of differentiation: well, moderately, and poorly differentiated.[55]

## Immunochemistry [edit]

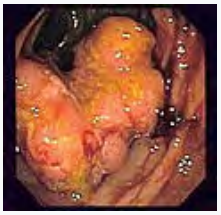
Most (50%) colorectal adenomas and (80–90%) colorectal cancer tumors are thought to over express the cyclooxygenase-2 (COX-2) enzyme.[56] This enzyme is generally not found in healthy colon tissue, but is thought to fuel abnormal cell growth.

### Macroscopy

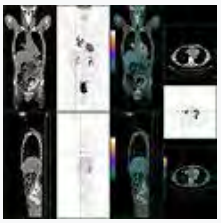


Appearance of the inside of the colon showing one invasive colorectal carcinoma (the crater-like, reddish, irregularly shaped tumor)

Gross appearance of a colectomy specimen containing two adenomatous polyps (the brownish oval tumors above the labels, attached to the normal beige lining by a stalk) and one invasive



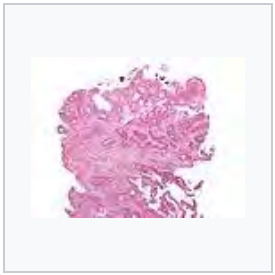
Endoscopic image of colon cancer identified in sigmoid colon on screening colonoscopy in the setting of Crohn's disease



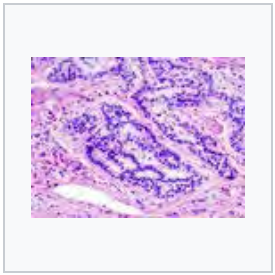
PET/CT of a staging exam of colon carcinoma. Besides the primary tumor a lot of lesions can be seen. On cursor position: lung nodule.

colorectal carcinoma (the crater-like, reddish, irregularly shaped tumor located above the label)

**Micrographs (H&E stain)**

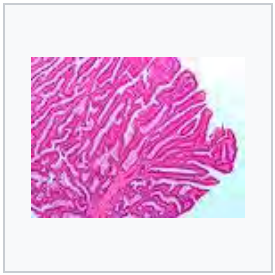


Cancer — Invasive adenocarcinoma (the most common type of colorectal cancer). The cancerous cells are seen in the center and at the bottom right of the image (blue). Near normal colon-lining cells are seen at the top right of the image.



Cancer — Histopathologic image of colonic carcinoid

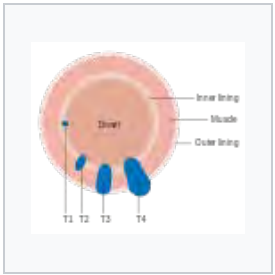
Precancer — Tubular adenoma (left of image), a type of colonic polyp and a precursor of colorectal cancer. Normal colorectal mucosa is seen on the right.



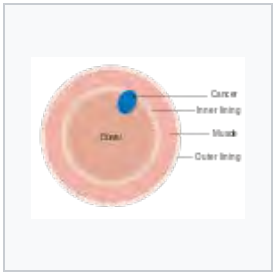
Precancer — Colorectal villous adenoma

## Staging [edit]

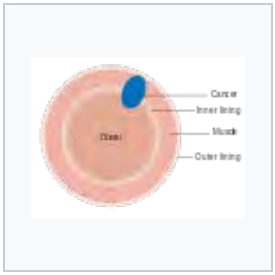
Staging is typically made according to the TNM staging system from the WHO organization, the UICC and the AJCC. The Astler-Coller classification (1954) and the Dukes classification (1932) are now less used.



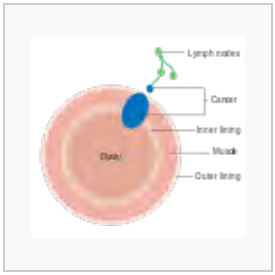

The T stages of bowel cancer.



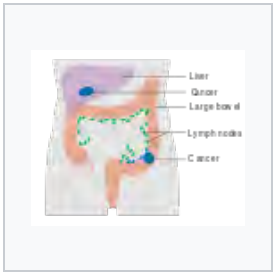

Dukes stage A bowel cancer; the cancer is only in the inner lining of the bowel.




Dukes stage B bowel cancer; the cancer has invaded the muscle.




Dukes stage C bowel cancer; the cancer has invaded the nearby lymph nodes.




Dukes stage D bowel cancer; the cancer has metastasized.

## Tumor budding [edit]

Tumor budding in colorectal cancer is loosely defined by the presence of individual cells and small clusters of tumor cells at the invasive front of carcinomas. It has been postulated to represent an epithelial–mesenchymal transition (EMT). Tumor budding is a well-established independent marker of a potentially poor outcome in colorectal carcinoma that may allow for dividing people into risk categories more meaningful than those defined by TNM staging, and also potentially guide treatment decisions, especially in T1 and T3 N0 (Stage II, Dukes' B) colorectal carcinoma. Unfortunately, its universal acceptance as a reportable factor has been held back by a lack of definitional uniformity with respect to both qualitative and quantitative aspects of tumor budding.[57]

# Prevention [edit]

It has been estimated that about half of colorectal cancer cases are due to lifestyle factors and about a quarter of

all cases are preventable.[58] Increasing surveillance, engaging in physical activity, consuming a diet high in fiber, and reducing smoking and alcohol consumption decrease the risk.[59][60]

## Lifestyle [edit]

Current dietary recommendations to prevent colorectal cancer include increasing the consumption of whole grains, fruits and vegetables, and reducing the intake of red meat and processed meats.[16][61] Higher physical activity is also recommended.[16][62] Physical exercise is associated with a modest reduction in colon but not rectal cancer risk.[63][64] High levels of physical activity reduce the risk of colon cancer by about 21%.[65] Sitting regularly for prolonged periods is associated with higher mortality from colon cancer. The risk is not negated by regular exercise, though it is lowered.[66] The evidence for any protective effect conferred by fiber and fruits and vegetables is, however, poor.[16][67] The risk of colon cancer can be reduced by maintaining a normal body weight.[68]

## Medication [edit]

Aspirin and celecoxib appear to decrease the risk of colorectal cancer in those at high risk.[69] Aspirin is recommended in those who are 50 to 60 years old, do not have an increased risk of bleeding, and are at risk for cardiovascular disease to prevent colorectal cancer.[70] It is not recommended in those at average risk.[71] There is tentative evidence for calcium supplementation but it is not sufficient to make a recommendation.[72] Vitamin D intake and blood levels are associated with a lower risk of colon cancer.[73][74]

## Screening [edit]

As more than 80% of colorectal cancers arise from adenomatous polyps, screening for this cancer is effective not only for early detection but also for prevention.[75] Diagnosis of cases of colorectal cancer through screening tends to occur 2–3 years before diagnosis of cases with symptoms.[15] Any polyps that are detected can be removed, usually by colonoscopy or sigmoidoscopy, and thus prevented from turning cancerous. Screening has the potential to reduce colorectal cancer deaths by 60%.[76]

The four main screening tests are fecal occult blood testing, flexible sigmoidoscopy, colonoscopy, and stool DNA screening test.[15] Of the three, only sigmoidoscopy cannot screen the right side of the colon where 42% of malignancies are found.[77] Virtual colonoscopy via a CT scan appears as good as standard colonoscopy for detecting cancers and large adenomas but is expensive, associated with radiation exposure, and cannot remove any detected abnormal growths like standard colonoscopy can.[15]

Fecal occult blood testing (FOBT) of the stool is typically recommended every two years and can be either guaiac based or immunochemical.[15] If abnormal FOBT results are found, participants are typically referred for a follow-up colonoscopy examination. Annual to biennial FOBT screening reduce colorectal cancer mortality by 16% and among those participating in screening colorectal cancer mortality can be reduced up to 23%, although it has not been proven to reduce all-cause mortality.[78] Immunochemical tests are highly accurate and do not require dietary or medication changes before testing.[79]

The multitarget stool DNA screening test is a noninvasive test used to screen for the presence of colorectal cancer or precancerous lesions. It uses a stool sample to identify biomarkers associated with colorectal cancer and precancerous lesions, including altered DNA and blood hemoglobin. A positive result may indicate the presence of precancerous lesions or colorectal cancer, and should be followed by colonoscopy. The American Cancer Society recommends screening with multitarget sDNA testing every 3 years, starting at age 50.[*citation needed*]

## Recommendations [edit]

In the United States screening is typically recommended between the age of 50 and 75 years.[6] For those between 76 and 85 years of age the decision to screen should be individualized.[6] A number of screening methods can be used including stool based tests every 3 years, sigmoidoscopy every 5 years and colonoscopy every 10 years. For those at high risk, screenings usually begin at around 40.[15][80] It is unclear which of these two methods is better.[81] Colonoscopy may find more cancers in the first part of the colon but is associated with greater cost and more complications.[81] For people with average risk who have had a high-quality colonoscopy with normal results, the American Gastroenterological Association does not recommend any type of screening in the 10 years following the colonoscopy.[82][83] For people over 75 or those with a life expectancy of less than 10 years, screening is not recommended.[84] It takes about 10 years after screening for one out of a 1000 people [85]

to benefit.

In Canada, among those 50 to 75 at normal risk, fecal immunochemical testing or FOBT is recommended every two years or sigmoidoscopy every 10 years.[86] Colonoscopy is less preferred.[86]

Some countries have national colorectal screening programs which offer FOBT screening for all adults within a certain age group, typically starting between age 50 and 60. Examples of countries with organised screening include the United Kingdom,[87] Australia[88] and the Netherlands.[89]

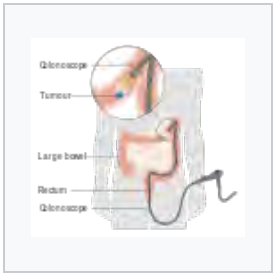
## Management [edit]

The treatment of colorectal cancer can be aimed at cure or palliation. The decision on which aim to adopt depends on various factors, including the person's health and preferences, as well as the stage of the tumor.[90] When colorectal cancer is caught early, surgery can be curative. However, when it is detected at later stages (for which metastases are present), this is less likely and treatment is often directed at palliation, to relieve symptoms caused by the tumour and keep the person as comfortable as possible.[15]

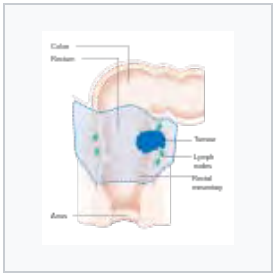
### Surgery [edit]

If the cancer is found at a very early stage, it may be removed during a colonoscopy.[1] For people with localized cancer, the preferred treatment is complete surgical removal with adequate margins, with the attempt of achieving a cure. This can either be done by an open laparotomy or sometimes laparoscopically.[15] The colon may then be reconnected or a person may have a colostomy.[1]

If there are only a few metastases in the liver or lungs they may also be removed. Sometimes chemotherapy is used before surgery to shrink the cancer before attempting to remove it. The two most common sites of recurrence of colorectal cancer are the liver and lungs.[15]




A diagram of a local resection of early stage colon cancer




A diagram of local surgery for rectal cancer

### Chemotherapy [edit]

In both cancer of the colon and rectum, chemotherapy may be used in addition to surgery in certain cases. The decision to add chemotherapy in management of colon and rectal cancer depends on the stage of the disease.

In Stage I colon cancer, no chemotherapy is offered, and surgery is the definitive treatment. The role of chemotherapy in Stage II colon cancer is debatable, and is usually not offered unless risk factors such as T4 tumor or inadequate lymph node sampling is identified. It is also known that the patients who carry abnormalities of the mismatch repair genes do not benefit from chemotherapy. For stage III and Stage IV colon cancer, chemotherapy is an integral part of treatment.[15]

If cancer has spread to the lymph nodes or distant organs, which is the case with stage III and stage IV colon cancer respectively, adding chemotherapy agents fluorouracil, capecitabine or oxaliplatin increases life expectancy. If the lymph nodes do not contain cancer, the benefits of chemotherapy are controversial. If the cancer is widely metastatic or unresectable, treatment is then palliative. Typically in this setting, a number of different chemotherapy medications may be used.[15] Chemotherapy drugs for this condition may include capecitabine, fluorouracil, irinotecan, oxaliplatin and UFT.[91] The drugs capecitabine and fluorouracil are interchangeable, with capecitabine being an oral medication while fluorouracil being an intravenous medicine. Some specific regimens used for CRC are FOLFOX, FOLFOXIRI, and FOLFIRI.[92] Antiangiogenic drugs such as bevacizumab are often added in first line therapy. Another class of drugs used in the second line setting are epidermal growth factor receptor inhibitors, of which the two FDA approved ones are cetuximab and panitumumab.[93]

The primary difference in the approach to low stage rectal cancer is the incorporation of radiation therapy. Often,

it is used in conjunction with chemotherapy in a neoadjuvant fashion to enable surgical resection, so that ultimately as colostomy is not required. However, it may not be possible in low lying tumors, in which case, a permanent colostomy may be required. Stage IV rectal cancer is treated similar to stage IV colon cancer.

## Radiation therapy [edit]

While a combination of radiation and chemotherapy may be useful for rectal cancer,[15] its use in colon cancer is not routine due to the sensitivity of the bowels to radiation.[94] Just as for chemotherapy, radiotherapy can be used in the neoadjuvant and adjuvant setting for some stages of rectal cancer.

## Palliative care [edit]

Palliative care is medical care which focuses on treatment of symptoms from serious illness, like cancer, and improving quality of life.[95] Palliative care is recommended for any person who has advanced colon cancer or has significant symptoms.[96]

Involvement of palliative care may be beneficial to improve the quality of life for both the person and his or her family, by improving symptoms, anxiety and preventing admissions to the hospital.[97]

In people with incurable colorectal cancer, palliative care can consist of procedures that relieve symptoms or complications from the cancer but do not attempt to cure the underlying cancer, thereby improving quality of life. Surgical options may include non-curative surgical removal of some of the cancer tissue, bypassing part of the intestines, or stent placement. These procedures can be considered to improve symptoms and reduce complications such as bleeding from the tumor, abdominal pain and intestinal obstruction.[98] Non-operative methods of symptomatic treatment include radiation therapy to decrease tumor size as well as pain medications.[99]

## Follow-up [edit]

The aims of follow-up are to diagnose, in the earliest possible stage, any metastasis or tumors that develop later, but did not originate from the original cancer (metachronous lesions).

The U.S. National Comprehensive Cancer Network and American Society of Clinical Oncology provide guidelines for the follow-up of colon cancer.[100][101] A medical history and physical examination are recommended every 3 to 6 months for 2 years, then every 6 months for 5 years. Carcinoembryonic antigen blood level measurements follow the same timing, but are only advised for people with T2 or greater lesions who are candidates for intervention. A CT-scan of the chest, abdomen and pelvis can be considered annually for the first 3 years for patients who are at high risk of recurrence (for example, those who had poorly differentiated tumors or venous or lymphatic invasion) and are candidates for curative surgery (with the aim to cure). A colonoscopy can be done after 1 year, except if it could not be done during the initial staging because of an obstructing mass, in which case it should be performed after 3 to 6 months. If a villous polyp, a polyp >1 centimeter or high grade dysplasia is found, it can be repeated after 3 years, then every 5 years. For other abnormalities, the colonoscopy can be repeated after 1 year.

Routine PET or ultrasound scanning, chest X-rays, complete blood count or liver function tests are not recommended.[100][101] A 2016 systematic review concluded that more intense surveillance and close follow-up does not provide additional survival benefits in non-metastatic colorectal cancers.[102]

## Exercise [edit]

Exercise may be recommended in the future as secondary therapy to cancer survivors. In epidemiological studies, exercise may decrease colorectal cancer-specific mortality and all-cause mortality. Results for the specific amounts of exercise needed to observe a benefit were conflicting. These differences may reflect differences in tumour biology and expression of biomarkers. Patients with tumors that lacked CTNNB1 expression (β-catenin), involved in Wnt signalling pathway, required more than 18 Metabolic equivalent (MET) hours per week, a measure of exercise, to observe a reduction in colorectal cancer mortality. The mechanism of how exercise benefits survival may be involved in immune surveillance and inflammation pathways. In clinical studies, a pro-inflammatory response was found in patients with stage II-III colorectal cancer who underwent 2 weeks of moderate exercise after completing their primary therapy. Oxidative balance may be another possible mechanism for benefits observed. A significant decrease in 8-oxo-dG was found in the urine of patients who underwent 2 weeks of moderate exercise after primary therapy. Other possible mechanisms may involve metabolic hormone and sex-steroid hormones, although these pathways may be involved in other types of cancers[103][104]

Another potential biomarker may be p27. Survivors with tumors that expressed p27 and performed greater and equal to 18 MET hours per week were found to have reduced colorectal-cancer mortality survival compared to those with less than 18 MET hours per week. Survivors without p27 expression who exercised were shown to have

worse outcomes. The constitutive activation of PI3K/AKT/mTOR pathway may explain the loss of p27 and excess energy balance may up-regulate p27 to stop cancer cells from dividing.[104]

## Prognosis [edit]

In Europe the five-year survival rate for colorectal cancer is less than 60%. In the developed world about a third of people who get the disease die from it.[15]

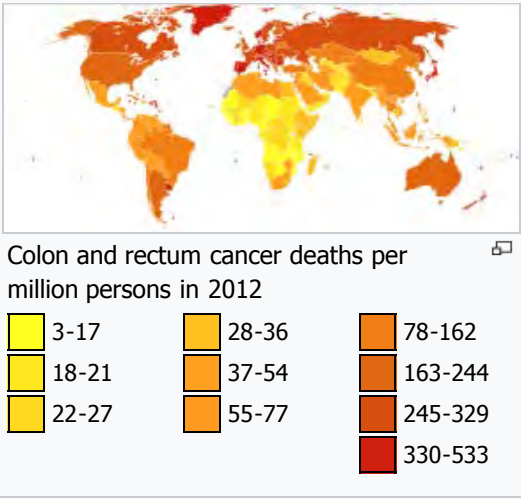
Survival is directly related to detection and the type of cancer involved, but overall is poor for symptomatic cancers, as they are typically quite advanced. Survival rates for early stage detection is about five times that of late stage cancers. People with a tumor that has not breached the muscularis mucosa (TNM stage Tis, N0, M0) have a five-year survival rate of 100%, while those with invasive cancer of T1 (within the submucosal layer) or T2 (within the muscular layer) have an average five-year survival rate of approximately 90%. Those with a more invasive tumor yet without node involvement (T3-4, N0, M0) have an average five-year survival rate of approximately 70%. Patients with positive regional lymph nodes (any T, N1-3, M0) have an average five-year survival rate of approximately 40%, while those with distant metastases (any T, any N, M1) have an average five-year survival rate of approximately 5%.[105]

According to American Cancer Society statistics in 2006,[106] over 20% of people with colorectal cancer come to medical attention when the disease is already advanced (stage IV), and up to 25% of this group will have isolated liver metastasis that is potentially resectable. In this selective group, those who undergo curative resection experience a five-year survival outcome in a third of the cases.[107]

## Epidemiology [edit]

Globally more than 1 million people get colorectal cancer every year[15] resulting in about 715,000 deaths as of 2010 up from 490,000 in 1990.[108]

As of 2012, it is the second most common cause of cancer in women (9.2% of diagnoses) and the third most common in men (10.0%)[109] with it being the fourth most common cause of cancer death after lung, stomach, and liver cancer.[110] It is more common in developed than developing countries.[111] Globally incidences vary 10-fold with highest rates in Australia, New Zealand, Europe and the US and lowest rates in Africa and South-Central Asia.[112]



Colon and rectum cancer deaths per million persons in 2012

### United States [edit]

Based on rates from 2007 to 2009, 4.96% of US men and women born today will be diagnosed with colorectal cancer during their lifetime.[113] From 2005 to 2009, the median age at diagnosis for cancer of the colon and rectum in the US was 69 years of age. Approximately 0.1% were diagnosed under age 20; 1.1% between 20 and 34; 4.0% between 35 and 44; 13.4% between 45 and 54; 20.4% between 55 and 64; 24.0% between 65 and 74; 25.0% between 75 and 84; and 12.0% 85+ years of age. Rates are higher among males (54 per 100,000 c.f. 40 per 100,000 for females).

## History [edit]

*See also: Timeline of colorectal cancer*

Rectal cancer has been diagnosed in an Ancient Egyptian mummy who had lived in the Dakhleh Oasis during the Ptolemaic period.[114]

The Biblical king Jehoram of Judah was recorded in 2 Chronicles 21 to be cursed with an incurable disease of the bowel, leading to his death, due to his supposed evil deeds. Modern scholarship indicates that his condition was most likely colon cancer.[115]

## Society and culture [edit]

[76]

In the United States, March is colorectal cancer awareness month.

### Notable cases [edit]

*Main article: List of people diagnosed with colorectal cancer*

- Corazon Aquino, former president of the Philippines[116]
- Pope John Paul II[117]
- Ronald Reagan, actor and former President of the United States[118]
- Howard Marks, Welsh drug smuggler and author [119]
- Harold Wilson, former Prime Minister of the United Kingdom[120]
- Robin Gibb, musician and member of the Bee Gees[121]
- Humayun Ahmed, Bengali writer and film maker[122]
- J.B.S. Haldane, Geneticist; polymath, popular science author[123]
- Stephen Sutton, Charity activist[124]

## Research [edit]

Preliminary in-vitro evidence suggests lactic acid bacteria (e.g., lactobacilli, streptococci or lactococci) may be protective against the development and progression of colorectal cancer through several mechanisms such as antioxidant activity, immunomodulation, promoting programmed cell death, antiproliferative effects, and epigenetic modification of cancer cells.[125]

Large-scale genome sequencing studies have been done to identify mutations in colorectal cancer patients' genome.[126]

The bacteria clostridium novyi-NT, is also being studied.[127]

- Mouse models of colorectal and intestinal cancer
- The Cancer Genome Atlas[35]
- The Colorectal Cancer Atlas integrating genomic and proteomic data pertaining to colorectal cancer tissues and cell lines have been developed.[128]

## References [edit]


1. ^ *a b c d e f* "Colon Cancer Treatment (PDQ®)". *NCI*. 2014-05-12. Retrieved 29 June 2014.
2. ^ "Defining Cancer". *National Cancer Institute*. Retrieved 10 June 2014.
3. ^ *a b c* "General Information About Colon Cancer". *NCI*. 2014-05-12. Retrieved 29 June 2014.
4. ^ *a b c d e f g h i* *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 5.5. ISBN 9283204298.
5. ^ *a b c* "Colorectal Cancer Prevention (PDQ®)". *National Cancer Institute*. 2014-02-27. Retrieved 29 June 2014.
6. ^ *a b c d* Bibbins-Domingo, Kirsten; Grossman, David C.; Curry, Susan J.; Davidson, Karina W.; Epling, John W.; García, Francisco A. R.; Gillman, Matthew W.; Harper, Diane M.; Kemper, Alex R.; Krist, Alex H.; Kurth, Ann E.; Landefeld, C. Seth; Mangione, Carol M.; Owens, Douglas K.; Phillips, William R.; Phipps, Maureen G.; Pignone, Michael P.; Siu, Albert L. (21 June 2016). "Screening for Colorectal Cancer". *JAMA*. **315** (23): 2564. doi:10.1001/jama.2016.5989.
7. ^ Thorat, MA; Cuzick, J (Dec 2013). "Role of aspirin in cancer prevention.". *Current Oncology Reports*. **15** (6): 533–40. doi:10.1007/s11912-013-0351-3. PMID 24114189.
8. ^ "Routine aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer: recommendation statement.". *American Family Physician*. **76** (1): 109–13. 2007. PMID 17668849.
9. ^ "SEER Stat Fact Sheets: Colon and Rectum Cancer". *NCI*. Retrieved 18 June 2014.
10. ^ *a b* *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 1.1. ISBN 9283204298.
11. ^ Alpers, David H.; Kalloo, Anthony N.; Kaplowitz, Neil; Owyang, Chung; Powell, Don W. (2008). Yamada, Tadataka, ed. *Principles of clinical gastroenterology*. Chichester, West Sussex: Wiley-Blackwell. p. 381. ISBN 978-1-4051-6910-3.
12. ^ *a b* Astin M, Griffin, T, Neal, RD, Rose, P, Hamilton, W (May 2011). "The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review". *The British Journal of General Practice*. **61** (586): 231–43. doi:10.3399/bjgp11X572427. PMC 3080228. PMID 21619747.
13. ^ Adelstein BA, Macaskill, P, Chan, SF, Katelaris, PH, Irwig, L (2011). "Most bowel cancer symptoms do not indicate colorectal cancer and polyps: a systematic review". *BMC Gastroenterology*. **11**: 65. doi:10.1186/1471-230X-11-65. PMC 3120795. PMID 21624112.
14. ^ *a b* Watson AJ, Collins, PD (2011). "Colon cancer: a civilization disorder". *Digestive Diseases*. **29** (2): 222–8. doi:10.1159/000323926. PMID 21734388.
15. ^ *a b c d e f g h i j k l m n o p q* Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, Starling N (2010).

"Colorectal cancer". *Lancet*. **375** (9719): 1030–47. doi:10.1016/S0140-6736(10)60353-4. PMID 20304247.

16. ^ [a b c d] "Colorectal Cancer 2011 Report: Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer" (PDF). World Cancer Research Fund & American Institute for Cancer Research. 2011.
17. ^ Lee, I-Min; Shiroma, Eric J; Lobelo, Felipe; Puska, Pekka; Blair, Steven N; Katzmarzyk, Peter T (1 July 2012). "Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy". *The Lancet*. **380** (9838): 219–29. doi:10.1016/S0140-6736(12)61031-9. PMC 3645500. PMID 22818936.
18. ^ Fedirko V, Tramacere, I, Bagnardi, V, Rota, M, Scotti, L, Islami, F, Negri, E, Straif, K, Romieu, I, La Vecchia, C, Boffetta, P, Jenab, M (Sep 2011). "Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies". *Annals of Oncology*. **22** (9): 1958–72. doi:10.1093/annonc/mdq653. PMID 21307158.
19. ^ Valtin, H (November 2002). " "Drink at least eight glasses of water a day." Really? Is there scientific evidence for "8 x 8"? ". *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*. **283** (5): R993–1004. doi:10.1152/ajpregu.00365.2002. PMID 12376390.
20. ^ Jawad N, Direkze, N, Leedham, SJ (2011). "Inflammatory bowel disease and colon cancer". *Recent Results in Cancer Research*. Recent Results in Cancer Research. **185**: 99–115. doi:10.1007/978-3-642-03503-6_6. ISBN 978-3-642-03502-9. PMID 21822822.
21. ^ [a b] Xie J, Itzkowitz, SH (2008). "Cancer in inflammatory bowel disease". *World Journal of Gastroenterology*. **14** (3): 378–89. doi:10.3748/wjg.14.378. PMC 2679126. PMID 18200660.
22. ^ [a b c d] Triantafillidis JK, Nasioulas, G, Kosmidis, PA (Jul 2009). "Colorectal cancer and inflammatory bowel disease: epidemiology, risk factors, mechanisms of carcinogenesis and prevention strategies". *Anticancer Research*. **29** (7): 2727–37. PMID 19596953.
23. ^ Juhn E, Khachemoune, A (2010). "Gardner syndrome: skin manifestations, differential diagnosis and management". *American Journal of Clinical Dermatology*. **11** (2): 117–22. doi:10.2165/11311180-000000000-00000. PMID 20141232.
24. ^ Half E, Bercovich, D, Rozen, P (2009). "Familial adenomatous polyposis". *Orphanet Journal of Rare Diseases*. **4**: 22. doi:10.1186/1750-1172-4-22. PMC 2772987. PMID 19822006.
25. ^ Möslein G, Pistorius S, Saeger H, Schackert HK (February 2003). "Preventive surgery for colon cancer in familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer syndrome". *Langenbecks Arch. Surg*. **388** (1): 9–16. doi:10.1007/s00423-003-0364-8. PMID 12690475.
26. ^ Stein, Ulrike; Walther, Wolfgang; Arlt, Franziska; Schwabe, Holger; Smith, Janice; Fichtner, Iduna; Birchmeier, Walter; Schlag, Peter M (2008). "MACC1, a newly identified key regulator of HGF-MET signaling, predicts colon cancer metastasis". *Nature Medicine*. **15** (1): 59–67. doi:10.1038/nm.1889. PMID 19098908.
27. ^ Stein U (2013) MACC1 - a novel target for solid cancers. Expert Opin Ther Targets
28. ^ Schuebel, Kornel E.; Chen, Wei; Cope, Leslie; Glöckner, Sabine C.; Suzuki, Hiromu; Yi, Joo-Mi; Chan, Timothy A.; Van Neste, Leander; Van Criekinge, Wim; van den Bosch, Sandra; van Engeland, Manon; Ting, Angela H.; Jair, Kamwing; Yu, Wayne; Toyota, Minoru; Imai, Kohzoh; Ahuja, Nita; Herman, James G.; Baylin, Stephen B. (2007). "Comparing the DNA Hypermethylome with Gene Mutations in Human Colorectal Cancer". *PLoS Genetics*. **3** (9): e157. doi:10.1371/journal.pgen.0030157. Retrieved 28 August 2015.
29. ^ Ionov Y, Peinado MA, Malkhosyan S, Shibata D, Perucho M (1993). "Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis". *Nature*. **363** (6429): 558–61. doi:10.1038/363558a0. PMID 8505985.
30. ^ Srikumar Chakravarthi; Baba Krishnan; Malathy Madhavan (1999). "Apoptosis and expression of p53 in colorectal neoplasms". *Indian J. Med. Res*. **86** (7): 95–102.
31. ^ Khalek FJ, Gallicano GI, Mishra L (May 2010). "Colon Cancer Stem Cells". *Gastrointest. Cancer Res.*: S16–S23. PMC 3047031. PMID 21472043.
32. ^ [a b c d] Markowitz SD, Bertagnolli MM (December 2009). "Molecular Origins of Cancer: Molecular Basis of Colorectal Cancer". *N. Engl. J. Med*. **361** (25): 2449–60. doi:10.1056/NEJMra0804588. PMC 2843693. PMID 20018966.
33. ^ Mehlen P, Fearon ER (August 2004). "Role of the dependence receptor DCC in colorectal cancer pathogenesis". *J. Clin. Oncol*. **22** (16): 3420–8. doi:10.1200/JCO.2004.02.019. PMID 15310786.
34. ^ Vogelstein, B; Kinzler, KW (2004). "Cancer genes and the pathways they control". *Nature Medicine*. **10** (8): 789–99. doi:10.1038/nm1087. PMID 15286780.
35. ^ [a b c] Muzny, DM.; Bainbridge, MN.; Chang, K.; Dinh, HH.; Drummond, JA.; Fowler, G.; Kovar, CL.; Lewis, LR.; Morgan, MB.; Newsham, Irene F.; Reid, Jeffrey G.; Santibanez, Jireh; Shinbrot, Eve; Trevino, Lisa R.; Wu, Yuan-Qing; Wang, Min; Gunaratne, Preethi; Donehower, Lawrence A.; Creighton, Chad J.; Wheeler, David A.; Gibbs, Richard A.; Lawrence, Michael S.; Voet, Douglas; Jing, Rui; Cibulskis, Kristian; Sivachenko, Andrey; Stojanov, Petar; McKenna, Aaron; Lander, Eric S.; Gabriel, Stacey (Jul 2012). "Comprehensive molecular characterization of human colon and rectal cancer". *Nature*. **487** (7407): 330–7. doi:10.1038/nature11252. PMC 3401966. PMID 22810696.
36. ^ Slaughter, DP; Southwick, HW; Smejkal, W (1953). "Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin". *Cancer*. **6** (5): 963–8. doi:10.1002/1097-0142(195309)6:5<963::AID-CNCR2820060515>3.0.CO;2-Q. PMID 13094644.
37. ^ Giovannucci, E; Ogino, S (Sep 21, 2005). "DNA methylation, field effects, and colorectal cancer.". *Journal of the National Cancer Institute*. **97** (18): 1317–9. doi:10.1093/jnci/dji305. PMID 16174847.
38. ^ [a b] Bernstein, C; Prasad, AR; Nfonsam, V; Bernstein, H. (2013). "DNA Damage, DNA Repair and Cancer". In Chen, Clark. *New Research Directions in DNA Repair*. InTech. ISBN 978-953-51-1114-6.
39. ^ Bernstein, C; Bernstein, H; Payne, CM; Dvorak, K; Garewal, H (2008). "Field defects in progression to gastrointestinal tract cancers". *Cancer Letters*. **260** (1–2): 1–10. doi:10.1016/j.canlet.2007.11.027. PMC 2744582. PMID 18164807.
40. ^ Nguyen, H; Loustaunau, C; Facista, A; Ramsey, L; Hassounah, N; Taylor, H; Krouse, R; Payne, CM; Tsikitis, VL;

Goldschmid, S; Banerjee, B; Perini, RF; Bernstein, C (2010). "Deficient Pms2, ERCC1, Ku86, CcOI in field defects during progression to colon cancer". *Journal of Visualized Experiments* (41): 1931. doi:10.3791/1931. PMC 3149991. PMID 20689513. 28 minute video

41. ^ Rubin, H (2011). "Fields and field cancerization: The preneoplastic origins of cancer: Asymptomatic hyperplastic fields are precursors of neoplasia, and their progression to tumors can be tracked by saturation density in culture". *BioEssays*. **33** (3): 224–31. doi:10.1002/bies.201000067. PMID 21254148.
42. ^ Tsao, JL; Yatabe, Y; Salovaara, R; Järvinen, HJ; Mecklin, JP; Aaltonen, LA; Tavaré, S; Shibata, D (2000). "Genetic reconstruction of individual colorectal tumor histories". *Proceedings of the National Academy of Sciences of the United States of America*. **97** (3): 1236–41. doi:10.1073/pnas.97.3.1236. PMC 15581. PMID 10655514.
43. ^ [a] [b] Vogelstein, B; Papadopoulos, N; Velculescu, VE; Zhou, S; Diaz Jr, LA; Kinzler, KW (2013). "Cancer genome landscapes". *Science*. **339** (6127): 1546–58. doi:10.1126/science.1235122. PMC 3749880. PMID 23539594.
44. ^ Lochhead P, Chan AT, Nishihara R, Fuchs CS, Beck AH, Giovannucci E, Ogino S. (2014). "Etiologic field effect: reappraisal of the field effect concept in cancer predisposition and progression". *Mod. Pathol*. **28**: 14–29. doi:10.1038/modpathol.2014.81. PMID 24925058.
45. ^ Balaguer F, Link A, Lozano JJ, et al. (August 2010). "Epigenetic silencing of miR-137 is an early event in colorectal carcinogenesis". *Cancer Res*. **70** (16): 6609–18. doi:10.1158/0008-5472.CAN-10-0622. PMC 2922409. PMID 20682795.
46. ^ Deng, G; Kakar, S; Kim, YS (2011). "MicroRNA-124a and microRNA-34b/c are frequently methylated in all histological types of colorectal cancer and polyps, and in the adjacent normal mucosa". *Oncology Letters*. **2** (1): 175–180. doi:10.3892/ol.2010.222. PMC 3412539. PMID 22870149.
47. ^ Grady, WM; Parkin, RK; Mitchell, PS; Lee, JH; Kim, YH; Tsuchiya, KD; Washington, MK; Paraskeva, C; Willson, JK; Kaz, AM; Kroh, EM; Allen, A; Fritz, BR; Markowitz, SD; Tewari, M (2008). "Epigenetic silencing of the intronic microRNA hsa-miR-342 and its host gene EVL in colorectal cancer". *Oncogene*. **27** (27): 3880–8. doi:10.1038/onc.2008.10. PMID 18264139.
48. ^ Kanwal, R; Gupta, S (2012). "Epigenetic modifications in cancer". *Clinical Genetics*. **81** (4): 303–11. doi:10.1111/j.1399-0004.2011.01809.x. PMC 3590802. PMID 22082348.
49. ^ Baldassarre, G; Battista, S; Belletti, B; Thakur, S; Pentimalli, F; Trapasso, F; Fedele, M; Pierantoni, G; Croce, CM; Fusco, A (2003). "Negative regulation of BRCA1 gene expression by HMGA1 proteins accounts for the reduced BRCA1 protein levels in sporadic breast carcinoma". *Molecular and Cellular Biology*. **23** (7): 2225–38. doi:10.1128/MCB.23.7.2225-2238.2003. PMC 150734. PMID 12640109.
50. ^ [a] [b] Schnekenburger, M; Diederich, M (2012). "Epigenetics Offer New Horizons for Colorectal Cancer Prevention". *Current Colorectal Cancer Reports*. **8** (1): 66–81. doi:10.1007/s11888-011-0116-z. PMC 3277709. PMID 22389639.
51. ^ Jacinto FV, Esteller M (July 2007). "Mutator pathways unleashed by epigenetic silencing in human cancer". *Mutagenesis*. **22** (4): 247–53. doi:10.1093/mutage/gem009. PMID 17412712.
52. ^ Lahtz C, Pfeifer GP (February 2011). "Epigenetic changes of DNA repair genes in cancer". *J. Mol. Cell. Biol*. **3** (1): 51–8. doi:10.1093/jmcb/mjq053. PMC 3030973. PMID 21278452.
53. ^ Bernstein C, Nfonsam V, Prasad AR, Bernstein H (March 2013). "Epigenetic field defects in progression to cancer". *World J. Gastrointest. Oncol*. **5** (3): 43–9. doi:10.4251/wjgo.v5.i3.43. PMC 3648662. PMID 23671730.
54. ^ Weerakkody, Yuranga; Gaillard, Frank. "Colorectal carcinoma". Radiopaedia.org. Retrieved 13 September 2014.
55. ^ "Moderately differentiated adenocarcinoma (colon)". *pathologyatlas.ro*.
56. ^ Sostres C, Gargallo CJ, Lanas A (February 2014). "Aspirin, cyclooxygenase inhibition and colorectal cancer". *World J. Gastrointest. Pharmacol. Ther*. **5** (1): 40–9. doi:10.4292/wjgpt.v5.i1.40. PMC 3944468. PMID 24605250.
57. ^ Mitrovic, B.; Schaeffer, D. F.; Riddell, R. H.; Kirsch, R. (2012). "Tumor budding in colorectal carcinoma: Time to take notice". *Modern Pathology*. **25** (10): 1315–25. doi:10.1038/modpathol.2012.94. PMID 22790014.
58. ^ Parkin, D. M.; Boyd, L.; Walker, L. C. (2011-12-06). "16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010". *British Journal of Cancer*. **105** (S2): S77–S81. doi:10.1038/bjc.2011.489. ISSN 0007-0920. PMC 3252065. PMID 22158327.
59. ^ Searke, David (2006). *Cancer Epidemiology and Prevention* (3 ed.). Oxford University Press. p. 809. ISBN 9780199747979.
60. ^ Rennert, Gad (2007). *Cancer Prevention*. Springer. p. 179. ISBN 9783540376965.
61. ^ Campos FG, Logullo Waitzberg, AG, Kiss, DR, Waitzberg, DL, Habr-Gama, A, Gama-Rodrigues, J (Jan 2005). "Diet and colorectal cancer: current evidence for etiology and prevention". *Nutricion Hospitalaria*. **20** (1): 18–25. PMID 15762416.
62. ^ Pérez-Cueto, Federico J. A.; Verbeke, Wim (2012-04-01). "Consumer implications of the WCRF's permanent update on colorectal cancer". *Meat Science*. **90** (4): 977–978. doi:10.1016/j.meatsci.2011.11.032. ISSN 1873-4138. PMID 22196090.
63. ^ Harriss DJ, Atkinson, G, Batterham, A, George, K, Cable, NT, Reilly, T, Haboubi, N, Renehan, AG, Colorectal Cancer, Lifestyle, Exercise And Research, Group (Sep 2009). "Lifestyle factors and colorectal cancer risk (2): a systematic review and meta-analysis of associations with leisure-time physical activity". *Colorectal Disease*. **11** (7): 689–701. doi:10.1111/j.1463-1318.2009.01767.x. PMID 19207713.
64. ^ Robsahm TE, Aagnes B, Hjartåker A, Langseth H, Bray FI, Larsen IK (November 2013). "Body mass index, physical activity, and colorectal cancer by anatomical subsites: A systematic review and meta-analysis of cohort studies.". *Eur. J. Cancer Prev*. **22** (6): 492–505. doi:10.1097/CEJ.0b013e328360f434. PMID 23591454.
65. ^ Kyu, Hmwe H; Bachman, Victoria F; Alexander, Lily T; Mumford, John Everett; Afshin, Ashkan; Estep, Kara; Veerman, J Lennert; Delwiche, Kristen; Iannarone, Marissa L; Moyer, Madeline L; Cercy, Kelly; Vos, Theo; Murray, Christopher J L; Forouzanfar, Mohammad H (9 August 2016). "Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic

heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013". *BMJ*: i3857. doi:10.1136/bmj.i3857.
66. ^ Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA (2015). "Sedentary Time and Its Association With Risk for Disease Incidence, Mortality, and Hospitalization in Adults: A Systematic Review and Meta-analysis". *Annals of Internal Medicine*. **162** (2): 123–32. doi:10.7326/M14-1651. PMID 25599350.
67. ^ Doyle VC, Logullo Waitzberg, AG, Kiss, DR, Waitzberg, DL, Habr-Gama, A, Gama-Rodrigues, J (May 2007). "Nutrition and colorectal cancer risk: a literature review". *Gastroenterology Nursing*. **30** (3): 178–82; quiz 182–3. doi:10.1097/01.SGA.0000278165.05435.c0. PMID 17568255.
68. ^ Lauby-Secretan, B; Scoccianti, C; Loomis, D; Grosse, Y; Bianchini, F; Straif, K; International Agency for Research on Cancer Handbook Working, Group (25 August 2016). "Body Fatness and Cancer - Viewpoint of the IARC Working Group.". *The New England Journal of Medicine*. **375** (8): 794–798. doi:10.1056/nejmsr1606602. PMID 27557308.
69. ^ Cooper K, Squires, H, Carroll, C, Papaioannou, D, Booth, A, Logan, RF, Maguire, C, Hind, D, Tappenden, P (Jun 2010). "Chemoprevention of colorectal cancer: systematic review and economic evaluation". *Health Technology Assessment*. **14** (32): 1–206. doi:10.3310/hta14320. PMID 20594533.
70. ^ Bibbins-Domingo, Kirsten (12 April 2016). "Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement". *Annals of Internal Medicine*. **164**: 836–45. doi:10.7326/M16-0577. PMID 27064677.
71. ^ Agency for Healthcare Research and Quality. "Aspirin or Nonsteroidal Anti-inflammatory Drugs for the Primary Prevention of Colorectal Cancer". United States Department of Health & Human Services. "2010/2011"
72. ^ Weingarten MA, Zalmanovici, A, Yaphe, J (2008). Weingarten, Michael Asher MA, ed. "Dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps". *Cochrane Database of Systematic Reviews* (1): CD003548. doi:10.1002/14651858.CD003548.pub4. PMID 18254022.
73. ^ Ma Y, Zhang, P, Wang, F, Yang, J, Liu, Z, Qin, H (2011). "Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies". *Journal of Clinical Oncology*. **29** (28): 3775–82. doi:10.1200/JCO.2011.35.7566. PMID 21876081.
74. ^ Yin L, Grandi, N, Raum, E, Haug, U, Arndt, V, Brenner, H (Jul 2011). "Meta-analysis: Serum vitamin D and colorectal adenoma risk". *Preventive Medicine*. **53** (1–2): 10–6. doi:10.1016/j.ypmed.2011.05.013. PMID 21672549.
75. ^ "What Can I Do to Reduce My Risk of Colorectal Cancer?". Centers for Disease Control and Prevention. April 2, 2014. Retrieved March 5, 2015.
76. ^ [a] [b] He J, Efron, JE (2011). "Screening for colorectal cancer". *Advances in Surgery*. **45**: 31–44. doi:10.1016/j.yasu.2011.03.006. PMID 21954677.
77. ^ Siegel RL, Ward EM, Jemal A (Mar 2012). "Trends in Colorectal Cancer Incidence Rates in the United States by Tumor Location and Stage, 1992–2008". *Cancer Epidemiology, Biomarkers & Prevention*. **21** (3): 411–6. doi:10.1158/1055-9965.EPI-11-1020. PMID 22219318. Retrieved September 16, 2012.
78. ^ Hewitson, P; Glasziou, P; Watson, E; Towler, B; Irwig, L (June 2008). "Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update". *The American Journal of Gastroenterology*. **103** (6): 1541–9. doi:10.1111/j.1572-0241.2008.01875.x. PMID 18479499.
79. ^ Lee, Jeffrey K.; Liles, Elizabeth G.; Bent, Stephen; Levin, Theodore R.; Corley, Douglas A. (4 February 2014). "Accuracy of Fecal Immunochemical Tests for Colorectal Cancer". *Annals of Internal Medicine*. **160** (3): 171–181. doi:10.7326/M13-1484.
80. ^ "Screening for Colorectal Cancer". *U.S. Preventive Services Task Force*. 2008.
81. ^ [a] [b] Brenner, H.; Stock, C.; Hoffmeister, M. (9 April 2014). "Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies". *BMJ*. **348** (apr09 1): g2467–g2467. doi:10.1136/bmj.g2467.
82. ^ American Gastroenterological Association. "Five Things Physicians and Patients Should Question" (PDF). *Choosing Wisely: an initiative of the ABIM Foundation*. American Gastroenterological Association. Archived from the original (PDF) on August 9, 2012. Retrieved August 17, 2012.
83. ^ Winawer, S; Fletcher, R; Rex, D; Bond, J; Burt, R; Ferrucci, J; Ganiats, T; Levin, T; Woolf, S; Johnson, D; Kirk, L; Litin, S; Simmang, C; Gastrointestinal Consortium, Panel (February 2003). "Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence". *Gastroenterology*. **124** (2): 544–60. doi:10.1053/gast.2003.50044. PMID 12557158.
84. ^ Qaseem A, Denberg TD, Hopkins RH Jr, et al. (2012). "Screening for Colorectal Cancer: A Guidance Statement From the American College of Physicians". *Annals of Internal Medicine*. **156** (5): 378–386. doi:10.7326/0003-4819-156-5-201203060-00010. PMID 22393133.
85. ^ Tang, V; Boscardin, WJ; Stijacic-Cenzer, I; Lee, SJ (16 April 2015). "Time to benefit for colorectal cancer screening: survival meta-analysis of flexible sigmoidoscopy trials.". *BMJ*. **350**: h1662. doi:10.1136/bmj.h1662. PMID 25881903.
86. ^ [a] [b] Bacchus, CM; Dunfield, L; Connor Gorber, S; Holmes, NM; Birtwhistle, R; Dickinson, JA; Lewin, G; Singh, H; Klarenbach, S; Mai, V; Tonelli, M; Canadian Task Force on Preventive Health, Care (22 February 2016). "Recommendations on screening for colorectal cancer in primary care.". *CMAJ : Canadian Medical Association*. **188**: 340–8. doi:10.1503/cmaj.151125. PMID 26903355.
87. ^ "NHS Bowel Cancer Screening Programme". *cancerscreening.nhs.uk*.
88. ^ "Home - Bowel Cancer Australia". *bowelcanceraustralia.org*. Archived from the original on December 24, 2014.
89. ^ "Bevolkingsonderzoek darmkanker". *rivm.nl*.
90. ^ Stein A, Atanackovic, D, Bokemeyer, C (Sep 2011). "Current standards and new trends in the primary treatment of colorectal cancer". *European Journal of Cancer*. **47** (Suppl 3): S312–4. doi:10.1016/S0959-8049(11)70183-6. PMID 21943995.

91. ^ "Chemotherapy of metastatic colorectal cancer". *Prescrire International*. **19** (109): 219–24. October 2010. PMID 21180382.
92. ^ Akhtar R, Chandel S, Sarotra P, Medhi B (2014). "Current status of pharmacological treatment of colorectal cancer". *World J Gastrointest Oncol*. **6** (6): 177–83. doi:10.4251/wjgo.v6.i6.177. PMC 4058725. PMID 24936228.
93. ^ Shaib, W; Mahajan, R; El-Rayes, B (2013). "Markers of resistance to anti-EGFR therapy in colorectal cancer". *Journal of Gastrointestinal Oncology*. **4** (3): 308–18. doi:10.3978/j.issn.2078-6891.2013.029. PMC 3712296. PMID 23997942.
94. ^ authors, editors, Vincent T. DeVita Jr., Theodore S. Lawrence, Steven A. Rosenberg ; associate scientific advisors, Robert A. Weinberg, Ronald A. DePinho ; with 421 contributing (2008). *DeVita, Hellman, and Rosenberg's cancer : principles & practice of oncology* (8th ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins. p. 1258. ISBN 978-0-7817-7207-5.
95. ^ "Palliative or Supportive Care". American Cancer Society. Retrieved 20 August 2014.
96. ^ "ASCO Provisional Clinical Opinion: The Integration of Palliative Care into Standard Oncology Care". ASCO. Archived from the original on August 21, 2014. Retrieved 20 August 2014.
97. ^ Higginson, IJ; Evans, CJ (Sep–Oct 2010). "What is the evidence that palliative care teams improve outcomes for cancer patients and their families?". *Cancer Journal*. **16** (5): 423–35. doi:10.1097/PPO.0b013e3181f684e5. PMID 20890138.
98. ^ Wasserberg N, Kaufman HS (December 2007). "Palliation of colorectal cancer". *Surg. Oncol.* **16** (4): 299–310. doi:10.1016/j.suronc.2007.08.008. PMID 17913495.
99. ^ Amersi F, Stamos MJ, Ko CY (July 2004). "Palliative care for colorectal cancer". *Surg. Oncol. Clin. N. Am*. **13** (3): 467–77. doi:10.1016/j.soc.2004.03.002. PMID 15236729.
100. ^ *a b* "National Comprehensive Cancer Network" (PDF). *nccn.org*.
101. ^ *a b* Desch CE, Benson AB 3rd, Somerfield MR, et al.; American Society of Clinical Oncology (2005). "Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline". *J. Clin. Oncol.* **23** (33): 8512–9. doi:10.1200/JCO.2005.04.0063. PMID 16260687.
102. ^ Jeffery, M; Hickey, BE; Hider, PN; See, AM (24 November 2016). "Follow-up strategies for patients treated for non-metastatic colorectal cancer.". *The Cochrane database of systematic reviews*. **11**: CD002200. doi:10.1002/14651858.CD002200.pub3. PMID 27884041.
103. ^ Betof AS, Dewhirst MW, Jones LW (March 2013). "Effects and potential mechanisms of exercise training on cancer progression: A translational perspective". *Brain Behav. Immun*. **30**: S75–87. doi:10.1016/j.bbi.2012.05.001. PMC 3638811. PMID 22610066.
104. ^ *a b* Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM (May 2012). "Physical activity, biomarkers, and disease outcomes in cancer survivors: A systematic review". *J. Natl. Cancer Inst.* **104** (11): 815–40. doi:10.1093/jnci/djs207. PMC 3465697. PMID 22570317.
105. ^ Box 3-1, Page 107 in: Elizabeth D Agabegi; Agabegi, Steven S. (2008). *Step-Up to Medicine (Step-Up Series)*. Hagerstwon, MD: Lippincott Williams & Wilkins. ISBN 0-7817-7153-6.
106. ^ [1] Archived September 25, 2006, at the Wayback Machine.
107. ^ Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M (April 2006). "Surgical resection of hepatic metastases from colorectal cancer: A systematic review of published studies". *Br. J. Cancer*. **94** (7): 982–99. doi:10.1038/sj.bjc.6603033. PMC 2361241. PMID 16538219.
108. ^ Lozano R, Naghavi M, Foreman K, et al. (December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
109. ^ *World Cancer Report 2014*. International Agency for Research on Cancer, World Health Organization. 2014. ISBN 978-92-832-0432-9.
110. ^ WHO (February 2010). "Cancer". World Health Organization. Retrieved January 5, 2011.
111. ^ Merika E, Saif, MW, Katz, A, Syrigos, K, Morse, M (Sep 2010). "Review. Colon cancer vaccines: an update". *In Vivo*. **24** (5): 607–28. PMID 20952724.
112. ^ Colorectal Cancer Incidence, Mortality and Prevalence Worldwide in 2008 — Summary Archived October 17, 2012, at the Wayback Machine.. Available from: Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. (2010) GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer. Accessed on 11 Oct 2012.
113. ^ Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). *SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations)*. Bethesda, MD: National Cancer Institute. Based on November 2011 SEER data submission, posted to the SEER web site, 2012.
114. ^ Rehemtulla, Alnawaz (December 2010). "Dinosaurs and Ancient Civilizations: Reflections on the Treatment of Cancer". *Neoplasia*. **12** (12): 957–968. doi:10.1593/neo.101588. PMC 3003131. PMID 21170260.
115. ^ Louba, Liubov (December 2004). "Colorectal carcinoma that afflicted King Jehoram.". *Minerva Med*. **95** (6): 557–561. PMID 15785440.
116. ^ [2] [*dead link*]
117. ^ "Pope John Paul II". *ABC News Online*.
118. ^ "Reagan turns 90". *BBC News: Americas*. 6 February 2001.
119. ^ http://www.dailymail.co.uk/news/article-2925482/Drug-smuggler-turned-celebrity-author-Howard-Marks-69-reveals-inoperable-bowel-cancer.html
120. ^ Goodman, Geoffrey (1 July 2005). "Harold Wilson | Politics". *The Guardian*. London. Retrieved 10 April 2014.
121. ^ Klein, Sarah (2012-04-23). "12 Famous Faces Touched By Colorectal Cancer". *Huffington Post*.

122. ^ "Humayun Ahmed dies". *Bdnews24.com*. 2012-07-19. Retrieved July 19, 2012.
123. ^ Krishna Dronamraju (May 2010). "J.B.S. Haldane's Last Years: His Life and Work in India [1957-1964]". *Genetics*. **185** (1): 5–10. doi:10.1534/genetics.110.116632. PMC 2870975. PMID 20516291.
124. ^ "Cancer fundraiser Stephen Sutton dies aged 19". *BBC News*.
125. ^ Zhong L, Zhang X, Covasa M (June 2014). "Emerging roles of lactic acid bacteria in protection against colorectal cancer". *World J. Gastroenterol.* **20** (24): 7878–86. doi:10.3748/wjg.v20.i24.7878. PMC 4069315. PMID 24976724.
126. ^ Liu, Y; Zhang, X; Han, C; Wan, G; Huang, X; Ivan, C; Jiang, D; Rodriguez-Aguayo, C; Lopez-Berestein, G; Rao, PH; Maru, DM; Pahl, A; He, X; Sood, AK; Ellis, LM; Anderl, J; Lu, X (30 April 2015). "TP53 loss creates therapeutic vulnerability in colorectal cancer.". *Nature*. **520** (7549): 697–701. doi:10.1038/nature14418. PMID 25901683.
127. ^ Mone, Amy. "New Treatment and Research". The Johns Hopkins Kimmel Cancer Center.
128. ^ "Colorectal Cancer Atlas".


## External links [edit]

- Colorectal cancer at DMOZ

Wikimedia Commons has media related to *Colorectal cancer*.

| v · t · e | **Diseases of the digestive system (primarily K20–K93, 530–579)** | |
|---|---|---|
| **Upper GI tract** | **Esophagus** | Esophagitis (Candidal · Eosinophilic · Herpetiform · · *Rupture* (Boerhaave syndrome · Mallory-Weiss syndrome · · UES (Zenker's diverticulum · · LES (Barrett's esophagus · · Esophageal motility disorder (Nutcracker esophagus · Achalasia · Diffuse esophageal spasm · Gastroesophageal reflux disease (GERD) · · Laryngopharyngeal reflux (LPR) · Esophageal stricture · Megaesophagus · |
| | **Stomach** | Gastritis (Atrophic · Ménétrier's disease · Gastroenteritis · · Peptic (gastric) ulcer (Cushing ulcer · Dieulafoy's lesion · · Dyspepsia · Pyloric stenosis · Achlorhydria · Gastroparesis · Gastroptosis · Portal hypertensive gastropathy · Gastric antral vascular ectasia · Gastric dumping syndrome · Gastric volvulus · |
| **Lower GI tract: Intestinal/ Enteropathy** | **Small intestine (Duodenum/Jejunum/Ileum)** | Enteritis (Duodenitis · Jejunitis · Ileitis · · Peptic (duodenal) ulcer (Curling's ulcer · · Malabsorption: Coeliac · Tropical sprue · Blind loop syndrome · Small bowel bacterial overgrowth syndrome · Whipple's · Short bowel syndrome · Steatorrhea · Milroy disease · Bile acid malabsorption · |
| | **Large intestine (Appendix/Colon)** | Appendicitis · Colitis (Pseudomembranous · Ulcerative · Ischemic · Microscopic · Collagenous · Lymphocytic · · Functional colonic disease (IBS · Intestinal pseudoobstruction / Ogilvie syndrome · · Megacolon / Toxic megacolon · Diverticulitis/Diverticulosis · |
| | **Large and/or small** | Enterocolitis (Necrotizing · · Gastroenterocolitis · IBD (Crohn's disease · · *Vascular*: Abdominal angina · Mesenteric ischemia · Angiodysplasia · Bowel obstruction: Ileus · Intussusception · Volvulus · Fecal impaction · Constipation · Diarrhea (Infectious · · Intestinal adhesions · |
| | **Rectum** | Proctitis (Radiation proctitis · · Proctalgia fugax · Rectal prolapse · Anismus · |
| | **Anal canal** | Anal fissure/Anal fistula · Anal abscess · Anal dysplasia · Pruritus ani · |
| **GI bleeding/BIS** | Upper (Hematemesis · Melena · · Lower (Hematochezia · · | |
| | **Liver** | Hepatitis (Viral hepatitis · Autoimmune hepatitis · Alcoholic hepatitis · · Cirrhosis (PBC · · Fatty liver (NASH · · *Vascular* (Budd-Chiari syndrome · Hepatic veno-occlusive disease · Portal hypertension · Nutmeg liver · · Alcoholic liver disease · Liver failure (Hepatic encephalopathy · Acute liver failure · |

| | | |
|---|---|---|
| **Accessory** | | · Liver abscess (Pyogenic · Amoebic · · Hepatorenal syndrome · Peliosis hepatis · Metabolic disorders (Wilson's disease · Hemochromatosis · · |
| | **Gallbladder** | Cholecystitis · Gallstones/Cholecystolithiasis · Cholesterolosis · Rokitansky-Aschoff sinuses · Postcholecystectomy syndrome · Porcelain gallbladder · |
| | **Bile duct/ Other biliary tree** | Cholangitis (Primary sclerosing cholangitis · Secondary sclerosing cholangitis · Ascending · · Cholestasis/Mirizzi's syndrome · Biliary fistula · Haemobilia · Gallstones/Cholelithiasis · *Common bile duct* (Choledocholithiasis · Biliary dyskinesia · · Sphincter of Oddi dysfunction · |
| | **Pancreatic** | Pancreatitis (Acute · Chronic · Hereditary · Pancreatic abscess · · Pancreatic pseudocyst · Exocrine pancreatic insufficiency · Pancreatic fistula · |
| **Abdominopelvic** | **Hernia** | Diaphragmatic (Congenital · · Hiatus · Inguinal (Indirect · Direct · · Umbilical · Femoral · Obturator · Spigelian · *Lumbar* (Petit's · Grynfeltt-Lesshaft · · *Undefined location* (Incisional · Internal hernia · Richter's · · |
| | **Peritoneal** | Peritonitis (Spontaneous bacterial peritonitis · · Hemoperitoneum · Pneumoperitoneum · |

| v · t · e · | **Digestive system neoplasia (C15–C26/D12–D13, 150–159/211)** | | |
|---|---|---|---|
| **GI tract** | **Upper** | **Esophagus** | Squamous cell carcinoma · Adenocarcinoma · |
| | | **Stomach** | Gastric carcinoma · Signet ring cell carcinoma · Gastric lymphoma (MALT lymphoma · · Linitis plastica · |
| | **Lower** | **Small intestine** | Duodenal cancer (Adenocarcinoma · · |
| | | **Appendix** | Carcinoid · Pseudomyxoma peritonei · |
| | | **Colon/rectum** | *colorectal polyp:* Peutz–Jeghers syndrome · Juvenile polyposis syndrome · Familial adenomatous polyposis/Gardner's syndrome · Cronkhite–Canada syndrome · *neoplasm:* Adenocarcinoma · Familial adenomatous polyposis · Hereditary nonpolyposis colorectal cancer · |
| | | **Anus** | Squamous cell carcinoma · |
| | **Upper and/or lower** | | Gastrointestinal stromal tumor · Krukenberg tumor (metastatic) · |
| **Accessory** | **Liver** | | *malignant:* Hepatocellular carcinoma (Fibrolamellar · · Hepatoblastoma · *benign:* Hepatocellular adenoma · Cavernous hemangioma · *hyperplasia:* Focal nodular hyperplasia · Nodular regenerative hyperplasia · |
| | **Biliary tract** | | *bile duct:* Cholangiocarcinoma · Klatskin tumor · *gallbladder:* Gallbladder cancer · |
| | **Pancreas** | | *exocrine pancreas:* Adenocarcinoma · Pancreatic ductal carcinoma · *cystic neoplasms*: Serous microcystic adenoma · Intraductal papillary mucinous neoplasm · Mucinous cystic neoplasm · Solid pseudopapillary neoplasm · Pancreatoblastoma · |
| **Peritoneum** | | | Primary peritoneal carcinoma · Peritoneal mesothelioma · Desmoplastic small round cell tumor · |

**Biology portal** **Medicine portal**

Categories: Conditions diagnosed by stool test | Colorectal cancer | Infectious causes of cancer


# Endometrial cancer





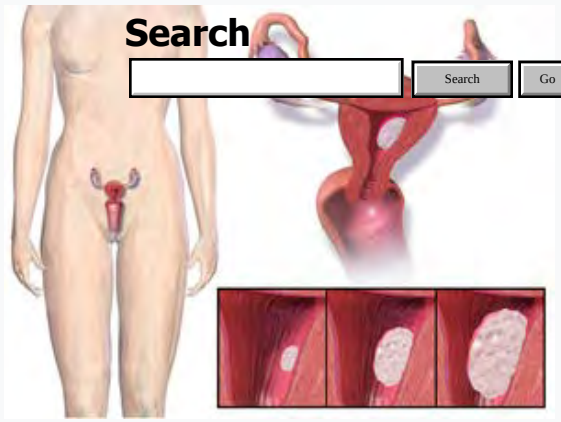
From Wikipedia, the free encyclopedia

**Endometrial cancer** is a cancer that arises from the endometrium (the lining of the uterus or womb).[1] It is the result of the abnormal growth of cells that have the ability to invade or spread to other parts of the body.[2] The first sign is most often vaginal bleeding not associated with a menstrual period. Other symptoms include pain with urination or sexual intercourse, or pelvic pain.[1] Endometrial cancer occurs most commonly after menopause.[3]

Approximately 40% of cases are related to obesity.[4] Endometrial cancer is also associated with excessive estrogen exposure, high blood pressure and diabetes.[1] Whereas taking estrogen alone increases the risk of endometrial cancer, taking both estrogen and a progestogen in combination, as in most birth control pills, decreases the risk.[1][4] Between two and five percent of cases are related to genes inherited from the parents.[4] Endometrial cancer is sometimes loosely referred to as "uterine cancer", although it is distinct from other forms of uterine cancer such as cervical cancer, uterine sarcoma, and trophoblastic disease.[5] The most frequent type of endometrial cancer is endometrioid carcinoma, which accounts for more than 80% of cases.[4] Endometrial cancer is commonly diagnosed by endometrial biopsy or by taking samples during a procedure known as dilation and curettage. A pap smear is not typically sufficient to show endometrial cancer.[6] Regular screening in those at normal risk is not called for.[7]

The leading treatment option for endometrial cancer is abdominal hysterectomy (the total removal by surgery of the uterus), together with removal of the fallopian tubes and ovaries on both sides, called a bilateral salpingo-oophorectomy. In more advanced cases, radiation therapy, chemotherapy or hormone therapy may also be recommended. If the disease is diagnosed at an early stage, the outcome is favorable,[6] and the overall five-year survival rate in the United States is greater than 80%.[8]

In 2012, endometrial cancers occurred in 320,000 women and caused 76,000 deaths.[4] This makes it the third most common cause of death in cancers which only affect women, behind ovarian and cervical cancer. It is more common in the developed world[4] and is the most common cancer of the female reproductive tract in developed countries.[6] Rates of endometrial cancer have risen in a number of countries between the 1980s and 2010.[4] This is believed to be due to the increasing number of elderly people and increasing rates of obesity.[9]



The location and development of endometrial cancer.

| Classification and external resources | |
|---|---|
| **Specialty** | Oncology, gynecology |
| **ICD-10** | C54.1 |
| **ICD-9-CM** | 182.0 |
| **OMIM** | 608089 |
| **DiseasesDB** | 4252 |
| **MedlinePlus** | 000910 |
| **eMedicine** | med/674 radio/253 |
| **Patient UK** | Endometrial cancer |
| **MeSH** | D016889 |

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Contents

## Classification [edit]

There are several types of endometrial cancer, including the most common endometrial carcinomas, which are divided into Type I and Type II subtypes. There are also rarer types including uterine papillary serous carcinoma, adenosquamous carcinoma, carcinomasarcoma and uterine clear-cell carcinoma.[10]

## Signs and symptoms [edit]

Vaginal bleeding or spotting in women after menopause occurs in 90% of endometrial cancer.[3][11] Bleeding is especially common with adenocarcinoma, occurring in two-thirds of all cases.[3][7] Abnormal menstrual cycles or extremely long, heavy, or frequent episodes of bleeding in women before menopause may also be a sign of endometrial cancer.[7]

Symptoms other than bleeding are not common. Other symptoms include thin white or clear vaginal discharge in postmenopausal women. More advanced disease shows more obvious symptoms or signs that can be detected on a physical examination. The uterus may become enlarged or the cancer may spread, causing lower abdominal pain or pelvic cramping.[7] Painful sexual intercourse or painful or difficult urination are less common signs of endometrial cancer.[5] The uterus may also fill with pus (pyometrea).[12] Of women with these less common symptoms (vaginal discharge, pelvic pain, and pus), 10–15% have cancer.[13]

## Risk factors [edit]

Risk factors for endometrial cancer include obesity, diabetes mellitus, breast cancer, use of tamoxifen, never having had a child, late menopause, high levels of estrogen, and increasing age.[12][13] Immigration studies (migration studies), which examine the change in cancer risk in populations moving between countries with different rates of cancer, show that there is some environmental component to endometrial cancer.[14] These environmental risk factors are not well characterized.[15]

### Hormones [edit]

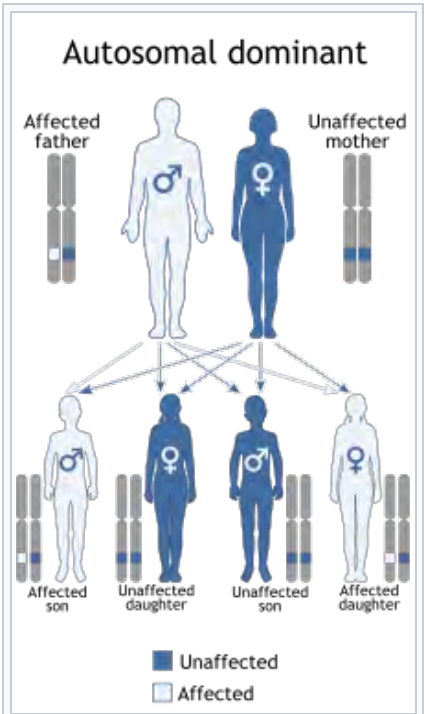
Most of the risk factors for endometrial cancer involve high levels of estrogens. An estimated 40% of cases are thought to be related to obesity.[4] In obesity, the excess of adipose tissue increases conversion of androstenedione into estrone, an estrogen. Higher levels of estrone in the blood causes less or no ovulation and exposes the endometrium to continuously high levels of estrogens.[9][16] Obesity also causes less estrogen to be removed from the blood.[16] Polycystic ovary syndrome (PCOS), which also causes irregular or no ovulation, is associated with higher rates of endometrial cancer for the same reasons as obesity.[14] Specifically, obesity, type II diabetes, and insulin resistance are risk factors for Type I endometrial cancer.[17] Obesity increases the risk for endometrial cancer

by 300–400%.[18]

Estrogen replacement therapy during menopause when not balanced (or "opposed") with progestin is another risk factor. Higher doses or longer periods of estrogen therapy have higher risks of endometrial cancer.[16] Women of lower weight are at greater risk from unopposed estrogen.[4] A longer period of fertility—either from an early first menstrual period or late menopause—is also a risk factor.[19] Unopposed estrogen raises an individual's risk of endometrial cancer by 2–10 fold, depending on weight and length of therapy.[4] In trans men who take testosterone and have not had a hysterectomy, the conversion of testosterone into estrogen via androstenedione may lead to a higher risk of endometrial cancer.[20]

## Genetics [edit]

Genetic disorders can also cause endometrial cancer. Overall, genetic causes contribute to 2–10% of endometrial cancer cases.[4][21] Lynch syndrome, an autosomal dominant genetic disorder that mainly causes colorectal cancer, also causes endometrial cancer, especially before menopause. Women with Lynch syndrome have a 40–60% risk of developing endometrial cancer, higher than their risk of developing colorectal (bowel) or ovarian cancer.[14] Ovarian and endometrial cancer develop simultaneously in 20% of people. Endometrial cancer nearly always develops before colon cancer, on average, 11 years before.[15] Carcinogenesis in Lynch syndrome comes from a mutation in MLH1 and/or MLH2: genes that participate in the process of mismatch repair, which allows a cell to correct mistakes in the DNA.[14] Other genes mutated in Lynch syndrome include MSH2, MSH6, and PMS2, which are also mismatch repair genes. Women with Lynch syndrome represent 2–3% of endometrial cancer cases; some sources place this as high as 5%.[15][18] Depending on the gene mutation, women with Lynch syndrome have different risks of endometrial cancer. With MLH1 mutations, the risk is 54%; with MSH2, 21%; and with MSH6, 16%.[22]



The autosomal dominant inheritance pattern seen in Lynch syndrome

Women with a family history of endometrial cancer are at higher risk.[5] Two genes most commonly associated with some other women's cancers, BRCA1 and BRCA2, do not cause endometrial cancer. There is an apparent link with these genes but it is attributable to the use of tamoxifen, a drug that itself can cause endometrial cancer, in breast and ovarian cancers.[14] The inherited genetic condition Cowden syndrome can also cause endometrial cancer. Women with this disorder have a 5–10% lifetime risk of developing endometrial cancer,[4] compared to the 2–3% risk for unaffected women.[15]

## Other health problems [edit]

Some therapies for other forms of cancer increase the lifetime risk of endometrial cancer, which is a baseline 2–3%.[15] Tamoxifen, a drug used to treat estrogen-positive breast cancers, has been associated with endometrial cancer in approximately 0.1% of users, particularly older women, but the benefits for survival from tamoxifen generally outweigh the risk of endometrial cancer.[23] A one to two-year course of tamoxifen approximately doubles the risk of endometrial cancer, and a five-year course of therapy quadruples that risk.[19] Raloxifene, a similar drug, did not raise the risk of endometrial cancer.[24] Previously having ovarian cancer is a risk factor for endometrial cancer,[25] as is having had previous radiotherapy to the pelvis. Specifically, ovarian granulosa cell tumors and thecomas are tumors associated with endometrial cancer.

Low immune function has also been implicated in endometrial cancer.[12] High blood pressure is also a risk factor,[18] but this may be because of its association with obesity.[22] Sitting regularly for prolonged periods is associated with higher mortality from endometrial cancer. The risk is not negated by regular exercise, though it is lowered.[26]

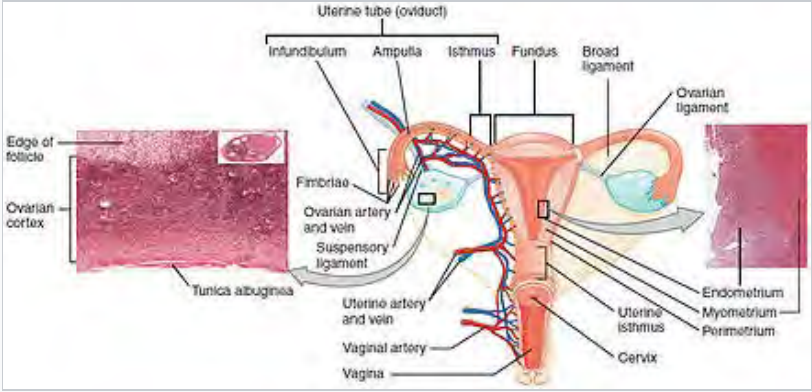
## Protective factors [edit]

Smoking and the use of progestin are both protective against endometrial cancer. Smoking provides protection by altering the metabolism of estrogen and promoting weight loss and early menopause. This protective effect lasts long after smoking is stopped. Progestin is present in the combined oral contraceptive pill and the hormonal intrauterine device (IUD).[14][27] Combined oral contraceptives reduce risk more the longer they are taken: by 56% after four

years, 67% after eight years, and 72% after twelve years. This risk reduction continues for at least fifteen years after contraceptive use has been stopped.[24] Obese women may need higher doses of progestin to be protected.[27] Having had more than five infants (grand multiparity) is also a protective factor,[12] and having at least one child reduces the risk by 35%. Breastfeeding for more than 18 months reduces risk by 23%. Increased physical activity reduces an individual's risk by 38–46%. There is preliminary evidence that consumption of soy is protective.[24]

## Pathophysiology [edit]

Endometrial cancer forms when there are errors in normal endometrial cell growth. Usually, when cells grow old or get damaged, they die, and new cells take their place. Cancer starts when new cells form unneeded, and old or damaged cells do not die as they should. The buildup of extra cells often forms a mass of tissue called a growth or tumor. These abnormal cancer cells have many genetic abnormalities that cause them to grow excessively.[5]



A diagram showing the female reproductive tract with the uterine wall enlarged and normal endometrium visible

**Mutations found in Type I and Type II endometrial cancers**[4][28]

| Gene mutated | Mutation type | Type I prevalence | Type II prevalence |
|---|---|---|---|
| ARID1A | point mutation | 40% | unknown |
| CTNNB1 | point mutation | 14–44% | unknown |
| FGFR2 | point mutation | 16% | unknown |
| KRAS | point mutation | 10–20% | unknown |
| PIK3R1 | point mutation | 43% | unknown |
| TP53 | point mutation | 10–20% | 90% |
| PTEN | point mutation | 37–61% | unknown |
| MLH1 | epigenetic silencing | 30% | unknown |
| RASSF1A | epigenetic silencing | 48% | unknown |
| SPRY2 | epigenetic silencing | 20% | unknown |
| PPP2R1A | point mutation | unknown | 17–41% |
| CDH1 | loss of heterozygosity | unknown | 80–90% |
| CDKN2A | loss of heterozygosity and/or epigenetic silencing | 20% | 40% |
| PIK3CA (oncogene) | point mutation or amplification | 24–39% | 20–30% |
| PIK3R1 (oncogene) | point mutation | unknown | 12% |
| STK15 (oncogene) | amplification | unknown | 60% |
| CCNE1 (oncogene) | amplification | unknown | 55% |
| ERBB2 (oncogene) | amplification | unknown | 30% |
| CCND1 (oncogene) | amplification | unknown | 26% |

In 10–20% of endometrial cancers, mostly Grade 3 (the highest histologic grade), mutations are found in a tumor suppressor gene, commonly p53 or PTEN. In 20% of endometrial hyperplasias and 50% of endometrioid cancers, PTEN suffers a loss-of-function mutation or a null mutation, making it less effective or completely ineffective.[29] Loss of PTEN function leads to up-regulation of the PI3k/Akt/mTOR pathway, which causes cell growth.[18] The p53 pathway can either be suppressed or highly activated in endometrial

cancer. When a mutant version of p53 is overexpressed, the cancer tends to be particularly aggressive.[29] P53 mutations and chromosome instability are associated with serous carcinomas, which tend to resemble ovarian and Fallopian carcinomas. Serous carcinomas are thought to develop from endometrial intraepithelial carcinoma.[18]

PTEN and p27 loss of function mutations are associated with a good prognosis, particularly in obese women. The Her2/neu oncogene, which indicates a poor prognosis, is expressed in 20% of endometrioid and serous carcinomas. CTNNB1 (beta-catenin; a transcription gene) mutations are found in 14–44% of endometrial cancers and may indicate a good prognosis, but the data is unclear.[29] Beta-catenin mutations are commonly found in endometrial cancers with squamous cells.[18] FGFR2 mutations are found in approximately 10% of endometrial cancers, and their prognostic significance is unclear.[29] SPOP is another tumor suppressor gene found to be mutated in some cases of endometrial cancer: 9% of clear cell endometrial carcinomas and 8% of serous endometrial carcinomas have mutations in this gene.[30]

Type I and Type II cancers (explained below) tend to have different mutations involved. ARID1A, which often carries a point mutation in Type I endometrial cancer, is also mutated in 26% of clear cell carcinomas of the endometrium, and 18% of serous carcinomas. Epigenetic silencing and point mutations of several genes are commonly found in Type I endometrial cancer.[4][28] Mutations in tumor suppressor genes are common in Type II endometrial cancer.[4] PIK3CA is commonly mutated in both Type I and Type II cancers.[28] In women with Lynch syndrome-associated endometrial cancer, microsatellite instability is common.[18]

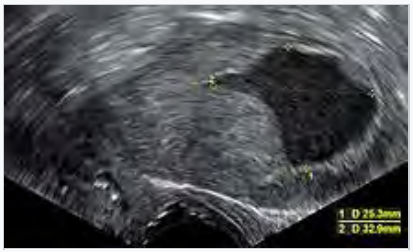
Development of an endometrial hyperplasia (overgrowth of endometrial cells) is a significant risk factor because hyperplasias can and often do develop into adenocarcinoma, though cancer can develop without the presence of a hyperplasia.[16] Within ten years, 8–30% of atypical endometrial hyperplasias develop into cancer, whereas 1–3% of non-atypical hyperplasias do so.[31] An atypical hyperplasia is one with visible abnormalities in the nuclei. Pre-cancerous endometrial hyperplasias are also referred to as endometrial intraepithelial neoplasia.[32] Mutations in the KRAS gene can cause endometrial hyperplasia and therefore Type I endometrial cancer.[29] Endometrial hyperplasia typically occurs after the age of 40.[5] Endometrial glandular dysplasia occurs with an overexpression of p53, and develops into a serous carcinoma.[12]

## Diagnosis [edit]

Diagnosis of endometrial cancer is made first by a physical examination and dilation and curettage (removal of endometrial tissue; D&C). This tissue is then examined histologically for characteristics of cancer. If cancer is found, medical imaging may be done to see whether the cancer has spread or invaded tissue.

### Examination [edit]

Routine screening of asymptomatic people is not indicated, since the disease is highly curable in its early, symptomatic stages. Instead, women, particularly menopausal women, should be aware of the symptoms and risk factors of endometrial cancer. A cervical screening test, such as a Pap smear, is not a useful diagnostic tool for endometrial cancer because the smear will be normal 50% of the time.[7] A Pap smear can detect disease that has spread to the cervix.[5] Results from a pelvic examination are frequently normal, especially in the early stages of disease. Changes in the size, shape or consistency of the uterus and/or its surrounding, supporting structures may exist when the disease is more advanced.[7] Cervical stenosis, the narrowing of the cervical opening, is a sign of endometrial cancer when pus or blood is found collected in the uterus (pyometra or hematometra).[11]



Vaginal ultrasonography with an endometrial fluid accumulation (darker area) in a postmenopausal uterus, a finding that is highly suspicious for endometrial cancer

Women with Lynch syndrome should begin to have annual biopsy screening at the age of 35. Some women with Lynch syndrome elect to have a prophylactic hysterectomy and salpingo-oophorectomy to greatly reduce the risk of endometrial and ovarian cancer.[7]

Transvaginal ultrasound to examine the endometrial thickness in women with postmenopausal bleeding is increasingly being used to aid in the diagnosis of endometrial cancer in the United States.[33] In the United Kingdom, both an endometrial biopsy and a transvaginal ultrasound used in conjunction are the standard of care for diagnosing endometrial cancer.[12] The homogeneity of the

Polypoidal endometrial carcinoma

tissue visible on transvaginal ultrasound can help to indicate whether the thickness is cancerous. Ultrasound findings alone are not conclusive in cases of endometrial cancer, so another screening method (for example endometrial biopsy) must be used in conjunction. Other imaging studies are of limited use. CT scans are used for preoperative imaging of tumors that appear advanced on physical exam or have a high-risk subtype (at high risk of metastasis).[34] They can also be used to investigate extrapelvic disease.[12] An MRI can be of some use in determining if the cancer has spread to the cervix or if it is an endocervical adenocarcinoma.[34] MRI is also useful for examining the nearby lymph nodes.[12]

Dilation and curettage or an endometrial biopsy are used to obtain a tissue sample for histological examination. Endometrial biopsy is the less invasive option, but it may not give conclusive results every time. Hysteroscopy only shows the gross anatomy of the endometrium, which is often not indicative of cancer, and is therefore not used, unless in conjunction with a biopsy.[34] Hysteroscopy can be used to confirm a diagnosis of cancer. New evidence shows that D&C has a higher false negative rate than endometrial biopsy.[18]

Before treatment is begun, several other investigations are recommended. These include a chest x-ray, liver function tests, kidney function tests,[18] and a test for levels of CA-125, a tumor marker that can be elevated in endometrial cancer.[5]

## Types [edit]

Endometrial cancer includes carcinomas, which are divided into Type I and Type II cancers and includes endometrioid adenocarcinoma, uterine papillary serous carcinoma, uterine clear-cell carcinoma, and several other very rare forms.

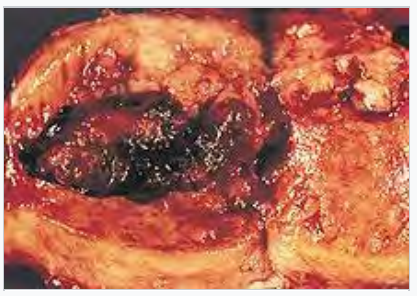
## Carcinoma [edit]

The vast majority of endometrial cancers are carcinomas (usually adenocarcinomas), meaning that they originate from the single layer of epithelial cells that line the endometrium and form the endometrial glands. There are many microscopic subtypes of endometrial carcinoma, but they are broadly organized into two categories, Type I and Type II, based on clinical features and pathogenesis. The two subtypes are genetically distinct.[7]

Type I endometrial carcinomas occur most commonly before and around the time of menopause. In the United States they are more common in whites, particularly those with a history of endometrial hyperplasia. Type I endometrial cancers are often low-grade, minimally invasive into the underlying uterine wall (myometrium), estrogen-dependent, and have a good outcome with treatment.[7] Type I carcinomas represent 75–90% of endometrial cancer.[12][35]

Type II endometrial carcinomas usually occur in older, post-menopausal people, in the United States are more common in black women, and are not associated with increased exposure to estrogen or a history of endometrial hyperplasia. Type II endometrial cancers are often high-grade, with deep invasion into the underlying uterine wall (myometrium), are of the serous or clear cell type, and carry a poorer prognosis. They can appear to be epithelial ovarian cancer on evaluation of symptoms.[7][35] They tend to present later than Type I tumors and are more aggressive, with a greater risk of relapse and/or metastasis.[12]

### Endometrioid adenocarcinoma [edit]

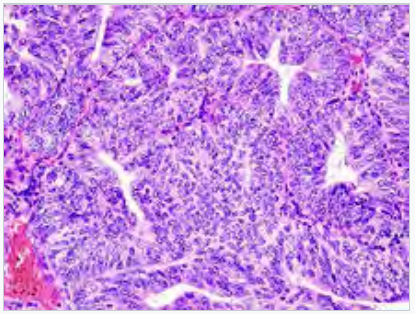


In endometrioid adenocarcinoma, the cancer cells grow in patterns reminiscent of normal endometrium, with many new glands formed from columnar epithelium with some abnormal nuclei. Low-grade endometrioid adenocarcinomas have well differentiated cells, have not invaded the myometrium, and are seen alongside endometrial hyperplasia. The tumor's glands form very close together, without the stromal tissue that normally separates them. Higher-grade endometrioid adenocarcinomas have less well-differentiated cells, have more solid sheets of tumor cells no longer organized into glands, and are associated with an atrophied endometrium. There are several subtypes of endometrioid adenocarcinoma with similar prognoses, including villoglandular, secretory, and ciliated cell variants.

There is also a subtype characterized by squamous differentiation. Some endometrioid adenocarcinomas have foci of mucinous carcinoma.[36]

The genetic mutations most commonly associated with endometrioid adenocarcinoma are in the genes PTEN, a tumor suppressor; PIK3CA, a kinase; KRAS, a GTPase that functions in signal transduction; and CTNNB1, involved in adhesion and cell signaling. The CTNNB1 (beta-catenin) gene is most commonly mutated in the squamous subtype of endometrioid adenocarcinoma.[37]

Gross pathology of an endometrial adenocarcinoma



A histologic view of an endometrial adenocarcinoma showing many abnormal nuclei

### Serous carcinoma [edit]

*See also: Uterine papillary serous carcinoma*

Serous carcinoma is a Type II endometrial tumor that makes up 5–10% of diagnosed endometrial cancer and is common in postmenopausal women with atrophied endometrium and black women. Serous endometrial carcinoma is aggressive and often invades the myometrium and metastasizes within the peritoneum (seen as omental caking) or the lymphatic system. Histologically, it appears with many atypical nuclei, papillary structures, and, in contrast to endometrioid adenocarcinomas, rounded cells instead of columnar cells. Roughly 30% of endometrial serous carcinomas also have psammoma bodies.[16][35] Serous carcinomas spread differently than most other endometrial cancers; they can spread outside the uterus without invading the myometrium.[16]

The genetic mutations seen in serous carcinoma are chromosomal instability and mutations in TP53, an important tumor suppressor gene.[37]

### Clear cell carcinoma [edit]

*See also: Uterine clear-cell carcinoma*

Clear cell carcinoma is a Type II endometrial tumor that makes up less than 5% of diagnosed endometrial cancer. Like serous cell carcinoma, it is usually aggressive and carries a poor prognosis. Histologically, it is characterized by the features common to all clear cells: the eponymous clear cytoplasm when H&E stained and visible, distinct cell membranes.[35] The p53 cell signaling system is not active in endometrial clear cell carcinoma.[12] This form of endometrial cancer is more common in postmenopausal women.[16]

### Mucinous carcinoma [edit]

Mucinous carcinomas are a rare form of endometrial cancer, making up less than 1–2% of all diagnosed endometrial cancer. Mucinous endometrial carcinomas are most often stage I and grade I, giving them a good prognosis. They typically have well-differentiated columnar cells organized into glands with the characteristic mucin in the cytoplasm. Mucinous carcinomas must be differentiated from cervical adenocarcinoma.[36]

### Mixed or undifferentiated carcinoma [edit]

Mixed carcinomas are those that have both Type I and Type II cells, with one making up at least 10% of the tumor.[36] These include the malignant mixed Müllerian tumor, which derives from endometrial epithelium and has a poor prognosis.[38]

Undifferentiated endometrial carcinomas make up less than 1–2% of diagnosed endometrial cancers. They have a worse prognosis than grade III tumors. Histologically, these tumors show sheets of identical epithelial cells with no identifiable pattern.[36]

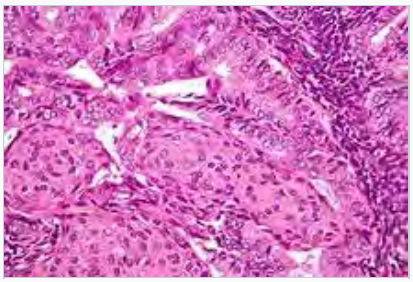
### Other carcinomas [edit]

Non-metastatic squamous cell carcinoma and transitional cell carcinoma are very rare in the endometrium. Squamous cell carcinoma of the endometrium has a poor prognosis.[36] It has been reported fewer than 100 times in the medical literature since its characterization in 1892. For primary squamous cell carcinoma of the endometrium (PSCCE) to be diagnosed, there must be no other primary cancer in the endometrium or cervix and it must not be connected to the cervical epithelium. Because of the rarity of this cancer, there are no guidelines for how it should be treated, nor any typical treatment. The common genetic causes remain uncharacterized.[39] Primary transitional cell carcinomas of the endometrium are even more rare; 16 cases had been reported as of 2008. Its pathophysiology and treatments have not been characterized.[40] Histologically, TCCE resembles endometrioid carcinoma and is distinct from other transitional cell carcinomas.[41]

## Sarcoma [edit]

*Main article: Endometrial stromal sarcoma*

In contrast to endometrial carcinomas, the uncommon endometrial stromal sarcomas are cancers that originate in the non-glandular connective tissue of the endometrium. They are generally non-aggressive and, if they recur, can take decades. Metastases to the lungs and pelvic or peritoneal cavities are the most frequent.[16] They typically have estrogen and/or progesterone receptors.[42] The prognosis for low-grade endometrial stromal sarcoma is good, with 60–90% five-year survival. High-grade undifferentiated endometrial sarcoma (HGUS) has a worse prognosis, with high rates of recurrence and 25% five-year survival.[43] HGUS prognosis is dictated by whether or not the cancer has invaded the arteries and veins. Without vascular invasion, the five-year survival is 83%; it drops to 17% when vascular invasion is observed. Stage I ESS has the best prognosis, with five-year survival of 98% and ten-year survival of 89%. ESS makes up 0.2% of uterine cancers.[44]



Endometrioid endometrial adenocarcinoma—very high magnification—H&E stain

## Metastasis [edit]

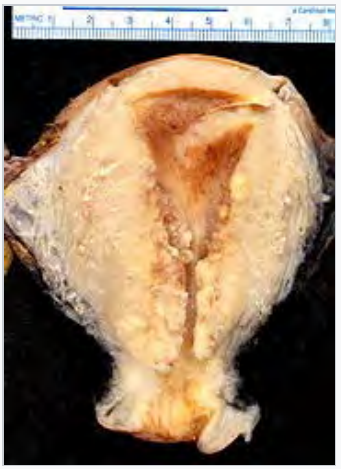
Endometrial cancer frequently metastasizes to the ovaries and Fallopian tubes[25] when the cancer is located in the upper part of the uterus, and the cervix when the cancer is in the lower part of the uterus. The cancer usually first spreads into the myometrium and the serosa, then into other reproductive and pelvic structures. When the lymphatic system is involved, the pelvic and para-aortic nodes are usually first to become involved, but in no specific pattern, unlike cervical cancer. More distant metastases are spread by the blood and often occur in the lungs, as well as the liver, brain, and bone.[45] Endometrial cancer metastasizes to the lungs 20–25% of the time, more than any other gynecologic cancer.[46]

## Histopathology [edit]

There is a three-tiered system for histologically classifying endometrial cancers, ranging from cancers with well-differentiated cells (grade I), to very poorly-differentiated cells (grade III).[19] Grade I cancers are the least aggressive and have the best prognosis, while grade III tumors are the most aggressive and likely to recur. Grade II cancers are intermediate between grades I and III in terms of cell differentiation and aggressiveness of disease.[10]

The histopathology of endometrial cancers is highly diverse. The most common finding is a well-differentiated endometrioid adenocarcinoma,[38] which is composed of numerous, small, crowded glands with varying degrees of nuclear atypia, mitotic activity, and stratification. This often appears on a background of endometrial hyperplasia. Frank adenocarcinoma may be distinguished from atypical hyperplasia by the finding of clear stromal invasion, or "back-to-back" glands which represent nondestructive replacement of the endometrial stroma by the cancer. With progression of the disease, the myometrium is infiltrated.[47]

A stage I, grade I section of an endometrial cancer after hysterectomy



A stage III endometrioid adenocarcinoma that has invaded the myometrium

## Staging [edit]

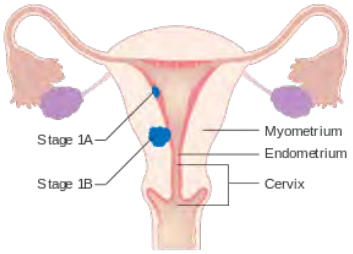
Endometrial carcinoma is surgically staged using the FIGO cancer staging system. The 2009 FIGO staging system is as follows:[48]

| Stage | Description |
|---|---|
| IA | Tumor is confined to the uterus with less than half myometrial invasion |
| IB | Tumor is confined to the uterus with more than half myometrial invasion |
| II | Tumor involves the uterus and the cervical stroma |
| IIIA | Tumor invades serosa or adnexa |
| IIIB | Vaginal and/or parametrial involvement |
| IIIC1 | Pelvic lymph node involvement |

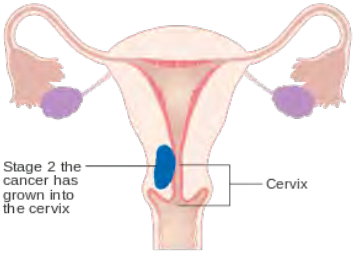
| | |
|---|---|
| IIIC2 | Para-aortic lymph node involvement, with or without pelvic node involvement |
| IVA | Tumor invades bladder mucosa and/or bowel mucosa |
| IVB | Distant metastases including abdominal metastases and/or inguinal lymph nodes |

Metastatic endometrial cancer seen in a removed lung

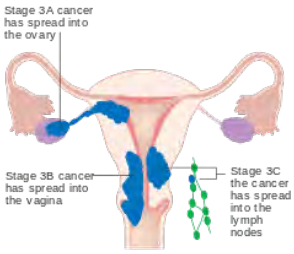
Myometrial invasion and involvement of the pelvic and para-aortic lymph nodes are the most commonly seen patterns of spread.[3] A Stage 0 is sometimes included, in this case it is referred to as "carcinoma in situ".[5] In 26% of presumably early-stage cancers, intraoperative staging revealed pelvic and distant metastases, making comprehensive surgical staging necessary.[22]



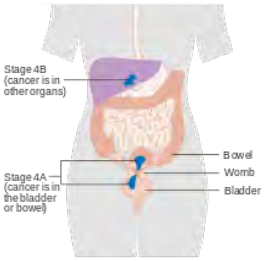

Stage IA and IB endometrial cancer




Stage II endometrial cancer




Stage III endometrial cancer

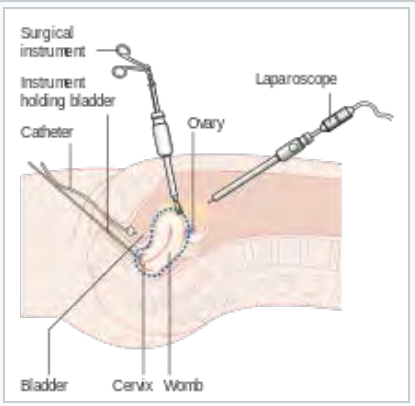



Stage IV endometrial cancer

## Management [edit]

### Surgery [edit]

The primary treatment for endometrial cancer is surgery; 90% of women with endometrial cancer are treated with some form of surgery.[19] Surgical treatment typically consists of hysterectomy including a bilateral salpingo-oophorectomy, which is the removal of the uterus, and both ovaries and Fallopian tubes. Lymphadenectomy, or removal of pelvic and para-aortic lymph nodes, is performed for tumors of histologic grade II or above.[13] Lymphadenectomy is routinely performed for all stages of endometrial cancer in the United States, but in the United Kingdom, the lymph nodes are typically only removed with disease of stage II or greater.[12] The topic of lymphadenectomy and what survival benefit it offers in stage I disease is still being debated.[18] In stage III and IV cancers, cytoreductive surgery is the norm,[13] and a biopsy of the omentum may also be included.[49] In stage IV disease, where there are distant metastases, surgery can be used as part of palliative therapy.[18] Laparotomy, an open-abdomen procedure, is the traditional surgical procedure; however, laparoscopy (keyhole surgery) is associated with lower operative morbidity. The two procedures have no difference in overall survival.[49] Removal of the uterus via the abdomen is recommended over removal of the uterus via the vagina because it gives the opportunity to examine and obtain washings of the abdominal cavity to detect any further evidence of cancer. Staging of the cancer is done during the surgery.[50]




A keyhole hysterectomy, one possible surgery to treat endometrial cancer

The few contraindications to surgery include inoperable tumor, massive obesity, a particularly high-risk operation, or a desire to preserve fertility.[50] These contraindications happen in about 5–10% of cases.[18] Women who wish to preserve their fertility and have low-grade stage I cancer can be treated with progestins, with or without concurrent tamoxifen therapy. This therapy can be continued until the cancer does not respond to treatment or until childbearing is done.[51] Uterine perforation may occur during a D&C or an endometrial biopsy.[52] Side effects of surgery to remove endometrial cancer can specifically include sexual dysfunction, temporary incontinence, and lymphedema, along with more common side effects of any surgery, including constipation.[5]

## Add-on therapy [edit]

There are a number of possible additional therapies. Surgery can be followed by radiation therapy and/or chemotherapy in cases of high-risk or high-grade cancers. This is called adjuvant therapy.[13]

## Chemotherapy [edit]

Adjuvant chemotherapy is a recent innovation, consisting of some combination of paclitaxel (or other taxanes like docetaxel), doxorubicin (and other anthracyclines), and platins (particularly cisplatin and carboplatin). Adjuvant chemotherapy has been found to increase survival in stage III and IV cancer more than added radiotherapy.[13][18][19][53] Mutations in mismatch repair genes, like those found in Lynch syndrome, can lead to resistance against platins, meaning that chemotherapy with platins is ineffective in people with these mutations.[54] Side effects of chemotherapy are common. These include hair loss, low neutrophil levels in the blood, and gastrointestinal problems.[13]

In cases where surgery is not indicated, palliative chemotherapy is an option; higher-dose chemotherapy is associated with longer survival.[13][19][53] Palliative chemotherapy, particularly using capecitabine and gemcitabine, is also often used to treat recurrent endometrial cancer.[53]

## Radiotherapy [edit]

Adjuvant radiotherapy is commonly used in early-stage (stage I or II) endometrial cancer. It can be delivered through vaginal brachytherapy (VBT), which is becoming the preferred route due to its reduced toxicity, or external beam radiotherapy (EBRT). Brachytherapy involves placing a radiation source in the organ affected; in the case of endometrial cancer a radiation source is placed directly in the vagina. External beam radiotherapy involves a beam of radiation aimed at the affected area from outside the body. VBT is used to treat any remaining cancer solely in the vagina, whereas EBRT can be used to treat remaining cancer elsewhere in the pelvis following surgery. However, the benefits of adjuvant radiotherapy are controversial. Though EBRT significantly reduces the rate of relapse in the pelvis, overall survival and metastasis rates are not improved.[3] VBT provides a better quality of life than EBRT.[18]

Radiotherapy can also be used before surgery in certain cases. When pre-operative imaging or clinical evaluation shows tumor invading the cervix, radiation can be given before a total hysterectomy is performed.[11] Brachytherapy and EBRT can also be used, singly or in combination, when there is a contraindication for hysterectomy.[18] Both delivery methods of radiotherapy are associated with side effects, particularly in the gastrointestinal tract.[3]

## Hormonal therapy [edit]

Hormonal therapy is only beneficial in certain types of endometrial cancer. It was once thought to be beneficial in most cases.[3][13] If a tumor is well-differentiated and known to have progesterone and estrogen receptors, progestins may be used in treatment.[53] About 25% of metastatic endometrioid cancers show a response to progestins. Also, endometrial stromal sarcomas can be treated with hormonal agents, including tamoxifen, hydroxyprogesterone caproate, letrozole, megestrol acetate, and medroxyprogesterone.[16] This treatment is effective in endometrial stromal sarcomas because they typically have estrogen and/or progestin receptors. Progestin receptors function as tumor suppressors in endometrial cancer cells.[55] Preliminary research and clinical trials have shown these treatments to have a high rate of response even in metastatic disease.[42]

## Monitoring [edit]

The tumor marker CA-125 is frequently elevated in endometrial cancer and can be used to monitor response to treatment, particularly in serous cell cancer or advanced disease.[25][34][56] Periodic MRIs or CT scans may be recommended in advanced disease and women with a history of endometrial cancer should receive more frequent pelvic examinations for the five years following treatment.[56] Examinations conducted every three to four months are recommended for the first two years following treatment, and every six months for the next three years.[18]

Women with endometrial cancer should not have routine surveillance imaging to monitor the cancer unless new symptoms appear or tumor markers begin rising. Imaging without these indications is discouraged because it is unlikely to detect a recurrence or improve survival, and because it has its own costs and side effects.[57] If a recurrence is suspected, PET/CT scanning is recommended.[18]

# Prognosis [edit]

## Survival rates [edit]

The five-year survival rate for endometrial adenocarcinoma following appropriate treatment is 80%.[59] Most women, over 70%, have FIGO stage I cancer, which has the best prognosis. Stage III and especially Stage IV cancers has a worse prognosis, but these are relatively rare, occurring in only 13% of cases. The median survival time for stage III-IV endometrial cancer is nine to ten months.[60] Older age indicates a worse prognosis.[13] In the United States, white women have a higher survival rate than black women, who tend to develop more aggressive forms of the disease by the time of their diagnosis.[61] Tumors with high progesterone receptor expression have a good prognosis compared to tumors with low progesterone receptor expression; 93% of women with high progesterone receptor disease survived to three years, compared with 36% of women with low progesterone receptor disease.[6] Heart disease is the most common cause of death among those who survive endometrial cancer,[62] with other obesity-related health problems also being common.[63]

**5-year relative survival rates in the US by FIGO stage:**[58]

| Stage | 5-year survival rate |
|---|---|
| I-A | 88% |
| I-B | 75% |
| II | 69% |
| III-A | 58% |
| III-B | 50% |
| III-C | 47% |
| IV-A | 17% |
| IV-B | 15% |

## Recurrence rates [edit]

Recurrence of early stage endometrial cancer ranges from 3 to 17%, depending on primary and adjuvant treatment.[59] Most recurrences (75–80%) occur outside of the pelvis, and most occur two to three years after treatment, 64% after two years and 87% after three years.[46]

Higher-staged cancers are more likely to recur, as are those that have invaded the myometrium or cervix, or that have metastasized into the lymphatic system. Papillary serous carcinoma, clear cell carcinoma, and endometrioid carcinoma are the subtypes at the highest risk of recurrence.[19] High-grade histological subtypes are also at elevated risk for recurrence.[12]

The most common site of recurrence is in the vagina;[3] vaginal relapses of endometrial cancer have the best prognosis. If relapse occurs from a cancer that has not been treated with radiation, EBRT is the first-line treatment and is often successful. If a cancer treated with radiation recurs, pelvic exenteration is the only option for curative treatment. Palliative chemotherapy, cytoreductive surgery, and radiation are also performed.[64] Radiation therapy (VBT and EBRT) for a local vaginal recurrence has a 50% five-year survival rate. Pelvic recurrences are treated with surgery and radiation, and abdominal recurrences are treated with radiation and, if possible, chemotherapy.[18] Other common recurrence sites are the pelvic lymph nodes, para-aortic lymph nodes, peritoneum (28% of recurrences), and lungs, though recurrences can also occur in the brain (<1%), liver (7%), adrenal glands (1%), bones (4–7%; typically the axial skeleton), lymph nodes outside the abdomen (0.4–1%), spleen, and muscle/soft tissue (2–6%).[46]

# Epidemiology [edit]

As of 2014, approximately 320,000 women are diagnosed with endometrial cancer worldwide each year and 76,000 die, making it the sixth most common cancer in women.[4] It is more common in developed countries, where the lifetime risk of endometrial cancer in people born with uteri is 1.6%, compared to 0.6% in developing countries.[13] It occurs in 12.9 out of 100,000 women annually in developed countries.[19]

In the United States, endometrial cancer is the most frequently diagnosed gynecologic cancer and, in women, the fourth most common cancer overall,[9][16] representing 6% of all cancer cases in women.[65] In that country, as of 2014 it was estimated that 52,630 women were diagnosed yearly and 8,590 would die from the disease.[22] Northern Europe, Eastern Europe, and North America have the highest rates of endometrial cancer, whereas Africa and West Asia have the lowest rates. Asia saw 41% of the world's endometrial cancer diagnoses in 2012, whereas Northern Europe, Eastern Europe, and North America together comprised 48% of diagnoses.[4] Unlike most cancers, the number of new cases has risen in recent years, including an increase of over 40% in the United Kingdom between 1993 and 2013.[13] Some of this rise may be due to the increase in obesity rates in developed countries,[19] increasing life expectancies, and lower birth rates.[9] The average lifetime risk for endometrial cancer is approximately 2–3% in people with uteruses.[15] In the UK, approximately 7,400 cases are diagnosed annually, and in the EU,

approximately 88,000.[18]

Endometrial cancer appears most frequently during perimenopause (the period just before, just after, and during menopause), between the ages of 50 and 65;[16] overall, 75% of endometrial cancer occurs after menopause.[3] Women younger than 40 make up 5% of endometrial cancer cases and 10–15% of cases occur in women under 50 years of age. This age group is at risk for developing ovarian cancer at the same time.[16] The worldwide median age of diagnosis is 63 years of age;[18] in the United States, the average age of diagnosis is 60 years of age. White American women are at higher risk for endometrial cancer than black American women, with a 2.88% and 1.69% lifetime risk respectively.[22] Japanese-American women and American Latina women have a lower rates and Native Hawaiian women have higher rates.[24]

## Research [edit]

There are several experimental therapies for endometrial cancer under research, including immunologic, hormonal, and chemotherapeutic treatments. Trastuzumab (Herceptin), an antibody against the Her2 protein, has been used in cancers known to be positive for the Her2/neu oncogene, but research is still underway. Immunologic therapies are also under investigation, particularly in uterine papillary serous carcinoma.[29]

Cancers can be analyzed using genetic techniques (including DNA sequencing and immunohistochemistry) to determine if certain therapies specific to mutated genes can be used to treat it. PARP inhibitors are used to treat endometrial cancer with PTEN mutations,[4] specifically, mutations that lower the expression of PTEN. The PARP inhibitor shown to be active against endometrial cancer is olaparib. Research is ongoing in this area as of the 2010s.[21][66][67]

Research is ongoing on the use of metformin, a diabetes medication, in obese women with endometrial cancer before surgery. Early research has shown it to be effective in slowing the rate of cancer cell proliferation.[17][28] Preliminary research has shown that preoperative metformin administration can reduce expression of tumor markers. Long-term use of metformin has not been shown to have a preventative effect against developing cancer, but may improve overall survival.[17]

Temsirolimus, an mTOR inhibitor, is under investigation as a potential treatment.[18] Research shows that mTOR inhibitors may be particularly effective for cancers with mutations in PTEN.[4] Ridaforolimus (deforolimus) is also being researched as a treatment for people who have previously had chemotherapy. Preliminary research has been promising, and a stage II trial for ridaforolimus was completed by 2013.[18] There has also been research on combined ridaforolimus/progestin treatments for recurrent endometrial cancer.[68] Bevacizumab and tyrosine kinase inhibitors, which inhibit angiogenesis, are being researched as potential treatments for endometrial cancers with high levels of vascular endothelial growth factor.[4] Ixabepilone is being researched as a possible chemotherapy for advanced or recurrent endometrial cancer.[68] Treatments for rare high-grade undifferentiated endometrial sarcoma are being researched, as there is no established standard of care yet for this disease. Chemotherapies being researched include doxorubicin and ifosfamide.[43]

There is also research in progress on more genes and biomarkers that may be linked to endometrial cancer. The protective effect of combined oral contraceptives and the IUD is being investigated. Preliminary research has shown that the levonorgestrel IUD placed for a year, combined with 6 monthly injections of gonadotropin-releasing hormone, can stop or reverse the progress of endometrial cancer in young women.[69] An experimental drug that combines a hormone with doxorubicin is also under investigation for greater efficacy in cancers with hormone receptors. Hormone therapy that is effective in treating breast cancer, including use of aromatase inhibitors, is also being investigated for use in endometrial cancer. One such drug is anastrozole, which is currently being researched in hormone-positive recurrences after chemotherapy.[68] Research into hormonal treatments for endometrial stromal sarcomas is ongoing as well. It includes trials of drugs like mifepristone, a progestin antagonist, and aminoglutethimide and letrozole, two aromatase inhibitors.[42]

Research continues into the best imaging method for detecting and staging endometrial cancer. In surgery, research has shown that complete pelvic lymphadenectomy along with hysterectomy in stage 1 endometrial cancer does not improve survival and increases the risk of negative side effects, including lymphedema. Other research is exploring the potential of identifying the sentinel lymph nodes for biopsy by injecting the tumor with dye that shines under infrared light. Intensity modulated radiation therapy is currently under investigation, and already used in some centers, for application in endometrial cancer, to reduce side effects from traditional radiotherapy. Its risk of recurrence has not yet been quantified. Research on hyperbaric oxygen therapy to reduce side effects is also ongoing. The results of the PORTEC 3 trial assessing combining adjuvant radiotherapy with chemotherapy were awaited in late [68]

2014.

## History and culture [edit]

Endometrial cancer is not widely known by the general populace, despite its frequency. There is low awareness of the symptoms, which can lead to later diagnosis and worse survival.[70]

## References [edit]


1. ^ a b c d "General Information About Endometrial Cancer". National Cancer Institute. 22 April 2014. Retrieved 3 September 2014.
2. ^ "Defining Cancer". National Cancer Institute. Retrieved 10 June 2014.
3. ^ a b c d e f g h i Kong, A; Johnson, N; Kitchener, HC; Lawrie, TA (18 April 2012). "Adjuvant radiotherapy for stage I endometrial cancer.". *The Cochrane database of systematic reviews*. **4**: CD003916. doi:10.1002/14651858.CD003916.pub4. PMID 22513918.
4. ^ a b c d e f g h i j k l m n o p q r s t International Agency for Research on Cancer (2014). *World Cancer Report 2014*. World Health Organization. Chapter 5.12. ISBN 978-92-832-0429-9.
5. ^ a b c d e f g h i "What You Need To Know: Endometrial Cancer". *NCI*. National Cancer Institute. Retrieved 6 August 2014.
6. ^ a b c d "Endometrial Cancer Treatment (PDQ®)". National Cancer Institute. 23 April 2014. Retrieved 3 September 2014.
7. ^ a b c d e f g h i j Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 823. ISBN 978-0-07-171672-7.
8. ^ "SEER Stat Fact Sheets: Endometrial Cancer". National Cancer Institute. Retrieved 18 June 2014.
9. ^ a b c d Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 817. ISBN 978-0-07-171672-7.
10. ^ a b Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 825. ISBN 978-0-07-171672-7.
11. ^ a b c Reynolds, RK; Loar III, PV (2010). "Gynecology". In Doherty, GM. *Current Diagnosis & Treatment: Surgery* (13th ed.). McGraw-Hill. ISBN 978-0-07-163515-8.
12. ^ a b c d e f g h i j k l m Saso, S; Chatterjee, J; Georgiou, E; Ditri, AM; Smith, JR; Ghaem-Maghami, S (2011). "Endometrial cancer". *BMJ*. **343**: d3954–d3954. doi:10.1136/bmj.d3954. PMID 21734165.
13. ^ a b c d e f g h i j k l Galaal, K; Al Moundhri, M; Bryant, A; Lopes, AD; Lawrie, TA (15 May 2014). "Adjuvant chemotherapy for advanced endometrial cancer.". *The Cochrane database of systematic reviews*. **5**: CD010681. doi:10.1002/14651858.CD010681.pub2. PMID 24832785.
14. ^ a b c d e f Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 818. ISBN 978-0-07-171672-7.
15. ^ a b c d e f Ma, J; Ledbetter, N; Glenn, L (2013). "Testing women with endometrial cancer for lynch syndrome: should we test all?". *Journal of the Advanced Practitioner in Oncology*. **4** (5): 322–30. PMC 4093445. PMID 25032011.
16. ^ a b c d e f g h i j k l Soliman, PT; Lu, KH (2013). "Neoplastic Diseases of the Uterus". In Lentz, GM; Lobo, RA; Gershenson, DM; Katz, VL. *Comprehensive Gynecology* (6th ed.). Mosby. ISBN 978-0-323-06986-1.
17. ^ a b c Sivalingam, VN; Myers, J; Nicholas, S; Balen, AH; Crosbie, EJ (2014). "Metformin in reproductive health, pregnancy and gynaecological cancer: established and emerging indications". *Human Reproduction Update*. **20** (6): 853–68. doi:10.1093/humupd/dmu037. PMID 25013215.
18. ^ a b c d e f g h i j k l m n o p q r s t u v Colombo, N; Preti, E; Landoni, F; Carinelli, S; Colombo, A; Marini, C; Sessa, C (October 2013). "Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Annals of Oncology*. 24 Suppl 6: vi33–8. doi:10.1093/annonc/mdt353. PMID 24078661.
19. ^ a b c d e f g h i Vale, CL; Tierney, J; Bull, SJ; Symonds, PR (15 August 2012). "Chemotherapy for advanced, recurrent or metastatic endometrial carcinoma.". *The Cochrane database of systematic reviews*. **8**: CD003915. doi:10.1002/14651858.CD003915.pub4. PMID 22895938.
20. ^ Committee on Health Care for Underserved Women (December 2011). "Health Care for Transgender Individuals: Committee Opinion No. 512". *Obstetrics and Gynecology*. American Committee for Obstetrics and Gynecology. pp. 1454–1458. doi:10.1097/aog.0b013e31823ed1c1. PMID 22105293.
21. ^ a b Reinbolt, RE; Hays, JL (2013). "The Role of PARP Inhibitors in the Treatment of Gynecologic Malignancies". *Frontiers in Oncology*. **3**: 237. doi:10.3389/fonc.2013.00237. PMC 3787651. PMID 24098868.
22. ^ a b c d e Burke WM, Orr J, Leitao M, Salom E, Gehrig P, Olawaiye AB, Brewer M, Boruta D, Villella J, Herzog T, Abu Shahin F (August 2014). "Endometrial cancer: A review and current management strategies: Part I". *Gynecologic Oncology*. **134** (2): 385–392. doi:10.1016/j.ygyno.2014.05.018. PMID 24905773.
23. ^ Staley, H; McCallum, I; Bruce, J (17 October 2012). "Postoperative tamoxifen for ductal carcinoma in situ.". *The Cochrane database of systematic reviews*. **10**: CD007847. doi:10.1002/14651858.CD007847.pub2. PMID 23076938. "There is

evidence from other reports that tamoxifen increases the risk of endometrial cancer although the data presented in this review describes only 10 events occurring in 1798 participants (0.5%) after seven years of follow-up."

24. ^ [a b c d] "Endometrial Cancer Prevention". *PDQ*. NIH. 28 February 2014.
25. ^ [a b c] Coleman, RL; Ramirez, PT; Gershenson, DM (2013). "Neoplastic Diseases of the Ovary". In Lentz, GM; Lobo, RA; Gershenson, DM; Katz, VL. *Comprehensive Gynecology* (6th ed.). Mosby. ISBN 978-0-323-06986-1.
26. ^ Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA (2015). "Sedentary Time and Its Association With Risk for Disease Incidence, Mortality, and Hospitalization in Adults: A Systematic Review and Meta-analysis". *Annals of Internal Medicine*. **162** (2): 123–32. doi:10.7326/M14-1651. PMID 25599350.
27. ^ [a b] Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 819. ISBN 978-0-07-171672-7.
28. ^ [a b c d] Suh, DH; Kim, JW; Kang, S; Kim, HJ; Lee, KH (2014). "Major clinical research advances in gynecologic cancer in 2013". *Journal of Gynecologic Oncology*. **25** (3): 236–248. doi:10.3802/jgo.2014.25.3.236. PMC 4102743. PMID 25045437.
29. ^ [a b c d e f] Thaker, PH; Sood, AK. "Molecular Oncology in Gynecologic Cancer". In Lentz, GM; Lobo, RA; Gershenson, DM; Katz, VL. *Comprehensive Gynecology* (6th ed.). Mosby. ISBN 978-0-323-06986-1.
30. ^ Mani, RS (September 2014). "The emerging role of speckle-type POZ protein (SPOP) in cancer development.". *Drug Discovery Today*. **19** (9): 1498–1502. doi:10.1016/j.drudis.2014.07.009. PMID 25058385. "A recent exome-sequencing study revealed that 8% of serious endometrial cancers and 9% of clear cell endometrial cancers have SPOP mutations"
31. ^ Luo, L; Luo, B; Zheng, Y; Zhang, H; Li, J; Sidell, N (5 June 2013). "Levonorgestrel-releasing intrauterine system for atypical endometrial hyperplasia.". *The Cochrane database of systematic reviews*. **6**: CD009458. doi:10.1002/14651858.CD009458.pub2. PMID 23737032.
32. ^ Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 820. ISBN 978-0-07-171672-7.
33. ^ Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 821. ISBN 978-0-07-171672-7.
34. ^ [a b c d] Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 824. ISBN 978-0-07-171672-7.
35. ^ [a b c d] Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 826. ISBN 978-0-07-171672-7.
36. ^ [a b c d e] Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 827. ISBN 978-0-07-171672-7.
37. ^ [a b] Colombo, N; Preti, E; Landoni, F; Carinelli, S; Colombo, A; Marini, C; Sessa, C (2011). "Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Annals of Oncology*. **22** (Supplement 6): vi35–vi39. doi:10.1093/annonc/mdr374. PMID 21908501.
38. ^ [a b] Johnson, N; Bryant, A; Miles, T; Hogberg, T; Cornes, P (5 October 2011). "Adjuvant chemotherapy for endometrial cancer after hysterectomy.". *The Cochrane database of systematic reviews* (10): CD003175. doi:10.1002/14651858.CD003175.pub2. PMID 21975736.
39. ^ Goodrich, S; Kebria-Moslemi, M; Broshears, J; Sutton, GP; Rose, P (September 2013). "Primary squamous cell carcinoma of the endometrium: two cases and a review of the literature". *Diagnostic Cytopathology*. **41** (9): 817–20. doi:10.1002/dc.22814. PMID 22241749.
40. ^ Mariño-Enríquez, A; González-Rocha, T; Burgos, E (November 2008). et al.. "Transitional cell carcinoma of the endometrium and endometrial carcinoma with transitional cell differentiation: a clinicopathologic study of 5 cases and review of the literature". *Human Pathology*. **39** (11): 1606–13. doi:10.1016/j.humpath.2008.03.005. PMID 18620731.
41. ^ Ahluwalia, M; Light, AM; Surampudi, K; Finn, CB (October 2006). "Transitional cell carcinoma of the endometrium: a case report and review of the literature". *International Journal of Gynecological Pathology*. **25** (4): 378–82. doi:10.1097/01.pgp.0000215296.53361.4b. PMID 16990716.
42. ^ [a b c] Sylvestre, VT; Dunton, CJ (April 2010). "Treatment of recurrent endometrial stromal sarcoma with letrozole: a case report and literature review". *Hormones and Cancer*. **1** (2): 112–5. doi:10.1007/s12672-010-0007-9. PMID 21761354.
43. ^ [a b] Hensley ML (2012). "Uterine sarcomas: histology and its implications on therapy". *American Society of Clinical Oncology educational book*: 356–61. doi:10.14694/EdBook_AM.2012.32.356. PMID 24451763.
44. ^ D'Angelo, E; Prat, J (January 2010). "Uterine sarcomas: a review". *Gynecologic Oncology*. **116** (1): 131–9. doi:10.1016/j.ygyno.2009.09.023. PMID 19853898.
45. ^ Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 828. ISBN 978-0-07-171672-7.
46. ^ [a b c] Kurra, V; Krajewski, KM; Jagannathan, J; Giardino, A; Berlin, S; Ramaiya, N (2013). "Typical and atypical metastatic sites of recurrent endometrial carcinoma". *Cancer Imaging*. **13**: 113–22. doi:10.1102/1470-7330.2013.0011. PMC 3613792. PMID 23545091.
47. ^ Weidner, N; Coté, R; Suster, S; Weiss, L, eds. (2002). *Modern Surgical Pathology (2 Volume Set)*. WB Saunders. ISBN 978-0-7216-7253-3.
48. ^ "Stage Information for Endometrial Cancer". National Cancer Institute. Retrieved 23 April 2014.
49. ^ [a b] Galaal, K; Bryant, A; Fisher, AD; Al-Khaduri, M; Kew, F; Lopes, AD (12 September 2012). "Laparoscopy versus laparotomy

for the management of early stage endometrial cancer.". *The Cochrane database of systematic reviews*. **9**: CD006655. doi:10.1002/14651858.CD006655.pub2. PMID 22972096.

50. ^ a b Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 829. ISBN 978-0-07-171672-7.
51. ^ Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 833. ISBN 978-0-07-171672-7.
52. ^ McGee, J; Covens, A (2013). "Gestational Trophoblastic Disease". In Lentz, GM; Lobo, RA; Gershenson, DM; Katz, VL. *Comprehensive Gynecology* (6th ed.). Mosby. ISBN 978-0-323-06986-1.
53. ^ a b c d Smith, JA; Jhingran, A (2013). "Principles of Radiation Therapy and Chemotherapy in Gynecologic Cancer". In Lentz, GM; Lobo, RA; Gershenson, DM; Katz, VL. *Comprehensive Gynecology* (6th ed.). Mosby. ISBN 978-0-323-06986-1.
54. ^ Guillotin, D; Martin, SA (2014). "Exploiting DNA mismatch repair deficiency as a therapeutic strategy". *Experimental Cell Research*. **329**: 110–115. doi:10.1016/j.yexcr.2014.07.004. PMID 25017099.
55. ^ Patel, B.; Elguero, S.; Thakore, S.; Dahoud, W.; Bedaiwy, M.; Mesiano, S. (2014). "Role of nuclear progesterone receptor isoforms in uterine pathophysiology". *Human Reproduction Update*. **21** (2): 155–173. doi:10.1093/humupd/dmu056. ISSN 1355-4786. PMC 4366574. PMID 25406186.
56. ^ a b Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 831. ISBN 978-0-07-171672-7.
57. ^ "Five Things Physicians and Patients Should Question". *Choosing Wisely*. Society of Gynecologic Oncology. 31 October 2013. Retrieved 27 July 2014.
58. ^ "Survival by stage of endometrial cancer". American Cancer Society. 2 March 2014. Retrieved 10 June 2014.
59. ^ a b Nicolaije, KA; Ezendam, NP; Vos, MC; Boll, D; Pijnenborg, JM; Kruitwagen, RF; Lybeert, ML; van de Poll-Franse, LV (2013). "Follow-up practice in endometrial cancer and the association with patient and hospital characteristics: A study from the population-based PROFILES registry". *Gynecologic Oncology*. **129** (2): 324–331. doi:10.1016/j.ygyno.2013.02.018. PMID 23435365.
60. ^ Ang, C; Bryant, A; Barton, DP; Pomel, C; Naik, R (4 February 2014). "Exenterative surgery for recurrent gynaecological malignancies.". *The Cochrane database of systematic reviews*. **2**: CD010449. doi:10.1002/14651858.CD010449.pub2. PMID 24497188.
61. ^ Soliman, PT; Lu, KH (2013). "Neoplastic Diseases of the Uterus". In Lentz, GM; Lobo, RA; Gershenson, DM; Katz, VL. *Comprehensive Gynecology* (6th ed.). Mosby. ISBN 978-0-323-06986-1.
62. ^ Ward, KK; Shah, NR; Saenz, CC; McHale, MT; Alvarez, EA; Plaxe, SC (August 2012). "Cardiovascular disease is the leading cause of death among endometrial cancer patients.". *Gynecologic Oncology*. **126** (2): 176–9. doi:10.1016/j.ygyno.2012.04.013. PMID 22507532.
63. ^ Fader, AN; Arriba, LN; Frasure, HE; von Gruenigen, VE (July 2009). "Endometrial cancer and obesity: epidemiology, biomarkers, prevention and survivorship.". *Gynecologic Oncology*. **114** (1): 121–7. doi:10.1016/j.ygyno.2009.03.039. PMID 19406460.
64. ^ Hoffman, BL; Schorge, JO; Schaffer, JI; Halvorson, LM; Bradshaw, KD; Cunningham, FG, eds. (2012). "Endometrial Cancer". *Williams Gynecology* (2nd ed.). McGraw-Hill. p. 834. ISBN 978-0-07-171672-7.
65. ^ "General Information about Endometrial Cancer". *Endometrial Cancer Treatment (PDQ)*. NIH. 23 April 2014.
66. ^ Lee, JM; Ledermann, JA; Kohn, EC (January 2014). "PARP Inhibitors for BRCA1/2 mutation-associated and BRCA-like malignancies". *Annals of Oncology*. **25** (1): 32–40. doi:10.1093/annonc/mdt384. PMID 24225019.
67. ^ Banerjee, S; Kaye, S (December 2011). "PARP inhibitors in BRCA gene-mutated ovarian cancer and beyond". *Current Oncology Reports*. **13** (6): 442–9. doi:10.1007/s11912-011-0193-9. PMID 21913063.
68. ^ a b c d "Womb cancer research". *CancerHelp UK*. Cancer Research UK. Retrieved 31 August 2014.
69. ^ Minig, L; Franchi, D; Boveri, S; Casadio, C; Bocciolone, L; Sideri, M (March 2011). "Progestin intrauterine device and GnRH analogue for uterus-sparing treatment of endometrial precancers and well-differentiated early endometrial carcinoma in young women.". *Annals of Oncology*. **22** (3): 643–9. doi:10.1093/annonc/mdq463. PMID 20876910.
70. ^ Carlisle, Daloni (21 September 2014). "Womb cancer: the most common diagnosis you've never heard of". The Guardian. Retrieved 29 September 2014.

## External links [edit]

- American Cancer Society's Detailed Guide: Endometrial Cancer
- U.S. National Cancer Institute: Endometrial cancer
- Anatomical pathology images

Wikimedia Commons has media related to *Endometrial cancer*.

| v · t · e | **Tumors: female urogenital neoplasia (C51–C58/D25–D28, 179–184/218–221)** | | | |
|---|---|---|---|---|
| | | **Glandular and epithelial/ surface epithelial-** | **CMS:** | Ovarian serous cystadenoma · Mucinous cystadenoma · Cystadenocarcinoma (Papillary serous cystadenocarcinoma · · Krukenberg tumor · |

| | | | |
|---|---|---|---|
| **Adnexa** | **Ovaries** | **stromal tumor** | Endometrioid tumor · Clear-cell ovarian carcinoma · Brenner tumour · |
| | | **Sex cord-gonadal stromal** | Leydig cell tumour · Sertoli cell tumour · Sertoli-Leydig cell tumour · Thecoma · Granulosa cell tumour · Luteoma · Sex cord tumour with annular tubules · Steroid cell tumor (NOS) · |
| | | **Germ cell** | Dysgerminoma · Nongerminomatous (Embryonal carcinoma · Endodermal sinus tumor · Gonadoblastoma · Teratoma/Struma ovarii · Choriocarcinoma · · |
| | | **Fibroma** | Meigs syndrome · |
| | **Fallopian tube** | Adenomatoid tumor · | |
| **Uterus** | **Myometrium** | Uterine fibroids/leiomyoma · Leiomyosarcoma · Adenomyoma · | |
| | **Endometrium** | Endometrioid tumor · Uterine papillary serous carcinoma · Clear cell carcinoma · Endometrial intraepithelial neoplasia · | |
| | **Cervix** | Cervical intraepithelial neoplasia · SCC · Glassy cell carcinoma · Villoglandular adenocarcinoma · | |
| | **Placenta** | Choriocarcinoma · Gestational trophoblastic disease · | |
| | **General** | Uterine sarcoma · Mixed Müllerian tumor · | |
| **Vagina** | SCC · Botryoid rhabdomyosarcoma · Clear cell adenocarcinoma of the vagina · Vaginal intraepithelial neoplasia · | | |
| **Vulva** | SCC · Melanoma · Papillary hidradenoma · Extramammary Paget's disease · Vulvar intraepithelial neoplasia · Bartholin gland carcinoma · | | |

| v · t · e · | **Women's health** | | |
|---|---|---|---|
| **Reproductive &Sexual health** | **Reproductive health** | **Reproductive tract** | External female genitalia (Clitoris (Clitoral hood · · Labia minora · Labia majora · · Vagina · Cervix · Uterus · Fallopian tube · Ovary · Reproductive system disease · |
| | | **Maternal health** | Pregnancy (Unintended pregnancy · Gravidity and parity · Obstetrics · Antenatal care · Adolescent pregnancy · Complications of pregnancy (Hyperemesis gravidarum · Ectopic pregnancy · Miscarriage · Obstetrical bleeding · Gestational diabetes · Hypertension (Preeclampsia · Eclampsia · · · · Childbirth (Midwifery · Preterm birth · Multiple births · Oxytocin · Obstructed labor · Cesarian section · Retained placenta · Obstetrical fistulae (Vesicovaginal fistula · Rectovaginal fistula · · Postpartum care · · Maternal deaths · Perinatal mortality · Stillbirths · Abortion · Mother-to-child transmission · Sterilization (Compulsory sterilization · · |
| | | **Reproductive life plan** | Infertility (Childlessness · Assisted reproductive technology · |

| | | | |
|---|---|---|---|
| | | | In vitro fertilization · · Parenting (Adoption · Fostering · · |
| | | **Contraception & Family planning** | Unsafe sex · Intrauterine devices · Oral contraceptives · Condoms · Contraceptive prevalence · Contraceptive security · Planned parenthood · |
| | | **Menstruation** | Menarche · Menstrual cycle · Menstrual aids (Tampons · Sanitary pads · · Dysmenorrhea · Menorrhagia · Amenorrhoea · Menopause (Hormone replacement therapy · · |
| | **Sexual health** | **Sexually transmitted infections** | HIV · Human papilloma virus (HPV vaccine · · Pelvic inflammatory disease · |
| | | | Female genital cutting (Clitoridectomy · Infibulation · · Child marriage · Forced marriage · Polygamy · Sexual intercourse · Orgasm · Dyspareunia · |
| | **Other** | | Sex differences · Sex education · Puberty · Breast health · Gynaecological disorders (Vaginitis · · |
| **Non-reproductive health** | **Violence against women** | | Domestic violence · Intimate partner violence · Misogyny · Sexual harassment · Sexual assault (Rape · · Femicide · Gender discrimination · |
| | **Non-communicable diseases** | **Cancer** | Lung cancer · Breast cancer · Uterine cancer (**Endometrial cancer** · Cervical cancer (Papanicolaou test · · · Ovarian cancer · |
| | | | Cardiovascular disease · Dementia (Alzheimer's disease · · Bone health (Osteoporosis (Hip fracture · · · Anaemia · |
| | | | Mental health (Anxiety · Depression (Major depressive disorder · · · Urinary tract (Urethra · Urinary tract infection · Urinary incontinence · · |
| **Sociocultural factors** | | | Poverty · Disadvantaged · Gender equality · Healthcare inequality · Gender disparities in health · Social determinants of health · Reproductive justice · Women's empowerment · |
| **Politics, Research & Advocacy** | **United Nations** | | The Convention on the Elimination of All Forms of Discrimination against Women · Declaration on the elimination of violence against women · International Day of the Girl Child · Commission on the Status of Women · UN Women · |
| | **United States** | | Office of Research on Women's Health · Women's Health Initiative · |
| | | | International Center for Research on Women · Nurses' Health Study · Black Women's Health Study · Cartwright Inquiry · Society for Women's Health Research · |
| **Women's health by country** | | | Women's health in China · Women's health in Ethiopia · Women's health in India (Family planning · · Birth control in the United States · |
| **Category · Commons · Portal · WikiProject ·** | | | |

Categories: Women's health | Gynaecological cancer

# Esophageal cancer

From Wikipedia, the free encyclopedia

**Esophageal cancer** is cancer arising from the esophagus—the food pipe that runs between the throat and the stomach.[1] Symptoms often include difficulty in swallowing and weight loss. Other symptoms may include pain when swallowing, a hoarse voice, enlarged lymph nodes ("glands") around the collarbone, a dry cough, and possibly coughing up or vomiting blood.[2]

The two main sub-types of the disease are esophageal squamous-cell carcinoma (often abbreviated to ESCC),[3] which is more common in the developing world, and esophageal adenocarcinoma (EAC), which is more common in the developed world.[1] A number of less common types also occur.[1] Squamous-cell carcinoma arises from the epithelial cells that line the esophagus.[4] Adenocarcinoma arises from glandular cells present in the lower third of the esophagus, often where they have already transformed to intestinal cell type (a condition known as Barrett's esophagus).[1][5] Causes of the squamous-cell type include tobacco, alcohol, very hot drinks, poor diet, and chewing betel nut.[6][7] The most common causes of the adenocarcinoma type are smoking tobacco, obesity, and acid reflux.[6]

The disease is diagnosed by biopsy done by an endoscope (a fiberoptic camera).[8] Prevention includes stopping smoking and eating a healthy diet.[1][2] Treatment is based on the cancer's stage and location, together with the person's general condition and individual preferences. Small localized squamous-cell cancers may be treated with surgery alone with the hope of a cure. In most other cases, chemotherapy with or without radiation therapy is used along with surgery.[8] Larger tumors may have their growth slowed with chemotherapy and radiation therapy.[1] In the presence of extensive disease or if the affected person is not fit enough to undergo surgery, palliative care is often recommended.[8]

As of 2012, esophageal cancer is the eighth-most common cancer globally with 456,000 new cases during the year.[1] It caused about 400,000 deaths that year, up from 345,000 in 1990.[1][9] Rates vary widely among countries, with about half of all cases occurring in China. It is around three times more common in men than in women.[1] Outcomes are related to the extent of the disease and other medical conditions, but generally tend to be fairly poor, as diagnosis is often late.[1][10] Five-year survival rates are around 13% to 18%.[2][11]

**Esophageal cancer**

**Synonyms** Oesophageal cancer

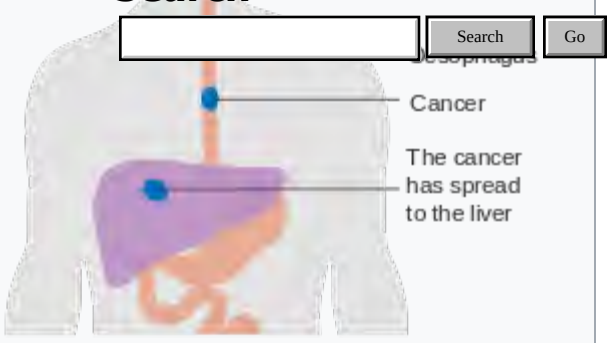



Diagram showing esophageal cancer in an advanced stage with spread to the liver

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Oncology, general surgery |
| **ICD-10** | C15 |
| **ICD-9-CM** | 150 |
| **OMIM** | 133239 |
| **DiseasesDB** | 9150 |
| **MedlinePlus** | 000283 |
| **eMedicine** | article/277930 article/368206 |
| **MeSH** | D004938 |

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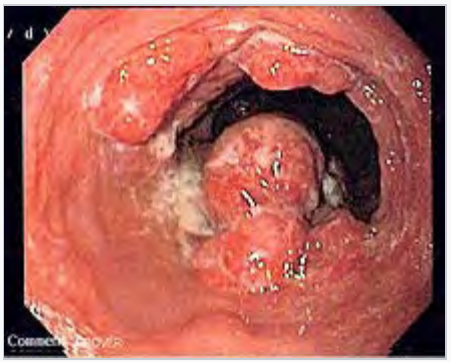
Contents

## Signs and symptoms [edit]



Endoscopic image of an esophageal adenocarcinoma

Prominent symptoms usually do not appear until the cancer has infiltrated over 60% of the circumference of the esophageal tube, by which time the tumor is already in an advanced stage.[12] Onset of symptoms is usually caused by narrowing of the tube due to the physical presence of the tumor.[13]

The first and the most common symptom is usually difficulty in swallowing, which is often experienced first with solid foods and later with softer foods and liquids.[2] Pain when swallowing is less usual at first.[2] Weight loss is often an initial symptom in cases of squamous-cell carcinoma, though not usually in cases of adenocarcinoma.[14] Eventual weight loss due to reduced appetite and undernutrition is common.[15] Pain behind the breastbone or in the region around the stomach often feels like heartburn. The pain can frequently be severe, worsening when food of any sort is swallowed. Another sign may be an unusually husky, raspy, or hoarse-sounding cough, a result of the tumor affecting the recurrent laryngeal nerve.

The presence of the tumor may disrupt the normal contractions of the esophagus when swallowing. This can lead to nausea and vomiting, regurgitation of food and coughing.[12] There is also an increased risk of aspiration pneumonia[12] due to food entering the airways through the abnormal connections (fistulas) that may develop between the esophagus and the trachea (windpipe).[10] Early signs of this serious complication may be coughing on drinking or eating.[16] The tumor surface may be fragile and bleed, causing vomiting of blood. Compression of local structures occurs in advanced disease, leading to such problems as upper airway obstruction and superior vena cava syndrome. Hypercalcemia (excess calcium in the blood) may occur.[12]

If the cancer has spread elsewhere, symptoms related to metastatic disease may appear. Common sites of spread include nearby lymph nodes, the liver, lungs and bone.[12] Liver metastasis can cause jaundice and abdominal swelling (ascites). Lung metastasis can cause, among other symptoms, impaired breathing due to excess fluid around the lungs (pleural effusion), and dyspnea (the feelings often associated with impaired breathing).

## Causes [edit]

The two main types (i.e. squamous-cell carcinoma and adenocarcinoma) have distinct sets of risk factors.[14] Squamous-cell carcinoma is linked to lifestyle factors such as smoking and alcohol.[17] Adenocarcinoma has been linked to effects of long-term acid reflux.[17] Tobacco is a risk factor for both types.[14] Both types are more common in men and in the over-60s.[18]

### Squamous-cell carcinoma [edit]

The two major risk factors for esophageal squamous-cell carcinoma are tobacco (smoking or chewing) and alcohol.[1] The combination of tobacco and alcohol has a strong synergistic effect.[19] Some data suggest that about half of all cases are due to tobacco and about one-third to alcohol, while over three-quarters of the cases in men are due to the combination of smoking and heavy drinking.[1] Risks associated with alcohol appear to be linked to its aldehyde metabolite and to mutations in certain related enzymes.[14] Such metabolic variants are relatively common in Asia.[1]

Other relevant risk factors include regular consumption of very hot drinks (over 65 °C)[20][21] and ingestion of caustic substances.[1] High levels of dietary exposure to nitrosamines (chemical compounds found both in tobacco smoke and certain foodstuffs) also appear to be a relevant risk factor.[14] Unfavorable dietary patterns seem to involve exposure to nitrosamines through processed and barbecued meats, pickled vegetables, etc., and a low intake of fresh foods.[1] Other associated factors include nutritional deficiencies, low socioeconomic status, and poor oral hygiene.[14] Chewing betel nut (areca) is an important risk factor in Asia.[7]

Physical trauma may increase the risk.[22] This may include the drinking of very hot drinks.[6]

### Adenocarcinoma [edit]

Male predominance is particularly strong in this type of esophageal cancer, which occurs about 7 to 10 times more frequently in men.[23] This imbalance may be related to the characteristics and interactions of other known risk factors, including acid reflux and obesity.[23]

The long-term erosive effects of acid reflux (an extremely common condition, also known as gastroesophageal reflux disease or GERD) have been strongly linked to this type of cancer.[24] Longstanding GERD can induce a change of cell type in the lower portion of the esophagus in response to erosion of its squamous lining.[24] This phenomenon, known as Barrett's esophagus, seems to appear about 20 years later in women than in men, maybe due to hormonal factors.[24] Having symptomatic GERD or bile reflux makes Barrett's esophagus more likely, which in turn raises the risk of further changes that can ultimately lead to adenocarcinoma.[14] The risk of developing adenocarcinoma in the presence of Barrett's esophagus is unclear, and may in the past have been overestimated.[1]

Being obese or overweight both appear to be associated with increased risk.[25] The association with obesity seems to be the strongest of any type of obesity-related cancer, though the reasons for this remain unclear.[26] Abdominal obesity seems to be of particular relevance, given the closeness of its association with this type of cancer, as well as with both GERD and Barrett's esophagus.[26] This type of obesity is characteristic of men.[26] Physiologically, it stimulates GERD and also has other chronic inflammatory effects.[24]

*Helicobacter pylori* infection (a common occurrence thought to have affected over half of the world's population) is not a risk factor for esophageal adnocarcinoma and actually appears to be protective. Despite being a cause of GERD and a risk factor for gastric cancer, the infection seems to be associated with a reduced risk of esophageal adenocarcinoma of as much as 50%.[27][28] The biological explanation for a protective effect is somewhat unclear.[28] One explanation is that some strains of *H. pylori* reduce stomach acid, thereby reducing damage by GERD.[29] Decreasing rates of *H. pylori* infection in Western populations over recent decades, which have been linked to better hygiene and increased refrigeration of food, could be a factor in the concurrent increase in esophageal adenocarcinoma.[27]

Female hormones may also have a protective effect, as EAC is not only much less common in women but develops later in life, by an average of 20 years. Although studies of many reproductive factors have not produced a clear picture, risk seems to decline for the mother in line with prolonged periods of breastfeeding.[27]

Tobacco smoking increases risk, but the effect in esophageal adenocarcinoma is slight compared to that in squamous cell carcinoma, and alcohol has not been demonstrated to be a cause.[27]

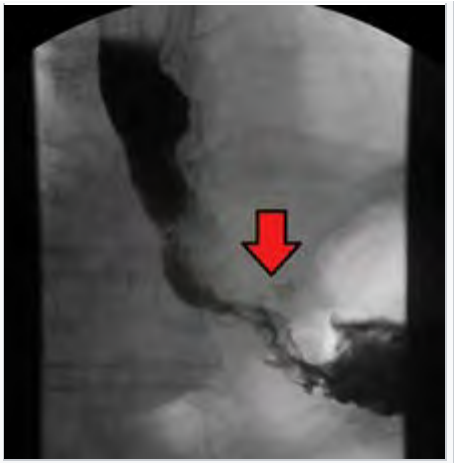
### Related conditions [edit]

- Head and neck cancer is associated with second primary tumors in the region, including esophageal squamous-cell carcinomas, due to field cancerization (i.e. a regional reaction to long-term carcinogenic exposure).[30][31]
- History of radiation therapy for other conditions in the chest is a risk factor for esophageal adenocarcinoma.[14]
- Corrosive injury to the esophagus by accidentally or intentionally swallowing caustic substances is a risk factor for squamous cell carcinoma.[1]
- Tylosis with esophageal cancer is a rare familial disease that has been linked to a mutation in the *RHBDF2* gene: it involves thickening of the skin of the palms and soles and a high lifetime risk of squamous cell carcinoma.[1][32]
- Achalasia (i.e. lack of the involuntary reflex in the esophagus after swallowing) appears to be a risk factor for both main types of esophageal cancer, at least in men, due to stagnation of trapped food and drink.[33]
- Plummer–Vinson syndrome (a rare disease that involves esophageal webs) is also a risk factor.[1]
- There is some evidence suggesting a possible causal association between human papillomavirus (HPV) and esophageal squamous-cell carcinoma.[34] The relationship is unclear.[35] Possible relevance of HPV could be greater in places that have a particularly high incidence of this form of the disease,[36] as in some Asian countries, including China.[37]
- There is an association between celiac disease and esophageal cancer. People with untreated celiac disease have a higher risk, but this risk decreases with time after diagnosis, probably due to the adoption of a gluten-free diet, which seems to have a protective role against development of malignancy in people with celiac disease. However, the delay in diagnosis and initiation of a gluten-free diet seems to increase the risk of malignancy. Moreover, in some cases the detection of celiac disease is due to the development of cancer, whose early symptoms are similar to some that may appear in celiac disease.[38]

## Diagnosis [edit]

### Clinical evaluation [edit]

Although an occlusive tumor may be suspected on a barium swallow or barium meal, the diagnosis is best made with an examination using an endoscope. This involves the passing of a flexible tube with a light and camera down the esophagus and examining the wall, and is called an esophagogastroduodenoscopy. Biopsies taken of suspicious lesions are

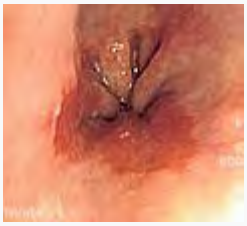


Esophageal cancer as shown by a filling defect during an upper GI series

then examined histologically for signs of malignancy.

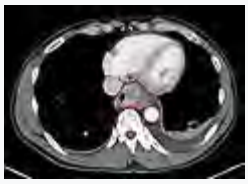
Additional testing is needed to assess how much the cancer has spread (see #Staging, below). Computed tomography (CT) of the chest, abdomen and pelvis can evaluate whether the cancer has spread to adjacent tissues or distant organs (especially liver and lymph nodes). The sensitivity of a CT scan is limited by its ability to detect masses (e.g. enlarged lymph nodes or involved organs) generally larger than 1 cm. Positron emission tomography is also used to estimate the extent of the disease and is regarded as more precise than CT alone. Esophageal endoscopic ultrasound can provide staging information regarding the level of tumor invasion, and possible spread to regional lymph nodes.

The location of the tumor is generally measured by the distance from the teeth. The esophagus (25 cm or 10 in long) is commonly divided into three parts for purposes of determining the location. Adenocarcinomas tend to occur nearer the stomach and squamous cell carcinomas nearer the throat, but either may arise anywhere in the esophagus.

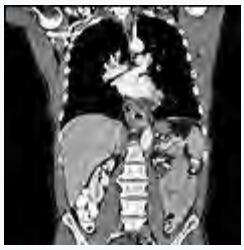


Endoscopic image of Barrett esophagus – a frequent precursor of esophageal adenocarcinoma

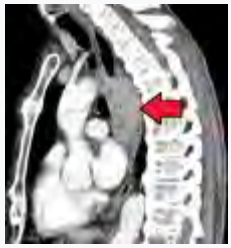
Endoscopy and radial endoscopic ultrasound images of a submucosal tumor in the central portion of the esophagus



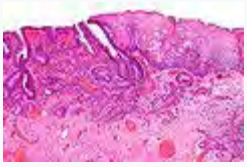
Contrast CT scan showing an esophageal tumor (axial view)



Contrast CT scan showing an esophageal tumor (coronal view)



Esophageal cancer



Micrograph showing histopathological appearance of an esophageal adenocarcinoma (dark blue – upper-left of image) and normal squamous

epithelium (upper-right of image) at H&E staining

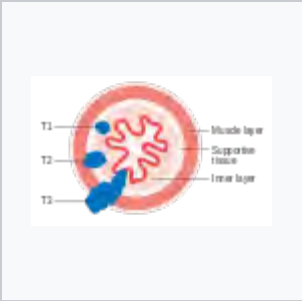
## Types [edit]

Esophageal cancers are typically carcinomas that arise from the epithelium, or surface lining, of the esophagus. Most esophageal cancers fall into one of two classes: esophageal squamous-cell carcinomas (ESCC), which are similar to head and neck cancer in their appearance and association with tobacco and alcohol consumption—and esophageal adenocarcinomas (EAC), which are often associated with a history of GERD and Barrett's esophagus. A rule of thumb is that a cancer in the upper two-thirds is likely to be ESCC and one in the lower one-third EAC.

Rare histologic types of esophageal cancer include different variants of squamous-cell carcinoma, and non-epithelial tumors, such as leiomyosarcoma, malignant melanoma, rhabdomyosarcoma and lymphoma, among others.[39][40]

## Staging [edit]

Staging is based on the TNM staging system, which classifies the amount of tumor invasion (T), involvement of lymph nodes (N), and distant metastasis (M).[14] The currently preferred classification is the 2010 AJCC staging system for cancer of the esophagus and the esophagogastric junction.[14] To help guide clinical decision making, this system also incorporates information on cell type (ESCC, EAC, etc.), grade (degree of differentiation – an indication of the biological aggressiveness of the cancer cells), and tumor location (upper, middle, lower, or junctional[41]).[42]




T1, T2, and T3 stages of esophageal cancer


Stage T4 esophageal cancer


Esophageal cancer with spread to lymph nodes

# Prevention [edit]

Prevention includes stopping smoking or chewing tobacco.[1] Overcoming addiction to areca chewing in Asia is another promising strategy for the prevention of esophageal squamous-cell carcinoma.[7] The risk can also be reduced by maintaining a normal body weight.[43]

According to the National Cancer Institute, "diets high in cruciferous (cabbage, broccoli/broccolini, cauliflower, Brussels sprouts) and green and yellow vegetables and fruits are associated with a decreased risk of esophageal cancer."[44] Dietary fiber is thought to be protective, especially against esophageal adenocarcinoma.[45] There is no evidence that vitamin supplements change the risk.[2]

## Screening [edit]

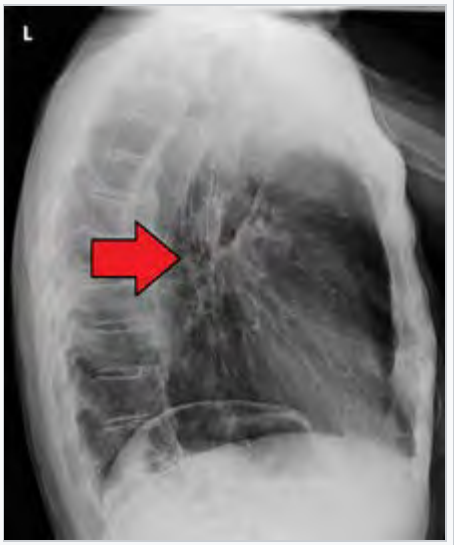
People with Barrett esophagus (a change in the cells lining the lower esophagus) are at much higher risk,[46] and may receive regular endoscopic screening for the early signs of cancer.[47] Because the benefit of screening for adenocarcinoma in people without symptoms is unclear,[1] it is not recommended in the

United States.[2] Some areas of the world with high rates of squamous-carcinoma have screening programs.[1]

## Management [edit]

Treatment is best managed by a multidisciplinary team covering the various specialties involved.[48][49] Adequate nutrition must be assured, and appropriate dental care is essential. Factors that influence treatment decisions include the stage and cellular type of cancer (EAC, ESCC, and other types), along with the person's general condition and any other diseases that are present.[14]

In general, treatment with a curative intention is restricted to localized disease, without distant metastasis: in such cases a combined approach that includes surgery may be considered. Disease that is widespread, metastatic or recurrent is managed palliatively: in this case, chemotherapy may be used to lengthen survival, while treatments such as radiotherapy or stenting may be used to relieve symptoms and make it easier to swallow.[14]



Esophageal stent for esophageal cancer


Esophageal stent for esophageal cancer

### Surgery [edit]

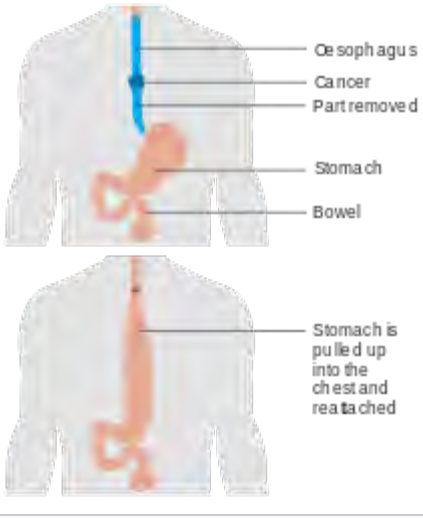
*Further information: Esophagectomy*

If the cancer has been diagnosed while still in an early stage, surgical treatment with a curative intention may be possible. Some small tumors that only involve the mucosa or lining of the esophagus may be removed by endoscopic mucosal resection (EMR).[50][51] Otherwise, curative surgery of early-stage lesions may entail removal of all or part of the esophagus (esophagectomy), although this is a difficult operation with a relatively high risk of mortality or post-operative difficulties. The benefits of surgery are less clear in early-stage ESCC than EAC. There are a number of surgical options, and the best choices for particular situations remain the subject of research and discussion.[48][52][53] As well as characteristics and location of the tumor, other factors include the patient's condition, and the type of operation the surgical team is most experienced with.

The likely quality of life after treatment is a relevant factor when considering surgery.[54] Surgical outcomes are likely better in large centers where the procedures are frequently performed.[52] If the cancer has spread to other parts of the body, esophagectomy is nowadays not normally performed.[52][55]

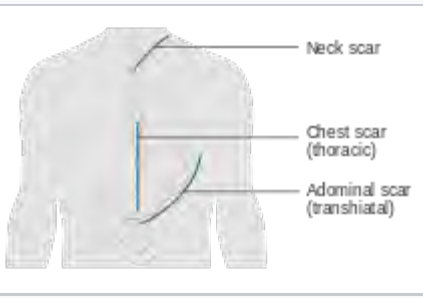
Esophagectomy is the removal of a segment of the esophagus; as this shortens the length of the remaining esophagus, some other segment of the digestive tract is pulled up through the chest cavity and interposed. This is usually the stomach or part of the large intestine (colon) or jejunum. Reconnection of the stomach to a shortened esophagus is called an esophagogastric anastomosis.[52]

Esophagectomy can be performed using several methods. The choice of the surgical approach depends on the characteristics and location of the tumor, and the preference of the surgeon. Clear evidence from clinical trials for which approaches give the best outcomes in different circumstances is lacking.[52] A first decision, regarding the point of




Before and after a total esophagectomy

entry, is between a transhiatial and a transthoracic procedure. The more recent transhiatial approach avoids the need to open the chest; instead the surgeon enters the body through an incision in the lower abdomen and another in the neck. The lower part of the esophagus is freed from the surrounding tissues and cut away as necessary. The stomach is then pushed through the esophageal hiatus (the hole where the esophagus passes through the diaphragm) and is joined to the remaining upper part of the esophagus at the neck.[52]




Typical scar lines after the two main methods of surgery

The traditional transthoracic approach enters the body through the chest, and has a number of variations. The thoracoabdominal approach opens the abdominal and thoracic cavities together, the two-stage Ivor Lewis (also called Lewis–Tanner) approach involves an initial laparotomy and construction of a gastric tube, followed by a right thoracotomy to excise the tumor and create an esophagogastric anastomosis. The three-stage McKeown approach adds a third incision in the neck to complete the cervical anastomosis. Recent approaches by some surgeons use what is called extended esophagectomy, where more surrounding tissue, including lymph nodes, is removed *en bloc*.[52]

If the person cannot swallow at all, an esophageal stent may be inserted to keep the esophagus open; stents may also assist in occluding fistulas. A nasogastric tube may be necessary to continue feeding while treatment for the tumor is given, and some patients require a gastrostomy (feeding hole in the skin that gives direct access to the stomach). The latter two are especially important if the patient tends to aspirate food or saliva into the airways, predisposing for aspiration pneumonia.

## Chemotherapy and radiotherapy [edit]

Chemotherapy depends on the tumor type, but tends to be cisplatin-based (or carboplatin or oxaliplatin) every three weeks with fluorouracil (5-FU) either continuously or every three weeks. In more recent studies, addition of epirubicin was better[*clarification needed*] than other comparable regimens in advanced nonresectable cancer.[56][*medical citation needed*] Chemotherapy may be given after surgery (adjuvant, i.e. to reduce risk of recurrence), before surgery (neoadjuvant) or if surgery is not possible; in this case, cisplatin and 5-FU are used. Ongoing trials compare various combinations of chemotherapy; the phase II/III REAL-2 trial – for example – compares four regimens containing epirubicin and either cisplatin or oxaliplatin, and either continuously infused fluorouracil or capecitabine.

Radiotherapy is given before, during, or after chemotherapy or surgery, and sometimes on its own to control symptoms. In patients with localised disease but contraindications to surgery, "radical radiotherapy" may be used with curative intent.

## Other approaches [edit]

Forms of endoscopic therapy have been used for stage 0 and I disease: endoscopic mucosal resection [57]

(EMR) and mucosal ablation using radiofrequency ablation, photodynamic therapy, Nd-YAG laser, or argon plasma coagulation.

Laser therapy is the use of high-intensity light to destroy tumor cells while affecting only the treated area. This is typically done if the cancer cannot be removed by surgery. The relief of a blockage can help with pain and difficulty swallowing. Photodynamic therapy, a type of laser therapy, involves the use of drugs that are absorbed by cancer cells; when exposed to a special light, the drugs become active and destroy the cancer cells.


Internal radiotherapy for esophageal cancer

Self-expandable metallic stents are sometimes used for palliative care

## Follow-up [edit]

Patients are followed closely after a treatment regimen has been completed. Frequently, other treatments are used to improve symptoms and maximize nutrition.

# Prognosis [edit]

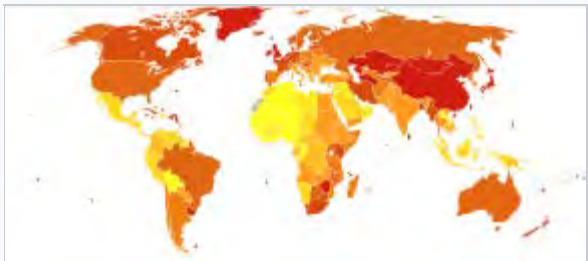
In general, the prognosis of esophageal cancer is quite poor, because most patients present with advanced disease. By the time the first symptoms (such as difficulty swallowing) appear, the disease has already progressed. The overall five-year survival rate (5YSR) in the United States is around 15%, with most people dying within the first year of diagnosis.[58] The latest survival data for England and Wales (patients diagnosed during 2007) show that only one in ten people survive esophageal cancer for at least ten years.[59]

Individualized prognosis depends largely on stage. Those with cancer restricted entirely to the esophageal mucosa have about an 80% 5YSR, but submucosal involvement brings this down to less than 50%. Extension into the muscularis propria (muscle layer of the esophagus) suggests a 20% 5YSR, and extension to the structures adjacent to the esophagus predict a 7% 5YSR. Patients with distant metastases (who are not candidates for curative surgery) have a less than 3% 5YSR.[*citation needed*]

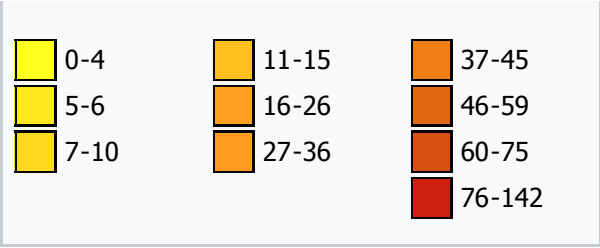
# Epidemiology [edit]

Esophageal cancer is the eighth most frequently diagnosed cancer worldwide,[1] and because of its poor prognosis it is the sixth most common cause of cancer-related death.[46] It caused about 400,000 deaths in 2012, accounting for about 5% of all cancer deaths (about 456,000 new cases were diagnosed, representing about 3% of all cancers).[1]

ESCC comprises 60–70% of all cases of esophageal cancer worldwide, while EAC accounts for a further 20–30% (melanomas, leiomyosarcomas, carcinoids and lymphomas are



Death from esophageal cancer per million persons in 2012




less common types).[60] The incidence of the two main types of esophageal cancer varies greatly between different geographical areas.[61] In general, ESCC is more common in the developing world, and EAC is more common in the developed world.[1]

The worldwide incidence rate of ESCC in 2012 was 5.2 new cases per 100,000 person-years, with a male predominance (7.7 per 100,000 in men vs. 2.8 in women).[62] It was the common type in 90% of the countries studied.[62] ESCC is particularly frequent in the so-called "Asian esophageal cancer belt", an area that passes through northern China, southern Russia, north-eastern Iran, northern Afghanistan and eastern Turkey.[60] In 2012, about 80% of ESCC cases worldwide occurred in central and south-eastern Asia, and over half (53%) of all cases were in China.[62] The countries with the highest estimated national incidence rates were (in Asia) Mongolia and Turkmenistan and (in Africa) Malawi, Kenya and Uganda.[62] The problem of esophageal cancer has long been recognized in the eastern and southern parts of Sub-Saharan Africa, where ESCC appears to predominate.[63]

In Western countries, EAC has become the dominant form of the disease, following an increase in incidence over recent decades (in contrast to the incidence of ESCC, which has remained largely stable).[8][27] In 2012, the global incidence rate for EAC was 0.7 per 100,000 with a strong male predominance (1.1 per 100,000 in men vs. 0.3 in women) Areas with particularly high incidence rates include northern and western Europe, North America and Oceania. The countries with highest recorded rates were the UK, Netherlands, Ireland, Iceland and New Zealand.[62]

### USA [edit]

In the United States, esophageal cancer is the seventh-leading cause of cancer death among males (making up 4% of the total).[64] The National Cancer Institute estimated there were about 18,000 new cases and more than 15,000 deaths from esophageal cancer in 2013 (the American Cancer Society estimated that during 2014, about 18,170 new esophageal cancer cases would be diagnosed, resulting in 15,450 deaths).[61][64] The squamous-cell carcinoma type is more common among African American males with a history of heavy smoking or alcohol use. Until the 1970s, squamous-cell carcinoma accounted for the vast majority of esophageal cancers in the United States. In recent decades, incidence of adenocarcinoma of the esophagus (which is associated with Barrett's esophagus) steadily rose in the United States to the point that it has now surpassed squamous-cell carcinoma. In contrast to squamous-cell carcinoma, esophageal adenocarcinoma is more common in Caucasian men (over the age of 60) than it is in African Americans. Multiple reports indicate esophageal adenocarcinoma incidence has increased during the past 20 years, especially in non-Hispanic white men. Esophageal adenocarcinoma age-adjusted incidence increased in New Mexico from 1973 to 1997. This increase was found in non-Hispanic whites and Hispanics and became predominant in non-Hispanic whites.[65] Esophageal cancer incidence and mortality rates for African Americans continue to be higher than the rate for Causasians. However, incidence and mortality of esophageal cancer has significantly decreased among African Americans since the early 1980s, whereas with Caucasians it has continued to increase.[66] Between 1975 and 2004, incidence of the adenocarcinoma type increased among white American males by over 460% and among white American females by 335%.[61]

### UK [edit]

The incidence of esophageal adenocarcinoma has risen considerably in the UK in recent decades.[14] Overall, esophageal cancer is the thirteenth most common cancer in the UK (around 8,300 people were diagnosed with the disease in 2011), and it is the sixth most common cause of cancer death (around 7,700 people died in 2012).[67]

## Society and culture [edit]

## Notable cases [edit]

*See also: Category:Deaths from esophageal cancer*

Christopher Hitchens, an author who is well known for the book "God is Not Great," also wrote about his life with esophageal cancer.[68]

Morrissey in October 2015 stated he has the disease and describes his experience when he first heard he had it.[69]

# Research directions [edit]

The risk of esophageal squamous-cell carcinoma may be reduced in people using aspirin or related NSAIDs,[70] but in the absence of randomized controlled trials the current evidence is inconclusive.[1][27]

# See also [edit]

- Esophagogastric junctional adenocarcinoma

# References [edit]


1. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z* Montgomery, EA; et al. (2014). "Oesophageal Cancer". In Stewart, BW; Wild, CP. *World Cancer Report 2014*. World Health Organization. pp. 528–543. ISBN 9283204298.
2. ^ *a b c d e f g* Ferri, FF, ed. (2012). "Esophageal Tumors". *Ferri's clinical advisor 2013*. Philadelphia, PA: Mosby (Elsevier). pp. 389–391. ISBN 9780323083737.
3. ^ Even by those using the British English spelling "oesophagus"
4. ^ Kelsen, David (2007). *Gastrointestinal oncology: principles and practices* (2nd ed.). Philadelphia, Pa.: Lippincott Williams & Wilkins. p. 4. ISBN 9780781776172.
5. ^ Whittemore, edited by David Schottenfeld, Joseph F. Fraumeni Jr.; associate editors, Graham A. Colditz, Jonathan M. Samet, Alice S. (2006). *Cancer epidemiology and prevention* (3rd ed.). Oxford: Oxford University Press. p. 697. ISBN 9780199747979.
6. ^ *a b c* Zhang, HZ; Jin, GF; Shen, HB (Jun 2012). "Epidemiologic differences in esophageal cancer between Asian and Western populations.". *Chinese journal of cancer*. **31** (6): 281–6. doi:10.5732/cjc.011.10390. PMC 3777490. PMID 22507220.
7. ^ *a b c* Akhtar, S (February 2013). "Areca nut chewing and esophageal squamous-cell carcinoma risk in Asians: a meta-analysis of case-control studies". *Cancer Causes & Control*. **24** (2): 257–65. doi:10.1007/s10552-012-0113-9. PMID 23224324.
8. ^ *a b c d* Stahl, M; Mariette, C; Haustermans, K; Cervantes, A; Arnold, D; ESMO Guidelines Working, Group (Oct 2013). "Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.". *Annals of Oncology*. 24 Suppl 6: vi51–6. doi:10.1093/annonc/mdt342. PMID 24078662.
9. ^ Lozano, R; Naghavi, M; Foreman, K; Lim, S; Shibuya, K; Aboyans, V; Abraham, J; Adair, T; et al. (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
10. ^ *a b* Enzinger PC, Mayer RJ (2003). "Esophageal cancer" (PDF). *N. Engl. J. Med.* **349** (23): 2241–52. doi:10.1056/NEJMra035010. PMID 14657432.
11. ^ "SEER Stat Fact Sheets: Esophageal Cancer". *National Cancer Institute*. Retrieved 18 June 2014.
12. ^ *a b c d e* Mayer RJ (2008). "Gastrointestinal Tract Cancer". In Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. *Harrison's principles of internal medicine*. **1** (18th ed.). New York: McGraw-Hill Medical Publishing Division. pp. 764–5. ISBN 978-0071748896.
13. ^ Cheifetz, Adam S; Brown, Alphonso; Curry, Michael; Moss, Alan C (2011). *Oxford American Handbook of Gastroenterology and Hepatology*. Oxford University Press. p. 106. ISBN 978-0-19-983012-1.
14. ^ *a b c d e f g h i j k l m* Pennathur A, Gibson MK, Jobe BA, Luketich JD (February 2013). "Oesophageal carcinoma". *Lancet*. **381** (9864): 400–12. doi:10.1016/S0140-6736(12)60643-6. PMID 23374478.
15. ^ Yamada, Tadataka (2011). *Textbook of Gastroenterology*. John Wiley & Sons. pp. 1590–1. ISBN 978-1-4443-

5941-1.
16. ^ Gerdes, Hans; Ferguson, Mark K (2002). "Palliation of Esophageal Cancer". In Posner, Mitchell C; Vokes, Everett E; Weichselbaum, Ralph R. *Cancer of the Upper Gastrointestinal Tract*. PMPH-USA. p. 184. ISBN 978-1-55009-101-4.
17. ^ a b Lao-Sirieix, P; Caldas, C; Fitzgerald, RC (June 2010). "Genetic predisposition to gastro-oesophageal cancer". *Current Opinion in Genetics & Development*. **20** (3): 210–7. doi:10.1016/j.gde.2010.03.002. PMID 20347291.
18. ^ Tobias JS, Hochhauser D (2013). *Cancer and its management* (6th ed.). p. 254. ISBN 1-11871-325-7.
19. ^ Prabhu, A; Obi, KO; Rubenstein, JH (June 2014). "The synergistic effects of alcohol and tobacco consumption on the risk of esophageal squamous cell carcinoma: a meta-analysis". *The American Journal of Gastroenterology*. **109** (6): 822–7. doi:10.1038/ajg.2014.71. PMID 24751582.
20. ^ Loomis, D; Guyton, KZ; Grosse, Y; et al. (July 2016). "Carcinogenicity of drinking coffee, mate, and very hot beverages." (PDF). *The Lancet. Oncology*. **17** (7): 877–8. doi:10.1016/s1470-2045(16)30239-x. PMID 27318851.
21. ^ "Q&A on Monographs Volume 116: Coffee, maté, and very hot beverages". *www.iarc.fr*. IARC / WHO. Archived from the original on 19 August 2013.
22. ^ Hunter, edited by Blair A. Jobe, Charles R. Thomas Jr., John G. (2009). *Esophageal cancer principles and practice*. New York: Demos Medical. p. 93. ISBN 9781935281177.
23. ^ a b Rutegård M, Lagergren P, Nordenstedt H, Lagergren J (July 2011). "Oesophageal adenocarcinoma: the new epidemic in men?". *Maturitas*. **69** (3): 244–8. doi:10.1016/j.maturitas.2011.04.003. PMID 21602001.
24. ^ a b c d de Jonge, PJ; van Blankenstein, M; Grady, WM; Kuipers, EJ (January 2014). "Barrett's oesophagus: epidemiology, cancer risk and implications for management". *Gut*. **63** (1): 191–202. doi:10.1136/gutjnl-2013-305490. PMID 24092861.
25. ^ Turati F, Tramacere I, La Vecchia C, Negri E (March 2013). "A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma". *Annals of Oncology*. **24** (3): 609–17. doi:10.1093/annonc/mds244. PMID 22898040.
26. ^ a b c Lagergren J (June 2011). "Influence of obesity on the risk of esophageal disorders". *Nature Reviews. Gastroenterology & Hepatology*. **8** (6): 340–7. doi:10.1038/nrgastro.2011.73. PMID 21643038.
27. ^ a b c d e f Lagergren, J; Lagergren, P (2013). "Recent developments in esophageal adenocarcinoma". *CA: A Cancer Journal for Clinicians*. **63** (4): 232–48. doi:10.3322/caac.21185. PMID 23818335.
28. ^ a b Falk, GW (July 2009). "Risk factors for esophageal cancer development" (PDF). *Surgical Oncology Clinics of North America*. **18** (3): 469–85. doi:10.1016/j.soc.2009.03.005. PMID 19500737.
29. ^ Harris, Randall E (2013). "Epidemiology of Esophageal Cancer". *Epidemiology of Chronic Disease: Global Perspectives*. Burlington, MA: Jones & Bartlett Publishers. pp. 157–161. ISBN 978-0-7637-8047-0.
30. ^ Priante AV, Castilho EC, Kowalski LP (April 2011). "Second primary tumors in patients with head and neck cancer". *Current Oncology Reports*. **13** (2): 132–7. doi:10.1007/s11912-010-0147-7. PMID 21234721.
31. ^ Scherübl H, Steinberg J, Schwertner C, Mir-Salim P, Stölzel U, de Villiers EM (June 2008). "'Field cancerization' im oberen Aerodigestivtrakt" [Coincidental squamous cell cancers of the esophagus, head, and neck: risk and screening]. *HNO* (in German). **56** (6): 603–8. doi:10.1007/s00106-007-1616-7. PMID 17928979.
32. ^ "Tylosis with esophageal cancer". *rarediseases.info.nih.gov*. Genetic and Rare Diseases Information Center (GARD) – NIH. 18 January 2013. Retrieved 16 August 2014.
33. ^ Nyrén O, Adami HO (2008). "Esophageal Cancer". In Adami HO, Hunter DJ, Trichopoulos D. *Textbook of Cancer Epidemiology*. Volume 1. Oxford University Press. p. 224. ISBN 978-0-19-531117-4.
34. ^ Liyanage SS, Rahman B, Ridda I, Newall AT, Tabrizi SN, Garland SM, Segelov E, Seale H, Crowe PJ, Moa A, Macintyre CR (2013). "The aetiological role of human papillomavirus in oesophageal squamous cell carcinoma: a meta-analysis". *PLOS ONE*. **8** (7): e69238. doi:10.1371/journal.pone.0069238. PMC 3722293. PMID 23894436.
35. ^ Sitas F, Egger S, Urban MI, Taylor PR, Abnet CC, Boffetta P, O'Connell DL, Whiteman DC, Brennan P, Malekzadeh R, Pawlita M, Dawsey SM, Waterboer T (January 2012). "InterSCOPE study: Associations between esophageal squamous cell carcinoma and human papillomavirus serological markers". *Journal of the National Cancer Institute*. **104** (2): 147–58. doi:10.1093/jnci/djr499. PMC 3260131. PMID 22228147.
36. ^ Syrjänen, K (January 2013). "Geographic origin is a significant determinant of human papillomavirus prevalence in oesophageal squamous cell carcinoma: systematic review and meta-analysis". *Scandinavian Journal of Infectious Diseases*. **45** (1): 1–18. doi:10.3109/00365548.2012.702281. PMID 22830571.
37. ^ Hardefeldt, HA; Cox, MR; Eslick, GD (June 2014). "Association between human papillomavirus (HPV) and oesophageal squamous cell carcinoma: a meta-analysis". *Epidemiology and Infection*. **142** (6): 1119–37. doi:10.1017/S0950268814000016. PMID 24721187.
38. ^ Han Y, Chen W, Li P, Ye J (2015). "Association Between Coeliac Disease and Risk of Any Malignancy and Gastrointestinal Malignancy: A Meta-Analysis.". *Medicine (Baltimore)*. **94** (38): e1612.

doi:10.1097/MD.0000000000001612. PMC 4635766. PMID 26402826.
39. ^ Shields TW, LoCicero JW, Reed CE, Feins RH (2009). *General Thoracic Surgery*. Lippincott Williams & Wilkins. pp. 2047–. ISBN 978-0-7817-7982-1.
40. ^ Halperin EC, Perez CA, Brady LW (2008). *Perez and Brady's Principles and Practice of Radiation Oncology*. Lippincott Williams & Wilkins. pp. 1137–. ISBN 978-0-7817-6369-1.
41. ^ Cancer arising at the junction between the esophagus and stomach is often classified as stomach cancer, as in ICD-10. See: "C16 - Malignant neoplasm of the stomach". *ICD-10 Version: 2015*. World Health Organization. Retrieved 14 November 2014.
42. ^ Rice TW, Blackstone EH, Rusch VW (March 2010). "A cancer staging primer: esophagus and esophagogastric junction". *The Journal of Thoracic and Cardiovascular Surgery*. **139** (3): 527–9. doi:10.1016/j.jtcvs.2009.11.002. PMID 20176201.
43. ^ Lauby-Secretan, B; Scoccianti, C; Loomis, D; Grosse, Y; Bianchini, F; Straif, K; International Agency for Research on Cancer Handbook Working, Group (25 August 2016). "Body Fatness and Cancer - Viewpoint of the IARC Working Group.". *The New England Journal of Medicine*. **375** (8): 794–798. doi:10.1056/NEJMsr1606602. PMID 27557308.
44. ^ NCI (2002). "Prevention: Dietary Factors, based on Chainani-Wu N. Diet and oral, pharyngeal, and esophageal cancer". *Nutr Cancer*. **44** (2): 104–26. doi:10.1207/S15327914NC4402_01. PMID 12734057.
45. ^ Coleman HG, Murray LJ, Hicks B, Bhat SK, Kubo A, Corley DA, Cardwell CR, Cantwell MM (July 2013). "Dietary fiber and the risk of precancerous lesions and cancer of the esophagus: a systematic review and meta-analysis". *Nutrition Reviews*. **71** (7): 474–82. doi:10.1111/nure.12032. PMID 23815145.
46. ^ *a b* Zhang Y (September 2013). "Epidemiology of esophageal cancer". *World J. Gastroenterol*. **19** (34): 5598–606. doi:10.3748/wjg.v19.i34.5598. PMC 3769895. PMID 24039351.
47. ^ Dunbar KB, Spechler SJ (May 2014). "Controversies in Barrett Esophagus". *Mayo Clin. Proc*. **89** (7): 973–984. doi:10.1016/j.mayocp.2014.01.022. PMID 24867396.
48. ^ *a b* Tobias, Jeffrey S.; Hochhauser, Daniel (2010). *Cancer and its Management* (6th ed.). p. 257. ISBN 1118713257.
49. ^ Berry 2014, p. S292
50. ^ Fernández-Esparrach, G; Calderón, A; de la Peña, J; et al. (April 2014). "Endoscopic submucosal dissection". *Endoscopy*. **46** (4): 361–70. doi:10.1055/s-0034-1364921. PMID 24671864.
51. ^ Sun, F; Yuan, P; Chen, T; Hu, J (7 May 2014). "Efficacy and complication of endoscopic submucosal dissection for superficial esophageal carcinoma: a systematic review and meta-analysis". *Journal of cardiothoracic surgery*. **9**: 78. doi:10.1186/1749-8090-9-78. PMC 4052291. PMID 24885614.
52. ^ *a b c d e f g* "Ch 79, "Treatment" ". *DeVita, Hellman, and Rosenberg's Cancer: Cancer: Principles & Practice of Oncology* (9th ed.). Lippincott Williams & Wilkins. 2011. ISBN 9781451105452. Online edition, with updates to 2014
53. ^ Berry, MF (May 2014). "Esophageal cancer: staging system and guidelines for staging and treatment.". *Journal of thoracic disease*. **6** (Suppl 3): S289–97. doi:10.3978/j.issn.2072-1439.2014.03.11. PMID 24876933.
54. ^ Parameswaran R, McNair A, Avery KN, Berrisford RG, Wajed SA, Sprangers MA, Blazeby JM (September 2008). "The role of health-related quality of life outcomes in clinical decision making in surgery for esophageal cancer: a systematic review". *Annals of Surgical Oncology*. **15** (9): 2372–9. doi:10.1245/s10434-008-0042-8. PMID 18626719.
55. ^ Berry 2014, p. S293
56. ^ Ross P, Nicolson M, Cunningham D, et al. (April 2002). "Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) With epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer". *Journal of clinical oncology*. **20** (8): 1996–2004. doi:10.1200/JCO.2002.08.105. PMID 11956258.
57. ^ Wang KK, Prasad G, Tian J (September 2010). "Endoscopic mucosal resection and endoscopic submucosal dissection in esophageal and gastric cancers". *Curr. Opin. Gastroenterol*. **26** (5): 453–8. doi:10.1097/MOG.0b013e32833e4712. PMC 3215503. PMID 20703112.
58. ^ Polednak AP (May 2003). "Trends in survival for both histologic types of esophageal cancer in US surveillance, epidemiology and end results areas". *Int. J. Cancer*. **105** (1): 98–100. doi:10.1002/ijc.11029. PMID 12672037.
59. ^ "Oesophageal cancer survival statistics". *Cancer Research UK*.
60. ^ *a b* Conteduca V, Sansonno D, Ingravallo G, Marangi S, Russi S, Lauletta G, Dammacco F (August 2012). "Barrett's esophagus and esophageal cancer: an overview". *International Journal of Oncology*. **41** (2): 414–24. doi:10.3892/ijo.2012.1481. PMID 22615011.
61. ^ *a b c* Napier KJ, Scheerer M, Misra S (May 2014). "Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities". *World Journal of Gastrointestinal Oncology*. **6** (5): 112–20. doi:10.4251/wjgo.v6.i5.112. PMC 4021327. PMID 24834141.
*a b c d e*

62. ^ Arnold M, Soerjomataram I, Ferlay J, Forman D (October 2014). "Global incidence of oesophageal cancer by histological subtype in 2012". *Gut*. **64**: 381–7. doi:10.1136/gutjnl-2014-308124. PMID 25320104.
63. ^ Kachala R (September 2010). "Systematic review: epidemiology of oesophageal cancer in Sub-Saharan Africa". *Malawi Medical Journal*. **22** (3): 65–70. doi:10.4314/mmj.v22i3.62190. PMC 3345777. PMID 21977849.
64. ^ *a b* "Cancer Facts and Figures 2014" (PDF). American Cancer Society. Retrieved 28 April 2014.
65. ^ Vega KJ, Jamal MM (September 2000). "Changing pattern of esophageal cancer incidence in New Mexico". *Am. J. Gastroenterol*. **95** (9): 2352–6. doi:10.1111/j.1572-0241.2000.02329.x. PMID 11007241.
66. ^ "Incidence and Mortality Rate Trends" (PDF). *A Snapshot of Esophageal Cancer*. National Cancer Institute. September 2006. Archived from the original (PDF) on 2007-03-16. Retrieved 2007-03-21.
67. ^ "Oesophageal cancer statistics". *Cancer Research UK*. Retrieved 3 October 2014.
68. ^ "Christopher Hitchens' widow on his death: "God never came up" ". *www.cbsnews.com*. Retrieved 2015-11-11.
69. ^ "Morrissey Talks Trump, Cancer Diagnosis, TSA Groping With Larry King". *Rolling Stone*. Retrieved 2015-11-11.
70. ^ Sun, L; Yu, S (Nov 2011). "Meta-analysis: non-steroidal anti-inflammatory drug use and the risk of esophageal squamous cell carcinoma.". *Diseases of the Esophagus*. **24** (8): 544–9. doi:10.1111/j.1442-2050.2011.01198.x. PMID 21539676.


## External links [edit]

- NCI esophageal cancer
- Cancer.Net: Esophageal Cancer
- Esophageal Cancer From Cancer Management: A Multidisciplinary Approach
- Learn More about Esophageal Cancer
- Oesophageal Cancer at Cancer Research UK
- National Comprehensive Cancer Network

Wikimedia Commons has media related to *Esophageal cancer*.

| v · t · e | **Digestive system neoplasia (C15–C26/D12–D13, 150–159/211)** | | |
|---|---|---|---|
| **GI tract** | **Upper** | **Esophagus** | Squamous cell carcinoma · Adenocarcinoma · |
| | | **Stomach** | Gastric carcinoma · Signet ring cell carcinoma · Gastric lymphoma (MALT lymphoma · · Linitis plastica · |
| | **Lower** | **Small intestine** | Duodenal cancer (Adenocarcinoma · · |
| | | **Appendix** | Carcinoid · Pseudomyxoma peritonei · |
| | | **Colon/rectum** | *colorectal polyp:* Peutz–Jeghers syndrome · Juvenile polyposis syndrome · Familial adenomatous polyposis/Gardner's syndrome · Cronkhite–Canada syndrome · *neoplasm:* Adenocarcinoma · Familial adenomatous polyposis · Hereditary nonpolyposis colorectal cancer · |
| | | **Anus** | Squamous cell carcinoma · |
| | **Upper and/or lower** | | Gastrointestinal stromal tumor · Krukenberg tumor (metastatic) · |
| **Accessory** | **Liver** | | *malignant:* Hepatocellular carcinoma (Fibrolamellar · · Hepatoblastoma · *benign:* Hepatocellular adenoma · Cavernous hemangioma · *hyperplasia:* Focal nodular hyperplasia · Nodular regenerative hyperplasia · |
| | **Biliary tract** | | *bile duct:* Cholangiocarcinoma · Klatskin tumor · *gallbladder:* Gallbladder cancer · |
| | | | *exocrine pancreas:* Adenocarcinoma · Pancreatic ductal carcinoma · |

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|---|---|---|
| | **Pancreas** | *cystic neoplasms*: Serous microcystic adenoma · Intraductal papillary mucinous neoplasm · Mucinous cystic neoplasm · Solid pseudopapillary neoplasm · Pancreatoblastoma · |
| **Peritoneum** | Primary peritoneal carcinoma · Peritoneal mesothelioma · Desmoplastic small round cell tumor · | |
| **Authority control** | NDL: 00572161 · | |

Categories: Gastrointestinal cancer




# Glioblastoma

From Wikipedia, the free encyclopedia
(Redirected from Glioblastoma multiforme)

**Glioblastoma**, also known as **glioblastoma multiforme** (**GBM**), is the most aggressive cancer that begins within the brain.[1] Signs and symptoms of glioblastoma are initially non-specific. They may include headaches, personality changes, nausea, and symptoms similar to those of a stroke.[2] Worsening of symptoms is often rapid. This can progress to unconsciousness.[3]

The cause of most cases is unclear.[3] Uncommon risk factors include genetic disorders such as neurofibromatosis and Li Fraumeni syndrome and previous radiation therapy.[3][4] Glioblastomas represent 15% of brain tumors.[2] They can either start from normal brain cells or develop from an already existing low-grade astrocytoma.[5] The diagnosis is typically made by a combination of CT scan, MRI scan, and tissue biopsy.[2]

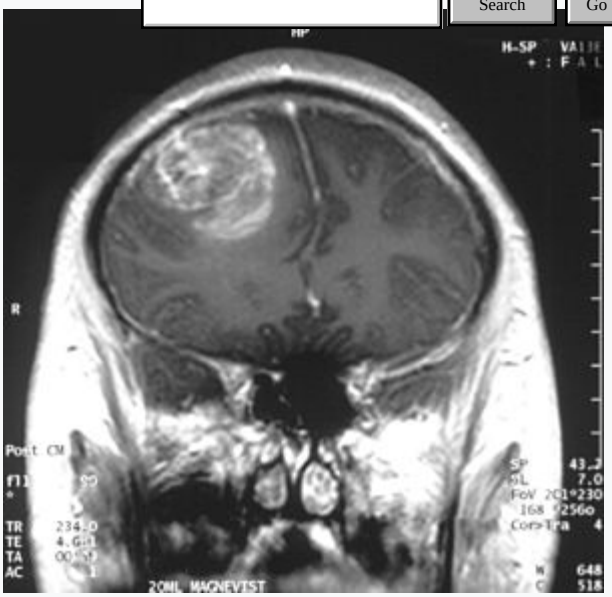
There is no clear way to prevent the disease. Typically treatment involves surgery after which chemotherapy and radiation therapy are used.[4] The medication temozolomide is frequently used as part of chemotherapy.[4][6][7] High dose steroids may be used to help reduce swelling and decrease symptoms.[2] It is unclear whether trying to remove all or simply most of the cancer is better.[8]

Despite maximum treatment, the cancer usually recurs.[4] The most common length of survival following diagnosis is 12 to 15 months with less than 3% to 5% of people surviving longer than five years.[3][4] Without treatment survival is typically 3 months.[9] It is the most common cancer that begins within the brain and the second most common brain tumor after meningioma.[1][10] About 3 per 100,000 people develop the disease a year.[4] It most often begins around 64 years of age and occurs more commonly in males than females.[3][4] Immunotherapy is being studied in glioblastoma with promising results.[11]

## Variants

**Glioblastoma**

**Synonyms** glioblastoma multiforme, grade IV astrocytoma




Coronal MRI with contrast of a glioblastoma WHO grade IV in a 15-year-old male

| Classification and external resources | |
|---|---|
| **Specialty** | Oncology, neurosurgery |
| **ICD-10** | C71 |
| **ICD-9-CM** | 191 |
| **ICD-O** | M9440/3 |
| **OMIM** | 137800 |
| **DiseasesDB** | 29448 |
| **eMedicine** | neuro/147 med/2692 |
| **MeSH** | D005909 |

[edit on Wikidata]

Contents

## Signs and symptoms [edit]

Although common symptoms of the disease include seizure, nausea and vomiting, headache, memory loss, and hemiparesis, the single most prevalent symptom is a progressive memory, personality, or neurological deficit due to temporal and frontal lobe involvement. The kind of symptoms produced depends more on the location of the tumor than on its pathological properties. The tumor can start producing symptoms quickly, but occasionally is an asymptomatic condition until it reaches an enormous size.

## Risk factors [edit]

For unknown reasons, GBM occurs more commonly in males.[12] Most glioblastoma tumors appear to be sporadic, without any genetic predisposition. No links have been found between glioblastoma and smoking,[13] consumption of cured meat,[14] or electromagnetic fields.[15][16][17][18] Alcohol consumption may be a possible risk factor.[19] Glioblastoma has been associated with the viruses SV40,[20] HHV-6,[21][22] and cytomegalovirus.[23] There also appears to be a small link between ionizing radiation and glioblastoma.[24] A 2006 analysis links brain cancer to lead exposure in the work-place.[25] There is an association of brain tumor incidence and malaria, suggesting that the anopheles mosquito, the carrier of malaria, might transmit a virus or other agent that could cause glioblastoma[26] or that the immunosuppression associated with malaria could enhance viral replication. Also HHV-6 reactivates in response to hypersensitivity reactions from drugs and environmental chemicals.[27]

Other risk factors include:[28]

- Sex: male (slightly more common in men than women)
- Age: over 50 years old
- Ethnicity: Caucasians, Hispanics, and Asians[29]
- Having a low-grade astrocytoma (brain tumor), which often, given enough time, develops into a higher-grade tumor
- Having one of the following genetic disorders is associated with an increased incidence of gliomas:
  - Neurofibromatosis
  - Tuberous sclerosis
  - Von Hippel-Lindau disease
  - Li-Fraumeni syndrome
  - Turcot syndrome

# Pathogenesis [edit]

Glioblastoma multiforme tumors are characterized by the presence of small areas of necrotizing tissue that are surrounded by anaplastic cells. This characteristic, as well as the presence of hyperplastic blood vessels, differentiates the tumor from Grade 3 astrocytomas, which do not have these features.

GBMs usually form in the cerebral white matter, grow quickly, and can become very large before producing symptoms. Less than 10% form more slowly following degeneration of low-grade astrocytoma or anaplastic astrocytoma. These are called secondary GBMs and are more common in younger patients (mean age 45 versus 62 years).[30] The tumor may extend into the meninges or ventricular wall, leading to high protein content in the cerebrospinal fluid (CSF) (> 100 mg/dL), as well as an occasional pleocytosis of 10 to 100 cells, mostly lymphocytes. Malignant cells carried in the CSF may spread (rarely) to the spinal cord or cause meningeal gliomatosis. However, metastasis of GBM beyond the central nervous system is extremely unusual. About 50% of GBMs occupy more than one lobe of a hemisphere or are bilateral. Tumors of this type usually arise from the cerebrum and may rarely exhibit the classic infiltration across the corpus callosum, producing a butterfly (bilateral) glioma.

The tumor may take on a variety of appearances, depending on the amount of hemorrhage, necrosis, or its age. A CT scan will usually show an inhomogeneous mass with a hypodense center and a variable ring of enhancement surrounded by edema. Mass effect from the tumor and edema may compress the ventricles and cause hydrocephalus.

## Molecular alterations [edit]

Four subtypes of glioblastoma have been identified:[31]

- Classical : Ninety-seven percent of tumors in the 'classical' subtype carry extra copies of the epidermal growth factor receptor (EGFR) gene, and most have higher than normal expression of epidermal growth factor receptor (EGFR), whereas the gene TP53, which is often mutated in glioblastoma, is rarely mutated in this subtype.[32]
- The Proneural subtype often has high rates of alterations in TP53, and in PDGFRA, the gene encoding a-type platelet-derived growth factor receptor, and in IDH1, the gene encoding isocitrate dehydrogenase-1.
- The Mesenchymal subtype is characterized by high rates of mutations or other alterations in NF1, the gene encoding Neurofibromin 1 and fewer alterations in the EGFR gene and less expression of EGFR than other types.[33]
- The Neural subtype was typified by the expression of neuron markers such as NEFL, GABRA1, SYT1 and SLC12A5.[31]

Many other genetic alterations have been described in glioblastoma, and the majority of them are clustered in three pathways, the P53, RB, and the PI3K/AKT.[34] Glioblastomas have alterations in 64-87%, 68-78% and 88% of these pathways, respectively.[1]

Another important alteration is methylation of MGMT, a "suicide" DNA repair enzyme. Methylation is described to impair DNA transcription and therefore, expression of the MGMT enzyme. Since an MGMT enzyme can only repair one DNA alkylation due to its suicide repair mechanism, reverse capacity is low and methylation of the MGMT gene promoter greatly affects DNA-repair capacity.[35][36] Indeed, MGMT methylation is associated with an improved response to treatment with DNA-damaging chemotherapeutics, such as temozolomide.[37]

## Glioblastoma stem-like cells [edit]

Cancer cells with stem cell-like properties have been found in glioblastomas (this may be a cause of their resistance to conventional treatments, and high recurrence rate).[38] These so-called glioblastoma stem-like cells reside in a niche around arterioles, which protects these cells against therapy by maintaining a relatively hypoxic environment.[39] A biomarker for cells in glioblastomas that exhibit cancer stem cell properties, the transcription factor Hes3, has been shown to regulate their number when placed in

culture.[40]

### Metabolism [edit]

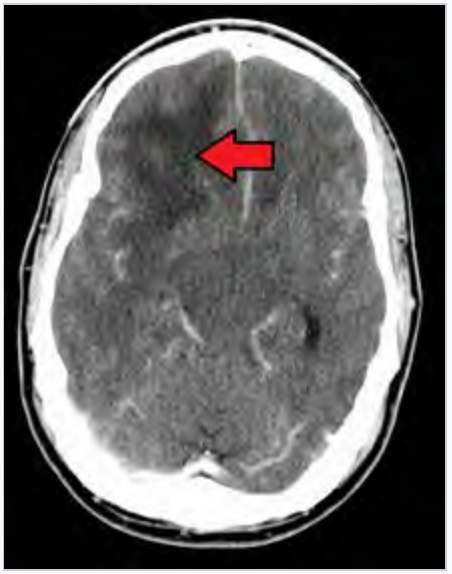
The *IDH1* gene encodes for the enzyme isocitrate dehydrogenase 1 and is frequently mutated in glioblastoma (primary GBM: 5%, secondary GBM >80%).[36] By producing very high concentrations of the "oncometabolite" D-2-hydroxyglutarate and dysregulating the function of the wild-type IDH1-enzyme it induces profound changes to the metabolism of *IDH1*-mutated glioblastoma, compared with *IDH1* wild-type glioblastoma or healthy astrocytes. Among others, it increases the glioblastoma cells' dependence on glutamine or glutamate as an energy source.[41] It has been hypothesized that *IDH1*-mutated glioblastoma are in a very high demand for glutamate and use this amino acid and neurotransmitter as a chemotactic signal. Since healthy astrocytes excrete glutamate, *IDH1*-mutated glioblastoma cells do not favor dense tumor structures but instead migrate, invade and disperse into healthy parts of the brain where glutamate concentrations are higher. This may explain the invasive behaviour of these *IDH1*-mutated glioblastoma.[42]

### Ion channels [edit]

Furthermore, glioblastoma multiforme exhibits numerous alterations in genes that encode for ion channels, including upregulation of gBK potassium channels and ClC-3 chloride channels. It has been hypothesized that by upregulating these ion channels, glioblastoma tumor cells can facilitate increased ion movement over the cell membrane, thereby increasing $H_2O$ movement through osmosis, which aids glioblastoma cells in changing cellular volume very rapidly. This is helpful in their extremely aggressive invasive behavior, because quick adaptations in cellular volume can facilitate movement through the sinuous extracellular matrix of the brain.[43]

## Diagnosis [edit]

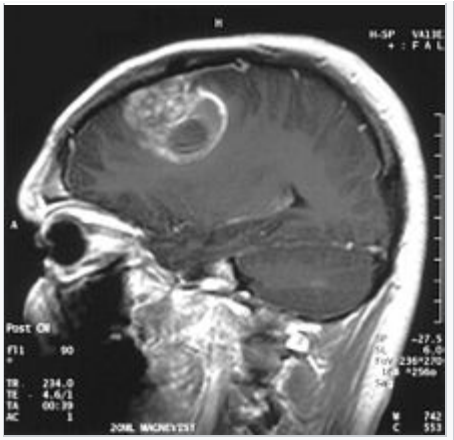
When viewed with MRI, glioblastomas often appear as ring-enhancing lesions. The appearance is not specific, however, as other lesions such as abscess, metastasis, tumefactive multiple sclerosis, and other entities may have a similar appearance.[44] Definitive diagnosis of a suspected GBM on CT or MRI requires a stereotactic biopsy or a craniotomy with tumor resection and pathologic confirmation. Because the tumor grade is based upon the most malignant portion of the tumor, biopsy or subtotal tumor resection can result in undergrading of the lesion. Imaging of tumor blood flow using perfusion MRI and measuring tumor metabolite concentration with MR spectroscopy may add value to standard MRI in select cases by showing increased relative cerebral blood volume and increased choline peak respectively, but pathology remains the gold standard for diagnosis and molecular characterization.



GBM in the frontal right lobe as seen on CT scan

It is important to distinguish primary glioblastoma from secondary glioblastoma. These tumors occur spontaneously (*de novo*) or have progressed from a lower-grade glioma, respectively.[45] Primary glioblastomas have a worse prognosis, different tumor biology and may have a different response to therapy, which makes this a critical evaluation to determine patient prognosis and therapy.[35] Over 80% of secondary glioblastoma carries a mutation in *IDH1*, whereas this mutation is rare in primary glioblastoma (5-10%). Thus, *IDH1* mutations are a useful tool to distinguish primary and secondary glioblastomas since histopathologically they are very similar and the distinction without molecular biomarkers is unreliable.[46]

## Treatment [edit]



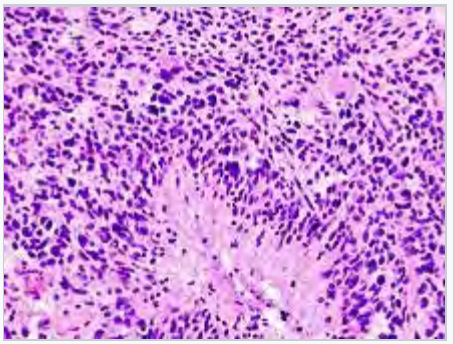
Sagittal MRI with contrast of a glioblastoma WHO grade IV in a 15-year-old boy.

It is very difficult to treat glioblastoma due to several complicating factors:[47]

- The tumor cells are very resistant to conventional therapies.
- The brain is susceptible to damage due to conventional therapy.
- The brain has a very limited capacity to repair itself.
- Many drugs cannot cross the blood–brain barrier to act on the tumor.

Treatment of primary brain tumors and brain metastases consists of both symptomatic and palliative therapies.

## Symptomatic therapy [edit]



Glioblastoma (histology slide)

Supportive treatment focuses on relieving symptoms and improving the patient's neurologic function. The primary supportive agents are anticonvulsants and corticosteroids.

- Historically, around 90% of patients with glioblastoma underwent anticonvulsant treatment, although it has been estimated that only approximately 40% of patients required this treatment. Recently, it has been recommended that neurosurgeons not administer anticonvulsants prophylactically, and should wait until a seizure occurs before prescribing this medication.[48] Those receiving phenytoin concurrent with radiation may have serious skin reactions such as erythema multiforme and Stevens–Johnson syndrome.
- Corticosteroids, usually dexamethasone given 4 to 8 mg every 4 to 6 h, can reduce peritumoral edema (through rearrangement of the blood–brain barrier), diminishing mass effect and lowering intracranial pressure, with a decrease in headache or drowsiness.

## Palliative therapy [edit]

Palliative treatment usually is conducted to improve quality of life and to achieve a longer survival time. It includes surgery, radiation therapy, and chemotherapy. A maximally feasible resection with maximal tumor-free margins is usually performed along with external beam radiation and chemotherapy. Gross total resection of tumor is associated with a better prognosis.

### Surgery [edit]

Surgery is the first stage of treatment of glioblastoma. An average GBM tumor contains $10^{11}$ cells, which is on average reduced to $10^{9}$ cells after surgery (a reduction of 99%). Benefits of surgery include resection for a pathological diagnosis, alleviation of symptoms related to mass effect, and potentially removing disease before secondary resistance to radiotherapy and chemotherapy occurs.

The greater the extent of tumor removal, the better. Removal of 98% or more of the tumor has been associated with a significantly longer healthier time than if less than 98% of the tumor is removed in retrospective analyses.[49] The chances of near-complete initial removal of the tumor may be increased if the surgery is guided by a fluorescent dye known as 5-aminolevulinic acid.[50] GBM cells are widely infiltrative through the brain at diagnosis, and so despite a "total resection" of all obvious tumor, most people with GBM later develop recurrent tumors either near the original site or at more distant locations within the brain. Other modalities, typically radiation and chemotherapy, are used after surgery in an effort

to suppress and slow recurrent disease.

### Radiotherapy [edit]

Subsequent to surgery, radiotherapy becomes the mainstay of treatment for people with glioblastoma. It is typically performed along with giving temozolomide (TMZ).[6] A pivotal clinical trial carried out in the early 1970s showed that among 303 GBM patients randomized to radiation or nonradiation therapy, those who received radiation had a median survival more than double those who did not.[51] Subsequent clinical research has attempted to build on the backbone of surgery followed by radiation. On average, radiotherapy after surgery can reduce the tumor size to $10^7$ cells. Whole-brain radiotherapy does not improve when compared to the more precise and targeted three-dimensional conformal radiotherapy.[52] A total radiation dose of 60–65 Gy has been found to be optimal for treatment.[53]

GBM tumors are well known to contain zones of tissue exhibiting hypoxia which are highly resistant to radiotherapy. Various approaches to chemotherapy radiosensitizers have been pursued with limited success as of 2016. As of 2010 newer research-approaches included preclinical and clinical investigations into the use of an oxygen diffusion-enhancing compound such as trans sodium crocetinate (TSC) as radiosensitizers,[54] and as of 2015 a clinical trial was underway.[55]

Boron neutron capture therapy has been tested as an alternative treatment for glioblastoma multiforme but is not in common use.

### Chemotherapy [edit]

Most studies show no benefit from the addition of chemotherapy. However, a large clinical trial of 575 participants randomized to standard radiation versus radiation plus temozolomide chemotherapy showed that the group receiving temozolomide survived a median of 14.6 months as opposed to 12.1 months for the group receiving radiation alone.[6][56] This treatment regime is now standard for most cases of glioblastoma where the person is not enrolled in a clinical trial.[57][58] Temozolomide seems to work by sensitizing the tumor cells to radiation.[59]

High doses of temozolomide in high-grade gliomas yield low toxicity, but the results are comparable to the standard doses.[60]

Antiangiogenic therapy with medications such as bevacizumab control symptoms but do not affect overall survival.[61]

### Other modalities [edit]

Alternating electric field therapy is an FDA-approved therapy for newly diagnosed[62] and recurrent glioblastoma.[63] In 2015, initial results from a phase-three randomized clinical trial of alternating electric field therapy plus temozolomide in newly diagnosed glioblastoma reported a three-month improvement in progression-free survival, and a five-month improvement in overall survival compared to temozolomide therapy alone,[64][65] representing the first large trial in a decade to show a survival improvement in this setting.[65] Despite these results, the efficacy of this approach remains controversial among medical experts.[66]

## Prognosis [edit]

The median survival time from the time of diagnosis without any treatment is 3 months, but with treatment survival of 1–2 years is common. Increasing age (> 60 years of age) carries a worse prognostic risk. Death is usually due to widespread tumor infiltration with cerebral edema and increased intracranial pressure.[67]

A good initial Karnofsky Performance Score (KPS) and MGMT methylation are associated with longer survival.[67] A DNA test can be conducted on glioblastomas to determine whether or not the promoter of the *MGMT* gene is methylated. Patients with a methylated MGMT promoter have longer survival than those

with an unmethylated MGMT promoter, due in part to increased sensitivity to temozolomide.[68] This DNA characteristic is intrinsic to the patient and currently cannot be altered externally. Another positive prognostic marker for glioblastoma patients is mutation of the *IDH1* gene,[1] which can be tested by DNA-based methods or by immunohistochemistry using an antibody against the most common mutation, namely IDH1-R132H.[69]

More prognostic power can be obtained by combining the mutational status of *IDH1* and the methylation status of *MGMT* into a two-gene predictor. Patients with both *IDH1* mutations and *MGMT* methylation have the longest survival, patients with an *IDH1* mutation or *MGMT* methylation an intermediate survival and patients without either genetic event have the shortest survival.[70]

Long-term benefits have also been associated with those patients who receive surgery, radiotherapy, and temozolomide chemotherapy.[67] However, much remains unknown about why some patients survive longer with glioblastoma. Age of under 50 is linked to longer survival in glioblastoma multiforme, as is 98%+ resection and use of temozolomide chemotherapy and better Karnofsky performance scores. A recent study confirms that younger age is associated with a much better prognosis, with a small fraction of patients under 40 years of age achieving a population-based cure. The population-based cure is thought to occur when a population's risk of death returns to that of the normal population, and in GBM, this is thought to occur after 10 years.[71]

UCLA Neuro-Oncology publishes real-time survival data for patients with this diagnosis.[72] They are the only institution in the United States that shows how their patients are performing. They also show a listing of chemotherapy agents used to treat GBM tumors. Despite a poor prognosis, there is a small number of survivors who have been GBM free for more than 10–20 years.

According to a 2003 study, glioblastoma multiforme prognosis can be divided into three subgroups dependent on KPS, the age of the patient, and treatment.[73]

| Recursive partitioning analysis (RPA) class | Definition | Historical Median Survival Time | Historical 1-Year Survival | Historical 3-Year Survival | Historical 5-Year Survival |
|---|---|---|---|---|---|
| III | Age < 50, KPS ≥ 90 | 17.1 months | 70% | 20% | 14% |
| IV | Age < 50, KPS < 90 | 11.2 months | 46% | 7% | 4% |
| | Age >= 50, KPS ≥ 70, surgical removal with good neurologic function | | | | |
| V + VI | Age ≥ 50, KPS ≥ 70, surgical removal with poor neurologic function | 7.5 months | 28% | 1% | 0% |
| | Age ≥ 50, KPS ≥ 70, no surgical removal | | | | |
| | Age ≥ 50, KPS < 70 | | | | |

## Epidemiology [edit]

About 3 per 100,000 people develop the disease a year.[4] It most often begins around 64 years of age and occurs more commonly in males than females.[3][4] It is the second most common central nervous system cancer after meningiomas, which arise from the meninges.[10]

## History [edit]

The term glioblastoma multiforme was introduced in 1926 by Percival Bailey and Harvey Cushing, based on the idea that the tumor originates from primitive precursors of glial cells (glioblasts), and the highly variable appearance due to the presence of necrosis, hemorrhage and cysts (multiform).[74]

# Research [edit]

A 2014 investigation made a screening of various drugs for anti-glioblastoma activity and identified 22 drugs with potent anti-glioblastoma activity, including the combination of irinotecan and statins.[75]

Laboratory research using genetically engineered stem cells to target glioblastomas in mice was reported in 2014 to show promise.[76]

## MicroRNA [edit]

RNA interference, usually microRNA, is being studied in tissue culture, pathology specimens and in preclinical animal studies.[77] MicroRNA-screening of plasma is used to determine the prognosis of glioblastoma.[78][79]

## Immunotherapy [edit]

Relapse of glioblastoma is attributed to the recurrence and persistence of tumor stem cells.[80] In a small trial, a tumor B-cell hybridoma vaccine against tumor stem cells elicited a specific tumor immune reaction thus enhancing immune response to the disease.[81] Larger trials, including tests of different EGFR signaling patterns and their relationship to tumor stem cells are being conducted.[*citation needed*] The test of rindopepimut failed in a phase III trial in 2016.[82] Other immunotherapeutic and vaccine-type approaches are at different stages of development, but conclusive results are not yet available.[83][84]

## Gene therapy [edit]

Gene therapy is a promising approach for fighting cancers including brain cancer.[85] Unlike current conventional cancer treatments such as chemotherapy and radiation therapy, gene transfer has the potential to selectively kill cancer cells while leaving healthy cells unharmed. Over the past two decades significant advances have been made in gene transfer technology and the field has matured to the point of clinical and commercial feasibility. Advances include vector (gene delivery vehicle) construction, vector producer cell efficiency and scale-up processes, preclinical models for target diseases and regulatory guidance regarding clinical trial design including endpoint definitions and measurements.

In one such approach, researchers at UCLA in 2005 reported a long-term survival benefit in an experimental brain tumor animal model.[86] Subsequently, in preparation for human clinical trials, this technology was further developed by Tocagen, and Toca 511 is since 2010 under clinical investigation in a Phase I trial for the potential treatment of recurrent high grade glioma including glioblastoma multiforme (GBM) and anaplastic astrocytoma.[87] Study due to complete July 2016.[87] As of January 2016 Six different trials of Toca 511 are registered.[88]

## Intranasal drug delivery [edit]

Direct nose-to-brain drug delivery is being explored as a means to achieve higher, and hopefully more effective, drug concentrations in the brain.[89][90] A clinical phase I/II study with glioblastoma patients in Brazil investigated the natural compound perillyl alcohol for intranasal delivery as an aerosol. The results were encouraging[91][92][93] and as of 2016 a similar trial has been initiated in the United States.[94]

# References [edit]

*a b c d*

1. ^ Bleeker, Fonnet E.; Molenaar, Remco J.; Leenstra, Sieger (2012). "Recent advances in the molecular understanding of glioblastoma". *Journal of Neuro-Oncology*. **108** (1): 11–27. doi:10.1007/s11060-011-0793-0. PMC 3337398. PMID 22270850.
2. ^ *a b c d* Young, RM; Jamshidi, A; Davis, G; Sherman, JH (June 2015). "Current trends in the surgical management and treatment of adult glioblastoma.". *Annals of Translational Medicine*. **3** (9): 121. doi:10.3978/j.issn.2305-5839.2015.05.10. PMC 4481356. PMID 26207249.
3. ^ *a b c d e f* *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 5.16. ISBN 9283204298.
4. ^ *a b c d e f g h i* Gallego, O (August 2015). "Nonsurgical treatment of recurrent glioblastoma.". *Current oncology (Toronto, Ont.)*. **22** (4): e273–81. doi:10.3747/co.22.2436. PMC 4530825. PMID 26300678.
5. ^ *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 3.8. ISBN 9283204298.
6. ^ *a b c* Khosla, D (February 2016). "Concurrent therapy to enhance radiotherapeutic outcomes in glioblastoma.". *Annals of translational medicine*. **4** (3): 54. doi:10.3978/j.issn.2305-5839.2016.01.25. PMC 4740000. PMID 26904576.
7. ^ Hart, MG; Garside, R; Rogers, G; Stein, K; Grant, R (30 April 2013). "Temozolomide for high grade glioma.". *The Cochrane database of systematic reviews*. **4**: CD007415. doi:10.1002/14651858.CD007415.pub2. PMID 23633341.
8. ^ Van Meir, E. G.; Hadjipanayis, C. G.; Norden, A. D.; Shu, H. K.; Wen, P. Y.; Olson, J. J. (2010). "Exciting New Advances in Neuro-Oncology: The Avenue to a Cure for Malignant Glioma". *CA: A Cancer Journal for Clinicians*. **60** (3): 166–93. doi:10.3322/caac.20069. PMC 2888474. PMID 20445000.
9. ^ Schapira, Anthony H.V. (2007). *Neurology and clinical neuroscience*. Philadelphia: Mosby Elsevier. p. 1336. ISBN 9780323070539.
10. ^ *a b* McNeill, Katharine A. "Epidemiology of Brain Tumors". *Neurologic Clinics*. **34** (4): 981–998. doi:10.1016/j.ncl.2016.06.014.
11. ^ "With Immunotherapy, Glimmers of Progress against Glioblastoma". *National Cancer Institute*. 9 December 2015. Retrieved 23 December 2015.
12. ^ Ohgaki, Hiroko; Kleihues, Paul (2005). "Population-Based Studies on Incidence, Survival Rates, and Genetic Alterations in Astrocytic and Oligodendroglial Gliomas". *Journal of Neuropathology & Experimental Neurology*. **64** (6): 479–89. PMID 15977639.
13. ^ Zheng, Tongzhang; Cantor, Kenneth P.; Zhang, (1): 61–70. doi:10.1007/s11060-006-9303-1 . PMID 17171441.
48. ^ Stevens, Glen H. J. (2006). "Antiepileptic therapy in patients with central nervous system malignancies". *Current Neurology and Neuroscience Reports*. **6** (4): 311–8. doi:10.1007/s11910-006-0024-9. PMID 16822352.
49. ^ Lacroix, Michel; Abi-Said, Dima; Fourney, Daryl R.; Gokaslan, Ziya L.; Shi, Weiming; Demonte, Franco; Lang, Frederick F.; McCutcheon, Ian E.; et al. (2001). "A multivariate analysis of 416 patients with glioblastoma multiforme: Prognosis, extent of resection, and survival". *Journal of Neurosurgery*. **95** (2): 190–8. doi:10.3171/jns.2001.95.2.0190. PMID 11780887.
50. ^ Stummer, Walter; Pichlmeier, Uwe; Meinel, Thomas; Wiestler, Otmar Dieter; Zanella, Friedhelm; Reulen, Hans-Jürgen; Ala-Glioma Study, Group (2006). "Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: A randomised controlled multicentre phase III trial". *The Lancet Oncology*. **7** (5): 392–401. doi:10.1016/S1470-2045(06)70665-9. PMID 16648043.
51. ^ Walker, Michael D.; Alexander, Eben; Hunt, William E.; MacCarty, Collin S.; Mahaley, M. Stephen; Mealey, John; Norrell, Horace A.; Owens, Guy; et al. (1978). "Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas". *Journal of Neurosurgery*. **49** (3): 333–43. doi:10.3171/jns.1978.49.3.0333. PMID 355604.
52. ^ Showalter, Timothy N.; Andrel, Jocelyn; Andrews, David W.; Curran, Walter J.; Daskalakis, Constantine; Werner-Wasik, Maria (2007). "Multifocal Glioblastoma Multiforme: Prognostic Factors and Patterns of Progression". *International Journal of Radiation Oncology*Biology*Physics*. **69** (3): 820–4. doi:10.1016/j.ijrobp.2007.03.045. PMID 17499453.
53. ^ Fulton, DS; Urtasun, RC; Scott-Brown, I; Johnson, ES; Mielke, B; Curry, B; Huyser-Wierenga, D; Hanson, J; Feldstein, M (1992). "Increasing radiation dose intensity using hyperfractionation in patients with malignant glioma. Final report of a prospective phase I-II dose response study". *Journal of Neuro-Oncology*. **14** (1): 63–72. doi:10.1007/BF00170946. PMID 1335044.
54. ^ Sheehan, Jason P; Shaffrey, Mark E; Gupta, Brinda; Larner, James; Rich, Jeremy N; Park, Deric M (2010). "Improving the radiosensitivity of radioresistant and hypoxic glioblastoma". *Future Oncology*. **6** (10): 1591–601. doi:10.2217/fon.10.123. PMID 21062158.
55. ^ Clinical trial number *NCT01465347* for "Safety and Efficacy Study of Trans Sodium Crocetinate (TSC) With Concomitant Radiation Therapy and Temozolomide in Newly Diagnosed Glioblastoma (GBM)" at ClinicalTrials.gov , accessed 2016-02-01
56. ^ Stupp, Roger; Mason, Warren P.; Van Den Bent, Martin J.; Weller, Michael; Fisher, Barbara;

Yawei; Chiu, Brian C. H.; Lynch, Charles F. (2001). "Risk of Brain Glioma not Associated with Cigarette Smoking or Use of Other Tobacco Products in Iowa". *Cancer Epidemiology, Biomarkers & Prevention*. **10** (4): 413–4. PMID 11319186.
14. ^ Wheeler, Lamar; Huncharek, Michael; Kupelnick, Bruce (2003). "Dietary Cured Meat and the Risk of Adult Glioma: A Meta-Analysis of Nine Observational Studies". *Journal of Environmental Pathology, Toxicology and Oncology*. **22** (2): 129–37. doi:10.1615/JEnvPathToxOncol.v22.i2.60. PMID 14533876.
15. ^ Savitz, David A.; Checkoway, Harvey; Loomis, Dana P. (1998). "Magnetic Field Exposure and Neurodegenerative Disease Mortality among Electric Utility Workers". *Epidemiology*. **9** (4): 398–404. doi:10.1097/00001648-199807000-00009. PMID 9647903.
16. ^ Inskip, Peter D.; Tarone, Robert E.; Hatch, Elizabeth E.; Wilcosky, Timothy C.; Shapiro, William R.; Selker, Robert G.; Fine, Howard A.; Black, Peter M.; et al. (2001). "Cellular-Telephone Use and Brain Tumors". *New England Journal of Medicine*. **344** (2): 79–86. doi:10.1056/NEJM200101113440201. PMID 11150357.
17. ^ Kan, Peter; Simonsen, Sara E.; Lyon, Joseph L.; Kestle, John R. W. (2007). "Cellular phone use and brain tumor: A meta-analysis". *Journal of Neuro-Oncology*. **86** (1): 71–8. doi:10.1007/s11060-007-9432-1. PMID 17619826.
18. ^ Hardell, Lennart; Carlberg, Michael; Hansson Mild, Kjell (2009). "Epidemiological evidence for an association between use of wireless phones and tumor diseases". *Pathophysiology*. **16** (2–3): 113–22. doi:10.1016/j.pathophys.2009.01.003. PMID 19268551.
19. ^ Baglietto, Laura; Giles, Graham G.; English, Dallas R.; Karahalios, Amalia; Hopper, John L.; Severi, Gianluca (2011). "Alcohol consumption and risk of glioblastoma; evidence from the Melbourne collaborative cohort study". *International Journal of Cancer*. **128** (8): 1929–1934. doi:10.1002/ijc.25770. PMID 21344375.
20. ^ Vilchez, Regis A; Kozinetz, Claudia A; Arrington, Amy S; Madden, Charles R; Butel, Janet S (2003). "Simian virus 40 in human cancers". *The American Journal of Medicine*. **114** (8): 675–84. doi:10.1016/S0002-9343(03)00087-1. PMID 12798456.
21. ^ Crawford, JR; Santi, MR; Thorarinsdottir, HK; Cornelison, R; Rushing, EJ; Zhang, H; Yao, K; Jacobson, S; MacDonald, TJ (2009). "Detection of human herpesvirus-6 variants in pediatric brain tumors: Association of viral antigen in low grade gliomas". *Journal of Clinical Virology*. **46** (1): 37–42. doi:10.1016/j.jcv.2009.05.011. PMC 2749001. PMID 19505845.
22. ^ Chi, J.; Gu, B.; Zhang, C.; Peng, G.; Zhou, F.; Chen, Y.; Zhang, G.; Guo, Y.; et al. (2012). "Human Herpesvirus 6 Latent Infection in Patients with Taphoorn, Martin J.B.; Belanger, Karl; Brandes, Alba A.; et al. (2005). "Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma". *New England Journal of Medicine*. **352** (10): 987–96. doi:10.1056/NEJMoa043330. PMID 15758009.
57. ^ Mason, Warren P.; Mirimanoff, René O.; Stupp, Roger (2006). "Radiotherapy with Concurrent and Adjuvant Temozolomide: A New Standard of Care for Glioblastoma Multiforme". *Progress in Neurotherapeutics and Neuropsychopharmacology*. **1** (1): 37–52. doi:10.1017/S1748232105000054. ISBN 978-0-521-86253-0.
58. ^ "Temozolomide Plus Radiation Helps Brain Cancer – National Cancer Institute". Archived from the original on August 15, 2007. Retrieved 2007-09-15.
59. ^ Chamberlain, Marc C.; Glantz, Michael J.; Chalmers, Lisa; Horn, Alixis; Sloan, Andrew E. (2006). "Early necrosis following concurrent Temodar and radiotherapy in patients with glioblastoma". *Journal of Neuro-Oncology*. **82** (1): 81–3. doi:10.1007/s11060-006-9241-y. PMID 16944309.
60. ^ Dall'Oglio, Stefano; d'Amico, Anna; Pioli, Fabio; Gabbani, Milena; Pasini, Felice; Passarin, Maria Grazia; Talacchi, Andrea; Turazzi, Sergio; Maluta, Sergio (2008). "Dose-intensity temozolomide after concurrent chemoradiotherapy in operated high-grade gliomas". *Journal of Neuro-Oncology*. **90** (3): 315–9. doi:10.1007/s11060-008-9663-9. PMID 18688571.
61. ^ Khasraw, M; Ameratunga, MS; Grant, R; Wheeler, H; Pavlakis, N (Sep 22, 2014). "Antiangiogenic therapy for high-grade glioma.". *The Cochrane database of systematic reviews*. **9**: CD008218. doi:10.1002/14651858.CD008218.pub3. PMID 25242542.
62. ^ "FDA approves expanded indication for medical device to treat a form of brain cancer". Retrieved 19 March 2016.
63. ^ "FDA approval letter - NovoTTF-100A System" (PDF). *www.fda.gov*. Retrieved 26 December 2014.
64. ^ Stupp, R; et al. (15 December 2015). "Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma". *JAMA*. **314** (23): 2535–43. doi:10.1001/jama.2015.16669. PMID 26670971.
65. ^ *a b* Sampson, John H. (15 December 2015). "Alternating Electric Fields for the Treatment of Glioblastoma". *JAMA*. **314** (23): 2511. doi:10.1001/jama.2015.16701.
66. ^ Wick, Wolfgang (25 February 2016). "TTFields: where does all the skepticism come from?". *Neuro-Oncology*. **18** (3): 303–305. doi:10.1093/neuonc/now012.
67. ^ *a b c* Krex, D.; Klink, B.; Hartmann, C.; Von Deimling, A.; Pietsch, T.; Simon, M.; Sabel, M.; Steinbach, J. P.; et al. (2007). "Long-term survival with glioblastoma multiforme". *Brain*. **130** (10):

Glioma". *Journal of Infectious Diseases*. **206** (9): 1394–8. doi:10.1093/infdis/jis513. PMID 22962688.
23. ^ "Target acquired", *The Economist*, May 29th, 2008
24. ^ Cavenee, WK (2000). "High-grade gliomas with chromosome 1p loss". *Journal of Neurosurgery*. **92** (6): 1080–1. doi:10.3171/jns.2000.92.6.1080. PMID 10839286.
25. ^ Van Wijngaarden, Edwin; Dosemeci, Mustafa (2006). "Brain cancer mortality and potential occupational exposure to lead: Findings from the National Longitudinal Mortality Study, 1979–1989". *International Journal of Cancer*. **119** (5): 1136–44. doi:10.1002/ijc.21947. PMID 16570286.
26. ^ Lehrer, Steven (2010). "Anopheles mosquito transmission of brain tumor". *Medical Hypotheses*. **74** (1): 167–8. doi:10.1016/j.mehy.2009.07.005. PMID 19656635.
27. ^ Pritchett, Joshua C.; Nanau, Radu M.; Neuman, Manuela G. (2012). "The Link between Hypersensitivity Syndrome Reaction Development and Human Herpes Virus-6 Reactivation". *International Journal of Hepatology*. **2012**: 1–19. doi:10.1155/2012/723062. PMC 3362035. PMID 22666603.
28. ^ Glioblastoma multiforme at Mount Sinai
29. ^ [1]
30. ^ Ohgaki, Hiroko; Kleihues, Paul (2009). "Genetic alterations and signaling pathways in the evolution of gliomas". *Cancer Science*. **100** (12): 2235–41. doi:10.1111/j.1349-7006.2009.01308.x. PMID 19737147.
31. ^ *a b* Verhaak, Roel G. W.; Hoadley, Katherine A.; Purdom, Elizabeth; Wang, Victoria; Qi, Yuan; Wilkerson, Matthew D.; Miller, C. Ryan; Ding, Li; et al. (January 2010). "Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in *PDGFRA*, *IDH1*, *EGFR*, and *NF1*". *Cancer Cell*. **17** (1): 98–110. doi:10.1016/j.ccr.2009.12.020. PMC 2818769. PMID 20129251.
32. ^ Hayden, Erika Check (2010). "Genomics boosts brain-cancer work". *Nature*. **463** (7279): 278. doi:10.1038/463278a. PMID 20090720.
33. ^ Kuehn, Bridget M. (2010). "Genomics Illuminates a Deadly Brain Cancer". *JAMA*. **303** (10): 925–7. doi:10.1001/jama.2010.236. PMID 20215599.
34. ^ Bleeker, FE; Lamba, S; Zanon, C; Molenaar, RJ; Hulsebos, TJ; Troost, D; van Tilborg, AA; Vandertop, WP; Leenstra, S; van Noorden, CJ; Bardelli, A (26 September 2014). "Mutational profiling of kinases in glioblastoma.". *BMC Cancer*. **14** (1): 718. doi:10.1186/1471-2407-14-718. PMID 25256166.
35. ^ *a b* Molenaar, RJ; Verbaan, D; Lamba, S; Zanon, C; Jeuken, JW; Boots-Sprenger, SH; Wesseling, P; Hulsebos, TJ; Troost, D; van Tilborg, AA; Leenstra, S; Vandertop, WP; Bardelli, A; van Noorden, CJ; 2596–606. doi:10.1093/brain/awm204. PMID 17785346.
68. ^ Martinez, Ramon; Schackert, Gabriele; Yaya-Tur, Ricard; Rojas-Marcos, Iñigo; Herman, James G.; Esteller, Manel (2006). "Frequent hypermethylation of the DNA repair gene MGMT in long-term survivors of glioblastoma multiforme". *Journal of Neuro-Oncology*. **83** (1): 91–3. doi:10.1007/s11060-006-9292-0. PMID 17164975.
69. ^ M. Preusser, A. Wöhrer, S. Stary, R. Höftberger, B. Streubel, J. A. Hainfellner (Aug 2011). "Value and limitations of immunohistochemistry and gene sequencing for detection of the IDH1-R132H mutation in diffuse glioma biopsy specimens.". *J Neuropathol Exp Neurol*. **70** (8): 715–723. doi:10.1097/NEN.0b013e31822713f0.
70. ^ Molenaar, Remco J. (2014). "The combination of *IDH1* mutations and *MGMT* methylation status predicts survival in glioblastoma better than either *IDH1* or *MGMT* alone". *Neuro-Oncology*. **16** (9): 1263–1273. doi:10.1093/neuonc/nou005. PMC 4136888. PMID 24510240.
71. ^ Smoll, Nicolas R.; Schaller, Karl; Gautschi, Oliver P. (2012). "The Cure Fraction of Glioblastoma Multiforme". *Neuroepidemiology*. **39** (1): 63–9. doi:10.1159/000339319. PMID 22776797.
72. ^ University of California, Los Angeles Neuro-Oncology : How Our Patients Perform : Glioblastoma Multiforme [GBM]. Neurooncology.ucla.edu. Retrieved on 2010-10-19.
73. ^ Shaw, E.G; Seiferheld, W; Scott, C; Coughlin, C; Leibel, S; Curran, W; Mehta, M (2003). "Reexamining the radiation therapy oncology group (RTOG) recursive partitioning analysis (RPA) for glioblastoma multiforme (GBM) patients". *International Journal of Radiation Oncology*Biology*Physics*. **57** (2): S135–6. doi:10.1016/S0360-3016(03)00843-5.
74. ^ Bailey & Cushing: Tumors of the Glioma Group JB Lippincott, Philadelphia, 1926.[*page needed*]
75. ^ Jiang PF (Jan 2014). "Novel anti-glioblastoma agents and therapeutic combinations identified from a collection of FDA approved drugs.". *J Transl Med*. **12** (1): 13. doi:10.1186/1479-5876-12-13. PMC 3898565. PMID 24433351.
76. ^ Stuckey, Daniel; Hingtgen, Shawn; Karaka, Nihal; Rich, Benjamin; Shah, Khalid (2014). "Engineering toxin-resistant therapeutic stem cells to treat brain tumors". *Stem Cells*. AlphaMed Express. **33**: 589–600. doi:10.1002/stem.1874. PMID 25346520.
77. ^ Møller, Heidi G.; Rasmussen, Andreas P.; Andersen, Hjalte H.; Johnsen, Kasper B.; Henriksen, Michael; Duroux, Meg (2012). "A Systematic Review of MicroRNA in Glioblastoma Multiforme: Micro-modulators in the Mesenchymal Mode of Migration and Invasion". *Molecular Neurobiology*. **47** (1): 131–44. doi:10.1007/s12035-012-8349-7. PMC 3538124. PMID 23054677.
78. ^ Henriksen, Michael; Johnsen, Kasper Bendix; Andersen, Hjalte Holm M; Pilgaard, Linda; Duroux,

Bleeker, FE (September 2014). "The combination of IDH1 mutations and MGMT methylation status predicts survival in glioblastoma better than either IDH1 or MGMT alone.". *Neuro-oncology*. **16** (9): 1263–73. doi:10.1093/neuonc/nou005. PMC 4136888. PMID 24510240.

36. ^ a b Molenaar, RJ; Radivoyevitch, T; Maciejewski, JP; van Noorden, CJ; Bleeker, FE (28 May 2014). "The driver and passenger effects of isocitrate dehydrogenase 1 and 2 mutations in oncogenesis and survival prolongation.". *Biochimica et Biophysica Acta*. **1846** (2): 326–341. doi:10.1016/j.bbcan.2014.05.004. PMID 24880135.
37. ^ Hegi, Monika E.; Diserens, Annie-Claire; Gorlia, Thierry; Hamou, Marie-France; De Tribolet, Nicolas; Weller, Michael; Kros, Johan M.; Hainfellner, Johannes A.; et al. (2005). "*MGMT* Gene Silencing and Benefit from Temozolomide in Glioblastoma". *New England Journal of Medicine*. **352** (10): 997–1003. doi:10.1056/NEJMoa043331. PMID 15758010.
38. ^ Murat, A.; Migliavacca, E.; Gorlia, T.; Lambiv, W. L.; Shay, T.; Hamou, M.-F.; De Tribolet, N.; Regli, L.; et al. (2008). "Stem Cell-Related 'Self-Renewal' Signature and High Epidermal Growth Factor Receptor Expression Associated with Resistance to Concomitant Chemoradiotherapy in Glioblastoma". *Journal of Clinical Oncology*. **26** (18): 3015–24. doi:10.1200/JCO.2007.15.7164. PMID 18565887.
39. ^ Hira, Vashendriya V. V.; Ploegmakers, Kimberley J.; Grevers, Frederieke; Verbovšek, Urška; Silvestre-Roig, Carlos; Aronica, Eleonora; Tigchelaar, Wikky; Turnšek, Tamara Lah; Molenaar, Remco J. (2015-07-01). "CD133+ and Nestin+ Glioma Stem-Like Cells Reside Around CD31+ Arterioles in Niches that Express SDF-1α, CXCR4, Osteopontin and Cathepsin K". *Journal of Histochemistry & Cytochemistry*. **63** (7): 481–493. doi:10.1369/0022155415581689. ISSN 0022-1554. PMID 25809793.
40. ^ Park, Deric M.; Jung, Jinkyu; Masjkur, Jimmy; Makrogkikas, Stylianos; Ebermann, Doreen; Saha, Sarama; Rogliano, Roberta; Paolillo, Nicoletta; Pacioni, Simone; McKay, Ron D.; Poser, Steve; Androutsellis-Theotokis, Andreas (2013). "Hes3 regulates cell number in cultures from glioblastoma multiforme with stem cell characteristics". *Scientific Reports*. **3**: 1095. Bibcode:2013NatSR...3E1095P. doi:10.1038/srep01095. PMC 3566603. PMID 23393614.
41. ^ van Lith, SA; Navis, AC; Verrijp, K; Niclou, SP; Bjerkvig, R; Wesseling, P; Tops, B; Molenaar, R; van Noorden, CJ; Leenders, WP (August 2014). "Glutamate as chemotactic fuel for diffuse glioma cells: are they glutamate suckers?". *Biochimica et Biophysica Acta*. **1846** (1): 66–74. doi:10.1016/j.bbcan.2014.04.004. PMID 24747768.
42. ^ van Lith, SA; Molenaar, R; van Noorden, CJ; Meg (2014). "MicroRNA Expression Signatures Determine Prognosis and Survival in Glioblastoma Multiforme—a Systematic Overview". *Molecular Neurobiology*. **50**: 896–913. doi:10.1007/s12035-014-8668-y. PMID 24619503.
79. ^ Niyazi, Maximilian; Zehentmayr, Franz; Niemöller, Olivier M; Eigenbrod, Sabina; Kretzschmar, Hans; Osthoff, Klaus-Schulze; Tonn, Jörg-Christian; Atkinson, Mike; Mörtl, Simone; Belka, Claus (2011). "MiRNA expression patterns predict survival in glioblastoma". *Radiation Oncology*. **6** (1): 153. doi:10.1186/1748-717X-6-153. PMC 3235977. PMID 22074483.
80. ^ Ghebeh, H; Bakr, MM; Dermime, S (2008). "Cancer stem cell immunotherapy: The right bullet for the right target". *Hematology/oncology and stem cell therapy*. **1** (1): 1–2. doi:10.1016/s1658-3876(08)50053-7. PMID 20063521.
81. ^ Moviglia, GA; Carrizo, AG; Varela, G; Gaeta, CA; Paes De Lima, A; Farina, P; Molina, H (2008). "Preliminary report on tumor stem cell/B cell hybridoma vaccine for recurrent glioblastoma multiforme". *Hematology/oncology and stem cell therapy*. **1** (1): 3–13. doi:10.1016/s1658-3876(08)50054-9. PMID 20063522.
82. ^ Celldex Brain Tumor Vaccine Fails Pivotal Clinical Trial. March 2016
83. ^ Yang L, Guo G, Niu XY, Liu J (2015). "Dendritic Cell-Based Immunotherapy Treatment for Glioblastoma Multiforme.". *Biomed. Res. Int.* **2015**: 717530. doi:10.1155/2015/717530. PMC 4488155. PMID 26167495.
84. ^ Hofman FM, Stathopoulos A, Kruse CA, Chen TC, Schijns VE (2013). "Immunotherapy of malignant gliomas using autologous and allogeneic tissue cells". *Anticancer Agents in Medicinal Chemistry*. **10** (6): 462–70. PMC 3999913. PMID 20879986.
85. ^ Fulci, Giulia; Chiocca, E Antonio (2007). "The status of gene therapy for brain tumors". *Expert Opinion on Biological Therapy*. **7** (2): 197–208. doi:10.1517/14712598.7.2.197. PMC 2819130. PMID 17250458.
86. ^ Tai, C; Wang, W; Chen, T; Kasahara, N (2005). "Single-Shot, Multicycle Suicide Gene Therapy by Replication-Competent Retrovirus Vectors Long-Term Survival Benefit in Experimental Glioma". *Molecular Therapy*. **12** (5): 842–51. doi:10.1016/j.ymthe.2005.03.017. PMID 16257382.
87. ^ a b Clinical trial number *NCT01156584* for "A Study of a Retroviral Replicating Vector Administered to Subjects With Recurrent Malignant Glioma" at ClinicalTrials.gov
88. ^ Toca 511 trials
89. ^ Matthias van Woensel; Nathalie Wauthoz; Rémi Rosière; Karim Amighi; Véronique Mathieu; Florence Lefranc; Stefaan W. van Gool; Steven de Vleeschouwer (2013). "Formulations for Intranasal Delivery of Pharmacological Agents to Combat Brain

Leenders, WP (December 2014). "Tumor cells in search for glutamate: an alternative explanation for increased invasiveness of IDH1 mutant gliomas.". *Neuro-oncology*. **16** (12): 1669–70. doi:10.1093/neuonc/nou152. PMID 25074540.

43. ^ Molenaar, Remco J. (2011). "Ion Channels in Glioblastoma". *ISRN Neurology*. **2011**: 1–7. doi:10.5402/2011/590249. PMC 3263536. PMID 22389824.
44. ^ Smirniotopoulos, J. G.; Murphy, F. M.; Rushing, E. J.; Rees, J. H.; Schroeder, J. W. (2007). "From the Archives of the AFIP: Patterns of Contrast Enhancement in the Brain and Meninges". *Radiographics*. **27** (2): 525–51. doi:10.1148/rg.272065155. PMID 17374867.
45. ^ Bleeker, FE; Molenaar, RJ; Leenstra, S (May 2012). "Recent advances in the molecular understanding of glioblastoma.". *Journal of Neuro-Oncology*. **108** (1): 11–27. doi:10.1007/s11060-011-0793-0. PMC 3337398. PMID 22270850.
46. ^ "The driver and passenger effects of isocitrate dehydrogenase 1 and 2 mutations in oncogenesis and survival prolongation.". *Biochim Biophys Acta*. **1846** (2): 326–41. Dec 2014. doi:10.1016/j.bbcan.2014.05.004. PMID 24880135.
47. ^ Lawson, H. Christopher; Sampath, Prakash; Bohan, Eileen; Park, Michael C.; Hussain, Namath; Olivi, Alessandro; Weingart, Jon; Kleinberg, Lawrence; Brem, Henry (2006). "Interstitial chemotherapy for malignant gliomas: The Johns Hopkins experience". *Journal of Neuro-Oncology*. **83**

Disease: A New Opportunity to Tackle GBM?". *Cancers (Basel)*. **5** (3): 1020–48. doi:10.3390/cancers5031020. PMC 3795377. PMID 24202332.

90. ^ Pardeshi CV, Belgamwar VS (2013). "Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood-brain barrier: an excellent platform for brain targeting". *Expert Opinion in Drug Delivery*. **10** (7): 957–72. doi:10.1517/17425247.2013.790887. PMID 23586809.
91. ^ Matthias van Woensel; Nathalie Wauthoz; Rémi Rosière; Karim Amighi; Véronique Mathieu; Florence Lefranc; Stefaan W. van Gool; Steven de Vleeschouwer (2013). "Formulations for Intranasal Delivery of Pharmacological Agents to Combat Brain Disease: A New Opportunity to Tackle GBM?". *Cancers (Basel)*. **5** (3): 1020–48. doi:10.3390/cancers5031020. PMC 3795377. PMID 24202332.
92. ^ Peterson A, Bansal A, Hofman F, Chen TC, Zada G (2014). "A systematic review of inhaled intranasal therapy for central nervous system neoplasms: an emerging therapeutic option". *Journal of Neurooncology*. **116** (3): 437–46. doi:10.1007/s11060-013-1346-5. PMID 24398618.
93. ^ Chen TC, Da Fonseca CO, Schönthal AH (2015). "Preclinical development and clinical use of perillyl alcohol for chemoprevention and cancer therapy". *American Journal of Cancer Research*. **5** (5): 1580–93. PMID 26175929.
94. ^ https://clinicaltrials.gov/ct2/show/NCT02704858

## External links [edit]

- Information about Glioblastoma Multiforme (GBM) from the American Brain Tumor Association
- AFIP Course Syllabus - Astrocytoma WHO Grading Lecture Handout
- Image Database – MR & CT of Glioblastoma

Wikimedia Commons has media related to *Glioblastoma multiforme*.

| v · t · e | **Nervous tissue tumors / NS neoplasm / Neuroectodermal tumor (ICD-O 9350–9589) (C70–C72, D32–D33, 191–192/225)** | | | |
|---|---|---|---|---|
| **Endocrine** | *Sellar:* | Craniopharyngioma · Pituicytoma · | | |
| | *Other:* | Pinealoma · | | |
| | | **Glioma** | **Astrocyte** | Astrocytoma (Pilocytic astrocytoma · Pleomorphic xanthoastrocytoma · Subependymal giant cell astrocytoma · Fibrillary astrocytoma · Anaplastic astrocytoma · Glioblastoma multiforme · · |
| | | | **Oligodendrocyte** | Oligodendroglioma · |

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|---|---|---|---|---|
| **CNS** | **Neuroepithelial (brain tumors, spinal tumors)** | | **Ependyma** | Ependymoma · Subependymoma · |
| | | | **Choroid plexus** | Choroid plexus tumor (Choroid plexus papilloma · Choroid plexus carcinoma · · |
| | | | **Multiple/unknown** | Oligoastrocytoma · Gliomatosis cerebri · Gliosarcoma · |
| | | **Mature neuron** | | Ganglioneuroma: Gangliоglioma · Retinoblastoma · Neurocytoma · Dysembryoplastic neuroepithelial tumour · Lhermitte–Duclos disease · |
| | | **PNET** | | Neuroblastoma (Esthesioneuroblastoma · Ganglioneuroblastoma · · Medulloblastoma · Atypical teratoid rhabdoid tumor · |
| | | **Primitive** | | Medulloepithelioma · |
| | **Meningiomas (Meninges)** | | | Meningioma · Hemangiopericytoma · |
| | **Hematopoietic** | | | Primary central nervous system lymphoma · |
| **PNS: NST** | *Cranial and paraspinal nerves:* Neurofibroma (Neurofibrosarcoma · Neurofibromatosis · · Neurilemmoma/Schwannoma (Acoustic neuroma · · Malignant peripheral nerve sheath tumor · | | | |
| *Note: Not all brain tumors are of nervous tissue, and not all nervous tissue tumors are in the brain (see brain metastasis).* | | | | |
| **Authority control** | GND: 4157617-2 · | | | |

Categories: Brain tumor

# Leukemia







*For the journal, see Leukemia (journal). For animal diseases, see Leucosis.*

**Leukemia**, also spelled **leukaemia**, is a group of cancers that usually begin in the bone marrow and result in high numbers of abnormal white blood cells.[2] These white blood cells are not fully developed and are called *blasts* or *leukemia cells*. Symptoms may include bleeding and bruising problems, feeling tired, fever, and an increased risk of infections.[3] These symptoms occur due to a lack of normal blood cells.[3] Diagnosis is typically made by blood tests or bone marrow biopsy.[3]

The exact cause of leukemia is unknown. Different kinds of leukemia are believed to have different causes. Both inherited and environmental (non-inherited) factors are believed to be involved.[4] Risk factors include smoking, ionizing radiation, some chemicals (such as benzene), prior chemotherapy, and Down syndrome.[4][5] People with a family history of leukemia are also at higher risk.[5] There are four main types of leukemia — acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML) — as well as a number of less common types.[5][6] Leukemias and lymphomas both belong to a broader group of tumors that affect the blood, bone marrow, and lymphoid system, known as tumors of the hematopoietic and lymphoid tissues.[7][8]

Treatment may involve some combination of chemotherapy, radiation therapy, targeted therapy, and bone marrow transplant, in addition to supportive care and palliative care as needed. Certain types of leukemia may be managed with watchful waiting.[5] The success of treatment depends on the type of leukemia and the age of the person. Outcomes have improved in the developed world.[6] The average five-year survival rate is 57% in the United States.[9] In children under 15, the five-year survival rate is greater than 60 to 85%, depending on the type of leukemia.[10] In children with acute leukemia who are cancer-free after five years, the cancer is unlikely to return.[10]

In 2012, leukemia developed in 352,000 people globally and caused 265,000 deaths.[6] It is the most common type of cancer in children, with three quarters of leukemia cases in children being the acute lymphoblastic type.[5] However, about 90% of all leukemias are diagnosed in adults, with AML and CLL being most common in adults.[5] It occurs more commonly in the developed world.[6]

Contents



Variants

A Wright's stained bone marrow aspirate smear from a person with precursor B-cell acute lymphoblastic leukemia.

**Pronunciation** /luːˈkiːmiːə/[1]

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Hematology and oncology |
| **ICD-10** | C91-C95 |
| **ICD-9-CM** | 208.9 |
| **ICD-O** | 9800-9940 |
| **DiseasesDB** | 7431 |
| **MedlinePlus** | 001299 |
| **eMedicine** | article/1201870 |
| **MeSH** | D007938 |

[edit on Wikidata]

## Classification [edit]

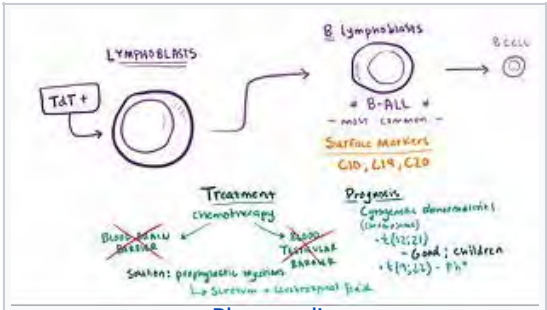
### General classification [edit]

**Four major kinds of leukemia**

| Cell type | Acute | Chronic |
|---|---|---|
| **Lymphocytic leukemia** (or "lymphoblastic") | Acute lymphoblastic leukemia (ALL) | Chronic lymphocytic leukemia (CLL) |
| **Myelogenous leukemia** ("myeloid" or "nonlymphocytic") | Acute myelogenous leukemia (AML or myeloblastic) | Chronic myelogenous leukemia (CML) |

Clinically and pathologically, leukemia is subdivided into a variety of large groups. The first division is between its *acute* and *chronic* forms:

- Acute leukemia is characterized by a rapid increase in the number of immature blood cells. The crowding that results from such cells makes the bone marrow unable to produce healthy blood cells. Immediate treatment is required in acute leukemia because of the rapid progression and accumulation of the malignant cells, which then spill over into the bloodstream and spread to other organs of the body. Acute forms of leukemia are the most common forms of leukemia in children.
- Chronic leukemia is characterized by the excessive buildup of relatively mature, but still abnormal, white blood cells. Typically taking months or years to progress, the cells are produced at a much higher rate than normal, resulting in many abnormal white blood cells. Whereas acute leukemia must be treated immediately, chronic forms are sometimes monitored for some time before treatment to ensure maximum effectiveness of therapy. Chronic leukemia mostly occurs in older people, but can occur in any age group.




Play media

An explanation of acute leukemia

Additionally, the diseases are subdivided according to which kind of blood cell is affected. This divides leukemias into lymphoblastic or *lymphocytic leukemias* and myeloid or *myelogenous leukemias*:

- In lymphoblastic or lymphocytic leukemias, the cancerous change takes place in a type of marrow cell that normally goes on to form lymphocytes, which are infection-fighting immune system cells. Most lymphocytic leukemias involve a specific subtype of lymphocyte, the B cell.
- In myeloid or myelogenous leukemias, the cancerous change takes place in a type of marrow cell that normally goes on to form red blood cells, some other types of white cells, and platelets.

Combining these two classifications provides a total of four main categories. Within each of these main categories, there are typically several subcategories. Finally, some rarer types are usually considered to be outside of this classification scheme.

### Specific types [edit]

- Acute lymphoblastic leukemia (ALL) is the most common type of leukemia in young children. It also affects adults, especially those 65 and older. Standard treatments involve chemotherapy and radiotherapy. The survival rates vary by age: 85% in children and 50% in adults.[11] Subtypes include precursor B acute lymphoblastic leukemia, precursor T acute lymphoblastic leukemia, Burkitt's leukemia, and acute biphenotypic leukemia.
- Chronic lymphocytic leukemia (CLL) most often affects adults over the age of 55. It sometimes occurs in younger adults, but it almost never affects children. Two-thirds of affected people are men. The five-year survival rate is 75%.[12] It is incurable, but there are many effective treatments. One subtype is B-cell prolymphocytic leukemia, a more aggressive disease.
- Acute myelogenous leukemia (AML) occurs more commonly in adults than in children, and more commonly in men than women. It is treated with chemotherapy. The five-year survival rate is 40%, except for APL (Acute Promyelocytic Leukemia), which has a survival rate greater than 90%.[13] Subtypes of AML include acute promyelocytic leukemia, acute myeloblastic leukemia, and acute megakaryoblastic leukemia.

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- Chronic myelogenous leukemia (CML) occurs mainly in adults; a very small number of children also develop this disease. It is treated with imatinib (Gleevec in United States, Glivec in Europe) or other drugs.[14] The five-year survival rate is 90%.[15][16] One subtype is chronic myelomonocytic leukemia.
- Hairy cell leukemia (HCL) is sometimes considered a subset of chronic lymphocytic leukemia, but does not fit neatly into this category. About 80% of affected people are adult men. No cases in children have been reported. HCL is incurable but easily treatable. Survival is 96% to 100% at ten years.[17]
- T-cell prolymphocytic leukemia (T-PLL) is a very rare and aggressive leukemia affecting adults; somewhat more men than women are diagnosed with this disease.[18] Despite its overall rarity, it is the most common type of mature T cell leukemia;[19] nearly all other leukemias involve B cells. It is difficult to treat, and the median survival is measured in months.
- Large granular lymphocytic leukemia may involve either T-cells or NK cells; like hairy cell leukemia, which involves solely B cells, it is a rare and indolent (not aggressive) leukemia.[20]
- Adult T-cell leukemia is caused by human T-lymphotropic virus (HTLV), a virus similar to HIV. Like HIV, HTLV infects CD4+ T-cells and replicates within them; however, unlike HIV, it does not destroy them. Instead, HTLV "immortalizes" the infected T-cells, giving them the ability to proliferate abnormally. Human T-cell lymphotropic virus types I and II (HTLV-I/II) are endemic in certain areas of the world.

## Signs and symptoms [edit]

Damage to the bone marrow, by way of displacing the normal bone marrow cells with higher numbers of immature white blood cells, results in a lack of blood platelets, which are important in the blood clotting process. This means people with leukemia may easily become bruised, bleed excessively, or develop pinprick bleeds (petechiae).

White blood cells, which are involved in fighting pathogens, may be suppressed or dysfunctional. This could cause the patient's immune system to be unable to fight off a simple infection or to start attacking other body cells. Because leukemia prevents the immune system from working normally, some patients experience frequent infection, ranging from infected tonsils, sores in the mouth, or diarrhea to life-threatening pneumonia or opportunistic infections.

Finally, the red blood cell deficiency leads to anemia, which may cause dyspnea and pallor.

Some patients experience other symptoms, such as feeling sick, having fevers, chills, night sweats, feeling fatigued and other flu-like symptoms. Some patients experience nausea or a feeling of fullness due to an enlarged liver and spleen; this can result in unintentional weight loss. Blasts affected by the disease may come together and become swollen in the liver or in the lymph nodes causing pain and leading to nausea.[22]

Common symptoms of chronic or acute leukemia[21]

If the leukemic cells invade the central nervous system, then neurological symptoms (notably headaches) can occur. Uncommon neurological symptoms like migraines, seizures, or coma can occur as a result of brain stem pressure. All symptoms associated with leukemia can be attributed to other diseases. Consequently, leukemia is always diagnosed through medical tests.

The word *leukemia*, which means 'white blood', is derived from the characteristic high white blood cell count that presents in most afflicted patients before treatment. The high number of white blood cells are apparent when a blood sample is viewed under a microscope, with the extra white blood cells frequently being immature or dysfunctional. The excessive number of cells can also interfere with the level of other cells, causing further harmful imbalance in the blood count.

Some leukemia patients do not have high white blood cell counts visible during a regular blood count. This less-common condition is called *aleukemia*. The bone marrow still contains cancerous white blood cells which disrupt the normal production of blood cells, but they remain in the marrow instead of entering the bloodstream, where they would be visible in a blood test. For an aleukemic patient, the white blood cell counts in the bloodstream can be normal or low. Aleukemia can occur in any of the four major types of leukemia, and is particularly common in hairy cell leukemia.[23]

## Causes [edit]

There is no single known cause for any of the different types of leukemias. The few known causes, which are not generally factors within the control of the average person, account for relatively few cases.[24] The cause for most cases of leukemia is unknown. The different leukemias likely have different causes.

Leukemia, like other cancers, results from mutations in the DNA. Certain mutations can trigger leukemia by activating oncogenes or deactivating tumor suppressor genes, and thereby disrupting the regulation of cell death, differentiation or [25]

division. These mutations may occur spontaneously or as a result of exposure to radiation or carcinogenic substances.

Among adults, the known causes are natural and artificial ionizing radiation, a few viruses such as human T-lymphotropic virus, and some chemicals, notably benzene and alkylating chemotherapy agents for previous malignancies.[26][27][28] Use of tobacco is associated with a small increase in the risk of developing acute myeloid leukemia in adults.[26] Cohort and case-control studies have linked exposure to some petrochemicals and hair dyes to the development of some forms of leukemia. Diet has very limited or no effect, although eating more vegetables may confer a small protective benefit.[24]

Viruses have also been linked to some forms of leukemia. For example, human T-lymphotropic virus (HTLV-1) causes adult T-cell leukemia.[29]

A few cases of maternal-fetal transmission (a baby acquires leukemia because its mother had leukemia during the pregnancy) have been reported.[26] Children born to mothers who use fertility drugs to induce ovulation are more than twice as likely to develop leukemia during their childhoods than other children.[30]

### Radiation [edit]

Large doses of Sr-90 emission from nuclear reactor, nicknamed bone seeker increases the risk of bone cancer and leukemia in animals, and is presumed to do so in people.[31]

### Genetic conditions [edit]

Some people have a genetic predisposition towards developing leukemia. This predisposition is demonstrated by family histories and twin studies.[26] The affected people may have a single gene or multiple genes in common. In some cases, families tend to develop the same kinds of leukemia as other members; in other families, affected people may develop different forms of leukemia or related blood cancers.[26]

In addition to these genetic issues, people with chromosomal abnormalities or certain other genetic conditions have a greater risk of leukemia.[27] For example, people with Down syndrome have a significantly increased risk of developing forms of acute leukemia (especially acute myeloid leukemia), and Fanconi anemia is a risk factor for developing acute myeloid leukemia.[26] Mutation in SPRED1 gene has been associated with a predisposition to childhood leukemia.[32]

### Non ionizing radiation [edit]

Whether or not non-ionizing radiation causes leukemia has been studied for several decades. The International Agency for Research on Cancer expert working group undertook a detailed review of all data on static and extremely low frequency electromagnetic energy, which occurs naturally and in association with the generation, transmission, and use of electrical power.[33] They concluded that there is limited evidence that high levels of ELF magnetic (but not electric) fields might cause some cases of childhood leukemia.[33] No evidence for a relationship to leukemia or another form of malignancy in adults has been demonstrated.[33] Since exposure to such levels of ELFs is relatively uncommon, the World Health Organization concludes that ELF exposure, if later proven to be causative, would account for just 100 to 2400 cases worldwide each year, representing 0.2 to 4.9% of the total incidence of childhood leukemia for that year (about 0.03 to 0.9% of all leukemias).[34]

## Diagnosis [edit]

Diagnosis is usually based on repeated complete blood counts and a bone marrow examination following observations of the symptoms. Sometimes, blood tests may not show that a person has leukemia, especially in the early stages of the disease or during remission. A lymph node biopsy can be performed to diagnose certain types of leukemia in certain situations.

Following diagnosis, blood chemistry tests can be used to determine the degree of liver and kidney damage or the effects of chemotherapy on the patient. When concerns arise about other damage due to leukemia, doctors may use an X-ray, MRI, or ultrasound. These can potentially show leukemia's effects on such body parts as bones (X-ray), the brain (MRI), or the kidneys, spleen, and liver (ultrasound). CT scans can be used to check lymph nodes in the chest, though this is almost never done.

Despite the use of these methods to diagnose whether or not a patient has leukemia, many people have not been diagnosed because many of the symptoms are vague, non-specific, and can refer to other diseases. For this reason, the American Cancer Society estimates that at least one-fifth of the people with leukemia have not yet been diagnosed.[23]

## Treatment [edit]

Most forms of leukemia are treated with pharmaceutical medication, typically combined into a multi-drug chemotherapy regimen. Some are also treated with radiation therapy. In some cases, a bone marrow transplant is effective.

### Acute lymphoblastic [edit]

*Further information: Acute lymphoblastic leukemia § Treatment*

Management of ALL is directed towards control of bone marrow and systemic (whole-body) disease. Additionally, treatment must prevent leukemic cells from spreading to other sites, particularly the central nervous system (CNS) e.g. monthly lumbar punctures. In general, ALL treatment is divided into several phases:

- *Induction chemotherapy* to bring about bone marrow remission. For adults, standard induction plans include prednisone, vincristine, and an anthracycline drug; other drug plans may include L-asparaginase or cyclophosphamide. For children with low-risk ALL, standard therapy usually consists of three drugs (prednisone, L-asparaginase, and vincristine) for the first month of treatment.
- *Consolidation therapy* or *intensification therapy* to eliminate any remaining leukemia cells. There are many different approaches to consolidation, but it is typically a high-dose, multi-drug treatment that is undertaken for a few months. Patients with low- to average-risk ALL receive therapy with antimetabolite drugs such as methotrexate and 6-mercaptopurine (6-MP). High-risk patients receive higher drug doses of these drugs, plus additional drugs.
- *CNS prophylaxis* (preventive therapy) to stop the cancer from spreading to the brain and nervous system in high-risk patients. Standard prophylaxis may include radiation of the head and/or drugs delivered directly into the spine.
- *Maintenance treatments* with chemotherapeutic drugs to prevent disease recurrence once remission has been achieved. Maintenance therapy usually involves lower drug doses, and may continue for up to three years.
- Alternatively, *allogeneic bone marrow transplantation* may be appropriate for high-risk or relapsed patients.[35]

## Chronic lymphocytic [edit]

*Further information: Chronic lymphocytic leukemia § Treatment*

### Decision to treat [edit]

Hematologists base CLL treatment on both the stage and symptoms of the individual patient. A large group of CLL patients have low-grade disease, which does not benefit from treatment. Individuals with CLL-related complications or more advanced disease often benefit from treatment. In general, the indications for treatment are:

- Falling hemoglobin or platelet count
- Progression to a later stage of disease
- Painful, disease-related overgrowth of lymph nodes or spleen
- An increase in the rate of lymphocyte production[36]

### Treatment approach [edit]

For most people with CLL, it is incurable by present treatments, so treatment is directed towards suppressing the disease for many years, rather than totally and permanently eliminating it. The primary chemotherapeutic plan is combination chemotherapy with chlorambucil or cyclophosphamide, plus a corticosteroid such as prednisone or prednisolone. The use of a corticosteroid has the additional benefit of suppressing some related autoimmune diseases, such as immunohemolytic anemia or immune-mediated thrombocytopenia. In resistant cases, single-agent treatments with nucleoside drugs such as fludarabine,[37] pentostatin, or cladribine may be successful. Younger and healthier patients may choose allogeneic or autologous bone marrow transplantation in the hope of a permanent cure.[38]

## Acute myelogenous [edit]

*Further information: Acute myeloid leukemia § Treatment*

Many different anti-cancer drugs are effective for the treatment of AML. Treatments vary somewhat according to the age of the patient and according to the specific subtype of AML. Overall, the strategy is to control bone marrow and systemic (whole-body) disease, while offering specific treatment for the central nervous system (CNS), if involved.

In general, most oncologists rely on combinations of drugs for the initial, *induction phase* of chemotherapy. Such combination chemotherapy usually offers the benefits of early remission and a lower risk of disease resistance. *Consolidation* and *maintenance* treatments are intended to prevent disease recurrence. Consolidation treatment often entails a repetition of induction chemotherapy or the intensification chemotherapy with additional drugs. By contrast, maintenance treatment involves drug doses that are lower than those administered during the induction phase.[39]

## Chronic myelogenous [edit]

*Further information: Chronic myelogenous leukemia § Treatment*

There are many possible treatments for CML, but the standard of care for newly diagnosed patients is imatinib (Gleevec) therapy.[40] Compared to most anti-cancer drugs, it has relatively few side effects and can be taken orally at home. With this drug, more than 90% of patients will be able to keep the disease in check for at least five years,[40] so that CML becomes a chronic, manageable condition.

In a more advanced, uncontrolled state, when the patient cannot tolerate imatinib, or if the patient wishes to attempt a permanent cure, then an allogeneic bone marrow transplantation may be performed. This procedure involves high-dose

chemotherapy and radiation followed by infusion of bone marrow from a compatible donor. Approximately 30% of patients die from this procedure.[40]

### Hairy cell [edit]

*Further information: Hairy cell leukemia § Treatment*

**Decision to treat**
Patients with hairy cell leukemia who are symptom-free typically do not receive immediate treatment. Treatment is generally considered necessary when the patient shows signs and symptoms such as low blood cell counts (e.g., infection-fighting neutrophil count below 1.0 K/μL), frequent infections, unexplained bruises, anemia, or fatigue that is significant enough to disrupt the patient's everyday life.

**Typical treatment approach**
Patients who need treatment usually receive either one week of cladribine, given daily by intravenous infusion or a simple injection under the skin, or six months of pentostatin, given every four weeks by intravenous infusion. In most cases, one round of treatment will produce a prolonged remission.[41]

Other treatments include rituximab infusion or self-injection with Interferon-alpha. In limited cases, the patient may benefit from *splenectomy* (removal of the spleen). These treatments are not typically given as the first treatment because their success rates are lower than cladribine or pentostatin.[42]

### T-cell prolymphocytic [edit]

*Further information: T-cell prolymphocytic leukemia § Treatment*

Most patients with T-cell prolymphocytic leukemia, a rare and aggressive leukemia with a median survival of less than one year, require immediate treatment.[43]

T-cell prolymphocytic leukemia is difficult to treat, and it does not respond to most available chemotherapeutic drugs.[43] Many different treatments have been attempted, with limited success in certain patients: purine analogues (pentostatin, fludarabine, cladribine), chlorambucil, and various forms of combination chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone CHOP, cyclophosphamide, vincristine, prednisone [COP], vincristine, doxorubicin, prednisone, etoposide, cyclophosphamide, bleomycin VAPEC-B). Alemtuzumab (Campath), a monoclonal antibody that attacks white blood cells, has been used in treatment with greater success than previous options.[43]

Some patients who successfully respond to treatment also undergo stem cell transplantation to consolidate the response.[43]

### Juvenile myelomonocytic [edit]

*Further information: Juvenile myelomonocytic leukemia § Treatment*

Treatment for juvenile myelomonocytic leukemia can include splenectomy, chemotherapy, and bone marrow transplantation.[44]

## Prognosis [edit]

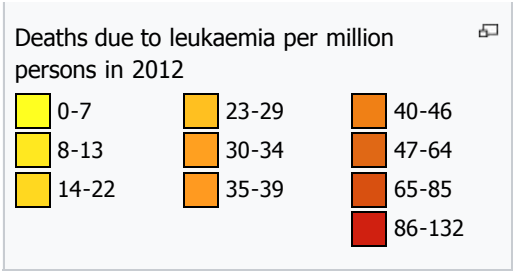
The success of treatment depends on the type of leukemia and the age of the person. Outcomes have improved in the developed world.[6] The average five-year survival rate is 57% in the United States.[9] In children under 15, the five-year survival rate is greater than 60 to 85%, depending on the type of leukemia.[10] In children with acute leukemia who are cancer-free after five years, the cancer is unlikely to return.[10]

Outcomes depend on whether it is acute, which is generally more severe, versus chronic; the specific abnormal white blood cell type; the stage of progression; the grade- degree of tissue abnormality; and the presence of proximal and/or distant metastasis and lymph node and bone marrow infiltration, the availability of current therapies and the skills of the health care team (cancer treatment outcomes are better at accredited academic cancer centers).[*citation needed*]

## Epidemiology [edit]

In 2010, globally, approximately 281,500 people died of leukemia.[45] In 2000, approximately 256,000 children and adults around the world developed a form of leukemia, and 209,000 died from it.[46] This represents about 3% of the almost seven million deaths due to cancer that year, and about 0.35% of all deaths from any cause.[46] Of the sixteen separate sites the body compared, leukemia was the 12th most common class of neoplastic disease, and the 11th most common cause of cancer-related death.[46] Leukemia occurs more commonly in the developed [47]

world.




## United States [edit]

About 245,000 people in the United States are affected with some form of leukemia, including those that have achieved remission or cure. Rates from 1975 to 2011 have increased by 0.7% per year among children.[48] Approximately 44,270 new cases of leukemia were diagnosed in the year 2008 in the US.[49] This represents 2.9% of all cancers (excluding simple basal cell and squamous cell skin cancers) in the United States, and 30.4% of all blood cancers.[50]

Among children with some form of cancer, about a third have a type of leukemia, most commonly acute lymphoblastic leukemia.[49] A type of leukemia is the second most common form of cancer in infants (under the age of 12 months) and the most common form of cancer in older children.[51] Boys are somewhat more likely to develop leukemia than girls, and white American children are almost twice as likely to develop leukemia than black American children.[51] Only about 3% cancer diagnoses among adults are for leukemias, but because cancer is much more common among adults, more than 90% of all leukemias are diagnosed in adults.[49]

Race is a risk factor in the United States. Hispanics, especially those under the age of 20, are at the highest risk for leukemia, while whites, Native Americans, Asian Americans, and Alaska Natives are at higher risk than African Americans.[52]

More men than women are diagnosed with leukemia and die from the disease. Around 30 percent more men than women have leukemia.[53]

## UK [edit]

Overall, leukaemia is the eleventh most common cancer in the UK (around 8,600 people were diagnosed with the disease in 2011), and it is the ninth most common cause of cancer death (around 4,800 people died in 2012).[54]

# History [edit]

*See also: Timeline of leukemia*

Leukemia was first described by anatomist and surgeon Alfred-Armand-Louis-Marie Velpeau in 1827. A more complete description was given by pathologist Rudolf Virchow in 1845. Observing an abnormally large number of white blood cells in a blood sample from a patient, Virchow called the condition *Leukämie* in German, which he formed from the two Greek words *leukos* (λευκός), meaning "white", and *haima* (αἷμα), meaning "blood". Around ten years after Virchow's findings, pathologist Franz Ernst Christian Neumann found that one deceased leukemia patient's bone marrow was colored "dirty green-yellow" as opposed to the normal red. This finding allowed Neumann to conclude that a bone marrow problem was responsible for the abnormal blood of leukemia patients.


Rudolf Virchow

By 1900 leukemia was viewed as a family of diseases as opposed to a single disease. By 1947 Boston pathologist Sidney Farber believed from past experiments that aminopterin, a folic acid mimic, could potentially cure leukemia in children. The majority of the children with ALL who were tested showed signs of improvement in, their bone marrow, but none of them were actually cured. This, however, led to further experiments.

In 1962, researchers Emil J. Freireich, Jr. and Emil Frei III used combination chemotherapy to attempt to cure leukemia. The tests were successful with some patients surviving long after the tests.[55]

# Society and culture [edit]

According to Susan Sontag, leukemia was often romanticized in 20th-century fiction, portrayed as a joy-ending, clean disease whose fair, innocent and gentle victims die young or at the wrong time. As such, it was the cultural successor to tuberculosis, which held this cultural position until it was discovered to be an infectious disease.[56] The 1970 romance novel *Love Story* is an example of this romanticization of leukemia.

In the United States, around $5.4 billion is spent on treatment a year.[57]

# Research directions [edit]

Significant research into the causes, prevalence, diagnosis, treatment, and prognosis of leukemia is being performed. Hundreds [58]

of clinical trials are being planned or conducted at any given time. Studies may focus on effective means of treatment, better ways of treating the disease, improving the quality of life for patients, or appropriate care in remission or after cures.

In general, there are two types of leukemia research: clinical or translational research and basic research. Clinical/translational research focuses on studying the disease in a defined and generally immediately patient-applicable way, such as testing a new drug in patients. By contrast, basic science research studies the disease process at a distance, such as seeing whether a suspected carcinogen can cause leukemic changes in isolated cells in the laboratory or how the DNA changes inside leukemia cells as the disease progresses. The results from basic research studies are generally less immediately useful to patients with the disease.[59]

Treatment through gene therapy is currently being pursued. One such approach used genetically modified T cells to attack cancer cells. In 2011, a year after treatment, two of the three patients with advanced chronic lymphocytic leukemia were reported to be cancer-free[60] and in 2013, three of five subjects who had acute lymphocytic leukemia were reported to be in remission for five months to two years.[61] Identifying stem cells that cause different types of leukaemia is also being researched.[62]

## Pregnancy [edit]

Leukemia is rarely associated with pregnancy, affecting only about 1 in 10,000 pregnant women.[63] How it is handled depends primarily on the type of leukemia. Nearly all leukemias appearing in pregnant women are acute leukemias.[64] Acute leukemias normally require prompt, aggressive treatment, despite significant risks of pregnancy loss and birth defects, especially if chemotherapy is given during the developmentally sensitive first trimester.[63] Chronic myelogenous leukemia can be treated with relative safety at any time during pregnancy with Interferon-alpha hormones.[63] Treatment for chronic lymphocytic leukemias, which are rare in pregnant women, can often be postponed until after the end of the pregnancy.[63][64]

## See also [edit]

- Acute erythroid leukemia
- Antileukemic drugs, medications used to kill leukemia cells
- Hematologic diseases, the large class of blood-related disorders, including leukemia
- Cancer-related fatigue

## References [edit]


1. ^ "Leukemia — Definition of Leukemia by Merriam-Webster".
2. ^ "Leukemia". *NCI*. Retrieved 13 June 2014.
3. ^ a b c d "What You Need To Know About™ Leukemia". *National Cancer Institute*. 23 December 2013. Retrieved 18 June 2014.
4. ^ a b Hutter, JJ (Jun 2010). "Childhood leukemia.". *Pediatrics in review / American Academy of Pediatrics*. **31** (6): 234–41. doi:10.1542/pir.31-6-234. PMID 20516235.
5. ^ a b c d e f "A Snapshot of Leukemia". *NCI*. Retrieved 18 June 2014.
6. ^ a b c d e *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 5.13. ISBN 9283204298.
7. ^ Vardiman, JW; Thiele, J; Arber, DA; Brunning, RD; Borowitz, MJ; Porwit, A; Harris, NL; Le Beau, MM; Hellström-Lindberg, E; Tefferi, A; Bloomfield, CD (30 Jul 2009). "The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes.". *Blood*. **114** (5): 937–51. doi:10.1182/blood-2009-03-209262. PMID 19357394.
8. ^ Cătoi, Alecsandru Ioan Baba, Cornel (2007). *Comparative oncology*. Bucharest: The Publishing House of the Romanian Academy. p. Chapter 17. ISBN 973-27-1457-3.
9. ^ a b "SEER Stat Fact Sheets: Leukemia". National Cancer Institute. 2011.
10. ^ a b c d American Cancer Society (2 March 2014). "Survival rates for childhood leukemia".
11. ^ Jameson, J. N. St C.; Dennis L. Kasper; Harrison, Tinsley Randolph; Braunwald, Eugene; Fauci, Anthony S.; Hauser, Stephen L; Longo, Dan L. (2005). *Harrison's principles of internal medicine*. New York: McGraw-Hill Medical Publishing
39. ^ American Cancer Society (22 March 2012). "Typical treatment of acute myeloid leukemia (except promyelocytic M3)". *Detailed Guide: Leukemia – Acute Myeloid (AML)*. American Cancer Society. Retrieved 31 October 2012.
40. ^ a b c Fausel C (October 2007). "Targeted chronic myeloid leukemia therapy: seeking a cure" (PDF). *J Manag Care Pharm*. **13** (8 Suppl A): 8–12. PMID 17970609.
41. ^ Robak, T; Jamroziak, K; Gora-Tybor, J; Blonski, J. Z.; Kasznicki, M; Dwilewicz-Trojaczek, J; Wiater, E; Zdunczyk, A; Dybowicz, J; Dmoszynska, A; Wojtaszko, M; Zdziarska, B; Calbecka, M; Kostyra, A; Hellmann, A; Lewandowski, K; Stella-Holowiecka, B; Sulek, K; Gawronski, K; Skotnicki, A. B.; Nowak, W; Zawilska, K; Molendowicz-Portala, L; Kloczko, J; Sokolowski, J; Warzocha, K; Seferynska, I; Ceglarek, B; Konopka, L (2007). "Cladribine in a weekly versus daily schedule for untreated active hairy cell leukemia: Final report from the Polish Adult Leukemia Group (PALG) of a prospective, randomized, multicenter trial". *Blood*. **109** (9): 3672–5. doi:10.1182/blood-2006-08-042929. PMID 17209059.
42. ^ Saven, A; Burian, C; Adusumalli, J; Koziol, J. A. (1999). "Filgrastim for cladribine-induced neutropenic fever in patients with hairy cell leukemia". *Blood*. **93** (8): 2471–7. PMID 10194424.
43. ^ a b c d Dearden CE, Matutes E, Cazin B (September 2001). "High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H". *Blood*. **98** (6): 1721–6. doi:10.1182/blood.V98.6.1721. PMID 11535503.
44. ^ "JMMLfoundation.org". JMMLfoundation.org. Archived from the original on 25 January 2009. Retrieved 29 August 2010.

Division. ISBN 0-07-140235-7.
12. ^ Finding Cancer Statistics » Cancer Stat Fact Sheets »Chronic Lymphocytic Leukemia National Cancer Institute.
13. ^ Colvin G. A.; Elfenbein G. J. (2003). "The latest treatment advances for acute myelogenous leukemia". *Medicine and Health, Rhode Island*. **86** (8): 243–6. PMID 14582219.
14. ^ "Novartis Oncology".
15. ^ Patients with Chronic Myelogenous Leukemia Continue to Do Well on Imatinib at 5-Year Follow-Up Medscape Medical News 2006.
16. ^ Updated Results of Tyrosine Kinase Inhibitors in CML ASCO 2006 Conference Summaries.
17. ^ Else, M., Ruchlemer, R., Osuji, N. (2005). "Long remissions in hairy cell leukemia with purine analogs: a report of 219 patients with a median follow-up of 12.5 years". *Cancer*. **104** (11): 2442–8. doi:10.1002/cncr.21447. PMID 16245328.
18. ^ Matutes Estella (1998). "T-cell prolymphocytic leukemia, a rare variant of mature post-thymic T-cell leukemias, has distinct clinical and laboratory characteristics and a poor prognosis". *Cancer Control Journal*. **5** (1).
19. ^ Valbuena JR, Herling M, Admirand JH, Padula A, Jones D, Medeiros LJ (March 2005). "T-cell prolymphocytic leukemia involving extramedullary sites". *American Journal of Clinical Pathology*. **123** (3): 456–64. doi:10.1309/93P4-2RNG-5XBG-3KBE. PMID 15716243.
20. ^ Elaine Sarkin Jaffe, Nancy Lee Harris, World Health Organization, International Agency for Research on Cancer, Harald Stein, J. W. Vardiman (2001). *Pathology and genetics of tumours of haematopoietic and lymphoid tissues*. World Health Organization Classification of Tumors. **3**. Lyon: IARC Press. ISBN 92-832-2411-6.
21. ^ Reference list is found at image description page in Wikimedia Commons
22. ^ "Leukemia". Columbia Electronic Encyclopedia, 6th Edition. Retrieved 4 November 2011.
23. ^ *a b* American Cancer Society (2010). "How is Leukemia Diagnosed?". *Detailed Guide: Leukemia – Adult Chronic*. American Cancer Society. Archived from the original on 5 April 2010. Retrieved 4 May 2010.
24. ^ *a b* Ross JA, Kasum CM, Davies SM, Jacobs DR, Folsom AR, Potter JD (August 2002). "Diet and risk of leukemia in the Iowa Women's Health Study". *Cancer Epidemiol. Biomarkers Prev*. **11** (8): 777–81. PMID 12163333.
25. ^ Radivoyevitch, T; Sachs, R K; Gale, R P; Molenaar, R J; Brenner, D J; Hill, B T; Kalaycio, M E; Carraway, H E; Mukherjee, S (2015). "Defining AML and MDS second cancer risk dynamics after diagnoses of first cancers treated or not with radiation". *Leukemia*. doi:10.1038/leu.2015.258.
26. ^ *a b c d e f* Wiernik, Peter H. (2001). *Adult leukemias*. New York: B. C. Decker. pp. 3–15. ISBN 1-55009-111-5.
27. ^ *a b* Robinette, Martin S.; Cotter, Susan; Van de Water (2001). *Quick Look Series in Veterinary Medicine: Hematology*. Teton NewMedia. p. 105. ISBN 1-893441-36-9.
28. ^ Stass, Sanford A.; Schumacher, Harold R.; Rock, William R. (2000). *Handbook of hematologic pathology*. New York, N.Y: Marcel Dekker. pp. 193–194. ISBN 0-8247-0170-4.
29. ^ Leonard, Barry (1998). *Leukemia: A Research Report*. DIANE Publishing. p. 7. ISBN 0-7881-7189-5.
30. ^ Rudant J, Amigou A, Orsi L, Althaus T, Leverger G, Baruchel A, Bertrand Y, Nelken B, Plat G, Michel G, Sirvent N, Chastagner P, Ducassou S, Rialland X, Hémon D, Clavel J (2013). "Fertility treatments, congenital malformations, fetal loss, and childhood acute leukemia: the ESCALE study (SFCE)". *Pediatr Blood Cancer*. **60** (2): 301–8. doi:10.1002/pbc.24192. PMID 22610722.
31. ^ "Sr-90 is known to increase the risk of bone cancer and leukemia in animals, and is presumed to do so in people; from google (nuclear reactor emit tritium) result 1, 2, 3".
32. ^ Pasmant, E; Ballerini, P; Lapillonne, H; Perot, C; Vidaud, D;
45. ^ Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA (December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
46. ^ *a b c* Mathers, Colin D, Cynthia Boschi-Pinto, Alan D Lopez and Christopher JL Murray (2001). "Cancer incidence, mortality and survival by site for 14 regions of the world" (PDF). *Global Programme on Evidence for Health Policy Discussion Paper No. 13*. World Health Organization.
47. ^ *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 5.13. ISBN 9283204298.
48. ^ Amitay, EL; Keinan-Boker, L (1 June 2015). "Breastfeeding and Childhood Leukemia Incidence: A Meta-analysis and Systematic Review.". *JAMA pediatrics*. **169** (6): e151025. doi:10.1001/jamapediatrics.2015.1025. PMID 26030516.
49. ^ *a b c* "Leukemia Facts & Statistics." The Leukemia & Lymphoma Society. Retrieved 2 July 2009.
50. ^ Horner MJ, Ries LAG, Krapcho M, Neyman N, et al. (eds). "SEER Cancer Statistics Review, 1975–2006". *Surveillance Epidemiology and End Results (SEER)*. Bethesda, MD: National Cancer Institute. Retrieved 3 November 2009. "Table 1.4: Age-Adjusted SEER Incidence and U.S. Death Rates and 5-Year Relative Survival Rates By Primary Cancer Site, Sex and Time Period"
51. ^ *a b* James G. Gurney, Malcolm A. Smith, Julie A. Ross (1999) *Cancer Incidence and Survival among Children and Adolescents, United States SEER program 1975–1995*, chapter on Leukemia Cancer Statistics Branch, National Cancer Institute, available online from the SEER web site
52. ^ Childhood Blood Cancers | The Leukemia & Lymphoma Society
53. ^ Facts 2012 from The Leukemia & Lymphoma Society

Leverger, G; Landman-Parker, J (2009). "SPRED1 disorder and predisposition to leukemia in children". *Blood*. **114** (5): 1131. doi:10.1182/blood-2009-04-218503. PMID 19643996.
33. ^ a b c *Non-Ionizing Radiation, Part 1: Static and Extremely Low-Frequency (ELF) Electric and Magnetic Fields (IARC Monographs on the Evaluation of the Carcinogenic Risks)*. Geneva: World Health Organisation. 2002. pp. 332–333, 338. ISBN 92-832-1280-0.
34. ^ "WHO | Electromagnetic fields and public health". Retrieved 18 February 2009.
35. ^ Hoffbrand, A.V.; Moss,, P.A.H.; Pettit, J.E. (2006). *Essential haematology* (5th ed.). Malden, Mass.: Blackwell Pub. ISBN 978-1-4051-3649-5.
36. ^ National Cancer Institute. "Chronic Lymphocytic Leukemia (PDQ) Treatment: Stage Information". Retrieved 4 September 2007.
37. ^ Eichhorst BF; Busch R; Hopfinger G; Pasold R; Hensel M; Steinbrecher C; Siehl S; Jäger U; Bergmann M; Stilgenbauer S; Schweighofer C; Wendtner CM; Döhner H; Brittinger G; Emmerich B; Hallek M; German CLL Study Group. (2006). "Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia". *Blood*. **107** (3): 885–91. doi:10.1182/blood-2005-06-2395. PMID 16219797.
38. ^ Gribben JG (January 2008). "Stem cell transplantation in chronic lymphocytic leukemia". *Biol. Blood Marrow Transplant.*
54. ^ "Leukaemia (all subtypes combined) statistics". *Cancer Research UK*. Retrieved 27 October 2014.
55. ^ Patlak, M (2002). "Targeting leukemia: From bench to bedside". *FASEB Journal*. **16** (3): 273. PMID 11874976.
56. ^ Sontag, Susan (1978). *Illness as Metaphor*. New York: Farrar, Straus and Giroux. p. 18. ISBN 0-374-17443-1.
57. ^ "A Snapshot of Leukemia". *NCI*. Retrieved 18 June 2014.
58. ^ "Search of: leukemia — List Results — ClinicalTrials.gov".
59. ^ "Understanding Clinical Trials for Blood Cancers" (PDF). Leukemia and Lymphoma Society. Retrieved 19 May 2010.
60. ^ Jaslow, Ryan. "New Leukemia Therapy Destroys Cancer by Turning Blood Cells into "Assassins" ". CBSnews.com HealthPop section. Retrieved 11 August 2011.
61. ^ Coghlan, Andy (26 March 2013) Gene therapy cures leukaemia in eight days The New Scientist, Retrieved 15 April 2013
62. ^ "How we're beating leukaemia". Leukaemia & Lymphoma Research. Retrieved 24 September 2013.
63. ^ a b c d Shapira T, Pereg D, Lishner M (September 2008). "How I treat acute and chronic leukemia in pregnancy". *Blood Rev*. **22** (5): 247–59. doi:10.1016/j.blre.2008.03.006. PMID 18472198.
64. ^ a b Koren G, Lishner M (2010). "Pregnancy and commonly used drugs in hematology practice". *Hematology Am Soc Hematol Educ Program*. **2010**: 160–5. doi:10.1182/asheducation-2010.1.160. PMID 21239787.

## External links [edit]

- Leukemia at DMOZ
- Leukaemia information from Cancer Research UK

Wikimedia Commons has media related to *Leukemia*.

| v · t · e · **Hematological malignancy/leukemia histology (ICD-O 9590–9989, C81–C96, 200–208)** **Lymphoid/Lymphoproliferative, Lymphomas/Lymphoid leukemias (9590–9739, 9800–9839)** | | | |
|---|---|---|---|
| **B cell (lymphoma, leukemia) (most CD19 CD20)** · | **By development/ marker** | **TdT+** | ALL (Precursor B acute lymphoblastic leukemia/lymphoma) · |
| | | **CD5+** | *naive B cell* (CLL/SLL) · *mantle zone* (Mantle cell) · |
| | | **CD22+** | Prolymphocytic · *CD11c+* (Hairy cell leukemia) · |
| | | **CD79a+** | *germinal center/follicular B cell* (Follicular · Burkitt's · GCB DLBCL · Primary cutaneous follicle center lymphoma) · *marginal zone/marginal zone B-cell* (Splenic marginal zone · MALT · Nodal marginal zone · Primary cutaneous marginal zone lymphoma) · |
| | | **RS (CD15+, CD30+)** | Classic Hodgkin's lymphoma (Nodular sclerosis) · *CD20+* (Nodular lymphocyte predominant Hodgkin's lymphoma) · |
| | | **PCDs/PP (CD38+/CD138+)** | *see immunoproliferative immunoglobulin disorders* · |
| | **By infection** | | *KSHV* (Primary effusion) · *EBV* (Lymphomatoid granulomatosis · Post-transplant lymphoproliferative disorder) · *HIV* (AIDS-related lymphoma) · *Helicobacter pylori* (MALT lymphoma) · |
| | **Cutaneous** | | Diffuse large B-cell lymphoma · Intravascular large B-cell lymphoma · Primary cutaneous marginal zone lymphoma · Primary cutaneous immunocytoma · Plasmacytoma · Plasmacytosis · Primary cutaneous follicle center lymphoma · |
| | **By development/ marker** | | TdT+: ALL (Precursor T acute lymphoblastic leukemia/lymphoma) · *prolymphocyte* (Prolymphocytic) · *CD30+* (Anaplastic large-cell lymphoma · Lymphomatoid papulosis type A) · |
| | | | *indolent:* Mycosis fungoides · Pagetoid reticulosis · Granulomatous slack skin · |

| | | | | |
|---|---|---|---|---|
| **T/NK** | **T cell (lymphoma, leukemia) (most CD3 CD4 · CD8) ·** | **Cutaneous** | **MF+variants** | *aggressive:* Sézary disease<br>Adult T-cell leukemia/lymphoma · |
| | | | **Non-MF** | CD30-:<br>Non-mycosis fungoides CD30− cutaneous large T-cell lymphoma · Pleomorphic T-cell lymphoma ·<br>Lymphomatoid papulosis type B ·<br>CD30+: CD30+ cutaneous T-cell lymphoma ·<br>Secondary cutaneous CD30+ large-cell lymphoma ·<br>Lymphomatoid papulosis type A · |
| | | **Other peripheral** | | Hepatosplenic · Angioimmunoblastic · Enteropathy-associated T-cell lymphoma ·<br>Peripheral T-cell lymphoma not otherwise specified (Lennert lymphoma) ·<br>Subcutaneous T-cell lymphoma · |
| | | **By infection** | | *HTLV-1* (Adult T-cell leukemia/lymphoma) · |
| | **NK cell / (most CD56)** | Aggressive NK-cell leukemia · Blastic NK cell lymphoma · | | |
| | **T or NK** | *EBV* (Extranodal NK-T-cell lymphoma/Angiocentric lymphoma) · Large granular lymphocytic leukemia · | | |
| **Lymphoid+ myeloid** | Acute biphenotypic leukaemia · | | | |
| **Lymphocytosis** | Lymphoproliferative disorders (X-linked lymphoproliferative disease · Autoimmune lymphoproliferative syndrome) ·<br>Leukemoid reaction · Diffuse infiltrative lymphocytosis syndrome · | | | |
| **Cutaneous lymphoid hyperplasia** | Cutaneous lymphoid hyperplasia (with bandlike and perivascular patterns · with nodular pattern · ·<br>Jessner lymphocytic infiltrate of the skin · | | | |

| v · t · e · **Myeloid hematological malignancy / leukemia histology (ICD-O 9590–9989, C81–C96, 200–208)** | | | | |
|---|---|---|---|---|
| **CFU-GM / and other granulocytes** | **CFU-GM** | **Myelocyte** | *AML:* | Acute myeloblastic leukemia · M0 · M1 · M2 · APL/M3 · |
| | | | *MP* | Chronic neutrophilic leukemia · |
| | | **Monocyte** | *AML* | AMoL/M5 · Myeloid dendritic cell leukemia · |
| | | | *CML* | Philadelphia chromosome ·<br>Accelerated phase chronic myelogenous leukemia · |
| | | **Myelomonocyte** | *AML* | M4 · |
| | | | *MD-MP* | Juvenile myelomonocytic leukemia ·<br>Chronic myelomonocytic leukemia · |
| | | **Other** | | Histiocytosis · |
| | **CFU-Baso** | *AML* | | Acute basophilic · |
| | **CFU-Eos** | *AML* | | Acute eosinophilic · |
| | | *MP* | | Chronic eosinophilic leukemia/Hypereosinophilic syndrome · |
| **MEP** | **CFU-Meg** | *AML* | | AMKL/M7 · |
| | | *MP* | | Essential thrombocytosis · |
| | **CFU-E** | *AML* | | Erythroleukemia/M6 · |
| | | *MP* | | Polycythemia vera · |
| | | *MD* | | Refractory anemia · Refractory anemia with excess of blasts ·<br>Chromosome 5q deletion syndrome · Sideroblastic anemia ·<br>Paroxysmal nocturnal hemoglobinuria · Refractory cytopenia with multilineage dysplasia · |
| **CFU-Mast** | *Mastocytoma* | | | Mast cell leukemia · Mast cell sarcoma · Systemic mastocytosis · |
| | Mastocytosis: | | | Diffuse cutaneous mastocytosis · Erythrodermic mastocytosis ·<br>Adult type of generalized eruption of cutaneous mastocytosis · Urticaria pigmentosa · |

| | | |
|---|---|---|
| | | Mast cell sarcoma · Solitary mastocytoma · |
| | Systemic mastocytosis | Xanthelasmoidal mastocytosis · |
| **Multiple/unknown** | *AML* | Acute panmyelosis with myelofibrosis · Myeloid sarcoma · |
| | *MP* | Myelofibrosis · Acute biphenotypic leukaemia · |
| **Authority control** | LCCN: sh85076285 · GND: 4035487-8 · NDL: 00562843 · | |

Categories: Leukemia | Lymphatic vessel diseases

# Lung cancer

From Wikipedia, the free encyclopedia

*This article is about lung carcinomas. For other lung tumors, see Lung tumor.*

**Lung cancer**, also known as **lung carcinoma**,[1] is a malignant lung tumor characterized by uncontrolled cell growth in tissues of the lung.[2] If left untreated, this growth can spread beyond the lung by the process of metastasis into nearby tissue or other parts of the body.[3] Most cancers that start in the lung, known as primary lung cancers, are carcinomas.[4] The two main types are small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC).[5] The most common symptoms are coughing (including coughing up blood), weight loss, shortness of breath, and chest pains.[6]

The vast majority (85%) of cases of lung cancer are due to long-term tobacco smoking.[7] About 10–15% of cases occur in people who have never smoked.[8] These cases are often caused by a combination of genetic factors and exposure to radon gas, asbestos, second-hand smoke, or other forms of air pollution.[7][9][10][11] Lung cancer may be seen on chest radiographs and computed tomography (CT) scans.[1] The diagnosis is confirmed by biopsy which is usually performed by bronchoscopy or CT-guidance.[12][13]

Prevention is by avoiding risk factors including smoking and air pollution.[14] Treatment and long-term outcomes depend on the type of cancer, the stage (degree of spread), and the person's overall health.[1] Most cases are not curable.[5] Common treatments include surgery, chemotherapy, and radiotherapy.[1] NSCLC is sometimes treated with surgery, whereas SCLC usually responds better to chemotherapy and radiotherapy.[15]

Worldwide in 2012, lung cancer occurred in 1.8 million people and resulted in 1.6 million deaths.[4] This makes it the most common cause of cancer-related death in men and second most common in women after breast cancer.[16] The most common age at diagnosis is 70 years. Overall, 17.4% of people in the United States diagnosed with lung cancer survive five years after the diagnosis,[17] while outcomes on average are worse in the developing world.[18]

## Contents

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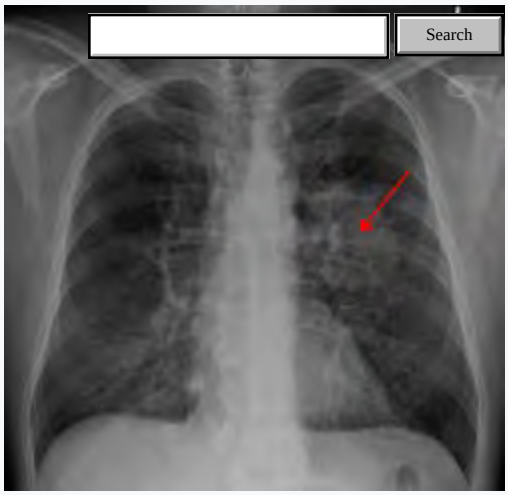



A chest X-ray showing a tumor in the lung (marked by arrow)

**Lung cancer**

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Oncology |
| **ICD-10** | C33-C34 |
| **ICD-9-CM** | 162 |
| **OMIM** | 211980 |
| **DiseasesDB** | 7616 |
| **MedlinePlus** | 007194 |
| **eMedicine** | med/1333 med/1336 emerg/335 radio/807 radio/405 radio/406 |
| **Patient UK** | Lung cancer |
| **MeSH** | D002283 |

[edit on Wikidata]

## Signs and symptoms [edit]

Signs and symptoms which may suggest lung cancer include:[6]

- Respiratory symptoms: coughing, coughing up blood, wheezing, or shortness of breath
- Systemic symptoms: weight loss, weakness, fever, or clubbing of the fingernails
- Symptoms due to the cancer mass pressing on adjacent structures: chest pain, bone pain, superior vena cava obstruction, or difficulty swallowing

If the cancer grows in the airways, it may obstruct airflow, causing breathing difficulties. The obstruction can lead to accumulation of secretions behind the blockage, and predispose to pneumonia.[6]

Depending on the type of tumor, paraneoplastic phenomena—symptoms not due to the local presence of cancer—may initially attract attention to the disease.[19] In lung cancer, these phenomena may include hypercalcemia, syndrome of inappropriate antidiuretic hormone (SIADH, abnormally concentrated urine and diluted blood), ectopic ACTH production, or Lambert–Eaton myasthenic syndrome (muscle weakness due to autoantibodies). Tumors in the top of the lung, known as Pancoast tumors, may invade the local part of the sympathetic nervous system, leading to Horner's syndrome (dropping of the eyelid and a small pupil on that side), as well as damage to the brachial plexus.[6]

Many of the symptoms of lung cancer (poor appetite, weight loss, fever, fatigue) are not specific.[12] In many people, the cancer has already spread beyond the original site by the time they have symptoms and seek medical attention.[20] Symptoms that suggest the presence of metastatic disease include weight loss, bone pain and neurological symptoms (headaches, fainting, convulsions, or limb weakness).[6] Common sites of spread include the brain, bone, adrenal glands, opposite lung, liver, pericardium, and kidneys.[20] About 10% of people with lung cancer do not have symptoms at diagnosis; these cancers are incidentally [13]

found on routine chest radiography.

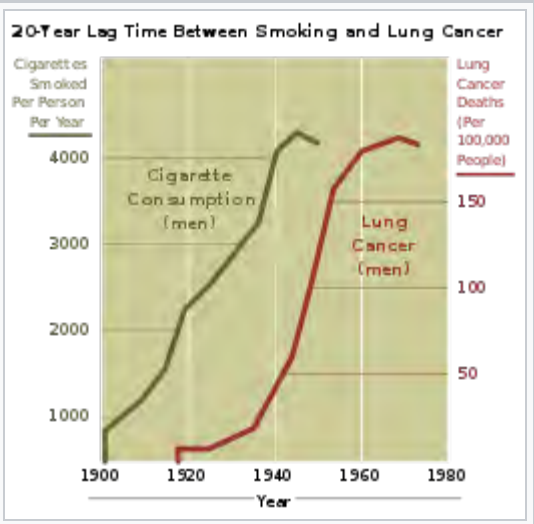


## Causes [edit]

Cancer develops following genetic damage to DNA and epigenetic changes. These changes affect the normal functions of the cell, including cell proliferation, programmed cell death (apoptosis) and DNA repair. As more damage accumulates, the risk of cancer increases.[21]

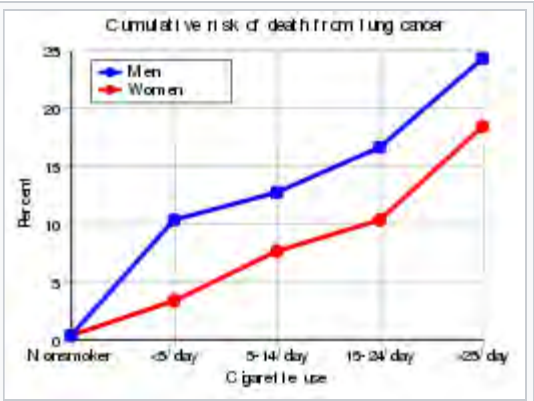
## Smoking [edit]

Smoking, particularly of cigarettes, is by far the main contributor to lung cancer.[22] Cigarette smoke contains at least 73 known carcinogens,[23] including benzo[*a*]pyrene,[24] NNK, 1,3-butadiene and a radioactive isotope of polonium, polonium-210.[23] Across the developed world, 90% of lung cancer deaths in men during the year 2000 were attributed to smoking (70% for women).[25] Smoking accounts for about 85% of lung cancer cases.[1]




Graph showing how a general increase in sales of tobacco products in the USA in the first four decades of the 20th century (cigarettes per person per year) led to a corresponding rapid increase in the rate of lung cancer during the 1930s, '40s and '50s (lung cancer deaths per 100,000 male population per year)

Passive smoking—the inhalation of smoke from another's smoking—is a cause of lung cancer in nonsmokers. A passive smoker can be defined as someone living or working with a smoker. Studies from the US,[26][27][28] Europe[29] and the UK[30] have consistently shown a significantly increased risk among those exposed to passive smoke.[31] Those who live with someone who smokes have a 20–30% increase in risk while those who work in an environment with secondhand smoke have a 16–19% increase in risk.[32] Investigations of sidestream smoke suggest it is more dangerous than direct smoke.[33] Passive smoking causes about 3,400 deaths from lung cancer each year in the USA.[28]




Risk of death from lung cancer is strongly correlated with smoking

Marijuana smoke contains many of the same carcinogens as those in tobacco smoke.[34] However, the effect of smoking cannabis on lung cancer risk is not clear.[35][36] A 2013 review did not find an increased risk from light to moderate use.[37] A 2014 review found that smoking cannabis doubled the risk of lung cancer.[38]

## Radon gas [edit]

Radon is a colourless and odorless gas generated by the breakdown of radioactive radium, which in turn is the decay product of uranium, found in the Earth's crust. The radiation decay products ionize genetic material, causing mutations that sometimes turn cancerous. Radon is the second-most common cause of lung cancer in the USA,[39] causing about 21,000 deaths each year.[40] The risk increases 8–16% for every 100 Bq/m³ increase in the radon concentration.[41] Radon gas levels vary by locality and the composition of the underlying soil and rocks. About one in 15 homes in the US has radon levels above the recommended guideline of 4 picocuries per liter (pCi/l) (148 Bq/m³).[42]

## Asbestos [edit]

Asbestos can cause a variety of lung diseases, including lung cancer. Tobacco smoking and asbestos have a

synergistic effect on the formation of lung cancer.[10] In smokers who work with asbestos, the risk of lung cancer is increased 45-fold compared to the general population.[43] Asbestos can also cause cancer of the pleura, called mesothelioma (which is different from lung cancer).[44]

### Air pollution [edit]

Outdoor air pollutants, especially chemicals released from the burning of fossil fuels, increase the risk of lung cancer.[7] Fine particulates ($PM_{2.5}$) and sulfate aerosols, which may be released in traffic exhaust fumes, are associated with slightly increased risk.[7][45] For nitrogen dioxide, an incremental increase of 10 parts per billion increases the risk of lung cancer by 14%.[46] Outdoor air pollution is estimated to account for 1–2% of lung cancers.[7]

Tentative evidence supports an increased risk of lung cancer from indoor air pollution related to the burning of wood, charcoal, dung or crop residue for cooking and heating.[47] Women who are exposed to indoor coal smoke have about twice the risk and a number of the by-products of burning biomass are known or suspected carcinogens.[48] This risk affects about 2.4 billion people globally,[47] and is believed to account for 1.5% of lung cancer deaths.[48]

### Genetics [edit]

About 8% of lung cancer is due to inherited factors.[49] In relatives of people with lung cancer, the risk is doubled. This is likely due to a combination of genes.[50] Polymorphisms on chromosomes 5, 6 and 15 are known to affect the risk of lung cancer.[51]

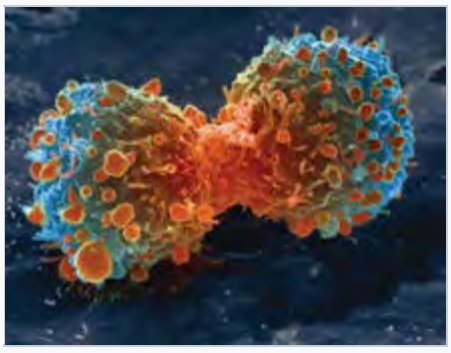
### Other causes [edit]

Numerous other substances, occupations, and environmental exposures have been linked to lung cancer. The International Agency for Research on Cancer (IARC) states there is "sufficient evidence" to show the following are carcinogenic in the lungs:[52]

- Some metals (aluminum production, cadmium and cadmium compounds, chromium(VI) compounds, beryllium and beryllium compounds, iron and steel founding, nickel compounds, arsenic and inorganic arsenic compounds, underground hematite mining)
- Some products of combustion (incomplete combustion, coal (indoor emissions from household coal burning), coal gasification, coal-tar pitch, coke production, soot, diesel engine exhaust)
- Ionizing radiation (X-radiation, gamma radiation, plutonium)
- Some toxic gases (methyl ether (technical grade), Bis-(chloromethyl) ether, sulfur mustard, MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture), fumes from painting)
- Rubber production and crystalline silica dust

## Pathogenesis [edit]

*See also: Carcinogenesis*



Similar to many other cancers, lung cancer is initiated by activation of oncogenes or inactivation of tumor suppressor genes.[53] Carcinogens cause mutations in these genes which induce the development of cancer.[54]

Mutations in the *K-ras* proto-oncogene are responsible for 10–30% of lung adenocarcinomas.[55][56] About 4% of non-small-cell lung carcinomas involve an EML4-ALK tyrosine kinase fusion gene.[57]

Epigenetic changes—such as alteration of DNA methylation, histone tail modification, or microRNA regulation—may lead to inactivation of tumor [58]

False-color scanning electron micrograph of a lung cancer cell dividing

suppressor genes.

The epidermal growth factor receptor (EGFR) regulates cell proliferation, apoptosis, angiogenesis, and tumor invasion.[55] Mutations and amplification of EGFR are common in non-small-cell lung carcinoma and provide the basis for treatment with EGFR-inhibitors. Her2/neu is affected less frequently.[55] Other genes that are often mutated or amplified are *c-MET*, *NKX2-1*, *LKB1*, *PIK3CA*, and *BRAF*.[55]

The cell lines of origin are not fully understood.[6] The mechanism may involve abnormal activation of stem cells. In the proximal airways, stem cells that express keratin 5 are more likely to be affected, typically leading to squamous-cell lung carcinoma. In the middle airways, implicated stem cells include club cells and neuroepithelial cells that express club cell secretory protein. Small-cell lung carcinoma may be derived from these cell lines[59] or neuroendocrine cells,[6] and may express CD44.[59]

Metastasis of lung cancer requires transition from epithelial to mesenchymal cell type. This may occur through activation of signaling pathways such as Akt/GSK3Beta, MEK-ERK, Fas, and Par6.[60]

## Diagnosis [edit]

Performing a chest radiograph is one of the first investigative steps if a person reports symptoms that may suggest lung cancer. This may reveal an obvious mass, widening of the mediastinum (suggestive of spread to lymph nodes there), atelectasis (collapse), consolidation (pneumonia) or pleural effusion.[1] CT imaging is typically used to provide more information about the type and extent of disease. Bronchoscopy or CT-guided biopsy is often used to sample the tumor for histopathology.[13]

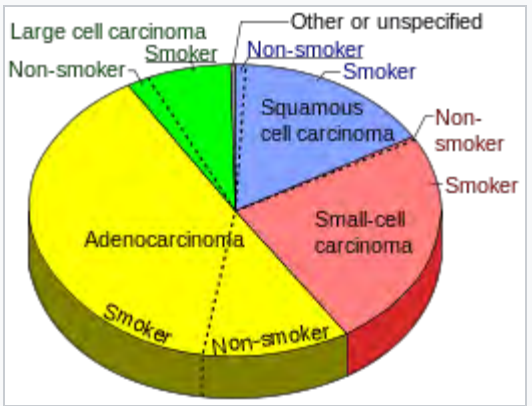
CT scan showing a cancerous tumor in the left lung

Lung cancer often appears as a solitary pulmonary nodule on a chest radiograph. However, the differential diagnosis is wide. Many other diseases can also give this appearance, including metastatic cancer, hamartomas, and infectious granulomas such as tuberculosis, histoplasmosis and coccidioidomycosis.[61] Lung cancer can also be an incidental finding, as a solitary pulmonary nodule on a chest radiograph or CT scan done for an unrelated reason.[62] The definitive diagnosis of lung cancer is based on histological examination of the suspicious tissue[6] in the context of the clinical and radiological features.[12]

Clinical practice guidelines recommend frequencies for pulmonary nodule surveillance.[63] CT imaging should not be used for longer or more frequently than indicated as extended surveillance exposes people to increased radiation.[63]

### Classification [edit]

Lung cancers are classified according to histological type.[12] This classification is important for determining management and predicting outcomes of the disease. Lung cancers are carcinomas—malignancies that arise from epithelial cells. Lung carcinomas are categorized by the size and appearance of the malignant cells seen by a histopathologist under a microscope. For therapeutic purposes, two broad classes are distinguished: non-small-cell lung carcinoma and small-cell lung carcinoma.[65]

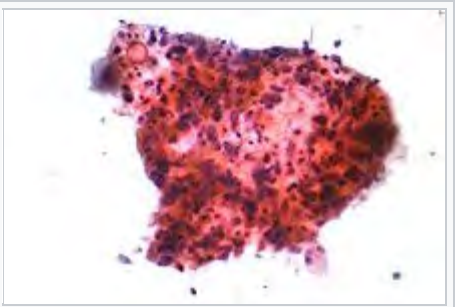



### Non-small-cell lung carcinoma [edit]

The three main subtypes of NSCLC are adenocarcinoma,

squamous-cell carcinoma and large-cell carcinoma.[6]

Nearly 40% of lung cancers are adenocarcinoma, which usually originates in peripheral lung tissue.[12] Although most cases of adenocarcinoma are associated with smoking, adenocarcinoma is also the most common form of lung cancer among people who have smoked fewer than 100 cigarettes in their lifetimes ("never-smokers")[6][66] and ex-smokers with a modest smoking history.[6]



Micrograph of squamous-cell carcinoma, a type of non-small-cell carcinoma, FNA specimen, Pap stain

A subtype of adenocarcinoma, the bronchioloalveolar carcinoma, is more common in female never-smokers, and may have a better long-term survival.[67]

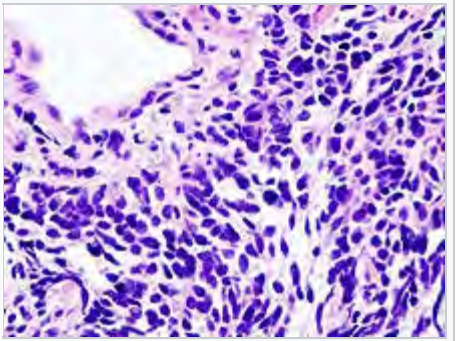
Squamous-cell carcinoma accounts for about 30% of lung cancers. They typically occur close to large airways. A hollow cavity and associated cell death are commonly found at the center of the tumor.[12] About 9% of lung cancers are large-cell carcinoma. These are so named because the cancer cells are large, with excess cytoplasm, large nuclei and conspicuous nucleoli.[12]

Pie chart showing incidences of non-small cell lung cancers as compared to small cell carcinoma shown at right, with fractions of smokers versus non-smokers shown for each type.[64]

**Age-adjusted incidence of lung cancer by histological type**[7]

| Histological type | Incidence per 100,000 per year |
|---|---|
| All types | 66.9 |
| Adenocarcinoma | 22.1 |
| Squamous-cell carcinoma | 14.4 |
| Small-cell carcinoma | 9.8 |

## Small-cell lung carcinoma [edit]



Small-cell lung carcinoma (microscopic view of a core needle biopsy)

In small-cell lung carcinoma (SCLC), the cells contain dense neurosecretory granules (vesicles containing neuroendocrine hormones), which give this tumor an endocrine/paraneoplastic syndrome association.[68] Most cases arise in the larger airways (primary and secondary bronchi).[13] Sixty to seventy percent have extensive disease (which cannot be targeted within a single radiation therapy field) at presentation.[6]

### Others [edit]

Four main histological subtypes are recognised, although some cancers may contain a combination of different subtypes,[65] such as adenosquamous carcinoma.[12] Rare subtypes include carcinoid tumors, bronchial gland carcinomas and sarcomatoid carcinomas.[12]

## Metastasis [edit]

The lung is a common place for the spread of tumors from other parts of the body. Secondary cancers are classified by the site of origin; e.g., breast cancer that has spread to the lung is called metastatic breast cancer. Metastases often have a characteristic round appearance on chest radiograph.[69]

Primary lung cancers themselves most commonly metastasize to the brain, bones, liver and adrenal glands.[12] Immunostaining of a biopsy is often helpful to determine the original source.[70] The presence of Napsin-A, TTF-1, CK7 and CK20 are helpful in confirming the subtype of lung carcinoma. SCLC derived from neuroendocrine cells may express CD56, neural cell adhesion molecule, synaptophysin or chromogranin.[6]

**Typical Napsin-A and TTF-1 immunostaining in primary lung carcinoma**[6]

| Histological type | Napsin-A | TTF-1 |
|---|---|---|
| Squamous-cell carcinoma | Negative | Negative |
| Adenocarcinoma | Positive | Positive |
| Small-cell carcinoma | Negative | Positive |

## Staging [edit]

*See also: Lung cancer staging*

Lung cancer staging is an assessment of the degree of spread of the cancer from its original source.[71] It is one of the factors affecting the prognosis and potential treatment of lung cancer.[6][71]

The evaluation of non-small-cell lung carcinoma (NSCLC) staging uses the TNM classification. This is based on the size of the primary **t**umor, lymph **n**ode involvement, and distant **m**etastasis.[6]

**TNM classification in lung cancer**[6][72]

| T: Primary tumor | | |
|---|---|---|
| TX | Any of: | Primary tumor cannot be assessed |
| | | Tumor cells present in sputum or bronchial washing, but tumor not seen with imaging or bronchoscopy |
| T0 | No evidence of primary tumor | |
| Tis | Carcinoma in situ | |
| T1 | Tumor size less than or equal to 3 cm across, surrounded by lung or visceral pleura, without invasion proximal to the lobar bronchus | |
| T1a | Tumor size less than or equal to 2 cm across | |
| T1b | Tumor size more than 2 cm but less than or equal to 3 cm across | |
| T2 | Any of: | Tumor size more than 3 cm but less than or equal to 7 cm across |
| | | Involvement of the main bronchus at least 2 cm distal to the carina |
| | | Invasion of visceral pleura |
| | | Atelectasis/obstructive pneumonitis extending to the hilum but not involving the whole lung |
| T2a | Tumor size more than 3 cm but less than or equal to 5 cm across | |
| T2b | Tumor size more than 5 cm but less than or equal to 7 cm across | |
| T3 | Any of: | Tumor size more than 7 cm across |
| | | Invasion into the chest wall, diaphragm, phrenic nerve, mediastinal pleura or parietal pericardium |
| | | Tumor less than 2 cm distal to the carina, but not involving the carina |
| | | Atelectasis/obstructive pneumonitis of the whole lung |
| | | Separate tumor nodule in the same lobe |
| T4 | Any of: | Invasion of the mediastinum, heart, great vessels, trachea, carina, recurrent laryngeal nerve, esophagus, or vertebra |
| | | Separate tumor nodule in a different lobe of the same lung |

| N: Lymph nodes | | |
|---|---|---|
| NX | Regional lymph nodes cannot be assessed | |
| N0 | No regional lymph node metastasis | |
| N1 | Metastasis to ipsilateral peribronchial and/or hilar lymph nodes | |
| N2 | Metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes | |
| N3 | Any of: | Metastasis to scalene or supraclavicular lymph nodes |
| | | Metastasis to contralateral hilar or mediastinal lymph nodes |

| M: Metastasis | | |
|---|---|---|
| MX | Distant metastasis cannot be assessed | |
| M0 | No distant metastasis | |
| M1a | Any of: | Separate tumor nodule in the other lung |
| | | Tumor with pleural nodules |
| | | Malignant pleural or pericardial effusion |
| M1b | Distant metastasis | |

Using the TNM descriptors, a group is assigned, ranging from occult cancer, through stages 0, IA (one-A),

IB, IIA, IIB, IIIA, IIIB and IV (four). This stage group assists with the choice of treatment and estimation of prognosis.[73]

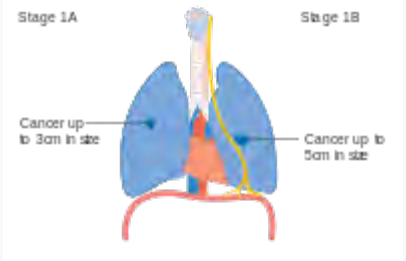
**Stage group according to TNM classification in lung cancer**[6]

| TNM | Stage group |
|---|---|
| T1a–T1b N0 M0 | IA |
| T2a N0 M0 | IB |
| T1a–T2a N1 M0 | IIA |
| T2b N0 M0 | |
| T2b N1 M0 | IIB |
| T3 N0 M0 | |
| T1a–T3 N2 M0 | IIIA |
| T3 N1 M0 | |
| T4 N0–N1 M0 | |
| N3 M0 | IIIB |
| T4 N2 M0 | |
| M1 | IV |

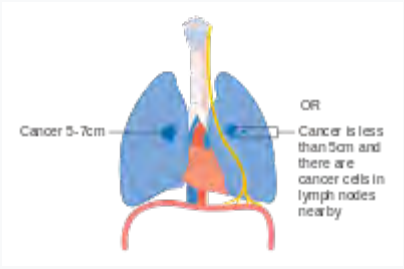
Small-cell lung carcinoma (SCLC) has traditionally been classified as "limited stage" (confined to one-half of the chest and within the scope of a single tolerable radiotherapy field) or "extensive stage" (more widespread disease).[6] However, the TNM classification and grouping are useful in estimating prognosis.[73]

For both NSCLC and SCLC, the two general types of staging evaluations are clinical staging and surgical staging. Clinical staging is performed prior to definitive surgery. It is based on the results of imaging studies (such as CT scans and PET scans) and biopsy results. Surgical staging is evaluated either during or after the operation and is based on the combined results of surgical and clinical findings, including surgical sampling of thoracic lymph nodes.[12]

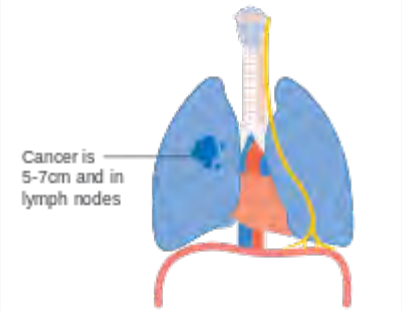
**Diagrams of main features of staging**



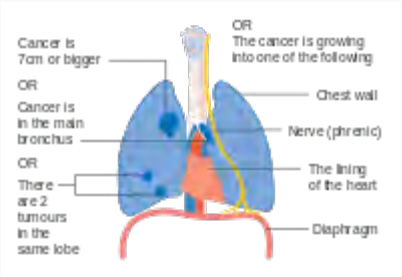

Stage IA and IB lung cancer



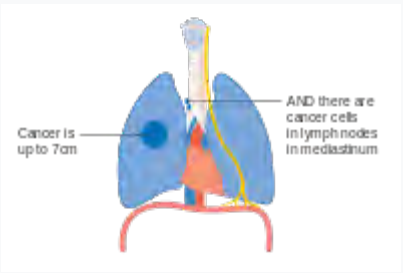

Stage IIA lung cancer



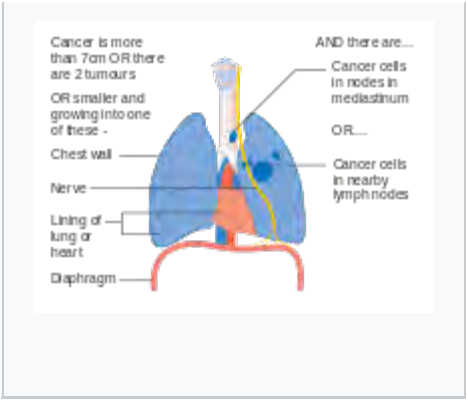

Stage IIB lung cancer



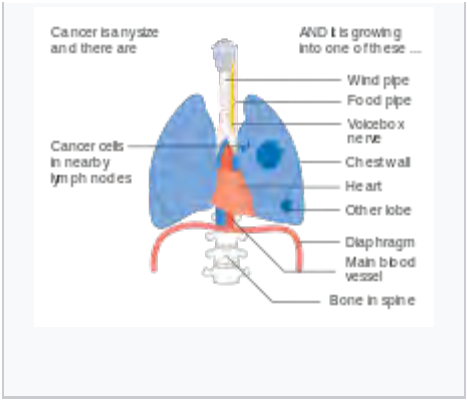

One option for stage IIB lung cancer, with T2b; but if tumor is within 2 cm of the carina, this is stage 3



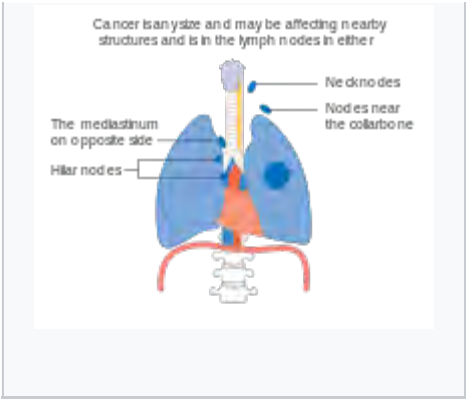

Stage IIIA lung cancer



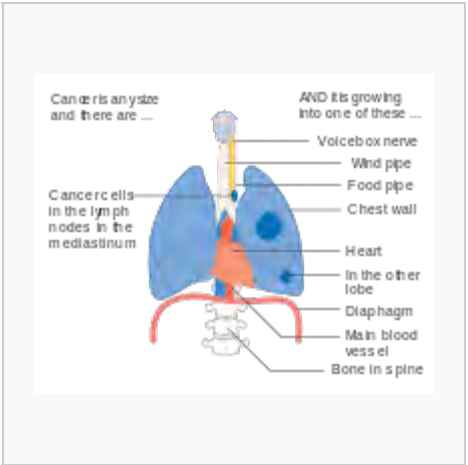

Stage IIIA lung cancer, if there is one feature from the list on each side



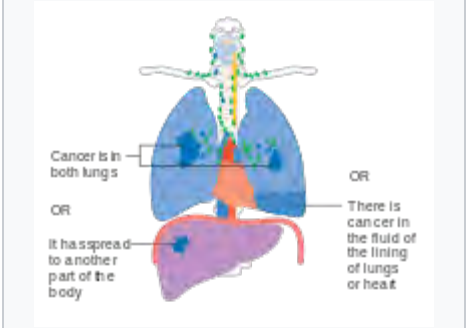

Stage IIIA lung cancer




Stage IIIB lung cancer




Stage IIIB lung cancer




Stage IV lung cancer

# Prevention [edit]

Smoking prevention and smoking cessation are effective ways of preventing the development of lung cancer.[74]

## Smoking ban [edit]

*See also: Smoking ban*

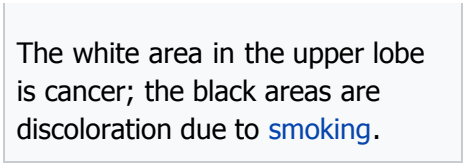
While in most countries industrial and domestic carcinogens have been identified and banned, tobacco smoking is still widespread. Eliminating tobacco smoking is a primary goal in the prevention of lung cancer, and smoking cessation is an important preventive tool in this process.[75]

Policy interventions to decrease passive smoking in public areas such as restaurants and workplaces have become more common in many Western countries.[76] Bhutan has had a complete smoking ban since 2005[77] while India introduced a ban on smoking in public in October 2008.[78] The World Health Organization has called for governments to institute a total ban on tobacco advertising to prevent young people from taking up smoking. They assess that such bans have reduced tobacco consumption by 16% where instituted.[79]

Cross section of a human lung:

## Screening [edit]

*Main article: Lung cancer screening*


The white area in the upper lobe is cancer; the black areas are discoloration due to smoking.

Cancer screening uses medical tests to detect disease in large groups of people who have no symptoms.[80] For individuals with high risk of developing lung cancer, computed tomography (CT) screening can detect cancer and give a person options to respond to it in a way that prolongs life.[63][81] This form of screening reduces the chance of death from lung cancer by an absolute amount of 0.3% (relative amount of 20%).[82][83] High risk people are those age 55–74 who have smoked equivalent amount of a pack of cigarettes daily for 30 years including time within the past 15 years.[63]

CT screening is associated with a high rate of falsely positive tests which may result in unneeded treatment.[84] For each true positive scan there are about 19 falsely positives scans.[85] Other concerns include radiation exposure[84] and the cost of testing along with follow up.[63] Research has not found two other available tests—sputum cytology or chest radiograph (CXR) screening tests—to have any benefit.[81][86]

The United States Preventive Services Task Force (USPSTF) recommends yearly screening using low-dose computed tomography in those who have a total smoking history of 30 pack-years and are between 55 and 80 years old until a person has not been smoking for more than 15 years.[87] Screening should not be done in those with other health problems that would make treatment of lung cancer if found not an option.[87] The English National Health Service was in 2014 re-examining the evidence for screening.[88]

## Other prevention strategies [edit]

The long-term use of supplemental vitamin A,[89][90] vitamin C,[89] vitamin D[91] or vitamin E[89] does not reduce the risk of lung cancer. Some studies suggest that people who eat diets with a higher proportion of vegetables and fruit tend to have a lower risk,[28][92] but this may be due to confounding—with the lower risk actually due to the association of a high fruit/vegetables diet with less smoking.[93] More rigorous studies have not demonstrated a clear association between diet and lung cancer risk.[6][92]

# Management [edit]

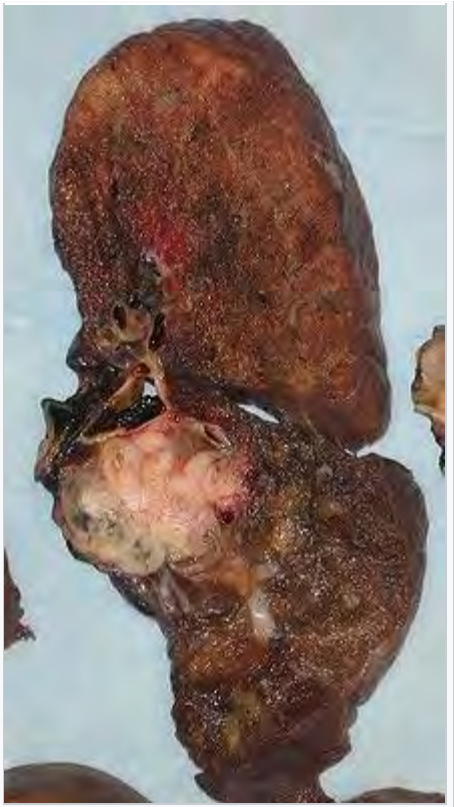
*Main article: Treatment of lung cancer*

Treatment for lung cancer depends on the cancer's specific cell type, how far it has spread, and the person's performance status. Common treatments include palliative care,[94] surgery, chemotherapy, and radiation therapy.[6] Targeted therapy of lung cancer is growing in importance for advanced lung cancer.

## Surgery [edit]

*Main article: Lung cancer surgery*

If investigations confirm NSCLC, the stage is assessed to determine whether the disease is localized and amenable to surgery or if it has spread to the point where it cannot be cured surgically. CT scan and positron emission tomography are used for this determination.[6] If mediastinal lymph node involvement is suspected, the nodes may be sampled to assist staging. Techniques used for this include transthoracic needle aspiration, transbronchial needle aspiration (with or without endobronchial ultrasound), endoscopic ultrasound with needle aspiration, mediastinoscopy, and thoracoscopy.[95] Blood tests and pulmonary function testing are used to assess whether a person is well enough for surgery.[13] If pulmonary function tests reveal poor respiratory reserve,
[6]



Pneumonectomy specimen containing a squamous-cell carcinoma, seen as a white area near the bronchi

surgery may not be possible.

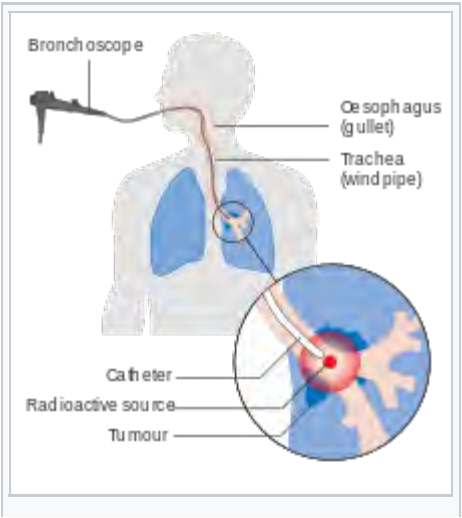
In most cases of early-stage NSCLC, removal of a lobe of lung (lobectomy) is the surgical treatment of choice. In people who are unfit for a full lobectomy, a smaller sublobar excision (wedge resection) may be performed. However, wedge resection has a higher risk of recurrence than lobectomy. Radioactive iodine brachytherapy at the margins of wedge excision may reduce the risk of recurrence. Rarely, removal of a whole lung (pneumonectomy) is performed.[96] Video-assisted thoracoscopic surgery (VATS) and VATS lobectomy use a minimally invasive approach to lung cancer surgery.[97] VATS lobectomy is equally effective compared to conventional open lobectomy, with less postoperative illness.[98]

In SCLC, chemotherapy and/or radiotherapy is typically used.[99] However the role of surgery in SCLC is being reconsidered. Surgery might improve outcomes when added to chemotherapy and radiation in early stage SCLC.[100]

## Radiotherapy [edit]

Radiotherapy is often given together with chemotherapy, and may be used with curative intent in people with NSCLC who are not eligible for surgery. This form of high-intensity radiotherapy is called radical radiotherapy.[101] A refinement of this technique is continuous hyperfractionated accelerated radiotherapy (CHART), in which a high dose of radiotherapy is given in a short time period.[102] Postoperative thoracic radiotherapy generally should not be used after curative intent surgery for NSCLC.[103] Some people with mediastinal N2 lymph node involvement might benefit from post-operative radiotherapy.[104]

For potentially curable SCLC cases, chest radiotherapy is often recommended in addition to chemotherapy.[12]




If cancer growth blocks a short section of bronchus, brachytherapy (localized radiotherapy) may be given directly inside the airway to open the passage. Compared to external beam radiotherapy, brachytherapy allows a reduction in treatment time and reduced radiation exposure to healthcare staff.[105] Evidence for brachytherapy, however, is less than that for external beam radiotherapy.[106]

Prophylactic cranial irradiation (PCI) is a type of radiotherapy to the brain, used to reduce the risk of metastasis. PCI is most useful in SCLC. In limited-stage disease, PCI increases three-year survival from 15% to 20%; in extensive disease, one-year survival increases from 13% to 27%.[107]

Recent improvements in targeting and imaging have led to the development of stereotactic radiation in the treatment of early-stage lung cancer. In this form of radiotherapy, high doses are delivered over

Internal radiotherapy for lung cancer given via the airway.

a number of sessions using stereotactic targeting techniques. Its use is primarily in patients who are not surgical candidates due to medical comorbidities.[108]

For both NSCLC and SCLC patients, smaller doses of radiation to the chest may be used for symptom control (palliative radiotherapy).[109]

## Chemotherapy [edit]

The chemotherapy regimen depends on the tumor type.[12] Small-cell lung carcinoma (SCLC), even relatively early stage disease, is treated primarily with chemotherapy and radiation.[110] In SCLC, cisplatin and etoposide are most commonly used.[111] Combinations with carboplatin, gemcitabine, paclitaxel, vinorelbine, topotecan, and irinotecan are also used.[112][113] In advanced non-small cell lung carcinoma (NSCLC), chemotherapy improves survival and is used as first-line treatment, provided the person is well enough for the treatment.[114] Typically, two drugs are used, of which one is often platinum-based (either cisplatin or carboplatin). Other commonly used drugs are gemcitabine, paclitaxel, docetaxel,[115][116] pemetrexed,[117] etoposide or vinorelbine.[116]

Adjuvant chemotherapy refers to the use of chemotherapy after apparently curative surgery to improve the outcome. In NSCLC, samples are taken of nearby lymph nodes during surgery to assist staging. If stage II or III disease is confirmed, adjuvant chemotherapy improves survival by 5% at five years.[118][119] The combination of vinorelbine and cisplatin is more effective than older regimens.[119] Adjuvant chemotherapy for people with stage IB cancer is controversial, as clinical trials have not clearly demonstrated a survival benefit.[120][121] Chemotherapy before surgery in NSCLC that can be removed surgically also appears to improve outcomes.[122]

Chemotherapy may be combined with palliative care in the treatment of the NSCLC. In advanced cases, appropriate chemotherapy improves average survival over supportive care alone, as well as improving quality of life.[123] With adequate physical fitness maintaining chemotherapy during lung cancer palliation offers 1.5 to 3 months of prolongation of survival, symptomatic relief, and an improvement in quality of life, with better results seen with modern agents.[124][125] The NSCLC Meta-Analyses Collaborative Group recommends if the recipient wants and can tolerate treatment, then chemotherapy should be considered in advanced NSCLC.[114][126]

## Targeted therapy [edit]

Several drugs that target molecular pathways in lung cancer are available, especially for the treatment of advanced disease. Erlotinib, gefitinib and afatinib inhibit tyrosine kinase at the epidermal growth factor receptor. Denosumab is a monoclonal antibody directed against receptor activator of nuclear factor kappa-B ligand. It may be useful in the treatment of bone metastases.[127]

## Bronchoscopy [edit]

Several treatments can be administered via bronchoscopy for the management of airway obstruction or bleeding. If an airway becomes obstructed by cancer growth, options include rigid bronchoscopy, balloon bronchoplasty, stenting, and microdebridement.[128] Laser photosection involves the delivery of laser light inside the airway via a bronchoscope to remove the obstructing tumor.[129]

## Palliative care [edit]

Palliative care when added to usual cancer care benefits people even when they are still receiving chemotherapy.[130] These approaches allow additional discussion of treatment options and provide opportunities to arrive at well-considered decisions.[131][132] Palliative care may avoid unhelpful but expensive care not only at the end of life, but also throughout the course of the illness. For individuals who [13][132]

have more advanced disease, hospice care may also be appropriate.

## Prognosis [edit]

Of all people with lung cancer in the US, 16.8% survive for at least five years after diagnosis.[17][133] In England and Wales, between 2010 and 2011, overall five-year survival for lung cancer was estimated at 9.5%.[134] Outcomes are generally worse in the developing world.[18] Stage is often advanced at the time of diagnosis. At presentation, 30–40% of cases of NSCLC are stage IV, and 60% of SCLC are stage IV.[12] Survival for lung cancer falls as the stage at diagnosis becomes more advanced: the English data suggest that around 70% of patients survive at least a year when diagnosed at the earliest stage, but this falls to just 14% for those diagnosed with the most advanced disease.[135]

**Outcomes in lung cancer according to clinical stage**[73]

| Clinical stage | Five-year survival (%) | |
|---|---|---|
| | Non-small-cell lung carcinoma | Small-cell lung carcinoma |
| IA | 50 | 38 |
| IB | 47 | 21 |
| IIA | 36 | 38 |
| IIB | 26 | 18 |
| IIIA | 19 | 13 |
| IIIB | 7 | 9 |
| IV | 2 | 1 |

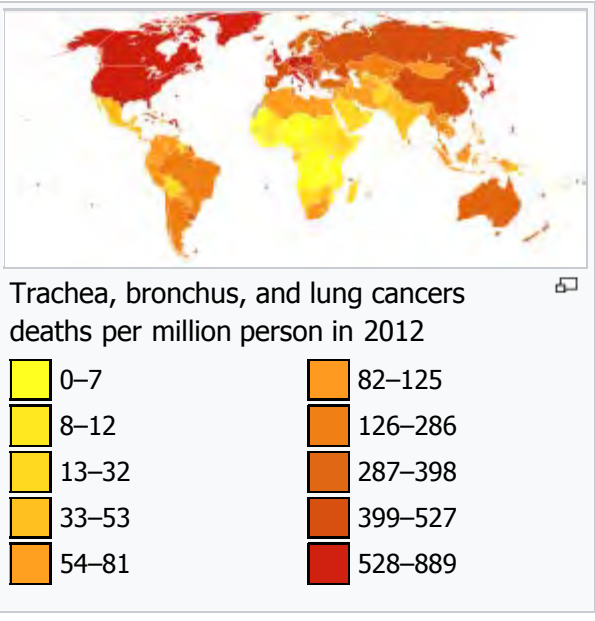
Prognostic factors in NSCLC include presence of pulmonary symptoms, large tumor size (>3 cm), nonsquamous cell type (histology), degree of spread (stage) and metastases to multiple lymph nodes, and vascular invasion. For people with inoperable disease, outcomes are worse in those with poor performance status and weight loss of more than 10%.[136] Prognostic factors in small cell lung cancer include performance status, gender, stage of disease, and involvement of the central nervous system or liver at the time of diagnosis.[137]

For NSCLC, the best prognosis is achieved with complete surgical resection of stage IA disease, with up to 70% five-year survival.[138] People with extensive-stage SCLC have an average five-year survival rate of less than 1%. The average survival time for limited-stage disease is 20 months, with a five-year survival rate of 20%.[1]

According to data provided by the National Cancer Institute, the median age at diagnosis of lung cancer in the United States is 70 years,[139] and the median age at death is 72 years.[140] In the US, people with medical insurance are more likely to have a better outcome.[141]

## Epidemiology [edit]

Worldwide, lung cancer is the most common cancer among men in terms of both incidence and mortality, and among women has the third highest incidence, and is second after breast cancer in mortality. In 2012, there were 1.82 million new cases globally, and 1.56 million deaths due to lung cancer, representing 19.4% of all deaths from cancer.[16] The highest rates are in North America, Europe and East Asia, with over a third of new cases in 2012 in China. Rates in Africa and South Asia are much lower.[142]




The population segment most likely to develop lung cancer is people aged over 50 who have a history of smoking. In contrast to the mortality rate in men, which began declining more than 20 years ago, women's lung cancer mortality rates have been rising over the last decades, and are just recently beginning to stabilize.[143] In the USA, the lifetime risk of developing lung cancer is 8% in men and 6% in women.[6]

For every 3–4 million cigarettes smoked, one lung cancer death occurs.[144] The influence of "Big Tobacco" plays a

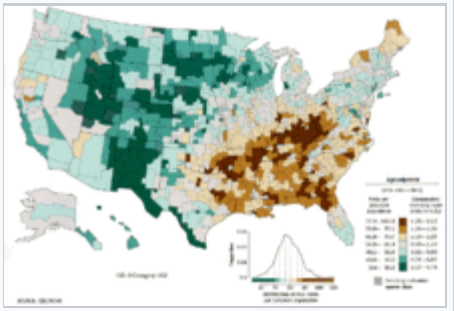
significant role in the smoking culture.[145] Young nonsmokers who see tobacco advertisements are more likely to take up smoking.[146] The role of passive smoking is increasingly being recognized as a risk factor for lung cancer,[31] leading to policy interventions to decrease undesired exposure of nonsmokers to others' tobacco smoke.[147]

In the United States, black men and women have a higher incidence.[148] Lung cancer rates are currently lower in developing countries.[149] With increased smoking in developing countries, the rates are expected to increase in the next few years, notably in China[150] and India.[151]

In the United States military veterans have a 25–50% higher rate of lung cancer primarily due to higher rates of smoking.[152] During World War Two and the Korean War asbestos also played a part and Agent Orange may have caused some problems during the Vietnam War.[153]

Lung cancer is the third most common cancer in the UK (around 46,400 people were diagnosed with the disease in 2014),[154] and it is the most common cause of cancer death (around 35,900 people died in 2014).[155]

From the 1960s, the rates of lung adenocarcinoma started to rise relative to other types of lung cancer. This is partly due to the introduction of filter cigarettes. The use of filters removes larger particles from tobacco smoke, thus reducing deposition in larger airways. However, the smoker has to inhale more deeply to receive the same amount of nicotine, increasing particle deposition in small airways where adenocarcinoma tends to arise.[156] The incidence of lung adenocarcinoma continues to rise.[157]



Lung cancer distribution for white males in the United States


Lung cancer, incidence, mortality and survival, England 1971–2011

## History [edit]

*See also: Timeline of lung cancer*

Lung cancer was uncommon before the advent of cigarette smoking; it was not even recognized as a distinct disease until 1761.[158] Different aspects of lung cancer were described further in 1810.[159] Malignant lung tumors made up only 1% of all cancers seen at autopsy in 1878, but had risen to 10–15% by the early 1900s.[160] Case reports in the medical literature numbered only 374 worldwide in 1912,[161] but a review of autopsies showed the incidence of lung cancer had increased from 0.3% in 1852 to 5.66% in 1952.[162] In Germany in 1929, physician Fritz Lickint recognized the link between smoking and lung cancer,[160] which led to an aggressive antismoking campaign.[163] The British Doctors' Study, published in the 1950s, was the first solid epidemiological evidence of the link between lung cancer and smoking.[164] As a result, in 1964 the Surgeon General of the United States recommended smokers should stop smoking.[165]

The connection with radon gas was first recognized among miners in the Ore Mountains near Schneeberg, Saxony. Silver has been mined there since 1470, and these mines are rich in uranium, with its accompanying radium and radon gas.[166] Miners developed a disproportionate amount of lung disease, eventually recognized as lung cancer in the 1870s.[167] Despite this discovery, mining continued into the 1950s, due to

the USSR's demand for uranium.[166] Radon was confirmed as a cause of lung cancer in the 1960s.[168]

The first successful pneumonectomy for lung cancer was performed in 1933.[169] Palliative radiotherapy has been used since the 1940s.[170] Radical radiotherapy, initially used in the 1950s, was an attempt to use larger radiation doses in patients with relatively early-stage lung cancer, but who were otherwise unfit for surgery.[171] In 1997, continuous hyperfractionated accelerated radiotherapy was seen as an improvement over conventional radical radiotherapy.[172] With small-cell lung carcinoma, initial attempts in the 1960s at surgical resection[173] and radical radiotherapy[174] were unsuccessful. In the 1970s, successful chemotherapy regimens were developed.[175]

## Research directions [edit]

Current research directions for lung cancer treatment include immunotherapy,[176] which encourages the body's immune system to attack the tumor cells, epigenetics, and new combinations of chemotherapy and radiotherapy, both on their own and together. Many of these new treatments work through immune checkpoint blockade, disrupting cancer's ability to evade the immune system.[176]

Ipilimumab blocks signaling through a receptor on T cells known as CTLA-4 which dampens down the immune system. It has been approved by the U.S. Food and Drug Administration (FDA) for treatment of melanoma and is undergoing clinical trials for both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[176]

Other immunotherapy treatments interfere with the binding of programmed cell death 1 (PD-1) protein with its ligand PD-1 ligand 1 (PD-L1). Signaling through PD-1 inactivates T cells. Some cancer cells appear to exploit this by expressing PD-L1 in order to switch off T cells that might recognise them as a threat. Monoclonal antibodies targeting both PD-1 and PD-L1, such as pembrolizumab and nivolumab[177] are currently in clinical trials for treatment for lung cancer.[176]

Epigenetics is the study of small, usually heritable, molecular modifications—or "tags"—that bind DNA and modify gene expression levels. Targeting these tags with drugs can kill cancer cells. Early-stage research in NSCLC using drugs aimed at epigenetic modifications shows that blocking more than one of these tags can kill cancer cells with fewer side effects.[178] Studies also show that giving patients these drugs before standard treatment can improve its effectiveness. Clinical trials are underway to evaluate how well these drugs kill lung cancer cells in humans.[178] Several drugs that target epigenetic mechanisms are in development. Histone deacetylase inhibitors in development include valproic acid, vorinostat, belinostat, panobinostat, entinostat, and romidepsin. DNA methyltransferase inhibitors in development include decitabine, azacytidine, and hydralazine.[58]

The TRACERx project is looking at how NSCLC develops and evolves, and how these tumors become resistant to treatment.[179] The project will look at tumor samples from 850 NSCLC patients at various stages including diagnosis, after first treatment, post-treatment, and relapse.[180] By studying samples at different points of tumor development, the researchers hope to identify the changes that drive tumor growth and resistance to treatment. The results of this project will help scientists and doctors gain a better understanding of NSCLC and potentially lead to the development of new treatments for the disease.[179]

For lung cancer cases that develop resistance to epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors, new drugs are in development. New EGFR inhibitors include afatinib and dacomitinib. An alternative signaling pathway, c-Met, can be inhibited by tivantinib and onartuzumab. New ALK inhibitors include crizotinib and ceritinib.[181]

## References [edit]


1. ^ *a b c d e f g* "Lung Carcinoma: Tumors of the Lungs". Merck Manual Professional Edition, Online edition. Retrieved 15 August 2007.
2. ^ "Non-Small Cell Lung Cancer Treatment –Patient Version (PDQ®)". *NCI*. May 12, 2015. Retrieved 5 March

2016.
3. ^ Falk, S; Williams, C (2010). "Chapter 1". *Lung Cancer—the facts* (3rd ed.). Oxford University Press. pp. 3–4. ISBN 978-0-19-956933-5.
4. ^ a b *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 5.1. ISBN 92-832-0429-8.
5. ^ a b "Lung Cancer—Patient Version". *NCI*. Retrieved 5 March 2016.
6. ^ a b c d e f g h i j k l m n o p q r s t u v w x Horn, L; Lovly, CM; Johnson, DH (2015). "Chapter 107: Neoplasms of the lung". In Kasper, DL; Hauser, SL; Jameson, JL; Fauci, AS; Longo, DL; Loscalzo, J. *Harrison's Principles of Internal Medicine* (19th ed.). McGraw-Hill. ISBN 978-0-07-180216-1.
7. ^ a b c d e f Alberg, AJ; Brock, MV; Samet, JM (2016). "52: Epidemiology of lung cancer". *Murray & Nadel's Textbook of Respiratory Medicine* (6th ed.). Saunders Elsevier. ISBN 978-1-4557-3383-5.
8. ^ Thun MJ, Hannan LM, Adams-Campbell LL, et al. (September 2008). "Lung cancer occurrence in never-smokers: an analysis of 13 cohorts and 22 cancer registry studies". *PLoS Medicine*. **5** (9): e185. doi:10.1371/journal.pmed.0050185. PMC 2531137. PMID 18788891.
9. ^ Carmona, RH (27 June 2006). "The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General". U.S. Department of Health and Human Services. "Secondhand smoke exposure causes disease and premature death in children and adults who do not smoke." Retrieved 2014-06-16
10. ^ a b O'Reilly, KM; Mclaughlin AM; Beckett WS; Sime PJ (March 2007). "Asbestos-related lung disease". *American Family Physician*. **75** (5): 683–688. PMID 17375514.
11. ^ "Tobacco Smoke and Involuntary Smoking" (PDF). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. WHO International Agency for Research on Cancer. **83**. 2004. "There is sufficient evidence that involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) causes lung cancer in humans. ... Involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) is carcinogenic to humans (Group 1)."
12. ^ a b c d e f g h i j k l m n Lu C, Onn A, Vaporciyan AA, et al. (2010). "78: Cancer of the Lung". *Holland-Frei Cancer Medicine* (8th ed.). People's Medical Publishing House. ISBN 978-1-60795-014-1.
13. ^ a b c d e f Collins, LG; Haines C; Perkel R; Enck RE (January 2007). "Lung cancer: diagnosis and management". *American Family Physician*. American Academy of Family Physicians. **75** (1): 56–63. PMID 17225705.
14. ^ "Lung Cancer Prevention–Patient Version (PDQ®)". *NCI*. November 4, 2015. Retrieved 5 March 2016.
15. ^ Chapman, S; Robinson G; Stradling J; West S (2009). "Chapter 31". *Oxford Handbook of Respiratory Medicine* (2nd ed.). Oxford University Press. ISBN 978-0-19-954516-2.
16. ^ a b *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 1.1. ISBN 92-832-0429-8.
17. ^ a b "Surveillance, Epidemiology and End Results Program". *National Cancer Institute*. Retrieved 5 Mar 2016.
18. ^ a b Majumder, edited by Sadhan (2009). *Stem cells and cancer* (Online-Ausg. ed.). New York: Springer. p. 193. ISBN 978-0-387-89611-3.
19. ^ Honnorat, J; Antoine JC (May 2007). "Paraneoplastic neurological syndromes". *Orphanet Journal of Rare Diseases*. BioMed Central. **2** (1): 22. doi:10.1186/1750-1172-2-22. PMC 1868710. PMID 17480225.
20. ^ a b Greene, Frederick L. (2002). *AJCC cancer staging manual*. Berlin: Springer-Verlag. ISBN 0-387-95271-3.
21. ^ Brown KM, Keats JJ, Sekulic A, et al. (2010). "Chapter 8". *Holland-Frei Cancer Medicine* (8th ed.). People's Medical Publishing House USA. ISBN 978-1-60795-014-1.
22. ^ Biesalski HK, Bueno de Mesquita B, Chesson A, et al. (1998). "European Consensus Statement on Lung Cancer: risk factors and prevention. Lung Cancer Panel". *CA Cancer J Clin*. Smoking is the major risk factor, accounting for about 90% of lung cancer incidence. **48** (3): 167–176; discussion 164–166. doi:10.3322/canjclin.48.3.167. PMID 9594919.
23. ^ a b Hecht, SS (2012). "Lung carcinogenesis by tobacco smoke". *International Journal of Cancer*. **131** (12): 2724–2732. doi:10.1002/ijc.27816. PMC 3479369. PMID 22945513.
24. ^ Kumar, V; Abbas AK; Aster JC (2013). "Chapter 5". *Robbins Basic Pathology* (9th ed.). Elsevier Saunders. p. 199. ISBN 978-1-4377-1781-5.
25. ^ Peto R, Lopez AD, Boreham J, et al. (2006). *Mortality from smoking in developed countries 1950–2000: Indirect estimates from National Vital Statistics*. Oxford University Press. ISBN 0-19-262535-7.
26. ^ California Environmental Protection Agency (1997). "Health effects of exposure to environmental tobacco smoke. California Environmental Protection Agency". *Tobacco Control*. **6** (4): 346–353. doi:10.1136/tc.6.4.346. PMC 1759599. PMID 9583639.
27. ^ Centers for Disease Control and Prevention (CDC) (December 2001). "State-specific prevalence of current cigarette smoking among adults, and policies and attitudes about secondhand smoke—United States, 2000". *Morbidity and Mortality Weekly Report*. Atlanta, Georgia: CDC. **50** (49): 1101–1106. PMID 11794619.
28. ^ a b c Alberg, AJ; Samet JM (September 2007). "Epidemiology of lung cancer". *Chest*. American College of Chest Physicians. **132** (S3): 29S–55S. doi:10.1378/chest.07-1347. PMID 17873159.

29. ^ Jaakkola, MS; Jaakkola JJ (August 2006). "Impact of smoke-free workplace legislation on exposures and health: possibilities for prevention". *European Respiratory Journal*. **28** (2): 397–408. doi:10.1183/09031936.06.00001306. PMID 16880370.
30. ^ Parkin, DM (December 2011). "Tobacco—attributable cancer burden in the UK in 2010". *British Journal of Cancer*. **105** (Suppl. 2): S6–S13. doi:10.1038/bjc.2011.475. PMC 3252064. PMID 22158323.
31. ^ [a] [b] Taylor, R; Najafi F; Dobson A (October 2007). "Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent". *International Journal of Epidemiology*. **36** (5): 1048–1059. doi:10.1093/ije/dym158. PMID 17690135.
32. ^ "Frequently asked questions about second hand smoke". *World Health Organization*. Retrieved 25 July 2012.
33. ^ Schick, S; Glantz S (December 2005). "Philip Morris toxicological experiments with fresh sidestream smoke: more toxic than mainstream smoke". *Tobacco Control*. **14** (6): 396–404. doi:10.1136/tc.2005.011288. PMC 1748121. PMID 16319363.
34. ^ Greydanus, DE; Hawver EK; Greydanus MM (October 2013). "Marijuana: current concepts". *Frontiers in Public Health*. **1** (42). doi:10.3389/fpubh.2013.00042. PMC 3859982. PMID 24350211.
35. ^ Owen, KP; Sutter, ME; Albertson, TE (February 2014). "Marijuana: respiratory tract effects.". *Clinical reviews in allergy & immunology*. **46** (1): 65–81. doi:10.1007/s12016-013-8374-y. PMID 23715638.
36. ^ Joshi, M; Joshi, A; Bartter, T (March 2014). "Marijuana and lung diseases.". *Current Opinion in Pulmonary Medicine*. **20** (2): 173–179. doi:10.1097/mcp.0000000000000026. PMID 24384575.
37. ^ Tashkin, DP (June 2013). "Effects of marijuana smoking on the lung.". *Annals of the American Thoracic Society*. **10** (3): 239–47. doi:10.1513/annalsats.201212-127fr. PMID 23802821.
38. ^ Underner, M; Urban T; Perriot J (June 2014). "Cannabis smoking and lung cancer". *Revue des Maladies Respiratoires*. **31** (6): 488–498. doi:10.1016/j.rmr.2013.12.002. PMID 25012035.
39. ^ Choi, H; Mazzone, P (September 2014). "Radon and lung cancer: assessing and mitigating the risk". *Cleveland Clinic Journal of Medicine*. **81** (9): 567–575. doi:10.3949/ccjm.81a.14046. PMID 25183848.
40. ^ "Radon (Rn) Health Risks". EPA.
41. ^ Schmid K, Kuwert T, Drexler H (March 2010). "Radon in Indoor Spaces: An Underestimated Risk Factor for Lung Cancer in Environmental Medicine". *Dtsch Arztebl Int*. **107** (11): 181–6. doi:10.3238/arztebl.2010.0181. PMC 2853156. PMID 20386676.
42. ^ EPA (February 2013). "Radiation information: radon". EPA.
43. ^ Tobias, J; Hochhauser D (2010). "Chapter 12". *Cancer and its Management* (6th ed.). Wiley-Blackwell. p. 199. ISBN 978-1-4051-7015-4.
44. ^ Davies, RJO; Lee YCG (2010). "18.19.3". *Oxford Textbook Medicine* (5th ed.). OUP Oxford. ISBN 978-0-19-920485-4.
45. ^ Chen, H; Goldberg MS; Villeneuve PJ (Oct–Dec 2008). "A systematic review of the relation between long-term exposure to ambient air pollution and chronic diseases". *Reviews on Environmental Health*. **23** (4): 243–297. doi:10.1515/reveh.2008.23.4.243. PMID 19235364.
46. ^ Clapp, RW; Jacobs MM; Loechler EL (Jan–Mar 2008). "Environmental and Occupational Causes of Cancer New Evidence, 2005–2007". *Reviews on Environmental Health*. **23** (1): 1–37. doi:10.1515/REVEH.2008.23.1.1. PMC 2791455. PMID 18557596.
47. ^ [a] [b] Lim, WY; Seow, A (January 2012). "Biomass fuels and lung cancer.". *Respirology (Carlton, Vic.)*. **17** (1): 20–31. doi:10.1111/j.1440-1843.2011.02088.x. PMID 22008241.
48. ^ [a] [b] Sood, A (December 2012). "Indoor fuel exposure and the lung in both developing and developed countries: an update.". *Clinics in chest medicine*. **33** (4): 649–65. doi:10.1016/j.ccm.2012.08.003. PMID 23153607.
49. ^ Yang, IA; Holloway, JW; Fong, KM (October 2013). "Genetic susceptibility to lung cancer and co-morbidities". *Journal of Thoracic Disease*. **5** (Suppl. 5): S454–S462. doi:10.3978/j.issn.2072-1439.2013.08.06. PMC 3804872. PMID 24163739.
50. ^ Dela Cruz, CS; Tanoue, LT; Matthay, RA (2015). "Chapter 109: Epidemiology of lung cancer". In Grippi, MA; Elias, JA; Fishman, JA; Kotloff, RM; Pack, AI; Senior, RM. *Fishman's Pulmonary Diseases and Disorders* (5th ed.). McGraw-Hill. p. 1673. ISBN 978-0-07-179672-9.
51. ^ Larsen, JE; Minna D (December 2011). "Molecular biology of lung cancer: clinical implications". *Clinics in Chest Medicine*. **32** (4): 703–740. doi:10.1016/j.ccm.2011.08.003. PMC 3367865. PMID 22054881.
52. ^ Cogliano, VJ; Baan, R; Straif, K; Grosse, Y; Lauby-Secretan, B; El Ghissassi, F; Bouvard, V; Benbrahim-Tallaa, L; Guha, N; Freeman, C; Galichet, L; Wild, CP (21 December 2011). "Preventable exposures associated with human cancers." (PDF). *Journal of the National Cancer Institute*. **103** (24): 1827–39. doi:10.1093/jnci/djr483. PMID 22158127.
53. ^ Cooper, WA; Lam DLC; O'Toole SA (October 2013). "Molecular biology of lung cancer" (PDF). *Journal of Thoracic Disease*. **5** (Suppl. 5): S. 479–490. doi:10.3978/j.issn.2072-1439.2013.08.03. PMC 3804875. PMID 24163741.

54. ^ Tobias, J; Hochhauser D (2010). "Chapter 12". *Cancer and its Management* (6th ed.). Wiley-Blackwell. p. 200. ISBN 978-1-4051-7015-4.
55. ^ *a b c d* Herbst, RS; Heymach JV; Lippman SM (September 2008). "Lung cancer". *New England Journal of Medicine*. **359** (13): 1367–1380. doi:10.1056/NEJMra0802714. PMID 18815398.
56. ^ Aviel-Ronen, S; Blackhall FH; Shepherd FA; Tsao MS (July 2006). "K-ras mutations in non-small-cell lung carcinoma: a review". *Clinical Lung Cancer*. Cancer Information Group. **8** (1): 30–38. doi:10.3816/CLC.2006.n.030. PMID 16870043.
57. ^ Kumar, V; Abbas AK; Aster JC (2013). "Chapter 5". *Robbins Basic Pathology* (9th ed.). Elsevier Saunders. p. 212. ISBN 978-1-4377-1781-5.
58. ^ *a b* Jakopovic, M; Thomas A; Balasubramaniam S (October 2013). "Targeting the epigenome in lung cancer: expanding approaches to epigenetic therapy" (PDF). *Frontiers in Oncology*. **3** (261). doi:10.3389/fonc.2013.00261. PMC 3793201. PMID 24130964.
59. ^ *a b* Mulvihill, MS; Kratz JR; Pham P (February 2013). "The role of stem cells in airway repair: implications for the origins of lung cancer". *Chinese Journal of Cancer*. **32** (2): 71–74. doi:10.5732/cjc.012.10097. PMC 3845611. PMID 23114089.
60. ^ Powell, CA; Halmos B; Nana-Sinkam SP (July 2013). "Update in lung cancer and mesothelioma 2012" (PDF). *American Journal of Respiratory and Critical Care Medicine*. **188** (2): 157–166. doi:10.1164/rccm.201304-0716UP. PMC 3778761. PMID 23855692.
61. ^ Ost, D (2015). "Chapter 110: Approach to the patient with pulmonary nodules". In Grippi, MA; Elias, JA; Fishman, JA; Kotloff, RM; Pack, AI; Senior, RM. *Fishman's Pulmonary Diseases and Disorders* (5th ed.). McGraw-Hill. p. 1685. ISBN 978-0-07-179672-9.
62. ^ Frank, L; Quint, LE (March 2012). "Chest CT incidentalomas: thyroid lesions, enlarged mediastinal lymph nodes, and lung nodules". *Cancer Imaging*. **12** (1): 41–48. doi:10.1102/1470-7330.2012.0006. PMC 3335330. PMID 22391408.
63. ^ *a b c d e* American College of Chest Physicians; American Thoracic Society (September 2013), "Five Things Physicians and Patients Should Question", *Choosing Wisely: an initiative of the ABIM Foundation*, American College of Chest Physicians and American Thoracic Society, retrieved 6 January 2013
64. ^ Smokers defined as current or former smoker of more than 1 year of duration. See image page in Commons for percentages in numbers. Reference: Table 2 in: Kenfield, S A; Wei, E K; Stampfer, M J; Rosner, B A; Colditz, G A (2008). "Comparison of aspects of smoking among the four histological types of lung cancer". *Tobacco Control*. **17** (3): 198–204. doi:10.1136/tc.2007.022582. PMC 3044470. PMID 18390646.
65. ^ *a b* Kumar, V; Abbas AK; Aster JC (2013). "12". *Robbins Basic Pathology* (9th ed.). Elsevier Saunders. p. 505. ISBN 978-1-4377-1781-5.
66. ^ Subramanian, J; Govindan R (February 2007). "Lung cancer in never smokers: a review". *Journal of Clinical Oncology*. American Society of Clinical Oncology. **25** (5): 561–570. doi:10.1200/JCO.2006.06.8015. PMID 17290066.
67. ^ Raz, DJ; He B; Rosell R; Jablons DM (March 2006). "Bronchioloalveolar carcinoma: a review". *Clinical Lung Cancer*. **7** (5): 313–322. doi:10.3816/CLC.2006.n.012. PMID 16640802.
68. ^ Rosti G, Bevilacqua G, Bidoli P, et al. (March 2006). "Small cell lung cancer". *Annals of Oncology*. **17** (Suppl. 2): 5–10. doi:10.1093/annonc/mdj910. PMID 16608983.
69. ^ Seo JB, Im JG, Goo JM, et al. (1 March 2001). "Atypical pulmonary metastases: spectrum of radiologic findings". *Radiographics*. **21** (2): 403–417. doi:10.1148/radiographics.21.2.g01mr17403. PMID 11259704.
70. ^ Tan D, Zander DS (2008). "Immunohistochemistry for Assessment of Pulmonary and Pleural Neoplasms: A Review and Update". *Int J Clin Exp Pathol*. **1** (1): 19–31. PMC 2480532. PMID 18784820.
71. ^ *a b* Connolly JL, Goldsmith JD, Wang HH, et al. (2010). "37: Principles of Cancer Pathology". *Holland-Frei Cancer Medicine* (8th ed.). People's Medical Publishing House. ISBN 978-1-60795-014-1.
72. ^ Chheang, S; Brown K (June 2013). "Lung cancer staging: clinical and radiologic perspectives". *Seminars in Interventional Radiology*. **30** (2): 99–113. doi:10.1055/s-0033-1342950. PMC 3709937. PMID 24436525.
73. ^ *a b c* Rami-Porta, R; Crowley JJ; Goldstraw P (February 2009). "The revised TNM staging system for lung cancer" (PDF). *Annals of Thoracic and Cardiovascular Surgery*. **15** (1): 4–9. PMID 19262443.
74. ^ Dela Cruz, CS; Tanoue LT; Matthay RA (December 2011). "Lung cancer: epidemiology, etiology, and prevention" (PDF). *Clinic in Chest Medicine*. **32** (4): 605–644. doi:10.1016/j.ccm.2011.09.001. PMC 3864624. PMID 22054876.
75. ^ Goodman, GE (November 2002). "Lung cancer. 1: prevention of lung cancer" (PDF). *Thorax*. **57** (11): 994–999. doi:10.1136/thorax.57.11.994. PMC 1746232. PMID 12403886.
76. ^ McNabola, A; Gill LW (February 2009). "The control of environmental tobacco smoke: a policy review". *International Journal of Environmental Research and Public Health*. **6** (2): 741–758. doi:10.3390/ijerph6020741.

PMC 2672352. PMID 19440413.
77. ^ Pandey, G (February 2005). "Bhutan's smokers face public ban". BBC. Retrieved 7 September 2007.
78. ^ Pandey, G (2 October 2008). "Indian ban on smoking in public". BBC. Retrieved 25 April 2012.
79. ^ "UN health agency calls for total ban on tobacco advertising to protect young" (Press release). United Nations News service. 30 May 2008.
80. ^ Gutierrez, A; Suh R; Abtin F (June 2013). "Lung cancer screening". *Seminars in Interventional Radiology*. **30** (2): 114–120. doi:10.1055/s-0033-1342951. PMC 3709936. PMID 24436526.
81. ^ [a] [b] Usman Ali, M; Miller, J; Peirson, L; Fitzpatrick-Lewis, D; Kenny, M; Sherifali, D; Raina, P (August 2016). "Screening for lung cancer: A systematic review and meta-analysis.". *Preventive medicine*. **89**: 301–14. doi:10.1016/j.ypmed.2016.04.015. PMID 27130532.
82. ^ Jaklitsch MT, Jacobson FL, Austin JH, et al. (July 2012). "The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups". *Journal of Thoracic and Cardiovascular Surgery*. **144** (1): 33–38. doi:10.1016/j.jtcvs.2012.05.060. PMID 22710039.
83. ^ Bach PB, Mirkin JN, Oliver TK, et al. (June 2012). "Benefits and harms of CT screening for lung cancer: a systematic review". *JAMA: The Journal of the American Medical Association*. **307** (22): 2418–2429. doi:10.1001/jama.2012.5521. PMC 3709596. PMID 22610500.
84. ^ [a] [b] Aberle, D. R.; Abtin, F.; Brown, K. (2013). "Computed Tomography Screening for Lung Cancer: Has It Finally Arrived? Implications of the National Lung Screening Trial". *Journal of Clinical Oncology*. **31** (8): 1002–1008. doi:10.1200/JCO.2012.43.3110. ISSN 0732-183X. PMID 23401434.
85. ^ Bach PB, Mirkin JN, Oliver TK, et al. (June 2012). "Benefits and harms of CT screening for lung cancer: a systematic review". *JAMA*. **307** (22): 2418–29. doi:10.1001/jama.2012.5521. PMC 3709596. PMID 22610500.
86. ^ Manser R, Lethaby A, Irving LB, Stone C, Byrnes G, Abramson MJ, Campbell D (2013). "Screening for lung cancer". *Cochrane Database of Systematic Reviews*. **6** (6): CD001991. doi:10.1002/14651858.CD001991.pub3. PMID 23794187.
87. ^ [a] [b] Moyer, VA; U.S. Preventive Services Task, Force (Mar 4, 2014). "Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement.". *Annals of Internal Medicine*. **160** (5): 330–8. doi:10.7326/M13-2771. PMID 24378917.
88. ^ Baldwin, DR; Hansell, DM; Duffy, SW; Field, JK (Mar 7, 2014). "Lung cancer screening with low dose computed tomography.". *BMJ (Clinical research ed.)*. **348**: g1970. doi:10.1136/bmj.g1970. PMID 24609921.
89. ^ [a] [b] [c] Fabricius, P; Lange P (July–September 2003). "Diet and lung cancer". *Monaldi Archives for Chest Disease*. **59** (3): 207–211. PMID 15065316.
90. ^ Fritz H, Kennedy D, Fergusson D, et al. (2011). "Vitamin A and Retinoid Derivatives for Lung Cancer: A Systematic Review and Meta Analysis". *PLoS ONE*. **6** (6): e21107. doi:10.1371/journal.pone.0021107. PMC 3124481. PMID 21738614.
91. ^ Herr C, Greulich T, Koczulla RA, et al. (March 2011). "The role of vitamin D in pulmonary disease: COPD, asthma, infection, and cancer". *Respiratory Research*. **12** (1): 31. doi:10.1186/1465-9921-12-31. PMC 3071319. PMID 21418564.
92. ^ [a] [b] Key, TJ (January 2011). "Fruit and vegetables and cancer risk". *British Journal of Cancer*. **104** (1): 6–11. doi:10.1038/sj.bjc.6606032. PMC 3039795. PMID 21119663.
93. ^ Bradbury, KE; Appleby, PN; Key, TJ (June 2014). "Fruit, vegetable, and fiber intake in relation to cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC)". *American Journal of Clinical Nutrition*. **100** (Suppl. 1): 394S–398S. doi:10.3945/ajcn.113.071357. PMID 24920034.
94. ^ Ferrell, B; Koczywas M; Grannis F; Harrington A (April 2011). "Palliative care in lung cancer". *Surgical Clinics of North America*. **91** (2): 403–417. doi:10.1016/j.suc.2010.12.003. PMID 21419260.
95. ^ Chang, L; Rivera, MP (2015). "Chapter 112: Clinical evaluation, diagnosis, and staging of lung cancer". In Grippi, MA; Elias, JA; Fishman, JA; Kotloff, RM; Pack, AI; Senior, RM. *Fishman's Pulmonary Diseases and Disorders* (5th ed.). McGraw-Hill. p. 1728. ISBN 978-0-07-179672-9.
96. ^ Reznik, SI; Smythe, WR (2015). "Chapter 113: Treatment of non-small-cell lung cancer: surgery". In Grippi, MA; Elias, JA; Fishman, JA; Kotloff, RM; Pack, AI; Senior, RM. *Fishman's Pulmonary Diseases and Disorders* (5th ed.). McGraw-Hill. p. 1737–1738. ISBN 978-0-07-179672-9.
97. ^ Alam, N; Flores RM (July–September 2007). "Video-assisted thoracic surgery (VATS) lobectomy: the evidence base". *Journal of the Society of Laparoendoscopic Surgeons*. **11** (3): 368–374. PMC 3015831. PMID 17931521.
98. ^ Rueth, NM; Andrade RS (June 2010). "Is VATS lobectomy better: perioperatively, biologically and oncologically?". *Annals of Thoracic Surgery*. **89** (6): S2107–S2111. doi:10.1016/j.athoracsur.2010.03.020. PMID 20493991.

99. ^ Simon GR, Turrisi A (September 2007). "Management of small cell lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition)". *Chest*. **132** (3 Suppl): 324S–339S. doi:10.1378/chest.07-1385. PMID 17873178.
100. ^ Goldstein, SD; Yang SC (October 2011). "Role of surgery in small cell lung cancer". *Surgical Oncology Clinics of North America*. **20** (4): 769–777. doi:10.1016/j.soc.2011.08.001. PMID 21986271.
101. ^ Arriagada, R; Goldstraw P; Le Chevalier T (2002). *Oxford Textbook of Oncology* (2nd ed.). Oxford University Press. p. 2094. ISBN 0-19-262926-3.
102. ^ Hatton, MQ; Martin JE (June 2010). "Continuous hyperfractionated accelerated radiotherapy (CHART) and non-conventionally fractionated radiotherapy in the treatment of non-small cell lung cancer: a review and consideration of future directions". *Clinical Oncology (Royal College of Radiologists)*. **22** (5): 356–364. doi:10.1016/j.clon.2010.03.010. PMID 20399629.
103. ^ PORT Meta-analysis Trialists Group (2005). Rydzewska, Larysa, ed. "Postoperative radiotherapy for non-small cell lung cancer". *Cochrane Database of Systematic Reviews* (2): CD002142. doi:10.1002/14651858.CD002142.pub2. PMID 15846628.
104. ^ Le Péchoux, C (2011). "Role of postoperative radiotherapy in resected non-small cell lung cancer: a reassessment based on new data". *Oncologist*. **16** (5): 672–681. doi:10.1634/theoncologist.2010-0150. PMC 3228187. PMID 21378080.
105. ^ Ikushima, H (February 2010). "Radiation therapy: state of the art and the future". *Journal of Medical Investigation*. **57** (1–2): 1–11. doi:10.2152/jmi.57.1. PMID 20299738.
106. ^ Reveiz, L; Rueda, JR; Cardona, AF (12 December 2012). "Palliative endobronchial brachytherapy for non-small cell lung cancer". *The Cochrane database of systematic reviews*. **12**: CD004284. doi:10.1002/14651858.CD004284.pub3. PMID 23235606.
107. ^ Paumier, A; Cuenca X; Le Péchoux C (June 2011). "Prophylactic cranial irradiation in lung cancer". *Cancer Treatment Reviews*. **37** (4): 261–265. doi:10.1016/j.ctrv.2010.08.009. PMID 20934256.
108. ^ Girard, N; Mornex F (October 2011). "Stereotactic radiotherapy for non-small cell lung cancer: From concept to clinical reality. 2011 update". *Cancer Radiothérapie*. **15** (6–7): 522–526. doi:10.1016/j.canrad.2011.07.241. PMID 21889901.
109. ^ Fairchild A, Harris K, Barnes E, et al. (August 2008). "Palliative thoracic radiotherapy for lung cancer: a systematic review". *Journal of Clinical Oncology*. **26** (24): 4001–4011. doi:10.1200/JCO.2007.15.3312. PMID 18711191.
110. ^ Hann CL, Rudin CM (30 November 2008). "Management of small-cell lung cancer: incremental changes but hope for the future". *Oncology (Williston Park)*. **22** (13): 1486–92. PMID 19133604.
111. ^ Murray, N; Turrisi AT (March 2006). "A review of first-line treatment for small-cell lung cancer". *Journal of Thoracic Oncology*. **1** (3): 270–278. PMID 17409868.
112. ^ Azim, HA; Ganti AK (March 2007). "Treatment options for relapsed small-cell lung cancer". *Anti-Cancer Drugs*. **18** (3): 255–261. doi:10.1097/CAD.0b013e328011a547. PMID 17264756.
113. ^ MacCallum, C; Gillenwater HH (July 2006). "Second-line treatment of small-cell lung cancer". *Current Oncology Reports*. **8** (4): 258–264. doi:10.1007/s11912-006-0030-8. PMID 17254525.
114. ^ [a] [b] NSCLC Meta-Analyses Collaborative Group (October 2008). "Chemotherapy in Addition to Supportive Care Improves Survival in Advanced Non–Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 16 Randomized Controlled Trials". *J. Clin. Oncol.* **26** (28): 4617–25. doi:10.1200/JCO.2008.17.7162. PMC 2653127. PMID 18678835.
115. ^ Carr, LL; Jett, JR (2015). "Chapter 114: Treatment of non-small-cell lung cancer: chemotherapy". In Grippi, MA; Elias, JA; Fishman, JA; Kotloff, RM; Pack, AI; Senior, RM. *Fishman's Pulmonary Diseases and Disorders* (5th ed.). McGraw-Hill. p. 1752. ISBN 978-0-07-179672-9.
116. ^ [a] [b] Clegg A, Scott DA, Hewitson P, et al. (January 2002). "Clinical and cost effectiveness of paclitaxel, docetaxel, gemcitabine, and vinorelbine in non-small cell lung cancer: a systematic review". *Thorax*. BMJ Publishing Group. **57** (1): 20–28. doi:10.1136/thorax.57.1.20. PMC 1746188. PMID 11809985.
117. ^ Fuld AD, Dragnev KH, Rigas JR (June 2010). "Pemetrexed in advanced non-small-cell lung cancer". *Expert Opin Pharmacother*. **11** (8): 1387–402. doi:10.1517/14656566.2010.482560. PMID 20446853.
118. ^ Carbone, DP; Felip E (September 2011). "Adjuvant therapy in non-small cell lung cancer: future treatment prospects and paradigms". *Clinical Lung Cancer*. **12** (5): 261–271. doi:10.1016/j.cllc.2011.06.002. PMID 21831720.
119. ^ [a] [b] Le Chevalier, T (October 2010). "Adjuvant chemotherapy for resectable non-small-cell lung cancer: where is it going?". *Annals of Oncology*. **21** (Suppl. 7): vii196–198. doi:10.1093/annonc/mdq376. PMID 20943614.
120. ^ Horn, L; Sandler AB; Putnam JB Jr; Johnson DH (May 2007). "The rationale for adjuvant chemotherapy in stage I non-small cell lung cancer". *Journal of Thoracic Oncology*. **2** (5): 377–383. doi:10.1097/01.JTO.0000268669.64625.bb. PMID 17473651.
121. ^ Wakelee, HA; Schiller JH; Gandara DR (July 2006). "Current status of adjuvant chemotherapy for stage IB non-

small-cell lung cancer: implications for the New Intergroup Trial". *Clinical Lung Cancer*. Cancer Information Group. **8** (1): 18–21. doi:10.3816/CLC.2006.n.028. PMID 16870041.
122. ^ NSCLC Meta-analysis Collaborative, Group (May 3, 2014). "Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data.". *Lancet*. **383** (9928): 1561–71. doi:10.1016/S0140-6736(13)62159-5. PMC 4022989. PMID 24576776.
123. ^ Souquet PJ, Chauvin F, Boissel JP, Bernard JP (April 1995). "Meta-analysis of randomised trials of systemic chemotherapy versus supportive treatment in non-resectable non-small cell lung cancer". *Lung Cancer*. 12 Suppl 1: S147–54. doi:10.1016/0169-5002(95)00430-9. PMID 7551923.
124. ^ Sörenson S, Glimelius B, Nygren P (2001). "A systematic overview of chemotherapy effects in non-small cell lung cancer". *Acta Oncologica*. **40** (2–3): 327–39. doi:10.1080/02841860151116402. PMID 11441939.
125. ^ Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N (2001). "A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer". *Health Technology Assessment*. **5** (32): 1–195. PMID 12065068.
126. ^ Non-Small Cell Lung Cancer Collaborative, Group (12 May 2010). "Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer.". *The Cochrane database of systematic reviews* (5): CD007309. doi:10.1002/14651858.CD007309.pub2. PMID 20464750.
127. ^ D'Antonio; Passaro A; Gori B (May 2014). "Bone and brain metastasis in lung cancer: recent advances in therapeutic strategies". *Therapeutic Advances in Medical Oncology*. **6** (3): 101–114. doi:10.1177/1758834014521110. PMC 3987652. PMID 24790650.
128. ^ Lazarus, DR; Eapen, GA (2014). "Chapter 16: Bronchoscopic interventions for lung cancer". In Roth, JA; Hong, WK; Komaki, RU. *Lung Cancer* (4th ed.). Wiley-Blackwell. ISBN 978-1-118-46874-6.
129. ^ Khemasuwan, D; Mehta, AC; Wang, KP (December 2015). "Past, present, and future of endobronchial laser photoresection". *Journal of Thoracic Disease*. **7** (Suppl. 4): S380–S388. doi:10.3978/j.issn.2072-1439.2015.12.55. PMC 4700383. PMID 26807285.
130. ^ Parikh, RB; Kirch, RA; Smith, TJ; Temel, JS (12 December 2013). "Early specialty palliative care--translating data in oncology into practice.". *The New England Journal of Medicine*. **369** (24): 2347–51. doi:10.1056/nejmsb1305469. PMC 3991113. PMID 24328469.
131. ^ Kelley AS, Meier DE (August 2010). "Palliative care—a shifting paradigm". *New England Journal of Medicine*. **363** (8): 781–2. doi:10.1056/NEJMe1004139. PMID 20818881.
132. ^ *a b* Prince-Paul M (April 2009). "When hospice is the best option: an opportunity to redefine goals". *Oncology (Williston Park, N.Y.)*. **23** (4 Suppl Nurse Ed): 13–7. PMID 19856592.
133. ^ Ridge, CA; McErlean AM; Ginsberg MS (June 2013). "Epidemiology of lung cancer". *Seminars in Interventional Radiology*. **30** (2): 93–98. doi:10.1055/s-0033-1342949. PMC 3709917. PMID 24436524.
134. ^ "Lung cancer survival statistics". Cancer Research UK.
135. ^ "Lung cancer survival statistics". Retrieved 28 October 2014.
136. ^ "Non-Small Cell Lung Cancer Treatment". *PDQ for Health Professionals*. National Cancer Institute. PMID 26389304. Retrieved 17 November 2015.
137. ^ "Small Cell Lung Cancer Treatment". *PDQ for Health Professionals*. National Cancer Institute. 2012. Retrieved 16 May 2012.
138. ^ Spiro, SG (2010). "18.19.1". *Oxford Textbook Medicine* (5th ed.). OUP Oxford. ISBN 978-0-19-920485-4.
139. ^ SEER data (SEER.cancer.gov) Median Age of Cancer Patients at Diagnosis 2002–2003
140. ^ SEER data (SEER.cancer.gov) Median Age of Cancer Patients at Death 2002–2006
141. ^ Slatore, CG; Au DH; Gould MK (November 2010). "An official American Thoracic Society systematic review: insurance status and disparities in lung cancer practices and outcomes". *American Journal of Respiratory and Critical Care Medicine*. **182** (9): 1195–1205. doi:10.1164/rccm.2009-038ST. PMID 21041563.
142. ^ Stewart, edited by Bernard W.; Wild, Christopher P. (2014). *World cancer report 2014*. Lyon: IARC Press. pp. 350–352. ISBN 978-92-832-0429-9.
143. ^ Jemal A, Tiwari RC, Murray T, et al. (2004). "Cancer statistics, 2004". *CA: A Cancer Journal for Clinicians*. **54** (1): 8–29. doi:10.3322/canjclin.54.1.8. PMID 14974761.
144. ^ Proctor, RN (March 2012). "The history of the discovery of the cigarette-lung cancer link: evidentiary traditions, corporate denial, global toll". *Tobacco Control*. **21** (2): 87–91. doi:10.1136/tobaccocontrol-2011-050338. PMID 22345227.
145. ^ Lum, KL; Polansky JR; Jackler RK; Glantz SA (October 2008). "Signed, sealed and delivered: "big tobacco" in Hollywood, 1927–1951". *Tobacco Control*. **17** (5): 313–323. doi:10.1136/tc.2008.025445. PMC 2602591. PMID 18818225.
146. ^ Lovato, C; Watts A; Stead LF (October 2011). "Impact of tobacco advertising and promotion on increasing adolescent smoking behaviours". *Cochrane Database of Systematic Reviews* (10): CD003439. doi:10.1002/14651858.CD003439.pub2. PMID 21975739.

147. ^ Kemp, FB (Jul–Sep 2009). "Smoke free policies in Europe. An overview". *Pneumologia*. **58** (3): 155–158. PMID 19817310.
148. ^ National Cancer Institute; SEER stat fact sheets: Lung and Bronchus. Surveillance Epidemiology and End Results. 2010 [1]
149. ^ "Gender in lung cancer and smoking research" (PDF). World Health Organization. 2004. Retrieved 26 May 2007.
150. ^ Zhang, J; Ou JX; Bai CX (November 2011). "Tobacco smoking in China: prevalence, disease burden, challenges and future strategies". *Respirology*. **16** (8): 1165–1172. doi:10.1111/j.1440-1843.2011.02062.x. PMID 21910781.
151. ^ Behera, D; Balamugesh T (2004). "Lung cancer in India" (PDF). *Indian Journal of Chest Diseases and Allied Sciences*. **46** (4): 269–281. PMID 15515828.
152. ^ "HONORING VETERANS WITH GOOD HEALTH". November 7, 2014. Retrieved 1 December 2015.
153. ^ "Lung Cancer As It Affects Veterans And Military". Retrieved 1 December 2015.
154. ^ "Cancer incidence statistics". *Cancer Research UK*. Retrieved 20 December 2016.
155. ^ "Lung cancer statistics". *Cancer Research UK*. Retrieved 20 December 2016.
156. ^ Charloux A, Quoix E, Wolkove N, et al. (February 1997). "The increasing incidence of lung adenocarcinoma: reality or artefact? A review of the epidemiology of lung adenocarcinoma". *International Journal of Epidemiology*. **26** (1): 14–23. doi:10.1093/ije/26.1.14. PMID 9126499.
157. ^ Kadara, H; Kabbout M; Wistuba II (January 2012). "Pulmonary adenocarcinoma: a renewed entity in 2011". *Respirology*. **17** (1): 50–65. doi:10.1111/j.1440-1843.2011.02095.x. PMID 22040022.
158. ^ Morgagni, Giovanni Battista (1761). *De sedibus et causis morborum per anatomen indagatis*. OL 24830495M.
159. ^ Bayle, Gaspard-Laurent (1810). *Recherches sur la phthisie pulmonaire* (in French). Paris. OL 15355651W.
160. ^ *a b* Witschi, H (November 2001). "A short history of lung cancer". *Toxicological Sciences*. **64** (1): 4–6. doi:10.1093/toxsci/64.1.4. PMID 11606795.
161. ^ Adler, I (1912). *Primary Malignant Growths of the Lungs and Bronchi*. New York: Longmans, Green, and Company. OCLC 14783544. OL 24396062M., cited in Spiro SG, Silvestri GA (2005). "One hundred years of lung cancer". *American Journal of Respiratory and Critical Care Medicine*. **172** (5): 523–529. doi:10.1164/rccm.200504-531OE. PMID 15961694.
162. ^ Grannis, FW. "History of cigarette smoking and lung cancer". smokinglungs.com. Archived from the original on 18 July 2007. Retrieved 6 August 2007.
163. ^ Proctor, R (2000). *The Nazi War on Cancer*. Princeton University Press. pp. 173–246. ISBN 0-691-00196-0.
164. ^ Doll, R; Hill AB (November 1956). "Lung Cancer and Other Causes of Death in Relation to Smoking". *British Medical Journal*. **2** (5001): 1071–1081. doi:10.1136/bmj.2.5001.1071. PMC 2035864. PMID 13364389.
165. ^ US Department of Health Education and Welfare (1964). "Smoking and health: report of the advisory committee to the Surgeon General of the Public Health Service" (PDF). Washington, DC: US Government Printing Office.
166. ^ *a b* Greaves, M (2000). *Cancer: the Evolutionary Legacy*. Oxford University Press. pp. 196–197. ISBN 0-19-262835-6.
167. ^ Greenberg, M; Selikoff IJ (February 1993). "Lung cancer in the Schneeberg mines: a reappraisal of the data reported by Harting and Hesse in 1879". *Annals of Occupational Hygiene*. **37** (1): 5–14. doi:10.1093/annhyg/37.1.5. PMID 8460878.
168. ^ Samet, JM (April 2011). "Radiation and cancer risk: a continuing challenge for epidemiologists". *Environmental Health*. **10** (Suppl. 1): S4. doi:10.1186/1476-069X-10-S1-S4. PMC 3073196. PMID 21489214.
169. ^ Horn, L; Johnson DH (July 2008). "Evarts A. Graham and the first pneumonectomy for lung cancer". *Journal of Clinical Oncology*. **26** (19): 3268–3275. doi:10.1200/JCO.2008.16.8260. PMID 18591561.
170. ^ Edwards, AT (1946). "Carcinoma of the Bronchus". *Thorax*. **1** (1): 1–25. doi:10.1136/thx.1.1.1. PMC 1018207. PMID 20986395.
171. ^ Kabela, M (1956). "Erfahrungen mit der radikalen Röntgenbestrahlung des Bronchienkrebses" [Experience with radical irradiation of bronchial cancer]. *Ceskoslovenská Onkológia* (in German). **3** (2): 109–115. PMID 13383622.
172. ^ Saunders M, Dische S, Barrett A, et al. (July 1997). "Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial". *Lancet*. Elsevier. **350** (9072): 161–165. doi:10.1016/S0140-6736(97)06305-8. PMID 9250182.
173. ^ Lennox SC, Flavell G, Pollock DJ, et al. (November 1968). "Results of resection for oat-cell carcinoma of the lung". *Lancet*. Elsevier. **2** (7575): 925–927. doi:10.1016/S0140-6736(68)91163-X. PMID 4176258.
174. ^ Miller, AB; Fox W; Tall R (September 1969). "Five-year follow-up of the Medical Research Council comparative trial of surgery and radiotherapy for the primary treatment of small-celled or oat-celled carcinoma of the bronchus". *Lancet*. Elsevier. **2** (7619): 501–505. doi:10.1016/S0140-6736(69)90212-8. PMID 4184834.
175. ^ Cohen M, Creaven PJ, Fossieck BE Jr et al. (1977). "Intensive chemotherapy of small cell bronchogenic carcinoma". *Cancer Treatment Reports*. **61** (3): 349–354. PMID 194691.

176. ^ a b c d Brahmer, JR (February 2014). "Immune checkpoint blockade: the hope for immunotherapy as a treatment of lung cancer?". *Seminars in oncology*. **41** (1): 126–32. doi:10.1053/j.seminoncol.2013.12.014. PMID 24565586.
177. ^ Powell, CA; Halmos, B; Nana-Sinkam, SP (July 2013). "Update in lung cancer and mesothelioma 2012". *American Journal of Respiratory and Critical Care Medicine*. **188** (2): 157–166. doi:10.1164/rccm.201304-0716UP. PMC 3778761. PMID 23855692.
178. ^ a b Forde, PM; Brahmer, JR; Kelly, RJ (1 May 2014). "New strategies in lung cancer: epigenetic therapy for non-small cell lung cancer.". *Clinical Cancer Research*. **20** (9): 2244–8. doi:10.1158/1078-0432.ccr-13-2088. PMID 24644000.
179. ^ a b Jamal-Hanjani, M; Hackshaw, A; Ngai, Y; et al. (July 2014). "Tracking genomic cancer evolution for precision medicine: the lung TRACERx study.". *PLOS Biology*. **12** (7): e1001906. doi:10.1371/journal.pbio.1001906. PMC 4086714. PMID 25003521.
180. ^ TRACERx project, Cancer Research UK science blog
181. ^ Spaans, JN; Goss, GD (August 2014). "Trials to overcome drug resistance to EGFR and ALK targeted therapies—past, present, and future". *Frontiers in Oncology*. **4** (233). doi:10.3389/fonc.2014.00233. PMC 4145253. PMID 25221748.


## External links [edit]

- Lung cancer at DMOZ

Wikimedia Commons has media related to *Lung cancers*.

| v · t · e · | **Tumours and neoplasia in the respiratory tract (C30–C34/D14, 160–163/212.0–212.4)** | | |
|---|---|---|---|
| **Upper RT** | *Nasal cavity*: Esthesioneuroblastoma · *Nasopharynx*: Nasopharyngeal carcinoma · Nasopharyngeal angiofibroma · *Larynx*: Laryngeal cancer · Laryngeal papillomatosis · | | |
| **Lower RT** | **Trachea** | Tracheal tumor · | |
| | **Lung** | **Non-small-cell lung carcinoma** | Squamous-cell carcinoma · Adenocarcinoma (Mucinous cystadenocarcinoma) · Large-cell lung carcinoma · Rhabdoid carcinoma · Sarcomatoid carcinoma · Carcinoid · Salivary gland–like carcinoma · Adenosquamous carcinoma · Papillary adenocarcinoma · Giant-cell carcinoma · |
| | | **Small-cell carcinoma** | Combined small-cell carcinoma · |
| | | **Non-carcinoma** | Sarcoma · Lymphoma · Immature teratoma · Melanoma · |
| | | **By location** | Pancoast tumor · Solitary pulmonary nodule · Central lung · Peripheral lung · |
| **Pleura** | Mesothelioma · Malignant solitary fibrous tumor · | | |
| **Authority control** | NDL: 00562782 · | | |

Categories: Lung cancer | Smoking


# Lymphoma

From Wikipedia, the free encyclopedia

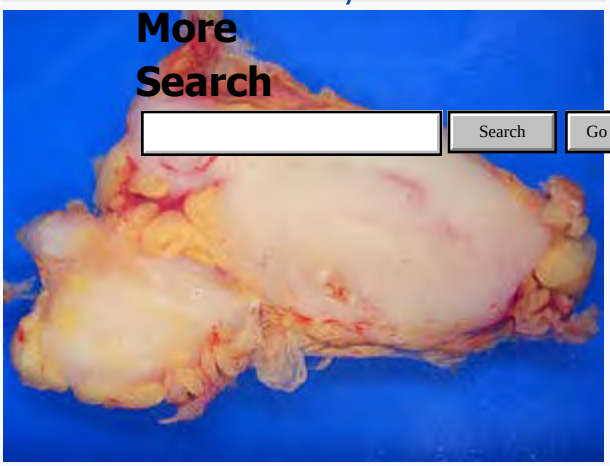
**Lymphoma** is a group of blood cell tumors that develop from lymphocytes (a type of white blood cell). The name often refers to just the cancerous ones rather than all such tumors.[1] Signs and symptoms may include enlarged lymph nodes, fever, drenching sweats, unintended weight loss, itching, and constantly feeling tired.[2][3] The enlarged lymph nodes are usually painless.[2] The sweats are most common at night.[2][3]

There are dozens of subtypes of lymphomas.[4] The two main categories of lymphomas are Hodgkin's lymphomas (HL) and the non-Hodgkin lymphomas (NHL).[5] The World Health Organization (WHO) includes two other categories as types of lymphoma: multiple myeloma and immunoproliferative diseases.[6] About 90% of lymphomas are non-Hodgkin lymphomas.[3][7] Lymphomas and leukemias are a part of the broader group of tumors of the hematopoietic and lymphoid tissues.[8]

Risk factors for Hodgkin lymphoma include infection with Epstein–Barr virus and a history of the disease in the family.[2] Risk factors for common types of non-Hodgkin lymphomas include autoimmune diseases, HIV/AIDS, infection with human T-lymphotropic virus, immunosuppressant medications, and some pesticides.[3] Eating large amounts of red meat and tobacco smoking may also increase the risk.[9][10][11] Diagnosis, if enlarged lymph nodes are present, is usually by lymph node biopsy.[2][3] Blood, urine, and bone marrow testing may also be useful in the diagnosis.[3] Medical imaging may then be done to determine if and where the cancer has spread.[2][3] Lymphoma most often spreads to the lungs, liver, and/or brain.[2][3]

Treatment may involve one or more of the following: chemotherapy, radiation therapy, targeted therapy, and surgery.[2][3] In some non-Hodgkin lymphomas, an increased amount of protein produced by the lymphoma cells causes the blood to become so thick that plasmapheresis is performed to remove the protein.[3] Watchful waiting may be appropriate for certain types.[3] The outcome depends on the subtype with some being curable and treatment prolonging survival in most.[5] The five-year survival rate in the United States for all Hodgkin lymphoma subtypes is 85%,[12] while that for non-Hodgkin lymphomas is 69%.[13] Worldwide, lymphomas developed in 566,000 people in 2012 and caused 305,000 deaths.[6] They make up 3–4% of all cancers, making them as a group the seventh-most common form.[6][14] In children, they are the third-most common cancer.[15] They occur more often in the developed world than the developing world.[6]

**Lymphoma**



Follicular lymphoma replacing a lymph node

| Classification and external resources | |
|---|---|
| **Specialty** | Hematology and oncology |
| **ICD-10** | C81–C96 |
| **ICD-9-CM** | 202.8 |
| **ICD-O** | 9590–9999 |
| **MedlinePlus** | 000580 *000581* |
| **MeSH** | D008223 |

[edit on Wikidata]

Contents

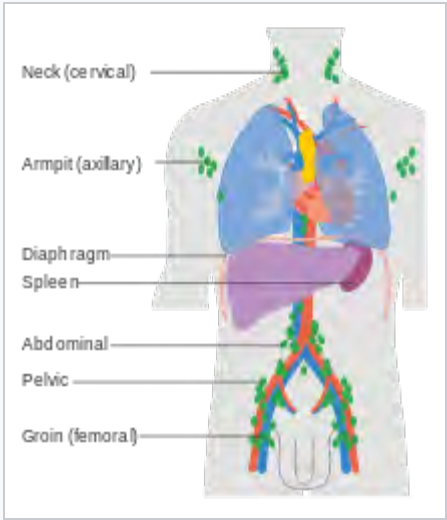




# Signs and symptoms [edit]

Lymphoma may present with certain nonspecific symptoms; if the symptoms are persistent, an evaluation to determine their cause, including possible lymphoma, should be undertaken.

- Lymphadenopathy[16][17] or swelling of lymph nodes, is the primary presentation in lymphoma.
- B symptoms (systemic symptoms) – can be associated with both Hodgkin lymphoma and non-Hodgkin lymphoma. They consist of:
  - Fever[16][17]
  - Night sweats[16][17]
  - Weight loss[16][17]
- Other symptoms:
  - Loss of appetite or anorexia[17]
  - Fatigue[16][17]
  - Respiratory distress or dyspnea[17]
  - Itching[16][17]

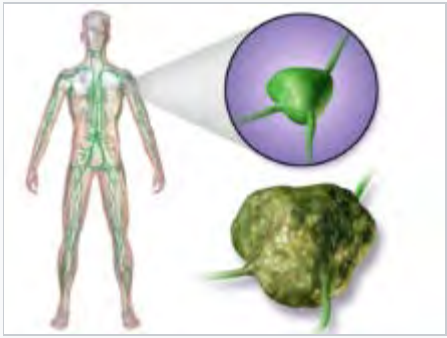



The lymph nodes where lymphoma most commonly develops

# Diagnosis [edit]

Lymphoma is definitively diagnosed by a lymph node biopsy, meaning a partial or total excision of a lymph node examined under the microscope.[18] This examination reveals histopathological features that may indicate lymphoma. After lymphoma is diagnosed, a variety of tests may be carried out to look for specific features characteristic of different types of lymphoma. These include:

- Immunophenotyping
- Flow cytometry
- Fluorescence *in situ* hybridization testing

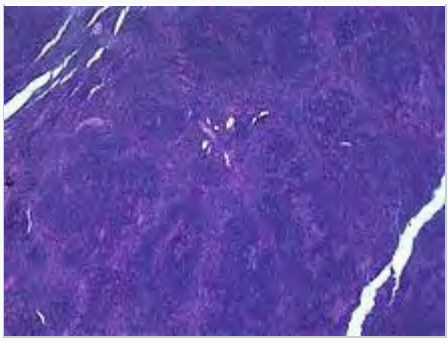


Lymphoma and lymphatic system

## Classification [edit]

Lymphomas *sensu stricto* are any neoplasms of the lymphatic tissues (*lympho-* + *-oma*) .[19] The main classes are malignant neoplasms (that

is, cancers) of the lymphocytes, a type of white blood cell that belongs to both the lymph and the blood and pervades both. Thus, lymphomas and leukemias are both tumors of the hematopoietic and lymphoid tissues, and as lymphoproliferative disorders, lymphomas and lymphoid leukemias are closely related, to the point that some of them are unitary disease entities that can be called by either name (for example, adult T-cell leukemia/lymphoma).



Lymph node with mantle cell lymphoma (low-power view, H&E)

Several classification systems have existed for lymphoma, which use histological and other findings to divide lymphoma into different categories. The classification of a lymphoma can affect treatment and prognosis. Classification systems generally classify lymphoma according to:

- Whether or not it is a Hodgkin lymphoma
- Whether the cell that is replicating is a T cell or B cell
- The site from which the cell arises

Lymphoma can also spread to the central nervous system, often around the brain in the meninges, known as lymphomatous meningitis (LM).[20]

## Hodgkin lymphoma [edit]

*Main article: Hodgkin lymphoma*

Hodgkin lymphoma is one of the most commonly known types of lymphoma,[*citation needed*] and differs from other forms of lymphoma in its prognosis and several pathological characteristics. A division into Hodgkin and non-Hodgkin lymphomas is used in several of the older classification systems. A Hodgkin lymphoma is marked by the presence of a type of cell called the Reed–Sternberg cell.[21][22]

## Non-Hodgkin lymphomas [edit]

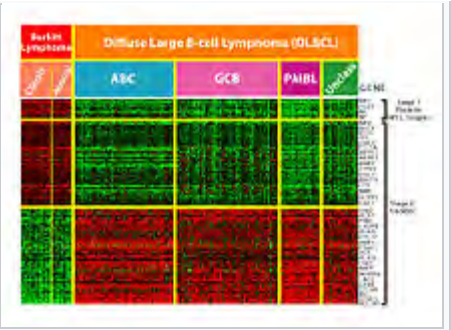
Non-Hodgkin lymphomas, which are defined as being all lymphomas except Hodgkin lymphoma, are more common than Hodgkin lymphoma. A wide variety of lymphomas are in this class, and the causes, the types of cells involved, and the prognosis vary by type. The incidence of non-Hodgkin lymphoma increases with age. It is further divided into several subtypes.

## WHO classification [edit]

The WHO classification, published in 2001 and updated in 2008,[23][24] is based upon the foundations laid within the "revised European-American lymphoma classification" (REAL). This system groups lymphomas by cell type (i.e. the normal cell type that most resembles the tumor) and defining phenotypic, molecular, or cytogenetic characteristics. The five groups are shown in the table. Hodgkin lymphoma is considered separately within the WHO and preceding classifications, although it is recognized as being a tumor of, albeit markedly abnormal, lymphocytes of mature B cell lineage.

Of the many forms of lymphoma, some are categorized as indolent (e.g. small lymphocytic lymphoma), compatible with a long life even without treatment, whereas other forms are aggressive (e.g. Burkitt's lymphoma), causing rapid deterioration and death. However, most of the aggressive lymphomas respond well to treatment and are curable. The prognosis, therefore, depends on the correct diagnosis and classification of the disease, which is established after examination of a biopsy by a pathologist (usually a hematopathologist).[25]

| Lymphoma subtypes (WHO 2008) |
| --- |
| **Mature B cell neoplasms** |
| ▪ B-cell chronic lymphocytic leukemia/small cell lymphoma<br>3 to 4% of lymphomas in adults<br>Small resting lymphocytes mixed with variable numbers of large |




DNA-microarray analysis of Burkitt's lymphoma and diffuse large B-cell lymphoma (DLBCL) showing differences in gene expression patterns. Colors indicate levels of expression; green indicates genes that are underexpressed in lymphoma cells (as compared to normal cells), whereas red indicates genes that are overexpressed in lymphoma cells.

activated cells, lymph nodes diffusely effaced
CD5, surface immunoglobulin
50%.[26]
Occurs in older adults, usually involves lymph nodes, bone marrow and spleen, most patients have peripheral blood involvement, indolent

- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma (such as Waldenström macroglobulinemia)
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Plasma cell neoplasms:
  - Plasma cell myeloma (also known as multiple myeloma)
  - Plasmacytoma
  - Monoclonal immunoglobulin deposition diseases
  - Heavy chain diseases
- Extranodal marginal zone B cell lymphoma, also called MALT lymphoma

  About 5% of lymphomas in adults
  Variable cell size and differentiation, 40% show plasma cell differentiation, homing of B cells to epithelium creates lymphoepithelial lesions.
  CD5, CD10, surface Ig
  Frequently occurs outside lymph nodes, very indolent, may be cured by local excision
- Nodal marginal zone B cell lymphoma
- Follicular lymphoma

  About 40% of lymphomas in adults
  Small "cleaved" cells (centrocytes) mixed with large activated cells (centroblasts), usually nodular ("follicular") growth pattern
  CD10, surface Ig
  72–77%[27]
  Occurs in older adults, usually involves lymph nodes, bone marrow and spleen, associated with t(14;18) translocation overexpressing Bcl-2, indolent
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma

  3 to 4% of lymphomas in adults
  Lymphocytes of small to intermediate size growing in diffuse pattern
  CD5
  50%[28] to 70%[28]
  Occurs mainly in adult males, usually involves lymph nodes, bone marrow, spleen and GI tract, associated with t(11;14) translocation overexpressing cyclin D1, moderately aggressive
- Diffuse large B cell lymphoma, not otherwise specified

  About 40 to 50% of lymphomas in adults
  Variable, most resemble B cells of large germinal centers, diffuse growth pattern
  Variable expression of CD10 and surface Ig
  5-year survival 60%[29]
  Occurs in all ages, but most commonly in older adults, may occur outside lymph nodes, aggressive
- Diffuse large B-cell lymphoma associated with chronic inflammation
- Epstein–Barr virus-positive DLBCL of the elderly
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma

ALK+ large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman's disease
- Burkitt lymphoma/leukemia

  < 1% of lymphomas in the United States
  Round lymphoid cells of intermediate size with several nucleoli, starry-sky appearance by diffuse spread with interspersed apoptosis
  CD10, surface Ig
  5-year survival 50%[30]
  Endemic in Africa, sporadic elsewhere, more common in immunocompromised and children, often visceral involvement, highly aggressive

**Mature T cell and natural killer (NK) cell neoplasms**

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocyte leukemia
- Aggressive NK cell leukemia
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Blastic NK cell lymphoma
- Mycosis fungoides / Sezary syndrome

  Most common cutaneous lymphoid malignancy
  Usually small lymphoid cells with convoluted nuclei that often infiltrate the epidermis, creating Pautrier microabscesseses
  CD4
  5-year survival 75%[31]
  Localized or more generalized skin symptoms, generally indolent, in a more aggressive variant, Sézary's disease, skin erythema and peripheral blood involvement
- Primary cutaneous CD30-positive T cell lymphoproliferative disorders
  - Primary cutaneous anaplastic large cell lymphoma
  - Lymphomatoid papulosis
- Peripheral T-cell lymphoma not otherwise specified

  Most common T cell lymphoma
  Variable, usually a mix small to large lymphoid cells with irregular nuclear contours
  CD3
  Probably consists of several rare tumor types, often disseminated and generally aggressive
- Angioimmunoblastic T cell lymphoma
- Anaplastic large cell lymphoma

**Precursor lymphoid neoplasms**

- B-lymphoblastic leukemia/lymphoma not otherwise specified
- B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
- T-lymphoblastic leukemia/lymphoma

  15% of childhood acute lymphoblastic leukemia and 90% of lymphoblastic lymphoma.[23]:635
  Lymphoblasts with irregular nuclear contours, condensed chromatin, small nucleoli and scant cytoplasm without granules
  TdT, CD2, CD7
  It often presents as a mediastinal mass because of involvement of the thymus. It is highly associated with *NOTCH1* mutations, and is most common in adolescent males.

**Hodgkin lymphoma**

- Classical Hodgkin lymphomas:
  - Nodular sclerosis form of Hodgkin lymphoma
    Most common type of Hodgkin lymphoma
    Reed-Sternberg cell variants and inflammation, usually broad sclerotic bands that consist of collagen
    CD15, CD30
    Most common in young adults, often arises in the mediastinum or cervical lymph nodes
  - Mixed cellularity Hodgkin lymphoma
    Second-most common form of Hodgkin lymphoma
    Many classic Reed-Sternberg cells and inflammation
    CD15, CD30
    Most common in men, more likely to be diagnosed at advanced stages than the nodular sclerosis form
    Epstein-Barr virus involved in 70% of cases
  - Lymphocyte-rich
  - Lymphocyte depleted or not depleted
- Nodular lymphocyte-predominant Hodgkin lymphoma

**Immunodeficiency-associated lymphoproliferative disorders**

- Associated with a primary immune disorder
- Associated with the human immunodeficiency virus (HIV)
- Post-transplant
- Associated with methotrexate therapy
- Primary central nervous system lymphoma occurs most often in immunocompromised patients, in particular those with AIDS, but it can occur in the immunocompetent, as well. It has a poor prognosis, particularly in those with AIDS. Treatment can consist of corticosteroids, radiotherapy, and chemotherapy, often with methotrexate.

## Previous classifications [edit]

Several previous classifications have been used, including Rappaport 1956, Lennert / Kiel 1974, BNLI, Working formulation (1982), and REAL (1994).

The Working formulation of 1982 was a classification of non-Hodgkin lymphoma. It excluded the Hodgkin lymphomas and divided the remaining lymphomas into four grades (low, intermediate, high, and miscellaneous) related to prognosis, with some further subdivisions based on the size and shape of affected cells. This purely histological classification included no information about cell surface markers, or genetics, and it made no distinction between T-cell lymphomas and B-cell lymphomas. It was widely accepted at the time of its publication, but is now obsolete.[32] It is still used by some cancer agencies for compilation of lymphoma statistics and historical rate comparisons.[*citation needed*]

In 1994, the Revised European-American Lymphoma (REAL) classification applied immunophenotypic and genetic features in identifying distinct clinicopathologic entities among all the lymphomas except Hodgkin lymphoma.[33] For coding purposes, the ICD-O (codes 9590–9999)[34] and ICD-10 (codes C81-C96)[35] are available.

## Staging [edit]

After a diagnosis and before treatment, a cancer is staged. This refers to determining if the cancer has spread, and if so, whether locally or to distant sites. Staging is reported as a grade between I (confined) and IV (spread). Staging is carried out because the stage of a cancer impacts its prognosis and treatment.[*citation needed*]

The Ann Arbor staging system is routinely used for staging of both HL and NHL. In this staging system, I represents a localized disease contained within a lymph node, II represents the presence of lymphoma

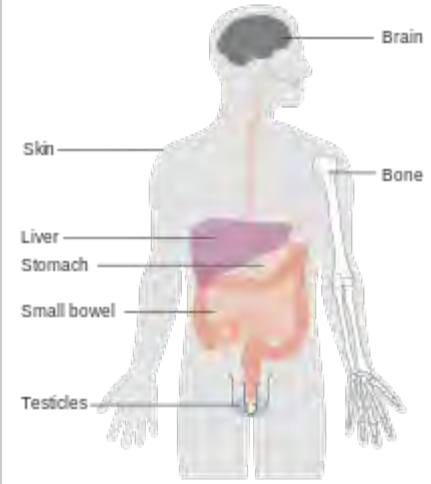
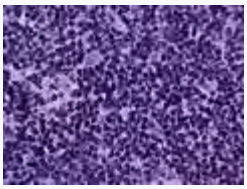



Diagram showing common sites where lymphoma spreads

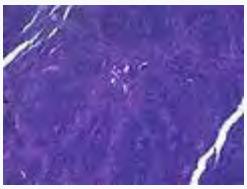
in two or more lymph nodes, III represents spread of the lymphoma to both sides of the diaphragm, and IV indicates tissue outside a lymph node.[*citation needed*]

CT scan or PET scan imaging modalities are used to stage a cancer.[*citation needed*]

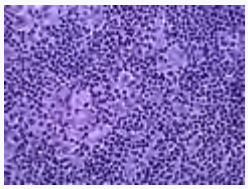
Age and poor performance status are established poor prognostic factors, as well.[36]



Mantle cell lymphoma: Notice the irregular nuclear contours of the medium-sized lymphoma cells and the presence of a pink histiocyte. By immunohistochemistry, the lymphoma cells expressed CD20, CD5, and Cyclin D1 (high-power view, H&E)



Hodgkin lymphoma, nodular lymphocyte predominant (low-power view): Notice the nodular architecture and the areas of "mottling".(H&E)



Hodgkin lymphoma, nodular lymphocyte predominant (high-power view): Notice the presence of L&H cells, also known as "popcorn cells". (H&E)

## Treatment [edit]

Prognoses and treatments are different for HL and between all the different forms of NHL,[37] and also depend on the grade of tumour, referring to how quickly a cancer replicates. Paradoxically, high-grade lymphomas are more readily treated and have better prognoses:[*citation needed*] Burkitt lymphoma, for example, is a high-grade tumour known to double within days, and is highly responsive to treatment. Lymphomas may be curable if detected in early stages with modern treatment.

### Low-grade lymphomas [edit]

Many low-grade lymphomas remain indolent for many years. Treatment of the nonsymptomatic patient is often avoided. In these forms of lymphoma, such as follicular lymphoma, watchful waiting is often the initial course of action. This is carried out because the harms and risks of treatment outweigh the benefits.[38] If a low-grade lymphoma is becoming symptomatic, radiotherapy or chemotherapy are the treatments of

choice; although they do not cure the lymphoma, they can alleviate the symptoms, particularly painful lymphadenopathy. Patients with these types of lymphoma can live near-normal lifespans, but the disease is incurable. Some centers advocate the use of single agent rituximab in the treatment of follicular lymphoma rather than the wait and watch approach. Watchful waiting is not a good strategy for all patients, as it leads to significant distress and anxiety in some patients. It has been equated with watch and worry.[39]

### High-grade lymphomas [edit]

Treatment of some other, more aggressive, forms of lymphoma[*which?*] can result in a cure in the majority of cases, but the prognosis for patients with a poor response to therapy is worse.[40] Treatment for these types of lymphoma typically consists of aggressive chemotherapy, including the CHOP or R-CHOP regimen. A number of people are cured with first-line chemotherapy. Most relapses occur within the first two years, and the relapse risk drops significantly thereafter.[41] For people who relapse, high-dose chemotherapy followed by autologous stem cell transplantation is a proven approach.[42]

### Hodgkin lymphoma [edit]

Hodgkin lymphoma typically is treated with radiotherapy alone, as long as it is localized.[43]

Advanced Hodgkin disease requires systemic chemotherapy, sometimes combined with radiotherapy.[44] Chemotherapy used includes the ABVD regimen, which is commonly used in the United States. Other regimens used in the management of Hodgkin lymphoma include BEACOPP and Stanford V. Considerable controversy exists regarding the use of ABVD or BEACOPP. Briefly, both regimens are effective, but BEACOPP is associated with more toxicity. Encouragingly, a significant number of people who relapse after ABVD can still be salvaged by stem cell transplant.[45]

### Palliative care [edit]

Palliative care, a specialized medical care focused on the symptoms, pain, and stress of a serious illness, is recommended by multiple national cancer treatment guidelines as an accompaniment to curative treatments for people suffering from lymphoma.[46][47] It is used to address both the direct symptoms of lymphoma and many unwanted side effects that arise from treatments.[48][49] Palliative care can be especially helpful for children who develop lymphoma, helping both children and their families deal with the physical and emotional symptoms of the disease.[48][50][51][52] For these reasons, palliative care is especially important for patients requiring bone marrow transplants.[53][54]

## Prognosis [edit]

| Five-year relative survival by stage at diagnosis[55] | | |
|---|---|---|
| Stage at diagnosis | Five-year relative survival (%) | Percentage of cases (%) |
| Localized (confined to primary site) | 82.3 | 26 |
| Regional (spread to regional lymph nodes) | 78.3 | 19 |
| Distant (cancer has metastasized) | 62.7 | 47 |
| Unknown (unstaged) | 68.6 | 8 |

## Epidemiology [edit]

Lymphoma is the most common form of hematological malignancy, or "blood cancer", in the developed world.

Taken together, lymphomas represent 5.3% of all cancers (excluding simple basal cell and squamous cell skin cancers) in the United States and 55.6% of all blood cancers.[56]

According to the U.S. National Institutes of Health, lymphomas account for about 5%, and Hodgkin lymphoma in particular accounts for less than 1% of all cases of cancer in the United States.

Because the whole system is part of the body's immune system, patients with a weakened immune system such as from HIV infection or from certain drugs or medication also have a higher incidence of lymphoma.[57]

Deaths from lymphomas and multiple myeloma per million persons in 2012

| | | |
|---|---|---|
| 0-13 | 23-28 | 43-57 |
| 14-18 | 29-34 | 58-88 |
| 19-22 | 35-42 | 89-121 |
| | | 122-184 |

## History [edit]

*See also: Timeline of lymphoma*

Thomas Hodgkin published the first description of lymphoma in 1832, specifically of the form named after him.[58] Since then, many other forms of lymphoma have been described.

## Research [edit]

The two types of lymphoma research are clinical or translational research and basic research. Clinical/translational research focuses on studying the disease in a defined and generally immediately patient-applicable way, such as testing a new drug in patients. Studies may focus on effective means of treatment, better ways of treating the disease, improving the quality of life for patients, or appropriate care in remission or after cures. Hundreds of clinical trials are being planned or conducted at any given time.[59]

Basic science research studies the disease process at a distance, such as seeing whether a suspected carcinogen can cause healthy cells to turn into lymphoma cells in the laboratory or how the DNA changes inside lymphoma cells as the disease progresses. The results from basic research studies are generally less immediately useful to patients with the disease,[60] but can improve scientists' understanding of lymphoma and form the foundation for future, more effective treatments.

## Other animals [edit]

*Main article: Lymphoma in animals*

## References [edit]


1. ^ Taylor, Elizabeth J. (2000). *Dorland's Illustrated medical dictionary*. (29th ed.). Philadelphia: Saunders. p. 1038. ISBN 0721662544.
2. ^ *a b c d e f g h* "General Information About Adult Hodgkin Lymphoma". *National Cancer Institute*. 2014-04-23. Retrieved 20 June 2014.
3. ^ *a b c d e f g h i j* "General Information About Adult Non-Hodgkin Lymphoma". *National Cancer Institute*. 2014-04-25. Retrieved 20 June 2014.
4. ^ Aditya Bardia (2010). *Johns Hopkins Patients' Guide to Lymphoma*. Jones & Bartlett Learning. p. 6. ISBN 9781449631413.

31. ^ Kirova YM, Piedbois Y, Haddad E, Levy E, Calitchi E, Marinello G, Le Bourgeois JP (May 1999). "Radiotherapy in the management of mycosis fungoides: indications, results, prognosis. Twenty years experience". *Radiother Oncol.* **51** (2): 147–51. doi:10.1016/S0167-8140(99)00050-X. PMID 10435806.
32. ^ Clarke CA, Glaser SL, Dorfman RF, Bracci PM, Eberle E, Holly EA (January 2004). "Expert review of non-Hodgkin lymphomas in a population-based cancer registry: reliability of diagnosis and subtype classifications". *Cancer Epidemiol. Biomarkers Prev*.

5. ^ *a b c The Lymphoma Guide Information for Patients and Caregivers* (pdf). *Leukemia and Lymphoma Society*. 2013. Retrieved 20 June 2014.
6. ^ *a b c d World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 5.13. ISBN 9283204298.
7. ^ "Lymphoma". *NCI*. Retrieved 13 June 2014.
8. ^ Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, Harris NL, Le Beau MM, Hellström-Lindberg E, Tefferi A, Bloomfield CD (Jul 30, 2009). "The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes.". *Blood*. **114** (5): 937–51. doi:10.1182/blood-2009-03-209262. PMID 19357394.
9. ^ Yang, L; Dong, J; Jiang, S; Shi, W; Xu, X; Huang, H; You, X; Liu, H (November 2015). "Red and Processed Meat Consumption Increases Risk for Non-Hodgkin Lymphoma: A PRISMA-Compliant Meta-Analysis of Observational Studies.". *Medicine*. **94** (45): e1729. doi:10.1097/MD.0000000000001729. PMC 4912242. PMID 26559248.
10. ^ Solimini, AG; Lombardi, AM; Palazzo, C; De Giusti, M (May 2016). "Meat intake and non-Hodgkin lymphoma: a meta-analysis of observational studies.". *Cancer causes & control : CCC*. **27** (5): 595–606. doi:10.1007/s10552-016-0745-2. PMID 27076059.
11. ^ Kamper-Jørgensen, M; Rostgaard, K; Glaser, SL; Zahm, SH; Cozen, W; Smedby, KE; Sanjosé, S; Chang, ET; Zheng, T; La Vecchia, C; Serraino, D; Monnereau, A; Kane, EV; Miligi, L; Vineis, P; Spinelli, JJ; McLaughlin, JR; Pahwa, P; Dosman, JA; Vornanen, M; Foretova, L; Maynadie, M; Staines, A; Becker, N; Nieters, A; Brennan, P; Boffetta, P; Cocco, P; Hjalgrim, H (September 2013). "Cigarette smoking and risk of Hodgkin lymphoma and its subtypes: a pooled analysis from the International Lymphoma Epidemiology Consortium (InterLymph).". *Annals of oncology : official journal of the European Society for Medical Oncology*. **24** (9): 2245–55. PMID 23788758.
12. ^ "Hodgkin Lymphoma—SEER Stat Fact Sheets". Seer.cancer.gov. Retrieved 2012-08-26.
13. ^ "SEER Stat Fact Sheets: Non-Hodgkin Lymphoma". *NCI*. Retrieved 18 June 2014.
14. ^ Marcus, Robert (2013). *Lymphoma : pathology, diagnosis and treatment* (Second ed.). p. 1. ISBN 9781107010598.
15. ^ Tepper, John E. Niederhuber, James O. Armitage, James H. Doroshow, Michael B. Kastan, Joel E. (2014). "Childhood lymphoma". *Abeloff's clinical oncology* (Fifth ed.). p. Chapter 97. ISBN 1455728659.
16. ^ *a b c d e f* "About Lymphoma". Lymphoma Research Foundation. Retrieved 22 December 2012.
17. ^ *a b c d e f g h* "Warning Signs of Lymphoma — First **13** (1): 138–43. doi:10.1158/1055-9965.EPI-03-0250. PMID 14744745.
33. ^ *Non-Hodgkin Lymphoma* at eMedicine
34. ^ Archived June 27, 2004, at the Wayback Machine.
35. ^ who.int
36. ^ International Prognostic Index N Engl J Med. 1993;329(14):987–94
37. ^ Sweetenham JW (November 2009). "Treatment of lymphoblastic lymphoma in adults". *Oncology (Williston Park, N.Y.)*. **23** (12): 1015–20. PMID 20017283.
38. ^ Elphee EE (May 2008). "Understanding the concept of uncertainty in patients with indolent lymphoma". *Oncol Nurs Forum*. **35** (3): 449–54. doi:10.1188/08.ONF.449-454. PMID 18467294.
39. ^ Ansell SM (2014). "Follicular lymphoma: Watch and wait is watch and worry". *The Lancet Oncology*. **15** (4): 368–9. doi:10.1016/S1470-2045(14)70066-X. PMID 24602759.
40. ^ Bernstein SH, Burack WR; Burack (2009). "The incidence, natural history, biology, and treatment of transformed lymphomas". *Hematology Am Soc Hematol Educ Program*. **2009**: 532–41. doi:10.1182/asheducation-2009.1.532. PMID 20008238.
41. ^ Jenkins EC (Jan 1972). "Wire-loop application of liquid emulsion to slides for autoradiography in light microscopy.". *Stain technology*. **47** (1): 23–6. doi:10.3109/10520297209116530. PMID 4550425.
42. ^ Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, Sonneveld P, Gisselbrecht C, Cahn JY, Harousseau JL (Dec 7, 1995). "Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma.". *The New England Journal of Medicine*. **333** (23): 1540–5. doi:10.1056/nejm199512073332305. PMID 7477169.
43. ^ Martin NE, Ng AK; Ng (November 2009). "Good things come in small packages: low-dose radiation as palliation for indolent non-Hodgkin lymphomas". *Leuk. Lymphoma*. **50** (11): 1765–72. doi:10.3109/10428190903186510. PMID 19883306.
44. ^ Kuruvilla J (2009). "Standard therapy of advanced Hodgkin lymphoma". *Hematology Am Soc Hematol Educ Program*. **2009**: 497–506. doi:10.1182/asheducation-2009.1.497. PMID 20008235.
45. ^ Viviani S, Zinzani PL, Rambaldi A, Brusamolino E, Levis A, Bonfante V, Vitolo U, Pulsoni A, Liberati AM, Specchia G, Valagussa P, Rossi A, Zaja F, Pogliani EM, Pregno P, Gotti M, Gallamini A, Rota Scalabrini D, Bonadonna G, Gianni AM (2011). "ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned". *New England Journal of Medicine*. **365** (3): 203–12.

Signs of Lymphoma". Lymphoma.about.com. Retrieved 2012-12-01.
18. ^ Mallick, Indranil. "How Is Lymphoma Diagnosed? ". lymphoma.about.com. Retrieved 22 December 2012.
19. ^ Elsevier, *Dorland's Illustrated Medical Dictionary*, Elsevier.
20. ^ Canova, F; Marino, D; Trentin, C; Soldà, C; Ghiotto, C; Aversa, SM (August 2011). "Intrathecal chemotherapy in lymphomatous meningitis.". *Critical reviews in oncology/hematology*. **79** (2): 127–34. PMID 20696592.
21. ^ National Cancer Institute, "Hodgkin Lymphoma", http://www.cancer.gov/cancertopics/types/hodgkin, accessed on 2013-08-05
22. ^ National Cancer Institute. "What You Need To Know About Hodgkin Lymphoma". U.S. Dept of Health and Human Services, (online at http://www.cancer.gov/cancertopics/wyntk/hodgkin.pdf), pg 4.
23. ^ *a b* Jaffe, ES; Harris, NL; Vardiman, JW; Campo, E; Arber, DA. (2011). *Hematopathology* (1st ed.). Elsevier Saunders. ISBN 9780721600406.
24. ^ Swerdlow, Steven H.; International Agency for Research on Cancer; World Health Organization (2008). *WHO classification of tumours of haematopoietic and lymphoid tissues*. World Health Organization classification of tumours. **2** (4th ed.). International Agency for Research on Cancer. ISBN 9789283224310.
25. ^ Wagman LD. (2008). "Principles of Surgical Oncology". In Pazdur R, Wagman LD, Camphausen KA, Hoskins WJ. *Cancer Management: A Multidisciplinary Approach* (11th ed.). CMPMedica. ISBN 9781891483622.
26. ^ "Chronic Leukemias". *The Merck Manual of Geriatrics*.
27. ^ *Lymphoma, Follicular* at eMedicine
28. ^ *a b*
    50% for limited stage: Leitch HA, Gascoyne RD, Chhanabhai M, Voss NJ, Klasa R, Connors JM (October 2003). "Limited-stage mantle-cell lymphoma". *Ann. Oncol.* **14** (10): 1555–61. doi:10.1093/annonc/mdg414. PMID 14504058.
    70% for advanced stage: Herrmann A, Hoster E, Zwingers T, Brittinger G, Engelhard M, Meusers P, Reiser M, Forstpointner R, Metzner B, Peter N, Wörmann B, Trümper L, Pfreundschuh M, Einsele H, Hiddemann W, Unterhalt M, Dreyling M (February 2009). "Improvement of overall survival in advanced stage mantle cell lymphoma". *J. Clin. Oncol.* **27** (4): 511–8. doi:10.1200/JCO.2008.16.8435. doi:10.1056/NEJMoa1100340 . PMID 21774708 .
46. ^ Ferrell B, Connor SR, Cordes A, Dahlin CM, Fine PG, Hutton N, Leenay M, Lentz J, Person JL, Meier DE, Zuroski K (2007). "The national agenda for quality palliative care: the National Consensus Project and the National Quality Forum". *J Pain Symptom Manage*. **33** (6): 737–44. doi:10.1016/j.jpainsymman.2007.02.024. PMID 17531914.
47. ^ *The American Society of Clinical Oncology made this recommendation based on various cancers. See American Society of Clinical Oncology, "Five Things Physicians and Patients Should Question" (PDF), *Choosing Wisely: an initiative of the ABIM Foundation*, American Society of Clinical Oncology, retrieved August 14, 2012
48. ^ *a b* Higginson IJ, Evans CJ; Evans (2010). "What is the evidence that palliative care teams improve outcomes for cancer patients and their families?". *Cancer J.* **16** (5): 423–35. doi:10.1097/PPO.0b013e3181f684e5. PMID 20890138.
49. ^ "Palliative Care: It's for Caregivers Too, Says Study". Retrieved 2014-08-21.
50. ^ Heath JA, Clarke NE, Donath SM, McCarthy M, Anderson VA, Wolfe J (2010). "Symptoms and suffering at the end of life in children with cancer: an Australian perspective". *Med J Aust*. **192** (2): 71–5. PMID 20078405.
51. ^ Schmidt P, Otto M, Hechler T, Metzing S, Wolfe J, Zernikow B (2013). "Did increased availability of pediatric palliative care lead to improved palliative care outcomes in children with cancer?". *J Palliat Med*. **16** (9): 1034–9. doi:10.1089/jpm.2013.0014. PMID 23901834.
52. ^ Tang ST, Chang WC, Chen JS, Wang HM, Shen WC, Li CY, Liao YC (2013). "Course and predictors of depressive symptoms among family caregivers of terminally ill cancer patients until their death". *Psychooncology*. **22** (6): 1312–8. doi:10.1002/pon.3141. PMID 22836818.
53. ^ Chung HM, Lyckholm LJ, Smith TJ (2009). "Palliative care in BMT". *Bone Marrow Transplant*. **43** (4): 265–73. doi:10.1038/bmt.2008.436. PMID 19151797.
54. ^ "Providing Palliative Care to Family Caregivers Throughout the Bone Marrow Transplantation Trajectory". Retrieved 2014-08-21.
55. ^ "SEER Stat Fact Sheets: Lymphoma". Archived from the original on 2013-10-10.
56. ^ Horner MJ, Ries LG, Krapcho M, Neyman N. "SEER Cancer Statistics Review, 1975–2006". *Surveillance Epidemiology and End Results (SEER)*. Bethesda, MD: National Cancer Institute. Retrieved 3 November 2009. "Table 1.4: Age-Adjusted SEER Incidence and U.S. Death Rates and 5-Year Relative Survival Rates By Primary Cancer Site, Sex and Time Period"
57. ^ Tran H, Nourse J, Hall S, Green M, Griffiths L, Gandhi MK (Sep 2008). "Immunodeficiency-

PMID 19075279.

29. ^ Turgeon, Mary Louise (2005). *Clinical Hematology: Theory and Procedures*. **936** (4 ed.). Lippincott Williams & Wilkins. pp. 285–6. ISBN 978-0-7817-5007-3.
30. ^ Diviné M, Casassus P, Koscielny S, Bosq J, Sebban C, Le Maignan C, Stamattoulas A, Dupriez B, Raphaël M, Pico JL, Ribrag V (December 2005). "Burkitt lymphoma in adults: a prospective study of 72 patients treated with an adapted pediatric LMB protocol". *Ann. Oncol.* **16** (12): 1928–35. doi:10.1093/annonc/mdi403. PMID 16284057.

associated lymphomas". *Blood Reviews*. **22** (5): 261–281. doi:10.1016/j.blre.2008.03.009. PMID 18456377.

58. ^ Hellman, Samuel; Mauch, P.M. Ed. (1999). *Hodgkin's Disease*. Chapter 1: Lippincott Williams & Wilkins. p. 5. ISBN 0-7817-1502-4.
59. ^ http://www.clinicaltrials.gov/ct2/results?term=lymphoma
60. ^ "Understanding Clinical Trials for Blood Cancers" (pdf). *The Leukemia & Lymphoma Society*. Leukemia and Lymphoma Society. Retrieved 19 May 2010.

## External links [edit]

- Lymphoma at DMOZ

| v · t · e · | Arthritis in children | |
|---|---|---|
| **Inflammatory** | **Idiopathic** | Juvenile idiopathic arthritis · |
| | **Inflammatory disease** | Inflammatory bowel disease · Sarcoidosis · Cystic fibrosis · Autoimmune hepatitis · |
| | **Hematological malignancy** | Acute lymphoblastic leukemia · **Lymphoma** · |
| | **Malignancy** | Neuroblastoma · |
| | **Reactive** | post-streptococcal · Rheumatic fever · postenteric, post-viral · |
| | **Infection** | Septic arthritis · Osteomyelitis · Tuberculosis · Lyme arthritis · |
| **Mechanical** | Osgood–Schlatter disease · | |
| **Tumours of cartilage bone or muscle** | **Benign** | Osteoid osteoma · Pigmented villonodular synovitis · Hemangioma · |
| | **Malignant** | Synovial sarcoma · Rhabdomyosarcoma · Ewing's sarcoma · |
| **Central Nervous System** | Idiopathic pain syndromes · **Local:** Complex regional pain syndrome/Reflex sympathetic dystrophy · **Generalized:** Fibromyalgia · | |

Categories: Lymphoma | Anatomical pathology | Hematology | Pediatrics

# Melanoma

From Wikipedia, the free encyclopedia

**Melanoma**, also known as **malignant melanoma**, is a type of cancer that develops from the pigment-containing cells known as melanocytes.[1] Melanomas typically occur in the skin but may rarely occur in the mouth, intestines, or eye.[1][2] In women they most commonly occur on the legs, while in men they are most common on the back.[2] Sometimes they develop from a mole with concerning changes including an increase in size, irregular edges, change in color, itchiness, or skin breakdown.[1]

The primary cause of melanoma is ultraviolet light (UV) exposure in those with low levels of skin pigment.[2][3] The UV light may be from either the sun or from other sources, such as tanning devices. About 25% develop from moles.[2] Those with many moles, a history of affected family members, and who have poor immune function are at greater risk.[1] A number of rare genetic defects such as xeroderma pigmentosum also increase risk.[4] Diagnosis is by biopsy of any concerning skin lesion.[1]

Using sunscreen and avoiding UV light may prevent melanoma.[2] Treatment is typically removal by surgery. In those with slightly larger cancers, nearby lymph nodes may be tested for spread. Most people are cured if spread has not occurred. For those in whom melanoma has spread, immunotherapy, biologic therapy, radiation therapy, or chemotherapy may improve survival.[1] With treatment the five-year survival rates in the United States is 98% among those with localized disease and 17% among those in whom spread has occurred.[5] The likelihood that it will come back or spread depends how thick the melanoma is, how fast the cells are dividing, and whether or not the overlying skin has broken down.[2]

Melanoma is the most dangerous type of skin cancer. Globally, in 2012, it occurred in 232,000 people and resulted in 55,000 deaths. Australia and New Zealand have the highest rates of melanoma in the world. There are also high rates in Europe and North America while it is less common in Asia, Africa, and Latin America.[2] Melanoma is more common in men than women.[4] Melanoma has become more common since the 1960s in areas that are mostly Caucasian.[2][4]

**Melanoma**

A melanoma of approximately 2.5 cm by 1.5 cm

**Pronunciation** /ˌmɛləˈnoʊmə/

| Classification and external resources | |
|---|---|
| **Specialty** | Oncology and dermatology |
| **ICD-10** | C43 |
| **ICD-9-CM** | 172.9 |
| **ICD-O** | M8720/3 |
| **OMIM** | 155600 |
| **DiseasesDB** | 7947 |
| **MedlinePlus** | 000850 |
| **eMedicine** | derm/257 med/1386 ent/27 plastic/456 |
| **MeSH** | D008545 |

[edit on Wikidata]

Contents

## Signs and symptoms [edit]

Early signs of melanoma are changes to the shape or color of existing moles or, in the case of nodular melanoma, the appearance of a new lump anywhere on the skin. At later stages, the mole may itch, ulcerate or bleed.[6] Early signs of melanoma are summarized by the mnemonic "ABCDE":

- **A**symmetry
- **B**orders (irregular with edges and corners)
- **C**olor (variegated)
- **D**iameter (greater than 6 mm (0.24 in), about the size of a pencil eraser)
- **E**volving over time

These classifications do not, however, apply to the most dangerous form of melanoma, nodular melanoma, which has its own classifications:

- **E**levated above the skin surface
- **F**irm to the touch
- **G**rowing

Metastatic melanoma may cause nonspecific paraneoplastic symptoms, including loss of appetite, nausea, vomiting and fatigue. Metastasis of early melanoma is possible, but relatively rare: less than a fifth of melanomas diagnosed early become metastatic. Brain metastases are particularly common in patients with metastatic melanoma.[7] It can also spread to the liver, bones, abdomen or distant lymph nodes.

## Cause [edit]

Melanomas are usually caused by DNA damage resulting from exposure to ultraviolet (UV) light from the sun. Genetics also play a role.

### UV radiation [edit]

The ultraviolet radiation from tanning beds increases the risk of melanoma.[8] The International Agency for Research on Cancer finds that tanning beds are "carcinogenic to humans" and that people who begin using tanning devices before age 30 are 75% more likely to develop melanoma.[9]

Those who work in airplanes also appear to have an increased risk, believed to be due to greater exposure to UV.[10]

Ultraviolet UVB light (wavelengths between 315 – 280 nm) from the sun is absorbed by skin cell DNA and results in a type of direct DNA damage called cyclobutane pyrimidine dimers (CPDs). Thymine-thymine, cytosine-cytosine or cytosine-thymine dimers are formed by the joining of two adjacent pyrimidine bases within a DNA strand. Somewhat similarly to UVB, UVA light (longer wavelengths between 400 – 315 nm) from the sun or from tanning beds can also be directly absorbed by skin DNA (at about 100 to 1000 fold lower efficiency than UVB is absorbed).[11]

Studies suggest that exposure to ultraviolet radiation (UVA[12] and UVB) is one of the major contributors to the development of melanoma. Occasional extreme sun exposure (resulting in "sunburn") is causally related to melanoma.[13] Melanoma is most common on the back in men and on legs in women (areas of intermittent sun exposure). The risk appears to be strongly influenced by socio-economic conditions rather than indoor versus outdoor occupations; it is more common in professional and administrative workers than unskilled workers.[14][15] Other factors are mutations in or total loss of tumor suppressor genes. Use of sunbeds (with deeply penetrating UVA rays) has been linked to the development of skin cancers, including melanoma.[16]

Possible significant elements in determining risk include the intensity and duration of sun exposure, the age at which sun exposure occurs, and the degree of skin pigmentation. Melanoma rates tend to be highest in countries settled by migrants from northern Europe that have a large amount of direct, intense sunlight that the skin of the settlers is not adapted to, most notably Australia. Exposure during childhood is a more important risk factor than exposure in adulthood. This is seen in migration studies in Australia.[17]

### Genetics [edit]

A number of rare mutations, which often run in families, greatly increase melanoma susceptibility. Several genes increase risks. Some rare genes have a relatively high risk of causing melanoma; some more common genes, such as a gene called MC1R that causes red hair, have a relatively lower elevated risk. Genetic testing can be used to search for the mutations.

One class of mutations affects the gene CDKN2A. An alternative reading frame mutation in this gene leads to the destabilization of p53, a transcription factor involved in apoptosis and in fifty percent of human cancers. Another mutation in the same gene results in a nonfunctional inhibitor of CDK4, a cyclin-dependent kinase that promotes cell division. Mutations that cause the skin condition xeroderma pigmentosum (XP) also increase melanoma susceptibility. Scattered throughout the genome, these mutations reduce a cell's ability to repair DNA. Both CDKN2A and XP mutations are highly penetrant (the chances of a carrier to express the phenotype is high).

Familial melanoma is genetically heterogeneous,[18] and loci for familial melanoma appear on the chromosome arms 1p, 9p and 12q. Multiple genetic events have been related to melanoma's pathogenesis (disease development).[19] The multiple tumor suppressor 1 (CDKN2A/MTS1) gene encodes p16INK4a – a low-molecular weight protein inhibitor of cyclin-dependent protein kinases (CDKs) – which has been localised to the p21 region of human chromosome 9.[20]

Other mutations confer lower risk, but are more common in the population. People with mutations in the MC1R gene, for example, are two to four times more likely to develop melanoma than those with two wild-type (typical unaffected type) copies. MC1R mutations are very common; in fact, all red-haired people have a mutated copy. Mutation of the MDM2 SNP309 gene is associated with increased risks for younger women.[21]

Fair- and red-haired people, persons with multiple atypical nevi or dysplastic nevi and persons born with giant congenital melanocytic nevi are at increased risk.[22]

A family history of melanoma greatly increases a person's risk because mutations in several genes have been found in melanoma-prone families.[23] People with a history of one melanoma are at increased risk of developing a second primary tumor.[24]

## Pathophysiology [edit]

The earliest stage of melanoma starts when melanocytes begin out-of-control growth. Melanocytes are found between the outer layer of the skin (the epidermis) and the next layer (the dermis). This early stage of the disease is called the radial growth phase, when the tumor is less than 1 mm thick. Because the cancer cells have not yet reached the blood vessels deeper in the skin, it is very unlikely that this early-stage melanoma will spread to other parts of the body. If the melanoma is detected at this stage, then it can usually be completely removed with surgery.

When the tumor cells start to move in a different direction — vertically up into the epidermis and into the papillary dermis — cell behaviour changes dramatically.[25]

The next step in the evolution is the invasive radial growth phase, which is a confusing term; however, it explains the process of the radial growth, in which individual cells start to acquire invasive potential. From this point on the melanoma is capable of spreading. The Breslow's depth of the lesion is usually less than 1 mm (0.04 in), while the Clark level is usually 2.

The vertical growth phase (VGP) following is the invasive melanoma. The tumor becomes able to grow into the surrounding tissue and can spread around the body through blood or lymph vessels. The tumor thickness is usually more than 1 mm (0.04 in), and the tumor involves the deeper parts of the dermis.

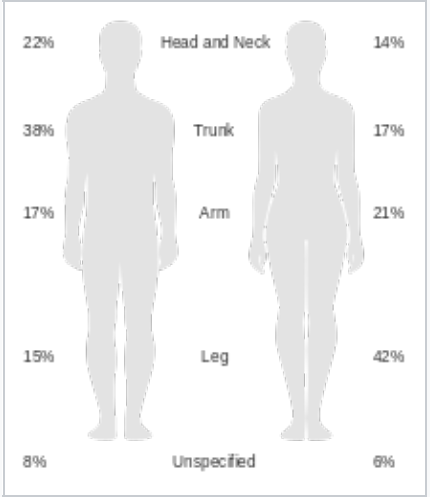
The host elicits an immunological reaction against the tumor during the VGP,[26] which is judged by the presence and activity of the tumor infiltrating lymphocytes (TILs). These cells sometimes completely destroy the primary tumor; this is called regression, which is the latest stage of development. In certain cases, the primary tumor is completely destroyed and only the metastatic tumor is discovered. About 40% of human melanomas contain activating mutations affecting the structure of the B-Raf protein, resulting in constitutive signaling through the Raf to MAP kinase pathway.[27]

In general, cancers are caused by damage to DNA.[28] UVA light mainly causes thymine-thymine dimers.[29] UVA also produces reactive oxygen species and these inflict other DNA damage, primarily single-strand breaks, oxidized pyrimidines and the oxidized purine 8-oxoguanine (a mutagenic DNA change) at 1/10th, 1/10th and 1/3rd the frequencies of UVA-induced thymine-thymine dimers, respectively.

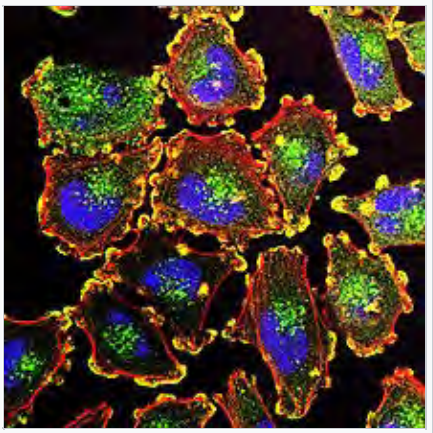
If unrepaired, CPD photoproducts can lead to mutations by inaccurate translesion synthesis during DNA replication or repair. The most frequent mutations due to inaccurate synthesis past CPDs are cytosine to thymine (C>T) or CC>TT transition mutations. These are commonly referred to as UV fingerprint mutations, as they are the most specific mutation caused by UV, being frequently found in sun-exposed skin but rarely found in internal organs.[30] Errors in DNA repair of UV photoproducts, or inaccurate synthesis past these photoproducts, can also lead to deletions, insertions and chromosomal translocations.

The entire genomes of 25 melanomas were sequenced.[31] On average, about 80,000 mutated bases (mostly C>T transitions) and about 100 structural rearragements were found per melanoma genome. This is much higher than the approximately 70 mutations across generations (parent to child).[32][33] Among the 25 melanomas, about 6,000 protein-coding genes had missense, nonsense or splice site mutations.

UV radiation causes damage to the DNA of cells, typically thymine dimerization, which when unrepaired can create mutations in the cell's genes. When the cell divides, these mutations are propagated to new generations of cells. If the mutations occur in protooncogenes or tumor suppressor genes, the rate of mitosis in the mutation-bearing cells can become uncontrolled, leading to the formation of a tumor. Data from patients suggest that aberrant levels of activating transcription factor in the nucleus of melanoma cells are associated with increased metastatic activity of melanoma cells;[34][35][36] studies from mice on skin cancer tend to confirm a role for activating transcription factor-2 in cancer progression.[37][38]



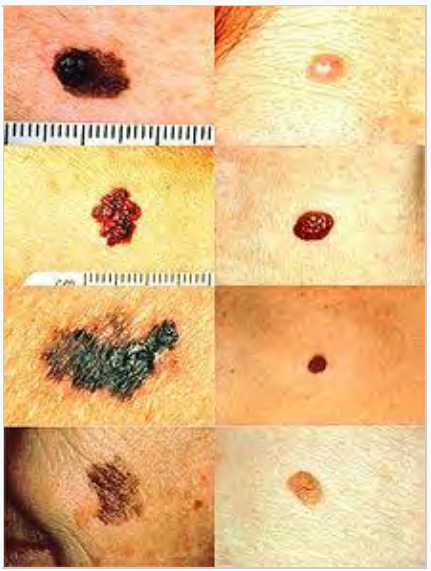
Where melanoma is most likely to develop


Molecular basis for melanoma cell motility: actin-rich podosomes (yellow), along with cell nuclei (blue), actin (red), and an actin regulator (green).

Cancer stem cells may also be involved.[39]

## Diagnosis [edit]

Visual inspection is the most common diagnostic technique.[40] Moles that are irregular in color or shape are typically treated as candidates. To detect melanomas (and increase survival rates), it is recommended to learn to recognize them (see "ABCDE" mnemonic above), to regularly examine moles for changes (shape, size, color, itching or bleeding) and to consult a qualified physician when a candidate appears.[41][42]



ABCD rule illustration: On the left side from top to bottom: melanomas showing (A) Asymmetry, (B) a border that is uneven, ragged, or notched, (C) coloring of different shades of brown, black, or tan and (D) diameter that had changed in size. The normal moles on the right side do not have abnormal characteristics (no asymmetry, even border, even color, no change in diameter).

### ABCDE [edit]

A popular method for remembering the signs and symptoms of melanoma is the mnemonic "ABCDE":

- **A**symmetrical skin lesion.
- **B**order of the lesion is irregular.
- **C**olor: melanomas usually have multiple colors.
- **D**iameter: moles greater than 6 mm are more likely to be melanomas than smaller moles.
- **E**nlarging: Enlarging or evolving

However, many melanomas present as lesions smaller than 6 mm in diameter; and all melanomas are malignant when they first appear as a small dot. Physicians typically examine all moles, including those less than 6 mm in diameter. Seborrheic keratosis may meet some or all of the ABCD criteria, and can lead to false alarms. Doctors can generally distinguish seborrheic keratosis from melanoma upon examination, or with dermatoscopy.

Some advocate replacing enlarging with evolution. Certainly moles that change and evolve will be a concern. Alternatively, some practitioners prefer elevation. Elevation can help identify a melanoma, but lack of elevation does not mean that the lesion is not a melanoma. Most melanomas in the US are detected before they become elevated. By the time elevation is visible, they may have progressed to the more dangerous invasive stage.

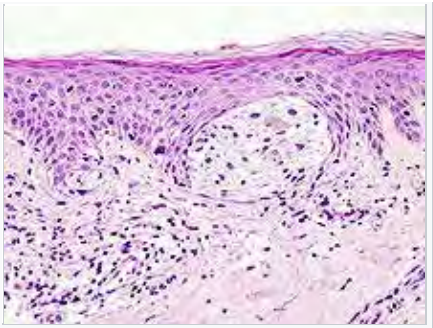
Nodular melanomas do not fulfill these criteria, having their own mnemonic, "EFG":

- **E**levated: the lesion is raised above the surrounding skin.
- **F**irm: the nodule is solid to the touch.
- **G**rowing: the nodule is increasing in size.

A dermatoscope

### Ugly duckling [edit]

A recent and novel method is the "ugly duckling sign".[43] It is simple, easy to teach, and highly effective. Correlation of common lesion characteristics is made. Lesions that greatly deviate from the common characteristics are labeled an "Ugly Duckling", and a further professional exam is required. The "Little Red Riding Hood" sign[43] suggests that individuals with fair skin and light-colored hair might have difficult-to-diagnose amelanotic melanomas. Extra care is required when examining such individuals, as they might have multiple melanomas and severely dysplastic nevi. A dermatoscope must be used to detect "ugly ducklings", as many melanomas in these individuals resemble non-melanomas or are considered to be "wolves in sheep's clothing".[44] These fair-skinned individuals often have lightly pigmented or amelanotic melanomas that do not present easy-to-observe color changes and variations. Their borders are often indistinct, complicating visual identification without a dermatoscope.



Melanoma in skin biopsy with H&E stain — this case may represent superficial spreading melanoma.

Amelanotic melanomas and melanomas arising in fair-skinned individuals are very difficult to detect, as they fail to show many of the characteristics in the ABCD rule, break the "Ugly Duckling" sign and are hard to distinguish from acne scarring, insect bites, dermatofibromas, or lentigines.

## Biopsy [edit]

Following a visual examination and a dermatoscopic exam,[44] or *in vivo* diagnostic tools such as a confocal microscope, the doctor may biopsy the suspicious mole. A skin biopsy performed under local anesthesia is often required to assist in making or confirming the diagnosis and in defining severity. Elliptical excisional biopsies may remove the tumor, followed by histological analysis and Breslow scoring. Punch biopsies are contraindicated in suspected melanomas, for fear of seeding tumor cells and hastening the spread of malignant cells.

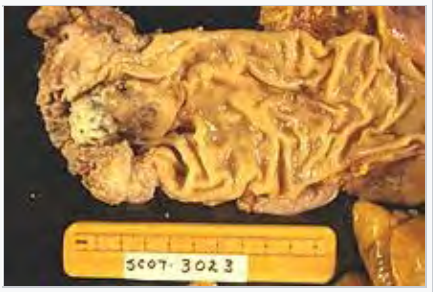
Total body photography, which involves photographic documentation of as much body surface as possible, is often used during follow-up for high-risk patients. The technique has been reported to enable early detection and provides a cost-effective approach (with any digital camera), but its efficacy has been questioned due to its inability to detect macroscopic changes.[40] The diagnosis method should be used in conjunction with (and not as a replacement for) dermoscopic imaging, with a combination of both methods appearing to give extremely high rates of detection.

Lymph node with almost complete replacement by metastatic melanoma. The brown pigment is focal deposition of melanin.

## Classification [edit]

Melanoma is divided into the following types:[45]

- Lentigo maligna
- Lentigo maligna melanoma
- Superficial spreading melanoma
- Acral lentiginous melanoma
- Mucosal melanoma
- Nodular melanoma
- Polypoid melanoma
- Desmoplastic melanoma
- Amelanotic melanoma
- Soft-tissue melanoma




An anal melanoma

See also:[46]

- Melanoma with small nevus-like cells
- Melanoma with features of a Spitz nevus
- Uveal melanoma

## Laboratory [edit]

Lactate dehydrogenase (LDH) tests are often used to screen for metastases, although many patients with metastases (even end-stage) have a normal LDH; extraordinarily high LDH often indicates metastatic spread of the disease to the liver.

It is common for patients diagnosed with melanoma to have chest X-rays and an LDH test, and in some cases CT, MRI, PET and/or PET/CT scans. Although controversial, sentinel lymph node biopsies and examination of the lymph nodes are also performed in patients to assess spread to the lymph nodes. A diagnosis of melanoma is

supported by the presence of the S-100 protein marker.

HMB-45 is a monoclonal antibody that reacts against an antigen present in melanocytic tumors such as melanomas. It is used in anatomic pathology as a marker for such tumors. The antibody was generated to an extract of melanoma. It reacts positively against melanocytic tumors but not other tumors, thus demonstrating specificity and sensitivity. The antibody also reacts positively against junctional nevus cells but not intradermal nevi, and against fetal melanocytes but not normal adult melanocytes.

HMB-45 is nonreactive with almost all non-melanoma human malignancies, with the exception of rare tumors showing evidence of melanogenesis (e.g., pigmented schwannoma, clear cell sarcoma) or tumors associated with tuberous sclerosis complex (angiomyolipoma and lymphangiomyoma).

## Staging [edit]

*Further context on cancer staging is available at TNM.*

Also of importance are the "Clark level" and "Breslow's depth", which refer to the microscopic depth of tumor invasion.[47]

Melanoma stages:[48] 5 year survival rates:

**Stage 0**: Melanoma *in situ* (Clark Level I), 99.9% survival

**Stage I / II**: Invasive melanoma, 89–95% survival

- T1a: Less than 1.0 mm primary tumor thickness, without ulceration, and mitosis < 1/mm2
- T1b: Less than 1.0 mm primary tumor thickness, with ulceration or mitoses ≥ 1/mm2
- T2a: 1.01–2.0 mm primary tumor thickness, without ulceration

**Stage II**: High risk melanoma, 45–79% survival

- T2b: 1.01–2.0 mm primary tumor thickness, with ulceration
- T3a: 2.01–4.0 mm primary tumor thickness, without ulceration
- T3b: 2.01–4.0 mm primary tumor thickness, with ulceration
- T4a: Greater than 4.0 mm primary tumor thickness, without ulceration
- T4b: Greater than 4.0 mm primary tumor thickness, with ulceration

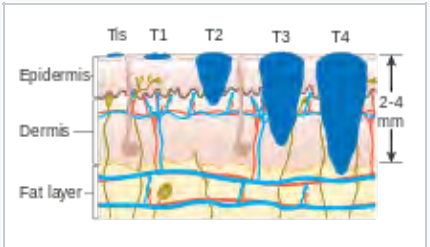
**Stage III**: Regional metastasis, 24–70% survival

- N1: Single positive lymph node
- N2: Two to three positive lymph nodes *or* regional skin/in-transit metastasis
- N3: Four positive lymph nodes *or* one lymph node and regional skin/in-transit metastases

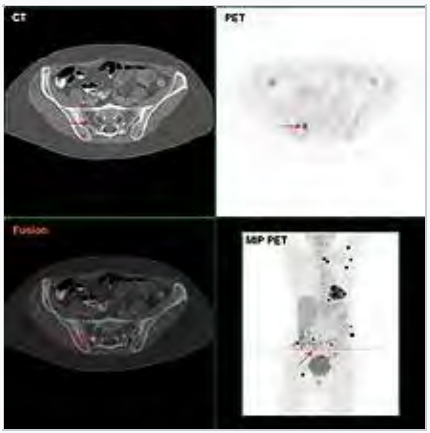
**Stage IV**: Distant metastasis, 7–19% survival

- M1a: Distant skin metastasis, normal LDH
- M1b: Lung metastasis, normal LDH
- M1c: Other distant metastasis *or* any distant metastasis with elevated LDH

*Based upon AJCC five-year survival from initial melanoma diagnosis with proper treatment.*



T stages of melanoma



F18-FDG PET/CT in a melanoma patient showing multiple lesions, most likely metastases

# Prevention [edit]

## Avoiding ultraviolet radiation [edit]

Minimizing exposure to sources of ultraviolet radiation (the sun and sunbeds),[49] following sun protection measures and wearing sun protective clothing (long-sleeved shirts, long trousers, and broad-brimmed hats) can offer protection.

Using artificial light for tanning was once believed to help prevent skin cancers, but it can actually lead to an [50]

increased incidence of melanomas. Even though tanning beds emit mostly UVA, which causes tanning, it by itself might be enough to induce melanomas.

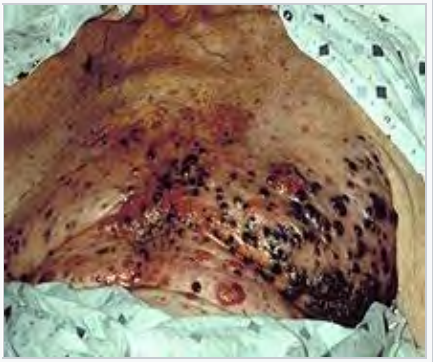
To decrease ultraviolet light exposure it is recommended to avoid the sun between the hours of 9 a.m. and 3 p.m. or avoid the sun when one's shadow is shorter than one's height.

### Sunscreen [edit]

Sunscreen appears to be effective in preventing melanoma.[2][51] In the past, use of sunscreens with a sun protection factor (SPF) rating of 50 or higher on exposed areas were recommended; as older sunscreens more effectively blocked UVA with higher SPF.[52] Currently, newer sunscreen ingredients (avobenzone, zinc oxide, and titanium dioxide) effectively block both UVA and UVB even at lower SPFs. Sunscreen also protects against squamous cell carcinoma, another skin cancer.[53]

## Treatment [edit]

Confirmation of the clinical diagnosis is done with a skin biopsy. This is usually followed up with a wider excision of the scar or tumor. Depending on the stage, a sentinel lymph node biopsy is done, as well, although controversy exists around trial evidence for this procedure.[54] Treatment of advanced malignant melanoma is performed from a multidisciplinary approach.



Extensive malignant melanoma on a person's chest

### Surgery [edit]

Excisional biopsies may remove the tumor, but further surgery is often necessary to reduce the risk of recurrence. Complete surgical excision with adequate surgical margins and assessment for the presence of detectable metastatic disease along with short- and long-term followup is standard. Often this is done by a wide local excision (WLE) with 1 to 2 cm margins. Melanoma-in-situ and lentigo malignas are treated with narrower surgical margins, usually 0.2 to 0.5 cm. Many surgeons consider 0.5 cm the standard of care for standard excision of melanoma-in-situ,[55] but 0.2 cm margin might be acceptable for margin controlled surgery (Mohs surgery, or the double-bladed technique with margin control). The wide excision aims to reduce the rate of tumor recurrence at the site of the original lesion. This is a common pattern of treatment failure in melanoma. Considerable research has aimed to elucidate appropriate margins for excision with a general trend toward less aggressive treatment during the last decades.[56]

Mohs surgery has been reported with cure rate as low as 77%[57] and as high as 98.0% for melanoma-in-situ.[58] CCPDMA and the "double scalpel" peripheral margin controlled surgery is equivalent to Mohs surgery in effectiveness on this "intra-epithelial" type of melanoma.

Melanomas that spread usually do so to the lymph nodes in the area of the tumor before spreading elsewhere. Attempts to improve survival by removing lymph nodes surgically (lymphadenectomy) were associated with many complications, but no overall survival benefit. Recently, the technique of sentinel lymph node biopsy has been developed to reduce the complications of lymph node surgery while allowing assessment of the involvement of nodes with tumor.[59]

Biopsy of sentinel lymph nodes is a widely used procedure when treating cutaneous melanoma.[60][61]

Neither sentinel lymph node biopsy nor other diagnostic tests should be performed to evaluate early, thin melanoma, including melanoma in situ, T1a melanoma or T1b melanoma ≤ 0.5mm.[62] People with these conditions are unlikely to have the cancer spread to their lymph nodes or anywhere else and already have a 97% 5-year survival rate.[62] Because of these things, sentinel lymph node biopsy is unnecessary health care for them.[62] Furthermore, baseline blood tests and radiographic studies should not be performed only based on identifying this kind of melanoma, as there are more accurate tests for detecting cancer and these tests have high false-positive rates.[62]

Sentinel lymph node biopsy is often performed, especially for T1b/T2+ tumors, mucosal tumors, ocular

melanoma and tumors of the limbs.[*citation needed*] A process called lymphoscintigraphy is performed in which a radioactive tracer is injected at the tumor site to localize the sentinel node(s). Further precision is provided using a blue tracer dye, and surgery is performed to biopsy the node(s). Routine hematoxylin and eosin (H&E) and immunoperoxidase staining will be adequate to rule out node involvement. Polymerase chain reaction (PCR) tests on nodes, usually performed to test for entry into clinical trials, now demonstrate that many patients with a negative sentinel lymph node actually had a small number of positive cells in their nodes. Alternatively, a fine-needle aspiration biopsy may be performed and is often used to test masses.

If a lymph node is positive, depending on the extent of lymph node spread, a radical lymph node dissection will often be performed. If the disease is completely resected, the patient will be considered for adjuvant therapy. Excisional skin biopsy is the management of choice. Here, the suspect lesion is totally removed with an adequate (but minimal, usually 1 or 2 mm) ellipse of surrounding skin and tissue.[63] To avoid disruption of the local lymphatic drainage, the preferred surgical margin for the initial biopsy should be narrow (1 mm). The biopsy should include the epidermal, dermal, and subcutaneous layers of the skin. This enables the histopathologist to determine the thickness of the melanoma by microscopic examination. This is described by Breslow's thickness (measured in millimeters). However, for large lesions, such as suspected lentigo maligna, or for lesions in surgically difficult areas (face, toes, fingers, eyelids), a small punch biopsy in representative areas will give adequate information and will not disrupt the final staging or depth determination. In no circumstances should the initial biopsy include the final surgical margin (0.5 cm, 1.0 cm, or 2 cm), as a misdiagnosis can result in excessive scarring and morbidity from the procedure. A large initial excision will disrupt the local lymphatic drainage and can affect further lymphangiogram-directed lymphnode dissection. A small punch biopsy can be used at any time where for logistical and personal reasons a patient refuses more invasive excisional biopsy. Small punch biopsies are minimally invasive and heal quickly, usually without noticeable scarring.

## Add on treatment [edit]

High-risk melanomas may require adjuvant treatment, although attitudes to this vary in different countries. In the United States, most patients in otherwise good health will begin up to a year of high-dose interferon treatment, which has severe side effects, but may improve the patient's prognosis slightly.[64] However British Association of Dermatologist guidelines on melanoma state that interferon is not recommended as a standard adjuvant treatment for melanoma.[65] A 2011 meta-analysis showed that interferon could lengthen the time before a melanoma comes back but increased survival by only 3% at 5 years. The unpleasant side effects also greatly decrease quality of life.[66]

In Europe, interferon is usually not used outside the scope of clinical trials.[67][68]

Metastatic melanomas can be detected by X-rays, CT scans, MRIs, PET and PET/CTs, ultrasound, LDH testing and photoacoustic detection.[69]

## Chemotherapy and immunotherapy [edit]

Various chemotherapy agents, including temozolomide, dacarbazine (also termed DTIC), immunotherapy (with interleukin-2 (IL-2) or interferon (IFN)), as well as local perfusion, are used by different centers. The overall success in metastatic melanoma is quite limited.[70]

IL-2 (Proleukin) was the first new therapy approved (1990 Europe, 1992 USA) for the treatment of metastatic melanoma in 20 years. Studies have demonstrated that IL-2 offers the possibility of a complete and long-lasting remission in this disease, although only in a small percentage of patients.[71] Intralesional IL-2 for in-transit metastases has a high complete response rate ranging from 40 to 100%.[72]

By 2005 a number of new agents and novel approaches were under evaluation and showed promise.[73]

In 2009 Clinical trial participation was considered the standard of care for metastatic melanoma.[74]

Therapies for metastatic melanoma include biologic immunotherapy agents ipilimumab, pembrolizumab, and nivolumab; BRAF inhibitors, such as vemurafenib and dabrafenib; and a MEK inhibitor trametinib.[72]

Ongoing research is looking at treatment by adoptive cell transfer.[75] For this purpose, application of prestimulated or modified T cells [76] or dendritic cells is possible.[77]

## Lentigo maligna [edit]

Standard excision is still being done by most surgeons. Unfortunately, the recurrence rate is exceedingly high (up to 50%). This is due to the ill-defined visible surgical margin, and the facial location of the lesions (often forcing the surgeon to use a narrow surgical margin). The narrow surgical margin used, combined with the limitation of the standard "bread-loafing" technique of fixed tissue histology — result in a high "false negative" error rate, and frequent recurrences. Margin control (peripheral margins) is necessary to eliminate the false negative errors. If bread loafing is used, distances from sections should approach 0.1 mm to assure that the method approaches complete margin control.

Mohs surgery has been done with cure rate reported to be as low as 77%,[57] and as high as 95% by another author.[58] The "double scalpel" peripheral margin controlled excision method approximates the Mohs method in margin control, but requires a pathologist intimately familiar with the complexity of managing the vertical margin on the thin peripheral sections and staining methods.[78]

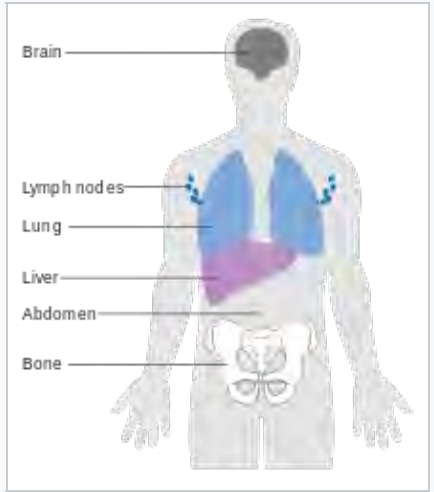
Some melanocytic nevi, and melanoma-in-situ (lentigo maligna) have resolved with an experimental treatment, imiquimod (Aldara) topical cream, an immune enhancing agent. Some dermasurgeons are combining the 2 methods: surgically excising the cancer and then treating the area with Aldara cream postoperatively for three months.

### Radiation therapy [edit]

Radiation therapy is often used after surgical resection for patients with locally or regionally advanced melanoma or for patients with unresectable distant metastases. Kilovoltage x-ray beams are often used for these treatments and have the property of the maximum radiation dose occurring close to the skin surface.[79] It may reduce the rate of local recurrence but does not prolong survival.[80] Radioimmunotherapy of metastatic melanoma is currently under investigation. Radiotherapy has a role in the palliation of metastatic melanoma.[81]

## Prognosis [edit]

Features that affect prognosis are tumor thickness in millimeters (Breslow's depth), depth related to skin structures (Clark level), type of melanoma, presence of ulceration, presence of lymphatic/perineural invasion, presence of tumor-infiltrating lymphocytes (if present, prognosis is better), location of lesion, presence of satellite lesions, and presence of regional or distant metastasis.[82] Certain types of melanoma have worse prognoses but this is explained by their thickness. Interestingly, less invasive melanomas even with lymph node metastases carry a better prognosis than deep melanomas without regional metastasis at time of staging. Local recurrences tend to behave similarly to a primary unless they are at the site of a wide local excision (as opposed to a staged excision or punch/shave excision) since these recurrences tend to indicate lymphatic invasion.



A diagram showing the most common sites for melanoma to spread

When melanomas have spread to the lymph nodes, one of the most important factors is the number of nodes with malignancy. Extent of malignancy within a node is also important; micrometastases in which malignancy is only microscopic have a more favorable prognosis than macrometastases. In some cases micrometastases may only be detected by special staining, and if malignancy is only detectable by a rarely employed test known as the polymerase chain reaction (PCR), the prognosis is better. Macrometastases in which malignancy is clinically apparent (in some cases cancer completely replaces a node) have a far worse prognosis, and if nodes are matted or if there is extracapsular extension, the prognosis is worse still.

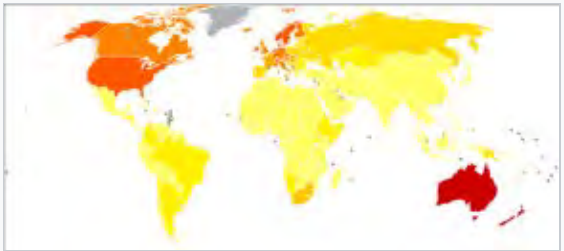
When there is distant metastasis, the cancer is generally considered incurable. The five-year survival rate is less than 10%.[48] The median survival is 6–12 months. Treatment is palliative, focusing on life extension and quality of life. In some cases, patients may live many months or even years with metastatic melanoma (depending on the aggressiveness of the treatment). Metastases to skin and lungs have a better prognosis. Metastases to brain, bone and liver are associated with a worse prognosis. Survival is better with metastasis in which the location of the primary tumor is unknown.[83]

There is not enough definitive evidence to adequately stage, and thus give a prognosis for, ocular melanoma and melanoma of soft parts, or mucosal melanoma (e.g. rectal melanoma), although these tend to metastasize more easily. Even though regression may increase survival, when a melanoma has regressed, it is impossible to know its original size and thus the original tumor is often worse than a pathology report might indicate.

## Epidemiology [edit]

Globally, in 2012, melanoma occurred in 232,000 people and resulted in 55,000 deaths.[2] Australia and New Zealand have the highest rates of melanoma in the world.[2] It has become more common in the last 20 years in areas that are mostly Caucasian.[2]

The rate of melanoma has increased in the recent years, but it is not clear to what extent changes in behavior, in the environment, or in early detection are involved.[85]



Age-standardized new cases per year of melanoma of the skin per 100,000 inhabitants in 2008.[84]

| | |
|---|---|
| no data | 8.76–10.50 |
| less than 1.75 | 10.51–12.25 |
| 1.76–3.50 | 12.26–14.00 |
| 3.51–5.25 | 14.01–15.75 |
| 5.26–7.00 | 15.76–17.50 |
| 7.01–8.75 | 17.76–19.25 |
| | more than 19.25 |

Deaths from melanoma and other skin cancers per million persons in 2012

| | | |
|---|---|---|
| 0-2 | 7-8 | 14-18 |
| 3-5 | 9-9 | 19-37 |
| 6-6 | 10-13 | 38-51 |
| | | 52-114 |

### Australia [edit]

Australia has a very high - and increasing - rate of melanoma. In 2012, deaths from melanoma occurred in 7.3-9.8 per 100,000 population. In Australia, melanoma is the third most common cancer in either sex; indeed, its incidence is higher than for lung cancer, although the latter accounts for more deaths. It is estimated that in 2012, more than 12,000 Australians were diagnosed with melanoma: given Australia's modest population, this is better expressed as 59.6 new cases per 100,000 population per year; >1 in 10 of all new cancer cases were melanomas.[86] Melanoma incidence in Australia is matter of significance, for the following reasons:

- Australian melanoma incidence has increased by more than 30 per cent between 1991 and 2009.
- Australian melanoma age-standardised incidence rates were, as of 2008, at least 12 times higher than the world average.
- Australian melanoma incidence is, by some margin, the highest in the world.
- Overall age-standardised cancer incidence in Australia is the highest in the world, and this is attributable to melanoma alone. Age-standardised overall cancer incidence is similar to New Zealand, but there is a statistically-significant difference between Australia and all other parts of the developed world including North America, Western Europe, and the Mediterranean.

### United States [edit]

In the United States about 9,000 people die from melanoma a year.[87] In 2011 it affected 19.7 per 100,000, and resulted in death in 2.7 per 100,000.[87]

## History [edit]

*See also: Timeline of melanoma*

Although melanoma is not a new disease, evidence for its occurrence in antiquity is rather scarce. However, one example lies in a 1960s examination of nine Peruvian mummies, radiocarbon dated to be approximately 2400 years old, which showed apparent signs of melanoma: melanotic masses in the skin and diffuse metastases to the bones.[88]

John Hunter is reported to be the first to operate on metastatic melanoma in 1787. Although not knowing precisely what it was, he described it as a "cancerous fungous excrescence". The excised tumor was preserved in the Hunterian Museum of the Royal College of Surgeons of England. It was not until 1968 that microscopic examination of the specimen revealed it to be an example of metastatic melanoma.[89]

The French physician René Laennec was the first to describe melanoma as a disease entity. His report was initially presented during a lecture for the Faculté de Médecine de Paris in 1804 and then published as a bulletin in 1806.[90] The first English language report of melanoma was presented by an English general practitioner from Stourbridge, William Norris in 1820.[91] In his later work in 1857 he remarked that there is a familial predisposition for development of melanoma (*Eight Cases of Melanosis with Pathological and Therapeutical Remarks on That Disease*). Norris was also a pioneer in suggesting a link between nevi and melanoma and the possibility of a relationship between melanoma and environmental exposures, by observing that most of his patients had pale complexions.[92] He also described that melanomas could be amelanotic and later showed the metastatic nature of melanoma by observing that they can disseminate to other visceral organs.

The first formal acknowledgment of advanced melanoma as untreatable came from Samuel Cooper in 1840. He stated that the only chance for a cure depends upon the early removal of the disease (i.e., early excision of the malignant mole) ...'[93] More than one and a half centuries later this situation remains largely unchanged.

The world melanoma is from the Greek μέλας *melas* meaning "dark".[94]

## Research [edit]

Pharmacotherapy research for unresectable or metastatic malignant melanoma offers new treatment possibilities.[95] In addition to the advances with recently approved agents, ongoing research into combination therapy, such as dabrafenib and trametinib, may reveal a more effective and better-tolerated option for patients with metastatic melanoma. One important pathway in melanin synthesis involves the transcription factor MITF. The MITF gene is highly conserved and is found in people, mice, birds, and even fish. MITF production is regulated via a fairly straightforward pathway. UV radiation causes increased expression of transcription factor p53 in keratinocytes, and p53 causes these cells to produce melanocyte-stimulating hormone (MSH), which binds to melanocortin 1 receptors (MC1R) on melanocytes. Ligand-binding at MC1R receptors activates adenylate cyclases, which produce cAMP, which activates CREB, which promote MITF expression. The targets of MITF include p16 (a CDK inhibitor) and Bcl2, a gene essential to melanocyte survival. It is often difficult to design drugs that interfere with transcription factors, but perhaps new drugs will be discovered that can impede some reaction in the pathway upstream of MITF.

Studies of chromatin structure also promise to shed light on transcriptional regulation in melanoma cells.[96] It has long been assumed that nucleosomes are positioned randomly on DNA, but murine studies of genes involved in melanin production now suggest that nucleosomes are stereotypically positioned on DNA. When a gene is undergoing transcription, its transcription start site is almost always nucleosome-free. When the gene is silent, however, nucleosomes often block the transcriptional start site, suggesting that nucleosome position may play a role in gene regulation. In addition to genetic mutations, evidence demonstrates that epigenetic events (e.g. loss of DNA hydroxymethylation 5-hydroxymethylcytosine) also play roles in melanoma tumorigenesis.[97]

Finally, given the fact that melanin helps protect skin cells from UV-induced damage, new melanoma prevention strategies could involve attempts to induce melanin synthesis in individuals who would otherwise get sunburns. Redheads, for example, do not tan because they have MC1R mutations. In mice, it has been shown that the melanin production pathway can be rescued downstream of MC1R.[*citation needed*]

### Targeted therapies [edit]

In clinical research setting other therapies, such as adoptive cell therapy or gene therapy, are being tested.[98]

Two kinds of experimental treatments developed at the National Cancer Institute (NCI), have been used in metastatic melanoma with tentative success.[25]

The first treatment involves adoptive cell therapy (ACT) using TILs immune cells (tumor infiltrating lymphocytes) isolated from a person's own melanoma tumor.[72] These cells are grown in large numbers in a laboratory and returned to the patient after a treatment that temporarily reduces normal T cells in the patient's body. TIL therapy following lymphodepletion can result in durable complete response in a variety of setups.[99][100]

The second treatment, adoptive transfer of genetically altered autologous lymphocytes, depends on delivering genes that encode so called T cell receptors (TCRs), into patient's lymphocytes.[72] After that manipulation lymphocytes recognize and bind to certain molecules found on the surface of melanoma cells and kill them.[101]

A vaccine to train the immune system to fight cancer showed modest benefit in late-stage testing in 2009 against melanoma.[102][103]

## BRAF inhibitors [edit]

About 60% of melanomas contain a mutation in the B-Raf gene. Early clinical trials suggested that B-Raf inhibitors including Plexxicon's vemurafenib could lead to substantial tumor regression in a majority of patients if their tumor contain the B-Raf mutation.[104] In June 2011, a large clinical trial confirmed the positive findings from those earlier trials.[105][106]

In August 2011 Vemurafenib received FDA approval for the treatment of late-stage melanoma. In May 2013 the US FDA approved dabrafenib as a single agent treatment for patients with BRAF V600E mutation-positive advanced melanoma.[107]

Some researchers believe that combination therapies that simultaneously block multiple pathways may improve efficacy by making it more difficult for the tumor cells to mutate before being destroyed. In October 2012 a study reported that combining Dabrafenib with a MEK inhibitor trametinib led to even better outcomes. Compared to Dabrafenib alone, progression-free survival was increased to 41% from 9%, and the median progression-free survival increased to 9.4 months versus 5.8 months. Some side effects were, however, increased in the combined study. [108][109]

In January 2014, the FDA approved the combination of dabrafenib and trametinib for the treatment of patients with BRAF V600E/K-mutant metastatic melanoma.[110]

Eventual resistance to BRAF and MEK inhibitors may be due to a cell surface protein known as EphA2 which is now being investigated.[111]

## Ipilimumab [edit]

At the American Society of Clinical Oncology Conference in June 2010, the Bristol-Myers Squibb pharmaceutical company reported the clinical findings of their drug ipilimumab. The study found an increase in median survival from 6.4 to 10 months in patients with advanced melanomas treated with the monoclonal ipilimumab, versus an experimental vaccine. It also found a one-year survival rate of 25% in the control group using the vaccine, 44% in the vaccine and ipilimumab group, and 46% in the group treated with ipilimumab alone.[112] However, some have raised concerns about this study for its use of the unconventional control arm, rather than comparing the drug against a placebo or standard treatment.[113][114] The criticism was that although Ipilimumab performed better than the vaccine, the vaccine has not been tested before and may be causing toxicity, making the drug appear better by comparison.

Ipilimumab was approved by the FDA in March 2011 to treat patients with late-stage melanoma that has spread or cannot be removed by surgery.[115][116][117]

In June 2011, a clinical trial of ipilimumab plus dacarbazine combined this immune system booster with the standard chemotherapy drug that targets cell division. It showed an increase in median survival for these late stage patients to 11 months instead of the 9 months normally seen. Researchers were also hopeful that perhaps 10–20% of patients could live a long time. Some serious side-effects of revving up the immune system were seen in some patients. A course of treatment costs $120,000. The drug's brandname is Yervoy.[105][118]

## Surveillance methods [edit]

Advances in high resolution ultrasound scanning have enabled surveillance of metastatic burden to the sentinel lymph nodes.[119] The Screening and Surveillance of Ultrasound in Melanoma trial (SUNMEL) is evaluating ultrasound as an alternative to invasive surgical methods.[120]

## Oncolytic virotherapy [edit]

In some countries oncolytic virotherapy methods are studied and used to treat melanoma. Oncolytic virotherapy is a promising branch of virotherapy, where oncolytic viruses are used to treat diseases; viruses can increase metabolism, reduce anti-tumor immunity and disorganize vasculature.[121] Talimogene laherparepvec (T-VEC) (which is a herpes simplex virus type 1–derived oncolytic immunotherapy), was shown to be useful against metastatic melanoma in 2015 with an increased survival of 4.4 months.[122]

## References [edit]


1. ^ *a b c d e f* "Melanoma Treatment–for health professionals (PDQ®)". *National Cancer Institute*. June 26, 2015. Retrieved 30 June 2015.
2. ^ *a b c d e f g h i j k l* *World Cancer Report 2014.* (PDF). World Health Organization. 2014. pp. Chapter 5.14. ISBN 9283204298.
3. ^ Kanavy HE, Gerstenblith MR (December 2011). "Ultraviolet radiation and melanoma". *Semin Cutan Med Surg*. **30** (4): 222–8. doi:10.1016/j.sder.2011.08.003. PMID 22123420.
4. ^ *a b c* Azoury, SC; Lange, JR (October 2014). "Epidemiology, risk factors, prevention, and early detection of melanoma.". *The Surgical clinics of North America*. **94** (5): 945–62, vii. doi:10.1016/j.suc.2014.07.013. PMID 25245960.
5. ^ "SEER Stat Fact Sheets: Melanoma of the Skin". *NCI*. Retrieved June 2015. Check date values in: `|access-date=` (help)
6. ^ "MelanomaWarningSigns.com".
7. ^ Fiddler IJ (October 1995). "Melanoma metastasis". *Cancer Control*. **2** (5): 398–404. PMID 10862180.
8. ^ Boniol, M; Autier, P; Boyle, P; Gandini, S (Jul 24, 2012). "Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis.". *BMJ (Clinical research ed.)*. **345**: e4757. doi:10.1136/bmj.e4757. PMC 3404185. PMID 22833605.
9. ^ WHO International Agency for Research on Cancer Monograph Working Group (August 2009). "A Review of Human Carcinogens—Part D:Radiation". *The Lancet Oncology*. **10** (8): 751–2. doi:10.1016/S1470-2045(09)70213-X. PMID 19655431.
10. ^ Sanlorenzo, Martina; Wehner, Mackenzie R.; Linos, Eleni; Kornak, John; Kainz, Wolfgang; Posch, Christian; Vujic, Igor; Johnston, Katia; Gho, Deborah; Monico, Gabriela; McGrath, James T.; Osella-Abate, Simona; Quaglino, Pietro; Cleaver, James E.; Ortiz-Urda, Susana (3 September 2014). "The Risk of Melanoma in Airline Pilots and Cabin Crew". *JAMA Dermatology*. doi:10.1001/jamadermatol.2014.1077.
11. ^ Rünger TM, Farahvash B, Hatvani Z, Rees A (January 2012). "Comparison of DNA damage responses following equimutagenic doses of UVA and UVB: a less effective cell cycle arrest with UVA may render UVA-induced pyrimidine dimers more mutagenic than UVB-induced ones". *Photochem. Photobiol. Sci*. **11** (1): 207–15. doi:10.1039/c1pp05232b. PMID 22005748.
12. ^ Wang S, Setlow R, Berwick M, Polsky D, Marghoob A, Kopf A, Bart R (2001). "Ultraviolet A and melanoma: a review". *J Am Acad Dermatol*. **44** (5): 837–46. doi:10.1067/mjd.2001.114594. PMID 11312434.
13. ^ Oliveria S, Saraiya M, Geller A, Heneghan M, Jorgensen C (2006). "Sun exposure and risk of melanoma". *Arch Dis Child*. **91** (2): 131–8. doi:10.1136/adc.2005.086918. PMC 2082713. PMID 16326797.
14. ^ Lee J, Strickland D (1980). "Malignant melanoma: social status and outdoor work". *Br J Cancer*. **41** (5): 757–63. doi:10.1038/bjc.1980.138. PMC 2010319. PMID 7426301.
15. ^ Pion IA, Rigel DS, Garfinkel L, Silverman MK, Kopf AW (January 1995). "Occupation and the risk of malignant melanoma". *Cancer*. **75** (2 Suppl): 637–44. doi:10.1002/1097-0142(19950115)75:2. PMID 7804988.
16. ^ The World Health Organization recommends that no person under 18 should use a sunbed
17. ^ Khlat M, Vail A, Parkin M, Green A (1992). "Mortality from melanoma in migrants to Australia: variation by age at arrival and duration of stay". *Am J Epidemiol*. **135** (10): 1103–13. PMID 1632422.
18. ^ Greene MH. (1998). "The genetics of hereditary melanoma and nevi". *Cancer*. **86** (11): 2464–77. doi:10.1002/(SICI)1097-0142(19991201)86:11. PMID 10630172.
19. ^ Halachmi S, Gilchrest BA (2001). "Update on genetic events in the pathogenesis of melanoma". *Current Opinion in Oncology*. **13** (2): 129–136. doi:10.1097/00001622-200103000-00008. PMID 11224711.
20. ^ CDKN2A cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4) from Entrez Gene
21. ^ Firoz for Cancer Research, EF; Warycha, M; Zakrzewski, J; Pollens, D; Wang, G; Shapiro, R; Berman, R; Pavlick, A; Manga, P; Ostrer, H.; Celebi, J. T.; Kamino, H.; Darvishian, F.; Rolnitzky, L.; Goldberg, J. D.; Osman, I.; Polsky, D. (2009). "Association of MDM2 SNP309, Age of Onset, and Gender in Cutaneous Melanoma.". *Clinical Cancer Research*. **15** (7): 2573–80. doi:10.1158/1078-0432.CCR-08-2678. PMID 19318491.
22. ^ Bliss J, Ford D, Swerdlow A, Armstrong B, Cristofolini M, Elwood J, Green A, Holly E, Mack T, MacKie R (1995). "Risk of cutaneous melanoma associated with pigmentation characteristics and freckling: systematic overview of 10 case-control studies. The International Melanoma Analysis Group (IMAGE)". *Int J Cancer*. **62** (4): 367–76. doi:10.1002/ijc.2910620402. PMID 7635560.
23. ^ Miller A, Mihm M (2006). "Melanoma". *N Engl J Med*. **355** (1): 51–65. doi:10.1056/NEJMra052166. PMID 16822996.

24. ^ Rhodes A, Weinstock M, Fitzpatrick T, Mihm M, Sober A (1987). "Risk factors for cutaneous melanoma. A practical method of recognizing predisposed individuals". *JAMA*. **258** (21): 3146–54. doi:10.1001/jama.258.21.3146. PMID 3312689.
25. ^ [a] [b] Hershkovitz L, Schachter J, Treves AJ, Besser MJ (2010). "Focus on adoptive T cell transfer trials in melanoma". *Clin. Dev. Immunol*. **2010**: 260267. doi:10.1155/2010/260267. PMC 3018069. PMID 21234353.
26. ^ "ASCO Annual Meeting Proceedings Part I. Abstract: Protective effect of a brisk tumor infiltrating lymphocyte infiltrate in melanoma: An EORTC melanoma group study". *Journal of Clinical Oncology*. **25** (18S): 8519. 2007.
27. ^ Davies, M A; Samuels, Y (2010). "Analysis of the genome to personalize therapy for melanoma". *Oncogene*. **29** (41): 5545–5555. doi:10.1038/onc.2010.323. PMC 3169242. PMID 20697348.
28. ^ Bernstein C, Prasad AR, Nfonsam V, Bernstein H. (2013). DNA Damage, DNA Repair and Cancer, New Research Directions in DNA Repair, Prof. Clark Chen (Ed.), ISBN 978-953-51-1114-6, InTech, http://www.intechopen.com/books/new-research-directions-in-dna-repair/dna-damage-dna-repair-and-cancer
29. ^ Sage E, Girard PM, Francesconi S (January 2012). "Unravelling UVA-induced mutagenesis". *Photochem. Photobiol. Sci*. **11** (1): 74–80. doi:10.1039/c1pp05219e. PMID 21901217.
30. ^ Budden T, Bowden NA (2013). "The Role of Altered Nucleotide Excision Repair and UVB-Induced DNA Damage in Melanomagenesis". *Int J Mol Sci*. **14** (1): 1132–51. doi:10.3390/ijms14011132. PMC 3565312. PMID 23303275.
31. ^ Berger MF, Hodis E, Heffernan TP, Deribe YL, Lawrence MS, Protopopov A, Ivanova E, Watson IR, Nickerson E, Ghosh P, Zhang H, Zeid R, Ren X, Cibulskis K, Sivachenko AY, Wagle N, Sucker A, Sougnez C, Onofrio R, Ambrogio L, Auclair D, Fennell T, Carter SL, Drier Y, Stojanov P, Singer MA, Voet D, Jing R, Saksena G, Barretina J, Ramos AH, Pugh TJ, Stransky N, Parkin M, Winckler W, Mahan S, Ardlie K, Baldwin J, Wargo J, Schadendorf D, Meyerson M, Gabriel SB, Golub TR, Wagner SN, Lander ES, Getz G, Chin L, Garraway LA (May 2012). "Melanoma genome sequencing reveals frequent PREX2 mutations". *Nature*. **485** (7399): 502–6. doi:10.1038/nature11071. PMC 3367798. PMID 22622578.
32. ^ Roach JC, Glusman G, Smit AF, et al. (April 2010). "Analysis of genetic inheritance in a family quartet by whole-genome sequencing". *Science*. **328** (5978): 636–9. doi:10.1126/science.1186802. PMC 3037280. PMID 20220176.
33. ^ Campbell CD, Chong JX, Malig M, et al. (November 2012). "Estimating the human mutation rate using autozygosity in a founder population". *Nat. Genet*. **44** (11): 1277–81. doi:10.1038/ng.2418. PMC 3483378. PMID 23001126.
34. ^ Leslie MC, Bar-Eli M (January 2005). "Regulation of gene expression in melanoma: new approaches for treatment". *J. Cell. Biochem*. **94** (1): 25–38. doi:10.1002/jcb.20296. PMID 15523674.
35. ^ Bhoumik A, Singha N, O'Connell MJ, Ronai ZA (June 2008). "Regulation of TIP60 by ATF2 modulates ATM activation". *J. Biol. Chem*. **283** (25): 17605–14. doi:10.1074/jbc.M802030200. PMC 2427333. PMID 18397884.
36. ^ Bhoumik A, Jones N, Ronai Z (March 2004). "Transcriptional switch by activating transcription factor 2-derived peptide sensitizes melanoma cells to apoptosis and inhibits their tumorigenicity". *Proc. Natl. Acad. Sci. U.S.A*. **101** (12): 4222–7. doi:10.1073/pnas.0400195101. PMC 384722. PMID 15010535.
37. ^ Vlahopoulos SA, Logotheti S, Mikas D, Giarika A, Gorgoulis V, Zoumpourlis V (April 2008). "The role of ATF-2 in oncogenesis". *BioEssays*. **30** (4): 314–27. doi:10.1002/bies.20734. PMID 18348191.
38. ^ Huang Y, Minigh J, Miles S, Niles RM (2008). "Retinoic acid decreases ATF-2 phosphorylation and sensitizes melanoma cells to taxol-mediated growth inhibition". *J Mol Signal*. **3**: 3. doi:10.1186/1750-2187-3-3. PMC 2265711. PMID 18269766.
39. ^ Parmiani, G (11 March 2016). "Melanoma Cancer Stem Cells: Markers and Functions.". *Cancers*. **8** (3). PMID 26978405.
40. ^ [a] [b] Wurm EM, Soyer HP (October 2010). "Scanning for melanoma". *Australian Prescriber* (33): 150–5.
41. ^ "Prevention: ABCD's of Melanoma". American Melanoma Foundation.
42. ^ Friedman R, Rigel D, Kopf A (1985). "Early detection of malignant melanoma: the role of physician examination and self-examination of the skin". *CA Cancer J Clin*. **35** (3): 130–51. doi:10.3322/canjclin.35.3.130. PMID 3921200.
43. ^ [a] [b] Mascaro JM, Mascaro JM (November 1998). "The dermatologist's position concerning nevi: a vision ranging from "the ugly duckling" to "little red riding hood" ". *Arch Dermatol*. **134** (11): 1484–5. doi:10.1001/archderm.134.11.1484. PMID 9828892.
44. ^ [a] [b] "Introduction to Dermoscopy". DermNet New Zealand.
45. ^ James, William D.; Berger, Timothy G.; et al. (2006). *Andrews' Diseases of the Skin: clinical Dermatology*. Saunders Elsevier. pp. 694–9. ISBN 0-7216-2921-0.
46. ^ Rapini, Ronald P.; Bolognia, Jean L.; Jorizzo, Joseph L. (2007). *Dermatology: 2-Volume Set*. St. Louis: Mosby. ISBN 1-4160-2999-0.
47. ^ "Malignant Melanoma: staging". *Collaborative Hypertext of Radiology*. Medical College of Wisconsin. 1 September 2006. Archived from the original on 2010-07-18.
48. ^ [a] [b] Balch C, Buzaid A, Soong S, Atkins M, Cascinelli N, Coit D, Fleming I, Gershenwald J, Houghton A, Kirkwood J, McMasters K, Mihm M, Morton D, Reintgen D, Ross M, Sober A, Thompson J, Thompson J (2001). "Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma". *J Clin Oncol*. **19** (16): 3635–48. PMID 11504745.
49. ^ Autier P (2005). "Cutaneous malignant melanoma: facts about sunbeds and sunscreen". *Expert Rev Anticancer Ther*. **5** (5): 821–33. doi:10.1586/14737140.5.5.821. PMID 16221052.

50. ^ Clough-Gorr KM, Titus-Ernstoff L, Perry AE, Spencer SK, Ernstoff MS (September 2008). "Exposure to sunlamps, tanning beds, and melanoma risk". *Cancer Causes Control*. **19** (7): 659–69. doi:10.1007/s10552-008-9129-6. PMID 18273687.
51. ^ Kanavy HE, Gerstenblith MR (December 2011). "Ultraviolet radiation and melanoma". *Semin Cutan Med Surg*. **30** (4): 222–8. doi:10.1016/j.sder.2011.08.003. PMID 22123420.
52. ^ Can Melanoma Be Prevented? Archived June 27, 2006, at the Wayback Machine.
53. ^ Burnett M.E.; Wang S.Q. (April 2011). "Current sunscreen controversies: a critical review". *Photodermatology, Photoimmunology & Photomedicine*. **27** (2): 58–67. doi:10.1111/j.1600-0781.2011.00557.x. PMID 21392107.
54. ^ "The Sentinel Node Biopsy Procedure in Melanoma does not offer a survival advantage". Malignant Melanoma. 2008-01-08. Retrieved 2012-08-13.
55. ^ Clark GS, Pappas-Politis EC, Cherpelis BS, et al. (July 2008). "Surgical management of melanoma in situ on chronically sun-damaged skin". *Cancer Control*. **15** (3): 216–24. PMID 18596673.
56. ^ Balch C, Urist M, Karakousis C, Smith T, Temple W, Drzewiecki K, Jewell W, Bartolucci A, Mihm M, Barnhill R (1993). "Efficacy of 2-cm surgical margins for intermediate-thickness melanomas (1 to 4 mm). Results of a multi-institutional randomized surgical trial". *Ann Surg*. **218** (3): 262–7; discussion 267–9. doi:10.1097/00000658-199309000-00005. PMC 1242959. PMID 8373269.
57. ^ *a b* Mohs, Frederic Edward; Mikhail, George R. (January 1991). *Mohs micrographic surgery*. W.B. Saunders. pp. 13–14. ISBN 978-0-7216-3415-9.
58. ^ *a b* Bene NI, Healy C, Coldiron BM (May 2008). "Mohs micrographic surgery is accurate 95.1% of the time for melanoma in situ: a prospective study of 167 cases". *Dermatol Surg*. **34** (5): 660–4. doi:10.1111/j.1524-4725.2007.34124.x. PMID 18261099. "Cure rate as high as 98% for small melanoma in situ, and as high as 95% noted for lentigo maligna variant of melanona in situ has been reported with Mohs surgery."
59. ^ "The Screening and Surveillance of Ultrasound in Melanoma trial (SUNMEL)". Archived from the original on 2009-01-06.
60. ^ Crowson, AN; Haskell, H (Oct 2013). "The role of sentinel lymph-node biopsy in the management of cutaneous melanoma.". *Giornale italiano di dermatologia e venereologia : organo ufficiale, Societa italiana di dermatologia e sifilografia*. **148** (5): 493–9. PMID 24005142.
61. ^ Ross, MI; Gershenwald, JE (May–Jun 2013). "Sentinel lymph node biopsy for melanoma: a critical update for dermatologists after two decades of experience.". *Clinics in dermatology*. **31** (3): 298–310. doi:10.1016/j.clindermatol.2012.08.004. PMID 23608449.
62. ^ *a b c d* American Academy of Dermatology (February 2013), "Five Things Physicians and Patients Should Question", *Choosing Wisely: an initiative of the ABIM Foundation*, American Academy of Dermatology, retrieved 5 December 2013, which cites
    - Bichakjian, CK; Halpern, AC; Johnson, TM; Foote Hood, A; Grichnik, JM; Swetter, SM; Tsao, H; Barbosa, VH; Chuang, TY; Duvic, M; Ho, VC; Sober, AJ; Beutner, KR; Bhushan, R; Smith Begolka, W; American Academy of Dermatology (Nov 2011). "Guidelines of care for the management of primary cutaneous melanoma. American Academy of Dermatology.". *Journal of the American Academy of Dermatology*. **65** (5): 1032–47. doi:10.1016/j.jaad.2011.04.031. PMID 21868127.
    - American Joint Committee on Cancer (2010). Stephen B. Edge, ed. *AJCC cancer staging manual* (7th ed.). New York: Springer. ISBN 978-0-387-88440-0.
    - National Comprehensive Cancer Network (2012), *National Comprehensive Cancer Network clinical practice guidelines in oncology (NCCN Guidelines): melanoma* (PDF), Fort Washington, Pennsylvania: National Comprehensive Cancer Network, retrieved 5 December 2013
63. ^ Swanson N, Lee K, Gorman A, Lee H (2002). "Biopsy techniques. Diagnosis of melanoma". *Intensive 2011: The Third International Conference on Resource Intensive Applications and Services*. **20** (4): 677–80. doi:10.1016/S0733-8635(02)00025-6. PMID 12380054.
64. ^ Kirkwood J, Strawderman M, Ernstoff M, Smith T, Borden E, Blum R (1996). "Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684". *J Clin Oncol*. **14** (1): 7–17. PMID 8558223.
65. ^ English (2010). Neil H. Cox; John S.C., eds. *British Association of Dermatologists' management guidelines*. Chichester, West Sussex: Wiley-Blackwell. ISBN 978-1-4443-3552-1. Retrieved 19 August 2013.
66. ^ Wheatley K, Ives N, Eggermont A, et al. (2007). "Adjuvant therapy for melanoma: an individual patient meta-analysis of randomised trials". *J Clin Oncol*. **25**: 8526.
67. ^ Kirkwood J, Ibrahim J, Sondak V, Richards J, Flaherty L, Ernstoff M, Smith T, Rao U, Steele M, Blum R (2000). "High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190". *J Clin Oncol*. **18** (12): 2444–58. PMID 10856105.
68. ^ Kirkwood J, Ibrahim J, Sondak V, Ernstoff M, Ross M (2002). "Interferon alfa-2a for melanoma metastases". *Lancet*. **359** (9310): 978–9. doi:10.1016/S0140-6736(02)08001-7. PMID 11918944.
69. ^ Weight RM, Viator JA, Dale PS, Caldwell CW, Lisle AE (2006). "Photoacoustic detection of metastatic melanoma cells in the human circulatory system". *Opt Lett*. **31** (20): 2998–3000. doi:10.1364/OL.31.002998. PMID 17001379.
70. ^ Bajetta E, Del Vecchio M, Bernard-Marty C, Vitali M, Buzzoni R, Rixe O, Nova P, Aglione S, Taillibert S, Khayat D (2002).

"Metastatic melanoma: chemotherapy". *Semin Oncol.* **29** (5): 427–45. doi:10.1053/sonc.2002.35238. PMID 12407508.
71. ^ Buzaid A (2004). "Management of metastatic cutaneous melanoma". *Oncology (Williston Park).* **18** (11): 1443–50; discussion 1457–9. PMID 15609471.
72. ^ *a b c d* Maverakis E, Cornelius LA, Bowen GM, Phan T, Patel FB, Fitzmaurice S, He Y, Burrall B, Duong C, Kloxin AM, Sultani H, Wilken R, Martinez SR, Patel F (2015). "Metastatic melanoma - a review of current and future treatment options". *Acta Derm Venereol.* **95** (5): 516–524. doi:10.2340/00015555-2035. PMID 25520039.
73. ^ Danson S, Lorigan P (2005). "Improving outcomes in advanced malignant melanoma: update on systemic therapy". *Drugs.* **65** (6): 733–43. doi:10.2165/00003495-200565060-00002. PMID 15819587.
74. ^ Bhatia S, Tykodi SS, Thompson JA (2009). "Treatment of Metastatic Melanoma: An Overview". *Oncology.* **23** (6): 488–96. PMC 2737459. PMID 19544689.
75. ^ Rosenberg, SA; Restifo, NP (3 April 2015). "Adoptive cell transfer as personalized immunotherapy for human cancer.". *Science.* **348** (6230): 62–8. doi:10.1126/science.aaa4967. PMID 25838374.
76. ^ Med Sci Monit. 2014 Jun 10;20:953-9. doi: 10.12659/MSM.890496. Clinical application of adoptive T cell therapy in solid tumors. Zang YW, Gu XD, Xiang JB, Chen ZY
77. ^ Van Lint, S; Wilgenhof, S; Heirman, C; Corthals, J; Breckpot, K; Bonehill, A; Neyns, B; Thielemans, K (September 2014). "Optimized dendritic cell-based immunotherapy for melanoma: the TriMix-formula.". *Cancer immunology, immunotherapy : CII.* **63** (9): 959–67. doi:10.1007/s00262-014-1558-3. PMID 24878889.
78. ^ Johnson TM, Headington JT, Baker SR, Lowe L (November 1997). "Usefulness of the staged excision for lentigo maligna and lentigo maligna melanoma: the "square" procedure". *J. Am. Acad. Dermatol.* **37** (5 Pt 1): 758–64. doi:10.1016/S0190-9622(97)70114-2. PMID 9366823.
79. ^ Hill, R; Healy, B; Holloway, L; Kuncic, Z; Thwaites, D; Baldock, C (21 March 2014). "Advances in kilovoltage x-ray beam dosimetry.". *Physics in medicine and biology.* **59** (6): R183–231. doi:10.1088/0031-9155/59/6/r183. PMID 24584183.
80. ^ Bastiaannet E, Beukema J, Hoekstra H (2005). "Radiation therapy following lymph node dissection in melanoma patients: treatment, outcome and complications". *Cancer Treat Rev.* **31** (1): 18–26. doi:10.1016/j.ctrv.2004.09.005. PMID 15707701.
81. ^ Boyer (1999). *Primary Care Oncology*. Ford.
82. ^ Homsi J, Kashani-Sabet M, Messina J, Daud A (2005). "Cutaneous melanoma: prognostic factors" (PDF). *Cancer Control.* **12** (4): 223–9. PMID 16258493.
83. ^ Bae, JM; Choi, YY; Kim, DS; Lee, JH; Jang, HS; Lee, JH; Kim, H; Oh, BH; Roh, MR; Nam, KA; Chung, KY (January 2015). "Metastatic melanomas of unknown primary show better prognosis than those of known primary: a systematic review and meta-analysis of observational studies.". *Journal of the American Academy of Dermatology.* **72** (1): 59–70. doi:10.1016/j.jaad.2014.09.029. PMID 25440435.
84. ^ "CANCERMondial (GLOBOCAN)". *GLOBOCAN*. 2010. Retrieved 12 August 2010.
85. ^ Berwick M, Wiggins C (2006). "The current epidemiology of cutaneous malignant melanoma". *Front Biosci.* **11**: 1244–54. doi:10.2741/1877. PMID 16368510.
86. ^ "Cancer in Australia: an overview 2012". AIHW.
87. ^ *a b* "Vital Signs: Melanoma Incidence and Mortality Trends and Projections — United States, 1982–2030". *Morbidity and Mortality Weekly Report*. June 2, 2015.
88. ^ Urteaga O, Pack G (1966). "On the antiquity of melanoma". *Cancer.* **19** (5): 607–10. doi:10.1002/1097-0142(196605)19:5<607::AID-CNCR2820190502>3.0.CO;2-8. PMID 5326247.
89. ^ Bodenham D (1968). "A study of 650 observed malignant melanomas in the South-West region". *Annals of the Royal College of Surgeons of England.* **43** (4): 218–39. PMC 2312310. PMID 5698493.
90. ^ Laennec RTH (1806). "Sur les melanoses". *Bulletin de la Faculte de Medecine de Paris.* **1**: 24–26.
91. ^ Norris, W. (1820). "A case of fungoid disease". *Edinb. Med. Surg. J.* **16**: 562–5.
92. ^ Norris W. Eight cases of Melanosis with pathological and therapeutical remarks on that disease. London: Longman; 1857.
93. ^ Cooper, Samuel (1840). *First lines of theory and practice of surgery*. London: Longman, Orme, Brown, Green and Longman.
94. ^ μέλας, Henry George Liddell, Robert Scott, *A Greek-English Lexicon*, on Perseus
95. ^ "Drugs in Clinical Development for Melanoma". *Pharmaceutical Medicine.* **26** (3): 171–183. 23 December 2012. doi:10.1007/BF03262391.
96. ^ Bastonini E; et al. (Sep 2014). "Chromatin barcodes as biomarkers for melanoma". *Pigment Cell Melanoma Res.* **27** (5): 788–800. doi:10.1111/pcmr.12258.
97. ^ Lian, Christine Guo; Xu, Yufei; Ceol, Craig; Wu, Feizhen; Larson, Allison; Dresser, Karen; Xu, Wenqi; Tan, Li; Hu, Yeguang. "Loss of 5-Hydroxymethylcytosine Is an Epigenetic Hallmark of Melanoma". *Cell.* **150** (6): 1135–1146. doi:10.1016/j.cell.2012.07.033. ISSN 0092-8674. PMC 3770275. PMID 22980977.
98. ^ Sotomayor M, Yu H, Antonia S, Sotomayor E, Pardoll D (2002). "Advances in gene therapy for malignant melanoma". *Cancer Control* (PDF). **9** (1): 39–48. PMID 11907465.
99. ^ Dudley ME, Yang JC, Sherry R, et al. (November 2008). "Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens". *J. Clin. Oncol.* **26** (32): 5233–9.

doi:10.1200/JCO.2008.16.5449. PMC 2652090. PMID 18809613.
100. ^ Besser MJ, Shapira-Frommer R, Treves AJ, et al. (May 2010). "Clinical responses in a phase II study using adoptive transfer of short-term cultured tumor infiltration lymphocytes in metastatic melanoma patients". *Clin. Cancer Res.* **16** (9): 2646–55. doi:10.1158/1078-0432.CCR-10-0041. PMID 20406835.
101. ^ "New Method of Gene Therapy Alters Immune Cells for Treatment of Advanced Melanoma; Technique May Also Apply to Other Common Cancers". 30 December 2015.
102. ^ "Immune System Taught To Fight Melanoma". CBSNews. 30 May 2009.
103. ^ Schwartzentruber, D. J.; Lawson, D. H.; Richards, J. M.; Conry, R. M.; Miller, D. M.; Treisman, J.; Gailani, F.; Riley, L.; Conlon, K.; Pockaj, B.; Kendra, K. L.; White, R. L.; Gonzalez, R.; Kuzel, T. M.; Curti, B.; Leming, P. D.; Whitman, E. D.; Balkissoon, J.; Reintgen, D. S.; Kaufman, H.; Marincola, F. M.; Merino, M. J.; Rosenberg, S. A.; Choyke, P.; Vena, D.; Hwu, P. (2011). "Gp100 Peptide Vaccine and Interleukin-2 in Patients with Advanced Melanoma". *New England Journal of Medicine*. **364** (22): 2119–2127. doi:10.1056/NEJMoa1012863.
104. ^ Harmon, Amy (February 21, 2010). "A Roller Coaster Chase for a Cure". *The New York Times*.
105. ^ *a b* Andrew Pollack (June 5, 2011). "Drugs Show Promise Slowing Advanced Melanoma". New York Times.
106. ^ Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M, Hogg D, Lorigan P, Lebbe C, Jouary T, Schadendorf D, Ribas A, O'Day SJ, Sosman JA, Kirkwood JM, Eggermont AM, Dreno B, Nolop K, Li J, Nelson B, Hou J, Lee RJ, Flaherty KT, McArthur GA, BRIM-3 Study Group (30 June 2011). "Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation". *New England Journal of Medicine*. **364** (26): 2507–2516. doi:10.1056/NEJMoa1103782. PMC 3549296. PMID 21639808.
107. ^ "GSK melanoma drugs add to tally of U.S. drug approvals". Reuters. May 30, 2013.
108. ^ "Combination of dabrafenib and trametinib delays development of treatment resistance in MM patients". News Medical. October 1, 2012.
109. ^ Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, Hamid O, Schuchter L, Cebon J, Ibrahim N, Kudchadkar R, Burris HA 3rd, Falchook G, Algazi A, Lewis K, Long GV, Puzanov I, Lebowitz P, Singh A, Little S, Sun P, Allred A, Ouellet D, Kim KB, Patel K, Weber J (1 November 2012). "Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations". *New England Journal of Medicine*. **367** (18): 1694–1703. doi:10.1056/NEJMoa1210093. PMC 3549295. PMID 23020132.
110. ^ "Dabrafenib/Trametinib Combination Approved for Advanced Melanoma". OncLive. January 9, 2014.
111. ^ "Counteracting Drug Resistance in Melanoma". 2015.
112. ^ "Bristol drug cuts death risk in advanced melanoma". *Reuters*. June 5, 2010.
113. ^ "The Risk For Bristol". *Forbes*. Archived from the original on 2011-03-15.
114. ^ "Phase 3 clinical study: Ipilimumab boosts, sustains immune system responses against melanoma tumors". News-medical.net. 2010-06-09. Retrieved 2012-08-13.
115. ^ Jefferson E (2011-03-25). "FDA approves new treatment for a type of late-stage skin cancer" (Press release). U.S. Food and Drug Administration (FDA). Retrieved 2011-03-25.
116. ^ Pollack, Andrew (2011-03-25). "Approval for Drug That Treats Melanoma". *The New York Times*. Retrieved 2011-03-27.
117. ^ Drugs.com: Yervoy
118. ^ Robert C, Thomas L, Bondarenko I, et al. (June 2011). "Ipilimumab plus dacarbazine for previously untreated metastatic melanoma". *N. Engl. J. Med.* **364** (26): 2517–26. doi:10.1056/NEJMoa1104621. PMID 21639810.
119. ^ Voit C, Van Akkooi AC, Schäfer-Hesterberg G, et al. (February 2010). "Ultrasound morphology criteria predict metastatic disease of the sentinel nodes in patients with melanoma". *J. Clin. Oncol.* **28** (5): 847–52. doi:10.1200/JCO.2009.25.7428. PMID 20065175.
120. ^ "malignant-melanoma.org". Archived from the original on 2011-10-14.
121. ^ Forbes, NE; Abdelbary, H; Lupien, M; Bell, JC; Diallo, JS (Sep 20, 2013). "Exploiting tumor epigenetics to improve oncolytic virotherapy.". *Frontiers in Genetics*. **4**: 184. doi:10.3389/fgene.2013.00184. PMID 24062768.
122. ^ "Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma". *Journal of Clinical Oncology*. **33**: 2780–2788. 2015. doi:10.1200/JCO.2014.58.3377.

## External links [edit]

- Melanoma at DMOZ

Look up *melanoma* in Wiktionary, the free dictionary.

Wikimedia Commons has media related to *Melanoma*.

| v • t • e • | Diseases of the skin and appendages by morphology | | | | |
|---|---|---|---|---|---|
| **Growths** | **Epidermal** | wart • callus • seborrheic keratosis • acrochordon • molluscum contagiosum • actinic keratosis • squamous-cell carcinoma • basal-cell carcinoma • Merkel-cell carcinoma • nevus sebaceous • trichoepithelioma • | | | |
| | **Pigmented** | Freckles • lentigo • melasma • nevus • **melanoma** • | | | |
| | **Dermal and subcutaneous** | epidermal inclusion cyst • hemangioma • dermatofibroma (benign fibrous histiocytoma) • keloid • lipoma • neurofibroma • xanthoma • Kaposi's sarcoma • infantile digital fibromatosis • granular cell tumor • leiomyoma • lymphangioma circumscriptum • myxoid cyst • | | | |
| **Rashes** | **With epidermal involvement** | **Eczematous** | contact dermatitis • atopic dermatitis • seborrheic dermatitis • stasis dermatitis • lichen simplex chronicus • Darier's disease • glucagonoma syndrome • langerhans cell histiocytosis • lichen sclerosus • pemphigus foliaceus • Wiskott–Aldrich syndrome • Zinc deficiency • | | |
| | | **Scaling** | psoriasis • tinea (corporis • cruris • pedis • manuum • faciei) • pityriasis rosea • secondary syphilis • mycosis fungoides • systemic lupus erythematosus • pityriasis rubra pilaris • parapsoriasis • ichthyosis • | | |
| | | **Blistering** | herpes simplex • herpes zoster • varicella • bullous impetigo • acute contact dermatitis • pemphigus vulgaris • bullous pemphigoid • dermatitis herpetiformis • porphyria cutanea tarda • epidermolysis bullosa simplex • | | |
| | | **Papular** | scabies • insect bite reactions • lichen planus • miliaria • keratosis pilaris • lichen spinulosus • transient acantholytic dermatosis • lichen nitidus • pityriasis lichenoides et varioliformis acuta • | | |
| | | **Pustular** | acne vulgaris • acne rosacea • folliculitis • impetigo • candidiasis • gonococcemia • dermatophyte • coccidioidomycosis • subcorneal pustular dermatosis • | | |
| | | **Hypopigmented** | tinea versicolor • vitiligo • pityriasis alba • postinflammatory hyperpigmentation • tuberous sclerosis • idiopathic guttate hypomelanosis • leprosy • hypopigmented mycosis fungoides • | | |
| | **Without epidermal involvement** | **Red** | **Blanchable Erythema** | **Generalized** | drug eruptions • viral exanthems • toxic erythema • systemic lupus erythematosus • |
| | | | | **Localized** | cellulitis • abscess • boil • erythema nodosum • carcinoid syndrome • fixed drug eruption • |
| | | | | **Specialized** | urticaria • erythema (multiforme • migrans • gyratum repens • annulare centrifugum • ab igne) • |
| | | | **Nonblanchable** | **Macular** | thrombocytopenic purpura • actinic/solar purpura • |

| | | | | | |
|---|---|---|---|---|---|
| | | | **Purpura** | **Papular** | disseminated intravascular coagulation · vasculitis · |
| | | **Indurated** | scleroderma/morphea · granuloma annulare · lichen sclerosis et atrophicus · necrobiosis lipoidica · | | |
| **Miscellaneous disorders** | **Ulcers** | | | | |
| | **Hair** | telogen effluvium · androgenic alopecia · trichotillomania · alopecia areata · systemic lupus erythematosus · tinea capitis · loose anagen syndrome · lichen planopilaris · folliculitis decalvans · acne keloidalis nuchae · | | | |
| | **Nail** | onychomycosis · psoriasis · paronychia · ingrown nail · | | | |
| | **Mucous membrane** | Aphthous stomatitis · oral candidiasis · lichen planus · leukoplakia · pemphigus vulgaris · mucous membrane pemphigoid · cicatricial pemphigoid · herpesvirus · coxsackievirus · syphilis · systemic histoplasmosis · squamous-cell carcinoma · | | | |

| v · t · e · | **Tumors: Skin neoplasm, nevi and melanomas (C43/D22, 172/216, ICD-O 8720-8799)** |
|---|---|
| **Melanoma** | Mucosal melanoma · Superficial spreading melanoma · Nodular melanoma · *lentigo* (Lentigo maligna/Lentigo maligna melanoma · Acral lentiginous melanoma · · Amelanotic melanoma · Desmoplastic melanoma · Melanoma with features of a Spitz nevus · Melanoma with small nevus-like cells · Polypoid melanoma · Nevoid melanoma · Melanocytic tumors of uncertain malignant potential · |
| **Nevus/ melanocytic nevus** | Nevus of Ito/Nevus of Ota · Compound nevus · Spitz nevus (Pigmented spindle cell nevus · · Halo nevus · Junctional nevus · Pseudomelanoma · |
| | Blue nevus (of Jadassohn–Tièche · Cellular · Epithelioid · Deep penetrating · Amelanotic · Malignant · · |
| | Congenital melanocytic nevus (Giant · Medium-sized · Small-sized) · |
| | Balloon cell nevus · Dysplastic nevus/Dysplastic nevus syndrome · |
| | Acral nevus · Becker's nevus · Benign melanocytic nevus · Nevus spilus · |
| **Authority control** | LCCN: sh85083381 · GND: 4074707-4 · |

Categories: Melanoma

# Mesothelioma

From Wikipedia, the free encyclopedia

**Mesothelioma** is a type of cancer that develops from the thin layer of tissue that covers many of the internal organs (known as the mesothelium).[1] The most common area affected is the lining of the lungs and chest wall.[2][3] Less commonly the lining of the abdomen and rarely the sac surrounding the heart,[4] or the sac surrounding the testis may be affected.[2][5] Signs and symptoms of mesothelioma may include shortness of breath due to fluid around the lung, a swollen abdomen, chest wall pain, cough, feeling tired, and weight loss.[2] These symptoms typically come on slowly.[6]

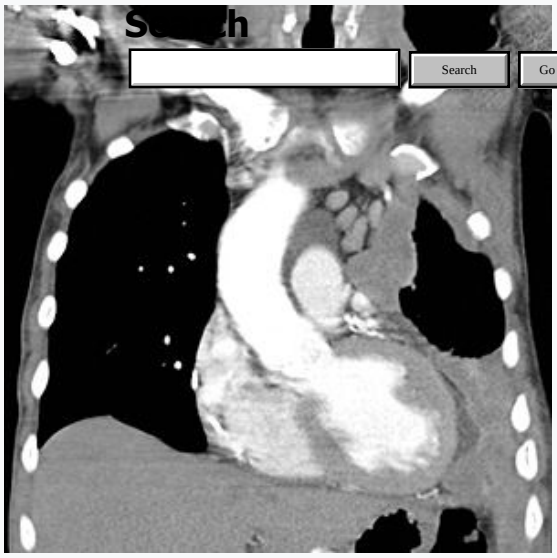
Greater than 80% of mesothelioma cases are caused by exposure to asbestos. The greater the exposure the greater the risk.[3] As of 2013 about 125 million people have been exposed to asbestos at work.[7] High rates of disease occur in people who mine asbestos, produce products from asbestos, work with asbestos products, live with asbestos workers, or work in buildings containing asbestos. Often it is around 40 years between exposure and the cancer starting.[3] Washing the clothing of someone who worked with asbestos also increases the risk.[3] Other risk factors include genetics and infection with the simian virus 40.[3] The diagnosis may be suspected based on chest X-ray and CT scan findings, and is confirmed by either examining fluid produced by the cancer or by a tissue biopsy of the cancer.[6]

Prevention centers around reducing exposure to asbestos.[8] Treatment often includes surgery, radiation therapy, and chemotherapy. A procedure known as pleurodesis, which involves using substances such as talc to scar together the pleura, may be used to prevent more fluid from building up around the lungs.[9] Chemotherapy often includes the medications cisplatin and pemetrexed.[6] The percentage of people that survive five years following diagnosis is on average 8% in the United States.[10]

In 2013 about 50,000 people had mesothelioma and 34,000 died from the disease.[11][12] Rates of mesothelioma vary in different areas of the world. Rates are higher in Australia, the United Kingdom, and lower in Japan.[3] It occurs in about 3,000 people per year in the United States.[13] It occurs more often in males than females. Rates of disease have increased since the 1950s. Diagnosis typically occurs after the age of 65 and most deaths occur around 70 years old. The disease was rare before the commercial use of asbestos.[3]

**Mesothelioma**
More

**Synonyms** malignant mesothelioma



CT scan showing a left sided mesothelioma with an enlarged mediastinal lymph node

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Oncology |
| **ICD-10** | C45 |
| **ICD-9-CM** | 163 |
| **ICD-O** | M9050/3-9055 |
| **OMIM** | 156240 |
| **DiseasesDB** | 8074 |
| **MedlinePlus** | 000115 |
| **eMedicine** | med/1457 |
| **MeSH** | D008654 |

[edit on Wikidata]

Contents

## Signs and symptoms [edit]

### Pleural mesothelioma [edit]

Symptoms or signs of mesothelioma may not appear until 20 to 50 years (or more) after exposure to asbestos. Shortness of breath, cough, and pain in the chest due to an accumulation of fluid in the pleural space (pleural effusion) are often symptoms of pleural mesothelioma.[14]

Mesothelioma that affects the pleura can cause these signs and symptoms:[14]

- Chest wall pain
- Pleural effusion, or fluid surrounding the lung
- Shortness of breath
- Fatigue or anemia
- Wheezing, hoarseness, or a cough
- Blood in the sputum (fluid) coughed up (hemoptysis)

In severe cases, the person may have many tumor masses. The individual may develop a pneumothorax, or collapse of the lung. The disease may metastasize, or spread to other parts of the body.

### Peritoneal mesothelioma [edit]

The most common symptoms of peritoneal mesothelioma are abdominal swelling and pain due to ascites (a buildup of fluid in the abdominal cavity). Other features may include weight loss, fever, night sweats, poor appetite, vomiting, constipation, and umbilical hernia.[15] If the cancer has spread beyond the mesothelium to other parts of the body, symptoms may include pain, trouble swallowing, or swelling of the neck or face.[*citation needed*] These symptoms may be caused by mesothelioma or by other, less serious conditions.

Tumors that affect the abdominal cavity often do not cause symptoms until they are at a late stage. Symptoms include:[*citation needed*]

- Abdominal pain
- Ascites, or an abnormal buildup of fluid in the abdomen
- A mass in the abdomen
- Problems with bowel function
- Weight loss

A mesothelioma does not usually spread to the bone, brain, or adrenal glands. Pleural tumors are usually found only on one side of the lungs.[*citation needed*]

### Pericardial mesothelioma [edit]

Pericardial mesothelioma is not well characterized, but observed cases have included cardiac symptoms, specifically constrictive pericarditis, heart failure, pulmonary embolism, and cardiac tamponade. They have also included nonspecific symptoms, including substernal chest pain, orthopnea (shortness of breath when lying flat), and cough. These symptoms are caused by the tumor encasing or infiltrating the heart.[4]

### End stage mesothelioma [edit]

In severe cases of the disease, the following signs and symptoms may be present:[*citation needed*]

- Blood clots in the veins, which may cause thrombophlebitis
- Disseminated intravascular coagulation, a disorder causing severe bleeding in many body organs
- Jaundice, or yellowing of the eyes and skin
- Low blood sugar level
- Pleural effusion
- Pulmonary emboli, or blood clots in the arteries of the lungs
- Severe ascites

## Cause [edit]

Working with asbestos is the most common risk factor for mesothelioma.[16] In the United States, asbestos is considered the major cause of malignant mesothelioma[17] and has been considered "indisputably"[18] associated with the development of mesothelioma. Indeed, the relationship between asbestos and mesothelioma is so strong that many consider mesothelioma a "signal" or "sentinel" tumor.[19][20][21][22] A history of asbestos exposure exists in most cases. However, mesothelioma has been reported in some individuals without any known exposure to asbestos. In rare cases, mesothelioma has also been associated with irradiation of the chest or abdomen, intrapleural thorium dioxide (thorotrast) as a contrast medium, and inhalation of other fibrous silicates, such as erionite or talc.[5][23] Some studies suggest that simian virus 40 (SV40) may act as a cofactor in the development of mesothelioma.[23] This has been confirmed in animal studies,[24][25] but studies in humans are inconclusive.[24][26][27] Pericardial mesothelioma may not be associated with asbestos exposure.[4]

Asbestos was known in antiquity, but it was not mined and widely used commercially until the late 19th century. Its use greatly increased during World War II. Since the early 1940s, millions of American workers have been exposed to asbestos dust. Initially, the risks associated with asbestos exposure were not publicly known. However, an increased risk of developing mesothelioma was later found among naval personnel (e.g., Navy, Marine Corps, and Coast Guard), shipyard workers, people who work in asbestos mines and mills, producers of asbestos products, workers in the heating and construction industries, and other tradespeople. Today, the official position of the U.S. Occupational Safety and Health Administration (OSHA) and the U.S. EPA is that protections and "permissible exposure limits" required by U.S. regulations, while adequate to prevent most asbestos-related non-malignant disease, are *not* adequate to prevent or protect against asbestos-related cancers such as mesothelioma.[28] Likewise, the British Government's Health and Safety Executive (HSE) states formally that any threshold for exposure to asbestos must be at a very low level and it is widely agreed that if any such threshold does exist at all, then it cannot currently be quantified. For practical purposes, therefore, HSE assumes that no such "safe" threshold exists. Others have noted as well that there is no evidence of a threshold level below which there is no risk of mesothelioma.[29] There appears to be a linear, dose-response relationship, with increasing dose producing increasing disease.[30] Nevertheless, mesothelioma may be related to brief, low level or indirect exposures to asbestos.[18] The dose necessary for effect appears to be lower for asbestos-induced mesothelioma than for pulmonary asbestosis or lung cancer.[18] Again, there

is no known safe level of exposure to asbestos as it relates to increased risk of mesothelioma.

The duration of exposure to asbestos causing mesothelioma can be short. For example, cases of mesothelioma have been documented with only 1–3 months of exposure.[31][32] People who work with asbestos wear personal protective equipment to lower their risk of exposure.[*citation needed*]

Latency, the time from first exposure to manifestation of disease, is prolonged in the case of mesothelioma. It is virtually never less than fifteen years and peaks at 30–40 years.[18] In a review of occupationally related mesothelioma cases, the median latency was 32 years.[33] Based upon the data from Peto *et al.*, the risk of mesothelioma appears to increase to the third or fourth power from first exposure.[30]

## Environmental exposures [edit]

The incidence of mesothelioma has been found to be higher in populations living near naturally occurring asbestos. People can be exposed to naturally occurring asbestos in areas where mining or road construction is occurring, or when the asbestos-containing rock is naturally weathered. Another common route of exposure is through asbestos-containing soil, which is used to whitewash, plaster, and roof houses in Greece.[7] In central Cappadocia, Turkey, mesothelioma was causing 50% of all deaths in three small villages—Tuzköy, Karain, and Sarıhıdır. Initially, this was attributed to erionite. Environmental exposure to asbestos has caused mesothelioma in places other than Turkey, including Corsica, Greece, Cyprus, China, and California.[7][34][35] In Metsovo, this exposure had resulted in mesothelioma incidence around 300 times more than expected in asbestos free populations and was associated with very frequent pleural calcification known as "Metsovo Lung".[36][37]

The documented presence of asbestos fibers in water supplies and food products has fostered concerns about the possible impact of long-term and, as yet, unknown exposure of the general population to these fibers.[*citation needed*]

Exposure to talc is also a risk factor for mesothelioma; exposure can affect those who live near talc mines, work in talc mines, or work in talc mills.[23]

## Occupational [edit]

Exposure to asbestos fibers has been recognized as an occupational health hazard since the early 20th century. Numerous epidemiological studies have associated occupational exposure to asbestos with the development of pleural plaques, diffuse pleural thickening, asbestosis, carcinoma of the lung and larynx, gastrointestinal tumors, and diffuse malignant mesothelioma of the pleura and peritoneum. Asbestos has been widely used in many industrial products, including cement, brake linings, gaskets, roof shingles, flooring products, textiles, and insulation.[38]

Commercial asbestos mining at Wittenoom, Western Australia, took place from 1937 to 1966. The first case of mesothelioma in the town occurred in 1960. The second case was in 1969, and new cases began to appear more frequently thereafter. The lag time between initial exposure to asbestos and the development of mesothelioma varied from 12 years 9 months up to 58 years.[39] A cohort study of miners employed at the mine reported that 85 deaths attributable to mesothelioma had occurred by 1985. By 1994, 539 reported deaths due to mesothelioma had been reported in Western Australia.[*citation needed*]

Occupational exposure to asbestos in the United States mainly occurs when people are maintaining buildings that already have asbestos. Approximately 1.3 million US workers are exposed to asbestos annually; in 2002, an estimated 44,000 miners were potentially exposed to asbestos.[23]

## Paraoccupational secondary exposure [edit]

Family members and others living with asbestos workers have an increased risk of developing mesothelioma, and possibly other asbestos-related diseases.[5][40][41] This risk may be the result of exposure to asbestos dust brought home on the clothing and hair of asbestos workers via washing a worker's clothes or coming into contact with asbestos-contaminated work clothing.[7][23] To reduce the chance of exposing family members to asbestos fibres, asbestos workers are usually required to shower and change their clothing before leaving the workplace.[*citation needed*]

## Asbestos in buildings [edit]

Many building materials used in both public and domestic premises prior to the banning of asbestos may contain asbestos. Those performing renovation works or DIY activities may expose themselves to asbestos dust. In the UK use of Chrysotile asbestos was banned at the end of 1999. Brown and blue asbestos was banned in the UK around 1985. Buildings built or renovated prior to these dates may contain asbestos materials.[*citation needed*]

## Genetic disposition [edit]

In a recent research carried on white American population in 2012, it was found that people with a germline mutation in their BAP1 gene are at higher risk of developing mesothelioma and uveal melanoma.[42]

## Erionite [edit]

Erionite is a zeolite mineral with similar properties to asbestos and is known to cause mesothelioma.[5] Detailed epidemiological investigation has shown that erionite causes mesothelioma mostly in families with a genetic predisposition.[7][34][35] Erionite is found in deposits in the Western United States, where it is used in gravel for road surfacing, and in Turkey, where it is used to construct homes. In Turkey, the United States, and Mexico, erionite has been associated with mesothelioma and has thus been designated a "known human carcinogen" by the US National Toxicology Program.[35]

# Pathophysiology [edit]

The mesothelium consists of a single layer of flattened to cuboidal cells forming the epithelial lining of the serous cavities of the body including the peritoneal, pericardial and pleural cavities. Deposition of asbestos fibers in the parenchyma of the lung may result in the penetration of the visceral pleura from where the fiber can then be carried to the pleural surface, thus leading to the development of malignant mesothelial plaques. The processes leading to the development of peritoneal mesothelioma remain unresolved, although it has been proposed that asbestos fibers from the lung are transported to the abdomen and associated organs via the lymphatic system. Additionally, asbestos fibers may be deposited in the gut after ingestion of sputum contaminated with asbestos fibers.[*citation needed*]

Diffuse pleural mesothelioma with extensive involvement of the pericardium.

Pleural contamination with asbestos or other mineral fibers has been shown to cause cancer. Long thin asbestos fibers (blue asbestos, amphibole fibers) are more potent carcinogens than "feathery fibers" (chrysotile or white asbestos fibers).[18] However, there is now evidence that smaller particles may be more dangerous than the larger fibers. They remain suspended in the air where they can be inhaled, and may penetrate more easily and deeper into the lungs. "We probably will find out a lot more about the health aspects of asbestos from [the World Trade Center attack], unfortunately," said Dr. Alan Fein, chief of pulmonary and critical-care medicine at North Shore-Long Island Jewish Health System.[43]

Mesothelioma development in rats has been demonstrated following intra-pleural inoculation of phosphorylated chrysotile fibers. It has been suggested that in humans, transport of fibers to the pleura is critical to the pathogenesis of mesothelioma. This is supported by the observed recruitment of significant numbers of macrophages and other cells of the immune system to localized lesions of accumulated asbestos fibers in the pleural and peritoneal cavities of rats. These lesions continued to attract and accumulate macrophages as the disease progressed, and cellular changes within the lesion culminated in a morphologically malignant tumor.[*citation needed*]

Experimental evidence suggests that asbestos acts as a complete carcinogen with the development of mesothelioma occurring in sequential stages of initiation and promotion. The molecular mechanisms underlying the malignant transformation of normal mesothelial cells by asbestos fibers remain unclear despite the demonstration of its oncogenic capabilities (see next-but-one paragraph). However, complete in vitro transformation of normal human mesothelial cells to malignant phenotype following exposure to asbestos fibers has not yet been achieved. In general, asbestos fibers are thought to act through direct physical interactions with the cells of the mesothelium in conjunction with indirect effects following interaction with inflammatory cells such as macrophages.[*citation needed*]

Analysis of the interactions between asbestos fibers and DNA has shown that phagocytosed fibers are able to make contact with chromosomes, often adhering to the chromatin fibers or becoming entangled within the chromosome. This contact between the asbestos fiber and the chromosomes or structural proteins of the spindle apparatus can induce complex abnormalities. The most common abnormality is monosomy of chromosome 22. Other frequent abnormalities include structural rearrangement of 1p, 3p, 9p and 6q chromosome arms.[*citation needed*]

Common gene abnormalities in mesothelioma cell lines include deletion of the tumor suppressor genes:[*citation needed*]

- Neurofibromatosis type 2 at 22q12
- $P16^{INK4A}$ [44]
- $P14^{ARF}$

Asbestos has also been shown to mediate the entry of foreign DNA into target cells. Incorporation of this foreign DNA may lead to mutations and oncogenesis by several possible mechanisms:

- Inactivation of tumor suppressor genes
- Activation of oncogenes
- Activation of proto-oncogenes due to incorporation of foreign DNA containing a promoter region
- Activation of DNA repair enzymes, which may be prone to error
- Activation of telomerase
- Prevention of apoptosis

Several genes are commonly mutated in mesothelioma, and may be prognostic factors. These include epidermal growth factor receptor (EGFR) and C-Met, receptor tyrosine kinasesoverexpressed in many mesotheliomas. Some association has been found with EGFR and epithelioid histology but no clear association has been found between EGFR overexpression and overall survival. Expression of AXL receptor tyrosine kinase is a negative prognostic factor. Expression of PDGFRB is a positive prognostic factor.[45] In general, mesothelioma is characterized by loss of function in tumor suppressor genes, rather than by an overexpression or gain of function in oncogenes.[46]

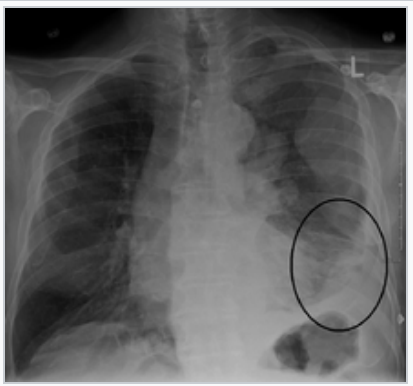
Asbestos fibers have been shown to alter the function and secretory properties of macrophages, ultimately creating conditions which favour the development of mesothelioma. Following asbestos phagocytosis, macrophages generate increased amounts of hydroxyl radicals, which are normal by-products of cellular anaerobic metabolism. However, these free radicals are also known clastogenic and membrane-active agents thought to promote asbestos carcinogenicity. These oxidants can participate in the oncogenic process by directly and indirectly interacting with DNA, modifying membrane-associated cellular events, including oncogene activation and perturbation of cellular antioxidant defences.[*citation needed*]

Asbestos also may possess immunosuppressive properties. For example, chrysotile fibres have been shown to depress the in vitro proliferation of phytohemagglutinin-stimulated peripheral blood lymphocytes, suppress natural killer cell lysis and significantly reduce lymphokine-activated killer cell viability and recovery. Furthermore, genetic alterations in asbestos-activated macrophages may result in the release of potent mesothelial cell mitogens such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) which in turn, may induce the chronic stimulation and proliferation of mesothelial cells after injury by asbestos fibres.[*citation needed*]

As an environmentally triggered malignancy, mesothelioma tumors have been found to be polyclonal in origin by performing a X-inactivation based assay on epitheloid and biphasic tumors obtained from female patients.[47] These results suggest that an environmental factor, e.g. asbestos exposure, may damage and transform a group of cells in the tissue, therefore result in a population of tumor cells that are, albeit slightly, genetically different.[*citation needed*]

## Diagnosis [edit]

Diagnosis of mesothelioma can be suspected with imaging but is confirmed with biopsy. It must be clinically and histologically differentiated from other pleural and pulmonary malignancies, including reactive pleural disease, primary lung carcinoma, pleural metastases of other cancers, and other primary pleural cancers.[5] Primary pericardial mesothelioma is often diagnosed after it has metastasized to lymph nodes or the lungs.[4]



CXR demonstrating a mesothelioma

### Imaging [edit]

Diagnosing mesothelioma is often difficult because the symptoms are similar to those of a number of other conditions. Diagnosis begins with a review of the patient's medical history. A history of exposure to asbestos may increase clinical suspicion for mesothelioma. A physical examination is performed, followed by chest X-ray and often lung function tests. The X-ray may reveal pleural thickening commonly seen after asbestos exposure and increases suspicion of mesothelioma.[14] A CT (or CAT) scan or an MRI is usually performed. If a large amount of fluid is present, abnormal cells may be detected by cytopathology if this fluid is aspirated with a syringe.[4] For pleural fluid, this is done by thoracentesis or tube thoracostomy (chest tube); for ascites, with paracentesis or ascitic drain; and for pericardial effusion with pericardiocentesis. While absence of malignant cells on cytology does not completely exclude mesothelioma, it makes it much more unlikely, especially if an alternative diagnosis can be made (e.g. tuberculosis, heart failure).[*citation needed*] However, with primary pericardial mesothelioma, pericardial

fluid may not contain malignant cells and a tissue biopsy is more useful in diagnosis.[4] Using conventional cytology diagnosis of malignant mesothelioma is difficult, but immunocytochemistry has greatly enhanced the accuracy of cytology.[*citation needed*]

## Biopsy [edit]

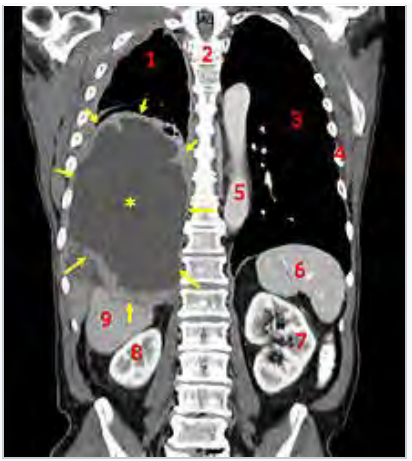
Generally, a biopsy is needed to confirm a diagnosis of malignant mesothelioma. A doctor removes a sample of tissue for examination under a microscope by a pathologist. A biopsy may be done in different ways, depending on where the abnormal area is located. If the cancer is in the chest, the doctor may perform a thoracoscopy. In this procedure, the doctor makes a small cut through the chest wall and puts a thin, lighted tube called a thoracoscope into the chest between two ribs. Thoracoscopy allows the doctor to look inside the chest and obtain tissue samples. Alternatively, the chest surgeon might directly open the chest (thoracotomy). If the cancer is in the abdomen, the doctor may perform a laparoscopy. To obtain tissue for examination, the doctor makes a small incision in the abdomen and inserts a special instrument into the abdominal cavity. If these procedures do not yield enough tissue, more extensive diagnostic surgery may be necessary.[*citation needed*]

## Immunochemistry [edit]

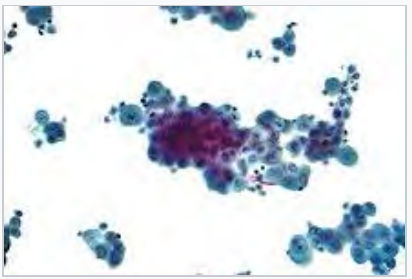
Immunohistochemical studies play an important role for the pathologist in differentiating malignant mesothelioma from neoplastic mimics, such as breast or lung cancer that has metastasized to the pleura. There are numerous tests and panels available, but no single test is perfect for distinguishing mesothelioma from carcinoma or even benign versus malignant. The positive markers indicate that mesothelioma is present; if other markers are positive it may indicate another type of cancer, such as breast or lung adenocarcinoma. Calretinin is a particularly important marker in distinguishing mesothelioma from metastatic breast or lung cancer.[5]

**Typical immunohistochemistry results**

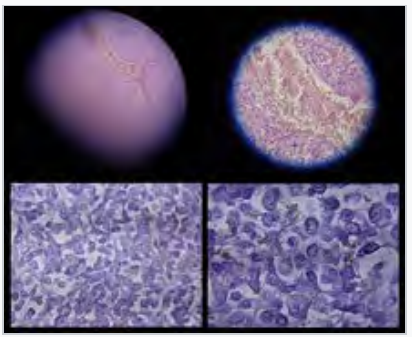
| Positive | Negative |
|---|---|
| EMA (epithelial membrane antigen) in a membranous distribution | CEA (carcinoembryonic antigen)[5] |
| WT1 (Wilms' tumour 1)[5] | B72.3 |
| Calretinin[5] | MOC-3 1 |
| Mesothelin[5] | CD15 |
| Cytokeratin 5[5] | Ber-EP4 |
| HBME-1 (human mesothelial cell 1) | TTF-1 (thyroid transcription factor-1)[5] |
| Podoplanin (PDPN)[5] | Claudin-4[5] |
| Osteopontin[5] | Epithelial cell adhesion molecule (EpCAM)[5] |
| | Estrogen receptor alpha[5] |
| | Mammaglobin[5] |




CT scan of a patient with mesothelioma, coronal section (the section follows the plane that divides the body in a front and a back half). The mesothelioma is indicated by yellow arrows, the central pleural effusion (fluid collection) is marked with a yellow star. Red numbers: (1) right lung, (2) spine, (3) left lung, (4) ribs, (5) descending part of the aorta, (6) spleen, (7) left kidney, (8) right kidney, (9) liver.



Micrograph of a pleural fluid cytopathology specimen showing mesothelioma.



Micrographs showing mesothelioma in a core biopsy.

## Subtypes [edit]

There are three main histological subtypes of malignant mesothelioma: epithelioid, sarcomatous, and biphasic. Epithelioid and biphasic mesothelioma make up approximately 75-95% of mesotheliomas and have been well characterized histologically, whereas sarcomatous mesothelioma has not been studied extensively. Most mesotheliomas express high levels of cytokeratin 5 regardless of subtype.[5]

Epithelioid mesothelioma is characterized by high levels of calretinin.[5]

Sarcomatous mesothelioma does not express high levels of calretinin.[5]

Other morphological subtypes have been described:

- Desmoplastic
- Clear cell
- Deciduoid
- Adenomatoid
- Glandular
- Mucohyaline
- Cartilaginous and osseous metaplasia
- Lymphohistiocytic

## Differential diagnosis [edit]

- Metastatic adenocarcinoma
- Pleural sarcoma
- Synovial sarcoma
- Thymoma
- Metastatic clear cell renal cell carcinoma
- Metastatic osteosarcoma

## Staging [edit]

Staging of mesothelioma is based on the recommendation by the International Mesothelioma Interest Group.[48] TNM classification of the primary tumor, lymph node involvement, and distant metastasis is performed. Mesothelioma is staged Ia–IV (one-A to four) based on the TNM status.[48][49]

# Prevention [edit]

Mesothelioma can be prevented in most cases by preventing exposure to asbestos. The US National Institute for Occupational Safety and Health maintains a recommended exposure limit of 0.1 asbestos fiber per cubic centimeter.[23]

# Screening [edit]

There is no universally agreed protocol for screening people who have been exposed to asbestos. Screening tests might diagnose mesothelioma earlier than conventional methods thus improving the survival prospects for patients. The serum osteopontin level might be useful in screening asbestos-exposed people for mesothelioma. The level of soluble mesothelin-related protein is elevated in the serum of about 75% of patients at diagnosis and it has been suggested that it may be useful for screening.[50] Doctors have begun testing the Mesomark assay which measures levels of soluble mesothelin-related proteins (SMRPs) released by diseased mesothelioma cells.[51]

# Treatment [edit]

Mesothelioma is generally resistant to radiation and chemotherapy treatment. Long-term survival and cures are exceedingly rare.[5] Treatment of malignant mesothelioma at earlier stages has a better prognosis. Clinical behavior of the malignancy is affected by several factors including the continuous mesothelial surface of the pleural cavity which favors local metastasis via exfoliated cells, invasion to underlying tissue and other organs within the pleural cavity, and the extremely long latency period between asbestos exposure and development of the disease. The histological subtype and the patient's age and health status also help predict prognosis. The epithelioid histology responds better

to treatment and has a survival advantage over sarcomatoid histology.[52]

## Surgery [edit]

Surgery, by itself, has proved disappointing. In one large series, the median survival with surgery (including extrapleural pneumonectomy) was only 11.7 months.[53] However, research indicates varied success when used in combination with radiation and chemotherapy (Duke, 2008), or with one of the latter. A pleurectomy/decortication is the most common surgery, in which the lining of the chest is removed. Less common is an extrapleural pneumonectomy (EPP), in which the lung, lining of the inside of the chest, the hemi-diaphragm and the pericardium are removed.[*citation needed*] In localized pericardial mesothelioma, pericardectomy can be curative; when the tumor has metastasized, pericardectomy is a palliative care option. The entire tumor is not often able to be removed.[4]

## Radiation [edit]

For patients with localized disease, and who can tolerate a radical surgery, radiation can be given post-operatively as a consolidative treatment. The entire hemithorax is treated with radiation therapy, often given simultaneously with chemotherapy. Delivering radiation and chemotherapy after a radical surgery have led to extended life expectancy in selected patient populations. It can also induce severe side-effects, including fatal pneumonitis.[54] As part of a curative approach to mesothelioma, radiotherapy is commonly applied to the sites of chest drain insertion, in order to prevent growth of the tumor along the track in the chest wall.[*citation needed*]

Although mesothelioma is generally resistant to curative treatment with radiotherapy alone, palliative treatment regimens are sometimes used to relieve symptoms arising from tumor growth, such as obstruction of a major blood vessel. Radiation therapy, when given alone with curative intent, has never been shown to improve survival from mesothelioma. The necessary radiation dose to treat mesothelioma that has not been surgically removed would be very toxic.[*citation needed*] Radiotherapy is of some use in pericardial mesothelioma.[4]

## Chemotherapy [edit]

Chemotherapy is the only treatment for mesothelioma that has been proven to improve survival in randomised and controlled trials. The landmark study published in 2003 by Vogelzang and colleagues compared cisplatin chemotherapy alone with a combination of cisplatin and pemetrexed (brand name Alimta) chemotherapy in patients who had not received chemotherapy for malignant pleural mesothelioma[55] previously and were not candidates for more aggressive "curative" surgery.[56] This trial was the first to report a survival advantage from chemotherapy in malignant pleural mesothelioma, showing a statistically significant improvement in median survival from 10 months in the patients treated with cisplatin alone to 13.3 months in the group of patients treated with cisplatin in the combination with pemetrexed and who also received supplementation with folate and vitamin $B_{12}$. Vitamin supplementation was given to most patients in the trial and pemetrexed related side effects were significantly less in patients receiving pemetrexed when they also received daily oral folate 500mcg and intramuscular vitamin $B_{12}$ 1000mcg every 9 weeks compared with patients receiving pemetrexed without vitamin supplementation. The objective response rate increased from 20% in the cisplatin group to 46% in the combination pemetrexed group. Some side effects such as nausea and vomiting, stomatitis, and diarrhoea were more common in the combination pemetrexed group but only affected a minority of patients and overall the combination of pemetrexed and cisplatin was well tolerated when patients received vitamin supplementation; both quality of life and lung function tests improved in the combination pemetrexed group. In February 2004, the United States Food and Drug Administration approved pemetrexed for treatment of malignant pleural mesothelioma. However, there are still unanswered questions about the optimal use of chemotherapy, including when to start treatment, and the optimal number of cycles to give.[*citation needed*] Cisplatin and pemetrexed together give patients a median survival of 12.1 months.[5]

Cisplatin in combination with raltitrexed has shown an improvement in survival similar to that reported for pemetrexed in combination with cisplatin, but raltitrexed is no longer commercially available for this indication. For patients unable to tolerate pemetrexed, cisplatin in combination with gemcitabine or vinorelbine is an alternative, or vinorelbine on its own, although a survival benefit has not been shown for these drugs. For patients in whom cisplatin cannot be used, carboplatin can be substituted but non-randomised data have shown lower response rates and high rates of haematological toxicity for carboplatin-based combinations, albeit with similar survival figures to patients receiving cisplatin.[57]

In January 2009, the United States FDA approved using conventional therapies such as surgery in combination with radiation and or chemotherapy on stage I or II Mesothelioma after research conducted by a nationwide study by Duke University concluded an almost 50 point increase in remission rates.[*citation needed*]

In pericardial mesothelioma, chemotherapy - typically adriamycin and/or cisplatin - is primarily used to shrink the

tumor and is not curative.[4]

### Immunotherapy [edit]

Treatment regimens involving immunotherapy have yielded variable results. For example, intrapleural inoculation of Bacillus Calmette-Guérin (BCG) in an attempt to boost the immune response, was found to be of no benefit to the patient (while it may benefit patients with bladder cancer). Mesothelioma cells proved susceptible to in vitro lysis by LAK cells following activation by interleukin-2 (IL-2), but patients undergoing this particular therapy experienced major side effects. Indeed, this trial was suspended in view of the unacceptably high levels of IL-2 toxicity and the severity of side effects such as fever and cachexia. Nonetheless, other trials involving interferon alpha have proved more encouraging with 20% of patients experiencing a greater than 50% reduction in tumor mass combined with minimal side effects.[*citation needed*]

### Heated intraoperative intraperitoneal chemotherapy [edit]

This technique is used in conjunction with surgery,[58] including in patients with malignant pleural mesothelioma.[59] The surgeon removes as much of the tumor as possible followed by the direct administration of a chemotherapy agent, heated to between 40 and 48 °C, in the abdomen. The fluid is perfused for 60 to 120 minutes and then drained. High concentrations of selected drugs are then administered into the abdominal and pelvic surfaces. Heating the chemotherapy treatment increases the penetration of the drugs into tissues. Also, heating itself damages the malignant cells more than the normal cells.[*citation needed*]

### Multimodality therapy [edit]

All of the standard approaches to treating solid tumors—radiation, chemotherapy, and surgery—have been investigated in patients with malignant pleural mesothelioma. Although surgery, by itself, is not very effective, surgery combined with adjuvant chemotherapy and radiation (trimodality therapy) has produced significant survival extension (3–14 years) among patients with favorable prognostic factors.[60] However, other large series of examining multimodality treatment have only demonstrated modest improvement in survival (median survival 14.5 months and only 29.6% surviving 2 years).[53] Reducing the bulk of the tumor with cytoreductive surgery is key to extending survival. Two surgeries have been developed: extrapleural pneumonectomy and pleurectomy/decortication. The indications for performing these operations are unique. The choice of operation namely depends on the size of the patient's tumor. This is an important consideration because tumor volume has been identified as a prognostic factor in mesothelioma.[61] Pleurectomy/decortication spares the underlying lung and is performed in patients with early stage disease when the intention is to remove all gross visible tumor (macroscopic complete resection), not simply palliation.[62] Extrapleural pneumonectomy is a more extensive operation that involves resection of the parietal and visceral pleurae, underlying lung, ipsilateral (same side) diaphragm, and ipsilateral pericardium. This operation is indicated for a subset of patients with more advanced tumors, who can tolerate a pneumonectomy.[63]

## Prognosis [edit]

Mesothelioma often has a poor prognosis. Typical survival despite surgery is between 12 and 21 months depending on the stage of disease at diagnosis with about 7.5% of people surviving for 5 years.[64]

Women, young people, people with low-stage cancers, and people with epithelioid cancers have better prognoses.[5] Negative prognostic factors include sarcomatoid or biphasic histology, high platelet counts (above 400,000), age over 50 years, white blood cell counts above 15.5, low glucose levels in the pleural fluid, low albumin levels, and high fibrinogen levels. Several markers are under investigation as prognostic factors, including nuclear grade, and serum c-reactive protein. Long-term survival is rare.[45]

Pericardial mesothelioma has a 10-month median survival time.[4]

In peritoneal mesothelioma, high expression of WT-1 protein indicates a worse prognosis.[5]

## Epidemiology [edit]

Although reported incidence rates have increased in the past 20 years, mesothelioma is still a relatively rare cancer. The incidence rate varies from one country to another, from a low rate of less than 1 per 1,000,000 in Tunisia and Morocco, to the highest rate in Britain, Australia and Belgium: 30 per 1,000,000 per year.[65] For comparison, populations with high levels of smoking can have a lung cancer incidence of over 1,000 per 1,000,000. Incidence of

malignant mesothelioma currently ranges from about 7 to 40 per 1,000,000 in industrialized Western nations, depending on the amount of asbestos exposure of the populations during the past several decades.[66] Worldwide incidence is estimated at 1-6 per 1,000,000.[5] Incidence of mesothelioma lags behind that of asbestosis due to the longer time it takes to develop; due to the cessation of asbestos use in developed countries, mesothelioma incidence is expected to decrease.[23] Incidence is expected to continue increasing in developing countries due to continuing use of asbestos.[5] Mesothelioma occurs more often in men than in women and risk increases with age, but this disease can appear in either men or women at any age. Approximately one fifth to one third of all mesotheliomas are peritoneal.[*citation needed*] Less than 5% of mesotheliomas are pericardial. The prevalence of pericardial mesothelioma is less than 0.002%; it is more common in men than women. It typically occurs in a person's 50s-70s.[4][67]

Between 1940 and 1979, approximately 27.5 million people were occupationally exposed to asbestos in the United States.[68] Between 1973 and 1984, the incidence of pleural mesothelioma among Caucasian males increased 300%. From 1980 to the late 1990s, the death rate from mesothelioma in the USA increased from 2,000 per year to 3,000, with men four times more likely to acquire it than women.[*citation needed*] More than 80% of mesotheliomas are caused by asbestos exposure.[5]

The incidence of peritoneal mesothelioma is 0.5–3.0 per million per year in men, and 0.2–2.0 per million per year in women.[69]

### UK [edit]

Mesothelioma accounts for less than 1% of all cancers diagnosed in the UK, (around 2,600 people were diagnosed with the disease in 2011), and it is the seventeenth most common cause of cancer death (around 2,400 people died in 2012).[70]

## History [edit]

The connection between asbestos exposure and mesothelioma was discovered in the 1970s. In the United States, asbestos manufacture stopped in 2002. Asbestos exposure thus shifted from workers in asbestos textile mills, friction product manufacturing, cement pipe fabrication, and insulation manufacture and installation to maintenance workers in asbestos-containing buildings.[23]

## Society and culture [edit]

### Notable cases [edit]

Mesothelioma, though rare, has had a number of notable patients:

- Bernie Banton, an Australian workers' rights activist, fought a long battle for compensation from James Hardie after he contracted mesothelioma after working for that company. He claimed James Hardie knew of the dangers of asbestos before he began work with the substance making insulation for power stations. Mesothelioma eventually took his life along with his brothers' and hundreds of James Hardie workers'. James Hardie made an undisclosed settlement with Banton only when his mesothelioma had reached its final stages and he was expected to have no more than 48 hours to live. Australian Prime Minister Kevin Rudd mentioned Banton's extended struggle in his acceptance speech after winning the 2007 Australian federal election.
- Steve McQueen, American actor, was diagnosed with peritoneal mesothelioma on December 22, 1979. He was not offered surgery or chemotherapy because doctors felt the cancer was too advanced. McQueen subsequently sought alternative treatments at clinics in Mexico. He died of a heart attack on November 7, 1980, in Juárez, Mexico, following cancer surgery. He may have been exposed to asbestos while serving with the U.S. Marines as a young adult—asbestos was then commonly used to insulate ships' piping—or from its use as an insulating material in automobile racing suits (McQueen was an avid racing driver and fan).[71]
- Cynthia Stelljes, oboist and founding member of the Canadian classical quartet Quartetto Gelato, died from the disease on December 29, 2006.[*citation needed*]
- Bill Tait, the husband of early anti-asbestos campaigner Nancy Tait, died of the condition in 1968, sparking his wife's subsequent activism.
- Bruce Vento, U.S. Congressman, died of mesothelioma in 2000. The Bruce Vento Hopebuilder award is given yearly by his wife at the MARF Symposium to persons or organizations who have done the most to support mesothelioma research and advocacy.
- Warren Zevon, an American rock singer-songwriter, was diagnosed with inoperable peritoneal mesothelioma in

2002. Zevon refused treatments due to concerns that they would serve to only incapacitate him, and instead opted to record his final album. He died on September 7, 2003, at the age of 56, in his Los Angeles home. His album, The Wind, was nominated for several Grammy awards, winning two.

Although life expectancy with this disease is typically limited, there are notable survivors. In July 1982, Stephen Jay Gould, a well-regarded paleontologist, was diagnosed with peritoneal mesothelioma. After his diagnosis, Gould wrote "The Median Isn't the Message",[72] in which he argued that statistics such as median survival are useful abstractions, not destiny. Gould lived for another 20 years, eventually succumbing to cancer not linked to his mesothelioma.

Paul Kraus, diagnosed in 1997, is considered the longest currently living (as of 2016) mesothelioma survivor in the world.[73]

## Legal issues [edit]

*Main article: Asbestos and the law*

Some people who were exposed to asbestos have collected damages for an asbestos-related disease, including mesothelioma. Compensation via asbestos funds or class action lawsuits is an important issue in law practices regarding mesothelioma.[*citation needed*]

The first lawsuits against asbestos manufacturers were in 1929. Since then, many lawsuits have been filed against asbestos manufacturers and employers, for neglecting to implement safety measures after the links between asbestos, asbestosis, and mesothelioma became known (some reports seem to place this as early as 1898). The liability resulting from the sheer number of lawsuits and people affected has reached billions of dollars.[74] The amounts and method of allocating compensation have been the source of many court cases, reaching up to the United States Supreme Court, and government attempts at resolution of existing and future cases. However, to date, the US Congress has not stepped in and there are no federal laws governing asbestos compensation.[75] In 2013, the "Furthering Asbestos Claim Transparency (FACT) Act of 2013" passed the US House of representatives and was sent to the US Senate, where it was referred to the Senate Judiciary Committee.[76] As the Senate did not vote on it before the end of the 113th Congress, it died in committee. It was revived in the 114th Congress, where it has not yet been brought before the House for a vote.[77]

### History

The first lawsuit against asbestos manufacturers was brought in 1929. The parties settled that lawsuit, and as part of the agreement, the attorneys agreed not to pursue further cases. In 1960, an article published by Wagner et al. was seminal in establishing mesothelioma as a disease arising from exposure to asbestos.[78] The article referred to over 30 case studies of people who had suffered from mesothelioma in South Africa. Some exposures were transient and some were mine workers. Prior to the use of advanced microscopy techniques, malignant mesothelioma was often diagnosed as a variant form of lung cancer.[79] In 1962 McNulty reported the first diagnosed case of malignant mesothelioma in an Australian asbestos worker.[80] The worker had worked in the mill at the asbestos mine in Wittenoom from 1948 to 1950.[*citation needed*]

In the town of Wittenoom, asbestos-containing mine waste was used to cover schoolyards and playgrounds. In 1965 an article in the British Journal of Industrial Medicine established that people who lived in the neighbourhoods of asbestos factories and mines, but did not work in them, had contracted mesothelioma.[*citation needed*]

Despite proof that the dust associated with asbestos mining and milling causes asbestos-related disease, mining began at Wittenoom in 1943 and continued until 1966. In 1974 the first public warnings of the dangers of blue asbestos were published in a cover story called "Is this Killer in Your Home?" in Australia's *Bulletin* magazine. In 1978 the Western Australian Government decided to phase out the town of Wittenoom, following the publication of a Health Dept. booklet, "The Health Hazard at Wittenoom", containing the results of air sampling and an appraisal of worldwide medical information.[*citation needed*]

By 1979 the first writs for negligence related to Wittenoom were issued against CSR and its subsidiary ABA, and the Asbestos Diseases Society was formed to represent the Wittenoom victims.[*citation needed*]

In Leeds, England the Armley asbestos disaster involved several court cases against Turner & Newall where local residents who contracted mesothelioma claimed compensation because of the asbestos pollution from the company's factory. One notable case was that of June Hancock, who contracted the disease in 1993 and died in 1997.[81]

# Research [edit]

*See also: Mesothelioma Applied Research Foundation*

The WT-1 protein is overexpressed in mesothelioma and is being researched as a potential target for drugs.[5]

## References [edit]


*This article includes information from a public domain U.S. National Cancer Institute fact sheet.*

1. ^ "Malignant Mesothelioma—Patient Version". *NCI*. Retrieved 3 April 2016.
2. ^ a b c "Malignant Mesothelioma Treatment–Patient Version (PDQ®)". *NCI*. September 4, 2015. Retrieved 3 April 2016.
3. ^ a b c d e f Robinson, BM (November 2012). "Malignant pleural mesothelioma: an epidemiological perspective.". *Annals of cardiothoracic surgery*. **1** (4): 491–6. doi:10.3978/j.issn.2225-319X.2012.11.04. PMC 3741803. PMID 23977542.
4. ^ a b c d e f g h i j k Sardar, MR; Kuntz, C; Patel, T; Saeed, W; Gnall, E; Imaizumi, S; Lande, L (2012). "Primary pericardial mesothelioma unique case and literature review.". *Texas Heart Institute journal / from the Texas Heart Institute of St. Luke's Episcopal Hospital, Texas Children's Hospital*. **39** (2): 261–4. PMC 3384041. PMID 22740748.
5. ^ a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac Panou, V; Vyberg, M; Weinreich, UM; Meristoudis, C; Falkmer, UG; Røe, OD (June 2015). "The established and future biomarkers of malignant pleural mesothelioma.". *Cancer treatment reviews*. **41** (6): 486–95. doi:10.1016/j.ctrv.2015.05.001. PMID 25979846.
6. ^ a b c Kondola, S; Manners, D; Nowak, AK (12 February 2016). "Malignant pleural mesothelioma: an update on diagnosis and treatment options.". *Therapeutic advances in respiratory disease*. **10**: 275–88. doi:10.1177/1753465816628800. PMID 26873306.
7. ^ a b c d e f Gulati, M; Redlich, CA (March 2015). "Asbestosis and environmental causes of usual interstitial pneumonia.". *Current Opinion in Pulmonary Medicine*. **21** (2): 193–200. doi:10.1097/MCP.0000000000000144. PMC 4472384. PMID 25621562.
8. ^ Whittemore, Alice S. (2006). *Cancer epidemiology and prevention* (3rd ed.). Oxford: Oxford University Press. p. 669. ISBN 9780199747979.
9. ^ "Malignant Mesothelioma Treatment–Patient Version (PDQ®)". *NCI*. September 4, 2015. Retrieved 3 April 2016.
10. ^ "Age-Adjusted SEER Incidence and U.S. Death Rates and 5-Year Relative Survival (Percent) By Primary Cancer Site, Sex and Time Period" (pdf). *NCI*. Retrieved 3 April 2016.
11. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/S0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
12. ^ GBD 2013 Mortality and Causes of Death, Collaborators (10 January 2015). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
13. ^ "What are the key statistics about malignant mesothelioma?". *American Cancer Society*. 2016-02-17. Retrieved 3 April 2016.
14. ^ a b c Barreiro, TJ; Katzman, PJ (2006). "Malignant mesothelioma: a case presentation and review". *The Journal of the American Osteopathic Association*. **106** (12): 699–704. PMID 17242414.
15. ^ Raza, A; Huang, WC; Takabe, K (2014). "Advances in the management of peritoneal mesothelioma". *World Journal of Gastroenterology*. **20** (33): 11700–11712. doi:10.3748/wjg.v20.i33.11700. PMC 4155360. PMID 25206274.
16. ^ EBSCO database verified by URAC; accessed from Mount Sinai Hospital, New York
17. ^ Kanarek, Marty S., Phd., MPH, Annals of Epidemiology Volume 21, Issue 9 , Pages 688-697, September 2011
18. ^ a b c d e Roggli VL, Sharma A, Butnor KJ, Sporn T, Vollmer RT (2002). "Malignant mesothelioma and occupational exposure to asbestos: a clinicopathological correlation of 1445 cases". *Ultrastruct Pathol*. **26** (2): 55–65. doi:10.1080/01913120252959227. PMID 12036093.
19. ^ Sporn TA, Roggli VL (2004). "Mesothelioma". In Roggli VL, Oury TD, Sporn TA. *Pathology of Asbestos-associated Diseases* (2nd ed.). Springer. p. 104.
20. ^ Gennaro V, Finkelstein MM, Ceppi M, et al. (March 2000). "Mesothelioma and lung tumors attributable to asbestos among petroleum workers". *Am. J. Ind. Med.* **37** (3): 275–82. doi:10.1002/(SICI)1097-0274(200003)37:3<275::AID-AJIM5>3.0.CO;2-I. PMID 10642417.
21. ^ Selikoff IJ (1986). "Occupational Respiratory Diseases". *Public Health and Preventative Medicine* (12th ed.). Appleton-Century-Crofts. p. 532.
22. ^ Henderson DW, et al. (2004). "After Helsinki: A multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997–2004". *Pathology*. **36** (6): 517–550. doi:10.1080/00313020400010955. PMID 15841689.
23. ^ a b c d e f g h "CDC - NIOSH Publications and Products - Current Intelligence Bulletin 62: Asbestos Fibers and Other Elongate Meneral Particles: State of the Science and Roadmap for Research". *www.cdc.gov*. Retrieved 2015-08-25.
24. ^ a b Broaddus VC, Robinson BW (2010). "Chapter 75". *Murray & Nadel's Textbook of Respiratory Medicine* (5th ed.). Saunders Elsevier. ISBN 978-1-4160-4710-0.
25. ^ Holland-Frei (2010). "Chapter 79". *Cancer Medicine* (8th ed.). People's Medical Publishing House USA. ISBN 978-1607950141.

26. ^ *Fishman's Pulmonary Diseases and Disorders* (4th ed.). McGraw-Hill. 2008. p. 1537. ISBN 0-07-145739-9.
27. ^ Maitra, A; Kumar V (2007). *Robbins Basic Pathology* (8th ed.). Saunders Elsevier. p. 536. ISBN 978-1-4160-2973-1.
28. ^ NIOSH Working Group Paper from the Centers for Disease Control, 1980
29. ^ Hillerdal G (August 1999). "Mesothelioma: cases associated with non-occupational and low dose exposures". *Occup Environ Med*. **56** (8): 505–13. doi:10.1136/oem.56.8.505. PMC 1757769. PMID 10492646.
30. ^ [a] [b] Peto J, Seidman H, Selikoff IJ (January 1982). "Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment". *Br. J. Cancer*. **45** (1): 124–35. doi:10.1038/bjc.1982.15. PMC 2010947. PMID 7059455.
31. ^ Burdorf A, Dahhan M, Swuste P (2003). "Occupational characteristics of cases with asbestos-related diseases in The Netherlands". *Ann Occup Hyg*. **47** (6): 485–92. doi:10.1093/annhyg/meg062. PMID 12890657.
32. ^ "Hygiene standards for airborne amosite asbestos dust. British Occupational Hygiene Society Committee on Hygiene Standards". *Ann Occup Hyg*. **16** (1): 1–5. 1973. doi:10.1093/annhyg/16.1.1. PMID 4775386.
33. ^ Lanphear BP, Buncher CR (July 1992). "Latent period for malignant mesothelioma of occupational origin". *J Occup Med*. **34** (7): 718–21. PMID 1494965.
34. ^ [a] [b] Constantopoulos SH. Environmental mesothelioma associated with tremolite asbestos: Lessons from the experiences of Turkey, Greece, Corsica, New Caledonia and Cyprus. Regulatory Toxicology and Pharmacology, 2008; 52: S110-S115
35. ^ [a] [b] [c] Weissman, David; Kiefer, Max (22 November 2011). "Erionite: An Emerging North American Hazard". National Institute for Occupational Safety and Health.
36. ^ Dogan, Umran (2003). "Mesothelioma in Cappadocian villages". *Indoor and Built Environment*. Ankara: Sage. **12** (6): 367–375. doi:10.1177/1420326X03039065. ISSN 1420-326X.
37. ^ Carbone, Michelle; Emri, Salih; Steele, Ian; Tuncer, Murat; Pass, Harvey I.; Baris, Y. Izzettin; et al. (2007). "A mesothelioma epidemic in Cappadocia: scientific developments and unexpected social outcomes". *Nature Reviews Cancer*. **7** (2): 147–54. doi:10.1038/nrc2068. PMID 17251920. Missing |last3= in Authors list (help)
38. ^ "Learn About Asbestos". US Environmental Protection Agency. Retrieved 2016-07-08.
39. ^ Berry, G; Reid, A; Aboagye-Sarfo, P (2012). "Malignant mesotheliomas in former miners and millers of crocidolite at Wittenoom (Western Australia) after more than 50 years follow-up". *British Journal of Cancer*. **106** (5): 1016–1020. doi:10.1038/bjc.2012.23. PMC 3305966. PMID 22315054.
40. ^ Protecting Workers' Families: A Research Agenda of the Workers' Family Protection Task Force. National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2002-113.
41. ^ Peipins LA, Lewin M, Campolucci S, et al. (November 2003). "Radiographic abnormalities and exposure to asbestos-contaminated vermiculite in the community of Libby, Montana, USA". *Environ. Health Perspect*. **111** (14): 1753–9. doi:10.1289/ehp.6346. PMC 1241719. PMID 14594627.
42. ^ Germline BAP1 mutations predispose to malignant mesothelioma Testa et al. 43(10):1022-5 - Nature Genetics
43. ^ "The Junkman's Answer to Terrorism: Use More Asbestos" (PDF). Center for Media and Democracy: Prwatch.org. 2001. Retrieved 2010-08-20.
44. ^ Chiosea, S; Krasinskas, A; Cagle, PT; Mitchell, KA; Zander, DS; Dacic, S (June 2008). "Diagnostic importance of 9p21 homozygous deletion in malignant mesotheliomas.". *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc*. **21** (6): 742–7. doi:10.1038/modpathol.2008.45. PMID 18327208.
45. ^ [a] [b] Davidson, Ben (2015-06-01). "Prognostic factors in malignant pleural mesothelioma". *Human Pathology*. **46** (6): 789–804. doi:10.1016/j.humpath.2015.02.006. ISSN 1532-8392. PMID 25824607.
46. ^ Reid, Glen (2015-06-01). "MicroRNAs in mesothelioma: from tumour suppressors and biomarkers to therapeutic targets". *Journal of Thoracic Disease*. **7** (6): 1031–1040. doi:10.3978/j.issn.2072-1439.2015.04.56. ISSN 2072-1439. PMC 4466421. PMID 26150916.
47. ^ Evaluation of clonal origin of malignant mesothelioma Comertpay et al.- Journal of Translational Medicine 2014, 12:301
48. ^ [a] [b] Ceresoli GL, Gridelli C, Santoro A, Santoro A (July 2007). "Multidisciplinary treatment of malignant pleural mesothelioma". *Oncologist*. **12** (7): 850–863. doi:10.1634/theoncologist.12-7-850. PMID 17673616.
49. ^ Rusch, VW (October 1995). "A proposed new international TNM staging system for malignant pleural mesothelioma" (PDF). *Chest*. **108** (4): 1122–8. doi:10.1378/chest.108.4.1122. PMID 7555126.
50. ^ Robinson BW, Creaney J, Lake R, et al. (July 2005). "Soluble mesothelin-related protein—a blood test for mesothelioma". *Lung Cancer*. **49** (Suppl 1): S109–11. doi:10.1016/j.lungcan.2005.03.020. PMID 15950789.
51. ^ Beyer HL, Geschwindt RD, et al. (April 2007). "MESOMARK: a potential test for malignant pleural mesothelioma". *Clinical Chemistry*. **53** (4): 666–672. doi:10.1373/clinchem.2006.079327. PMID 17289801.
52. ^ Haber SE, Haber JM (2011). "Malignant mesothelioma: a clinical study of 238 cases". *Ind Health*. **49** (2): 166–72. doi:10.2486/indhealth.MS1147. PMID 21173534.
53. ^ [a] [b] Borasio P, Berruti A, Billé A, et al. (February 2008). "Malignant pleural mesothelioma: clinicopathologic and survival characteristics in a consecutive series of 394 patients". *Eur J Cardiothorac Surg*. **33** (2): 307–13. doi:10.1016/j.ejcts.2007.09.044. PMID 18164622.
54. ^ Fatal pneumonitis associated with intensity-modulated radiation therapy for mesothelioma, Allen AM and alt, in Int J Radiat Oncol Biol Phys, 2006 Jul 1;65(3):640-5.
55. ^ "Pleural Mesothelioma". Retrieved 20 October 2014.
56. ^ Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. (July 2003). "Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma". *J. Clin. Oncol*. **21** (14): 2636–44. doi:10.1200/JCO.2003.11.136. PMID 12860938.

57. ^ Santoro A, O'Brien ME, Stahel RA, et al. (July 2008). "Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaïve patients with malignant pleural mesothelioma: results of the International Expanded Access Program". *J Thorac Oncol*. **3** (7): 756–63. doi:10.1097/JTO.0b013e31817c73d6. PMID 18594322.
58. ^ Sugarbaker PH, Welch LS, Mohamed F, Glehen O (July 2003). "A review of peritoneal mesothelioma at the Washington Cancer Institute". *Surg Oncol Clin N Am*. **12** (3): 605–21, xi. doi:10.1016/S1055-3207(03)00045-0. PMID 14567020.
Online manual: Management of Peritoneal Surface Malignancy.
59. ^ Richards WG, Zellos L, Bueno R, et al. (April 2006). "Phase I to II study of pleurectomy/decortication and intraoperative intracavitary hyperthermic cisplatin lavage for mesothelioma". *J. Clin. Oncol*. **24** (10): 1561–7. doi:10.1200/JCO.2005.04.6813. PMID 16575008.
60. ^ Sugarbaker DJ, Flores RM, Jaklitsch MT, et al. (January 1999). "Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients". *J Thorac Cardiovasc Surg*. **117** (1): 54–63; discussion 63–5. doi:10.1016/S0022-5223(99)70469-1. PMID 9869758.
61. ^ Pass HI, Temeck BK, Kranda K, et al. (1998). "Preoperative tumor volume is associated with outcome in malignant pleural mesothelioma". *J Thorac Cardiovasc Surg*. **115** (2): 310–7; discussion 317–8. doi:10.1016/S0022-5223(98)70274-0. PMID 9475525.
62. ^ Sugarbaker, DJ (2006). "Macroscopic complete resection: the goal of primary surgery in multimodality therapy for pleural mesothelioma". *J Thorac Oncol*. **1** (2): 175–176. doi:10.1097/01243894-200602000-00014. PMID 17409850.
63. ^ Sugarbaker DJ, Jaklitsch MT, Bueno R, et al. (2004). "Prevention, early detection, and management of complications after 328 consecutive extrapleural pneumonectomies". *J Thorac Cardiovasc Surg*. **128** (1): 138–146. doi:10.1016/j.jtcvs.2004.02.021. PMID 15224033.
64. ^ "Survival statistics for mesothelioma". *www.cancer.org*. 17 February 2016. Retrieved 28 November 2016.
65. ^ Bianchi, C; Bianchi T (June 2007). "Malignant mesothelioma: global incidence and relationship with asbestos". *Industrial Health*. **45** (3): 379–387. doi:10.2486/indhealth.45.379. PMID 17634686.
66. ^ Robinson BW, Lake RA (October 2005). "Advances in malignant mesothelioma". *The New England Journal of Medicine*. **353** (15): 1591–603. doi:10.1056/NEJMra050152. PMID 16221782.
67. ^ Restrepo, Carlos S.; Vargas, Daniel; Ocazionez, Daniel; Martínez-Jiménez, Santiago; Betancourt Cuellar, Sonia L.; Gutierrez, Fernando R. (2013-10-01). "Primary pericardial tumors". *Radiographics: A Review Publication of the Radiological Society of North America, Inc*. **33** (6): 1613–1630. doi:10.1148/rg.336135512. ISSN 1527-1323. PMID 24108554.
68. ^ "DB-397.0.REPORT.JN.ppt" (PDF). Retrieved 2010-08-20.
69. ^ Boffetta, P (June 2007). "Epidemiology of peritoneal mesothelioma: a review". *Annals of Oncology*. **18** (6): 985–990. doi:10.1093/annonc/mdl345. PMID 17030547.
70. ^ "Mesothelioma statistics". *Cancer Research UK*. Retrieved 28 October 2014.
71. ^ Lerner, Barron H. (2005-11-15). "McQueen's Legacy of Laetrile". New York Times. Retrieved May 12, 2010.
72. ^ Gould, Stephen Jay. "The Median Isn't the Message" (PDF). Retrieved May 23, 2013.
73. ^ Branley, Alison (7 May 2013). "Survivor sees his illness as a 'gift'". *Herald News*. Retrieved 7 May 2013.
74. ^ ORTIZ V. FIBREBOARD CORP. (97-1704) 527 U.S. 815 (1999) had individual liability from a single corporation and its insurance carriers of nearly $2 billion.
75. ^ ORTIZ V. FIBREBOARD CORP. (97-1704) 527 U.S. 815 (1999)
76. ^ "H.R.982 - 113th Congress (2013-2014): Furthering Asbestos Claim Transparency (FACT) Act of 2013 - Congress.gov - Library of Congress". Library of Congress. Retrieved 20 October 2014.
77. ^ "H.R.526 - 114th Congress (2015-2016): Furthering Asbestos Claim Transparency (FACT) Act of 2015 - Congress.gov - Library of Congress". Library of Congress. Retrieved 1 Dec 2015.
78. ^ Wagner JC, Sleggs CA, Marchand P (October 1960). "Diffuse Pleural Mesothelioma and Asbestos Exposure in the North Western Cape Province". *Br J Ind Med*. **17** (4): 260–71. doi:10.1136/oem.17.4.260. PMC 1038078. PMID 13782506.
79. ^ Alastair J Moore, Robert J Parker, John Wiggins (2008). "Malignant mesothelioma". *Orphanet Journal of Rare Diseases*. **3** (34): 1750–1172. doi:10.1186/1750-1172-3-34. PMC 2652430. PMID 19099560.
80. ^ McNulty JC (December 1962). "Malignant pleural mesothelioma in an asbestos worker". *Med J Aust*. **49** (2): 953–4. PMID 13932248.
81. ^ "June Hancock Research Fund". Retrieved 2010-03-01.


## External links [edit]

Mesothelioma at DMOZ

Wikinews has news related to: *Asbestos*

Wikibooks has a book on the topic of: *Radiation Oncology/Lung/Mesothelioma*

v · t · e **Connective/soft tissue tumors and sarcomas (ICD-O 8800–9059) (C45–C49/D17–D21, 171/214–215)**

| | | | |
|---|---|---|---|
| **Not otherwise specified** | Soft-tissue sarcoma · Desmoplastic small-round-cell tumor · | | |
| **Connective tissue neoplasm** | **Fibromatous** | **Fibroma/fibrosarcoma:** | Dermatofibrosarcoma protuberans · Desmoplastic fibroma · |
| | | **Fibroma/fibromatosis:** | Aggressive infantile fibromatosis · Aponeurotic fibroma · Collagenous fibroma · Diffuse infantile fibromatosis · Familial myxovascular fibromas · Fibroma of tendon sheath · Fibromatosis colli · Infantile digital fibromatosis · Juvenile hyaline fibromatosis · Plantar fibromatosis · Pleomorphic fibroma · Oral submucous fibrosis · |
| | | **Histiocytoma/histiocytic sarcoma:** | Benign fibrous histiocytoma · Malignant fibrous histiocytoma · Atypical fibroxanthoma · Solitary fibrous tumor · |
| | **Myxomatous** | Myxoma/myxosarcoma (Cutaneous myxoma · Superficial acral fibromyxoma · · Angiomyxoma · Ossifying fibromyxoid tumour · | |
| | **Fibroepithelial** | Brenner tumour · Fibroadenoma · Phyllodes tumor · | |
| | **Synovial-like** | Synovial sarcoma · Clear-cell sarcoma · | |
| **Lipomatous** | Lipoma/liposarcoma (Myelolipoma · Myxoid liposarcoma · · PEComa (Angiomyolipoma · · Chondroid lipoma · Intradermal spindle cell lipoma · Pleomorphic lipoma · Lipoblastomatosis · Spindle cell lipoma · Hibernoma · | | |
| **Myomatous** | *general:* | Myoma/myosarcoma · | |
| | *smooth muscle:* | Leiomyoma/leiomyosarcoma · | |
| | *skeletal muscle:* | Rhabdomyoma/rhabdomyosarcoma: Embryonal rhabdomyosarcoma (Sarcoma botryoides · · Alveolar rhabdomyosarcoma · | |
| | Leiomyoma · Angioleiomyoma · Angiolipoleiomyoma · Genital leiomyoma · Leiomyosarcoma · Multiple cutaneous and uterine leiomyomatosis syndrome · Multiple cutaneous leiomyoma · Neural fibrolipoma · Solitary cutaneous leiomyoma · STUMP · | | |
| **Complex mixed and stromal** | Adenomyoma · Pleomorphic adenoma · Mixed Müllerian tumor · Mesoblastic nephroma · Wilms' tumor · Malignant rhabdoid tumour · Clear-cell sarcoma of the kidney · Hepatoblastoma · Pancreatoblastoma · Carcinosarcoma · | | |
| **Mesothelial** | **Mesothelioma** · Adenomatoid tumor · | | |

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|---|---|---|---|
| v · t · e · | **Tumours and neoplasia in the respiratory tract (C30–C34/D14, 160–163/212.0–212.4)** | | |
| **Upper RT** | *Nasal cavity*: Esthesioneuroblastoma · *Nasopharynx*: Nasopharyngeal carcinoma · Nasopharyngeal angiofibroma · *Larynx*: Laryngeal cancer · Laryngeal papillomatosis · | | |
| | **Trachea** | Tracheal tumor · | |
| | | **Non-small-cell lung carcinoma** | Squamous-cell carcinoma · Adenocarcinoma (Mucinous cystadenocarcinoma) · Large-cell lung carcinoma · Rhabdoid carcinoma · Sarcomatoid carcinoma · Carcinoid · |

| | | | |
|---|---|---|---|
| **Lower RT** | **Lung** | | Salivary gland–like carcinoma · Adenosquamous carcinoma · Papillary adenocarcinoma · Giant-cell carcinoma · |
| | | **Small-cell carcinoma** | Combined small-cell carcinoma · |
| | | **Non-carcinoma** | Sarcoma · Lymphoma · Immature teratoma · Melanoma · |
| | | **By location** | Pancoast tumor · Solitary pulmonary nodule · Central lung · Peripheral lung · |
| **Pleura** | **Mesothelioma** · Malignant solitary fibrous tumor · | | |

| v · t · e · | **Occupational safety and health** |
|---|---|
| **General topics** | Environment, health and safety · Ergonomics · Health physics · Hospital-acquired infection · Indoor air quality · Occupational asthma · Occupational disease · Occupational hygiene · Occupational injury · Risk management · Process safety management · Public health · Repetitive strain injury · |
| **Professions** | Environmental health · Industrial engineering · Occupational health nursing · Occupational health psychology · Occupational medicine · Occupational therapist · Safety engineering · |
| **Specific disorders** | Acrodynia · Asbestosis · Berylliosis · Brucellosis · Byssinosis ("brown lung") · Chalicosis · Chimney sweeps' carcinoma · Chronic solvent-induced encephalopathy (CSE) · Coalworker's pneumoconiosis ("black lung") · Concussions in sport · De Quervain syndrome · Exposure to human nail dust · Farmer's lung · Fiddler's neck · Flock worker's lung · Glassblower's cataract · Golfer's elbow · Hearing Loss · Indium lung · Laboratory animal allergy · Lead poisoning · Mad hatter disease · **Mesothelioma** · Metal fume fever · Mule spinners' cancer · Noise-induced hearing loss · Phossy jaw · Pneumoconiosis · Radium jaw · Silicosis · Silo-filler's disease · Surfer's ear · Tennis elbow · Tinnitus · Writer's cramp · |
| **Organizations** | European Agency for Safety and Health at Work · Health and Safety Executive · International Labour Organization · National Institute for Occupational Safety and Health · Occupational Safety and Health Administration · World Health Organization · |
| **Standards** | Occupational Safety and Health Convention, 1981 · OHSAS 18001 · Worker Protection Standard (US) · Working Environment Convention, 1977 · |
| **See also** | Bangladesh Accord · Environmental toxicology · International Chemical Safety Card · Safety data sheet (SDS) · Sports injuries · Toxic tort · Workers' compensation · National Day of Mourning (Canadian observance) · |
| **Category** · Occupational diseases · **Commons** · Journals · Organizations · | |

| | |
|---|---|
| **Authority control** | NDL: 01166679 · |

Categories: Mesothelioma | Diseases of pleura | Connective and soft tissue neoplasms | Asbestos | Occupational diseases | Rare diseases | Rare cancers | Pleura neoplasia | Infectious causes of cancer

# Ovarian cancer

From Wikipedia, the free encyclopedia

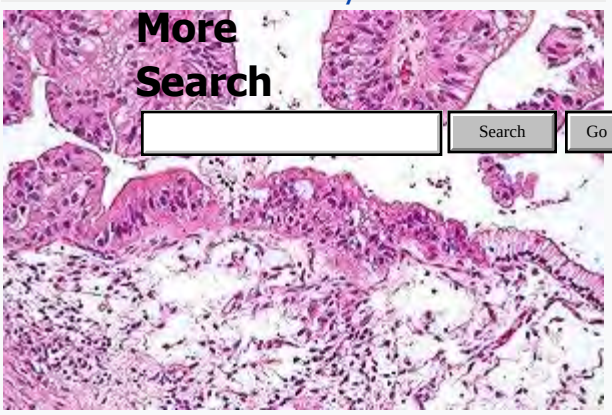
**Ovarian cancer** is a cancer that forms in an ovary.[1] It results in abnormal cells that have the ability to invade or spread to other parts of the body.[2] When this process begins, there may be no or only vague symptoms. Symptoms become more noticeable as the cancer progresses.[3][4] These symptoms may include bloating, pelvic pain, abdominal swelling, and loss of appetite, among others.[3] Common areas to which the cancer may spread include the lining of the abdomen, lining of the bowel and bladder, lymph nodes, lungs, and liver.[5][6]

The risk of ovarian cancer increases in women who have ovulated more over their lifetime. This includes those who have never had children, those who begin ovulation at a younger age or reach menopause at an older age.[7] Other risk factors include hormone therapy after menopause, fertility medication, and obesity.[1][8] Factors that decrease risk include hormonal birth control, tubal ligation, and breast feeding.[8] About 10% of cases are related to inherited genetic risk; women with mutations in the genes *BRCA1* or *BRCA2* have about a 50% chance of developing the disease. The most common type of ovarian cancer, comprising more than 95% of cases, is ovarian carcinoma. There are five main subtypes of ovarian carcinoma, of which high-grade serous carcinoma is the most common. These tumors are believed to start in the cells covering the ovaries,[7] though some may form at the Fallopian tubes.[9] Less common types of ovarian cancer include germ cell tumors and sex cord stromal tumors.[7] A diagnosis of ovarian cancer is confirmed through a biopsy of tissue, usually removed during surgery.[3]

Screening is not recommended in women who are at average risk, as evidence does not support a reduction in death and the high rate of false positive tests may lead to unneeded surgery, which is accompanied by its own risks.[10] Those at very high risk may have their ovaries removed as a preventive measure.[1] If caught and treated in an early stage, ovarian cancer may be curable. Treatment usually includes some combination of surgery, radiation therapy, and chemotherapy.[3] Outcomes depend on the extent of the disease and the subtype of the cancer present.[7] The overall five-year survival rate in the United States is 45%.[11] Outcomes are worse in the developing world.[7]

In 2012, ovarian cancer occurred in 239,000 women and resulted in 152,000 deaths worldwide. This makes it, among women, the seventh-most common cancer and the eighth-most common cause of death from cancer.[7] The typical age of diagnosis is 63.[12] Death from ovarian cancer is more common in North [7]

**Ovarian cancer (human)**



Micrograph of a mucinous ovarian carcinoma stained by H&E.

| Classification and external resources | |
|---|---|
| **Specialty** | Oncology, gynecology |
| **ICD-10** | C56 |
| **ICD-9-CM** | 183, 220 |
| **ICD-O** | varied |
| **DiseasesDB** | 9418 |
| **MedlinePlus** | 000889 |
| **eMedicine** | med/1698 |
| **Patient UK** | Ovarian cancer |
| **MeSH** | D010051 |

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America and Europe than in Africa and Asia.





## Signs and symptoms [edit]

Signs and symptoms of ovarian cancer are frequently absent in early stages; even when they do exist, they may be subtle. In most cases, symptoms exist for several months before being recognized and diagnosed, or they may initially be misdiagnosed as a condition such as irritable bowel syndrome.[13] The early stages of ovarian cancer tend to be painless unless the growing mass causes ovarian torsion.[14] Early symptoms can include bloating, abdominopelvic pain, and pain in the side.[15] The most typical symptoms of ovarian cancer include bloating, abdominal or pelvic pain or discomfort, back pain, irregular menstruation or postmenopausal vaginal bleeding, pain or bleeding after or during sexual intercourse, difficulty eating, loss of appetite, fatigue, diarrhea, indigestion, heartburn, constipation, nausea, early satiety, and possibly urinary symptoms (including frequent urination and urgent urination); typically these symptoms are caused by a mass pressing on the other abdominopelvic organs or from metastases.[14][15][16] If these symptoms start to occur more often or more severely than usual, especially after no significant history of such symptoms, ovarian cancer should be considered.[14][17][18] Metastases may cause a Sister Mary Joseph nodule.[16]

In adolescents or children with ovarian tumors, the presenting symptoms can include severe abdominal pain, irritation of the peritoneum, or bleeding.[19] As the cancer becomes more advanced, it can cause an

accumulation of fluid in the abdomen. If the malignancy has not been diagnosed by the time it causes ascites, it is typically diagnosed shortly thereafter.[14] Advanced cancers can also cause abdominal masses, lymph node masses, or pleural effusion.[16]

Ovarian cancer symptoms can vary based on the subtype.[14] Low malignant potential (LMP) tumors, also known as borderline tumors, do not cause an increase in CA125 levels and are not identifiable with an ultrasound. The typical symptoms of a LMP tumor can include abdominal distension or pelvic pain. Particularly large masses tend to be benign or borderline.[18] Rarely, teratomas can cause growing teratoma syndrome or peritoneal gliomatosis.[16] The symptoms of sex cord-stromal tumors belie their ability to produce hormones. In prepubertal children, early puberty is the main symptom; abdominal pain and distension are also common. Rather than early puberty, adolescents with sex cord-stromal tumors may experience amenorrhea. Adults instead experience menometrorrhagia and abnormal vaginal bleeding after menopause in most cases. Other common symptoms include hirsutism, abdominal pain, virilization, and an adnexal mass.[20]

## Risk factors [edit]

Most of the risk for ovarian cancer is related to the amount of time spent in ovulation. Thus not having children is a risk factor for ovarian cancer, likely because ovulation is not suppressed via pregnancy. Both obesity and hormone replacement therapy also raise the risk.[14]

Things that halt ovulation: breast feeding, oral contraceptive use with estrogen/progesterone combination meds, multiple pregnancies, and pregnancy at an early age, all decrease risk of ovarian cancer. These conditions decrease the overall time during one's lifetime spent ovulating. A positive family history of ovarian cancer is a risk factor for ovarian cancer. People with hereditary nonpolyposis colon cancer (Lynch Syndrome), and those with BRCA-1 and BRCA-2 genetic abnormalities are at increased risk.

### Hormones [edit]

Use of fertility medication may contribute to borderline ovarian tumor formation, but the link between the two is disputed and difficult to study.[13] Fertility drugs may be associated with a higher risk of borderline tumors.[16] Those who have been treated for infertility but remain nulliparous are at higher risk for epithelial ovarian cancer; however, those who are successfully treated for infertility and subsequently give birth are at no higher risk. This may be due to shedding of precancerous cells during pregnancy but the cause remains unclear.[18] The risk factor may instead be infertility itself, not the treatment.[21]

Hormonal conditions such as polycystic ovary syndrome and endometriosis are associated with ovarian cancer, but the link is not completely confirmed.[13] Postmenopausal hormone replacement therapy (HRT) with estrogen likely increases the risk of ovarian cancer. The association has not been confirmed in a large-scale study,[18][22] but notable studies including the Million Women Study have supported this link. Postmenopausal HRT with combined estrogen and progesterone may increase contemporaneous risk if used for over 5 years, but this risk returns to normal after cessation of therapy.[21] Estrogen HRT with or without progestins increases the risk of endometrioid and serous tumors but lowers the risk of mucinous tumors. Higher doses of estrogen increase this risk.[16]

Long periods of continuous ovulation are thought to be the main non-genetic cause of epithelial ovarian cancer. This is because during the cells are constantly stimulated to divide while ovulatory cycles continue. Therefore, people who have not borne children are at twice the risk of ovarian cancer than those who have. A longer period of ovulation caused by early first menstruation or late menopause is also a risk factor.[18][21][23]

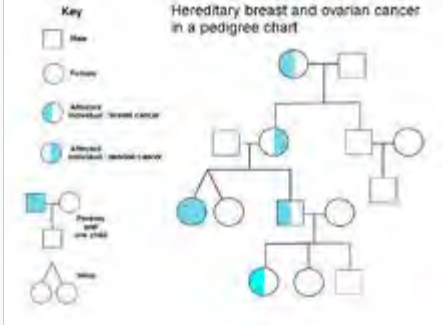
Endometriosis is another risk factor for ovarian cancer,[21] as is pain with menstruation. Endometriosis is associated with clear-cell and endometrioid subtypes, low-grade serous tumors, stage I and II tumors, grade 1 tumors, and lower mortality.[16]

Before menopause, obesity can increase a person's risk of ovarian cancer, but this risk is not present after

menopause. This risk is also relevant in those who are both obese and have never used HRT. A similar association with ovarian cancer appears in taller people.[21]

## Genetics [edit]

*Further information: Hereditary breast–ovarian cancer syndrome*




Ovarian and breast cancer patients in a pedigree chart of a family

In general, a family history of ovarian cancer can indicate a predisposition to developing it. The major genetic risk factor for ovarian cancer is a mutation in *BRCA1* or *BRCA2* DNA mismatch repair genes, which is present in 10% of ovarian cancer cases. Only one allele need be mutated to place a person at high risk, because the risky mutations are autosomal dominant. The gene can be inherited through either the maternal or paternal line, but has variable penetrance.[14][18] Though mutations in these genes are usually associated with increased risk of breast cancer, they also carry a substantial lifetime risk of ovarian cancer, a risk that peaks in a person's 40s and 50s. The lowest risk cited is 30% and the highest 60%.[13][14][18] Mutations in BRCA1 have a lifetime risk of developing ovarian cancer of 15–45%.[16] Mutations in *BRCA2* are less risky than those with *BRCA1*, with a lifetime risk of 10% (lowest risk cited) to 40% (highest risk cited).[14][16] On average, BRCA-associated cancers develop 15 years before their sporadic counterparts, because people who inherit the mutations on one copy of their gene only need one mutation to start the process of carcinogenesis, whereas people with two normal genes would need to acquire two mutations.[18]

In the United States, five of 100 women with a first-degree relative with ovarian cancer will eventually get ovarian cancer themselves, placing those with affected family members at triple the risk of women with unaffected family members. Seven of 100 women with two or more relatives with ovarian cancer will eventually get ovarian cancer.[18][24] In general, 5–10% of ovarian cancer cases have a genetic cause.[18] BRCA mutations are associated with high-grade serous nonmucinous epithelial ovarian cancer.[16]

A strong family history of endometrial cancer, colon cancer, or other gastrointestinal cancers may indicate the presence of a syndrome known as hereditary nonpolyposis colorectal cancer (also known as Lynch syndrome), which confers a higher risk for developing a number of cancers, including ovarian cancer. Lynch syndrome is caused by mutations in mismatch repair genes, including *MSH2*, *MLH1*, *MLH6*, *PMS1*, and *PMS2*.[14] The risk of ovarian cancer for an individual with Lynch syndrome is between 10 and 12 percent.[14][18] People of Icelandic descent, European Jewish descent/Ashkenazi Jewish descent, and Hungarian descent are at higher risk for epithelial ovarian cancer.[18] Estrogen receptor beta gene (ESR2) seems to be a key to pathogenesis and response to therapy.[25] Other genes that have been associated with ovarian cancer are *BRIP1*, *MSH6*, *RAD51C* and *RAD51D*.[26] *CDH1*, *CHEK2*, *PALB2* and *RAD50* have also been associated with ovarian cancer.[27]

Several rare genetic disorders are associated with specific subtypes of ovarian cancer. Peutz–Jeghers syndrome, a rare genetic disorder, also predisposes people to sex cord tumour with annular tubules.[13][14] Ollier disease and Maffucci syndrome are associated with granulosa cell tumors in children and may also be associated with Sertoli-Leydig tumors. Benign fibromas are associated with nevoid basal cell carcinoma syndrome.[14]

## Environmental factors [edit]

Industrialized nations, with the exception of Japan, have high rates of epithelial ovarian cancer, which may be due to diet in those countries. White people are at a 30–40% higher risk for ovarian cancer when compared to Black and Hispanic people, likely due to socioeconomic factors; white women tend to have fewer children and different rates of gynecologic surgeries that affect risk for ovarian cancer.[18]

Cohort studies have found a correlation between dairy consumption and ovarian cancer, but case-control studies do not show this correlation. There is mixed evidence regarding the effect of red meat and processed meat in ovarian cancer.[16]

Tentative evidence suggests that talc, pesticides, and herbicides increase the risk of ovarian cancer.[28] The American Cancer Society notes that as of now, no study has been able to accurately link any single chemical in the environment, or in the human diet, directly to mutations that cause ovarian cancer.[29]

## Other [edit]

Alcohol consumption does not appear to be related to ovarian cancer.[16][30] Other factors that have been investigated, such as smoking, low levels of vitamin D in the blood,[31] presence of inclusion ovarian cysts, and infection with human papilloma virus (the cause of some cases of cervical cancer), have been disproven as risk factors for ovarian cancer.[13][16] The carcinogenicity of perineal talc is controversial, because it can act as an irritant if it travels through the reproductive tract to the ovaries.[16][18][21] Case-control studies have shown that use of perineal talc does increase the risk of ovarian cancer, but using talc more often does not create a greater risk.[16] Use of talc elsewhere on the body is unrelated to ovarian cancer.[21] Sitting regularly for prolonged periods is associated with higher mortality from epithelial ovarian cancer. The risk is not negated by regular exercise, though it is lowered.[32]

Increased age (up to the 70s) is a risk factor for epithelial ovarian cancer because more mutations in cells can accumulate and eventually cause cancer. Those over 80 are at slightly lower risk.[18]

Smoking tobacco is associated with a higher risk of mucinous ovarian cancer; after smoking cessation, the risk eventually returns to normal.A diet high in animal fats may be associated with ovarian cancer, but the connection is unclear. Diet seems to play a very small role, if any, in ovarian cancer risk.[21]

Trans men who have ovaries may be at higher risk of ovarian cancer, but the reason for this is unknown. Potential factors include testosterone therapy and lower rates of protective factors.[33]

Higher levels of C-reactive protein are associated with a higher risk of developing ovarian cancer.[16]

## Protective factors [edit]

Suppression of ovulation, which would otherwise cause damage to the ovarian epithelium and, consequently, inflammation, is generally protective. This effect can be achieved by having children, taking combined oral contraceptives, and breast feeding, all of which are protective factors.[14] A longer period of breastfeeding correlates with a larger decrease in the risk of ovarian cancer.[21] Each birth decreases risk of ovarian cancer more, and this effect is seen with up to five births. Combined oral contraceptives reduce the risk of ovarian cancer by up to 50%, and the protective effect of combined oral contraceptives can last 25–30 years after they are discontinued.[18][21] Regular use of aspirin or acetaminophen (paracetamol) may be associated with a lower risk of ovarian cancer; other NSAIDs do not seem to have a similar protective effect.[16]

Tubal ligation is protective because carcinogens are unable to reach the ovary and fimbriae via the vagina, uterus, and Fallopian tubes.[14] Tubal ligation is also protective in women with the BRCA1 mutation, but not the BRCA2 mutation.[16] Hysterectomy reduces the risk, and removal of both Fallopian tubes and ovaries (bilateral salpingo-oophorectomy) dramatically reduces the risk of not only ovarian cancer, but breast cancer as well.[13] This is still a topic of research, as the link between hysterectomy and lower ovarian cancer risk is controversial. The reasons that hysterectomy may be protective have not been elucidated as of 2015.[21]

A diet that includes large amounts of carotene, fiber, and vitamins with low amounts of fat—specifically, a diet with non-starchy vegetables (e.g. broccoli and onions)—may be protective,[18] though research is still ongoing in this area.[21] Higher caffeine intake and consumption of more than two cups of tea a day have both been associated with lower ovarian cancer risk.[16] Smoking tobacco is protective for sex cord-stromal

tumors.[20]

## Pathophysiology [edit]

Ovarian cancer forms when errors in normal ovarian cell growth occur. Usually, when cells grow old or get damaged, they die, and new cells take their place. Cancer starts when new cells form unneeded, and old or damaged cells do not die as they should. The buildup of extra cells often forms a mass of tissue called a growth or tumor. These abnormal cancer cells have many genetic abnormalities that cause them to grow excessively.[36] When an ovary releases an egg, the egg follicle bursts open and becomes the corpus luteum. This structure needs to be repaired by dividing cells in the ovary.[21] Continuous ovulation for a long time means more repair of the ovary by dividing cells, which can acquire mutations in each division.[18]

Overall, the most common gene mutations in ovarian cancer occur in *NF1*, *BRCA1*, *BRCA2*, and *CDK12*. Type I ovarian cancers, which tend to be less aggressive, tend to have microsatellite instability in several genes, including both oncogenes (most notably *BRAF* and *KRAS*) and tumor suppressors (most notably *PTEN*).[13] The most common mutations in Type I cancers are *KRAS*, *BRAF*, *ERBB2*, *PTEN*, *PIK3CA*, and *ARID1A*.[16] Type II cancers, the more aggressive type, have different genes mutated, including *p53*, *BRCA1*, and *BRCA2*.[13] Low-grade cancers tend to have mutations in KRAS, whereas cancers of any grade that develop from low malignant potential tumors tend to have mutations in p53.[18] Type I cancers tend to develop from precursor lesions, whereas Type II cancers can develop from a serous tubal intraepithelial carcinoma.[16] Serous cancers that have BRCA

**Mutations found in ovarian cancer subtypes**[13][16][34]

| Gene mutated | Mutation type | Subtype | Prevalence |
|---|---|---|---|
| *AKT1* | amplification | | 3% |
| *AKT2* | amplification/mutation | | 6%,[13] 20%[34] |
| *ARID1A* | point mutation | endometrioid and clear cell | |
| *BECN1* | deletion[35] | | |
| *BRAF* | point mutation | low-grade serous | 0.5% |
| *BRCA1* | nonsense mutation | high-grade serous | 5% |
| *BRCA2* | frameshift mutation | high-grade serous | 3% |
| *CCND1* | amplification | | 4% |
| *CCND2* | upregulation | | 15% |
| *CCNE1* | amplification | | 20% |
| *CDK12* | | high-grade serous | |
| *CDKN2A* | downregulation (30%) and deletion (2%) | | 32% |
| *CTNNB1* | | clear cell | |
| DICER1 | missense mutation (somatic) | nonepithelial | 29% |
| DYNLRB1 (km23) | mutation | | 42% |
| EGFR | amplification/overexpression | | 20% |
| *ERBB2* (Her2/neu) | amplification/overexpression | mucinous and low-grade serous | 30% |
| FMS | coexpression with CSF-1 | | 50% |
| FOXL2 | point mutation (402 C to G) | adult granulosa cell | ~100% |
| *JAG1* | amplification | | 2% |
| *JAG2* | amplification | | 3% |
| *KRAS* | amplification | mucinous and low-grade serous | 11% |

mutations also inevitably have p53 mutations, indicating that the removal of both functional genes is important for cancer to develop.[18]

In 50% of high-grade serous cancers, homologous recombination DNA repair is dysfunctional, as are the notch and FOXM1 signaling pathways. They also almost always have p53 mutations. Other than this, mutations in high-grade serous carcinoma are hard to characterize beyond their high degree of genomic instability. *BRCA1* and *BRCA2* are essential for homologous recombination DNA repair, and germline mutations in these genes are found in about 15% of people with ovarian cancer.[13] The most common mutations in BRCA1 and BRCA2 are the frameshift mutations that originated in a small founding population of Ashkenazi Jews.[18]

Autophagy regulator beclin-1 has been implicated in ovarian cancer tumorigenesis and tumor progression; it has one copy deleted in many ovarian tumors.[35]

Almost 100% of rare mucinous carcinomas have mutations in *KRAS* and amplifications of *ERBB2* (also known as *Her2/neu*).[13] Overall, 20% of ovarian cancers have mutations in *Her2/neu*.[14]

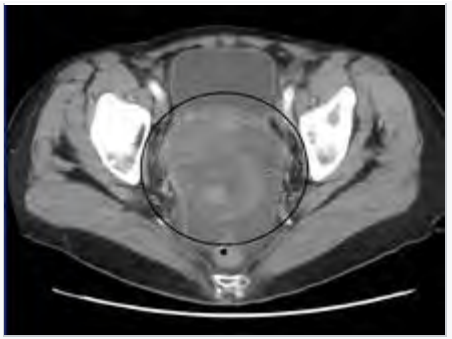
| | | | |
|---|---|---|---|
| *MAML1* | amplification and point mutation | | 2% |
| *MAML2* | amplification and point mutation | | 4% |
| *MAML3* | amplification | | 2% |
| MLH1 | | | 1% |
| *NF1* | deletion (8%) and point mutation (4%) | high-grade serous | 12% |
| *NOTCH3* | amplification and point mutation | | 11% |
| *NRAS* | | low-grade serous | |
| PIK3C3 (PI3K3) | amplification/mutation | | 12–20% |
| *PIK3CA* | amplification | endometrioid and clear cell | 18% |
| *PPP2R1A* | | endometrioid and clear cell | |
| *PTEN* | deletion | endometrioid and clear cell | 7% |
| *RB1* | deletion (8%) and point mutation (2%) | | 10% |
| TGF-β | mutation/overexpression | | 12% |
| *TP53* | mutation/overexpression | high-grade serous | 20–50% |
| TβRI | mutation | | 33% |
| TβRII | mutation | | 25% |
| USP36 | overexpression | | |

Serous carcinomas may develop from serous tubal intraepithelial carcinoma, rather than developing spontaneously from ovarian tissue. Other carcinomas develop from cortical inclusion cysts, which are groups of epithelial ovarian cells inside the stroma.[18]

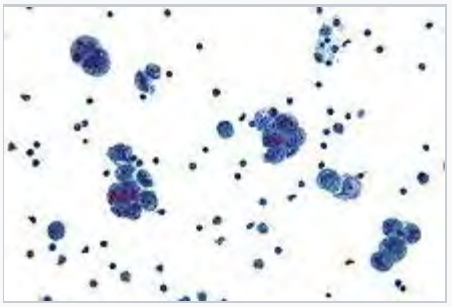
# Diagnosis [edit]

## Examination [edit]

Diagnosis of ovarian cancer starts with a physical examination (including a pelvic examination), a blood test (for CA-125 and sometimes other markers), and transvaginal ultrasound.[14] Sometimes a rectovaginal examination is used to help plan a surgery.[18] The diagnosis must be confirmed with surgery to inspect the abdominal cavity, take biopsies (tissue samples for microscopic analysis), and look for cancer cells in the abdominal fluid. This helps to determine if an ovarian mass is benign or malignant.[14]



A very large ovarian cancer as seen on CT



Micrograph of serous carcinoma, a type of ovarian cancer, diagnosed in peritoneal fluid

Ovarian cancer's early stages (I/II) are difficult to diagnose because most symptoms are nonspecific and thus of little use in diagnosis; as a result, it is rarely diagnosed until it spreads and advances to later stages (III/IV).[37] Additionally, symptoms of ovarian cancer may appear similar to irritable bowel syndrome. In patients in whom pregnancy is a possibility, BHCG level should be measured during the diagnosis process. Serum alpha-fetoprotein, neuron-specific enolase, and lactate dehydrogenase should be measured in young girls and adolescents with suspected ovarian tumors as younger patients are more likely to have malignant germ cell tumors.[14][16]

A physical examination, including a pelvic examination, and a pelvic ultrasound (transvaginal or otherwise) are both essential for diagnosis: physical examination may reveal increased abdominal girth and/or ascites (fluid within the abdominal cavity), while pelvic examination may reveal an ovarian or abdominal mass.[13] An adnexal mass is a significant finding that often indicates ovarian cancer, especially if it is fixed, nodular, irregular, solid, and/or bilateral. 13–21% of adnexal masses are caused by malignancy; however, there are other benign causes of adnexal masses, including ovarian follicular cyst, leiomyoma, endometriosis, ectopic pregnancy, hydrosalpinx, tuboovarian abscess, ovarian torsion, dermoid cyst, cystadenoma (serous or mucinous), diverticular or appendiceal abscess, nerve sheath tumor, pelvic kidney, ureteral or bladder diverticulum, benign cystic mesothelioma of the peritoneum, peritoneal tuberculosis, or paraovarian cyst. Ovaries that can be felt are also a sign of ovarian cancer in postmenopausal women. Other parts of a physical examination for suspected ovarian cancer can include a breast examination and a digital rectal exam. Palpation of the supraclavicular, axillary, and inguinal lymph nodes may reveal lymphadenopathy, which can be indicative of metastasis. Another indicator may be the presence of a pleural effusion, which can be noted on auscultation.[16]

When an ovarian malignancy is included in a list of diagnostic possibilities, a limited number of laboratory tests are indicated. A complete blood count and serum electrolyte test should be obtained in all patients;[38] when an ovarian cancer is present, these tests often show a high number of platelets (20–25% of people) and low blood sodium levels due to chemical signals secreted by the tumor.[18] A positive test for inhibin A and inhibin B can indicate a granulosa cell tumor.[16]

A blood test for a marker molecule called CA-125 is useful in differential diagnosis and in follow up of the disease, but it by itself has not been shown to be an effective method to screen for early-stage ovarian cancer due to its unacceptable low sensitivity and specificity.[38] CA-125 levels in premenopausal people over 200 U/mL may indicate ovarian cancer, as may any elevation in CA-125 above 35 U/mL in post-menopausal people. CA-125 levels are not accurate in early stage ovarian cancer, as fully half of stage I ovarian cancer patients have a normal CA-125 level.[16][18] CA-125 may also be elevated in benign (non-cancerous) conditions, including endometriosis, pregnancy, uterine fibroids, menstruation, ovarian cysts, systemic lupus erythematosus, liver disease, inflammatory bowel disease, pelvic inflammatory disease, and leiomyoma.[16][39] HE4 is another candidate for ovarian cancer testing, though it has not been extensively tested. Other tumor markers for ovarian cancer include CA19-9, CA72-4, CA15-3, immunosuppressive acidic protein, haptoglobin-alpha, OVX1, mesothelin, lysophosphatidic acid, osteopontin, and fibroblast growth factor 23.[16]

Use of blood test panels may help in diagnosis.[16][38] The OVA1 panel includes CA-125, beta-2 microglobulin, transferrin, apolipoprotein A1, and transthyretin. OVA1 above 5.0 in premenopausal people and 4.4 in postmenopausal people indicates a high risk for cancer.[18] A different set of laboratory tests is used for detecting sex cord-stromal tumors. High levels of testosterone or dehydroepiandrosterone sulfate, combined with other symptoms and high levels of inhibin A and inhibin B can be indicative of an SCST of any type.[20]

Current research is looking at ways to consider tumor marker proteomics in combination with other indicators of disease (i.e. radiology and/or symptoms) to improve diagnostic accuracy. The challenge in such an approach is that the disparate prevalence of ovarian cancer means that even testing with very high sensitivity and specificity will still lead to a number of false positive results, which in turn may lead to issues such as performing surgical procedures in which cancer is not found intraoperatively.[40] Genomics approaches have not yet been developed for ovarian cancer.[16]

CT scanning is preferred to assess the extent of the tumor in the abdominopelvic cavity, though magnetic resonance imaging can also be used.[13] CT scanning can also be useful for finding omental caking or differentiating fluid from solid tumor in the abdomen, especially in low malignant potential tumors. However, it may not detect smaller tumors. Sometimes, a chest x-ray is used to detect metastases in the chest or pleural effusion. Another test for metastatic disease, though it is infrequently used, is a barium enema, which can show if the rectosigmoid colon is involved in the disease. Positron emission tomography, bone scans, and paracentesis are of limited use; in fact, paracentesis can cause metastases to form at the needle insertion site and may not provide useful results.[18] However, paracentesis can be used in cases where there is no pelvic mass and ascites is still present.[18] A physician suspecting ovarian cancer may also perform mammography or an endometrial biopsy (in the case of abnormal bleeding) to assess the possibility of breast malignancies and endometrial malignancy, respectively. Vaginal ultrasonography is often the first-line imaging study performed when an adnexal mass is found. Several characteristics of an adnexal mass indicate ovarian malignancy; they usually are solid, irregular, multilocular, and/or large; and they typically have papillary features, central vessels, and/or irregular internal septations.[16] However, SCST has no definitive characteristics on radiographic study.[20]

To definitively diagnose ovarian cancer, a surgical procedure to inspect the abdomen is required. This can be an open procedure (laparotomy, incision through the abdominal wall) or keyhole surgery (laparoscopy). During this procedure, suspicious tissue is removed and sent for microscopic analysis. Usually, this includes a unilateral salpingo-oophorectomy, removal of a single affected ovary and Fallopian tube. Fluid from the abdominal cavity can also be analyzed for cancerous cells. If cancer is found, this procedure can also be used to determine the extent of its spread (which is a form of tumor staging).[14]

## Risk scoring [edit]

A widely recognized method of estimating the risk of malignant ovarian cancer is the risk of malignancy index (RMI), calculated based on an initial workup.[13][41] An RMI score of over 200 or 250 is generally felt to indicate high risk for ovarian cancer.[13][16]

The RMI is calculated as:

RMI = ultrasound score x menopausal score x CA-125 level in U/ml.[13]

Two methods can be used to determine the ultrasound score and menopausal score, with the resultant scores being referred to as RMI 1 and RMI 2, respectively, depending on what method is used.

| Feature | RMI 1[13] | RMI 2[16][42] |
|---|---|---|
| Ultrasound abnormalities:<br>▪ multilocular cyst<br>▪ solid areas<br>▪ ascites<br>▪ intra-abdominal metastases | 0 = no abnormality<br>1 = one abnormality<br>3 = two or more abnormalities | 0 = none<br>1 = one abnormality<br>4 = two or more abnormalities |

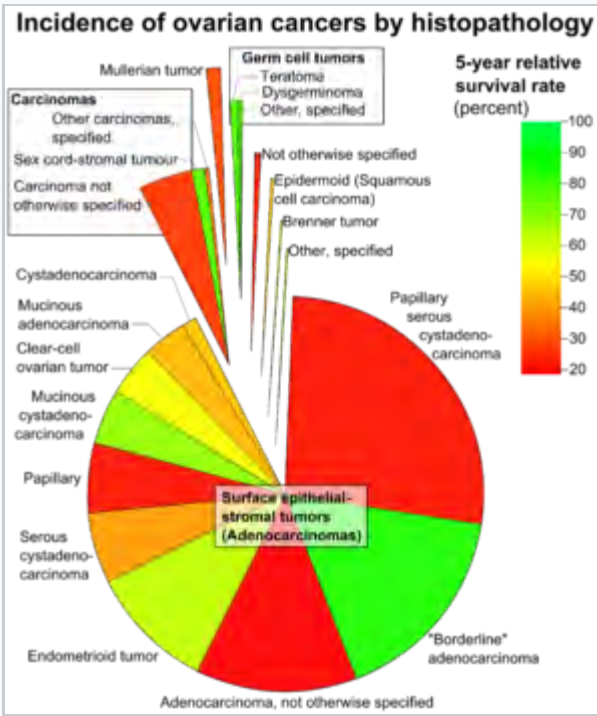
| | | |
|---|---|---|
| Menopausal score | 1 = premenopausal<br>3 = postmenopausal | 1 = premenopausal<br>4 = postmenopausal |
| CA-125 | Quantity in U/ml | Quantity in U/ml |

Another method for quantifying risk of ovarian cancer is the Risk of Ovarian Cancer Algorithm (ROCA), observes levels over time and determines if they are increasing rapidly enough to warrant transvaginal ultrasound.[18] The Risk of Ovarian Malignancy algorithm uses CA-125 levels and HE4 levels to calculate the risk of ovarian cancer; it may be more effective than RMI. The Assessment of Different Neoplasias in the Adnexa (ADNEX) model can be used to assess risk of malignancy in an adnexal mass, based on its characteristics and risk factors. The QCancer (Ovary) algorithm is used to predict likelihood of ovarian cancer from risk factors.[16]

## Pathology [edit]

Ovarian cancers are classified according to the microscopic appearance of their structures (histology or histopathology). Histology dictates many aspects of clinical treatment, management, and prognosis. The gross pathology of ovarian cancers is very similar regardless of histologic type: tumors have solid and cystic masses.[18] According to SEER, the types of ovarian cancers in women age 20 and over are:[43]

| Percent of ovarian cancers in women age 20+ | Percent of ovarian cancers in women age 20+ by subdivision | Histology | Five-year RSR |
|---|---|---|---|
| 89.7 | | Surface epithelial-stromal tumor (adenocarcinoma) | 54.4 |
| | 26.4 | Papillary serous cystadenocarcinoma | 21.0 |
| | 15.9 | "Borderline" adenocarcinoma (underestimated - short data collection interval) | 98.2 |
| | 12.6 | Adenocarcinoma, not otherwise specified | 18.3 |
| | 9.8 | Endometrioid tumor | 70.9 |
| | 5.8 | Serous cystadenocarcinoma | 44.2 |
| | 5.5 | Papillary | 21.0 |
| | 4.2 | Mucinous cystadenocarcinoma | 77.7 |
| | 4.0 | Clear-cell ovarian tumor | 61.5 |
| | 3.4 | Mucinous adenocarcinoma | 49.1 |
| | 1.3 | Cystadenocarcinoma | 50.7 |
| 5.5 | | Carcinoma | |



Ovarian cancers in women aged 20+, with area representing relative incidence and color representing five-year relative survival rate[43]

| | | | |
|---|---|---|---|
| | 4.1 | Carcinoma not otherwise specified | 26.8 |
| | 1.1 | Sex cord-stromal tumour | 87.8 |
| | 0.3 | Other carcinomas, specified | 37.3 |
| 1.7 | | Mullerian tumor | 29.8 |
| 1.5 | | Germ cell tumor | 91.0 |
| | 0.8 | Teratoma | 89.1 |
| | 0.5 | Dysgerminoma | 96.8 |
| | 0.3 | Other, specified | 85.1 |
| 0.6 | | Not otherwise specified | 23.0 |
| 0.5 | | Epidermoid (squamous cell carcinoma) | 51.3 |
| 0.2 | | Brenner tumor | 67.9 |
| 0.2 | | Other, specified | 71.7 |

Ovarian cancers are histologically and genetically divided into type I or type II. Type I cancers are of low histological grade, and include endometrioid, mucinous, and clear-cell carcinomas. Type II cancers are of higher histological grade and include serous carcinoma and carcinosarcoma.[13]

## Epithelial carcinoma [edit]

Surface epithelial-stromal tumour, also known as ovarian epithelial carcinoma, is the most common type of ovarian cancer, representing approximately 90% of ovarian cancers. It includes serous tumour, endometrioid tumor, and mucinous cystadenocarcinoma. Less common tumors are malignant Brenner tumor and transitional cell carcinoma of the ovary. Epithelial ovarian cancers develop from the epithelium, a layer of cells that covers the ovary.[44]

A pathological specimen of ovarian carcinoma

### Serous carcinoma [edit]

Most people with epithelial ovarian carcinoma, about two-thirds, have a serous carcinoma,[13] though this proportion is estimated as high as 80%.[16][45] Low-grade serous carcinoma is less aggressive than high-grade serous carcinomas, though it does not typically respond well to chemotherapy or hormonal treatments.[13] Serous carcinomas are thought to begin in the Fallopian tube.[44] Histologically, serous adenocarcinomas have psammoma bodies. Low-grade serous adenocarcinomas resemble Fallopian tube epithelium, whereas high-grade serous adenocarcinomas show anaplasia and nuclear atypia.[18]

50% of the time, serous carcinomas are bilateral, and in 85% of cases, they have spread beyond the ovary at the time of diagnosis. Most have a diameter over 15 cm.[45]

### Small-cell carcinoma [edit]

Small-cell ovarian carcinoma is rare and aggressive, with two main subtypes: hypercalcemic and pulmonary. It is typically fatal within 2 years of diagnosis. Hypercalcemic small cell ovarian carcinoma overwhelmingly affects those in their 20s, causes high blood calcium levels, and affects one ovary. Pulmonary small cell ovarian cancer usually affects both ovaries of older women and looks like oat-cell carcinoma of the lung.[18]

### Primary peritoneal carcinoma [edit]

*Main article: Primary peritoneal carcinoma*

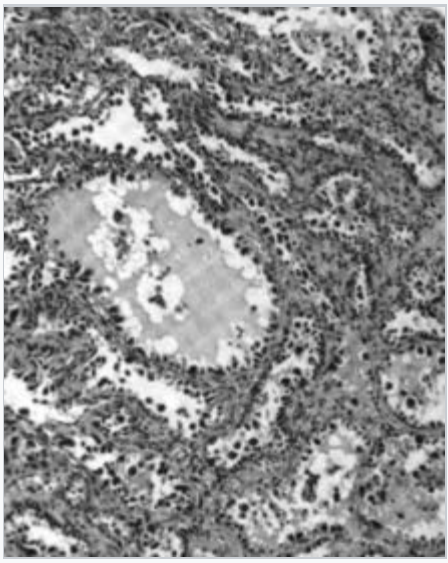
Primary peritoneal carcinomas develop from the peritoneum, a membrane that covers the abdominal cavity that has the same embryonic origin as the ovary. They are often discussed and classified with ovarian cancers when they affect the ovary.[44][46] They can develop even after the ovaries have been removed and may appear similar to mesothelioma.[18]

### Clear-cell carcinoma [edit]

Clear-cell ovarian carcinomas do not typically respond well to chemotherapy and may be related to endometriosis.[13] They represent approximately 5% of all endometrial cancers. Japanese women develop clear-cell ovarian cancer more frequently than other groups of women.[16]

### Clear-cell adenocarcinoma [edit]

Clear-cell adenocarcinomas are histopathologically similar to other clear cell carcinomas, with clear cells and hobnail cells. They represent approximately 5–10% of epithelial ovarian cancers and are associated with endometriosis in the pelvic cavity. They are typically early-stage and therefore curable by surgery, but advanced clear-cell adenocarcinomas (approximately 20%) have a poor prognosis and are often resistant to platinum chemotherapy.[18]



Hobnail cells seen in a clear cell carcinoma sample

### Endometrioid [edit]

Endometrioid adenocarcinomas make up approximately 15–20% of epithelial ovarian cancers. Because they are typically low-grade, endometrioid adenocarcinomas have a good prognosis. These tumors frequently co-occur with endometriosis or endometrial cancer.[18]

### Malignant mixed müllerian tumor (carcinosarcoma) [edit]

Mixed müllerian tumors make up less than 1% of ovarian cancer. They have epithelial and mesenchymal cells visible and tend to have a poor prognosis.[18]

### Mucinous [edit]

Mucinous tumors include mucinous adenocarcinoma and mucinous cystadenocarcinoma.[18]

### Mucinous adenocarcinoma [edit]

*Main article: Mucinous adenocarcinoma*

Mucinous adenocarcinomas make up 5–10% of epithelial ovarian cancers. Histologically, they are similar to intestinal or cervical adenocarcinomas, and are often actually metastases of appendiceal or colon cancers. Advanced mucinous adenocarcinomas have a poor prognosis, generally worse than serous tumors, and are often resistant to platinum chemotherapy, though they are rare.[18]

### Pseudomyxoma peritonei [edit]

*Main article: Pseudomyxoma peritonei*

*Pseudomyxoma peritonei* refers to a collection of encapsulated mucous or gelatinous material in the abdominopelvic cavity, which is very rarely caused by a primary mucinous ovarian tumor. More commonly, it is associated with ovarian metastases of intestinal cancer.[18]

### Undifferentiated epithelial [edit]

Undifferentiated cancers - those where the cell type cannot be determined - make up about 10% of epithelial ovarian cancers and have a comparatively poor prognosis.[18][44] When examined under the microscope, these tumors have very abnormal cells that are arranged in clumps or sheets. Usually there are [18]

recognizable clumps of serous cells inside the tumor.

### Malignant Brenner tumor [edit]

*Main article: Brenner tumor*

Malignant Brenner tumors are rare. Histologically, they have dense fibrous stroma with areas of transitional epithelium, and some squamous differentiation. To be classified as a malignant Brenner tumor, it must have Brenner tumor foci and transitional cell carcinoma. The transitional cell carcinoma component is typically poorly differentiated and resembles urinary tract cancer.[18]

### Transitional cell carcinoma [edit]

*Main article: Transitional cell carcinoma*

Transitional cell carcinomas represent less than 5% of ovarian cancers. Histologically, they appear similar to bladder carcinoma. The prognosis is intermediate - better than most epithelial cancers but worse than malignant Brenner tumors.[18]

## Sex cord-stromal tumor [edit]

*Main article: Sex cord-stromal tumor*

Sex cord-stromal tumor, including estrogen-producing granulosa cell tumor, the benign thecoma, and virilizing Sertoli-Leydig cell tumor or arrhenoblastoma, accounts for 7% of ovarian cancers. They occur most frequently in women between 50 and 69 years of age, but can occur in women of any age, including young girls. They are not typically aggressive and are usually unilateral;[14] they are therefore usually treated with surgery alone. Sex cord-stromal tumors are the main hormone-producing ovarian tumors.[20]

Several different cells from the mesenchyme can give rise to sex-cord or stromal tumors. These include fibroblasts and endocrine cells. The symptoms of a sex-cord or stromal ovarian tumor can differ from other types of ovarian cancer. Common signs and symptoms include ovarian torsion, hemorrhage from or rupture of the tumor, an abdominal mass, and hormonal disruption. In children, isosexual precocious pseudopuberty may occur with granulosa cell tumors since they produce estrogen. These tumors cause abnormalities in menstruation (excessive bleeding, infrequent menstruation, or no menstruation) or postmenopausal bleeding. Because these tumors produce estrogen, they can cause or occur at the same time as endometrial cancer or breast cancer. Other sex-cord/stromal tumors present with distinct symptoms. Sertoli-Leydig cell tumors cause virilization and excessive hair growth due to the production of testosterone and androstenedione, which can also cause Cushing's syndrome in rare cases. Also, sex-cord stromal tumors occur that do not cause a hormonal imbalance, including benign fibromas, which cause ascites and hydrothorax.[14] With germ cell tumors, sex cord-stromal tumors are the most common ovarian cancer diagnosed in women under 20.[20]

### Granulosa cell tumor [edit]

Granulosa cell tumors are the most common sex-cord stromal tumors, making up 70% of cases, and are divided into two histologic subtypes: adult granulosa cell tumors, which develop in women over 50, and juvenile granulosa tumors, which develop before puberty or before the age of 30. Both develop in the ovarian follicle from a population of cells that surrounds germinal cells.[20]

### Adult granulosa cell tumor [edit]

Adult granuosa cell tumors are characterized by later onset (30+ years, 50 on average). These tumors produce high levels of estrogen, which causes its characteristic symptoms: menometrorrhagia; endometrial hyperplasia; tender, enlarged breasts; postmenopausal bleeding; and secondary amenorrhea. The mass of the tumor can cause other symptoms, including abdominal pain and distension, or symptoms similar to an ectopic pregnancy if the tumor bleeds and ruptures.[20]

### Juvenile granulosa cell tumor [edit]

### Sertoli-Leydig cell tumor [edit]

Sertoli-Leydig tumors are most common in women before the age of 30, and particularly common before puberty.[20]

### Sclerosing stromal tumors [edit]

Sclerosing stromal tumors typically occur in girls before puberty or women before the age of 30.[20]

## Germ cell tumor [edit]

*Main article: Germ cell tumor*

Germ cell tumors of the ovary develop from the ovarian germ cells.[44] Germ cell tumor accounts for about 30% of ovarian tumors, but only 5% of ovarian cancers, because most germ-cell tumors are teratomas and most teratomas are benign. Malignant teratomas tend to occur in older women, when one of the germ layers in the tumor develops into a squamous cell carcinoma.[14] Germ-cell tumors tend to occur in young women (20s–30s) and girls, making up 70% of the ovarian cancer seen in that age group.[19] Germ-cell tumors can include dysgerminomas, teratomas, yolk sac tumors/endodermal sinus tumors, and choriocarcinomas, when they arise in the ovary. Some germ-cell tumors have an isochromosome 12, where one arm of chromosome 12 is deleted and replaced with a duplicate of the other.[14] Most germ-cell cancers have a better prognosis than other subtypes and are more sensitive to chemotherapy. They are more likely to be stage I at diagnosis.[20] Overall, they metastasize more frequently than epithelial ovarian cancers. In addition, the cancer markers used vary with tumor type: choriocarcinomas are monitored with beta-HCG and endodermal sinus tumors with alpha-fetoprotein.[14]

Germ-cell tumors are typically discovered when they become large, palpable masses. However, like sex cord tumors, they can cause ovarian torsion or hemorrhage and, in children, isosexual precocious puberty. They frequently metastasize to nearby lymph nodes, especially para-aortic and pelvic lymph nodes.[14] The most common symptom of germ cell tumors is subacute abdominal pain caused by the tumor bleeding, necrotizing, or stretching the ovarian capsule. If the tumor ruptures, causes significant bleeding, or torses the ovary, it can cause acute abdominal pain, which occurs in less than 10% of those with germ-cell tumors. They can also secrete hormones which change the menstrual cycle. In 25% of germ-cell tumors, the cancer is discovered during a routine examination and does not cause symptoms.[20]

Diagnosing germ cell tumors may be difficult because the normal menstrual cycle and puberty can cause pain and pelvic symptoms, and a young woman may even believe these symptoms to be those of pregnancy, and not seek treatment due to the stigma of teen pregnancy. Blood tests for alpha-fetoprotein, karyotype, human chorionic gonadotropin, and liver function are used to diagnose germ cell tumor and potential co-occurring gonadal dysgenesis. A germ cell tumor may be initially mistaken for a benign ovarian cyst.[20]

### Dysgerminoma [edit]

*Main article: Dysgerminoma*

Dysgerminoma accounts for 35% of ovarian cancer in young women and is the most likely germ cell tumor to metastasize to the lymph nodes; nodal metastases occur in 25–30% of cases.[19][20] These tumors may have mutations in the *KIT* gene, a mutation known for its role in gastrointestinal stromal tumor. People with an XY karyotype and ovaries (gonadal dysgenesis) or an X,0 karyotype and ovaries (Turner syndrome) who develop a unilateral dysgerminoma are at risk for a gonadoblastoma in the other ovary, and in this case, both ovaries are usually removed when a unilateral dysgerminoma is discovered to avoid the risk of another malignant tumor. Gonadoblastomas in people with Swyer or Turner syndrome become malignant in approximately 40% of cases. However, in general, dysgerminomas are bilateral 10–20% of the time.[14][20]

They are composed of cells that cannot differentiate further and develop directly from germ cells or from gonadoblastomas. Dysgerminomas contain syncytiotrophoblasts in approximately 5% of cases, and can therefore cause elevated hCG levels. On gross appearance, dysgerminomas are typically pink to tan-colored, have multiple lobes, and are solid. Microscopically, they appear identical to seminomas and very close to embryonic primordial germ cells, having large, polyhedral, rounded clear cells. The nuclei are

uniform and round or square with prominent nucleoli and the cytoplasm has high levels of glycogen. Inflammation is another prominent histologic feature of dysgerminomas.[20]

### Choriocarcinoma [edit]

*Main article: Choriocarcinoma*

Choriocarcinoma can occur as a primary ovarian tumor developing from a germ cell, though it is usually a gestational disease that metastasizes to the ovary. Primary ovarian choriocarcinoma has a poor prognosis and can occur without a pregnancy. They produce high levels of hCG and can cause early puberty in children or menometrorrhagia (irregular, heavy menstruation) after menarche.[20]

### Immature (solid) teratoma [edit]

*Main article: Immature teratoma*

Immature, or solid, teratomas are the most common type of ovarian germ cell tumor, making up 40–50% of cases. Teratomas are characterized by the presence of disorganized tissues arising from all three embryonic germ layers: ectoderm, mesoderm, and endoderm; immature teratomas also have undifferentiated stem cells that make them more malignant than mature teratomas (dermoid cysts). The different tissues are visible on gross pathology and often include bone, cartilage, hair, mucus, or sebum, but these tissues are not visible from the outside, which appears to be a solid mass with lobes and cysts. Histologically, they have large amounts of neuroectoderm organized into sheets and tubules along with glia; the amount of neural tissue determines the histologic grade. Immature teratomas usually only affect one ovary (10% co-occur with dermoid cysts) and usually metastasize throughout the peritoneum. They can also cause mature teratoma implants to grow throughout the abdomen in a disease called growing teratoma syndrome; these are usually benign but will continue to grow during chemotherapy, and often necessitate further surgery. Unlike mature teratomas, immature teratomas form many adhesions, making them less likely to cause ovarian torsion. There is no specific marker for immature teratomas, but carcinoembryonic antigen (CEA), CA-125, CA19-9, or AFP can sometimes indicate an immature teratoma.[20]

Stage I teratomas make up the majority (75%) of cases and have the best prognosis, with 98% of patients surviving 5 years; if a Stage I tumor is also grade 1, it can be treated with unilateral surgery only. Stage II though IV tumors make up the remaining quarter of cases and have a worse prognosis, with 73–88% of patients surviving 5 years.[20]

### Mature teratoma (dermoid cyst) [edit]

*Main article: Dermoid cyst*

Mature teratomas, or dermoid cysts, are rare tumors consisting of mostly benign tissue that develop after menopause. The tumors consist of disorganized tissue with nodules of malignant tissue, which can be of various types. The most common malignancy is squamous cell carcinoma, but adenocarcinoma, basal-cell carcinoma, carcinoid tumor, neuroectodermal tumor, malignant melanoma, sarcoma, sebaceous tumor, and struma ovarii can also be part of the dermoid cyst. They are treated with surgery and adjuvant platinum chemotherapy or radiation.[20]

### Yolk sac tumor/endodermal sinus tumor [edit]

*Main article: Yolk sac tumor*

Yolk sac tumors, formerly called endodermal sinus tumors, make up approximately 10–20% of ovarian germ cell malignancies, and have the worst prognosis of all ovarian germ cell tumors. They occur both before menarche (in one-third of cases) and after menarche (the remaining two-thirds of cases). Half of people with yolk sac tumors are diagnosed in stage I. Typically, they are unilateral until metastasis, which occurs within the peritoneal cavity and via the bloodstream to the lungs. Yolk sac tumors grow quickly and recur easily, and are not easily treatable once they have recurred. Stage I yolk sac tumors are highly treatable, with a 5-year disease free survival rate of 93%, but stage II-IV tumors are less treatable, with survival rates of 64–91%.[20]

Their gross appearance is solid, friable, and yellow, with necrotic and hemorrhagic areas. They also often contain cysts that can degenerate or rupture. Histologically, yolk sac tumors are characterized by the presence of Schiller-Duval bodies (which are pathognomonic for yolk sac tumors) and a reticular pattern. Yolk sac tumors commonly secrete alpha-fetoprotein and can be immunohistochemically stained for its presence; the level of alpha-fetoprotein in the blood is a useful marker of recurrence.[20]

### Embryonal carcinoma [edit]

*Main article: Embryonal carcinoma*

Embryonal carcinomas, a rare tumor type usually found in mixed tumors, develop directly from germ cells but are not terminally differentiated; in rare cases they may develop in dysgenetic gonads. They can develop further into a variety of other neoplasms, including choriocarcinoma, yolk sac tumor, and teratoma. They occur in younger people, with an average age at diagnosis of 14, and secrete both alpha-fetoprotein (in 75% of cases) and hCG.[20]

Histologically, embryonal carcinoma appears similar to the embryonic disc, made up of epithelial, anaplastic cells in disorganized sheets, with gland-like spaces and papillary structures.[20]

### Polyembryoma [edit]

*Main article: Polyembryoma*

Polyembryomas, the most immature form of teratoma and very rare ovarian tumors, are histologically characterized by having several embryo-like bodies with structures resembling a germ disk, yolk sac, and amniotic sac. Syncytiotrophoblast giant cells also occur in polyembryomas.[20]

## Squamous cell carcinoma [edit]

Primary ovarian squamous cell carcinomas are rare and have a poor prognosis when advanced. More typically, ovarian squamous cell carcinomas are cervical metastases, areas of differentiation in an endometrioid tumor, or derived from a mature teratoma.[18]

## Mixed tumors [edit]

Mixed tumors contain elements of more than one of the above classes of tumor histology. To be classed as a mixed tumor, the minor type must make up more than 10% of the tumor.[16] Though mixed carcinomas can have any combination of cell types, mixed ovarian cancers are typically serous/endometrioid or clear cell/endometrioid.[18] Mixed germ cell tumors make up approximately 25–30% of all germ cell ovarian cancers, with combinations of dysgerminoma, yolk sac tumor, and/or immature teratoma. The prognosis and treatment vary based on the component cell types.[20]

## Secondary ovarian cancer [edit]

Ovarian cancer can also be a secondary cancer, the result of metastasis from a primary cancer elsewhere in the body.[14] About 7% of ovarian cancers are due to metastases, while the rest are primary cancers.[*citation needed*] Common primary cancers are breast cancer, colon cancer, appendiceal cancer, and stomach cancer (primary gastric cancers that metastasize to the ovary are called Krukenberg tumors).[14] Krukenberg tumors have signet ring cells and mucinous cells.[18] Endometrial cancer and lymphomas can also metastasize to the ovary.[45]

## Low malignant potential tumors [edit]

Low malignant potential ovarian tumors, also called borderline tumors, have some benign and some malignant features.[18] LMP tumors make up approximately 10%-15% of all ovarian tumors.[16][44] They develop earlier than epithelial ovarian cancer, around the age of 40–49. They typically do not have extensive invasion; 10% of LMP tumors have areas of stromal microinvasion (<3mm, <5% of tumor). LMP

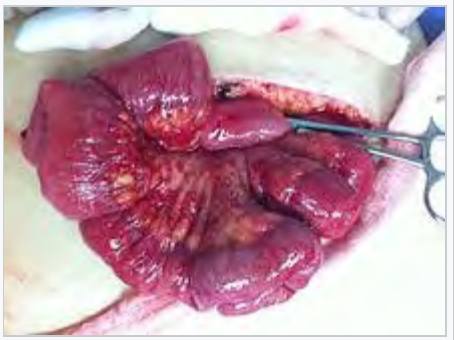
tumors have other abnormal features, including increased mitosis, changes in cell size or nucleus size, abnormal nuclei, cell stratification, and small projections on cells (papillary projections). Serous and/or mucinous characteristics can be seen on histological examination, and serous histology makes up the overwhelming majority of advanced LMP tumors. More than 80% of LMP tumors are Stage I; 15% are stage II and III and less than 5% are stage IV.[18] Implants of LMP tumors are often non-invasive.[44]

## Staging [edit]

Ovarian cancer is staged using the FIGO staging system and uses information obtained after surgery, which can include a total abdominal hysterectomy via midline laparotomy, removal of (usually) both ovaries and Fallopian tubes, (usually) the omentum, pelvic (peritoneal) washings, assessment of retroperitoneal lymph nodes (including the pelvic and para-aortic lymph nodes), appendectomy in suspected mucinous tumors, and pelvic/peritoneal biopsies for cytopathology.[13][14][16][47] Around 30% of ovarian cancers that appear confined to the ovary have metastasized microscopically, which is why even stage-I cancers must be staged completely.[14] 22% of cancers presumed to be stage I are observed to have lymphatic metastases.[16] The AJCC stage is the same as the FIGO stage. The AJCC staging system describes the extent of the primary tumor (T), the absence or presence of metastasis to nearby lymph nodes (N), and the absence or presence of distant metastasis (M).[48] The most common stage at diagnosis is stage IIIc, with over 70% of diagnoses.[14]

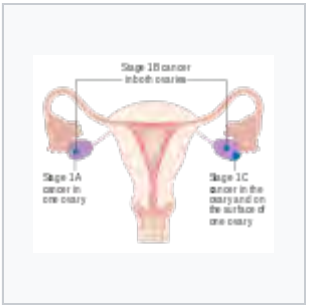
**FIGO stages of ovarian cancer**[13][47]

| Stage | | | | Description |
|---|---|---|---|---|
| I | | | | Cancer is completely limited to the ovary |
| | IA | | | involves one ovary, capsule intact, no tumor on ovarian surface, negative washings |
| | IB | | | involves both ovaries; capsule intact; no tumor on ovarian surface; negative washings |
| | IC | | | tumor involves one or both ovaries |
| | IC1 | | | surgical spill |
| | IC2 | | | capsule has ruptured or tumor on ovarian surface |
| | IC3 | | | positive ascites or washings |
| II | | | | pelvic extension of the tumor (must be confined to the pelvis) or primary peritoneal tumor, involves one or both ovaries |
| | IIA | | | tumor found on uterus or fallopian tubes |
| | IIB | | | tumor elsewhere in the pelvis |
| III | | | | cancer found outside the pelvis or in the retroperitoneal lymph nodes, involves one or both ovaries |
| | IIIA | | | metastasis in retroperitoneal lymph nodes or microscopic extrapelvic metastasis |
| | | IIIA1 | | metastasis in retroperitoneal lymph nodes |

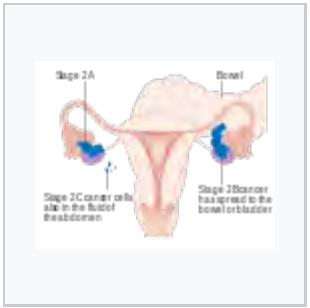


Ovarian adenocarcinoma deposit in the mesentery of the small bowel

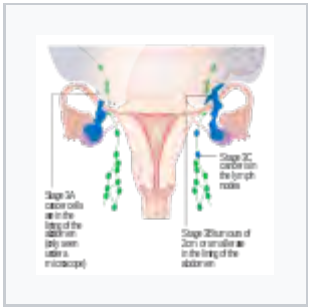
| | | | | |
|---|---|---|---|---|
| | | | IIIA1(i) | the metastasis is less than 10 mm in diameter |
| | | | IIIA1(ii) | the metastasis is greater than 10 mm in diameter |
| | | IIIA2 | | microscopic metastasis in the peritoneum, regardless of retroperitoneal lymph node status |
| | IIIB | | | metastasis in the peritoneum less than or equal to 2 cm in diameter, regardless of retroperitoneal lymph node status; or metastasis to liver or spleen capsule |
| | IIIC | | | metastasis in the peritoneum greater than 2 cm in diameter, regardless of retroperitoneal lymph node status; or metastasis to liver or spleen capsule |
| IV | | | | distant metastasis (i.e. outside of the peritoneum) |
| | IVA | | | pleural effusion containing cancer cells |
| | IVB | | | metastasis to distant organs (including the parenchyma of the spleen or liver), or metastasis to the inguinal and extra-abdominal lymph nodes |



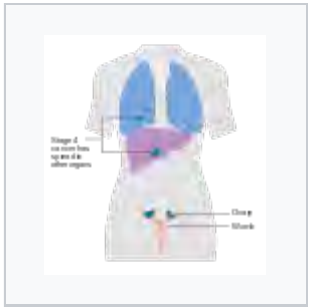
Stage 1 ovarian cancer



Stage 2 ovarian cancer



Stage 3 ovarian cancer



Stage 4 ovarian cancer

The AJCC/TNM staging system indicates where the tumor has developed, spread to lymph nodes, and metastasis.[16]

**AJCC/TNM stages of ovarian cancer**[16]

| Stage | | | Description |
|---|---|---|---|
| T | | | Primary tumor |
| | Tx | | Cannot be assessed |
| | T0 | | No evidence |
| | T1 | | Tumor limited to ovary/ovaries |
| | | T1a | One ovary with intact capsule, no surface tumor, and negative ascites/peritoneal washings |
| | | T1b | Both ovaries with intact capsules, no surface tumor, and negative ascites/peritoneal washings |
| | | T1c | One or both ovaries with ruptured capsule or capsules, surface tumor, positive ascites/peritoneal washings |

| | | | |
|---|---|---|---|
| | T2 | | Tumor is in ovaries and pelvis (extension or implantation) |
| | | T2a | Expansion to uterus or Fallopian tubes, negative ascites/peritoneal washings |
| | | T2b | Expansion in other pelvic tissues, negative ascites/peritoneal washings |
| | | T2c | Expansion to any pelvic tissue, positive ascites/peritoneal washings |
| | T3 | | Tumor is in ovaries and has metastasized outside the pelvis to the peritoneum (including the liver capsule) |
| | | T3a | Microscopic metastasis |
| | | T3b | Macroscopic metastasis less than 2 cm diameter |
| | | T3c | Macroscopic metastasis greater than 2 cm diameter |
| N | | | Regional lymph node metastasis |
| | Nx | | Cannot be assessed |
| | N0 | | No metastasis |
| | N1 | | Metastasis present |
| M | | | Distant metastasis |
| | M0 | | No metastasis |
| | M1 | | Metastasis present (excluding liver capsule, including liver parenchyma and cytologically confirmed pleural effusion) |

The AJCC/TNM stages can be correlated with the FIGO stages:[16]

| FIGO | T | N | M |
|---|---|---|---|
| I | T1 | N0 | M0 |
| IA | T1a | N0 | M0 |
| IB | T1b | N0 | M0 |
| IC | T1c | N0 | M0 |
| II | T2 | N0 | M0 |
| IIA | T2a | N0 | M0 |
| IIB | T2b | N0 | M0 |
| IIC | T2c | N0 | M0 |
| III | T3 | N0 | M0 |
| IIIA | T3a | N0 | M0 |
| IIIB | T3b | N0 | M0 |
| IIIC | T3c | N0/N1 | M0 |
| IV | Any | Any | M1 |

In addition to being staged, like all cancers, ovarian cancer is also graded. The histologic grade of a tumor measures how abnormal or malignant its cells look under the microscope. The four grades indicate the likelihood of the cancer to spread and the higher the grade, the more likely for this to occur. Grade 0 is used to describe noninvasive tumors. Grade 0 cancers are also referred to as borderline tumors.[49] Grade 1 tumors have well differentiated cells (look very similar to the normal tissue) and are the ones with the best prognosis. Grade 2 tumors are also called moderately well-differentiated and they are made up of cells that resemble the normal tissue. Grade 3 tumors have the worst prognosis and their cells are abnormal, referred to as poorly differentiated.[50]

Metastasis in ovarian cancer is very common in the abdomen, and occurs via exfoliation, where cancer cells

burst through the ovarian capsule and are able to move freely throughout the peritoneal cavity. Ovarian cancer metastases usually grow on the surface of organs rather than the inside; they are also common on the omentum and the peritoneal lining. Cancer cells can also travel through the lymphatic system and metastasize to lymph nodes connected to the ovaries via blood vessels; i.e. the lymph nodes along the infundibulopelvic ligament, the broad ligament, and the round ligament. The most commonly affected groups include the paraaortic, hypogastric, external iliac, obturator, and inguinal lymph nodes. Usually, ovarian cancer does not metastasize to the liver, lung, brain, or kidneys unless it is recurrent disease; this differentiates ovarian cancer from many other forms of cancer.[18]

## Screening [edit]

The only screening recommended for all women is an annual pelvic examination. This is not very effective in detecting early ovarian cancer because it is usually only palpable in advanced stages.[18] Ovarian cancer screening is of high clinical interest because the disease is not typically detectable at its early stages, when it is the most curable. Screening is not recommended using CA-125 measurements, HE4 levels, ultrasound, or adnexal palpation in women who are at average risk. Screening for any type of cancer must be accurate and reliable—it needs to accurately detect the disease and it must not give false positive results in people who do not have cancer.[14][51]

Ovarian cancer has low prevalence, even in the high-risk group of women from the ages of 50 to 60 (about one in 2000), and screening of women with average risk is more likely to give ambiguous results than detect a problem which requires treatment. Because ambiguous results are more likely than detection of a treatable problem, and because the usual response to ambiguous results is invasive interventions, in women of average risk, the potential harms of having screening without an indication outweigh the potential benefits. The purpose of screening is to diagnose ovarian cancer at an early stage, when it is more likely to be treated successfully.[14][51]

Screening with transvaginal ultrasound, pelvic examination, and CA-125 levels can be used instead of preventative surgery in women who have BRCA1 or BRCA2 mutations. This strategy has shown some success.[18]

## Prevention [edit]

People with strong genetic risk for ovarian cancer may consider the surgical removal of their ovaries as a preventative measure. This is often done after completion of childbearing years. This reduces the chances of developing both breast cancer (by around 50%) and ovarian cancer (by about 96%) in people at high risk. Women with *BRCA* gene mutations usually also have their Fallopian tubes removed at the same time (salpingo-oophorectomy), since they also have an increased risk of Fallopian tube cancer. However, these statistics may overestimate the risk reduction because of how they have been studied.[14][51]

People with a significant family history for ovarian cancer are often referred to a genetic counselor to see if they should be tested for BRCA mutations.[18]

## Management [edit]

Treatment usually involves chemotherapy and surgery, and sometimes radiotherapy, regardless of the subtype of ovarian cancer.[44] Surgical treatment may be sufficient for well-differentiated malignant tumors and confined to the ovary. Addition of chemotherapy may be required for more aggressive tumors confined to the ovary. For patients with advanced disease, a combination of surgical reduction with a combination chemotherapy regimen is standard. Borderline tumors, even following spread outside of the ovary, are managed well with surgery, and chemotherapy is not seen as useful.[52] Second-look surgery and maintenance chemotherapy have not been shown to provide benefit.[18]

### Surgery [edit]

Surgery is the preferred treatment and is frequently necessary to obtain a tissue specimen for differential diagnosis via its histology. The type of surgery depends upon how widespread the cancer is when diagnosed (the cancer stage), as well as the presumed type and grade of cancer. The surgeon, who is usually a specialized gynecologic oncology surgeon, may remove one (unilateral oophorectomy) or both ovaries (bilateral oophorectomy), the Fallopian tubes (salpingectomy), the uterus (hysterectomy), and the omentum (omentectomy). Typically, all of these are removed. For low-grade, unilateral stage-IA cancers, only the involved ovary (which must be unruptured) and Fallopian tube will be removed. This can be done especially in young people who wish to preserve their fertility. However, a risk of microscopic metastases exists and staging must be completed.[13] If any metastases are found, a second surgery to remove the remaining ovary and uterus is needed.[52] Tranexamic acid can be administered prior to surgery to reduce the need for blood transfusions due to blood loss during the surgery.[16]

If a tumor in a premenopausal woman is determined to be a low malignant potential tumor during surgery, and it is clearly stage I cancer, only the affected ovary is removed. For postmenopausal women with low malignant potential tumors, hysterectomy with bilateral salpingo-oophorectomy is still the preferred option. During staging, the appendix should be examined or removed. This is particularly important with mucinous tumors.[18] In children or adolescents with ovarian cancer, surgeons typically attempt to preserve one ovary to allow for the completion of puberty, but if the cancer has spread, this is not always possible. Dysgerminomas in particular tend to affect both ovaries: 8–15% of dysgerminomas are present in both ovaries.[19] People with low-grade (well-differentiated) tumors are typically treated only with surgery,[14] which is often curative.[44] In general, germ cell tumors can be treated with unilateral surgery unless the cancer is widespread or fertility is not a factor.[20]

In advanced cancers, where complete removal is not an option, as much tumor as possible is removed in a procedure called debulking surgery. This surgery is not always successful, and is less likely to be successful in women with extensive metastases in the peritoneum, stage- IV disease, cancer in the transverse fissure of the liver, mesentery, or diaphragm, and large areas of ascites. Debulking surgery is usually only done once.[13] More complete debulking is associated with better outcomes: women with no macroscopic evidence of disease after debulking have a median survival of 39 months, as opposed to 17 months with less complete surgery.[14] By removing metastases, many cells that are resistant to chemotherapy are removed, and any clumps of cells that have died are also removed. This allows chemotherapy to better reach the remaining cancer cells, which are more likely to be fast-growing and therefore chemosensitive.[18]

Interval debulking surgery is another protocol used, where neoadjuvant chemotherapy is given, debulking surgery is performed, and chemotherapy is finished after debulking.[52] Though no definitive studies have been completed, it is shown to be approximately equivalent to primary debulking surgery in terms of survival, and shows slightly lower morbidity.[18]

There are several different surgical procedures that can be employed to treat ovarian cancer. For stage I and II cancer, laparascopic (keyhole) surgery can be used, but metastases may not be found. For advanced cancer, laparoscopy is not used, since debulking metastases requires access to the entire peritoneal cavity. Depending on the extent of the cancer, procedures may include a bilateral salpingo-oophorectomy, biopsies throughout the peritoneum and abdominal lymphatic system, omentectomy, splenectomy, bowel resection, diaphragm stripping or resection, appendectomy, or even a posterior pelvic exenteration.[18]

To fully stage ovarian cancer, lymphadenectomy should be included in the surgery, but a significant survival benefit to this practice may not happen.[13] This is particularly important in germ cell tumors because they frequently metastasize to nearby lymph nodes.[14]

If ovarian cancer recurs, secondary surgery is sometimes a treatment option. This depends on how easily the tumor can be removed, how much fluid has accumulated in the abdomen, and overall health.[13] It can be helpful in people who had their first surgery done by a generalist and in epithelial ovarian cancer.[16] Secondary surgery can be effective in dysgerminomas and immature teratomas.[20]

The major side effect of an oophorectomy in younger women is early menopause, which can cause osteoporosis. After surgery, hormone replacement therapy can be considered, especially in younger women.

This therapy can consist of a combination of estrogen and progesterone, or estrogen alone. Estrogen alone is safe after hysterectomy; when the uterus is still present, unopposed estrogen dramatically raises the risk of endometrial cancer.[13] Estrogen therapy after surgery does not change survival rates.[16] People having ovarian cancer surgery are typically hospitalized afterwards for 3–4 days and spend around a month recovering at home.[53] Surgery outcomes are best at hospitals that do a large number of ovarian cancer surgeries.[18]

It is unclear if laparoscopy or laparotomy is better or worse for FIGO stage I ovarian cancer.[54][*needs update*] There is also no apparent difference between total abdominal hysterectomy and supracervical hysterectomy for advanced cancers. Approximately 2.8% of people having a first surgery for advanced ovarian cancer die within two weeks of the surgery (2.8% perioperative mortality rate).[16] More aggressive surgeries are associated with better outcomes in advanced (stage III or IV) ovarian cancer.[18]

## Chemotherapy [edit]

Chemotherapy has been a general standard of care for ovarian cancer for decades, although with highly variable protocols. Chemotherapy is used after surgery to treat any residual disease, if appropriate. In some cases, there may be reason to perform chemotherapy first, followed by surgery. This is called "neoadjuvant chemotherapy", and is common when a tumor cannot be completely removed or optimally debulked via surgery. Though it has not been shown to increase survival, it can reduce the risk of complications after surgery. If a unilateral salpingo-oophorectomy or other surgery is performed, additional chemotherapy, called "adjuvant chemotherapy", can be given.[13][16] Adjuvant chemotherapy is used in stage 1 cancer typically if the tumor is of a high histologic grade (grade 3) or the highest substage (stage 1c), provided the cancer has been optimally staged during surgery.[16][52] Bevacizumab may be used as an adjuvant chemotherapy if the tumor is not completely removed during surgery or if the cancer is stage IV; it can extend progression-free survival but has not been shown to extend overall survival.[16] Chemotherapy is curative in approximately 20% of advanced ovarian cancers;[18] it is more often curative with malignant germ cell tumors than epithelial tumors.[20]

Chemotherapy in ovarian cancer typically consists of platins, a group of platinum-based drugs, combined with non-platins. Common therapies can include paclitaxel, cisplatin, topotecan, doxorubicin, epirubicin, and gemcitabine. Carboplatin is typically given in combination with either paclitaxel or docetaxel; the typical combination is carboplatin with paclitaxel.[13][16] Carboplatin is superior to cisplatin in that it is less toxic and has fewer side effects, generally allowing for an improved quality of life in comparison, though both are similarly effective.[16] Three-drug regimens have not been found to be more effective,[13] and platins alone or nonplatins alone are less effective than platins and nonplatins in combination.[16] Chemotherapy can be given intravenously or in the peritoneal cavity.[14] Though intraperitoneal chemotherapy is associated with longer progression-free survival and overall survival, it also causes more adverse side effects than intravenous chemotherapy.[16] It is mainly used when the cancer has been optimally debulked. Intraperitoneal chemotherapy can be highly effective because ovarian cancer mainly spreads inside the peritoneal cavity, and higher doses of the drugs can reach the tumors this way.[18]

Chemotherapy can cause anemia; intravenous iron has been found to be more effective than oral iron supplements in reducing the need for blood transfusions.[16] Typical cycles of treatment involve one treatment every 3 weeks, repeated for 6 weeks or more.[55] Fewer than 6 weeks (cycles) of treatment is less effective than 6 weeks or more.[16] Germ-cell malignancies are treated differently than other ovarian cancers - a regimen of bleomycin, etoposide, and cisplatin (BEP) is used with 5 days of chemotherapy administered every 3 weeks for 3 to 4 cycles.[14][20] Chemotherapy for germ cell tumors has not been shown to cause amenorrhea, infertility, birth defects, or miscarriage.[20] Maintenance chemotherapy has not been shown to be effective.[16]

In people with *BRCA* mutations, platinum chemotherapy is more effective.[13] Germ-cell tumors and malignant sex-cord/stromal tumors are treated with chemotherapy, though dysgerminomas and sex-cord tumors are not typically very responsive.[14][19]

## Platinum-sensitive or platinum-resistant [edit]

If ovarian cancer recurs, it is considered partially platinum-sensitive or platinum-resistant, based on the time since the last recurrence treated with platins: partially platinum-sensitive cancers recurred 6–12 months after last treatment, and platinum-resistant cancers have an interval of less than 6 months. Second-line chemotherapy should be given only after the cancer becomes symptomatic, because no difference in survival is seen between treating asymptomatic (elevated CA-125) and symptomatic recurrences.

For platinum-sensitive tumors, platins are the drugs of choice for second-line chemotherapy, in combination with other cytotoxic agents. Regimens include carboplatin combined with pegylated liposomal doxorubicin, gemcitabine, or paclitaxel.[14] Carboplatin-doublet therapy can be combined with paclitaxel for increased efficacy in some cases. Another potential adjuvant therapy for platinum-sensitive recurrences is olaparib, which may improve progression-free survival but has not been shown to improve overall survival.[16] (Olaparib, a PARP inhibitor, was approved by the US FDA for use in BRCA-associated ovarian cancer that had previously been treated with chemotherapy.[56]) For recurrent germ cell tumors, an additional 4 cycles of BEP chemotherapy is the first-line treatment for those tho have been treated with surgery or platins.

If the tumor is determined to be platinum-resistant, vincristine, dactinomycin, and cyclophosphamide (VAC) or some combination of paclitaxel, gemcitabine, and oxaliplatin may be used as a second-line therapy.[20]

For platinum-resistant tumors, there are no high-efficacy chemotherapy options. Single-drug regimens (doxorubicin or topotecan) do not have high response rates,[13] but single-drug regimens of topotecan, pegylated liposomal doxorubicin, or gemcitabine are used in some cases.[14][16] Topotecan cannot be used in people with an intestinal blockage. Paclitaxel used alone is another possible regimen, or it may be combined with liposomal doxorubicin, gemcitabine, cisplatin, topotecan, etoposide, or cyclophosphamide.[55] ( See also Palliative care below.)

## Radiation therapy [edit]

Dysgerminomas are most effectively treated with radiation,[19] though this can cause infertility and is being phased out in favor of chemotherapy.[14] Radiation therapy does not improve survival in people with well-differentiated tumors.[14]

In stage 1c and 2 cancers, radiation therapy is used after surgery if there is the possibility of residual disease in the pelvis but the abdomen is cancer-free. Radiotherapy can also be used in palliative care of advanced cancers. A typical course of radiotherapy for ovarian cancer is 5 days a week for 3–4 weeks. Common side effects of radiotherapy include diarrhea, constipation, and frequent urination.[57]

## Hormonal therapy [edit]

Despite the fact that 60% of ovarian tumors have estrogen receptors, ovarian cancer is only rarely responsive to hormonal treatments. Estrogen alone does not have an effect on the cancer, and tamoxifen and letrozole are rarely effective.[13]

## Immunotherapy [edit]

Immunotherapy is a topic of current research in ovarian cancer. In some cases, the antibody drug bevacizumab, though still a topic of active research, is used to treat advanced cancer along with chemotherapy.[52] It has been approved for this use in the European Union.[58]

## Follow-up [edit]

Specific follow-up depends on, for example, the type and stage of ovarian cancer, the treatment, and the presence of any symptoms. Usually, a check-up appointment is made about every 2 to 3 months initially, followed by twice per year for up to 5 years.[59] For epithelial ovarian cancers, the most common test upon follow-up is CA-125 level. However, treatment based only on elevated CA-125 levels and not any symptoms

can increase side effects without any prolongation of life, so the implication of the outcome of a CA-125 test should be discussed before taking it.[60] The recommendation as of 2014 is recurrent cancer may be present if the CA-125 level is twice normal.[13] Treating a recurrence detected by CA-125 does not improve survival.[16]

For women with germ-cell tumors, follow-up tests generally include alpha-fetoprotein (AFP) and/or human chorionic gonadotropin. For women with stromal cancers, tests for hormones like estrogen, testosterone, and inhibin are sometimes helpful.[60] Inhibin can also be useful for monitoring the progress of sex-cord tumors, along with mullerian inhibiting substance. AFP can also be used to monitor Sertoli-Leydig tumors.[14] In dysgerminomas, lactate dehydrogenase and its two isozymes (LDH-1 and LDH-2) are used to test for recurrence.[20]

Women with ovarian cancer should not have routine surveillance imaging to monitor the cancer unless new symptoms appear or tumor markers begin rising.[61] Imaging without these indications is discouraged because it is unlikely to detect a recurrence, improve survival, and because it has its own costs and side effects.[61] However, CT imaging can be used if desired, though this is not common.[13] If a tumor is easily imaged, imaging may be used to monitor the progress of treatment.[62]

### Palliative care [edit]

Palliative care focuses on relieving symptoms and increasing or maintaining quality of life. It has been recommended as part of the treatment plan for any person with advanced ovarian cancer or patients with significant symptoms.[63] In platinum-refractory and platinum-resistant cases, palliative non-platin chemotherapy is the main treatment.[18]

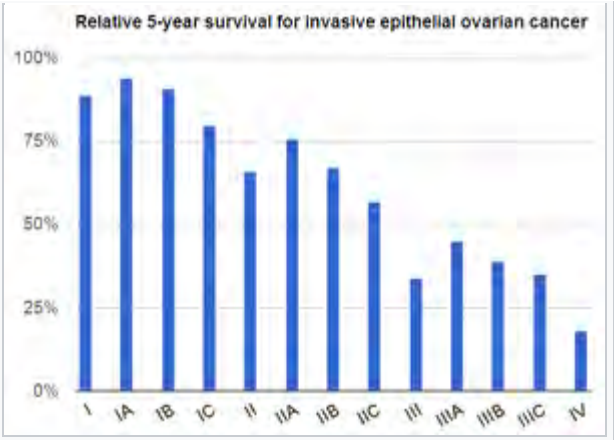
Palliative care can entail treatment of symptoms and complications of the cancer, including pain, nausea, constipation, ascites, bowel obstruction, edema, pleural effusion, and mucositis. Especially if the cancer advances and becomes incurable, treatment of symptoms becomes one of the main goals of therapy. Palliative care can also entail helping with decision-making such as if or when hospice care is appropriate, and the preferred place for the patient at end of life care.[16][64]

Bowel obstruction can be treated with palliative surgery (colostomy, ileostomy, or internal bypass) or medicine, but surgery has been shown to increase survival time.[13][16] Palliative surgery may result in short bowel syndrome, enterocutaneous fistula, or re-obstruction; or may not be possible due to the extent of obstruction.[18] Other treatments of complications can include total parenteral nutrition, a low-residue diet, palliative gastrostomy, and adequate pain control.[13] Bowel obstruction can also be treated with octreotide when palliative surgery is not an option. Cancer can also block the ureters, which can be relieved by a nephrostomy or a ureteric stent. Ascites can be relieved by repeated paracentesis or placement of a drain to increase comfort.[5] Pleural effusions can be treated in a similar manner, with repeated thoracentesis, pleurodesis, or placement of a drain.[18]

Radiation therapy can be used as part of the palliative care of advanced ovarian cancer, since it can help to shrink tumors that are causing symptoms. Palliative radiotherapy typically lasts for only a few treatments, a much shorter course of therapy than non-palliative radiotherapy.[57] It is also used for palliation of chemotherapy-resistant germ cell tumors.[20]

## Prognosis [edit]

Ovarian cancer usually has a relatively poor prognosis. It is disproportionately deadly because it lacks any clear early detection or screening test, meaning most cases are not diagnosed until they have reached advanced stages.[66] However, in some cases, ovarian cancer recurrences are chronically treatable.[13]



Relative five-year survival of invasive epithelial ovarian cancer by stage[65]

Ovarian cancer metastasizes early in its development, often before it has been diagnosed. High-grade tumors metastasize more readily than low-grade tumors. Typically, tumor cells begin to metastasize by growing in the peritoneal cavity.[14] More than 60% of women presenting with ovarian cancer have stage-III or stage-IV cancer, when it has already spread beyond the ovaries. Ovarian cancers shed cells into the naturally occurring fluid within the abdominal cavity. These cells can then implant on other abdominal (peritoneal) structures, including the uterus, urinary bladder, bowel, lining of the bowel wall, and omentum, forming new tumor growths before cancer is even suspected.

The five-year survival rate for all stages of ovarian cancer is 46%; the one-year survival rate is 72% and the ten-year survival rate is 35%.[67] For cases where a diagnosis is made early in the disease, when the cancer is still confined to the primary site, the five-year survival rate is 92.7%.[68] About 70% of women with advanced disease respond to initial treatment, most of whom attain complete remission, but half of these women experience a recurrence 1–4 years after treatment.[14] Brain metastasis is more common in stage III/IV cancer but can still occur in cancers staged at I/II. People with brain metastases survive a median of 8.2 months, though surgery, chemotherapy, and whole brain radiation therapy can improve survival.[16]

Ovarian cancer survival varies significantly with subtype. Dysgerminomas have a very favorable prognosis. In early stages, they have a five-year survival rate of 96.9%.[19] Around two-thirds of dysgerminomas are diagnosed at stage I.[20] Stage-III dysgerminomas have a five-year survival of 61%; when treated with BEP chemotherapy after incomplete surgical removal, dysgerminomas have a 95% two-year survival rate. Sex-cord-stromal malignancies also have a favorable prognosis; because they are slow-growing, even those with metastatic disease can survive a decade or more.[14] Low malignant potential tumors usually only have a bad prognosis when there are invasive tumor implants found in the peritoneal cavity.[18]

Complications of ovarian cancer can include spread of the cancer to other organs, progressive function loss of various organs, ascites, and intestinal obstructions, which can be fatal. Intestinal obstructions in multiple sites are the most common proximate cause of death.[13] Intestinal obstruction in ovarian cancer can either be a true obstruction, where tumor blocks the intestinal lumen, or a pseudo-obstruction, when tumor prevents normal peristalsis.[69] Continuous accumulation of ascites can be treated by placing a drain that can be self-drained.[13]

## Prognostic factors [edit]

There are a number of prognostic factors in ovarian cancer. Positive prognostic factors - those indicating better chances of survival - include no residual disease after surgery (stage III/IV), complete macroscopic resection (stage IV), BRCA2 mutations, young age (under 45 years), nonserous type, low histologic grade, early stage, co-occurrence with endometrial cancer, and low CA-125 levels. There is conflicting evidence for BRCA1 as a prognostic factor. Conversely, negative prognostic factors - those that indicate a worse chance of survival - include rupture of the ovarian capsule during surgery, older age (over 45 years), mucinous type, stage IV, high histologic grade, clear cell type, upper abdominal involvement, high CA-125 levels, the presence of tumor cells in the blood, and elevated cyclooxygenase-2.[16]

Expression of various mRNAs can also be prognostic for ovarian cancer. High levels of Drosha and Dicer are associated with improved survival, whereas high levels of let-7b, HIF1A, EphA1, and poly(ADP-ribose)

polymerase are associated with worse survival. Cancers that are positive for WT1 carry a worse prognosis; estrogen-receptor positive cancers have a better prognosis.[16]

## Survival rates [edit]

Overall five-year survival rates for all types of ovarian cancer are presented below by stage and histologic grade:[14]

| Stage | Survival |
|---|---|
| I | 90–95% |
| II | 70–80% |
| III | 20–50% |
| IV | 1–5% |

| Histologic grade | Survival |
|---|---|
| Low grade | 88% |
| Intermediate grade | 58% |
| High grade | 27% |

The survival rates given below are for the different types of ovarian cancer, according to American Cancer Society.[70] They come from the National Cancer Institute, SEER, and are based on patients diagnosed from 2004 to 2010.

| Invasive epithelial ovarian cancer | |
|---|---|
| **Stage** | **Relative five-year survival rate** |
| I | 90% |
| IA | 94% |
| IB | 92% |
| IC | 85% |
| II | 70% |
| IIA | 78% |
| IIB | 73% |
| III | 39% |
| IIIA | 59% |
| IIIB | 52% |
| IIIC | 39% |
| IV | 17% |

| Ovarian stromal tumors | |
|---|---|
| **Stage** | **Relative five-year survival rate** |
| I | 95% |
| II | 78% |
| III | 65% |
| IV | 35% |

| Germ cell tumors of the ovary | |
|---|---|
| **Stage** | **Relative 5-yr Survival Rate** |
| I | 98% |
| II | 94% |
| III | 87% |
| IV | 69% |

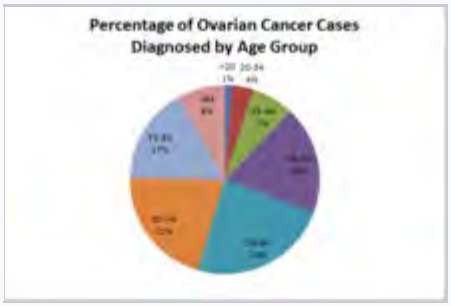
| Fallopian tube carcinoma | |
|---|---|
| **Stage** | **Relative five-year survival rate** |
| I | 87% |
| II | 86% |
| III | 52% |
| IV | 40% |

| Low malignant potential tumors[18] | |
|---|---|
| **Stage** | **Relative five-year survival rate** |
| I | 99% |
| II | 98% |
| III | 96% |
| IV | 77% |

## Recurrence rates [edit]

Ovarian cancer frequently recurs after treatment. Overall, in a 5-year period, 20% of stage I and II cancers recur. Most recurrences are in the abdomen.[18] If a recurrence occurs in advanced disease, it typically occurs within 18 months of initial treatment (18 months progression-free survival). Recurrences can be treated, but the disease-free interval tends to shorten and chemoresistance increases with each recurrence.[13] When a dysgerminoma recurs, it is most likely to recur within a year of diagnosis, and other malignant germ cell tumors recur within 2 years 90% of the time. Germ cell tumors other than dysgerminomas have a poor prognosis when they relapse, with a 10% long-term survival rate.[20] Low malignant potential tumors rarely relapse, even when fertility-sparing surgery is the treatment of choice. 15% of LMP tumors relapse after unilateral surgery in the previously unaffected ovary, and they are typically easily treated with surgery. More advanced tumors may take up to 20 years to relapse, if they relapse at all, and are only treated with surgery unless the tumor has changed its histological characteristics or grown very quickly. In these cases, and when there is significant ascites, chemotherapy may also be used. Relapse is usually indicated by rising CA-125 levels and then progresses to symptomatic relapse within 2–6 months.[18] Recurrent sex cord-stromal tumors are typically unresponsive to treatment but not aggressive.[20]

## Epidemiology [edit]




Ovarian cancer cases diagnosed by age group[68]

Globally, as of 2010, about 160,000 people died from ovarian cancer, up from 113,000 in 1990.[72] As of 2014, more than 220,000 diagnoses of epithelial ovarian cancer were made yearly.[13] In 2010, in the United States, an estimated 21,880 new cases were diagnosed and 13,850 women died of ovarian cancer. Around 1800 of the new diagnoses were sex-cord or stromal tumors.[14] In the United Kingdom as of 2014, approximately 7,000–7,100 yearly diagnoses were made and 4,200 deaths occurred.[13][21] It is the 5th most common cancer in UK women.[16][21] Ovarian cancer is most commonly diagnosed after menopause,[21] between the ages of 60 and 64. 90% of ovarian cancer occurs in women over the age of 45 and 80% in women over 50.[16] Germ cell tumors and sex cord-stromal tumors are far less common than epithelial tumors in US women, with incidence of 0.4 per 100,000 women and 0.2 per 100,000 women, respectively. When diagnosed in young people, they make up 1% of overall ovarian cancer.[20]

Age-standardized death from ovarian cancer per 100,000 inhabitants in 2004[71]

| | |
|---|---|
| no data | 3–3.6 |
| less than 0.6 | 3.6–4.2 |
| 0.6–1.2 | 4.2–4.8 |
| 1.2–1.8 | 4.8–5.4 |
| 1.8–2.4 | 5.4–6 |
| 2.4–3 | 6–7 |
| | more than 7 |

The overall lifetime risk is around 1.6%[14] (one woman in 48–70).[16] The risk in the UK is similar, at 1.7% (one woman in 60). Ashkenazi Jewish women carry mutated *BRCA* alleles at a rate five times that of the rest of the population, putting them at higher risk for ovarian cancer.[13] Black women are at double the risk for sex cord-stromal tumors compared to non-Black women.[20]

In the US, ovarian cancer affects 1.3–1.4% and is the cause of death of about 1% of women.[18][73] This made it the fifth-leading cause of cancer-related deaths with an estimated 15,000 deaths in 2008.[14][73] Ovarian cancer represents approximately 4% of cancers diagnosed in women.[16] It occurs more commonly in developed countries.[73] Ovarian cancer is the fifth-most common cancer in women in the UK (around 7,100 women were diagnosed with the disease in 2011), and it is the fifth-most common cause of cancer death in women (around 4,300 women died in 2012).[74] In the United States, it is also the fifth-most common cancer in women but the fourth-most common cause of cancer death.[16] It is the most deadly

gynecologic cancer.[18] In 2014, the incidence rate for women in developed countries was about 9.4 per 100,000, compared to 5.0 per 100,000 in developing countries.[13] In the US, the incidence rate in women over 50 is approximately 33 per 100,000.[75] In the UK, the incidence rate over the whole population is 21.6 per 100,000. In Europe, Lithuania, Latvia, Ireland, Slovakia, and the Czech Republic have the highest incidences of ovarian cancer, whereas Portugal and Cyprus have the lowest incidences. The overall incidence in Europe is approximately 5–15 per 100,000 women.[16]

The rate of ovarian cancer between 1993 and 2008 decreased in women of the 40–49 age cohort and in the 50–64 age cohort, possibly due to this group's widespread adoption of oral contraceptives.[13] This decrease made it the ninth-most common cancer in women.[18]

## In pregnancy [edit]

Malignant germ cell tumors are the type of ovarian cancer most likely to occur during pregnancy. They are typically diagnosed when an adnexal mass is found on examination (in 1–2% of all pregnancies), a tumor is seen on ultrasound, or the parent's level of alpha-fetoprotein is elevated. Dermoid cysts and dysgerminomas are the most common germ cell tumors during pregnancy. Germ cell tumors diagnosed during pregnancy are unlikely to have metastasized and can be treated by surgery and, in some cases, chemotherapy, which carries the risk of birth defects. Yolk sac tumors and immature teratomas grow particularly quickly and are usually treated with chemotherapy even during pregnancy; however, dysgerminomas that have been optimally debulked may be treated after childbirth.[20]

## Other animals [edit]

Ovarian tumors have been reported in equine mares. Reported tumor types include teratoma,[76][77] cystadenocarcinoma,[78] and particularly granulosa cell tumor.[79][80][81][82][83]

## Research [edit]

Researchers are assessing different ways to screen for ovarian cancer. Screening tests that could potentially be used alone or in combination for routine screening include the CA-125 marker and transvaginal ultrasound.[84] Doctors can measure the levels of the CA-125 protein in a woman's blood; high levels could be a sign of ovarian cancer, but this is not always the case, and not all women with ovarian cancer have high CA-125 levels. Transvaginal ultrasound involves using an ultrasound probe to scan the ovaries from inside the vagina, giving a clearer image than scanning the abdomen. The UK Collaborative Trial of Ovarian Cancer Screening is testing a screening technique that combines CA-125 blood tests with transvaginal ultrasound. Several large studies are going on, but none has identified an effective technique.[13][85] In 2009, however, early results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) showed that a technique combining annual CA-125 tests with ultrasound imaging did help to detect the disease at an early stage.[58][86] However, it's not yet clear if this approach could actually help to save lives —the full results of the trial will be published in 2015.[87] One major problem with screening is no clear progression of the disease from stage I (noninvasive) to stage III (invasive) is seen, and it may not be possible to find cancers before they reach stage III. Another problem is that screening methods tend to find too many suspicious lesions, most of which are not cancer, but malignancy can only be assessed with surgery.[13] The ROCA method combined with transvaginal ultrasonography is being researched in high-risk women to determine if it is a viable screening method. It is also being investigated in normal-risk women as it has shown promise in the wider population.[18] Studies are also in progress to determine if screening helps detect cancer earlier in people with BRCA mutations.[58]

Research into various prognostic factors for ovarian cancer is also going on. Recent research shows that thrombocytosis predicts lower survival and higher stage cancer.[13] Ongoing research is also investigating the benefits of surgery for recurrent ovarian cancer.[58]

While an active area of research, no immunotherapy has been shown to be effective as of 2013.[88] However, trials of the antibody and VEGF inhibitor bevacizumab, which can slow the growth of new blood vessels in the cancer, have shown promising results, especially in combination with pazopanib, which also slows the process of blood vessel growth. Bevacizumab has been particularly effective in preliminary studies on stage-III and -IV cancer[13] and has been cited as having at least a 15% response rate.[14] It is being investigated particularly in mucinous ovarian cancers.[58] Bevacizumab can also be combined with platinum chemotherapy, a combination that has had positive preliminary results in PFS, but equivocal results regarding overall survival. One disadvantage to these treatments is the side effect profile, which includes high blood pressure and proteinuria. The drug can also exacerbate bowel disease, leading to fistulae or bowel perforation. Vintafolide, which consists of an antifolate conjugated with vinblastine, is also in clinical trials; it may prove beneficial because folate receptors are overexpressed in many ovarian cancers.[13] Another potential immunotherapy is trastuzumab (Herceptin), which is active against tumors positive for Her2/neu mutations.[14] Other angiogenesis inhibitors are also being investigated as potential ovarian cancer treatments. Combretastatin and pazopanib are being researched in combination for recurrent ovarian cancer. Trebananib and tasquinimod are other angiogenesis inhibitors being investigated. The monoclonal antibody farletuzumab is being researched as an adjuvant to traditional chemotherapy. Another type of immunotherapy involves vaccines, including TroVax.[58]

An alternative to BEP chemotherapy, a regimen of 3 cycles of carboplatin and etoposide, is a current topic of research for germ cell malignancies.[20]

Intraperitoneal chemotherapy has also been under investigation during the 2000s and 2010s for its potential to deliver higher doses of cytotoxic agent to tumors. Preliminary trials with cisplatin and paclitaxel have shown it is not well tolerated, but does improve survival, and more tolerable regimens are being researched.[13] Cisplatin and paclitaxel are both being researched as intraperitoneal chemotherapy agents. A specific chemotherapy regimen for rare clear-cell cancers is also under investigation: irinotecan combined with cisplatin.[58]

PARP inhibitors have also shown promise in early trials, particularly in people with *BRCA* gene mutations, since the BRCA protein interacts with the PARP pathway. It is also being studied in recurrent ovarian cancer in general, where preliminary studies have shown longer PFS. Specifically, olaparib has shown greater survival compared to doxorubicin, though this treatment is still being investigated. It is not clear yet which biomarkers are predictive of responsiveness to PARP inhibitors.[13] Rucaparib is another PARP inhibitor being researched in BRCA-positive and BRCA-negative recurrent advanced ovarian cancer. Niraparib is a PARP inhibitor being tested in BRCA-positive recurrent ovarian cancer.[58]

mTOR inhibitors were a highly investigated potential treatment in the 2000s and 2010s, but the side effects of these drugs (particularly hyperglycemia and hyperlipidemia) were not well tolerated and the survival benefit not confirmed. PI3 kinase inhibitors have been of interest, but they tend to be highly toxic and cause diarrhea. Another investigated drug is selumetinib, a MAPK inhibitor. It improved survival, but did not correlate with any mutations found in tumors.[13]

Tyrosine kinase inhibitors are another investigational drug class that may have applications in ovarian cancer. Angiogenesis inhibitors in the receptor tyrosine kinase inhibitor group, including pazopanib, cediranib, and nintedanib, have also been shown to increase progression free survival (PFS), but their benefit for overall survival has not been investigated as of 2015.[13] Preliminary research showed that cediranib combined with platins in recurrent ovarian cancer increased the time to second recurrence by 3–4 months and increased survival by 3 months.[58] MK-1775 is a tyrosine kinase inhibitor that is being used in combination with paclitaxel and carboplatin in platinum-sensitive cancers with p53 mutations. Nintedanib is being researched as a potential therapy in combination with cyclophosphamide for people with recurrences.[58]

Hormone therapies are a topic of current research in ovarian cancer, particularly, the value of certain medications used to treat breast cancer. These include tamoxifen, letrozole, and anastrozole. Preliminary studies have showed a benefit for tamoxifen in a small number of people with advanced ovarian cancer. Letrozole may help to slow or stop growth of estrogen receptor positive ovarian cancer. Anastrozole is being investigated in postmenopausal people with estrogen receptor-positive cancer.[58]

Research into mitigating side effects of ovarian cancer treatment is also ongoing. Radiation fibrosis, the formation of scar tissue in an area treated with radiation, may be relieved with hyperbaric oxygen therapy, but research has not been completed in this area. Treatment of ovarian cancer may also cause people to experience psychiatric difficulties, including depression. Research is ongoing to determine how counseling and psychotherapy can help people who have ovarian cancer during treatment.[58]

## References [edit]


1. ^ a b c "Ovarian Cancer Prevention (PDQ®)". *NCI*. December 6, 2013. Retrieved 1 July 2014.
2. ^ "Defining Cancer". *National Cancer Institute*. Retrieved 10 June 2014.
3. ^ a b c d "Ovarian Epithelial Cancer Treatment (PDQ®)". *NCI*. 2014-05-12. Retrieved 1 July 2014.
4. ^ Ebell, MH; Culp, MB; Radke, TJ (March 2016). "A Systematic Review of Symptoms for the Diagnosis of Ovarian Cancer.". *American journal of preventive medicine*. **50** (3): 384–94. doi:10.1016/j.amepre.2015.09.023. PMID 26541098.
5. ^ a b "Treating advanced ovarian cancer". *www.cancerresearchuk.org*. Retrieved 2015-05-16.
6. ^ Ruddon, Raymond W. (2007). *Cancer biology* (4th ed.). Oxford: Oxford University Press. p. 223. ISBN 9780195175431.
7. ^ a b c d e f g *World Cancer Report 2014*. World Health Organization. 2014. Chapter 5.12. ISBN 9283204298.
8. ^ a b "Ovarian Cancer Prevention (PDQ®)". *NCI*. 2014-06-20. Retrieved 1 July 2014.
9. ^ Piek JM, van Diest PJ, Verheijen RH (2008). "Ovarian carcinogenesis: an alternative hypothesis". *Adv. Exp. Med. Biol*. Advances in Experimental Medicine and Biology. **622**: 79–87. doi:10.1007/978-0-387-68969-2_7. ISBN 978-0-387-68966-1. PMID 18546620.
10. ^ Moyer VA (Dec 18, 2012). "Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement.". *Annals of Internal Medicine*. **157** (12): 900–4. doi:10.7326/0003-4819-157-11-201212040-00539. PMID 22964825.
11. ^ "SEER Stat Fact Sheets: Ovary Cancer". *NCI*. Retrieved 18 June 2014.
12. ^ "What are the risk factors for ovarian cancer?". *www.cancer.org*. 02/04/2016. Retrieved 18 May 2016. Check date values in: `|date=` (help)
13. ^ a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af ag ah ai aj ak al am an ao ap aq ar as at au av aw ax ay az ba bb bc bd be bf Jayson GC, Kohn EC, Kitchener HC, Ledermann JA (October 2014). "Ovarian cancer". *Lancet*. **384** (9951): 1376–88. doi:10.1016/S0140-6736(13)62146-7. PMID 24767708.
14. ^ a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af ag ah ai aj ak al am an ao ap aq ar as at au av aw ax ay az ba bb bc Seiden MV (2012). "Gynecologic Malignancies". In Longo DL, Kasper DL, Jameson JL, Fauci AS, Hauser SL, Loscalzo J. *Harrison's Principles of Internal Medicine* (18th ed.). McGraw-Hill. ISBN 978-0-07-174889-6.
15. ^ a b "Ovarian cancer symptoms". *www.cancerresearchuk.org*. Retrieved 2015-05-16.
16. ^ a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af ag ah ai aj ak al am an ao ap aq ar as at au av aw ax ay az ba bb bc bd be bf bg bh bi bj bk bl bm bn bo bp bq br bs "Ovarian cancer". DynaMed. June 18, 2015. (subscription required (help)).
17. ^ Goff BA (June 2012). "Ovarian cancer: screening and early detection". *Obstetrics and gynecology clinics of North America*. **39** (2): 183–94. doi:10.1016/j.ogc.2012.02.007. PMID 22640710.
18. ^ a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af ag ah ai aj ak al am an ao ap aq ar as at au av aw ax ay az ba bb bc bd be bf bg bh bi bj bk bl bm bn bo bp bq br bs bt Hoffman, Barbara L.; Schorge, John O.; Schaffer, Joseph I.; Halvorson, Lisa M.; Bradshaw, Karen D.; Cunningham, F. Gary (2012). "Epithelial Ovarian Cancer". *Williams Gynecology* (2nd ed.). McGraw Hill Medical. pp. 853–878. ISBN 978-0-07-171672-7.
19. ^ a b c d e f g DeCherney, Alan; Nathan, Lauren; Goodwin, T. Murphy; Laufer, Neri; Roman, Ashley (2012). "Pediatric and Adolescent Gynecology". *Current Diagnosis & Treatment Obstetrics & Gynecology* (11th ed.). ISBN 978-0071638562.
20. ^ a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af ag ah ai aj ak al am an ao Hoffman BL, Schorge JO, Schaffer JI, Halvorson LM, Bradshaw KD, Cunningham F, Calver LE (2012). *Ovarian Germ Cell and Sex Cord-Stromal Tumors*. *Williams Gynecology* (2nd ed.). McGraw Hill.
21. ^ a b c d e f g h i j k l m n o p "Ovarian cancer risks and causes". Cancer Research UK. 15 January 2014. Retrieved 29 January 2015.
22. ^ Manson JE, Bassuk SS (2012). "The Menopause Transition and Postmenopausal Hormone Therapy". In Longo DL, Kasper DL, Jameson JL, Fauci AS, Hauser SL, Loscalzo J. *Harrison's Principles of Internal Medicine* (18th ed.).

McGraw-Hill. ISBN 978-0-07-174889-6.
23. ^ Gong, Ting-Ting; Wu, Qi-Jun; Vogtmann, Emily; Lin, Bei; Wang, Yong-Lai (2013-06-15). "Age at menarche and risk of ovarian cancer: a meta-analysis of epidemiological studies". *International Journal of Cancer. Journal International Du Cancer*. **132** (12): 2894–2900. doi:10.1002/ijc.27952. ISSN 0020-7136. PMC 3806278. PMID 23175139.
24. ^ "Ovarian Cancer Prevention (PDQ®)". National Cancer Institute. 2013. Retrieved 2013-12-30.
25. ^ Kyriakidis I, Papaioannidou P (2016). "Estrogen receptor beta and ovarian cancer: a key to pathogenesis and response to therapy". *Arch Gynecol Oncol*. **293** (6): 1161–8. doi:10.1007/s00404-016-4027-8. PMID 26861465.
26. ^ Norquist BM, Harrell MI, Brady MF, Walsh T, Lee MK, Gulsuner S, Bernards SS, Casadei S, Yi Q, Burger RA, Chan JK, Davidson SA, Mannel RS, DiSilvestro PA, Lankes HA, Ramirez NC, King MC, Swisher EM, Birrer MJ (2015). "Inherited mutations in women With ovarian carcinoma". *JAMA Oncol*. **30**: 1–9. doi:10.1001/jamaoncol.2015.5495.
27. ^ Kuusisto KM, Bebel A, Vihinen M, Schleutker J, Sallinen SL (2011). "Screening for BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD50, and CDH1 mutations in high-risk Finnish BRCA1/2-founder mutation-negative breast and/or ovarian cancer individuals". *Breast Cancer Res*. **13** (1): R20. doi:10.1186/bcr2832.
28. ^ Salehi, Fariba; Dunfield, Lesley; Phillips, Karen P.; Krewski, Daniel; Vanderhyden, Barbara C. (1 March 2008). "Risk factors for ovarian cancer: an overview with emphasis on hormonal factors". *Journal of Toxicology and Environmental Health. Part B, Critical Reviews*. **11**: 301–321. doi:10.1080/10937400701876095. PMID 18368558.
29. ^ "Do we know what causes ovarian cancer?". *www.cancer.org*.
30. ^ Hjartåker A, Meo MS, Weiderpass E (January 2010). "Alcohol and gynecological cancers: an overview". *European Journal of Cancer Prevention*. **19** (1): 1–10. doi:10.1097/CEJ.0b013e328333fb3a. PMID 19926999.
31. ^ Zhang X, Nicosia SV, Bai W (2006). "Vitamin D receptor is a novel drug target for ovarian cancer treatment". *Curr Cancer Drug Targets*. **6** (3): 229–44. doi:10.2174/156800906776842939. PMID 16712459.
32. ^ Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA (2015). "Sedentary Time and Its Association With Risk for Disease Incidence, Mortality, and Hospitalization in Adults: A Systematic Review and Meta-analysis". *Annals of Internal Medicine*. **162** (2): 123–32. doi:10.7326/M14-1651. PMID 25599350.
33. ^ Margolies, Liz (7 October 2013). "Ovarian Cancer in Transgender Men". National LGBT Cancer Network. Retrieved 5 May 2015.
34. ^ *a b* Odunsi, Kunle; Pejovic, Tanja; Anderson, Matthew L. (2011). *Molecular Biology of Gynecologic Cancers*. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. Wolters Kluwer/Lippincott Williams & Wilkins. pp. 1302–1310. ISBN 978-1-4511-0545-2.
35. ^ *a b* Chen, Ning; Karantza-Wadsworth, Vassiliki (2009-09-01). "Role and regulation of autophagy in cancer". *Biochimica et Biophysica Acta*. **1793** (9): 1516–1523. doi:10.1016/j.bbamcr.2008.12.013. ISSN 0006-3002. PMC 3155287. PMID 19167434.
36. ^ "Genetics of Breast and Ovarian Cancer (PDQ®)". NCI. 2 October 2014. Retrieved 27 October 2014.
37. ^ Rossing MA, Wicklund KG, Cushing-Haugen KL, Weiss NS (2010-01-28). "Predictive Value of Symptoms for Early Detection of Ovarian Cancer". *J Natl Cancer Inst*. **102** (4): 222–9. doi:10.1093/jnci/djp500. PMC 2826180. PMID 20110551.
38. ^ *a b c* Miller RW, Ueland FR (March 2012). "Risk of malignancy in sonographically confirmed ovarian tumors.". *Clinical obstetrics and gynecology*. **55** (1): 52–64. doi:10.1097/GRF.0b013e31824970cf. PMID 22343229.
39. ^ "Ovarian cancer tests". *www.cancerresearchuk.org*. Retrieved 2015-05-16.
40. ^ Dunn, J. D. (ed.). "Associated Title(s): PROTEOMICS – Clinical Applications". **11** (15). ISSN 1615-9861.
41. ^ "Guideline CG122. Ovarian cancer: The recognition and initial management of ovarian cancer, Appendix D: Risk of malignancy index (RMI I)." . *NICE clinical guidelines*. April 2011.
42. ^ Geomini, Peggy; Kruitwagen, Roy; Bremer, Gérard L.; Cnossen, Jeltsje; Mol, Ben W. J. (Feb 2009). "The accuracy of risk scores in predicting ovarian malignancy: a systematic review". *Obstetrics and Gynecology*. **113** (2 Pt 1): 384–394. doi:10.1097/AOG.0b013e318195ad17. ISSN 0029-7844. PMID 19155910.
43. ^ *a b* Kosary, Carol L. (2007). "Chapter 16: Cancers of the Ovary" (PDF). In Baguio, RNL; Young, JL; Keel, GE; Eisner, MP; Lin, YD; Horner, M-J. *SEER Survival Monograph: Cancer Survival Among Adults: US SEER Program, 1988–2001, Patient and Tumor Characteristics*. SEER Program. NIH Pub. No. 07-6215. Bethesda, MD: National Cancer Institute. pp. 133–144.
44. ^ *a b c d e f g h i* "Types of ovarian cancer". *www.cancerresearchuk.org*. Retrieved 2015-05-16.
45. ^ *a b c* Levy, Gary; Purcell; Karen (2013). DeCherney, AH; Nathan, L; Laufer, N; et al., eds. *Premalignant & Malignant Disorders of the Ovaries & Oviducts*. *CURRENT Diagnosis & Treatment: Obstetrics & Gynecology, 11e*. McGraw-Hill.

46. ^ "Primary peritoneal carcinoma" . *www.cancerresearchuk.org*. Retrieved 2015-05-16.
47. ^ a b "Ovarian Cancer Staging" (PDF). Society for Gynecologic Oncology. 1 January 2014.
48. ^ "How is ovarian cancer staged?". Retrieved July 27, 2010.
49. ^ "Diagnosis and Staging". Retrieved July 27, 2010.
50. ^ "Stages of ovarian cancer". *www.cancerresearchuk.org*. Retrieved 2015-05-16.
51. ^ a b c Croswell JM, Brawley OW, Kramer BS (2012). "Prevention and Early Detection of Cancer". In Longo DL, Kasper DL, Jameson JL, Fauci AS, Hauser SL, Loscalzo J. *Harrison's Principles of Internal Medicine* (18th ed.). McGraw-Hill. ISBN 978-0-07-174889-6.
52. ^ a b c d e "Types of treatment for ovarian cancer". *www.cancerresearchuk.org*. Retrieved 2015-05-16.
53. ^ "Surgery for ovarian cancer". *www.cancerresearchuk.org*. Retrieved 2015-05-16.
54. ^ Lawrie, TA; Medeiros, LR; Rosa, DD; da Rosa, MI; Edelweiss, MI; Stein, AT; Zelmanowicz, A; Ethur, AB; Zanini, RR (28 February 2013). "Laparoscopy versus laparotomy for FIGO stage I ovarian cancer.". *The Cochrane database of systematic reviews*. **2**: CD005344. doi:10.1002/14651858.CD005344.pub3. PMID 23450560.
55. ^ a b "Drugs used for ovarian cancer". *www.cancerresearchuk.org*. Retrieved 2015-05-16.
56. ^ Yao, Stephanie (19 December 2014). "FDA approves Lynparza to treat advanced ovarian cancer: First LDT companion diagnostic test also approved to identify appropriate patients". U.S. Food and Drug Administration.
57. ^ a b "Radiotherapy for ovarian cancer". *www.cancerresearchuk.org*. Retrieved 2015-05-16.
58. ^ a b c d e f g h i j k l "Ovarian cancer research". *www.cancerresearchuk.org*. Retrieved 2015-05-16.
59. ^ "Follow up for ovarian cancer". Cancer Research UK.
60. ^ a b Follow-up care from American Cancer Society. Last Medical Review: 03/21/2013. Last Revised: 02/06/2014
61. ^ a b Society of Gynecologic Oncology (February 2014), "Five Things Physicians and Patients Should Question", *Choosing Wisely: an initiative of the ABIM Foundation*, Society of Gynecologic Oncology, retrieved 19 February 2013, which cites
    - Bhosale P, Peungjesada S, Wei W, Levenback CF, Schmeler K, Rohren E, Macapinlac HA, Iyer RB (August 2010). "Clinical Utility of Positron Emission Tomography/Computed Tomography in the Evaluation of Suspected Recurrent Ovarian Cancer in the Setting of Normal CA-125 Levels". *International Journal of Gynecological Cancer*. **20** (6): 936–944. doi:10.1111/IGC.0b013e3181e82a7f. PMID 20683399.
62. ^ "Chemotherapy for ovarian cancer". *www.cancerresearchuk.org*. Retrieved 2015-05-16.
63. ^ "ASCO Provisional Clinical Opinion: The Integration of Palliative Care into Standard Oncology Care". ASCO. Archived from the original on 21 August 2014. Retrieved 20 August 2014.
64. ^ Radwany SM, von Gruenigen VE (Mar 2012). "Palliative and end-of-life care for patients with ovarian cancer.". *Clinical obstetrics and gynecology*. **55** (1): 173–84. doi:10.1097/grf.0b013e31824b1af1. PMID 22343236.
65. ^ "Survival rates for ovarian cancer". American Cancer Society. April 22, 2013. Retrieved 2013-12-30.
66. ^ Society of Gynecologic Oncology (February 2014), "Five Things Physicians and Patients Should Question", *Choosing Wisely: an initiative of the ABIM Foundation*, Society of Gynecologic Oncology, retrieved 19 February 2013, which cites
    - Smith TJ, Temin S, Alesi ER, Abernethy AP, Balboni TA, Basch EM, Ferrell BR, Loscalzo M, Meier DE, Paice JA, Peppercorn JM, Somerfield M, Stovall E, Von Roenn JH (6 February 2012). "American Society of Clinical Oncology Provisional Clinical Opinion: The Integration of Palliative Care Into Standard Oncology Care". *Journal of Clinical Oncology*. **30** (8): 880–887. doi:10.1200/JCO.2011.38.5161. PMID 22312101.
    - Rezk Y, Timmins PF, Smith HS (26 December 2010). "Review Article: Palliative Care in Gynecologic Oncology". *American Journal of Hospice and Palliative Medicine*. **28** (5): 356–374. doi:10.1177/1049909110392204. PMID 21187291.
    - Lewin SN, Buttin BM, Powell MA, Gibb RK, Rader JS, Mutch DG, Herzog TJ (November 2005). "Resource utilization for ovarian cancer patients at the end of life: How much is too much?". *Gynecologic Oncology*. **99** (2): 261–266. doi:10.1016/j.ygyno.2005.07.102. PMID 16140364.
67. ^ "Statistics and outlook for ovarian cancer". *www.cancerresearchuk.org*. Retrieved 2015-05-16.
68. ^ a b Survival rates based on SEER incidence and NCHS mortality statistics, as cited by the National Cancer Institute in SEER Stat Fact Sheets — Cancer of the Ovary
69. ^ Gucalp R, Dutcher J (2012). "Oncologic Emergencies". In Longo DL, Kasper DL, Jameson JL, Fauci AS, Hauser SL, Loscalzo J. *Harrison's Principles of Internal Medicine* (18th ed.). McGraw-Hill. ISBN 978-0-07-174889-6.
70. ^ "Survival rates for ovarian cancer, by stage". *American Cancer Society*. Retrieved 29 October 2014.
71. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved November 11, 2009.
72. ^ Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al. (15 December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.

73. ^ [a] [b] [c] Ramirez, Pedro T.; Gershenson, David M. (September 2013). "Ovarian Cancer". *The Merck Manual for Health Care Professionals*.
74. ^ "Ovarian cancer statistics". *Cancer Research UK*. Retrieved 28 October 2014.
75. ^ Hennessy, Bryan T.; Suh, Grace K.; Markman, Maurie (2011). Kantarjian, HM; Wolff, RA; Koller, CA, eds. *Ovarian Cancer*. *The MD Anderson Manual of Medical Oncology*. McGraw-Hill.
76. ^ Catone G, Marino G, Mancuso R, Zanghì A (April 2004). "Clinicopathological features of an equine ovarian teratoma". *Reprod. Domest. Anim*. **39** (2): 65–9. doi:10.1111/j.1439-0531.2003.00476.x. PMID 15065985.
77. ^ Lefebvre R, Theoret C, Doré M, Girard C, Laverty S, Vaillancourt D (November 2005). "Ovarian teratoma and endometritis in a mare". *Can. Vet. J.* **46** (11): 1029–33. PMC 1259148. PMID 16363331.
78. ^ Son YS, Lee CS, Jeong WI, Hong IH, Park SJ, Kim TH, Cho EM, Park TI, Jeong KS (May 2005). "Cystadenocarcinoma in the ovary of a Thoroughbred mare". *Aust. Vet. J.* **83** (5): 283–4. doi:10.1111/j.1751-0813.2005.tb12740.x. PMID 15957389.
79. ^ Frederico LM, Gerard MP, Pinto CR, Gradil CM (May 2007). "Bilateral occurrence of granulosa-theca cell tumors in an Arabian mare". *Can. Vet. J.* **48** (5): 502–5. PMC 1852596. PMID 17542368.
80. ^ Hoque S, Derar RI, Osawa T, Taya K, Watanabe G, Miyake Y (June 2003). "Spontaneous repair of the atrophic contralateral ovary without ovariectomy in the case of a granulosa theca cell tumor (GTCT) affected mare" ( – Scholar search). *J. Vet. Med. Sci*. **65** (6): 749–51. doi:10.1292/jvms.65.749. PMID 12867740.[*dead link*]
81. ^ Sedrish SA, McClure JR, Pinto C, Oliver J, Burba DJ (November 1997). "Ovarian torsion associated with granulosa-theca cell tumor in a mare". *J. Am. Vet. Med. Assoc*. **211** (9): 1152–4. PMID 9364230.
82. ^ Moll HD, Slone DE, Juzwiak JS, Garrett PD (1987). "Diagonal paramedian approach for removal of ovarian tumors in the mare". *Vet Surg*. **16** (6): 456–8. doi:10.1111/j.1532-950X.1987.tb00987.x. PMID 3507181.
83. ^ Doran R, Allen D, Gordon B (January 1988). "Use of stapling instruments to aid in the removal of ovarian tumours in mares". *Equine Vet. J.* **20** (1): 37–40. doi:10.1111/j.2042-3306.1988.tb01450.x. PMID 2835223.
84. ^ Russell MR, Walker MJ, Williamson AJ, Gentry-Maharaj A, Ryan A, Kalsi J, Skates S, D'Amato A, Dive C, Pernemalm M, Humphryes PC, Fourkala EO, Whetton AD, Menon U, Jacobs I, Graham RL (2016). "Protein Z: A putative novel biomarker for early detection of ovarian cancer". *Int. J. Cancer*. **138** (12): 2984–92. doi:10.1002/ijc.30020. PMC 4840324. PMID 26815306.
85. ^ Partridge E, Kreimer AR, Greenlee RT, Williams C, Xu JL, Church TR, Kessel B, Johnson CC, Weissfeld JL, Isaacs C, Andriole GL, Ogden S, Ragard LR, Buys SS (April 2009). "Results from four rounds of ovarian cancer screening in a randomized trial". *Obstet Gynecol*. **113** (4): 775–82. doi:10.1097/AOG.0b013e31819cda77. PMC 2728067. PMID 19305319.
86. ^ Menon U, Gentry-Maharaj A, Hallett R, Ryan A, Burnell M, Sharma A, Lewis S, Davies S, Philpott S, Lopes A, Godfrey K, Oram D, Herod J, Williamson K, Seif MW, Scott I, Mould T, Woolas R, Murdoch J, Dobbs S, Amso NN, Leeson S, Cruickshank D, McGuire A, Campbell S, Fallowfield L, Singh N, Dawnay A, Skates SJ, Parmar M, Jacobs I (April 2009). "Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)". *Lancet Oncol*. **10** (4): 327–40. doi:10.1016/S1470-2045(09)70026-9. PMID 19282241. Lay summary – *Cancer Research UK, Science Update blog* (March 2009).
87. ^ Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, Amso NN, Apostolidou S, Benjamin E, Cruickshank D, Crump DN, Davies SK, Dawnay A, Dobbs S, Fletcher G, Ford J, Godfrey K, Gunu R, Habib M, Hallett R, Herod J, Jenkins H, Karpinskyj C, Leeson S, Lewis SJ, Liston WR, Lopes A, Mould T, Murdoch J, Oram D, Rabideau DJ, Reynolds K, Scott I, Seif MW, Sharma A, Singh N, Taylor J, Warburton F, Widschwendter M, Williamson K, Woolas R, Fallowfield L, McGuire AJ, Campbell S, Parmar M, Skates SJ (2016). "Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial". *Lancet*. **387** (10022): 945–56. doi:10.1016/S0140-6736(15)01224-6. PMC 4779792. PMID 26707054.
88. ^ Leffers N, Daemen T, Helfrich W, Boezen HM, Cohlen BJ, Melief CJ, Nijman HW (Sep 17, 2014). "Antigen-specific active immunotherapy for ovarian cancer". *The Cochrane database of systematic reviews*. **9**: CD007287. doi:10.1002/14651858.CD007287.pub3. PMID 25229990.


## Further reading [edit]


- Cannistra SA (December 2004). "Cancer of the ovary". *N. Engl. J. Med*. **351** (24): 2519–29. doi:10.1056/NEJMra041842. PMID 15590954.


## External links [edit]

- "Ovarian Cancer". American Cancer Society.
- Petrucelli N, Daly MB, Feldman GL (2013). *BRCA1 and BRCA2 Hereditary Breast/Ovarian Cancer*. PMID 20301425. NBK1247. In Pagon RA, Bird TD, Dolan CR, et al., eds. (1993–). *GeneReviews™ [Internet]*. Seattle WA: University of Washington, Seattle. Check date values in: `|date=` (help)
- Interactive Health Tutorials Medline Plus: Ovarian cancer Using animated graphics and you can also listen to the tutorial
- UK statistics for ovarian cancer
- "Ovarian cancer". *About Cancer*. Cancer Research UK.
- What is Ovarian Cancer Infographic, information on ovarian cancer - Mount Sinai Hospital, New York


| v · t · e · | **Tumors: female urogenital neoplasia (C51–C58/D25–D28, 179–184/218–221)** | | |
|---|---|---|---|
| **Adnexa** | **Ovaries** | **Glandular and epithelial/ surface epithelial-stromal tumor** | **CMS:** Ovarian serous cystadenoma · Mucinous cystadenoma · Cystadenocarcinoma (Papillary serous cystadenocarcinoma · · Krukenberg tumor · |
| | | | Endometrioid tumor · Clear-cell ovarian carcinoma · Brenner tumour · |
| | | **Sex cord-gonadal stromal** | Leydig cell tumour · Sertoli cell tumour · Sertoli-Leydig cell tumour · Thecoma · Granulosa cell tumour · Luteoma · Sex cord tumour with annular tubules · Steroid cell tumor (NOS) · |
| | | **Germ cell** | Dysgerminoma · Nongerminomatous (Embryonal carcinoma · Endodermal sinus tumor · Gonadoblastoma · Teratoma/Struma ovarii · Choriocarcinoma · · |
| | | **Fibroma** | Meigs syndrome · |
| | **Fallopian tube** | Adenomatoid tumor · | |
| **Uterus** | **Myometrium** | Uterine fibroids/leiomyoma · Leiomyosarcoma · Adenomyoma · | |
| | **Endometrium** | Endometrioid tumor · Uterine papillary serous carcinoma · Clear cell carcinoma · Endometrial intraepithelial neoplasia · | |
| | **Cervix** | Cervical intraepithelial neoplasia · SCC · Glassy cell carcinoma · Villoglandular adenocarcinoma · | |
| | **Placenta** | Choriocarcinoma · Gestational trophoblastic disease · | |
| | **General** | Uterine sarcoma · Mixed Müllerian tumor · | |
| **Vagina** | SCC · Botryoid rhabdomyosarcoma · Clear cell adenocarcinoma of the vagina · Vaginal intraepithelial neoplasia · | | |
| **Vulva** | SCC · Melanoma · Papillary hidradenoma · Extramammary Paget's disease · Vulvar intraepithelial neoplasia · Bartholin gland carcinoma · | | |
| **Authority control** | NDL: 00569292 · | | |

Categories: Ovarian cancer | Gynaecological cancer | Gynaecology


# Pancreatic cancer



From Wikipedia, the free encyclopedia

**Pancreatic cancer** arises when cells in the pancreas, a glandular organ behind the stomach, begin to multiply out of control and form a mass. These cancerous cells have the ability to invade other parts of the body.[1] There are a number of types of pancreatic cancer. The most common, **pancreatic adenocarcinoma**, accounts for about 85% of cases, and the term "pancreatic cancer" is sometimes used to refer only to that type. These adenocarcinomas start within the part of the pancreas which makes digestive enzymes. Several other types of cancer, which collectively represent the majority of the non-adenocarcinomas, can also arise from these cells. One to two percent of cases of pancreatic cancer are neuroendocrine tumors, which arise from the hormone-producing cells of the pancreas. These are generally less aggressive than pancreatic adenocarcinoma.[2]

Signs and symptoms of the most common form of pancreatic cancer may include yellow skin, abdominal or back pain, unexplained weight loss, light-colored stools, dark urine and loss of appetite.[3] There are usually no symptoms in the disease's early stages, and symptoms that are specific enough to suggest pancreatic cancer typically do not develop until the disease has reached an advanced stage.[3][4] By the time of diagnosis, pancreatic cancer has often spread to other parts of the body.[2][5]

Pancreatic cancer rarely occurs before the age of 40, and more than half of cases of pancreatic adenocarcinoma occur in those over 70.[4] Risk factors for pancreatic cancer include tobacco smoking, obesity, diabetes, and certain rare genetic conditions.[4] About 25% of cases are linked to smoking,[6] and 5–10% are linked to inherited genes.[4] Pancreatic cancer is usually diagnosed by a combination of medical imaging techniques such as ultrasound or computed tomography, blood tests, and examination of tissue samples (biopsy).[6][7] The disease is divided into stages, from early (stage I) to late (stage IV).[5] Screening the general population has not been found to be effective.[8]

The risk of developing pancreatic cancer is lower among non-smokers, and people who maintain a healthy weight and limit their consumption of red or processed meat.[9] A smoker's chance of developing the disease decreases if they stop smoking, and almost returns to that of the rest of the population after 20 years.[2] Pancreatic cancer can be treated with surgery, radiotherapy, chemotherapy, palliative care, or

**Pancreatic cancer**

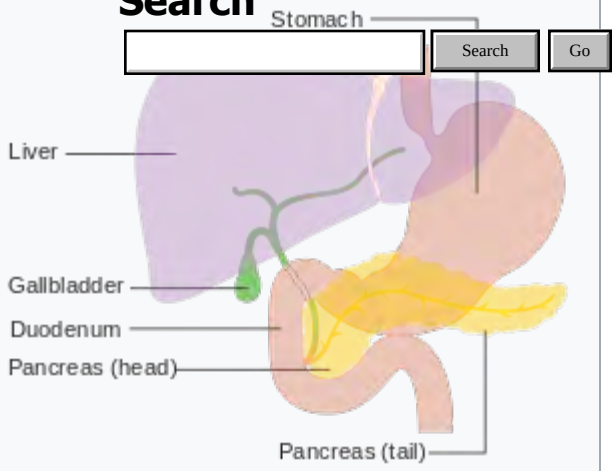



Diagram showing the position of the pancreas, behind the stomach (which is transparent in this schematic).

| Classification and external resources | |
|---|---|
| **Specialty** | Oncology |
| **ICD-10** | C25 |
| **ICD-9-CM** | 157 |
| **OMIM** | 260350 |
| **DiseasesDB** | 9510 |
| **MedlinePlus** | 000236 |
| **eMedicine** | med/1712 |
| **MeSH** | D010190 |

[edit on Wikidata]

a combination of these. Treatment options are partly based on the cancer stage. Surgery is the only treatment that can cure pancreatic adenocarcinoma,[5] and may also be done to improve quality of life without the potential for cure.[3][5] Pain management and medications to improve digestion are sometimes needed.[5] Early palliative care is recommended even for those receiving treatment that aims for a cure.[10][11]

In 2012, pancreatic cancers of all types were the seventh most common cause of cancer deaths, resulting in 330,000 deaths globally.[2] Pancreatic cancer is the fifth most common cause of death from cancer in the United Kingdom,[12] and the fourth most common in the United States.[13][14] The disease occurs most often in the developed world, where about 70% of the new cases in 2012 originated.[2] Pancreatic adenocarcinoma typically has a very poor prognosis: after diagnosis, 25% of people survive one year and 5% live for five years.[2][15] For cancers diagnosed early, the five-year survival rate rises to about 20%.[16] Neuroendocrine cancers have better outcomes; at five years from diagnosis, 65% of those diagnosed are living, though survival varies considerably depending on the type of tumor.[2]

Contents

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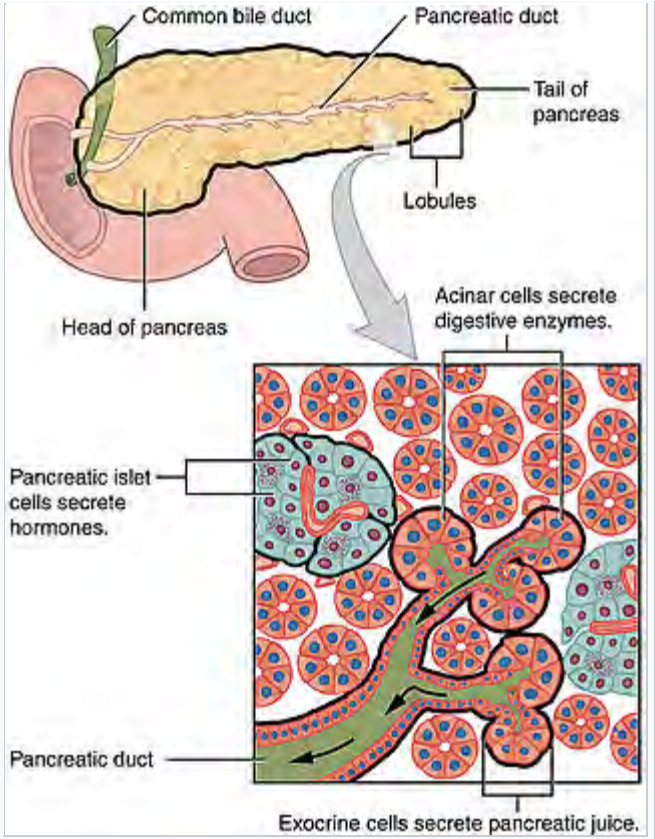
Video explanation

## Types [edit]

The many types of pancreatic cancer can be divided into two general groups. The vast majority of cases (about 99%) occur in the part of the pancreas which produces digestive enzymes, known as the exocrine component. There are several sub-types of exocrine pancreatic cancers, but their diagnosis and treatment have much in common. The small minority of cancers that arise in the hormone-producing (endocrine) tissue of the pancreas




The pancreas has multiple functions, served by the endocrine cells in the islets of Langerhans and the exocrine acinar cells. Pancreatic cancer may arise from any of these and disrupt any of their functions.

have different clinical characteristics. Both groups occur mainly (but not exclusively) in people over 40, and are slightly more common in men, but some rare sub-types mainly occur in women or children.[17][18]

## Exocrine cancers [edit]

The exocrine group is dominated by pancreatic adenocarcinoma (variations of this name may add "invasive" and "ductal"), which is by far the most common type, representing about 85% of all pancreatic cancers.[4] Nearly all these start in the ducts of the pancreas, and pancreatic ductal adenocarcinoma is often abbreviated as PDAC.[19] This is despite the fact that the tissue from which it arises – the pancreatic ductal epithelium – represents less than 10% of the pancreas by cell volume.[20] This cancer originates in the ducts that carry secretions (such as enzymes and bicarbonate) away from the pancreas. About 60–70% of adenocarcinomas occur in the 'head' of the pancreas.[4]

The next most common type, acinar cell carcinoma of the pancreas, arises in the clusters of cells that produce these enzymes, and represents 5% of exocrine pancreas cancers.[21] Like the 'functioning' endocrine cancers described below, acinar cell carcinomas may cause over-production of certain molecules, in this case digestive enzymes, which may cause symptoms such as skin rashes and joint pain.

Cystadenocarcinomas account for 1% of pancreatic cancers, and they have a better prognosis than the other exocrine types.[21]

Pancreatoblastoma is a rare form, mostly occurring in childhood, and with a relatively good prognosis. Other exocrine cancers include adenosquamous carcinomas, signet ring cell carcinomas, hepatoid carcinomas, colloid carcinomas, undifferentiated carcinomas, and undifferentiated carcinomas with osteoclast-like giant cells. Solid pseudopapillary tumor is a rare low-grade neoplasm that mainly affects younger women, and generally has a very good prognosis.[4][22]

Pancreatic mucinous cystic neoplasms are a broad group of pancreas tumors that have varying malignant potential. They are being detected at a greatly increased rate as CT scans become more powerful and common, and discussion continues as how best to assess and treat them, given that many are benign.[23]

## Neuroendocrine [edit]

*Main article: Pancreatic neuroendocrine tumor*

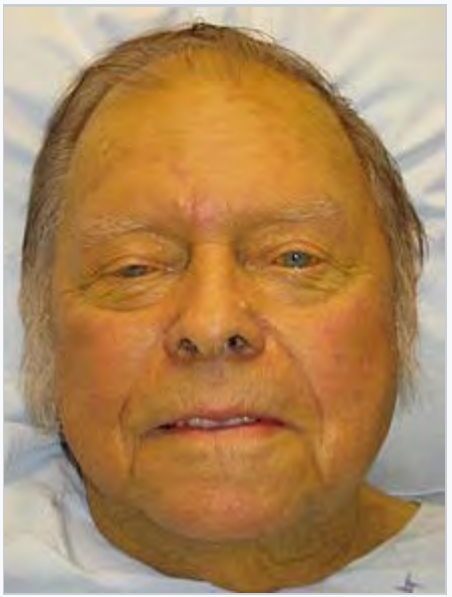
The small minority of tumors that arise elsewhere in the pancreas are mainly pancreatic neuroendocrine tumors (PanNETs).[24] Neuroendocrine tumors (NETs) are a diverse group of benign or malignant tumors that arise from the body's neuroendocrine cells, which are responsible for integrating the nervous and endocrine systems. NETs can start in most organs of the body, including the pancreas, where the various malignant types are all considered to be rare. PanNETs are grouped into 'functioning' and 'non-functioning'

types, depending on the degree to which they produce hormones. The functioning types secrete hormones such as insulin, gastrin, and glucagon into the bloodstream, often in large quantities, giving rise to serious symptoms such as low blood sugar, but also favoring relatively early detection. The most common functioning PanNETs are insulinomas and gastrinomas, named after the hormones they secrete. The non-functioning types do not secrete hormones in a sufficient quantity to give rise to overt clinical symptoms. For this reason, non-functioning PanNETs are often diagnosed only after the cancer has spread to other parts of the body.[25]

As with other neuroendocrine tumors, the history of the terminology and classification of PanNETs is complex.[24] PanNETs are sometimes called "islet cell cancers",[26] even though it is now known that they do not actually arise from islet cells as previously thought.[25]

## Signs and symptoms [edit]

Since pancreatic cancer usually does not cause recognizable symptoms in its early stages, the disease is typically not diagnosed until it has spread beyond the pancreas itself.[7] This is one of the main reasons for the generally poor survival rates. Exceptions to this are the functioning PanNETs, where over-production of various active hormones can give rise to symptoms (which depend on the type of hormone).[27]



Jaundice can be a symptom, due to biliary obstruction from a pancreatic tumor

Bearing in mind that the disease is rarely diagnosed before the age of 40, common symptoms of pancreatic adenocarcinoma occurring before diagnosis include:

- Pain in the upper abdomen or back, often spreading from around the stomach to the back. The location of the pain can indicate the part of the pancreas where a tumor is located. The pain may be worse at night and may increase over time to become severe and unremitting.[21] It may be slightly relieved by bending forward. In the UK, about half of new cases of pancreatic cancer are diagnosed following a visit to a hospital emergency department for pain or jaundice. In up to two-thirds of people abdominal pain is the main symptom, for 46% of the total accompanied by jaundice, with 13% having jaundice without pain.[5]
- Jaundice, a yellow tint to the whites of the eyes or skin, with or without pain, and possibly in combination with darkened urine. This results when a cancer in the head of the pancreas obstructs the common bile duct as it runs through the pancreas.[28]
- Unexplained weight loss, either from loss of appetite, or loss of exocrine function resulting in poor digestion.[5]
- The tumor may compress neighboring organs, disrupting digestive processes and making it difficult for the stomach to empty, which may cause nausea and a feeling of fullness. The undigested fat leads to foul-smelling, fatty feces that are difficult to flush away.[5] Constipation is common.[29]
- At least 50% of people with pancreatic adenocarcinoma have diabetes at the time of diagnosis.[4] While long-standing diabetes is a known risk factor for pancreatic cancer (see Risk factors), the cancer can itself cause diabetes, in which case recent onset of diabetes could be considered an early sign of the disease.[30] People over 50 who develop diabetes have eight times the usual risk of developing pancreatic adenocarcinoma within three years, after which the relative risk declines.[5]

### Other findings [edit]

- Trousseau's syndrome, in which blood clots form spontaneously in the portal blood vessels, the deep veins of the extremities, or the superficial veins anywhere on the body, may be associated with pancreatic cancer, and is found in about 10% of cases.[6]

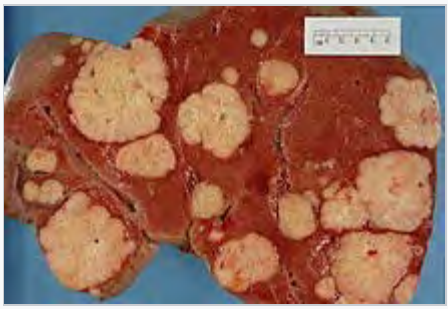
- Clinical depression has been reported in association with pancreatic cancer in some 10–20% of cases, and can be a hindrance to optimal management. The depression sometimes appears before the diagnosis of cancer, suggesting that it may be brought on by the biology of the disease.[6]

Other common manifestations of the disease include: weakness and tiring easily; dry mouth; sleep problems; and a palpable abdominal mass."[29]

## Symptoms of spread (metastasis) [edit]

The spread of pancreatic cancer to other organs (metastasis) may also cause symptoms. Typically, pancreatic adenocarcinoma first spreads to nearby lymph nodes, and later to the liver or to the peritoneal cavity, large intestine or lungs.[6] It is uncommon for it to spread to the bones or brain.[31]

Cancers in the pancreas may also be secondary cancers that have spread from other parts of the body. This is uncommon, found in only about 2% of cases of pancreatic cancer. Kidney cancer is by far the most common cancer to spread to the pancreas, followed by colorectal cancer, and then cancers of the skin, breast, and lung. Surgery may be performed on the pancreas in such cases, whether in hope of a cure or to alleviate symptoms.[32]



Cross section of a human liver, at autopsy, showing multiple large pale tumor deposits, that are secondary tumors derived from pancreatic cancer

## Risk factors [edit]

Risk factors for pancreatic adenocarcinoma include:[2][4][5][33]

- Age, gender, and ethnicity; the risk of developing pancreatic cancer increases with age. Most cases occur after age 65,[2] while cases before age 40 are uncommon. The disease is slightly more common in men than women, and in the United States is over 1.5 times more common in African Americans, though incidence in Africa is low.[2]
- Cigarette smoking is the best-established avoidable risk factor for pancreatic cancer, approximately doubling risk among long-term smokers, the risk increasing with the number of cigarettes smoked and the years of smoking. The risk declines slowly after smoking cessation, taking some 20 years to return to almost that of non-smokers.[34]
- Obesity; a BMI greater than 35 increases relative risk by about half.[5]
- Family history; 5–10% of pancreatic cancer cases have an inherited component, where people have a family history of pancreatic cancer.[4][35] The risk escalates greatly if more than one first-degree relative had the disease, and more modestly if they developed it before the age of 50.[7] Most of the genes involved have not been identified.[4][36] Hereditary pancreatitis gives a greatly increased lifetime risk of pancreatic cancer of 30–40% to the age of 70.[6] Screening for early pancreatic cancer may be offered to individuals with hereditary pancreatitis on a research basis.[37] Some people may choose to have their pancreas surgically removed to prevent cancer developing in the future.[6]
  Pancreatic cancer has been associated with the following other rare hereditary syndromes: Peutz–Jeghers syndrome due to mutations in the *STK11* tumor suppressor gene (very rare, but a very strong risk factor); dysplastic nevus syndrome (or familial atypical multiple mole and melanoma syndrome, FAMMM-PC) due to mutations in the *CDKN2A* tumor suppressor gene; autosomal recessive ataxia-telangiectasia and autosomal dominantly inherited mutations in the *BRCA2* gene and *PALB2* gene; hereditary non-polyposis colon cancer (Lynch syndrome); and familial adenomatous polyposis. PanNETs have been associated with multiple endocrine neoplasia type 1 (MEN1) and von Hippel Lindau syndromes.[4][6][7]
- Chronic pancreatitis appears to almost triple risk, and as with diabetes, new-onset pancreatitis may be a symptom of a tumor.[6] The risk of pancreatic cancer in individuals with familial pancreatitis is [6][36]

particularly high.
- Diabetes mellitus is a risk factor for pancreatic cancer and (as noted in the Signs and symptoms section) new-onset diabetes may also be an early sign of the disease. People who have been diagnosed with Type 2 diabetes for longer than ten years may have a 50% increased risk, as compared with non-diabetics.[6]
- Specific types of food (as distinct from obesity) have not been clearly shown to increase the risk of pancreatic cancer.[4] Dietary factors for which there is some evidence of slightly increased risk include processed meat, red meat, and meat cooked at very high temperatures (e.g. by frying, broiling or barbecuing).[38][39]

### Alcohol [edit]

Drinking alcohol excessively is a major cause of chronic pancreatitis, which in turn predisposes to pancreatic cancer. However, considerable research has failed to firmly establish alcohol consumption as a direct risk factor for pancreatic cancer. Overall, the association is consistently weak and the majority of studies have found no association, with smoking a strong confounding factor. The evidence is stronger for a link with heavy drinking, of at least six drinks per day.[6][40]

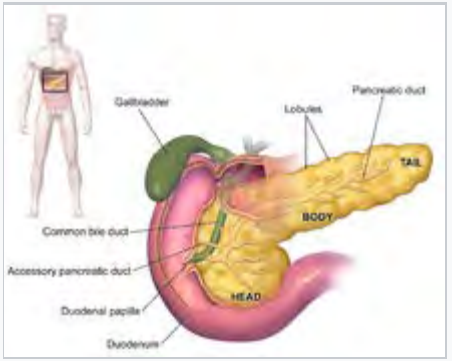
## Diagnosis [edit]

The symptoms of pancreatic adenocarcinoma do not usually appear in the disease's early stages, and are individually not distinctive to the disease.[5][6][28] The symptoms at diagnosis vary according to the location of the cancer in the pancreas, which anatomists divide (from left to right on most diagrams) into the thick head, the neck, and the tapering body, ending in the tail.

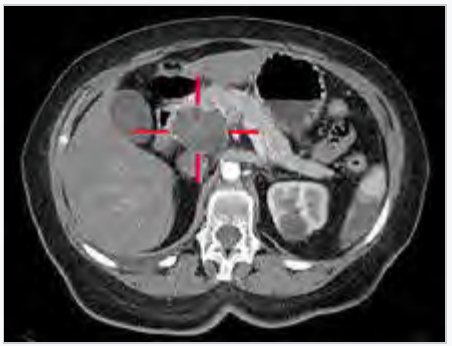
Regardless of a tumor's location, the most common symptom is unexplained weight loss, which may be considerable. A large minority (between 35% and 47%) of people diagnosed with the disease will have had nausea, vomiting or a feeling of weakness. Tumors in the head of the pancreas typically also cause jaundice, pain, loss of appetite, dark urine, and light-colored stools. Tumors in the body and tail typically also cause pain.[28]

People sometimes have recent onset of atypical type 2 diabetes that is difficult to control, a history of recent but unexplained blood vessel inflammation caused by blood clots (thrombophlebitis) known as Trousseau sign, or a previous attack of pancreatitis.[28] A doctor may suspect pancreatic cancer when the onset of diabetes in someone over 50 years old is accompanied by typical symptoms such as unexplained weight loss, persistent abdominal or back pain, indigestion, vomiting, or fatty feces.[5] Jaundice accompanied by a painlessly swollen gallbladder (known as Courvoisier's sign) may also raise suspicion, and can help differentiate pancreatic cancer from gallstones.[41]

Medical imaging techniques, such as computed tomography (CT scan) and endoscopic ultrasound (EUS) are used both to confirm the diagnosis and to help decide whether the tumor can be surgically removed (its "resectability").[5] Magnetic resonance imaging and positron emission tomography may also be used,[4] and magnetic resonance cholangiopancreatography may be useful in some cases.[28] Abdominal ultrasound is less sensitive and will miss small tumors, but can identify cancers that have spread to the liver and build-up of fluid in the peritoneal cavity (ascites).[5] It may be used for a quick and cheap first [42]



The head, body and tail of the pancreas. The stomach is faded out in this image to show the entire pancreas, of which the body and tail lie behind the stomach, and the neck partially behind.


Axial CT image with i.v. contrast and added color. Cross lines towards top left surround a macrocystic adenocarcinoma of

examination before other techniques.

the pancreatic head.

A biopsy by fine needle aspiration, often guided by endoscopic ultrasound, may be used where there is uncertainty over the diagnosis, but a histologic diagnosis is not usually required for removal of the tumor by surgery to go ahead.[5]

Liver function tests can show a combination of results indicative of bile duct obstruction (raised conjugated bilirubin, γ-glutamyl transpeptidase and alkaline phosphatase levels). CA19-9 (carbohydrate antigen 19.9) is a tumor marker that is frequently elevated in pancreatic cancer. However, it lacks sensitivity and specificity, not least because 5% of people lack the Lewis (a) antigen and cannot produce CA19-9. It has a sensitivity of 80% and specificity of 73% in detecting pancreatic adenocarcinoma, and is used for following known cases rather than diagnosis.[4][5]

The most common form of pancreatic cancer (adenocarcinoma) is typically characterized by moderately to poorly differentiated glandular structures on microscopic examination. There is typically considerable desmoplasia or formation of a dense fibrous stroma or structural tissue consisting of a range of cell types (including myofibroblasts, macrophages, lymphocytes and mast cells) and deposited material (such as type I collagen and hyaluronic acid). This creates a tumor microenvironment that is short of blood vessels (hypovascular) and so of oxygen (tumor hypoxia).[4] It is thought that this prevents many chemotherapy drugs from reaching the tumor, as one factor making the cancer especially hard to treat.[4][6]

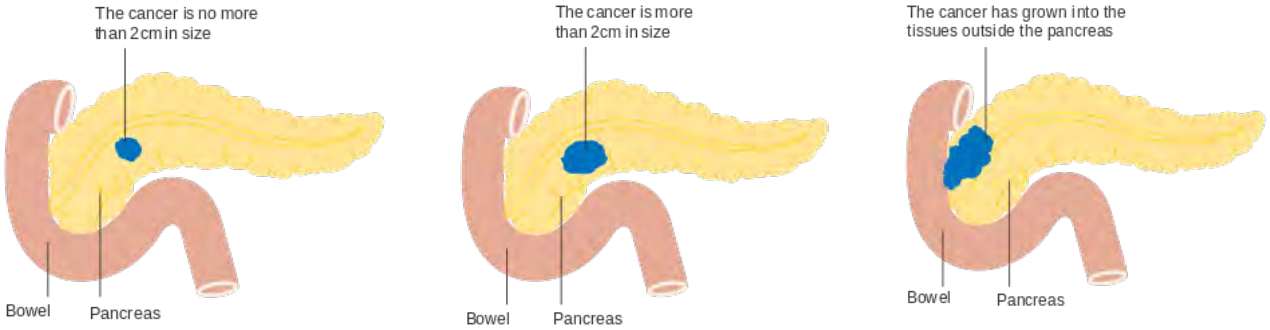
## Staging [edit]

### Exocrine cancers [edit]

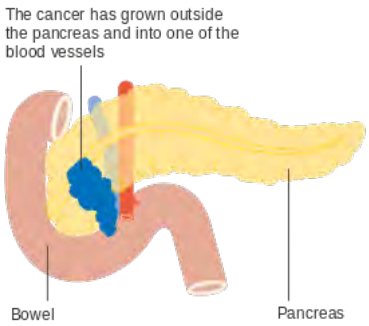
Pancreatic cancer is usually staged following a CT scan.[28] The most widely used cancer staging system for pancreatic cancer is the one formulated by the American Joint Committee on Cancer (AJCC) together with the Union for International Cancer Control (UICC). The AJCC-UICC staging system designates four main overall stages, ranging from early to advanced disease, based on TNM classification of **T**umor size, spread to lymph **N**odes, and **M**etastasis.[43]

To help decide treatment, the tumors are also divided into three broader categories based on whether surgical removal seems possible: in this way, tumors are judged to be "resectable", "borderline resectable", or "unresectable".[44] When the disease is still in an early stage (AJCC-UICC stages I and II), without spread to large blood vessels or distant organs such as the liver or lungs, surgical resection of the tumor can normally be performed, if the patient is willing to undergo this major operation and is thought to be sufficiently fit.[5] The AJCC-UICC staging system allows distinction between stage III tumors that are judged to be "borderline resectable" (where surgery is technically feasible because the celiac axis and superior mesenteric artery are still free) and those that are "unresectable" (due to more locally advanced disease); in terms of the more detailed TNM classification, these two groups correspond to T3 and T4 respectively.[6]

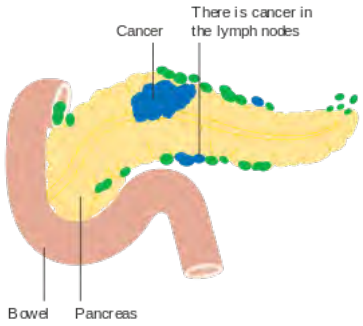
**Pancreatic cancer staging (TNM classification)**




Stage T1 pancreatic cancer  Stage T2 pancreatic cancer  Stage T3 pancreatic cancer

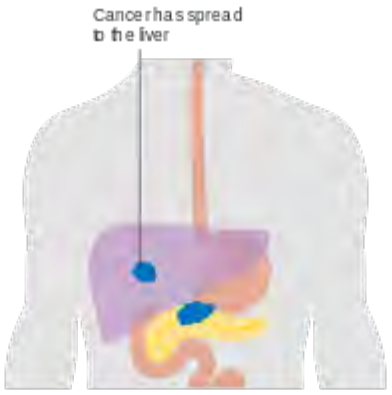



Stage T4 pancreatic cancer




Pancreatic cancer in nearby lymph nodes – Stage N1

Locally advanced adenocarcinomas have spread into neighboring organs, which may be any of the following (in roughly decreasing order of frequency): the duodenum, stomach, transverse colon, spleen, adrenal gland, or kidney. Very often they also spread to the important blood or lymphatic vessels and nerves that run close to the pancreas, making surgery far more difficult. Typical sites for metastatic spread (stage IV disease) are the liver, peritoneal cavity and lungs, all of which occur in 50% or more of fully advanced cases.[45]



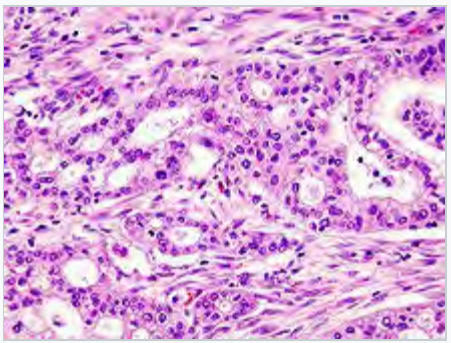

Pancreatic cancer metastasized – stage M1

## PanNETs [edit]

The 2010 WHO classification of tumors of the digestive system grades all the pancreatic neuroendocrine tumors (PanNETs) into three categories, based on their degree of cellular differentiation (from "NET G1" through to the poorly differentiated "NET G3").[18] The U.S. National Comprehensive Cancer Network recommends use of the same AJCC-UICC staging system as pancreatic adenocarcinoma.[46]:52 Using this scheme, the stage-by-stage outcomes for PanNETs are dissimilar to those of the exocrine cancers.[47] A different TNM system for PanNETs has been proposed by the European Neuroendocrine Tumor Society.[18]

# Precursors [edit]

## Exocrine cancers [edit]

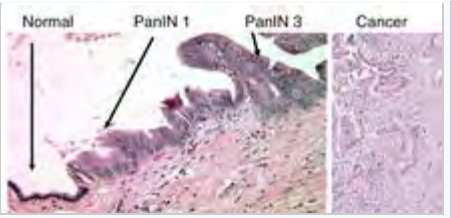


Micrograph of pancreatic ductal adenocarcinoma (the most common type of pancreatic cancer). H&E stain.

These cancers are thought to arise from several types of precancerous lesions within the pancreas. But these lesions do not always progress to cancer, and the increased numbers detected as a by-product of the increasing use of CT scans for other reasons are not all treated.[6] Apart from pancreatic serous cystadenomas (SCNs), which are almost always benign, three types of precancerous lesion are recognized.

The first is pancreatic intraepithelial neoplasia. These are microscopic abnormalities in the pancreas, which are often found in autopsies of people with no diagnosed cancer. These may progress from low to high grade and then to a tumor. More than 90% of cases at all grades carry a faulty *KRAS* gene, while in grades 2 and 3 damage to three further genes – *CDKN2A* (*p16*), *p53* and *SMAD4* – are increasingly often found.[4]

Secondly, intraductal papillary mucinous neoplasms (IPMNs) are macroscopic lesions, which occur in about 2% of all adults, rising to




Micrographs of normal pancreas, pancreatic intraepithelial neoplasia (precursors to pancreatic carcinoma) and pancreatic carcinoma. H&E stain.

about 10% by age 70, and have about a 25% risk of developing into invasive cancer. They also very often have *KRAS* gene mutations, in about 40–65% of cases, and in the GNAS Gs alpha subunit and RNF43, affecting the Wnt signaling pathway.[4] Even if removed surgically, there remains a considerably increased risk of pancreatic cancer developing subsequently.[6]

The last type, pancreatic mucinous cystic neoplasms (MCNs) mainly occur in women, and may remain benign or progress to cancer.[48] If they become large, cause symptoms, or have suspicious features, they can usually be successfully removed by surgery.[6]

The genetic events found in ductal adenocarcinoma have been well characterized, and complete exome sequencing has been done for the common types of tumor. Four genes have each been found to be mutated in the majority of adenocarcinomas: *KRAS* (in 95% of cases), *CDKN2A* (also in 95%), *TP53* (75%), and *SMAD4* (55%). The last of these are especially associated with a poor prognosis.[6] *SWI/SNF* mutations/deletions occur in about 10–15% of the adenocarcinomas.[4] The genetic alterations in several other types of pancreatic cancer and precancerous lesions have also been researched.[6]

### PanNETs [edit]

The genes often found mutated in PanNETs are different from those in pancreatic adenocarcinoma.[49] For example, *KRAS* mutation is normally absent. Instead, hereditary *MEN1* gene mutations give rise to MEN1 syndrome, in which primary tumors occur in two or more endocrine glands. About 40–70% of people born with a *MEN1* mutation eventually develop a PanNet.[50] Other genes that are frequently mutated include *DAXX*, *mTOR* and *ATRX*.[25]

## Prevention and screening [edit]

Apart from not smoking, the American Cancer Society recommends keeping a healthy weight, and increasing consumption of fruits, vegetables, and whole grains, while decreasing consumption of red and processed meat, although there is no consistent evidence this will prevent or reduce pancreatic cancer specifically.[51] A 2014 review of research concluded that there was evidence that consumption of citrus fruits and curcumin reduced risk of pancreatic cancer, while there was possibly a beneficial effect from whole grains, folate, selenium, and non-fried fish.[40]

In the general population, screening of large groups is not currently considered effective, although newer techniques, and the screening of tightly targeted groups, are being evaluated.[52][53] Nevertheless, regular screening with endoscopic ultrasound and MRI/CT imaging is recommended for those at high risk from inherited genetics.[7][42][53][54]

## Management [edit]

### Exocrine cancer [edit]

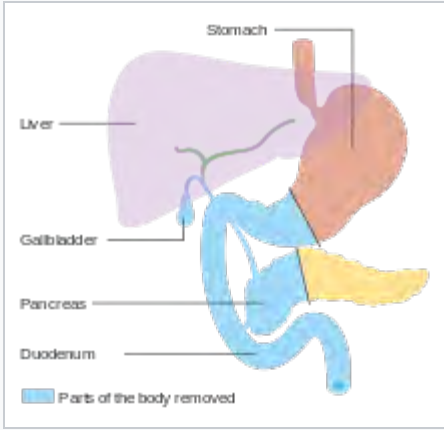
A key assessment that is made after diagnosis is whether surgical removal of the tumor is possible (see Staging), as this is the only cure for this cancer. Whether or not surgical resection can be offered depends on how much the cancer has spread. The exact location of the tumor is also a significant factor, and CT can show how it relates to the major blood vessels passing close to the pancreas. The general health of the person must also be assessed, though age in itself is not an obstacle to surgery.[6]

Chemotherapy and, to a lesser extent, radiotherapy are likely to be offered to most people, whether or not

surgery is possible. Specialists advise that the management of pancreatic cancer should be in the hands of a multidisciplinary team including specialists in several aspects of oncology, and is, therefore, best conducted in larger centers.[4][6]

## Surgery [edit]

Surgery with the intention of a cure is only possible in around one-fifth (20%) of new cases.[5] Although CT scans help, in practice it can be difficult to determine whether the tumor can be fully removed (its "resectability"), and it may only become apparent during surgery that it is not possible to successfully remove the tumor without damaging other vital tissues. Whether or not surgical resection can be offered depends on various factors, including the precise extent of local anatomical adjacency to, or involvement of, the venous or arterial blood vessels,[4] as well as surgical expertise and a careful consideration of projected post-operative recovery.[55][56] The age of the person is not in itself a reason not to operate, but their general performance status needs to be adequate for a major operation.[5]

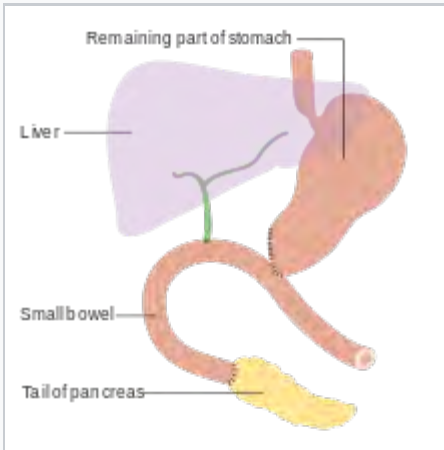


Parts of the body removed in Whipple's operation

One particular feature that is evaluated is the encouraging presence, or discouraging absence, of a clear layer or plane of fat creating a barrier between the tumor and the vessels.[6] Traditionally, an assessment is made of the tumor's proximity to major venous or arterial vessels, in terms of "abutment" (defined as the tumor touching no more than half a blood vessel's circumference without any fat to separate it), "encasement" (when the tumor encloses most of the vessel's circumference), or full vessel involvement.[57]:22 A resection that includes encased sections of blood vessels may be possible in some cases,[58][59] particularly if preliminary neoadjuvant therapy is feasible,[60][61][62] using chemotherapy[56][57]:36[63] and/or radiotherapy.[57]:29–30

Even when the operation appears to have been successful, cancerous cells are often found around the edges ("margins") of the removed tissue, when a pathologist examines them microscopically (this will always be done), indicating the cancer has not been entirely removed.[4] Furthermore, cancer stem cells are usually not evident microscopically, and if they are present they may continue to develop and spread.[64][65] An exploratory laparoscopy (a small, camera-guided surgical procedure) may therefore be performed to gain a clearer idea of the outcome of a full operation.[66][*needs update*]

For cancers involving the head of the pancreas, the Whipple procedure is the most commonly attempted curative surgical treatment. This is a major operation which involves removing the pancreatic head and the curve of the duodenum together ("pancreato-duodenectomy"), making a bypass for food from the stomach to the jejunum ("gastro-jejunostomy") and attaching a loop of jejunum to the cystic duct to drain bile ("cholecysto-jejunostomy"). It can be performed only if the person is likely to survive major surgery and if the cancer is localized without invading local structures or metastasizing. It can, therefore, be performed only in a minority of cases. Cancers of the tail of the pancreas can be resected using a procedure known as a distal pancreatectomy, which often also entails removal of the spleen.[4][6] Nowadays, this can often be done using minimally invasive surgery.[4][6]



How the pancreas and bowel are joined back together after a Whipple's operation

Although curative surgery no longer entails the very high death rates that occurred until the 1980s, a high proportion of people (about 30–45%) still have to be treated for a post-operative sickness that is not caused by the cancer itself. The most common complication of surgery is difficulty in emptying the stomach.[6] Certain more limited surgical procedures may also be used to ease symptoms (see Palliative care).

For instance, if the cancer is invading or compressing the duodenum or colon. In such cases, bypass surgery might overcome the obstruction and improve quality of life but is not intended as a cure.[5]

## Chemotherapy [edit]

After surgery, adjuvant chemotherapy with gemcitabine or 5-FU can be offered if the person is sufficiently fit, after a recovery period of one to two months.[7][42] In people not suitable for curative surgery, chemotherapy may be used to extend life or improve its quality.[6] Before surgery, neoadjuvant chemotherapy or chemoradiotherapy may be used in cases that are considered to be "borderline resectable" (see Staging) in order to reduce the cancer to a level where surgery could be beneficial. In other cases neoadjuvant therapy remains controversial, because it delays surgery.[6][7][67]

Gemcitabine was approved by the United States Food and Drug Administration (FDA) in 1997, after a clinical trial reported improvements in quality of life and a 5-week improvement in median survival duration in people with advanced pancreatic cancer.[68] This was the first chemotherapy drug approved by the FDA primarily for a nonsurvival clinical trial endpoint.[69] Chemotherapy using gemcitabine alone was the standard for about a decade, as a number of trials testing it in combination with other drugs failed to demonstrate significantly better outcomes. However, the combination of gemcitabine with erlotinib was found to increase survival modestly, and erlotinib was licensed by the FDA for use in pancreatic cancer in 2005.[70]

The FOLFIRINOX chemotherapy regimen using four drugs was found more effective than gemcitabine, but with substantial side effects, and is thus only suitable for people with good performance status. This is also true of protein-bound paclitaxel (nab-paclitaxel), which was licensed by the FDA in 2013 for use with gemcitabine in pancreas cancer.[71] By the end of 2013, both FOLFIRINOX and nab-paclitaxel with gemcitabine were regarded as good choices for those able to tolerate the side-effects, and gemcitabine remained an effective option for those who were not. A head-to-head trial between the two new options is awaited, and trials investigating other variations continue. However, the changes of the last few years have only increased survival times by a few months.[68] Clinical trials are often conducted for novel adjuvant therapies.[7]

## Radiotherapy [edit]

The role of radiotherapy as an auxiliary (adjuvant) treatment after potentially curative surgery has been controversial since the 1980s.[6] The European Society for Medical Oncology recommends that adjuvant radiotherapy should only be used for people enrolled in clinical trials.[42] However, there is a continuing tendency for clinicians in the US to be more ready to use adjuvant radiotherapy than those in Europe. Many clinical trials have tested a variety of treatment combinations since the 1980s, but have failed to settle the matter conclusively.[6][7]

Radiotherapy may form part of treatment to attempt to shrink a tumor to a resectable state, but its use on unresectable tumors remains controversial as there are conflicting results from clinical trials. The preliminary results of one trial, presented in 2013, "markedly reduced enthusiasm" for its use on locally advanced tumors.[4]

## PanNETs [edit]

*Main articles: Neuroendocrine tumor and Pancreatic neuroendocrine tumor*

Treatment of PanNETs, including the less common malignant types, may include a number of approaches.[46][72][73][74] Some small tumors of less than 1 cm. that are identified incidentally, for example on a CT scan performed for other purposes, may be followed by watchful waiting.[46] This depends on the assessed risk of surgery which is influenced by the site of the tumor and the presence of other medical problems.[46] Tumors within the pancreas only (localized tumors), or with limited metastases, for example to the liver, may be removed by surgery. The type of surgery depends on the tumor location, and the degree of spread to lymph nodes.[18]

For localized tumors, the surgical procedure may be much less extensive than the types of surgery used to treat pancreatic adenocarcinoma described above, but otherwise surgical procedures are similar to those for exocrine tumors. The range of possible outcomes varies greatly; some types have a very high survival rate after surgery while others have a poor outlook. As all this group are rare, guidelines emphasize that treatment should be undertaken in a specialized center.[18][25] Use of liver transplantation may be considered in certain cases of liver metastasis.[75]

For functioning tumors, the somatostatin analog class of medications, such as octreotide, can reduce the excessive production of hormones.[18] Lanreotide can slow tumor growth.[76] If the tumor is not amenable to surgical removal and is causing symptoms, targeted therapy with everolimus or sunitinib can reduce symptoms and slow progression of the disease.[25][77][78] Standard cytotoxic chemotherapy is generally not very effective for PanNETs, but may be used when other drug treatments fail to prevent the disease from progressing,[25][79] or in poorly differentiated PanNET cancers.[80]

Radiation therapy is occasionally used if there is pain due to anatomic extension, such as metastasis to bone. Some PanNETs absorb specific peptides or hormones, and these PanNETs may respond to nuclear medicine therapy with radiolabeled peptides or hormones such as iobenguane (iodine-131-MIBG).[81][82][83][84] Radiofrequency ablation (RFA), cryoablation, and hepatic artery embolization may also be used.[85][86]

### Palliative care [edit]

Palliative care is medical care which focuses on treatment of symptoms from serious illness, such as cancer, and improving quality of life.[87] Because pancreatic adenocarcinoma is usually diagnosed after it has progressed to an advanced stage, palliative care as a treatment of symptoms is often the only treatment possible.[88]

Palliative care focuses not on treating the underlying cancer, but on treating symptoms such as pain or nausea, and can assist in decision-making, including when or if hospice care will be beneficial.[89] Pain can be managed with medications such as opioids or through procedural intervention, by a nerve block on the celiac plexus (CPB). This alters or, depending on the technique used, destroys the nerves that transmit pain from the abdomen. CPB is a safe and effective way to reduce the pain, which generally reduces the need to use opioid painkillers, which have significant negative side effects.[6][90]

Other symptoms or complications that can be treated with palliative surgery are obstruction by the tumor of the intestines or bile ducts. For the latter, which occurs in well over half of cases, a small metal tube called a stent may be inserted by endoscope to keep the ducts draining.[28] Palliative care can also help treat depression that often comes with the diagnosis of pancreatic cancer.[6]

Both surgery and advanced inoperable tumors often lead to digestive system disorders from a lack of the exocrine products of the pancreas (exocrine insufficiency). These can be treated by taking pancreatin which contains manufactured pancreatic enzymes, and is best taken with food.[5] Difficulty in emptying the stomach (delayed gastric emptying) is common and can be a serious problem, involving hospitalization. Treatment may involve a variety of approaches, including draining the stomach by nasogastric aspiration and drugs called proton-pump inhibitors or H2 antagonists, which both reduce production of gastric acid.[5]

## Outcomes [edit]

Pancreatic adenocarcinoma and the other less common exocrine cancers have a very poor prognosis, as they are normally diagnosed at a late stage when the cancer is already locally advanced or has spread to other parts of the body.[4] Outcomes are much better for PanNETs: many are benign and completely without clinical symptoms, and even those cases not treatable with surgery have an average five-year survival rate of

**Outcomes in pancreatic cancers according to clinical stage**[44]

| Clinical stage | Five-year survival (%) – U.S., diagnoses 1992–98 | |
|---|---|---|
| | Exocrine pancreatic cancer | Neuroendocrine treated with surgery |
| **IA / I** | 14 | 61 |

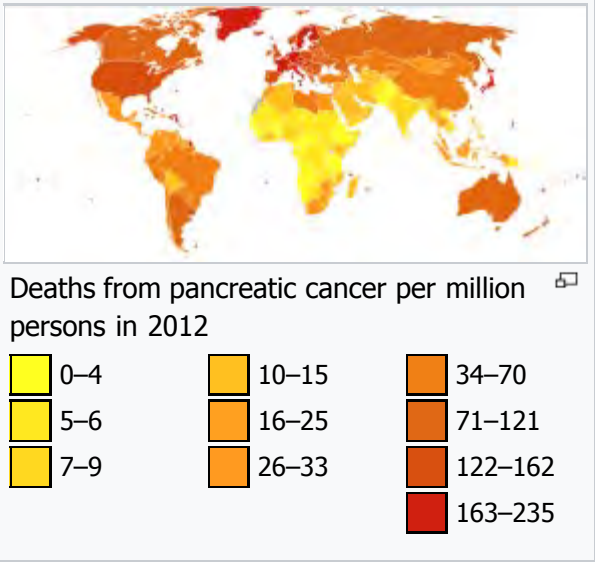
16%,[44] although the outlook varies considerably according to the type.[27]

| | | |
|---|---|---|
| **IB** | 12 | |
| **IIA / II** | 7 | 52 |
| **IIB** | 5 | |
| **III** | 3 | 41 |
| **IV** | 1 | 16 |

For locally advanced and metastatic pancreatic adenocarcinomas, which together represent over 80% of cases, numerous recent trials comparing chemotherapy regimes have shown increased survival times, but not to more than one year.[4][68] Overall five-year survival for pancreatic cancer in the US has improved from 2% in cases diagnosed in 1975–77, and 4% in 1987–89 diagnoses, to 6% in 2003–09.[91] In the less than 20% of cases of pancreatic adenocarcinoma with a diagnosis of a localized and small cancerous growth (less than 2 cm in Stage T1), about 20% of Americans survive to five years.[16]

## Distribution [edit]

As of 2012, pancreatic cancer resulted in 330,000 deaths globally,[2] up from 310,000 in 2010 and 200,000 in 1990.[92] In 2014, an estimated 46,000 people in the US are expected to be diagnosed with pancreatic cancer and 40,000 to die of it.[4] Although it accounts for only 2.5% of new cases, pancreatic cancer is responsible for 6% of cancer deaths each year.[93] It is the seventh highest cause of death from cancer worldwide.[2]




Globally pancreatic cancer is the 11th most common cancer in women and the 12th most common in men.[2] The majority of recorded cases occur in developed countries.[2] People from the United States have an average lifetime risk of about 1 in 67 (or 1.5%) of developing the disease,[94] slightly higher than the figure for the UK.[95] The disease is more common in men than women,[2][4] though the difference in rates has narrowed over recent decades, probably reflecting earlier increases in female smoking. In the United States the risk for African Americans is over 50% greater than for whites, but the rates in Africa and East Asia are much lower than those in North America or Europe. The United States, Central and eastern Europe, and Argentina and Uruguay all have high rates.[2]

Pancreatic cancer is the 10th most common cancer in the UK (around 8,800 people were diagnosed with the disease in 2011), and it is the 5th most common cause of cancer death (around 8,700 people died in 2012).[96]

### PanNETs [edit]

The annual incidence of clinically recognized PanNETs is low (about 5 per one million person-years) and is dominated by the non-functioning types.[22] Somewhere between 45% and 90% of PanNETs are thought to be of the non-functioning types.[18][25] Studies of autopsies have uncovered small PanNETs rather frequently, suggesting that the prevalence of tumors that remain inert and asymptomatic may be relatively high.[25] Overall PanNETs are thought to account for about 1 to 2% of all pancreatic tumors.[22] The definition and classification of PanNETs has changed over time, affecting what is known about their epidemiology and clinical relevance.[49]

## History [edit]

*See also: Timeline of pancreatic cancer*

The earliest recognition of pancreatic cancer has been attributed to the 18th-century Italian scientist Giovanni Battista Morgagni, the historical father of modern-day anatomic pathology, who claimed to have traced several cases of cancer in the pancreas. Many 18th and 19th-century physicians were skeptical about the existence of the disease, given the similar appearance of pancreatitis. Some case reports were published in the 1820s and 1830s, and a genuine histopathologic diagnosis was eventually recorded by the American clinician Jacob Mendes Da Costa, who also doubted the reliability of Morgagni's interpretations. By the start of the 20th century, cancer of the head of the pancreas had become a well-established diagnosis.[97]

Regarding the recognition of PanNETs, the possibility of cancer of the islet cells was initially suggested in 1888. The first case of hyperinsulinism due to a tumor of this type was reported in 1927. Recognition of a non-insulin-secreting type of PanNET is generally ascribed to the American surgeons, R. M. Zollinger and E. H. Ellison, who gave their names to Zollinger–Ellison syndrome, after postulating the existence of a gastrin-secreting pancreatic tumor in a report of two cases of unusually severe peptic ulcers published in 1955.[97] In 2010, the WHO recommended that PanNETs be referred to as "neuroendocrine" rather than "endocrine" tumors.[24]

The first reported partial pancreaticoduodenectomy was performed by the Italian surgeon Alessandro Codivilla in 1898, but the patient only survived 18 days before succumbing to complications. Early operations were compromised partly because of mistaken beliefs that people would die if their duodenum were removed, and also, at first, if the flow of pancreatic juices stopped. Later it was thought, also mistakenly, that the pancreatic duct could simply be tied up without serious adverse effects; in fact, it will very often leak later on. In 1907–08, after some more unsuccessful operations by other surgeons, experimental procedures were tried on corpses by French surgeons.[98]

In 1912 the German surgeon Walther Kausch was the first to remove large parts of the duodenum and pancreas together (*en bloc*). This was in Breslau, now Wrocław in Poland. In 1918 it was demonstrated in operations on dogs that total removal of the duodenum is compatible with life, but this was not reported in human surgery until 1935, when the American surgeon Allen Oldfather Whipple published the results of a series of three operations at Columbia Presbyterian Hospital in New York. Only one of the patients had the duodenum totally removed, but he survived for two years before dying of metastasis to the liver. The first operation was unplanned, as cancer was only discovered in the operating theater. Whipple's success showed the way for the future, but the operation remained a difficult and dangerous one until recent decades. He published several refinements to his procedure, including the first total removal of the duodenum in 1940, but he only performed a total of 37 operations.[98]

The discovery in the late 1930s that vitamin K prevented bleeding with jaundice, and the development of blood transfusion as an everyday process, both improved post-operative survival,[98] but about 25% of people never left hospital alive as late as the 1970s.[99] In the 1970s a group of American surgeons wrote urging that the procedure was too dangerous and should be abandoned. Since then outcomes in larger centers have improved considerably, and mortality from the operation is often less than 4%.[20] In 2006 a report was published of a series of 1,000 consecutive pancreaticoduodenectomies performed by a single surgeon from Johns Hopkins Hospital between 1969 and 2003. The rate of these operations had increased steadily over this period, with only three of them before 1980, and the median operating time reduced from 8.8 hours in the 1970s to 5.5 hours in the 2000s, and mortality within 30 days or in hospital was only 1%.[98][99] Another series of 2,050 operations at the Massachusetts General Hospital between 1941 and 2011 showed a similar picture of improvement.[100]

Small precancerous neoplasms for many pancreatic cancers are being detected at greatly increased rates by modern medical imaging. One type, the intraductal papillary mucinous neoplasm (IPMN) was first described by Japanese researchers in 1982. It was noted in 2010 that: "For the next decade, little attention was paid to this report; however, over the subsequent 15 years, there has been a virtual explosion in the recognition of this tumor."[45]

## Research directions [edit]

Worldwide efforts on many levels are underway to understand pancreatic cancer, but progress has been slow, particularly into understanding the disease's causes.[101] There are several fundamental unanswered questions.[102][103] The nature of the changes that lead to the disease are being intensely investigated, such as the roles played by genes such as *KRAS* and *p53*.[36][104][105] A key question is the timing of events as the disease develops and progresses – particularly the role of diabetes,[106] and how and when the disease spreads.[107]

Research on early detection is ongoing.[52][53] For instance, the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) trial is aiming to determine whether regular screening is appropriate for people with a family history of the disease, or who have hereditary pancreatitis.[108] The knowledge that new onset of diabetes can be an early sign of the disease could facilitate timely diagnosis and prevention if a workable screening strategy can be developed.[106][109][110]

Another area of interest is in assessing whether keyhole surgery (laparoscopy) would be better than Whipple's procedure in treating the disease surgically, particularly in terms of recovery time.[111] Irreversible electroporation is a relatively novel ablation technique that has shown promise in downstaging and prolonging survival in persons with locally advanced disease. It is especially suitable for treatment of tumors that are in proximity to peri-pancreatic vessels without risk of vascular trauma.[112][113] The limited success of outcomes after surgery has led to a number of trials that were running in 2014 to test outcomes using chemotherapy or radiochemotherapy before surgery. This had previously not been found to be helpful, but is being trialed again, using drug combinations which have emerged from the many trials of post-operative therapies, such as FOLFIRINOX.[4]

Efforts are underway to develop new drugs.[36][114] Some of these involve targeted therapies against the cancer cells' molecular mechanisms.[115][116][117] Others aim to target the highly resistant cancer stem cells.[65][118] Still others aim to affect the non-neoplastic stroma and microenvironment of the tumor, which is known to influence cell proliferation and metastasis.[117][118][119][120][121] A further approach involves the use of immunotherapy, such as oncolytic viruses.[122][123]

## See also [edit]

- Gastrointestinal cancer
- Pancreatic Cancer Action (organization in the UK)
- Lustgarten Foundation for Pancreatic Cancer Research (organization in the US)
- List of people diagnosed with pancreatic cancer

## References [edit]


1. ^ "What is Cancer? Defining Cancer". National Cancer Institute, National Institutes of Health. 7 March 2014. Retrieved 5 December 2014.
2. ^ *a b c d e f g h i j k l m n o p* *World Cancer Report 2014*. World Health Organization. 2014. Chapter 5.7. ISBN 92-832-0429-8.
3. ^ *a b c* "Pancreatic Cancer Treatment (PDQ®) Patient Version". *National Cancer Institute*. National Institutes of Health. 17 April 2014. Retrieved 8 June 2014.
4. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae* Ryan DP, Hong TS, Bardeesy N (September 2014). "Pancreatic adenocarcinoma" (PDF). *N. Engl. J. Med.* **371** (11): 1039–49. doi:10.1056/NEJMra1404198. PMID 25207767.
5. ^ *a b c d e f g h i j k l m n o p q r s t u v w* Bond-Smith G, Banga N, Hammond TM, Imber CJ (2012). "Pancreatic adenocarcinoma" (PDF). *BMJ (Clinical research ed.)*. **344**: e2476. doi:10.1136/bmj.e2476. PMID 22592847.
6. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af* Wolfgang CL, Herman JM, Laheru DA, Klein AP, Erdek MA, Fishman EK, Hruban RH (September 2013). "Recent progress in pancreatic cancer". *CA: A Cancer Journal for Clinicians*. **63** (5): 318–48. doi:10.3322/caac.21190. PMC 3769458. PMID 23856911.
7. ^ *a b c d e f g h i* Vincent A, Herman J, Schulick R, Hruban RH, Goggins M (August 2011). "Pancreatic cancer

(PDF). *Lancet*. **378** (9791): 607–20. doi:10.1016/S0140-6736(10)62307-0 . PMID 21620466 .
8. ^ Bussom S, Saif MW (5 March 2010). "Methods and rationale for the early detection of pancreatic cancer. Highlights from the "2010 ASCO Gastrointestinal Cancers Symposium". Orlando, FL, USA. January 22–24, 2010". *JOP : Journal of the pancreas*. **11** (2): 128–30. PMID 20208319.
9. ^ "Can pancreatic cancer be prevented?". *American Cancer Society*. 11 June 2014. Retrieved 13 November 2014.
10. ^ Shahrokni A, Saif MW (10 July 2013). "Metastatic pancreatic cancer: the dilemma of quality vs. quantity of life". *JOP : Journal of the pancreas*. **14** (4): 391–4. doi:10.6092/1590-8577/1663. PMID 23846935.
11. ^ Bardou M, Le Ray I (December 2013). "Treatment of pancreatic cancer: A narrative review of cost-effectiveness studies". *Best practice & research. Clinical gastroenterology*. **27** (6): 881–92. doi:10.1016/j.bpg.2013.09.006. PMID 24182608.
12. ^ Pancreatic Cancer Research Fund, 2015
13. ^ Hariharan D, Saied A, Kocher HM (2008). "Analysis of mortality rates for pancreatic cancer across the world". *HPB*. **10** (1): 58–62. doi:10.1080/13651820701883148. PMC 2504856. PMID 18695761.
14. ^ "Lifetime Risk of Developing or Dying From Cancer". *American Cancer Society*. 1 October 2014. Retrieved 1 December 2014.. The top three vary by gender, and include breast cancer for women and prostate cancer for men.
15. ^ "Cancer Facts & Figures 2010" (PDF). *American Cancer Society*. 2010. Retrieved 5 December 2014. See p. 4 for incidence estimates, and p. 19 for survival percentages.
16. ^ *a b* "Pancreatic Cancer Treatment (PDQ®) Health Professional Version". *National Cancer Institute*. National Institutes of Health. 21 February 2014. Retrieved 24 November 2014. "The highest cure rate occurs if the tumor is truly localized to the pancreas; however, this stage of disease accounts for less than 20% of cases. In cases with localized disease and small cancers (<2 cm) with no lymph node metastases and no extension beyond the capsule of the pancreas, complete surgical resection is associated with an actuarial five-year survival rate of 18% to 24%."
17. ^ Harris, RE (2013). "Epidemiology of pancreatic cancer". *Epidemiology of Chronic Disease*. Jones & Bartlett. pp. 181–190. ISBN 978-0-7637-8047-0.
18. ^ *a b c d e f g* Öberg K, Knigge U, Kwekkeboom D, Perren A (October 2012). "Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Annals of Oncology*. 23 Suppl 7: vii124–30. doi:10.1093/annonc/mds295. PMID 22997445. (Table 5 outlines the proposed TNM staging system for PanNETs.)
19. ^ *Handbook of Pancreatic Cancer*. New York: Springer. 2009. p. 288. ISBN 978-0-387-77497-8. Retrieved 12 June 2016.
20. ^ *a b* Govindan R (2011). *DeVita, Hellman, and Rosenberg's Cancer: Cancer: Principles & Practice of Oncology* (9th ed.). Lippincott Williams & Wilkins. Chapter 35: Cancer of the Pancreas: Surgical Management. ISBN 978-1-4511-0545-2. Online edition, with updates to 2014
21. ^ *a b c* Tobias JS, Hochhauser D (2014). *Cancer and its Management* (7th ed.). p. 297. ISBN 978-1-118-46871-5.
22. ^ *a b c* "Types of Pancreas Tumors". *The Sol Goldman Pancreas Cancer Research Center*. Johns Hopkins Medicine. 2012. Retrieved 18 November 2014.
23. ^ Farrell JJ, Fernández-del Castillo C (June 2013). "Pancreatic cystic neoplasms: management and unanswered questions". *Gastroenterology*. **144** (6): 1303–15. doi:10.1053/j.gastro.2013.01.073. PMID 23622140.
24. ^ *a b c* The PanNET denomination is in line with WHO guidelines for the classification of tumors of the digestive system [1] published in 2010. Historically, PanNETs have also been referred to by a variety of terms, and are still commonly called "pancreatic endocrine tumors". See: Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S (August 2010). "The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems" (PDF). *Pancreas*. **39** (6): 707–12. doi:10.1097/MPA.0b013e3181ec124e. PMID 20664470.
25. ^ *a b c d e f g h* Burns WR, Edil BH (March 2012). "Neuroendocrine pancreatic tumors: guidelines for management and update". *Current treatment options in oncology*. **13** (1): 24–34. doi:10.1007/s11864-011-0172-2. PMID 22198808.
26. ^ The Medical Subject Headings indexing system refers to "islet cell carcinoma", which is subdivided into gastrinoma, glucagonoma, somatostatinoma and VIPoma. See: 2014 MeSH tree at "Pancreatic Neoplasms [C04.588.322.475]" 16 October 2014
27. ^ *a b* "Islet Cell Tumors of the Pancreas / Endocrine Neoplasms of the Pancreas". *The Sol Goldman Pancreas Cancer Research Center*. Johns Hopkins Medicine. 2012. Retrieved 5 January 2015.
28. ^ *a b c d e f g* De La Cruz MS, Young AP, Ruffin MT (April 2014). "Diagnosis and management of pancreatic cancer". *Am Fam Physician*. **89** (8): 626–32. PMID 24784121.
29. ^ *a b* Alberts, SR; Goldberg, RM (2009). "Chapter 9: Gastrointestinal tract cancers". In Casciato, DA; Territo, MC. *Manual of clinical oncology*. Lippincott Williams & Wilkins. pp. 188–236. ISBN 978-0-7817-6884-9.
30. ^ Pannala R, Basu A, Petersen GM, Chari ST (January 2009). "New-onset diabetes: a potential clue to the early

diagnosis of pancreatic cancer". *The Lancet. Oncology*. **10** (1): 88–95. doi:10.1016/S1470-2045(08)70337-1. PMC 2795483. PMID 19111249.

31. ^ "Chapter 15; Pancreas". *Manual for Staging of Cancer* (PDF) (2nd ed.). American Joint Committee on Cancer. pp. 95–8. See page 95 for citation regarding "... lesser degree of involvement of bones and brain and other anatomical sites."
32. ^ Sperti C, Moletta L, Patanè G (15 October 2014). "Metastatic tumors to the pancreas: The role of surgery". *World Journal of Gastrointestinal Oncology*. **6** (10): 381–92. doi:10.4251/wjgo.v6.i10.381. PMID 25320654.
33. ^ "Causes of pancreatic cancer". *NHS Choices*. National Health Service, England. 7 October 2014. Retrieved 5 December 2014.
34. ^ Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, Negri E, Li D, Risch HA, Olson SH, Gallinger S, Miller AB, Bueno-de-Mesquita HB, Talamini R, Polesel J, Ghadirian P, Baghurst PA, Zatonski W, Fontham E, Bamlet WR, Holly EA, Bertuccio P, Gao YT, Hassan M, Yu H, Kurtz RC, Cotterchio M, Su J, Maisonneuve P, Duell EJ, Boffetta P, La Vecchia C (July 2012). "Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4)". *Annals of Oncology*. **23** (7): 1880–8. doi:10.1093/annonc/mdr541. PMID 22104574.
35. ^ Peters, ML; Tseng, JF; Miksad, RA (31 March 2016). "Genetic Testing in Pancreatic Ductal Adenocarcinoma: Implications for Prevention and Treatment.". *Clinical therapeutics*. **38**: 1622–35. doi:10.1016/j.clinthera.2016.03.006. PMID 27041411.
36. ^ *a b c d* Reznik R, Hendifar AE, Tuli R (2014). "Genetic determinants and potential therapeutic targets for pancreatic adenocarcinoma". *Front Physiol*. **5**: 87. doi:10.3389/fphys.2014.00087. PMC 3939680. PMID 24624093.
37. ^ Greenhalf W, Grocock C, Harcus M, Neoptolemos J (2009). "Screening of high-risk families for pancreatic cancer". *Pancreatology*. **9** (3): 215–22. doi:10.1159/000210262. PMID 19349734.
38. ^ "Cancer Facts and Figures 2014" (PDF). *American Cancer Society*. Retrieved 5 January 2015., p. 19, "Though evidence is still accumulating, consumption of red or processed meat, or meat cooked at very high temperatures, may slightly increase risk."
39. ^ Larsson SC, Wolk A (January 2012). "Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies". *Br J Cancer*. Online first (3): 603–7. doi:10.1038/bjc.2011.585. PMC 3273353. PMID 22240790.
40. ^ *a b* Pericleous M, Rossi RE, Mandair D, Whyand T, Caplin ME (January 2014). "Nutrition and pancreatic cancer.". *Anticancer research*. **34** (1): 9–21. PMID 24403441.
41. ^ Fitzgerald JE, White MJ, Lobo DN (April 2009). "Courvoisier's gallbladder: law or sign?" (PDF). *World Journal of Surgery*. **33** (4): 886–91. doi:10.1007/s00268-008-9908-y. PMID 19190960.
42. ^ *a b c d* Seufferlein T, Bachet JB, Van Cutsem E, Rougier P (October 2012). "Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Annals of Oncology*. 23 Suppl 7: vii33–40. doi:10.1093/annonc/mds224. PMID 22997452.
43. ^ Cascinu S, Falconi M, Valentini V, Jelic S (May 2010). "Pancreatic cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Annals of Oncology*. 21 Suppl 5: v55–8. doi:10.1093/annonc/mdq165. PMID 20555103.
44. ^ *a b c* "Staging of pancreatic cancer". *American Cancer Society*. 11 June 2014. Retrieved 29 September 2014.
45. ^ *a b* Zyromski, Nicholas J.; Nakeeb, Attila; Lillemoe, Keith D. (2010). Silberman, Howard; Silberman, Allan W., eds. *Principles and practice of surgical oncology : multidisciplinary approach to difficult problems* (online ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins. Chapter 35. ISBN 978-0-7817-6546-6. Retrieved 3 November 2014.
46. ^ *a b c d* "Neuroendocrine tumors, NCCN Guidelines Version 1.2015" (PDF). *NCCN Guidelines*. National Comprehensive Cancer Network, Inc. November 11, 2014. Retrieved December 25, 2014.
47. ^ National Cancer Institute. Pancreatic Neuroendocrine Tumors (Islet Cell Tumors) Treatment (PDQ®) Incidence and Mortality [2]
48. ^ Delpu Y, Hanoun N, Lulka H, Sicard F, Selves J, Buscail L, Torrisani J, Cordelier P (2011). "Genetic and epigenetic alterations in pancreatic carcinogenesis". *Curr Genomics*. **12** (1): 15–24. doi:10.2174/138920211794520132. PMC 3129039. PMID 21886451.
49. ^ *a b* Lewis MA, Yao JC (Feb 2014). "Molecular pathology and genetics of gastrointestinal neuroendocrine tumours". *Current Opinion in Endocrinology & Diabetes and Obesity*. **21** (1): 22–7. doi:10.1097/MED.0000000000000033. PMID 24310147.
50. ^ Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML (September 2012). "Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1)" (PDF). *The Journal of Clinical Endocrinology and Metabolism*. **97** (9): 2990–3011. doi:10.1210/jc.2012-1230. PMID 22723327.
51. ^ "Diet and activity factors that affect risks for certain cancers: Pancreatic cancer section". *American Cancer*

*Society*. 20 August 2012. Retrieved 4 November 2014.

52. ^ [a] [b] He XY, Yuan YZ (August 2014). "Advances in pancreatic cancer research: moving towards early detection". *World J. Gastroenterol*. **20** (32): 11241–8. doi:10.3748/wjg.v20.i32.11241. PMC 4145762. PMID 25170208.
53. ^ [a] [b] [c] Okano K, Suzuki Y (August 2014). "Strategies for early detection of resectable pancreatic cancer". *World J. Gastroenterol*. **20** (32): 11230–40. doi:10.3748/wjg.v20.i32.11230. PMC 4145761. PMID 25170207.
54. ^ Stoita A, Penman ID, Williams DB (May 2011). "Review of screening for pancreatic cancer in high risk individuals". *World J. Gastroenterol*. **17** (19): 2365–71. doi:10.3748/wjg.v17.i19.2365. PMC 3103788. PMID 21633635.
55. ^ Gurusamy KS, Kumar S, Davidson BR, Fusai G (2014). "Cochrane Database of Systematic Reviews". *The Cochrane database of systematic reviews*. **2** (2): CD010244. doi:10.1002/14651858.CD010244.pub2. PMID 24578248.
56. ^ [a] [b] Mollberg N, Rahbari NN, Koch M, Hartwig W, Hoeger Y, Büchler MW, Weitz J (2011). "Arterial resection during pancreatectomy for pancreatic cancer: A systematic review and meta-analysis". *Annals of Surgery*. **254** (6): 882–93. doi:10.1097/SLA.0b013e31823ac299. PMID 22064622.
57. ^ [a] [b] [c] "Pancreatic adenocarcinoma. NCCN Guidelines Version 1.2015" (PDF). *NCCN Guidelines*. National Comprehensive Cancer Network, Inc. December 4, 2014. Retrieved December 26, 2014.
58. ^ Alamo JM, Marín LM, Suarez G, Bernal C, Serrano J, Barrera L, Gómez MA, Muntané J, Padillo FJ (2014). "Improving outcomes in pancreatic cancer: key points in perioperative management". *World J. Gastroenterol*. **20** (39): 14237–45. doi:10.3748/wjg.v20.i39.14237. PMC 4202352. PMID 25339810.
59. ^ Lopez NE, Prendergast C, Lowy AM (2014). "Borderline resectable pancreatic cancer: definitions and management". *World J. Gastroenterol*. **20** (31): 10740–51. doi:10.3748/wjg.v20.i31.10740. PMC 4138454. PMID 25152577.
60. ^ Polistina F, Di Natale G, Bonciarelli G, Ambrosino G, Frego M (2014). "Neoadjuvant strategies for pancreatic cancer". *World J. Gastroenterol*. **20** (28): 9374–83. doi:10.3748/wjg.v20.i28.9374 (inactive 2016-06-20). PMC 4110569. PMID 25071332.
61. ^ Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J (2010). "Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages". *PLoS Med*. **7** (4): e1000267. doi:10.1371/journal.pmed.1000267. PMC 2857873. PMID 20422030.
62. ^ Christians KK, Evans DB (2014). "Additional Support for Neoadjuvant Therapy in the Management of Pancreatic Cancer". *Ann. Surg. Oncol*. **22** (6): 1755–8. doi:10.1245/s10434-014-4307-0. PMID 25519932.
63. ^ Tsvetkova EV, Asmis TR (2014). "Role of neoadjuvant therapy in the management of pancreatic cancer: is the era of biomarker-directed therapy here?". *Curr Oncol*. **21** (4): e650–7. doi:10.3747/co.21.2006. PMC 4117630. PMID 25089113.
64. ^ Zhan HX, Xu JW, Wu D, Zhang TP, Hu SY (2015). "Pancreatic cancer stem cells: New insight into a stubborn disease". *Cancer Lett*. **357** (2): 429–37. doi:10.1016/j.canlet.2014.12.004. PMID 25499079.
65. ^ [a] [b] Tanase CP, Neagu AI, Necula LG, Mambet C, Enciu AM, Calenic B, Cruceru ML, Albulescu R (2014). "Cancer stem cells: Involvement in pancreatic cancer pathogenesis and perspectives on cancer therapeutics". *World Journal of Gastroenterology*. **20** (31): 10790–801. doi:10.3748/wjg.v20.i31.10790. PMC 4138459. PMID 25152582.
66. ^ Allen VB, Gurusamy KS, Takwoingi Y, Kalia A, Davidson BR (2013). "Diagnostic accuracy of laparoscopy following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer". *Cochrane Database Syst Rev*. **11** (11): CD009323. doi:10.1002/14651858.CD009323.pub2. PMID 24272022.
67. ^ Heinemann V, Haas M, Boeck S (October 2013). "Neoadjuvant treatment of borderline resectable and non-resectable pancreatic cancer.". *Annals of Oncology*. **24** (10): 2484–92. doi:10.1093/annonc/mdt239. PMID 23852311.
68. ^ [a] [b] [c] Thota R, Pauff JM, Berlin JD (January 2014). "Treatment of metastatic pancreatic adenocarcinoma: a review". *Oncology (Williston Park, N.Y.)*. **28** (1): 70–4. PMID 24683721.
69. ^ Ryan, DP (8 July 2014). "Chemotherapy for advanced exocrine pancreatic cancer: Topic 2475, Version 46.0" (subscription required). *UpToDate*. Wolters Kluwer Health. Retrieved 18 November 2014.
70. ^ "Cancer Drug Information: FDA Approval for Erlotinib Hydrochloride". *National Cancer Institute*. National Institutes of Health. 3 July 2013. Retrieved 5 December 2014.
71. ^ Borazanci E, Von Hoff DD; Von Hoff, DD (September 2014). "Nab-paclitaxel and gemcitabine for the treatment of people with metastatic pancreatic cancer". *Expert Rev Gastroenterol Hepatol*. **8** (7): 739–47. doi:10.1586/17474124.2014.925799. PMID 24882381.
72. ^ Falconi M, Bartsch DK, Eriksson B, Klöppel G, Lopes JM, O'Connor JM, Salazar R, Taal BG, Vullierme MP, O'Toole D (2012). "ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: Well-differentiated pancreatic non-functioning tumors". *Neuroendocrinology*. **95** (2): 120–34.

doi:10.1159/000335587. PMID 22261872.
73. ^ Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, Scoazec JY, Salazar R, Sauvanet A, Kianmanesh R (2012). "ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: Functional pancreatic endocrine tumor syndromes". *Neuroendocrinology*. **95** (2): 98–119. doi:10.1159/000335591. PMC 3701449. PMID 22261919.
74. ^ Pavel M, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, Anlauf M, Wiedenmann B, Salazar R (2012). "ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary". *Neuroendocrinology*. **95** (2): 157–76. doi:10.1159/000335597. PMID 22262022.
75. ^ Rossi RE, Massironi S, Conte D, Peracchi M (2014). "Therapy for metastatic pancreatic neuroendocrine tumors". *Annals of Translational Medicine*. **2** (1): 8. doi:10.3978/j.issn.2305-5839.2013.03.01 (inactive 2016-06-20). PMC 4200651. PMID 25332984.
76. ^ Nick Mulcahy (December 17, 2014). "FDA Approves Lanreotide for Neuroendocrine Tumors". *Medscape Medical News*. WebMD LLC. Retrieved December 25, 2014.
77. ^ Everolimus Approved for Pancreatic Neuroendocrine Tumors The ASCO Post. May 15, 2011, Volume 2, Issue 8
78. ^ National Cancer Institute. Cancer Drug Information. FDA Approval for Sunitinib Malate. Pancreatic Neuroendocrine Tumors
79. ^ Tejani MA, Saif MW (2014). "Pancreatic neuroendocrine tumors: Does chemotherapy work?". *JOP: Journal of the pancreas*. **15** (2): 132–4. doi:10.6092/1590-8577/2301 (inactive 2016-06-20). PMID 24618436.
80. ^ Text is available electronically (but may require free registration) See: Benson AB, Myerson RJ, Sasson AR. *Pancreatic, neuroendocrine GI, and adrenal cancers. Cancer Management: A Multidisciplinary Approach 13th edition 2010.* ISBN 978-0-615-41824-7.
81. ^ Gulenchyn KY, Yao X, Asa SL, Singh S, Law C (2012). "Radionuclide therapy in neuroendocrine tumours: A systematic review". *Clinical Oncology*. **24** (4): 294–308. doi:10.1016/j.clon.2011.12.003. PMID 22221516.
82. ^ Vinik AI (2014). "Advances in Diagnosis and Treatment of Pancreatic Neuroendocrine Tumors (PNETS)". *Endocrine Practice*. **20** (11): 1–23. doi:10.4158/EP14373.RA. PMID 25297671.
83. ^ Kwekkeboom DJ, de Herder WW, van Eijck CH, Kam BL, van Essen M, Teunissen JJ, Krenning EP (2010). "Peptide receptor radionuclide therapy in patients with gastroenteropancreatic neuroendocrine tumors". *Seminars in Nuclear Medicine*. **40** (2): 78–88. doi:10.1053/j.semnuclmed.2009.10.004. PMID 20113677.
84. ^ Bodei L, Cremonesi M, Kidd M, Grana CM, Severi S, Modlin IM, Paganelli G (2014). "Peptide receptor radionuclide therapy for advanced neuroendocrine tumors". *Thoracic Surgery Clinics*. **24** (3): 333–49. doi:10.1016/j.thorsurg.2014.04.005. PMID 25065935.
85. ^ Castellano D, Grande E, Valle J, Capdevila J, Reidy-Lagunes D, O'Connor JM, Raymond E (2014). "Expert consensus for the management of advanced or metastatic pancreatic neuroendocrine and carcinoid tumors". *Cancer Chemotherapy and Pharmacology*. **75** (6): 1099–114. doi:10.1007/s00280-014-2642-2. PMID 25480314.
86. ^ Singh S, Dey C, Kennecke H, Kocha W, Maroun J, Metrakos P, Mukhtar T, Pasieka J, Rayson D, Rowsell C, Sideris L, Wong R, Law C (2014). "Consensus Recommendations for the Diagnosis and Management of Pancreatic Neuroendocrine Tumors: Guidelines from a Canadian National Expert Group". *Annals of Surgical Oncology*. **22** (8): 2685–99. doi:10.1245/s10434-014-4145-0. PMID 25366583.
87. ^ "Palliative or Supportive Care". American Cancer Society. 2014. Retrieved 20 August 2014.
88. ^ Buanes TA (14 August 2014). "Pancreatic cancer-improved care achievable". *World Journal of Gastroenterology*. **20** (30): 10405–18. doi:10.3748/wjg.v20.i30.10405. PMC 4130847. PMID 25132756.
89. ^ "If treatment for pancreatic cancer stops working". American Cancer Society. 11 June 2014. Archived from the original on 2014-10-22. Retrieved 20 August 2014.
90. ^ Arcidiacono PG, Calori G, Carrara S, McNicol ED, Testoni PA (2011). Arcidiacono PG, ed. "Celiac plexus block for pancreatic cancer pain in adults". *Cochrane Database Syst Rev* (3): CD007519. doi:10.1002/14651858.CD007519.pub2. PMID 21412903.
91. ^ "Cancer Facts and Figures 2014" (PDF). *American Cancer Society*. Retrieved 5 January 2015., Table, p. 18, rates adjusted for normal life expectancy
92. ^ Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, et al. (December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
93. ^ Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ (2007). "Cancer statistics, 2007". *CA*. **57** (1): 43–66. doi:10.3322/canjclin.57.1.43. PMID 17237035.
94. ^ "What are the key statistics about pancreatic cancer?". *American Cancer Society*. 11 June 2014. Retrieved 11 November 2014.
95. ^ "Pancreatic cancer statistics". *Cancer Research UK*. Retrieved 18 December 2014.; "In 2010, in the UK, the lifetime risk of developing pancreatic cancer is 1 in 73 for men and 1 in 74 for women", noting "The lifetime risk ...

has been calculated ... using the 'Current Probability' method; this is a different method used from most other cancer sites since the possibility of having more than one diagnosis of pancreatic cancer over the course of their lifetime is very low"

96. ^ "Pancreatic cancer statistics". *Cancer Research UK*. Retrieved 28 October 2014.
97. ^ *a b* Busnardo AC, DiDio LJ, Tidrick RT, Thomford NR (1983). "History of the pancreas" (PDF). *American Journal of Surgery*. **146** (5): 539–50. doi:10.1016/0002-9610(83)90286-6. PMID 6356946.
98. ^ *a b c d* Are C, Dhir M, Ravipati L (June 2011). "History of pancreaticoduodenectomy: early misconceptions, initial milestones and the pioneers". *HPB*. **13** (6): 377–84. doi:10.1111/j.1477-2574.2011.00305.x. PMC 3103093. PMID 21609369.
99. ^ *a b* Cameron JL, Riall TS, Coleman J, Belcher KA (July 2006). "One thousand consecutive pancreaticoduodenectomies". *Annals of Surgery*. **244** (1): 10–5. doi:10.1097/01.sla.0000217673.04165.ea. PMC 1570590. PMID 16794383.
100. ^ Fernández-del Castillo C, Morales-Oyarvide V, McGrath D, Wargo JA, Ferrone CR, Thayer SP, Lillemoe KD, Warshaw AL (September 2012). "Evolution of the Whipple procedure at the Massachusetts General Hospital". *Surgery*. **152** (3 Suppl 1): S56–63. doi:10.1016/j.surg.2012.05.022. PMC 3806095. PMID 22770961.
101. ^ Wolpin BM, Stampfer MJ (July 2009). "Defining determinants of pancreatic cancer risk: are we making progress?". *J. Natl. Cancer Inst.* **101** (14): 972–3. doi:10.1093/jnci/djp182. PMID 19561317.
102. ^ "What's new in pancreatic cancer research and treatment?". *American Cancer Society*. 11 June 2014. Retrieved 17 July 2014.
103. ^ "Pancreatic cancer research". *Cancer Research UK*. Retrieved 17 July 2014.
104. ^ "Australian Pancreatic Genome Initiative". Garvan Institute. Retrieved 17 July 2014.
105. ^ Biankin AV, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, Miller DK, Wilson PJ, et al. (November 2012). "Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes". *Nature*. **491** (7424): 399–405. Bibcode:2012Natur.491..399.. doi:10.1038/nature11547. PMC 3530898. PMID 23103869.
106. ^ *a b* Pannala R, Basu A, Petersen GM, Chari ST (January 2009). "New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer". *Lancet Oncol.* **10** (1): 88–95. doi:10.1016/S1470-2045(08)70337-1. PMC 2795483. PMID 19111249.
107. ^ Graham JS, Jamieson NB, Rulach R, Grimmond SM, Chang DK, Biankin AV (November 2014). "Pancreatic cancer genomics: where can the science take us?". *Clin. Genet.* **88** (3): 213–9. doi:10.1111/cge.12536. PMID 25388820.
108. ^ "About EUROPAC". *European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC)*. University of Liverpool. Retrieved 17 July 2014.
109. ^ Zhang C, Yang G, Ling Y, Chen G, Zhou T (December 2014). "The early diagnosis of pancreatic cancer and diabetes: what's the relationship?". *Journal of Gastrointestinal Oncology*. **5** (6): 481–8. doi:10.3978/j.issn.2078-6891.2014.055 (inactive 2016-06-20). PMC 4226830. PMID 25436129.
110. ^ Bruenderman EH, Martin RC (13 October 2014). "High-risk population in sporadic pancreatic adenocarcinoma: guidelines for screening". *The Journal of surgical research*. **194** (1): 212–219. doi:10.1016/j.jss.2014.06.046. PMC 4559279. PMID 25479908.
111. ^ Subar D, Gobardhan PD, Gayet B (2014). "Laparoscopic pancreatic surgery". *Best Practice & Research Clinical Gastroenterology*. **28** (1): 123–32. doi:10.1016/j.bpg.2013.11.011.
112. ^ Weiss MJ, Wolfgang CL (2013). "Irreversible electroporation: a novel pancreatic cancer therapy". *Current Problems in Cancer*. **37** (5): 262–5. doi:10.1016/j.currproblcancer.2013.10.002. PMID 24331180.
113. ^ Moir J, White SA, French JJ, Littler P, Manas DM (December 2014). "Systematic review of irreversible electroporation in the treatment of advanced pancreatic cancer". *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. **40** (12): 1598–1604. doi:10.1016/j.ejso.2014.08.480. PMID 25307210.
114. ^ Al Haddad AH, Adrian TE (November 2014). "Challenges and future directions in therapeutics for pancreatic ductal adenocarcinoma". *Expert Opin Investig Drugs*. **23** (11): 1499–515. doi:10.1517/13543784.2014.933206. PMID 25078674.
115. ^ Adiseshaiah, Pavan P.; Crist, Rachael M.; Hook, Sara S.; McNeil, Scott E. (2016). "Nanomedicine strategies to overcome the pathophysiological barriers of pancreatic cancer". *Nature Reviews Clinical Oncology*. **13**: 750–765. doi:10.1038/nrclinonc.2016.119. ISSN 1759-4774.
116. ^ Kleger A, Perkhofer L, Seufferlein T (July 2014). "Smarter drugs emerging in pancreatic cancer therapy". *Ann. Oncol.* **25** (7): 1260–70. doi:10.1093/annonc/mdu013. PMID 24631947.
117. ^ *a b* Tang SC, Chen YC (August 2014). "Novel therapeutic targets for pancreatic cancer". *World Journal of Gastroenterology*. **20** (31): 10825–44. doi:10.3748/wjg.v20.i31.10825. PMC 4138462. PMID 25152585.
118. ^ *a b* Schober M, Jesenofsky R, Faissner R, Weidenauer C, Hagmann W, Michl P, Heuchel RL, Haas SL, Löhr JM

(2014). "Desmoplasia and chemoresistance in pancreatic cancer". *Cancers (Basel)*. **6** (4): 2137–54. doi:10.3390/cancers6042137. PMC 4276960. PMID 25337831.
119. ^ Rossi ML, Rehman AA, Gondi CS (2014). "Therapeutic options for the management of pancreatic cancer". *World J. Gastroenterol*. **20** (32): 11142–59. doi:10.3748/wjg.v20.i32.11142. PMC 4145755. PMID 25170201.
120. ^ Neesse A, Krug S, Gress TM, Tuveson DA, Michl P (2013). "Emerging concepts in pancreatic cancer medicine: targeting the tumor stroma". *Onco Targets Ther*. **7**: 33–43. doi:10.2147/OTT.S38111. PMC 3872146. PMID 24379681.
121. ^ Heinemann V, Reni M, Ychou M, Richel DJ, Macarulla T, Ducreux M (February 2014). "Tumour-stroma interactions in pancreatic ductal adenocarcinoma: rationale and current evidence for new therapeutic strategies". *Cancer Treat. Rev*. **40** (1): 118–28. doi:10.1016/j.ctrv.2013.04.004. PMID 23849556.
122. ^ Fong Y, Ady J, Heffner J, Klein E (2014). "Oncolytic viral therapy for pancreatic cancer: current research and future directions". *Oncolytic Virotherapy*: 35. doi:10.2147/OV.S53858.
123. ^ Pavelic J (October 2014). "Editorial: combined cancer therapy". *Curr. Pharm. Des*. **20** (42): 6511–2. doi:10.2174/1381612820666140826154834. PMID 25341927.

## External links [edit]

- Pancreatic cancer at DMOZ

Wikimedia Commons has media related to *Pancreatic cancer*.

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|---|---|---|---|
| **GI tract** | **Upper** | **Esophagus** | Squamous cell carcinoma · Adenocarcinoma · |
| | | **Stomach** | Gastric carcinoma · Signet ring cell carcinoma · Gastric lymphoma (MALT lymphoma · · Linitis plastica · |
| | **Lower** | **Small intestine** | Duodenal cancer (Adenocarcinoma · · |
| | | **Appendix** | Carcinoid · Pseudomyxoma peritonei · |
| | | **Colon/rectum** | *colorectal polyp:* Peutz–Jeghers syndrome · Juvenile polyposis syndrome · Familial adenomatous polyposis/Gardner's syndrome · Cronkhite–Canada syndrome · *neoplasm:* Adenocarcinoma · Familial adenomatous polyposis · Hereditary nonpolyposis colorectal cancer · |
| | | **Anus** | Squamous cell carcinoma · |
| | **Upper and/or lower** | | Gastrointestinal stromal tumor · Krukenberg tumor (metastatic) · |
| **Accessory** | **Liver** | | *malignant:* Hepatocellular carcinoma (Fibrolamellar · · Hepatoblastoma · *benign:* Hepatocellular adenoma · Cavernous hemangioma · *hyperplasia:* Focal nodular hyperplasia · Nodular regenerative hyperplasia · |
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| | **Pancreas** | | *exocrine pancreas:* Adenocarcinoma · Pancreatic ductal carcinoma · *cystic neoplasms*: Serous microcystic adenoma · Intraductal papillary mucinous neoplasm · Mucinous cystic neoplasm · Solid pseudopapillary neoplasm · Pancreatoblastoma · |

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| **Peritoneum** | Primary peritoneal carcinoma · Peritoneal mesothelioma · Desmoplastic small round cell tumor · |

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| **Pancreas** | **Pancreatic cancer** · Pancreatic neuroendocrine tumor · α: Glucagonoma · β: Insulinoma · δ: Somatostatinoma · G: Gastrinoma · VIPoma · |
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| **Parathyroid** | Parathyroid neoplasm · Adenoma · Carcinoma · |
| **Pineal gland** | Pinealoma · Pinealoblastoma · Pineocytoma · |
| **MEN** | 1 · 2A · 2B · |

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Categories: Pancreatic cancer | Gastrointestinal cancer | Pancreas disorders

# Prostate cancer

From Wikipedia, the free encyclopedia

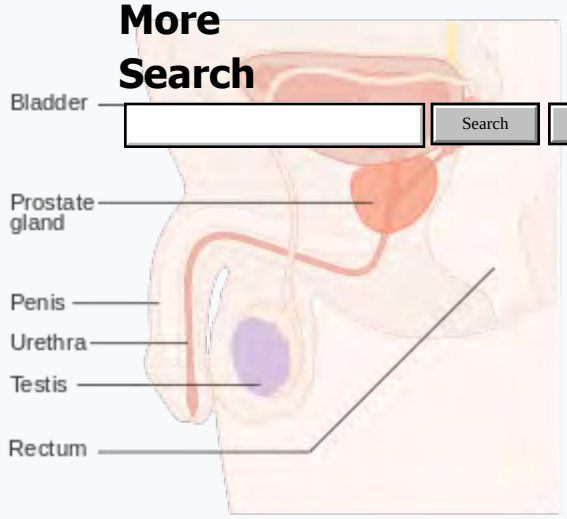
**Prostate cancer**, also known as **carcinoma of the prostate**, is the development of cancer in the prostate, a gland in the male reproductive system.[1] Most prostate cancers are slow growing; however, some grow relatively quickly.[2][3] The cancer cells may spread from the prostate to other parts of the body, particularly the bones and lymph nodes.[4] It may initially cause no symptoms.[3] In later stages it can lead to difficulty urinating, blood in the urine, or pain in the pelvis, back or when urinating.[5] A disease known as benign prostatic hyperplasia may produce similar symptoms. Other late symptoms may include feeling tired due to low levels of red blood cells.[3]

Factors that increase the risk of prostate cancer include: older age, a family history of the disease, and race. About 99% of cases occur in those over the age of 50. Having a first-degree relative with the disease increases the risk two to threefold. In the United States it is more common in the African American population than the white American population. Other factors that may be involved include a diet high in processed meat, red meat, or milk products or low in certain vegetables.[2] An association with gonorrhea has been found, but a reason for this relationship has not been identified.[6] Prostate cancer is diagnosed by biopsy. Medical imaging may then be done to determine if the cancer has spread to other parts of the body.[5]

Prostate cancer screening is controversial.[2][3] Prostate-specific antigen (PSA) testing increases cancer detection but does not decrease mortality.[7] The United States Preventive Services Task Force recommends against screening using the PSA test, due to the risk of overdiagnosis and overtreatment, as most cancer diagnosed would remain asymptomatic. The USPSTF concludes that the potential benefits of testing do not outweigh the expected harms.[8] While 5α-reductase inhibitors appear to decrease low-grade cancer risk they do not affect high-grade cancer risk and thus are not recommended for prevention.[2] Supplementation with vitamins or minerals does not appear to affect the risk.[2][9]

Many cases can be safely followed with active surveillance or watchful waiting. Other treatments may include a combination of surgery, radiation therapy, hormone therapy or chemotherapy.[5] When it only occurs inside the prostate it may be curable.[3] In those in whom the disease has spread to the bones, pain medications, bisphosphonates and targeted therapy, among others, may be useful. Outcomes depend on a

**Prostate cancer**




Position of the prostate

| Classification and external resources | |
|---|---|
| **Specialty** | Oncology |
| **ICD-10** | C61 |
| **ICD-9-CM** | 185 |
| **OMIM** | 176807 |
| **DiseasesDB** | 10780 |
| **MedlinePlus** | 000380 |
| **eMedicine** | radio/574 |
| **Patient UK** | Prostate cancer |
| **MeSH** | D011471 |

[edit on Wikidata]

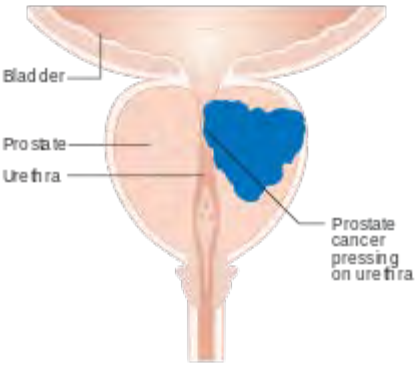
person's age and other health problems as well as how aggressive and extensive the cancer is. Most people with prostate cancer do not end up dying from the disease.[5] The 5-year survival rate in the United States is 99%.[10] Globally it is the second most common type of cancer and the fifth leading cause of cancer-related death in men.[11] In 2012 it occurred in 1.1 million men and caused 307,000 deaths.[11] It was the most common cancer in males in 84 countries,[2] occurring more commonly in the developed world. Rates have been increasing in the developing world.[12] Detection increased significantly in the 1980s and 1990s in many areas due to increased PSA testing.[2] Studies of males who died from unrelated causes have found prostate cancer in 30% to 70% of those over age 60.[3]

**Contents**



## Signs and symptoms [edit]

Early prostate cancer usually has no clear symptoms. Sometimes, however, prostate cancer does cause symptoms, often similar to those of diseases such as benign prostatic hyperplasia. These include frequent urination, nocturia (increased urination at night), difficulty starting and maintaining a steady stream of urine, hematuria (blood in the urine),



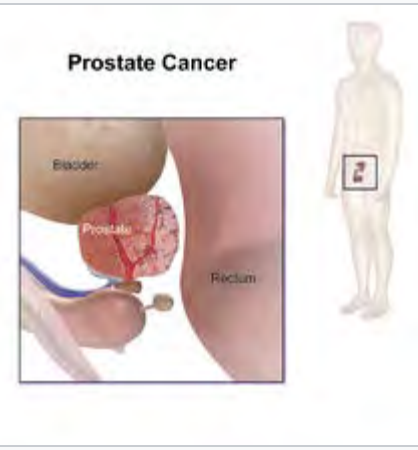

A diagram of prostate cancer pressing on the urethra, which can cause symptoms.

and dysuria (painful urination). A study based on the 1998 Patient Care Evaluation in the US found that about a third of patients diagnosed with prostate cancer had one or more such symptoms, while two-thirds had no symptoms.[13]

Edit links

Prostate cancer is associated with urinary dysfunction as the prostate gland surrounds the prostatic urethra. Changes within the gland, therefore, directly affect urinary function. Because the *vas deferens* deposits seminal fluid into the prostatic urethra, and secretions from the prostate gland itself are included in semen content, prostate cancer may also cause problems with sexual function and performance, such as difficulty achieving erection or painful ejaculation.[13]

Metastatic prostate cancer that has spread to other parts of the body can cause additional symptoms. The most common symptom is bone pain, often in the vertebrae (bones of the spine), pelvis, or ribs. Spread of cancer into other bones such as the femur is usually to the proximal or nearby part of the bone. Prostate cancer in the spine can also compress the spinal cord, causing tingling, leg weakness and urinary and fecal incontinence.[14]




Prostate cancer

## Risk factors [edit]

A complete understanding of the causes of prostate cancer remains elusive.[15] The primary risk factors are obesity, age and family history. Prostate cancer is very uncommon in men younger than 45, but becomes more common with advancing age. The average age at the time of diagnosis is 70.[16] However, many men never know they have prostate cancer. Autopsy studies of Chinese, German, Israeli, Jamaican, Swedish, and Ugandan men who died of other causes have found prostate cancer in 30% of men in their fifties, and in 80% of men in their seventies.[17] Men who have first-degree family members with prostate cancer appear to have double the risk of getting the disease compared to men without prostate cancer in the family.[18] This risk appears to be greater for men with an affected brother than for men with an affected father. In the United States in 2005, there were an estimated 230,000 new cases of prostate cancer and 30,000 deaths due to prostate cancer.[19] Men with high blood pressure are more likely to develop prostate cancer.[20] There is a small increased risk of prostate cancer associated with lack of exercise.[21] A 2010 study found that prostate basal cells were the most common site of origin for prostate cancers.[22]

### Genetic [edit]

Genetic background may contribute to prostate cancer risk, as suggested by associations with race, family, and specific gene variants. Men who have a first-degree relative (father or brother) with prostate cancer have twice the risk of developing prostate cancer, and those with two first-degree relatives affected have a fivefold greater risk compared with men with no family history.[23] In the United States, prostate cancer more commonly affects black men than white or Hispanic men, and is also more deadly in black men.[24][25] In contrast, the incidence and mortality rates for Hispanic men are one third lower than for non-Hispanic whites. Studies of twins in Scandinavia suggest that 40% of prostate cancer risk can be explained by inherited factors.[26]

No single gene is responsible for prostate cancer; many different genes have been implicated. Mutations in

*BRCA1* and *BRCA2*, important risk factors for ovarian cancer and breast cancer in women, have also been implicated in prostate cancer.[27] Other linked genes include the Hereditary Prostate cancer gene 1 (HPC1), the androgen receptor, and the vitamin D receptor.[24] TMPRSS2-ETS gene family fusion, specifically TMPRSS2-ERG or TMPRSS2-ETV1/4 promotes cancer cell growth.[28]

Two large genome-wide association studies linking single nucleotide polymorphisms (SNPs) to prostate cancer were published in 2008.[29][30] These studies identified several SNPs which substantially affect the risk of prostate cancer. For example, individuals with TT allele pair at SNP rs10993994 were reported to be at 1.6 times higher risk of prostate cancer than those with the CC allele pair. This SNP explains part of the increased prostate cancer risk of African American men as compared to American men of European descent, since the C allele is much more prevalent in the latter; this SNP is located in the promoter region of the *MSMB* gene, thus affects the amount of MSMB protein synthesized and secreted by epithelial cells of the prostate.[31]

## Dietary [edit]

While some dietary factors have been associated with prostate cancer the evidence is still tentative.[32] Evidence supports little role for dietary fruits and vegetables in prostate cancer occurrence.[33] Red meat and processed meat also appear to have little effect in human studies.[34] Higher meat consumption has been associated with a higher risk in some studies.[35]

Lower blood levels of vitamin D may increase the risk of developing prostate cancer.[36]

Folic acid supplements have no effect on the risk of developing prostate cancer.[37]

## Medication exposure [edit]

There are also some links between prostate cancer and medications, medical procedures, and medical conditions.[38] Use of the cholesterol-lowering drugs known as the statins may also decrease prostate cancer risk.[39]

Infection or inflammation of the prostate (prostatitis) may increase the chance for prostate cancer while another study shows infection may help prevent prostate cancer by increasing blood to the area. In particular, infection with the sexually transmitted infections chlamydia, gonorrhea, or syphilis seems to increase risk.[40] Finally, obesity[41] and elevated blood levels of testosterone[42] may increase the risk for prostate cancer. There is an association between vasectomy and prostate cancer; however, more research is needed to determine if this is a causative relationship.[43]

Research released in May 2007, found that US war veterans who had been exposed to Agent Orange had a 48% increased risk of prostate cancer recurrence following surgery.[44]

## Infectious disease [edit]

An association with gonorrhea has been found, but a mechanism for this relationship has not been identified.[6]

In 2006, a previously unknown retrovirus, Xenotropic MuLV-related virus or XMRV, was associated with human prostate tumors,[45] but subsequent reports on the virus were contradictory,[46][47] and the original 2006 finding was instead due to a previously undetected contamination.[48] The journals *Science* and *PlosONE* both retracted XMRV related articles.[49][50]

## Sexual factors [edit]

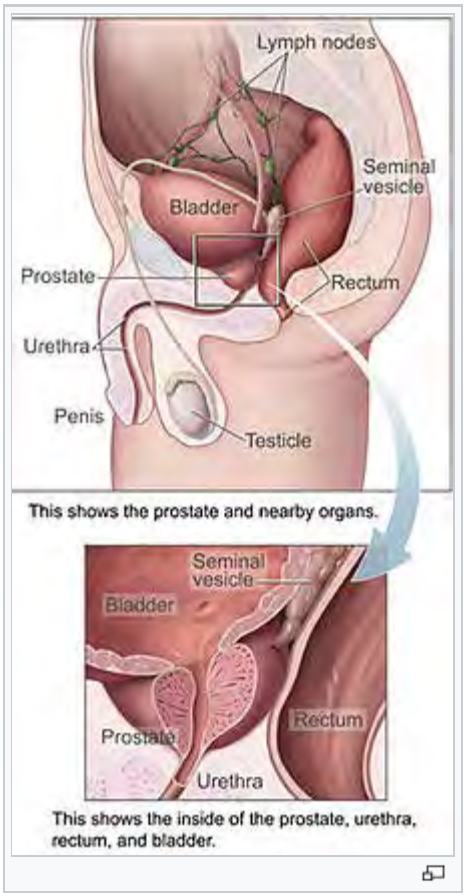
Several case-control studies have shown that having many lifetime sexual partners or starting sexual activity early in life substantially increases the risk of prostate cancer.[51][52][53]

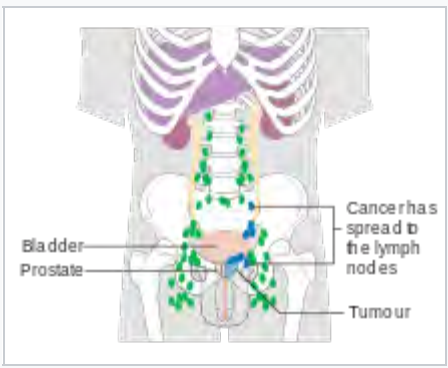
While the available evidence is weak,[54] tentative results suggest that frequent ejaculation may decrease

the risk of prostate cancer.[55] A study, over eight years, showed that those that ejaculated most frequently (over 21 times per month on average) were less likely to get prostate cancer (however, the researchers asserted "ejaculation frequency was not statistically significantly associated with risk of advanced prostate cancer" and concluded "our results suggest that ejaculation frequency is not related to increased risk of prostate cancer").[56] The results were broadly similar to the findings of a smaller Australian study.[57]

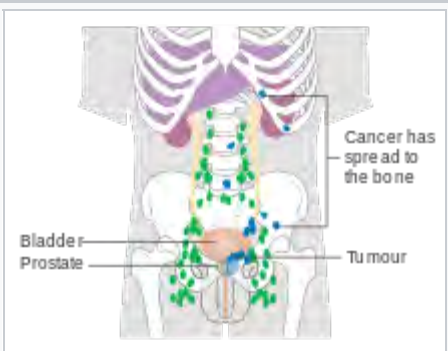
## Pathophysiology [edit]

The prostate is a part of the male reproductive system that helps make and store seminal fluid. In adult men, a typical prostate is about 3 centimeters long and weighs about 20 grams.[58] It is located in the pelvis, under the urinary bladder and in front of the rectum. The prostate surrounds part of the urethra, the tube that carries urine from the bladder during urination and semen during ejaculation.[59] Because of its location, prostate diseases often affect urination, ejaculation, and rarely defecation. The prostate contains many small glands which make about 20% of the fluid constituting semen.[60] In prostate cancer, the cells of these prostate glands mutate into cancer cells. The prostate glands require male hormones, known as androgens, to work properly. Androgens include testosterone, which is made in the testes; dehydroepiandrosterone, made in the adrenal glands; and dihydrotestosterone, which is converted from testosterone within the prostate itself. Androgens are also responsible for secondary sex characteristics such as facial hair and increased muscle mass.




Prostate cancer that has metastasized to the lymph nodes




Prostate cancer that has metastasized to the bone

Prostate cancer is classified as an adenocarcinoma, or glandular cancer, that begins when normal semen-secreting prostate gland cells mutate into cancer cells. The region of prostate gland where the adenocarcinoma is most common is the peripheral zone. Initially, small clumps of cancer cells remain confined to otherwise normal prostate glands, a condition known as carcinoma in situ or prostatic intraepithelial neoplasia (PIN). Although there is no proof that PIN is a cancer precursor, it is closely associated with cancer. Over time, these cancer cells begin to multiply and spread to the surrounding prostate tissue (the stroma) forming a tumor. Eventually, the tumor may grow large enough to invade nearby organs such as the seminal vesicles or the rectum, or the tumor cells may develop the ability to travel in the bloodstream and lymphatic system. Prostate cancer is considered a malignant tumor because it is a mass of cells that can invade other parts of the body. This invasion of other organs is called metastasis. Prostate cancer most commonly metastasizes to the bones, lymph nodes, and may invade rectum, bladder and lower ureters after local progression. The route of metastasis to bone is thought to be venous as the prostatic venous plexus draining the prostate connects with the vertebral veins.[61]

The prostate is a zinc-accumulating, citrate-producing organ. The protein ZIP1 is responsible for the active transport of zinc into prostate cells. One of the zinc's important roles is to change the metabolism of the cell in order to produce citrate, an important component of semen. The process of zinc accumulation, alteration of metabolism, and citrate

production is energy inefficient, and prostate cells sacrifice enormous amounts of energy (ATP) in order to accomplish this task. Prostate cancer cells are generally devoid of zinc. This allows prostate cancer cells to save energy not making citrate, and utilize the new abundance of energy to grow and spread. The absence of zinc is thought to occur via a silencing of the gene that produces the transporter protein ZIP1. ZIP1 is now called a tumor suppressor gene product for the gene SLC39A1. The cause of the epigenetic silencing is unknown. Strategies which transport zinc into transformed prostate cells effectively eliminate these cells in animals. Zinc inhibits NF-κB pathways, is anti-proliferative and induces apoptosis in abnormal cells. Unfortunately, oral ingestion of zinc is ineffective since high concentrations of zinc into prostate cells is not possible without the active transporter, ZIP1.[62]

Loss of cancer suppressor genes, early in the prostatic carcinogenesis, have been localized to chromosomes *8p*, *10q*, *13q*, and *16q*. P53 mutations in the primary prostate cancer are relatively low and are more frequently seen in metastatic settings, hence, p53 mutations are a late event in the pathology of prostate cancer. Other tumor suppressor genes that are thought to play a role in prostate cancer include PTEN (gene) and KAI1. "Up to 70 percent of men with prostate cancer have lost one copy of the PTEN gene at the time of diagnosis"[63] Relative frequency of loss of E-cadherin and CD44 has also been observed.

RUNX2 is a transcription factor that prevents cancer cells from undergoing apoptosis thereby contributing to the development of prostate cancer.[64]

The PI3k/Akt signaling cascade works with the transforming growth factor beta/SMAD signaling cascade to ensure prostate cancer cell survival and protection against apoptosis.[65] X-linked inhibitor of apoptosis (XIAP) is hypothesized to promote prostate cancer cell survival and growth and is a target of research because if this inhibitor can be shut down then the apoptosis cascade can carry on its function in preventing cancer cell proliferation.[66] Macrophage inhibitory cytokine-1 (MIC-1) stimulates the focal adhesion kinase (FAK) signaling pathway which leads to prostate cancer cell growth and survival.[67]

The androgen receptor helps prostate cancer cells to survive and is a target for many anti cancer research studies; so far, inhibiting the androgen receptor has only proven to be effective in mouse studies.[68] Prostate specific membrane antigen (PSMA) stimulates the development of prostate cancer by increasing folate levels for the cancer cells to use to survive and grow; PSMA increases available folates for use by hydrolyzing glutamated folates.[69]

## Diagnosis [edit]

The American Cancer Society's position regarding early detection is "Research has not yet proven that the potential benefits of testing outweigh the harms of testing and treatment. The American Cancer Society believes that men should not be tested without learning about what we know and don't know about the risks and possible benefits of testing and treatment. Starting at age 50, (45 if African American or brother or father suffered from condition before age 65) talk to your doctor about the pros and cons of testing so you can decide if testing is the right choice for you."[70]

The only test that can fully confirm the diagnosis of prostate cancer is a biopsy, the removal of small pieces of the prostate for microscopic examination. However, prior to a biopsy, less invasive testing can be conducted.

There are also several other tests that can be used to gather more information about the prostate and the urinary tract. Digital rectal examination (DRE) may allow a doctor to detect prostate abnormalities. Cystoscopy shows the urinary tract from inside the bladder, using a thin, flexible camera tube inserted down the urethra. Transrectal ultrasonography creates a picture of the prostate using sound waves from a probe in the rectum.

### Prostate imaging [edit]

Ultrasound (US) and magnetic resonance imaging (MRI) are the two main imaging methods used for prostate cancer detection. Urologists use transrectal ultrasound during prostate biopsy and can sometimes see a hypoechoic area (tissues or structures that reflect relatively less of the ultrasound waves directed at

them). However, the US has poor tissue resolution and thus, is generally not clinically used.

Prostate MRI has better soft tissue resolution than ultrasound.[71]

MRI in those who are at low risk might help people choose active surveillance, in those who are at intermediate risk it may help with determining the stage of disease, while in those who are at high risk it might help find bone disease.[72]

Currently (2011), MRI is used to identify targets for prostate biopsy using fusion MRI with ultrasound (US) or MRI-guidance alone. In men who are candidates for active surveillance, fusion MR/US guided prostate biopsy detected 33% of cancers compared to 7% with standard ultrasound guided biopsy.[73]

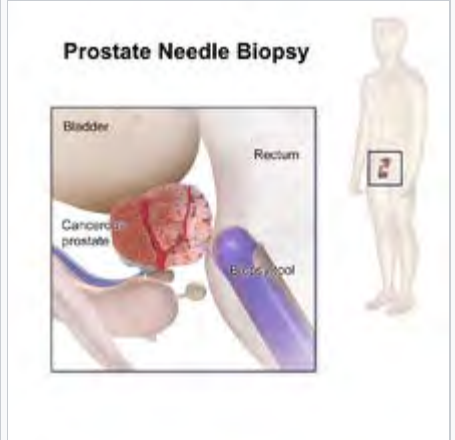
Prostate MRI is also used for surgical planning for men undergoing robotic prostatectomy. It has also shown to help surgeons decide whether to resect or spare the neurovascular bundle, determine return to urinary continence, and help assess surgical difficulty.[74]

For Prostate MRI exists the PI-RADS Reporting system. PI-RADS is an acronym for Prostate Imaging-Reporting and Data System, defining standards of high-quality clinical service for multi-parametric Magnetic Resonance Imaging (mpMRI), including image creation and reporting.

## Biopsy [edit]

*Main article: Prostate biopsy*

If cancer is suspected, a biopsy is offered expediently. During a biopsy a urologist or radiologist obtains tissue samples from the prostate via the rectum. A biopsy gun inserts and removes special hollow-core needles (usually three to six on each side of the prostate) in less than a second. Prostate biopsies are routinely done on an outpatient basis and rarely require hospitalization. Antibiotics should be used to prevent complications like fever, urinary tract infections, and sepsis.[75] Fifty-five percent of men report discomfort during prostate biopsy.[76]

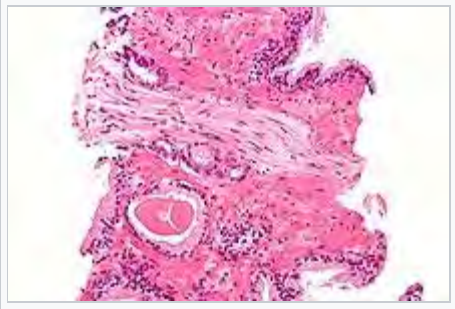


Prostate needle biopsy

## Gleason score [edit]

*Main article: Gleason score*

The tissue samples are then examined under a microscope to determine whether cancer cells are present, and to evaluate the microscopic features (or Gleason score) of any cancer found. Prostate specific membrane antigen is a transmembrane carboxypeptidase and exhibits folate hydrolase activity.[77] This protein is overexpressed in prostate cancer tissues and is associated with a higher Gleason score.[77]


Micrograph showing a prostate cancer (conventional adenocarcinoma) with perineural invasion. H&E stain.

## Tumor markers [edit]

Tissue samples can be stained for the presence of PSA and other tumor markers in order to determine the origin of malignant cells that have metastasized.[78]

Small cell carcinoma is a very rare (1%[79]) type of prostate cancer that cannot be diagnosed using the PSA.[79][80] As of 2009 researchers were researching ways to screen for this type of prostate cancer, because it is relatively unknown and rare, but very serious and quick to spread to other parts of the body.[80] Possible methods include chromatographic separation methods by mass spectrometry, or protein capturing by immunoassays or immunized antibodies. The test method will involve quantifying the amount of the biomarker PCI, with reference to the Gleason Score. This test quick and sensitive. It can detect patients in the diagnostic grey zone, particularly those with a serum free to total

Prostate Specific Antigen ratio of 10-20%.[81]

The oncoprotein BCL-2 is associated with the development of androgen-independent prostate cancer, due to its high levels of expression in androgen-independent tumours in advanced stages of the pathology. The upregulation of BCL-2 after androgen ablation in prostate carcinoma cell lines and in a castrated-male rat model further established a connection between BCL-2 expression and prostate cancer progression.[82]

The expression of Ki-67 by immunohistochemistry may be a significant predictor of patient outcome for men with prostate cancer.[83]

ERK5 is a protein that may be used as a marker. It is present in abnormally high levels in cases of prostate cancer, including invasive cancer that has metastasized. It is also present in relapsed cancer following previous hormone therapy. Reducing the amount of ERK5 in cancerous cells reduces their invasiveness.[84]

## Staging [edit]

*Main article: Prostate cancer staging*

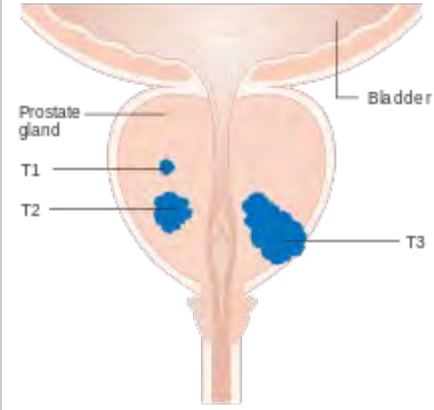
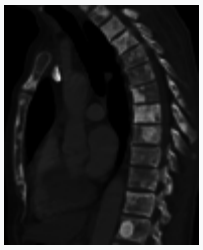


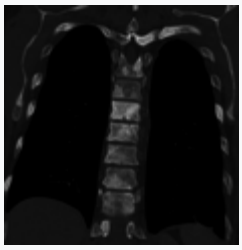
Diagram showing T1-3 stages of prostate cancer.

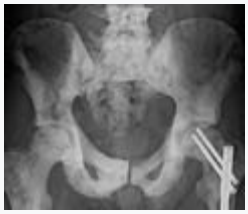
An important part of evaluating prostate cancer is determining the stage, or how far the cancer has spread. Knowing the stage helps define prognosis and is useful when selecting therapies. The most common system is the four-stage TNM system (abbreviated from Tumor/Nodes/Metastases). Its components include the size of the tumor, the number of involved lymph nodes, and the presence of any other metastases.[85]

The most important distinction made by any staging system is whether or not the cancer is still confined to the prostate. In the TNM system, clinical T1 and T2 cancers are found only in the prostate, while T3 and T4 cancers have spread elsewhere. Several tests can be used to look for evidence of spread. Medical specialty professional organizations recommend against the use of PET scans, CT scans, or bone scans when a physician stages early prostate cancer with low risk for metastasis.[86] Those tests would be appropriate in such cases as when a CT scan evaluates spread within the pelvis, a bone scan look for spread to the bones, and endorectal coil magnetic resonance imaging to closely evaluate the prostatic capsule and the seminal vesicles. Bone scans should reveal osteoblastic appearance due to *increased* bone density in the areas of bone metastasis—opposite to what is found in many other cancers that metastasize.

After a prostate biopsy, a pathologist looks at the samples under a microscope. If cancer is present, the pathologist reports the grade of the tumor. The grade tells how much the tumor tissue differs from normal prostate tissue and suggests how fast the tumor is likely to grow. The Gleason system is used to grade prostate tumors from 2 to 10, where a Gleason score of 10 indicates the most abnormalities. The pathologist assigns a number from 1 to 5 for the most common pattern observed under the microscope, then does the same for the second-most-common pattern. The sum of these two numbers is the Gleason score. The Whitmore-Jewett stage is another method sometimes used.


Sclerosis of the bones of the thoracic spine


Sclerosis of the bones of the thoracic spine


Sclerosis of the bones of the pelvis due to

due to prostate cancer metastases (CT image)

due to prostate cancer metastases (CT image)

prostate cancer metastases

# Prevention [edit]

## Diet and lifestyle [edit]

The data on the relationship between diet and prostate cancer is poor.[87] In light of this the rate of prostate cancer is linked to the consumption of the Western diet.[87] There is little if any evidence to support an association between trans fat, saturated fat and carbohydrate intake and risk of prostate cancer.[87][88] Evidence regarding the role of omega-3 fatty acids in preventing prostate cancer does not suggest that they reduce the risk of prostate cancer, although additional research is needed.[87][89] Vitamin supplements appear to have no effect and some may increase the risk.[9][87] High calcium intake has been linked to advanced prostate cancer.[90] Consuming fish may lower prostate cancer deaths but does not appear to affect its occurrence.[91] Some evidence supports lower rates of prostate cancer with a vegetarian diet.[92] There is some tentative evidence for foods containing lycopene and selenium.[93] Diets rich in cruciferous vegetables, soy, beans and other legumes may be associated with a lower risk of prostate cancer, especially more advanced cancers.[94]

Men who get regular exercise may have a slightly lower risk, especially vigorous activity and the risk of advanced prostate cancer.[94]

## Medications [edit]

In those who are being regularly screened 5-alpha-reductase inhibitor (finasteride and dutasteride) reduce the overall risk of being diagnosed with prostate cancer however there is insufficient data to determine if they have an effect on the risk of death and may increase the chance of more serious cases.[95]

# Screening [edit]

*Main article: Prostate cancer screening*

Prostate cancer screening is an attempt to find unsuspected cancers. Initial screens may lead to more invasive follow-up tests such as a biopsy.[96] Options include the digital rectal exam (DRE) and the prostate-specific antigen (PSA) blood test. Such screening is controversial and, in some people, may lead to unnecessary disruption and possibly harmful consequences.[97] Routine screening with either a DRE or PSA is not supported by the evidence as there is no mortality benefit from screening.[7]

The United States Preventive Services Task Force (USPSTF) recommends against the PSA test for prostate cancer screening in healthy men regardless of age.[98] They concluded that the potential benefit of testing does not outweigh the expected harms.[8][99] The Centers for Disease Control and Prevention shared that conclusion.[100] The American Society of Clinical Oncology and the American College of Physicians discourages screening for those who are expected to live less than ten to fifteen years, while in those with a greater life expectancy a decision should be made by the person in question based on the potential risks and benefits.[101] In general, they concluded, "it is uncertain whether the benefits associated with PSA testing for prostate cancer screening are worth the harms associated with screening and subsequent unnecessary treatment."[102] American Urological Association (AUA 2013) guidelines call for weighing the benefits of preventing prostate cancer mortality in 1 man for every 1,000 men screened over a ten-year period against the known harms associated with diagnostic tests and treatment. The AUA recommends screening decisions in those 55 to 69 be based on shared decision making, and that if screening is performed it should occur no more often than every two years.[103]

# Management [edit]

*Main article: Management of prostate cancer*

The first decision to be made in managing prostate cancer is whether treatment is needed. Prostate cancer, especially low-grade forms found in elderly men, often grows so slowly that no treatment is required.[104] Treatment may also be inappropriate if a person has other serious health problems or is not expected to live long enough for symptoms to appear.

Which option is best depends on the stage of the disease, the Gleason score, and the PSA level. Other important factors are age, general health, and a person's views about potential treatments and their possible side effects. Because most treatments can have significant side effects, such as erectile dysfunction and urinary incontinence, treatment discussions often focus on balancing the goals of therapy with the risks of lifestyle alterations. A combination of the treatment options is often recommended for managing prostate cancer.[105][106][107]

Guidelines for treatment for specific clinical situations requires a good estimation of a person's long-term life expectancy.[108] People can also use an 18-item questionnaire to learn whether they have good knowledge and understanding about their treatment options before they choose. Most of those who are newly diagnosed and made a treatment choice can not correctly answer over half of the questions.[108]

If radiation therapy is done first, and fails, then radical prostatectomy becomes a very technically challenging surgery and may not be feasible. On the other hand, radiation therapy done after surgical failure may have many complications.[109] It is associated with a small increase in bladder and colon cancer.[110]

In localized disease, it is unknown if radical prostatectomy is better or worse than watchful waiting.[111]

A meta-analysis on the effects of voiding position during urination in males with prostate enlargement showed that sitting was superior to standing. Bladder emptying was significantly improved, while there was a trend towards a higher urinary flow and shorter voiding time.[112]

## Surveillance [edit]

Many men diagnosed with low-risk prostate cancer are eligible for *active surveillance*. This term implies careful observation of the tumor over time, with the intention of treatment for a cure if there are signs of cancer progression. Active surveillance is *not* synonymous with watchful waiting, an older term which implies no treatment or specific program of monitoring, with the assumption that *palliative*, not curative, treatment would be used if advanced, symptomatic disease develops.

Active surveillance involves monitoring the tumor for signs of growth or the appearance of symptoms. The monitoring process may involve serial PSA, physical examination of the prostate, and/or repeated biopsies. The goal of surveillance is to avoid overtreatment and the sometimes serious, permanent side effects of treatment for a slow-growing or self-limited tumor that would never cause any problems for the person. This approach is not used for aggressive cancers, but it may cause anxiety for people who wrongly believe that all cancer is deadly or themselves to have life-threatening cancer. For 50% to 75% of people with prostate cancer it will cause no harm before a person dies from other causes.[113]

## Aggressive cancer [edit]

Treatment of aggressive prostate cancers may involve surgery (i.e. radical prostatectomy), radiation therapy including brachytherapy (prostate brachytherapy) and external beam radiation therapy, high-intensity focused ultrasound (HIFU), chemotherapy, oral chemotherapeutic drugs (Temozolomide/TMZ), cryosurgery, hormonal therapy, or some combination.[114][115]

Although the widespread use of prostate-specific antigen (PSA) screening in the USA has resulted in diagnosis at earlier age and cancer stage, the vast majority of cases are still diagnosed in men older than 65 years, and approximately 25% of cases are diagnosed in men older than 75 years.[116] Though US

National Comprehensive Cancer Network guidelines recommend using life expectancy greater than or less than 10 years to help make treatment decisions, in practice, many elderly patients are not offered curative treatment options such as radical prostatectomy or radiation therapy and are instead treated with hormonal therapy or watchful waiting.[117] This pattern can be attributed to factors such as medical co-morbidity and patient preferences is regard to quality of life in addition to prostate cancer specific risk factors such as pretreatment PSA, Gleason score and clinical stage. As the average life expectancy increases due to advances in the treatment of cardiovascular, pulmonary and other chronic diseases, it is likely that more elderly patients will be living long enough to suffer the consequences of their prostate cancer. Therefore, there is currently much interest in the role of aggressive prostate cancer treatment modalities such as with surgery or radiation in the elderly population who have localized disease.

If the cancer has spread beyond the prostate, treatment options significantly change, so most doctors that treat prostate cancer use a variety of nomograms to predict the probability of spread. Treatment by watchful waiting/active surveillance, external beam radiation therapy, brachytherapy, cryosurgery, HIFU, and surgery are, in general, offered to men whose cancer remains within the prostate. Hormonal therapy and chemotherapy are often reserved for disease that has spread beyond the prostate. However, there are exceptions: radiation therapy may be used for some advanced tumors, and hormonal therapy is used for some early stage tumors. Cryotherapy (the process of freezing the tumor), hormonal therapy, and chemotherapy may also be offered if initial treatment fails and the cancer progresses.

Sipuleucel-T, a cancer vaccine has been found to result in a benefit (a four-month increase in survival) for men with metastatic prostate cancer.[118]

## Castration-resistant [edit]

*Main article: Castration-resistant prostate cancer*

Most hormone dependent cancers become resistant to treatment after one to three years and resume growth despite hormone therapy. Previously considered "hormone-refractory prostate cancer" or "androgen-independent prostate cancer", the term castration-resistant has replaced "hormone refractory" because while they are no longer responsive to castration treatment (reduction of available androgen/testosterone/DHT by chemical or surgical means), these cancers still show reliance upon hormones for androgen receptor activation.[119]

The cancer chemotherapic docetaxel has been used as treatment for CRPC with a median survival benefit of 2 to 3 months.[120][121] A second-line chemotherapy treatment is cabazitaxel.[122] A combination of bevacizumab, docetaxel, thalidomide and prednisone appears effective in the treatment of CRPC.[123]

The immunotherapy treatment with sipuleucel-T in CRPC increases survival by 4 months.[124] The second line hormonal therapy abiraterone increases survival by 4.6 months when compared to placebo.[125] Enzalutamide is another second line hormonal agent with a 5-month survival advantage over placebo. Both abiraterone and enzalutamide are currently being tested in clinical trials in those with CRPC who have not previously received chemotherapy.[126][127]

Only a subset of people respond to androgen signaling blocking drugs and certain cells with characteristics resembling stem cells remain unaffected.[128][129] Therefore, the desire to improve outcome of people with CRPC has resulted in the claims of increasing doses further or combination therapy with synergistic androgen signaling blocking agents.[130] But even these combination will not affect stem-like cells that do not exhibit androgen signaling. It is possible that for further advances, a combination of androgen signaling blocking agent with stem-like cell directed differentiation therapy drug would prove ideal.[131]

## Palliative care [edit]

Palliative care is medical care which focuses on treatment of symptoms of serious illness, like cancer, and improving quality of life.[132] One of the goals of treatment in palliative care is symptom control rather than a cure of the underlying cancer. Pain is common in metastatic prostate cancer, and cancer pain related to bone metastases can be treated with bisphosphonates, medications such as opioids, and palliative radiation therapy to known metastases. Spinal cord compression can occur with metastases to the spine and can be

treated with steroids, surgery, or radiation therapy. Other symptoms that can be addressed through palliative care include fatigue, delirium, lymphedema in the scrotum or penis, nausea, vomiting, and weight loss.[133]

## Prognosis [edit]

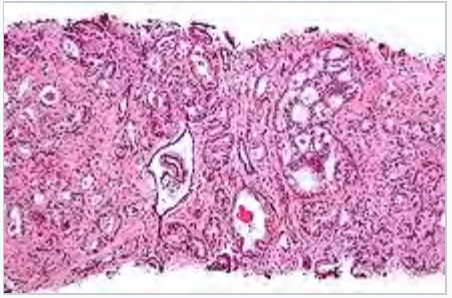
Prostate cancer rates are higher and prognoses are poorer in developed countries than in the rest of the world. Many of the risk factors for prostate cancer are more prevalent in the developed world, including longer life expectancy and diets high in red meat. Also, where there is more access to screening programs, there is a higher detection rate. Prostate cancer affected 18% of American men and caused death in 3% in 2005.[19] In the United States, prostate cancers that are local or regional at the time of diagnosis have a 5-year survival rate of nearly 100%, while those with distant metastases have a 5-year survival rate of 28%.[134] In Japan, death from prostate cancer was one-fifth to one-half the rates in the United States and Europe in the 1990s.[135] In India in the 1990s, half of the people with prostate cancer confined to the prostate died within 19 years.[136] African-American men have 50–60 times more prostate cancer and prostate cancer deaths than men in Shanghai, China.[137] In Nigeria, 2% of men develop prostate cancer, and 64% of them are dead after 2 years.[138]

In patients who undergo treatment, the most important clinical prognostic indicators of disease outcome are the stage, pretherapy PSA level, and Gleason score. In general, the higher the grade and the stage, the poorer the prognosis. Nomograms can be used to calculate the estimated risk of the individual patient. The predictions are based on the experience of large groups of patients suffering from cancers at various stages.[139]

In 1941, Charles Huggins reported that androgen ablation therapy causes regression of primary and metastatic androgen-dependent prostate cancer.[140] He was awarded the 1966 Nobel Prize for Physiology or Medicine for this discovery. Androgen ablation therapy causes remission in 80-90% of patients undergoing therapy, resulting in a median progression-free survival of 12 to 33 months. After remission, an androgen-independent phenotype typically emerges, wherein the median overall survival is 23–37 months from the time of initiation of androgen ablation therapy.[141] It is not clear how the prostate cancer becomes androgen-independent or how it reestablishes progression, although a few possibilities (on how) have been proposed.[142] And the way the cancer changes, to overcome the lack of androgen, may vary between individual patients.

### Classification systems [edit]

Many prostate cancers are not destined to be lethal, and most men will ultimately not die as a result of the disease. Decisions about treatment type and timing may, therefore, be informed by an estimation of the risk that the tumor will ultimately recur after treatment and/or progress to metastases and mortality. Several tools are available to help predict outcomes, such as pathologic stage and recurrence after surgery or radiation therapy. Most combine stage, grade, and PSA level, and some also add the number or percentage of biopsy cores positive, age, and/or other information.



Micrograph of prostate adenocarcinoma, acinar type, the most common type of prostate cancer. Needle biopsy, H&E stain

- The *D'Amico classification* stratifies men by low, intermediate, or high risk based on stage, grade, and PSA. It is used widely in clinical practice and research settings. The major downside to the 3-level system is that it does not account for multiple adverse parameters (e.g., high Gleason score *and* high PSA) in stratifying patients.
- The Partin tables[143] predict pathologic outcomes (margin status, extraprostatic extension, and seminal vesicle invasion) based on the same three variables and are published as lookup tables.
- The *Kattan nomograms* predict recurrence after surgery and/or radiation therapy, based on data

available either at the time of diagnosis or after surgery. The nomograms can be calculated using paper graphs or software available on a website or for handheld computers. The Kattan score represents the likelihood of remaining free of disease at a given time interval following treatment.
- The UCSF *Cancer of the Prostate Risk Assessment (CAPRA) score* predicts both pathologic status and recurrence after surgery. It offers comparable accuracy as the Kattan preoperative nomogram and can be calculated without paper tables or a calculator. Points are assigned based on PSA, Grade, stage, age, and percentage of cores positive; the sum yields a 0–10 score, with every 2 points representing roughly a doubling of risk of recurrence. The CAPRA score was derived from community-based data in the CaPSURE database. It has been validated among over 10,000 prostatectomy patients, including patients from CaPSURE;[144] the SEARCH registry, representing data from several Veterans Administration and active military medical centers;[145] a multi-institutional cohort in Germany;[146] and the prostatectomy cohort at Johns Hopkins University.[147] More recently, it has been shown to predict metastasis and mortality following prostatectomy, radiation therapy, watchful waiting, or androgen deprivation therapy.[148]

## Life expectancy [edit]

Life expectancy projections are averages for an entire male population, and many medical and lifestyle factors modify these numbers. For example, studies have shown that a 40-year-old man will lose 3.1 years of life if he is overweight (BMI 25-29) and 5.8 years of life if he is obese (BMI 30 or more), compared to men of normal weight. If he is both overweight and a smoker, he will lose 6.7 years, and if obese and a smoker, he will lose 13.7 years.[149]

At this time, there is no evidence that either surgery or beam radiation has an advantage over the other in this regard, the lower death rates reported with surgery appear to occur because surgery is more likely to be offered to younger men with less serious forms of cancer. Insufficient information is available to determine whether seed radiation extends life more readily than the other treatments, but data so far do not suggest that it does.[150]

People with low-grade disease (Gleason 2-4) were unlikely to die of prostate cancer within 15 years of diagnosis. Older men (age 70-75) with low-grade disease had an approximately 20% overall survival at 15 years due to deaths from competing causes. Men with high-grade disease (Gleason 8-10) experienced high prostate cancer mortality within 15 years of diagnosis, regardless of their age at diagnosis, underscoring the very aggressive nature of poorly differentiated prostate cancer.[151]

# Epidemiology [edit]

As of 2012, prostate cancer is the second most frequently diagnosed cancer (at 15% of all male cancers)[153] and the sixth leading cause of cancer death in males worldwide.[154] In 2010 it resulted in 256,000 deaths up from 156,000 deaths in 1990.[155] Rates of prostate cancer vary widely across the world. Although the rates vary widely between countries, it is least common in South and East Asia, and more common in Europe, North America, Australia and New Zealand.[156] Prostate cancer is least common among Asian men and most common among black men, with figures for white men in between.[157][158] The average annual incidence rate of prostate cancer between 1988 and 1992 among Chinese men in the United States was 15 times higher than that of their counterparts living in Shanghai and Tianjin.[157][158][159] However, these high rates may be affected by increasing rates of detection.[160] Many suggest that prostate cancer may be under reported, yet BPH incidence in China and Japan is similar to rates in Western countries.[161][162] In Europe in 2012 it was the 3rd most diagnosed cancer after breast and colorectal at 417,000

Age-standardized death from prostate cancer per 100,000 inhabitants in 2004.[152]

| | | |
|---|---|---|
| no data | 12-16 | 28-32 |
| <4 | 16-20 | 32-36 |
| 4-8 | 20-24 | 36-40 |
| 8-12 | 24-28 | 40-44 |
| | | >44 |

cases.[163]

Prostate cancer develops primarily in men over fifty. It is the most common type of cancer in men in the United States, with 186,000 new cases in 2008 and 28,600 deaths.[164] It is the second leading cause of cancer death in U.S. men after lung cancer. In the United Kingdom it is also the second most common cause of cancer death after lung cancer, where around 35,000 cases are diagnosed every year and of which around 10,000 die of it.[165]

More than 80% of men will develop prostate cancer by the age of 80.[166] However, in the majority of cases, it will be slow-growing and harmless. In such men, diagnosing prostate cancer is overdiagnosis—the needless identification of a technically aberrant condition that will never harm the patient—and treatment in such men exposes them to all of the adverse effects, with no possibility of extending their lives.[167]

## History [edit]

Although the prostate was first described by Venetian anatomist Niccolò Massa in 1536, and illustrated by Flemish anatomist Andreas Vesalius in 1538, prostate cancer was not identified until 1853.[168] Prostate cancer was initially considered a rare disease, probably because of shorter life expectancies and poorer detection methods in the 19th century. The first treatments of prostate cancer were surgeries to relieve urinary obstruction.[169] Removal of the entire gland (radical perineal prostatectomy) was first performed in 1904 by Hugh H. Young at Johns Hopkins Hospital.[170] Surgical removal of the testes (orchiectomy) to treat prostate cancer was first performed in the 1890s, but with limited success. Transurethral resection of the prostate (TURP) replaced radical prostatectomy for symptomatic relief of obstruction in the middle of the 20th century because it could better preserve penile erectile function. Radical retropubic prostatectomy was developed in 1983 by Patrick Walsh.[171] This surgical approach allowed for removal of the prostate and lymph nodes with maintenance of penile function.

In 1941, Charles B. Huggins published studies in which he used estrogen to oppose testosterone production in men with metastatic prostate cancer. This discovery of "chemical castration" won Huggins the 1966 Nobel Prize in Physiology or Medicine.[172] The role of the gonadotropin-releasing hormone (GnRH) in reproduction was determined by Andrzej W. Schally and Roger Guillemin, who both won the 1977 Nobel Prize in Physiology or Medicine for this work. GnRH receptor agonists, such as leuprolide and goserelin, were subsequently developed and used to treat prostate cancer.[173][174]

Radiation therapy for prostate cancer was first developed in the early 20th century and initially consisted of intraprostatic radium implants. External beam radiotherapy became more popular as stronger [X-ray] radiation sources became available in the middle of the 20th century. Brachytherapy with implanted seeds (for prostate cancer) was first described in 1983.[175]

Systemic chemotherapy for prostate cancer was first studied in the 1970s. The initial regimen of cyclophosphamide and 5-fluorouracil was quickly joined by multiple regimens using a host of other systemic chemotherapy drugs.[176]

### Cell-of-origin [edit]

A series of studies published in *Science* involved introduced viruses known to cause cancerous mutation in prostate cells: AKT, ERG, and AR into isolated samples of basal and luminal cells and grafted the treated tissue into mice. After 16 weeks, none of the luminal samples had undergone malignant mutation, while the basal samples had mutated into prostate-like tubules which had then developed malignancy and formed cancerous tumors, which appeared identical to human samples under magnification. This led to the conclusion that the prostate basal cell may be the most likely "site of origin" of prostate cancer.[22]

## Society and culture [edit]

People with prostate cancer generally encounter significant disparities in awareness, funding, media

coverage, and research—and therefore, inferior treatment and poorer outcomes—compared to other cancers of equal prevalence.[177] In 2001, *The Guardian* noted that Britain had 3,000 nurses specializing in breast cancer, compared to only one for prostate cancer. It also discovered that the waiting time between referral and diagnosis was two weeks for breast cancer but three months for prostate cancer.[178] A 2007 report by the U.S.-based National Prostate Cancer Coalition stated that for every prostate cancer drug on the market, there were seven used to treat breast cancer. *The Times* also noted an "anti-male bias in cancer funding" with a four-to-one discrepancy in the United Kingdom by both the government and by cancer charities such as Cancer Research UK.[177][179] Equality campaigners such as author Warren Farrell cite such stark spending inequalities as a clear example of governments unfairly favouring women's health over men's health.[180]

Disparities also extend into areas such as detection, with governments failing to fund or mandate prostate cancer screening while fully supporting breast cancer programs. For example, a 2007 report found 49 U.S. states mandate insurance coverage for routine breast cancer screening, compared to 28 for prostate cancer.[177][181] Prostate cancer also experiences significantly less media coverage than other, equally prevalent cancers, with a study by Prostate Coalition showing 2.6 breast cancer stories for each one covering cancer of the prostate.[177]

Prostate Cancer Awareness Month takes place in September in a number of countries. A light blue ribbon is used to promote the cause.[182][183]

## Research [edit]

### CRPC [edit]

MDV3100 was in phase III trials for CRPC (chemo-naive and post-chemo patient populations)[184] and gained FDA approval in 2012 as enzalutamide for the treatment of castration-resistant prostate cancer.[126][127]

Alpharadin completed a phase 3 trial for CRPC patients with bone metastasis. A pre-planned interim analysis showed improved survival and quality of life. The study was stopped for ethical reasons to give the placebo group the same treatment. Alpharadin uses bone targeted Radium-223 isotopes to kill cancer cells by alpha radiation.[185] It was approved by the U.S. Food and Drug Administration (FDA) on May, 15th 2013 ahead of schedule under the priority review program.[186] Alpharadin still waits for approval by the European Medicines Agency (EMA).

As of 2016 PARP inhibitor olaparib has shown promise in clinical trials for CRPC.[187] Also in trials for CRPC are : checkpoint inhibitor ipilimumab, CYP17 inhibitor galeterone (TOK-001), and immunotherapy PROSTVAC.[187]

### Pre-clinical [edit]

Arachidonate 5-lipoxygenase has been identified as playing a significant role in the survival of prostate cancer cells.[188][189][190] Medications which target this enzyme may be an effective therapy for limiting tumor growth and cancer metastasis as well as inducing programmed cell death in cancer cells.[188][189][190] In particular, arachidonate 5-lipoxygenase inhibitors produce massive, rapid programmed cell death in prostate cancer cells.[188][189][190]

### Cancer models [edit]

Scientists have established a few prostate cancer cell lines to investigate the mechanism involved in the progression of prostate cancer. LNCaP, PC-3 (PC3), and DU-145 (DU145) are commonly used prostate cancer cell lines. The LNCaP cancer cell line was established from a human lymph node metastatic lesion of prostatic adenocarcinoma. PC-3 and DU-145 cells were established from human prostatic adenocarcinoma metastatic to bone and to brain, respectively. LNCaP cells express androgen receptor (AR); however, PC-3

and DU-145 cells express very little or no AR. AR, an androgen-activated transcription factor, belongs to the steroid nuclear receptor family. Development of the prostate is dependent on androgen signaling mediated through AR, and AR is also important during the development of prostate cancer. The proliferation of LNCaP cells is androgen-dependent but the proliferation of PC-3 and DU-145 cells is androgen-insensitive. Elevation of AR expression is often observed in advanced prostate tumors in patients.[191][192] Some androgen-independent LNCaP sublines have been developed from the ATCC androgen-dependent LNCaP cells after androgen deprivation for study of prostate cancer progression. These androgen-independent LNCaP cells have elevated AR expression and express prostate specific antigen upon androgen treatment. The paradox is that androgens inhibit the proliferation of these androgen-independent prostate cancer cells.[193][194][195]

## Diagnosis [edit]

At present, an active area of research and non-clinically applied investigations involve non-invasive methods of prostate tumor detection.

A molecular test that detects the presence of cell-associated PCA3 mRNA in fluid massaged from the prostate by the doctor and first-void urinated out has also been under investigation. PCA3 mRNA is expressed almost exclusively by prostate cells and has been shown to be highly over-expressed in prostate cancer cells. The test result is currently reported as a specimen ratio of PCA3 mRNA to PSA mRNA. Although not a replacement for serum PSA level, the PCA3 test is an additional tool to help decide whether, in men suspected of having prostate cancer (especially if an initial biopsy fails to explain the elevated serum PSA), a biopsy/rebiopsy is really needed. The higher the expression of PCA3 in the sample, the greater the likelihood of a positive biopsy; i.e., the presence of cancer cells in the prostate.[196]

# References [edit]


1. ^ "Prostate Cancer". *National Cancer Institute*. Retrieved 12 October 2014.
2. ^ a b c d e f g *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 5.11. ISBN 9283204298.
3. ^ a b c d e f "Prostate Cancer Treatment (PDQ) – Health Professional Version". National Cancer Institute. 2014-04-11. Retrieved 1 July 2014.
4. ^ Ruddon, Raymond W. (2007). *Cancer biology* (4th ed.). Oxford: Oxford University Press. p. 223. ISBN 9780195175431.
5. ^ a b c d "Prostate Cancer Treatment (PDQ) – Patient Version". National Cancer Institute. 2014-04-08. Retrieved 1 July 2014.
6. ^ a b Caini, Saverio; Gandini, Sara; Dudas, Maria; Bremer, Viviane; Severi, Ettore; Gherasim, Alin (2014). "Sexually transmitted infections and prostate cancer risk: A systematic review and meta-analysis". *Cancer Epidemiology*. **38** (4): 329–338. doi:10.1016/j.canep.2014.06.002. PMID 24986642.
7. ^ a b Djulbegovic M, Beyth RJ, Neuberger MM, Stoffs TL, Vieweg J, Djulbegovic B, Dahm P (2010). "Screening for prostate cancer: systematic review and meta-analysis of randomized controlled trials". *BMJ*. **341**: c4543. doi:10.1136/bmj.c4543. PMC 2939952. PMID 20843937.
8. ^ a b "Talking With Your Patients About Screening for Prostate Cancer" (PDF). Retrieved 2012-07-02.
9. ^ a b Stratton J, Godwin M (2011). "The effect of supplemental vitamins and minerals on the development of prostate cancer: A systematic review and meta-analysis". *Family practice*. **28** (3): 243–52. doi:10.1093/fampra/cmq115. PMID 21273283.
10. ^ "SEER Stat Fact Sheets: Prostate Cancer". *NCI*. Retrieved 18 June 2014.
11. ^ a b *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 1.1. ISBN 9283204298.
12. ^ Baade PD, Youlden DR, Krnjacki LJ (February 2009). "International epidemiology of prostate cancer: geographical distribution and secular trends". *Molecular nutrition & food research*. **53** (2): 171–84. doi:10.1002/mnfr.200700511. PMID 19101947.
13. ^ a b Miller DC, Hafez KS, Stewart A, Montie JE, Wei JT (September 2003). "Prostate carcinoma presentation, diagnosis, and staging: an update form the National Cancer Data Base". *Cancer*. **98** (6): 1169–78. doi:10.1002/cncr.11635. PMID 12973840.
14. ^ van der Cruijsen-Koeter IW, Vis AN, Roobol MJ, Wildhagen MF, de Koning HJ, van der Kwast TH, Schröder FH (July 2005). "Comparison of screen detected and clinically diagnosed prostate cancer in the European randomized

study of screening for prostate cancer, section rotterdam". *Urol*. **174** (1): 121–5. doi:10.1097/01.ju.0000162061.40533.0f. PMID 15947595.
15. ^ Hsing AW, Chokkalingam AP (2006). "Prostate cancer epidemiology". *Frontiers in Bioscience*. **11**: 1388–413. doi:10.2741/1891. PMID 16368524.
16. ^ Hankey BF, Feuer EJ, Clegg LX, Hayes RB, Legler JM, Prorok PC, Ries LA, Merrill RM, Kaplan RS (June 16, 1999). "Cancer surveillance series: interpreting trends in prostate cancer—part I: Evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates". *J Natl Cancer Inst*. **91** (12): 1017–24. doi:10.1093/jnci/91.12.1017. PMID 10379964.
17. ^ Breslow N, Chan CW, Dhom G, Drury RA, Franks LM, Gellei B, Lee YS, Lundberg S, Sparke B, Sternby NH, Tulinius H (November 15, 1977). "Latent carcinoma of prostate at autopsy in seven areas. The International Agency for Research on Cancer, Lyons, France". *Int J Cancer*. **20** (5): 680–8. doi:10.1002/ijc.2910200506. PMID 924691.
18. ^ Zeegers MP, Jellema A, Ostrer H (2003). "Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma: a meta-analysis". *Cancer*. **97** (8): 1894–903. doi:10.1002/cncr.11262. PMID 12673715.
19. ^ *a b* Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ (2005). "Cancer statistics, 2005". *CA Cancer J Clin*. **55** (1): 10–30. doi:10.3322/canjclin.55.1.10. PMID 15661684.
20. ^ Martin RM, Vatten L, Gunnell D, Romundstad P (March 2010). "Blood pressure and risk of prostate cancer: cohort Norway (CONOR)". *Cancer Causes Control*. **21** (3): 463–72. doi:10.1007/s10552-009-9477-x. PMID 19949849.
21. ^ Friedenreich CM, Neilson HK, Lynch BM (Sep 2010). "State of the epidemiological evidence on physical activity and cancer prevention". *European journal of cancer (Oxford, England : 1990)*. **46** (14): 2593–604. doi:10.1016/j.ejca.2010.07.028. PMID 20843488.
22. ^ *a b* Goldstein AS, Huang J, Guo C, Garraway IP, Witte ON (July 2010). "Identification of a cell of origin for human prostate cancer". *Science*. **329** (5991): 568–71. doi:10.1126/science.1189992. PMC 2917982. PMID 20671189.
23. ^ Steinberg GD, Carter BS, Beaty TH, Childs B, Walsh PC (1990). "Family history and the risk of prostate cancer". *Prostate*. **17** (4): 337–47. doi:10.1002/pros.2990170409. PMID 2251225.
24. ^ *a b* Gallagher RP, Fleshner N (October 1998). "Prostate cancer: 3. Individual risk factors" (PDF). *CMAJ*. **159** (7): 807–13. PMC 1232741. PMID 9805030.
25. ^ Hoffman RM, Gilliland FD, Eley JW, Harlan LC, Stephenson RA, Stanford JL, Albertson PC, Hamilton AS, Hunt WC, Potosky AL (March 2001). "Racial and ethnic differences in advanced-stage prostate cancer: the Prostate Cancer Outcomes Study". *J. Natl. Cancer Inst*. **93** (5): 388–95. doi:10.1093/jnci/93.5.388. PMID 11238701.
26. ^ Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K (July 2000). "Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland". *N. Engl. J. Med*. **343** (2): 78–85. doi:10.1056/NEJM200007133430201. PMID 10891514.
27. ^ Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, Tucker MA (May 1997). "The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews". *N. Engl. J. Med*. **336** (20): 1401–8. doi:10.1056/NEJM199705153362001. PMID 9145676.
28. ^ Beuzeboc P, Soulié M, Richaud P, Salomon L, Staerman F, Peyromaure M, Mongiat-Artus P, Cornud F, Paparel P, Davin JL, Molinié V (December 2009). "[Fusion genes and prostate cancer. From discovery to prognosis and therapeutic perspectives]". *Prog. Urol.* (in French). **19** (11): 819–24. doi:10.1016/j.purol.2009.06.002. PMID 19945666.
29. ^ Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, Jugurnauth SK, Mulholland S, Leongamornlert DA, Edwards SM, Morrison J, Field HI, Southey MC, Severi G, Donovan JL, Hamdy FC, Dearnaley DP, Muir KR, Smith C, Bagnato M, Ardern-Jones AT, Hall AL, O'Brien LT, Gehr-Swain BN, Wilkinson RA, Cox A, Lewis S, Brown PM, Jhavar SG, Tymrakiewicz M, Lophatananon A, Bryant SL, Horwich A, Huddart RA, Khoo VS, Parker CC, Woodhouse CJ, Thompson A, Christmas T, Ogden C, Fisher C, Jamieson C, Cooper CS, English DR, Hopper JL, Neal DE, Easton DF (March 2008). "Multiple newly identified loci associated with prostate cancer susceptibility". *Nature Genetics*. **40** (3): 316–21. doi:10.1038/ng.90. PMID 18264097.
30. ^ Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, Yu K, Chatterjee N, Welch R, Hutchinson A, Crenshaw A, Cancel-Tassin G, Staats BJ, Wang Z, Gonzalez-Bosquet J, Fang J, Deng X, Berndt SI, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cussenot O, Valeri A, Andriole GL, Crawford ED, Tucker M, Gerhard DS, Fraumeni JF, Hoover R, Hayes RB, Hunter DJ, Chanock SJ (March 2008). "Multiple loci identified in a genome-wide association study of prostate cancer". *Nature Genetics*. **40** (3): 310–5. doi:10.1038/ng.91. PMID 18264096.
31. ^ Whitaker HC, Kote-Jarai Z, Ross-Adams H, Warren AY, Burge J, George A, Bancroft E, Jhavar S, Leongamornlert D, Tymrakiewicz M, Saunders E, Page E, Mitra A, Mitchell G, Lindeman GJ, Evans DG, Blanco I, Mercer C, Rubinstein WS, Clowes V, Douglas F, Hodgson S, Walker L, Donaldson A, Izatt L, Dorkins H, Male A, Tucker K, Stapleton A, Lam J, Kirk J, Lilja H, Easton D, Cooper C, Eeles R, Neal DE (Oct 13, 2010). Vickers A, ed. "The rs10993994 risk allele for prostate cancer results in clinically relevant changes in microseminoprotein-beta expression in tissue and urine".

*PLoS ONE*. **5** (10): e13363. doi:10.1371/journal.pone.0013363. PMC 2954177. PMID 20967219.

32. ^ Venkateswaran V, Klotz LH (Aug 2010). "Diet and prostate cancer: mechanisms of action and implications for chemoprevention". *Nature Reviews Urology*. **7** (8): 442–53. doi:10.1038/nrurol.2010.102. PMID 20647991.
33. ^ Key TJ (2011). "Fruit and vegetables and cancer risk". *British Journal of Cancer*. **104** (1): 6–11. doi:10.1038/sj.bjc.6606032. PMC 3039795. PMID 21119663. "For other common cancers, including colorectal, breast and prostate cancer, epidemiological studies suggest little or no association between total fruit and vegetable consumption and risk."
34. ^ Alexander DD, Mink PJ, Cushing CA, Sceurman B (2010). "A review and meta-analysis of prospective studies of red and processed meat intake and prostate cancer". *Nutrition journal*. **9**: 50. doi:10.1186/1475-2891-9-50. PMC 2987772. PMID 21044319.
35. ^ "Chemicals in Meat Cooked at High Temperatures and Cancer Risk". *National Cancer Institute*.
36. ^ Wigle DT, Turner MC, Gomes J, Parent ME (March 2008). "Role of hormonal and other factors in human prostate cancer". *Journal of Toxicology and Environmental Health. Part B, Critical Reviews*. **11** (3–4): 242–59. doi:10.1080/10937400701873548. PMID 18368555.
37. ^ Qin X, Cui Y, Shen L, Sun N, Zhang Y, Li J, Xu X, Wang B, Xu X, Huo Y, Wang X (Jan 22, 2013). "Folic acid supplementation and cancer risk: A meta-analysis of randomized controlled trials". *International Journal of Cancer. Journal International Du Cancer*. **133** (5): 1033–41. doi:10.1002/ijc.28038. PMID 23338728.
38. ^ Jacobs EJ, Rodriguez C, Mondul AM, Connell CJ, Henley SJ, Calle EE, Thun MJ (July 2005). "A large cohort study of aspirin and other nonsteroidal anti-inflammatory drugs and prostate cancer incidence". *J. Natl. Cancer Inst*. **97** (13): 975–80. doi:10.1093/jnci/dji173. PMID 15998950.
39. ^ Shannon J, Tewoderos S, Garzotto M, Beer TM, Derenick R, Palma A, Farris PE (August 2005). "Statins and prostate cancer risk: a case-control study". *Am. J. Epidemiol*. **162** (4): 318–25. doi:10.1093/aje/kwi203. PMID 16014776.
40. ^ Dennis LK, Lynch CF, Torner JC (July 2002). "Epidemiologic association between prostatitis and prostate cancer". *Urology*. **60** (1): 78–83. doi:10.1016/S0090-4295(02)01637-0. PMID 12100928.
41. ^ Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ (April 2003). "Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults". *N. Engl. J. Med*. **348** (17): 1625–38. doi:10.1056/NEJMoa021423. PMID 12711737.
42. ^ Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ (August 1996). "Prospective study of sex hormone levels and risk of prostate cancer". *J. Natl. Cancer Inst*. **88** (16): 1118–26. doi:10.1093/jnci/88.16.1118. PMID 8757191.
43. ^ "?". Retrieved 9 August 2010.
44. ^ "Veterans exposed to Agent Orange have higher rates of prostate cancer recurrence". *Medical College of Georgia News*. May 20, 2007.
45. ^ Urisman A, Molinaro RJ, Fischer N, Plummer SJ, Casey G, Klein EA, Malathi K, Magi-Galluzzi C, Tubbs RR, Ganem D, Silverman RH, DeRisi JL (March 2006). "Identification of a Novel Gammaretrovirus in Prostate Tumors of Patients Homozygous for R462Q RNASEL Variant". *PLoS Pathog*. **2** (3): e25. doi:10.1371/journal.ppat.0020025. PMC 1434790. PMID 16609730.
46. ^ Schlaberg R, Choe DJ, Brown KR, Thaker HM, Singh IR (September 2009). "XMRV is present in malignant prostatic epithelium and is associated with prostate cancer, especially high-grade tumors". *Proc. Natl. Acad. Sci. U.S.A*. **106** (38): 16351–6. doi:10.1073/pnas.0906922106. PMC 2739868. PMID 19805305.
47. ^ Hohn O, Krause H, Barbarotto P, Niederstadt L, Beimforde N, Denner J, Miller K, Kurth R, Bannert N (2009). "Lack of evidence for xenotropic murine leukemia virus-related virus (XMRV) in German prostate cancer patients". *Retrovirology*. **6**: 92. doi:10.1186/1742-4690-6-92. PMC 2770519. PMID 19835577.
48. ^ Lee D, Das Gupta J, Gaughan C, Steffen I, Tang N, Luk KC, Qiu X, Urisman A, Fischer N, Molinaro R, Broz M, Schochetman G, Klein EA, Ganem D, Derisi JL, Simmons G, Hackett J, Silverman RH, Chiu CY (2012). Tachedjian G, ed. "In-Depth Investigation of Archival and Prospectively Collected Samples Reveals No Evidence for XMRV Infection in Prostate Cancer". *PLoS ONE*. **7** (9): e44954. doi:10.1371/journal.pone.0044954. PMC 3445615. PMID 23028701.
49. ^ Alberts B (Dec 23, 2011). "Retraction". *Science*. **334** (6063): 1636. doi:10.1126/science.334.6063.1636-a. PMID 22194552.
50. ^ Ross, Susan, ed. (September 2012). "Retraction. Identification of a novel gammaretrovirus in prostate tumors of patients homozygous for R462Q RNASEL variant". *PLoS Pathogens*. **8** (9): 10.1371/annotation/7e2efc01–2e9b–4e9b–aef0–87ab0e4e4732. doi:10.1371/annotation/7e2efc01-2e9b-4e9b-aef0-87ab0e4e4732. PMC 3445601. PMID 23028303.
51. ^ Dennis LK, Dawson DV (January 2002). "Meta-analysis of measures of sexual activity and prostate cancer". *Epidemiology (Cambridge, Mass.)*. **13** (1): 72–9. doi:10.1097/00001648-200201000-00012. PMID 11805589.
52. ^ Rosenblatt KA, Wicklund KG, Stanford JL (Jun 15, 2001). "Sexual factors and the risk of prostate cancer".

*American Journal of Epidemiology*. **153** (12): 1152–8. doi:10.1093/aje/153.12.1152. PMID 11415949.
53. ^ Sarma AV, McLaughlin JC, Wallner LP, Dunn RL, Cooney KA, Schottenfeld D, Montie JE, Wei JT (September 2006). "Sexual behavior, sexually transmitted diseases and prostatitis: the risk of prostate cancer in black men". *The Journal of Urology*. **176** (3): 1108–13. doi:10.1016/j.juro.2006.04.075. PMID 16890703.
54. ^ *Male Reproductive Cancers*. Springer New York. 2010. p. 27. ISBN 9781441904508.
55. ^ Scardino, Peter (2005). *Comprehensive textbook of genitourinary oncology* (3rd ed.). Philadelphia: Lippincott Williams & Wilkins. p. 16. ISBN 9780781749848.
56. ^ Leitzmann, MF; Platz, EA; Stampfer, MJ; Willett, WC; Giovannucci, E (7 April 2004). "Ejaculation frequency and subsequent risk of prostate cancer.". *JAMA*. **291** (13): 1578–86. doi:10.1001/jama.291.13.1578. PMID 15069045.
57. ^ Giles, GG; Severi, G; English, DR; McCredie, MR; Borland, R; Boyle, P; Hopper, JL (August 2003). "Sexual factors and prostate cancer.". *BJU international*. **92** (3): 211–6. doi:10.1046/j.1464-410x.2003.04319.x. PMID 12887469.
58. ^ Aumüller, G. (1979). *Prostate Gland and Seminal Vesicles*. Berlin-Heidelberg: Springer-Verlag.
59. ^ Moore, K.; Dalley, A. (1999). *Clinically Oriented Anatomy*. Baltimore, Maryland: Lippincott Williams & Wilkins. ISBN 0-683-06132-1.
60. ^ Steive, H. (1930). "*Männliche Genitalorgane*". Handbuch der mikroskopischen Anatomie des Menschen. *Vol. VII Part 2*. Berlin: Springer. pp. 1–399.
61. ^ "Male Genitals - Prostate Neoplasms". *Pathology study images*. University of Virginia School of Medicine. Archived from the original on 2011-04-28. Retrieved 2011-04-28. "There are many connections between the prostatic venous plexus and the vertebral veins. The veins forming the prostatic plexus do not contain valves and it is thought that straining to urinate causes prostatic venous blood to flow in a reverse direction and enter the vertebral veins carrying malignant cells to the vertebral column."
62. ^ Journal-molecular cancer, review, 2006 5:17, doi:10.1186/1476-4598-5-17
63. ^ "Scientists Discover Anti-Cancer Mechanism that Arrests Early Prostate Cancer". August 4, 2005.
64. ^ Leav I, Plescia J, Goel HL, Li J, Jiang Z, Cohen RJ, Languino LR, Altieri DC (January 2010). "Cytoprotective Mitochondrial Chaperone TRAP-1 As a Novel Molecular Target in Localized and Metastatic Prostate Cancer". *Am. J. Pathol*. **176** (1): 393–401. doi:10.2353/ajpath.2010.090521. PMC 2797899. PMID 19948822.
65. ^ Zha J, Huang YF (September 2009). "[TGF-beta/Smad in prostate cancer: an update]". *Zhonghua Nan Ke Xue* (in Chinese). **15** (9): 840–3. PMID 19947572.
66. ^ Watanabe SI, Miyata Y, Kanda S, Iwata T, Hayashi T, Kanetake H, Sakai H (November 2009). "Expression of X-linked inhibitor of apoptosis protein in human prostate cancer specimens with and without neo-adjuvant hormonal therapy". *J Cancer Res Clin Oncol*. **136** (5): 787–93. doi:10.1007/s00432-009-0718-x. PMID 19946707.
67. ^ Senapati S, Rachagani S, Chaudhary K, Johansson SL, Singh RK, Batra SK (March 2010). "Overexpression of macrophage inhibitory cytokine-1 induces metastasis of human prostate cancer cells through the FAK–RhoA signaling pathway". *Oncogene*. **29** (9): 1293–302. doi:10.1038/onc.2009.420. PMC 2896817. PMID 19946339.
68. ^ Narizhneva NV, Tararova ND, Ryabokon P, Shyshynova I, Prokvolit A, Komarov PG, Purmal AA, Gudkov AV, Gurova KV (December 2009). "Small molecule screening reveals a transcription-independent pro-survival function of androgen receptor in castration-resistant prostate cancer". *Cell Cycle*. **8** (24): 4155–67. doi:10.4161/cc.8.24.10316. PMC 2896895. PMID 19946220.
69. ^ Yao V, Berkman CE, Choi JK, O'Keefe DS, Bacich DJ (February 2010). "Expression of prostate-specific membrane antigen (PSMA), increases cell folate uptake and proliferation and suggests a novel role for PSMA in the uptake of the non-polyglutamated folate, folic acid". *Prostate*. **70** (3): 305–16. doi:10.1002/pros.21065. PMID 19830782.
70. ^ http://www.cancer.org/Healthy/FindCancerEarly/CancerScreeningGuidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer American Cancer Society American Cancer Society Guidelines for the early detection of cancer Cited: September 2011
71. ^ Bonekamp D, Jacobs MA, El-Khouli R, Stoianovici D, Macura KJ (May–June 2011). "Advancements in MR Imaging of the Prostate: From Diagnosis to Interventions". *Radiographics*. **31** (3 Suppl): 677–703. doi:10.1148/rg.313105139. PMC 3093638. PMID 21571651.
72. ^ Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, Rouviere O, Logager V, Fütterer JJ (2012). "ESUR prostate MR guidelines 2012". *European Radiology*. **22** (4): 746–57. doi:10.1007/s00330-011-2377-y. PMC 3297750. PMID 22322308.
73. ^ Natarajan S, Marks LS, Margolis DJ, Huang J, Macairan ML, Lieu P, Fenster A (May 2011). "Clinical application of a 3D ultrasound-guided prostate biopsy system". *Urol Oncol*. **29** (3 Suppl): 334–42. doi:10.1016/j.urolonc.2011.02.014. PMC 3432280. PMID 21555104.
74. ^ Tan N, Margolis DJ, McClure TD, Thomas A, Finley DS, Reiter RE, Huang J, Raman SS (October 2011). "Radical prostatectomy: value of prostate MRI in surgical planning". *Abdominal Imaging*. **37** (4): 664–74. doi:10.1007/s00261-011-9805-y. PMID 21993567.

75. ^ Mohand Yaghi Kehinde EO (2015). "Oral antibiotics in trans-rectal prostate biopsy and its efficacy to reduce infectious complications: Systematic review". *Urol Ann*. **7** (4): 417–427. doi:10.4103/0974-7796.164860. PMC 4660689. PMID 26538868.
76. ^ Essink-Bot ML, de Koning HJ, Nijs HG, Kirkels WJ, van der Maas PJ, Schröder FH (June 1998). "Short-term effects of population-based screening for prostate cancer on health-related quality of life". *J. Natl. Cancer Inst.* **90** (12): 925–31. doi:10.1093/jnci/90.12.925. PMID 9637143.
77. ^ *a b* Figueiredo JC, Grau MV, Haile RW, Sandler RS, Summers RW, Bresalier RS, Burke CA, McKeown-Eyssen GE, Baron JA (March 2009). "Folic Acid and Risk of Prostate Cancer: Results From a Randomized Clinical Trial". *J. Natl. Cancer Inst.* **101** (6): 432–5. doi:10.1093/jnci/djp019. PMC 2657096. PMID 19276452.
78. ^ Chuang AY, DeMarzo AM, Veltri RW, Sharma RB, Bieberich CJ, Epstein JI (August 2007). "Immunohistochemical differentiation of high-grade prostate carcinoma from urothelial carcinoma". *Am. J. Surg. Pathol.* **31** (8): 1246–55. doi:10.1097/PAS.0b013e31802f5d33. PMID 17667550.
79. ^ *a b* Nutting C, Horwich A, Fisher C, Parsons C, Dearnaley DP (June 1997). "Small-cell carcinoma of the prostate". *Journal of the Royal Society of Medicine*. **90** (6): 340–1. PMC 1296316. PMID 9227387.
80. ^ *a b* Wei ZF, Xu H, Wang H, Wei W, Cheng W, Zhou WQ, Ge JP, Zhang ZY, Gao JP, Yin HL (September 2009). "[Clinicopathological characterization of prostatic small cell carcinoma: a case report and review of the literature]". *Zhonghua Nan Ke Xue* (in Chinese). **15** (9): 829–32. PMID 19947569.
81. ^ "Biomarker for Prostate Cancer" (PDF). Freepatentsonline.com. Retrieved 2011-08-29.
82. ^ Catz SD, Johnson JL (January 2003). "BCL-2 in prostate cancer: a minireview". *Apoptosis*. **8** (1): 29–37. doi:10.1023/A:1021692801278. PMID 12510149.
83. ^ Srikumar Chakravarthi; David Low Wee Yang; Thanikachalam P; Nagaraja HS; Nadeem Irfan Bukhari (2009). "Assessment of proliferative index and its association with Ki-67 antigen molecule expression in nodular hyperplasia of prostate". *Indian Journal of Science & Technology*. **2** (8): 1–4.
84. ^ British Journal of Cancer - 15 Feb 2011
85. ^ BMJ Group (8 December 2009). "Prostate cancer: How far has your cancer spread? The TNM system". London: Guardian.co.uk. Retrieved 9 August 2010.
86. ^ American Society of Clinical Oncology (2013). "Five things physicians and patients should question" (PDF). *The Journal of the Oklahoma State Medical Association*. **106** (4): 150–1. PMID 23795527.
    - Makarov DV, Desai RA, Yu JB, Sharma R, Abraham N, Albertsen PC, Penson DF, Gross CP (2012). "The population level prevalence and correlates of appropriate and inappropriate imaging to stage incident prostate cancer in the medicare population". *The Journal of Urology*. **187** (1): 97–102. doi:10.1016/j.juro.2011.09.042. PMID 22088337.
    - National Comprehensive Cancer Network - Prostate (2012). "NCCN Clinical Practice Guidelines in Oncology". *nccn.org*. Retrieved 15 November 2012.
    - Thompson I, Thrasher JB, Aus G, Burnett AL, Canby-Hagino ED, Cookson MS, D'Amico AV, Dmochowski RR, Eton DT, Forman JD, Goldenberg SL, Hernandez J, Higano CS, Kraus SR, Moul JW, Tangen CM (2007). "Guideline for the management of clinically localized prostate cancer: 2007 update". *The Journal of Urology*. **177** (6): 2106–31. doi:10.1016/j.juro.2007.03.003. PMID 17509297.
87. ^ *a b c d e* Masko EM, Allott EH, Freedland SJ (Nov 15, 2012). "The Relationship Between Nutrition and Prostate Cancer: Is More Always Better?". *European Urology*. **63** (5): 810–20. doi:10.1016/j.eururo.2012.11.012. PMC 3597758. PMID 23219353.
88. ^ Thompson AK, Shaw DI, Minihane AM, Williams CM (Dec 2008). "Trans-fatty acids and cancer: the evidence reviewed". *Nutrition research reviews*. **21** (2): 174–88. doi:10.1017/S0954422408110964. PMID 19087370.
89. ^ Heinze VM, Actis AB (February 2012). "Dietary conjugated linoleic acid and long-chain n-3 fatty acids in mammary and prostate cancer protection: a review". *International journal of food sciences and nutrition*. **63** (1): 66–78. doi:10.3109/09637486.2011.598849. PMID 21762028.
90. ^ Datta M, Schwartz GG (2012). "Calcium and vitamin D supplementation during androgen deprivation therapy for prostate cancer: a critical review". *The oncologist*. **17** (9): 1171–9. doi:10.1634/theoncologist.2012-0051. PMC 3448410. PMID 22836449.
91. ^ Szymanski KM, Wheeler DC, Mucci LA (Nov 2010). "Fish consumption and prostate cancer risk: a review and meta-analysis". *The American Journal of Clinical Nutrition*. **92** (5): 1223–33. doi:10.3945/ajcn.2010.29530. PMID 20844069.
92. ^ American Dietetic Association and Dieticians of Canada (June 2003). "Position of the American Dietetic Association and Dietitians of Canada: Vegetarian diets". *Journal of the American Dietetic Association*. **103** (6): 748–65. doi:10.1053/jada.2003.50142. PMID 12778049.
93. ^ Research, World Cancer Research Fund ; American Institute for Cancer (2007). *Food, nutrition, physical activity, and the prevention of cancer a global perspective* (PDF). Washington, D.C.: American Institute for Cancer Research. p. 76. ISBN 978-0-9722522-2-5.

94. ^ [a] [b] "American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention" (pdf). *Last Revised: 1/11/2012*.
95. ^ Wilt TJ, MacDonald R, Hagerty K, Schellhammer P, Kramer BS (2008). Wilt TJ, ed. "Five-alpha-reductase Inhibitors for prostate cancer prevention". *Cochrane Database Syst Rev* (2): CD007091. doi:10.1002/14651858.CD007091. PMID 18425978.
96. ^ The Editorial Board (November 25, 2015). "A Better Way to Screen for Prostate Cancer". *New York Times*. Retrieved November 26, 2015.
97. ^ Marcione, Marilyn (12 October 2011). "Prostate testing's dark side: Men who were harmed". Associated Press. Retrieved 2011-10-13.
98. ^ Moyer VA (May 2012). "Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement". *Annals of Internal Medicine*. doi:10.1059/0003-4819-157-2-201207170-00459. PMID 22615453.
99. ^ Chou R, Croswell JM, Dana T, Bougatsos C, Blazina I, Fu R, Gleitsmann K, Koenig HC, Lam C, Maltz A, Rugge JB, Lin K (December 2011). "Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force". *Annals of Internal Medicine*. **155** (11): 762–71. doi:10.1059/0003-4819-155-11-201112060-00375. PMID 21984740.
100. ^ Prostate Cancer Screening CDC, updated April 6, 2010
101. ^ Qaseem A, Barry MJ, Denberg TD, Owens DK, Shekelle P (April 2013). "Screening for Prostate Cancer: A Guidance Statement From the Clinical Guidelines Committee of the American College of Physicians". *Annals of Internal Medicine*. **158** (10): 761–9. doi:10.7326/0003-4819-158-10-201305210-00633. PMID 23567643.
102. ^ Basch E, Oliver TK, Vickers A, Thompson I, Kantoff P, Parnes H, Loblaw DA, Roth B, Williams J, Nam RK (Jul 16, 2012). "Screening for Prostate Cancer With Prostate-Specific Antigen Testing: American Society of Clinical Oncology Provisional Clinical Opinion" (PDF). *Journal of Clinical Oncology*. **30** (24): 3020–5. doi:10.1200/JCO.2012.43.3441. PMC 3776923. PMID 22802323.
103. ^ "EARLY DETECTION OF PROSTATE CANCER: AUA GUIDELINE". *American Urological Association*. 2013. Retrieved 10 May 2013.
104. ^ Kolata, Gina (21 November 2011). "'Cancer' or 'Weird Cells': Which Sounds Deadlier?". *The New York Times*.
105. ^ Lu-Yao GL, Albertsen PC, Moore DF, Shih W, Lin Y, DiPaola RS, Barry MJ, Zietman A, O'Leary M, Walker-Corkery E, Yao SL (September 2009). "Outcomes of Localized Prostate Cancer Following Conservative Management". *The Journal of the American Medical Association*. **302** (11): 1202–09. doi:10.1001/jama.2009.1348. PMC 2822438. PMID 19755699.
106. ^ Mongiat-Artus P, Peyromaure M, Richaud P, Droz JP, Rainfray M, Jeandel C, Rebillard X, Moreau JL, Davin JL, Salomon L, Soulié M (December 2009). "[Recommendations for the treatment of prostate cancer in the elderly man: A study by the oncology committee of the French association of urology]". *Prog. Urol.* (in French). **19** (11): 810–7. doi:10.1016/j.purol.2009.02.008. PMID 19945664.
107. ^ Picard JC, Golshayan AR, Marshall DT, Opfermann KJ, Keane TE (November 2009). "The multi-disciplinary management of high-risk prostate cancer". *Urol. Oncol.* **30** (1): 3–15. doi:10.1016/j.urolonc.2009.09.002. PMID 19945310.
108. ^ [a] [b] Mohan R, Schellhammer PF (August 2011). "Treatment options for localized prostate cancer". *Am Fam Physician*. **84** (4): 413–20. PMID 21842788.
109. ^ Mouraviev V, Evans B, Polascik TJ (2006). "Salvage prostate cryoablation after primary interstitial brachytherapy failure: a feasible approach". *Prostate Cancer Prostatic Dis.* **9** (1): 99–101. doi:10.1038/sj.pcan.4500853. PMID 16314889.
110. ^ Wallis, Christopher J D; Mahar, Alyson L; Choo, Richard; Herschorn, Sender; Kodama, Ronald T; Shah, Prakesh S; Danjoux, Cyril; Narod, Steven A; Nam, Robert K (2 March 2016). "Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis". *BMJ*: i851. doi:10.1136/bmj.i851.
111. ^ Hegarty J, Beirne PV, Walsh E, Comber H, Fitzgerald T, Wallace Kazer M (Nov 10, 2010). Hegarty J, ed. "Radical prostatectomy versus watchful waiting for prostate cancer". *Cochrane database of systematic reviews (Online)* (11): CD006590. doi:10.1002/14651858.CD006590.pub2. PMID 21069689.
112. ^ de Jong, Y; Pinckaers, JH; Ten Brinck, RM; Lycklama À Nijeholt, AA; Dekkers, OM (2014). "Urinating Standing versus Sitting: Position Is of Influence in Men with Prostate Enlargement. A Systematic Review and Meta-Analysis.". *PLoS ONE*. **9** (7): e101320. doi:10.1371/journal.pone.0101320. PMC 4106761. PMID 25051345.
113. ^ "Active Surveillance May Be Preferred Option in Some Men with Prostate Cancer". Cancer.gov. 2011-04-19. Retrieved 2011-08-29.
114. ^ Hong H, Zhang Y, Sun J, Cai W (November 2009). "Positron emission tomography imaging of prostate cancer". *Amino Acids*. **39** (1): 11–27. doi:10.1007/s00726-009-0394-9. PMC 2883014. PMID 19946787.
115. ^ Peyromaure M, Valéri A, Rebillard X, Beuzeboc P, Richaud P, Soulié M, Salomon L (December 2009). "[Characteristics of prostate cancer in men less than 50-year-old]". *Prog. Urol.* (in French). **19** (11): 803–9.

doi:10.1016/j.purol.2009.04.010. PMID 19945663.
116. ^ Fitzpatrick JM (2008). "Management of localized prostate cancer in senior adults: the crucial role of comorbidity". *BJU international*. 101 Suppl 2: 16–22. doi:10.1111/j.1464-410X.2007.07487.x. PMID 18307688.
117. ^ "Evidence-Based Cancer Guidelines, Oncology Drug Compendium, Oncology Continuing Medical Education". NCCN. Retrieved 2011-08-29.
118. ^ Hammerstrom AE, Cauley DH, Atkinson BJ, Sharma P (August 2011). "Cancer immunotherapy: sipuleucel-T and beyond". *Pharmacotherapy*. **31** (8): 813–28. doi:10.1592/phco.31.8.813. PMID 21923608.
119. ^ Seruga B, Ocana A, Tannock IF (January 2011). "Drug resistance in metastatic castration-resistant prostate cancer". *Nature Reviews Clinical Oncology*. **8** (1): 12–23. doi:10.1038/nrclinonc.2010.136. PMID 20859283.
120. ^ Clarke NW (c. 2005). "Docetaxel for the Treatment of Hormone Refractory Prostate Cancer" (PDF).
121. ^ "Prostate cancer (hormone-refractory) - docetaxel". National Institute for Health and Clinical Excellence. 2010-12-10. Retrieved 2011-07-04.
122. ^ de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, Gravis G, Bodrogi I, Mackenzie MJ, Shen L, Roessner M, Gupta S, Sartor AO (October 2010). "Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial". *Lancet*. **376** (9747): 1147–54. doi:10.1016/S0140-6736(10)61389-X. PMID 20888992.
123. ^ "Avastin, Thalomid, Taxotere, and Prednisone Effective for Men with Hormone Refractory Prostate Cancer". March 2010. Retrieved 10 May 2010.
124. ^ Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB, Xu Y, Frohlich MW, Schellhammer PF (July 2010). "Sipuleucel-T immunotherapy for castration-resistant prostate cancer". *N. Engl. J. Med.* **363** (5): 411–22. doi:10.1056/NEJMoa1001294. PMID 20818862.
125. ^ "FDA approves Zytiga for late-stage prostate cancer". U.S. Food and Drug Administration. 2011-04-28.
126. ^ [a] [b] "FDA approves new treatment for a type of late stage prostate cancer". *press release*. United States Food and Drug Administration. 2012-08-31.
127. ^ [a] [b] Anna Azvolinsky (September 4, 2012). "FDA Approves Enzalutamide (Xtandi) for Late-Stage Prostate Cancer". CancerNetwork.
128. ^ Qin J, Liu X, Laffin B, Chen X, Choy G, Jeter CR, Calhoun-Davis T, Li H, Palapattu GS, Pang S, Lin K, Huang J, Ivanov I, Li W, Suraneni MV, Tang DG (2012). "The PSA−/lo Prostate Cancer Cell Population Harbors Self-Renewing Long-Term Tumor-Propagating Cells that Resist Castration". *Cell Stem Cell*. **10** (5): 556–69. doi:10.1016/j.stem.2012.03.009. PMC 3348510. PMID 22560078.
129. ^ Maitland NJ, Collins AT (2008). "Prostate cancer stem cells—a new target for therapy". *Journal of Clinical Oncology*. **26** (17): 2862–70. doi:10.1200/JCO.2007.15.1472. PMID 18539965.
130. ^ Attard G, Richards J, de Bono JS (2011). "New strategies in metastatic prostate cancer: targeting the androgen receptor signaling pathway". *Clinical Cancer Research*. **17** (7): 1649–57. doi:10.1158/1078-0432.CCR-10-0567. PMC 3513706. PMID 21372223.
131. ^ Rane JK, Pellacani D, Maitland NJ (2012). "Advanced prostate cancer—a case for adjuvant differentiation therapy". *Nature Reviews Urology*. **9** (10): 595–602. doi:10.1038/nrurol.2012.157. PMID 22890299.
132. ^ "Palliative or Supportive Care". American Cancer Society. Retrieved 20 August 2014.
133. ^ Thompson, JC; Wood, J; Feuer, D (2007). "Prostate cancer: palliative care and pain relief.". *British medical bulletin*. **83**: 341–54. doi:10.1093/bmb/ldm018. PMID 17628024.
134. ^ "Survival rates for prostate cancer". American Cancer Society. Last Medical Review: 12/22/2014
135. ^ Wakai K (February 2005). "[Descriptive epidemiology of prostate cancer in Japan and Western countries]". *Nippon Rinsho* (in Japanese). **63** (2): 207–12. PMID 15714967.
136. ^ Jaubert de Beaujeu M, Chavrier Y (January 1976). "[Deformations of the anterior thoracic wall (author's transl)]". *Ann Chir Thorac Cardiovasc* (in French). **15** (1): 1–6. PMID 1259345.
137. ^ Hsing AW, Tsao L, Devesa SS (January 2000). "International trends and patterns of prostate cancer incidence and mortality". *Int. J. Cancer*. **85** (1): 60–7. doi:10.1002/(SICI)1097-0215(20000101)85:1<60::AID-IJC11>3.0.CO;2-B. PMID 10585584.
138. ^ Osegbe DN (April 1997). "Prostate cancer in Nigerians: facts and nonfacts". *J. Urol*. **157** (4): 1340–3. doi:10.1016/S0022-5347(01)64966-8. PMID 9120935.
139. ^ Di Blasio CJ, Rhee AC, Cho D, Scardino PT, Kattan MW (October 2003). "Predicting clinical end points: treatment nomograms in prostate cancer". *Semin. Oncol.* **30** (5): 567–86. doi:10.1016/S0093-7754(03)00351-8. PMID 14571407.
140. ^ Huggins C, Steven RE, Hodges CV (1941). "Studies on prostatic cancer". *Arch. Surg*. **43** (2): 209–223. doi:10.1001/archsurg.1941.01210140043004.
141. ^ Hellerstedt BA, Pienta KJ (2002). "The current state of hormonal therapy for prostate cancer". *CA Cancer J Clin*. **52** (3): 154–79. doi:10.3322/canjclin.52.3.154. PMID 12018929.
142. ^ Feldman BJ, Feldman D (October 2001). "The development of androgen-independent prostate cancer". *Nature*

*Reviews Cancer*. **1** (1): 34–45. doi:10.1038/35094009. PMID 11900250.
143. ^ Eifler J. B.; Feng Z.; Lin B. M.; Partin M. T.; Humphreys E. B.; Han M.; Epstein J. I.; Walsh P. C.; Trock B. J.; et al. (2013). "An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011". *BJU International*. **111**: 22–29. doi:10.1111/j.1464-410X.2012.11324.x.
144. ^ Cooperberg MR, Pasta DJ, Elkin EP, Litwin MS, Latini DM, Du Chane J, Carroll PR (June 2005). "The UCSF Cancer of the Prostate Risk Assessment (CAPRA) Score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy". *J. Urol*. **173** (6): 1938–42. doi:10.1097/01.ju.0000158155.33890.e7. PMC 2948569. PMID 15879786.
145. ^ Cooperberg MR, Freedland SJ, Pasta DJ, Elkin EP, Presti JC, Amling CL, Terris MK, Aronson WJ, Kane CJ, Carroll PR (November 2006). "Multiinstitutional validation of the UCSF cancer of the prostate risk assessment for prediction of recurrence after radical prostatectomy". *Cancer*. **107** (10): 2384–91. doi:10.1002/cncr.22262. PMID 17039503.
146. ^ May M, Knoll N, Siegsmund M, Fahlenkamp D, Vogler H, Hoschke B, Gralla O (November 2007). "Validity of the CAPRA score to predict biochemical recurrence-free survival after radical prostatectomy. Results from a European multicenter survey of 1,296 patients". *J. Urol*. **178** (5): 1957–62; discussion 1962. doi:10.1016/j.juro.2007.07.043. PMID 17868719.
147. ^ Zhao KH, Hernandez DJ, Han M, Humphreys EB, Mangold LA, Partin AW (August 2008). "External validation of University of California, San Francisco, Cancer of the Prostate Risk Assessment score". *Urology*. **72** (2): 396–400. doi:10.1016/j.urology.2007.11.165. PMID 18372031.
148. ^ Cooperberg MR, Broering JM, Carroll PR (June 2009). "Risk Assessment for Prostate Cancer Metastasis and Mortality at the Time of Diagnosis". *J. Natl. Cancer Inst*. **101** (12): 878–87. doi:10.1093/jnci/djp122. PMC 2697208. PMID 19509351.
149. ^ "CDC FastStats". Centers for Disease Control.
150. ^ "Treatment Choices for Men With Early-Stage Prostate Cancer". National Cancer Institute.
151. ^ "Gleason 6 Prostate Cancer: Translating Biology into Population Health.". *J Urol*. **194**: 626–634. Apr 2015. doi:10.1016/j.juro.2015.01.126. PMID 25849602.
152. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved Nov 11, 2009.
153. ^ *World Cancer Report 2014*. International Agency for Research on Cancer, World Health Organization. 2014. ISBN 978-92-832-0432-9.
154. ^ Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011). "Global cancer statistics". *CA – A Cancer Journal for Clinicians*. **61** (2): 69–90. doi:10.3322/caac.20107. PMID 21296855.
155. ^ Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al. (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
156. ^ "Prostate Cancer Statistics". Laparoscopic Urology. Retrieved 19 June 2016.
157. ^ *a b* Overview: Prostate Cancer—What Causes Prostate Cancer? American Cancer Society (2 May 2006). Retrieved on 5 April 2007
158. ^ *a b* Prostate Cancer FAQs. State University of New York School of Medicine Department of Urology (31 August 2006). Retrieved on 5 April 2007
159. ^ Lee MM, Gomez SL, Chang JS, Wey M, Wang RT, Hsing AW (Jul 2003). "Soy and isoflavone consumption in relation to prostate cancer risk in China". *Cancer Epidemiol Biomarkers Prev*. **12** (7): 665–8. PMID 12869409.
160. ^ Potosky AL, Miller BA, Albertsen PC, Kramer BS (February 1995). "The role of increasing detection in the rising incidence of prostate cancer". *JAMA*. **273** (7): 548–52. doi:10.1001/jama.273.7.548. PMID 7530782.
161. ^ Hanno P.M., Malcowicz S. B., Wein A. J., "Clinical Manual of Urology" McGraw Hill 2001
162. ^ Homma Y, Kawabe K, Tsukamoto T, Yamanaka H, Okada K, Okajima E, Yoshida O, Kumazawa J, Gu FL, Lee C, Hsu TC, dela Cruz RC, Tantiwang A, Lim PH, Sheikh MA, Bapat SD, Marshall VR, Tajima K, Aso Y (1997). "Epidemiologic survey of lower urinary tract symptoms in Asia and Australia using the international prostate symptom score". *International Journal of Urology*. **4** (1): 40–46. doi:10.1111/j.1442-2042.1997.tb00138.x. PMID 9179665.
163. ^ Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, Forman D, Bray F (April 2013). "Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012". *European journal of cancer (Oxford, England : 1990)*. **49** (6): 1374–403. doi:10.1016/j.ejca.2012.12.027. PMID 23485231.
164. ^ Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ (March 2008). "Cancer Statistics, 2008". *CA Cancer J Clin*. **58** (2): 71–96. doi:10.3322/CA.2007.0010. PMID 18287387.
165. ^ "Prostate cancer statistics". *Cancer Research UK*. Retrieved 3 October 2014.
166. ^ Bostwick, David G.; Eble, John N. (2007). *Urological Surgical Pathology*. St. Louis: Mosby. p. 468. ISBN 0-323-01970-6.

167. ^ Woloshin, Steve; Schwartz, Lisa A. (2011). *Overdiagnosed: Making People Sick in the Pursuit of Health*. USA: Beacon Press. pp. 45–60. ISBN 0-8070-2200-4.
168. ^ Adams J (1853). "The case of scirrhous of the prostate gland with corresponding affliction of the lymphatic glands in the lumbar region and in the pelvis". *Lancet*. **1** (1547): 393–394. doi:10.1016/S0140-6736(02)68759-8.
169. ^ Lytton B (June 2001). "Prostate cancer: a brief history and the discovery of hormonal ablation treatment". *The Journal of Urology*. **165** (6 Pt 1): 1859–62. doi:10.1016/S0022-5347(05)66228-3. PMID 11371867.
170. ^ Young HH (1905). "Four cases of radical prostatectomy". *Johns Hopkins Bull*. **16**.
171. ^ Walsh PC, Lepor H, Eggleston JC (1983). "Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations". *The Prostate*. **4** (5): 473–85. doi:10.1002/pros.2990040506. PMID 6889192.
172. ^ Huggins CB, Hodges CV (1941). "Studies on prostate cancer: 1. The effects of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate". *Cancer Res*. **1** (4): 293.
173. ^ Schally AV, Kastin AJ, Arimura A (November 1971). "Hypothalamic follicle-stimulating hormone (FSH) and luteinizing hormone (LH)-regulating hormone: structure, physiology, and clinical studies". *Fertility and Sterility*. **22** (11): 703–21. PMID 4941683.
174. ^ Tolis G, Ackman D, Stellos A, Mehta A, Labrie F, Fazekas AT, Comaru-Schally AM, Schally AV (March 1982). "Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists". *Proc. Natl. Acad. Sci. U.S.A.* **79** (5): 1658–62. doi:10.1073/pnas.79.5.1658. PMC 346035. PMID 6461861.
175. ^ Denmeade SR, Isaacs JT (May 2002). "A history of prostate cancer treatment". *Nature Reviews Cancer*. **2** (5): 389–96. doi:10.1038/nrc801. PMID 12044015.
176. ^ Scott WW, Johnson DE, Schmidt JE, Gibbons RP, Prout GR, Joiner JR, Saroff J, Murphy GP (December 1975). "Chemotherapy of advanced prostatic carcinoma with cyclophosphamide or 5-fluorouracil: results of first national randomized study". *The Journal of Urology*. **114** (6): 909–11. PMID 1104900.
177. ^ *a b c d* Arnst, Catherine (2007-06-13). "A Gender Gap in Cancer". Businessweek.com. Retrieved 2011-08-29.
178. ^ Browne, Anthony (2001-10-07). "Cancer bias puts breasts first". *The Guardian*. London.
179. ^ Men lose out in battle for cancer cash - Times Online Archived May 24, 2011, at the Wayback Machine.
180. ^ *Does feminism discriminate against ... - Google Books*. Books.google.co.uk. 2008-07-24. ISBN 978-0-19-531283-6. Retrieved 2011-08-29.
181. ^ [1] Archived May 24, 2011, at the Wayback Machine.
182. ^ "Breast cancer receives much more research funding, publicity than prostate cancer despite similar number of victims". The Daily Caller. 2010-10-05. Retrieved 2011-08-29.
183. ^ "Prostate cancer in shadow of female counterpart". MSNBC. 2005-03-28. Retrieved 2011-08-29.
184. ^ http://www.clinicaltrials.gov/ct2/results?intr=%22MDV3100%22 ClinicalTrials.gov listing of MDV3100 articles
185. ^ "Positive Outcome of Interim Analysis of pivotal Alpharadin study: Primary endpoint met in Phase III ALSYMPCA study". *Press Release*. Algeta.com. 2011-06-06. Retrieved 2011-07-04.
186. ^ "FDA approves new drug for advanced prostate cancer" (Press release). Food and Drug Administration. 15 May 2013.
187. ^ *a b* Geethakumari PR, Cookson MS, Kelly WK (15 February 2016). "The Evolving Biology of Castration-Resistant Prostate Cancer: Review of Recommendations From the Prostate Cancer Clinical Trials Working Group 3". *Oncology*. Cancer Network. **30** (2): 187–195, 199.
188. ^ *a b c* Ghosh J, Myers CE (October 1998). "Inhibition of arachidonate 5-lipoxygenase triggers massive apoptosis in human prostate cancer cells". *Proc. Natl. Acad. Sci. U.S.A.* **95** (22): 13182–13187. doi:10.1073/pnas.95.22.13182. PMC 23752. PMID 9789062. "Inhibition of 5-lipoxygenase by MK886 completely blocks 5-HETE production and induces massive apoptosis in both hormone-responsive (LNCaP) and -nonresponsive (PC3) human prostate cancer cells. This cell death is very rapid"
189. ^ *a b c* Greene ER, Huang S, Serhan CN, Panigrahy D (November 2011). "Regulation of inflammation in cancer by eicosanoids". *Prostaglandins Other Lipid Mediat*. **96** (1-4): 27–36. doi:10.1016/j.prostaglandins.2011.08.004. PMC 4051344. PMID 21864702. "The 5-lipoxygenase (5-LOX) pathway is implicated in the development and progression of human cancers. 5-LOX, whose crystal structure was recently identified (118), is a key enzyme in metabolizing arachidonic acid to leukotrienes. 5-LOX can be induced by pro-inflammatory stimuli and is expressed in epithelial cancers including lung, prostate, breast, and colon (113). Hence, 5-LOX inhibitors have been targeted for their chemopreventive effects. Inhibition of 5-LOX activity is shown to block prostate cancer cell proliferation as well as carcinogen-induced lung tumorigenesis (119, 120). ... Both 5-HETE and 12-HETE are also products of lipoxygenase and are involved in tumor progression (12). Exogenous 5-HETE can stimulate the proliferation of prostate cancer cells and act as a survival factor (137, 138). These results require relatively high concentrations (at a concentration of 10 μM). Blocking the formation of 5-HETE, by inhibiting 5-lipoxygenase, results in massive apoptosis of human prostate cancer cells (139)."
190. ^ *a b c* Bishayee K, Khuda-Bukhsh AR (September 2013). "5-lipoxygenase antagonist therapy: a new approach

towards targeted cancer chemotherapy". *Acta Biochim. Biophys. Sin. (Shanghai)*. **45** (9): 709–719. doi:10.1093/abbs/gmt064. PMID 23752617. "Recent studies demonstrated the involvement of growth factors, such as epidermal growth factor (EGF) and neurotensin in the 5-LOX-mediated tumor progression in prostate cancer [22,23]. Recent studies with 5-LOX siRNA [10] and specific blocker of 5-LOX [24] revealed the relation of this gene with the tumor cell proliferation. ... Meclofenamate sodium (MS) is known for its anti-inflammatory activity, and apart from this, Boctor et al. [37] reported that it caused reduction in the formation of 5-HETE in human leucocytes when used. MS can thus be considered a dual inhibitor of 5-LOX and COX pathways of arachidonic acid cascade. Further investigation with this substance revealed that it could interfere with the LT receptors in the lung carcinoma [38]. In a recent study, a group of scientists have shown the effect of MS on prostate cancer cells both in vitro and in vivo [39], and their result suggests a profound reduction in the tumor growth and cancer metastasis. ... While the commonly used inhibitors produced strong cytotoxicity, notably, zileuton, the only commercialized 5-LOX inhibitor, failed to induce an anti-proliferative or cytotoxic response in all other types of tumor cells where 5-LOX was in inactive state (e.g. HeLa cells); however, where 5-LOX was in active state, zileuton could effectively inhibit progression, as in case of prostate cancer."

191. ^ Linja MJ, Savinainen KJ, Saramäki OR, Tammela TL, Vessella RL, Visakorpi T (May 2001). "Amplification and overexpression of androgen receptor gene in hormone-refractory prostate cancer". *Cancer Research*. **61** (9): 3550–5. PMID 11325816.
192. ^ Ford OH, Gregory CW, Kim D, Smitherman AB, Mohler JL (November 2003). "Androgen receptor gene amplification and protein expression in recurrent prostate cancer". *The Journal of Urology*. **170** (5): 1817–21. doi:10.1097/01.ju.0000091873.09677.f4. PMID 14532783.
193. ^ Kokontis J, Takakura K, Hay N, Liao S (March 1994). "Increased androgen receptor activity and altered c-myc expression in prostate cancer cells after long-term androgen deprivation". *Cancer Research*. **54** (6): 1566–73. PMID 7511045.
194. ^ Umekita Y, Hiipakka RA, Kokontis JM, Liao S (October 1996). "Human prostate tumor growth in athymic mice: inhibition by androgens and stimulation by finasteride". *Proc. Natl. Acad. Sci. U.S.A.* **93** (21): 11802–7. doi:10.1073/pnas.93.21.11802. PMC 38139. PMID 8876218.
195. ^ Kokontis JM, Hsu S, Chuu CP, Dang M, Fukuchi J, Hiipakka RA, Liao S (December 2005). "Role of androgen receptor in the progression of human prostate tumor cells to androgen independence and insensitivity". *The Prostate*. **65** (4): 287–98. doi:10.1002/pros.20285. PMID 16015608.
196. ^ Bourdoumis A, Papatsoris AG, Chrisofos M, Efstathiou E, Skolarikos A, Deliveliotis C (2010). "The novel prostate cancer antigen 3 (PCA3) biomarker". *Int Braz J Urol*. **36** (6): 665–8; discussion 669. doi:10.1590/S1677-55382010000600003. PMID 21176272.

## External links [edit]

- Prostate cancer at DMOZ
- Patient-centered information from the European Urological Association

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| v · t · e · | **Tumors: male urogenital neoplasia (C60–C63/D29, 185–187/222)** · | | |
|---|---|---|---|
| | | **Sex cord-** | Sertoli-Leydig cell tumour (Sertoli cell tumour · Leydig cell tumour · · |

| | | | | |
|---|---|---|---|---|
| **Internal** | **Testicles** | **gonadal stromal** | | |
| | | **Germ cell** | **G** | Seminoma (Spermatocytic seminoma · Intratubular germ cell neoplasia · · |
| | | | **NG** | Embryonal carcinoma · Endodermal sinus tumor · Gonadoblastoma · Teratoma · Choriocarcinoma · Embryoma · |
| | **Prostate** | | | Adenocarcinoma · High-grade prostatic intraepithelial neoplasia (HGPIN · · Small-cell carcinoma · Transitional cell carcinoma · |
| **External** | **Penis** | | | Carcinoma (Extramammary Paget's disease · · Bowen's disease · Bowenoid papulosis · Erythroplasia of Queyrat · Hirsuties coronae glandis · |
| **Authority control** | GND: 4047511-6 · NDL: 00575400 · | | | |

Categories: Male genital neoplasia | Neoplastic and hyperplastic prostate disorders | Histopathology | Prostate cancer | Infectious causes of cancer




# Skin cancer

From Wikipedia, the free encyclopedia

**Skin cancers** are cancers that arise from the skin. They are due to the development of abnormal cells that have the ability to invade or spread to other parts of the body.[1] There are three main types of skin cancers: basal-cell skin cancer (BCC), squamous-cell skin cancer (SCC) and melanoma.[2] The first two together along with a number of less common skin cancers are known as nonmelanoma skin cancer (NMSC).[3][4] Basal-cell cancer grows slowly and can damage the tissue around it but is unlikely to spread to distant areas or result in death.[3] It often appears as a painless raised area of skin, that may be shiny with small blood vessels running over it or may present as a raised area with an ulcer.[2] Squamous-cell cancer is more likely to spread.[3] It usually presents as a hard lump with a scaly top but may also form an ulcer.[5] Melanomas are the most aggressive. Signs include a mole that has changed in size, shape, color, has irregular edges, has more than one color, is itchy or bleeds.[6]

Greater than 90% of cases are caused by exposure to ultraviolet radiation from the Sun.[7] This exposure increases the risk of all three main types of skin cancer.[7] Exposure has increased partly due to a thinner ozone layer.[3][8] Tanning beds are becoming another common source of ultraviolet radiation.[7] For melanomas and basal-cell cancers exposure during childhood is particularly harmful.[9] For squamous-cell cancers total exposure, irrespective of when it occurs, is more important.[7] Between 20% and 30% of melanomas develop from moles.[9] People with light skin are at higher risk[2] as are those with poor immune function such as from medications or HIV/AIDS.[3][10] Diagnosis is by biopsy.[6]

Decreasing exposure to ultraviolet radiation and the use of sunscreen appear to be effective methods of preventing melanoma and squamous-cell cancer.[9][11] It is not clear if sunscreen affects the risk of basal-cell cancer.[11] Nonmelanoma skin cancer is usually curable.[3] Treatment is generally by surgical removal but may less commonly involve radiation therapy or topical medications such as fluorouracil.[2] Treatment of melanoma may involve some combination of surgery, chemotherapy, radiation therapy, and targeted therapy.[6] In those people whose disease has spread to other areas of their bodies, palliative care may be used to improve quality of life.[6] Melanoma has one of the higher survival rates among cancers, with over 86% of people in the UK and more than 90% in the United States surviving more than 5 years.[12][13]

Skin cancer is the most common form of cancer, globally accounting for at least 40% of cases.[3][14] It is

**Skin cancer**

A basal-cell skin cancer. Note the pearly appearance and telangiectasia.

| Classification and external resources | |
|---|---|
| **Specialty** | Oncology and dermatology |
| **ICD-10** | C43-C44 |
| **ICD-9-CM** | 172, 173 |
| **ICD-O** | 8010-8720 |
| **MedlinePlus** | 001442 |
| **eMedicine** | article/276624, article/870538, article/1100753, article/1965430 |
| **MeSH** | D012878 |

[edit on Wikidata]

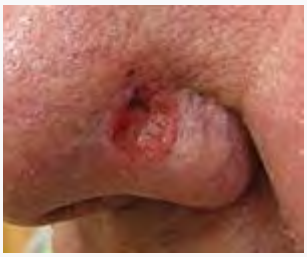
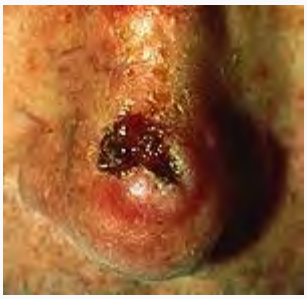
especially common among people with light skin.[15] The most common type is nonmelanoma skin cancer, which occurs in at least 2-3 million people per year.[9][16] This is a rough estimate, however, as good statistics are not kept.[2] Of nonmelanoma skin cancers, about 80% are basal-cell cancers and 20% squamous-cell cancers.[4] Basal-cell and squamous-cell cancers rarely result in death.[9] In the United States they were the cause of less than 0.1% of all cancer deaths.[2] Globally in 2012 melanoma occurred in 232,000 people, and resulted in 55,000 deaths.[9] Australia and New Zealand have the highest rates of melanoma in the world.[9] The three main types of skin cancer have become more common in the last 20 to 40 years, especially in those areas which are mostly Caucasian.[3][9]

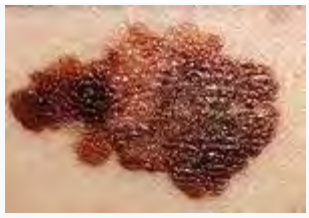
**Contents**



## Classification [edit]

There are three main types of skin cancer: basal-cell skin cancer (basal-cell carcinoma) (BCC), squamous-cell skin cancer (squamous-cell carcinoma) (SCC) and malignant melanoma.

| Cancer | Description | Illustration |
|---|---|---|
| Basal-cell carcinoma | Note the pearly translucency to fleshy color, tiny blood vessels on the surface, and sometime ulceration which can be characteristics. The key term is translucency. |  |
| Squamous-cell carcinoma | Commonly presents as a red, crusted, or scaly patch or bump. Often a very rapid growing tumor. |  |
| Malignant melanoma | The common appearance is an asymmetrical area, with an irregular border, color variation, and often greater than 6 mm diameter.[17] | |



Basal-cell carcinomas are present on sun-exposed areas of the skin, especially the face. They rarely metastasize and rarely cause death. They are easily treated with surgery or radiation. Squamous-cell skin cancer are common, but much less common than basal-cell cancers. They metastasize more frequently than BCCs. Even then, the metastasis rate is quite low, with the exception of SCC of the lip, ear, and in people who are immunosuppressed. Melanoma are the least frequent of the 3 common skin cancers. They frequently metastasize, and could potentially cause death once they spread.

Less common skin cancers include: dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, and angiosarcoma.

BCC and SCC often carry a UV-signature mutation indicating that these cancers are caused by UVB radiation via direct DNA damage. However malignant melanoma is predominantly caused by UVA radiation via indirect DNA damage. The indirect DNA damage is caused by free radicals and reactive oxygen species. Research indicates that the absorption of three sunscreen ingredients into the skin, combined with a 60-minute exposure to UV, leads to an increase of free radicals in the skin, if applied in too little quantities and too infrequently.[18] However, the researchers add that newer creams often do not contain these specific compounds, and that the combination of other ingredients tends to retain the compounds on the surface of the skin. They also add the frequent re-application reduces the risk of radical formation.

## Signs and symptoms [edit]

There are a variety of different skin cancer symptoms. These include changes in the skin that do not heal, ulcering in the skin, discolored skin, and changes in existing moles, such as jagged edges to the mole and enlargement of the mole.

### Basal-cell skin cancer [edit]

Basal-cell skin cancer (BCC) usually presents as a raised, smooth, pearly bump on the sun-exposed skin of the head, neck or shoulders. Sometimes small blood vessels (called telangiectasia) can be seen within the tumor. Crusting and bleeding in the center of the tumor frequently develops. It is often mistaken for a sore that does not heal. This form of skin cancer is the least deadly and with proper treatment can be completely eliminated, often without scarring.

### Squamous-cell skin cancer [edit]

Squamous-cell skin cancer (SCC) is commonly a red, scaling, thickened patch on sun-exposed skin. Some are firm hard nodules and dome shaped like keratoacanthomas. Ulceration and bleeding may occur. When SCC is not treated, it may develop into a large mass. Squamous-cell is the second most common skin cancer. It is dangerous, but not nearly as dangerous as a melanoma.

### Melanoma [edit]

Most melanoma consist of various colours from shades of brown to black. A small number of melanoma are pink, red or fleshy in colour; these are called amelanotic melanoma and tend to be more aggressive. Warning signs of malignant melanoma include change in the size, shape, color or elevation of a mole. Other signs are the appearance of a new mole during adulthood or pain, itching, ulceration, redness around the site, or bleeding at the site. An often-used mnemonic is "ABCDE", where A is for "asymmetrical", B for "borders" (irregular: "Coast of Maine sign"), C for "color" (variegated), D for "diameter" (larger than 6 mm—[19][20]

the size of a pencil eraser) and E for "evolving."

### Other [edit]

Merkel cell carcinomas are most often rapidly growing, non-tender red, purple or skin colored bumps that are not painful or itchy. They may be mistaken for a cyst or another type of cancer.[21]

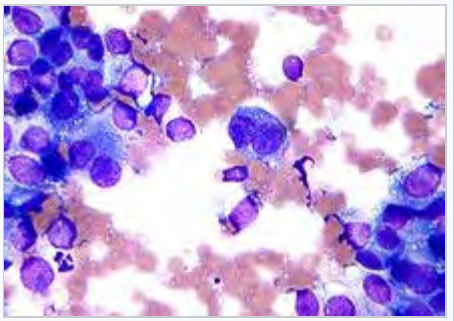
## Causes [edit]

Ultraviolet radiation from sun exposure is the primary environmental cause of skin cancer.[22][23][24] Other risk factors that play a role include:

- Smoking tobacco[23]
- HPV infections increase the risk of squamous-cell carcinoma.[23]
- Some genetic syndromes[23] including congenital melanocytic nevi syndrome which is characterized by the presence of nevi (birthmarks or moles) of varying size which are either present at birth, or appear within 6 months of birth. Nevi larger than 20 mm (3/4") in size are at higher risk for becoming cancerous.
- Chronic non-healing wounds.[23] These are called Marjolin's ulcers based on their appearance, and can develop into squamous-cell carcinoma.
- Ionizing radiation, environmental carcinogens, artificial UV radiation (e.g. tanning beds), aging, and light skin color.[23] It is believed that tanning beds are the cause of hundreds of thousands of basal and squamous-cell carcinomas.[25] The World Health Organization now places people who use artificial tanning beds in its highest risk category for skin cancer.[26] Alcohol consumption, specifically excessive drinking increase the risk of sunburns.[27]
- The use of many immunosuppressive medications increases the risk of skin cancer. Cyclosporin A, a calcineurin inhibitor for example increases the risk approximately 200 times, and azathioprine about 60 times.[28]

## Pathophysiology [edit]

A malignant epithelial tumor that primarily originates in the epidermis, in squamous mucosa or in areas of squamous metaplasia is referred to as a squamous-cell carcinoma.[29]



Micrograph of melanoma. FNA specimen. Field stain

Macroscopically, the tumor is often elevated, fungating, or may be ulcerated with irregular borders. Microscopically, tumor cells destroy the basement membrane and form sheets or compact masses which invade the subjacent connective tissue (dermis). In well differentiated carcinomas, tumor cells are pleomorphic/atypical, but resembling normal keratinocytes from prickle layer (large, polygonal, with abundant eosinophilic (pink) cytoplasm and central nucleus).[29]

Their disposal tends to be similar to that of normal epidermis: immature/basal cells at the periphery, becoming more mature to the centre of the tumor masses. Tumor cells transform into keratinized squamous cells and form round nodules with concentric, laminated layers, called "cell nests" or "epithelial/keratinous pearls". The surrounding stroma is reduced and contains inflammatory infiltrate (lymphocytes). Poorly differentiated squamous carcinomas contain more pleomorphic cells and no keratinization.[29]

## Prevention [edit]

[30] [31]

Sunscreen is effective and thus recommended to prevent melanoma and squamous-cell carcinoma. There is little evidence that it is effective in preventing basal-cell carcinoma.[32] Other advice to reduce rates of skin cancer includes avoiding sunburning, wearing protective clothing, sunglasses and hats, and attempting to avoid sun exposure or periods of peak exposure.[33] The U.S. Preventive Services Task Force recommends that people between 9 and 25 years of age be advised to avoid ultraviolet light.[34]

The risk of developing skin cancer can be reduced through a number of measures including decreasing indoor tanning and mid day sun exposure, increasing the use of sunscreen,[35] and avoiding the use of tobacco products.

There is insufficient evidence either for or against screening for skin cancers.[36] Vitamin supplements and antioxidant supplements have not been found to have an effect in prevention.[37] Evidence for a benefit from dietary measures is tentative.[38]

Zinc oxide and titanium oxide are often used in sun screen to provide broad protection from UVA and UVB ranges.[39]

Eating certain foods may decrease the risk of sunburns but this is much less than the protection provided by sunscreen.[40]

## Treatment [edit]

Treatment is dependent on type of cancer, location of the cancer, age of the person, and whether the cancer is primary or a recurrence. Treatment is also determined by the specific type of cancer. For a small basal-cell cancer in a young person, the treatment with the best cure rate (Mohs surgery or CCPDMA) might be indicated. In the case of an elderly frail man with multiple complicating medical problems, a difficult to excise basal-cell cancer of the nose might warrant radiation therapy (slightly lower cure rate) or no treatment at all. Topical chemotherapy might be indicated for large superficial basal-cell carcinoma for good cosmetic outcome, whereas it might be inadequate for invasive nodular basal-cell carcinoma or invasive squamous-cell carcinoma.[*citation needed*]. In general, melanoma is poorly responsive to radiation or chemotherapy.

For low-risk disease, radiation therapy (external beam radiotherapy[41] or brachytherapy), topical chemotherapy (imiquimod or 5-fluorouracil) and cryotherapy (freezing the cancer off) can provide adequate control of the disease; all of them, however, may have lower overall cure rates than certain type of surgery. Other modalities of treatment such as photodynamic therapy, topical chemotherapy, electrodesiccation and curettage can be found in the discussions of basal-cell carcinoma and squamous-cell carcinoma.

Mohs' micrographic surgery (Mohs surgery) is a technique used to remove the cancer with the least amount of surrounding tissue and the edges are checked immediately to see if tumor is found. This provides the opportunity to remove the least amount of tissue and provide the best cosmetically favorable results. This is especially important for areas where excess skin is limited, such as the face. Cure rates are equivalent to wide excision. Special training is required to perform this technique. An alternative method is CCPDMA and can be performed by a pathologist not familiar with Mohs surgery.

In the case of disease that has spread (metastasized), further surgical procedures or chemotherapy may be required.[42]

Treatments for metastatic melanoma include biologic immunotherapy agents ipilimumab, pembrolizumab, and nivolumab; BRAF inhibitors, such as vemurafenib and dabrafenib; and a MEK inhibitor trametinib.[43]

### Reconstruction [edit]

Currently, surgical excision is the most common form of treatment for skin cancers. The goal of reconstructive surgery is restoration of normal appearance and function. The choice of technique in reconstruction is dictated by the size and location of the defect. Excision and reconstruction of facial skin cancers is generally more challenging due to presence of highly visible and functional anatomic structures in the face.

When skin defects are small in size, most can be repaired with simple repair where skin edges are approximated and closed with sutures. This will result in a linear scar. If the repair is made along a natural skin fold or wrinkle line, the scar will be hardly visible. Larger defects may require repair with a skin graft, local skin flap, pedicled skin flap, or a microvascular free flap. Skin grafts and local skin flaps are by far more common than the other listed choices.

Skin grafting is patching of a defect with skin that is removed from another site in the body. The skin graft is sutured to the edges of the defect, and a bolster dressing is placed atop the graft for seven to ten days, to immobilize the graft as it heals in place. There are two forms of skin grafting: split thickness and full thickness. In a split thickness skin graft, a shaver is used to shave a layer of skin from the abdomen or thigh. The donor site regenerates skin and heals over a period of two weeks. In a full thickness skin graft, a segment of skin is totally removed and the donor site needs to be sutured closed.[44]

Split thickness grafts can be used to repair larger defects, but the grafts are inferior in their cosmetic appearance. Full thickness skin grafts are more acceptable cosmetically. However, full thickness grafts can only be used for small or moderate sized defects.

Local skin flaps are a method of closing defects with tissue that closely matches the defect in color and quality. Skin from the periphery of the defect site is mobilized and repositioned to fill the deficit. Various forms of local flaps can be designed to minimize disruption to surrounding tissues and maximize cosmetic outcome of the reconstruction. Pedicled skin flaps are a method of transferring skin with an intact blood supply from a nearby region of the body. An example of such reconstruction is a pedicled forehead flap for repair of a large nasal skin defect. Once the flap develops a source of blood supply form its new bed, the vascular pedicle can be detached.[45]

## Prognosis [edit]

The mortality rate of basal-cell and squamous-cell carcinoma are around 0.3%, causing 2000 deaths per year in the US. In comparison, the mortality rate of melanoma is 15–20% and it causes 6500 deaths per year.[46]:29,31 Even though it is much less common, malignant melanoma is responsible for 75% of all skin cancer-related deaths.[47]

The survival rate for people with melanoma depends upon when they start treatment. The cure rate is very high when melanoma is detected in early stages, when it can easily be removed surgically. The prognosis is less favorable if the melanoma has spread to other parts of the body.[48] As of 2003 the overall five year cure rate with Mohs' micrographic surgery was around 95 percent for recurrent basal cell carcinoma.[49]

Australia and New Zealand exhibit one of the highest rates of skin cancer incidence in the world, almost four times the rates registered in the United States, the UK and Canada. Around 434,000 people receive treatment for non-melanoma skin cancers and 10,300 are treated for melanoma. Melanoma is the most common type of cancer in people between 15–44 years in both countries. The incidence of skin cancer has been increasing.[50] The incidence of melanoma among Auckland residents of European descent in 1995 was 77.7 cases per 100,000 people per year, and was predicted to increase in the 21st century because of "the effect of local stratospheric ozone depletion and the time lag from sun exposure to melanoma development."[51]

## Epidemiology [edit]

Skin cancers result in 80,000 deaths a year as of 2010, 49,000 of which are due to melanoma and 31,000 of which are due to non-melanoma skin cancers.[53] This is up from 51,000 in 1990.[53]

In the US in 2008, 59,695 people were diagnosed with melanoma, and 8,623 people died from it.[54] In Australia more than 12,500 new cases of melanoma are reported each year, out of which more than 1,500 die from the disease. Australia has the highest per capita incidence of

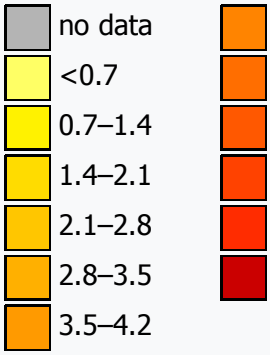
Age-standardized death from

melanoma in the world.[55]

More than 3.5 million cases of skin cancer are diagnosed annually in the United States, which makes it the most common form of cancer in that country. According to the Skin Cancer Foundation, one in five Americans will develop skin cancer at some point of their lives. The most common form of skin cancer is basal-cell carcinoma, followed by squamous cell carcinoma. Although the incidence of many cancers in the United States is falling, the incidence of melanoma keeps growing, with approximately 68,729 melanomas diagnosed in 2004 according to reports of the National Cancer Institute.[56]

Skin cancer (malignant melanoma) is the fifth most common cancer in the UK (around 13,300 people were diagnosed with malignant melanoma in 2011), and the disease accounts for 1% all cancer deaths (around 2,100 people died in 2012).[57]

melanoma and other skin cancers per 100,000 inhabitants in 2004[52]




## References [edit]


1. ^ "Defining Cancer". *National Cancer Institute*. Retrieved 10 June 2014.
2. ^ *a b c d e f* "Skin Cancer Treatment (PDQ®)". *NCI*. 2013-10-25. Retrieved 30 June 2014.
3. ^ *a b c d e f g h* Cakir, BÖ; Adamson, P; Cingi, C (November 2012). "Epidemiology and economic burden of nonmelanoma skin cancer.". *Facial plastic surgery clinics of North America*. **20** (4): 419–22. doi:10.1016/j.fsc.2012.07.004. PMID 23084294.
4. ^ *a b* Marsden, edited by Sajjad Rajpar, Jerry (2008). *ABC of skin cancer*. Malden, Mass.: Blackwell Pub. pp. 5–6. ISBN 9781444312508.
5. ^ Lynne M Dunphy (2011). *Primary Care: The Art and Science of Advanced Practice Nursing*. F.A. Davis. p. 242. ISBN 9780803626478.
6. ^ *a b c d* "General Information About Melanoma". *NCI*. 2014-04-17. Retrieved 30 June 2014.
7. ^ *a b c d* Gallagher, RP; Lee, TK; Bajdik, CD; Borugian, M (2010). "Ultraviolet radiation.". *Chronic diseases in Canada*. 29 Suppl 1: 51–68. PMID 21199599.
8. ^ Maverakis E, Miyamura Y, Bowen MP, Correa G, Ono Y, Goodarzi H (2010). "Light, including ultraviolet". *J Autoimmun*. **34** (3): J247–57. doi:10.1016/j.jaut.2009.11.011. PMID 20018479.
9. ^ *a b c d e f g h* *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 5.14. ISBN 9283204298.
10. ^ Chiao, EY; Krown, SE (September 2003). "Update on non-acquired immunodeficiency syndrome-defining malignancies.". *Current opinion in oncology*. **15** (5): 389–97. doi:10.1097/00001622-200309000-00008. PMID 12960522.
11. ^ *a b* Jou, PC; Feldman, RJ; Tomecki, KJ (June 2012). "UV protection and sunscreens: what to tell patients.". *Cleveland Clinic journal of medicine*. **79** (6): 427–36. doi:10.3949/ccjm.79a.11110. PMID 22660875.
12. ^ "SEER Stat Fact Sheets: Melanoma of the Skin". *NCI*. Retrieved 18 June 2014.
13. ^ "Release: Cancer Survival Rates, Cancer Survival in England, Patients Diagnosed 2005-2009 and Followed up to 2010". *Office for National Statistics*. 15 November 2011. Retrieved 30 June 2014.
14. ^ Dubas, LE; Ingraffea, A (February 2013). "Nonmelanoma skin cancer.". *Facial plastic surgery clinics of North America*. **21** (1): 43–53. doi:10.1016/j.fsc.2012.10.003. PMID 23369588.
15. ^ Leiter, U; Garbe, C (2008). "Epidemiology of melanoma and nonmelanoma skin cancer--the role of sunlight.". *Advances in experimental medicine and biology*. **624**: 89–103. doi:10.1007/978-0-387-77574-6_8. PMID 18348450.
16. ^ "How common is skin cancer?". *World Health Organization*. Retrieved 30 June 2014.
17. ^ "Malignant Melanoma: eMedicine Dermatology".
18. ^ Hanson Kerry M.; Gratton Enrico; Bardeen Christopher J (2006). "Sunscreen enhancement of UV-induced reactive oxygen species in the skin". *Free Radical Biology and Medicine*. **41** (8): 1205–1212. doi:10.1016/j.freeradbiomed.2006.06.011. PMID 17015167.
19. ^ "What You Need To Know About: Melanoma and Other Skin Cancers" (PDF). National Cancer Institute.
20. ^ "Melanoma Skin Cancer" (PDF). American Cancer Society. 2012.
21. ^ Bickle K, Glass, LF, Messina, JL, Fenske, NA, Siegrist, K (March 2004). "Merkel cell carcinoma: a clinical, histopathologic, and immunohistochemical review.". *Seminars in cutaneous medicine and surgery*. **23** (1): 46–53.

doi:10.1016/s1085-5629(03)00087-7. PMID 15095915.
22. ^ Narayanan DL, Saladi, RN, Fox, JL (September 2010). "Ultraviolet radiation and skin cancer.". *International Journal of Dermatology*. **49** (9): 978–86. doi:10.1111/j.1365-4632.2010.04474.x. PMID 20883261.
23. ^ *a b c d e f* Saladi RN, Persaud, AN (January 2005). "The causes of skin cancer: a comprehensive review.". *Drugs of today (Barcelona, Spain : 1998)*. **41** (1): 37–53. doi:10.1358/dot.2005.41.1.875777. PMID 15753968.
24. ^ Gordon, Randy (2013-08-01). "Skin cancer: an overview of epidemiology and risk factors". *Seminars in Oncology Nursing*. **29** (3): 160–169. doi:10.1016/j.soncn.2013.06.002. ISSN 1878-3449. PMID 23958214.
25. ^ Wehner, MR; Shive, ML; Chren, MM; Han, J; Qureshi, AA; Linos, E (October 2, 2012). "Indoor tanning and non-melanoma skin cancer: systematic review and meta-analysis.". *BMJ (Clinical research ed.)*. **345**: e5909. doi:10.1136/bmj.e5909. PMC 3462818. PMID 23033409.
26. ^ Arndt, K.A. (2010).*Skin Care and Repair*.Chestnut Hill, MA:Harvard Health Publications.
27. ^ Saladi, R. N.; Nektalova, T.; Fox, J. L. (2010-01-01). "Induction of skin carcinogenicity by alcohol and ultraviolet light". *Clinical and Experimental Dermatology*. **35** (1): 7–11. doi:10.1111/j.1365-2230.2009.03465.x. ISSN 1365-2230. PMID 19778305.
28. ^ Kuschal C, Thoms, KM; Schubert, S; Schäfer, A; Boeckmann, L; Schön, MP; Emmert, S (January 2012). "Skin cancer in organ transplant recipients: effects of immunosuppressive medications on DNA repair.". *Experimental Dermatology*. **21** (1): 2–6. doi:10.1111/j.1600-0625.2011.01413.x. PMID 22151386.
29. ^ *a b c* ""Squamous cell carcinoma (epidermoid carcinoma) — skin" pathologyatlas.ro". Retrieved 2007-07-21.
30. ^ Kanavy HE, Gerstenblith MR (December 2011). "Ultraviolet radiation and melanoma". *Semin Cutan Med Surg*. **30** (4): 222–8. doi:10.1016/j.sder.2011.08.003. PMID 22123420.
31. ^ Burnett ME, Wang SQ (April 2011). "Current sunscreen controversies: a critical review". *Photodermatol Photoimmunol Photomed*. **27** (2): 58–67. doi:10.1111/j.1600-0781.2011.00557.x. PMID 21392107.
32. ^ Kütting B, Drexler H (December 2010). "UV-induced skin cancer at workplace and evidence-based prevention". *Int Arch Occup Environ Health*. **83** (8): 843–54. doi:10.1007/s00420-010-0532-4. PMID 20414668.
33. ^ Council on Environmental H, Section on, Dermatology, Balk, SJ (March 2011). "Ultraviolet radiation: a hazard to children and adolescents.". *Pediatrics*. **127** (3): 588–97. doi:10.1542/peds.2010-3501. PMID 21357336.
34. ^ Lin JS, Eder, M, Weinmann, S (February 2011). "Behavioral counseling to prevent skin cancer: a systematic review for the U.S. Preventive Services Task Force.". *Annals of Internal Medicine*. **154** (3): 190–201. doi:10.1059/0003-4819-154-3-201102010-00009. PMID 21282699.
35. ^ Lin JS, Eder, M, Weinmann, S (2011). "Behavioral counseling to prevent skin cancer: a systematic review for the U.S. Preventive Services Task Force.". *Annals of Internal Medicine*. **154** (3): 190–201. doi:10.1059/0003-4819-154-3-201102010-00009. PMID 21282699.
36. ^ Bibbins-Domingo, Kirsten; Grossman, David C.; Curry, Susan J.; Davidson, Karina W.; Ebell, Mark; Epling, John W.; García, Francisco A. R.; Gillman, Matthew W.; Kemper, Alex R.; Krist, Alex H.; Kurth, Ann E.; Landefeld, C. Seth; Mangione, Carol M.; Phillips, William R.; Phipps, Maureen G.; Pignone, Michael P.; Siu, Albert L. (26 July 2016). "Screening for Skin Cancer". *JAMA*. **316** (4): 429. doi:10.1001/jama.2016.8465.
37. ^ Chang YJ, Myung, SK, Chung, ST, Kim, Y, Lee, EH, Jeon, YJ, Park, CH, Seo, HG, Huh, BY (2011). "Effects of vitamin treatment or supplements with purported antioxidant properties on skin cancer prevention: a meta-analysis of randomized controlled trials.". *Dermatology (Basel, Switzerland)*. **223** (1): 36–44. doi:10.1159/000329439. PMID 21846961.
38. ^ Jensen, JD; Wing, GJ; Dellavalle, RP (November–December 2010). "Nutrition and melanoma prevention.". *Clinics in dermatology*. **28** (6): 644–9. doi:10.1016/j.clindermatol.2010.03.026. PMID 21034988.
39. ^ Smijs, Threes G; Pavel, Stanislav (2011-10-13). "Titanium dioxide and zinc oxide nanoparticles in sunscreens: focus on their safety and effectiveness". *Nanotechnology, Science and Applications*. **4**: 95–112. doi:10.2147/NSA.S19419. ISSN 1177-8903. PMC 3781714. PMID 24198489.
40. ^ Stahl, W; Sies, H (November 2012). "β-Carotene and other carotenoids in protection from sunlight.". *The American Journal of Clinical Nutrition*. **96** (5): 1179S–84S. doi:10.3945/ajcn.112.034819. PMID 23053552.
41. ^ Hill, R; Healy, B; Holloway, L; Kuncic, Z; Thwaites, D; Baldock, C (21 March 2014). "Advances in kilovoltage x-ray beam dosimetry.". *Physics in medicine and biology*. **59** (6): R183–231. doi:10.1088/0031-9155/59/6/r183. PMID 24584183.
42. ^ Doherty, Gerard M.; Mulholland, Michael W. (2005). *Greenfield's Surgery: Scientific Principles And Practice*. Baltimore: Williams & Wilkins. ISBN 0-7817-5626-X.
43. ^ Maverakis E, Cornelius LA, Bowen GM, Phan T, Patel FB, Fitzmaurice S, He Y, Burrall B, Duong C, Kloxin AM, Sultani H, Wilken R, Martinez SR, Patel F (2015). "Metastatic melanoma - a review of current and future treatment options". *Acta Derm Venereol*. **95** (5): 516–524. doi:10.2340/00015555-2035. PMID 25520039.
44. ^ Maurice M Khosh, MD, FACS. "Skin Grafts, Full-Thickness". *eMedicine*.
45. ^ Skin Cancer Reconstruction
46. ^ C. C. Boring; T. S. Squires; T. Tong (1991). "Cancer statistics, 1991". *SA Cancer Journal for Clinician*. **41** (1): 19–

36. doi:10.3322/canjclin.41.1.19. PMID 1984806.
47. ^ Jerant AF, Johnson JT, Sheridan CD, Caffrey TJ (July 2000). "Early Detection and Treatment of Skin Cancer". *American Family Physician*. **62** (2): 357–68, 375–6, 381–2. PMID 10929700.
48. ^ "Malignant Melanoma Cancer". Retrieved 2010-07-02.
49. ^ Wong, C S M (4 October 2003). "Basal cell carcinoma". *BMJ*. **327** (7418): 794–798. doi:10.1136/bmj.327.7418.794. PMC 214105. PMID 14525881.
50. ^ "Skin Cancer Facts and Figures". Retrieved 2013-12-01. "From 1982 to 2007 melanoma diagnoses increased by around 50%. From 1998 to 2007, GP consultations to treat non-melanoma skin cancer increased by 14%, to reach 950,000 visits each year."
51. ^ Jones WO, Harman CR, Ng AK, Shaw JH (1999). "Incidence of malignant melanoma in Auckland, New Zealand: The highest rates in the world". *World Journal of Surgery*. **23** (7): 732–5. doi:10.1007/pl00012378.
52. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved November 11, 2009.
53. ^ *a b* Lozano, R (December 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
54. ^ CDC - Skin Cancer Statistics
55. ^ [1] Melanoma facts and statistics
56. ^ "Skin Cancer Facts". Retrieved 2010-07-02.
57. ^ "Skin cancer statistics". *Cancer Research UK*. Retrieved 28 October 2014.

## External links [edit]

- Skin cancer at DMOZ
- Skin cancer procedures: text, images and videos

Wikimedia Commons has media related to *Skin cancers*.

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|---|---|---|
| **Conditions** | **Benign tumors** | Hyperplasia · Cyst · Pseudocyst · Hamartoma · |
| | **Malignant progression** | Dysplasia · Carcinoma in situ · Cancer · Metastasis · Primary tumor · Sentinel lymph node · |
| | **Topography** | Head/Neck (Oral, Nasopharyngeal) · Digestive system · Respiratory system · Bone · **Skin** · Blood · Urogenital · Nervous system · Endocrine system · |
| | **Histology** | Carcinoma · Sarcoma · Blastoma · Papilloma · Adenoma · |
| | **Other** | Precancerous condition · Paraneoplastic syndrome · |
| **Staging/grading** | TNM · Ann Arbor · Prostate cancer staging · Gleason grading system · Dukes classification · | |
| **Carcinogenesis** | Cancer cell · Carcinogen · Tumor suppressor genes/oncogenes · Clonally transmissible cancer · Oncovirus · Cancer bacteria · | |
| **Misc.** | Research · List of oncology-related terms · History · Cancer pain · Cancer and nausea · | |

| v · t · e · | **Tumors: Skin neoplasm, nevi and melanomas (C43/D22, 172/216, ICD-O 8720-8799)** |
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| **Melanoma** | Mucosal melanoma · Superficial spreading melanoma · Nodular melanoma · *lentigo* (Lentigo maligna/Lentigo maligna melanoma · Acral lentiginous melanoma · · Amelanotic melanoma · Desmoplastic melanoma · Melanoma with features of a Spitz nevus · Melanoma with small nevus-like cells · Polypoid melanoma · Nevoid melanoma · Melanocytic tumors of uncertain malignant potential · |

| | |
|---|---|
| **Nevus/ melanocytic nevus** | Nevus of Ito/Nevus of Ota · Compound nevus · Spitz nevus (Pigmented spindle cell nevus · · Halo nevus · Junctional nevus · Pseudomelanoma · |
| | Blue nevus (of Jadassohn–Tièche · Cellular · Epithelioid · Deep penetrating · Amelanotic · Malignant · · |
| | Congenital melanocytic nevus (Giant · Medium-sized · Small-sized) · |
| | Balloon cell nevus · Dysplastic nevus/Dysplastic nevus syndrome · |
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|---|---|---|---|
| **Tumor** | **Carcinoma** | **BCC** | Forms (Aberrant · Cicatricial · Cystic · Fibroepithelioma of Pinkus · Infiltrative · Micronodular · Nodular · Pigmented · Polypoid · Pore-like · Rodent ulcer · Superficial · · Nevoid basal cell carcinoma syndrome · |
| | | **SCC** | Forms (Adenoid · Basaloid · Clear cell · Signet-ring-cell · Spindle-cell · · Marjolin's ulcer · Bowen's disease · Bowenoid papulosis · Erythroplasia of Queyrat · Actinic keratosis · |
| | | **Adenocarcinoma** | Aggressive digital papillary adenocarcinoma · Extramammary Paget's disease · |
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| | **Benign tumors** | **Acanthoma** | Forms (Large cell · Fissuring · Clear cell · Epidermolytic · · Melanoacanthoma · Pilar sheath acanthoma · Seboacanthoma · Seborrheic keratosis · Warty dyskeratoma · |
| | | **Keratoacanthoma** | Generalized eruptive · Keratoacanthoma centrifugum marginatum · Multiple · Solitary · |
| | | **Wart** | Verruca vulgaris · Verruca plana · Plantar wart · Periungual wart · |
| **Other** | **Epidermal nevus** | | Syndromes (Epidermal nevus syndrome · Schimmelpenning syndrome · Nevus comedonicus syndrome · · Nevus comedonicus · Inflammatory linear verrucous epidermal nevus · Linear verrucous epidermal nevus · Pigmented hairy epidermal nevus syndrome · Systematized epidermal nevus · Phakomatosis pigmentokeratotica · |
| | **Other nevus** | | Nevus unius lateris · Patch blue nevus · Unilateral palmoplantar verrucous nevus · Zosteriform speckled lentiginous nevus · |
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|---|---|---|---|
| **Dermis** | Benign fibrous histiocytoma/dermatofibrosarcoma protuberans · Dermatofibrosarcoma protuberans · | | |
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| | | *urogenital:* | Hirsuties coronae glandis · |
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| **Subcutaneous tumors** | **Other** | | Palisaded encapsulated neuroma · Infantile neuroblastoma · Neuroma cutis · |
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| | | *nevus:* | Nevus anemicus · Nevus flammeus · Nevus flammeus nuchae · Nevus lipomatosus superficialis · Nevus oligemicus · Connective tissue nevus · Midline nevus flammeus · Porokeratotic eccrine ostial and dermal duct nevus · |
| | | *histiocytoma:* | Pleomorphic undifferentiated sarcoma · Plexiform fibrohistiocytic tumor · Progressive nodular histiocytoma · |
| | | | Teratoma · Adenoma sebaceum · Metastatic carcinoma · Giant-cell tumor of the tendon sheath · Glomus tumor · Granular cell tumor · Carcinoid · Desmoid tumor · Neurothekeoma · Angiokeratoma · Zosteriform metastasis · Keratinizing metaplasia · Epithelioid sarcoma · |

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Categories: Integumentary neoplasia | Sun tanning


# Stomach cancer

From Wikipedia, the free encyclopedia

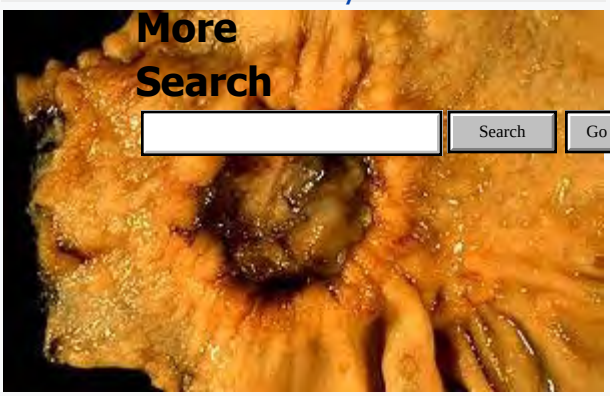
**Stomach cancer**, also known as **gastric cancer**, is cancer developing from the lining of the stomach.[1] Early symptoms may include heartburn, upper abdominal pain, nausea and loss of appetite. Later signs and symptoms may include weight loss, yellowing of the skin and whites of the eyes, vomiting, difficulty swallowing, and blood in the stool among others.[2] The cancer may spread from the stomach to other parts of the body, particularly the liver, lungs, bones, lining of the abdomen and lymph nodes.[3]

The most common cause is infection by the bacterium *Helicobacter pylori*, which accounts for more than 60% of cases.[4][5][6] Certain types of *H. pylori* have greater risks than others. Other common causes include eating pickled vegetables and smoking. About 10% of cases run in families and between 1% and 3% of cases are due to genetic syndromes inherited from a person's parents such as hereditary diffuse gastric cancer. Most cases of stomach cancers are gastric carcinomas. This type can be divided into a number of subtypes. Lymphomas and mesenchymal tumors may also develop in the stomach. Most of the time, stomach cancer develops in stages over years.[5] Diagnosis is usually by biopsy done during endoscopy. This is followed by medical imaging to determine if the disease has spread to other parts of the body.[2] Japan and South Korea, two countries that have high rates of the disease, screen for stomach cancer.[5]

A Mediterranean diet lowers the risk of cancer as does the stopping of smoking. There is tentative evidence that treating *H. pylori* decreases the future risk.[5][7] If cancer is treated early, many cases can be cured.[5] Treatments may include some combination of surgery, chemotherapy, radiation therapy, and targeted therapy.[2] If treated late, palliative care may be advised.[5] Outcomes are often poor with a less than 10% 5-year survival rate globally. This is largely because most people with the condition present with advanced disease.[8] In the United States 5-year survival is 28% while in South Korea it is over 65% partly due to screening efforts.[5]

Globally stomach cancer is the fifth leading cause of cancer and the third leading cause of death from cancer making up 7% of cases and 9% of deaths.[10] In 2012 it occurred in 950,000 people and caused 723,000 deaths.[10] Before the 1930s in much of the world, including most Western developed countries, it was the most common cause of death from cancer.[11][12][13] Rates of death have been decreasing in many areas of the world since then.[5] This is believed to be due to the eating of less salted and pickled foods as [14]

**Stomach cancer**



A stomach ulcer that was diagnosed as cancer on biopsy and surgically removed.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Oncology |
| **ICD-10** | C16 |
| **ICD-9-CM** | 151 |
| **OMIM** | 137215 |
| **DiseasesDB** | 12445 |
| **MedlinePlus** | 000223 |
| **eMedicine** | med/845 |
| **MeSH** | D013274 |
| **GeneReviews** | Hereditary Diffuse Gastric Cancer |

[edit on Wikidata]

a result of the development of refrigeration as a method of keeping food fresh. Stomach cancer occurs most commonly in East Asia and Eastern Europe. It occurs twice as often in males as in females.[5]

Contents





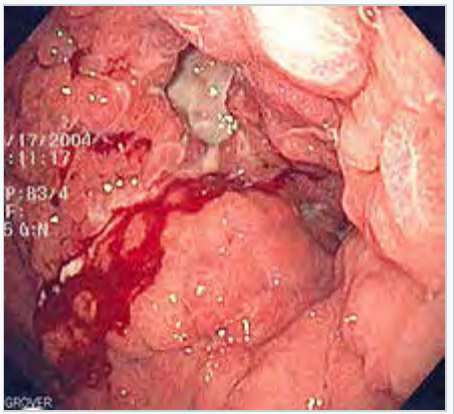
## Signs and symptoms [edit]

Stomach cancer is often either asymptomatic (producing no noticeable symptoms) or it may cause only nonspecific symptoms (symptoms that are not specific to stomach cancer and to other related or unrelated disorders) in its early stages. By the time symptoms occur, the cancer has often reached an advanced stage (see below) and may have metastasized (spread to other, perhaps distant, parts of the body), which is one of the main reasons for its relatively poor prognosis.[15] Stomach cancer can cause the following signs and symptoms:

Early cancers may be associated with indigestion or a burning sensation (heartburn). However, less than 1 in every 50 people referred for endoscopy due to indigestion has cancer.[16] Abdominal discomfort and loss of appetite, especially for meat, can occur.

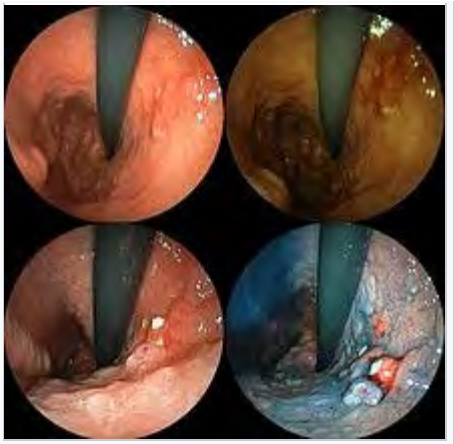
Gastric cancers that have enlarged and invaded normal tissue can cause weakness, fatigue, bloating of the stomach after meals, abdominal pain in the upper abdomen, nausea and occasional vomiting, diarrhea or constipation. Further enlargement may cause weight loss or bleeding with vomiting blood or having blood in the stool, the latter apparent as black discolouration (melena) and sometimes leading to anemia. Dysphagia suggests a tumour in the cardia or extension of the gastric tumour into the esophagus.

These can be symptoms of other problems such as a stomach virus, gastric ulcer, or tropical sprue.



Endoscopic image of linitis plastica, a type of stomach cancer where the entire stomach is invaded, leading to a leather bottle-like appearance with blood coming out of it.

## Causes [edit]



Endoscopic images of the stomach cancer in early stage. Its histology was poorly differentiated adenocarcinoma with signet ring cells. Left above: normal, right above: FICE, left low: acetate stained, right low: AIM stained

Gastric cancer occurs as a result of many factors.[17] It occurs twice as common in males as females. Estrogen may protect women against the development of this cancer form.[18][19]

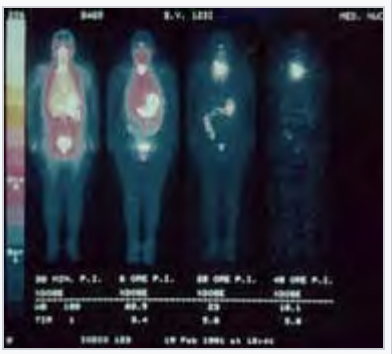
## Infections [edit]

*Helicobacter pylori* infection is an essential risk factor in 65–80% of gastric cancers, but only 2% of people with Helicobacter infections develop stomach cancer.[20][21] The mechanism by which *H. pylori* induces stomach cancer potentially involves chronic inflammation, or the action of *H. pylori* virulence factors such as CagA.[22] It was estimated that Epstein–Barr virus is responsible for 84,000 cases per year.[23] Other factors associated with increased risk are AIDS.[21]

## Smoking [edit]

Smoking increases the risk of developing gastric cancer significantly, from 40% increased risk for current smokers to 82% increase for heavy smokers. Gastric cancers due to smoking mostly occur in the upper part of the stomach near the esophagus.[24][25][26] Some studies show increased risk with alcohol consumption as well.[21][27]

## Diet [edit]



Sequence of 123-iodine human scintiscans after an intravenous injection: (from left) after 30 minutes, 20 hours and 48 hours. A high and rapid concentration of radio-iodine is evident in gastric mucosa of the stomach, in salivary glands, oral mucosa and in the periencephalic and cerebrospinal fluid (left). In the thyroid gland, I- concentration is more

Dietary factors are not proven causes,[29] but some foods including smoked foods,[30] salt and salt-rich foods, red meat, processed meat, pickled vegetables,[21] and bracken[31] are associated with a higher risk of stomach cancer. Nitrates and nitrites in cured meats can be converted by certain bacteria, including *H. pylori*, into compounds that have been found to cause stomach cancer in animals.

Fresh fruit and vegetable intake, citrus fruit intake, and antioxidant intake are associated with a lower risk of stomach cancer.[21][24] A Mediterranean diet is associated with lower rates of stomach cancer,[32] as is regular aspirin use.[21]

Obesity is a physical risk factor that has been found to increase the risk of gastric adenocarcinoma by contributing to the development of gastroesophageal reflux disease (GERD).[33] The exact mechanism by which obesity causes GERD is not completely known. Studies hypothesize that increased dietary fat leading to increased pressure on the stomach and the lower esophageal sphincter, due to excess adipose tissue, could play a role, yet no statistically significant data has been collected.[34] However, the risk of gastric cardia adenocarcinoma, with GERD present, has been found to increase more than 2 times for an obese person.[33] There is a correlation between iodine deficiency and gastric cancer.[35][36][37]

## Genetics [edit]

About 10% of cases run in families and between 1% and 3% of cases are

due to genetic syndromes inherited from a person's parents such as hereditary diffuse gastric cancer.[5]

A genetic risk factor for gastric cancer is a genetic defect of the CDH1 gene known as hereditary diffuse gastric cancer (HDGC). The CDH1 gene, which codes for E-cadherin, lies on the 16th chromosome.[38] When the gene experiences a particular mutation, gastric cancer develops through a mechanism that is not fully understood.[38] This mutation is considered autosomal dominant meaning that half of a carrier's children will likely experience the same mutation.[38] Diagnosis of hereditary diffuse gastric cancer usually takes place when at least two cases involving a family member, such as a parent or grandparent, are diagnosed, with at least one diagnosed before the age of 50.[38] The diagnosis can also be made if there are at least three cases in the family, in which case age is not considered.[38]

progressive, also in the reservoir (from 1% after 30 minutes to 5.8 % after 48 hours, of the total injected dose).[28]

The International Cancer Genome Consortium is leading efforts to identify genomic changes involved in stomach cancer.[39][40] A very small percentage of diffuse-type gastric cancers (see Histopathology below) arise from an inherited abnormal *CDH1* gene. Genetic testing and treatment options are available for families at risk.[41]

### Other [edit]

Other risks include diabetes,[42] pernicious anemia,[27] chronic atrophic gastritis,[43] Menetrier's disease (hyperplastic, hypersecretory gastropathy),[44] and intestinal metaplasia.[45]

## Diagnosis [edit]

To find the cause of symptoms, the doctor asks about the patient's medical history, does a physical exam, and may order laboratory studies. The patient may also have one or all of the following exams:

- Gastroscopic exam is the diagnostic method of choice. This involves insertion of a fibre optic camera into the stomach to visualise it.[27]
- Upper GI series (may be called barium roentgenogram).
- Computed tomography or CT scanning of the abdomen may reveal gastric cancer. It is more useful to determine invasion into adjacent tissues or the presence of spread to local lymph nodes. Wall thickening of more than 1 cm that is focal, eccentric and enhancing favours malignancy.[46]

In 2013, Chinese and Israeli scientists reported a successful pilot study of a breathalyzer-style breath test intended to diagnose stomach cancer by analyzing exhaled chemicals without the need for an intrusive endoscopy.[47] A larger-scale clinical trial of this technology was completed in 2014.[48]

Abnormal tissue seen in a gastroscope examination will be biopsied by the surgeon or gastroenterologist. This tissue is then sent to a pathologist for histological examination under a microscope to check for the presence of cancerous cells. A biopsy, with subsequent histological analysis, is the only sure way to confirm the presence of cancer cells.[27]

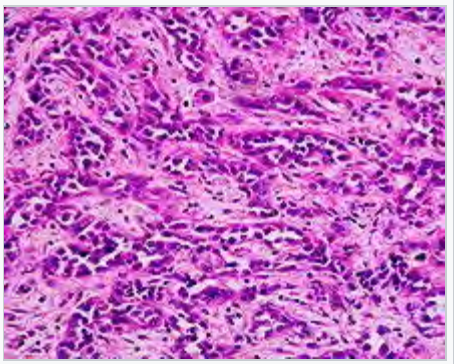
Various gastroscopic modalities have been developed to increase yield of detected mucosa with a dye that accentuates the cell structure and can identify areas of dysplasia. *Endocytoscopy* involves ultra-high magnification to visualise cellular structure to better determine areas of dysplasia. Other gastroscopic modalities such as optical coherence tomography are being tested investigationally for similar applications.[49]

A number of cutaneous conditions are associated with gastric cancer. A condition of darkened hyperplasia of the skin, frequently of the axilla and groin, known as acanthosis nigricans, is associated with intra-abdominal cancers such as gastric cancer. Other cutaneous manifestations of gastric cancer include *tripe palms* (a similar darkening hyperplasia of the skin of the palms) and the Leser-Trelat sign, which is the rapid development of skin lesions known as seborrheic keratoses.[50]

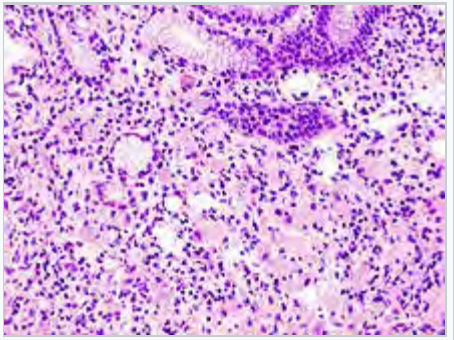
Various blood tests may be done including a complete blood count (CBC) to check for anaemia, and a fecal occult blood test to check for blood in the stool.

## Histopathology [edit]

- *Gastric adenocarcinoma* is a malignant epithelial tumour, originating from glandular epithelium of the gastric mucosa. Stomach cancers are overwhelmingly adenocarcinomas (90%).[51] Histologically, there are two major types of gastric adenocarcinoma (Lauren classification): intestinal type or diffuse type. Adenocarcinomas tend to aggressively invade the gastric wall, infiltrating the muscularis mucosae, the submucosa and thence the muscularis propria. Intestinal type adenocarcinoma tumour cells describe irregular tubular structures, harbouring pluristratification, multiple lumens, reduced stroma ("back to back" aspect). Often, it associates intestinal metaplasia in neighbouring mucosa. Depending on glandular architecture, cellular pleomorphism and mucosecretion, adenocarcinoma may present 3 degrees of differentiation: well, moderate and poorly differentiated. Diffuse type adenocarcinoma (mucinous, colloid, linitis plastica, leather-bottle stomach) tumour cells are discohesive and secrete mucus, which is delivered in the interstitium, producing large pools of mucus/colloid (optically "empty" spaces). It is poorly differentiated. If the mucus remains inside the tumour cell, it pushes the nucleus to the periphery: "*signet-ring cell*".
- Around 5% of gastric malignancies are lymphomas (MALTomas, or MALT lymphoma).[52]
- Carcinoid and stromal tumors may occur.



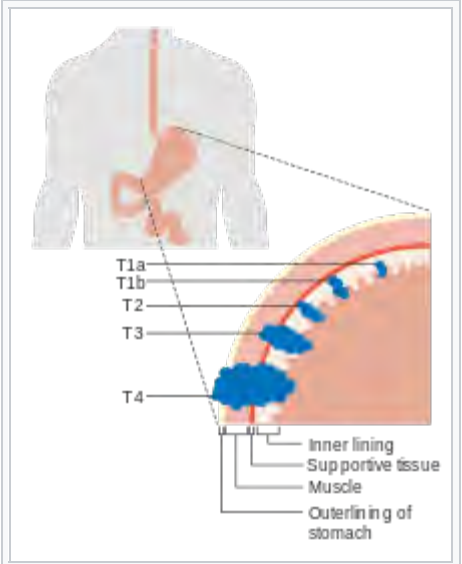
Poor to moderately differentiated adenocarcinoma of the stomach. H&E stain.



Gastric signet ring cell carcinoma. H&E stain.

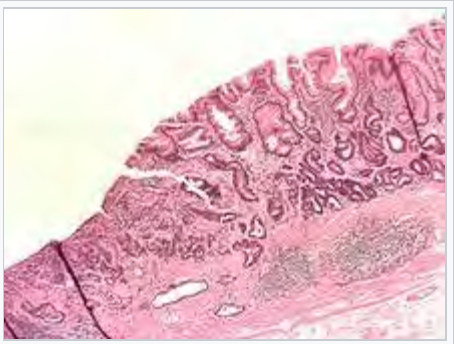
## Staging [edit]

If cancer cells are found in the tissue sample, the next step is to stage, or find out the extent of the disease. Various tests determine whether the cancer has spread and, if so, what parts of the body are affected. Because stomach cancer can spread to the liver, the pancreas, and other organs near the stomach as well as to the lungs, the doctor may order a CT scan, a PET scan,[53] an endoscopic ultrasound exam, or other tests to check these areas. Blood tests for tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) may be ordered, as their levels correlate to extent of metastasis, especially to the liver, and the cure rate.




T stages of stomach cancer

Staging may not be complete until after surgery. The surgeon removes nearby lymph nodes and possibly samples of tissue from other areas in the abdomen for examination by a pathologist.



Adenocarcinoma of the stomach and intestinal metaplasia. H&E stain.

The clinical stages of stomach cancer are:[54][55]

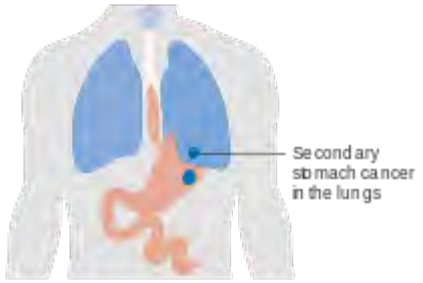
- **Stage 0.** Limited to the inner lining of the stomach. Treatable by endoscopic mucosal resection when found very early (in routine screenings); otherwise by gastrectomy and lymphadenectomy without need for chemotherapy or

radiation.

- **Stage I.** Penetration to the second or third layers of the stomach **(Stage 1A)** or to the second layer and nearby lymph nodes **(Stage 1B)**. Stage 1A is treated by surgery, including removal of the omentum. Stage 1B may be treated with chemotherapy (5-fluorouracil) and radiation therapy.
- **Stage II.** Penetration to the second layer and more distant lymph nodes, or the third layer and only nearby lymph nodes, or all four layers but not the lymph nodes. Treated as for Stage I, sometimes with additional neoadjuvant chemotherapy.
- **Stage III.** Penetration to the third layer and more distant lymph nodes, or penetration to the fourth layer and either nearby tissues or nearby or more distant lymph nodes. Treated as for Stage II; a cure is still possible in some cases.
- **Stage IV.** Cancer has spread to nearby tissues and more distant lymph nodes, or has metastasized to other organs. A cure is very rarely possible at this stage. Some other techniques to prolong life or improve symptoms are used, including laser treatment, surgery, and/or stents to keep the digestive tract open, and chemotherapy by drugs such as 5-fluorouracil, cisplatin, epirubicin, etoposide, docetaxel, oxaliplatin, capecitabine or irinotecan.

The TNM staging system is also used.[56]

In a study of open-access endoscopy in Scotland, patients were diagnosed 7% in Stage I 17% in Stage II, and 28% in Stage III.[57] A Minnesota population was diagnosed 10% in Stage I, 13% in Stage II, and 18% in Stage III.[58] However, in a high-risk population in the Valdivia Province of southern Chile, only 5% of patients were diagnosed in the first two stages and 10% in stage III.[59]




Stomach cancer metastasized to the lungs

## Prevention [edit]

Getting rid of *H. pylori* in those who are infected decreases the risk of stomach cancer, at least in those who are Asian.[60] A 2014 meta-analysis of observational studies found that a diet high in fruits, mushrooms, garlic, soybeans, and green onions was associated with a lower risk of stomach cancer in the Korean population.[61] Low doses of vitamins, especially from a healthy diet, decrease the risk of stomach cancer.[62] A previous review of antioxidant supplementation did not find supporting evidence and possibly worse outcomes.[63][64]

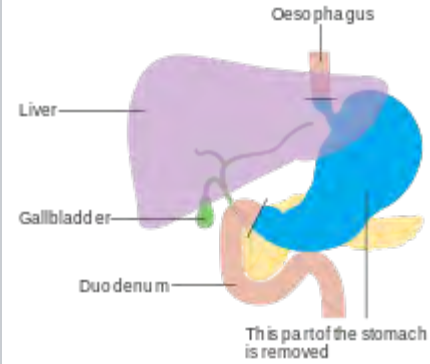
## Management [edit]

Cancer of the stomach is difficult to cure unless it is found at an early stage (before it has begun to spread). Unfortunately, because early stomach cancer causes few symptoms, the disease is usually advanced when the diagnosis is made.[65]

Treatment for stomach cancer may include surgery,[66] chemotherapy, and/or radiation therapy.[67] New treatment approaches such as biological therapy and improved ways of using current methods are being studied in clinical trials.[68]

### Surgery [edit]

Surgery remains the only curative therapy for stomach cancer.[8] Of the different surgical techniques, endoscopic mucosal resection (EMR) is a treatment for early gastric cancer (tumor only involves the mucosa) that was pioneered in Japan and is available in the United States at some centers.[8] In this procedure, the tumor, together with the inner lining of stomach (mucosa), is removed from the wall of the stomach using an electrical wire loop through the endoscope. The advantage is that it is a much smaller operation than removing the stomach.[8] Endoscopic



Anatomy before Roux-en-y surgery to resect stomach cancer.

submucosal dissection (ESD) is a similar technique pioneered in Japan, used to resect a large area of mucosa in one piece.[8] If the pathologic examination of the resected specimen shows incomplete resection or deep invasion by tumor, the patient would need a formal stomach resection.[8] A 2016 Cochrane review found low quality evidence of no difference in short-term mortality between laparoscopic and open gastrectomy (removal of stomach), and that benefits or harms of laparoscopic gastrectomy cannot be ruled out.[69]

Those with metastatic disease at the time of presentation may receive palliative surgery and while it remains controversial, due to the possibility of complications from the surgery itself and the fact that it may delay chemotherapy the data so far is mostly positive, with improved survival rates being seen in those treated with this approach.[8][70]

### Chemotherapy [edit]

The use of chemotherapy to treat stomach cancer has no firmly established standard of care. Unfortunately, stomach cancer has not been particularly sensitive to these drugs, and chemotherapy, if used, has usually served to palliatively reduce the size of the tumor, relieve symptoms of the disease and increase survival time. Some drugs used in stomach cancer treatment have included: 5-FU (fluorouracil) or its analog capecitabine, BCNU (carmustine), methyl-CCNU (semustine) and doxorubicin (Adriamycin), as well as mitomycin C, and more recently cisplatin and taxotere, often using drugs in various combinations. The relative benefits of these different drugs, alone and in combination, are unclear.[71] Clinical researchers have explored the benefits of giving chemotherapy before surgery to shrink the tumor, or as adjuvant therapy after surgery to destroy remaining cancer cells.[8]

### Targeted therapy [edit]

Recently, treatment with human epidermal growth factor receptor 2 (*HER2*) inhibitor, trastuzumab, has been demonstrated to increase overall survival in inoperable locally advanced or metastatic gastric carcinoma over-expressing the HER2/neu gene.[8] In particular, *HER2* is overexpressed in 13-22% of patients with gastric cancer.[68][72] Of note, *HER2* overexpression in gastric neoplasia is heterogeneous and comprises a minority of tumor cells (less than 10% of gastric cancers overexpress *HER2* in more than 5% of tumor cells). Hence, this heterogeneous expression should be taken into account for *HER2* testing, particularly in small samples such as biopsies, requiring the evaluation of more than one bioptic sample.[72]

### Radiation [edit]

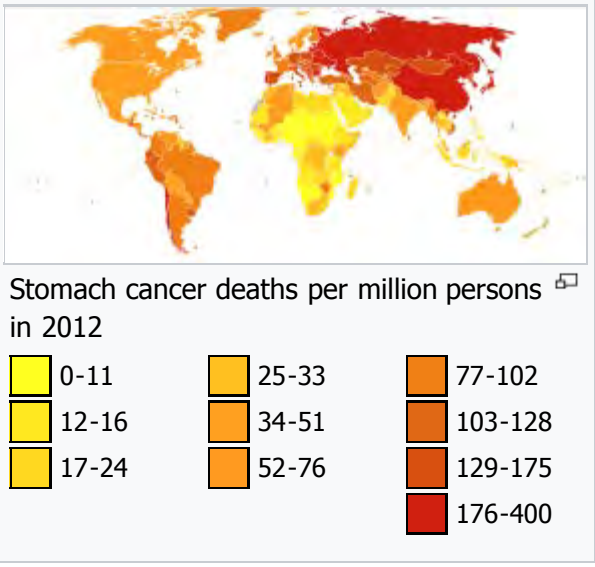
Radiation therapy (also called radiotherapy) may be used to treat stomach cancer, often as an adjuvant to chemotherapy and/or surgery.[8]

## Prognosis [edit]

The prognosis of stomach cancer is generally poor, due to the fact the tumour has often metastasised by the time of discovery and the fact that most people with the condition are elderly (median age is between 70 and 75 years) at presentation.[73] The five-year survival rate for stomach cancer is reported to be less than 10 percent.[8]

## Epidemiology [edit]

Worldwide, stomach cancer is the fifth most common cancer with 952,000 cases diagnosed in 2012.[10] It is more common in men and in developing countries.[74][75] In 2012, it represented 8.5% of cancer cases in men, making it the fourth most common cancer in men.[76] In 2012 number of deaths were 700,000 having decreased slightly from 774,000 in 1990 making it the third leading cause of cancer death after lung cancer and liver cancer.[77][78]




Less than 5% of stomach cancers occur in people under 40 years of age with 81.1% of that 5% in the age-group of 30 to 39 and 18.9% in the age-group of 20 to 29.[79]

In 2014, stomach cancer accounted for 0.61% of deaths (13,303 cases) in the United States.[80] In China, stomach cancer accounted for 3.56% of all deaths (324,439 cases).[81] The highest rate of stomach cancer was in Mongolia, at 28 cases per 100,000 people.[82]

In the United Kingdom, stomach cancer is the fifteenth most common cancer (around 7,100 people were diagnosed with stomach cancer in 2011), and it is the tenth most common cause of cancer death (around 4,800 people died in 2012).[83]

Incidence and mortality rates of gastric cancer vary greatly in Africa. The GLOBOCAN system is currently the most widely used method to compare these rates between countries, but African incidence and mortality rates are seen to differ among countries possibly due to the lack of universal access to a registry system for all countries.[84] Variation as drastic as estimated rates from 0.3/100000 in Botswana to 20.3/100000 in Mali have been observed.[84] In Uganda, the incidence of gastric cancer has increased from the 1960s measurement of 0.8/100000 to 5.6/100000.[84] Gastric cancer, though present, is relatively low when compared to countries with high incidence like Japan or China. One suspected cause of the variation within Africa and between other countries is due to different strains of the Helicobacter pylori bacteria. The trend commonly seen is that H. pylori infection increases the risk for gastric cancer, however this is not the case in Africa giving this phenomenon the name the "African enigma."[85] Although this bacteria is found in Africa, evidence has supported that different strains with mutations in the bacterial genotype may contribute to the difference in cancer development between African countries and others outside of the continent.[85] However, increasing access to health care and treatment measures have been commonly associated with the rising incidence, particularly in Uganda.[84]

## Other animals [edit]

The stomach is a muscular organ of the gastrointestinal tract that holds food and begins the digestive process by secreting gastric juice. The most common cancers of the stomach are adenocarcinomas but other histological types have been reported. Signs vary but may include vomiting (especially if blood is present), weight loss, anemia, and lack of appetite. Bowel movements may be dark and tarry in nature. In order to determine whether cancer is present in the stomach, special X-rays and/or abdominal ultrasound may be performed. Gastroscopy, a test using an instrument called endoscope to examine the stomach, is a useful diagnostic tool that can also take samples of the suspected mass for histopathological analysis to confirm or rule out cancer. The most definitive method of cancer diagnosis is through open surgical biopsy.[86] Most stomach tumors are malignant with evidence of spread to lymph nodes or liver, making treatment difficult. Except for lymphoma, surgery is the most frequent treatment option for stomach cancers but it is associated with significant risks.

# References [edit]


1. ^ "Stomach (Gastric) Cancer". *NCI*. Retrieved 1 July 2014.
2. ^ a b c "Gastric Cancer Treatment (PDQ®)". *NCI*. 2014-04-17. Retrieved 1 July 2014.
3. ^ Ruddon, Raymond W. (2007). *Cancer biology* (4th ed.). Oxford: Oxford University Press. p. 223. ISBN 9780195175431.
4. ^ Sim, edited by Fiona; McKee, Martin (2011). *Issues in public health* (2nd ed.). Maidenhead: Open University Press. p. 74. ISBN 9780335244225.
5. ^ a b c d e f g h i j *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 5.4. ISBN 9283204298.
6. ^ Chang, A. H.; Parsonnet, J. (2010). "Role of Bacteria in Oncogenesis". *Clinical Microbiology Reviews*. **23** (4): 837–857. doi:10.1128/CMR.00012-10. ISSN 0893-8512. PMC 2952975. PMID 20930075.
7. ^ "Stomach (Gastric) Cancer Prevention (PDQ®)". *NCI*. 2014-02-27. Retrieved 1 July 2014.
8. ^ a b c d e f g h i j k Orditura, M; Galizia, G; Sforza, V; Gambardella, V; Fabozzi, A; Laterza, MM; Andreozzi, F; Ventriglia, J; Savastano, B; Mabilia, A; Lieto, E; Ciardiello, F; De Vita, F (February 2014). "Treatment of gastric cancer." (PDF). *World Journal of Gastroenterology*. **20** (7): 1635–49. doi:10.3748/wjg.v20.i7.1635. PMC 3930964. PMID 24587643.
9. ^ "SEER Stat Fact Sheets: Stomach Cancer". *NCI*. Retrieved 18 June 2014.
10. ^ a b c "Chapter 1.1". *World Cancer Report 2014*. World Health Organization. 2014. ISBN 9283204298.
11. ^ Hochhauser, Jeffrey Tobias, Daniel (2010). *Cancer and its management* (6th ed.). Chichester, West Sussex, UK: Wiley-Blackwell. p. 259. ISBN 9781444306378.
12. ^ Khleif, Edited by Roland T. Skeel, Samir N. (2011). *Handbook of cancer chemotherapy* (8th ed.). Philadelphia: Wolter Kluwer. p. 127. ISBN 9781608317820.
13. ^ Joseph A Knight (2010). *Human Longevity: The Major Determining Factors*. Author House. p. 339. ISBN 9781452067223.
14. ^ Moore, edited by Rhonda J.; Spiegel, David (2004). *Cancer, culture, and communication*. New York: Kluwer Academic. p. 139. ISBN 9780306478857.
15. ^ "Statistics and outlook for stomach cancer". Cancer Research UK. Retrieved 19 February 2014.
16. ^ "Guidance on Commissioning Cancer Services Improving Outcomes in Upper Gastro-intestinal Cancers" (PDF). NHS. Jan 2001.
17. ^ Lee YY, Derakhshan MH (Jun 2013). "Environmental and lifestyle risk factors of gastric cancer". *Arch. Iran. Med.* **16** (6): 358–65. PMID 23725070.
18. ^ Chandanos E, Lagergren J. Oestrogen and the enigmatic male predominance of gastric cancer. Eur J Cancer. 2008 Nov;44(16):2397-403.
19. ^ Qin J, Liu M, Ding Q, Ji X, Hao Y, Wu X, Xiong J. The direct effect of estrogen on cell viability and apoptosis in human gastric cancer cells. Mol Cell Biochem. 2014 Oct;395(1-2):99-107.
20. ^ "Proceedings of the fourth Global Vaccine Research Forum" (PDF). *Initiative for Vaccine Research team of the Department of Immunization, Vaccines and Biologicals*. WHO. April 2004. Retrieved 2009-05-11. "Epidemiology of *Helicobacter pylori* and gastric cancer..."
21. ^ a b c d e f González CA, Sala N, Rokkas T; Sala; Rokkas (2013). "Gastric cancer: epidemiologic aspects". *Helicobacter*. **18** (Supplement 1): 34–38. doi:10.1111/hel.12082. PMID 24011243.
22. ^ Hatakeyama, M. & Higashi, H; Higashi (2005). "Helicobacter pylori CagA: a new paradigm for bacterial carcinogenesis". *Cancer Science*. **96** (12): 835–843. doi:10.1111/j.1349-7006.2005.00130.x. PMID 16367902.
23. ^ http://www.cancerresearchuk.org/about-us/cancer-news/press-release/2014-03-24-developing-a-vaccine-for-the-epstein-barr-virus-could-prevent-up-to-200000-cancers-globally-say
24. ^ a b "What Are The Risk Factors For Stomach Cancer(Website)". American Cancer Society. Retrieved 2010-03-31.
25. ^ Nomura A, Grove JS, Stemmermann GN, Severson RK; Grove; Stemmermann; Severson (1990). "Cigarette smoking and stomach cancer". *Cancer Research*. **50** (21): 7084. PMID 2208177.
26. ^ Trédaniel J, Boffetta P, Buiatti E, Saracci R, Hirsch A; Boffetta; Buiatti; Saracci; Hirsch (August 1997). "Tobacco smoking and gastric cancer: Review and meta-analysis". *International Journal of Cancer*. **72** (4): 565–73. doi:10.1002/(SICI)1097-0215(19970807)72:4<565::AID-IJC3>3.0.CO;2-O. PMID 9259392.
27. ^ a b c d Thrumurthy SG, Chaudry MA, Hochhauser D, Ferrier K, Mughal M; Chaudry; Hochhauser; Mughal (2013). "The diagnosis and management of gastric cancer". *British Medical Journal*. **347** (16): 1695–6. doi:10.1136/bmj.f6367. PMID 24191271.
28. ^ Venturi, S.; Donati, F.M.; Venturi, A.; Venturi, M. (2000). "Environmental Iodine Deficiency: A Challenge to the Evolution of Terrestrial Life?". *Thyroid*. **10** (8): 727–9. doi:10.1089/10507250050137851. PMID 11014322.

29. ^ *Tumors of the GI Tract* at Merck Manual of Diagnosis and Therapy Professional Edition
30. ^ Jakszyn P, González CA; Gonzalez (2006). "Nitrosamine and related food intake and gastric and oesophageal cancer risk: A systematic review of the epidemiological evidence" (PDF). *World J Gastroenterol*. **12** (27): 4296–4303. PMC 4087738. PMID 16865769.
31. ^ Alonso-Amelot ME, Avendaño M; Avendaño (March 2002). "Human carcinogenesis and bracken fern: a review of the evidence". *Current Medicinal Chemistry*. **9** (6): 675–86. doi:10.2174/0929867023370743. PMID 11945131.
32. ^ Buckland G, Agudo A, Lujan L, Jakszyn P, Bueno-De-Mesquita HB, Palli D, Boeing H, Carneiro F, Krogh V; Agudo; Luján; Jakszyn; Bueno-De-Mesquita; Palli; Boeing; Carneiro; Krogh; Sacerdote; Tumino; Panico; Nesi; Manjer; Regnér; Johansson; Stenling; Sanchez; Dorronsoro; Barricarte; Navarro; Quirós; Allen; Key; Bingham; Kaaks; Overvad; Jensen; Olsen; et al. (2009). "Adherence to a Mediterranean diet and risk of gastric adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study". *American Journal of Clinical Nutrition*. **91** (2): 381–90. doi:10.3945/ajcn.2009.28209. PMID 20007304.
33. ^ *a b* Crew K, Neugut A (January 2006). "Epidemiology of gastric cancer". *World Journal of Gastroenterology*. **12** (3): 354–62. doi:10.3748/wjg.v12.i3.354. PMC 4066052. PMID 16489633.
34. ^ Hampel Howard; Abraham Neena S.; El-Serag Hashem B. (August 2005). "Meta-Analysis: obesity and the risk for gastroesophageal reflux disease and its complications". *Annals of Internal Medicine*. **143** (3): 199–211. doi:10.7326/0003-4819-143-3-200508020-00006.
35. ^ Josefssson, M.; Ekblad, E. (2009). "22. Sodium Iodide Symporter (NIS) in Gastric Mucosa: Gastric Iodide Secretion". In Preedy, Victor R.; Burrow, Gerard N.; Watson, Ronald. *Comprehensive Handbook of Iodine: Nutritional, Biochemical, Pathological and Therapeutic Aspects*. Elsevier. pp. 215–220. ISBN 978-0-12-374135-6.
36. ^ Venturi, Sebastiano (2011). "Evolutionary Significance of Iodine". *Current Chemical Biology-*. **5** (3): 155–162. doi:10.2174/187231311796765012. ISSN 1872-3136.
37. ^ Venturi II, S.; Donati, F.M.; Venturi, A.; Venturi, M.;; Venturi, A; Venturi, M; Grossi, L; Guidi, A (2000). "Role of iodine in evolution and carcinogenesis of thyroid, breast and stomach.". *Adv Clin Path*. **4** (1): 11–17. PMID 10936894.
38. ^ *a b c d e* "Hereditary Diffuse Cancer". *No Stomach for Cancer*. Retrieved 21 Oct 2014.
39. ^ "Gastric Cancer — Adenocarcinoma". International Cancer Genome Consortium. Retrieved 24 February 2014.
40. ^ "Gastric Cancer — Intestinal- and diffuse-type". International Cancer Genome Consortium. Retrieved 24 February 2014.
41. ^ Brooks-Wilson AR, Kaurah P, Suriano G, Leach S, Senz J, Grehan N, Butterfield YS, Jeyes J, Schinas J; Kaurah; Suriano; Leach; Senz; Grehan; Butterfield; Jeyes; Schinas; Bacani; Kelsey; Ferreira; MacGillivray; MacLeod; Micek; Ford; Foulkes; Australie; Greenberg; Lapointe; Gilpin; Nikkel; Gilchrist; Hughes; Jackson; Monaghan; Oliveira; Seruca; Gallinger; et al. (2004). "Germline E-cadherin mutations in hereditary diffuse gastric cancer: assessment of 42 new families and review of genetic screening criteria". *Journal of Medical Genetics*. **41** (7): 508–17. doi:10.1136/jmg.2004.018275. PMC 1735838. PMID 15235021.
42. ^ Tseng C-H, Tseng F-H; Tseng (2014). "Diabetes and gastric cancer: The potential links". *World J Gastroenterol*. **20** (7): 1701–11. doi:10.3748/wjg.v20.i7.1701. PMC 3930970. PMID 24587649.
43. ^ Crosby DA, Donohoe CL, Fitzgerald L, Muldoon C, Hayes B, O'Toole D, Reynolds JV; Donohoe; Fitzgerald; Muldoon; Hayes; O'Toole; Reynolds (2004). "Gastric Neuroendocrine Tumours". *Digestive Surgery*. **29** (4): 331–348. doi:10.1159/000342988. PMID 23075625.
44. ^ Kim J, Cheong JH, Chen J, Hyung WJ, Choi SH, Noh SH; Cheong; Chen; Hyung; Choi; Noh (2004). "Menetrier's Disease in Korea: Report of Two Cases and Review of Cases in a Gastric Cancer Prevalent Region" (PDF). *Yonsei Medical Journal*. **45** (3): 555–560. doi:10.3349/ymj.2004.45.3.555. PMID 15227748.
45. ^ Tsukamoto T, Mizoshita T, Tatematsu M; Mizoshita; Tatematsu (2006). "Gastric-and-intestinal mixed-type intestinal metaplasia: aberrant expression of transcription factors and stem cell intestinalization". *Gastric Cancer*. **9** (3): 156–166. doi:10.1007/s10120-006-0375-6. PMID 16952033.
46. ^ Virmani, V; Khandelwal, A; Sethi, V; Fraser-Hill, M; Fasih, N; Kielar, A (2012). "Neoplastic stomach lesions and their mimickers: Spectrum of imaging manifestations". *Cancer Imaging*. **12**: 269–78. doi:10.1102/1470-7330.2012.0031. PMC 3458788. PMID 22935192.
47. ^ Xu ZQ, Broza YY, Ionsecu R, et al. (March 2013). "A nanomaterial-based breath test for distinguishing gastric cancer from benign gastric conditions". *Br. J. Cancer*. **108** (4): 941–50. doi:10.1038/bjc.2013.44. PMC 3590679. PMID 23462808. Lay summary – *Medical News Today* ("Breath Test Could Detect and Diagnose Stomach Cancer") (6 March 2013).
48. ^ "Detection of precancerous gastric lesions and gastric cancer through exhaled breath". *Gut*. 13 April 2015. doi:10.1136/gutjnl-2014-308536.
49. ^ Inoue H, Kudo S-, Shiokawa A; Kudo; Shiokawa (2005). "Technology Insight: laser-scanning confocal microscopy and endocytoscopy for cellular observation of the gastrointestinal tract". *Nature Clinical Practice Gastroenterology &*

*Hepatology*. **2** (1): 31–7. doi:10.1038/ncpgasthep0072. PMID 16265098.
50. ^ Pentenero M, Carrozzo M, Pagano M, Gandolfo S; Carrozzo; Pagano; Gandolfo (2004). "Oral acanthosis nigricans, tripe palms and sign of leser-trelat in a patient with gastric adenocarcinoma". *International Journal of Dermatology*. **43** (7): 530–2. doi:10.1111/j.1365-4632.2004.02159.x. PMID 15230897.
51. ^ Kumar; et al. (2010). *Pathologic Basis of Disease* (8th ed.). Saunders Elsevier. p. 784. ISBN 978-1-4160-3121-5.
52. ^ Kumar 2010, p. 786
53. ^ Lim JS, Yun MJ, Kim MJ, Hyung WJ, Park MS, Choi JY, Kim TS, Lee JD, Noh SH, Kim KW; Yun; Kim; Hyung; Park; Choi; Kim; Lee; Noh; Kim (2006). "CT and PET in stomach cancer: preoperative staging and monitoring of response to therapy". *Radiographics*. **26** (1): 143–156. doi:10.1148/rg.261055078. PMID 16418249.
54. ^ "Detailed Guide: Stomach Cancer Treatment Choices by Type and Stage of Stomach Cancer". American Cancer Society. 2009-11-03.
55. ^ Guy Slowik (October 2009). "What Are The Stages Of Stomach Cancer?". ehealthmd.com.
56. ^ "Detailed Guide: Stomach Cancer: How Is Stomach Cancer Staged?". American Cancer Society.
57. ^ Paterson HM, McCole D, Auld CD; McCole; Auld (2006). "Impact of open-access endoscopy on detection of early oesophageal and gastric cancer 1994–2003: population-based study". *Endoscopy*. **38** (5): 503–7. doi:10.1055/s-2006-925124. PMID 16767587.
58. ^ Crane SJ, Locke GR, Harmsen WS, Zinsmeister AR, Romero Y, Talley NJ; Locke Gr; Harmsen; Zinsmeister; Romero; Talley (2008). "Survival Trends in Patients With Gastric and Esophageal Adenocarcinomas: A Population-Based Study". *Mayo Clinic Proceedings*. **83** (10): 1087–94. doi:10.4065/83.10.1087. PMC 2597541. PMID 18828967.
59. ^ Heise K, Bertran E, Andia ME, Ferreccio C; Bertran; Andia; Ferreccio (2009). "Incidence and survival of stomach cancer in a high-risk population of Chile". *World Journal of Gastroenterology*. **15** (15): 1854–62. doi:10.3748/wjg.15.1854. PMC 2670413. PMID 19370783.
60. ^ Ford, AC; Forman, D; Hunt, RH; Yuan, Y; Moayyedi, P (20 May 2014). "Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials.". *BMJ*. **348**: g3174. doi:10.1136/bmj.g3174. PMC 4027797. PMID 24846275.
61. ^ Woo HD, Park S, Oh K, Kim HJ, Shin HR, Moon HK, Kim J (2014). "Diet and cancer risk in the Korean population: a meta- analysis" (PDF). *Asian Pacific Journal of Cancer Prevention*. **15** (19): 8509–19. doi:10.7314/apjcp.2014.15.19.8509. PMID 25339056.
62. ^ Kong, P; Cai, Q; Geng, Q; Wang, J; Lan, Y; Zhan, Y; Xu, D (2014). "Vitamin intake reduce the risk of gastric cancer: meta-analysis and systematic review of randomized and observational studies.". *PLOS ONE*. **9** (12): e116060. doi:10.1371/journal.pone.0116060. PMC 4280145. PMID 25549091.
63. ^ Bjelakovic, G; Nikolova, D; Simonetti, RG; Gluud, C (16 July 2008). "Antioxidant supplements for preventing gastrointestinal cancers.". *Cochrane Database of Systematic Reviews* (3): CD004183. doi:10.1002/14651858.CD004183.pub3. PMID 18677777.
64. ^ Bjelakovic, G; Nikolova, D; Gluud, LL; Simonetti, RG; Gluud, C (14 March 2012). "Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases.". *Cochrane Database of Systematic Reviews*. **3**: CD007176. doi:10.1002/14651858.CD007176.pub2. PMID 22419320.
65. ^ Roopma Wadhwa, Takashi Taketa, Kazuki Sudo, Mariela A. Blum, Jaffer A. Ajani; Taketa; Sudo; Blum; Ajani (2013). "Modern Oncological Approaches to Gastric Adenocarcinoma". *Gastroenterology Clinics of North America*. **42** (2): 359–369. doi:10.1016/j.gtc.2013.01.011. PMID 23639645.
66. ^ Ke Chen, Xiao-Wu Xu, Ren-Chao Zhang, Yu Pan, Di Wu, Yi-Ping Mou; Xu; Zhang; Pan; Wu; Mou (2013). "Systematic review and meta-analysis of laparoscopy-assisted and open total gastrectomy for gastric cancer". *World J Gastroenterol*. **19** (32): 5365–76. doi:10.3748/wjg.v19.i32.5365. PMC 3752573. PMID 23983442.
67. ^ Jennifer L. Pretz, Jennifer Y. Wo, Harvey J. Mamon, Lisa A. Kachnic, Theodore S. Hong; Wo; Mamon; Kachnic; Hong (2011). "Chemoradiation Therapy: Localized Esophageal, Gastric, and Pancreatic Cancer". *Surgical Oncology Clinics of North America*. **22** (3): 511–524. doi:10.1016/j.soc.2013.02.005. PMID 23622077.
68. ^ [a] [b] Judith Meza-Junco, Heather-Jane Au, Michael B Sawyer; Au; Sawyer (2011). "Critical appraisal of trastuzumab in treatment of advanced stomach cancer". *Cancer Management and Research*. **2011** (3): 57–64. doi:10.2147/CMAR.S12698. PMC 3085240. PMID 21556317.
69. ^ Best, LM; Mughal, M; Gurusamy, KS (31 March 2016). "Laparoscopic versus open gastrectomy for gastric cancer.". *The Cochrane database of systematic reviews*. **3**: CD011389. doi:10.1002/14651858.CD011389.pub2. PMID 27030300. Retrieved 5 April 2016.
70. ^ Sun, J; Song, Y; Wang, Z; Chen, X; Gao, P; Xu, Y; Zhou, B; Xu, H (December 2013). "Clinical significance of palliative gastrectomy on the survival of patients with incurable advanced gastric cancer: a systematic review and meta-analysis." (PDF). *BMC Cancer*. **13** (1): 577. doi:10.1186/1471-2407-13-577. PMID 24304886.
71. ^ Scartozzi M, Galizia E, Verdecchia L, Berardi R, Antognoli S, Chiorrini S, Cascinu S; Galizia; Verdecchia; Berardi; Antognoli; Chiorrini; Cascinu (2007). "Chemotherapy for advanced gastric cancer: across the years for a standard of

care". *Expert Opinion on Pharmacotherapy*. **8** (6): 797–808. doi:10.1517/14656566.8.6.797. PMID 17425475.
72. ^ [a] [b] Fusco N, Rocco EG, Del Conte C, Pellegrini C, Bulfamante G, Di Nuovo F, Romagnoli S, Bosari S (Jun 2013). "HER2 in gastric cancer: a digital image analysis in pre-neoplastic, primary and metastatic lesions". *Mod Pathol*. **26** (6): 816–24. doi:10.1038/modpathol.2012.228. PMID 23348899.
73. ^ Cabebe, EC; Mehta, VK; Fisher, G, Jr (21 January 2014). Talavera, F; Movsas, M; McKenna, R; Harris, JE, eds. "Gastric Cancer". *Medscape Reference*. WebMD. Retrieved 4 April 2014.
74. ^ Parkin DM, Bray F, Ferlay J, Pisani P; Bray; Ferlay; Pisani (2005). "Global Cancer Statistics, 2002". *CA: A Cancer Journal for Clinicians*. **55** (2): 74–108. doi:10.3322/canjclin.55.2.74. PMID 15761078.
75. ^ "Are the number of cancer cases increasing or decreasing in the world?". *WHO Online Q&A*. WHO. 1 April 2008. Retrieved 2009-05-11.
76. ^ *World Cancer Report 2014*. International Agency for Research on Cancer, World Health Organization. 2014. ISBN 978-92-832-0432-9.
77. ^ Lozano, R; Naghavi, M; Foreman, K; Lim, S; Shibuya, K; Aboyans, V; Abraham, J; Adair, T; Aggarwal, R; Ahn, SY; Alvarado, M; Anderson, HR; Anderson, LM; Andrews, KG; Atkinson, C; Baddour, LM; Barker-Collo, S; Bartels, DH; Bell, ML; Benjamin, EJ; Bennett, D; Bhalla, K; Bikbov, B; Bin Abdulhak, A; Birbeck, G; Blyth, F; Bolliger, I; Boufous, S; Bucello, C; et al. (15 December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
78. ^ "PRESS RELEASE N° 224 Global battle against cancer won't be won with treatment alone: Effective prevention measures urgently needed to prevent cancer crisis" (PDF). *World Health Organization*. 3 February 2014. Retrieved 14 March 2014.
79. ^ "Gastric Cancer in Young Adults". *Revista Brasileira de Cancerologia*. **46** (3). Jul 2000.
80. ^ "Health profile: United States". Le Duc Media. Retrieved 31 Jan 2016.
81. ^ "Health profile: China". Le Duc Media. Retrieved 31 Jan 2016.
82. ^ "Stomach Cancer: Death Rate Per 100,000". Le Duc Media. Retrieved 13 March 2014.
83. ^ "Stomach cancer statistics". *Cancer Research UK*. Retrieved 28 October 2014.
84. ^ [a] [b] [c] [d] Asombang Akwi W; Rahman Rubayat; Ibdah Jamal A (2014). "Gastric cancer in Africa: Current management and outcomes". *World Journal of Gastroenterology*. **20**: 3875–79. doi:10.3748/wjg.v20.i14.3875.
85. ^ [a] [b] Louw J. A.; Kidd M. S. G.; Kummer A. F.; Taylor K.; Kotze U.; Hanslo D. (November 2001). "The relationship between helicobacter pylori infection, the virulence genotypes of the infecting strain and gastric cancer in the African setting". *Helicobacter*. **6** (4): 268–73. doi:10.1046/j.1523-5378.2001.00044.x.
86. ^ Withrow SJ, MacEwen EG, eds. (2001). *Small Animal Clinical Oncology* (3rd ed.). W.B. Saunders.

## External links [edit]

- National Cancer Institute Gastric cancer treatment guidelines

Wikimedia Commons has media related to *Stomach cancer*.

| v · t · e | **Digestive system neoplasia (C15–C26/D12–D13, 150–159/211)** | | |
|---|---|---|---|
| **GI tract** | **Upper** | **Esophagus** | Squamous cell carcinoma · Adenocarcinoma · |
| | | **Stomach** | Gastric carcinoma · Signet ring cell carcinoma · Gastric lymphoma (MALT lymphoma · · Linitis plastica · |
| | **Lower** | **Small intestine** | Duodenal cancer (Adenocarcinoma · · |
| | | **Appendix** | Carcinoid · Pseudomyxoma peritonei · |
| | | **Colon/rectum** | *colorectal polyp:* Peutz–Jeghers syndrome · Juvenile polyposis syndrome · Familial adenomatous polyposis/Gardner's syndrome · Cronkhite–Canada syndrome · *neoplasm:* Adenocarcinoma · Familial adenomatous polyposis · |

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| | | | Hereditary nonpolyposis colorectal cancer · |
| | | **Anus** | Squamous cell carcinoma · |
| | **Upper and/or lower** | | Gastrointestinal stromal tumor · Krukenberg tumor (metastatic) · |
| **Accessory** | **Liver** | | *malignant:* Hepatocellular carcinoma (Fibrolamellar · · Hepatoblastoma · *benign:* Hepatocellular adenoma · Cavernous hemangioma · *hyperplasia:* Focal nodular hyperplasia · Nodular regenerative hyperplasia · |
| | **Biliary tract** | | *bile duct:* Cholangiocarcinoma · Klatskin tumor · *gallbladder:* Gallbladder cancer · |
| | **Pancreas** | | *exocrine pancreas:* Adenocarcinoma · Pancreatic ductal carcinoma · *cystic neoplasms*: Serous microcystic adenoma · Intraductal papillary mucinous neoplasm · Mucinous cystic neoplasm · Solid pseudopapillary neoplasm · Pancreatoblastoma · |
| **Peritoneum** | | | Primary peritoneal carcinoma · Peritoneal mesothelioma · Desmoplastic small round cell tumor · |
| **Authority control** | | | NDL: 00563908 · |

Categories: Stomach cancer | Abdomen | Epstein–Barr virus-associated diseases | Infectious causes of cancer

# Book:Ophthalmology

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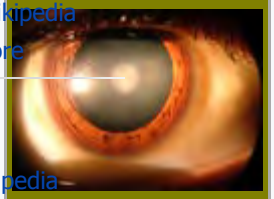

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# Amblyopia

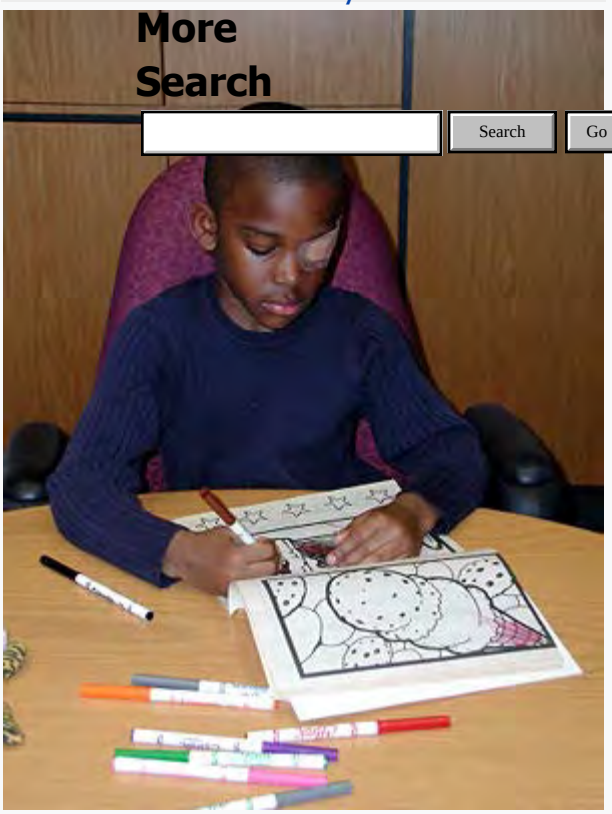
From Wikipedia, the free encyclopedia

**Amblyopia**, also called **lazy eye**, is a disorder of sight due to the eye and brain not working well together. It results in decreased vision in an eye that otherwise typically appears normal. It is the most common cause of decreased vision in a single eye among children and younger adults.[1]

The cause of amblyopia can be any condition that interferes with focusing during early childhood.[1][2] This can occur from poor alignment of the eyes, an eye being irregularly shaped such that focusing is difficult, one eye being more nearsighted or farsighted than the other, or clouding of the lens of an eye.[1] After the underlying cause is fixed, vision is not fully restored as the mechanism also involves the brain.[2][3] Amblyopia can be difficult to detect and therefore vision testing is recommended for all children around the ages of four to five.[4]

Early detection improves treatment success.[4] Eye glasses may be all the treatment needed for some children.[4][5] If this is not sufficient, treatments which force the child to use the weaker eye are used. This is done by either using a patch or putting atropine in the stronger eye. Without treatment amblyopia typically persists into adulthood. Evidence regarding treatments for adults is poor.[1]

Amblyopia was first described in the 1600s.[6] It begins by the age of five.[4] In adults the disorder is estimated to affect 1–5% of the population.[7] While treatment improves vision it does not typically restore it to normal in the affected eye.[4] The condition may make people ineligible to be pilots or police officers.[4] The word "amblyopia" is from Greek αμβλυωπία, meaning "blunt vision".[6]



A child wearing an adhesive eyepatch to correct amblyopia

| Classification and external resources | |
|---|---|
| **Specialty** | Ophthalmology |
| **ICD-10** | H53.0 |
| **ICD-9-CM** | 368.0 |
| **DiseasesDB** | 503 |
| **MedlinePlus** | 001014 |
| **eMedicine** | oph/316 |
| **Patient UK** | Amblyopia |
| **MeSH** | D000550 |

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Contents

## Signs and symptoms [edit]

Many people with amblyopia, especially those who only have a mild form, are not aware they have the condition until tested at older ages, since the vision in their stronger eye is normal. People typically have poor stereo vision, however, since it requires both eyes. Those with amblyopia further may have, on the affected eye, poor pattern recognition, poor visual acuity, and low sensitivity to contrast and motion.[8]

Amblyopia is characterized by several functional abnormalities in spatial vision, including reductions in visual acuity (VA), contrast sensitivity function (CSF), and vernier acuity as well as spatial distortion, abnormal spatial interactions, and impaired contour detection. In addition, individuals with amblyopia suffer from binocular abnormalities such as impaired stereoacuity (stereoscopic acuity) and abnormal binocular summation.[9] Also, a crowding phenomenon is present.[10] These deficits are usually specific to the amblyopic eye. However, sub-clinical deficits of the "better" eye have also been demonstrated.[11]

People with amblyopia also have problems of binocular vision such as limited stereoscopic depth perception and usually have difficulty seeing the three-dimensional images in hidden stereoscopic displays such as autostereograms.[12] Perception of depth, however, from monocular cues such as size, perspective, and motion parallax remains normal.

## Types [edit]

Amblyopia has three main causes:

- Strabismic: by strabismus (misaligned eyes)
- Refractive: by anisometropia (high degrees of nearsightedness, farsightedness, or astigmatism in one or both eyes)
- Deprivational: by deprivation of vision early in life by vision-obstructing disorders such as congenital cataract

### Strabismus amblyopia [edit]

Strabismus, sometimes also incorrectly called *lazy eye*, is a condition in which the eyes are misaligned.[13] Strabismus usually results in normal vision in the preferred sighting (or "fellow") eye (the eye that the person prefers to use), but may cause abnormal vision in the deviating or strabismic eye due to the difference between the images projecting to the brain from the two eyes.[14] Adult-onset strabismus usually causes double vision (diplopia), since the two eyes are not fixed on the same object. Children's brains, however, are more neuroplastic, and therefore can more easily adapt by suppressing images from one of the eyes, eliminating the double vision. This plastic response of the brain, however, interrupts the brain's normal development, resulting in the amblyopia. Recent evidence points to a cause of infantile strabismus lying with the input to the visual cortex.[15]

Those with strabismic amblyopia tend to show ocular motion deficits when reading, even when they use the nonamblyopic eye. In particular, they tend to make more saccades per line than persons with normal stereo vision, and to have a reduced reading speed, especially when reading a text with small font size.[16][17]

Strabismic amblyopia is treated by clarifying the visual image with glasses, or encouraging use of the amblyopic eye with an eyepatch over the dominant eye or pharmacologic penalization of the better eye. Penalization usually consists of applying atropine drops to temporarily dilate the pupil, which leads to blurring of vision in the good eye. This helps to prevent the bullying and teasing associated with wearing a patch, although sometimes application of the eye drops is more challenging. The ocular alignment itself may be treated with surgical or non-surgical methods, depending on the type and severity of the strabismus.[18]

### Refractive or anisometropic amblyopia [edit]

Refractive amblyopia may result from anisometropia (unequal refractive error between the two eyes).[19][20] Anisometropia exists when there is a difference in the power between the two eyes. The eye which provides the brain with a clearer image typically becomes the dominant eye. The image in the other eye is blurred, which results in abnormal development of one half of the visual system. Refractive amblyopia is usually less severe than strabismic amblyopia and is commonly missed by primary care physicians because of its less dramatic appearance and lack of obvious physical manifestation, such as with strabismus.[21] Given that the refractive correction of anisometropia by means of spectacles typically leads to different image magnification for the two eyes, which may in turn prevent binocular vision, a refractive correction using contact lenses is to be considered. Also pediatric refractive surgery is a treatment option, in particular if conventional approaches have failed due to aniseikonia or lack of compliance or both.[22]

Frequently, amblyopia is associated with a combination of anisometropia and strabismus. In some cases, the vision between the eyes can differ to the point where one eye has twice average vision while the other eye is completely blind.

### Deprivation and occlusion amblyopia [edit]

Deprivation amblyopia (*Amblyopia ex anopsia*) results when the ocular media become opaque, such as is the case with congenital cataract or corneal haziness.[23] These opacities prevent adequate visual input from reaching the eye, and therefore disrupt development. If not treated in a timely fashion, amblyopia may persist even after the cause of the opacity is removed. Sometimes, drooping of the eyelid (ptosis) or some other problem causes the upper eyelid to physically occlude a child's vision, which may cause amblyopia quickly. Occlusion amblyopia may be a complication of a hemangioma that blocks some or all of the eye. Other possible causes of deprivation and occlusion amblyopia include obstruction in the vitreous and aphakia.[24] Deprivation amblyopia accounts for less than 3% of all individuals affected by amblyopia.[24]

## Pathophysiology [edit]

Amblyopia is a developmental problem in the brain, not any intrinsic, organic neurological problem in the eyeball (although organic problems can lead to amblyopia which can continue to exist after the organic problem has resolved by medical intervention).[25] The part of the brain receiving images from the affected eye is not stimulated properly and does not develop to its full visual potential. This has been confirmed by direct brain examination. David H. Hubel and Torsten Wiesel won the Nobel Prize in Physiology or Medicine in 1981 for their work in showing the extent of the damage to ocular dominance columns produced in kittens by sufficient visual deprivation during the so-called "critical period." The maximum "critical period" in humans is from birth to two years old.[26]

## Diagnosis [edit]

Amblyopia is diagnosed by identifying low visual acuity in one or both eyes, out of proportion to the structural abnormality of the eye and excluding other visual disorders as causes for the lowered visual acuity.

It can be defined as an inter-ocular difference of two lines or more in acuity (e.g. on Snellen chart) when the eye optics is maximally corrected.[27]

In young children, visual acuity is difficult to measure and can be estimated by observing the reactions of the patient reacts when one eye is covered, including observing the patient's ability to follow objects with one eye.

Stereotests like the Lang stereotest are not reliable exclusion tests for amblyopia: A patient who passes the Lang stereotest test is unlikely to have strabismic amblyopia, but could nonetheless have refractive or deprivational amblyopia.[28] It has been suggested that binocular retinal birefringence scanning may be

able to identify, already in very young children, amblyopia that is associated with strabismus, microstrabismus, or reduced fixation accuracy.

It is essential to diagnose and treat amblyopia as early as possible in order to keep the vision loss to a minimum.

## Treatment [edit]

Treatment of strabismic or anisometropic amblyopia consists of correcting the optical deficit (wearing the necessary spectacle prescription) and often forcing use of the amblyopic eye, by patching the good eye, or instilling topical atropine in the good eye, or both.[13]:130[29]

Concerning patching versus atropine, there is a drawback in using atropine: the drops can have a side effect of creating nodules in the eye which a correctional ointment can counteract. One should also be wary of over-patching or over-penalizing the good eye when treating amblyopia, as this can create so-called "reverse amblyopia".[18][30] Eye patching is usually done on a part-time schedule of about 4–6 hours a day. Treatment is continued as long as vision improves. It is not worthwhile continuing to patch for more than 6 months if there is no improvement.[31]

Treatment of individuals age 9 through adult is possible through applied perceptual learning.[32][33]

*Deprivation amblyopia* is treated by removing the opacity as soon as possible followed by patching or penalizing the good eye to encourage the use of the amblyopic eye.[18] The earlier the treatment is initiated, the easier and faster the treatment is and the less psychologically damaging. There is also a greater chance of achieving 20/20 vision if treatment is initiated as early as possible.[34]

One of the German public health insurance providers, Barmer, has changed its policy to cover, as of 1 April 2014, the costs for an app for amblyopic children whose condition has so far not improved through patching. The app offers dedicated eye exercises which the patient performs while wearing an eyepatch.[35]

### Older age [edit]

Although the best outcome is achieved if treatment is started before age 8, research has shown that children older than age 12 and some adults can show improvement in the affected eye. Children from 9 to 11 who wore an eye patch and performed near point activities (vision therapy) were four times as likely to show a two line improvement on a standard 11 line eye chart than children with amblyopia who did not receive treatment. Adolescents aged 13 to 17 showed improvement as well, albeit in smaller amounts than younger children. It is uncertain whether such improvements are only temporary, however, particularly if treatment is discontinued.[18][36]

There is tentative evidence that perceptual training may be beneficial in adults.[37][38][39]

Virtual reality computer games where each eye receives different signals of the virtual world that the player's brain must combine in order to successfully play the game have shown some promise in improving both monocularity in the affected eye as well as binocularity.[40][41]

## Epidemiology [edit]

Between 2% and 5% of the population in western countries have amblyopia.[27][42] In the U.K., 90% of visual health appointments in the child are concerning amblyopia.[43]

Depending on the chosen criterion for diagnosis, between 1% and 4% of the children have amblyopia.[44]

## Research [edit]

A 2009 study,[45] widely reported in the popular press,[46] has suggested that repetitive transcranial

magnetic stimulation may temporarily improve contrast sensitivity and spatial resolution in the affected eye of adults with amblyopia. This approach is still under development,[47] and the results await verification by other researchers. It has also been suggested that comparable results can be achieved using different types of brain stimulation[48] such as anodal transcranial direct current stimulation[49] and theta burst rTMS.[50]

A 2013 study concluded that there is converging evidence that decorrelated binocular experience plays a pivotal role in the genesis of amblyopia and the associated residual deficits.[51] Another study of 2013[52] suggests that playing a version of the popular game Tetris that is modified such that each eye sees separate components of the game may also help to treat this condition in adults.[53] Furthermore, it has been proposed that the effects of this kind of therapy may be further enhanced by non-invasive brain stimulation[48] as shown by a recent study using anodal tDCS.[54]

A 2014 Cochrane Review sought to determine the effectiveness of occlusion treatment on patients with sensory deprivation amblyopia, however no trials were found eligible to be included in the review.[24] However, it is suggested that good outcomes from occlusion treatment for sensory deprivation amblyopia rely on compliance with the treatment.

## References [edit]


1. ^ *a b c d* "Facts About Amblyopia". *National Eye Institute*. September 2013. Retrieved 27 July 2016.
2. ^ *a b* Schwartz, editor, M. William (2002). *The 5-minute pediatric consult* (3rd ed.). Philadelphia: Lippincott Williams & Wilkins. p. 110. ISBN 9780781735391.
3. ^ Levi, D. (2013). "Linking assumptions in amblyopia.". *Visual neuroscience*. **30** (5-6): 277–287. doi:10.1017/S0952523813000023. PMID 23879956.
4. ^ *a b c d e f* Jefferis, JM; Connor, AJ; Clarke, MP (12 November 2015). "Amblyopia.". *BMJ (Clinical research ed.)*. **351**: h5811. doi:10.1136/bmj.h5811. PMID 26563241.
5. ^ Maconachie, GD; Gottlob, I (December 2015). "The challenges of amblyopia treatment.". *Biomedical journal*. **38** (6): 510–6. doi:10.1016/j.bj.2015.06.001. PMID 27013450.
6. ^ *a b* "Chapter 2 - Visual development in childhood". *Visual Impairments and Developmental Disorders: From diagnosis to rehabilitation Mariani Foundation Paediatric Neurology*. John Libbey Eurotext. 2016. ISBN 9782742014828. Retrieved 27 July 2016.
7. ^ Webber, AL; Wood, Joanne (2005). "Amblyopia: Prevalence, Natural History, Functional Effects and Treatment". *Clinical and Experimental Optometry*. **88** (6): 365–375. doi:10.1111/j.1444-0938.2005.tb05102.x. PMID 16329744.
8. ^ Hess, R.F., Mansouri, B., Dakin, S.C., & Allen, H.A. (2006). "Integration of local motion is normal in amblyopia". *J. Opt. Soc. Am. A*. **23** (5): 986–992. doi:10.1364/JOSAA.23.000986. PMID 16642175.
9. ^ Polat U, Ma-Naim T, Belkin M, Sagi D (April 2004). "Improving vision in adult amblyopia by perceptual learning". *Proc. Natl. Acad. Sci. U.S.A.* **101**: 6692–7. doi:10.1073/pnas.0401200101. PMC 404107. PMID 15096608.
10. ^ A study of separation difficulty. Its relationship to
31. ^ Emmett T. Cunningham; Paul Riordan-Eva. *Vaughan & Asbury's general ophthalmology.* (18th ed.). McGraw-Hill Medical. ISBN 978-0071634205.
32. ^ Zhou, Y; et al. (2005). "Perceptual Learning Improves Contrast Sensitivity and Visual Acuity in Adults with Anisometropic Amblyopia". *Vision Research*. **46** (5): 739–50. doi:10.1016/j.visres.2005.07.031. PMID 16153674.
33. ^ Polat, U; et al. (2004). "Improving Vision in Adult Amblyopia by Perceptual Learning". *PNAS*. **101** (17): 6692–7. doi:10.1073/pnas.0401200101. PMC 404107. PMID 15096608.
34. ^ Williams, C; Northstone, K; Harrad, K A; Sparrow, J M; Harvey, I; Alspac Study, Team (2002). "Amblyopia treatment outcomes after screening before or at age 3 years: follow up from randomised trial". *BMJ*. **324** (7353): 1549. doi:10.1136/bmj.324.7353.1549. PMC 116606. PMID 12089090.
35. ^ "App auf Rezept: Barmer bezahlt internetbasierte Behandlung" [Prescription app: Barmer pays for internet-based treatment]. *www.aerztezeitung.de* (in German). 28 March 2014. Retrieved 29 March 2014.
36. ^ Pediatric Eye Disease Investigator Group (2005). "Randomized trial of treatment of amblyopia in children aged 7 to 17 years". *Archives of Ophthalmology*. **123** (April): 437–447. doi:10.1001/archopht.123.4.437. PMID 15824215.
37. ^ Polat, U; Polat, Uri; Ma-Naim, Tova; Belkin, Michael; Sagi, Dov (27 April 2004). "Improving vision in adult amblyopia by perceptual learning". *PNAS*. **101** (17): 6692–6697. doi:10.1073/pnas.0401200101. PMC 404107. PMID 15096608.
38. ^ Astle, AT; Webb, BS; McGraw, PV (Nov 2011). "Can perceptual learning be used to treat amblyopia

visual acuity in normal and amblyopic eyes.
11. ^ Simonis K (2005). "Amblyopia Characterization, Treatment, and Prophylaxis". *Survey of Ophthalmolgy*. **50** (2): 123–166. doi:10.1016/j.survophthal.2004.12.005.
12. ^ Tyler, C.W. (2004). "*Binocular Vision In, Duane's Foundations of Clinical Ophthalmology*. Vol. 2, Tasman W., Jaeger E.A. (Eds.), J.B. Lippincott Co.: Philadelphia".
13. ^ [a] [b] Wright, Kenneth W.; Spiegel, Peter H.; Thompson, Lisa S. (2006). *Handbook of Pediatric Strabismus and Amblyopia*. New York, New York: Springer. ISBN 978-0-387-27924-4.
14. ^ Levi, D.M. (2006). "Visual processing in amblyopia: human studies". *Strabismus*. **14** (1): 11–19. doi:10.1080/09273970500536243. PMID 16513566.
15. ^ Tychsen, Lawrence (2012). "The cause of infantile strabismus lies upstairs in the cerebral cortex, not downstairs in the brainstem". *Archives of Ophthalmology*. **130** (8): 1060–1061. doi:10.1001/archophthalmol.2012.1481.
16. ^ Kanonidou E., Gottlob I., Proudlock F.A. *The effect of font size on reading performance in strabismic amblyopia: an eye movement investigation, Invest. Ophthalmol. Vis. Sci.* 2014 January; Vol. 55, Nr. 1, pp. 451-459, doi:10.1167/iovs.13-13257.
17. ^ Kanonidou E, Proudlock FA, Gottlob I. *Reading strategies in mild to moderate strabismic amblyopia: an eye movement investigation.*, Invest. Ophthalmol. *Vis. Sci.* 2010; Vol. 51, Nr. 7, pp. 3502-3508, doi:10.1167/iovs.09-4236.
18. ^ [a] [b] [c] [d] Holmes, Repka, Kraker & Clarke (2006). "The treatment of amblyopia". *Strabismus*. **15** (1): 37–42. doi:10.1080/09273970500536227. PMID 16513568.
19. ^ Robert F. Rutstein; David Corliss (April 1999). "Relationship between Anisometropia, Amblyopia, and Binocularity". *Optometry & Vision Science*.
20. ^ David R Weakley Jr. (January 2001). "The association between nonstrabismic anisometropia, amblyopia, and subnormal binocularity". *Ophthalmology*. pp. 163–171. doi:10.1016/s0161-6420(00)00425-5.
21. ^ "Commonly Missed Diagnoses in the Childhood Eye Examination". American Family Physician. August 15, 2001.
22. ^ William F. Astle; Jamalia Rahmat; April D. Ingram; Peter T. Huang (December 2007). "Laser-assisted subepithelial keratectomy for anisometropic amblyopia in children: Outcomes at 1 year". *Journal of Cataract & Refractive Surgery*. **33** (12): 2028–2034. doi:10.1016/j.jcrs.2007.07.024.
23. ^ Angell; Robb, RM; Berson, FG; et al. (1981). "Visual prognosis in patients with ruptures in Descemet's membrane due to forceps injuries". *Arch Ophthalmol*. **99** (12): 2137–9. doi:10.1001/archopht.1981.03930021013004. PMID 7305711.
beyond the critical period of visual development?". *Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists)*. **31** (6): 564–73. doi:10.1111/j.1475-1313.2011.00873.x. PMID 21981034.
39. ^ Levi DM (June 2012). "Prentice award lecture 2011: Removing the brakes on plasticity in the amblyopic brain". *Optometry and Vision Science: Official Publication of the American Academy of Optometry*. **89** (6): 827–38. doi:10.1097/OPX.0b013e318257a187. PMC 3369432. PMID 22581119.
40. ^ BBC News: Video games tackle 'lazy eye'
41. ^ Eastgate, RM; Griffiths, GD; Waddingham, PE; Moody, AD; Butler, TKH; Cobb, SV; Comaish, IF; Haworth, SM; Gregson, R; Ash, IM; Brown, SM (2006). "Modified virtual reality technology for treatment of amblyopia". *Eye*. **20** (3): 370–374. doi:10.1038/sj.eye.6701882. PMID 15832182.
42. ^ Elflein, Heike M.; Fresenius, Suzanne; Lamparter, Julia; Pitz, first4 (2015-05-08). "The prevalence of amblyopia in Germany: data from the prospective, population-based gutenberg health study" (pdf). *Deutsches Ärzteblatt International*. **112**: 338–344. doi:10.3238/arztebl.2015.0338. ISSN 1866-0452. PMC 4458790. PMID 26043421.
43. ^ Stewart, C. E.; Fielder, A. R.; Stephens, D. A.; Moseley, M. J. (2002-08-01). "Design of the Monitored Occlusion Treatment of Amblyopia Study (MOTAS)". *British Journal of Ophthalmology*. **86**: 915–919. doi:10.1136/bjo.86.8.915. ISSN 1468-2079. PMC 1771248. PMID 12140215.
44. ^ Birch, Eileen E. (March 2013). "Amblyopia and binocular vision". *Progress in Retinal and Eye Research*. **33**: 67–84. doi:10.1016/j.preteyeres.2012.11.001. PMC 3577063. PMID 23201436.
45. ^ Benjamin Thompson; Behzad Mansouri; Lisa Koski; Robert F. Hess (2008). "Brain Plasticity in the Adult: Modulation of Function in Amblyopia with rTMS". *Current Biology*. **18** (14): 1067–1071. doi:10.1016/j.cub.2008.06.052. PMID 18635353.
46. ^ National Public Radio. "Magnetic Pulses To Brain Help 'Lazy Eye'".
47. ^ Robert F. Hess; Benjamin Thompson (February 2013). "New insights into amblyopia: binocular therapy and noninvasive brain stimulation". *Journal of AAPOS*. **17** (1). pp. 89–93. doi:10.1016/j.jaapos.2012.10.018.
48. ^ [a] [b] Hess Robert F.; Thompson Benjamin; Baker Daniel H. (2014). "Binocular vision in amblyopia: structure, suppression and plasticity". *Ophthalmic and Physiological Optics*. **34** (2): 146–162. doi:10.1111/opo.12123.
49. ^ Spiegel Daniel P.; et al. (2013). "Anodal Transcranial Direct Current Stimulation Transiently Improves Contrast Sensitivity and Normalizes Visual Cortex Activation in Individuals With Amblyopia". *Neurorehabilitation and neural repair*. **27** (8): 760–

24. ^ a b c Antonio-Santos A, Vedula SS, Hatt RR, Powell C (2014). "Occlusion for stimulus deprivation amblyopia". *Cochrane Database Syst Rev*. **2**: CD005136. doi:10.1002/14651858.CD005136.pub3. PMC 4260153. PMID 24504975.
25. ^ McKee, SP., Levi, DM., Movshon, JA. (2003). "The pattern of visual deficits in amblyopia" (PDF). *J Vision*. **4** (5): 380–405. doi:10.1167/3.5.5. PMID 12875634.
26. ^ Jeffrey Cooper; Rachel Cooper. "All About Strabismus". Optometrists Network. Retrieved 9 March 2008.
27. ^ a b Wright, W. K. (2006). *Handbook of Pediatric Strabismus and Amblyopia*. New-York: Springer. pp. 103–137.
28. ^ Ulrich Schiefer; Helmut Wilhelm; William Hart (11 September 2007). *Clinical Neuro-Ophthalmology: A Practical Guide*. Springer Science & Business Media. p. 16. ISBN 978-3-540-32708-0.
29. ^ Coats DK and Paysse EA. Overview of amblyopia UpToDate. Last updated: Sep 25, 2014
30. ^ Amblyopia NEI Health Information Archived 11 September 2005 at the Wayback Machine.
769. doi:10.1177/1545968313491006.
50. ^ Clavagnier Simon; Thompson Benjamin; Hess Robert F (2013). "Long lasting effects of daily theta burst rTMS sessions in the human amblyopic cortex". *Brain stimulation*. **6** (6): 860–867. doi:10.1016/j.brs.2013.04.002.
51. ^ Birch, Eileen E. (2013). "Amblyopia and binocular vision". *Progress in Retinal and Eye Research* (Review). **33**: 67–84. doi:10.1016/j.preteyeres.2012.11.001. ISSN 1350-9462. PMC 3577063. PMID 23201436.
52. ^ Jinrong Li; Benjamin Thompson; Daming Deng; Lily Y.L. Chan; Minbin Yu; Robert F. Hess (2013). "Dichoptic training enables the adult amblyopic brain to learn". *Current Biology*. **23** (8): R308–9. doi:10.1016/j.cub.2013.01.059. PMID 23618662. Retrieved 28 September 2013.
53. ^ Joseph Nordqvist: Tetris Video Game Helps Treat Lazy Eye, Medical News Today (MNT), 23 April 2013.
54. ^ Spiegel Daniel P.; et al. (2013). "Transcranial direct current stimulation enhances recovery of stereopsis in adults with amblyopia". *Neurotherapeutics*. **10** (4): 831–839. doi:10.1007/s13311-013-0200-y.


## Further reading [edit]


- Birch EE (March 2013). "Amblyopia and binocular vision". *Progress in Retinal and Eye Research* (review). **33**: 67–84. doi:10.1016/j.preteyeres.2012.11.001. PMC 3577063. PMID 23201436.
- Daw, Nigel W. (2014). *Visual Development* (Third ed.). Springer. ISBN 978-1461490586.
  - Chapter What is Amblyopia? pp. 123–145, doi:10.1007/978-1-4614-9059-3_8,
  - Chapter Treatment of Amblyopia pp. 167–180, doi:10.1007/978-1-4614-9059-3_10.
- Stewart, Catherine E.; Moseley, Merrick J.; Fielder, Alistair R. (2011). "Amblyopia Therapy: An Update". *Strabismus*. **19** (3): 91–98. doi:10.3109/09273972.2011.600421. ISSN 0927-3972.
- Sengpiel F (September 2014). "Plasticity of the visual cortex and treatment of amblyopia". *Current Biology* (review). **24** (18): R936–R940. doi:10.1016/j.cub.2014.05.063. PMID 25247373.
- Hamm LM, Black J, Dai S, Thompson B (2014). "Global processing in amblyopia: a review". *Frontiers in Psychology* (review). **5**: 583. doi:10.3389/fpsyg.2014.00583. PMC 4060804. PMID 24987383.


## External links [edit]

- National Eye Institute (NEI) Resource Guide
- International Orthoptics Association
- Lazy Eye Site from the National Health Service, UK
- Stereo Sue at TEDx
- Daniel R. Morgan : Amblyopia therapy options expand beyond patching for children and adults , Primary Care Optometry News, October 2012, helio.com (overview over recent methods of amblyopia treatment)

Wikimedia Commons has media related to *Amblyopia*.

| v · t · e | **Diseases of the human eye (H00–H59 · 360–379) ·** | |
|---|---|---|
| | **Adnexa** | |
| | **Inflammation** | Stye · Chalazion · Blepharitis · |

| | | |
|---|---|---|
| **Eyelid** | | Entropion · Ectropion · Lagophthalmos · Blepharochalasis · Ptosis · Blepharophimosis · Xanthelasma · |
| | **Eyelash** | Trichiasis · Madarosis · |
| **Lacrimal apparatus** | | Dacryoadenitis · Epiphora · Dacryocystitis · Xerophthalmia · |
| **Orbit** | | Exophthalmos · Enophthalmos · Orbital cellulitis · Orbital lymphoma · Periorbital cellulitis · |
| **Conjunctiva** | | Conjunctivitis (allergic · · Pterygium · Pinguecula · Subconjunctival hemorrhage · |
| **Globe** | | |
| **Fibrous tunic** | **Sclera** | Scleritis · Episcleritis · |
| | **Cornea** | Keratitis (herpetic · acanthamoebic · fungal · · Corneal ulcer · Photokeratitis · Thygeson's superficial punctate keratopathy · Corneal dystrophy (Fuchs' · Meesmann · · Corneal ectasia (Keratoconus · Pellucid marginal degeneration · Keratoglobus · Terrien's marginal degeneration · Post-LASIK ectasia · · Keratoconjunctivitis (sicca · · Corneal neovascularization · Kayser–Fleischer ring · Haab's striae · Arcus senilis · Band keratopathy · |
| **Vascular tunic** | **Iris · Ciliary body ·** | Uveitis · Intermediate uveitis · Hyphema · Rubeosis iridis · Persistent pupillary membrane · Iridodialysis · Synechia · |
| | **Choroid** | Choroideremia · Choroiditis (Chorioretinitis · · |
| **Lens** | | Cataract (Congenital cataract · Childhood cataract · · Aphakia · Ectopia lentis · |
| **Retina** | | Retinitis (Chorioretinitis · Cytomegalovirus retinitis · · Retinal detachment · Retinoschisis · Ocular ischemic syndrome / Central retinal vein occlusion · Central retinal artery occlusion · Retinopathy (diabetic · hypertensive · Purtscher's · of prematurity · Bietti's crystalline dystrophy · Coats' disease · · Macular degeneration · Retinitis pigmentosa · Retinal haemorrhage · Central serous retinopathy · Macular edema · Epiretinal membrane (Macular pucker) · Vitelliform macular dystrophy · Leber's congenital amaurosis · Birdshot chorioretinopathy · |
| **Other** | | Glaucoma / Ocular hypertension / Primary juvenile glaucoma · Floater · Leber's hereditary optic neuropathy · Red eye · Globe rupture · Keratomycosis · Phthisis bulbi · Persistent fetal vasculature / Persistent hyperplastic primary vitreous · Persistent tunica vasculosa lentis · Familial exudative vitreoretinopathy · |
| **Pathways** | | |
| **Optic nerve**<br>**Optic disc** | | Optic neuritis (optic papillitis · · Papilledema (Foster Kennedy syndrome · · Optic atrophy · Optic disc drusen · |
| | **Optic neuropathy** | Ischemic (anterior (AION) · posterior (PION) · · Kjer's · Leber's hereditary · Toxic and nutritional · |
| **Strabismus**<br>**Extraocular muscles**<br>**Binocular vision**<br>**Accommodation** | **Paralytic strabismus** | Ophthalmoparesis · Chronic progressive external ophthalmoplegia · Kearns–Sayre syndrome · |
| | **palsies** | Oculomotor (III) · Fourth-nerve (IV) · Sixth-nerve (VI) · |
| | **Other strabismus** | Esotropia / Exotropia · Hypertropia · Heterophoria (Esophoria · Exophoria · · Cyclotropia · Brown's syndrome · Duane syndrome · |
| | **Other binocular** | Conjugate gaze palsy · Convergence insufficiency · Internuclear ophthalmoplegia · One and a half syndrome · |

| | |
|---|---|
| **Refraction** | Refractive error (Hyperopia · Myopia · · Astigmatism · Anisometropia / Aniseikonia · Presbyopia · |
| **Vision disorders Blindness** | **Amblyopia** · Leber's congenital amaurosis · Diplopia · Scotoma · Color blindness (Achromatopsia · Dichromacy · Monochromacy · · Nyctalopia (Oguchi disease · · Blindness / Vision loss / Visual impairment · |
| **Anopsia** | Hemianopsia (binasal · bitemporal · homonymous · · Quadrantanopia · |
| **subjective** | Asthenopia · Hemeralopia · Photophobia · Scintillating scotoma · |
| **Pupil** | Anisocoria · Argyll Robertson pupil · Marcus Gunn pupil · Adie syndrome · Miosis · Mydriasis · Cycloplegia · Parinaud's syndrome · |
| **Other** | Nystagmus · Childhood blindness · |
| **Infections** | |
| Trachoma · Onchocerciasis · | |
| **Authority control** | NDL: 00574975 · |

Categories: Visual disturbances and blindness

# Cataract

From Wikipedia, the free encyclopedia
(Redirected from Cataracts)

*For other uses, see Cataract (disambiguation).*

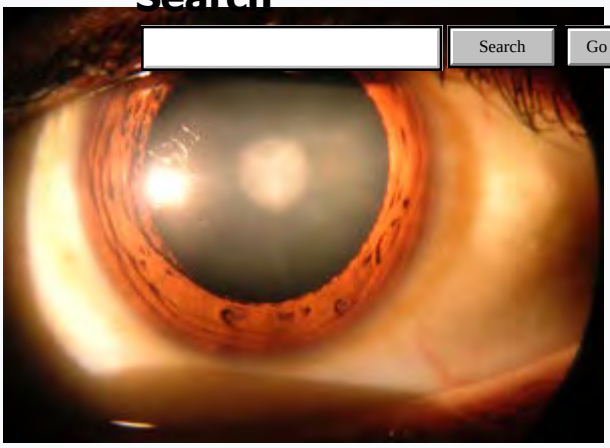
A **cataract** is a clouding of the lens in the eye which leads to a decrease in vision. Cataracts often develop slowly and can affect one or both eyes. Symptoms may include faded colors, blurry vision, halos around light, trouble with bright lights, and trouble seeing at night.[1] This may result in trouble driving, reading, or recognizing faces.[2] Poor vision caused by cataracts may also result in an increased risk of falling and depression.[3] Cataracts are the cause of half of blindness and 33% of visual impairment worldwide.[4][5]

Cataracts are most commonly due to aging but may also occur due to trauma or radiation exposure, be present from birth, or occur following eye surgery for other problems.[1][6] Risk factors include diabetes, smoking tobacco, prolonged exposure to sunlight, and alcohol. Either clumps of protein or yellow-brown pigment may be deposited in the lens reducing the transmission of light to the retina at the back of the eye. Diagnosis is by an eye examination.[1]

Prevention includes wearing sunglasses and not smoking. Early on the symptoms may be improved with glasses. If this does not help, surgery to remove the cloudy lens and replace it with an artificial lens is the only effective treatment. Surgery is only needed if the cataracts are causing problems and generally results in an improved quality of life.[1][7] Cataract surgery is not readily available in many countries, which is especially true for women, those living in rural areas, and those who do not know how to read.[6][8]

About 20 million people are blind due to cataracts.[6] It is the cause of approximately 5% of blindness in the United States and nearly 60% of blindness in parts of Africa and South America.[8] Blindness from cataracts occurs in about 10 to 40 per 100,000 children in the developing world, and 1 to 4 per 100,000 children in the developed world.[9] Cataracts become more common with age. More than half the people in the United States had cataracts by the age of 80.[1]

**Cataract**



Magnified view of a cataract seen on examination with a slit lamp

**Classification and external resources**

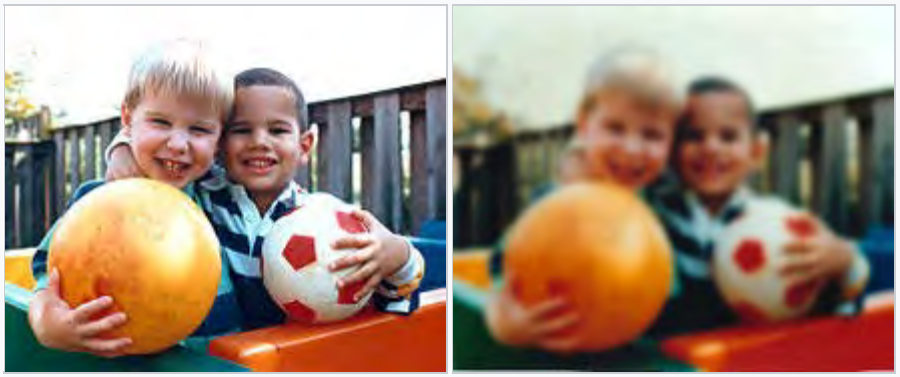
| | |
|---|---|
| **Specialty** | Ophthalmology |
| **ICD-10** | H25-H26, H28, Q12.0 |
| **ICD-9-CM** | 366 |
| **DiseasesDB** | 2179 |
| **MedlinePlus** | 001001 |
| **eMedicine** | article/1210914 |
| **MeSH** | D002386 |

[edit on Wikidata]

**Contents**

## Signs and symptoms [edit]

Signs and symptoms vary depending on the type of cataract, though considerable overlap occurs. People with nuclear sclerotic or brunescent cataracts often notice a reduction of vision. Those with posterior subcapsular cataracts usually complain of glare as their major symptom.[10]



An example of normal vision on the left versus vision with cataracts on the right

The severity of cataract formation, assuming no other eye disease is present, is judged primarily by a visual acuity test. The appropriateness of surgery depends on a patient's particular functional and visual needs and other risk factors, all of which may vary widely.[11]

## Causes [edit]

### Age [edit]

Age is the most common cause.[1][6] Lens proteins denature and degrade over time, and this process is accelerated by diseases such as diabetes mellitus and hypertension. Environmental factors, including toxins, radiation, and ultraviolet light, have cumulative effects, which are worsened by the loss of protective and restorative mechanisms due to alterations in gene expression and chemical processes within the eye.[12]

Bilateral cataracts in an infant due to congenital rubella syndrome

### [edit]

## Trauma

Svenska
Tagalog
Tatarça/tatarça
Türkçe
Українська
Tiếng Việt
Walon
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Edit links

Blunt trauma causes swelling, thickening, and whitening of the lens fibers. While the swelling normally resolves with time, the white color may remain. In severe blunt trauma, or in injuries that penetrate the eye, the capsule in which the lens sits can be damaged. This damage allows fluid from other parts of the eye to rapidly enter the lens leading to swelling and then whitening, obstructing light from reaching the retina at the back of the eye. Cataracts may develop in 0.7 to 8.0% of cases following electrical injuries.[13] Blunt trauma can also result in star- or petal-shaped cataracts.[14]

## Radiation [edit]

Ultraviolet light, specifically UVB, has been shown to cause cataracts, and some evidence indicates sunglasses worn at an early age can slow its development in later life.[15] Microwave radiation has also been found to cause cataracts. The mechanism is unclear, but it may include changes in heat-sensitive enzymes that normally protect cell proteins in the lens. Another possible mechanism is direct damage to the lens from pressure waves induced in the aqueous humor.

Cataracts have been associated with ionizing radiation such as X-rays. The addition of damage to the DNA of the lens cells has been considered.[16] Finally, electric and heat injuries denature and whiten the lens as a result of direct protein coagulation.[12] This same process makes the clear albumen of an egg become white and opaque after cooking. Cataracts of this type are often seen in glassblowers and furnace workers. Lasers of sufficient power output are known to damage the eyes and skin.

## Genetics [edit]

The genetic component is strong in the development of cataracts,[17] most commonly through mechanisms that protect and maintain the lens. The presence of cataracts in childhood or early life can occasionally be due to a particular syndrome. Examples of chromosome abnormalities associated with cataracts include 1q21.1 deletion syndrome, cri-du-chat syndrome, Down syndrome, Patau's syndrome, trisomy 18 (Edward's syndrome), and Turner's syndrome, and in the case of neurofibromatosis type 2, juvenile cataract on one or both sides may be noted. Examples of single-gene disorder include Alport's syndrome, Conradi's syndrome, myotonic dystrophy, and oculocerebrorenal syndrome or Lowe syndrome.

## Skin diseases [edit]

The skin and the lens have the same embryological origin and so can be affected by similar diseases.[18] Those with atopic dermatitis and eczema occasionally develop shield ulcers cataracts. Ichthyosis is an autosomal recessive disorder associated with cuneiform cataracts and nuclear sclerosis. Basal-cell nevus and pemphigus have similar associations.

## Smoking and alcohol [edit]

Cigarette smoking has been shown to double the rate of nuclear sclerotic cataracts and triple the rate of posterior subcapsular cataracts.[19] Evidence is conflicting over the effect of alcohol. Some surveys have shown a link, but others which followed people over longer terms have not.[20]

## Inadequate vitamin C [edit]

Low vitamin C intake and serum levels have been associated with greater cataract rates.[21] However, use of supplements of vitamin C has not demonstrated benefit.[22]

## Medications [edit]

Some medications, such as inhaled corticosteroids, may increase the risk of cataract development.[23] People with schizophrenia often have risk factors for lens opacities (such as diabetes, hypertension, and [24] [25]

poor nutrition) but antipsychotic medications are unlikely to contribute to cataract formation. Miotics and triparanol may increase the risk.[26]

### Post-operative [edit]

Nearly every person who undergoes a vitrectomy—without ever having had cataract surgery—will experience progression of nuclear sclerosis after the operation.[27] This may be because the native vitreous humor is different to the solutions used to replace the vitreous (vitreous substitutes), such as BSS Plus.[28] This may also be because the native vitreous humour contains ascorbic acid which helps neutralize oxidative damage to the lens and because traditional vitreous substitutes do not contain ascorbic acid.[29][30] As such, for phakic patients requiring a vitrectomy it is becoming increasingly common for ophthalmologists to offer the vitrectomy with a combined prophylactic cataract surgery procedure to prophylactically prevent cataract formation.[31]

### Other diseases [edit]

- Metabolic and nutritional diseases
  - Aminoaciduria or Lowe's syndrome
  - Diabetes mellitus
  - Fabry's disease
  - Galactosemia / galactosemic cataract
  - Homocystinuria
  - Hyperparathyroidism
  - Hypoparathyroidism
  - Hypervitaminosis D
  - Hypothyroidism
  - Hypocalcaemia
  - Mucopolysaccharidoses
  - Wilson's disease
- Congenital
  - Congenital syphilis
  - Cytomegalic inclusion disease
  - Rubella
  - Cockayne syndrome
- Genetic syndromes
  - Down syndrome
  - Patau syndrome
  - Edwards syndrome
- Infections:
  - Cysticercosis
  - Leprosy
  - Onchocerciasis
  - Toxoplasmosis
  - Varicella
- Secondary to other eye diseases:
  - Retinopathy of prematurity
  - Aniridia
  - Uveitis
  - Retinal detachment
  - Retinitis pigmentosa

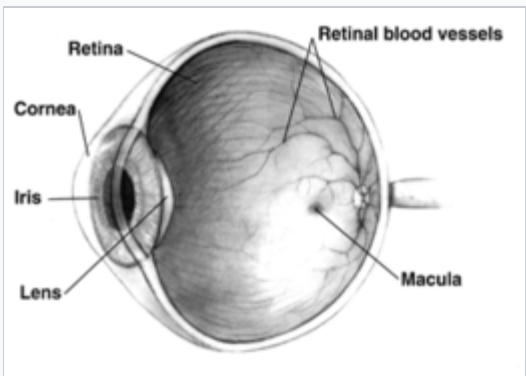
A cat with cataracts in both eyes.

## Classification [edit]

Cataracts may be partial or complete, stationary or progressive, or hard or soft. The main types of age-related cataracts are nuclear sclerosis, cortical, and posterior subcapsular.

Nuclear sclerosis is the most common type of cataract, and involves the central or 'nuclear' part of the lens. This eventually becomes hard, or 'sclerotic', due to condensation on the lens nucleus and the deposition of brown pigment within the lens. In its advanced stages it is called a brunescent cataract. This type of cataract can present with a shift to nearsightedness, causing problems with distance vision though reading is less affected.[32]

Cortical cataracts are due to the lens cortex (outer layer) becoming opaque. They occur when changes in the fluid contained in the periphery of the lens causes fissuring. When these cataracts are viewed through an ophthalmoscope, or other magnification




Cross-sectional view, showing the position of the human lens

system, the appearance is similar to white spokes of a wheel.
Symptoms often include problems with glare and light scatter at night.[32]

Posterior subcapsular cataracts are cloudy at the back of the lens adjacent to the capsule (or bag) in which the lens sits. Because light becomes more focused toward the back of the lens, they can cause disproportionate symptoms for their size.

An immature cataract has some transparent protein, but with a mature cataract, all the lens protein is opaque. In a hypermature or Morgagnian cataract, the lens proteins have become liquid. Congenital cataract, which may be detected in adulthood, has a different classification and includes lamellar, polar, and sutural cataracts.[33][34]

Cataracts can be classified by using the lens opacities classification system LOCS III. In this system, cataracts are classified based on type as nuclear, cortical, or posterior. The cataracts are further classified based on severity on a scale from 1 to 5. The LOCS III system is highly reproducible.[35]

## Prevention [edit]

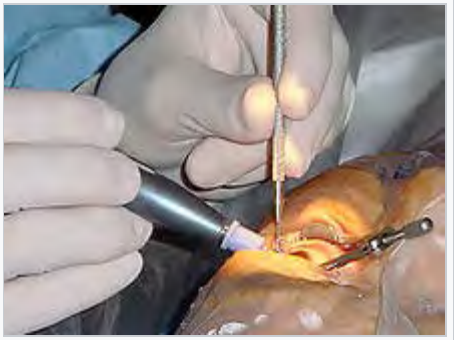
Risk factors such as UVB exposure and smoking can be addressed, but are unlikely to make a large difference to visual function. Although no means of preventing cataracts has been scientifically proven, wearing sunglasses that counteract ultraviolet light may slow their development.[36][37] While adequate intake of antioxidants (such as vitamins A, C, and E) has been thought to protect against the risk of cataracts, clinical trials have shown no benefit from supplements;[22] though evidence is mixed, but weakly positive, for a potential protective effect of the nutrients lutein and zeaxanthin.[38] Statin use is somewhat associated with a lower risk of nuclear sclerotic cataracts.[39]

## Treatment [edit]

### Surgical [edit]

*Main article: Cataract surgery*

Cataract removal can be performed at any stage and no longer requires ripening of the lens. Surgery is usually 'outpatient' and performed using local anesthesia. About 9 of 10 patients can achieve a corrected vision of 20/40 or better after surgery.[32]



Cataract surgery, using a temporal-approach phacoemulsification probe (in right hand) and "chopper" (in left hand) being done under operating microscope at a navy medical center

Several recent evaluations found that cataract surgery can meet expectations only when significant functional impairment due to cataracts exists prior to surgery. Visual function estimates such as VF-14 have been found to give more realistic estimates than visual acuity testing alone.[32][40] In some developed countries, a trend to overuse cataract surgery has been noted, which may lead to disappointing results.[41]

Phacoemulsification is the most widely used cataract surgery in the developed world.[42][43] This procedure uses ultrasonic energy to emulsify the cataract lens. Phacoemulsification typically comprises six steps:

- Anaesthetic – The eye is numbed with either a subtenon injection around the eye (see: retrobulbar block) or topical anesthetic eye drops. The former also provides paralysis of the eye muscles.
- Corneal incision – Two cuts are made at the margin of the clear cornea to allow insertion of instruments into the eye.
- Capsulorhexis – A needle or small pair of forceps is used to create a

Slit lamp photo of posterior capsular opacification visible a few months after implantation of intraocular lens in eye, seen on retroillumination

circular hole in the capsule in which the lens sits.
- Phacoemulsification – A handheld ultrasonic probe is used to break up and emulsify the lens into liquid using the energy of ultrasound waves. The resulting 'emulsion' is sucked away.
- Irrigation and aspiration – The cortex, which is the soft outer layer of the cataract, is aspirated or sucked away. Fluid removed is continually replaced with a saline solution to prevent collapse of the structure of the anterior chamber (the front part of the eye).
- Lens insertion – A plastic, foldable lens is inserted into the capsular bag that formerly contained the natural lens. Some surgeons also inject an antibiotic into the eye to reduce the risk of infection. The final step is to inject salt water into the corneal wounds to cause the area to swell and seal the incision.

Extracapsular cataract extraction (ECCE) consists of removing the lens manually, but leaving the majority of the capsule intact.[44] The lens is expressed through a 10- to 12-mm incision which is closed with sutures at the end of surgery. ECCE is less frequently performed than phacoemulsification, but can be useful when dealing with very hard cataracts or other situations where emulsification is problematic. Manual small incision cataract surgery (MSICS) has evolved from ECCE. In MSICS, the lens is removed through a self-sealing scleral tunnel wound in the sclera which, ideally, is watertight and does not require suturing. Although "small", the incision is still markedly larger than the portal in phacoemulsion. This surgery is increasingly popular in the developing world where access to phacoemulsification is still limited.

Intracapsular cataract extraction (ICCE) is rarely performed.[45] The lens and surrounding capsule are removed in one piece through a large incision while pressure is applied to the vitreous membrane. The surgery has a high rate of complications.

## Prognosis [edit]

### Postoperative care [edit]

Slit lamp photo of anterior capsular opacification visible a few months after implantation of intraocular lens in eye, magnified view

The postoperative recovery period (after removing the cataract) is usually short. The patient is usually ambulatory on the day of surgery, but is advised to move cautiously and avoid straining or heavy lifting for about a month. The eye is usually patched on the day of surgery and use of an eye shield at night is often suggested for several days after surgery.[11]

In all types of surgery, the cataractous lens is removed and replaced with an artificial lens, known as an intraocular lens, which stays in the eye permanently. Intraocular lenses are usually monofocal, correcting for either distance or near vision. Multifocal lenses may be implanted to improve near and distance vision simultaneously, but these lenses may increase the chance of unsatisfactory vision.[12]

### Complications [edit]

Serious complications of cataract surgery include retinal detachment and endophthalmitis.[46] In both cases, patients notice a sudden decrease in vision. In endophthalmitis, patients often describe pain. Retinal detachment frequently presents with unilateral visual field defects, blurring of vision, flashes of light, or floating spots.

The risk of retinal detachment was estimated as about 0.4% within 5.5

A South African woman experiences newfound eyesight after a patch was removed after surgery to remove an eye cataract.

years, corresponding to a 2.3-fold risk increase compared to naturally expected incidence, with older studies reporting a substantially higher risk. The incidence is increasing over time in a somewhat linear manner, and the risk increase lasts for at least 20 years after the procedure. Particular risk factors are younger age, male sex, longer axial length, and complications during surgery. In the highest risk group of patients, the incidence of pseudophakic retinal detachment may be as high as 20%.[47][48]

The risk of endophthalmitis occurring after surgery is less than one in 1000.[49]

Corneal edema and cystoid macular edema are less serious but more common, and occur because of persistent swelling at the front of the eye in corneal edema or back of the eye in cystoid macular edema.[50] They are normally the result of excessive inflammation following surgery, and in both cases, patients may notice blurred, foggy vision. They normally improve with time and with application of anti-inflammatory drops. The risk of either occurring is around one in 100.

Posterior capsular opacification, also known as after-cataract, is a condition in which months or years after successful cataract surgery, vision deteriorates or problems with glare and light scattering recur, usually due to thickening of the back or posterior capsule surrounding the implanted lens, so-called 'posterior lens capsule opacification'. Growth of natural lens cells remaining after the natural lens was removed may be the cause, and the younger the patient, the greater the chance of this occurring. Management involves cutting a small, circular area in the posterior capsule with targeted beams of energy from a laser, called Nd:YAG laser capsulotomy, after the type of laser used. The laser can be aimed very accurately, and the small part of the capsule which is cut falls harmlessly to the bottom of the inside of the eye. This procedure leaves sufficient capsule to hold the lens in place, but removes enough to allow light to pass directly through to the retina. Serious side effects are rare.[51] Posterior capsular opacification is common and occurs following up to one in four operations, but these rates are decreasing following the introduction of modern intraocular lenses together with a better understanding of the causes.

Vitreous touch syndrome is a possible complication of intracapsular cataract extraction.[52]

## Epidemiology [edit]

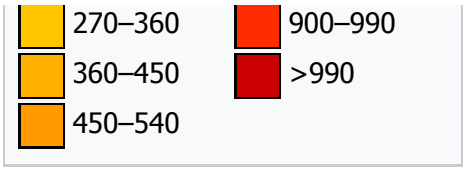
Age-related cataracts are responsible for 51% of world blindness, about 20 million people.[54] Globally, cataracts cause moderate to severe disability in 53.8 million (2004), 52.2 million of whom are in low and middle income countries.[55]

In many countries, surgical services are inadequate, and cataracts remain the leading cause of blindness.[54] Even where surgical services are available, low vision associated with cataracts may still be prevalent as a result of long waits for, and barriers to, surgery, such as cost, lack of information and transportation problems.

In the United States, age-related lens changes have been reported in 42% between the ages of 52 and 64,[56] 60% between the ages 65 and 74,[57] and 91% between the ages of 75 and 85.[56] Cataracts affect nearly 22 million Americans age 40 and older. By age 80, more than half of all Americans have cataracts. Direct medical costs for cataract treatment are estimated at $6.8 billion annually.[58]

Disability-adjusted life years for cataracts per 100,000 inhabitants in 2004:[53]

| | |
|---|---|
| no data | 540–630 |
| <90 | 630–720 |
| 90–180 | 720–810 |
| 180–270 | 810–900 |




In the eastern Mediterranean region, cataracts are responsible for over 51% of blindness. Access to eye care in many countries in this region is limited.[59]

## History [edit]

*See also: Cataract surgery § History*

The first references to cataracts and their treatment in Ancient Rome are found in 29 AD in *De Medicinae*, the work of the Latin encyclopedist Aulus Cornelius Celsus.[60] Archaeological evidence of eye surgery in the Roman era also exists.[61]

Other early accounts are found in Sanskrit. Cataract surgery was described by the Indian physician, Suśruta (about 200 AD).[62]

Muslim ophthalmologist Ammar ibn Ali, in his *Choice of Eye Diseases*, written *circa* 1000, wrote of his invention of a syringe and the technique of cataract extraction while experimenting with it on a patient.[63]

### Etymology [edit]

"Cataract" is derived from the Latin *cataracta*, meaning "waterfall", and from the Ancient Greek καταρράκτης (*katarrhaktēs*), "down-rushing",[64] from καταράσσω (*katarassō*) meaning "to dash down"[65] (from *kata-*, "down"; *arassein*, "to strike, dash").[66] As rapidly running water turns white, so the term may have been used metaphorically to describe the similar appearance of mature ocular opacities. In Latin, *cataracta* had the alternative meaning "portcullis"[67] and the name possibly passed through French to form the English meaning "eye disease" (early 15th century), on the notion of "obstruction".[68] Early Persian physicians called the term *nazul-i-ah*, or "descent of the water"—vulgarised into waterfall disease or cataract—believing such blindness to be caused by an outpouring of corrupt humour into the eye.[69]

## Research [edit]

N-Acetylcarnosine drops have been investigated as a medical treatment for cataracts. The drops are believed to work by reducing oxidation and glycation damage in the lens, particularly reducing crystallin crosslinking.[70][71] Some benefit has been shown in small manufacturer sponsored randomized controlled trials but further independent corroboration is still required.[72]

Femtosecond laser mode-locking, used during cataract surgery, was originally used to cut accurate and predictable flaps in LASIK surgery, and has been introduced to cataract surgery. The incision at the junction of the sclera and cornea and the hole in capsule during capsulorhexis, traditionally made with a handheld blade, needle, and forceps, are dependent on skill and experience of the surgeon. Sophisticated three-dimensional images of the eyes can be used to guide lasers to make these incisions. Nd:YAG laser can also then break up the cataract as in phacoemulsification.[73]

Stem cells have been used in a clinical trial for lens regeneration in twelve children under the age of two with cataracts present at birth.[74] The children were followed for six months, so it is unknown what the long-term results will be, and it is unknown if this procedure would work in adults.[74]

## References [edit]

1. ^ *a b c d e f* "Facts About Cataract". September 2009. Retrieved 24 May 2015.
2. ^ Allen D, Vasavada A (2006). "Cataract and surgery for cataract". *BMJ*. **333** (7559): 128–32.
(1): 135–44. doi:10.1001/archopht.1979.01020010069017. PMID 758890.
35. ^ Yanoff, Myron; Duker, Jay S. (2008).

doi:10.1136/bmj.333.7559.128. PMC 1502210. PMID 16840470.
3. ^ Gimbel, HV; Dardzhikova, AA (January 2011). "Consequences of waiting for cataract surgery.". *Current Opinion in Ophthalmology*. **22** (1): 28–30. doi:10.1097/icu.0b013e328341425d. PMID 21076306.
4. ^ "Visual impairment and blindness Fact Sheet N °282". August 2014. Retrieved 23 May 2015.
5. ^ *GLOBAL DATA ON VISUAL IMPAIRMENTS 2010* (PDF). WHO. 2012. p. 6.
6. ^ *a b c d* "Priority eye diseases". Retrieved 24 May 2015.
7. ^ Lamoureux, EL; Fenwick, E; Pesudovs, K; Tan, D (January 2011). "The impact of cataract surgery on quality of life.". *Current Opinion in Ophthalmology*. **22** (1): 19–27. doi:10.1097/icu.0b013e3283414284. PMID 21088580.
8. ^ *a b* Rao, GN; Khanna, R; Payal, A (January 2011). "The global burden of cataract.". *Current Opinion in Ophthalmology*. **22** (1): 4–9. doi:10.1097/icu.0b013e3283414fc8. PMID 21107260.
9. ^ Pandey, Suresh K. (2005). *Pediatric cataract surgery techniques, complications, and management*. Philadelphia: Lippincott Williams & Wilkins. p. 20. ISBN 9780781743075.
10. ^ "Posterior Supcapsular Cataract". *Digital Reference of Ophthalmology*. Edward S. Harkness Eye Institute, Department of Ophthalmology of Columbia University. 2003. Retrieved 2 April 2013.
11. ^ *a b* Emmett T. Cunningham; Paul Riordan-Eva. *Vaughan & Asbury's general ophthalmology.* (18th ed.). McGraw-Hill Medical. ISBN 978-0071634205.[*page needed*]
12. ^ *a b c* Duker, Jay S.; Myron Yanoff MD; Yanoff, Myron; Jay S. Duker MD (2009). *Ophthalmology*. St. Louis, Mo: Mosby/Elsevier. ISBN 0-323-04332-1.[*page needed*]
13. ^ Reddy SC (1999). "Electric cataract: a case report and review of the literature". *European Journal of Ophthalmology*. **9** (2): 134–8. PMID 10435427.
14. ^ Ram, Jagat; Gupta, Rohit (2016). "Petaloid Cataract". *New England Journal of Medicine*. **374** (18): e22. doi:10.1056/NEJMicm1507349.
15. ^ Sliney DH (1994). "UV radiation ocular exposure dosimetry". *Doc. Ophthalmol.* **88** (3-4): 243–54. doi:10.1007/bf01203678. PMID 7634993.
16. ^ Lipman RM, Tripathi BJ, Tripathi RC (1988). "Cataracts induced by microwave and ionizing radiation". *Surv. Ophthalmol.* **33** (3): 200–10. doi:10.1016/0039-6257(88)90088-4. PMID 3068822.
17. ^ Hejtmancik; Smaoui (2003), "Molecular Genetics of Cataract", *Genetics in Ophthalmology*, Karger Medical and Scientific Publishers, p. 77, ISBN 9783805575782
*Ophthalmology* (3rd ed.). Edinburgh: Mosby. p. 412. ISBN 978-0323057516.
36. ^ Neale RE, Purdie JL, Hirst LW, Green AC (November 2003). "Sun exposure as a risk factor for nuclear cataract". *Epidemiology*. **14** (6): 707–712. doi:10.1097/01.ede.0000086881.84657.98. PMID 14569187.
37. ^ Javitt JC, Wang F, West SK (1996). "Blindness Due to Cataract: Epidemiology and Prevention" (PDF). *Annual Review of Public Health*. **17**: 159–77. doi:10.1146/annurev.pu.17.050196.001111. PMID 8724222. Archived from the original (PDF) on April 6, 2008. Cited in *Five-Year Agenda for the National Eye Health Education Program (NEHEP)*, p. B-2; National Eye Institute, U.S. National Institutes of Health
38. ^ Barker FM (August 2010). "Dietary supplementation: effects on visual performance and occurrence of AMD and cataracts". *Curr. Med. Res. Opin.* **26** (8): 2011–23. doi:10.1185/03007995.2010.494549. PMID 20590393.
39. ^ Klein BE, Klein R, Lee KE, Grady LM (2006). "Statin Use and Incident Nuclear Cataract". *Journal of the American Medical Association*. **295** (23): 2752–8. doi:10.1001/jama.295.23.2752. PMID 16788130.
40. ^ Davis JC, McNeill H, Wasdell M, Chunick S, Bryan S (2012). "Focussing both eyes on health outcomes: Revisiting cataract surgery". *BMC Geriatrics*. **12**: 50. doi:10.1186/1471-2318-12-50. PMC 3497611. PMID 22943071.
41. ^ Black N, Browne J, van der Meulen J, Jamieson L, Copley L, Lewsey J (2008). "Is there overutilisation of cataract surgery in England?". *British Journal of Ophthalmology*. **93** (1): 13–17. doi:10.1136/bjo.2007.136150. PMID 19098042.
42. ^ Eunbi Kim; Sam Young Yoon; Young Joo Shin (2014), *Studies on the Cornea and Lens*, Springer, p. 4, ISBN 9781493919352
43. ^ Hasler, Pascal (2013), *Essential Principles of Phacoemulsification*, JP Medical Ltd, ISBN 9789962678618[*page needed*]
44. ^ Henderson, Bonnie (2007), "Extracapsular Cataract Extraction", *Essentials of Cataract Surgery*, SLACK, p. 187, ISBN 9781556428029
45. ^ Goes, Frank (2013), *The Eye in History*, JP Medical, p. 367, ISBN 9789350902745
46. ^ Naumann; Holbach; Kruse, eds. (2008), "Complications After Cataract Surgery", *Applied Pathology for Ophthalmic Microsurgeons*, Springer Science & Business, p. 247, ISBN 9783540683667
47. ^ Olsen T, Jeppesen P (2012). "The Incidence of Retinal Detachment After Cataract Surgery". *The Open Ophthalmology Journal*. **6**: 79–82. doi:10.2174/1874364101206010079. PMC 3447164. PMID 23002414.
48. ^ Herrmann W, Helbig H, Heimann H (2011). "Pseudophakie-Ablatio". *Klinische Monatsblätter für Augenheilkunde*. **228** (3): 195–200. doi:10.1055/s-

18. ^ Yanoff, Myron; Duker, Jay (2009), *Ophthalmology*, Elsevier Health Sciences, p. 507, ISBN 9780323043328
19. ^ Christen WG, Manson JE, Seddon JM, Glynn RJ, Buring JE, Rosner B, Hennekens CH (August 1992). "A prospective study of cigarette smoking and risk of cataract in men". *JAMA*. **268** (8): 989–93. doi:10.1001/jama.1992.03490080063025. PMID 1501324.
20. ^ Wang S, Wang JJ, Wong TY (2008). "Alcohol and eye diseases". *Surv. Ophthalmol*. **53** (5): 512–25. doi:10.1016/j.survophthal.2008.06.003. PMID 18929762.
21. ^ Wei, L.; Liang, G.; Cai, C.; Lv, J. (May 2016). "Association of vitamin C with the risk of age-related cataract: a meta-analysis". *Acta ophthalmologica*. **94** (3): e170–6. doi:10.1111/aos.12688. PMID 25735187.
22. ^ *a b* Mathew MC, Ervin AM, Tao J, Davis RM (Jun 13, 2012). "Antioxidant vitamin supplementation for preventing and slowing the progression of age-related cataract.". *Cochrane Database of Systematic Reviews*. **6**: CD004567. doi:10.1002/14651858.CD004567.pub2. PMC 4410744. PMID 22696344.
23. ^ Weatherall, M; Clay, J; James, K; Perrin, K; Shirtcliffe, P; Beasley, R (September 2009). "Dose-response relationship of inhaled corticosteroids and cataracts: a systematic review and meta-analysis.". *Respirology (Carlton, Vic.)*. **14** (7): 983–90. doi:10.1111/j.1440-1843.2009.01589.x. PMID 19740259.
24. ^ Uçok A, Gaebel W (February 2008). "Side effects of atypical antipsychotics: a brief overview.". *World Psychiatry*. **7** (1): 58–62. doi:10.1002/j.2051-5545.2008.tb00154.x. PMC 2327229. PMID 18458771.
25. ^ van den Brûle J, Degueldre F, Galand A (December 1998). "Cataractes incitées de médicament" [Drug-induced cataracts]. *Revue Médicale de Liège* (in French). **53** (12): 766–9. PMID 9927876.
26. ^ "Triperanol". *MeSH*. National Library of Medicine. Retrieved 2013-02-06.
27. ^ Almony, Arghavan; Holekamp, Nancy M; Bai, Fang; Shui, Ying-Bo; Beebe, David (2012). "Small-gauge vitrectomy does not protect against nuclear sclerotic cataract". *Retina*. **32** (3): 499–505. doi:10.1097/IAE.0b013e31822529cf. PMID 22392091.
28. ^ Kokavec, Jan; Min, San H; Tan, Mei H; Gilhotra, Jagjit S; Newland, Henry S; Durkin, Shane R; Grigg, John; Casson, Robert J (2016). "Biochemical analysis of the living human vitreous". *Clinical & Experimental Ophthalmology*. doi:10.1111/ceo.12732.
29. ^ Donati, Simone; Caprani, Simona Maria; Airaghi, Giulia; Vinciguerra, Riccardo; Bartalena, Luigi; Testa, Francesco; Mariotti, Cesare; Porta, Giovanni; Simonelli, Francesca; Azzolini, Claudio (2014). "Vitreous Substitutes: The Present and the Future". 0029-1246116. PMID 21374539.
49. ^ Behndig A, Montan P, Stenevi U, Kugelberg M, Lundström M (August 2011). "One million cataract surgeries: Swedish National Cataract Register 1992-2009". *J. Cataract Refract. Surg*. **37** (8): 1539–45. doi:10.1016/j.jcrs.2011.05.021. PMID 21782099.
50. ^ Gault, Janice; Vander, James (2015), *Ophthalmology Secrets in Color*, Elsevier Health Sciences, p. 221, ISBN 9780323378024
51. ^ "Posterior capsule opacification – why laser treatment is sometimes needed following cataract surgery". *rnib.org.uk*.
52. ^ Dr. Kushal Banerjee (2006). "A review and clinical evaluation of per-operative and post-operative complications in case of manual small incision cataract surgery and extracapsular cataract extraction with posterior chamber intra-ocular lens implantation" (PDF). Retrieved 1 June 2014.
53. ^ "Death and DALY estimates for 2004 by cause for WHO Member States" (xls). *World Health Organization*. who.int. 2004.
54. ^ *a b* "Priority eye diseases: Cataract". *Prevention of Blindness and Visual Impairment*. World Health Organization.
55. ^ *The global burden of disease : 2004 update*. Geneva, Switzerland: World Health Organization. 2008. p. 35. ISBN 9789241563710.
56. ^ *a b* Sperduto RD, Seigel D (Jul 1980). "Senile lens and senile macular changes in a population-based sample". *Am. J. Ophthalmol*. **90** (1): 86–91. doi:10.1016/s0002-9394(14)75081-0. PMID 7395962.
57. ^ Kahn HA, Leibowitz HM, Ganley JP, Kini MM, Colton T, Nickerson RS, Dawber TR (Jul 1977). "The Framingham Eye Study. I. Outline and major prevalence findings". *Am. J. Epidemiol*. **106** (1): 17–32. PMID 879158.
58. ^ "Eye Health Statistics at a Glance" (PDF). Archived from the original (PDF) on March 17, 2015.
59. ^ "Health Topics: Cataract". World Health Organization – Eastern Mediterranean Regional Office.
60. ^ Aulus Cornelius Celsus, G. F. Collier (transl.) (1831). *De Medicinae*. OL 5225311W.
61. ^ Elliott, Jane (February 9, 2008). "The Romans carried out cataract ops". *BBC News*.
62. ^ Suśruta, P. V. Sharma (trans.) (2000). *Suśruta-Saṃhitā*. **1**. Varanasi: Caukhambha Visvabharati. p. iv. OL 160267M.
63. ^ Finger, Stanley (1994). *Origins of Neuroscience: A History of Explorations Into Brain Function*. Oxford University Press. p. 70. ISBN 0-19-514694-8.
64. ^ καταρράκτης, Henry George Liddell, Robert Scott, *A Greek-English Lexicon*, on Perseus
65. ^ καταράσσω, Henry George Liddell, Robert Scott,*A Greek-English Lexicon*, on Perseus
66. ^ "cataract". *Word of the Day*. Dictionary.com. 29 October 2003.

*BioMed Research International*. **2014**: 351804. doi:10.1155/2014/351804. PMC 4024399. PMID 24877085.
30. ^ Shui, Ying-Bo; Holekamp, Nancy M.; Kramer, Benjamin C.; Crowley, Jan R.; Wilkins, Mark A.; Chu, Fred; Malone, Paula E.; Mangers, Shayna J.; Hou, Joshua H.; Siegfried, Carla J.; Beebe, David C. (2009). "The Gel State of the Vitreous and Ascorbate-Dependent Oxygen Consumption". *Archives of Ophthalmology*. **127** (4): 475–82. doi:10.1001/archophthalmol.2008.621. PMC 2683478. PMID 19365028.
31. ^ Jalil, A; Steeples, L; Subramani, S; Bindra, M S; Dhawahir-Scala, F; Patton, N (2014). "Microincision cataract surgery combined with vitrectomy: a case series". *Eye*. **28** (4): 386–9. doi:10.1038/eye.2013.300. PMC 3983625. PMID 24406418.
32. ^ *a b c d* Bollinger KE, Langston RH (2008). "What can patients expect from cataract surgery?". *Cleveland Clinic Journal of Medicine*. **75** (3): 193–196, 199–196. doi:10.3949/ccjm.75.3.193. PMID 18383928.
33. ^ Spencer RW, Andelman SY (1965). "Steroid cataracts. Posterior subcapsular cataract formation in rheumatoid arthritis patients on long term steroid therapy". *Arch. Ophthalmol*. **74**: 38–41. doi:10.1001/archopht.1965.00970040040009. PMID 14303339.
34. ^ Greiner JV, Chylack LT (1979). "Posterior subcapsular cataracts: histopathologic study of steroid-associated cataracts". *Arch. Ophthalmol*. **97**
"cataract". *Oxford Dictionaries*. Oxford University Press.
67. ^ cataracta, Charlton T. Lewis, Charles Short, *A Latin Dictionary*, on Perseus
68. ^ Online Etymology Dictionary, etymonline.com
69. ^ Mistaken Science — Topic Powered by eve community, Wordcraft Forums, wordcraft.infopop.cc
70. ^ Williams DL, Munday P (2006). "The effect of a topical antioxidant formulation including N-acetyl carnosine on canine cataract: a preliminary study". *Vet Ophthalmol*. **9** (5): 311–6. doi:10.1111/j.1463-5224.2006.00492.x. PMID 16939459.
71. ^ Guo Y, Yan H (2006). "Preventive effect of carnosine on cataract development". *Yan Ke Xue Bao*. **22** (2): 85–8. PMID 17162883.
72. ^ Toh T, Morton J, Coxon J, Elder MJ (2007). "Medical treatment of cataract". *Clin. Experiment. Ophthalmol*. **35** (7): 664–71. doi:10.1111/j.1442-9071.2007.01559.x. PMID 17894689.
73. ^ Friedman NJ, Palanker DV, Schuele G, Andersen D, Marcellino G, Seibel BS, Batlle J, Feliz R, Talamo JH, Blumenkranz MS, Culbertson WW (July 2011). "Femtosecond laser capsulotomy". *J. Cataract Refract. Surg*. **37** (7): 1189–98. doi:10.1016/j.jcrs.2011.04.022. PMID 21700099. as PDF The authors declare a financial interest in a company producing femtosecond laser equipment.
74. ^ *a b* "Stem cells used to repair children's eyes after cataracts". *NHS*. March 10, 2016. Retrieved 11 March 2016.

## External links [edit]

- Cataract at DMOZ
- Pictures of different types of cataracts
- Video describing history and science of seeing cataracts in your own eye on YouTube

| v · t · e | Diseases of the human eye (H00–H59 · 360–379) · | |
|---|---|---|
| **Adnexa** | | |
| **Eyelid** | **Inflammation** | Stye · Chalazion · Blepharitis · |
| | Entropion · Ectropion · Lagophthalmos · Blepharochalasis · Ptosis · Blepharophimosis · Xanthelasma · | |
| | **Eyelash** | Trichiasis · Madarosis · |
| **Lacrimal apparatus** | Dacryoadenitis · Epiphora · Dacryocystitis · Xerophthalmia · | |
| **Orbit** | Exophthalmos · Enophthalmos · Orbital cellulitis · Orbital lymphoma · Periorbital cellulitis · | |
| **Conjunctiva** | Conjunctivitis (allergic · · Pterygium · Pinguecula · Subconjunctival hemorrhage · | |
| **Globe** | | |
| | **Sclera** | Scleritis · Episcleritis · |

| | | |
|---|---|---|
| **Fibrous tunic** | **Cornea** | Keratitis (herpetic · acanthamoebic · fungal · · Corneal ulcer · Photokeratitis · Thygeson's superficial punctate keratopathy · Corneal dystrophy (Fuchs' · Meesmann · · Corneal ectasia (Keratoconus · Pellucid marginal degeneration · Keratoglobus · Terrien's marginal degeneration · Post-LASIK ectasia · · Keratoconjunctivitis (sicca · · Corneal neovascularization · Kayser–Fleischer ring · Haab's striae · Arcus senilis · Band keratopathy · |
| **Vascular tunic** | **Iris · Ciliary body ·** | Uveitis · Intermediate uveitis · Hyphema · Rubeosis iridis · Persistent pupillary membrane · Iridodialysis · Synechia · |
| | **Choroid** | Choroideremia · Choroiditis (Chorioretinitis · · |
| **Lens** | **Cataract** (Congenital cataract · Childhood cataract · · Aphakia · Ectopia lentis · | |
| **Retina** | Retinitis (Chorioretinitis · Cytomegalovirus retinitis · · Retinal detachment · Retinoschisis · Ocular ischemic syndrome / Central retinal vein occlusion · Central retinal artery occlusion · Retinopathy (diabetic · hypertensive · Purtscher's · of prematurity · Bietti's crystalline dystrophy · Coats' disease · · Macular degeneration · Retinitis pigmentosa · Retinal haemorrhage · Central serous retinopathy · Macular edema · Epiretinal membrane (Macular pucker) · Vitelliform macular dystrophy · Leber's congenital amaurosis · Birdshot chorioretinopathy · | |
| **Other** | Glaucoma / Ocular hypertension / Primary juvenile glaucoma · Floater · Leber's hereditary optic neuropathy · Red eye · Globe rupture · Keratomycosis · Phthisis bulbi · Persistent fetal vasculature / Persistent hyperplastic primary vitreous · Persistent tunica vasculosa lentis · Familial exudative vitreoretinopathy · | |
| **Pathways** | | |
| **Optic nerve Optic disc** | Optic neuritis (optic papillitis · · Papilledema (Foster Kennedy syndrome · · Optic atrophy · Optic disc drusen · | |
| | **Optic neuropathy** | Ischemic (anterior (AION) · posterior (PION) · · Kjer's · Leber's hereditary · Toxic and nutritional · |
| **Strabismus Extraocular muscles Binocular vision Accommodation** | **Paralytic strabismus** | Ophthalmoparesis · Chronic progressive external ophthalmoplegia · Kearns–Sayre syndrome · |
| | **palsies** | Oculomotor (III) · Fourth-nerve (IV) · Sixth-nerve (VI) · |
| | **Other strabismus** | Esotropia / Exotropia · Hypertropia · Heterophoria (Esophoria · Exophoria · · Cyclotropia · Brown's syndrome · Duane syndrome · |
| | **Other binocular** | Conjugate gaze palsy · Convergence insufficiency · Internuclear ophthalmoplegia · One and a half syndrome · |
| **Refraction** | Refractive error (Hyperopia · Myopia · · Astigmatism · Anisometropia / Aniseikonia · Presbyopia · | |
| **Vision disorders Blindness** | Amblyopia · Leber's congenital amaurosis · Diplopia · Scotoma · Color blindness (Achromatopsia · Dichromacy · Monochromacy · · Nyctalopia (Oguchi disease · · Blindness / Vision loss / Visual impairment · | |
| | **Anopsia** | Hemianopsia (binasal · bitemporal · homonymous · · Quadrantanopia · |
| | **subjective** | Asthenopia · Hemeralopia · Photophobia · Scintillating scotoma · |
| **Pupil** | Anisocoria · Argyll Robertson pupil · Marcus Gunn pupil · Adie syndrome · Miosis · Mydriasis · Cycloplegia · Parinaud's syndrome · | |

| | |
|---|---|
| **Other** | Nystagmus · Childhood blindness · |
| **Infections** | |
| | Trachoma · Onchocerciasis · |
| **Authority control** | LCCN: sh85020947 · GND: 4158095-3 · BNF: cb11953097t (data) · NDL: 00562858 · BNE: XX526157 · |

Categories: Ophthalmology | Eye | Vision | Aging-associated diseases | Blindness | Disorders of lens | Diseases of the eye and adnexa




# Color blindness

From Wikipedia, the free encyclopedia

(Redirected from Color blind)

*"Colorblind" redirects here. For color blindness in other species, see Color vision. For other uses, see Colorblind (disambiguation).*

**Color blindness**, also known as **color vision deficiency**, is the decreased ability to see color or differences in color.[2] Color blindness can make some educational activities difficult. Buying fruit, picking clothing, and reading traffic lights can also be more challenging. Problems, however, are generally minor and most people adapt. People with total color blindness may also have decreased visual acuity and be uncomfortable in bright environments.[2]

The most common cause of color blindness is a fault in the development of one or more of the three sets of color sensing cones in the eye. Males are more likely to be color blind than females as the genes responsible for the most common forms of color blindness are on the X chromosome. As females have two X chromosomes, a defect in one is typically compensated for by the other, while males only have one X chromosome. Color blindness can also result from physical or chemical damage to the eye, optic nerve, or parts of the brain. Diagnosis is typically with the Ishihara color test; however a number of other testing methods also exist.[2]

There is no cure for color blindness.[2] Diagnosis may allow a person's teacher to change their method of teaching to accommodate the decreased ability to recognize color.[1] Special lenses may help people with red–green color blindness when under bright conditions. There are also mobile apps that can help people identify colors.[2]

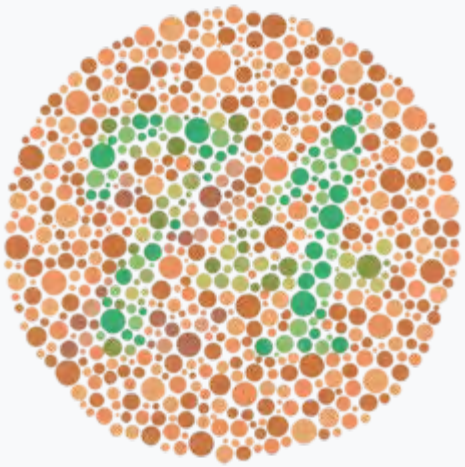
Red–green color blindness is the most common form, followed by blue–yellow color blindness and total color blindness.[2] Red–green color blindness affects up to 8% of males and 0.5% of females of Northern European descent. The ability to see color also decreases in old age.[2] Being color blind may make people ineligible for certain jobs in certain countries. This may include pilot, train driver, and armed forces. The effect of color blindness on artistic ability, however, is controversial. The ability to draw appears to be unchanged and a number of famous artists are believed to have been color blind.[1]

Contents



**Color blindness**

**Synonyms** ... vision[1]



Example of an Ishihara color test plate. Depending on the computer displays, people with normal vision should see the number "74". Many people who are color blind see it as "21", and those with total color blindness may not see any numbers.

**Classification and external resources**

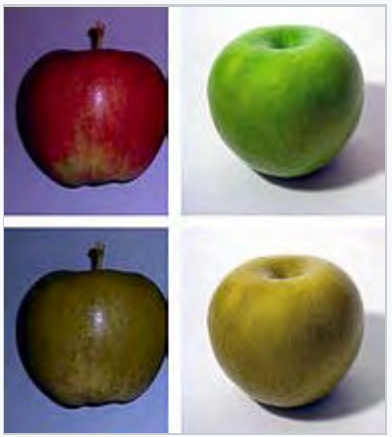
| | |
|---|---|
| **Specialty** | Ophthalmology |
| **ICD-10** | H53.5 |
| **ICD-9-CM** | 368.5 |
| **DiseasesDB** | 2999 |
| **MedlinePlus** | 001002 |
| **MeSH** | D003117 |

[edit on Wikidata]

## Signs and symptoms [edit]

In almost all cases, color blind people retain blue–yellow discrimination, and most color-blind individuals are anomalous trichromats rather than complete dichromats. In practice, this means that they often retain a limited discrimination along the red–green axis of color space, although their ability to separate colors in this dimension is severely reduced. Color blindness very rarely means complete monochromatism.[*citation needed*]

Dichromats often confuse red and green items. For example, they may find it difficult to distinguish a Braeburn apple from a Granny Smith and in some cases, the red and green of traffic lights without other clues—for example, shape or position. The vision of dichromats may also be compared to images produced by a color printer that has run out of the ink in one of its three color cartridges (for protanopes and deuteranopes, the red cartridge, and for tritanopes, the yellow cartridge). Dichromats tend to learn to use texture and shape clues and so are often able to penetrate camouflage that has been designed to deceive individuals with color-normal vision.[3]



Simulation of the normal (above) and dichromatic (below) perception of red and green apples[*citation needed*]

Colors of traffic lights are confusing to some dichromats, as there is insufficient apparent difference between the red/amber traffic lights, and that of sodium street lamps; also, the green can be confused with a grubby white lamp. This is a risk factor on high-speed undulating roads where angular cues cannot be used. British Rail color lamp signals use more easily identifiable colors: The red is blood red, the amber is yellow and the green is a bluish color. Most British road traffic lights are mounted vertically on a black rectangle with a white border (forming a "sighting board") and so dichromats can look for the position of the light within the rectangle—top,

Horizontal traffic light in Halifax, Nova Scotia, Canada

middle or bottom. In the eastern provinces of Canada horizontally mounted traffic lights are generally differentiated by shape to facilitate identification for those with color blindness. In the United States, this is not done by shape but by position, as the red light is always on the left if the light is horizontal, or on top if the light is vertical. However, a single flashing light (red indicating cars must stop, yellow for caution/yield) is indistinguishable, but these are rare.



Normal sight

Deuteranopia sight

Tritanopia sight

Monochromacy sight

## Causes [edit]

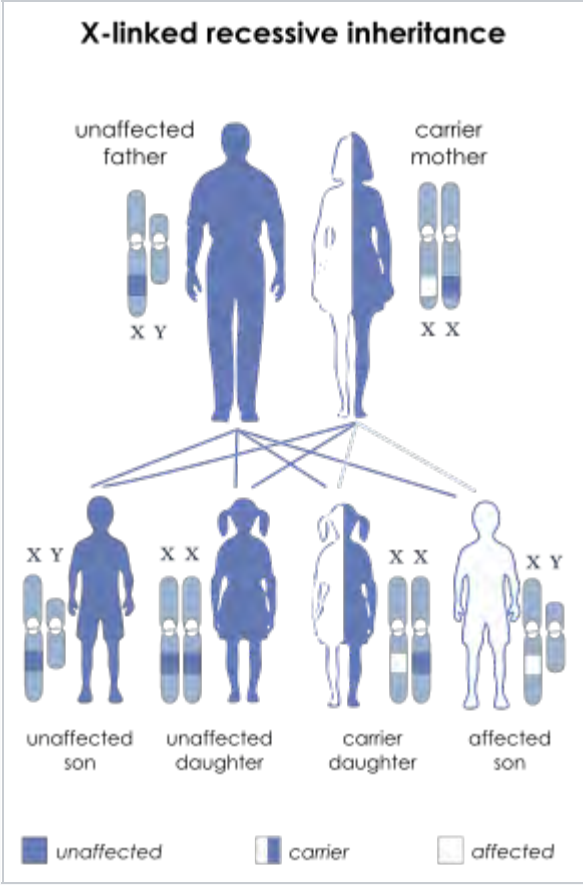
Color vision deficiencies can be classified as acquired or inherited.

- Acquired: Diseases, drugs (e.g., Plaquenil), and chemicals may cause color blindness.[4][5]
- Inherited: There are three types of inherited or congenital color vision deficiencies: monochromacy, dichromacy, and anomalous trichromacy.
  - Monochromacy, also known as "total color blindness", is the lack of ability to distinguish colors (and thus the person views everything as if it were on a black and white television); caused by cone defect or absence. Monochromacy occurs when two or all three of the cone pigments are missing and color and lightness vision is reduced to one dimension.
    - Rod monochromacy (achromatopsia) is an exceedingly rare, nonprogressive inability to distinguish any colors as a result of absent or nonfunctioning retinal cones. It is associated with light sensitivity (photophobia), involuntary eye oscillations (nystagmus), and poor vision.
    - Cone monochromacy is a rare total color blindness that is accompanied by relatively normal vision, electroretinogram, and electrooculogram. Cone monochromacy can also be a result of having more than one type of dichromatic color blindness. People who have, for instance, both protanopia and tritanopia are considered to have cone monochromacy. Since cone monochromacy is the lack of/damage of more than one cone in retinal environment, having two types of dichromacy would be an equivalent.
  - Dichromacy is a moderately severe color vision defect in which one of the three basic color mechanisms is absent or not functioning. It is hereditary and, in the case of protanopia or deuteranopia, sex-linked, affecting predominantly males. Dichromacy occurs when one of the cone pigments is missing and color is reduced to two dimensions. Dichromacy conditions are labeled based on whether the "first" (Greek: *prot-*, referring to the red photoreceptors), "second" (*deuter-*, the green), or "third" (*trit-*, the blue) photoreceptors are affected.
    - Protanopia is a severe type of color vision deficiency caused by the complete absence of red retinal photoreceptors. Protans have difficulties distinguishing between blue and green colors and also between red and green colors. It is a form of dichromatism in which the subject can only perceive light wavelengths from 400 to 650 nm, instead of the usual 700 nm. Pure reds cannot be seen, instead appearing black; purple colors cannot be distinguished from blues; more orange-tinted reds may appear as very dim yellows, and all orange–yellow–green shades of too long a wavelength to stimulate the blue receptors appear as a similar yellow hue. It is hereditary, sex-linked, and present in 1% of males.
    - Deuteranopia is a type of color vision deficiency where the green photoreceptors are absent. It affects hue discrimination in the same way as protanopia, but without the dimming effect. Like protanopia, it is hereditary, sex-linked, and found in about 1% of the male population.[6]
    - Tritanopia is a very rare color vision disturbance in which there are only two cone pigments present and a total absence of blue retinal receptors. Blues appear greenish, yellows and oranges appear pinkish, and purple colors appear deep red. It is related to chromosome 7. Unlike protanopia and deuteranopia, tritanopia and tritanomaly are not sex-linked traits and can be acquired rather than inherited and can be reversed in some cases.
  - Anomalous trichromacy is a common type of inherited color vision deficiency, occurring when one of the three cone pigments is altered in its spectral sensitivity.
    - Protanomaly is a mild color vision defect in which an altered spectral sensitivity of red retinal receptors (closer to green receptor response) results in poor red–green hue discrimination. It is hereditary, sex-linked, and present in 1% of males. The difference with protanopia is that in this case the L-cone is present but malfunctioning, whereas in the earlier the L-cone is completely missing.[7]
    - Deuteranomaly, caused by a similar shift in the green retinal receptors, is by far the most common type of color vision deficiency, mildly affecting red–green hue discrimination in 5% of European males. It is hereditary and sex-linked. The difference with deuteranopia is that in this

case the green sensitive cones are not missing but malfunctioning.[8]
- Tritanomaly is a rare, hereditary color vision deficiency affecting blue–green and yellow–red/pink hue discrimination. It is related to chromosome "7".[9] The difference is that the S-cone is malfunctioning but not missing.[10]

## Genetics [edit]

Color blindness is typically inherited. It is most commonly inherited from mutations on the X chromosome but the mapping of the human genome has shown there are many causative mutations—mutations capable of causing color blindness originate from at least 19 different chromosomes and 56 different genes (as shown online at the Online Mendelian Inheritance in Man (OMIM)). Two of the most common inherited forms of color blindness are protanopia and deuteranopia.[11] One of the common color vision defects is red–green deficiency which is present in about 8 percent of males and 0.5 percent of females of Northern European ancestry.[12]



X-linked recessive inheritance

Some of the inherited diseases known to cause color blindness are:

- cone dystrophy
- cone-rod dystrophy
- achromatopsia (a.k.a. rod monochromatism, stationary cone dystrophy or cone dysfunction syndrome)
- blue cone monochromatism (a.k.a. blue cone monochromacy or X-linked achromatopsia)
- Leber's congenital amaurosis
- retinitis pigmentosa (initially affects rods but can later progress to cones and therefore color blindness).

Inherited color blindness can be congenital (from birth), or it can commence in childhood or adulthood. Depending on the mutation, it can be stationary, that is, remain the same throughout a person's lifetime, or progressive. As progressive phenotypes involve deterioration of the retina and other parts of the eye, certain forms of color blindness can progress to legal blindness, i.e., an acuity of 6/60 (20/200) or worse, and often leave a person with complete blindness.

Color blindness always pertains to the cone photoreceptors in retinas, as the cones are capable of detecting the color frequencies of light.

About 8 percent of males, and 0.5 percent of females, are color blind in some way or another, whether it is one color, a color combination, or another mutation.[13] The reason males are at a greater risk of inheriting an X linked mutation is that males only have one X chromosome (XY, with the Y chromosome carrying altogether different genes than the X chromosome), and females have two (XX); if a woman inherits a normal X chromosome in addition to the one that carries the mutation, she will not display the mutation. Men do not have a second X chromosome to override the chromosome that carries the mutation. If 5% of variants of a given gene are defective, the probability of a single copy being defective is 5%, but the probability that two copies are both defective is $0.05 \times 0.05 = 0.0025$, or just 0.25%.

## Other causes [edit]

Other causes of color blindness include brain or retinal damage caused by shaken baby syndrome, accidents and other trauma which produce swelling of the brain in the occipital lobe, and damage to the retina caused by exposure to ultraviolet light (10–300 nm). Damage often presents itself later on in life.

Color blindness may also present itself in the spectrum of degenerative diseases of the eye, such as age-related macular degeneration, and as part of the retinal damage caused by diabetes. Another factor that may affect color blindness includes a deficiency in Vitamin A.[14]

## Types [edit]

Based on clinical appearance, color blindness may be described as total or partial. Total color blindness is much less common than partial color blindness.[15] There are two major types of color blindness: those who have difficulty distinguishing between red and green, and who have difficulty distinguishing between blue and yellow.[16][17]

- Total color blindness
- Partial color blindness
  - Red–green
    - Dichromacy (protanopia and deuteranopia)
    - Anomalous trichromacy (protanomaly and deuteranomaly)
  - Blue–yellow
    - Dichromacy (tritanopia)
    - Anomalous trichromacy (tritanomaly)
    - Blue–green trichromacy (tritanomaly)

Immunofluorescent imaging is a way to determine red–green color coding. Conventional color coding is difficult for individuals with red–green color blindness (protanopia or deuteranopia) to discriminate. Replacing red with magenta or green with turquoise improves visibility for such individuals.[18]

The different kinds of inherited color blindness result from partial or complete loss of function of one or more of the different cone systems. When one cone system is compromised, dichromacy results. The most frequent forms of human color blindness result from problems with either the middle or long wavelength sensitive cone systems, and involve difficulties in discriminating reds, yellows, and greens from one another. They are collectively referred to as "red–green color blindness", though the term is an over-simplification and is somewhat misleading. Other forms of color blindness are much more rare. They include problems in discriminating blues from greens and yellows from reds/pinks, and the rarest forms of all, complete color blindness or *monochromacy*, where one cannot distinguish any color from grey, as in a black-and-white movie or photograph.

Protanopes, deuteranopes, and tritanopes are dichromats; that is, they can match any color they see with some mixture of just two primary colors (whereas normally humans are trichromats and require three primary colors). These individuals normally know they have a color vision problem and it can affect their lives on a daily basis. Two percent of the male population exhibit severe difficulties distinguishing between red, orange, yellow, and green. A certain pair of colors, that seem very different to a normal viewer, appear to be the same color (or different shades of same color) for such a dichromat. The terms protanopia, deuteranopia, and tritanopia come from Greek and literally mean "inability to see (*anopia*) with the first (*prot-*), second (*deuter-*), or third (*trit-*) [cone]", respectively.

Anomalous trichromacy is the least serious type of color deficiency.[19] People with protanomaly, deuteranomaly, or tritanomaly are trichromats, but the color matches they make differ from the normal. They are called anomalous trichromats. In order to match a given spectral yellow light, protanomalous observers need more red light in a red/green mixture than a normal observer, and deuteranomalous observers need more green. From a practical standpoint though, many protanomalous and deuteranomalous people have very little difficulty carrying out tasks that require normal color vision. Some may not even be aware that their color perception is in any way different from normal.

Protanomaly and deuteranomaly can be diagnosed using an instrument called an anomaloscope, which mixes spectral red and green lights in variable proportions, for comparison with a fixed spectral yellow. If this is done in front of a large audience of males, as the proportion of red is increased from a low value, first a small proportion of the audience will declare a match, while most will see the mixed light as greenish; these are the deuteranomalous observers. Next, as more red is added the majority will say that a match

has been achieved. Finally, as yet more red is added, the remaining, protanomalous, observers will declare a match at a point where normal observers will see the mixed light as definitely reddish.[*citation needed*]

## Red–green color blindness [edit]

Protanopia, deuteranopia, protanomaly, and deuteranomaly are commonly inherited forms of red–green color blindness which affect a substantial portion of the human population. Those affected have difficulty with discriminating red and green hues due to the absence or mutation of the red or green retinal photoreceptors. This deficiency does not cause difficulty discerning red from green.[11][20] It is sex-linked: genetic red–green color blindness affects males much more often than females, because the genes for the red and green color receptors are located on the X chromosome, of which males have only one and females have two. Females (46, XX) are red–green color blind only if *both* their X chromosomes are defective with a similar deficiency, whereas males (46, XY) are color blind if their single X chromosome is defective.[*citation needed*]

The gene for red–green color blindness is transmitted from a color blind male to all his daughters who are heterozygote carriers and are usually unaffected. In turn, a carrier woman has a fifty percent chance of passing on a mutated X chromosome region to each of her male offspring. The sons of an affected male will not inherit the trait from him, since they receive his Y chromosome and not his (defective) X chromosome. Should an affected male have children with a carrier or colorblind woman, their daughters may be colorblind by inheriting an affected X chromosome from each parent.[*citation needed*]

Because one X chromosome is inactivated at random in each cell during a woman's development, it is possible for her to have four different cone types, as when a carrier of protanomaly has a child with a deuteranomalic man. Denoting the normal vision alleles by P and D and the anomalous by p and d, the carrier is PD pD and the man is Pd. The daughter is either PD Pd or pD Pd. Suppose she is pD Pd. Each cell in her body expresses either her mother's chromosome pD or her father's Pd. Thus her red–green sensing will involve both the normal and the anomalous pigments for both colors. Such females are tetrachromats, since they require a mixture of four spectral lights to match an arbitrary light.[*citation needed*]

Red–green color blindness can be caused by ethambutol.[21]

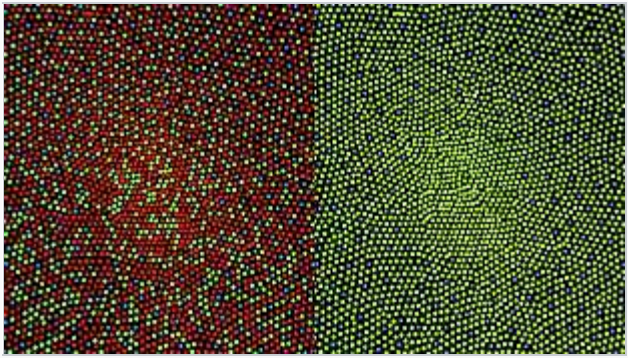


Illustration of the distribution of cone cells in the fovea of an individual with normal color vision (left), and a color blind (protanopic) retina. The center of the fovea holds very few blue-sensitive cones.

- **Protanopia** (1% of males): Lacking the red cones for long-wavelength sensitive retinal cones, those with this condition are unable to distinguish between colors in the green–yellow–red section of the spectrum. They have a neutral point at a cyan-like wavelength around 492 nm (see spectral color for comparison) – that is, they cannot discriminate light of this wavelength from white. For a protanope, the brightness of red, orange, and yellow are much reduced compared to normal. This dimming can be so pronounced that reds may be confused with black or dark gray, and red traffic lights may appear to be extinguished. They may learn to distinguish reds from yellows primarily on the basis of their apparent brightness or lightness, not on any perceptible hue difference. Violet, lavender, and purple are indistinguishable from various shades of blue because their reddish components are so dimmed as to be invisible. For example, pink flowers, reflecting both red light and blue light, may appear just blue to the protanope. A very few people have been found who have one normal eye and one protanopic eye. These *unilateral dichromats* report that with only their protanopic eye open, they see wavelengths shorter than neutral point as blue and those longer than it as yellow. This is a rare form of color blindness.

- **Deuteranopia** (1% of males): Lacking the green cones for medium-wavelength cones, those affected

are again unable to distinguish between colors in the green–yellow–red section of the spectrum. Their neutral point is at a slightly longer wavelength, 498 nm, a more greenish hue of cyan. A deuteranope suffers the same hue discrimination problems as protanopes, but without the abnormal dimming. Purple colors are not perceived as something opposite to spectral colors; all these appear similarly. This form of colorblindness is also known as *Daltonism* after John Dalton (his diagnosis was confirmed as deuteranopia in 1995, some 150 years after his death, by DNA analysis of his preserved eyeball). Equivalent forms for daltonism in Romanic languages such as *daltonismo* (Spanish, Portuguese and Italian), *daltonisme* (French), *daltonism* (Romanian) are still used to describe color blindess in a broad sense or deuteranopia in a more restricted sense. Deuteranopic unilateral dichromats report that with only their deuteranopic eye open, they see wavelengths shorter than neutral point as blue and longer than it as yellow.[22]

- **Protanomaly** (1% of males, 0.01% of females):[23] Having a mutated form of the long-wavelength (red) pigment, whose peak sensitivity is at a shorter wavelength than in the normal retina, protanomalous individuals are less sensitive to red light than normal. This means that they are less able to discriminate colors, and they do not see mixed lights as having the same colors as normal observers. They also suffer from a darkening of the red end of the spectrum. This causes reds to reduce in intensity to the point where they can be mistaken for black. Protanomaly is a fairly rare form of color blindness, making up about 1% of the male population. Both protanomaly and deuteranomaly are carried on the X chromosome.

- **Deuteranomaly** (most common—6% of males, 0.4% of females):[23] These individuals have a mutated form of the medium-wavelength (green) pigment. The medium-wavelength pigment is shifted towards the red end of the spectrum resulting in a reduction in sensitivity to the green area of the spectrum. Unlike protanomaly the intensity of colors is unchanged. The deuteranomalous person is considered "green weak". For example, in the evening, dark green cars appear to be black to Deuteranomalous people. Similar to the protanomates, deuteranomates are poor at discriminating small differences in hues in the red, orange, yellow, green region of the spectrum. They make errors in the naming of hues in this region because the hues appear somewhat shifted towards green. One very important difference between deuteranomalous individuals and protanomalous individuals is deuteranomalous individuals do *not* have the loss of "brightness" problem.

## Blue–yellow color blindness [edit]

Those with tritanopia and tritanomaly have difficulty discriminating between bluish and greenish hues, as well as yellowish and reddish hues.

Color blindness involving the inactivation of the short-wavelength sensitive cone system (whose absorption spectrum peaks in the bluish-violet) is called **tritanopia** or, loosely, blue–yellow color blindness. The tritanope's neutral point occurs near a yellowish 570 nm; green is perceived at shorter wavelengths and red at longer wavelengths.[24] Mutation of the short-wavelength sensitive cones is called **tritanomaly**. Tritanopia is equally distributed among males and females. Jeremy H. Nathans (with the Howard Hughes Medical Institute) demonstrated that the gene coding for the blue receptor lies on chromosome 7, which is shared equally by males and females. Therefore, it is not sex-linked. This gene does not have any neighbor whose DNA sequence is similar. Blue color blindness is caused by a simple mutation in this gene.

- **Tritanopia** (less than 1% of males and females): Lacking the short-wavelength cones, those affected see short-wavelength colors (blue, indigo and a spectral violet) greenish and drastically dimmed, some of these colors even as black. Yellow is indistinguishable from pink, and purple colors are perceived as various shades of red. This form of color blindness is not sex-linked.

- **Tritanomaly** (equally rare for males and females [0.01% for both]):[23] Having a mutated form of the short-wavelength (blue) pigment. The short-wavelength pigment is shifted towards the green area of the spectrum. This is the rarest form of anomalous trichromacy color blindness. Unlike the other anomalous trichromacy color deficiencies, the mutation for this color blindness is carried on chromosome

7. Therefore, it is equally prevalent in both male & female populations. The OMIM gene code for this mutation is 304000 "Colorblindness, Partial Tritanomaly".[25]

### Total color blindness [edit]

Total color blindness is defined as the inability to see color. Although the term may refer to acquired disorders such as cerebral achromatopsia also known as color agnosia, it typically refers to congenital color vision disorders (i.e. more frequently rod monochromacy and less frequently cone monochromacy).[26][27]

In cerebral achromatopsia, a person cannot perceive colors even though the eyes are capable of distinguishing them. Some sources do not consider these to be true color blindness, because the failure is of perception, not of vision. They are forms of visual agnosia.[27]

Monochromacy is the condition of possessing only a single channel for conveying information about color. Monochromats possess a complete inability to distinguish any colors and perceive only variations in brightness. It occurs in two primary forms:

1. Rod monochromacy, frequently called *achromatopsia*, where the retina contains no cone cells, so that in addition to the absence of color discrimination, vision in lights of normal intensity is difficult. While normally rare, achromatopsia is very common on the island of Pingelap, a part of the Pohnpei state, Federated States of Micronesia, where it is called *maskun*: about 10% of the population there has it, and 30% are unaffected carriers. The island was devastated by a storm in the 18th century (an example of a genetic bottleneck) and one of the few male survivors carried a gene for achromatopsia. The population grew to several thousand before foreign troops introduced diseases to the island in the 1940s.
2. Cone monochromacy is the condition of having both rods and cones, but only a single kind of cone. A cone monochromat can have good pattern vision at normal daylight levels, but will not be able to distinguish hues. Blue cone monochromacy (X chromosome) is caused by lack of functionality of L and M cones (red and green). It is encoded at the same place as red–green color blindness on the X chromosome. Peak spectral sensitivities are in the blue region of the visible spectrum (near 440 nm). People with this condition generally show nystagmus ("jiggling eyes"), photophobia (light sensitivity), reduced visual acuity, and myopia (nearsightedness).[28] Visual acuity usually falls to the 20/50 to 20/400 range.

## Mechanism [edit]

*See also: Trichromatic color vision*

The typical human retina contains two kinds of light cells: the rod cells (active in low light) and the cone cells (active in normal daylight). Normally, there are three kinds of cone cells, each containing a different pigment, which are activated when the pigments absorb light. The spectral sensitivities of the cones differ; one is most sensitive to short wavelengths, one to medium wavelengths, and the third to medium-to-long wavelengths within the visible spectrum, with their peak sensitivities in the blue, green, and yellow-green regions of the spectrum, respectively. The absorption spectra of the three systems overlap, and combine to cover the visible spectrum. These receptors are known as short (S), medium (M),and long (L) wavelength cones, but are also often referred to as blue, green, and red cones, although this terminology is inaccurate.[29]

The receptors are each responsive to a wide range of wavelengths. For example, the long wavelength "red" receptor has its peak sensitivity in the yellow-green, some way from the red end (longest wavelength) of the visible spectrum. The sensitivity of normal color vision actually depends on the overlap between the absorption ranges of the three systems: different colors are recognized when the different types of cone are stimulated to different degrees. Red light, for example, stimulates the long wavelength cones much more than either of the others, and reducing the wavelength causes the other two cone systems to be increasingly stimulated, causing a gradual change in hue.

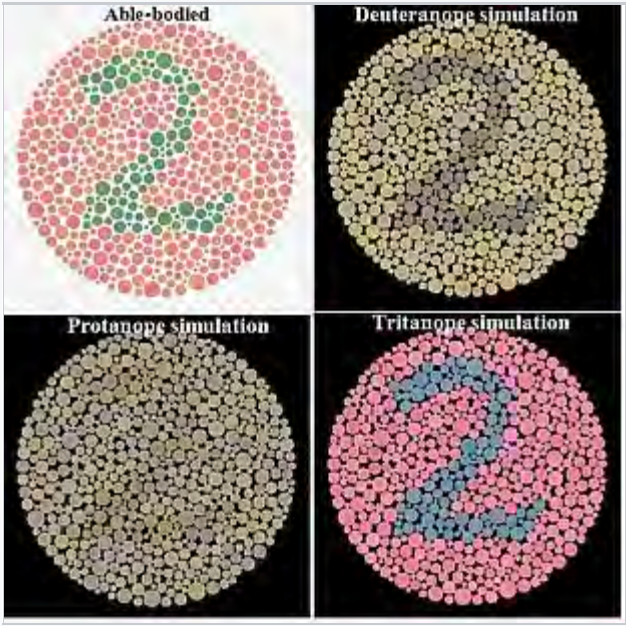
Many of the genes involved in color vision are on the X chromosome, making color blindness much more common in males than in females because males only have one X chromosome, while females have two. Because this is an X-linked trait, an estimated 2–3% of women have a 4th color cone[30] and can be

considered tetrachromats. One such woman has been reported to be a true or functional tetrachromat, as she can discriminate colors most other people can't.[31][32]

## Diagnosis [edit]

The Ishihara color test, which consists of a series of pictures of colored spots, is the test most often used to diagnose red–green color deficiencies.[33] A figure (usually one or more Arabic digits) is embedded in the picture as a number of spots in a slightly different color, and can be seen with normal color vision, but not with a particular color defect. The full set of tests has a variety of figure/background color combinations, and enable diagnosis of which particular visual defect is present. The anomaloscope, described above, is also used in diagnosing anomalous trichromacy.

> Position yourself about 75cm from your monitor so that the colour test image you are looking at is at eye level, read the description of the image and see what you can see!! It is not necessary in all cases to use the entire set of images. In a large scale examination the test can be simplified to 6 tests; test, one of tests 2 or 3, one of tests 4, 5, 6 or 7, one of tests 8 or 9, one of tests 10, 11, 12 or 13 and one of tests 14 or 15.[*this quote needs a citation*]




An Ishihara test image as seen by subjects with normal color vision and by those with a variety of color deficiencies

Because the Ishihara color test contains only numerals, it may not be useful in diagnosing young children, who have not yet learned to use numerals. In the interest of identifying these problems early on in life, alternative color vision tests were developed using only symbols (square, circle, car).

Besides the Ishihara color test, the US Navy and US Army also allow testing with the Farnsworth Lantern Test. This test allows 30% of color deficient individuals, whose deficiency is not too severe, to pass.

Another test used by clinicians to measure chromatic discrimination is the Farnsworth-Munsell 100 hue test. The patient is asked to arrange a set of colored caps or chips to form a gradual transition of color between two anchor caps.[34]

The HRR color test (developed by Hardy, Rand, and Rittler) is a red–green color test that, unlike the Ishihara, also has plates for the detection of the tritan defects.[35]

Most clinical tests are designed to be fast, simple, and effective at identifying broad categories of color blindness. In academic studies of color blindness, on the other hand, there is more interest in developing flexible tests to collect thorough datasets, identify copunctal points, and measure just noticeable differences.[36]

## Management [edit]

There is generally no treatment to cure color deficiencies. "The American Optometric Association reports a contact lens on one eye can increase the ability to differentiate between colors, though nothing can make you truly see the deficient color."[37]

### Lenses [edit]

Optometrists can supply colored spectacle lenses or a single red-tint contact lens to wear on the non-dominant eye, but although this may improve discrimination of some colors, it can make other colors more difficult to distinguish. A 1981 review of various studies to evaluate the effect of the X-chrom contact lens concluded that, while the lens may allow the wearer to achieve a better score on certain color vision tests, it did not correct color vision in the natural environment.[38] A case history using the X-Chrom lens for a rod monochromat is reported[39] and an X-Chrom manual is online.[40]

Lenses that filter certain wavelengths of light can allow people with a cone anomaly, but not dichromacy, to see a better spectrum of colors, especially those with classic "red/green" color blindness. They work by notching out wavelengths that strongly stimulate both red and green cones in a deuter- or protanomalous person, improving the distinction between the two cones' signals. As of 2013, sunglasses that enhance colors for many colorblind people are available commercially.[41][42][43]

### Apps [edit]

Many applications for iPhone and iPad have been developed to help colorblind people to view the colors in a better way. Many applications launch a sort of simulation of colorblind vision to make normal-view people understand how the color-blinds see the world. Others allow a correction of the image grabbed from the camera with a special "daltonizer" algorithm.

The GNOME desktop environment provides colorblind accessibility using the gnome-mag and the libcolorblind software. Using a gnome applet, the user may switch a color filter on and off, choosing from a set of possible color transformations that will displace the colors in order to disambiguate them. The software enables, for instance, a colorblind person to see the numbers in the Ishihara test.

## Epidemiology [edit]

Color blindness affects a large number of individuals, with protanopia and deuteranopia being the most common types.[11] In individuals with Northern European ancestry, as many as 8 percent of men and 0.4 percent of women experience congenital color deficiency.[45]

**Rates of color blindness**[*clarification needed*][44]

| | Males | Females |
|---|---|---|
| **Dichromacy** | 2.4% | 0.03% |
| Protanopia (red deficient: L cone absent) | 1.3% | 0.02% |
| Deuteranopia (green deficient: M cone absent) | 1.2% | 0.01% |
| Tritanopia (blue deficient: S cone absent) | 0.001% | 0.03% |
| **Anomalous trichromacy** | 6.3% | 0.37% |
| Protanomaly (red deficient: L cone defect) | 1.3% | 0.02% |
| Deuteranomaly (green deficient: M cone defect) | 5.0% | 0.35% |
| Tritanomaly (blue deficient: S cone defect) | 0.0001% | 0.0001% |

The number affected varies among groups. Isolated communities with a restricted gene pool sometimes produce high proportions of color blindness, including the less usual types. Examples include rural Finland, Hungary, and some of the Scottish islands. In the United States, about 7 percent of the male population—or about 10.5 million men—and 0.4 percent of the female population either cannot distinguish red from green, or see red and green differently from how others do (Howard Hughes Medical Institute, 2006 [*clarification needed*]). More than 95 percent of all variations in human color vision involve the red and green receptors in male eyes. It is very rare for males or females to be "blind" to the blue end of the spectrum.[46]

### Red–green color blindness [edit]

| Population | N | % |
|---|---|---|
| Arabs (Druzes) | 337 | 10.0 |
| | | |

| | | |
|---|---|---|
| Aboriginal Australians | 4,455 | 1.9 |
| Belgians | 9,540 | 7.4 |
| Bosnians | 4,836 | 6.2 |
| Britons | 16,180 | 6.6 |
| Chinese | 1,164 | 6.9 |
| Dutch | 3,168 | 8.0 |
| Eskimo | 297 | 2.5 |
| Fiji Islanders | 608 | 0.8 |
| French | 1,243 | 8.6 |
| Germans | 7,861 | 7.7 |
| Hutu | 1,000 | 2.9 |
| Indians (Andhra Pradesh) | 292 | 7.5 |
| Iranians | 16,180 | 6.6 |
| Japanese | 259,000 | 4.0 |
| Navajo | 571 | 2.3 |
| Norwegians | 9,047 | 9.0 |
| Mexicans | 571 | 2.3 |
| Russians | 1,343 | 9.2 |
| Scots | 463 | 7.8 |
| Swiss | 2,000 | 8.0 |
| Tibetans | 241 | 5.0 |
| Tswana | 407 | 2.0 |
| Tutsi | 1,000 | 2.5 |
| Vojvodinians | 4,750 | 7.4 |
| DR Congolese | 929 | 1.7 |

[47]

## History [edit]

The first scientific paper on the subject of color blindness, *Extraordinary facts relating to the vision of colours*, was published by the English chemist John Dalton in 1798[48] after the realization of his own color blindness. Because of Dalton's work, the general condition has been called *daltonism*, although in English this term is now used only for deuteranopia.

## Society and culture [edit]

### Design implications [edit]

> This section **needs additional citations for verification**. Please help improve this article by adding citations to reliable sources.

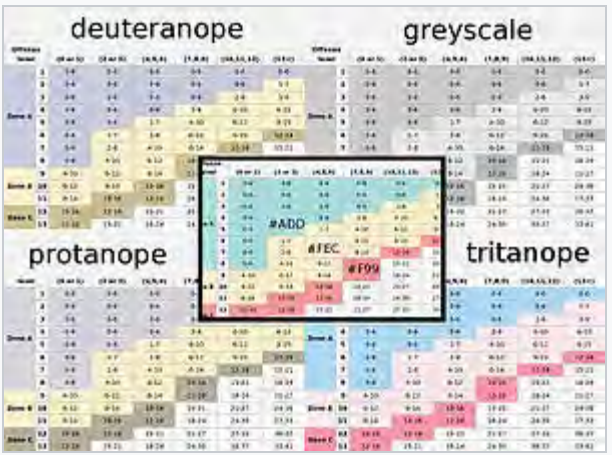

An 1895 illustration of normal vision and various kinds of color blindness



Color codes present particular problems for those with color deficiencies as they are often difficult or impossible for them to perceive.

Good graphic design avoids using color coding or using color contrasts alone to express information;[49] this not only helps color blind people, but also aids understanding by normally sighted people.

Designers need to take into account that color-blindness is highly sensitive to differences in material. For example, a red–green colorblind person who is incapable of distinguishing colors on a map printed on paper may have no such difficulty when viewing the map on a computer screen or television. In addition, some color blind people find it easier to distinguish problem colors on artificial materials, such as plastic or in acrylic paints, than on natural materials, such as paper or wood. Third, for some color blind people, color can only be distinguished if there is a sufficient "mass" of color: thin lines might appear black, while a thicker line of the same color can be perceived as having color.[*citation needed*]




Testing the colors of a web chart, *(center)*, to ensure that no information is lost to the various forms of color-blindness.

Designers should also note that red–blue and yellow–blue color combinations are generally safe. So instead of the ever-popular "red means bad and green means good" system, using these combinations can lead to a much higher ability to use color coding effectively. This will still cause problems for those with monochromatic color blindness, but it is still something worth considering.[50]

When the need to process visual information as rapidly as possible arises, for example in an emergency situation, the visual system may operate only in shades of gray, with the extra information load in adding color being dropped.[*citation needed*] This is an important possibility to consider when designing, for example, emergency brake handles or emergency phones.

## Occupations [edit]

Color blindness may make it difficult or impossible for a person to engage in certain occupations. Persons with color blindness may be legally or practically barred from occupations in which color perception is an essential part of the job (*e.g.,* mixing paint colors), or in which color perception is important for safety (*e.g.,* operating vehicles in response to color-coded signals). This occupational safety principle originates

from the Lagerlunda train crash of 1875 in Sweden. Following the crash, Professor Alarik Frithiof Holmgren, a physiologist, investigated and concluded that the color blindness of the engineer (who had died) had caused the crash. Professor Holmgren then created the first test using different-colored skeins to exclude people from jobs in the transportation industry on the basis of color blindness.[51] However, there is a claim that there is no firm evidence that color deficiency did cause the collision, or that it might have not been the sole cause.[52]

Color vision is important for occupations using telephone or computer networking cabling, as the individual wires inside the cables are color-coded using green, orange, brown, blue and white colors.[53] Electronic wiring, transformers, resistors, and capacitors are color-coded as well, using black, brown, red, orange, yellow, green, blue, violet, gray, white, silver, gold.[54]

## Driving [edit]

Some countries (for example, Romania) have refused to grant driving licenses to individuals with color blindness. In Romania, there is an ongoing campaign to remove the legal restrictions that prohibit colorblind citizens from getting drivers' licenses.[55]

The usual justification for such restrictions is that drivers of motor vehicles must be able to recognize color-coded signals, such as traffic lights or warning lights.[50]

## Piloting aircraft [edit]

While many aspects of aviation depend on color coding, only a few of them are critical enough to be interfered with by some milder types of color blindness. Some examples include color-gun signaling of aircraft that have lost radio communication, color-coded glide-path indications on runways, and the like. Some jurisdictions restrict the issuance of pilot credentials to persons who suffer from color blindness for this reason. Restrictions may be partial, allowing color-blind persons to obtain certification but with restrictions, or total, in which case color-blind persons are not permitted to obtain piloting credentials at all.[*citation needed*]

In the United States, the Federal Aviation Administration requires that pilots be tested for normal color vision as part of their medical clearance in order to obtain the required medical certificate, a prerequisite to obtaining a pilot's certification. If testing reveals color blindness, the applicant may be issued a license with restrictions, such as no night flying and no flying by color signals—such a restriction effectively prevents a pilot from holding certain flying occupations, such as that of an airline pilot, although commercial pilot certification is still possible, and there are a few flying occupations that do not require night flight and thus are still available to those with restrictions due to color blindness (e.g., agricultural aviation). The government allows several types of tests, including medical standard tests (*e.g.,* the Ishihara, Dvorine, and others) and specialized tests oriented specifically to the needs of aviation. If an applicant fails the standard tests, they will receive a restriction on their medical certificate that states: "Not valid for night flying or by color signal control". They may apply to the FAA to take a specialized test, administered by the FAA. Typically, this test is the "color vision light gun test". For this test an FAA inspector will meet the pilot at an airport with an operating control tower. The color signal light gun will be shone at the pilot from the tower, and they must identify the color. If they pass they may be issued a waiver, which states that the color vision test is no longer required during medical examinations. They will then receive a new medical certificate with the restriction removed. This was once a Statement of Demonstrated Ability (SODA), but the SODA was dropped, and converted to a simple waiver (letter) early in the 2000s.[56]

Research published in 2009 carried out by the City University of London's Applied Vision Research Centre, sponsored by the UK's Civil Aviation Authority and the US Federal Aviation Administration, has established a more accurate assessment of color deficiencies in pilot applicants' red–green and yellow–blue color range which could lead to a 35% reduction in the number of prospective pilots who fail to meet the minimum medical threshold.[57]

## Art [edit]

Inability to distinguish color does not necessarily preclude the ability to become a celebrated artist. The 20th century expressionist painter Clifton Pugh, three-time winner of Australia's Archibald Prize, on biographical, gene inheritance and other grounds has been identified as a protanope.[58] 19th century French artist Charles Méryon became successful by concentrating on etching rather than painting after he was diagnosed as having a red–green deficiency.[59]

### Rights of the color blind [edit]

A famous traffic light on Tipperary Hill in Syracuse, New York, is upside-down due to the sentiments of its Irish American community, but has been criticized due to the potential hazard it poses for color-blind persons.[60]

### Brazil [edit]

A Brazilian court ruled that people with color blindness are protected by the Inter-American Convention on the Elimination of All Forms of Discrimination against Person with Disabilities.[61][62][63]

At trial, it was decided that the carriers of color blindness have a right of access to wider knowledge, or the full enjoyment of their human condition.

## Research [edit]

Some tentative evidence finds that color blind people are better at penetrating certain color camouflages. Such findings may give an evolutionary reason for the high rate of red–green color blindness.[3] There is also a study suggesting that people with some types of color blindness can distinguish colors that people with normal color vision are not able to distinguish.[64] In World War II, color blind observers were used to penetrate camouflage.[65]

In September 2009, the journal *Nature* reported that researchers at the University of Washington and University of Florida were able to give trichromatic vision to squirrel monkeys, which normally have only dichromatic vision, using gene therapy.[66]

In 2003, a cybernetic device called eyeborg was developed to allow the wearer to hear sounds representing different colors.[67] Achromatopsic artist Neil Harbisson was the first to use such a device in early 2004; the eyeborg allowed him to start painting in color by memorizing the sound corresponding to each color. In 2012, at a TED Conference, Harbisson explained how he could now perceive colors outside the ability of human vision.[68] Portuguese Designer Miguel Neiva developed a code system, named Coloradd, based on five basic shapes that, when combined, make it easier to identify various colors for colorblind people. Its use is currently[*when?*] expanding in Portugal (hospitals, transportation, education) and in other countries.

## See also [edit]

- Motion blindness
- RG color space
- Tetrachromacy

## References [edit]


1. ^ *a b c* Gordon, N (March 1998). "Colour blindness.". *Public health*. **112** (2): 81–4. doi:10.1038/sj.ph.1900446. PMID 9581449.
2. ^ *a b c d e f g* "Facts About Color Blindness". *NEI*. February 2015. Retrieved 29 July 2016.
3. ^ *a b* Morgan, M. J.; Adam, A.; Mollon, J. D. (June 1992). "Dichromats detect colour-camouflaged objects that are not detected by trichromats". *Proc. Biol. Sci.* **248** (1323): 291–5. doi:10.1098/rspb.1992.0074. PMID 1354367.
4. ^ Acquired Colour Vision Defects. colourblindawareness.org

5. ^ MedlinePlus Encyclopedia *Color blindness*
6. ^ "Types of Color Deficiencies". *Konan Medical*. Retrieved 2014-04-26.
7. ^ Protanopia – Red–Green Color Blindness. color-blindness.com
8. ^ Deuteranopia – Red–Green Color Blindness. color-blindness.com
9. ^ Tovee, Martin J. (2008). *An Introduction to the Visual System*. Cambridge University Press. ISBN 0-521-70964-4.
10. ^ Tritanopia – Blue–Yellow Color Blindness. color-blindness.com
11. ^ *a b c* Wong, Bang (2011). "Color blindness". *Nature Methods*. **8** (6): 441. doi:10.1038/nmeth.1618. PMID 21774112.
12. ^ Albrecht, Mario (2010). "Color blindness". *Nature Methods*. **7** (10): 775–775. doi:10.1038/nmeth1010-775a. ISSN 1548-7091.
13. ^ Sharpe, L.T.; Stockman, A.; Jägle, H.; Nathans, J. (1999). "Opsin genes, cone photopigments, color vision and color blindness". In Gegenfurtner, K. R.; Sharpe, L. T. *Color Vision: From Genes to Perception*. Cambridge University Press. ISBN 978-0-521-00439-8.
14. ^ American Medical Association (2003). Leikin, Jerrold B.; Lipsky, Martin S., eds. *Complete Medical Encyclopedia* (encyclopedia) (First ed.). New York, NY: Random House Reference. p. 388. ISBN 0-8129-9100-1.
15. ^ Spring, Kenneth R.; Parry-Hill, Matthew J.; Fellers, Thomas J.; Davidson, Michael W. "Human Vision and Color Perception". Florida State University. Retrieved 2007-04-05.
16. ^ Hoffman, Paul S. "Accommodating Color Blindness" (PDF). Archived from the original (PDF) on 15 May 2008. Retrieved 2009-07-01.
17. ^ Neitz, Maureen E. "Severity of Colorblindness Varies". Medical College of Wisconsin. Archived from the original on 5 February 2007. Retrieved 2007-04-05.
18. ^ Jones, Sara A; Shim, Sang-Hee; He, Jiang; Zhuang, Xiaowei (2011). "Fast, three-dimensional super-resolution imaging of live cells". *Nature Methods*. **8** (6): 499–508. doi:10.1038/nmeth.1605. PMC 3137767. PMID 21552254.
19. ^ Simunovic, M P (2010). "Colour vision deficiency". *Eye*. **24** (5): 747–55. doi:10.1038/eye.2009.251. PMID 19927164.
20. ^ Neitz, Jay; Neitz, Maureen (2011). "The genetics of normal and defective color vision". *Vision Research*. **51** (7): 633–51. doi:10.1016/j.visres.2010.12.002. PMC 3075382. PMID 21167193.
21. ^ "Myambutol (Ethambutol) Drug Information: Description, User Reviews, Drug Side Effects, Interactions – Prescribing Information at RxList". Rxlist.com. Retrieved 2014-05-24.
22. ^ David L. MacAdam (ed.) and Deane B. Judd (1979). *Contributions to color science*. NBS. p. 584.
23. ^ *a b c* Kalloniatis, Michael; Luu, Charles (July 9, 2007). "The Perception of Color". In Kolb, Helga; Fernandez, Eduardo; Nelson, Ralph. *Webvision: The Organization of the Retina and Visual System*. PMID 21413396.
24. ^ Goldstein, E. Bruce (2007). *Sensation and perception* (7th ed.). Wadsworth: Thomson. p. 152. ISBN 978-0-534-55810-9.
25. ^ "Disease-causing Mutations and protein structure". UCL Biochemistry BSM Group. Retrieved 2007-04-02.
26. ^ "Types of Colour Blindness". *Colour Blind Awareness*.
27. ^ *a b* Blom, Jan Dirk (2009). *A Dictionary of Hallucinations*. Springer. p. 4. ISBN 978-1-4419-1222-0.
28. ^ Weiss, A. H.; Biersdorf, W. R. (1989). "Blue cone monochromatism". *J Pediatr Ophthalmol Strabismus*. **26** (5): 218–23. PMID 2795409.
29. ^ "Colour vision deficiency – Causes". NHS Choices. 2012-12-14. Retrieved 2014-05-24.
30. ^ Roth, Mark (13 September 2006). "Some women may see 100,000,000 colors, thanks to their genes". Pittsburgh Post-Gazette.
31. ^ Didymus, JohnThomas (Jun 19, 2012), "Scientists find woman who sees 99 million more colors than others", *Digital Journal*
32. ^ Jordan, Gabriele; Deeb, Samir S.; Bosten, Jenny M.; Mollon, J. D. (July 2010). "The dimensionality of color vision in carriers of anomalous trichromacy". *Journal of Vision*. **10** (12): 12. doi:10.1167/10.8.12. PMID 20884587.
33. ^ Gordon, N (1998). "Colour blindness". *Public Health*. **112** (2): 81–4. doi:10.1038/sj.ph.1900446. PMID 9581449.
34. ^ Kinnear, PR; Sahraie, A (2002). "New Farnsworth-Munsell 100 hue test norms of normal observers for each year of age 5–22 and for age decades 30–70". *The British Journal of Ophthalmology*. **86** (12): 1408–11. doi:10.1136/bjo.86.12.1408. PMC 1771429. PMID 12446376.
35. ^ Cole, Barry L; Lian, Ka-Yee; Lakkis, Carol (2006). "The new Richmond HRR pseudoisochromatic test for colour vision is better than the Ishihara test". *Clinical and Experimental Optometry*. **89** (2): 73–80. doi:10.1111/j.1444-0938.2006.00015.x. PMID 16494609.
36. ^ Toufeeq, A (2004). "Specifying colours for colour vision testing using computer graphics". *Eye*. **18** (10): 1001–5. doi:10.1038/sj.eye.6701378. PMID 15192692.
37. ^ Color Vision Deficiency. American Optometric Association

38. ^ Siegel, I. M. (1981). "The X-Chrom lens. On seeing red". *Surv Ophthalmol*. **25** (5): 312–24. PMID 6971497.
39. ^ Zeltzer, HI (1979). "Use of modified X-Chrom for relief of light dazzlement and color blindness of a rod monochromat". *Journal of the American Optometric Association*. **50** (7): 813–8. PMID 315420.
40. ^ An X-Chrom manual. Artoptical.com. Retrieved on 2016-12-10.
41. ^ A Scientist Accidentally Developed Sunglasses That Could Correct Color Blindness. Smithsonianmag.com (2015-03-03). Retrieved on 2016-12-10.
42. ^ Introducing EnChroma. Enchroma.com. Retrieved on 2016-12-10.
43. ^ Pogue, David (15 August 2013). "Glasses That Solve Colorblindness, for a Big Price Tag". The New York Times. Retrieved 22 July 2015.
44. ^ "Causes and Incidence of Colorblindness". *Causes of Color*. Retrieved 27 February 2014.[*unreliable source?*]
45. ^ Chan, Xin; Goh, Shi; Tan, Ngiap (2014). "Subjects with colour vision deficiency in the community: what do primary care physicians need to know?". *Asia Pacific Family Medicine*. **13** (1): 10. doi:10.1186/s12930-014-0010-3.
46. ^ Ananya, Mandal. "Color Blindness Prevalence". *Health*. Retrieved 27 February 2014.
47. ^ Harrison, G.A. et al. (1977): *Human Biology*, Oxford University Press, Oxford, ISBN 0-19-857164-X.
48. ^ Dalton, J (1798). "Extraordinary facts relating to the vision of colours: with observations". *Memoirs of the Literary and Philosophical Society of Manchester*. **5**: 28–45. OCLC 9879327.
49. ^ Crow, Kevin L. (2008). "Four Types of Disabilities: Their Impact on Online Learning". *TechTrends*. **52** (1): 51–5. doi:10.1007/s11528-008-0112-6.
50. ^ *a b* Habibzadeh, Parham (2015-01-01). "Our red–green world". *Australian Health Review*. **40** (4): 474. doi:10.1071/ah15161.
51. ^ Algis, J.; Vingrys, J.; Cole, Barry L. (1986). "Origins of colour vision standards within the transport industry". *Ophthalmic & Physiological Optics*. **6** (4): 369–75. doi:10.1111/j.1475-1313.1986.tb01155.x. PMID 3306566.
52. ^ Mollon, JD; Cavonius, LR (2012). "The Lagerlunda Collision and the Introduction of Color Vision Testing". *Survey of Ophthalmology*. **57** (2): 178–94. doi:10.1016/j.survophthal.2011.10.003. PMID 22301271.
53. ^ Meyers, Michael (2002). *All in One A+ Certification Exam Guide* (4th ed.). Berkeley, California: McGraw-Hill/Osborne. ISBN 0-07-222274-3.[*page needed*]
54. ^ Grob, Bernard (2001). *Basic Electronics*. Columbus, Ohio: Glencoe/McGraw-Hill. ISBN 0-02-802253-X.[*page needed*]
55. ^ "Petition to European Union on Colorblind's condition in Romania". Retrieved 2007-08-21.[*self-published source?*]
56. ^ "Aerospace Medical Dispositions — Color vision". Retrieved 2009-04-11.
57. ^ Warburton, Simon (29 May 2009). "Colour-blindness research could clear more pilots to fly: UK CAA". *Air transport*. Reed Business Information. Retrieved 29 October 2009.
58. ^ Cole, Barry L; Harris, Ross W (2009). "Colour blindness does not preclude fame as an artist: celebrated Australian artist Clifton Pugh was a protanope". *Clinical and Experimental Optometry*. **92** (5): 421–8. doi:10.1111/j.1444-0938.2009.00384.x. PMID 19515095.
59. ^ Anon. "Charles Meryon". *Art Encyclopedia. The Concise Grove Dictionary of Art*. Oxford University Press. Retrieved 7 January 2010.
60. ^ Zhang, Sarah. "The Story Behind Syracuse's Upside-Down Traffic Light". *Gizmodo*.
61. ^ "Full text of the decision of the court – in Portuguese language". Retrieved 2012-03-09.
62. ^ "Decree issued by president of a republic ratifying Legislative Decree No. 198, of june 13, which approved the Inter-American Convention AG/RES. 1608 – in Portuguese language". Retrieved 2012-03-09.
63. ^ "Inter-American Convention on the Elimination of All Forms of Discrimination against Person with Disabilities.". Retrieved 2012-03-09.
64. ^ Bosten, J.M.; Robinson, J.D.; Jordan, G.; Mollon, J.D. (2005). "Multidimensional scaling reveals a color dimension unique to 'color-deficient' observers". *Current Biology*. **15** (23): R950–2. doi:10.1016/j.cub.2005.11.031. PMID 16332521.
65. ^ "Colour blindness not all it seems". *BBC News*. 6 December 2015. Retrieved 21 June 2016.
66. ^ Dolgin, Elie (2009). "Colour blindness corrected by gene therapy". *Nature*. doi:10.1038/news.2009.921.
67. ^ Alfredo M. Ronchi: *Eculture: Cultural Content in the Digital Age.* Springer (New York, 2009). p. 319 ISBN 978-3-540-75273-8
68. ^ "I listen to color", Neil Harbisson at TED Global, 27 June 2012.


## Further reading [edit]


- Kaiser, Peter K.; Boynton, Robert M. (1996). *Human color vision*. Washington, DC: Optical Society of

America. ISBN 1-55752-461-0. OCLC 472932250.
- McIntyre, Donald (2002). *Colour blindness: causes and effects*. Chester: Dalton Publishing. ISBN 0-9541886-0-8. OCLC 49204679.
- Rubin, Melvin L.; Cassin, Barbara; Solomon, Sheila (1984). *Dictionary of eye terminology*. Gainesville, Fla: Triad Pub. Co. ISBN 0-937404-07-1. OCLC 10375427.
- Shevell, Steven K. (2003). *The science of color*. Amsterdam: Elsevier. ISBN 0-444-51251-9. OCLC 52271315.
- Hilbert, David; Byrne, Alexander (1997). *Readings on color*. Cambridge, Mass: MIT Press. ISBN 0-262-52231-4. OCLC 35762680.
- Stiles, W. S.; Wyszecki, Günter (2000). *Color science: concepts and methods, quantitative data and formulae*. Chichester: John Wiley & Sons. ISBN 0-471-39918-3. OCLC 799532137.
- Kuchenbecker, J.; Broschmann, D. (2014). *Plates for color vision testing*. New York: Thieme. ISBN 978-3-13-175481-3.

## External links [edit]

- Color blindness at DMOZ
- "A Glossary of Color Science."

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|---|---|
| Gaze · Accommodation · Intraocular pressure · Visual field · Color vision (**Color blindness** · Opponent process · Monochromacy · Dichromacy · Trichromacy · Tetrachromacy · Pentachromacy · · | |

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| **Pathways** | | |
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# Conjunctivitis

From Wikipedia, the free encyclopedia

*"Pinkeye" redirects here. For other uses, see Pinkeye (disambiguation).*

**Conjunctivitis**, also known as **pink eye**, is inflammation of the outermost layer of the white part of the eye and the inner surface of the eyelid.[1] It makes the eye appear pink or reddish. There may also be pain, burning, scratchiness, or itchiness. The affected eye may have increased tears or be "stuck shut" in the morning. Swelling of the white part of the eye may also occur.[2] Itching of the eye is more common in cases due to allergies.[3] Conjunctivitis can affect one or both eyes.[2]

The most common infectious causes are viral followed by bacterial.[3] The viral infection may occur along with other symptoms of a common cold. Viral and bacterial cases are easily spread between people.[2] Allergies to pollen or animal hair is also a common cause.[3] Diagnosis is often based on signs and symptoms. Occasionally a sample of the discharge is sent for culture.[2]

Prevention is partly by handwashing. Treatment depends on the underlying cause.[2] In the majority of viral cases, there is no specific treatment.[3] Most cases due to a bacterial infection will also resolve without treatment; however, antibiotics can shorten the illness.[2][3] Those who wear contact lens and those with either gonorrhea or chlamydia as the cause should be treated. Allergic cases can be treated with antihistamine or mast cell inhibitor drops.[3]

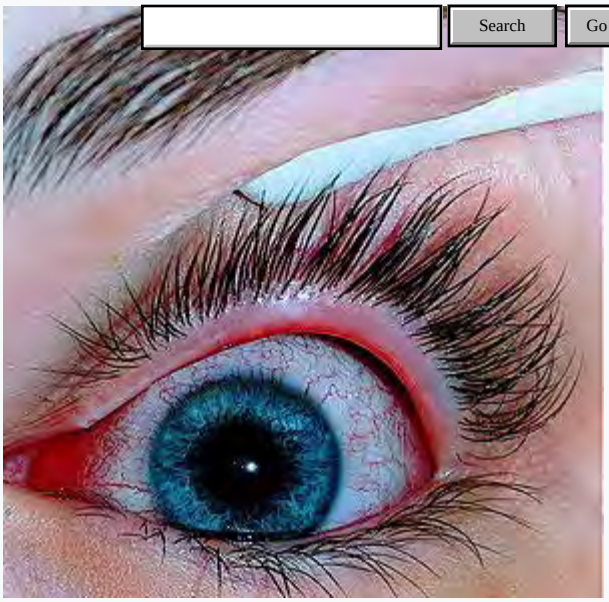
About 3 to 6 million people get conjunctivitis each year in the United States.[2][3] In adults viral causes are more common, while in children bacterial causes are more common.[3] Typically people get better in one or two weeks.[2][3] If there is visual loss, significant pain, sensitivity to light, signs of herpes, or a person is not improving after a week, further diagnosis and treatment may be required.[3] Conjunctivitis in a newborn, known as neonatal conjunctivitis, may also require specific treatment.[2]

Contents



**Conjunctivitis**

**Synonyms** Pink eye, Madras eye



An eye with viral conjunctivitis

| Classification and external resources | |
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| **Specialty** | Ophthalmology |
| **ICD-10** | H10 |
| **ICD-9-CM** | 372.0 |
| **DiseasesDB** | 3067 |
| **MedlinePlus** | 001010 |
| **eMedicine** | emerg/110 |
| **Patient UK** | Conjunctivitis |
| **MeSH** | D003231 |

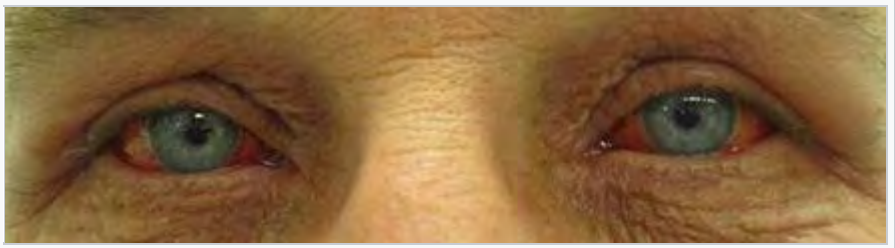
[edit on Wikidata]

## Signs and symptoms [edit]

Red eye, swelling of conjunctiva and watering of the eyes are symptoms common to all forms of conjunctivitis. However, the pupils should be normally reactive, and the visual acuity normal.

### Viral [edit]

Viral conjunctivitis is often associated with an infection of the upper respiratory tract, a common cold, and/or a sore throat. Its symptoms include excessive watering and itching. The infection usually begins with one eye, but may spread easily to the other.



Conjunctivitis due to a viral infection resulting in some bleeding

Viral conjunctivitis shows a fine, diffuse pinkness of the conjunctiva, which is easily mistaken for the ciliary infection of iris (iritis), but there are usually corroborative signs on microscopy, particularly numerous lymphoid follicles on the tarsal conjunctiva, and sometimes a punctate keratitis.

Some other viruses that can infect the eye include Herpes simplex virus and Varicella zoster.[4]

### Allergic [edit]

Allergic conjunctivitis is inflammation of the conjunctiva (the membrane covering the white part of the eye) due to allergy.[5] Allergens differ among patients.

Symptoms consist of redness (mainly due to vasodilation of the peripheral small blood vessels), swelling of the conjunctiva, itching, and increased lacrimation (production of tears). If this is combined with rhinitis, the condition is termed "allergic rhinoconjunctivitis". The symptoms are due to release of histamine and other active substances by mast cells, which stimulate dilation of blood vessels, irritate nerve endings, and increase secretion of tears.

An eye with allergic conjunctivitis showing conjunctival

### Bacterial [edit]

edema

An eye with bacterial conjunctivitis

Bacterial conjunctivitis causes the rapid onset of conjunctival redness, swelling of the eyelid, and mucopurulent discharge. Typically, symptoms develop first in one eye, but may spread to the other eye within 2–5 days.Bacterial conjunctivitis due to common pyogenic (pus-producing) bacteria causes marked grittiness/irritation and a stringy, opaque, greyish or yellowish mucopurulent discharge that may cause the lids to stick together, especially after sleep. Severe crusting of the infected eye and the surrounding skin may also occur. The gritty and/or scratchy feeling is sometimes localized enough for patients to insist they must have a foreign body in the eye. The more acute pyogenic infections can be painful.[*citation needed*] Common bacteria responsible for non-acute bacterial conjunctivitis are Staphylococci, Streptococci,[6] Haemophilus sp. Less commonly Chlamydia trachomatis is involved.[7]

Bacteria such as *Chlamydia trachomatis* or *Moraxella* can cause a non-exudative but persistent conjunctivitis without much redness. Bacterial conjunctivitis may cause the production of membranes or pseudomembranes that cover the conjunctiva. Pseudomembranes consist of a combination of inflammatory cells and exudates, and are loosely adherent to the conjunctiva, while true membranes are more tightly adherent and cannot be easily peeled away. Cases of bacterial conjunctivitis that involve the production of membranes or pseudomembranes are associated with Neisseria gonorrhoeae, β-hemolytic streptococci, and C. diphtheriae. *Corynebacterium diphtheriae* causes membrane formation in conjunctiva of non-immunized children.[*citation needed*]

## Chemical [edit]

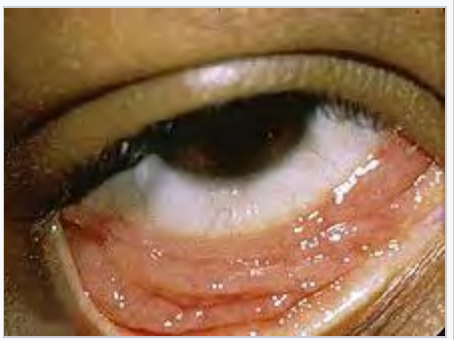
Chemical eye injury is due to either an acidic or alkali substance getting in the eye.[8] Alkalis are typically worse than acidic burns.[9] Mild burns will produce conjunctivitis, while more severe burns may cause the cornea to turn white.[9] Litmus paper is an easy way to rule out the diagnosis by verifying that the pH is within the normal range of 7.0—7.2.[8] Large volumes of irrigation is the treatment of choice and should continue until the pH is 6—8.[9] Local anaesthetic eye drops can be used to decrease the pain.[9]

Irritant or toxic conjunctivitis show primarily marked redness. If due to splash injury, it is often present in only the lower conjunctival sac. With some chemicals, above all with caustic alkalis such as sodium hydroxide, there may be necrosis of the conjunctiva with a deceptively white eye due to vascular closure, followed by sloughing of the dead epithelium. This is likely to be associated with slit-lamp evidence of anterior uveitis.

## Other [edit]

Inclusion conjunctivitis of the newborn (ICN) is a conjunctivitis that may be caused by the bacteria *Chlamydia trachomatis*, and may lead to acute, purulent conjunctivitis.[10] However, it is usually self-healing.[10]

Conjunctivitis is identified by irritation and redness of the conjunctiva. Except in obvious pyogenic or toxic/chemical conjunctivitis, a slit lamp (biomicroscope) is needed to have any confidence in the diagnosis. Examination of the tarsal conjunctiva is usually more diagnostic than the bulbar conjunctiva.



An eye with chlamydial conjunctivitis

# Causes [edit]

Conjunctivitis when caused by an infection is most commonly caused by a viral infection.[11] Bacterial infections, allergies, other irritants and dryness are also common causes. Both bacterial and viral infections are contagious and passed from person

to person, but can also spread through contaminated objects or water.

The most common cause of viral conjunctivitis is adenoviruses (see: Adenoviral keratoconjunctivitis).[12] Herpetic keratoconjunctivitis (caused by herpes simplex viruses) can be serious and requires treatment with acyclovir. Acute hemorrhagic conjunctivitis is a highly contagious disease caused by one of two enteroviruses, Enterovirus 70 and Coxsackievirus A24. These were first identified in an outbreak in Ghana in 1969, and have spread worldwide since then, causing several epidemics.[13]

The most common causes of acute bacterial conjunctivitis are *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.[12] Though very rare, hyperacute cases are usually caused by *Neisseria gonorrhoeae* or *N. meningitidis*. Chronic cases of bacterial conjunctivitis are those lasting longer than 3 weeks, and are typically caused by *Staphylococcus aureus*, *Moraxella lacunata*, or gram-negative enteric flora.

Conjunctivitis may also be caused by allergens such as pollen, perfumes, cosmetics, smoke,[14] dust mites, Balsam of Peru,[15] and eye drops.[16]

Conjunctivitis is part of the triad of reactive arthritis, which is thought to be caused by autoimmune cross-reactivity following certain bacterial infections. Reactive arthritis is highly associated with HLA-B27. Conjunctivitis is associated with the autoimmune disease relapsing polychondritis.[17][18]

## Diagnosis [edit]

Cultures are not often taken or needed as most cases resolve either with time or typical antibiotics. Swabs for bacterial culture are necessary if the history and signs suggest bacterial conjunctivitis but there is no response to topical antibiotics. Viral culture may be appropriate in epidemic case clusters.

A patch test is used to identify the causative allergen in the case where conjunctivitis is caused by allergy.[19]

Conjunctival scrapes for cytology can be useful in detecting chlamydial and fungal infections, allergy, and dysplasia, but are rarely done because of the cost and the general lack of laboratory staff experienced in handling ocular specimens. Conjunctival incisional biopsy is occasionally done when granulomatous diseases (*e.g.*, sarcoidosis) or dysplasia are suspected.

### Classification [edit]

Classification can be either by cause or by extent of the inflamed area.

### Causes [edit]

- Allergic conjunctivitis, caused by allergens such as pollen, perfumes, cosmetics, smoke,[14] dust mites, Balsam of Peru (used in food and drink for flavoring, in perfumes and toiletries for fragrance, and in medicine and pharmaceutical items for healing properties),[15] and eye drops.[16] A patch test is used to diagnose it and identify the causative allergen.[19]
- Bacterial conjunctivitis
- Viral conjunctivitis
- Chemical conjunctivitis
- Neonatal conjunctivitis is often defined separately due to different organisms
- Autoimmune

### By extent of involvement [edit]

Blepharoconjunctivitis is the dual combination of conjunctivitis with blepharitis (inflammation of the eyelids).

Keratoconjunctivitis is the combination of conjunctivitis and keratitis (corneal inflammation).

### Differential diagnosis [edit]

There are more serious conditions that can present with a red eye such as infectious keratitis, angle closure glaucoma, or iritis. These conditions require the urgent attention of an ophthalmologist. Signs of such conditions include decreased vision, significantly increased sensitivity to light, inability to keep eye open, a pupil that does not respond to light, or a severe headache with nausea.[20] Fluctuating blurring is common, due to tearing and mucoid discharge. Mild photophobia is common. However, if any of these symptoms are prominent, it is important to consider other diseases such as glaucoma, uveitis, keratitis and even meningitis or carotico-cavernous fistula.

A more comprehensive differential diagnosis for the red or painful eye includes:[20]

- corneal abrasion
- subconjunctival hemorrhage
- pinguecula
- blepharitis
- dacryocystitis
- keratoconjunctivitis sicca (dry eye)
- keratitis
- herpes simplex
- herpes zoster
- episcleritis - an inflammatory condition that produces a similar appearance to conjunctivitis, but without discharge or tearing.
- uveitis
- acute angle-closure glaucoma
- enophthalmitis

## Prevention [edit]

The best effective prevention is hygiene and not rubbing the eyes by infected hands. Vaccination against adenovirus, haemophilus influenzae, pneumococcus, and neisseria meningitidis is also effective.[*citation needed*]

Povidone-iodine eye solution has been found to prevent conjunctivitis following birth.[21] As it is less expensive it is being more commonly used for this purpose globally.[21]

## Management [edit]

Conjunctivitis resolves in 65% of cases without treatment, within two to five days. The prescription of antibiotics is not necessary in most cases.[22]

### Viral [edit]

Viral conjunctivitis usually resolves on its own and does not require any specific treatment.[11] Antihistamines (e.g., diphenhydramine) or mast cell stabilizers (e.g., cromolyn) may be used to help with the symptoms.[11] Povidone iodine has been suggested as a treatment, but as of 2008 evidence to support it was poor.[23]

### Allergic [edit]

For the allergic type, cool water poured over the face with the head inclined downward constricts capillaries, and artificial tears sometimes relieve discomfort in mild cases. In more severe cases, nonsteroidal anti-inflammatory medications and antihistamines may be prescribed. Persistent allergic conjunctivitis may also require topical steroid drops.

### Bacterial [edit]

Bacterial conjunctivitis usually resolves without treatment.[11] Topical antibiotics may be needed only if no improvement is observed after three days.[24] In people who received no antibiotics, recovery was in 4.8 days, with immediate antibiotics it was 3.3 days, and with delayed antibiotics 3.9 days. No serious effects were noted either with or without treatment.[25] As they do speed healing in bacterial conjunctivitis, their use is also reasonable.[26]

In those who wear contact lenses, are immunocompromised, have disease which is thought to be due to chlamydia or gonorrhea, have a fair bit of pain, or who have lots of discharge, antibiotics are recommended.[11] Gonorrhea or chlamydia infections require both oral and topical antibiotics.[11]

When appropriate, the choice of antibiotic varies, differing based on the cause (if known) or the likely cause of the conjunctivitis. Fluoroquinolones, sodium sulfacetamide, or trimethoprim/polymyxin may be used, typically for 7–10 days.[12] Cases of meningococcal conjunctivitis can also be treated with systemic penicillin, as long as the strain is sensitive to penicillin.

When investigated as a treatment, Povidone-iodine ophthalmic solution has also been observed to have some effectiveness against bacterial and chlamydial conjunctivitis, with a possible role suggested in locations where topical antibiotics are unavailable or costly.[27]

### Chemical [edit]

Conjunctivitis due to chemicals is treated via irrigation with Ringer's lactate or saline solution. Chemical injuries (particularly alkali burns) are medical emergencies, as they can lead to severe scarring and intraocular damage. People with chemically induced conjunctivitis should not touch their eyes, regardless of whether or not their hands are clean, as they run the risk of spreading the condition to another eye.

## Epidemiology [edit]

Conjunctivitis is the most common eye disease.[28]

## History [edit]

A former superintendent of the Regional Institute of Ophthalmology in the city of Madras (the present-day Chennai) in India, Kirk Patrick, was the first to have found the adenovirus that caused conjunctivitis, leading to the name "Madras eye" for the disease.[29]

## See also [edit]

- Conjunctival suffusion
- Episcleritis

## References [edit]


1. ^ Richards A, Guzman-Cottrill JA (May 2010). "Conjunctivitis". *Pediatr Rev*. **31** (5): 196–208. doi:10.1542/pir.31-5-196. PMID 20435711.
2. ^ *a b c d e f g h i* "Facts About Pink Eye". *National Eye Institute*. November 2015. Retrieved 8 March 2016.
3. ^ *a b c d e f g h i j* Azari, AA; Barney, NP (23 October 2013). "Conjunctivitis: a systematic review of diagnosis and treatment.". *JAMA*. **310** (16): 1721–9. doi:10.1001/jama.2013.280318. PMID 24150468.
4. ^ Forbes BA, Sahm DF, Weissfeld AS. *Bailey & Scott's Diagnostic Microbiology*. 12th Edition. Mosby Elsevier, 2007. p. 834.
5. ^ Bielory L, Friedlaender MH (February 2008). "Allergic conjunctivitis". *Immunol Allergy Clin North Am*. **28** (1): 43–58, vi. doi:10.1016/j.iac.2007.12.005. PMID 18282545.
6. ^ "Pink Eye (Conjunctivitis)". MedicineNet.

7. ^ "Acute Bacterial Conjunctivitis - Eye Disorders - Merck Manuals Professional Edition" . *Merck Manuals Professional Edition*. Retrieved 31 December 2016.
8. ^ *a b* Zentani A, Burslem J (December 2009). "Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 4: use of litmus paper in chemical eye injury". *Emerg Med J*. **26** (12): 887. doi:10.1136/emj.2009.086124. PMID 19934140.
9. ^ *a b c d* Hodge C, Lawless M (July 2008). "Ocular emergencies". *Aust Fam Physician*. **37** (7): 506–9. PMID 18592066.
10. ^ *a b* Fisher, Bruce; Harvey, Richard P.; Champe, Pamela C. (2007). *Lippincott's Illustrated Reviews: Microbiology (Lippincott's Illustrated Reviews Series)*. Hagerstown MD: Lippincott Williams & Wilkins. ISBN 0-7817-8215-5.
11. ^ *a b c d e f* Azari, AA; Barney, NP (23 October 2013). "Conjunctivitis: a systematic review of diagnosis and treatment.". *JAMA: the Journal of the American Medical Association*. **310** (16): 1721–9. doi:10.1001/jama.2013.280318. PMID 24150468.
12. ^ *a b c* Yanoff, Myron; Duker, Jay S. (2008). *Ophthalmology* (3rd ed.). Edinburgh: Mosby. pp. 227–236. ISBN 978-0-323-05751-6.
13. ^ Lévêque N, Huguet P, Norder H, Chomel JJ (April 2010). "[Enteroviruses responsible for acute hemorrhagic conjunctivitis]". *Med Mal Infect* (in French). **40** (4): 212–8. doi:10.1016/j.medmal.2009.09.006. PMID 19836177.
14. ^ *a b* "Allergic Conjunctivitis". familydoctor.org. Retrieved 2015-09-18.[*unreliable medical source?*]
15. ^ *a b* Pamela Brooks – (2012-10-25). *The Daily Telegraph: Complete Guide to Allergies*. Retrieved 2014-04-15.
16. ^ *a b* "What Is Allergic Conjunctivitis? What Causes Allergic Conjunctivitis?". medicalnewstoday.com. Retrieved 2010-04-06.
17. ^ Puéchal, X; Terrier, B; Mouthon, L; Costedoat-Chalumeau, N; Guillevin, L; Le Jeunne, C (March 2014). "Relapsing polychondritis.". *Joint, bone, spine : revue du rhumatisme*. **81** (2): 118–24. doi:10.1016/j.jbspin.2014.01.001. PMID 24556284.
18. ^ Cantarini, Luca; Vitale, Antonio; Brizi, Maria Giuseppina; Caso, Francesco; Frediani, Bruno; Punzi, Leonardo; Galeazzi, Mauro; Rigante, Donato (2014). "Diagnosis and classification of relapsing polychondritis". *Journal of Autoimmunity*. 48-49: 53–59. doi:10.1016/j.jaut.2014.01.026. ISSN 0896-8411. PMID 24461536.
19. ^ *a b* Mark J. Mannis; Marian S. Macsai; Arthur C. Huntley (1996). *Eye and skin disease*. Lippincott-Raven. Retrieved 2014-04-23.
20. ^ *a b* Longo, DL (2012). "Disorders of the Eye(Horton JC)". *Harrison's Principles of Internal Medicine*. McGra-Hill.
21. ^ *a b* Isenberg, SJ (2003). "The ocular application of povidone-iodine.". *Community eye health / International Centre for Eye Health*. **16** (46): 30–1. PMID 17491857.
22. ^ Rose P (August 2007). "Management strategies for acute infective conjunctivitis in primary care: a systematic review". *Expert Opin Pharmacother*. **8** (12): 1903–21. doi:10.1517/14656566.8.12.1903. PMID 17696792.
23. ^ Jimmy D. Bartlett; Siret D. Jaanus (2008). *Clinical Ocular Pharmacology*. Elsevier Health Sciences. pp. 454–. ISBN 0-7506-7576-4.
24. ^ Visscher, KL; Hutnik, CM; Thomas, M (November 2009). "Evidence-based treatment of acute infective conjunctivitis: Breaking the cycle of antibiotic prescribing.". *Canadian Family Physician*. **55** (11): 1071–5. PMC 2776793. PMID 19910590.
25. ^ Sheikh A, Hurwitz B (2006). Sheikh, Aziz, ed. "Antibiotics versus placebo for acute bacterial conjunctivitis". *Cochrane Database Syst Rev* (2): CD001211. doi:10.1002/14651858.CD001211.pub2. PMID 16625540.
26. ^ Sheikh, A; Hurwitz, B; van Schayck, CP; McLean, S; Nurmatov, U (12 September 2012). "Antibiotics versus placebo for acute bacterial conjunctivitis.". *Cochrane database of systematic reviews (Online)*. **9**: CD001211. doi:10.1002/14651858.CD001211.pub3. PMID 22972049.
27. ^ Isenberg, SJ; Apt, L; Valenton, M; Del Signore, M; Cubillan, L; Labrador, MA; Chan, P; Berman, NG (November 2002). "A controlled trial of povidone-iodine to treat infectious conjunctivitis in children". *American Journal of Ophthalmology*. **134** (5): 681–688. doi:10.1016/S0002-9394(02)01701-4. PMID 12429243.
28. ^ Smeltzer, Suzanne C. (2010). *Brunner & Suddarth's textbook of medical-surgical nursing.* (12th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 1787. ISBN 9780781785891.
29. ^ "Chennai's medical history unveiled". *The Times of India*. Chennai. 23 August 2011. Retrieved 16 September 2012.


## External links [edit]

- Conjunctivitis at DMOZ

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|---|---|---|
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| | | Entropion · Ectropion · Lagophthalmos · Blepharochalasis · Ptosis · Blepharophimosis · Xanthelasma · |
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| **Conjunctiva** | | **Conjunctivitis** (allergic · · Pterygium · Pinguecula · Subconjunctival hemorrhage · |
| **Globe** | | |
| **Fibrous tunic** | **Sclera** | Scleritis · Episcleritis · |
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| **Other** | | Glaucoma / Ocular hypertension / Primary juvenile glaucoma · Floater · Leber's hereditary optic neuropathy · Red eye · Globe rupture · Keratomycosis · Phthisis bulbi · Persistent fetal vasculature / Persistent hyperplastic primary vitreous · Persistent tunica vasculosa lentis · Familial exudative vitreoretinopathy · |
| **Pathways** | | |
| **Optic nerve Optic disc** | | Optic neuritis (optic papillitis · · Papilledema (Foster Kennedy syndrome · · Optic atrophy · Optic disc drusen · |
| | **Optic neuropathy** | Ischemic (anterior (AION) · posterior (PION) · · Kjer's · Leber's hereditary · Toxic and nutritional · |
| | | Ophthalmoparesis · Chronic progressive external ophthalmoplegia · |

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|---|---|---|
| **Strabismus**<br>**Extraocular muscles**<br>**Binocular vision**<br>**Accommodation** | **Paralytic strabismus** | Kearns–Sayre syndrome ·<br>**palsies** Oculomotor (III) · Fourth-nerve (IV) · Sixth-nerve (VI) · |
| | **Other strabismus** | Esotropia / Exotropia · Hypertropia · Heterophoria (Esophoria · Exophoria · · Cyclotropia · Brown's syndrome · Duane syndrome · |
| | **Other binocular** | Conjugate gaze palsy · Convergence insufficiency · Internuclear ophthalmoplegia · One and a half syndrome · |
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| **Pupil** | Anisocoria · Argyll Robertson pupil · Marcus Gunn pupil · Adie syndrome · Miosis · Mydriasis · Cycloplegia · Parinaud's syndrome · | |
| **Other** | Nystagmus · Childhood blindness · | |

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|---|
| Trachoma · Onchocerciasis · |

| v · t · e · **Inflammation** | | | |
|---|---|---|---|
| **Acute** | **Plasma derived mediators** | Bradykinin · *complement* (C3 · C5a · MAC · · *coagulation* (Factor XII · Plasmin · Thrombin · · | |
| | **Cell derived mediators** | *preformed:* | Lysosome granules · *biogenic amines* (Histamine · Serotonin · · |
| | | *synthesized on demand:* | *cytokines* (IFN-γ · IL-8 · TNF-α · IL-1 · · *eicosanoids* (Leukotriene B4 · Prostaglandins · · Nitric oxide · Kinins · |
| **Chronic** | Macrophage · Epithelioid cell · Giant cell · Granuloma · | | |
| **Processes** | **Traditional:** | Rubor · Calor · Tumor · Dolor · Functio laesa · | |
| | **Modern:** | Acute-phase reaction/Fever · Vasodilation · Increased vascular permeability · Exudate · Leukocyte extravasation · Chemotaxis · | |
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| | **Respiratory** | *upper* (Sinusitis · Rhinitis · Pharyngitis · Laryngitis · · *lower* (Tracheitis · | |

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|---|---|---|---|
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| | **Endocrine** | | Insulitis · Hypophysitis · Thyroiditis · Parathyroiditis · Adrenalitis · |
| | **Lymphatic** | | Lymphangitis · Lymphadenitis · |
| **Authority control** | NDL: 00565682 · | | |

Categories: Disorders of conjunctiva | Inflammations | Measles

# Retinal detachment

From Wikipedia, the free encyclopedia
(Redirected from Detached retina)

**Retinal detachment** is a disorder of the eye in which the retina separates from the layer underneath.[1] Symptoms include an increase in the number of floaters, flashes of light, and worsening of the outer part of the visual field.[1][2] This may be described as a curtain over part of the field of vision.[2] In about 7% of cases both eyes are affected.[3] Without treatment permanent loss of vision may occur.[4]

The mechanism most commonly involves a break in the retina that then allows the fluid in the eye to get behind the retina. A break in the retina can occur from a posterior vitreous detachment, injury to the eye, or inflammation of the eye. Other risk factors include being short sighted and previous cataract surgery. Retinal detachments also rarely occur due to a choroidal tumor.[1] Diagnosis is by either looking at the back of the eye with an ophthalmoscope or by ultrasound.[1][4]

In those with a retinal tear, efforts to prevent it becoming a detachment include cryotherapy using a cold probe or photocoagulation using a laser. Treatment of retinal detachment should be carried out in a timely manner. This may include scleral buckling where silicone is sutured to the outside of the eye, pneumatic retinopexy where gas is injected into the eye, or vitrectomy where the vitreous is partly removed and replaced with either gas or oil.[1]

Retinal detachments affect between 0.6 and 1.8 people per 10,000 per year.[3] About 0.3% of people are affected at some point in their life.[5] It is most common in people who are in their 60s or 70s. Males are more often affected than females. The long term outcomes depend on the duration of the detachment and whether the macula was detached.[1] If treated before the macula detaches outcomes are generally good.[1][5]

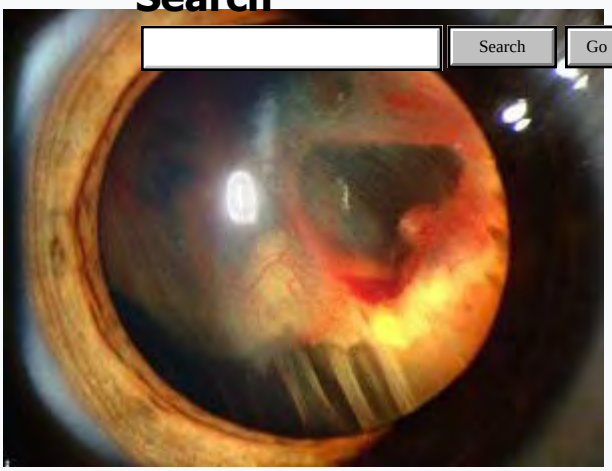
Contents





**Retinal detachment**

**Synonyms** Detached retina



Slit lamp photograph showing retinal detachment.

| Classification and external resources | |
|---|---|
| **Specialty** | Ophthalmology |
| **ICD-10** | H33 |
| **ICD-9-CM** | 361 |
| **DiseasesDB** | 11417 |
| **MedlinePlus** | 001027 |
| **eMedicine** | oph/504 |
| **Patient UK** | Retinal detachment |
| **MeSH** | D012163 |

[edit on Wikidata]

## Signs and symptoms [edit]

A rhegmatogenous retinal detachment is commonly preceded by a posterior vitreous detachment which gives rise to these symptoms:

- flashes of light (photopsia) – very brief in the extreme peripheral (outside of center) part of vision
- a sudden dramatic increase in the number of floaters
- a ring of floaters or hairs just to the temporal (skull) side of the central vision

Although most posterior vitreous detachments do not progress to retinal detachments, those that do produce the following symptoms:

- a dense shadow that starts in the peripheral vision and slowly progresses towards the central vision
- the impression that a veil or curtain was drawn over the field of vision
- straight lines (scale, edge of the wall, road, etc.) that suddenly appear curved (positive Amsler grid test)
- central visual loss

In the event of an appearance of sudden flashes of light or floaters, an eye doctor needs to be consulted immediately.[6] A shower of floaters or any loss of vision, too, is a medical emergency.

## Risk factors [edit]

Risk factors for retinal detachment include severe myopia, retinal tears, trauma, family history, as well as complications from cataract surgery.[5][7]

Retinal detachment can be mitigated in some cases when the warning signs[8] are caught early. The most effective means of prevention and risk reduction is through education of the initial signs, and encouragement for people to seek ophthalmic medical attention if they have symptoms suggestive of a posterior vitreous detachment.[9] Early examination allows detection of retinal tears which can be treated with laser or cryotherapy. This reduces the risk of retinal detachment in those who have tears from around 1:3 to 1:20. For this reason, the governing bodies in some sports require regular eye examination.

Trauma-related cases of retinal detachment can occur in high-impact sports or in high speed sports. Although some recommend avoiding activities that increase pressure in the eye, including diving and skydiving, there is little evidence to support this recommendation, especially in the general population. Nevertheless, ophthalmologists generally advise people with high degrees of myopia to try to avoid exposure to activities that have the potential for trauma, increase pressure on or within the eye itself, or include rapid acceleration and deceleration, such as bungee jumping or roller coaster rides.

Intraocular pressure spikes occur during any activity accompanied by the Valsalva maneuver, including weightlifting.[10] An epidemiological study suggests that heavy manual lifting at work may be associated with increased risk of rhegmatogenous retinal detachment, but this relationship is not strong.[11][12] In this study, obesity also appeared to increase the risk of retinal detachment. A high Body Mass Index (BMI) and elevated blood pressure have been identified as a risk factor in non-myopic individuals.[13]

Genetic factors promoting local inflammation and photoreceptor degeneration may also be involved in the development of the disease.[14]

Other risk factors include the following:

- Glaucoma[*citation needed*]
- AIDS[15]
- Cataract surgery[16]
- Diabetic retinopathy[15][17]
- Eclampsia[18]
- Family history of retinal detachment[19]
- Homocysteinuria[20]
- Malignant hypertension[15][18]
- Metastatic cancer, which spreads to the eye (eye cancer)[21]
- Retinoblastoma[22]
- Severe myopia[7]
- Smoking and passive smoking[23][24]
- Stickler syndrome[15]
- Von Hippel-Lindau disease[25]

## Diagnosis [edit]

Retinal detachment can be examined by fundus photography or ophthalmoscopy. Fundus photography generally needs a considerably larger instrument than the ophthalmoscope, but has the advantage of availing the image to be examined by a specialist at another location and/or time, as well as providing photo documentation for future reference. Modern fundus photographs generally recreate considerably larger areas of the fundus than what can be seen at any one time with handheld ophthalmoscopes.

A physician using a "three-mirror glass" to diagnose retinal detachment

Ultrasound has diagnostic accuracy similar to that of examination by an ophthalmologist.[26] The recent meta-analysis[*which?*] shows the diagnostic accuracy of emergency department (ED) ocular ultrasonography is high. The sensitivity and specificity ranged from 97% to 100% and 83% to 100%. The typical feature of retinal detachment when viewed on ultrasound is "flying angel sign". It shows the detached retina moving with a fixed point under the B mode, linear probe 10MHz.[27]

Retinal detachment, flying angel sign on ultrasound

### Types [edit]

- Rhegmatogenous retinal detachment – A rhegmatogenous retinal detachment occurs due to a break in the retina (called a *retinal tear*) that allows fluid to pass from the vitreous space into the subretinal space between the sensory retina and the retinal pigment epithelium. Retinal breaks are divided into three types – holes, tears and dialyses. Holes form due to retinal atrophy especially within an area of lattice degeneration. Tears are due to vitreoretinal traction. Dialyses are very peripheral and circumferential, and may be either tractional or atrophic. The atrophic form most often occurs as idiopathic dialysis of the young.
- Exudative, serous, or secondary retinal detachment – An exudative retinal detachment occurs due to inflammation, injury or vascular abnormalities that results in fluid accumulating underneath the retina without the presence of a hole, tear, or break. In evaluation of retinal detachment it is critical to exclude exudative detachment as surgery will make the situation worse, not better. Although rare, exudative detachment can be caused by the growth of a tumor on the layers of tissue beneath the retina, namely the choroid. This cancer is called a choroidal melanoma.
- Tractional retinal detachment – A tractional retinal detachment occurs when fibrous or fibrovascular

tissue, caused by an injury, inflammation or neovascularization, pulls the sensory retina from the retinal pigment epithelium.

A minority of retinal detachments result from trauma, including blunt blows to the orbit, penetrating trauma, and concussions to the head. A retrospective Indian study of more than 500 cases of rhegmatogenous detachments found that 11% were due to trauma, and that gradual onset was the norm, with over 50% presenting more than one month after the inciting injury.[28]

# Treatment [edit]

There are several methods of treating a detached retina, each of which depends on finding and closing the breaks that have formed in the retina. All three of the procedures follow the same three general principles:

1. Find all retinal breaks
2. Seal all retinal breaks
3. Relieve present (and future) vitreoretinal traction

## Cryopexy and laser photocoagulation [edit]

Cryotherapy (freezing) or laser photocoagulation are occasionally used alone to wall off a small area of retinal detachment so that the detachment does not spread.

## Scleral buckle surgery [edit]

Scleral buckle surgery is an established treatment in which the eye surgeon sews one or more silicone bands (or tyres) to the sclera (the white outer coat of the eyeball). The bands push the wall of the eye inward against the retinal hole, closing the break or reducing fluid flow through it and reducing the effect of vitreous traction thereby allowing the retina to re-attach. Cryotherapy (freezing) is applied around retinal breaks prior to placing the buckle. Often subretinal fluid is drained as part of the buckling procedure. The buckle remains in situ. The most common side effect of a scleral operation is myopic shift. That is, the operated eye will be more short sighted after the operation. Radial scleral buckle is indicated for U-shaped tears or Fishmouth tears, and posterior breaks. Circumferential scleral buckle is indicated for multiple breaks, anterior breaks and wide breaks. Encircling buckles are indicated for breaks covering more than 2 quadrants of retinal area, lattice degeneration located on more than 2 quadrant of retinal area, undetectable breaks, and proliferative vitreous retinopathy.

## Pneumatic retinopexy [edit]

This operation is generally performed in the doctor's office under local anesthesia. It is another method of repairing a retinal detachment in which a gas bubble ($SF_6$ or $C_3F_8$ gas) is injected into the eye after which laser or freezing treatment is applied to the retinal hole. The patient's head is then positioned so that the bubble rests against the retinal hole. Patients may have to keep their heads tilted for several days to keep the gas bubble in contact with the retinal hole. The surface tension of the gas/water interface seals the hole in the retina, and allows the retinal pigment epithelium to pump the subretinal space dry and "suck the retina back into place". This strict positioning requirement makes the treatment of the retinal holes and detachments that occurs in the lower part of the eyeball impractical. This procedure is usually combined with cryopexy or laser photocoagulation. Pneumatic retinopexy has significantly lower success rates compared to scleral buckle surgery and vitrectomy. Some initially successful cases will fail during the weeks and months after surgery. In some of the failed cases, an area of the retina which was healthy and attached prior to the initial pneumatic retinopexy repair procedure develops new tears and/or becomes detached. A recent Cochrane Review compared outcomes from patients receiving retinal reattachment from pneumatic retinopexy versus scleral buckle.[29] Though the quality of evidence from two randomized controlled trials was low, eyes having received the pneumatic retinopexy procedure were more likely to have a recurrence of retinal detachment by follow-up, and were 11% less likely to achieve retinal reattachment, compared to scleral buckle.[29]

### Vitrectomy [edit]

Vitrectomy is an increasingly used treatment for retinal detachment. It involves the removal of the vitreous gel and is usually combined with filling the eye with either a gas bubble ($SF_6$ or $C_3F_8$ gas) or silicone oil (PDMS). An advantage of using gas in this operation is that there is no myopic shift after the operation and gas is absorbed within a few weeks. PDMS, if used, needs to be removed after a period of 2–8 months depending on surgeon's preference. Silicone oil is more commonly used in cases associated with proliferative vitreo-retinopathy (PVR). A disadvantage is that a vitrectomy always leads to more rapid progression of a cataract in the operated eye. In many places vitrectomy is the most commonly performed operation for the treatment of retinal detachment. A recent Cochrane Review assessing various tamponade agents for patients with retinal detachment associated with PVR found that patients treated with $C_3F_8$ gas and standard silicone oil had visual and anatomic advantages over patients using $SF_6$.[30] Heavy silicone oil did not show any advantages over regular silicone oil.[30]

## Prognosis [edit]

85 percent of cases will be successfully treated with one operation with the remaining 15 percent requiring 2 or more operations. After treatment patients gradually regain their vision over a period of a few weeks, although the visual acuity may not be as good as it was prior to the detachment, particularly if the macula was involved in the area of the detachment.

Up until the early 20th century, the prognosis for rhegmatogenous retinal detachment was very poor, and no effective treatments were available. Currently, about 95 percent of cases of retinal detachment can be repaired successfully.[31] Treatment failures usually involve either the failure to recognize all sites of detachment, the formation of new retinal breaks, or proliferative vitreoretinopathy.[31]

Involvement of the macula portends a worse prognosis. In cases where the macula is not involved (detached), 90 percent of patients have 20/40 vision or better after reattachment surgery.[31] Some damage to vision may occur during reattachment surgery, and 10 percent of patients with normal vision experience some vision loss after a successful reattachment surgery.

## Epidemiology [edit]

The incidence of retinal detachment in otherwise normal eyes is around 5 new cases in 100,000 persons per year.[32] Detachment is more frequent in middle-aged or elderly populations, with rates of around 20 in 100,000 per year.[33] The lifetime risk in normal individuals is about 1 in 300.[5] Asymptomatic retinal breaks are present in about 6% of eyes in both clinical and autopsy studies.[34][*needs update*]

- Retinal detachment is more common in people with severe myopia (above 5–6 diopters), in whom the retina is more thinly stretched. In such patients, lifetime risk rises to 1 in 20.[35][*not in citation given*] About two-thirds of cases of retinal detachment occur in myopics. Myopic retinal detachment patients tend to be younger than non-myopic ones.
- Retinal detachment is more frequent after surgery for cataracts. The estimated long-term prevalence of retinal detachment after cataract surgery is in the range of 5 to 16 per 1000 cataract operations,[36] but is much higher in patients who are highly myopic, with a prevalence of up to 7% being reported in one study.[37] One study found that the probability of experiencing retinal detachment within 10 years of cataract surgery may be about 5 times higher than in the absence of treatment.[38]
- Tractional retinal detachments can also occur in patients with proliferative diabetic retinopathy[39] or those with proliferative retinopathy of sickle cell disease.[40] In proliferative retinopathy, abnormal blood vessels (neovascularization) grow within the retina and extend into the vitreous. In advanced disease, the vessels can pull the retina away from the back wall of the eye, leading to tractional retinal detachment.

Although retinal detachment usually occurs in just one eye, there is a 15% chance of it developing in the

other eye, and this risk increases to 25–30% in patients who have had a retinal detachment and cataracts extracted from both eyes.[35]

## See also [edit]

- Cystathionine beta synthase deficiency
- Retinoschisis
- Retinal regeneration
- Moore's lightning streaks

## References [edit]


1. ^ a b c d e f Fraser, S; Steel, D (24 November 2010). "Retinal detachment.". *BMJ clinical evidence*. **2010**. PMC 3275330. PMID 21406128.
2. ^ a b "Facts About Retinal Detachment". *National Eye Institute*. October 2009. Retrieved 26 July 2016.
3. ^ a b Mitry, D; Charteris, DG; Fleck, BW; Campbell, H; Singh, J (June 2010). "The epidemiology of rhegmatogenous retinal detachment: geographical variation and clinical associations.". *The British journal of ophthalmology*. **94** (6): 678–84. doi:10.1136/bjo.2009.157727. PMID 19515646.
4. ^ a b c Gelston, CD (15 October 2013). "Common eye emergencies.". *American family physician*. **88** (8): 515–9. PMID 24364572.
5. ^ a b c d Gariano RF, Kim CH (2004). "Evaluation and management of suspected retinal detachment". *American family physician*. **69** (7): 1691–1698. PMID 15086041.
6. ^ "Retinal Detachment". Retrieved July 26, 2013.
7. ^ a b Haug SJ, Bhisitkul RB (2012). "Risk factors for retinal detachment following cataract surgery". *Current Opinion in Ophthalmology*. **23** (1): 7–11. doi:10.1097/ICU.0b013e32834cd653. PMID 22081033.
8. ^ Detachment – NHS Choices
9. ^ Byer NE (1994). "Natural history of posterior vitreous detachment with early management as the premier line of defense against retinal detachment". *Ophthalmology*. **101** (9): 1503–13; discussion 1513–4. doi:10.1016/S0161-6420(94)31141-9. PMID 8090453.
10. ^ Dickerman RD, Smith GH, Langham-Roof L, McConathy WJ, East JW, Smith AB (1999). "Intra-ocular pressure changes during maximal isometric contraction: does this reflect intra-cranial pressure or retinal venous pressure?". *Neurol. Res*. **21** (3): 243–6. PMID 10319330.
11. ^ Mattioli S, De Fazio R, Buiatti E, Truffelli D, Zanardi F, Curti S, Cooke RM, Baldasseroni A, Miglietta B, Bonfiglioli R, Tassinari G, Violante FS (2008). "Physical exertion (lifting) and retinal detachment among people with myopia". *Epidemiology*. **19** (6): 868–71. doi:10.1097/EDE.0b013e318187a7da. PMID 18854710.
24. ^ AJ Franklin1, M Yu2 and RK Maturi3 (2002). "Tobacco Smoking Negatively Affects the Outcome of Retinal Detachment Repair". *Invest Ophthalmol Vis Sci*. **43**.
25. ^ Goldman 2011, pp. 2390–2391
26. ^ Vrablik, ME; Snead, GR; Minnigan, HJ; Kirschner, JM; Emmett, TW; Seupaul, RA (February 2015). "The Diagnostic Accuracy of Bedside Ocular Ultrasonography for the Diagnosis of Retinal Detachment: A Systematic Review and Meta-analysis.". *Annals of Emergency Medicine*. **65** (2): 199–203.e1. doi:10.1016/j.annemergmed.2014.02.020. PMID 24680547.
27. ^ "The Diagnostic Accuracy of Bedside Ocular Ultrasonography for the Diagnosis of Retinal Detachment: A Systematic Review and Meta-analysis". *Annals of Emergency Medicine*. **65** (2): 199–203.e1. February 2015. doi:10.1016/j.annemergmed.2014.02.020. PMID 24680547.
28. ^ Shukla Manoj; Ahuja OP; Jamal Nasir (1986). "Traumatic retinal detachment". *Indian J Ophthalmol*. **34**: 29–32. PMID 3443496.
29. ^ a b Hatef E, Sena DF, Fallano KA, Crews J, Do DV (2015). "Pneumatic retinopexy versus scleral buckle for repairing simple rhegmatogenous retinal detachments". *Cochrane Database Syst Rev*. **5**: CD008350. doi:10.1002/14651858.CD008350.pub2. PMID 25950286.
30. ^ a b Schwartz SG, Flynn Jr HW, Lee WH, Wang X (2014). "Tamponade in surgery for retinal detachment associated with proliferative vitreoretinopathy". *Cochrane Database Syst Rev*. **2**: CD006126. doi:10.1002/14651858.CD006126.pub3. PMC 3990035. PMID 24532038.
31. ^ a b c Yanoff & Duker 2008, pp. 725
32. ^ Ivanisević M, Bojić L, Eterović D (2000). "Epidemiological study of nontraumatic phakic rhegmatogenous retinal detachment". *Ophthalmic Res*. **32** (5): 237–9. doi:10.1159/000055619. PMID 10971186.

12. ^ Mattioli S, Curti S, De Fazio R, Farioli A, Cooke RM, Zanardi F, Violante FS (2009). "Risk Factors for Retinal Detachment". *Epidemiology*. **20** (3): 465–466. doi:10.1097/EDE.0b013e31819f1b17. PMID 19363359.
13. ^ Farioli A, Hemmingsson T, Kriebel D : Vascular risk factors and rhegmatogenous retinal detachment: a follow-up of a national cohort of Swedish men. British Journal of Ophthalmology 2016; 100: 907-913.
14. ^ Delyfer MN, Raffelsberger W, Mercier D, Korobelnik JF, Gaudric A, Charteris DG, Tadayoni R, Metge F, Caputo G, Barale PO, Ripp R, Muller JD, Poch O, Sahel JA, Léveillard T (2011). Barnes, Steven, ed. "Transcriptomic Analysis of Human Retinal Detachment Reveals Both Inflammatory Response and Photoreceptor Death". *PLoS ONE*. **6** (12): e28791. doi:10.1371/journal.pone.0028791. PMC 3235162. PMID 22174898.
15. ^ *a b c d* Yanoff & Duker 2008, pp. 724
16. ^ Yanoff & Duker 2008, pp. 492
17. ^ Goldman 2011, pp. e236-13
18. ^ *a b* Goldman 2011, pp. 2467
19. ^ "Retinal detachment". *MedlinePlus Medical Encyclopedia*. National Institutes of Health. 2005. Retrieved 2006-07-18.
20. ^ Goldman 2011, pp. 1362
21. ^ Goldman 2011, pp. 2442
22. ^ Goldman 2011, pp. 2441
23. ^ Sema DÜNDAR1, Fatih ÖZCURA2, İbrahim METEOĞLU3, Mehmet Erkut KARA4 (2012). "Effects of long-term passive smoking on the vascular endothelial growth factor and apoptosis marker expression in the retina and choroid" (PDF). *Turk J Med Sci*. **42** (3): 377–383.
33. ^ Li X (2003). "Incidence and epidemiological characteristics of rhegmatogenous retinal detachment in Beijing, China". *Ophthalmology*. **110** (12): 2413–7. doi:10.1016/S0161-6420(03)00867-4. PMID 14644727.
34. ^ Wilkinson CP (2012). "Interventions for asymptomatic retinal breaks and lattice degeneration for preventing retinal detachment". *Cochrane Database Syst Rev*. **3**: CD003170. doi:10.1002/14651858.CD003170.pub3. PMC 4730545. PMID 22419286.
35. ^ *a b* "eMedicine –Retinal Detachment : Article by Gregory Luke Larkin, MD, MSPH, MSEng, FACEP". Retrieved 2007-06-04.
36. ^ Ramos M, Kruger EF, Lashkari K (2002). "Biostatistical analysis of pseudophakic and aphakic retinal detachments". *Seminars in ophthalmology*. **17** (3–4): 206–13. doi:10.1076/soph.17.3.206.14784. PMID 12759852.
37. ^ Hyams SW, Bialik M, Neumann E (1975). "Myopia-aphakia. I. Prevalence of retinal detachment". *The British journal of ophthalmology*. **59** (9): 480–2. doi:10.1136/bjo.59.9.480. PMC 1042658. PMID 1203233.
38. ^ Rowe JA, Erie JC, Baratz KH, Hodge DO, Gray DT, Butterfield L, Robertson DM (1999). "Retinal detachment in Olmsted County, Minnesota, 1976 through 1995". *Ophthalmology*. **106** (1): 154–159. doi:10.1016/S0161-6420(99)90018-0. PMID 9917797.
39. ^ "Diabetic Retinopathy: Retinal Disorders: Merck Manual Home Health Handbook". Retrieved 2007-06-04.
40. ^ "IU Opt Online CE: Retinal Vascular Disease: Sickle Cell Retinopathy". Retrieved 2007-06-04.


### Notes


- Goldman, Lee (2011). *Goldman's Cecil Medicine* (24th ed.). Philadelphia: Elsevier Saunders. p. 1362. ISBN 1437727883.
- Yanoff, Myron; Duker, Jay S. (2008). *Ophthalmology* (3rd ed.). Edinburgh: Mosby. ISBN 978-0323057516.


## External links [edit]

- Retinal Detachment Resource Guide from the National Eye Institute (NEI).
- Overview of retinal detachment from eMedicine
- Guidelines from the American Academy of Family Physicians
- Retinal detachment information from WebMD
- Retinal detachment information from the Merck Manual

Wikimedia Commons has media related to *Retinal detachment*.

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|---|---|---|
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Categories: Medical emergencies | Disorders of choroid and retina

# Sjögren's syndrome

From Wikipedia, the free encyclopedia

*Not to be confused with Sjögren–Larsson syndrome, a skin disorder.*

**Sjögren's syndrome** (**SS**) is a long-term autoimmune disease in which the moisture-producing glands of the body are affected.[2] This results primarily in the development of a dry mouth and dry eyes.[3] Other symptoms can include dry skin, a chronic cough, vaginal dryness, numbness in the arms and legs, feeling tired, muscle and joint pains, and thyroid problems.[2] Those affected are at an increased risk (5%) of lymphoma.[3][4]

While the exact cause is unclear it is believed to involve a combination of genetics and an environmental trigger such as exposure to a virus or bacteria.[2] It can occur independently of other health problems (primary Sjögren's syndrome) or as a result of another connective tissue disorder (secondary Sjögren's syndrome).[5] The inflammation that results progressively damages the glands.[4] Diagnosis is by biopsy of moisture-producing glands and blood tests looking for specific antibodies.[3] On biopsy there is typically lymphocyte within the glands.[3]

Treatment is directed at the person's symptoms. For dry eyes artificial tears, medications to reduce inflammation, or surgery to shut the tear ducts, may be tried. For a dry mouth, chewing gum, sipping water, or a saliva substitute may be used. In those with joint or muscle pain, ibuprofen may be used. Medications that can cause dryness may also be stopped such as antihistamines.[2]

The disease was described in 1933 by Henrik Sjögren after whom it is named; however, a number of earlier descriptions of people with the symptoms exist.[5] Between 0.2% and 1.2% of the population are affected, with half having the primary form and half the secondary form.[4] Females are affected about ten times as often as males and it commonly begins in middle age;[3][5] however, anyone can be affected.[3] Among those without other autoimmune disorders, life expectancy is unchanged.[6]

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**Sjögren syndrome**

**Synonyms** Sjögren syndrome

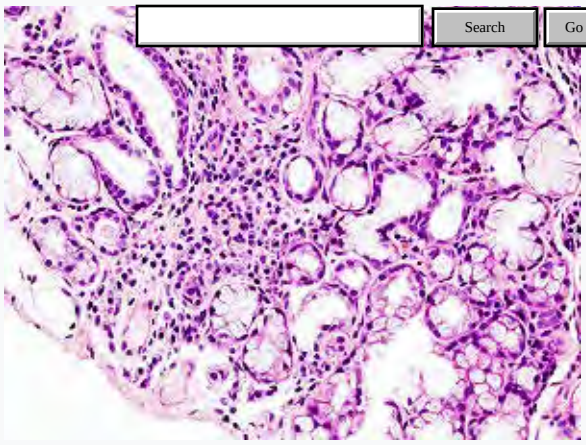


Image with a microscope of focal lymphoid infiltration in the minor salivary gland associated with Sjögren's syndrome, H & E stain

**Pronunciation** English /ˈʃoʊgrɪn/ or /ˈʃɜːrgrɛn/[1] Swedish [ˈɧøːgreːn]

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Rheumatology |
| **ICD-10** | M35.0 |
| **ICD-9-CM** | 710.2 |
| **OMIM** | 270150 |
| **DiseasesDB** | 12155 |
| **MedlinePlus** | 000456 |
| **eMedicine** | med/2136 emerg/537 derm/846 ped/2811 oph/477 oph/695 |
| **Patient UK** | Sjögren's syndrome |
| **MeSH** | D012859 |

[edit on Wikidata]

## Signs and symptoms [edit]

The hallmark symptom of SS is a generalized dryness, typically including dry mouth and keratoconjunctivitis sicca (dry eyes), part of what are known as sicca symptoms. Sicca syndrome also incorporates vaginal dryness and chronic bronchitis. SS may cause skin, nose, and vaginal dryness, and may affect other organs of the body, including the muscles (myositis), kidneys, blood vessels, lungs, liver, biliary system, pancreas, peripheral nervous system (distal axonal sensorimotor neuropathy or small fiber peripheral neuropathy) and brain. Some patients have gastric issues such as GERD, achlorhydria and/or gastroparesis, and chronic pain with accompanying fatigue and brain fog.

Skin dryness in some people with SS may be the result of lymphocytic infiltration into skin glands. The symptoms may develop insidiously, with the diagnosis often not considered for several years, because the complaints of sicca may be otherwise attributed to medications, a dry environment, aging, or may be regarded as not of severity warranting the level of investigation necessary to establish the presence of the specific underlying autoimmune disorder condition.[7]

SS can damage vital organs of the body with symptoms that may plateau or worsen, or go into remission as with other autoimmune diseases. Some people may experience only the mild symptoms of dry eyes and mouth, while others have symptoms of severe disease. Many patients can treat problems symptomatically. Others are forced to cope with blurred vision, constant eye discomfort, recurrent mouth infections, swollen parotid glands, dysphonia (vocal disorders including hoarseness), and difficulty in swallowing and eating. Debilitating fatigue and joint pain can seriously impair quality of life. Some patients can develop renal involvement (autoimmune tubulointerstitial nephritis) leading to proteinuria (excess protein in urine), urinary concentrating defect, and distal renal tubular acidosis.

### Associated conditions [edit]

SS is associated with a number of other medical conditions, many of which are autoimmune or rheumatic disorders, such as celiac disease,[8][9] fibromyalgia, autoimmune thyroiditis, multiple sclerosis and spondyloarthropathy,[10] and several malignancies, principally non-Hodgkin lymphoma.[10][11]

## Cause [edit]

Although the cause of SS is unknown, it is believed to be under the influence of a combination of genetic, environmental, and several other factors, as is the case with many other autoimmune disorders.[12]

### Genetic factors [edit]

The observation of high rates of autoimmune disorders in families of SS is linked with a genetic predisposition to the syndrome.[13] Studies on the polymorphisms of human leukocyte antigen (HLA)-DR and HLA-DQ gene regions in SS patients show differential susceptibility to the syndrome due to different types of the resulting autoantibody production.[13]

### Hormonal factors [edit]

Since SS is associated with a high prevalence in women, sex hormones, especially estrogen, are believed to affect humoral and cell-mediated immune responses affecting susceptibility to the syndrome.[13] Androgens are generally considered to prevent autoimmunity.[14] Studies on mice models suggest estrogen deficiency stimulates presentation of autoantigens, inducing SS-like symptoms.[13]

### Microchimerism factors [edit]

Microchimerism of fetal cells (offspring lymphoid cells in maternal circulation) may generate autoimmunity in women who have been previously pregnant.[14][15] Generation of an autoimmune potential via microchimerism may lead to a switch from a silent form of autoimmunity with age-dependent decrease in self-tolerance.[14]

### Environmental factors [edit]

Viral proteins, engulfed molecules, or degraded self-structures may initiate autoimmunity by molecular mimicry and increase the chances of SS development.[14] Epstein-Barr virus, hepatitis C, and human T-cell leukemia virus-1 are among the most studied infectious agents in SS.[14] Damaged self-structures targeted for apoptosis may be mistakenly exposed to the immune system, triggering autoimmunity in exocrine glands which are often prone to autoimmune responses.[14]

## Pathogenesis [edit]

The pathogenetic mechanisms of SS have not been fully elucidated, resulting in the lack of pathophysiology knowledge of the management of this autoimmune exocrinopathy. Although the numerous factors contributing to the progression of this disease have made it difficult to find out the exact origin and cause, major advances over the past decade have contributed to a proposed set of pathogenic events that occur prior to the diagnosis of SS.[16]

SS was originally proposed to be a specific, self-perpetuating immune system-mediated loss of exocrine glands, specifically acinar and ductal cells. Although this explains the more obvious symptoms (e.g., the lack of salivary and lacrimal fluid), it does not explain the more widespread systemic effects seen in the progression of the disease.

In the presence of a susceptible genetic background, both environmental and hormonal factors are thought to be capable of triggering the infiltration of lymphocytes, specifically CD4+ T cells, B cells, and plasma cells, causing glandular dysfunction in the salivary and lacrimal glands.[16]

SS is associated with increased levels in cerebrospinal fluid (CSF) of IL-1RA, an interleukin 1 antagonist. This suggests that the disease begins with increased activity in the interleukin 1 system, followed by an autoregulatory up-regulation of IL-1RA to reduce the successful binding of interleukin 1 to its receptors. Interleukin 1 likely is the marker for fatigue, but increased IL-1RA is observed in the CSF and is associated with increased fatigue through cytokine-induced sickness behavior.[17] SS, though, is characterized by decreased levels of IL-1ra in saliva, which could be responsible for mouth inflammation and dryness.[18] Patients with secondary SS also often exhibit signs and symptoms of their primary rheumatic disorders, such as systemic lupus erythematosus, rheumatoid arthritis, or systemic sclerosis.

### Genetic predisposition [edit]

The genetic locus most significantly associated with primary SS is the major histocompatibility complex/human leukocyte antigen (MHC/HLA) region, as demonstrated by the preliminary results of the first genome-wide

association study (GWAS).[19] This GWAS included data from a discovery cohort of 395 patients of European ancestry with primary SS, and 1,975 healthy control individuals, and from a replication study that comprised 1,234 cases and 4,779 healthy controls. Associations with polymorphisms located at six independent loci were also detected; *IRF5, STAT4, BLK, IL12A, TNIP1,* and *CXCR5*. This also suggested the activation of the innate immune system, notably through the IFN system, B-cell activation through *CXCR5*-directed recruitment to lymphoid follicles and B-cell receptor (BCR) activation involving *BLK*, and T-cell activation owing to HLA susceptibility and the IL-12-IFN-γ-axis.[20]

Patients of different ethnic origin carry different HLA susceptibility alleles, of which, HLA-DR and HLA-DQ are involved in the pathogenesis of SS. For example, patients from Northern and Western Europe and from North America show a high prevalence of *B8, DRw52,* and *DR3* genes.[21] HLA class II alleles are associated with the presence of specific subsets of autoantibodies, rather than with the disease itself.[22] Autoantibodies refer to the loss of B-cell tolerance leading to production of antibodies directed against diverse organ-specific and organ nonspecific antigens.[16] Association between HLA and SS is restricted to patients with anti-SSA/Ro or anti-SSB/La antibodies. Seropositivity for anti-Ro and anti-La is associated with greater severity and longer duration of disease, and findings of their high abundance from the salivary glands of SS patients suggests their imperative role in the pathogenesis of SS.[23]

Beyond genetics, epigenetic abnormality related to DNA methylation, histone acetylation, or microRNA expression probably have key roles in the pathogenesis of autoimmune diseases, including SS, though research in this area is very limited and minimal.[24]

## Environmental triggers [edit]

Environmental factors, such as glandular viral infection, could prompt epithelial cells to activate the HLA-independent innate immune system through toll-like receptors.[25] Although a number of infectious, exogenous agents have been implicated in the pathogenesis of SS, such as Epstein-Barr virus (EBV), human T-lymphotropic virus 1, and hepatitis C virus, their association with appears weak. While EBV is present in the salivary glands of normal individuals, a high incidence of EBV reactivation in SS patients has been reported with increased levels of EBV DNA. This indicates viral reactivation and inability of lymphoid infiltrates to control EBV replication in SS, leading to the initiation or perpetuation of an immune response in target organs. Nonetheless, it remains to be clarified exactly how reactivation of EBV is induced in lesions of patients with SS, and which specific molecular mechanisms are involved in the process of viral reactivation.[26]

## Inflammation [edit]

Epithelial cells in SS lesions are active participants in the induction and perpetuation of the inflammatory process. Environmental and hormonal factors, in concert with an appropriate genetic background, are believed to trigger SS, which dysregulates epithelial cells and allows aberrant homing and activation of dendritic cells (DCs), T cells, and B cells.[27] Dendritic cells are antigen-presenting cells which process antigen material and present it to other T cells. Following the migration of lymphocytes into the glands in response to chemokines and specific adhesion molecules, T cells interact with epithelial cells. Epithelial cells are further activated by proinflammatory cytokines (IL-1β, IFN-γ, and TNF), which are produced by adjacent T cells. The early accumulation of plasmacytoid dendritic cells in the target tissues, which produce high levels of type 1 IFNs, seems to be important, as these cells can further dysregulate the immune response through abnormal retention of lymphocytes in the tissues and their subsequent activation. IFN-α stimulates the production of B-cell activating factor (BAFF) by epithelial cells, DCs, and T cells. BAFF stimulates aberrant B-cell maturation, leading to the emergence of self-reactive B cells, which locally produce autoantibodies, in a germinal centre-like structure (GC-like), which is also the location of lymphomagenesis (origin of lymphoma).[16]

## Programmed cell death [edit]

Dysregulation of apoptosis (programmed cell death) is believed to play a role in the pathogenesis of a variety of autoimmune diseases, though its role in SS is controversial. Both the Fas and Fas ligand proteins are overexpressed in primary SS patients, while expression of BCL-1, which is known to downregulate apoptosis, was found to be significantly reduced in acinar and ductal epithelial cells of SS patients compared to healthy people.[28][29] *In situ* studies did not show increased apoptosis among glandular epithelial cells, but did show reduced apoptosis among infiltrating mononuclear cells. Reduced apoptosis was also implicated in the

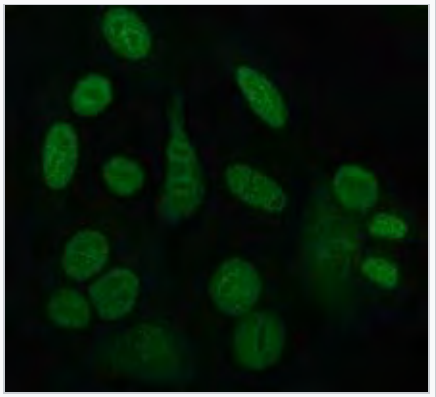
accumulation of autoreactive B-cells found in the glands. The relationship of autoantibodies expressed in SS with apoptosis is still being researched.[12]

### Hormonal factors [edit]

Sex hormones seem to influence humoral and cell-mediated immune response, with estrogen being considered one of the biggest factors responsible for sex-immunologic dimorphism.[30] Estrogen deficiency appears to play a role in development of SS.[31] It has been hypothesized that androgen administration to the ocular surface may serve as an effective therapy for dry eyes.[32]

## Diagnosis [edit]

Diagnosing SS is complicated by the range of symptoms a patient may manifest, and the similarity between symptoms of SS and those of other conditions. Also, patients who have symptoms of SS approach different specialities regarding their symptoms which make the diagnosis difficult. Since the symptoms of this autoimmune disorder such as dry eyes and dry mouth are very common among people, and mostly observed from the age of 40 and above, it is often mistaken as age-related, thus ignored. However, some medications can also cause symptoms that are similar to those of SS. The combination of several tests, which can be done in a series, can eventually lead to the diagnosis of SS.[15][33]



Speckled Immunofluorescence staining pattern of antinuclear antibodies on HEp-20-10 cells

SS is usually classified as either 'primary' or 'secondary'. Primary Sjögren's syndrome occurs by itself and secondary Sjögren's syndrome occurs when another connective tissue disease is present.

Blood tests can be done to determine if a patient has high levels of antibodies that are indicative of the condition, such as antinuclear antibody (ANA) and rheumatoid factor (because SS frequently occurs secondary to rheumatoid arthritis), which are associated with autoimmune diseases. Typical SS ANA patterns are SSA/Ro and SSB/La, of which SSB/La is far more specific; SSA/Ro is associated with numerous other autoimmune conditions, but are often present in SS. However, SSA and SSB tests are frequently not positive in SS.

The rose bengal test uses a stain that measures state and function of the lacrimal glands. This test involves placing the non-toxic dye rose bengal on the eyes. The dye's distinctive colour helps in determining the state and functioning of tear film and the rate of tear evaporation. Any distinctive colour change observed will be indicative of SS, but many related diagnostic tools will be used to confirm the condition of SS.[33]

Schirmer's test measures the production of tears: a strip of filter paper is held inside the lower eyelid for five minutes, and its wetness is then measured with a ruler. Producing less than 5 mm (0.20 in) of liquid is usually indicative of SS. This measurement analysis varies among people depending on other eye-related conditions and medications in use when the test is taken.[33] A slit-lamp examination can reveal dryness on the surface of the eye.

Symptoms of dry mouth and dryness in the oral cavity are caused by the reduced production of saliva from the salivary glands (parotid gland, submandibular gland, and sublingual gland). To check the status of salivary glands and the production of saliva, a salivary flow-rate test is performed, in which the person is asked to spit as much as they can into a cup, and the resulting saliva sample is collected and weighed. This test's results can determine whether the salivary glands are functioning adequately. Not enough saliva produced could mean the person has SS.[33] An alternative test is non-stimulated whole saliva flow collection, in which the person spits into a test tube every minute for 15 minutes. A resultant collection of less than 1.5 ml (0.053 imp fl oz; 0.051 US fl oz) is considered a positive result.[34]

A lip/salivary gland biopsy takes a tissue sample that can reveal lymphocytes clustered around salivary glands, and damage to these glands due to inflammation. This test involves removing a sample of tissue from a person's inner lip/salivary gland and examining it under a microscope. In addition, a sialogram, a special X-ray test, is performed to see if any blockage is present in the salivary gland ducts (i.e. parotid duct) and the amount of saliva that flows into the mouth.[33]

Also, a radiological procedure is available as a reliable and accurate test for SS. A contrast agent is injected into the parotid duct, which opens from the cheek into the vestibule of the mouth opposite the neck of the upper second molar tooth. Histopathology studies should show focal lymphocytic sialadenitis. Objective evidence of salivary gland involvement is tested through ultrasound examinations, the level of unstimulated whole salivary flow, a parotid sialography or salivary scintigraphy, and autoantibodies against Ro (SSA) and/or La (SSB) antigens.

SS can be excluded from people with past head and neck radiation therapy, acquired immunodeficiency syndrome, pre-existing lymphoma, sarcoidosis, graft-versus-host disease, and use of anticholinergic drugs.

## Prevention [edit]

There is no prevention mechanism for SS due to its complexity as an autoimmune disorder. However, lifestyle changes can reduce the risk factors of getting SS or reduce the severity of the condition with patients who have already been diagnosed. Diet is strongly associated with inflammation that is mostly seen in many autoimmune related diseases including SS. An experimental study show that SS patients show high sensitivity to gluten that directly relates to inflammation.[35] Moderate exercise is also found to be helpful in SS patients mainly reducing the effect of lung inflammation.[36]

## Treatment [edit]

Neither a cure for SS nor a specific treatment is known to permanently restore gland secretion. Instead, treatment is generally symptomatic and supportive.

### Eye care [edit]

Moisture replacement therapies such as artificial tears may ease the symptoms of dry eyes. Some patients with more severe problems use goggles to increase local humidity or have punctal plugs inserted to help retain tears on the ocular surface for a longer time.

Additionally, cyclosporine (Restasis) is available by prescription to help treat chronic dry eye by suppressing the inflammation that disrupts tear secretion. Prescription drugs are also available that help to stimulate salivary flow, such as cevimeline (Evoxac) and pilocarpine. Salagen, a manufactured form of pilocarpine, can be used to help produce tears, as well as saliva in the mouth and intestines. It is derived from the jaborandi plant.

### Vaginal dryness [edit]

In women with SS, vaginal dryness, vulvodynia and dyspareunia (painful sexual intercourse) are often reported; personal lubricants are recommended to help lessen irritation or pain that may result from dryness in the vaginal and vulvar areas.[33]

### Musculoskeletal [edit]

Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used to treat musculoskeletal symptoms. For individuals with severe complications, corticosteroids or immunosuppressive drugs may be prescribed, and sometimes IVIG (intravenous immunoglobulin). Also, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate may be helpful. Hydroxychloroquine (Plaquenil) is another option and is generally considered safer than methotrexate. However, these prescribed drugs have a range of side effects such as nausea, loss of appetite, dizziness, hair loss, stomach aches/cramps, headache, liver toxicity, and increased risk of infections. Also, people who take drugs to suppress the immune system are more likely to develop cancer later.[33]

### Systemic [edit]

For systemic symptoms, including fatigue, joint pain, myositis and neuropathy, biologic immunosuppressant drugs such as Rituxan and Benlysta that work via B-cell pathology are often used and have less toxic profiles than traditional immunosuppressive regimens.

### Dental care [edit]

Preventive dental treatment is also necessary (and often overlooked by the patient), as the lack of saliva associated with xerostomia creates an ideal environment for the proliferation of bacteria that cause cavities.[37] Treatments include at-home topical fluoride application to strengthen tooth enamel and frequent teeth cleanings by a dental hygienist. Existing cavities must also be treated, as cavities that extend into the tooth can not be effectively treated through teeth cleaning alone, and are at a high risk of spreading into the pulp of the tooth, leading to the loss of vitality and need for extraction or root canal therapy. This treatment regimen is the same as that used for all xerostomia patients, such as those undergoing head and neck radiation therapy which often damages the salivary glands, as they are more susceptible to radiation than other body tissues.

Unfortunately, many patients, not realizing the need for dental treatment, do not see a dentist until most of their teeth are beyond the point of restoration. It is not uncommon for a dentist to see a xerostomia patient with severe, untreatable cavities in almost every tooth. In severe cases, the only viable treatment may be to extract all of the patient's teeth and treat with prosthetics such as dentures or implants.

## Prognosis [edit]

Published studies on the survival of SS patients are limited in varied respects, perhaps owing to the relatively small sample sizes, and secondary SS is associated with other autoimmune diseases. However, results from a number of studies indicated, compared to other autoimmune diseases, SS is associated with a notably high incidence of malignant non-Hodgkin lymphoma (NHL).[16] NHL is the cancer derived from white blood cells. About 5% of patients with SS will develop some form of lymphoid malignancy.[38] Patients with severe cases are much more likely to develop lymphomas than patients with mild or moderate cases.[39] The most common lymphomas are salivary extranodal marginal zone B cell lymphomas (MALT lymphomas in the salivary glands)[40] and diffuse large B-cell lymphoma.[39]

Lymphomagenesis in primary SS patients is considered as a multistep process, with the first step being chronic stimulation of autoimmune B cells, especially B cells that produce rheumatoid factor at sites targeted by the disease.[41][42] This increases the frequency of oncogenic mutation, leading to any dysfunction at checkpoints of autoimmune B-cell activation to transform into malignancy. A study's finding has concluded the continuous stimulation of autoimmune B cells, leading to subtle germinal abnormalities in genes having specific consequences in B cells, which underlies the susceptibility to lymphoma.[43]

Apart from this notably higher incidence of malignant NHL, SS patients show only modest or clinically insignificant deterioration in specific organ-related function, which explains the only slight increases in mortality rates of SS patients in comparison with the remainder of the population.[16]

## Complications [edit]

Among the complications discussed above, women with anti-Ro/SSA and anti-La/SSA antibodies who become pregnant, have an increased rate of neonatal lupus erythematosus with congenital heart block requiring a pacemaker.[44] Type I cryoglobulinemia is a known complication of SS.[45]

## Epidemiology [edit]

SS is the third most common rheumatic autoimmune disorder, behind rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[46] There are no geographical differences in the rates of SS.[47] SS has been reported in all areas of the world, although regional rates have not been well studied.[47][48] Depending on the criteria for determining prevalence, studies estimate the prevalence of SS at 500,000 to 2 million people in the United States. Moreover, other broader studies of prevalence of SS range widely with some reports of up to a prevalence of 3% of the population.[46] A few studies that have been conducted on the incidence of SS report that the incidence of the syndrome varies between 3 and 6 per 100,000 per year.[46][49]

Nine out of ten SS patients are reported to be women.[12][48] In addition to prevalence in women, having a first-degree relative with an autoimmune disease and previous pregnancies have been identified as

epidemiological risk factors.[50] Differences in prevalence due to race and ethnicity are unknown.

Although SS occurs in all age groups, the average age of onset is between ages 40 and 60, although experts note that up to half of all cases may be left undiagnosed or unreported.[12][46][51][52] The prevalence of SS generally increases with age.[46]

SS has been known to be reported in 30-50% of people with rheumatoid arthritis, as well as 10-25% with systemic lupus erythematosus.[12]

## History [edit]


Henrik Samuel Conrad Sjögren

Johann von Mikulicz-Radecki (1850–1905) is generally credited with the first description of SS. In 1892, he described a 42-year-old man with enlargement of the parotid and lacrimal glands associated with a round-cell infiltrate and acinar atrophy.[33][53] However, the criteria Mikulicz established for diagnosis, often led to misdiagnosis of Mikulicz's syndrome. Many conditions, such as tuberculosis, infections, sarcoidosis, and lymphoma present with similar conditions to those listed under Mikulicz's syndrome.[33] Nevertheless, the term "Mikulicz's syndrome" is still used occasionally to describe the appearance of lymphocytic infiltrates on salivary-gland biopsies.[33]

In 1930, Henrik Sjögren (1899–1986), an ophthalmologist in Jönköping, Sweden, observed a patient with low secretions from the lacrimal and salivary glands.[54] Sjögren introduced the term keratoconjunctivitis sicca for the symptom of dry eyes (keratoconjunctivitis). In 1933, he published his doctoral thesis, describing 19 females, most of whom were postmenopausal and had arthritis, showing clinical and pathological manifestations of the syndrome.[53] Sjögren clarifies that keratoconjunctivitis sicca, resulting from water deficiency, had no relation to xerophthalmia, resulting from vitamin A deficiency.[53] Sjögren's thesis was not well received as the Board of Examiners criticized some clinical aspects.[54]

After extensive research and data collection, Sjögren published an essential paper in 1951, describing 80 patients with keratoconjunctivitis sicca, 50 of whom also had arthritis.[54] His subsequent follow-up conference trips pertaining to his paper led to an international interest in SS.[54] The term *keratoconjunctivitis sicca* was coined by Sjögren himself began to be identified as SS in literature,[54] although it can now have more general usage.

## Research [edit]

Research on multifactorial autoimmune diseases such as SS focuses on expanding the knowledge surrounding the disorder, improving diagnostic tools and finding ways to prevent, manage, and cure the disorder. The United Kingdom Primary Sjögren's Syndrome Registry, a tissue biobank of samples taken for research, supported by the Medical Research Council, UK was established in 2010.[55]

As an autoimmune disease, susceptibility to SS is greatly influenced by the human leukocyte antigen.[56] DQA1*05:01, DQB1*02:01, and DRB1*03:01 alleles were identified as risk factors, while DQA1*02:01, DQA1*03:01 and DQB1*05:01 alleles were found to be protective factors for the disease.[57] The relationship between alleles and specific race was also established.[58] HLA-DQ2 and HLA-B8 are generally found in Caucasian patients, while HLA-DR5 is related to Greek and Israeli patients.[58] Multiple genome-wide association scans may be conducted in the future to identify key risk variants.[56]

Viruses that can trigger the immune response of the syndrome include


Singer-actress Carrie Ann Inaba is the National Awareness Ambassador and Spokesperson for the Sjogren's Syndrome Foundation.

human T-lymphotropic virus type 1 (HTLV-1), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV) and hepatitis C virus (HCV).[58] The UK Primary Sjögren's Syndrome Registry supports clinical trials and genetic studies of SS and is open to patients wishing to participate in research studies and researchers studying the disease.[55]

Some research showed that the lack of vitamin A and vitamin D are associated with this disease.[58] Vitamin D deficiency was found to be related to neurological manifestations and the presence of lymphoma among patients. On the other hand, vitamin A levels were inversely associated with extra-glandular manifestations of the disease.[58]

Saliva is a potential diagnostic tool of SS because the salivary component is changed after onset of the disease.[59] With the new miniaturization technology, called 'lab on a chip', the diagnosis can be more convenient.[59]

With regard to therapeutics, multiple monoclonal antibodies were under investigation in 2007.[60] The most promising seemed to be the anti-CD20 rituximab and the anti-CD22 epratuzumab, while the anti-TNF-α and IFN-α seemed less effective.[60]

In 2014, the Sjögren's Syndrome Foundation announced a five-year goal to cut the time to diagnoses in half.[61]

## Notable cases [edit]

- Shannon Boxx (U.S. Olympic soccer player) has both SS and lupus.[62]
- Carrie Ann Inaba (singer-actress) is the National Awareness Ambassador & Spokesperson for the Sjogren Syndrome Foundation.[63]
- Venus Williams (world champion tennis player) has been diagnosed with SS and said she had struggled with fatigue for years.[64]

## See also [edit]

- Benign lymphoepithelial lesion
- Invisible disability
- Keratoconjunctivitis sicca
- List of cutaneous conditions
- Parotitis
- Xerostomia

## References [edit]

- The original text from this article was obtained from a public domain resource at NIH


1. ^ Elsevier, *Dorland's Illustrated Medical Dictionary*, Elsevier.
2. ^ *a b c d* "What Is Sjögren's Syndrome? Fast Facts". *NIAMS*. November 2014. Retrieved 15 July 2016.
3. ^ *a b c d e f* Brito-Zerón, P; Baldini, C; Bootsma, H; Bowman, SJ; Jonsson, R; Mariette, X; Sivils, K; Theander, E; Tzioufas, A; Ramos-Casals, M (7 July 2016). "Sjögren syndrome.". *Nature reviews. Disease primers*. **2**: 16047. doi:10.1038/nrdp.2016.47. PMID 27383445.
4. ^ *a b c* John H., Klippel (2008). *Primer on the rheumatic diseases* (13th ed.). New York, NY: Springer. p. 389. ISBN 9780387685663. Retrieved 15 July 2016.
5. ^ *a b c* Ng, Wan-Fai (2016). *Sjogren's Syndrome*. Oxford University Press. pp. 10–11. ISBN 9780198736950.
6. ^ Singh, AG; Singh, S; Matteson, EL (March 2016). "Rate, risk factors and causes of mortality in patients with Sjögren's syndrome: a systematic review and meta-analysis of cohort studies.". *Rheumatology (Oxford, England)*. **55** (3): 450–60. doi:10.1093/rheumatology/kev354. PMID 26412810.
7. ^ Fox, R. I., Stern, M. & Michelson, P. Update in Sjögren syndrome. Curr. Opin. Rheumatol. 12, 391-398 (2000).
8. ^ Lundin KE, Wijmenga C (Sep 2015). "Coeliac disease and autoimmune disease–genetic overlap and screening". *Nat Rev Gastroenterol Hepatol* (Review). **12** (9): 507–15. doi:10.1038/nrgastro.2015.136. PMID 26303674.
9. ^ Denham JM, Hill ID (Aug 2013). "Celiac disease and autoimmunity: review and controversies". *Curr Allergy Asthma Rep* (Review). **13** (4): 347–53. doi:10.1007/s11882-013-0352-1. PMC 3725235. PMID 23681421.
10. ^ *a b* Gabriel SE, Michaud K (2009). "Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases". *Arthritis Res Ther* (Review). **11** (3): 229. doi:10.1186/ar2669. PMC 2714099. PMID 19519924.
11. ^ Papageorgiou A, Voulgarelis M, Tzioufas AG (Jul 2015). "Clinical picture, outcome and predictive factors of lymphoma in Sjögren syndrome". *Autoimmun Rev* (Review). **14** (7): 641–9. doi:10.1016/j.autrev.2015.03.004. PMID 25808075.
12. ^ *a b c d e* Borchers A. T., Naguwa S. M., Keen C. L., Gershwin M. E. (2003). "Immunopathogenesis of Sjögren's syndrome". *Clin. Rev. Allergy Immunol*. **25**: 89–104. doi:10.1385/criai:25:1:89.
13. ^ *a b c d* Voulgarelis M., Tzioufas A. G. (2010). "Pathogenetic mechanisms in the initiation and perpetuation of Sjögren's syndrome". *Nature reviews. Rheumatology*. **6**: 529–537. doi:10.1038/nrrheum.2010.118.
14. ^ *a b c d e f* Delaleu N., Jonsson R., Koller M. M. (2005). "Sjögren's syndrome". *Eur. J. Oral Sci*. **113**: 101–113. doi:10.1111/j.1600-0722.2004.00183.x.
34. ^ Dr. J. Parks, Ancaster ON Canada
35. ^ Liden M.; et al. (2007). "Gluten sensitivity in patients with primary Sjogren's syndrome". *Scand. J. Gastroenterol*. **42**: 962–962. doi:10.1080/00365520701195345. PMID 17613926.
36. ^ Strombeck B.E., *et al*, Effects of exercise on aerobic capacity and fatigue in women with primary Sjögren's syndrome, *Rheumatology*, 46:868–871, 2007. PMID 17308315. Accessed 2016-11-12.
37. ^ Xin W, Leung KC, Lo EC, Mok MY, Leung MH, A randomized, double-blind, placebo-controlled clinical trial of fluoride varnish in preventing dental caries of Sjögren's syndrome patients, *BMC Oral Health*, 16(1):102, Sep 23, 2016. PMID 27664129. doi:10.1186/s12903-016-0296-7. Accessed 2016-11-12.
38. ^ Tzioufas, Athanasios G.; Voulgarelis, Michael (2007). "Update on Sjögren's syndrome autoimmune epithelitis: from classification to increased neoplasias". *Best Pract Res Clin Rheumatol*. **21** (6): 989–1010. doi:10.1016/j.berh.2007.09.001. PMID 18068857.
39. ^ *a b* Smedby, K. E.; Baecklund, E.; Askling, J. (2006). "Malignant lymphomas in autoimmunity and inflammation: a review of risks, risk factors, and lymphoma characteristics". *Cancer Epidemiol. Biomarkers Prev*. **15** (11): 2069–77. doi:10.1158/1055-9965.EPI-06-0300. PMID 17119030.
40. ^ Voulgarelis, Michael; Skopouli, Fotini N. (2007). "Clinical, immunologic, and molecular factors predicting lymphoma development in Sjogren's syndrome patients". *Clin Rev Allergy Immunol*. **32** (3): 265–74. doi:10.1007/s12016-007-8001-x. PMID 17992593.
41. ^ Martin T.; et al. (2000). "Salivary gland lymphomas in patients with Sjögren's syndrome may frequently develop from rheumatoid factor B cells". *Arthritis Rheum*. **43**: 908–916. doi:10.1002/1529-0131(200004)43:4<908::aid-anr24>3.0.co;2-k.
42. ^ Bende R. J.; et al. (2005). "Among B cell non-Hodgkin's lymphomas, MALT lymphomas express a unique antibody repertoire with frequent rheumatoid factor reactivity". *J. Exp. Med*. **201**: 1229–1241. doi:10.1084/jem.20050068.
43. ^ Nocturne, G. et al. Germinal and somatic genetic variants of TNFAIP3 promote lymphomagenesis process complicating primary Sjögren's syndrome [abstract OP0023]" *Ann. Rheum. Dis* 72 (Suppl. 3), 55 (2013).
44. ^ Manthorpe, R; Svensson, A; Wirestrand, LE (November 2004). "Late neonatal lupus erythematosus onset in a child born of a mother with primary Sjögren's syndrome". *Ann. Rheum. Dis*. **63** (11): 1496–7. doi:10.1136/ard.2003.014944. PMC 1754813. PMID 15479901.
45. ^ Ramos-Casals, Manel; Cervera, Ricard; Yagüe, Jordi; García-Carrasco, Mario; Trejo, Olga; Jiménez, Sonia; Morlà, Rosa M; Font, Josep; Ingelmo, Miguel (Dec 1998). "Cryoglobulinemia in primary Sjögren's syndrome: prevalence and clinical characteristics in a series of 115 patients". *Semin Arthritis Rheum*. **28** (3): 200–5. doi:10.1016/S0049-0172(98)80037-1. PMID 9872481.

15. ^ [a] [b] Whitacre C. C. (2001). "Sex differences in autoimmune disease". *Nat. Immunol*. **2**: 777–780. doi:10.1038/ni0901-777.
16. ^ [a] [b] [c] [d] [e] [f] Voulgarelis M., Tzioufas A. G. (2010). "Pathogenetic mechanisms in the initiation and perpetuation of SjÖgren's syndrome". *Nature Reviews Rheumatology*. **6**: 529–537. doi:10.1038/nrrheum.2010.118.
17. ^ Harboe, Erna; Tjensvoll, Anne Bolette; Vefring, Hege K.; Gøransson, Lasse G.; Kvaløy, Jan Terje; Omdal, Roald (2009). "Fatigue in primary Sjögren's syndrome – A link to sickness behaviour in animals?". *Brain, Behavior, and Immunity*. **23** (8): 1104–8. doi:10.1016/j.bbi.2009.06.151. PMID 19560535.
18. ^ Perrier, S; Coussediere, C; Dubost, JJ; Albuisson, E; Sauvezie, B (1998). "IL-1 receptor antagonist (IL-1RA) gene polymorphism in Sjögren's syndrome and rheumatoid arthritis". *Clinical immunology and immunopathology*. **87** (3): 309–13. doi:10.1006/clin.1998.4520. PMID 9646842.
19. ^ Reveille JD: The molecular genetics of systemic lupus erythematosus and Sjögren's syndrome. Curr Opin Rheumatol 1992, 4:644-656.
20. ^ Lessard, C. J. et al. Identification of multiple Sjögren's syndrome susceptibility loci [abstract OP0020]. Ann.Rheum. Dis. 72 (Suppl. 3), 54 (2013).
21. ^ Kang HI, Fei HM, Saito I, Sawada S, Chen SL, Yi D, Chan E, Peebles C, Bugawan TL, Erlich HA; et al. ": Comparison of HLA class II genes in Caucasoid, Chinese, and Japanese patients with primary Sjögren's syndrome". *J Immunol*. **1993** (150): 3615–3623.
22. ^ Bolstad AI, Wassmuth R, Haga HJ, Jonsson R. "HLA markers and clinical characteristics in Caucasians with primary Sjögren's syndrome". *J Rheumatol*. **2001** (28): 1554–1562.
23. ^ Fei HM, Kang H, Scharf S, Erlich H, Peebles C, Fox R. "Specific HLA-DQA and HLA-DRB1 alleles confer susceptibility to Sjögren's syndrome and autoantibody production". *J Clin Lab Anal*. **1991** (5): 382–391.
24. ^ Lu Q (2013). "The critical importance of epigenetics in autoimmunity". *J. Autoimmun*. **41**: 1–5. doi:10.1016/j.jaut.2013.01.010.
25. ^ Takeda, K., Kaisho, T. & Akira, S. Toll-like receptors" *Annu. Rev. Immunol* 2003; 21, 335–376
26. ^ Pflugfelder S. C.; et al. (1993). "Epstein–Barr virus and the lacrimal gland pathology of Sjögren's syndrome". *Am. J. Pathol*. **143**: 49–64.
27. ^ Manoussakis M. N.; et al. (2007). "Rates of infiltration by macrophages and dendritic cells and expression of interleukin-18 and interleukin-12 in the chronic inflammatory lesions of Sjögren's syndrome: correlation with certain features of immune hyperactivity and factors associated with high risk of lymphoma development". *Arthritis Rheum*. **56**: 3977–3988. doi:10.1002/art.23073.
28. ^ Ohlsson M.; et al. (2002). "CD40, CD154, Bax and Bcl-2 expression in Sjögren's syndrome salivary glands: a putative anti-apoptotic role during its effector phases". *Scand. J. Immunol*. **56**: 561–571. doi:10.1046/j.1365-3083.2002.01168.x.
29. ^ Ohlsson M.; et al. (2001). "Fas-induced apoptosis is a *Lab. Invest*. **81**:
46. ^ [a] [b] [c] [d] [e] Fox R. I., Stern M., Michelson P. (2000). "Update in Sjögren syndrome". *Curr. Opin. Rheumatol*. **12**: 391–398.
47. ^ [a] [b] Mavragani C. P., Moutsopoulos H. M. (2010). "The geoepidemiology of Sjogren's syndrome". *Autoimmunity Reviews*. **9**: A305–A310. doi:10.1016/j.autrev.2009.11.004. PMID 19903539.
48. ^ [a] [b] Jonsson R., Vogelsang P., Volchenkov R., Espinosa A. (2011). "The complexity of Sjogren's syndrome: Novel aspects on pathogenesis". *Immunol. Lett*. **141**: 1–9. doi:10.1016/j.imlet.2011.06.007. PMID 21777618.
49. ^ Alamanos Y.; et al. (2006). "Epidemiology of primary Sjögren's syndrome in north-west Greece, 1982-2003". *Rheumatology (Oxford)*. **45**: 187–191. doi:10.1093/rheumatology/kei107. PMID 16332955.
50. ^ Priori R.; et al. (2007). "Risk factors for Sjögren's syndrome: a case-control study". *Clin. Exp. Rheumatol*. **25**: 378.
51. ^ Haugen A. J.; et al. (2008). "Estimation of the prevalence of primary Sjögren's syndrome in two age-different community-based populations using two sets of classification criteria: the Hordaland Health Study. Scand". *J. Rheumatol*. **37**: 30–34. doi:10.1080/03009740701678712. PMID 18189192.
52. ^ García-Carrasco M.; et al. (2002). "Primary Sjögren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients". *Medicine*. **81**: 270–280. doi:10.1097/00005792-200207000-00003.
53. ^ [a] [b] [c] Parke A. L., Buchanan W. W. (1998). "Sjögren's syndrome: History, clinical and pathological features". *Inflammopharmacology*. **6**: 271–287. doi:10.1007/s10787-998-0012-6.
54. ^ [a] [b] [c] [d] [e] Murube, J. Henrik Sjögren, 1899-1986. The ocular surface 8, 2-2 (2010)
55. ^ [a] [b] Ng, W.-F.; Bowman, S. J.; Griffiths, B.; Ukpssr Study, Group (January 2011). "United Kingdom Primary Sjogren's Syndrome Registry--a united effort to tackle an orphan rheumatic disease". *Rheumatology (Oxford)*. **50** (1): 32–9. doi:10.1093/rheumatology/keq240. PMID 20693261.
56. ^ [a] [b] Ice, John A.; Li, He; Adrianto, Indra; Lin, Paul Chee; Kelly, Jennifer A.; Montgomery, Courtney G.; Lessard, Christopher J.; Moser, Kathy L. (August 2012). "Genetics of Sjögren's syndrome in the genome-wide association era". *J. Autoimmun*. **39** (1–2): 57–63. doi:10.1016/j.jaut.2012.01.008. PMC 3518871. PMID 22289719.
57. ^ Cruz-Tapias, Paola; Rojas-Villarraga, Adriana; Maier-Moore, Shannon; Anaya, Juan-Manuel (February 2012). "HLA and Sjögren's syndrome susceptibility. A meta-analysis of worldwide studies". *Autoimmun Rev*. **11** (4): 281–7. doi:10.1016/j.autrev.2011.10.002. PMID 22001416.
58. ^ [a] [b] [c] [d] [e] Peri, Yogev; Agmon-Levin, Nancy; Theodor, Emanuel; Shoenfeld, Yehuda (February 2012). "Sjögren's syndrome, the old and the new". *Best Pract Res Clin Rheumatol*. **26** (1): 105–17. doi:10.1016/j.berh.2012.01.012. PMID 22424197.

95–105. doi:10.1038/labinvest.3780215.
30. ^ Cutolo M, Sulli A, Capellino S, Villaggio B, Montagna P, Seriolo B, Straub RH (2004). "Sex hormones influence on the immune system: basic and clinical aspects in autoimmunity.". *Lupus*. **13** (9): 635–8. doi:10.1191/0961203304lu1094oa. PMID 15485092.
31. ^ Mavragani CP, Fragoulis GE, Moutsopoulos HM (Dec 2012). "Endocrine alterations in primary Sjogren's syndrome: an overview". *J Autoimmun* (Review). **39** (4): 354–8. doi:10.1016/j.jaut.2012.05.011. PMID 22695186.
32. ^ Sullivan DA, Wickham LA, Rocha EM, Krenzer KL, Sullivan BD, Steagall R, Cermak JM, Dana MR, Ullman MD, Sato EH, Gao J, Rocha FJ, Ono M, Silveira LA, Lambert RW, Kelleher RS, Tolls DB, Toda I (1999). "Androgens and dry eye in Sjögren's syndrome.". *Ann N Y Acad Sci*. **22** (876): 312–24. PMID 10415627.
33. ^ *a b c d e f g h i j* Fox R. I. (2005). "Sjögren's syndrome". *Lancet*. **366**: 321–331. doi:10.1016/s0140-6736(05)66990-5.
59. ^ *a b* Liu, Jingyi; Duan, Yixiang (July 2012). "Saliva: a potential media for disease diagnostics and monitoring". *Oral Oncol*. **48** (7): 569–77. doi:10.1016/j.oraloncology.2012.01.021. PMID 22349278.
60. ^ *a b* Meijer, Jiska M.; Pijpe, Justin; Bootsma, Hendrika; Vissink, Arjan; Kallenberg, Cees G. M. (June 2007). "The future of biologic agents in the treatment of SS". *Clin Rev Allergy Immunol*. **32** (3): 292–7. doi:10.1007/s12016-007-8005-6. PMC 2071970. PMID 17992596.
61. ^ "'"Breakthrough Goal" SSF Launches 5-Year Breakthrough Goal/"To shorten the time to diagnose Sjögren's by 50% in 5 years!"'". Sjogren's Syndrome Foundation. August 2016.
62. ^ "Olympic soccer player Shannon Boxx's battle with lupus". CNN. 2012. Retrieved 18 February 2014.
63. ^ Sjogren's Syndrome Foundation Thanks Carrie Ann Inaba for Helping Raise Awareness
64. ^ "Williams Says She Struggled With Fatigue for Years". NY Times. 2011. Retrieved 18 February 2014.

## External links [edit]

- Sjögren's Syndrome Foundation (SSF)
- Patient-friendly introductory educational video from SSF, "Sjögren's Syndrome: A Place to Begin"
- Sjögren's Registry
- Sjögren's Syndrome at NHS Choices
- Questions and Answers about Sjögren's Syndrome - US National Institute of Arthritis and Musculoskeletal and Skin Diseases

Wikimedia Commons has media related to *Sjögren's syndrome*.

| v · t · e · | **Systemic connective tissue disorders (M32–M36, 710)** | |
|---|---|---|
| **General** | **Systemic lupus erythematosus** | Drug-induced SLE · Libman-Sacks endocarditis · |
| | **Inflammatory myopathy** | Myositis · Dermatopolymyositis (Dermatomyositis/Juvenile dermatomyositis · Polymyositis* Inclusion body myositis · · |
| | **Scleroderma** | Systemic scleroderma (Progressive systemic sclerosis · CREST syndrome · · |
| | Overlap syndrome / Mixed connective tissue disease · | |
| **Other hypersensitivity/autoimmune** | **Sjögren's syndrome** · | |
| **Other** | Behçet's disease · Polymyalgia rheumatica · Eosinophilic fasciitis · Eosinophilia–myalgia syndrome · fibrillin (Marfan syndrome · Congenital contractural arachnodactyly · · | |

| v · t · e · | **Hypersensitivity and autoimmune diseases (279.5–6)** | |
|---|---|---|
| **Type I/allergy/atopy (IgE)** | **Foreign** | Atopic eczema · Allergic urticaria · Allergic rhinitis (Hay fever) · Allergic asthma · Anaphylaxis · Food allergy (common allergies include: Milk · Egg · Peanut · Tree nut · Seafood · Soy · Wheat · · Penicillin allergy · |
| | **Autoimmune** | Eosinophilic esophagitis · |

| | | | |
|---|---|---|---|
| **Type II/ADCC (IgM · IgG · ·** | **Foreign** | Hemolytic disease of the newborn · | |
| | **Autoimmune** | **Cytotoxic** | Autoimmune hemolytic anemia · Immune thrombocytopenic purpura · Bullous pemphigoid · Pemphigus vulgaris · Rheumatic fever · Goodpasture's syndrome · Guillain–Barré syndrome · |
| | | **"Type V"/receptor** | Graves' disease · Myasthenia gravis · Pernicious anemia · |
| **Type III (Immune complex)** | **Foreign** | Henoch–Schönlein purpura · Hypersensitivity vasculitis · Reactive arthritis · Farmer's lung · Post-streptococcal glomerulonephritis · Serum sickness · Arthus reaction · | |
| | **Autoimmune** | Systemic lupus erythematosus · Subacute bacterial endocarditis · Rheumatoid arthritis · | |
| **Type IV/cell-mediated (T cells)** | **Foreign** | Allergic contact dermatitis · Mantoux test · | |
| | **Autoimmune** | Diabetes mellitus type 1 · Hashimoto's thyroiditis · Multiple sclerosis · Coeliac disease · Giant-cell arteritis · Postorgasmic illness syndrome · Reactive arthritis · | |
| | **GVHD** | Transfusion-associated graft versus host disease · | |
| **Unknown/ multiple** | **Foreign** | Hypersensitivity pneumonitis (Allergic bronchopulmonary aspergillosis · · Transplant rejection · Latex allergy (I+IV) · | |
| | **Autoimmune** | **Sjögren's syndrome** · Autoimmune hepatitis · Autoimmune polyendocrine syndrome (APS1 · APS2 · · Autoimmune adrenalitis · Systemic autoimmune disease · | |

v · t · e · **Oral and maxillofacial pathology (K00–K06, K11–K14, 520–525, 527–529)**

**Lips**

Cheilitis (Actinic · Angular · Plasma cell · · Cleft lip · Congenital lip pit · Eclabium · Herpes labialis · Macrocheilia · Microcheilia · Nasolabial cyst · Sun poisoning · Trumpeter's wart ·

**Tongue**

Ankyloglossia · Black hairy tongue · Caviar tongue · Crenated tongue · Cunnilingus tongue · Fissured tongue · Foliate papillitis · Glossitis (Geographic tongue · Median rhomboid glossitis · Transient lingual papillitis · · Glossoptosis · Hypoglossia · Lingual thyroid · Macroglossia · Microglossia · Rhabdomyoma ·

**Palate**

Bednar's aphthae · Cleft palate · High-arched palate · Palatal cysts of the newborn · Inflammatory papillary hyperplasia · Stomatitis nicotina · Torus palatinus ·

**Oral mucosa** - *Lining of mouth*

Amalgam tattoo · Angina bullosa haemorrhagica · Behçet syndrome · Bohn's nodules · Burning mouth syndrome · Candidiasis · Condyloma acuminatum · Darier's disease · Epulis fissuratum · Erythema multiforme · Erythroplakia · Fibroma (Giant-cell · · Focal epithelial hyperplasia · Fordyce spots · Hairy leukoplakia · Hand, foot and mouth disease · Hereditary benign intraepithelial dyskeratosis · Herpangina · Herpes zoster · Intraoral dental sinus · Leukoedema · Leukoplakia · Lichen planus · Linea alba · Lupus erythematosus · Melanocytic nevus · Melanocytic oral lesion · Molluscum contagiosum · Morsicatio buccarum · Oral cancer (*Benign:* Squamous cell papilloma · Keratoacanthoma · *Malignant:* Adenosquamous carcinoma · Basaloid squamous carcinoma · Mucosal melanoma · Spindle cell carcinoma · Squamous cell carcinoma · Verrucous carcinoma · · Oral florid papillomatosis · Oral melanosis (Smoker's melanosis · ·

Pemphigoid (Benign mucous membrane · · Pemphigus · Plasmoacanthoma · Stomatitis (Aphthous · Denture-related · Herpetic · · Smokeless tobacco keratosis · Submucous fibrosis · Ulceration · Verruca vulgaris · Verruciform xanthoma · White sponge nevus ·

**Teeth (pulp, dentin, enamel)**

Amelogenesis imperfecta · Ankylosis · Anodontia · Caries (Early childhood caries · · Concrescence · Failure of eruption of teeth · Dens evaginatus (Talon cusp · · Dentin dysplasia · Dentin hypersensitivity · Dentinogenesis imperfecta · Dilaceration · Discoloration · Ectopic enamel · Enamel hypocalcification · Enamel hypoplasia (Turner's hypoplasia · · Enamel pearl · Fluorosis · Fusion · Gemination · Hyperdontia · Hypodontia (Maxillary lateral incisor agenesis · · Impaction (Wisdom tooth impaction · · Macrodontia · Meth mouth · Microdontia · Odontogenic tumors (Keratocystic odontogenic tumour · · Odontoma (Dens in dente · · Open contact · Premature eruption (Neonatal teeth · · Pulp calcification (Pulp stone · · Pulp canal obliteration · Pulp necrosis · Pulp polyp · Pulpitis · Regional odontodysplasia · Resorption · Shovel-shaped incisors · Supernumerary root · Taurodontism · Trauma (Avulsion · Cracked tooth syndrome · Vertical root fracture · Occlusal · · Tooth loss (Edentulism · · Tooth wear (Abrasion · Abfraction · Acid erosion · Attrition · ·

**Periodontium (gingiva, periodontal ligament, cementum, alveolus) -** *Gums and tooth-supporting structures*

Cementicle · Cementoblastoma (Gigantiform · · Cementoma · Eruption cyst · Epulis (Pyogenic granuloma · Congenital epulis · · Gingival enlargement · Gingival cyst of the adult · Gingival cyst of the newborn · Gingivitis (Desquamative · Granulomatous · Plasma cell · · Hereditary gingival fibromatosis · Hypercementosis · Hypocementosis · Linear gingival erythema · Necrotizing periodontal diseases (Acute necrotizing ulcerative gingivitis · · Pericoronitis · Peri-implantitis · Periodontal abscess · Periodontal trauma · Periodontitis (Aggressive · As a manifestation of systemic disease · Chronic · · Perio-endo lesion · Teething ·

**Periapaical, mandibular and maxillary hard tissues -** *Bones of jaws*

Agnathia · Alveolar osteitis · Buccal exostosis · Cherubism · Idiopathic osteosclerosis · Mandibular fracture · Microgenia · Micrognathia · Intraosseous cysts (*Odontogenic:* periapical · Dentigerous · Buccal bifurcation · Lateral periodontal · Globulomaxillary · Calcifying odontogenic · Glandular odontogenic · *Non-odontogenic:* Nasopalatine duct · Median mandibular · Median palatal · Traumatic bone · · Osteoma · Osteomyelitis · Osteonecrosis (Bisphosphonate-associated · Neuralgia-inducing cavitational osteonecrosis · Osteoradionecrosis · · Osteoporotic bone marrow defect · Paget's disease of bone · Periapical abscess (Phoenix abscess · · Periapical periodontitis · Stafne defect · Torus mandibularis ·

**Temporomandibular joints, muscles of mastication and malocclusions -** *Jaw joints, chewing muscles and bite abnormalities*

Bruxism · Condylar resorption · Mandibular dislocation · Malocclusion (Crossbite · Open bite · Overbite · Overjet · Prognathia · Retrognathia · · Temporomandibular joint dysfunction ·

**Salivary glands**

Benign lymphoepithelial lesion · Ectopic salivary gland tissue · Frey's syndrome · HIV salivary gland disease · Necrotizing sialometaplasia · Mucocele (Ranula · · Pneumoparotitis · Salivary duct stricture · Salivary gland aplasia · Salivary gland atresia · Salivary gland diverticulum · Salivary gland fistula · Salivary gland hyperplasia · Salivary gland hypoplasia · Salivary gland neoplasms (*Benign:* Basal cell adenoma · Canalicular adenoma · Ductal papilloma · Monomorphic adenoma · Myoepithelioma · Oncocytoma · Papillary cystadenoma lymphomatosum · Pleomorphic adenoma · Sebaceous adenoma · *Malignant:* Acinic cell carcinoma · Adenocarcinoma · Adenoid cystic carcinoma · Carcinoma ex pleomorphic adenoma · Lymphoma · Mucoepidermoid carcinoma · · Sclerosing polycystic adenosis · Sialadenitis (Parotitis · Chronic sclerosing sialadenitis · · Sialectasis · Sialocele · Sialodochitis · Sialosis · Sialolithiasis · **Sjögren's syndrome** ·

**Orofacial soft tissues -** *Soft tissues around the mouth*

Actinomycosis · Angioedema · Basal cell carcinoma · Cutaneous sinus of dental origin · Cystic hygroma · Gnathophyma · Ludwig's angina · Macrostomia · Melkersson–Rosenthal syndrome · Microstomia · Noma · Oral Crohn's disease ·

Orofacial granulomatosis · Perioral dermatitis · Pyostomatitis vegetans ·

**Other**

Eagle syndrome · Hemifacial hypertrophy · Facial hemiatrophy · Oral manifestations of systemic disease ·

**Authority control** NDL: 00571353 ·

Categories: Ailments of unknown etiology | Autoimmune diseases | Connective tissue diseases | Hepatitis C virus-associated diseases | Salivary gland pathology | Syndromes | Systemic connective tissue disorders



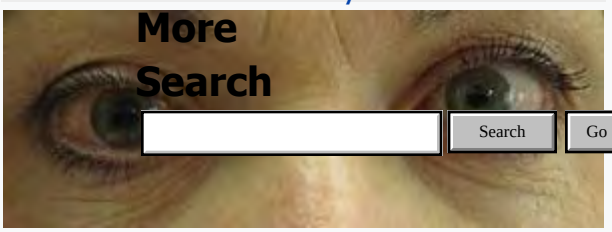

# Glaucoma

From Wikipedia, the free encyclopedia

**Glaucoma** is a group of eye diseases which result in damage to the optic nerve and vision loss.[1] The most common type is open-angle glaucoma with less common types including closed-angle glaucoma and normal-tension glaucoma. Open-angle glaucoma develops slowly over time and there is no pain. Side vision may begin to decrease followed by central vision resulting in blindness if not treated.[1] Closed-angle glaucoma can present gradually or suddenly.[2] The sudden presentation may involve severe eye pain, blurred vision, mid-dilated pupil, redness of the eye, and nausea.[1][2] Vision loss from glaucoma, once it has occurred, is permanent.[1]

Risk factors for glaucoma include increased pressure in the eye, a family history of the condition, migraines, high blood pressure, and obesity.[1] For eye pressures a value of greater than 21 mmHg or 2.8 kPa is often used with higher pressures leading to a greater risk.[2][3] However, some may have high eye pressure for years and never develop damage.[2] Conversely, optic nerve damage may occur with normal pressure, known as normal-tension glaucoma.[4] The mechanism of open-angle glaucoma is believed to be slow exit of aqueous humor through the trabecular meshwork while in closed-angle glaucoma the iris blocks the trabecular meshwork.[2] Diagnosis is by a dilated eye examination.[1] Often the optic nerve shows an abnormal amount of cupping.[2]

**Glaucoma**



Acute angle closure glaucoma of the right eye. Note the mid-sized pupil, which was nonreactive to light, and redness of the whites of the eyes.

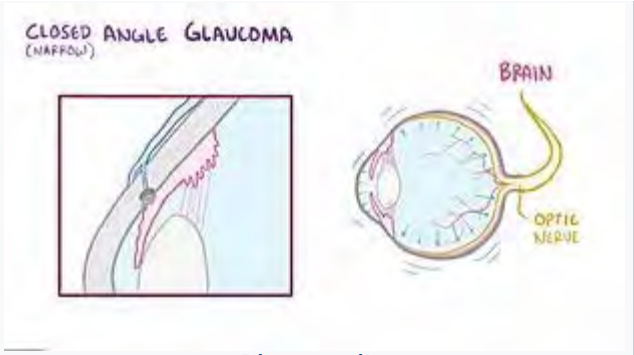
| Classification and external resources | |
|---|---|
| **Specialty** | Ophthalmology |
| **ICD-10** | H40-H42 |
| **ICD-9-CM** | 365 |
| **DiseasesDB** | 5226 |
| **MedlinePlus** | 001620 |
| **eMedicine** | oph/578 |
| **MeSH** | D005901 |

[edit on Wikidata]

If treated early it is possible to slow or stop the progression of disease with medication, laser treatment, or surgery.[1] The goal of these treatments is to decrease eye pressure. A number of different classes of glaucoma medication are available. Laser treatments may be effective in both open-angle and closed-angle glaucoma. A number of types of glaucoma surgeries may be used in people who do not respond sufficiently to other measures.[2] Treatment of closed-angle glaucoma is a medical emergency.[1]

About 11 to 67 million people have glaucoma globally.[2][5] The disease affects about 2 million people in the United States.[2] It occurs more commonly among older people.[1] Closed-angle glaucoma is more common in women.[2] Glaucoma has been called the "silent thief of sight" because the loss of vision usually occurs slowly over a long period of time.[6] Worldwide, glaucoma is the second-leading cause of blindness after cataracts.[2][7] The word "glaucoma" is from ancient Greek *glaukos* which means blue, green, or gray.[8] In English, the word was used as early as 1587 but did not become commonly used until after 1850, when the development of the ophthalmoscope allowed people to see the optic nerve damage.[9]

Contents




Play media

Video explanation

## Signs and symptoms [edit]

Open-angle glaucoma is painless and does not have acute attacks, thus the lack of clear symptoms make screening via regular eye check-ups important. The only signs are gradually progressive visual field loss, and optic nerve changes (increased cup-to-disc ratio on fundoscopic examination).

About 10% of people with closed angles present with acute angle closure characterized by sudden ocular pain, seeing halos around lights, red eye, very high intraocular pressure (>30 mmHg), nausea and vomiting, suddenly decreased vision, and a fixed, mid-dilated pupil. It is also associated with an oval pupil in some cases. Acute angle closure is an emergency.

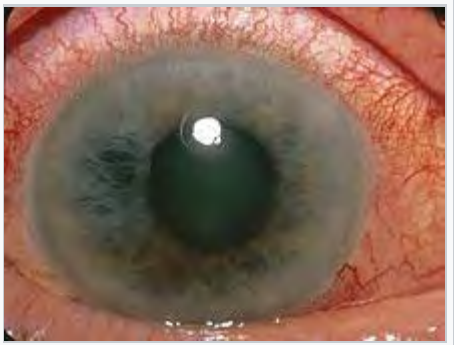


Photo showing conjunctival vessels dilated at the corneal edge (ciliary flush, circumcorneal flush) and hazy cornea characteristic of acute angle closure glaucoma

## Causes [edit]

Of the several causes for glaucoma, ocular hypertension (increased pressure within the eye) is the most important risk factor in most glaucomas, but in some populations, only 50% of people with primary open-angle glaucoma actually have elevated ocular pressure.[10]

Open-angle glaucoma accounts for 90% of glaucoma cases in the United States. Closed-angle glaucoma accounts for less than 10% of glaucoma cases in the United States, but as many as half of glaucoma cases in other nations (particularly East Asian countries).

A normal range of vision

The same view with advanced vision loss from glaucoma

## Dietary [edit]



No clear evidence indicates vitamin deficiencies cause glaucoma in humans. It follows, then, that oral vitamin supplementation is not a recommended treatment for glaucoma.[11] Caffeine increases intraocular pressure in those with glaucoma, but does not appear to affect normal individuals.[12]

## Ethnicity [edit]

Many people of East Asian descent are prone to developing angle closure glaucoma due to shallower anterior chamber depths, with the majority of cases of glaucoma in this population consisting of some form of angle closure.[13] Higher rates of glaucoma have also been reported for Eskimo populations, compared to white populations, in Canada and Greenland.[14]

## Genetics [edit]

Positive family history is a risk factor for glaucoma. The relative risk of having primary open-angle glaucoma (P.O.A.G.) is increased about two- to four-fold for people who have a sibling with glaucoma.[15] Glaucoma, particularly primary open-angle glaucoma, is associated with mutations in several genes, including *MYOC*, *ASB10*, *WDR36*, *NTF4*, and *TBK1*,[16] although most cases of glaucoma do not involve these genetic mutations. Normal-tension glaucoma, which comprises one-third of POAG, is also associated with genetic mutations (including *OPA1* and *OPTN* genes).[17]

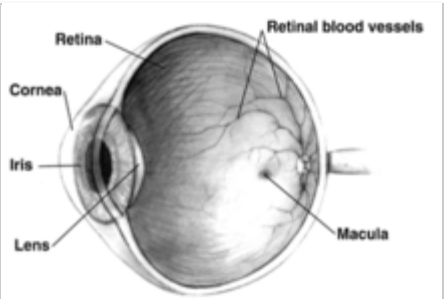
Various rare congenital/genetic eye malformations are associated with glaucoma. Occasionally, failure of the normal third-trimester gestational atrophy of the hyaloid canal and the tunica vasculosa lentis is associated with other anomalies. Angle closure-induced ocular hypertension and glaucomatous optic neuropathy may also occur with these anomalies,[18][19][20] and has been modelled in mice.[21]

## Other [edit]

Other factors can cause glaucoma, known as "secondary glaucoma", including prolonged use of steroids (steroid-induced glaucoma); conditions that severely restrict blood flow to the eye, such as severe diabetic retinopathy and central retinal vein occlusion (neovascular glaucoma); ocular trauma (angle-recession glaucoma); and inflammation of the middle layer of the pigmented vascular eye structure (uveitis), known as uveitic glaucoma.

# Pathophysiology [edit]

The underlying cause of open-angle glaucoma remains unclear. Several theories exist on its exact etiology. However, the major risk factor for most glaucomas and the focus of treatment is increased intraocular pressure. Intraocular pressure is a function of production of liquid aqueous humor by the ciliary processes of the eye, and its drainage through the trabecular meshwork. Aqueous humor flows from the ciliary processes into the posterior chamber, bounded posteriorly by the lens



Human eye cross-sectional view

and the zonules of Zinn, and anteriorly by the iris. It then flows through the pupil of the iris into the anterior chamber, bounded posteriorly by the iris and anteriorly by the cornea. From here, the trabecular meshwork drains aqueous humor via Schlemm's canal into scleral plexuses and general blood circulation.[22]

In open/wide-angle glaucoma, flow is reduced through the trabecular meshwork, due to the degeneration and obstruction of the trabecular meshwork, whose original function is to absorb the aqueous humor. Loss of aqueous humor absorption leads to increased resistance and thus a chronic, painless buildup of pressure in the eye.[23]

In close/narrow-angle, the iridocorneal angle is completely closed because of forward displacement of the final roll and root of the iris against the cornea, resulting in the inability of the aqueous fluid to flow from the posterior to the anterior chamber and then out of the trabecular network. This accumulation of aqueous humor causes an acute increase in pressure and pain.

The inconsistent relationship of glaucomatous optic neuropathy with increased intraocular pressure has provoked hypotheses and studies on anatomic structure, eye development, nerve compression trauma, optic nerve blood flow, excitatory neurotransmitter, trophic factor, retinal ganglion cell/axon degeneration, glial support cell, immune system, aging mechanisms of neuron loss, and severing of the nerve fibers at the scleral edge.[24][25][26][27][28][29][30][31][32][33][34][35]

## Diagnosis [edit]

Screening for glaucoma is usually performed as part of a standard eye examination performed by optometrists and ophthalmologists. Testing for glaucoma should include measurements of the intraocular pressure via tonometry,[36] anterior chamber angle examination or gonioscopy, and examination of the optic nerve to look for any visible damage to it, or change in the cup-to-disc ratio and also rim appearance and vascular change. A formal visual field test should be performed. The retinal nerve fiber layer can be assessed with imaging techniques such as optical coherence tomography, scanning laser polarimetry, and/or scanning laser ophthalmoscopy (Heidelberg retinal tomogram).[37][38][39]

Owing to the sensitivity of all methods of tonometry to corneal thickness, methods such as Goldmann tonometry should be augmented with pachymetry to measure the central corneal thickness (CCT). A thicker-than-average cornea can result in a pressure reading higher than the 'true' pressure whereas a thinner-than-average cornea can produce a pressure reading lower than the 'true' pressure.

Because pressure measurement error can be caused by more than just CCT (i.e., corneal hydration, elastic properties, etc.), it is impossible to 'adjust' pressure measurements based only on CCT measurements. The frequency doubling illusion can also be used to detect glaucoma with the use of a frequency doubling technology perimeter.[40]

Examination for glaucoma also could be assessed with more attention given to sex, race, history of drug use, refraction, inheritance and family history.[37]

**Glaucoma tests**[41][42][43]

| | What test examines | How it is accomplished |
|---|---|---|
| Tonometry | Inner eye pressure | The eye is numbed via eye drops. The examiner then uses a tonometer to measure the inner pressure of the eye through pressure applied by a puff of warm air or a tiny tool. |

| | | |
|---|---|---|
| Ophthalmoscopy (dilated eye examination) | Shape and color of the optic nerve | The pupil is dilated via the application of eye drops. Using a small magnification device with a light on the end, the examiner can examine the magnified optic nerve. |
| Perimetry (visual field test) | Complete field of vision | The patient looks straight ahead and is asked to indicate when light passes the patient's peripheral field of vision. This allows the examiner to map the patient's field of vision. |
| Gonioscopy | Angle in the eye where the iris meets the cornea | Eyedrops are used to numb the eye. A hand-held contact lens with a mirror is placed gently on the eye to allow the examiner to see the angle between the cornea and the iris. |
| Pachymetry | Thickness of the cornea | The examiner places a pachymeter gently on the front of the eye to measure its thickness. |
| Nerve fiber analysis | Thickness of the nerve fiber layer | Using one of several techniques, the nerve fibers are examined. |

Glaucoma has been classified into specific types:[44]

## Primary glaucoma and its variants [edit]

Primary glaucoma (H40.1-H40.2)

- Primary open-angle glaucoma, also known as chronic open-angle glaucoma, chronic simple glaucoma, glaucoma simplex
  - High-tension glaucoma
  - Low-tension glaucoma
- Primary angle closure glaucoma, also known as primary closed-angle glaucoma, narrow-angle glaucoma, pupil-block glaucoma, acute congestive glaucoma
  - Acute angle closure glaucoma (*aka* AACG)[45]
  - Chronic angle closure glaucoma
  - Intermittent angle closure glaucoma
  - Superimposed on chronic open-angle closure glaucoma ("combined mechanism" – uncommon)

Variants of primary glaucoma

- Pigmentary glaucoma
- Exfoliation glaucoma, also known as pseudoexfoliative glaucoma or glaucoma capsulare
- Primary juvenile glaucoma

**Primary angle closure glaucoma** is caused by contact between the iris and trabecular meshwork, which in turn obstructs outflow of the aqueous humor from the eye. This contact between iris and trabecular meshwork (TM) may gradually damage the function of the meshwork until it fails to keep pace with aqueous production, and the pressure rises. In over half of all cases, prolonged contact between iris and TM causes the formation of synechiae (effectively "scars").

These cause permanent obstruction of aqueous outflow. In some cases, pressure may rapidly build up in the eye, causing pain and redness (symptomatic, or so-called "acute" angle closure). In this situation, the vision may become blurred, and halos may be seen around bright lights. Accompanying symptoms may include a headache and vomiting.

Diagnosis is made from physical signs and symptoms: pupils mid-dilated and unresponsive to light, cornea edematous (cloudy), reduced vision, redness, and pain. However, the majority of cases are asymptomatic. Prior to the very severe loss of vision, these cases can only be identified by examination, generally by an eye care professional.

Once any symptoms have been controlled, the first line (and often definitive) treatment is laser iridotomy. This may be performed using either Nd:YAG or argon lasers, or in some cases by conventional incisional surgery. The goal of treatment is to reverse and prevent, contact between the iris and trabecular meshwork. In early to moderately advanced cases, iridotomy is successful in opening the angle in around

75% of cases. In the other 25%, laser iridoplasty, medication (pilocarpine) or incisional surgery may be required.

**Primary open-angle glaucoma** is when optic nerve damage results in a progressive loss of the visual field.[46] This is associated with increased pressure in the eye. Not all people with primary open-angle glaucoma have eye pressure that is elevated beyond normal, but decreasing the eye pressure further has been shown to stop progression even in these cases.

The increased pressure is caused by trabecular blockage. Because the microscopic passageways are blocked, the pressure builds up in the eye and causes imperceptible very gradual vision loss. Peripheral vision is affected first, but eventually the entire vision will be lost if not treated.

Diagnosis is made by looking for cupping of the optic nerve. Prostaglandin agonists work by opening uveoscleral passageways. Beta-blockers, such as timolol, work by decreasing aqueous formation. Carbonic anhydrase inhibitors decrease bicarbonate formation from ciliary processes in the eye, thus decreasing the formation of Aqueous humor. Parasympathetic analogs are drugs that work on the trabecular outflow by opening up the passageway and constricting the pupil. Alpha 2 agonists (brimonidine, apraclonidine) both decrease fluid production (via. inhibition of AC) and increase drainage.

## Developmental glaucoma [edit]

Developmental glaucoma (Q15.0)

- Primary congenital glaucoma
- Infantile glaucoma
- Glaucoma associated with hereditary or familial diseases

## Secondary glaucoma [edit]

Secondary glaucoma (H40.3-H40.6)

- Inflammatory glaucoma
  - Uveitis of all types
  - Fuchs heterochromic iridocyclitis
- Phacogenic glaucoma
  - Angle-closure glaucoma with mature cataract
  - Phacoanaphylactic glaucoma secondary to rupture of lens capsule
  - Phacolytic glaucoma due to phacotoxic meshwork blockage
  - Subluxation of lens
- Glaucoma secondary to intraocular hemorrhage
  - Hyphema
  - Hemolytic glaucoma, also known as erythroclastic glaucoma
- Traumatic glaucoma
  - Angle recession glaucoma: Traumatic recession on anterior chamber angle
  - Postsurgical glaucoma
    - Aphakic pupillary block
    - Ciliary block glaucoma
- Neovascular glaucoma (see below for more details)
- Drug-induced glaucoma
  - Corticosteroid induced glaucoma
  - Alpha-chymotrypsin glaucoma. Postoperative ocular hypertension from use of alpha chymotrypsin.
- Glaucoma of miscellaneous origin
  - Associated with intraocular tumors
  - Associated with retinal detachments
  - Secondary to severe chemical burns of the eye

- Associated with essential iris atrophy
- Toxic glaucoma

**Neovascular glaucoma**, an uncommon type of glaucoma, is difficult or nearly impossible to treat, and is often caused by proliferative diabetic retinopathy (PDR) or central retinal vein occlusion (CRVO). It may also be triggered by other conditions that result in ischemia of the retina or ciliary body. Individuals with poor blood flow to the eye are highly at risk for this condition.

Neovascular glaucoma results when new, abnormal vessels begin developing in the angle of the eye that begin blocking the drainage. Patients with such condition begin to rapidly lose their eyesight. Sometimes, the disease appears very rapidly, especially after cataract surgery procedures. A new treatment for this disease, as first reported by Kahook and colleagues, involves the use of a novel group of medications known as anti-VEGF agents. These injectable medications can lead to a dramatic decrease in new vessel formation and, if injected early enough in the disease process, may lead to normalization of intraocular pressure. Currently, there are no high-quality controlled trials demonstrating a beneficial effect of anti-VEGF treatments in lowering IOP in people with neovascular glaucoma.[47]

**Toxic glaucoma** is open angle glaucoma with an unexplained significant rise of intraocular pressure following unknown pathogenesis. Intraocular pressure can sometimes reach 80 mmHg (11 kPa). It characteristically manifests as ciliary body inflammation and massive trabecular oedema that sometimes extends to Schlemm's canal. This condition is differentiated from malignant glaucoma by the presence of a deep and clear anterior chamber and a lack of aqueous misdirection. Also, the corneal appearance is not as hazy. A reduction in visual acuity can occur followed neuroretinal breakdown.

Associated factors include inflammation, drugs, trauma and intraocular surgery, including cataract surgery and vitrectomy procedures. Gede Pardianto (2005) reported on four patients who had toxic glaucoma. One of them underwent phacoemulsification with small particle nucleus drops. Some cases can be resolved with some medication, vitrectomy procedures or trabeculectomy. Valving procedures can give some relief, but further research is required.[48]

## Absolute glaucoma [edit]

Absolute glaucoma (H44.5) is the end stage of all types of glaucoma. The eye has no vision, absence of pupillary light reflex and pupillary response, and has a stony appearance. Severe pain is present in the eye. The treatment of absolute glaucoma is a destructive procedure like cyclocryoapplication, cyclophotocoagulation, or injection of 99% alcohol.

## Types [edit]

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Glaucoma is an umbrella term for eye conditions which damage the optic nerve, and which can lead to a loss of vision.[49] The main cause of damage to the optic nerve is intraocular pressure (IOP), excessive fluid pressure within the eye, which can be due to various reasons including blockage of drainage ducts, and narrowing or closure of the angle between the iris and cornea.

The primary division in categorizing different types of glaucoma is open-angle and closed-angle (or angle-closure) glaucoma. The open angle refers to the angle where the iris meets the cornea being as wide and open as it should be, allowing the fluid from inside the eye to drain, thus relieving the internal pressure. Where this angle is narrowed or closed, pressure can build up, and eventually damage the optic nerve leading to loss of vision.

Primary open-angle glaucoma (also, *primary glaucoma*, *chronic glaucoma*) refers to slow clogging of the drainage canals resulting in increased eye pressure which causes progressive optic nerve damage. This manifests as a gradual loss of the visual field, starting with a loss of peripheral vision, but eventually the entire vision will be lost if not treated.[46] This is the most common type of glaucoma, accounting for 90%

of cases in the United States, but fewer in Asian countries. Onset is slow and painless, and loss of vision is gradual and irreversible.

Narrow-angle glaucoma (also *closed-angle glaucoma*) the iris bows forward, narrowing the angle that drains the eye, increasing pressure within the eye. If untreated, it can lead to the medical emergency of angle-closure glaucoma.

In angle-closure glaucoma (also *closed-angle glaucoma*, *primary angle-closure glaucoma*, *acute glaucoma*) the iris bows forward and causes physical contact between the iris and trabecular meshwork, which blocks the outflow of aqueous humor from within the eye. This contact may gradually damage the draining function of the meshwork until it fails to keep pace with aqueous production, and the intraocular pressure rises. The onset of symptoms is sudden and causes pain and other symptoms that are noticeable; it is treated as a medical emergency. Unlike open-angle glaucoma, angle-closure glaucoma is a result of the angle between the iris and cornea closing. This tends to occur in the far-sighted, who have smaller-than-normal anterior chambers, making physical contact between the iris and trabecular meshwork more likely.

Normal-tension glaucoma (also *NTG*, *low-tension glaucoma*, *normal-pressure glaucoma*) is a condition where the optic nerve is damaged although intraocular pressure (IOP) is in the normal range (12-22mm Hg). Individuals with a family history of NTG, those of Japanese ancestry, and those with a history of systemic heart disease are at higher than average risk of developing NTG. The cause of NTG is unknown.

Secondary glaucoma refers to any case in which another disease, trauma, drug or procedure causes increased eye pressure, resulting in optic nerve damage and vision loss, and may be mild or severe. It can be due to an eye injury, inflammation, a tumor, or advanced cases of cataracts or diabetes. It can also be caused by certain drugs such as steroids. Treatment depends on whether it is open-angle or angle-closure glaucoma.

In pseudoexfoliation glaucoma (also, *PEX*, *exfoliation glaucoma*) the pressure is due to the accumulation of microscopic granular protein fibers, which can block normal drainage of the aqueous humor. PEX is prevalent in Scandinavia, primarily in those over 70, and more commonly in women.

Pigmentary glaucoma (also, pigmentary dispersion syndrome) is caused by pigment cells sloughing off from the back of the iris and floating around in the aqueous humor. Over time, these pigment cells can accumulate in the anterior chamber in such a way that it can begin to clog the trabecular meshwork. It is a rare condition that occurs mostly among Caucasians, mostly males in their mid-20s to 40s, and most are nearsighted.

Primary juvenile glaucoma is a neonate or juvenile abnormality where ocular hypertension is evident at birth or shortly thereafter and is caused by abnormalities in the anterior chamber angle development that blocks the outflow of the aqueous humor.

Uveitic Glaucoma is due to uveitis, the swelling and inflammation of the uvea, the middle layer of the eye. The uvea provides most of the blood supply to the retina. Increased eye pressure in uveitis can result from the inflammation itself or from the steroids used to treat it.

## Screening [edit]

The United States Preventive Services Task Force as of 2013 states there is insufficient evidence to recommend for or against screening for glaucoma.[50] Therefore, there is no national screening program in the US. Screening, however, is recommended starting at age 40 by the American Academy of Ophthalmology.[2]

There is a glaucoma screening program in the UK. Those at risk are advised to have a dilated eye examination at least once a year.[51]

## Treatment [edit]

The modern goals of glaucoma management are to avoid glaucomatous damage and nerve damage, and

preserve visual field and total quality of life for patients, with minimal side effects.[52][53] This requires appropriate diagnostic techniques and follow-up examinations, and judicious selection of treatments for the individual patient. Although intraocular pressure is only one of the major risk factors for glaucoma, lowering it via various pharmaceuticals and/or surgical techniques is currently the mainstay of glaucoma treatment.

Vascular flow and neurodegenerative theories of glaucomatous optic neuropathy have prompted studies on various neuroprotective therapeutic strategies, including nutritional compounds, some of which may be regarded by clinicians as safe for use now, while others are on trial.

## Medication [edit]

*Main article: Glaucoma medication*

Latanoprost

Intraocular pressure can be lowered with medication, usually eye drops. Several classes of medications are used to treat glaucoma, with several medications in each class.

Each of these medicines may have local and systemic side effects. Adherence to medication protocol can be confusing and expensive; if side effects occur, the patient must be willing either to tolerate them or to communicate with the treating physician to improve the drug regimen. Initially, glaucoma drops may reasonably be started in either one or in both eyes.[54]

Poor compliance with medications and follow-up visits is a major reason for vision loss in glaucoma patients. A 2003 study of patients in an HMO found half failed to fill their prescriptions the first time, and one-fourth failed to refill their prescriptions a second time.[55] Patient education and communication must be ongoing to sustain successful treatment plans for this lifelong disease with no early symptoms.

The possible neuroprotective effects of various topical and systemic medications are also being investigated.[11][56][57][58]

- Prostaglandin analogs, such as latanoprost, bimatoprost and travoprost, increase uveoscleral outflow of aqueous humor. Bimatoprost also increases trabecular outflow.
- Topical beta-adrenergic receptor antagonists, such as timolol, levobunolol, and betaxolol, decrease aqueous humor production by the epithelium of the ciliary body.
- Alpha2-adrenergic agonists, such as brimonidine and apraclonidine, work by a dual mechanism, decreasing aqueous humor production and increasing uveoscleral outflow.
- Less-selective alpha agonists, such as epinephrine, decrease aqueous humor production through vasoconstriction of ciliary body blood vessels, useful only in open-angle glaucoma. Epinephrine's mydriatic effect, however, renders it unsuitable for closed-angle glaucoma due to further narrowing of the uveoscleral outflow (i.e. further closure of trabecular meshwork, which is responsible for absorption of aqueous humor).
- Miotic agents (parasympathomimetics), such as pilocarpine, work by contraction of the ciliary muscle, opening the trabecular meshwork and allowing increased outflow of the aqueous humour. Echothiophate, an acetylcholinesterase inhibitor, is used in chronic glaucoma.
- Carbonic anhydrase inhibitors, such as dorzolamide, brinzolamide, and acetazolamide, lower secretion of aqueous humor by inhibiting carbonic anhydrase in the ciliary body.

## Laser [edit]

Argon laser trabeculoplasty (ALT) may be used to treat open-angle glaucoma, but this is a temporary solution, not a cure. A 50-μm argon laser spot is aimed at the trabecular meshwork to stimulate the opening of the mesh to allow more outflow of aqueous fluid. Usually, half of the angle is treated at a time. Traditional laser trabeculoplasty uses a thermal argon laser in an argon laser trabeculoplasty procedure.

A newer type of laser trabeculoplasty uses a "cold" (nonthermal) laser to stimulate drainage in the trabecular meshwork. This newer procedure, selective laser trabeculoplasty (SLT), uses a 532-nm, frequency-doubled, Q-switched Nd:YAG laser, which selectively targets melanin pigment in the trabecular

meshwork cells. Studies show SLT is as effective as ALT at lowering eye pressure. In addition, SLT may be repeated three to four times, whereas ALT can usually be repeated only once.

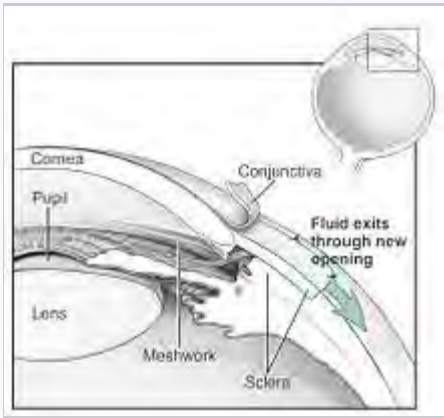
Nd:YAG laser peripheral iridotomy (LPI) may be used in patients susceptible to or affected by angle closure glaucoma or pigment dispersion syndrome. During laser iridotomy, laser energy is used to make a small, full-thickness opening in the iris to equalize the pressure between the front and back of the iris, thus correcting any abnormal bulging of the iris. In people with narrow angles, this can uncover the trabecular meshwork. In some cases of intermittent or short-term angle closure, this may lower the eye pressure. Laser iridotomy reduces the risk of developing an attack of acute angle closure. In most cases, it also reduces the risk of developing chronic angle closure or of adhesions of the iris to the trabecular meshwork.

Diode laser cycloablation lowers IOP by reducing aqueous secretion by destroying secretory ciliary epithelium.[37]

## Surgery [edit]

*Main article: Glaucoma surgery*

Both laser and conventional surgeries are performed to treat glaucoma. Surgery is the primary therapy for those with congenital glaucoma.[59] Generally, these operations are a temporary solution, as there is not yet a cure for glaucoma.




Conventional surgery to treat glaucoma makes a new opening in the trabecular meshwork, which helps fluid to leave the eye and lowers intraocular pressure.

## Canaloplasty [edit]

Canaloplasty is a nonpenetrating procedure using microcatheter technology. To perform a canaloplasty, an incision is made into the eye to gain access to the Schlemm's canal in a similar fashion to a viscocanalostomy. A microcatheter will circumnavigate the canal around the iris, enlarging the main drainage channel and its smaller collector channels through the injection of a sterile, gel-like material called viscoelastic. The catheter is then removed and a suture is placed within the canal and tightened.

By opening the canal, the pressure inside the eye may be relieved, although the reason is unclear, since the canal (of Schlemm) does not have any significant fluid resistance in glaucoma or healthy eyes. Long-term results are not available.[60][61]

## Trabeculectomy [edit]

The most common conventional surgery performed for glaucoma is the trabeculectomy. Here, a partial thickness flap is made in the scleral wall of the eye, and a window opening is made under the flap to remove a portion of the trabecular meshwork. The scleral flap is then sutured loosely back in place to allow fluid to flow out of the eye through this opening, resulting in lowered intraocular pressure and the formation of a bleb or fluid bubble on the surface of the eye.

Scarring can occur around or over the flap opening, causing it to become less effective or lose effectiveness altogether. Traditionally, chemotherapeutic adjuvants, such as mitomycin C (MMC) or 5-fluorouracil (5-FU), are applied with soaked sponges on the wound bed to prevent filtering blebs from scarring by inhibiting fibroblast proliferation. Contemporary alternatives to prevent the scarring of the meshwork opening include the sole or combinative implementation of nonchemotherapeutic adjuvants such as the ologen collagen matrix, which has been clinically shown to increase the success rates of surgical treatment.[62][63][64][65]

Collagen matrix prevents scarring by randomizing and modulating fibroblast proliferation in addition to mechanically preventing wound contraction and adhesion.

## Glaucoma drainage implants [edit]

*Main article: Glaucoma valve*

Professor Anthony Molteno developed the first glaucoma drainage implant, in Cape Town in 1966.[66] Since then, several types of implants have followed on from the original, the Baerveldt tube shunt, or the valved implants, such as the Ahmed glaucoma valve implant or the ExPress Mini Shunt and the later generation pressure ridge Molteno implants. These are indicated for glaucoma patients not responding to maximal medical therapy, with previous failed guarded filtering surgery (trabeculectomy). The flow tube is inserted into the anterior chamber of the eye, and the plate is implanted underneath the conjunctiva to allow a flow of aqueous fluid out of the eye into a chamber called a bleb.

- The first-generation Molteno and other nonvalved implants sometimes require the ligation of the tube until the bleb formed is mildly fibrosed and water-tight.[67] This is done to reduce postoperative hypotony—sudden drops in postoperative intraocular pressure.
- Valved implants, such as the Ahmed glaucoma valve, attempt to control postoperative hypotony by using a mechanical valve.
- Ab interno implants, such as the Xen Gel Stent, are transscleral implants by an ab interno procedure to channel aqueous humor into the non-dissected Tenon's space, creating a subconjunctival drainage area similar to a bleb.[68][69] The implants are transscleral and different from more other ab interno implants that do not create a transscleral drainage, such as iStent, CyPass, or Hydrus.[70]

The ongoing scarring over the conjunctival dissipation segment of the shunt may become too thick for the aqueous humor to filter through. This may require preventive measures using antifibrotic medications, such as 5-fluorouracil or mitomycin-C (during the procedure), or other nonantifibrotic medication methods, such as collagen matrix implant,[71][72] or biodegradable spacer, or later on create a necessity for revision surgery with the sole or combinative use of donor patch grafts or collagen matrix implant.[73][74] And for glaucomatous painful blind eye and some cases of glaucoma, cyclocryotherapy for ciliary body ablation could be considered to be performed.[75]

### Laser-assisted nonpenetrating deep sclerectomy [edit]

The most common surgical approach currently used for the treatment of glaucoma is trabeculectomy, in which the sclera is punctured to alleviate intraocular pressure.

Nonpenetrating deep sclerectomy (NPDS) surgery is a similar, but modified, procedure, in which instead of puncturing the scleral bed and trabecular meshwork under a scleral flap, a second deep scleral flap is created, excised, with further procedures of deroofing the Schlemm's canal, upon which, percolation of liquid from the inner eye is achieved and thus alleviating intraocular pressure, without penetrating the eye. NPDS is demonstrated to cause significantly fewer side effects than trabeculectomy.[*citation needed*] However, NPDS is performed manually and requires higher level of skills that may be assisted with instruments.[*citation needed*] In order to prevent wound adhesion after deep scleral excision and to maintain good filtering results, NPDS as with other non-penetrating procedures is sometimes performed with a variety of biocompatible spacer or devices, such as the Aquaflow collagen wick,[76] ologen Collagen Matrix,[64][77][78] or Xenoplast glaucoma implant.[79]

Laser-assisted NPDS is performed with the use of a $CO_2$ laser system. The laser-based system is self-terminating once the required scleral thickness and adequate drainage of the intraocular fluid have been achieved. This self-regulation effect is achieved as the $CO_2$ laser essentially stops ablating as soon as it comes in contact with the intraocular percolated liquid, which occurs as soon as the laser reaches the optimal residual intact layer thickness.

## Prognosis [edit]

In open-angle glaucoma, the typical progression from normal vision to complete blindness takes about 25 years to 70 years without treatment, depending on the method of estimation used.[80] The intraocular pressure can also have an effect, with higher pressures reducing the time until blindness.[81]

[edit]

# Epidemiology

As of 2010, there were 44.7 million people in the world with open angle glaucoma.[83] The same year, there were 2.8 million people in the United States with open angle glaucoma.[83] By 2020, the prevalence is projected to increase to 58.6 million worldwide and 3.4 million the United States.[83]

Both internationally and in the United States glaucoma is the second-leading cause of blindness.[2] Globally cataracts are a more common cause. Glaucoma is also the leading cause of blindness in African Americans, who have higher rates of primary open angle glaucoma.[84][85] Bilateral vision loss can negatively affect mobility and interfere with driving.[86]

A meta-analysis published in 2009 found that people with primary open angle glaucoma do *not* have increased mortality rates, or increased risk of cardiovascular death.[87]

Disability-adjusted life year for glaucoma per 100,000 inhabitants in 2004[82]

| | |
|---|---|
| no data | 112–135 |
| fewer than 20 | 135–158 |
| 20–43 | 158–181 |
| 43–66 | 181–204 |
| 66–89 | 204–227 |
| 89–112 | 227–250 |
| | more than 250 |

# History [edit]

The association of elevated intraocular pressure (IOP) and the eye disease glaucoma was first described by Englishman Richard Bannister in 1622: "...that the Eye be grown more solid and hard, then naturally it should be...".[88] The invention of the ophthalmoscope by Hermann Helmholtz in 1851 enabled ophthalmologists for the first time to identify the pathological hallmark of glaucoma, the excavation of the optic nerve head due to retinal ganglion cell loss. The first reliable instrument to measure intraocular pressure was invented by Norwegian ophthalmologist Hjalmar August Schiøtz in 1905. About half a century later, Hans Goldmann in Berne, Switzerland, developed his applanation tonometer which still today - despite numerous new innovations in diagnostics - is considered the gold standard of determining this crucial pathogenic factor. In the late 20th century, further pathomechanisms beyond elevated IOP were discovered and became the subject of research like insufficient blood supply - often associated with low or irregular blood pressure - to the retina and optic nerve head.[89] The first drug to reduce IOP, pilocarpine, was introduced in the 1870s. Early surgical techniques like iridectomy and fistulating methods have recently been supplemented by less invasive procedures like small implants, a range of options now widely called MIGS (micro-invasive glaucoma surgery).

## Etymology [edit]

The word "glaucoma" comes from the Greek γλαύκωμα, a derivative of γλαυκός, which commonly described the color of eyes which were not dark (i.e. blue, green, light gray). Eyes described as γλαυκός due to disease might have had a gray cataract in the Hippocratic era, or, in the early Common Era, the greenish pupillary hue sometimes seen in angle-closure glaucoma.[8][90]

# Research [edit]

## Rho kinase inhibitors [edit]

Rho kinase inhibitors, such as ripasudil, work by inhibition of the actin cytoskeleton, resulting in the morphological changes in the trabecular meshwork and increased aqueous outflow. More compounds in this class are being investigated in phase 2 and phase 3 trials.[91]

Play media

scientists track eye movements in glaucoma patients to check vision impairment while driving

## Neuroprotective agents [edit]

A 2013 Cochrane Systematic Review compared the effect of brimonidine and timolol in slowing the progression of open angle glaucoma in adult participants.[92] The results showed that participants assigned to brimonidine showed less visual field progression that those assigned to timolol, though the results were not significant, given the heavy loss-to-followup and limited evidence.[92] The mean intraocular pressures for both groups were similar. Participants in the brimonidine group had a higher occurrence of side effects caused by medication than participants in the timolol group.[92]

## Cannabis [edit]

Studies in the 1970s reported that the use of cannabis may lower intraocular pressure.[93][94][95] In an effort to determine whether marijuana, or drugs derived from it, might be effective as a glaucoma treatment, the US National Eye Institute supported research studies from 1978 to 1984. These studies demonstrated some derivatives of marijuana lowered intraocular pressure when administered orally, intravenously, or by smoking, but not when topically applied to the eye.

In 2003, the American Academy of Ophthalmology released a position statement stating that cannabis was not more effective than prescription medications. Furthermore, no scientific evidence has been found that demonstrates increased benefits and/or diminished risks of cannabis use to treat glaucoma compared with the wide variety of pharmaceutical agents now available.[95][96]

In 2012 the American Glaucoma Society published a position paper discrediting the use of cannabis as a legitimate treatment for elevated intraocular pressure, for reasons including short duration of action and side effects that limit many activities of daily living.[97]

# References [edit]


1. ^ *a b c d e f g h i* "Facts About Glaucoma". *National Eye Institute*. Retrieved 29 March 2016.
2. ^ *a b c d e f g h i j k l m* Mantravadi, AV; Vadhar, N (September 2015). "Glaucoma.". *Primary Care*. Saunders (Elsevier). **42** (3): 437–49. doi:10.1016/j.pop.2015.05.008. ISSN 0095-4543. PMID 26319348 – via Elsevier Science Direct. (subscription required (help)).
3. ^ Rhee, Douglas J. (2012). *Glaucoma* (2 ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 180. ISBN 9781609133375. OCLC 744299538.
4. ^ Mi, Xue-Song; Yuan, Ti-Fei; So, Kwok-Fai (16 September 2014). "The current research status of normal tension glaucoma". *Clinical Interventions in Aging*. **9**: 1563–71. doi:10.2147/CIA.S67263. PMID 25258525.
5. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/S0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
6. ^ "Glaucoma: The 'silent thief' begins to tell its secrets" (Press release). National Eye Institute. 21 January 2014.
7. ^ Resnikoff, Serge; Pascolini, Donatella; Etya'Ale, Daniel; Kocur, Ivo; Pararajasegaram, Ramachandra; Pokharel, Gopal P.; Mariotti, Silvio P. (2004). "Global data on visual impairment in the year 2002". *Bulletin of the World Health Organization*. **82** (11): 844–51. doi:10.1590/S0042-96862004001100009 (inactive 2015-01-01). PMC 2623053. PMID 15640920.
8. ^ *a b* Leffler, CT; Schwartz, SG; Giliberti, FM; Young, MT; Bermudez, D (2015). "What was Glaucoma Called Before the 20th Century?". *Ophthalmology and Eye Diseases*. Libertas Academica. **7**: 21–33. doi:10.4137/OED.S32004.

ISSN 1179-1721. PMC 4601337. PMID 26483611.
9. ^ Leffler CT, Schwartz SG, Stackhouse R, Davenport B, Spetzler K (2013). "Evolution and impact of eye and vision terms in written English". *JAMA Ophthalmology*. **131** (12): 1625–31. doi:10.1001/jamaophthalmol.2013.917. PMID 24337558.
10. ^ Sommer A, Tielsch JM, Katz J, et al. (August 1991). "Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey". *Archives of Ophthalmology*. **109** (8): 1090–5. doi:10.1001/archopht.1991.01080080050026. PMID 1867550. (subscription required (help)).
11. ^ *a b* Rhee DJ, Katz LJ, Spaeth GL, Myers JS (2001). "Complementary and alternative medicine for glaucoma". *Survey of Opthalmology*. **46** (1): 43–55. doi:10.1016/S0039-6257(01)00233-8. PMID 11525790. (subscription required (help)).
12. ^ Li, M; Wang, M; Guo, W; Wang, J; Sun, X (March 2011). "The effect of caffeine on intraocular pressure: a systematic review and meta-analysis". *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv für klinische und experimentelle Ophthalmologie*. Springer. **249** (3): 435–42. doi:10.1007/s00417-010-1455-1. ISSN 1435-702X. PMID 20706731. (subscription required (help)).
13. ^ Wang N, Wu H, Fan Z (November 2002). "Primary angle closure glaucoma in Chinese and Western populations". *Chinese Medical Journal*. **115** (11): 1706–15. PMID 12609093.
14. ^ Friedman D, Vedula SS (2006). "Lens extraction for chronic angle-closure glaucoma". *Cochrane Database Syst Rev*. **3**: CD005555. doi:10.1002/14651858.CD005555.pub2. PMC 4438535. PMID 16856103.
15. ^ Myron Yanoff; Jay S. Duker (2009). *Ophthalmology* (3rd ed.). Mosby Elsevier. p. 1096. ISBN 9780323043328.
16. ^ Online Mendelian Inheritance in Man (OMIM) GLAUCOMA, PRIMARY OPEN ANGLE; POAG -137760
17. ^ Online Mendelian Inheritance in Man (OMIM) GLAUCOMA, NORMAL TENSION, SUSCEPTIBILITY TO -606657
18. ^ Pardianto G, et al. (2005). "Aqueous Flow and the Glaucoma". *Mimbar Ilmiah Oftalmologi Indonesia*. **2**: 12–5.
19. ^ Chaum E, et al. "A 5-year-old girl who failed her school vision screening. Case presentation of Persistent fetal vasculature (PFV), also called persistent hyperplastic primary vitreous (PHPV)". *Digital Journal of Ophthalmology*.
20. ^ Hunt A, Rowe N, Lam A, Martin F (July 2005). "Outcomes in persistent hyperplastic primary vitreous". *Br J Ophthalmol*. **89** (7): 859–63. doi:10.1136/bjo.2004.053595. PMC 1772745. PMID 15965167.
21. ^ Chang B, Smith RS, Peters M, et al. (2001). "Haploinsufficient Bmp4 ocular phenotypes include anterior segment dysgenesis with elevated intraocular pressure". *BMC Genet*. **2**: 18. doi:10.1186/1471-2156-2-18. PMC 59999. PMID 11722794.
22. ^ Alguire P (1990). "The Eye Chapter 118 Tonometry>Basic Science". In Walker HK, Hall WD, Hurst JW. *Clinical methods: the history, physical, and laboratory examinations* (3rd ed.). London: Butterworths. ISBN 0-409-90077-X.
23. ^ Mozaffarieh M, Grieshaber MC, Flammer J (2008). "Oxygen and blood flow: players in the pathogenesis of glaucoma". *Mol Vis*. **14**: 224–33. PMC 2267728. PMID 18334938.
24. ^ Hasnain, Syed S (2006). "Scleral edge, not optic disc or retina is the primary site of injury in chronic glaucoma". *Medical Hypotheses*. **67** (6): 1320–1325. doi:10.1016/j.mehy.2006.05.030. PMID 16824694.
25. ^ Osborne NN, Wood JP, Chidlow G, Bae JH, Melena J, Nash MS (August 1999). "Ganglion cell death in glaucoma: what do we really know?". *Br J Ophthalmol*. **83** (8): 980–6. doi:10.1136/bjo.83.8.980. PMC 1723166. PMID 10413706.
26. ^ Levin LA, Peeples P (February 2008). "History of neuroprotection and rationale as a therapy for glaucoma". *Am J Manag Care*. **14** (1 Suppl): S11–4. PMID 18284310.
27. ^ Varma R, Peeples P, Walt JG, Bramley TJ (February 2008). "Disease progression and the need for neuroprotection in glaucoma management". *Am J Manag Care*. **14** (1 Suppl): S15–9. PMID 18284311.
28. ^ Hernández M, Urcola JH, Vecino E (May 2008). "Retinal ganglion cell neuroprotection in a rat model of glaucoma following brimonidine, latanoprost or combined treatments". *Exp Eye Res*. **86** (5): 798–806. doi:10.1016/j.exer.2008.02.008. PMID 18394603.
29. ^ Cantor LB (December 2006). "Brimonidine in the treatment of glaucoma and ocular hypertension". *Ther Clin Risk Manag*. **2** (4): 337–46. doi:10.2147/tcrm.2006.2.4.337. PMC 1936355. PMID 18360646.
30. ^ Schwartz M (June 2007). "Modulating the immune system: a vaccine for glaucoma?". *Can J Ophthalmol*. **42** (3): 439–41. doi:10.3129/I07-050. PMID 17508041.
31. ^ Morrison JC (2006). "INTEGRINS IN THE OPTIC NERVE HEAD: POTENTIAL ROLES IN GLAUCOMATOUS OPTIC NEUROPATHY (AN AMERICAN OPHTHALMOLOGICAL SOCIETY THESIS)". *Trans Am Ophthalmol Soc*. **104**: 453–77. PMC 1809896. PMID 17471356.
32. ^ Knox DL, Eagle RC, Green WR (March 2007). "Optic nerve hydropic axonal degeneration and blocked retrograde axoplasmic transport: histopathologic features in human high-pressure secondary glaucoma". *Arch Ophthalmol*. **125** (3): 347–53. doi:10.1001/archopht.125.3.347. PMID 17353405.
33. ^ Tezel G, Luo C, Yang X (March 2007). "Accelerated Aging in Glaucoma: Immunohistochemical Assessment of Advanced Glycation End Products in the Human Retina and Optic Nerve Head". *Invest. Ophthalmol. Vis. Sci*. **48**

(3): 1201–11. doi:10.1167/iovs.06-0737. PMC 2492883. PMID 17325164.
34. ^ Berry FB, Mirzayans F, Walter MA (April 2006). "Regulation of FOXC1 stability and transcriptional activity by an epidermal growth factor-activated mitogen-activated protein kinase signaling cascade". *J Biol Chem*. **281** (15): 10098–104. doi:10.1074/jbc.M513629200. PMID 16492674.
35. ^ "Issue on neuroprotection". *Can J Ophthalmol*. **42** (3). June 2007. ISSN 1715-3360.
36. ^ Farandos, NM; Yetisen, AK; Monteiro, MJ; Lowe, CR; Yun, SH (November 2014). "Contact Lens Sensors in Ocular Diagnostics". *Advanced Healthcare Materials*. **4**: 792–810. doi:10.1002/adhm.201400504. PMID 25400274.
37. ^ *a b c* Pardianto G et al. Some difficulties on Glaucoma. Mimbar Ilmiah Oftalmologi Indonesia.2006;3: 49–52.
38. ^ Thomas R, Parikh RS (September 2006). "How to assess a patient for glaucoma". *Community Eye Health*. **19** (59): 36–7. PMC 1705629. PMID 17491713.
39. ^ Michelessi M, Lucenteforte E, Oddone F, Brazzelli M, Parravano M, Franchi S, Ng SM, Virgili G (2015). "Optic nerve head and fibre layer imaging for diagnosing glaucoma". *Cochrane Database Syst Rev*. **11**: CD008803. doi:10.1002/14651858.CD008803.pub2. PMID 26618332.
40. ^ Johnson, Chris A. The use of a visual illusion to detect glaucoma. In *Visual Perception: The Influence of H. W. Leibowitz*, eds. Andre, J., Owens, D. A., and Harvey, Jr., L. O. (2003); 45–56. Washington, D.C.: The American Psychological Association.
41. ^ Foundation, G. R. (n.d.). "Five common Glaucoma Tests". Glaucoma.org. Retrieved 2014-02-20.
42. ^ Troy Bedinghaus, O (2010). "Six Tests for Glaucoma". Vision.about.com. Retrieved 2014-02-20.
43. ^ "Nerve Fiber Analysis". *Glaucoma Associates of Texas*. White Rabbit Communications, Inc. 2010. Retrieved 9 December 2012.
44. ^ Paton D, Craig JA; Craig (1976). "Glaucomas. Diagnosis and management". *Clin Symp*. **28** (2): 1–47. PMID 1053095.
45. ^ Logan, Carolynn M.; Rice, M. Katherine (1987). *Logan's Medical and Scientific Abbreviations*. Philadelphia: J. B. Lippincott Company. p. 3. ISBN 0-397-54589-4.
46. ^ *a b* "Primary Open-Angle Glaucoma: Glaucoma: Merck Manual Professional". Merck.com. Retrieved 2011-01-24.
47. ^ Simha A, Braganza A, Abraham L, Samuel P, Lindsley K (2013). "Anti-vascular endothelial growth factor for neovascular glaucoma". *Cochrane Database Syst Rev*. **10**: CD007920. doi:10.1002/14651858.CD007920.pub2. PMC 4261636. PMID 24089293.
48. ^ Pardianto G, Difficulties on glaucoma in Mimbar Ilmiah Oftalmologi Indonesia.2006;3: 48–9.[*verification needed*]
49. ^ Arthur J. Sit, MD (April 23, 2006). "Many types of glaucoma, one kind of damage to optic nerve". Chicago Tribune. Archived from the original on 2012-10-06. Retrieved 2015-08-18. "Glaucoma is a broad term for a number of different conditions that damage the optic nerve, the 'cable' that carries visual information from the eye to the brain, thereby causing changes in vision."
50. ^ Moyer, Virginia A. (9 July 2013). "Screening for Glaucoma: U.S. Preventive Services Task Force Recommendation Statement". *Annals of Internal Medicine*. doi:10.7326/0003-4819-159-6-201309170-00685.
51. ^ "Glaucoma – National Institutes of Health". Nihseniorhealth.gov. Retrieved 2011-01-24.
52. ^ Noecker RJ (June 2006). "The management of glaucoma and intraocular hypertension: current approaches and recent advances". *Ther Clin Risk Manag*. **2** (2): 193–206. doi:10.2147/tcrm.2006.2.2.193. PMC 1661659. PMID 18360593.
53. ^ Parikh RS, Parikh SR, Navin S, Arun E, Thomas R (1 May 2008). "Practical approach to medical management of glaucoma". *Indian J Ophthalmol*. **56** (3): 223–30. doi:10.4103/0301-4738.40362. PMC 2636120. PMID 18417824.
54. ^ Leffler CT, Amini L (2007). "Interpretation of uniocular and binocular trials of glaucoma medications: an observational case series". *BMC Ophthalmol*. **7**: 17. doi:10.1186/1471-2415-7-17. PMC 2093925. PMID 17916260.
55. ^ Jaret, Peter. "A New Understanding of Glaucoma". NYTimes.com. Retrieved 2014-02-20.
56. ^ Ritch R (June 2007). "Natural compounds: evidence for a protective role in eye disease". *Can J Ophthalmol*. **42** (3): 425–38. doi:10.3129/I07-044. PMID 17508040.
57. ^ Tsai JC, Song BJ, Wu L, Forbes M (September 2007). "Erythropoietin: a candidate neuroprotective agent in the treatment of glaucoma". *J Glaucoma*. **16** (6): 567–71. doi:10.1097/IJG.0b013e318156a556. PMID 17873720.
58. ^ Mozaffarieh M, Flammer J (November 2007). "Is there more to glaucoma treatment than lowering IOP?". *Surv Ophthalmol*. **52** (Suppl 2): S174–9. doi:10.1016/j.survophthal.2007.08.013. PMID 17998043.
59. ^ Online Mendelian Inheritance in Man (OMIM) Glaucoma, Congenital: GLC3 Buphthalmos -231300
60. ^ Shingleton B, Tetz M, Korber N (March 2008). "Circumferential viscodilation and tensioning of Schlemm's canal (canaloplasty) with temporal clear corneal phacoemulsification cataract surgery for open-angle glaucoma and visually significant cataract: one-year results". *J Cataract Refract Surg*. **34** (3): 433–40. doi:10.1016/j.jcrs.2007.11.029. PMID 18299068.
61. ^ Lewis RA, von Wolff K, Tetz M, et al. (July 2007). "Canaloplasty: circumferential viscodilation and tensioning of

Schlemm's canal using a flexible microcatheter for the treatment of open-angle glaucoma in adults: interim clinical study analysis". *J Cataract Refract Surg*. **33** (7): 1217–26. doi:10.1016/j.jcrs.2007.03.051. PMID 17586378.
62. ^ Dada T, Sharma R, Sinha G, Angmo D, Temkar S (2016). "Cyclodialysis-enhanced trabeculectomy with triple Ologen implantation". *Eur J Ophthalmol*. **26** (1): 95–7. doi:10.5301/ejo.5000633. PMID 26044372.
63. ^ Yuan, F; Li, L; Chen; Yan; Wang (2015). "Biodegradable 3D-Porous Collagen Matrix (Ologen) Compared with Mitomycin C for Treatment of Primary Open-Angle Glaucoma: Results at 5 Years". *Journal of Ophthalmology*. **2015** (637537): 1–7. doi:10.1155/2015/637537. PMC 4452460. PMID 26078875.
64. ^ [a] [b] Dada, Tanuj; Amit S; Saptorshi M; Meenakshi G (May 2013). "Combined Subconjunctival and Subscleral ologen Implant Insertion in Trabeculectomy". *Eye (Lond.)*. **27** (7): 889. doi:10.1038/eye.2013.76. PMC 3709396. PMID 23640614.
65. ^ Cillino, S; Casuccio A; Di Pace F; Cagini C; Ferraro LL (Mar 2016). "Biodegradable collagen matrix implant versus mitomycin-C in trabeculectomy: five-year follow-up". *BMC Ophthalmol*. **16** (24). doi:10.1186/s12886-016-0198-0. PMC 4779569. PMID 26946419.
66. ^ "Eyelights Newsletter: About Glaucoma New Zealand" (PDF). Glaucoma.org. Retrieved 2014-02-20.
67. ^ Molteno AC, Polkinghorne PJ, Bowbyes JA (November 1986). "The vicryl tie technique for inserting a draining implant in the treatment of secondary glaucoma". *Aust N Z J Ophthalmol*. **14** (4): 343–54. doi:10.1111/j.1442-9071.1986.tb00470.x. PMID 3814422.
68. ^ Lewis RA (Aug 2014). "Ab interno approach to the subconjunctival space using a collagen glaucoma stent.". *J Cataract Refract Surg*. **40** (8): 1301–6. doi:10.1016/j.jcrs.2014.01.032. PMID 24943904.
69. ^ "Xen Gel Stent". *AqueSys*. AqueSys. Retrieved 27 June 2015.
70. ^ "Advances in Glaucoma Filtration Surgery". Glaucoma Today. Retrieved 27 June 2015.
71. ^ Rosentreter, Andre; Andre M. Schild; Sven Dinslage; Thomas S. Dietlein (Jan 2011). "Biodegradable implant for tissue repair after glaucoma drainage device surgery". *J Glaucoma*. **21** (2): 76–8. doi:10.1097/IJG.0b013e3182027ab0. PMID 21278584.
72. ^ Rosentreter, Andre; Anne C. Mellein; Walter W. Konen; Thomas S. Dietlein (Sep 2010). "Capsule excision and ologenTM implantation for revision after glaucoma drainage device surgery". *Graefes Arch Clin Exp Ophthalmol*. **248** (9): 1319–24. doi:10.1007/s00417-010-1385-y. PMID 20405139.
73. ^ Rosentreter, A; Mellein AC; Konen WW; Dietlein TS (2010). "Capsule excision and ologenTM implantation for revision after glaucoma drainage device surgery". *Graefes Arch Clin Exp Ophthalmol*. **248** (9): 1319–24. doi:10.1007/s00417-010-1385-y. PMID 20405139.
74. ^ Oana, Stirbu; Jorge Vila (December 2012). Shaarawy, Tarek, ed. "Tube Exposure Repair". *Journal of Current Glaucoma Practice*. **6** (3): 139–142. doi:10.5005/jp-journals-10008-1121.
75. ^ Pardianto G, et al. (2006). "Some difficulties on Glaucoma". *Mimbar Ilmiah Oftalmologi Indonesia*. **3**: 49–50.
76. ^ Iqbal "Ike" K. Ahmed (1 September 2005). "Making the Case for Nonpenetrating Surgery". *Review of Ophthamology*. **12** (9). Archived from the original on 11 October 2007.
77. ^ Aptel, F; Dumas S; Denis P (2009). "Ultrasound biomicroscopy and optical coherence tomography imaging of filtering blebs after deep sclerectomy with new collagen implant". *Eur J Ophthalmol*. **19** (2): 223–30. PMID 19253238.
78. ^ Matthew, SJ; Sarkisian S; Nathan B; James MR (2012). "Initial experience using a collagen matrix implant (ologen) as a wound modulator with canaloplasty: 12 month results". Ft. Lauderdale: ARVO Congress.
79. ^ Anisimova SY, Anisimova SI, Larionov EV (2012). "Biological drainage – Xenoplast in glaucoma surgery (experimental and 10-year of clinical follow-up)" (PDF). Copenhagen: EGS Congress.
80. ^ Heijl, Anders; Bengtsson, Boel; Hyman, Leslie; Leske, M. Cristina (Dec 2009). "Natural History of Open-Angle Glaucoma". *Ophthalmology*. **116** (12): 2271–2276. doi:10.1016/j.ophtha.2009.06.042. PMID 19854514.
81. ^ "Glaucoma". Coopereyecare.com. 2013-07-25. Retrieved 2014-02-20.
82. ^ "Death and DALY estimates for 2004 by cause for WHO Member States" (xls). *World Health Organization*. 2004.
83. ^ [a] [b] [c] Quigley, H A; Broman, AT (March 2006). "The number of people with glaucoma worldwide in 2010 and 2020". *British Journal of Ophthalmology*. **90** (3): 262–267. doi:10.1136/bjo.2005.081224. PMC 1856963. PMID 16488940.
84. ^ Sommer, Alfred; Tielsch, James M.; Katz, Joanne; Quigley, Harry A.; Gottsch, John D.; Javitt, Jonathan C.; Martone, James F.; Royall, Richard M.; Witt, Kathe A.; Ezrine, Sandi (Nov 14, 1991). "Racial Differences in the Cause-Specific Prevalence of Blindness in East Baltimore". *New England Journal of Medicine*. **325** (20): 1412–1417. doi:10.1056/NEJM199111143252004. PMID 1922252.
85. ^ "Glaucoma and Marijuana use". National Eye Institute. June 21, 2005.
86. ^ Ramulu, Pradeep (March 2009). "Glaucoma and disability: which tasks are affected, and at what stage of disease?". *Current opinion in ophthalmology*. **20** (2): 92–8. doi:10.1097/ICU.0b013e32832401a9. PMC 2692230. PMID 19240541.
87. ^ Akbari, M.; Akbari, S.; Pasquale, L. R. (February 2009). "The Association of Primary Open-angle Glaucoma With

Mortality: A Meta-analysis of Observational Studies". *Archives of Ophthalmology*. **127** (2): 204–210. doi:10.1001/archophthalmol.2008.571. PMID 19204241.
88. ^ Richard Bannister: Treatise of One Hundred and Thirteen Diseases of the Eyes and Eyelids. London 1622
89. ^ Daniel Albert and Diane Edwards: The History of Ophthalmologist. Cambridge, Mass. 1996
90. ^ Leffler CT, Schwartz SG, Hadi TM, Salman A, Vasuki V (2015). "The early history of glaucoma: the glaucous eye (800 BC to 1050 AD)". *Clinical Ophthalmology*. **2015** (9): 207–15. doi:10.2147/OPTH.S77471. PMID 25673972.
91. ^ Sean K Wang, Robert T Chang (2014). "An emerging treatment option for glaucoma: Rho kinase inhibitors". *Clin Ophthalmol*. **8**: 883–89. doi:10.2147/OPTH.S41000. PMC 4025933. PMID 24872673.
92. ^ *a b c* Sena DF, Lindsley K (2013). "Neuroprotection for treatment of glaucoma in adults". *Cochrane Database Syst Rev*. **2** (2): CD006539. doi:10.1002/14651858.CD006539.pub3. PMC 4261923. PMID 23450569.
93. ^ "Marijuana and Medicine: Assessing the Science Base". Nap.edu. Retrieved 2014-02-20.
94. ^ "Marijuana and Medicine: Assessing the Science Base (1999), Institute of Medicine, National Academies Press". Nap.edu. Retrieved 2011-06-22.
95. ^ *a b* "Complementary Therapy Assessment: Marijuana in the Treatment of Glaucoma". American Academy of Ophthalmology. Retrieved 2011-05-04.
96. ^ "Complementary Therapy Assessments : American Academy of Ophthalmology". One.aao.org. Retrieved 2011-01-24.
97. ^ Jampel, Henry (2010). "American Glaucoma Society Position Statement: Marijuana and the Treatment of Glaucoma". *J Glaucoma*. **19** (2): 75.

## External links [edit]

- Glaucoma at DMOZ
- GeneReview/NCBI/NIH/UW entry on Primary Congenital Glaucoma
- *Glaucoma*, by Gary Heiting, OD and Marilyn Haddrill, *All About Vision*

| v · t · e · | **Diseases of the human eye (H00–H59 · 360–379) ·** | |
|---|---|---|
| **Adnexa** | | |
| **Eyelid** | **Inflammation** | Stye · Chalazion · Blepharitis · |
| | | Entropion · Ectropion · Lagophthalmos · Blepharochalasis · Ptosis · Blepharophimosis · Xanthelasma · |
| | **Eyelash** | Trichiasis · Madarosis · |
| **Lacrimal apparatus** | | Dacryoadenitis · Epiphora · Dacryocystitis · Xerophthalmia · |
| **Orbit** | | Exophthalmos · Enophthalmos · Orbital cellulitis · Orbital lymphoma · Periorbital cellulitis · |
| **Conjunctiva** | | Conjunctivitis (allergic · · Pterygium · Pinguecula · Subconjunctival hemorrhage · |
| **Globe** | | |
| **Fibrous tunic** | **Sclera** | Scleritis · Episcleritis · |
| | **Cornea** | Keratitis (herpetic · acanthamoebic · fungal · · Corneal ulcer · Photokeratitis · Thygeson's superficial punctate keratopathy · Corneal dystrophy (Fuchs' · Meesmann · · Corneal ectasia (Keratoconus · Pellucid marginal degeneration · Keratoglobus · Terrien's marginal degeneration · Post-LASIK ectasia · · Keratoconjunctivitis (sicca · · Corneal neovascularization · Kayser–Fleischer ring · Haab's striae · Arcus senilis · Band keratopathy · |
| **Vascular tunic** | **Iris · Ciliary body ·** | Uveitis · Intermediate uveitis · Hyphema · Rubeosis iridis · Persistent pupillary membrane · Iridodialysis · Synechia · |

| | | |
|---|---|---|
| | **Choroid** | Choroideremia · Choroiditis (Chorioretinitis · · |
| **Lens** | Cataract (Congenital cataract · Childhood cataract · · Aphakia · Ectopia lentis · | |
| **Retina** | Retinitis (Chorioretinitis · Cytomegalovirus retinitis · · Retinal detachment · Retinoschisis · Ocular ischemic syndrome / Central retinal vein occlusion · Central retinal artery occlusion · Retinopathy (diabetic · hypertensive · Purtscher's · of prematurity · Bietti's crystalline dystrophy · Coats' disease · · Macular degeneration · Retinitis pigmentosa · Retinal haemorrhage · Central serous retinopathy · Macular edema · Epiretinal membrane (Macular pucker) · Vitelliform macular dystrophy · Leber's congenital amaurosis · Birdshot chorioretinopathy · | |
| **Other** | **Glaucoma** / Ocular hypertension / Primary juvenile glaucoma · Floater · Leber's hereditary optic neuropathy · Red eye · Globe rupture · Keratomycosis · Phthisis bulbi · Persistent fetal vasculature / Persistent hyperplastic primary vitreous · Persistent tunica vasculosa lentis · Familial exudative vitreoretinopathy · | |
| **Pathways** | | |
| **Optic nerve Optic disc** | Optic neuritis (optic papillitis · · Papilledema (Foster Kennedy syndrome · · Optic atrophy · Optic disc drusen · | |
| | **Optic neuropathy** | Ischemic (anterior (AION) · posterior (PION) · · Kjer's · Leber's hereditary · Toxic and nutritional · |
| **Strabismus Extraocular muscles Binocular vision Accommodation** | **Paralytic strabismus** | Ophthalmoparesis · Chronic progressive external ophthalmoplegia · Kearns–Sayre syndrome · |
| | **palsies** | Oculomotor (III) · Fourth-nerve (IV) · Sixth-nerve (VI) · |
| | **Other strabismus** | Esotropia / Exotropia · Hypertropia · Heterophoria (Esophoria · Exophoria · · Cyclotropia · Brown's syndrome · Duane syndrome · |
| | **Other binocular** | Conjugate gaze palsy · Convergence insufficiency · Internuclear ophthalmoplegia · One and a half syndrome · |
| **Refraction** | Refractive error (Hyperopia · Myopia · · Astigmatism · Anisometropia / Aniseikonia · Presbyopia · | |
| **Vision disorders Blindness** | Amblyopia · Leber's congenital amaurosis · Diplopia · Scotoma · Color blindness (Achromatopsia · Dichromacy · Monochromacy · · Nyctalopia (Oguchi disease · · Blindness / Vision loss / Visual impairment · | |
| | **Anopsia** | Hemianopsia (binasal · bitemporal · homonymous · · Quadrantanopia · |
| | **subjective** | Asthenopia · Hemeralopia · Photophobia · Scintillating scotoma · |
| **Pupil** | Anisocoria · Argyll Robertson pupil · Marcus Gunn pupil · Adie syndrome · Miosis · Mydriasis · Cycloplegia · Parinaud's syndrome · | |
| **Other** | Nystagmus · Childhood blindness · | |
| **Infections** | | |
| Trachoma · Onchocerciasis · | | |

| | |
|---|---|
| **Authority control** | LCCN: sh85055227 · GND: 4021210-5 · SUDOC: 027278808 · BNF: cb11935553n (data) · NDL: 00569850 · BNE: XX529246 · |

Categories: Glaucoma | Blindness


# Macular degeneration

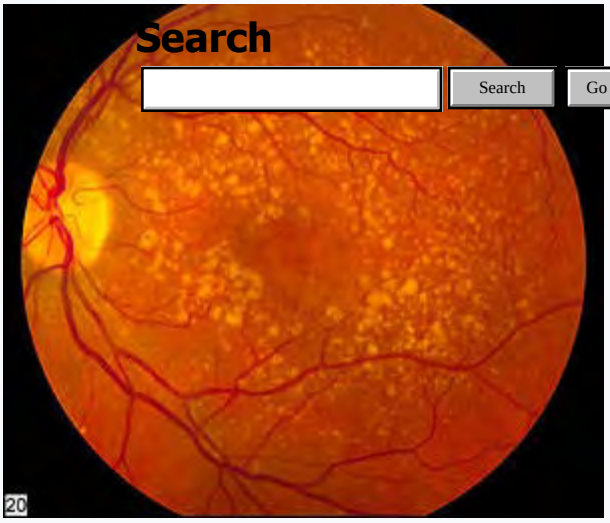
From Wikipedia, the free encyclopedia

**Macular degeneration**, also known as **age-related macular degeneration** (**AMD** or **ARMD**), is a medical condition which may result in blurred or no vision in the center of the visual field.[1] Early on there are often no symptoms. Over time, however, some people experience a gradual worsening of vision that may affect one or both eyes. While it does not result in complete blindness, loss of central vision can make it hard to recognize faces, drive, read, or perform other activities of daily life. Visual hallucinations may also occur but these do not represent a mental illness.[1]

Macular degeneration typically occurs in older people. Genetic factors and smoking also play a role. It is due to damage to the macula of the retina. Diagnosis is by a complete eye exam. The severity is divided into early, intermediate, and late types.[1] The late type is additionally divided into "dry" and "wet" forms with the dry form making up 90% of cases.[1][2]

Prevention includes exercising, eating well, and not smoking.[1] Antioxidant vitamins and minerals do not appear to be useful for prevention.[3] There is no cure or treatment that returns vision already lost. In the wet form, anti-VEGF medication injected into the eye or less commonly laser coagulation or photodynamic therapy may slow worsening.[1] Supplements in those who already have the disease may slow progression.[4]

In 2010 it affected 23.5 million people globally.[5] In 2013 moderate to severe disease affected 13.4 million and it is the fourth most common cause of blindness after cataracts, preterm birth, and glaucoma.[6] It most commonly occurs in people over the age of fifty and in the United States is the most common cause of vision loss in this age group.[1][2] About 0.4% of people between 50 and 60 have the disease, while it occurs in 0.7% of people 60 to 70, 2.3% of those 70 to 80, and nearly 12% of people over 80 years old.[2]



Picture of the back of the eye showing intermediate age-related macular degeneration

| Classification and external resources | |
|---|---|
| **Specialty** | Ophthalmology |
| **ICD-10** | H35.3 |
| **ICD-9-CM** | 362.50 |
| **DiseasesDB** | 11948 |
| **MedlinePlus** | 001000 |
| **eMedicine** | article/1223154 |
| **Patient UK** | Macular degeneration |
| **MeSH** | D008268 |

[edit on Wikidata]

Contents

## Signs and symptoms [edit]

Signs and symptoms of macular degeneration include:

**Visual symptoms**

- Distorted vision in the form of metamorphopsia, in which a grid of straight lines appears wavy and parts of the grid may appear blank: Patients often first notice this when looking at things like miniblinds in their home or telephone poles while driving. There may also be central scotomas, shadows or missing areas of vision
- Slow recovery of visual function after exposure to bright light (photostress test)
- Visual acuity drastically decreasing (two levels or more), e.g.: 20/20 to 20/80
- Blurred vision: Those with nonexudative macular degeneration may be asymptomatic or notice a gradual loss of central vision, whereas those with exudative macular degeneration often notice a rapid onset of vision loss (often caused by leakage and bleeding of abnormal blood vessels).
- Trouble discerning colors, specifically dark ones from dark ones and light ones from light ones
- A loss in contrast sensitivity

Normal vision

The same view with age-related macular degeneration (National Eye Institute)

Macular degeneration by itself will not lead to total blindness. For that matter, only a very small number of people with visual impairment are totally blind. In almost all cases, some vision remains, mainly peripheral. Other complicating conditions may possibly lead to such an acute condition (severe stroke or trauma, untreated glaucoma, etc.), but few macular degeneration patients experience total visual loss.[7]

The area of the macula comprises only about 2.1% of the retina, and the remaining 97.9% (the peripheral field) remains unaffected by the disease. Even though the macula provides such a small fraction of the visual field, almost half of the visual cortex is devoted to processing macular information.[8]

The loss of central vision profoundly affects visual functioning. It is quite difficult, for example, to read

without central vision. Pictures that attempt to depict the central visual loss of macular degeneration with a black spot do not really do justice to the devastating nature of the visual loss. This can be demonstrated by printing letters six inches high on a piece of paper and attempting to identify them while looking straight ahead and holding the paper slightly to the side. Most people find this difficult to do.

## Risk factors [edit]

- **Ageing**: Advanced age is the strongest predictor of AMD.[*medical citation needed*] .
- **Family history:**

### Environment and lifestyle [edit]

- **Smoking**: Smoking tobacco increases the risk of AMD by two to three times that of someone who has never smoked, and may be the most important modifiable factor in its prevention. A review of previous studies found "a strong association between current smoking and AMD. ... Cigarette smoking is likely to have toxic effects on the retina."[9]
- **Hypertension** (high blood pressure): In the ALIENOR study 2013, early and late AMD were not significantly associated with systolic or diastolic BP, hypertension, or use of antihypertensive medications, but elevated pulse pressure ((PP) systolic BP minus diastolic BP) was significantly associated with an increased risk of late AMD.[10]
- **Atherosclerosis**:
- **High cholesterol**: Elevated cholesterol may increase the risk of AMD[11]
- **Obesity**: Abdominal obesity is a risk factor, especially among men[12]
- **Fat intake**: Consuming high amounts of certain fats including saturated fats, trans fats and omega-6 fatty acids likely contributes to AMD, while monounsaturated fats are potentially protective.[13] In particular, ω-3 fatty acids may decrease the risk of AMD.[14]
- **Exposure to sunlight**,[*dubious – discuss*] especially blue light: Evidence is conflicting as to whether exposure to sunlight contributes to the development of macular degeneration. A recent study on 446 subjects found it does not.[15] Other research, however, has shown high-energy visible light may contribute to AMD.[16][17]

### Genetics [edit]

Recurrence ratios for siblings of an affected individual are three- to sixfold higher than in the general population.[18] Genetic linkage analysis has identified 5 sets of gene variants at three locations on different chromosomes (1, 6 and 10) as explaining at least 50% of the risk. These genes have roles regulating immune response, inflammatory processes and homeostasis of the retina. Variants of these genes give rise to different kinds of dysfunction in these processes. Over time, this results in accumulation of intracellular and extracellular metabolic debris. This can cause scarring of the retina or breakdown of its vascularization.

Genetic tests are available for some of these gene variations. However, pathogenesis of macular degeneration is a complex interaction between genetics, environment and lifestyle, and presence of unfavorable genetic factors doesn't necessarily predict progression to disease. The three loci where identified gene variants are found are designated:

- Complement Factor H (CFH) on chromosome 1 at location 1q31.3
- HTRA serine peptidase 1/Age Related Maculopathy Susceptibility 2 (HTRA1/ARMS2) on chromosome 10 at location 10q26
- Complement Factor B/Complement Component 2 (CFB/CC2) on chromosome 6 at 6p21.3

### Specific genes [edit]

- **Polymorphisms in genes for complement system proteins**: The genes for the complement system proteins factor H (CFH), factor B (CFB) and factor 3 (C3) are strongly associated with a person's risk for developing AMD. CFH is involved in inhibiting the inflammatory response. The mutation in CFH (*Y402H*) results in reduced ability of CFH to regulate complement on critical surfaces such as the retina

and leads to increased inflammatory response within the macula. Absence of the complement factor H-related genes *R3* and *R1* protects against AMD.[19][20] Two independent studies in 2007 showed a certain common mutation *Arg80Gly* in the C3 gene, which is a central protein of the complement system, is strongly associated with the occurrence of AMD.[21][22] The authors of both papers consider their study to underscore the influence of the complement pathway in the pathogenesis of this disease.

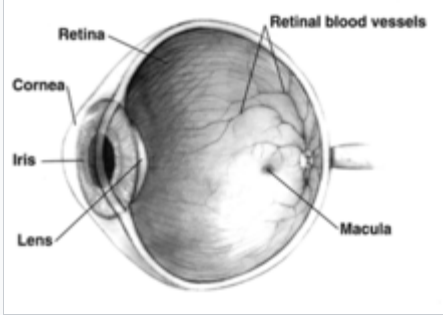
- In two 2006 studies, another gene that has implications for the disease, called *HTRA1* (encoding a secreted serine protease), was identified.[23][24]
- Six mutations of the gene *SERPING1* (Serpin Peptidase Inhibitor, Clade G (C1 Inhibitor), Member 1) are associated with AMD. Mutations in this gene can also cause hereditary angioedema.[25]
- **Fibulin-5 mutation**: Rare forms of the disease are caused by genetic defects in fibulin-5, in an autosomal dominant manner. In 2004, Stone *et al.* performed a screen on 402 AMD patients and revealed a statistically significant correlation between mutations in fibulin-5 and incidence of the disease.

### Mitochondrial related gene polymorphisms [edit]

such as that in the MT-ND2 molecule, predicts wet AMD.[26][27]

## Pathophysiology [edit]

The pathogenesis of age-related macular degeneration is not well known, although a number of theories have been put forward, including oxidative stress, mitochondrial dysfunction, and inflammatory processes.



Human eye cross-sectional view

The imbalance between production of damaged cellular components and degradation leads to the accumulation of detrimental products, for example, intracellular lipofuscin and extracellular drusen. Incipient atrophy is demarcated by areas of retinal pigment epithelium (RPE) thinning or depigmentation that precede geographic atrophy in the early stages of AMD. In advanced stages of AMD, atrophy of the RPE (geographic atrophy) and/or development of new blood vessels (neovascularization) result in death of photoreceptors and central vision loss.

In the dry (nonexudative) form, cellular debris called drusen accumulates between the retina and the choroid, causing atrophy and scarring to the retina. In the wet (exudative) form, which is more severe, blood vessels grow up from the choroid (neovascularization) behind the retina which can leak exudate and fluid and also cause hemorrhaging.

Early work demonstrated a family of immune mediators was plentiful in drusen.[28] Complement factor H (CFH) is an important inhibitor of this inflammatory cascade, and a disease-associated polymorphism in the CFH gene strongly associates with AMD.[29][30][31][32][33] Thus an AMD pathophysiological model of chronic low grade complement activation and inflammation in the macula has been advanced.[34][35] Lending credibility to this has been the discovery of disease-associated genetic polymorphisms in other elements of the complement cascade including complement component 3 (C3).[36]

A powerful predictor of AMD is found on chromosome *10q26* at LOC 387715. An insertion/deletion polymorphism at this site reduces expression of the *ARMS2* gene though destabilization of its mRNA through deletion of the polyadenylation signal.[37] ARMS2 protein may localize to the mitochondria and participate in energy metabolism, though much remains to be discovered about its function.

Other gene markers of progression risk includes tissue inhibitor of metalloproteinase 3 (TIMP3), suggesting a role for intracellular matrix metabolism in AMD progression.[38] Variations in cholesterol metabolising genes such as the hepatic lipase, cholesterol ester transferase, lipoprotein lipase and the ABC-binding cassette A1 correlate with disease progression. The early stigmata of disease, drusen, are rich in cholesterol, offering face validity to the results of genome-wide association studies.[39]

## Stages [edit]

In AMD there is a progressive accumulation of characteristic yellow deposits, called drusen (buildup of extracellular proteins and lipids), in the macula (a part of the retina), between the retinal pigment epithelium and the underlying choroid which is believed to damage the retina over time. Amyloid beta, which builds up in Alzheimer's disease brains, is one the proteins accumulating in AMD, which is one of the reasons AMD is sometimes called "Alzheimer's of the eye" or "Alzheimer's of the retina".[40] AMD can be divided into 3 stages: early, intermediate, and late, based partially on the extent (size and number) of drusen.[1]

AMD-like pathology begins with small yellow deposits (drusen) in the macula, between the retinal pigment epithelium and the underlying choroid. Most people with these early changes (referred to as age-related maculopathy) still have good vision. People with drusen may or may not develop AMD, in fact the majority of people over age 60 have drusen with no negative effects. The risk of developing symptoms is higher when the drusen are large and numerous and associated with disturbance in the pigmented cell layer under the macula. Large and soft drusen are thought to be related to elevated cholesterol deposits.

## Early AMD [edit]

Early AMD is diagnosed based on the presence of medium-sized drusen, about the width of an average human hair. Early AMD is usually asymptomatic.[1]

## Intermediate AMD [edit]

Intermediate AMD is diagnosed by large drusen, irreversible retinal damage (atrophy) caused by cell death, or both. Intermediate AMD may cause some vision loss, however, like Early AMD, it is usually asymptomatic.[1]

## Late AMD [edit]

In late AMD, enough retinal damage occurs that people have symptomatic central vision loss in addition to drusen. The damage can ether be worsening of atrophy from Intermediate AMD or the onset of Neovascular disease. Late AMD is further divided into two subtypes based on the types of damage: Dry AMD, and Wet AMD (also called Neovascular AMD).[1]

### Dry AMD [edit]

In dry AMD (also called atrophic AMD), patients have symptomatic central vision loss due to retinal atrophy. This form is the most common type of clinical AMD, accounting for 80–90% of cases and progresses slowly. In 10–20% of people, it progresses to the wet type.

### Wet AMD [edit]

Neovascular or exudative AMD, the "wet" form of advanced AMD, causes vision loss due to abnormal blood vessel growth (choroidal neovascularization) in the choriocapillaris, through Bruch's membrane. It is usually, but not always, preceded by the dry form of AMD. The proliferation of abnormal blood vessels in the retina is stimulated by vascular endothelial growth factor (VEGF). Unfortunately, because these blood vessels are abnormal, these new vessels are fragile, ultimately leading to blood and protein leakage below the macula. Bleeding, leaking, and scarring from these blood vessels eventually cause irreversible damage to the photoreceptors and rapid vision loss if left untreated.

## Oxidative stress [edit]

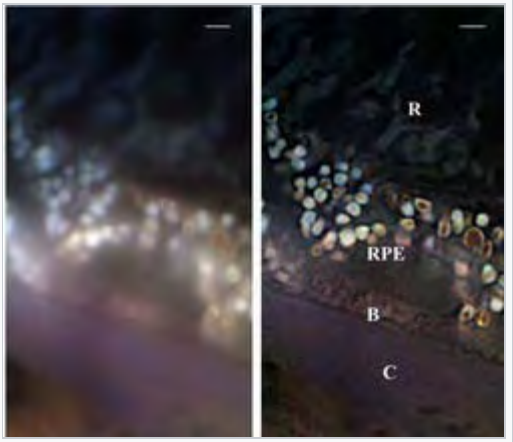
Age-related accumulation of low-molecular-weight, phototoxic, pro-oxidant melanin oligomers within lysosomes in the retinal pigment epithelium (RPE) may be partly responsible for decreasing the digestive rate of photoreceptor outer rod segments (POS) by the RPE – autophagy. A decrease in the digestive rate of POS has been shown to be associated with lipofuscin formation – a classic sign associated with AMD.[41][42]

The role of retinal oxidative stress in the etiology of AMD by causing further inflammation of the macula is suggested by the enhanced rate of disease in smokers and those exposed to UV irradiation.[43][44][45]

Mitochondrial dysfunction may play a role.[46]

## Diagnosis [edit]

Diagnosis of age-related macular degeneration rests on signs in the macula, irrespective of visual acuity. Diagnosis of AMD may include the following procedures and tests:



Super resolution microscopic investigation of human eye tissue affected by AMD

- There is a loss of contrast sensitivity, so that contours, shadows, and color vision are less vivid. The loss in contrast sensitivity can be quickly and easily measured by a contrast sensitivity test like Pelli Robson performed either at home or by an eye specialist.
- When viewing an Amsler grid, some straight lines appear wavy and some patches appear blank
- When viewing a Snellen chart, at least 2 lines decline
- Preferential hyperacuity perimetry changes (for wet AMD)[47][48]
- In dry macular degeneration, which occurs in 85–90 percent of AMD cases, drusen spots can be seen in Fundus photography
- In wet macular degeneration, angiography can visualize the leakage of bloodstream behind the macula. Fluorescein angiography allows for the identification and localization of abnormal vascular processes.
- Using an electroretinogram, points in the macula with a weak or absent response compared to a normal eye may be found
- Farnsworth-Munsell 100 hue test and Maximum Color Contrast Sensitivity test (MCCS) for assessing color acuity and color contrast sensitivity
- Optical coherence tomography is now used by most ophthalmologists in the diagnosis and the follow-up evaluation of the response to treatment with antiangiogenic drugs.

### Histology [edit]

- Pigmentary changes in the retina – In addition to the pigmented cells in the iris (the colored part of the eye), there are pigmented cells beneath the retina. As these cells break down and release their pigment, dark clumps of released pigment and later, areas that are less pigmented may appear
- Exudative changes: hemorrhages in the eye, hard exudates, subretinal/sub-RPE/intraretinal fluid
- Drusen, tiny accumulations of extracellular material that build up on the retina. While there is a tendency for drusen to be blamed for the progressive loss of vision, drusen deposits can be present in the retina without vision loss. Some patients with large deposits of drusen have normal visual acuity. If normal retinal reception and image transmission are sometimes possible in a retina when high concentrations of drusen are present, then, even if drusen can be implicated in the loss of visual function, there must be at least one other factor that accounts for the loss of vision.

## Prevention [edit]

A 2012 Cochrane review found the use of vitamin and mineral supplements, alone or in combination, by the general population had no effect on whether or not AMD started.[3]

## Management [edit]

Supplements that include lutein and zeaxanthin may slow down the worsening of AMD.[4][49] They have; however, not been shown to prevent the disease.[49] There is not enough evidence to determine if statins

have a role in preventing or slowing the progression of AMD.[50] Antiangiogenic steroids such as anecortave acetate and triamcinolone acetonide have shown no evidence in preventing visual loss in people with neovascular AMD.[51]

## Dry AMD [edit]

No medical or surgical treatment is available for this condition.

## Wet AMD [edit]

It can be treated with laser coagulation, and more commonly with medication that stops and sometimes reverses the growth of blood vessels.[52][53]

A randomized control trial found that bevacizumab and ranibizumab had similar efficacy, and reported no significant increase in adverse events with bevacizumab.[54] A 2014 Cochrane review found that the systemic safety of bevacizumab and ranibizumab are similar when used to treat neovascular AMD, except for gastrointestinal disorders.[55] Bevacizumab however is not FDA approved for treatment of macular degeneration. A controversy in the UK involved the off-label use of cheaper bevacizumab over the approved, but expensive, ranibizumab.[56] Ranibizumab is a smaller fragment, Fab fragment, of the parent bevacizumab molecule specifically designed for eye injections. Other approved antiangiogenic drugs for the treatment of neo-vascular AMD include pegaptanib[57] and aflibercept.[58]

The American Academy of Ophthalmology practice guidelines do not recommend laser coagulation therapy for macular degeneration, but state that it may be useful in people with new blood vessels in the choroid outside of the fovea who don't respond to drug treatment.[59][60] There is strong evidence that laser coagulation will result in the disappearance of drusen but does not affect choroidal neovascularisation.[61] A 2007 Cochrane review on found that laser photocoagulation of new blood vessels in the choroid outside of the fovea is effective and economical method, but that the benefits are limited for vessels next to or below the fovea.[62]

Photodynamic therapy has also been used to treat wet AMD.[63] The drug verteporfin is administered intravenously; light of a certain wavelength is then applied to the abnormal blood vessels. This activates the verteporfin destroying the vessels.

Cataract surgery could possibly improve visual outcomes for people with AMD, though there have been concerns of surgery increasing the progression of AMD. A randomized controlled trial found that people who underwent immediate cataract surgery (within 2 weeks) had improved visual acuity and better quality of life outcomes than those who underwent delayed cataract surgery (6 months).[64]

## Adaptive devices [edit]

Because peripheral vision is not affected, people with macular degeneration can learn to use their remaining vision to partially compensate.[65] Assistance and resources are available in many countries and every state in the U.S.[66] Classes for "independent living" are given and some technology can be obtained from a state department of rehabilitation.

Adaptive devices can help people read. These include magnifying glasses, special eyeglass lenses, computer screen readers, and TV systems that enlarge reading material.

Computer screen readers such as JAWS or Thunder work with standard Windows computers. Also Apple devices provide wide range of features (voice over,screen readers, Braille etc.,

Video cameras can be fed into standard or special-purpose computer monitors, and the image can be zoomed in and magnified. These

Josef Tal, an Israeli composer who was affected by macular degeneration, checks a manuscript using a CCTV desktop

systems often include a movable table to move the written material.

Accessible publishing provides larger fonts for printed books, patterns to make tracking easier, audiobooks and DAISY books with both text and audio.

unit.

## Epidemiology [edit]

Age-related macular degeneration accounts for more than 54% of all vision loss in the white population in the USA. An estimated 8 million Americans are affected with early age-related macular degeneration, of whom over 1 million will develop advanced age-related macular degeneration within the next 5 years. In the UK, age-related macular degeneration is the cause of blindness in almost 42% of those who go blind aged 65–74 years, almost two-thirds of those aged 75–84 years, and almost three-quarters of those aged 85 years or older.

Macular degeneration is more likely to be found in Caucasians than in people of African descent.[68][69]

Disability-adjusted life year for macular degeneration and other (sense organ diseases) per 100,000 inhabitants in 2004[67]

| | |
|---|---|
| no data | 156–170 |
| less than 100 | 170–184 |
| 100–114 | 184–198 |
| 114–128 | 198–212 |
| 128–142 | 212–226 |
| 142–156 | 226–240 |
| | more than 240 |

## Research directions [edit]

### Association with other age-related diseases [edit]

Studies indicate drusen associated with AMD are similar in molecular composition to Beta-Amyloid (βA) plaques and deposits in other age-related diseases such as Alzheimer's disease and atherosclerosis. This suggests that similar pathways may be involved in the etiologies of AMD and other age-related diseases.[70]

### Genetic testing [edit]

A practical application of AMD-associated genetic markers is in the prediction of progression of AMD from early stages of the disease to neovascularization.[71][72]

### Stem cell transplant [edit]

*See also: Adeno associated virus and gene therapy of the human retina*

Cell based therapies using bone marrow stem cells as well as Retinal pigment epithelial transplantation are being studied.[73] Recent advancements within the field of stem cell research in the United States have led to the first human embryonic stem cell trial for dry AMD, which reports positive results.[74]

## Other types [edit]

There are a few other (rare) kinds of macular degeneration with similar symptoms but unrelated in etiology to Wet or Dry age-related macular degeneration. They are all genetic disorders that may occur in childhood or middle age.

- Best's disease
- Sorsby's fundus dystrophy is an autosomal dominant, retinal disease characterized by sudden acuity loss resulting from untreatable submacular neovascularisation
- Stargardt's disease (juvenile macular degeneration, STGD) is an autosomal recessive retinal disorder characterized by a juvenile-onset macular dystrophy, alterations of the peripheral retina, and subretinal

deposition of lipofuscin-like material.

Similar symptoms with a very different etiology and different treatment can be caused by epiretinal membrane or macular pucker or any other condition affecting the macula, such as central serous retinopathy.

## Notable cases [edit]

- Judi Dench[75]
- Joan Plowright[76]
- Peter Sallis,[77] notable of voices of Wallace from *Wallace and Gromit* until 2012
- Rosanne Barr[78]

## See also [edit]

- Cherry-red spot
- Fuchs spot
- Micropsia

## References [edit]


1. ^ *a b c d e f g h i j k* "Facts About Age-Related Macular Degeneration". *National Eye Institute*. June 2015. Retrieved 21 December 2015.
2. ^ *a b c* Mehta, S (September 2015). "Age-Related Macular Degeneration.". *Primary care*. **42** (3): 377–91. doi:10.1016/j.pop.2015.05.009. PMID 26319344.
3. ^ *a b* Evans JR, Lawrenson JG (2012). Evans, Jennifer R, ed. "Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration". *Cochrane Database Syst Rev*. **6**: CD000253. doi:10.1002/14651858.CD000253.pub3. PMID 22696317.
4. ^ *a b* Evans, JR; Lawrenson, JG (14 November 2012). "Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration.". *The Cochrane database of systematic reviews*. **11**: CD000254. doi:10.1002/14651858.CD000254.pub3. PMID 23152201.
5. ^ Velez-Montoya, R; Oliver, SC; Olson, JL; Fine, SL; Quiroz-Mercado, H; Mandava, N (March 2014). "Current knowledge and trends in age-related macular degeneration: genetics, epidemiology, and prevention.". *Retina (Philadelphia, Pa.)*. **34** (3): 423–41. doi:10.1097/iae.0000000000000036. PMID 24285245.
6. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
7. ^ Roberts, DL (September 2006). "The First Year—Age Related Macular Degeneration". *(Marlowe & Company)*: 100.
8. ^ Roberts, DL (September 2006). "The First Year—Age Related Macular Degeneration". *(Marlowe & Company)*: 20.
9. ^ Thornton, J; Edwards, R; Mitchell, P; Harrison, RA; Buchan, I; Kelly, SP (September 2005). "Smoking and age-related macular degeneration: a review of association.". *Eye (London, England)*. **19** (9): 935–44. doi:10.1038/sj.eye.6701978. PMID 16151432.
10. ^ Cougnard-Grégoire, A; et al. (March 2013). "Long-term blood pressure and age-related macular degeneration: the ALIENOR study". *Invest Ophthalmol Vis Sci*. **54** (3): 1905–12. doi:10.1167/iovs.12-10192. PMID 23404120.
11. ^ Dasari, Bhanu; Prasanthi, Jaya RP; Marwarha, Gurdeep; Singh, Brij B; Ghribi, Othman (18 August 2011). "Cholesterol-enriched diet causes age-related macular degeneration-like pathology in rabbit retina". *BMC Ophthalmology*. **11**: 22. doi:10.1186/1471-2415-11-22. PMC 3170645. PMID 21851605.
12. ^ Adams MK, Simpson JA, Aung KZ, et al. (1 June 2011). "Abdominal obesity and age-related macular degeneration". *Am J Epidemiol*. **173** (11): 1246–55. doi:10.1093/aje/kwr005. PMID 21422060. Retrieved 29 July 2012.
13. ^ Parekh N, Voland RP, Moeller SM, et al. (November 2009). "Association between dietary fat intake and age-related macular degeneration in the Carotenoids in Age-Related Eye Disease Study (CAREDS): an ancillary study of the Women's Health Initiative". *Arch Ophthalmol*. **127** (11): 1483–93. doi:10.1001/archophthalmol.2009.130. PMC 3144752. PMID 19901214.

14. ^ John Paul SanGiovanni; Emily Y. Chew; Traci E. Clemons; Matthew D. Davis; Frederick L. Ferris III; Gary R. Gensler; Natalie Kurinij; Anne S. Lindblad; Roy C. Milton; Johanna M. Seddon; Robert D. Sperduto (May 5, 2007). "The Relationship of Dietary Lipid Intake and Age-Related Macular Degeneration in a Case-Control Study". *Archives of Ophthalmology*.
15. ^ Khan JC, Shahid H, Thurlby DA, Bradley M, Clayton DG, Moore AT, Bird AC, Yates JR, Genetic Factors in AMD Study (January 2006). "Age related macular degeneration and sun exposure, iris colour, and skin sensitivity to sunlight". *The British Journal of Ophthalmology*. **90** (1): 29–32. doi:10.1136/bjo.2005.073825. PMC 1856929. PMID 16361662.
16. ^ Glazer-Hockstein, C; Dunaief JL (January 2006). "Could blue light-blocking lenses decrease the risk of age-related macular degeneration?". *Retina*. **26** (1): 1–4. doi:10.1097/00006982-200601000-00001. PMID 16395131.
17. ^ Margrain, TH; Boulton M; Marshall J; Sliney DH (September 2004). "Do blue light filters confer protection against age-related macular degeneration?". *Progress in Retinal and Eye Research*. **23** (5): 523–31. doi:10.1016/j.preteyeres.2004.05.001. PMID 15302349.
18. ^ Maller, J; et al. (September 2006). "Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration.". *Nat. Genet*. **38** (9): 1055–9. doi:10.1038/ng1873. PMID 16936732.
19. ^ Hughes, Anne E; Orr, Nick; Esfandiary, Hossein; Diaz-Torres, Martha; Goodship, Timothy; Chakravarthy, Usha (2006). "A common CFH haplotype, with deletion of CFHR1 and CFHR3, is associated with lower risk of age-related macular degeneration". *Nature Genetics*. **38** (10): 1173–1177. doi:10.1038/ng1890. PMID 16998489.
20. ^ Fritsche, L. G.; Lauer, N.; Hartmann, A.; Stippa, S.; et al. (2010). "An imbalance of human complement regulatory proteins CFHR1, CFHR3 and factor H influences risk for age-related macular degeneration (AMD)". *Human Molecular Genetics*. **19** (23): 4694–4704. doi:10.1093/hmg/ddq399. PMID 20843825.
21. ^ Yates JR, Sepp T, Matharu BK, Khan JC, Thurlby DA, Shahid H, Clayton DG, Hayward C, Morgan J, Wright AF, Armbrecht AM, Dhillon B, Deary IJ, Redmond E, Bird AC, Moore AT (2007). "Complement C3 Variant and the Risk of Age-Related Macular Degeneration". *N Engl J Med*. **357** (6): 553–561. doi:10.1056/NEJMoa072618. PMID 17634448.
22. ^ Maller JB, Fagerness JA, Reynolds RC, Neale BM, Daly MJ, Seddon JM (2007). "Variation in Complement Factor 3 is Associated with Risk of Age-Related Macular Degeneration". *Nature Genetics*. **39** (10): 1200–1201. doi:10.1038/ng2131. PMID 17767156.
23. ^ Yang Z, Camp NJ, Sun H, Tong Z, Gibbs D, Cameron DJ, Chen H, Zhao Y, Pearson E, et al. (Nov 2006). "A variant of the HTRA1 gene increases susceptibility to age-related macular degeneration". *Science*. **314** (5801): 992–3. doi:10.1126/science.1133811. PMID 17053109.
24. ^ Dewan A, Liu M, Hartman S, et al. (November 2006). "HTRA1 Promoter Polymorphism in Wet Age-Related Macular Degeneration". *Science*. **314** (5801): 989–92. doi:10.1126/science.1133807. PMID 17053108.
25. ^ Hirschler, Ben (2008-10-07). "Gene discovery may help hunt for blindness cure". Reuters. Archived from the original on October 11, 2008. Retrieved 2008-10-07.
26. ^ Udar N, Atilano SR, Memarzadeh M, Boyer D, Chwa M, Lu S (2009). "Mitochondrial DNA Haplogroups Associated with Age-Related Macular Degeneration". *Invest Ophthalmol Vis Sci*. **50** (6): 2966–74. doi:10.1167/iovs.08-2646. PMID 19151382.
27. ^ Canter JA, Olson LM, Spencer K, Schnetz-Boutaud N, Anderson B, Hauser MA (2008). Nicholas Weedon, Michael, ed. "Mitochondrial DNA polymorphism A4917G is independently associated with age-related macular degeneration". *PLoS ONE*. **3** (5): e2091. doi:10.1371/journal.pone.0002091. PMC 2330085. PMID 18461138.
28. ^ Mullins RF, Russell SR, Anderson DH, Hageman GS (2000). "Drusen associated with aging and age-related macular degeneration contain proteins common to extracellular deposits associated with atherosclerosis, elastosis, amyloidosis, and dense deposit disease". *FASEB J*. **14** (7): 835–46. PMID 10783137.
29. ^ Hageman GS, Anderson DH, Johnson LV, Hancox LS, Taiber AJ, Hardisty LI (2005). "A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration". *Proc Natl Acad Sci USA*. **102** (20): 7227–32. doi:10.1073/pnas.0501536102. PMC 1088171. PMID 15870199.
30. ^ Chen LJ, Liu DT, Tam PO, Chan WM, Liu K, Chong KK (2006). "Association of complement factor H polymorphisms with exudative age-related macular degeneration". *Mol. Vis*. **12**: 1536–42. PMID 17167412.
31. ^ Despriet DD, Klaver CC, Witteman JC, Bergen AA, Kardys I, de Maat MP (2006). "Complement factor H polymorphism, complement activators, and risk of age-related macular degeneration". *JAMA*. **296** (3): 301–9. doi:10.1001/jama.296.3.301. PMID 16849663.
32. ^ Li M, Tmaca-Sonmez P, Othman M, Branham KE, Khanna R, Wade MS (2006). "CFH haplotypes without the Y402H coding variant show strong association with susceptibility to age-related macular degeneration". *Nature Genetics*. **38** (9): 1049–54. doi:10.1038/ng1871. PMC 1941700. PMID 16936733.
33. ^ Haines JL, Hauser MA, Schmidt S, Scott WK, Olson LM, Gallins P (2005). "Complement factor H variant increases the risk of age-related macular degeneration". *Science*. **308** (5720): 419–21. doi:10.1126/science.1110359.

PMID 15761120.
34. ^ Rohrer B, Long Q, Coughlin B, Renner B, Huang Y, Kunchithapautham K (2010). "A targeted inhibitor of the complement alternative pathway reduces RPE injury and angiogenesis in models of age-related macular degeneration". *Adv Exp Med Biol*. Advances in Experimental Medicine and Biology. **703**: 137–49. doi:10.1007/978-1-4419-5635-4_10. ISBN 978-1-4419-5634-7. PMID 20711712.
35. ^ Kunchithapautham K, Rohrer B (May 2011). "Sublytic Membrane-Attack-Complex (MAC) Activation Alters Regulated Rather than Constitutive Vascular Endothelial Growth Factor (VEGF) Secretion in Retinal Pigment Epithelium Monolayers". *J Biol Chem*. **286** (27): 23717–23724. doi:10.1074/jbc.M110.214593. PMC 3129152. PMID 21566137.
36. ^ Yates JR, Sepp T, Matharu BK, Khan JC, Thurlby DA, Shahid H (2007). "Complement C3 variant and the risk of age-related macular degeneration". *NEJM*. **357** (6): 553–61. doi:10.1056/NEJMoa072618. PMID 17634448.
37. ^ Fritsche LG, Loenhardt T, Janssen A, Fisher SA, Rivera A, Keilhauer CN (2008). "Age-related macular degeneration is associated with an unstable ARMS2 (LOC387715) mRNA DNA damage and repair in age-related macular degeneration". *Nat. Genet*. **40** (7): 892–896. doi:10.1038/ng.170.
38. ^ Chen W, Stambolian D, Edwards AO, Branham KE, Othman M, Jakobsdottir J (2010). "Genetic variants near TIMP3 and high-density lipoprotein–associated loci influence susceptibility to age-related macular degeneration". *Proc Natl Acad Sci U S A*. **107** (16): 7401–6. doi:10.1073/pnas.0912702107. PMC 2867722. PMID 20385819.
39. ^ Neale BM, Fagerness J, Reynolds R, Sobrin L, Parker M, Raychaudhuri S (2010). "Genome-wide association study of advanced age-related macular degeneration identifies a role of the hepatic lipase gene (LIPC)". *Proc Natl Acad Sci U S A*. **107** (16): 7395–400. doi:10.1073/pnas.0912019107. PMC 2867697. PMID 20385826.
40. ^ Ratnayaka JA, Serpell LC, Lotery AJ (2015). "Dementia of the eye: the role of amyloid beta in retinal degeneration". *Eye (Lond)*. **29**: 1013–26. doi:10.1038/eye.2015.100. PMC 4541342. PMID 26088679.
41. ^ "Melanin aggregation and polymerization: possible implications in age related macular degeneration." *Ophthalmic Research*, 2005; volume 37: pages 136–141.
42. ^ John Lacey, "Harvard Medical signs agreement with Merck to develop potential therapy for macular degeneration", 23-May-2006
43. ^ Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP (2005). "Smoking and age-related macular degeneration: a review of association". *Eye*. **19** (9): 935–44. doi:10.1038/sj.eye.6701978. PMID 16151432.
44. ^ Tomany SC, Cruickshanks KJ, Klein R, Klein BE, Knudtson MD (2004). "Sunlight and the 10-year incidence of age-related maculopathy: the Beaver Dam Eye Study". *Arch Ophthalmol*. **122** (5): 750–7. doi:10.1001/archopht.122.5.750. PMID 15136324.
45. ^ Szaflik JP, Janik-Papis K, Synowiec E, Ksiazek D, Zaras M, Wozniak K (2009). "DNA damage and repair in age-related macular degeneration". *Mutat Res*. **669** (1–2): 167–176. doi:10.1016/j.mrfmmm.2009.06.008.
46. ^ Barot, M; Gokulgandhi, MR; Mitra, AK (December 2011). "Mitochondrial dysfunction in retinal diseases". *Current Eye Research*. **36** (12): 1069–77. doi:10.3109/02713683.2011.607536. PMC 4516173. PMID 21978133.
47. ^ http://www.revoptom.com/index.asp?page=2_14021.htm. Retrieved August 4, 2009. Missing or empty `|title=` (help)[*dead link*]
48. ^ "Preferential Hyperacuity Perimetry (PHP) as an Adjunct Diagnostic Tool to Funduscopy in Age–related Macular Degeneration – Ophthalmology Technology Spotlight". Medcompare. Retrieved 2011-01-11.
49. ^ *a b* Hobbs, RP; Bernstein, PS (2013). "Nutrient Supplementation for Age-related Macular Degeneration, Cataract, and Dry Eye.". *Journal of ophthalmic & vision research*. **9** (4): 487–93. doi:10.4103/2008-322X.150829. PMC 4329711. PMID 25709776.
50. ^ Gehlbach, P; Li, T; Hatef, E (11 February 2015). "Statins for age-related macular degeneration.". *The Cochrane database of systematic reviews*. **2**: CD006927. doi:10.1002/14651858.CD006927.pub4. PMID 25675254.
51. ^ Geltzer A, Turalba A, Vedula SS (2013). "Surgical implantation of steroids with antiangiogenic characteristics for treating neovascular age-related macular degeneration". *Cochrane Database Syst Rev*. **1**: CD005022. doi:10.1002/14651858.CD005022.pub3. PMC 4269233. PMID 23440797.
52. ^ de Jong PT (2006). "Age-related macular degeneration". *N Engl J Med.* **355** (14): 1474–1485. doi:10.1056/NEJMra062326. PMID 17021323.
53. ^ Ch. 25, Disorders of the Eye, Jonathan C. Horton, in Harrison's Principles of Internal Medicine, 16th ed.
54. ^ Chakravarthy, U; Harding, SP; Rogers, CA; Downes, SM; Lotery, AJ; Culliford, LA; Reeves, BC; on behalf of the IVAN study, investigators (Jul 18, 2013). "Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial.". *Lancet*. **382** (9900): 1258–67. doi:10.1016/S0140-6736(13)61501-9. PMID 23870813.
55. ^ Moja, L; Lucenteforte, E; Kwag, KH; Bertele, V; Campomori, A; Chakravarthy, U; D'Amico, R; Dickersin, K; Kodjikian, L; Lindsley, K; Loke, Y; Maguire, M; Martin, DF; Mugelli, A; Mühlbauer, B; Püntmann, I; Reeves, B; Rogers, C; Schmucker, C; Subramanian, ML; Virgili, G (Sep 15, 2014). "Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration.". *The Cochrane database of systematic reviews*.

**9**: CD011230. doi:10.1002/14651858.CD011230.pub2. PMC 4262120. PMID 25220133.
56. ^ Copley, Caroline; Hirschler, Ben (April 24, 2012). "Novartis challenges UK Avastin use in eye disease". Reuters.
57. ^ "FDA Approves New Drug Treatment for Age-Related Macular Degeneration". *FDA.gov*. U.S. Food and Drug Administration.
58. ^ FDA approves Eylea for macular degeneration
59. ^ "Age-Related Macular Degeneration PPP - Updated 2015". American Academy of Ophthalmology Preferred Practice Pattern. 29 January 2015. Retrieved 22 October 2016.
60. ^ Lindsley, K; Li, T; Ssemanda, E; Virgili, G; Dickersin, K (April 2016). "Interventions for Age-Related Macular Degeneration: Are Practice Guidelines Based on Systematic Reviews?". *Ophthalmology*. **123** (4): 884–97. doi:10.1016/j.ophtha.2015.12.004. PMID 26804762.
61. ^ Virgili G, Michelessi M, Parodi MB, Bacherini D, Evans JR (2015). "Laser treatment of drusen to prevent progression to advanced age-related macular degeneration". *Cochrane Database Syst Rev*. **10**: CD006537. doi:10.1002/14651858.CD006537.pub3. PMID 26493180.
62. ^ Virgili, G; Bini, A (18 July 2007). "Laser photocoagulation for neovascular age-related macular degeneration.". *The Cochrane database of systematic reviews* (3): CD004763. doi:10.1002/14651858.CD004763.pub2. PMID 17636773.
63. ^ "Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation". *Health Technology Assessment*. **7** (9). 2003. doi:10.3310/hta7090.
64. ^ Casparis H, Lindsley K, Kuo IC, Sikder S, Bressler NM (2012). "Surgery for cataracts in people with age-related macular degeneration". *Cochrane Database Syst Rev*. **6**: CD006757. doi:10.1002/14651858.CD006757.pub3. PMC 3480178. PMID 22696359.
65. ^ "Low Vision Rehabilitation Delivery Model". Mdsupport.org. Retrieved 2011-01-11.
66. ^ "Agencies, Centers, Organizations, & Societies". Mdsupport.org. 2005-09-01. Retrieved 2011-01-11.
67. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved Nov 11, 2009.
68. ^ Age-Related Eye Disease Study Research Group (Dec 2000). "Risk Factors Associated with Age-Related Macular Degeneration: A Case-control Study in the Age-Related Eye Disease Study: Age-Related Eye Disease Study Report Number 3". *Ophthalmology*. **107** (12): 2224–32. doi:10.1016/S0161-6420(00)00409-7. PMC 1470467. PMID 11097601.
69. ^ Clemons TE, Milton RC, Klein R, Seddon JM, Ferris FL (April 2005). "Risk Factors for the Incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS) AREDS Report No. 19". *Ophthalmology*. **112** (4): 533–9. doi:10.1016/j.ophtha.2004.10.047. PMC 1513667. PMID 15808240.
70. ^ Mullins, RF; et al. (May 2000). "Drusen associated with aging and age-related macular degeneration contain proteins common to extracellular deposits associated with atherosclerosis, elastosis, amyloidosis, and dense deposit disease". *FASEB J.* **14** (7): 835–46. PMID 10783137.
71. ^ Chen W, Stambolian D, Edwards AO, Branham KE, Othman M, Jakobsdottir J (2010). "Genetic variants near TIMP3 and high-density lipoprotein–associated loci influence susceptibility to age-related macular degeneration". *Proc Natl Acad Sci U S A*. **107** (16): 7401–7406. doi:10.1073/pnas.0912702107. PMC 2867722. PMID 20385819.
72. ^ Neale BM, Fagerness J, Reynolds R, Sobrin L, Parker M, Raychaudhuri S (2010). "Genome-wide association study of advanced age-related macular degeneration identifies a role of the hepatic lipase gene (LIPC)". *Proc Natl Acad Sci U S A*. **107** (16): 7395–7400. doi:10.1073/pnas.0912019107. PMC 2867697. PMID 20385826.
73. ^ John S, et al. (2013). "Choice of cell source in cell based therapies for retinal damage due to age related macular degeneration (AMD): A review". *Journal of Ophthalmology*. **2013**: 1–9. doi:10.1155/2013/465169.
74. ^ Lanza, R; Schwartz, SD (25 Feb 2012). "Embryonic stem cell trials for macular degeneration: a preliminary report". *Lancet*. **379**: 713–720. doi:10.1016/s0140-6736(12)60028-2.
75. ^ "Judi Dench 'can't read any more due to failing eye site", The Guardian, 23 February 2014
76. ^ "Joan bows out to a standing ovation", The Guardian, 13 May 2014
77. ^ "Patrons of the Macular Society", Macular Society
78. ^ "Roseanne Barr's blindness and how to prevent her diseases", CNN

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- Macular degeneration at DMOZ

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Categories: Visual disturbances and blindness | Disorders of choroid and retina | Senescence




# Refractive error

From Wikipedia, the free encyclopedia

**Refractive error**, also known as **refraction error**, is a problem with focusing of light on the retina due to the shape of the eye.[1] The most common types of refractive error are near-sightedness, far-sightedness, astigmatism, and presbyopia. Near-sightedness results in far objects being blurry, far-sightedness result in close objects being blurry, astigmatism causes objects to appear stretched out or blurry, and presbyopia results in a poor ability to focus on close objects. Other symptoms may include double vision, headaches, and eye strain.[1]

Near-sightedness is due to the length of the eyeball being too long, far-sightedness the eyeball too short, astigmatism the cornea being the wrong shape, and presbyopia aging of the lens of the eye such that it cannot change shape sufficiently. Some refractive errors are inherited from a person's parents. Diagnosis is by eye examination.[1]

Refractive errors are corrected with eyeglasses, contact lenses, or surgery. Eyeglasses are the easiest and safest method of correction. Contact lenses can provide a wider field of vision; however are associated with a risk of infection. Refractive surgery permanently changes the shape of the cornea.[1]

**Refraction error**

Glasses are a common treatment for refractive errors

| Classification and external resources | |
|---|---|
| **Specialty** | ophthalmology |
| **ICD-10** | H52.0-H52.4 |
| **ICD-9-CM** | 367.0-367.2-367.9 |
| **DiseasesDB** | 29645 |
| **MeSH** | D012030 |

[edit on Wikidata]

The number of people globally with refractive errors has been estimated at one to two billion. Rates vary between regions of the world with about 25% of Europeans and 80% of Asians affected.[2] Near-sightedness is the most common disorder.[3] Rates among adults are between 15-49% while rates among children are between 1.2-42%.[4] Far-sightedness more commonly affects young child and the elderly.[5][6] Presbyopia affects most people over the age of 35.[1] The number of people with refractive errors that have not been corrected was estimated at 660 million (10 per 100 people) in 2013.[7] Of these 9.5 million were blind due to the refractive error.[7] It is one of the most common causes of vision loss along with cataracts, macular degeneration, and vitamin A deficiency.[8]

Contents

## Classification [edit]

An eye that has no refractive error when viewing distant objects is said to have *emmetropia* or be *emmetropic* meaning the eye is in a state in which it can focus parallel rays of light (light from distant objects) on the retina, without using any accommodation. A distant object in this case is defined as an object 8 meters or further away from the eye.

An eye that has refractive error when viewing distant objects is said to have *ametropia* or be *ametropic*. This eye cannot focus parallel rays of light (light from distant objects) on the retina, or needs accommodation to do so.

The word "ametropia" can be used interchangeably with "refractive error". Types of ametropia include myopia, hyperopia and astigmatism. They are frequently categorized as spherical errors and cylindrical errors:

- Spherical errors occur when the optical power of the eye is either too large or too small to focus light on the retina. People with refractive error frequently have blurry vision.
  - **Nearsightedness**: When the optics are too powerful for the length of the eyeball one has myopia or nearsightedness. This can arise from a cornea or crystalline lens with too much curvature (refractive myopia) or an eyeball that is too long (axial myopia). Myopia can be corrected with a concave lens which causes the divergence of light rays before they reach the cornea.
  - **Farsightedness**: When the optics are too weak for the length of the eyeball, one has hyperopia or farsightedness. This can arise from a cornea or crystalline lens with not enough curvature (refractive hyperopia) or an eyeball that is too short (axial hyperopia). This can be corrected with convex lenses which cause light rays to converge prior to hitting the cornea.
  - **Presbyopia**: When the flexibility of the lens declines, typically due to age. The individual would experience difficulty in near vision, often relieved by reading glasses, bifocal, or progressive lenses.
- Cylindrical errors cause astigmatism, when the optical power of the eye is too powerful or too weak across one meridian, such as if the corneal curvature tends towards a cylindrical shape. The angle between that meridian and the horizontal is known as the axis of the cylinder.
  - **Astigmatism**: A person with astigmatic refractive error sees lines of a particular orientation less more clearly than lines at right angles to them. This defect can be corrected by refracting light more in one meridian than the other. Cylindrical lenses serve this purpose.

## Risk factors [edit]

### Genetics [edit]


Fundus of person with retinitis pigmentosa, early stage

The Online Mendelian Inheritance in Man (OMIM) database has listed 261 genetic disorders in which myopia is one of the symptoms.[9] Myopia may be present in heritable connective tissue disorders such as: Knobloch syndrome (OMIM 267750); Marfan syndrome (OMIM 154700); and Stickler syndrome (type 1, OMIM 108300; type 2, OMIM 604841).[10] Myopia is present in heritable connective tissue disorders such as: Knobloch syndrome (OMIM 267750); Marfan syndrome (OMIM 154700); and Stickler syndrome (type 1, OMIM 108300; type 2, OMIM 604841).[10] Myopia has also been reported in X-linked disorders caused by mutations in loci involved in retinal photoreceptor function (NYX, RP2, MYP1) such as: autosomal recessive congenital stationary night blindness (CSNB; OMIM 310500); retinitis pigmentosa 2 (RP2; OMIM 312600); Bornholm eye disease (OMIM 310460).[11] Many genes that have been associated with refractive error are clustered into common biological networks involved in connective tissue growth and extracellular matrix organization.[10] Although a large number of chromosomal localisations have been associated with myopia (MYP1-MYP17), few specific genes have been identified.[9]

## Environmental [edit]

In studies of the genetic predisposition of refractive error, there is a correlation between environmental factors and the risk of developing myopia.[12] Myopia has been observed in individuals with visually intensive occupations.[11] Reading has also been found to be a predictor of myopia in children. It has been reported that children with myopia spent significantly more time reading than non-myopic children who spent more time playing outdoors.[11] Socioeconomic status and higher levels of education have also been reported to be a risk factor for myopia.

# Diagnosis [edit]

Blurry vision may result from any number of conditions not necessarily related to refractive errors. The diagnosis of a refractive error is usually confirmed by an eye care professional during an eye examination using a large number of lenses of different optical powers, and often a retinoscope (a procedure entitled *retinoscopy*) to measure objectively in which the patient views a distant spot while the clinician changes the lenses held before the patient's eye and watches the pattern of reflection of a small light shone on the eye. Following that "objective refraction" the clinician typically shows the patient lenses of progressively higher or weaker powers in a process known as *subjective refraction*. Cycloplegic agents are frequently used to more accurately determine the amount of refractive error, particularly in children[13]

A doctor uses a trial frame and trial lenses to measure the patient's refractive error.

An automated refractor is an instrument that is sometimes used in place of retinoscopy to objectively estimate a person's refractive error.[14] Shack–Hartmann wavefront sensor and its inverse[15] can also be used to characterize eye aberrations in a higher level of resolution and accuracy.

Vision defects caused by refractive error can be distinguished from other problems using a pinhole occluder, which will improve vision only in the case of refractive error.

# Management [edit]

How refractive errors are treated or managed depends upon the amount and severity of the condition. Those who possess mild amounts of refractive error may elect to leave the condition uncorrected, particularly if the patient is asymptomatic. For those who are symptomatic, glasses, contact lenses, refractive surgery, or a combination of the three are typically used.

In the case of myopia, however, some believe that such treatments may also have the long-term effect of exacerbating that refractive error — i.e., making the patient even more nearsighted. This would be due to the very same prescription that is tailored for use at a 12-to-20-foot distance also commonly being used for close-up work as well, thus artificially amplifying the focusing stress that would normally be presented to the accommodation mechanisms of the eye at that distance.[*citation needed*]

However, this exacerbating effect is not generally believed to exist in the general case, although in cases where the myopia is due to accommodative spasm, removing the corrective lenses for a time may lead to improvement.[*citation needed*]

# Epidemiology [edit]

The number of people globally with refractive errors that have not

been corrected was estimated at 660 million (10 per 100 people) in 2013.[7]

The number of people globally with refractive errors has been estimated from 800 million to 2.3 billion.

DALYs per 100,000 people due to refractive errors in 2004.[16]

| | |
|---|---|
| no data | 380-450 |
| less than 100 | 450-520 |
| 100-170 | 520-590 |
| 170-240 | 590-660 |
| 240-310 | 660-730 |
| 310-380 | 730-800 |
| | more than 800 |

## References [edit]


1. ^ a b c d e "Facts About Refractive Errors". *NEI*. October 2010. Retrieved 29 July 2016.
2. ^ Denniston, Alastair; Murray, Philip (2014). *Oxford Handbook of Ophthalmology* (3 ed.). OUP Oxford. p. 826. ISBN 9780191057021.
3. ^ Foster, PJ; Jiang, Y (February 2014). "Epidemiology of myopia.". *Eye (London, England)*. **28** (2): 202–8. doi:10.1038/eye.2013.280. PMC 3930282. PMID 24406412.
4. ^ Pan, CW; Ramamurthy, D; Saw, SM (January 2012). "Worldwide prevalence and risk factors for myopia.". *Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists)*. **32** (1): 3–16. doi:10.1111/j.1475-1313.2011.00884.x. PMID 22150586.
5. ^ Castagno, VD; Fassa, AG; Carret, ML; Vilela, MA; Meucci, RD (23 December 2014). "Hyperopia: a meta-analysis of prevalence and a review of associated factors among school-aged children.". *BMC ophthalmology*. **14**: 163. doi:10.1186/1471-2415-14-163. PMC 4391667. PMID 25539893.
6. ^ Grosvenor, Theodore (2007). *Primary care optometry* (5 ed.). St. Louis (Miss.): Butterworth Heinemann, Elsevier. p. 70. ISBN 9780750675758.
7. ^ a b c Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
8. ^ Pan, CW; Dirani, M; Cheng, CY; Wong, TY; Saw, SM (March 2015). "The age-specific prevalence of myopia in Asia: a meta-analysis.". *Optometry and vision science : official publication of the American Academy of Optometry*. **92** (3): 258–66. doi:10.1097/opx.0000000000000516. PMID 25611765.
9. ^ a b Morgan, Ian; Kyoko Ohno-Matsui (May 2012). "Myopia". *The Lancet*. **379** (9827): 1739–1748. doi:10.1016/S0140-6736(12)60272-4.
10. ^ a b c Wojciechowski, Robert (April 2011). "Nature and Nurture: the complex genetics of myopia and refractive error". *Clin Genet*. **79** (4): 301–320. doi:10.1111/j.1399-0004.2010.01592.x.
11. ^ a b c Wojcienchowski, Robert (April 2011). "Nature and Nurture: the complex genetics of myopia and refractive error". *National Institutes of Health*. **79** (4): 301–320. doi:10.1111/j.1399-0004.2010.01592.x.
12. ^ Barnes, Katherine (February 2013). "Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia". *Nature Genetics*. **45** (3): 314–8. doi:10.1038/ng.2554. PMC 3740568. PMID 23396134.
13. ^ *Roque, B. Refractive errors in children.* November 2, 2005.
14. ^ "Frequently Asked Questions: How do you measure refractive errors?". *The New York Eye And Ear Infirmary*. Retrieved 2006-09-13.

15. ^ "NETRA: Inverse Shack-Hartmann Wavefront Sensor using High Resolution Mobile Phone Display". *Vitor F. Pamplona, Ankit Mohan, Manuel M. Oliveira, Ramesh Raskar*. Retrieved 2011-12-13.
16. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved Nov 11, 2009.

## External links [edit]

| v · t · e · | **Diseases of the human eye (H00–H59 · 360–379) ·** | |
|---|---|---|
| **Adnexa** | | |
| **Eyelid** | **Inflammation** | Stye · Chalazion · Blepharitis · |
| | Entropion · Ectropion · Lagophthalmos · Blepharochalasis · Ptosis · Blepharophimosis · Xanthelasma · | |
| | **Eyelash** | Trichiasis · Madarosis · |
| **Lacrimal apparatus** | Dacryoadenitis · Epiphora · Dacryocystitis · Xerophthalmia · | |
| **Orbit** | Exophthalmos · Enophthalmos · Orbital cellulitis · Orbital lymphoma · Periorbital cellulitis · | |
| **Conjunctiva** | Conjunctivitis (allergic · · Pterygium · Pinguecula · Subconjunctival hemorrhage · | |
| **Globe** | | |
| **Fibrous tunic** | **Sclera** | Scleritis · Episcleritis · |
| | **Cornea** | Keratitis (herpetic · acanthamoebic · fungal · · Corneal ulcer · Photokeratitis · Thygeson's superficial punctate keratopathy · Corneal dystrophy (Fuchs' · Meesmann · · Corneal ectasia (Keratoconus · Pellucid marginal degeneration · Keratoglobus · Terrien's marginal degeneration · Post-LASIK ectasia · · Keratoconjunctivitis (sicca · · Corneal neovascularization · Kayser–Fleischer ring · Haab's striae · Arcus senilis · Band keratopathy · |
| **Vascular tunic** | **Iris · Ciliary body ·** | Uveitis · Intermediate uveitis · Hyphema · Rubeosis iridis · Persistent pupillary membrane · Iridodialysis · Synechia · |
| | **Choroid** | Choroideremia · Choroiditis (Chorioretinitis · · |
| **Lens** | Cataract (Congenital cataract · Childhood cataract · · Aphakia · Ectopia lentis · | |
| **Retina** | Retinitis (Chorioretinitis · Cytomegalovirus retinitis · · Retinal detachment · Retinoschisis · Ocular ischemic syndrome / Central retinal vein occlusion · Central retinal artery occlusion · Retinopathy (diabetic · hypertensive · Purtscher's · of prematurity · Bietti's crystalline dystrophy · Coats' disease · · Macular degeneration · Retinitis pigmentosa · Retinal haemorrhage · Central serous retinopathy · Macular edema · Epiretinal membrane (Macular pucker) · Vitelliform macular dystrophy · Leber's congenital amaurosis · Birdshot chorioretinopathy · | |
| **Other** | Glaucoma / Ocular hypertension / Primary juvenile glaucoma · Floater · Leber's hereditary optic neuropathy · Red eye · Globe rupture · Keratomycosis · Phthisis bulbi · Persistent fetal vasculature / Persistent hyperplastic primary vitreous · Persistent tunica vasculosa lentis · Familial exudative vitreoretinopathy · | |
| **Pathways** | | |
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| **Optic disc** | | Ischemic (anterior (AION) · posterior (PION) · · Kjer's · |

| | | |
|---|---|---|
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| | **palsies** | Oculomotor (III) · Fourth-nerve (IV) · Sixth-nerve (VI) · |
| | **Other strabismus** | Esotropia / Exotropia · Hypertropia · Heterophoria (Esophoria · Exophoria · · Cyclotropia · Brown's syndrome · Duane syndrome · |
| | **Other binocular** | Conjugate gaze palsy · Convergence insufficiency · Internuclear ophthalmoplegia · One and a half syndrome · |
| **Refraction** | **Refractive error** (Hyperopia · Myopia · · Astigmatism · Anisometropia / Aniseikonia · Presbyopia · | |
| **Vision disorders**<br>**Blindness** | Amblyopia · Leber's congenital amaurosis · Diplopia · Scotoma · Color blindness (Achromatopsia · Dichromacy · Monochromacy · · Nyctalopia (Oguchi disease · · Blindness / Vision loss / Visual impairment · | |
| | **Anopsia** | Hemianopsia (binasal · bitemporal · homonymous · · Quadrantanopia · |
| | **subjective** | Asthenopia · Hemeralopia · Photophobia · Scintillating scotoma · |
| **Pupil** | Anisocoria · Argyll Robertson pupil · Marcus Gunn pupil · Adie syndrome · Miosis · Mydriasis · Cycloplegia · Parinaud's syndrome · | |
| **Other** | Nystagmus · Childhood blindness · | |
| **Infections** | | |
| Trachoma · Onchocerciasis · | | |

Categories: Vision | Disorders of ocular muscles, binocular movement, accommodation and refraction | Refraction

# Trachoma





**Trachoma**, also called **granular conjunctivitis**, **Egyptian ophthalmia**,[1] and **blinding trachoma**, is an infectious disease caused by bacterium *Chlamydia trachomatis*. The infection causes a roughening of the inner surface of the eyelids. This roughening can lead to pain in the eyes, breakdown of the outer surface or cornea of the eyes, and eventual blindness. Untreated, repeated trachoma infections can result in a form of permanent blindness when the eyelids turn inward.[2]

The bacteria that cause the disease can be spread by both direct and indirect contact with an affected person's eyes or nose. Indirect contact includes through clothing or flies that have come in to contact with an affected person's eyes or nose. Children spread the disease more often than adults. Poor sanitation, crowded living conditions, and not enough clean water and toilets also increase spread.[2]

Efforts to prevent the disease include improving access to clean water and decreasing the number of people infected by treatment with antibiotics.[2] This may include treating, all at once, whole groups of people in whom the disease is known to be common.[3] Washing by itself is not enough to prevent disease but may be useful with other measures.[4] Treatment options include oral azithromycin and topical tetracycline.[3] Azithromycin is preferred because it can be used as a single oral dose.[5] After scarring of the eyelid has occurred, surgery may be required to correct the position of the eyelashes and prevent blindness.[2]

Globally, about 80 million people have an active infection.[6] In some areas infections may be present in as many as 60–90% of children and it more commonly affects women than men likely due to their closer contact with children.[2] The disease is the cause of decreased vision in 2.2 million people of whom 1.2 million are completely blind.[2] It commonly occurs in 53 countries of Africa, Asia, Central and South America with about 230 million people at risk.[2] It results in US$8 billion of economic losses a year.[2] It belongs to a group of diseases known as neglected tropical diseases.[6]



**Trachoma**

Surgical repair of in-turned eyelid and eyelashes resulting from trachoma

| Classification and external resources | |
|---|---|
| **Specialty** | infectious disease |
| **ICD-10** | A71 |
| **ICD-9-CM** | 076 |
| **DiseasesDB** | 29100 |
| **MedlinePlus** | 001486 |
| **eMedicine** | oph/118 |
| **Patient UK** | Trachoma |
| **MeSH** | D014141 |

[edit on Wikidata]

Edit links

## Signs and symptoms [edit]

The bacterium has an incubation period of 5 to 12 days, after which the affected individual experiences symptoms of conjunctivitis, or irritation similar to "pink eye." Blinding endemic trachoma results from multiple episodes of reinfection that maintains the intense inflammation in the conjunctiva. Without reinfection, the inflammation will gradually subside.[7]

The conjunctival inflammation is called "active trachoma" and usually is seen in children, especially pre-school children. It is characterized by white lumps in the undersurface of the upper eyelid (conjunctival follicles or lymphoid germinal centres) and by non-specific inflammation and thickening often associated with papillae. Follicles may also appear at the junction of the cornea and the sclera (limbal follicles). Active trachoma will often be irritating and have a watery discharge. Bacterial secondary infection may occur and cause a purulent discharge.

The later structural changes of trachoma are referred to as "cicatricial trachoma". These include scarring in the eyelid (tarsal conjunctiva) that leads to distortion of the eyelid with buckling of the lid (tarsus) so the lashes rub on the eye (trichiasis). These lashes will lead to corneal opacities and scarring and then to blindness. Linear scar present in the Sulcus subtarsalis is called Arlt's line (named after Carl Ferdinand von Arlt). In addition, blood vessels and scar tissue can invade the upper cornea (pannus). Resolved limbal follicles may leave small gaps in pannus (Herbert's Pits).

Most commonly children with active trachoma will not present with any symptoms as the low-grade irritation and ocular discharge is just accepted as normal. However, further symptoms may include:

- Eye discharge
- Swollen eyelids
- Trichiasis (turned-in eyelashes)
- Swelling of lymph nodes in front of the ears
- Sensitivity to bright lights
- Increased heart rate
- Further ear, nose and throat complications.

The major complication or the most important one is corneal ulcer occurring due to rubbing by concentrations, or trichiasis with superimposed bacterial infection.

## Cause [edit]

Trachoma is caused by *Chlamydia trachomatis*, serotypes (serovars) A, B, and C.[8] It is spread by direct contact with eye, nose, and throat secretions from affected individuals, or contact with fomites[9]

(inanimate objects that carry infectious agents), such as towels and/or washcloths, that have had similar contact with these secretions. Flies can also be a route of mechanical transmission.[9] Untreated, repeated trachoma infections result in entropion—a painful form of permanent blindness when the eyelids turn inward, causing the eyelashes to scratch the cornea. Children are the most susceptible to infection due to their tendency to easily get dirty, but the blinding effects or more severe symptoms are often not felt until adulthood.

Blinding endemic trachoma occurs in areas with poor personal and family hygiene. Many factors are indirectly linked to the presence of trachoma including lack of water, absence of latrines or toilets, poverty in general, flies, close proximity to cattle, crowding, and so forth.[7][10] However, the final common pathway seems to be the presence of dirty faces in children that facilitates the frequent exchange of infected ocular discharge from one child's face to another. Most transmission of trachoma occurs within the family.[7]

## Diagnosis [edit]

### McCallan's classification [edit]

McCallan in 1908 divided the clinical course of trachoma into 4 stages

| Stage 1 (Incipient trachoma) | Stage 2 (Established trachoma) | Stage 3 (Cicatrising trachoma) | Stage 4 (Healed trachoma) |
|---|---|---|---|
| Hyperaemia of palpebral conjunctiva | Appearance of mature follicle & papillae | Scarring of palpebral conjunctiva | Disease is cured or is not markable |
| Immature follicle | Progressive corneal pannus | Scars are easily visible as white bands | Sequelae to cicatrisation cause symptoms |

### WHO classification [edit]

The World Health Organization recommends a simplified grading system for trachoma.[11] The Simplified WHO Grading System is summarized below:

Trachomatous inflammation, follicular (TF)—Five or more follicles of >0.5 mm on the upper tarsal conjunctiva

Trachomatous inflammation, intense (TI)—Papillary hypertrophy and inflammatory thickening of the upper tarsal conjunctiva obscuring more than half the deep tarsal vessels

Trachomatous scarring (TS)—Presence of scarring in tarsal conjunctiva.

Trachomatous trichiasis (TT)—At least one ingrown eyelash touching the globe, or evidence of epilation (eyelash removal)

Corneal opacity (CO)—Corneal opacity blurring part of the pupil margin

## Prevention [edit]

Although trachoma was eliminated from much of the developed world in the 20th century, this disease persists in many parts of the developing world, particularly in communities without adequate access to water and sanitation.[12]

### Environmental measures [edit]

Environmental improvement: Modifications in water use, fly control, latrine use, health education, and proximity to domesticated animals have all been proposed to reduce transmission of *C. trachomatis*. These

changes pose numerous challenges for implementation. It seems likely that these environmental changes ultimately impact on the transmission of ocular infection by means of lack of facial cleanliness.[7] Particular attention is required for environmental factors that limit clean faces.

A systematic review examining the effectiveness of environmental sanitary measures on the prevalence of active trachoma in endemic areas showed that usage of insecticide spray resulted in significant reductions of trachoma and fly density in some studies.[13] Health education also resulted in reductions of active trachoma when implemented.[13] Improved water supply did not result in a reduction of trachoma incidence.[13]

### Antibiotics [edit]

Antibiotic therapy: WHO Guidelines recommend that a region should receive community-based, mass antibiotic treatment when the prevalence of active trachoma among one- to nine-year-old children is greater than 10 percent.[14] Subsequent annual treatment should be administered for three years, at which time the prevalence should be reassessed. Annual treatment should continue until the prevalence drops below five percent. At lower prevalences, antibiotic treatment should be family-based.

## Management [edit]

### Antibiotics [edit]

Antibiotic selection: Azithromycin (single oral dose of 20 mg/kg) or topical tetracycline (one percent eye ointment twice a day for six weeks). Azithromycin is preferred because it is used as a single oral dose. Although it is expensive, it is generally used as part of the international donation program organized by Pfizer through the International Trachoma Initiative.[5] Azithromycin can be used in children from the age of six months and in pregnancy.[7] As a community-based antibiotic treatment, some evidence suggests that oral azithromycin was more effective than topical tetracycline; however, there was no consistent evidence that supported oral or topical antibiotics as being more effective.[3] Antibiotic treatment reduces the risk of active trachoma in individuals infected with chlamydia trachomatis.[3]

### Surgery [edit]

Surgery: For individuals with trichiasis, a bilamellar tarsal rotation procedure is warranted to direct the lashes away from the globe.[15] Evidence suggests that usage of a lid clamp and absorbable sutures would result in reduced lid contour abnormalities and granuloma formulation post-surgery.[16] Early intervention is beneficial as the rate of recurrence is higher in more advanced disease.[17]

### Lifestyle measures [edit]

Facial cleanliness: Children with grossly visible nasal discharge, ocular discharge, or flies on their faces are at least twice as likely to have active trachoma as children with clean faces.[7] Intensive community-based health education programs to promote face-washing can significantly reduce the prevalence of active trachoma, especially intense trachoma (TI). If an individual is already infected washing one's face is strongly encouraged, especially a child, in order to prevent re-infection.[18] Some evidence exists that washing the face combined with topical tetracycline might be more effective in reducing severe trachoma compared to topical tetracycline alone.[4] The same trial found no statistically significant benefit of eye washing alone or in combination with tetracycline eye drops in reducing follicular trachoma amongst children.[4]

National governments in collaboration with numerous non-profit organizations implement trachoma control programs using the WHO-recommended SAFE strategy, which includes:

- Surgery to correct advanced stages of the disease;

Antibiotics to treat active infection, using azithromycin
- Facial cleanliness to reduce disease transmission;
- Environmental change to increase access to clean water and improved sanitation.

## Prognosis [edit]

If not treated properly with oral antibiotics, the symptoms may escalate and cause blindness, which is the result of ulceration and consequent scarring of the cornea. Surgery may also be necessary to fix eyelid deformities.

Without intervention, trachoma keeps families shackled within a cycle of poverty, as the disease and its long-term effects are passed from one generation to the next.

## Epidemiology [edit]

As of 2008, between 40–80 million people are infected,[6] and between 1.3 million and 8 million have permanent blindness due to trachoma.[19][20] It is common in more than 50 countries worldwide.[19] In many of these communities, women are three times more likely than men to be blinded by the disease, due to their roles as caregivers in the family.[21] About 110 million people live in endemic areas and need treatment. An additional 210 million live where trachoma is suspected endemic.

Disability-adjusted life year for trachoma per 100,000 inhabitants in 2004

| | |
|---|---|
| no data | 100–200 |
| ≤10 | 200–300 |
| 10–20 | 300–400 |
| 20–40 | 400–500 |
| 40–60 | 500–600 |
| 60–80 | ≥600 |
| 80–100 | |

Ghana, Mexico, Saudi Arabia, Iran, Morocco and Oman report that the disease nationally eliminated.[22] Australia is the only developed country to still have endemic blinding trachoma.[23] In 2008, trachoma was found in half of Australia's very remote communities at endemic levels.[23]

The WHO has set a target to eliminate trachoma as a public health problem by 2020.[24] The International Coalition for Trachoma Control (ICTC) has produced a strategic plan called 2020 INSight that lays out actions and milestones to achieve global elimination of blinding trachoma by the year 2020.[25] "We can make this disease history, and this document lays out a plan to do so," said Dr. Paul Emerson, program director of the International Trachoma Initiative (ITI) and former director of the Carter Center's Trachoma Control Program. "There is an urgent need for action to avoid additional suffering and unnecessary blindness for hundreds of thousands of people." The International Trachoma Initiative (ITI) coordinated the publication of 2020 INSight, which was produced with input from a diverse set of stakeholders.

The Trachoma Atlas is an open-access resource on the geographical distribution of trachoma. It features maps that show the prevalence of trachoma. The maps are free to use and download.[26]

## History [edit]

The disease is one of the earliest known eye afflictions, having been identified in Egypt as early as 15 B.C.[7]

Its presence was also recorded in ancient China and Mesopotamia. Trachoma became a problem as people moved into crowded settlements or towns where hygiene was poor. It became a particular problem in Europe in the 19th century. After the Egyptian Campaign (1798–1802) and the Napoleonic Wars (1798–1815), trachoma was rampant in the army barracks of Europe and spread to those living in towns as troops returned home. Stringent control measures were introduced and by the early 20th century, trachoma was

essentially controlled in Europe, although cases were reported up until the 1950s.[7] Today, most victims of trachoma live in underdeveloped and poverty-stricken countries in Africa, the Middle East, and Asia.

In the United States, the Centers for Disease Control says "No national or international surveillance [for trachoma] exists. Blindness due to trachoma has been eliminated from the United States. The last cases were found among Native American populations and in Appalachia, and those in the boxing, wrestling, and sawmill industries (prolonged exposure to combinations of sweat and sawdust often lead to the disease). In the late 19th century and early 20th century, trachoma was the main reason for an immigrant coming through Ellis Island to be deported."[27][28]

In 1913, President Woodrow Wilson signed an act designating funds for the eradication of the disease.[29][30] Immigrants who attempted to enter the U.S. through Ellis Island, New York had to be checked for trachoma.[27] During this time treatment for the disease was by topical application of copper sulfate. By the late 1930s, a number of ophthalmologists reported success in treating trachoma with sulfonamide antibiotics.[31] In 1948, Vincent Tabone (who was later to become the President of Malta) was entrusted with the supervision of a campaign in Malta to treat trachoma using sulfonamide tablets and drops.[32]

Thanks to improved sanitation and overall living conditions, trachoma virtually disappeared from the industrialized world by the 1950s. However, it continues to plague the developing world to this day. Epidemiological studies were conducted in 1956-63 by the Trachoma Control Pilot Project in India under the Indian Council for Medical Research.[33] This potentially blinding disease remains endemic in the poorest regions of Africa, Asia, and the Middle East and in some parts of Latin America and Australia. Currently, 8 million people are visually impaired as a result of trachoma, and 41 million suffer from active infection.

Of the 54 countries that WHO cited as still having blinding trachoma occurring, Australia is the only developed country - Australian Aboriginal people who live in remote communities with inadequate sanitation are still blinded by this infectious eye disease.[34]

## Etymology [edit]

The term is derived from New Latin *trāchōma*, from Greek τράχωμα *trākhōma*, from τραχύς *trākhus* "rough."[35]

# References [edit]


1. ^ Swanner, Yann A. Meunier ; with contributions from Michael Hole, Takudzwa Shumba & B.J. (2014). *Tropical diseases : a practical guide for medical practitioners and students*. Oxford: Oxford University Press, USA. p. 199. ISBN 9780199997909.
2. ^ *a b c d e f g h* "Blinding Trachoma Fact sheet N°382". *World Health Organization*. November 2013. Retrieved 14 March 2014.
3. ^ *a b c d* Evans JR1, Solomon AW (March 2011). "Antibiotics for trachoma". *Cochrane Database Syst Rev*. **16** (3): CD001860. doi:10.1002/14651858.CD001860.pub3. PMID 21412875.
4. ^ *a b c* Ejere, HO; Alhassan, MB; Rabiu, M (20 February 2015). "Face washing promotion for preventing active trachoma.". *Cochrane Database of Systematic Reviews*. **2** (2): CD003659. doi:10.1002/14651858.CD003659.pub4. PMID 25697765.
5. ^ *a b* Mariotti SP (November 2004). "New steps toward eliminating blinding trachoma". *N. Engl. J. Med*. **351** (19): 2004–7. doi:10.1056/NEJMe048205. PMID 15525727.
6. ^ *a b c* Fenwick, A (Mar 2012). "The global burden of neglected tropical diseases.". *Public health*. **126** (3): 233–6. doi:10.1016/j.puhe.2011.11.015. PMID 22325616.
7. ^ *a b c d e f g h* Taylor, Hugh (2008). *Trachoma: A Blinding Scourge from the Bronze Age to the Twenty-first Century*. Centre for Eye Research Australia. ISBN 0-9757695-9-6.
8. ^ Mackern-Oberti, J. P.; Motrich, R. N. D. O.; Breser, M. A. L.; Sánchez, L. R.; Cuffini, C.; Rivero, V. E. (2013). "Chlamydia trachomatis infection of the male genital tract: An update". *Journal of Reproductive Immunology*. **100**: 37–53. doi:10.1016/j.jri.2013.05.002.
9. ^ *a b* Goldman, Lee (2011). *Goldman's Cecil Medicine* (24th ed.). Philadelphia: Elsevier Saunders. pp. e326–2.

ISBN 1437727883.
10. ^ Wright HR, Turner A, Taylor HR (June 2008). "Trachoma". *Lancet*. **371** (9628): 1945–54. doi:10.1016/S0140-6736(08)60836-3. PMID 18539226.
11. ^ Thylefors B, Dawson CR, Jones BR, West SK, Taylor HR (1987). "A simple system for the assessment of trachoma and its complications". *Bull. World Health Organ.* **65** (4): 477–83. PMC 2491032. PMID 3500800.
12. ^ Stocks, Meredith E. (2014). "Effect of Water, Sanitation, and Hygiene on the Prevention of Trachoma: A Systematic Review and Meta-Analysis". *PLOS Medicine*. **11**: e1001605. doi:10.1371/journal.pmed.1001605.
13. ^ *a b c* Rabiu M, Alhassan MB, Ejere HO, Evans JR (2012). "Environmental sanitary interventions for preventing active trachoma". *Cochrane Database Syst Rev*. **2**: CD004003. doi:10.1002/14651858.CD004003.PUB4. PMID 22336798.
14. ^ Solomon, AW; Zondervan M; Kuper H; et al. (2006). "Trachoma control: a guide for programme managers (PDF). World Health Organization.
15. ^ Reacher M, Foster A, Huber J. "Trichiasis Surgery for Trachoma. The Bilamellar Tarsal Rotation Procedure." 1993; World Health Organization, Geneva: WHO/PBL/93.29.
16. ^ Burton M, Habtamu E, Ho D, Gower EW (2015). "Interventions for trachoma trichiasis". *Cochrane Database Syst Rev*. **11**: CD004008. doi:10.1002/14651858.CD004008.pub3. PMC 4661324. PMID 26568232.
17. ^ Burton MJ, Kinteh F, Jallow O, et al. (October 2005). "A randomised controlled trial of azithromycin following surgery for trachomatous trichiasis in the Gambia". *Br J Ophthalmol*. **89** (10): 1282–8. doi:10.1136/bjo.2004.062489. PMC 1772881. PMID 16170117.
18. ^ Prevention-Trachoma 18 July 2008-24 March 2009
19. ^ *a b* Burton MJ, Mabey DC (2009). Brooker, Simon, ed. "The global burden of trachoma: a review". *PLoS Negl Trop Dis*. **3** (10): e460. doi:10.1371/journal.pntd.0000460. PMC 2761540. PMID 19859534.
20. ^ "Trachoma". World Health Organization. 2012. Retrieved 9 December 2012.
21. ^ What is Trachoma? International Trachoma Initiative.
22. ^ Elizabeth Farrelly (16 November 2009). "A shamed nation turns a blind eye". The Sydney Morning Herald. Archived from the original on 12 April 2011. Retrieved 11 April 2013.
23. ^ *a b* "Eye health in Aboriginal and Torres Strait Islander people". Australian Institute of Health and Welfare. 2008. Archived from the original on 28 October 2012. Retrieved 11 April 2013.
24. ^ http://www.who.int/mediacentre/news/notes/2006/np09/en/
25. ^ "Global strategy lays out concrete action plan to eliminate blinding trachoma by 2020". International Coalition for Trachoma Control. July 2011. Retrieved November 8, 2014.
26. ^ www.trachomaatlas.org
27. ^ *a b* Yew, E (Jun 1980). "Medical inspection of immigrants at Ellis Island, 1891-1924.". *Bulletin of the New York Academy of Medicine*. **56** (5): 488–510. PMC 1805119. PMID 6991041.
28. ^ Disease Listing, Trachoma, Technical Information | CDC Bacterial, Mycotic Diseases.
29. ^ Allen SK, Semba RD (2002). "The trachoma menace in the United States, 1897-1960". *Surv Ophthalmol*. **47** (5): 500–9. doi:10.1016/S0039-6257(02)00340-5. PMID 12431697.
30. ^ Leupp, Constance D. (August 1914). "Removing The Blinding Curse Of The Mountains: How Dr. McMullen, Of The Public Health Service Is Organizing The War Against Trachoma In The Appalachians". *The World's Work: A History of Our Time*. **XLIV** (2): 426–430. Retrieved 2009-08-04.
31. ^ Thygeson P (1939). "The Treatment of Trachoma with Sulfanilamide: A Report of 28 Cases". *Trans Am Ophthalmol Soc*. **37**: 395–403. PMC 1315791. PMID 16693194.
32. ^ Ophthalmology in Malta, C. Savona Ventura, University of Malta, 2003.
33. ^ Gupta, UC and Preobragenski, W (1964), Trachoma in India—Endemicity and Epidemiological study, Indian Journal of Ophthalmology, Volume 12, issue 2, pages 39-49.
34. ^ Taylor, Hugh R. (2001). "Trachoma in Australia". *Medical Journal of Australia*. **175** (7): 371–372. PMID 11700815.
35. ^ "tra·cho·ma". *The American Heritage Dictionary of the English Language, Fourth Edition*. TheFreeDictionary. Retrieved 19 January 2014.

## External links [edit]

- CDC Disease Info *trachoma*
- New York Times article *Preventable Disease Blinds Poor in Third World* Published: March 31, 2006
- Photographs of trachoma patients

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# Attention deficit hyperactivity disorder

From Wikipedia, the free encyclopedia
(Redirected from ADHD)

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## Variants

*"ADD" and "A.D.H.D." redirect here. For other uses, see ADD (disambiguation) and A.D.H.D. (disambiguation).*
*"Minimal brain dysfunction" redirects here. It is not to be confused with mild cognitive impairment.*

**Attention deficit hyperactivity disorder** (**ADHD**) is a mental disorder of the neurodevelopmental type.[1][2] It is characterized by problems paying attention, excessive activity, or difficulty controlling behavior which is not appropriate for a person's age.[3][4] These symptoms begin by age six to twelve, are present for more than six months, and cause problems in at least two settings (such as school, home, or recreational activities).[5][6] In children, problems paying attention may result in poor school performance.[3] Although it causes impairment, particularly in modern society, many children with ADHD have a good attention span for tasks they find interesting.[7]

Despite being the most commonly studied and diagnosed mental disorder in children and adolescents, the exact cause is unknown in the majority of cases.[8] It affects about 5–7% of children when diagnosed via the DSM-IV criteria[9][4] and 1–2% when diagnosed via the ICD-10 criteria.[10] The World Health Organization (WHO) estimated that it affected about 39 million people as of 2013.[11] Rates are similar between countries and depend mostly on how it is diagnosed.[12] ADHD is diagnosed approximately three times more often in boys than in girls, although the disorder is often overlooked in girls due to their symptoms differing from those of boys.[13][14][15] About 30–50% of people diagnosed in childhood continue to have symptoms into adulthood and between 2–5% of adults have the condition.[16][17][18] The condition can be difficult to tell apart from other disorders, as well as to distinguish from high levels of activity that are still within the normal-range.[6]

ADHD management recommendations vary by country and usually involve some combination of counseling, lifestyle changes, and medications.[3] The British guideline only recommends medications as a first-line treatment in children who have severe symptoms and for medication to be considered in those with moderate symptoms who either refuse or fail to improve with counseling, though for adults medications are a first-line treatment.[19] Canadian and American guidelines recommend that medications and behavioral therapy be used together as a first-line therapy, except in preschool-aged children.[20][21] Stimulant medication therapy is not recommended as a first-line therapy in preschool-aged children in either guideline.[19][21] Treatment with stimulants is effective for up to 14 months; however, its long term effectiveness is unclear.[19][22][23][24] Adolescents and adults tend to develop coping skills which make up for some or all of their impairments.[25]

The medical literature has described symptoms similar to ADHD since the 19th century.[26] ADHD, its diagnosis, and its treatment have been considered controversial since the 1970s.[27] The controversies have involved

**Attention deficit hyperactivity disorder**

| | |
|---|---|
| **Synonyms** | attention deficit disorder, hyperkinetic disorder (ICD-10) |

Children with ADHD may find it more difficult to focus and to complete their schoolwork.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Psychiatry |
| **ICD-10** | F90 |
| **ICD-9-CM** | 314.00, 314.01 |
| **OMIM** | 143465 |
| **DiseasesDB** | 6158 |
| **MedlinePlus** | 001551 |
| **eMedicine** | med/3103 ped/177 |
| **Patient UK** | Attention deficit hyperactivity disorder |
| **MeSH** | D001289 |

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clinicians, teachers, policymakers, parents, and the media. Topics include ADHD's causes and the use of stimulant medications in its treatment.[28] Most healthcare providers accept ADHD as a genuine disorder in children and adults, and the debate in the scientific community mainly centers on how it is diagnosed and treated.[29][30][31] The condition was officially known as **attention deficit disorder** (**ADD**) from 1980 to 1987 while before this it was known as **hyperkinetic reaction of childhood**.[32][33]





## Signs and symptoms [edit]



Inattention, hyperactivity (restlessness in adults), disruptive behavior, and impulsivity are common in ADHD.[34][35] Academic difficulties are frequent as are problems with relationships.[34] The symptoms can be difficult to define as it is hard to draw a line at where normal levels of inattention, hyperactivity, and impulsivity end and significant levels requiring interventions begin.[36]


Play media

Video explaining ADHD

According to the DSM-5, symptoms must be present for six months or more to a degree that is much greater than others of the same age[4] and they must cause significant problems functioning in at least two settings (e.g., social, school/work, or home).[4] The full criteria must have been met prior to age 12 in order to receive a diagnosis of ADHD.[4]

ADHD is divided into three subtypes: predominantly inattentive (ADHD-PI or ADHD-I), predominantly hyperactive-impulsive (ADHD-PH), and combined type (ADHD-C).[4][36]

A child with ADHD inattentive type has most or all of following symptoms, excluding situations where these symptoms are better explained by another psychiatric or medical condition:[4][37]

- Be easily distracted, miss details, forget things, and frequently switch from one activity to another
- Have difficulty maintaining focus on one task
- Become bored with a task after only a few minutes, unless doing something enjoyable
- Have difficulty focusing attention on organizing and completing a task or learning something new

- Have trouble completing or turning in homework assignments, often losing things (e.g., pencils, toys, assignments) needed to complete tasks or activities
- Seem to not be listening when spoken to
- Daydream, become easily confused, and move slowly
- Have difficulty processing information as quickly and accurately as others
- Struggle to follow instructions
- Have trouble understanding minute details

A child with ADHD hyperactive/impulsive type has most or all of the following symptoms, excluding situations where these symptoms are better explained by another psychiatric or medical condition:[4][37]

- Fidget and squirm in their seats
- Talk nonstop
- Dash around, touching or playing with anything and everything in sight
- Have trouble sitting still during dinner, school, doing homework, and story time
- Be constantly in motion
- Have difficulty doing quiet tasks or activities
- Be very impatient
- Blurt out inappropriate comments, show their emotions without restraint, and act without regard for consequences
- Have difficulty waiting for things they want or waiting their turns in games
- Often interrupt conversations or others' activities

Symptoms of hyperactivity tend to go away with age and turn into "inner restlessness" in teens and adults with ADHD.[16]

People with ADHD of all ages are more likely to have problems with social skills, such as social interaction and forming and maintaining friendships. This is true for all subtypes. About half of children and adolescents with ADHD experience social rejection by their peers compared to 10–15% of non-ADHD children and adolescents. People with attention deficits are prone to having difficulty processing verbal and nonverbal language which can negatively affect social interaction. They also may drift off during conversations, and miss social cues.[38]

Difficulties managing anger are more common in children with ADHD[39] as are poor handwriting[40] and delays in speech, language and motor development.[41][42] Although it causes significant impairment, particularly in modern society, many children with ADHD have a good attention span for tasks they find interesting.[7]

## Associated disorders [edit]

In children, ADHD occurs with other disorders about ⅔ of the time.[7] Some commonly associated conditions include:

- Learning disabilities have been found to occur in about 20–30% of children with ADHD. Learning disabilities can include developmental speech and language disorders and academic skills disorders.[43] ADHD, however, is not considered a learning disability, but it very frequently causes academic difficulties.[43]
- Tourette syndrome has been found to occur more commonly in the ADHD population.[3]
- Oppositional defiant disorder (ODD) and conduct disorder (CD), which occur with ADHD in about 50% and 20% of cases respectively.[44] They are characterized by antisocial behaviors such as stubbornness, aggression, frequent temper tantrums, deceitfulness, lying, and stealing.[45] About half of those with hyperactivity and ODD or CD develop antisocial personality disorder in adulthood.[46] Brain imaging supports that conduct disorder and ADHD are separate conditions.[47]
- Primary disorder of vigilance, which is characterized by poor attention and concentration, as well as difficulties staying awake. These children tend to fidget, yawn and stretch and appear to be hyperactive in order to remain alert and active.[45]
- Mood disorders (especially bipolar disorder and major depressive disorder). Boys diagnosed with the combined ADHD subtype are more likely to have a mood disorder.[48] Adults with ADHD sometimes also have bipolar disorder, which requires careful assessment to accurately diagnose and treat both conditions.[49]
- Anxiety disorders have been found to occur more commonly in the ADHD population.[48]
- Obsessive-compulsive disorder (OCD) can co-occur with ADHD and shares many of its characteristics.[45]
- Substance use disorders. Adolescents and adults with ADHD are at increased risk of substance abuse.[16] This is most commonly seen with alcohol or cannabis.[16] The reason for this may be an altered reward pathway in the brains of ADHD individuals.[16] This makes the evaluation and treatment of ADHD more difficult, with serious substance misuse problems usually treated first due to their greater risks.[19][50]

- Restless legs syndrome has been found to be more common in those with ADHD and is often due to iron deficiency anaemia.[51][52] However, restless legs can simply be a part of ADHD and requires careful assessment to differentiate between the two disorders.[53]
- Sleep disorders and ADHD commonly co-exist. They can also occur as a side effect of medications used to treat ADHD. In children with ADHD, insomnia is the most common sleep disorder with behavioral therapy the preferred treatment.[54][55] Problems with sleep initiation are common among individuals with ADHD but often they will be deep sleepers and have significant difficulty getting up in the morning.[56] Melatonin is sometimes used in children who have sleep onset insomnia.[57]
- People with ADHD have an increased risk of persistent bed wetting.[58]
- A 2016 systematic review found a well established association between ADHD and obesity, asthma and sleep disorders, and tentative evidence for association with celiac disease and migraine,[59] while another 2016 systematic review did not support a clear link between celiac disease and ADHD, and stated that routine screening for celiac disease in people with ADHD is discouraged.[60]

### Intelligence [edit]

Overall, studies have shown that people with ADHD tend to have lower scores on intelligence quotient (IQ) tests.[61] The significance of this is controversial due to the differences between people with ADHD and the difficulty determining the influence of symptoms, such as distractibility, on lower scores rather than intellectual capacity.[61] In studies of ADHD, higher IQs may be over represented because many studies exclude individuals who have lower IQs despite those with ADHD scoring on average 9 points lower on standardized intelligence measures.[62]

## Cause [edit]

The cause of most cases of ADHD is unknown; however, it is believed to involve interactions between genetic and environmental factors.[63][64] Certain cases are related to previous infection of or trauma to the brain.[63]

### Genetics [edit]

Twin studies indicate that the disorder is often inherited from one's parents with genetics determining about 75% of cases.[19][65][66] Siblings of children with ADHD are three to four times more likely to develop the disorder than siblings of children without the disorder.[67] Genetic factors are also believed to be involved in determining whether ADHD persists into adulthood.[68]

Typically, a number of genes are involved, many of which directly affect dopamine neurotransmission.[69][70] Those involved with dopamine include DAT, DRD4, DRD5, TAAR1, MAOA, COMT, and DBH.[70][71][72] Other genes associated with ADHD include SERT, HTR1B, SNAP25, GRIN2A, ADRA2A, TPH2, and BDNF.[69][70] A common variant of a gene called LPHN3 is estimated to be responsible for about 9% of cases and when this variant is present, people are particularly responsive to stimulant medication.[73] The 7 repeat variant of dopamine receptor D4 (DRD4–7R) causes increased inhibitory effects induced by dopamine and is associated with ADHD. The DRD4 receptor is a G protein-coupled receptor that inhibits adenylyl cyclase. The DRD4–7R mutation results in a wide range of behavioral phenotypes, including ADHD symptoms reflecting split attention.[74]

Evolution may have played a role in the high rates of ADHD, particularly hyperactive and impulsive traits in males.[75] Some have hypothesized that some women may be more attracted to males who are risk takers, increasing the frequency of genes that predispose to hyperactivity and impulsivity in the gene pool.[76] Others have claimed that these traits may be an adaptation that helped males face stressful or dangerous environment with, for example, increased impulsivity and exploratory behavior.[75][76] In certain situations, ADHD traits may have been beneficial to society as a whole even while being harmful to the individual.[75][76][77] The high rates and heterogeneity of ADHD may have increased reproductive fitness and benefited society by adding diversity to the gene pool despite being detrimental to the individual.[77] In certain environments, some ADHD traits may have offered personal advantages to individuals, such as quicker response to predators or superior hunting skills.[78]

People with Down syndrome are more likely to have ADHD.[79]

### Environment [edit]

*See also: Diet and attention deficit hyperactivity disorder*

In addition to genetics, some environmental factors might play a role.[80] Alcohol intake during pregnancy can

cause fetal alcohol spectrum disorders which can include ADHD or symptoms like it.[81] Children exposed to certain toxic substances, such as lead or polychlorinated biphenyls, may develop problems which resemble ADHD.[8][82] Exposure to the organophosphate insecticides chlorpyrifos and dialkyl phosphate is associated with an increased risk; however, the evidence is not conclusive.[83] Exposure to tobacco smoke during pregnancy can cause problems with central nervous system development and can increase the risk of ADHD.[8][84]

Extreme premature birth, very low birth weight, and extreme neglect, abuse, or social deprivation also increase the risk[8][85] as do certain infections during pregnancy, at birth, and in early childhood. These infections include, among others, various viruses (measles, varicella zoster encephalitis, rubella, enterovirus 71).[86] At least 30% of children with a traumatic brain injury later develop ADHD[87] and about 5% of cases are due to brain damage.[88]

Some studies suggest that in a minority of children, artificial food dyes or preservative may be associated with an increased prevalence of ADHD or ADHD-like symptoms[8][89] but the evidence is weak and may only apply to children with food sensitivities.[89][90][91] The United Kingdom and the European Union have put in place regulatory measures based on these concerns.[92] In a minority of children, intolerances or allergies to certain foods may worsen ADHD symptoms.[93]

Research does not support popular beliefs that ADHD is caused by eating too much refined sugar, watching too much television, parenting, poverty or family chaos; however, they might worsen ADHD symptoms in certain people.[35]

### Society [edit]

The diagnosis of ADHD can represent family dysfunction or a poor educational system rather than an individual problem.[94] Some cases may be explained by increasing academic expectations, with a diagnosis being a method for parents in some countries to get extra financial and educational support for their child.[88] The youngest children in a class have been found to be more likely to be diagnosed as having ADHD possibly due to their being developmentally behind their older classmates.[95][96] Behaviors typical of ADHD occur more commonly in children who have experienced violence and emotional abuse.[19]

The social construct theory of ADHD suggests that because the boundaries between "normal" and "abnormal" behavior are socially constructed, i.e. jointly created and validated by all members of society, and in particular by physicians, parents, and teachers, it then follows that subjective valuations and judgements determine which diagnostic criteria are used and, thus, the number of people affected.[97] This could lead to the situation where the DSM-IV arrives at levels of ADHD three to four times higher than those obtained with the ICD-10.[15] Thomas Szasz, a supporter of this theory, has argued that ADHD was "invented and not discovered."[98][99]

## Pathophysiology [edit]

Current models of ADHD suggest that it is associated with functional impairments in some of the brain's neurotransmitter systems, particularly those involving dopamine and norepinephrine.[100][101] The dopamine and norepinephrine pathways that originate in the ventral tegmental area and locus coeruleus project to diverse regions of the brain and govern a variety of cognitive processes.[100][102] The dopamine pathways and norepinephrine pathways which project to the prefrontal cortex and striatum are directly responsible for modulating executive function (cognitive control of behavior), motivation, reward perception, and motor function;[100][101][102] these pathways are known to play a central role in the pathophysiology of ADHD.[100][102][103][104] Larger models of ADHD with additional pathways have been proposed.[101][103][104]

### Brain structure [edit]

In children with ADHD, there is a general reduction of volume in certain brain structures, with a proportionally greater decrease in the volume in the left-sided prefrontal cortex.[101][105] The posterior parietal cortex also shows thinning in ADHD individuals compared to controls.[101] Other brain structures in the prefrontal-striatal-cerebellar and prefrontal-striatal-thalamic circuits have also been found to differ between people with and without ADHD.[101][103][104]

### Neurotransmitter pathways [edit]

Previously it was thought that the elevated number of dopamine transporters in people with ADHD was part of the pathophysiology but it appears that the elevated numbers are due to adaptation to exposure to stimulants.[106] Current models involve the mesocorticolimbic dopamine pathway and the locus coeruleus-noradrenergic

system.[100][101][102] ADHD psychostimulants possess treatment efficacy because they increase neurotransmitter activity in these systems.[101][102][107] There may additionally be abnormalities in serotoninergic, glutamatergic, or cholinergic pathways.[107][108][109]

### Executive function and motivation [edit]

The symptoms of ADHD arise from a deficiency in certain executive functions (e.g., attentional control, inhibitory control, and working memory).[56][101][102][110] Executive functions are a set of cognitive processes that are required to successfully select and monitor behaviors that facilitate the attainment of one's chosen goals.[56][102][110] The executive function impairments that occur in ADHD individuals result in problems with staying organized, time keeping, excessive procrastination, maintaining concentration, paying attention, ignoring distractions, regulating emotions, and remembering details.[56][101][102] People with ADHD appear to have unimpaired long-term memory, and deficits in long-term recall appear to be attributed to impairments in working memory.[56][111] The criteria for an executive function deficit are met in 30–50% of children and adolescents with ADHD.[112] One study found that 80% of individuals with ADHD were impaired in at least one executive function task, compared to 50% for individuals without ADHD.[113] Due to the rates of brain maturation and the increasing demands for executive control as a person gets older, ADHD impairments may not fully manifest themselves until adolescence or even early adulthood.[56]

ADHD has also been associated with motivational deficits in children.[114] Children with ADHD find it difficult to focus on long-term over short-term rewards, and exhibit impulsive behavior for short-term rewards.[114]

## Diagnosis [edit]

ADHD is diagnosed by an assessment of a person's childhood behavioral and mental development, including ruling out the effects of drugs, medications and other medical or psychiatric problems as explanations for the symptoms.[19] It often takes into account feedback from parents and teachers[6] with most diagnoses begun after a teacher raises concerns.[88] It may be viewed as the extreme end of one or more continuous human traits found in all people.[19] Whether someone responds to medications does not confirm or rule out the diagnosis. As imaging studies of the brain do not give consistent results between individuals, they are only used for research purposes and not diagnosis.[115]

In North America, DSM-5 criteria are used for diagnosis, while European countries usually use the ICD-10. With the DSM-IV criteria a diagnosis of ADHD is 3–4 times more likely than with the ICD-10 criteria.[15] It is classified as neurodevelopmental psychiatric disorder.[2][16] Additionally, it is classified as a disruptive behavior disorder along with oppositional defiant disorder, conduct disorder, and antisocial personality disorder.[116] A diagnosis does not imply a neurological disorder.[19]

Associated conditions that should be screened for include anxiety, depression, oppositional defiant disorder, conduct disorder, and learning and language disorders. Other conditions that should be considered are other neurodevelopmental disorders, tics, and sleep apnea.[117]

Diagnosis of ADHD using quantitative electroencephalography (QEEG) is an ongoing area of investigation, although the value of QEEG in ADHD is currently unclear.[118][119] In the United States, the Food and Drug Administration has approved the use of QEEG to evaluate the morbidity of ADHD.[120]

Self-rating scales, such as the ADHD rating scale and the Vanderbilt ADHD diagnostic rating scale are used in the screening and evaluation of ADHD.[121]

### Diagnostic and Statistical Manual [edit]

As with many other psychiatric disorders, formal diagnosis should be made by a qualified professional based on a set number of criteria. In the United States, these criteria are defined by the American Psychiatric Association in the DSM. Based on the DSM criteria, there are three sub-types of ADHD:[4]

1. ADHD predominantly inattentive type (ADHD-PI) presents with symptoms including being easily distracted, forgetful, daydreaming, disorganization, poor concentration, and difficulty completing tasks.[5][4]
2. ADHD, predominantly hyperactive-impulsive type presents with excessive fidgetiness and restlessness, hyperactivity, difficulty waiting and remaining seated, immature behavior; destructive behaviors may also be present.[5][4]
3. ADHD, combined type is a combination of the first two subtypes.[5][4]

This subdivision is based on presence of at least six out of nine long-term (lasting at least six months) symptoms of inattention, hyperactivity–impulsivity, or both.[122] To be considered, the symptoms must have appeared by the age of six to twelve and occur in more than one environment (e.g. at home and at school or work).[5] The symptoms must be not appropriate for a child of that age[5][123] and there must be evidence that it is causing social, school or work related problems.[122]

## International Classification of Diseases [edit]

In the ICD-10, the symptoms of "hyperkinetic disorder" are analogous to ADHD in the DSM-5. When a conduct disorder (as defined by ICD-10)[41] is present, the condition is referred to as *hyperkinetic conduct disorder*. Otherwise, the disorder is classified as *disturbance of activity and attention*, *other hyperkinetic disorders* or *hyperkinetic disorders, unspecified*. The latter is sometimes referred to as *hyperkinetic syndrome*.[41]

In the preliminary draft for ICD-11 (planned for 2018), ADHD is classified under 6A42 *(Attention deficit hyperactivity disorder)* and everything seems to be fully identical now to DSM-5.[124]

## Adults [edit]

*Main article: Adult attention deficit hyperactivity disorder*

Adults with ADHD are diagnosed under the same criteria, including that their signs must have been present by the age of six to twelve. Questioning parents or guardians as to how the person behaved and developed as a child may form part of the assessment; a family history of ADHD also adds weight to a diagnosis.[16] While the core symptoms of ADHD are similar in children and adults they often present differently in adults than in children, for example excessive physical activity seen in children may present as feelings of restlessness and constant mental activity in adults.[16]

It is estimated that between 2–5% of adults have ADHD.[16] Around 25-50% of children with ADHD continue to experience ADHD symptoms into adulthood, while the rest experiences fewer or no symptoms.[4][16] Currently, most adults remain untreated.[125] Many adults with ADHD without diagnosis and treatment have a disorganized life and some use non-prescribed drugs or alcohol as a coping mechanism.[25] Other problems may include relationship and job difficulties, and an increased risk of criminal activities.[16] Associated mental health problems include: depression, anxiety disorder, and learning disabilities.[25]

Some ADHD symptoms in adults differ from those seen in children. While children with ADHD may climb and run about excessively, adults may experience an inability to relax, or they talk excessively in social situations. Adults with ADHD may start relationships impulsively, display sensation-seeking behavior, and be short-tempered. Addictive behavior such as substance abuse and gambling are common. The DSM-V criteria do specifically deal with adults, unlike those in DSM-IV, which were criticized for not being appropriate for adults; those who presented differently may lead to the claim that they outgrew the diagnosis.[16]

## Differential diagnosis [edit]

Symptoms of ADHD such as low mood and poor self-image, mood swings, and irritability can be confused with dysthymia, cyclothymia or bipolar disorder as well as with borderline personality disorder.[16] Some symptoms that are due to anxiety disorders, antisocial personality disorder, developmental disabilities or mental retardation or the effects of substance abuse such as intoxication and

| ADHD symptoms which are related to other disorders[126] | | |
|---|---|---|
| **Depression** | **Anxiety disorder** | **Bipolar disorder** |
| ▪ feelings of hopelessness, low self-esteem, or unhappiness<br>▪ loss of interest in hobbies or regular activities<br>▪ fatigue<br>▪ sleep problems<br>▪ difficulty maintaining attention<br>▪ change in appetite<br>▪ irritability or hostility<br>▪ low tolerance for stress<br>▪ thoughts of death<br>▪ unexplained pain | ▪ persistent feeling of anxiety<br>▪ irritability<br>▪ occasional feelings of panic or fear<br>▪ being hyperalert<br>▪ inability to pay attention<br>▪ tire easily<br>▪ low tolerance for stress<br>▪ difficulty maintaining attention | **in manic state**<br>▪ excessive happiness<br>▪ hyperactivity<br>▪ racing thoughts<br>▪ aggression<br>▪ excessive talking<br>▪ grandiose delusions<br>▪ decreased need for sleep<br>▪ inappropriate social behavior<br>▪ difficulty maintaining attention<br>**in depressive state**<br>▪ same symptoms as in |

| | | |
|---|---|---|
| withdrawal can overlap with some ADHD. | | depression section |

These disorders can also sometimes occur along with ADHD. Medical conditions which can cause ADHD type symptoms include: hyperthyroidism, seizure disorder, lead toxicity, hearing deficits, hepatic disease, sleep apnea, drug interactions, untreated celiac disease, and head injury.[25][60]

Primary sleep disorders may affect attention and behavior and the symptoms of ADHD may affect sleep.[127] It is thus recommended that children with ADHD be regularly assessed for sleep problems.[128] Sleepiness in children may result in symptoms ranging from the classic ones of yawning and rubbing the eyes, to hyperactivity and inattentiveness.[129] Obstructive sleep apnea can also cause ADHD type symptoms.[129]

### Biomarker research [edit]

Reviews of ADHD biomarkers have noted that platelet monoamine oxidase expression, urinary norepinephrine, urinary MHPG, and urinary phenethylamine levels consistently differ between ADHD individuals and healthy control.[130][131] These measurements could potentially serve as diagnostic biomarkers for ADHD, but more research is needed to establish their diagnostic utility.[131] Urinary and blood plasma phenethylamine concentrations are lower in ADHD individuals relative to controls and the two most commonly prescribed drugs for ADHD, amphetamine and methylphenidate, increase phenethylamine biosynthesis in treatment-responsive individuals with ADHD.[71][130][131] Lower urinary phenethylamine concentrations are also associated with symptoms of inattentiveness in ADHD individuals.[131]

## Management [edit]

*Main article: Attention deficit hyperactivity disorder management*

The management of ADHD typically involves counseling or medications either alone or in combination. While treatment may improve long-term outcomes, it does not get rid of negative outcomes entirely.[132] Medications used include stimulants, atomoxetine, alpha-2 adrenergic receptor agonists, and sometimes antidepressants.[48][107] In those who have trouble focussing on long-term rewards, a large amount of positive reinforcement improves task performance.[114] ADHD stimulants also improve persistence and task performance in children with ADHD.[101][114]

### Behavioral therapies [edit]

There is good evidence for the use of behavioral therapies in ADHD and they are the recommended first line treatment in those who have mild symptoms or are preschool-aged.[133][134] Psychological therapies used include: psychoeducational input, behavior therapy, cognitive behavioral therapy (CBT), interpersonal psychotherapy, family therapy, school-based interventions, social skills training, behavioral peer intervention, organization training,[135] parent management training,[19] and neurofeedback.[136] Behavior modification and neurofeedback have the best support.[137]

Parent training and education have been found to have short-term benefits.[138][139] There is little high quality research on the effectiveness of family therapy for ADHD, but the evidence that exists shows that it is similar to community care and better than a placebo.[140] Several ADHD specific support groups exist as informational sources and may help families cope with ADHD.[141]

Training in social skills, behavioral modification and medication may have some limited beneficial effects. The most important factor in reducing later psychological problems, such as major depression, criminality, school failure, and substance use disorders is formation of friendships with people who are not involved in delinquent activities.[142]

Regular physical exercise, particularly aerobic exercise, is an effective add-on treatment for ADHD in children and adults, particularly when combined with stimulant medication, although the best intensity and type of aerobic exercise for improving symptoms are not currently known.[143][144][145] In particular, the long-term effects of regular aerobic exercise in ADHD individuals include better behavior and motor abilities, improved executive functions (including attention, inhibitory control, and planning, among other cognitive domains), faster information processing speed, and better memory.[143][144][145] Parent-teacher ratings of behavioral and socio-emotional outcomes in response to regular aerobic exercise include: better overall function, reduced ADHD symptoms, better self-esteem, reduced levels of anxiety and depression, fewer somatic complaints, better academic and classroom behavior, and improved social behavior.[143] Exercising while on stimulant medication augments the effect of [143]

stimulant medication on executive function. It is believed that these short-term effects of exercise are mediated by an increased abundance of synaptic dopamine and norepinephrine in the brain.[143]

## Medication [edit]

Stimulant medications are the pharmaceutical treatment of choice.[146][147] They have at least some effect on symptoms in the short term in about 80% of people.[24] Methylphenidate appears to improve symptoms as reported by teachers and parents.[148] Stimulants may also reduce the risk of injuries in children with ADHD.[149]

Methylphenidate (Ritalin) 10 mg tablets

There are a number of non-stimulant medications, such as atomoxetine, bupropion, guanfacine, and clonidine that may be used as alternatives, or added to stimulant therapy.[146][150] There are no good studies comparing the various medications; however, they appear more or less equal with respect to side effects.[151] Stimulants appear to improve academic performance while atomoxetine does not.[152] Atomoxetine, due to its lack of addiction liability, may be preferred in those who are at risk of recreational or compulsive stimulant use.[16] There is little evidence on the effects of medication on social behaviors.[151] As of June 2015, the long-term effects of ADHD medication have yet to be fully determined.[153][154] Magnetic resonance imaging studies suggest that long-term treatment with amphetamine or methylphenidate decreases abnormalities in brain structure and function found in subjects with ADHD.[155][156][157]

Guidelines on when to use medications vary by country, with the United Kingdom's National Institute for Health and Care Excellence recommending use for children only in severe cases, though for adults medication is a first-line treatment, while most United States guidelines recommend medications in most age groups.[20] Medications are not recommended for preschool children.[19][158] Underdosing of stimulants may occur and result in a lack of response or later loss of effectiveness.[159] This is particularly common in adolescents and adults as approved dosing is based on school-aged children, causing some practitioners to use weight based or benefit based off-label dosing instead.[160][161][162]

While stimulants and atomoxetine are usually safe, there are side-effects and contraindications to their use.[146] A large overdose on ADHD stimulants is commonly associated with symptoms such as stimulant psychosis and mania;[163] although very rare, at therapeutic doses these events appear to occur in approximately 0.1% of individuals within the first several weeks after starting amphetamine or methylphenidate therapy.[164][163][165] Administration of an antipsychotic medication has been found to effectively resolve the symptoms of acute amphetamine psychosis.[163] Regular monitoring has been recommended in those on long-term treatment.[166] Stimulant therapy should be stopped periodically to assess continuing need for medication, decrease possible growth delay, and reduce tolerance.[167][168] Long-term misuse of stimulant medications at doses above the therapeutic range for ADHD treatment is associated with addiction and dependence.[169][170] Untreated ADHD, however, is also associated with elevated risk of substance use disorders and conduct disorders.[169] The use of stimulants appears to either reduce this risk or have no effect on it.[16][153][169] The safety of these medications in pregnancy is unclear.[171]

## Diet [edit]

Dietary modifications may be of benefit to a small proportion of children with ADHD.[172] A 2013 meta-analysis found less than a third of children with ADHD see some improvement in symptoms with free fatty acid supplementation or decreased eating of artificial food coloring.[90] These benefits may be limited to children with food sensitivities or those who are simultaneously being treated with ADHD medications.[90] This review also found that evidence does not support removing other foods from the diet to treat ADHD.[90] A 2014 review found that an elimination diet results in a small overall benefit.[93] A 2016 review stated that the use of a gluten-free diet as standard ADHD treatment is discouraged.[60] Iron, magnesium and iodine may also have an effect on ADHD symptoms.[173] There is a small amount of evidence that lower tissue zinc levels may be associated with ADHD.[174] In the absence of a demonstrated zinc deficiency (which is rare outside of developing countries), zinc supplementation is not recommended as treatment for ADHD.[175] However, zinc supplementation may reduce the minimum effective dose of amphetamine when it is used with amphetamine for the treatment of ADHD.[176] There

is evidence of a modest benefit of omega 3 fatty acid supplementation, but it is not recommended in place of traditional medication.[177][178]

## Prognosis [edit]

An 8-year follow up of children diagnosed with ADHD (combined type) found that they often have difficulties in adolescence, regardless of treatment or lack thereof.[179] In the USA, fewer than 5% of individuals with ADHD get a college degree,[180] compared to 28% of the general population aged 25 years and older.[181] The proportion of children meeting criteria for ADHD drops by about half in the three years following the diagnosis and this occurs regardless of treatments used.[182][183] ADHD persists into adulthood in about 30–50% of cases.[17] Those affected are likely to develop coping mechanisms as they mature, thus compensating to some extent for their previous symptoms.[25]

## Epidemiology [edit]

*Main article: Epidemiology of attention deficit hyperactive disorder*

ADHD is estimated to affect about 6–7% of people aged 18 and under when diagnosed via the DSM-IV criteria.[9] When diagnosed via the ICD-10 criteria rates in this age group are estimated at 1–2%.[10] Children in North America appear to have a higher rate of ADHD than children in Africa and the Middle East; this is believed to be due to differing methods of diagnosis rather than a difference in underlying frequency.[184] If the same diagnostic methods are used, the rates are more or less the same between countries.[12] It is diagnosed approximately three times more often in boys than in girls.[14][15] This difference between sexes may reflect either a difference in susceptibility or that females with ADHD are less likely to be diagnosed than males.[185]

Rates of diagnosis and treatment have increased in both the United Kingdom and the United States since the 1970s.[186] This is believed to be primarily due to changes in how the condition is diagnosed[186] and how readily people are willing to treat it with medications rather than a true change in how common the condition is.[10] It is believed that changes to the diagnostic criteria in 2013 with the release of the DSM-5 will increase the percentage of people diagnosed with ADHD, especially among adults.[187]

## History [edit]

*Main article: History of attention deficit hyperactivity disorder*

Hyperactivity has long been part of the human condition. Sir Alexander Crichton describes "mental restlessness" in his book *An inquiry into the nature and origin of mental derangement* written in 1798.[188][189] ADHD was first clearly described by George Still in 1902.[186]

The terminology used to describe the condition has changed over time and has included: in the DSM-I (1952) "minimal brain dysfunction", in the DSM-II (1968) "hyperkinetic reaction of childhood", in the DSM-III (1980) "attention-deficit disorder (ADD) with or without hyperactivity".[186] In 1987 this was changed to ADHD in the DSM-III-R and the DSM-IV in 1994 split the diagnosis into three subtypes, ADHD inattentive type, ADHD hyperactive-impulsive type and ADHD combined type.[190] These terms were kept in the DSM-5 in 2013.[4] Other terms have included "minimal brain damage" used in the 1930s.[191]

The use of stimulants to treat ADHD was first described in 1937.[192] In 1934, Benzedrine became the first amphetamine medication approved for use in the United States.[193] Methylphenidate was introduced in the 1950s, and enantiopure dextroamphetamine in the 1970s.[186]

## Society and culture [edit]

### Controversies [edit]

*Main article: Attention deficit hyperactivity disorder controversies*

ADHD, its diagnosis, and its treatment have been controversial since the 1970s.[27][28][194] The controversies involve clinicians, teachers, policymakers, parents, and the media. Positions range from the view that ADHD is within the normal range of behavior[19][195] to the hypothesis that ADHD is a genetic condition.[196] Other areas

of controversy include the use of stimulant medications in children,[28][197] the method of diagnosis, and the possibility of overdiagnosis.[197] In 2012, the National Institute for Health and Care Excellence, while acknowledging the controversy, states that the current treatments and methods of diagnosis are based on the dominant view of the academic literature.[19] In 2014, Keith Conners, one of the early advocates for recognition of the disorder, spoke out against overdiagnosis in a *New York Times* article.[198] In contrast, a 2014 peer-reviewed medical literature review indicated that ADHD is underdiagnosed in adults.[18]

With widely differing rates of diagnosis across countries, states within countries, races, and ethnicities, some suspect factors other than the presence of the symptoms of ADHD are playing a role in diagnosis.[95] Some sociologists consider ADHD to be an example of the medicalization of deviant behavior, that is, the turning of the previously non-medical issue of school performance into a medical one.[27][88] Most healthcare providers accept ADHD as a genuine disorder, at least in the small number of people with severe symptoms.[88] Among healthcare providers the debate mainly centers on diagnosis and treatment in the much greater number of people with less severe symptoms.[30][31][88]

As of 2009, 8% of all United States Major League Baseball players had been diagnosed with ADHD, making the disorder common among this population. The increase coincided with the League's 2006 ban on stimulants, which has raised concern that some players are mimicking or falsifying the symptoms or history of ADHD to get around the ban on the use of stimulants in sport.[199]

## Media commentary [edit]

A number of public figures have given controversial statements regarding ADHD. Tom Cruise has described the medications Ritalin (methylphenidate) and Adderall (a mixed-salt amphetamine formulation) as "street drugs".[200] Ushma S. Neill criticized this view, stating that the doses of stimulants used in the treatment of ADHD do not cause addiction and that there is some evidence of a reduced risk of later substance addiction in children treated with stimulants.[201] In the UK, Susan Greenfield spoke out publicly in 2007 in the House of Lords about the need for a wide-ranging inquiry into the dramatic increase in the diagnosis of ADHD, and possible causes. Her comments followed a BBC *Panorama* program that highlighted research that suggested medications are no better than other forms of therapy in the long term.[202] In 2010, the BBC Trust criticized the 2007 *Panorama* program for summarizing the research as showing "no demonstrable improvement in children's behaviour after staying on ADHD medication for three years" when in actuality "the study found that medication did offer a significant improvement over time" although the long-term benefits of medication were found to be "no better than children who were treated with behavior therapy."[203]

# References [edit]


1. ^ Sroubek, A; Kelly, M; Li, X (February 2013). "Inattentiveness in attention-deficit/hyperactivity disorder". *Neuroscience Bulletin*. **29** (1): 103–10. doi:10.1007/s12264-012-1295-6. PMID 23299717.
2. ^ *a b* Caroline, SC, ed. (2010). *Encyclopedia of Cross-Cultural School Psychology*. Springer Science & Business Media. p. 133. ISBN 9780387717982.
3. ^ *a b c d* "Attention Deficit Hyperactivity Disorder". *National Institute of Mental Health*. March 2016. Retrieved 5 March 2016.
4. ^ *a b c d e f g h i j k l m n* American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington: American Psychiatric Publishing. pp. 59–65. ISBN 0890425558.
5. ^ *a b c d e f* "Symptoms and Diagnosis". *Attention-Deficit / Hyperactivity Disorder (ADHD)*. Division of Human Development, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention. 29 September 2014. Retrieved 3 November 2014.
6. ^ *a b c* Dulcan, MK; Lake, MB (2011). *Concise Guide to Child and Adolescent Psychiatry* (4th illustrated ed.). American Psychiatric Publishing. p. 34. ISBN 9781585624164.
7. ^ *a b c* Walitza, S; Drechsler, R; Ball, J (August 2012). "Das schulkind mit ADHS" [The school child with ADHD]. *Ther Umsch* (in German). **69** (8): 467–73. doi:10.1024/0040-5930/a000316. PMID 22851461.
8. ^ *a b c d e* NIMH (2013). "Attention Deficit Hyperactivity Disorder (Easy-to-Read)". National Institute of Mental Health. Retrieved 17 Apr 2016.
9. ^ *a b* Willcutt, EG (July 2012). "The prevalence of DSM-IV attention-deficit/hyperactivity disorder: A meta-analytic review". *Neurotherapeutics*. **9** (3): 490–9. doi:10.1007/s13311-012-0135-8. PMC 3441936. PMID 22976615.
10. ^ *a b c* Cowen, P; Harrison, P; Burns, T (2012). *Shorter Oxford Textbook of Psychiatry* (6th ed.). Oxford University Press. p. 546. ISBN 9780199605613.
11. ^ Global Burden of Disease Study 2013, Collaborators (5 June 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386**: 743–800. doi:10.1016/S0140-

6736(15)60692-4. PMC 4561509. PMID 26063472.
12. ^ a b Faraone, SV (2011). "Ch. 25: Epidemiology of Attention Deficit Hyperactivity Disorder". In Tsuang, MT; Tohen, M; Jones, P. *Textbook of Psychiatric Epidemiology* (3rd ed.). John Wiley & Sons. p. 450. ISBN 9780470977408.
13. ^ "Gender differences in ADHD". *http://www.apa.org/*. American Psychological Association. External link in |website= (help)
14. ^ a b Emond, V; Joyal, C; Poissant, H (April 2009). "Neuroanatomie structurelle et fonctionnelle du trouble déficitaire d'attention avec ou sans hyperactivité (TDAH)" [Structural and functional neuroanatomy of attention-deficit hyperactivity disorder (ADHD)]. *Encephale* (in French). **35** (2): 107–14. doi:10.1016/j.encep.2008.01.005. PMID 19393378.
15. ^ a b c d Singh, I (December 2008). "Beyond polemics: Science and ethics of ADHD". *Nature Reviews Neuroscience*. **9** (12): 957–64. doi:10.1038/nrn2514. PMID 19020513.
16. ^ a b c d e f g h i j k l m n o Kooij, SJ; Bejerot, S; Blackwell, A; Caci, H; et al. (2010). "European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD". *BMC Psychiatry*. **10**: 67. doi:10.1186/1471-244X-10-67. PMC 2942810. PMID 20815868.
17. ^ a b Bálint, S; Czobor, P; Mészáros, A; Simon, V; et al. (2008). "Neuropszichológiai károsodásokat felnőtt figyelemhiányos hiperaktivitás zavar(ADHD): A szakirodalmi áttekintés" [Neuropsychological impairments in adult attention deficit hyperactivity disorder: A literature review]. *Psychiatria Hungarica* (in Hungarian). **23** (5): 324–335. PMID 19129549.
18. ^ a b Ginsberg Y, Quintero J, Anand E, Casillas M, Upadhyaya HP (2014). "Underdiagnosis of attention-deficit/hyperactivity disorder in adult patients: a review of the literature". *Prim Care Companion CNS Disord*. **16** (3). doi:10.4088/PCC.13r01600. PMC 4195639. PMID 25317367. "Reports indicate that ADHD affects 2.5%–5% of adults in the general population,[5–8] compared with 5%–7% of children.[9,10] ... However, fewer than 20% of adults with ADHD are currently diagnosed and/or treated by psychiatrists.[7,15,16]"
19. ^ a b c d e f g h i j k l m National Collaborating Centre for Mental Health (2009). *Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in Children, Young People and Adults*. British Psychological Society. pp. 19–27, 38, 130, 133, 317. ISBN 9781854334718.
20. ^ a b "Canadian ADHD Practice Guidelines" (PDF). *Canadian ADHD Alliance*. Retrieved 4 February 2011.
21. ^ a b "Attention-Deficit / Hyperactivity Disorder (ADHD): Recommendations". Centers for Disease Control and Prevention. 24 June 2015. Retrieved 13 July 2015.
22. ^ Huang, YS; Tsai, MH (July 2011). "Long-term outcomes with medications for attention-deficit hyperactivity disorder: Current status of knowledge". *CNS Drugs*. **25** (7): 539–554. doi:10.2165/11589380-000000000-00000. PMID 21699268.
23. ^ Arnold, LE; Hodgkins, P; Caci, H; Kahle, J; et al. (February 2015). "Effect of treatment modality on long-term outcomes in attention-deficit/hyperactivity disorder: A systematic review". *PLoS ONE*. **10** (2): e0116407. doi:10.1371/journal.pone.0116407. PMC 4340791. PMID 25714373.
24. ^ a b Parker J, Wales G, Chalhoub N, Harpin V (September 2013). "The long-term outcomes of interventions for the management of attention-deficit hyperactivity disorder in children and adolescents: a systematic review of randomized controlled trials". *Psychol. Res. Behav. Manag*. **6**: 87–99. doi:10.2147/PRBM.S49114. PMC 3785407. PMID 24082796. "Results suggest there is moderate-to-high-level evidence that combined pharmacological and behavioral interventions, and pharmacological interventions alone can be effective in managing the core ADHD symptoms and academic performance at 14 months. However, the effect size may decrease beyond this period. ... Only one paper examining outcomes beyond 36 months met the review criteria. ... There is high level evidence suggesting that pharmacological treatment can have a major beneficial effect on the core symptoms of ADHD (hyperactivity, inattention, and impulsivity) in approximately 80% of cases compared with placebo controls, in the short term.22"
25. ^ a b c d e Gentile JP, Atiq R, Gillig PM (August 2006). "Adult ADHD: Diagnosis, Differential Diagnosis, and Medication Management". *Psychiatry (Edgmont)*. **3** (8): 25–30. PMC 2957278. PMID 20963192.
26. ^ Lange, KW; Reichl, S; Lange, KM; Tucha, L; et al. (December 2010). "The history of attention deficit hyperactivity disorder". *ADHD Attention Deficit and Hyperactivity Disorders*. **2** (4): 241–55. doi:10.1007/s12402-010-0045-8. PMC 3000907. PMID 21258430.
27. ^ a b c Parrillo VN (2008). *Encyclopedia of Social Problems*. SAGE. p. 63. ISBN 9781412941655. Retrieved 2 May 2009.
28. ^ a b c Mayes R, Bagwell C, Erkulwater J (2008). "ADHD and the rise in stimulant use among children". *Harv Rev Psychiatry*. **16** (3): 151–166. doi:10.1080/10673220802167782. PMID 18569037.
29. ^ Sim MG, Hulse G, Khong E (August 2004). "When the child with ADHD grows up" (PDF). *Aust Fam Physician*. **33** (8): 615–618. PMID 15373378. Retrieved 8 November 2014.
30. ^ a b Silver LB (2004). *Attention-deficit/hyperactivity disorder* (3rd ed.). American Psychiatric Publishing. pp. 4–7. ISBN 9781585621316.
31. ^ a b Schonwald A, Lechner E (April 2006). "Attention deficit/hyperactivity disorder: complexities and controversies". *Curr. Opin. Pediatr*. **18** (2): 189–195. doi:10.1097/01.mop.0000193302.70882.70. PMID 16601502.
32. ^ Weiss, Lawrence G. (2005). *WISC-IV clinical use and interpretation scientist-practitioner perspectives* (1st ed.). Amsterdam: Elsevier Academic Press. p. 237. ISBN 9780125649315.
33. ^ "ADHD: The Diagnostic Criteria". PBS. Frontline. Retrieved 5 March 2016.
34. ^ a b Dobie C (2012). "Diagnosis and management of attention deficit hyperactivity disorder in primary care for school-age children and adolescents". Institute for Clinical Systems Improvement: 79.
35. ^ a b CDC (6 Jan 2016), *Facts About ADHD*, Centers for Disease Control and Prevention, retrieved 20 Mar 2016
a b

36. ^ Ramsay JR (2007). *Cognitive behavioral therapy for adult ADHD*. Routledge. pp. 4, 25–26. ISBN 0415955017.
37. ^ [a] [b] National Institute of Mental Health (2008). "Attention Deficit Hyperactivity Disorder (ADHD)". National Institutes of Health.
38. ^ Coleman WL (August 2008). "Social competence and friendship formation in adolescents with attention-deficit/hyperactivity disorder". *Adolesc Med State Art Rev*. **19** (2): 278–99, x. PMID 18822833.
39. ^ "ADHD Anger Management Directory". Webmd.com. Retrieved 17 January 2014.
40. ^ Racine MB, Majnemer A, Shevell M, Snider L (April 2008). "Handwriting performance in children with attention deficit hyperactivity disorder (ADHD)". *J. Child Neurol*. **23** (4): 399–406. doi:10.1177/0883073807309244. PMID 18401033.
41. ^ [a] [b] [c] "F90 Hyperkinetic disorders", *International Statistical Classification of Diseases and Related Health Problems 10th Revision*, World Health Organisation, 2010, retrieved 2 November 2014
42. ^ Bellani M, Moretti A, Perlini C, Brambilla P (December 2011). "Language disturbances in ADHD". *Epidemiol Psychiatr Sci*. **20** (4): 311–315. doi:10.1017/S2045796011000527. PMID 22201208.
43. ^ [a] [b] Bailey, Eileen. "ADHD and Learning Disabilities: How can you help your child cope with ADHD and subsequent Learning Difficulties? There is a way.". Remedy Health Media, LLC. Retrieved 15 November 2013.
44. ^ McBurnett, K; Pfiffner, LJ (November 2009). "Treatment of aggressive ADHD in children and adolescents: Conceptualization and treatment of comorbid behavior disorders". *Postgrad Med*. **121** (6): 158–165. doi:10.3810/pgm.2009.11.2084. PMID 19940426.
45. ^ [a] [b] [c] Krull, KR (5 December 2007). "Evaluation and diagnosis of attention deficit hyperactivity disorder in children". *Uptodate*. Wolters Kluwer Health. Retrieved 12 September 2008. (subscription required (help)).
46. ^ Hofvander B, Ossowski D, Lundström S, Anckarsäter H (2009). "Continuity of aggressive antisocial behavior from childhood to adulthood: The question of phenotype definition". *Int J Law Psychiatry*. **32** (4): 224–234. doi:10.1016/j.ijlp.2009.04.004. PMID 19428109.
47. ^ Rubia K (June 2011). "'Cool' inferior frontostriatal dysfunction in attention-deficit/hyperactivity disorder versus 'hot' ventromedial orbitofrontal-limbic dysfunction in conduct disorder: a review". *Biol. Psychiatry*. **69** (12): e69–87. doi:10.1016/j.biopsych.2010.09.023. PMID 21094938.
48. ^ [a] [b] [c] Wilens TE, Spencer TJ (September 2010). "Understanding attention-deficit/hyperactivity disorder from childhood to adulthood". *Postgrad Med*. **122** (5): 97–109. doi:10.3810/pgm.2010.09.2206. PMC 3724232. PMID 20861593.
49. ^ Baud P, Perroud N, Aubry JM (June 2011). "[Bipolar disorder and attention deficit/hyperactivity disorder in adults: differential diagnosis or comorbidity]". *Rev Med Suisse* (in French). **7** (297): 1219–1222. PMID 21717696.
50. ^ Wilens TE, Morrison NR (July 2011). "The intersection of attention-deficit/hyperactivity disorder and substance abuse". *Curr Opin Psychiatry*. **24** (4): 280–285. doi:10.1097/YCO.0b013e328345c956. PMC 3435098. PMID 21483267.
51. ^ Merino-Andreu M (March 2011). "Trastorno por déficit de atención/hiperactividad y síndrome de piernas inquietas en niños" [Attention deficit hyperactivity disorder and restless legs syndrome in children]. *Rev Neurol* (in Spanish). 52 Suppl 1: S85–95. PMID 21365608.
52. ^ Picchietti MA, Picchietti DL (August 2010). "Advances in pediatric restless legs syndrome: Iron, genetics, diagnosis and treatment". *Sleep Med*. **11** (7): 643–651. doi:10.1016/j.sleep.2009.11.014. PMID 20620105.
53. ^ Karroum E, Konofal E, Arnulf I (2008). "Restless-legs syndrome". *Rev. Neurol. (Paris)* (in French). **164** (8–9): 701–721. doi:10.1016/j.neurol.2008.06.006. PMID 18656214.
54. ^ Corkum P, Davidson F, Macpherson M (June 2011). "A framework for the assessment and treatment of sleep problems in children with attention-deficit/hyperactivity disorder". *Pediatr. Clin. North Am*. **58** (3): 667–683. doi:10.1016/j.pcl.2011.03.004. PMID 21600348.
55. ^ Tsai MH, Huang YS (May 2010). "Attention-deficit/hyperactivity disorder and sleep disorders in children". *Med. Clin. North Am*. **94** (3): 615–632. doi:10.1016/j.mcna.2010.03.008. PMID 20451036.
56. ^ [a] [b] [c] [d] [e] [f] Brown TE (October 2008). "ADD/ADHD and Impaired Executive Function in Clinical Practice". *Curr Psychiatry Rep*. **10** (5): 407–411. doi:10.1007/s11920-008-0065-7. PMID 18803914.
57. ^ Bendz LM, Scates AC (January 2010). "Melatonin treatment for insomnia in pediatric patients with attention-deficit/hyperactivity disorder". *Annals of Pharmacotherapy*. **44** (1): 185–191. doi:10.1345/aph.1M365. PMID 20028959.
58. ^ Shreeram S, He JP, Kalaydjian A, Brothers S, Merikangas KR (January 2009). "Prevalence of enuresis and its association with attention-deficit/hyperactivity disorder among United States children: results from a nationally representative study". *J Am Acad Child Adolesc Psychiatry*. **48** (1): 35–41. doi:10.1097/CHI.0b013e318190045c. PMC 2794242. PMID 19096296.
59. ^ Instanes JT, Klungsøyr K, Halmøy A, Fasmer OB, Haavik J (2016). "Adult ADHD and Comorbid Somatic Disease: A Systematic Literature Review.". *J Atten Disord* (Systematic Review). doi:10.1177/1087054716669589. PMID 27664125.
60. ^ [a] [b] [c] Ertürk, E; Wouters, S; Imeraj, L; Lampo, A (29 January 2016). "Association of ADHD and Celiac Disease: What Is the Evidence? A Systematic Review of the Literature.". *Journal of Attention Disorders* (Review). doi:10.1177/1087054715611493. PMID 26825336. "Up till now, there is no conclusive evidence for a relationship between ADHD and CD. Therefore, it is not advised to perform routine screening of CD when assessing ADHD (and vice versa) or to implement GFD as a standard treatment in ADHD. Nevertheless, the possibility of untreated CD predisposing to ADHD-like behavior should be kept in mind. ... It is possible that in untreated patients with CD, neurologic symptoms such as chronic fatigue, inattention, pain, and headache could predispose patients to ADHD-like behavior (mainly symptoms of inattentive type), which may be alleviated after GFD treatment. *(CD: celiac disease; GFD: gluten-free diet)*"
61. ^ [a] [b] Frazier, TW; Demaree, HA; Youngstrom, EA (July 2004). "Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder.". *Neuropsychology*. **18** (3): 543–55. doi:10.1037/0894-4105.18.3.543. PMID 15291732.

62. ^ Mackenzie, GB; Wonders, E (2016). "Rethinking Intelligence Quotient Exclusion Criteria Practices in the Study of Attention Deficit Hyperactivity Disorder.". *Frontiers in psychology*. **7**: 794. doi:10.3389/fpsyg.2016.00794. PMC 4886698. PMID 27303350.
63. ^ [a] [b] Millichap, J. Gordon (2010). "Chapter 2: Causative Factors". *Attention Deficit Hyperactivity Disorder Handbook: A Physician's Guide to ADHD* (2nd ed.). New York, NY: Springer Science. p. 26. doi:10.1007/978-104419-1397-5. ISBN 978-1-4419-1396-8. LCCN 2009938108.
64. ^ Thapar A, Cooper M, Eyre O, Langley K (January 2013). "What have we learnt about the causes of ADHD?". *J Child Psychol Psychiatry*. **54** (1): 3–16. doi:10.1111/j.1469-7610.2012.02611.x. PMC 3572580. PMID 22963644.
65. ^ Neale, BM; Medland, SE; Ripke, S; et al. (September 2010). "Meta-analysis of genome-wide association studies of attention-deficit/hyperactivity disorder". *J Am Acad Child Adolesc Psychiatry*. **49** (9): 884–897. doi:10.1016/j.jaac.2010.06.008. PMC 2928252. PMID 20732625.
66. ^ Burt SA (July 2009). "Rethinking environmental contributions to child and adolescent psychopathology: a meta-analysis of shared environmental influences". *Psychol Bull*. **135** (4): 608–637. doi:10.1037/a0015702. PMID 19586164.
67. ^ Nolen-Hoeksema S (2013). *Abnormal Psychology* (Sixth ed.). p. 267. ISBN 9780078035388.
68. ^ Franke B, Faraone SV, Asherson P, Buitelaar J, Bau CH, Ramos-Quiroga JA, Mick E, Grevet EH, Johansson S, Haavik J, Lesch KP, Cormand B, Reif A (October 2012). "The genetics of attention deficit/hyperactivity disorder in adults, a review". *Mol. Psychiatry*. **17** (10): 960–987. doi:10.1038/mp.2011.138. PMC 3449233. PMID 22105624.
69. ^ [a] [b] Gizer IR, Ficks C, Waldman ID (July 2009). "Candidate gene studies of ADHD: a meta-analytic review". *Hum. Genet*. **126** (1): 51–90. doi:10.1007/s00439-009-0694-x. PMID 19506906.
70. ^ [a] [b] [c] Kebir O, Tabbane K, Sengupta S, Joober R (March 2009). "Candidate genes and neuropsychological phenotypes in children with ADHD: review of association studies". *J Psychiatry Neurosci*. **34** (2): 88–101. PMC 2647566. PMID 19270759.
71. ^ [a] [b] Berry, MD (January 2007). "The potential of trace amines and their receptors for treating neurological and psychiatric diseases". *Reviews on Recent Clinical Trials*. **2** (1): 3–19. doi:10.2174/157488707779318107. PMID 18473983. "Although there is little direct evidence, changes in trace amines, in particular PE, have been identified as a possible factor for the onset of attention deficit/hyperactivity disorder (ADHD). … Further, amphetamines, which have clinical utility in ADHD, are good ligands at trace amine receptors. Of possible relevance in this aspect is modafanil, which has shown beneficial effects in ADHD patients and has been reported to enhance the activity of PE at TAAR1. Conversely, methylphenidate, …showed poor efficacy at the TAAR1 receptor. In this respect it is worth noting that the enhancement of functioning at TAAR1 seen with modafanil was not a result of a direct interaction with TAAR1."
72. ^ Sotnikova TD, Caron MG, Gainetdinov RR (August 2009). "Trace amine-associated receptors as emerging therapeutic targets". *Mol. Pharmacol*. **76** (2): 229–235. doi:10.1124/mol.109.055970. PMC 2713119. PMID 19389919.
73. ^ Arcos-Burgos M, Muenke M (November 2010). "Toward a better understanding of ADHD: LPHN3 gene variants and the susceptibility to develop ADHD". *Atten Defic Hyperact Disord*. **2** (3): 139–147. doi:10.1007/s12402-010-0030-2. PMC 3280610. PMID 21432600.
74. ^ Nikolaidis A, Gray JR (Jun 2010). "ADHD and the DRD4 exon III 7-repeat polymorphism: an international meta-analysis". *Social Cognitive and Affective Neuroscience*. **5** (2-3): 188–193. doi:10.1093/scan/nsp049. PMC 2894686. PMID 20019071.
75. ^ [a] [b] [c] Glover V (April 2011). "Annual Research Review: Prenatal stress and the origins of psychopathology: an evolutionary perspective". *J Child Psychol Psychiatry*. **52** (4): 356–67. doi:10.1111/j.1469-7610.2011.02371.x. PMID 21250994.
76. ^ [a] [b] [c] Williams J, Taylor E (June 2006). "The evolution of hyperactivity, impulsivity and cognitive diversity". *J R Soc Interface*. **3** (8): 399–413. doi:10.1098/rsif.2005.0102. PMC 1578754. PMID 16849269.
77. ^ [a] [b] Cardo E, Nevot A, Redondo M, et al. (March 2010). "Trastorno por déficit de atención/hiperactividad: ¿un patrón evolutivo?" [Attention deficit disorder and hyperactivity: a pattern of evolution?]. *Rev Neurol* (in Spanish). 50 Suppl 3: S143–7. PMID 20200842.
78. ^ Adriani, Walter; Zoratto, Francesca; Laviola, Giovanni (13 January 2012). "Brain Processes in Discounting: Consequences of Adolescent Methylphenidate Exposure". In Stanford, Clare; Tannock, Rosemary. *Behavioral neuroscience of attention deficit hyperactivity disorder and its treatment*. Current Topics in Behavioral Neurosciences. Volume 9. New York: Springer. pp. 132–134. ISBN 978-3-642-24611-1.
79. ^ Ekstein, Sivan; Glick, Benjamin; Weill, Michal; Kay, Barrie; Berger, Itai (2011-10-01). "Down Syndrome and Attention-Deficit/Hyperactivity Disorder (ADHD)". *Journal of Child Neurology*. **26** (10): 1290–1295. doi:10.1177/0883073811405201. ISSN 0883-0738. PMID 21628698.
80. ^ CDC (16 Mar 2016), *Attention-Deficit / Hyperactivity Disorder (ADHD)*, Centers for Disease Control and Prevention, retrieved 17 Apr 2016
81. ^ Burger PH, Goecke TW, Fasching PA, Moll G, Heinrich H, Beckmann MW, Kornhuber J (September 2011). "[How does maternal alcohol consumption during pregnancy affect the development of attention deficit/hyperactivity syndrome in the child]". *Fortschr Neurol Psychiatr* (Review) (in German). **79** (9): 500–506. doi:10.1055/s-0031-1273360. PMID 21739408.
82. ^ Eubig PA, Aguiar A, Schantz SL (December 2010). "Lead and PCBs as risk factors for attention deficit/hyperactivity disorder". *Environ. Health Perspect.* (Review. Research Support, N.I.H., Extramural. Research Support, U.S. Gov't, Non-P.H.S.). **118** (12): 1654–1667. doi:10.1289/ehp.0901852. PMC 3002184. PMID 20829149.
83. ^ de Cock M, Maas YG, van de Bor M (August 2012). "Does perinatal exposure to endocrine disruptors induce autism spectrum and attention deficit hyperactivity disorders? Review". *Acta Paediatr.* (Review. Research Support, Non-U.S. Gov't). **101** (8): 811–818. doi:10.1111/j.1651-2227.2012.02693.x. PMID 22458970.
84. ^ Abbott LC, Winzer-Serhan UH (April 2012). "Smoking during pregnancy: lessons learned from epidemiological studies and

experimental studies using animal models". *Crit. Rev. Toxicol.* (Review). **42** (4): 279–303. doi:10.3109/10408444.2012.658506. PMID 22394313.

85. ^ Thapar, A.; Cooper, M.; Jefferies, R.; Stergiakouli, E. (March 2012). "What causes attention deficit hyperactivity disorder? ". *Arch Dis Child* (Review. Research Support, Non-U.S. Gov't). **97** (3): 260–5. doi:10.1136/archdischild-2011-300482. PMID 21903599.
86. ^ Millichap JG (February 2008). "Etiologic classification of attention-deficit/hyperactivity disorder". *Pediatrics* (Review). **121** (2): e358–65. doi:10.1542/peds.2007-1332. PMID 18245408.
87. ^ Eme, R (April 2012). "ADHD: an integration with pediatric traumatic brain injury". *Expert Rev Neurother* (Review). **12** (4): 475–83. doi:10.1586/ern.12.15. PMID 22449218.
88. ^ *a b c d e f* Mayes R, Bagwell C, Erkulwater JL (2009). *Medicating Children: ADHD and Pediatric Mental Health* (illustrated ed.). Harvard University Press. pp. 4–24. ISBN 9780674031630.
89. ^ *a b* Millichap, JG; Yee, MM (February 2012). "The diet factor in attention-deficit/hyperactivity disorder". *Pediatrics*. **129** (2): 330–7. doi:10.1542/peds.2011-2199. PMID 22232312.
90. ^ *a b c d* Sonuga-Barke EJ, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, Stevenson J, Danckaerts M, van der Oord S, Döpfner M, Dittmann RW, Simonoff E, Zuddas A, Banaschewski T, Buitelaar J, Coghill D, Hollis C, Konofal E, Lecendreux M, Wong IC, Sergeant J (March 2013). "Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments". *Am J Psychiatry*. **170** (3): 275–289. doi:10.1176/appi.ajp.2012.12070991. PMID 23360949. "Free fatty acid supplementation and artificial food color exclusions appear to have beneficial effects on ADHD symptoms, although the effect of the former are small and those of the latter may be limited to ADHD patients with food sensitivities..."
91. ^ Tomaska LD and Brooke-Taylor, S. *Food Additives – General* pp. 449–454 in Encyclopedia of Food Safety, Vol 2: Hazards and Diseases. Eds, Motarjemi Y et al. Academic Press, 2013. ISBN 9780123786135
92. ^ FDA (March 2011), *Background Document for the Food Advisory Committee: Certified Color Additives in Food and Possible Association with Attention Deficit Hyperactivity Disorder in Children* (PDF), U.S. Food and Drug Administration
93. ^ *a b* Nigg JT, Holton K (Oct 2014). "Restriction and elimination diets in ADHD treatment". *Child Adolesc Psychiatr Clin N Am* (Review). **23** (4): 937–53. doi:10.1016/j.chc.2014.05.010. PMC 4322780. PMID 25220094. "an elimination diet produces a small aggregate effect but may have greater benefit among some children. Very few studies enable proper evaluation of the likelihood of response in children with ADHD who are not already preselected based on prior diet response."
94. ^ "Mental health of children and adolescents" (PDF). 15 January 2005. Archived from the original (PDF) on 24 October 2009. Retrieved 13 October 2011.
95. ^ *a b* Elder TE (September 2010). "The importance of relative standards in ADHD diagnoses: evidence based on exact birth dates". *J Health Econ*. **29** (5): 641–656. doi:10.1016/j.jhealeco.2010.06.003. PMC 2933294. PMID 20638739.
96. ^ Parritz, R (2013). *Disorders of Childhood: Development and Psychopathology*. Cengage Learning. p. 151. ISBN 9781285096063.
97. ^ Parens E, Johnston J (2009). "Facts, values, and Attention-Deficit Hyperactivity Disorder (ADHD): an update on the controversies". *Child Adolesc Psychiatry Ment Health*. **3** (1): 1. doi:10.1186/1753-2000-3-1. PMC 2637252. PMID 19152690.
98. ^ Chriss, James J. (2007). *Social control: an introduction*. Cambridge, UK: Polity. p. 230. ISBN 0-7456-3858-9.
99. ^ Szasz, Thomas Stephen (2001). *Pharmacracy: medicine and politics in America*. New York: Praeger. p. 212. ISBN 0-275-97196-1.
100. ^ *a b c d e* Chandler DJ, Waterhouse BD, Gao WJ (May 2014). "New perspectives on catecholaminergic regulation of executive circuits: evidence for independent modulation of prefrontal functions by midbrain dopaminergic and noradrenergic neurons". *Front. Neural Circuits*. **8**: 53. doi:10.3389/fncir.2014.00053. PMC 4033238. PMID 24904299.
101. ^ *a b c d e f g h i j k* Malenka RC, Nestler EJ, Hyman SE (2009). "Chapters 10 and 13". In Sydor A, Brown RY. *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience* (2nd ed.). New York: McGraw-Hill Medical. pp. 266, 315, 318–323. ISBN 9780071481274. "Early results with structural MRI show thinning of the cerebral cortex in ADHD subjects compared with age-matched controls in prefrontal cortex and posterior parietal cortex, areas involved in working memory and attention."
102. ^ *a b c d e f g h* Malenka RC, Nestler EJ, Hyman SE (2009). "Chapter 6: Widely Projecting Systems: Monoamines, Acetylcholine, and Orexin". In Sydor A, Brown RY. *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience* (2nd ed.). New York: McGraw-Hill Medical. pp. 148, 154–157. ISBN 9780071481274. "DA has multiple actions in the prefrontal cortex. It promotes the "cognitive control" of behavior: the selection and successful monitoring of behavior to facilitate attainment of chosen goals. Aspects of cognitive control in which DA plays a role include working memory, the ability to hold information "on line" in order to guide actions, suppression of prepotent behaviors that compete with goal-directed actions, and control of attention and thus the ability to overcome distractions. Cognitive control is impaired in several disorders, including attention deficit hyperactivity disorder. ... Noradrenergic projections from the LC thus interact with dopaminergic projections from the VTA to regulate cognitive control. ... it has not been shown that 5HT makes a therapeutic contribution to treatment of ADHD."
*NOTE: DA: dopamine, LC: locus coeruleus, VTA: ventral tegmental area, 5HT: serotonin (5-hydroxytryptamine)*
103. ^ *a b c* Castellanos FX, Proal E (January 2012). "Large-scale brain systems in ADHD: beyond the prefrontal-striatal model". *Trends Cogn. Sci. (Regul. Ed.)*. **16** (1): 17–26. doi:10.1016/j.tics.2011.11.007. PMC 3272832. PMID 22169776. "Recent conceptualizations of ADHD have taken seriously the distributed nature of neuronal processing [10,11,35,36]. Most of the candidate networks have focused on prefrontal-striatal-cerebellar circuits, although other posterior regions are also being proposed [10]."

104. ^ [a] [b] [c] Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, Castellanos FX (October 2012). "Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies". *Am J Psychiatry*. **169** (10): 1038–1055. doi:10.1176/appi.ajp.2012.11101521. PMC 3879048. PMID 22983386.
105. ^ Krain AL, Castellanos FX (August 2006). "Brain development and ADHD". *Clin Psychol Rev*. **26** (4): 433–444. doi:10.1016/j.cpr.2006.01.005. PMID 16480802.
106. ^ Fusar-Poli P, Rubia K, Rossi G, Sartori G, Balottin U (March 2012). "Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? A meta-analysis". *Am J Psychiatry*. **169** (3): 264–72. doi:10.1176/appi.ajp.2011.11060940. PMID 22294258.
107. ^ [a] [b] [c] Bidwell LC, McClernon FJ, Kollins SH (August 2011). "Cognitive enhancers for the treatment of ADHD". *Pharmacol. Biochem. Behav.* **99** (2): 262–274. doi:10.1016/j.pbb.2011.05.002. PMC 3353150. PMID 21596055.
108. ^ Cortese S (September 2012). "The neurobiology and genetics of Attention-Deficit/Hyperactivity Disorder (ADHD): what every clinician should know". *Eur. J. Paediatr. Neurol.* **16** (5): 422–433. doi:10.1016/j.ejpn.2012.01.009. PMID 22306277.
109. ^ Lesch KP, Merker S, Reif A, Novak M (June 2013). "Dances with black widow spiders: dysregulation of glutamate signalling enters centre stage in ADHD". *Eur Neuropsychopharmacol*. **23** (6): 479–491. doi:10.1016/j.euroneuro.2012.07.013. PMID 22939004.
110. ^ [a] [b] Diamond A (2013). "Executive functions". *Annu. Rev. Psychol.* **64**: 135–168. doi:10.1146/annurev-psych-113011-143750. PMC 4084861. PMID 23020641. "EFs and prefrontal cortex are the first to suffer, and suffer disproportionately, if something is not right in your life. They suffer first, and most, if you are stressed (Arnsten 1998, Liston et al. 2009, Oaten & Cheng 2005), sad (Hirt et al. 2008, von Hecker & Meiser 2005), lonely (Baumeister et al. 2002, Cacioppo & Patrick 2008, Campbell et al. 2006, Tun et al. 2012), sleep deprived (Barnes et al. 2012, Huang et al. 2007), or not physically fit (Best 2010, Chaddock et al. 2011, Hillman et al. 2008). Any of these can cause you to appear to have a disorder of EFs, such as ADHD, when you do not."
111. ^ Skodzik T, Holling H, Pedersen A (November 2013). "Long-Term Memory Performance in Adult ADHD: A Meta-Analysis". *J. Atten. Disord*. doi:10.1177/1087054713510561. PMID 24232170.
112. ^ Lambek R, Tannock R, Dalsgaard S, Trillingsgaard A, Damm D, Thomsen PH (August 2010). "Validating neuropsychological subtypes of ADHD: how do children with and without an executive function deficit differ?". *J Child Psychol Psychiatry*. **51** (8): 895–904. doi:10.1111/j.1469-7610.2010.02248.x. PMID 20406332.
113. ^ Nigg JT, Willcutt EG, Doyle AE, Sonuga-Barke EJ (June 2005). "Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes?". *Biol. Psychiatry*. **57** (11): 1224–1230. doi:10.1016/j.biopsych.2004.08.025. PMID 15949992.
114. ^ [a] [b] [c] [d] Modesto-Lowe V, Chaplin M, Soovajian V, Meyer A (2013). "Are motivation deficits underestimated in patients with ADHD? A review of the literature". *Postgrad Med*. **125** (4): 47–52. doi:10.3810/pgm.2013.07.2677. PMID 23933893. "Behavioral studies show altered processing of reinforcement and incentives in children with ADHD. These children respond more impulsively to rewards and choose small, immediate rewards over larger, delayed incentives. Interestingly, a high intensity of reinforcement is effective in improving task performance in children with ADHD. Pharmacotherapy may also improve task persistence in these children. ... Previous studies suggest that a clinical approach using interventions to improve motivational processes in patients with ADHD may improve outcomes as children with ADHD transition into adolescence and adulthood."
115. ^ "MerckMedicus Modules: ADHD –Pathophysiology". August 2002. Archived from the original on 1 May 2010.
116. ^ Wiener JM, Dulcan MK (2004). *Textbook Of Child and Adolescent Psychiatry* (illustrated ed.). American Psychiatric Publishing. ISBN 9781585620579. Retrieved 2 November 2014.
117. ^ Wolraich M, Brown L, Brown RT, DuPaul G, Earls M, Feldman HM, Ganiats TG, Kaplanek B, Meyer B, Perrin J, Pierce K, Reiff M, Stein MT, Visser S (November 2011). "ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents". *Pediatrics*. **128** (5): 1007–1022. doi:10.1542/peds.2011-2654. PMID 22003063.
118. ^ Sand T, Breivik N, Herigstad A (February 2013). "[Assessment of ADHD with EEG]". *Tidsskr. Nor. Laegeforen.* (in Norwegian). **133** (3): 312–316. doi:10.4045/tidsskr.12.0224. PMID 23381169.
119. ^ Millichap JG, Millichap JJ, Stack CV (July 2011). "Utility of the electroencephalogram in attention deficit hyperactivity disorder". *Clin EEG Neurosci*. **42** (3): 180–184. doi:10.1177/155005941104200307. PMID 21870470.
120. ^ "FDA permits marketing of first brain wave test to help assess children and teens for ADHD". United States Food and Drug Administration. 15 July 2013.
121. ^ Smith, B.H.; Barkley, R.A.; Shapiro, C.J. (2007). "Attention-Deficit/Hyperactivity Disorder". In Mash, Eric J.; Barkley, Russell A. *Assessment of Childhood Disorders* (4th ed.). New York, NY: Guilford Press. pp. 53–131. ISBN 978-1593854935.
122. ^ [a] [b] Steinau S (2013). "Diagnostic Criteria in Attention Deficit Hyperactivity Disorder – Changes in DSM 5". *Front Psychiatry*. **4**: 49. doi:10.3389/fpsyt.2013.00049. PMC 3667245. PMID 23755024.
123. ^ Berger I (September 2011). "Diagnosis of attention deficit hyperactivity disorder: much ado about something" (PDF). *Isr. Med. Assoc. J.* **13** (9): 571–574. PMID 21991721.
124. ^ ICD-11 Beta Draft. who.int
125. ^ Culpepper L, Mattingly G (2010). "Challenges in identifying and managing attention-deficit/hyperactivity disorder in adults in the primary care setting: a review of the literature". *Prim Care Companion J Clin Psychiatry*. **12** (6): PCC.10r00951. doi:10.4088/PCC.10r00951pur. PMC 3067998. PMID 21494335.
126. ^ Consumer Reports; Drug Effectiveness Review Project (March 2012). "Evaluating Prescription Drugs Used to Treat: Attention Deficit Hyperactivity Disorder (ADHD) Comparing Effectiveness, Safety, and Price" (PDF). *Best Buy Drugs*. Consumer Reports: 2. Retrieved 12 April 2013.

127. ^ Owens JA (October 2008). "Sleep disorders and attention-deficit/hyperactivity disorder". *Curr Psychiatry Rep*. **10** (5): 439–444. doi:10.1007/s11920-008-0070-x. PMID 18803919.
128. ^ Walters AS, Silvestri R, Zucconi M, Chandrashekariah R, Konofal E (December 2008). "Review of the possible relationship and hypothetical links between attention deficit hyperactivity disorder (ADHD) and the simple sleep related movement disorders, parasomnias, hypersomnias, and circadian rhythm disorders". *J Clin Sleep Med*. **4** (6): 591–600. PMC 2603539. PMID 19110891.
129. ^ *a b* Lal C, Strange C, Bachman D (June 2012). "Neurocognitive impairment in obstructive sleep apnea". *Chest*. **141** (6): 1601–1610. doi:10.1378/chest.11-2214. PMID 22670023.
130. ^ *a b* Irsfeld, M; Spadafore, M; Prüß, BM (September 2013). "β-phenylethylamine, a small molecule with a large impact". *Webmedcentral*. **4** (9). PMC 3904499. PMID 24482732. "While diagnosis of ADHD is usually done by analysis of the symptoms (American Psychiatric Association, 2000), PEA was recently described as a biomarker for ADHD"
131. ^ *a b c d* Scassellati C, Bonvicini C, Faraone SV, Gennarelli M (October 2012). "Biomarkers and attention-deficit/hyperactivity disorder: a systematic review and meta-analyses". *J. Am. Acad. Child Adolesc. Psychiatry*. **51** (10): 1003–1019.e20. doi:10.1016/j.jaac.2012.08.015. PMID 23021477.
132. ^ Shaw M, Hodgkins P, Caci H, Young S, Kahle J, Woods AG, Arnold LE (4 September 2012). "A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment". *BMC Med*. **10**: 99. doi:10.1186/1741-7015-10-99. PMC 3520745. PMID 22947230.
133. ^ Fabiano GA, Pelham WE, Coles EK, Gnagy EM, Chronis-Tuscano A, O'Connor BC (March 2009). "A meta-analysis of behavioral treatments for attention-deficit/hyperactivity disorder". *Clin Psychol Rev*. **29** (2): 129–140. doi:10.1016/j.cpr.2008.11.001. PMID 19131150.
134. ^ Kratochvil CJ, Vaughan BS, Barker A, Corr L, Wheeler A, Madaan V (March 2009). "Review of pediatric attention deficit/hyperactivity disorder for the general psychiatrist". *Psychiatr. Clin. North Am*. **32** (1): 39–56. doi:10.1016/j.psc.2008.10.001. PMID 19248915.
135. ^ Evans, SW; Owens, JS; Bunford, N (2014). "Evidence-based psychosocial treatments for children and adolescents with attention-deficit/hyperactivity disorder.". *Journal of Clinical Child and Adolescent Psychology*. **43** (4): 527–51. doi:10.1080/15374416.2013.850700. PMID 24245813.
136. ^ Arns M, de Ridder S, Strehl U, Breteler M, Coenen A (July 2009). "Efficacy of neurofeedback treatment in ADHD: the effects on inattention, impulsivity and hyperactivity: a meta-analysis". *Clin EEG Neurosci*. **40** (3): 180–189. doi:10.1177/155005940904000311. PMID 19715181.
137. ^ Hodgson, K; Hutchinson, AD; Denson, L (May 2014). "Nonpharmacological treatments for ADHD: a meta-analytic review.". *Journal of Attention Disorders*. **18** (4): 275–82. doi:10.1177/1087054712444732. PMID 22647288.
138. ^ Pliszka S (July 2007). "Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder". *J Am Acad Child Adolesc Psychiatry*. **46** (7): 894–921. doi:10.1097/chi.0b013e318054e724. PMID 17581453.
139. ^ Antshel, KM (January 2015). "Psychosocial interventions in attention-deficit/hyperactivity disorder: update.". *Child and adolescent psychiatric clinics of North America*. **24** (1): 79–97. doi:10.1016/j.chc.2014.08.002. PMID 25455577.
140. ^ Bjornstad G, Montgomery P (2005). Bjornstad GJ, ed. "Family therapy for attention-deficit disorder or attention-deficit/hyperactivity disorder in children and adolescents". *Cochrane Database Syst Rev* (2): CD005042. doi:10.1002/14651858.CD005042.pub2. PMID 15846741.
141. ^ Turkington, C; Harris, J (2009). *The Encyclopedia of the Brain and Brain Disorders*. Infobase Publishing. p. 47. ISBN 9781438127033.
142. ^ Mikami AY (June 2010). "The importance of friendship for youth with attention-deficit/hyperactivity disorder". *Clin Child Fam Psychol Rev*. **13** (2): 181–98. doi:10.1007/s10567-010-0067-y. PMC 2921569. PMID 20490677.
143. ^ *a b c d e* Den Heijer AE, Groen Y, Tucha L, Fuermaier AB, Koerts J, Lange KW, Thome J, Tucha O (July 2016). "Sweat it out? The effects of physical exercise on cognition and behavior in children and adults with ADHD: a systematic literature review". *J. Neural. Transm. (Vienna)*. doi:10.1007/s00702-016-1593-7. PMID 27400928. "Beneficial chronic effects of cardio exercise were found on various functions as well, including executive functions, attention and behavior."
144. ^ *a b* Kamp CF, Sperlich B, Holmberg HC (July 2014). "Exercise reduces the symptoms of attention-deficit/hyperactivity disorder and improves social behaviour, motor skills, strength and neuropsychological parameters". *Acta Paediatr*. **103** (7): 709–714. doi:10.1111/apa.12628. PMID 24612421. Retrieved 14 March 2015. "We may conclude that all different types of exercise ... attenuate the characteristic symptoms of ADHD and improve social behaviour, motor skills, strength and neuropsychological parameters without any undesirable side effects. Available reports do not reveal which type, intensity, duration and frequency of exercise is most effective"
145. ^ *a b* Rommel AS, Halperin JM, Mill J, Asherson P, Kuntsi J (September 2013). "Protection from genetic diathesis in attention-deficit/hyperactivity disorder: possible complementary roles of exercise". *J. Am. Acad. Child Adolesc. Psychiatry*. **52** (9): 900–910. doi:10.1016/j.jaac.2013.05.018. PMC 4257065. PMID 23972692. "The findings from these studies provide some support for the notion that exercise has the potential to act as a protective factor for ADHD."
146. ^ *a b c* Wigal SB (2009). "Efficacy and safety limitations of attention-deficit hyperactivity disorder pharmacotherapy in children and adults". *CNS Drugs*. 23 Suppl 1: 21–31. doi:10.2165/00023210-200923000-00004. PMID 19621975.
147. ^ Castells X, Ramos-Quiroga JA, Bosch R, Nogueira M, Casas M (2011). Castells X, ed. "Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults". *Cochrane Database Syst. Rev.* (6): CD007813. doi:10.1002/14651858.CD007813.pub2. PMID 21678370.
148. ^ Storebø, OJ; Ramstad, E; Krogh, HB; Nilausen, TD; Skoog, M; Holmskov, M; Rosendal, S; Groth, C; Magnusson, FL; Moreira-Maia, CR; Gillies, D; Buch Rasmussen, K; Gauci, D; Zwi, M; Kirubakaran, R; Forsbøl, B; Simonsen, E; Gluud, C (25 November 2015). "Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD).". *The*

*Cochrane database of systematic reviews*. **11**: CD009885. doi:10.1002/14651858.CD009885.pub2. PMID 26599576.

149. ^ Dalsgaard, Søren; Leckman, James F.; Mortensen, Preben Bo; Nielsen, Helena Skyt; Simonsen, Marianne (2015-08-01). "Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study". *The Lancet. Psychiatry*. **2** (8): 702–709. doi:10.1016/S2215-0366(15)00271-0. ISSN 2215-0374. PMID 26249301.
150. ^ Childress, A. C.; Sallee, F. R. (2012). "Revisiting clonidine: an innovative add-on option for attention-deficit/hyperactivity disorder". *Drugs of Today (Barcelona, Spain: 1998)*. **48** (3): 207–217. doi:10.1358/dot.2012.48.3.1750904. ISSN 1699-3993. PMID 22462040.
151. ^ [a] [b] McDonagh MS, Peterson K, Thakurta S, Low A (December 2011). "Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder". United States Library of Medicine. PMID 22420008.
152. ^ Prasad V, Brogan E, Mulvaney C, Grainge M, Stanton W, Sayal K (April 2013). "How effective are drug treatments for children with ADHD at improving on-task behaviour and academic achievement in the school classroom? A systematic review and meta-analysis". *Eur Child Adolesc Psychiatry*. **22** (4): 203–216. doi:10.1007/s00787-012-0346-x. PMID 23179416.
153. ^ [a] [b] Kiely B, Adesman A (June 2015). "What we do not know about ADHD… yet". *Curr. Opin. Pediatr*. **27** (3): 395–404. doi:10.1097/MOP.0000000000000229. PMID 25888152. "In addition, a consensus has not been reached on the optimal diagnostic criteria for ADHD. Moreover, the benefits and long-term effects of medical and complementary therapies for this disorder continue to be debated. These gaps in knowledge hinder the ability of clinicians to effectively recognize and treat ADHD."
154. ^ Hazell P (July 2011). "The challenges to demonstrating long-term effects of psychostimulant treatment for attention-deficit/hyperactivity disorder". *Current Opinion in Psychiatry*. **24** (4): 286–290. doi:10.1097/YCO.0b013e32834742db. PMID 21519262.
155. ^ Hart H, Radua J, Nakao T, Mataix-Cols D, Rubia K (February 2013). "Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects". *JAMA Psychiatry*. **70** (2): 185–198. doi:10.1001/jamapsychiatry.2013.277. PMID 23247506.
156. ^ Spencer TJ, Brown A, Seidman LJ, Valera EM, Makris N, Lomedico A, Faraone SV, Biederman J (September 2013). "Effect of psychostimulants on brain structure and function in ADHD: a qualitative literature review of magnetic resonance imaging-based neuroimaging studies". *J. Clin. Psychiatry*. **74** (9): 902–917. doi:10.4088/JCP.12r08287. PMC 3801446. PMID 24107764.
157. ^ Frodl T, Skokauskas N (February 2012). "Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects.". *Acta psychiatrica Scand*. **125** (2): 114–126. doi:10.1111/j.1600-0447.2011.01786.x. PMID 22118249. "Basal ganglia regions like the right globus pallidus, the right putamen, and the nucleus caudatus are structurally affected in children with ADHD. These changes and alterations in limbic regions like ACC and amygdala are more pronounced in non-treated populations and seem to diminish over time from child to adulthood. Treatment seems to have positive effects on brain structure."
158. ^ Greenhill LL, Posner K, Vaughan BS, Kratochvil CJ (April 2008). "Attention deficit hyperactivity disorder in preschool children". *Child and Adolescent Psychiatric Clinics of North America*. **17** (2): 347–366, ix. doi:10.1016/j.chc.2007.11.004. PMID 18295150.
159. ^ Stevens, Jonathan R.; Wilens, Timothy E.; Stern, Theodore A. (2013). "Using Stimulants for Attention-Deficit/Hyperactivity Disorder: Clinical Approaches and Challenges". *The Primary Care Companion for CNS Disorders*. **15** (2). doi:10.4088/PCC.12f01472. ISSN 2155-7772. PMC 3733520. PMID 23930227.
160. ^ Young, Joel L. (2010). "Individualizing Treatment for Adult ADHD: An Evidence-Based Guideline". *Medscape*. Retrieved 19 June 2016.
161. ^ Biederman, Joseph (2003). "New-Generation Long-Acting Stimulants for the Treatment of Attention-Deficit/Hyperactivity Disorder". *Medscape*. Retrieved 19 June 2016. "As most treatment guidelines and prescribing information for stimulant medications relate to experience in school-aged children, prescribed doses for older patients are lacking. Emerging evidence for both methylphenidate and Adderall indicate that when weight-corrected daily doses, equipotent with those used in the treatment of younger patients, are used to treat adults with ADHD, these patients show a very robust clinical response consistent with that observed in pediatric studies. These data suggest that older patients may require a more aggressive approach in terms of dosing, based on the same target dosage ranges that have already been established -- for methylphenidate, 1-1.5-2 mg/kg/day, and for D,L-amphetamine, 0.5-0.75-1 mg/kg/day....
In particular, adolescents and adults are vulnerable to underdosing, and are thus at potential risk of failing to receive adequate dosage levels. As with all therapeutic agents, the efficacy and safety of stimulant medications should always guide prescribing behavior: careful dosage titration of the selected stimulant product should help to ensure that each patient with ADHD receives an adequate dose, so that the clinical benefits of therapy can be fully attained."
162. ^ Kessler, S. (1996). "Drug therapy in attention-deficit hyperactivity disorder". *Southern Medical Journal*. **89** (1): 33–38. doi:10.1097/00007611-199601000-00005. ISSN 0038-4348. PMID 8545689.
163. ^ [a] [b] [c] Shoptaw SJ, Kao U, Ling W (January 2009). Shoptaw SJ, Ali R, ed. "Treatment for amphetamine psychosis". *Cochrane Database Syst. Rev.* (1): CD003026. doi:10.1002/14651858.CD003026.pub3. PMID 19160215. "A minority of individuals who use amphetamines develop full-blown psychosis requiring care at emergency departments or psychiatric hospitals. In such cases, symptoms of amphetamine psychosis commonly include paranoid and persecutory delusions as well as auditory and visual hallucinations in the presence of extreme agitation. More common (about 18%) is for frequent amphetamine users to report psychotic symptoms that are sub-clinical and that do not require high-intensity intervention ... About 5–15% of the users who develop an amphetamine psychosis fail to recover completely (Hofmann 1983) ... Findings from one trial indicate use of antipsychotic medications effectively resolves symptoms of acute amphetamine psychosis."
164. ^ "Adderall XR Prescribing Information" (PDF). *United States Food and Drug Administration*. Shire US Inc. December

2013. Retrieved 30 December 2013. "Treatment-emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without prior history of psychotic illness or mania can be caused by stimulants at usual doses. ... In a pooled analysis of multiple short-term, placebo controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients."

165. ^ Mosholder AD, Gelperin K, Hammad TA, Phelan K, Johann-Liang R (February 2009). "Hallucinations and other psychotic symptoms associated with the use of attention-deficit/hyperactivity disorder drugs in children". *Pediatrics*. **123** (2): 611–616. doi:10.1542/peds.2008-0185. PMID 19171629.
166. ^ Kraemer M, Uekermann J, Wiltfang J, Kis B (July 2010). "Methylphenidate-induced psychosis in adult attention-deficit/hyperactivity disorder: report of 3 new cases and review of the literature". *Clin Neuropharmacol*. **33** (4): 204–6. doi:10.1097/WNF.0b013e3181e29174. PMID 20571380.
167. ^ van de Loo-Neus GH, Rommelse N, Buitelaar JK (August 2011). "To stop or not to stop? How long should medication treatment of attention-deficit hyperactivity disorder be extended?". *Eur Neuropsychopharmacol*. **21** (8): 584–599. doi:10.1016/j.euroneuro.2011.03.008. PMID 21530185.
168. ^ Ibrahim, Kinda; Donyai, Parastou (2015). "Drug Holidays From ADHD Medication: International Experience Over the Past Four Decades" (PDF). *Journal of Attention Disorders*. **19** (7): 551–568. doi:10.1177/1087054714548035. ISSN 1557-1246. PMID 25253684.
169. ^ *a b c* Malenka, RC; Nestler, EJ; Hyman, SE (2009). Sydor, A; Brown, RY, eds. *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience* (2nd ed.). New York: McGraw-Hill Medical. pp. 323, 368. ISBN 9780071481274. "supervised use of stimulants at therapeutic doses may decrease risk of experimentation with drugs to self-medicate symptoms. Second, untreated ADHD may lead to school failure, peer rejection, and subsequent association with deviant peer groups that encourage drug misuse. ... amphetamines and methylphenidate are used in low doses to treat attention deficit hyperactivity disorder and in higher doses to treat narcolepsy (Chapter 12). Despite their clinical uses, these drugs are strongly reinforcing, and their long-term use at high doses is linked with potential addiction"
170. ^ Oregon Health & Science University (2009). "Black box warnings of ADHD drugs approved by the US Food and Drug Administration". Portland, Oregon: United States National Library of Medicine. Retrieved 17 January 2014.
171. ^ Ashton H, Gallagher P, Moore B (September 2006). "The adult psychiatrist's dilemma: psychostimulant use in attention deficit/hyperactivity disorder". *J. Psychopharmacol. (Oxford)*. **20** (5): 602–610. doi:10.1177/0269881106061710. PMID 16478756.
172. ^ Nigg JT, Lewis K, Edinger T, Falk M (January 2012). "Meta-analysis of attention-deficit/hyperactivity disorder or attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives". *J Am Acad Child Adolesc Psychiatry*. **51** (1): 86–97. doi:10.1016/j.jaac.2011.10.015. PMID 22176942.
173. ^ Konikowska K, Regulska-Ilow B, Rózańska D (2012). "The influence of components of diet on the symptoms of ADHD in children". *Rocz Panstw Zakl Hig*. **63** (2): 127–134. PMID 22928358.
174. ^ Arnold LE, DiSilvestro RA (2005). "Zinc in attention-deficit/hyperactivity disorder". *Journal of child and adolescent psychopharmacology*. **15** (4): 619–27. doi:10.1089/cap.2005.15.619. PMID 16190793.
175. ^ Bloch, MH; Mulqueen, J (October 2014). "Nutritional supplements for the treatment of ADHD.". *Child and adolescent psychiatric clinics of North America*. **23** (4): 883–97. doi:10.1016/j.chc.2014.05.002. PMID 25220092.
176. ^ Krause J (April 2008). "SPECT and PET of the dopamine transporter in attention-deficit/hyperactivity disorder". *Expert Rev. Neurother*. **8** (4): 611–625. doi:10.1586/14737175.8.4.611. PMID 18416663. "Zinc binds at ... extracellular sites of the DAT [103], serving as a DAT inhibitor. In this context, controlled double-blind studies in children are of interest, which showed positive effects of zinc [supplementation] on symptoms of ADHD [105,106]. It should be stated that at this time [supplementation] with zinc is not integrated in any ADHD treatment algorithm."
177. ^ Bloch MH, Qawasmi A (October 2011). "Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: systematic review and meta-analysis". *J Am Acad Child Adolesc Psychiatry*. **50** (10): 991–1000. doi:10.1016/j.jaac.2011.06.008. PMC 3625948. PMID 21961774.
178. ^ Königs A, Kiliaan AJ (July 2016). "Critical appraisal of omega-3 fatty acids in attention-deficit/hyperactivity disorder treatment". *Neuropsychiatr. Dis. Treat*. **12**: 1869–1882. doi:10.2147/NDT.S68652. PMC 4968854. PMID 27555775.
179. ^ Molina BS, Hinshaw SP, Swanson JM, et al. (May 2009). "The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study". *Journal of the American Academy of Child and Adolescent Psychiatry*. **48** (5): 484–500. doi:10.1097/CHI.0b013e31819c23d0. PMC 3063150. PMID 19318991.
180. ^ Cimera, Robert E. (2002). *Making ADHD a gift : teaching Superman how to fly*. Lanham, Md.: Scarecrow Press. p. 116. ISBN 978-0-8108-4318-9. Retrieved 17 January 2014.
181. ^ Bergman, Mike (28 March 2005). "College Degree Nearly Doubles Annual Earnings, Census Bureau Reports". *U.S. Census Bureau*. Archived from the original on 23 September 2008. Retrieved 2 October 2008.
182. ^ Jensen PS, Arnold LE, Swanson JM (August 2007). "3-year follow-up of the NIMH MTA study". *Journal of the American Academy of Child and Adolescent Psychiatry*. **46** (8): 989–1002. doi:10.1097/CHI.0b013e3180686d48. PMID 17667478.
183. ^ "What is the evidence for using CNS stimulants to treat ADHD in children?". *Therapeutics Initiative*. University of British Columbia. March 2008. Archived from the original on 6 September 2010.
184. ^ Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (June 2007). "The worldwide prevalence of ADHD: a systematic review and metaregression analysis". *The American Journal of Psychiatry*. **164** (6): 942–8. doi:10.1176/appi.ajp.164.6.942. PMID 17541055.
185. ^ Staller J, Faraone SV (2006). "Attention-deficit hyperactivity disorder in girls: epidemiology and management". *CNS Drugs*. **20** (2): 107–23. doi:10.2165/00023210-200620020-00003. PMID 16478287.
186. ^ *a b c d e* "ADHD Throughout the Years" (PDF). Center For Disease Control and Prevention. Retrieved 2 August 2013.
187. ^ Dalsgaard, S (February 2013). "Attention-deficit/hyperactivity disorder (ADHD)". *European child & adolescent psychiatry*.

22 Suppl 1: S43–8. doi:10.1007/s00787-012-0360-z. PMID 23202886.
188. ^ Palmer ED, Finger S (May 2001). "An early description of ADHD (inattentive subtype): Dr Alexander Crichton and 'Mental restlessness' (1798)". *Child and Adolescent Mental Health*. **6** (2): 66–73. doi:10.1111/1475-3588.00324.
189. ^ Crichton A (1798). *An inquiry into the nature and origin of mental derangement: comprehending a concise system of the physiology and pathology of the human mind and a history of the passions and their effects*. United Kingdom: AMS Press. p. 271. ISBN 9780404082123. Retrieved 17 January 2014.
190. ^ Millichap, J. Gordon (2010). "Chapter 1: Definition and History of ADHD". *Attention Deficit Hyperactivity Disorder Handbook: A Physician's Guide to ADHD* (2nd ed.). Springer Science. pp. 2–3. doi:10.1007/978-104419-1397-5. ISBN 978-1-4419-1396-8. LCCN 2009938108.
191. ^ Weiss M (2010). *ADHD in Adulthood: A Guide to Current Theory, Diagnosis, and Treatment*. JHU Press. ISBN 9781421401317. Retrieved 17 January 2014.
192. ^ Patrick KS, Straughn AB, Perkins JS, González MA (January 2009). "Evolution of stimulants to treat ADHD: transdermal methylphenidate". *Human Psychopharmacology*. **24** (1): 1–17. doi:10.1002/hup.992. PMC 2629554. PMID 19051222.
193. ^ Rasmussen N (July 2006). "Making the first anti-depressant: amphetamine in American medicine, 1929–1950". *J . Hist. Med. Allied Sci*. **61** (3): 288–323. doi:10.1093/jhmas/jrj039. PMID 16492800.
194. ^ Foreman DM (February 2006). "Attention deficit hyperactivity disorder: legal and ethical aspects". *Archives of Disease in Childhood*. **91** (2): 192–194. doi:10.1136/adc.2004.064576. PMC 2082674. PMID 16428370.
195. ^ Faraone, Stephen V (2005). "The scientific foundation for understanding attention-deficit/hyperactivity disorder as a valid psychiatric disorder". *Eur Child Adolesc Psychiatry*. **14** (1): 1–10. doi:10.1007/s00787-005-0429-z. PMID 15756510.
196. ^ Boseley, Sarah (30 September 2010). "Hyperactive children may suffer from genetic disorder, says study". The Guardian.
197. ^ *a b* Cormier E (October 2008). "Attention deficit/hyperactivity disorder: a review and update". *J Pediatr Nurs*. **23** (5): 345–357. doi:10.1016/j.pedn.2008.01.003. PMID 18804015.
198. ^ Schwarz, Alan (14 December 2013). "The Selling of Attention Deficit Disorder" (14 December 2013). The New York Times. Retrieved 26 February 2015.
199. ^ Saletan, William (12 January 2009). "Doping Deficit Disorder. Need performance-enhancing drugs? Claim ADHD". Slate. Archived from the original on 21 May 2009. Retrieved 2 May 2009.
200. ^ "A Couch Tom Cruise Won't Jump On". Washington Post. June 25, 2005. Retrieved 22 September 2015.
201. ^ Neill US (August 2005). "Tom Cruise is dangerous and irresponsible". *J. Clin. Invest*. **115** (8): 1964–5. doi:10.1172/JCI26200. PMC 1180571. PMID 16075033.
202. ^ "Peer calls for ADHD care review". BBC News. 14 November 2007. Retrieved 29 January 2012.
203. ^ Singh A (25 February 2010). "BBC must broadcast apology over inaccurate Panorama programme". *The Telegraph*. Retrieved 29 January 2012.

## External links [edit]

- Attention deficit hyperactivity disorder at DMOZ
- National Institute of Mental Health on ADHD
- New Zealand MOH Guidelines for the Assessment and Treatment of Attention-Deficit/Hyperactivity Disorder
- AACAP Practice Parameters for the Assessment and Treatment of attention deficit hyperactivity disorder

Wikimedia Commons has media related to *Attention Deficit Hyperactivity Disorder*.

| v · t · e · | **Attention deficit hyperactivity disorder (F90, 314)** |
|---|---|
| **Main articles** | History of ADHD · ADHD in adults · ADHD controversies · ADHD management · List of ADHD organizations · Social construct theory of ADHD · ADHD coaching · *Major characteristics:* Attention · Hyperactivity · Impulsivity · |
| **Sub-types** | ADHD predominantly inattentive (ADHD-I, formerly **ADD**) · **ADHD predominantly hyperactive** (ADHD-H, formerly **ADHD**) · **ADHD combined type** (ADHD-C) · |
| **Notable publications** | *Driven to Distraction* (1994) · *Delivered from Distraction* (2005) · |
| **Medications** | *Stimulants:* · Methylphenidate (Ritalin, Concerta, and others) · Dexmethylphenidate (Focalin, Focalin XR) · Amphetamine (Evekeo, Adderall, Adzenys XR, Dyanavel XR) · Dextroamphetamine (Dexedrine, Zenzedi, ProCentra, and others) · Lisdexamfetamine (Vyvanse) · *Non-stimulant:* · Atomoxetine (Strattera) · Guanfacine (Tenex *(off-label)*, Intuniv) · Clonidine (Catapres *(off-* |

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| | *label)*, Kapvay) · |
| **Related or outdated topics** | Auditory processing disorder · Deficits in attention, motor control and perception · Developmental coordination disorder · Low arousal theory · Sluggish cognitive tempo · Sensory processing disorder · |

| v · t · e · | **ADHD pharmacotherapies** | |
|---|---|---|
| **Central nervous system (CNS) stimulants** | **Amphetamine** | *Adderall* · *Adzenys* · *Dyanavel* · *Evekeo* · |
| | **Dextroamphetamine** | *Dexedrine* · *ProCentra* · *Zenzedi* · |
| | **Lisdexamfetamine** | *Vyvanse* · |
| | **Methamphetamine** | *Desoxyn* · |
| | **Methylphenidate** | *Ritalin* · *Concerta* · *Aptensio* · *Biphentin* · *Daytrana* · *Equasym* · *Medikinet* · *Metadate* · *Methylin* · *Quillivant* · |
| | **Dexmethylphenidate** | *Focalin* · |
| **Non-classical CNS stimulants** | Atomoxetine · Modafinil · | |
| **$\alpha_2$ adrenoceptor agonists** | Clonidine · Guanfacine · | |
| **Antidepressants / Anxiolytics** | Amitriptyline · Bupropion · Buspirone · Desipramine · Duloxetine · Imipramine · Milnacipran · Moclobemide · Nortriptyline · Reboxetine · Venlafaxine · | |
| **Miscellaneous others** | Amantadine · Carbamazepine · Memantine · | |
| **Related articles** | **Attention deficit hyperactivity disorder** (ADHD) · *Attention deficit hyperactivity disorder management* · Monoamine releasing agent · Dopamine (DA) · Dopamine transporter (DAT) · Dopamine reuptake inhibitor (DRI) · Norepinephrine (NE) · Norepinephrine transporter (NET) · Norepinephrine reuptake inhibitor (NRI) · Serotonin (5-HT) · Serotonin transporter (SERT) · Selective serotonin reuptake inhibitor (SSRI) · Serotonin-norepinephrine reuptake inhibitor (SNRI) · Norepinephrine-dopamine reuptake inhibitor (NDRI) · Serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI) · | |

| v · t · e · | **Amphetamine** | |
|---|---|---|
| **Main articles and pharmaceuticals** | **Amphetamine** | *Adderall* · *Adzenys* · *Dyanavel* · *Evekeo* · |
| | **Levoamphetamine** | N/A |
| | **Dextroamphetamine** | *Dexedrine* · *ProCentra* · *Zenzedi* · |
| | **Lisdexamfetamine** | *Vyvanse* · |
| **Neuropharmacology** | **Biomolecular targets** | TAAR1 (full agonist) · CART (mRNA inducer) · 5-HT1A receptor (low affinity ligand) · MAO (weak competitive inhibitor) · |
| | **Inhibited transporters** | DAT · NET · SERT · VMAT1 · VMAT2 · EAAT3 · SLC22A3 · SLC22A5 · |
| **Active metabolites** | 4-Hydroxyamphetamine · 4-Hydroxynorephedrine · Norephedrine · | |
| **Related articles** | ADD · **ADHD** · ADHD management · Amphetamine psychosis · Dopamine · Doping in sport · Formetorex · ΔFosB · History and culture of substituted amphetamines · History of Benzedrine · Methamphetamine · Methylphenidate · *N*-Methylphenethylamine · Narcolepsy · Nootropic · Norepinephrine · Performance-enhancing substance · Pharmaceutical drug · Phenethylamine · Phentermine · Phenylacetone · Recreational drug use · Serotonin · Substituted amphetamine · Trace amine · | |

| v · t · e · | **Emotional and behavioral disorders (F90–F98, 312–314)** |
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| **Emotional/behavioral** | **ADHD** · Conduct disorder · Oppositional defiant disorder · Emotional/behavioral disorder (EBD) · Separation anxiety · *Social functioning* (Selective mutism · RAD · DAD · · *Tic disorders* (Tourette syndrome · · *Speech disorders* (Stuttering · Cluttering · · Stereotypic movement disorder · *Body-focused repetitive behavior* (Nose-picking · Nail biting · Hair pulling · Skin picking · · *Elimination disorders* (Enuresis · Encopresis · · |

| v · t · e · **Mental and behavioral disorders (F 290–319)** | | |
|---|---|---|
| **Neurological/symptomatic** | | |
| **Dementia** | Mild cognitive impairment · Alzheimer's disease · Vascular dementia · Pick's disease · Creutzfeldt–Jakob disease · Huntington's disease · Parkinson's disease · AIDS dementia complex · Frontotemporal dementia · Sundowning · Wandering · | |
| **Autism spectrum** | Autism · Asperger syndrome · Savant syndrome · PDD-NOS · High-functioning autism · | |
| **Other** | Delirium · Post-concussion syndrome · Organic brain syndrome · | |
| **Psychoactive substances, substance abuse, drug abuse and substance-related disorders** | | |
| Intoxication/Drug overdose · Physical dependence · Substance dependence · Rebound effect · Double rebound · Withdrawal · | | |
| **Schizophrenia, schizotypal and delusional** | | |
| **Psychosis** | Schizoaffective disorder · Schizophreniform disorder · Brief reactive psychosis · | |
| **Schizophrenia** | Disorganized schizophrenia · Paranoid schizophrenia · Simple-type schizophrenia · | |
| **Delusional disorders** | Delusional disorder · Folie à deux · | |
| **Mood (affective)** | | |
| Mania · Bipolar disorder · (Bipolar I · Bipolar II · Cyclothymia · Bipolar NOS) · Depression · (Major depressive disorder · Dysthymia · Seasonal affective disorder · Atypical depression · Melancholic depression) · | | |
| **Neurotic, stress-related and somatoform** | | |
| **Anxiety disorder** | **Phobia** | Agoraphobia · Social anxiety · Social phobia · (Anthropophobia) · Specific phobia · (Claustrophobia) · Specific social phobia · |
| | **Other** | Panic disorder · Panic attack · Generalized anxiety disorder · OCD · *stress* · (Acute stress reaction · PTSD) · |
| **Adjustment disorder** | Adjustment disorder with depressed mood · | |
| **Somatic symptom disorder** | Somatization disorder · Body dysmorphic disorder · Hypochondriasis · Nosophobia · Da Costa's syndrome · Psychalgia · Conversion disorder · (Ganser syndrome · Globus pharyngis) · Neurasthenia · Mass psychogenic illness · | |
| **Dissociative disorder** | Dissociative identity disorder · Psychogenic amnesia · Fugue state · Depersonalization disorder · | |
| **Physiological/physical behavioral** | | |
| **Eating disorder** | Anorexia nervosa · Bulimia nervosa · Rumination syndrome · NOS · | |
| **Nonorganic sleep disorders** | (Nonorganic hypersomnia · Nonorganic insomnia) · Parasomnia · (REM sleep behavior disorder · Night terror · Nightmare) · | |
| **Sexual dysfunction** | *sexual desire* · (Hypoactive sexual desire disorder · Hypersexuality) · *sexual arousal* · (Female sexual arousal disorder) · Erectile dysfunction · *orgasm* · (Anorgasmia · Delayed ejaculation · Premature ejaculation · Sexual anhedonia) · *pain* · (Vaginismus · Dyspareunia) · | |
| **Postnatal** | Postpartum depression · Postpartum psychosis · | |
| **Adult personality and behavior** | | |
| *Gender dysphoria* | Sexual maturation disorder · Ego-dystonic sexual orientation · Sexual relationship disorder · Paraphilia · | |

| | |
|---|---|
| | (Voyeurism · Fetishism) · |
| **Other** | Personality disorder · Impulse control disorder · (Kleptomania · Trichotillomania · Pyromania · Dermatillomania) · Body-focused repetitive behavior · Factitious disorder · (Münchausen syndrome) · |
| **Disorders typically diagnosed in childhood** | |
| **Intellectual disability** | X-linked intellectual disability · (Lujan–Fryns syndrome) · |
| **Psychological development (developmental disabilities)** | Specific · Pervasive · Autism spectrum · |
| **Emotional and behavioral** | **ADHD** · Conduct disorder · (ODD) · Emotional/behavioral disorder · (Separation anxiety disorder) · *social functioning* · (Selective mutism · RAD · DAD) · Tic disorder · (Tourette syndrome) · *Speech* · (Stuttering · Cluttering) · Movement disorder · (Stereotypic) · |
| **Symptoms and uncategorized** | |
| Catatonia · False pregnancy · Intermittent explosive disorder · Psychomotor agitation · Stereotypy · Psychogenic non-epileptic seizures · Klüver–Bucy syndrome · | |

**Medicine portal** **Pervasive developmental disorders portal**

Categories: Amphetamine | Attention | Attention deficit hyperactivity disorder | Attention disorders | Childhood psychiatric disorders | Educational psychology | Emotional and behavioral disorders in childhood and adolescence | Learning disabilities | Methylphenidate | Psychiatric diagnosis

# Alcoholism

From Wikipedia, the free encyclopedia

*"Alcoholic" redirects here. For alcoholic beverages, see alcoholic beverage. For the song by Starsailor, see Alcoholic (song).*

**Alcoholism**, also known as **alcohol use disorder** (**AUD**), is a broad term for any drinking of alcohol that results in problems.[1] It was previously divided into two types: alcohol abuse and alcohol dependence.[2][3] In a medical context, alcoholism is said to exist when two or more of the following conditions is present: a person drinks large amounts over a long time period, has difficulty cutting down, acquiring and drinking alcohol takes up a great deal of time, alcohol is strongly desired, usage results in not fulfilling responsibilities, usage results in social problems, usage results in health problems, usage results in risky situations, withdrawal occurs when stopping, and alcohol tolerance has occurred with use.[3] Risky situations include drinking and driving or having unsafe sex among others.[3] Alcohol use can affect all parts of the body but particularly affects the brain, heart, liver, pancreas, and immune system. This can result in mental illness, Wernicke–Korsakoff syndrome, an irregular heart beat, liver failure, and an increase in the risk of cancer, among other diseases.[4][5] Drinking during pregnancy can cause damage to the baby resulting in fetal alcohol spectrum disorders.[6] Generally women are more sensitive to alcohol's harmful physical and mental effects than men.[7]

Both environmental factors and genetics are associated with alcoholism with about half the risk attributed to each. A person with a parent or sibling with alcoholism is three to four times more likely to be alcoholic themselves.[4] Environmental factors include social, cultural, and behavioral influences.[8] High stress levels, anxiety, as well as inexpensive easily accessible alcohol increases risk.[4][9] People may continue to drink partly to prevent or improve symptoms of withdrawal. A low level of withdrawal may last for months following stopping.[9] Medically, alcoholism is considered both a physical and mental illness.[10][11] Both questionnaires and certain blood tests may detect people with possible alcoholism. Further information is then collected to confirm the diagnosis.[4]

Prevention of alcoholism is possible by regulating and limiting

**Alcoholism**

**Synonyms** alcohol dependence syndrome


"King Alcohol and his Prime Minister" c. 1820

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Psychiatry, toxicology |
| **ICD-10** | F10.2 |
| **ICD-9-CM** | 303 |
| **OMIM** | 103780 |
| **MedlinePlus** | 000944 |
| **eMedicine** | article/285913 |
| **MeSH** | D000437 |

[edit on Wikidata]

the sale of alcohol, taxing alcohol to increase its cost, and providing inexpensive treatment.[12] Treatment may take several steps. Because of the medical problems that can occur during withdrawal, alcohol detoxification should be carefully controlled. One common method involves the use of benzodiazepine medications, such as diazepam. This can be either given while admitted to a health care institution or occasionally while a person remains in the community with close supervision.[13] Other addictions or mental illness may complicate treatment.[14] After detoxification support such as group therapy or support groups are used to help keep a person from returning to drinking.[15][16] One commonly used form of support is the group Alcoholics Anonymous.[17] The medications acamprosate, disulfiram, or naltrexone may also be used to help prevent further drinking.[18]

The World Health Organization estimates that as of 2010 there were 208 million people with alcoholism worldwide (4.1% of the population over 15 years of age).[7][19] In the United States about 17 million (7%) of adults and 0.7 million (2.8%) of those age 12 to 17 years of age are affected.[20] It is more common among males and young adults, becoming less common in middle and old age.[4] It is the least common in Africa at 1.1% and has the highest rates in Eastern Europe at 11%.[4] Alcoholism directly resulted in 139,000 deaths in 2013 up from 112,000 deaths in 1990.[21] A total of 3.3 million deaths (5.9% of all deaths) are believed to be due to alcohol.[20] It often reduces a person's life expectancy by around ten years.[22] In the United States it resulted in economic costs of $224 billion USD in 2006.[20] Many terms, some insulting and others informal, have been used to refer to people affected by alcoholism including: tippler, drunkard, dipsomaniac, and souse.[23] In 1979, the World Health Organization discouraged the use of "alcoholism" due to its inexact meaning, preferring "alcohol dependence syndrome".[24]

**Contents**

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# Signs and symptoms

*See also: long-term effects of alcohol*

## Early signs

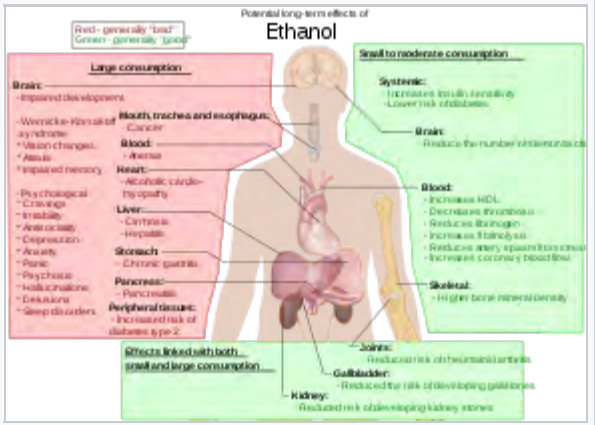
The risk of alcohol dependence begins at low levels of drinking and increases directly with both the volume of alcohol consumed and a pattern of drinking larger amounts on an occasion, to the point of intoxication, which is sometimes called "binge drinking". Young adults are particularly at risk of engaging in binge drinking.

Play media

Effects of alcohol on the body

## Long-term misuse

Alcoholism is characterised by an increased tolerance to alcohol–which means that an individual can consume more alcohol–and physical dependence on alcohol, which makes it hard for an individual to control their consumption. The physical dependency caused by alcohol can lead to an affected individual having a very strong urge to drink alcohol. These characteristics play a role decreasing an alcoholic's ability to stop drinking.[25] Alcoholism can have adverse effects on mental health, causing psychiatric disorders and increasing the risk of suicide. A depressed mood is a common symptom of heavy alcohol drinkers.[26][27]




Some of the possible long-term effects of ethanol an individual may develop. Additionally, in pregnant women, alcohol can cause fetal alcohol syndrome.

## Warning signs

Warning signs of alcoholism include the consumption of increasing amounts of alcohol and frequent intoxication, preoccupation with drinking to the exclusion of other activities, promises to quit drinking and failure to keep them, the inability to remember what was said or done while drinking (colloquially known as "blackouts"), personality changes associated with drinking, denial or the making of excuses for drinking, the refusal to admit excessive drinking, dysfunction or other problems at work and/or school, the loss of interest in personal appearance or hygiene, marital and economic problems, and the complaint of poor health, with loss of appetite, respiratory infections, or increased anxiety.[28]

## Physical

### Short-term effects

*Main article: Short-term effects of alcohol*

Drinking enough to cause a blood alcohol concentration (BAC) of 0.03–0.12% typically causes an overall improvement in mood and possible euphoria (a "happy" feeling), increased self-confidence and sociability, decreased anxiety, a flushed, red appearance in the face and impaired judgment and fine muscle coordination. A BAC of 0.09% to 0.25% causes lethargy, sedation, balance problems and blurred vision. A BAC from 0.18% to 0.30% causes profound confusion, impaired speech (e.g., slurred speech), staggering, dizziness and vomiting. A BAC from 0.25% to 0.40% causes stupor, unconsciousness, anterograde amnesia,

vomiting (death may occur due to inhalation of vomit (pulmonary aspiration) while unconscious and respiratory depression (potentially life-threatening). A BAC from 0.35% to 0.80% causes a coma (unconsciousness), life-threatening respiratory depression and possibly fatal alcohol poisoning. With all alcoholic beverages, drinking while driving, operating an aircraft or heavy machinery increases the risk of an accident; many countries have penalties against drunk driving.

### Long-term effects

*See also: Long-term effects of alcohol consumption*

Drinking more than one drink a day for women or two drinks for men increases the risk of heart disease, high blood pressure, atrial fibrillation, and stroke.[29] Risk is greater in younger people due to binge drinking which may result in violence or accidents.[29] About 3.3 million deaths (5.9% of all deaths) are believed to be due to alcohol each year.[20] Alcoholism reduces a person's life expectancy by around ten years[22] and alcohol use is the third leading cause of early death in the United States.[29] No professional medical association recommends that people who are nondrinkers should start drinking wine.[29][30] Long-term alcohol abuse can cause a number of physical symptoms, including cirrhosis of the liver, pancreatitis, epilepsy, polyneuropathy, alcoholic dementia, heart disease, nutritional deficiencies, peptic ulcers[31] and sexual dysfunction, and can eventually be fatal. Other physical effects include an increased risk of developing cardiovascular disease, malabsorption, alcoholic liver disease, and cancer. Damage to the central nervous system and peripheral nervous system can occur from sustained alcohol consumption.[32][33] A wide range of immunologic defects can result and there may be a generalized skeletal fragility, in addition to a recognized tendency to accidental injury, resulting a propensity to bone fractures.[34]

Women develop long-term complications of alcohol dependence more rapidly than do men. Additionally, women have a higher mortality rate from alcoholism than men.[35] Examples of long-term complications include brain, heart, and liver damage[36] and an increased risk of breast cancer. Additionally, heavy drinking over time has been found to have a negative effect on reproductive functioning in women. This results in reproductive dysfunction such as anovulation, decreased ovarian mass, problems or irregularity of the menstrual cycle, and early menopause.[35] Alcoholic ketoacidosis can occur in individuals who chronically abuse alcohol and have a recent history of binge drinking.[37][38] The amount of alcohol that can be biologically processed and its effects differ between sexes. Equal dosages of alcohol consumed by men and women generally result in women having higher blood alcohol concentrations (BACs), since women generally have a higher percentage of body fat and therefore a lower volume of distribution for alcohol than men, and because the stomachs of men tend to metabolize alcohol more quickly.[39]

## Psychiatric

Long-term misuse of alcohol can cause a wide range of mental health problems. Severe cognitive problems are common; approximately 10 percent of all dementia cases are related to alcohol consumption, making it the second leading cause of dementia.[40] Excessive alcohol use causes damage to brain function, and psychological health can be increasingly affected over time.[41]Social skills are significantly impaired in people suffering from alcoholism due to the neurotoxic effects of alcohol on the brain, especially the prefrontal cortex area of the brain. The social skills that are impaired by alcohol abuse include impairments in perceiving facial emotions, prosody perception problems and theory of mind deficits; the ability to understand humour is also impaired in alcohol abusers.[42] Psychiatric disorders are common in alcoholics, with as many as 25 percent suffering severe psychiatric disturbances. The most prevalent psychiatric symptoms are anxiety and depression disorders. Psychiatric symptoms usually initially worsen during alcohol withdrawal, but typically improve or disappear with continued abstinence.[43] Psychosis, confusion, and organic brain syndrome may be caused by alcohol misuse, which can lead to a misdiagnosis such as schizophrenia.[44] Panic disorder can develop or worsen as a direct result of long-term alcohol misuse.[45][46]

The co-occurrence of major depressive disorder and alcoholism is well documented.[47][48][49] Among those

with comorbid occurrences, a distinction is commonly made between depressive episodes that remit with alcohol abstinence ("substance-induced"), and depressive episodes that are primary and do not remit with abstinence ("independent" episodes).[50][51][52] Additional use of other drugs may increase the risk of depression.[53] Psychiatric disorders differ depending on gender. Women who have alcohol-use disorders often have a co-occurring psychiatric diagnosis such as major depression, anxiety, panic disorder, bulimia, post-traumatic stress disorder (PTSD), or borderline personality disorder. Men with alcohol-use disorders more often have a co-occurring diagnosis of narcissistic or antisocial personality disorder, bipolar disorder, schizophrenia, impulse disorders or attention deficit/hyperactivity disorder (ADHD).[54] Women with alcoholism are more likely to experience physical or sexual assault, abuse and domestic violence than women in the general population,[54] which can lead to higher instances of psychiatric disorders and greater dependence on alcohol.

## Social effects

*See also: Drug-related crime*

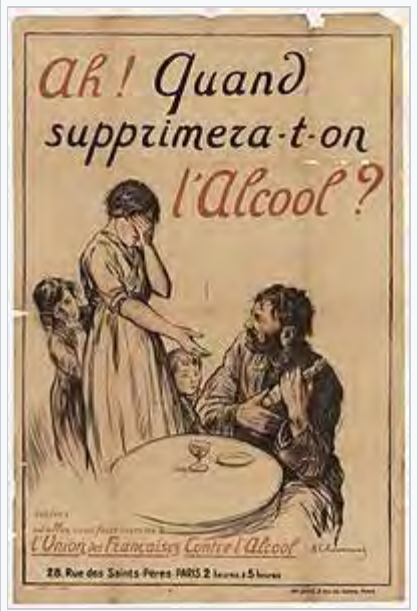
The social problems arising from alcoholism are serious, caused by the pathological changes in the brain and the intoxicating effects of alcohol.[40][55] Alcohol abuse is associated with an increased risk of committing criminal offences, including child abuse, domestic violence, rape, burglary and assault.[56] Alcoholism is associated with loss of employment,[57] which can lead to financial problems. Drinking at inappropriate times, and behavior caused by reduced judgment, can lead to legal consequences, such as criminal charges for drunk driving[58] or public disorder, or civil penalties for tortious behavior, and may lead to a criminal sentence. An alcoholic's behavior and mental impairment, while drunk, can profoundly affect those surrounding them and lead to isolation from family and friends. This isolation can lead to marital conflict and divorce, or contribute to domestic violence. Alcoholism can also lead to child neglect, with subsequent lasting damage to the emotional development of the alcoholic's children.[59] For this reason, children of alcoholic parents can develop a number of emotional problems. For example, they can become afraid of their parents, because of their unstable mood behaviors. In addition, they can develop considerable amount of shame over their inadequacy to liberate their parents from alcoholism. As a result of this failure, they develop wretched self-images, which can lead to depression.[60]

## Alcohol withdrawal

*Main article: Alcohol withdrawal syndrome*
*See also: Kindling (sedative-hypnotic withdrawal)*

As with similar substances with a sedative-hypnotic mechanism, such as barbiturates and benzodiazepines, withdrawal from alcohol dependence can be fatal if it is not properly managed.[55][61] Alcohol's primary effect is the increase in stimulation of the $GABA_A$ receptor, promoting central nervous system depression. With repeated heavy consumption of alcohol, these receptors are desensitized and reduced in number, resulting in tolerance and physical dependence. When alcohol consumption is stopped too abruptly, the person's nervous system suffers from uncontrolled synapse firing. This can result in symptoms that include anxiety, life-threatening seizures, delirium tremens, hallucinations, shakes and possible heart failure.[62][63] Other neurotransmitter systems are also involved, especially dopamine, NMDA and glutamate.[25][64]

Severe acute withdrawal symptoms such as delirium tremens and seizures rarely occur after 1-week post cessation of alcohol. The acute withdrawal phase can be defined as lasting between one and three weeks. In the period of 3 – 6 weeks following cessation increased anxiety, depression, as well as sleep disturbance, is common;[65] fatigue and tension can persist for up to 5 weeks as part of the post-acute withdrawal syndrome; about a quarter of alcoholics experience anxiety and depression for up to 2 years.



A French temperance poster

from the Union des Françaises contre l'Alcool (this translates as "Union of French People Against Alcohol"). The poster states "Ah! Quand supprimera-t'on l'alcool?", which translates as "Ah! When will we [the nation] abolish alcohol?"

These post-acute withdrawal symptoms have also been demonstrated in animal models of alcohol dependence and withdrawal.[66] A kindling effect also occurs in alcoholics whereby each subsequent withdrawal syndrome is more severe than the previous withdrawal episode; this is due to neuroadaptations which occur as a result of periods of abstinence followed by re-exposure to alcohol. Individuals who have had multiple withdrawal episodes are more likely to develop seizures and experience more severe anxiety during withdrawal from alcohol than alcohol-dependent individuals without a history of past alcohol withdrawal episodes. The kindling effect leads to persistent functional changes in brain neural circuits as well as to gene expression.[67] Kindling also results in the intensification of psychological symptoms of alcohol withdrawal.[65] There are decision tools and questionnaires which help guide physicians in evaluating alcohol withdrawal. For example, the CIWA-Ar objectifies alcohol withdrawal symptoms in order to guide therapy decisions which allows for an efficient interview while at the same time retaining clinical usefulness, validity, and reliability, ensuring proper care for withdrawal patients, who can be in danger of death.[68]

# Causes

William Hogarth's *Gin Lane*, 1751

A complex mixture of genetic and environmental factors influences the risk of the development of alcoholism.[69] Genes that influence the metabolism of alcohol also influence the risk of alcoholism, and may be indicated by a family history of alcoholism.[70] One paper has found that alcohol use at an early age may influence the expression of genes which increase the risk of alcohol dependence.[71] Individuals who have a genetic disposition to alcoholism are also more likely to begin drinking at an earlier age than average.[72] Also, a younger age of onset of drinking is associated with an increased risk of the development of alcoholism,[72] and about 40 percent of alcoholics will drink excessively by their late adolescence. It is not entirely clear whether this association is causal, and some researchers have been known to disagree with this view.[73]

Severe childhood trauma is also associated with a general increase in the risk of drug dependency.[69] Lack of peer and family support is associated with an increased risk of alcoholism developing.[69] Genetics and adolescence are associated with an increased sensitivity to the neurotoxic effects of chronic alcohol abuse. Cortical degeneration due to the neurotoxic effects increases impulsive behaviour, which may contribute to the development, persistence and severity of alcohol use disorders. There is evidence that with abstinence, there is a reversal of at least some of the alcohol induced central nervous system damage.[74] The use of cannabis was associated with later problems with alcohol use.[75] Alcohol use was associated with an increased probability of later use of tobacco, cannabis, and other illegal drugs.[76]

## Availability

Alcohol is the most available, widely consumed, and widely abused recreational drug. Beer alone is the world's most widely consumed[77] alcoholic beverage; it is the third-most popular drink overall, after water and tea.[78] It is thought by some to be the oldest fermented beverage.[79][80][81][82]

## Gender difference

Based on combined data from SAMHSA's 2004–2005 National Surveys on Drug Use & Health, the rate of past-year alcohol dependence or abuse among persons aged 12 or older varied by level of alcohol use: 44.7% of past month heavy drinkers, 18.5% binge drinkers, 3.8% past month non-binge drinkers, and

1.3% of those who did not drink alcohol in the past month met the criteria for alcohol dependence or abuse in the past year. Males had higher rates than females for all measures of drinking in the past month: any alcohol use (57.5% vs. 45%), binge drinking (30.8% vs. 15.1%), and heavy alcohol use (10.5% vs. 3.3%), and males were twice as likely as females to have met the criteria for alcohol dependence or abuse in the past year (10.5% vs. 5.1%).[83]

### Genetic variation

*See also: Human genetic variation*

Genetic differences exist between different racial groups which affect the risk of developing alcohol dependence. For example, there are differences between African, East Asian and Indo-racial groups in how they metabolize alcohol. These genetic factors are believed to, in part, explain the differing rates of alcohol dependence among racial groups.[84][85] The alcohol dehydrogenase allele ADH1 B*3 causes a more rapid metabolism of alcohol. The allele ADH1 B*3 is only found in those of African descent and certain Native American tribes. African Americans and Native Americans with this allele have a reduced risk of developing alcoholism.[86] Native Americans however, have a significantly higher rate of alcoholism than average; it is unclear why this is the case.[87] Other risk factors such as cultural environmental effects e.g. trauma have been proposed to explain the higher rates of alcoholism among Native Americans compared to alcoholism levels in caucasians.[88][89]

## Diagnosis

*See also: Addiction medicine*

### Definition

Misuse, problem use, abuse, and heavy use of alcohol refer to improper use of alcohol which may cause physical, social, or moral harm to the drinker.[90] Moderate use is defined by *The Dietary Guidelines for Americans* as no more than two alcoholic beverages a day for men and no more than one alcoholic beverage a day for women.[91] Some drinkers may drink more than 600 ml of alcohol per day during a heavy drinking period.[92] The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines binge drinking as the amount of alcohol leading to a blood alcohol content (BAC) of 0.08, which, for most adults, would be reached by consuming five drinks for men or four for women over a two-hour period. According to the NIAAA, men may be at risk for alcohol-related problems if their alcohol consumption exceeds 14 standard drinks per week or 4 drinks per day, and women may be at risk if they have more than 7 standard drinks per week or 3 drinks per day. It defines a standard drink as one 12-ounce bottle of beer, one 5-ounce glass of wine, or 1.5 ounces of distilled spirits.[93] Despite this risk, a 2014 report in the National Survey on Drug Use and Health found that only 10% of either "heavy drinkers" or "binge drinkers" defined according to the above criteria also met the criteria for alcohol dependence, while only 1.3% of non-binge drinkers met this criteria. An inference drawn from this study is that evidence-based policy strategies and clinical preventive services may effectively reduce binge drinking without requiring addiction treatment in most cases.[94]

A picture of a man drinking from a bottle of alcohol while sitting on a boardwalk, ca. 1905-1914. Picture by Austrian photographer Emil Mayer.

### Alcoholism

The term *alcoholism* is commonly used amongst laypeople, but it is poorly defined. The WHO calls *alcoholism* "a term of long-standing use and variable meaning", and use of the term was disfavored by a 1979 WHO expert committee. *The Big Book* (from Alcoholics Anonymous) states that once a person is an

alcoholic, they are always an alcoholic, but does not define what is meant by the term *alcoholic* in this context. In 1960, Bill W., co-founder of Alcoholics Anonymous (AA), said:

> We have never called alcoholism a disease because, technically speaking, it is not a disease entity. For example, there is no such thing as heart disease. Instead there are many separate heart ailments, or combinations of them. It is something like that with alcoholism. Therefore we did not wish to get in wrong with the medical profession by pronouncing alcoholism a disease entity. Therefore we always called it an illness, or a malady—a far safer term for us to use.[95] In professional and research contexts, the term "alcoholism" sometimes encompasses both alcohol abuse and alcohol dependence,[96] and sometimes is considered equivalent to alcohol dependence. Talbot (1989) observes that alcoholism in the classical disease model follows a progressive course: if a person continues to drink, their condition will worsen. This will lead to harmful consequences in their life, physically, mentally, emotionally and socially.[97]

## Johnson's typologies

Johnson (1980) explores the emotional progression of the addict's response to alcohol. He looks at this in four phases. The first two are considered "normal" drinking and the last two are viewed as "typical" alcoholic drinking.[98][99] Johnson's four phases consist of:

1. Learning the mood swing. A person is introduced to alcohol (in some cultures this can happen at a relatively young age), and the person enjoys the happy feeling it produces. At this stage there is no emotional cost.
2. Seeking the mood swing. A person will drink to regain that feeling of euphoria experienced in phase 1; the drinking will increase as more intoxication is required to achieve the same effect. Again at this stage, there are no significant consequences.
3. At the third stage there are physical and social consequences, i.e., hangovers, family problems, work problems, etc. A person will continue to drink excessively, disregarding the problems.
4. The fourth stage can be detrimental, as Johnson cites it as a risk for premature death. As a person now drinks to feel normal, they block out the feelings of overwhelming guilt, remorse, anxiety, and shame they experience when sober.[100]

## Milam & Ketcham's physical deterioration stages

Other theorists such as Milam & Ketcham (1983) focus on the physical deterioration that alcohol consumption causes. They describe the process in three stages:

1. Adaptive stage – The person will not experience any negative symptoms, and they believe they have capacity for drinking alcohol without problems. Physiological changes are happening with the increase in tolerance, but this will not be noticeable to the drinker or others.
2. Dependent stage – At this stage, symptoms build up gradually. Hangover symptoms from excessive drinking may be confused with withdrawal symptoms. Many addicts will maintain their drinking to avoid withdrawal sickness, drinking small amounts frequently. They will try to hide their drinking problem from others, and will avoid gross intoxication.
3. Deterioration stage – Various organs are damaged due to long-term drinking. Medical treatment in a rehabilitation center will be required; otherwise the pathological changes will cause death.

## DSM and ICD

In psychology and psychiatry, the DSM is the most common global standard, while in medicine, the standard is ICD. The terms they recommend are similar but not identical.

| Organization | Preferred term(s) | Definition |
|---|---|---|
| | "alcohol | ▪ alcohol abuse = repeated use despite recurrent adverse consequences.[101]<br>▪ alcohol dependence = *alcohol abuse* combined with tolerance, |

| | | |
|---|---|---|
| APA's DSM-IV | abuse" and "alcohol dependence" | withdrawal, and an uncontrollable drive to drink.[101] The term "alcoholism" was split into "alcohol abuse" and "alcohol dependence" in 1980's DSM-III, and in 1987's DSM-III-R behavioral symptoms were moved from "abuse" to "dependence".[102] It has been suggested that DSM-V merge alcohol abuse and alcohol dependence into a single new entry,[103] named "alcohol-use disorder".[104] |
| WHO's ICD-10 | "alcohol harmful use" and "alcohol dependence syndrome" | Definitions are similar to that of the DSM-IV. The World Health Organisation uses the term "alcohol dependence syndrome" rather than alcoholism.[24] The concept of "harmful use" (as opposed to "abuse") was introduced in 1992's ICD-10 to minimize underreporting of damage in the absence of dependence.[102] The term "alcoholism" was removed from ICD between ICD-8/ICDA-8 and ICD-9.[105] |

The DSM-IV diagnosis of alcohol dependence represents one approach to the definition of alcoholism. In part, this is to assist in the development of research protocols in which findings can be compared to one another. According to the DSM-IV, an alcohol dependence diagnosis is: "maladaptive alcohol use with clinically significant impairment as manifested by at least three of the following within any one-year period: tolerance; withdrawal; taken in greater amounts or over longer time course than intended; desire or unsuccessful attempts to cut down or control use; great deal of time spent obtaining, using, or recovering from use; social, occupational, or recreational activities given up or reduced; continued use despite knowledge of physical or psychological sequelae."[106] Despite the imprecision inherent in the term, there have been attempts to define how the word *alcoholism* should be interpreted when encountered. In 1992, it was defined by the National Council on Alcoholism and Drug Dependence (NCADD) and ASAM as "a primary, chronic disease characterized by impaired control over drinking, preoccupation with the drug alcohol, use of alcohol despite adverse consequences, and distortions in thinking."[107] MeSH has had an entry for "alcoholism" since 1999, and references the 1992 definition.[108]

AA describes alcoholism as an illness that involves a physical allergy[109]:28 (where "allergy" has a different meaning than that used in modern medicine.[110]) and a mental obsession.[109]:23[111] The doctor and addiction specialist Dr. William D. Silkworth M.D. writes on behalf of AA that "Alcoholics suffer from a "(physical) craving beyond mental control".[109]:XXVI A 1960 study by E. Morton Jellinek is considered the foundation of the modern disease theory of alcoholism.[112] Jellinek's definition restricted the use of the word *alcoholism* to those showing a particular natural history. The modern medical definition of *alcoholism* has been revised numerous times since then. The American Medical Association uses the word alcoholism to refer to a particular chronic primary disease.[113]

## Social barriers

Attitudes and social stereotypes can create barriers to the detection and treatment of alcohol abuse. This is more of a barrier for women than men. Fear of stigmatization may lead women to deny that they are suffering from a medical condition, to hide their drinking, and to drink alone. This pattern, in turn, leads family, physicians, and others to be less likely to suspect that a woman they know is an alcoholic.[35] In contrast, reduced fear of stigma may lead men to admit that they are suffering from a medical condition, to display their drinking publicly, and to drink in groups. This pattern, in turn, leads family, physicians, and others to be more likely to suspect that a man they know is an alcoholic.[54]

## Screening

Several tools may be used to detect a loss of control of alcohol use. These tools are mostly self-reports in questionnaire form. Another common theme is a score or tally that sums up the general severity of alcohol use.[114]

The CAGE questionnaire, named for its four questions, is one such example that may be used to screen patients quickly in a doctor's office.

Two "yes" responses indicate that the respondent should be investigated further.

The questionnaire asks the following questions:

1. Have you ever felt you needed to **C**ut down on your drinking?
2. Have people **A**nnoyed you by criticizing your drinking?
3. Have you ever felt **G**uilty about drinking?
4. Have you ever felt you needed a drink first thing in the morning (**E**ye-opener) to steady your nerves or to get rid of a hangover?[115][116]

The CAGE questionnaire has demonstrated a high effectiveness in detecting alcohol-related problems; however, it has limitations in people with less severe alcohol-related problems, white women and college students.[117]

Other tests are sometimes used for the detection of alcohol dependence, such as the Alcohol Dependence Data Questionnaire, which is a more sensitive diagnostic test than the CAGE questionnaire. It helps distinguish a diagnosis of alcohol dependence from one of heavy alcohol use.[118] The Michigan Alcohol Screening Test (MAST) is a screening tool for alcoholism widely used by courts to determine the appropriate sentencing for people convicted of alcohol-related offenses,[119] driving under the influence being the most common. The Alcohol Use Disorders Identification Test (AUDIT), a screening questionnaire developed by the World Health Organization, is unique in that it has been validated in six countries and is used internationally. Like the CAGE questionnaire, it uses a simple set of questions – a high score earning a deeper investigation.[120] The Paddington Alcohol Test (PAT) was designed to screen for alcohol-related problems amongst those attending Accident and Emergency departments. It concords well with the AUDIT questionnaire but is administered in a fifth of the time.[121] Certain blood tests may also indicate possible alcoholism.[4]

## Genetic predisposition testing

Psychiatric geneticists John I. Nurnberger, Jr., and Laura Jean Bierut suggest that alcoholism does not have a single cause—including genetic—but that genes do play an important role "by affecting processes in the body and brain that interact with one another and with an individual's life experiences to produce protection or susceptibility". They also report that fewer than a dozen alcoholism-related genes have been identified, but that more likely await discovery.[122] At least one genetic test exists for an allele that is correlated to alcoholism and opiate addiction.[123] Human dopamine receptor genes have a detectable variation referred to as the DRD2 TaqI polymorphism. Those who possess the A1 allele (variation) of this polymorphism have a small but significant tendency towards addiction to opiates and endorphin-releasing drugs like alcohol.[124] Although this allele is slightly more common in alcoholics and opiate addicts, it is not by itself an adequate predictor of alcoholism, and some researchers argue that evidence for DRD2 is contradictory.[122]

## Urine and blood tests

There are reliable tests for the actual use of alcohol, one common test being that of blood alcohol content (BAC).[125] These tests do not differentiate alcoholics from non-alcoholics; however, long-term heavy drinking does have a few recognizable effects on the body, including:[126]

- Macrocytosis (enlarged MCV)
- Elevated GGT
- Moderate elevation of AST and ALT and an AST: ALT ratio of 2:1
- High carbohydrate deficient transferrin (CDT)

With regard to alcoholism, BAC is useful to judge alcohol tolerance, which in turn is sign of alcoholism.[4]

However, none of these blood tests for biological markers is as sensitive as screening questionnaires.

# Prevention

The World Health Organization, the European Union and other regional bodies, national governments and parliaments have formed alcohol policies in order to reduce the harm of alcoholism.[127][128] Targeting adolescents and young adults is regarded as an important step to reduce the harm of alcohol abuse. Increasing the age at which licit drugs of abuse such as alcohol can be purchased, the banning or restricting advertising of alcohol has been recommended as additional ways of reducing the harm of alcohol dependence and abuse. Credible, evidence based educational campaigns in the mass media about the consequences of alcohol abuse have been recommended. Guidelines for parents to prevent alcohol abuse amongst adolescents, and for helping young people with mental health problems have also been suggested.[129]

# Management

Treatments are varied because there are multiple perspectives of alcoholism. Those who approach alcoholism as a medical condition or disease recommend differing treatments from, for instance, those who approach the condition as one of social choice. Most treatments focus on helping people discontinue their alcohol intake, followed up with life training and/or social support to help them resist a return to alcohol use. Since alcoholism involves multiple factors which encourage a person to continue drinking, they must all be addressed to successfully prevent a relapse. An example of this kind of treatment is detoxification followed by a combination of supportive therapy, attendance at self-help groups, and ongoing development of coping mechanisms. The treatment community for alcoholism typically supports an abstinence-based zero tolerance approach; however, some prefer a harm-reduction approach.[130]

## Detoxification

*Main article: Alcohol detoxification*

Alcohol detoxification or 'detox' for alcoholics is an abrupt stop of alcohol drinking coupled with the substitution of drugs, such as benzodiazepines, that have similar effects to prevent alcohol withdrawal. Individuals who are only at risk of mild to moderate withdrawal symptoms can be detoxified as outpatients. Individuals at risk of a severe withdrawal syndrome as well as those who have significant or acute comorbid conditions are generally treated as inpatients. Detoxification does not actually treat alcoholism, and it is necessary to follow up detoxification with an appropriate treatment program for alcohol dependence or abuse to reduce the risk of relapse.[13] Some symptoms of alcohol withdrawal such as depressed mood and anxiety typically take weeks or months to abate while other symptoms persist longer due to persisting neuroadaptations.[65] Alcoholism has serious adverse effects on brain function; on average it takes one year of abstinence to recover from the cognitive deficits incurred by chronic alcohol abuse.[131]

## Psychological

Various forms of group therapy or psychotherapy can be used to deal with underlying psychological issues that are related to alcohol addiction, as well as provide relapse prevention skills. The mutual-help group-counseling approach is one of the most common ways of helping alcoholics maintain sobriety.[15] Alcoholics Anonymous was one of the first organizations formed to provide mutual, nonprofessional counseling, and it is still the largest. Others include LifeRing Secular Recovery, SMART Recovery, Women For Sobriety, and Secular Organizations for Sobriety.[132] Rationing and moderation programs such as Moderation Management and DrinkWise do not mandate complete abstinence. While most alcoholics are unable to limit their drinking in this way, some return to moderate drinking. A 2002 US study by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) showed that 17.7 percent of

A regional service center for Alcoholics Anonymous.

individuals diagnosed as alcohol dependent more than one year prior returned to low-risk drinking. This group, however, showed fewer initial symptoms of dependency.[133] A follow-up study, using the same subjects that were judged to be in remission in 2001–2002, examined the rates of return to problem drinking in 2004–2005. The study found abstinence from alcohol was the most stable form of remission for recovering alcoholics.[134] A long-term (60 year) follow-up of two groups of alcoholic men concluded that "return to controlled drinking rarely persisted for much more than a decade without relapse or evolution into abstinence."[135]

## Medications

In the United States there are four currently approved medications for alcoholism: disulfiram, two forms of naltrexone, and acamprosate.[136] Several other drugs are also used and many are under investigation.

- Acamprosate (Campral) may stabilise the brain chemistry that is altered due to alcohol dependence via antagonising the actions of glutamate, a neurotransmitter which is hyperactive in the post-withdrawal phase.[137] By reducing excessive NMDA activity which occurs at the onset of alcohol withdrawal, acamprosate can reduce or prevent alcohol withdrawal related neurotoxicity.[138] Acamprosate reduces the risk of relapse amongst alcohol dependent persons.[139][140]
- Benzodiazepines, while useful in the management of acute alcohol withdrawal, if used long-term can cause a worse outcome in alcoholism. Alcoholics on chronic benzodiazepines have a lower rate of achieving abstinence from alcohol than those not taking benzodiazepines. This class of drugs is commonly prescribed to alcoholics for insomnia or anxiety management.[141] Initiating prescriptions of benzodiazepines or sedative-hypnotics in individuals in recovery has a high rate of relapse with one author reporting more than a quarter of people relapsed after being prescribed sedative-hypnotics. Those who are long-term users of benzodiazepines should not be withdrawn rapidly, as severe anxiety and panic may develop, which are known risk factors for relapse into alcohol abuse. Taper regimes of 6–12 months have been found to be the most successful, with reduced intensity of withdrawal.[142][143]
- Calcium carbimide (Temposil) works in the same way as disulfiram; it has an advantage in that the occasional adverse effects of disulfiram, hepatotoxicity and drowsiness, do not occur with calcium carbimide.[144]
- Disulfiram (Antabuse) prevents the elimination of acetaldehyde, a chemical the body produces when breaking down ethanol. Acetaldehyde itself is the cause of many hangover symptoms from alcohol use. The overall effect is severe discomfort when alcohol is ingested: an extremely fast-acting and long-lasting uncomfortable hangover. This discourages an alcoholic from drinking in significant amounts while they take the medicine.
- Naltrexone is a competitive antagonist for opioid receptors, effectively blocking the effects of endorphins and opiates. Naltrexone is used to decrease cravings for alcohol and encourage abstinence. Alcohol causes the body to release endorphins, which in turn release dopamine and activate the reward pathways; hence when naltrexone is in the body there is a reduction in the pleasurable effects from consuming alcohol.[145] Evidence supports a reduced risk of relapse among alcohol dependent persons and a decrease in excessive drinking.[140] Nalmefene also appears effective and works by a similar manner.[140]

The Sinclair method is a method of using opiate antagonists to treat alcoholism by having the person take the medication about an hour before they drink alcohol, and only then.[146][147] The opioid blocks the positive reinforcement effects of ethanol and hopefully allows the person to stop drinking or drink less.[147]

Evidence does not support the use of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), antipsychotics, or gabapentin.[140]

## Dual addictions and dependences

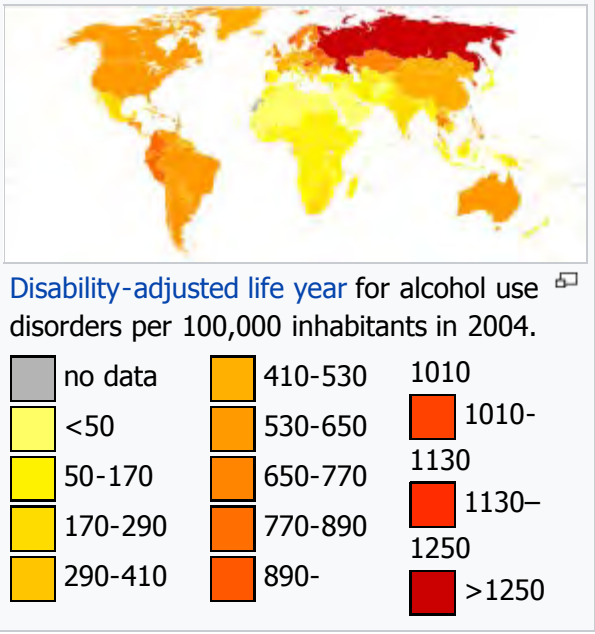
Alcoholics may also require treatment for other psychotropic drug addictions and drug dependences. The most common dual dependence syndrome with alcohol dependence is benzodiazepine dependence, with studies showing 10–20 percent of alcohol-dependent individuals had problems of dependence and/or

misuse problems of benzodiazepine drugs such as valium or clonazopam. These drugs are, like alcohol, depressants. Benzodiazepines may be used legally, if they are prescribed by doctors for anxiety problems or other mood disorders, or they may be purchased as illegal drugs "on the street" through illicit channels. Benzodiazepine use increases cravings for alcohol and the volume of alcohol consumed by problem drinkers.[148] Benzodiazepine dependency requires careful reduction in dosage to avoid benzodiazepine withdrawal syndrome and other health consequences. Dependence on other sedative-hypnotics such as zolpidem and zopiclone as well as opiates and illegal drugs is common in alcoholics. Alcohol itself is a sedative-hypnotic and is cross-tolerant with other sedative-hypnotics such as barbiturates, benzodiazepines and nonbenzodiazepines. Dependence upon and withdrawal from sedative-hypnotics can be medically severe and, as with alcohol withdrawal, there is a risk of psychosis or seizures if not managed properly.[149]

# Epidemiology

The World Health Organization estimates that as of 2010 there are 208 million people with alcoholism worldwide (4.1% of the population over 15 years of age).[7][19] Substance use disorders are a major public health problem facing many countries. "The most common substance of abuse/dependence in patients presenting for treatment is alcohol."[130] In the United Kingdom, the number of 'dependent drinkers' was calculated as over 2.8 million in 2001.[151] About 12% of American adults have had an alcohol dependence problem at some time in their life.[152] In the United States and Western Europe, 10 to 20 percent of men and 5 to 10 percent of women at some point in their lives will meet criteria for alcoholism.[153]

Within the medical and scientific communities, there is a broad consensus regarding alcoholism as a disease state. For example, the American Medical Association considers alcohol a drug and states that "drug addiction is a chronic, relapsing brain disease characterized by compulsive drug seeking and use despite often devastating consequences. It results from a complex interplay of biological vulnerability, environmental exposure, and developmental factors (e.g., stage of brain maturity)."[113] Alcoholism has a higher prevalence among men, though, in recent decades, the proportion of female alcoholics has increased.[36] Current evidence indicates that in both men and women, alcoholism is 50–60 percent genetically determined, leaving 40–50 percent for environmental influences.[154] Most alcoholics develop alcoholism during adolescence or young adulthood.[69] 31 percent of college students show signs of alcohol abuse, while six percent are dependent on alcohol. Under the DSM's new definition of alcoholics, that means about 37 percent of college students may meet the criteria.[155]

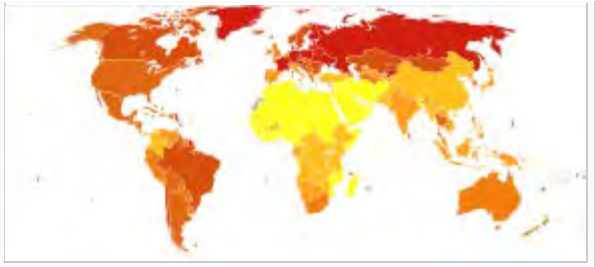



Disability-adjusted life year for alcohol use disorders per 100,000 inhabitants in 2004.

Total recorded yearly alcohol per capita consumption (15+), in litres of pure alcohol[150]

# Prognosis

Alcoholism often reduces a person's life expectancy by around ten years.[22] The most common cause of death in alcoholics is from cardiovascular complications.[156] There is a high rate of suicide in chronic alcoholics, which increases the longer a



Alcohol use disorders deaths per million persons in 2012

| | | |
|---|---|---|
| 0-0 | 7-13 | 38-52 |
| 1-3 | 14-20 | 53-255 |
| 4-6 | 21-37 | |

person drinks. Approximately 3–15 percent of alcoholics commit suicide,[157] and research has found that over 50 percent of all suicides are associated with alcohol or drug dependence. This is believed to be due to alcohol causing physiological distortion of brain chemistry, as well as social isolation. Suicide is also very common in adolescent alcohol abusers, with 25 percent of suicides in adolescents being related to alcohol abuse.[158] Among those with alcohol dependence after one year, some met the criteria for low-risk drinking, even though only 25.5 percent of the group received any treatment, with the breakdown as follows: 25 percent were found to be still dependent, 27.3 percent were in partial remission (some symptoms persist), 11.8 percent asymptomatic drinkers (consumption increases chances of relapse) and 35.9 percent were fully recovered — made up of 17.7 percent low-risk drinkers plus 18.2 percent abstainers.[159] In contrast, however, the results of a long-term (60-year) follow-up of two groups of alcoholic men indicated that "return to controlled drinking rarely persisted for much more than a decade without relapse or evolution into abstinence."[160] There was also "return-to-controlled drinking, as reported in short-term studies, is often a mirage."

## History

Adriaen Brouwer, *Inn with Drunken Peasants*, 1620s

Historically the name "dipsomania" was coined by German physician C. W. Hufeland in 1819 before it was superseded by "alcoholism".[161][162] That term now has a more specific meaning.[163] The term "alcoholism" was first used in 1849 by the Swedish physician Magnus Huss to describe the systematic adverse effects of alcohol.[164] Alcohol has a long history of use and misuse throughout recorded history. Biblical, Egyptian and Babylonian sources record the history of abuse and dependence on alcohol. In some ancient cultures alcohol was worshiped and in others, its abuse was condemned. Excessive alcohol misuse and drunkenness were recognized as causing social problems even thousands of years ago. However, the defining of habitual drunkenness as it was then known as and its adverse consequences were not well established medically until the 18th century. In 1647 a Greek monk named Agapios was the first to document that chronic alcohol misuse was associated with toxicity to the nervous system and body which resulted in a range of medical disorders such as seizures, paralysis, and internal bleeding. In 1920 the effects of alcohol abuse and chronic drunkenness led to the failed prohibition of alcohol being considered and eventually enforced briefly in America. In 2005 the cost of alcohol dependence and abuse was estimated to cost the US economy approximately 220 billion dollars per year, more than cancer and obesity.[165]

## Society and culture

The various health problems associated with long-term alcohol consumption are generally perceived as detrimental to society, for example, money due to lost labor-hours, medical costs due to injuries due to drunkenness and organ damage from long-term use, and secondary treatment costs, such as the costs of


1904 advertisement describing alcoholism as a disease.

rehabilitation facilities and detoxification centers. Alcohol use is a major contributing factor for head injuries, motor vehicle accidents (due to drunk driving), domestic violence, and assaults. Beyond the financial costs that alcohol consumption imposes, there are also significant social costs to both the alcoholic and their family and friends.[55] For instance, alcohol consumption by a pregnant woman can lead to fetal alcohol syndrome,[166] an incurable and damaging condition.[167] Estimates of the economic costs of alcohol abuse, collected by the World Health Organization, vary from one to six percent of a country's GDP.[168] One Australian estimate pegged alcohol's social costs at 24% of all drug abuse costs; a similar Canadian study concluded alcohol's share was 41%.[169] One study quantified the cost to the UK of *all* forms of alcohol misuse in 2001 as £18.5–20 billion.[151][170] All economic costs in the United States in 2006 have been estimated at $223.5 billion.[171]

Stereotypes of alcoholics are often found in fiction and popular culture. The "town drunk" is a stock character in Western popular culture. Stereotypes of drunkenness may be based on racism or xenophobia, as in the fictional depiction of the Irish as heavy drinkers.[172] Studies by social psychologists Stivers and Greeley attempt to document the perceived prevalence of high alcohol consumption amongst the Irish in America.[173] Alcohol consumption is relatively similar between many European cultures, the United States, and Australia. In Asian countries that have a high gross domestic product, there is heightened drinking compared to other Asian countries, but it is nowhere near as high as it is in other countries like the United States. It is also inversely seen, with countries that have very low gross domestic product showing high alcohol consumption.[174] In a study done on Korean immigrants in Canada, they reported alcohol was even an integral part of their meal, and is the only time solo drinking should occur. They also believe alcohol is necessary at any social event as it helps conversations start.[175]

Caucasians have a much lower abstinence rate (11.8%) and much higher tolerance to symptoms (3.4±2.45 drinks) of alcohol than Chinese (33.4% and 2.2±1.78 drinks respectively). Also, the more acculturation there is between cultures, the more influenced the culture is to adopt Caucasians drinking practices.[176] Peyote, a psychoactive agent, has even shown promise in treating alcoholism. Alcohol had actually replaced peyote as Native Americans' psychoactive agent of choice in rituals when peyote was outlawed.[177]

# Research

## Topiramate

Topiramate, a derivative of the naturally occurring sugar monosaccharide D-fructose, has been found effective in helping alcoholics quit or cut back on the amount they drink. Evidence suggests that topiramate antagonizes excitatory glutamate receptors, inhibits dopamine release, and enhances inhibitory gamma-aminobutyric acid function. A 2008 review of the effectiveness of topiramate concluded that the results of

published trials are promising, however as of 2008, data was insufficient to support using topiramate in conjunction with brief weekly compliance counseling as a first-line agent for alcohol dependence.[178] A 2010 review found that topiramate may be superior to existing alcohol pharmacotherapeutic options. Topiramate effectively reduces craving and alcohol withdrawal severity as well as improving quality-of-life-ratings.[179]

### Baclofen

Baclofen, a GABAB receptor agonist, is under study for the treatment of alcoholism.[180] A 2015 systematic review concluded that there is insufficient evidence for the use of baclofen for withdrawal symptoms in alcoholism.[181] There is tentative data supporting baclofen in alcohol dependence however further trials are needed as of 2013.[182]

### Ondansetron

Ondansetron, a 5HT3 antagonist, appears to have promise as a treatment.[183]

## See also

- Addictive personality
- Alcohol-related traffic crashes in the United States
- Alcohol Use Disorders Identification Test
- Alcoholism in family systems
- Collaborative Study On The Genetics of Alcoholism
- CRAFFT Screening Test
- High-functioning alcoholic
- List of countries by alcohol consumption

## References


1. ^ Jill Littrell (2014). *Understanding and Treating Alcoholism Volume I: An Empirically Based Clinician's Handbook for the Treatment of Alcoholism:volume Ii: Biological, Psychological, and Social Aspects of Alcohol Consumption and Abuse.* Hoboken: Taylor and Francis. p. 55. ISBN 9781317783145. "The World Health Organization defines alcoholism as any drinking which results in problems"
2. ^ Hasin, Deborah (December 2003). "Classification of Alcohol Use Disorders". *http://pubs.niaaa.nih.gov/*. Retrieved 28 February 2015. External link in `|website=` (help)
3. ^ *a b c* "Alcohol Use Disorder: A Comparison Between DSM–IV and DSM–5". November 2013. Retrieved 9 May 2015.
4. ^ *a b c d e f g h i* Association, American Psychiatric (2013). *Diagnostic and statistical manual of mental disorders : DSM-5.* (5 ed.). Washington, D.C.: American Psychiatric Association. pp. 490–497. ISBN 9780890425541.
5. ^ "Alcohol's Effects on the Body". Retrieved 9 May 2015.
6. ^ "Fetal Alcohol Exposure". Retrieved 9 May 2015.
7. ^ *a b c Global status report on alcohol and health 2014* (PDF). World Health Organization. 2014.
87. ^ Ehlers CL (2007). "Variations in ADH and ALDH in Southwest California Indians". *Alcohol Res Health*. **30** (1): 14–7. PMID 17718395.
88. ^ Szlemko WJ, Wood JW, Thurman PJ (October 2006). "Native Americans and alcohol: past, present, and future". *J Gen Psychol*. **133** (4): 435–51. doi:10.3200/GENP.133.4.435-451. PMID 17128961.
89. ^ Spillane NS, Smith GT (May 2007). "A theory of reservation-dwelling American Indian alcohol use risk". *Psychol Bull*. **133** (3): 395–418. doi:10.1037/0033-2909.133.3.395. PMID 17469984.
90. ^ American Heritage Dictionaries (12 April 2006). *The American Heritage dictionary of the English language* (4 ed.). Boston: Houghton Mifflin. ISBN 978-0-618-70172-8. "To use wrongly or improperly; misuse: abuse alcohol"
91. ^ "Dietary Guidelines for Americans 2005". USA: health.gov. 2005. Dietary Guidelines
92. ^ See question 16 of the Severity of Alcohol Dependence Questionnaire.
93. ^ http://pubs.niaaa.nih.gov/publications/aa68/aa68.htm

p. s8,51. ISBN 9789240692763.
8. ^ Agarwal-Kozlowski K, Agarwal DP (April 2000). "[Genetic predisposition for alcoholism]". *Ther Umsch*. **57** (4): 179–84. doi:10.1024/0040-5930.57.4.179. PMID 10804873.
9. ^ Moonat, S; Pandey, SC (2012). "Stress, epigenetics, and alcoholism.". *Alcohol research : current reviews*. **34** (4): 495–505. PMID 23584115.
10. ^ Mersy, DJ (1 April 2003). "Recognition of alcohol and substance abuse.". *American family physician*. **67** (7): 1529–32. PMID 12722853.
11. ^ "HEALTH AND ETHICS POLICIES OF THE AMA HOUSE OF DELEGATES" (PDF). June 2008. p. 33. Retrieved 10 May 2015. "H-30.997 Dual Disease Classification of Alcoholism: The AMA reaffirms its policy endorsing the dual classification of alcoholism under both the psychiatric and medical sections of the International Classification of Diseases. (Res. 22, I-79; Reaffirmed: CLRPD Rep. B, I-89; Reaffirmed: CLRPD Rep. B, I-90; Reaffirmed by CSA Rep. 14, A-97; Reaffirmed: CSAPH Rep. 3, A-07)"
12. ^ World Health Organization (January 2015). "Alcohol". Retrieved 10 May 2015.
13. ^ *a b* Blondell RD (February 2005). "Ambulatory detoxification of patients with alcohol dependence". *Am Fam Physician*. **71** (3): 495–502. PMID 15712624.
14. ^ DeVido, JJ; Weiss, RD (December 2012). "Treatment of the depressed alcoholic patient.". *Current psychiatry reports*. **14** (6): 610–8. doi:10.1007/s11920-012-0314-7. PMID 22907336.
15. ^ *a b* Morgan-Lopez AA, Fals-Stewart W (May 2006). "Analytic complexities associated with group therapy in substance abuse treatment research: problems, recommendations, and future directions". *Exp Clin Psychopharmacol*. **14** (2): 265–73. doi:10.1037/1064-1297.14.2.265. PMID 16756430.
16. ^ Albanese, AP (November 2012). "Management of alcohol abuse.". *Clinics in liver disease*. **16** (4): 737–62. doi:10.1016/j.cld.2012.08.006. PMID 23101980.
17. ^ Tusa, AL; Burgholzer, JA (2013). "Came to believe: spirituality as a mechanism of change in alcoholics anonymous: a review of the literature from 1992 to 2012.". *Journal of addictions nursing*. **24** (4): 237–46. doi:10.1097/jan.0000000000000003. PMID 24335771.
18. ^ Testino, G; Leone, S; Borro, P (December 2014). "Treatment of alcohol dependence: recent progress and reduction of consumption.". *Minerva medica*. **105** (6): 447–66. PMID 25392958.
19. ^ *a b* "Global Population Estimates by Age, 1950–2050". Retrieved 10 May 2015.
20. ^ *a b c d* "Alcohol Facts and Statistics". Retrieved 9 May 2015.
94. ^ Esser, Marissa B.; Hedden, Sarra L.; Kanny, Dafna; Brewer, Robert D.; Gfroerer, Joseph C.; Naimi, Timothy S. (20 November 2014). "Prevalence of Alcohol Dependence Among US Adult Drinkers, 2009–2011". *Preventing Chronic Disease*. **11**. doi:10.5888/pcd11.140329.
95. ^ Thomas F. McGovern; William L. White (20 May 2003). *Alcohol Problems in the United States: Twenty Years of Treatment Perspective*. Routledge. pp. 7–. ISBN 978-0-7890-2049-9. Retrieved 17 April 2010.
96. ^ "alcoholism" at *Dorland's Medical Dictionary*
97. ^ Thombs, Dennis L (1999). *Introductive To Addictive Behaviors 2ed*. London: The Guildford Press. p. 64.
98. ^ Thombs, Dennis L (1999). *Introduction to Addictive Behaviours 2ed*. London: The Guildford Press. p. 64.
99. ^ Thombs, Dennis (1999). *Introduction to Addictive Behaviors*. London: The Guildford Press. p. 64.
100. ^ Thombs, Dennis L (1999). *Introduction to Addictive Behaviors 2ed*. London: The Guildford Press. p. 65.
101. ^ *a b* VandenBos, Gary R. (15 July 2006). *APA dictionary of psychology*. Washington, DC: American Psychological Association. ISBN 978-1-59147-380-0.
102. ^ *a b* "Diagnostic Criteria for Alcohol Abuse and Dependence – Alcohol Alert No. 30-1995". Archived from the original on 27 March 2010. Retrieved 17 April 2010.
103. ^ Martin CS, Chung T, Langenbucher JW (August 2008). "How Should We Revise Diagnostic Criteria for Substance Use Disorders in the DSM—V?". *J Abnorm Psychol*. **117** (3): 561–75. doi:10.1037/0021-843X.117.3.561. PMC 2701140. PMID 18729609.
104. ^ "Proposed Revision | APA DSM-5". Archived from the original on 25 March 2010. Retrieved 17 April 2010.
105. ^ "A System to Convert ICD Diagnostic Codes for Alcohol Research". Retrieved 17 April 2010.
106. ^ *Diagnostic and statistical manual of mental disorders: DSM-IV*. Washington, DC: American Psychiatric Association. 31 July 1994. ISBN 978-0-89042-025-6.
107. ^ Morse RM, Flavin DK (August 1992). "The definition of alcoholism. The Joint Committee of the National Council on Alcoholism and Drug Dependence and the American Society of Addiction Medicine to Study the Definition and Criteria for the Diagnosis of Alcoholism". *JAMA: The Journal of the American Medical Association*. **268** (8): 1012–4. doi:10.1001/jama.1992.03490080086030. ISSN 0098-7484. PMID 1501306.
108. ^ Alcoholism at the US National Library of Medicine Medical Subject Headings (MeSH)
109. ^ *a b c* The first 100 members of AA (2001) [1939]. *Alcoholics Anonymous: the story of how many thousands of men and women have recovered from*

21. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013." *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
22. ^ *a b c* Schuckit, MA (27 November 2014). "Recognition and management of withdrawal delirium (delirium tremens).". *The New England Journal of Medicine*. **371** (22): 2109–13. doi:10.1056/NEJMra1407298. PMID 25427113.
23. ^ *Chambers English Thesaurus*. Allied Publishers. p. 175. ISBN 9788186062043.
24. ^ *a b* WHO. "Lexicon of alcohol and drug terms published by the World Health Organization". World Health Organisation.
25. ^ *a b* Hoffman PL, Tabakoff B (July 1996). "Alcohol dependence: a commentary on mechanisms". *Alcohol Alcohol*. **31** (4): 333–40. doi:10.1093/oxfordjournals.alcalc.a008159. PMID 8879279.
26. ^ Dunn N, Cook CC (March 1999). "Psychiatric aspects of alcohol misuse". *Hospital medicine (London, England : 1998)*. **60** (3): 169–72. doi:10.12968/hosp.1999.60.3.1060. ISSN 1462-3935. PMID 10476237.
27. ^ Wilson, Richard; Kolander, Cheryl A. (2003). *Drug abuse prevention: a school and community partnership*. Sudbury, Mass.: Jones and Bartlett. pp. 40–45. ISBN 978-0-7637-1461-1.
28. ^ "Biology". *The Volume Library*. **1**. Nashville, TN: The Southwestern Company. 2009. p. 29. ISBN 978-0-87197-208-8.
29. ^ *a b c d* O'Keefe, JH; Bhatti, SK; Bajwa, A; DiNicolantonio, JJ; Lavie, CJ (March 2014). "Alcohol and cardiovascular health: the dose makes the poison ... or the remedy.". *Mayo Clinic Proceedings*. **89** (3): 382–93. doi:10.1016/j.mayocp.2013.11.005. PMID 24582196.
30. ^ *Alcohol and Heart Health* American Heart Association
31. ^ American Medical Association (2003). Leiken, Jerrold B. MD; Lipsky, Martin S. MD, eds. *Complete Medical Encyclopedia* (Encyclopedia) (First ed.). New York, NY: Random House Reference. p. 485. ISBN 0-8129-9100-1.
32. ^ Müller D, Koch RD, von Specht H, Völker W, Münch EM (March 1985). "[Neurophysiologic findings in chronic alcohol abuse]". *Psychiatr Neurol Med Psychol (Leipz)* (in German). **37** (3): 129–32. PMID 2988001.
33. ^ Testino G (2008). "Alcoholic diseases in hepato-gastroenterology: a point of view". *Hepatogastroenterology*. **55** (82–83): 371–7. PMID 18613369.
34. ^ 10th Special Report to the U.S. Congress on *alcoholism*. New York City: Alcoholics Anonymous World Services. xxxii, 575 p. ISBN 1-893007-16-2.
110. ^ Kay AB (2000). "Overview of 'allergy and allergic diseases: with a view to the future'". *Br. Med. Bull.* **56** (4): 843–64. doi:10.1258/0007142001903481. ISSN 0007-1420. PMID 11359624.
111. ^ "The Big Book Self Test:". intoaction.us. Retrieved 19 February 2008.
112. ^ "OCTOBER 22 DEATHS". todayinsci.com. Archived from the original on 7 February 2008. Retrieved 18 February 2008.
113. ^ *a b* Nora Volkow. "Science of Addiction" (PDF). American Medical Association.
114. ^ Kahan M (April 1996). "Identifying and managing problem drinkers". *Can Fam Physician*. **42**: 661–71. PMC 2146411. PMID 8653034.
115. ^ Ewing JA (October 1984). "Detecting alcoholism. The CAGE questionnaire". *JAMA: The Journal of the American Medical Association*. **252** (14): 1905–7. doi:10.1001/jama.252.14.1905. ISSN 0098-7484. PMID 6471323.
116. ^ "CAGE questionnaire – screen for alcohol misuse" (PDF).
117. ^ Dhalla S, Kopec JA (2007). "The CAGE questionnaire for alcohol misuse: a review of reliability and validity studies". *Clin Invest Med*. **30** (1): 33–41. PMID 17716538.
118. ^ Raistrick, D.; Dunbar, G.; Davidson, R. (1983). "Alcohol Dependence Data Questionnaire (SADD)". European Monitoring Centre for Drugs and Drug Addiction.
119. ^ "Michigan Alcohol Screening Test". The National Council on Alcoholism and Drug Dependence.
120. ^ Thomas F. Babor; John C. Higgins-Biddle; John B. Saunders; Maristela G. Monteiro (2001). "The Alcohol Use Disorders Identification Test, Guidelines for Use in Primary Care" (PDF). World Health Organization.
121. ^ Smith SG, Touquet R, Wright S, Das Gupta N (September 1996). "Detection of alcohol misusing patients in accident and emergency departments: the Paddington alcohol test (PAT)". *Journal of Accident and Emergency Medicine*. British Association for Accident and Emergency Medicine. **13** (5): 308–312. doi:10.1136/emj.13.5.308. ISSN 1351-0622. PMC 1342761. PMID 8894853.
122. ^ *a b* Nurnberger, Jr., John I., and Bierut, Laura Jean. "Seeking the Connections: Alcoholism and our Genes." *Scientific American*, April 2007, Vol. 296, Issue 4.
123. ^ New York Daily News (William Sherman) Test targets addiction gene[*permanent dead link*] 11 February 2006
124. ^ Berggren U, Fahlke C, Aronsson E, Karanti A, Eriksson M, Blennow K, Thelle D, Zetterberg H, Balldin J (September 2006). "The taqI DRD2 A1 allele is associated with alcohol-dependence although its effect size is small" (Free full text). *Alcohol and alcoholism (Oxford, Oxfordshire)*. **41** (5): 479–85.

Alcohol and Health, 2000, U.S. Department of Health and Human Services, Public Health Service National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism.

35. ^ a b c Blum, Laura N.; Nielsen, Nancy H.; Riggs, Joseph A.; Council on Scientific Affairs, American Medical Association (September 1998). "Alcoholism and alcohol abuse among women: report of the council on scientific affairs". *Journal of Women's Health*. Mary Ann Liebert, Inc. **7** (7): 861–870. doi:10.1089/jwh.1998.7.861.
36. ^ a b Walter H, Gutierrez K, Ramskogler K, Hertling I, Dvorak A, Lesch OM (November 2003). "Gender-specific differences in alcoholism: implications for treatment". *Archives of Women's Mental Health*. **6** (4): 253–8. doi:10.1007/s00737-003-0014-8. PMID 14628177.
37. ^ Mihai B, Lăcătuşu C, Graur M (April–June 2008). "[Alcoholic ketoacidosis]". *Rev Med Chir Soc Med Nat Iasi*. **112** (2): 321–6. PMID 19294998.
38. ^ Sibaï K, Eggimann P (September 2005). "[Alcoholic ketoacidosis: not rare cause of metabolic acidosis]". *Rev Med Suisse*. **1** (32): 2106, 2108–10, 2112–5. PMID 16238232.
39. ^ Cederbaum AI (2012). "Alcohol metabolism". *Clin Liver Dis*. **16** (4): 667–85. doi:10.1016/j.cld.2012.08.002. PMC 3484320. PMID 23101976.
40. ^ a b Georgy Bakalkin (8 July 2008). "Alcoholism-associated molecular adaptations in brain neurocognitive circuits". eurekalert.org. Retrieved 11 January 2012.
41. ^ Oscar-Berman M, Marinkovic K (2003). "Alcoholism and the brain: an overview". *Alcohol Res Health*. **27** (2): 125–33. PMID 15303622.
42. ^ Uekermann J, Daum I (May 2008). "Social cognition in alcoholism: a link to prefrontal cortex dysfunction?". *Addiction*. **103** (5): 726–35. doi:10.1111/j.1360-0443.2008.02157.x. PMID 18412750.
43. ^ Wetterling T, Junghanns K (September 2000). "Psychopathology of alcoholics during withdrawal and early abstinence". *Eur Psychiatry*. **15** (8): 483–8. doi:10.1016/S0924-9338(00)00519-8. ISSN 0924-9338. PMID 11175926.
44. ^ Schuckit MA (November 1983). "Alcoholism and other psychiatric disorders". *Hosp Community Psychiatry*. **34** (11): 1022–7. doi:10.1176/ps.34.11.1022. ISSN 0022-1597. PMID 6642446.
45. ^ Cowley DS (24 January 1992). "Alcohol abuse, substance abuse, and panic disorder". *Am J Med*. **92** (1A): 41S–48S. doi:10.1016/0002-9343(92)90136-Y. ISSN 0002-9343. PMID 1346485.
46. ^ Cosci F, Schruers KR, Abrams K, Griez EJ (June 2007). "Alcohol use disorders and panic disorder: a review of the evidence of a direct relationship". *J Clin Psychiatry*. **68** (6): 874–80. doi:10.1093/alcalc/agl043. ISSN 0735-0414. PMID 16751215.
125. ^ Jones AW (2006). "Urine as a biological specimen for forensic analysis of alcohol and variability in the urine-to-blood relationship". *Toxicol Rev*. **25** (1): 15–35. doi:10.2165/00139709-200625010-00002. PMID 16856767.
126. ^ Das SK, Dhanya L, Vasudevan DM (2008). "Biomarkers of alcoholism: an updated review". *Scand J Clin Lab Invest*. **68** (2): 81–92. doi:10.1080/00365510701532662. PMID 17852805.
127. ^ World Health Organisation (2010). "Alcohol".
128. ^ "Alcohol policy in the WHO European Region: current status and the way forward" (PDF). World Health Organisation. 12 September 2005.
129. ^ Crews F, He J, Hodge C (February 2007). "Adolescent cortical development: a critical period of vulnerability for addiction". *Pharmacol Biochem Behav*. **86** (2): 189–99. doi:10.1016/j.pbb.2006.12.001. PMID 17222895.
130. ^ a b Gabbard, Glen O. (2001). *Treatments of psychiatric disorders* (3 ed.). Washington, DC: American Psychiatric Press. ISBN 978-0-88048-910-2.
131. ^ Stavro K, Pelletier J, Potvin S (January 2012). "Widespread and sustained cognitive deficits in alcoholism: a meta-analysis.". *Addict Biol*. **18** (2): 203–13. doi:10.1111/j.1369-1600.2011.00418.x. PMID 22264351.
132. ^ Smith, M.A., Melinda; Saisan, M.S.W., Joanna (2016). "Self-Help Groups for Alcohol Addiction".
133. ^ Dawson DA, Grant BF, Stinson FS, Chou PS, Huang B, Ruan WJ (2005). "Recovery from DSM-IV alcohol dependence: United States, 2001–2002". *Addiction*. **100** (3): 281–92. doi:10.1111/j.1360-0443.2004.00964.x. PMID 15733237.
134. ^ Dawson DA, Goldstein RB, Grant BF (2007). "Rates and correlates of relapse among individuals in remission from DSM-IV alcohol dependence: a 3-year follow-up". *Alcoholism: Clinical and Experimental Research*. **31** (12): 2036–45. doi:10.1111/j.1530-0277.2007.00536.x. PMID 18034696.
135. ^ Vaillant GE (2003). "A 60-year follow-up of alcoholic men". *Addiction (Abingdon, England)*. **98** (8): 1043–51. doi:10.1046/j.1360-0443.2003.00422.x. PMID 12873238.
136. ^ National Institute on Alcohol Abuse and Alcoholism. http://pubs.niaaa.nih.gov/publications/AA76/AA76.htm
137. ^ Mason BJ, Heyser CJ (January 2010). "The neurobiology, clinical efficacy and safety of acamprosate in the treatment of alcohol dependence". *Expert Opin Drug Saf*. **9** (1): 177–88. doi:10.1517/14740330903512943. PMID 20021295.
138. ^ Mason BJ, Heyser CJ (March 2010). "Acamprosate:

doi:10.4088/JCP.v68n0608. ISSN 0160-6689. PMID 17592911.
47. ^ Grant BF, Harford TC (October 1995). "Comorbidity between DSM-IV alcohol use disorders and major depression: results of a national survey". *Drug Alcohol Depend*. **39** (3): 197–206. doi:10.1016/0376-8716(95)01160-4. ISSN 0376-8716. PMID 8556968.
48. ^ Kandel DB, Huang FY, Davies M (October 2001). "Comorbidity between patterns of substance use dependence and psychiatric syndromes". *Drug Alcohol Depend*. **64** (2): 233–41. doi:10.1016/S0376-8716(01)00126-0. ISSN 0376-8716. PMID 11543993.
49. ^ Cornelius JR, Bukstein O, Salloum I, Clark D (2003). "Alcohol and psychiatric comorbidity". *Recent Dev Alcohol*. Recent Developments in Alcoholism. **16**: 361–74. doi:10.1007/0-306-47939-7_24. ISBN 0-306-47258-9. ISSN 0738-422X. PMID 12638646.
50. ^ Schuckit MA, Tipp JE, Bergman M, Reich W, Hesselbrock VM, Smith TL (July 1997). "Comparison of induced and independent major depressive disorders in 2,945 alcoholics". *Am J Psychiatry*. **154** (7): 948–57. doi:10.1176/ajp.154.7.948. ISSN 0002-953X. PMID 9210745.
51. ^ Schuckit MA, Tipp JE, Bucholz KK, Nurnberger JI, Hesselbrock VM, Crowe RR, Kramer J (October 1997). "The life-time rates of three major mood disorders and four major anxiety disorders in alcoholics and controls". *Addiction*. **92** (10): 1289–304. doi:10.1111/j.1360-0443.1997.tb02848.x. ISSN 0965-2140. PMID 9489046.
52. ^ Schuckit MA, Smith TL, Danko GP, Pierson J, Trim R, Nurnberger JI, Kramer J, Kuperman S, Bierut LJ, Hesselbrock V (November 2007). "A comparison of factors associated with substance-induced versus independent depressions". *J Stud Alcohol Drugs*. **68** (6): 805–12. doi:10.15288/jsad.2007.68.805. ISSN 1937-1888. PMID 17960298.
53. ^ Schuckit M (June 1983). "Alcoholic patients with secondary depression". *Am J Psychiatry*. **140** (6): 711–4. doi:10.1176/ajp.140.6.711. ISSN 0002-953X. PMID 6846629.
54. ^ *a b c* Karrol Brad R. (2002). "Women and alcohol use disorders: a review of important knowledge and its implications for social work practitioners". *Journal of social work*. **2** (3): 337–356. doi:10.1177/146801730200200305.
55. ^ *a b c* McCully, Chris (2004). *Goodbye Mr. Wonderful. Alcohol, Addition and Early Recovery*. London: Jessica Kingsley Publishers. ISBN 978-1-84310-265-6.
56. ^ Isralowitz, Richard (2004). *Drug use: a reference handbook*. Santa Barbara, Calif.: ABC-CLIO. pp. 122–123. ISBN 978-1-57607-708-5.
57. ^ Langdana, Farrokh K. (27 March 2009). *Macroeconomic Policy: Demystifying Monetary and Fiscal Policy* (2nd ed.). Springer. p. 81. ISBN 978-
A prototypic neuromodulator in the treatment of alcohol dependence". *CNS Neurol Disord Drug Targets*. **9** (1): 23–32. doi:10.2174/187152710790966641. PMC 2853976. PMID 20201812.
139. ^ Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M (2010). Rösner S, ed. "Acamprosate for alcohol dependence". *Cochrane Database of Systematic Reviews* (9): CD004332. doi:10.1002/14651858.CD004332.pub2. PMID 20824837.
140. ^ *a b c d* Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, Kim MM, Shanahan E, Gass CE, Rowe CJ, Garbutt JC (14 May 2014). "Pharmacotherapy for Adults With Alcohol Use Disorders in Outpatient Settings". *JAMA*. **311** (18): 1889–900. doi:10.1001/jama.2014.3628. PMID 24825644.
141. ^ Lindsay, S.J.E.; Powell, Graham E., eds. (28 July 1998). *The Handbook of Clinical Adult Psychology* (2nd ed.). Routledge. p. 402. ISBN 978-0-415-07215-1.
142. ^ Gitlow, Stuart (1 October 2006). *Substance Use Disorders: A Practical Guide* (2nd ed.). USA: Lippincott Williams and Wilkins. pp. 52 and 103–121. ISBN 978-0-7817-6998-3.
143. ^ Kushner MG, Abrams K, Borchardt C (March 2000). "The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings". *Clin Psychol Rev*. **20** (2): 149–71. doi:10.1016/S0272-7358(99)00027-6. PMID 10721495.
144. ^ Ogborne AC (June 2000). "Identifying and treating patients with alcohol-related problems". *CMAJ*. **162** (12): 1705–8. PMC 1232509. PMID 10870503.
145. ^ Soyka M, Rösner S (November 2008). "Opioid antagonists for pharmacological treatment of alcohol dependence – a critical review". *Curr Drug Abuse Rev*. **1** (3): 280–91. doi:10.2174/1874473710801030280. PMID 19630726.
146. ^ Anderson, Kenneth (Jul 28, 2013). "Drink Your Way Sober with Naltrexone". *Psychology Today*. Retrieved 18 July 2016.
147. ^ *a b* Sinclair, JD (2001). "Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism.". *Alcohol and alcoholism (Oxford, Oxfordshire)*. **36** (1): 2–10. doi:10.1093/alcalc/36.1.2. PMID 11139409.
148. ^ Poulos CX, Zack M (November 2004). "Low-dose diazepam primes motivation for alcohol and alcohol-related semantic networks in problem drinkers". *Behav Pharmacol*. **15** (7): 503–12. doi:10.1097/00008877-200411000-00006. ISSN 0955-8810. PMID 15472572.
149. ^ Johansson BA, Berglund M, Hanson M, Pöhlén C, Persson I (November 2003). "Dependence on legal psychotropic drugs among alcoholics" (PDF).

0-387-77665-1.
58. ^ Gifford, Maria (22 October 2009). *Alcoholism (Biographies of Disease)*. Greenwood Press. pp. 89–91. ISBN 978-0-313-35908-8.
59. ^ Schadé, Johannes Petrus (October 2006). *The Complete Encyclopedia of Medicine and Health*. Foreign Media Books. pp. 132–133. ISBN 978-1-60136-001-4.
60. ^ Gold, Mark. "Children of Alcoholics". Psych Central. Retrieved 27 November 2011.
61. ^ Galanter, Marc; Kleber, Herbert D. (1 July 2008). *The American Psychiatric Publishing Textbook of Substance Abuse Treatment* (4th ed.). United States of America: American Psychiatric Publishing Inc. p. 58. ISBN 978-1-58562-276-4.
62. ^ Dart, Richard C. (1 December 2003). *Medical Toxicology* (3rd ed.). USA: Lippincott Williams & Wilkins. pp. 139–140. ISBN 978-0-7817-2845-4.
63. ^ Idemudia SO, Bhadra S, Lal H (June 1989). "The pentylenetetrazol-like interoceptive stimulus produced by ethanol withdrawal is potentiated by bicuculline and picrotoxinin". *Neuropsychopharmacology*. **2** (2): 115–22. doi:10.1016/0893-133X(89)90014-6. ISSN 0893-133X. PMID 2742726.
64. ^ Chastain G (October 2006). "Alcohol, neurotransmitter systems, and behavior". *The Journal of General Psychology*. **133** (4): 329–35. doi:10.3200/GENP.133.4.329-335. ISSN 0022-1309. PMID 17128954.
65. ^ *a b c* Heilig M, Egli M, Crabbe JC, Becker HC (April 2010). "Acute withdrawal, protracted abstinence and negative affect in alcoholism: are they linked?". *Addict Biol*. **15** (2): 169–84. doi:10.1111/j.1369-1600.2009.00194.x. PMC 3268458. PMID 20148778.
66. ^ Johnson, Bankole A. (2011). *Addiction medicine : science and practice*. New York: Springer. pp. 301–303. ISBN 978-1-4419-0337-2.
67. ^ Breese GR, Sinha R, Heilig M (February 2011). "Chronic alcohol neuroadaptation and stress contribute to susceptibility for alcohol craving and relapse.". *Pharmacol Ther*. **129** (2): 149–71. doi:10.1016/j.pharmthera.2010.09.007. PMC 3026093. PMID 20951730.
68. ^ Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM (November 1989). "Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar).". *Br J Addict*. **84** (11): 1353–7. doi:10.1111/j.1360-0443.1989.tb00737.x. PMID 2597811.
69. ^ *a b c d* Enoch MA (December 2006). "Genetic and environmental influences on the development of alcoholism: resilience vs. risk". *Annals of the New York Academy of Sciences*. **1094** (1): 193–201. doi:10.1196/annals.1376.019. PMID 17347351.
70. ^ Bierut LJ, Schuckit MA, Hesselbrock V, Reich T (2000). "Co-occurring risk factors for alcohol dependence and habitual smoking". *Alcohol Res Alcohol Alcohol*. **38** (6): 613–8. doi:10.1093/alcalc/agg123. ISSN 0735-0414. PMID 14633651.
150. ^ Catherine Le Galès-Camus (2004). *Global Status Report on Alcohol 2004* (PDF). World Health Organization. ISBN 92-4-156272-2.
151. ^ *a b* "Alcohol misuse: How much does it cost?" (PDF). Cabinet Office Strategy Unit. September 2003.
152. ^ Hasin DS, Stinson FS, Ogburn E, Grant BF (2007). "Prevalence, Correlates, Disability, and Comorbidity of DSM-IV Alcohol Abuse and Dependence in the United States". *Archives of General Psychiatry*. **64** (7): 830–42. doi:10.1001/archpsyc.64.7.830. PMID 17606817.
153. ^ "alcoholism". Encyclopædia Britannica. 2010.
154. ^ Dick DM, Bierut LJ (April 2006). "The genetics of alcohol dependence". *Current psychiatry reports*. **8** (2): 151–7. doi:10.1007/s11920-006-0015-1. ISSN 1523-3812. PMID 16539893.
155. ^ "About 37 percent of college students could now be considered alcoholics". *Emerald Media*.
156. ^ Zuskin E, Jukić V, Lipozencić J, Matosić A, Mustajbegović J, Turcić N, Poplasen-Orlovac D, Bubas M, Prohić A (December 2006). "[Alcoholism—how it affects health and working capacity]". *Arh Hig Rada Toksikol*. **57** (4): 413–26. PMID 17265681.
157. ^ *American Psychiatric Association practice guidelines for the treatment of psychiatric disorders.* Arlington, Virg.: American Psychiatric Association. 2006. p. 1346. ISBN 9780890423851.
158. ^ O'Connor, Rory; Sheehy, Noel (29 January 2000). *Understanding suicidal behaviour*. Leicester: BPS Books. pp. 33–37. ISBN 978-1-85433-290-5.
159. ^ The National Institute on Alcohol Abuse and Alcoholism; U.S. Department of Health and Human Services, NIH News (18 January 2005). "2001–2002 Survey Finds That Many Recover From Alcoholism". National Institutes of Health.
160. ^ Vaillant GE (August 2003). "A 60-year follow-up of alcoholic men". *Addiction*. **98** (8): 1043–51. doi:10.1046/j.1360-0443.2003.00422.x. ISSN 0965-2140. PMID 12873238.
161. ^ Peters, Uwe Henrik (30 April 2007). *Lexikon Psychiatrie, Psychotherapie, Medizinische Psychologie*. Urban Fischer bei Elsev. ISBN 978-3-437-15061-6.
162. ^ Valverde, Mariana (1998). *Diseases of the Will*. Cambridge: Cambridge University Press. p. 48. ISBN 978-0-521-64469-3.
163. ^ Tracy, Sarah J. (25 May 2005). *Alcoholism in America: from reconstruction to prohibition*. Baltimore: Johns Hopkins University Press. pp. 31–52. ISBN 978-0-8018-8119-0.
164. ^ *Alcoholismus chronicus, eller Chronisk alkoholssjukdom:*. Stockholm und Leipzig. 1852. Retrieved 19 February 2008.
165. ^ Potter, James V. (14 January 2008). *Substances of Abuse*. **2**. AFS Publishing Co. pp. 1–13. ISBN 978-1-930327-46-7.

*Health*. **24** (4): 233–41. PMID 15986718.
71. ^ Agrawal A, Sartor CE, Lynskey MT, Grant JD, Pergadia ML, Grucza R, Bucholz KK, Nelson EC, Madden PA, Martin NG, Heath AC (2009). "Evidence for an Interaction Between Age at 1st Drink and Genetic Influences on DSM-IV Alcohol Dependence Symptoms". *Alcoholism: Clinical and Experimental Research*. **33** (12): 2047–56. doi:10.1111/j.1530-0277.2009.01044.x. PMC 2883563. PMID 19764935.
72. ^ *a b* "Early Age At First Drink May Modify Tween/Teen Risk For Alcohol Dependence". Medical News Today. 21 September 2009.
73. ^ Schwandt ML, Lindell SG, Chen S, Higley JD, Suomi SJ, Heilig M, Barr CS (February 2010). "Alcohol Response and Consumption in Adolescent Rhesus Macaques: Life History and Genetic Influences". *Alcohol*. **44** (1): 67–80. doi:10.1016/j.alcohol.2009.09.034. PMC 2818103. PMID 20113875.
74. ^ Crews FT, Boettiger CA (September 2009). "Impulsivity, Frontal Lobes and Risk for Addiction". *Pharmacol Biochem Behav*. **93** (3): 237–47. doi:10.1016/j.pbb.2009.04.018. PMC 2730661. PMID 19410598.
75. ^ Weinberger, A. H.; Platt, J; Goodwin, R. D. (2016). "Is cannabis use associated with an increased risk of onset and persistence of alcohol use disorders? A three-year prospective study among adults in the United States". *Drug and Alcohol Dependence*. **161**: 363–7. doi:10.1016/j.drugalcdep.2016.01.014. PMID 26875671.
76. ^ Kirby, T; Barry, A. E. (2012). "Alcohol as a gateway drug: A study of US 12th graders" (PDF). *Journal of School Health*. **82** (8): 371–9. doi:10.1111/j.1746-1561.2012.00712.x. PMID 22712674.
77. ^ "Volume of World Beer Production". *European Beer Guide*. Archived from the original on 28 October 2006. Retrieved 17 October 2006.
78. ^ Nelson, Max (2005). *The Barbarian's Beverage: A History of Beer in Ancient Europe*. Abingdon, Oxon: Routledge. p. 1. ISBN 0-415-31121-7. Retrieved 21 September 2010.
79. ^ Rudgley, Richard (1993). *The Alchemy of Culture: Intoxicants in Society*. London: British Museum Press. p. 411. ISBN 978-0-7141-1736-2. Retrieved 13 January 2012.
80. ^ Arnold, John P (2005). *Origin and History of Beer and Brewing: From Prehistoric Times to the Beginning of Brewing Science and Technology*. Cleveland, Ohio: Reprint Edition by BeerBooks. p. 411. ISBN 0-9662084-1-2. Retrieved 13 January 2012.
81. ^ Joshua J. Mark (2011). Beer. Ancient History Encyclopedia.
82. ^ *World's Best Beers: One Thousand*. Google Books. 6 October 2009. ISBN 978-1-4027-6694-7. Retrieved 7 August 2010.
166. ^ Julie Louise Gerberding; José Cordero; R. Louise Floyd (May 2005). "Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis" (PDF). USA: Centers for Disease Control and Prevention.
167. ^ Streissguth, Ann Pytkowicz (1 September 1997). *Fetal alcohol syndrome: a guide for families and communities*. Baltimore, MD, USA: Paul H Brookes Pub. ISBN 978-1-55766-283-5.
168. ^ "Global Status Report on Alcohol 2004" (PDF). World Health Organization. Archived (PDF) from the original on 30 December 2006. Retrieved 3 January 2007.
169. ^ "Economic cost of alcohol consumption". World Health Organization Global Alcohol Database. Retrieved 3 January 2007.
170. ^ "Q&A: The costs of alcohol". BBC. 19 September 2003.
171. ^ Bouchery EE, Harwood HJ, Sacks JJ, Simon CJ, Brewer RD (2011). "Economic Costs of Excessive Alcohol Consumption in the U.S., 2006". *American Journal of Preventive Medicine*. **41** (5): 516–524. doi:10.1016/j.amepre.2011.06.045. PMID 22011424.
172. ^ "World/Global Alcohol/Drink Consumption". Finfacts Ireland. 2009.
173. ^ Stivers, Richard (May 2000). *Hair of the dog: Irish drinking and its American stereotype*. New York: Continuum. ISBN 978-0-8264-1218-8.
174. ^ Chen CC, Yin SJ (2008). "Alcohol abuse and related factors in Asia". *International Review of Psychiatry*. **20** (5): 425–433. doi:10.1080/09540260802344075. PMID 19012127.
175. ^ Wooksoo, K. (2009). Drinking Culture of Elderly Korean Immigrants in Canada: A Focus Group Study. Journal of Cross-Cultural Gerontology, 24(4), 339–353.
176. ^ Li, H. Z., & Rosenblood, L. (1994). Exploring factors influencing alcohol consumption patterns among Chinese and Caucasians. Journal of Studies on Alcohol, 55(4), 427. Retrieved from EBSCOhost.
177. ^ French, L. (2008). Psychoactive agents and Native American spirituality: Past and present. Contemporary Justice Review, 11(2), 155–163.
178. ^ Olmsted CL, Kockler DR (October 2008). "Topiramate for alcohol dependence". *Ann Pharmacother*. **42** (10): 1475–80. doi:10.1345/aph.1L157. ISSN 1060-0280. PMID 18698008.
179. ^ Kenna GA, Lomastro TL, Schiesl A, Leggio L, Swift RM (May 2009). "Review of topiramate: an antiepileptic for the treatment of alcohol dependence". *Curr Drug Abuse Rev*. **2** (2): 135–42. doi:10.2174/1874473710902020135. PMID 19630744.
180. ^ Leggio L, Garbutt JC, Addolorato G (March 2010). "Effectiveness and safety of baclofen in the treatment of alcohol dependent patients.". *CNS & neurological disorders drug targets*. **9** (1): 33–44.

83. ^ "Gender differences in alcohol use and alcohol dependence or abuse: 2004 or 2005." The NSDUH Report. Accessed 22 June 2012.
84. ^ Moore S, Montane-Jaime LK, Carr LG, Ehlers CL (2007). "Variations in alcohol-metabolizing enzymes in people of East Indian and African descent from Trinidad and Tobago". *Alcohol Res Health*. **30** (1): 28–30. PMID 17718398.
85. ^ Eng MY, Luczak SE, Wall TL (2007). "ALDH2, ADH1B, and ADH1C genotypes in Asians: a literature review". *Alcohol Res Health*. **30** (1): 22–7. PMID 17718397.
86. ^ Scott DM, Taylor RE (2007). "Health-related effects of genetic variations of alcohol-metabolizing enzymes in African Americans". *Alcohol Res Health*. **30** (1): 18–21. PMID 17718396.
181. ^ Liu, J; Wang, LN (3 April 2015). "Baclofen for alcohol withdrawal.". *The Cochrane database of systematic reviews*. **4**: CD008502. doi:10.1002/14651858.CD008502.pub4. PMID 25836263.
182. ^ "Baclofen and severe alcohol dependence: an uncertain harm-benefit balance as of early 2013.". *Prescrire Int*. **22** (141): 214–7. September 2013. PMID 24171218.
183. ^ Kenna GA (2010). "Medications acting on the serotonergic system for the treatment of alcohol dependent patients.". *Current pharmaceutical design*. **16** (19): 2126–35. doi:10.2174/138161210791516396. PMID 20482508.



doi:10.2174/187152710790966614. PMID 20201813.


## Further reading


- Cannon, Eoin F. (2013). *The Saloon and the Mission: Addiction, Conversion, and the Politics of Redemption in American Culture.* Amherst, MA: University of Massachusetts Press.
- Galanter, Marc (2005). *Alcohol Problems in Adolescents and Young Adults: Epidemiology, Neurobiology, Prevention, Treatment*. New York, NY: Kluwer Academic/Plenum. ISBN 0-306-48625-3. OCLC 133155628.
- Hedblom, Jack H. (2007). *Last Call: Alcoholism and Recovery*. Baltimore, MD: Johns Hopkins University Press. ISBN 978-0-8018-8677-5. OCLC 237901552.
- National Institute on Alcohol Abuse and Alcoholism. "Etiology and Natural History of Alcoholism".
- The Online Resource for Addiction Recovery, Addiction Treatment & Addiction help. "Addiction Recovery".
- O'Farrell, Timothy J. and William Fals-Stewart (2006). *Behavioral Couples Therapy for Alcoholism and Drug Abuse*. New York, NY: Guilford Press. ISBN 1-59385-324-6. OCLC 64336035.
- Osborn, Matthew Warner (2014). *Rum Maniacs: Alcoholic Insanity in the Early American Republic.* Chicago: University of Chicago Press.
- Pence, Gregory, "Kant on Whether Alcoholism is a Disease," Ch. 2, *The Elements of Bioethics*, McGraw-Hill Books, 2007.
- Plant, Martin A. and Moira Plant (2006). *Binge Britain: Alcohol and the National Response*. Oxford, UK; New York, NY: Oxford University Press. ISBN 0-19-929940-4. OCLC 238809013.
- Smart, Lesley (2007). *Alcohol and Human Health*. Oxford, UK: Oxford University Press. ISBN 978-0-19-923735-7. OCLC 163616466.
- Sutton, Philip M. (2007). "Alcoholism and Drug Abuse". In Michael L. Coulter; Stephen M. Krason; Richard S. Myers; Joseph A. Varacalli. *Encyclopedia of Catholic Social Thought, Social Science, and Social Policy*. Lanham, MD; Toronto, Canada; Plymouth, UK: Scarecrow Press. pp. 22–24. ISBN 978-0-8108-5906-7.
- Thompson, Warren, MD, FACP. "Alcoholism." Emedicine.com, 6 June 2007. Retrieved 2007-09-02.
- Erdozain AM, Callado LF (2014). "Neurobiological alterations in alcohol addiction: a review". *Adicciones*. **26** (4): 360–370. PMID 25578004.


## External links

- Alcohol at DMOZ
- CAGE Questionnaire on NIH
- CIWA-Ar Score for Alcohol Withdrawal

Find more about
**Alcoholism**
at Wikipedia's sister projects

Definitions from Wiktionary
Media from Commons
Quotations from Wikiquote

| v · t · e · | Reinforcement disorders: Addiction and Dependence | |
|---|---|---|
| Addiction | Drug | **Alcoholism** · Amphetamine · Cocaine · Ethanol · Methamphetamine · Methylphenidate · Nicotine · Opioid · |
| | Behavioral | Financial (Gambling · Shopping · · Media (Computer · Internet · Video game · · Palatable food · Sex-related (Cybersex · Intercourse · Pornography · · |
| | Cellular mechanisms | Transcriptional (**ΔFosB** · c-Fos · Cdk5 · CREB · GluR2 · NF-κB · · Epigenetic (**G9a** · G9a-like protein · **HDAC1** · **HDAC2** · **HDAC3** · HDAC4 · HDAC5 · HDAC9 · HDAC10 · SIRT1 · SIRT2 · ... · · |
| Dependence | Concepts | Physical dependence · Psychological dependence · Withdrawal · |
| | Disorders | **Alcoholism** · Amphetamine · Barbiturate · Benzodiazepine · Caffeine · Cannabis · Cocaine · Nicotine · Opioid · Substituted amphetamine · |
| See also | Category:Addiction · Cognitive behavioral therapy · Harm reduction · Support groups (Addiction recovery groups · List of twelve-step groups · NoFap · · | |

| v · t · e · | Alcohol and health | |
|---|---|---|
| Specific interactions | Note: see Template:Psychoactive substance use for diagnoses<br>Aging · Alcohol-induced mood disorders · Brain · Cancer (breast cancer · · Sleep · Tolerance · Weight · | |
| Substance abuse prevention | Sobriety | Alcohol-free zone · Alcohol detoxification · Alcohol rehabilitation · Alcoholics Anonymous · Sober companion · |
| | Alcohol limitation | 0-0-1-3 · Ban on caffeinated alcoholic beverages · Alcohol education · Alcohol server training · Recommended maximum intake of alcoholic beverages · |
| | Addiction medicine | **Alcoholism** · Anti-addictive psychedelics: Ibogaine, *Salvia divinorum* · |
| Religion and alcohol | Christian views on alcohol (alcohol in the Bible · · Islam and alcohol · Dionysian Mysteries · | |
| Social issues | Alcohol advertising (on college campuses · · Alcohol-free beverage definition controversy · Alcohol self-medication · Native Americans · Binge drinking (0.08 BAC · · Blackout (alcohol-related amnesia) · College student alcoholism · Domestic violence · Drinking games / pregaming · Driving under the influence · Drunkorexia · Dry January · Adult Children of Alcoholics · Family systems · French paradox · High-functioning alcoholic (HFA) · moonshine contamination · Rum-running (black market · · Sex · Sin tax / Pigovian tax · | |
| General | Short-term effects of alcohol consumption · Long-term effects of alcohol consumption · | |

| v · t · e · | Psychoactive substance-related disorder (F10–F19, 291–292; 303–305) | |
|---|---|---|
| General | SID (Substance intoxication / Drug overdose · Withdrawal · Substance-induced psychosis · · SUD (Substance abuse · Physical dependence / Substance dependence · · | |

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|---|---|---|---|---|
| **Alcohol** | **SID** | **Diseases** | **Neurological disorders** | Alcoholic hallucinosis · Alcohol withdrawal · Fetal alcohol spectrum disorder (FASD) · Fetal alcohol syndrome (FAS) · Korsakoff's syndrome · Wernicke–Korsakoff syndrome · Wernicke's encephalopathy · |
| | | | **Digestive system** | Alcoholic hepatitis · Alcoholic liver disease · Auto-brewery syndrome · |
| | | | **Nervous system** | Alcohol-related dementia · Alcoholic hallucinosis · Hangover · |
| | | | **Cardiovascular system** | Alcoholic cardiomyopathy · Alcohol flush reaction · |
| | **SUD** | **Alcoholism** · Alcohol dependence · Alcohol abuse · | | |
| **Opioids** | SID (Opioid overdose · · SUD (Opioid addiction and dependence · · | | | |
| **Caffeine** | SID (Effect of caffeine on memory · Caffeine-induced sleep disorder · · SUD (Caffeine dependence · · | | | |
| **Cannabis** | SID (Effects of cannabis · Long-term effects of cannabis · · SUD (Cannabis dependence · · | | | |
| **Sedative / hypnotic** | *benzodiazepine:* SID (Benzodiazepine overdose · Benzodiazepine withdrawal · · SUD (Benzodiazepine misuse · Benzodiazepine dependence · · *barbiturate:* SID (Barbiturate overdose · · SUD (Barbiturate dependence · · | | | |
| **Cocaine** | SID (Cocaine intoxication · · SUD (Cocaine dependence · · | | | |
| **Stimulants** | SID (Stimulant psychosis · · SUD (Amphetamine dependence · · | | | |
| **Hallucinogen** | SID (Hallucinogen persisting perception disorder · · | | | |
| **Tobacco** | SID (Nicotine poisoning · Nicotine withdrawal · · | | | |
| **Volatile solvent** | Inhalant abuse: Toluene toxicity · | | | |
| **Multiple** | Poly drug use · | | | |

| v · t · e · | **Alcoholics Anonymous** |
|---|---|
| | History · Effectiveness · |
| **Concepts** | Twelve Steps · Twelve Traditions · Higher Power · Serenity Prayer · |
| **Literature** | The Big Book · *Twelve Steps and Twelve Traditions* · *The Little Red Book* · *Day by Day* · |
| **People** | Bill W. · Dr. Bob · Jim Burwell · Sister Ignatia · Marty Mann · Carl Jung · Lois W. · William Duncan Silkworth · Rowland Hazard III · Ebby Thacher · |
| **Related** | Al-Anon/Alateen · **Alcoholism** · Bill Wilson House · Disease theory of alcoholism · Hazelden Foundation · The Oxford Group · Stepping Stones · Charles B. Towns · |
| **Drama** | *Bill W. and Dr. Bob* · *My Name Is Bill W.* · *When Love Is Not Enough: The Lois Wilson Story* · *Bill W. (2012)* · |
| | Category:Alcoholics Anonymous |

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| **Authority control** | GND: 4001220-7 · BNF: cb11964742x (data) · NDL: 00560352 · |

Categories: Alcohol abuse | Drinking culture | Psychiatric diagnosis | Substance dependence




# Anorexia nervosa

From Wikipedia, the free encyclopedia

*"Anorexia" and "Anorectic" redirect here. For the medication, see Anorectic. For other uses, see Anorexia (disambiguation).*

## Variants

**Anorexia nervosa**, often referred to simply as **anorexia**,[1] is an eating disorder characterized by a low weight, fear of gaining weight, a strong desire to be thin, and food restriction.[2] Many people with anorexia see themselves as overweight even though they are in fact underweight.[2][3] If asked they usually deny they have a problem with low weight.[4] Often they weigh themselves frequently, eat only small amounts, and only eat certain foods. Some will exercise excessively, force themselves to vomit, or use laxatives to produce weight loss. Complications may include osteoporosis, infertility and heart damage, among others.[2] Women will often stop having menstrual periods.[4]

The cause is not known. There appear to be some genetic components with identical twins more often affected than non-identical twins.[3] Cultural factors also appear to play a role with societies that value thinness having higher rates of disease.[4] Additionally, it occurs more commonly among those involved in activities that value thinness such as high-level athletics, modelling, and dancing.[4][5] Anorexia often begins following a major life change or stress-inducing event. The diagnosis requires a significantly low weight. The severity of disease is based on body mass index (BMI) in adults with mild disease having a BMI of greater than 17, moderate a BMI of 16 to 17, severe a BMI of 15 to 16, and extreme a BMI less than 15. In children a BMI for age percentile of less than the 5th percentile is often used.[4]

Treatment of anorexia involves restoring a healthy weight, treating the underlying psychological problems, and addressing behaviors that promote the problem. While medications do not help with weight gain, they may be used to help with associated anxiety or depression.[2] A number of types of therapy may be useful including an approach where parents assume responsibility for feeding their child, known as Maudsley family therapy and cognitive behavioral therapy.[2][6] Sometimes people require admission to hospital to restore weight.[7] Evidence for benefit from nasogastric tube feeding; however, is unclear.[8] Some people will just have a single episode and recover while others may have many episodes over years.[7] Many complications improve or

**Anorexia nervosa**


"Miss A—" pictured in 1866 and in 1870 after treatment. She was one of the earliest case studies of anorexia. From the published medical papers of Sir William Gull

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Psychiatry |

resolve with regaining of weight.[7]

Globally, anorexia is estimated to affect two million people as of 2013.[9] It is estimated to occur in 0.9% to 4.3% of women and 0.2% to 0.3% of men in Western countries at some point in their life.[10] About 0.4% of young females are affected in a given year and it is estimated to occur ten times less commonly in males.[4][10] Rates in most of the developing world are unclear.[4] Often it begins during the teen years or young adulthood.[2] While anorexia became more commonly diagnosed during the 20th century it is unclear if this was due to an increase in its frequency or simply better diagnosis.[3] In 2013 it directly resulted in about 600 deaths globally up from 400 deaths in 1990.[11] Eating disorders also increase a person's risk of death from a wide range of other causes including suicide.[2][10] About 5% of people with anorexia die from complications over a ten-year period, a nearly 6 times increased risk.[4][12] The term anorexia nervosa was first used in 1873 by William Gull to describe this condition.[13]

| | |
|---|---|
| **ICD-10** | F50.0-F50.1 |
| **ICD-9-CM** | 307.1 |
| **OMIM** | 606788 |
| **DiseasesDB** | 749 |
| **MedlinePlus** | 000362 |
| **eMedicine** | emerg/34 med/144 |
| **Patient UK** | Anorexia nervosa |
| **MeSH** | D000856 |

[edit on Wikidata]



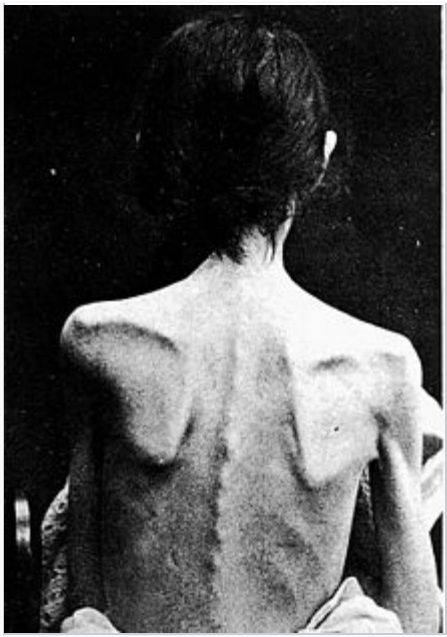



Play media

Video explanation

## Signs and symptoms [edit]

Anorexia nervosa is an eating disorder characterized by attempts to lose weight, to the point of starvation. A person with anorexia nervosa may exhibit a number of signs and symptoms, the type and severity of which may vary and may be present but not readily apparent.[14]



The back of a person with anorexia

Anorexia nervosa, and the associated malnutrition that results from self-imposed starvation, can cause complications in every major organ system in the body.[15] Hypokalaemia, a drop in the level of potassium in the blood, is a sign of anorexia nervosa.[16][17] A significant drop in potassium can cause abnormal heart rhythms, constipation, fatigue, muscle damage and paralysis.[18] Some individuals may lack awareness that they are ill.

Symptoms may include:

- A low body mass index for ones age, height and weight.
- Amenorrhea, a symptom that occurs after prolonged weight loss; causes menses to stop, hair becomes brittle, and skin becomes yellow and unhealthy.
- Fear of even the slightest weight gain; taking all precautionary measures to avoid weight gain or becoming "overweight".[19]
- Rapid, continuous weight loss.[20]
- Lanugo: soft, fine hair growing over the face and body.[17]
- An Obsession with counting calories and monitoring fat contents of food.
- Preoccupation with food, recipes, or cooking; may cook elaborate dinners for others, but not eat the food themselves or consume a very small portion.
- Food restrictions despite being underweight or at a healthy weight.
- Food rituals, such as cutting food into tiny pieces, refusing to eat around others and hiding or discarding of food.
- Purging: May use laxatives, diet pills, ipecac syrup, or water pills to flush food out of their system after eating or may engage in self-induced vomiting though this is a more common symptom of bulimia.
- Excessive exercise[21] including micro-exercising, for example making small persistent movements of fingers or toes.[22]
- Perception of self as overweight, even though they might not be.
- Intolerance to cold and frequent complaints of being cold; body temperature may lower (hypothermia) in an effort to conserve energy due to malnutrition.[23]
- Hypotension or orthostatic hypotension.
- Bradycardia or tachycardia.
- Depression, anxiety disorders and insomnia.
- Solitude: may avoid friends and family and become more withdrawn and secretive.
- Abdominal distension.
- Halitosis (from vomiting or starvation-induced ketosis).
- Dry hair and skin, as well as hair thinning.
- Chronic fatigue.[19]
- Rapid mood swings.
- Being protective of ones social media accounts due to eating disorder content.
- Having feet discoloration causing an orange appearance.
- Having severe muscle tension + aches and pains.
- Seeming on edge more often than usual.
- Having teary eyes and suicidal tendencies.
- Evidence/habits of self harming or self-loathing.
- Admiration of thinner people.

## Associated problems [edit]

Other psychological issues may factor into anorexia nervosa; some fulfill the criteria for a separate Axis I diagnosis or a personality disorder which is coded Axis II and thus are considered comorbid to the diagnosed eating disorder. Some people have a previous disorder which may increase their vulnerability to developing an eating disorder and some develop them afterwards.[*medical citation needed*] The presence of Axis I or Axis II psychiatric comorbidity has been shown to affect the severity and type of anorexia nervosa symptoms in both adolescents and adults.[*medical citation needed*]

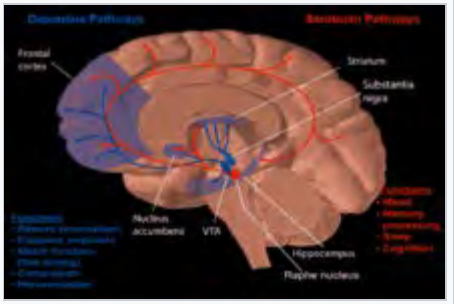
Obsessive-compulsive disorder (OCD) and obsessive-compulsive personality disorder (OCPD) are highly comorbid with AN, particularly the restrictive subtype.[24] Obsessive-compulsive personality disorder is linked with more severe symptomatology and worse prognosis.[25] The causality between personality disorders and eating disorders has yet to be fully established.[*medical citation needed*] Other comorbid conditions include depression,[26] alcoholism,[27] borderline and other personality disorders,[28][29] anxiety disorders,[30] attention deficit hyperactivity disorder,[31] and body dysmorphic disorder (BDD).[32] Depression and anxiety are the most common comorbidities,[33] and depression is associated with a worse outcome.[33]

Autism spectrum disorders occur more commonly among people with eating disorders than in the general population.[34] Zucker *et al.* (2007) proposed that conditions on the autism spectrum make up the cognitive endophenotype underlying anorexia nervosa and appealed for increased interdisciplinary collaboration.[35]

## Causes [edit]

There is evidence for biological, psychological, developmental, and sociocultural risk factors, but the exact cause of eating disorders is unknown.[36]

### Biological [edit]



Dysregulation of the serotonin pathways has been implicated in the etiology, pathogenesis and pathophysiology of anorexia nervosa.[36]

- Genetics: anorexia nervosa is highly heritable.[36] Twin studies have shown a heritability rate of between 28 and 58%.[37] Association studies have been performed, studying 128 different polymorphisms related to 43 genes including genes involved in regulation of eating behavior, motivation and reward mechanics, personality traits and emotion. Consistent associations have been identified for polymorphisms associated with agouti-related peptide, brain derived neurotrophic factor, catechol-o-methyl transferase, SK3 and opioid receptor delta-1.[38] Epigenetic modifications, such as DNA methylation, may contribute to the development or maintenance of anorexia nervosa, though clinical research in this area is in its infancy.[39]
- Obstetric complications: prenatal and perinatal complications may factor into the development of anorexia nervosa, such as maternal anemia, diabetes mellitus, preeclampsia, placental infarction, and neonatal cardiac abnormalities. Neonatal complications may also have an influence on harm avoidance, one of the personality traits associated with the development of AN.[*medical citation needed*]
- Neuroendocrine dysregulation: altered signalling of peptides that facilitate communication between the gut, brain and adipose tissue, such as ghrelin, leptin, neuropeptide Y and orexin, may contribute to the pathogenesis of anorexia nervosa by disrupting regulation of hunger and satiety.[40][41]
- Gastrointestinal diseases: people with gastrointestinal disorders may be more risk of developing disorders eating practices than the general population, principally restrictive eating disturbances.[42] An association of anorexia nervosa with celiac disease has been found.[43] The role that gastrointestinal symptoms play in the development of eating disorders seems rather complex. Some authors report that unresolved symptoms prior to gastrointestinal disease diagnosis may create a food aversion in these

persons, causing alterations to their eating patterns. Other authors report that greater symptoms throughout their diagnosis led to greater risk. It has been documented that some people with celiac disease, irritable bowel syndrome or inflammatory bowel disease who are not conscious about the importance of strictly following their diet, choose to consume their trigger foods to promote weight loss. On the other hand, individuals with good dietary management may develop anxiety, food aversion and eating disorders because of concerns around cross contamination of their foods.[42] Some authors suggest that medical professionals should evaluate the presence of an unrecognized celiac disease in all people with eating disorder, especially if they present any gastrointestinal symptom (such as decreased appetite, abdominal pain, bloating, distension, vomiting, diarrhea or constipation), weight loss, or growth failure; and also routinely ask celiac patients about weight or body shape concerns, dieting or vomiting for weight control, to evaluate the possible presence of eating disorders,[43] specially in women.[44]

Studies have hypothesized the continuance of disordered eating patterns may be epiphenomena of starvation. The results of the Minnesota Starvation Experiment showed normal controls exhibit many of the behavioral patterns of anorexia nervosa (AN) when subjected to starvation. This may be due to the numerous changes in the neuroendocrine system, which results in a self-perpetuating cycle.[45][46][47]

Another hypothesis is that anorexia nervosa is more likely to occur in populations in which obesity is more prevalent, and results from a sexually selected evolutionary drive to appear youthful in populations in which size becomes the primary indicator of age.[48]

Anorexia nervosa is more likely to occur in a person's pubertal years. Some explanatory hypotheses for the rising prevalence of eating disorders in adolescence are "increase of adipose tissue in girls, hormonal changes of puberty, societal expectations of increased independence and autonomy that are particularly difficult for anorexic adolescents to meet; [and] increased influence of the peer group and its values." [49]

## Psychological [edit]

Early theories of the cause of anorexia linked it to childhood sexual abuse or dysfunctional families;[50][51] evidence is conflicting, and well-designed research is needed.[36] The fear of food is known as *sitiophobia*,[52] *cibophobia*,[53] or *sitophobia* and is part of the differential diagnosis.[54][55] Other psychological causes of Anorexia includes low self-esteem, feeling like there is lack of control, depression, anxiety, and loneliness.[56] Peer pressure and constant pressure media and others around can lead to low self-esteem and other psychological symptoms and causes eating disorders like Anorexia.[57]

## Sociological [edit]

Anorexia nervosa has been increasingly diagnosed since 1950;[58] the increase has been linked to vulnerability and internalization of body ideals.[49] People in professions where there is a particular social pressure to be thin (such as models and dancers) were more likely to develop anorexia,[*medical citation needed*] and those with anorexia have much higher contact with cultural sources that promote weight loss.[*medical citation needed*] This trend can also be observed for people who partake in certain sports, such as jockeys and wrestlers.[59] There is a higher incidence and prevalence of anorexia nervosa in sports with an emphasis on aesthetics, where low body fat is advantageous, and sports in which one has to make weight for competition.[60] Family dynamics can play big part in the cause of anorexia.[61] When there is a constant pressure from people to be thin, teasing, bullying can cause low self-esteem and other psychological symptoms.[56]

## Media effects [edit]

Constant exposure to media that presents body ideals may constitute a risk factor for body dissatisfaction and anorexia nervosa. The cultural ideal for body shape for men versus women continues to favor slender women and athletic, V-shaped muscular men. A 2002 review found that, of the magazines most popular among people aged 18 to 24 years, those read by men, unlike those read by women, were more likely to [*unreliable medical source?*][62]

feature ads and articles on shape than on diet. Body dissatisfaction and internalization of body ideals are risk factors for anorexia nervosa that threaten the health of both male and female populations.[*medical citation needed*]

Websites that stress the importance of attainment of body ideals extol and promote anorexia nervosa through the use of religious metaphors, lifestyle descriptions, "thinspiration" or "fitspiration" (inspirational photo galleries and quotes that aim to serve as motivators for attainment of body ideals).[63] Pro-anorexia websites reinforce internalization of body ideals and the importance of their attainment.[63]

The media gives men and women a false view of what people truly look like. In magazines, movies and even on billboards most of the actors/models are photoshopped in multiple ways. People then strive to look like these "perfect" role models when in reality they aren't any where near perfection themselves.[64]

## Mechanisms [edit]

- Serotonin dysregulation: brain imaging studies implicate alterations of 5-HT1A and 5-HT2A receptors and the 5-HT transporter.[36] Alterations of these circuits may affect mood and impulse control as well as the motivating and hedonic aspects of feeding behavior.[65] Starvation has been hypothesized to be a response to these effects, as it is known to lower tryptophan and steroid hormone metabolism, which might reduce serotonin levels at these critical sites and ward off anxiety.[65]
- Addiction to the chemicals released in the brain during starving and physical activity:[66][67] people affected with anorexia often report getting some sort of high from not eating. The effect of food restriction and intense activity causes symptoms similar to anorexia in female rats,[66] though it is not explained why this addiction affects only females.
- Resting state fMRI has identified the insular cortex and corticolimbic circuitry as likely brain areas responsible for the symptomology of anorexia nervosa.[68]

## Diagnosis [edit]

A diagnostic assessment includes the person's current circumstances, biographical history, current symptoms, and family history. The assessment also includes a mental state examination, which is an assessment of the person's current mood and thought content, focusing on views on weight and patterns of eating.

### DSM-5 [edit]

Anorexia nervosa is classified under the Feeding and Eating Disorders in the latest revision of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM 5).

Relative to the previous version of the DSM (DSM-IV-TR), the 2013 revision (DSM5) reflects changes in the criteria for anorexia nervosa, most notably that of the amenorrhea criterion being removed.[7][69] Amenorrhea was removed for several reasons: it does not apply to males, it is not applicable for females before or after the age of menstruation or taking birth control pills, and some women who meet the other criteria for AN still report some menstrual activity.[7]

### Subtypes [edit]

There are two subtypes of AN:[15][70]

- Binge-eating/purging type: the individual utilizes binge eating or displays purging behavior as a means for losing weight.[70] It is different from bulimia nervosa in terms of the individual's weight. An individual with binge-eating/purging type anorexia does not maintain a healthy or normal weight but is significantly underweight. People with bulimia nervosa on the other hand can sometimes be overweight.[19]
- Restricting type: the individual uses restricting food intake, fasting, diet pills, or exercise as a means for

losing weight;[15] they may exercise excessively to keep off weight or prevent weight gain, and some individuals eat only enough to stay alive.[15][19]

## Levels of severity [edit]

Body mass index (BMI) is used by the DSM-5 as an indicator of the level of severity of anorexia nervosa. The DSM-5 states these as follows:[71]

- Mild: BMI of greater than 17
- Moderate: BMI of 16–16.99
- Severe: BMI of 15–15.99
- Extreme: BMI of less than 15

## Investigations [edit]

Medical tests to check for signs of physical deterioration in anorexia nervosa may be performed by a general physician or psychiatrist, including:

- Complete Blood Count (CBC): a test of the white blood cells, red blood cells and platelets used to assess the presence of various disorders such as leukocytosis, leukopenia, thrombocytosis and anemia which may result from malnutrition.[72]
- Urinalysis: a variety of tests performed on the urine used in the diagnosis of medical disorders, to test for substance abuse, and as an indicator of overall health[73]
- Chem-20: Chem-20 also known as SMA-20 a group of twenty separate chemical tests performed on blood serum. Tests include cholesterol, protein and electrolytes such as potassium, chlorine and sodium and tests specific to liver and kidney function.[74]
- Glucose tolerance test: Oral glucose tolerance test (OGTT) used to assess the body's ability to metabolize glucose. Can be useful in detecting various disorders such as diabetes, an insulinoma, Cushing's Syndrome, hypoglycemia and polycystic ovary syndrome.[75]
- Serum cholinesterase test: a test of liver enzymes (acetylcholinesterase and pseudocholinesterase) useful as a test of liver function and to assess the effects of malnutrition.[76]
- Liver Function Test: A series of tests used to assess liver function some of the tests are also used in the assessment of malnutrition, protein deficiency, kidney function, bleeding disorders, and Crohn's Disease.[77]
- Lh response to GnRH: Luteinizing hormone (Lh) response to gonadotropin-releasing hormone (GnRH): Tests the pituitary glands' response to GnRh a hormone produced in the hypothalamus. Hypogonadism is often seen in anorexia nervosa cases.[16]
- Creatine Kinase Test (CK-Test): measures the circulating blood levels of creatine kinase an enzyme found in the heart (CK-MB), brain (CK-BB) and skeletal muscle (CK-MM).[78]
- Blood urea nitrogen (BUN) test: urea nitrogen is the byproduct of protein metabolism first formed in the liver then removed from the body by the kidneys. The BUN test is primarily used to test kidney function. A low BUN level may indicate the effects of malnutrition.[79]
- BUN-to-creatinine ratio: A BUN to creatinine ratio is used to predict various conditions. A high BUN/creatinine ratio can occur in severe hydration, acute kidney failure, congestive heart failure, and intestinal bleeding. A low BUN/creatinine ratio can indicate a low protein diet, celiac disease, rhabdomyolysis, or cirrhosis of the liver.[80][81]
- Electrocardiogram (EKG or ECG): measures electrical activity of the heart. It can be used to detect various disorders such as hyperkalemia[82]
- Electroencephalogram (EEG): measures the electrical activity of the brain. It can be used to detect abnormalities such as those associated with pituitary tumors.[83]
- Thyroid Screen TSH, t4, t3 :test used to assess thyroid functioning by checking levels of thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3)[84]

## Differential diagnoses [edit]

*Main article: Anorexia nervosa (differential diagnoses)*

A variety of medical and psychological conditions have been misdiagnosed as anorexia nervosa; in some cases the correct diagnosis was not made for more than ten years.

The distinction between the diagnoses of anorexia nervosa, bulimia nervosa and eating disorder not otherwise specified (EDNOS) is often difficult to make as there is considerable overlap between people diagnosed with these conditions. Seemingly minor changes in a people's overall behavior or attitude can change a diagnosis from anorexia: binge-eating type to bulimia nervosa. A main factor differentiating binge-purge anorexia from bulimia is the gap in physical weight. Someone with bulimia nervosa is ordinarily at a healthy weight, or slightly overweight. Someone with binge-purge anorexia is commonly underweight.[85] People with the binge-purging subtype of AN may be significantly underweight and typically do not binge-eat large amounts of food, yet they purge the small amount of food they eat.[85] In contrast, those with bulimia nervosa tend to be at normal weight or overweight and binge large amounts of food.[85] It is not unusual for a person with an eating disorder to "move through" various diagnoses as their behavior and beliefs change over time.[35]

## Treatment [edit]

There is no conclusive evidence that any particular treatment for anorexia nervosa works better than others; however, there is enough evidence to suggest that early intervention and treatment are more effective.[86] Treatment for anorexia nervosa tries to address three main areas.

- Restoring the person to a healthy weight;
- Treating the psychological disorders related to the illness;
- Reducing or eliminating behaviours or thoughts that originally led to the disordered eating.[87]

Although restoring the person's weight is the primary task at hand, optimal treatment also includes and monitors behavioral change in the individual as well.[88] There is some evidence that hospitalisation might adversely affect long term outcome.[89]

Psychotherapy for individuals with AN is challenging as they may value being thin and may seek to maintain control and resist change.[90] Some studies demonstrate that family based therapy in adolescents with AN is superior to individual therapy.[91]

Treatment of people with AN is difficult because they are afraid of gaining weight. Initially developing a desire to change may be important.[92]

### Diet [edit]

Diet is the most essential factor to work on in people with anorexia nervosa, and must be tailored to each person's needs. Food variety is important when establishing meal plans as well as foods that are higher in energy density.[93] People must consume adequate calories, starting slowly, and increasing at a measured pace.[21] Evidence of a role for zinc supplementation during refeeding is unclear.[8]

### Therapy [edit]

Family-based treatment (FBT) has been shown to be more successful than individual therapy for adolescents with AN.[12][94] Various forms of family-based treatment have been proven to work in the treatment of adolescent AN including conjoint family therapy (CFT), in which the parents and child are seen together by the same therapist, and separated family therapy (SFT) in which the parents and child attend therapy separately with different therapists.[12] Proponents of Family therapy for adolescents with AN assert that it is important to include parents in the adolescent's treatment.[12]

A four- to five-year follow up study of the Maudsley family therapy, an evidence-based manualized model, showed full recovery at rates up to 90%.[95] Although this model is recommended by the NIMH,[96] critics claim that it has the potential to create power struggles in an intimate relationship and may disrupt equal

partnerships.[97]

Cognitive behavioral therapy (CBT) is useful in adolescents and adults with anorexia nervosa;[98] acceptance and commitment therapy is a type of CBT, which has shown promise in the treatment of AN.[99] Cognitive remediation therapy (CRT) is used in treating anorexia nervosa.[100]

### Medication [edit]

Pharmaceuticals have limited benefit for anorexia itself.[101]

### Admission to hospital [edit]

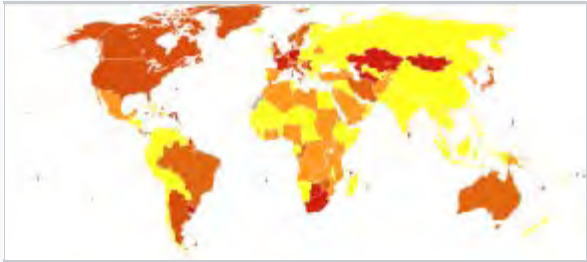
AN has a high mortality[102] and patients admitted in a severely ill state to medical units are at particularly high risk. Diagnosis can be challenging, risk assessment may not be performed accurately, consent and the need for compulsion may not be assessed appropriately, refeeding syndrome may be missed or poorly treated and the behavioural and family problems in AN may be missed or poorly managed.[103] The MARSIPAN guidelines recommend that medical and psychiatric experts work together in managing severely ill people with AN.[104]

### Nutrition [edit]

The rate of refeeding can be difficult to establish, because the fear of refeeding syndrome (RFS) can lead to underfeeding. It is thought that RFS, with falling phosphate and potassium levels, is more likely to occur when BMI is very low, and when medical comorbidities such as infection or cardiac failure, are present. In those circumstances, it is recommended to start refeeding slowly but to build up rapidly as long as RFS does not occur. Recommendations on energy requirements vary, from 5–10 kCal/Kg/day in the most medically compromised patients, who appear to have the highest risk of RFS to 1900 Kcal/day[105][106]

## Prognosis [edit]

AN has the highest mortality rate of any psychological disorder.[12] The mortality rate is 6 to 12 times higher than expected, and the suicide risk is 56 times higher; half of women with AN achieve a full recovery, while an additional 20–30% may partially recover.[12][16] Not all people with anorexia recover completely: about 20% develop anorexia nervosa as a chronic disorder.[86] If anorexia nervosa is not treated, serious complications such as heart conditions[14] and kidney failure can arise and eventually lead to death.[107] The average number of years from onset to remission of AN is seven for women and three for men. After ten to fifteen years, 70% of people no longer meet the diagnostic criteria, but many still continue to have eating-related problems.[108]




Alexithymia influences treatment outcome.[101] Recovery is also viewed on a spectrum rather than black and white. According to the Morgan-Russell criteria, individuals can have a good, intermediate, or poor outcome. Even when a person is classified as having a "good" outcome, weight only has to be within 15% of average, and normal menstruation must be present in females. The good outcome also excludes psychological health. Recovery for people with anorexia nervosa is undeniably positive, but recovery does not mean a return to normal.[*medical citation needed*]

### Complications [edit]

Anorexia nervosa can have serious implications if its duration and severity are significant and if onset occurs

before the completion of growth, pubertal maturation, or the attainment of peak bone mass.[*medical citation needed*] Complications specific to adolescents and children with anorexia nervosa can include the following: Growth retardation may occur, as height gain may slow and can stop completely with severe weight loss or chronic malnutrition. In such cases, provided that growth potential is preserved, height increase can resume and reach full potential after normal intake is resumed.[*medical citation needed*] Height potential is normally preserved if the duration and severity of illness are not significant or if the illness is accompanied with delayed bone age (especially prior to a bone age of approximately 15 years), as hypogonadism may negate the deleterious effects of undernutrition on stature by allowing for a longer duration of growth compared to controls.[*medical citation needed*] In such cases, appropriate early treatment can preserve height potential and may even help to increase it in some post-anorexic subjects due to the aforementioned reasons in addition to factors such as long-term reduced estrogen-producing adipose tissue levels compared to premorbid levels.[*medical citation needed*] In some cases, especially where onset is pre-pubertal, physical consequences such as stunted growth and pubertal delay are usually fully reversible.[109]

Anorexia nervosa causes alterations in the female reproductive system; significant weight loss, as well as psychological stress and intense exercise, typically results in a cessation of menstruation in women who are past puberty. In patients with anorexia nervosa, there is a reduction of the secretion of gonadotropin releasing hormone in the central nervous system, preventing ovulation.[110] Anorexia nervosa can also result in pubertal delay or arrest. Both height gain and pubertal development are dependent on the release of growth hormone and gonadotrophins (LH and FSH) from the pituitary gland. Suppression of gonadotrophins in people with anorexia nervosa has been documented.[111] Typically, growth hormone (GH) levels are high, but levels of IGF-1, the downstream hormone that should be released in response to GH are low; this indicates a state of "resistance" to GH due to chronic starvation.[112] IGF-1 is necessary for bone formation, and decreased levels in anorexia nervosa contribute to a loss of bone density and potentially contribute to osteopenia or osteoporosis.[112] Anorexia nervosa can also result in reduction of peak bone mass. Buildup of bone is greatest during adolescence, and if onset of anorexia nervosa occurs during this time and stalls puberty, low bone mass may be permanent.[113] Hepatic steatosis, or fatty infiltration of the liver, can also occur, and is an indicator of malnutrition in children.[114] Neurological disorders that may occur as complications include seizures and tremors. Wernicke encephalopathy, which results from vitamin B1 deficiency, has been reported in patients who are extremely malnourished; symptoms include confusion, oculomotor dysfunction, and abnormalities in walking gait.

The most common gastrointestinal complications of anorexia nervosa are delayed stomach emptying and constipation, but also include elevated liver function tests, diarrhea, acute pancreatitis, heartburn, difficulty swallowing, and, rarely, superior mesenteric artery syndrome.[115] Delayed stomach emptying, or gastroparesis, often develops following food restriction and weight loss; the most common symptom is bloating with gas and abdominal distension, and often occurs after eating. Other symptoms of gastroparesis include early satiety, fullness, nausea, and vomiting. The symptoms may inhibit efforts at eating and recovery, but can be managed by limiting high-fiber foods, using liquid nutritional supplements, or using metoclopramide to increase emptying of food from the stomach.[115] Gastroparesis generally resolves when weight is regained.

## Cardiac complications [edit]

Anorexia nervosa increases the risk of sudden cardiac death, though the precise cause is unknown. Cardiac complications include structural and functional changes to the heart.[116] Some of these cardiovascular changes are mild and are reversible with treatment, while others may be life-threatening. Cardiac complications can include arrhythmias, abnormally slow heart beat, low blood pressure, decreased size of the heart muscle, reduced heart volume, mitral valve prolapse, myocardial fibrosis, and pericardial effusion.[116]

Abnormalities in conduction and repolarization of the heart that can result from anorexia nervosa include QT prolongation, increased QT dispersion, conduction delays, and junctional escape rhythms.[116] Electrolyte abnormalities, particularly hypokalemia and hypomagnesemia can cause anomalies in the electrical activity of the heart, and result in life-threatening arrhythmias. Hypokalemia most commonly results in anorexic patients when restricting is accompanied by purging (induced vomiting or laxative use). Hypotension (low

blood pressure) is common, and symptoms include fatigue and weakness. Orthostatic hypotension, a marked decrease in blood pressure when standing from a supine position, may also occur. Symptoms include lightheadedness upon standing, weakness, and cognitive impairment, and may result in fainting or near-fainting.[116] Orthostasis in anorexia nervosa indicates worsening cardiac function and may indicate a need for hospitalization.[116] Hypotension and orthostasis generally resolve upon recovery to a normal weight. The weight loss in anorexia nervosa also causes atrophy of cardiac muscle. This leads to decreased ability to pump blood, a reduction in the ability to sustain exercise, a diminished ability to increase blood pressure in response to exercise, and a subjective feeling of fatigue.[117] Some individuals may also have a decrease in cardiac contractility. Cardiac complications can be life-threatening, but the heart muscle generally improves with weight gain, and the heart normalizes in size normalizes over weeks to months, with recovery.[117] Atrophy of the heart muscle is a marker of the severity of the disease, and while it is reversible with treatment and refeeding, it is possible that it may cause permanent, microscopic changes to the heart muscle that increase the risk of sudden cardiac death.[116] Individuals with anorexia nervosa may experience chest pain or palpitations; these can be a result of mitral valve prolapse. Mitral valve prolapse occurs because the size of the heart muscle decreases while the tissue of the mitral valve remains the same size. Studies have shown rates of mitral valve prolapse of around 20 percent in those with anorexia nervosa, while the rate in the general population is estimated at 2–4 percent.[118] It has been suggested that there is an association between mitral valve prolapse and sudden cardiac death, but it has not been proven to be causative, either in patients with anorexia nervosa or in the general population.[116]

### Relapse [edit]

Relapse occurs in approximately a third of people in hospital, and is greatest in the first six to eighteen months after release from an institution.[119]

## Epidemiology [edit]

Anorexia is estimated to occur in 0.9% to 4.3% of women and 0.2% to 0.3% of men in Western countries at some point in their life.[10] About 0.4% of young females are affected in a given year and it is estimated to occur three to ten times less commonly in males.[4][10][119] Rates in most of the developing world are unclear.[4] Often it begins during the teen years or young adulthood.[2]

The lifetime rate of atypical anorexia nervosa, a form of ED-NOS in which not all of the diagnostic criteria for AN are met, is much higher, at 5–12%.[120]

While anorexia become more commonly diagnosed during the 20th century it is unclear if this was due to an increase in its frequency or simply better diagnosis.[3] Most studies show that since at least 1970 the incidence of AN in adult women is fairly constant, while there is some indication that the incidence may have been increasing for girls aged between 14 and 20.[121]

### Underrepresentation [edit]

Eating disorders are less reported in preindustrial, non-westernized countries than in Western countries. In Africa, not including South Africa, the only data presenting information about eating disorders occurs in case reports and isolated studies, not studies investigating prevalence. Data shows in research that in westernized civilizations, ethnic minorities have very similar rates of eating disorders, contrary to the belief that eating disorders predominantly occur in Caucasian people.[*medical citation needed*]

Due to different standards of beauty for men and women, men are often not diagnosed as anorexic. Generally men who alter their bodies do so to be lean and muscular rather than thin. In addition, men who might otherwise be diagnosed with anorexia may not meet the DSM IV criteria for BMI since they have muscle weight, but have very little fat.[122] Men and women athletes are often overlooked as anorexic.[122] Research emphasizes the importance to take athletes' diet, weight and symptoms into account when diagnosing anorexia, instead of just looking at weight and BMI. For athletes, ritualized activities such as weigh-ins place emphasis on weight, which may promote the development of eating disorders among

them.[*citation needed*] While women use diet pills, which is an indicator of unhealthy behavior and an eating disorder, men use steroids, which contextualizes the beauty ideals for genders. This also shows men having a preoccupation with their body, which is an indicator of an eating disorder.[36] In a Canadian study, 4% of boys in grade nine used anabolic steroids.[36] Anorexic men are sometimes referred to as *manorexic*.[123]

## History [edit]

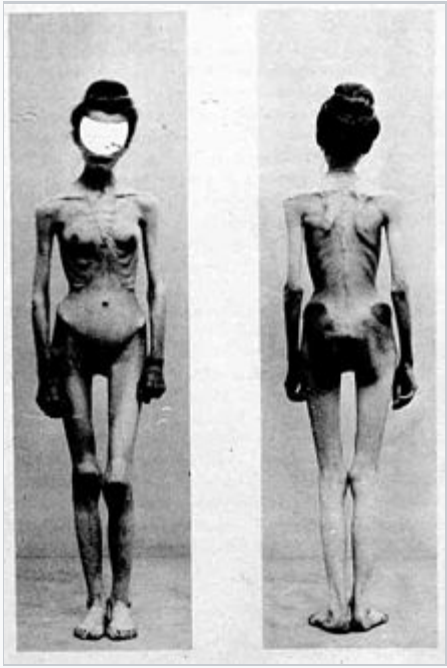
*Main article: History of anorexia nervosa*

The term *anorexia nervosa* was coined in 1873 by Sir William Gull, one of Queen Victoria's personal physicians.[124] The history of anorexia nervosa begins with descriptions of religious fasting dating from the Hellenistic era[125] and continuing into the medieval period. The medieval practice of self-starvation by women, including some young women, in the name of religious piety and purity also concerns anorexia nervosa; it is sometimes referred to as *anorexia mirabilis*.[126][127]

The earliest medical descriptions of anorexic illnesses are generally credited to English physician Richard Morton in 1689.[125] Case descriptions fitting anorexic illnesses continued throughout the 17th, 18th and 19th centuries.[128]

In the late 19th century anorexia nervosa became widely accepted by the medical profession as a recognized condition. In 1873, Sir William Gull, one of Queen Victoria's personal physicians, published a seminal paper which coined the term *anorexia nervosa* and provided a number of detailed case descriptions and treatments.[128] In the same year, French physician Ernest-Charles Lasègue similarly published details of a number of cases in a paper entitled *De l'Anorexie hystérique*.[129]

Awareness of the condition was largely limited to the medical profession until the latter part of the 20th century, when German-American psychoanalyst Hilde Bruch published *The Golden Cage: the Enigma of Anorexia Nervosa* in 1978. Despite major advances in neuroscience,[130] Bruch's theories tend to dominate popular thinking. A further important event was the death of the popular singer and drummer Karen Carpenter in 1983, which prompted widespread ongoing media coverage of eating disorders.[131]



Two images of an anorexic female person published in 1900 in "Nouvelle Iconographie de la Salpêtrière". The case was entitiled "Un cas d'anorexie hysterique" *(A case of hysteria anorexia).*

### Etymology [edit]

The term is of Greek origin: *an-* (ἀν-, prefix denoting negation) and *orexis* (ὄρεξις, "appetite"), translating literally to a nervous loss of appetite.[132]

## See also [edit]

- List of people with anorexia nervosa
- Eating recovery
- National Association of Anorexia Nervosa and Associated Disorders
- Orthorexia nervosa
- Pro-ana
- Inedia

## References [edit]

1. ^ Sari Fine Shepphird (2009). *100 Questions & Answers About Anorexia Nervosa*. Jones & Bartlett Learning. p. xvi. ISBN 978-1-4496-3079-9.
2. ^ *a b c d e f g h* "What are Eating Disorders?". *NIMH*. Retrieved 24 May 2015.
3. ^ *a b c d* Attia E (2010). "Anorexia Nervosa: Current Status and Future Directions". *Annual Review of Medicine*. **61** (1): 425–35. doi:10.1146/annurev.med.050208.200745. PMID 19719398.
4. ^ *a b c d e f g h i j* *Diagnostic and statistical manual of mental disorders : DSM-5* (5 ed.). Washington: American Psychiatric Publishing. 2013. pp. 338–345. ISBN 978-0-89042-555-8.
5. ^ Arcelus, J; Witcomb, GL; Mitchell, A (March 2014). "Prevalence of eating disorders amongst dancers: a systemic review and meta-analysis.". *European eating disorders review : the journal of the Eating Disorders Association*. **22** (2): 92–101. doi:10.1002/erv.2271. PMID 24277724.
6. ^ Hay, P (July 2013). "A systematic review of evidence for psychological treatments in eating disorders: 2005–2012.". *The International Journal of Eating Disorders*. **46** (5): 462–9. doi:10.1002/eat.22103. PMID 23658093.
7. ^ *a b c d e* "Feeding and eating disorders" (PDF). American Psychiatric Publishing. 2013. Retrieved 9 April 2015.
8. ^ *a b* British Psychological Society (2004). "Eating Disorders: Core Interventions in the Treatment and Management of Anorexia Nervosa, Bulimia Nervosa and Related Eating Disorders." (PDF): 103. PMID 23346610.
9. ^ Global Burden of Disease Study 2013, Collaborators (5 June 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/S0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
10. ^ *a b c d e* Smink, FR; van Hoeken, D; Hoek, HW (August 2012). "Epidemiology of eating disorders: incidence, prevalence and mortality rates.". *Current psychiatry reports*. **14** (4): 406–14. doi:10.1007/s11920-012-0282-y. PMC 3409365. PMID 22644309.
11. ^ GBD 2013 Mortality and Causes of Death Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013". *Lancet*. **385** (9963): 117–171. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
12. ^ *a b c d e f* Espie J, Eisler I (2015). "Focus on anorexia nervosa: modern psychological treatment
60. ^ Baum A (2006). "Eating Disorders in the Male Athlete" (PDF). *Sports medicine (Auckland, N.Z.)*. **36** (1): 1–6. doi:10.2165/00007256-200636010-00001. PMID 16445307.
61. ^ "Eating Disorders Anorexia Causes | Eating Disorders". *Psychiatric Disorders and Mental Health Issues*. Retrieved 1 March 2016.
62. ^ Labre MP (2002). "Adolescent boys and the muscular male body ideal". *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*. **30** (4): 233–42. PMID 11927235.
63. ^ *a b* Norris ML, Boydell KM, Pinhas L, Katzman DK (2006). "Ana and the Internet: A review of pro-anorexia websites". *International Journal of Eating Disorders*. **39** (6): 443–7. doi:10.1002/eat.20305. PMID 16721839.
64. ^ Harrison, Kristen (2001). "Ourselves, Our Bodies: Thin-Ideal Media, Self-Discrepancies, and Eating Disorder Symptomatology in Adolescents". *Journal of Social and Clinical Psychology*. **20** (3): 289. doi:10.1521/jscp.20.3.289.22303.
65. ^ *a b* Kaye WH, Frank GK, Bailer UF, Henry SE, Meltzer CC, Price JC, Mathis CA, Wagner A (2005). "Serotonin alterations in anorexia and bulimia nervosa: new insights from imaging studies". *Physiol. Behav*. **85** (1): 73–81. doi:10.1016/j.physbeh.2005.04.013. PMID 15869768.
66. ^ *a b* Bergh C, Södersten P (1996). "Anorexia nervosa, self–starvation and the reward of stress". *Nature Medicine*. **2** (1): 21–22. doi:10.1038/nm0196-21. PMID 8564826.
67. ^ Keating C (2011). "Sex differences precipitating anorexia nervosa in females: the estrogen paradox and a novel framework for targeting sex-specific neurocircuits and behavior". *Biological Basis of Sex Differences in Psychopharmacology*. *Current Topics in Behavioral Neurosciences*. **8**. pp. 189–207. doi:10.1007/7854_2010_99. ISBN 978-3-642-20005-2. PMID 21769727. [*verification needed*]
68. ^ Gaudio S, Wiemerslage L, Brooks SJ, Schiöth HB (2016). "A systematic review of resting-state functional-MRI studies in anorexia nervosa: Evidence for functional connectivity impairment in cognitive control and visuospatial and body-signal integration". *Neurosci Biobehav Rev*. **71**: 578–589. doi:10.1016/j.neubiorev.2016.09.032. PMID 27725172.
69. ^ Estour B, Galusca B, Germain N (2014). "Constitutional thinness and anorexia nervosa: a possible misdiagnosis?". *Front Endocrinol (Lausanne)*. **5**: 175. doi:10.3389/fendo.2014.00175. PMC 4202249. PMID 25368605.
70. ^ *a b* Peat C, Mitchell JE, Hoek HW, Wonderlich SA (2009). "Validity and utility of subtyping anorexia nervosa". *Int J Eat Disord*. **42** (7): 590–4.

and guidelines for the adolescent patient". *Adolesc Health Med Ther*. **6**: 9–16. doi:10.2147/AHMT.S70300. PMC 4316908. PMID 25678834.
13. ^ Gull, WW (September 1997). "Anorexia nervosa (apepsia hysterica, anorexia hysterica). 1868.". *Obesity Research*. **5** (5): 498–502. doi:10.1002/j.1550-8528.1997.tb00677.x. PMID 9385628.
14. ^ *a b* Surgenor LJ, Maguire S (2013). "Assessment of anorexia nervosa: an overview of universal issues and contextual challenges". *J Eat Disord*. **1** (1): 29. doi:10.1186/2050-2974-1-29. PMC 4081667. PMID 24999408.
15. ^ *a b c d* Strumia R (2009). "Skin signs in anorexia nervosa". *Dermatoendocrinol*. **1** (5): 268–70. doi:10.4161/derm.1.5.10193. PMC 2836432. PMID 20808514.
16. ^ *a b c* Miller KK (2013). "Endocrine effects of anorexia nervosa". *Endocrinol. Metab. Clin. North Am*. **42** (3): 515–28. doi:10.1016/j.ecl.2013.05.007. PMC 3769686. PMID 24011884.
17. ^ *a b* Walsh JM, Wheat ME, Freund K (2000). "Detection, evaluation, and treatment of eating disorders the role of the primary care physician". *J Gen Intern Med*. **15** (8): 577–90. doi:10.1046/j.1525-1497.2000.02439.x. PMC 1495575. PMID 10940151.
18. ^ Stargrove MB, Treasure J, McKee DL (2008). *Herb, Nutrient, and Drug Interactions: Clinical Implications and Therapeutic Strategies*. Elsevier Health Sciences. ISBN 0-323-02964-7. Retrieved 9 April 2015.
19. ^ *a b c d* Nolen-Hoeksema S (2013). *Abnormal Psychology*. New York: McGraw Hill. pp. 339–41. ISBN 978-0-07-803538-8.
20. ^ "Anorexia Nervosa". National Association of Anorexia Nervosa and Associated Disorders. Retrieved 15 April 2014.
21. ^ *a b* Marzola E, Nasser JA, Hashim SA, Shih PA, Kaye WH (2013). "Nutritional rehabilitation in anorexia nervosa: review of the literature and implications for treatment". *BMC Psychiatry*. **13** (1): 290. doi:10.1186/1471-244X-13-290. PMC 3829207. PMID 24200367.
22. ^ Robinson, Paul H. (2006). *Community treatment of eating disorders*. Chichester: John Wiley & Sons. p. 66. ISBN 978-0-470-01676-3.
23. ^ Haller E (1992). "Eating disorders. A review and update". *The Western Journal of Medicine*. **157** (6): 658–62. PMC 1022101. PMID 1475950.
24. ^ Godier LR, Park RJ (2014). "Compulsivity in anorexia nervosa: a transdiagnostic concept". *Front Psychol*. **5**: 778. doi:10.3389/fpsyg.2014.00778. PMC 4101893. PMID 25101036.
doi:10.1002/eat.20717. PMC 2844095. PMID 19598270.
71. ^ Singleton, Joanne K. (12 November 2014). *Primary Care, Second Edition: An Interprofessional Perspective*. Springer Publishing Company. ISBN 978-0-8261-7147-4. Retrieved 9 April 2015.
72. ^ "CBC". MedlinePlus : U.S. National Library of Medicine. Retrieved 31 May 2013.
73. ^ Urinalysis at Medline. Nlm.nih.gov (26 January 2012). Retrieved on 2012-02-04.
74. ^ Chem-20 at Medline. Nlm.nih.gov. Retrieved on 4 February 2012.
75. ^ Lee H, Oh JY, Sung YA, Chung H, Cho WY (2009). "The prevalence and risk factors for glucose intolerance in young Korean women with polycystic ovary syndrome". *Endocrine*. **36** (2): 326–32. doi:10.1007/s12020-009-9226-7. PMID 19688613.
76. ^ Montagnese C, Scalfi L, Signorini A, De Filippo E, Pasanisi F, Contaldo F (2007). "Cholinesterase and other serum liver enzymes in underweight outpatients with eating disorders". *The International Journal of Eating Disorders*. **40** (8): 746–50. doi:10.1002/eat.20432. PMID 17610252.
77. ^ Narayanan V, Gaudiani JL, Harris RH, Mehler PS (2010). "Liver function test abnormalities in anorexia nervosa—cause or effect". *The International Journal of Eating Disorders*. **43** (4): 378–81. doi:10.1002/eat.20690. PMID 19424979.
78. ^ Walder A, Baumann P (2008). "Increased creatinine kinase and rhabdomyolysis in anorexia nervosa". *The International Journal of Eating Disorders*. **41** (8): 766–7. doi:10.1002/eat.20548. PMID 18521917.
79. ^ BUN at Medline. Nlm.nih.gov (26 January 2012). Retrieved on 2012-02-04.
80. ^ Sheridan AM, Bonventre JV (2000). "Cell biology and molecular mechanisms of injury in ischemic acute renal failure". *Current Opinion in Nephrology and Hypertension*. **9** (4): 427–34. doi:10.1097/00041552-200007000-00015. PMID 10926180.
81. ^ Nelsen DA (2002). "Gluten-sensitive enteropathy (celiac disease): more common than you think". *American Family Physician*. **66** (12): 2259–66. PMID 12507163.
82. ^ Pepin J, Shields C (Feb 2012). "Advances in diagnosis and management of hypokalemic and hyperkalemic emergencies". *Emerg Med Pract*. **14** (2): 1–17. PMID 22413702.
83. ^ "Electroencephalogram". *Medline Plus*. 26 January 2012. Retrieved 4 February 2012.
84. ^ Madhusmita M, Klibanski A (2011). "The neuroendocrine basis of anorexia nervosa and its impact on bone metabolism". *Neuroendocrinology*. **93** (2): 65–73. doi:10.1159/000323771. ISSN 1423-0194. PMC 3214929. PMID 21228564.
85. ^ *a b c* Nolen-Hoeksema S (2014). "Eating

25. ^ Crane AM, Roberts ME, Treasure J (2007). "Are Obsessive-Compulsive Personality Traits Associated with a Poor Outcome in Anorexia Nervosa? A Systematic Review of Randomized Controlled Trials and Naturalistic Outcome Studies". *International Journal of Eating Disorders*. **40** (7): 581–8. doi:10.1002/eat.20419. PMID 17607713.
26. ^ Casper RC (1998). "Depression and eating disorders". *Depression and Anxiety*. **8** (Suppl 1): 96–104. doi:10.1002/(SICI)1520-6394(1998)8:1+<96::AID-DA15>3.0.CO;2-4. PMID 9809221.
27. ^ Zernig G, Saria A, Kurz M, O'Malley S (24 March 2000). *Handbook of Alcoholism*. CRC Press. p. 293. ISBN 978-1-4200-3696-1.
28. ^ Sansone RA, Levitt JL (21 August 2013). *Personality Disorders and Eating Disorders: Exploring the Frontier*. Routledge. p. 28. ISBN 1-135-44280-0.
29. ^ Halmi KA (2013). "Perplexities of treatment resistance in eating disorders". *BMC Psychiatry*. **13**: 292. doi:10.1186/1471-244X-13-292. PMC 3829659. PMID 24199597.
30. ^ Swinbourne JM, Touyz SW (2007). "The co-morbidity of eating disorders and anxiety disorders: a review". *European Eating Disorders Review : the Journal of the Eating Disorders Association*. **15** (4): 253–74. doi:10.1002/erv.784. PMID 17676696.
31. ^ Cortese S, Bernardina BD, Mouren MC (2007). "Attention-deficit/hyperactivity disorder (ADHD) and binge eating". *Nutrition Reviews*. **65** (9): 404–11. doi:10.1111/j.1753-4887.2007.tb00318.x. PMID 17958207.
32. ^ Wilhelm S, Phillips KA, Steketee G (18 December 2012). *Cognitive-Behavioral Therapy for Body Dysmorphic Disorder: A Treatment Manual*. Guilford Press. p. 270. ISBN 978-1-4625-0790-0.
33. ^ *a b* Berkman ND, Bulik CM, Brownley KA, Lohr KN, Sedway JA, Rooks A, Gartlehner G (2006). "Management of eating disorders" (PDF). *Evid Rep Technol Assess (Full Rep)* (135): 1–166. PMC 4780981. PMID 17628126.
34. ^ Huke V, Turk J, Saeidi S, Kent A, Morgan JF (2013). "Autism spectrum disorders in eating disorder populations: a systematic review". *Eur Eat Disord Rev*. **21** (5): 345–51. doi:10.1002/erv.2244. PMID 23900859.
35. ^ *a b* Zucker NL, Losh M, Bulik CM, LaBar KS, Piven J, Pelphrey KA (2007). "Anorexia nervosa and autism spectrum disorders: guided investigation of social cognitive endophenotypes" (PDF). *Psychological Bulletin*. **133** (6): 976–1006. doi:10.1037/0033-2909.133.6.976. PMID 17967091.
36. ^ *a b c d e f g* Rikani AA, Choudhry Z, Choudhry AM, Ikram H, Asghar MW, Kajal D, Waheed A, Mobassarah NJ (2013). "A critique of the literature on etiology of eating disorders". *Annals of Neurosciences*. **20** (4): 157–161. doi:10.5214/ans.0972.7531.200409. PMC 4117136
disorders". *Abnormal Psychology* (Sixth ed.). New York: McGraw-Hill Education. p. 341. ISBN 978-0-07-803538-8.
86. ^ *a b* Lock JD, Fitzpatrick KK (2009). "Anorexia nervosa". *BMJ Clin Evid*. **2009**. PMC 2907776. PMID 19445758.
87. ^ National Institute of Mental Health. "Eating disorders". Retrieved 23 March 2015.
88. ^ National Collaborating Centre for Mental Health (2004). Eating Disorders: Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders. London, The British Psychological Society and The Royal College of Psychiatrists.
89. ^ Gowers S. G.; et al. (2000). "Impact of hospitalisation on the outcome of adolescent anorexia nervosa". *Br J Psychiatry*. **176** (2): 138–141. doi:10.1192/bjp.176.2.138.
90. ^ Nolen-Hoeksema, S (2014). *Abnormal Psychology* (Sixth ed.). McGraw-Hill Education. p. 357. ISBN 978-1-259-06072-4.
91. ^ Blessitt, E., et al. (2015). "Family therapy for adolescent anorexia nervosa." Curr Opin Psychiatry 28(6): 455–460.
92. ^ Garner, David M.; Garfinkel, Paul E. (1997-01-01). *Handbook of Treatment for Eating Disorders*. Guilford Press. ISBN 978-1-57230-186-3.
93. ^ Whitnet E, Rolfes SR (2011). *Understanding Nutrition*. United States: Wadsworth Cengage Learning. p. 255. ISBN 1-133-58752-6.
94. ^ Russell, Gerald (1987). "An Evaluation of Family Therapy in Anorexia Nervosa and Bulimia Nervosa". *Arch Gen Psychiatry*. **44** (12): 1047–56. doi:10.1001/archpsyc.1987.01800240021004. PMID 3318754.
95. ^ le Grange D, Eisler I (2009). "Family interventions in adolescent anorexia nervosa". *Child and Adolescent Psychiatric Clinics of North America*. **18** (1): 159–73. doi:10.1016/j.chc.2008.07.004. PMID 19014864.
96. ^ "Eating Disorders". National Institute of Mental Health (NIMH). 2011. Retrieved 29 September 2013.
97. ^ "Couples Therapy Helps Combat Anorexia Nervosa". *Eating Disorders Review*. **23** (6). 2012.
98. ^ Whitfield G, Davidson A (2007). *Cognitive Behavioural Therapy Explained*. Radcliffe Publishing. ISBN 978-1-85775-603-6. Retrieved 9 April 2015.
99. ^ Keltner NL, Steele D (6 August 2014). *Psychiatric Nursing*. Elsevier Health Sciences. ISBN 978-0-323-29352-5. Retrieved 9 April 2015.
100. ^ Tchanturia K, Lounes N, Holttum S (2014). "Cognitive remediation in anorexia nervosa and related conditions: a systematic review". *Eur Eat Disord Rev*. **22** (6): 454–62. doi:10.1002/erv.2326. PMID 25277720.
101. ^ *a b* Pinna F, Sanna L, Carpiniello B (2015). "Alexithymia in eating disorders: therapeutic implications". *Psychol Res Behav Manag*. **8**: 1–15.

. PMID 25206042.
37. ^ Thornton LM, Mazzeo SE, Bulik CM (2011). "The heritability of eating disorders: methods and current findings". *Behavioral Neurobiology of Eating Disorders. Current Topics in Behavioral Neurosciences*. **6**. pp. 141–56. doi:10.1007/7854_2010_91. ISBN 978-3-642-15130-9. PMC 3599773. PMID 21243474.
38. ^ Rask-Andersen M, Olszewski PK, Levine AS, Schiöth HB (2009). "Molecular mechanisms underlying anorexia nervosa: Focus on human gene association studies and systems controlling food intake". *Brain Res Rev*. **62** (2): 147–64. doi:10.1016/j.brainresrev.2009.10.007. PMID 19931559.
39. ^ Pjetri E, Schmidt U, Kas MJ, Campbell IC (2012). "Epigenetics and eating disorders". *Curr Opin Clin Nutr Metab Care*. **15** (4): 330–5. doi:10.1097/MCO.0b013e3283546fd3. PMID 22617563.
40. ^ Davis JF, Choi DL, Benoit SC (2011). "24. Orexigenic Hypothalamic Peptides Behavior and Feeding – 24.5 Orexin". In Preedy VR, Watson RR, Martin CR. *Handbook of Behavior, Food and Nutrition*. Springer. pp. 361–2. ISBN 978-0-387-92271-3.
41. ^ Smitka K, Papezova H, Vondra K, Hill M, Hainer V, Nedvidkova J (2013). "The role of "mixed" orexigenic and anorexigenic signals and autoantibodies reacting with appetite-regulating neuropeptides and peptides of the adipose tissue-gut-brain axis: relevance to food intake and nutritional status in patients with anorexia nervosa and bulimia nervosa". *Int J Endocrinol*. **2013**: 483145. doi:10.1155/2013/483145. PMC 3782835. PMID 24106499.
42. ^ [a] [b] Satherley R, Howard R, Higgs S (Jan 2015). "Disordered eating practices in gastrointestinal disorders". *Appetite* (Review). **84**: 240–50. doi:10.1016/j.appet.2014.10.006. PMID 25312748.
43. ^ [a] [b] Bern EM, O'Brien RF (Aug 2013). "Is it an eating disorder, gastrointestinal disorder, or both?". *Curr Opin Pediatr* (Review). **25** (4): 463–70. doi:10.1097/MOP.0b013e328362d1ad. PMID 23838835. "Several case reports brought attention to the association of anorexia nervosa and celiac disease.(...) Some patients present with the eating disorder prior to diagnosis of celiac disease and others developed anorexia nervosa after the diagnosis of celiac disease. Healthcare professionals should screen for celiac disease with eating disorder symptoms especially with gastrointestinal symptoms, weight loss, or growth failure.(...) Celiac disease patients may present with gastrointestinal symptoms such as diarrhea, steatorrhea, weight loss, vomiting, abdominal pain, anorexia, constipation, bloating, and distension due to malabsorption. Extraintestinal presentations include anemia, osteoporosis,
doi:10.2147/PRBM.S52656. PMC 4278740. PMID 25565909.
102. ^ Arcelus J.; et al. (2011). "Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies". *Arch Gen Psychiatry*. **68** (7): 724–731. doi:10.1001/archgenpsychiatry.2011.74.
103. ^ Robinson P (2012) Avoiding deaths in hospital from anorexia nervosa: the MARSIPAN project. Psychiatrist, 36: 109–13.]
104. ^ Royal_College_of_Psychiatrists (2014). MARSIPAN: Management of Really Sick Patients with Anorexia Nervosa. Second edition. Page 6
105. ^ O'Connor, G. and D. Nicholls (2013). "Refeeding hypophosphatemia in adolescents with anorexia nervosa: a systematic review." Nutr Clin Pract 28(3): 358–364.
106. ^ http://%5Bhttps://www.nice.org.uk/guidance/cg32/chapter/1-Guidance#what-to-give-in-hospital-and-the-community%20NICE%20guideline%20on%20Nutrition%20support%5D
107. ^ Bouquegneau A, Dubois BE, Krzesinski JM, Delanaye P (2012). "Anorexia nervosa and the kidney". *Am. J. Kidney Dis.* **60** (2): 299–307. doi:10.1053/j.ajkd.2012.03.019. PMID 22609034.
108. ^ Nolen-Hoeksema S (2014). "Eating Disorders". *Abnormal Psychology* (Sixth ed.). New York: McGraw Hill Education. p. 342. ISBN 978-0-07-803538-8.
109. ^ "Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders" (PDF). *National Collaborating Centre for Mental Health*. 2004.
110. ^ Vyver E, Steinegger C, Katzman DK (2008). "Eating disorders and menstrual dysfunction in adolescents". *Ann. N. Y. Acad. Sci*. **1135**: 253–64. doi:10.1196/annals.1429.013. PMID 18574232.
111. ^ Devlin MJ, Walsh BT, Katz JL, Roose SP, Linkie DM, Wright L, Vande Wiele R, Glassman AH (1989). "Hypothalamic-pituitary-gonadal function in anorexia nervosa and bulimia". *Psychiatry Res*. **28** (1): 11–24. doi:10.1016/0165-1781(89)90193-5. PMID 2500676.
112. ^ [a] [b] Støving RK, Chen JW, Glintborg D, Brixen K, Flyvbjerg A, Hørder K, Frystyk J (2007). "Bioactive insulin-like growth factor (IGF) I and IGF-binding protein-1 in anorexia nervosa". *J. Clin. Endocrinol. Metab*. **92** (6): 2323–9. doi:10.1210/jc.2006-1926. PMID 17389700.
113. ^ Misra, Madhusmita; Klibanski, Anne (1 June 2014). "Anorexia nervosa and bone". *Journal of Endocrinology*. **221** (3): R163–R176. doi:10.1530/JOE-14-0039. ISSN 0022-0795. PMC 4047520. PMID 24898127.
114. ^ Kleinman R (1 April 2008). *Walker's Pediatric Gastrointestinal Disease*. PMPH-USA. ISBN 978-1-55009-364-3. Retrieved 9 April 2015.

dermatitis herpetiformis, short stature, delayed puberty, fatigue, aphthous stomatitis, elevated transaminases, neurologic problems, or dental enamel hypoplasia.(...) it has become clear that symptomatic and diagnosed celiac disease is the tip of the iceberg; the remaining 90% or more of children are asymptomatic and undiagnosed."

44. ^ Quick VM, Byrd-Bredbenner C, Neumark-Sztainer D (1 May 2013). "Chronic illness and disordered eating: a discussion of the literature". *Adv Nutr* (Review). **4** (3): 277–86. doi:10.3945/an.112.003608. PMC 3650496. PMID 23674793.
45. ^ Zandian M, Ioakimidis I, Bergh C, Södersten P (2007). "Cause and treatment of anorexia nervosa". *Physiology & Behavior*. **92** (1–2): 283–90. doi:10.1016/j.physbeh.2007.05.052. PMID 17585973.
46. ^ Thambirajah MS (2007). *Case Studies in Child and Adolescent Mental Health*. Radcliffe Publishing. p. 145. ISBN 978-1-85775-698-2. OCLC 84150452.
47. ^ Kaye W (2008). "Neurobiology of Anorexia and Bulimia Nervosa Purdue Ingestive Behavior Research Center Symposium Influences on Eating and Body Weight over the Lifespan: Children and Adolescents". *Physiology & Behavior*. **94** (1): 121–35. doi:10.1016/j.physbeh.2007.11.037. PMC 2601682. PMID 18164737.
48. ^ Lozano GA (2008). "Obesity and sexually selected anorexia nervosa". *Medical Hypotheses*. **71** (6): 933–940. doi:10.1016/j.mehy.2008.07.013. PMID 18760541.
49. ^ *a b* Herpertz-Dahlmann B, Bühren K, Remschmidt H (2013). "Growing up is hard: Mental disorders in adolescence". *Deutsches Arzteblatt international*. **110** (25): 432–9; quiz 440. doi:10.3238/arztebl.2013.0432. PMC 3705204. PMID 23840288.
50. ^ Wonderlich SA, Brewerton TD, Jocic Z, Dansky BS, Abbott DW (1997). "Relationship of childhood sexual abuse and eating disorders". *J Am Acad Child Adolesc Psychiatry*. **36** (8): 1107–15. doi:10.1097/00004583-199708000-00018. PMID 9256590.
51. ^ Connors ME, Morse W (1993). "Sexual abuse and eating disorders: A review". *The International Journal of Eating Disorders*. **13** (1): 1–11. doi:10.1002/1098-108x(199301)13:1<1::aid-eat2260130102>3.0.co;2-p. PMID 8477269.
52. ^ Worthen, Dennis (2001). *P & G Pharmacy Handbook*. p. 65.
53. ^ Ensminger, Audrey (1983). *Foods & nutrition encyclopedia*. p. 423.
54. ^ Colman, Andrew (2015). *A Dictionary of Psychology*. OUP Oxford. p. 851. ISBN 978-0-19-105784-7.
55. ^ *Textbook of Clinical Gastroenterology and Hepatology* (2 ed.). John Wiley & Sons. 2012.
115. ^ *a b* Norris ML, Harrison ME, Isserlin L, Robinson A, Feder S, Sampson M (2016). "Gastrointestinal complications associated with anorexia nervosa: A systematic review". *Int J Eat Disord*. **49** (3): 216–37. doi:10.1002/eat.22462. PMID 26407541.
116. ^ *a b c d e f g* Sachs KV, Harnke B, Mehler PS, Krantz MJ (2016). "Cardiovascular complications of anorexia nervosa: A systematic review". *Int J Eat Disord*. **49** (3): 238–48. doi:10.1002/eat.22481. PMID 26710932.
117. ^ *a b* Goldberg SJ, Comerci GD, Feldman L (1988). "Cardiac output and regional myocardial contraction in anorexia nervosa". *J Adolesc Health Care*. **9** (1): 15–21. doi:10.1016/0197-0070(88)90013-7. PMID 3335466.
118. ^ Johnson GL, Humphries LL, Shirley PB, Mazzoleni A, Noonan JA (1986). "Mitral valve prolapse in patients with anorexia nervosa and bulimia". *Arch. Intern. Med*. **146** (8): 1525–9. doi:10.1001/archinte.1986.00360200083014. PMID 3460535.
119. ^ *a b* Hasan TF, Hasan H (2011). "Anorexia nervosa: a unified neurological perspective". *Int J Med Sci*. **8** (8): 679–703. doi:10.7150/ijms.8.679. PMC 3204438. PMID 22135615.
120. ^ Zanetti T (2013). "Epidemiology of Eating Disorders". *Eating Disorders and the Skin*. pp. 9–15. doi:10.1007/978-3-642-29136-4_2. ISBN 978-3-642-29135-7.
121. ^ Smink FR, van Hoeken D, Hoek HW (2012). "Epidemiology of Eating Disorders: Incidence, Prevalence and Mortality Rates". *Current Psychiatry Reports*. **14** (4): 406–414. doi:10.1007/s11920-012-0282-y. PMC 3409365. PMID 22644309.
122. ^ *a b* Bonci CM, Bonci LJ, Granger LR, Johnson CL, Malina RM, Milne LW, Ryan RR, Vanderbunt EM (2008). "National athletic trainers' association position statement: Preventing, detecting, and managing disordered eating in athletes". *Journal of Athletic Training*. **43** (1): 80–108. doi:10.4085/1062-6050-43.1.80. PMC 2231403. PMID 18335017.
123. ^ Crilly L (2 April 2012). *Hope with Eating Disorders*. Hay House, Inc. ISBN 978-1-84850-906-1. Retrieved 9 April 2015.
124. ^ Gull WW (1997). "Anorexia nervosa (apepsia hysterica, anorexia hysterica). 1868". *Obesity Research*. **5** (5): 498–502. doi:10.1002/j.1550-8528.1997.tb00677.x. PMID 9385628.
125. ^ *a b* Pearce JM (2004). "Richard Morton: Origins of Anorexia nervosa". *European Neurology*. **52** (4): 191–192. doi:10.1159/000082033. PMID 15539770.
126. ^ Espi Forcen F (2013). "Anorexia mirabilis: the practice of fasting by Saint Catherine of Siena in the late Middle Ages". *Am J Psychiatry*. **170** (4): 370–1. doi:10.1176/appi.ajp.2012.12111457. PMID 23545792.
127. ^ Harris JC (2014). "Anorexia nervosa and anorexia

p. 69. ISBN 978-1-118-32142-3.
56. ^ a b "Factors That May Contribute to Eating Disorders | National Eating Disorders Association". *www.nationaleatingdisorders.org*. Retrieved 1 March 2016.
57. ^ Field, Alison E.; Camargo, Carlos A.; Taylor, C. Barr; Berkey, Catherine S.; Roberts, Susan B.; Colditz, Graham A. (1 January 2001). "Peer, Parent, and Media Influences on the Development of Weight Concerns and Frequent Dieting Among Preadolescent and Adolescent Girls and Boys". *Pediatrics*. **107** (1): 54–60. doi:10.1542/peds.107.1.54. ISSN 0031-4005. PMID 11134434.
58. ^ "Eating disorders and culture". *Harvard Mental Health Letter*. **20** (9): 7. 1 March 2004. PMID 15044128.
59. ^ Anderson-Fye, Eileen P. and Becker, Anne E. (2004) "Sociocultural Aspects of Eating Disorders" pp. 565–89 in *Handbook of Eating Disorders and Obesity*, J. Kevin (ed.). Thompson. Hoboken, NJ: John Wiley & Sons.
mirabilis: Miss K. R—and St Catherine Of Siena". *JAMA Psychiatry*. **71** (11): 1212–3. doi:10.1001/jamapsychiatry.2013.2765. PMID 25372187.
128. ^ a b Gull, Sir William Withey (1894). T D Acland, ed. *Medical Papers*. p. 309.
129. ^ Lasègue E (6 September 1873). "On Hysterical Anorexia". Medical Times and Gazette. See also PMID 9385627
130. ^ Arnold, Carrie (2012) *Decoding Anorexia: How Breakthroughs in Science Offer Hope for Eating Disorders*, Routledge Press. ISBN 0-415-89867-6
131. ^ Arnold, Carrie (29 March 2016). "Anorexia: you don't just grow out of it". *The Guardian*. Retrieved 29 March 2016.
132. ^ Klein DA, Walsh BT (2004). "Eating disorders: clinical features and pathophysiology". *Physiol. Behav*. **81** (2): 359–74. doi:10.1016/j.physbeh.2004.02.009. PMID 15159176.

## Further reading [edit]

- Bailey AP, Parker AG, Colautti LA, Hart LM, Liu P, Hetrick SE (2014). "Mapping the evidence for the prevention and treatment of eating disorders in young people". *J Eat Disord*. **2** (1): 5. doi:10.1186/2050-2974-2-5. PMC 4081733. PMID 24999427.
- Coelho GM, Gomes AI, Ribeiro BG, Soares Ede A (2014). "Prevention of eating disorders in female athletes". *Open Access J Sports Med*. **5**: 105–13. doi:10.2147/OAJSM.S36528. PMC 4026548. PMID 24891817.
- Luca A, Luca M, Calandra C (2015). "Eating Disorders in Late-life". *Aging Dis*. **6** (1): 48–55. doi:10.14336/AD.2014.0124. PMC 4306473. PMID 25657852.

## External links [edit]

- National Association of Anorexia Nervosa and Associated Disorders
- International Eating Disorder Referral and Information Center
- Anorexia nervosa
- Society of Clinical Psychology—Anorexia

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# Anxiety disorder

From Wikipedia, the free encyclopedia

**Anxiety disorders** are a group of mental disorders characterized by feelings of anxiety and fear.[2] Anxiety is a worry about future events and fear is a reaction to current events. These feelings may cause physical symptoms, such as a fast heart rate and shakiness. There are a number of anxiety disorders: including generalized anxiety disorder, specific phobia, social anxiety disorder, separation anxiety disorder, agoraphobia, and panic disorder. The disorder differs by what results in the symptoms. People often have more than one anxiety disorder.[2]

The cause of anxiety disorders is a combination of genetic and environmental factors.[3] Risk factors include a history of child abuse, family history of mental disorders, and poverty. Anxiety disorders often occur with other mental disorders, particularly major depressive disorder, personality disorder, and substance use disorder.[4] To be diagnosed symptoms typically need to be present at least six months, be more than would be expected for the situation, and decrease functioning.[2][4] Other problems that may result in similar symptoms including hyperthyroidism, heart disease, caffeine, alcohol, or cannabis use, and withdrawal from certain drugs, among others.[4][5]

Without treatment, anxiety disorders tend to remain.[2][3] Treatment may include lifestyle changes, counselling, and medications. Counselling is typically with a type of cognitive behavioural therapy.[4] Medications, such as antidepressants or beta blockers, may improve symptoms.[3]

About 12% of people are affected by an anxiety disorder in a given year and between 5-30% are affected at some point in their life.[4][6] They occur about twice as often in females as males, and generally begin before the age of 25.[2][4] The most common are specific phobia which affects nearly 12% and social anxiety disorder which affects 10% at some point in their life. They affect those between the ages of 15 and 35 the most and become less common after the age of 55. Rates appear to be higher in the United States and Europe.[4]

Contents



**Anxiety disorder**

*The Scream* (Norwegian: *Skrik*) a painting by Norwegian artist Edvard Munch[1]

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## Classification [edit]

### Generalized [edit]

*Main article: Generalized anxiety disorder*

Facial expression of someone with chronic anxiety

Generalized anxiety disorder (GAD) is a common, chronic disorder characterized by long-lasting anxiety that is not focused on any one object or situation. Those suffering from generalized anxiety disorder experience non-specific persistent fear and worry, and become overly concerned with everyday matters. Generalized anxiety disorder is "characterized by chronic excessive worry accompanied by three or more of the following symptoms: restlessness, fatigue, concentration problems, irritability, muscle tension, and sleep disturbance".[7] Generalized anxiety disorder is the most common anxiety disorder to affect older adults.[8] Anxiety can be a symptom of a medical or substance abuse problem, and medical professionals must be aware of this. A diagnosis of GAD is made when a person has been excessively worried about an everyday problem for six months or more.[9] A person may find that they have problems making daily decisions and remembering commitments as a result of lack of concentration/preoccupation with worry.[10] Appearance looks strained, with increased sweating from the hands, feet, and axillae,[11] and they may be tearful, which can suggest depression.[12] Before a diagnosis of anxiety disorder is made, physicians must rule out drug-induced anxiety and other medical causes.[13]

In children GAD may be associated with headaches, restlessness, abdominal pain, and heart palpitations.[14]

Typically it begins around 8 to 9 years of age.[14]

## Phobias [edit]

*Main article: Phobia*

The single largest category of anxiety disorders is that of phobic disorders, which includes all cases in which fear and anxiety are triggered by a specific stimulus or situation. Between 5% and 12% of the population worldwide suffer from phobic disorders.[9] Sufferers typically anticipate terrifying consequences from encountering the object of their fear, which can be anything from an animal to a location to a bodily fluid to a particular situation. Sufferers understand that their fear is not proportional to the actual potential danger but still are overwhelmed by it.[15]

## Panic disorder [edit]

*Main article: Panic disorder*

With panic disorder, a person has brief attacks of intense terror and apprehension, often marked by trembling, shaking, confusion, dizziness, nausea, and/or difficulty breathing. These panic attacks, defined by the APA as fear or discomfort that abruptly arises and peaks in less than ten minutes, can last for several hours.[16] Attacks can be triggered by stress, fear, or even exercise; the specific cause is not always apparent.

In addition to recurrent unexpected panic attacks, a diagnosis of panic disorder requires that said attacks have chronic consequences: either worry over the attacks' potential implications, persistent fear of future attacks, or significant changes in behavior related to the attacks. As such, those suffering from panic disorder experience symptoms even outside specific panic episodes. Often, normal changes in heartbeat are noticed by a panic sufferer, leading them to think something is wrong with their heart or they are about to have another panic attack. In some cases, a heightened awareness (hypervigilance) of body functioning occurs during panic attacks, wherein any perceived physiological change is interpreted as a possible life-threatening illness (i.e., extreme hypochondriasis).

## Agoraphobia [edit]

*Main article: Agoraphobia*

Agoraphobia is the specific anxiety about being in a place or situation where escape is difficult or embarrassing or where help may be unavailable.[17] Agoraphobia is strongly linked with panic disorder and is often precipitated by the fear of having a panic attack. A common manifestation involves needing to be in constant view of a door or other escape route. In addition to the fears themselves, the term agoraphobia is often used to refer to avoidance behaviors that sufferers often develop.[18] For example, following a panic attack while driving, someone suffering from agoraphobia may develop anxiety over driving and will therefore avoid driving. These avoidance behaviors can often have serious consequences and often reinforce the fear they are caused by.

## Social anxiety disorder [edit]

*Main article: Social anxiety disorder*

Social anxiety disorder (SAD; also known as social phobia) describes an intense fear and avoidance of negative public scrutiny, public embarrassment, humiliation, or social interaction. This fear can be specific to particular social situations (such as public speaking) or, more typically, is experienced in most (or all) social interactions. Social anxiety often manifests specific physical symptoms, including blushing, sweating, and difficulty speaking. As with all phobic disorders, those suffering from social anxiety often will attempt to avoid the source of their anxiety; in the case of social anxiety this is particularly problematic, and in severe cases can lead to complete social isolation.

Social physique anxiety (SPA) is a subtype of social anxiety. It is concern over the evaluation of one's body by others.[19] SPA is common among adolescents, especially females.

## Post-traumatic stress disorder [edit]

*Main article: Post-traumatic stress disorder*

Post-traumatic stress disorder (PTSD) is an anxiety disorder that results from a traumatic experience. Post-traumatic stress can result from an extreme situation, such as combat, natural disaster, rape, hostage situations, child abuse, bullying, or even a serious accident. It can also result from long-term (chronic) exposure to a severe stressor,[20] for example soldiers who endure individual battles but cannot cope with continuous combat. Common symptoms include hypervigilance, flashbacks, avoidant behaviors, anxiety, anger and depression.[21] There are a number of treatments that form the basis of the care plan for those suffering with PTSD. Such treatments include cognitive behavioral therapy (CBT), psychotherapy and support from family and friends.[9]

Posttraumatic stress disorder (PTSD) research began with Vietnam veterans, as well as natural and non natural disaster victims. Studies have found the degree of exposure to a disaster has been found to be the best predictor of PTSD.[22]

## Separation anxiety [edit]

*Main article: Separation anxiety disorder*

Separation anxiety disorder (SepAD) is the feeling of excessive and inappropriate levels of anxiety over being separated from a person or place. Separation anxiety is a normal part of development in babies or children, and it is only when this feeling is excessive or inappropriate that it can be considered a disorder.[23] Separation anxiety disorder affects roughly 7% of adults and 4% of children, but the childhood cases tend to be more severe; in some instances, even a brief separation can produce panic.[24][25] Treating a child earlier may prevent problems. This may include training the parents and family on how to deal with it. Often, the parents will reinforce the anxiety because they do not know how to properly work through it with the child. In addition to parent training and family therapy, medication, such as SSRI's, can be used to treat separation anxiety.[26]

## Situational anxiety [edit]

Situational anxiety is caused by new situations or changing events. It can also be caused by various events that make that particular individual uncomfortable. Its occurrence is very common. Often, an individual will experience panic attacks or extreme anxiety in specific situations. A situation that causes one individual to experience anxiety may not affect another individual at all. For example, some people become uneasy in crowds or tight spaces, so standing in a tightly packed line, say at the bank or a store register, may cause them to experience extreme anxiety, possibly a panic attack.[27] Others, however, may experience anxiety when major changes in life occur, such as entering college, getting married, having children, etc.

## Obsessive–compulsive disorder [edit]

*Main article: Obsessive–compulsive disorder*

Obsessive–compulsive disorder (OCD) is not classified as an anxiety disorder by the DSM-5 but is by the ICD-10. It was previously classified as an anxiety disorder in the DSM-4. It is a condition where the person has obsessions (distressing, persistent, and intrusive thoughts or images) and/or compulsions (urges to repeatedly perform specific acts or rituals), that are not caused by drugs or physical order, and which cause distress or social dysfunction.[28][29] The compulsive rituals are personal rules followed to relieve the anxiety.[29] OCD affects roughly 1-2% of adults (somewhat more women than men), and under 3% of children and adolescents.[28][29]

A person with OCD knows that the symptoms are unreasonable and struggles against both the thoughts and the behavior.[28][30] Their symptoms could be related to external events they fear (such as their home burning down because they forget to turn off the stove) or worry that they will behave inappropriately.[30]

It is not certain why some people have OCD, but behavioral, cognitive, genetic, and neurobiological factors may be involved.[29] Risk factors include family history, being single (although that may result from the disorder), and higher socioeconomic class or not being in paid employment.[29] OCD is chronic; about 20% of people will overcome it, and symptoms will at least reduce over time for most people (a further 50%).[28]

## Causes [edit]

### Drugs [edit]

Anxiety and depression can be caused by alcohol abuse, which in most cases improves with prolonged abstinence. Even moderate, sustained alcohol use may increase anxiety levels in some individuals.[31] Caffeine, alcohol and benzodiazepine dependence can worsen or cause anxiety and panic attacks.[32] Anxiety commonly occurs during the acute withdrawal phase of alcohol and can persist for up to 2 years as part of a post-acute withdrawal syndrome, in about a quarter of people recovering from alcoholism.[33] In one study in 1988–1990, illness in approximately half of patients attending mental health services at one British hospital psychiatric clinic, for conditions including anxiety disorders such as panic disorder or social phobia, was determined to be the result of alcohol or benzodiazepine dependence. In these patients, an initial increase in anxiety occurred during the withdrawal period followed by a cessation of their anxiety symptoms.[34]

There is evidence that chronic exposure to organic solvents in the work environment can be associated with anxiety disorders. Painting, varnishing and carpet-laying are some of the jobs in which significant exposure to organic solvents may occur.[35]

Taking caffeine may cause or worsen anxiety disorders,[36][37] including panic disorder.[38][39][40] Those with anxiety disorders can have high caffeine sensitivity.[41][42] Caffeine-induced anxiety disorder is a subclass of the DSM-5 diagnosis of substance/medication-induced anxiety disorder. Substance/medication-induced anxiety disorder falls under the category of anxiety disorders, and not the category of substance-related and addictive disorders, even though the symptoms are due to the effects of a substance.[43]

Cannabis use is associated with anxiety disorders. However, the precise relationship between cannabis use and anxiety still needs to be established.[44][45]

### Medical conditions [edit]

Occasionally, an anxiety disorder may be a side-effect of an underlying endocrine disease that causes nervous system hyperactivity, such as pheochromocytoma[46][47] or hyperthyroidism.[48]

### Stress [edit]

Anxiety disorders can arise in response to life stresses such as financial worries or chronic physical illness. Anxiety among adolescents and young adults is common due to the stresses of social interaction, evaluation, and body image. Anxiety is also common among older people who have dementia. On the other hand, anxiety disorder is sometimes misdiagnosed among older adults when doctors misinterpret symptoms of a physical ailment (for instance, racing heartbeat due to cardiac arrhythmia) as signs of anxiety.[8]

### Genetics [edit]

GAD runs in families and is six times more common in the children of someone with the condition.[49]

While anxiety arose as an adaptation, in modern times it is almost always thought of negatively in the context of anxiety disorders. People with these disorders have highly sensitive systems; hence, their systems tend to overreact to seemingly harmless stimuli. Sometimes anxiety disorders occur in those who have had traumatic youths, demonstrating an increased prevalence of anxiety when it appears a child will have a difficult future.[50] In these cases, the disorder arises as a way to predict that the individual's

environment will continue to pose threats.

### Persistence of anxiety [edit]

At a low level, anxiety is not a bad thing. In fact, the hormonal response to anxiety has evolved as a benefit, as it helps humans react to dangers. Researchers in evolutionary medicine believe this adaptation allows humans to realize there is a potential threat and to act accordingly in order to ensure greatest possibility of protection. It has actually been shown that those with low levels of anxiety have a greater risk of death than those with average levels. This is because the absence of fear can lead to injury or death.[50] Additionally, patients with both anxiety and depression were found to have lower morbidity than those with depression alone.[51] The functional significance of the symptoms associated with anxiety includes: greater alertness, quicker preparation for action, and reduced probability of missing threats.[51] In the wild, vulnerable individuals, for example those who are hurt or pregnant, have a lower threshold for anxiety response, making them more alert.[51] This demonstrates a lengthy evolutionary history of the anxiety response.

### Evolutionary mismatch [edit]

It has been theorized that high rates of anxiety are a reaction to how the social environment has changed from the Paleolithic era. For example, in the Stone Age there was greater skin-to-skin contact and more handling of babies by their mothers, both of which are strategies that reduce anxiety.[50] Additionally, there is greater interaction with strangers in present times as opposed to interactions solely between close-knit tribes. Researchers posit that the lack of constant social interaction, especially in the formative years, is a driving cause of high rates of anxiety.

Many current cases are likely to have resulted from an evolutionary mismatch, which has been specifically termed a "psychopathogical mismatch." In evolutionary terms, a mismatch occurs when an individual possesses traits that were adapted for an environment that differs from the individual's current environment. For example, even though an anxiety reaction may have been evolved to help with life-threatening situations, for highly sensitized individuals in Westernized cultures simply hearing bad news can elicit a strong reaction.[52]

An evolutionary perspective may provide insight into alternatives to current clinical treatment methods for anxiety disorders. Simply knowing some anxiety is beneficial may alleviate some of the panic associated with mild conditions. Some researchers believe that, in theory, anxiety can be mediated by reducing a patient's feeling of vulnerability and then changing their appraisal of the situation.[52]

## Mechanisms [edit]

### Biological [edit]

Low levels of GABA, a neurotransmitter that reduces activity in the central nervous system, contribute to anxiety. A number of anxiolytics achieve their effect by modulating the GABA receptors.[53][54][55]

Selective serotonin reuptake inhibitors, the drugs most commonly used to treat depression, are frequently considered as a first line treatment for anxiety disorders.[56]

### Amygdala [edit]

The amygdala is central to the processing of fear and anxiety, and its function may be disrupted in anxiety disorders.[57] Sensory information enters the amygdala through the nuclei of the basolateral complex (consisting of lateral, basal, and accessory basal nuclei). The basolateral complex processes sensory-related fear memories and communicates their threat importance to memory and sensory processing elsewhere in the brain, such as the medial prefrontal cortex and sensory cortices.

Another important area is the adjacent central nucleus of the amygdala, which controls species-specific fear

responses, via connections to the brainstem, hypothalamus, and cerebellum areas. In those with general anxiety disorder, these connections functionally seem to be less distinct, with greater gray matter in the central nucleus. Another difference is that the amygdala areas have decreased connectivity with the insula and cingulate areas that control general stimulus salience, while having greater connectivity with the parietal cortex and prefrontal cortex circuits that underlie executive functions.[57]

The latter suggests a compensation strategy for dysfunctional amygdala processing of anxiety. Researchers have noted "Amygdalofrontoparietal coupling in generalized anxiety disorder patients may ... reflect the habitual engagement of a cognitive control system to regulate excessive anxiety."[57] This is consistent with cognitive theories that suggest the use in this disorder of attempts to reduce the involvement of emotions with compensatory cognitive strategies.

Clinical and animal studies suggest a correlation between anxiety disorders and difficulty in maintaining balance.[58][59][60][61] A possible mechanism is malfunction in the parabrachial area, a brain structure that, among other functions, coordinates signals from the amygdala with input concerning balance.[62]

Anxiety processing in the basolateral amygdala has been implicated with dendritic arborization of the amygdaloid neurons. SK2 potassium channels mediate inhibitory influence on action potentials and reduce arborization. By overexpressing SK2 in the basolateral amygdala, anxiety in experimental animals can be reduced together with general levels of stress-induced corticosterone secretion.[63]

## Prevention [edit]

Focus is increasing on prevention of anxiety disorders.[64] There is tentative evidence to support the use of cognitive behavior therapy[64] and mindfulness therapy.[65][66] As of 2013, there are no effective measures to prevent GAD in adults.[67]

## Diagnosis [edit]

Anxiety disorders are often severe chronic conditions, which can be present from an early age or begin suddenly after a triggering event. They are prone to flare up at times of high stress and are frequently accompanied by physiological symptoms such as headache, sweating, muscle spasms, tachycardia, palpitations, and hypertension, which in some cases lead to fatigue.

In casual discourse the words "anxiety" and "fear" are often used interchangeably; in clinical usage, they have distinct meanings: "anxiety" is defined as an unpleasant emotional state for which the cause is either not readily identified or perceived to be uncontrollable or unavoidable, whereas "fear" is an emotional and physiological response to a recognized external threat.[68] The term "anxiety disorder" includes fears (phobias) as well as anxieties.[*medical citation needed*]

The diagnosis of anxiety disorders is difficult because there are no objective biomarkers, it is based on symptoms,[69] which typically need to be present at least six months, be more than would be expected for the situation, and decrease functioning.[2][4] Several generic anxiety questionnaires can be used to detect anxiety symptoms, such as the State-Trait Anxiety Inventory (STAI), the Generalized Anxiety Disorder 7 (GAD-7), the Beck Anxiety Inventory (BAI), the Zung Self-Rating Anxiety Scale, and the Taylor Manifest Anxiety Scale.[70] Other questionnaires combine anxiety and depression measurement, such as the Hamilton Anxiety Rating Scale, the Hospital Anxiety and Depression Scale (HADS), the Patient Health Questionnaire (PHQ), and the Patient-Reported Outcomes Measurement Information System (PROMIS).[70] Examples of specific anxiety questionnaires include the Liebowitz Social Anxiety Scale (LSAS), the Social Interaction Anxiety Scale (SIAS), the Social Phobia Inventory (SPIN), the Social Phobia Scale (SPS), and the Social Anxiety Questionnaire (SAQ-A30).[71]

Anxiety disorders often occur along with other mental disorders, in particular depression, which may occur in as many as 60% of people with anxiety disorders. The fact that there is considerable overlap between symptoms of anxiety and depression, and that the same environmental triggers can provoke symptoms in [72]

either condition, may help to explain this high rate of comorbidity.

Studies have also indicated that anxiety disorders are more likely among those with family history of anxiety disorders, especially certain types.[73]

Sexual dysfunction often accompanies anxiety disorders, although it is difficult to determine whether anxiety causes the sexual dysfunction or whether they arise from a common cause. The most common manifestations in individuals with anxiety disorder are avoidance of intercourse, premature ejaculation or erectile dysfunction among men and pain during intercourse among women. Sexual dysfunction is particularly common among people affected by panic disorder (who may fear that a panic attack will occur during sexual arousal) and posttraumatic stress disorder.[74]

### Differential diagnosis [edit]

The diagnosis of an anxiety disorder requires first ruling out an underlying medical cause.[5][68] Diseases that may present similar to an anxiety disorder, including certain endocrine diseases (hypo- and hyperthyroidism, hyperprolactinemia),[4][5][68][75] metabolic disorders (diabetes),[5][76] deficiency states (low levels of vitamin D, B2, B12, folic acid),[5] gastrointestinal diseases (celiac disease, non-celiac gluten sensitivity, inflammatory bowel disease),[77][78][79] heart diseases,[4][5] blood diseases (anemia),[5] and brain degenerative diseases (Parkinson's disease, dementia, multiple sclerosis, Huntington's disease).[5][80][81][82]

Also, several drugs can cause or worsen anxiety, whether in intoxication, withdrawal, or from chronic use. These include alcohol, tobacco, cannabis, sedatives (including prescription benzodiazepines), opioids (including prescription pain killers and illicit drugs like heroin), stimulants (such as caffeine, cocaine and amphetamines), hallucinogens, and inhalants.[4][83]

## Treatment [edit]

Treatment options include lifestyle changes, therapy, and medications. There is no good evidence as to whether therapy or medication is more effective; the choice of which is up to the person with the anxiety disorder and most choose therapy first.[84] The other may be offered in addition to the first choice or if the first choice fails to relieve symptoms.[84]

### Lifestyle changes [edit]

Lifestyle changes include exercise, for which there is moderate evidence for some improvement, regularizing sleep patterns, reduce caffeine intake, and stopping smoking.[84] Stopping smoking has benefits in anxiety as large as or larger than those of medications.[85]

### Therapy [edit]

Cognitive behavioral therapy (CBT) is effective for anxiety disorders and is a first line treatment.[84][86][87][88] CBT appears to be equally effective when carried out via the internet.[89] While evidence for mental health apps is promising it is preliminary.[90]

Self-help books can contribute to the treatment of people with anxiety disorders.[91]

Mindfulness based programs also appear to be effective for managing anxiety disorders.[92][93] It is unclear if meditation has an effect on anxiety and transcendental meditation appears to be no different than other types of meditation.[94]

### Medications [edit]

Medications include SSRIs or SNRIs are first line choices for generalized anxiety disorder; there is no good evidence for any member of the class being better than another, so cost often drives drug choice.[84]

Buspirone, quetiapine and pregabalin are second line treatments for people who do not respond to SSRIs or SNRIs; there is also evidence that benzodiazepines including diazepam and clonazepam are effective but these are not preferred due to the risk of dependence.[84]

Medications need to be used with care among older adults, who are more likely to have side effects because of coexisting physical disorders. Adherence problems are more likely among older people, who may have difficulty understanding, seeing, or remembering instructions.[8]

In general medications are not seen as helpful in specific phobia but a benzodiazepine is sometimes used to help resolve acute episodes; as 2007 data were sparse for efficacy of any drug.[95]

### Alternative medicine [edit]

Many other remedies have been used for anxiety disorder. These include kava, where the potential for benefit seems greater than that for harm with short-term use in those with mild to moderate anxiety.[96][97] The American Academy of Family Physicians (AAFP) recommends use of kava for those with mild to moderate anxiety disorders who are not using alcohol or taking other medicines metabolized by the liver, but who wish to use "natural" remedies.[98] Side effects of kava in the clinical trials were rare and mild.

Inositol has been found to have modest effects in people with panic disorder or obsessive-compulsive disorder.[99] There is insufficient evidence to support the use of St. John's wort, valerian or passionflower.[99]

Aromatherapy has shown some tentative benefits for anxiety reduction in people with cancer when done with massages, although it not clear whether it could just enhance the effect of massage itself.[100]

### Children [edit]

Several methods of treatment have been found to be effective in treating childhood anxiety disorders. Therapy is strongly preferred to medication.[101]

Cognitive behavioral therapy (CBT), a well-established treatment for anxiety related disorders in children and adolescents, is a good first therapy approach.[101] Studies have also gathered substantial evidence for treatments that are not CBT based as being effective forms of treament, expanding treatment options for those who do not respond to CBT.[101] Like adults, children may undergo psychotherapy, cognitive-behavioral therapy, or counseling. Family therapy is a form of treatment in which the child meets with a therapist together with the primary guardians and siblings. Each family member may attend individual therapy, but family therapy is typically a form of group therapy. Art and play therapy are also used. Art therapy is most commonly used when the child will not or cannot verbally communicate, due to trauma or a disability in which they are nonverbal. Participating in art activities allows the child to express what they otherwise may not be able to communicate to others.[102] In play therapy, the child is allowed to play however they please as a therapist observes them. The therapist may intercede from time to time with a question, comment, or suggestion. This is often most effective when the family of the child plays a significant role in the treatment.[103]

In children and adolescents, a medication option is warranted, antidepressants such as SSRIs, SNRIs as well as tricyclic antidepressants can be effective.[104]

## Prognosis [edit]

The prognosis varies on the severity of each case and utilization of treatment for each individual. [105]

If these children are left untreated, they face risks such as poor results at school, avoidance of important social activities, and substance abuse. Children who have an anxiety disorder are likely to have other disorders such as depression, eating disorders, attention deficit disorders both hyperactive and inattentive.

## Epidemiology [edit]

Globally as of 2010 approximately 273 million (4.5% of the population) had an anxiety disorder.[106] It is more common in females (5.2%) than males (2.8%).[106]

In Europe, Africa and Asia, lifetime rates of anxiety disorders are between 9 and 16%, and yearly rates are between 4 and 7%.[107] In the United States, the lifetime prevalence of anxiety disorders is about 29%[108] and between 11 and 18% of adults have the condition in a given year.[107] This difference is affected by the range of ways in which different cultures interpret anxiety symptoms and what they consider to be normative behavior.[109][110] In general, anxiety disorders represent the most prevalent psychiatric condition in the United States, outside of substance use disorder.[111]

## Children [edit]

Like adults, children can experience anxiety disorders; between 10 and 20 percent of all children will develop a full-fledged anxiety disorder prior to the age of 18,[112] making anxiety the most common mental health issue in young people. Anxiety disorders in children are often more challenging to identify than their adult counterparts owing to the difficulty many parents face in discerning them from normal childhood fears. Likewise, anxiety in children is sometimes misdiagnosed as an attention deficit disorder or, due to the tendency of children to interpret their emotions physically (as stomach aches, head aches, etc.), anxiety disorders may initially be confused with physical ailments.[113]

Anxiety in children has a variety of causes; sometimes anxiety is rooted in biology, and may be a product of another existing condition, such as Autism or Asperger's Disorder.[114] Gifted children are also often more prone to excessive anxiety than non-gifted children.[115] Other cases of anxiety arise from the child having experienced a traumatic event of some kind, and in some cases, the cause of the child's anxiety cannot be pinpointed.[116]

Anxiety in children tends to manifest along age-appropriate themes, such as fear of going to school (not related to bullying) or not performing well enough at school, fear of social rejection, fear of something happening to loved ones, etc. What separates disordered anxiety from normal childhood anxiety is the duration and intensity of the fears involved.[113]

A small child will usually experience separation anxiety, for example, but he or she will generally grow out of it by about the age of 6, whereas in an anxious child it may linger for years longer, hindering the child's development.[117] Similarly, most children will fear the dark or losing their parents at some point, but this fear will dissipate over time without interfering a great deal in that child's normal day-to-day activities. In a child with an anxiety disorder, fearing the dark or loss of loved ones may grow into a lasting obsession which the child tries to deal with in compulsive ways which erode his or her quality of life.[117] The presence of co- occurring depressive symptoms in anxiety disorders may mark the transition to a more severe and detrimental and impairing disorder in preschool and early school age.[118]

Children, similar to adults, may suffer from a range of different anxiety disorders, including:

Generalized anxiety disorder: The child experiences persistent anxiety regarding a wide variety of situations, and this anxiety may adapt to fit each new situation that arises or be based largely on imagined situations which have yet to occur. Reassurance often has little effect.[113][117]

Separation anxiety disorder: A child who is older than 6 or 7 who has an extremely difficult time being away from his or her parents may be experiencing Separation Anxiety Disorder. Children with this disorder often fear that they will lose their loved ones during times of absence. As such, they frequently refuse to attend school.[119]

Social anxiety disorder should not be confused with shyness or introversion; shyness is frequently normal, especially in very young children. Children with social anxiety disorder often wish to engage in social activity (unlike introverts) but find themselves held back by obsessive fears of being disliked. They often convince

themselves they have made a poor impression on others, regardless of evidence to the contrary. Over time, they may develop a phobia of social situations.[120] This disorder affects older children and preteens more often than younger children. Social phobia in children may also be caused by some traumatic event, such as not knowing an answer when called on in class.[121]

While uncommon in children, OCD can occur. Rates are between two and four percent.[122] Like adults, children rely on "magical thinking" in order to allay their anxiety, i.e., he or she must perform certain rituals (often based in counting, organizing, cleaning, etc.) in order to "prevent" the calamity he or she feels is imminent. Unlike normal children, who can leave their magical thinking-based activities behind when called upon to do so, children with OCD are literally unable to cease engaging in these activities, regardless of the consequences.[117][123]

Panic disorder is more common in older children, though younger children sometimes also suffer from it. Panic disorder is frequently mistaken for a physical illness by children suffering from it, likely due to its strongly physical symptoms (a racing heartbeat, sweating, dizziness, nausea, etc.) These symptoms are, however, usually accompanied by extreme fear, particularly the fear of dying. Like adults with Panic Disorder, children may attempt to avoid any situation they feel is a "trigger" for their attacks.[117]

## References [edit]


1. ^ Peter Aspden (21 April 2012). "So, what does 'The Scream' mean?". *Financial Times*.
2. ^ *a b c d e f* *Diagnostic and Statistical Manual of Mental DisordersAmerican Psychiatric Associati.* (5th ed.). Arlington: American Psychiatric Publishing. 2013. pp. 189–195. ISBN 978-0890425558.
3. ^ *a b c* "Anxiety Disorders". *NIMH*. March 2016. Retrieved 14 August 2016.
4. ^ *a b c d e f g h i j k* Craske, MG; Stein, MB (24 June 2016). "Anxiety.". *Lancet (London, England)*. doi:10.1016/S0140-6736(16)30381-6. PMID 27349358.
5. ^ *a b c d e f g h* Testa A, Giannuzzi R, Daini S, Bernardini L, Petrongolo L, Gentiloni Silveri N (2013). "Psychiatric emergencies (part III): psychiatric symptoms resulting from organic diseases" (PDF). *Eur Rev Med Pharmacol Sci* (Review). 17 Suppl 1: 86–99. PMID 23436670.
6. ^ Kessler; et al. (2007). "Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative". *World Psychiatry*. **6** (3): 168–76. PMC 2174588. PMID 18188442.
7. ^ Schacter, D. L., Gilbert, D. T., & Wegner, D.M. (2011). *Psychology: Second Edition*. New York, NY: Worth.
8. ^ *a b c* Calleo J, Stanley M (2008). "Anxiety Disorders in Later Life: Differentiated Diagnosis and Treatment Strategies". *Psychiatric Times*. **26** (8).
9. ^ *a b c* Phil Barker (7 October 2003). *Psychiatric and mental health nursing: the craft of caring*. London: Arnold. ISBN 978-0-340-81026-2. Retrieved 17 December 2010.
10. ^ *Psychology*, Michael Passer, Ronald Smith, Nigel Holt, Andy Bremner, Ed Sutherland, Michael Vliek (2009) McGrath Hill Education, UK: McGrath Hill Companies Inc. p 790
11. ^ http://www.webmd.com/anxiety-panic/guide/mental-health-anxiety-disorders
12. ^ *Psychiatry*, Michael Gelder, Richard Mayou, John Geddes 3rd ed. Oxford; New York: Oxford University Press, c 2005 p. 75
13. ^ Varcarolis. E (2010). *Manual of Psychiatric Nursing Care Planning: Assessment Guides, Diagnoses and Psychopharmacology*. 4th ed. New York: Saunders Elsevier. p 109.
14. ^ *a b* Keeton, CP; Kolos, AC; Walkup, JT (2009). "Pediatric generalized anxiety disorder: epidemiology, diagnosis, and management.". *Paediatric drugs*. **11** (3): 171–83. doi:10.2165/00148581-200911030-00003. PMID 19445546.
15. ^ *Psychology*. Michael Passer, Ronald Smith, Nigel Holt, Andy Bremner, Ed Sutherland, Michael Vliek. (2009) McGrath Hill Higher Education; UK: McGrath Hill companies Inc.
16. ^ "Panic Disorder". *Center for the Treatment and Study of Anxiety, University of Pennsylvania*.
17. ^ Craske 2003 Gorman, 2000
18. ^ Jane E. Fisher; William T. O'Donohue (27 July 2006). *Practitioner's Guide to Evidence-Based Psychotherapy*. Springer. p. 754. ISBN 978-0387283692.
19. ^ *The Oxford Handbook of Exercise Psychology*. Oxford University Press. 2012. p. 56. ISBN 9780199930746.
20. ^ *Post-Traumatic Stress Disorder and the Family*. Veterans Affairs Canada. 2006. ISBN 0-662-42627-4.
21. ^ Psychological Disorders, Psychologie Anglophone

22. ^ Fullerton, Carol (1997). *Posttraumatic Stress Disorder*. Washington, D.C.: American Psychiatric Press Inc. pp. 8–9. ISBN 0-88048-751-8.
23. ^ Siegler, Robert (2006). *How Children Develop, Exploring Child Develop Student Media Tool Kit & Scientific American Reader to Accompany How Children Develop*. New York: Worth Publishers. ISBN 0-7167-6113-0.
24. ^ "Adult Separation Anxiety Often Overlooked Diagnosis – Arehart-Treichel 41 (13): 30 – Psychiatr News". Psychiatric News. Retrieved 20 February 2012.
25. ^ Shear, K.; Jin, R.; Ruscio, AM.; Walters, EE.; Kessler, RC. (June 2006). "Prevalence and correlates of estimated DSM-IV child and adult separation anxiety disorder in the National Comorbidity Survey Replication". *Am J Psychiatry*. **163** (6): 1074–1083. doi:10.1176/appi.ajp.163.6.1074. PMC 1924723. PMID 16741209.
26. ^ Mohatt, Justin; Bennett, Shannon M.; Walkup, John T. (2014-07-01). "Treatment of Separation, Generalized, and Social Anxiety Disorders in Youths". *American Journal of Psychiatry*. **171** (7): 741–748. doi:10.1176/appi.ajp.2014.13101337. ISSN 0002-953X.
27. ^ Situational Panic Attacks. (n.d.). Retrieved from http://www.sound-mind.org/situational-panic-attacks.html
28. ^ *a b c d* National Collaborating Centre for Mental Health, (UK) (2006). "Obsessive-Compulsive Disorder: Core Interventions in the Treatment of Obsessive-Compulsive Disorder and Body Dysmorphic Disorder,". *NICE Clinical Guidelines* (31). PMID 21834191. Retrieved 21 November 2015.
29. ^ *a b c d e* Soomro, GM (18 January 2012). "Obsessive compulsive disorder.". *BMJ clinical evidence*. **2012**. PMC 3285220. PMID 22305974.
30. ^ *a b* Institute for Quality and Efficiency in Health Care (IQWiG). "Obsessive-compulsive disorder: overview". *PubMed Health*. Institute for Quality and Efficiency in Health Care (IQWiG). Retrieved 21 November 2015.
31. ^ Evans, Katie; Sullivan, Michael J. (1 March 2001). *Dual Diagnosis: Counseling the Mentally Ill Substance Abuser* (2nd ed.). Guilford Press. pp. 75–76. ISBN 978-1-57230-446-8.
32. ^ Lindsay, S.J.E.; Powell, Graham E., eds. (28 July 1998). *The Handbook of Clinical Adult Psychology* (2nd ed.). Routledge. pp. 152–153. ISBN 978-0-415-07215-1.
33. ^ Johnson, Bankole A. (2011). *Addiction medicine : science and practice*. New York: Springer. pp. 301–303. ISBN 978-1-4419-0337-2.
34. ^ Cohen SI (February 1995). "Alcohol and benzodiazepines generate anxiety, panic and phobias". *J R Soc Med*. **88** (2): 73–77. PMC 1295099. PMID 7769598.
35. ^ Morrow LA; et al. (2000). "Increased incidence of anxiety and depressive disorders in persons with organic solvent exposure". *Psychosomat Med*. **62** (6): 746–750. doi:10.1097/00006842-200011000-00002. PMID 11138992.
36. ^ Scott, Trudy (2011). *The Antianxiety Food Solution: How the Foods You Eat Can Help You Calm Your Anxious Mind, Improve Your Mood, and End Cravings*. New Harbinger Publications. p. 59. ISBN 1-57224-926-9. Retrieved 7 October 2012.
37. ^ Winston AP (2005). "Neuropsychiatric effects of caffeine". *Advances in Psychiatric Treatment*. **11** (6): 432–439. doi:10.1192/apt.11.6.432.
38. ^ Hughes RN (June 1996). "Drugs Which Induce Anxiety: Caffeine". *New Zealand Journal of Psychology*. **25** (1): 36–42.
39. ^ Vilarim MM, Rocha Araujo DM, Nardi AE (August 2011). "Caffeine challenge test and panic disorder: a systematic literature review". *Expert Rev Neurother*. **11** (8): 1185–95. doi:10.1586/ern.11.83. PMID 21797659.
40. ^ Vilarim, Marina Machado; Rocha Araujo, Daniele Marano; Nardi, Antonio Egidio (2011). "Caffeine challenge test and panic disorder: A systematic literature review". *Expert Review of Neurotherapeutics*. **11** (8): 1185–95. doi:10.1586/ern.11.83. PMID 21797659.
41. ^ Bruce, Malcolm; Scott, N; Shine, P; Lader, M (1992). "Anxiogenic Effects of Caffeine in Patients with Anxiety Disorders". *Archives of General Psychiatry*. **49** (11): 867–9. doi:10.1001/archpsyc.1992.01820110031004. PMID 1444724.
42. ^ Nardi, Antonio E.; Lopes, Fabiana L.; Valença, Alexandre M.; Freire, Rafael C.; Veras, André B.; De-Melo-Neto, Valfrido L.; Nascimento, Isabella; King, Anna Lucia; Mezzasalma, Marco A.; Soares-Filho, Gastão L.; Zin, Walter A. (2007). "Caffeine challenge test in panic disorder and depression with panic attacks". *Comprehensive Psychiatry*. **48** (3): 257–63. doi:10.1016/j.comppsych.2006.12.001. PMID 17445520.
43. ^ American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. American Psychiatric Publishing. pp. 226–230. ISBN 978-0-89042-555-8.
44. ^ Kedzior, Karina Karolina; Laeber, Lisa Tabata (2014-05-10). "A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies". *BMC Psychiatry*. **14**: 136. doi:10.1186/1471-244X-14-136. ISSN 1471-244X. PMC 4032500. PMID 24884989.
45. ^ Crippa, José Alexandre; Zuardi, Antonio Waldo; Martín-Santos, Rocio; Bhattacharyya, Sagnik; Atakan, Zerrin; McGuire, Philip; Fusar-Poli, Paolo (2009-10-01). "Cannabis and anxiety: a critical review of the evidence". *Human Psychopharmacology: Clinical and Experimental*. **24** (7): 515–523. doi:10.1002/hup.1048. ISSN 1099-1077.

PMID 19693792.
46. ^ Kantorovich V, Eisenhofer G, Pacak K (2008). "Pheochromocytoma: an endocrine stress mimicking disorder". *Ann. N. Y. Acad. Sci*. **1148**: 462–8. doi:10.1196/annals.1410.081. PMC 2693284. PMID 19120142.
47. ^ Guller U, Turek J, Eubanks S, Delong ER, Oertli D, Feldman JM (2006). "Detecting pheochromocytoma: defining the most sensitive test". *Ann. Surg*. **243**: 102–7. doi:10.1097/01.sla.0000193833.51108.24. PMC 1449983. PMID 16371743.
48. ^ http://www.medscape.com/viewarticle/723663_6
49. ^ Patel, G; Fancher, TL (3 Dec 2013). "In the clinic. Generalized anxiety disorder.". *Annals of Internal Medicine*. **159** (11): ITC6–1, ITC6–2, ITC6–3, ITC6–4, ITC6–5, ITC6–6, ITC6–7, ITC6–8, ITC6–9, ITC6–10, ITC6–11; quiz ITC6–12. doi:10.7326/0003-4819-159-11-201312030-01006. PMID 24297210.
50. ^ *a b c* Grinde, B (2005). "An approach to the prevention of anxiety-related disorders based on evolutionary medicine" (PDF). *Preventative Medicine*. **40** (6): 904–909. doi:10.1016/j.ypmed.2004.08.001. PMID 15850894.
51. ^ *a b c* Bateson, M; B. Brilot; D. Nettle (2011). "Anxiety: An evolutionary approach" (PDF). *Canadian Journal of Psychiatry*. **56** (12): 707–715.
52. ^ *a b* Price, John S. (September 2003). "Evolutionary aspects of anxiety disorders". *Dialogues in Clinical Neuroscience*. **5** (3): 223–236. PMC 3181631. PMID 22033473.
53. ^ Lydiard RB (2003). "The role of GABA in anxiety disorders". *J Clin Psychiatry*. **64** (Suppl 3): 21–27. PMID 12662130.
54. ^ Nemeroff CB (2003). "The role of GABA in the pathophysiology and treatment of anxiety disorders". *Psychopharmacol Bull*. **37** (4): 133–146. PMID 15131523.
55. ^ Enna SJ (1984). "Role of gamma-aminobutyric acid in anxiety". *Psychopathology*. **17** (Suppl 1): 15–24. doi:10.1159/000284073. PMID 6143341.
56. ^ Dunlop BW, Davis PG (2008). "Combination treatment with benzodiazepines and SSRIs for comorbid anxiety and depression: a review". *Prim Care Companion J Clin Psychiatry*. **10** (3): 222–228. doi:10.4088/PCC.v10n0307. PMC 2446479. PMID 18615162.
57. ^ *a b c* Etkin A, Prater KE, Schatzberg AF, Menon V, Greicius MD (2009). "Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder". *Arch Gen Psychiatry*. **66** (12): 1361–1372. doi:10.1001/archgenpsychiatry.2009.104. PMID 19996041.
58. ^ Kalueff AV, Ishikawa K, Griffith AJ (10 January 2008). "Anxiety and otovestibular disorders: linking behavioral phenotypes in men and mice". *Behav. Brain Res*. **186** (1): 1–11. doi:10.1016/j.bbr.2007.07.032. PMID 17822783.
59. ^ Nagaratnam N, Ip J, Bou-Haidar P (May–June 2005). "The vestibular dysfunction and anxiety disorder interface: a descriptive study with special reference to the elderly". *Arch Gerontol Geriatr*. **40** (3): 253–264. doi:10.1016/j.archger.2004.09.006. PMID 15814159.
60. ^ Lepicard EM, Venault P, Perez-Diaz F, Joubert C, Berthoz A, Chapouthier G (20 December 2000). "Balance control and posture differences in the anxious BALB/cByJ mice compared to the non anxious C57BL/6J mice". *Behav. Brain Res*. **117** (1–2): 185–195. doi:10.1016/S0166-4328(00)00304-1. PMID 11099772.
61. ^ Simon NM, Pollack MH, Tuby KS, Stern TA (June 1998). "Dizziness and panic disorder: a review of the association between vestibular dysfunction and anxiety". *Ann Clin Psychiatry*. **10** (2): 75–80. doi:10.3109/10401239809147746. PMID 9669539.
62. ^ Balaban CD, Thayer JF (January–April 2001). "Neurological bases for balance-anxiety links". *J Anxiety Disord*. **15** (1–2): 53–79. doi:10.1016/S0887-6185(00)00042-6. PMID 11388358.
63. ^ Mitra R, Ferguson D, Sapolsky RM (10 February 2009). "SK2 potassium channel overexpression in basolateral amygdala reduces anxiety, stress-induced corticosterone secretion and dendritic arborization". *Mol. Psychiatry*. **14** (9): 847–855, 827. doi:10.1038/mp.2009.9. PMC 2763614. PMID 19204724.
64. ^ *a b* Bienvenu, OJ; Ginsburg, GS (December 2007). "Prevention of anxiety disorders". *International review of psychiatry (Abingdon, England)*. **19** (6): 647–54. doi:10.1080/09540260701797837. PMID 18092242.
65. ^ Khoury B, Lecomte T, Fortin G, et al. (Aug 2013). "Mindfulness-based therapy: a comprehensive meta-analysis". *Clin Psychol Rev*. **33** (6): 763–71.
66. ^ Sharma M, Rush SE (Jul 2014). "Mindfulness-based stress reduction as a stress management intervention for healthy individuals: a systematic review". *J Evid Based Complementary Altern Med*. **19** (4): 271–86. doi:10.1177/2156587214543143. PMID 25053754.
67. ^ Patel, G; Fancher, TL (3 December 2013). "In the clinic. Generalized anxiety disorder." (PDF). *Annals of Internal Medicine*. **159** (11): ITC6–1, ITC6–2, ITC6–3, ITC6–4, ITC6–5, ITC6–6, ITC6–7, ITC6–8, ITC6–9, ITC6–10, ITC6–11; quiz ITC6–12. doi:10.7326/0003-4819-159-11-201312030-01006. PMID 24297210. "currently there is no evidence on the effectiveness of preventive measures for GAD in adult"
*a b c*

68. ^ World Health Organization (2009). *Pharmacological Treatment of Mental Disorders in Primary Health Care* (PDF). Geneva. ISBN 978-92-4-154769-7.
69. ^ Rose M, Devine J (2014). "Assessment of patient-reported symptoms of anxiety". *Dialogues Clin Neurosci* (Review). **16** (2): 197–211 (Table 1). PMC 4140513. PMID 25152658.
70. ^ *a b* Rose M, Devine J (2014). "Assessment of patient-reported symptoms of anxiety". *Dialogues Clin Neurosci* (Review). **16** (2): 197–211 (Table 1). PMC 4140513. PMID 25152658.
71. ^ Rose M, Devine J (2014). "Assessment of patient-reported symptoms of anxiety". *Dialogues Clin Neurosci* (Review). **16** (2): 197–211 (Table 2). PMC 4140513. PMID 25152658.
72. ^ Cameron OG (1 December 2007). "Understanding Comorbid Depression and Anxiety". *Psychiatric Times*. **24** (14).
73. ^ McLaughlin K; Behar E; Borkovec T (25 August 2005). "Family history of psychological problems in generalized anxiety disorder". *Journal of Clinical Psychology*. **64** (7): 905–918. doi:10.1002/jclp.20497. PMID 18509873.
74. ^ Coretti G, Baldi I (1 August 2007). "The Relationship Between Anxiety Disorders and Sexual Dysfunction". *Psychiatric Times*. **24** (9).
75. ^ Samuels MH (2008). "Cognitive function in untreated hypothyroidism and hyperthyroidism". *Curr Opin Endocrinol Diabetes Obes* (Review). **15** (5): 429–33. doi:10.1097/MED.0b013e32830eb84c. PMID 18769215.
76. ^ Grigsby AB, Anderson RJ, Freedland KE, Clouse RE, Lustman PJ (2002). "Prevalence of anxiety in adults with diabetes: a systematic review". *J Psychosom Res* (Systematic Review). **53** (6): 1053–60. PMID 12479986.
77. ^ Zingone F, Swift GL, Card TR, Sanders DS, Ludvigsson JF, Bai JC (Apr 2015). "Psychological morbidity of celiac disease: A review of the literature". *United European Gastroenterol J* (Review). **3** (2): 136–45. doi:10.1177/2050640614560786. PMC 4406898. PMID 25922673.
78. ^ Molina-Infante J, Santolaria S, Sanders DS, Fernández-Bañares F (May 2015). "Systematic review: noncoeliac gluten sensitivity". *Aliment Pharmacol Ther* (Systematic Review). **41** (9): 807–20. doi:10.1111/apt.13155. PMID 25753138.
79. ^ Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H (2016). "Depression and anxiety in patients with Inflammatory Bowel Disease: A systematic review". *J Psychosom Res* (Systematic Review). **87**: 70–80. doi:10.1016/j.jpsychores.2016.06.001. PMID 27411754.
80. ^ Zhao QF, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. (2016). "The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis". *J Affect Disord* (Systematic Review). **190**: 264–71. doi:10.1016/j.jad.2015.09.069. PMID 26540080.
81. ^ Wen MC, Chan LL, Tan LC, Tan EK (2016). "Depression, anxiety, and apathy in Parkinson's disease: insights from neuroimaging studies". *Eur J Neurol* (Review). **23** (6): 1001–19. doi:10.1111/ene.13002. PMC 5084819. PMID 27141858.
82. ^ Marrie RA, Reingold S, Cohen J, Stuve O, Trojano M, Sorensen PS, et al. (2015). "The incidence and prevalence of psychiatric disorders in multiple sclerosis: a systematic review". *Mult Scler* (Systematic Review). **21** (3): 305–17. doi:10.1177/1352458514564487. PMC 4429164. PMID 25583845.
83. ^ American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders, fifth edition*. Arlington, VA: American Psychiatric Association. ISBN 978-0890425558.
84. ^ *a b c d e f* Stein, MB; Sareen, J (19 November 2015). "Clinical Practice: Generalized Anxiety Disorder.". *The New England Journal of Medicine*. **373** (21): 2059–68. doi:10.1056/nejmcp1502514. PMID 26580998.
85. ^ Taylor, G.; McNeill, A.; Girling, A.; Farley, A.; Lindson-Hawley, N.; Aveyard, P. (13 February 2014). "Change in mental health after smoking cessation: systematic review and meta-analysis". *BMJ*. **348** (feb13 1): g1151–g1151. doi:10.1136/bmj.g1151. PMC 3923980. PMID 24524926.
86. ^ Cuijpers, P; Sijbrandij, M; Koole, S; Huibers, M; Berking, M; Andersson, G (Mar 2014). "Psychological treatment of generalized anxiety disorder: A meta-analysis.". *Clinical Psychology Review*. **34** (2): 130–140. doi:10.1016/j.cpr.2014.01.002. PMID 24487344.
87. ^ Otte, C (2011). "Cognitive behavioral therapy in anxiety disorders: current state of the evidence.". *Dialogues in clinical neuroscience*. **13** (4): 413–21. PMC 3263389. PMID 22275847.
88. ^ Pompoli, A; Furukawa, TA; Imai, H; Tajika, A; Efthimiou, O; Salanti, G (13 April 2016). "Psychological therapies for panic disorder with or without agoraphobia in adults: a network meta-analysis.". *The Cochrane database of systematic reviews*. **4**: CD011004. doi:10.1002/14651858.CD011004.pub2. PMID 27071857.
89. ^ Olthuis, JV; Watt, MC; Bailey, K; Hayden, JA; Stewart, SH (12 March 2016). "Therapist-supported Internet cognitive behavioural therapy for anxiety disorders in adults.". *The Cochrane database of systematic reviews*. **3**: CD011565. doi:10.1002/14651858.CD011565.pub2. PMID 26968204.
90. ^ Donker, T; Petrie, K; Proudfoot, J; Clarke, J; Birch, MR; Christensen, H (15 November 2013). "Smartphones for smarter delivery of mental health programs: a systematic review.". *Journal of medical Internet research*. **15** (11): e247. doi:10.2196/jmir.2791. PMC 3841358. PMID 24240579.
91. ^ Warren Mansell (1 June 2007). "Reading about self-help books on cognitive-behavioural therapy for anxiety

disorders". Pb.rcpsych.org. Retrieved 20 February 2012.
92. ^ Roemer L, Williston SK, Eustis EH (Nov 2013). "Mindfulness and acceptance-based behavioral therapies for anxiety disorders". *Curr Psychiatry Rep*. **15** (11): 410. doi:10.1007/s11920-013-0410-3.
93. ^ Lang AJ (May 2013). "What mindfulness brings to psychotherapy for anxiety and depression". *Depress Anxiety*. **30** (5): 409–12. doi:10.1002/da.22081.
94. ^ Krisanaprakornkit, T; Krisanaprakornkit, W; Piyavhatkul, N; Laopaiboon, M (25 January 2006). "Meditation therapy for anxiety disorders.". *The Cochrane database of systematic reviews* (1): CD004998. doi:10.1002/14651858.CD004998.pub2. PMID 16437509.
95. ^ Choy, Y; Fyer, AJ; Lipsitz, JD (April 2007). "Treatment of specific phobia in adults.". *Clinical Psychology Review*. **27** (3): 266–86. doi:10.1016/j.cpr.2006.10.002. PMID 17112646.
96. ^ Pittler MH, Ernst E (2003). Pittler MH, ed. "Kava extract for treating anxiety". *Cochrane Database of Systematic Reviews* (1): CD003383. doi:10.1002/14651858.CD003383. PMID 12535473.
97. ^ Witte S, Loew D, Gaus W (March 2005). "Meta-analysis of the efficacy of the acetonic kava-kava extract WS1490 in patients with non-psychotic anxiety disorders". *Phytother Res*. **19** (3): 183–188. doi:10.1002/ptr.1609. PMID 15934028.
98. ^ Saeed SA, Bloch RM, Antonacci DJ (August 2007). "Herbal and dietary supplements for treatment of anxiety disorders". *Am Fam Physician*. **76** (4): 549–556. PMID 17853630.
99. ^ *a b* Saeed, SA; Bloch, RM; Antonacci, DJ (15 Aug 2007). "Herbal and dietary supplements for treatment of anxiety disorders". *American family physician*. **76** (4): 549–56. PMID 17853630.
100. ^ Fellowes, D.; Barnes, K.; Wilkinson, S. (2004-01-01). "Aromatherapy and massage for symptom relief in patients with cancer". *The Cochrane Database of Systematic Reviews* (2): CD002287. doi:10.1002/14651858.CD002287.pub2. ISSN 1469-493X. PMID 15106172.
101. ^ *a b c* Higa-McMillan, CK; Francis, SE; Rith-Najarian, L; Chorpita, BF (18 June 2015). "Evidence Base Update: 50 Years of Research on Treatment for Child and Adolescent Anxiety.". *Journal of Clinical Child and Adolescent Psychology*: 1–23. doi:10.1080/15374416.2015.1046177. PMID 26087438.
102. ^ Kozlowska K.; Hanney L. (1999). "Family assessment and intervention using an interactive are exercise". *Australia and New Zealand Journal of Family Therapy*. **20** (2): 61–69. doi:10.1002/j.1467-8438.1999.tb00358.x.
103. ^ Bratton, S.C., & Ray, D. (2002). Humanistic play therapy. In D.J. Cain (Ed.), *Humanistic psychotherapies: Handbook of research and practice* (pp. 369-402). Washington, DC: American Psychological Association.
104. ^ *Social Phobia* at eMedicine
105. ^ Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences. "Principles and Practice of Geriatric Psychology, Second Edition". *Principles and Practice of Geriatric Psychiatry*. Pamela J. Swales, Erin L. Cassidy. Javaid I. Sheikh: 555–557. doi:10.1002/0470846410.ch101. Retrieved 13 February 2012.
106. ^ *a b* Vos, T; Flaxman, AD; Naghavi, M; Lozano, R; Michaud, C; Ezzati, M; Shibuya, K; Salomon, JA; Abdalla, S; et al. (15 Dec 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2163–96. doi:10.1016/S0140-6736(12)61729-2. PMID 23245607.
107. ^ *a b* Simpson, Helen Blair, ed. (2010). *Anxiety disorders : theory, research, and clinical perspectives* (1. publ. ed.). Cambridge, UK: Cambridge University Press. p. 7. ISBN 978-0-521-51557-3.
108. ^ Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (June 2005). "Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication". *Arch. Gen. Psychiatry*. **62** (6): 593–602. doi:10.1001/archpsyc.62.6.593. PMID 15939837.
109. ^ Brockveld, Kelia C.; Perini, Sarah J.; Rapee, Ronald M. (2014). "6". In Hofmann, Stefan G.; DiBartolo, Patricia M. *Social Anxiety: Clinical, Developmental, and Social Perspectives* (3 ed.). Elsevier. ISBN 978-0-12-394427-6.
110. ^ Hofmann, Stefan G.; Asnaani, Anu (December 2010). "Cultural Aspects in Social Anxiety and Social Anxiety Disorder". *Depress Anxiety*. **27** (12): 1117–1127. doi:10.1002/da.20759. PMC 3075954. PMID 21132847.
111. ^ Fricchione, Gregory (12 August 2004). "Generalized Anxiety Disorder". *New England Journal of Medicine*. **351** (7): 675–682. doi:10.1056/NEJMcp022342.
112. ^ Essau, Cecilia A. (2006). *Child and Adolescent Psychopathology: Theoretical and Clinical Implications*. 27 church road, Hove, East Sussex: Routledge. p. 79.
113. ^ *a b c* AnxietyBC. "GENERALIZED ANXIETY". *AnxietyBC*. AnxietyBC. Retrieved 11 June 2015.
114. ^ Merrill, Anna. "Anxiety and Autism Spectrum Disorders". *Indiana Resource Center for Autism*. Indiana Resource Center for Autism. Retrieved 10 June 2015.
115. ^ Guignard, Jacques-Henri; Jacquet, Anne-Yvonne; Lubart, Todd I. "Perfectionism and Anxiety: A Paradox in Intellectual Giftedness?". *PLOS*. PLOS. Retrieved 10 June 2015.
116. ^ Rapee, Ronald M.; Schniering, Carolyn A.; Hudson, Jennifer L. "Anxiety Disorders During Childhood and Adolescence: Origins and Treatment" (PDF). Annual Review of Clinical Psychology.
*a b c d e*

117. ^ Shenfield, Tali. "A Primer on Child and Adolescent Anxiety" . *Advanced Psychology*.
118. ^ Klitzing K von, White LO, Otto Y, Fuchs S, Egger HL, Klein AM: Depressive comorbidity in preschool anxiety disorder. J Child Psychol Psychiatr 2014; 55: 1107–16.
119. ^ "Separation Anxiety in Children". *WebMD*. WebMD. Retrieved 11 June 2015.
120. ^ "SOCIAL ANXIETY DISORDER". *AnxietyBC*. AnxietyBC. Retrieved 11 June 2015.
121. ^ Biegel, D.E. (1995). Caregiver burden. In G.E. Maddox (Ed.), *The encyclopedia of aging* (2,d ed., pp. 138-141). New York: Springer
122. ^ Boileau, B (2011). "A review of obsessive-compulsive disorder in children and adolescents.". *Dialogues in clinical neuroscience*. **13** (4): 401–11. PMC 3263388. PMID 22275846.
123. ^ Harvard Medical School (2004a). "December). Children's fears and anxieties". *Harvard Mental Health Letter*. **21** (6): 1–3.


## Further reading [edit]


- Khouzam, HR (March 2009). "Anxiety Disorders: Guidelines for Effective Primary Care. Part 1: Diagnosis". *Consultant*. **49** (3).
- Khouzam, HR (April 2009). "Anxiety Disorders: Guidelines for Effective Primary Care. Part 2: Treatment". *Consultant*. **49** (4).
- Vanin, John; Helsley, James (2007). *Anxiety Disorders: A Pocket Guide For Primary Care*. Humana Press. ISBN 978-1-58829-923-9.
- Craske, Michelle Genevieve (2003). *Origins of Phobias and Anxiety Disorders: Why More Women than Men?*. Amsterdam: Elsevier. ISBN 0-08-044032-0.
- Schutz, Samantha (2006). *I Don't Want to Be Crazy: A Memoir of Anxiety Disorder*. *www.samanthaschutz.net*. PUSH. ISBN 978-0-439-80518-6.


## External links [edit]

- Support Group Providers for Anxiety disorder at DMOZ

| v · t · e · | **Mental and behavioral disorders (F 290–319)** |
|---|---|
| | **Neurological/symptomatic** |
| **Dementia** | Mild cognitive impairment · Alzheimer's disease · Vascular dementia · Pick's disease · Creutzfeldt–Jakob disease · Huntington's disease · Parkinson's disease · AIDS dementia complex · Frontotemporal dementia · Sundowning · Wandering · |
| **Autism spectrum** | Autism · Asperger syndrome · Savant syndrome · PDD-NOS · High-functioning autism · |
| **Other** | Delirium · Post-concussion syndrome · Organic brain syndrome · |
| | **Psychoactive substances, substance abuse, drug abuse and substance-related disorders** |
| | Intoxication/Drug overdose · Physical dependence · Substance dependence · Rebound effect · Double rebound · Withdrawal · |
| | **Schizophrenia, schizotypal and delusional** |
| **Psychosis** | Schizoaffective disorder · Schizophreniform disorder · Brief reactive psychosis · |
| **Schizophrenia** | Disorganized schizophrenia · Paranoid schizophrenia · Simple-type schizophrenia · |
| **Delusional disorders** | Delusional disorder · Folie à deux · |
| | **Mood (affective)** |
| | Mania · Bipolar disorder · (Bipolar I · Bipolar II · Cyclothymia · Bipolar NOS) · Depression · (Major depressive disorder · |

Dysthymia · Seasonal affective disorder · Atypical depression · Melancholic depression) ·

| Neurotic, stress-related and somatoform | | |
|---|---|---|
| **Anxiety disorder** | **Phobia** | Agoraphobia · Social anxiety · Social phobia · (Anthropophobia) · Specific phobia · (Claustrophobia) · Specific social phobia · |
| | **Other** | Panic disorder · Panic attack · Generalized anxiety disorder · OCD · *stress* · (Acute stress reaction · PTSD) · |
| **Adjustment disorder** | | Adjustment disorder with depressed mood · |
| **Somatic symptom disorder** | | Somatization disorder · Body dysmorphic disorder · Hypochondriasis · Nosophobia · Da Costa's syndrome · Psychalgia · Conversion disorder · (Ganser syndrome · Globus pharyngis) · Neurasthenia · Mass psychogenic illness · |
| **Dissociative disorder** | | Dissociative identity disorder · Psychogenic amnesia · Fugue state · Depersonalization disorder · |

| Physiological/physical behavioral | |
|---|---|
| **Eating disorder** | Anorexia nervosa · Bulimia nervosa · Rumination syndrome · NOS · |
| **Nonorganic sleep disorders** | (Nonorganic hypersomnia · Nonorganic insomnia) · Parasomnia · (REM sleep behavior disorder · Night terror · Nightmare) · |
| **Sexual dysfunction** | *sexual desire* · (Hypoactive sexual desire disorder · Hypersexuality) · *sexual arousal* · (Female sexual arousal disorder) · Erectile dysfunction · *orgasm* · (Anorgasmia · Delayed ejaculation · Premature ejaculation · Sexual anhedonia) · *pain* · (Vaginismus · Dyspareunia) · |
| **Postnatal** | Postpartum depression · Postpartum psychosis · |

| Adult personality and behavior | |
|---|---|
| *Gender dysphoria* | Sexual maturation disorder · Ego-dystonic sexual orientation · Sexual relationship disorder · Paraphilia · (Voyeurism · Fetishism) · |
| **Other** | Personality disorder · Impulse control disorder · (Kleptomania · Trichotillomania · Pyromania · Dermatillomania) · Body-focused repetitive behavior · Factitious disorder · (Münchausen syndrome) · |

| Disorders typically diagnosed in childhood | |
|---|---|
| **Intellectual disability** | X-linked intellectual disability · (Lujan–Fryns syndrome) · |
| **Psychological development (developmental disabilities)** | Specific · Pervasive · Autism spectrum · |
| **Emotional and behavioral** | ADHD · Conduct disorder · (ODD) · Emotional/behavioral disorder · (Separation anxiety disorder) · *social functioning* · (Selective mutism · RAD · DAD) · Tic disorder · (Tourette syndrome) · *Speech* · (Stuttering · Cluttering) · Movement disorder · (Stereotypic) · |

**Symptoms and uncategorized**

Catatonia · False pregnancy · Intermittent explosive disorder · Psychomotor agitation · Stereotypy · Psychogenic non-epileptic seizures · Klüver–Bucy syndrome ·

| | |
|---|---|
| **Authority control** | GND: 4295459-9 · NDL: 01084829 · |

Categories: Abnormal psychology | Anxiety disorders | Neurotic, stress-related and somatoform disorders | Psychiatric diagnosis




# Asperger syndrome

From Wikipedia, the free encyclopedia

**Asperger syndrome** (**AS**), also known as **Asperger's**, is a developmental disorder characterized by significant difficulties in social interaction and nonverbal communication, along with restricted and repetitive patterns of behavior and interests.[1] As a milder autism spectrum disorder (ASD), it differs from other ASDs by relatively normal language and intelligence.[2] Although not required for diagnosis, physical clumsiness and unusual use of language are common.[3][4] Signs usually begin before two years old and typically last for a person's entire life.[1]

The exact cause of Asperger's is unknown.[1] While it is probably partly inherited, the underlying genetics have not been determined conclusively.[3][5] Environmental factors are also believed to play a role.[1] Brain imaging has not identified a common underlying problem.[3] The diagnosis of Asperger's was removed in the 2013 fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), and people with these symptoms are now included within the autism spectrum disorder along with autism and pervasive developmental disorder not otherwise specified.[1][6] It remains within the tenth edition of the *International Classification of Diseases* (ICD-10) as of 2015.[2]

There is no single treatment, and the effectiveness of particular interventions is supported by only limited data.[3] Treatment is aimed at improving poor communication skills, obsessive or repetitive routines, and physical clumsiness.[7] Interventions may include social skills training, cognitive behavioral therapy, physical therapy, speech therapy, parent training, and medications for associated problems such as mood or anxiety.[7] Most children improve as they grow up, but social and communication difficulties usually persist.[8] Some researchers and people on the autism spectrum have advocated a shift in attitudes toward the view that autism spectrum disorder is a difference, rather than a disease that must be treated or cured.[9][10]

In 2013, Asperger's was estimated to affect 31 million people globally.[11] The syndrome is named after the Austrian

**Asperger syndrome**

**Synonyms** Asperger's syndrome, Asperger disorder (AD), Asperger's

Restricted interests or repetitive behaviors, such as this boy's interest in playing with a toy model of molecules, may be features of Asperger's.

| Classification and external resources | |
|---|---|
| **Specialty** | Psychiatry |
| **ICD-10** | F84.5 |
| **ICD-9-CM** | 299.80 |
| **OMIM** | 608638 |
| **DiseasesDB** | 31268 |
| **MedlinePlus** | 001549 |
| **eMedicine** | ped/147 |
| **Patient UK** | Asperger syndrome |
| **MeSH** | *F03.550.325.100* |

[edit on Wikidata]

pediatrician Hans Asperger who, in 1944, described children in his practice who lacked nonverbal communication, had limited understanding of others' feelings, and were physically clumsy.[12] The modern conception of Asperger syndrome came into existence in 1981 and went through a period of popularization.[13][14][15] It became a standardized diagnosis in the early 1990s.[16] Many questions and controversies remain about aspects of the disorder.[8] There is doubt about whether it is distinct from high-functioning autism (HFA).[17] Partly because of this, the percentage of people affected is not firmly established.[3]

**Contents**





# Classification


Play media

Autism spectrum disorder video

The extent of the overlap between AS and high-functioning autism (HFA—autism unaccompanied by intellectual disability) is unclear.[17][18][19] The ASD classification is to some extent an artifact of how autism was discovered,[20] and may not reflect the true nature of the spectrum;[21] methodological problems have beset Asperger syndrome as a valid diagnosis from the outset.[22][23] In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), published in May 2013,[24] AS, as a separate diagnosis, was eliminated and folded into autism spectrum disorder.[25] Like the diagnosis of Asperger syndrome,[26] the change was controversial[26][27] and AS was not removed from the WHO's ICD-10.

The World Health Organization (WHO) defines Asperger syndrome (AS) as one of the autism spectrum disorders (ASD) or pervasive developmental disorders (PDD), which are a spectrum of psychological conditions that are characterized by abnormalities of social interaction and communication that pervade the individual's functioning, and by restricted and repetitive interests and behavior. Like other psychological development disorders, ASD begins in infancy or childhood, has a steady course without remission or relapse, and has impairments that result from maturation-related changes in various systems of the brain.[28] ASD, in turn, is a subset of the broader autism phenotype,[29]

which describes individuals who may not have ASD but do have autistic-like traits, such as social deficits. Of the other four ASD forms, autism is the most similar to AS in signs and likely causes, but its diagnosis requires impaired communication and allows delay in cognitive development; Rett syndrome and childhood disintegrative disorder share several signs with autism but may have unrelated causes; and pervasive developmental disorder not otherwise specified (PDD-NOS) is diagnosed when the criteria for a more specific disorder are unmet.[30]

# Characteristics

As a pervasive developmental disorder, Asperger syndrome is distinguished by a pattern of symptoms rather than a single symptom. It is characterized by qualitative impairment in social interaction, by stereotyped and restricted patterns of behavior, activities and interests, and by no clinically significant delay in cognitive development or general delay in language.[31] Intense preoccupation with a narrow subject, one-sided verbosity, restricted prosody, and physical clumsiness are typical of the condition, but are not required for diagnosis.[17] Suicidal behavior appears to occur at rates similar to those without ASD.[32]

People with Asperger syndrome often display restricted or specialized interests, such as this boy's interest in stacking cans.

## Social interaction

*Further information: Asperger syndrome and interpersonal relationships*

A lack of demonstrated empathy affects aspects of communal living for persons with Asperger syndrome.[4] Individuals with AS experience difficulties in basic elements of social interaction, which may include a failure to develop friendships or to seek shared enjoyments or achievements with others (for example, showing others objects of interest), a lack of social or emotional reciprocity (social "games" give-and-take mechanic), and impaired nonverbal behaviors in areas such as eye contact, facial expression, posture, and gesture.[3]

People with AS may not be as withdrawn around others, compared with those with other, more debilitating forms of autism; they approach others, even if awkwardly. For example, a person with AS may engage in a one-sided, long-winded speech about a favorite topic, while misunderstanding or not recognizing the listener's feelings or reactions, such as a wish to change the topic of talk or end the interaction.[17] This social awkwardness has been called "active but odd".[3] This failure to react appropriately to social interaction may appear as disregard for other people's feelings, and may come across as insensitive.[17] However, not all individuals with AS will approach others. Some of them may even display selective mutism, speaking not at all to most people and excessively to specific people. Some may choose only to talk to people they like.[33]

The cognitive ability of children with AS often allows them to articulate social norms in a laboratory context,[3] where they may be able to show a theoretical understanding of other people's emotions; however, they typically have difficulty acting on this knowledge in fluid, real-life situations.[17] People with AS may analyze and distill their observations of social interaction into rigid behavioral guidelines, and apply these rules in awkward ways, such as forced eye contact, resulting in a demeanor that appears rigid or socially naive. Childhood desire for companionship can become numbed through a history of failed social encounters.[3]

The hypothesis that individuals with AS are predisposed to violent or criminal behavior has been investigated, but is not supported by data.[3][34] More evidence suggests children with AS are victims rather than victimizers.[35] A 2008 review found that an overwhelming number of reported violent criminals with AS had coexisting psychiatric disorders such as schizoaffective disorder.[36]

## Restricted and repetitive interests and behavior

People with Asperger syndrome can display behavior, interests, and activities that are restricted and repetitive and are sometimes abnormally intense or focused. They may stick to inflexible routines, move in stereotyped and repetitive ways, preoccupy themselves with parts of objects or compulsive behaviors like lining things up in patterns.[31]

Pursuit of specific and narrow areas of interest is one of the most striking possible features of AS.[3] Individuals with AS may collect volumes of detailed information on a relatively narrow topic such as weather data or star names, without necessarily having a genuine understanding of the broader topic.[3][17] For example, a child might memorize camera model numbers while caring little about photography.[3] This behavior is usually apparent by age 5 or 6.[3] Although these special interests may change from time to time, they typically become more unusual and narrowly focused, and often dominate social interaction so much that the entire family may become immersed. Because narrow topics often capture the interest of children, this symptom may go unrecognized.[17]

Stereotyped and repetitive motor behaviors are a core part of the diagnosis of AS and other ASDs.[37] They include hand movements such as flapping or twisting, and complex whole-body movements.[31] These are typically repeated in longer bursts and look more voluntary or ritualistic than tics, which are usually faster, less rhythmical and less often symmetrical.[38]

According to the Adult Asperger Assessment (AAA) diagnostic test, a lack of interest in fiction and a positive preference towards non-fiction is common among adults with AS.[39]

## Speech and language

Although individuals with Asperger syndrome acquire language skills without significant general delay and their speech typically lacks significant abnormalities, language acquisition and use is often atypical.[17] Abnormalities include verbosity, abrupt transitions, literal interpretations and miscomprehension of nuance, use of metaphor meaningful only to the speaker, auditory perception deficits, unusually pedantic, formal or idiosyncratic speech, and oddities in loudness, pitch, intonation, prosody, and rhythm.[3] Echolalia has also been observed in individuals with AS.[40]

Three aspects of communication patterns are of clinical interest: poor prosody, tangential and circumstantial speech, and marked verbosity. Although inflection and intonation may be less rigid or monotonic than in classic autism, people with AS often have a limited range of intonation: speech may be unusually fast, jerky or loud. Speech may convey a sense of incoherence; the conversational style often includes monologues about topics that bore the listener, fails to provide context for comments, or fails to suppress internal thoughts. Individuals with AS may fail to detect whether the listener is interested or engaged in the conversation. The speaker's conclusion or point may never be made, and attempts by the listener to elaborate on the speech's content or logic, or to shift to related topics, are often unsuccessful.[17]

Children with AS may have an unusually sophisticated vocabulary at a young age and have been colloquially called "little professors", but have difficulty understanding figurative language and tend to use language literally.[3] Children with AS appear to have particular weaknesses in areas of nonliteral language that include humor, irony, teasing, and sarcasm. Although individuals with AS usually understand the cognitive basis of humor, they seem to lack understanding of the intent of humor to share enjoyment with others.[18] Despite strong evidence of impaired humor appreciation, anecdotal reports of humor in individuals with AS seem to challenge some psychological theories of AS and autism.[41]

## Motor and sensory perception

Individuals with Asperger syndrome may have signs or symptoms that are independent of the diagnosis, but can affect the individual or the family.[42] These include differences in perception and problems with motor skills, sleep, and emotions.

Individuals with AS often have excellent auditory and visual perception.[43] Children with ASD often

demonstrate enhanced perception of small changes in patterns such as arrangements of objects or well-known images; typically this is domain-specific and involves processing of fine-grained features.[44] Conversely, compared with individuals with high-functioning autism, individuals with AS have deficits in some tasks involving visual-spatial perception, auditory perception, or visual memory.[3] Many accounts of individuals with AS and ASD report other unusual sensory and perceptual skills and experiences. They may be unusually sensitive or insensitive to sound, light, and other stimuli;[45] these sensory responses are found in other developmental disorders and are not specific to AS or to ASD. There is little support for increased fight-or-flight response or failure of habituation in autism; there is more evidence of decreased responsiveness to sensory stimuli, although several studies show no differences.[46]

Hans Asperger's initial accounts[3] and other diagnostic schemes[47] include descriptions of physical clumsiness. Children with AS may be delayed in acquiring skills requiring motor dexterity, such as riding a bicycle or opening a jar, and may seem to move awkwardly or feel "uncomfortable in their own skin". They may be poorly coordinated, or have an odd or bouncy gait or posture, poor handwriting, or problems with visual-motor integration.[3][17] They may show problems with proprioception (sensation of body position) on measures of developmental coordination disorder (motor planning disorder), balance, tandem gait, and finger-thumb apposition. There is no evidence that these motor skills problems differentiate AS from other high-functioning ASDs.[3]

Children with AS are more likely to have sleep problems, including difficulty in falling asleep, frequent nocturnal awakenings, and early morning awakenings.[48][49] AS is also associated with high levels of alexithymia, which is difficulty in identifying and describing one's emotions.[50] Although AS, lower sleep quality, and alexithymia are associated, their causal relationship is unclear.[49]

## Causes

*Further information: Causes of autism*

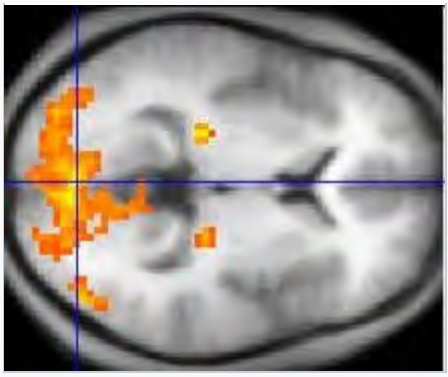
Hans Asperger described common symptoms among his patients' family members, especially fathers, and research supports this observation and suggests a genetic contribution to Asperger syndrome. Although no specific gene has yet been identified, multiple factors are believed to play a role in the expression of autism, given the phenotypic variability seen in children with AS.[3][51] Evidence for a genetic link is the tendency for AS to run in families and an observed higher incidence of family members who have behavioral symptoms similar to AS but in a more limited form (for example, slight difficulties with social interaction, language, or reading).[7] Most research suggests that all autism spectrum disorders have shared genetic mechanisms, but AS may have a stronger genetic component than autism.[3] There is probably a common group of genes where particular alleles render an individual vulnerable to developing AS; if this is the case, the particular combination of alleles would determine the severity and symptoms for each individual with AS.[7]

A few ASD cases have been linked to exposure to teratogens (agents that cause birth defects) during the first eight weeks from conception. Although this does not exclude the possibility that ASD can be initiated or affected later, it is strong evidence that it arises very early in development.[52] Many environmental factors have been hypothesized to act after birth, but none has been confirmed by scientific investigation.[53]

## Mechanism

*Further information: Autism § Mechanism*

Asperger syndrome appears to result from developmental factors that affect many or all functional brain systems, as opposed to localized effects.[56] Although the specific underpinnings of AS or factors that distinguish it from other ASDs are unknown, and no clear pathology [3]



Functional magnetic resonance imaging provides some evidence for both underconnectivity and mirror neuron theories.[54][55]

common to individuals with AS has emerged, it is still possible that AS's mechanism is separate from other ASDs.[57] Neuroanatomical studies and the associations with teratogens strongly suggest that the mechanism includes alteration of brain development soon after conception.[52] Abnormal migration of embryonic cells during fetal development may affect the final structure and connectivity of the brain, resulting in alterations in the neural circuits that control thought and behavior.[58] Several theories of mechanism are available; none are likely to provide a complete explanation.[59]

The underconnectivity theory hypothesizes underfunctioning high-level neural connections and synchronization, along with an excess of low-level processes.[54] It maps well to general-processing theories such as weak central coherence theory, which hypothesizes that a limited ability to see the big picture underlies the central disturbance in ASD.[60] A related theory—enhanced perceptual functioning—focuses more on the superiority of locally oriented and perceptual operations in autistic individuals.[61]

The mirror neuron system (MNS) theory hypothesizes that alterations to the development of the MNS interfere with imitation and lead to Asperger's core feature of social impairment.[55][62] For example, one study found that activation is delayed in the core circuit for imitation in individuals with AS.[63] This theory maps well to social cognition theories like the theory of mind, which hypothesizes that autistic behavior arises from impairments in ascribing mental states to oneself and others,[64] or hyper-systemizing, which hypothesizes that autistic individuals can systematize internal operation to handle internal events but are less effective at empathizing by handling events generated by other agents.[65]

## Diagnosis

*Main article: Diagnosis of Asperger syndrome*

Standard diagnostic criteria require impairment in social interaction and repetitive and stereotyped patterns of behavior, activities and interests, without significant delay in language or cognitive development. Unlike the international standard,[28] the DSM-IV-TR criteria also required significant impairment in day-to-day functioning;[31] DSM-5 eliminated AS as a separate diagnosis in 2013, and folded it into the umbrella of autism spectrum disorders.[25] Other sets of diagnostic criteria have been proposed by Szatmari *et al.*[66] and by Gillberg and Gillberg.[67]

Diagnosis is most commonly made between the ages of four and eleven.[3] A comprehensive assessment involves a multidisciplinary team[4][7][68] that observes across multiple settings,[3] and includes neurological and genetic assessment as well as tests for cognition, psychomotor function, verbal and nonverbal strengths and weaknesses, style of learning, and skills for independent living.[7] The "gold standard" in diagnosing ASDs combines clinical judgment with the Autism Diagnostic Interview-Revised (ADI-R)—a semistructured parent interview—and the Autism Diagnostic Observation Schedule (ADOS)—a conversation and play-based interview with the child.[8] Delayed or mistaken diagnosis can be traumatic for individuals and families; for example, misdiagnosis can lead to medications that worsen behavior.[68][69]

Underdiagnosis and overdiagnosis may be problems. The cost and difficulty of screening and assessment can delay diagnosis. Conversely, the increasing popularity of drug treatment options and the expansion of benefits has motivated providers to overdiagnose ASD.[70] There are indications AS has been diagnosed more frequently in recent years, partly as a residual diagnosis for children of normal intelligence who are not autistic but have social difficulties.[71]

There are questions about the external validity of the AS diagnosis. That is, it is unclear whether there is a practical benefit in distinguishing AS from HFA and from PDD-NOS;[71] the same child can receive different diagnoses depending on the screening tool.[7] The debate about distinguishing AS from HFA is partly due to a tautological dilemma where disorders are defined based on severity of impairment, so that studies that appear to confirm differences based on severity are to be expected.[72]

### Differential diagnosis

Many children with AS are initially misdiagnosed with attention deficit hyperactivity disorder (ADHD).[3] Diagnosing adults is more challenging, as standard diagnostic criteria are designed for children and the expression of AS changes with age.[73] Adult diagnosis requires painstaking clinical examination and thorough medical history gained from both the individual and other people who know the person, focusing on childhood behavior.[39] Conditions that must be considered in a differential diagnosis include other ASDs, the schizophrenia spectrum, ADHD, obsessive–compulsive disorder, major depressive disorder, semantic pragmatic disorder, nonverbal learning disorder,[68] Tourette syndrome,[38] stereotypic movement disorder, bipolar disorder,[51] and social-cognitive deficits due to brain damage from alcohol abuse.[74]

There are considerable similarities and overlap between Asperger's syndrome and obsessive–compulsive personality disorder (OCPD),[75] such as list-making, inflexible adherence to rules, and obsessive aspects of Asperger's syndrome, though the former may be distinguished from OCPD especially regarding affective behaviors, worse social skills, difficulties with theory of mind and intense intellectual interests, e.g. an ability to recall every aspect of a hobby.[76]

## Screening

Parents of children with Asperger syndrome can typically trace differences in their children's development to as early as 30 months of age.[51] Developmental screening during a routine check-up by a general practitioner or pediatrician may identify signs that warrant further investigation.[3][7] The United States Preventive Services Task Force in 2016 found it was unclear if screening was beneficial or harmful among children in whom there is no concerns.[77]

The diagnosis of AS is complicated by the use of several different screening instruments,[7][47] including the Asperger Syndrome Diagnostic Scale (ASDS), Autism Spectrum Screening Questionnaire (ASSQ), Childhood Autism Spectrum Test (CAST) (previously called the Childhood Asperger Syndrome Test),[78] Gilliam Asperger's disorder scale (GADS), Krug Asperger's Disorder Index (KADI),[79] and the Autism-spectrum quotient (AQ; with versions for children,[80] adolescents[81] and adults[82]). None have been shown to reliably differentiate between AS and other ASDs.[3]

## Management

*Further information: Autism therapies*

Asperger syndrome treatment attempts to manage distressing symptoms and to teach age-appropriate social, communication and vocational skills that are not naturally acquired during development,[3] with intervention tailored to the needs of the individual based on multidisciplinary assessment.[83] Although progress has been made, data supporting the efficacy of particular interventions are limited.[3][84]

### Therapies

The ideal treatment for AS coordinates therapies that address core symptoms of the disorder, including poor communication skills and obsessive or repetitive routines. While most professionals agree that the earlier the intervention, the better, there is no single best treatment package.[7] AS treatment resembles that of other high-functioning ASDs, except that it takes into account the linguistic capabilities, verbal strengths,

and nonverbal vulnerabilities of individuals with AS.[3] A typical program generally includes:[7]

- A positive behavior support procedure includes training and support of parents and school faculty in behavior management strategies to use in the home and school;
- An applied behavior analysis (ABA) technique called social skills training for more effective interpersonal interactions;[85]
- Cognitive behavioral therapy to improve stress management relating to anxiety or explosive emotions[86] and to cut back on obsessive interests and repetitive routines;
- Medication, for coexisting conditions such as major depressive disorder and anxiety disorder;[87]
- Occupational or physical therapy to assist with poor sensory processing and motor coordination;
- Social communication intervention, which is specialized speech therapy to help with the pragmatics of the give and take of normal conversation.[88]

Of the many studies on behavior-based early intervention programs, most are case reports of up to five participants and typically examine a few problem behaviors such as self-injury, aggression, noncompliance, stereotypies, or spontaneous language; unintended side effects are largely ignored.[89] Despite the popularity of social skills training, its effectiveness is not firmly established.[90] A randomized controlled study of a model for training parents in problem behaviors in their children with AS showed that parents attending a one-day workshop or six individual lessons reported fewer behavioral problems, while parents receiving the individual lessons reported less intense behavioral problems in their AS children.[91] Vocational training is important to teach job interview etiquette and workplace behavior to older children and adults with AS, and organization software and personal data assistants can improve the work and life management of people with AS.[3]

## Medications

No medications directly treat the core symptoms of AS.[87] Although research into the efficacy of pharmaceutical intervention for AS is limited,[3] it is essential to diagnose and treat comorbid conditions.[4] Deficits in self-identifying emotions or in observing effects of one's behavior on others can make it difficult for individuals with AS to see why medication may be appropriate.[87] Medication can be effective in combination with behavioral interventions and environmental accommodations in treating comorbid symptoms such as anxiety disorder, major depressive disorder, inattention and aggression.[3] The atypical antipsychotic medications risperidone and olanzapine have been shown to reduce the associated symptoms of AS;[3] risperidone can reduce repetitive and self-injurious behaviors, aggressive outbursts and impulsivity, and improve stereotypical patterns of behavior and social relatedness. The selective serotonin reuptake inhibitors (SSRIs) fluoxetine, fluvoxamine, and sertraline have been effective in treating restricted and repetitive interests and behaviors.[3][4][51]

Care must be taken with medications, as side effects may be more common and harder to evaluate in individuals with AS, and tests of drugs' effectiveness against comorbid conditions routinely exclude individuals from the autism spectrum.[87] Abnormalities in metabolism, cardiac conduction times, and an increased risk of type 2 diabetes have been raised as concerns with these medications,[92][93] along with serious long-term neurological side effects.[89] SSRIs can lead to manifestations of behavioral activation such as increased impulsivity, aggression, and sleep disturbance.[51] Weight gain and fatigue are commonly reported side effects of risperidone, which may also lead to increased risk for extrapyramidal symptoms such as restlessness and dystonia[51] and increased serum prolactin levels.[94] Sedation and weight gain are more common with olanzapine,[93] which has also been linked with diabetes.[92] Sedative side-effects in school-age children[95] have ramifications for classroom learning. Individuals with AS may be unable to identify and communicate their internal moods and emotions or to tolerate side effects that for most people would not be problematic.[96]

# Prognosis

There is some evidence that children with AS may see a lessening of symptoms; up to 20% of children may no longer meet the diagnostic criteria as adults, although social and communication difficulties may persist.[8] As of 2006, no studies addressing the long-term outcome of individuals with Asperger syndrome are available and there are no systematic long-term follow-up studies of children with AS.[17] Individuals with AS appear to have normal life expectancy, but have an increased prevalence of comorbid psychiatric conditions, such as major depressive disorder and anxiety disorder that may significantly affect prognosis.[3][8] Although social impairment may be lifelong, the outcome is generally more positive than with individuals with lower functioning autism spectrum disorders;[3] for example, ASD symptoms are more likely to diminish with time in children with AS or HFA.[97] Most students with AS/HFA have average mathematical ability and test slightly worse in mathematics than in general intelligence, but some are gifted in mathematics.[98] AS has potentially been linked to some accomplishments, such as Vernon L. Smith winning the Nobel Memorial Prize in Economic Sciences;[99] however, Smith is self-diagnosed.[100]

Although many attend regular education classes, some children with AS may utilize special education services because of their social and behavioral difficulties.[17] Adolescents with AS may exhibit ongoing difficulty with self care or organization, and disturbances in social and romantic relationships. Despite high cognitive potential, most young adults with AS remain at home, yet some do marry and work independently.[3] The "different-ness" adolescents experience can be traumatic.[101] Anxiety may stem from preoccupation over possible violations of routines and rituals, from being placed in a situation without a clear schedule or expectations, or from concern with failing in social encounters;[3] the resulting stress may manifest as inattention, withdrawal, reliance on obsessions, hyperactivity, or aggressive or oppositional behavior.[86] Depression is often the result of chronic frustration from repeated failure to engage others socially, and mood disorders requiring treatment may develop.[3] Clinical experience suggests the rate of suicide may be higher among those with AS, but this has not been confirmed by systematic empirical studies.[102]

Education of families is critical in developing strategies for understanding strengths and weaknesses;[4] helping the family to cope improves outcomes in children.[35] Prognosis may be improved by diagnosis at a younger age that allows for early interventions, while interventions in adulthood are valuable but less beneficial.[4] There are legal implications for individuals with AS as they run the risk of exploitation by others and may be unable to comprehend the societal implications of their actions.[4]

# Epidemiology

*Further information: Conditions comorbid to autism spectrum disorders*

Prevalence estimates vary enormously. A 2003 review of epidemiological studies of children found autism prevalence rates ranging from 0.03 to 4.84 per 1,000, with the ratio of autism to Asperger syndrome ranging from 1.5:1 to 16:1;[103] combining the geometric mean ratio of 5:1 with a conservative prevalence estimate for autism of 1.3 per 1,000 suggests indirectly that the prevalence of AS might be around 0.26 per 1,000.[104] Part of the variance in estimates arises from differences in diagnostic criteria. For example, a relatively small 2007 study of 5,484 eight-year-old children in Finland found 2.9 children per 1,000 met the ICD-10 criteria for an AS diagnosis, 2.7 per 1,000 for Gillberg and Gillberg criteria, 2.5 for DSM-IV, 1.6 for Szatmari *et al.*, and 4.3 per 1,000 for the union of the four criteria. Boys seem to be more likely to have AS than girls; estimates of the sex ratio range from 1.6:1 to 4:1, using the Gillberg and Gillberg criteria.[105] Females with autism spectrum disorders may be underdiagnosed.[106]

Anxiety disorder and major depressive disorder are the most common conditions seen at the same time; comorbidity of these in persons with AS is estimated at 65%.[3] Reports have associated AS with medical conditions such as aminoaciduria and ligamentous laxity, but these have been case reports or small studies and no factors have been associated with AS across studies.[3] One study of males with AS found an increased rate of epilepsy and a high rate (51%) of nonverbal learning disorder.[107] AS is associated with tics, Tourette syndrome, and bipolar disorder, and the repetitive behaviors of AS have many similarities with the symptoms of obsessive–compulsive disorder and obsessive–compulsive personality disorder.[108]

However many of these studies are based on clinical samples or lack standardized measures; nonetheless, comorbid conditions are relatively common.[8]

# History

*Main article: History of Asperger syndrome*

Named after the Austrian pediatrician Hans Asperger (1906–1980), Asperger syndrome is a relatively new diagnosis in the field of autism.[109] As a child, Asperger appears to have exhibited some features of the very condition named after him, such as remoteness and talent in language.[110][111] In 1944, Asperger described four children in his practice[4] who had difficulty in integrating themselves socially. The children lacked nonverbal communication skills, failed to demonstrate empathy with their peers, and were physically clumsy. Asperger called the condition "autistic psychopathy" and described it as primarily marked by social isolation.[7] Fifty years later, several standardizations of AS as a diagnosis were tentatively proposed, many of which diverge significantly from Asperger's original work.[112]

Unlike today's AS, autistic psychopathy could be found in people of all levels of intelligence, including those with intellectual disability.[113] Asperger defended the value of high-functioning autistic individuals, writing "We are convinced, then, that autistic people have their place in the organism of the social community. They fulfill their role well, perhaps better than anyone else could, and we are talking of people who as children had the greatest difficulties and caused untold worries to their care-givers."[12] Asperger also believed some would be capable of exceptional achievement and original thought later in life.[4] His paper was published during wartime and in German, so it was not widely read elsewhere.

Lorna Wing popularized the term *Asperger syndrome* in the English-speaking medical community in her 1981 publication[114] of a series of case studies of children showing similar symptoms,[109] and Uta Frith translated Asperger's paper to English in 1991.[12] Sets of diagnostic criteria were outlined by Gillberg and Gillberg in 1989 and by Szatmari *et al.* in the same year.[105] AS became a standard diagnosis in 1992, when it was included in the tenth edition of the World Health Organization's diagnostic manual, *International Classification of Diseases* (ICD-10); in 1994, it was added to the fourth edition of the American Psychiatric Association's diagnostic reference, *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).[7]

Hundreds of books, articles and websites now describe AS, and prevalence estimates have increased dramatically for ASD, with AS recognized as an important subgroup.[109] Whether it should be seen as distinct from high-functioning autism is a fundamental issue requiring further study,[4] and there are questions about the empirical validation of the DSM-IV and ICD-10 criteria.[17] In 2013, DSM-5 eliminated AS as a separate diagnosis, folding it into the autism spectrum on a severity scale.[25]

# Society and culture

*See also: Sociological and cultural aspects of autism*

People identifying with Asperger syndrome may refer to themselves in casual conversation as *aspies* (a term first used in print by Liane Holliday Willey in 1999).[115] The word *neurotypical* (abbreviated *NT*) describes a person whose neurological development and state are typical, and is often used to refer to non-autistic people. The Internet has allowed individuals with AS to communicate with each other in a way that was not previously possible because of their rarity and geographic dispersal, forming a subculture composed of people with Asperger's. Internet sites like Wrong Planet have made it easier for individuals to connect.[9]

Students and families walk

Some autistic people have advocated a shift in perception of autism spectrum disorders as complex syndromes rather than diseases that must

to support Autism Awareness Month.

be cured. Proponents of this view reject the notion that there is an "ideal" brain configuration and that any deviation from the norm is pathological; they promote tolerance for what they call neurodiversity.[116] These views are the basis for the autistic rights and autistic pride movements.[117] There is a contrast between the attitude of adults with self-identified AS, who typically do not want to be cured and are proud of their identity, and parents of children with AS, who typically seek assistance and a cure for their children.[118]

Some researchers have argued that AS can be viewed as a different cognitive style, not a disorder,[9] and that it should be removed from the standard *Diagnostic and Statistical Manual*, much as homosexuality was removed.[119] In a 2002 paper, Simon Baron-Cohen wrote of those with AS, "In the social world, there is no great benefit to a precise eye for detail, but in the worlds of maths, computing, cataloging, music, linguistics, engineering, and science, such an eye for detail can lead to success rather than failure." Baron-Cohen cited two reasons why it might still be useful to consider AS to be a disability: to ensure provision for legally required special support, and to recognize emotional difficulties from reduced empathy.[10] Baron-Cohen argues that the genes for Asperger's combination of abilities have operated throughout recent human evolution and have made remarkable contributions to human history.[120]

By contrast, Pier Jaarsma and Welin wrote in 2011 that the "broad version of the neurodiversity claim, covering low-functioning as well as high-functioning autism, is problematic. Only a narrow conception of neurodiversity, referring exclusively to high-functioning autists, is reasonable."[121] They say that "higher functioning" individuals with autism may "not [be] benefited with such a psychiatric defect-based diagnosis ... some of them are being harmed by it, because of the disrespect the diagnosis displays for their natural way of being", but "think that it is still reasonable to include other categories of autism in the psychiatric diagnostics. The narrow conception of the neurodiversity claim should be accepted but the broader claim should not."[121] Jonathan Mitchell, an autistic author and blogger who advocates a cure for autism, has described autism as having "prevented me from making a living or ever having a girlfriend. It's given me bad fine motor coordination problems where I can hardly write. I have an impaired ability to relate to people. I can't concentrate or get things done."[122] He describes neurodiversity as a "tempting escape valve".[123]

# References


1. ^ *a b c d e* "Autism Spectrum Disorder". *National Institute of Mental Health*. September 2015. Retrieved 12 March 2016.
2. ^ *a b* "F84.5 Asperger syndrome". *World Health Organization*. 2015. Retrieved 13 March 2016.
3. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af ag ah ai aj ak al am an ao ap aq* McPartland J, Klin A (2006). "Asperger's syndrome". *Adolesc Med Clin*. **17** (3): 771–88. doi:10.1016/j.admecli.2006.06.010. PMID 17030291.
4. ^ *a b c d e f g h i j k* Baskin JH, Sperber M, Price BH (2006). "Asperger syndrome revisited". *Rev Neurol Dis*. **3** (1): 1–7. PMID 16596080.
5. ^ Klauck SM (2006). "Genetics of autism spectrum disorder" (PDF). *European Journal of Human Genetics*. **14** (6): 714–720. doi:10.1038/sj.ejhg.5201610. PMID 16721407.
6. ^ "Autism Spectrum Disorder". *National Institute of Mental Health*. Retrieved 12 March 2016.
7. ^ *a b c d e f g h i j k l m* National Institute of Neurological Disorders and Stroke (NINDS) (31 July 2007). "Asperger syndrome fact sheet". Archived from the original on 21 August 2007. Retrieved 24 August 2007. NIH Publication No. 05-5624.
8. ^ *a b c d e f* Woodbury-Smith MR, Volkmar FR (January 2009). "Asperger syndrome". *Eur Child Adolesc Psychiatry*. **18** (1): 2–11. doi:10.1007/s00787-008-0701-0. PMID 18563474.
9. ^ *a b c* Clarke J, van Amerom G (2007). "'Surplus suffering': differences between organizational understandings of Asperger's syndrome and those people who claim the 'disorder'". *Disabil Soc*. **22** (7): 761–76. doi:10.1080/09687590701659618.
10. ^ *a b* Baron-Cohen S (2002). "Is Asperger syndrome necessarily viewed as a disability?". *Focus Autism Other Dev Disabl*. **17** (3): 186–91. doi:10.1177/10883576020170030801. A preliminary, freely readable draft, with slightly

different wording in the quoted text, is in: Baron-Cohen S (2002). "Is Asperger's syndrome necessarily a disability? " (PDF). Cambridge: Autism Research Centre. Archived (PDF) from the original on 17 December 2008. Retrieved 2 December 2008.

11. ^ Global Burden of Disease Study 2013, Collaborators (5 June 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013." . *Lancet (London, England)*. **386**: 743–800. doi:10.1016/S0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
12. ^ a b c Asperger H; tr.; annot. Frith U (1991) [1944]. "'Autistic psychopathy' in childhood". In Frith U. *Autism and Asperger syndrome*. Cambridge University Press. pp. 37–92. ISBN 0-521-38608-X.
13. ^ Klin A, Pauls D, Schultz R, Volkmar F (2005). "Three diagnostic approaches to Asperger syndrome: Implications for research". *J Autism Dev Dis*. **35** (2): 221–34. doi:10.1007/s10803-004-2001-y. PMID 15909408.
14. ^ Wing L (1998). "The history of Asperger syndrome". In Schopler E, Mesibov GB, Kunce LJ. *Asperger syndrome or high-functioning autism?*. New York: Plenum press. pp. 11–25. ISBN 0-306-45746-6.
15. ^ Woodbury-Smith M, Klin A, Volkmar F (2005). "Asperger's Syndrome: A Comparison of Clinical Diagnoses and Those Made According to the ICD-10 and DSM-IV". *J Autism Dev Disord*. **35** (2): 235–240. doi:10.1007/s10803-004-2002-x. PMID 15909409.
16. ^ Baker, Linda (2004). *Asperger's Syndrome: Intervening in Schools, Clinics, and Communities*. Routledge. p. 44. ISBN 9781135624149.
17. ^ a b c d e f g h i j k l m n Klin A (2006). "Autism and Asperger syndrome: an overview". *Rev Bras Psiquiatr*. **28** (suppl 1): S3–S11. doi:10.1590/S1516-44462006000500002. PMID 16791390.
18. ^ a b Kasari C, Rotheram-Fuller E (2005). "Current trends in psychological research on children with high-functioning autism and Asperger disorder". *Current Opinion in Psychiatry*. **18** (5): 497–501. doi:10.1097/01.yco.0000179486.47144.61. PMID 16639107.
19. ^ Witwer AN, Lecavalier L (2008). "Examining the validity of autism spectrum disorder subtypes". *J Autism Dev Disord*. **38** (9): 1611–24. doi:10.1007/s10803-008-0541-2. PMID 18327636.
20. ^ Sanders JL (2009). "Qualitative or quantitative differences between Asperger's Disorder and autism? historical considerations". *J Autism Dev Disord*. **39** (11): 1560–7. doi:10.1007/s10803-009-0798-0. PMID 19548078.
21. ^ Szatmari P (2000). "The classification of autism, Asperger's syndrome, and pervasive developmental disorder". *Can J Psychiatry*. **45** (8): 731–38. PMID 11086556.
22. ^ Matson JL, Minshawi NF (2006). "History and development of autism spectrum disorders". *Early intervention for autism spectrum disorders: a critical analysis*. Amsterdam: Elsevier Science. p. 21. ISBN 0-08-044675-2.
23. ^ Schopler E (1998). "Premature popularization of Asperger syndrome". In Schopler E, Mesibov GB, Kunce LJ. *Asperger syndrome or high-functioning autism?*. New York: Plenum press. pp. 388–90. ISBN 0-306-45746-6.
24. ^ "DSM-5 development". American Psychiatric Association. 2010. Archived from the original on 13 February 2010. Retrieved 20 February 2010.
25. ^ a b c "299.80 Asperger's Disorder". *DSM-5 Development*. American Psychiatric Association. Archived from the original on 25 December 2010. Retrieved 21 December 2010.
26. ^ a b Ghaziuddin M (2010). "Should the DSM V drop Asperger syndrome?". *J Autism Dev Disord*. **40** (9): 1146–8. doi:10.1007/s10803-010-0969-z. PMID 20151184.
27. ^ Faras H, Al Ateeqi N, Tidmarsh L (2010). "Autism spectrum disorders". *Ann Saudi Med*. **30** (4): 295–300. doi:10.4103/0256-4947.65261. PMC 2931781. PMID 20622347.
28. ^ a b World Health Organization (2006). "F84. Pervasive developmental disorders". *International Statistical Classification of Diseases and Related Health Problems* (10th (ICD-10) ed.). ISBN 92-4-154419-8.
29. ^ Piven J, Palmer P, Jacobi D, Childress D, Arndt S (1997). "Broader autism phenotype: evidence from a family history study of multiple-incidence autism families". *Am J Psychiatry*. **154** (2): 185–90. doi:10.1176/ajp.154.2.185. PMID 9016266.
30. ^ Lord C, Cook EH, Leventhal BL, Amaral DG (2000). "Autism spectrum disorders". *Neuron*. **28** (2): 355–63. doi:10.1016/S0896-6273(00)00115-X. PMID 11144346.
31. ^ a b c d American Psychiatric Association (2000). "Diagnostic criteria for 299.80 Asperger's Disorder (AD)". *Diagnostic and Statistical Manual of Mental Disorders* (4th, text revision (DSM-IV-TR) ed.). ISBN 0-89042-025-4. Retrieved 28 June 2007.
32. ^ Hannon, G; Taylor, EP (December 2013). "Suicidal behaviour in adolescents and young adults with ASD: findings from a systematic review.". *Clinical Psychology Review*. **33** (8): 1197–204. doi:10.1016/j.cpr.2013.10.003. PMID 24201088.
33. ^ Brasic JR (7 July 2010). "Asperger's Syndrome". *Medscape eMedicine*. Retrieved 25 November 2010.
34. ^ Allen D, Evans C, Hider A, Hawkins S, Peckett H, Morgan H (2008). "Offending behaviour in adults with Asperger syndrome". *J Autism Dev Disord*. **38** (4): 748–58. doi:10.1007/s10803-007-0442-9. PMID 17805955.

35. ^ [a] [b] Tsatsanis KD (2003). "Outcome research in Asperger syndrome and autism". *Child Adolesc Psychiatr Clin N Am*. **12** (1): 47–63. doi:10.1016/S1056-4993(02)00056-1. PMID 12512398.
36. ^ Newman SS, Ghaziuddin M (2008). "Violent crime in Asperger syndrome: the role of psychiatric comorbidity". *J Autism Dev Disord*. **38** (10): 1848–52. doi:10.1007/s10803-008-0580-8. PMID 18449633.
37. ^ South M, Ozonoff S, McMahon WM (2005). "Repetitive behavior profiles in Asperger syndrome and high-functioning autism". *J Autism Dev Disord*. **35** (2): 145–58. doi:10.1007/s10803-004-1992-8. PMID 15909401.
38. ^ [a] [b] Rapin I (2001). "Autism spectrum disorders: relevance to Tourette syndrome". *Adv Neurol*. **85**: 89–101. PMID 11530449.
39. ^ [a] [b] Roy M, Dillo W, Emrich HM, Ohlmeier MD (2009). "Asperger's syndrome in adulthood". *Dtsch Arztebl Int*. **106** (5): 59–64. doi:10.3238/arztebl.2009.0059. PMC 2695286. PMID 19562011.
40. ^ Frith U (January 1996). "Social communication and its disorder in autism and Asperger syndrome". *J. Psychopharmacol. (Oxford)*. **10** (1): 48–53. doi:10.1177/026988119601000108. PMID 22302727.
41. ^ Lyons V, Fitzgerald M (2004). "Humor in autism and Asperger syndrome". *J Autism Dev Disord*. **34** (5): 521–31. doi:10.1007/s10803-004-2547-8. PMID 15628606.
42. ^ Filipek PA, Accardo PJ, Baranek GT, et al. (1999). "The screening and diagnosis of autistic spectrum disorders". *J Autism Dev Disord*. **29** (6): 439–84. doi:10.1023/A:1021943802493. PMID 10638459.
43. ^ Frith U (2004). "Emanuel Miller lecture: confusions and controversies about Asperger syndrome". *J Child Psychol Psychiatry*. **45** (4): 672–86. doi:10.1111/j.1469-7610.2004.00262.x. PMID 15056300.
44. ^ Prior M, Ozonoff S (2007). "Psychological factors in autism". In Volkmar FR. *Autism and Pervasive Developmental Disorders* (2nd ed.). Cambridge University Press. pp. 69–128. ISBN 0-521-54957-4.
45. ^ Bogdashina O (2003). *Sensory Perceptional Issues in Autism and Asperger Syndrome: Different Sensory Experiences, Different Perceptual Worlds*. Jessica Kingsley. ISBN 1-84310-166-1.
46. ^ Rogers SJ, Ozonoff S (2005). "Annotation: what do we know about sensory dysfunction in autism? A critical review of the empirical evidence". *J Child Psychol Psychiatry*. **46** (12): 1255–68. doi:10.1111/j.1469-7610.2005.01431.x. PMID 16313426.
47. ^ [a] [b] Ehlers S, Gillberg C (1993). "The epidemiology of Asperger's syndrome. A total population study". *J Child Psychol Psychiat*. **34** (8): 1327–50. doi:10.1111/j.1469-7610.1993.tb02094.x. PMID 8294522.
48. ^ Polimeni MA, Richdale AL, Francis AJ (2005). "A survey of sleep problems in autism, Asperger's disorder and typically developing children". *J Intellect Disabil Res*. **49** (4): 260–8. doi:10.1111/j.1365-2788.2005.00642.x. PMID 15816813.
49. ^ [a] [b] Tani P, Lindberg N, Joukamaa M, et al. (2004). "Asperger syndrome, alexithymia and perception of sleep". *Neuropsychobiology*. **49** (2): 64–70. doi:10.1159/000076412. PMID 14981336.
50. ^ Alexithymia and AS:
    - Fitzgerald M, Bellgrove MA (2006). "The overlap between alexithymia and Asperger's syndrome". *J Autism Dev Disord*. **36** (4): 573–6. doi:10.1007/s10803-006-0096-z. PMC 2092499. PMID 16755385.
    - Hill E, Berthoz S (2006). "Response". *J Autism Dev Disord*. **36** (8): 1143–5. doi:10.1007/s10803-006-0287-7. PMID 17080269.
    - Lombardo MV, Barnes JL, Wheelwright SJ, Baron-Cohen S (2007). Zak P, ed. "Self-referential cognition and empathy in autism". *PLoS ONE*. **2** (9): e883. doi:10.1371/journal.pone.0000883. PMC 1964804. PMID 17849012.
51. ^ [a] [b] [c] [d] [e] [f] Foster B, King BH (2003). "Asperger syndrome: to be or not to be?". *Current Opinion in Pediatrics*. **15** (5): 491–4. doi:10.1097/00008480-200310000-00008. PMID 14508298.
52. ^ [a] [b] Arndt TL, Stodgell CJ, Rodier PM (2005). "The teratology of autism". *Int J Dev Neurosci*. **23** (2–3): 189–99. doi:10.1016/j.ijdevneu.2004.11.001. PMID 15749245.
53. ^ Rutter M (2005). "Incidence of autism spectrum disorders: changes over time and their meaning". *Acta Paediatr*. **94** (1): 2–15. doi:10.1111/j.1651-2227.2005.tb01779.x. PMID 15858952.
54. ^ [a] [b] Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ (2007). "Functional and anatomical cortical underconnectivity in autism: evidence from an FMRI study of an executive function task and corpus callosum morphometry". *Cereb Cortex*. **17** (4): 951–61. doi:10.1093/cercor/bhl006. PMC 4500121. PMID 16772313.
55. ^ [a] [b] Iacoboni M, Dapretto M (2006). "The mirror neuron system and the consequences of its dysfunction". *Nature Reviews Neuroscience*. **7** (12): 942–51. doi:10.1038/nrn2024. PMID 17115076.
56. ^ Müller RA (2007). "The study of autism as a distributed disorder". *Ment Retard Dev Disabil Res Rev*. **13** (1): 85–95. doi:10.1002/mrdd.20141. PMC 3315379. PMID 17326118.
57. ^ Rinehart NJ, Bradshaw JL, Brereton AV, Tonge BJ (2002). "A clinical and neurobehavioural review of high-functioning autism and Asperger's disorder". *Aust N Z J Psychiatry*. **36** (6): 762–70. doi:10.1046/j.1440-1614.2002.01097.x. PMID 12406118.

58. ^ Berthier ML, Starkstein SE, Leiguarda R (1990). "Developmental cortical anomalies in Asperger's syndrome: neuroradiological findings in two patients". *J Neuropsychiatry Clin Neurosci*. **2** (2): 197–201. PMID 2136076.
59. ^ Happé F, Ronald A, Plomin R (2006). "Time to give up on a single explanation for autism". *Nature Neuroscience*. **9** (10): 1218–20. doi:10.1038/nn1770. PMID 17001340.
60. ^ Happé F, Frith U (2006). "The weak coherence account: detail-focused cognitive style in autism spectrum disorders". *J Autism Dev Disord*. **36** (1): 5–25. doi:10.1007/s10803-005-0039-0. PMID 16450045.
61. ^ Mottron L, Dawson M, Soulières I, Hubert B, Burack J (2006). "Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception". *J Autism Dev Disord*. **36** (1): 27–43. doi:10.1007/s10803-005-0040-7. PMID 16453071.
62. ^ Ramachandran VS, Oberman LM (2006). "Broken mirrors: a theory of autism" (PDF). *Sci Am*. **295** (5): 62–9. doi:10.1038/scientificamerican1106-62. PMID 17076085. Archived (PDF) from the original on 5 February 2009. Retrieved 13 February 2009.
63. ^ Nishitani N, Avikainen S, Hari R (2004). "Abnormal imitation-related cortical activation sequences in Asperger's syndrome". *Annals of Neurology*. **55** (4): 558–62. doi:10.1002/ana.20031. PMID 15048895.
64. ^ Baron-Cohen S, Leslie AM, Frith U (1985). "Does the autistic child have a 'theory of mind'?" (PDF). *Cognition*. **21** (1): 37–46. doi:10.1016/0010-0277(85)90022-8. PMID 2934210. Archived (PDF) from the original on 28 June 2007. Retrieved 28 June 2007.
65. ^ Baron-Cohen S (2006). "The hyper-systemizing, assortative mating theory of autism" (PDF). *Prog Neuropsychopharmacol Biol Psychiatry*. **30** (5): 865–72. doi:10.1016/j.pnpbp.2006.01.010. PMID 16519981. Archived from the original (PDF) on 14 June 2007. Retrieved 8 June 2009.
66. ^ Szatmari P, Bremner R, Nagy J (1989). "Asperger's syndrome: a review of clinical features". *Can J Psychiatry*. **34** (6): 554–60. PMID 2766209.
67. ^ Gillberg IC, Gillberg C (1989). "Asperger syndrome—some epidemiological considerations: a research note". *J Child Psychol Psychiatry*. **30** (4): 631–8. doi:10.1111/j.1469-7610.1989.tb00275.x. PMID 2670981.
68. ^ [a] [b] [c] Fitzgerald M, Corvin A (2001). "Diagnosis and differential diagnosis of Asperger syndrome". *Adv Psychiatric Treat*. **7** (4): 310–8. doi:10.1192/apt.7.4.310.
69. ^ Leskovec TJ, Rowles BM, Findling RL (2008). "Pharmacological treatment options for autism spectrum disorders in children and adolescents". *Harv Rev Psychiatry*. **16** (2): 97–112. doi:10.1080/10673220802075852. PMID 18415882.
70. ^ Shattuck PT, Grosse SD (2007). "Issues related to the diagnosis and treatment of autism spectrum disorders". *Ment Retard Dev Disabil Res Rev*. **13** (2): 129–35. doi:10.1002/mrdd.20143. PMID 17563895.
71. ^ [a] [b] Klin A, Volkmar FR (2003). "Asperger syndrome: diagnosis and external validity". *Child Adolesc Psychiatr Clin N Am*. **12** (1): 1–13. doi:10.1016/S1056-4993(02)00052-4. PMID 12512395.
72. ^ Toth K, King BH (2008). "Asperger's syndrome: diagnosis and treatment". *Am J Psychiatry*. **165** (8): 958–63. doi:10.1176/appi.ajp.2008.08020272. PMID 18676600.
73. ^ Tantam D (2003). "The challenge of adolescents and adults with Asperger syndrome". *Child Adolesc Psychiatr Clin N Am*. **12** (1): 143–63. doi:10.1016/S1056-4993(02)00053-6. PMID 12512403.
74. ^ Uekermann J, Daum I (May 2008). "Social cognition in alcoholism: a link to prefrontal cortex dysfunction?". *Addiction*. **103** (5): 726–35. doi:10.1111/j.1360-0443.2008.02157.x. PMID 18412750.
75. ^ Gillberg, C; Billstedt, E (November 2000). "Autism and Asperger syndrome: coexistence with other clinical disorders.". *Acta Psychiatrica Scandinavica*. **102** (5): 321–30. doi:10.1034/j.1600-0447.2000.102005321.x. PMID 11098802.
76. ^ Fitzgerald, M. (1 July 2001). "Diagnosis and differential diagnosis of Asperger syndrome". *Advances in Psychiatric Treatment*. **7** (4): 310–318. doi:10.1192/apt.7.4.310.
77. ^ Siu, AL; US Preventive Services Task Force, (USPSTF); Bibbins-Domingo, K; Grossman, DC; Baumann, LC; Davidson, KW; Ebell, M; García, FA; Gillman, M; Herzstein, J; Kemper, AR; Krist, AH; Kurth, AE; Owens, DK; Phillips, WR; Phipps, MG; Pignone, MP (16 February 2016). "Screening for Autism Spectrum Disorder in Young Children: US Preventive Services Task Force Recommendation Statement.". *JAMA*. **315** (7): 691–6. doi:10.1001/jama.2016.0018. PMID 26881372.
78. ^ The **CAST** has been renamed from the *Childhood Asperger Syndrome Test* to the *Childhood Autism Spectrum Test*, reflecting the removal of Asperger's Syndrome from the DSM-5
79. ^ Campbell JM (2005). "Diagnostic assessment of Asperger's disorder: a review of five third-party rating scales". *J Autism Dev Disord*. **35** (1): 25–35. doi:10.1007/s10803-004-1028-4. PMID 15796119.
80. ^ Auyeung B, Baron-Cohen S, Wheelwright S, Allison C (2008). "The Autism Spectrum Quotient: Children's Version (AQ-Child)" (PDF). *J Autism Dev Disord*. **38** (7): 1230–40. doi:10.1007/s10803-007-0504-z. PMID 18064550. Archived (PDF) from the original on 5 February 2009. Retrieved 2 January 2009.
81. ^ Baron-Cohen S, Hoekstra RA, Knickmeyer R, Wheelwright S (2006). "The Autism-Spectrum Quotient (AQ)—adolescent version" (PDF). *J Autism Dev Disord*. **36** (3): 343–50. doi:10.1007/s10803-006-0073-6. (PDF)

PMID 16552625 . Archived (PDF) from the original on 5 February 2009. Retrieved 2 January 2009.
82. ^ Woodbury-Smith MR, Robinson J, Wheelwright S, Baron-Cohen S (2005). "Screening adults for Asperger Syndrome using the AQ: a preliminary study of its diagnostic validity in clinical practice" (PDF). *J Autism Dev Disord*. **35** (3): 331–5. doi:10.1007/s10803-005-3300-7. PMID 16119474. Archived (PDF) from the original on 17 December 2008. Retrieved 2 January 2009.
83. ^ Khouzam HR, El-Gabalawi F, Pirwani N, Priest F (2004). "Asperger's disorder: a review of its diagnosis and treatment". *Compr Psychiatry*. **45** (3): 184–91. doi:10.1016/j.comppsych.2004.02.004. PMID 15124148.
84. ^ Attwood T (2003). "Frameworks for behavioral interventions". *Child Adolesc Psychiatr Clin N Am*. **12** (1): 65–86. doi:10.1016/S1056-4993(02)00054-8. PMID 12512399.
85. ^ Krasny L, Williams BJ, Provencal S, Ozonoff S (2003). "Social skills interventions for the autism spectrum: essential ingredients and a model curriculum". *Child Adolesc Psychiatr Clin N Am*. **12** (1): 107–22. doi:10.1016/S1056-4993(02)00051-2. PMID 12512401.
86. ^ *a b* Myles BS (2003). "Behavioral forms of stress management for individuals with Asperger syndrome". *Child Adolesc Psychiatr Clin N Am*. **12** (1): 123–41. doi:10.1016/S1056-4993(02)00048-2. PMID 12512402.
87. ^ *a b c d* Towbin KE (2003). "Strategies for pharmacologic treatment of high functioning autism and Asperger syndrome". *Child Adolesc Psychiatr Clin N Am*. **12** (1): 23–45. doi:10.1016/S1056-4993(02)00049-4. PMID 12512397.
88. ^ Paul R (2003). "Promoting social communication in high functioning individuals with autistic spectrum disorders". *Child Adolesc Psychiatr Clin N Am*. **12** (1): 87–106. doi:10.1016/S1056-4993(02)00047-0. PMID 12512400.
89. ^ *a b* Matson JL (2007). "Determining treatment outcome in early intervention programs for autism spectrum disorders: a critical analysis of measurement issues in learning based interventions". *Res Dev Disabil*. **28** (2): 207–18. doi:10.1016/j.ridd.2005.07.006. PMID 16682171.
90. ^ Rao PA, Beidel DC, Murray MJ (2008). "Social skills interventions for children with Asperger's syndrome or high-functioning autism: a review and recommendations". *J Autism Dev Disord*. **38** (2): 353–61. doi:10.1007/s10803-007-0402-4. PMID 17641962.
91. ^ Sofronoff K, Leslie A, Brown W (2004). "Parent management training and Asperger syndrome: a randomized controlled trial to evaluate a parent based intervention". *Autism*. **8** (3): 301–17. doi:10.1177/1362361304045215. PMID 15358872.
92. ^ *a b* Newcomer JW (2007). "Antipsychotic medications: metabolic and cardiovascular risk". *J Clin Psychiatry*. **68** (suppl 4): 8–13. PMID 17539694.
93. ^ *a b* Chavez B, Chavez-Brown M, Sopko MA, Rey JA (2007). "Atypical antipsychotics in children with pervasive developmental disorders". *Pediatr Drugs*. **9** (4): 249–66. doi:10.2165/00148581-200709040-00006. PMID 17705564.
94. ^ Staller J (2006). "The effect of long-term antipsychotic treatment on prolactin". *J Child Adolesc Psychopharmacol*. **16** (3): 317–26. doi:10.1089/cap.2006.16.317. PMID 16768639.
95. ^ Stachnik JM, Nunn-Thompson C (2007). "Use of atypical antipsychotics in the treatment of autistic disorder". *Annals of Pharmacotherapy*. **41** (4): 626–34. doi:10.1345/aph.1H527. PMID 17389666.
96. ^ Blacher J, Kraemer B, Schalow M (2003). "Asperger syndrome and high functioning autism: research concerns and emerging foci". *Current Opinion in Psychiatry*. **16** (5): 535–542. doi:10.1097/00001504-200309000-00008.
97. ^ Coplan J, Jawad AF (2005). "Modeling clinical outcome of children with autistic spectrum disorders". *Pediatrics*. **116** (1): 117–22. doi:10.1542/peds.2004-1118. PMID 15995041. Lay summary – *press release* (5 July 2005).
98. ^ Chiang HM, Lin YH (2007). "Mathematical ability of students with Asperger syndrome and high-functioning autism" (PDF). *Autism*. **11** (6): 547–56. doi:10.1177/1362361307083259. PMID 17947290. Archived from the original on 7 April 2009. Retrieved 6 March 2009. – via SAGE Journals (subscription required)
99. ^ Herera S (25 February 2005). "Mild autism has 'selective advantages'". CNBC. Archived from the original on 1 November 2007. Retrieved 14 November 2007.
100. ^ "Autism Spectrum: Are You On It?". *NYMag.com*. Retrieved 8 April 2016.
101. ^ Moran M (2006). "Asperger's may be answer to diagnostic mysteries". *Psychiatr News*. **41** (19): 21–36. doi:10.1176/pn.41.19.0021.
102. ^ Gillberg C (2008). "Asperger syndrome—mortality and morbidity". In Rausch JL, Johnson ME, Casanova MF. *Asperger's Disorder*. Informa Healthcare. pp. 63–80. ISBN 0-8493-8360-9.
103. ^ Fombonne E, Tidmarsh L (2003). "Epidemiologic data on Asperger disorder". *Child Adolesc Psychiatr Clin N Am*. **12** (1): 15–21. doi:10.1016/S1056-4993(02)00050-0. PMID 12512396.
104. ^ Fombonne E (2007). "Epidemiological surveys of pervasive developmental disorders". In Volkmar FR. *Autism and Pervasive Developmental Disorders* (2nd ed.). Cambridge University Press. pp. 33–68. ISBN 0-521-54957-4.
105. ^ *a b* Mattila ML, Kielinen M, Jussila K, et al. (2007). "An epidemiological and diagnostic study of Asperger syndrome according to four sets of diagnostic criteria". *J Am Acad Child Adolesc Psychiatry*. **46** (5): 636–46.

doi:10.1097/chi.0b013e318033ff42. PMID 17450055.
106. ^ Galanopoulos, Anastasios; Robertson, Dene; Woodhouse, Emma (4 January 2016). "The assessment of autism spectrum disorders in adults". *Advances in Autism*. **2** (1): 31–40. doi:10.1108/AIA-09-2015-0017.
107. ^ Cederlund M, Gillberg C (2004). "One hundred males with Asperger syndrome: a clinical study of background and associated factors". *Dev Med Child Neurol*. **46** (10): 652–60. doi:10.1111/j.1469-8749.2004.tb00977.x. PMID 15473168.
108. ^ Gillberg C, Billstedt E (2000). "Autism and Asperger syndrome: coexistence with other clinical disorders". *Acta Psychiatr Scand*. **102** (5): 321–30. doi:10.1034/j.1600-0447.2000.102005321.x. PMID 11098802.
109. ^ *a b c* Baron-Cohen S, Klin A (2006). "What's so special about Asperger Syndrome?" (PDF). *Brain Cogn*. **61** (1): 1–4. doi:10.1016/j.bandc.2006.02.002. PMID 16563588.
110. ^ Lyons V, Fitzgerald M (2007). "Did Hans Asperger (1906–1980) have Asperger Syndrome?". *J Autism Dev Disord*. **37** (10): 2020–1. doi:10.1007/s10803-007-0382-4. PMID 17917805.
111. ^ Osborne L (2002). *American Normal: The Hidden World of Asperger Syndrome*. Copernicus. p. 19. ISBN 0-387-95307-8.
112. ^ Hippler K, Klicpera C (February 2003). "A retrospective analysis of the clinical case records of 'autistic psychopaths' diagnosed by Hans Asperger and his team at the University Children's Hospital, Vienna". *Philosophical Transactions of the Royal Society B*. **358** (1430): 291–301. doi:10.1098/rstb.2002.1197. PMC 1693115. PMID 12639327.
113. ^ Wing L (1991). "The relationship between Asperger's syndrome and Kanner's autism". In Frith U. *Autism and Asperger syndrome*. Cambridge University Press. pp. 93–121. ISBN 0-521-38608-X.
114. ^ Wing L (1981). "Asperger's syndrome: a clinical account". *Psychol Med*. **11** (1): 115–29. doi:10.1017/S0033291700053332. PMID 7208735. Archived from the original on 17 August 2007. Retrieved 15 August 2007.
115. ^ Willey LH (1999). *Pretending to be Normal: Living with Asperger's Syndrome*. Jessica Kingsley. pp. 71, 104. ISBN 1-85302-749-9.
116. ^ Williams CC (2005). "In search of an Asperger". In Stoddart KP. *Children, Youth and Adults with Asperger Syndrome: Integrating Multiple Perspectives*. Jessica Kingsley. pp. 242–52. ISBN 1-84310-319-2. "The life prospects of people with AS would change if we shifted from viewing AS as a set of dysfunctions, to viewing it as a set of differences that have merit."
117. ^ Dakin CJ (2005). "Life on the outside: A personal perspective of Asperger syndrome". In Stoddart KP. *Children, Youth and Adults with Asperger Syndrome: Integrating Multiple Perspectives*. Jessica Kingsley. pp. 352–61. ISBN 1-84310-319-2.
118. ^ Clarke J, van Amerom G (2008). "Asperger's syndrome: differences between parents' understanding and those diagnosed". *Soc Work Health Care*. **46** (3): 85–106. doi:10.1300/J010v46n03_05. PMID 18551831.
119. ^ Allred S (2009). "Reframing Asperger syndrome: lessons from other challenges to the *Diagnostic and Statistical Manual* and ICIDH approaches". *Disabil Soc*. **24** (3): 343–55. doi:10.1080/09687590902789511.
120. ^ Baron-Cohen S (2008). "The evolution of brain mechanisms for social behavior". In Crawford C; Krebs D. *Foundations of Evolutionary Psychology*. Lawrence Erlbaum. pp. 415–32. ISBN 0-8058-5957-8.
121. ^ *a b* Jaarsma P, Welin S (February 2011). "Autism as a Natural Human Variation: Reflections on the Claims of the Neurodiversity Movement" (PDF). *Health Care Anal*. **20** (1): 20–30. doi:10.1007/s10728-011-0169-9. PMID 21311979. Archived from the original (PDF) on 1 November 2013.
122. ^ Hamilton, Jon. "Shortage of Brain Tissue Hinders Autism Research". *NPR*. Retrieved 10 May 2015.
123. ^ Solomon A (2008-05-25). "The autism rights movement". *New York*. Archived from the original on 27 May 2008. Retrieved 2008-05-27.

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- Asperger's Syndrome at DMOZ

*Pervasive developmental disorders portal*

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# Autism

From Wikipedia, the free encyclopedia

## Variants

*This article is about the classic autistic disorder. For other conditions sometimes called "autism", see Autism spectrum.*

**Autism** is a neurodevelopmental disorder characterized by impaired social interaction, verbal and non-verbal communication, and restricted and repetitive behavior. Parents usually notice signs in the first two years of their child's life.[1] These signs often develop gradually, though some children with autism reach their developmental milestones at a normal pace and then regress.[2] The diagnostic criteria require that symptoms become apparent in early childhood, typically before age three.[3]

While autism is highly heritable, researchers suspect both environmental and genetic factors as causes.[4] Some cases are strongly associated with certain infections during pregnancy including rubella and use of alcohol or cocaine.[5] Controversies surround other proposed environmental causes;[6] for example, the vaccine hypotheses, which have since been disproven. Autism affects information processing in the brain by altering how nerve cells and their synapses connect and organize; how this occurs is not well understood.[7] In the DSM V it is included within the autism spectrum (ASDs), along with Asperger syndrome, which lacks delays in cognitive development and language, and pervasive developmental disorder, not otherwise specified (commonly abbreviated as PDD-NOS), which is diagnosed when the full set of criteria for autism or Asperger syndrome are not met.[8][3]

Early speech or behavioral interventions can help children with autism gain self-care, social, and communication skills.[1] Although there is no known cure,[1] there have been reported cases of children who recovered.[9] Not many children with autism live independently after reaching adulthood, though some become successful.[10] An autistic culture has developed, with some individuals seeking a cure and others believing autism should be accepted as a difference and not treated as a disorder.[11]

Globally, autism is estimated to affect 21.7 million people as of 2013.[12] As of 2010, the number of people affected is estimated at about 1–2 per 1,000 worldwide. It occurs four to five times more often in boys than girls. About 1.5% of children in the United States (one in 68) are diagnosed with ASD as of 2014, a 30% increase from one in 88 in 2012.[13][14][15] The rate of autism among adults aged 18 years and over in the United Kingdom is 1.1%.[16] The number of people diagnosed has been increasing dramatically since the 1980s, partly due to changes in diagnostic practice and government-subsidized financial incentives for named diagnoses;[15] the question of whether actual rates have increased is unresolved.[17]



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Repetitively stacking or lining up objects is associated with autism.

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# Characteristics

Autism is a highly variable neurodevelopmental disorder[18] that first appears during infancy or childhood, and generally follows a steady course without remission.[19] People with autism may be severely impaired in some respects but normal, or even superior, in others.[20] Overt symptoms gradually begin after the age of six months, become established by age two or three years,[21] and tend to continue through adulthood, although often in more muted form.[22] It is distinguished not by a single symptom, but by a characteristic triad of symptoms: impairments in social interaction; impairments in communication; and restricted interests and repetitive behavior. Other aspects, such as atypical eating, are also common but are not essential for diagnosis.[23] Autism's individual symptoms occur in the general population and appear not to associate highly, without a sharp line separating pathologically severe from common traits.[24]


Play media

Autism spectrum disorder video

## Social development

Social deficits distinguish autism and the related autism spectrum disorders (ASD; see Classification) from other developmental disorders.[22] People with autism have social impairments and often lack the intuition about others that many people take for granted. Noted autistic Temple Grandin described her inability to understand the social communication of neurotypicals, or people with normal neural development, as leaving her feeling "like an anthropologist on Mars".[25]

Unusual social development becomes apparent early in childhood. Autistic infants show less attention to social stimuli, smile and look at others less often, and respond less to their own name. Autistic toddlers differ more strikingly from social norms; for example, they have less eye contact and turn-taking, and do not have the ability to use simple movements to express themselves, such as pointing at things.[26] Three- to five-year-old children with autism are less likely to exhibit social understanding, approach others spontaneously, imitate and respond to emotions, communicate nonverbally, and take turns with others. However, they do form attachments to their primary caregivers.[27] Most children with autism display moderately less attachment security than neurotypical children, although this difference disappears in children with higher mental development or less severe ASD.[28] Older children and adults with ASD perform worse on tests of face and emotion recognition[29] although this may

be partly due to a lower ability to define a person's own emotions.[30]

Children with high-functioning autism suffer from more intense and frequent loneliness compared to non-autistic peers, despite the common belief that children with autism prefer to be alone. Making and maintaining friendships often proves to be difficult for those with autism. For them, the quality of friendships, not the number of friends, predicts how lonely they feel. Functional friendships, such as those resulting in invitations to parties, may affect the quality of life more deeply.[31]

There are many anecdotal reports, but few systematic studies, of aggression and violence in individuals with ASD. The limited data suggest that, in children with intellectual disability, autism is associated with aggression, destruction of property, and tantrums.[32]

## Communication

About a third to a half of individuals with autism do not develop enough natural speech to meet their daily communication needs.[33] Differences in communication may be present from the first year of life, and may include delayed onset of babbling, unusual gestures, diminished responsiveness, and vocal patterns that are not synchronized with the caregiver. In the second and third years, children with autism have less frequent and less diverse babbling, consonants, words, and word combinations; their gestures are less often integrated with words. Children with autism are less likely to make requests or share experiences, and are more likely to simply repeat others' words (echolalia)[34][35] or reverse pronouns.[36] Joint attention seems to be necessary for functional speech, and deficits in joint attention seem to distinguish infants with ASD:[8] for example, they may look at a pointing hand instead of the pointed-at object,[26][35] and they consistently fail to point at objects in order to comment on or share an experience.[8] Children with autism may have difficulty with imaginative play and with developing symbols into language.[34][35]

In a pair of studies, high-functioning children with autism aged 8–15 performed equally well as, and adults better than, individually matched controls at basic language tasks involving vocabulary and spelling. Both autistic groups performed worse than controls at complex language tasks such as figurative language, comprehension and inference. As people are often sized up initially from their basic language skills, these studies suggest that people speaking to autistic individuals are more likely to overestimate what their audience comprehends.[37]

## Repetitive behavior

Autistic individuals display many forms of repetitive or restricted behavior, which the Repetitive Behavior Scale-Revised (RBS-R) categorizes as follows.[38]

A young boy with autism who has arranged his toys in a row

- Stereotyped behaviors: Repetitive movements, such as hand flapping, head rolling, or body rocking.
- Compulsive behaviors: Time-consuming behaviors intended to reduce anxiety that an individual feels compelled to perform repeatedly or according to rigid rules, such as placing objects in a specific order, checking things, or hand washing.
- Sameness: Resistance to change; for example, insisting that the furniture not be moved or refusing to be interrupted.
- Ritualistic behavior: Unvarying pattern of daily activities, such as an unchanging menu or a dressing ritual. This is closely associated with sameness and an independent validation has suggested combining the two factors.[38]
- Restricted interests: Interests or fixations that are abnormal in theme or intensity of focus, such as preoccupation with a single television program, toy, or game.
- Self-injury: Behaviors such as eye-poking, skin-picking, hand-biting and head-banging.[8]

No single repetitive or self-injurious behavior seems to be specific to autism, but autism appears to have an elevated pattern of occurrence and severity of these behaviors.[39]

## Other symptoms

Autistic individuals may have symptoms that are independent of the diagnosis, but that can affect the individual or the family.[23] An estimated 0.5% to 10% of individuals with ASD show unusual abilities, ranging from splinter skills such as the memorization of trivia to the extraordinarily rare talents of prodigious autistic savants.[40] Many individuals with ASD show superior skills in perception and attention, relative to the general population.[41] Sensory abnormalities are found in over 90% of those with autism, and are considered core features by some,[42]

although there is no good evidence that sensory symptoms differentiate autism from other developmental disorders.[43] Differences are greater for under-responsivity (for example, walking into things) than for over-responsivity (for example, distress from loud noises) or for sensation seeking (for example, rhythmic movements).[44] An estimated 60%–80% of autistic people have motor signs that include poor muscle tone, poor motor planning, and toe walking;[42] deficits in motor coordination are pervasive across ASD and are greater in autism proper.[45]

Unusual eating behavior occurs in about three-quarters of children with ASD, to the extent that it was formerly a diagnostic indicator. Selectivity is the most common problem, although eating rituals and food refusal also occur;[46] this does not appear to result in malnutrition. Although some children with autism also have gastrointestinal symptoms, there is a lack of published rigorous data to support the theory that children with autism have more or different gastrointestinal symptoms than usual;[47] studies report conflicting results, and the relationship between gastrointestinal problems and ASD is unclear.[48]

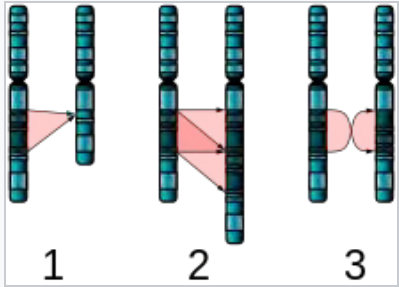
Parents of children with ASD have higher levels of stress.[26] Siblings of children with ASD report greater admiration of and less conflict with the affected sibling than siblings of unaffected children and were similar to siblings of children with Down syndrome in these aspects of the sibling relationship. However, they reported lower levels of closeness and intimacy than siblings of children with Down syndrome; siblings of individuals with ASD have greater risk of negative well-being and poorer sibling relationships as adults.[49]

## Causes

*Main article: Causes of autism*

It has long been presumed that there is a common cause at the genetic, cognitive, and neural levels for autism's characteristic triad of symptoms.[50] However, there is increasing suspicion that autism is instead a complex disorder whose core aspects have distinct causes that often co-occur.[50][51]

Autism has a strong genetic basis, although the genetics of autism are complex and it is unclear whether ASD is explained more by rare mutations with major effects, or by rare multigene interactions of common genetic variants.[53][54] Complexity arises due to interactions among multiple genes, the environment, and epigenetic factors which do not change DNA sequencing but are heritable and influence gene expression.[22] Many genes have been associated with autism through sequencing the genomes of affected individuals and their parents.[55]



Deletion (1), duplication (2) and inversion (3) are all chromosome abnormalities that have been implicated in autism.[52]

Studies of twins suggest that heritability is 0.7 for autism and as high as 0.9 for ASD, and siblings of those with autism are about 25 times more likely to be autistic than the general population.[42] However, most of the mutations that increase autism risk have not been identified. Typically, autism cannot be traced to a Mendelian (single-gene) mutation or to a single chromosome abnormality, and none of the genetic syndromes associated with ASDs have been shown to selectively cause ASD.[53] Numerous candidate genes have been located, with only small effects attributable to any particular gene.[53] Most loci individually explain less than 1% of cases of autism.[56] The large number of autistic individuals with unaffected family members may result from spontaneous structural variation — such as deletions, duplications or inversions in genetic material during meiosis.[57][58] Hence, a substantial fraction of autism cases may be traceable to genetic causes that are highly heritable but not inherited: that is, the mutation that causes the autism is not present in the parental genome.[52]

Several lines of evidence point to synaptic dysfunction as a cause of autism.[7] Some rare mutations may lead to autism by disrupting some synaptic pathways, such as those involved with cell adhesion.[59] Gene replacement studies in mice suggest that autistic symptoms are closely related to later developmental steps that depend on activity in synapses and on activity-dependent changes.[60] All known teratogens (agents that cause birth defects) related to the risk of autism appear to act during the first eight weeks from conception, and though this does not exclude the possibility that autism can be initiated or affected later, there is strong evidence that autism arises very early in development.[61]

Exposure to air pollution during pregnancy, especially heavy metals and particulates, may increase the risk of autism.[62] Environmental factors that have been claimed without evidence to contribute to or exacerbate autism include certain foods, infectious diseases, solvents, diesel exhaust, PCBs, phthalates and phenols used in plastic [17]

products, pesticides, brominated flame retardants, alcohol, smoking, illicit drugs, vaccines, and prenatal stress. No evidence has been found for these claims, and some such as the MMR vaccine have been completely disproven.[63]

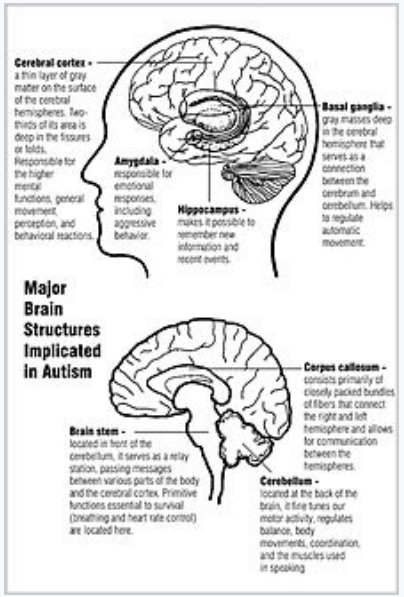
Parents may first become aware of autistic symptoms in their child around the time of a routine vaccination. This has led to unsupported theories blaming vaccine "overload", a vaccine preservative, or the MMR vaccine for causing autism.[64] The latter theory was supported by a litigation-funded study that has since been shown to have been "an elaborate fraud".[65] Although these theories lack convincing scientific evidence and are biologically implausible,[64] parental concern about a potential vaccine link with autism has led to lower rates of childhood immunizations, outbreaks of previously controlled childhood diseases in some countries, and the preventable deaths of several children.[66][67]

# Mechanism

Autism's symptoms result from maturation-related changes in various systems of the brain. How autism occurs is not well understood. Its mechanism can be divided into two areas: the pathophysiology of brain structures and processes associated with autism, and the neuropsychological linkages between brain structures and behaviors.[68] The behaviors appear to have multiple pathophysiologies.[24]

## Pathophysiology

Unlike many other brain disorders, such as Parkinson's, autism does not have a clear unifying mechanism at either the molecular, cellular, or systems level; it is not known whether autism is a few disorders caused by mutations converging on a few common molecular pathways, or is (like intellectual disability) a large set of disorders with diverse mechanisms.[18] Autism appears to result from developmental factors that affect many or all functional brain systems,[70] and to disturb the timing of brain development more than the final product.[69] Neuroanatomical studies and the associations with teratogens strongly suggest that autism's mechanism includes alteration of brain development soon after conception.[61] This anomaly appears to start a cascade of pathological events in the brain that are significantly influenced by environmental factors.[71] Just after birth, the brains of children with autism tend to grow faster than usual, followed by normal or relatively slower growth in childhood. It is not known whether early overgrowth occurs in all children with autism. It seems to be most prominent in brain areas underlying the development of higher cognitive specialization.[42] Hypotheses for the cellular and molecular bases of pathological early overgrowth include the following:



Autism affects the amygdala, cerebellum, and many other parts of the brain.[69]

- An excess of neurons that causes local overconnectivity in key brain regions.[72]
- Disturbed neuronal migration during early gestation.[73][74]
- Unbalanced excitatory–inhibitory networks.[74]
- Abnormal formation of synapses and dendritic spines,[74] for example, by modulation of the neurexin–neuroligin cell-adhesion system,[75] or by poorly regulated synthesis of synaptic proteins.[76][77] Disrupted synaptic development may also contribute to epilepsy, which may explain why the two conditions are associated.[78]

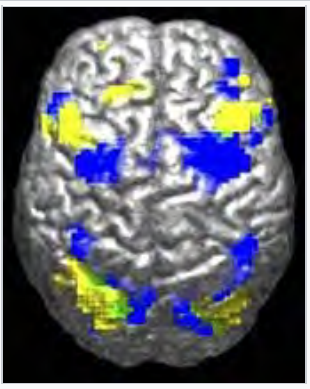
The immune system is thought to play an important role in autism. Children with autism have been found by researchers to have inflammation of both the peripheral and central immune systems as indicated by increased levels of pro-inflammatory cytokines and significant activation of microglia.[79][80][81] Biomarkers of abnormal immune function have also been associated with increased impairments in behaviors that are characteristic of the core features of autism such as deficits in social interactions and communication.[80] Interactions between the immune system and the nervous system begin early during the embryonic stage of life, and successful neurodevelopment depends on a balanced immune response. It is thought that activation of a pregnant mother's immune system such as from environmental toxicants or infection can contribute to causing autism through causing a disruption of brain development.[82][83][84] This is supported by recent studies that have found that infection during pregnancy is associated with an increased risk of autism.[85][86]

The relationship of neurochemicals to autism is not well understood; several have been investigated, with the most evidence for the role of serotonin and of genetic differences in its transport.[7] The role of group I metabotropic

glutamate receptors (mGluR) in the pathogenesis of fragile X syndrome, the most common identified genetic cause of autism, has led to interest in the possible implications for future autism research into this pathway.[87] Some data suggests neuronal overgrowth potentially related to an increase in several growth hormones[88] or to impaired regulation of growth factor receptors. Also, some inborn errors of metabolism are associated with autism, but probably account for less than 5% of cases.[89]

The mirror neuron system (MNS) theory of autism hypothesizes that distortion in the development of the MNS interferes with imitation and leads to autism's core features of social impairment and communication difficulties. The MNS operates when an animal performs an action or observes another animal perform the same action. The MNS may contribute to an individual's understanding of other people by enabling the modeling of their behavior via embodied simulation of their actions, intentions, and emotions.[90] Several studies have tested this hypothesis by demonstrating structural abnormalities in MNS regions of individuals with ASD, delay in the activation in the core circuit for imitation in individuals with Asperger syndrome, and a correlation between reduced MNS activity and severity of the syndrome in children with ASD.[91] However, individuals with autism also have abnormal brain activation in many circuits outside the MNS[92] and the MNS theory does not explain the normal performance of children with autism on imitation tasks that involve a goal or object.[93]

ASD-related patterns of low function and aberrant activation in the brain differ depending on whether the brain is doing social or nonsocial tasks.[95] In autism there is evidence for reduced functional connectivity of the default network, a large-scale brain network involved in social and emotional processing, with intact connectivity of the task-positive network, used in sustained attention and goal-directed thinking[*clarification needed*]. In people with autism the two networks are not negatively correlated in time, suggesting an imbalance in toggling between the two networks, possibly reflecting a disturbance of self-referential thought.[96]



Autistic individuals tend to use different areas of the brain (yellow) for a movement task compared to a control group (blue).[94]

The underconnectivity theory of autism hypothesizes that autism is marked by underfunctioning high-level neural connections and synchronization, along with an excess of low-level processes.[97] Evidence for this theory has been found in functional neuroimaging studies on autistic individuals[37] and by a brainwave study that suggested that adults with ASD have local overconnectivity in the cortex and weak functional connections between the frontal lobe and the rest of the cortex.[98] Other evidence suggests the underconnectivity is mainly within each hemisphere of the cortex and that autism is a disorder of the association cortex.[99]

From studies based on event-related potentials, transient changes to the brain's electrical activity in response to stimuli, there is considerable evidence for differences in autistic individuals with respect to attention, orientation to auditory and visual stimuli, novelty detection, language and face processing, and information storage; several studies have found a preference for nonsocial stimuli.[100] For example, magnetoencephalography studies have found evidence in children with autism of delayed responses in the brain's processing of auditory signals.[101]

In the genetic area, relations have been found between autism and schizophrenia based on duplications and deletions of chromosomes; research showed that schizophrenia and autism are significantly more common in combination with 1q21.1 deletion syndrome. Research on autism/schizophrenia relations for chromosome 15 (15q13.3), chromosome 16 (16p13.1) and chromosome 17 (17p12) are inconclusive.[102]

Functional connectivity studies have found both hypo- and hyper-connectivity in brains of people with autism. Hypo-connectivity seems to dominate, especially for interhemispheric and cortico-cortical functional connectivity.[103]

## Neuropsychology

Two major categories of cognitive theories have been proposed about the links between autistic brains and behavior.

The first category focuses on deficits in social cognition. Simon Baron-Cohen's empathizing–systemizing theory postulates that autistic individuals can systemize—that is, they can develop internal rules of operation to handle events inside the brain—but are less effective at empathizing by handling events generated by other agents. An extension, the extreme male brain theory, hypothesizes that autism is an extreme case of the male brain, defined psychometrically as individuals in whom systemizing is better than empathizing.[104] These theories are somewhat related to Baron-Cohen's earlier theory of mind approach, which hypothesizes that autistic behavior arises from an inability to ascribe mental states to oneself and others. The theory of mind hypothesis is supported by the atypical responses of children with autism to the Sally–Anne test for reasoning about others' motivations,[104] and the

mirror neuron system theory of autism described in *Pathophysiology* maps well to the hypothesis.[91] However, most studies have found no evidence of impairment in autistic individuals' ability to understand other people's basic intentions or goals; instead, data suggests that impairments are found in understanding more complex social emotions or in considering others' viewpoints.[105]

The second category focuses on nonsocial or general processing: the executive functions such as working memory, planning, inhibition. In his review, Kenworthy states that "the claim of executive dysfunction as a causal factor in autism is controversial", however, "it is clear that executive dysfunction plays a role in the social and cognitive deficits observed in individuals with autism".[106] Tests of core executive processes such as eye movement tasks indicate improvement from late childhood to adolescence, but performance never reaches typical adult levels.[107] A strength of the theory is predicting stereotyped behavior and narrow interests;[108] two weaknesses are that executive function is hard to measure[106] and that executive function deficits have not been found in young children with autism.[29]

Weak central coherence theory hypothesizes that a limited ability to see the big picture underlies the central disturbance in autism. One strength of this theory is predicting special talents and peaks in performance in autistic people.[109] A related theory—enhanced perceptual functioning—focuses more on the superiority of locally oriented and perceptual operations in autistic individuals.[110] These theories map well from the underconnectivity theory of autism.

Neither category is satisfactory on its own; social cognition theories poorly address autism's rigid and repetitive behaviors, while the nonsocial theories have difficulty explaining social impairment and communication difficulties.[51] A combined theory based on multiple deficits may prove to be more useful.[111]

## Diagnosis

Diagnosis is based on behavior, not cause or mechanism.[24][112] Under the DSM-5, autism is characterized by persistent deficits in social communication and interaction across multiple contexts, as well as restricted, repetitive patterns of behavior, interests, or activities. These deficits are present in early childhood, typically before age three, and lead to clinically significant functional impairment. Sample symptoms include lack of social or emotional reciprocity, stereotyped and repetitive use of language or idiosyncratic language, and persistent preoccupation with unusual objects. The disturbance must not be better accounted for by Rett syndrome, intellectual disability or global developmental delay.[3] ICD-10 uses essentially the same definition.[19]

Several diagnostic instruments are available. Two are commonly used in autism research: the Autism Diagnostic Interview-Revised (ADI-R) is a semistructured parent interview, and the Autism Diagnostic Observation Schedule (ADOS)[113] uses observation and interaction with the child. The Childhood Autism Rating Scale (CARS) is used widely in clinical environments to assess severity of autism based on observation of children.[26]

A pediatrician commonly performs a preliminary investigation by taking developmental history and physically examining the child. If warranted, diagnosis and evaluations are conducted with help from ASD specialists, observing and assessing cognitive, communication, family, and other factors using standardized tools, and taking into account any associated medical conditions.[114] A pediatric neuropsychologist is often asked to assess behavior and cognitive skills, both to aid diagnosis and to help recommend educational interventions.[115] A differential diagnosis for ASD at this stage might also consider intellectual disability, hearing impairment, and a specific language impairment[114] such as Landau–Kleffner syndrome.[116] The presence of autism can make it harder to diagnose coexisting psychiatric disorders such as depression.[117]

Clinical genetics evaluations are often done once ASD is diagnosed, particularly when other symptoms already suggest a genetic cause.[118] Although genetic technology allows clinical geneticists to link an estimated 40% of cases to genetic causes,[119] consensus guidelines in the US and UK are limited to high-resolution chromosome and fragile X testing.[118] A genotype-first model of diagnosis has been proposed, which would routinely assess the genome's copy number variations.[120] As new genetic tests are developed several ethical, legal, and social issues will emerge. Commercial availability of tests may precede adequate understanding of how to use test results, given the complexity of autism's genetics.[121] Metabolic and neuroimaging tests are sometimes helpful, but are not routine.[118]

ASD can sometimes be diagnosed by age 14 months, although diagnosis becomes increasingly stable over the first three years of life: for example, a one-year-old who meets diagnostic criteria for ASD is less likely than a three-year-old to continue to do so a few years later.[122] In the UK the National Autism Plan for Children recommends at most 30 weeks from first concern to completed diagnosis and assessment, though few cases are handled that quickly in practice.[114] Although the symptoms of autism and ASD begin early in childhood, they are sometimes

missed; years later, adults may seek diagnoses to help them or their friends and family understand themselves, to help their employers make adjustments, or in some locations to claim disability living allowances or other benefits.

Underdiagnosis and overdiagnosis are problems in marginal cases, and much of the recent increase in the number of reported ASD cases is likely due to changes in diagnostic practices. The increasing popularity of drug treatment options and the expansion of benefits has given providers incentives to diagnose ASD, resulting in some overdiagnosis of children with uncertain symptoms. Conversely, the cost of screening and diagnosis and the challenge of obtaining payment can inhibit or delay diagnosis.[123] It is particularly hard to diagnose autism among the visually impaired, partly because some of its diagnostic criteria depend on vision, and partly because autistic symptoms overlap with those of common blindness syndromes or blindisms.[124]

## Classification

Autism is one of the five pervasive developmental disorders (PDD), which are characterized by widespread abnormalities of social interactions and communication, and severely restricted interests and highly repetitive behavior.[19] These symptoms do not imply sickness, fragility, or emotional disturbance.[22]

Of the five PDD forms, Asperger syndrome is closest to autism in signs and likely causes; Rett syndrome and childhood disintegrative disorder share several signs with autism, but may have unrelated causes; PDD not otherwise specified (PDD-NOS; also called *atypical autism*) is diagnosed when the criteria are not met for a more specific disorder.[125] Unlike with autism, people with Asperger syndrome have no substantial delay in language development.[126] The terminology of autism can be bewildering, with autism, Asperger syndrome and PDD-NOS often called the *autism spectrum disorders* (ASD)[1] or sometimes the *autistic disorders*,[127] whereas autism itself is often called *autistic disorder*, *childhood autism*, or *infantile autism*. In this article, *autism* refers to the classic autistic disorder; in clinical practice, though, *autism*, *ASD*, and *PDD* are often used interchangeably.[118] ASD, in turn, is a subset of the broader autism phenotype, which describes individuals who may not have ASD but do have autistic-like traits, such as avoiding eye contact.[128]

The manifestations of autism cover a wide spectrum, ranging from individuals with severe impairments—who may be silent, developmentally disabled, and locked into hand flapping and rocking—to high functioning individuals who may have active but distinctly odd social approaches, narrowly focused interests, and verbose, pedantic communication.[129] Because the behavior spectrum is continuous, boundaries between diagnostic categories are necessarily somewhat arbitrary.[42] Sometimes the syndrome is divided into low-, medium- or high-functioning autism (LFA, MFA, and HFA), based on IQ thresholds,[130] or on how much support the individual requires in daily life; these subdivisions are not standardized and are controversial. Autism can also be divided into syndromal and non-syndromal autism; the syndromal autism is associated with severe or profound intellectual disability or a congenital syndrome with physical symptoms, such as tuberous sclerosis.[131] Although individuals with Asperger syndrome tend to perform better cognitively than those with autism, the extent of the overlap between Asperger syndrome, HFA, and non-syndromal autism is unclear.[132]

Some studies have reported diagnoses of autism in children due to a loss of language or social skills, as opposed to a failure to make progress, typically from 15 to 30 months of age. The validity of this distinction remains controversial; it is possible that regressive autism is a specific subtype,[2][34][122][133] or that there is a continuum of behaviors between autism with and without regression.[134]

Research into causes has been hampered by the inability to identify biologically meaningful subgroups within the autistic population[135] and by the traditional boundaries between the disciplines of psychiatry, psychology, neurology and pediatrics.[136] Newer technologies such as fMRI and diffusion tensor imaging can help identify biologically relevant phenotypes (observable traits) that can be viewed on brain scans, to help further neurogenetic studies of autism;[137] one example is lowered activity in the fusiform face area of the brain, which is associated with impaired perception of people versus objects.[7] It has been proposed to classify autism using genetics as well as behavior.[138]

# Screening

About half of parents of children with ASD notice their child's unusual behaviors by age 18 months, and about four-fifths notice by age 24 months.[122] According to an article failure to meet any of the following milestones "is an absolute indication to proceed with further evaluations. Delay in referral for such testing may delay early diagnosis and treatment and affect the long-term outcome".[23]

- No babbling by 12 months.
- No gesturing (pointing, waving, etc.) by 12 months.

No single words by 16 months.
- No two-word (spontaneous, not just echolalic) phrases by 24 months.
- Any loss of any language or social skills, at any age.

The United States Preventive Services Task Force in 2016 found it was unclear if screening was beneficial or harmful among children in whom there is no concerns.[139] The Japanese practice is to screen all children for ASD at 18 and 24 months, using autism-specific formal screening tests. In contrast, in the UK, children whose families or doctors recognize possible signs of autism are screened. It is not known which approach is more effective.[7] Screening tools include the Modified Checklist for Autism in Toddlers (M-CHAT), the Early Screening of Autistic Traits Questionnaire, and the First Year Inventory; initial data on M-CHAT and its predecessor, the Checklist for Autism in Toddlers (CHAT), on children aged 18–30 months suggests that it is best used in a clinical setting and that it has low sensitivity (many false-negatives) but good specificity (few false-positives).[122] It may be more accurate to precede these tests with a broadband screener that does not distinguish ASD from other developmental disorders.[140] Screening tools designed for one culture's norms for behaviors like eye contact may be inappropriate for a different culture.[141] Although genetic screening for autism is generally still impractical, it can be considered in some cases, such as children with neurological symptoms and dysmorphic features.[142]

## Prevention

Infection with rubella during pregnancy causes fewer than 1% of cases of autism;[143] vaccination against rubella can prevent many of those cases.[144]

## Management

*Main article: Autism therapies*

A three-year-old with autism points to fish in an aquarium, as part of an experiment on the effect of intensive shared-attention training on language development.[94]

The main goals when treating children with autism are to lessen associated deficits and family distress, and to increase quality of life and functional independence. In general, higher IQs are correlated with greater responsiveness to treatment and improved treatment outcomes.[145][146] No single treatment is best and treatment is typically tailored to the child's needs.[1] Families and the educational system are the main resources for treatment.[7] Studies of interventions have methodological problems that prevent definitive conclusions about efficacy,[147] however the development of evidence-based interventions has advanced in recent years.[145] Although many psychosocial interventions have some positive evidence, suggesting that some form of treatment is preferable to no treatment, the methodological quality of systematic reviews of these studies has generally been poor, their clinical results are mostly tentative, and there is little evidence for the relative effectiveness of treatment options.[148] Intensive, sustained special education programs and behavior therapy early in life can help children acquire self-care, social, and job skills,[1] and often improve functioning and decrease symptom severity and maladaptive behaviors;[149] claims that intervention by around age three years is crucial are not substantiated.[150] Available approaches include applied behavior analysis (ABA), developmental models, structured teaching, speech and language therapy, social skills therapy, and occupational therapy.[1] Among these approaches, interventions either treat autistic features comprehensively, or focalize treatment on a specific area of deficit.[145] There is some evidence that early intensive behavioral intervention (EIBI), an early intervention model based on ABA for 20 to 40 hours a week for multiple years, is an effective treatment for some children with ASD.[151] Two theoretical frameworks outlined for early childhood intervention include applied behavioral analysis (ABA) and developmental social pragmatic models (DSP).[145] One interventional strategy utilizes a parent training model, which teaches parents how to implement various ABA and DSP techniques, allowing for parents to disseminate interventions themselves.[145] Various DSP programs have been developed to explicitly deliver intervention systems through at-home parent implementation. Despite the recent development of parent training models, these interventions have demonstrated effectiveness in numerous studies, being evaluated as a probable efficacious mode of treatment.[145]

### Education

Educational interventions can be effective to varying degrees in most children: intensive ABA treatment has demonstrated effectiveness in enhancing global functioning in preschool children[152] and is well-established for improving intellectual performance of young children.[149] Similarly, teacher-implemented intervention that utilizes an ABA combined with a developmental social pragmatic approach has been found to be a well-established treatment in improving social-communication skills in young children, although there is less evidence in its treatment of global symptoms.[145] Neuropsychological reports are often poorly communicated to educators, resulting in a gap between what a report recommends and what education is provided.[115] It is not known whether treatment programs for children lead to significant improvements after the children grow up,[149] and the limited research on the effectiveness of adult residential programs shows mixed results.[153] The appropriateness of including children with varying severity of autism spectrum disorders in the general education population is a subject of current debate among educators and researchers.[154]

### Medication

Many medications are used to treat ASD symptoms that interfere with integrating a child into home or school when behavioral treatment fails.[22][155] More than half of US children diagnosed with ASD are prescribed psychoactive drugs or anticonvulsants, with the most common drug classes being antidepressants, stimulants, and antipsychotics.[156] Antipsychotics, such as risperidone and aripiprazole, have been found to be useful for treating irritability, repetitive behavior, and sleeplessness that often occurs with autism, however their side effects must be weighed against their potential benefits, and people with autism may respond atypically.[157] There is scant reliable research about the effectiveness or safety of drug treatments for adolescents and adults with ASD.[158] No known medication relieves autism's core symptoms of social and communication impairments.[159] Experiments in mice have reversed or reduced some symptoms related to autism by replacing or modulating gene function,[60][87] suggesting the possibility of targeting therapies to specific rare mutations known to cause autism.[59][160]

### Alternative medicine

Although many alternative therapies and interventions are available, few are supported by scientific studies.[29][161] Treatment approaches have little empirical support in quality-of-life contexts, and many programs focus on success measures that lack predictive validity and real-world relevance.[31] Scientific evidence appears to matter less to service providers than program marketing, training availability, and parent requests.[162] Some alternative treatments may place the child at risk. A 2008 study found that compared to their peers, autistic boys have significantly thinner bones if on casein-free diets;[163] in 2005, botched chelation therapy killed a five-year-old child with autism.[164] There has been early research looking at hyperbaric treatments in children with autism.[165]

Although popularly used as an alternative treatment for people with autism, there is no good evidence that a gluten-free diet is of benefit.[166][167][168] In the subset of people who have gluten sensitivity there is limited evidence that suggests that a gluten free diet may improve some autistic behaviors.[166][169][170][171]

### Cost

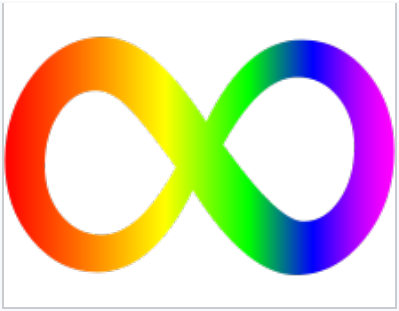
Treatment is expensive; indirect costs are more so. For someone born in 2000, a US study estimated an average lifetime cost of $4.11 million (net present value in 2017 dollars, inflation-adjusted from 2003 estimate),[172] with about 10% medical care, 30% extra education and other care, and 60% lost economic productivity.[173] Publicly supported programs are often inadequate or inappropriate for a given child, and unreimbursed out-of-pocket medical or therapy expenses are associated with likelihood of family financial problems;[174] one 2008 US study found a 14% average loss of annual income in families of children with ASD,[175] and a related study found that ASD is associated with higher probability that child care problems will greatly affect parental employment.[176] US states increasingly require private health insurance to cover autism services, shifting costs from publicly funded education programs to privately funded health insurance.[177] After childhood, key treatment issues include residential care, job training and placement, sexuality, social skills, and estate planning.[178]

## Society and culture

*Main article: Sociological and cultural aspects of autism*

The emergence of the autism rights movement has served as an attempt to encourage people to be more tolerant of those with autism.[179] Through this

movement, people hope to cause others to think of autism as a difference instead of a disease. Proponents of this movement wish to seek "acceptance, not cures."[180] There have also been many worldwide events promoting autism awareness such as World Autism Awareness Day, Light It Up Blue, Autism Sunday, Autistic Pride Day, Autreat, and others.[181][182][183][184][185] There have also been many organizations dedicated to increasing the awareness of autism and the effects that autism has on someone's life. These organizations include Autism Speaks, Autism National Committee, Autism Society of America, and many others.[186] Social-science scholars have had an increased focused on studying those with autism in hopes to learn more about "autism as a culture, transcultural comparisons… and research on social movements."[187] Media has had an influence on how the public perceives those with autism. *Rain Man*, a film that won 4 Oscars including Best Picture, depicts a character with autism who has incredible talents and abilities.[188] While many autistics don't have these special abilities, there are some autistic individuals who have been successful in their fields.[189][190][191]



The rainbow-colored infinity is often used as a symbol for the diversity of the autism spectrum as well as neurodiversity in general.

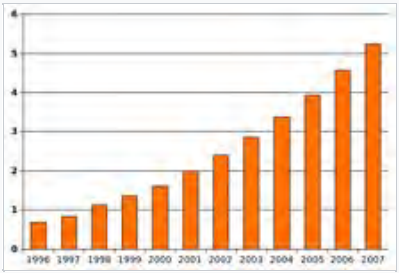
## Prognosis

There is no known cure.[1][7] Children recover occasionally, so that they lose their diagnosis of ASD;[9] this occurs sometimes after intensive treatment and sometimes not. It is not known how often recovery happens;[149] reported rates in unselected samples of children with ASD have ranged from 3% to 25%.[9] Most children with autism acquire language by age five or younger, though a few have developed communication skills in later years.[192] Most children with autism lack social support, meaningful relationships, future employment opportunities or self-determination.[31] Although core difficulties tend to persist, symptoms often become less severe with age.[22]

Few high-quality studies address long-term prognosis. Some adults show modest improvement in communication skills, but a few decline; no study has focused on autism after midlife.[193] Acquiring language before age six, having an IQ above 50, and having a marketable skill all predict better outcomes; independent living is unlikely with severe autism.[194] Most people with autism face significant obstacles in transitioning to adulthood.[195]

## Epidemiology

*Main article: Epidemiology of autism*




Reports of autism cases per 1,000 children grew dramatically in the US from 1996 to 2007. It is unknown how much, if any, growth came from changes in rates of autism.

Most recent reviews tend to estimate a prevalence of 1–2 per 1,000 for autism and close to 6 per 1,000 for ASD,[17] and 11 per 1,000 children in the United States for ASD as of 2008;[14][143] because of inadequate data, these numbers may underestimate ASD's true rate.[118] Globally, autism affects an estimated 21.7 million people as of 2013, while Asperger syndrome affects a further 31.1 million.[12] In 2012, the NHS estimated that the overall prevalence of autism among adults aged 18 years and over in the UK was 1.1%.[16] Rates of PDD-NOS's has been estimated at 3.7 per 1,000, Asperger syndrome at roughly 0.6 per 1,000, and childhood disintegrative disorder at 0.02 per 1,000.[196] CDC's most recent estimate is that 1 out of every 68 children, or 14.7 per 1,000, has an ASD as of 2010.[197]

The number of reported cases of autism increased dramatically in the 1990s and early 2000s. This increase is largely attributable to changes in diagnostic practices, referral patterns, availability of services, age at diagnosis, and public awareness,[196][198] though unidentified environmental risk factors cannot be ruled out.[6] The available evidence does not rule out the possibility that autism's true prevalence has increased;[196] a real increase would suggest directing more attention and funding toward changing environmental factors instead of continuing to focus on genetics.[199]

Boys are at higher risk for ASD than girls. The sex ratio averages 4.3:1 and is greatly modified by cognitive impairment: it may be close to 2:1 with intellectual disability and more than 5.5:1 without.[17] Several theories

about the higher prevalence in males have been investigated, but the cause of the difference is unconfirmed;[83] one theory is that females are underdiagnosed.[200]

Although the evidence does not implicate any single pregnancy-related risk factor as a cause of autism, the risk of autism is associated with advanced age in either parent, and with diabetes, bleeding, and use of psychiatric drugs in the mother during pregnancy.[83][201] The risk is greater with older fathers than with older mothers; two potential explanations are the known increase in mutation burden in older sperm, and the hypothesis that men marry later if they carry genetic liability and show some signs of autism.[42] Most professionals believe that race, ethnicity, and socioeconomic background do not affect the occurrence of autism.[202]

Several other conditions are common in children with autism.[7] They include:

- **Genetic disorders**. About 10–15% of autism cases have an identifiable Mendelian (single-gene) condition, chromosome abnormality, or other genetic syndrome,[203] and ASD is associated with several genetic disorders.[204]
- **Intellectual disability**. The percentage of autistic individuals who also meet criteria for intellectual disability has been reported as anywhere from 25% to 70%, a wide variation illustrating the difficulty of assessing autistic intelligence.[205] In comparison, for PDD-NOS the association with intellectual disability is much weaker,[206] and by definition, the diagnosis of Asperger's excludes intellectual disability.[207]
- **Anxiety disorders** are common among children with ASD; there are no firm data, but studies have reported prevalences ranging from 11% to 84%. Many anxiety disorders have symptoms that are better explained by ASD itself, or are hard to distinguish from ASD's symptoms.[208]
- **Epilepsy**, with variations in risk of epilepsy due to age, cognitive level, and type of language disorder.[209]
- Several **metabolic defects**, such as phenylketonuria, are associated with autistic symptoms.[89]
- **Minor physical anomalies** are significantly increased in the autistic population.[210]
- **Preempted diagnoses**. Although the DSM-IV rules out concurrent diagnosis of many other conditions along with autism, the full criteria for Attention deficit hyperactivity disorder (ADHD), Tourette syndrome, and other of these conditions are often present and these comorbid diagnoses are increasingly accepted.[211]
- **Sleep problems** affect about two-thirds of individuals with ASD at some point in childhood. These most commonly include symptoms of insomnia such as difficulty in falling asleep, frequent nocturnal awakenings, and early morning awakenings. Sleep problems are associated with difficult behaviors and family stress, and are often a focus of clinical attention over and above the primary ASD diagnosis.[212]

## History

*Further information: History of Asperger syndrome*

A few examples of autistic symptoms and treatments were described long before autism was named. The *Table Talk* of Martin Luther, compiled by his notetaker, Mathesius, contains the story of a 12-year-old boy who may have been severely autistic.[213] Luther reportedly thought the boy was a soulless mass of flesh possessed by the devil, and suggested that he be suffocated, although a later critic has cast doubt on the veracity of this report.[214] The earliest well-documented case of autism is that of Hugh Blair of Borgue, as detailed in a 1747 court case in which his brother successfully petitioned to annul Blair's marriage to gain Blair's inheritance.[215] The Wild Boy of Aveyron, a feral child caught in 1798, showed several signs of autism; the medical student Jean Itard treated him with a behavioral program designed to help him form social attachments and to induce speech via imitation.[216]

Leo Kanner introduced the label *early infantile autism* in 1943.

The New Latin word *autismus* (English translation *autism*) was coined by the Swiss psychiatrist Eugen Bleuler in 1910 as he was defining symptoms of schizophrenia. He derived it from the Greek word *autós* (αὐτός, meaning "self"), and used it to mean morbid self-admiration, referring to "autistic withdrawal of the patient to his fantasies, against which any influence from outside becomes an intolerable disturbance".[217]

The word *autism* first took its modern sense in 1938 when Hans Asperger of the Vienna University Hospital adopted Bleuler's terminology *autistic psychopaths* in a lecture in German about child psychology.[218] Asperger was investigating an ASD now known as Asperger syndrome, though for various reasons it was not widely recognized as a separate diagnosis until 1981.[216] Leo Kanner of the Johns Hopkins Hospital first used *autism* in its modern sense in English when he introduced the label *early infantile autism* in a 1943 report of 11 children with striking behavioral similarities.[36] Almost all the characteristics described in Kanner's first paper on the subject, notably "autistic aloneness" and

"insistence on sameness", are still regarded as typical of the autistic spectrum of disorders.[51] It is not known whether Kanner derived the term independently of Asperger.[219]

Kanner's reuse of *autism* led to decades of confused terminology like *infantile schizophrenia*, and child psychiatry's focus on maternal deprivation led to misconceptions of autism as an infant's response to "refrigerator mothers". Starting in the late 1960s autism was established as a separate syndrome by demonstrating that it is lifelong, distinguishing it from intellectual disability and schizophrenia and from other developmental disorders, and demonstrating the benefits of involving parents in active programs of therapy.[220] As late as the mid-1970s there was little evidence of a genetic role in autism; now it is thought to be one of the most heritable of all psychiatric conditions.[221] Although the rise of parent organizations and the destigmatization of childhood ASD have deeply affected how we view ASD,[216] parents continue to feel social stigma in situations where their child's autistic behavior is perceived negatively by others,[222] and many primary care physicians and medical specialists still express some beliefs consistent with outdated autism research.[223]

The Internet has helped autistic individuals bypass nonverbal cues and emotional sharing that they find so hard to deal with, and has given them a way to form online communities and work remotely.[224] Sociological and cultural aspects of autism have developed: some in the community seek a cure, while others believe that autism is simply another way of being.[11][225]

# References


1. ^ *a b c d e f g h* Myers SM, Johnson CP (2007). "Management of children with autism spectrum disorders". *Pediatrics*. **120** (5): 1162–82. doi:10.1542/peds.2007-2362. PMID 17967921.
2. ^ *a b* Stefanatos GA (2008). "Regression in autistic spectrum disorders". *Neuropsychol Rev*. **18** (4): 305–19. doi:10.1007/s11065-008-9073-y. PMID 18956241.
3. ^ *a b c* Autism Spectrum Disorder, 299.00 (F84.0). In: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. American Psychiatric Publishing; 2013.
4. ^ Chaste P, Leboyer M (2012). "Autism risk factors: genes, environment, and gene-environment interactions". *Dialogues in Clinical Neuroscience*. **14**: 281–92. PMC 3513682. PMID 23226953.
5. ^ Ornoy A, Weinstein-Fudim L, Ergaz Z (2015), "Prenatal factors associated with autism spectrum disorder (ASD)", *Reproductive Toxicology*, **56**: 155–169, doi:10.1016/j.reprotox.2015.05.007, PMID 26021712
6. ^ *a b* Rutter M (2005). "Incidence of autism spectrum disorders: changes over time and their meaning". *Acta Paediatr*. **94** (1): 2–15. doi:10.1111/j.1651-2227.2005.tb01779.x. PMID 15858952.
7. ^ *a b c d e f g h* Levy SE, Mandell DS, Schultz RT (2009). "Autism". *Lancet*. **374** (9701): 1627–38. doi:10.1016/S0140-6736(09)61376-3. PMC 2863325. PMID 19819542.
8. ^ *a b c d* Johnson CP, Myers SM (2007). "Identification and evaluation of children with autism spectrum disorders". *Pediatrics*. **120** (5): 1183–215. doi:10.1542/peds.2007-2361. PMID 17967920. Archived from the original on 8 February 2009.
9. ^ *a b c* Helt M, Kelley E, Kinsbourne M, Pandey J, Boorstein H, Herbert M, Fein D (2008). "Can children with autism recover? if so, how?". *Neuropsychol Rev*. **18** (4): 339–66. doi:10.1007/s11065-008-9075-9. PMID 19009353.
10. ^ Howlin P, Goode S, Hutton J, Rutter M (2004). "Adult outcome for children with autism". *J Child Psychol Psychiatry*. **45** (2): 212–29. doi:10.1111/j.1469-7610.2004.00215.x. PMID 14982237.
11. ^ *a b* Silverman C (2008). "Fieldwork on another planet: social science perspectives on the autism spectrum". *Biosocieties*. **3** (3): 325–41. doi:10.1017/S1745855208006236.
12. ^ *a b* Global Burden of Disease Study 2013 Collaborators (2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **386**: 743–800. doi:10.1016/S0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
13. ^ "ASD Data and Statistics". *CDC.gov*. Archived from the original on 18 April 2014. Retrieved 5 April 2014.
14. ^ *a b* "Prevalence of autism spectrum disorders — autism and developmental disabilities monitoring network, 14 sites, United States, 2008". *MMWR Surveill Summ*. **61** (3): 1–19. 2012. PMID 22456193. Archived from the original on 25 March 2014.
15. ^ *a b* Blumberg SJ, Bramlett MD, Kogan MD, Schieve LA, Jones JR, Lu MC (2013). "Changes in prevalence of parent-reported autism spectrum disorder in school-aged U.S. children: 2007 to 2011–2012" (PDF). *Natl Health Stat Report* (65): 1–11. PMID 24988818. Archived (PDF) from the original on 21 September 2013.
16. ^ *a b* Brugha T, Cooper SA, McManus S, et al. (31 January 2012). "Estimating the prevalence of autism spectrum conditions in adults: extending the 2007 Adult Psychiatric Morbidity Survey" (PDF). *The Information Centre for Health and Social Care*. National Health Service, UK. Retrieved 29 December 2014.
17. ^ *a b c d* Newschaffer CJ, Croen LA, Daniels J, Giarelli E, Grether JK, Levy SE, Mandell DS, Miller LA, Pinto-Martin J, Reaven J, Reynolds AM, Rice CE, Schendel D, Windham GC (2007). "The epidemiology of autism spectrum disorders" (PDF). *Annu Rev Public Health*. **28**: 235–58. doi:10.1146/annurev.publhealth.28.021406.144007. PMID 17367287. Archived from the

original (PDF) on 3 September 2013.
18. ^ a b Geschwind DH (2008). "Autism: many genes, common pathways?". *Cell*. **135** (3): 391–5. doi:10.1016/j.cell.2008.10.016. PMC 2756410. PMID 18984147.
19. ^ a b c "F84. Pervasive developmental disorders". *ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision*. World Health Organization. 2007. Archived from the original on 21 April 2013. Retrieved 10 October 2009.
20. ^ Pinel JPG. *Biopsychology*. Boston, Massachusetts: Pearson; 2011. ISBN 978-0-205-03099-6. p. 235.
21. ^ Rogers SJ (2009). "What are infant siblings teaching us about autism in infancy?". *Autism Res*. **2** (3): 125–37. doi:10.1002/aur.81. PMC 2791538. PMID 19582867.
22. ^ a b c d e f Rapin I, Tuchman RF (2008). "Autism: definition, neurobiology, screening, diagnosis". *Pediatr Clin North Am*. **55** (5): 1129–46. doi:10.1016/j.pcl.2008.07.005. PMID 18929056.
23. ^ a b c Filipek PA, Accardo PJ, Baranek GT, Cook EH, Dawson G, Gordon B, Gravel JS, Johnson CP, Kallen RJ, Levy SE, Minshew NJ, Ozonoff S, Prizant BM, Rapin I, Rogers SJ, Stone WL, Teplin S, Tuchman RF, Volkmar FR (1999). "The screening and diagnosis of autistic spectrum disorders". *J Autism Dev Disord*. **29** (6): 439–84. doi:10.1023/A:1021943802493. PMID 10638459. This paper represents a consensus of representatives from nine professional and four parent organizations in the US.
24. ^ a b c London E (2007). "The role of the neurobiologist in redefining the diagnosis of autism". *Brain Pathol*. **17** (4): 408–11. doi:10.1111/j.1750-3639.2007.00103.x. PMID 17919126.
25. ^ Sacks O. *An Anthropologist on Mars: Seven Paradoxical Tales*. Knopf; 1995. ISBN 978-0-679-43785-7.
26. ^ a b c d *Handbook of Autism and Pervasive Developmental Disorders, Assessment, Interventions, and Policy*. John Wiley & Sons; 2014 [Retrieved 24 December 2014]. ISBN 1-118-28220-5. p. 301.
27. ^ Sigman M, Dijamco A, Gratier M, Rozga A (2004). "Early detection of core deficits in autism". *Ment Retard Dev Disabil Res Rev*. **10** (4): 221–33. CiteSeerX 10.1.1.492.9930. doi:10.1002/mrdd.20046. PMID 15666338.
28. ^ Rutgers AH, Bakermans-Kranenburg MJ, van Ijzendoorn MH, van Berckelaer-Onnes IA (2004). "Autism and attachment: a meta-analytic review". *J Child Psychol Psychiatry*. **45** (6): 1123–34. doi:10.1111/j.1469-7610.2004.t01-1-00305.x. PMID 15257669.
29. ^ a b c Sigman M, Spence SJ, Wang AT (2006). "Autism from developmental and neuropsychological perspectives". *Annu Rev Clin Psychol*. **2**: 327–55. doi:10.1146/annurev.clinpsy.2.022305.095210. PMID 17716073.
30. ^ Bird, G.; Cook, R. (2013-07-23). "Mixed emotions: the contribution of alexithymia to the emotional symptoms of autism". *Translational Psychiatry*. **3** (7): e285. doi:10.1038/tp.2013.61. PMC 3731793. PMID 23880881.
31. ^ a b c Burgess AF, Gutstein SE (2007). "Quality of life for people with autism: raising the standard for evaluating successful outcomes" (PDF). *Child Adolesc Ment Health*. **12** (2): 80–6. doi:10.1111/j.1475-3588.2006.00432.x. Archived (PDF) from the original on 21 December 2013.
32. ^ Matson JL, Nebel-Schwalm M (November 2007). "Assessing challenging behaviors in children with autism spectrum disorders: A review". *Research in Developmental Disabilities*. **28** (6): 567–79. doi:10.1016/j.ridd.2006.08.001. PMID 16973329.
33. ^ Noens I, van Berckelaer-Onnes I, Verpoorten R, van Duijn G (2006). "The ComFor: an instrument for the indication of augmentative communication in people with autism and intellectual disability". *J Intellect Disabil Res*. **50** (9): 621–32. doi:10.1111/j.1365-2788.2006.00807.x. PMID 16901289.
34. ^ a b c Landa R (2007). "Early communication development and intervention for children with autism". *Ment Retard Dev Disabil Res Rev*. **13** (1): 16–25. doi:10.1002/mrdd.20134. PMID 17326115.
35. ^ a b c Tager-Flusberg H, Caronna E (2007). "Language disorders: autism and other pervasive developmental disorders". *Pediatr Clin North Am*. **54** (3): 469–81. doi:10.1016/j.pcl.2007.02.011. PMID 17543905.
36. ^ a b Kanner L (1943). "Autistic disturbances of affective contact". *Nerv Child*. **2**: 217–50. Reprinted in Kanner L (1968). "Autistic disturbances of affective contact". *Acta Paedopsychiatr*. **35** (4): 100–36. PMID 4880460.
37. ^ a b Williams DL, Goldstein G, Minshew NJ (2006). "Neuropsychologic functioning in children with autism: further evidence for disordered complex information-processing". *Child Neuropsychol*. **12** (4–5): 279–98. doi:10.1080/09297040600681190. PMC 1803025. PMID 16911973.
38. ^ a b Lam KS, Aman MG (2007). "The Repetitive Behavior Scale-Revised: independent validation in individuals with autism spectrum disorders". *J Autism Dev Disord*. **37** (5): 855–66. doi:10.1007/s10803-006-0213-z. PMID 17048092.
39. ^ Bodfish JW, Symons FJ, Parker DE, Lewis MH (2000). "Varieties of repetitive behavior in autism: comparisons to mental retardation". *J Autism Dev Disord*. **30** (3): 237–43. doi:10.1023/A:1005596502855. PMID 11055459.
40. ^ Treffert DA (2009). "The savant syndrome: an extraordinary condition. A synopsis: past, present, future". *Philosophical Transactions of the Royal Society B*. **364** (1522): 1351–7. doi:10.1098/rstb.2008.0326. PMC 2677584. PMID 19528017. Lay summary – *Wisconsin Medical Society*.
41. ^ Plaisted Grant K, Davis G (2009). "Perception and apperception in autism: rejecting the inverse assumption". *Philosophical Transactions of the Royal Society B*. **364** (1522): 1393–8. doi:10.1098/rstb.2009.0001. PMC 2677593. PMID 19528022.
42. ^ a b c d e f Geschwind DH (2009). "Advances in autism". *Annu Rev Med*. **60**: 367–80. doi:10.1146/annurev.med.60.053107.121225. PMC 3645857. PMID 19630577.
43. ^ Rogers SJ, Ozonoff S (2005). "Annotation: what do we know about sensory dysfunction in autism? A critical review of the empirical evidence". *J Child Psychol Psychiatry*. **46** (12): 1255–68. doi:10.1111/j.1469-7610.2005.01431.x. PMID 16313426.

44. ^ Ben-Sasson A, Hen L, Fluss R, Cermak SA, Engel-Yeger B, Gal E (2009). "A meta-analysis of sensory modulation symptoms in individuals with autism spectrum disorders". *J Autism Dev Disord*. **39** (1): 1–11. doi:10.1007/s10803-008-0593-3. PMID 18512135.
45. ^ Fournier KA, Hass CJ, Naik SK, Lodha N, Cauraugh JH (2010). "Motor coordination in autism spectrum disorders: a synthesis and meta-analysis". *J Autism Dev Disord*. **40**: 1227–40. doi:10.1007/s10803-010-0981-3. PMID 20195737.
46. ^ Dominick KC, Davis NO, Lainhart J, Tager-Flusberg H, Folstein S (2007). "Atypical behaviors in children with autism and children with a history of language impairment". *Res Dev Disabil*. **28** (2): 145–62. doi:10.1016/j.ridd.2006.02.003. PMID 16581226.
47. ^ Erickson CA, Stigler KA, Corkins MR, Posey DJ, Fitzgerald JF, McDougle CJ (2005). "Gastrointestinal factors in autistic disorder: a critical review". *J Autism Dev Disord*. **35** (6): 713–27. doi:10.1007/s10803-005-0019-4. PMID 16267642.
48. ^ Buie T, Campbell DB, Fuchs GJ, Furuta GT, Levy J, Vandewater J, Whitaker AH, Atkins D, Bauman ML, Beaudet AL, Carr EG, Gershon MD, Hyman SL, Jirapinyo P, Jyonouchi H, Kooros K, Kushak R, Levitt P, Levy SE, Lewis JD, Murray KF, Natowicz MR, Sabra A, Wershil BK, Weston SC, Zeltzer L, Winter H (2010). "Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report". *Pediatrics*. **125** (Suppl 1): S1–18. doi:10.1542/peds.2009-1878C. PMID 20048083. Archived from the original on 6 July 2010.
49. ^ Orsmond GI, Seltzer MM (2007). "Siblings of individuals with autism spectrum disorders across the life course" (PDF). *Ment Retard Dev Disabil Res Rev*. **13** (4): 313–20. doi:10.1002/mrdd.20171. PMID 17979200. Archived from the original (PDF) on 30 May 2013.
50. ^ [a] [b] Happé F, Ronald A (2008). "The 'fractionable autism triad': a review of evidence from behavioural, genetic, cognitive and neural research". *Neuropsychol Rev*. **18** (4): 287–304. doi:10.1007/s11065-008-9076-8. PMID 18956240.
51. ^ [a] [b] [c] Happé F, Ronald A, Plomin R (2006). "Time to give up on a single explanation for autism". *Nature Neuroscience*. **9** (10): 1218–20. doi:10.1038/nn1770. PMID 17001340.
52. ^ [a] [b] Beaudet AL (2007). "Autism: highly heritable but not inherited". *Nat Med*. **13** (5): 534–6. doi:10.1038/nm0507-534. PMID 17479094.
53. ^ [a] [b] [c] Abrahams BS, Geschwind DH (2008). "Advances in autism genetics: on the threshold of a new neurobiology". *Nature Reviews Genetics*. **9** (5): 341–55. doi:10.1038/nrg2346. PMC 2756414. PMID 18414403.
54. ^ Buxbaum JD (2009). "Multiple rare variants in the etiology of autism spectrum disorders". *Dialogues Clin Neurosci*. **11** (1): 35–43. PMC 3181906. PMID 19432386.
55. ^ Sanders, Stephan J.; He, Xin; Willsey, A. Jeremy; Ercan-Sencicek, A. Gulhan; Samocha, Kaitlin E.; Cicek, A. Ercument; Murtha, Michael T.; Bal, Vanessa H.; Bishop, Somer L.; Dong, Shan; Goldberg, Arthur P.; Jinlu, Cai; Keaney, John F.; Klei, Lambertus; Mandell, Jeffrey D.; Moreno-De-Luca, Daniel; Poultney, Christopher S.; Robinson, Elise B.; Smith, Louw; Solli-Nowlan, Tor; Su, Mack Y.; Teran, Nicole A.; Walker, Michael F.; Werling, Donna M.; Beaudet, Arthur L.; Cantor, Rita M.; Fombonne, Eric; Geschwind, Daniel H.; Grice, Dorothy E.; Lord, Catherine; Lowe, Jennifer K.; Mane, Shrikant M.; Martin, Donna M.; Morrow, Eric M.; Talkowski, Michael E.; Sutcliffe, James S.; Walsh, Christopher A.; Yu, Timothy W.; Ledbetter, David H.; Martin, Christa Lese; Cook, Edwin H.; Buxbaum, Joseph D.; Daly, Mark J.; Devlin, Bernie; Roeder, Kathryn; State, Matthew W. (September 2015). "Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci". *Neuron*. **87** (6): 1215–1233. doi:10.1016/j.neuron.2015.09.016. PMC 4624267. PMID 26402605.
56. ^ Persico, Antonio M.; Napolioni, Valerio (August 2013). "Autism genetics". *Behavioural Brain Research*. **251**: 95–112. doi:10.1016/j.bbr.2013.06.012.
57. ^ Cook EH, Scherer SW (2008). "Copy-number variations associated with neuropsychiatric conditions". *Nature*. **455** (7215): 919–23. doi:10.1038/nature07458. PMID 18923514.
58. ^ Brandler, William M.; Antaki, Danny; Gujral, Madhusudan; Noor, Amina; Rosanio, Gabriel; Chapman, Timothy R.; Barrera, Daniel J.; Lin, Guan Ning; Malhotra, Dheeraj; Watts, Amanda C.; Wong, Lawrence C.; Estabillo, Jasper A.; Gadomski, Therese E.; Hong, Oanh; Fajardo, Karin V. Fuentes; Bhandari, Abhishek; Owen, Renius; Baughn, Michael; Yuan, Jeffrey; Solomon, Terry; Moyzis, Alexandra G.; Maile, Michelle S.; Sanders, Stephan J.; Reiner, Gail E.; Vaux, Keith K.; Strom, Charles M.; Zhang, Kang; Muotri, Alysson R.; Akshoomoff, Natacha; Leal, Suzanne M.; Pierce, Karen; Courchesne, Eric; Iakoucheva, Lilia M.; Corsello, Christina; Sebat, Jonathan (March 2016). "Frequency and Complexity of De Novo Structural Mutation in Autism". *The American Journal of Human Genetics*. **98** (4): 1–13. doi:10.1016/j.ajhg.2016.02.018.
59. ^ [a] [b] Betancur C, Sakurai T, Buxbaum JD (2009). "The emerging role of synaptic cell-adhesion pathways in the pathogenesis of autism spectrum disorders". *Trends Neurosci*. **32** (7): 402–12. doi:10.1016/j.tins.2009.04.003. PMID 19541375.
60. ^ [a] [b] Walsh CA, Morrow EM, Rubenstein JL (2008). "Autism and brain development". *Cell*. **135** (3): 396–400. doi:10.1016/j.cell.2008.10.015. PMC 2701104. PMID 18984148.
61. ^ [a] [b] Arndt TL, Stodgell CJ, Rodier PM (2005). "The teratology of autism". *Int J Dev Neurosci*. **23** (2–3): 189–99. doi:10.1016/j.ijdevneu.2004.11.001. PMID 15749245.
62. ^ Lyall K, Schmidt RJ, Hertz-Picciotto I (April 2014). "Maternal lifestyle and environmental risk factors for autism spectrum disorders". *Int J Epidemiol*. **43** (2): 443–64. doi:10.1093/ije/dyt282. PMID 24518932.
63. ^ Kinney DK, Munir KM, Crowley DJ, Miller AM (2008). "Prenatal stress and risk for autism". *Neurosci Biobehav Rev*. **32** (8): 1519–32. doi:10.1016/j.neubiorev.2008.06.004. PMC 2632594. PMID 18598714.
64. ^ [a] [b] Gerber JS, Offit PA (2009). "Vaccines and autism: a tale of shifting hypotheses". *Clin Infect Dis*. **48** (4): 456–61. doi:10.1086/596476. PMC 2908388. PMID 19128068. Archived from the original on 31 October 2013.
65. ^ Godlee F, Smith J, Marcovitch H (2011). "Wakefield's article linking MMR vaccine and autism was fraudulent". *BMJ*. **342**: c7452. doi:10.1136/bmj.c7452. PMID 21209060. Archived from the original on 11 November 2013.
66. ^ Vaccines and autism:
    - Doja A, Roberts W (2006). "Immunizations and autism: a review of the literature". *Can J Neurol Sci*. **33** (4): 341–6.

doi:10.1017/s031716710000528x. PMID 17168158.
- Gerber JS, Offit PA (2009). "Vaccines and autism: a tale of shifting hypotheses". *Clin Infect Dis*. **48** (4): 456–61. doi:10.1086/596476. PMC 2908388. PMID 19128068. Archived from the original on 31 October 2013.
- Gross L (2009). "A broken trust: lessons from the vaccine–autism wars". *PLoS Biol*. **7** (5): e1000114. doi:10.1371/journal.pbio.1000114. PMC 2682483. PMID 19478850.
- Paul R (2009). "Parents ask: am I risking autism if I vaccinate my children?". *J Autism Dev Disord*. **39** (6): 962–3. doi:10.1007/s10803-009-0739-y. PMID 19363650.
- Poland GA, Jacobson RM (13 January 2011). "The Age-Old Struggle against the Antivaccinationists". *N Engl J Med*. **364**: 97–9. doi:10.1056/NEJMp1010594. PMID 21226573. Archived from the original on 23 April 2014.

67. ^ McBrien J, Murphy J, Gill D, Cronin M, O'Donovan C, Cafferkey MT (2003). "Measles outbreak in Dublin, 2000". *Pediatr. Infect. Dis. J.* **22** (7): 580–4. doi:10.1097/00006454-200307000-00002. PMID 12867830.
68. ^ Penn HE (2006). "Neurobiological correlates of autism: a review of recent research". *Child Neuropsychol*. **12** (1): 57–79. doi:10.1080/09297040500253546. PMID 16484102.
69. ^ [a] [b] Amaral DG, Schumann CM, Nordahl CW (2008). "Neuroanatomy of autism". *Trends Neurosci*. **31** (3): 137–45. doi:10.1016/j.tins.2007.12.005. PMID 18258309.
70. ^ Müller RA (2007). "The study of autism as a distributed disorder". *Ment Retard Dev Disabil Res Rev*. **13** (1): 85–95. doi:10.1002/mrdd.20141. PMC 3315379. PMID 17326118.
71. ^ Casanova MF (2007). "The neuropathology of autism". *Brain Pathol*. **17** (4): 422–33. doi:10.1111/j.1750-3639.2007.00100.x. PMID 17919128.
72. ^ Courchesne E, Pierce K, Schumann CM, Redcay E, Buckwalter JA, Kennedy DP, Morgan J (2007). "Mapping early brain development in autism". *Neuron*. **56** (2): 399–413. doi:10.1016/j.neuron.2007.10.016. PMID 17964254.
73. ^ Schmitz C, Rezaie P (2008). "The neuropathology of autism: where do we stand?". *Neuropathol Appl Neurobiol*. **34** (1): 4–11. doi:10.1111/j.1365-2990.2007.00872.x. PMID 17971078.
74. ^ [a] [b] [c] Persico AM, Bourgeron T (2006). "Searching for ways out of the autism maze: genetic, epigenetic and environmental clues". *Trends Neurosci*. **29** (7): 349–58. doi:10.1016/j.tins.2006.05.010. PMID 16808981.
75. ^ Südhof TC (2008). "Neuroligins and neurexins link synaptic function to cognitive disease". *Nature*. **455** (7215): 903–11. doi:10.1038/nature07456. PMC 2673233. PMID 18923512.
76. ^ Kelleher RJ, Bear MF (2008). "The autistic neuron: troubled translation?". *Cell*. **135** (3): 401–6. doi:10.1016/j.cell.2008.10.017. PMID 18984149.
77. ^ Bear MF, Dölen G, Osterweil E, Nagarajan N (2008). "Fragile X: translation in action.". *Neuropsychopharmacology*. **33** (1): 84–7. doi:10.1038/sj.npp.1301610. PMID 17940551.
78. ^ Tuchman R, Moshé SL, Rapin I (2009). "Convulsing toward the pathophysiology of autism". *Brain Dev*. **31** (2): 95–103. doi:10.1016/j.braindev.2008.09.009. PMC 2734903. PMID 19006654.
79. ^ Hsiao EY (2013). "Immune dysregulation in autism spectrum disorder.". *International Review of Neurobiology*. **113**: 269–302. doi:10.1016/B978-0-12-418700-9.00009-5. PMID 24290389.
80. ^ [a] [b] Onore C, Careaga M, Ashwood P (August 2011). "The role of immune dysfunction in the pathophysiology of autism". *Brain, Behavior and Immunity*. **26** (3): 383–92. doi:10.1016/j.bbi.2011.08.007. PMID 21906670.
81. ^ Rossignol DA, Frye RE (2014). "Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism.". *Frontiers in Physiology*. **5**: 150. doi:10.3389/fphys.2014.00150. PMID 24795645.
82. ^ Patterson PH (July 2011). "Maternal infection and immune involvement in autism.". *Trends in Molecular Medicine*. **17** (7): 389–94. doi:10.1016/j.molmed.2011.03.001. PMID 21482187.
83. ^ [a] [b] [c] Chaste P, Leboyer M (2012). "Autism risk factors: genes, environment, and gene-environment interactions". *Dialogues Clin Neurosci*. **14** (3): 281–92. PMC 3513682. PMID 23226953.
84. ^ Ashwood P, Wills S, Van de Water J (2006). "The immune response in autism: a new frontier for autism research". *J Leukoc Biol*. **80** (1): 1–15. CiteSeerX 10.1.1.329.777. doi:10.1189/jlb.1205707. PMID 16698940.
85. ^ Lee BK, Magnusson C, Gardner RM, Blomström S, Newschaffer CJ, Burstyn I, Karlsson H, Dalman C (September 2014). "Maternal hospitalization with infection during pregnancy and risk of autism spectrum disorders.". *Brain, Behavior and Immunity*. **44**: 100–105. doi:10.1016/j.bbi.2014.09.001. PMID 25218900.
86. ^ Atladóttir HO, Thorsen P, Østergaard L, Schendel DE, Lemcke S, Abdallah M, Parner ET (December 2010). "Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders.". *Journal of Autism and Developmental Disorders*. **40** (12): 1423–30. doi:10.1007/s10803-010-1006-y. PMID 20414802.
87. ^ [a] [b] Dölen G, Osterweil E, Rao BS, Smith GB, Auerbach BD, Chattarji S, Bear MF (2007). "Correction of fragile X syndrome in mice". *Neuron*. **56** (6): 955–62. doi:10.1016/j.neuron.2007.12.001. PMC 2199268. PMID 18093519.
88. ^ Hughes JR (2009). "Update on autism: A review of 1300 reports published in 2008". *Epilepsy Behav*. **16** (4): 569–589. doi:10.1016/j.yebeh.2009.09.023. PMID 19896907.
89. ^ [a] [b] Manzi B, Loizzo AL, Giana G, Curatolo P (2008). "Autism and metabolic diseases". *J Child Neurol*. **23** (3): 307–14. doi:10.1177/0883073807308698. PMID 18079313.
90. ^ MNS and autism:
    - Williams JH (2008). "Self–other relations in social development and autism: multiple roles for mirror neurons and other brain bases". *Autism Res*. **1** (2): 73–90. doi:10.1002/aur.15. PMID 19360654.
    - Dinstein I, Thomas C, Behrmann M, Heeger DJ (2008). "A mirror up to nature". *Curr Biol*. **18** (1): R13–8. doi:10.1016/j.cub.2007.11.004. PMC 2517574. PMID 18177704.
91. ^ [a] [b] Iacoboni M, Dapretto M (2006). "The mirror neuron system and the consequences of its dysfunction". *Nature Reviews Neuroscience*. **7** (12): 942–51. doi:10.1038/nrn2024. PMID 17115076.

92. ^ Frith U, Frith CD (2003). "Development and neurophysiology of mentalizing" (PDF). *Philosophical Transactions of the Royal Society B*. **358** (1431): 459–73. doi:10.1098/rstb.2002.1218. PMC 1693139. PMID 12689373.
93. ^ Hamilton AF (2008). "Emulation and mimicry for social interaction: a theoretical approach to imitation in autism". *Q J Exp Psychol*. **61** (1): 101–15. doi:10.1080/17470210701508798. PMID 18038342.
94. ^ [a] [b] Powell K (2004). "Opening a window to the autistic brain". *PLoS Biol*. **2** (8): E267. doi:10.1371/journal.pbio.0020267. PMC 509312. PMID 15314667. Archived from the original on 26 May 2013.
95. ^ Di Martino A, Ross K, Uddin LQ, Sklar AB, Castellanos FX, Milham MP (2009). "Functional brain correlates of social and nonsocial processes in autism spectrum disorders: an activation likelihood estimation meta-analysis". *Biol Psychiatry*. **65** (1): 63–74. doi:10.1016/j.biopsych.2008.09.022. PMC 2993772. PMID 18996505.
96. ^ Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ (2009). "Default-mode brain dysfunction in mental disorders: a systematic review". *Neurosci Biobehav Rev*. **33** (3): 279–96. doi:10.1016/j.neubiorev.2008.09.002. PMID 18824195.
97. ^ Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ (2007). "Functional and anatomical cortical underconnectivity in autism: evidence from an FMRI study of an executive function task and corpus callosum morphometry". *Cereb Cortex*. **17** (4): 951–61. doi:10.1093/cercor/bhl006. PMC 4500121. PMID 16772313. Archived from the original on 7 July 2010.
98. ^ Murias M, Webb SJ, Greenson J, Dawson G (2007). "Resting state cortical connectivity reflected in EEG coherence in individuals with autism". *Biol Psychiatry*. **62** (3): 270–3. doi:10.1016/j.biopsych.2006.11.012. PMC 2001237. PMID 17336944.
99. ^ Minshew NJ, Williams DL (2007). "The new neurobiology of autism: cortex, connectivity, and neuronal organization". *Arch Neurol*. **64** (7): 945–50. doi:10.1001/archneur.64.7.945. PMC 2597785. PMID 17620483.
100. ^ Jeste SS, Nelson CA (2009). "Event related potentials in the understanding of autism spectrum disorders: an analytical review". *J Autism Dev Disord*. **39** (3): 495–510. doi:10.1007/s10803-008-0652-9. PMID 18850262.
101. ^ Roberts TP, Schmidt GL, Egeth M, Blaskey L, Rey MM, Edgar JC, Levy SE (2008). "Electrophysiological signatures: magnetoencephalographic studies of the neural correlates of language impairment in autism spectrum disorders". *Int J Psychophysiol*. **68** (2): 149–60. doi:10.1016/j.ijpsycho.2008.01.012. PMC 2397446. PMID 18336941.
102. ^ Crespi B, Stead P, Elliot M (2010). "Evolution in health and medicine Sackler colloquium: Comparative genomics of autism and schizophrenia". *Proceedings of the National Academy of Sciences of the United States of America*. **107** (Suppl 1): 1736–41. doi:10.1073/pnas.0906080106. PMC 2868282. PMID 19955444.
103. ^ Ha S, Sohn IJ, Kim N, Sim HJ, Cheon KA (Dec 2015). "Characteristics of Brains in Autism Spectrum Disorder: Structure, Function and Connectivity across the Lifespan". *Exp Neurobiol* (Review). **24** (4): 273–84. doi:10.5607/en.2015.24.4.273. PMC 4688328. PMID 26713076.
104. ^ [a] [b] Baron-Cohen S (2009). "Autism: the empathizing–systemizing (E-S) theory" (PDF). *Annals of the New York Academy of Sciences*. **1156**: 68–80. doi:10.1111/j.1749-6632.2009.04467.x. PMID 19338503. Archived from the original (PDF) on 14 December 2013.
105. ^ Hamilton AF (2009). "Goals, intentions and mental states: challenges for theories of autism". *J Child Psychol Psychiatry*. **50** (8): 881–92. CiteSeerX 10.1.1.621.6275. doi:10.1111/j.1469-7610.2009.02098.x. PMID 19508497.
106. ^ [a] [b] Kenworthy L, Yerys BE, Anthony LG, Wallace GL (2008). "Understanding executive control in autism spectrum disorders in the lab and in the real world". *Neuropsychol Rev*. **18** (4): 320–38. doi:10.1007/s11065-008-9077-7. PMC 2856078. PMID 18956239.
107. ^ O'Hearn K, Asato M, Ordaz S, Luna B (2008). "Neurodevelopment and executive function in autism". *Dev Psychopathol*. **20** (4): 1103–32. doi:10.1017/S0954579408000527. PMID 18838033.
108. ^ Hill EL (2004). "Executive dysfunction in autism". *Trends Cogn Sci*. **8** (1): 26–32. doi:10.1016/j.dr.2004.01.001. PMID 14697400.
109. ^ Happé F, Frith U (2006). "The weak coherence account: detail-focused cognitive style in autism spectrum disorders". *J Autism Dev Disord*. **36** (1): 5–25. doi:10.1007/s10803-005-0039-0. PMID 16450045.
110. ^ Mottron L, Dawson M, Soulières I, Hubert B, Burack J (2006). "Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception". *J Autism Dev Disord*. **36** (1): 27–43. doi:10.1007/s10803-005-0040-7. PMID 16453071.
111. ^ Rajendran G, Mitchell P (2007). "Cognitive theories of autism". *Dev Rev*. **27** (2): 224–60. doi:10.1016/j.dr.2007.02.001.
112. ^ Baird G, Cass H, Slonims V (2003). "Diagnosis of autism". *BMJ*. **327** (7413): 488–93. doi:10.1136/bmj.327.7413.488. PMC 188387. PMID 12946972. Archived from the original on 6 March 2009.
113. ^ Gotham K, Risi S, Dawson G, Tager-Flusberg H, Joseph R, Carter A, Hepburn S, McMahon W, Rodier P, Hyman SL, Sigman M, Rogers S, Landa R, Spence MA, Osann K, Flodman P, Volkmar F, Hollander E, Buxbaum J, Pickles A, Lord C (2008). "A replication of the Autism Diagnostic Observation Schedule (ADOS) revised algorithms". *J Am Acad Child Adolesc Psychiatry*. **47** (6): 642–51. doi:10.1097/CHI.0b013e31816bffb7. PMC 3057666. PMID 18434924.
114. ^ [a] [b] [c] Dover CJ, Le Couteur A (2007). "How to diagnose autism". *Arch Dis Child*. **92** (6): 540–5. doi:10.1136/adc.2005.086280. PMC 2066173. PMID 17515625.
115. ^ [a] [b] Kanne SM, Randolph JK, Farmer JE (2008). "Diagnostic and assessment findings: a bridge to academic planning for children with autism spectrum disorders". *Neuropsychol Rev*. **18** (4): 367–84. doi:10.1007/s11065-008-9072-z. PMID 18855144.
116. ^ Mantovani JF (2000). "Autistic regression and Landau–Kleffner syndrome: progress or confusion?". *Dev Med Child Neurol*. **42** (5): 349–53. doi:10.1017/S0012162200210621. PMID 10855658.
117. ^ Matson JL, Neal D (2009). "Cormorbidity: diagnosing comorbid psychiatric conditions". *Psychiatr Times*. **26** (4). Archived from the original on 3 April 2013.

118. ^ [a b c d e] Caronna EB, Milunsky JM, Tager-Flusberg H (2008). "Autism spectrum disorders: clinical and research frontiers". *Arch Dis Child*. **93** (6): 518–23. doi:10.1136/adc.2006.115337. PMID 18305076.
119. ^ Schaefer GB, Mendelsohn NJ (2008). "Archived copy". *Genet Med*. pp. 4–12. doi:10.1097/GIM.0b013e31815efdd7. PMID 18197051. Archived from the original on 1 September 2010. Retrieved 2008-02-07. Lay summary – *Medical News Today* (7 February 2008).
120. ^ Ledbetter DH (2008). "Cytogenetic technology—genotype and phenotype". *N Engl J Med*. **359** (16): 1728–30. doi:10.1056/NEJMe0806570. PMID 18784093.
121. ^ McMahon WM, Baty BJ, Botkin J (2006). "Genetic counseling and ethical issues for autism". *American Journal of Medical Genetics*. **142C** (1): 52–7. doi:10.1002/ajmg.c.30082. PMID 16419100.
122. ^ [a b c d] Landa RJ (2008). "Diagnosis of autism spectrum disorders in the first 3 years of life". *Nat Clin Pract Neurol*. **4** (3): 138–47. doi:10.1038/ncpneuro0731. PMID 18253102.
123. ^ Shattuck PT, Grosse SD (2007). "Issues related to the diagnosis and treatment of autism spectrum disorders". *Ment Retard Dev Disabil Res Rev*. **13** (2): 129–35. doi:10.1002/mrdd.20143. PMID 17563895.
124. ^ Cass H (1998). "Visual impairment and autism: current questions and future research". *Autism*. **2** (2): 117–38. doi:10.1177/1362361398022002.
125. ^ Volkmar FR, State M, Klin A (2009). "Autism and autism spectrum disorders: diagnostic issues for the coming decade". *J Child Psychol Psychiatry*. **50** (1–2): 108–15. doi:10.1111/j.1469-7610.2008.02010.x. PMID 19220594.
126. ^ American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-IV*. 4 ed. Washington, DC: American Psychiatric Association; 2000. ISBN 978-0-89042-025-6. OCLC 768475353. Diagnostic criteria for 299.00 Autistic Disorder.
127. ^ Freitag CM (2007). "The genetics of autistic disorders and its clinical relevance: a review of the literature". *Mol Psychiatry*. **12** (1): 2–22. doi:10.1038/sj.mp.4001896. PMID 17033636.
128. ^ Piven J, Palmer P, Jacobi D, Childress D, Arndt S (1997). "Broader autism phenotype: evidence from a family history study of multiple-incidence autism families". *Am J Psychiatry*. **154** (2): 185–90. doi:10.1176/ajp.154.2.185. PMID 9016266.
129. ^ Happé F (1999). "Understanding assets and deficits in autism: why success is more interesting than failure" (PDF). *Psychologist*. **12** (11): 540–7. Archived from the original (PDF) on 17 May 2012.
130. ^ Baron-Cohen S (2006). "The hyper-systemizing, assortative mating theory of autism" (PDF). *Prog Neuropsychopharmacol Biol Psychiatry*. **30** (5): 865–72. doi:10.1016/j.pnpbp.2006.01.010. PMID 16519981. Archived from the original (PDF) on 13 May 2012.
131. ^ Cohen D, Pichard N, Tordjman S, Baumann C, Burglen L, Excoffier E, Lazar G, Mazet P, Pinquier C, Verloes A, Héron D (2005). "Specific genetic disorders and autism: clinical contribution towards their identification". *J Autism Dev Disord*. **35** (1): 103–16. doi:10.1007/s10803-004-1038-2. PMID 15796126.
132. ^ Validity of ASD subtypes:
    - Klin A (2006). "Autism and Asperger syndrome: an overview". *Rev Bras Psiquiatr*. **28** (suppl 1): S3–S11. doi:10.1590/S1516-44462006000500002. PMID 16791390.[*dead link*]
    - Witwer AN, Lecavalier L (2008). "Examining the validity of autism spectrum disorder subtypes". *J Autism Dev Disord*. **38** (9): 1611–24. doi:10.1007/s10803-008-0541-2. PMID 18327636.
133. ^ Volkmar F, Chawarska K, Klin A (2005). "Autism in infancy and early childhood". *Annu Rev Psychol*. **56**: 315–36. doi:10.1146/annurev.psych.56.091103.070159. PMID 15709938. A partial update is in: Volkmar FR, Chawarska K (2008). "Autism in infants: an update". *World Psychiatry*. **7** (1): 19–21. PMC 2366821. PMID 18458791.
134. ^ Ozonoff S, Heung K, Byrd R, Hansen R, Hertz-Picciotto I (2008). "The onset of autism: patterns of symptom emergence in the first years of life". *Autism Res*. **1** (6): 320–328. doi:10.1002/aur.53. PMC 2857525. PMID 19360687.
135. ^ Altevogt BM, Hanson SL, Leshner AI (2008). "Autism and the environment: challenges and opportunities for research". *Pediatrics*. **121** (6): 1225–9. doi:10.1542/peds.2007-3000. PMID 18519493. Archived from the original on 15 January 2010.
136. ^ Reiss AL (2009). "Childhood developmental disorders: an academic and clinical convergence point for psychiatry, neurology, psychology and pediatrics". *J Child Psychol Psychiatry*. **50** (1–2): 87–98. doi:10.1111/j.1469-7610.2008.02046.x. PMID 19220592.
137. ^ Piggot J, Shirinyan D, Shemmassian S, Vazirian S, Alarcón M (2009). "Neural systems approaches to the neurogenetics of autism spectrum disorders". *Neuroscience*. **164** (1): 247–56. doi:10.1016/j.neuroscience.2009.05.054. PMID 19482063.
138. ^ Stephan DA (2008). "Unraveling autism". *American Journal of Human Genetics*. **82** (1): 7–9. doi:10.1016/j.ajhg.2007.12.003. PMC 2253980. PMID 18179879.
139. ^ Siu, AL; US Preventive Services Task Force, (USPSTF); Bibbins-Domingo, K; Grossman, DC; Baumann, LC; Davidson, KW; Ebell, M; García, FA; Gillman, M; Herzstein, J; Kemper, AR; Krist, AH; Kurth, AE; Owens, DK; Phillips, WR; Phipps, MG; Pignone, MP (16 February 2016). "Screening for Autism Spectrum Disorder in Young Children: US Preventive Services Task Force Recommendation Statement.". *JAMA*. **315** (7): 691–6. doi:10.1001/jama.2016.0018. PMID 26881372.
140. ^ Wetherby AM, Brosnan-Maddox S, Peace V, Newton L (2008). "Validation of the Infant–Toddler Checklist as a broadband screener for autism spectrum disorders from 9 to 24 months of age". *Autism*. **12** (5): 487–511. doi:10.1177/1362361308094501. PMC 2663025. PMID 18805944.
141. ^ Wallis KE, Pinto-Martin J (2008). "The challenge of screening for autism spectrum disorder in a culturally diverse society". *Acta Paediatr*. **97** (5): 539–40. doi:10.1111/j.1651-2227.2008.00720.x. PMID 18373717.
142. ^ Lintas C, Persico AM (2009). "Autistic phenotypes and genetic testing: state-of-the-art for the clinical geneticist". *Journal of Medical Genetics*. **46** (1): 1–8. doi:10.1136/jmg.2008.060871. PMC 2603481. PMID 18728070. Archived from the original on 30 October 2013.
143. ^ [a b] Duchan E, Patel DR (2012). "Epidemiology of autism spectrum disorders". *Pediatr. Clin. North Am*. **59** (1): 27–43, ix–

x. doi:10.1016/j.pcl.2011.10.003. PMID 22284791.
144. ^ Lambert N, Strebel P, Orenstein W, Icenogle J, Poland GA (7 January 2015). "Rubella". *Lancet*. **385**: 2297–307. doi:10.1016/S0140-6736(14)60539-0. PMID 25576992.
145. ^ *a b c d e f g* Smith, Tristram; Iadarola, Suzannah (2015-11-02). "Evidence Base Update for Autism Spectrum Disorder". *Journal of Clinical Child & Adolescent Psychology*. **44** (6): 897–922. doi:10.1080/15374416.2015.1077448. ISSN 1537-4416. PMID 26430947.
146. ^ Eldevik, Sigmund; Hastings, Richard P.; Hughes, J. Carl; Jahr, Erik; Eikeseth, Svein; Cross, Scott (2009-05-19). "Meta-Analysis of Early Intensive Behavioral Intervention for Children With Autism". *Journal of Clinical Child & Adolescent Psychology*. **38** (3): 439–450. doi:10.1080/15374410902851739. ISSN 1537-4416. PMID 19437303.
147. ^ Ospina MB, Krebs Seida J, Clark B, Karkhaneh M, Hartling L, Tjosvold L, Vandermeer B, Smith V (2008). "Behavioural and developmental interventions for autism spectrum disorder: a clinical systematic review". *PLoS ONE*. **3** (11): e3755. doi:10.1371/journal.pone.0003755. PMC 2582449. PMID 19015734. Archived from the original on 5 November 2013.
148. ^ Seida JK, Ospina MB, Karkhaneh M, Hartling L, Smith V, Clark B (2009). "Systematic reviews of psychosocial interventions for autism: an umbrella review". *Dev Med Child Neurol*. **51** (2): 95–104. doi:10.1111/j.1469-8749.2008.03211.x. PMID 19191842.
149. ^ *a b c d* Rogers SJ, Vismara LA (2008). "Evidence-based comprehensive treatments for early autism". *J Clin Child Adolesc Psychol*. **37** (1): 8–38. doi:10.1080/15374410701817808. PMC 2943764. PMID 18444052.
150. ^ Howlin P, Magiati I, Charman T (2009). "Systematic review of early intensive behavioral interventions for children with autism". *Am J Intellect Dev Disabil*. **114** (1): 23–41. doi:10.1352/2009.114:23-41. PMID 19143460.
151. ^ Reichow B, Barton EE, Boyd BA, Hume K (2012). "Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD)". *Cochrane Database of Systematic Reviews*. **10**: CD009260. doi:10.1002/14651858.CD009260.pub2. PMID 23076956.
152. ^ Eikeseth S (2009). "Outcome of comprehensive psycho-educational interventions for young children with autism". *Res Dev Disabil*. **30** (1): 158–78. CiteSeerX 10.1.1.615.3336. doi:10.1016/j.ridd.2008.02.003. PMID 18385012.
153. ^ Van Bourgondien ME, Reichle NC, Schopler E (2003). "Effects of a model treatment approach on adults with autism". *J Autism Dev Disord*. **33** (2): 131–40. doi:10.1023/A:1022931224934. PMID 12757352.
154. ^ Simpson RL, de Boer-Ott SR, Smith-Myles B (2003). "Inclusion of Learners with Autism Spectrum Disorders in General Education Settings". *Topics in Language Disorders*. **23** (2): 116–133. doi:10.1097/00011363-200304000-00005. Archived from the original on 2011-07-14.
155. ^ Leskovec TJ, Rowles BM, Findling RL (2008). "Pharmacological treatment options for autism spectrum disorders in children and adolescents". *Harv Rev Psychiatry*. **16** (2): 97–112. doi:10.1080/10673220802075852. PMID 18415882.
156. ^ Oswald DP, Sonenklar NA (2007). "Medication use among children with autism spectrum disorders". *J Child Adolesc Psychopharmacol*. **17** (3): 348–55. doi:10.1089/cap.2006.17303. PMID 17630868.
157. ^ Ji N, Findling RL (Mar 2015). "An update on pharmacotherapy for autism spectrum disorder in children and adolescents". *Curr Opin Psychiatry*. **28** (2): 91–101. doi:10.1097/YCO.0000000000000132. PMID 25602248.
158. ^ Lack of research on drug treatments:
    - Angley M, Young R, Ellis D, Chan W, McKinnon R (2007). "Children and autism—part 1—recognition and pharmacological management" (PDF). *Aust Fam Physician*. **36** (9): 741–4. PMID 17915375. Archived from the original (PDF) on 7 April 2013.
    - Broadstock M, Doughty C, Eggleston M (2007). "Systematic review of the effectiveness of pharmacological treatments for adolescents and adults with autism spectrum disorder". *Autism*. **11** (4): 335–48. doi:10.1177/1362361307078132. PMID 17656398.
159. ^ Buitelaar JK (2003). "Why have drug treatments been so disappointing?". *Novartis Found Symp*. **251**: 235–44; discussion 245–9, 281–97. doi:10.1002/0470869380.ch14. PMID 14521196.
160. ^ Dölen G, Carpenter RL, Ocain TD, Bear MF (2010). "Mechanism-based approaches to treating fragile X". *Pharmacol Ther*. **127** (1): 78–93. doi:10.1016/j.pharmthera.2010.02.008. PMID 20303363.
161. ^ Lack of support for interventions:
    - Francis K (2005). "Autism interventions: a critical update" (PDF). *Dev Med Child Neurol*. **47** (7): 493–9. doi:10.1017/S0012162205000952. PMID 15991872.
    - Levy SE, Hyman SL (2008). "Complementary and alternative medicine treatments for children with autism spectrum disorders". *Child Adolesc Psychiatr Clin N Am*. **17** (4): 803–20, ix. doi:10.1016/j.chc.2008.06.004. PMC 2597185. PMID 18775371.
    - Rao PA, Beidel DC, Murray MJ (2008). "Social skills interventions for children with Asperger's syndrome or high-functioning autism: a review and recommendations". *J Autism Dev Disord*. **38** (2): 353–61. doi:10.1007/s10803-007-0402-4. PMID 17641962.
162. ^ Stahmer AC, Collings NM, Palinkas LA (2005). "Early intervention practices for children with autism: descriptions from community providers". *Focus Autism Other Dev Disabl*. **20** (2): 66–79. doi:10.1177/10883576050200020301. PMC 1350798. PMID 16467905.
163. ^ Hediger ML, England LJ, Molloy CA, Yu KF, Manning-Courtney P, Mills JL (2008). "Archived copy". *J Autism Dev Disord*. pp. 848–56. doi:10.1007/s10803-007-0453-6. PMID 17879151. Archived from the original on 1 October 2013. Retrieved 2008-04-17. Lay summary – *NIH News* (29 January 2008).
164. ^ Brown MJ, Willis T, Omalu B, Leiker R (2006). "Deaths resulting from hypocalcemia after administration of edetate disodium: 2003–2005". *Pediatrics*. **118** (2): e534–6. doi:10.1542/peds.2006-0858. PMID 16882789. Archived from the original on 27 July 2009.
165. ^ Warren Z, Veenstra-VanderWeele J, Stone W, et al. (April 2011). "Therapies for Children With Autism Spectrum Disorders": 8. PMID 21834171. "Hyperbaric therapy, in which oxygen is administered in special chambers that maintain a

higher air pressure, has shown possible effects in other chronic neurologic conditions and has also undergone preliminary exploration in ASDs."
166. ^ [a] [b] Buie T (2013). "The relationship of autism and gluten". *Clin Ther* (Review). **35** (5): 578–83. doi:10.1016/j.clinthera.2013.04.011. PMID 23688532. "At this time, the studies attempting to treat symptoms of autism with diet have not been sufficient to support the general institution of a gluten-free or other diet for all children with autism."
167. ^ Marí-Bauset S, Zazpe I, Mari-Sanchis A, Llopis-González A, Morales-Suárez-Varela M (Dec 2014). "Evidence of the gluten-free and casein-free diet in autism spectrum disorders: a systematic review". *J Child Neurol*. **29** (12): 1718–27. doi:10.1177/0883073814531330. hdl:10171/37087. PMID 24789114.
168. ^ Millward C, Ferriter M, Calver S, Connell-Jones G (2008). Ferriter M, ed. "Gluten- and casein-free diets for autistic spectrum disorder". *Cochrane Database Syst Rev* (2): CD003498. doi:10.1002/14651858.CD003498.pub3. PMC 4164915. PMID 18425890.
169. ^ Volta U, Caio G, De Giorgio R, Henriksen C, Skodje G, Lundin KE (Jun 2015). "Non-celiac gluten sensitivity: a work-in-progress entity in the spectrum of wheat-related disorders". *Best Pract Res Clin Gastroenterol*. **29** (3): 477–91. doi:10.1016/j.bpg.2015.04.006. PMID 26060112. "autism spectrum disorders (ASD) have been hypothesized to be associated with NCGS [47,48]. Notably, a gluten- and casein-free diet might have a positive effect in improving hyperactivity and mental confusion in some patients with ASD. This very exciting association between NCGS and ASD deserves further study before conclusions can be firmly drawn."
170. ^ San Mauro I, Garicano E, Collado L, Ciudad MJ (Dec 2014). "[Is gluten the great etiopathogenic agent of disease in the XXI century?] [Article in Spanish]". *Nutr Hosp*. **30** (6): 1203–10. doi:10.3305/nh.2014.30.6.7866. PMID 25433099.
171. ^ Catassi C, Bai JC, Bonaz B, Bouma G, Calabrò A, Carroccio A, Castillejo G, Ciacci C, Cristofori F, Dolinsek J, Francavilla R, Elli L, Green P, Holtmeier W, Koehler P, Koletzko S, Meinhold C, Sanders D, Schumann M, Schuppan D, Ullrich R, Vécsei A, Volta U, Zevallos V, Sapone A, Fasano A (Sep 2013). "Non-Celiac Gluten sensitivity: the new frontier of gluten related disorders". *Nutrients*. **5** (10): 3839–53. doi:10.3390/nu5103839. PMC 3820047. PMID 24077239. "The above data suggest that removing gluten from the diet may positively affect the clinical outcome in some children diagnosed with ASD, indicating that autism may be part of the spectrum of NCGS, at least in some cases. However, a word of caution is necessary to stress the fact that only a small, selected sub-group of children affected by ASD may benefit from an elimination diet. Additional investigations are required in order to identify phenotypes based on best- and non-response to dietary modifications and assess any biological correlates including anthropometry before considering a dietary intervention."
172. ^ Federal Reserve Bank of Minneapolis Community Development Project. "Consumer Price Index (estimate) 1800–". Federal Reserve Bank of Minneapolis. Retrieved January 2, 2017.
173. ^ Ganz ML (2007). "The lifetime distribution of the incremental societal costs of autism". *Arch Pediatr Adolesc Med*. **161** (4): 343–9. doi:10.1001/archpedi.161.4.343. PMID 17404130. Archived from the original on 12 December 2009. Lay summary – *Harvard School of Public Health* (25 April 2006).
174. ^ Sharpe DL, Baker DL (2007). "Financial issues associated with having a child with autism". *J Fam Econ Iss*. **28** (2): 247–64. doi:10.1007/s10834-007-9059-6.
175. ^ Montes G, Halterman JS (2008). "Association of childhood autism spectrum disorders and loss of family income". *Pediatrics*. **121** (4): e821–6. doi:10.1542/peds.2007-1594. PMID 18381511. Archived from the original on 4 March 2010.
176. ^ Montes G, Halterman JS (2008). "Child care problems and employment among families with preschool-aged children with autism in the United States". *Pediatrics*. **122** (1): e202–8. doi:10.1542/peds.2007-3037. PMID 18595965. Archived from the original on 6 December 2009.
177. ^ Reinke T (2008). "States increasingly mandate special autism services". *Manag Care*. **17** (8): 35–6, 39. PMID 18777788. Archived from the original on 24 March 2014.
178. ^ Aman MG (2005). "Treatment planning for patients with autism spectrum disorders". *J Clin Psychiatry*. **66** (Suppl 10): 38–45. PMID 16401149.
179. ^ Trivedi, Bijal. "Autistic and proud of it". *New Scientist*. Retrieved 2015-11-10.
180. ^ Shapiro, Joseph (2006-06-26). "Autism Movement Seeks Acceptance, Not Cures". *NPR.org*. Retrieved 2015-11-10.
181. ^ "World Autism Awareness Day, 2 April". *United Nations*. Retrieved 2015-11-17.
182. ^ "What is LIUB". *Autism Speaks*. Retrieved 2015-11-17.
183. ^ Bascom, Julia (2015-06-18). "Autistic Pride Day 2015: A Message to the Autistic Community". Retrieved 2015-11-18.
184. ^ "Autism Sunday - Home". *Autism Sunday*. 2010. Retrieved 2015-11-17.
185. ^ "About Autreat". *Autreat.com*. 2013. Retrieved 2015-11-17.
186. ^ "Other Autism Organizations". *Autism Speaks*. 2012-07-25. Retrieved 2015-11-17.
187. ^ Silverman, Chloe (2008). "Fieldwork on Another Planet: Social Science Perspectives on the Autism Spectrum". *BioSocieties*. **3** (3): 325–341. doi:10.1017/S1745855208006236. ISSN 1745-8552.
188. ^ "Rain Man (1988) - IMDb". *IMDb*. Retrieved 2015-11-17.
189. ^ "American RadioWorks: Fast Food and Animal Rights - Kill Them With Kindness, Page 1". *American Public Media*. Retrieved 2015-11-17.
190. ^ Page, Tim (2007-08-20). "Parallel Play". *New Yorker*. Retrieved 2015-11-17.
191. ^ "Famous People With Autism Spectrum Disorder: Autistic Celebrities (List)". *Mental Health Daily*. Retrieved 2015-11-18.
192. ^ Pickett E, Pullara O, O'Grady J, Gordon B (2009). "Speech acquisition in older nonverbal individuals with autism: a review of features, methods, and prognosis". *Cogn Behav Neurol*. **22** (1): 1–21. doi:10.1097/WNN.0b013e318190d185. PMID 19372766.
193. ^ Seltzer MM, Shattuck P, Abbeduto L, Greenberg JS (2004). "Trajectory of development in adolescents and adults with autism". *Ment Retard Dev Disabil Res Rev*. **10** (4): 234–47. doi:10.1002/mrdd.20038. PMID 15666341.

194. ^ Tidmarsh L, Volkmar FR (2003). "Diagnosis and epidemiology of autism spectrum disorders". *Can J Psychiatry*. **48** (8): 517–25. PMID 14574827.
195. ^ Hendricks DR, Wehman P (24 March 2009). "Transition From School to Adulthood for Youth With Autism Spectrum Disorders: Review and Recommendations". *Focus on Autism and Other Developmental Disabilities*. **24** (2): 77–88. doi:10.1177/1088357608329827.
196. ^ [a] [b] [c] Fombonne E (2009). "Epidemiology of pervasive developmental disorders". *Pediatr Res*. **65** (6): 591–8. doi:10.1203/PDR.0b013e31819e7203. PMID 19218885.
197. ^ CDC | Home | Autism Spectrum Disorder (ASD) | NCBDDD
198. ^ Wing L, Potter D (2002). "The epidemiology of autistic spectrum disorders: is the prevalence rising?". *Ment Retard Dev Disabil Res Rev*. **8** (3): 151–61. doi:10.1002/mrdd.10029. PMID 12216059.
199. ^ Szpir M (2006). "Tracing the origins of autism: a spectrum of new studies". *Environ Health Perspect*. **114** (7): A412–8. doi:10.1289/ehp.114-a412. PMC 1513312. PMID 16835042.
200. ^ Schaafsma SM, Pfaf DW (August 2014). "Etiologies underlying sex differences in Autism Spectrum Disorders". *Frontiers in neuroendocrinology*. **35** (3): 255–71. doi:10.1016/j.yfrne.2014.03.006. PMID 24705124.
201. ^ Gardener H, Spiegelman D, Buka SL (2009). "Prenatal risk factors for autism: comprehensive meta-analysis". *Br J Psychiatry*. **195** (1): 7–14. doi:10.1192/bjp.bp.108.051672. PMC 3712619. PMID 19567888.
202. ^ Bertoglio K, Hendren RL (2009). "New developments in autism". *Psychiatr Clin North Am*. **32** (1): 1–14. doi:10.1016/j.psc.2008.10.004. PMID 19248913.
203. ^ Folstein SE, Rosen-Sheidley B (2001). "Genetics of autism: complex aetiology for a heterogeneous disorder". *Nature Reviews Genetics*. **2** (12): 943–55. doi:10.1038/35103559. PMID 11733747.
204. ^ Zafeiriou DI, Ververi A, Vargiami E (2007). "Childhood autism and associated comorbidities". *Brain Dev*. **29** (5): 257–72. doi:10.1016/j.braindev.2006.09.003. PMID 17084999.
205. ^ Learning in autism. In: Byrne JH (ed.-in-chief), Roediger HL III (vol. ed.). *Learning and Memory: A Comprehensive Reference*. Vol. 2. Academic Press; 2008 [Retrieved 26 July 2008]. doi:10.1016/B978-012370509-9.00152-2. ISBN 978-0-12-370504-4. p. 759–72.
206. ^ Chakrabarti S, Fombonne E (2001). "Pervasive developmental disorders in preschool children". *JAMA*. **285** (24): 3093–9. doi:10.1001/jama.285.24.3093. PMID 11427137. Archived from the original on 28 August 2010.
207. ^ *DSM-IV-TR Diagnostical and Statistical Manual of Mental Disorders Fourth edition text revision*. American Psychiatric Association, Washington DC; 2000. p. 80.
208. ^ White SW, Oswald D, Ollendick T, Scahill L (2009). "Anxiety in children and adolescents with autism spectrum disorders". *Clin Psychol Rev*. **29** (3): 216–29. doi:10.1016/j.cpr.2009.01.003. PMC 2692135. PMID 19223098.
209. ^ Spence SJ, Schneider MT (2009). "The role of epilepsy and epileptiform EEGs in autism spectrum disorders". *Pediatr Res*. **65** (6): 599–606. doi:10.1203/PDR.0b013e31819e7168. PMC 2692092. PMID 19454962.
210. ^ Ozgen HM, Hop JW, Hox JJ, Beemer FA, van Engeland H (2010). "Minor physical anomalies in autism: a meta-analysis". *Mol Psychiatry*. **15** (3): 300–7. doi:10.1038/mp.2008.75. PMID 18626481.
211. ^ Steyaert JG, De la Marche W (2008). "What's new in autism?". *Eur J Pediatr*. **167** (10): 1091–101. doi:10.1007/s00431-008-0764-4. PMID 18597114.
212. ^ Richdale AL, Schreck KA (2009). "Sleep problems in autism spectrum disorders: prevalence, nature, & possible biopsychosocial aetiologies". *Sleep Med Rev*. **13** (6): 403–11. doi:10.1016/j.smrv.2009.02.003. PMID 19398354.
213. ^ Wing L (1997). "The history of ideas on autism: legends, myths and reality". *Autism*. **1** (1): 13–23. doi:10.1177/1362361397011004.
214. ^ Miles M (2005). "Martin Luther and childhood disability in 16th century Germany: what did he write? what did he say?". Independent Living Institute. Archived from the original on 3 November 2013. Retrieved 23 December 2008.
215. ^ *Autism in History: The Case of Hugh Blair of Borgue*. Blackwell; 2000. ISBN 978-0-631-22089-3.
216. ^ [a] [b] [c] Wolff S (2004). "The history of autism". *Eur Child Adolesc Psychiatry*. **13** (4): 201–8. doi:10.1007/s00787-004-0363-5. PMID 15365889.
217. ^ Kuhn R (2004). "Eugen Bleuler's concepts of psychopathology". *Hist Psychiatry*. **15** (3): 361–6. doi:10.1177/0957154X04044603. PMID 15386868. The quote is a translation of Bleuler's 1910 original.
218. ^ Asperger H (1938). "Das psychisch abnormale Kind" [The psychically abnormal child]. *Wien Klin Wochenschr* (in German). **51**: 1314–7.
219. ^ Lyons V, Fitzgerald M (2007). "Asperger (1906–1980) and Kanner (1894–1981), the two pioneers of autism". *J Autism Dev Disord*. **37** (10): 2022–3. doi:10.1007/s10803-007-0383-3. PMID 17922179.
220. ^ Fombonne E (2003). "Modern views of autism". *Can J Psychiatry*. **48** (8): 503–5. PMID 14574825.
221. ^ Szatmari P. Genetic epidemiology of autism spectrum disorders. In: Volkmar FR. *Autism and Pervasive Developmental Disorders*. 2nd ed. Cambridge University Press; 2007. ISBN 978-0-521-54957-8. p. 157–78.
222. ^ Chambres P, Auxiette C, Vansingle C, Gil S (2008). "Adult attitudes toward behaviors of a six-year-old boy with autism". *J Autism Dev Disord*. **38** (7): 1320–7. doi:10.1007/s10803-007-0519-5. PMID 18297387.
223. ^ Heidgerken AD, Geffken G, Modi A, Frakey L (2005). "A survey of autism knowledge in a health care setting". *J Autism Dev Disord*. **35** (3): 323–30. doi:10.1007/s10803-005-3298-x. PMID 16119473.
224. ^ Biever C (2007). "Web removes social barriers for those with autism". *New Sci* (2610): 26–7. Archived from the original on 20 October 2012.
225. ^ Harmon A (20 December 2004). "How about not 'curing' us, some autistics are pleading". *The New York Times*. Archived from the original on 11 May 2013.

## Further reading


- Sicile-Kira, C. *Autism spectrum disorder: the complete guide to understanding autism*. Revised Perigee trade paperback ed. New York, New York: Perigee; 2014. ISBN 978-0-399-16663-1.
- Waltz, M. *Autism: A Social and Medical History*. 1st ed. Palgrave Macmillan; 22 March 2013. ISBN 978-0-230-52750-8.
- Silberman, S. *NeuroTribes: The Legacy of Autism and How to Think Smarter About People Who Think Differently*. 1st ed. Crows Nest, New South Wales: Allen & Unwin; 2015. ISBN 978-1-760-11363-6.


## External links

- Autism at DMOZ

Find more about
**Autism**
at Wikipedia's sister projects

- Definitions from Wiktionary
- Media from Commons
- News from Wikinews
- Textbooks from Wikibooks
- Data from Wikidata

| v · t · e · | **Pervasive developmental disorders and autism spectrum (F84, 299)** |
|---|---|
| **Main** | Causes · Comorbid conditions · Epidemiology · Heritability · Sociological and cultural aspects · Medical model · Therapies · |
| **Diagnoses** | Autism spectrum (High-functioning autism · **Classic Autism** · Asperger syndrome · Pervasive developmental disorder not otherwise specified · Childhood disintegrative disorder · Rett syndrome) · |
| **Related conditions** | Alexithymia · Attention deficit hyperactivity disorder · Anxiety disorder (obsessive–compulsive disorder) · Einstein syndrome · Epilepsy · Fragile X syndrome · Hyperlexia · Savant syndrome · Schizotypal autism · Sensory processing disorder · Intellectual disability · Developmental coordination disorder · Multiple complex developmental disorder · |
| **Controversies** | Autism rights movement · Autistic enterocolitis · Facilitated communication · MMR vaccine · Thiomersal (Chelation) · |
| **Diagnostic scales** | Gilliam Asperger's disorder scale · Autism Diagnostic Observation Schedule · Autism Diagnostic Interview · Autism-spectrum quotient · Childhood Autism Rating Scale · |
| **Lists** | Autism-related topics · Fictional characters · Schools · |

| v · t · e · | **Mental and behavioral disorders (F 290–319)** |
|---|---|
| | **Neurological/symptomatic** |
| **Dementia** | Mild cognitive impairment · Alzheimer's disease · Vascular dementia · Pick's disease · Creutzfeldt–Jakob disease · Huntington's disease · Parkinson's disease · AIDS dementia complex · Frontotemporal dementia · Sundowning · Wandering · |
| **Autism spectrum** | **Autism** · Asperger syndrome · Savant syndrome · PDD-NOS · High-functioning autism · |
| **Other** | Delirium · Post-concussion syndrome · Organic brain syndrome · |
| | **Psychoactive substances, substance abuse, drug abuse and substance-related disorders** |
| | Intoxication/Drug overdose · Physical dependence · Substance dependence · Rebound effect · Double rebound · Withdrawal · |

| Schizophrenia, schizotypal and delusional | | |
|---|---|---|
| **Psychosis** | Schizoaffective disorder · Schizophreniform disorder · Brief reactive psychosis · | |
| **Schizophrenia** | Disorganized schizophrenia · Paranoid schizophrenia · Simple-type schizophrenia · | |
| **Delusional disorders** | Delusional disorder · Folie à deux · | |
| **Mood (affective)** | | |
| Mania · Bipolar disorder · (Bipolar I · Bipolar II · Cyclothymia · Bipolar NOS) · Depression · (Major depressive disorder · Dysthymia · Seasonal affective disorder · Atypical depression · Melancholic depression) · | | |
| **Neurotic, stress-related and somatoform** | | |
| **Anxiety disorder** | **Phobia** | Agoraphobia · Social anxiety · Social phobia · (Anthropophobia) · Specific phobia · (Claustrophobia) · Specific social phobia · |
| | **Other** | Panic disorder · Panic attack · Generalized anxiety disorder · OCD · *stress* · (Acute stress reaction · PTSD) · |
| **Adjustment disorder** | Adjustment disorder with depressed mood · | |
| **Somatic symptom disorder** | Somatization disorder · Body dysmorphic disorder · Hypochondriasis · Nosophobia · Da Costa's syndrome · Psychalgia · Conversion disorder · (Ganser syndrome · Globus pharyngis) · Neurasthenia · Mass psychogenic illness · | |
| **Dissociative disorder** | Dissociative identity disorder · Psychogenic amnesia · Fugue state · Depersonalization disorder · | |
| **Physiological/physical behavioral** | | |
| **Eating disorder** | Anorexia nervosa · Bulimia nervosa · Rumination syndrome · NOS · | |
| **Nonorganic sleep disorders** | (Nonorganic hypersomnia · Nonorganic insomnia) · Parasomnia · (REM sleep behavior disorder · Night terror · Nightmare) · | |
| **Sexual dysfunction** | *sexual desire* · (Hypoactive sexual desire disorder · Hypersexuality) · *sexual arousal* · (Female sexual arousal disorder) · Erectile dysfunction · *orgasm* · (Anorgasmia · Delayed ejaculation · Premature ejaculation · Sexual anhedonia) · *pain* · (Vaginismus · Dyspareunia) · | |
| **Postnatal** | Postpartum depression · Postpartum psychosis · | |
| **Adult personality and behavior** | | |
| *Gender dysphoria* | Sexual maturation disorder · Ego-dystonic sexual orientation · Sexual relationship disorder · Paraphilia · (Voyeurism · Fetishism) · | |
| **Other** | Personality disorder · Impulse control disorder · (Kleptomania · Trichotillomania · Pyromania · Dermatillomania) · Body-focused repetitive behavior · Factitious disorder · (Münchausen syndrome) · | |
| **Disorders typically diagnosed in childhood** | | |
| **Intellectual disability** | X-linked intellectual disability · (Lujan–Fryns syndrome) · | |
| **Psychological development (developmental disabilities)** | Specific · Pervasive · Autism spectrum · | |
| **Emotional and behavioral** | ADHD · Conduct disorder · (ODD) · Emotional/behavioral disorder · (Separation anxiety disorder) · *social functioning* · (Selective mutism · RAD · DAD) · Tic disorder · (Tourette syndrome) · *Speech* · (Stuttering · Cluttering) · Movement disorder · (Stereotypic) · | |
| **Symptoms and uncategorized** | | |
| Catatonia · False pregnancy · Intermittent explosive disorder · Psychomotor agitation · Stereotypy · Psychogenic non-epileptic seizures · Klüver–Bucy syndrome · | | |

| v · t · e · | **Autism resources** |
|---|---|

| **Autism** (outline · spectrum · · | |
|---|---|
| **Awareness** | Autism friendly · Autism Sunday · Communication Shutdown · World Autism Awareness Day · |
| **Culture** | Autistic art · Autism spectrum disorders in the media · Fictional characters · Films about autism · Circle of Friends · Neurodiversity · Medical model of autism · Sociological and cultural aspects of autism · |

| **Therapies** | |
|---|---|
| **Psychotropic medication (antipsychotics)** | Aripiprazole · Risperidone · |
| **Applied behavior analysis (ABA)** | Cognitive behavior therapy (social skills training · · Discrete trial training (Lovaas) · Early start denver model · Pivotal response treatment · Schoolwide positive behavior support · |
| **Developmental** | Floortime (The PLAY Project) · |
| **Controversial** | Auditory integration training · Aversive therapy/Electric shocks (Judge Rotenberg Educational Center) · Chelation of mercury · Ethical challenges to autism treatment · Facilitated communication · Gluten-free casein-free diet · Hug machine · Hyperbaric oxygen therapy · Holding therapy · Relationship development intervention · Secretin · Sensory integration therapy · Son-Rise · Vitamin B12 · |
| **Related** | Occupational therapy · Picture Exchange Communication System (PECS) · Social Stories · Speech therapy · SSRI antidepressants · Structured teaching (TEACCH) · |

| **Centers** | | |
|---|---|---|
| **Research** | United States | Association for Science in Autism Treatment · Simons Foundation Autism Research Initiative · Autism Research Institute · Autism Science Foundation · National Alliance for Autism Research · Yale Child Study Center · |
| | United Kingdom | Autism Research Centre (UK) · |
| | other / see also | Conditions and research areas · Researchers · |
| **Therapy** | United States | Center for Autism and Related Disorders (CARD) · MIND Institute · |
| **Schools** | ESPA College (UK) · Exceptional Minds (USA) · Pathlight School (Singapore) · Sunfield Children's Home (UK) · TreeHouse School (UK) · Western Autistic School (Australia) · *List of schools* · | |

| **Organizations** | | |
|---|---|---|
| **Americas** | United States | Athletes Against Autism · Autism National Committee · Autism Network International · Autism Science Foundation · Autistic Self Advocacy Network · Autism Society of America · Autism Speaks · Daniel Jordan Fiddle Foundation · Generation Rescue · Interactive Autism Network · LENA Foundation · Talk About Curing Autism · |
| | other | Centro Ann Sullivan (Peru) · Filipino-Canadian Autism Parent Support Group (Canada) · |
| **Asia** | Action for Autism (India) · Autism Resource Centre (Singapore) · GetVidya (India) · | |
| **Caribbean** | Autistic Society (Trinidad and Tobago) · Maia Chung Autism and Disabilities Foundation (Jamaica) · | |
| **Europe** | UK | Autism Anglia · The Autism Directory · Autism Awareness Campaign UK · Autism Cymru · Autism Plus · Autistica · National Autistic Society · Sacar · |
| | other | Specialisterne (Denmark) · Aspies For Freedom · Alliance Autiste · |
| **Oceania** | Luke Priddis Foundation (Australia) · | |
| **International** | Autism rights movement · Wrong Planet · | |

| **Literature** | |
|---|---|
| | *The Accidental Teacher: Life Lessons from My Silent Son* · *Aspergirls: Empowering Females with Asperger's Syndrome* · *Animals in Translation* · |

| | |
|---|---|
| **Non-fiction** | *Autism's False Prophets* · *Freaks, Geeks, and Asperger Syndrome: A User Guide to Adolescence* · *Like Colour to the Blind* · *Look Me in the Eye* · *Mother Warriors* · *Nobody Nowhere* · *Overcoming Autism* · *Somebody Somewhere* · *Son-Rise: The Miracle Continues* · *Strange Son* · *Switched On* · *Unstrange Minds* · *Extreme Love: Autism* · |
| **Fiction** | *The Mu Rhythm Bluff* · *The Curious Incident of the Dog in the Night-Time* · *Dear John* · *House Rules* · *Mockingbird* · *Saving Max* · *Speed of Dark* · *The Winter Journey* · *With the Light* · |
| **For younger people** | *Everybody Is Different: A Book for Young People Who Have Brothers or Sisters With Autism* · *Ian's Walk: A Story about Autism* · *Marcelo in the Real World* · *Rage: A Love Story* · *Rules* · |
| **Journals** | *Autism* · *Journal of Autism and Developmental Disorders* · *Molecular Autism* · *Research in Autism Spectrum Disorders* · |

| v · t · e · | **Autism-related films** |
|---|---|
| **Documentary** | *Autism Every Day* · *Autism Is a World* · *Autism: The Musical* · *Best Kept Secret* · *Children of the Stars* · *Dad's in Heaven with Nixon* · *Educating Peter* · *Graduating Peter* · *The Horse Boy* · *How to Dance in Ohio* · *Normal People Scare Me* · *Recovered: Journeys Through the Autism Spectrum and Back* · *Refrigerator Mothers* · *Too Sane for This World* · *The Wall or psychoanalysis put to the test for autism* · |
| **Docudrama and Biopic** | *After Thomas* · *Cries from the Heart* · *Marathon* · *Son-Rise: A Miracle of Love* · *Temple Grandin* · *Wretches & Jabberers* · |
| **Educational** | *The Transporters* · |
| **Fictional** | *Adam* · *Backstreet Dreams* · *Barfi!* · *Ben X* · *The Black Balloon* · *Bless the Child* · *The Boy Who Could Fly* · *Breaking and Entering* · *Burning Bright* · *Carne* · *Change of Habit* · *A Child Is Waiting* · *Chocolate* · *Cube* · *Dark Floors* · *David's Mother* · *Dear John* · *Dr. Pomerantz* · *Elling* · *Eeshwar* · *Extremely Loud and Incredibly Close* · *Family Pictures* · *Fly Away* · *Forrest Gump* · *God's Ears* · *Haridas* · *Henry & Verlin* · *House of Cards* · *I Am Sam* · *Imagination* · *Joyful Noise* · *Killer Diller* · *Koi... Mil Gaya* · *Mabul* · *Mario* · *Mary and Max* · *Mercury Rising* · *Midwinter Night's Dream* · *Miracle Run* · *Molly* · *Mozart and the Whale* · *My Name Is Khan* · *Nell* · *Nightworld: Lost Souls* · *Ocean Heaven* · *The Other Sister* · *Quantum Apocalypse* · *Raam* · *Rain Man* · *Relative Fear* · *Run Wild, Run Free* · *Salmon Fishing in the Yemen* · *Season of Miracles* · *Swati Mutyam* · *Swathi Muthu* · *Silent Fall* · *Simple Simon* · *Snow Cake* · *The Story of Luke* · *Touch* · *Under the Piano* · *When the Bough Breaks* · *White Frog* · *Zig Zag* · |

**Pervasive developmental disorders portal**

Categories: Autism | Communication disorders | Mental and behavioural disorders | Neurological disorders | Neurological disorders in children | Pervasive developmental disorders | Psychiatric diagnosis

# Bipolar disorder



From Wikipedia, the free encyclopedia

*"Manic depression" redirects here. For other uses, see Manic depression (disambiguation).*
*"Bipolar disorders" redirects here. For the medical journal, see Bipolar Disorders (journal).*

**Bipolar disorder**, also known as **manic depression**, is a mental disorder with periods of depression and periods of elevated mood.[2][3] The elevated mood is significant and is known as mania or hypomania, depending on its severity, or whether symptoms of psychosis are present. During mania, an individual behaves or feels abnormally energetic, happy or irritable.[2] Individuals often make poorly thought out decisions with little regard to the consequences. The need for sleep is usually reduced during manic phases.[3] During periods of depression there may be crying, a negative outlook on life, and poor eye contact with others.[2] The risk of suicide among those with the illness is high at greater than 6 percent over 20 years, while self-harm occurs in 30–40 percent.[2] Other mental health issues such as anxiety disorders and substance use disorder are commonly associated.[2]

The causes are not clearly understood, but both environmental and genetic factors play a role.[2] Many genes of small effect contribute to risk.[2][4] Environmental factors include a history of childhood abuse, and long-term stress.[2] The condition is divided into bipolar I disorder if there is at least one manic episode and bipolar II disorder if there are at least one hypomanic episode and one major depressive episode. In those with less severe symptoms of a prolonged duration the condition cyclothymic disorder may be diagnosed. If due to drugs or medical problems it is classified separately.[3] Other conditions that may present in a similar manner include attention deficit hyperactivity disorder, personality disorders, schizophrenia, and substance use disorder as well as a number of medical conditions.[2] Medical testing is not required for a diagnosis, though blood tests or medical imaging can be done to rule out other problems.[5]

Treatment commonly includes psychotherapy, as well as medications such as mood stabilizers and antipsychotics. Examples of mood stabilizers that are commonly used include lithium and various anticonvulsants. Treatment in hospital against a person's consent may be required if a person is at risk to themselves or others but refuses treatment. Severe behavioral problems may be managed with short term antipsychotics or benzodiazepines. In periods of mania it is recommended that antidepressants be stopped. If antidepressants are used for

**Bipolar disorder**

| | |
|---|---|
| **Synonyms** | bipolar affective disorder, bipolar illness, manic depression, bipolar disease[1] |

Bipolar disorder is characterized by episodes of depression and mania.

**Classification and external resources**

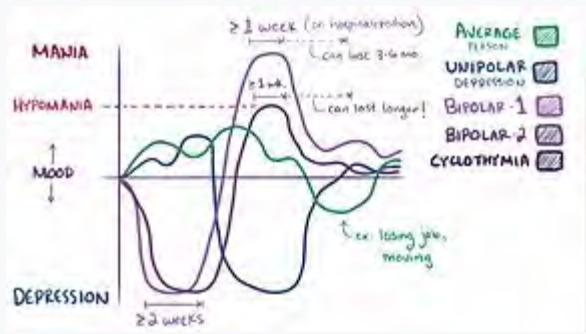
| | |
|---|---|
| **Specialty** | Psychiatry |
| **ICD-10** | F31 |
| **ICD-9-CM** | 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8 |
| **OMIM** | 125480 309200 |
| **DiseasesDB** | 7812 |
| **MedlinePlus** | 000926 |
| **eMedicine** | med/229 |
| **Patient UK** | Bipolar disorder |
| **MeSH** | D001714 |

[edit on Wikidata]

periods of depression they should be used with a mood stabilizer. Electroconvulsive therapy (ECT) may be helpful for those who do not respond to other treatments. If treatments are stopped, it is recommended that this be done slowly. Many individuals have financial, social or work-related problems due to the illness. These difficulties occur a quarter to a third of the time on average. The risk of death from natural causes such as heart disease is twice that of the general population. This is due to poor lifestyle choices and the side effects from medications.[2]

About 3 percent of people in the US are estimated to have bipolar disorder at some point in their life.[6] Lower rates of around 1 percent are found in other countries. The most common age at which symptoms begin is 25.[2] Rates appear to be similar in females and males.[7] The economic costs of the disorder has been estimated at $45 billion for the United States in 1991.[8] A large proportion of this was related to a higher number of missed work days, estimated at 50 per year.[8] People with bipolar disorder often face problems with social stigma.[2]






Play media

Video explanation

# Signs and symptoms

[9]

Mania is the defining feature of bipolar disorder, and can occur with different levels of severity. With milder levels of mania, known as hypomania, individuals are energetic, excitable, and may be highly productive.[10] As hypomania worsens, individuals begin to exhibit erratic and impulsive behavior, often making poor decisions due to unrealistic ideas about the future, and sleep very reduced.[10] At the extreme, manic individuals can experience distorted or delusional beliefs about the universe, hallucinate, hear voices, to the point of psychosis.[10] A depressive episode commonly follows an episode of mania.[10] The biological mechanisms responsible for switching from a manic or hypomanic episode to a depressive episode, or vice versa, remain poorly understood.[11]

An image from the past - when people with bipolar disorder were consigned to an asylum

## Manic episodes

Nineteenth-century drawing of a woman deprived of her dignity in old age.

Mania is a distinct period of at least one week of elevated or irritable mood, which can range from euphoria to delirium, and those experiencing hypo- or mania may exhibit three or more of the following behaviors: speak in a rapid, uninterruptible manner, short attention span, racing thoughts, increased goal-oriented activities, agitation, or they may exhibit behaviors characterized as impulsive or high-risk, such as hypersexuality or excessive spending.[9] To meet the definition for a manic episode, these behaviors must impair the individual's ability to socialize or work.[9][10] If untreated, a manic episode usually lasts three to six months.[12]

People with hypomania or mania may experience a decreased need of sleep, speak excessively in addition to speaking rapidly, and impaired judgment.[10][13] Manic individuals often have a history of substance abuse developed over years as a form of "self-medication".[14] At the more extreme, a person in a full blown manic state can experience psychosis; a break with reality, a state in which thinking is affected along with mood.[10] They may feel unstoppable, or as if they have been "chosen" and are on a "special mission", or have other grandiose or delusional ideas.[15] This may lead to violent behavior and, sometimes, hospitalization in an inpatient psychiatric hospital.[10][13] The severity of manic symptoms can be measured by rating scales such as the Young Mania Rating Scale, though questions remain about their reliability.[16]

The onset of a manic (or depressive) episode is often foreshadowed by sleep disturbances.[17] Mood changes, psychomotor and appetite changes, and an increase in anxiety can also occur up to three weeks before a manic episode develops.[18]

## Hypomanic episodes

Hypomania is the milder form of mania, defined as at least four days of the same criteria as mania,[10] but does not cause a significant decrease in the individual's ability to socialize or work, lacks psychotic features such as delusions or hallucinations, and does not require psychiatric hospitalization.[9] Overall functioning may actually increase during episodes of hypomania and is thought to serve as a defense mechanism against depression by some.[19] Hypomanic episodes rarely progress to full blown manic episodes.[19] Some people who experience hypomania show increased creativity[10] while others are irritable or demonstrate poor judgment.

Hypomania may feel good to some persons who experience it, though most people who experience hypomania state that the stress of the experience is very painful.[10] Bipolar people who go hypo, however, tend to forget the effects of their actions on those around them. Even when family and friends recognize mood swings, the individual will often deny that anything is wrong.[20] What might be called a "hypomanic event", if not accompanied by depressive episodes, is often not deemed problematic, unless the mood changes are uncontrollable, volatile or mercurial.[19] Most commonly, symptoms continue for a few weeks to a few months.[21]

## Depressive episodes

Symptoms of the depressive phase of bipolar disorder include persistent feelings of sadness, irritability or anger, loss of interest in previously enjoyed activities, excessive or inappropriate guilt, hopelessness, sleeping too much or not enough, changes in appetite and/or weight, fatigue, problems concentrating, self-loathing or feelings of worthlessness, and thoughts of death or suicidal ideation.[22] In severe cases, the individual may develop symptoms of psychosis, a condition also known as severe bipolar disorder with psychotic features. These symptoms include delusions and hallucinations. A major depressive episode persists for at least two weeks, and may result in suicide if left untreated.[23]


Depression.

The earlier the age of onset, the more likely the first few episodes are to be depressive.[24] Because a bipolar diagnosis requires a manic or hypomanic episode, many patients are initially diagnosed and treated as having major depression and then incorrectly prescribed antidepressants.[25]

## Mixed affective episodes

*Main article: Mixed affective state*

In bipolar disorder, mixed state is a condition during which symptoms of both mania and depression occur simultaneously.[26] Individuals experiencing a mixed state may have manic symptoms such as grandiose thoughts while simultaneously experiencing depressive symptoms such as excessive guilt or feeling suicidal.[26] Mixed states are considered to be high-risk for suicidal behavior since depressive emotions such as hopelessness are often paired with mood swings or difficulties with impulse control.[26] Anxiety disorder occurs more frequently as a comorbidity in mixed bipolar episodes than in non-mixed bipolar depression or mania.[26] Substance abuse (including alcohol) also follows this trend, thereby appearing to depict bipolar symptoms as no more than a consequence of substance abuse.[26]

## Associated features

*Main article: Associated features of bipolar disorder*

Associated features are clinical phenomena that often accompany the disorder but are not part of the diagnostic criteria. In adults with the condition, bipolar disorder is often accompanied by changes in cognitive processes and abilities. These include reduced attentional and executive capabilities and impaired memory. How the individual processes the universe also depends on the phase of the disorder, with differential characteristics between the manic, hypomanic and depressive states.[18] Some studies have found a significant association between bipolar disorder and creativity.[27] Those with bipolar disorder may have difficulty in maintaining relationships.[28] There are several common childhood precursors seen in children who later receive a diagnosis of bipolar disorder; these disorders include mood abnormalities, full major depressive episodes, and attention deficit hyperactivity disorder (ADHD).[29]

## Comorbid conditions

The diagnosis of bipolar disorder can be complicated by coexisting (comorbid) psychiatric conditions including the following: obsessive-compulsive disorder, substance abuse, eating disorders, attention deficit hyperactivity disorder, social phobia, premenstrual syndrome (including premenstrual dysphoric disorder), or panic disorder.[14][22][30][31] A careful longitudinal analysis of symptoms and episodes, enriched if possible by discussions with friends and family members, is crucial to establishing a treatment plan where these comorbidities exist.[32]

# Causes

The causes of bipolar disorder likely vary between individuals and the exact mechanism underlying the disorder remains unclear.[33] Genetic influences are believed to account for 60–80 percent of the risk of developing the disorder indicating a strong hereditary component.[30] The overall heritability of the bipolar spectrum has been estimated at 0.71.[34] Twin studies have been limited by relatively small sample sizes but have indicated a substantial genetic contribution, as well as environmental influence. For bipolar disorder type I, the (probandwise) concordance rates in modern studies have been consistently estimated at around 40 percent in identical twins (same genes), compared to about 5 percent in fraternal twins.[9][35] A combination of bipolar I, II and cyclothymia produced concordance rates of 42 percent vs. 11 percent, with a relatively lower ratio for bipolar II that likely reflects heterogeneity. There is overlap with unipolar depression and if this is also counted in the co-twin the concordance with bipolar disorder rises to 67 percent in monozygotic twins and 19 percent in dizygotic.[36] The relatively low concordance between dizygotic twins brought up together suggests that shared family environmental effects are limited, although the ability to detect them has been limited by small sample sizes.[34]

## Genetic

Genetic studies have suggested that many chromosomal regions and candidate genes are related to bipolar disorder susceptibility with each gene exerting a mild to moderate effect.[30] The risk of bipolar disorder is nearly ten-fold higher in first degree-relatives of those affected with bipolar disorder when compared to the general population; similarly, the risk of major depressive disorder is three times higher in relatives of those with bipolar disorder when compared to the general population.[9]

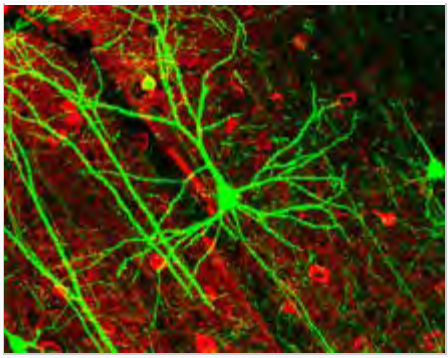
Although the first genetic linkage finding for mania was in 1969,[37] the linkage studies have been inconsistent.[9] The largest and most recent genome-wide association study failed to find any particular locus that exerts a large effect reinforcing the idea that no single gene is responsible for bipolar disorder in most cases.[38]

Findings point strongly to heterogeneity, with different genes being implicated in different families.[39] Robust and replicable genome-wide significant associations showed several common single nucleotide polymorphisms, including variants within the genes CACNA1C, ODZ4, and NCAN.[30][38]

Advanced paternal age has been linked to a somewhat increased chance of bipolar disorder in offspring, consistent with a hypothesis of increased new genetic mutations.[40]

## Physiological

Abnormalities in the structure and/or function of certain brain circuits could underlie bipolar. Meta-analyses of structural MRI studies in bipolar disorder report an increase in the volume of the lateral ventricles, globus pallidus and increase in the rates of deep white matter hyperintensities.[41][42][43] Functional MRI findings suggest that abnormal modulation between ventral prefrontal and limbic regions, especially the amygdala, are likely contribute to poor emotional [44]



Brain imaging studies have revealed differences in the volume of various brain regions between BD patients and healthy control subjects

regulation and mood symptoms.

Euthymic bipolar people show decreased activity in the lingual gyrus, while people who are manic demonstrated decreased activity in the inferior frontal cortex, while no differences were found in people with depressed bipolar.[45] People with bipolar have increased activation of left hemisphere ventral limbic areas and decreased activation of right hemisphere cortical structures related to cognition.[46]

One proposed model for bipolar suggests that hypersensitivity of reward circuits consisting of fronto-striatal circuits causes mania and hyposensitivity of these circuits cause depression.[47]

According to the "kindling" hypothesis, when people who are genetically predisposed toward bipolar disorder experience stressful events, the stress threshold at which mood changes occur becomes progressively lower, until the episodes eventually start (and recur) spontaneously. There is evidence supporting an association between early-life stress and dysfunction of the hypothalamic-pituitary-adrenal axis (HPA axis) leading to its over activation, which may play a role in the pathogenesis of bipolar disorder.[48][49]

Other brain components which have been proposed to play a role are the mitochondria[33] and a sodium ATPase pump.[50] Circadian rhythms and melatonin activity also seem to be altered.[51]

## Environmental

Environmental factors play a significant role in the development and course of bipolar disorder, and individual psychosocial variables may interact with genetic dispositions.[52] It is probable that recent life events and interpersonal relationships contribute to the likelihood of onsets and recurrences of bipolar mood episodes, as they do for onsets and recurrences of unipolar depression.[53] In surveys, 30–50 percent of adults diagnosed with bipolar disorder report traumatic/abusive experiences in childhood, which is associated on average with earlier onset, a higher rate of suicide attempts, and more co-occurring disorders such as PTSD.[54] The number of reported stressful events in childhood is higher in those with an adult diagnosis of bipolar spectrum disorder compared to those without, particularly events stemming from a harsh environment rather than from the child's own behavior.[55]

## Neurological

Less commonly bipolar disorder, or a bipolar-like disorder, may occur as a result of or in association with a neurological condition or injury. Such conditions and injuries include (but are not limited to) stroke, traumatic brain injury, HIV infection, multiple sclerosis, porphyria, and rarely temporal lobe epilepsy.[56]

## Neurochemical

Dopamine, a known neurotransmitter responsible for mood cycling, has been shown to have increased transmission during the manic phase.[11][57] The dopamine hypothesis states that the increase in dopamine results in secondary homeostatic down regulation of key systems and receptors such as an increase in dopamine mediated G protein-coupled receptors. This results in decreased dopamine transmission characteristic of the depressive phase.[11] The depressive phase ends with homeostatic up regulation potentially restarting the cycle over again.[58]

Glutamate is significantly increased within the left dorsolateral prefrontal cortex during the manic phase of bipolar disorder, and returns to normal levels once the phase is over.[59] The increase in GABA is possibly caused by a disturbance in early development causing a disturbance of cell migration and the formation of normal lamination, the layering of brain structures commonly associated with the cerebral cortex.[60]

Medications use to treat bipolar may exert their effect by modulating intracellular signaling, such as through depleting myo-inositol levels, inhibition of cAMP signaling, and through altering G coupled proteins[61]

Decreased levels of 5-HIAA in the CSF of bipolar patients during both depressed and manic phases. Increased dopaminergic activity has been hypothesized in manic states due to the ability of dopamine agonist to stimulant mania in bipolar patients. Decreased sensitivity of regulatory a2 adrenergic receptors as well as increased cell counts in the locus coeruleus indicated increased noradrenergic activity in manic patients. Low plasma GABA levels on both sides of the mood spectrum have been found.[62] One review found no difference in monoamine levels, but found abnormal norepinephrine turnover in bipolar patients.[63] Tyrosine depletion was found to attenuate the effects of methamphetamine in bipolar patients as well as symptoms of mania, implicating dopamine in mania. VMAT2 binding was found to be increased in one study of bipolar manic patients.[64]

# Prevention

Attempts at prevention of bipolar disorder have focused on stress (such as childhood adversity or highly conflictual families) which, although not a diagnostically specific causal agent for bipolar, does place genetically and biologically vulnerable individuals at risk for a more pernicious course of illness.[65] There has been debate regarding the causal relationship between usage of cannabis and bipolar disorder.[66]

# Diagnosis

Bipolar disorder is commonly diagnosed during adolescence or early adulthood, but onset can occur throughout the life cycle.[3][67] The disorder can be difficult to distinguish from unipolar depression and the average delay in diagnosis is 5–10 years after symptoms begin.[68] Diagnosis of bipolar disorder takes several factors into account and considers the self-reported experiences of the symptomatic individual, abnormal behavior reported by family members, friends or co-workers, observable signs of illness as assessed by a clinician, and often a medical work-up to rule-out medical causes. In diagnosis, caregiver-scored rating scales, specifically the mother, has been found to be more accurate than teacher and youth report in predicting identifying youths with bipolar disorder.[69] Assessment is usually done on an outpatient basis; admission to an inpatient facility is considered if there is a risk to oneself or others. The most widely used criteria for diagnosing bipolar disorder are from the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) and the World Health Organization's (WHO) *International Statistical Classification of Diseases and Related Health Problems*, 10th Edition (ICD-10). The ICD-10 criteria are used more often in clinical settings outside of the U.S. while the DSM criteria are used clinically within the U.S. and are the prevailing criteria used internationally in research studies. The DSM-5, published in 2013, included further and more accurate specifiers compared to its predecessor, the DSM-IV-TR.[70] Semi structured interviews such as the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) and the Structured Clinical Interview for DSM-IV (SCID) are used for diagnostic confirmation of bipolar disorder.

Several rating scales for the screening and evaluation of bipolar disorder exist,[71] including the Bipolar spectrum diagnostic scale, Mood Disorder Questionnaire, the General Behavior Inventory and the Hypomania Checklist.[72] The use of evaluation scales can not substitute a full clinical interview but they serve to systematize the recollection of symptoms.[72] On the other hand, instruments for screening bipolar disorder tend to have lower sensitivity.[71]

## Differential diagnosis

There are several other mental disorders with symptoms similar to those seen in bipolar disorder. These disorders include schizophrenia, major depressive disorder,[73] attention deficit hyperactivity disorder (ADHD), and certain personality disorders, such as borderline personality disorder.[74][75][76]

Although there are no biological tests that are diagnostic of bipolar disorder,[38] blood tests and/or imaging may be carried out to exclude medical illnesses with clinical presentations similar to that of bipolar disorder such as hypothyroidism or hyperthyroidism, metabolic disturbance, a chronic disease, or an infection such as HIV or syphilis.[67] A review of current and recent medications and drug use is considered to rule out these causes; common medications that can cause manic symptoms include antidepressants, prednisone, Parkinson's disease medications, thyroid hormone, stimulants (including cocaine and methamphetamine), and certain antibiotics.[77] An EEG may be used to exclude neurological disorders such as epilepsy, and a CT scan or MRI of the head may be used to exclude brain lesions.[67] Additional testing is especially indicated when age of first onset is mid to late life.[3] Investigations are not generally repeated for a relapse unless there is a specific medical indication.[*citation needed*]

## Bipolar spectrum

Bipolar spectrum disorders includes: bipolar I disorder, bipolar II disorder, cyclothymic disorder and cases where subthreshold symptoms are found to cause clinically significant impairment or distress.[3][67] These disorders involve major depressive episodes that alternate with manic or hypomanic episodes, or with mixed episodes that feature symptoms of both mood states.[3] The concept of the bipolar spectrum is similar to that of Emil Kraepelin's original concept of manic depressive illness.[78]

Unipolar hypomania without accompanying depression has been noted in the medical literature.[79] There is speculation as to whether this condition may occur with greater frequency in the general, untreated population; successful social function of these potentially high-achieving individuals may lead to being labeled as normal, rather than as individuals with substantial dysregulation.

## Criteria and subtypes

The DSM and the ICD characterize bipolar disorder as a spectrum of disorders occurring on a continuum. The DSM-5 lists three specific subtypes:[3]

- Bipolar I disorder: At least one manic episode is necessary to make the diagnosis;[80] depressive episodes are common in the vast majority of cases with bipolar disorder I, but are unnecessary for the diagnosis.[9] Specifiers such as "mild, moderate, moderate-severe, severe" and "with psychotic features" should be added as applicable to indicate the presentation and course of the disorder.[3]
- Bipolar II disorder: No manic episodes and one or more hypomanic episodes and one or more major depressive episode.[80] Hypomanic episodes do not go to the full extremes of mania (*i.e.*, do not usually cause severe social or occupational impairment, and are without psychosis), and this can make bipolar II more difficult to diagnose, since the hypomanic episodes may simply appear as periods of successful high productivity and are reported less frequently than a distressing, crippling depression.
- Cyclothymia: A history of hypomanic episodes with periods of depression that do not meet criteria for major depressive episodes.[81]

When relevant, specifiers for *peripartum onset* and *with rapid cycling* should be used with any subtype. Individuals who have subthreshold symptoms that cause clinically significant distress or impairment, but do not meet full criteria for one of the three subtypes may be diagnosed with other specified or unspecified bipolar disorder. Other specified bipolar disorder is used when a clinician chooses to provide an explanation for why the full criteria were not met (e.g., hypomania without a prior major depressive episode).[3]

## Rapid cycling

Most people who meet criteria for bipolar disorder experience a number of episodes, on average 0.4 to 0.7 per year, lasting three to six months.[82] *Rapid cycling*, however, is a course specifier that may be applied to any of the above subtypes. It is defined as having four or more mood disturbance episodes within a one-

year span and is found in a significant proportion of individuals with bipolar disorder.[22] These episodes are separated from each other by a remission (partial or full) for at least two months or a switch in mood polarity (i.e., from a depressive episode to a manic episode or vice versa).[9] The definition of rapid cycling most frequently cited in the literature (including the DSM) is that of Dunner and Fieve: at least four major depressive, manic, hypomanic or mixed episodes are required to have occurred during a 12-month period.[83] Ultra-rapid (days) and ultra-ultra rapid or ultradian (within a day) cycling have also been described.[84] The literature examining the pharmacological treatment of rapid cycling is sparse and there is no clear consensus with respect to its optimal pharmacological management.[85]

# Management

*Main article: Treatment of bipolar disorder*

There are a number of pharmacological and psychotherapeutic techniques used to treat bipolar disorder. Individuals may use self-help and pursue recovery.

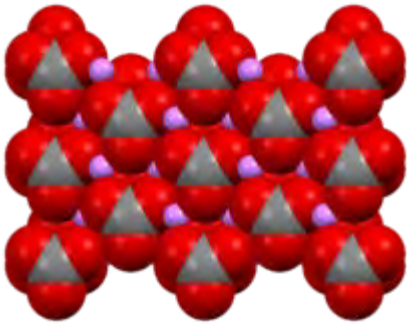
Hospitalization may be required especially with the manic episodes present in bipolar I. This can be voluntary or (if mental health legislation allows and varying state-to-state regulations in the USA) involuntary (called civil or involuntary commitment). Long-term inpatient stays are now less common due to deinstitutionalization, although these can still occur.[86] Following (or in lieu of) a hospital admission, support services available can include drop-in centers, visits from members of a community mental health team or an Assertive Community Treatment team, supported employment and patient-led support groups, intensive outpatient programs. These are sometimes referred to as partial-inpatient programs.[87]

## Psychosocial

Psychotherapy is aimed at alleviating core symptoms, recognizing episode triggers, reducing negative expressed emotion in relationships, recognizing prodromal symptoms before full-blown recurrence, and, practicing the factors that lead to maintenance of remission.[88][89][90] Cognitive behavioral therapy, family-focused therapy, and psychoeducation have the most evidence for efficacy in regard to relapse prevention, while interpersonal and social rhythm therapy and cognitive-behavioral therapy appear the most effective in regard to residual depressive symptoms. Most studies have been based only on bipolar I, however, and treatment during the acute phase can be a particular challenge.[91] Some clinicians emphasize the need to talk with individuals experiencing mania, to develop a therapeutic alliance in support of recovery.[92]

## Medication

A number of medications are used to treat bipolar disorder.[53] The medication with the best evidence is lithium, which is effective in treating acute manic episodes and preventing relapses; lithium is also an effective treatment for bipolar depression.[93] Lithium reduces the risk of suicide, self-harm, and death in people with bipolar disorder.[94] It is unclear if ketamine is useful in bipolar as of 2015.[95]



Lithium carbonate is one of many treatments for bipolar disorder

Four anticonvulsants are used in the treatment of bipolar disorder. Carbamazepine effectively treats manic episodes, with some evidence it has greater benefit in rapid-cycling bipolar disorder, or those with more psychotic symptoms or a more schizoaffective clinical picture. It is less effective in preventing relapse than lithium or valproate.[96][97] Carbamazepine became a popular treatment option for bipolar in the late 1980s and early 1990s, but was displaced by sodium valproate in the 1990s.[*citation needed*] Since then, valproate has become a commonly prescribed treatment, and is effective in treating manic episodes.[98] Lamotrigine has some efficacy in treating bipolar depression, and this benefit is greatest in more severe [99]

depression. It has also been shown to have some benefit in preventing further episodes, though there are concerns about the studies done, and is of no benefit in rapid cycling disorder.[100] The effectiveness of topiramate is unknown.[101] Depending on the severity of the case, anticonvulsants may be used in combination with lithium or on their own.[*citation needed*]

Antipsychotic medications are effective for short-term treatment of bipolar manic episodes and appear to be superior to lithium and anticonvulsants for this purpose.[53] However, other medications such as lithium are preferred for long-term use.[53] Olanzapine is effective in preventing relapses, although the evidence is not as solid as the evidence for lithium.[102] Antidepressants have not been found to be of any benefit over that found with mood stabilizers.[103]

Short courses of benzodiazepines may be used in addition to other medications until mood stabilizing become effective.[104]

### Alternative medicine

Several studies have suggested that omega 3 fatty acids may have beneficial effects on depressive symptoms, but not manic symptoms. However, only a few small studies of variable quality have been published and there is not enough evidence to draw any firm conclusions.[105]

## Prognosis

A lifelong condition with periods of partial or full recovery in between recurrent episodes of relapse,[22][105] bipolar disorder is considered to be a major health problem worldwide because of the increased rates of disability and premature mortality.[105] It is also associated with co-occurring psychiatric and medical problems and high rates of initial under- or misdiagnosis, causing a delay in appropriate treatment interventions and contributing to poorer prognoses.[24] After a diagnosis is made, it remains is difficult to achieve complete remission of all symptoms with the currently available psychiatric medications and symptoms often become progressively more severe over time.[71][106]

Compliance with medications is one of the most significant factors that can decrease the rate and severity of relapse and have a positive impact on overall prognosis.[107] However, the types of medications used in treating BD commonly cause side effects[108] and more than 75% of individuals with BD inconsistently take their medications for various reasons.[107]

Of the various types of the disorder, rapid cycling (four or more episodes in one year) is associated with the worst prognosis due to higher rates of self-harm and suicide.[22] Individuals diagnosed with bipolar who have a family history of bipolar disorder are at a greater risk for more frequent manic/hypomanic episodes.[109] Early onset and psychotic features are also associated with worse outcomes,[110][111] as well as subtypes that are nonresponsive to lithium.[106]

Early recognition and intervention also improve prognosis as the symptoms in earlier stages are less severe and more responsive to treatment.[106] Onset after adolescence is connected to better prognoses for both genders, and being male is a protective factor against higher levels of depression. For women, better social functioning prior to developing bipolar disorder and being a parent are protective towards suicide attempts.[109]

### Functioning

People with bipolar disorder often experience a decline in cognitive functioning during (or possibly before) their first episode, after which a certain degree of cognitive dysfunction typically becomes permanent, with more severe impairment during acute phases and moderate impairment during periods of remission. As a result, two-thirds of people with BD continue to experience impaired psychosocial functioning in between episodes even when their mood symptoms are in full remission. A similar pattern in seen in both BD-I and BD-II, but people with BD-II experience a lesser degree of impairment.[108] Cognitive deficits typically

increase over the course of the illness. Higher degrees of impairment correlate with the number of previous manic episodes and hospitalizations, and with the presence psychotic symptoms.[112] Early intervention can slow the progression of cognitive impairment, while treatment at later stages can help reduce distress and negative consequences related to cognitive dysfunction.[106]

Despite the overly ambitious goals that are frequently part of manic episodes, symptoms of mania undermine the ability to achieve these goals and often interfere an individual's social and occupational functioning. One third of people with BD remain unemployed for one year following a hospitalization for mania.[113] Depressive symptoms during and between episodes, which occur much more frequently for most people than hypomanic or manic symptoms over the course of illness, are associated with lower functional recovery in between episodes, including unemployment or underemployment for both BD-I and BD-II.[3][114] However, the course of illness (duration, age of onset, number of hospitalizations, and presence or not of rapid cycling) and cognitive performance are the best predictors of employment outcomes in individuals with bipolar disorder, followed by symptoms of depression and years of education.[114]

### Recovery and recurrence

A naturalistic study from first admission for mania or mixed episode (representing the hospitalized and therefore most severe cases) found that 50 percent achieved syndromal recovery (no longer meeting criteria for the diagnosis) within six weeks and 98 percent within two years. Within two years, 72 percent achieved symptomatic recovery (no symptoms at all) and 43 percent achieved functional recovery (regaining of prior occupational and residential status). However, 40 percent went on to experience a new episode of mania or depression within 2 years of syndromal recovery, and 19 percent switched phases without recovery.[115]

Symptoms preceding a relapse (prodromal), specially those related to mania, can be reliably identified by people with bipolar disorder.[116] There have been intents to teach patients coping strategies when noticing such symptoms with encouraging results.[117]

### Suicide

Bipolar disorder can cause suicidal ideation that leads to suicidal attempts. Individuals whose bipolar disorder begins with a depressive or mixed affective episode seem to have a poorer prognosis and an increased risk of suicide.[73] One out of two people with bipolar disorder attempt suicide at least once during their lifetime and many attempts are successfully completed.[30] The annual average suicide rate is 0.4 percent, which is 10–20 times that of the general population.[118] The standardized mortality ratio from suicide in bipolar disorder is between 18 and 25.[119] The lifetime risk of suicide has been estimated to be as high as 20 percent in those with bipolar disorder.[9]

## Epidemiology

Bipolar disorder is the sixth leading cause of disability worldwide and has a lifetime prevalence of about 3 percent in the general population.[6][120] However, a reanalysis of data from the National Epidemiological Catchment Area survey in the United States suggested that 0.8 percent of the population experience a manic episode at least once (the diagnostic threshold for bipolar I) and a further 0.5 percent have a hypomanic episode (the diagnostic threshold for bipolar II or cyclothymia). Including sub-threshold diagnostic criteria, such as one or two symptoms over a short time-period, an additional 5.1 percent of the population, adding up to a total of 6.4 percent, were classified as having a bipolar spectrum disorder.[121] A more recent analysis of data from a second US National Comorbidity Survey found that 1 percent met

Burden of bipolar disorder around the world: disability-adjusted life years per 100,000 inhabitants in 2004.

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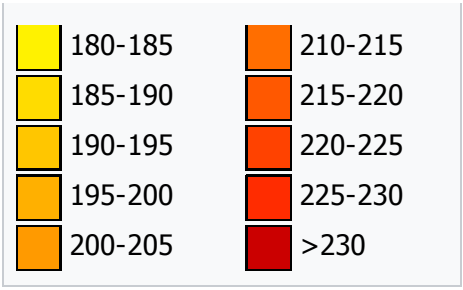
lifetime prevalence criteria for bipolar I, 1.1 percent for bipolar II, and 2.4 percent for subthreshold symptoms.[122]




There are conceptual and methodological limitations and variations in the findings. Prevalence studies of bipolar disorder are typically carried out by lay interviewers who follow fully structured/fixed interview schemes; responses to single items from such interviews may suffer limited validity. In addition, diagnoses (and therefore estimates of prevalence) vary depending on whether a categorical or spectrum approach is used. This consideration has led to concerns about the potential for both underdiagnosis and overdiagnosis.[123]

The incidence of bipolar disorder is similar in men and women[124] as well as across different cultures and ethnic groups.[125] A 2000 study by the World Health Organization found that prevalence and incidence of bipolar disorder are very similar across the world. Age-standardized prevalence per 100,000 ranged from 421.0 in South Asia to 481.7 in Africa and Europe for men and from 450.3 in Africa and Europe to 491.6 in Oceania for women. However, severity may differ widely across the globe. Disability-adjusted life year rates, for example, appear to be higher in developing countries, where medical coverage may be poorer and medication less available.[126] Within the United States, Asian Americans have significantly lower rates than their African and European American counterparts.[127]

Late adolescence and early adulthood are peak years for the onset of bipolar disorder.[128][129] One study also found that in 10 percent of bipolar cases, the onset of mania had happened after the patient had turned 50.[130]

## History

*Main article: History of bipolar disorder*

German psychiatrist Emil Kraepelin first distinguished between manic–depressive illness and "dementia praecox" (now known as schizophrenia) in the late 19th century

Variations in moods and energy levels have been observed as part of the human experience since throughout history. The words "melancholia", an old word for depression, and "mania" originated in Ancient Greece. The word melancholia is derived from *melas* (μελας), meaning "black", and *chole* (χολη), meaning "bile" or "gall",[131] indicative of the term's origins in pre-Hippocratic humoral theory. Within the humoral theories, mania was viewed as arising from an excess of yellow bile, or a mixture of black and yellow bile. The linguistic origins of mania, however, are not so clear-cut. Several etymologies were proposed by the Ancient Roman physician Caelius Aurelianus, including the Greek word *ania*, meaning "to produce great mental anguish", and *manos*, meaning "relaxed" or "loose", which would contextually approximate to an excessive relaxing of the mind or soul.[132] There are at least five other candidates, and part of the confusion surrounding the exact etymology of the word mania is its varied usage in the pre-Hippocratic poetry and mythology.[132]

In the early 1800s, French psychiatrist Jean-Étienne Dominique Esquirol's lypemania, one of his affective monomanias, was the first elaboration on what was to become modern depression.[133] The basis of the current conceptualisation of bipolar illness can be traced back to the 1850s; on January 31, 1854, Jules Baillarger described to the French Imperial Académie Nationale de Médecine a biphasic mental illness causing recurrent oscillations between mania and depression, which he termed *folie à double forme* (dual-form insanity).[134] Two weeks later, on February 14, 1854, Jean-Pierre Falret presented a description to the Academy on what was essentially the same disorder, and which he

called *folie circulaire* (circular insanity).[135]

These concepts were developed by the German psychiatrist Emil Kraepelin (1856–1926), who, using Kahlbaum's concept of cyclothymia,[136] categorized and studied the natural course of untreated bipolar patients. He coined the term *manic depressive psychosis*, after noting that periods of acute illness, manic or depressive, were generally punctuated by relatively symptom-free intervals where the patient was able to function normally.[137]

The term "manic–depressive *reaction*" appeared in the first version of the DSM in 1952, influenced by the legacy of Adolf Meyer.[138] Subtyping into "unipolar" depressive disorders and bipolar disorders was first proposed by German psychiatrists Karl Kleist and Karl Leonhard in the 1950s and they have regarded as a separate conditions since publication of the DSM-III. The subtypes bipolar II and rapid cycling have been included since the DSM-IV, based on work from the 1970s by David Dunner, Elliot Gershon, Frederick Goodwin, Ronald Fieve and Joseph Fleiss.[139][140][141]

## Society and culture

*See also: List of people with bipolar disorder, Category:Books about bipolar disorder, and Category:Films about bipolar disorder*

There are widespread problems with social stigma, stereotypes, and prejudice against individuals with a diagnosis of bipolar disorder.[142]

Kay Redfield Jamison, a clinical psychologist and professor of psychiatry at the Johns Hopkins University School of Medicine, profiled her own bipolar disorder in her memoir *An Unquiet Mind* (1995).[143] In his autobiography *Manicdotes: There's Madness in His Method* (2008) Chris Joseph describes his struggle between the creative dynamism which allowed the creation of his multimillion-pound advertising agency Hook Advertising, and the money-squandering dark despair of his bipolar illness.[144]

Several dramatic works have portrayed characters with traits suggestive of the diagnosis that has been the subject of discussion by psychiatrists and film experts alike. A notable example is *Mr. Jones* (1993), in which Mr. Jones (Richard Gere) swings from a manic episode into a depressive phase and back again, spending time in a psychiatric hospital and displaying many of the features of the syndrome.[145] In *The Mosquito Coast* (1986), Allie Fox (Harrison Ford) displays some features including recklessness, grandiosity, increased goal-directed activity and mood lability, as well as some paranoia.[146] Psychiatrists have suggested that Willy Loman, the main character in Arthur Miller's classic play *Death of a Salesman*, suffers from bipolar disorder,[147] though that specific term for the condition did not exist when the play was written.

Singer Rosemary Clooney's public revelation of bipolar disorder in 1977 made her an early celebrity spokeswoman for mental illness[*citation needed*]

TV specials, for example the BBC's *Stephen Fry: The Secret Life of the Manic Depressive*,[148] MTV's *True Life: I'm Bipolar*, talk shows, and public radio shows, and the greater willingness of public figures to discuss their own bipolar disorder, have focused on psychiatric conditions, thereby, raising public awareness.

On April 7, 2009, the nighttime drama *90210* on the CW network, aired a special episode where the character Silver was diagnosed with bipolar disorder.[149] Stacey Slater, a character from the BBC soap EastEnders, has been diagnosed with the disorder. The storyline was developed as part of the BBC's Headroom campaign.[150] The Channel 4 soap *Brookside* had earlier featured a story about bipolar disorder when the character Jimmy Corkhill was diagnosed with the condition.[151] 2011 Showtime's political thriller drama *Homeland* protagonist Carrie Mathison is bipolar, which she has kept secret since her school days.[152] In April 2014, ABC premiered a medical drama, *Black Box*, in which the main character, a world-

renowned neuroscientist, is bipolar.[153]

# Specific populations

## Children

*Main article: Bipolar disorder in children*

In the 1920s, Emil Kraepelin noted that manic episodes are rare before puberty.[154] In general, bipolar disorder in children was not recognized in the first half of the twentieth century. This issue diminished with an increased following of the DSM criteria in the last part of the twentieth century.[154][155]

Lithium is the only medication approved by the FDA for treating mania in children

While in adults the course of bipolar disorder is characterized by discrete episodes of depression and mania with no clear symptomatology between them, in children and adolescents very fast mood changes or even chronic symptoms are the norm.[156] Pediatric bipolar disorder is commonly characterized by outbursts of anger, irritability and psychosis, rather than euphoric mania, which is more likely to be seen in adults.[154][156] Early onset bipolar disorder is more likely to manifest as depression rather than mania or hypomania.[157]

The diagnosis of childhood bipolar disorder is controversial,[156] although it is not under discussion that the typical symptoms of bipolar disorder have negative consequences for minors suffering them.[154] The debate is mainly centered on whether what is called bipolar disorder in children refers to the same disorder as when diagnosing adults,[154] and the related question of whether the criteria for diagnosis for adults are useful and accurate when applied to children.[156] Regarding diagnosis of children, some experts recommend following the DSM criteria.[156] Others believe that these criteria do not correctly separate children with bipolar disorder from other problems such as ADHD, and emphasize fast mood cycles.[156] Still others argue that what accurately differentiates children with bipolar disorder is irritability.[156] The practice parameters of the AACAP encourage the first strategy.[154][156] American children and adolescents diagnosed with bipolar disorder in community hospitals increased 4-fold reaching rates of up to 40 percent in 10 years around the beginning of the 21st century, while in outpatient clinics it doubled reaching 6 percent.[156] Studies using DSM criteria show that up to 1 percent of youth may have bipolar disorder.[154]

Treatment involves medication and psychotherapy.[156] Drug prescription usually consists in mood stabilizers and atypical antipsychotics.[156] Among the former, lithium is the only compound approved by the FDA for children.[154] Psychological treatment combines normally education on the disease, group therapy and cognitive behavioral therapy.[156] Chronic medication is often needed.[156]

Current research directions for bipolar disorder in children include optimizing treatments, increasing the knowledge of the genetic and neurobiological basis of the pediatric disorder and improving diagnostic criteria.[156] Some treatment research suggests that psychosocial interventions that involve the family, psychoeducation, and skills building (through therapies such as CBT, DBT, and IPSRT) can benefit in a pharmocotherapy.[158] Unfortunately, the literature and research on the effects of psychosocial therapy on BPSD is scarce, making it difficult to determine the efficacy of various therapies.[158] The DSM-5 has proposed a new diagnosis which is considered to cover some presentations currently thought of as childhood-onset bipolar.[159]

## Elderly

There is a relative lack of knowledge about bipolar disorder in late life. There is evidence that it becomes

less prevalent with age but nevertheless accounts for a similar percentage of psychiatric admissions; that older bipolar patients had first experienced symptoms at a later age; that later onset of mania is associated with more neurologic impairment; that substance abuse is considerably less common in older groups; and that there is probably a greater degree of variation in presentation and course, for instance individuals may develop new-onset mania associated with vascular changes, or become manic only after recurrent depressive episodes, or may have been diagnosed with bipolar disorder at an early age and still meet criteria. There is also some weak and not conclusive evidence that mania is less intense and there is a higher prevalence of mixed episodes, although there may be a reduced response to treatment. Overall, there are likely more similarities than differences from younger adults.[160][161] In the elderly, recognition and treatment of bipolar disorder may be complicated by the presence of dementia or the side effects of medications being taken for other conditions.[162]

## See also

- Bipolar disorders research
- *Bipolar Disorders* (journal)

## Notes


1. ^ Coyle, Nessa; Paice, Judith A. (2015). *Oxford Textbook of Palliative Nursing*. Oxford University Press, Incorporated. p. 623. ISBN 9780199332342.
2. ^ *a b c d e f g h i j k l* Anderson IM, Haddad PM, Scott J (Dec 27, 2012). "Bipolar disorder". *BMJ (Clinical research ed.)*. **345**: e8508. doi:10.1136/bmj.e8508. PMID 23271744.
3. ^ *a b c d e f g h i j k* American Psychiatry Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington: American Psychiatric Publishing. pp. 123–154. ISBN 0-89042-555-8.
4. ^ Goodwin, Guy M. "Bipolar disorder". *Medicine*. **40** (11): 596–598. doi:10.1016/j.mpmed.2012.08.011.
5. ^ NIMH (April 2016). "Bipolar Disorder". National Institutes of Health. Retrieved August 13, 2016.
6. ^ *a b* Schmitt A, Malchow B, Hasan A, Falkai P (February 2014). "The impact of environmental factors in severe psychiatric disorders". *Front Neurosci*. **8** (19). doi:10.3389/fnins.2014.00019. PMC 3920481. PMID 24574956.
7. ^ Diflorio, A; Jones, I (2010). "Is sex important? Gender differences in bipolar disorder". *International Review of Psychiatry (Abingdon, England)*. **22** (5): 437–52. doi:10.3109/09540261.2010.514601. PMID 21047158.
8. ^ *a b* Hirschfeld, RM; Vornik, LA (Jun 2005). "Bipolar disorder—costs and comorbidity.". *The American journal of managed care*. **11** (3 Suppl): S85–90. PMID 16097719.
9. ^ *a b c d e f g h i j* Barnett JH, Smoller JW (2009). "The genetics of bipolar disorder". *Neuroscience*. **164** (1): 331–43. doi:10.1016/j.neuroscience.2009.03.080. PMC 3637882. PMID 19358880.
10. ^ *a b c d e f g h i j k* Beentjes TA, Goossens PJ, Poslawsky IE (October 2012). "Caregiver burden in bipolar hypomania and mania: a systematic review". *Perspect Psychiatr Care*. **48** (4): 187–97. doi:10.1111/j.1744-6163.2012.00328.x. PMID 23005586.
11. ^ *a b c* Salvadore G, Quiroz JA, Machado-Vieira R, Henter ID, Manji HK, Zarate CA (November 2010). "The neurobiology of the switch process in bipolar disorder: a review". *J Clin Psychiatry*. **71** (11): 1488–1501. doi:10.4088/JCP.09r05259gre. PMC 3000635. PMID 20492846.
12. ^ Titmarsh S (May–June 2013). "Characteristics and duration of mania: implications for continuation treatment". *Progress in Neurology and Psychiatry*. **17** (3): 26–7. doi:10.1002/pnp.283.
13. ^ *a b* Tarr GP, Glue P, Herbison P (November 2011). "Comparative efficacy and acceptability of mood stabilizer and second generation antipsychotic monotherapy for acute mania—a systematic review and meta-analysis". *J Affect Disord*. **134** (1–3): 14–9. doi:10.1016/j.jad.2010.11.009. PMID 21145595.
14. ^ *a b* Post RM, Kalivas P (March 2013). "Bipolar disorder and substance misuse: pathological and therapeutic implications of their comorbidity and cross-sensitisation". *Br J Psychiatry*. **202** (3): 172–6. doi:10.1192/bjp.bp.112.116855. PMID 23457180.
15. ^ Knowles R, McCarthy-Jones S, Rowse G (June 2011). "Grandiose delusions: a review and theoretical integration of cognitive and affective perspectives". *Clin Psychol Rev*. **31** (4): 684–96. doi:10.1016/j.cpr.2011.02.009. PMID 21482326.
16. ^ Furukawa TA (2010). "Assessment of mood: Guides for clinicians". *Journal of Psychosomatic Research*. **68** (6):

581–589. doi:10.1016/j.jpsychores.2009.05.003 . PMID 20488276 .
17. ^ McKenna BS, Eyler LT (November 2012). "Overlapping prefrontal systems involved in cognitive and emotional processing in euthymic bipolar disorder and following sleep deprivation: a review of functional neuroimaging studies". *Clin Psychol Rev*. **32** (7): 650–63. doi:10.1016/j.cpr.2012.07.003. PMC 3922056. PMID 22926687.
18. ^ a b Mansell W, Pedley R (Mar 2008). "The ascent into mania: a review of psychological processes associated with the development of manic symptoms.". *Clinical Psychology Review*. **28** (3): 494–520. doi:10.1016/j.cpr.2007.07.010. PMID 17825463.
19. ^ a b c Bowins B (2007). "Cognitive regulatory control therapies". *Am J Psychother*. **67** (3): 215–36. PMID 24236353.
20. ^ "Bipolar Disorder: NIH Publication No. 95-3679". U.S. National Institutes of Health. September 1995. Archived from the original on April 29, 2008.
21. ^ "Bipolar II Disorder Symptoms and Signs". Web M.D. Retrieved December 6, 2010.
22. ^ a b c d e Muneer A (June 2013). "Treatment of the depressive phase of bipolar affective disorder: a review". *J Pak Med Assoc*. **63** (6): 763–9. PMID 23901682.
23. ^ "Practice Guideline for the Treatment of Patients With Bipolar Disorder Second Edition". *APA Practice Guidelines for the Treatment of Psychiatric Disorders: Comprehensive Guidelines and Guideline Watches*. **1**. 2006. doi:10.1176/appi.books.9780890423363.50051. ISBN 978-0-89042-336-3.
24. ^ a b Bowden CL (January 2001). "Strategies to reduce misdiagnosis of bipolar depression". *Psychiatr Serv*. **52** (1): 51–5. doi:10.1176/appi.ps.52.1.51. PMID 11141528.
25. ^ Muzina DJ, Kemp DE, McIntyre RS (October–December 2007). "Differentiating bipolar disorders from major depressive disorders: treatment implications". *Ann Clin Psychiatry*. **19** (4): 305–12. doi:10.1080/10401230701653591. PMID 18058287.
26. ^ a b c d e Swann AC, Lafer B, Perugi G, Frye MA, Bauer M, Bahk WM, Scott J, Ha K, Suppes T (January 2013). "Bipolar mixed states: an international society for bipolar disorders task force report of symptom structure, course of illness, and diagnosis". *Am J Psychiatry*. **170** (1): 31–42. doi:10.1176/appi.ajp.2012.12030301. PMID 23223893.
27. ^ Srivastava S, Ketter TA (December 2010). "The link between bipolar disorders and creativity: evidence from personality and temperament studies.". *Current psychiatry reports*. **12** (6): 522–30. doi:10.1007/s11920-010-0159-x. PMID 20936438.
28. ^ Goodwin & Jamison 2007, p. 338.
29. ^ Reinhardt MC, Reinhardt CA (March–April 2013). "Attention deficit-hyperactivity disorder, comorbidities, and risk situations". *J Pediatr (Rio J)*. **89** (2): 124–30. doi:10.1016/j.jped.2013.03.015. PMID 23642421.
30. ^ a b c d e Kerner B (February 2014). "Genetics of bipolar disorder". *Appl Clin Genet*. **7**: 33–42. doi:10.2147/tacg.s39297. PMC 3966627. PMID 24683306.
31. ^ Cirillo PC, Passos RB, Bevilaqua MC, López JR, Nardi AE (December 2012). "Bipolar disorder and Premenstrual Syndrome or Premenstrual Dysphoric Disorder comorbidity: a systematic review". *Rev Bras Psiquiatr*. **34** (4): 467–79. doi:10.1016/j.rbp.2012.04.010. PMID 23429819.
32. ^ Sagman D, Tohen M (2009). "Comorbidity in Bipolar Disorder: The Complexity of Diagnosis and Treatment". *Psychiatric Times*.
33. ^ a b Nierenberg AA, Kansky C, Brennan BP, Shelton RC, Perlis R, Iosifescu DV (January 2013). "Mitochondrial modulators for bipolar disorder: a pathophysiologically informed paradigm for new drug development". *Aust N Z J Psychiatry*. **47** (1): 26–42. doi:10.1177/0004867412449303. PMID 22711881.
34. ^ a b Edvardsen J, Torgersen S, Røysamb E, Lygren S, Skre I, Onstad S, Oien PA (2008). "Heritability of bipolar spectrum disorders. Unity or heterogeneity?". *Journal of Affective Disorders*. **106** (3): 229–240. doi:10.1016/j.jad.2007.07.001. PMID 17692389.
35. ^ Kieseppä T, Partonen T, Haukka J, Kaprio J, Lönnqvist J (2004). "High Concordance of Bipolar I Disorder in a Nationwide Sample of Twins". *American Journal of Psychiatry*. **161** (10): 1814–1821. doi:10.1176/appi.ajp.161.10.1814. PMID 15465978.
36. ^ McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A (2003). "The Heritability of Bipolar Affective Disorder and the Genetic Relationship to Unipolar Depression". *Archives of General Psychiatry*. **60** (5): 497–502. doi:10.1001/archpsyc.60.5.497. PMID 12742871.
37. ^ Reich T, Clayton PJ, Winokur G (1969). "Family history studies: V. The genetics of mania". *The American Journal of Psychiatry*. **125** (10): 1358–1369. doi:10.1176/ajp.125.10.1358. PMID 5304735.
38. ^ a b c Craddock N, Sklar P (May 2013). "Genetics of bipolar disorder". *Lancet*. **381** (9878): 1654–62. doi:10.1016/S0140-6736(13)60855-7. PMID 23663951.
39. ^ Segurado R, Detera-Wadleigh SD, Levinson DF, Lewis CM, Gill M, Nurnberger JI, Craddock N, DePaulo JR, Baron M, Gershon ES, Ekholm J, Cichon S, Turecki G, Claes S, Kelsoe JR, Schofield PR, Badenhop RF, Morissette J, Coon H, Blackwood D, McInnes LA, Foroud T, Edenberg HJ, Reich T, Rice JP, Goate A, McInnis MG, McMahon FJ, Badner JA,

Goldin LR, Bennett P, Willour VL, Zandi PP, Liu J, Gilliam C, Juo SH, Berrettini WH, Yoshikawa T, Peltonen L, Lönnqvist J, Nöthen MM, Schumacher J, Windemuth C, Rietschel M, Propping P, Maier W, Alda M, Grof P, Rouleau GA, Del-Favero J, Van Broeckhoven C, Mendlewicz J, Adolfsson R, Spence MA, Luebbert H, Adams LJ, Donald JA, Mitchell PB, Barden N, Shink E, Byerley W, Muir W, Visscher PM, Macgregor S, Gurling H, Kalsi G, McQuillin A, Escamilla MA, Reus VI, Leon P, Freimer NB, Ewald H, Kruse TA, Mors O, Radhakrishna U, Blouin JL, Antonarakis SE, Akarsu N (2003). "Genome Scan Meta-Analysis of Schizophrenia and Bipolar Disorder, Part III: Bipolar Disorder". *The American Journal of Human Genetics*. **73** (1): 49–62. doi:10.1086/376547. PMC 1180589. PMID 12802785.

40. ^ Frans EM, Sandin S, Reichenberg A, Lichtenstein P, Långström N, Hultman CM (2008). "Advancing Paternal Age and Bipolar Disorder". *Archives of General Psychiatry*. **65** (9): 1034–1040. doi:10.1001/archpsyc.65.9.1034. PMID 18762589.
41. ^ Kempton MJ, Geddes JR, Ettinger U, Williams SC, Grasby PM (2008). "Meta-analysis, Database, and Meta-regression of 98 Structural Imaging Studies in Bipolar Disorder". *Archives of General Psychiatry*. **65** (9): 1017–1032. doi:10.1001/archpsyc.65.9.1017. PMID 18762588.
42. ^ Arnone D, Cavanagh J, Gerber D, Lawrie SM, Ebmeier KP, McIntosh AM (2009). "Magnetic resonance imaging studies in bipolar disorder and schizophrenia: Meta-analysis". *The British Journal of Psychiatry*. **195** (3): 194–201. doi:10.1192/bjp.bp.108.059717. PMID 19721106.
43. ^ "Bipolar MRI Database". *Bipolar Disorder Neuroimaging Database (BiND)*.
44. ^ Strakowski SM, Adler CM, Almeida J, Altshuler LL, Blumberg HP, Chang KD, DelBello MP, Frangou S, McIntosh A, Phillips ML, Sussman JE, Townsend JD (2012). "The functional neuroanatomy of bipolar disorder: A consensus model". *Bipolar Disorders*. **14** (4): 313–325. doi:10.1111/j.1399-5618.2012.01022.x. PMID 22631617.
45. ^ Chen, Chi-Hua; Suckling, John; Lennox, Belinda R.; Ooi, Cinly; Bullmore, Ed T. (1 February 2011). "A quantitative meta-analysis of fMRI studies in bipolar disorder". *Bipolar Disorders*. **13** (1): 1–15. doi:10.1111/j.1399-5618.2011.00893.x. ISSN 1399-5618. PMID 21320248.
46. ^ Houenou, Josselin; Frommberger, Juliane; Carde, Soufiane; Glasbrenner, Manuela; Diener, Carsten; Leboyer, Marion; Wessa, Michèle (1 April 2011). "Neuroimaging-based markers of bipolar disorder: Evidence from two meta-analyses". *Journal of Affective Disorders*. **132** (3): 344–355. doi:10.1016/j.jad.2011.03.016. ISSN 1573-2517.
47. ^ Nusslock, Robin; Young, Christina B.; Damme, Katherine S. F. (1 November 2014). "Elevated reward-related neural activation as a unique biological marker of bipolar disorder: assessment and treatment implications". *Behaviour Research and Therapy*. **62**: 74–87. doi:10.1016/j.brat.2014.08.011. ISSN 1873-622X. PMID 25241675.
48. ^ Bender RE, Alloy LB (April 2011). "Life stress and kindling in bipolar disorder: review of the evidence and integration with emerging biopsychosocial theories". *Clin Psychol Rev*. **31** (3): 383–98. doi:10.1016/j.cpr.2011.01.004. PMC 3072804. PMID 21334286.
49. ^ Lee HJ, Son GH, Geum D (September 2013). "Circadian Rhythm Hypotheses of Mixed Features, Antidepressant Treatment Resistance, and Manic Switching in Bipolar Disorder". *Psychiatry Investig*. **10** (3): 225–32. doi:10.4306/pi.2013.10.3.225. PMC 3843013. PMID 24302944.
50. ^ Brown & Basso 2004, p. 16.
51. ^ Dallaspezia S, Benedetti F (December 2009). "Melatonin, circadian rhythms, and the clock genes in bipolar disorder". *Curr Psychiatry Rep*. **11** (6): 488–93. doi:10.1007/s11920-009-0074-1. PMID 19909672.
52. ^ Serretti A, Mandelli L (2008). "The genetics of bipolar disorder: Genome 'hot regions,' genes, new potential candidates and future directions". *Molecular Psychiatry*. **13** (8): 742–771. doi:10.1038/mp.2008.29. PMID 18332878.
53. ^ *a b c d* Geddes JR, Miklowitz DJ (May 11, 2013). "Treatment of bipolar disorder". *Lancet*. **381** (9878): 1672–82. doi:10.1016/S0140-6736(13)60857-0. PMID 23663953.
54. ^ Brietzke E, Kauer Sant'anna M, Jackowski A, Grassi-Oliveira R, Bucker J, Zugman A, Mansur RB, Bressan RA (December 2012). "Impact of childhood stress on psychopathology" (PDF). *Rev Bras Psiquiatr*. **34** (4): 480–8. doi:10.1016/j.rbp.2012.04.009. PMID 23429820.
55. ^ Miklowitz DJ, Chang KD (2008). "Prevention of bipolar disorder in at-risk children: Theoretical assumptions and empirical foundations". *Development and Psychopathology*. **20** (3): 881–897. doi:10.1017/S0954579408000424. PMC 2504732. PMID 18606036.
56. ^ Murray ED, Buttner N, Price BH. (2012) Depression and Psychosis in Neurological Practice. In: Neurology in Clinical Practice, 6th Edition. Bradley WG, Daroff RB, Fenichel GM, Jankovic J (eds.) Butterworth Heinemann. April 12, 2012. ISBN 1-4377-0434-4 | ISBN 978-1-4377-0434-1
57. ^ Lahera G, Freund N, Sáiz-Ruiz J (January–March 2013). "Salience and dysregulation of the dopaminergic system" (PDF). *Rev Psquiatr Salud Ment*. **6** (1): 45–51. doi:10.1016/j.rpsm.2012.05.003. PMID 23084802.
58. ^ Berk M, Dodd S, Kauer-Sant'anna M, Malhi GS, Bourin M, Kapczinski F, Norman T (2007). "Dopamine dysregulation syndrome: implications for a dopamine hypothesis of bipolar disorder". *Acta Psychiatr Scanda Suppl*. **116** (Supplement s434): 41–49. doi:10.1111/j.1600-0447.2007.01058.x. PMID 17688462.

59. ^ Michael N, Erfurth A, Ohrmann P, Gössling M, Arolt V, Heindel W, Pfleiderer B (2003). "Acute mania is accompanied by elevated glutamate/glutamine levels within the left dorsolateral prefrontal cortex". *Psychopharmacology*. **168** (3): 344–346. doi:10.1007/s00213-003-1440-z. PMID 12684737.
60. ^ Benes FM, Berretta S (2001). "GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder". *Neuropsychopharmacology*. **25** (1): 1–27. doi:10.1016/S0893-133X(01)00225-1. PMID 11377916.
61. ^ Manji, Husseini K.; Lenox, Robert H. (September 2000). "Signaling: Cellular Insights into the Pathophysiology of Bipolar Disorder". *Biological Psychiatry*. **48** (6): 518–530. doi:10.1016/S0006-3223(00)00929-X. PMID 11018224.
62. ^ Kapczinski, Flávio; Frey, Benício Noronha; Zannatto, Vanessa (1 October 2004). "[Physiopathology of bipolar disorders: what have changed in the last 10 years?]". *Revista Brasileira De Psiquiatria (Sao Paulo, Brazil: 1999)*. 26 Suppl 3: 17–21. doi:10.1590/S1516-44462004000700005. ISSN 1516-4446. PMID 15597134.
63. ^ Berns, Gregory S.; Nemeroff, Charles B. (15 November 2003). "The neurobiology of bipolar disorder". *American Journal of Medical Genetics*. **123C** (1): 76–84. doi:10.1002/ajmg.c.20016. ISSN 1552-4868.
64. ^ Manji, Husseini K.; Quiroz, Jorge A.; Payne, Jennifer L.; Singh, Jaskaran; Lopes, Barbara P.; Viegas, Jenilee S.; Zarate, Carlos A. (5 December 2016). "The underlying neurobiology of bipolar disorder". *World Psychiatry*. **2** (3): 136–146. ISSN 1723-8617. PMC 1525098. PMID 16946919.
65. ^ Miklowitz DJ, Chang KD (Summer 2008). "Prevention of bipolar disorder in at-risk children: theoretical assumptions and empirical foundations.". *Development and Psychopathology*. **20** (3): 881–97. doi:10.1017/s0954579408000424. PMC 2504732. PMID 18606036.
66. ^ Khan MA, Akella S (December 2009). "Cannabis-Induced Bipolar Disorder with Psychotic Features: A Case Report". *Psychiatry (Edgmont)*. **6** (12): 44–8. PMC 2811144. PMID 20104292.
67. ^ *a b c d* Price AL, Marzani-Nissen GR (March 2012). "Bipolar disorders: a review". *Am Fam Physician*. **85** (5): 483–93. PMID 22534227.
68. ^ Phillips ML, Kupfer DJ (May 2013). "Bipolar disorder diagnosis: challenges and future directions". *Lancet*. **381** (9878): 1663–71. doi:10.1016/S0140-6736(13)60989-7. PMID 23663952.
69. ^ Youngstrom, Eric Arden; Genzlinger, Jacquelynne E; Egerton, Gregory A.; Van Meter, Anna R. "Multivariate Meta-Analysis of the Discriminative Validity of Caregiver, Youth, and Teacher Rating Scales for Pediatric Bipolar Disorder: Mother Knows Best About Mania". *Archives of Scientific Psychology*. **3** (1): 112–137. doi:10.1037/arc0000024. Retrieved 7 December 2016.
70. ^ Perugi, G.; Ghaemi, S. N.; Akiskal, H. (2006). "Diagnostic and Clinical Management Approaches to Bipolar Depression, Bipolar II and Their Comorbidities". *Bipolar Psychopharmacotherapy*. *Caring for the Patient*. pp. 193–234. doi:10.1002/0470017953.ch11. ISBN 978-0-470-01795-1.
71. ^ *a b c* Carvalho, AF; et al. (Feb 2015). "Screening for bipolar spectrum disorders: A comprehensive meta-analysis of accuracy studies". *J Affective Disorders*. **172**: 337–46. doi:10.1016/j.jad.2014.10.024. PMID 25451435.
72. ^ *a b* Picardi A (2009). "Rating scales in bipolar disorder". *Current Opinion in Psychiatry*. **22** (1): 42–49. doi:10.1097/YCO.0b013e328315a4d2. PMID 19122534.
73. ^ *a b* Baldessarini RJ, Faedda GL, Offidani E, Vázquez GH, Marangoni C, Serra G, Tondo L (May 2013). "Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: a review". *J Affect Disord*. **148** (1): 129–35. doi:10.1016/j.jad.2012.10.033. PMID 23219059.
74. ^ Sood AB, Razdan A, Weller EB, Weller RA (2005). "How to differentiate bipolar disorder from attention deficit hyperactivity disorder and other common psychiatric disorders: A guide for clinicians". *Current psychiatry reports*. **7** (2): 98–103. doi:10.1007/s11920-005-0005-8. PMID 15802085.
75. ^ Magill CA (2004). "The boundary between borderline personality disorder and bipolar disorder: Current concepts and challenges". *Canadian Journal of Psychiatry*. **49** (8): 551–556. PMID 15453104.
76. ^ Bassett D (2012). "Borderline personality disorder and bipolar affective disorder. Spectra or spectre? A review". *Australian and New Zealand Journal of Psychiatry*. **46** (4): 327–339. doi:10.1177/0004867411435289. PMID 22508593.
77. ^ Peet, M; Peters, S (1995). "Drug-induced mania". *Drug Safety*. **12** (2): 146–53. doi:10.2165/00002018-199512020-00007. PMID 7766338.
78. ^ Korn ML. "Across the Bipolar Spectrum: From Practice to Research". Medscape.
79. ^ Beesdo K, Höfler M, Leibenluft E, Lieb R, Bauer M, Pfennig A (September 2009). "Mood episodes and mood disorders: patterns of incidence and conversion in the first three decades of life". *Bipolar Disord*. **11** (6): 637–49. doi:10.1111/j.1399-5618.2009.00738.x. PMC 2796427. PMID 19689506.
80. ^ *a b* Renk K, White R, Lauer BA, McSwiggan M, Puff J, Lowell A (February 2014). "Bipolar Disorder in Children". *Psychiatry J*. **2014** (928685): 1–19. doi:10.1155/2014/928685. PMC 3994906. PMID 24800202.
81. ^ Van Meter AR, Youngstrom EA, Findling RL (June 2012). "Cyclothymic disorder: a critical review". *Clin Psychol Rev*. **32** (4): 229–43. doi:10.1016/j.cpr.2012.02.001. PMID 22459786.
82. ^ Angst J, Sellaro R (2000). "Historical perspectives and natural history of bipolar disorder". *Biological Psychiatry*. **48**

(6): 445–457. doi:10.1016/s0006-3223(00)00909-4. PMID 11018218.
83. ^ Bauer M, Beaulieu S, Dunner DL, Lafer B, Kupka R (February 2008). "Rapid cycling bipolar disorder – diagnostic concepts". *Bipolar Disorders*. **10** (1 Pt 2): 153–62. doi:10.1111/j.1399-5618.2007.00560.x. PMID 18199234.
84. ^ Tillman R, Geller B (2003). "Definitions of Rapid, Ultrarapid, and Ultradian Cycling and of Episode Duration in Pediatric and Adult Bipolar Disorders: A Proposal to Distinguish Episodes from Cycles". *Journal of Child and Adolescent Psychopharmacology*. **13** (3): 267–271. doi:10.1089/104454603322572598. PMID 14642014.
85. ^ Fountoulakis KN, Kontis D, Gonda X, Yatham LN (March 2013). "A systematic review of the evidence on the treatment of rapid cycling bipolar disorder". *Bipolar Disord*. **15** (2): 115–37. doi:10.1111/bdi.12045. PMID 23437958.
86. ^ Becker T, Kilian R (2006). "Psychiatric services for people with severe mental illness across western Europe: What can be generalized from current knowledge about differences in provision, costs and outcomes of mental health care?". *Acta Psychiatrica Scandinavica*. **113** (429): 9–16. doi:10.1111/j.1600-0447.2005.00711.x. PMID 16445476.
87. ^ McGurk SR, Mueser KT, Feldman K, Wolfe R, Pascaris A (2007). "Cognitive Training for Supported Employment: 2–3 Year Outcomes of a Randomized Controlled Trial". *American Journal of Psychiatry*. **164** (3): 437–441. doi:10.1176/appi.ajp.164.3.437. PMID 17329468.
88. ^ Lam et al., 1999; Miklowitz & Goldstein, 1997; Frank, 2005.[*full citation needed*]
89. ^ Leahy & Johnson 2003.
90. ^ Basco & Rush 2005.
91. ^ Zaretsky AE, Rizvi S, Parikh SV (2007). "How well do psychosocial interventions work in bipolar disorder?". *Canadian Journal of Psychiatry*. **52** (1): 14–21. PMID 17444074.
92. ^ Havens LL, Ghaemi SN (2005). "Existential despair and bipolar disorder: The therapeutic alliance as a mood stabilizer". *American journal of psychotherapy*. **59** (2): 137–147. PMID 16170918.
93. ^ Brown KM, Tracy DK (June 2013). "Lithium: the pharmacodynamic actions of the amazing ion". *Ther Adv Psychopharmacol*. **3** (3): 163–76. doi:10.1177/2045125312471963. PMC 3805456. PMID 24167688.
94. ^ Cipriani A, Hawton K, Stockton S, Geddes JR (2013). "Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis". *BMJ*. **346**: f3646. doi:10.1136/bmj.f3646. PMID 23814104.
95. ^ McCloud, TL; Caddy, C; Joachim, J; Rendell, JM; Diamond, PR; Shuttleworth, C; Brett, D; Amit, BH; McShane, R; Hamadi, L; Hawton, K; Cipriani, A (September 29, 2015). "Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults.". *The Cochrane database of systematic reviews*. **9**: CD011611. doi:10.1002/14651858.CD011611.pub2. PMID 26415966.
96. ^ Post RM, Ketter TA, Uhde T, Ballenger JC (2007). "Thirty years of clinical experience with carbamazepine in the treatment of bipolar illness: Principles and practice". *CNS Drugs*. **21** (1): 47–71. doi:10.2165/00023210-200721010-00005. PMID 17190529.
97. ^ Rapoport SI, Basselin M, Kim HW, Rao JS (October 2009). "Bipolar disorder and mechanisms of action of mood stabilizers". *Brain Res Rev*. **61** (2): 185–209. doi:10.1016/j.brainresrev.2009.06.003. PMC 2757443. PMID 19555719.
98. ^ Macritchie K, Geddes JR, Scott J, Haslam D, de Lima M, Goodwin G (2003). "Valproate for acute mood episodes in bipolar disorder". In Reid K. *Cochrane Database of Systematic Reviews*. *Cochrane database of systematic reviews (Online)*. pp. CD004052. doi:10.1002/14651858.CD004052. PMID 12535506.
99. ^ Geddes JR, Calabrese JR, Goodwin GM (2008). "Lamotrigine for treatment of bipolar depression: Independent meta-analysis and meta-regression of individual patient data from five randomised trials". *The British Journal of Psychiatry*. **194** (1): 4–9. doi:10.1192/bjp.bp.107.048504. PMID 19118318.
100. ^ van der Loos ML, Kölling P, Knoppert-van der Klein EA, Nolen WA (2007). "Lamotrigine in the treatment of bipolar disorder, a review". *Tijdschrift voor psychiatrie*. **49** (2): 95–103. PMID 17290338.
101. ^ Vasudev K, Macritchie K, Geddes J, Watson S, Young A (2006). "Topiramate for acute affective episodes in bipolar disorder". In Young AH. *Cochrane Database of Systematic Reviews*. *Cochrane database of systematic reviews (Online)*. pp. CD003384. doi:10.1002/14651858.CD003384.pub2. PMID 16437453.
102. ^ Cipriani A, Rendell JM, Geddes J (2009). Cipriani A, ed. "Olanzapine in long-term treatment for bipolar disorder". *Cochrane database of systematic reviews (Online)* (1): CD004367. doi:10.1002/14651858.CD004367.pub2. PMID 19160237.
103. ^ El-Mallakh RS, Elmaadawi AZ, Loganathan M, Lohano K, Gao Y (July 2010). "Bipolar disorder: an update". *Postgraduate Medicine*. **122** (4): 24–31. doi:10.3810/pgm.2010.07.2172. PMID 20675968.
104. ^ "Benzodiazepines for Bipolar Disorder". WebMD.com. Retrieved February 13, 2013.
105. ^ *a b c* Montgomery P, Richardson AJ (April 16, 2008). Montgomery P, ed. "Omega-3 fatty acids for bipolar disorder". *The Cochrane database of systematic reviews* (2): CD005169. doi:10.1002/14651858.CD005169.pub2. PMID 18425912. "Currently, there is simply not enough existing evidence, and what evidence is currently available is of such a varied and often-times questionable nature that no reliable conclusions may be drawn."

106. ^ [a] [b] [c] [d] Muneer, Ather (2016), "Staging Models in Bipolar Disorder: A Systematic Review of the Literature", *Clinical Psychopharmacology & Neuroscience*, **14** (2): 117–30, doi:10.9758/cpn.2016.14.2.117, PMC 4857867, PMID 27121423
107. ^ [a] [b] Jann, Michael W. (2014), "Diagnosis and Treatment of Bipolar Disorders in Adults: A Review of the Evidence on Pharmacologic Treatments", *American Health & Drug Benefits*, **7** (9): 489–499, PMC 4296286, PMID 25610528
108. ^ [a] [b] Tsitsipa, Eirini; Fountoulakis, Konstantinos N. (1 December 2015), "The Neurocognitive Functioning in Bipolar Disorder: A Systematic Review of Data", *Annals of General Psychiatry*, **14**: 42, doi:10.1186/s12991-015-0081-z, PMC 4666163, PMID 26628905
109. ^ [a] [b] Maciukiewicz M, Pawlak J, Kapelski P, Łabędzka M, Skibinska M, Zaremba D, Leszczynska-Rodziewicz A, Dmitrzak-Weglarz M, Hauser J (2016). "Can Psychological, Social and Demographical Factors Predict Clinical Characteristics Symptomatology of Bipolar Affective Disorder and Schizophrenia?". *Psychiatr Q*. **87** (3): 501–13. doi:10.1007/s11126-015-9405-z. PMC 4945684. PMID 26646576.
110. ^ Kennedy KP, Cullen KR, DeYoung CG, Klimes-Dougan B (2015). "The genetics of early-onset bipolar disorder: A systematic review". *J Affect Disord*. **184**: 1–12. doi:10.1016/j.jad.2015.05.017. PMID 26057335.
111. ^ Serafini G, Pompili M, Borgwardt S, Houenou J, Geoffroy PA, Jardri R, Girardi P, Amore M (2014). "Brain changes in early-onset bipolar and unipolar depressive disorders: a systematic review in children and adolescents". *Eur Child Adolesc Psychiatry*. **23** (11): 1023–41. doi:10.1007/s00787-014-0614-z. PMID 25212880.
112. ^ Bortolato B, Miskowiak KW, Köhler CA, Vieta E, Carvalho AF (2015). "Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses". *Neuropsychiatr Dis Treat*. **11**: 3111–25. doi:10.2147/NDT.S76700. PMC 4689290. PMID 26719696.
113. ^ Johnson, Sheri L. (2005), "Mania and Dysregulation in Goal Pursuit: A Review", *Clinical Psychology Review*, **25** (2): 241–62, doi:10.1016/j.cpr.2004.11.002, PMC 2847498, PMID 15642648
114. ^ [a] [b] Tse S, Chan S, Ng KL, Yatham LN (2014). "Meta-analysis of predictors of favorable employment outcomes among individuals with bipolar disorder". *Bipolar Disord*. **16** (3): 217–29. doi:10.1111/bdi.12148. PMID 24219657.
115. ^ Tohen M, Zarate CA, Hennen J, Khalsa HM, Strakowski SM, Gebre-Medhin P, Salvatore P, Baldessarini RJ (2003). "The McLean-Harvard First-Episode Mania Study: Prediction of recovery and first recurrence". *The American Journal of Psychiatry*. **160** (12): 2099–2107. doi:10.1176/appi.ajp.160.12.2099. PMID 14638578.
116. ^ Jackson A, Cavanagh J, Scott J (2003). "A systematic review of manic and depressive prodromes". *Journal of Affective Disorders*. **74** (3): 209–217. doi:10.1016/s0165-0327(02)00266-5. PMID 12738039.
117. ^ Lam D, Wong G (2005). "Prodromes, coping strategies and psychological interventions in bipolar disorders". *Clinical Psychology Review*. **25** (8): 1028–1042. doi:10.1016/j.cpr.2005.06.005. PMID 16125292.
118. ^ Sadock, Kaplan & Sadock 2007, p. 388.
119. ^ Roger S. McIntyre, MD; Joanna K. Soczynska & Jakub Konarski. "Bipolar Disorder: Defining Remission and Selecting Treatment". Psychiatric Times, October 2006, Vol. XXIII, No. 11.
120. ^ Boland EM, Alloy LB (February 2013). "Sleep disturbance and cognitive deficits in bipolar disorder: toward an integrated examination of disorder maintenance and functional impairment". *Clin Psychol Rev*. **33** (1): 33–44. doi:10.1016/j.cpr.2012.10.001. PMC 3534911. PMID 23123569.
121. ^ Judd LL, Akiskal HS (2003). "The prevalence and disability of bipolar spectrum disorders in the US population: Re-analysis of the ECA database taking into account subthreshold cases". *Journal of Affective Disorders*. **73** (1–2): 123–131. doi:10.1016/s0165-0327(02)00332-4. PMID 12507745.
122. ^ Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC (2007). "Lifetime and 12-Month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication". *Archives of General Psychiatry*. **64** (5): 543–552. doi:10.1001/archpsyc.64.5.543. PMC 1931566. PMID 17485606.
123. ^ Phelps J (2006). "Bipolar Disorder: Particle or Wave? DSM Categories or Spectrum Dimensions?". *Psychiatric Times*.
124. ^ Farren CK, Hill KP, Weiss RD (December 2012). "Bipolar disorder and alcohol use disorder: a review". *Curr Psychiatry Rep*. **14** (6): 659–66. doi:10.1007/s11920-012-0320-9. PMC 3730445. PMID 22983943.
125. ^ Ferrari, AJ; Baxter, AJ; Whiteford, HA (2011). "A systematic review of the global distribution and availability of prevalence data for bipolar disorder". *J Affective Disorders*. Elsevier. **134**: 1–13. doi:10.1016/j.jad.2010.11.007. PMID 21131055.
126. ^ Ayuso-Mateos, Jose Luis. "Global burden of bipolar disorder in the year 2000" (PDF). World Health Organization. Retrieved December 9, 2012.
127. ^ Kurasaki, Karen S. (2002). *Asian American Mental Health: Assessment Theories and Methods*. pp. 14–15.
128. ^ Christie KA, Burke JD, Regier DA, Rae DS, Boyd JH, Locke BZ (1988). "Epidemiologic evidence for early onset of mental disorders and higher risk of drug abuse in young adults". *The American Journal of Psychiatry*. **145** (8): 971–

975. doi:10.1176/ajp.145.8.971 . PMID 3394882 .
129. ^ Goodwin & Jamison 2007, p. 1945.
130. ^ Monczor M (2010). "Bipolar disorder in the elderly". *Vertex (Buenos Aires, Argentina)*. **21** (92): 275–283. PMID 21188315.
131. ^ Liddell & Scott 1980.
132. ^ *a b* Angst J, Marneros A (December 2001). "Bipolarity from ancient to modern times: conception, birth and rebirth". *J Affect Disord*. **67** (1–3): 3–19. doi:10.1016/S0165-0327(01)00429-3. PMID 11869749.
133. ^ Borch-Jacobsen M (October 2010). "Which came first, the condition or the drug?". *London Review of Books*. **32** (19): 31–33. "at the beginning of the 19th century with Esquirol's 'affective monomanias' (notably 'lypemania', the first elaboration of what was to become our modern depression)"
134. ^ Pichot P (2004). "Circular insanity, 150 years on". *Bulletin de l'Academie nationale de medecine* (in French). **188** (2): 275–284. PMID 15506718.
135. ^ Sedler MJ (1983). "Falret's discovery: The origin of the concept of bipolar affective illness. Translated by M. J. Sedler and Eric C. Dessain". *The American Journal of Psychiatry*. **140** (9): 1127–1133. doi:10.1176/ajp.140.9.1127. PMID 6351641.
136. ^ Millon 1996, p. 290.
137. ^ Kraepelin, Emil (1921), *Manic–depressive Insanity and Paranoia*, ISBN 0-405-07441-7
138. ^ Goodwin & Jamison 2007, Chapter 1.
139. ^ Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy Carlos A. Zarate Jr., Husseini K. Manji, Springer Science & Business Media, April 16, 2009
140. ^ The course of bipolar disorder Kate E. A. Saunders and Guy M. Goodwin, Advances in Psychiatric Treatment (2010) 16: 318-328 doi:10.1192/apt.bp.107.004903
141. ^ DAVID L.DUNNER Interviewed by Thomas A. Ban for the ANCP, Waikoloa, Hawaii, December 13, 2001
142. ^ Elgie R. Morselli PL (Feb–Mar 2007). "Social functioning in bipolar patients: the perception and perspective of patients, relatives and advocacy organizations – a review". *Bipolar disorders*. **9** (1–2): 144–57. doi:10.1111/j.1399-5618.2007.00339.x. PMID 17391357.
143. ^ Jamison 1995.
144. ^ Joseph 2008.
145. ^ Robinson 2003, pp. 78–81.
146. ^ Robinson 2003, pp. 84–85.
147. ^ McKinley, Jesse (February 28, 1999). "Get That Man Some Prozac; If the Dramatic Tension Is All in His Head". *The New York Times*. Retrieved March 3, 2012.
148. ^ "The Secret Life of the Manic Depressive". BBC. 2006. Archived from the original on January 18, 2010. Retrieved February 20, 2007.
149. ^ "Child and Adolescent Bipolar Foundation special 90210 website". CABF. 2009. Retrieved April 7, 2009.[*dead link*]
150. ^ "EastEnders' Stacey faces bipolar disorder". BBC Press Office. May 14, 2009. Retrieved May 28, 2009.
151. ^ Tinniswood, Rachael (May 14, 2003). "The Brookie boys who shone at soap awards show". *Liverpool Echo*. Mirror Group Newspapers. Retrieved April 26, 2014.
152. ^ "Pilot". *Homeland*. Season 1. Episode 1. October 2, 2011. Showtime.
153. ^ "Catherine Black by Kelly Reilly". *abc.go.com*. ABC. Archived from the original on May 23, 2014. Retrieved May 22, 2014.
154. ^ *a b c d e f g h* McClellan J, Kowatch R, Findling RL (2007). Work Group on Quality Issues. "Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder". *Journal of the American Academy of Child & Adolescent Psychiatry*. **46** (1): 107–125. doi:10.1097/01.chi.0000242240.69678.c4. PMID 17195735.
155. ^ Anthony, J.; Scott, P. (1960). "Manic–depressive Psychosis in Childhood". *Journal of Child Psychology and Psychiatry*. **1**: 53–72. doi:10.1111/j.1469-7610.1960.tb01979.x.
156. ^ *a b c d e f g h i j k l m n* Leibenluft E, Rich BA (2008). "Pediatric Bipolar Disorder". *Annual Review of Clinical Psychology*. **4**: 163–187. doi:10.1146/annurev.clinpsy.4.022007.141216. PMID 17716034.
157. ^ Cosgrove VE, Roybal D, Chang KD (April 2013). "Bipolar depression in pediatric populations: epidemiology and management". *Paediatr Drugs*. **15** (2): 83–91. doi:10.1007/s40272-013-0022-8. PMID 23529869.
158. ^ *a b* Fristad, MA; MacPherson, HA (2014). "Evidence-based psychosocial treatments for child and adolescent bipolar spectrum disorders.". *Journal of Clinical Child and Adolescent Psychology*. **43** (3): 339–55. doi:10.1080/15374416.2013.822309. PMID 23927375.
159. ^ Roy, AK; et al. (Sep 2014). "Disruptive mood dysregulation disorder: a new diagnostic approach to chronic irritability in youth". *Am J Psychiatry*. **171** (9): 918–24. doi:10.1176/appi.ajp.2014.13101301. PMC 4390118. PMID 25178749.
160. ^ Vasudev A, Thomas A (July 2010). "'Bipolar disorder' in the elderly: what's in a name?". *Maturitas*. **66** (3): 231–5.

doi:10.1016/j.maturitas.2010.02.013. PMID 20307944.
161. ^ Depp CA, Jeste DV (2004). "Bipolar disorder in older adults: A critical review". *Bipolar Disorders*. **6** (5): 343–367. doi:10.1111/j.1399-5618.2004.00139.x. PMID 15383127.
162. ^ Trinh NH, Forester B (2007). "Bipolar Disorder in the Elderly: Differential Diagnosis and Treatment". *Psychiatric Times*. **24** (14).

## References


- Basco, Monica Ramirez; Rush, A. John (2005). *Cognitive-Behavioral Therapy for Bipolar Disorder* (Second ed.). New York: The Guilford Press. ISBN 978-1-59385-168-2. OCLC 300306925.
- Brown, Malcomb R.; Basso, Michael R. (2004). *Focus on Bipolar Disorder Research*. Nova Science Publishers. ISBN 978-1-59454-059-2.
- Joseph, Chris (2008). *Manicdotes: There's Madness in His Method*. London: Austin & Macauley. ISBN 978-1-905609-07-9. Amazon review.
- Goodwin, F. K.; Jamison, K. R. (2007). *Manic–depressive illness: bipolar disorders and recurrent depression* (2nd. ed.). Oxford University Press. ISBN 978-0-19-513579-4. OCLC 70929267. Retrieved April 2, 2016.
- Jamison, Kay Redfield (1995). *An Unquiet Mind: A Memoir of Moods and Madness*. New York: Knopf. ISBN 978-0-330-34651-1.
- Leahy, Robert L.; Johnson, Sheri L. (2003). *Psychological Treatment of Bipolar Disorder*. New York: The Guilford Press. ISBN 978-1-57230-924-1. OCLC 52714775.
- Liddell, Henry George; Scott, Robert (1980). *A Greek-English Lexicon* (Abridged ed.). Oxford University Press. ISBN 978-0-19-910207-5.
- Millon, Theordore (1996). *Disorders of Personality: DSM-IV-TM and Beyond*. New York: John Wiley and Sons. ISBN 978-0-471-01186-6.
- Robinson, D. J. (2003). *Reel Psychiatry: Movie Portrayals of Psychiatric Conditions*. Port Huron, Michigan: Rapid Psychler Press. ISBN 978-1-894328-07-4.
- Sadock, Benjamin J.; Kaplan, Harold I.; Sadock, Virginia A. (2007). *Kaplan & Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry* (Tenth ed.). ISBN 978-0-7817-7327-0. Retrieved April 2, 2016.


## Further reading


- Healy, David (2011). *Mania: A Short History of Bipolar Disorder*. Baltimore: Johns Hopkins University Press. ISBN 978-1-4214-0397-7.
- Mondimore, Francis Mark (2014). *Bipolar Disorder: A Guide for Patients and Families* (3rd ed.). Baltimore: Johns Hopkins University Press. ISBN 978-1-4214-1206-1.
- Yatham, Lakshmi (2010). *Bipolar Disorder*. New York: Wiley. ISBN 978-0-470-72198-8.


## External links

- Bipolar Disorder at DMOZ
- Bipolar Disorder overview from the U.S. National Institute of Mental Health website
- NICE Bipolar Disorder clinical guidelines from the U.K. National Institute for Health and Clinical Excellence website

Media from Commons
News from Wikinews
Textbooks from Wikibooks
Data from Wikidata

| v · t · e · | **Mental and behavioral disorders (F 290–319)** |
|---|---|
| **Neurological/symptomatic** | |
| **Dementia** | Mild cognitive impairment · Alzheimer's disease · Vascular dementia · Pick's disease · Creutzfeldt–Jakob disease · Huntington's disease · Parkinson's disease · AIDS dementia complex · Frontotemporal dementia · Sundowning · Wandering · |
| **Autism spectrum** | Autism · Asperger syndrome · Savant syndrome · PDD-NOS · High-functioning autism · |
| **Other** | Delirium · Post-concussion syndrome · Organic brain syndrome · |
| **Psychoactive substances, substance abuse, drug abuse and substance-related disorders** | |
| Intoxication/Drug overdose · Physical dependence · Substance dependence · Rebound effect · Double rebound · Withdrawal · | |
| **Schizophrenia, schizotypal and delusional** | |
| **Psychosis** | Schizoaffective disorder · Schizophreniform disorder · Brief reactive psychosis · |
| **Schizophrenia** | Disorganized schizophrenia · Paranoid schizophrenia · Simple-type schizophrenia · |
| **Delusional disorders** | Delusional disorder · Folie à deux · |
| **Mood (affective)** | |
| Mania · **Bipolar disorder** · (Bipolar I · Bipolar II · Cyclothymia · Bipolar NOS) · Depression · (Major depressive disorder · Dysthymia · Seasonal affective disorder · Atypical depression · Melancholic depression) · | |
| **Neurotic, stress-related and somatoform** | |
| **Anxiety disorder** | **Phobia**: Agoraphobia · Social anxiety · Social phobia · (Anthropophobia) · Specific phobia · (Claustrophobia) · Specific social phobia · |
| | **Other**: Panic disorder · Panic attack · Generalized anxiety disorder · OCD · *stress* · (Acute stress reaction · PTSD) · |
| **Adjustment disorder** | Adjustment disorder with depressed mood · |
| **Somatic symptom disorder** | Somatization disorder · Body dysmorphic disorder · Hypochondriasis · Nosophobia · Da Costa's syndrome · Psychalgia · Conversion disorder · (Ganser syndrome · Globus pharyngis) · Neurasthenia · Mass psychogenic illness · |
| **Dissociative disorder** | Dissociative identity disorder · Psychogenic amnesia · Fugue state · Depersonalization disorder · |
| **Physiological/physical behavioral** | |
| **Eating disorder** | Anorexia nervosa · Bulimia nervosa · Rumination syndrome · NOS · |
| **Nonorganic sleep disorders** | (Nonorganic hypersomnia · Nonorganic insomnia) · Parasomnia · (REM sleep behavior disorder · Night terror · Nightmare) · |

| | |
|---|---|
| **Sexual dysfunction** | *sexual desire* · (Hypoactive sexual desire disorder · Hypersexuality) · *sexual arousal* · (Female sexual arousal disorder) · Erectile dysfunction · *orgasm* · (Anorgasmia · Delayed ejaculation · Premature ejaculation · Sexual anhedonia) · *pain* · (Vaginismus · Dyspareunia) · |
| **Postnatal** | Postpartum depression · Postpartum psychosis · |

**Adult personality and behavior**

| | |
|---|---|
| *Gender dysphoria* | Sexual maturation disorder · Ego-dystonic sexual orientation · Sexual relationship disorder · Paraphilia · (Voyeurism · Fetishism) · |
| **Other** | Personality disorder · Impulse control disorder · (Kleptomania · Trichotillomania · Pyromania · Dermatillomania) · Body-focused repetitive behavior · Factitious disorder · (Münchausen syndrome) · |

**Disorders typically diagnosed in childhood**

| | |
|---|---|
| **Intellectual disability** | X-linked intellectual disability · (Lujan–Fryns syndrome) · |
| **Psychological development (developmental disabilities)** | Specific · Pervasive · Autism spectrum · |
| **Emotional and behavioral** | ADHD · Conduct disorder · (ODD) · Emotional/behavioral disorder · (Separation anxiety disorder) · *social functioning* · (Selective mutism · RAD · DAD) · Tic disorder · (Tourette syndrome) · *Speech* · (Stuttering · Cluttering) · Movement disorder · (Stereotypic) · |

**Symptoms and uncategorized**

Catatonia · False pregnancy · Intermittent explosive disorder · Psychomotor agitation · Stereotypy · Psychogenic non-epileptic seizures · Klüver–Bucy syndrome ·

V · T · E · **Mood disorder (F30–F39, 296)**

| | | |
|---|---|---|
| **History** | Emil Kraepelin · Karl Leonhard · John Cade · Mogens Schou · Frederick K. Goodwin · Kay Redfield Jamison · | |
| **Symptoms** | Hallucination · Delusion · Emotional dysregulation (Anhedonia · Dysphoria · Suicidal ideation · · Mood swing · *sleep disorder* (Hypersomnia · Insomnia · · Psychosis · Racing thoughts · Reduced affect display · Depression (differential diagnoses) · | |
| **Spectrum** | **Bipolar disorder** (Bipolar I · Bipolar II · Cyclothymia · Bipolar NOS · · Depression · (Major depressive disorder · Dysthymia · Seasonal affective disorder · Atypical depression · Melancholic depression) · Schizoaffective disorder · Mania · Mixed affective state · Hypomania · Major depressive episode · Rapid cycling · | |
| **Treatment** | **Anticonvulsants** | Carbamazepine · Lamotrigine · Oxcarbazepine · Valproate (Sodium valproate · Valproate semisodium · · |
| | **Sympathomimetics, SSRIs & similar** | Dextroamphetamine · Methylphenidate · Bupropion · Sertraline · Fluoxetine · Escitalopram · |
| | **Other mood stabilizers** | Antipsychotics · Lithium (Lithium carbonate · Lithium citrate · Lithium sulfate · · Atypical antipsychotics · |
| | **Non-pharmaceutical** | Clinical psychology · Electroconvulsive therapy · Involuntary commitment · Light therapy · Psychotherapy · Transcranial magnetic stimulation · |

| | | |
|---|---|---|
| | | Cognitive behavioral therapy · Dialectical behavior therapy · |
| **Authority control** | NDL: 00571488 · | |

Categories: Bipolar disorder | Mood disorders | Psychiatric diagnosis | Depression (psychology)




# Borderline personality disorder

From Wikipedia, the free encyclopedia

**Borderline personality disorder** (**BPD**), also known as **emotionally unstable personality disorder**, is a long-term pattern of abnormal behavior characterized by unstable relationships with other people, unstable sense of self, and unstable emotions.[3][4] There is often an extreme fear of abandonment, frequent dangerous behavior, a feeling of emptiness, and self-harm. Symptoms may be brought on by seemingly normal events.[3] The behavior typically begins by early adulthood, and occurs across a variety of situations.[4] Substance abuse, depression, and eating disorders are commonly associated with BPD.[3] About 10% of those with BPD die by suicide.[3][4]

BPD's causes are unclear, but seem to involve genetic, brain, environment, and social factors. It occurs about five times more often in a person who has an affected close relative.[3] Adverse life events also appear to play a role. The underlying mechanism appears to involve the frontolimbic network of neurons.[5] BPD is recognized by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) as a personality disorder, along with nine other such disorders.[4] Diagnosis is based on the symptoms while a medical exam may be done to rule out other problems.[3] The condition must be differentiated from an identity problem or substance use disorders, among other possibilities.[4]

Borderline personality disorder is typically treated with therapy, such as cognitive behavioral therapy (CBT). Another type, dialectical behavior therapy (DBT) has been found to reduce the risk of suicide. Therapy may occur one-on-one, or in a group. While medications do not cure BPD, they may be used to help with the associated symptoms. Some people require care in hospital.[3]

About 1.6% of people have BPD in a given year.[3] Females are diagnosed about three times as often as males. It appears to become less common among older people. Up to half of people improve over a ten-year period. People affected typically use a high amount of healthcare resources.[4] There is an ongoing debate about the naming of the disorder, especially the suitability of the word "borderline".[3]

**Contents**

**Borderline personality disorder**

**Synonyms** emotionally unstable personality disorder, impulsive or borderline type,[1] emotional intensity disorder,[2] neurotic psychopathy[1]

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Psychiatry |
| **ICD-10** | F60.3 |
| **ICD-9-CM** | 301.83 |
| **MedlinePlus** | 000935 |
| **eMedicine** | article/913575 |
| **Patient UK** | Borderline personality disorder |
| **MeSH** | D001883 |

[edit on Wikidata]

**Personality disorders**

**Cluster A (odd)**
Paranoid · Schizoid · Schizotypal ·

**Cluster B (dramatic)**
Antisocial · **Borderline** · Histrionic · Narcissistic ·

**Cluster C (anxious)**
Avoidant · Dependent · Obsessive–compulsive ·

**Not specified**
Depressive · Passive-aggressive · Sadistic · Self-defeating · Psychopathic ·

V · T · E ·

## Signs and symptoms [edit]

Borderline personality disorder may be characterized by the following signs and symptoms:

- Markedly disturbed sense of identity
- Frantic efforts to avoid real or imagined abandonment and extreme reactions to such
- Splitting ("black-and-white" thinking)
- Severe impulsivity
- Intense or uncontrollable emotional reactions that often seem disproportionate to the event or situation
- Unstable and chaotic interpersonal relationships
- Self-damaging behavior
- Distorted self-image[3]
- Dissociation

- Frequently accompanied by depression, anxiety, anger, substance abuse, or rage

The most distinguishing symptoms of BPD are marked sensitivity to rejection or criticism, and intense fear of possible abandonment.[6] Overall, the features of BPD include unusually intense sensitivity in relationships with others, difficulty regulating emotions, and impulsivity. Other symptoms may include feeling unsure of one's personal identity, morals, and values; having paranoid thoughts when feeling stressed; dissociation and depersonalization; and, in moderate to severe cases, stress-induced breaks with reality or psychotic episodes.

## Emotions [edit]

People with BPD feel emotions more easily, more deeply, and longer than others do.[7][8] In addition, emotions may repeatedly resurge and persist a long time.[8] Consequently, it may take more time for people with BPD than others to return to a stable emotional baseline following an intense emotional experience.[9] People with BPD often engage in idealization and devaluation of others, alternating between high positive regard and great disappointment.[10]

In Marsha Linehan's view, the sensitivity, intensity, and duration with which people with BPD feel emotions have both positive and negative effects.[9] People with BPD are often exceptionally enthusiastic, idealistic, joyful, and loving.[11] However, they may feel overwhelmed by negative emotions ("anxiety, depression, guilt/shame, worry, anger, etc."), experiencing intense grief instead of sadness, shame and humiliation instead of mild embarrassment, rage instead of annoyance, and panic instead of nervousness.[11]

People with BPD are also especially sensitive to feelings of rejection, criticism, isolation, and perceived failure.[12] Before learning other coping mechanisms, their efforts to manage or escape from their very negative emotions may lead to emotional isolation, self-injury or suicidal behavior.[13] They are often aware of the intensity of their negative emotional reactions and, since they cannot regulate them, they shut them down entirely.[9] This can be harmful to people with BPD, since negative emotions alert people to the presence of a problematic situation and move them to address it which the person with BPD would normally be aware of only to cause further distress.[9]

While people with BPD feel joy intensely, they are especially prone to dysphoria, depression, and/or feelings of mental and emotional distress. Zanarini et al. recognized four categories of dysphoria that are typical of this condition: extreme emotions, destructiveness or self-destructiveness, feeling fragmented or lacking identity, and feelings of victimization.[14] Within these categories, a BPD diagnosis is strongly associated with a combination of three specific states: feeling betrayed, "feeling like hurting myself", and feeling out of control.[14] Since there is great variety in the types of dysphoria experienced by people with BPD, the amplitude of the distress is a helpful indicator of borderline personality disorder.[14]

In addition to intense emotions, people with BPD experience emotional lability; or in other words, changeability. Although the term emotional lability suggests rapid changes between depression and elation, the mood swings in people with this condition actually fluctuate more frequently between anger and anxiety and between depression and anxiety.[15]

## Behavior [edit]

Impulsive behavior is common, including substance or alcohol abuse, eating disorders, unprotected sex or indiscriminate sex with multiple partners, reckless spending, and reckless driving.[16] Impulsive behavior may also include leaving jobs or relationships, running away, and self-injury.[17]

People with BPD act impulsively because it gives them immediate relief from their emotional pain.[17] However, in the long term, people with BPD suffer increased pain from the shame and guilt that follow such actions.[17] A cycle often begins in which people with BPD feel emotional pain, engage in impulsive behavior to relieve that pain, feel shame and guilt over their actions, feel emotional pain from the shame and guilt, and then experience stronger urges to engage in impulsive behavior to relieve the new pain.[17] As time goes on, impulsive behavior may become an automatic response to emotional pain.[17]

## Self-harm and suicide [edit]

Self-harming or suicidal behavior is one of the core diagnostic criteria in the DSM-5.[4] The lifetime risk of suicide among people with BPD is between 3% and 10%.[6][18] There is evidence that men diagnosed with BPD are approximately twice as likely to complete suicide as women diagnosed with BPD.[19] There is also evidence that a considerable percentage of men who complete suicide may have undiagnosed BPD.[20]

Self-harm such as cutting oneself is a common sign in borderline personality disorder.[3] Here in different states of wound healing.

Self-harm, such as cutting, is common and takes place with or without suicidal intent.[3][21][22] The reported reasons for non-suicidal self-injury (NSSI) differ from the reasons for suicide attempts.[13] Nearly 70% of people with BPD self-harm without trying to end their life.[23] Reasons for NSSI include expressing anger, self-punishment, generating normal feelings (often in response to dissociation), and distracting oneself from emotional pain or difficult circumstances.[13] In contrast, suicide attempts typically reflect a belief that others will be better off following the suicide.[13] Both suicidal and non-suicidal self-injury are a response to feeling negative emotions.[13]

Sexual abuse can be a particular trigger for suicidal behavior in adolescents with BPD tendencies.[24][*quantify*]

## Interpersonal relationships [edit]

People with BPD can be very sensitive to the way others treat them, by feeling intense joy and gratitude at perceived expressions of kindness, and intense sadness or anger at perceived criticism or hurtfulness.[25] Their feelings about others often shift from admiration or love to anger or dislike after a disappointment, a threat of losing someone, or a perceived loss of esteem in the eyes of someone they value. This phenomenon, sometimes called splitting, includes a shift from idealizing others to devaluing them.[26] Combined with mood disturbances, idealization and devaluation can undermine relationships with family, friends, and co-workers.[27] Self-image can also change rapidly from healthy to unhealthy.

While strongly desiring intimacy, people with BPD tend toward insecure, avoidant or ambivalent, or fearfully preoccupied attachment patterns in relationships,[28] and they often view the world as dangerous and malevolent.[25] BPD, like other personality disorders, is linked to increased levels of chronic stress and conflict in romantic relationships, decreased satisfaction on the part of romantic partners, abuse, and unwanted pregnancy.[29]

## Sense of self [edit]

People with BPD tend to have trouble seeing a clear picture of their identity. In particular, they tend to have difficulty knowing what they value, believe, prefer, and enjoy.[30] They are often unsure about their long-term goals for relationships and jobs. This difficulty with knowing who they are and what they value can cause people with BPD to experience feeling "empty" and "lost".[30]

## Cognitions [edit]

The often intense emotions experienced by people with BPD can make it difficult for them to control the focus of their attention—to concentrate.[30] In addition, people with BPD may tend to dissociate, which can be thought of as an intense form of "zoning out".[31] Dissociation often occurs in response to experiencing a painful event (or experiencing something that triggers the memory of a painful event). It involves the mind automatically redirecting attention away from that event, presumably to protect against experiencing intense emotion and unwanted behavioral impulses that such emotion might otherwise trigger.[31]

Although the mind's habit of blocking out intense painful emotions may provide temporary relief, it can also

have the unwanted side effect of blocking or blunting the experience of ordinary emotions, reducing the access of people with BPD to the information contained in those emotions, which helps guide effective decision-making in daily life.[31] Sometimes, it is possible for another person to tell when someone with BPD is dissociating, because their facial or vocal expressions may become flat or expressionless, or they may appear to be distracted; at other times, dissociation may be barely noticeable.[31]

### Disability [edit]

BPD is related to lower functioning and disability, even when socioeconomic status, medical conditions, and all psychiatric disorders were controlled.[32] Further, it is more common for females with BPD to experience disabilities than males with BPD.[32] More research is necessary to determine if this is due to a genetic sex difference or social reasons, but more females with BPD are diagnosed than males.[32]

## Causes [edit]

As is the case with other mental disorders, the causes of BPD are complex and not fully agreed upon.[33] Evidence suggests that BPD and post-traumatic stress disorder (PTSD) may be related in some way.[34] Most researchers agree that a history of childhood trauma can be a contributing factor,[35] but less attention has historically been paid to investigating the causal roles played by congenital brain abnormalities, genetics, neurobiological factors, and environmental factors other than trauma.[33][36]

Social factors include how people interact in their early development with their family, friends, and other children.[37] Psychological factors include the individual's personality and temperament, shaped by his or her environment and learned coping skills that deal with stress.[37] These different factors together suggest that there are multiple factors that may contribute to the disorder.

### Genetics [edit]

The heritability of BPD has been estimated at 40%.[38] That is, 40 percent of the variability in liability underlying BPD in the population can be explained by genetic differences. Twin studies may overestimate the effect of genes on variability in personality disorders due to the complicating factor of a shared family environment.[39] Nonetheless, the researchers of this study concluded that personality disorders "seem to be more strongly influenced by genetic effects than almost any axis I disorder [e.g., bipolar disorder, depression, eating disorders], and more than most broad personality dimensions."[40] Moreover, the study found that BPD was estimated to be the third most-heritable personality disorder out of the 10 personality disorders reviewed.[40]

Twin, sibling, and other family studies indicate partial heritability for impulsive aggression, but studies of serotonin-related genes have suggested only modest contributions to behavior.[41]

Families with twins in the Netherlands were participants of an ongoing study by Trull and colleagues, in which 711 pairs of siblings and 561 parents were examined to identify the location of genetic traits that influenced the development of BPD.[42] Research collaborators found that genetic material on chromosome nine was linked to BPD features.[42] The researchers concluded "that genetic factors play a major role in individual differences of borderline personality disorder features."[42] These same researchers had earlier concluded in a previous study that 42 percent of variation in BPD features was attributable to genetic influences and 58 percent was attributable to environmental influences.[42]

Genes currently under investigation include the 7-repeat polymorphism of the dopamine D4 receptor (DRD4), which has been linked to disorganized attachment, whilst the combined effect of the 7-repeat polymorphism and the 10/10 dopamine transporter (DAT) genotype has been linked to abnormalities in inhibitory control, both noted features of BPD.[43] There is a possible connection to chromosome 5.[44]

### Brain abnormalities [edit]

A number of neuroimaging studies in BPD have reported findings of reductions in regions of the brain involved in the regulation of stress responses and emotion, affecting the hippocampus, the orbitofrontal cortex, and the amygdala, amongst other areas.[43] A smaller number of studies have used magnetic resonance spectroscopy to explore changes in the concentrations of neurometabolites in certain brain regions of BPD patients, looking specifically at neurometabolites such as N-acetylaspartate, creatine, glutamate-related compounds, and choline-containing compounds.[43]

### Hippocampus [edit]

The hippocampus tends to be smaller in people with BPD, as it is in people with post-traumatic stress disorder (PTSD). However, in BPD, unlike PTSD, the amygdala also tends to be smaller.[45]

### Amygdala [edit]

The amygdalas are smaller and more active in people with BPD.[45] Decreased amygdala volume has also been found in people with obsessive-compulsive disorder.[46] One study has found unusually strong activity in the left amygdalas of people with BPD when they experience and view displays of negative emotions.[47] Since the amygdala generates all emotions (including unpleasant ones), this unusually strong activity may explain the unusual strength and longevity of fear, sadness, anger, and shame experienced by people with BPD, as well as their heightened sensitivity to displays of these emotions in others.[45]

### Prefrontal cortex [edit]

The prefrontal cortex tends to be less active in people with BPD, especially when recalling memories of abandonment.[48] This relative inactivity occurs in the right anterior cingulate (areas 24 and 32).[48] Given its role in regulating emotional arousal, the relative inactivity of the prefrontal cortex might explain the difficulties people with BPD experience in regulating their emotions and responses to stress.[49]

### Hypothalamic-pituitary-adrenal axis [edit]

The hypothalamic-pituitary-adrenal axis (HPA axis) regulates cortisol production, which is released in response to stress. Cortisol production tends to be elevated in people with BPD, indicating a hyperactive HPA axis in these individuals.[50] This causes them to experience a greater biological stress response, which might explain their greater vulnerability to irritability.[51] Since traumatic events can increase cortisol production and HPA axis activity, one possibility is that the prevalence of higher than average activity in the HPA axis of people with BPD may simply be a reflection of the higher than average prevalence of traumatic childhood and maturational events among people with BPD.[51] Another possibility is that, by heightening their sensitivity to stressful events, increased cortisol production may predispose those with BPD to experience stressful childhood and maturational events as traumatic.

Increased cortisol production is also associated with an increased risk of suicidal behavior.[52]

## Neurobiological factors [edit]

### Estrogen [edit]

Individual differences in women's estrogen cycles may be related to the expression of BPD symptoms in female patients.[53] A 2003 study found that women's BPD symptoms were predicted by changes in estrogen levels throughout their menstrual cycles, an effect that remained significant when the results were controlled for a general increase in negative affect.[54]

## Developmental factors [edit]

### Childhood trauma [edit]

There is a strong correlation between child abuse, especially child sexual abuse, and development of BPD.[55][56][57] Many individuals with BPD report a history of abuse and neglect as young children, but causation is still debated.[58] Patients with BPD have been found to be significantly more likely to report having been verbally, emotionally, physically, or sexually abused by caregivers of either gender. They also report a high incidence of incest and loss of caregivers in early childhood.[59]

Individuals with BPD were also likely to report having caregivers of both sexes deny the validity of their thoughts and feelings. Caregivers were also reported to have failed to provide needed protection and to have neglected their child's physical care. Parents of both sexes were typically reported to have withdrawn from the child emotionally and to have treated the child inconsistently.[59] Additionally, women with BPD who reported a previous history of neglect by a female caregiver and abuse by a male caregiver were significantly more likely to experience sexual abuse by a non-caregiver.[59]

It has been suggested that children who experience chronic early maltreatment and attachment difficulties may go on to develop borderline personality disorder.[60]

Writing in the psychoanalytic tradition, Otto Kernberg argues that a child's failure to achieve the developmental task of psychic clarification of self and other and failure to overcome splitting might increase the risk of developing a borderline personality.[61]

A child's inability to tolerate delayed gratification at age 4 does not predict later development of BPD.[62]

## Neurological patterns [edit]

The intensity and reactivity of a person's negative affectivity, or tendency to feel negative emotions, predicts BPD symptoms more strongly than does childhood sexual abuse.[63] This finding, differences in brain structure (see Brain abnormalities), and the fact that some patients with BPD do not report a traumatic history,[64] suggest that BPD is distinct from the post-traumatic stress disorder which frequently accompanies it. Thus, researchers examine developmental causes in addition to childhood trauma.

Research published in January 2013 by Dr. Anthony Ruocco at the University of Toronto has highlighted two patterns of brain activity that may underlie the dysregulation of emotion indicated in this disorder: (1) increased activity in the brain circuits responsible for the experience of heightened emotional pain, coupled with (2) reduced activation of the brain circuits that normally regulate or suppress these generated painful emotions. These two neural networks are seen to be dysfunctionally operative in the frontolimbic regions, but the specific regions vary widely in individuals, which calls for the analysis of more neuroimaging studies.[65]

Also (contrary to the results of earlier studies) sufferers of BPD showed less activation in the amygdala in situations of increased negative emotionality than the control group. Dr. John Krystal, editor of the journal *Biological Psychiatry*, wrote that these results "[added] to the impression that people with borderline personality disorder are 'set-up' by their brains to have stormy emotional lives, although not necessarily unhappy or unproductive lives".[65] Their emotional instability has been found to correlate with differences in several brain regions.[66]

## Mediating and moderating factors [edit]

### Executive function [edit]

While high rejection sensitivity is associated with stronger symptoms of borderline personality disorder, executive function appears to mediate the relationship between rejection sensitivity and BPD symptoms.[62] That is, a group of cognitive processes that include planning, working memory, attention, and problem-solving might be the mechanism through which rejection sensitivity impacts BPD symptoms. A 2008 study found that the relationship between a person's rejection sensitivity and BPD symptoms was stronger when executive function was lower and that the relationship was weaker when executive function was higher.[62] This suggests that high executive function might help protect people with high rejection sensitivity against symptoms of BPD.[62]

A 2012 study found that problems in working memory might contribute to greater impulsivity in people with BPD.[67]

### Family environment [edit]

Family environment mediates the effect of child sexual abuse on the development of BPD. An unstable family environment predicts the development of the disorder, while a stable family environment predicts a lower risk. One possible explanation is that a stable environment buffers against its development.[68]

### Self-complexity [edit]

Self-complexity, or considering one's self to have many different characteristics, appears to moderate the relationship between Actual-Ideal self-discrepancy and the development of BPD symptoms. That is, for individuals who believe that their actual characteristics do not match the characteristics that they hope to acquire, high self-complexity reduces the impact of their conflicted self-image on BPD symptoms.[69]

However, self-complexity does not moderate the relationship between Actual-Ought self-discrepancy and the development of BPD symptoms. That is, for individuals who believe that their actual characteristics do not match the characteristics that they should already have, high self-complexity does not reduce the impact of their conflicted self-image on BPD symptoms. The protective role of self-complexity in Actual-Ideal self-discrepancy, but not in Actual-Ought self-discrepancy, suggests that the impact of conflicted or unstable self-image in BPD depends on whether the individual views self in terms of characteristics that they hope to acquire, or in terms of characteristics that they should already have acquired.[69]

### Thought suppression [edit]

A 2005 study found that thought suppression, or conscious attempts to avoid thinking certain thoughts, mediates the relationship between emotional vulnerability and BPD symptoms.[63] A later study found that the relationship between emotional vulnerability and BPD symptoms is not necessarily mediated by thought suppression. However, this study did find that thought suppression mediates the relationship between an invalidating environment and BPD symptoms.[70]

## Diagnosis [edit]

Diagnosis of borderline personality disorder is based on a clinical assessment by a mental health professional. The best method is to present the criteria of the disorder to a person and to ask them if they feel that these characteristics accurately describe them.[6] Actively involving people with BPD in determining their diagnosis can help them become more willing to accept it.[6] Although some clinicians prefer not to tell people with BPD what their diagnosis is, either from concern about the stigma attached to this condition or because BPD used to be considered untreatable, it is usually helpful for the person with BPD to know their diagnosis.[6] This helps them know that others have had similar experiences and can point them toward effective treatments.[6]

In general, the psychological evaluation includes asking the patient about the beginning and severity of symptoms, as well as other questions about how symptoms impact the patient's quality of life. Issues of particular note are suicidal ideations, experiences with self-harm, and thoughts about harming others.[71] Diagnosis is based both on the person's report of their symptoms and on the clinician's own observations.[71] Additional tests for BPD can include a physical exam and laboratory tests to rule out other possible triggers for symptoms, such as thyroid conditions or substance abuse.[71]

The ICD-10 manual refers to the disorder as *emotionally unstable personality disorder* and has similar diagnostic criteria. In the DSM-5, the name of the disorder remains the same as in the previous editions.[4]

### Diagnostic and Statistical Manual [edit]

The Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) has removed the multiaxial system. Consequently, all disorders, including personality disorders, are listed in Section II of the manual. A person must meet 5 of 9 criteria to receive a diagnosis of borderline personality disorder.[72] The DSM-5 defines the main features of BPD as a pervasive pattern of instability in interpersonal relationships, self image, and affect, as well as markedly impulsive behavior.[72]

In addition, the DSM-5 proposes alternative diagnostic criteria for Borderline personality disorder in section III, "Alternative DSM-5 Model for Personality Disorders." These alternative criteria are based on trait research and include specifying at least four of seven maladaptive traits.[73]

According to Marsha Linehan, many mental health professionals find it challenging to diagnose BPD using the DSM criteria, since these criteria describe such a wide variety of behaviors.[74] To address this issue, Linehan has grouped the symptoms of BPD under five main areas of dysregulation: emotions, behavior, interpersonal relationships, sense of self, and cognition.[74]

## International Classification of Disease [edit]

The World Health Organization's ICD-10 defines a disorder that is conceptually similar to borderline personality disorder, called *(F60.3) Emotionally unstable personality disorder*. Its two subtypes are described below.[75]

### F60.30 Impulsive type

At least three of the following must be present, one of which must be (2):

1. marked tendency to act unexpectedly and without consideration of the consequences;
2. marked tendency to engage in quarrelsome behavior and to have conflicts with others, especially when impulsive acts are thwarted or criticized;
3. liability to outbursts of anger or violence, with inability to control the resulting behavioral explosions;
4. difficulty in maintaining any course of action that offers no immediate reward;
5. unstable and capricious (impulsive, whimsical) mood.

### F60.31 Borderline type

At least three of the symptoms mentioned in *F60.30 Impulsive type* must be present [see above], with at least two of the following in addition:

1. disturbances in and uncertainty about self-image, aims, and internal preferences;
2. liability to become involved in intense and unstable relationships, often leading to emotional crisis;
3. excessive efforts to avoid abandonment;
4. recurrent threats or acts of self-harm;
5. chronic feelings of emptiness.
6. demonstrates impulsive behavior, e.g., speeding, substance abuse[76]

The ICD-10 also describes some general criteria that define what is considered a Personality disorder.

## Millon's subtypes [edit]

Theodore Millon has proposed four subtypes of BPD. He suggests that an individual diagnosed with BPD may exhibit none, one, or more of the following:[77]

| Subtype | Features |
|---|---|
| **Discouraged** (including avoidant features) | Pliant, submissive, loyal, humble; feels vulnerable and in constant jeopardy; feels hopeless, depressed, helpless, and powerless. |
| **Petulant** (including negativistic features) | Negativistic, impatient, restless, as well as stubborn, defiant, sullen, pessimistic, and resentful; easily slighted and quickly disillusioned. |
| **Impulsive** (including histrionic or antisocial features) | Capricious, superficial, flighty, distractible, frenetic, and seductive; fearing loss, becomes agitated, and gloomy and irritable; potentially suicidal. |

| | |
|---|---|
| **Self-destructive** (including depressive or masochistic features) | Inward-turning, intropunitively angry; conforming, deferential, and ingratiating behaviors have deteriorated; increasingly high-strung and moody; possible suicide. |

## Misdiagnosis [edit]

People with BPD may be misdiagnosed for a variety of reasons. One reason for misdiagnosis is BPD has symptoms that coexist with other disorders such as depression, PTSD, and bipolar disorder. The tests to narrow down what disorder a person has are also similar in questions that if the patient doesn't respond with the answers that have the word usually, then the disorder will go untreated due to improper diagnosis.[78][79]

## Family members [edit]

People with BPD are prone to feeling angry at members of their family and alienated from them. On their part, family members often feel angry and helpless at how their BPD family members relate to them.[6]

Parents of adults with BPD are often both over-involved and under-involved in family interactions.[80] In romantic relationships, BPD is linked to increased levels of chronic stress and conflict, decreased satisfaction of romantic partners, abuse, and unwanted pregnancy. However, these links may apply to personality disorders in general.[29]

## Adolescence [edit]

Onset of symptoms typically occurs during adolescence or young adulthood, although symptoms suggestive of this disorder can sometimes be observed in children.[81] Symptoms among adolescents that predict the development of BPD in adulthood may include problems with body-image, extreme sensitivity to rejection, behavioral problems, non-suicidal self-injury, attempts to find exclusive relationships, and severe shame.[6] Many adolescents experience these symptoms without going on to develop BPD, but those who experience them are 9 times as likely as their peers to develop BPD. They are also more likely to develop other forms of long-term social disabilities.[6]

Clinicians are discouraged from diagnosing anyone with BPD before the age of 18, due to the normal ups and downs of adolescence and a still-developing personality. However, BPD can sometimes be diagnosed before age 18, in which case the features must have been present and consistent for at least 1 year.[82]

A BPD diagnosis in adolescence might predict that the disorder will continue into adulthood.[82][83] Among adolescents who warrant a BPD diagnosis, there appears to be one group in which the disorder remains stable over time and another group in which the individuals move in and out of the diagnosis.[84] Earlier diagnoses may be helpful in creating a more effective treatment plan for the adolescent.[82][83] Family therapy is considered a helpful component of treatment for adolescents with BPD.[85]

## Differential diagnosis and comorbidity [edit]

Lifetime comorbid (co-occurring) conditions are common in BPD. Compared to those diagnosed with other personality disorders, people with BPD showed a higher rate of also meeting criteria for[86]

- mood disorders, including major depression and bipolar disorder
- anxiety disorders, including panic disorder, social anxiety disorder, and post-traumatic stress disorder (PTSD)
- other personality disorders
- substance abuse
- eating disorders, including anorexia nervosa and bulimia
- attention deficit hyperactivity disorder[87][*non-primary source needed*]
- somatoform disorders

dissociative disorders

A diagnosis of a personality disorder should not be made during an untreated mood episode/disorder, unless the lifetime history supports the presence of a personality disorder.

## Comorbid Axis I disorders [edit]

A 2008 study found that at some point in their lives, 75 percent of people with BPD meet criteria for mood disorders, especially major depression and Bipolar I, and nearly 75 percent meet criteria for an anxiety disorder.[88] Nearly 73 percent meet criteria for substance abuse or dependency, and about 40 percent for PTSD.[88] It is noteworthy that less than half of the participants with BPD in this study presented with PTSD, a prevalence similar to that reported in an earlier study.[86] The finding that less than half of patients with BPD experience PTSD during their lives challenges the theory that BPD and PTSD are the same disorder.[86]

**Gender differences in Axis I lifetime comorbid diagnosis, 2008[88] and 1998[86]**

| Axis I diagnosis | Overall (%) | Male (%) | Female (%) |
|---|---|---|---|
| **Mood disorders** | **75.0** | **68.7** | **80.2** |
| Major depressive disorder | 32.1 | 27.2 | 36.1 |
| Dysthymia | 9.7 | 7.1 | 11.9 |
| Bipolar I disorder | 31.8 | 30.6 | 32.7 |
| Bipolar II disorder | 7.7 | 6.7 | 8.5 |
| **Anxiety disorders** | **74.2** | **66.1** | **81.1** |
| Panic disorder with agoraphobia | 11.5 | 7.7 | 14.6 |
| Panic disorder without agoraphobia | 18.8 | 16.2 | 20.9 |
| Social phobia | 29.3 | 25.2 | 32.7 |
| Specific phobia | 37.5 | 26.6 | 46.6 |
| PTSD | 39.2 | 29.5 | 47.2 |
| Generalized anxiety disorder | 35.1 | 27.3 | 41.6 |
| Obsessive-compulsive disorder** | 15.6 | --- | --- |
| **Substance use disorders** | **72.9** | **80.9** | **66.2** |
| Any alcohol use disorder | 57.3 | 71.2 | 45.6 |
| Any drug use disorder | 36.2 | 44.0 | 29.8 |
| **Eating disorders**** | **53.0** | **20.5** | **62.2** |
| Anorexia nervosa** | 20.8 | 7 * | 25 * |
| Bulimia nervosa** | 25.6 | 10 * | 30 * |
| Eating disorder not otherwise specified** | 26.1 | 10.8 | 30.4 |
| **Somatoform disorders**** | **10.3** | **10 *** | **10 *** |
| Somatization disorder** | 4.2 | --- | --- |
| Hypochondriasis** | 4.7 | --- | --- |
| Somatoform pain disorder** | 4.2 | --- | --- |
| **Psychotic disorders**** | **1.3** | **1 *** | **1 *** |

* Approximate values
** Values from 1998 study[86]
--- Value not provided by study

There are marked gender differences in the types of comorbid conditions a person with BPD is likely to have—[86] a higher percentage of males with BPD meet criteria for substance-use disorders, while a higher percentage of females with BPD meet criteria for PTSD and eating disorders.[86][88][89] In one study, 38% of participants with BPD met the criteria for a diagnosis of ADHD.[87] In another study, 6 of 41 participants (15%) met the criteria for an autism spectrum disorder (a subgroup that had significantly more frequent suicide attempts).[90]

Regardless that it is an infradiagnosed disorder, a few studies have shown that the "lower expressions" of it might lead to wrong diagnoses. The many and shifting Axis I disorders in people with BPD can sometimes cause clinicians to miss the presence of the underlying personality disorder. However, since a complex pattern of Axis I diagnoses has been found to strongly predict the presence of BPD, clinicians can use the feature of a complex pattern of comorbidity as a clue that BPD might be present.[86]

### Mood disorders [edit]

Many people with borderline personality disorder also have mood disorders, such as major depressive disorder or a bipolar disorder.[27] Some characteristics of BPD are similar to those of mood disorders, which can complicate the diagnosis.[91][92][93] It is especially common for people to be misdiagnosed with bipolar disorder when they have borderline personality disorder or vice versa.[94] For someone with bipolar disorder, behavior suggestive of BPD might appear while the client is experiencing an episode of major depression or mania, only to disappear once the client's mood has stabilized.[95] For this reason, it is ideal to wait until the client's mood has stabilized before attempting to make a diagnosis.[95]

At face value, the affective lability of BPD and the rapid mood cycling of bipolar disorders can seem very similar.[96] It can be difficult even for experienced clinicians, if they are unfamiliar with BPD, to differentiate between the mood swings of these two conditions.[97] However, there are some clear differences.[94]

First, the mood swings of BPD and bipolar disorder tend to have different durations. In some people with bipolar disorder, episodes of depression or mania last for at least two weeks at a time, which is much longer than moods last in people with BPD.[94] Even among those who experience bipolar disorder with more rapid mood shifts, their moods usually last for days, while the moods of people with BPD can change in minutes or hours.[97] So while euphoria and impulsivity in someone with BPD might resemble a manic episode, the experience would be too brief to qualify as a manic episode.[95][97]

Second, the moods of bipolar disorder do not respond to changes in the environment, while the moods of BPD do respond to changes in the environment.[95] That is, a positive event would not lift the depressed mood caused by bipolar disorder, but a positive event would potentially lift the depressed mood of someone with BPD. Similarly, an undesirable event would not dampen the euphoria caused by bipolar disorder, but an undesirable event would dampen the euphoria of someone with borderline personality disorder.[95]

Third, when people with BPD experience euphoria, it is usually without the racing thoughts and decreased need for sleep that are typical of hypomania,[95] though a later 2013 study of data collected in 2004 found that borderline personality disorder diagnosis and symptoms were associated with chronic sleep disturbances, including difficulty initiating sleep, difficulty maintaining sleep, and waking earlier than desired, as well as with the consequences of poor sleep, and noted that "[f]ew studies have examined the experience of chronic sleep disturbances in those with borderline personality disorder".[98]

Because the two conditions have a number of similar symptoms, BPD was once considered to be a mild form of bipolar disorder[99][100] or to exist on the bipolar spectrum. However, this would require that the underlying mechanism causing these symptoms be the same for both conditions. Differences in phenomenology, family history, longitudinal course, and responses to treatment indicate that this is not the case.[101] Researchers have found "only a modest association" between bipolar disorder and borderline personality disorder, with "a strong spectrum relationship with [BPD and] bipolar disorder extremely unlikely."[102] Benazzi et al. suggest that the DSM-IV BPD diagnosis combines two unrelated characteristics: an affective instability dimension related to Bipolar II and an impulsivity dimension not related to Bipolar II.[103]

### Premenstrual dysphoric disorder [edit]

Premenstrual dysphoric disorder (PMDD) occurs in 3–8 percent of women.[104] Symptoms begin 5–11 days before menstruation and cease a few days after it begins.[*citation needed*] Symptoms may include marked mood swings, irritability, depressed mood, feeling hopeless or suicidal, a subjective sense of being overwhelmed or out of control, anxiety, binge eating, difficulty concentrating, and substantial impairment of

interpersonal relationships.[105][106] People with PMDD typically begin to experience symptoms in their early twenties, although many do not seek treatment until their early thirties.[105]

Although some of the symptoms of PMDD and BPD are similar, they are different disorders. They are distinguishable by the timing and duration of symptoms, which are markedly different: the symptoms of PMDD occur only during the luteal phase of the menstrual cycle,[105] whereas BPD symptoms occur persistently at all stages of the menstrual cycle. In addition, the symptoms of PMDD do not include impulsivity.[105]

### Comorbid Axis II disorders [edit]

More than two-thirds of people diagnosed with BPD also meet the criteria for another Axis II personality disorder at some point in their lives. (In a 2008 study, the rate was 73.9 percent.)[88] Cluster A disorders, which include paranoid, schizoid, and schizotypal, are the most common, with a prevalence of 50.4 percent in people with BPD.[88]

**Percentage of people with BPD and a lifetime comorbid Axis II diagnosis, 2008**[88]

| Axis II diagnosis | Overall ( % ) | Male ( % ) | Female ( % ) |
|---|---|---|---|
| **Any Cluster A** | **50.4** | **49.5** | **51.1** |
| Paranoid | 21.3 | 16.5 | 25.4 |
| Schizoid | 12.4 | 11.1 | 13.5 |
| Schizotypal | 36.7 | 38.9 | 34.9 |
| **Any Other Cluster B** | **49.2** | **57.8** | **42.1** |
| Antisocial | 13.7 | 19.4 | _9.0 |
| Histrionic | 10.3 | 10.3 | 10.3 |
| Narcissistic | 38.9 | 47.0 | 32.2 |
| **Any Cluster C** | **29.9** | **27.0** | **32.3** |
| Avoidant | 13.4 | 10.8 | 15.6 |
| Dependent | _3.1 | _2.6 | _3.5 |
| Obsessive-compulsive | 22.7 | 21.7 | 23.6 |

The second most common is another Cluster B disorder, which includes antisocial, histrionic, and narcissistic. These have an overall prevalence of 49.2 percent in people with BPD, with narcissistic being the most common, at 38.9 percent; antisocial the second most common, at 13.7 percent; and histrionic the least common, at 10.3 percent.[88] The least common are Cluster C disorders, which include avoidant, dependent, and obsessive-compulsive, and have a prevalence of 29.9 percent in people with BPD.[88] The percentages for specific comorbid Axis II disorders can be found in the adjacent table.

## Management [edit]

*Main article: Management of borderline personality disorder*

Psychotherapy is the primary treatment for borderline personality disorder.[5] Treatments should be based on the needs of the individual, rather than upon the general diagnosis of BPD. Medications are useful for treating comorbid disorders, such as depression and anxiety.[107] Short-term hospitalization has not been found to be more effective than community care for improving outcomes or long-term prevention of suicidal behavior in those with BPD.[108]

### Psychotherapy [edit]

Long-term psychotherapy is currently the treatment of choice for BPD.[109] There are six such treatments available: dynamic deconstructive psychotherapy (DDP),[110] mentalization-based treatment (MBT), transference-focused psychotherapy, dialectical behavior therapy (DBT), general psychiatric management, and schema-focused therapy.[6] While DBT is the therapy that has been studied the most, empirical research and case studies have shown that all of these treatments are effective for treating BPD, except for

schema-focused therapy.[6][*ambiguous*] Long-term therapy of any kind, including schema-focused therapy, is better than no treatment, especially in reducing urges to self-injure.[109]

Cognitive behavioral therapy (CBT) is also a type of psychotherapy used for treatment of BPD. This type of therapy relies on changing people's behaviors and beliefs by identifying problems from the disorder. CBT is known to reduce some anxiety and mood symptoms as well as reduce suicidal thoughts and self-harming behaviors.[3]

Mentalization-based therapy and transference-focused psychotherapy are based on psychodynamic principles, and dialectical behavior therapy is based on cognitive-behavioral principles and mindfulness.[109] General psychiatric management combines the core principles from each of these treatments, and it is considered easier to learn and less intensive.[6] Randomized controlled trials have shown that DBT and MBT may be the most effective, and the two share many similarities.[111][112] However, a naturalistic study indicated that DDP may be more effective than DBT.[113] Researchers are interested in developing shorter versions of these therapies to increase accessibility, to relieve the financial burden on patients, and to relieve the resource burden on treatment providers.[109][112]

From a psychodynamic perspective, a special problem of psychotherapy with people with BPD is intense projection. It requires the psychotherapist to be flexible in considering negative attributions by the patient rather than quickly interpreting the projection.[114]

Some research indicates that mindfulness meditation may bring about favorable structural changes in the brain, including changes in brain structures that are associated with BPD.[115][116][117] Mindfulness-based interventions also appear to bring about an improvement in symptoms characteristic of BPD, and some clients who underwent mindfulness-based treatment no longer met a minimum of five of the DSM-IV-TR diagnostic criteria for BPD.[117][118]

## Medications [edit]

A 2010 review by the Cochrane collaboration found that no medications show promise for "the core BPD symptoms of chronic feelings of emptiness, identity disturbance and abandonment." However, the authors found that some medications may impact isolated symptoms associated with BPD or the symptoms of comorbid conditions.[119][*needs update*]

Of the typical antipsychotics studied in relation to BPD, haloperidol may reduce anger and flupenthixol may reduce the likelihood of suicidal behavior. Among the atypical antipsychotics, one trial found that aripiprazole may reduce interpersonal problems and impulsivity.[119] Olanzapine may decrease affective instability, anger, psychotic paranoid symptoms, and anxiety, but a placebo had a greater ameliorative impact on suicidal ideation than olanzapine did. The effect of ziprasidone was not significant.[119]

Of the mood stabilizers studied, valproate semisodium may ameliorate depression, interpersonal problems, and anger. Lamotrigine may reduce impulsivity and anger; topiramate may ameliorate interpersonal problems, impulsivity, anxiety, anger, and general psychiatric pathology. The effect of carbamazepine was not significant. Of the antidepressants, amitriptyline may reduce depression, but mianserin, fluoxetine, fluvoxamine, and phenelzine sulfate showed no effect. Omega-3 fatty acid may ameliorate suicidality and improve depression. As of 2010, trials with these medications had not been replicated and the effect of long-term use had not been assessed.[119]

Because of weak evidence and the potential for serious side effects from some of these medications, the UK National Institute for Health and Clinical Excellence (NICE) 2009 clinical guideline for the treatment and management of BPD recommends, "Drug treatment should not be used specifically for borderline personality disorder or for the individual symptoms or behavior associated with the disorder." However, "drug treatment may be considered in the overall treatment of comorbid conditions." They suggest a "review of the treatment of people with borderline personality disorder who do not have a diagnosed comorbid mental or physical illness and who are currently being prescribed drugs, with the aim of reducing and stopping unnecessary drug treatment."[120]

### Services [edit]

There is a significant difference between the number of those who would benefit from treatment and the number of those who are treated. The so-called "treatment gap" is a function of the disinclination of the afflicted to submit for treatment, an underdiagnosing of the disorder by healthcare providers, and the limited availability and access to state-of-the-art treatments.[121] Nonetheless, individuals with BPD accounted for about 20 percent of psychiatric hospitalizations in one survey.[122] The majority of individuals with BPD who are in treatment continue to use outpatient treatment in a sustained manner for several years, but the number using the more restrictive and costly forms of treatment, such as inpatient admission, declines with time.[123]

Experience of services varies.[124] Assessing suicide risk can be a challenge for clinicians, and patients themselves tend to underestimate the lethality of self-injurious behaviors. People with BPD typically have a chronically elevated risk of suicide much above that of the general population and a history of multiple attempts when in crisis.[125] Approximately half the individuals who commit suicide meet criteria for a personality disorder. Borderline personality disorder remains the most commonly associated personality disorder with suicide.[126]

## Prognosis [edit]

With treatment, the majority of people with BPD can find relief from distressing symptoms and achieve remission, defined as a consistent relief from symptoms for at least two years.[127][128] This longitudinal study tracking the symptoms of people with BPD found that 34.5% achieved remission within two years from the beginning of the study. Within four years, 49.4% had achieved remission, and within six years, 68.6% had achieved remission. By the end of the study, 73.5% of participants were found to be in remission.[127] Moreover, of those who achieved recovery from symptoms, only 5.9% experienced recurrences. A later study found that ten years from baseline (during a hospitalization), 86% of patients had sustained a stable recovery from symptoms.[129]

Patient personality can play an important role during the therapeutic process, leading to better clinical outcomes. Recent research has shown that BPD patients undergoing Dialectical Behavior Therapy (DBT) exhibit better clinical outcomes correlated with higher levels of the trait of agreeableness in the patient, compared to patients either low in agreeableness or not being treated with DBT. This association was mediated through the strength of a working alliance between patient and therapist; that is, more agreeable patients developed stronger working alliances with their therapists, which in turn, led to better clinical outcomes.[130]

In addition to recovering from distressing symptoms, people with BPD also achieve high levels of psychosocial functioning. A longitudinal study tracking the social and work abilities of participants with BPD found that six years after diagnosis, 56% of participants had good function in work and social environments, compared to 26% of participants when they were first diagnosed. Vocational achievement was generally more limited, even compared to those with other personality disorders. However, those whose symptoms had remitted were significantly more likely to have good relationships with a romantic partner and at least one parent, good performance at work and school, a sustained work and school history, and good psychosocial functioning overall.[131]

## Epidemiology [edit]

The prevalence of BPD was initially estimated to be 1 to 2 percent of the general population[128][132] and to occur three times more often in women than in men.[133][134] However, the lifetime prevalence of BPD in a 2008 study was found to be 5.9% of the general population, occurring in 5.6% of men and 6.2% of women.[88] The difference in rates between men and women in this study was not found to be statistically significant.[88]

Borderline personality disorder is estimated to contribute to 20 percent of psychiatric hospitalizations and to

occur among 10 percent of outpatients.[135]

29.5 percent of new inmates in Iowa USA, fit a diagnosis of borderline personality disorder in 2007,[136] and the overall prevalence of BPD in the U.S.-prison population is thought to be 17 percent.[135] These high numbers may be related to the high frequency of substance abuse and substance use disorders among people with BPD, which is estimated at 38 percent.[135]

## History [edit]

The coexistence of intense, divergent moods within an individual was recognized by Homer, Hippocrates, and Aretaeus, the latter describing the vacillating presence of impulsive anger, melancholia, and mania within a single person. The concept was revived by Swiss physician Théophile Bonet in 1684 who, using the term *folie maniaco-mélancolique*,[140] described the phenomenon of unstable moods that followed an unpredictable course. Other writers noted the same pattern, including the American psychiatrist C. Hughes in 1884 and J.C. Rosse in 1890, who called the disorder "borderline insanity".[141] In 1921, Kraepelin identified an "excitable personality" that closely parallels the borderline features outlined in the current concept of BPD.[142]

Idealization in Edvard Munch's *The Brooch. Eva Mudocci* (1903)

The first significant psychoanalytic work to use the term "borderline" was written by Adolf Stern in 1938.[143] It described a group of patients suffering from what he thought to be a mild form of schizophrenia, on the *borderline* between neurosis and psychosis.

The 1960s and 1970s saw a shift from thinking of the condition as borderline schizophrenia to thinking of it as a borderline affective disorder (mood disorder), on the fringes of bipolar disorder, cyclothymia, and dysthymia. In the DSM-II, stressing the intensity and variability of moods, it was called cyclothymic personality (affective personality).[82] While the term "borderline" was evolving to refer to a distinct category of disorder, psychoanalysts such as Otto Kernberg were using it to refer to a broad spectrum of issues, describing an intermediate level of personality organization[142] between neurosis and psychosis.[144]

Devaluation in Edvard Munch's *Salome* (1903). Idealization and devaluation of others in personal relations is a highly specific trait in BPD (introduction and main text). The painter Edvard Munch depicted his new friend, the violinist Eva Mudocci, in both ways

After standardized criteria were developed[145] to distinguish it from mood disorders and other Axis I disorders, BPD became a personality disorder diagnosis in 1980 with the publication of the DSM-III.[128] The diagnosis was distinguished from sub-syndromal schizophrenia, which was termed "Schizotypal personality disorder".[144] The DSM-IV Axis II Work Group of the American Psychiatric Association finally decided on the name "borderline personality disorder," which is still in use by the DSM-5 today.[4] However, the term "borderline" has been described as uniquely inadequate for describing the symptoms characteristic of this disorder.[146]

## Controversies [edit]

### Credibility and validity of testimony [edit]

The credibility of individuals with personality disorders has been questioned at least since the 1960s.[147] Two concerns are the incidence of dissociation episodes among people with BPD and the belief that lying is a key component of this condition.

within days. First as "a woman seen by a man in love", then as "a bloodthirsty and cannibalistic Salome".[137] In modern times, Munch has been diagnosed by psychiatrists as having had BPD, including by an authority in the field, James F. Masterson.[138][139]

## Dissociation [edit]

Researchers disagree about whether dissociation, or a sense of detachment from emotions and physical experiences, impacts the ability of people with BPD to recall the specifics of past events. A 1999 study reported that the specificity of autobiographical memory was decreased in BPD patients.[148] The researchers found that decreased ability to recall specifics was correlated with patients' levels of dissociation.[148]

## Lying as a feature [edit]

Some theorists argue that patients with BPD often lie.[149] However, others write that they have rarely seen lying among patients with BPD in clinical practice.[149] Regardless, lying is not one of the diagnostic criteria for BPD.

The belief that lying is a distinguishing characteristic of BPD can impact the quality of care that people with this diagnosis receive in the legal and healthcare systems. For instance, Jean Goodwin relates an anecdote of a patient with multiple personality disorder, now called dissociative identity disorder, who suffered from pelvic pain due to traumatic events in her childhood.[150] Due to their disbelief in her accounts of these events, physicians diagnosed her with borderline personality disorder, reflecting a belief that lying is a key feature of BPD. Based upon her BPD diagnosis, the physicians then disregarded the patient's assertion that she was allergic to adhesive tape. The patient was in fact allergic to adhesive tape, which later caused complications in the surgery to relieve her pelvic pain.[150]

## Gender [edit]

Since BPD can be a stigmatizing diagnosis even within the mental health community, some survivors of childhood abuse who are diagnosed with BPD are re-traumatized by the negative responses they receive from healthcare providers.[151] One camp argues that it would be better to diagnose these men or women with post-traumatic stress disorder, as this would acknowledge the impact of abuse on their behavior. Critics of the PTSD diagnosis argue that it medicalizes abuse rather than addressing the root causes in society.[152] Regardless, a diagnosis of PTSD does not encompass all aspects of the disorder (see Brain abnormalities and Terminology).

Joel Paris states that "In the clinic ... Up to 80% of patients are women. That may not be true in the community."[153] He offers the following explanations regarding these gender discrepancies:

> "The most probable explanation for gender differences in clinical samples is that women are more likely to develop the kind of symptoms that bring patients in for treatment. Twice as many women as men in the community suffer from depression (Weissman & Klerman, 1985). In contrast, there is a preponderance of men meeting criteria for substance abuse and psychopathy (Robins & Regier, 1991), and males with these disorders do not necessarily present in the mental health system. Men and women with similar psychological problems may express distress differently. Men tend to drink more and carry out more crimes. Women tend to turn their anger on themselves, leading to depression as well as the cutting and overdosing that characterize BPD. Thus, anti-social personality disorder (ASPD) and borderline personality disorders might derive from similar underlying pathology but present with symptoms strongly influenced by gender (Paris, 1997a; Looper & Paris, 2000). We have even more specific evidence that men with BPD may not seek help. In a study of completed suicides among people aged 18 to 35 years (Lesage et al., 1994), 30% of the suicides involved individuals with BPD (as confirmed by psychological autopsy, in which symptoms were assessed by interviews with family members). Most of the suicide completers were men, and very few were in treatment. Similar findings emerged from a later study conducted by our own research group (McGirr, Paris, Lesage, Renaud, & Turecki, 2007)."[20]

In short, men are less likely to seek or accept appropriate treatment, more likely to be treated for symptoms of BPD such as substance abuse rather than BPD itself (furthermore, the symptoms of BPD and ASPD may derive from a similar underlying aetiology) and possibly men are simply more likely to commit suicide prior to diagnosis.

Among men diagnosed with BPD there is also evidence of a higher suicide rate: "men are more than twice as likely as women—18 percent versus 8 percent"—to die by suicide.[19]

There are also sex differences in borderline personality disorders.[154] Men with BPD are more likely to abuse substances, have explosive temper, high levels of novelty seeking and have anti-social, narcissistic, passive-aggressive or sadistic personality traits.[154] Women with BPD are more likely to have eating disorders, mood disorders, anxiety and post-traumatic stress.[154]

## Manipulative behavior [edit]

Manipulative behavior to obtain nurturance is considered by the DSM-IV-TR and many mental health professionals to be a defining characteristic of borderline personality disorder.[155] However, Marsha Linehan notes that doing so relies upon the assumption that people with BPD who communicate intense pain, or who engage in self-harm and suicidal behavior, do so with the intention of influencing the behavior of others.[156] The impact of such behavior on others—often an intense emotional reaction in concerned friends, family members, and therapists—is thus assumed to have been the person's intention.[156]

However, since people with BPD lack the ability to successfully manage painful emotions and interpersonal challenges, their frequent expressions of intense pain, self-harming, or suicidal behavior may instead represent a method of mood regulation or an escape mechanism from situations that feel unbearable.[157] Linehan notes that if, for example, one were to withhold pain medication from burn victims and cancer patients, leaving them unable to regulate their severe pain, they would also exhibit "attention-seeking" and self-destructive behavior in order to cope.[158]

## Stigma [edit]

The features of BPD include emotional instability; intense, unstable interpersonal relationships; a need for intimacy; and a fear of rejection. As a result, people with BPD often evoke intense emotions in those around them. Pejorative terms to describe people with BPD, such as "difficult", "treatment resistant", "manipulative", "demanding", and "attention seeking", are often used and may become a self-fulfilling prophecy, as the negative treatment of these individuals triggers further self-destructive behavior.[159]

## Physical violence [edit]

The stigma surrounding borderline personality disorder includes the belief that people with BPD are prone to violence toward others.[160] While movies and visual media often sensationalize people with BPD by portraying them as violent, the majority of researchers agree that people with BPD are unlikely to physically harm others.[160] Although people with BPD often struggle with experiences of intense anger, a defining characteristic of BPD is that they direct it inward toward themselves.[161] One of the key differences between BPD and antisocial personality disorder (ASPD) is that people with BPD tend to internalize anger by hurting themselves, while people with ASPD tend to externalize it by hurting others.[161]

In addition, adults with BPD have often experienced abuse in childhood, so many people with BPD adopt a "no-tolerance" policy toward expressions of anger of any kind.[161] Their extreme aversion to violence can cause many people with BPD to overcompensate and experience difficulties being assertive and expressing their needs.[161] This is one way in which people with BPD choose to harm themselves over potentially causing harm to others.[161] Another way in which people with BPD avoid expressing their anger through violence is by causing physical damage to themselves, such as engaging in non-suicidal self-injury.[13][160]

## Mental healthcare providers [edit]

People with BPD are considered to be among the most challenging groups of patients to work with in therapy, requiring a high level of skill and training in the psychiatrists, therapists and nurses involved in their treatment.[162] A majority of psychiatric staff report finding individuals with BPD moderately to extremely difficult to work with and more difficult than other client groups.[163] Efforts are ongoing to improve public and staff attitudes toward people with BPD.[164][165]

In psychoanalytic theory, the stigmatization among mental healthcare providers may be thought to reflect countertransference (when a therapist projects his or her own feelings on to a client). Thus, a diagnosis of BPD "often says more about the clinician's negative reaction to the patient than it does about the patient" and "explains away the breakdown in empathy between the therapist and the patient and becomes an institutional epithet in the guise of pseudoscientific jargon".[144] This inadvertent countertransference can give rise to inappropriate clinical responses, including excessive use of medication, inappropriate mothering, and punitive use of limit setting and interpretation.[166]

Some clients feel the diagnosis is helpful, allowing them to understand that they are not alone and to connect with others with BPD who have developed helpful coping mechanisms. However, others experience the term "borderline personality disorder" as a pejorative label rather than an informative diagnosis. They report concerns that their self-destructive behavior is incorrectly perceived as manipulative and that the stigma surrounding this disorder limits their access to healthcare.[167][*non-primary source needed*] Indeed, mental health professionals frequently refuse to provide services to those who have received a BPD diagnosis.[168]

### Terminology [edit]

Because of the above concerns, and because of a move away from the original theoretical basis for the term (see history), there is ongoing debate about renaming borderline personality disorder. While some clinicians agree with the current name, others argue that it should be changed,[169] since many who are labelled with borderline personality disorder find the name unhelpful, stigmatizing, or inaccurate.[169][170] Valerie Porr, president of Treatment and Research Advancement Association for Personality Disorders states that "the name BPD is confusing, imparts no relevant or descriptive information, and reinforces existing stigma."[171]

Alternative suggestions for names include *emotional regulation disorder* or *emotional dysregulation disorder*. *Impulse disorder* and *interpersonal regulatory disorder* are other valid alternatives, according to John Gunderson of McLean Hospital in the United States.[172] Another term suggested by psychiatrist Carolyn Quadrio is *post traumatic personality disorganization* (PTPD), reflecting the condition's status as (often) both a form of chronic post traumatic stress disorder (PTSD) as well as a personality disorder.[57] However, although many with BPD do have traumatic histories, some do not report any kind of traumatic event, which suggests that BPD is not necessarily a trauma spectrum disorder.[64]

The Treatment and Research Advancements National Association for Personality Disorders (TARA-APD) campaigned unsuccessfully to change the name and designation of BPD in DSM-5, published in May 2013, in which the name "borderline personality disorder" remains unchanged and it is not considered a trauma- and stressor-related disorder.[173]

## Society and culture [edit]

### Film and television [edit]

There are several films and television shows that portray characters either explicitly diagnosed or with traits suggestive of BPD. These may be misleading if they are thought to depict this disorder accurately. Unfortunately, dramatic portrayals of people with BPD in movies and other forms of visual media contribute to the stigma surrounding borderline personality disorder, especially the myth that people with BPD are violent toward others.[160] The majority of researchers agree that in reality, people with BPD are very unlikely to harm others.[160]

The films *Play Misty for Me*[174] and *Girl, Interrupted* (based on the memoir of the same name) both suggest the emotional instability of the disorder; however, the first case shows a person more aggressive to others than to herself, which is not characteristic of the disorder.[175] The 1992 film *Single White Female*, like the first example, also suggests characteristics, some of which are actually atypical of the disorder: the character Hedy had markedly disturbed sense of identity and reacts drastically to abandonment.[176]

Films attempting to depict characters with the disorder include *A Thin Line Between Love and Hate*, *Filth*, *Fatal Attraction*, *The Crush*, *Mad Love*, *Malicious*, *Interiors*, *The Cable Guy*, *Mr. Nobody*, *Cracks*,[177] and *Welcome to Me*.[178][179] Psychiatrists Eric Bui and Rachel Rodgers argue that the character of Anakin Skywalker/Darth Vader in the *Star Wars* films meets six of the nine diagnostic criteria; Bui also found Anakin a useful example to explain BPD to medical students. In particular, Bui points to the character's abandonment issues, uncertainty over his identity, and dissociative episodes.[180]

## Awareness [edit]

In early 2008, the United States House of Representatives declared the month of May as Borderline Personality Disorder Awareness Month.[181][182]

# Notes [edit]


1. ^ a b Maj, Mario (2005). *Personality disorders*. Chichester: J. Wiley & Sons. p. 126. ISBN 9780470090367.
2. ^ Blom, Jan Dirk (2010). *A dictionary of hallucinations* (1 ed.). New York: Springer. p. 74. ISBN 9781441912237.
3. ^ a b c d e f g h i j k l m "Borderline Personality Disorder". *NIMH*. Retrieved 16 March 2016.
4. ^ a b c d e f g h i *Diagnostic and statistical manual of mental disorders : DSM-5* (5th ed.). Washington [etc.]: American Psychiatric Publishing. 2013. pp. 645, 663–6. ISBN 9780890425558.
5. ^ a b Leichsenring, F; Leibing, E; Kruse, J; New, AS; Leweke, F (1 January 2011). "Borderline personality disorder.". *Lancet (London, England)*. **377** (9759): 74–84. doi:10.1016/s0140-6736(10)61422-5. PMID 21195251.
6. ^ a b c d e f g h i j k l Gunderson, John G. (26 May 2011). "Borderline Personality Disorder". *The New England Journal of Medicine*. **364** (21): 2037–2042. doi:10.1056/NEJMcp1007358. PMID 21612472.
7. ^ Linehan 1993, p. 43
8. ^ a b Manning 2011, p. 36
9. ^ a b c d Linehan 1993, p. 45
10. ^ Linehan 1993, p. 146
11. ^ a b Linehan 1993, p. 44
12. ^ Stiglmayr CE, Grathwol T, Linehan MM, Ihorst G, Fahrenberg J, Bohus M (May 2005). "Aversive tension in patients with borderline personality disorder: a computer-based controlled field study". *Acta Psychiatr Scand*. **111** (5): 372–9. doi:10.1111/j.1600-0447.2004.00466.x. PMID 15819731.
13. ^ a b c d e f Brown MZ, Comtois KA, Linehan MM (February 2002). "Reasons for suicide attempts and nonsuicidal self-injury in women with borderline personality disorder". *J Abnorm Psychol*. **111** (1): 198–202. doi:10.1037/0021-843X.111.1.198. PMID 11866174.
14. ^ a b c Zanarini MC, Frankenburg FR, DeLuca CJ, Hennen J, Khera GS, Gunderson JG (1998). "The pain of being borderline: dysphoric states specific to borderline personality disorder". *Harv Rev Psychiatry*. **6** (4): 201–7. doi:10.3109/10673229809000330. PMID 10370445.
15. ^ Koenigsberg HW, Harvey PD, Mitropoulou V, et al. (May 2002). "Characterizing affective instability in borderline personality disorder". *Am J Psychiatry*. **159** (5): 784–8. doi:10.1176/appi.ajp.159.5.784. PMID 11986132.
16. ^ National Education Alliance for Borderline Personality Disorder. "A BPD Brief" (PDF). p. 4. Archived from the original (PDF) on 12 September 2012. Retrieved 30 June 2013.
17. ^ a b c d e Manning 2011, p. 18
18. ^ Gunderson, John G.; Links, Paul S. (2008). *Borderline Personality Disorder: A Clinical Guide* (2nd ed.). American Psychiatric Publishing, Inc. p. 9. ISBN 978-1585623358.
19. ^ a b Kreisman J, Strauss H (2004). *Sometimes I Act Crazy. Living With Borderline Personality Disorder*. Wiley & Sons. p. 206.
20. ^ a b Paris J (2008). *Treatment of Borderline Personality Disorder. A Guide to Evidence-Based Practice*. The Guilford Press. pp. 21–22.

21. ^ Soloff P.H.; Lis J.A.; Kelly T.; et al. (1994). "Self-mutilation and suicidal behavior in borderline personality disorder". *Journal of Personality Disorders*. **8** (4): 257–67. doi:10.1521/pedi.1994.8.4.257.
22. ^ Gardner D.L.; Cowdry R.W. (1985). "Suicidal and parasuicidal behavior in borderline personality disorder". *Psychiatric Clinics of North America*. **8** (2): 389–403. PMID 3895199.
23. ^ Urnes, O (30 April 2009). "[Self-harm and personality disorders].". *Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke*. **129** (9): 872–6. doi:10.4045/tidsskr.08.0140. PMID 19415088.
24. ^ Horesh N, Sever J, Apter A (July–August 2003). "A comparison of life events between suicidal adolescents with major depression and borderline personality disorder". *Compr Psychiatry*. **44** (4): 277–83. doi:10.1016/S0010-440X(03)00091-9. PMID 12923705.
25. ^ *a b* Arntz, Arnoud (September 2005). "Introduction to special issue: cognition and emotion in borderline personality disorder". *Journal of Behavior Therapy and Experimental Psychiatry*. **36** (3): 167–72. doi:10.1016/j.jbtep.2005.06.001. PMID 16018875.
26. ^ "What Is BPD: Symptoms". Retrieved 31 January 2013.
27. ^ *a b* Robinson, David J. (2005). *Disordered Personalities*. Rapid Psychler Press. pp. 255–310. ISBN 1-894328-09-4.
28. ^ Levy KN, Meehan KB, Weber M, Reynoso J, Clarkin JF (2005). "Attachment and borderline personality disorder: implications for psychotherapy". *Psychopathology*. **38** (2): 64–74. doi:10.1159/000084813. PMID 15802944.
29. ^ *a b* Daley SE, Burge D, Hammen C (August 2000). "Borderline personality disorder symptoms as predictors of 4-year romantic relationship dysfunction in young women: addressing issues of specificity". *J Abnorm Psychol*. **109** (3): 451–60. doi:10.1037/0021-843X.109.3.451. PMID 11016115.
30. ^ *a b c* Manning 2011, p. 23
31. ^ *a b c d* Manning 2011, p. 24
32. ^ *a b c* Grant, Chou, Goldstein, Huang, Stinson, Saha, Smith, Dawson, Pulay, Pickering, Ruan (April 2008). "Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: Results from the Wave 2 National Epidemiologic survey on alcohol and related conditions". *Journal of Clinical Psychology* (69): 533–545.
33. ^ *a b* "Borderline personality disorder". Mayo Clinic. Retrieved 15 May 2008.
34. ^ Gunderson, JG; Sabo, AN (1993). "The phenomenological and conceptual interface between borderline personality disorder and PTSD". *Am J Psychiatry*. **150** (1): 19–27. doi:10.1176/ajp.150.1.19. PMID 8417576.
35. ^ Kluft, Richard P. (1990). *Incest-Related Syndromes of Adult Psychopathology*. American Psychiatric Pub, Inc. pp. 83, 89. ISBN 0-88048-160-9.
36. ^ Zanarini, MC; Frankenburg, FR (1997). "Pathways to the development of borderline personality disorder". *J. Pers. Disord*. **11** (1): 93–104. doi:10.1521/pedi.1997.11.1.93. PMID 9113824.
37. ^ *a b* Grohol, John M. (30 January 2013). "Borderline Personality Disorder". psychcentral.com.
38. ^ Amad, A; Ramoz, N; Thomas, P; Jardri, R; Gorwood, P (March 2014). "Genetics of borderline personality disorder: systematic review and proposal of an integrative model.". *Neuroscience and biobehavioral reviews*. **40**: 6–19. doi:10.1016/j.neubiorev.2014.01.003. PMID 24456942.
39. ^ Torgersen, S (March 2000). "Genetics of patients with borderline personality disorder". *Psychiatr. Clin. North Am*. **23** (1): 1–9. doi:10.1016/S0193-953X(05)70139-8. PMID 10729927.
40. ^ *a b* Torgersen, S; Lygren, S; Oien, PA; et al. (2000). "A twin study of personality disorders". *Compr Psychiatry*. **41** (6): 416–25. doi:10.1053/comp.2000.16560. PMID 11086146.
41. ^ Goodman, M; New, A; Siever, L (December 2004). "Trauma, genes, and the neurobiology of personality disorders". *Annals of the New York Academy of Sciences*. **1032**: 104–16. Bibcode:2004NYASA1032..104G. doi:10.1196/annals.1314.008. PMID 15677398.
42. ^ *a b c d* "Possible Genetic Causes Of Borderline Personality Disorder Identified". sciencedaily.com. 20 December 2008.
43. ^ *a b c* O'Neil, Aisling; Thomas Frodl (18 January 2012). "Brain structure and function in borderline personality disorder". *Brain Structure and Function*. **217**: 767–782. doi:10.1007/s00429-012-0379-4. Retrieved 6 May 2014.
44. ^ Lubke, GH; Laurin, C; Amin, N; Hottenga, JJ; Willemsen, G; van Grootheest, G; Abdellaoui, A; Karssen, LC; Oostra, BA; van Duijn, CM; Penninx, BW; Boomsma, DI (August 2014). "Genome-wide analyses of borderline personality features.". *Molecular Psychiatry*. **19** (8): 923–9. doi:10.1038/mp.2013.109. PMID 23979607.
45. ^ *a b c* Chapman & Gratz 2007, p. 47
46. ^ Szeszko PR, Robinson D, Alvir JM, et al. (October 1999). "Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder". *Arch. Gen. Psychiatry*. **56** (10): 913–9. doi:10.1001/archpsyc.56.10.913. PMID 10530633.
47. ^ Herpertz SC, Dietrich TM, Wenning B, et al. (August 2001). "Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study". *Biol. Psychiatry*. **50** (4): 292–8. doi:10.1016/S0006-

3223(01)01075-7 . PMID 11522264 .
48. ^ a b Schmahl CG, Elzinga BM, Vermetten E, Sanislow C, McGlashan TH, Bremner JD (July 2003). "Neural correlates of memories of abandonment in women with and without borderline personality disorder". *Biol. Psychiatry*. **54** (2): 142–51. doi:10.1016/S0006-3223(02)01720-1. PMID 12873804.
49. ^ Chapman & Gratz 2007, p. 48
50. ^ Grossman R, Yehuda R, Siever L (June 1997). "The dexamethasone suppression test and glucocorticoid receptors in borderline personality disorder". *Annals of the New York Academy of Sciences*. **821**: 459–64. Bibcode:1997NYASA.821..459G. doi:10.1111/j.1749-6632.1997.tb48305.x. PMID 9238229.
51. ^ a b Chapman & Gratz 2007, p. 49
52. ^ van Heeringen K, Audenaert K, Van de Wiele L, Verstraete A (November 2000). "Cortisol in violent suicidal behaviour: association with personality and monoaminergic activity". *J Affect Disord*. **60** (3): 181–9. doi:10.1016/S0165-0327(99)00180-9. PMID 11074106.
53. ^ DeSoto, M. Catherine (2007). "Borderline Personality Disorder, Gender and Serotonin: Does Estrogen Play a Role?". In Czerbska, Martina T. *Psychoneuroendocrinology Research Trends*. Nova Biomedical. Nova Science Publishers. pp. 149–60. ISBN 978-1-60021-665-7.
54. ^ DeSoto MC, Geary DC, Hoard MK, Sheldon MS, Cooper L (August 2003). "Estrogen fluctuations, oral contraceptives and borderline personality". *Psychoneuroendocrinology*. **28** (6): 751–66. doi:10.1016/S0306-4530(02)00068-9. PMID 12812862.
55. ^ Cohen P (September 2008). "Child development and personality disorder". *Psychiatr Clin North Am*. **31** (3): 477–93. doi:10.1016/j.psc.2008.03.005. PMID 18638647.
56. ^ Herman, Judith Lewis; Judith Herman MD (1992). *Trauma and recovery*. New York: BasicBooks. ISBN 0-465-08730-2.
57. ^ a b Quadrio, C (December 2005). "Axis One/Axis Two: A disordered borderline". *Australian and New Zealand Journal of Psychiatry*. **39**: A107. doi:10.1111/j.1440-1614.2005.01674_39_s1.x.
58. ^ Ball JS, Links PS (February 2009). "Borderline personality disorder and childhood trauma: evidence for a causal relationship". *Curr Psychiatry Rep*. **11** (1): 63–8. doi:10.1007/s11920-009-0010-4. PMID 19187711.
59. ^ a b c Zanarini MC, Frankenburg FR, Reich DB, et al. (2000). "Biparental failure in the childhood experiences of borderline patients". *J Personal Disord*. **14** (3): 264–73. doi:10.1521/pedi.2000.14.3.264. PMID 11019749.
60. ^ Dozier, Mary; Stovall-McClough, K. Chase; Albus, Kathleen E. (1999). "Attachment and psychopathology in adulthood". In Cassidy, Jude; Shaver, Phillip R. *Handbook of attachment*. New York: Guilford Press. pp. 497–519.
61. ^ Kernberg, Otto F. *Borderline conditions and pathological narcissism*. Northvale, N.J.: J. Aronson. ISBN 0-87668-762-1.[*page needed*]
62. ^ a b c d Ayduk O, Zayas V, Downey G, Cole AB, Shoda Y, Mischel W (February 2008). "Rejection Sensitivity and Executive Control: Joint predictors of Borderline Personality features". *J Res Pers*. **42** (1): 151–168. doi:10.1016/j.jrp.2007.04.002. PMC 2390893. PMID 18496604.
63. ^ a b Rosenthal, MZ; Cheavens, JS; Lejuez, CW; Lynch, TR (September 2005). "Thought suppression mediates the relationship between negative affect and borderline personality disorder symptoms". *Behav Res There*. **43** (9): 1173–85. doi:10.1016/j.brat.2004.08.006. PMID 16005704.
64. ^ a b Chapman & Gratz 2007, p. 52
65. ^ a b Ruocco, Anthony C.; Amirthavasagam, Sathya, Choi-Kain, Lois W.; McMain, Shelley F. (2013). "Neural Correlates of Negative Emotionality in Borderline Personality Disorder: An Activation-Likelihood-Estimation Meta-Analysis". *Biological Psychiatry*. **73** (2): 153–160. doi:10.1016/j.biopsych.2012.07.014.
66. ^ Koenigsberg, Harold W; Siever, Larry J; Lee, Hedok; Pizzarello, Scott; New, Antonia S; Goodman, Marianne; Cheng, Hu; Flory, Janine; Prohovnik, Isak (2009). "Neural correlates of emotion processing in borderline personality disorder.". *Psychiatry Research*. **172** (3): 192–9. doi:10.1016/j.pscychresns.2008.07.010. PMC 4153735. PMID 19394205. Lay summary. "BPD patients demonstrated greater differences in activation than controls, when viewing negative pictures compared with rest, in the amygdala, fusiform gyrus, primary visual areas, superior temporal gyrus (STG), and premotor areas, while healthy controls showed greater differences than BPD patients in the insula, middle temporal gyrus and dorsolateral prefrontal cortex."
67. ^ Lazzaretti, Matteo; Morandotti, Niccolò; Sala, Michela; Isola, Miriam; Frangou, Sophia; De Vidovich, Giulia; Marraffini, Elisa; Gambini, Francesca; et al. (2012). "Impaired working memory and normal sustained attention in borderline personality disorder". *Acta Neuropsychiatrica*. **24** (6): 349–55. doi:10.1111/j.1601-5215.2011.00630.x.
68. ^ Bradley R, Jenei J, Westen D (January 2005). "Etiology of borderline personality disorder: disentangling the contributions of intercorrelated antedents". *J. Nerv. Ment. Dis.* **193** (1): 24–31. doi:10.1097/01.nmd.0000149215.88020.7c. PMID 15674131.
69. ^ a b Parker, AG; Boldero, JM; Bell, RC (September 2006). "Borderline personality disorder features: the role of self-discrepancies and self-complexity". *Psychol Psychother*. **79** (Pt 3): 309–21. doi:10.1348/147608305X70072.

PMID 16945194.
70. ^ Sauer, SE; Baer, Ruth A.; Baer, RA (February 2009). "Relationships between thought suppression and symptoms of borderline personality disorder". *J. Pers. Disord.* **23** (1): 48–61. doi:10.1521/pedi.2009.23.1.48. PMID 19267661.
71. ^ *a b c* "Personality Disorders: Tests and Diagnosis". Mayo Clinic. Retrieved 13 June 2013.
72. ^ *a b* American Psychiatric Association 2013, pp. 663–8
73. ^ American Psychiatric Association 2013, pp. 766–7
74. ^ *a b* Manning 2011, p. 13
75. ^ Emotionally unstable personality disorder – International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) – World Health Organization
76. ^ Carlson, Neil R.; Heth, C. Donald (2010). *Psychology: The Science of Behavior*. Pearson Canada. p. 570.
77. ^ Millon, Theodore (2004). *Personality Disorders in Modern Life*. Hoboken, New Jersey: John Wiley & Sons. p. 4. ISBN 0-471-23734-5.
78. ^ Chanen, Andrew M; Thompson, Katherine N (1 April 2016). "Prescribing and borderline personality disorder". *Australian Prescriber*. **39** (2): 49–53. doi:10.18773/austprescr.2016.019. PMC 4917638. PMID 27340322.
79. ^ Meaney, Rebecca; Hasking, Penelope; Reupert, Andrea (2016). "Borderline Personality Disorder Symptoms in College Students:The Complex Interplay Between Alexithymia, Emotional Dysregulation and Rumination". *PLOS ONE*.
80. ^ Allen DM, Farmer RG (1996). "Family relationships of adults with borderline personality disorder". *Compr Psychiatry*. **37** (1): 43–51. doi:10.1016/S0010-440X(96)90050-4. PMID 8770526.
81. ^ Linehan 1993, p. 49
82. ^ *a b c d* American Psychiatric Association 2000[*page needed*]
83. ^ *a b* Netherton, S.D.; Holmes, D.; Walker, C.E. (1999). *Child and Adolescent Psychological Disorders: Comprehensive Textbook*. New York, NY: Oxford University Press.[*page needed*]
84. ^ Miller AL, Muehlenkamp JJ, Jacobson CM (July 2008). "Fact or fiction: diagnosing borderline personality disorder in adolescents". *Clin Psychol Rev*. **28** (6): 969–81. doi:10.1016/j.cpr.2008.02.004. PMID 18358579.
85. ^ Linehan 1993, p. 98
86. ^ *a b c d e f g h* Zanarini MC, Frankenburg FR, Dubo ED, et al. (December 1998). "Axis I comorbidity of borderline personality disorder". *Am J Psychiatry*. **155** (12): 1733–9. doi:10.1176/ajp.155.12.1733. PMID 9842784.
87. ^ *a b* Ferrer M, Andión O, Matalí J, et al. (December 2010). "Comorbid attention-deficit/hyperactivity disorder in borderline patients defines an impulsive subtype of borderline personality disorder". *J. Pers. Disord.* **24** (6): 812–22. doi:10.1521/pedi.2010.24.6.812. PMID 21158602.[*non-primary source needed*]
88. ^ *a b c d e f g h i j k* Grant BF, Chou SP, Goldstein RB, et al. (April 2008). "Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions". *J Clin Psychiatry*. **69** (4): 533–45. doi:10.4088/JCP.v69n0404. PMC 2676679. PMID 18426259.
89. ^ Gregory, Robert J. (1 November 2006). "Clinical Challenges in Co-occurring Borderline Personality and Substance Use Disorders". *Psychiatric Times*.
90. ^ Rydén, Göran; Rydén, Eleonore; Hetta, Jerker (2008). "Borderline personality disorder and autism spectrum disorder in females: A cross-sectional study" (PDF). *Clinical Neuropsychiatry*. **5** (1): 22–30. Retrieved 7 February 2013.
91. ^ Bolton S, Gunderson JG (September 1996). "Distinguishing borderline personality disorder from bipolar disorder: differential diagnosis and implications". *Am J Psychiatry*. **153** (9): 1202–7. doi:10.1176/ajp.153.9.1202. PMID 8780426.
92. ^ American Psychiatric Association Practice Guidelines (October 2001). "Practice guideline for the treatment of patients with borderline personality disorder. American Psychiatric Association". *Am J Psychiatry*. **158** (10 Suppl): 1–52. doi:10.1176/appi.ajp.158.1.1. PMID 11665545.
93. ^ "Differential Diagnosis of Borderline Personality Disorder". *BPD Today*.
94. ^ *a b c* Chapman & Gratz 2007, p. 87
95. ^ *a b c d e f* Jamison, Kay R.; Goodwin, Frederick Joseph (1990). *Manic-depressive illness*. Oxford [Oxfordshire]: Oxford University Press. p. 108. ISBN 0-19-503934-3.
96. ^ Mackinnon DF, Pies R (February 2006). "Affective instability as rapid cycling: theoretical and clinical implications for borderline personality and bipolar spectrum disorders". *Bipolar Disord*. **8** (1): 1–14. doi:10.1111/j.1399-5618.2006.00283.x. PMID 16411976.
97. ^ *a b c* Chapman & Gratz 2007, p. 88
98. ^ Selby EA (October 2013). "Chronic sleep disturbances and borderline personality disorder symptoms". *J Consult*

*Clin Psychol*. **81** (5): 941–7. doi:10.1037/a0033201. PMC 4129646. PMID 23731205.
99. ^ Akiskal HS, Yerevanian BI, Davis GC, King D, Lemmi H (February 1985). "The nosologic status of borderline personality: clinical and polysomnographic study". *Am J Psychiatry*. **142** (2): 192–8. doi:10.1176/ajp.142.2.192. PMID 3970243.
100. ^ Gunderson JG, Elliott GR (March 1985). "The interface between borderline personality disorder and affective disorder". *Am J Psychiatry*. **142** (3): 277–88. doi:10.1176/ajp.142.3.277. PMID 2857532.
101. ^ Paris J (2004). "Borderline or bipolar? Distinguishing borderline personality disorder from bipolar spectrum disorders". *Harv Rev Psychiatry*. **12** (3): 140–5. doi:10.1080/10673220490472373. PMID 15371068.
102. ^ Jamison, Kay R.; Goodwin, Frederick Joseph (1990). *Manic-depressive illness*. Oxford [Oxfordshire]: Oxford University Press. p. 336. ISBN 0-19-503934-3.
103. ^ Benazzi F (January 2006). "Borderline personality-bipolar spectrum relationship". *Prog. Neuropsychopharmacol. Biol. Psychiatry*. **30** (1): 68–74. doi:10.1016/j.pnpbp.2005.06.010. PMID 16019119.
104. ^ Rapkin, AJ; Lewis, EI (November 2013). "Treatment of premenstrual dysphoric disorder". *Womens Health (Lond Engl)*. **9** (6): 537–56. doi:10.2217/whe.13.62. PMID 24161307.
105. ^ *a b c d* Grady-Weliky, TA (January 2003). "Premenstrual dysphoric disorder". *N. Engl. J. Med*. **348** (5): 433–8. doi:10.1056/NEJMcp012067. PMID 12556546.
106. ^ Steriti, Ronald. "Premenstrual Dysphoric Disorder" (PDF). Archived from the original (PDF) on 20 October 2014.
107. ^ "CG78 Borderline personality disorder (BPD): NICE guideline". Nice.org.uk. 28 January 2009. Retrieved 12 August 2009.
108. ^ Paris J (June 2004). "Is hospitalization useful for suicidal patients with borderline personality disorder?". *J. Pers. Disord*. **18** (3): 240–7. doi:10.1521/pedi.18.3.240.35443. PMID 15237044.
109. ^ *a b c d* Zanarini MC (November 2009). "Psychotherapy of borderline personality disorder". *Acta Psychiatr Scand*. **120** (5): 373–7. doi:10.1111/j.1600-0447.2009.01448.x. PMC 3876885. PMID 19807718.
110. ^ Gabbard, G.O. (2014). Psychodynamic psychiatry in clinical practice. 5th Edition. American Psychiatric Publishing: Washington, D.C., pp. 445-448.
111. ^ Linehan MM, Comtois KA, Murray AM, et al. (July 2006). "Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder". *Arch. Gen. Psychiatry*. **63** (7): 757–66. doi:10.1001/archpsyc.63.7.757. PMID 16818865.
112. ^ *a b* Paris J (February 2010). "Effectiveness of different psychotherapy approaches in the treatment of borderline personality disorder". *Curr Psychiatry Rep*. **12** (1): 56–60. doi:10.1007/s11920-009-0083-0. PMID 20425311.
113. ^ Sachdeva S.; Goldman G.; Mustata G.; Deranja E.; Gregory R. J. (2013). "Naturalistic outcomes of evidence-based therapies for borderline personality disorder at a university clinic: A quasi-randomized trial". *Journal of the American Psychoanalytic Association*. **61**: 578–584. doi:10.1177/0003065113490637.
114. ^ Blechner, Mark J. (July 1994). "Projective identification, countertransference, and the 'maybe-me'". *Contemporary Psychoanalysis*. **30** (3): 619–30. doi:10.1080/00107530.1994.10746876.
115. ^ >Tang YY, Posner MI (Jan 2013). "Special issue on mindfulness neuroscience". *Social Cognitive & Affective Neuroscience*. **8** (1): 1–3. doi:10.1093/scan/nss104.
116. ^ Posner MI, Tang YY, Lynch G (2014). "Mechanisms of white matter change induced by meditation training". *Frontiers in Psychology*. **5** (1220): 297–302. doi:10.3389/fpsyg.2014.01220.
117. ^ *a b* Chafos VH, Economou P (July 2014). "Beyond Borderline Personality Disorder: The Mindful Brain". *Social Work*. **59** (4): 297–302. doi:10.1093/sw/swu030.
118. ^ Sachse S, Keville S, Feigenbaum J (Jun 2011). "A feasibility study of mindfulness-based cognitive therapy for individuals with borderline personality disorder". *Psychology and Psychotherapy*. **84** (2): 184–200. doi:10.1348/147608310X516387.
119. ^ *a b c d* Binks CA, Fenton M, McCarthy L, Lee T, Adams CE, Duggan C (2006). Binks C, ed. "Pharmacological interventions for people with borderline personality disorder". *Cochrane Database of Systematic Reviews* (1): CD005653. doi:10.1002/14651858.CD005653. PMID 16437535.
120. ^ "The UK National Institute for Health and Clinical Excellence (NICE) 2009 clinical guideline for the treatment and management of BPD" (PDF). Retrieved 6 September 2011.
121. ^ Johnson, R. Skip (26 July 2014). "Treatment of Borderline Personality Disorder". BPDFamily.com. Retrieved 5 August 2014.
122. ^ Zanarini MC, Frankenburg FR, Khera GS, Bleichmar J (2001). "Treatment histories of borderline inpatients". *Compr Psychiatry*. **42** (2): 144–50. doi:10.1053/comp.2001.19749. PMID 11244151.
123. ^ Zanarini MC, Frankenburg FR, Hennen J, Silk KR (January 2004). "Mental health service utilization by borderline personality disorder patients and Axis II comparison subjects followed prospectively for 6 years". *J Clin Psychiatry*. **65** (1): 28–36. doi:10.4088/JCP.v65n0105. PMID 14744165.
124. ^ Fallon P (August 2003). "Travelling through the system: the lived experience of people with borderline personality

disorder in contact with psychiatric services". *J Psychiatr Ment Health Nurs*. **10** (4): 393–401. doi:10.1046/j.1365-2850.2003.00617.x. PMID 12887630.
125. ^ Links, Paul S.; Bergmans, Yvonne; Warwar, Serine H. (1 July 2004). "Assessing Suicide Risk in Patients With Borderline Personality Disorder". *Psychiatric Times*.
126. ^ Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M (2004). "Borderline personality disorder". *Lancet*. **364** (9432): 453–61. doi:10.1016/S0140-6736(04)16770-6. PMID 15288745.
127. ^ *a b* Zanarini MC, Frankenburg FR, Hennen J, Silk KR (February 2003). "A longitudinal course of borderline psychopathology: 6-year prospective follow-up of the phenomenology of borderline personality disorder". *Am J Psychiatry*. **160** (2): 274–83. doi:10.1176/appi.ajp.160.2.274. PMID 12562573.
128. ^ *a b c* Oldham, John M. (July 2004). "Borderline Personality Disorder: An Overview". *Psychiatric Times*.
129. ^ Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G (June 2010). "Time to attainment of recovery from borderline personality disorder and stability of recovery: A 10-year prospective follow-up study". *Am J Psychiatry*. **167** (6): 663–7. doi:10.1176/appi.ajp.2009.09081130. PMC 3203735. PMID 20395399. Lay summary – *McLean Hospital* (15 April 2010).
130. ^ Hirsh JB, Quilty LC, Bagby RM, McMain SF (August 2012). "The relationship between agreeableness and the development of the working alliance in patients with borderline personality disorder". *J. Pers. Disord*. **26** (4): 616–27. doi:10.1521/pedi.2012.26.4.616. PMID 22867511.
131. ^ Zanarini MC, Frankenburg FR, Hennen J, Reich DB, Silk KR (February 2005). "Psychosocial functioning of borderline patients and axis II comparison subjects followed prospectively for six years". *J. Pers. Disord*. **19** (1): 19–29. doi:10.1521/pedi.19.1.19.62178. PMID 15899718.
132. ^ Swartz, Marvin; Blazer, Dan; George, Linda; Winfield, Idee (1990). "Estimating the Prevalence of Borderline Personality Disorder in the Community". *Journal of Personality Disorders*. **4** (3): 257–272. doi:10.1521/pedi.1990.4.3.257.
133. ^ Skodol AE, Bender DS (2003). "Why are women diagnosed borderline more than men?". *Psychiatr Q*. **74** (4): 349–60. doi:10.1023/A:1026087410516. PMID 14686459.
134. ^ Korzekwa MI, Dell PF, Links PS, Thabane L, Webb SP (2008). "Estimating the prevalence of borderline personality disorder in psychiatric outpatients using a two-phase procedure". *Compr Psychiatry*. **49** (4): 380–6. doi:10.1016/j.comppsych.2008.01.007. PMID 18555059.
135. ^ *a b c* "BPD Fact Sheet". National Educational Alliance for Borderline Personality Disorder. 2013.
136. ^ Black DW, Gunter T, Allen J, et al. (2007). "Borderline personality disorder in male and female offenders newly committed to prison". *Compr Psychiatry*. **48** (5): 400–5. doi:10.1016/j.comppsych.2007.04.006. PMID 17707246.
137. ^ Tove Aarkrog: *Edvard Munch: the life of a person with borderline personality as seen through his art*, Lundbeck Pharma A/S, Denmark 1990, ISBN 8798352415, p. 34-35.
138. ^ James F. Masterson: *Search For The Real Self. Unmasking The Personality Disorders Of Our Age*, Chapter 12: The Creative Solution: Sartre, Munch, and Wolfe, p. 208–230, Simon and Schuster, New York 1988, ISBN 1451668910, p. 212-213.
139. ^ Tove Aarkrog: *Edvard Munch: the life of a person with borderline personality as seen through his art*, Lundbeck Pharma A/S, Denmark 1990, ISBN 8798352415.
140. ^ Millon, Grossman & Meagher 2004, p. 172
141. ^ C. Hughes (1884). "Borderline psychiatric records – prodronal symptoms of physical impairments". *Alienists & Neurology*. **5**: 85–90.
142. ^ *a b* Millon 1996, pp. 645–690
143. ^ Stern, Adolf (1938). "Psychoanalytic investigation of and therapy in the borderline group of neuroses". *Psychoanalytic Quarterly*. **7**: 467–489.
144. ^ *a b c* Aronson TA (August 1985). "Historical perspectives on the borderline concept: a review and critique". *Psychiatry*. **48** (3): 209–22. PMID 3898174.
145. ^ Gunderson JG, Kolb JE, Austin V (July 1981). "The diagnostic interview for borderline patients". *Am J Psychiatry*. **138** (7): 896–903. doi:10.1176/ajp.138.7.896. PMID 7258348.
146. ^ Stone MH (2005). "Borderline Personality Disorder: History of the Concept". In Zanarini MC. *Borderline personality disorder*. Boca Raton, FL: Taylor & Francis. pp. 1–18. ISBN 0-8247-2928-5.
147. ^ Kluft, Richard; Goodwin, Jean (1985). *Childhood Antecedents of Multiple Personality Disorder: Credibility Problems in Multiple Personality Disorder Patients and Abused Children*. American Psychiatric Publishing, Inc. p. 2.
148. ^ *a b* Startup, M.; B. Jones; H. Heard; M. Swales; J.M.G. Williams; R.S.P. Jones (November 1999). "Autobiographical memory and dissociation in borderline personality disorder". *Psychological Medicine*. **29** (6): 1397–1404. doi:10.1017/S0033291799001208. PMID 10616945.
149. ^ *a b* Linehan 1993, p. 17

150. ^ [a] [b] Kluft, Richard; Goodwin, Jean (1985). *Childhood Antecedents of Multiple Personality Disorder: Credibility Problems in Multiple Personality Disorder Patients and Abused Children*. American Psychiatric Publishing, Inc. p. 3.
151. ^ Nehls N (1998). "Borderline personality disorder: gender stereotypes, stigma, and limited system of care". *Issues Ment Health Nurs*. **19** (2): 97–112. doi:10.1080/016128498249105. PMID 9601307.(subscription required)
152. ^ Becker D (October 2000). "When she was bad: borderline personality disorder in a posttraumatic age". *Am J Orthopsychiatry*. **70** (4): 422–32. doi:10.1037/h0087769. PMID 11086521.
153. ^ Paris J (2008). *Treatment of Borderline Personality Disorder. A Guide to Evidence-Based Practice*. The Guilford Press. p. 21.
154. ^ [a] [b] [c] Sansone, Randy A.; Sansone, Lori A. (1 May 2011). "Gender Patterns in Borderline Personality Disorder". *Innovations in Clinical Neuroscience*. **8** (5): 16–20. ISSN 2158-8333. PMC 3115767. PMID 21686143.
155. ^ American Psychiatric Association 2000, p. 705
156. ^ [a] [b] Linehan 1993, p. 14
157. ^ Linehan 1993, p. 15
158. ^ Linehan 1993, p. 18
159. ^ Aviram RB, Brodsky BS, Stanley B (2006). "Borderline personality disorder, stigma, and treatment implications". *Harv Rev Psychiatry*. **14** (5): 249–56. doi:10.1080/10673220600975121. PMID 16990170.
160. ^ [a] [b] [c] [d] [e] Chapman & Gratz 2007, p. 31
161. ^ [a] [b] [c] [d] [e] Chapman & Gratz 2007, p. 32
162. ^ Hinshelwood RD (March 1999). "The difficult patient. The role of 'scientific psychiatry' in understanding patients with chronic schizophrenia or severe personality disorder". *Br J Psychiatry*. **174** (3): 187–90. doi:10.1192/bjp.174.3.187. PMID 10448440.
163. ^ Cleary M, Siegfried N, Walter G (September 2002). "Experience, knowledge and attitudes of mental health staff regarding clients with a borderline personality disorder". *Int J Ment Health Nurs*. **11** (3): 186–91. doi:10.1046/j.1440-0979.2002.00246.x. PMID 12510596.
164. ^ Deans C, Meocevic E (2006). "Attitudes of registered psychiatric nurses towards patients diagnosed with borderline personality disorder". *Contemp Nurse*. **21** (1): 43–9. doi:10.5172/conu.2006.21.1.43. PMID 16594881.
165. ^ Krawitz R (July 2004). "Borderline personality disorder: attitudinal change following training". *Aust N Z J Psychiatry*. **38** (7): 554–9. doi:10.1111/j.1440-1614.2004.01409.x. PMID 15255829.
166. ^ Vaillant GE (1992). "The beginning of wisdom is never calling a patient a borderline; or, the clinical management of immature defenses in the treatment of individuals with personality disorders". *J Psychother Pract Res*. **1** (2): 117–34. PMC 3330289. PMID 22700090.
167. ^ Nehls N (August 1999). "Borderline personality disorder: the voice of patients". *Res Nurs Health*. **22** (4): 285–93. doi:10.1002/(SICI)1098-240X(199908)22:4<285::AID-NUR3>3.0.CO;2-R. PMID 10435546.
168. ^ Manning 2011, p. ix
169. ^ [a] [b] Bogod, Elizabeth. "Borderline Personality Disorder Label Creates Stigma". Archived from the original on 2 May 2015.
170. ^ "Understanding Borderline Personality Disorder". Treatment and Research Advancements Association for Personality Disorder. 2004.
171. ^ Porr, Valerie (2001). "How Advocacy is Bringing Borderline Personality Disorder Into the Light". Archived from the original on 20 October 2014.
172. ^ Gunderson, John G.; Hoffman, Perry D. (2005). *Understanding and Treating Borderline Personality Disorder A Guide for Professionals and Families*. Arlington, Virginia: American Psychiatric Publishing.[*page needed*]
173. ^ American Psychiatric Association 2013, pp. 663–6
174. ^ Robinson, David J. (2003). *Reel Psychiatry: Movie Portrayals of Psychiatric Conditions*. Port Huron, Michigan: Rapid Psychler Press. p. 234. ISBN 1-894328-07-8.
175. ^ Wedding D, Boyd MA, Niemiec RM (2005). *Movies and Mental Illness: Using Films to Understand Psychopathology*. Cambridge, MA: Hogrefe. p. 59. ISBN 0-88937-292-6.
176. ^ Robinson (*Reel Psychiatry: Movie Portrayals of Psychiatric Conditions*), p. 235
177. ^ Robinson, David J. (1999). *The Field Guide to Personality Disorders*. Rapid Psychler Press. p. 113. ISBN 0-9680324-6-X.
178. ^ O'Sullivan, Michael (7 May 2015). "Kristen Wiig earns awkward laughs and silence in 'Welcome to Me'". *Washington Post*. Retrieved 3 June 2015.
179. ^ Chang, Justin (11 September 2014). "Toronto Film Review: 'Welcome to Me': Kristen Wiig plays a woman with borderline personality disorder in this startlingly inspired comedy from Shira Piven". *Variety*. Retrieved 3 June 2015.
180. ^ Hsu, Jeremy (8 June 2010). "The Psychology of Darth Vader Revealed". *LiveScience*. TopTenReviews. Retrieved

8 June 2010.
181. ^ HR 1005, 4/1/08
182. ^ "BPD Awareness Month – Congressional History". *BPD Today*. Mental Health Today. Retrieved 1 November 2010.

## References [edit]


- Chapman, Alexander L.; Gratz, Kim L. (2007). *The Borderline Personality Disorder Survival Guide: Everything You Need to Know About Living with BPD*. Oakland, CA: New Harbinger Publications. ISBN 978-1-57224-507-5.
- Linehan, Marsha M.; Comtois, Katherine Anne; Murray, Angela M.; Brown, Milton Z.; Gallop, Robert J.; Heard, Heidi L.; Korslund, Kathryn E.; Tutek, Darren A.; et al. (2006). "Two-Year Randomized Controlled Trial and Follow-up of Dialectical Behavior Therapy vs Therapy by Experts for Suicidal Behaviors and Borderline Personality Disorder". *Archives of General Psychiatry*. **63** (7): 757–66. doi:10.1001/archpsyc.63.7.757. PMID 16818865.
- Linehan, Marsha (1993). *Cognitive-behavioral treatment of borderline personality disorder*. New York: Guilford Press. ISBN 0-89862-183-6.
- Manning, Shari (2011). *Loving Someone with Borderline Personality Disorder*. The Guilford Press. ISBN 978-1-59385-607-6.
- Millon, Theodore (1996). *Disorders of Personality: DSM-IV-TM and Beyond*. New York: John Wiley & Sons. ISBN 0-471-01186-X.
- Millon, Theodore (2004). *Personality Disorders in Modern Life*. ISBN 0-471-32355-1.
- Millon, Theodore; Grossman, Seth; Meagher, Sarah E. (2004). *Masters of the mind: exploring the story of mental illness from ancient times to the new millennium*. John Wiley & Sons. ISBN 978-0-471-46985-8.
- Millon, Theodore (2006). "Personality Subtypes". *Institute for Advanced Studies in Personology and Psychopathology*. Dicandrien, Inc. Retrieved 1 November 2010.
- American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.). American Psychiatric Association. ISBN 978-0-89042-025-6.
- American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). American Psychiatric Publishing. ISBN 978-0-89042-555-8.


## External links [edit]

- Borderline personality disorder at DMOZ
- "Borderline personality disorder". National Institute of Mental Health.
- APA DSM 5 Definition of Borderline personality disorder
- APA Division 12 treatment page for Borderline personality disorder

| v · t · e | **Borderline personality disorder** |
|---|---|
| **General** | Dimensional models of personality disorders · Impulse control disorders · Trauma model of mental disorders · |
| **Symptoms and behaviors** | Dissociation · Eating disorders · Dysregulation · Feelings of emptiness · Hypersexuality · Idealization and devaluation · Impulsivity · Mood swings · Projection · Self-harm · Splitting · Suicidal ideation · |
| **Management** | Dialectical behavior therapy · Dynamic deconstructive psychotherapy · McLean Hospital · Mentalization-based treatment · Schema therapy · Social psychiatry · Transference focused psychotherapy · |
| **Family challenges** | BPDFamily (support group) · Codependency · Complex PTSD · Emotional blackmail · Family estrangement · Personal boundaries · |

| v · t · e | **DSM personality disorders** |
|---|---|
| **DSM-III-R only** | Sadistic · Self-defeating (masochistic) · |
| | Personality disorder not otherwise specified |

| | | |
|---|---|---|
| **DSM-IV only** | **Appendix B (proposed)** | Depressive · Negativistic (passive-aggressive) · |
| **DSM-5 (Categorical model)** | **Cluster A (odd)** | Paranoid · Schizoid · Schizotypal · |
| | **Cluster B (dramatic)** | Antisocial · **Borderline** · Histrionic · Narcissistic · |
| | **Cluster C (anxious)** | Avoidant · Dependent · Obsessive-compulsive · |
| **DSM-5** | Alternative hybrid categorical and dimensional model in Section III included to stimulate further research | |

| V · T · E · | **ICD-10 personality disorders** |
|---|---|
| **Schizotypal** | Schizotypal · |
| **Specific** | Anankastic · Anxious (avoidant) · Dependent · Dissocial · Emotionally unstable · Histrionic · Paranoid · Schizoid · |
| **Other** | Eccentric · Haltlose type · Immature · Narcissistic · Passive-aggressive · Psychoneurotic · |
| **Unspecified** | Unspecified · |

| | |
|---|---|
| **Authority control** | GND: 1045493465 · |

Categories: Borderline personality disorder | Abnormal psychology | Cluster B personality disorders | Personality disorders | Psychiatric diagnosis | Suffering | Women and psychology

# Bulimia nervosa

From Wikipedia, the free encyclopedia

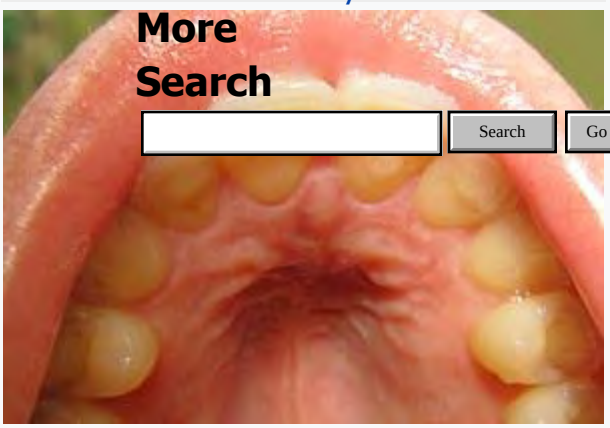
**Bulimia nervosa**, also known as simply **bulimia**, is an eating disorder characterized by binge eating followed by purging. Binge eating refers to eating a large amount of food in a short amount of time. Purging refers to the attempts to get rid of the food consumed. This may be done by vomiting or taking laxatives.[1] Other efforts to lose weight may include the use of diuretics, stimulants, water fasting, or excessive exercise.[1][2] Most people with bulimia are at a normal weight.[3] The forcing of vomiting may result in thickened skin on the knuckles and breakdown of the teeth. Bulimia is frequently associated with other mental disorders such as depression, anxiety, and problems with drugs or alcohol.[1] There is also a higher risk of suicide and self-harm.[4]

Bulimia is more common among those who have a close relative with the condition.[1] The percentage risk that is estimated to be due to genetics is between 30% and 80%.[2] Other risk factors for the disease include psychological stress, cultural pressure to attain a certain body type, poor self-esteem, and obesity.[1][2] Living in a culture that promotes dieting and having parents that worry about weight are also risks.[2] Diagnosis is based on a person's medical history,[5] however this is difficult as people are usually secretive about their binge eating and purging habits.[2] Furthermore, the diagnosis of anorexia nervosa takes precedence over that of bulimia.[2] Other similar disorders include binge eating disorder, Kleine-Levin syndrome, and borderline personality disorder.[5]

Cognitive behavioral therapy is the primary treatment for bulimia.[1][6] Antidepressants of the selective serotonin reuptake inhibitors (SSRI) or tricyclic antidepressant class may have a modest benefit.[2][7] While outcomes with bulimia are typically better than in those of anorexia, the risk of death among those affected is higher than that of the general population.[4] At 10 years after receiving treatment about 50% of people are fully recovered.[2]

Globally, bulimia was estimated to affect 6.5 million people in 2013.[8] About 1% of young women have bulimia at a given point in time and about 2% to 3% of women have the condition at some point in their lives.[4] The condition is less common in the developing world.[2] Bulimia is about nine times more likely to occur in women than men. Among women, rates are highest in young adults.[5] Bulimia was named and first described by the British psychiatrist Gerald Russell in 1979.[9][10]

**Bulimia nervosa**

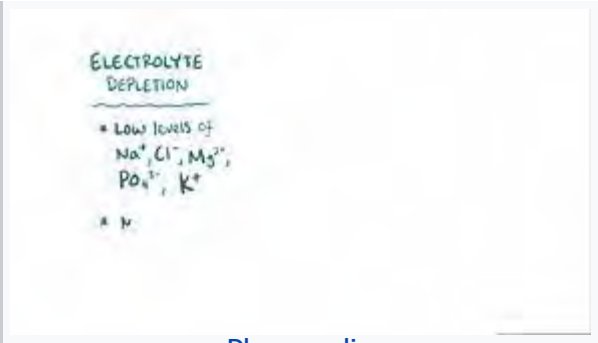


Loss of enamel from the inside of the upper front teeth as a result of bulimia

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Psychiatry |
| **ICD-10** | F50.2 |
| **ICD-9-CM** | 307.51 |
| **OMIM** | 607499 |
| **DiseasesDB** | 1770 |
| **MedlinePlus** | 000341 |
| **eMedicine** | emerg/810 med/255 |
| **Patient UK** | Bulimia nervosa |
| **MeSH** | D052018 |

[edit on Wikidata]



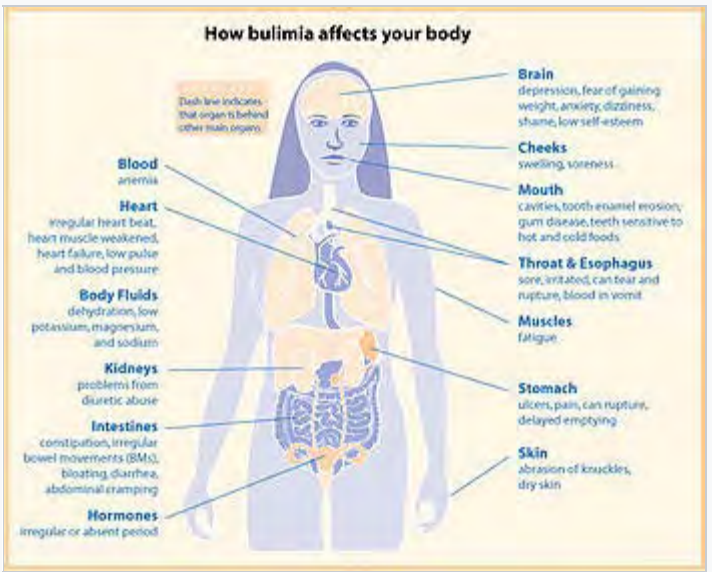

Play media

Video explanation

## Signs and symptoms [edit]

Bulimia typically involves rapid and out-of-control eating, which may stop when the bulimic is interrupted by another person or the stomach hurts from over-extension, followed by self-induced vomiting or other forms of purging. This cycle may be repeated several times a week or, in more serious cases, several times a day[12] and may directly cause:

- Chronic gastric reflux after eating, secondary to vomiting[13]
- Dehydration and hypokalemia due to renal potassium loss in the presence of alkalosis and frequent vomiting[14]
- Electrolyte imbalance, which can lead to abnormal heart rhythms, cardiac arrest, and even death
- Esophagitis, or inflammation of the esophagus
- Mallory-Weiss tears
- Boerhaave syndrome, a rupture in the esophageal wall due to vomiting
- Oral trauma, in which repetitive insertion of fingers or other objects causes lacerations to the lining of the mouth or throat
- Russell's sign: calluses on knuckles and back of hands due to repeated trauma from incisors[15][16]
- Perimolysis, or severe dental erosion of tooth enamel[17]
- Swollen salivary glands (for example, in the neck, under the jaw line)[17][18]
- Gastroparesis or delayed emptying
- Constipation
- Peptic ulcers
- Infertility
- Constant weight fluctuations are common




How bulimia affects the body

The erosion on the lower teeth was caused by bulimia. For comparison, the upper teeth were

restored with porcelain veneers.[11]

These are some of the many signs that may indicate whether someone has bulimia nervosa:[19]

- A fixation on the number of calories consumed.
- A fixation on and extreme consciousness of ones weight.
- Low self-esteem and/or self harming.
- Suicidal tendencies
- low blood pressure
- An irregular menstrual cycle in woman.
- Regular trips to the bathroom, especially soon after eating.
- Depression, anxiety disorders and sleep disorders.
- Frequent occurrences involving consumption of abnormally large portions of food.[20]
- The use of laxatives and diet pills.
- Unhealthy/dry skin, hair, nails and lips.
- A lack of energy.

As with many psychiatric illnesses, delusions can occur, in conjunction with other signs and symptoms, leaving the person with a false belief that is not ordinarily accepted by others.[21]

People with bulimia nervosa may also exercise to a point that excludes other activities.[21]

### Related disorders [edit]

Bulimics are much more likely than non-bulimics to have an affective disorder, such as depression or general anxiety disorder: A 1985 Columbia University study on female bulimics at New York State Psychiatric Institute found 70% had suffered depression some time in their lives (as opposed to 25.8% for adult females in a control sample from the general population), rising to 88% for all affective disorders combined.[22] Another study by the Royal Children's Hospital in Melbourne on a cohort of 2,000 adolescents similarly found that those meeting at least two of the DSM-IV criteria for bulimia nervosa or anorexia nervosa had a sixfold increase in risk of anxiety and a doubled risk for substance dependency.[23] Some sufferers of anorexia nervosa exhibit episodes of bulimic tendencies through purging (either through self-induced vomiting or laxatives) as a way to quickly remove food in their system.[24] Bulimia also has negative effects on the sufferer's dental health due to the acid passed through the mouth from frequent vomiting causing acid erosion, mainly on the posterior dental surface.

## Diagnosis [edit]

The onset of bulimia nervosa is often during adolescence, between 13 and 20 years of age, and many cases have previously suffered from obesity, with many sufferers relapsing in adulthood into episodic bingeing and purging even after initially successful treatment and remission.[25] A lifetime prevalence of 0.5 percent and 0.9 percent for adult and adolescent sufferers, respectively, is estimated among the United States population.[26] Bulimia nervosa may affect up to 1% of young women and, after 10 years of diagnosis, half will recover fully, a third will recover partially, and 10–20% will still have symptoms.[2]

Adolescents with bulimia nervosa are more likely to have self-imposed perfectionism and compulsivity issues in eating compared to their peers. This means that the high expectations and unrealistic goals that these individuals set for themselves are internally motivated rather than by social views or expectations.[27]

### Criteria [edit]

Bulimia nervosa can be difficult to detect, compared to anorexia nervosa, because bulimics tend to be of average or slightly above or below average weight. Many bulimics may also engage in significantly disordered eating and exercise patterns without meeting the full diagnostic criteria for bulimia nervosa.[28] Recently, the *Diagnostic and Statistical Manual of Mental Disorders* was revised, which resulted in the loosening of criteria regarding the diagnoses of bulimia nervosa and anorexia nervosa.[29] The diagnostic

criteria utilized by the DSM-5 includes repetitive episodes of binge eating (a discrete episode of overeating during which the individual feels out of control of consumption) compensated for by excessive or inappropriate measures taken to avoid gaining weight.[30] The diagnosis also requires the episodes of compensatory behaviors and binge eating to happen a minimum of once a week for a consistent time period of 3 months.[31] The diagnosis is made only when the behavior is not a part of the symptom complex of anorexia nervosa and when the behavior reflects an overemphasis on physical mass or appearance. Purging often is a common characteristic of a more severe case of bulimia nervosa.[32]

## Causes [edit]

### Biological [edit]

As with anorexia nervosa, there is evidence of genetic predispositions contributing to the onset of this eating disorder.[33] Abnormal levels of many hormones, notably serotonin, have been shown to be responsible for some disordered eating behaviors. Brain-derived neurotrophic factor (BDNF) is under investigation as a possible mechanism.[34][35]

There is evidence that sex hormones may influence appetite and eating in women, and the onset of bulimia nervosa. Studies have shown that women with hyperandrogenism and polycystic ovary syndrome have a dysregulation of appetite, along with carbohydrates and fats. This dysregulation of appetite is also seen in women with bulimia nervosa. In addition, gene knockout studies in mice have shown that mice that have the gene encoding estrogen receptors have decreased fertility due to ovarian dysfunction and dysregulation of androgen receptors. In humans, there is evidence that there is an association between polymorphisms in the ERβ (estrogen receptor β) and bulimia, suggesting there is a correlation between sex hormones and bulimia nervosa.[36]

Bulimia has been compared to drug addiction, though the empirical support for this characterization is limited.[37] However, people with bulimia nervosa may share dopamine D2 receptor-related vulnerabilities with those with substance abuse disorders.[38]

Dieting, a common behaviour in bulimics, is associated with lower plasma tryptophan levels.[*citation needed*] Decreased tryptophan levels in the brain, and thus the synthesis of serotonin, increases bulimic urges in currently and formerly bulimic individuals within hours.[39][40]

### Social [edit]

Media portrayals of an 'ideal' body shape are widely considered to be a contributing factor to bulimia.[21] In a 1991 study by Weltzin, Hsu, Pollicle, and Kaye, it was stated that 19% of bulimics undereat, 37% of bulimics eat an amount of food that is normal for an average human being, and 44% of bulimics overeat.[41] A survey of 15- to 18-year-old high school girls in Nadroga, Fiji, found the self-reported incidence of purging rose from 0% in 1995 (a few weeks after the introduction of television in the province) to 11.3% in 1998.[42] In addition, the suicide rate among people with bulimia nervosa is 7.5 times higher than in the general population.[43]

When attempting to decipher the origin of bulimia nervosa in a cognitive context, Christopher Fairburn *et al.*'s cognitive behavioral model is often considered the golden standard. Fairburn et al.'s model discusses the process in which an individual falls into the binge-purge cycle and thus develops bulimia. Fairburn *et al.* argue that extreme concern with weight and shape coupled with low self-esteem will result in strict, rigid, and inflexible dietary rules. Accordingly, this would lead to unrealistically restricted eating, which may consequently induce an eventual "slip" where the individual commits a minor infraction of the strict and inflexible dietary rules. Moreover, the cognitive distortion due to dichotomous thinking leads the individual to binge. The binge subsequently should trigger a perceived loss of control, promoting the individual to purge in hope of counteracting the binge. However, Fairburn *et al.* assert the cycle repeats itself, and thus consider the binge-purge cycle to be self-perpetuating.[44][*citation needed*]

In contrast, Byrne and Mclean's findings differed slightly from Fairburn *et al.*'s cognitive behavioral model of bulimia nervosa in that the drive for thinness was the major cause of purging as a way of controlling weight. In turn, Byrne and Mclean argued that this makes the individual vulnerable to binging, indicating that it is not a binge-purge cycle but rather a purge-binge cycle in that purging comes before bingeing. Similarly, Fairburn *et al.*'s cognitive behavioral model of bulimia nervosa is not necessarily applicable to every individual and is certainly reductionist. Everyone differs from another, and taking such a complex behavior like bulimia and applying the same one theory to everyone would certainly be invalid. In addition, the cognitive behavioral model of bulimia nervosa is very cultural bound in that it may not be necessarily applicable to cultures outside of the Western society. To evaluate, Fairburn *et al*.'s model and more generally the cognitive explanation of bulimia nervosa is more descriptive than explanatory, as it does not necessarily explain how bulimia arises. Furthermore, it is difficult to ascertain cause and effect, because it may be that distorted eating leads to distorted cognition rather than vice versa.[45][46]

A considerable amount of literature has identified a correlation between sexual abuse and the development of bulimia nervosa. The reported incident rate of unwanted sexual contact is higher among those with bulimia nervosa than anorexia nervosa.[47]

When exploring the etiology of bulimia through a socio-cultural perspective, the "thin ideal internalization" is significantly responsible. The thin ideal internalization is the extent to which individuals adapt to the societal ideals of attractiveness. Studies have shown that young females that read fashion magazines tend to have more bulimic symptoms than those females who do not. This further demonstrates the impact of media on the likelihood of developing the disorder.[48] Individuals first accept and "buy into" the ideals, and then attempt to transform themselves in order to reflect the societal ideals of attractiveness. J. Kevin Thompson and Eric Stice claim that family, peers, and most evidently media reinforce the thin ideal, which may lead to an individual accepting and "buying into" the thin ideal. In turn, Thompson and Stice assert that if the thin ideal is accepted, one could begin to feel uncomfortable with their body shape or size since it may not necessarily reflect the thin ideal set out by society. Thus, people feeling uncomfortable with their bodies may result in suffering from body dissatisfaction and may develop a certain drive for thinness. Consequently, body dissatisfaction coupled with a drive for thinness is thought to promote dieting and negative effects, which could eventually lead to bulimic symptoms such as purging or bingeing. Binges lead to self-disgust which causes purging to prevent weight gain.[49]

A study dedicated to investigating the thin ideal internalization as a factor of bulimia nervosa is Thompson's and Stice's research. The aim of their study was to investigate how and to what degree does media affect the thin ideal internalization. Thompson and Stice used randomized experiments (more specifically programs) dedicated to teaching young women how to be more critical when it comes to media, in order to reduce thin ideal internalization. The results showed that by creating more awareness of the media's control of the societal ideal of attractiveness, the thin ideal internalization significantly dropped. In other words, less thin ideal images portrayed by the media resulted in less thin ideal internalization. Therefore, Thompson and Stice concluded that media affected greatly the thin ideal internalization.[50] Papies showed that it is not the thin ideal itself, but rather the self-association with other persons of a certain weight that decide how someone with bulimia nervosa feels. People that associate themselves with thin models get in a positive attitude when they see thin models and people that associate with overweight get in a negative attitude when they see thin models. Moreover, it can be taught to associate with thinner people.[51]

## Treatment [edit]

There are two main types of treatment given to those suffering with bulimia nervosa; psychopharmacological and psychosocial treatments.[52]

### Psychotherapy [edit]

There are several supported psychosocial treatments for bulimia. Cognitive behavioral therapy (CBT), which involves teaching a person to challenge automatic thoughts and engage in behavioral experiments (for example, in session eating of "forbidden foods") has a small amount of evidence supporting its use.[53]

By using CBT people record how much food they eat and periods of vomiting with the purpose of

identifying and avoiding emotional fluctuations that bring on episodes of bulimia on a regular basis.[54] Barker (2003) states that research has found 40–60% of people using cognitive behaviour therapy to become symptom free. He states in order for the therapy to work, all parties must work together to discuss, record and develop coping strategies. Barker (2003) claims by making people aware of their actions they will think of alternatives.[55][56] People undergoing CBT who exhibit early behavioral changes are most likely to achieve the best treatment outcomes in the long run.[57] Researchers have also reported some positive outcomes for interpersonal psychotherapy and dialectical behavior therapy.[58][59]

Maudsley family therapy, developed at the Maudsley Hospital in London for the treatment of anorexia has been shown promising results in bulimia.[60]

The use of Cognitive Behavioral Therapy (CBT) has been shown to be quite effective for treating bulimia nervosa (BN) in adults, but little research has been done on effective treatments of BN for adolescents.[61] Although CBT is seen as more cost efficient and helps individuals with BN in self-guided care, Family Based Treatment (FBT) might be more helpful to younger adolescents who need more support and guidance from their families. Adolescents are at the stage where their brains are still quite malleable and developing gradually.[62] Therefore, young adolescents with BN are less likely to realize the detrimental consequences of becoming bulimic and have less motivation to change,[63] which is why FBT would be useful to have families intervene and support the teens.[61] Working with BN patients and their families in FBT can empower the families by having them involved in their adolescent's food choices and behaviors, taking more control of the situation in the beginning and gradually letting the adolescent become more autonomous when they have learned healthier eating habits.[61]

### Medication [edit]

Antidepressants of the selective serotonin reuptake inhibitors (SSRI) class may have a modest benefit.[7] This includes fluoxetine, which is FDA approved, for the treatment of bulimia, other antidepressants such as sertraline may also be effective against bulimia. Topiramate may also be useful but has greater side effects.[7]

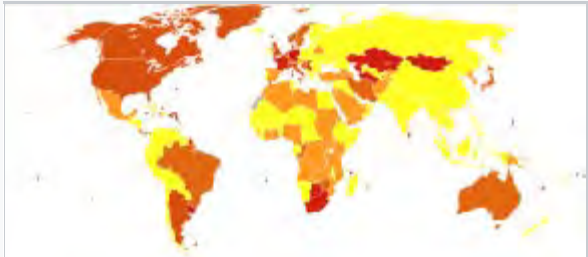
It is not known if combining medication with counseling improve the outcomes. Any trials which originally suggested that such combinations should improve the outcome have not proven to be exceptionally powerful. Some positive outcomes of treatments can include: abstinence from binge eating, a decrease in obsessive behaviors to lose weight and in shape preoccupation, less severe psychiatric symptoms, a desire to counter the effects of binge eating, as well as an improvement in social functioning and reduced relapse rates.[2]

### Alternative medicine [edit]

Some researchers have also claimed positive outcomes in hypnotherapy.[64]

## Epidemiology [edit]

There is little data on the percentage of people with bulimia in general populations. Most studies conducted thus far have been on convenience samples from hospital patients, high school or university students. These have yielded a wide range of results: between 0.1% and 1.4% of males, and between 0.3% and 9.4% of females.[65] Studies on time trends in the prevalence of bulimia nervosa have also yielded inconsistent results.[66] According to Gelder, Mayou and Geddes (2005) bulimia nervosa is prevalent between 1 and 2 percent of women aged 15–40 years. Bulimia nervosa occurs more frequently in developed countries[54] and in cities, with one



Deaths due to eating disorders per million persons in 2012

0-0 2-2 4-25


study finding that bulimia is five times more prevalent in cities than in rural areas.[67] There is a perception that bulimia is most prevalent amongst girls from middle-class families;[68] however, in a 2009 study girls from families in the lowest income bracket studied were 153 percent more likely to be bulimic than girls from the highest income bracket.[69]

There are higher rates of eating disorders in groups involved in activities which idealize a slim physique, such as dance,[70] gymnastics, modeling, cheerleading, running, acting, swimming, diving, rowing and figure skating. Bulimia is thought to be more prevalent among Caucasians;[71] however, a more recent study showed that African-American teenage girls were 50 percent more likely than white girls to exhibit bulimic behavior, including both binging and purging.[72]

| Country | Year | Sample size and type | % affected | |
|---|---|---|---|---|
| Australia | 2008 | 1,943 adolescents (ages 15–17) | 1.0% male | 6.4% female[23] |
| Portugal | 2006 | 2,028 high school students | | 0.3% female[73] |
| Brazil | 2004 | 1,807 students (ages 7–19) | 0.8% male | 1.3% female[74] |
| Spain | 2004 | 2,509 female adolescents (ages 13–22) | | 1.4% female[75] |
| Hungary | 2003 | 580 Budapest residents | 0.4% male | 3.6% female[70] |
| Australia | 1998 | 4,200 high school students | 0.3% combined[76] | |
| United States | 1996 | 1,152 college students | 0.2% male | 1.3% female[77] |
| Norway | 1995 | 19,067 psychiatric patients | 0.7% male | 7.3% female[78] |
| Canada | 1995 | 8,116 (random sample) | 0.1% male | 1.1% female[79] |
| Japan | 1995 | 2,597 high school students | 0.7% male | 1.9% female[80] |
| United States | 1992 | 799 college students | 0.4% male | 5.1% female[81] |

## History [edit]

### Etymology [edit]

The term *bulimia* comes from Greek βουλιμία *boulīmia*, "ravenous hunger", a compound of βοῦς *bous*, "ox" and λιμός, *līmos*, "hunger".[82] Literally, the scientific name of the disorder, *bulimia nervosa*, translates to "nervous ravenous hunger".

### Before the 20th century [edit]

Although diagnostic criteria for bulimia nervosa did not appear until 1979, evidence suggests that binging and purging were popular in certain ancient cultures. The first documented account of behavior resembling bulimia nervosa was recorded in Xenophon's Anabasis around 370 B.C, in which Greek soldiers purged themselves in the mountains of Asia Minor. It is unclear whether this purging was preceded by binging.[83] In ancient Egypt, physicians recommended purging once a month for three days in order to preserve health.[84] This practice stemmed from the belief that human diseases were caused by the food itself. In ancient Rome, elite society members would vomit in order to "make room" in their stomachs for more food at all day banquets.[84] Emperors Claudius and Vitellius both were gluttonous and obese, and they often resorted to habitual purging.[84]

Historical records also suggest that some saints who developed anorexia (as a result of a life of asceticism)

may also have displayed bulimic behaviors.[84] Saint Mary Magdalen de Pazzi (1566–1607) and Saint Veronica Giuliani (1660–1727) were both observed binge eating—giving in, as they believed, to the temptations of the devil.[84] Saint Catherine of Siena (1347–1380) is known to have supplemented her strict abstinence from food by purging as reparation for her sins. Catherine died from starvation at age thirty-three.[84]

While the psychological disorder "bulimia nervosa" is relatively new, the word "bulimia," signifying overeating, has been present for centuries.[84] The Babylon Talmud referenced practices of "bulimia," yet scholars believe that this simply referred to overeating without the purging or the psychological implications bulimia nervosa.[84] In fact, a search for evidence of bulimia nervosa from the 17th to late 19th century revealed that only a quarter of the overeating cases they examined actually vomited after the binges. There was no evidence of deliberate vomiting or an attempt to control weight.[84]

## 20th century [edit]

At the turn of the century, bulimia (overeating) was described as a clinical symptom, but rarely in the context of weight control.[85] Purging, however, was seen in anorexic patients and attributed to gastric pain rather than another method of weight control.[85]

In 1930, admissions of anorexia nervosa patients to the Mayo Clinic from 1917 to 1929 were compiled. Fifty-five to sixty-five percent of these patients were reported to be voluntarily vomiting in order to relieve weight anxiety.[85] Records show that purging for weight control continued throughout the mid-1900s. Several case studies from this era reveal patients suffering from the modern description of bulimia nervosa.[85] In 1939, Rahman and Richardson reported that out of their six anorexic patients, one had periods of overeating and another practiced self-induced vomiting.[85] Wulff, in 1932, treated "Patient D," who would have periods of intense cravings for food and overeat for weeks, which often resulted in frequent vomiting.[84] Patient D, who grew up with a tyrannical father, was repulsed by her weight and would fast for a few days, rapidly losing weight. Ellen West, a patient described by Ludwig Binswanger in 1958, was teased by friends for being fat and excessively took thyroid pills to lose weight, later using laxatives and vomiting.[84] She reportedly consumed dozens of oranges and several pounds of tomatoes each day, yet would skip meals. After being admitted to a psychiatric facility for depression, Ellen ate ravenously yet lost weight, presumably due to self-induced vomiting.[84] However, while these patients may have met modern criteria for bulimia nervosa, they cannot technically be diagnosed with the disorder, as it had not yet appeared in the Diagnostic and Statistical Manual of Mental Disorders at the time of their treatment.[84]

An explanation for the increased instances of bulimic symptoms may be due to the 20th century's new ideals of thinness.[85] The shame of being fat emerged in the 1940s, when teasing remarks about weight became more common. The 1950s, however, truly introduced the trend of an aspiration for thinness.[85]

In 1979, Gerald Russell first published a description of bulimia nervosa, in which he studied patients with a "morbid fear of becoming fat" who overate and purged afterwards.[9] He specified treatment options and indicated the seriousness of the disease, which can be accompanied by depression and suicide.[9] In 1980, bulimia nervosa first appeared in the DSM-III.[9]

After its appearance in the DSM-III, there was a sudden rise in the documented incidences of bulimia nervosa.[84] In the early 1980s, incidences of the disorder rose to about 40 in every 100,000 people.[84] This decreased to about 27 in every 100,000 people at the end of the 1980s/early 1990s.[84] However, bulimia nervosa's prevalence was still much higher than anorexia nervosa's, which at the time occurred in about 14 people per 100,000.[84]

In 1991, Kendler et al. documented the cumulative risk for bulimia nervosa for those born before 1950, from 1950 to 1959, and after 1959.[86] The risk for those born after 1959 is much higher than those in either of the other cohorts.[86]

## See also [edit]

- Anorectic Behavior Observation Scale
- Eating disorders and development
- Eating recovery
- Binge eating disorder
- List of people with bulimia nervosa

Wikimedia Commons has media related to *Bulimia nervosa*.

## References [edit]


1. ^ a b c d e f "Bulimia nervosa fact sheet". *Office on Women's Health*. July 16, 2012. Retrieved 27 June 2015.
2. ^ a b c d e f g h i j k Hay PJ, Claudino AM; Claudino (2010). "Bulimia nervosa". *Clinical Evidence*. **2010**: 1009. PMC 3275326. PMID 21418667.
3. ^ Bulik, CM; Marcus, MD; Zerwas, S; Levine, MD; La Via, M (October 2012). "The changing "weightscape" of bulimia nervosa.". *The American Journal of Psychiatry*. **169** (10): 1031–6. doi:10.1176/appi.ajp.2012.12010147. PMID 23032383.
4. ^ a b c Smink, FR; van Hoeken, D; Hoek, HW (August 2012). "Epidemiology of eating disorders: incidence, prevalence and mortality rates.". *Current psychiatry reports*. **14** (4): 406–14. doi:10.1007/s11920-012-0282-y. PMC 3409365. PMID 22644309.
5. ^ a b c American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (Fifth ed.). Arlington, VA: American Psychiatric Publishing. pp. 345–349. ISBN 978-0-89042-555-8.
6. ^ Hay, P (July 2013). "A systematic review of evidence for psychological treatments in eating disorders: 2005–2012.". *The International Journal of Eating Disorders*. **46** (5): 462–9. doi:10.1002/eat.22103. PMID 23658093.
7. ^ a b c McElroy, SL; Guerdjikova, AI; Mori, N; O'Melia, AM (October 2012). "Current pharmacotherapy options for bulimia nervosa and binge eating disorder.". *Expert opinion on pharmacotherapy*. **13** (14): 2015–26. doi:10.1517/14656566.2012.721781. PMID 22946772.
8. ^ Global Burden of Disease Study 2013, Collaborators (5 June 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386**: 743–800. doi:10.1016/S0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
9. ^ a b c d Russell G (1979). "Bulimia nervosa: An ominous variant of anorexia nervosa". *Psychological Medicine*. **9** (3): 429–48. doi:10.1017/S0033291700031974. PMID 482466.
10. ^ Palmer R (2004). "Bulimia nervosa: 25 years on". *The British Journal of Psychiatry*. **185** (6): 447–8. doi:10.1192/bjp.185.6.447. PMID 15572732.
11. ^ Dorfman J, The Center for Special Dentistry.
12. ^ "Bulimia Nervosa" (PDF). *Let's Talk Facts*. American Psychiatric Association: 1. 2005. Retrieved 13 September 2013.
13. ^ Mehler PS (2003). "Bulimia Nervosa". *The New England Journal of Medicine*. **349** (9): 875–81. doi:10.1056/NEJMcp022813. PMID 12944574.
14. ^ Mehler, PS.; Crews, C.; Weiner, K. (2004). "Bulimia: medical complications.". *J Womens Health (Larchmt)*. **13** (6): 668–75. doi:10.1089/1540999041783127. PMID 15333281.
15. ^ Joseph AB, Herr B; Herr (1985). "Finger calluses in bulimia". *The American Journal of Psychiatry*. **142** (5): 655. PMID 3857013.
16. ^ Wynn DR, Martin MJ; Martin (1984). "A physical sign of bulimia". *Mayo Clinic Proceedings*. **59** (10): 722. doi:10.1016/s0025-6196(12)62063-1. PMID 6592415.
17. ^ a b "Eating Disorders". *Oral Health Topics A–Z*. American Dental Association. Archived from the original on Feb 3, 2009.
18. ^ Mcgilley BM, Pryor TL; Pryor (June 1998). "Assessment and Treatment of Bulimia Nervosa". *American Family Physician*. **57** (11): 2743–50. PMID 9636337.
19. ^ "Symptoms Of Bulimia Nervosa". *Illawarra Mercury*. February 23, 2001.[*unreliable source?*]
20. ^ "Bulimia Nervosa". *Proud2BME*. The National Eating Disorders Association. Retrieved 5 December 2014.
21. ^ a b c Barker, P (2003). *Psychiatric and Mental Health Nursing: The Craft of Caring*. Great Britain: Arnold. ISBN 0340810262.[*page needed*]
22. ^ Walsh BT, Roose SP, Glassman AH, Gladis M, Sadik C (1985). "Bulimia and depression". *Psychosomatic Medicine*. **47** (2): 123–31. doi:10.1097/00006842-198503000-00003. PMID 3863157.

23. ^ [a] [b] Patton GC, Coffey C, Carlin JB, Sanci L, Sawyer S (2008). "Prognosis of adolescent partial syndromes of eating disorder". *The British Journal of Psychiatry*. **192** (4): 294–9. doi:10.1192/bjp.bp.106.031112. PMID 18378993.
24. ^ Carlson, N.R., et al. (2007). Psychology: The Science of Behaviour – 4th Canadian ed. Toronto, ON: Pearson Education Canada.[*page needed*]
25. ^ Shader, Richard I. (2004). *Manual of Psychiatric Therapeutics*. Hagerstwon, MD: Lippincott Williams & Wilkins. ISBN 0-7817-4459-8.[*page needed*]
26. ^ [Nolen-Hoeksema, S. (2013)."(Ab)normal Psychology"(6th edition). McGraw-Hill. p.344]
27. ^ Castro-Fornieles J, Gual P, Lahortiga F, Gila A, Casulà V, Fuhrmann C, Imirizaldu M, Saura B, Martínez E, Toro J (September 2007). "Self-oriented perfectionism in eating disorders". *The International Journal of Eating Disorders*. **40** (6): 562–568. doi:10.1002/eat.20393. PMID 17510925.
28. ^ Walsh JM, Wheat ME, Freund K (2000). "Detection, evaluation, and treatment of eating disorders". *Journal of General Internal Medicine*. **15** (8): 577–90. doi:10.1046/j.1525-1497.2000.02439.x. PMC 1495575. PMID 10940151.
29. ^ [Nolen-Hoeksema, S. (2013)."(Ab)normal Psychology"(6th edition). McGraw-Hill. p.343]
30. ^ American Psychiatric Association (2000). "Diagnostic criteria for 307.51 Bulimia Nervosa". *Diagnostic and Statistical Manual of Mental Disorders* (4th, text revision (DSM-IV-TR) ed.). ISBN 0-89042-025-4.
31. ^ [Nolen-Hoeksema, S. (2013)."(Ab)normal Psychology" (6th edition). McGraw-Hill. p.343]
32. ^ Nolan-Hoeksema, Susan (2014). *Abnormal Psychology* (6 ed.). McGraw-Hill Education. p. 345. ISBN 978-0-07-803538-8.
33. ^ "Biological Causes of Anorexia Nervosa and Bulimia Nervosa". Retrieved 4 July 2016.
34. ^ Ribasés M, Gratacòs M, Fernández-Aranda F, Bellodi L, Boni C, Anderluh M, Cavallini MC, Cellini E, Di Bella D, Erzegovesi S, Foulon C, Gabrovsek M, Gorwood P, Hebebrand J, Hinney A, Holliday J, Hu X, Karwautz A, Kipman A, Komel R, Nacmias B, Remschmidt H, Ricca V, Sorbi S, Wagner G, Treasure J, Collier DA, Estivill X (2004). "Association of BDNF with anorexia, bulimia and age of onset of weight loss in six European populations". *Human Molecular Genetics*. **13** (12): 1205–1212. doi:10.1093/hmg/ddh137. PMID 15115760.
35. ^ Wonderlich, Stephen; Mitchell, James E.; de Zwaan, Martina; Steiger, Howard, eds. (2008). "1". *Annual Review of Eating Disorders – part 2*. Radcliffe Publishing. pp. 14–15. ISBN 978-1-84619-244-9.
36. ^ Hirschberg AL (2012). "Sex hormones, appetite and eating behaviour in women". *Maturitas*. **71** (3): 248–56. doi:10.1016/j.maturitas.2011.12.016. PMID 22281161.
37. ^ Broft A, Shingleton R, Kaufman J, Liu F, Kumar D, Slifstein M, Abi-Dargham A, Schebendach J, Van Heertum R, Attia E, Martinez D, Walsh BT (July 2012). "Striatal dopamine in bulimia nervosa: A pet imaging study". *The International Journal of Eating Disorders*. **45** (5): 648–656. doi:10.1002/eat.20984. PMC 3640453. PMID 22331810.
38. ^ Kaye WH, Wierenga CE, Bailer UF, Simmons AN, Wagner A, Bischoff-Grethe A (2013). "Does a Shared Neurobiology for Foods and Drugs of Abuse Contribute to Extremes of Food Ingestion in Anorexia and Bulimia Nervosa?". *Biological Psychiatry*. **73** (9): 836–42. doi:10.1016/j.biopsych.2013.01.002. PMID 23380716.
39. ^ Smith KA, Fairburn CG, Cowen PJ (1999). "Symptomatic Relapse in Bulimia Nervosa Following Acute Tryptophan Depletion". *Archives of General Psychiatry*. **56** (2): 171–6. doi:10.1001/archpsyc.56.2.171. PMID 10025442.
40. ^ Weltzin TE, Fernstrom MH, Fernstrom JD, Neuberger SK, Kaye WH (1995). "Acute tryptophan depletion and increased food intake and irritability in bulimia nervosa". *The American Journal of Psychiatry*. **152** (11): 1668–71. PMID 7485633.
41. ^ Carlson, Neil R.; Buskist, William; Heth, C. Donald; Schmaltz, Rod (2010). *Psychology: the science of behaviour* (4th Canadian ed.). Toronto: Pearson Education Canada. p. 415. ISBN 978-0-205-70286-2.
42. ^ Becker AE, Burwell RA, Gilman SE, Herzog DB, Hamburg P (2002). "Eating behaviours and attitudes following prolonged exposure to television among ethnic Fijian adolescent girls". *The British Journal of Psychiatry*. **180** (6): 509–14. doi:10.1192/bjp.180.6.509. PMID 12042229.
43. ^ Nolen-Hoeksema, Susan (2014). "Bulimia Nervosa" *Abnormal Psychology*. 6e. pg 344.
44. ^ Fairburn, C. G.; Beglin, S. J. (April 1, 1990). "Studies of the epidemiology of bulimia nervosa". *American Journal of Psychiatry*. **147** (4): 401–408. doi:10.1176/ajp.147.4.401. ISSN 0002-953X. PMID 2180327. Retrieved 2015-04-12.
45. ^ Trull, Thimothy (2010-10-08). *Abnormal Psychology and Life: A Dimensional Approach*. Belmont CA: Wadsworth, Cengage Learning. pp. 236–8. ISBN 978-1-111-34376-7.
46. ^ Byrne SM, McLean NJ; McLean (2002). "The cognitive-behavioral model of bulimia nervosa: A direct evaluation". *The International Journal of Eating Disorders*. **31** (1): 17–31. doi:10.1002/eat.10002. PMID 11835294.
47. ^ Waller, G (1992). "Sexual abuse and the severity of bulimic symptoms". *The British Journal of Psychiatry*. **161**: 90–3. doi:10.1192/bjp.161.1.90. PMID 1638336.
48. ^ Nolen-Hoeksema, Susan (2013). *(Ab)normal Psychology*. McGraw Hill. p. 338. ISBN 0078035384.
49. ^ Zieve, David. "Bulimia". PubMed Health. Retrieved April 18, 2011.

50. ^ Thompson, J. Kevin; Stice, Eric (2001). "Thin-Ideal Internalization: Mounting Evidence for a New Risk Factor for Body-Image Disturbance and Eating Pathology". *Current Directions in Psychological Science*. **10** (5): 181–3. doi:10.1111/1467-8721.00144. JSTOR 20182734.
51. ^ Papies EK, Nicolaije KA; Nicolaije (2012). "Inspiration or deflation? Feeling similar or dissimilar to slim and plus-size models affects self-evaluation of restrained eaters". *Body Image*. **9** (1): 76–85. doi:10.1016/j.bodyim.2011.08.004. PMID 21962524.
52. ^ Hoste RR, Labuschagne Z, Le Grange D (2012). "Adolescent Bulimia Nervosa". *Current Psychiatry Reports*. **14** (4): 391–7. doi:10.1007/s11920-012-0280-0. PMID 22614677.
53. ^ Hay, PP; Bacaltchuk, J; Stefano, S; Kashyap, P (7 October 2009). "Psychological treatments for bulimia nervosa and binging.". *The Cochrane database of systematic reviews* (4): CD000562. doi:10.1002/14651858.CD000562.pub3. PMID 19821271.
54. ^ [a] [b] Gelder, Michael Graham; Mayou, Richard; Geddes, John (2005). *Psychiatry*. ISBN 978-0-19-852863-0.[*page needed*]
55. ^ Agras WS, Crow SJ, Halmi KA, Mitchell JE, Wilson GT, Kraemer HC (2000). "Outcome Predictors for the Cognitive Behavior Treatment of Bulimia Nervosa: Data from a Multisite Study". *The American Journal of Psychiatry*. **157** (8): 1302–8. doi:10.1176/appi.ajp.157.8.1302. PMID 10910795.
56. ^ Wilson GT, Loeb KL, Walsh BT, Labouvie E, Petkova E, Liu X, Waternaux C (1999). "Psychological versus pharmacological treatments of bulimia nervosa: Predictors and processes of change". *Journal of Consulting and Clinical Psychology*. **67** (4): 451–9. doi:10.1037/0022-006X.67.4.451. PMID 10450615.
57. ^ Trunko ME, Rockwell RE, Curry E, Runfola C, Kaye WH (2007). "Management of bulimia nervosa". *Women's Health (London, England)*. **3** (2): 255–65. doi:10.2217/17455057.3.2.255. PMID 19803857.
58. ^ Fairburn CG, Agras WS, Walsh BT, Wilson GT, Stice E (2004). "Prediction of Outcome in Bulimia Nervosa by Early Change in Treatment". *The American Journal of Psychiatry*. **161** (12): 2322–4. doi:10.1176/appi.ajp.161.12.2322. PMID 15569910.
59. ^ Safer DL, Telch CF, Agras WS (2001). "Dialectical Behavior Therapy for Bulimia Nervosa". *The American Journal of Psychiatry*. **158** (4): 632–4. doi:10.1176/appi.ajp.158.4.632. PMID 11282700.
60. ^ Lock J, le Grange D; Le Grange (2005). "Family-based treatment of eating disorders". *The International Journal of Eating Disorders*. **37**: S64–7; discussion S87–9. doi:10.1002/eat.20122. PMID 15852323.
61. ^ [a] [b] [c] Keel PK, Haedt A; Haedt (2008). "Evidence-Based Psychosocial Treatments for Eating Problems and Eating Disorders". *Journal of Clinical Child and Adolescent Psychology*. **37** (1): 39–61. doi:10.1080/15374410701817832. PMID 18444053.
62. ^ Le Grange D, Lock J, Dymek M (2003). "Family-based therapy for adolescents with bulimia nervosa". *American Journal of Psychotherapy*. **57** (2): 237–51. PMID 12817553.
63. ^ Castro-Fornieles J, Bigorra A, Martinez-Mallen E, Gonzalez L, Moreno E, Font E, Toro J (2011). "Motivation to change in adolescents with bulimia nervosa mediates clinical change after treatment". *European Eating Disorders Review : the Journal of the Eating Disorders Association*. **19** (1): 46–54. doi:10.1002/erv.1045. PMID 20872926.
64. ^ Barabasz M (2007). "Efficacy of Hypnotherapy in the Treatment of Eating Disorders". *The International Journal of Clinical and Experimental Hypnosis*. **55** (3): 318–35. doi:10.1080/00207140701338688. PMID 17558721.
65. ^ Makino M, Tsuboi K, Dennerstein L (2004). "Prevalence of eating disorders: a comparison of Western and non-Western countries". *MedGenMed : Medscape General Medicine*. **6** (3): 49. PMC 1435625. PMID 15520673.
66. ^ Hay PJ, Mond J, Buttner P, Darby A (2008). Murthy RS, ed. "Eating Disorder Behaviors Are Increasing: Findings from Two Sequential Community Surveys in South Australia". *PLOS ONE*. **3** (2): e1541. doi:10.1371/journal.pone.0001541. PMC 2212110. PMID 18253489.
67. ^ van Son GE, van Hoeken D, Bartelds AI, van Furth EF, Hoek HW (2006). "Urbanisation and the incidence of eating disorders". *The British Journal of Psychiatry*. **189** (6): 562–3. doi:10.1192/bjp.bp.106.021378. PMID 17139044.
68. ^ "Bulimia". *finddoctorsonline.com*.[*permanent dead link*]
69. ^ Grohol, John (March 19, 2009). "Black Girls At Risk for Bulimia".
70. ^ [a] [b] Tölgyes T, Nemessury J; Nemessury (2004). "Epidemiological studies on adverse dieting behaviours and eating disorders among young people in Hungary". *Social Psychiatry and Psychiatric Epidemiology*. **39** (8): 647–54. doi:10.1007/s00127-004-0783-z. PMID 15300375.
71. ^ Franko DL, Becker AE, Thomas JJ, Herzog DB (2007). "Cross-ethnic differences in eating disorder symptoms and related distress". *The International Journal of Eating Disorders*. **40** (2): 156–64. doi:10.1002/eat.20341. PMID 17080449.
72. ^ McBride, Hugh. "Study Reveals Stunning Prevalence of Bulimia Among African-American Girls". Archived from the original on Feb 10, 2012.
73. ^ Machado PP, Machado BC, Gonçalves S, Hoek HW (2007). "The prevalence of eating disorders not otherwise specified". *The International Journal of Eating Disorders*. **40** (3): 212–7. doi:10.1002/eat.20358. PMID 17173324.

74. ^ Vilela JE, Lamounier JA, Dellaretti Filho MA, Barros Neto JR, Horta GM (2004). "Transtornos alimentares em escolares" [Eating disorders in school children]. *Jornal De Pediatria* (in Portuguese). **80** (1): 49–54. doi:10.1590/S0021-75572004000100010. PMID 14978549.
75. ^ Lahortiga-Ramos F, De Irala-Estévez J, Cano-Prous A, Gual-García P, Martínez-González MA, Cervera-Enguix S (2005). "Incidence of eating disorders in Navarra (Spain)". *European Psychiatry : the Journal of the Association of European Psychiatrists*. **20** (2): 179–85. doi:10.1016/j.eurpsy.2004.07.008. PMID 15797704.
76. ^ Hay P (1998). "The epidemiology of eating disorder behaviors: An Australian community-based survey". *The International Journal of Eating Disorders*. **23** (4): 371–82. doi:10.1002/(SICI)1098-108X(199805)23:4<371::AID-EAT4>3.0.CO;2-F. PMID 9561427.
77. ^ Pemberton AR, Vernon SW, Lee ES (1996). "Prevalence and Correlates of Bulimia Nervosa and Bulimic Behaviors in a Racially Diverse Sample of Undergraduate Students in Two Universities in Southeast Texas". *American Journal of Epidemiology*. **144** (5): 450–5. doi:10.1093/oxfordjournals.aje.a008950. PMID 8781459.
78. ^ Götestam KG, Eriksen L, Hagen H (1995). "An epidemiological study of eating disorders in Norwegian psychiatric institutions". *The International Journal of Eating Disorders*. **18** (3): 263–8. doi:10.1002/1098-108X(199511)18:3<263::AID-EAT2260180308>3.0.CO;2-O. PMID 8556022.
79. ^ Garfinkel PE, Lin E, Goering P, Spegg C, Goldbloom DS, Kennedy S, Kaplan AS, Woodside DB (July 1995). "Bulimia nervosa in a Canadian community sample: prevalence and comparison of subgroups". *The American Journal of Psychiatry*. **152** (7): 1052–8. PMID 7793442.
80. ^ Suzuki K, Takeda A, Matsushita S (1995). "Coprevalence of bulimia with alcohol abuse and smoking among Japanese male and female high school students". *Addiction (Abingdon, England)*. **90** (7): 971–5. doi:10.1111/j.1360-0443.1995.tb03506.x. PMID 7663319.
81. ^ Heatherton TF, Nichols P, Mahamedi F, Keel P (November 1995). "Body weight, dieting, and eating disorder symptoms among college students, 1982 to 1992". *The American Journal of Psychiatry*. **152** (11): 1623–9. PMID 7485625.
82. ^ Douglas Harper (November 2001). "Online Etymology Dictionary: bulimia". *Online Etymology Dictionary*. Retrieved 2008-04-06.
83. ^ Giannini, A. J. (1993). "A history of bulimia". In *The Eating disorders* (pp. 18–21). Springer New York.
84. ^ *a b c d e f g h i j k l m n o p q* Russell, G. (1997). *The history of bulimia nervosa*. D. Garner & P. Garfinkel (Eds.), Handbook of Treatment for Eating Disorders (2nd ed., pp. 11–24). New York, NY: The Guilford Press.
85. ^ *a b c d e f g* Casper, Regina C. (1983). "On the emergence of bulimia nervosa as a syndrome a historical view". *International Journal of Eating Disorders*. **2** (3): 3–16. doi:10.1002/1098-108X(198321)2:3<3::AID-EAT2260020302>3.0.CO;2-D.
86. ^ *a b* Kendler KS, MacLean C, Neale M, Kessler R, Heath A, Eaves L (1991). "The genetic epidemiology of bulimia nervosa". *The American Journal of Psychiatry*. **148** (12): 1627–37. PMID 1842216.



| v · t · e · | **Mental and behavioral disorders (F 290–319)** |
|---|---|
| | **Neurological/symptomatic** |
| **Dementia** | Mild cognitive impairment · Alzheimer's disease · Vascular dementia · Pick's disease · Creutzfeldt–Jakob disease · Huntington's disease · Parkinson's disease · AIDS dementia complex · Frontotemporal dementia · Sundowning · Wandering · |
| **Autism spectrum** | Autism · Asperger syndrome · Savant syndrome · PDD-NOS · High-functioning autism · |
| **Other** | Delirium · Post-concussion syndrome · Organic brain syndrome · |
| | **Psychoactive substances, substance abuse, drug abuse and substance-related disorders** |
| | Intoxication/Drug overdose · Physical dependence · Substance dependence · Rebound effect · Double rebound · Withdrawal · |
| | **Schizophrenia, schizotypal and delusional** |
| **Psychosis** | Schizoaffective disorder · Schizophreniform disorder · Brief reactive psychosis · |
| **Schizophrenia** | Disorganized schizophrenia · Paranoid schizophrenia · Simple-type schizophrenia · |
| **Delusional disorders** | Delusional disorder · Folie à deux · |

| Mood (affective) | | |
|---|---|---|
| Mania · Bipolar disorder · (Bipolar I · Bipolar II · Cyclothymia · Bipolar NOS) · Depression · (Major depressive disorder · Dysthymia · Seasonal affective disorder · Atypical depression · Melancholic depression) · | | |
| **Neurotic, stress-related and somatoform** | | |
| **Anxiety disorder** | **Phobia** | Agoraphobia · Social anxiety · Social phobia · (Anthropophobia) · Specific phobia · (Claustrophobia) · Specific social phobia · |
| | **Other** | Panic disorder · Panic attack · Generalized anxiety disorder · OCD · *stress* · (Acute stress reaction · PTSD) · |
| **Adjustment disorder** | Adjustment disorder with depressed mood · | |
| **Somatic symptom disorder** | Somatization disorder · Body dysmorphic disorder · Hypochondriasis · Nosophobia · Da Costa's syndrome · Psychalgia · Conversion disorder · (Ganser syndrome · Globus pharyngis) · Neurasthenia · Mass psychogenic illness · | |
| **Dissociative disorder** | Dissociative identity disorder · Psychogenic amnesia · Fugue state · Depersonalization disorder · | |
| **Physiological/physical behavioral** | | |
| **Eating disorder** | Anorexia nervosa · **Bulimia nervosa** · Rumination syndrome · NOS · | |
| **Nonorganic sleep disorders** | (Nonorganic hypersomnia · Nonorganic insomnia) · Parasomnia · (REM sleep behavior disorder · Night terror · Nightmare) · | |
| **Sexual dysfunction** | *sexual desire* · (Hypoactive sexual desire disorder · Hypersexuality) · *sexual arousal* · (Female sexual arousal disorder) · Erectile dysfunction · *orgasm* · (Anorgasmia · Delayed ejaculation · Premature ejaculation · Sexual anhedonia) · *pain* · (Vaginismus · Dyspareunia) · | |
| **Postnatal** | Postpartum depression · Postpartum psychosis · | |
| **Adult personality and behavior** | | |
| *Gender dysphoria* | Sexual maturation disorder · Ego-dystonic sexual orientation · Sexual relationship disorder · Paraphilia · (Voyeurism · Fetishism) · | |
| **Other** | Personality disorder · Impulse control disorder · (Kleptomania · Trichotillomania · Pyromania · Dermatillomania) · Body-focused repetitive behavior · Factitious disorder · (Münchausen syndrome) · | |
| **Disorders typically diagnosed in childhood** | | |
| **Intellectual disability** | X-linked intellectual disability · (Lujan–Fryns syndrome) · | |
| **Psychological development (developmental disabilities)** | Specific · Pervasive · Autism spectrum · | |
| **Emotional and behavioral** | ADHD · Conduct disorder · (ODD) · Emotional/behavioral disorder · (Separation anxiety disorder) · *social functioning* · (Selective mutism · RAD · DAD) · Tic disorder · (Tourette syndrome) · *Speech* · (Stuttering · Cluttering) · Movement disorder · (Stereotypic) · | |
| **Symptoms and uncategorized** | | |
| Catatonia · False pregnancy · Intermittent explosive disorder · Psychomotor agitation · Stereotypy · Psychogenic non-epileptic seizures · Klüver–Bucy syndrome · | | |

Categories: Eating disorders | Culture-bound syndromes | Vomiting | Psychiatric diagnosis




# Eating disorder

From Wikipedia, the free encyclopedia

**Eating disorders** are mental disorders defined by abnormal eating habits that negatively affect a person's physical or mental health. They include binge eating disorder where people eat a large amount in a short period of time, anorexia nervosa where people eat very little and thus have a low body weight, bulimia nervosa where people eat a lot and then try to rid themselves of the food, pica where people eat non-food items, rumination disorder where people regurgitate food, avoidant/restrictive food intake disorder where people have a lack of interest in food, and a group of other specified feeding or eating disorders. Anxiety disorders, depression, and substance abuse are common among people with eating disorders.[1] These disorders do not include obesity.[2]

**Eating disorders**

| Classification and external resources | |
|---|---|
| Specialty | Psychiatry |
| ICD-10 | |
| ICD-9-CM | 307.5 |
| MeSH | D001068 |

[edit on Wikidata]

The cause of eating disorders is not clear.[3] Both biological and environmental factors appear to play a role.[1][3] Cultural idealization of thinness is believed to contribute.[3] Eating disorders affect about 12 percent of dancers.[4] Those who have experienced sexual abuse are also more likely to develop eating disorders.[5] Some disorders such as pica and rumination disorder occur more often in people with intellectual disabilities. Only one eating disorder can be diagnosed at a given time.[2]

Treatment can be effective for many eating disorders. This typically involves counselling, a proper diet, a normal amount of exercise, and the reduction of efforts to eliminate food. Hospitalization is occasionally needed. Medications may be used to help with some of the associated symptoms.[1] At five years about 70% of people with anorexia and 50% of people with bulimia recover. Recovery from binge eating disorder is less clear and estimated at 20% to 60%. Both anorexia and bulimia increase the risk of death.[6]

In the developed world binge eating disorder affects about 1.6% of women and 0.8% of men in a given year. Anorexia affects about 0.4% and bulimia affects about 1.3% of young women in a given year.[2] During the entire life up to 4% of women have anorexia, 2% have bulimia, and 2% have binge eating disorder.[6] Anorexia and bulimia occur nearly ten times more often in females than males.[2] Typically they begin in late childhood or early adulthood.[1] Rates of other eating disorders are not clear.[2] Rates of eating disorders appear to be lower in less developed countries.[7]

Contents

## Classification [edit]

Bulimia nervosa is a disorder characterized by binge eating and purging, as well as excessive evaluation of one's self-worth in terms of body weight or shape.[8] Purging can include self-induced vomiting, over-exercising, and the use of diuretics, enemas, and laxatives. Anorexia nervosa is characterized by extreme food restriction and excessive weight loss, accompanied by the fear of being fat.[9] The extreme weight loss often causes women and girls who have begun menstruating to stop having menstrual periods, a condition known as amenorrhea. Although amenorrhea was once a required criterion for the disorder, it is no longer required to meet criteria for anorexia nervosa due to its exclusive nature for sufferers who are male, post-menopause, or who do not menstruate for other reasons.[10] The DSM-5 specifies two subtypes of anorexia nervosa—the restricting type and the binge/purge type. Those who suffer from the restricting type of anorexia nervosa restrict food intake and do not engage in binge eating, whereas those suffering from the binge/purge type lose control over their eating at least occasionally and may compensate for these binge episodes.[11] The most notable difference between anorexia nervosa binge/purge type and bulimia nervosa is the body weight of the person. Those diagnosed with anorexia nervosa binge/purge type are underweight, while those with bulimia nervosa may have a body weight that falls within the range from normal to obese.[12][13]

### ICD and DSM [edit]

These eating disorders are specified as mental disorders in standard medical manuals, such as in the ICD-10,[14] the DSM-5, or both.

- Anorexia nervosa (AN), characterized by lack of maintenance of a healthy body weight, an obsessive fear of gaining weight or refusal to do so, and an unrealistic perception, or non-recognition of the seriousness, of current low body weight.[15] Anorexia can cause menstruation to stop, and often leads to bone loss, loss of skin integrity, etc. It greatly stresses the heart, increasing the risk of heart attacks and related heart problems. The risk of death is greatly increased in individuals with this disease.[16] The most underlining factor researchers are starting to take notice of is that it may not just be a vanity, social, or media issue, but it could also be related to biological and or genetic components.[17] The DSM-5 contains many changes that better represent patients with these conditions. The DSM-IV required amenorrhea (the absence of the menstrual cycle) to be present in order to diagnose a patient with anorexia.[18] This is no longer a requirement in the DSM-5.
- Bulimia nervosa (BN), characterized by recurrent binge eating followed by compensatory behaviors such as purging (self-induced vomiting, eating to the point of vomiting, excessive use of laxatives/diuretics, or excessive exercise). Fasting and over-exercising may also be used as a method of purging following a binge.
- Muscle dysmorphia is characterized by appearance preoccupation that one's own body is too small, too skinny, insufficiently muscular, or insufficiently lean. Muscle dysmorphia affects mostly males.

- Binge Eating Disorder (BED), characterized by recurring binge eating at least once a week for over a period of 3 months while experiencing lack of control[18] and guilt after overeating.[19] The disorder can develop within individuals of a wide range of ages and socioeconomic classes.[20][21]
- Other Specified Feeding or Eating Disorder (OSFED) is an eating or feeding disorder that does not meet full DSM-5 criteria for AN, BN, or BED. Examples of otherwise-specified eating disorders include individuals with atypical anorexia nervosa, who meet all criteria for AN except being underweight, despite substantial weight loss; atypical bulimia nervosa, who meet all criteria for BN except that bulimic behaviors are less frequent or have not been ongoing for long enough; purging disorder; and night eating syndrome.

### Other [edit]

- Compulsive overeating (COE), in which individuals habitually graze on large quantities of food rather than binging, as would be typical of binge eating disorder.
- Prader-Willi syndrome
- Diabulimia, characterized by the deliberate manipulation of insulin levels by diabetics in an effort to control their weight.
- Food maintenance, characterized by a set of aberrant eating behaviors of children in foster care.[22]
- Orthorexia nervosa, a term used by Steven Bratman to characterize an obsession with a "pure" diet, in which people develop an obsession with avoiding unhealthy foods to the point where it interferes with a person's life.[23]
- Selective eating disorder, also called picky eating, is an extreme sensitivity to how something tastes. A person with SED may or may not be a supertaster.
- Drunkorexia, commonly characterized by purposely restricting food intake in order to reserve food calories for alcoholic calories, exercising excessively in order to burn calories consumed from drinking, and over-drinking alcohols in order to purge previously consumed food.[24]
- Pregorexia, characterized by extreme dieting and over-exercising in order to control pregnancy weight gain. Undernutrition during pregnancy is associated with low birth weight, coronary heart disease, type 2 diabetes, stroke, hypertension, cardiovascular disease risk, and depression.[25]
- Gourmand syndrome, a rare condition occurring after damage to the frontal lobe, resulting in an obsessive focus on fine foods.[26]

## Signs and symptoms [edit]

Symptoms and complications vary according to the nature and severity of the eating disorder:[27]

**Possible Symptoms and Complications of Eating Disorders**

| | | | |
|---|---|---|---|
| acne | xerosis | amenorrhoea | tooth loss, cavities |
| constipation | diarrhea | water retention and/or edema | lanugo |
| telogen effluvium | cardiac arrest | hypokalemia | death |
| osteoporosis[28] | electrolyte imbalance | hyponatremia | brain atrophy[29][30] |
| pellagra[31] | scurvy | kidney failure | suicide[32][33][34] |

Some physical symptoms of eating disorders are weakness, fatigue, sensitivity to cold, reduced beard growth in men, reduction in waking erections, reduced libido, weight loss and failure of growth.[35] Unexplained hoarseness may be a symptom of an underlying eating disorder, as the result of acid reflux, or entry of acidic gastric material into the laryngoesophageal tract. Patients who induce vomiting, such as those with anorexia nervosa, binge eating-purging type or those with purging-type bulimia nervosa are at risk for acid reflux.[36] Polycystic ovary syndrome (PCOS) is the most common endocrine disorder to affect women. Though often associated with obesity it can occur in normal weight individuals. PCOS has been associated with binge eating and bulimic behavior.[37][38][39][40][41][42]

### Pro-Ana subculture [edit]

Several websites promote eating disorders, and can provide a means for individuals to communicate in order to maintain eating disorders. Members of these websites typically feel that their eating disorder is the only aspect of a chaotic life that they can control.[43] These websites are often interactive and have discussion boards where individuals can share strategies, ideas, and experiences, such as diet and exercise plans that achieve extremely low weights.[44] A study comparing the personal web-blogs that were pro-eating disorder with those focused on recovery found that the pro-eating disorder blogs contained language reflecting lower cognitive processing, used a more closed-minded writing style, contained less emotional expression and fewer social references, and focused more on eating-related contents than did the recovery blogs.[45]

### Psychopathology [edit]

The psychopathology of eating disorders centers around body image disturbance, such as concerns with weight and shape; self-worth being too dependent on weight and shape; fear of gaining weight even when underweight; denial of how severe the symptoms are and a distortion in the way the body is experienced.[35]

## Causes [edit]

The cause of eating disorder is not clear.

Many people with eating disorders suffer also from body dysmorphic disorder, altering the way a person sees themself.[46][47] Studies have found that a high proportion of individuals diagnosed with body dysmorphic disorder also had some type of eating disorder, with 15% of individuals having either anorexia nervosa or bulimia nervosa.[46] This link between body dysmorphic disorder and anorexia stems from the fact that both BDD and anorexia nervosa are characterized by a preoccupation with physical appearance and a distortion of body image.[47] There are also many other possibilities such as environmental, social and interpersonal issues that could promote and sustain these illnesses.}[48] Also, the media are oftentimes blamed for the rise in the incidence of eating disorders due to the fact that media images of idealized slim physical shape of people such as models and celebrities motivate or even force people to attempt to achieve slimness themselves. The media are accused of distorting reality, in the sense that people portrayed in the media are either naturally thin and thus unrepresentative of normality or unnaturally thin by forcing their bodies to look like the ideal image by putting excessive pressure on themselves to look a certain way. While past findings have described the causes of eating disorders as primarily psychological, environmental, and sociocultural, new studies have uncovered evidence that there is a prevalent genetic/heritable aspect of the causes of eating disorders.[49]

### Genetics [edit]

- Genetic: Numerous studies have been undertaken that show a possible genetic predisposition toward eating disorders as a result of Mendelian inheritance.[50][50][51] It has also been shown that eating disorders can be heritable. Recent twin studies have found slight instances of genetic variance when considering the different criterion of both anorexia nervosa and bulimia nervosa as endophenotypes contributing to the disorders as a whole.[48] In another recent study, twin and family studies led researchers to discover a genetic link on chromosome 1 that can be found in multiple family members of an individual with anorexia nervosa, indicating an inheritance pattern found between family members of others that have been previously diagnosed with an eating disorder.[49] A study found that an individual who is a first degree relative of someone who has suffered or currently suffers from an eating disorder is seven to twelve times more likely to suffer from an eating disorder themselves.[52] Twin studies also have shown that at least a portion of the vulnerability to develop eating disorders can be inherited, and there has been sufficient evidence to show that there is a genetic locus that shows susceptibility for developing anorexia nervosa.[52]

- Epigenetics: Epigenetic mechanisms are means by which environmental effects alter gene expression via methods such as DNA methylation; these are independent of and do not alter the underlying DNA sequence. They are heritable, but also may occur throughout the lifespan, and are potentially reversible. Dysregulation of dopaminergic neurotransmission due to epigenetic mechanisms has been implicated in various eating disorders.[53][54] One study has found that "epigenetic mechanisms may contribute to the known alterations of ANP homeostasis in women with eating disorders."[53][55] Other candidate genes for epigenetic studies in eating disorders include leptin, pro-opiomelanocortin (POMC) and brain-derived neurotrophic factor (BDNF).[56]

## Psychological [edit]

Eating disorders are classified as Axis I[57] disorders in the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-IV) published by the American Psychiatric Association. There are various other psychological issues that may factor into eating disorders, some fulfill the criteria for a separate Axis I diagnosis or a personality disorder which is coded Axis II and thus are considered comorbid to the diagnosed eating disorder. Axis II disorders are subtyped into 3 "clusters": A, B and C. The causality between personality disorders and eating disorders has yet to be fully established.[58] Some people have a previous disorder which may increase their vulnerability to developing an eating disorder.[59][60][61] Some develop them afterwards.[62] The severity and type of eating disorder symptoms have been shown to affect comorbidity.[63] The DSM-IV should not be used by laypersons to diagnose themselves, even when used by professionals there has been considerable controversy over the diagnostic criteria used for various diagnoses, including eating disorders. There has been controversy over various editions of the DSM including the latest edition, DSM-V, due in May 2013.[64][65][66][67][68]

## Cognitive attentional bias issues [edit]

Attentional bias may have an effect on eating disorders. Many studies have been performed to test this theory.

**Comorbid Disorders**

| Axis I | Axis II |
|---|---|
| depression[69] | obsessive compulsive personality disorder[70] |
| substance abuse, alcoholism[71] | borderline personality disorder[72] |
| anxiety disorders[73] | narcissistic personality disorder[74] |
| obsessive compulsive disorder[75][76] | histrionic personality disorder[77] |
| Attention-deficit hyperactivity disorder[78][79][80][81] | avoidant personality disorder[82] |

## Personality traits [edit]

There are various childhood personality traits associated with the development of eating disorders.[83] During adolescence these traits may become intensified due to a variety of physiological and cultural influences such as the hormonal changes associated with puberty, stress related to the approaching demands of maturity and socio-cultural influences and perceived expectations, especially in areas that concern body image. Eating disorders have been associated with a fragile sense of self and with disordered mentalization.[84] Many personality traits have a genetic component and are highly heritable. Maladaptive levels of certain traits may be acquired as a result of anoxic or traumatic brain injury, neurodegenerative diseases such as Parkinson's disease, neurotoxicity such as lead exposure, bacterial infection such as Lyme disease or viral infection such as Toxoplasma gondii as well as hormonal influences. While studies are still continuing via the use of various imaging techniques such as fMRI; these traits have been shown to originate in various regions of the brain[85] such as the amygdala[86][87] and the prefrontal cortex.[88] Disorders in the prefrontal cortex and the executive functioning system have been shown to affect eating [89][90]

behavior.

## Celiac disease [edit]

People with gastrointestinal disorders may be more risk of developing disordered eating practices than the general population, principally restrictive eating disturbances.[91] An association of anorexia nervosa with celiac disease has been found.[92] The role that gastrointestinal symptoms play in the development of eating disorders seems rather complex. Some authors report that unresolved symptoms prior to gastrointestinal disease diagnosis may create a food aversion in these persons, causing alterations to their eating patterns. Other authors report that greater symptoms throughout their diagnosis led to greater risk. It has been documented that some people with celiac disease, irritable bowel syndrome or inflammatory bowel disease who are not conscious about the importance of strictly following their diet, choose to consume their trigger foods to promote weight loss. On the other hand, individuals with good dietary management may develop anxiety, food aversion and eating disorders because of concerns around cross contamination of their foods.[91] Some authors suggest that medical professionals should evaluate the presence of an unrecognized celiac disease in all people with eating disorder, especially if they present any gastrointestinal symptom (such as decreased appetite, abdominal pain, bloating, distension, vomiting, diarrhea or constipation), weight loss, or growth failure; and also routinely ask celiac patients about weight or body shape concerns, dieting or vomiting for weight control, to evaluate the possible presence of eating disorders,[92] specially in women.[93]

## Environmental influences [edit]

## Child maltreatment [edit]

Child abuse which encompasses physical, psychological and sexual abuse, as well as neglect has been shown to approximately triple the risk of an eating disorder.[94] Sexual abuse appears to about double the risk of bulimia; however, the association is less clear for anorexia.[94]

## Social isolation [edit]

Social isolation has been shown to have a deleterious effect on an individual's physical and emotional well-being. Those that are socially isolated have a higher mortality rate in general as compared to individuals that have established social relationships. This effect on mortality is markedly increased in those with pre-existing medical or psychiatric conditions, and has been especially noted in cases of coronary heart disease. "The magnitude of risk associated with social isolation is comparable with that of cigarette smoking and other major biomedical and psychosocial risk factors." (Brummett *et al.*)

Social isolation can be inherently stressful, depressing and anxiety-provoking. In an attempt to ameliorate these distressful feelings an individual may engage in emotional eating in which food serves as a source of comfort. The loneliness of social isolation and the inherent stressors thus associated have been implicated as triggering factors in binge eating as well.[95][96][97][98]

Waller, Kennerley and Ohanian (2007) argued that both bingeing–vomiting and restriction are emotion suppression strategies, but they are just utilized at different times. For example, restriction is used to pre-empt any emotion activation, while bingeing–vomiting is used after an emotion has been activated.[99]

## Parental influence [edit]

Parental influence has been shown to be an intrinsic component in the development of eating behaviors of children. This influence is manifested and shaped by a variety of diverse factors such as familial genetic predisposition, dietary choices as dictated by cultural or ethnic preferences, the parents' own body shape and eating patterns, the degree of involvement and expectations of their children's eating behavior as well as the interpersonal relationship of parent and child. This is in addition to the general psychosocial climate of the home and the presence or absence of a nurturing stable environment. It has been shown that maladaptive parental behavior has an important role in the development of eating disorders. As to the more

subtle aspects of parental influence, it has been shown that eating patterns are established in early childhood and that children should be allowed to decide when their appetite is satisfied as early as the age of two. A direct link has been shown between obesity and parental pressure to eat more.

Coercive tactics in regard to diet have not been proven to be efficacious in controlling a child's eating behavior. Affection and attention have been shown to affect the degree of a child's finickiness and their acceptance of a more varied diet.[100][101][102][103][104][105]

Hilde Bruch, a pioneer in the field of studying eating disorders, asserts that anorexia nervosa often occurs in girls who are high achievers, obedient, and always trying to please their parents. Their parents have a tendency to be over-controlling and fail to encourage the expression of emotions, inhibiting daughters from accepting their own feelings and desires. Adolescent females in these overbearing families lack the ability to be independent from their families, yet realize the need to, often resulting in rebellion. Controlling their food intake may make them feel better, as it provides them with a sense of control.[106]

## Peer pressure [edit]

In various studies such as one conducted by The McKnight Investigators, peer pressure was shown to be a significant contributor to body image concerns and attitudes toward eating among subjects in their teens and early twenties.

Eleanor Mackey and co-author, Annette M. La Greca of the University of Miami, studied 236 teen girls from public high schools in southeast Florida. "Teen girls' concerns about their own weight, about how they appear to others and their perceptions that their peers want them to be thin are significantly related to weight-control behavior", says psychologist Eleanor Mackey of the Children's National Medical Center in Washington and lead author of the study. "Those are really important."

According to one study, 40% of 9- and 10-year-old girls are already trying to lose weight.[107] Such dieting is reported to be influenced by peer behavior, with many of those individuals on a diet reporting that their friends also were dieting. The number of friends dieting and the number of friends who pressured them to diet also played a significant role in their own choices.[108][109][110][111]

Elite athletes have a significantly higher rate in eating disorders. Female athletes in sports such as gymnastics, ballet, diving, etc. are found to be at the highest risk among all athletes. Women are more likely than men to acquire an eating disorder between the ages of 13–30. 0–15% of those with bulimia and anorexia are men.[112]

## Cultural pressure [edit]

There is a cultural emphasis on thinness which is especially pervasive in western society. There is an unrealistic stereotype of what constitutes beauty and the ideal body type as portrayed by the media, fashion and entertainment industries. "The cultural pressure on men and women to be 'perfect' is an important predisposing factor for the development of eating disorders".[113][114] Further, when women of all races base their evaluation of their self upon what is considered the culturally ideal body, the incidence of eating disorders increases.[115] Eating disorders are becoming more prevalent in non-Western countries where thinness is not seen as the ideal, showing that social and cultural pressures are not the only causes of eating disorders.[116] For example, observations of anorexia in all of the non-Western regions of the world point to the disorder not being "culture-bound" as once thought.[117] However, studies on rates of bulimia suggest that it might be culturally bound. In non-Western countries, bulimia is less prevalent than anorexia, but these non-Western countries where it is observed can be said to have probably or definitely been influenced or exposed to Western culture and ideology.[118]

Socioeconomic status (SES) has been viewed as a risk factor for eating disorders, presuming that possessing more resources allows for an individual to actively choose to diet and reduce body weight.[119] Some studies have also shown a relationship between increasing body dissatisfaction with increasing SES.[120] However, once high socioeconomic status has been achieved, this relationship weakens and, in some cases, no longer exists.[117]

The media plays a major role in the way in which people view themselves. Countless magazine ads and commercials depict thin celebrities like Lindsay Lohan, Nicole Richie, Victoria Beckham and Mary Kate Olsen, who appear to gain nothing but attention from their looks. Society has taught people that being accepted by others is necessary at all costs.[121] Unfortunately this has led to the belief that in order to fit in one must look a certain way. Televised beauty competitions such as the Miss America Competition contribute to the idea of what it means to be beautiful because competitors are evaluated on the basis of their opinion.[122]

In addition to socioeconomic status being considered a cultural risk factor so is the world of sports. Athletes and eating disorders tend to go hand in hand, especially the sports where weight is a competitive factor. Gymnastics, horse back riding, wrestling, body building, and dancing are just a few that fall into this category of weight dependent sports. Eating disorders among individuals that participate in competitive activities, especially women, often lead to having physical and biological changes related to their weight that often mimic prepubescent stages. Oftentimes as women's bodies change they lose their competitive edge which leads them to taking extreme measures to maintain their younger body shape. Men often struggle with binge eating followed by excessive exercise while focusing on building muscle rather than losing fat, but this goal of gaining muscle is just as much an eating disorder as obsessing over thinness. The following statistics taken from Susan Nolen-Hoeksema's book, *(ab)normal psychology*, shows the estimated percentage of athletes that struggle with eating disorders based on the category of sport.

- Aesthetic sports (dance, figure skating, gymnastics) – 35%
- Weight dependent sports (judo, wrestling) – 29%
- Endurance sports (cycling, swimming, running) – 20%
- Technical sports (golf, high jumping) – 14%
- Ball game sports (volleyball, soccer) – 12%

Although most of these athletes develop eating disorders to keep their competitive edge, others use exercise as a way to maintain their weight and figure. This is just as serious as regulating food intake for competition. Even though there is mixed evidence showing at what point athletes are challenged with eating disorders, studies show that regardless of competition level all athletes are at higher risk for developing eating disorders that non-athletes, especially those that participate in sports where thinness is a factor.[123]

Pressure from society is also seen within the homosexual community. Homosexual men are at greater risk of eating disorder symptoms than heterosexual men.[124] Within the gay culture, muscularity gives the advantages of both social and sexual desirability and also power.[125] These pressures and ideas that another homosexual male may desire a mate who is thinner or muscular can possibly lead to eating disorders. The higher eating disorder symptom score reported, the more concern about how others perceive them and the more frequent and excessive exercise sessions occur.[125] High levels of body dissatisfaction are also linked to external motivation to working out and old age; however, having a thin and muscular body occurs within younger homosexual males than older.[124][125]

It is important to realize some of the limitations and challenges of many studies that try to examine the roles of culture, ethnicity, and SES. For starters, most of the cross-cultural studies use definitions from the DSM-IV-TR, which has been criticized as reflecting a Western cultural bias. Thus, assessments and questionnaires may not be constructed to detect some of the cultural differences associated with different disorders. Also, when looking at individuals in areas potentially influenced by Western culture, few studies have attempted to measure how much an individual has adopted the mainstream culture or retained the traditional cultural values of the area. Lastly, the majority of the cross-cultural studies on eating disorders and body image disturbances occurred in Western nations and not in the countries or regions being examined.[126]

While there are many influences to how an individual processes their body image, the media does play a major role. Along with the media, parental influence, peer influence, and self-efficacy beliefs also play a large role in an individual's view of themselves. The way the media presents images can have a lasting effect on an individual's perception of their body image. Eating disorders are a worldwide issue and while women are more likely to be affected by an eating disorder it still affects both genders (Schwitzer 2012). The media influences eating disorders whether shown in a positive or negative light, it then has a

responsibility to use caution when promoting images that projects an ideal that many turn to eating disorders to attain.[127]

To try to address unhealthy body image in the fashion world, in 2015, France passed a law requiring models to be declared healthy by a doctor to participate in fashion shows. It also requires re-touched images to be marked as such in magazines.[128]

There is a relationship between "thin ideal" social media content and body dissatisfaction and eating disorders among young adult women, especially in the Western hemisphere.[129] New research points to an "internalization" of distorted images online, as well as negative comparisons among young adult women.[130] Most studies have been based in the U.S, the U.K, and Australia, these are places where the thin ideal is strong among women, as well as the strive for the "perfect" body.[130]

In addition to mere media exposure, there is an online "pro-eating disorder" community. Through personal blogs and Twitter, this community promotes eating disorders as a "lifestyle", and continuously posts pictures of emaciated bodies, and tips on how to stay thin. The hashtag "#proana" (pro-anorexia), is a product of this community,[131] as well as images promoting weight loss, tagged with the term "thinspiration". According to social comparison theory, young women have a tendency to compare their appearance to others, which can result in a negative view of their own bodies and altering of eating behaviors, that in turn can develop disordered eating behaviors.[132]

When body parts are isolated and displayed in the media as objects to be looked at, it is called objectification, and women are affected most by this phenomenon. Objectification increases self-objectification, where women judge their own body parts as a mean of praise and pleasure for others. There is a significant link between self-objectification, body dissatisfaction, and disordered eating, as the beauty ideal is altered through social media.[129]

## Mechanisms [edit]

- Biochemical: Eating behavior is a complex process controlled by the neuroendocrine system, of which the Hypothalamus-pituitary-adrenal-axis (HPA axis) is a major component. Dysregulation of the HPA axis has been associated with eating disorders,[133][134] such as irregularities in the manufacture, amount or transmission of certain neurotransmitters, hormones[135] or neuropeptides[136] and amino acids such as homocysteine, elevated levels of which are found in AN and BN as well as depression.[137]
  - Serotonin: a neurotransmitter involved in depression also has an inhibitory effect on eating behavior.[138][139][140][141][142]
  - Norepinephrine is both a neurotransmitter and a hormone; abnormalities in either capacity may affect eating behavior.[143][144]
  - Dopamine: which in addition to being a precursor of norepinephrine and epinephrine is also a neurotransmitter which regulates the rewarding property of food.[145][146]
  - Neuropeptide Y also known as NPY is a hormone that encourages eating and decreases metabolic rate.[147] Blood levels of NPY are elevated in patients with anorexia nervosa, and studies have shown that injection of this hormone into the brain of rats with restricted food intake increases their time spent running on a wheel. Normally the hormone stimulates eating in healthy patients, but under conditions of starvation it increases their activity rate, probably to increase the chance of finding food.[147] The increased levels of NPY in the blood of patients with eating disorders can in some ways explain the instances of extreme over-exercising found in most anorexia nervosa patients.
- Leptin and ghrelin: leptin is a hormone produced primarily by the fat cells in the body; it has an inhibitory effect on appetite by inducing a feeling of satiety. Ghrelin is an appetite inducing hormone produced in the stomach and the upper portion of the small intestine. Circulating levels of both hormones are an important factor in weight control. While often associated with obesity, both hormones and their respective effects have been implicated in the pathophysiology of anorexia nervosa and bulimia nervosa.[148] Leptin can also be used to distinguish between constitutional thinness found in a [48][149]

healthy person with a low BMI and an individual with anorexia nervosa.
- Gut bacteria and immune system: studies have shown that a majority of patients with anorexia and bulimia nervosa have elevated levels of autoantibodies that affect hormones and neuropeptides that regulate appetite control and the stress response. There may be a direct correlation between autoantibody levels and associated psychological traits.[150][151] Later study revealed that autoantibodies reactive with alpha-MSH are, in fact, generated against ClpB, a protein produced by certain gut bacteria e.g. Escherichia coli. ClpB protein was identified as a conformational antigen-mimetic of alpha-MSH. In patients with eating disorders plasma levels of anti-ClpB IgG and IgM correalated with patients' psychological traits[152]
- Infection: PANDAS, is an abbreviation for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections. Children with PANDAS "have obsessive-compulsive disorder (OCD) and/or tic disorders such as Tourette syndrome, and in whom symptoms worsen following infections such as "strep throat" and scarlet fever". (NIMH) There is a possibility that PANDAS may be a precipitating factor in the development of anorexia nervosa in some cases, (PANDAS AN).[153]
- Lesions: studies have shown that lesions to the right frontal lobe or temporal lobe can cause the pathological symptoms of an eating disorder.[154][155][156]
- Tumors: tumors in various regions of the brain have been implicated in the development of abnormal eating patterns.[157][158][159][160][161]
- Brain calcification: a study highlights a case in which prior calcification of the right thalumus may have contributed to development of anorexia nervosa.[162]
- somatosensory homunculus: is the representation of the body located in the somatosensory cortex, first described by renowned neurosurgeon Wilder Penfield. The illustration was originally termed "Penfield's Homunculus", homunculus meaning little man. "In normal development this representation should adapt as the body goes through its pubertal growth spurt. However, in AN it is hypothesized that there is a lack of plasticity in this area, which may result in impairments of sensory processing and distortion of body image". (Bryan Lask, also proposed by VS Ramachandran)
- Obstetric complications: There have been studies done which show maternal smoking, obstetric and perinatal complications such as maternal anemia, very pre-term birth (less than 32 weeks), being born small for gestational age, neonatal cardiac problems, preeclampsia, placental infarction and sustaining a cephalhematoma at birth increase the risk factor for developing either anorexia nervosa or bulimia nervosa. Some of this developmental risk as in the case of placental infarction, maternal anemia and cardiac problems may cause intrauterine hypoxia, umbilical cord occlusion or cord prolapse may cause ischemia, resulting in cerebral injury, the prefrontal cortex in the fetus and neonate is highly susceptible to damage as a result of oxygen deprivation which has been shown to contribute to executive dysfunction, ADHD, and may affect personality traits associated with both eating disorders and comorbid disorders such as impulsivity, mental rigidity and obsessionality. The problem of perinatal brain injury, in terms of the costs to society and to the affected individuals and their families, is extraordinary. (Yafeng Dong, PhD)[163][164][165][166][167][168][169][170][171][172][173]
- Symptom of starvation: Evidence suggests that the symptoms of eating disorders are actually symptoms of the starvation itself, not of a mental disorder. In a study involving thirty-six healthy young men that were subjected to semi-starvation, the men soon began displaying symptoms commonly found in patients with eating disorders.[147][174] In this study, the healthy men ate approximately half of what they had become accustomed to eating and soon began developing symptoms and thought patterns (preoccupation with food and eating, ritualistic eating, impaired cognitive ability, other physiological changes such as decreased body temperature) that are characteristic symptoms of anorexia nervosa.[147] The men used in the study also developed hoarding and obsessive collecting behaviors, even though they had no use for the items, which revealed a possible connection between eating disorders and obsessive compulsive disorder.[147]

## Diagnosis [edit]

The initial diagnosis should be made by a competent medical professional. "The medical history is the most powerful tool for diagnosing eating disorders"(American Family Physician).[175] There are many medical disorders that mimic eating disorders and comorbid psychiatric disorders. All organic causes should be ruled

out prior to a diagnosis of an eating disorder or any other psychiatric disorder. In the past 30 years eating disorders have become increasingly conspicuous and it is uncertain whether the changes in presentation reflect a true increase.[*citation needed*] Anorexia nervosa and bulimia nervosa are the most clearly defined subgroups of a wider range of eating disorders. Many patients present with subthreshold expressions of the two main diagnoses: others with different patterns and symptoms.[176]

## Medical [edit]

The diagnostic workup typically includes complete medical and psychosocial history and follows a rational and formulaic approach to the diagnosis. Neuroimaging using fMRI, MRI, PET and SPECT scans have been used to detect cases in which a lesion, tumor or other organic condition has been either the sole causative or contributory factor in an eating disorder. "Right frontal intracerebral lesions with their close relationship to the limbic system could be causative for eating disorders, we therefore recommend performing a cranial MRI in all patients with suspected eating disorders" (Trummer M *et al.* 2002), "intracranial pathology should also be considered however certain is the diagnosis of early-onset anorexia nervosa. Second, neuroimaging plays an important part in diagnosing early-onset anorexia nervosa, both from a clinical and a research prospective".(O'Brien *et al.* 2001).[156][177]

## Psychological [edit]

**Eating Disorder Specific Psychometric Tests**

| | |
|---|---|
| Eating Attitudes Test[178] | SCOFF questionnaire[179] |
| Body Attitudes Test[180] | Body Attitudes Questionnaire[181] |
| Eating Disorder Inventory[182] | Eating Disorder Examination Interview[183] |

After ruling out organic causes and the initial diagnosis of an eating disorder being made by a medical professional, a trained mental health professional aids in the assessment and treatment of the underlying psychological components of the eating disorder and any comorbid psychological conditions. The clinician conducts a clinical interview and may employ various psychometric tests. Some are general in nature while others were devised specifically for use in the assessment of eating disorders. Some of the general tests that may be used are the Hamilton Depression Rating Scale[184] and the Beck Depression Inventory.[185][186] longitudinal research showed that there is an increase in chance that a young adult female would develop bulimia due to their current psychological pressure and as the person ages and matures, their emotional problems change or are resolved and then the symptoms decline.[187]

## Differential diagnoses [edit]

There are multiple medical conditions which may be misdiagnosed as a primary psychiatric disorder, complicating or delaying treatment. These may have a synergistic effect on conditions which mimic an eating disorder or on a properly diagnosed eating disorder.

- Lyme disease which is known as the "great imitator", as it may present as a variety of psychiatric or neurological disorders including anorexia nervosa.[188][189]
- Gastrointestinal diseases,[91] such as celiac disease, Crohn's disease, peptic ulcer, eosinophilic esophagitis[92] or non-celiac gluten sensitivity,[190] among others. Celiac disease is also known as the "great imitator", because it may involve several organs and cause an extensive variety of non-gastrointestinal symptoms, such as psychiatric and neurological disorders,[191][192][193] including anorexia nervosa.[92]
- Addison's Disease is a disorder of the adrenal cortex which results in decreased hormonal production. Addison's disease, even in subclinical form may mimic many of the symptoms of anorexia nervosa.[194]
- Gastric adenocarcinoma is one of the most common forms of cancer in the world. Complications due to this condition have been misdiagnosed as an eating disorder.[195]
- Hypothyroidism, hyperthyroidism, hypoparathyroidism and hyperparathyroidism may mimic some of the symptoms of, can occur concurrently with, be masked by or exacerbate an eating

disorder.[196][197][198][199][200][201][202][203]

- Toxoplasma seropositivity: even in the absence of symptomatic toxoplasmosis, toxoplasma gondii exposure has been linked to changes in human behavior and psychiatric disorders including those comorbid with eating disorders such as depression. In reported case studies the response to antidepressant treatment improved only after adequate treatment for toxoplasma.[204]
- Neurosyphilis: It is estimated that there may be up to one million cases of untreated syphilis in the US alone. "The disease can present with psychiatric symptoms alone, psychiatric symptoms that can mimic any other psychiatric illness". Many of the manifestations may appear atypical. Up to 1.3% of short term psychiatric admissions may be attributable to neurosyphilis, with a much higher rate in the general psychiatric population. (Ritchie, M Perdigao J,)[205]
- Dysautonomia: a wide variety of autonomic nervous system (ANS) disorders may cause a wide variety of psychiatric symptoms including anxiety, panic attacks and depression. Dysautonomia usually involves failure of sympathetic or parasympathetic components of the ANS system but may also include excessive ANS activity. Dysautonomia can occur in conditions such as diabetes and alcoholism.

Psychological disorders which may be confused with an eating disorder, or be co-morbid with one:

- Emetophobia is an anxiety disorder characterized by an intense fear of vomiting. A person so afflicted may develop rigorous standards of food hygiene, such as not touching food with their hands. They may become socially withdrawn to avoid situations which in their perception may make them vomit. Many who suffer from emetophobia are diagnosed with anorexia or self-starvation. In severe cases of emetophobia they may drastically reduce their food intake.[206][207]
- Phagophobia is an anxiety disorder characterized by a fear of eating, it is usually initiated by an adverse experience while eating such as choking or vomiting. Persons with this disorder may present with complaints of pain while swallowing.[208]
- Body dysmorphic disorder (BDD) is listed as a somatoform disorder that affects up to 2% of the population. BDD is characterized by excessive rumination over an actual or perceived physical flaw. BDD has been diagnosed equally among men and women. While BDD has been misdiagnosed as anorexia nervosa, it also occurs comorbidly in 39% of eating disorder cases. BDD is a chronic and debilitating condition which may lead to social isolation, major depression and suicidal ideation and attempts. Neuroimaging studies to measure response to facial recognition have shown activity predominately in the left hemisphere in the left lateral prefrontal cortex, lateral temporal lobe and left parietal lobe showing hemispheric imbalance in information processing. There is a reported case of the development of BDD in a 21-year-old male following an inflammatory brain process. Neuroimaging showed the presence of a new atrophy in the frontotemporal region.[209][210][211][212]

## Prevention [edit]

Prevention aims to promote a healthy development before the occurrence of eating disorders. It also intends early identification of an eating disorder before it is too late to treat. Children as young as ages 5–7 are aware of the cultural messages regarding body image and dieting. Prevention comes in bringing these issues to the light. The following topics can be discussed with young children (as well as teens and young adults).

- Emotional Bites: a simple way to discuss emotional eating is to ask children about why they might eat besides being hungry. Talk about more effective ways to cope with emotions, emphasizing the value of sharing feelings with a trusted adult.
- Say No to Teasing: another concept is to emphasize that it is wrong to say hurtful things about other people's body sizes.
- Body Talk: emphasize the importance of listening to one's body. That is, eating when you are hungry (not starving) and stopping when you are satisfied (not stuffed). Children intuitively grasp these concepts.
- Fitness Comes in All Sizes: educate children about the genetics of body size and the normal changes occurring in the body. Discuss their fears and hopes about growing bigger. Focus on fitness and a balanced diet.[213]

Internet and modern technologies provide new opportunities for prevention. On-line programs have the

potential to increase the use of prevention programs. The development and practice of prevention programs via on-line sources make it possible to reach a wide range of people at minimal cost.[214] Such an approach can also make prevention programs to be sustainable.

## Treatment [edit]

Treatment varies according to type and severity of eating disorder, and usually more than one treatment option is utilized.[215] There is no well-established treatment for eating disorders, meaning that current views about treatment are based mainly on clinical experience. Family doctors play an important role in early treatment of people with eating disorders by encouraging those who are also reluctant to see a psychiatrist.[216] Treatment can take place in a variety of different settings such as community programs, hospitals, day programs, and groups.[217] That said, some treatment methods are:

- Cognitive behavioral therapy (CBT),[218][219][220] which postulates that an individual's feelings and behaviors are caused by their own thoughts instead of external stimuli such as other people, situations or events; the idea is to change how a person thinks and reacts to a situation even if the situation itself does not change. See Cognitive behavioral treatment of eating disorders.
  - Acceptance and commitment therapy: a type of CBT[221]
  - Cognitive Remediation Therapy (CRT), a set of cognitive drills or compensatory interventions designed to enhance cognitive functioning.[222][223][224][225]
- Dialectical behavior therapy[226]
- Family therapy[227] including "conjoint family therapy" (CFT), "separated family therapy" (SFT) and Maudsley Family Therapy.[228][229]
- Behavioral therapy: focuses on gaining control and changing unwanted behaviors.[230]
- Interpersonal psychotherapy (IPT)[231]
- Cognitive Emotional Behaviour Therapy (CEBT)[232]
- Music Therapy
- Recreation Therapy
- Art therapy[233]
- Nutrition counseling[234] and Medical nutrition therapy[235][236][237]
- Medication: Orlistat is used in obesity treatment. Olanzapine seems to promote weight gain as well as the ability to ameliorate obsessional behaviors concerning weight gain. zinc supplements have been shown to be helpful, and cortisol is also being investigated.[238][239][240][241][242][243]
- Self-help and guided self-help have been shown to be helpful in AN, BN and BED;[220][244][245][246] this includes support groups and self-help groups such as Eating Disorders Anonymous and Overeaters Anonymous.[247][248]
- Psychoanalysis
- Inpatient care

There are few studies on the cost-effectiveness of the various treatments.[249] Treatment can be expensive;[250][251] due to limitations in health care coverage, people hospitalized with anorexia nervosa may be discharged while still underweight, resulting in relapse and rehospitalization.[252]

For children with anorexia, the only well-established treatment is the family treatment-behavior.[253] For other eating disorders in children, however, there is no well-established treatments, though family treatment-behavior has been used in treating bulimia.[253]

## Outcomes [edit]

Outcome estimates are complicated by non-uniform criteria used by various studies, but for anorexia nervosa, bulimia nervosa, and binge eating disorder, there seems to be general agreement that full recovery rates are in the 50% to 85% range, with larger proportions of people experiencing at least partial

remission.[247][254][255][256] The outcomes of eating disorders (ED) vary among the cases. For many, it can be a lifelong struggle or it can be overcome within months. In the United States, twenty million women and ten million men have an eating disorders at least once in their lifetime.[257] The mortality rate for those with anorexia nervosa is 5.4 per 1000 individuals per year. Roughly 1.3 deaths were due to suicide. A person who is or had been in an inpatient setting had a rate of 4.6 deaths per 1000. Of individuals with bulimia nervosa about 2 persons per 1000 persons die per year and among those with EDNOS about 3.3 per 1000 people die per year.[258]

- Miscarriages: Pregnant women with a Binge Eating Disorder have shown to have a greater chance of having a miscarriage compared to pregnant women with any other eating disorders. According to a study done, out of a group of pregnant women being evaluated, 46.7% of the pregnancies ended with a miscarriage in women that were diagnosed with BED, with 23.0% in the control. In the same study, 21.4% of women diagnosed with Bulimia Nervosa had their pregnancies end with miscarriages and only 17.7% of the controls.[259]
- Relapse: An individual who is in remission from BN and EDNOS (Eating Disorder Not Otherwise Specified) is at a high risk of falling back into the habit of self-harming themselves. Factors such as high stress regarding their job, pressures from society, as well as other occurrences that inflict stress on a person, can push a person back to what they feel will ease the pain. A study tracked a group of selected people that were either diagnosed with BN or EDNOS for 60 months. After the 60 months were complete, the researchers recorded whether or not the patients were suffering from a relapse. The results found that the probability of a person previously diagnosed with EDNOS had a 41% chance of relapsing; a person with BN had a 47% chance.[260]
- Attachment insecurity: People who are showing signs of attachment anxiety will most likely have trouble communicating their emotional status as well as having trouble seeking effective social support. Signs that a person has adopted this symptom include not showing recognition to their caregiver or when he/she is feeling pain. In a clinical sample, it is clear that at the pretreatment step of a patient's recovery, more severe eating disorder symptoms directly corresponds to higher attachment anxiety. The more this symptom increases, the more difficult it is to achieve eating disorder reduction prior to treatment.[261]

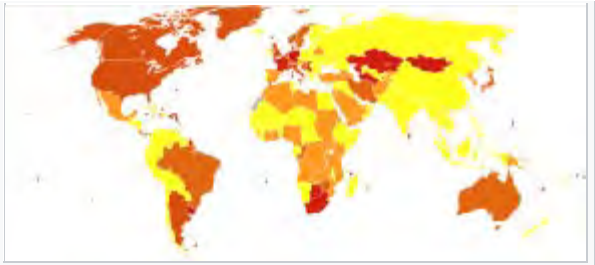
Anorexia Nervosa symptoms include the increasing chance of getting osteoporosis. This disease causes the bones of an individual to become brittle, weak, and low in density. Thinning of the hair as well as dry hair and skin is also very common. The muscles of the heart will also start to change if no treatment is inflicted on the patient. This causes the heart to have an abnormally slow heart rate along with low blood pressure. Heart failure becomes a major consideration when this begins to occur. Muscles throughout the body begin to lose their strength. This will cause the individual to begin feeling faint, drowsy, and weak. Along with these symptoms, the body will begin to grow a layer of hair called lanugo. The human body does this in response to the lack of heat and insulation due to the low percentage of body fat.[257]

Bulimia nervosa symptoms include heart problems like an irregular heartbeat that can lead to heart failure and death may occur. This occurs because of the electrolyte imbalance that is a result of the constant binge and purge process. The probability of a gastric rupture increases. A gastric rupture is when there is a sudden rupture of the stomach lining that can be fatal.The acids that are contained in the vomit can cause a rupture in the esophagus as well as tooth decay. As a result, to laxative abuse, irregular bowel movements may occur along with constipation. Sores along the lining of the stomach called peptic ulcers begin to appear and the chance of developing pancreatitis increases.[257]

Binge eating symptoms include high blood pressure, which can cause heart disease if it is not treated. Many patients recognize an increase in the levels of cholesterol. The chance of being diagnosed with gallbladder disease increases, which affects an individual's digestive tract.[257]

## Epidemiology [edit]

Eating disorders result in about 7,000 deaths a year as of 2010, making them the mental illnesses with the highest mortality rate.[262]



Deaths due to eating disorders per million persons in 2012

0-0 1-1 2-2 3-3 4-25

One study in the United States found a higher rate in college students who are transgender.[263]

## Economics [edit]

- Total costs in USA for hospital stays involving eating disorders rose from $165 million in 1999–2000 to $277 million in 2008–2009; this was a 68% increase. The mean cost per discharge of a person with an eating disorder rose by 29% over the decade, from $7,300 to $9,400.
- Over the decade, hospitalizations involving eating disorders increased among all age groups. The greatest increases occurred among those 45 to 65 years of age (an 88% increase), followed by hospitalizations among people younger than 12 years of age (a 72% increase).
- The majority of eating disorder inpatients were female. During 2008–2009, 88% of cases involved females, and 12% were males. The report also showed a 53% increase in hospitalizations for males with a principal diagnosis of an eating disorder, from 10% to 12% over the decade.[264]

## See also [edit]

- Weight phobia

## References [edit]


1. ^ *a b c d* "What are Eating Disorders?". *NIMH*. Retrieved 24 May 2015.
2. ^ *a b c d e* American Psychiatry Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington: American Psychiatric Publishing. pp. 329–354. ISBN 0-89042-555-8.
3. ^ *a b c* Rikani, AA; Choudhry, Z; Choudhry, AM; Ikram, H; Asghar, MW; Kajal, D; Waheed, A; Mobassarah, NJ (October 2013). "A critique of the literature on etiology of eating disorders.". *Annals of Neurosciences*. **20** (4): 157–61. doi:10.5214/ans.0972.7531.200409. PMC 4117136. PMID 25206042.
4. ^ Arcelus, J; Witcomb, GL; Mitchell, A (March 2014). "Prevalence of eating disorders amongst dancers: a systemic review and meta-analysis.". *European eating disorders review : the journal of the Eating Disorders Association*. **22** (2): 92–101. doi:10.1002/erv.2271. PMID 24277724.
5. ^ Chen, L; Murad, MH; Paras, ML; Colbenson, KM; Sattler, AL; Goranson, EN; Elamin, MB; Seime, RJ; Shinozaki, G; Prokop, LJ; Zirakzadeh, A (July 2010). "Sexual Abuse and Lifetime Diagnosis of Psychiatric Disorders: Systematic Review and Meta-analysis". *Mayo Clinic Proceedings*. **85** (7): 618–629. doi:10.4065/mcp.2009.0583. PMID 20458101.
6. ^ *a b* Smink, FR; van Hoeken, D; Hoek, HW (November 2013). "Epidemiology, course, and



"Gastrointestinal hormones regulating appetite". *Philosophical Transactions of the Royal Society B*. **361** (1471): 1187–209. doi:10.1098/rstb.2006.1856. PMC 1642697. PMID 16815798.
136. ^ Gendall, KA; Kaye, WH; Altemus, M; McConaha, CW; La Via, MC (1999). "Leptin, neuropeptide Y, and peptide YY in long-term recovered eating disorder patients". *Biological Psychiatry*. **46** (2): 292–9. doi:10.1016/S0006-3223(98)00292-3. PMID 10418705.
137. ^ Wilhelm, J; Müller, E; De Zwaan, M; Fischer, J; Hillemacher, T; Kornhuber, J; Bleich, S; Frieling, H (2010). "Elevation of homocysteine levels is only partially reversed after therapy in females with eating disorders". *Journal of neural transmission (Vienna, Austria : 1996)*. **117** (4): 521–7. doi:10.1007/s00702-010-0379-6. PMID 20191295.
138. ^ Jimerson, DC; Lesem, MD; Kaye, WH; Hegg, AP; Brewerton, TD (1990). "Eating disorders and depression: is there a serotonin connection?". *Biological Psychiatry*. **28** (5): 443–54. doi:10.1016/0006-3223(90)90412-U. PMID 2207221.
139. ^ Leibowitz, SF (1990). "The role of serotonin in eating disorders". *Drugs*. 39 Suppl 3: 33–48. doi:10.2165/00003495-199000393-00005. PMID 2197074.

outcome of eating disorders.". *Current opinion in psychiatry*. **26** (6): 543–8. doi:10.1097/yco.0b013e328365a24f. PMID 24060914.
7. ^ Pike, KM; Hoek, HW; Dunne, PE (November 2014). "Cultural trends and eating disorders.". *Current opinion in psychiatry*. **27** (6): 436–42. doi:10.1097/yco.0000000000000100. PMID 25211499.
8. ^ American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5 ed.). Washington, D.C.: American Psychiatric Publishing. ISBN 978-0-89042-555-8.
9. ^ "Anorexia Nervosa". *Nationaleatingdisorders.org*. Retrieved 2013-02-13.
10. ^ Nolen-Hoeksma (2014). *Abnormal Psychology* (6th ed.). US: McGraw-Hill. p. 339. ISBN 1-308-21150-3.
11. ^ Yale, Susan Nolen-Hoeksema, (2014). *Abnormal psychology* (6th ed.). New York, NY: McGraw Hill Education. pp. 340–341. ISBN 978-0-07-803538-8.
12. ^ "Eating Disorders". American Psychiatric Association. Retrieved 4 December 2014.
13. ^ "NAMI National Alliance on Mental Illness". Retrieved 4 December 2014.
14. ^ "CD 10 Codes For Psychiatry". Priory Lodge Education Ltd. 2011.
15. ^ Thompson, S.B.N. "Eating disorders: a guide for health professionals." London: Chapman & Hall 1993."
16. ^ Neumaker, K.J. (2000). "Morality rates and causes of death". *European Eating Disorders Review*. **8** (2): 181–187. doi:10.1002/(SICI)1099-0968(200003)8:2<181::AID-ERV336>3.0.CO;2-#.
17. ^ Psychology Second Edition 2009, chap. 8 Eating Disorders by Schacter, Daniel L.
18. ^ *a b* "Archived copy" (PDF). Archived from the original (PDF) on 2015-05-01. Retrieved 2015-04-09.
19. ^ "Binge Eating Disorder".
20. ^ Striegel-Moore, RH; Franko, DL (2008). "Should binge eating disorder be included in the DSM-V? A critical review of the state of the evidence". *Annual Review of Clinical Psychology*. **4**: 305–24. doi:10.1146/annurev.clinpsy.4.022007.141149. PMID 18370619.
21. ^ Teaching Students with Mental Health Disorders: Resources for Teachers. Victoria: British Columbia Ministry of Education, Special Programs Branch, 2001. Print.
22. ^ Tarren-Sweeney, M; Hazell, P (2006). "Mental health of children in foster and kinship care in New South Wales, Australia". *Journal of paediatrics and child health*. **42** (3): 89–97. doi:10.1111/j.1440-1754.2006.00804.x. PMID 16509906.
23. ^ Too Much #Fitspo: When Healthy Eating Becomes an Eating Disorder, Glammonitor.com, 2015-4-29
24. ^ Barry, E; Piazza-Gardner, K (2012). "Drunkorexia: Understanding the Co-occurrence of Alcohol Consumption and Eating/Exercise Weight
140. ^ Blundell, JE; Lawton, CL; Halford, JC (1995). "Serotonin, eating behavior, and fat intake". *Obesity Research*. 3 Suppl 4: 471S–476S. doi:10.1002/j.1550-8528.1995.tb00214.x. PMID 8697045.
141. ^ Kaye, WH (1997). "Anorexia nervosa, obsessional behavior, and serotonin". *Psychopharmacology bulletin*. **33** (3): 335–44. PMID 9550876.
142. ^ Bailer, UF; Price, JC; Meltzer, CC; Mathis, CA; Frank, GK; Weissfeld, L; McConaha, CW; Henry, SE; Brooks-Achenbach, S; Barbarich, NC; Kaye, WH (2004). "Altered 5-HT(2A) receptor binding after recovery from bulimia-type anorexia nervosa: relationships to harm avoidance and drive for thinness". *Neuropsychopharmacology*. **29** (6): 1143–55. doi:10.1038/sj.npp.1300430. PMID 15054474.
143. ^ Hainer, V; Kabrnova, K; Aldhoon, B; Kunesova, M; Wagenknecht, M (2006). "Serotonin and norepinephrine reuptake inhibition and eating behavior". *Annals of the New York Academy of Sciences*. **1083**: 252–69. Bibcode:2006NYASA1083..252H. doi:10.1196/annals.1367.017. PMID 17148744.
144. ^ George, DT; Kaye, WH; Goldstein, DS; Brewerton, TD; Jimerson, DC (July 1990). "Altered norepinephrine regulation in bulimia: effects of pharmacological challenge with isoproterenol". *Psychiatry Res*. **33** (1): 1–10. doi:10.1016/0165-1781(90)90143-S. PMID 2171006.
145. ^ Wang, GJ; Volkow, ND; Logan, J; Pappas, NR; Wong, CT; Zhu, W; Netusil, N; Fowler, JS (2001). "Brain dopamine and obesity". *Lancet*. **357** (9253): 354–7. doi:10.1016/S0140-6736(00)03643-6. PMID 11210998.
146. ^ Zhulenko, VN; Georgieva, GN; Smirnova, LA (1975). "Mercury content in the organs and tissues of slaughter animals". *Veterinariia* (4): 96–8. PMID 1216579.
147. ^ *a b c d e* Carlson, Neil (2013). "Ingestive Behavior". *Physiology of Behavior*. University of Massachusetts, Amherst: Pearson. pp. 428–432. ISBN 0-205-23939-0.
148. ^ Frederich, R; Hu, S; Raymond, N; Pomeroy, C (2002). "Leptin in anorexia nervosa and bulimia nervosa: importance of assay technique and method of interpretation". *The Journal of laboratory and clinical medicine*. **139** (2): 72–9. doi:10.1067/mlc.2002.121014. PMID 11919545.
149. ^ Ferron, F; Considine, R; Peino, R; Lado; I (1997). "Serum leptin concentrations in patients with anorexia nervosa, bulimia nervosa, and non-specific eating disorders correlate with the body mass index but are independent of the respective disease". *Clinical Endocrinology*. **46** (3): 289–293. doi:10.1046/j.1365-2265.1997.1260938.x. PMID 9156037.
150. ^ Fetissov, SO; Harro, J; Jaanisk, M; Järv, A; Podar, I; Nilsson, I; Sakthivel, P; Lefvert, AK; et al. (2005).

Management Behaviors". *Journal of American College Health*. **60** (3): 236–243. doi:10.1080/07448481.2011.587487. PMID 22420701.
25. ^ Mathieu, J (2009). "What Is Pregorexia?". *Journal of the American Dietetic Association*. **109** (6): 976–979. doi:10.1016/j.jada.2009.04.021. PMID 19465173.
26. ^ Regard, M; Landis, T (1997). " "Gourmand syndrome": Eating passion associated with right anterior lesions". *Neurology*. **48** (5): 1185–90. doi:10.1212/wnl.48.5.1185. PMID 9153440.
27. ^ Strumia, R (2005). "Dermatologic signs in patients with eating disorders". *American journal of clinical dermatology*. **6** (3): 165–73. doi:10.2165/00128071-200506030-00003. PMID 15943493.
28. ^ Joyce, JM; Warren, DL; Humphries, LL; Smith, AJ; Coon, JS (1990). "Osteoporosis in women with eating disorders: comparison of physical parameters, exercise, and menstrual status with SPA and DPA evaluation". *Journal of Nuclear Medicine*. **31** (3): 325–31. PMID 2308003.
29. ^ Drevelengas, A; Chourmouzi, D; Pitsavas, G; Charitandi, A; Boulogianni, G (2001). "Reversible brain atrophy and subcortical high signal on MRI in a patient with anorexia nervosa". *Neuroradiology*. **43** (10): 838–40. doi:10.1007/s002340100589. PMID 11688699.
30. ^ Addolorato, G; Taranto, C; Capristo, E; Gasbarrini, G (1998). "A case of marked cerebellar atrophy in a woman with anorexia nervosa and cerebral atrophy and a review of the literature". *The International Journal of Eating Disorders*. **24** (4): 443–7. doi:10.1002/(SICI)1098-108X(199812)24:4<443::AID-EAT13>3.0.CO;2-4. PMID 9813771.
31. ^ Jagielska, G; Tomaszewicz-Libudzic, EC; Brzozowska, A (2007). "Pellagra: a rare complication of anorexia nervosa". *European child & adolescent psychiatry*. **16** (7): 417–20. doi:10.1007/s00787-007-0613-4. PMID 17712518.
32. ^ Pompili, M; Mancinelli, I; Girardi, P; Accorrà, D; Ruberto, A; Tatarelli, R (2003). "Suicide and attempted suicide in anorexia nervosa and bulimia nervosa". *Annali dell'Istituto Superiore di Sanità*. **39** (2): 275–81. PMID 14587228.
33. ^ Franko, DL; Keel, PK; Dorer, DJ; Blais, MA; Delinsky, SS (2004). "What predicts suicide attempts in women with eating disorders?". *Psychological Medicine*. **34** (5): 843–53. doi:10.1017/S0033291703001545. PMID 15500305.
34. ^ Fedorowicz, VJ; Falissard, B; Foulon, C; Dardennes, R; Divac, SM (2007). "Factors associated with suicidal behaviors in a large French sample of inpatients with eating disorders". *The International Journal of Eating Disorders*. **40** (7): 589–95. doi:10.1002/eat.20415. PMID 17607699.
35. ^ *a b* Treasure, J; Claudino, AM; Zucker, N (2010). "Autoantibodies against neuropeptides are associated with psychological traits in eating disorders". *Proceedings of the National Academy of Sciences of the United States of America*. **102** (41): 14865–70. Bibcode:2005PNAS..10214865F. doi:10.1073/pnas.0507204102. PMC 1253594. PMID 16195379.
151. ^ Sinno, MH; Do Rego, JC; Coëffier, M; Bole-Feysot, C; Ducrotté, P; Gilbert, D; Tron, F; Costentin, J; Hökfelt, T; Déchelotte, P; Fetissov, SO (2009). "Regulation of feeding and anxiety by alpha-MSH reactive autoantibodies". *Psychoneuroendocrinology*. **34** (1): 140–9. doi:10.1016/j.psyneuen.2008.08.021. PMID 18842346.
152. ^ "Bacterial ClpB heat-shock protein, an antigen-mimetic of the anorexigenic peptide α-MSH, at the origin of eating disorders". *Translational Psychiatry*. **4**: e458. 2014. doi:10.1038/tp.2014.98.
153. ^ Sokol, MS (2000). "Infection-triggered anorexia nervosa in children: clinical description of four cases". *Journal of child and adolescent psychopharmacology*. **10** (2): 133–45. doi:10.1089/cap.2000.10.133. PMID 10933123.
154. ^ Uher, R; Treasure, J (2005). "Brain lesions and eating disorders". *Journal of neurology, neurosurgery, and psychiatry*. **76** (6): 852–7. doi:10.1136/jnnp.2004.048819. PMC 1739667. PMID 15897510.
155. ^ Houy, E; Debono, B; Dechelotte, P; Thibaut, F (2007). "Anorexia nervosa associated with right frontal brain lesion". *The International Journal of Eating Disorders*. **40** (8): 758–61. doi:10.1002/eat.20439. PMID 17683096.
156. ^ *a b* Trummer, M; Eustacchio, S; Unger, F; Tillich, M; Flaschka, G (2002). "Right hemispheric frontal lesions as a cause for anorexia nervosa report of three cases". *Acta neurochirurgica*. **144** (8): 797–801. doi:10.1007/s00701-002-0934-5. PMID 12181689.
157. ^ Winston, AP; Barnard, D; D'souza, G; Shad, A; Sherlala, K (2006). "Pineal germinoma presenting as anorexia nervosa: Case report and review of the literature". *The International Journal of Eating Disorders*. **39** (7): 606–8. doi:10.1002/eat.20322. PMID 17041920.
158. ^ Chipkevitch, E; Fernandes, AC (1993). "Hypothalamic tumor associated with atypical forms of anorexia nervosa and diencephalic syndrome". *Arquivos de neuro-psiquiatria*. **51** (2): 270–4. doi:10.1590/S0004-282X1993000200022. PMID 8274094.
159. ^ Rohrer, TR; Fahlbusch, R; Buchfelder, M; Dörr, HG (2006). "Craniopharyngioma in a female adolescent presenting with symptoms of anorexia nervosa". *Klinische Pädiatrie*. **218** (2): 67–71. doi:10.1055/s-2006-921506. PMID 16506105.
160. ^ Chipkevitch, E (1994). "Brain tumors and anorexia nervosa syndrome". *Brain & development*. **16** (3):

"Eating disorders". *The Lancet*. **375** (9714): 583–93. doi:10.1016/S0140-6736(09)61748-7. PMID 19931176.

36. ^ "Unexplained Hoarseness: One Clue to an Eating Disorder". *Eating Disorders Review*. **24** (1). 2013.[*author missing*]
37. ^ Hirschberg, AL; Naessén, S; Stridsberg, M; Byström, B; Holtet, J (2004). "Impaired cholecystokinin secretion and disturbed appetite regulation in women with polycystic ovary syndrome". *Gynecological Endocrinology*. **19** (2): 79–87. doi:10.1080/09513590400002300. PMID 15624269.
38. ^ Naessén, S; Carlström, K; Garoff, L; Glant, R; Hirschberg, AL (2006). "Polycystic ovary syndrome in bulimic women—an evaluation based on the new diagnostic criteria". *Gynecological Endocrinology*. **22** (7): 388–94. doi:10.1080/09513590600847421. PMID 16864149.
39. ^ McCluskey, S; Evans, C; Lacey, JH; Pearce, JM; Jacobs, H (1991). "Polycystic ovary syndrome and bulimia". *Fertility and Sterility*. **55** (2): 287–91. PMID 1991526.
40. ^ Jahanfar, S; Eden, JA; Nguyent, TV (1995). "Bulimia nervosa and polycystic ovary syndrome". *Gynecological Endocrinology*. **9** (2): 113–7. doi:10.3109/09513599509160199. PMID 7502686.
41. ^ Morgan, JF; McCluskey, SE; Brunton, JN; Hubert Lacey, J (2002). "Polycystic ovarian morphology and bulimia nervosa: a 9-year follow-up study". *Fertility and Sterility*. **77** (5): 928–31. doi:10.1016/S0015-0282(02)03063-7. PMID 12009345.
42. ^ Lujan, ME; Chizen, DR; Pierson, RA (2008). "Diagnostic Criteria for Polycystic Ovary Syndrome: Pitfalls and Controversies". *Journal of obstetrics and gynaecology Canada : JOGC*. **30** (8): 671–9. PMC 2893212. PMID 18786289.
43. ^ Gailey, J (2009). "Starving is the most fun a girl can have: The Pro-Ana subculture as edgework". *Critical Criminology*. **17** (2): 93–108. doi:10.1007/s10612-009-9074-z.
44. ^ Borzekowski, D; Schenk, S; Wilson, J; Peebles, R (2010). "E-Ana and e-mia: A content analysis of pro-eating disorder web sites". *American Journal of Public Health*. **100** (8): 1526–1534. doi:10.2105/AJPH.2009.172700. PMC 2901299. PMID 20558807.
45. ^ Wolf, M; Theis, F; Kordy, H (2013). "Language Use in Eating Disorder Blogs: Psychological Implications of Social Online Activity". *Journal of Language and Social Psychology*. **32** (2): 212–226. doi:10.1177/0261927x12474278.
46. ^ [a] [b] Ruffolo, J; Phillips, K; Menard, W; Fay, C; Weisberg, R (2006). "Comorbidity of Body Dysmorphic Disorder and Eating Disorders: Severity of Psychopathology and Body Image Disturbance". *The International Journal of Eating Disorders*. **39** (1): 11–19. doi:10.1002/eat.20219.

175–9. doi:10.1016/0387-7604(94)90064-7. PMID 7943600.

161. ^ Lin, L; Liao, SC; Lee, YJ; Tseng, MC; Lee, MB (2003). "Brain tumor presenting as anorexia nervosa in a 19-year-old man". *Journal of the Formosan Medical Association, Taiwan yi zhi*. **102** (10): 737–40. PMID 14691602.
162. ^ Conrad, R; Wegener, I; Geiser, F; Imbierowicz, K; Liedtke, R (2008). "Nature against nurture: calcification in the right thalamus in a young man with anorexia nervosa and obsessive-compulsive personality disorder". *CNS spectrums*. **13** (10): 906–10. PMID 18955946.
163. ^ Burke, CJ; Tannenberg, AE; Payton, DJ (1997). "Ischaemic cerebral injury, intrauterine growth retardation, and placental infarction". *Developmental medicine and child neurology*. **39** (11): 726–30. doi:10.1111/j.1469-8749.1997.tb07373.x. PMID 9393885.
164. ^ Cnattingius, S; Hultman, CM; Dahl, M; Sparén, P (1999). "Very preterm birth, birth trauma, and the risk of anorexia nervosa among girls". *Archives of General Psychiatry*. **56** (7): 634–8. doi:10.1001/archpsyc.56.7.634. PMID 10401509.
165. ^ Favaro, A; Tenconi, E; Santonastaso, P (2006). "Perinatal factors and the risk of developing anorexia nervosa and bulimia nervosa". *Archives of General Psychiatry*. **63** (1): 82–8. doi:10.1001/archpsyc.63.1.82. PMID 16389201.
166. ^ Favaro, A; Tenconi, E; Santonastaso, P (2008). "The relationship between obstetric complications and temperament in eating disorders: a mediation hypothesis". *Psychosomatic Medicine*. **70** (3): 372–7. doi:10.1097/PSY.0b013e318164604e. PMID 18256341.
167. ^ Decker, MJ; Hue, GE; Caudle, WM; Miller, GW (2003). "Episodic neonatal hypoxia evokes executive dysfunction and regionally specific alterations in markers of dopamine signaling". *Neuroscience*. **117** (2): 417–25. doi:10.1016/S0306-4522(02)00805-9. PMID 12614682.
168. ^ Decker, MJ; Rye, DB (2002). "Neonatal intermittent hypoxia impairs dopamine signaling and executive functioning". *Sleep & breathing*. **6** (4): 205–10. doi:10.1007/s11325-002-0205-y. PMID 12524574.
169. ^ Scher, MS (2003). "Fetal and neonatal neurologic case histories: assessment of brain disorders in the context of fetal-maternal-placental disease. Part 1: Fetal neurologic consultations in the context of antepartum events and prenatal brain development". *Journal of child neurology*. **18** (2): 85–92. doi:10.1177/08830738030180020901. PMID 12693773.
170. ^ Scher, MS; Wiznitzer, M; Bangert, BA (2002). "Cerebral infarctions in the fetus and neonate: maternal-placental-fetal considerations". *Clinics in perinatology*. **29** (4): 693–724, vi–vii. doi:10.1016/S0095-5108(02)00055-6. PMID 12516742.

PMID 16254870.
47. ^ a b Grant, JE; Kim, SW; Eckert, ED (November 2002). "Body dysmorphic disorder in patients with anorexia nervosa: prevalence, clinical features, and delusionality of body image.". *The International Journal of Eating Disorders*. **32** (3): 291–300. doi:10.1002/eat.10091. PMID 12210643.
48. ^ a b c Bulick, C; Hebebrand, J; Keski-Rahkonen, A; Klump, K; Reichborn, T; Mazzeo, SE; Wade, TD (2007). "Genetic Epidemiology, Endophenotypes, and Eating Disorder Classification". *The International Journal of Eating Disorders*. **40**: S52–S60. doi:10.1002/eat.20398. PMID 17573683.
49. ^ a b DeAngelis, T (2002). "A genetic link to anorexia". *American Psychological Association*. **33** (3): 34.
50. ^ a b Klump, KL; Kaye, WH; Strober, M (2001). "The evolving genetic foundations of eating disorders". *The Psychiatric clinics of North America*. **24** (2): 215–25. doi:10.1016/S0193-953X(05)70218-5. PMID 11416922.
51. ^ Mazzeo, SE; Bulik, CM (2009). "Environmental and genetic risk factors for eating disorders: What the clinician needs to know". *Child and adolescent psychiatric clinics of North America*. **18** (1): 67–82. doi:10.1016/j.chc.2008.07.003. PMC 2719561. PMID 19014858.
52. ^ a b Patel, P; Wheatcroft, R; Park, R; Stein, A (2002). "The Children of Mothers With Eating Disorders". *Clinical Child and Family Psychology Review*. **5** (1): 1–19. doi:10.1023/A:1014524207660. PMID 11993543.
53. ^ a b Frieling, H; Römer, KD; Scholz, S; Mittelbach, F; Wilhelm, J; De Zwaan, M; Jacoby, GE; Kornhuber, J; Hillemacher, T; Bleich, S (2010). "Epigenetic dysregulation of dopaminergic genes in eating disorders". *The International Journal of Eating Disorders*. **43** (7): 577–83. doi:10.1002/eat.20745. PMID 19728374.
54. ^ Frieling, Helge; Römer, Konstanze D.; Scholz, Sarah; Mittelbach, Franziska; Wilhelm, Julia; De Zwaan, Martina; Jacoby, Georg E.; Kornhuber, Johannes; Hillemacher, Thomas (2010-11-01). "Epigenetic dysregulation of dopaminergic genes in eating disorders". *International Journal of Eating Disorders*. **43** (7): 577–583. doi:10.1002/eat.20745. ISSN 1098-108X. PMID 19728374.
55. ^ Frieling, H; Bleich, S; Otten, J; Römer, KD; Kornhuber, J; et al. (2008). "Epigenetic downregulation of atrial natriuretic peptide but not vasopressin mRNA expression in females with eating disorders is related to impulsivity". *Neuropsychopharmacology*. **33** (11): 2605–9. doi:10.1038/sj.npp.1301662. PMID 18172431.
56. ^ Campbell, Iain C.; Mill, Jonathan; Uher, Rudolf; Schmidt, Ulrike (2011-01-01). "Eating disorders, gene–environment interactions and epigenetics".
171. ^ Burke, CJ; Tannenberg, AE (1995). "Prenatal brain damage and placental infarction- an autopsy study". *Developmental medicine and child neurology*. **37** (6): 555–62. doi:10.1111/j.1469-8749.1995.tb12042.x. PMID 7789664.
172. ^ Squier, M; Keeling, JW (1991). "The incidence of prenatal brain injury". *Neuropathology and applied neurobiology*. **17** (1): 29–38. doi:10.1111/j.1365-2990.1991.tb00691.x. PMID 2057048.
173. ^ Al Mamun, A; Lawlor, DA; Alati, R; O'Callaghan, MJ (2006). "Does maternal smoking during pregnancy have a direct effect on future offspring obesity? Evidence from a prospective birth cohort study". *American Journal of Epidemiology*. **164** (4): 317–25. doi:10.1093/aje/kwj209. PMID 16775040.
174. ^ Keys, A; Brozek, J; Henschel, A; Mickelsen, O; Taylor, H (1950). *The Biology of Human Starvation*. University of Minnesota Press.
175. ^ Pritts, SD; Susman, J (2003). "Diagnosis of eating disorders in primary care". *American family physician*. **67** (2): 297–304. PMID 12562151.
176. ^ Gelder, Mayou, Geddes (2005). Psychiatry: Page 161. New York, NY; Oxford University Press Inc.
177. ^ O'Brien, A; Hugo, P; Stapleton, S; Lask, B (2001). "'"Anorexia saved my life": coincidental anorexia nervosa and cerebral meningioma". *The International Journal of Eating Disorders*. **30** (3): 346–9. doi:10.1002/eat.1095. PMID 11746295.
178. ^ Garfinkel, PE; Newman, A (2001). "The eating attitudes test: twenty-five years later". *Eating and weight disorders : EWD*. **6** (1): 1–24. doi:10.1007/bf03339747. PMID 11300541.
179. ^ Rueda, GE; Díaz, LA; Campo, A; Barros, JA; Avila, GC (2005). "Validation of the SCOFF questionnaire for screening of eating disorders in university women". *Biomedica : revista del Instituto Nacional de Salud*. **25** (2): 196–202. PMID 16022374.
180. ^ Probst, M; Pieters, G; Vanderlinden, J (2008). "Evaluation of body experience questionnaires in eating disorders in female patients (AN/BN) and nonclinical participants". *The International Journal of Eating Disorders*. **41** (7): 657–65. doi:10.1002/eat.20531. PMID 18446834.
181. ^ Ben-Tovim, DI; Walker, MK (1992). "A quantitative study of body-related attitudes in patients with anorexia and bulimia nervosa". *Psychological Medicine*. **22** (4): 961–9. doi:10.1017/S0033291700038538. PMID 1488491.
182. ^ Olson, MS; Williford, HN; Richards, LA; Brown, JA; Pugh, S (1996). "Self-reports on the Eating Disorder Inventory by female aerobic instructors". *Perceptual and motor skills*. **82** (3 Pt 1): 1051–8. doi:10.2466/pms.1996.82.3.1051. PMID 8774050.
183. ^ Wilfley, DE; Schwartz, MB; Spurrell, EB; Fairburn, CG (2000). "Using the eating disorder examination to identify the specific psychopathology of binge eating disorder". *The International Journal of Eating*

*Neuroscience & Biobehavioral Reviews*. **35** (3): 784–793. doi:10.1016/j.neubiorev.2010.09.012. PMID 20888360.
57. ^ Westen, D; Harnden-Fischer, J (2001). "Personality profiles in eating disorders: rethinking the distinction between axis I and axis II". *The American Journal of Psychiatry*. **158** (4): 547–62. doi:10.1176/appi.ajp.158.4.547. PMID 11282688.
58. ^ Rosenvinge, JH; Martinussen, M; Ostensen, E (2000). "The comorbidity of eating disorders and personality disorders: a meta-analytic review of studies published between 1983 and 1998". *Eating and weight disorders*. **5** (2): 52–61. doi:10.1007/bf03327480. PMID 10941603.
59. ^ Kaye, WH; Bulik, CM; Thornton, L; Barbarich, N; Masters, K (2004). "Comorbidity of anxiety disorders with anorexia and bulimia nervosa". *The American Journal of Psychiatry*. **161** (12): 2215–21. doi:10.1176/appi.ajp.161.12.2215. PMID 15569892.
60. ^ Thornton, C; Russell, J (1997). "Obsessive compulsive comorbidity in the dieting disorders". *The International Journal of Eating Disorders*. **21** (1): 83–7. doi:10.1002/(SICI)1098-108X(199701)21:1<83::AID-EAT10>3.0.CO;2-P. PMID 8986521.
61. ^ Vitousek, K; Manke, F (1994). "Personality variables and disorders in anorexia nervosa and bulimia nervosa". *Journal of Abnormal Psychology*. **103** (1): 137–47. doi:10.1037/0021-843X.103.1.137. PMID 8040475.
62. ^ Braun, DL; Sunday, SR; Halmi, KA (1994). "Psychiatric comorbidity in patients with eating disorders". *Psychological Medicine*. **24** (4): 859–67. doi:10.1017/S0033291700028956. PMID 7892354.
63. ^ Spindler, A; Milos, G (2007). "Links between eating disorder symptom severity and psychiatric comorbidity". *Eating behaviors*. **8** (3): 364–73. doi:10.1016/j.eatbeh.2006.11.012. PMID 17606234.
64. ^ Collier, R (2010). "DSM revision surrounded by controversy". *Canadian Medical Association Journal*. **182** (1): 16–7. doi:10.1503/cmaj.109-3108. PMC 2802599. PMID 19920166.
65. ^ Kutchins, H; Kirk, SA (1989). "DSM-III-R: the conflict over new psychiatric diagnoses". *Health & social work*. **14** (2): 91–101. PMID 2714710.
66. ^ Busko, Marlene. "DSM-IV Diagnostic Criteria for Eating Disorders May Be Too Stringent". *Medscape*.
67. ^ Murdoch, CJ (10 September 2009). "The Politics of Disease Definition: A Summer of DSM-V Controversy in Review. Stanford Center for Law and the Biosciences".
68. ^ "Psychiatry manual's secrecy criticized". *Los Angeles Times*. 29 December 2008.
69. ^ Casper, RC (1998). "Depression and eating *Disorders*. **27** (3): 259–69. doi:10.1002/(SICI)1098-108X(200004)27:3<259::AID-EAT2>3.0.CO;2-G. PMID 10694711.
184. ^ Ehle, G; Wahlstab, A; Ott, J (1982). "Psychodiagnostic findings in anorexia nervosa and post-pill amenorrhea". *Psychiatrie, Neurologie, und medizinische Psychologie*. **34** (11): 647–56. PMID 7170321.
185. ^ Kennedy, SH; Kaplan, AS; Garfinkel, PE; Rockert, W (1994). "Depression in anorexia nervosa and bulimia nervosa: discriminating depressive symptoms and episodes". *Journal of psychosomatic research*. **38** (7): 773–82. doi:10.1016/0022-3999(94)90030-2. PMID 7877132.
186. ^ Camargo, EE (2001). "Brain SPECT in neurology and psychiatry". *Journal of Nuclear Medicine*. **42** (4): 611–23. PMID 11337551.
187. ^ Abebe, D; Lein, L; von Soest (2012). "The development of bulimic symptoms from adolescence to young adulthood in females and males: A population based longitudinal cohort study". *International Journal of Eating Disorders*. **45** (6): 737–745. doi:10.1002/eat.20950. PMID 22886952.
188. ^ Fallon, BA; Nields, JA (1994). "Lyme disease: a neuropsychiatric illness". *The American Journal of Psychiatry*. **151** (11): 1571–83. doi:10.1176/ajp.151.11.1571. PMID 7943444.
189. ^ Pachner, AR (1988). "Borrelia burgdorferi in the nervous system: the new "great imitator" ". *Annals of the New York Academy of Sciences*. **539**: 56–64. Bibcode:1988NYASA.539...56P. doi:10.1111/j.1749-6632.1988.tb31838.x. PMID 3190104.
190. ^ Volta U, Caio G, De Giorgio R, Henriksen C, Skodje G, Lundin KE (Jun 2015). "Non-celiac gluten sensitivity: a work-in-progress entity in the spectrum of wheat-related disorders". *Best Pract Res Clin Gastroenterol* (Review). **29** (3): 477–91. doi:10.1016/j.bpg.2015.04.006. PMID 26060112. "Among psychiatric disorders, a minority (6%) of patients with NCGS showed a previous clinical history of eating behavior abnormalities *(NCGS = non-celiac gluten sensitivity)*"
191. ^ Duggan JM (May 17, 2004). "Coeliac disease: the great imitator" (PDF). *Med J Aust* (Review). **180** (10): 524–6. PMID 15139831.
192. ^ Zingone F, Swift GL, Card TR, Sanders DS, Ludvigsson JF, Bai JC (Apr 2015). "Psychological morbidity of celiac disease: A review of the literature". *United European Gastroenterol J* (Review). **3** (2): 136–45. doi:10.1177/2050640614560786. PMC 4406898. PMID 25922673.
193. ^ Jackson JR, Eaton WW, Cascella NG, Fasano A, Kelly DL (Mar 2012). "Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity". *Psychiatr Q*. **83** (1): 91–102. doi:10.1007/s11126-011-9186-y. PMC 3641836.

disorders". *Depression and Anxiety*. **8** (Suppl 1): 96–104. doi:10.1002/(SICI)1520-6394(1998)8:1+<96::AID-DA15>3.0.CO;2-4. PMID 9809221.
70. ^ Serpell, L; Livingstone, A; Neiderman, M; Lask, B (2002). "Anorexia nervosa: obsessive-compulsive disorder, obsessive-compulsive personality disorder, or neither?". *Clinical Psychology Review*. **22** (5): 647–69. doi:10.1016/S0272-7358(01)00112-X. PMID 12113200.
71. ^ Bulik, CM; Klump, KL; Thornton, L; Kaplan, AS; Devlin, B (2004). "Alcohol use disorder comorbidity in eating disorders: a multicenter study". *The Journal of Clinical Psychiatry*. **65** (7): 1000–6. doi:10.4088/JCP.v65n0718. PMID 15291691.
72. ^ Larsson, JO; Hellzén, M (2004). "Patterns of personality disorders in women with chronic eating disorders". *Eating and weight disorders : EWD*. **9** (3): 200–5. doi:10.1007/bf03325067. PMID 15656014.
73. ^ Swinbourne, JM; Touyz, SW (2007). "The co-morbidity of eating disorders and anxiety disorders: a review". *European eating disorders review : the journal of the Eating Disorders Association*. **15** (4): 253–74. doi:10.1002/erv.784. PMID 17676696.
74. ^ Ronningstam, E (1996). "Pathological narcissism and narcissistic personality disorder in Axis I disorders". *Harvard Review of Psychiatry*. **3** (6): 326–40. doi:10.3109/10673229609017201. PMID 9384963.
75. ^ Anderluh, MB; Tchanturia, K; Rabe-Hesketh, S; Treasure, J (2003). "Childhood obsessive-compulsive personality traits in adult women with eating disorders: defining a broader eating disorder phenotype". *The American Journal of Psychiatry*. **160** (2): 242–7. doi:10.1176/appi.ajp.160.2.242. PMID 12562569.
76. ^ Pinto, A; Mancebo, MC; Eisen, JL; Pagano, ME; Rasmussen, SA (2006). "The Brown Longitudinal Obsessive Compulsive Study: clinical features and symptoms of the sample at intake". *The Journal of Clinical Psychiatry*. **67** (5): 703–11. doi:10.4088/JCP.v67n0503. PMC 3272757. PMID 16841619.
77. ^ Lucka, I; Cebella, A (2004). "Characteristics of the forming personality in children suffering from anorexia nervosa". *Psychiatria polska*. **38** (6): 1011–8. PMID 15779665.
78. ^ Biederman, J; Ball, SW; Monuteaux, MC; Surman, CB; Johnson, JL; Zeitlin, S (2007). "Are girls with ADHD at risk for eating disorders? Results from a controlled, five-year prospective study". *Journal of developmental and behavioral pediatrics : JDBP*. **28** (4): 302–7. doi:10.1097/DBP.0b013e3180327917. PMID 17700082.
79. ^ Dukarm, CP (May 2005). "Bulimia nervosa and attention deficit hyperactivity disorder: a possible role for stimulant medication". *Journal of Women's Health*. **14** (4): 345–50. doi:10.1089/jwh.2005.14.345. PMID 15916509. PMID 21877216.
194. ^ Adams, R; Hinkebein, MK; McQuillen, M; Sutherland, S (1998). "Prompt differentiation of Addison's disease from anorexia nervosa during weight loss and vomiting". *Southern Medical Journal*. **91** (2): 208–11. doi:10.1097/00007611-199802000-00017. PMID 9496878.
195. ^ Siew, LC; Huang, C; Fleming, J (2010). "Gastric adenocarcinoma mistakenly diagnosed as an eating disorder: case report". *The International Journal of Eating Disorders*. **43** (3): 286–8. doi:10.1002/eat.20678. PMID 19365820.
196. ^ Mannucci, E; Ricca, V; Filetti, S; Boldrini, M; Rotella, CM (2003). "Eating behavior and thyroid disease in female obese patients". *Eating behaviors*. **4** (2): 173–9. doi:10.1016/S1471-0153(03)00012-6. PMID 15000980.
197. ^ Byerley, B; Black, DW; Grosser, BI (1983). "Anorexia nervosa with hyperthyroidism: case report". *The Journal of Clinical Psychiatry*. **44** (8): 308–9. PMID 6874653.
198. ^ Krahn, D (1990). "Thyrotoxicosis and bulimia nervosa". *Psychosomatics*. **31** (2): 222–4. doi:10.1016/S0033-3182(90)72201-3. PMID 2330406.
199. ^ Tiller, J; MacRae, A; Schmidt, U; Bloom, S; Treasure, J (1994). "The prevalence of eating disorders in thyroid disease: a pilot study". *Journal of psychosomatic research*. **38** (6): 609–16. doi:10.1016/0022-3999(94)90058-2. PMID 7990069.
200. ^ Fonseca, V; Wakeling, A; Havard, CW (1990). "Hyperthyroidism and eating disorders". *BMJ (Clinical research ed.)*. **301** (6747): 322–3. doi:10.1136/bmj.301.6747.322. PMC 1663651. PMID 2393739.
201. ^ Birmingham, CL; Gritzner, S; Gutierrez, E (2006). "Hyperthyroidism in anorexia nervosa: case report and review of the literature". *The International Journal of Eating Disorders*. **39** (7): 619–20. doi:10.1002/eat.20308. PMID 16958126.
202. ^ Mattingly, D; Bhanji, S (April 1995). "Hypoglycaemia and anorexia nervosa". *J R Soc Med*. **88** (4): 191–195. PMC 1295161. PMID 7745563.
203. ^ Ozawa, Y; Koyano, H; Akama, T (1999). "Complete recovery from intractable bulimia nervosa by the surgical cure of primary hyperparathyroidism". *The International Journal of Eating Disorders*. **26** (1): 107–10. doi:10.1002/(SICI)1098-108X(199907)26:1<107::AID-EAT15>3.0.CO;2-U. PMID 10349592.
204. ^ Kar, N; Misra, B (2004). "Toxoplasma seropositivity and depression: a case report". *BMC Psychiatry*. **4**: 1. doi:10.1186/1471-244X-4-1. PMC 356918. PMID 15018628.
205. ^ Ritchie MA, Perdigao JA. Neurosyphilis: Considerations for a Psychiatrist. Louisiana State University School of Medicine Department of

80. ^ Mikami, AY; Hinshaw, SP; Arnold, LE; Hoza, B; Hechtman, L (2010). "Bulimia nervosa symptoms in the multimodal treatment study of children with ADHD". *The International Journal of Eating Disorders*. **43** (3): 248–59. doi:10.1002/eat.20692. PMID 19378318.
81. ^ Cortese, S; Bernardina, BD; Mouren, MC (2007). "Attention-deficit/hyperactivity disorder (ADHD) and binge eating". *Nutrition Reviews*. **65** (9): 404–11. doi:10.1111/j.1753-4887.2007.tb00318.x. PMID 17958207.
82. ^ Bruce, KR; Steiger, H; Koerner, NM; Israel, M; Young, SN (2004). "Bulimia nervosa with co-morbid avoidant personality disorder: behavioural characteristics and serotonergic function". *Psychological Medicine*. **34** (1): 113–24. doi:10.1017/S003329170300864X. PMID 14971632.
83. ^ Podar, I; Hannus, A; Allik, J (1999). "Personality and affectivity characteristics associated with eating disorders: a comparison of eating disordered, weight-preoccupied, and normal samples". *Journal of Personality Assessment*. **73** (1): 133–47. doi:10.1207/S15327752JPA730109. PMID 10497805.
84. ^ Skårderud, F and Fonagy, P "Eating Disorders" in Bateman, A and Fonagy, P (Eds) Handbook of mentalizing in Mental Health Practice. American Psychiatric Publishing, Washington DC, 2012. Pages 347-383
85. ^ Gardini, S; Cloninger, CR; Venneri, A (2009). "Individual differences in personality traits reflect structural variance in specific brain regions". *Brain Research Bulletin*. **79** (5): 265–70. doi:10.1016/j.brainresbull.2009.03.005. PMID 19480986.
86. ^ Marsh, AA; Finger, EC; Mitchell, DG; Reid, ME; Sims, C (2008). "Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders". *The American Journal of Psychiatry*. **165** (6): 712–20. doi:10.1176/appi.ajp.2007.07071145. PMID 18281412.
87. ^ Iidaka, T; Matsumoto, A; Ozaki, N; Suzuki, T; Iwata, N (2006). "Volume of left amygdala subregion predicted temperamental trait of harm avoidance in female young subjects. A voxel-based morphometry study". *Brain Research*. **1125** (1): 85–93. doi:10.1016/j.brainres.2006.09.015. PMID 17113049.
88. ^ Rubino, V; Blasi, G; Latorre, V; Fazio, L; D'errico, I (2007). "Activity in medial prefrontal cortex during cognitive evaluation of threatening stimuli as a function of personality style". *Brain Research Bulletin*. **74** (4): 250–7. doi:10.1016/j.brainresbull.2007.06.019. PMID 17720547.
89. ^ Spinella, M; Lyke, J (2004). "Executive personality traits and eating behavior". *The International journal* Psychiatry Neurosyphilis
206. ^ Lipsitz, JD; Fyer, AJ; Paterniti, A; Klein, DF (2001). "Emetophobia: preliminary results of an internet survey". *Depression and Anxiety*. **14** (2): 149–52. doi:10.1002/da.1058. PMID 11668669.
207. ^ Boschen, MJ (2007). "Reconceptualizing emetophobia: a cognitive-behavioral formulation and research agenda". *Journal of anxiety disorders*. **21** (3): 407–19. doi:10.1016/j.janxdis.2006.06.007. PMID 16890398.
208. ^ Shapiro, J; Franko, DL; Gagne, A (1997). "Phagophobia: a form of psychogenic dysphagia. A new entity". *Annals of Otology, Rhinology, and Laryngology*. **106** (4): 286–90. PMID 9109717.
209. ^ Gabbay, V; Asnis, GM; Bello, JA; Alonso, CM (2003). "New onset of body dysmorphic disorder following frontotemporal lesion". *Neurology*. **61** (1): 123–5. doi:10.1212/01.WNL.0000069607.30528.D5. PMID 12847173.
210. ^ Phillips, KA; McElroy, SL; Keck Jr, PE; Hudson, JI; Pope Jr, HG (1994). "A comparison of delusional and nondelusional body dysmorphic disorder in 100 cases". *Psychopharmacology bulletin*. **30** (2): 179–86. PMID 7831453.
211. ^ Feusner, JD; Townsend, J; Bystritsky, A; Bookheimer, S (2007). "Visual information processing of faces in body dysmorphic disorder". *Archives of General Psychiatry*. **64** (12): 1417–25. doi:10.1001/archpsyc.64.12.1417. PMID 18056550.
212. ^ Feusner, JD; Yaryura-Tobias, J; Saxena, S (2008). "The pathophysiology of body dysmorphic disorder". *Body Image*. **5** (1): 3–12. doi:10.1016/j.bodyim.2007.11.002. PMID 18314401.
213. ^ Zeckhausen, Dina (2005). "Prevention: It's never too young to start". *Eating Disoreders Recovery Today*. **3** (2).
214. ^ National Research Council & Institute of Medicine. (2009b). Preventing mental, emotional, and behavioral disorders among young people: Progress and possibilities (M. E. O'Connell, T. Boat, & K. E. Warner,Eds.).Washington, DC: National Academies Press.[*page needed*]
215. ^ Halmi, KA (2005). "The multimodal treatment of eating disorders". *World Psychiatry*. World Psychiatric Association. **4** (2): 69–73. PMC 1414734. PMID 16633511.
216. ^ Gelder, Mayou, Geddes (2005). Psychiatry. New York, NY: Oxford University Press Inc.[*page needed*]
217. ^ (Downey, 2014)
218. ^ Pike, KM; Walsh, BT; Vitousek, K; Wilson, GT; Bauer, J (2003). "Cognitive behavior therapy in the posthospitalization treatment of anorexia nervosa". *The American Journal of Psychiatry*. **160** (11): 2046–9. doi:10.1176/appi.ajp.160.11.2046. PMID 14594754.
219. ^ Yeh, HW; Tzeng, NS; Lai, TJ; Chou, KR (2006).

*of neuroscience*. **114** (1): 83–93. doi:10.1080/00207450490249356. PMID 14660070.

90. ^ Sinai, C; Hirvikoski, T; Vansvik, ED; Nordström, AL; Linder, J (2009). "Thyroid hormones and personality traits in attempted suicide". *Psychoneuroendocrinology*. **34** (10): 1526–32. doi:10.1016/j.psyneuen.2009.05.009. PMID 19525070.
91. ^ *a b c* Satherley R, Howard R, Higgs S (Jan 2015). "Disordered eating practices in gastrointestinal disorders". *Appetite* (Review). **84**: 240–50. doi:10.1016/j.appet.2014.10.006. PMID 25312748.
92. ^ *a b c d* Bern EM, O'Brien RF (Aug 2013). "Is it an eating disorder, gastrointestinal disorder, or both?". *Curr Opin Pediatr* (Review). **25** (4): 463–70. doi:10.1097/MOP.0b013e328362d1ad. PMID 23838835. "Several case reports brought attention to the association of anorexia nervosa and celiac disease.(...) Some patients present with the eating disorder prior to diagnosis of celiac disease and others developed anorexia nervosa after the diagnosis of celiac disease. Healthcare professionals should screen for celiac disease with eating disorder symptoms especially with gastrointestinal symptoms, weight loss, or growth failure.(...) Celiac disease patients may present with gastrointestinal symptoms such as diarrhea, steatorrhea, weight loss, vomiting, abdominal pain, anorexia, constipation, bloating, and distension due to malabsorption. Extraintestinal presentations include anemia, osteoporosis, dermatitis herpetiformis, short stature, delayed puberty, fatigue, aphthous stomatitis, elevated transaminases, neurologic problems, or dental enamel hypoplasia.(...) it has become clear that symptomatic and diagnosed celiac disease is the tip of the iceberg; the remaining 90% or more of children are asymptomatic and undiagnosed."
93. ^ Quick VM, Byrd-Bredbenner C, Neumark-Sztainer D (May 1, 2013). "Chronic illness and disordered eating: a discussion of the literature". *Adv Nutr* (Review). **4** (3): 277–86. doi:10.3945/an.112.003608. PMC 3650496. PMID 23674793.
94. ^ *a b* Caslini, M; Bartoli, F; Crocamo, C; Dakanalis, A; Clerici, M; Carrà, G (January 2016). "Disentangling the Association Between Child Abuse and Eating Disorders: A Systematic Review and Meta-Analysis.". *Psychosomatic medicine*. **78** (1): 79–90. doi:10.1097/psy.0000000000000233. PMID 26461853.
95. ^ Troop, NA; Bifulco, A (2002). "Childhood social arena and cognitive sets in eating disorders". *The British journal of clinical psychology*. The British Psychological Society. **41** (Pt 2): 205–11. doi:10.1348/014466502163976. PMID 12034006.
96. ^ Nonogaki, K; Nozue, K; Oka, Y (2007). "Social "Cognitive behavioral therapy for eating disorders". *Hu li za zhi the journal of nursing*. **53** (4): 65–73. PMID 16874604.
220. ^ *a b* Schmidt, U; Lee, S; Beecham, J; Perkins, S; Treasure, J (2007). "A randomized controlled trial of family therapy and cognitive behavior therapy guided self-care for adolescents with bulimia nervosa and related disorders". *The American Journal of Psychiatry*. **164** (4): 591–8. doi:10.1176/appi.ajp.164.4.591. PMID 17403972.
221. ^ Berman, MI; Boutelle, KN; Crow, SJ (2009). "A case series investigating acceptance and commitment therapy as a treatment for previously treated, unremitted patients with anorexia nervosa". *European eating disorders review*. **17** (6): 426–34. doi:10.1002/erv.962. PMID 19760625.
222. ^ Wykes, T; Brammer, M; Mellers, J; Bray, P; Reeder, C; et al. (2002). "Effects on the brain of a psychological treatment: cognitive remediation therapy: functional magnetic resonance imaging in schizophrenia". *The British Journal of Psychiatry*. **181**: 144–52. doi:10.1192/bjp.181.2.144. PMID 12151286.
223. ^ Cognitive Remediation Therapy for Anorexia Nervosa by Kate Tchanturia Publisher: Cambridge University Press; 1 edition (April 30, 2010) Language: English ISBN 0-521-74816-X ISBN 978-0-521-74816-2
224. ^ Tchanturia, K; Davies, H; Campbell, IC (2007). "Cognitive remediation therapy for patients with anorexia nervosa: preliminary findings". *Annals of General Psychiatry*. **6** (1): 14. doi:10.1186/1744-859X-6-14. PMC 1892017. PMID 17550611.
225. ^ Cwojdzińska, A; Markowska-Regulska, K; Rybakowski, F (2009). "Cognitive remediation therapy in adolescent anorexia nervosa—case report". *Psychiatria polska*. **43** (1): 115–24. PMID 19694406.
226. ^ Safer, DL; Telch, CF; Agras, WS (2001). "Dialectical behavior therapy for bulimia nervosa". *The American Journal of Psychiatry*. **158** (4): 632–4. doi:10.1176/appi.ajp.158.4.632. PMID 11282700.
227. ^ Eisler, I; Dare, C; Hodes, M; Russell, G (2000). "Family therapy for adolescent anorexia nervosa: the results of a controlled comparison of two family interventions". *Journal of child psychology and psychiatry, and allied disciplines*. **41** (6): 727–36. doi:10.1111/1469-7610.00660. PMID 11039685.
228. ^ Rhodes, P; Brown, J; Madden, S (2009). "The Maudsley model of family-based treatment for anorexia nervosa: a qualitative evaluation of parent-to-parent consultation". *Journal of marital and family therapy*. **35** (2): 181–92. doi:10.1111/j.1752-0606.2009.00115.x. PMID 19302516.
229. ^ Wallis, A; Rhodes, P; Kohn, M; Madden, S (2007). "Five-years of family based treatment for anorexia nervosa: the Maudsley Model at the Children's

isolation affects the development of obesity and type 2 diabetes in mice". *Endocrinology*. **148** (10): 4658–66. doi:10.1210/en.2007-0296. PMID 17640995.
97. ^ Esplen, MJ; Garfinkel, P; Gallop, R (2000). "Relationship between self-soothing, aloneness, and evocative memory in bulimia nervosa". *The International Journal of Eating Disorders*. **27** (1): 96–100. doi:10.1002/(SICI)1098-108X(200001)27:1<96::AID-EAT11>3.0.CO;2-S. PMID 10590454.
98. ^ Larson, R; Johnson, C (1985). "Bulimia: disturbed patterns of solitude". *Addictive behaviors*. **10** (3): 281–90. doi:10.1016/0306-4603(85)90009-7. PMID 3866486.
99. ^ Fox, John (July 2009). "Eating Disorders and Emotions". *Clinical Psychology & Psychotherapy*. **16** (237–239): 237–239. doi:10.1002/cpp.625.
100. ^ Johnson, JG; Cohen, P; Kasen, S; Brook, JS (2002). "Childhood adversities associated with risk for eating disorders or weight problems during adolescence or early adulthood". *The American Journal of Psychiatry*. **159** (3): 394–400. doi:10.1176/appi.ajp.159.3.394. PMID 11870002.
101. ^ Klesges, RC; Coates, TJ; Brown, G; Sturgeon-Tillisch, J; Moldenhauer-Klesges, LM (1983). "Parental influences on children's eating behavior and relative weight". *Journal of applied behavior analysis*. **16** (4): 371–8. doi:10.1901/jaba.1983.16-371. PMC 1307898. PMID 6654769.
102. ^ Galloway, AT; Fiorito, L; Lee, Y; Birch, LL (2005). "Parental Pressure, Dietary Patterns, and Weight Status among Girls Who Are "Picky Eaters" ". *Journal of the American Dietetic Association*. **105** (4): 541–8. doi:10.1016/j.jada.2005.01.029. PMC 2530930. PMID 15800554.
103. ^ Jones, C; Harris, G; Leung, N (2005). "Parental rearing behaviours and eating disorders: the moderating role of core beliefs". *Eating behaviors*. **6** (4): 355–64. doi:10.1016/j.eatbeh.2005.05.002. PMID 16257809.
104. ^ Brown, R; Ogden, J (2004). "Children's eating attitudes and behaviour: a study of the modelling and control theories of parental influence". *Health education research*. **19** (3): 261–71. doi:10.1093/her/cyg040. PMID 15140846.
105. ^ Savage, JS; Fisher, JO; Birch, LL (2007). "Parental Influence on Eating Behavior: Conception to Adolescence". *The Journal of law, medicine & ethics : a journal of the American Society of Law, Medicine & Ethics*. **35** (1): 22–34. doi:10.1111/j.1748-720X.2007.00111.x. PMC 2531152. PMID 17341215.
106. ^ Nolen-Hoeksema, Susan. *Abnormal Psychology, 6e*. McGraw-Hill Education, 2014. p. 359-360.
107. ^ Schreiber, GB; Robins, M; Striegel-Moore, R; Obarzanek, E (1996). "Weight modification efforts reported by black and white preadolescent girls: National Heart, Lung, and Blood Institute Growth and Hospital at Westmead". *International journal of adolescent medicine and health*. **19** (3): 277–83. doi:10.1515/IJAMH.2007.19.3.277. PMID 17937144.
230. ^ Gray, JJ; Hoage, CM (1990). "Bulimia nervosa: group behavior therapy with exposure plus response prevention". *Psychological reports*. **66** (2): 667–74. doi:10.2466/PR0.66.2.667-674. PMID 1971954.
231. ^ McIntosh, VV; Bulik, CM; McKenzie, JM; Luty, SE; Jordan, J (2000). "Interpersonal psychotherapy for anorexia nervosa". *The International Journal of Eating Disorders*. **27** (2): 125–39. doi:10.1002/(SICI)1098-108X(200003)27:2<125::AID-EAT1>3.0.CO;2-4. PMID 10657886.
232. ^ Corstorphine, E (2006). "Cognitive Emotional Behavioural Therapy for the eating disorders; working with beliefs about emotions". *European Eating Disorders Review*. **14** (6): 448–461. doi:10.1002/erv.747.
233. ^ Frisch, MJ; Franko, DL; Herzog, DB (2006). "Arts-based therapies in the treatment of eating disorders". *Eating disorders*. **14** (2): 131–42. doi:10.1080/10640260500403857. PMID 16777810.
234. ^ Latner, JD; Wilson, GT (2000). "Cognitive-behavioral therapy and nutritional counseling in the treatment of bulimia nervosa and binge eating". *Eating behaviors*. **1** (1): 3–21. doi:10.1016/S1471-0153(00)00008-8. PMID 15001063.
235. ^ Perelygina, L; Patrusheva, I; Manes, N; Wildes, MJ (2003). "Quantitative real-time PCR for detection of monkey B virus (Cercopithecine herpesvirus 1) in clinical samples". *Journal of Virological Methods*. **109** (2): 245–51. doi:10.1016/S0166-0934(03)00078-8. PMID 12711069.
236. ^ Whisenant, SL; Smith, BA (1995). "Eating disorders: current nutrition therapy and perceived needs in dietetics education and research". *Journal of the American Dietetic Association*. **95** (10): 1109–12. doi:10.1016/S0002-8223(95)00301-0. PMID 7560681.
237. ^ American Dietetic Association (2006). "Position of the American Dietetic Association: Nutrition intervention in the treatment of anorexia nervosa, bulimia nervosa, and other eating disorders". *Journal of the American Dietetic Association*. **106** (12): 2073–82. doi:10.1016/j.jada.2006.09.007. PMID 17186637.
238. ^ Casper, RC (2002). "How useful are pharmacological treatments in eating disorders?". *Psychopharmacology bulletin*. **36** (2): 88–104. PMID 12397843.
239. ^ Goldberg, SC; Halmi, KA; Eckert, ED; Casper, RC; Davis, JM (1979). "Cyproheptadine in anorexia nervosa". *The British Journal of Psychiatry*. **134**: 67–70. doi:10.1192/bjp.134.1.67. PMID 367480.
240. ^ Walsh, BT; Wilson, GT; Loeb, KL; Devlin, MJ; Pike, KM (1997). "Medication and psychotherapy in the treatment of bulimia nervosa". *The American Journal*

Health Study". *Pediatrics*. **98** (1): 63–70. PMID 8668414.
108. ^ Page, RM; Suwanteerangkul, J (2007). "Dieting among Thai adolescents: having friends who diet and pressure to diet". *Eating and weight disorders : EWD*. **12** (3): 114–24. doi:10.1007/bf03327638. PMID 17984635.
109. ^ McKnight, Investigators (2003). "Risk factors for the onset of eating disorders in adolescent girls: results of the McKnight longitudinal risk factor study". *The American Journal of Psychiatry*. **160** (2): 248–54. doi:10.1176/appi.ajp.160.2.248. PMID 12562570.
110. ^ Paxton, SJ; Schutz, HK; Wertheim, EH; Muir, SL (1999). "Friendship clique and peer influences on body image concerns, dietary restraint, extreme weight-loss behaviors, and binge eating in adolescent girls". *Journal of Abnormal Psychology*. **108** (2): 255–66. doi:10.1037/0021-843X.108.2.255. PMID 10369035.
111. ^ Rukavina, T; Pokrajac-Bulian, A (2006). "Thin-ideal internalization, body dissatisfaction and symptoms of eating disorders in Croatian adolescent girls". *Eating and weight disorders : EWD*. **11** (1): 31–7. doi:10.1007/bf03327741. PMID 16801743.
112. ^ [ Nolen-Hoeksema, Susan (2014). (Ab)normal psychology. New York, NY: McGraw Hill. p. 323. ISBN 978-0-07-803538-8.
113. ^ Garner, DM; Garfinkel, PE (2009). "Socio-cultural factors in the development of anorexia nervosa". *Psychological Medicine*. **10** (4): 647–56. doi:10.1017/S0033291700054945. PMID 7208724.
114. ^ Eisenberg, ME; Neumark-Sztainer, D; Story, M; Perry, C (2005). "The role of social norms and friends' influences on unhealthy weight-control behaviors among adolescent girls". *Social Science & Medicine*. **60** (6): 1165–73. doi:10.1016/j.socscimed.2004.06.055. PMID 15626514.
115. ^ Jung, J; Lennon, SJ (2003). "Body Image, Appearance Self-Schema, and Media Images". *Family and Consumer Sciences Research Journal*. **32**: 27–51. doi:10.1177/1077727X03255900.
116. ^ Simpson, KJ (2002). "Anorexia nervosa and culture". *Journal of Psychiatric and Mental Health Nursing*. **9** (1): 65–71. doi:10.1046/j.1351-0126.2001.00443.x. PMID 11896858.
117. ^ *a b* Soh, NL; Touyz, SW; Surgenor, LJ (2006). "Eating and body image disturbances across cultures: A review". *European Eating Disorders Review*. **14** (1): 54–65. doi:10.1002/erv.678.
118. ^ Keel, PK; Klump, KL (2003). "Are eating disorders culture-bound syndromes? Implications for conceptualizing their etiology". *Psychological Bulletin*. **129** (5): 747–69. doi:10.1037/0033-2909.129.5.747. PMID 12956542.
119. ^ Nevonen, L; Norring, C (2004). "Socio-economic variables and eating disorders: A comparison of Psychiatry. **154** (4): 523–31. PMID 9090340.
241. ^ Marrazzi, MA; Markham, KM; Kinzie, J; Luby, ED (1995). "Binge eating disorder: response to naltrexone". *International journal of obesity and related metabolic disorders*. International Association for the Study of Obesity. **19** (2): 143–5. PMID 7735342.
242. ^ Vandereycken, W; Pierloot, R (1982). "Pimozide combined with behavior therapy in the short-term treatment of anorexia nervosa. A double-blind placebo-controlled cross-over study". *Acta Psychiatrica Scandinavica*. **66** (6): 445–50. doi:10.1111/j.1600-0447.1982.tb04501.x. PMID 6758492.
243. ^ Birmingham, CL; Gritzner, S (2006). "How does zinc supplementation benefit anorexia nervosa?". *Eating and weight disorders : EWD*. **11** (4): e109–11. PMID 17272939.
244. ^ Perkins, SJ; Murphy, R; Schmidt, U; Williams, C; Schmidt, UUS (2006). "Self-help and guided self-help for eating disorders". *Cochrane database of systematic reviews (Online)*. **3** (3): CD004191. doi:10.1002/14651858.CD004191.pub2. PMID 16856036.
245. ^ Carter, JC; Olmsted, MP; Kaplan, AS; McCabe, RE (2003). "Self-help for bulimia nervosa: a randomized controlled trial". *The American Journal of Psychiatry*. **160** (5): 973–8. doi:10.1176/appi.ajp.160.5.973. PMID 12727703.
246. ^ Thiels, C; Schmidt, U; Treasure, J; Garthe, R (2003). "Four-year follow-up of guided self-change for bulimia nervosa". *Eating and weight disorders : EWD*. **8** (3): 212–7. doi:10.1007/bf03325016. PMID 14649785.
247. ^ *a b* Peterson, CB; Mitchell, JE; Crow, SJ; Crosby, RD; Wonderlich, SA (2009). "The Efficacy of Self-Help Group Treatment and Therapist-Led Group Treatment for Binge Eating Disorder". *The American Journal of Psychiatry*. **166** (12): 1347–54. doi:10.1176/appi.ajp.2009.09030345. PMC 3041988. PMID 19884223.
248. ^ Delinsky, SS; Latner, JD; Wilson, GT (2006). "Binge eating and weight loss in a self-help behavior modification program". *Obesity*. **14** (7): 1244–9. doi:10.1038/oby.2006.141. PMID 16899805.
249. ^ Bulik, CM; Berkman, ND; Brownley, KA; Sedway, JA; Lohr, KN (2007). "Anorexia nervosa treatment: a systematic review of randomized controlled trials". *The International Journal of Eating Disorders*. **40** (4): 310–20. doi:10.1002/eat.20367. PMID 17370290.
250. ^ Agras, WS (2001). "The consequences and costs of the eating disorders". *The Psychiatric clinics of North America*. **24** (2): 371–9. doi:10.1016/S0193-953X(05)70232-X. PMID 11416936.
251. ^ Palmer, RL; Birchall, H; Damani, S; Gatward, N (2003). "A dialectical behavior therapy program for people with an eating disorder and borderline personality disorder—description and outcome". *The*

between patients and normal controls". *Eating and Weight Disorders*. **9** (4): 279–84. doi:10.1007/BF03325082. PMID 15844400.
120. ^ Polivy, J; Herman, CP (2002). "Causes of eating disorders". *Annual Review of Psychology*. **53**: 187–213. doi:10.1146/annurev.psych.53.100901.135103. PMID 11752484.
121. ^ Essick, Ellen (2006). "Eating Disorders and Sexuality". In Steinberg, Shirley R.; Parmar, Priya; Richard, Birgit. *Contemporary Youth Culture: An International Encyclopedia*. Greenwood. pp. 276–80. ISBN 978-0-313-33729-1.
122. ^ DeMonte, Alexandria. "Beauty Pageants". M.E. Sharpe. Retrieved 24 September 2013.[*dead link*]
123. ^ Nolen-Hoeksema, Susan (2014). *abnormal psychology* (6th ed.). New York: McGraw-Hill Education. pp. 353–354. ISBN 978-0-07-803538-8.
124. ^ *a b* Harrell, WA; Boisvert, JA (2009). "Homosexuality as a Risk Factor for Eating Disorder Symptomatology in Men". *The Journal of Men's Studies*. **17** (3): 210–25. doi:10.3149/jms.1703.210.
125. ^ *a b c* Burton, CL; Allomong, TW; Halkitis, PN; Siconolfi, D (2009). "Body Dissatisfaction and Eating Disorders in a Sample of Gay and Bisexual Men". *International Journal of Men's Health*. **8** (3): 254–64. doi:10.3149/jmh.0803.254.
126. ^ Mash, Eric Jay; Wolfe, David Allen (2010). "Eating Disorders and Related Conditions". *Abnormal Child Psychology*. Belmont, CA: Wadsworth: Cengage Learning. pp. 415–26. ISBN 978-0-495-50627-0.
127. ^ Schwitzer, AM (2012). "Diagnosing, Conceptualizing, and Treating Eating Disorders Not Otherwise Specified: A Comprehensive Practice Model". *Journal of Counseling & Development*. **90** (3): 281–9. doi:10.1002/j.1556-6676.2012.00036.x.
128. ^ Kim Willsher, Models in France must provide doctor's note to work, The Guardian, 18 December.
129. ^ *a b* Ghaznavi, Jannath; Taylor, Laramie D. (2015-06-01). "Bones, body parts, and sex appeal: An analysis of #thinspiration images on popular social media". *Body Image*. **14**: 54–61. doi:10.1016/j.bodyim.2015.03.006.
130. ^ *a b* Perloff, Richard M. (2014-05-29). "Social Media Effects on Young Women's Body Image Concerns: Theoretical Perspectives and an Agenda for Research". *Sex Roles*. **71** (11-12): 363–377. doi:10.1007/s11199-014-0384-6. ISSN 0360-0025.
131. ^ Arseniev-Koehler, Alina; Lee, Hedwig; McCormick, Tyler; Moreno, Megan A. "#Proana: Pro-Eating Disorder Socialization on Twitter". *Journal of Adolescent Health*. **58** (6): 659–664. doi:10.1016/j.jadohealth.2016.02.012.
132. ^ Yu, U.-J. "Deconstructing College Students' Perceptions of Thin-Idealized Versus Nonidealized *International Journal of Eating Disorders*. **33** (3): 281–6. doi:10.1002/eat.10141. PMID 12655624.
252. ^ Baran, SA; Weltzin, TE; Kaye, WH (1995). "Low discharge weight and outcome in anorexia nervosa". *The American Journal of Psychiatry*. **152** (7): 1070–2. PMID 7793445.
253. ^ *a b* Lock, J (2015). "An Update on Evidence-Based Psychosocial Treatments for Eating Disorders in Children and Adolescents.". *Journal of Clinical Child and Adolescent Psychology*. **44** (5): 707–21. doi:10.1080/15374416.2014.971458. PMID 25580937.
254. ^ Vandereycken, W (2003). "Prognosis of anorexia nervosa". *The American Journal of Psychiatry*. **160** (9): 1708. doi:10.1176/appi.ajp.160.9.1708. PMID 12944354.
255. ^ Bergh, C; Brodin, U; Lindberg, G; Södersten, P (2002). "Randomized controlled trial of a treatment for anorexia and bulimia nervosa". *Proceedings of the National Academy of Sciences of the United States of America*. **99** (14): 9486–91. Bibcode:2002PNAS...99.9486B. doi:10.1073/pnas.142284799. PMC 123167. PMID 12082182.
256. ^ Herzog, DB; Dorer, DJ; Keel, PK; Selwyn, SE; Ekeblad, ER (1999). "Recovery and relapse in anorexia and bulimia nervosa: a 7.5-year follow-up study". *Journal of the American Academy of Child and Adolescent Psychiatry*. **38** (7): 829–37. doi:10.1097/00004583-199907000-00012. PMID 10405500.
257. ^ *a b c d* "Health Consequences of Eating Disorders". National Eating Disorder Association.
258. ^ Arcelus, Jon (2011-07-04). "Mortality Rates in Patients With Anorexia Nervosa and Other Eating Disorders". *Archives of General Psychiatry*. **68** (7). doi:10.1001/archgenpsychiatry.2011.74. ISSN 0003-990X.
259. ^ Linna Milla S.; Raevuori Anu; Haukka Jari; Suvisaari Jaana M.; Suokas Jaana T.; Gissler Mika (2013). "Reproductive Health Outcomes in Eating Disorders". *International Journal of Eating Disorders*. **46** (8): 826–33. doi:10.1002/eat.22179.
260. ^ Grilo Carlos M.; Pagano Maria E.; Stout Robert L.; Markowitz John C.; Ansell Emily B.; Pinto Anthony; Zanarini Mary C.; Yen Shirley; Skodol Andrew E. (2012). "Stressful Life Events Predict Eating Disorder Relapse following Remission: Six year Prospective Outcomes". *International Journal of Eating Disorders*. **45** (2): 185–92. doi:10.1002/eat.20909.
261. ^ Illing Vanessa A.; Tasca Giorgio; Balfour Louise; Bissada Hany (2010). "Attachment Insecurity Predicts Eating Disorder Symptoms and Treatment Outcomes in a Clinical Sample of Women". *The Journal of Nervous and Mental Disease*. **198** (9): 653–59. doi:10.1097/nmd.0b013e3181ef34b2.
262. ^ Lozano, R; Naghavi, M; Foreman, K; Lim, S; Shibuya, K; Aboyans, V; Abraham, J; Adair, T; et al.

Media Images on Body Dissatisfaction and Advertising Effectiveness". *Clothing and Textiles Research Journal*. **32** (3): 153–169. doi:10.1177/0887302x14525850.
133. ^ Gross, MJ; Kahn, JP; Laxenaire, M; Nicolas, JP; Burlet, C (1994). "Corticotropin-releasing factor and anorexia nervosa: reactions of the hypothalamus-pituitary-adrenal axis to neurotropic stress". *Annales d'endocrinologie*. **55** (6): 221–8. PMID 7864577.
134. ^ Licinio, J; Wong, ML; Gold, PW (1996). "The hypothalamic-pituitary-adrenal axis in anorexia nervosa". *Psychiatry Research*. **62** (1): 75–83. doi:10.1016/0165-1781(96)02991-5. PMID 8739117.
135. ^ Chaudhri, O; Small, C; Bloom, S (2006). (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
263. ^ Diemer, EW; Grant, JD; Munn-Chernoff, MA; Patterson, DA; Duncan, AE (August 2015). "Gender Identity, Sexual Orientation, and Eating-Related Pathology in a National Sample of College Students.". *The Journal of Adolescent Health*. **57** (2): 144–9. doi:10.1016/j.jadohealth.2015.03.003. PMID 25937471.
264. ^ "Hospitalizations for Eating Disorders Rose Over the Past Decade". *Eating Disorders Review*. **24** (2). 2013.

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| **Autism spectrum** | Autism · Asperger syndrome · Savant syndrome · PDD-NOS · High-functioning autism · |
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| **Psychoactive substances, substance abuse, drug abuse and substance-related disorders** | |
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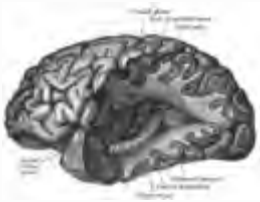

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Categories: Abnormal psychology | Behavioral neuroscience | Eating disorders | Mind–body interventions | Neuroscience | Behavioural syndromes associated with physiological disturbances and physical factors | Psychiatric specialities | Psychiatric diagnosis




# Major depressive disorder

From Wikipedia, the free encyclopedia

*For other types of depression, see Mood disorder.*

**Major depressive disorder** (**MDD**), also known simply as **depression**, is a mental disorder characterized by at least two weeks of low mood that is present across most situations.[1] It is often accompanied by low self-esteem, loss of interest in normally enjoyable activities, low energy, and pain without a clear cause.[1] People may also occasionally have false beliefs or see or hear things that others cannot.[1] Some people have periods of depression separated by years in which they are normal while others nearly always have symptoms present.[2] Major depressive disorder can negatively affects a person's personal, work, or school life, as well as sleeping, eating habits, and general health.[1][2] Between 2–7% of adults with major depression die by suicide,[3] and up to 60% of people who die by suicide had depression or another mood disorder.[4]

The cause is believed to be a combination of genetic, environmental, and psychological factors.[1] Risk factors include a family history of the condition, major life changes, certain medications, chronic health problems, and substance abuse.[1][2] About 40% of the risk appears to be related to genetics.[2] The diagnosis of major depressive disorder is based on the person's reported experiences and a mental status examination.[5] There is no laboratory test for major depression.[2] Testing, however, may be done to rule out physical conditions that can cause similar symptoms.[5] Major depression should be differentiated from sadness which is a normal part of life and is less severe.[2] The United States Preventive Services Task Force (USPSTF) recommends screening for depression among those over the age 12,[6][7] while a prior Cochrane review found insufficient evidence for screening.[8]

Typically, people are treated with counselling and antidepressant medication.[1] Medication appears to be effective, but the effect may only be significant in the most severely depressed.[9][10] It is unclear whether medications affect the risk of suicide.[11] Types of counselling used include

**Major depressive disorder**

| | |
|---|---|
| **Synonyms** | clinical depression, major depression, unipolar depression, unipolar disorder, recurrent depression |

Vincent van Gogh's 1890 painting *Sorrowing old man ('At Eternity's Gate')*

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Psychiatry |
| **ICD-10** | F32, F33 |
| **ICD-9-CM** | 296.2, 296.3 |
| **OMIM** | 608516 |
| **DiseasesDB** | 3589 |
| **MedlinePlus** | 003213 |

cognitive behavioral therapy (CBT) and interpersonal therapy.[1][12] If other measures are not effective electroconvulsive therapy (ECT) may be tried.[1] Hospitalization may be necessary in cases with a risk of harm to self and may occasionally occur against a person's wishes.[13]

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| **eMedicine** | med/532 |
| **Patient UK** | Major depressive disorder |
| **MeSH** | D003865 |

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Major depressive disorder affected approximately 253 million (3.6%) of people in 2013.[14] The percentage of people who are affected at one point in their life varies from 7% in Japan to 21% in France.[15] Lifetime rates are higher in the developed world (15%) compared to the developing world (11%).[15] It causes the second most years lived with disability after low back pain.[16] The most common time of onset is in a person in their 20s and 30s. Females are affected about twice as often as males.[2][15] The American Psychiatric Association added "major depressive disorder" to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) in 1980.[17] It was a split of the previous depressive neurosis in the DSM-II which also encompassed the conditions now known as dysthymia and adjustment disorder with depressed mood.[17] Those currently or previously affected may be stigmatized.[18]

**Contents**




Play media

Video explanation of depression

# Signs and symptoms

Major depression significantly affects a person's family and personal

relationships, work or school life, sleeping and eating habits, and general health.[19] Its impact on functioning and well-being has been compared to that of other chronic medical conditions such as diabetes.[20]

An 1892 lithograph of a woman diagnosed with depression

A person having a major depressive episode usually exhibits a very low mood, which pervades all aspects of life, and an inability to experience pleasure in activities that were formerly enjoyed. Depressed people may be preoccupied with, or ruminate over, thoughts and feelings of worthlessness, inappropriate guilt or regret, helplessness, hopelessness, and self-hatred.[21] In severe cases, depressed people may have symptoms of psychosis. These symptoms include delusions or, less commonly, hallucinations, usually unpleasant.[22] Other symptoms of depression include poor concentration and memory (especially in those with melancholic or psychotic features),[23] withdrawal from social situations and activities, reduced sex drive, irritability,[24] and thoughts of death or suicide. Insomnia is common among the depressed. In the typical pattern, a person wakes very early and cannot get back to sleep.[25] Hypersomnia, or oversleeping, can also happen.[25] Some antidepressants may also cause insomnia due to their stimulating effect.[26]

A depressed person may report multiple physical symptoms such as fatigue, headaches, or digestive problems; physical complaints are the most common presenting problem in developing countries, according to the World Health Organization's criteria for depression.[27] Appetite often decreases, with resulting weight loss, although increased appetite and weight gain occasionally occur.[21] Family and friends may notice that the person's behavior is either agitated or lethargic.[25] Older depressed people may have cognitive symptoms of recent onset, such as forgetfulness,[23] and a more noticeable slowing of movements.[28] Depression often coexists with physical disorders common among the elderly, such as stroke, other cardiovascular diseases, Parkinson's disease, and chronic obstructive pulmonary disease.[29]

Depressed children may often display an irritable mood rather than a depressed mood,[21] and show varying symptoms depending on age and situation.[30] Most lose interest in school and show a decline in academic performance. They may be described as clingy, demanding, dependent, or insecure.[25] Diagnosis may be delayed or missed when symptoms are interpreted as normal moodiness.[21]

## Associated conditions

Major depression frequently co-occurs with other psychiatric problems. The 1990–92 *National Comorbidity Survey* (US) reports that half of those with major depression also have lifetime anxiety and its associated disorders such as generalized anxiety disorder.[31] Anxiety symptoms can have a major impact on the course of a depressive illness, with delayed recovery, increased risk of relapse, greater disability and increased suicide attempts.[32] There are increased rates of alcohol and drug abuse and particularly dependence,[33] and around a third of individuals diagnosed with ADHD develop comorbid depression.[34] Post-traumatic stress disorder and depression often co-occur.[19] Depression may also coexist with attention deficit hyperactivity disorder (ADHD), complicating the diagnosis and treatment of both.[35]

Depression and pain often co-occur. One or more pain symptoms are present in 65% of depressed patients, and anywhere from 5 to 85% of patients with pain will be suffering from depression, depending on the setting; there is a lower prevalence in general practice, and higher in specialty clinics. The diagnosis of depression is often delayed or missed, and the outcome worsens. The outcome can also worsen if the depression is noticed but completely misunderstood.[36]

Depression is also associated with a 1.5- to 2-fold increased risk of cardiovascular disease, independent of other known risk factors, and is itself linked directly or indirectly to risk factors such as smoking and

obesity. People with major depression are less likely to follow medical recommendations for treating and preventing cardiovascular disorders, which further increases their risk of medical complications.[37] In addition, cardiologists may not recognize underlying depression that complicates a cardiovascular problem under their care.[38]

# Causes

The biopsychosocial model proposes that biological, psychological, and social factors all play a role in causing depression.[2][39] The diathesis–stress model specifies that depression results when a preexisting vulnerability, or diathesis, is activated by stressful life events. The preexisting vulnerability can be either genetic,[40][41] implying an interaction between nature and nurture, or schematic, resulting from views of the world learned in childhood.[42]

## Biological

*Main article: Biology of depression*

## Monoamine hypothesis

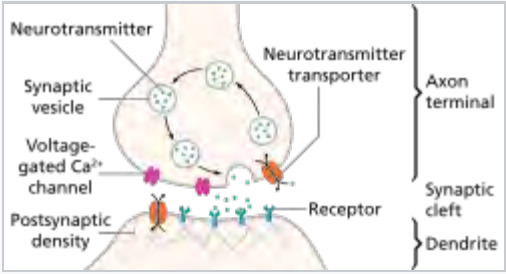



Diagram of a chemical synapse between two neurons. Most antidepressants influence the overall balance of three neurotransmitters: serotonin, norepinephrine, and dopamine. Some antidepressants act on neurotransmitter receptors.

Most antidepressant medications alter the levels of one or more of the monoamines—the neurotransmitters serotonin, norepinephrine and dopamine—in the synaptic cleft between neurons in the brain. Some medications affect the monoamine receptors directly.

Serotonin is hypothesized to regulate other neurotransmitter systems; decreased serotonin activity may allow these systems to act in unusual and erratic ways.[43] According to this "permissive hypothesis", depression arises when low serotonin levels promote low levels of norepinephrine, another monoamine neurotransmitter.[44] Some antidepressants enhance the levels of norepinephrine directly, whereas others raise the levels of dopamine, a third monoamine neurotransmitter. These observations gave rise to the monoamine hypothesis of depression. In its contemporary formulation, the monoamine hypothesis postulates that a deficiency of certain neurotransmitters is responsible for the corresponding features of depression: "Norepinephrine may be related to alertness and energy as well as anxiety, attention, and interest in life; [lack of] serotonin to anxiety, obsessions, and compulsions; and dopamine to attention, motivation, pleasure, and reward, as well as interest in life."[45] The proponents of this theory recommend the choice of an antidepressant with mechanism of action that impacts the most prominent symptoms. Anxious and irritable patients should be treated with SSRIs or norepinephrine reuptake inhibitors, and those experiencing a loss of energy and enjoyment of life with norepinephrine- and dopamine-enhancing drugs.[45]

However, since the 1990s, research has uncovered multiple limitations of the monoamine hypothesis, and its inadequacy has been criticized within the psychiatric community.[46] For one thing, serotonin system dysfunction cannot be the sole cause of depression; antidepressants usually bring serotonin levels up to normal very quickly, but it often takes at least two to four weeks before mood improves significantly. Intensive investigation has failed to find convincing evidence of a primary dysfunction of a specific monoamine system in patients with major depressive disorders. The antidepressants that do not act through the monoamine system, such as tianeptine and opipramol, have been known for a long time. There has also been inconsistency with regards to serum 5-HIAA levels, a metabolite of serotonin.[47] Experiments with pharmacological agents that cause depletion of monoamines have shown that this depletion does not cause depression in healthy people.[48][49] However depletion of tryptophan, tyrosine and phenylalanine does result in decreased mood in those with a predisposition to depression[50] Already limited, the

monoamine hypothesis has been further oversimplified when presented to the general public.[51]

## Drug and alcohol use

*See also: Substance-induced mood disorders*

Very high levels of substance abuse occur in the psychiatric population, especially alcohol, sedatives and cannabis. Depression and other mental health problems can have a substance induced cause; making a differential or dual diagnosis regarding whether mental ill-health is substance related or not or co-occurring is an important part of a psychiatric evaluation.[52] According to the DSM-IV, a diagnosis of mood disorder cannot be made if the cause is believed to be due to "the direct physiological effects of a substance"; when a syndrome resembling major depression is believed to be caused immediately by substance abuse or by an adverse drug reaction, it is referred to as, "substance-induced mood disturbance". Alcoholism or excessive alcohol consumption significantly increases the risk of developing major depression.[53][54] Like alcohol, the benzodiazepines are central nervous system depressants; this class of medication is commonly used to treat insomnia, anxiety, and muscular spasms. Similar to alcohol, benzodiazepines increase the risk of developing major depression. This increased risk of depression may be due in part to the adverse or toxic effects of sedative-hypnotic drugs including alcohol on neurochemistry,[54] such as decreased levels of serotonin and norepinephrine,[55] or activation of immune mediated inflammatory pathways in the brain.[56] Chronic use of benzodiazepines also can cause or worsen depression,[57] or depression may be part of a protracted withdrawal syndrome.[58][59] About a quarter of people recovering from alcoholism experience anxiety and depression, which can persist for up to 2 years.[60] Methamphetamine abuse is also commonly associated with depression.[61]

## Estrogens

The hormone estrogen has been implicated in depressive disorders due to the increase in risk of depressive episodes after puberty, the antenatal period, and reduced rates after menopause.[62] On the converse, the premenstrual and postpartum periods of low estrogen levels are also associated with increased risk.[62] Sudden withdrawal of, fluctuations in or periods of sustained low levels of estrogen have been linked to significant mood lowering. Clinical recovery from depression postpartum, perimenopause, and postmenopause was shown to be effective after levels of estrogen were stabilized or restored.[63][64]

## HPA Axis

There is some evidence that major depression may be caused in part by an overactive hypothalamic-pituitary-adrenal axis (HPA axis) that results in an effect similar to the neuro-endocrine response to stress. Investigations reveal increased levels of the hormone cortisol and enlarged pituitary and adrenal glands, suggesting disturbances of the endocrine system may play a role in some psychiatric disorders, including major depression. Oversecretion of corticotropin-releasing hormone from the hypothalamus is thought to drive this, and is implicated in the cognitive and arousal symptoms.[65]

## Genetics

Reviews and meta-analyses have contradicted one another with regard to genetic associations with depression.[66][67][68]

## Immune

Other research has explored potential roles of molecules necessary for overall cellular functioning: cytokines. The symptoms of major depressive disorder are nearly identical to those of sickness behavior, the response of the body when the immune system is fighting an infection. This raises the possibility that depression can result from a maladaptive manifestation of sickness behavior as a result of abnormalities in circulating cytokines.[69] The involvement of pro-inflammatory cytokines in depression is strongly suggested by a meta-analysis of the clinical literature showing higher blood concentrations of IL-6 and TNF-α in

depressed subjects compared to controls.[70] These immunological abnormalities may cause excessive prostaglandin E production and likely excessive COX-2 expression. Abnormalities in how indoleamine 2,3-dioxygenase enzyme activates as well as the metabolism of tryptophan-kynurenine may lead to excessive metabolism of tryptophan-kynurenine and lead to increased production of the neurotoxin quinolinic acid, contributing to major depression. N-Methyl-D-aspartic acid activation leading to excessive glutamatergic neurotransmission, may also contribute.[71] A number of factors that increase inflammation have been linked to depression including a poor diet, smoking, and obesity.[72]

### Trauma

Depression may be directly caused by damage to the cerebellum as is seen in cerebellar cognitive affective syndrome.[73][74][75]

## Social

Poverty and social isolation are associated with increased risk of mental health problems in general.[76] Child abuse (physical, emotional, sexual, or neglect) is also associated with increased risk of developing depressive disorders later in life.[77] Such a link has good face validity given that it is during the years of development that a child is learning how to become a social being. Abuse of the child by the caregiver is bound to distort the developing personality and create a much greater risk for depression and many other debilitating mental and emotional states. Disturbances in family functioning, such as parental (particularly maternal) depression, severe marital conflict or divorce, death of a parent, or other disturbances in parenting are additional risk factors.[76] In adulthood, stressful life events are strongly associated with the onset of major depressive episodes.[78] In this context, life events connected to social rejection appear to be particularly related to depression.[79][80] Evidence that a first episode of depression is more likely to be immediately preceded by stressful life events than are recurrent ones is consistent with the hypothesis that people may become increasingly sensitized to life stress over successive recurrences of depression.[81][82]

The relationship between stressful life events and social support has been a matter of some debate; the lack of social support may increase the likelihood that life stress will lead to depression, or the absence of social support may constitute a form of strain that leads to depression directly.[83] There is evidence that neighborhood social disorder, for example, due to crime or illicit drugs, is a risk factor, and that a high neighborhood socioeconomic status, with better amenities, is a protective factor.[84] Adverse conditions at work, particularly demanding jobs with little scope for decision-making, are associated with depression, although diversity and confounding factors make it difficult to confirm that the relationship is causal.[85]

Depression can be caused by prejudice. This can occur when people hold negative self-stereotypes about themselves. This "deprejudice" can be related to a group membership (e.g., Me-Gay-Bad) or not (Me-Bad). If someone has prejudicial beliefs about a stigmatized group and then becomes a member of that group, they may internalize their prejudice and develop depression. For example, a boy growing up in the United States may learn the negative stereotype that gay men are immoral. When he grows up and realizes he is gay, he may direct this prejudice inward on himself and become depressed. People may also show prejudice internalization through self-stereotyping because of negative childhood experiences such as verbal and physical abuse.[86]

## Evolutionary

*Main article: Evolutionary approaches to depression*

Depression is maladaptive and difficult to explain using evolutionary psychology; its heterogeneity also makes such explanations difficult. It may be however that some types of MDD may involve "exaggerated or distorted derivatives of human social behaviors which have survived over the eons because they conveyed enhanced survival", such as the behaviors relating to attachment and social rank.[87]

# Diagnosis

## Clinical assessment

*Further information: Rating scales for depression*

A diagnostic assessment may be conducted by a suitably trained general practitioner, or by a psychiatrist or psychologist,[19] who records the person's current circumstances, biographical history, current symptoms, and family history. The broad clinical aim is to formulate the relevant biological, psychological, and social factors that may be impacting on the individual's mood. The assessor may also discuss the person's current ways of regulating mood (healthy or otherwise) such as alcohol and drug use. The assessment also includes a mental state examination, which is an assessment of the person's current mood and thought content, in particular the presence of themes of hopelessness or pessimism, self-harm or suicide, and an absence of positive thoughts or plans.[19] Specialist mental health services are rare in rural areas, and thus diagnosis and management is left largely to primary-care clinicians.[88] This issue is even more marked in developing countries.[89] The mental health examination may include the use of a rating scale such as the Hamilton Rating Scale for Depression[90] or the Beck Depression Inventory[91] or the Suicide Behaviors Questionnaire-Revised.[92] The score on a rating scale alone is insufficient to diagnose depression to the satisfaction of the DSM or ICD, but it provides an indication of the severity of symptoms for a time period, so a person who scores above a given cut-off point can be more thoroughly evaluated for a depressive disorder diagnosis.[93] Several rating scales are used for this purpose.[93]

Primary-care physicians and other non-psychiatrist physicians have more difficulty with underrecognition and undertreatment of depression compared to psychiatric physicians, in part because of the physical symptoms that often accompany depression, in addition to the many potential patient, provider, and system barriers that the authors describe. A review found that non-psychiatrist physicians miss about two-thirds of cases, though this has improved somewhat in more recent studies.[94]

Before diagnosing a major depressive disorder, in general a doctor performs a medical examination and selected investigations to rule out other causes of symptoms. These include blood tests measuring TSH and thyroxine to exclude hypothyroidism; basic electrolytes and serum calcium to rule out a metabolic disturbance; and a full blood count including ESR to rule out a systemic infection or chronic disease.[95] Adverse affective reactions to medications or alcohol misuse are often ruled out, as well. Testosterone levels may be evaluated to diagnose hypogonadism, a cause of depression in men.[96] Vitamin D levels are often checked now, as low levels of vitamin D have been associated with greater risk for depression.[97]

Subjective cognitive complaints appear in older depressed people, but they can also be indicative of the onset of a dementing disorder, such as Alzheimer's disease.[98][99] Cognitive testing and brain imaging can help distinguish depression from dementia.[100] A CT scan can exclude brain pathology in those with psychotic, rapid-onset or otherwise unusual symptoms.[101] In general, investigations are not repeated for a subsequent episode unless there is a medical indication.

No biological tests confirm major depression.[102] Biomarkers of depression have been sought to provide an objective method of diagnosis. There are several potential biomarkers, including Brain-Derived Neurotrophic Factor and various functional MRI techniques. One study developed a decision tree model of interpreting a series of fMRI scans taken during various activities. In their subjects, the authors of that study were able to achieve a sensitivity of 80% and a specificity of 87%, corresponding to a negative predictive value of 98% and a positive predictive value of 32% (positive and negative likelihood ratios were 6.15, 0.23, respectively). However, much more research is needed before these tests could be used clinically.[103]

## DSM-IV-TR and ICD-10 criteria

The most widely used criteria for diagnosing depressive conditions are found in the American Psychiatric Association's revised fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), and the World Health Organization's *International Statistical Classification of Diseases and Related Health Problems* (ICD-10), which uses the name *depressive episode* for a single episode and *recurrent depressive disorder* for repeated episodes.[104] The latter system is typically used in European countries,[105]

while the former is used in the US and many other non-European nations, and the authors of both have worked towards conforming one with the other.[106]

Both DSM-IV-TR and ICD-10 mark out typical (main) depressive symptoms.[107] ICD-10 defines three typical depressive symptoms (depressed mood, anhedonia, and reduced energy), two of which should be present to determine depressive disorder diagnosis.[108][109] According to DSM-IV-TR, there are two main depressive symptoms—depressed mood and anhedonia. At least one of these must be present to make a diagnosis of major depressive episode.[110]

Major depressive disorder is classified as a mood disorder in DSM-IV-TR.[111] The diagnosis hinges on the presence of single or recurrent major depressive episodes.[21] Further qualifiers are used to classify both the episode itself and the course of the disorder. The category Depressive Disorder Not Otherwise Specified is diagnosed if the depressive episode's manifestation does not meet the criteria for a major depressive episode. The ICD-10 system does not use the term *major depressive disorder* but lists very similar criteria for the diagnosis of a depressive episode (mild, moderate or severe); the term *recurrent* may be added if there have been multiple episodes without mania.[104]

## Major depressive episode

*Main article: Major depressive episode*

A major depressive episode is characterized by the presence of a severely depressed mood that persists for at least two weeks.[21] Episodes may be isolated or recurrent and are categorized as mild (few symptoms in excess of minimum criteria), moderate, or severe (marked impact on social or occupational functioning). An episode with psychotic features—commonly referred to as *psychotic depression*—is automatically rated as severe. If the patient has had an episode of mania or markedly elevated mood, a diagnosis of bipolar disorder is made instead.[112] Depression without mania is sometimes referred to as *unipolar* because the mood remains at one emotional state or "pole".[113]

DSM-IV-TR excludes cases where the symptoms are a result of bereavement, although it is possible for normal bereavement to evolve into a depressive episode if the mood persists and the characteristic features of a major depressive episode develop.[114] The criteria have been criticized because they do not take into account any other aspects of the personal and social context in which depression can occur.[115] In addition, some studies have found little empirical support for the DSM-IV cut-off criteria, indicating they are a diagnostic convention imposed on a continuum of depressive symptoms of varying severity and duration:[116] Excluded are a range of related diagnoses, including dysthymia, which involves a chronic but milder mood disturbance;[117] recurrent brief depression, consisting of briefer depressive episodes;[118][119] minor depressive disorder, whereby only some symptoms of major depression are present;[120] and adjustment disorder with depressed mood, which denotes low mood resulting from a psychological response to an identifiable event or stressor.[121]

## Subtypes

The DSM-IV-TR recognizes five further subtypes of MDD, called *specifiers*, in addition to noting the length, severity and presence of psychotic features:

- **Melancholic depression** is characterized by a loss of pleasure in most or all activities, a failure of reactivity to pleasurable stimuli, a quality of depressed mood more pronounced than that of grief or loss, a worsening of symptoms in the morning hours, early-morning waking, psychomotor retardation, excessive weight loss (not to be confused with anorexia nervosa), or excessive guilt.[122]
- **Atypical depression** is characterized by mood reactivity (paradoxical anhedonia) and positivity, significant weight gain or increased appetite (comfort eating), excessive sleep or sleepiness (hypersomnia), a sensation of heaviness in limbs known as leaden paralysis, and significant social impairment as a consequence of hypersensitivity to perceived interpersonal rejection.[123]
- **Catatonic depression** is a rare and severe form of major depression involving disturbances of motor behavior and other symptoms. Here, the person is mute and almost stuporous, and either remains

immobile or exhibits purposeless or even bizarre movements. Catatonic symptoms also occur in schizophrenia or in manic episodes, or may be caused by neuroleptic malignant syndrome.[124]

- **Postpartum depression**, or **mental and behavioral disorders associated with the puerperium, not elsewhere classified**,[104] refers to the intense, sustained and sometimes disabling depression experienced by women after giving birth. Postpartum depression has an incidence rate of 10–15% among new mothers. The DSM-IV mandates that, in order to qualify as postpartum depression, onset occur within one month of delivery. It has been said that postpartum depression can last as long as three months.[125]
- **Seasonal affective disorder** (SAD) is a form of depression in which depressive episodes come on in the autumn or winter, and resolve in spring. The diagnosis is made if at least two episodes have occurred in colder months with none at other times, over a two-year period or longer.[126]

## Screening

In 2016 the United States Preventive Services Task Force (USPSTF) recommended screening in the adult populations with evidence that it increases the detection of people with depression and with proper treatment improves outcomes.[6] They recommend screening in those between the age of 12 to 18 as well.[7]

A Cochrane review from 2005 found screening programs do not significantly improve detection rates, treatment, or outcome.[8]

## Differential diagnoses

*Main article: Depression (differential diagnoses)*

To confer major depressive disorder as the most likely diagnosis, other potential diagnoses must be considered, including dysthymia, adjustment disorder with depressed mood, or bipolar disorder. Dysthymia is a chronic, milder mood disturbance in which a person reports a low mood almost daily over a span of at least two years. The symptoms are not as severe as those for major depression, although people with dysthymia are vulnerable to secondary episodes of major depression (sometimes referred to as *double depression*).[117] Adjustment disorder with depressed mood is a mood disturbance appearing as a psychological response to an identifiable event or stressor, in which the resulting emotional or behavioral symptoms are significant but do not meet the criteria for a major depressive episode.[121] Bipolar disorder, also known as *manic–depressive disorder*, is a condition in which depressive phases alternate with periods of mania or hypomania. Although depression is currently categorized as a separate disorder, there is ongoing debate because individuals diagnosed with major depression often experience some hypomanic symptoms, indicating a mood disorder continuum.[127]

Other disorders need to be ruled out before diagnosing major depressive disorder. They include depressions due to physical illness, medications, and substance abuse. Depression due to physical illness is diagnosed as a Mood disorder due to a general medical condition. This condition is determined based on history, laboratory findings, or physical examination. When the depression is caused by a medication, drug of abuse, or exposure to a toxin, it is then diagnosed as a specific mood disorder (previously called *Substance-induced mood disorder* in the DSM-IV-TR).[2]

# Prevention

Preventative efforts may result in decreases in rates of the condition of between 22 and 38%.[128] Eating large amounts of fish may also reduce the risk.[129]

Behavioral interventions, such as interpersonal therapy and cognitive-behavioral therapy, are effective at preventing new onset depression.[128][130][131] Because such interventions appear to be most effective when delivered to individuals or small groups, it has been suggested that they may be able to reach their large target audience most efficiently through the Internet.[132]

However, an earlier meta-analysis found preventive programs with a competence-enhancing component to be superior to behavior-oriented programs overall, and found behavioral programs to be particularly unhelpful for older people, for whom social support programs were uniquely beneficial. In addition, the programs that best prevented depression comprised more than eight sessions, each lasting between 60 and 90 minutes, were provided by a combination of lay and professional workers, had a high-quality research design, reported attrition rates, and had a well-defined intervention.[133]

The Netherlands mental health care system provides preventive interventions, such as the "Coping with Depression" course (CWD) for people with sub-threshold depression. The course is claimed to be the most successful of psychoeducational interventions for the treatment and prevention of depression (both for its adaptability to various populations and its results), with a risk reduction of 38% in major depression and an efficacy as a treatment comparing favorably to other psychotherapies.[130][134]

# Management

*Main article: Management of depression*

The three most common treatments for depression are psychotherapy, medication, and electroconvulsive therapy. Psychotherapy is the treatment of choice (over medication) for people under 18. The UK National Institute for Health and Care Excellence (NICE) 2004 guidelines indicate that antidepressants should not be used for the initial treatment of mild depression, because the risk-benefit ratio is poor. The guidelines recommend that antidepressants treatment in combination with psychosocial interventions should be considered for:

- People with a history of moderate or severe depression
- Those with mild depression that has been present for a long period
- As a second line treatment for mild depression that persists after other interventions
- As a first line treatment for moderate or severe depression.

The guidelines further note that antidepressant treatment should be continued for at least six months to reduce the risk of relapse, and that SSRIs are better tolerated than tricyclic antidepressants.[135]

American Psychiatric Association treatment guidelines recommend that initial treatment should be individually tailored based on factors including severity of symptoms, co-existing disorders, prior treatment experience, and patient preference. Options may include pharmacotherapy, psychotherapy, exercise, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) or light therapy. Antidepressant medication is recommended as an initial treatment choice in people with mild, moderate, or severe major depression, and should be given to all patients with severe depression unless ECT is planned.[136]

Treatment options are much more limited in developing countries, where access to mental health staff, medication, and psychotherapy is often difficult. Development of mental health services is minimal in many countries; depression is viewed as a phenomenon of the developed world despite evidence to the contrary, and not as an inherently life-threatening condition.[137] A 2014 Cochrane review found insufficient evidence to determine the effectiveness of psychological versus medical therapy in children.[138]

## Lifestyle

*Further information: Neurobiological effects of physical exercise § Major depressive disorder*

Physical exercise is recommended for management of mild depression,[139] and has a moderate effect on symptoms.[140] Exercise has also been found to be effective for (unipolar) major depression.[141] It is equivalent to the use of medications or psychological therapies in most people.[140] In the older people it does appear to decrease depression.[142] Exercise may be recommended to people who are willing, motivated, and physically healthy enough to participate in an exercise program as treatment.[141]

There is a small amount of evidence that skipping a night's sleep may improve depressive symptoms, with the effects usually showing up within a day. This effect is usually temporary. Besides sleepiness, this method can cause a side effect of mania or hypomania.[143]

In observational studies smoking cessation has benefits in depression as large as or larger than those of medications.[144]

## Counselling

Psychotherapy can be delivered, to individuals, groups, or families by mental health professionals. A 2015 review found that cognitive behavioral therapy appears to be similar to antidepressant medication in terms of effect.[145] A 2012 review found psychotherapy to be better than no treatment but not other treatments.[146] With more complex and chronic forms of depression, a combination of medication and psychotherapy may be used.[147][148] A 2014 Cochrane review found that work-directed interventions combined with clinical interventions helped to reduce sick days taken by people with depression.[149]

Psychotherapy has been shown to be effective in older people.[150][151] Successful psychotherapy appears to reduce the recurrence of depression even after it has been terminated or replaced by occasional booster sessions.

## Cognitive behavioral therapy

*See also: Behavioral theories of depression*

Cognitive behavioral therapy (CBT) currently has the most research evidence for the treatment of depression in children and adolescents, and CBT and interpersonal psychotherapy (IPT) are preferred therapies for adolescent depression.[152] In people under 18, according to the National Institute for Health and Clinical Excellence, medication should be offered only in conjunction with a psychological therapy, such as CBT, interpersonal therapy, or family therapy.[153] Cognitive behavioral therapy has also been shown to reduce the number of sick days taken by people with depression, when used in conjunction with primary care.[149]

The most-studied form of psychotherapy for depression is CBT, which teaches clients to challenge self-defeating, but enduring ways of thinking (cognitions) and change counter-productive behaviors. Research beginning in the mid-1990s suggested that CBT could perform as well or as better than antidepressants in patients with moderate to severe depression.[154][155] CBT may be effective in depressed adolescents,[156] although its effects on severe episodes are not definitively known.[157] Several variables predict success for cognitive behavioral therapy in adolescents: higher levels of rational thoughts, less hopelessness, fewer negative thoughts, and fewer cognitive distortions.[158] CBT is particularly beneficial in preventing relapse.[159][160]

Cognitive behavioral therapy and occupational programs (including modification of work activities and assistance) have been shown to be effective in reducing sick days taken by workers with depression.[161]

### Variants

Several variants of cognitive behavior therapy have been used in those with depression, the most notable being rational emotive behavior therapy,[162] and mindfulness-based cognitive therapy.[163] Mindfulness based stress reduction programs may reduce depression symptoms.[164][165] Mindfulness programs also appear to be a promising intervention in youth.[166]

## Psychoanalysis

Psychoanalysis is a school of thought, founded by Sigmund Freud, which emphasizes the resolution of unconscious mental conflicts.[167] Psychoanalytic techniques are used by some practitioners to treat clients presenting with major depression.[168] A more widely practiced, eclectic technique, called psychodynamic psychotherapy, is loosely based on psychoanalysis and has an additional social and interpersonal focus.[169] In a meta-analysis of three controlled trials of Short Psychodynamic Supportive Psychotherapy, this modification was found to be as effective as medication for mild to moderate depression.[170]

## Antidepressants

*Main article: Antidepressant*


Sertraline (Zoloft) is used primarily to treat major depression in adults.

Conflicting results have arisen from studies that look at the effectiveness of antidepressants in people with acute, mild to moderate depression. Stronger evidence supports the usefulness of antidepressants in the treatment of depression that is chronic (dysthymia) or severe.

While small benefits were found, researchers Irving Kirsch and Thomas Moore state they may be due to issues with the trials rather than a true effect of the medication.[171] In a later publication, Kirsch concluded that the overall effect of new-generation antidepressant medication is below recommended criteria for clinical significance.[10] Similar results were obtained in a meta analysis by Fornier.[9]

A review commissioned by the National Institute for Health and Care Excellence concluded that there is strong evidence that SSRIs have greater efficacy than placebo on achieving a 50% reduction in depression scores in moderate and severe major depression, and that there is some evidence for a similar effect in mild depression.[172] Similarly, a Cochrane systematic review of clinical trials of the generic antidepressant amitriptyline concluded that there is strong evidence that its efficacy is superior to placebo.[173]

In 2014 the U.S. FDA published a systematic review of all antidepressant maintenance trials submitted to the agency between 1985 and 2012. The authors concluded that maintenance treatment reduced the risk of relapse by 52% compared to placebo, and that this effect was primarily due to recurrent depression in the placebo group rather than a drug withdrawal effect.[9]

To find the most effective antidepressant medication with minimal side-effects, the dosages can be adjusted, and if necessary, combinations of different classes of antidepressants can be tried. Response rates to the first antidepressant administered range from 50–75%, and it can take at least six to eight weeks from the start of medication to remission.[174] Antidepressant medication treatment is usually continued for 16 to 20 weeks after remission, to minimize the chance of recurrence,[174] and even up to one year of continuation is recommended.[175] People with chronic depression may need to take medication indefinitely to avoid relapse.[19]

Selective serotonin reuptake inhibitors (SSRIs) are the primary medications prescribed, owing to their relatively mild side-effects, and because they are less toxic in overdose than other antidepressants.[176] People who do not respond to one SSRI can be switched to another antidepressant, and this results in improvement in almost 50% of cases.[177] Another option is to switch to the atypical antidepressant bupropion.[178] Venlafaxine, an antidepressant with a different mechanism of action, may be modestly more effective than SSRIs.[179] However, venlafaxine is not recommended in the UK as a first-line treatment because of evidence suggesting its risks may outweigh benefits,[180] and it is specifically discouraged in children and adolescents.[181][182]

For child and adolescent depression, fluoxetine is recommended if medication are used.[183] Fluoxetine; however, appears to have only slight benefit in children,[183][184] while other antidepressants have not been shown to be effective.[185] There is also insufficient evidence to determine effectiveness in those with depression complicated by dementia.[186] Any antidepressant can cause low serum sodium levels (also called hyponatremia);[187] nevertheless, it has been reported more often with SSRIs.[176] It is not uncommon for SSRIs to cause or worsen insomnia; the sedating antidepressant mirtazapine can be used in such cases.[188][189]

Irreversible monoamine oxidase inhibitors, an older class of antidepressants, have been plagued by potentially life-threatening dietary and drug interactions. They are still used only rarely, although newer and better-tolerated agents of this class have been developed.[190] The safety profile is different with reversible

monoamine oxidase inhibitors such as moclobemide where the risk of serious dietary interactions is negligible and dietary restrictions are less strict.[191]

For children, adolescents, and probably young adults between 18 and 24 years old, there is a higher risk of both suicidal ideations and suicidal behavior in those treated with SSRIs.[192][193] For adults, it is unclear whether SSRIs affect the risk of suicidality. One review found no connection;[194] another an increased risk;[195] and a third no risk in those 25–65 years old and a decrease risk in those more than 65.[196] A black box warning was introduced in the United States in 2007 on SSRI and other antidepressant medications due to increased risk of suicide in patients younger than 24 years old.[197] Similar precautionary notice revisions were implemented by the Japanese Ministry of Health.[198]

## Other medications

There is some evidence that fish oil supplements containing high levels of eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA) may be effective in major depression,[199] but other meta-analysis of the research conclude that positive effects may be due to publication bias.[200] There is some preliminary evidence that COX-2 inhibitors have a beneficial effect on major depression.[71] Lithium appears effective at lowering the risk of suicide in those with bipolar disorder and unipolar depression to nearly the same levels as the general population.[201] There is a narrow range of effective and safe dosages of lithium thus close monitoring may be needed.[202] Low-dose thyroid hormone may be added to existing antidepressants to treat persistent depression symptoms in people who have tried multiple courses of medication.[203]

## Electroconvulsive therapy

Electroconvulsive therapy (ECT) is a standard psychiatric treatment in which seizures are electrically induced in patients to provide relief from psychiatric illnesses.[204]:1880 ECT is used with informed consent[205] as a last line of intervention for major depressive disorder.[206]

A round of ECT is effective for about 50% of people with treatment-resistant major depressive disorder, whether it is unipolar or bipolar.[207] Follow-up treatment is still poorly studied, but about half of people who respond, relapse with twelve months.[208]

Aside from effects in the brain, the general physical risks of ECT are similar to those of brief general anesthesia.[209]:259 Immediately following treatment, the most common adverse effects are confusion and memory loss.[206][210] ECT is considered one of the least harmful treatment options available for severely depressed pregnant women.[211]

A usual course of ECT involves multiple administrations, typically given two or three times per week until the patient is no longer suffering symptoms ECT is administered under anesthetic with a muscle relaxant.[212] Electroconvulsive therapy can differ in its application in three ways: electrode placement, frequency of treatments, and the electrical waveform of the stimulus. These three forms of application have significant differences in both adverse side effects and symptom remission. After treatment, drug therapy is usually continued, and some patients receive maintenance ECT.[206]

ECT appears to work in the short term via an anticonvulsant effect mostly in the frontal lobes, and longer term via neurotrophic effects primarily in the medial temporal lobe.[213]

## Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) or deep transcranial magnetic stimulation is a noninvasive method used to stimulate small regions of the brain.[214] TMS was approved by the FDA for treatment-resistant major depressive disorder in 2008[215] and as of 2014 evidence supports that it is probably effective.[216] The American Psychiatric Association[217] the Canadian Network for Mood and Anxiety Disorders,[218] and the Royal Australia and New Zealand College of Psychiatrists have endorsed rTMS for trMDD.[219]

### Other

Bright light therapy reduces depression symptom severity, with benefit was found for both seasonal affective disorder and for nonseasonal depression, and an effect similar to those for conventional antidepressants. For non-seasonal depression, adding light therapy to the standard antidepressant treatment was not effective.[220] For non-seasonal depression where light was used mostly in combination with antidepressants or wake therapy a moderate effect was found, with response better than control treatment in high-quality studies, in studies that applied morning light treatment, and with people who respond to total or partial sleep deprivation.[221] Both analyses noted poor quality, short duration, and small size of most of the reviewed studies.

## Prognosis

Major depressive episodes often resolve over time whether or not they are treated. Outpatients on a waiting list show a 10–15% reduction in symptoms within a few months, with approximately 20% no longer meeting the full criteria for a depressive disorder.[222] The median duration of an episode has been estimated to be 23 weeks, with the highest rate of recovery in the first three months.[223]

Studies have shown that 80% of those suffering from their first major depressive episode will suffer from at least 1 more during their life,[224] with a lifetime average of 4 episodes.[225] Other general population studies indicate that around half those who have an episode recover (whether treated or not) and remain well, while the other half will have at least one more, and around 15% of those experience chronic recurrence.[226] Studies recruiting from selective inpatient sources suggest lower recovery and higher chronicity, while studies of mostly outpatients show that nearly all recover, with a median episode duration of 11 months. Around 90% of those with severe or psychotic depression, most of whom also meet criteria for other mental disorders, experience recurrence.[227][228]

Recurrence is more likely if symptoms have not fully resolved with treatment. Current guidelines recommend continuing antidepressants for four to six months after remission to prevent relapse. Evidence from many randomized controlled trials indicates continuing antidepressant medications after recovery can reduce the chance of relapse by 70% (41% on placebo vs. 18% on antidepressant). The preventive effect probably lasts for at least the first 36 months of use.[229]

Those people experiencing repeated episodes of depression require ongoing treatment in order to prevent more severe, long-term depression. In some cases, people must take medications for long periods of time or for the rest of their lives.[230]

Cases when outcome is poor are associated with inappropriate treatment, severe initial symptoms that may include psychosis, early age of onset, more previous episodes, incomplete recovery after 1 year, pre-existing severe mental or medical disorder, and family dysfunction as well.[231]

Depressed individuals have a shorter life expectancy than those without depression, in part because depressed patients are at risk of dying by suicide.[232] However, they also have a higher rate of dying from other causes,[233] being more susceptible to medical conditions such as heart disease.[234] Up to 60% of people who die by suicide have a mood disorder such as major depression, and the risk is especially high if a person has a marked sense of hopelessness or has both depression and borderline personality disorder.[235] The lifetime risk of suicide associated with a diagnosis of major depression in the US is estimated at 3.4%, which averages two highly disparate figures of almost 7% for men and 1% for women[236] (although suicide attempts are more frequent in women).[237] The estimate is substantially lower than a previously accepted figure of 15%, which had been derived from older studies of hospitalized patients.[238]

Depression is often associated with unemployment and poverty.[239] Major depression is currently the leading cause of disease burden in North America and other high-income countries, and the fourth-leading cause worldwide. In the year 2030, it is predicted to be the second-leading cause of disease burden worldwide after HIV, according to the World Health Organization.[240] Delay or failure in seeking treatment

after relapse, and the failure of health professionals to provide treatment, are two barriers to reducing disability.[241]

# Epidemiology

*Main article: Epidemiology of depression*

Disability-adjusted life year for unipolar depressive disorders per 100,000 inhabitants in 2004.[242]

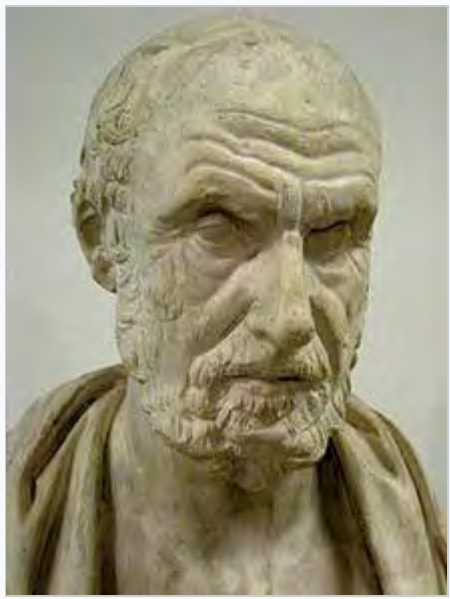
| | |
|---|---|
| no data | 1000–1075 |
| <700 | 1075–1150 |
| 700–775 | 1150–1225 |
| 775–850 | 1225–1300 |
| 850–925 | 1300–1375 |
| 925–1000 | 1375–1450 |
| | >1450 |

Major depressive disorder affects approximately 253 million people in 2013 (3.6% of the global population).[14] The percentage of people who are affected at one point in their life varies from 7% in Japan to 21% in France.[15] In most countries the number of people who have depression during their lives falls within an 8–18% range.[15] In North America, the probability of having a major depressive episode within a year-long period is 3–5% for males and 8–10% for females.[243][244] Major depression to be about twice as common in women as in men, although it is unclear why this is so, and whether factors unaccounted for are contributing to this.[245] The relative increase in occurrence is related to pubertal development rather than chronological age, reaches adult ratios between the ages of 15 and 18, and appears associated with psychosocial more than hormonal factors.[245] Depression is a major cause of disability worldwide.[246]

People are most likely to develop their first depressive episode between the ages of 30 and 40, and there is a second, smaller peak of incidence between ages 50 and 60.[247] The risk of major depression is increased with neurological conditions such as stroke, Parkinson's disease, or multiple sclerosis, and during the first year after childbirth.[248] It is also more common after cardiovascular illnesses, and is related more to a poor outcome than to a better one.[234][249] Studies conflict on the prevalence of depression in the elderly, but most data suggest there is a reduction in this age group.[250] Depressive disorders are more common to observe in urban than in rural population and the prevalence is in groups with stronger socioeconomic factors i.e. homelessness.[251]

# History

*Main article: History of depression*



The Ancient Greek physician Hippocrates described a syndrome of melancholia as a distinct disease with particular mental and physical symptoms; he characterized all "fears and despondencies, if they last a long time" as being symptomatic of the ailment.[252] It was a similar but far broader concept than today's depression; prominence was given to a clustering of the symptoms of sadness, dejection, and despondency, and often fear, anger, delusions and obsessions were included.[253]

The term *depression* itself was derived from the Latin verb *deprimere*, "to press down".[254] From the 14th century, "to depress" meant to subjugate or to bring down in spirits. It was used in 1665 in English author Richard Baker's *Chronicle* to refer to someone having "a great depression of spirit", and by English author Samuel Johnson in a similar sense in 1753.[255] The term also came into use in physiology and economics. An early usage referring to a psychiatric symptom was by French psychiatrist Louis Delasiauve in 1856, and by the 1860s it was

appearing in medical dictionaries to refer to a physiological and metaphorical lowering of emotional function.[256] Since Aristotle, melancholia had been associated with men of learning and intellectual brilliance, a hazard of contemplation and creativity. The newer concept abandoned these associations and through the 19th century, became more associated with women.[253]

Diagnoses of depression go back at least as far as Hippocrates


A historical caricature of a man with an approaching depression

Although *melancholia* remained the dominant diagnostic term, *depression* gained increasing currency in medical treatises and was a synonym by the end of the century; German psychiatrist Emil Kraepelin may have been the first to use it as the overarching term, referring to different kinds of melancholia as *depressive states*.[257]

Sigmund Freud likened the state of melancholia to mourning in his 1917 paper *Mourning and Melancholia*. He theorized that objective loss, such as the loss of a valued relationship through death or a romantic break-up, results in subjective loss as well; the depressed individual has identified with the object of affection through an unconscious, narcissistic process called the *libidinal cathexis* of the ego. Such loss results in severe melancholic symptoms more profound than mourning; not only is the outside world viewed negatively but the ego itself is compromised.[258] The patient's decline of self-perception is revealed in his belief of his own blame, inferiority, and unworthiness.[259] He also emphasized early life experiences as a predisposing factor.[253] Adolf Meyer put forward a mixed social and biological framework emphasizing *reactions* in the context of an individual's life, and argued that the term *depression* should be used instead of *melancholia*.[260] The first version of the DSM (DSM-I, 1952) contained *depressive reaction* and the DSM-II (1968) *depressive neurosis*, defined as an excessive reaction to internal conflict or an identifiable event, and also included a depressive type of manic-depressive psychosis within Major affective disorders.[261]

In the mid-20th century, researchers theorized that depression was caused by a chemical imbalance in neurotransmitters in the brain, a theory based on observations made in the 1950s of the effects of reserpine and isoniazid in altering monoamine neurotransmitter levels and affecting depressive symptoms.[262]

The term "unipolar" (along with the related term "bipolar") was coined by the neurologist and psychiatrist Karl Kleist, and subsequently used by his disciples Edda Neele and Karl Leonhard.[263]

The term *Major depressive disorder* was introduced by a group of US clinicians in the mid-1970s as part of proposals for diagnostic criteria based on patterns of symptoms (called the "Research Diagnostic Criteria", building on earlier Feighner Criteria),[264] and was incorporated into the DSM-III in 1980.[265] To maintain consistency the ICD-10 used the same criteria, with only minor alterations, but using the DSM diagnostic threshold to mark a *mild depressive episode*, adding higher threshold categories for moderate and severe episodes.[107][265] The ancient idea of *melancholia* still survives in the notion of a melancholic subtype.

The new definitions of depression were widely accepted, albeit with some conflicting findings and views. There have been some continued empirically based arguments for a return to the diagnosis of melancholia.[266][267] There has been some criticism of the expansion of coverage of the diagnosis, related to the development and promotion of antidepressants and the biological model since the late 1950s.[268]

## Society and culture

*See also: List of people with major depressive disorder*

## Terminology

The 16th American president Abraham Lincoln had "melancholy", a condition that now may be referred to as clinical depression.[269]

The term "depression" is used in a number of different ways. It is often used to mean this syndrome but may refer to other mood disorders or simply to a low mood. People's conceptualizations of depression vary widely, both within and among cultures. "Because of the lack of scientific certainty," one commentator has observed, "the debate over depression turns on questions of language. What we call it—'disease,' 'disorder,' 'state of mind'—affects how we view, diagnose, and treat it."[270] There are cultural differences in the extent to which serious depression is considered an illness requiring personal professional treatment, or is an indicator of something else, such as the need to address social or moral problems, the result of biological imbalances, or a reflection of individual differences in the understanding of distress that may reinforce feelings of powerlessness, and emotional struggle.[271][272]

The diagnosis is less common in some countries, such as China. It has been argued that the Chinese traditionally deny or somatize emotional depression (although since the early 1980s, the Chinese denial of depression may have modified).[273] Alternatively, it may be that Western cultures reframe and elevate some expressions of human distress to disorder status. Australian professor Gordon Parker and others have argued that the Western concept of depression "medicalizes" sadness or misery.[274][275] Similarly, Hungarian-American psychiatrist Thomas Szasz and others argue that depression is a metaphorical illness that is inappropriately regarded as an actual disease.[276] There has also been concern that the DSM, as well as the field of descriptive psychiatry that employs it, tends to reify abstract phenomena such as depression, which may in fact be social constructs.[277] American archetypal psychologist James Hillman writes that depression can be healthy for the soul, insofar as "it brings refuge, limitation, focus, gravity, weight, and humble powerlessness."[278] Hillman argues that therapeutic attempts to eliminate depression echo the Christian theme of resurrection, but have the unfortunate effect of demonizing a soulful state of being.

## Stigma

Historical figures were often reluctant to discuss or seek treatment for depression due to social stigma about the condition, or due to ignorance of diagnosis or treatments. Nevertheless, analysis or interpretation of letters, journals, artwork, writings, or statements of family and friends of some historical personalities has led to the presumption that they may have had some form of depression. People who may have had depression include English author Mary Shelley,[279] American-British writer Henry James,[280] and American president Abraham Lincoln.[281] Some well-known contemporary people with possible depression include Canadian songwriter Leonard Cohen[282] and American playwright and novelist Tennessee Williams.[283] Some pioneering psychologists, such as Americans William James[284][285] and John B. Watson,[286] dealt with their own depression.

There has been a continuing discussion of whether neurological disorders and mood disorders may be linked to creativity, a discussion that goes back to Aristotelian times.[287][288] British literature gives many examples of reflections on depression.[289] English philosopher John Stuart Mill experienced a several-months-long period of what he called "a dull state of nerves", when one is "unsusceptible to enjoyment or pleasurable excitement; one of those moods when what is pleasure at other times, becomes insipid or indifferent". He quoted English poet Samuel Taylor Coleridge's "Dejection" as a perfect description of his case: "A grief without a pang, void, dark and drear, / A drowsy, stifled, unimpassioned grief, / Which finds no natural outlet or relief / In word, or sigh, or tear."[290][291] English writer Samuel Johnson used the term

"the black dog" in the 1780s to describe his own depression,[292] and it was subsequently popularized by depression sufferer former British Prime Minister Sir Winston Churchill.[292]

Social stigma of major depression is widespread, and contact with mental health services reduces this only slightly. Public opinions on treatment differ markedly to those of health professionals; alternative treatments are held to be more helpful than pharmacological ones, which are viewed poorly.[293] In the UK, the Royal College of Psychiatrists and the Royal College of General Practitioners conducted a joint Five-year Defeat Depression campaign to educate and reduce stigma from 1992 to 1996;[294] a MORI study conducted afterwards showed a small positive change in public attitudes to depression and treatment.[295]

## Research

Trials are looking at the effects of botulinum toxins on depression. The idea is that the drug is used to make the person look less frowning and that this stops the negative facial feedback from the face.[296] In 2015 it turned out, however, that the partly positive effects that had been observed until then could have been placebo effects.[297]

MDD has been studied by taking MRI scans of patients with depression have revealed a number of differences in brain structure compared to those who are not depressed. Meta-analyses of neuroimaging studies in major depression reported that, compared to controls, depressed patients had increased volume of the lateral ventricles and adrenal gland and smaller volumes of the basal ganglia, thalamus, hippocampus, and frontal lobe (including the orbitofrontal cortex and gyrus rectus).[298][299] Hyperintensities have been associated with patients with a late age of onset, and have led to the development of the theory of vascular depression.[300]

## Elderly

*See also: Late life depression*

Depression is especially common among those over 65 years of age and increases in frequency with age beyond this age.[301] In addition the risk of depression increases in relation to the age and frailty of the individual.[301] Depression is one the most important factors which negatively impact quality of life in adults as well as the elderly.[301] Both symptoms and treatment among the elderly differ from those of the rest of the adult populations.[301]

As with many other diseases it is common among the elderly not to present classical depressive symptoms.[301] Diagnosis and treatment is further complicated in that the elderly are often simultaneously treated with a number of other drugs, and often have other concurrent diseases.[301] Treatment differs in that studies of SSRI-drugs have shown lesser and often inadequate effect among the elderly, while other drugs with more clear effects have adverse effects which can be especially difficult to handle among the elderly.[301] Duloxetine is an SNRI-drug with documented effect on recurring depression among the elderly, but has adverse effects in form of dizziness, dryness of the mouth, diarrhea, and constipation.[301]

Problem solving therapy was as of 2015 the only psychological therapy with proven effect, and can be likened to a simpler form of cognitive behavioral therapy.[301] However, elderly with depression are seldom offered any psychological treatment, and the evidence surrounding which other treatments are effective is incomplete.[301] Electroconvulsive therapy (ECT or electric-shock therapy) has been used as treatment of the elderly, and register-studies suggest it is effective although less so among the elderly than among the rest of the adult population.[301]

The risks involved with treatment of depression among the elderly as opposed to benefits is not entirely clear.[301] Awaiting more evidence on how depression-treatment among the elderly is best designed it is important to follow up treatment results, and to reconsider changing treatments if it does not help.[301]

# Other animals

*Further information: Animal psychopathology § Depression*

# References


1. ^ a b c d e f g h i "Depression". *NIMH*. May 2016. Retrieved 31 July 2016.
2. ^ a b c d e f g h i American Psychiatric Association (2013), *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.), Arlington: American Psychiatric Publishing, pp. 160–168, ISBN 978-0-89042-555-8, retrieved 22 July 2016
3. ^ Richards, C. Steven; O'Hara, Michael W. (2014). *The Oxford Handbook of Depression and Comorbidity*. Oxford University Press. p. 254. ISBN 9780199797042.
4. ^ Lynch, Virginia A.; Duval, Janet Barber (2010). *Forensic Nursing Science*. Elsevier Health Sciences. p. 453. ISBN 0323066380.
5. ^ a b Patton, Lauren L. (2015). *The ADA Practical Guide to Patients with Medical Conditions* (2 ed.). John Wiley & Sons. p. 339. ISBN 9781118929285.
6. ^ a b Siu, AL; US Preventive Services Task Force, (USPSTF); Bibbins-Domingo, K; Grossman, DC; Baumann, LC; Davidson, KW; Ebell, M; García, FA; Gillman, M; Herzstein, J; Kemper, AR; Krist, AH; Kurth, AE; Owens, DK; Phillips, WR; Phipps, MG; Pignone, MP (26 January 2016). "Screening for Depression in Adults: US Preventive Services Task Force Recommendation Statement.". *JAMA*. **315** (4): 380–7. doi:10.1001/jama.2015.18392. PMID 26813211.
7. ^ a b Siu, AL; U.S. Preventive Services Task, Force (1 March 2016). "Screening for Depression in Children and Adolescents: U.S. Preventive Services Task Force Recommendation Statement.". *Annals of Internal Medicine*. **164** (5): 360–6. doi:10.7326/M15-2957. PMID 26858097.
8. ^ a b Gilbody S, House AO, Sheldon TA (2005). "Screening and case finding instruments for depression". *Cochrane Database of Systematic Reviews* (4): CD002792. doi:10.1002/14651858.CD002792.pub2. PMID 16235301.
9. ^ a b c Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, Fawcett J (January 2010). "Antidepressant drug effects and depression severity: a patient-level meta-analysis". *JAMA*. **303** (1): 47–53. doi:10.1001/jama.2009.1943. PMC 3712503. PMID 20051569.
10. ^ a b Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT (February 2008). "Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration". *PLoS Med*. **5** (2): e45. doi:10.1371/journal.pmed.0050045. PMC 2253608. PMID 18303940.
11. ^ Braun, C; Bschor, T; Franklin, J; Baethge, C (2016). "Suicides and Suicide Attempts during Long-Term Treatment with Antidepressants: A Meta-Analysis of 29 Placebo-Controlled Studies Including 6,934 Patients with Major Depressive Disorder.". *Psychotherapy and psychosomatics*. **85** (3): 171–9. doi:10.1159/000442293. PMID 27043848.
12. ^ Driessen Ellen; Hollon Steven D (2010). "Cognitive Behavioral Therapy for Mood Disorders: Efficacy, Moderators and Mediators". *Psychiatric Clinics of North America*. **33** (3): 537–55. doi:10.1016/j.psc.2010.04.005. PMC 2933381. PMID 20599132.
13. ^ Association, American Psychiatric. *American Psychiatric Association Practice Guidelines for the Treatment of Psychiatric Disorders: Compendium 2006*. American Psychiatric Pub. p. 780. ISBN 9780890423851.
14. ^ a b Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/S0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
15. ^ a b c d e Kessler, RC; Bromet, EJ (2013). "The epidemiology of depression across cultures.". *Annual review of public health*. **34**: 119–38. doi:10.1146/annurev-publhealth-031912-114409. PMC 4100461. PMID 23514317.
16. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/S0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
17. ^ a b Hersen, Michel; Rosqvist, Johan (2008). *Handbook of Psychological Assessment, Case Conceptualization, and Treatment, Volume 1: Adults*. John Wiley & Sons. p. 32. ISBN 9780470173565.
18. ^ Strakowski, Stephen M.; Nelson, Erik. "Introduction". *Major Depressive Disorder*. Oxford University Press. p. Chapter 1. ISBN 9780190206185.
19. ^ a b c d e *Depression* (PDF). National Institute of Mental Health (NIMH). Retrieved 7 September 2008.

20. ^ Hays RD, Wells KB, Sherbourne CD, Rogers W, Spritzer K (1995). "Functioning and well-being outcomes of patients with depression compared with chronic general medical illnesses". *Archives of General Psychiatry*. **52** (1): 11–19. doi:10.1001/archpsyc.1995.03950130011002. PMID 7811158.
21. ^ *a b c d e f* American Psychiatric Association 2000a, p. 349
22. ^ American Psychiatric Association 2000a, p. 412
23. ^ *a b* Delgado PL, Schillerstrom J (2009). "Cognitive Difficulties Associated With Depression: What Are the Implications for Treatment?". *Psychiatric Times*. **26** (3).
24. ^ Judd, LL; Schettler, PJ; Coryell, W; Akiskal, HS; Fiedorowicz, JG (2013). "Overt irritability/anger in unipolar major depressive episodes: past and current characteristics and implications for long-term course". *JAMA Psychiatry*. **70** (11): 1171–80. doi:10.1001/jamapsychiatry.2013.1957. PMID 24026579.
25. ^ *a b c d* American Psychiatric Association 2000a, p. 350
26. ^ "Insomnia: Assessment and Management in Primary Care". *American Family Physician*. **59** (11): 3029–38. 1999. Retrieved 12 November 2014.
27. ^ Patel V, Abas M, Broadhead J (2001). "Depression in developing countries: Lessons from Zimbabwe". *BMJ*. **322** (7284): 482–84. doi:10.1136/bmj.322.7284.482.
28. ^ Faculty of Psychiatry of Old Age, NSW Branch, RANZCP; Kitching D Raphael B (2001). *Consensus Guidelines for Assessment and Management of Depression in the Elderly* (PDF). North Sydney, New South Wales: NSW Health Department. p. 2. ISBN 0-7347-3341-0.
29. ^ Yohannes AM, Baldwin RC (2008). "Medical Comorbidities in Late-Life Depression". *Psychiatric Times*. **25** (14).
30. ^ American Psychiatric Association 2000a, p. 354
31. ^ Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG (1996). "Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey". *British Journal of Psychiatry*. **168** (suppl 30): 17–30. PMID 8864145.
32. ^ Hirschfeld RM (2001). "The Comorbidity of Major Depression and Anxiety Disorders: Recognition and Management in Primary Care". *Primary Care Companion to the Journal of Clinical Psychiatry*. **3** (6): 244–254. PMC 181193. PMID 15014592.
33. ^ Grant BF (1995). "Comorbidity between DSM-IV drug use disorders and major depression: Results of a national survey of adults". *Journal of Substance Abuse*. **7** (4): 481–87. doi:10.1016/0899-3289(95)90017-9. PMID 8838629.
34. ^ Hallowell EM, Ratey JJ (2005). *Delivered from distraction: Getting the most out of life with Attention Deficit Disorder*. New York: Ballantine Books. pp. 253–55. ISBN 0-345-44231-8.
35. ^ Brunsvold GL, Oepen G (2008). "Comorbid Depression in ADHD: Children and Adolescents". *Psychiatric Times*. **25** (10).
36. ^ Bair MJ, Robinson RL, Katon W, Kroenke K (2003). "Depression and Pain Comorbidity: A Literature Review". *Archives of Internal Medicine*. **163** (20): 2433–45. doi:10.1001/archinte.163.20.2433. PMID 14609780.
37. ^ Swardfager W, Herrmann N, Marzolini S, Saleem M, Farber SB, Kiss A, Oh PI, Lanctôt KL (2011). "Major depressive disorder predicts completion, adherence, and outcomes in cardiac rehabilitation: a prospective cohort study of 195 patients with coronary artery disease.". *Journal of Clinical Psychiatry*. **72** (9): 1181–8. doi:10.4088/jcp.09m05810blu. PMID 21208573.
38. ^ Schulman J, Shapiro BA (2008). "Depression and Cardiovascular Disease: What Is the Correlation?". *Psychiatric Times*. **25** (9).
39. ^ Department of Health and Human Services (1999). "The fundamentals of mental health and mental illness" (PDF). *Mental Health: A Report of the Surgeon General*. Retrieved 11 November 2008.
40. ^ Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R (July 2003). "Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene". *Science*. **301** (5631): 386–89. Bibcode:2003Sci...301..386C. doi:10.1126/science.1083968. PMID 12869766.
41. ^ Haeffel GJ, Getchell M, Koposov RA, Yrigollen CM, Deyoung CG, Klinteberg BA, Oreland L, Ruchkin VV, Grigorenko EL (2008). "Association between polymorphisms in the dopamine transporter gene and depression: evidence for a gene-environment interaction in a sample of juvenile detainees" (PDF). *Psychol Sci*. **19** (1): 62–9. doi:10.1111/j.1467-9280.2008.02047.x. PMID 18181793.
42. ^ Slavich GM (2004). "Deconstructing depression: A diathesis-stress perspective (Opinion)". *APS Observer*. Retrieved 11 November 2008.
43. ^ Barlow 2005, p. 226
44. ^ Shah N, Eisner T, Farrell M, Raeder C (July–August 1999). "An overview of SSRIs for the treatment of depression" (PDF). *Journal of the Pharmacy Society of Wisconsin*. Retrieved 10 November 2008.
45. ^ *a b* Nutt DJ (2008). "Relationship of neurotransmitters to the symptoms of major depressive disorder". *Journal of Clinical Psychiatry*. 69 Suppl E1: 4–7. PMID 18494537.
46. ^ Hirschfeld RM (2000). "History and evolution of the monoamine hypothesis of depression". *Journal of Clinical*

*Psychiatry*. 61 Suppl 6: 4–6. PMID 10775017.
47. ^ Jacobsen, Jacob P. R.; Medvedev, Ivan O.; Caron, Marc G. (5 September 2012). "The 5-HT deficiency theory of depression: perspectives from a naturalistic 5-HT deficiency model, the tryptophan hydroxylase 2Arg439His knockin mouse". *Philosophical Transactions of the Royal Society B: Biological Sciences*. **367** (1601): 2444–2459. doi:10.1098/rstb.2012.0109. ISSN 0962-8436. PMC 3405680. PMID 22826344.
48. ^ Delgado PL, Moreno FA (2000). "Role of norepinephrine in depression". *J Clin Psychiatry*. 61 Suppl 1: 5–12. PMID 10703757.
49. ^ Delgado PL (2000). "Depression: the case for a monoamine deficiency". *Journal of Clinical Psychiatry*. 61 Suppl 6: 7–11. PMID 10775018.
50. ^ Ruhe, HG; Mason, NS; Schene, AH (2007). "Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies". *Molecular Psychiatry*. **12**: 331–359. doi:10.1038/sj.mp.4001949. PMID 17389902.
51. ^ Lacasse, Jeffrey R.; Leo, Jonathan (8 November 2005). "Serotonin and Depression: A Disconnect between the Advertisements and the Scientific Literature". *PLoS Medicine*. **2** (12): e392. doi:10.1371/journal.pmed.0020392. PMC 1277931. PMID 16268734.
52. ^ Cottencin O (December 2009). "[Severe depression and addictions]". *Encephale* (in French). 35 Suppl 7: S264–8. doi:10.1016/S0013-7006(09)73483-9. PMID 20141784.
53. ^ Falk DE, Yi HY, Hilton ME (2008). "Age of onset and temporal sequencing of lifetime DSM-IV alcohol use disorders relative to comorbid mood and anxiety disorders". *Drug Alcohol Depend*. **94** (1–3): 234–45. doi:10.1016/j.drugalcdep.2007.11.022. PMC 2386955. PMID 18215474.
54. ^ *a b* Boden JM, Fergusson DM (May 2011). "Alcohol and depression". *Addiction*. **106** (5): 906–14. doi:10.1111/j.1360-0443.2010.03351.x. PMID 21382111.
55. ^ Professor Heather Ashton (2002). "Benzodiazepines: How They Work and How to Withdraw".
56. ^ Kelley KW, Dantzer R (June 2011). "Alcoholism and inflammation: neuroimmunology of behavioral and mood disorders". *Brain Behav. Immun*. 25 Suppl 1: S13–20. doi:10.1016/j.bbi.2010.12.013. PMID 21193024.
57. ^ Semple, David; Roger Smyth; Jonathan Burns; Rajan Darjee; Andrew McIntosh (2007) [2005]. "13". *Oxford Handbook of Psychiatry*. United Kingdom: Oxford University Press. p. 540. ISBN 0-19-852783-7.
58. ^ Collier, Judith; Longmore, Murray (2003). "4". In Scally, Peter. *Oxford Handbook of Clinical Specialties* (6 ed.). Oxford University Press. p. 366. ISBN 978-0-19-852518-9.
59. ^ Janicak, Philip G.; Marder, Stephen R.; Pavuluri, Mani N. (2011). *Principles and practice of psychopharmacotherap*. Philadelphia: Wolters Kluwer Health/Lippincott Williams Wilkins. pp. 507–508. ISBN 978-1-60547-565-3.
60. ^ Johnson, Bankole A. (2011). *Addiction medicine : science and practic*. New York: Springer. pp. 301–303. ISBN 978-1-4419-0337-2.
61. ^ Marshall BD, Werb D (June 2010). "Health outcomes associated with methamphetamine use among young people: a systematic review". *Addiction*. **105** (6): 991–1002. doi:10.1111/j.1360-0443.2010.02932.x. PMID 20659059.
62. ^ *a b* Cutter WJ, Norbury R, Murphy DG (2003). "Oestrogen, brain function, and neuropsychiatric disorders". *Journal of Neurology, Neurosurgery and Psychiatry*. **74** (7): 837–40. doi:10.1136/jnnp.74.7.837. PMC 1738534. PMID 12810759.
63. ^ Douma SL, Husband C, O'Donnell ME, Barwin BN, Woodend AK (2005). "Estrogen-related Mood Disorders Reproductive Life Cycle Factors". *Advances in Nursing Science*. **28** (4): 364–375. doi:10.1097/00012272-200510000-00008. PMID 16292022.
64. ^ Lasiuk GC, Hegadoren KM (2007). "The Effects of Estradiol on Central Serotonergic Systems and Its Relationship to Mood in Women". *Biological Research for Nursing*. **9** (2): 147–160. doi:10.1177/1099800407305600. PMID 17909167.
65. ^ Monteleone P (2001). "Endocrine disturbances and psychiatric disorders". *Current Opinion in Psychiatry*. Lippincott Williams & Wilkins, Inc. **14** (6): 605–10. doi:10.1097/00001504-200111000-00020. ISSN 0951-7367.
66. ^ Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR (June 2009). "Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis". *JAMA*. **301** (23): 2462–71. doi:10.1001/jama.2009.878. PMC 2938776. PMID 19531786.
67. ^ Munafò MR, Durrant C, Lewis G, Flint J (February 2009). "Gene X environment interactions at the serotonin transporter locus". *Biol. Psychiatry*. **65** (3): 211–9. doi:10.1016/j.biopsych.2008.06.009. PMID 18691701.
68. ^ Uher R, McGuffin P (January 2010). "The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression: 2009 update". *Mol. Psychiatry*. **15** (1): 18–22. doi:10.1038/mp.2009.123. PMID 20029411.
69. ^ Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW (2008). "From inflammation to sickness and depression: when the immune system subjugates the brain". *Nature Reviews Neuroscience*. **9** (1): 46–56. doi:10.1038/nrn2297. PMC 2919277. PMID 18073775.

70. ^ Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL (2010). "A meta-analysis of cytokines in major depression". *Biological Psychiatry*. **67** (5): 446–457. doi:10.1016/j.biopsych.2009.09.033. PMID 20015486.
71. ^ [a] [b] Müller N, Myint AM, Schwarz MJ (February 2011). "Inflammatory biomarkers and depression". *Neurotox Res*. **19** (2): 308–18. doi:10.1007/s12640-010-9210-2. PMID 20658274.
72. ^ Berk, Michael; Williams, Lana J.; Jacka, Felice N.; O'Neil, Adrienne; Pasco, Julie A.; Moylan, Steven; Allen, Nicholas B.; Stuart, Amanda L.; Hayley, Amie C. (1 January 2013). "So depression is an inflammatory disease, but where does the inflammation come from?". *BMC Medicine*. **11**: 200. doi:10.1186/1741-7015-11-200. ISSN 1741-7015. PMC 3846682. PMID 24228900.
73. ^ Schmahmann JD (2004). "Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome". *J Neuropsychiatry Clin Neurosci*. **16** (3): 367–78. doi:10.1176/appi.neuropsych.16.3.367. PMID 15377747.
74. ^ Konarski JZ, McIntyre RS, Grupp LA, Kennedy SH (May 2005). "Is the cerebellum relevant in the circuitry of neuropsychiatric disorders?". *J Psychiatry Neurosci*. **30** (3): 178–86. PMID 15944742.
75. ^ Schmahmann JD, Weilburg JB, Sherman JC (2007). "The neuropsychiatry of the cerebellum – insights from the clinic". *Cerebellum*. **6** (3): 254–67. doi:10.1080/14734220701490995. PMID 17786822.
76. ^ [a] [b] Raphael B (2000). "Unmet Need for Prevention". In Andrews G, Henderson S. *Unmet Need in Psychiatry:Problems, Resources, Responses*. Cambridge University Press. pp. 138–39. ISBN 0-521-66229-X.
77. ^ Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB (2008). "The link between childhood trauma and depression: insights from HPA axis studies in humans". *Psychoneuroendocrinology*. **33** (6): 693–710. doi:10.1016/j.psyneuen.2008.03.008. PMID 18602762.
78. ^ Kessler RC (1997). "The effects of stressful life events on depression". *Annual Review of Psychology*. **48**: 191–214. doi:10.1146/annurev.psych.48.1.191. PMID 9046559.
79. ^ Kendler KS, Hettema JM, Butera F, Gardner CO, Prescott CA (2003). "Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety". *Archives of General Psychiatry*. **60** (8): 789–796. doi:10.1001/archpsyc.60.8.789. PMID 12912762.
80. ^ Slavich GM, Thornton T, Torres LD, Monroe SM, Gotlib IH (2009). "Targeted rejection predicts hastened onset of major depression". *Journal of Social and Clinical Psychology*. **28**: 223–243. doi:10.1521/jscp.2009.28.2.223. PMC 2847269. PMID 20357895.
81. ^ Monroe SM, Slavich GM, Torres LD, Gotlib IH (2007). "Major life events and major chronic difficulties are differentially associated with history of major depressive episodes". *Journal of Abnormal Psychology*. **116** (1): 116–124. doi:10.1037/0021-843X.116.1.116. PMID 17324022.
82. ^ Sadock 2002, p. 540
83. ^ Vilhjalmsson R (1993). "Life stress, social support and clinical depression: A reanalysis of the literature". *Social Science & Medicine*. **37** (3): 331–42. doi:10.1016/0277-9536(93)90264-5. PMID 8356482.
84. ^ Kim D (2008). "Blues from the neighborhood? Neighborhood characteristics and depression". *Epidemiologic reviews*. **30**: 101–17. doi:10.1093/epirev/mxn009. PMID 18753674.
85. ^ Bonde JP (2008). "Psychosocial factors at work and risk of depression: A systematic review of the epidemiological evidence". *Journal of Occupational and Environmental Medicine*. **65** (7): 438–45. doi:10.1136/oem.2007.038430. PMID 18417557.
86. ^ Cox WT, Abramson LY, Devine PG, Hollon SD (2012). "Stereotypes, Prejudice, and Depression: The Integrated Perspective". *Perspectives on Psychological Science*. **7** (5): 427–449. doi:10.1177/1745691612455204. PMID 26168502.
87. ^ Sloman L, Gilbert P, Hasey G (2003). "Evolved mechanisms in depression: The role and interaction of attachment and social rank in depression". *Journal of Affective Disorders*. **74** (2): 107–21. doi:10.1016/S0165-0327(02)00116-7. PMID 12706512.
88. ^ Kaufmann IM (1 September 1993). "Rural psychiatric services. A collaborative model". *Canadian Family Physician*. **39**: 1957–61. PMC 2379905. PMID 8219844.
89. ^ "Call for action over Third World depression". *BBC News (Health)*. British Broadcasting Corporation (BBC). 1 November 1999. Retrieved 11 October 2008.
90. ^ Zimmerman M, Chelminski I, Posternak M (September 2004). "A Review of Studies of the Hamilton Depression Rating Scale in Healthy Controls: Implications for the Definition of Remission in Treatment Studies Of Depression". *J Nerv Ment Dis*. **192** (9): 595–601. doi:10.1097/01.nmd.0000138226.22761.39. PMID 15348975.
91. ^ McPherson A, Martin CR (February 2010). "A Narrative Review of the Beck Depression Inventory (BDI) and Implications for its Use in an Alcohol-Dependent Population". *J Psychiatr Ment Health Nurs*. **17** (1): 19–30. doi:10.1111/j.1365-2850.2009.01469.x. PMID 20100303.
92. ^ Osman, A.; Bagge, C. L.; Gutierrez, P. M.; Konick, L. C.; Kopper, B. A.; Barrios, F. X. (1 December 2001). "The Suicidal Behaviors Questionnaire-Revised (SBQ-R):Validation with Clinical and Nonclinical Samples". *Assessment*. **8**

(4): 443–454. doi:10.1177/107319110100800409. PMID 11785588.
93. ^ a b Sharp LK, Lipsky MS (2002). "Screening for depression across the lifespan: a review of measures for use in primary care settings". *American Family Physician*. **66** (6): 1001–8. PMID 12358212.
94. ^ Cepoiu M, McCusker J, Cole MG, Sewitch M, Belzile E, Ciampi A (2008). "Recognition of depression by non-psychiatric physicians—a systematic literature review and meta-analysis". *J Gen Intern Med*. **23** (1): 25–36. doi:10.1007/s11606-007-0428-5. PMC 2173927. PMID 17968628.
95. ^ Dale J, Sorour E, Milner G (2008). "Do psychiatrists perform appropriate physical investigations for their patients? A review of current practices in a general psychiatric inpatient and outpatient setting". *Journal of Mental Health*. **17** (3): 293–98. doi:10.1080/09638230701498325.
96. ^ Orengo CA, Fullerton G, Tan R (2004). "Male depression: A review of gender concerns and testosterone therapy". *Geriatrics*. **59** (10): 24–30. PMID 15508552.
97. ^ Ju, SY (2013). "Serum 25-hydroxyvitamin D levels and the risk of depression: a systematic review and meta-analysis". *J Nutr Health Aging*. **17** (5): 447–55. doi:10.1007/s12603-012-0418-0. PMID 23636546.
98. ^ Reid LM, Maclullich AM (2006). "Subjective memory complaints and cognitive impairment in older people". *Dementia and geriatric cognitive disorders*. **22** (5–6): 471–85. doi:10.1159/000096295. PMID 17047326.
99. ^ Katz IR (1998). "Diagnosis and treatment of depression in patients with Alzheimer's disease and other dementias". *The Journal of Clinical Psychiatry*. 59 Suppl 9: 38–44. PMID 9720486.
100. ^ Wright SL, Persad C (2007). "Distinguishing between depression and dementia in older persons: Neuropsychological and neuropathological correlates". *Journal of Geriatric Psychiatry and Neurology*. **20** (4): 189–98. doi:10.1177/0891988707308801. PMID 18004006.
101. ^ Sadock 2002, p. 108
102. ^ Sadock 2002, p. 260
103. ^ Hahn T, Marquand AF, Ehlis AC, Dresler T, Kittel-Schneider S, Jarczok TA, Lesch KP, Jakob PM, Mourao-Miranda J, Brammer MJ, Fallgatter AJ (December 2010). "Integrating Neurobiological Markers of Depression". *Arch. Gen. Psychiatry*. **68** (4): 361–368. doi:10.1001/archgenpsychiatry.2010.178. PMID 21135315. Retrieved 1 April 2011.
104. ^ a b c "Mental and behavioural disorders: Mood [affective] disorders". World Health Organization. 2010. Retrieved 8 November 2008.
105. ^ Sadock 2002, p. 288
106. ^ American Psychiatric Association 2000a, p. xxix
107. ^ a b Gruenberg, A.M., Goldstein, R.D., Pincus, H.A. (2005). "Classification of Depression: Research and Diagnostic Criteria: DSM-IV and ICD-10" (PDF). *Biology of Depression: From Novel Insights to Therapeutic Strategies (eds J. Licinio and M.-L. Wong)*. Wiley-VCH Verlag GmbH. doi:10.1002/9783527619672.ch1. Retrieved 30 October 2008.
108. ^ "The ICD-10 Classification of Mental and Behavioural Disorders: Clinical descriptions and diagnostic guidelines" (PDF). World Health Organization. 2010. Retrieved 12 November 2014.
109. ^ The ICD-10 classification of mental and behavioral disorders. Clinical description and diagnostic guideline. Geneva: World Health Organization, 1992
110. ^ American Psychiatric Association 2000a
111. ^ American Psychiatric Association 2000a, p. 345
112. ^ American Psychiatric Association 2000a, p. 372
113. ^ Parker 1996, p. 173
114. ^ American Psychiatric Association 2000a, p. 352
115. ^ Wakefield JC, Schmitz MF, First MB, Horwitz AV (2007). "Extending the bereavement exclusion for major depression to other losses: Evidence from the National Comorbidity Survey". *Archives of General Psychiatry*. **64** (4): 433–40. doi:10.1001/archpsyc.64.4.433. PMID 17404120. Lay summary – *The Washington Post* (3 April 2007).
116. ^ Kendler KS, Gardner CO (1 February 1998). "Boundaries of major depression: An evaluation of DSM-IV criteria". *American Journal of Psychiatry*. **155** (2): 172–77. PMID 9464194.
117. ^ a b Sadock 2002, p. 552
118. ^ American Psychiatric Association 2000a, p. 778
119. ^ Carta MG, Altamura AC, Hardoy MC, Pinna F, Medda S, Dell'Osso L, Carpiniello B, Angst J (2003). "Is recurrent brief depression an expression of mood spectrum disorders in young people?". *European Archives of Psychiatry and Clinical Neuroscience*. **253** (3): 149–53. doi:10.1007/s00406-003-0418-5. PMID 12904979.
120. ^ Rapaport MH, Judd LL, Schettler PJ, Yonkers KA, Thase ME, Kupfer DJ, Frank E, Plewes JM, Tollefson GD, Rush AJ (2002). "A descriptive analysis of minor depression". *American Journal of Psychiatry*. **159** (4): 637–43. doi:10.1176/appi.ajp.159.4.637. PMID 11925303.
121. ^ a b American Psychiatric Association 2000a, p. 355
122. ^ American Psychiatric Association 2000a, pp. 419–20

123. ^ American Psychiatric Association 2000a, pp. 421–22
124. ^ American Psychiatric Association 2000a, pp. 417–18
125. ^ Nonacs, Ruta M (4 December 2007). "Postpartum depression". eMedicine. Retrieved 30 October 2008.
126. ^ American Psychiatric Association 2000a, p. 425
127. ^ Akiskal HS, Benazzi F (2006). "The DSM-IV and ICD-10 categories of recurrent [major] depressive and bipolar II disorders: Evidence that they lie on a dimensional spectrum". *Journal of Affective Disorders*. **92** (1): 45–54. doi:10.1016/j.jad.2005.12.035. PMID 16488021.
128. ^ [a] [b] Cuijpers P, van Straten A, Smit F, Mihalopoulos C, Beekman A (2008). "Preventing the onset of depressive disorders: a meta-analytic review of psychological interventions". *Am J Psychiatry*. **165** (10): 1272–80. doi:10.1176/appi.ajp.2008.07091422. PMID 18765483.
129. ^ Li, F; Liu, X; Zhang, D (10 September 2015). "Fish consumption and risk of depression: a meta-analysis.". *Journal of epidemiology and community health*: jech–2015–206278. doi:10.1136/jech-2015-206278. PMID 26359502.
130. ^ [a] [b] Muñoz RF, Beardslee WR, Leykin Y (May–June 2012). "Major depression can be prevented". *The American Psychologist*. **67** (4): 285–95. doi:10.1037/a0027666. PMC 4533896. PMID 22583342.
131. ^ Cuijpers, P (20 September 2012). *Prevention and early treatment of mental ill-health* (PDF). PSYCHOLOGY FOR HEALTH: Contributions to Policy Making, Brussels.
132. ^ Griffiths, K.M.; Farrer, L.; Christensen, H. (2010). "The efficacy of internet interventions for depression and anxiety disorders: a review of randomised controlled trials" (PDF). *Medical Journal of Australia*. **192** (11): 4–11. Retrieved 12 November 2014.
133. ^ Jané-Llopis E, Hosman C, Jenkins R, Anderson P (2003). "Predictors of efficacy in depression prevention programmes" (PDF). *British Journal of Psychiatry*. Retrieved 2 April 2009.
134. ^ Cuijpers P, Muñoz RF, Clarke GN, Lewinsohn PM (2009). "Psychoeducational treatment and prevention of depression: the "Coping with Depression" course thirty years later". *Clinical Psychology Review*. **29** (5): 449–458. doi:10.1016/j.cpr.2009.04.005. PMID 19450912.
135. ^ "Depression". National Institute for Health and Care Excellence. December 2004. Archived from the original on 15 November 2008. Retrieved 20 March 2013.
136. ^ "PsychiatryOnline | APA Practice Guidelines | Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition".
137. ^ Patel V, Araya R, Bolton P (2004). "Editorial: Treating depression in the developing world". *Tropical Medicine & International Health*. **9** (5): 539–41. doi:10.1111/j.1365-3156.2004.01243.x. PMID 15117296. (subscription required (help)).
138. ^ Cox GR, Callahan P, Churchill R, Hunot V, Merry SN, Parker AG, Hetrick SE (30 November 2014). "Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents.". *The Cochrane database of systematic reviews*. **11**: CD008324. doi:10.1002/14651858.CD008324.pub3. PMID 25433518.
139. ^ "Management of depression in primary and secondary care" (PDF). *National Clinical Practice Guideline Number 23*. National Institute for Health and Clinical Excellence. 2007. Retrieved 4 November 2008.
140. ^ [a] [b] Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, McMurdo M, Mead GE (12 September 2013). Mead, Gillian E, ed. "Exercise for depression". *Cochrane Database of Systematic Reviews*. **9**: CD004366. doi:10.1002/14651858.CD004366.pub6. PMID 24026850.
141. ^ [a] [b] Josefsson, T.; Lindwall, M.; Archer, T. (2014). "Physical exercise intervention in depressive disorders: Meta-analysis and systematic review". *Scandinavian Journal of Medicine & Science in Sports*. **24** (2): 259–272. doi:10.1111/sms.12050. ISSN 0905-7188. PMID 23362828.
142. ^ Bridle C, Spanjers K, Patel S, Atherton NM, Lamb SE (September 2012). "Effect of exercise on depression severity in older people: systematic review and meta-analysis of randomised controlled trials". *Br J Psychiatry*. **201** (3): 180–5. doi:10.1192/bjp.bp.111.095174. PMID 22945926.
143. ^ Giedke H, Schwärzler F (2002). "Therapeutic use of sleep deprivation in depression". *Sleep Medicine Reviews*. **6** (5): 361–77. doi:10.1053/smrv.2002.0235. PMID 12531127.
144. ^ Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P (13 February 2014). "Change in mental health after smoking cessation: systematic review and meta-analysis". *BMJ*. **348** (feb13 1): g1151–g1151. doi:10.1136/bmj.g1151. PMC 3923980. PMID 24524926.
145. ^ Amick, HR; Gartlehner, G; Gaynes, BN; Forneris, C; Asher, GN; Morgan, LC; Coker-Schwimmer, E; Boland, E; Lux, LJ; Gaylord, S; Bann, C; Pierl, CB; Lohr, KN (8 December 2015). "Comparative benefits and harms of second generation antidepressants and cognitive behavioral therapies in initial treatment of major depressive disorder: systematic review and meta-analysis.". *BMJ (Clinical research ed.)*. **351**: h6019. PMC 4673103. PMID 26645251.
146. ^ Khan A, Faucett J, Lichtenberg P, Kirsch I, Brown WA (30 July 2012). "A Systematic Review of Comparative Efficacy of Treatments and Controls for Depression". *PLOS ONE*. **7** (7): e41778.

doi:10.1371/journal.pone.0041778. PMC 3408478. PMID 22860015.
147. ^ Thase ME (1999). "When are psychotherapy and pharmacotherapy combinations the treatment of choice for major depressive disorder?". *Psychiatric Quarterly*. **70** (4): 333–46. doi:10.1023/A:1022042316895. PMID 10587988.
148. ^ Cordes, J. (2013). "Depression". *Encyclopedia of Sciences and Religions*. p. 610. doi:10.1007/978-1-4020-8265-8_301. ISBN 978-1-4020-8264-1.
149. ^ *a b* Nieuwenhuijsen, Karen; Faber, Babs; Verbeek, Jos H.; Neumeyer-Gromen, Angela; Hees, Hiske L.; Verhoeven, Arco C.; van der Feltz-Cornelis, Christina M.; Bültmann, Ute (2014). "Interventions to improve return to work in depressed people". *The Cochrane Database of Systematic Reviews*. **12**: CD006237. doi:10.1002/14651858.CD006237.pub3. ISSN 1469-493X. PMID 25470301.
150. ^ Wilson KC, Mottram PG, Vassilas CA (2008). "Psychotherapeutic treatments for older depressed people". *Cochrane Database of Systematic Reviews*. **23** (1): CD004853. doi:10.1002/14651858.CD004853.pub2. PMID 18254062.
151. ^ Cuijpers P, van Straten A, Smit F (2006). "Psychological treatment of late-life depression: a meta-analysis of randomized controlled trials". *International Journal of Geriatric Psychiatry*. **21** (12): 1139–49. doi:10.1002/gps.1620. PMID 16955421.
152. ^ Childhood Depression. abct.org. Last updated: 30 July 2010
153. ^ NICE (2005). *NICE guidelines: Depression in children and adolescents*. London: NICE. p. 5. ISBN 1-84629-074-0. Retrieved 16 August 2008.
154. ^ Dobson KS (1989). "A meta-analysis of the efficacy of cognitive therapy for depression". *J Consult Clin Psychol*. **57** (3): 414–9. doi:10.1037/0022-006X.57.3.414. PMID 2738214.
155. ^ Roth, Anthony; Fonagy, Peter (2005) [1996]. *What Works for Whom? Second Edition: A Critical Review of Psychotherapy Research*. Guilford Press. p. 78. ISBN 1-59385-272-X.
156. ^ Weersing VR, Walker PN (2008). "Review: Cognitive behavioural therapy for adolescents with depression". *Evidence-Based Mental Health*. **11** (3): 76. doi:10.1136/ebmh.11.3.76. PMID 18669678. Retrieved 27 November 2008.
157. ^ Harrington R, Whittaker J, Shoebridge P, Campbell F (1998). "Systematic review of efficacy of cognitive behaviour therapies in childhood and adolescent depressive disorder". *BMJ*. **316** (7144): 1559–63. doi:10.1136/bmj.316.7144.1559. PMC 28555. PMID 9596592.
158. ^ Becker SJ (2008). "Cognitive-Behavioral Therapy for Adolescent Depression: Processes of Cognitive Change". *Psychiatric Times*. **25** (14).
159. ^ Almeida AM, Lotufo Neto F (2003). "Cognitive-behavioral therapy in prevention of depression relapses and recurrences: a review". *Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999)*. **25** (4): 239–44. PMID 15328551.
160. ^ Paykel ES (2007). "Cognitive therapy in relapse prevention in depression". *The International Journal of Neuropsychopharmacology*. **10** (1): 131–6. doi:10.1017/S1461145706006912. PMID 16787553.
161. ^ Nieuwenhuijsen K, Faber B, Verbeek JH, Neumeyer-Gromen A, Hees HL, Verhoeven AC, van der Feltz-Cornelis CM, Bültmann U (2014). "Interventions to improve return to work in depressed people". *The Cochrane Database of Systematic Reviews*. **12**: CD006237. doi:10.1002/14651858.CD006237.pub3. PMID 25470301.
162. ^ Beck 1987, p. 10
163. ^ Coelho HF, Canter PH, Ernst E (2007). "Mindfulness-based cognitive therapy: Evaluating current evidence and informing future research". *Journal of Consulting and Clinical Psychology*. **75** (6): 1000–05. doi:10.1037/0022-006X.75.6.1000. PMID 18085916.
164. ^ Khoury B, Lecomte T, Fortin G, Masse M, Therien P, Bouchard V, Chapleau MA, Paquin K, Hofmann SG (August 2013). "Mindfulness-based therapy: a comprehensive meta-analysis". *Clin Psychol Rev*. **33** (6): 763–71. doi:10.1016/j.cpr.2013.05.005. PMID 23796855.
165. ^ Jain FA, Walsh RN, Eisendrath SJ, et al. (2014). "Critical Analysis of the Efficacy of Meditation Therapies for Acute and Subacute Phase Treatment of Depressive Disorders: A systematic Review". *Psychosomatics*. **56**: 297–302. doi:10.1016/j.psym.2014.10.007.
166. ^ Simkin DR, Black NB (July 2014). "Meditation and mindfulness in clinical practice.". *Child and adolescent psychiatric clinics of North America*. **23** (3): 487–534. doi:10.1016/j.chc.2014.03.002. PMID 24975623.
167. ^ Dworetzky J (1997). *Psychology*. Pacific Grove, CA, USA: Brooks/Cole Pub. Co. p. 602. ISBN 0-314-20412-1.
168. ^ Doidge N, Simon B, Lancee WJ, First M, Brunshaw J, Brauer L, Grant DC, Stevens A, Oldham JM, Mosher P (2002). "Psychoanalytic patients in the US, Canada, and Australia: II. A DSM-III-R validation study". *Journal of the American Psychoanalytic Association*. **50** (2): 615–27. doi:10.1177/00030651020500021101. PMID 12206545.
169. ^ Barlow 2005, p. 20
170. ^ de Maat S, Dekker J, Schoevers R, van Aalst G, Gijsbers-van Wijk C, Hendriksen M, Kool S, Peen J, Van R, de Jonghe F (2007). "Short Psychodynamic Supportive Psychotherapy, antidepressants, and their combination in the treatment of major depression: A mega-analysis based on three Randomized Clinical Trials". *Depression and Anxiety*. **25** (7): 565–74. doi:10.1002/da.20305. PMID 17557313.

171. ^ Kirsch I, Moore TJ, Scoboria A, Nicholls SS (2002). "The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration". *Prevention & Treatment*. **5**. doi:10.1037/1522-3736.5.1.523a.
172. ^ "The treatment and management of depression in adults" (PDF). NICE. October 2009. Retrieved 12 November 2014.
173. ^ Leucht C, Huhn M, Leucht S (2012). Leucht, C, ed. "Amitriptyline versus placebo for major depressive disorder". *Cochrane Database of Systematic Reviews*. **12**: CD009138. doi:10.1002/14651858.CD009138.pub2. PMID 23235671.
174. ^ *a b* Karasu TB, Gelenberg A, Merriam A, Wang P (April 2000). "Practice Guideline for the Treatment of Patients With Major Depressive Disorder (Second Edition)". *Am J Psychiatry*. **157** (4 Suppl): 1–45. PMID 10767867.; Third edition doi:10.1176/appi.books.9780890423363.48690
175. ^ Thase ME (2006). "Preventing relapse and recurrence of depression: a brief review of therapeutic options". *CNS spectrums*. **11** (12 Suppl 15): 12–21. PMID 17146414.
176. ^ *a b* Royal Pharmaceutical Society of Great Britain 2008, p. 204
177. ^ Whooley MA, Simon GE (2000). "Managing Depression in Medical Outpatients". *New England Journal of Medicine*. **343** (26): 1942–50. doi:10.1056/NEJM200012283432607. PMID 11136266. Retrieved 11 November 2008.
178. ^ Zisook S, Rush AJ, Haight BR, Clines DC, Rockett CB (2006). "Use of bupropion in combination with serotonin reuptake inhibitors". *Biological Psychiatry*. **59** (3): 203–10. doi:10.1016/j.biopsych.2005.06.027. PMID 16165100.
179. ^ Papakostas GI, Thase ME, Fava M, Nelson JC, Shelton RC (2007). "Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents". *Biological Psychiatry*. **62** (11): 1217–27. doi:10.1016/j.biopsych.2007.03.027. PMID 17588546.
180. ^ Gordon Duff (31 May 2006). "Updated prescribing advice for venlafaxine (Efexor/Efexor XL)". Medicines and Healthcare products Regulatory Agency (MHRA).
181. ^ "Depression in children and young people: Identification and management in primary, community and secondary care" (PDF). NHS National Institute for Health and Clinical Excellence. 2005. Retrieved 12 November 2014.
182. ^ Mayers AG, Baldwin DS (2005). "Antidepressants and their effect on sleep". *Human Psychopharmacology*. **20** (8): 533–59. doi:10.1002/hup.726. PMID 16229049.
183. ^ *a b* Cipriani, A; Zhou, X; Del Giovane, C; Hetrick, SE; Qin, B; Whittington, C; Coghill, D; Zhang, Y; Hazell, P; Leucht, S; Cuijpers, P; Pu, J; Cohen, D; Ravindran, AV; Liu, Y; Michael, KD; Yang, L; Liu, L; Xie, P (27 August 2016). "Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis.". *Lancet (London, England)*. **388** (10047): 881–90. doi:10.1016/S0140-6736(16)30385-3. PMID 27289172.
184. ^ Tsapakis EM, Soldani F, Tondo L, Baldessarini RJ (2008). "Efficacy of antidepressants in juvenile depression: meta-analysis". *Br J Psychiatry*. **193** (1): 10–7. doi:10.1192/bjp.bp.106.031088. PMID 18700212.
185. ^ Cipriani A, Zhou X, Del Giovane C, Hetrick SE, Qin B, Whittington C, Coghill D, Zhang Y, Hazell P, Leucht S, Cuijpers P, Pu J, Cohen D, Ravindran AV, Liu Y, Michael KD, Yang L, Liu L, Xie P (8 June 2016). "Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis". *Lancet*. **388**: 881–90. doi:10.1016/S0140-6736(16)30385-3. PMID 27289172.
186. ^ Nelson JC, Devanand DP (April 2011). "A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia". *Journal of the American Geriatrics Society*. **59** (4): 577–85. doi:10.1111/j.1532-5415.2011.03355.x. PMID 21453380.
187. ^ Palmer BF, Gates JR, Lader M (2003). "Causes and Management of Hyponatremia". *Annals of Pharmacotherapy*. **37** (11): 1694–702. doi:10.1345/aph.1D105. PMID 14565794.
188. ^ Guaiana G, Barbui C, Hotopf M (2007). "Amitriptyline for depression". *Cochrane Database of Systematic Reviews*. **18** (3): 11–7. doi:10.1002/14651858.CD004186.pub2. PMID 17636748.
189. ^ Anderson IM (2000). "Selective serotonin reuptake inhibitors versus tricyclic antidepressants: A meta-analysis of efficacy and tolerability". *Journal of Affective Disorders*. **58** (1): 19–36. doi:10.1016/S0165-0327(99)00092-0. PMID 10760555.
190. ^ Krishnan KR (2007). "Revisiting monoamine oxidase inhibitors". *Journal of Clinical Psychiatry*. 68 Suppl 8: 35–41. PMID 17640156.
191. ^ Bonnet U (2003). "Moclobemide: therapeutic use and clinical studies". *CNS Drug Rev*. **9** (1): 97–140. doi:10.1111/j.1527-3458.2003.tb00245.x. PMID 12595913.
192. ^ Hammad TA (16 August 2004). "Review and evaluation of clinical data. Relationship between psychiatric drugs and pediatric suicidality" (PDF). FDA. pp. 42; 115. Retrieved 29 May 2008.
193. ^ Hetrick, SE; McKenzie, JE; Cox, GR; Simmons, MB; Merry, SN (14 November 2012). "Newer generation

antidepressants for depressive disorders in children and adolescents.". *The Cochrane database of systematic reviews*. **11**: CD004851. doi:10.1002/14651858.CD004851.pub3. PMID 23152227.
194. ^ Gunnell D, Saperia J, Ashby D (2005). "Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review". *BMJ*. **330** (7488): 385. doi:10.1136/bmj.330.7488.385. PMC 549105. PMID 15718537.
195. ^ Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, Hutton B (2005). "Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials". *BMJ*. **330** (7488): 396. doi:10.1136/bmj.330.7488.396. PMC 549110. PMID 15718539.
196. ^ Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, Hammad TA, Temple R, Rochester G (11 August 2009). "Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration". *BMJ (Clinical research ed.)*. **339**: b2880. doi:10.1136/bmj.b2880. PMC 2725270. PMID 19671933.
197. ^ "FDA Proposes New Warnings About Suicidal Thinking, Behavior in Young Adults Who Take Antidepressant Medications". FDA. 2 May 2007. Retrieved 29 May 2008.
198. ^ Medics and Foods Department. Pharmaceuticals and Medical Devices Safety Information (PDF) (Report). 261 (in Japanese). Ministry of Health, Labour and Welfare (Japan).
199. ^ Sublette ME, Ellis SP, Geant AL, Mann JJ (September 2011). "Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression". *J Clin Psychiatry*. **72** (12): 1577–84. doi:10.4088/JCP.10m06634. PMC 3534764. PMID 21939614.
200. ^ Bloch MH, Hannestad J (September 2011). "Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis". *Mol Psychiatry*. **17** (12): 1272–82. doi:10.1038/mp.2011.100. PMC 3625950. PMID 21931319.
201. ^ Cipriani A, Hawton K, Stockton S, Geddes JR (27 June 2013). "Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis". *BMJ*. **346** (jun27 4): f3646–f3646. doi:10.1136/bmj.f3646. PMID 23814104.
202. ^ Nolen-Hoeksema, Susan. (2014) "Treatment of Mood Disorders". In (6th ed.) *Abnormal Psychology* p. 196. New York: McGraw-Hill. ISBN 978-0-07-803538-8.
203. ^ Gelenberg, Alan J.; Freeman, Marlene P.; Markowitz, John C. "Practice Guideline for the Treatment of Patients with Major Depressive Disorder. 3rd edition." (PDF). American Psychiatric Association (APA). Retrieved 3 November 2014.
204. ^ Rudorfer, MV, Henry, ME, Sackeim, HA (2003). "Electroconvulsive therapy". In A Tasman, J Kay, JA Lieberman (eds) *Psychiatry, Second Edition*. Chichester: John Wiley & Sons Ltd, 1865–1901.
205. ^ Beloucif S (2013). "Informed consent for special procedures: electroconvulsive therapy and psychosurgery". *Curr Opin Anaesthesiol*. **26** (2): 182–5. doi:10.1097/ACO.0b013e32835e7380. PMID 23385317.
206. ^ *a b c* FDA. FDA Executive Summary. Prepared for the 27–28 January 2011 meeting of the Neurological Devices Panel Meeting to Discuss the Classification of Electroconvulsive Therapy Devices (ECT). Quote, p38: "Three major practice guidelines have been published on ECT. These guidelines include: APA Task Force on ECT (2001); Third report of the Royal College of Psychiatrists' Special Committee on ECT (2004); National Institute for Health and Clinical Excellence (NICE 2003; NICE 2009). There is significant agreement between the three sets of recommendations."
207. ^ Dierckx B, Heijnen WT, van den Broek WW, Birkenhäger TK; Heijnen, WT; Van Den Broek, WW; Birkenhäger, TK (2012). "Efficacy of electroconvulsive therapy in bipolar versus unipolar major depression: A meta-analysis". *Bipolar Disorders*. **12** (2): 146–150. doi:10.1111/j.1399-5618.2012.00997.x. PMID 22420590.
208. ^ Jelovac A, et al. (Nov 2013). "Relapse following successful electroconvulsive therapy for major depression: a meta-analysis". *Neuropsychopharmacology*. **38** (12): 2467–74. doi:10.1038/npp.2013.149. PMC 3799066. PMID 23774532.
209. ^ Surgeon General (1999). *Mental Health: A Report of the Surgeon General*, chapter 4.
210. ^ American Psychiatric Association; Committee on Electroconvulsive Therapy; Richard D. Weiner (chairperson); et al. (2001). *The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging* (2nd ed.). Washington, DC: American Psychiatric Publishing. ISBN 978-0-89042-206-9.
211. ^ Pompili M, et al. (Dec 2014). "Electroconvulsive treatment during pregnancy: a systematic review". *Expert Rev Neurother*. **14** (12): 1377–90. doi:10.1586/14737175.2014.972373. PMID 25346216.
212. ^ "5 Outdated Beliefs About ECT". *Psych Central.com*.
213. ^ Abbott, C. C.; Gallegos, P.; Rediske, N.; Lemke, N. T.; Quinn, D. K. (2013). "A Review of Longitudinal Electroconvulsive Therapy: Neuroimaging Investigations". *Journal of Geriatric Psychiatry and Neurology*. **27** (1): 33–46. doi:10.1177/0891988713516542. PMID 24381234.
214. ^ "NiCE. January 2014 Transcranial magnetic stimulation for treating and preventing migraine".
215. ^ "Melkerson, MN (2008-12-16). "Special Premarket 510(k) Notification for NeuroStar® TMS Therapy System for

Major Depressive Disorder" (pdf). Food and Drug Administration. Retrieved 2010-07-16." (PDF).
216. ^ Lefaucheur, JP; André-Obadia, N (November 2014). "Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS).". *Clinical Neurophysiology*. **125** (11): 2150–206. doi:10.1016/j.clinph.2014.05.021. PMID 25034472.
217. ^ "American Psychiatric Association (2010). (eds: Gelenberg, AJ, Freeman, MP, Markowitz, JC, Rosenbaum, JF, Thase, ME, Trivedi, MH, Van Rhoads, RS). Practice Guidelines for the Treatment of Patients with Major Depressive Disorder, 3rd Edition" (PDF).
218. ^ "Journal of Affective Disorders" (PDF). 2009. pp. S1–S64.
219. ^ Rush, A. John; Marangell, Lauren B.; Sackeim, Harold A.; George, Mark S.; Brannan, Stephen K.; Davis, Sonia M.; Howland, Robert; Kling, Mitchel A.; Rittberg, Barry R.; Burke, William J.; Rapaport, Mark H.; Zajecka, John; Nierenberg, Andrew A.; Husain, Mustafa M.; Ginsberg, David; Cooke, Robert G. (2005). "The Royal Australian and New Zealand College of Psychiatrists. (2013) Position Statement 79. Repetitive Transcranial Magnetic Stimulation. Practice and Partnerships Committee". *Biological Psychiatry*. **58** (5): 347–54. doi:10.1016/j.biopsych.2005.05.025. PMID 16139580.
220. ^ Golden RN, Gaynes BN, Ekstrom RD, Hamer RM, Jacobsen FM, Suppes T, Wisner KL, Nemeroff CB (April 2005). "The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence". *American Journal of Psychiatry*. **162** (4): 656–62. doi:10.1176/appi.ajp.162.4.656. PMID 15800134.
221. ^ Tuunainen A, Kripke DF, Endo T (2004). Tuunainen, Arja, ed. "Light therapy for non-seasonal depression". *Cochrane Database Syst Rev* (2): CD004050. doi:10.1002/14651858.CD004050.pub2. PMID 15106233.
222. ^ Posternak MA, Miller I (2001). "Untreated short-term course of major depression: A meta-analysis of outcomes from studies using wait-list control groups". *Journal of Affective Disorders*. **66** (2–3): 139–46. doi:10.1016/S0165-0327(00)00304-9. PMID 11578666.
223. ^ Posternak MA, Solomon DA, Leon AC, Mueller TI, Shea MT, Endicott J, Keller MB (2006). "The naturalistic course of unipolar major depression in the absence of somatic therapy". *Journal of Nervous and Mental Disease*. **194** (5): 324–29. doi:10.1097/01.nmd.0000217820.33841.53. PMID 16699380.
224. ^ Fava GA, Park SK, Sonino N (2006). "Treatment of recurrent depression.". *Expert Review of Neurotherapeutics*. **6** (11): 1735–1740. doi:10.1586/14737175.6.11.1735. PMID 17144786.
225. ^ Limosin F, Mekaoui L, Hautecouverture S (2007). "Stratégies thérapeutiques prophylactiques dans la dépression unipolaire [Prophylactic treatment for recurrent major depression]". *La Presse Médicale*. **36** (11–C2): 1627–1633. doi:10.1016/j.lpm.2007.03.032. PMID 17555914.
226. ^ Eaton WW, Shao H, Nestadt G, Lee HB, Lee BH, Bienvenu OJ, Zandi P (2008). "Population-based study of first onset and chronicity in major depressive disorder". *Archives of General Psychiatry*. **65** (5): 513–20. doi:10.1001/archpsyc.65.5.513. PMC 2761826. PMID 18458203.
227. ^ Holma KM, Holma IA, Melartin TK, Rytsälä HJ, Isometsä ET (2008). "Long-term outcome of major depressive disorder in psychiatric patients is variable". *Journal of Clinical Psychiatry*. **69** (2): 196–205. doi:10.4088/JCP.v69n0205. PMID 18251627.
228. ^ Kanai T, Takeuchi H, Furukawa TA, Yoshimura R, Imaizumi T, Kitamura T, Takahashi K (2003). "Time to recurrence after recovery from major depressive episodes and its predictors". *Psychological Medicine*. **33** (5): 839–45. doi:10.1017/S0033291703007827. PMID 12877398.
229. ^ Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, Goodwin GM (2003). "Relapse prevention with antidepressant drug treatment in depressive disorders: A systematic review". *Lancet*. **361** (9358): 653–61. doi:10.1016/S0140-6736(03)12599-8. PMID 12606176.
230. ^ "Major Depression". *MedlinePlus*. 10 March 2014. Retrieved 16 July 2010.
231. ^ "Depression, Major: Prognosis". *MDGuidlines*. Guardian Life Insurance Company of America. Retrieved 16 July 2010.
232. ^ Cassano P, Fava M (2002). "Depression and public health: an overview". *J Psychosom Res*. **53** (4): 849–57. doi:10.1016/S0022-3999(02)00304-5. PMID 12377293.
233. ^ Rush AJ (2007). "The varied clinical presentations of major depressive disorder". *The Journal of Clinical Psychiatry*. **68** (Supplement 8): 4–10. PMID 17640152.
234. ^ [a] [b] Alboni P, Favaron E, Paparella N, Sciammarella M, Pedaci M (2008). "Is there an association between depression and cardiovascular mortality or sudden death?". *Journal of cardiovascular medicine (Hagerstown, Md.)*. **9** (4): 356–62. doi:10.2459/JCM.0b013e3282785240. PMID 18334889.
235. ^ Barlow DH; Durand VM (2005). *Abnormal psychology: An integrative approach (5th ed.)*. Belmont, CA, USA: Thomson Wadsworth. pp. 248–49. ISBN 0-534-63356-0.
236. ^ Blair-West GW, Mellsop GW (2001). "Major depression: Does a gender-based down-rating of suicide risk challenge its diagnostic validity?". *Australian and New Zealand Journal of Psychiatry*. **35** (3): 322–28. doi:10.1046/j.1440-1614.2001.00895.x. PMID 11437805.
237. ^ Oquendo MA, Bongiovi-Garcia ME, Galfalvy H, Goldberg PH, Grunebaum MF, Burke AK, Mann JJ (2007). "Sex differences in clinical predictors of suicidal acts after major depression: a prospective study". *The American*

*Journal of Psychiatry*. **164** (1): 134–41. doi:10.1176/ajp.2007.164.1.134. PMC 3785095. PMID 17202555.
238. ^ Bostwick JM, Pankratz VS (2000). "Affective disorders and suicide risk: A reexamination". *American Journal of Psychiatry*. **157** (12): 1925–32. doi:10.1176/appi.ajp.157.12.1925. PMID 11097952.
239. ^ Weich S, Lewis G (1998). "Poverty, unemployment, and common mental disorders: Population based cohort study". *BMJ*. **317** (7151): 115–19. doi:10.1136/bmj.317.7151.115. PMC 28602. PMID 9657786. Retrieved 16 September 2008.
240. ^ Mathers CD, Loncar D (2006). "Projections of global mortality and burden of disease from 2002 to 2030". *PLoS Med*. **3** (11): e442. doi:10.1371/journal.pmed.0030442. PMC 1664601. PMID 17132052.
241. ^ Andrews G (2008). "In Review: Reducing the Burden of Depression". *Canadian Journal of Psychiatry*. **53** (7): 420–27. PMID 18674396.
242. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved 11 November 2009.
243. ^ Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005). "Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication". *Archives of General Psychiatry*. **62** (6): 593–602. doi:10.1001/archpsyc.62.6.593. PMID 15939837.
244. ^ Murphy JM, Laird NM, Monson RR, Sobol AM, Leighton AH (2000). "A 40-year perspective on the prevalence of depression: The Stirling County Study". *Archives of General Psychiatry*. **57** (3): 209–15. doi:10.1001/archpsyc.57.3.209. PMID 10711905.
245. ^ *a b* Kuehner C (2003). "Gender differences in unipolar depression: An update of epidemiological findings and possible explanations". *Acta Psychiatrica Scandinavica*. **108** (3): 163–74. doi:10.1034/j.1600-0447.2003.00204.x. PMID 12890270.
246. ^ "The world health report 2001 – Mental Health: New Understanding, New Hope". *WHO website*. World Health Organization. 2001. Retrieved 19 October 2008.
247. ^ Eaton WW, Anthony JC, Gallo J, Cai G, Tien A, Romanoski A, Lyketsos C, Chen LS (1997). "Natural history of diagnostic interview schedule/DSM-IV major depression. The Baltimore Epidemiologic Catchment Area follow-up". *Archives of General Psychiatry*. **54** (11): 993–99. doi:10.1001/archpsyc.1997.01830230023003. PMID 9366655.
248. ^ Rickards H (2005). "Depression in neurological disorders: Parkinson's disease, multiple sclerosis, and stroke". *Journal of Neurology Neurosurgery and Psychiatry*. **76**: i48–i52. doi:10.1136/jnnp.2004.060426. PMC 1765679. PMID 15718222.
249. ^ Strik JJ, Honig A, Maes M (2001). "Depression and myocardial infarction: relationship between heart and mind". *Progress in neuro-psychopharmacology & biological psychiatry*. **25** (4): 879–92. doi:10.1016/S0278-5846(01)00150-6. PMID 11383983.
250. ^ Jorm AF (2000). "Does old age reduce the risk of anxiety and depression? A review of epidemiological studies across the adult life span". *Psychological Medicine*. **30** (1): 11–22. doi:10.1017/S0033291799001452. PMID 10722172.
251. ^ Gelder, M., Mayou, R. and Geddes, J. 2005. Psychiatry. 3rd ed. New York: Oxford. pp105.
252. ^ Hippocrates, *Aphorisms*, Section 6.23
253. ^ *a b c* Radden, J (2003). "Is this dame melancholy? Equating today's depression and past melancholia". *Philosophy, Psychiatry, & Psychology*. **10** (1): 37–52. doi:10.1353/ppp.2003.0081.
254. ^ depress. (n.d.). Online Etymology Dictionary. Retrieved 30 June 2008, from Dictionary.com
255. ^ Wolpert, L (1999). "Malignant Sadness: The Anatomy of Depression". *The New York Times*. Retrieved 30 October 2008.
256. ^ Berrios GE (1988). "Melancholia and depression during the 19th century: A conceptual history". *British Journal of Psychiatry*. **153** (3): 298–304. doi:10.1192/bjp.153.3.298. PMID 3074848.
257. ^ Davison, K (2006). "Historical aspects of mood disorders". *Psychiatry*. **5** (4): 115–18. doi:10.1383/psyt.2006.5.4.115.
258. ^ Carhart-Harris RL, Mayberg HS, Malizia AL, Nutt D (2008). "Mourning and melancholia revisited: Correspondences between principles of Freudian metapsychology and empirical findings in neuropsychiatry". *Annals of General Psychiatry*. **7**: 9. doi:10.1186/1744-859X-7-9. PMC 2515304. PMID 18652673.
259. ^ Freud, S (1984). "Mourning and Melancholia". In Richards A. *11.On Metapsychology: The Theory of Psycholoanalysis*. Aylesbury, Bucks: Pelican. pp. 245–69. ISBN 0-14-021740-1.
260. ^ Lewis, AJ (1934). "Melancholia: A historical review". *Journal of Mental Science*. **80** (328): 1–42. doi:10.1192/bjp.80.328.1.
261. ^ American Psychiatric Association (1968). "Schizophrenia". *Diagnostic and statistical manual of mental disorders: DSM-II* (PDF). Washington, DC: American Psychiatric Publishing, Inc. pp. 36–37, 40. Retrieved 3 August 2008.
262. ^ Schildkraut JJ (1965). "The catecholamine hypothesis of affective disorders: A review of supporting evidence". *American Journal of Psychiatry*. **122** (5): 509–22. doi:10.1176/ajp.122.5.509. PMID 5319766.
263. ^ Angst J. Terminology, history and definition of bipolar spectrum. In: Maj M, Akiskal HS, López-Ibor JJ, Sartorius N (eds.), *Bipolar disorders*. Chichester: Wiley & Sons, LTD; 2002. pp. 53–55.

264. ^ Spitzer RL, Endicott J, Robins E (1975). "The development of diagnostic criteria in psychiatry" (PDF). Retrieved 8 November 2008.
265. ^ a b Philipp M, Maier W, Delmo CD (1991). "The concept of major depression. I. Descriptive comparison of six competing operational definitions including ICD-10 and DSM-III-R". *European Archives of Psychiatry and Clinical Neuroscience*. **240** (4–5): 258–65. doi:10.1007/BF02189537. PMID 1829000.
266. ^ Bolwig, Tom G.; Shorter, Edward (2007). "Melancholia: Beyond DSM, beyond neurotransmitters. Proceedings of a conference, May 2006, Copenhagen, Denmark". *Acta Psychiatrica Scandinavica Suppl*. **115** (433): 4–183. doi:10.1111/j.1600-0447.2007.00956.x. PMID 17280564.
267. ^ Fink M, Bolwig TG, Parker G, Shorter E (2007). "Melancholia: Restoration in psychiatric classification recommended". *Acta Psychiatrica Scandinavica*. **115** (2): 89–92. doi:10.1111/j.1600-0447.2006.00943.x. PMC 3712974. PMID 17244171.
268. ^ Healy, David (1999). *The Antidepressant Era*. Cambridge, MA: Harvard University Press. p. 42. ISBN 0-674-03958-0.
269. ^ Wolf, Joshua "Lincoln's Great Depression", *The Atlantic*, October 2005, Retrieved 10 October 2009
270. ^ Maloney F (3 November 2005). "The Depression Wars: Would Honest Abe Have Written the Gettysburg Address on Prozac?". *Slate magazine*. Washington Post. Retrieved 3 October 2008.
271. ^ Karasz A (2005). "Cultural differences in conceptual models of depression". *Social Science in Medicine*. **60** (7): 1625–35. doi:10.1016/j.socscimed.2004.08.011. PMID 15652693.
272. ^ Tilbury, F; Rapley, M (2004). "'There are orphans in Africa still looking for my hands': African women refugees and the sources of emotional distress". *Health Sociology Review*. **13** (1): 54–64. doi:10.5172/hesr.13.1.54.
273. ^ Parker G, Gladstone G, Chee KT (2001). "Depression in the planet's largest ethnic group: The Chinese". *American Journal of Psychiatry*. **158** (6): 857–64. doi:10.1176/appi.ajp.158.6.857. PMID 11384889.
274. ^ Parker G (2007). "Is depression overdiagnosed? Yes". *BMJ*. **335** (7615): 328. doi:10.1136/bmj.39268.475799.AD. PMC 1949440. PMID 17703040.
275. ^ Pilgrim D, Bentall R (1999). "The medicalisation of misery: A critical realist analysis of the concept of depression". *Journal of Mental Health*. **8** (3): 261–74. doi:10.1080/09638239917580.
276. ^ Steibel W (Producer) (1998). "Is depression a disease?". *Debatesdebates*. Retrieved 16 November 2008.
277. ^ Blazer DG (2005). *The age of melancholy: "Major depression" and its social origins*. New York, NY, USA: Routledge. ISBN 978-0-415-95188-3.
278. ^ Hillman J (T Moore, Ed.) (1989). *A blue fire: Selected writings by James Hillman*. New York, NY, USA: Harper & Row. pp. 152–53. ISBN 0-06-016132-9.
279. ^ Seymour, Miranda (2002). *Mary Shelley*. Grove Press. pp. 560–61. ISBN 0-8021-3948-5.
280. ^ "Biography of Henry James". pbs.org. Retrieved 19 August 2008.
281. ^ Burlingame, Michael (1997). *The Inner World of Abraham Lincoln*. Urbana: University of Illinois Press. pp. xvii, 92–113. ISBN 0-252-06667-7.
282. ^ Pita E (26 September 2001). "An Intimate Conversation with...Leonard Cohen". Retrieved 3 October 2008.
283. ^ Jeste ND, Palmer BW, Jeste DV (2004). "Tennessee Williams". *American Journal of Geriatric Psychiatry*. **12** (4): 370–75. doi:10.1097/00019442-200407000-00004. PMID 15249274.
284. ^ James H (Ed.) (1920). *Letters of William James (Vols. 1 and 2)*. Montana USA: Kessinger Publishing Co. pp. 147–48. ISBN 978-0-7661-7566-2.
285. ^ Hergenhahn 2005, p. 311
286. ^ Cohen D (1979). *J. B. Watson: The Founder of Behaviourism*. London, UK: Routledge & Kegan Paul. p. 7. ISBN 0-7100-0054-5.
287. ^ Andreasen NC (2008). "The relationship between creativity and mood disorders". *Dialogues in clinical neuroscience*. **10** (2): 251–5. PMC 3181877. PMID 18689294.
288. ^ Simonton, DK (2005). "Are genius and madness related? Contemporary answers to an ancient question". *Psychiatric Times*. **22** (7).
289. ^ Heffernan CF (1996). *The melancholy muse: Chaucer, Shakespeare and early medicine*. Pittsburgh, PA, USA: Duquesne University Press. ISBN 0-8207-0262-5.
290. ^ Mill JS (2003). "A crisis in my mental history: One stage onward". *Autobiography* (txt). Project Gutenberg EBook. pp. 1826–32. ISBN 1-4212-4200-1. Retrieved 9 August 2008.
291. ^ Sterba R (1947). "The 'Mental Crisis' of John Stuart Mill". *Psychoanalytic Quarterly*. **16** (2): 271–72. Retrieved 5 November 2008.
292. ^ a b "Churchill's Black Dog?: The History of the 'Black Dog' as a Metaphor for Depression" (PDF). *Black Dog Institute website*. Black Dog Institute. 2005. Retrieved 18 August 2008.
293. ^ Jorm AF, Angermeyer M, Katschnig H (2000). "Public knowledge of and attitudes to mental disorders: a limiting factor in the optimal use of treatment services". In Andrews G, Henderson S. *Unmet Need in Psychiatry:Problems, Resources, Responses*. Cambridge University Press. p. 409. ISBN 0-521-66229-X.

294. ^ Paykel ES, Tylee A, Wright A, Priest RG, Rix S, Hart D (1997). "The Defeat Depression Campaign: psychiatry in the public arena". *American Journal of Psychiatry*. **154** (6 Suppl): 59–65. doi:10.1176/ajp.154.6.59. PMID 9167546.
295. ^ Paykel ES, Hart D, Priest RG (1998). "Changes in public attitudes to depression during the Defeat Depression Campaign". *British Journal of Psychiatry*. **173** (6): 519–22. doi:10.1192/bjp.173.6.519. PMID 9926082.
296. ^ Kruger TH, Wollmer MA (2015). "Depression – An emerging indication for botulinum toxin treatment". *Toxicon*. **107** (Pt A): 154–7. doi:10.1016/j.toxicon.2015.09.035. PMID 26415901.
297. ^ Milev, R (2015). "Response of Depression to Botulinum Toxin Treatment: Agitation as a Predictor". *Frontiers in Psychiatry*. **6**: 55. doi:10.3389/fpsyt.2015.00055. PMC 4403301. PMID 25941497..
298. ^ Kempton MJ, Salvador Z, Munafò MR, Geddes JR, Simmons A, Frangou S, Williams SC (2011). "Structural Neuroimaging Studies in Major Depressive Disorder: Meta-analysis and Comparison With Bipolar Disorder". *Arch Gen Psychiatry*. **68** (7): 675–90. doi:10.1001/archgenpsychiatry.2011.60. PMID 21727252. see also MRI database at www.depressiondatabase.org
299. ^ Arnone D, McIntosh AM, Ebmeier KP, Munafò MR, Anderson IM (July 2011). "Magnetic resonance imaging studies in unipolar depression: Systematic review and meta-regression analyses". *Eur Neuropsychopharmacol*. **22** (1): 1–16. doi:10.1016/j.euroneuro.2011.05.003. PMID 21723712.
300. ^ Herrmann LL, Le Masurier M, Ebmeier KP (2008). "White matter hyperintensities in late life depression: a systematic review". *Journal of Neurology, Neurosurgery, and Psychiatry*. **79** (6): 619–24. doi:10.1136/jnnp.2007.124651. PMID 17717021.
301. ^ *a b c d e f g h i j k l m* Services, Swedish Council on Health Technology Assessmentl. "Depression treatment for the elderly". *www.sbu.se*. Retrieved 16 June 2016.


## Cited works


- American Psychiatric Association (2000a). *Diagnostic and statistical manual of mental disorders, Fourth Edition, Text Revision: DSM-IV-TR*. Washington, DC: American Psychiatric Publishing, Inc. ISBN 0-89042-025-4.
- Barlow DH; Durand VM (2005). *Abnormal psychology: An integrative approach (5th ed.)*. Belmont, CA, USA: Thomson Wadsworth. ISBN 0-534-63356-0.
- Beck AT, Rush J, Shaw BF, Emery G (1987) [1979]. *Cognitive Therapy of depression*. New York, NY, USA: Guilford Press. ISBN 0-89862-919-5.
- Hergenhahn BR (2005). *An Introduction to the History of Psychology* (5th ed.). Belmont, CA, USA: Thomson Wadsworth. ISBN 0-534-55401-6.
- May R (1994). *The discovery of being: Writings in existential psychology*. New York, NY, USA: W. W. Norton & Company. ISBN 0-393-31240-2.
- Hadzi-Pavlovic, Dusan; Parker, Gordon (1996). *Melancholia: a disorder of movement and mood: a phenomenological and neurobiological review*. Cambridge, UK: Cambridge University Press. ISBN 0-521-47275-X.
- Royal Pharmaceutical Society of Great Britain (2008). *British National Formulary (BNF 56)*. UK: BMJ Group and RPS Publishing. ISBN 978-0-85369-778-7.
- Sadock, Virginia A.; Sadock, Benjamin J.; Kaplan, Harold I. (2003). *Kaplan & Sadock's synopsis of psychiatry: behavioral sciences/clinical psychiatry*. Philadelphia: Lippincott Williams & Wilkins. ISBN 0-7817-3183-6.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| **Other** | Personality disorder · Impulse control disorder · (Kleptomania · Trichotillomania · Pyromania · Dermatillomania) · Body-focused repetitive behavior · Factitious disorder · (Münchausen syndrome) · |
| **Disorders typically diagnosed in childhood** | |
| **Intellectual disability** | X-linked intellectual disability · (Lujan–Fryns syndrome) · |
| **Psychological development (developmental disabilities)** | Specific · Pervasive · Autism spectrum · |
| **Emotional and behavioral** | ADHD · Conduct disorder · (ODD) · Emotional/behavioral disorder · (Separation anxiety disorder) · *social functioning* · (Selective mutism · RAD · DAD) · Tic disorder · (Tourette syndrome) · *Speech* · (Stuttering · Cluttering) · Movement disorder · (Stereotypic) · |
| **Symptoms and uncategorized** | |
| Catatonia · False pregnancy · Intermittent explosive disorder · Psychomotor agitation · Stereotypy · Psychogenic non-epileptic seizures · Klüver–Bucy syndrome · | |

| v · t · e · | **Mood disorder (F30–F39, 296)** | |
|---|---|---|
| **History** | Emil Kraepelin · Karl Leonhard · John Cade · Mogens Schou · Frederick K. Goodwin · Kay Redfield Jamison · | |
| **Symptoms** | Hallucination · Delusion · Emotional dysregulation (Anhedonia · Dysphoria · Suicidal ideation · · Mood swing · *sleep disorder* (Hypersomnia · Insomnia · · Psychosis · Racing thoughts · Reduced affect display · Depression (differential diagnoses) · | |
| **Spectrum** | Bipolar disorder (Bipolar I · Bipolar II · Cyclothymia · Bipolar NOS · · Depression · (**Major depressive disorder** · Dysthymia · Seasonal affective disorder · Atypical depression · Melancholic depression) · Schizoaffective disorder · Mania · Mixed affective state · Hypomania · Major depressive episode · Rapid cycling · | |
| **Treatment** | **Anticonvulsants** | Carbamazepine · Lamotrigine · Oxcarbazepine · Valproate (Sodium valproate · Valproate semisodium · · |
| | **Sympathomimetics, SSRIs & similar** | Dextroamphetamine · Methylphenidate · Bupropion · Sertraline · Fluoxetine · Escitalopram · |
| | **Other mood stabilizers** | Antipsychotics · Lithium (Lithium carbonate · Lithium citrate · Lithium sulfate · · Atypical antipsychotics · |
| | **Non-pharmaceutical** | Clinical psychology · Electroconvulsive therapy · Involuntary commitment · Light therapy · Psychotherapy · Transcranial magnetic stimulation · Cognitive behavioral therapy · Dialectical behavior therapy · |
| **Authority control** | NDL: 01190900 · | |

Categories: Abnormal psychology | Bipolar spectrum | History of medicine | Mood disorders | Depression (psychology) | Psychiatric diagnosis


# Obsessive–compulsive disorder

From Wikipedia, the free encyclopedia
(Redirected from Obsessive–compulsive disorder)

*"OCD" redirects here. For other uses, see OCD (disambiguation). Not to be confused with Obsessive–compulsive personality disorder.*

**Obsessive–compulsive disorder** (**OCD**) is a mental disorder where people feel the need to check things repeatedly, perform certain routines repeatedly (called "rituals"), or have certain thoughts repeatedly. People are unable to control either the thoughts or the activities for more than a short period of time. Common activities include hand washing, counting of things, and checking to see if a door is locked. Some may have difficulty throwing things out. These activities occur to such a degree that the person's daily life is negatively affected.[1] Often they take up more than an hour a day.[2] Most adults realize that the behaviors do not make sense.[1] The condition is associated with tics, anxiety disorder, and an increased risk of suicide.[2][3]

The cause is unknown.[1] There appear to be some genetic components with both identical twins more often affected than both non-identical twins. Risk factors include a history of child abuse or other stress inducing event. Some cases have been documented to occur following infections. The diagnosis is based on the symptoms and requires ruling out other drug related or medical causes.[2] Rating scales such as the Yale–Brown Obsessive Compulsive Scale can be used to assess the severity.[4] Other disorders with similar symptoms include anxiety disorder, major depressive disorder, eating disorders, tic disorders, and obsessive–compulsive personality disorder.[2]

Treatment involves counselling, such as cognitive behavioral therapy (CBT), and sometimes medication, typically selective serotonin reuptake inhibitors (SSRIs).[5][6] CBT for OCD involves increasing exposure to what causes the problems while not allowing the repetitive behavior to occur.[5] While clomipramine appears to work as well as SSRIs, it has greater side effects.[5] Atypical antipsychotics may be useful when used in addition to an SSRI in treatment-resistant cases but are also associated with an increased risk of side effects.[6][7] Without treatment, the condition often lasts decades.[2]

Obsessive–compulsive disorder affects about 2.3% of people at some point in their life.[8] Rates during a given year are about 1.2% and it occurs worldwide.[2] It is unusual for symptoms to begin after the age of thirty-five, and half of people develop problems before twenty.[1][2] Males and females are affected about equally.[1] In English the phrase *obsessive–compulsive* is often used in an informal manner unrelated to OCD to describe someone who is excessively meticulous, perfectionistic, absorbed, or otherwise fixated.[9]

Contents



Obsess...

Frequent, excessive hand washing occurs in some people with OCD

| Classification and external resources | |
|---|---|
| **Specialty** | Psychiatry |
| **ICD-10** | F42 |
| **ICD-9-CM** | 300.3 |
| **OMIM** | 164230 |
| **DiseasesDB** | 33766 |
| **MedlinePlus** | 000929 |
| **eMedicine** | article/287681 |
| **MeSH** | D009771 |

[edit on Wikidata]

# Signs and symptoms

## Obsessions

*Main article: Intrusive thought*

Obsessions are thoughts that recur and persist despite efforts to ignore or confront them.[10] People with OCD frequently perform tasks, or compulsions, to seek relief from obsession-related anxiety. Within and among individuals, the initial obsessions, or intrusive thoughts, vary in their clarity and vividness. A relatively vague obsession could involve a general sense of disarray or tension accompanied by a belief that life cannot proceed as normal while the imbalance remains. A more intense obsession could be a preoccupation with the thought or image of someone close to them dying[11][12] or intrusions related to "relationship rightness."[13] Other obsessions concern the possibility that someone or something other than oneself—such as God, the Devil, or disease—will harm either the person with OCD or the people or things that the person cares about. Other individuals with OCD may experience the sensation of invisible protrusions emanating from their bodies, or have the feeling that inanimate objects are ensouled.[14]

People with OCD may face intrusive thoughts, such as thoughts about the Devil (shown is a painted interpretation of Hell)

Some people with OCD experience sexual obsessions that may involve intrusive thoughts or images of "kissing, touching, fondling, oral sex, anal sex, intercourse, incest and rape" with "strangers, acquaintances, parents, children, family members, friends, coworkers, animals and religious figures", and can include "heterosexual or homosexual content" with persons of any age.[15] As with other intrusive, unpleasant thoughts or images, some disquieting sexual thoughts at times are normal, but people with OCD may attach extraordinary significance to the thoughts. For example, obsessive fears about sexual orientation can appear to the person with OCD, and even to those around them, as a crisis of sexual identity.[16][17] Furthermore, the doubt that accompanies OCD leads to uncertainty regarding whether one might act on the troubling thoughts, resulting in self-criticism or self-loathing.[15]

People with OCD understand that their notions do not correspond with reality; however, they feel that they must act as though their notions are correct. For example, an individual who engages in compulsive hoarding might be inclined to treat inorganic matter as if it had the sentience or rights of living organisms, while accepting that such behavior is irrational on a more intellectual level.

## Primarily obsessional

*Main article: Primarily Obsessional OCD*

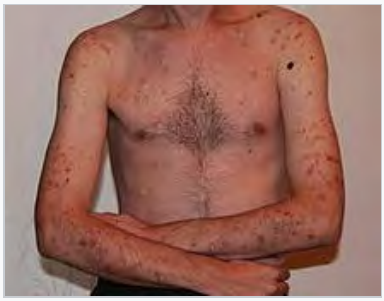
OCD sometimes manifests without overt compulsions.[18] Nicknamed "Pure-O",[19] or referred to as Primarily Obsessional OCD, OCD without overt compulsions could, by one estimate, characterize as many as 50 percent to 60 percent of OCD cases.[20] Primarily obsessional OCD has been called one of the most distressing and challenging forms of OCD.[21] People with this form of OCD have distressing and unwanted thoughts emerging frequently, and these thoughts typically center on a fear that one may do something totally uncharacteristic of oneself, possibly something potentially fatal to oneself or others.[21] The thoughts may likely be of an aggressive or sexual nature.[21]

Rather than engaging in observable compulsions, the person with this subtype might perform more covert, mental rituals, or

might feel driven to avoid the situations in which particular thoughts seem likely to intrude.[19] As a result of this avoidance, people can struggle to fulfill both public and private roles, even if they place great value on these roles and even if they had fulfilled the roles successfully in the past.[19] Moreover, the individual's avoidance can confuse others who do not know its origin or intended purpose, as it did in the case of a man whose wife began to wonder why he would not hold their infant child.[19] The covert mental rituals can take up a great deal of a person's time during the day.

## Compulsions

*Main article: Compulsive behavior*


Skin-picking disorder

Some people with OCD perform compulsive rituals because they inexplicably feel they have to, others act compulsively so as to mitigate the anxiety that stems from particular obsessive thoughts. The person might feel that these actions somehow either will prevent a dreaded event from occurring, or will push the event from their thoughts. In any case, the individual's reasoning is so idiosyncratic or distorted that it results in significant distress for the individual with OCD or for those around them. Excessive skin picking, hair-pulling, nail biting, and other body-focused repetitive behavior disorders are all on the obsessive–compulsive spectrum.[2] Some individuals with OCD are aware that their behaviors are not rational, but feel compelled to follow through with them to fend off feelings of panic or dread.[2][22]

Some common compulsions include hand washing, cleaning, checking things (e.g., locks on doors), repeating actions (e.g., turning on and off switches), ordering items in a certain way, and requesting reassurance.[23] Compulsions are different than tics (such as touching, tapping, rubbing, or blinking)[24] and stereotyped movements (such as head banging, body rocking, or self-biting), which usually aren't as complex as compulsions and aren't precipitated by obsessions.[2] It can sometimes be difficult to tell the difference between compulsions and complex tics.[2] About 10% to 40% of individuals with OCD also have a lifetime tic disorder.[25]

People rely on compulsions as an escape from their obsessive thoughts; however, they are aware that the relief is only temporary, that the intrusive thoughts will soon return. Some people use compulsions to avoid situations that may trigger their obsessions. Although some people do certain things over and over again, they do not necessarily perform these actions compulsively. For example, bedtime routines, learning a new skill, and religious practices are not compulsions. Whether or not behaviors are compulsions or mere habit depends on the context in which the behaviors are performed. For example, arranging and ordering DVDs for eight hours a day would be expected of one who works in a video store, but would seem abnormal in other situations. In other words, habits tend to bring efficiency to one's life, while compulsions tend to disrupt it.[26]

In addition to the anxiety and fear that typically accompanies OCD, sufferers may spend hours performing such compulsions every day. In such situations, it can be hard for the person to fulfill their work, family, or social roles. In some cases, these behaviors can also cause adverse physical symptoms. For example, people who obsessively wash their hands with antibacterial soap and hot water can make their skin red and raw with dermatitis.[27]

People with OCD can use rationalizations to explain their behavior; however, these rationalizations do not apply to the overall behavior but to each instance individually. For example, a person compulsively checking the front door may argue that the time taken and stress caused by one more check of the front door is much less than the time and stress associated with being robbed, and thus checking is the better option. In practice, after that check, the person is *still* not sure and deems it is *still* better to perform one more check, and this reasoning can continue as long as necessary.

## Overvalued ideas

Some people with OCD exhibit what is known as *overvalued ideas*. In such cases, the person with OCD will truly be uncertain whether the fears that cause them to perform their compulsions are irrational or not. After some discussion, it is possible to convince the individual that their fears may be unfounded. It may be more difficult to do ERP therapy on such people because they may be unwilling to cooperate, at least initially. There are severe cases in which the person has an unshakeable belief in the context of OCD that is difficult to differentiate from psychotic disorders.[28]

## Cognitive performance

A 2013 meta-analysis confirmed people with OCD to have mild but wide-ranging cognitive deficits; significantly regarding spatial memory, to a lesser extent with verbal memory, fluency, executive function and processing speed, while auditory attention was not significantly affected.[29] People with OCD show impairment in formulating an organizational strategy for coding information, set-shifting, motor and cognitive inhibition.[30]

## Associated conditions

People with OCD may be diagnosed with other conditions, as well or instead of OCD, such as the aforementioned obsessive–compulsive personality disorder, major depressive disorder, bipolar disorder,[31] generalized anxiety disorder, anorexia

nervosa, social anxiety disorder, bulimia nervosa, Tourette syndrome, Asperger syndrome, attention deficit hyperactivity disorder, dermatillomania (compulsive skin picking), body dysmorphic disorder, and trichotillomania (hair pulling). In 2009 it was reported that depression among those with OCD is particularly alarming because their risk of suicide is high; more than 50 percent of people experience suicidal tendencies, and 15 percent have attempted suicide.[4] Individuals with OCD have also been found to be affected by delayed sleep phase syndrome at a substantially higher rate than the general public.[32] Moreover, severe OCD symptoms are consistently associated with greater sleep disturbance. Reduced total sleep time and sleep efficiency have been observed in people with OCD, with delayed sleep onset and offset and an increased prevalence of delayed sleep phase disorder.[33]

Behaviorally, there is some research demonstrating a link between drug addiction and the disorder as well. For example, there is a higher risk of drug addiction among those with any anxiety disorder (possibly as a way of coping with the heightened levels of anxiety), but drug addiction among people with OCD may serve as a type of compulsive behavior and not just as a coping mechanism. Depression is also extremely prevalent among people with OCD. One explanation for the high depression rate among OCD populations was posited by Mineka, Watson, and Clark (1998), who explained that people with OCD (or any other anxiety disorder) may feel depressed because of an "out of control" type of feeling.[34]

Someone exhibiting OCD signs does not necessarily have OCD. Behaviors that present as (or seem to be) obsessive or compulsive can also be found in a number of other conditions as well, including obsessive–compulsive *personality* disorder (OCPD), autism, disorders where perseveration is a possible feature (ADHD, PTSD, bodily disorders or habit problems),[35] or sub-clinically.

Some with OCD present with features typically associated with Tourette's syndrome, such as compulsions that may appear to resemble motor tics; this has been termed "tic-related OCD" or "Tourettic OCD".[36][37]

There is tentative evidence that OCD may be associated with above-average intelligence or at least a small increase in intelligence.[38][39]

# Causes

*Main article: Cause of obsessive-compulsive disorder*

The cause is unknown.[1] Both environmental and genetic factors are believed to play a role. Risk factors include a history of child abuse or other stress-inducing event.[2]

## Genetics

There appear to be some genetic components with identical twins more often affected than non-identical twins.[2] Further, individuals with OCD are more likely to have first-degree family members exhibiting the same disorders than do matched controls. In cases where OCD develops during childhood, there is a much stronger familial link in the disorder than cases in which OCD develops later in adulthood. In general, genetic factors account for 45–65% of the variability in OCD symptoms in children diagnosed with the disorder.[40] Recent evidence supports the possibility of a heritable predisposition for neurological development favoring OCD.[41]

A mutation has been found in the human serotonin transporter gene, hSERT, in unrelated families with OCD.[42]

Per evolutionary psychology moderate versions of compulsive behavior may have had evolutionary advantages. Examples would be moderate constant checking of hygiene, the hearth, or the environment for enemies. Similarly, hoarding may have had evolutionary advantages. In this view OCD may be the extreme statistical "tail" of such behaviors possibly due to a high amount of predisposing genes.[43]

## Infection

A controversial hypothesis[44] is that some cases of rapid onset of OCD in children and adolescents may be caused by a syndrome connected to Group A streptococcal infections, known as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).[44][45]

# Mechanisms

*Main article: Biology of obsessive–compulsive disorder*

Brain scans of people with OCD have shown that they have different patterns of brain activity than people without OCD and that different functioning of circuitry within a certain part of the brain, the striatum, may cause the disorder. Differences in other parts of the brain and neurotransmitter dysregulation, especially serotonin and dopamine, may also contribute to OCD.[46] Independent studies have consistently found unusual dopamine and serotonin activity in various regions of the brain in people with OCD. These can be defined as dopaminergic hypofunction in the prefrontal cortex (mesocortical dopamine pathway) and serotonergic hypofunction in the basal ganglia.[47][48][49] Glutamate dysregulation has also been the subject of

recent research,[50][51] although its role in the disorder's etiology is not yet clear. Glutamate is known to act as a cotransmitter with dopamine in dopamine pathways that project out of the ventral tegmental area.

People with OCD evince increased grey matter volumes in bilateral lenticular nuclei, extending to the caudate nuclei, with decreased grey matter volumes in bilateral dorsal medial frontal/anterior cingulate gyri.[52][53] These findings contrast with those in people with other anxiety disorders, who evince decreased (rather than increased) grey matter volumes in bilateral lenticular / caudate nuclei, while also decreased grey matter volumes in bilateral dorsal medial frontal/anterior cingulate gyri.[53] Orbitofrontal cortex overactivity is attenuated in people who have successfully responded to SSRI medication, a result believed to be caused by increased stimulation of serotonin receptors 5-HT2A and 5-HT2C.[54] The striatum, linked to planning and the initiation of appropriate actions, has also been implicated; mice genetically engineered with a striatal abnormality exhibit OCD-like behavior, grooming themselves three times as frequently as ordinary mice.[55]

A meta analysis of functional neuroimaging in OCD reported the only consistent findings have been in the orbital gyrus and head of the caudate nucleus.[56]

# Diagnosis

Formal diagnosis may be performed by a psychologist, psychiatrist, clinical social worker, or other licensed mental health professional. To be diagnosed with OCD, a person must have obsessions, compulsions, or both, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM). The Quick Reference to the 2000 edition of the DSM states that several features characterize clinically significant obsessions and compulsions. Such obsessions, the DSM says, are recurrent and persistent thoughts, impulses, or images that are experienced as intrusive and that cause marked anxiety or distress. These thoughts, impulses, or images are of a degree or type that lies outside the normal range of worries about conventional problems.[57] A person may attempt to ignore or suppress such obsessions, or to neutralize them with some other thought or action, and will tend to recognize the obsessions as idiosyncratic or irrational.

Compulsions become clinically significant when a person feels driven to perform them in response to an obsession, or according to rules that must be applied rigidly, and when the person consequently feels or causes significant distress. Therefore, while many people who do not suffer from OCD may perform actions often associated with OCD (such as ordering items in a pantry by height), the distinction with clinically significant OCD lies in the fact that the person who suffers from OCD *must* perform these actions, otherwise they will experience significant psychological distress. These behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these activities are not logically or practically connected to the issue, or they are excessive. In addition, at some point during the course of the disorder, the individual must realize that their obsessions or compulsions are unreasonable or excessive.

Moreover, the obsessions or compulsions must be time-consuming (taking up more than one hour per day) or cause impairment in social, occupational, or scholastic functioning.[57] It is helpful to quantify the severity of symptoms and impairment before and during treatment for OCD. In addition to the peron's estimate of the time spent each day harboring obsessive-compulsive thoughts or behaviors, concrete tools can be used to gauge the people's condition. This may be done with rating scales, such as the Yale–Brown Obsessive Compulsive Scale (Y-BOCS). With measurements like these, psychiatric consultation can be more appropriately determined because it has been standardized.[4]

OCD is sometimes placed in a group of disorders called the obsessive–compulsive spectrum.[58]

## Differential diagnosis

OCD is often confused with the separate condition obsessive–compulsive personality disorder (OCPD). OCD is egodystonic, meaning that the disorder is incompatible with the sufferer's self-concept.[59][60] Because ego dystonic disorders go against a person's self-concept, they tend to cause much distress. OCPD, on the other hand, is egosyntonic—marked by the person's acceptance that the characteristics and behaviours displayed as a result are compatible with their self-image, or are otherwise appropriate, correct or reasonable.

As a result, people with OCD are often aware that their behavior is not rational, are unhappy about their obsessions but nevertheless feel compelled by them.[61] By contrast people with OCPD are not aware of anything abnormal; they will readily explain why their actions are rational, it is usually impossible to convince them otherwise, and they tend to derive pleasure from their obsessions or compulsions.[61]

# Management

A form of psychotherapy called "cognitive behavioral therapy" (CBT) and psychotropic medications are first-line treatments for OCD.[1][62] Other forms of psychotherapy, such as psychodynamic and psychoanalysis may help in managing some aspects of the disorder, but in 2007 the American Psychiatric Association (APA) noted a lack of controlled studies showing their effectiveness "in dealing with the core symptoms of OCD".[63] The fact that many individuals do not seek treatment may be due in part to stigma associated with OCD.[*citation needed*]

## Therapy

The specific technique used in CBT is called exposure and response prevention (ERP) which involves teaching the person to deliberately come into contact with the situations that trigger the obsessive thoughts and fears ("exposure"), without carrying out the usual compulsive acts associated with the obsession ("response prevention"), thus gradually learning to tolerate the discomfort and anxiety associated with not performing the ritualistic behavior. At first, for example, someone might touch something only very mildly "contaminated" (such as a tissue that has been touched by another tissue that has been touched by the end of a toothpick that has touched a book that came from a "contaminated" location, such as a school.) That is the "exposure". The "ritual prevention" is not washing. Another example might be leaving the house and checking the lock only once (exposure) without going back and checking again (ritual prevention). The person fairly quickly habituates to the anxiety-producing situation and discovers that their anxiety level drops considerably; they can then progress to touching something more "contaminated" or not checking the lock at all—again, without performing the ritual behavior of washing or checking.[64]

One exposure and ritual prevention activity would be to check the lock only once, and then leave.

ERP has a strong evidence base, and it is considered the most effective treatment for OCD.[64] However, this claim was doubted by some researchers in 2000 who criticized the quality of many studies.[65]

It has generally been accepted that psychotherapy, in combination with psychiatric medication, is more effective than either option alone. However, more recent studies have shown no difference in outcomes for those treated with the combination of medicine and CBT versus CBT alone.[66]

## Medication

The medications most frequently used are the selective serotonin reuptake inhibitors (SSRIs).[5] Clomipramine, a medication belonging to the class of tricyclic antidepressants appears to work as well as SSRIs but has a higher rate of side effects.[5]

A blister pack of clomipramine under the brand name "Anafranil".

SSRIs are a second line treatment of adult obsessive compulsive disorder (OCD) with mild functional impairment and as first line treatment for those with moderate or severe impairment. In children, SSRIs can be considered as a second line therapy in those with moderate-to-severe impairment, with close monitoring for psychiatric adverse effects.[62] SSRIs are efficacious in the treatment of OCD; people treated with SSRIs are about twice as likely to respond to treatment as those treated with placebo.[67][68] Efficacy has been demonstrated both in short-term (6–24 weeks) treatment trials and in discontinuation trials with durations of 28–52 weeks.[69][70][71]

In 2006, the National Institute of Clinical and Health Excellence (NICE) guidelines recommended anti-psychotics for OCD that does not improve with SSRI treatment.[6] For OCD the evidence for the atypical antipsychotic drugs risperidone and quetiapine is tentative with insufficient evidence for olanzapine.[72] A 2014 review article found two studies that indicated that aripiprazole was "effective in the short-term" and found that "[t]here was a small effect-size for risperidone or anti-psychotics in general in the short-term"; however, the study authors found "no evidence for the effectiveness of quetiapine or olanzapine in comparison to placebo."[6] While quetiapine may be useful when used in addition to an SSRI in treatment-resistant OCD, these drugs are often poorly tolerated, and have metabolic side effects that limit their use. None of the atypical antipsychotics appear to be useful when used alone.[7]

A guideline by the APA suggested that dextroamphetamine may be considered by itself after more well supported treatments have been tried.[73]

## Procedures

Electroconvulsive therapy (ECT) has been found to have effectiveness in some severe and refractory cases.[74]

Surgery may be used as a last resort in people who do not improve with other treatments. In this procedure, a surgical lesion is made in an area of the brain (the cingulate cortex). In one study, 30% of participants benefited significantly from this procedure.[75] Deep-brain stimulation and vagus nerve stimulation are possible surgical options that do not require destruction of brain tissue. In the US, the Food and Drug Administration approved deep-brain stimulation for the treatment of OCD under a humanitarian device exemption requiring that the procedure be performed only in a hospital with specialist qualifications to do so.[76]

In the US, psychosurgery for OCD is a treatment of last resort and will not be performed until the person has failed several attempts at medication (at the full dosage) with augmentation, and many months of intensive cognitive–behavioral therapy

with exposure and ritual/response prevention.[77] Likewise, in the United Kingdom, psychosurgery cannot be performed unless a course of treatment from a suitably qualified cognitive–behavioral therapist has been carried out.

### Children

Therapeutic treatment may be effective in reducing ritual behaviors of OCD for children and adolescents.[78] Similar to the treatment of adults with OCD, CBT stands as an effective and validated first line of treatment of OCD in children.[79] Family involvement, in the form of behavioral observations and reports, is a key component to the success of such treatments.[80] Parental interventions also provide positive reinforcement for a child who exhibits appropriate behaviors as alternatives to compulsive responses. In a recent meta-analysis of evidenced-based treatment of OCD in children, family-focused individual CBT was labeled as "probably efficacious", establishing it as one of the leading psychosocial treatments for youth with OCD.[79] After one or two years of therapy, in which a child learns the nature of his or her obsession and acquires strategies for coping, that child may acquire a larger circle of friends, exhibit less shyness, and become less self-critical.[81]

Although the causes of OCD in younger age groups range from brain abnormalities to psychological preoccupations, life stress such as bullying and traumatic familial deaths may also contribute to childhood cases of OCD, and acknowledging these stressors can play a role in treating the disorder.[82]

## Epidemiology

Obsessive–compulsive disorder affects about 2.3% of people at some point in their life.[8] Rates during a given year are about 1.2% and it occurs worldwide.[2] It is unusual for symptoms to begin after the age of thirty five and half of people develop problems before twenty.[1][2] Males and females are affected about equally.[1]

Age-standardized disability-adjusted life year estimated rates for obsessive-compulsive disorder per 100,000 inhabitants in 2004.

| | |
|---|---|
| no data | 75–82.5 |
| <45 | 82.5–90 |
| 45–52.5 | 90–97.5 |
| 52.5–60 | 97.5–105 |
| 60–67.5 | 105–112.5 |
| 67.5–75 | 112.5–120 |
| | >120 |

## Prognosis

Psychological interventions such as behavioral therapy and cognitive-behavioral therapy as well as medication can lead to a reduction of OCD symptoms for a number of people. However, symptoms may persist at moderate levels even following adequate treatment courses, and completely symptom-free periods are uncommon.[83]

## History

From the 14th to the 16th century in Europe, it was believed that people who experienced blasphemous, sexual, or other obsessive thoughts were possessed by the Devil.[59] Based on this reasoning, treatment involved banishing the "evil" from the "possessed" person through exorcism.[84][85] In the early 1910s, Sigmund Freud attributed obsessive–compulsive behavior to unconscious conflicts that manifest as symptoms.[84] Freud describes the clinical history of a typical case of "touching phobia" as starting in early childhood, when the person has a strong desire to touch an item. In response, the person develops an "external prohibition" against this type of touching. However, this "prohibition does not succeed in abolishing" the desire to touch; all it can do is repress the desire and "force it into the unconscious".[86]

## Society and culture

### Notable cases

Some notable historical and contemporary figures known to have had OCD are listed below.

- The American aviator and filmmaker Howard Hughes is known to have had OCD.[87] Friends of Hughes have also mentioned his obsession with minor flaws in clothing.[88] This was conveyed in the *The Aviator* (2004), a film biography of Hughes.[89]
- British poet, essayist, and lexicographer Samuel Johnson is an example of an historical figure with a retrospective diagnosis of OCD. He had elaborate rituals for crossing the thresholds of doorways, and repeatedly walked up and down staircases counting the steps.[90]

### Art, entertainment, and media

Movies and television shows often portray idealized representations of disorders such as OCD. These depictions may lead to increased public awareness, understanding, and sympathy for such

disorders.[91]

- In the film *As Good as it Gets* (1997), actor Jack Nicholson portrays a man "with Obsessive Compulsive Disorder (OCD)".[92] "Throughout the film, [he] engages in ritualistic behaviors (i.e., compulsions) that disrupt his interpersonal and professional life", a "cinematic representation of psychopathology [that] accurately depicts the functional interference and distress associated with OCD".[92]
- The film *Matchstick Men* (2003), directed by Ridley Scott, portrays a con-man named Roy (Nicolas Cage) who has obsessive-compulsive disorder. The film "opens with Roy, at home, suffering with his numerous obsessive compulsive symptoms, which take the form of a need for order and cleanliness and a compulsion to open and close doors three times, whilst counting aloud, before he can walk through them."[93]
- In the USA Network American comedy-drama detective mystery television series *Monk* (2002–2009), the titular Adrian Monk fears both human contact and dirt.[94][95]

This ribbon represents Trichotillomania and other body focused repetitive behaviors. Concept for the ribbon was started by Jenne Schrader. Colors were voted on by the Trichotillomania Facebook community, and made official by Trichotillomania Learning Center in August 2013

## Research

The naturally occurring sugar inositol has been suggested as a treatment for OCD.[96]

Nutrition deficiencies may also contribute to OCD and other mental disorders. Vitamin and mineral supplements may aid in such disorders and provide nutrients necessary for proper mental functioning.[97]

μ-Opioids, such as hydrocodone and tramadol, may improve OCD symptoms.[98] Administration of opiate treatment may be contraindicated in individuals concurrently taking CYP2D6 inhibitors such as fluoxetine and paroxetine.[99]

Much current research is devoted to the therapeutic potential of the agents that affect the release of the neurotransmitter glutamate or the binding to its receptors. These include riluzole,[51] memantine, gabapentin, N-acetylcysteine, topiramate and lamotrigine.[*citation needed*]

## Other animals

*See also: Animal psychopathology § Obsessive compulsive disorder (OCD)*

## References


1. ^ *a b c d e f g h i* The National Institute of Mental Health (NIMH) (January 2016). "What is Obsessive-Compulsive Disorder (OCD)?". *U.S. National Institutes of Health (NIH)*. Retrieved 24 July 2016.
2. ^ *a b c d e f g h i j k l m n o* *Diagnostic and statistical manual of mental disorders : DSM-5* (5 ed.). Washington: American Psychiatric Publishing. 2013. pp. 237–242. ISBN 9780890425558.
3. ^ Angelakis, I; Gooding, P; Tarrier, N; Panagioti, M (25 March 2015). "Suicidality in obsessive compulsive disorder (OCD): A systematic review and meta-analysis.". *Clinical Psychology Review*. **39**: 1–15. doi:10.1016/j.cpr.2015.03.002. PMID 25875222.
4. ^ *a b c* Fenske JN, Schwenk TL (August 2009). "Obsessive compulsive disorder: diagnosis and management". *Am Fam Physician*. **80** (3): 239–45. PMID 19621834.
5. ^ *a b c d e* Grant JE (14 August 2014). "Clinical practice: Obsessive-compulsive disorder.". *The New England Journal of Medicine*. **371** (7): 646–53. doi:10.1056/NEJMcp1402176. PMID 25119610.
6. ^ *a b c d* Veale, D; Miles, S; Smallcombe, N; Ghezai, H; Goldacre, B; Hodsoll, J (29 November 2014). "Atypical antipsychotic augmentation in SSRI treatment refractory obsessive-compulsive disorder: a systematic review and meta-analysis.". *BMC Psychiatry*. **14**: 317. doi:10.1186/s12888-014-0317-5. PMC 4262998. PMID 25432131.
7. ^ *a b* Decloedt EH, Stein DJ (2010). "Current trends in drug treatment of obsessive-compulsive disorder". *Neuropsychiatr Dis Treat*. **6**: 233–42. doi:10.2147/NDT.S3149. PMC 2877605. PMID 20520787.
52. ^ Radua J, Mataix-Cols D (November 2009). "Voxel-wise meta-analysis of grey matter changes in obsessive–compulsive disorder". *British Journal of Psychiatry*. **195** (5): 393–402. doi:10.1192/bjp.bp.108.055046. PMID 19880927.
53. ^ *a b* Radua J, van den Heuvel OA, Surguladze S, Mataix-Cols D (5 July 2010). "Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders". *Archives of General Psychiatry*. **67** (7): 701–711. doi:10.1001/archgenpsychiatry.2010.70. PMID 20603451.
54. ^ Kim KW, Lee DY (2002). "Obsessive-Compulsive Disorder Associated With a Left Orbitofrontal Infarct". *Journal of Neuropsychiatry and Clinical Neurosciences*. **14** (1): 88–89. doi:10.1176/appi.neuropsych.14.1.88. PMID 11884667.
55. ^ Welch JM, Lu J, Rodriguiz RM, Trotta NC, Peca J, Ding JD, Feliciano C, Chen M, Adams JP, Luo J, Dudek SM, Weinberg RJ, Calakos N, Wetsel WC, Feng G (August 2007). "Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice". *Nature*. **448** (7156): 894–900. doi:10.1038/nature06104. PMC 2442572. PMID 17713528.
56. ^ Whiteside, Stephen P.; Port, John D.; Abramowitz, Jonathan S. (2004). "A meta–analysis of functional neuroimaging in obsessive–compulsive disorder". *Psychiatry Research: Neuroimaging*. **132** (1): 69–79. doi:10.1016/j.pscychresns.2004.07.001. PMID 15546704.

8. ^ [a] [b] Goodman, WK; Grice, DE; Lapidus, KA; Coffey, BJ (September 2014). "Obsessive-compulsive disorder.". *The Psychiatric clinics of North America*. **37** (3): 257–67. doi:10.1016/j.psc.2014.06.004. PMID 25150561.
9. ^ Bynum, W.F.; Porter, Roy; Shepherd, Michael (1985). "Obsessional Disorders: A Conceptual History. Terminological and Classificatory Issues.". *The anatomy of madness : essays in the history of psychiatry*. London: Routledge. pp. 166–187. ISBN 9780415323826.
10. ^ Markarian Y, Larson MJ, Aldea MA, Baldwin SA, Good D, Berkeljon A, Murphy TK, Storch EA, McKay D (February 2010). "Multiple pathways to functional impairment in obsessive-compulsive disorder". *Clin Psychol Rev*. **30** (1): 78–88. doi:10.1016/j.cpr.2009.09.005. PMID 19853982.
11. ^ Baer (2001), p. 33, 78
12. ^ Baer (2001), p. xiv.
13. ^ Doron G, Szepsenwol O, Karp E, Gal N (2013). "Obsessing About Intimate-Relationships: Testing the Double Relationship-Vulnerability Hypothesis". *Journal of Behavior Therapy and Experimental Psychiatry*. **44** (4): 433–440. doi:10.1016/j.jbtep.2013.05.003. PMID 23792752.
14. ^ Mash, E. J., & Wolfe, D. A. (2005). *Abnormal child psychology* (3rd ed.). Belmont, CA: Thomson Wadsworth, p. 197.
15. ^ [a] [b] Osgood-Hynes, Deborah. Thinking Bad Thoughts (PDF). MGH/McLean OCD Institute, Belmont, MA, published by the *OCD Foundation*, Milford, CT. Retrieved on 30 December 2006.
16. ^ Steven Phillipson I Think It Moved Center for Cognitive-Behavioral Psychotherapy, OCDOnline.com. Retrieved on 14 May 2009.
17. ^ Mark-Ameen Johnson, I'm Gay and You're Not : Understanding Homosexuality Fears brainphysics.com. Retrieved on 14 May 2009.
18. ^ Freeston M, Ladouceur R (2003). "What do patients do with their obsessive thoughts?". *Behaviour Research and Therapy*. **35** (4): 335–348. doi:10.1016/S0005-7967(96)00094-0.
19. ^ [a] [b] [c] [d] Hyman, B. M., & Pedrick, C. (2005). *The OCD workbook: Your guide to breaking free from obsessive–compulsive disorder* (2nd ed.). Oakland, CA: New Harbinger, pp. 125–126.
20. ^ Weisman M.M.; Bland R.C.; Canino G.J.; Greenwald S.; Hwu H.G.; Lee C.K.; et al. (1994). "The cross national epidemiology of obsessive–compulsive disorder". *Journal of Clinical Psychiatry*. **55**: 5–10.
21. ^ [a] [b] [c] Hyman, Bruce and Troy DeFrene. *Coping with OCD*. 2008. New Harbinger Publications.
22. ^ *Highlights of Changes from DSM-IV-TR to DSM-5* (PDF), American Psychiatric Association, 2013, p. 7, retrieved 12 Apr 2016
23. ^ Boyd MA (2007). *Psychiatric Nursing*. Lippincott Williams & Wilkins. p. 418. ISBN 0-397-55178-9.
24. ^ Storch; et al. (2008), "Obsessive-compulsive disorder in youth with and without a chronic tic disorder", *Depression and Anxiety*, **25** (9): 761–767, doi:10.1002/da.20304, PMID 17345600
25. ^ Conelea; et al. (2014), "Tic-related obsessive-compulsive disorder (OCD): phenomenology and treatment outcome in the Pediatric OCD Treatment Study II", *Journal of the American Academy of Child & Adolescent Psychiatry*, **53** (12): 1308–16, doi:10.1016/j.jaac.2014.09.014, PMC 4254546, PMID 25457929
26. ^ "Obsessive-Compulsive Disorder, (2005)". Retrieved 15 December 2009.
27. ^ "Hygiene of the Skin: When Is Clean Too Clean? Subtopic: "Skin Barrier Properties and Effect of Hand Hygiene Practices", Paragraph 5.". Retrieved 26 March 2009.
28. ^ O'Dwyer, Anne-Marie Carter, Obsessive–compulsive disorder and delusions revisited, The British Journal of Psychiatry (2000) 176: 281–284
57. ^ [a] [b] *Quick Reference to the Diagnostic Criteria from DSM-IV-TR*. Arlington, VA: American Psychiatric Association, 2000.
58. ^ Starcevic, V; Janca, A (January 2011). "Obsessive-compulsive spectrum disorders: still in search of the concept-affirming boundaries.". *Current opinion in psychiatry*. **24** (1): 55–60. doi:10.1097/yco.0b013e32833f3b58. PMID 20827198.
59. ^ [a] [b] Aardema F., O'Connor (2007). "The menace within: obsessions and the self". *International Journal of Cognitive Therapy*. **21**: 182–197. doi:10.1891/088983907781494573.
60. ^ Aardema F., O'Connor (2003). "Seeing white bears that are not there: Inference processes in obsessions". *Journal of Cognitive Psychotherapy*. **17**: 23–37. doi:10.1891/jcop.17.1.23.58270.
61. ^ [a] [b] Carter, K. "Obsessive–compulsive personality disorder." PSYC 210 lecture: Oxford College of Emory University. Oxford, GA. 11 April 2006.
62. ^ [a] [b] National Institute for Health and Clinical Excellence (NICE) (November 2005). "Obsessive-compulsive disorder: Core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder". Information about NICE Clinical Guideline 31. UK National Health Service (NHS). Retrieved 24 July 2016.
63. ^ Koran LM, Hanna GL, Hollander E, Nestadt G, Simpson HB (July 2007). "Practice guideline for the treatment of patients with obsessive-compulsive disorder". *The American Journal of Psychiatry*. **164** (7 Suppl): 5–53. PMID 17849776.
64. ^ [a] [b] Huppert & Roth: (2003) Treating Obsessive-Compulsive Disorder with Exposure and Response Prevention. *The Behavior Analyst Today, 4 (1),* 66 – 70 BAO
65. ^ Klein DF (2000). "Flawed meta-analyses comparing psychotherapy with pharmacotherapy". *Am J Psychiatry*. **157** (8): 1204–11. doi:10.1176/appi.ajp.157.8.1204. PMID 10910778.
66. ^ Foa EB, Liebowitz MR, Kozak MJ, Davies S, Campeas R, Franklin ME, Huppert JD, Kjernisted K, Rowan V, Schmidt AB, Simpson HB, Tu X (2005). "Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive–compulsive disorder". *Am J Psychiatry*. **162** (1): 151–61. doi:10.1176/appi.ajp.162.1.151. PMID 15625214.
67. ^ Arroll B, Elley CR, Fishman T, Goodyear-Smith FA, Kenealy T, Blashki G, Kerse N, Macgillivray S (2009). Arroll, Bruce, ed. "Antidepressants versus placebo for depression in primary care". *The Cochrane Database of Systematic Reviews* (3): CD007954. doi:10.1002/14651858.CD007954. PMID 19588448.
68. ^ "Review Finds SSRIs Modestly Effective in Short-Term Treatment of OCD". Archived from the original on 13 April 2013.
69. ^ Fineberg NA, Brown A, Reghunandanan S, Pampaloni I (2012). "Evidence-based pharmacotherapy of obsessive-compulsive disorder". *The International Journal of Neuropsychopharmacology*. **15** (8): 1173–91. doi:10.1017/S1461145711001829. PMID 22226028.
70. ^ "Sertraline prescribing information" (PDF). Retrieved 30 January 2015.
71. ^ "Paroxetine prescribing information" (PDF). Retrieved 30 January 2015.
72. ^ Komossa, K; Depping, AM; Meyer, M; Kissling, W; Leucht, S (8 Dec 2010). "Second-generation antipsychotics for obsessive compulsive disorder.". *The Cochrane database of systematic reviews* (12): CD008141. doi:10.1002/14651858.CD008141.pub2. PMID 21154394.
73. ^ Koran, Lorrin; Hanna, Gregory; Hollander, Eric; Nestadt, Gerald; Helen, Simpson. "Practice Guideline for the Treatment of Patients With Obsessive-Compulsive Disorder" (PDF). *American Psychiatric Association*. American Psychiatric Association.
74. ^ Cybulska Eva M (2006). "Obsessive Compulsive disorder, the

29. ^ Shin NY, Lee TY, Kim E, Kwon JS (19 July 2013). "Cognitive functioning in obsessive-compulsive disorder: a meta-analysis". *Psychological Medicine*. **44**: 1–10. doi:10.1017/S0033291713001803. PMID 23866289.
30. ^ Çetinay Aydın P, Güleç Öyekçin D (2013). "Cognitive functions in patients with obsessive compulsive disorder". *Turk psikiyatri dergisi (Turkish journal of psychiatry)*. **24** (4): 266–74. doi:10.5080/u7172. PMID 24310094.
31. ^ Chen YW, Dilsaver SC (1995). "Comorbidity for obsessive-compulsive disorder in bipolar and unipolar disorders". *Psychiatry Research*. **59** (1–2): 57–64. doi:10.1016/0165-1781(95)02752-1. PMID 8771221.
32. ^ Turner J, Drummond LM, Mukhopadhyay S, Ghodse H, White S, Pillay A, Fineberg NA (June 2007). "A prospective study of delayed sleep phase syndrome in patients with severe resistant obsessive–compulsive disorder". *World Psychiatry*. **6** (2): 108–111. PMC 2219909. PMID 18235868.
33. ^ Paterson JL, Reynolds AC, Ferguson SA, Dawson D (2013). "Sleep and obsessive-compulsive disorder (OCD)". *Sleep Medicine Reviews*. **17** (6): 465–74. doi:10.1016/j.smrv.2012.12.002. PMID 23499210.
34. ^ Mineka S, Watson D, Clark LA (1998). "Comorbidity of anxiety and unipolar mood disorders". *Annual Review of Psychology*. **49**: 377–412. doi:10.1146/annurev.psych.49.1.377. PMID 9496627.
35. ^ Pediatric Obsessive-Compulsive Disorder Differential Diagnoses – 2012
36. ^ Mansueto CS, Keuler DJ (2005). "Tic or compulsion?: it's Tourettic OCD.". *Behavior Modification*. **29** (5): 784–99. doi:10.1177/0145445505279261. PMID 16046664.
37. ^ "OCD and Tourette Syndrome: Re-examining the Relationship". International OCD Foundation. Retrieved 30 October 2013.
38. ^ Clark, David (2012). *Cognitive-Behavioral Therapy for OCD*. Guilford Press. p. Chapter 4. ISBN 9781462506651.
39. ^ Ozertugrul,, Engin (April 21, 2015). *Interview with OCD: Forty-five Days to End of a New Beginning*.
40. ^ Abramowitz JS, Taylor S, McKay D (2009). "Obsessive-compulsive disorder". *Lancet*. **374** (9688): 491–9. doi:10.1016/S0140-6736(09)60240-3. PMID 19665647.
41. ^ Menzies L, Achard S, Chamberlain SR, Fineberg N, Chen CH, del Campo N, Sahakian BJ, Robbins TW, Bullmore E (2007). "Neurocognitive endophenotypes of obsessive-compulsive disorder". *Brain*. **130** (Pt 12): 3223–36. doi:10.1093/brain/awm205. PMID 17855376.
42. ^ Ozaki N, Goldman D, Kaye WH, Plotnicov K, Greenberg BD, Lappalainen J, Rudnick G, Murphy DL (2003). "Serotonin transporter missense mutation associated with a complex neuropsychiatric phenotype". *Mol. Psychiatry*. **8** (11): 933–6. doi:10.1038/sj.mp.4001365. PMID 14593431.
43. ^ Bracha HS (2006). "Human brain evolution and the "Neuroevolutionary Time-depth Principle:" Implications for the Reclassification of fear-circuitry-related traits in DSM-V and for studying resilience to warzone-related posttraumatic stress disorder". *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. **30** (5): 827–853. doi:10.1016/j.pnpbp.2006.01.008. PMID 16563589.
44. ^ [a] [b] Boileau B (2011). "A review of obsessive-compulsive disorder in children and adolescents". *Dialogues Clin Neurosci*. **13** (4): 401–11. PMC 3263388. PMID 22275846.
45. ^ Moretto, Germana; Pasquini, Massimo; et al. (2008), "What every psychiatrist should know about PANDAS: a review", *Clinical Practice and Epidemiology in Mental Health*, Department of Psychiatric Sciences and Psychological Medicine, Sapienza University of Rome
46. ^ "Obsessive-Compulsive Disorder (OCD) – Cause". WebMD. 21 June 2010. Retrieved 10 December 2011.
47. ^ van der Wee NJ, Stevens H, Hardeman JA, Mandl RC, Denys DA, van Megen HJ, Kahn RS, Westenberg HM (2004). brain and electroconvulsive therapy". *British Journal of Hospital Medicine*. **67** (2): 77–82. doi:10.12968/hmed.2006.67.2.20466.
75. ^ Barlow, D. H. and V. M. Durand. *Essentials of Abnormal Psychology*. California: Thomson Wadsworth, 2006.
76. ^ Barlas S (8 April 2009). "FDA Approves Pioneering Treatment for Obsessive- Compulsive Disorder". *Psychiatric Times*. **26** (4).
77. ^ Surgical Procedures for Obsessive–Compulsive Disorder, by M. Jahn and M. Williams, Ph.D,. BrainPhysics OCD Resource, Accessed 6 July 2008.
78. ^ O'Donohue William; Ferguson Kyle E (2006). "Evidence-Based Practice in Psychology and Behavior Analysis". *The Behavior Analyst Today*. **7** (3): 335–347. doi:10.1037/h0100155.
79. ^ [a] [b] Freeman, J; Garcia, A; Frank, H; Benito, K; Conelea, C; Walther, M; Edmunds, J (2014). "Evidence base update for psychosocial treatments for pediatric obsessive-compulsive disorder". *Journal of Clinical Child and Adolescent Psychology*. **43** (1): 7–26. doi:10.1080/15374416.2013.804386. PMID 23746138.
80. ^ Rapoport, J. E. (1989). Obsessive-compulsive Disorder In Children & Adolescents. Washington: American Psychiatric Press.
81. ^ Adams, P. L. (1973). Obsessive Children: A Sociopsychiatric Study. Philadelphia: Brunner / Mazel.
82. ^ D'Alessandro TM (2009). "Factors influencing the onset of childhood obsessive compulsive disorder". *Pediatr Nurs*. **35** (1): 43–6. PMID 19378573.
83. ^ Eddy KT, Dutra L, Bradley R, Westen D (2004). "A multidimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive-compulsive disorder". *Clin Psychol Rev*. **24** (8): 1011–30. doi:10.1016/j.cpr.2004.08.004. PMID 15533282.
84. ^ [a] [b] M. A. Jenike; Baer, L.; & W. E. Minichiello. *Obsessive Compulsive Disorders: Theory and Management*. Littleton, MA: PSG Publishing, 1986.
85. ^ Berrios G E (1989). "Obsessive Compulsive Disorder: Its conceptual history in France during the 19th Century". *Comprehensive Psychiatry*. **30**: 283–95. doi:10.1016/0010-440x(89)90052-7.
86. ^ Freud S (1950). *Totem and Taboo:Some Points of Agreement between the Mental Lives of Savages and Neurotics*. trans. Strachey. New York: W. W. Norton & Company. ISBN 0-393-00143-1. p. 29.
87. ^ Dittmann, M (July–August 2005). "Hughes's germ phobia revealed in psychological autopsy". *American Psychological Association*. Retrieved 9 January 2015.
88. ^ M. Dittmann (July–August 2005). "Hughes's germ phobia revealed in psychological autopsy". *APA Online: Monitor on Psychology*. **36** (7).
89. ^ Chosak, Anne (12 October 2012). "The Aviator: A real-life portrayal of OCD in the media". *=Massachusetts General Hospital OCD and Related Disorders Program*. Retrieved 9 January 2015.
90. ^ "SAMUEL JOHNSON (1709–1784): A Patron Saint of OCD? by Fred Penzel, Ph.D. from the Scientific Advisory Board of the International OCD Foundation". *Westsuffolkpsych.homestead.com*. Retrieved 29 November 2013.
91. ^ Goldberg FR (2007). *Turn box office movies into mental health opportunities: A literature review and resource guide for clinicians and educators* (PDF). Beneficial Film Guides, Inc. p. 8. Retrieved February 17, 2010.
92. ^ [a] [b] Berman, Noah (5 October 2012). "Is This 'As Good as It Gets?': Popular Media's Representation of OCD". *Massachusetts General Hospital OCD and Related Disorders Program*. Retrieved 9 January 2015.
93. ^ Almeida. "Royal College of Psychiatrists, Discover Psychiatry, Minds on Film Blog, Matchstick Men". *Royal College of*

"Enhanced dopamine transporter density in psychotropic-naive patients with obsessive-compulsive disorder shown by [123I]{beta}-CIT SPECT". *Am J Psychiatry*. **161** (12): 2201–6. doi:10.1176/appi.ajp.161.12.2201. PMID 15569890.
48. ^ Kim CH, Cheon KA, Koo MS, Ryu YH, Lee JD, Chang JW, Lee HS (2007). "Dopamine transporter density in the basal ganglia in obsessive-compulsive disorder, measured with [123I]IPT SPECT before and after treatment with serotonin reuptake inhibitors". *Neuropsychobiology*. **55** (3–4): 156–62. doi:10.1159/000106474. PMID 17657168.
49. ^ Harsányi A, Csigó K, Demeter G, Németh A (2007). "New approach to obsessive-compulsive disorder: Dopaminergic theories". *Psychiatria Hungarica : A Magyar Pszichiatriai Tarsasag tudomanyos folyoirata*. **22** (4): 248–258. PMID 18167420.
50. ^ Pittenger C, Bloch MH, Williams K (2011). "Glutamate abnormalities in obsessive compulsive disorder: Neurobiology, pathophysiology, and treatment". *Pharmacology & Therapeutics*. **132** (3): 314–332. doi:10.1016/j.pharmthera.2011.09.006. PMC 3205262. PMID 21963369.
51. ^ [a] [b] Wu K, Hanna GL, Rosenberg DR, Arnold PD (2012). "The *Psychiatrists*. Retrieved 14 January 2015.
94. ^ Stewart, Susan (September 16, 2007). "Happy to Be Neurotic, at Least Once a Week". *The New York Times*. Retrieved December 8, 2008.
95. ^ Aniety Disorders Association of America. "WHAT IS OCD?". *USA Network*. Retrieved December 8, 2008.
96. ^ Camfield DA, Sarris J, Berk M (1 June 2011). "Nutraceuticals in the treatment of obsessive compulsive disorder (OCD): a review of mechanistic and clinical evidence". *Progress in neuro-psychopharmacology & biological psychiatry*. **35** (4): 887–95. doi:10.1016/j.pnpbp.2011.02.011. PMID 21352883.
97. ^ Lakhan SE, Vieira KF (2008). "Nutritional therapies for mental disorders". *Nutr J.* **7**: 2. doi:10.1186/1475-2891-7-2. PMC 2248201. PMID 18208598.
98. ^ Davidson J, Bjorgvinsson T (June 2003). "Current and potential pharmacological treatments for obsessive-compulsive disorder". *Expert Opinion on Investigational Drugs*. **12** (6): 993–1001. doi:10.1517/13543784.12.6.993. PMID 12783603.
99. ^ Koran LM (2007). "Obsessive-Compulsive Disorder: An Update for the Clinician". *Focus* (5): 3.

## External links

- Obsessive–compulsive disorder at DMOZ
- National Institute Of Mental Health
- American Psychiatric Association
- APA Division 12 treatment page for obsessive-compulsive disorder
- Davis, Lennard J. (2008). *Obsession: A History*. University of Chicago Press. ISBN 978-0-226-13782-7.

Wikimedia Commons has media related to *Obsessive–compulsive disorder*.

| v · t · e · | **Mental and behavioral disorders (F 290–319)** |
|---|---|
| | **Neurological/symptomatic** |
| **Dementia** | Mild cognitive impairment · Alzheimer's disease · Vascular dementia · Pick's disease · Creutzfeldt–Jakob disease · Huntington's disease · Parkinson's disease · AIDS dementia complex · Frontotemporal dementia · Sundowning · Wandering · |
| **Autism spectrum** | Autism · Asperger syndrome · Savant syndrome · PDD-NOS · High-functioning autism · |
| **Other** | Delirium · Post-concussion syndrome · Organic brain syndrome · |
| | **Psychoactive substances, substance abuse, drug abuse and substance-related disorders** |
| | Intoxication/Drug overdose · Physical dependence · Substance dependence · Rebound effect · Double rebound · Withdrawal · |
| | **Schizophrenia, schizotypal and delusional** |
| **Psychosis** | Schizoaffective disorder · Schizophreniform disorder · Brief reactive psychosis · |
| **Schizophrenia** | Disorganized schizophrenia · Paranoid schizophrenia · Simple-type schizophrenia · |
| **Delusional disorders** | Delusional disorder · Folie à deux · |
| | **Mood (affective)** |
| | Mania · Bipolar disorder · (Bipolar I · Bipolar II · Cyclothymia · Bipolar NOS) · Depression · (Major depressive disorder · Dysthymia · Seasonal affective disorder · Atypical depression · Melancholic depression) · |
| | **Neurotic, stress-related and somatoform** |
| **Anxiety disorder** | **Phobia**: Agoraphobia · Social anxiety · Social phobia · (Anthropophobia) · Specific phobia · (Claustrophobia) · Specific social phobia · |
| | **Other**: Panic disorder · Panic attack · Generalized anxiety disorder · **OCD** · *stress* · (Acute stress reaction · PTSD) · |
| **Adjustment disorder** | Adjustment disorder with depressed mood · |

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|---|---|
| **Somatic symptom disorder** | Somatization disorder · Body dysmorphic disorder · Hypochondriasis · Nosophobia · Da Costa's syndrome · Psychalgia · Conversion disorder · (Ganser syndrome · Globus pharyngis) · Neurasthenia · Mass psychogenic illness · |
| **Dissociative disorder** | Dissociative identity disorder · Psychogenic amnesia · Fugue state · Depersonalization disorder · |
| **Physiological/physical behavioral** | |
| **Eating disorder** | Anorexia nervosa · Bulimia nervosa · Rumination syndrome · NOS · |
| **Nonorganic sleep disorders** | (Nonorganic hypersomnia · Nonorganic insomnia) · Parasomnia · (REM sleep behavior disorder · Night terror · Nightmare) · |
| **Sexual dysfunction** | *sexual desire* · (Hypoactive sexual desire disorder · Hypersexuality) · *sexual arousal* · (Female sexual arousal disorder) · Erectile dysfunction · *orgasm* · (Anorgasmia · Delayed ejaculation · Premature ejaculation · Sexual anhedonia) · *pain* · (Vaginismus · Dyspareunia) · |
| **Postnatal** | Postpartum depression · Postpartum psychosis · |
| **Adult personality and behavior** | |
| *Gender dysphoria* | Sexual maturation disorder · Ego-dystonic sexual orientation · Sexual relationship disorder · Paraphilia · (Voyeurism · Fetishism) · |
| **Other** | Personality disorder · Impulse control disorder · (Kleptomania · Trichotillomania · Pyromania · Dermatillomania) · Body-focused repetitive behavior · Factitious disorder · (Münchausen syndrome) · |
| **Disorders typically diagnosed in childhood** | |
| **Intellectual disability** | X-linked intellectual disability · (Lujan–Fryns syndrome) · |
| **Psychological development (developmental disabilities)** | Specific · Pervasive · Autism spectrum · |
| **Emotional and behavioral** | ADHD · Conduct disorder · (ODD) · Emotional/behavioral disorder · (Separation anxiety disorder) · *social functioning* · (Selective mutism · RAD · DAD) · Tic disorder · (Tourette syndrome) · *Speech* · (Stuttering · Cluttering) · Movement disorder · (Stereotypic) · |
| **Symptoms and uncategorized** | |
| Catatonia · False pregnancy · Intermittent explosive disorder · Psychomotor agitation · Stereotypy · Psychogenic non-epileptic seizures · Klüver–Bucy syndrome · | |

| v · t · e · | **Obsessive–compulsive disorder (F42, 300.3)** | | |
|---|---|---|---|
| **History** | Yale–Brown Obsessive Compulsive Scale · | | |
| **Biology** | **Neuroanatomy** | Basal ganglia (striatum) · Orbitofrontal cortex · Cingulate cortex · Brain-derived neurotrophic factor · | |
| | **Receptors** | 5-$HT_{1D}\beta$ · 5-$HT_{2A}$ · 5-$HT_{2C}$ · μ Opioid · $H_2$ · $NK_1$ · $M_4$ · NMDA · | |
| **Symptoms** | Obsessions (associative · diagnostic · injurious · scrupulous · pathogenic · sexual) · Compulsions (impulses, rituals · tics) · Thought suppression (avoidance) · Hoarding (animals, books · possessions) · | | |
| **Treatment** | **Serotonergics** | **Selective serotonin reuptake inhibitors** | Escitalopram · Fluoxetine · Fluvoxamine · Paroxetine · Sertraline · Citalopram · Nefazodone · |
| | | **Serotonin–norepinephrine reuptake inhibitors** | Venlafaxine · Desvenlafaxine · Duloxetine · |
| | | **Serotonin–norepinephrine–dopamine reuptake inhibitors** | Nefazodone · |
| | | **Monoamine oxidase inhibitors** | Phenelzine · Tranylcypromine · |
| | | **Tricyclic antidepressants** | Clomipramine · |

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|---|---|---|---|
| | | **Serotonergic psychedelics** | Lysergic acid diethylamide · Psilocin · |
| | | **Nootropics** | Inositol · |
| | | **Atypical antipsychotics** | Aripiprazole · Quetiapine · |
| | **Mu opioidergics** | Hydrocodone · Morphine · Tramadol · | |
| | **Anticholinergics** | Diphenhydramine · | |
| | **NMDA glutamatergics** | Riluzole · | |
| | **NK-1 tachykininergics** | Aprepitant · | |
| | **Other** | Nicotine · Memantine · Tautomycin · | |
| | **Behavioral** | Cognitive behavioral therapy (Exposure and response prevention) · | |
| **Organizations** | International OCD Foundation · OCD Action · | | |
| **Notable people** | Edna B. Foa · Stanley Rachman · Adam S. Radomsky · Jeffrey M. Schwartz · Susan Swedo · Emily Colas · | | |
| **Popular culture** | **Literature/Comics** | **Fictional** | *Matchstick Men* · *Plyushkin* · *Xenocide* · |
| | | **Nonfiction** | *Everything in Its Place* · *Just Checking* · |
| | **Media** | *As Good as It Gets* · *The Aviator* · *Matchstick Men* · Adrian Monk · "$pringfield" · | |
| **Related** | Obsessive–compulsive personality disorder · Obsessional jealousy · Primarily Obsessional OCD · Relationship obsessive–compulsive disorder · Social anxiety disorder · Tourette syndrome · | | |

| v · t · e · | **OCD pharmacotherapies** |
|---|---|
| **Antidepressants** | SSRIs (e.g., fluoxetine, sertraline, escitalopram) · SNRIs (e.g., venlafaxine) · TCAs (e.g., clomipramine) · MAOIs (e.g., phenelzine) · |
| **Others** | Antiandrogens (e.g., cyproterone acetate, triptorelin) · Antipsychotics (e.g., aripiprazole) · Benzodiazepines · Lamotrigine · Memantine · Mirtazapine · N-Acetylcysteine · Ondansetron · Pregabalin · Psychedelics (e.g., psilocybin) · Riluzole · Topiramate · |

| | |
|---|---|
| **Authority control** | GND: 4234004-4 · NDL: 00991324 · |

Categories: Obsessive–compulsive disorder | Habit and impulse disorders | Magical thinking | Neurotic, stress-related and somatoform disorders | Ritual | Psychiatric diagnosis | Anxiety

# Phobia

From Wikipedia, the free encyclopedia

*This article is about the clinical psychology. For other uses, see Phobia (disambiguation).*

A **phobia** is a type of anxiety disorder, defined by a persistent fear of an object or situation.[1] The phobia typically results in a rapid onset of fear and is present for more than six months. The affected person will go to great lengths to avoid the situation or object, typically to a degree greater than the actual danger posed. If the feared object or situation cannot be avoided, the affected person will have significant distress. With blood or injury phobia, fainting may occur.[1] Agoraphobia is often associated with panic attacks.[2] Usually a person has phobias to a number of objects or situations.[1]

Phobias can be divided into specific phobias, social phobia, and agoraphobia.[1][3] Types of specific phobias include to certain animals, natural environment situations, blood or injury, and specific situations.[1] The most common are fear of spiders, fear of snakes, and fear of heights.[4] Occasionally they are triggered by a negative experience with the object or situation. Social phobia is when the situation is feared as the person is worried about others judging them. Agoraphobia is when fear of a situation occurs because it is felt that escape would not be possible.[1]

Specific phobias should be treated with exposure therapy where the person is introduced to the situation or object in question until the fear resolves. Medications are not useful in this type of phobia.[3] Social phobia and agoraphobia are often treated with some combination of counselling and medication.[5][6] Medications used include antidepressants, benzodiazepines, or beta-blockers.[5]

Specific phobias affect about 6-8% of people in the Western world and 2-4% of people in Asian, Africa, and Latin America in a given year.[1] Social phobia affects about 7% of people in the United States and 0.5-2.5% of people in the rest of the world. Agoraphobia affects about 1.7% of people.[2] Women are affected about twice as often as men. Typically onset is around the age of 10 to 17. Rates become lower as people get older.[1][2] People with phobias are at a higher risk of suicide.[1]

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**Variants**

**More Phobia**

A fear of spiders is one of the more common phobias

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Psychiatry |
| **ICD-10** | F40.9 |
| **ICD-9-CM** | 300.20 |
| **OMIM** | 608251 |
| **MedlinePlus** | 000956 |
| **eMedicine** | article/288016 |
| **MeSH** | D010698 |

[edit on Wikidata]


Play media

Video explanation

# Classification [edit]

Most phobias are classified into three categories and, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V), such phobias are considered to be sub-types of anxiety disorder. The categories are:

1. Specific phobias: Fear of particular objects or social situations that immediately results in anxiety and can sometimes lead to panic attacks. Specific phobia may be further subdivided into five categories: animal type, natural environment type, situational type, blood-injection-injury type, and other.[7]
2. Agoraphobia: a generalized fear of leaving home or a small familiar 'safe' area, and of possible panic attacks that might follow. It may also be caused by various specific phobias such as fear of open spaces, social embarrassment (social agoraphobia), fear of contamination (fear of germs, possibly complicated by obsessive-compulsive disorder) or PTSD (post traumatic stress disorder) related to a trauma that occurred out of doors.
3. Social phobia, also known as social anxiety disorder, is when the situation is feared as the person is worried about others judging them.[1]

Phobias vary in severity among individuals. Some individuals can simply avoid the subject of their fear and suffer relatively mild anxiety over that fear. Others suffer full-fledged panic attacks with all the associated disabling symptoms. Most individuals understand that they are suffering from an irrational fear, but are powerless to override their panic reaction. These individuals often report dizziness, loss of bladder or bowel control, tachypnea, feelings of pain, and shortness of breath.[8]

## Specific phobias [edit]

A specific phobia is a marked and persistent fear of an object or situation which brings about an excessive or unreasonable fear when in the presence of, or anticipating, a specific object; the specific phobias may also include concerns with losing control, panicking, and fainting which is the direct result of an encounter with the phobia.[9] Specific phobias are defined in relation to objects or situations whereas social phobias emphasize social fear and the evaluations that might accompany them.

The DSM breaks specific phobias into five subtypes: animal, natural environment, blood-injection-injury, situational, and other.[10] In children, phobias involving animals, natural environment (darkness), and blood-injection-injury usually develop between the ages of 7 and 9, and these are reflective of normal

development. Additionally, specific phobias are most prevalent in children between ages 10 and 13.[11]

## Social phobia [edit]

*See also: Social anxiety disorder*

Unlike specific phobias, social phobias include fear of public situations and scrutiny which leads to embarrassment or humiliation in the diagnostic criteria.

# Causes [edit]

## Environmental [edit]

Rachman proposed three pathways to acquiring fear conditioning: classical conditioning, vicarious acquisition and informational/instructional acquisition:[12]

Much of the progress in understanding the acquisition of fear responses in phobias can be attributed to classical conditioning (Pavlovian model).[13] When an aversive stimulus and a neutral one are paired together, for instance when an electric shock is given in a specific room, the subject can start to fear not only the shock but the room as well. In behavioral terms, this is described as a conditioned stimulus (CS) *(the room)* that is paired with an aversive unconditioned stimulus (UCS) *(the shock)*, which leads to a conditioned response (CR) *(fear for the room)* (CS+UCS=CR).[13] For instance, in case of the fear of heights (acrophobia), the CS is heights such as a balcony on the top floors of a high rise building. The UCS originates from an aversive or traumatizing event in the person's life, such as almost falling down from a great height. The original fear of almost falling down is associated with being on a high place, leading to a fear of heights. In other words, the CS *(heights)* associated with the aversive UCS *(almost falling down)* leads to the CR *(fear)*. This direct conditioning model, though very influential in the theory of fear acquisition, is not the only way to acquire a phobia.

Vicarious fear acquisition is learning to fear something, not by a subject's own experience of fear, but by watching others reacting fearfully (observational learning). For instance, when a child sees a parent reacting fearfully to an animal, the child can become afraid of the animal as well.[14] Through observational learning, humans are able to learn to fear potentially dangerous objects;a reaction which also been observed in non-human primates.[15] In a study focusing on non-human primates, results showed that the primates learned to fear snakes at a fast rate after observing parents' fearful reactions.[15] An increase of fearful behaviors was observed as the non-human primates continued to observe their parents' fearful reaction.[15] Even though observational learning has been proven to be effective in creating reactions of fear and phobias, it has also been shown that by physically experiencing an event, chances increase of fearful and phobic behaviors.[15] In some cases physically experiencing an event, may increase the fear and phobia more so than observing a fearful reaction of another human or non-human primate.

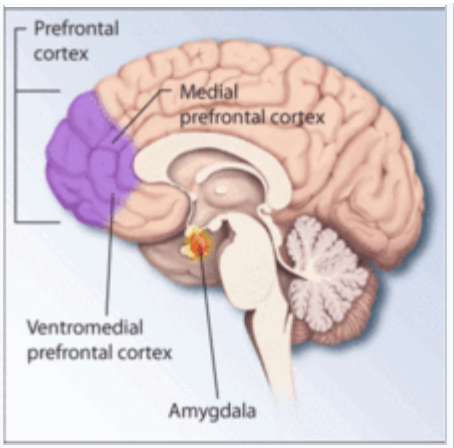
Informational/instructional fear acquisition is learning to fear something by getting information. For instance, fearing electrical wire after having heard that touching it will result in an electric shock.[16]

A conditioned fear response to an object or situation is not always a phobia. To meet the criteria for a phobia there must also be symptoms of impairment and avoidance. Impairment is defined as being unable to complete routine tasks whether occupational, academic or social. In acrophobia an impairment of occupation could result from not taking a job solely because of its location at the top floor of a building, or socially not participating in a social event at a theme park. The avoidance aspect is defined as behavior that results in the omission of an aversive event that would otherwise occur with the goal of the preventing anxiety.[17]

# Mechanism [edit]

Beneath the lateral fissure in the cerebral cortex, the insula, or insular

cortex, of the brain has been identified as part of the limbic system, along with cingulated gyrus, hippocampus, corpus callosum, and other nearby cortices. This system has been found to play a role in emotion processing[19] and the insula, in particular, may contribute through its role in maintaining autonomic functions.[20] Studies by Critchley et al. indicate the insula as being involved in the experience of emotion by detecting and interpreting threatening stimuli.[21] Similar studies involved in monitoring the activity of the insula show a correlation between increased insular activation and anxiety.[19]



Regions of the brain associated with phobias[18]

In the frontal lobes, other cortices involved with phobia and fear are the anterior cingulate cortex and the medial prefrontal cortex. In the processing of emotional stimuli, studies on phobic reactions to facial expressions have indicated these areas to be involved in processing and responding to negative stimuli.[22] The ventromedial prefrontal cortex has been said to influence the amygdala by monitoring its reaction to emotional stimuli or even fearful memories.[19] Most specifically, the medial prefrontal cortex is active during extinction of fear and is responsible for long term extinction. Stimulation of this area decreases conditioned fear responses and so its role may be in inhibiting the amygdala and its reaction to fearful stimuli.[23]

The hippocampus is a horseshoe shaped structure that plays an important part in the brain's limbic system because of its role in forming memories and connecting them with emotions and the senses. When dealing with fear, the hippocampus receives impulses from the amygdala that allows it to connect the fear with a certain sense, such as a smell or sound.

## Amygdala [edit]

The amygdala is an almond shaped mass of nuclei that is located deep in the brain's medial temporal lobe. It processes the events associated with fear and is being linked to social phobia and other anxiety disorders. The amygdala's ability to respond to fearful stimuli occurs through the process of fear conditioning. Similar to classical conditioning, the amygdala learns to associate a conditioned stimulus with a negative or avoidant stimulus, creating a conditioned fear response that is often seen in phobic individuals. In this way the amygdala is responsible for not only recognizing certain stimuli or cues as dangerous, but plays a role in the storage of threatening stimuli to memory. The basolateral nuclei (or basolateral amygdala) and the hippocampus interact with the amygdala in the storage of memory, which suggests why memories are often remembered more vividly if they have emotional significance.[24]

In addition to memory, the amygdala also triggers the secretion of hormones that affect fear and aggression. When the fear or aggression response is initiated, the amygdala releases hormones into the body to put the human body into an "alert" state, which prepares the individual to move, run, fight, etc.[25] This defensive "alert" state and response is generally referred to in psychology as the fight-or-flight response.[*citation needed*]

Inside the brain, however, this stress response can be observed in the hypothalamic-pituitary-adrenal axis (HPA).This circuit incorporates the process of receiving stimuli, interpreting it, and releasing certain hormones into the blood stream. The parvocellular neurosecretary neurons of the hypothalamus release corticotropin-releasing hormone(CRH) which is sent to the anterior pituitary. Here the pituitary releases adrenocorticotropic hormone (ACTH) which ultimately stimulates the release of cortisol. In relation to anxiety, the amygdala is responsible for activating this circuit, while the hippocampus is responsible for suppressing it. Glucocorticoid receptors in the hippocampus monitor the amount of cortisol in the system and through negative feedback can tell the hypothalamus to stop releasing CRH.[20]

Studies on mice engineered to have high concentrations of CRH showed higher levels of anxiety, while those engineered to have no or low amounts of CRH receptors were less anxious. In phobic patients, therefore, high amounts of cortisol may be present, or alternatively, there may be low levels of glucocorticoid receptors or even serotonin (5-HT).[20]

### Disruption by damage [edit]

For the areas in the brain involved in emotion—most specifically fear— the processing and response to emotional stimuli can be significantly altered when one of these regions becomes lesioned or damaged. Damage to the cortical areas involved in the limbic system such as the cingulate cortex or frontal lobes have resulted in extreme changes in emotion.[20] Other types of damage include Klüver–Bucy syndrome and Urbach–Wiethe disease. In Klüver–Bucy syndrome, a temporal lobectomy, or removal of the temporal lobes results in changes involving fear and aggression. Specifically, the removal of these lobes results in decreased fear, confirming its role in fear recognition and response. Bilateral damage to the medial temporal lobes, which is known as Urbach–Wiethe disease exhibits similar symptoms of decreased fear and aggression, but also an inability to recognize emotional expressions, especially angry or fearful faces.[20]

The amygdala's role in learned fear includes interactions with other brain regions in the neural circuit of fear. While lesions in the amygdala can inhibit its ability to recognize fearful stimuli, other areas such as the ventromedial prefrontal cortex and the basolateral nuclei of the amygdala can affect the region's ability to not only become conditioned to fearful stimuli, but to eventually extinguish them. The basolateral nuclei, through receiving stimulus info, undergo synaptic changes which allow the amygdala to develop a conditioned response to fearful stimuli. Lesions in this area, therefore, have been shown to disrupt the acquisition of learned responses to fear.[20] Likewise, lesions in the ventromedial prefrontal cortex (the area responsible for monitoring the amygdala) have been shown to not only slow down the speed of extinguishing a learned fear response, but also how effective or strong the extinction is. This suggests there is a pathway or circuit among the amygdala and nearby cortical areas that process emotional stimuli and influence emotional expression, all of which can be disrupted when an area becomes damaged.[19]

## Diagnosis [edit]

The terms *distress* and *impairment* as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV-TR) should also take into account the context of the person's environment if attempting a diagnosis. The DSM-IV-TR states that if a phobic stimulus, whether it be an object or a social situation, is absent entirely in an environment — a diagnosis cannot be made. An example of this situation would be an individual who has a fear of mice but lives in an area devoid of mice. Even though the concept of mice causes marked distress and impairment within the individual, because the individual does not encounter mice in the environment no actual distress or impairment is ever experienced. Proximity and the degree to which escape from the phobic stimulus is impossible should also be considered. As the person approaches a phobic stimulus, anxiety levels increase (e.g. as one gets closer to a snake, fear increases in ophidiophobia), and the degree to which escape of the phobic stimulus is limited has the effect of varying the intensity of fear in instances such as riding an elevator (e.g. anxiety increases at the midway point between floors and decreases when the floor is reached and the doors open).[26]

## Treatments [edit]

There are various methods used to treat phobias. These methods include: systematic desensitization, progressive relaxation, virtual reality, modeling, medications, and hypnotherapy.

### Therapy [edit]

Cognitive behavioral therapy (CBT) can be beneficial. Cognitive behavioral therapy allows the patient to challenge dysfunctional thoughts or beliefs by being mindful of their own feelings with the aim that the patient will realize their fear is irrational. CBT may be conducted in a group setting. Gradual desensitisation treatment and CBT are often successful, provided the patient is willing to endure some discomfort.[27][28] In one clinical trial, 90% of patients were observed to no longer have a phobic reaction after successful CBT treatment.[28][29][30][31]

CBT is also an effective treatment for phobias in children and adolescents, and it has been adapted to be

appropriate for use with this age. One example of a CBT program targeted towards children is the Coping Cat. This treatment program can be used with children between the ages of 7 and 13 to treat social phobia. This program works to decrease negative thinking, increase problem solving, and to provide a functional coping outlook in the child.[32] Another CBT program was developed by Ann Marie Albano to treat social phobia in adolescents. This program has five stages: Psychoeducation, Skill Building, Problem Solving, Exposure, and Generalization and Maintenance. Psycho education focuses on identifying and understanding symptoms. Skill Building focuses on learning cognitive restructuring, social skills, and problem solving skills. Problem Solving focuses on identifying problems and using a proactive approach to solving them. Exposure involves exposing the adolescent to social situations in a hierarchical approach. Finally, Generalization and Maintenance involves practicing the skills learned.[33]

Eye movement desensitization and reprocessing (EMDR) has been demonstrated in peer-reviewed clinical trials to be effective in treating some phobias. Mainly used to treat post-traumatic stress disorder, EMDR has been demonstrated as effective in easing phobia symptoms following a specific trauma, such as a fear of dogs following a dog bite.[34]

Another method psychologists and psychiatrists use to treat patients with extreme phobias is prolonged exposure. Prolonged exposure is used in psychotherapy when the person with the phobia is exposed to the object of their fear over a long period of time. This technique is only tested[*clarification needed*] when a person has overcome avoidance of or escape from the phobic object or situation. People with slight distress from their phobias usually do not need prolonged exposure to their fear.[35]

## Systematic desensitization [edit]

A method used in the treatment of a phobia is systematic desensitization, a process in which the patients seeking help slowly become accustomed to their phobia, and ultimately overcome it. Traditional systematic desensitization involves a person being exposed to the object they are afraid of over time, so that the fear and discomfort do not become overwhelming. This controlled exposure to the anxiety provoking stimulus is key to the effectiveness of exposure therapy in the treatment of specific phobia's. One form of systematic desensitization involves, humor. It has been shown that humor is an excellent alternative to the traditional systematic desensitization, when it does not efficiently rid someone of a phobia.[36] Humor systematic desensitization involves a series of treatment activities that consist of activities that elicit humor with the feared object.[36] Previously learned progressive muscle relaxation procedures can be used as the activities become more difficult in a person's own hierarchy level. Progressive muscle relaxation helps patients relax their muscles before and during exposures to the phobic object.

Participant modeling has been proven to be effective for children and adolescents. Participant modeling consists of a therapist modeling how the patients should respond to their fears.[37] This encourages the patients to practice this behavior and reinforces their efforts. Similar to systematic desensitization, patients are gradually introduced to the phobic objects. The main difference between participant modeling and systematic desensitization, involves observations and modeling. Participant modeling encompasses a therapist modeling positive behavior(s), observing the positive behavior(s), and gradual exposure to the phobic object.[37]

Virtual reality therapy is a type of therapy that helps patients imagine scenes with the phobic object, like systematic desensitization therapy. Using virtual reality, virtual reality therapy generates scenes that may not have been possible in the physical world. There are several advantages that virtual reality therapy has over systematic desensitization therapy: patients have the ability to control the scenes produced, patients can endure more phobic scenes (i.e. they may not be able to experience/handle these harsh scenes in real life), it is more realistic than simply imagining a scene, it occurs in a private room, and is very efficient.[38]

## Medications [edit]

Medications can help regulate the apprehension and fear that comes from thinking about or being exposed to a particular fearful object or situation. Antidepressant medications such as SSRIs or MAOIs may be helpful in some cases of phobia. SSRIs (antidepressants) act with serotonin, a neurotransmitter in the brain. Since serotonin impacts mood, patients may be prescribed an antidepressant. Another type of medication

used for treating patients with phobias are sedatives. Benzodiazepines are sedatives, which can help patients relax by reducing the amount of anxiety they feel.[39] Benzodiazepines may be useful in acute treatment of severe symptoms, but the risk-benefit ratio is against their long-term use in phobic disorders.[40] Though once believed to be highly addictive, these prescriptions have been recently shown as addictive if used with negative behaviors (i.e. alcohol abuse) .[39] Despite this recent positive finding, benzodiazepines should be used with caution. Beta blockers are another medication that can be used as a treatment for phobias. Beta blockers stop the stimulating effects of adrenaline in a person's body. These effects include: sweating, increased heart rate, elevated blood pressure, tremors, and the feeling of a pounding heart.[39] By taking beta blockers before a phobic event, these symptoms are decreased, causing the event to be less frightening.

### Hypnotherapy [edit]

Hypnotherapy can be used alone and in conjunction with systematic desensitization to treatment phobias.[41] Hypnotherapy can help people with phobias, resolve their issue, by uncovering the underlying cause of the phobia. The cause of phobias may be from a past event that the patient does not remember. When a traumatic event has occurred and the person who experienced it does not remember the event, the term is called repression. Repression is a mechanism our mind uses to keep the memory of the trauma out of our conscious mind until we are ready to deal with it. Hypnotherapy may also eliminate the conditioned responses that occur during different situations: the phobic object is within eyesight of the patient, the patient is placed in a phobic situation, or the patient is attempting to complete a phobic task. Patients are first placed into a hypnotic trance (i.e. an extremely relaxed state).[42] The unconscious can be retrieved during the hypnotic trance. This state allows for patients to be open to suggestion, which helps bring about a desired change.[42] Addressing old memories consciously helps individuals understand the event and see the event in a way which is no longer threatening.

## Epidemiology [edit]

Phobias are a common form of anxiety disorders and distributions are heterogeneous by age and gender. An American study by the National Institute of Mental Health (NIMH) found that between 8.7 percent and 18.1 percent of Americans suffer from phobias,[43] making it the most common mental illness among women in all age groups and the second most common illness among men older than 25. Between 4 percent and 10 percent of all children experience specific phobias during their lives,[11] and social phobias occur in one percent to three percent of children and adolescents.[*citation needed*]

A Swedish study found that females have a higher incidence than males (26.5 percent for females and 12.4 percent for males).[44] Among adults, 21.2 percent of women and 10.9 percent of men have a single specific phobia, while multiple phobias occur in 5.4 percent of females and 1.5 percent of males.[44] Women are nearly four times as likely as men to have a fear of animals (12.1 percent in women and 3.3 percent in men) — a higher dimorphic than with all specific or generalized phobias or social phobias.[44] Social phobias are more common in girls than in boys,[45] while situational phobia occurs in 17.4 percent of women and 8.5 percent of men.[44]

## Society and culture [edit]

### Terminology [edit]

*Main article: List of phobias*

The word *phobia* comes from the Greek: φόβος (*phóbos*), meaning "aversion", "fear", or "morbid fear". In popular culture, it is common for specific phobias to be given a name based on a Greek word for the object of the fear, plus the suffix *-phobia*. Creating these terms is something of a word game. Few of these terms are found in medical literature.[46] In ancient Greek mythology Phobos was the twin brother of Deimos

(terror).

The word *phobia* may also refer to conditions other than true phobias. For example, the term *hydrophobia* is an old name for rabies, since an aversion to water is one of that disease's symptoms. A specific phobia to water is called aquaphobia instead. A hydrophobe is a chemical compound which repels water. Similarly, the term *photophobia* usually refers to a physical complaint (aversion to light due to inflamed eyes or excessively dilated pupils), rather than an irrational fear of light.

## Non medical use [edit]

A number of terms with the suffix -phobia are used non-clinically. Examples include:

- Chemophobia – Negative attitudes and mistrust towards chemistry and synthetic chemicals.
- Xenophobia – Fear or dislike of strangers or the unknown, sometimes used to describe nationalistic political beliefs and movements.
- Homophobia – Negative attitudes and feelings toward homosexuality or people who are identified or perceived as being lesbian, gay, bisexual or transgender (LGBT).

Such terms are not phobias. They are derogatory terms for negative attitudes towards certain categories of people or other things, used in an invalid analogy with the medical usage of the term. These terms were coined with the purpose of shedding a negative light on the people within these opposing groups, by suggesting that everyone within has an irrational fear towards the objects of the terms. Usually these kinds of "phobias" are described as fear, dislike, disapproval, prejudice, hatred, discrimination, or hostility towards the object of the "phobia".[47]

# References [edit]


1. ^ *a b c d e f g h i j* American Psychiatric Association (2013), *Diagnostic and Statistical Manual of Mental Disorders (5th ed.)*, Arlington: American Psychiatric Publishing, pp. 190, 197–202, ISBN 0890425558
2. ^ *a b c* American Psychiatric Association (2013), *Diagnostic and Statistical Manual of Mental Disorders (5th ed.)*, Arlington: American Psychiatric Publishing, pp. 204, 218–219, ISBN 0890425558
3. ^ *a b* Hamm, AO (September 2009). "Specific phobias.". *The Psychiatric clinics of North America*. **32** (3): 577–91. doi:10.1016/j.psc.2009.05.008. PMID 19716991.
4. ^ "Specific Phobias". *USVA*. Retrieved 26 July 2016.
5. ^ *a b* "Anxiety Disorders". *NIMH*. March 2016. Retrieved 27 July 2016.
6. ^ Perugi, G; Frare, F; Toni, C (2007). "Diagnosis and treatment of agoraphobia with panic disorder.". *CNS Drugs*. **21** (9): 741–64. doi:10.2165/00023210-200721090-00004. PMID 17696574.
7. ^ LeBeau RT, Glenn D, Liao B, Wittchen HU, Beesdo-Baum K, Ollendick T, Craske MG (2010). "Specific phobia: a review of DSM-IV specific phobia and preliminary recommendations for DSM-V". *Depress Anxiety*. **27** (2): 148–67. doi:10.1002/da.20655. PMID 20099272.
8. ^ Tamparo, Carol; Lewis, Marcia (2011). *Diseases of the Human Body*. Philadelphia, PA: F.A. Davis Company. p. 153. ISBN 9780803625051.
9. ^ *Diagnostic and Statistical Manual of Mental Disorders, 4th ed*. Washington D.C.: American



062-9.
27. ^ Hall, Lynne L. *Fighting Phobias, the Things That Go Bump in the Mind*, FDA Consumer Magazine, Volume 31 No. 2, March 1997.
28. ^ *a b* Wolpe, Joseph (1958). *Psychotherapy by reciprocal inhibition.* (PDF). Stanford University Press.
29. ^ E. B., Foa; Blau, J. S.; Prout, M.; Latimer, P. (1977). "Is horror a necessary component of flooding (implosion)?". *Behaviour Research and Therapy*. **15**: 397–402. doi:10.1016/0005-7967(77)90043-2.
30. ^ Craske, Michelle; Martin M. Antony; David H. Barlow (2006). *Mastering your fears and phobias,*. US: Oxford University Press. ISBN 978-0-19-518917-9.
31. ^ Eysenck, Hans (1977). *You and Neurosis*.
32. ^ Kendall, P. C., Aschenbrand, S. G., & Hudson, J. L. (2003). Child-focused treatment of anxiety. In A. E. Kazdin, J. R. Weisz (Eds.) , Evidence-based psychotherapies for children and adolescents (pp. 81–100). New York, NY US: Guilford Press
33. ^ Albano, A. (2003). Treatment of social anxiety disorder. In M. A. Reinecke, F. M. Dattilio, A. Freeman (Eds.) , Cognitive therapy with children and adolescents: A casebook for clinical practice (2nd ed.) (pp. 128–161). New York, NY US: Guilford Press.
34. ^ De Jongh, A; Ten Broeke, E; Renssen, M R. (1999). "Treatment of specific phobias with Eye Movement Desensitization and Reprocessing (EMDR): protocol, empirical status, and conceptual issues". *Journal of anxiety disorders*. **13** (1–2): 69–85. doi:10.1016/S0887-6185(98)00040-1.

Psychiatric Association. 1994. p. 405. ISBN 0-89042-062-9.
10. ^ http://www.dsm5.org/proposedrevision/pages/proposedrevision.aspx?rid=162
11. ^ a b Bolton, D.; Eley, T. C.; O'Connor, T. G.; Perrin, S.; Rabe-Hesketh, S.; Rijsdijk, F.; Smith, P. (2006). "Prevalence and genetic and environmental influences on anxiety disorders in 6-year-old twins". *Psychological Medicine*. **36** (3): 335–344. doi:10.1017/S0033291705006537. PMID 16288680.
12. ^ Rachman, S.J. (1978). *Fear and Courage*. San Francisco: WH Freeman & Co.
13. ^ a b Myers; Davis, K. M. (2007). "Mechanisms of fear extinction". *Molecular Psychiatry*. **12** (2): 120–150. doi:10.1038/sj.mp.4001939. PMID 17160066. Retrieved April 25, 2011.
14. ^ "vicarious conditioning". BehaveNet. Retrieved 2013-06-21.
15. ^ a b c d Mineka, S.; Davidson, M.; Cook, M.; Keir, R. (1984). "Observational conditioning of snake fear in rhesus monkeys.". *Journal of Abnormal Psychology*. **93** (4): 355–372. doi:10.1037/0021-843x.93.4.355.
16. ^ Andreas Olsson; Elizabeth A. Phelps (2004). "Learned Fear of *Unseen* Faces After Pavlovian, Observational, and Instructed Fear" (PDF). *Psychological Science*. **15** (12): 822–828. doi:10.1111/j.0956-7976.2004.00762.x. PMID 15563327.
17. ^ Bolles, R. C. (1970). "Species-specific Defense Reactions and Avoidance Learning". *Psychological Review*. **77**: 32–38. doi:10.1037/h0028589.
18. ^ "NIMH · Post Traumatic Stress Disorder Research Fact Sheet". *National Institutes of Health*.
19. ^ a b c d Tillfors, Maria (15 March 2003). "Why do some individuals develop social phobia? A review with emphasis on the neurobiological influences". *Nord J. Psychiatry*. Taylor & Francis. **58** (4). doi:10.1080/0839480410005774.
20. ^ a b c d e f Mark F. Bear; Barry W. Connors; Michael A. Paradiso, eds. (2007). *Neuroscience: Exploring the Brain* (3rd ed.). Lippincott Williams & Wilkins. ISBN 9780781760034.
21. ^ Straube, T.; Mentzel, H.; Miltner, W. R. (2005). "Neuropsychobiology". *Common and District Brain Activation to Threat and Safety Signals in Social Phobia*. **52** (3): 163–8. doi:10.1159/000087987.
22. ^ Etkin, Amit; Tobias Egner; Raffael Kalisch (February 2011). "Emotional processing in the anterior cingulate and medial prefrontal cortex". *Trends Cogn Sci*. **15** (2): 85–93. doi:10.1016/j.tics.2010.11.004. PMC 3035157. PMID 21167765.
23. ^ Akirav, Irit; Mouna Maroun (15 May 2006). "The Role of the Medial Prefrontal Cortex-Amygdala Circuit in Stress Effects on the Extinction of Fear". *Neural* PMID 10225501.
35. ^ Watson, J.P.; Marks (2 January 1971). "Prolonged Exposure: A Rapid Treatment For Phobias". *British Medical Journal*. **1** (5739): 13–15. doi:10.1136/bmj.1.5739.13. JSTOR 25413031.
36. ^ a b Ventis, L.B; Higbee, G; Murdock, S.A. (2001). "Using humor in systematic desensitization to reduce fear". *Journal of General Psychology*. **128**: 241–253. doi:10.1080/00221300109598911.
37. ^ a b Love, S.R; Matson, J.L.; West, D (1990). "Mothers as effective therapists for autistic children's phobias". *Journal of Applied Behavior Analysis*. **23**: 379–385. doi:10.1901/jaba.1990.23-379.
38. ^ North, M.M.; North, S.M.; Coble, J.R. (1997). *Virtual reality therapy: An effective treatment for psychological disorders*. Amsterdam, Netherlands: IOS Press.
39. ^ a b c Marshall (1995). "Integrated treatment of social phobia". *Bulletin of the Menninger Clinic*. 59(2,Suppl A): A27-A37.
40. ^ Stein, Dan J. (16 February 2004). "Specific Phobia". *Clinical Manual of Anxiety Disorders* (1st ed.). USA: American Psychiatric Press Inc. p. 53. ISBN 978-1-58562-076-0. "Fears are common in children and adolescents. However, for some youth, these fears persist and develop into specific phobias. A specific phobia is an intense, enduring fear of an identifiable object or situation that may lead to panic symptoms, distress, and avoidance (e.g., fears of dogs, snakes, storms, heights, costumed characters, the dark, and similar objects or situations). Moreover, phobias can affect a youngster's quality of life by interfering with school, family, friends, and free-time. It is estimated that 5% to 10% of youth will develop a phobia before reaching the age of 16."
41. ^ Iglesias, Alex; Iglesias, Adam (2013). "I-95 Phobia Treated With Hypnotic Systematic Desensitization: A Case Report". *American Journal of Clinical Hypnosis*. **52** (6): 143–151. doi:10.1080/00029157.2013.785930. PMID 24665816.
42. ^ a b Vickers, A.; Zollman, C.; Payne, D.K. (1990). "Hypnosis and relaxation therapies". *Western Journal of Medicine*. **175** (4): 269–272. doi:10.1136/ewjm.175.4.269. PMC 1071579. PMID 11577062.
43. ^ Kessler et al., *Prevalence, Severity, and Comorbidity of 12-Month DSM-IV Disorders in the National Comorbidity Survey Replication*, June 2005, Archive of General Psychiatry, Volume 20
44. ^ a b c d Fredrikson, M; Annas, P; Fischer, H; Wik, G (1996). "Gender and age differences in the prevalence of specific fears and phobias". *Behaviour research and therapy*. **34** (1): 33–9. doi:10.1016/0005-7967(95)00048-3. PMID 8561762.
45. ^ Essau, C. A.; Conradt, J.; Petermann, F. (1999). "Frequency and comorbidity of social phobia and

*Plasticity*. **2007**: 1–11. doi:10.1155/2007/30873 .
24. ^ Paul J. Whalen; Elizabeth A. Phelps, eds. (2009). *The Human Amygdala*. New York: The Guilford Press.
25. ^ Winerman, Lea. "Figuring Out Phobia", American Psychology Association: Monitor on Psychology, August 2007.
26. ^ *Diagnostic and Statistical Manual of Mental Disorders, 4th ed*. Washington D.C.: American Psychiatric Association. 1994. p. 406. ISBN 0-89042-
social fears in adolescents". *Behaviour Research and Therapy*. **37** (9): 831–843. doi:10.1016/S0005-7967(98)00179-X. PMID 10458047.
46. ^ Abbasi, Jennifer (25 Jul 2011), "Is Trypophobia a real phobia?", *Popular Science*, retrieved 10 Apr 2016
47. ^ R.L.G. (15 July 2011). "Changes in meaning: Homophobe". *The Economist*. The Economist. Retrieved 18 August 2015.

## External links [edit]

- Social Anxiety at DMOZ
- Diagnostic criteria for specific phobia in the DSM-IV

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| v · t · e | **Mental and behavioral disorders (F 290–319)** | |
|---|---|---|
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| **Autism spectrum** | Autism · Asperger syndrome · Savant syndrome · PDD-NOS · High-functioning autism · | |
| **Other** | Delirium · Post-concussion syndrome · Organic brain syndrome · | |
| **Psychoactive substances, substance abuse, drug abuse and substance-related disorders** | | |
| Intoxication/Drug overdose · Physical dependence · Substance dependence · Rebound effect · Double rebound · Withdrawal · | | |
| **Schizophrenia, schizotypal and delusional** | | |
| **Psychosis** | Schizoaffective disorder · Schizophreniform disorder · Brief reactive psychosis · | |
| **Schizophrenia** | Disorganized schizophrenia · Paranoid schizophrenia · Simple-type schizophrenia · | |
| **Delusional disorders** | Delusional disorder · Folie à deux · | |
| **Mood (affective)** | | |
| Mania · Bipolar disorder · (Bipolar I · Bipolar II · Cyclothymia · Bipolar NOS) · Depression · (Major depressive disorder · Dysthymia · Seasonal affective disorder · Atypical depression · Melancholic depression) · | | |
| **Neurotic, stress-related and somatoform** | | |
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| | **Other** | Panic disorder · Panic attack · Generalized anxiety disorder · OCD · *stress* · (Acute stress reaction · PTSD) · |

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| **Adjustment disorder** | Adjustment disorder with depressed mood · |
| **Somatic symptom disorder** | Somatization disorder · Body dysmorphic disorder · Hypochondriasis · Nosophobia · Da Costa's syndrome · Psychalgia · Conversion disorder · (Ganser syndrome · Globus pharyngis) · Neurasthenia · Mass psychogenic illness · |
| **Dissociative disorder** | Dissociative identity disorder · Psychogenic amnesia · Fugue state · Depersonalization disorder · |
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| **Nonorganic sleep disorders** | (Nonorganic hypersomnia · Nonorganic insomnia) · Parasomnia · (REM sleep behavior disorder · Night terror · Nightmare) · |
| **Sexual dysfunction** | *sexual desire* · (Hypoactive sexual desire disorder · Hypersexuality) · *sexual arousal* · (Female sexual arousal disorder) · Erectile dysfunction · *orgasm* · (Anorgasmia · Delayed ejaculation · Premature ejaculation · Sexual anhedonia) · *pain* · (Vaginismus · Dyspareunia) · |
| **Postnatal** | Postpartum depression · Postpartum psychosis · |
| **Adult personality and behavior** | |
| *Gender dysphoria* | Sexual maturation disorder · Ego-dystonic sexual orientation · Sexual relationship disorder · Paraphilia · (Voyeurism · Fetishism) · |
| **Other** | Personality disorder · Impulse control disorder · (Kleptomania · Trichotillomania · Pyromania · Dermatillomania) · Body-focused repetitive behavior · Factitious disorder · (Münchausen syndrome) · |
| **Disorders typically diagnosed in childhood** | |
| **Intellectual disability** | X-linked intellectual disability · (Lujan–Fryns syndrome) · |
| **Psychological development (developmental disabilities)** | Specific · Pervasive · Autism spectrum · |
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| **Symptoms and uncategorized** | |
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Categories: Abnormal psychology | Phobias | Psychiatric diagnosis

# Posttraumatic stress disorder

From Wikipedia, the free encyclopedia

(Redirected from Post traumatic stress disorder)

*"PTSD" redirects here. For the album by Pharoahe Monch, see PTSD (album).*

**Posttraumatic stress disorder** (**PTSD**)[note 1] is a mental disorder that can develop after a person is exposed to a traumatic event, such as sexual assault, warfare, traffic collisions, or other threats on a person's life.[1] Symptoms may include disturbing thoughts, feelings, or dreams related to the events, mental or physical distress to trauma-related cues, attempts to avoid trauma-related cues, alterations in how a person thinks and feels, and increased arousal. These symptoms last for more than a month after the event. Young children are less likely to show distress but instead may express their memories through play.[1] Those with PTSD are at a higher risk of suicide.[2]

Most people who have experienced a traumatic event will not develop PTSD.[2] People who experience interpersonal trauma (for example rape or child abuse) are more likely to develop PTSD, as compared to people who experience non-assault based trauma such as accidents and natural disasters.[3] About half of people develop PTSD following rape.[2] Children are less likely than adults to develop PTSD after trauma, especially if they are under ten years of age.[4] Diagnosis is based on the presence of specific symptoms following a traumatic event.[2]

Prevention may be possible when therapy is targeted at those with early symptoms but is not effective when carried out among all people following trauma.[2] The main treatments for people with PTSD are counselling and medication.[5] A number of different types of therapy may be useful.[6] This may occur one-on-one or in a group.[5] Antidepressants of the selective serotonin reuptake inhibitor type are the first-line medications for PTSD and result in benefit in about half of people.[7] These benefits are less than those seen with therapy.[2] It is unclear if using medications and therapy together has greater benefit.[2][8] Other medications do not have enough evidence to support their use and in the case of benzodiazepines may worsen outcomes.[9][10]

In the United States about 3.5% of adults have PTSD in a given year, and 9% of people develop it at some point in their life.[1] In much of the rest of the world, rates during a given year are between 0.5% and 1%.[1] Higher rates may occur in regions of armed conflict.[2] It is more common in women than men.[5]

## Variants


Art therapy project created by a U.S. Marine with posttraumatic stress disorder

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Psychiatry |
| **ICD-10** | F43.1 |
| **ICD-9-CM** | 309.81 |
| **DiseasesDB** | 33846 |
| **MedlinePlus** | 000925 |
| **eMedicine** | med/1900 |
| **Patient UK** | Posttraumatic stress disorder |
| **MeSH** | D013313 |

[edit on Wikidata]

Symptoms of trauma-related mental disorders have been documented since at least the time of the ancient Greeks.[11] During the World Wars study increased and it was known under various terms including "shell shock" and "combat neurosis".[12] The term "posttraumatic stress disorder" came into use in the 1970s in large part due to the diagnoses of US military veterans of the Vietnam War.[13] It was officially recognized by the American Psychiatric Association in 1980 in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III).[14]





Play media

Video explanation

# Classification



PTSD was classified as an anxiety disorder in the DSM-IV, but has since been reclassified as a "trauma- and stressor-related disorder" in the DSM-5. The characteristic symptoms are not present before exposure to the traumatic event. In the typical case, the individual with PTSD persistently avoids trauma-related thoughts and emotions, and discussion of the traumatic event, and may even have amnesia of the event. However, the event is commonly relived by the individual through intrusive, recurrent recollections, flashbacks, and nightmares.[15] While it is common to have symptoms after any traumatic event, these must persist to a sufficient degree (i.e., causing dysfunction in life or clinical levels of distress) for longer than one month after the trauma to be classified as PTSD (clinically significant dysfunction or distress for less than one month after the trauma may be acute stress disorder).[1][16][17][18]

# Risk factors

Persons considered at risk include, for example, combat military personnel, victims of natural disasters, concentration camp survivors, and victims of violent crime. Individuals frequently experience "survivor's guilt" for remaining alive while others died. Causes of the symptoms of PTSD are the experiencing or witnessing of a stressor event involving death, serious injury or such threat to the self or others in a situation in which the individual felt intense fear, horror, or powerlessness.[20] Persons employed in occupations that expose them to violence (such as soldiers) or disasters (such as emergency service workers) are also at risk.[20] Other occupations that are at higher risk, including police officers, firefighters, ambulance personnel, health care professionals, train drivers, divers, journalists, and sailors, in addition to people who work at banks, post offices or in stores.[21] The size of the hippocampus is inversely related to post-traumatic stress disorder and treatment success; the smaller the higher risk of PTSD.[22]

*No quieren (They do not want to)* by Francisco Goya (1746–1828) depicts an elderly woman wielding a knife in defense of a girl being assaulted by a soldier.[19]

## Trauma

*See also: Psychological resilience*

PTSD is believed to be caused by the experience of a wide range of traumatic events and, in particular if the trauma is extreme, can occur in persons with no predisposing conditions.[23][24] Most people will experience at least one traumatizing event in their lifetime.[25] Men are more likely to experience a traumatic event, but women are more likely to experience the kind of high-impact traumatic event that can lead to PTSD, such as interpersonal violence and sexual assault.[4]

Posttraumatic stress reactions have not been studied as well in children and adolescents as adults.[4] The rate of PTSD may be lower in children than adults, but in the absence of therapy, symptoms may continue for decades.[4] One estimate suggests that the proportion of children and adolescents having PTSD in a non-wartorn population in a developed country may be 1% compared to 1.5% to 3% of adults, and much lower below the age of 10 years.[4] On average, 16% of children exposed to a traumatic event develop PTSD, varying according to type of exposure and gender.[26]

Predictor models have consistently found that childhood trauma, chronic adversity, and familial stressors increase risk for PTSD as well as risk for biological markers of risk for PTSD after a traumatic event in adulthood.[27][28][29] Experiencing bullying as a child or an adult has been correlated with the development of PTSD.[30] Peritraumatic dissociation in children is a predictive indicator of the development of PTSD later in life.[31] This effect of childhood trauma, which is not well-understood, may be a marker for both traumatic experiences and attachment problems.[32][33] Proximity to, duration of, and severity of the trauma make an impact, and interpersonal traumas cause more problems than impersonal ones.[34]

Quasi-experimental studies have demonstrated a relationship between intrusive thoughts and intentional control responses such that suppression increases the frequency of unwanted intrusive thoughts. These results suggest that suppression of intrusive thoughts may be important in the development and maintenance of PTSD.[35]

## Foster care

Adults who were in foster care as children have a higher rate of PTSD.[*medical citation needed*]

## Domestic violence

An individual that has been exposed to domestic violence is predisposed to the development of PTSD.

However, being exposed to a traumatic experience does not automatically indicate that an individual will develop PTSD.[16] There is a strong association between the development of PTSD in mothers that experienced domestic violence during the perinatal period of their pregnancy.[36]

## Military experience

Early intervention appears to be a critical preventive measure.[37] Studies have shown that soldiers prepared for the potential of a traumatic experience are more prepared to deal with the stress of a traumatic experience and therefore less likely to develop PTSD.[16]

A U.S. Long-Range Patrol team leader in Vietnam, 1968.

Among American troops in Vietnam a greater portion of women experienced high levels of war-zone stress compared to theater men—39.9 percent versus 23.5 percent. The key to this fact is that the vast majority (6,250 or 83.3%) of the women who served in the war zone were nurses who dealt almost daily with death. Black veterans had nearly 2.5 fold the risk of developing war zone-related PTSD as compared to white/other veterans. Hispanics had more than three times the risk. But the most revealing fact, theater veterans injured or wounded in combat had nearly four times the risk of developing PTSD compared to those not injured/wounded according to two key studies—the August 2014 *National Vietnam Veterans Longitudinal Study* (NVVLS). Paired with the late 1980s *National Vietnam Veterans Readjustment Study* (NVVRS).[38]

The long-term medical consequence of PTSD among male veterans who served in the Vietnam War was that they were almost twice as likely to die in the quarter of a century between the two key studies than those who did not have PTSD. PTSD can have numerous clinical and occupational effects. It was also found those with PTSD were more likely to die of chronic conditions such as cancer, nervous system disorders, and musculoskeletal problems. The etiology of this relationship is not certain other than lingering stress from combat such as nightmares, intrusive memories, and hyper-vigilance are aggravating factors contributing to psychological and physiological illnesses.[38]

The racial similarity between Hispanic and Vietnamese soldiers, and the discrimination Hispanic soldiers faced from their own military, made it difficult for Hispanic soldiers to dehumanize their enemy. Hispanic veterans who reported experiencing racial discrimination during their service displayed more symptoms of PTSD than Hispanic veterans who did not.[39]

PTSD is under-diagnosed in female veterans.[40] Sexual assault in the military is a leading cause for female soldiers developing PTSD; a female soldier who is sexually assaulted while serving in the military is nine times more likely to develop PTSD than a female soldier who is not assaulted. A soldier's assailant may be her colleague or superior officer, making it difficult for her to both report the crime and to avoid interacting with her assailant again.[41] Until the Tailhook scandal drew attention to the problem, the role that sexual assault in the military plays in female veterans developing PTSD went largely unstudied.[42]

Protective effects include social support, which also helps with recovery if PTSD develops.[43][44] For more aggravating factors to recovery once home, see social alienation among returning war veterans.

## Genetics

*Main article: Genetics of posttraumatic stress disorder*

There is evidence that susceptibility to PTSD is hereditary. Approximately 30% of the variance in PTSD is caused from genetics alone. For twin pairs exposed to combat in Vietnam, having a monozygotic (identical) twin with PTSD was associated with an increased risk of the co-twin's having PTSD compared to twins that were dizygotic (non-identical twins).[45] There is evidence that those with a genetically smaller

hippocampus are more likely to develop PTSD following a traumatic event. Research has also found that PTSD shares many genetic influences common to other psychiatric disorders. Panic and generalized anxiety disorders and PTSD share 60% of the same genetic variance. Alcohol, nicotine, and drug dependence share greater than 40% genetic similarities.[31]

Several biological indicators have been identified that are related to later PTSD development. Heightened startle responses and a smaller hippocampal volume have been identified as biomarkers for the risk of developing PTSD.[22] Additionally, one study found that soldiers whose leukocytes had greater numbers of glucocorticoid receptors were more prone to developing PTSD after experiencing trauma.[46]

### Drug and substance abuse

Drug abuse and alcohol abuse commonly co-occur with PTSD.[47] Recovery from posttraumatic stress disorder or other anxiety disorders may be hindered, or the condition worsened, by medication or substance use; resolving these problems can bring about improvement in an individual's mental health status and anxiety levels.[48][49]

## Pathophysiology

### Neuroendocrinology

PTSD symptoms may result when a traumatic event causes an over-reactive adrenaline response, which creates deep neurological patterns in the brain. These patterns can persist long after the event that triggered the fear, making an individual hyper-responsive to future fearful situations.[16][50] During traumatic experiences the high levels of stress hormones secreted suppress hypothalamic activity that may be a major factor toward the development of PTSD.[51]

PTSD causes biochemical changes in the brain and body, that differ from other psychiatric disorders such as major depression. Individuals diagnosed with PTSD respond more strongly to a dexamethasone suppression test than individuals diagnosed with clinical depression.[52][53]

Most people with PTSD show a low secretion of cortisol and high secretion of catecholamines in urine,[54] with a norepinephrine/cortisol ratio consequently higher than comparable non-diagnosed individuals.[55] This is in contrast to the normative fight-or-flight response, in which both catecholamine and cortisol levels are elevated after exposure to a stressor.[56]

Brain catecholamine levels are high,[57] and corticotropin-releasing factor (CRF) concentrations are high.[58][59] Together, these findings suggest abnormality in the hypothalamic-pituitary-adrenal (HPA) axis.

The maintenance of fear has been shown to include the HPA axis, the locus coeruleus-noradrenergic systems, and the connections between the limbic system and frontal cortex. The HPA axis that coordinates the hormonal response to stress,[60] which activates the LC-noradrenergic system, is implicated in the over-consolidation of memories that occurs in the aftermath of trauma.[61] This over-consolidation increases the likelihood of one's developing PTSD. The amygdala is responsible for threat detection and the conditioned and unconditioned fear responses that are carried out as a response to a threat.[31]

The HPA axis is responsible for coordinating the hormonal response to stress.[31] Given the strong cortisol suppression to dexamethasone in PTSD, HPA axis abnormalities are likely predicated on strong negative feedback inhibition of cortisol, itself likely due to an increased sensitivity of glucocorticoid receptors.[62] PTSD has been hypothesized to be a maladaptive learning pathway to fear response through a hypersensitive, hyperreactive, and hyperresponsive HPA axis.[63]

Low cortisol levels may predispose individuals to PTSD: Following war trauma, Swedish soldiers serving in Bosnia and Herzegovina with low pre-service salivary cortisol levels had a higher risk of reacting with PTSD symptoms, following war trauma, than soldiers with normal pre-service levels.[64] Because cortisol is normally important in restoring homeostasis after the stress response, it is thought that trauma survivors

with low cortisol experience a poorly contained—that is, longer and more distressing—response, setting the stage for PTSD.

It is thought that the locus coeruleus-noradrenergic system mediates the over-consolidation of fear memory. High levels of cortisol reduce noradrenergic activity, and because people with PTSD tend to have reduced levels of cortisol, it has been proposed that individuals with PTSD cannot regulate the increased noradrenergic response to traumatic stress.[65] Intrusive memories and conditioned fear responses are thought to be a result of the response to associated triggers. Neuropeptide Y has been reported to reduce the release of norepinephrine and has been demonstrated to have anxiolytic properties in animal models. Studies have shown people with PTSD demonstrate reduced levels of NPY, possibly indicating their increased anxiety levels.[31]

Other studies indicate that people that suffer from PTSD have chronically low levels of serotonin, which contributes to the commonly associated behavioral symptoms such as anxiety, ruminations, irritability, aggression, suicidality, and impulsivity.[66] Serotonin also contributes to the stabilization of glucocorticoid production.

Dopamine levels in a person with PTSD can help contribute to the symptoms associated. Low levels of dopamine can contribute to anhedonia, apathy, impaired attention, and motor deficits. Increased levels of dopamine can cause psychosis, agitation, and restlessness.[66]

Hyperresponsiveness in the norepinephrine system can be caused by continued exposure to high stress. Overactivation of norepinephrine receptors in the prefrontal cortex can be connected to the flashbacks and nightmares frequently experienced by those with PTSD. A decrease in other norepinephrine functions (awareness of the current environment) prevents the memory mechanisms in the brain from processing that the experience, and emotions the person is experiencing during a flashback are not associated with the current environment.[66]

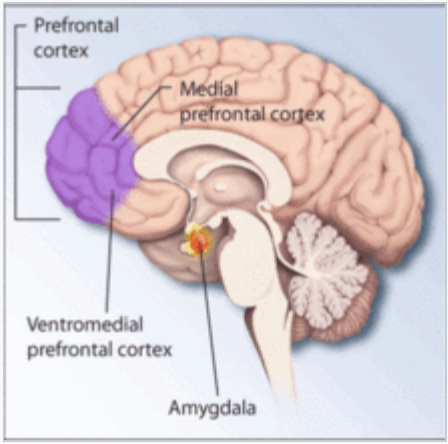
There is considerable controversy within the medical community regarding the neurobiology of PTSD. A 2012 review showed no clear relationship between cortisol levels and PTSD. The majority of reports indicate people with PTSD have elevated levels of corticotropin-releasing hormone, lower basal cortisol levels, and enhanced negative feedback suppression of the HPA axis by dexamethasone.[31][67]

## Neuroanatomy

The three brain areas with changed function are the prefrontal cortex, amygdala, and hippocampus. Much of this research stems from PTSD victims from the Vietnam War.

For example, a prospective study using the Vietnam Head Injury Study showed that damage to the prefrontal cortex may be protective against later development of PTSD.[69] PTSD patients have decreased brain activity in the dorsal and rostral anterior cingulate cortices and the ventromedial prefrontal cortex, areas linked to the experience and regulation of emotion.[70]

The amygdala is strongly involved in forming emotional memories, especially fear-related memories. Neuroimaging studies in humans have revealed aspects of PTSD morphology and function.[71] During high stress, the hippocampus, which is associated with placing memories in the correct context of space and time and memory recall, is suppressed. According to one theory this suppression may be the cause of the flashbacks that can affect people with PTSD. When someone with PTSD undergoes stimuli similar to the traumatic event, the body perceives the event as occurring again because the memory was never properly recorded in the person's memory.[31][72][*unreliable medical source?*]



Regions of the brain associated with stress and posttraumatic stress disorder[68]

The amygdalocentric model of PTSD proposes that the amygdala is very much aroused and insufficiently controlled by the medial prefrontal cortex and the hippocampus, in particular during extinction.[73] This is

consistent with an interpretation of PTSD as a syndrome of deficient extinction ability.[73][74]

A 2011 study found that fear extinction-induced IGF2/IGFBP7 signalling promotes the survival of hippocampal neurons in 2-3 week old newborn mice. This suggests that enhancing IGF2 signalling and adult neurogenesis might be suitable to treat diseases linked to excessive fear memory such as PTSD.[75] Further animal and clinical research into the amygdala and fear conditioning may suggest additional treatments for the condition.

The basolateral nucleus (BLA) of the amygdala is responsible for the comparison and development of associations between unconditioned and conditioned responses to stimuli, which results in the fear conditioning present in PTSD. The BLA activates the central nucleus (CeA) of the amygdala, which elaborates the fear response, (including behavioral response to threat and elevated startle response). Descending inhibitory inputs from the medial prefrontal cortex (mPFC) regulate the transmission from the BLA to the CeA, which is hypothesized to play a role in the extinction of conditioned fear responses.[31]

In a 2007 study Vietnam War combat veterans with PTSD showed a 20% reduction in the volume of their hippocampus compared with veterans having suffered no such symptoms.[76] This finding was not replicated in chronic PTSD patients traumatized at an air show plane crash in 1988 (Ramstein, Germany).[77] A 2016 study strengthened theory that a smaller hippocampus increases the risk for post-traumatic stress disorder, and a larger hippocampus increases the likelihood efficacious treatment.[78]

# Diagnosis

PTSD can be particularly difficult to diagnose, because numerous factors can lead to over-reporting (e.g., disability) and under-reporting (e.g., avoidance) symptoms, dysfunction and distress.

## Screening and assessment

A number of screening instruments are used for screening adults for PTSD, as well as youth, such as the UCLA PTSD Index for DSM-IV.[79] The Primary Care PTSD Screen,[80][81] PTSD Checklist,[82][83][84] GAD-7,[85] Child PTSD Symptom Scale,[86] and M3 Checklist[87] are other screening tools.[25][88]

The U.S. Department of Veterans Affairs' Evidence-based Synthesis Program published an exhaustive systematic review of studies about PTSD screening instruments, fully reviewing 15 of the highest quality studies. There were a total of 12 PTSD screening tools reviewed, 7 that screen for only PTSD and 5 that "screen for the psychiatric disorders commonly encountered and treated by primary care providers". The authors divided these into brief, intermediate, and multiple condition screens.[25] The brief screens (SIPS, ADD, and PDI-4A) were least useful due to poor discrimination. Of the intermediate screens (Breslau, M3,[87] PC-PTSD,[81] and SPAN), their performances were "comparable." The most used screen, the PCL (or PTSD Checklist),[84] was the longest one (17 items) and had the most variability in cut points across various clinical populations. While the 5 multidimensional screens—those that screened for multiple psychiatric conditions—performed less well than the PTSD-only screens, "this might be preferable, as 'false positives' on [multidimensional] screens may reflect psychiatric symptomatology requiring further evaluation." Of these multidimensional screens, "the M-3 performed better than the GAD-7 at identifying probable cases of PTSD." The M3 uses a "two-staged screening approach" that also assesses for depression, bipolar, and anxiety disorders. The study concludes with recommendations for future research.[25]

The American Academy of Child and Adolescent Psychiatry has a practice guideline for the assessment and treatment of PTSD in children and adolescents.[89] The American Psychiatric Association has a more general practice guideline for the assessment and management of acute stress disorder and PTSD.[90]

A revised form of the *Impact of Events* scale (IES-R) gives a total score ranging from 0 to 88.[91] A score of 24 or more confers a clinical concern for PTSD, and a score of 33 is suggested to represent the best cutoff for a probable diagnosis of PTSD.[92]

## Diagnostic and statistical manual

Since the introduction of DSM-IV, the number of possible events that might be used to diagnose PTSD has increased; one study suggests that the increase is around 50%.[93] Various scales to measure the severity and frequency of PTSD symptoms exist.[94][95] Standardized screening tools such as Trauma Screening Questionnaire[96] and PTSD Symptom Scale[97] can be used to detect possible symptoms of posttraumatic stress disorder and suggest the need for a formal diagnostic assessment.

In the May 2013 DSM-5, PTSD was classified as a trauma- and stress-related disorder.[1]

## International classification of diseases

The diagnostic criteria for PTSD, stipulated in the International Statistical Classification of Diseases and Related Health Problems 10 (ICD-10), may be summarized as:[98]

- Exposure to a stressful event or situation (either short or long lasting) of exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone.
- Persistent remembering, or "reliving" the stressor by intrusive flashbacks, vivid memories, recurring dreams, or by experiencing distress when exposed to circumstances resembling or associated with the stressor.
- Actual or preferred avoidance of circumstances resembling or associated with the stressor (not present before exposure to the stressor).
- Either (1) or (2):
  1. Inability to recall, either partially or completely, some important aspects of the period of exposure to the stressor
  2. Persistent symptoms of increased psychological sensitivity and arousal (not present before exposure to the stressor) shown by any two of the following:
- difficulty in falling or staying asleep
- irritability or outbursts of anger
- difficulty in concentrating
- hyper-vigilance
- exaggerated startle response.

The International Statistical Classification of Diseases and Related Health Problems 10 diagnostic guidelines state:[98] In general, this disorder should not be diagnosed unless there is evidence that it arose within 6 months of a traumatic event of exceptional severity. A "probable" diagnosis might still be possible if the delay between the event and the onset was longer than 6 months, provided that the clinical manifestations are typical and no alternative identification of the disorder (e.g., as an anxiety or obsessive-compulsive disorder or depressive episode) is plausible. In addition to evidence of trauma, there must be a repetitive, intrusive recollection or re-enactment of the event in memories, daytime imagery, or dreams. Conspicuous emotional detachment, numbing of feeling, and avoidance of stimuli that might arouse recollection of the trauma are often present but are not essential for the diagnosis. The autonomic disturbances, mood disorder, and behavioural abnormalities all contribute to the diagnosis but are not of prime importance. The late chronic sequelae of devastating stress, i.e. those manifest decades after the stressful experience, should be classified under F62.0.

## Differential diagnosis

A diagnosis of PTSD requires that the person has been exposed to an extreme stressor such as one that is life-threatening. Any stressor can result in a diagnosis of adjustment disorder and it is an appropriate diagnosis for a stressor and a symptom pattern that does not meet the criteria for PTSD, for example a partner being fired, or a spouse leaving. If any of the symptom pattern is present before the stressor, another diagnosis is required, such as brief psychotic disorder or major depressive disorder. Other differential diagnoses are schizophrenia or other disorders with psychotic features such as Psychotic disorders due to a general medical condition. Drug-induced psychotic disorders can be considered if substance abuse is involved.[15]

The symptom pattern for acute stress disorder must occur and be resolved within four weeks of the trauma. If it lasts longer, and the symptom pattern fits that characteristic of PTSD, the diagnosis may be changed.[15]

Obsessive compulsive disorder may be diagnosed for intrusive thoughts that are recurring but not related to a specific traumatic event.[15]

# Prevention

*See also: Traumatic memories*

Modest benefits have been seen from early access to cognitive behavioral therapy.[99] Critical incident stress management has been suggested as a means of preventing PTSD, but subsequent studies suggest the likelihood of its producing negative outcomes.[100][101] A review "...did not find any evidence to support the use of an intervention offered to everyone", and that "...multiple session interventions may result in worse outcome than no intervention for some individuals."[102] The World Health Organization recommends against the use of benzodiazepines and antidepressants in those having experienced trauma.[103] Some evidence supports the use of hydrocortisone for prevention in adults, however there is limited or no evidence supporting propranolol, escitalopram, temazepam, or gabapentin.[104]

## Psychological debriefing

Trauma-exposed individuals often receive treatment called *psychological debriefing* in an effort to prevent PTSD.[99] Several meta-analyses; however, find that psychological debriefing is unhelpful and is potentially harmful.[99][105][106] This is true for both single-session debriefing and multiple session interventions.[102] The American Psychological Association judges the status of psychological debriefing as *No Research Support/Treatment is Potentially Harmful*.[107]

Psychological debriefing was in the past, however, the most often used preventive measure, partly because of the relative ease with which this treatment can be given to individuals directly following an event. It consists of interviews that are meant to allow individuals to directly confront the event and share their feelings with the counselor and to help structure their memories of the event. This treatment has since been found to be potentially harmful.[99]

## Risk-targeted interventions

*For one such method, see trauma risk management.*

Risk-targeted interventions are those that attempt to mitigate specific formative information or events. It can target modeling normal behaviors, instruction on a task, or giving information on the event.[108][109]

# Management

*Further information: Treatments for combat-related PTSD*

Systematic reviews have found that combination therapy (psychological and pharmacotherapy) is no more effective than psychological therapy alone.[110]

An assistance dog trained to

## Psychotherapy

Many forms of psychotherapy have been found to be efficacious for trauma-related problems such as PTSD. Basic counseling practices common to many treatments for PTSD include education about the condition, and provision of safety and support.[16][97]

help veterans with PTSD

The psychotherapy programs with the strongest demonstrated efficacy include cognitive behavioral programs, variants of exposure therapy[*citation needed*], stress inoculation training (SIT), variants of cognitive therapy (CT), eye movement desensitization and reprocessing (EMDR),[111] mindfulness-based meditation[112] and many combinations of these procedures.[113] EMDR and trauma-focused cognitive behavioral therapy (TFCBT) were recommended as first-line treatments for trauma victims in a 2007 review; however, "the evidence base [for EMDR] was not as strong as that for TFCBT ... Furthermore, there was limited evidence that TFCBT and EMDR were superior to supportive/non-directive treatments, hence it is highly unlikely that their effectiveness is due to non-specific factors such as attention."[114] A meta-analytic comparison of EMDR and cognitive behavioral therapy found both protocols indistinguishable in terms of effectiveness in treating PTSD; however, "the contribution of the eye movement component in EMDR to treatment outcome" is unclear.[115]

Furthermore, the availability of school-based therapy is particularly important for children with PTSD. Children with PTSD are far more likely to pursue treatment at school (because of its proximity and ease) than at a free clinic.[116]

## Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) seeks to change the way a trauma victim feels and acts by changing the patterns of thinking or behavior, or both, responsible for negative emotions. CBT has been proven to be an effective treatment for PTSD and is currently considered the standard of care for PTSD by the United States Department of Defense.[117][118] In CBT, individuals learn to identify thoughts that make them feel afraid or upset and replace them with less distressing thoughts. The goal is to understand how certain thoughts about events cause PTSD-related stress.

Recent research on contextually based third-generation behavior therapies suggests that they may produce results comparable to some of the better validated therapies.[119] Many of these therapy methods have a significant element of exposure[120] and have demonstrated success in treating the primary problems of PTSD and co-occurring depressive symptoms.[121]

Exposure therapy is a type of cognitive behavioral therapy[122] that involves assisting trauma survivors to re-experience distressing trauma-related memories and reminders in order to facilitate habituation and successful emotional processing of the trauma memory. Most exposure therapy programs include both imaginal confrontation with the traumatic memories and real-life exposure to trauma reminders; this therapy modality is well supported by clinical evidence[*citation needed*]. The success of exposure-based therapies has raised the question of whether exposure is a necessary ingredient in the treatment of PTSD.[123] Some organizations[*which?*] have endorsed the need for exposure.[124][125] The US Department of Veterans Affairs has been actively training mental health treatment staff in prolonged exposure therapy[126] and Cognitive Processing Therapy[127] in an effort to better treat US veterans with PTSD.

## Eye movement desensitization and reprocessing

*Main article: Eye movement desensitization and reprocessing*

Eye movement desensitization and reprocessing (EMDR) is a form of psychotherapy developed and studied by Francine Shapiro.[128] She had noticed that, when she was thinking about disturbing memories herself, her eyes were moving rapidly. When she brought her eye movements under control while thinking, the thoughts were less distressing.[128]

In 2002, Shapiro and Maxfield published a theory of why this might work, called adaptive information processing.[129] This theory proposes that eye movement can be used to facilitate emotional processing of memories, changing the person's memory to attend to more adaptive information.[130] The therapist initiates voluntary rapid eye movements while the person focuses on memories, feelings or thoughts about a particular trauma.[4][131] The therapists uses hand movements to get the person to move their eyes backward and forward, but hand-tapping or tones can also be used.[4] EMDR closely resembles cognitive

behavior therapy as it combines exposure (re-visiting the traumatic event), working on cognitive processes and relaxation/self-monitoring.[4] However, exposure by way of being asked to think about the experience rather than talk about it has been highlighted as one of the more important distinguishing elements of EMDR.[132]

There have been multiple small controlled trials of four to eight weeks of EMDR in adults[133] as well as children and adolescents.[131] EMDR reduced PTSD symptoms enough in the short term that one in two adults no longer met the criteria for PTSD, but the number of people involved in these trials was small.[133] There was not enough evidence to know whether or not EMDR could eliminate PTSD.[133] There was some evidence that EMDR might prevent depression.[133] There were no studies comparing EMDR to other psychological treatments or to medication.[133] Adverse effects were largely unstudied.[133] The benefits were greater for women with a history of sexual assault compared with people who had experienced other types of traumatizing events (such as accidents, physical assaults and war). There is a small amount of evidence that EMDR may improve re-experiencing symptoms in children and adolescents, but EMDR has not been shown to improve other PTSD symptoms, anxiety, or depression.[131]

The eye movement component of the therapy may not be critical for benefit.[4][130] As there has been no major, high quality randomized trial of EMDR with eye movements versus EMDR without eye movements, the controversy over effectiveness is likely to continue.[132] Authors of a meta-analysis published in 2013 stated, "We found that people treated with eye movement therapy had greater improvement in their symptoms of post-traumatic stress disorder than people given therapy without eye movements….Secondly we found that that in laboratory studies the evidence concludes that thinking of upsetting memories and simultaneously doing a task that facilitates eye movements reduces the vividness and distress associated with the upsetting memories."[111]

## Interpersonal psychotherapy

Other approaches, in particular involving social supports,[43][44] may also be important. An open trial of interpersonal psychotherapy[134] reported high rates of remission from PTSD symptoms without using exposure.[135] A current, NIMH-funded trial in New York City is now (and into 2013) comparing interpersonal psychotherapy, prolonged exposure therapy, and relaxation therapy.[136][*full citation needed*][137][138]

## Medication

While many medications do not have enough evidence to support their use, three (fluoxetine, paroxetine, and venlafaxine) have been shown to have a small benefit over placebo.[10] This study concluded that "the drugs included were well tolerated overall." With many medications, residual PTSD symptoms following treatment is the rule rather than the exception.[139]

## Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) may have some benefit for PTSD symptoms.[10][140] Tricyclic antidepressants are equally effective but are less well tolerated.[141] Evidence provides support for a small or modest improvement with sertraline, fluoxetine, paroxetine, and venlafaxine.[10][142] Thus, these four medications are considered to be first-line medications for PTSD.[140][143]

## Benzodiazepines

Benzodiazepines are not recommended for the treatment of PTSD due to a lack of evidence of benefit and risk of worsening PTSD symptoms.[144] Some authors believe that the use of benzodiazepines is contraindicated for acute stress, as this group of drugs promotes dissociation and ulterior revivals.[145] Nevertheless, some use benzodiazepines with caution for short-term anxiety and insomnia.[146][147][148]

While benzodiazepines can alleviate acute anxiety, there is no consistent evidence that they can stop the development of PTSD and may actually increase the risk of developing PTSD 2-5 times.[9] Additionally, benzodiazepines may reduce the effectiveness of psychotherapeutic interventions, and there is some evidence that benzodiazepines may actually contribute to the development and chronification of PTSD. For those who already have PTSD, benzodiazepines may worsen and prolong the course of illness, by worsening psychotherapy outcomes, and causing or exacerbating aggression, depression (including suicidality), and substance use.[9] Drawbacks include the risk of developing a benzodiazepine dependence, tolerance (i.e., short-term benefits wearing off with time), and withdrawal syndrome; additionally, individuals with PTSD (even those without a history of alcohol or drug misuse) are at an increased risk of abusing benzodiazepines.[143][149] Due to a number of other treatments with greater efficacy for PTSD and less risks (e.g., prolonged exposure, cognitive processing therapy, eye movement desensitization and reprocessing, cognitive restructuring therapy, trauma-focused cognitive behavioral therapy, brief eclectic psychotherapy, narrative therapy, stress inoculation training, serotonergic antidepressants, adrenergic inhibitors, antipsychotics, and even anticonvulsants), benzodiazepines should be considered relatively contraindicated until all other treatment options are exhausted.[6][150] For those who argue that benzodiazepines should be used sooner in the most severe cases, the adverse risk of disinhibition (associated with suicidality, aggression and crimes) and clinical risks of delaying or inhibiting definitive efficacious treatments, make other alternative treatments preferable (e.g., inpatient, residential, partial hospitalization, intensive outpatient, dialectic behavior therapy; and other fast-acting sedating medications such as trazodone, mirtazapine, amitripytline, doxepin, prazosin, propranolol, guanfacine, clonidine, quetiapine, olanzapine, valproate, gabapentin).[7][150][151]

### Glucocorticoids

Glucocorticoids may be useful for short-term therapy to protect against neurodegeneration caused by the extended stress response that characterizes PTSD, but long-term use may actually promote neurodegeneration.[152]

### Cannabinoids

There is tentative evidence that medical cannabis may be effective at reducing PTSD symptoms, but, as of as of 2015, there is insufficient evidence to confirm its effectiveness for this condition.[153][154] Despite the uncertain evidence, use of cannabis or derived products is widespread among US veterans with PTSD.[155]

The cannabinoid nabilone is sometimes used off-label for nightmares in PTSD. Although some short-term benefit was shown, adverse effects are common and it has not been adequately studied to determine efficacy.[156] Additionally, there are other treatments with stronger efficacy and less risks (e.g., psychotherapy, serotonergic antidepressants, adrenergic inhibitors). The use of medical marijuana for PTSD is controversial, with only a handful of states permitting its use for that purpose.[157]

## Other

### Exercise, sport and physical activity

Physical activity can influence people's psychological wellbeing[158] and physical health.[159] The U.S. National Center for PTSD recommends moderate exercise as a way to distract from disturbing emotions, build self-esteem and increase feelings of being in control again. They recommend a discussion with a doctor before starting an exercise program.[160]

### Play therapy for children

Play is thought to help children link their inner thoughts with their outer world, connecting real experiences with abstract thought.[161] Repetitive play can also be one of the ways a child relives traumatic events, and that can be a symptom of traumatization in a child or young person.[162] Although it is commonly used, there have not been enough studies comparing outcomes in groups of children receiving and not receiving

play therapy, so the effects of play therapy are not yet understood.[4][161]

### Military programs

Many veterans of the wars in Iraq and Afghanistan have faced significant physical, emotional, and relational disruptions. In response, the United States Marine Corps has instituted programs to assist them in re-adjusting to civilian life, especially in their relationships with spouses and loved ones, to help them communicate better and understand what the other has gone through.[163] Walter Reed Army Institute of Research (WRAIR) developed the Battlemind program to assist service members avoid or ameliorate PTSD and related problems.

## Epidemiology

There is debate over the rates of PTSD found in populations, but, despite changes in diagnosis and the criteria used to define PTSD between 1997 and 2007, epidemiological rates have not changed significantly.[165]

The United Nations' World Health Organization publishes estimates of PTSD impact for each of its member states; the latest data available are for 2004. Considering only the 25 most populated countries ranked by overall age-standardized Disability-Adjusted Life Year (DALY) rate, the top half of the ranked list is dominated by Asian/Pacific countries, the US, and Egypt.[166] Ranking the countries by the male-only or female-only rates produces much the same result, but with less meaningfulness, as the score range in the single-sex rankings is much-reduced (4 for women, 3 for men, as compared with 14 for the overall score range), suggesting that the differences between female and male rates, within each country, is what drives the distinctions between the countries.[167][168]

Disability-adjusted life year rates for posttraumatic stress disorder per 100,000 inhabitants in 2004.[164]

| | |
|---|---|
| no data | 49.5-51 |
| < 43.5 | 51-52.5 |
| 43.5-45 | 52.5-54 |
| 45-46.5 | 54-55.5 |
| 46.5-48 | 55.5-57 |
| 48-49.5 | 57–58.5 |
| | > 58.5 |

**Age-standardized Disability-adjusted life year (DALY) rates for PTSD, per 100,000 inhabitants, in 25 most populous countries, ranked by overall rate (2004)**

| Region | Country | PTSD DALY rate, overall[166] | PTSD DALY rate, females[167] | PTSD DALY rate, males[168] |
|---|---|---|---|---|
| Asia / Pacific | Thailand | 59 | 86 | 30 |
| Asia / Pacific | Indonesia | 58 | 86 | 30 |
| Asia / Pacific | Philippines | 58 | 86 | 30 |
| Americas | USA | 58 | 86 | 30 |
| Asia / Pacific | Bangladesh | 57 | 85 | 29 |
| Africa | Egypt | 56 | 83 | 30 |
| Asia / Pacific | India | 56 | 85 | 29 |
| Asia / Pacific | Iran | 56 | 83 | 30 |

| | | | | |
|---|---|---|---|---|
| Asia / Pacific | Pakistan | 56 | 85 | 29 |
| Asia / Pacific | Japan | 55 | 80 | 31 |
| Asia / Pacific | Myanmar | 55 | 81 | 30 |
| Europe | Turkey | 55 | 81 | 30 |
| Asia / Pacific | Vietnam | 55 | 80 | 30 |
| Europe | France | 54 | 80 | 28 |
| Europe | Germany | 54 | 80 | 28 |
| Europe | Italy | 54 | 80 | 28 |
| Asia / Pacific | Russian Federation | 54 | 78 | 30 |
| Europe | United Kingdom | 54 | 80 | 28 |
| Africa | Nigeria | 53 | 76 | 29 |
| Africa | Dem. Republ. of Congo | 52 | 76 | 28 |
| Africa | Ethiopia | 52 | 76 | 28 |
| Africa | South Africa | 52 | 76 | 28 |
| Asia / Pacific | China | 51 | 76 | 28 |
| Americas | Mexico | 46 | 60 | 30 |
| Americas | Brazil | 45 | 60 | 30 |

## United States

The National Comorbidity Survey Replication has estimated that the lifetime prevalence of PTSD among adult Americans is 6.8%, with women (9.7%) more than twice as likely as men[66] (3.6%) to have PTSD at some point in their lives.[169] More than 60% of men and more than 60% of women experience at least one traumatic event in their life. The most frequently reported traumatic events by men are rape, combat, and childhood neglect or physical abuse. Women most frequently report instances of rape, sexual molestation, physical attack, being threatened with a weapon and childhood physical abuse.[66] 88% of men and 79% of women with lifetime PTSD have at least one comorbid psychiatric disorder. Major depressive disorder, 48% of men and 49% of women, and lifetime alcohol abuse or dependence, 51.9% of men and 27.9% of women, are the most common comorbid disorders.[170]

The United States Department of Veterans Affairs estimates that 830,000 Vietnam War veterans suffered symptoms of PTSD.[171] The *National Vietnam Veterans' Readjustment Study* (NVVRS) found 15.2% of male and 8.5% of female Vietnam veterans to suffer from current PTSD at the time of the study. Life-Time prevalence of PTSD was 30.9% for males and 26.9% for females. In a reanalysis of the NVVRS data, along with analysis of the data from the Matsunaga Vietnam Veterans Project, Schnurr, Lunney, Sengupta, and Waelde found that, contrary to the initial analysis of the NVVRS data, a large majority of Vietnam veterans suffered from PTSD symptoms (but not the disorder itself). Four out of five reported recent symptoms when interviewed 20–25 years after Vietnam.[172]

A 2011 study from Georgia State University and San Diego State University found that rates of PTSD diagnosis increased significantly when troops were stationed in combat zones, had tours of longer than a year, experienced combat, or were injured. Military personnel serving in combat zones were 12.1

percentage points more likely to receive a PTSD diagnosis than their active-duty counterparts in non-combat zones. Those serving more than 12 months in a combat zone were 14.3 percentage points more likely to be diagnosed with PTSD than those having served less than one year. Experiencing an enemy firefight was associated a 18.3 percentage point increase in the probability of PTSD, while being wounded or injured in combat was associated a 23.9 percentage point increase in the likelihood of a PTSD diagnosis. For the 2.16 million U.S. troops deployed in combat zones between 2001 and 2010, the total estimated two-year costs of treatment for combat-related PTSD are between $1.54 billion and $2.69 billion.[173]

As of 2013, rates of PTSD have been estimated at up to 20% for veterans returning from Iraq and Afghanistan.[25] As of 2013 13% of veterans returning from Iraq were unemployed.[174]

# Veterans

## United States

*Further information: Benefits for US Veterans with PTSD*

## United Kingdom

In the UK, there are various charities and service organisations dedicated to aiding veterans in readjusting to civilian life. The Royal British Legion and the more recently established Help for Heroes are two of Britain's more high-profile veterans' organisations which have actively advocated for veterans over the years. There has been some controversy that the NHS has not done enough in tackling mental health issues and is instead "dumping" veterans on charities such as Combat Stress.[175][176]

## Canada

Veterans Affairs Canada offers a new program that includes rehabilitation, financial benefits, job placement, health benefits program, disability awards, peer support[177][178][179] and family support.[180]

Vietnam Veterans Memorial, Washington, D.C.

# History

The 1952 edition of the DSM-I includes a diagnosis of "gross stress reaction", which has similarities to the modern definition and understanding of PTSD.[181] Gross stress reaction is defined as a "normal personality [utilizing] established patterns of reaction to deal with overwhelming fear" as a response to "conditions of great stress".[182] The diagnosis includes language which relates the condition to combat as well as to "civilian catastrophe".[182]

Early in 1978, the term was used in a working group finding presented to the Committee of Reactive Disorders.[183] The condition was added to the DSM-III, which was being developed in the 1980s, as posttraumatic stress disorder.[181][183] In the DSM-IV, the spelling "posttraumatic stress disorder" is used, while in the ICD-10, the spelling is "post-traumatic stress disorder".[184]

The addition of the term to the DSM-III was greatly influenced by the experiences and conditions of US military veterans of the Vietnam War.[185] Due to its association with the war in Vietnam, PTSD has become synonymous with many historical war-time diagnoses such as railway spine, stress syndrome, nostalgia, soldier's heart, shell shock, battle fatigue, combat stress reaction, or traumatic war neurosis.[186][187] Some of these terms date back to the 19th century, which is indicative of the universal nature of the condition. In a similar vein, psychiatrist Jonathan Shay has proposed that Lady Percy's soliloquy in the William Shakespeare play *Henry IV, Part 1* (act 2, scene 3, lines 40–62[188]), written around 1597, represents an

unusually accurate description of the symptom constellation of PTSD.[189]

Statue, *Three Servicemen*, Vietnam Veterans Memorial

The correlations between combat and PTSD are undeniable; according to Stéphane Audoin-Rouzeau and Annette Becker, "One-tenth of mobilized American men were hospitalized for mental disturbances between 1942 and 1945, and, after thirty-five days of uninterrupted combat, 98% of them manifested psychiatric disturbances in varying degrees."[190] In fact, much of the available published research regarding PTSD is based on studies done on veterans of the war in Vietnam. A study based on personal letters from soldiers of the 18th-century Prussian Army concludes that combatants may have had PTSD.[191]

The researchers from the Grady Trauma Project highlight the tendency people have to focus on the combat side of PTSD: "less public awareness has focused on civilian PTSD, which results from trauma exposure that is not combat related... " and "much of the research on civilian PTSD has focused on the sequelae of a single, disastrous event, such as the Oklahoma City bombing, September 11th attacks, and Hurricane Katrina".[192] Disparity in the focus of PTSD research affects the already popular perception of the exclusive interconnectedness of combat and PTSD. This is misleading when it comes to understanding the implications and extent of PTSD as a neurological disorder. Dating back to the definition of Gross stress reaction in the DSM-I, civilian experience of catastrophic or high stress events is included as a cause of PTSD in medical literature. The 2014 National Comorbidity Survey reports that "the traumas most commonly associated with PTSD are combat exposure and witnessing among men and rape and sexual molestation among women."[193] Because of the initial overt focus on PTSD as a combat related disorder when it was first fleshed out in the years following the war in Vietnam, in 1975 Ann Wolbert Burgess and Lynda Lytle Holmstrom defined Rape trauma syndrome, RTS, in order to draw attention to the striking similarities between the experiences of soldiers returning from war and of rape victims.[194] This paved the way for a more comprehensive understanding of causes of PTSD.

The DSM-IV classified PTSD under anxiety disorders, but the DSM-5 created a new category called "Trauma- and Stressor-Related Disorders," in which PTSD is now classified.[1]

## Terminology

The Diagnostic and Statistical Manual of Mental Disorders does not hyphenate 'post' and 'traumatic', thus, the DSM-5 lists the disorder as *posttraumatic stress disorder*. However, many scientific journal articles and other scholarly publications do hyphenate the name of the disorder, *viz.*, post-traumatic stress disorder.[195] Dictionaries also differ with regard to the preferred spelling of the disorder with the *Collins English Dictionary - Complete and Unabridged* using the hyphenated spelling, and the *American Heritage Dictionary of the English Language, Fifth Edition* and the *Random House Kernerman Webster's College Dictionary* giving the non-hyphenated spelling.[196]

## Research

Most knowledge regarding PTSD comes from studies in high-income countries.[197]

To recapitulate some of the neurological and neurobehavioral symptoms experienced by the veteran population of recent conflicts in Iraq and Afghanistan, researchers at the Roskamp Institute and the James A Haley Veteran's Hospital (Tampa) have developed an animal model to study the consequences of mild traumatic brain injury (mTBI) and PTSD.[198] In the laboratory, the researchers exposed mice to a repeated session of unpredictable stressor (i.e. predator odor while restrained), and physical trauma in the form of inescapable foot-shock, and this was also combined with a mTBI. In this study, PTSD animals demonstrated recall of traumatic memories, anxiety, and an impaired social behavior, while animals subject to both mTBI

and PTSD had a pattern of disinhibitory-like behavior. mTBI abrogated both contextual fear and impairments in social behavior seen in PTSD animals. In comparison with other animal studies,[198][199] examination of neuroendocrine and neuroimmune responses in plasma revealed a trend toward increase in corticosterone in PTSD and combination groups.

### Psychotherapy adjuncts

MDMA was used for psychedelic therapy for a variety of indications before its criminalization in the US in 1985. In response to its criminalization, the Multidisciplinary Association for Psychedelic Studies was founded as a nonprofit drug-development organization to develop MDMA into a legal prescription drug for use as an adjunct in psychotherapy.[200] The drug is hypothesized to facilitate psychotherapy by reducing fear, thereby allowing patients to reprocess and accept their traumatic memories without becoming emotionally overwhelmed. In this treatment, patients participate in an extended psychotherapy session during the acute activity of the drug, and then spend the night at the treatment facility. In the sessions with the drug, therapists are not directive and support the patients in exploring their inner experiences. Patients participate in standard psychotherapy sessions before the drug-assisted sessions, as well as after the drug-assisted psychotherapy to help them integrate their experiences with the drug.[201] Preliminary results suggest MDMA-assisted psychotherapy might be effective for individuals who have not responded favorably to other treatments. Future research employing larger sample sizes and an appropriate placebo condition, i.e., one in which subjects cannot discern if they are in the experimental or control condition, will increase confidence in the results of initial research.[202][203]

Clinical research is also investigating using D-cycloserine, hydrocortisone, and propranolol as adjuncts to more conventional exposure therapy.[203]

## Notes

1. ^ Acceptable variants of this term exist; see the *Terminology* section in this article.

## References


1. ^ *a b c d e f g* American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing. pp. 271–280. ISBN 978-0-89042-555-8.
2. ^ *a b c d e f g h* Bisson, JI; Cosgrove, S; Lewis, C; Robert, NP (26 November 2015). "Post-traumatic stress disorder.". *BMJ (Clinical research ed.)*. **351**: h6161. PMC 4663500. PMID 26611143.
3. ^ Zoladz, Phillip (June 2013). "Current status on behavioral and biological markers of PTSD: A search for clarity in a conflicting literature". *Neuroscience and Biobehavioral Reviews*. **37** (5): 860–895. doi:10.1016/j.neubiorev.2013.03.024. PMID 23567521.
4. ^ *a b c d e f g h i j* National Collaborating Centre for Mental Health (UK) (2005). "Post-Traumatic Stress Disorder: The Management of PTSD in Adults and Children in Primary and Secondary Care". *NICE Clinical Guidelines, No. 26*. Gaskell (Royal College of Psychiatrists). Lay summary – *Pubmed Health (plain English)*.
5. ^ *a b c* "Post-Traumatic Stress Disorder". *National Institute of Mental Health*. February 2016. Retrieved 10 March 2016.
6. ^ *a b* Haagen, JF; Smid, GE; Knipscheer, JW; Kleber, RJ (August 2015). "The efficacy of recommended treatments for veterans with PTSD: A metaregression analysis.". *Clinical Psychology Review*. **40**: 184–94. doi:10.1016/j.cpr.2015.06.008. PMID 26164548.
7. ^ *a b* Berger, W; Mendlowicz, MV; Marques-Portella, C; Kinrys, G; Fontenelle, LF; Marmar, CR; Figueira, I (17 March 2009). "Pharmacologic alternatives to antidepressants in posttraumatic stress disorder: a systematic review.". *Progress in neuro-psychopharmacology & biological psychiatry*. **33** (2): 169–80. doi:10.1016/j.pnpbp.2008.12.004. PMC 2720612. PMID 19141307.
8. ^ Hetrick, SE; Purcell, R; Garner, B; Parslow, R (7 July 2010). "Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD).". *The Cochrane database of systematic reviews* (7): CD007316. doi:10.1002/14651858.CD007316.pub2. PMID 20614457.
9. ^ *a b c* Guina, J; Rossetter, SR; DeRHODES, BJ; Nahhas, RW; Welton, RS (July 2015). "Benzodiazepines for PTSD: A

Systematic Review and Meta-Analysis.". *Journal of Psychiatric Practice*. **21** (4): 281–303. doi:10.1097/pra.0000000000000091. PMID 26164054.

10. ^ *a b c d* Hoskins, M.; Pearce, J.; Bethell, A.; Dankova, L.; Barbui, C.; Tol, WA.; van Ommeren, M.; de Jong, J.; Seedat, S. (February 2015). "Pharmacotherapy for post-traumatic stress disorder: systematic review and meta-analysis.". *Br J Psychiatry*. **206** (2): 93–100. doi:10.1192/bjp.bp.114.148551. PMID 25644881. "Some drugs have a small positive impact on PTSD symptoms"
11. ^ Carlstedt, Roland (2009). *Handbook of Integrative Clinical Psychology, Psychiatry, and Behavioral Medicine Perspectives, Practices, and Research.* New York: Springer Pub. Co. p. 353. ISBN 9780826110954.
12. ^ Herman, Judith (2015). *Trauma and Recovery: The Aftermath of Violence--From Domestic Abuse to Political Terror*. Basic Books. p. 9. ISBN 9780465098736.
13. ^ Klykylo, William M. (2012). *Clinical child psychiatry* (3. ed.). Chichester, West Sussex, UK: John Wiley & Sons. p. Chapter 15. ISBN 9781119967705.
14. ^ Friedman, MJ (October 2013). "Finalizing PTSD in DSM-5: getting here from there and where to go next.". *Journal of traumatic stress*. **26** (5): 548–56. doi:10.1002/jts.21840. PMID 24151001.
15. ^ *a b c d* American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders: DSM-IV*. Washington, DC: American Psychiatric Association. ISBN 0-89042-061-0.[*page needed*]; on-line.
16. ^ *a b c d e* Rothschild, Babette (2000). *The Body Remembers: The Psychophysiology of Trauma and Trauma Treatment*. New York: W.W. Norton & Company. ISBN 0-393-70327-4.[*page needed*]
17. ^ Kaplan, H. I.; Sadock, B. J. (1994). Grebb, J. A., ed. *Kaplan and Sadock's synopsis of psychiatry: Behavioral sciences, clinical psychiatry* (7th ed.). Baltimore: Williams & Williams. pp. 606–609.[*page needed*]
18. ^ Satcher D (1999). "Chapter 4". *Mental Health: A Report of the Surgeon General*. Surgeon General of the United States.
19. ^ Robinson, Maisah (May 27, 2006). "Review of Francisco Goya's Disasters of War". Associated Press. Archived from the original on 2014-07-28.[*unreliable source?*]
20. ^ *a b* Fullerton CS, Ursano RJ, Wang L (2004). "Acute Stress Disorder, Posttraumatic Stress Disorder, and Depression in Disaster or Rescue Workers". *Am J Psychiatry*. **161** (8): 1370–1376. doi:10.1176/appi.ajp.161.8.1370. PMID 15285961.
21. ^ Skogstad, M (2013). "Work-related post-traumatic stress disorder". *Occupational Medicine*. **63** (3): 175–182. doi:10.1093/occmed/kqt003. PMID 23564090. Retrieved 2016-07-15.
22. ^ *a b* Marcus ME (2003). "Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism". *Proceedings of the National Academy of Sciences*. **168** (15): 9039–9043. doi:10.1073/pnas.1530467100. PMC 166434. PMID 12853571.
23. ^ "Post-Traumatic Stress Disorder (PTSD)". *U.S. Department of Health and Human Services*. National Institute of Mental Health (NIMH). Retrieved 2011-12-16.
24. ^ Mayo Clinic staff. "Post-traumatic stress disorder (PTSD)". Mayo Foundation for Medical Education and Research. Retrieved 2011-12-16.[*scientific citation needed*]
25. ^ *a b c d e* Spoont, Michele; Arbisi, P; Fu, S; Greer, N; Kehle-Forbes, S; Meis, L; Rutks, I. (January 2013). "Screening for Post-Traumatic Stress Disorder (PTSD) in Primary Care: A Systematic Review". Washington DC: Department of Veterans Affairs. PMID 23487872. Lay summary – *Pubmed Health (plain English)*.
26. ^ Alisic; et al. "Rates of post-traumatic stress disorder in trauma-exposed children and adolescents: meta-analysis". *British Journal of Psychiatry*. **204** (5): 335–340. doi:10.1192/bjp.bp.113.131227.
27. ^ Koenen KC, Moffitt TE, Poulton R, Martin J, Caspi A (February 2007). "Early childhood factors associated with the development of post-traumatic stress disorder: results from a longitudinal birth cohort". *Psychol Med*. **37** (2): 181–92. doi:10.1017/S0033291706009019. PMC 2254221. PMID 17052377.
28. ^ Lapp KG, Bosworth HB, Strauss JL, Stechuchak KM, Horner RD, Calhoun PS, Meador KG, Lipper S, Butterfield MI (September 2005). "Lifetime sexual and physical victimization among male veterans with combat-related post-traumatic stress disorder". *Mil Med*. **170** (9): 787–90. PMID 16261985.
29. ^ Otte C, Neylan TC, Pole N, Metzler T, Best S, Henn-Haase C, Yehuda R, Marmar CR (January 2005). "Association between childhood trauma and catecholamine response to psychological stress in police academy recruits". *Biol. Psychiatry*. **57** (1): 27–32. doi:10.1016/j.biopsych.2004.10.009. PMID 15607297.
30. ^ Dobry, Y; Braquehais, MD; Sher, L (2013). "Bullying, psychiatric pathology and suicidal behavior.". *International journal of adolescent medicine and health*. **25** (3): 295–9. doi:10.1515/ijamh-2013-0065. PMID 24006324.
31. ^ *a b c d e f g h* Skelton K, Ressler KJ, Norrholm SD, Jovanovic T, Bradley-Davino B (2012). "PTSD and gene variants: New pathways and new thinking". *Neuropharmacology*. **62** (2): 628–637. doi:10.1016/j.neuropharm.2011.02.013. PMC 3136568. PMID 21356219.
32. ^ Laor N, Wolmer L, Mayes LC, Golomb A, Silverberg DS, Weizman R, Cohen DJ (May 1996). "Israeli preschoolers

under Scud missile attacks. A developmental perspective on risk-modifying factors". *Arch Gen Psychiatry*. **53** (5): 416–23. doi:10.1001/archpsyc.1996.01830050052008. PMID 8624185.
33. ^ Laor N, Wolmer L, Mayes LC, Gershon A, Weizman R, Cohen DJ (March 1997). "Israeli preschool children under Scuds: a 30-month follow-up". *J Am Acad Child Adolesc Psychiatry*. **36** (3): 349–56. doi:10.1097/00004583-199703000-00013. PMID 9055515. (subscription required (help)).
34. ^ Janoff-Bulman, R. (1992). *Shattered Assumptions: Toward a New Psychology of Trauma*. New York: Free Press.[*page needed*]
35. ^ Falsetti, Sherry A.; Monier, Jeannine; Resnick, Jeannine (2005). "Chapter 2: Intrusive Thoughts In Posttraumatic Stress Disorder". In Clark, David A. *Intrusive Thoughts In Clinical Disorders. Theory, Research, and Treatment*. The Guilford Press. pp. 40–41. ISBN 1-59385-083-2.
36. ^ Howard, LM; Oram, S; Galley, H; Trevillion, K; Feder, G (2013). "Domestic violence and perinatal mental disorders: a systematic review and meta-analysis.". *PLOS Medicine*. **10** (5): e1001452. doi:10.1371/journal.pmed.1001452. PMC 3665851. PMID 23723741.
37. ^ Glass, Albert Julius; Jones, Franklin D. "Psychiatry In The U.S. Army: Lessons for Community Psychiatry" (PDF).
38. ^ *a b* Chandler, Jerome Greer, (Aug. 2015) "PTSD Is Bad for your Physical Health," *VFW* magazine, pps: 30-32.
39. ^ Ruef, Anna; Litz, Brett; Schlenger, William (2000). "Hispanic Ethnicity and Risk for Combat-Related Posttraumatic Stress Disorder". *Cultural Diversity and Ethnic Minority Psychology*. **6** (3): 235–251. doi:10.1037/1099-9809.6.3.235.
40. ^ Pereira, Angela (January 2002). "Combat trauma and the diagnosis of post-traumatic stress disorder in female and male veterans". *Military Medicine*. **167** (1): 23–27.
41. ^ Suris, Alina; Lind, Lisa; Kashner, Michael; Borman, Patricia; Petty, Frederick (2004). "Sexual Assault in Women Veterans: An Examination of PTSD Risk, Health Care Utilization, and Cost of Care" (PDF). *Psychosomatic Medicine*: 749–756.
42. ^ Wolfe, Jessica; Sharkansky, Erica; Read, Jennifer; Dawson, Ree; Martin, James; Ouimette, Paige (1 February 1998). "Sexual Harassment and Assault as Predictors of PTSD Symptomatology Among U.S. Female Persian Gulf War Military Personnel" (PDF). *Journal of Interpersonal Violence*. **13**: 40–57. doi:10.1177/088626098013001003.
43. ^ *a b* Brewin CR, Andrews B, Valentine JD (October 2000). "Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults". *J Consult Clin Psychol*. **68** (5): 748–66. doi:10.1037/0022-006X.68.5.748. PMID 11068961.
44. ^ *a b* Ozer EJ, Best SR, Lipsey TL, Weiss DS (January 2003). "Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis". *Psychol Bull*. **129** (1): 52–73. doi:10.1037/0033-2909.129.1.52. PMID 12555794.
45. ^ True WR, Rice J, Eisen SA, Heath AC, Goldberg J, Lyons MJ, Nowak J (1993). "A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms". *Arch. Gen. Psychiatry*. **50** (4): 257–64. doi:10.1001/archpsyc.1993.01820160019002. PMID 8466386.
46. ^ Delahanty DL (2011). "Toward the predeployment detection of risk for PTSD". *American Journal of Psychiatry*. **168** (1): 9–11. doi:10.1176/appi.ajp.2010.10101519. PMID 21205813.
47. ^ Maxmen, J. S.; Ward, N. G. (2002). *Psychotropic drugs: fast facts* (3rd ed.). New York: W. W. Norton. p. 348. ISBN 0-393-70301-0.
48. ^ Cohen SI (February 1995). "Alcohol and benzodiazepines generate anxiety, panic and phobias". *J R Soc Med*. **88** (2): 73–77. PMC 1295099. PMID 7769598.
49. ^ Spates, R.; Souza, T. (2007). "Treatment of PTSD and Substance Abuse Comorbidity" (PDF). *The Behavior Analyst Today*. **9** (1): 11–26. doi:10.1037/h0100643. Archived (PDF) from the original on 2014-06-23.
50. ^ *The Secret Life of the Brain (Series), episode 4*. PBS. 2001. Retrieved 2014-01-29.
51. ^ Joseph Zohar; Alzbeta Juven-Wetzler; Viki Myers; Leah Fostic (2008). "Post-Traumatic stress disorder: Facts and Fiction". *Current opinion in psychiatry*. **21** (1): 70–eoa. doi:10.1097/YCO.0b013e3282f269ee. PMID 18281844.
52. ^ Yehuda R, Halligan SL, Golier JA, Grossman R, Bierer LM (2004). "Effects of trauma exposure on the cortisol response to dexamethasone administration in PTSD and major depressive disorder". *Psychoneuroendocrinology*. **29** (3): 389–404. doi:10.1016/S0306-4530(03)00052-0. PMID 14644068.
53. ^ Yehuda R, Halligan SL, Grossman R, Golier JA, Wong C (2002). "The cortisol and glucocorticoid receptor response to low dose dexamethasone administration in aging combat veterans and holocaust survivors with and without posttraumatic stress disorder". *Biol Psychiatry*. **52** (5): 393–403. doi:10.1016/S0006-3223(02)01357-4. PMID 12242055.
54. ^ Heim C, Ehlert U, Hellhammer DH (2000). "The potential role of hypocorticolism in the pathophysiology of stress-related bodily disorders". *Psychoneuroendocrinology*. **25** (1): 1–35. doi:10.1016/S0306-4530(99)00035-9. PMID 10633533.
55. ^ Mason JW, Giller EL, Kosten TR, Harkness L (1988). "Elevation of urinary norepinephrine/cortisol ratio in posttraumatic stress disorder". *J Nerv Ment Dis*. **176** (8): 498–502. doi:10.1097/00005053-198808000-00008.

PMID 3404142.
56. ^ Bohnen N, Nicolson N, Sulon J, Jolles J (1991). "Coping style, trait anxiety and cortisol reactivity during mental stress". *J Psychosom Res*. **35** (2–3): 141–7. doi:10.1016/0022-3999(91)90068-Y. PMID 2046048.
57. ^ Geracioti TD, Baker DG, Ekhator NN, West SA, Hill KK, Bruce AB, Schmidt D, Rounds-Kugler B, Yehuda R, Keck PE, Kasckow JW (2001). "CSF norepinephrine concentrations in posttraumatic stress disorder". *Am J Psychiatry*. **158** (8): 1227–30. doi:10.1176/appi.ajp.158.8.1227. PMID 11481155.
58. ^ Sautter FJ, Bissette G, Wiley J, Manguno-Mire G, Schoenbachler B, Myers L, Johnson JE, Cerbone A, Malaspina D (December 2003). "Corticotropin-releasing factor in posttraumatic stress disorder (PTSD) with secondary psychotic symptoms, nonpsychotic PTSD, and healthy control subjects". *Biol. Psychiatry*. **54** (12): 1382–8. doi:10.1016/S0006-3223(03)00571-7. PMID 14675802.
59. ^ de Kloet CS, Vermetten E, Geuze E, Lentjes EG, Heijnen CJ, Stalla GK, Westenberg HG (2008). "Elevated plasma corticotrophin-releasing hormone levels in veterans with posttraumatic stress disorder". *Prog. Brain Res*. Progress in Brain Research. **167**: 287–91. doi:10.1016/S0079-6123(07)67025-3. ISBN 978-0-444-53140-7. PMID 18037027.
60. ^ Radley JJ, Kabbaj M, Jacobson L, Heydendael W, Yehuda R, Herman JP (September 2011). "Stress risk factors and stress related pathology: Neuroplasticity epigenetics and endophenotypes". *Stress*. **14** (5): 481–497. doi:10.3109/10253890.2011.604751. PMC 3641164. PMID 21848436.
61. ^ Pitman RK (1989). "Post-traumatic stress disorder, hormones, and memory". *Biological Psychiatry*. **26** (3): 221–223. doi:10.1016/0006-3223(89)90033-4. PMID 2545287.
62. ^ Yehuda R (2001). "Biology of posttraumatic stress disorder". *J Clin Psychiatry*. 62. Suppl 17: 41–6. PMID 11495096.
63. ^ Yehuda R (2002). "Clinical relevance of biologic findings in PTSD". *Psychiatr Q*. **73** (2): 123–33. doi:10.1023/A:1015055711424. PMID 12025720.
64. ^ Aardal-Eriksson E, Eriksson TE, Thorell LH (2001). "Salivary cortisol, posttraumatic stress symptoms, and general health in the acute phase and during 9-month follow-up". *Biol. Psychiatry*. **50** (12): 986–93. doi:10.1016/S0006-3223(01)01253-7. PMID 11750895.
65. ^ Zohar J, Juven-Wetzler A, Myers V, Fostick L (January 2008). "Post traumatic stress disorder:facts and fiction". *Current opinion in psychiatry*. **21** (1): 74–7. doi:10.1097/YCO.0b013e3282f269ee. PMID 18281844.
66. ^ *a b c d e* Olszewski TM, Varrasse JF (2005). "The neurobiology of PTSD: implications for nurses". *Journal of Psychosocial Nursing and Mental Health Services*. **43** (6): 40–7. PMID 16018133.
67. ^ Lindley SE, Carlson EB, Benoit M (2004). "Basal and dexamethasone suppressed salivary cortisol concentrations in a community sample of patients with posttraumatic stress disorder". *Biol. Psychiatry*. **55** (9): 940–5. doi:10.1016/j.biopsych.2003.12.021. PMID 15110738.
68. ^ "NIMH · Post Traumatic Stress Disorder Research Fact Sheet". *National Institutes of Health*. Retrieved 2014-01-29.
69. ^ Newton, Philip. "From Mouse to Man; the Anatomy of Posttraumatic Stress Disorder". *Psychologytoday.com*. Retrieved 20 December 2009.
70. ^ Etkin, Amit; Wager, Tor D. (2007-10-01). "Functional Neuroimaging of Anxiety: A Meta-Analysis of Emotional Processing in PTSD, Social Anxiety Disorder, and Specific Phobia". *The American Journal of Psychiatry*. **164** (10): 1476–1488. doi:10.1176/appi.ajp.2007.07030504. ISSN 0002-953X. PMC 3318959. PMID 17898336.
71. ^ Newport DJ, Nemeroff CB; Nemeroff, Charles B (2010). "Neurobiology of posttraumatic stress disorder". *Current Opinion in Neurobiology*. **10** (2): 211–218. doi:10.1016/S0959-4388(00)00080-5. PMID 10753802.
72. ^ [*unreliable medical source?*] van der Kolk B (March 2000). "Posttraumatic stress disorder and the nature of trauma". *Dialogues in Clinical Neuroscience*. **2**: 7–22. PMC 3181584. PMID 22034447.
73. ^ *a b* Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, Zeidan MA, Handwerger K, Orr SP, Rauch SL (2009). "Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder". *Biol Psychiatry*. **66** (12): 1075–82. doi:10.1016/j.biopsych.2009.06.026. PMC 2787650. PMID 19748076.
74. ^ Stein MB, Paulus MP (2009). "Imbalance of approach and avoidance: the yin and yang of anxiety disorders". *Biol Psychiatry*. **66** (12): 1072–4. doi:10.1016/j.biopsych.2009.09.023. PMC 2825567. PMID 19944792.
75. ^ Agis-Balboa RC, Arcos-Diaz D, Wittnam J, Govindarajan N, Blom K, Burkhardt S, Haladyniak U, Agbemenyah HY, Zovoilis A, Salinas-Riester G, Opitz L, Sananbenesi F, Fischer A (August 2011). "A hippocampal insulin-growth factor 2 pathway regulates the extinction of fear memories". *EMBO J*. **30** (19): 4071–83. doi:10.1038/emboj.2011.293. PMC 3209781. PMID 21873981.
76. ^ Carlson, Neil R. (2007). Physiology of Behavior (9 ed.). Pearson Education, Inc.[*full citation needed*]
77. ^ Jatzko A, Rothenhöfer S, Schmitt A, Gaser C, Demirakca T, Weber-Fahr W, Wessa M, Magnotta V, Braus DF (2006). "Hippocampal volume in chronic posttraumatic stress disorder (PTSD): MRI study using two different evaluation methods" (PDF). *Journal of Affective Disorders*. **94** (1–3): 121–126. doi:10.1016/j.jad.2006.03.010. PMID 16701903. Retrieved 2014-01-29.

78. ^ Mikael Rubin, Erel Shvil , Santiago Papini , Binod T. Chhetry , Liat Helpman, John C. Markowitz, J. John Mann, Yuval Neria (30 June 2016). "Greater hippocampal volume is associated with PTSD treatment response". *Psychiatry Neroimaging*. pp. 36–39. doi:10.1016/j.pscychresns.2016.05.001.
79. ^ Elhai, Jon D.; Layne, Christopher M.; Steinberg, Alan M.; Brymer, Melissa J.; Briggs, Ernestine C.; Ostrowski, Sarah A.; Pynoos, Robert S. (2013-02-01). "Psychometric Properties of the UCLA PTSD Reaction Index. Part II: Investigating Factor Structure Findings in a National Clinic-Referred Youth Sample". *Journal of Traumatic Stress*. **26** (1): 10–18. doi:10.1002/jts.21755. ISSN 1573-6598.
80. ^ "Primary Care PTSD Screen (PC-PTSD)". *PTSD: National Center for PTSD*. Department of Veterans Affairs. "The Primary Care PTSD Screen (PC-PTSD) is a 4-item screen that was designed for use in primary care and other medical settings, and is currently used to screen for PTSD in Veterans using VA health care."
81. ^ *a b* Prins, Annabel; Ouimette, Paige; Kimerling, Rachel; Camerond, Rebecca P.; Hugelshofer, Daniela S.; Shaw-Hegwer, Jennifer; Thrailkill, Ann; Gusman, Fred D.; Sheikh, Javaid I. (1 January 2004). "The primary care PTSD screen (PC–PTSD): development and operating characteristics" (PDF). *Primary Care Psychiatry*. **9** (1): 9–14. doi:10.1185/135525703125002360. Retrieved 21 February 2016.
82. ^ Wortmann, Jennifer H.; Jordan, Alexander H.; Weathers, Frank W.; Resick, Patricia A.; Dondanville, Katherine A.; Hall-Clark, Brittany; Foa, Edna B.; Young-McCaughan, Stacey; Yarvis, Jeffrey S.; Hembree, Elizabeth A.; Mintz, Jim; Peterson, Alan L.; Litz, Brett T. (2016-01-11). "Psychometric analysis of the PTSD Checklist-5 (PCL-5) among treatment-seeking military service members". *Psychological Assessment*. doi:10.1037/pas0000260. ISSN 1939-134X. PMID 26751087.
83. ^ Bovin, Michelle J.; Marx, Brian P.; Weathers, Frank W.; Gallagher, Matthew W.; Rodriguez, Paola; Schnurr, Paula P.; Keane, Terence M. (2015-12-14). "Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5) in veterans". *Psychological Assessment*. doi:10.1037/pas0000254. ISSN 1939-134X. PMID 26653052.
84. ^ *a b* Blevins, Christy A.; Weathers, Frank W.; Davis, Margaret T.; Witte, Tracy K.; Domino, Jessica L. (2015-12-01). "The Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5): Development and initial psychometric evaluation". *Journal of Traumatic Stress*. **28** (6): 489–498. doi:10.1002/jts.22059. ISSN 1573-6598. Retrieved 2015-12-08.
85. ^ Beard, C (Aug 2014). "Beyond generalized anxiety disorder: psychometric properties of the GAD-7 in a heterogeneous psychiatric sample". *J Anxiety Disord*. Elsevier. **28** (6): 547–552. doi:10.1016/j.janxdis.2014.06.002. PMID 24983795.
86. ^ "The Child PTSD Symptom Scale (CPSS)". *National Center for PTSD*. U.S. Department of Veterans Affairs. 23 February 2016.
87. ^ *a b* Gaynes BN, DeVeaugh-Geiss J, Weir S, Gu H, MacPherson C, Schulberg HC, Culpepper L, Rubinow DR (March 2010). "Feasibility and Diagnostic Validity of the M-3 Checklist: a Brief, Self-rated Screen for Depressive, Bipolar, Anxiety, and Post-traumatic Stress Disorders in Primary Care". *Annals of Family Medicine*. **8** (2): 160–169. doi:10.1370/afm.1092. PMC 2834723. PMID 20212303. Retrieved 2016-07-15.
88. ^ Spoont, MR; Williams JW, Jr; Kehle-Forbes, S; Nieuwsma, JA; Mann-Wrobel, MC; Gross, R (4 August 2015). "Does This Patient Have Posttraumatic Stress Disorder?: Rational Clinical Examination Systematic Review.". *JAMA*. **314** (5): 501–10. doi:10.1001/jama.2015.7877. PMID 26241601.
89. ^ Cohen, JA; Bukstein, O; Walter, H; Benson, SR; Chrisman, A; Farchione, TR; Hamilton, J; Keable, H; Kinlan, J; Schoettle, U; Siegel, M; Stock, S; Medicus, J; AACAP Work Group On Quality, Issues (April 2010). "Practice parameter for the assessment and treatment of children and adolescents with posttraumatic stress disorder.". *Journal of the American Academy of Child and Adolescent Psychiatry*. **49** (4): 414–30. doi:10.1016/j.jaac.2009.12.020. PMID 20410735.
90. ^ Benedek, DM. "Guideline Watch (March 2009): Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder" (PDF). *American Psychiatric Association*. APA. Retrieved 2016-07-15.
91. ^ Weiss & Marmar (1996). "Impact of Event Scale - Revised (IES-R)". *United States Department of Veterans Affairs*. Last updated August 17, 2015
92. ^ (PDF). EMDR Humanitarian Assistance Programs http://www.emdrhap.org/content/wp-content/uploads/2014/07/VIII-E_Impact_of_Events_Scale_Revised.pdf. Retrieved 2016-02-08. Missing or empty `|title=` (help), in turn citing: Weiss, D.S. (2007). The Impact of Event Scale-Revised. In J.P. Wilson, & T.M. Keane (Eds.) Assessing psychological trauma and PTSD: a practitioner's handbook (2nd ed., pp. 168-189). New York: Guilford Press.
93. ^ Breslau N, Kessler RC (2001). "The stressor criterion in DSM-IV posttraumatic stress disorder: an empirical investigation". *Biol. Psychiatry*. **50** (9): 699–704. doi:10.1016/S0006-3223(01)01167-2. PMID 11704077.
94. ^ Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM (January 1995). "The development of a Clinician-Administered PTSD Scale". *J Trauma Stress*. **8** (1): 75–90. doi:10.1002/jts.2490080106. PMID 7712061.

[*incomplete short citation*]

95. ^ Foa E: The Post Traumatic Diagnostic Scale Manual. Minneapolis, NCS, 1995.
96. ^ Brewin CR, Rose S, Andrews B, Green J, Tata P, McEvedy C, Turner S, Foa EB (2002). "Brief screening instrument for post traumatic stress disorder". *British Journal of Psychiatry*. **181**: 158–162. doi:10.1192/bjp.181.2.158. PMID 12151288.
97. ^ a b Foa EB, Cashman L, Jaycox L, Perry K (1997). "The validation of a self-report measure of posttraumatic stress disorder: the Posttraumatic Diagnostic Scale". *Psychological Assessment*. **9** (4): 445–451. doi:10.1037/1040-3590.9.4.445.
98. ^ a b "The ICD-10 Classification of Mental and Behavioural Disorders" (PDF). World Health Organization. pp. 120–121. Retrieved 2014-01-29.
99. ^ a b c d Feldner MT, Monson CM, Friedman MJ (2007). "A critical analysis of approaches to targeted PTSD prevention: current status and theoretically derived future directions". *Behav Modif*. **31** (1): 80–116. doi:10.1177/0145445506295057. PMID 17179532.
100. ^ Carlier, IVE; Lamberts, RD; van Uchelen, AJ; Gersons, BPR (1998). "Disaster-related post-traumatic stress in police officers: A field study of the impact of debriefing". *Stress Medicine*. **14** (3): 143–8. doi:10.1002/(SICI)1099-1700(199807)14:3<143::AID-SMI770>3.0.CO;2-S.[*dead link*]
101. ^ Mayou RA, Ehlers A, Hobbs M (2000). "Psychological debriefing for road traffic accident victims. Three-year follow-up of a randomised controlled trial". *Br J Psychiatry*. **176** (6): 589–93. doi:10.1192/bjp.176.6.589. PMID 10974967.
102. ^ a b Roberts NP, Kitchiner NJ, Kenardy J, Bisson JI (2009). Roberts, Neil P, ed. "Multiple session early psychological interventions for the prevention of post-traumatic stress disorder". *Cochrane Database of Systematic Reviews* (3). Art. No. CD006869. doi:10.1002/14651858.CD006869.pub2. PMID 19588408. Archived from the original on 2014-04-21. Retrieved April 27, 2011. (subscription required)
103. ^ *Assessment and Management of Conditions Specifically Related to Stress* (PDF). Geneva: World Health Organization. 2013. ISBN 978-92-4-150593-2. Retrieved 2014-01-29.
104. ^ Amos, T; Stein, DJ; Ipser, JC (8 July 2014). "Pharmacological interventions for preventing post-traumatic stress disorder (PTSD).". *The Cochrane database of systematic reviews*. **7**: CD006239. doi:10.1002/14651858.CD006239.pub2. PMID 25001071.
105. ^ van Emmerik AA, Kamphuis JH, Hulsbosch AM, Emmelkamp PM (2002). "Single session debriefing after psychological trauma: a meta-analysis". *The Lancet*. **360** (9335): 766–771. doi:10.1016/S0140-6736(02)09897-5. PMID 12241834.
106. ^ Rose S, Bisson J, Churchill R, Wessely S (2002). Rose, Suzanna C, ed. "Psychological debriefing for preventing post traumatic stress disorder (PTSD)". *Cochrane Database of Systematic Reviews* (2). Art. No. CD000560. doi:10.1002/14651858.CD000560. PMID 12076399.
107. ^ "American Psychological Association on psychological debriefing". Archived from the original on 2013-11-10.
108. ^ Wiseman T, Foster K, Curtis K (Nov 2013). "Mental health following traumatic physical injury: an integrative literature review". *Injury*. **44** (11): 1383–90. doi:10.1016/j.injury.2012.02.015. PMID 22409991.
109. ^ Kassam-Adams N; et al. (Dec 2013). "Posttraumatic stress following pediatric injury: update on diagnosis, risk factors, and intervention". *JAMA Pediatr*. **167** (12): 1158–65. doi:10.1001/jamapediatrics.2013.2741. PMID 24100470.
110. ^ Hetrick S. E.; Purcell R.; Garner B.; Parslow R. (2010). "Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD)". *Cochrane Database Syst Rev*. **7** (7).
111. ^ a b Lee CW, Cuijpers P (2013). "A meta-analysis of the contribution of eye movements in processing emotional memories". *J. Behav. Ther. Exp. Psychiatry*. **44** (2): 231–9. doi:10.1016/j.jbtep.2012.11.001. PMID 23266601.
112. ^ Crawford C, Dawn B (Jul 2013). "A Systematic Review of Biopsychosocial Training Programs for the Self-Management of Emotional Stress: Potential Applications for the Military". *Evidence-Based Complementary and Alternative Medicine*. **2013**: 1–23. doi:10.1155/2013/747694.
113. ^ Cahill, S. P.; Foa, E. B. (2004). Taylor, S., ed. *Advances in the Treatment of Posttraumatic Stress Disorder: Cognitive-behavioral perspectives*. New York: Springer. pp. 267–313.
114. ^ Bisson JI, Ehlers A, Matthews R, Pilling S, Richards D, Turner S (2007). "Psychological treatments for chronic post-traumatic stress disorder. Systematic review and meta-analysis". *Br J Psychiatry*. **190** (2): 97–104. doi:10.1192/bjp.bp.106.021402. PMID 17267924.
115. ^ Seidler GH, Wagner FE (2006). "Comparing the efficacy of EMDR and trauma-focused cognitive-behavioral therapy in the treatment of PTSD: a meta-analytic study". *Psychol Med*. **36** (11): 1515–22. doi:10.1017/S0033291706007963. PMID 16740177.
116. ^ Rolfsnes E. S., Idsoe T. (2011). "School based intervention programs for PTSD symptoms: A review and meta analysis". *Journal of Traumatic Stress*. **24** (2): 155–165. doi:10.1002/jts.20622.
117. ^ "Treatment of PTSD - PTSD: National Center for PTSD". U.S. Department of Veterans Affairs. May 26, 2016.
118. ^ "PTSD Treatment Options". Defense Centers of Excellence. November 23, 2016.

119. ^ Mulick, P. S.; Landes, S.; Kanter, J. W. (2005). "Contextual Behavior Therapies in the Treatment of PTSD: A Review" (PDF). *International Journal of Behavioral Consultation and Therapy*. **1** (3): 223–228. doi:10.1037/h0100747.
120. ^ Hassija, CM; Gray, MJ (2007). "Behavioral Interventions for Trauma and Posttraumatic Stress Disorder". *International Journal of Behavioral Consultation and Therapy*. Behavior Analyst Online. **3** (2): 166–175. doi:10.1037/h0100797.
121. ^ Mulick, P. S.; Naugle, A. E. (2009). "Behavioral Activation in the Treatment of Comorbid Posttraumatic Stress Disorder and Major Depressive Disorder". *International Journal of Behavioral Consultation and Therapy*. **5** (2): 330–339.
122. ^ Grohol, JM. "What is Exposure Therapy?". *Psychcentral.com*. Retrieved 2010-07-14.
123. ^ Joseph, J. S.; Gray, M. J. (2008). "Exposure Therapy for Posttraumatic Stress Disorder" (PDF). *Journal of Behavior Analysis of Offender and Victim: Treatment and Prevention*. **1** (4): 69–80. doi:10.1037/h0100457. Archived from the original (PDF) on 2010-12-29. Retrieved 2010-05-10.
124. ^ Ursano RJ, Bell C, Eth S, Friedman M, Norwood A, Pfefferbaum B, Pynoos JD, Zatzick DF, Benedek DM, McIntyre JS, Charles SC, Altshuler K, Cook I, Cross CD, Mellman L, Moench LA, Norquist G, Twemlow SW, Woods S, Yager J (November 2004). Work Group on ASD PTSD, Steering Committee on Practice Guidelines. "Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder". *Am J Psychiatry*. **161** (11 Suppl): 3–31. PMID 15617511.
125. ^ *Committee on Treatment of Posttraumatic Stress Disorder, Institute of Medicine: Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence*. Washington, D.C.: National Academies Press. 2008. ISBN 0-309-10926-4.[*page needed*]
126. ^ "Prolonged Exposure Therapy". *U.S. Department of Veteran Affairs*. PTSD: National Center for PTSD. 2009-09-29. Retrieved 2010-07-14.[*dead link*]
127. ^ Karlin BE, Ruzek JI, Chard KM, Eftekhari A, Monson CM, Hembree EA, Resick PA, Foa EB (2010). "Dissemination of evidence-based psychological treatments for posttraumatic stress disorder in the Veterans Health Administration". *Journal of Traumatic Stress*. **23** (6): 663–673. doi:10.1002/jts.20588. PMID 21171126.
128. ^ *a b* Shapiro, Francine (April 1989). "Efficacy of the eye movement desensitization procedure in the treatment of traumatic memories". *Journal of Traumatic Stress*. **2** (2): 199–223. doi:10.1002/jts.2490020207.
129. ^ Shapiro F, Maxfield L (August 2002). "Eye Movement Desensitization and Reprocessing (EMDR): information processing in the treatment of trauma". *Journal of clinical psychology*. **58** (8): 933–46. doi:10.1002/jclp.10068. PMID 12115716.
130. ^ *a b* The Management of Post-Traumatic Stress Working Group (2010). "VA/DoD clinical practice guideline for management of post-traumatic stress". Department of Veterans Affairs, Department of Defense. p. Version 2.0. Retrieved 2 June 2013.
131. ^ *a b c* Gillies D, Taylor F, Gray C, O'Brien L, D'Abrew N (2012). Gillies, Donna, ed. "Psychological therapies for the treatment of post traumatic stress disorder in children and adolescents". *Cochrane Database of Systematic Reviews*. **12**: CD006726. doi:10.1002/14651858.CD006726.pub2. PMID 23235632. Lay summary – *Pubmed Health (plain English)*.
132. ^ *a b* Jeffries FW, Davis P; Davis, P. (May 2013). "What is the role of eye movements in eye movement desensitization and reprocessing (EMDR) for post-traumatic stress disorder (PTSD)? a review". *Behavioural and cognitive psychotherapy*. **41** (3): 290–300. doi:10.1017/S1352465812000793. PMID 23102050.
133. ^ *a b c d e f* Jonas, D. E.; Cusack, K.; Forneris, C. A. (April 2013). "Psychological and pharmacological treatments for adults with posttraumatic stress disorder (PTSD)". Comparative Effectiveness Reviews. Rockville, MD: US Agency for Healthcare Quality and Research. PMID 23658937. Lay summary – *Pubmed Health (plain English)*.
134. ^ Weissman, M. M.; Markowitz, J. C.; Klerman, G. L. (2007). *Clinician's Quick Guide to Interpersonal Psychotherapy*. New York: Oxford University Press.[*page needed*]
135. ^ Bleiberg KL, Markowitz JC (January 2005). "A pilot study of interpersonal psychotherapy for posttraumatic stress disorder". *Am J Psychiatry*. **162** (1): 181–3. doi:10.1176/appi.ajp.162.1.181. PMID 15625219.
136. ^ "Trauma and PTSD Program – Columbia University Department of Psychiatry". Columbiatrauma.org. Retrieved 2014-01-29.[*full citation needed*]
137. ^ Markowitz JC, Milrod B, Bleiberg K, Marshall RD (March 2009). "Interpersonal factors in understanding and treating posttraumatic stress disorder". *J Psychiatr Pract*. **15** (2): 133–40. doi:10.1097/01.pra.0000348366.34419.28. PMC 2852131. PMID 19339847.
138. ^ Markowitz JC (October 2010). "IPT and PTSD". *Depress Anxiety*. **27** (10): 879–81. doi:10.1002/da.20752. PMC 3683871. PMID 20886608.
139. ^ Krystal JH, Neumeister A; Alexander, Neumeister (2009). "Noradrenergic and serotonergic mechansims in the neurobiology of posttraumatic stress disorder and resilience". *Brain Research*. **1293**: 13–23.

doi:10.1016/j.brainres.2009.03.044. PMC 2761677. PMID 19332037.

140. ^ a b Jeffreys, Matthew; Capehart, Bruce; Friedman, Matthew J. (2012). "Pharmacotherapy for posttraumatic stress disorder: Review with clinical applications" (PDF). *The Journal of Rehabilitation Research and Development*. **49** (5): 703–15. doi:10.1682/JRRD.2011.09.0183. PMID 23015581. Retrieved 26 November 2015. "While evidence-based, trauma-focused psychotherapy is the preferred treatment for PTSD, pharmacotherapy is also an important treatment option. First-line pharmacotherapy agents include selective serotonin reuptake inhibitors and the selective serotonin-norepinephrine reuptake inhibitor venlafaxine."
141. ^ Puetz, T W; Youngstedt, S D; Herring, M P (28 May 2015). Hashimoto, K, ed. "Effects of Pharmacotherapy on Combat-Related PTSD, Anxiety, and Depression: A Systematic Review and Meta-Regression Analysis". *PLOS ONE*. **10** (5): e0126529. doi:10.1371/journal.pone.0126529. PMC 4447407. PMID 26020791. Retrieved 26 November 2015. "The cumulative evidence summarized in this review indicates that pharmacotherapy significantly reduces PTSD, anxiety, and depressive symptom severity among combat veterans with PTSD. The magnitude of the overall effects of pharmacotherapy on PTSD (Δ = 0.38), anxiety (Δ = 0.42), and depressive symptoms (Δ = 0.52) were moderate..."
142. ^ Kapfhammer, Hans-Peter (2014). "Patient-reported outcomes in post-traumatic stress disorder Part II: Focus on pharmacological treatment" (PDF). *Dialogues in Clinical Neuroscience* (in English, Spanish, and French). **16** (2): 227–237. PMC 4140515. PMID 25152660.
143. ^ a b Berger W, Mendlowicz MV, Marques-Portella C, Kinrys G, Fontenelle LF, Marmar CR, Figueira I (Mar 2009). "Pharmacologic alternatives to antidepressants in posttraumatic stress disorder: a systematic review". *Prog Neuropsychopharmacol Biol Psychiatry*. **33** (2): 169–80. doi:10.1016/j.pnpbp.2008.12.004. PMC 2720612. PMID 19141307.
144. ^ Jain S, Greenbaum MA, Rosen C (February 2012). "Concordance between psychotropic prescribing for veterans with PTSD and clinical practice guidelines". *Psychiatr Serv*. **63** (2): 154–60. doi:10.1176/appi.ps.201100199. PMID 22302333.
145. ^ Auxéméry Y (October 2012). "[Posttraumatic stress disorder (PTSD) as a consequence of the interaction between an individual genetic susceptibility, a traumatogenic event and a social context]". *Encephale* (in French). **38** (5): 373–80. doi:10.1016/j.encep.2011.12.003. PMID 23062450.
146. ^ Kapfhammer HP (December 2008). "[Therapeutic possibilities after traumatic experiences]". *Psychiatr Danub*. **20** (4): 532–45. PMID 19011595.
147. ^ Reist, C (2005). Post-traumatic Stress Disorder. Compendia, Build ID: F000005, published by Epocrates.com
148. ^ Maxmen, J. S.; Ward, N. G. (2002). *Psychotropic drugs: fast facts* (3rd ed.). New York: W. W. Norton. p. 349. ISBN 0-393-70301-0.
149. ^ Marténvi F (Mar 2005). "[Three paradigms in the treatment of posttraumatic stress disorder]". *Neuropsychopharmacol Hung*. **7** (1): 11–21. PMID 16167463.
150. ^ a b *Veterans Affairs and Department of Defense clinical practice guideline for management of post-traumatic stress*. VA/DoD. 2010.
151. ^ Bandelow, Borwin; Zohar, Joseph; Hollander, Eric; Kasper, Siegfried; Möller, Hans-Jürgen; Zohar, Joseph; Hollander, Eric; Kasper, Siegfried (2008-01-01). "World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision". *The World Journal of Biological Psychiatry*. **9** (4): 248–312. doi:10.1080/15622970802465807. ISSN 1562-2975. PMID 18949648. Missing | last6= in Authors list (help)
152. ^ Griffin, GD; Charron, D; Al-Daccak, R (November 2014). "Post-traumatic stress disorder: revisiting adrenergics, glucocorticoids, immune system effects and homeostasis.". *Clinical & translational immunology*. **3** (11): e27. doi:10.1038/cti.2014.26. PMID 25505957.
153. ^ Blessing EM, Steenkamp MM, Manzanares J, Marmar CR (2015). "Cannabidiol as a Potential Treatment for Anxiety Disorders". *Neurotherapeutics* (Review). **12** (4): 825–36. doi:10.1007/s13311-015-0387-1. PMC 4604171. PMID 26341731.
154. ^ Yarnell S (2015). "The Use of Medicinal Marijuana for Posttraumatic Stress Disorder: A Review of the Current Literature". *Prim Care Companion CNS Disord* (Review). **17** (3). doi:10.4088/PCC.15r01786. PMC 4578915. PMID 26644963.
155. ^ Betthauser K, Pilz J, Vollmer LE (2015). "Use and effects of cannabinoids in military veterans with posttraumatic stress disorder". *Am J Health Syst Pharm* (Review). **72** (15): 1279–84. doi:10.2146/ajhp140523. PMID 26195653.
156. ^ Canadian Agency for Drugs and Technologies in Health (Oct 2015). "Long-term Nabilone Use: A Review of the Clinical Effectiveness and Safety". *CADTH Rapid Response Reports*. PMID 26561692. Retrieved 19 November 2015.
157. ^ Gregg, K (2016-07-13). Providence Journal http://www.providencejournal.com/news/20160713/raimondo-signs-law-allowing-marijuana-for-treatment-of-ptsd. Retrieved 18 August 2016. Missing or empty | title= (help)

158. ^ Lawrence, Sue; De Silva, M; Henley, R (2010). Lawrence, Sue, ed. "Sports and games for post-traumatic stress disorder (PTSD)". *Cochrane Database of Systematic Reviews* (1). doi:10.1002/14651858.CD007171.pub2.
159. ^ Jankowski, K. "PTSD and physical health". *Information on trauma and PTSD for professionals, National Center for PTSD*. U.S. Department of Veterans Affairs. Retrieved 8 June 2013.[*dead link*]
160. ^ U.S. Department of Veterans Affairs. "Lifestyle Changes Recommended for PTSD Patients". *Information on trauma and PTSD for veterans, general public and family from the National Center for PTSD*. U.S. Department of Veterans Affairs. Retrieved 8 June 2013.[*dead link*]
161. ^ *a b* Wethington HR, Hahn RA, Fuqua-Whitley DS, Sipe TA, Crosby AE, Johnson RL, Liberman AM, Mościcki E, Price LN, Tuma FK, Kalra G, Chattopadhyay SK (31 August 2008). "The Effectiveness of Interventions to Reduce Psychological Harm from Traumatic Events Among Children and Adolescents". *American Journal of Preventive Medicine*. **35** (3): 287–313. doi:10.1016/j.amepre.2008.06.024. PMID 18692745.
162. ^ Fletcher, K. E.; Barkley, Russell A. (2003). "7". In Mash, Eric J. *Child psychopathology* (2nd ed.). New York: Guilford Press. pp. 330–371. ISBN 1-57230-609-2.
163. ^ "Marine Corps Offers Yoga, Massages to Marriages Strained by War". Fox News Channel. Associated Press. 2008-04-02. Retrieved 2008-04-03.
164. ^ "Mortality and Burden of Disease Estimates for WHO Member States in 2004". *World Health Organization*.
165. ^ Brunet A, Akerib V, Birmes P (2007). "Don't throw out the baby with the bathwater (PTSD is not overdiagnosed)" (PDF). *Can J Psychiatry*. **52** (8): 501–2; discussion 503. PMID 17955912. Retrieved 2008-03-12.
166. ^ *a b* "Mortality and Burden of Disease Estimates for WHO Member States: Persons, all ages (2004)" (xls). *World Health Organization*. 2004. Retrieved 2009-11-12.
167. ^ *a b* "Mortality and Burden of Disease Estimates for WHO Member States: Females, all ages (2004)" (xls). *World Health Organization*. 2004. Retrieved 2009-11-12.
168. ^ *a b* "Mortality and Burden of Disease Estimates for WHO Member States: Males, all ages (2004)" (xls). *World Health Organization*. 2004. Retrieved 2009-11-12.
169. ^ Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB (December 1995). "Posttraumatic stress disorder in the National Comorbidity Survey". *Arch Gen Psychiatry*. **52** (12): 1048–60. doi:10.1001/archpsyc.1995.03950240066012. PMID 7492257.
170. ^ Sher, Leo (2010). "Neurobiology of suicidal behavior in post-traumatic stress disorder". *Expert Reviews*. **10** (8): 1233–1235. doi:10.1586/ern.10.114. PMID 20662745.
171. ^ Mintz, S. (2007). "The War's Costs". *Digital History*. Archived from the original on 2003-09-07.
172. ^ Price, Jennifer L. "Findings from the National Vietnam Veterans' Readjustment Study – Factsheet". *United States Department of Veterans Affairs*. National Center for PTSD. Archived from the original on 2009-04-30.
173. ^ "Psychological Costs of War: Military Combat and Mental Health". Journalistsresource.org. Retrieved 2014-01-29.
174. ^ Meade, Barbara J.; Glenn, Margaret K.; Wirth, Oliver (March 29, 2013). "Mission Critical: Getting Vets With PTSD Back to Work". *NIOSH: Workplace Safety and Health*. Medscape & NIOSH.
175. ^ Dixon, Laura (February 28, 2009). "Lance Corporal Johnson Beharry accuses Government of neglecting soldiers". *The Times*. London. Retrieved 2009-08-29. (subscription required)
176. ^ "UK | Full interview: L/Cpl Johnson Beharry". BBC News. 2009-02-28. Archived from the original on 2014-02-19. Retrieved 2009-08-29.
177. ^ "The Operational Stress Injury Social Support (OSISS) Program for Canadian Veterans". See also "Evaluation of the OSISS Peer Support Network" (PDF). Dept. of National Defence and Veterans Affairs Canada. January 2005.
178. ^ Heber, A.; Grenier, S.; Richardson, D.; Darte, K. (2006). "Combining Clinical Treatment and Peer Support: A Unique Approach to Overcoming Stigma and Delivering Care" (PDF). *Human Dimensions in Military Operations – Military Leaders' Strategies for Addressing Stress and Psychological Support*. Neuilly-sur-Seine, France: Canadian Department Of National Defence. Retrieved 2014-01-30.
179. ^ J Don Richardson; Kathy Darte; Stéphane Grenier; Allan English; Joe Sharpe (2008). "Operational Stress Injury Social Support: a Canadian innovation in professional peer support". *Canadian Military Journal*. **9** (1): 57–64. Retrieved 2014-01-30.
180. ^ "The New Veterans Charter for CF Veterans and their Families". Vac-Acc.Gc.Ca. 2006-07-12. Archived from the original on 2006-06-19. Retrieved 2009-08-29.
181. ^ *a b* Andreasen, Nancy C. (2010). "Posttraumatic stress disorder: a history and a critique". *Annals of the New York Academy of Sciences*. **1208** (Psychiatric and Neurologic Aspects of War): 67–71. doi:10.1111/j.1749-6632.2010.05699.x.
182. ^ *a b* American Psychiatric Association (1952). *Diagnostic and Statistical Manual*. American Psychiatric Association Mental Hospital Service. p. 326.3. ISBN 978-0890420171.

183. ^ [a] [b] Shalev, Arieh Y.; Yehuda, Rachel; Alexander C. McFarlane (2000). *International handbook of human response to trauma*. New York: Kluwer Academic/Plenum Press. ISBN 0-306-46095-5.[*page needed*];on-line.
184. ^ "International Statistical Classification of Diseases and Related Health Problems 10th Revision Version for 2007". World Health Organization (UN). 2007. Retrieved October 3, 2011.
185. ^ "When trauma tips you over: PTSD Part 1". All in the Mind. Australian Broadcasting Commission. 9 October 2004.
186. ^ Andreasen, Nancy C. (Feb 19, 2004). *Brave New Brain: Conquering Mental Illness in the Era of the Genome*. New York: Oxford University Press. p. 303. ISBN 978-0-19-516728-3.
187. ^ Jones, Joshua A. 2013, VOL. 5 NO. 02 pp. 1-3. "Nostalgia to Post-Traumatic Stress Disorder: A Mass Society Theory of Psychological Reactions to Combat" *The International Student Journal*
188. ^ "Henry IV, Part I, Act II, Scene 3 : |: Open Source Shakespeare". Opensourceshakespeare.org. Retrieved 2014-01-30.
189. ^ Shay, Jonathan (1994). *Achilles in Vietnam: Combat Trauma and the Undoing of Character*. Scribner. pp. 165–66.
190. ^ World War One – A New Kind of War | Part II, From *14 – 18 Understanding the Great War*, by Stéphane Audoin-Rouzeau, Annette Becker[*incomplete short citation*]
191. ^ Möbius, Sascha (2015). "Im Kugelhagel der Musketen". *Damals* (in German). Vol. 47 no. 12. pp. 64–69.
192. ^ "Civilian PTSD Symptoms and Risk for Involvement in the Criminal Justice System". *Journal of the Academy of Psychiatry and the Law*. **40** (4): 522–529. 2012-12-01. ISSN 1093-6793. Retrieved 2014-11-29.
193. ^ Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB (December 1995). "Posttraumatic Stress Disorder in the National Comorbidity Survey". *Arch Gen Psychiatry*. **52** (12): 1048–1060. doi:10.1001/archpsyc.1995.03950240066012. PMID 7492257. Retrieved 2014-11-29.
194. ^ Holmstrom, Lynda Lyttle; Burgess, Ann Wolbert. *The Victim of Rape: Institutional Reactions*. Wiley-Interscience. ISBN 0471407852.
195. ^ "Search results: 'post-traumatic stress disorder' in the title of a journal article". *PubMed*. U.S. National Library of Medicine. Retrieved 21 January 2015.
196. ^ "PTSD". *TheFreeDictionary.com*. Farlex, Inc. Retrieved 21 January 2015.
197. ^ Fodor; et al. (2014). "Is traumatic stress research global? A bibliometric analysis". *European Journal of Psychotraumatology*. **5**. doi:10.3402/ejpt.v5.23269. Retrieved 1 August 2016.
198. ^ [a] [b] Ojo, J; Greenberg, M (December 2014). "Neurobehavioral, neuropathological and biochemical profiles in a novel mouse model of co-morbid post-traumatic stress disorder and mild traumatic brain injury". *Front Behav Neurosci*. **8**: 213. doi:10.3389/fnbeh.2014.00213. PMID 25002839.
199. ^ Poulos, AM; Reger, M (August 2014). "Amnesia for early life stress does not preclude the adult development of posttraumatic stress disorder symptoms in rats.". *Biol Psychiatry*. **15** (76): 306–14. doi:10.1016/j.biopsych.2013.10.007. PMID 24231200.
200. ^ Emerson A, Ponté L, Jerome L, Doblin R (2014). "History and future of the Multidisciplinary Association for Psychedelic Studies (MAPS)". *J Psychoactive Drugs*. **46** (1): 27–36. doi:10.1080/02791072.2014.877321. PMID 24830183.
201. ^ "A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder" (PDF). Multidisciplinary Association for Psychedelic Studies. 4 January 2013. Archived (PDF) from the original on 2014-06-23. Retrieved 31 May 2014.
202. ^ White, C. Michael (16 April 2014). "3,4-Methylenedioxymethamphetamine's (MDMA's) Impact on Posttraumatic Stress Disorder" (PDF). *Annals of Pharmacotherapy*. **48**: 908–915. doi:10.1177/1060028014532236.
203. ^ [a] [b] de Kleine RA, Rothbaum BO, van Minnen A (17 Oct 2014). "Pharmacological enhancement of exposure-based treatment in PTSD: a qualitative review" (PDF). *Eur J Psychotraumatology*. **4**. doi:10.3402/ejpt.v4i0.21626. PMC 3800126. PMID 24147208.


# External links

- Posttraumatic stress disorder at DMOZ
- Resources for the public from VA National PTSD Center
- Resources for professionals from VA National PTSD Center
- Post Traumatic Stress Disorder Information Resource from The University of Queensland School of Medicine
- Resources for Parents of Children with PTSD from The Children's Hospital of Philadelphia
- AACAP practice parameters for assessment and treatment for PTSD

| v · t · e · | **Mental and behavioral disorders (F 290–319)** |
|---|---|
| **Neurological/symptomatic** | |
| **Dementia** | Mild cognitive impairment · Alzheimer's disease · Vascular dementia · Pick's disease · Creutzfeldt–Jakob disease · Huntington's disease · Parkinson's disease · AIDS dementia complex · Frontotemporal dementia · Sundowning · Wandering · |
| **Autism spectrum** | Autism · Asperger syndrome · Savant syndrome · PDD-NOS · High-functioning autism · |
| **Other** | Delirium · Post-concussion syndrome · Organic brain syndrome · |
| **Psychoactive substances, substance abuse, drug abuse and substance-related disorders** | |
| Intoxication/Drug overdose · Physical dependence · Substance dependence · Rebound effect · Double rebound · Withdrawal · | |
| **Schizophrenia, schizotypal and delusional** | |
| **Psychosis** | Schizoaffective disorder · Schizophreniform disorder · Brief reactive psychosis · |
| **Schizophrenia** | Disorganized schizophrenia · Paranoid schizophrenia · Simple-type schizophrenia · |
| **Delusional disorders** | Delusional disorder · Folie à deux · |
| **Mood (affective)** | |
| Mania · Bipolar disorder · (Bipolar I · Bipolar II · Cyclothymia · Bipolar NOS) · Depression · (Major depressive disorder · Dysthymia · Seasonal affective disorder · Atypical depression · Melancholic depression) · | |
| **Neurotic, stress-related and somatoform** | |
| **Anxiety disorder** — **Phobia** | Agoraphobia · Social anxiety · Social phobia · (Anthropophobia) · Specific phobia · (Claustrophobia) · Specific social phobia · |
| **Anxiety disorder** — **Other** | Panic disorder · Panic attack · Generalized anxiety disorder · OCD · *stress* · (Acute stress reaction · **PTSD**) · |
| **Adjustment disorder** | Adjustment disorder with depressed mood · |
| **Somatic symptom disorder** | Somatization disorder · Body dysmorphic disorder · Hypochondriasis · Nosophobia · Da Costa's syndrome · Psychalgia · Conversion disorder · (Ganser syndrome · Globus pharyngis) · Neurasthenia · Mass psychogenic illness · |
| **Dissociative disorder** | Dissociative identity disorder · Psychogenic amnesia · Fugue state · Depersonalization disorder · |
| **Physiological/physical behavioral** | |
| **Eating disorder** | Anorexia nervosa · Bulimia nervosa · Rumination syndrome · NOS · |
| **Nonorganic sleep disorders** | (Nonorganic hypersomnia · Nonorganic insomnia) · Parasomnia · (REM sleep behavior disorder · Night terror · Nightmare) · |
| **Sexual dysfunction** | *sexual desire* · (Hypoactive sexual desire disorder · Hypersexuality) · *sexual arousal* · (Female sexual arousal disorder) · Erectile dysfunction · *orgasm* · (Anorgasmia · Delayed ejaculation · Premature ejaculation · Sexual anhedonia) · *pain* · (Vaginismus · Dyspareunia) · |
| **Postnatal** | Postpartum depression · Postpartum psychosis · |

| Adult personality and behavior | |
|---|---|
| *Gender dysphoria* | Sexual maturation disorder · Ego-dystonic sexual orientation · Sexual relationship disorder · Paraphilia · (Voyeurism · Fetishism) · |
| **Other** | Personality disorder · Impulse control disorder · (Kleptomania · Trichotillomania · Pyromania · Dermatillomania) · Body-focused repetitive behavior · Factitious disorder · (Münchausen syndrome) · |

| Disorders typically diagnosed in childhood | |
|---|---|
| **Intellectual disability** | X-linked intellectual disability · (Lujan–Fryns syndrome) · |
| **Psychological development (developmental disabilities)** | Specific · Pervasive · Autism spectrum · |
| **Emotional and behavioral** | ADHD · Conduct disorder · (ODD) · Emotional/behavioral disorder · (Separation anxiety disorder) · *social functioning* · (Selective mutism · RAD · DAD) · Tic disorder · (Tourette syndrome) · *Speech* · (Stuttering · Cluttering) · Movement disorder · (Stereotypic) · |

| Symptoms and uncategorized |
|---|
| Catatonia · False pregnancy · Intermittent explosive disorder · Psychomotor agitation · Stereotypy · Psychogenic non-epileptic seizures · Klüver–Bucy syndrome · |

| v · t · e · | Trauma | |
|---|---|---|
| **Principles** | Polytrauma · Major trauma · Traumatology · Triage · Resuscitation · Trauma triad of death · | |
| **Assessment** | **Clinical prediction rules** | Revised Trauma Score · Injury Severity Score · Abbreviated Injury Scale · NACA score · |
| | **Investigations** | Diagnostic peritoneal lavage · Focused assessment with sonography for trauma · |
| **Management** | **Principles** | Advanced trauma life support · Trauma surgery · Trauma center · Trauma team · Damage control surgery · Early appropriate care · |
| | **Procedures** | Resuscitative thoracotomy · |
| **Pathophysiology** | **Injury** | MSK (Bone fracture · Joint dislocation · Degloving · Soft tissue injury · · Resp (Flail chest · Pneumothorax · Hemothorax · Diaphragmatic rupture · Pulmonary contusion · · Cardio (Internal bleeding · Thoracic aorta injury · Cardiac tamponade · · GI (Blunt kidney trauma · Ruptured spleen · · Neuro (Penetrating head injury · Traumatic brain injury · Intracranial hemorrhage · · |
| | **Mechanism** | Blast injury · Blunt trauma · Burn · Penetrating trauma · Crush injury · Stab wound · Ballistic trauma · Electrocution · |
| | **Region** | Abdominal trauma · Chest trauma · Facial trauma · Head injury · Spinal cord injury · |
| | **Demographic** | Geriatric trauma · Pediatric trauma · |
| **Complications** | **Posttraumatic stress disorder** · Wound healing · Acute lung injury · Crush syndrome (Rhabdomyolysis · · Compartment syndrome · Contracture (Volkmann's contracture · · Fat embolism · Chronic traumatic encephalopathy · | |
| **Authority control** | GND: 4361388-3 · NDL: 01000003 · | |

Categories: Posttraumatic stress disorder | Abnormal psychology | Aftermath of war | Homelessness | Military medicine | Military personnel | Military psychiatry | Military sociology | Military veterans' affairs | Psychiatric diagnosis | Trauma and stressor related disorders

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# Schizophrenia

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*For other uses, see Schizophrenia (disambiguation).*

**Schizophrenia** is a mental disorder characterized by abnormal social behavior and failure to understand what is real.[2] Common symptoms include false beliefs, unclear or confused thinking, hearing voices that others do not, reduced social engagement and emotional expression, and a lack of motivation.[2][3] People with schizophrenia often have additional mental health problems such as anxiety disorders, major depressive illness, or substance use disorders.[4] Symptoms typically come on gradually, begin in young adulthood, and last a long time.[3][5]

The causes of schizophrenia include environmental and genetic factors.[6] Possible environmental factors include being raised in a city, cannabis use, certain infections, parental age, and poor nutrition during pregnancy.[6][7] Genetic factors include a variety of common and rare genetic variants.[8] Diagnosis is based on observed behavior, the person's reported experiences, and reports of others familiar with the person.[5] During diagnosis a person's culture must also be taken into account.[5] As of 2013 there is no objective test.[5] Schizophrenia does not imply a "split personality" or "multiple personality disorder" — conditions with which it is often confused in public perception.[9]

The mainstay of treatment is antipsychotic medication, along with counselling, job training, and social rehabilitation.[2][6] It is unclear whether typical or atypical antipsychotics are better.[10] In those who do not improve with other antipsychotics clozapine may be tried.[6] In more serious situations—where there is risk to self or others—involuntary hospitalization may be necessary, although hospital stays are now shorter and less frequent than they once

**Schizophrenia**

Self-portrait of a person with schizophrenia, representing that individual's perception of the distorted experience of reality in the disorder

**Pronunciation** /ˌskɪtsəˈfriːniə, ˌskɪdz-, -oʊ-, -ˈfrɛniə/[1]

| Classification and external resources | |
|---|---|
| **Specialty** | Psychiatry |
| **ICD-10** | F20 |
| **ICD-9-CM** | 295 |
| **OMIM** | 181500 |
| **DiseasesDB** | 11890 |
| **MedlinePlus** | 000928 |
| **eMedicine** | med/2072 emerg/520 |
| **Patient UK** | Schizophrenia |

| | |
|---|---|
| **MeSH** | *F03.700.750* |

[edit on Wikidata]

About 0.3–0.7% of people are affected by schizophrenia during their lifetimes.[12] In 2013 there were estimated to be 23.6 million cases globally.[13] Males are more often affected than females.[2] About 20% of people do well, and a few recover completely.[5] Social problems, such as long-term unemployment, poverty, and homelessness are common.[5][14] The average life expectancy of people with the disorder is ten to twenty-five years less than for the general population.[15] This is the result of increased physical health problems and a higher suicide rate (about 5%).[12][16] In 2013 an estimated 16,000 people worldwide died from behavior related to, or caused by, schizophrenia.[17]

**Contents**




Play media

Video explanation of schizophrenia

# Symptoms

*See also: Basic symptoms of schizophrenia*

Individuals with schizophrenia may experience hallucinations (most reported are hearing voices), delusions (often bizarre or persecutory in nature), and disorganized thinking and speech. The last may range from loss of train of thought, to sentences only loosely connected in meaning, to speech that is not understandable known as word salad. Social withdrawal, sloppiness of dress and hygiene, and loss of motivation and judgment are all common in schizophrenia.[18] Distortions of self-experience such as feeling as if one's thoughts or feelings are not really one's own to believing thoughts are being inserted into one's mind, sometimes termed passivity phenomena, are also common.[19] There is often an observable pattern of emotional difficulty, for example lack of [20]

*My Eyes at the Moment of the Apparitions* by German artist

responsiveness. Impairment in social cognition is associated with schizophrenia,[21] as are symptoms of paranoia. Social isolation commonly occurs.[22] Difficulties in working and long-term memory, attention, executive functioning, and speed of processing also commonly occur.[12] In one uncommon subtype, the person may be largely mute, remain motionless in bizarre postures, or exhibit purposeless agitation, all signs of catatonia.[23] About 30 to 50 percent of people with schizophrenia fail to accept that they have an illness or comply with their recommended treatment.[24] Treatment may have some effect on insight.[25] People with schizophrenia often find facial emotion perception to be difficult.[26]

People with schizophrenia may have a high rate of irritable bowel syndrome but they often do not mention it unless specifically asked.[27]

August Natterer, who had schizophrenia

Cloth embroidered by a person diagnosed with schizophrenia

## Positive and negative

Schizophrenia is often described in terms of positive and negative (or deficit) symptoms.[28] *Positive symptoms* are those that most individuals do not normally experience, but are present in people with schizophrenia. They can include delusions, disordered thoughts and speech, and tactile, auditory, visual, olfactory and gustatory hallucinations, typically regarded as manifestations of psychosis.[29] Hallucinations are also typically related to the content of the delusional theme.[30] Positive symptoms generally respond well to medication.[30]

*Negative symptoms* are deficits of normal emotional responses or of other thought processes, and are less responsive to medication.[18] They commonly include flat expressions or little emotion, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and lack of motivation. Negative symptoms appear to contribute more to poor quality of life, functional ability, and the burden on others than positive symptoms do.[31] People with greater negative symptoms often have a history of poor adjustment before the onset of illness, and response to medication is often limited.[18][32]

## Cognitive dysfunction

Deficits in cognitive abilities are widely recognized as a core feature of schizophrenia.[33][34][35] The extent of the cognitive deficits an individual experiences is a predictor of how functional an individual will be, the quality of occupational performance, and how successful the individual will be in maintaining treatment.[36] The presence and degree of cognitive dysfunction in individuals with schizophrenia has been reported to be a better indicator of functionality than the presentation of positive or negative symptoms.[33] The deficits impacting the cognitive function are found in a large number of areas: working memory, long-term memory,[37][38] verbal declarative memory,[39] semantic processing,[40] episodic memory,[36] attention, learning (particularly verbal learning).[37] Deficits in verbal memory are the most pronounced in individuals with schizophrenia, and are not accounted for by deficit in attention. Verbal memory impairment has been linked to a decreased ability in individuals with schizophrenia to semantically encode (process information relating to meaning), which is cited as a cause for another known deficit in long-term memory.[37] When given a list of words, healthy individuals remember positive words more frequently (known as the Pollyanna principle); however, individuals with schizophrenia tend to remember all words equally regardless of their connotations, suggesting that the experience of anhedonia impairs the semantic encoding of the words.[37] These deficits have been found in individuals before the onset of the illness to some extent.[33][35][41] First-degree family members of individuals with schizophrenia and other high-risk individuals also show a degree of deficit in cognitive abilities, and specifically in working memory.[41] A review of the literature on cognitive deficits in individuals with schizophrenia shows that the deficits may be present in early adolescence, or as early as childhood.[33] The deficits which an individual with schizophrenia presents tend to remain the same over time in most patients, or follow an identifiable course based upon environmental variables.[33][37]

Although the evidence that cognitive deficits remain stable over time is reliable and abundant,[36][37] much of the research in this domain focuses on methods to improve attention and working memory.[37][38] Efforts to improve learning ability in individuals with schizophrenia using a high- versus low-reward condition and an instruction-absent or instruction-present condition revealed that increasing reward leads to poorer performance while providing instruction leads to improved performance, highlighting that some treatments may exist to increase cognitive performance.[37] Training individuals with schizophrenia to alter their thinking, attention, and language behaviors by verbalizing tasks, engaging in cognitive rehearsal, giving self-instructions, giving coping statements to the self to handle failure, and providing self-reinforcement for success, significantly improves performance on recall tasks.[37] This type of training, known as self-instructional (SI) training, produced benefits such as lower number of nonsense verbalizations and improved recall while distracted.[37]

### Onset

*See also: Schizophrenia in children*

Late adolescence and early adulthood are peak periods for the onset of schizophrenia,[12] critical years in a young adult's social and vocational development.[42] In 40% of men and 23% of women diagnosed with schizophrenia, the condition manifested itself before the age of 19.[43] To minimize the developmental disruption associated with schizophrenia, much work has recently been done to identify and treat the prodromal (pre-onset) phase of the illness, which has been detected up to 30 months before the onset of symptoms.[42] Those who go on to develop schizophrenia may experience transient or self-limiting psychotic symptoms[44] and the non-specific symptoms of social withdrawal, irritability, dysphoria,[45] and clumsiness[46] during the prodromal phase.

## Causes

*Main article: Causes of schizophrenia*

A combination of genetic and environmental factors play a role in the development of schizophrenia.[9][12] People with a family history of schizophrenia who have a transient psychosis have a 20–40% chance of being diagnosed one year later.[47]

### Genetic

Estimates of heritability vary because of the difficulty in separating genetic and environmental influences;[48] averages of 0.80 have been given.[49] The greatest single risk factor for developing schizophrenia is having a first-degree relative with the disease (risk is 6.5%); more than 40% of monozygotic twins of those with schizophrenia are also affected.[9] If one parent is affected the risk is about 13% and if both are affected the risk is nearly 50%.[49]

Many genes are believed to be involved in schizophrenia, each of small effect and unknown transmission and expression.[8][9] Many possible candidates have been proposed, including specific copy number variations, *NOTCH4*, and histone protein loci.[50] A number of genome-wide associations such as zinc finger protein 804A have also been linked.[51] There appears to be overlap in the genetics of schizophrenia and bipolar disorder.[52] Evidence is emerging that the genetic architecture of schizophrenia involved both common and rare risk variation.[53]

Assuming a hereditary basis, one question from evolutionary psychology is why genes that *increase* the likelihood of psychosis evolved, assuming the condition would have been maladaptive from an evolutionary point of view. One idea is that genes are involved in the evolution of language and human nature, but to date such ideas remain little more than hypothetical in nature.[54][55]

### Environment

Environmental factors associated with the development of schizophrenia include the living environment, drug use, and prenatal stressors.[12]

Parenting style seems to have no major effect, although people with supportive parents do better than those with critical or hostile parents.[9] Childhood trauma, death of a parent, and being bullied or abused increase the risk of psychosis.[56] Living in an urban environment during childhood or as an adult has consistently been found to increase the risk of schizophrenia by a factor of two,[9][12] even after taking into account drug use, ethnic group, and size of social group.[57] Other factors that play an important role include social isolation and immigration related to social adversity, racial discrimination, family dysfunction, unemployment, and poor housing conditions.[9][58]

It has been hypothesized that in some people, development of schizophrenia is related to intestinal tract dysfunction such as seen with non-celiac gluten sensitivity or abnormalities in the intestinal flora.[59] A subgroup of persons with schizophrenia present an immune response to gluten different from that found in people with celiac, with elevated levels of certain serum biomarkers of gluten sensitivity such as anti-gliadin IgG or anti-gliadin IgA antibodies.[60]

### Substance use

About half of those with schizophrenia use drugs or alcohol excessively.[61] Amphetamine, cocaine, and to a lesser extent alcohol, can result in a transient stimulant psychosis or alcohol-related psychosis that presents very similarly to schizophrenia.[9][62] Although it is not generally believed to be a cause of the illness, people with schizophrenia use nicotine at much higher rates than the general population.[63]

Alcohol abuse can occasionally cause the development of a chronic, substance-induced psychotic disorder via a kindling mechanism.[64] Alcohol use is not associated with an earlier onset of psychosis.[65]

Cannabis can be a contributory factor in schizophrenia,[7][66][67] potentially causing the disease in those who are already at risk.[67] The increased risk may require the presence of certain genes within an individual[67] or may be related to preexisting psychopathology.[7] Early exposure is strongly associated with an increased risk.[7] The size of the increased risk is not clear,[68] but appears to be in the range of two to three times greater for psychosis.[66] Higher dosage and greater frequency of use are indicators of increased risk of chronic psychoses.[66]

Other drugs may be used only as coping mechanisms by individuals who have schizophrenia, to deal with depression, anxiety, boredom, and loneliness.[61][69]

### Developmental factors

Factors such as hypoxia and infection, or stress and malnutrition in the mother during fetal development, may result in a slight increase in the risk of schizophrenia later in life.[12] People diagnosed with schizophrenia are more likely to have been born in winter or spring (at least in the northern hemisphere), which may be a result of increased rates of viral exposures in utero.[9] The increased risk is about five to eight percent.[70] Other infections during pregnancy or around the time of birth that may increase the risk include *Toxoplasma gondi* and *Chlamydia*.[71]

## Mechanisms

*Main article: Mechanisms of schizophrenia*

A number of attempts have been made to explain the link between altered brain function and schizophrenia.[12] One of the most common is the dopamine hypothesis, which attributes psychosis to the mind's faulty interpretation of the misfiring of dopaminergic neurons.[12]

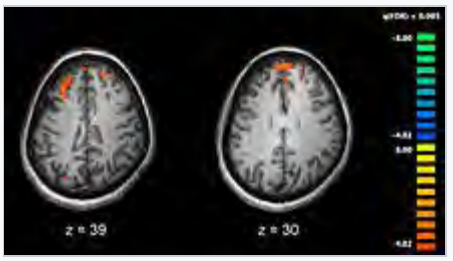
## Psychological

Many psychological mechanisms have been implicated in the development and maintenance of schizophrenia. Cognitive biases have been identified in those with the diagnosis or those at risk, especially when under stress or in confusing situations.[72] Some cognitive features may reflect global neurocognitive deficits such as memory loss, while others may be related to particular issues and experiences.[73][74]

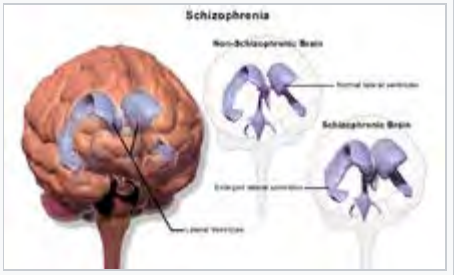
Despite a demonstrated appearance of blunted affect, recent findings indicate that many individuals diagnosed with schizophrenia are emotionally responsive, particularly to stressful or negative stimuli, and that such sensitivity may cause vulnerability to symptoms or to the disorder.[75][76] Some evidence suggests that the content of delusional beliefs and psychotic experiences can reflect emotional causes of the disorder, and that how a person interprets such experiences can influence symptomatology.[77][78][79] The use of "safety behaviors" (acts such as gestures or the use of words in specific contexts) to avoid or neutralize imagined threats may actually contribute to the chronicity of delusions.[80] Further evidence for the role of psychological mechanisms comes from the effects of psychotherapies on symptoms of schizophrenia.[81]

## Neurological

Schizophrenia is associated with subtle differences in brain structures, found in forty to fifty percent of cases, and in brain chemistry during acute psychotic states.[12] Studies using neuropsychological tests and brain imaging technologies such as fMRI and PET to examine functional differences in brain activity have shown that differences seem to occur most commonly in the frontal lobes, hippocampus and temporal lobes.[83] Reductions in brain volume, smaller than those found in Alzheimer's disease, have been reported in areas of the frontal cortex and temporal lobes. It is uncertain whether these volumetric changes are progressive or exist prior to the onset of the disease.[46] These differences have been linked to the neurocognitive deficits often associated with schizophrenia.[84] Because neural circuits are altered, it has alternatively been suggested that schizophrenia should be thought of as a collection of neurodevelopmental disorders.[85] There has been debate on whether treatment with antipsychotics can itself cause reduction of brain volume.[86]



Functional magnetic resonance imaging (fMRI) showing two levels of the brain; areas in orange were more active in healthy controls than in medicated people with schizophrenia.



People with schizophrenia who are medication compliant have an association with enlarged lateral ventricles in the brain.[82]

Particular attention has been paid to the function of dopamine in the mesolimbic pathway of the brain. This focus largely resulted from the accidental finding that phenothiazine drugs, which block dopamine function, could reduce psychotic symptoms. It is also supported by the fact that amphetamines, which trigger the release of dopamine, may exacerbate the psychotic symptoms in schizophrenia.[87] The influential dopamine hypothesis of schizophrenia proposed that excessive activation of $D_2$ receptors was the cause of (the positive symptoms of) schizophrenia. Although postulated for about 20 years based on the $D_2$ blockade effect common to all antipsychotics, it was not until the mid-1990s that PET and SPET imaging studies provided supporting evidence. The dopamine hypothesis is now thought to be simplistic, partly because newer antipsychotic medication (atypical antipsychotic medication) can be just as effective as older medication (typical antipsychotic medication), but also affects serotonin function and may have slightly less of a dopamine blocking effect.[88]

Interest has also focused on the neurotransmitter glutamate and the reduced function of the NMDA glutamate receptor in schizophrenia, largely because of the abnormally low levels of glutamate receptors [89]

found in the postmortem brains of those diagnosed with schizophrenia, and the discovery that glutamate-blocking drugs such as phencyclidine and ketamine can mimic the symptoms and cognitive problems associated with the condition.[90] Reduced glutamate function is linked to poor performance on tests requiring frontal lobe and hippocampal function, and glutamate can affect dopamine function, both of which have been implicated in schizophrenia; this has suggested an important mediating (and possibly causal) role of glutamate pathways in the condition.[91] But positive symptoms fail to respond to glutamatergic medication.[92]

# Diagnosis

*Main article: Diagnosis of schizophrenia*

Schizophrenia is diagnosed based on criteria in either the American Psychiatric Association's fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM 5), or the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD-10). These criteria use the self-reported experiences of the person and reported abnormalities in behavior, followed by a clinical assessment by a mental health professional. Symptoms associated with schizophrenia occur along a continuum in the population and must reach a certain severity before a diagnosis is made.[9] As of 2013 there is no objective test.[5]

## Criteria

In 2013, the American Psychiatric Association released the fifth edition of the DSM (DSM-5). To be diagnosed with schizophrenia, two diagnostic criteria have to be met over much of the time of a period of at least one month, with a significant impact on social or occupational functioning for at least six months. The person had to be suffering from delusions, hallucinations, or disorganized speech. A second symptom could be negative symptoms, or severely disorganized or catatonic behaviour.[93] The definition of schizophrenia remained essentially the same as that specified by the 2000 version of DSM (DSM-IV-TR), but DSM-5 makes a number of changes.

- Subtype classifications – such as catatonic and paranoid schizophrenia – are removed. These were retained in previous revisions largely for reasons of tradition, but had subsequently proved to be of little worth.[94]
- Catatonia is no longer so strongly associated with schizophrenia.[95]
- In describing a person's schizophrenia, it is recommended that a better distinction be made between the current state of the condition and its historical progress, to achieve a clearer overall characterization.[94]
- Special treatment of Schneider's first-rank symptoms is no longer recommended.[94]
- Schizoaffective disorder is better defined to demarcate it more cleanly from schizophrenia.[94]
- An assessment covering eight domains of psychopathology – such as whether hallucination or mania is experienced – is recommended to help clinical decision-making.[96]

The ICD-10 criteria are typically used in European countries, while the DSM criteria are used in the United States and to varying degrees around the world, and are prevailing in research studies. The ICD-10 criteria put more emphasis on Schneiderian first-rank symptoms. In practice, agreement between the two systems is high.[97] The current proposal for the ICD-11 criteria for schizophrenia recommends adding self-disorder as a symptom.[19]

If signs of disturbance are present for more than a month but less than six months, the diagnosis of schizophreniform disorder is applied. Psychotic symptoms lasting less than a month may be diagnosed as brief psychotic disorder, and various conditions may be classed as psychotic disorder not otherwise specified, while schizoaffective disorder is diagnosed if symptoms of mood disorder are substantially present alongside psychotic symptoms. If the psychotic symptoms are the direct physiological result of a general medical condition or a substance, then the diagnosis is one of a psychosis secondary to that condition.[93] Schizophrenia is not diagnosed if symptoms of pervasive developmental disorder are present unless prominent delusions or hallucinations are also present.[93]

## Subtypes

With the publication of DSM-5, the APA removed all sub-classifications of schizophrenia.[98] The five sub-classifications included in DSM-IV-TR were:[99][100]

- Paranoid type: Delusions or auditory hallucinations are present, but thought disorder, disorganized behavior, or affective flattening are not. Delusions are persecutory and/or grandiose, but in addition to these, other themes such as jealousy, religiosity, or somatization may also be present. (DSM code 295.3/ICD code F20.0)
- Disorganized type: Named *hebephrenic schizophrenia* in the ICD. Where thought disorder and flat affect are present together. (DSM code 295.1/ICD code F20.1)
- Catatonic type: The subject may be almost immobile or exhibit agitated, purposeless movement. Symptoms can include catatonic stupor and waxy flexibility. (DSM code 295.2/ICD code F20.2)
- Undifferentiated type: Psychotic symptoms are present but the criteria for paranoid, disorganized, or catatonic types have not been met. (DSM code 295.9/ICD code F20.3)
- Residual type: Where positive symptoms are present at a low intensity only. (DSM code 295.6/ICD code F20.5)

The ICD-10 defines two additional subtypes:[99]

- Post-schizophrenic depression: A depressive episode arising in the aftermath of a schizophrenic illness where some low-level schizophrenic symptoms may still be present. (ICD code F20.4)
- Simple schizophrenia: Insidious and progressive development of prominent negative symptoms with no history of psychotic episodes. (ICD code F20.6)

Latent schizophrenia (F21.1), schizophrenic reaction (F21.2), pseudoneurotic schizophrenia (F21.3), pseudopsychopathic schizophrenia (F21.4), "symptom-depleted" schizophrenia (F21.5) are in the Russian version of the ICD-10. They are in the category of "schizotypal" disorder in section F21 of chapter V.[101]

## Differential diagnosis

*See also: Dual diagnosis and Comparison of bipolar disorder and schizophrenia*

Psychotic symptoms may be present in several other mental disorders, including bipolar disorder,[102] borderline personality disorder,[103] drug intoxication and drug-induced psychosis. Delusions ("non-bizarre") are also present in delusional disorder, and social withdrawal in social anxiety disorder, avoidant personality disorder and schizotypal personality disorder. Schizotypal personality disorder has symptoms that are similar but less severe than those of schizophrenia.[5] Schizophrenia occurs along with obsessive-compulsive disorder (OCD) considerably more often than could be explained by chance, although it can be difficult to distinguish obsessions that occur in OCD from the delusions of schizophrenia.[104] A few people withdrawing from benzodiazepines experience a severe withdrawal syndrome which may last a long time. It can resemble schizophrenia and be misdiagnosed as such.[105]

A more general medical and neurological examination may be needed to rule out medical illnesses which may rarely produce psychotic schizophrenia-like symptoms, such as metabolic disturbance, systemic infection, syphilis, AIDS dementia complex, epilepsy, limbic encephalitis, and brain lesions. Stroke, multiple sclerosis, hyperthyroidism, hypothyroidism and dementias such as Alzheimer's disease, Huntington's disease, frontotemporal dementia and Lewy Body dementia may also be associated with schizophrenia-like psychotic symptoms.[106] It may be necessary to rule out a delirium, which can be distinguished by visual hallucinations, acute onset and fluctuating level of consciousness, and indicates an underlying medical illness. Investigations are not generally repeated for relapse unless there is a specific *medical* indication or possible adverse effects from antipsychotic medication. In children hallucinations must be separated from typical childhood fantasies.[5]

# Prevention

Prevention of schizophrenia is difficult as there are no reliable markers for the later development of the

disorder.[107] There is tentative evidence for the effectiveness of early interventions to prevent schizophrenia.[108] While there is some evidence that early intervention in those with a psychotic episode may improve short-term outcomes, there is little benefit from these measures after five years.[12] Attempting to prevent schizophrenia in the prodrome phase is of uncertain benefit and therefore as of 2009 is not recommended.[109] Cognitive behavioral therapy may reduce the risk of psychosis in those at high risk after a year[110] and is recommended in this group, by the National Institute for Health and Care Excellence (NICE).[111] Another preventative measure is to avoid drugs that have been associated with development of the disorder, including cannabis, cocaine, and amphetamines.[9]

# Management

*Main article: Management of schizophrenia*

The primary treatment of schizophrenia is antipsychotic medications, often in combination with psychological and social supports.[12] Hospitalization may occur for severe episodes either voluntarily or (if mental health legislation allows it) involuntarily. Long-term hospitalization is uncommon since deinstitutionalization beginning in the 1950s, although it still occurs.[11] Community support services including drop-in centers, visits by members of a community mental health team, supported employment[112] and support groups are common. Some evidence indicates that regular exercise has a positive effect on the physical and mental health of those with schizophrenia.[113]

## Medication


Risperidone (trade name Risperdal) is a common atypical antipsychotic medication.

The first-line psychiatric treatment for schizophrenia is antipsychotic medication,[114] which can reduce the positive symptoms of psychosis in about 7 to 14 days. Antipsychotics, however, fail to significantly improve the negative symptoms and cognitive dysfunction.[32][115] In those on antipsychotics, continued use decreases the risk of relapse.[116][117] There is little evidence regarding effects from their use beyond two or three years.[117]

The choice of which antipsychotic to use is based on benefits, risks, and costs.[12] It is debatable whether, as a class, typical or atypical antipsychotics are better.[10][118] Amisulpride, olanzapine, risperidone and clozapine may be more effective but are associated with greater side effects.[119] Typical antipsychotics have equal drop-out and symptom relapse rates to atypicals when used at low to moderate dosages.[120] There is a good response in 40–50%, a partial response in 30–40%, and treatment resistance (failure of symptoms to respond satisfactorily after six weeks to two or three different antipsychotics) in 20% of people.[32] Clozapine is an effective treatment for those who respond poorly to other drugs ("treatment-resistant" or "refractory" schizophrenia),[121] but it has the potentially serious side effect of agranulocytosis (lowered white blood cell count) in less than 4% of people.[9][12][122]

Most people on antipsychotics have side effects. People on typical antipsychotics tend to have a higher rate of extrapyramidal side effects while some atypicals are associated with considerable weight gain, diabetes and risk of metabolic syndrome; this is most pronounced with olanzapine, while risperidone and quetiapine are also associated with weight gain.[119] Risperidone has a similar rate of extrapyramidal symptoms to haloperidol.[119] It remains unclear whether the newer antipsychotics reduce the chances of developing neuroleptic malignant syndrome or tardive dyskinesia, a rare but serious neurological disorder.[123]

For people who are unwilling or unable to take medication regularly, long-acting depot preparations of antipsychotics may be used to achieve control.[124] They reduce the risk of relapse to a greater degree than [116]

oral medications. When used in combination with psychosocial interventions they may improve long-term adherence to treatment.[124] The American Psychiatric Association suggests considering stopping antipsychotics in some people if there are no symptoms for more than a year.[117]

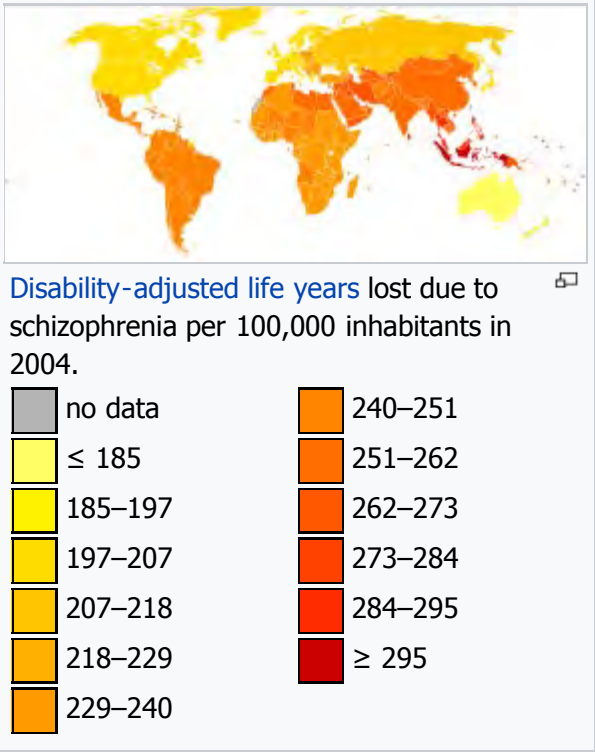
### Psychosocial

A number of psychosocial interventions may be useful in the treatment of schizophrenia including: family therapy,[125] assertive community treatment, supported employment, cognitive remediation,[126] skills training, token economic interventions, and psychosocial interventions for substance use and weight management.[127] Family therapy or education, which addresses the whole family system of an individual, may reduce relapses and hospitalizations.[125] Evidence for the effectiveness of cognitive-behavioral therapy (CBT) in either reducing symptoms or preventing relapse is minimal.[128][129] Art or drama therapy have not been well-researched.[130][131] Music therapy has been shown to improve mental state and social functioning when paired with regular care.[132]

## Prognosis

*Main article: Prognosis of schizophrenia*

Schizophrenia has great human and economic costs.[12] It results in a decreased life expectancy by 10–25 years.[15] This is primarily because of its association with obesity, poor diet, sedentary lifestyles, and smoking, with an increased rate of suicide playing a lesser role.[12][15][133] Antipsychotic medications may also increase the risk.[15] These differences in life expectancy increased between the 1970s and 1990s.[134]




Disability-adjusted life years lost due to schizophrenia per 100,000 inhabitants in 2004.

Schizophrenia is a major cause of disability, with active psychosis ranked as the third-most-disabling condition after quadriplegia and dementia and ahead of paraplegia and blindness.[135] Approximately three-fourths of people with schizophrenia have ongoing disability with relapses[32] and 16.7 million people globally are deemed to have moderate or severe disability from the condition.[136] Some people do recover completely and others function well in society.[137] Most people with schizophrenia live independently with community support.[12] About 85% are unemployed.[6] In people with a first episode of psychosis a good long-term outcome occurs in 42%, an intermediate outcome in 35% and a poor outcome in 27%.[138] Outcomes for schizophrenia appear better in the developing than the developed world.[139] These conclusions, however, have been questioned.[140][141]

There is a higher than average suicide rate associated with schizophrenia. This has been cited at 10%, but a more recent analysis revises the estimate to 4.9%, most often occurring in the period following onset or first hospital admission.[16][142] Several times more (20 to 40%) attempt suicide at least once.[5][143] There are a variety of risk factors, including male gender, depression, and a high intelligence quotient.[143]

Schizophrenia and smoking have shown a strong association in studies worldwide.[144][145] Use of cigarettes is especially high in individuals diagnosed with schizophrenia, with estimates ranging from 80 to 90% being regular smokers, as compared to 20% of the general population.[145] Those who smoke tend to smoke heavily, and additionally smoke cigarettes with high nicotine content.[146] Some evidence suggests

that paranoid schizophrenia may have a better prospect than other types of schizophrenia for independent living and occupational functioning.[147] Among people with schizophrenia use of cannabis is also common.[61]

# Epidemiology

*Main article: Epidemiology of schizophrenia*

Schizophrenia affects around 0.3–0.7% of people at some point in their life,[12] or 24 million people worldwide as of 2011.[148] It occurs 1.4 times more frequently in males than females and typically appears earlier in men[9]—the peak ages of onset are 25 years for males and 27 years for females.[149] Onset in childhood is much rarer,[150] as is onset in middle or old age.[151]

Deaths per million persons due to schizophrenia in 2012.

0-0 2-2 4-6
1-1 3-3 7-20

Despite the prior belief that schizophrenia occurs at similar rates worldwide, its frequency varies across the world,[5][152] within countries,[153] and at the local and neighborhood level.[154] This variation has been estimated to be fivefold.[6] It causes approximately one percent of worldwide disability adjusted life years[9] and resulted in 20,000 deaths in 2010.[155] The rate of schizophrenia varies up to threefold depending on how it is defined.[12]

In 2000, the World Health Organization found the percentage of people affected and the number of new cases that develop each year is roughly similar around the world, with age-standardized prevalence per 100,000 ranging from 343 in Africa to 544 in Japan and Oceania for men, and from 378 in Africa to 527 in Southeastern Europe for women.[156] About 1.1% of adults have schizophrenia in the United States.[157]

# History

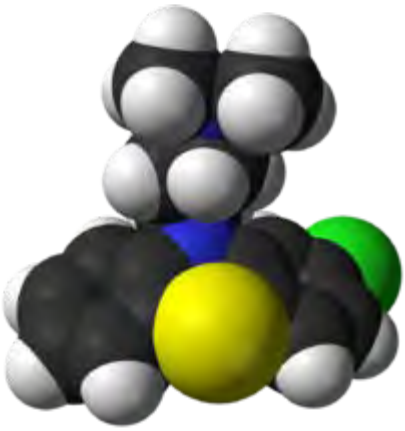
*Main article: History of schizophrenia*

In the early 20th century, the psychiatrist Kurt Schneider listed the forms of psychotic symptoms that he thought distinguished schizophrenia from other psychotic disorders. These are called *first-rank symptoms* or Schneider's first-rank symptoms. They include delusions of being controlled by an external force, the belief that thoughts are being inserted into or withdrawn from one's conscious mind, the belief that one's thoughts are being broadcast to other people, and hearing hallucinatory voices that comment on one's thoughts or actions or that have a conversation with other hallucinated voices.[158] Although they have significantly contributed to the current diagnostic criteria, the specificity of first-rank symptoms has been questioned. A review of the diagnostic studies conducted between 1970 and 2005 found that they allow neither a reconfirmation nor a rejection of Schneider's claims, and suggested that first-rank symptoms should be de-emphasized in future revisions of diagnostic systems.[159] The absence of first-rank symptoms should raise suspicion of a medical disorder, however.[19]

The term "schizophrenia" was coined by Eugen Bleuler.

The history of schizophrenia is complex and does not lend itself easily to a linear narrative.[160] Accounts of a schizophrenia-like syndrome are thought to be rare in historical records before the 19th century, although reports of irrational, unintelligible, or uncontrolled behavior were common. A detailed case

report in 1797 concerning James Tilly Matthews, and accounts by Philippe Pinel published in 1809, are often regarded as the earliest cases of the illness in the medical and psychiatric literature.[161] The Latinized term *dementia praecox* was first used by German alienist Heinrich Schule in 1886 and then in 1891 by Arnold Pick in a case report of a psychotic disorder (hebephrenia). In 1893 Emil Kraepelin borrowed the term from Schule and Pick and in 1899 introduced a broad new distinction in the classification of mental disorders between *dementia praecox* and mood disorder (termed manic depression and including both unipolar and bipolar depression).[162] Kraepelin believed that *dementia praecox* was probably caused by a long-term, smouldering systemic or "whole body" disease process that affected many organs and peripheral nerves in the body but which affected the brain after puberty in a final decisive cascade.[163] His use of the term "praecox" distinguished it from other forms of dementia such as Alzheimer's disease which typically occur later in life.[164] It is sometimes argued that the use of the term *démence précoce* in 1852 by the French physician Bénédict Morel constitutes the medical discovery of schizophrenia. However, this account ignores the fact that there is little to connect Morel's descriptive use of the term and the independent development of the *dementia praecox* disease concept at the end of the nineteenth century.[165]



Molecule of chlorpromazine (trade name Thorazine), which revolutionized treatment of schizophrenia in the 1950s

The word *schizophrenia*—which translates roughly as "splitting of the mind" and comes from the Greek roots *schizein* (σχίζειν, "to split") and *phrēn*, *phren-* (φρήν, φρεν-, "mind")[166]—was coined by Eugen Bleuler in 1908 and was intended to describe the separation of function between personality, thinking, memory, and perception. American and British interpretations of Bleuler led to the claim that he described its main symptoms as four *A*'s: flattened *affect*, *autism*, impaired *association* of ideas, and *ambivalence*.[167][168] Bleuler realized that the illness was *not* a dementia, as some of his patients improved rather than deteriorated, and thus proposed the term schizophrenia instead. Treatment was revolutionized in the mid-1950s with the development and introduction of chlorpromazine.[169]

In the early 1970s, the diagnostic criteria for schizophrenia were the subject of a number of controversies which eventually led to the operational criteria used today. It became clear after the 1971 US–UK Diagnostic Study that schizophrenia was diagnosed to a far greater extent in America than in Europe.[170] This was partly due to looser diagnostic criteria in the US, which used the DSM-II manual, contrasting with Europe and its ICD-9. David Rosenhan's 1972 study, published in the journal *Science* under the title "On being sane in insane places", concluded that the diagnosis of schizophrenia in the US was often subjective and unreliable.[171] These were some of the factors leading to the revision not only of the diagnosis of schizophrenia, but the revision of the whole DSM manual, resulting in the publication of the DSM-III in 1980.[172]

The term schizophrenia is commonly misunderstood to mean that affected persons have a "split personality". Although some people diagnosed with schizophrenia may hear voices and may experience the voices as distinct personalities, schizophrenia does not involve a person changing among distinct, multiple personalities; the confusion arises in part due to the literal interpretation of Bleuler's term "schizophrenia" (Bleuler originally associated schizophrenia with dissociation, and included split personality in his category of schizophrenia).[173][174] Dissociative identity disorder (having a "split personality") was also often misdiagnosed as schizophrenia based on the loose criteria in the DSM-II.[174][175] The first known misuse of the term to mean "split personality" was in an article by the poet T. S. Eliot in 1933.[176] Other scholars have traced earlier roots.[177] Rather, the term means a "splitting of mental functions", reflecting the presentation of the illness.[178]

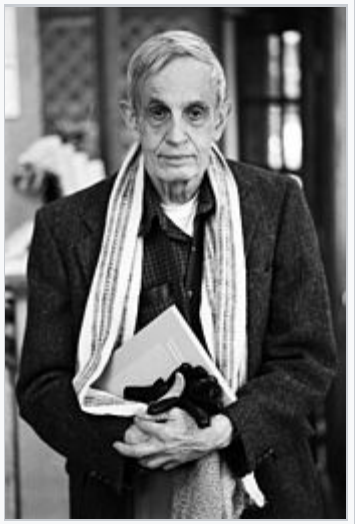
## Society and culture

*See also: Social construction of schizophrenia, List of people with schizophrenia, and Religion and*

*schizophrenia*

In 2002, the term for schizophrenia in Japan was changed from *seishin-bunretsu-byō* (精神分裂病?, lit. "mind-split disease") to *tōgō-shitchō-shō* (統合失調症?, lit. "integration disorder") to reduce stigma.[179] The new name was inspired by the biopsychosocial model; it increased the percentage of people who were informed of the diagnosis from 37 to 70% over three years.[180] A similar change was made in South Korea in 2012.[181] A professor of psychiatry, Jim van Os, has proposed changing the English term to "psychosis spectrum syndrome".[182]

In the United States, the cost of schizophrenia—including direct costs (outpatient, inpatient, drugs, and long-term care) and non-health care costs (law enforcement, reduced workplace productivity, and unemployment)—was estimated to be $62.7 billion in 2002.[183] The book and film *A Beautiful Mind* chronicles the life of John Forbes Nash, a Nobel Prize–winning mathematician who was diagnosed with schizophrenia.



John Nash, an American mathematician and joint recipient of the 1994 Nobel Prize for Economics, who had schizophrenia. His life was the subject of the 2001 Academy Award-winning film *A Beautiful Mind*.

## Violence

Individuals with severe mental illness, including schizophrenia, are at a significantly greater risk of being *victims* of both violent and non-violent crime.[184] Schizophrenia has been associated with a higher rate of violent acts, although this is primarily due to higher rates of drug use.[185] Rates of homicide linked to psychosis are similar to those linked to substance misuse, and parallel the overall rate in a region.[186] What role schizophrenia has on violence independent of drug misuse is controversial, but certain aspects of individual histories or mental states may be factors.[187] About 11% of people in prison for homicide have schizophrenia while 21% have mood disorders.[188] Another study found about 8-10% of people with schizophrenia had committed a violent act in the past year compared to 2% of the general population.[188]

Media coverage relating to violent acts by individuals with schizophrenia reinforces public perception of an association between schizophrenia and violence.[185] In a large, representative sample from a 1999 study, 12.8% of Americans believed that individuals with schizophrenia were "very likely" to do something violent against others, and 48.1% said that they were "somewhat likely" to. Over 74% said that people with schizophrenia were either "not very able" or "not able at all" to make decisions concerning their treatment, and 70.2% said the same of money-management decisions.[189] The perception of individuals with psychosis as violent has more than doubled in prevalence since the 1950s, according to one meta-analysis.[190]

# Research directions

*See also: Animal models of schizophrenia*

Research has found a tentative benefit in using minocycline to treat schizophrenia.[191] Nidotherapy or efforts to change the environment of people with schizophrenia to improve their ability to function, is also being studied; however, there is not enough evidence yet to make conclusions about its effectiveness.[192] Negative symptoms have proven a challenge to treat, as they are generally not made better by medication. Various agents have been explored for possible benefits in this area.[193] There have been trials on drugs with anti-inflammatory activity, based on the premise that inflammation might play a role in the pathology of schizophrenia.[194]

# References

1. ^ Jones, Daniel (2003) [1917], Peter Roach, James Hartmann and Jane Setter, eds., *English Pronouncing Dictionary*, Cambridge: Cambridge University Press, ISBN 3-12-539683-2
2. ^ a b c d "Schizophrenia Fact sheet N°397". *WHO*. September 2015. Retrieved 3 February 2016.
3. ^ a b "Schizophrenia". *National Institute of Mental Health*. January 2016. Retrieved 3 February 2016.
4. ^ Buckley PF; Miller BJ; Lehrer DS; Castle DJ (March 2009). "Psychiatric comorbidities and schizophrenia". *Schizophr Bull*. **35** (2): 383–402. doi:10.1093/schbul/sbn135. PMC 2659306. PMID 19011234.
5. ^ a b c d e f g h i j k American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington: American Psychiatric Publishing. pp. 101–05. ISBN 978-0890425558.
6. ^ a b c d e f Owen, MJ; Sawa, A; Mortensen, PB (14 January 2016). "Schizophrenia.". *Lancet (London, England)*. doi:10.1016/S0140-6736(15)01121-6. PMID 26777917.
7. ^ a b c d Chadwick B; Miller ML; Hurd YL (2013). "Cannabis Use during Adolescent Development: Susceptibility to Psychiatric Illness". *Front Psychiatry* (Review). **4**: 129. doi:10.3389/fpsyt.2013.00129. PMC 3796318. PMID 24133461.
8. ^ a b Kavanagh, D H; Tansey, K E; O'Donovan, M C; Owen, M J (2014). "Schizophrenia genetics: emerging themes for a complex disorder". *Molecular Psychiatry*. **20** (1): 72–76. doi:10.1038/mp.2014.148. ISSN 1359-4184.
9. ^ a b c d e f g h i j k l m n Picchioni MM; Murray RM (July 2007). "Schizophrenia". *BMJ*. **335** (7610): 91–5. doi:10.1136/bmj.39227.616447.BE. PMC 1914490. PMID 17626963.
10. ^ a b Kane JM; Correll CU (2010). "Pharmacologic treatment of schizophrenia". *Dialogues Clin Neurosci*. **12** (3): 345–57. PMC 3085113. PMID 20954430.
11. ^ a b Becker T; Kilian R (2006). "Psychiatric services for people with severe mental illness across western Europe: what can be generalized from current knowledge about differences in provision, costs and outcomes of mental health care?". *Acta Psychiatrica Scandinavica Supplement*. **113** (429): 9–16. doi:10.1111/j.1600-0447.2005.00711.x. PMID 16445476.
12. ^ a b c d e f g h i j k l m n o p q r s t van Os J, Kapur S (August 2009). "Schizophrenia" (PDF). *Lancet*. **374** (9690): 635–45. doi:10.1016/S0140-6736(09)60995-8. PMID 19700006.
13. ^ Global Burden of Disease Study 2013, Collaborators (5 June 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386**: 743–800. doi:10.1016/S0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
14. ^ Foster, A; Gable, J; Buckley, J (September 2012). "Homelessness in schizophrenia.". *The Psychiatric clinics of North America*. **35** (3): 717–34. doi:10.1016/j.psc.2012.06.010. PMID 22929875.
15. ^ a b c d Laursen TM, Munk-Olsen T, Vestergaard M (March 2012). "Life expectancy and cardiovascular mortality in persons with schizophrenia". *Current opinion in psychiatry*. **25** (2): 83–8. doi:10.1097/YCO.0b013e32835035ca. PMID 22249081.
16. ^ a b Hor K; Taylor M (November 2010). "Suicide and schizophrenia: a systematic review of rates and risk factors". *Journal of psychopharmacology (Oxford, England)*. **24** (4 Suppl): 81–90. doi:10.1177/1359786810385490. PMID 20923923.
17. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
18. ^ a b c Carson VB (2000). Mental health nursing: the nurse-patient journey W.B. Saunders. ISBN 978-0-7216-8053-8. p. 638.
19. ^ a b c Heinz, A.; Voss, M.; Lawrie, S. M.; Mishara, A.; Bauer, M.; Gallinat, J.; Juckel, G.; Lang, U.; Rapp, M. (2016-07-15). "Shall we really say goodbye to first rank symptoms". *European Psychiatry: The Journal of the Association of European Psychiatrists*. **37**: 8–13. doi:10.1016/j.eurpsy.2016.04.010. ISSN 1778-3585. PMID 27429167.
20. ^ Hirsch SR; Weinberger DR (2003). *Schizophrenia*. Wiley-Blackwell. p. 21. ISBN 978-0-632-06388-8.
21. ^ Brunet-Gouet E; Decety J (December 2006). "Social brain dysfunctions in schizophrenia: a review of neuroimaging studies". *Psychiatry Res*. **148** (2–3): 75–92. doi:10.1016/j.pscychresns.2006.05.001. PMID 17088049.
22. ^ Hirsch SR; WeinbergerDR (2003). *Schizophrenia*. Wiley-Blackwell. p. 481. ISBN 978-0-632-06388-8.
23. ^ Ungvari GS; Caroff SN; Gerevich J (March 2010). "The catatonia conundrum: evidence of psychomotor phenomena as a symptom dimension in psychotic disorders". *Schizophr Bull*. **36** (2): 231–8. doi:10.1093/schbul/sbp105. PMC 2833122. PMID 19776208.
24. ^ Baier M (August 2010). "Insight in schizophrenia: a review". *Current psychiatry reports*. **12** (4): 356–61. doi:10.1007/s11920-010-0125-7. PMID 20526897.

25. ^ Pijnenborg GH; van Donkersgoed RJ; David AS; Aleman A (March 2013). "Changes in insight during treatment for psychotic disorders: a meta-analysis". *Schizophrenia Research*. **144** (1–3): 109–17. doi:10.1016/j.schres.2012.11.018. PMID 23305612.
26. ^ Kohler CG; Walker JB; Martin EA; Healey KM; Moberg PJ (September 2010). "Facial emotion perception in schizophrenia: a meta-analytic review". *Schizophr Bull*. **36** (5): 1009–19. doi:10.1093/schbul/sbn192. PMC 2930336. PMID 19329561.
27. ^ Fadgyas-Stanculete, M; Buga, AM; Popa-Wagner, A; Dumitrascu, DL (2014). "The relationship between irritable bowel syndrome and psychiatric disorders: from molecular changes to clinical manifestations.". *Journal of molecular psychiatry*. **2** (1): 4. doi:10.1186/2049-9256-2-4. PMID 25408914.
28. ^ Sims A (2002). *Symptoms in the mind: an introduction to descriptive psychopathology*. Philadelphia: W. B. Saunders. ISBN 0-7020-2627-1.
29. ^ Kneisl C. and Trigoboff E. (2009). Contemporary Psychiatric- Mental Health Nursing. 2nd edition. London: Pearson Prentice Ltd. p. 371
30. ^ *a b* American Psychiatric Association. Task Force on DSM-IV. (2000). Diagnostic and statistical manual of mental disorders: DSM-IV-TR. American Psychiatric Pub. ISBN 978-0-89042-025-6. p. 299
31. ^ Velligan DI & Alphs LD (1 March 2008). "Negative Symptoms in Schizophrenia: The Importance of Identification and Treatment". *Psychiatric Times*. **25** (3).
32. ^ *a b c d* Smith T; Weston C; Lieberman J (August 2010). "Schizophrenia (maintenance treatment)". *Am Fam Physician*. **82** (4): 338–9. PMID 20704164.
33. ^ *a b c d e* Bozikas, Vasilis P.; Andreou, Christina (2011-02-01). "Longitudinal Studies of Cognition in First Episode Psychosis: A Systematic Review of the Literature". *Australian and New Zealand Journal of Psychiatry*. **45** (2): 93–108. doi:10.3109/00048674.2010.541418. ISSN 0004-8674. PMID 21320033.
34. ^ Dauvermann, Maria R.; Whalley, Heather C.; Schmidt, André; Lee, Graham L.; Romaniuk, Liana; Roberts, Neil; Johnstone, Eve C.; Lawrie, Stephen M.; Moorhead, Thomas WJ (2014-01-01). "Computational neuropsychiatry – schizophrenia as a cognitive brain network disorder". *Schizophrenia*. **5**: 30. doi:10.3389/fpsyt.2014.00030. PMC 3971172. PMID 24723894.
35. ^ *a b* Shah, JN; Qureshi, SU; Jawaid, A; Schulz, PE (June 2012). "Is there evidence for late cognitive decline in chronic schizophrenia?". *The Psychiatric quarterly*. **83** (2): 127–44. doi:10.1007/s11126-011-9189-8. PMID 21863346.
36. ^ *a b c* Goldberg, Terry E.; Keefe, Richard S. E.; Goldman, Robert S.; Robinson, Delbert G.; Harvey, Philip D. (2010-04-01). "Circumstances Under Which Practice Does Not Make Perfect: A Review of the Practice Effect Literature in Schizophrenia and Its Relevance to Clinical Treatment Studies". *Neuropsychopharmacology*. **35** (5): 1053–1062. doi:10.1038/npp.2009.211. ISSN 0893-133X. PMC 3055399. PMID 20090669.
37. ^ *a b c d e f g h i j* Kurtz, Matthew M.; Moberg, Paul J.; Gur, Ruben C.; Gur, Raquel E. (2001-12-01). "Approaches to Cognitive Remediation of Neuropsychological Deficits in Schizophrenia: A Review and Meta-Analysis". *Neuropsychology Review*. **11** (4): 197–210. doi:10.1023/A:1012953108158. ISSN 1040-7308.
38. ^ *a b* Tan, Bhing-Leet (2009-08-01). "Profile of cognitive problems in schizophrenia and implications for vocational functioning". *Australian Occupational Therapy Journal*. **56** (4): 220–228. doi:10.1111/j.1440-1630.2008.00759.x. ISSN 1440-1630.
39. ^ Cirillo, Michael; Seidman, Larry (2003). "Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms". *Neuropsychology Review*. Retrieved 14 December 2015.
40. ^ Pomarol-Clotet, E.; Oh, T. M. S. S.; Laws, K. R.; McKenna, P. J. (2008-02-01). "Semantic priming in schizophrenia: systematic review and meta-analysis". *The British Journal of Psychiatry*. **192** (2): 92–97. doi:10.1192/bjp.bp.106.032102. ISSN 0007-1250. PMID 18245021.
41. ^ *a b* Barch, Deanna M. (2003-08-01). "Cognition in Schizophrenia Does Working Memory Work?". *Current Directions in Psychological Science*. **12** (4): 146–150. doi:10.1111/1467-8721.01251. ISSN 0963-7214.
42. ^ *a b* Addington J, Cadenhead KS, Cannon TD, et al. (2007). "North American prodrome longitudinal study: a collaborative multisite approach to prodromal schizophrenia research". *Schizophrenia Bulletin*. **33** (3): 665–72. doi:10.1093/schbul/sbl075. PMC 2526151. PMID 17255119.
43. ^ Cullen KR, Kumra S, Regan J, et al. (2008). "Atypical Antipsychotics for Treatment of Schizophrenia Spectrum Disorders". *Psychiatric Times*. **25** (3).
44. ^ Amminger GP, Leicester S, Yung AR, et al. (2006). "Early onset of symptoms predicts conversion to non-affective psychosis in ultra-high risk individuals". *Schizophrenia Research*. **84** (1): 67–76. doi:10.1016/j.schres.2006.02.018. PMID 16677803.
45. ^ Parnas J; Jorgensen A (1989). "Pre-morbid psychopathology in schizophrenia spectrum". *British Journal of Psychiatry*. **115**: 623–7. doi:10.1192/bjp.155.5.623. PMID 2611591.
46. ^ *a b* Coyle, Joseph (2006). "Chapter 54: The Neurochemistry of Schizophrenia". In Siegal, George J; et al. *Basic*

*Neurochemistry: Molecular, Cellular and Medical Aspects* (7th ed.). Burlington, MA: Elsevier Academic Press. pp. 876–78. ISBN 0-12-088397-X.

47. ^ Drake RJ; Lewis SW (March 2005). "Early detection of schizophrenia". *Current Opinion in Psychiatry*. **18** (2): 147–50. doi:10.1097/00001504-200503000-00007. PMID 16639167.
48. ^ O'Donovan MC; Williams NM; Owen MJ (October 2003). "Recent advances in the genetics of schizophrenia". *Hum. Mol. Genet*. 12 Spec No 2: R125–33. doi:10.1093/hmg/ddg302. PMID 12952866.
49. ^ *a b* Herson M (2011). "Etiological considerations". *Adult psychopathology and diagnosis*. John Wiley & Sons. ISBN 9781118138847.
50. ^ McLaren JA; Silins E; Hutchinson D; Mattick RP; Hall W (January 2010). "Assessing evidence for a causal link between cannabis and psychosis: a review of cohort studies". *Int. J. Drug Policy*. **21** (1): 10–9. doi:10.1016/j.drugpo.2009.09.001. PMID 19783132.
51. ^ O'Donovan MC; Craddock NJ; Owen MJ (July 2009). "Genetics of psychosis; insights from views across the genome". *Hum. Genet*. **126** (1): 3–12. doi:10.1007/s00439-009-0703-0. PMID 19521722.
52. ^ Craddock N; Owen MJ (2010). "The Kraepelinian dichotomy - going, going... But still not gone". *The British Journal of Psychiatry*. **196**: 92–95. doi:10.1192/bjp.bp.109.073429. PMC 2815936. PMID 20118450.
53. ^ Moore S; Kelleher E; Corvin A. (2011). "The shock of the new: progress in schizophrenia genomics". *Current Genomics*. **12** (7): 516–24. doi:10.2174/138920211797904089. PMC 3219846. PMID 22547958.
54. ^ Crow TJ (July 2008). "The 'big bang' theory of the origin of psychosis and the faculty of language". *Schizophrenia Research*. **102** (1–3): 31–52. doi:10.1016/j.schres.2008.03.010. PMID 18502103.
55. ^ Mueser KT; Jeste DV (2008). *Clinical Handbook of Schizophrenia*. New York: Guilford Press. pp. 22–23. ISBN 1-59385-652-0.
56. ^ Dvir Y; Denietolis B; Frazier JA (October 2013). "Childhood trauma and psychosis". *Child and adolescent psychiatric clinics of North America*. **22** (4): 629–41. doi:10.1016/j.chc.2013.04.006. PMID 24012077.
57. ^ Van Os J (2004). "Does the urban environment cause psychosis?". *British Journal of Psychiatry*. **184** (4): 287–288. doi:10.1192/bjp.184.4.287. PMID 15056569.
58. ^ Selten JP; Cantor-Graae E; Kahn RS (March 2007). "Migration and schizophrenia". *Current Opinion in Psychiatry*. **20** (2): 111–115. doi:10.1097/YCO.0b013e328017f68e. PMID 17278906.
59. ^ Nemani, K; Hosseini Ghomi, R; McCormick, B; Fan, X (2 January 2015). "Schizophrenia and the gut-brain axis.". *Progress in neuro-psychopharmacology & biological psychiatry*. **56**: 155–60. doi:10.1016/j.pnpbp.2014.08.018. PMID 25240858.
60. ^ Lachance LR, McKenzie K (Feb 2014). "Biomarkers of gluten sensitivity in patients with non-affective psychosis: a meta-analysis". *Schizophr Res* (Review). **152** (2–3): 521–7. doi:10.1016/j.schres.2013.12.001. PMID 24368154.
61. ^ *a b c* Gregg L; Barrowclough C; Haddock G (2007). "Reasons for increased substance use in psychosis". *Clin Psychol Rev*. **27** (4): 494–510. doi:10.1016/j.cpr.2006.09.004. PMID 17240501.
62. ^ Larson, Michael (30 March 2006). "Alcohol-Related Psychosis". *eMedicine*. WebMD. Retrieved 27 September 2006.
63. ^ Sagud M, Mihaljević-Peles A, Mück-Seler D, et al. (September 2009). "Smoking and schizophrenia" (PDF). *Psychiatr Danub*. **21** (3): 371–5. PMID 19794359.
64. ^ *Alcohol-Related Psychosis* at eMedicine
65. ^ Large M; Sharma S; Compton MT; Slade T; Nielssen O (June 2011). "Cannabis use and earlier onset of psychosis: a systematic meta-analysis". *Arch. Gen. Psychiatry*. **68** (6): 555–61. doi:10.1001/archgenpsychiatry.2011.5. PMID 21300939.
66. ^ *a b c* Niesink RJ; van Laar MW (2013). "Does cannabidiol protect against adverse psychological effects of THC?". *Frontiers in Psychiatry* (Review). **4**: 130. doi:10.3389/fpsyt.2013.00130. PMC 3797438. PMID 24137134.
67. ^ *a b c* Parakh P; Basu D (August 2013). "Cannabis and psychosis: have we found the missing links?". *Asian Journal of Psychiatry* (Review). **6** (4): 281–7. doi:10.1016/j.ajp.2013.03.012. PMID 23810133. "Cannabis acts as a component cause of psychosis, that is, it increases the risk of psychosis in people with certain genetic or environmental vulnerabilities, though by itself, it is neither a sufficient nor a necessary cause of psychosis."
68. ^ Gage, SH; Hickman, M; Zammit, S (12 August 2015). "Association Between Cannabis and Psychosis: Epidemiologic Evidence.". *Biological Psychiatry*. doi:10.1016/j.biopsych.2015.08.001. PMID 26386480.
69. ^ Leweke FM; Koethe D (June 2008). "Cannabis and psychiatric disorders: it is not only addiction". *Addict Biol*. **13** (2): 264–75. doi:10.1111/j.1369-1600.2008.00106.x. PMID 18482435.
70. ^ Yolken R (Jun 2004). "Viruses and schizophrenia: a focus on herpes simplex virus". *Herpes*. **11** (Suppl 2): 83A–88A. PMID 15319094.
71. ^ Arias, I; Sorlozano, A; Villegas, E; de Dios Luna, J; McKenney, K; Cervilla, J; Gutierrez, B; Gutierrez, J (April 2012). "Infectious agents associated with schizophrenia: a meta-analysis.". *Schizophrenia Research*. **136** (1-3): 128–36. doi:10.1016/j.schres.2011.10.026. PMID 22104141.
72. ^ Broome MR, Woolley JB, Tabraham P, et al. (November 2005). "What causes the onset of psychosis?". *Schizophr.*

*Res*. **79** (1): 23–34. doi:10.1016/j.schres.2005.02.007. PMID 16198238.
73. ^ Bentall RP; Fernyhough C; Morrison AP; Lewis S; Corcoran R (2007). "Prospects for a cognitive-developmental account of psychotic experiences". *Br J Clin Psychol*. **46** (Pt 2): 155–73. doi:10.1348/014466506X123011. PMID 17524210.
74. ^ Kurtz MM (2005). "Neurocognitive impairment across the lifespan in schizophrenia: an update". *Schizophrenia Research*. **74** (1): 15–26. doi:10.1016/j.schres.2004.07.005. PMID 15694750.
75. ^ Cohen AS; Docherty NM (2004). "Affective reactivity of speech and emotional experience in patients with schizophrenia". *Schizophrenia Research*. **69** (1): 7–14. doi:10.1016/S0920-9964(03)00069-0. PMID 15145465.
76. ^ Horan WP; Blanchard JJ (2003). "Emotional responses to psychosocial stress in schizophrenia: the role of individual differences in affective traits and coping". *Schizophrenia Research*. **60** (2–3): 271–83. doi:10.1016/S0920-9964(02)00227-X. PMID 12591589.
77. ^ Smith B, Fowler DG, Freeman D, et al. (September 2006). "Emotion and psychosis: links between depression, self-esteem, negative schematic beliefs and delusions and hallucinations". *Schizophr. Res*. **86** (1–3): 181–8. doi:10.1016/j.schres.2006.06.018. PMID 16857346.
78. ^ Beck, AT (2004). "A Cognitive Model of Schizophrenia". *Journal of Cognitive Psychotherapy*. **18** (3): 281–88. doi:10.1891/jcop.18.3.281.65649.
79. ^ Bell V; Halligan PW; Ellis HD (2006). "Explaining delusions: a cognitive perspective". *Trends in Cognitive Science*. **10** (5): 219–26. doi:10.1016/j.tics.2006.03.004. PMID 16600666.
80. ^ Freeman D; Garety PA; Kuipers E; Fowler D; Bebbington PE; Dunn G (January 2007). "Acting on persecutory delusions: the importance of safety seeking". *Behav Res Ther*. **45** (1): 89–99. doi:10.1016/j.brat.2006.01.014. PMID 16530161.
81. ^ Kuipers E; Garety P; Fowler D; Freeman D; Dunn G; Bebbington P (October 2006). "Cognitive, emotional, and social processes in psychosis: refining cognitive behavioral therapy for persistent positive symptoms". *Schizophr Bull*. 32 Suppl 1: S24–31. doi:10.1093/schbul/sbl014. PMC 2632539. PMID 16885206.
82. ^ Torres, US; Portela-Oliveira, E; Borgwardt, S; Busatto, GF (20 December 2013). "Structural brain changes associated with antipsychotic treatment in schizophrenia as revealed by voxel-based morphometric MRI: an activation likelihood estimation meta-analysis.". *BMC Psychiatry*. **13**: 342. doi:10.1186/1471-244x-13-342. PMC 3878502. PMID 24359128.
83. ^ Kircher, Tilo & Renate Thienel (2006). "Functional brain imaging of symptoms and cognition in schizophrenia". *The Boundaries of Consciousness*. Amsterdam: Elsevier. p. 302. ISBN 0-444-52876-8.
84. ^ Green MF (2006). "Cognitive impairment and functional outcome in schizophrenia and bipolar disorder". *Journal of Clinical Psychiatry*. **67** (Suppl 9): 3–8. doi:10.4088/jcp.1006e12. PMID 16965182.
85. ^ Insel TR (November 2010). "Rethinking schizophrenia". *Nature*. **468** (7321): 187–93. doi:10.1038/nature09552. PMID 21068826.
86. ^ "Antipsychotics for schizophrenia associated with subtle loss in brain volume". *ScienceDaily*. February 8, 2011. Retrieved 3 July 2014.
87. ^ Laruelle M, Abi-Dargham A, van Dyck CH, et al. (August 1996). "Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects". *Proc. Natl. Acad. Sci. U.S.A.* **93** (17): 9235–40. doi:10.1073/pnas.93.17.9235. PMC 38625. PMID 8799184.
88. ^ Jones HM; Pilowsky LS (2002). "Dopamine and antipsychotic drug action revisited". *British Journal of Psychiatry*. **181**: 271–275. doi:10.1192/bjp.181.4.271. PMID 12356650.
89. ^ Konradi C; Heckers S (2003). "Molecular aspects of glutamate dysregulation: implications for schizophrenia and its treatment". *Pharmacology and Therapeutics*. **97** (2): 153–79. doi:10.1016/S0163-7258(02)00328-5. PMID 12559388.
90. ^ Lahti AC; Weiler MA; Tamara Michaelidis BA; Parwani A; Tamminga CA (2001). "Effects of ketamine in normal and schizophrenic volunteers". *Neuropsychopharmacology*. **25** (4): 455–67. doi:10.1016/S0893-133X(01)00243-3. PMID 11557159.
91. ^ Coyle JT; Tsai G; Goff D (2003). "Converging evidence of NMDA receptor hypofunction in the pathophysiology of schizophrenia". *Annals of the New York Academy of Sciences*. **1003**: 318–27. doi:10.1196/annals.1300.020. PMID 14684455.
92. ^ Tuominen HJ; Tiihonen J; Wahlbeck K (2005). "Glutamatergic drugs for schizophrenia: a systematic review and meta-analysis". *Schizophrenia Research*. **72** (2–3): 225–34. doi:10.1016/j.schres.2004.05.005. PMID 15560967.
93. ^ *a b c* American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington: American Psychiatric Publishing. ISBN 978-0890425558.
94. ^ *a b c d* Tandon R, Gaebel W, Barch DM, et al. (October 2013). "Definition and description of schizophrenia in the DSM-5". *Schizophr. Res*. **150** (1): 3–10. doi:10.1016/j.schres.2013.05.028. PMID 23800613.
95. ^ As referenced from PMID 23800613, Heckers S; Tandon R; Bustillo J (March 2010). "Catatonia in the DSM--shall we move or not?". *Schizophr Bull* (Editorial). **36** (2): 205–7. doi:10.1093/schbul/sbp136. PMC 2833126.

PMID 19933711.
96. ^ Barch DM, Bustillo J, Gaebel W, et al. (October 2013). "Logic and justification for dimensional assessment of symptoms and related clinical phenomena in psychosis: relevance to DSM-5". *Schizophr. Res.* **150** (1): 15–20. doi:10.1016/j.schres.2013.04.027. PMID 23706415.
97. ^ Jakobsen KD, Frederiksen JN, Hansen T, et al. (2005). "Reliability of clinical ICD-10 schizophrenia diagnoses". *Nordic Journal of Psychiatry*. **59** (3): 209–12. doi:10.1080/08039480510027698. PMID 16195122.
98. ^ American Psychiatric Association DSM-5 Work Groups (2010) Proposed Revisions – Schizophrenia and Other Psychotic Disorders. Retrieved 17 February 2010.
99. ^ *a b* "The ICD-10 Classification of Mental and Behavioural Disorders" (PDF). World Health Organization. p. 26.
100. ^ "DSM-5 Changes: Schizophrenia & Psychotic Disorders". 29 May 2014. Retrieved 8 January 2016.
101. ^ МКБ-10: Классификация психических и поведенческих расстройств. F21 Шизотипическое расстройство [The ICD-10 Classification of Mental and Behavioural Disorders. F21 Schizotypal Disorder]. Russian.
102. ^ Pope HG (1983). "Distinguishing bipolar disorder from schizophrenia in clinical practice: guidelines and case reports". *Hospital and Community Psychiatry*. **34**: 322–28. doi:10.1176/ps.34.4.322. PMID 6840720.
103. ^ McGlashan TH (February 1987). "Testing DSM-III symptom criteria for schizotypal and borderline personality disorders". *Archives of General Psychiatry*. **44** (2): 143–8. doi:10.1001/archpsyc.1987.01800140045007. PMID 3813809.
104. ^ Bottas A (15 April 2009). "Comorbidity: Schizophrenia With Obsessive-Compulsive Disorder". *Psychiatric Times*. **26** (4).
105. ^ Gabbard GO (15 May 2007). *Gabbard's Treatments of Psychiatric Disorders, Fourth Edition (Treatments of Psychiatric Disorders)*. American Psychiatric Publishing. pp. 209–11. ISBN 1-58562-216-8.
106. ^ Murray ED; Buttner N; Price BH (2012). "Depression and Psychosis in Neurological Practice". In Bradley WG; Daroff RB; Fenichel GM; Jankovic J. *Bradley's neurology in clinical practice*. **1** (6th ed.). Philadelphia, PA: Elsevier/Saunders. pp. 92–111. ISBN 1-4377-0434-4.
107. ^ Cannon TD; Cornblatt B; McGorry P (May 2007). "The empirical status of the ultra high-risk (prodromal) research paradigm". *Schizophrenia Bulletin*. **33** (3): 661–4. doi:10.1093/schbul/sbm031. PMC 2526144. PMID 17470445.
108. ^ Marshall M; Rathbone J (Jun 15, 2011). "Early intervention for psychosis". *The Cochrane database of systematic reviews* (6): CD004718. doi:10.1002/14651858.CD004718.pub3. PMC 4163966. PMID 21678345.
109. ^ de Koning MB, Bloemen OJ, van Amelsvoort TA, et al. (June 2009). "Early intervention in patients at ultra high risk of psychosis: benefits and risks". *Acta Psychiatr Scand*. **119** (6): 426–42. doi:10.1111/j.1600-0447.2009.01372.x. PMID 19392813.
110. ^ Stafford MR; Jackson H; Mayo-Wilson E; Morrison AP; Kendall T (18 January 2013). "Early interventions to prevent psychosis: systematic review and meta-analysis". *BMJ (Clinical research ed.)*. **346**: f185. doi:10.1136/bmj.f185. PMC 3548617. PMID 23335473.
111. ^ "Psychosis and schizophrenia in adults: treatment and management" (PDF). *NICE*. Mar 2014. p. 7. Retrieved 19 April 2014.
112. ^ McGurk SR; Mueser KT; Feldman K; Wolfe R; Pascaris A (Mar 2007). "Cognitive training for supported employment: 2–3 year outcomes of a randomized controlled trial.". *American Journal of Psychiatry*. **164** (3): 437–41. doi:10.1176/appi.ajp.164.3.437. PMID 17329468.
113. ^ Gorczynski P; Faulkner G (2010). "Exercise therapy for schizophrenia". *Cochrane Database of Systematic Reviews* (5): CD004412. doi:10.1002/14651858.CD004412.pub2. PMID 20464730.
114. ^ National Collaborating Centre for Mental Health (25 March 2009). "Schizophrenia: Full national clinical guideline on core interventions in primary and secondary care" (PDF). Retrieved 25 November 2009.
115. ^ Tandon R; Keshavan MS; Nasrallah HA (March 2008). "Schizophrenia, "Just the Facts": what we know in 2008 part 1: overview" (PDF). *Schizophrenia Research*. **100** (1–3): 4–19. doi:10.1016/j.schres.2008.01.022. PMID 18291627.
116. ^ *a b* Leucht S, Tardy M, Komossa K, et al. (June 2012). "Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis". *Lancet*. **379** (9831): 2063–71. doi:10.1016/S0140-6736(12)60239-6. PMID 22560607.
117. ^ *a b c* Harrow M; Jobe TH (19 March 2013). "Does long-term treatment of schizophrenia with antipsychotic medications facilitate recovery?". *Schizophrenia bulletin*. **39** (5): 962–5. doi:10.1093/schbul/sbt034. PMC 3756791. PMID 23512950.
118. ^ Hartling L, Abou-Setta AM, Dursun S, et al. (14 August 2012). "Antipsychotics in Adults With Schizophrenia: Comparative Effectiveness of First-generation versus second-generation medications: a systematic review and meta-analysis". *Annals of Internal Medicine*. **157** (7): 498–511. doi:10.7326/0003-4819-157-7-201210020-00525. PMID 22893011.
119. ^ *a b c* Barry SJE; Gaughan TM; Hunter R (2012). "Schizophrenia". *BMJ Clinical Evidence*. **2012**. PMC 3385413.

PMID 23870705.
120. ^ Schultz SH; North SW; Shields CG (June 2007). "Schizophrenia: a review". *Am Fam Physician*. **75** (12): 1821–9. PMID 17619525.
121. ^ Taylor DM (2000). "Refractory schizophrenia and atypical antipsychotics". *J Psychopharmacol*. **14** (4): 409–418. doi:10.1177/026988110001400411. PMID 11198061.
122. ^ Essali A; Al-Haj Haasan N; Li C; Rathbone J (2009). "Clozapine versus typical neuroleptic medication for schizophrenia". *Cochrane Database of Systematic Reviews* (1): CD000059. doi:10.1002/14651858.CD000059.pub2. PMID 19160174.
123. ^ Ananth J; Parameswaran S; Gunatilake S; Burgoyne K; Sidhom T (April 2004). "Neuroleptic malignant syndrome and atypical antipsychotic drugs". *Journal of Clinical Psychiatry*. **65** (4): 464–70. doi:10.4088/JCP.v65n0403. PMID 15119907.
124. ^ *a b* McEvoy JP (2006). "Risks versus benefits of different types of long-acting injectable antipsychotics". *J Clin Psychiatry*. 67 Suppl 5: 15–8. PMID 16822092.
125. ^ *a b* Pharoah F; Mari J; Rathbone J; Wong W (2010). "Family intervention for schizophrenia". *Cochrane Database of Systematic Reviews*. **12** (12): CD000088. doi:10.1002/14651858.CD000088.pub3. PMID 21154340.
126. ^ Medalia A; Choi J (2009). "Cognitive remediation in schizophrenia." (PDF). *Neuropsychology Rev*. **19** (3): 353–364. doi:10.1007/s11065-009-9097-y. PMID 19444614.
127. ^ Dixon LB, Dickerson F, Bellack AS, et al. (January 2010). "The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements". *Schizophr Bull*. **36** (1): 48–70. doi:10.1093/schbul/sbp115. PMC 2800143. PMID 19955389.
128. ^ Jauhar S, McKenna PJ, Radua J, et al. (January 2014). "Cognitive-behavioural therapy for the symptoms of schizophrenia: systematic review and meta-analysis with examination of potential bias". *The British Journal of Psychiatry* (Review). **204** (1): 20–9. doi:10.1192/bjp.bp.112.116285. PMID 24385461.
129. ^ Jones C; Hacker D; Cormac I; Meaden A; Irving CB (2012). "Cognitive behaviour therapy versus other psychosocial treatments for schizophrenia". *Cochrane Database of Systematic Reviews*. **4** (4): CD008712. doi:10.1002/14651858.CD008712.pub2. PMID 22513966.
130. ^ Ruddy R; Milnes D (2005). "Art therapy for schizophrenia or schizophrenia-like illnesses.". *Cochrane Database of Systematic Reviews* (4): CD003728. doi:10.1002/14651858.CD003728.pub2. PMID 16235338.
131. ^ Ruddy RA; Dent-Brown K (2007). "Drama therapy for schizophrenia or schizophrenia-like illnesses.". *Cochrane Database of Systematic Reviews* (1): CD005378. doi:10.1002/14651858.CD005378.pub2. PMID 17253555.
132. ^ Mössler, K; Chen, X; Heldal, TO; Gold, C (7 December 2011). "Music therapy for people with schizophrenia and schizophrenia-like disorders.". *The Cochrane database of systematic reviews* (12): CD004025. doi:10.1002/14651858.CD004025.pub3. PMID 22161383.
133. ^ Erlangsen A; Eaton WW; Mortensen PB; Conwell Y (Feb 2012). "Schizophrenia--a predictor of suicide during the second half of life?". *Schizophrenia Research*. **134** (2-3): 111–7. doi:10.1016/j.schres.2011.09.032. PMID 22018943.
134. ^ Saha S; Chant D; McGrath J (October 2007). "A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time?". *Arch. Gen. Psychiatry*. **64** (10): 1123–31. doi:10.1001/archpsyc.64.10.1123. PMID 17909124.
135. ^ Ustün TB, Rehm J, Chatterji S, Saxena S, Trotter R, Room R, Bickenbach J (1999). "Multiple-informant ranking of the disabling effects of different health conditions in 14 countries". *The Lancet*. **354** (9173): 111–15. doi:10.1016/S0140-6736(98)07507-2. PMID 10408486.
136. ^ World Health Organization (2008). *The global burden of disease : 2004 update* ([Online-Ausg.] ed.). Geneva, Switzerland: World Health Organization. p. 35. ISBN 9789241563710.
137. ^ Warner R (July 2009). "Recovery from schizophrenia and the recovery model". *Current Opinion in Psychiatry*. **22** (4): 374–80. doi:10.1097/YCO.0b013e32832c920b. PMID 19417668.
138. ^ Menezes NM; Arenovich T; Zipursky RB (October 2006). "A systematic review of longitudinal outcome studies of first-episode psychosis". *Psychol Med*. **36** (10): 1349–62. doi:10.1017/S0033291706007951. PMID 16756689.
139. ^ Isaac M; Chand P; Murthy P (August 2007). "Schizophrenia outcome measures in the wider international community". *Br J Psychiatry Suppl*. **50**: s71–7. doi:10.1192/bjp.191.50.s71. PMID 18019048.
140. ^ Cohen A; Patel V; Thara R; Gureje O (March 2008). "Questioning an axiom: better prognosis for schizophrenia in the developing world?". *Schizophr Bull*. **34** (2): 229–44. doi:10.1093/schbul/sbm105. PMC 2632419. PMID 17905787.
141. ^ Burns J (August 2009). "Dispelling a myth: developing world poverty, inequality, violence and social fragmentation are not good for outcome in schizophrenia". *Afr J Psychiatry (Johannesbg)*. **12** (3): 200–5. doi:10.4314/ajpsy.v12i3.48494. PMID 19894340.
142. ^ Palmer BA; Pankratz VS; Bostwick JM (March 2005). "The lifetime risk of suicide in schizophrenia: a reexamination". *Archives of General Psychiatry*. **62** (3): 247–53. doi:10.1001/archpsyc.62.3.247.

PMID 15753237.
143. ^ a b Carlborg A; Winnerbäck K; Jönsson EG; Jokinen J; Nordström P (July 2010). "Suicide in schizophrenia". *Expert Rev Neurother*. **10** (7): 1153–64. doi:10.1586/ern.10.82. PMID 20586695.
144. ^ De Leon J; Diaz FJ (2005). "A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors". *Schizophrenia Research*. **76** (2–3): 135–57. doi:10.1016/j.schres.2005.02.010. PMID 15949648.
145. ^ a b Keltner NL; Grant JS (2006). "Smoke, Smoke, Smoke That Cigarette". *Perspectives in Psychiatric Care*. **42** (4): 256–61. doi:10.1111/j.1744-6163.2006.00085.x. PMID 17107571.
146. ^ American Psychiatric Association. Task Force on DSM-IV. (2000). Diagnostic and statistical manual of mental disorders: DSM-IV-TR. American Psychiatric Pub. ISBN 978-0-89042-025-6. p. 304
147. ^ American Psychiatric Association. Task Force on DSM-IV. (2000). Diagnostic and statistical manual of mental disorders: DSM-IV-TR. American Psychiatric Pub. ISBN 978-0-89042-025-6. p. 314
148. ^ "Schizophrenia". World Health Organization. 2011. Retrieved 27 February 2011.
149. ^ Cascio MT; Cella M; Preti A; Meneghelli A; Cocchi A (May 2012). "Gender and duration of untreated psychosis: a systematic review and meta-analysis". *Early intervention in psychiatry* (Review). **6** (2): 115–27. doi:10.1111/j.1751-7893.2012.00351.x. PMID 22380467.
150. ^ Kumra S; Shaw M; Merka P; Nakayama E; Augustin R (2001). "Childhood-onset schizophrenia: research update". *Canadian Journal of Psychiatry*. **46** (10): 923–30. PMID 11816313.
151. ^ Hassett A, Ames D, Chiu E, eds. (2005). *Psychosis in the Elderly*. London: Taylor and Francis. p. 6. ISBN 1-84184-394-6.
152. ^ Jablensky A, Sartorius N, Ernberg G, et al. (1992). "Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study". *Psychological Medicine Monograph Supplement*. **20**: 1–97. doi:10.1017/S0264180100000904. PMID 1565705.
153. ^ Kirkbride JB, Fearon P, Morgan C, et al. (March 2006). "Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study". *Archives of General Psychiatry*. **63** (3): 250–8. doi:10.1001/archpsyc.63.3.250. PMID 16520429.
154. ^ Kirkbride JB, Fearon P, Morgan C, et al. (2007). "Neighbourhood variation in the incidence of psychotic disorders in Southeast London". *Social Psychiatry and Psychiatric Epidemiology*. **42** (6): 438–45. doi:10.1007/s00127-007-0193-0. PMID 17473901.
155. ^ Lozano R, Naghavi M, Foreman K, et al. (December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
156. ^ Ayuso-Mateos JL. "Global burden of schizophrenia in the year 2000" (PDF). World Health Organization. Retrieved 27 February 2013.
157. ^ "Schizophrenia". Retrieved 29 December 2015.
158. ^ Schneider K (1959). *Clinical Psychopathology* (5 ed.). New York: Grune & Stratton.
159. ^ Nordgaard J; Arnfred SM; Handest P; Parnas J (January 2008). "The diagnostic status of first-rank symptoms". *Schizophrenia Bulletin*. **34** (1): 137–54. doi:10.1093/schbul/sbm044. PMC 2632385. PMID 17562695.
160. ^ =Yuhas, Daisy. "Throughout History, Defining Schizophrenia Has Remained a Challenge". Scientific American Mind (March/April 2013). Retrieved 3 March 2013.
161. ^ Heinrichs RW (2003). "Historical origins of schizophrenia: two early madmen and their illness". *Journal of the History of the Behavioral Sciences*. **39** (4): 349–63. doi:10.1002/jhbs.10152. PMID 14601041.
162. ^ Noll, Richard (2011). *American madness: the rise and fall of dementia praecox*. Cambridge, MA: Harvard University Press. ISBN 978-0-674-04739-6.
163. ^ Noll R (2012). "Whole body madness". *Psychiatric Times*. **29** (12): 13–14.
164. ^ Hansen RA; Atchison B (2000). *Conditions in occupational therapy: effect on occupational performance*. Hagerstown, MD: Lippincott Williams & Wilkins. ISBN 0-683-30417-8.
165. ^ Berrios G.E.; Luque R; Villagran J (2003). "Schizophrenia: a conceptual history". *International Journal of Psychology and Psychological Therapy*. **3** (2): 111–140.
166. ^ Kuhn R (2004). tr. Cahn CH. "Eugen Bleuler's concepts of psychopathology". *History of Psychiatry*. **15** (3): 361–6. doi:10.1177/0957154X04044603. PMID 15386868.
167. ^ Stotz-Ingenlath G (2000). "Epistemological aspects of Eugen Bleuler's conception of schizophrenia in 1911" (PDF). *Medicine, Health Care and Philosophy*. **3** (2): 153–9. doi:10.1023/A:1009919309015. PMID 11079343.
168. ^ McNally K (2009). "Eugen Bleuler's "Four A's" ". *History of Psychology*. **12** (2): 43–59. doi:10.1037/a0015934. PMID 19831234.
169. ^ Turner T (2007). "Unlocking psychosis". *British Medical Journal*. **334** (suppl): s7. doi:10.1136/bmj.39034.609074.94. PMID 17204765.
170. ^ Wing JK (January 1971). "International comparisons in the study of the functional psychoses". *British Medical*

*Bulletin*. **27** (1): 77–81. PMID 4926366.
171. ^ Rosenhan D (1973). "On being sane in insane places". *Science*. **179** (4070): 250–8. Bibcode:1973Sci...179..250R. doi:10.1126/science.179.4070.250. PMID 4683124.
172. ^ Wilson M (March 1993). "DSM-III and the transformation of American psychiatry: a history". *American Journal of Psychiatry*. **150** (3): 399–410. doi:10.1176/ajp.150.3.399. PMID 8434655.
173. ^ Stotz-Ingenlath G (2000). "Epistemological aspects of Eugen Bleuler's conception of schizophrenia in 1911". *Med Health Care Philos*. **3** (2): 153–159. doi:10.1023/A:1009919309015. PMID 11079343.
174. ^ *a b* Hayes J. A.; Mitchell J. C. (1994). "Mental health professionals' skepticism about multiple personality disorder". *Professional Psychology: Research and Practice*. **25** (4): 410–415. doi:10.1037/0735-7028.25.4.410.
175. ^ Putnam, Frank W. (1989). Diagnosis and Treatment of Multiple Personality Disorder. New York: The Guilford Press. pp. 351. ISBN 0-89862-177-1
176. ^ Berrios, G. E.; Porter, Roy (1995). *A history of clinical psychiatry: the origin and history of psychiatric disorders*. London: Athlone Press. ISBN 0-485-24211-7.
177. ^ McNally K (Winter 2007). "Schizophrenia as split personality/Jekyll and Hyde: the origins of the informal usage in the English language". *Journal of the history of the behavioral sciences*. **43** (1): 69–79. doi:10.1002/jhbs.20209. PMID 17205539.
178. ^ Baucum, Don (2006). *Psychology* (2nd ed.). Hauppauge, N.Y.: Barron's. p. 182. ISBN 9780764134210.
179. ^ Kim Y; Berrios GE (2001). "Impact of the term schizophrenia on the culture of ideograph: the Japanese experience". *Schizophr Bull*. **27** (2): 181–5. doi:10.1093/oxfordjournals.schbul.a006864. PMID 11354585.
180. ^ Sato M (2004). "Renaming schizophrenia: a Japanese perspective". *World Psychiatry*. **5** (1): 53–55. PMC 1472254. PMID 16757998.
181. ^ Lee YS; Kim JJ; Kwon JS (Aug 2013). "Renaming schizophrenia in South Korea". *The Lancet*. **382** (9893): 683–684. doi:10.1016/S0140-6736(13)61776-6. PMID 23972810.
182. ^ van Os, Jim (2 February 2016). "'Schizophrenia' does not exist". *BMJ*: i375. doi:10.1136/bmj.i375.
183. ^ Wu EQ (2005). "The economic burden of schizophrenia in the United States in 2002". *J Clin Psychiatry*. **66** (9): 1122–9. doi:10.4088/jcp.v66n0906. PMID 16187769.
184. ^ Maniglio R (March 2009). "Severe mental illness and criminal victimization: a systematic review". *Acta Psychiatr Scand*. **119** (3): 180–91. doi:10.1111/j.1600-0447.2008.01300.x. PMID 19016668.
185. ^ *a b* Fazel S; Gulati G; Linsell L; Geddes JR; Grann M (August 2009). "Schizophrenia and violence: systematic review and meta-analysis". *PLoS Med*. **6** (8): e1000120. doi:10.1371/journal.pmed.1000120. PMC 2718581. PMID 19668362.
186. ^ Large M; Smith G; Nielssen O (July 2009). "The relationship between the rate of homicide by those with schizophrenia and the overall homicide rate: a systematic review and meta-analysis". *Schizophr. Res*. **112** (1–3): 123–9. doi:10.1016/j.schres.2009.04.004. PMID 19457644.
187. ^ Bo S; Abu-Akel A; Kongerslev M; Haahr UH; Simonsen E (July 2011). "Risk factors for violence among patients with schizophrenia". *Clin Psychol Rev*. **31** (5): 711–26. doi:10.1016/j.cpr.2011.03.002. PMID 21497585.
188. ^ *a b* Valença, Alexandre Martins; de Moraes, Talvane Marins (1 October 2006). "[Relationship between homicide and mental disorders]". *Revista Brasileira De Psiquiatria (Sao Paulo, Brazil: 1999)*. 28 Suppl 2: S62–68. ISSN 1516-4446. PMID 17143446.
189. ^ Pescosolido BA; Monahan J; Link BG; Stueve A; Kikuzawa S (September 1999). "The public's view of the competence, dangerousness, and need for legal coercion of persons with mental health problems". *American Journal of Public Health*. **89** (9): 1339–45. doi:10.2105/AJPH.89.9.1339. PMC 1508769. PMID 10474550.
190. ^ Phelan JC; Link BG; Stueve A; Pescosolido BA (June 2000). "Public Conceptions of Mental Illness in 1950 and 1996: What Is Mental Illness and Is It to be Feared?". *Journal of Health and Social Behavior*. **41** (2): 188–207. doi:10.2307/2676305.
191. ^ Dean OM; Data-Franco J; Giorlando F; Berk M (1 May 2012). "Minocycline: therapeutic potential in psychiatry". *CNS Drugs*. **26** (5): 391–401. doi:10.2165/11632000-000000000-00000. PMID 22486246.
192. ^ Chamberlain IJ, Sampson S (28 March 2013). Chamberlain, Ian J, ed. "Nidotherapy for people with schizophrenia". *Cochrane Database of Systematic Reviews*. **3** (3): CD009929. doi:10.1002/14651858.CD009929.pub2. PMID 23543583.
193. ^ Chue P; LaLonde JK (2014). "Addressing the unmet needs of patients with persistent negative symptoms of schizophrenia: emerging pharmacological treatment options". *Neuropsychiatr Dis Treat*. **10**: 777–89. doi:10.2147/ndt.s43404. PMC 4020880. PMID 24855363.
194. ^ Keller WR; Kum LM; Wehring HJ; Koola MM; Buchanan RW; Kelly DL. (2013). "A review of anti-inflammatory agents for symptoms of schizophrenia". *J Psychopharmacol*. **27** (4): 337–42. doi:10.1177/0269881112467089. PMID 23151612.

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# Suicide

From Wikipedia, the free encyclopedia

*For other uses, see Suicide (disambiguation).*

**Suicide** is the act of intentionally causing one's own death.[1] Risk factors include mental disorders such as depression, bipolar disorder, schizophrenia, personality disorders, alcoholism, or substance misuse.[2][3] Others are impulsive acts due to stress such as from financial difficulties, troubles with relationships, or from bullying.[3][4] Those who have previously attempted suicide are at higher risk for future attempts.[3] Suicide prevention efforts include limiting access to method of suicide, such as firearms and poisons, treating mental disorders and substance misuse, proper media reporting of suicide, and improving economic conditions.[3] Although crisis hotlines are common, there is little evidence for their effectiveness.[5]

The most commonly used method of suicide varies between countries, and is partly related to the availability of effective means.[6] Common methods include hanging, pesticide poisoning, and firearms.[3][7] Suicide resulted in 842,000 deaths globally in 2013 (up from 712,000 deaths in 1990).[8] This makes it the 10th leading cause of death worldwide.[2][9] Approximately 0.5% to 1.4% of people die by suicide, about 12 per 100,000 persons per year.[9][10] Three quarters of suicides globally occur in the developing world.[3] Rates of completed suicides are generally higher in men than in women, ranging from 1.5 times as much in the developing world to 3.5 times in the developed world.[11] Suicide is generally most common among those over the age of 70; however, in certain countries those aged between 15 and 30 are at highest risk.[11] There are an estimated 10 to 20 million non-fatal attempted suicides every year.[12] Non-fatal suicide attempts may lead to injury and long-term disabilities. In the Western world, attempts are more common in young people and females.[10]

*The Suicide* by Édouard Manet 1877–1881

| Classification and external resources | |
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Views on suicide have been influenced by broad existential themes such as religion, honor, and the meaning of life.[13][14] The Abrahamic religions traditionally consider suicide an offense towards God due to the belief in the sanctity of life.[15] During the samurai era in Japan, a form of suicide known as seppuku was respected as a means of making up for failure or as a form of protest.[16] Sati, a practice outlawed by

the British Raj, expected the Indian widow to kill herself on her husband's funeral fire, either willingly or under pressure from the family and society.[17] Suicide and attempted suicide, while previously illegal, are no longer in most Western countries.[18] It remains a criminal offense in many countries.[19] In the 20th and 21st centuries, suicide has been used on rare occasions as a form of protest, and kamikaze and suicide bombings have been used as a military or terrorist tactic.[20] The word is from the Latin *suicidium*, which means "the killing of oneself".[21]

Contents





# Definitions

*Main article: Suicide terminology*

Suicide, also known as completed suicide, is the "act of taking one's own life".[1] Attempted suicide or non-fatal suicidal behavior is self-injury with the desire to end one's life that does not result in death.[22] Assisted suicide is when one individual helps another bring about their own death indirectly via providing either advice or the means to the end.[23] This is in contrast to euthanasia, where another person takes a more active role in bringing about a person's death.[23] Suicidal ideation is thoughts of ending one's life but not taking any active efforts to do so.[22]

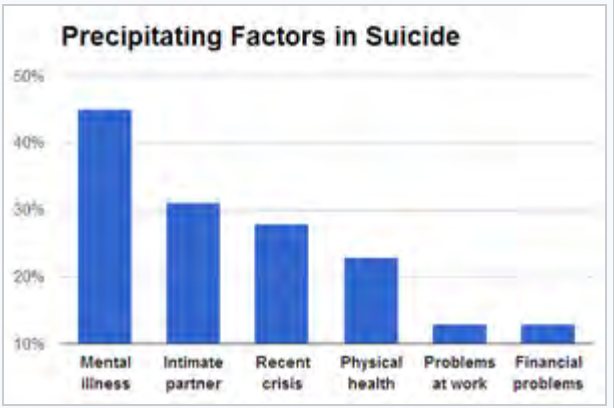
There is discussion about the appropriateness of the term *"commit"*, and its use to describe suicide. Those who object to the use of *commit* argue

A picture of a woman with depression who was suicidal

that it carries with it implications that suicide is a criminal, sinful or morally wrong act.[24] There is growing consensus that it is more appropriate to use "completed suicide," "died by suicide" or simply "killed him/herself" to describe the act of suicide, and this is reflected in mental health organisations' media guidance.[25][26][27][28] Despite these efforts, "committed suicide" and similar descriptions remain common in both scholarly research and journalism.[29][30]

## Risk factors for humans

Factors that affect the risk of suicide include mental disorders, drug misuse, psychological states, cultural, family and social situations, and genetics.[32] Mental disorders and substance misuse frequently co-exist.[33] Other risk factors include having previously attempted suicide,[10] the ready availability of a means to take one's life, a family history of suicide, or the presence of traumatic brain injury.[34] For example, suicide rates have been found to be greater in households with firearms than those without them.[35]




The precipitating circumstances for suicide from 16 American states in 2008[31]

Socio-economic problems such as unemployment, poverty, homelessness, and discrimination may trigger suicidal thoughts.[36][37] About 15–40% of people leave a suicide note.[38] Genetics appears to account for between 38% and 55% of suicidal behaviors.[39] War veterans have a higher risk of suicide due in part to higher rates of mental illness such as post traumatic stress disorder and physical health problems related to war.[40]

### Mental disorders

Mental disorders are often present at the time of suicide with estimates ranging from 27%[41] to more than 90%.[10] In Asia, rates of mental disorders appear to be lower than in Western countries.[11] Of those who have been admitted to a psychiatric unit, their lifetime risk of completed suicide is about 8.6%.[10] Half of all people who die by suicide may have major depressive disorder; having this or one of the other mood disorders such as bipolar disorder increases the risk of suicide 20-fold.[42] Other conditions implicated include schizophrenia (14%), personality disorders (8%),[43][44] bipolar disorder,[42] and posttraumatic stress disorder.[10] Others estimate that about half of people who complete suicide could be diagnosed with a personality disorder with borderline personality disorder being the most common.[45] About 5% of people with schizophrenia die of suicide.[46] Eating disorders are another high risk condition.[47]

In approximately 80% of completed suicides, the individual has seen a physician within the year before their death,[48] including 45% within the prior month.[49] Approximately 25–40% of those who completed

suicide had contact with mental health services in the prior year.[41][48] Antidepressants of the SSRI type appear to increase the risk of suicide in children but do not change the risk in adults.[50]

## Previous attempts and self-harm

A previous history of suicide attempts is the most accurate predictor of completed suicide.[10] Approximately 20% of suicides have had a previous attempt, and of those who have attempted suicide, 1% complete suicide within a year[10] and more than 5% die by suicide within 10 years.[47] Acts of self-harm are not usually suicide attempts and most who self-harm are not at high risk of suicide.[51] Some who self-harm, however, do still end their life by suicide, and risk for self-harm and suicide may overlap.[51]

## Substance use


"The Drunkard's Progress", 1846 demonstrating how alcoholism can lead to poverty, crime, and eventually suicide

Substance abuse is the second most common risk factor for suicide after major depression and bipolar disorder.[52] Both chronic substance misuse as well as acute intoxication are associated.[33][53] When combined with personal grief, such as bereavement, the risk is further increased.[53] Substance misuse is also associated with mental health disorders.[33]

Most people are under the influence of sedative-hypnotic drugs (such as alcohol or benzodiazepines) when they die by suicide[54] with alcoholism present in between 15% and 61% of cases.[33] Countries that have higher rates of alcohol use and a greater density of bars generally also have higher rates of suicide.[55] About 2.2–3.4% of those who have been treated for alcoholism at some point in their life die by suicide.[55] Alcoholics who attempt suicide are usually male, older, and have tried to take their own lives in the past.[33] Between 3 and 35% of deaths among those who use heroin are due to suicide (approximately 14 fold greater than those who do not use).[56] In adolescents who misuse alcohol, neurological and psychological dysfunctions may contribute to the increased risk of suicide.[57]

The misuse of cocaine and methamphetamine has a high correlation with suicide.[33][58] In those who use cocaine the risk is greatest during the withdrawal phase.[59] Those who used inhalants are also at significant risk with around 20% attempting suicide at some point and more than 65% considering it.[33] Smoking cigarettes is associated with the risk of suicide.[60] There is little evidence as to why this association exists; however it has been hypothesized that those who are predisposed to smoking are also predisposed to suicide, that smoking causes health problems which subsequently make people want to end their life, and that smoking affects brain chemistry causing a propensity for suicide.[60] Cannabis however does not appear to independently increase the risk.[33]

## Problem gambling

Problem gambling is associated with increased suicidal ideation and attempts compared to the general population.[61] Between 12 and 24% pathological gamblers attempt suicide.[62] The rate of suicide among their spouses is three times greater than that of the general population.[62] Other factors that increase the risk in problem gamblers include mental illness, alcohol and drug misuse.[63]

## Medical conditions

There is an association between suicidality and physical health problems such as[47] chronic pain,[64]

traumatic brain injury,[65] cancer,[66] kidney failure (requiring hemodialysis), HIV, and systemic lupus erythematosus.[47] The diagnosis of cancer approximately doubles the subsequent risk of suicide.[66] The prevalence of increased suicidality persisted after adjusting for depressive illness and alcohol abuse. In people with more than one medical condition the risk was particularly high. In Japan, health problems are listed as the primary justification for suicide.[67]

Sleep disturbances such as insomnia[68] and sleep apnea are risk factors for depression and suicide. In some instances the sleep disturbances may be a risk factor independent of depression.[69] A number of other medical conditions may present with symptoms similar to mood disorders, including hypothyroidism, Alzheimer's, brain tumors, systemic lupus erythematosus, and adverse effects from a number of medications (such as beta blockers and steroids).[10]

## Psychosocial states

A number of psychological states increase the risk of suicide including: hopelessness, loss of pleasure in life, depression and anxiousness.[42] A poor ability to solve problems, the loss of abilities one used to have, and poor impulse control also play a role.[42][70] In older adults the perception of being a burden to others is important.[71] Suicide in which the reason is that the person feels that they are not part of society is known as egoistic suicide.[72] Rates of suicide appear to decrease around Christmas.[73] One study however found the risk may be greater for males on their birthday.[74]

Recent life stresses such as a loss of a family member or friend, loss of a job, or social isolation (such as living alone) increase the risk.[42] Those who have never married are also at greater risk.[10] Being religious may reduce one's risk of suicide.[75] This has been attributed to the negative stance many religions take against suicide and to the greater connectedness religion may give.[75] Muslims, among religious people, appear to have a lower rate of suicide; however the data supporting this is not strong.[19] There does not appear to be a difference in rates of attempted suicide rates.[19] Young women in the Middle East may have higher rates.[76]

Some may take their own lives to escape bullying or prejudice.[77] A history of childhood sexual abuse[78] and time spent in foster care are also risk factors.[79] Sexual abuse is believed to contribute to about 20% of the overall risk.[39]

An evolutionary explanation for suicide is that it may improve inclusive fitness. This may occur if the person dying by suicide cannot have more children and takes resources away from relatives by staying alive. An objection is that deaths by healthy adolescents likely does not increase inclusive fitness. Adaptation to a very different ancestral environment may be maladaptive in the current one.[70][80]

Poverty is associated with the risk of suicide.[81] Increasing relative poverty compared to those around a person increases suicide risk.[82] Over 200,000 farmers in India have died by suicide since 1997, partly due to issues of debt.[83] In China suicide is three times as likely in rural regions as urban ones, partly, it is believed, due to financial difficulties in this area of the country.[84]

## Media

The media, which includes the Internet, plays an important role.[32] How it depicts suicide may have a negative effect, with high-volume, prominent, repetitive coverage glorifying or romanticizing suicide having the most impact.[85] When detailed descriptions of how to kill oneself by a specific means are portrayed, this method of suicide may increase in the population as a whole.[6]

This trigger of suicide contagion or copycat suicide is known as the *Werther effect*, named after the protagonist in

In Goethe's *The Sorrows of Young Werther*, the title character kills himself due to a love triangle involving Charlotte (pictured at his grave). Some admirers of the story were triggered into copycat suicide, known as the Werther effect.

Goethe's *The Sorrows of Young Werther* who killed himself and then was emulated by many admirers of the book.[86] This risk is greater in adolescents who may romanticize death.[87] It appears that while news media has a significant effect; that of the entertainment media is equivocal.[88][89] The opposite of the Werther effect is the proposed *Papageno effect*, in which coverage of effective coping mechanisms may have a protective effect. The term is based upon a character in Mozart's opera *The Magic Flute*, who (fearing the loss of a loved one) had planned to kill himself until his friends helped him out.[86] When media follows recommended reporting guidelines the risk of suicides can be decreased.[85] Getting buy-in from industry, however, can be difficult, especially in the long term.[85]

### Rational

Rational suicide is the reasoned taking of one's own life,[90] although others consider suicide as never rational.[90] The act of taking one's life for the benefit of others is known as altruistic suicide.[91] An example of this is an elder ending his or her life to leave greater amounts of food for the younger people in the community.[91] Suicide in some Inuit cultures has been seen as an act of respect, courage, or wisdom.[92]

A suicide attack is a political action where an attacker carries out violence against others which they understand will result in their own death.[93] Some suicide bombers are motivated by a desire to obtain martyrdoms.[40] Kamikaze missions were carried out as a duty to a higher cause or moral obligation.[92] Murder–suicide is an act of homicide followed within a week by suicide of the person who carried out the act.[94]

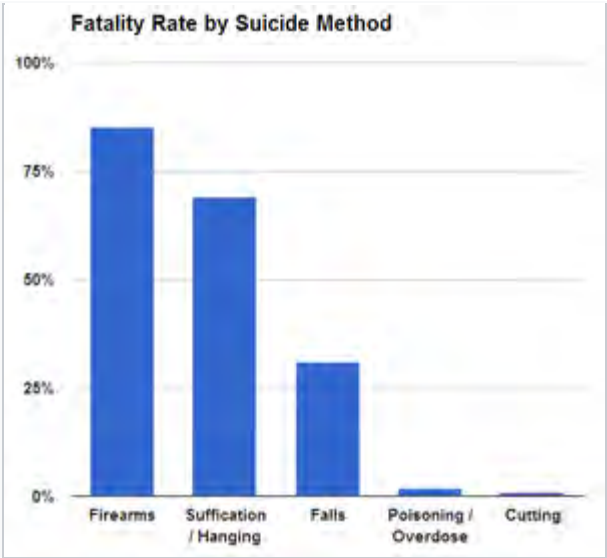
Mass suicides are often performed under social pressure where members give up autonomy to a leader.[95] Mass suicides can take place with as few as two people, often referred to as a suicide pact.[96]

In extenuating situations where continuing to live would be intolerable, some people use suicide as a means of escape.[97] Some inmates in Nazi concentration camps are known to have killed themselves by deliberately touching the electrified fences.[98]

## Methods

*Main article: Suicide methods*

The leading method of suicide varies among countries. The leading methods in different regions include hanging, pesticide poisoning, and firearms.[7] These differences are believed to be in part due to availability of the different methods.[6] A review of 56 countries found that hanging was [99]




Case fatality rate by suicide method in the United States[35]

the most common method in most of the countries, accounting for 53% of the male suicides and 39% of the female suicides.[100]

Worldwide, 30% of suicides are estimated to occur from pesticide poisoning, most of which occur in the developing world.[3] The use of this method varies markedly from 4% in Europe to more than 50% in the Pacific region.[101] It is also common in Latin America due to easy access within the farming populations.[6] In many countries, drug overdoses account for approximately 60% of suicides among women and 30% among men.[102] Many are unplanned and occur during an acute period of ambivalence.[6] The death rate varies by method: firearms 80-90%, drowning 65-80%, hanging 60-85%, car exhaust 40-60%, jumping 35-60%, charcoal burning 40-50%, pesticides 6-75%, and medication overdose 1.5-4%.[6] The most common attempted methods of suicide differ from the most common successful methods; up to 85% of attempts are via drug overdose in the developed world.[47]

In China, the consumption of pesticides is the most common method.[103] In Japan, self-disembowelment known as seppuku (or hara-kiri) still occurs;[103] however, hanging and jumping are the most common.[104] Jumping to one's death is common in both Hong Kong and Singapore at 50% and 80% respectively.[6] In Switzerland, firearms are the most frequent suicides method in young males, however this method has decreased relatively since guns have become less common.[105][106] In the United States, 57% of suicides involve the use of firearms, with this method being somewhat more common in men than women.[10] The next most common cause was hanging in males and self-poisoning in females.[10] Together these methods comprised about 40% of U.S. suicides.[107]

## Pathophysiology

There is no known unifying underlying pathophysiology for either suicide or depression.[10] It is however believed to result from an interplay of behavioral, socio-environmental and psychiatric factors.[6]

Low levels of brain-derived neurotrophic factor (BDNF) are both directly associated with suicide[108] and indirectly associated through its role in major depression, posttraumatic stress disorder, schizophrenia and obsessive–compulsive disorder.[109] Post-mortem studies have found reduced levels of BDNF in the hippocampus and prefrontal cortex, in those with and without psychiatric conditions.[110] Serotonin, a brain neurotransmitter, is believed to be low in those who die by suicide. This is partly based on evidence of increased levels of 5-HT2A receptors found after death.[111] Other evidence includes reduced levels of a breakdown product of serotonin, 5-Hydroxyindoleacetic acid, in the cerebral spinal fluid.[112] Direct evidence is however hard to gather.[111] Epigenetics, the study of changes in genetic expression in response to environmental factors which do not alter the underlying DNA, is also believed to play a role in determining suicide risk.[113]

## Prevention

*Main article: Suicide prevention*

Suicide prevention is a term used for the collective efforts to reduce the incidence of suicide through preventative measures. Reducing access to certain methods, such as firearms or toxins can reduce risk.[6][114] Other measures include reducing access to charcoal and barriers on bridges and subway platforms.[6][115] Treatment of drug and alcohol addiction, depression, and those who have attempted suicide in the past may also be effective.[114] Some have proposed reducing access to alcohol as a preventative strategy (such as reducing the number of bars).[33] Although crisis hotlines are common there is little evidence to support or refute their effectiveness.[5][116] In young adults who have recently thought about suicide, cognitive behavioral therapy appears to improve outcomes.[117] Economic development through its ability to reduce poverty may be able to decrease suicide rates.[81] Efforts to increase social connection, especially in elderly males, may be effective.[118] The World Suicide Prevention Day is observed annually on September 10 with the support of the International Association for Suicide Prevention and the World Health Organization.[119]


As a suicide prevention initiative, this sign promotes a special telephone available on the Golden Gate Bridge that connects to a crisis hotline.

## Screening

There is little data on the effects of screening the general population on the ultimate rate of suicide.[120][121] Screening those who come to the emergency departments with injuries from self harm have been shown to help identify suicide ideation and suicide intention. Psychometric tests such as the Beck Depression Inventory or the Geriatric Depression Scale for older people are being used.[122] As there is a high rate of people who test positive via these tools that are not at risk of suicide, there are concerns that screening may significantly increase mental health care resource utilization.[123] Assessing those at high risk however is recommended.[10] Asking about suicidality does not appear to increase the risk.[10]

## Mental illness

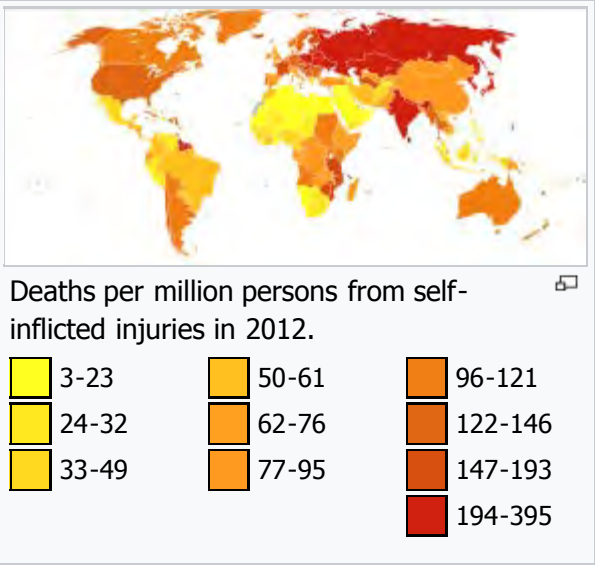
In those with mental health problems a number of treatments may reduce the risk of suicide. Those who are actively suicidal may be admitted to psychiatric care either voluntarily or involuntarily.[10] Possessions that may be used to harm oneself are typically removed.[47] Some clinicians get patients to sign suicide prevention contracts where they agree to not harm themselves if released.[10] Evidence however does not support a significant effect from this practice.[10] If a person is at low risk, outpatient mental health treatment may be arranged.[47] Short-term hospitalization has not been found to be more effective than community care for improving outcomes in those with borderline personality disorder who are chronically suicidal.[124][125]

There is tentative evidence that psychotherapy, specifically, dialectical behaviour therapy reduces suicidality in adolescents[126] as well as in those with borderline personality disorder.[127] It may also be useful in decreasing suicide attempts in adults at high risk.[128] Evidence however has not found a decrease in completed suicides.[126]

There is controversy around the benefit-versus-harm of antidepressants.[32] In young persons, the newer antidepressants such as SSRIs appear to increase the risk of suicidality from 25 per 1000 to 40 per 1000.[129] In older persons however they might decrease the risk.[10] Lithium appears effective at lowering the risk in those with bipolar disorder and unipolar depression to nearly the same levels as the general population.[130][131] Clozapine may decrease the thoughts of suicide in some people with schizophrenia.[132]

# Epidemiology

*Main article: Epidemiology of suicide*

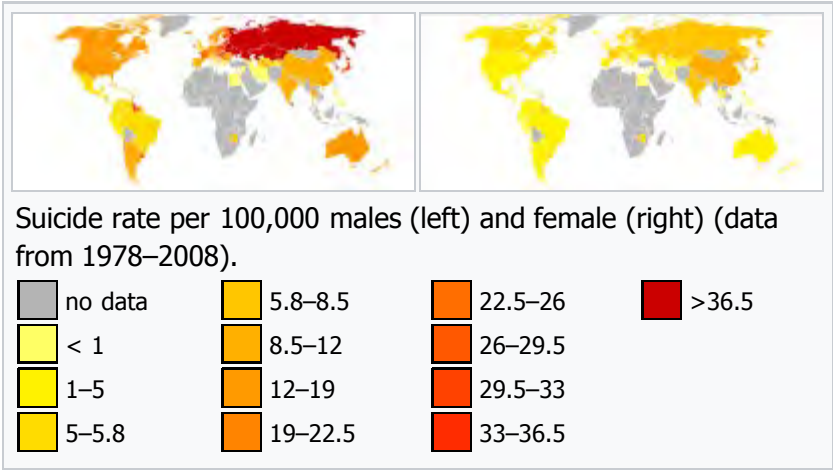



Approximately 0.5% to 1.4% of people die by suicide, a mortality rate of 11.6 per 100,000 persons per year.[9][10] Suicide resulted in 842,000 deaths in 2013 up from 712,000 deaths in 1990.[8] Rates of suicide have increased by 60% from the 1960s to 2012,[114] with these increases seen primarily in the developing world.[2] Globally, as of 2008/2009, suicide is the tenth leading cause of death.[2] For every suicide that results in death there are between 10 and 40 attempted suicides.[10]

Suicide rates differ significantly between countries and over time.[9] As a percentage of deaths in 2008 it was: Africa 0.5%, South-East Asia 1.9%, Americas 1.2% and Europe 1.4%.[9] Rates per 100,000 were: Australia 8.6, Canada 11.1, China 12.7, India 23.2, United Kingdom 7.6, United States 11.4 and South Korea 28.9.[133][134] It was ranked as the 10th leading cause of death in the United States in 2009 at about 36,000 cases a year,[135] with about 650,000 people seen in emergency departments yearly due to attempting suicide.[10] The country's rate among men in their 50s rose by nearly half in the decade 1999–2010.[136] Lithuania, Japan and Hungary have the highest rates.[9] Around 75% of suicides occur in the developing world.[3] The countries with the greatest absolute numbers of suicides are China and India, accounting for over half the total.[9] In China, suicide is the 5th leading cause of death.[137]

## Sex

*Main article: Gender differences in suicide*




Globally as of 2012 death by suicide occur about 1.8 times more often in males than female.[9][138]

In the Western world, males die three to four times more often by means of suicide than do females.[9] This difference is even more pronounced in those over the age of 65, with tenfold more males than females dying by suicide.[139] Suicide attempts and self-harm are between two and four times more frequent in females.[10][140][141] Some researchers have attributed this to males using more lethal means to end their lives.[139] However, separating intentional suicide attempts, from non-suicidal self-harm, is not currently done in the United States, when gathering statistics at the national level.[142]

China has one of the highest female suicide rates in the world and is the only country where it is higher than that of men (ratio of 0.9).[9][137] In the Eastern Mediterranean, suicide rates are nearly equivalent between males and females.[9] The highest rate of female suicide is found in South Korea at 22 per 100,000, with high rates in South-East Asia and the Western Pacific generally.[9]

Due in part to social stigmatisation and the resulting depression, people whose gender identity does not align with their assigned sex are at a high risk of suicide.[143]

In Sweden, same-sex married men have a suicide risk nearly three times higher than their heterosexual counterparts and same-sex married women have a tentatively elevated suicide risk.[144]

### Age

In many countries the rate of suicide is highest in the middle-aged[145] or elderly.[6] The absolute number of suicides however is greatest in those between 15 and 29 years old due to the number of people in this age group.[9] In the United States it is greatest in Caucasian men older than 80 years, even though younger people more frequently attempt suicide.[10] It is the second most common cause of death in adolescents[32] and in young males is second only to accidental death.[145] In young males in the developed world it is the cause of nearly 30% of mortality.[145] In the developing world rates are similar, but it makes up a smaller proportion of overall deaths due to higher rates of death from other types of trauma.[145] In South-East Asia in contrast to other areas of the world, deaths from suicide occur at a greater rate in young females than elderly females.[9]

## History

*Main article: History of suicide*

In ancient Athens, a person who committed suicide without the approval of the state was denied the honors of a normal burial. The person would be buried alone, on the outskirts of the city, without a headstone or marker.[146] However, it was deemed to be an acceptable method to deal with military defeat.[147] In Ancient Rome, while suicide was initially permitted, it was later deemed a crime against the state due to its economic costs.[148]

*The Death of Seneca* (1684), painting by Luca Giordano, depicting the suicide of Seneca the Younger in Ancient Rome

Suicide came to be regarded as a sin in Christian Europe and was condemned at the Council of Arles in 452 as the work of the Devil. In the Middle Ages, the Church had drawn-out discussions as to when the desire for martyrdom was suicidal, as in the case of martyrs of Córdoba. Despite these disputes and occasional official rulings, Catholic doctrine was not entirely settled on the subject of suicide until the later 17th century. A criminal ordinance issued by Louis XIV of France in 1670 was extremely severe, even for the times: the dead person's body was drawn through the streets, face down, and then hung or thrown on a garbage heap. Additionally, all of the person's property was confiscated.[149][150]

Attitudes towards suicide slowly began to shift during the Renaissance. John Donne's work *Biathanatos*, contained one of the first modern defences of suicide, bringing proof from the conduct of Biblical figures, such as Jesus, Samson and Saul, and presenting arguments on grounds of reason and nature to sanction suicide in certain circumstances.[151]

The secularization of society that began during The Enlightenment questioned traditional religious attitudes toward suicide and brought a more modern perspective to the issue. David Hume denied that suicide was a crime as it affected no one and was potentially to the advantage of the individual. In his 1777 *Essays on Suicide and the Immortality of the Soul* he rhetorically asked, "Why should I prolong a miserable existence, because of some frivolous advantage which the public may perhaps receive from me?"[151] A shift in public opinion at large can also be discerned; *The Times* in 1786 initiated a spirited debate on the motion "Is suicide an act of courage?".[152]

By the 19th-century, the act of suicide had shifted from being viewed as caused by sin to being caused by insanity in Europe.[150] Although suicide remained illegal during this period, it increasingly became the target of satirical comments, such as the Gilbert and Sullivan musical *The Mikado* that satirized the idea of executing someone who had already killed himself.

By 1879, English law began to distinguish between suicide and homicide, although suicide still resulted in forfeiture of estate.[153] In 1882, the deceased were permitted daylight burial in England[154] and by the middle of the 20th century, suicide had become legal in much of the western world.

# Social and culture

## Legislation

*Main article: Suicide legislation*

In most Western countries, suicide is no longer a crime.[18] It was, however, in most Western European countries from the Middle Ages until at least the 1800s.[153] It remains a criminal offense in most Muslim-majority nations.[19]

A *tantō* knife prepared for *seppuku* (abdomen-cutting)

In Australia suicide is not a crime.[155] It however is a crime to counsel, incite, or aid and abet another in attempting to die by suicide, and the law explicitly allows any person to use "such force as may reasonably be necessary" to prevent another from taking their own life.[156] The Northern Territory of Australia briefly had legal physician-assisted suicide from 1996 to 1997.[157]

No country in Europe currently considers suicide or attempted suicide to be a crime.[158] England and Wales decriminalized suicide via the Suicide Act 1961 and the Republic of Ireland in 1993.[158] The word "commit" was used in reference to it being illegal, however many organisations have stopped it because of the negative connotation.[159][160]

Samurai about to perform seppuku

In India, suicide used to be illegal and surviving family could face legal difficulties.[161] The government of India decided to repeal the law in 2014.[162] In Germany, active euthanasia is illegal and anyone present during suicide may be prosecuted for failure to render aid in an emergency.[163] Switzerland has recently taken steps to legalize assisted suicide for the chronically mentally ill. The high court in Lausanne, in a 2006 ruling, granted an anonymous individual with longstanding psychiatric difficulties the right to end his own life.[164]

In the United States, suicide is not illegal but may be associated with penalties for those who attempt it.[158] Physician-assisted suicide is legal in the state of Washington for people with terminal diseases.[165] In Oregon, people with terminal diseases may request medications to help end their life.[166]

Canadians who have attempted suicide may be barred from entering the US. US laws allow border guards to deny access to people who have a mental illness, including those with previous suicide attempts.[167][168]

## Religious views

*Main article: Religious views on suicide*

In most forms of Christianity, suicide is considered a sin, based mainly on the writings of influential Christian thinkers of the Middle Ages, such as St. Augustine and St. Thomas Aquinas, but suicide was not considered a sin under the Byzantine Christian code of Justinian, for

A Hindu widow burning herself with the corpse of her husband, 1820s

instance.[169][170] In Catholic doctrine, the argument is based on the commandment "Thou shalt not kill" (made applicable under the New Covenant by Jesus in Matthew 19:18), as well as the idea that life is a gift given by God which should not be spurned, and that suicide is against the "natural order" and thus interferes with God's master plan for the world.[171] Traditionally suiciders were buried in the forest without ceremonies, like horses or cows.[*citation needed*]

However, it is believed that mental illness or grave fear of suffering diminishes the responsibility of the one completing suicide.[172] Counter-arguments include the following: that the sixth commandment is more accurately translated as "thou shalt not murder" (not necessarily applying to the self), that God has given free will to humans, that taking one's own life no more violates God's Law than does curing a disease and that a number of suicides by followers of God are recorded in the Bible with no dire condemnation.[173]

Judaism focuses on the importance of valuing this life, and as such, suicide is tantamount to denying God's goodness in the world. Despite this, under extreme circumstances when there has seemed no choice but to either be killed or forced to betray their religion, Jews have committed individual suicide or mass suicide (see Masada, First French persecution of the Jews, and York Castle for examples) and as a grim reminder there is even a prayer in the Jewish liturgy for "when the knife is at the throat", for those dying "to sanctify God's Name" (see Martyrdom). These acts have received mixed responses by Jewish authorities, regarded by some as examples of heroic martyrdom, while others state that it was wrong for them to take their own lives in anticipation of martyrdom.[174]

Islamic religious views are against suicide.[19] The Qu'ran forbids it by stating "do not kill or destroy yourself".[175] The hadiths also state individual suicide to be unlawful and a sin.[19] Stigma is often associated with suicide in Islamic countries.[175]

In Hinduism, suicide is generally frowned upon and is considered equally sinful as murdering another in contemporary Hindu society. Hindu Scriptures state that one who dies by suicide will become part of the spirit world, wandering earth until the time one would have otherwise died, had one not taken one's own life.[176] However, Hinduism accepts a man's right to end one's life through the non-violent practice of fasting to death, termed *Prayopavesa*.[177] But Prayopavesa is strictly restricted to people who have no desire or ambition left, and no responsibilities remaining in this life.[177] Jainism has a similar practice named *Santhara*. Sati, or self-immolation by widows, was prevalent in Hindu society during the Middle Ages.[178]

## Philosophy

*Main article: Philosophy of suicide*

A number of questions are raised within the philosophy of suicide, included what constitutes suicide, whether or not suicide can be a rational choice, and the moral permissibility of suicide.[179] Arguments as to acceptability of suicide in moral or social terms range from the position that the act is inherently immoral and unacceptable under any circumstances to a regard for suicide as a sacrosanct right of anyone who believes they have rationally and conscientiously come to the decision to end their own lives, even if they are young and healthy.

Opponents to suicide include Christian philosophers such as Augustine of Hippo, Thomas Aquinas,[179] Immanuel Kant[180] and, arguably, John Stuart Mill – Mill's focus on the importance of liberty and autonomy meant that he rejected choices which would prevent a person from making future autonomous decisions.[181] Others view suicide as a legitimate matter of personal choice. Supporters of this position maintain that no one should be forced to suffer against their will, particularly from conditions such as incurable disease, mental illness, and old age, with no possibility of improvement. They reject the belief that

suicide is always irrational, arguing instead that it can be a valid last resort for those enduring major pain or trauma.[182] A stronger stance would argue that people should be allowed to autonomously choose to die regardless of whether they are suffering. Notable supporters of this school of thought include Scottish empiricist David Hume[179] and American bioethicist Jacob Appel.[164][183]

## Advocacy

*See also: Advocacy of suicide*

Advocacy of suicide has occurred in many cultures and subcultures. The Japanese military during World War II encouraged and glorified kamikaze attacks, which were suicide attacks by military aviators from the Empire of Japan against Allied naval vessels in the closing stages of the Pacific theater of World War II. Japanese society as a whole has been described as "suicide tolerant"[185] (see Suicide in Japan).

Internet searches for information on suicide return webpages that 10-30% of the time encourage or facilitate suicide attempts. There is some concern that such sites may push those predisposed over the edge. Some people form suicide pacts online, either with pre-existing friends or people they have recently encountered in chat rooms or message boards. The Internet, however, may also help prevent suicide by providing a social group for those who are isolated.[186]

In this painting by Alexandre-Gabriel Decamps, the palette, pistol, and note lying on the floor suggest that the event has just taken place; an artist has taken his own life.[184]

## Locations

*See also: List of suicide sites*

Some landmarks have become known for high levels of suicide attempts.[187] These include San Francisco's Golden Gate Bridge, Japan's Aokigahara Forest,[188] England's Beachy Head[187] and Toronto's Bloor Street Viaduct.[189]

As of 2010, the Golden Gate Bridge has had more than 1,300 die by suicide by jumping since its construction in 1937.[190] Many locations where suicide is common have constructed barriers to prevent it;[191] this includes the Luminous Veil in Toronto,[189] the Eiffel Tower in Paris and Empire State Building in New York City.[191] As of 2011, a barrier is being constructed for the Golden Gate Bridge.[192] They appear to be generally effective.[192]

## Notable cases

*Main article: List of suicides*

An example of mass suicide is the 1978 Jonestown killings/suicide in which 909 members of the Peoples Temple, an American religious group led by Jim Jones, ended their lives by drinking grape Flavor Aid laced with cyanide.[193][194][195] Thousands of Japanese civilians took their own lives in the last days of the Battle of Saipan in 1944, some jumping from "Suicide Cliff" and "Banzai Cliff".[196]

The 1981 hunger strikes, led by Bobby Sands, resulted in 10 deaths. The cause of death was recorded by the coroner as "starvation, self-imposed" rather than suicide; this was modified to simply "starvation" on the death certificates after protest from the dead strikers' families.[197] During World War II, Erwin Rommel was found to have foreknowledge of the July 20 Plot on Hitler's life; he was threatened with public trial, execution and reprisals on his family unless he took his own life.[198]

Japanese general Hideki Tojo, receiving life-saving treatment immediately after attempted suicide, 1945

# Other species

*Main article: Animal suicide*

As suicide requires a willful attempt to die, some feel it therefore cannot be said to occur in non-human animals.[147] Suicidal behavior has been observed in salmonella seeking to overcome competing bacteria by triggering an immune system response against them.[199] Suicidal defenses by workers are also noted in the Brazilian ant *Forelius pusillus*, where a small group of ants leaves the security of the nest after sealing the entrance from the outside each evening.[200]

Pea aphids, when threatened by a ladybug, can explode themselves, scattering and protecting their brethren and sometimes even killing the ladybug.[201] Some species of termites have soldiers that explode, covering their enemies with sticky goo.[202][203]

There have been anecdotal reports of dogs, horses and dolphins killing themselves, though with little conclusive evidence.[204] There has been little scientific study of animal suicide.[205]

# References


1. ^ *a b* *Stedman's Medical Dictionary* (28th ed.). Philadelphia: Lippincott Williams & Wilkins. 2006. ISBN 978-0-7817-3390-8.
2. ^ *a b c d* Hawton K, van Heeringen K (April 2009). "Suicide". *Lancet*. **373** (9672): 1372–81. doi:10.1016/S0140-6736(09)60372-X. PMID 19376453.
3. ^ *a b c d e f g h* "Suicide Fact sheet N°398". *WHO*. April 2016. Retrieved 3 March 2016.
4. ^ Bottino, SM; Bottino, CM; Regina, CG; Correia, AV; Ribeiro, WS (March 2015). "Cyberbullying and adolescent mental health: systematic review.". *Cadernos de Saúde Pública*. **31** (3): 463–75. doi:10.1590/0102-311x00036114. PMID 25859714.
5. ^ *a b* Sakinofsky, I (June 2007). "The current evidence base for the clinical care of suicidal patients: strengths and weaknesses". *Canadian Journal of Psychiatry*. **52** (6 Suppl 1): 7S–20S. PMID 17824349.
6. ^ *a b c d e f g h i j k* Yip, PS; Caine, E; Yousuf, S; Chang, SS; Wu, KC; Chen, YY (Jun 23, 2012). "Means restriction for suicide prevention". *Lancet*. **379** (9834): 2393–9. doi:10.1016/S0140-6736(12)60521-2. PMID 22726520.
7. ^ *a b* Ajdacic-Gross V, Weiss MG, Ring M, et al. (September 2008). "Methods of suicide: international suicide patterns derived from the WHO mortality database". *Bull. World Health Organ.* **86** (9): 726–32. doi:10.2471/BLT.07.043489. PMC 2649482. PMID 18797649.
8. ^ *a b* GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385**: 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
9. ^ *a b c d e f g h i j k l m n* Värnik, P (March 2012). "Suicide in the world". *International Journal of Environmental Research and Public Health*. **9** (3): 760–71. doi:10.3390/ijerph9030760. PMC 3367275. PMID 22690161.
10. ^ *a b c d e f g h i j k l m n o p q r s t u v w x* Chang, B; Gitlin, D; Patel, R (September 2011). "The depressed patient and suicidal patient in the emergency department: evidence-based management and treatment strategies". *Emergency medicine practice*. **13** (9): 1–23; quiz 23–4. PMID 22164363.
11. ^ *a b c* *Preventing suicide: a global imperative*. WHO. 2014. pp. 7, 20, 40. ISBN 9789241564779.
12. ^ Bertolote JM, Fleischmann A (October 2002). "Suicide and psychiatric diagnosis: a worldwide perspective". *World Psychiatry*. **1** (3): 181–5. PMC 1489848. PMID 16946849.
13. ^ Tomer, Adrian (2013). *Existential and Spiritual Issues in Death Attitudes*. Psychology Press. p. 282. ISBN 9781136676901.
14. ^ Ritzer, edited by George; Stepnisky, Jeffrey (2011). *The Wiley-Blackwell companion to major social theorists*. Malden, MA: Wiley-Blackwell. p. 65. ISBN 9781444396607.
15. ^ *God, Religion, Science, Nature, Culture, and Morality*. Archway Publishing. 2014. p. 254. ISBN 9781480811249.
16. ^ Colt, George Howe (1992). *The enigma of suicide* (1st Touchstone ed.). New York: Simon & Schuster. p. 139. ISBN 9780671760717.
17. ^ "Indian woman commits sati suicide". Bbc.co.uk. 2002-08-07. Retrieved 2010-08-26.
18. ^ *a b* White, Tony (2010). *Working with suicidal individuals : a guide to providing understanding, assessment and*

*support*. London: Jessica Kingsley Publishers. p. 12. ISBN 978-1-84905-115-6.
19. ^ [a b c d e f] Lester, D (2006). "Suicide and Islam". *Archives of Suicide Research*. **10** (1): 77–97. doi:10.1080/13811110500318489. PMID 16287698.
20. ^ Aggarwal, N (2009). "Rethinking suicide bombing". *Crisis*. **30** (2): 94–7. doi:10.1027/0227-5910.30.2.94. PMID 19525169.
21. ^ *Issues in Law & Medicine, Volume 3*. National Legal Center for the Medically Dependent & Disabled, Incorporated, and the Horatio R. Storer Foundation, Incorporated. 1987. p. 39.
22. ^ [a b] Krug, Etienne (2002). *World Report on Violence and Health (Vol. 1)*. Genève: World Health Organization. p. 185. ISBN 978-92-4-154561-7.
23. ^ [a b] Gullota, edited by Thomas P; Bloom, Martin (2002). *Encyclopedia of Primary Prevention and Health Promotion*. New York: Kluwer Academic/Plenum. p. 1112. ISBN 978-0-306-47296-1.
24. ^ Ball, P. Bonny (2005). "The Power of words". Canadian Association of Suicide Prevention. Retrieved 16 May 2013.
25. ^ Beck, A.T.; Resnik, H.L.P. & Lettieri, D.J, eds. (1974). "Development of suicidal intent scales". *The prediction of suicide*. Bowie, MD: Charles Press. p. 41. ISBN 978-0913486139.
26. ^ "Recommendations for Reporting on Suicide" (PDF). National Institute of Mental Health. 2001. Retrieved 15 May 2013.
27. ^ "Reporting Suicide and Self Harm". Time To Change. 2008. Retrieved 2 Jan 2016.
28. ^ "Media Guidelines for Reporting Suicide" (PDF). 2013. Retrieved 2 Jan 2016.
29. ^ Olson, Robert (2011). "Suicide and Language". *Centre for Suicide Prevention*. InfoExchange (3): 4. Retrieved 15 May 2013.
30. ^ Beaton, Susan; Forster, Peter; Maple, Myfanwy (February 2013). "Suicide and Language: Why we Shouldn't Use the 'C' Word". *In Psych*. Melbourne: Australian Psychological Society. **35** (1): 30–31.
31. ^ Karch, DL; Logan, J; Patel, N (Aug 26, 2011). "Surveillance for violent deaths—National Violent Death Reporting System, 16 states, 2008". *Morbidity and mortality weekly report. Surveillance summaries (Washington, D.C.: 2002)*. **60** (10): 1–49. PMID 21866088.
32. ^ [a b c d] Hawton, K; Saunders, KE; O'Connor, RC (Jun 23, 2012). "Self-harm and suicide in adolescents". *Lancet*. **379** (9834): 2373–82. doi:10.1016/S0140-6736(12)60322-5. PMID 22726518.
33. ^ [a b c d e f g h i] Vijayakumar, L; Kumar, MS; Vijayakumar, V (May 2011). "Substance use and suicide". *Current opinion in psychiatry*. **24** (3): 197–202. doi:10.1097/YCO.0b013e3283459242. PMID 21430536.
34. ^ Simpson, G; Tate, R (December 2007). "Suicidality in people surviving a traumatic brain injury: prevalence, risk factors and implications for clinical management". *Brain injury: [BI]*. **21** (13–14): 1335–51. doi:10.1080/02699050701785542. PMID 18066936.
35. ^ [a b] Miller, M; Azrael, D; Barber, C (April 2012). "Suicide mortality in the United States: the importance of attending to method in understanding population-level disparities in the burden of suicide". *Annual Review of Public Health*. **33**: 393–408. doi:10.1146/annurev-publhealth-031811-124636. PMID 22224886.
36. ^ Qin P, Agerbo E, Mortensen PB (April 2003). "Suicide risk in relation to socioeconomic, demographic, psychiatric, and familial factors: a national register-based study of all suicides in Denmark, 1981–1997". *Am J Psychiatry*. **160** (4): 765–72. doi:10.1176/appi.ajp.160.4.765. PMID 12668367.
37. ^ Centers for Disease Control and Prevention, (CDC) (May 3, 2013). "Suicide among adults aged 35-64 years--United States, 1999-2010.". *MMWR. Morbidity and mortality weekly report*. **62** (17): 321–5. PMID 23636024.
38. ^ Gilliland, Richard K. James, Burl E. (2012-05-08). *Crisis intervention strategies* (7th ed.). Belmont, CA: Brooks/Cole. p. 215. ISBN 978-1-111-18677-7.
39. ^ [a b] Brent, DA; Melhem, N (June 2008). "Familial transmission of suicidal behavior". *The Psychiatric clinics of North America*. **31** (2): 157–77. doi:10.1016/j.psc.2008.02.001. PMC 2440417. PMID 18439442.
40. ^ [a b] Rozanov, V; Carli, V (July 2012). "Suicide among war veterans". *International Journal of Environmental Research and Public Health*. **9** (7): 2504–19. doi:10.3390/ijerph9072504. PMC 3407917. PMID 22851956.
41. ^ [a b] University of Manchester Centre for Mental Health and Risk. "The National Confidential Inquiry into Suicide and Homicide by People with Mental Illness" (PDF). Retrieved 25 July 2012.
42. ^ [a b c d e] Chehil, Stan Kutcher, Sonia (2012). *Suicide Risk Management A Manual for Health Professionals.* (2nd ed.). Chicester: John Wiley & Sons. pp. 30–33. ISBN 978-1-119-95311-1.
43. ^ Pompili, M; Girardi, P; Ruberto, A; Tatarelli, R (2005). "Suicide in borderline personality disorder: a meta-analysis.". *Nordic Journal of Psychiatry*. **59** (5): 319–24. doi:10.1080/08039480500320025. PMID 16757458.
44. ^ Bertolote, JM; Fleischmann, A; De Leo, D; Wasserman, D (2004). "Psychiatric diagnoses and suicide: revisiting the evidence". *Crisis*. **25** (4): 147–55. doi:10.1027/0227-5910.25.4.147. PMID 15580849.
45. ^ Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M (2004). "Borderline personality disorder". *Lancet*. **364** (9432): 453–61. doi:10.1016/S0140-6736(04)16770-6. PMID 15288745. "Between 40% and 65% of individuals

who commit suicide meet criteria for a personality disorder, with borderline personality disorder being the most commonly associated."

46. ^ van Os J, Kapur S (August 2009). "Schizophrenia" (PDF). *Lancet*. **374** (9690): 635–45. doi:10.1016/S0140-6736(09)60995-8. PMID 19700006.
47. ^ *a b c d e f g* Tintinalli, Judith E. (2010). *Emergency Medicine: A Comprehensive Study Guide (Emergency Medicine (Tintinalli))*. New York: McGraw-Hill Companies. pp. 1940–1946. ISBN 0-07-148480-9.
48. ^ *a b* Pirkis, J; Burgess, P (December 1998). "Suicide and recency of health care contacts. A systematic review". *The British Journal of Psychiatry*. **173** (6): 462–74. doi:10.1192/bjp.173.6.462. PMID 9926074.
49. ^ Luoma, JB; Martin, CE; Pearson, JL (June 2002). "Contact with mental health and primary care providers before suicide: a review of the evidence". *The American Journal of Psychiatry*. **159** (6): 909–16. doi:10.1176/appi.ajp.159.6.909. PMID 12042175.
50. ^ Sharma, Tarang; Guski, Louise Schow; Freund, Nanna; Gøtzsche, Peter C (27 January 2016). "Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports". *BMJ*: i65. doi:10.1136/bmj.i65.
51. ^ *a b* Greydanus, DE; Shek, D (September 2009). "Deliberate self-harm and suicide in adolescents". *The Keio journal of medicine*. **58** (3): 144–51. doi:10.2302/kjm.58.144. PMID 19826208.
52. ^ Perrotto, Jerome D. Levin, Joseph Culkin, Richard S. (2001). *Introduction to chemical dependency counseling*. Northvale, N.J.: Jason Aronson. pp. 150–152. ISBN 978-0-7657-0289-0.
53. ^ *a b* Fadem, Barbara (2004). *Behavioral science in medicine*. Philadelphia: Lippincott Williams & Wilkins. p. 217. ISBN 978-0-7817-3669-5.
54. ^ Youssef NA, Rich CL (2008). "Does acute treatment with sedatives/hypnotics for anxiety in depressed patients affect suicide risk? A literature review". *Ann Clin Psychiatry*. **20** (3): 157–69. doi:10.1080/10401230802177698. PMID 18633742.
55. ^ *a b* Sher, L (January 2006). "Alcohol consumption and suicide". *QJM : monthly journal of the Association of Physicians*. **99** (1): 57–61. doi:10.1093/qjmed/hci146. PMID 16287907.
56. ^ Darke S, Ross J (November 2002). "Suicide among heroin users: rates, risk factors and methods". *Addiction*. **97** (11): 1383–94. doi:10.1046/j.1360-0443.2002.00214.x. PMID 12410779.
57. ^ Sher L (2007). "Functional magnetic resonance imaging in studies of the neurobiology of suicidal behavior in adolescents with alcohol use disorders". *Int J Adolesc Med Health*. **19** (1): 11–8. doi:10.1515/ijamh.2007.19.1.11. PMID 17458319.
58. ^ Darke, S; Kaye, S; McKetin, R; Duflou, J (May 2008). "Major physical and psychological harms of methamphetamine use". *Drug and alcohol review*. **27** (3): 253–62. doi:10.1080/09595230801923702. PMID 18368606.
59. ^ Jr, Frank J. Ayd, (2000). *Lexicon of psychiatry, neurology, and the neurosciences* (2nd ed.). Philadelphia [u.a.]: Lippincott Williams & Wilkins. p. 256. ISBN 978-0-7817-2468-5.
60. ^ *a b* Hughes, JR (Dec 1, 2008). "Smoking and suicide: a brief overview". *Drug and Alcohol Dependence*. **98** (3): 169–78. doi:10.1016/j.drugalcdep.2008.06.003. PMC 2585177. PMID 18676099.
61. ^ Pallanti, Stefano; Rossi, Nicolò Baldini; Hollander, Eric (2006). "11. Pathological Gambling". In Hollander, Eric; Stein, Dan J. *Clinical manual of impulse-control disorders*. American Psychiatric Pub. p. 253. ISBN 978-1-58562-136-1.
62. ^ *a b* Oliveira, MP; Silveira, DX; Silva, MT (June 2008). "Pathological gambling and its consequences for public health". *Revista de saude publica*. **42** (3): 542–9. doi:10.1590/S0034-89102008005000026. PMID 18461253.
63. ^ Hansen, M; Rossow, I (Jan 17, 2008). "Gambling and suicidal behaviour". *Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke*. **128** (2): 174–6. PMID 18202728.
64. ^ Manthorpe, J; Iliffe, S (December 2010). "Suicide in later life: public health and practitioner perspectives". *International journal of geriatric psychiatry*. **25** (12): 1230–8. doi:10.1002/gps.2473. PMID 20104515.
65. ^ Simpson GK, Tate RL (August 2007). "Preventing suicide after traumatic brain injury: implications for general practice". *Med. J. Aust*. **187** (4): 229–32. PMID 17708726.
66. ^ *a b* Anguiano, L; Mayer, DK; Piven, ML; Rosenstein, D (Jul–Aug 2012). "A literature review of suicide in cancer patients". *Cancer nursing*. **35** (4): E14–26. doi:10.1097/NCC.0b013e31822fc76c. PMID 21946906.
67. ^ Yip, edited by Paul S.F. (2008). *Suicide in Asia : causes and prevention*. Hong Kong: Hong Kong University Press. p. 11. ISBN 978-962-209-943-2.
68. ^ Ribeiro, JD; Pease, JL; Gutierrez, PM; Silva, C; Bernert, RA; Rudd, MD; Joiner TE, Jr (February 2012). "Sleep problems outperform depression and hopelessness as cross-sectional and longitudinal predictors of suicidal ideation and behavior in young adults in the military". *Journal of Affective Disorders*. **136** (3): 743–50. doi:10.1016/j.jad.2011.09.049. PMID 22032872.
69. ^ Bernert, RA; Joiner, TE, Jr; Cukrowicz, KC; Schmidt, NB; Kraków, B (September 2005). "Suicidality and sleep

disturbances". *Sleep*. **28** (9): 1135–41. PMID 16268383.

70. ^ [a] [b] Joiner TE, Jr; Brown, JS; Wingate, LR (2005). "The psychology and neurobiology of suicidal behavior". *Annual Review of Psychology*. **56**: 287–314. doi:10.1146/annurev.psych.56.091103.070320. PMID 15709937.
71. ^ Van Orden, K; Conwell, Y (June 2011). "Suicides in late life". *Current psychiatry reports*. **13** (3): 234–41. doi:10.1007/s11920-011-0193-3. PMC 3085020. PMID 21369952.
72. ^ Stein, edited by George; Wilkinson, Greg (2007). *Seminars in general adult psychiatry* (2. ed.). London: Gaskell. p. 144. ISBN 9781904671442.
73. ^ Carley, S; Hamilton, M (November 2004). "Best evidence topic report. Suicide at christmas.". *Emergency medicine journal : EMJ*. **21** (6): 716–7. doi:10.1136/emj.2004.019703. PMC 1726490. PMID 15496706.
74. ^ Williams, A; While, D; Windfuhr, K; Bickley, H; Hunt, IM; Shaw, J; Appleby, L; Kapur, N (2011). "Birthday blues: examining the association between birthday and suicide in a national sample.". *Crisis*. **32** (3): 134–42. doi:10.1027/0227-5910/a000067. PMID 21616762.
75. ^ [a] [b] Koenig, HG (May 2009). "Research on religion, spirituality, and mental health: a review" (PDF). *Canadian Journal of Psychiatry*. **54** (5): 283–91. PMID 19497160.
76. ^ Rezaeian, M (2010). "Suicide among young Middle Eastern Muslim females.". *Crisis*. **31** (1): 36–42. doi:10.1027/0227-5910/a000005. PMID 20197256.
77. ^ Cox, William T. L.; Abramson, Lyn Y.; Devine, Patricia G.; Hollon, Steven D. (2012). "Stereotypes, Prejudice, and Depression: The Integrated Perspective". *Perspectives on Psychological Science*. **7** (5): 427–449. doi:10.1177/1745691612455204. PMID 26168502.
78. ^ Wegman, HL; Stetler, C (October 2009). "A meta-analytic review of the effects of childhood abuse on medical outcomes in adulthood". *Psychosomatic Medicine*. **71** (8): 805–12. doi:10.1097/PSY.0b013e3181bb2b46. PMID 19779142.
79. ^ Oswald, SH; Heil, K; Goldbeck, L (June 2010). "History of maltreatment and mental health problems in foster children: a review of the literature". *Journal of pediatric psychology*. **35** (5): 462–72. doi:10.1093/jpepsy/jsp114. PMID 20007747.
80. ^ Confer, Jaime C.; Easton, Judith A.; Fleischman, Diana S.; Goetz, Cari D.; Lewis, David M. G.; Perilloux, Carin; Buss, David M. (1 January 2010). "Evolutionary psychology: Controversies, questions, prospects, and limitations". *American Psychologist*. **65** (2): 110–126. doi:10.1037/a0018413. PMID 20141266.
81. ^ [a] [b] Stark, CR; Riordan, V; O'Connor, R (2011). "A conceptual model of suicide in rural areas". *Rural and remote health*. **11** (2): 1622. PMID 21702640.
82. ^ Daly, Mary (Sep 2012). "Relative Status and Well-Being: Evidence from U.S. Suicide Deaths" (PDF). *Federal Reserve Bank of San Francisco Working Paper Series*.
83. ^ Lerner, George (Jan 5, 2010). "Activist: Farmer suicides in India linked to debt, globalization". *CNN World*. Retrieved 13 February 2013.
84. ^ Law, S; Liu, P (February 2008). "Suicide in China: unique demographic patterns and relationship to depressive disorder". *Current psychiatry reports*. **10** (1): 80–6. doi:10.1007/s11920-008-0014-5. PMID 18269899.
85. ^ [a] [b] [c] Bohanna, I; Wang, X (2012). "Media guidelines for the responsible reporting of suicide: a review of effectiveness". *Crisis*. **33** (4): 190–8. doi:10.1027/0227-5910/a000137. PMID 22713977.
86. ^ [a] [b] Sisask, M; Värnik, A (January 2012). "Media roles in suicide prevention: a systematic review". *International journal of environmental research and public health*. **9** (1): 123–38. doi:10.3390/ijerph9010123. PMC 3315075. PMID 22470283.
87. ^ Stack S (April 2005). "Suicide in the media: a quantitative review of studies based on non-fictional stories". *Suicide Life Threat Behav*. **35** (2): 121–33. doi:10.1521/suli.35.2.121.62877. PMID 15843330.
88. ^ Pirkis J (July 2009). "Suicide and the media". *Psychiatry*. **8** (7): 269–271. doi:10.1016/j.mppsy.2009.04.009.
89. ^ Shrivastava, Amresh; Kimbrell,, Megan; editors, David Lester, (2012). *Suicide from a global perspective : psychosocial approaches*. New York: Nova Science Publishers. pp. 115–118. ISBN 978-1-61470-965-7.
90. ^ [a] [b] Loue, Sana (2008). *Encyclopedia of aging and public health : with 19 tables*. New York, NY: Springer. p. 696. ISBN 978-0-387-33753-1.
91. ^ [a] [b] Moody, Harry R. (2010). *Aging : concepts and controversies* (6th ed.). Los Angeles: Pine Forge Press. p. 158. ISBN 978-1-4129-6966-6.
92. ^ [a] [b] Hales, edited by Robert I. Simon, Robert E. (2012). *The American Psychiatric Publishing textbook of suicide assessment and management* (2nd ed.). Washington, DC: American Psychiatric Pub. p. 714. ISBN 978-1-58562-414-0.
93. ^ editor, Tarek Sobh, (2010). *Innovations and advances in computer sciences and engineering* (Online-Ausg. ed.). Dordrecht: Springer Verlag. p. 503. ISBN 978-90-481-3658-2.
94. ^ Eliason, S (2009). "Murder-suicide: a review of the recent literature". *The journal of the American Academy of Psychiatry and the Law*. **37** (3): 371–6. PMID 19767502.

95. ^ Smith, William Kornblum in collaboration with Carolyn D. (2011-01-31). *Sociology in a changing world* (9e [9th ed]. ed.). Belmont, CA: Wadsworth Cengage Learning. p. 27. ISBN 978-1-111-30157-6.
96. ^ Campbell, Robert Jean (2004). *Campbell's psychiatric dictionary* (8th ed.). Oxford: Oxford University Press. p. 636. ISBN 978-0-19-515221-0.
97. ^ Veatch, ed. by Robert M. (1997). *Medical ethics* (2. ed.). Sudbury, Mass. [u.a.]: Jones and Bartlett. p. 292. ISBN 978-0-86720-974-7.
98. ^ Gutman, Yisrael; Berenbaum, Michael (ed); et al. (1998). *Anatomy of the Auschwitz death camp* (1st pbk. ed.). Bloomington: Publ. in association with the United States Holocaust Memorial Museum, Washington, D.C. by Indiana University Press. p. 400. ISBN 978-0-253-20884-2.
99. ^ Ajdacic-Gross, V; Weiss, MG; Ring, M; Hepp, U; Bopp, M; Gutzwiller, F; Rössler, W (September 2008). "Methods of suicide: international suicide patterns derived from the WHO mortality database.". *Bulletin of the World Health Organization*. **86** (9): 726–32. doi:10.2471/BLT.07.043489. PMC 2649482. PMID 18797649.
100. ^ O'Connor, Rory C.; Platt, Stephen; Gordon, Jacki, eds. (1 June 2011). *International Handbook of Suicide Prevention: Research, Policy and Practice*. John Wiley and Sons. p. 34. ISBN 978-1-119-99856-3.
101. ^ Gunnell D.; Eddleston M.; Phillips M.R.; Konradsen F. (2007). "The global distribution of fatal pesticide self-poisoning: systematic review". *BMC Public Health*. **7**: 357. doi:10.1186/1471-2458-7-357. PMC 2262093. PMID 18154668.
102. ^ Geddes, John; Price, Jonathan; Gelder, Rebecca McKnight; with Michael; Mayou, Richard (2012-01-05). *Psychiatry* (4th ed.). Oxford: Oxford University Press. p. 62. ISBN 978-0-19-923396-0.
103. ^ [a] [b] Krug, Etienne (2002). *World Report on Violence and Health, Volume 1*. Genève: World Health Organization. p. 196. ISBN 978-92-4-154561-7.
104. ^ Yoshioka, E; Hanley, SJ; Kawanishi, Y; Saijo, Y (6 November 2014). "Time trends in method-specific suicide rates in Japan, 1990-2011.". *Epidemiology and psychiatric sciences*: 1–11. doi:10.1017/S2045796014000675. PMID 25373686.
105. ^ Reisch, T; Steffen, T; Habenstein, A; Tschacher, W (September 2013). "Change in suicide rates in Switzerland before and after firearm restriction resulting from the 2003 "Army XXI" reform.". *The American Journal of Psychiatry*. **170** (9): 977–84. doi:10.1176/appi.ajp.2013.12091256. PMID 23897090.
106. ^ Eshun, edited by Sussie; Gurung, Regan A.R. (2009). *Culture and mental health sociocultural influences, theory, and practice*. Chichester, U.K.: Wiley-Blackwell. p. 301. ISBN 978-1-4443-0581-4.
107. ^ "U.S. Suicide Statistics (2005)". Retrieved 2008-03-24.
108. ^ Pjevac, M; Pregelj, P (October 2012). "Neurobiology of suicidal behaviour". *Psychiatria Danubina*. 24 Suppl 3: S336–41. PMID 23114813.
109. ^ Sher, L (2011). "The role of brain-derived neurotrophic factor in the pathophysiology of adolescent suicidal behavior". *International journal of adolescent medicine and health*. **23** (3): 181–5. doi:10.1515/ijamh.2011.041. PMID 22191181.
110. ^ Sher, L (May 2011). "Brain-derived neurotrophic factor and suicidal behavior". *QJM : monthly journal of the Association of Physicians*. **104** (5): 455–8. doi:10.1093/qjmed/hcq207. PMID 21051476.
111. ^ [a] [b] Dwivedi, Yogesh (2012). *The neurobiological basis of suicide*. Boca Raton, FL: Taylor & Francis/CRC Press. p. 166. ISBN 978-1-4398-3881-5.
112. ^ Stein, edited by George; Wilkinson, Greg (2007). *Seminars in general adult psychiatry* (2. ed.). London: Gaskell. p. 145. ISBN 978-1-904671-44-2.
113. ^ Autry, AE; Monteggia, LM (Nov 1, 2009). "Epigenetics in suicide and depression". *Biological Psychiatry*. **66** (9): 812–3. doi:10.1016/j.biopsych.2009.08.033. PMC 2770810. PMID 19833253.
114. ^ [a] [b] [c] "Suicide prevention". *WHO Sites: Mental Health*. World Health Organization. Aug 31, 2012. Retrieved 2013-01-13.
115. ^ Cox, GR; Owens, C; Robinson, J; Nicholas, A; Lockley, A; Williamson, M; Cheung, YT; Pirkis, J (Mar 9, 2013). "Interventions to reduce suicides at suicide hotspots: a systematic review". *BMC Public Health*. **13**: 214. doi:10.1186/1471-2458-13-214. PMC 3606606. PMID 23496989.
116. ^ "Suicide". *The United States Surgeon General*. Retrieved 4 September 2011.
117. ^ Robinson, J; Hetrick, SE; Martin, C (January 2011). "Preventing suicide in young people: systematic review". *The Australian and New Zealand Journal of Psychiatry*. **45** (1): 3–26. doi:10.3109/00048674.2010.511147. PMID 21174502.
118. ^ Fässberg, MM; van Orden, KA; Duberstein, P; Erlangsen, A; Lapierre, S; Bodner, E; Canetto, SS; De Leo, D; Szanto, K; Waern, M (March 2012). "A systematic review of social factors and suicidal behavior in older adulthood". *International journal of environmental research and public health*. **9** (3): 722–45. doi:10.3390/ijerph9030722. PMC 3367273. PMID 22690159.
119. ^ "World Suicide Prevention Day -10 September, 2013". IASP. Retrieved 29 October 2013.
120. ^ Williams, SB; O'Connor, EA; Eder, M; Whitlock, EP (April 2009). "Screening for child and adolescent depression in

primary care settings: a systematic evidence review for the US Preventive Services Task Force". *Pediatrics*. **123** (4): e716–35. doi:10.1542/peds.2008-2415. PMID 19336361.
121. ^ LeFevre, ML; U.S. Preventive Services Task Force (May 20, 2014). "Screening for suicide risk in adolescents, adults, and older adults in primary care: u.s. Preventive services task force recommendation statement.". *Annals of Internal Medicine*. **160** (10): 719–26. doi:10.7326/M14-0589. PMID 24842417.
122. ^ Meier, Marshall B. Clinard, Robert F. (2008). *Sociology of deviant behavior* (14th ed.). Belmont, CA: Wadsworth Cengage Learning. p. 169. ISBN 978-0-495-81167-1.
123. ^ Horowitz, LM; Ballard, ED; Pao, M (October 2009). "Suicide screening in schools, primary care and emergency departments". *Current Opinion in Pediatrics*. **21** (5): 620–7. doi:10.1097/MOP.0b013e3283307a89. PMC 2879582. PMID 19617829.
124. ^ Paris, J (June 2004). "Is hospitalization useful for suicidal patients with borderline personality disorder?". *Journal of personality disorders*. **18** (3): 240–7. doi:10.1521/pedi.18.3.240.35443. PMID 15237044.
125. ^ Goodman, M; Roiff, T; Oakes, AH; Paris, J (February 2012). "Suicidal risk and management in borderline personality disorder". *Current psychiatry reports*. **14** (1): 79–85. doi:10.1007/s11920-011-0249-4. PMID 22113831.
126. ^ *a b* Canadian Agency for Drugs and Technologies in Health, (CADTH) (2010). "Dialectical behaviour therapy in adolescents for suicide prevention: systematic review of clinical-effectiveness". *CADTH technology overviews*. **1** (1): e0104. PMC 3411135. PMID 22977392.
127. ^ Stoffers, JM; Völlm, BA; Rücker, G; Timmer, A; Huband, N; Lieb, K (Aug 15, 2012). Lieb, Klaus, ed. "Psychological therapies for people with borderline personality disorder". *Cochrane database of systematic reviews (Online)*. **8**: CD005652. doi:10.1002/14651858.CD005652.pub2. PMID 22895952.
128. ^ Elizabeth O'Connor; Bradley N. Gaynes; Brittany U. Burda; Clara Soh; Evelyn P. Whitlock (April 2013). "Screening for and Treatment of Suicide Risk Relevant to Primary Care: A Systematic Review for the U.S. Preventive Services Task Force". *Annals of Internal Medicine*. **158** (10): 741–54. doi:10.7326/0003-4819-158-10-201305210-00642. PMID 23609101.
129. ^ Hetrick, SE; McKenzie, JE; Cox, GR; Simmons, MB; Merry, SN (Nov 14, 2012). Hetrick, Sarah E, ed. "Newer generation antidepressants for depressive disorders in children and adolescents". *Cochrane database of systematic reviews (Online)*. **11**: CD004851. doi:10.1002/14651858.CD004851.pub3. PMID 23152227.
130. ^ Baldessarini, RJ; Tondo, L; Hennen, J (2003). "Lithium treatment and suicide risk in major affective disorders: update and new findings". *The Journal of Clinical Psychiatry*. 64 Suppl 5: 44–52. PMID 12720484.
131. ^ Cipriani, A.; Hawton, K.; Stockton, S.; Geddes, J. R. (27 June 2013). "Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis". *BMJ*. **346** (jun27 4): f3646–f3646. doi:10.1136/bmj.f3646. PMID 23814104.
132. ^ Wagstaff, A; Perry, C (2003). "Clozapine: in prevention of suicide in patients with schizophrenia or schizoaffective disorder.". *CNS Drugs*. **17** (4): 273–80; discussion 281–3. doi:10.2165/00023210-200317040-00004. PMID 12665398.
133. ^ "Deaths estimates for 2008 by cause for WHO Member States". World Health Organization. Retrieved 10 February 2013.
134. ^ "Suicide rates Data by country". *who.int*. Retrieved 23 November 2014.
135. ^ Haney, EM; O'Neil, ME; Carson, S; Low, A; Peterson, K; Denneson, LM; Oleksiewicz, C; Kansagara, D (March 2012). "Suicide Risk Factors and Risk Assessment Tools: A Systematic Review". PMID 22574340.
136. ^ "CDC finds suicide rates among middle-aged adults increased from 1999 to 2010". Centers for Disease Control and Prevention. May 2, 2013. Retrieved 15 July 2013.
137. ^ *a b* Weiyuan, C (December 2009). "Women and suicide in rural China". *Bulletin of the World Health Organization*. **87** (12): 888–9. doi:10.2471/BLT.09.011209. PMC 2789367. PMID 20454475.
138. ^ "Estimates for 2000–2012". *WHO*. Retrieved 24 August 2016.
139. ^ *a b* David Sue, Derald Wing Sue, Stanley Sue, Diane Sue (2012-01-01). *Understanding abnormal behavior* (Tenth ed., [student ed.] ed.). Belmont, CA: Wadsworth/Cengage Learning. p. 255. ISBN 978-1-111-83459-3.
140. ^ Stern, Theodore A.; Fava, Maurizio; Wilens, Timothy E.; Rosenbaum, Jerrold F. (2015). *Massachusetts General Hospital Comprehensive Clinical Psychiatry* (2 ed.). Elsevier Health Sciences. p. 589. ISBN 9780323328999.
141. ^ Krug, Etienne G. (2002). *World Report on Violence and Health*. World Health Organization. p. 191. ISBN 9789241545617.
142. ^ "Suicide Statistics — AFSP". *American Foundation for Suicide Prevention*. Retrieved 3 September 2016.
143. ^ "http://www.thetaskforce.org/downloads/reports/reports/ntds_full.pdf" (PDF). 2011. Retrieved 25 July 2016. External link in |title= (help)
144. ^ Björkenstam, Charlotte; et al. (11 May 2016). "Suicide in married couples in Sweden: Is the risk greater in same-sex couples". *European Journal of Epidemiology*. doi:10.1007/s10654-016-0154-6. Retrieved 27 November 2016.

145. ^ a b c d Pitman, A; Krysinska, K; Osborn, D; King, M (Jun 23, 2012). "Suicide in young men". *The Lancet*. **379** (9834): 2383–92. doi:10.1016/S0140-6736(12)60731-4. PMID 22726519.
146. ^ Szasz, Thomas (1999). *Fatal freedom : the ethics and politics of suicide*. Westport, Conn.: Praeger. p. 11. ISBN 978-0-275-96646-1.
147. ^ a b Maris, Ronald (2000). *Comprehensive textbook of suicidology*. New York [u.a.]: Guilford Press. pp. 97–103. ISBN 978-1-57230-541-0.
148. ^ Dickinson, Michael R. Leming, George E. (2010-09-02). *Understanding dying, death, and bereavement* (7th ed.). Belmont, CA: Wadsworth Cengage Learning. p. 290. ISBN 978-0-495-81018-6.
149. ^ W. S. F. Pickering; Geoffrey Walford (2000). *Durkheim's Suicide : a century of research and debate* (1. publ. ed.). London [u.a.]: Routledge. p. 69. ISBN 978-0-415-20582-5.
150. ^ a b Maris, Ronald (2000). *Comprehensive textbook of suicidology*. New York [u.a.]: Guilford Press. p. 540. ISBN 978-1-57230-541-0.
151. ^ a b "Suicide". Stanford Encyclopedia of Philosophy.
152. ^ Paula R. Backscheider; Catherine Ingrassia (2008). *A Companion to the Eighteenth-Century English Novel and Culture*. John Wiley & Sons. p. 530. ISBN 9781405154505.
153. ^ a b Paperno, Irina (1997). *Suicide as a cultural institution in Dostoevsky's Russia*. Ithaca: Cornell university press. p. 60. ISBN 978-0-8014-8425-4.
154. ^ Norman St. John-Stevas (2002). *Life, Death and the Law: Law and Christian Morals in England and the United States*. Beard Books. p. 233. ISBN 9781587981135.
155. ^ al.], David Lanham ... [et (2006). *Criminal laws in Australia*. Annandale, N.S.W.: The Federation Press. p. 229. ISBN 978-1-86287-558-6.
156. ^ Duffy, Michael Costa, Mark (1991). *Labor, prosperity and the nineties : beyond the bonsai economy* (2nd ed.). Sydney: Federation Press. p. 315. ISBN 978-1-86287-060-4.
157. ^ Quill, Constance E. Putnam ; foreword by Timothy E. (2002). *Hospice or hemlock? : searching for heroic compassion*. Westport, Conn.: Praeger. p. 143. ISBN 978-0-89789-921-5.
158. ^ a b c McLaughlin, Columba (2007). *Suicide-related behaviour understanding, caring and therapeutic responses*. Chichester, England: John Wiley & Sons. p. 24. ISBN 978-0-470-51241-8.
159. ^ Holt, Gerry."When suicide was illegal". BBC News. 3 August 2011. Accessed 11 August 2011.
160. ^ "Guardian & Observer style guide". *Guardian website*. The Guardian. Retrieved 29 November 2011.
161. ^ Srivastava, editors, Nitish Dogra, Sangeet (2012-01-01). *Climate change and disease dynamics in India*. New Delhi: The Energy and Resources Institute. p. 256. ISBN 978-81-7993-412-8.
162. ^ "Govt decides to repeal Section 309 from IPC; attempt to suicide no longer a crime". Zee News. December 10, 2014. Retrieved December 10, 2014.
163. ^ "German politician Roger Kusch helped elderly woman to die". Times Online. July 2, 2008.
164. ^ a b Appel, JM (May 2007). "A Suicide Right for the Mentally Ill? A Swiss Case Opens a New Debate". *Hastings Center Report*. **37** (3): 21–23. doi:10.1353/hcr.2007.0035. PMID 17649899.
165. ^ "Chapter 70.245 RCW, The Washington death with dignity act". *Washington State Legislature*.
166. ^ "Oregon Revised Statute - 127.800 s.1.01. Definitions". Oregon State Legislature.
167. ^ "CBCNews.ca Mobile". Cbc.ca. 1999-02-01. Retrieved 2014-08-06.
168. ^ Claude Adams (April 15, 2014). "US border suicide profiling must stop: Report". *globalnews.ca*. Retrieved 7 August 2014.
169. ^ Ronald Roth, D.Acu. "Suicide & Euthanasia – a Biblical Perspective". Acu-cell.com. Retrieved 2009-05-06.
170. ^ "Norman N. Holland, Literary Suicides: A Question of Style". Clas.ufl.edu. Retrieved 2009-05-06.
171. ^ "Catechism of the Catholic Church – PART 3 SECTION 2 CHAPTER 2 ARTICLE 5". Scborromeo.org. 1941-06-01. Retrieved 2009-05-06.
172. ^ "Catechism of the Catholic Church – PART 3 SECTION 2 CHAPTER 2 ARTICLE 5". Scborromeo.org. 1941-06-01. Retrieved 2009-05-06.
173. ^ "The Bible and Suicide". Religioustolerance.org. Retrieved 2009-05-06.
174. ^ "Euthanasia and Judaism: Jewish Views of Euthanasia and Suicide". ReligionFacts.com. Retrieved 2008-09-16.
175. ^ a b Gearing, RE; Lizardi, D (September 2009). "Religion and suicide.". *Journal of religion and health*. **48** (3): 332–41. doi:10.1007/s10943-008-9181-2. PMID 19639421.
176. ^ Hindu Website. Hinduism and suicide
177. ^ a b "Hinduism – Euthanasia and Suicide". BBC. 2009-08-25.
178. ^ BBC News, "India wife dies on husband's pyre", Aug. 22, 2006.
179. ^ a b c "Suicide (Stanford Encyclopedia of Philosophy)". Plato.stanford.edu. Retrieved 2009-05-06.
180. ^ Kant, Immanuel. (1785) *Kant: The Metaphysics of Morals*, M. Gregor (trans.), Cambridge: Cambridge University

Press, 1996. ISBN 978-0-521-56673-5. p177.
181. ^ Safranek John P (1998). "Autonomy and Assisted Suicide: The Execution of Freedom". *The Hastings Center Report*. **28** (4): 33. doi:10.2307/3528611.
182. ^ Raymond Whiting: A natural right to die: twenty-three centuries of debate, pp. 13–17; Praeger (2001) ISBN 0-313-31474-8
183. ^ Wesley J. Smith, Death on Demand: The assisted-suicide movement sheds its fig leaf, *The Weekly Standard*, June 5, 2007
184. ^ "The Suicide". The Walters Art Museum.
185. ^ Ozawa-de Silva, C (December 2008). "Too lonely to die alone: internet suicide pacts and existential suffering in Japan". *Culture, medicine and psychiatry*. **32** (4): 516–51. doi:10.1007/s11013-008-9108-0. PMID 18800195.
186. ^ Durkee, T; Hadlaczky, G; Westerlund, M; Carli, V (October 2011). "Internet pathways in suicidality: a review of the evidence". *International journal of environmental research and public health*. **8** (10): 3938–52. doi:10.3390/ijerph8103938. PMC 3210590. PMID 22073021.
187. ^ *a b* Robinson, edited by David Picard, Mike (2012-11-28). *Emotion in motion : tourism, affect and transformation*. Farnham, Surrey: Ashgate. p. 176. ISBN 978-1-4094-2133-7.
188. ^ Robinson, ed. by Peter; Heitmann, Sine; Dieke, Peter (2010). *Research themes for tourism*. Oxfordshire [etc.]: CABI. p. 172. ISBN 978-1-84593-684-6.
189. ^ *a b* Dennis, Richard (2008). *Cities in modernity : representations and productions of metropolitan space, 1840 – 1930* (Repr. ed.). Cambridge [u.a.]: Cambridge Univ. Press. p. 20. ISBN 978-0-521-46841-1.
190. ^ McDougall, Tim; Armstrong, Marie; Trainor, Gemma (2010). *Helping children and young people who self-harm : an introduction to self-harming and suicidal behaviours for health professionals*. Abingdon, Oxon: Routledge. p. 23. ISBN 978-0-415-49913-2.
191. ^ *a b* Bateson, John (2008). *Building hope : leadership in the nonprofit world*. Westport, Conn.: Praeger. p. 180. ISBN 978-0-313-34851-8.
192. ^ *a b* Miller, David (2011). *Child and Adolescent Suicidal Behavior: School-Based Prevention, Assessment, and Intervention*. p. 46. ISBN 978-1-60623-997-1.
193. ^ Hall 1987, p.282
194. ^ *Alternative Considerations of Jonestown and Peoples Temple*. San Diego State University.Archived January 24, 2011, at WebCite
195. ^ "1978:Mass Suicide Leaves 900 Dead". Retrieved 9 November 2011.
196. ^ John Toland, *The Rising Sun: The Decline and Fall of the Japanese Empire 1936–1945*, Random House, 1970, p. 519
197. ^ Suicide and Self-Starvation, Terence M. O'Keeffe, *Philosophy*, Vol. 59, No. 229 (Jul., 1984), pp. 349–363
198. ^ Watson, Bruce (2007). *Exit Rommel: The Tunisian Campaign, 1942–43*. Stackpole Books. p. 170. ISBN 978-0-8117-3381-6.
199. ^ Chang, Kenneth (August 25, 2008). "In Salmonella Attack, Taking One for the Team". New York Times.
200. ^ Tofilski,Adam; Couvillon, MJ; Evison, SEF; Helantera, H; Robinson, EJH; Ratnieks, FLW (2008). "Preemptive Defensive Self-Sacrifice by Ant Workers" (PDF). *The American Naturalist*. **172** (5): E239–E243. doi:10.1086/591688. PMID 18928332.
201. ^ Larry O'Hanlon (Mar 10, 2010). "Animal Suicide Sheds Light on Human Behavior". Discovery News.
202. ^ "Life In The Undergrowth". BBC.
203. ^ Bordereau, C; Robert, A.; Van Tuyen, V.; Peppuy, A. (August 1997). "Suicidal defensive behaviour by frontal gland dehiscence in Globitermes sulphureus Haviland soldiers (Isoptera)". *Insectes Sociaux*. Birkhäuser Basel. **44** (3): 289–297. doi:10.1007/s000400050049.
204. ^ Nobel, Justin (Mar 19, 2010). "Do Animals Commit Suicide? A Scientific Debate". Time.
205. ^ Stoff, David; Mann, J. John (1997). "Suicide Research". *Annals of the New York Academy of Sciences*. Annals of the New York Academy of Sciences. **836** (Neurobiology of Suicide, The : From the Bench to the Clinic): 1–11. Bibcode:1997NYASA.836....1S. doi:10.1111/j.1749-6632.1997.tb52352.x.

# Further reading

- Gambotto, Antonella (2004). *The Eclipse: A Memoir of Suicide*. Australia: Broken Ankle Books. ISBN 0-9751075-1-8.
- Goeschel, Christian (2009). *Suicide in Nazi Germany*. Oxford University Press. ISBN 0-19-953256-7.

# External links

- Suicide at DMOZ
- *Preventing suicide: a global imperative.* (PDF). WHO. 2014. ISBN 9789241564779.
- Freakonomics podcast: The Suicide Paradox

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# Book:Rheumatology

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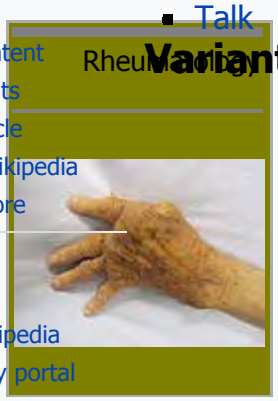


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# Carpal tunnel syndrome

From Wikipedia, the free encyclopedia

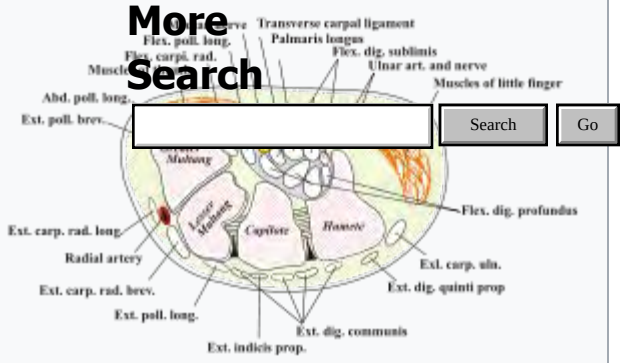
**Carpal tunnel syndrome** (**CTS**) is a medical condition due to compression of the median nerve as it travels through the wrist at the carpal tunnel.[1] The main symptoms are pain, numbness, and tingling, in the thumb, index finger, middle finger, and the thumb side of the ring fingers.[1] Symptoms typically start gradually and during the night.[2] Pain may extend up the arm.[2] Weak grip strength may occur and after a long period of time the muscles at the base of the thumb may waste away.[2] In more than half of cases both sides are affected.[1]

Risk factors include obesity, repetitive wrist work, pregnancy, and rheumatoid arthritis.[3][4] There is tentative evidence that hypothyroidism increases the risk.[5] It is unclear if diabetes plays a role. The use of birth control pills does not affect the risk. Types of work that are associated include computer work, work with vibrating tools, and work that requires a strong grip.[3] Diagnosis is suspected based on signs, symptoms, and specific physical tests and may be confirmed with electrodiagnostic tests.[2] If muscle wasting at the base of the thumb is present, the diagnosis is likely.[3]

Being physically active can decrease the risk of developing CTS. Symptoms can be improved by wearing a wrist splint or with corticosteroid injections. Taking NSAIDs or gabapentin does not appear to be useful. Surgery to cut the transverse carpal ligament is effective with better results at a year compared to non surgical options. Further splinting after surgery is not needed. Evidence does not support magnet therapy.[3]

About 5% of people in the United States have carpal tunnel syndrome.[6] It usually begins in adulthood and women are more commonly affected than men.[2] Up to 33% of people may improve without specific treatment over approximately a year.[1] Carpal tunnel syndrome was first fully described after World War II.[7]

**Carpal tunnel syndrome**




Transverse section at the wrist. The median nerve is colored yellow. The carpal tunnel consists of the bones and transverse carpal ligament.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Orthopedic surgery, plastic surgery |
| **ICD-10** | G56.0 |
| **ICD-9-CM** | 354.0 |
| **OMIM** | 115430 |
| **DiseasesDB** | 2156 |
| **MedlinePlus** | 000433 |
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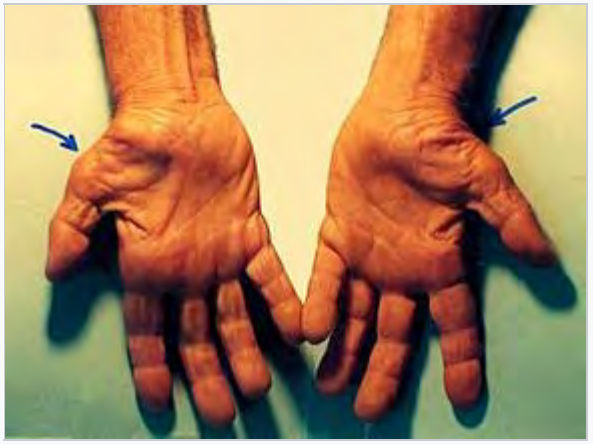
## Signs and symptoms [edit]

People with CTS experience numbness, tingling, or burning sensations in the thumb and fingers, in particular the index and middle fingers and radial half of the ring finger, because these receive their sensory and motor function (muscle control) from the median nerve. Ache and discomfort can possibly be felt more proximally in the forearm or even the upper arm.[8] Less-specific symptoms may include pain in the wrists or hands, loss of grip strength,[9] and loss of manual dexterity.[10]



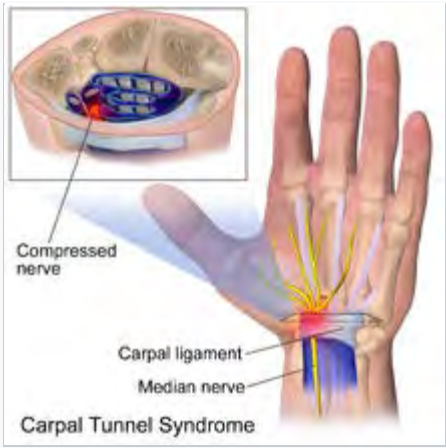
Untreated carpal tunnel syndrome, showing how the muscles at the base of the thumb have wasted away.

Some suggest that median nerve symptoms can arise from compression at the level of the thoracic outlet or the area where the median nerve passes between the two heads of the pronator teres in the forearm,[11] although this is debated.

Numbness and paresthesias in the median nerve distribution are the hallmark neuropathic symptoms (NS) of carpal tunnel entrapment syndrome. Weakness and atrophy of the thumb muscles may occur if the condition remains untreated, because the muscles are not receiving sufficient nerve stimulation.[12] Discomfort is usually worse at night and in the morning.[13]

## Causes [edit]

Most cases of CTS are of unknown cause.[14] Carpal tunnel syndrome can be associated with any condition that causes pressure on the median nerve at the wrist. Some common conditions that can lead to CTS include obesity, hypothyroidism, arthritis, diabetes, prediabetes (impaired glucose tolerance), and trauma.[15] Genetics play a role.[16] The use of birth control pills does not affect the risk.[3] Carpal tunnel is




Anatomy of the carpal tunnel showing the median nerve passing through the tight space it shares with the finger tendons.

a feature of a form of Charcot-Marie-Tooth syndrome type 1 called hereditary neuropathy with liability to pressure palsies.

Other causes of this condition include intrinsic factors that exert pressure within the tunnel, and extrinsic factors (pressure exerted from outside the tunnel), which include benign tumors such as lipomas, ganglion, and vascular malformation.[17] Carpal tunnel syndrome often is a symptom of transthyretin amyloidosis-associated polyneuropathy and prior carpal tunnel syndrome surgery is very common in individuals who later present with transthyretin amyloid-associated cardiomyopathy, suggesting that transthyretin amyloid deposition may cause carpal tunnel syndrome.[18][19][20][21][22][23][24]

The median nerve can usually move up to 9.6 mm to allow the wrist to flex, and to a lesser extent during extension.[25] Long-term compression of the median nerve can inhibit nerve gliding, which may lead to injury and scarring. When scarring occurs, the nerve will adhere to the tissue around it and become locked into a fixed position, so that less movement is apparent.[26]

Normal pressure of the carpal tunnel has been defined as a range of 2–10 mm, and wrist flexion increases this pressure 8-fold, while extension increases it 10-fold.[25] Repetitive flexion and extension in the wrist significantly increase the fluid pressure in the tunnel through thickening of the synovial tissue that lines the tendons within the carpal tunnel.[27]

## Work related [edit]

The international debate regarding the relationship between CTS and repetitive motion in work is ongoing. The Occupational Safety and Health Administration (OSHA) has adopted rules and regulations regarding cumulative trauma disorders. Occupational risk factors of repetitive tasks, force, posture, and vibration have been cited. The relationship between work and CTS is controversial; in many locations, workers diagnosed with carpal tunnel syndrome are entitled to time off and compensation.[28][29]

Some speculate that carpal tunnel syndrome is provoked by repetitive movement and manipulating activities and that the exposure can be cumulative. It has also been stated that symptoms are commonly exacerbated by forceful and repetitive use of the hand and wrists in industrial occupations,[30] but it is unclear as to whether this refers to pain (which may not be due to carpal tunnel syndrome) or the more typical numbness symptoms.[31]

A review of available scientific data by the National Institute for Occupational Safety and Health (NIOSH) indicated that job tasks that involve highly repetitive manual acts or specific wrist postures were associated with incidents of CTS, but causation was not established, and the distinction from work-related arm pains that are not carpal tunnel syndrome was not clear. It has been proposed that repetitive use of the arm can affect the biomechanics of the upper limb or cause damage to tissues. It has also been proposed that postural and spinal assessment along with ergonomic assessments should be included in the overall determination of the condition. Addressing these factors has been found to improve comfort in some studies.[32] A 2010 survey by NIOSH showed that 2/3 of the 5 million carpal tunnel cases in the US that year were related to work.[33] Women have more work-related carpal tunnel syndrome than men.[34]

Speculation that CTS is work-related is based on claims such as CTS being found mostly in the working adult population, though evidence is lacking for this. For instance, in one recent representative series of a consecutive experience, most patients were older and not working.[35] Based on the claimed increased incidence in the workplace, arm use is implicated, but the weight of evidence suggests that this is an

inherent, genetic, slowly but inevitably progressive idiopathic peripheral mononeuropathy.[36]

### Associated conditions [edit]

A variety of patient factors can lead to CTS, including heredity, size of the carpal tunnel, associated local and systematic diseases, and certain habits.[37] Non-traumatic causes generally happen over a period of time, and are not triggered by one certain event. Many of these factors are manifestations of physiologic aging.[38]

Examples include:

- Rheumatoid arthritis and other diseases that cause inflammation of the flexor tendons.
- With hypothyroidism, generalized myxedema causes deposition of mucopolysaccharides within both the perineurium of the median nerve, as well as the tendons passing through the carpal tunnel.
- During pregnancy women experience CTS due to hormonal changes (high progesterone levels) and water retention (which swells the synovium), which are common during pregnancy.
- Previous injuries including fractures of the wrist.
- Medical disorders that lead to fluid retention or are associated with inflammation such as: inflammatory arthritis, Colles' fracture, amyloidosis, hypothyroidism, diabetes mellitus, acromegaly, and use of corticosteroids and estrogens.
- Carpal tunnel syndrome is also associated with repetitive activities of the hand and wrist, in particular with a combination of forceful and repetitive activities[15]
- Acromegaly causes excessive growth hormones. This causes the soft tissues and bones around the carpel tunnel to grow and compress the median nerve.[39]
- Tumors (usually benign), such as a ganglion or a lipoma, can protrude into the carpal tunnel, reducing the amount of space. This is exceedingly rare (less than 1%).
- Obesity also increases the risk of CTS: individuals classified as obese (BMI > 29) are 2.5 times more likely than slender individuals (BMI < 20) to be diagnosed with CTS.[40]
- *Double-crush syndrome* is a debated hypothesis that compression or irritation of nerve branches contributing to the median nerve in the neck, or anywhere above the wrist, increases sensitivity of the nerve to compression in the wrist. There is little evidence, however, that this syndrome really exists.[41]
- Heterozygous mutations in the gene SH3TC2, associated with Charcot-Marie-Tooth, confer susceptibility to neuropathy, including the carpal tunnel syndrome.[42]

## Pathophysiology [edit]

*Main article: Carpal tunnel*

The carpal tunnel is an anatomical compartment located at the base of the palm. Nine flexor tendons and the median nerve pass through the carpal tunnel that is surrounded on three sides by the carpal bones that form an arch. The median nerve provides feeling or sensation to the thumb, index finger, long finger, and half of the ring finger. At the level of the wrist, the median nerve supplies the muscles at the base of the thumb that allow it to abduct, move away from the other four fingers, as well as move out of the plane of the palm. The carpal tunnel is located at the middle third of the base of the palm, bounded by the bony prominence of the scaphoid tubercle and trapezium at the base of the thumb, and the hamate hook that can be palpated along the axis of the ring finger. From the anatomical position, the carpal tunnel is bordered on the anterior surface by the transverse carpal ligament, also known as the flexor retinaculum. The flexor retinaculum is a strong, fibrous band that attaches to the pisiform and the hamulus of the hamate. The proximal boundary is the distal wrist skin crease, and the distal boundary is approximated by a line known as Kaplan's cardinal line.[43] This line uses surface landmarks, and is drawn between the apex of the skin fold between the thumb and index finger to the palpated hamate hook.[44] The median nerve can be compressed by a decrease in the size of the canal, an increase in the size of the contents (such as the swelling of lubrication tissue around the flexor tendons), or both.[45] Since the carpal tunnel is bordered by carpal bones on one side and a ligament on the other, when the pressure builds up inside the tunnel, there is nowhere for it to escape and thus it ends up pressing up against and damaging the median nerve.

Simply flexing the wrist to 90 degrees will decrease the size of the canal.

Compression of the median nerve as it runs deep to the transverse carpal ligament (TCL) causes atrophy of the thenar eminence, weakness of the flexor pollicis brevis, opponens pollicis, abductor pollicis brevis, as well as sensory loss in the digits supplied by the median nerve. The superficial sensory branch of the median nerve, which provides sensation to the base of the palm, branches proximal to the TCL and travels superficial to it. Thus, this branch spared in carpal tunnel syndrome, and there is no loss of palmar sensation.[46]

## Diagnosis [edit]

There is no consensus reference standard for the diagnosis of carpal tunnel syndrome. A combination of described symptoms, clinical findings, and electrophysiological testing may be used. CTS work up is the most common referral to the electrodiagnostic lab. Historically, diagnosis has been made with the combination of a thorough history and physical examination in conjunction with the use of electrodiagnostic (EDX) testing for confirmation. Additionally, evolving technology has included the use of ultrasonography in the diagnosis of CTS. However, it is well established that physical exam provocative maneuvers lack both sensitivity and specificity. Furthermore, EDX cannot fully exclude the diagnosis of CTS due to the lack of sensitivity. A Joint report published by the American Association of Neuromuscular and Electrodiagostic Medicine (AANEM), the American Academy of Physical Medicine and Rehabilitation (AAPM&R) and the American Academy of Neurology defines practice parameters, standards and guidelines for EDX studies of CTS based on an extensive critical literature review. This joint review concluded median and sensory nerve conduction studies are valid and reproducible in a clinical laboratory setting and a clinical diagnosis of CTS can be made with a sensitivity greater than 85% and specificity greater than 95%. Given the key role of electrodiagnostic testing in the diagnosis of CTS, The American Association of Neuromuscular & Electrodiagnostic Medicine has issued evidence-based practice guidelines, both for the diagnosis of carpal tunnel syndrome.

Numbness in the distribution of the median nerve, nocturnal symptoms, thenar muscle weakness/atrophy, positive Tinel's sign at the carpal tunnel, and abnormal sensory testing such as two-point discrimination have been standardized as clinical diagnostic criteria by consensus panels of experts.[47][48] Pain may also be a presenting symptom, although less common than sensory disturbances.

Electrodiagnostic testing (electromyography and nerve conduction velocity) can objectively verify the median nerve dysfunction. Normal nerve conduction studies, however, do not exclude the diagnosis of CTS. Clinical assessment by history taking and physical examination can support a diagnosis of CTS. If clinical suspicion of CTS is high, treatment should be initiated despite normal electrodiagnostic testing.

### Physical exam [edit]

The use of Phalen test, Tinel sign, Flick sign, or upper limb nerve test alone is not sufficient for diagnosis.[3]

- Phalen's maneuver is performed by flexing the wrist gently as far as possible, then holding this position and awaiting symptoms.[49] A positive test is one that results in numbness in the median nerve distribution when holding the wrist in acute flexion position within 60 seconds. The quicker the numbness starts, the more advanced the condition. Phalen's sign is defined as pain and/or paresthesias in the median-innervated fingers with one minute of wrist flexion. Only this test has been shown to correlate with CTS severity when studied prospectively.[37]
- Tinel's sign, a classic — though less sensitive - test is a way to detect irritated nerves. Tinel's is performed by lightly tapping the skin over the flexor retinaculum to elicit a sensation of tingling or "pins and needles" in the nerve distribution. Tinel's sign (pain and/or paresthesias of the median-innervated fingers with percussion over the median nerve) is less sensitive, but slightly more specific than Phalen's sign.[37]
- Durkan test, *carpal compression test*, or applying firm pressure to the palm over the nerve for up to 30 seconds to elicit symptoms has also been proposed.[50][51]
- Hand elevation test The hand elevation test has higher sensitivity and specificity than Tinel's test,

Phalen's test, and carpal compression test. Chi-square statistical analysis confirms the hand elevation test is not ineffective compared with Tinel's test, Phalen's test, and carpal compression test.[52]

As a note, a patient with true carpal tunnel syndrome (entrapment of the median nerve within the carpal tunnel) will not have any sensory loss over the thenar eminence (bulge of muscles in the palm of hand and at the base of the thumb). This is because the palmar branch of the median nerve, which innervates that area of the palm, branches off of the median nerve and passes over the carpal tunnel.[53] This feature of the median nerve can help separate carpal tunnel syndrome from thoracic outlet syndrome, or pronator teres syndrome.

Other conditions may also be misdiagnosed as carpal tunnel syndrome. Thus, if history and physical examination suggest CTS, patients will sometimes be tested electrodiagnostically with nerve conduction studies and electromyography. The goal of electrodiagnostic testing is to compare the speed of conduction in the median nerve with conduction in other nerves supplying the hand. When the median nerve is compressed, as in CTS, it will conduct more slowly than normal and more slowly than other nerves. There are many electrodiagnostic tests used to make a diagnosis of CTS, but the most sensitive, specific, and reliable test is the Combined Sensory Index (also known as Robinson index).[54] Electrodiagnosis rests upon demonstrating impaired median nerve conduction across the carpal tunnel in context of normal conduction elsewhere. Compression results in damage to the myelin sheath and manifests as delayed latencies and slowed conduction velocities [37] However, normal electrodiagnostic studies do not preclude the presence of carpal tunnel syndrome, as a threshold of nerve injury must be reached before study results become abnormal and cut-off values for abnormality are variable.[48] Carpal tunnel syndrome with normal electrodiagnostic tests is very, very mild at worst.

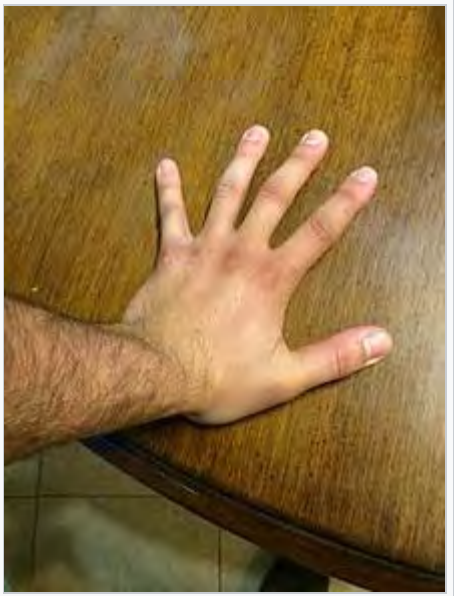
The role of MRI or ultrasound imaging in the diagnosis of carpal tunnel syndrome is unclear.[55][56][57] Their routine use is not recommended.[3]

### Differential diagnosis [edit]

Carpal tunnel syndrome is sometimes applied as a label to anyone with pain, numbness, swelling, and/or burning in the radial side of the hands and/or wrists. When pain is the primary symptom, carpal tunnel syndrome is unlikely to be the source of the symptoms.[31] As a whole, the medical community is not currently embracing or accepting trigger point theories due to lack of scientific evidence supporting their effectiveness.

## Prevention [edit]

Suggested healthy habits such as avoiding repetitive stress, work modification through use of ergonomic equipment (wrist rest, mouse pad), taking proper breaks, using keyboard alternatives (digital pen, voice recognition, and dictation), and have been proposed as methods to help prevent carpal tunnel syndrome. The potential role of B-vitamins in preventing or treating carpal tunnel syndrome has not been proven.[58][59][*unreliable medical source?*] There is little or no data to support the concept that activity adjustment prevents carpal tunnel syndrome.[60]


Carpal tunnel prevention

Stretches and isometric exercises will aid in prevention for persons at risk. Stretching before the activity and during breaks will aid in alleviating tension at the wrist.[61] Place the hand firmly on a flat surface and gently press for a few seconds to stretch the wrist and fingers. An example for an isometric exercise of the wrist is done by clenching the fist tightly, releasing and fanning out fingers.[61] None of these stretches or exercises should cause pain or discomfort.

Biological factors such as genetic predisposition and anthropometric features had significantly stronger causal association with carpal tunnel

syndrome than occupational/environmental factors such as repetitive hand use and stressful manual work.[60] This suggests that carpal tunnel syndrome might not be preventable simply by avoiding certain activities or types of work/activities.

stretch[*citation needed*]

# Treatment [edit]

Generally accepted treatments include: physiotherapy, steroids either orally or injected locally, splinting, and surgical release of the transverse carpal ligament.[62] There is insufficient evidence for ultrasound, yoga, lasers, vitamin B6, and exercise.[62] Change in activity may include avoiding activities that worsen symptoms.[16]

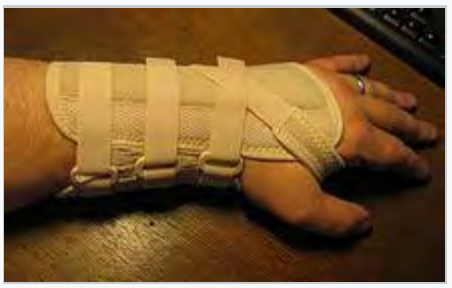
The American Academy of Orthopedic Surgeons recommends proceeding conservatively with a course of nonsurgical therapies tried before release surgery is considered.[63] A different treatment should be tried if the current treatment fails to resolve the symptoms within 2 to 7 weeks. Early surgery with carpal tunnel release is indicated where there is evidence of median nerve denervation or a person elects to proceed directly to surgical treatment.[63] Recommendations may differ when carpal tunnel syndrome is found in association with the following conditions: diabetes mellitus, coexistent cervical radiculopathy, hypothyroidism, polyneuropathy, pregnancy, rheumatoid arthritis, and carpal tunnel syndrome in the workplace.[63]

## Splints [edit]

The importance of wrist braces and splints in the carpal tunnel syndrome therapy is known, but many people are unwilling to use braces. In 1993, The American Academy of Neurology recommend a non-invasive treatment for the CTS at the beginning (except for sensitive or motor deficit or grave report at EMG/ENG): a therapy using splints was indicated for light and moderate pathology.[64] Current recommendations generally don't suggest immobilizing braces, but instead activity modification and non-steroidal anti-inflammatory drugs as initial therapy, followed by more aggressive options or specialist referral if symptoms do not improve.[65][66]

A rigid splint can keep the wrist straight

Many health professionals suggest that, for the best results, one should wear braces at night and, if possible, during the activity primarily causing stress on the wrists.[67][68]



A different type of rigid splint used in carpal tunnel syndrome.

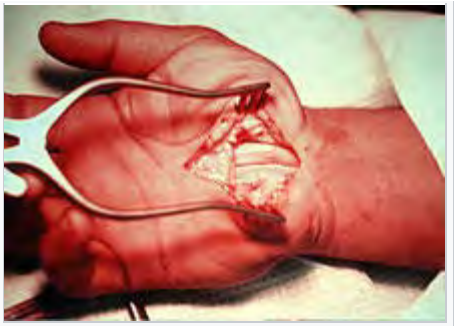
## Corticosteroids [edit]

Corticosteroid injections can be effective for temporary relief from symptoms while a person develops a long-term strategy that fits their lifestyle.[69] The injections are done under local anæsthesia.[70][71] This treatment is not appropriate for extended periods, however. In general, local steroid injections are only used until other treatment options can be identified.

## Surgery [edit]

*Main article: Carpal tunnel surgery*

Release of the transverse carpal ligament is known as "carpal tunnel release" surgery. It is recommended when there is static (constant, not just intermittent) numbness, muscle weakness, or atrophy, and when night-splinting or other conservative interventions no longer control [72]



Carpal Tunnel Syndrome Operation

intermittent symptoms. The surgery may be done with local[73][74][75] or regional anesthesia[76][77] with[78] or without[74] sedation, or under general anesthesia.[75][77][79] In general, milder cases can be controlled for months to years, but severe cases are unrelenting symptomatically and are likely to result in surgical treatment.[80]

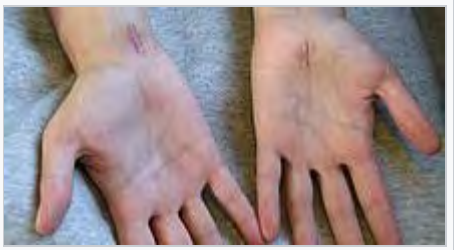
Surgery is more beneficial in the short term to alleviate symptoms (up to six months) than wearing an orthosis for a minimum of 6 weeks. However, surgery and wearing a brace resulted in similar symptom relief in the long term (12-18 month outcomes).[81]

### Physical therapy [edit]

A recent evidence based guideline produced by the American Academy of Orthopedic Surgeons assigned various grades of recommendation to physiotherapy (also called physical therapy) and other nonsurgical treatments.[82] One of the primary issues with physiotherapy is that it attempts to reverse (often) years of pathology inside the carpal tunnel. Practitioners caution that any physiotherapy such as myofascial release may take weeks of persistent application to effectively manage carpal tunnel syndrome.[83]

Again, some claim that pro-active ways to reduce stress on the wrists, which alleviates wrist pain and strain, involve adopting a more ergonomic work and life environment. For example, some have claimed that switching from a QWERTY computer keyboard layout to a more optimised ergonomic layout such as Dvorak was commonly cited as beneficial in early CTS studies, however some meta-analyses of these studies claim that the evidence that they present is limited.[84][85]

## Prognosis [edit]



Scars from carpal tunnel release surgery. Two different techniques were used. The left scar is 6 weeks old, the right scar is 2 weeks old. Also note the muscular atrophy of the thenar eminence in the left hand, a common sign of advanced CTS

Most people relieved of their carpal tunnel symptoms with conservative or surgical management find minimal residual or "nerve damage".[86] Long-term chronic carpal tunnel syndrome (typically seen in the elderly) can result in permanent "nerve damage", i.e. irreversible numbness, muscle wasting, and weakness. Those that undergo a carpal tunnel release are nearly twice as likely as those not having surgery to develop trigger thumb in the months following the procedure.[87]

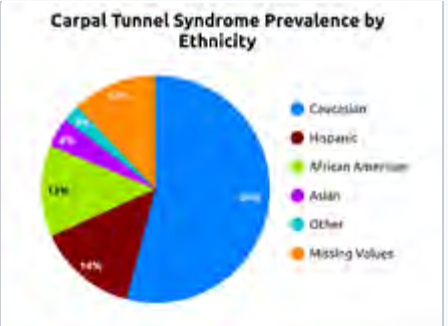
While outcomes are generally good, certain factors can contribute to poorer results that have little to do with nerves, anatomy, or surgery type. One study showed that mental status parameters or alcohol use yields much poorer overall results of treatment.[88]

Recurrence of carpal tunnel syndrome after successful surgery is rare.[89] If a person has hand pain after surgery, it is most likely not caused by carpal tunnel syndrome. It may be the case that the illness of a person with hand pain after carpal tunnel release was diagnosed incorrectly, such that the carpal tunnel release has had no positive effect upon the patient's symptoms.[*citation needed*]

## Epidemiology [edit]

Carpal tunnel syndrome can affect anyone. It accounts for about 90% of [90]

all nerve compression syndromes. In the U.S., 5% of people have the effects of carpal tunnel syndrome. Caucasians have the highest risk of CTS compared with other races such as non-white South Africans.[91] Women suffer more from CTS than men with a ratio of 3:1 between the ages of 45–60 years. Only 10% of reported cases of CTS are younger than 30 years.[91] Increasing age is a risk factor. CTS is also common in pregnancy.




Rates of carpal tunnel syndrome by ethnicity. CTS is much more common in Caucasians.

## Occupational [edit]

As of 2010, 8% of U.S. workers reported ever having carpal tunnel syndrome and 4% reported carpal tunnel syndrome in the past 12 months. Prevalence rates for carpal tunnel syndrome in the past 12 months were higher among females than among males; among workers aged 45–64 than among those aged 18–44. Overall, 67% of current carpal tunnel syndrome cases among current/recent workers were reportedly attributed to work by health professionals, indicating that the prevalence rate of work-related carpal tunnel syndrome among workers was 2%, and that there were approximately 3.1 million cases of work-related carpal tunnel syndrome among U.S. workers in 2010. Among current carpal tunnel syndrome cases attributed to specific jobs, 24% were attributed to jobs in the manufacturing industry, a proportion 2.5 times higher than the proportion of current/recent workers employed in the manufacturing industry, suggesting that jobs in this industry are associated with an increased risk of work-related carpal tunnel syndrome.[92]

# History [edit]

The condition known as carpal tunnel syndrome had major appearances throughout the years but it was most commonly heard of in the years following World War II.[7] Individuals who had suffered from this condition have been depicted in surgical literature for the mid-19th century.[7] In 1854, Sir James Paget was the first to report median nerve compression at the wrist in a distal radius fracture.[93] Following the early 20th century there were various cases of median nerve compression underneath the transverse carpal ligament.[93] Carpal Tunnel Syndrome was most commonly noted in medical literature in the early 20th century but the first use of the term was noted 1939. Physician Dr. George S. Phalen of the Cleveland Clinic identified the pathology after working with a group of patients in the 1950s and 1960s.

# Notable cases [edit]

- HRH Prince Philip, husband of Queen Elizabeth II[94]
- Mike Dirnt, bassist with the band Green Day[95]

# References [edit]


1. ^ *a b c d* Burton, C; Chesterton, LS; Davenport, G (May 2014). "Diagnosing and managing carpal tunnel syndrome in primary care.". *The British journal of general practice : the journal of the Royal College of General Practitioners*. **64** (622): 262–3. doi:10.3399/bjgp14x679903. PMC 4001168. PMID 24771836.
2. ^ *a b c d e* "Carpal Tunnel Syndrome Fact Sheet". *National Institute of Neurological Disorders and Stroke*. January 28, 2016. Retrieved 4 March 2016.
3. ^ *a b c d e f g* American Academy of Orthopaedic Surgeons (February 29, 2016). "Management of Carpal Tunnel Syndrome Evidence-Based Clinical Practice Guideline.".
4. ^ Osterman, M; Ilyas, AM; Matzon, JL (October 2012). "Carpal tunnel syndrome in pregnancy.". *The Orthopedic clinics of North America*. **43** (4): 515–20. doi:10.1016/j.ocl.2012.07.020. PMID 23026467.
5. ^ Shiri, R (December 2014). "Hypothyroidism and carpal tunnel syndrome: a meta-analysis.". *Muscle & nerve*. **50**

(6): 879–83. doi:10.1002/mus.24453. PMID 25204641.
6. ^ Bickel, KD (January 2010). "Carpal tunnel syndrome.". *The Journal of hand surgery*. **35** (1): 147–52. doi:10.1016/j.jhsa.2009.11.003. PMID 20117319.
7. ^ [a] [b] [c] Amadio, Peter C. (2007). "History of carpal tunnel syndrome". In Luchetti, Riccardo; Amadio, Peter C. *Carpal Tunnel Syndrome*. Berlin: Springer. pp. 3–9. ISBN 978-3-540-22387-0.
8. ^ "Carpal tunnel syndrome - Symptoms". *NHS Choices*. Retrieved 2016-05-21. Page last reviewed: 18/09/2014
9. ^ Atroshi, I.; Gummesson, C; Johnsson, R; Ornstein, E; Ranstam, J; Rosén, I (1999). "Prevalence of Carpal Tunnel Syndrome in a General Population". *JAMA*. **282** (2): 153–158. doi:10.1001/jama.282.2.153. PMID 10411196.
10. ^ "Carpal Tunnel Syndrome Information Page". National Institute of Neurological Disorders and Stroke. December 28, 2010.
11. ^ Netter, Frank (2011). *Atlas of Human Anatomy* (5th ed.). Philadelphia, PA: Saunders Elsevier. pp. 412, 417, 435. ISBN 978-0-8089-2423-4.
12. ^ Lazaro, R (1997). "Neuropathic symptoms and musculoskeletal pain in carpal tunnel syndrome: Prognostic and therapeutic implications". *Surgical Neurology*. **47** (2): 115–7; discussion 117–9. doi:10.1016/S0090-3019(95)00457-2. PMID 9040810.
13. ^ Tamparo, Carol (2011). *Fifth Edition: Diseases of the Human Body*. Philadelphia, PA: F. A. Davis Company. p. 231. ISBN 978-0-8036-2505-1.
14. ^ Sternbach, G (1999). "The carpal tunnel syndrome". *Journal of Emergency Medicine*. **17** (3): 519–23. doi:10.1016/S0736-4679(99)00030-X. PMID 10338251.
15. ^ [a] [b] Katz, Jeffrey N.; Simmons, Barry P. (2002). "Carpal Tunnel Syndrome". *New England Journal of Medicine*. **346** (23): 1807–12. doi:10.1056/NEJMcp013018. PMID 12050342.
16. ^ [a] [b] "Carpal Tunnel Syndrome". American Academy of Orthopaedic Surgeons. December 2009.
17. ^ Tiong, W. H. C.; Ismael, T.; Regan, P. J. (2005). "Two rare causes of carpal tunnel syndrome". *Irish Journal of Medical Science*. **174** (3): 70–8. doi:10.1007/BF03170208. PMID 16285343.
18. ^ Almeida M.R.; et al. (2005). "Small transthyretin (TTR) ligands as possible therapeutic agents in TTR amyloidosis". *Curr. Drug Targets: CNS Neurol. Disord*. **4**: 587–596. doi:10.2174/156800705774322076.
19. ^ Izumoto S.; et al. (1992). "Familial amyloidotic polyneuropathy presenting with carpal tunnel syndrome and a new transthyretin mutation, asparagine 70". *Neurology*. **42**: 2094–102. doi:10.1212/wnl.42.11.2094.
20. ^ Jacobson D.R.; et al. (1997). "Transthyretin ILE20, a new variant associated with late-onset cardiac amyloidosis". *Hum. Mutat*. **9**: 83–85. doi:10.1002/(sici)1098-1004(1997)9:1<83::aid-humu19>3.3.co;2-j.
21. ^ Kodaira M.; et al. "Non-senile wild-type transthyretin systemic amyloidosis presenting as bilateral carpal tunnel syndrome". *J Peripher Nerv Syst*. **2008** (13): 148–50.
22. ^ Koike H.; et al. (2009). "The significance of carpal tunnel syndrome in transthyretin Val30Met familial amyloid polyneuropathy". *Amyloid*. **16**: 142–148. doi:10.1080/13506120903094074. PMID 19626479.
23. ^ Sekijima Y.; et al. (2011). "High prevalence of wild-type transthyretin deposition in patients with idiopathic carpal tunnel syndrome: a common cause of carpal tunnel syndrome in the elderly". *Hum Pathol*. **42**: 1785–91. doi:10.1016/j.humpath.2011.03.004. PMID 21733562.
24. ^ Tojo K.; et al. (2010). "Upper limb neuropathy such as carpal tunnel syndrome as an initial manifestation of ATTR Val30Met familial amyloid polyneuropathy". *Amyloid*. **17**: 32–35. doi:10.3109/13506121003619369. PMID 20132088.
25. ^ [a] [b] Ibrahim I.; Khan W. S.; Goddard N.; Smitham P. (2012). "Suppl 1: Carpal Tunnel Syndrome: A Review of the Recent Literature". *The Open Orthopaedics Journal*. **6**: 69–76. doi:10.2174/1874325001206010069.
26. ^ Armstrong T., Chaffin D. (1979). "Capral tunnel syndrome and selected personal attributes". *Journal of Occupational Medicine*. **21** (7).
27. ^ Schuind F.; Ventura M.; Pasteels J. (1990). "Idiopathic carpal tunnel syndrome: Histologic study of flexor tendon synovium". *The Journal of Hand Surgery*. **15** (3).
28. ^ Derebery, J (2006). "Work-related carpal tunnel syndrome: the facts and the myths". *Clinics in occupational and environmental medicine*. **5** (2): 353–67, viii. doi:10.1016/j.coem.2005.11.014 (inactive 2015-01-11). PMID 16647653.
29. ^ Office of Communications and Public Liaison (December 18, 2009). "National Institute of Neurological Disorders and Stroke".
30. ^ Werner, Robert A. (2006). "Evaluation of Work-Related Carpal Tunnel Syndrome". *Journal of Occupational Rehabilitation*. **16** (2): 201–16. doi:10.1007/s10926-006-9026-3. PMID 16705490.
31. ^ [a] [b] Graham, B. (1 December 2008). "The Value Added by Electrodiagnostic Testing in the Diagnosis of Carpal Tunnel Syndrome". *The Journal of Bone and Joint Surgery*. **90** (12): 2587–2593. doi:10.2106/JBJS.G.01362. PMID 19047703.
32. ^ Cole, Donald C.; Hogg-Johnson, Sheilah; Manno, Michael; Ibrahim, Selahadin; Wells, Richard P.; Ferrier, Sue E.; Worksite Upper Extremity Research Group (2006). "Reducing musculoskeletal burden through ergonomic program

implementation in a large newspaper". *International Archives of Occupational and Environmental Health*. **80** (2): 98–108. doi:10.1007/s00420-006-0107-6. PMID 16736193.
33. ^ Luckhaupt, Sara E.; Burris, Dara L. (24 June 2013). "How Does Work Affect the Health of the U.S. Population? Free Data from the 2010 NHIS-OHS Provides the Answers". National Institute for Occupational Safety and Health. Retrieved 18 January 2015.
34. ^ Swanson, Naomi; Tisdale-Pardi, Julie; MacDonald, Leslie; Tiesman, Hope M. (13 May 2013). "Women's Health at Work". National Institute for Occupational Safety and Health. Retrieved 21 January 2015.
35. ^ LOZANOCALDERON, S; PAIVA, A; RING, D (1 March 2008). "Patient Satisfaction After Open Carpal Tunnel Release Correlates With Depression". *The Journal of Hand Surgery*. **33** (3): 303–307. doi:10.1016/j.jhsa.2007.11.025. PMID 18343281.
36. ^ LOZANOCALDERON, S; ANTHONY, S; RING, D (1 April 2008). "The Quality and Strength of Evidence for Etiology: Example of Carpal Tunnel Syndrome". *The Journal of Hand Surgery*. **33** (4): 525–538. doi:10.1016/j.jhsa.2008.01.004. PMID 18406957.
37. ^ *a b c d* Scott, Kevin R.; Kothari, Milind J. (October 5, 2009). "Treatment of carpal tunnel syndrome". UpToDate.
38. ^ Stevens JC, Beard CM, O'Fallon WM, Kurland LT (1992). "Conditions associated with carpal tunnel syndrome". *Mayo Clin Proc*. **67** (6): 541–548. doi:10.1016/S0025-6196(12)60461-3. PMID 1434881.
39. ^ "Carpel Tunnel Syndrome in Acromegaly". Treatmentandsymptoms.com. Retrieved 2011-10-05.
40. ^ Werner, Robert A.; Albers, James W.; Franzblau, Alfred; Armstrong, Thomas J. (1994). "The relationship between body mass index and the diagnosis of carpal tunnel syndrome". *Muscle & Nerve*. **17** (6): 632–6. doi:10.1002/mus.880170610.
41. ^ Wilbourn AJ, Gilliatt RW (1997). "Double-crush syndrome: a critical analysis". *Neurology*. **49** (1): 21–27. doi:10.1212/WNL.49.1.21. PMID 9222165.
42. ^ Lupski, James R.; Reid, Jeffrey G.; Gonzaga-Jauregui, Claudia; Rio Deiros, David; Chen, David C.Y.; Nazareth, Lynne; Bainbridge, Matthew; Dinh, Huyen; et al. (2010). "Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy". *New England Journal of Medicine*. **362** (13): 1181–91. doi:10.1056/NEJMoa0908094. PMID 20220177.
43. ^ Brooks, JJ; Schiller, JR; Allen, SD; Akelman, E (Oct 2003). "Biomechanical and anatomical consequences of carpal tunnel release". *Clinical biomechanics (Bristol, Avon)*. **18** (8): 685–93. doi:10.1016/S0268-0033(03)00052-4. PMID 12957554.
44. ^ Vella, JC; Hartigan, BJ; Stern, PJ (Jul–Aug 2006). "Kaplan's cardinal line". *The Journal of hand surgery*. **31** (6): 912–8. doi:10.1016/j.jhsa.2006.03.009. PMID 16843150.
45. ^ RH Gelberman; PT Hergenroeder; AR Hargens; GN Lundborg; WH Akeson (1 March 1981). "The carpal tunnel syndrome. A study of carpal canal pressures". *The Journal of Bone and Joint Surgery*. **63** (3): 380–383. PMID 7204435.
46. ^ Norvell, Jeffrey G.; Steele, Mark (September 10, 2009). "Carpal Tunnel Syndrome". eMedicine.
47. ^ Rempel, D; Evanoff B; Amadio PC; et al. (1998). "Consensus criteria for the classification of carpal tunnel syndrome in epidemiologic studies". *Am J Public Health*. **88** (10): 1447–1451. doi:10.2105/AJPH.88.10.1447. PMC 1508472. PMID 9772842.
48. ^ *a b* Graham, B; Regehr G; Naglie G; Wright JG (2006). "Development and validation of diagnostic criteria for carpal tunnel syndrome". *Journal of Hand Surgery*. **31A** (6): 919–924.
49. ^ Cush JJ, Lipsky PE (2004). "Approach to articular and musculoskeletal disorders". *Harrison's Principles of Internal Medicine* (16th ed.). McGraw-Hill Professional. p. 2035. ISBN 0-07-140235-7.
50. ^ Gonzalezdelpino, J; Delgadomartinez, A; Gonzalezgonzalez, I; Lovic, A (1997). "Value of the carpal compression test in the diagnosis of carpal tunnel syndrome". *The Journal of Hand Surgery: Journal of the British Society for Surgery of the Hand*. **22**: 38–41. doi:10.1016/S0266-7681(97)80012-5.
51. ^ Durkan, JA (1991). "A new diagnostic test for carpal tunnel syndrome". *The Journal of bone and joint surgery. American volume*. **73** (4): 535–8. PMID 1796937.
52. ^ Ma H, Kim I (November 2012). "The diagnostic assessment of hand elevation test in carpal tunnel syndrome". *Journal of Korean Neurosurgical Society*. **52** (5): 472–5. doi:10.3340/jkns.2012.52.5.472. PMC 3539082. PMID 23323168.
53. ^ Netter, Frank (2011). *Atlas of Human Anatomy* (5th ed.). Philadelphia, PA: Saunders Elsevier. p. 447. ISBN 978-0-8089-2423-4.
54. ^ Robinson, L (2007). "Electrodiagnosis of Carpal Tunnel Syndrome". *Physical Medicine and Rehabilitation Clinics of North America*. **18** (4): 733–46. doi:10.1016/j.pmr.2007.07.008. PMID 17967362.
55. ^ Wilder-Smith, Einar P; Seet, Raymond C S; Lim, Erle C H (2006). "Diagnosing carpal tunnel syndrome—clinical criteria and ancillary tests". *Nature Clinical Practice Neurology*. **2** (7): 366–74. doi:10.1038/ncpneuro0216. PMID 16932587.
56. ^ Bland, Jeremy DP (2005). "Carpal tunnel syndrome". *Current Opinion in Neurology*. **18** (5): 581–5.

doi:10.1097/01.wco.0000173142.58068.5a. PMID 16155444.
57. ^ Jarvik, J; Yuen, E; Kliot, M (2004). "Diagnosis of carpal tunnel syndrome: electrodiagnostic and MR imaging evaluation". *Neuroimaging Clinics of North America*. **14** (1): 93–102, viii. doi:10.1016/j.nic.2004.02.002. PMID 15177259.
58. ^ Spooner, GR; Desai, HB; Angel, JF; Reeder, BA; Donat, JR (Oct 1993). "Using pyridoxine to treat carpal tunnel syndrome. Randomized control trial". *Canadian Family Physician*. **39**: 2122–7. PMC 2379872. PMID 8219859.
59. ^ Scangas, G; Lozano-Calderón, S; Ring, D (Sep 2008). "Disparity between popular (Internet) and scientific illness concepts of carpal tunnel syndrome causation". *The Journal of hand surgery*. **33** (7): 1076–80. doi:10.1016/j.jhsa.2008.03.001. PMID 18762100.
60. ^ *a b* Lozano-Calderón, Santiago; Shawn Anthony; David Ring (April 2008). "The Quality and Strength of Evidence for Etiology: Example of Carpal Tunnel Syndrome". *The Journal of Hand Surgery*. **33** (4): 525–538. doi:10.1016/j.jhsa.2008.01.004. PMID 18406957.
61. ^ *a b* "Nadal, Roger, and Susan Lintsworth. "Getting a Hand up on Carpal Tunnel Syndrome. Tips for Beating the Malady of the Information Age." PTA Today. EBSCO Host, Apr. 2002. Web. 24 Jan. 2014. http://wnyptot.com/articles/info_education/carpal_tunnel.pdf"
62. ^ *a b* Piazzini, DB; Aprile, I; Ferrara, PE; Bertolini, C; Tonali, P; Maggi, L; Rabini, A; Piantelli, S; Padua, L (Apr 2007). "A systematic review of conservative treatment of carpal tunnel syndrome". *Clinical rehabilitation*. **21** (4): 299–314. doi:10.1177/0269215507077294. PMID 17613571.
63. ^ *a b c Clinical Practice Guideline on the Treatment of Carpal Tunnel Syndrome* (PDF). American Academy of Orthopaedic Surgeons. September 2008.[*page needed*]
64. ^ American Academy of Neurology (2006). "Quality Standards Subcommittee: Practice parameter for carpal tunnel syndrome". *Neurology*. **43**: 2406–2409. PMID 8232968.
65. ^ Katz, Jeffrey N.; Simmons, Barry P. (2002). "Carpal Tunnel Syndrome". *New England Journal of Medicine*. **346** (23): 1807–1812. doi:10.1056/NEJMcp013018. PMID 12050342.
66. ^ Harris JS, ed. (1998). *Occupational Medicine Practice Guidelines: evaluation and management of common health problems and functional recovery in workers*. Beverly Farms, Mass.: OEM Press. ISBN 978-1-883595-26-5.[*page needed*]
67. ^ Premoselli, S; Sioli, P; Grossi, A; Cerri, C (2006). "Neutral wrist splinting in carpal tunnel syndrome: a 3- and 6-months clinical and neurophysiologic follow-up evaluation of night-only splint therapy". *Europa medicophysica*. **42** (2): 121–6. PMID 16767058.
68. ^ Michlovitz, SL (2004). "Conservative interventions for carpal tunnel syndrome". *The Journal of orthopaedic and sports physical therapy*. **34** (10): 589–600. doi:10.2519/jospt.2004.34.10.589. PMID 15552705.
69. ^ Marshall, Shawn C; Tardif, Gaetan; Ashworth, Nigel L; Marshall, Shawn C (2007). Marshall, Shawn C, ed. "Local corticosteroid injection for carpal tunnel syndrome". *Cochrane Database of Systematic Reviews*. doi:10.1002/14651858.CD001554.pub2.
70. ^ "Carpal Tunnel Steroid Injection". Medscape. Retrieved July 9, 2015.
71. ^ "Carpal Tunnel Injection Information". EBSCO – via The Mount Sinai Hospital.
72. ^ Hui, A.C.F.; Wong, S.M.; Tang, A.; Mok, V.; Hung, L.K.; Wong, K.S. (2004). "Long-term outcome of carpal tunnel syndrome after conservative treatment". *International Journal of Clinical Practice*. **58** (4): 337–9. doi:10.1111/j.1368-5031.2004.00028.x. PMID 15161116.
73. ^ "Open Carpal Tunnel Surgery for Carpal Tunnel Syndrome". WebMD. Retrieved July 9, 2015.
74. ^ *a b* al Youha, Sarah; Lalonde, Donald (May 2014). "Update/Review: Changing of Use of Local Anesthesia in the Hand". *Plastic and Reconstructive Surgery Global Open*. **2**: e150. doi:10.1097/GOX.0000000000000095. PMC 4174079. PMID 25289343.
75. ^ *a b* Nabhan A, Ishak B, Al-Khayat J, Steudel W-I (April 25, 2008). "Endoscopic Carpal Tunnel Release using a modified application technique of local anesthesia: safety and effectiveness". *Journal of Brachial Plexus and Peripheral Nerve Injury*. **3** (11): 11. doi:10.1186/1749-7221-3-11. PMC 2383895. PMID 18439257.
76. ^ "A Patient's Guide to Open Carpal Tunnel Release". Houston Methodist Orthopedics & Sports Medicine. Retrieved July 9, 2015.
77. ^ *a b* "AAOS Informed Patient Tutorial - Carpal Tunnel Release Surgery". The American Academy of Orthopaedic Surgeons. Retrieved July 9, 2015.
78. ^ Lee J-J, Hwang SM, Jang JS, Lim SY, Heo D-H, Cho YJ (2010). "Remifentanil-Propofol Sedation as an Ambulatory Anesthesia for Carpal Tunnel Release" (PDF). *Journal of Korean Neurosurgical Society*. **48** (5): 429–433. doi:10.3340/jkns.2010.48.5.429. PMC 3030083. PMID 21286480.
79. ^ "Information on Anesthesia Options". Long Beach, California: The Hand & Wrist Center. Retrieved July 9, 2015.
80. ^ Kouyoumdjian, JA; Morita, MP; Molina, AF; Zanetta, DM; Sato, AK; Rocha, CE; Fasanella, CC (2003). "Long-term outcomes of symptomatic electrodiagnosed carpal tunnel syndrome". *Arquivos de neuro-psiquiatria*. **61** (2A): 194–8.

doi:10.1590/S0004-282X2003000200007. PMID 12806496.
81. ^ D'Angelo, Kevin; Sutton, Deborah; Côté, Pierre; Dion, Sarah; Wong, Jessica J.; Yu, Hainan; Randhawa, Kristi; Southerst, Danielle; Varatharajan, Sharanya. "The Effectiveness of Passive Physical Modalities for the Management of Soft Tissue Injuries and Neuropathies of the Wrist and Hand: A Systematic Review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration". *Journal of Manipulative and Physiological Therapeutics*. **38** (7): 493–506. doi:10.1016/j.jmpt.2015.06.006.
82. ^ Keith, M. W.; Masear, V.; Chung, K. C.; Amadio, P. C.; Andary, M.; Barth, R. W.; Maupin, K.; Graham, B.; Watters, W. C.; Turkelson, C. M.; Haralson, R. H.; Wies, J. L.; McGowan, R. (4 January 2010). "American Academy of Orthopaedic Surgeons Clinical Practice Guideline on The Treatment of Carpal Tunnel Syndrome". *The Journal of Bone and Joint Surgery*. **92** (1): 218–219. doi:10.2106/JBJS.I.00642. PMID 20048116.
83. ^ Siu, G.; Jaffee, J.D.; Rafique, M.; Weinik, M.M. (1 March 2012). "Osteopathic Manipulative Medicine for Carpal Tunnel Syndrome". *The Journal of the American Osteopathic Association*. **112** (3): 127–139. PMID 22411967.
84. ^ Lincoln, A; Vernick, JS; Ogaitis, S; Smith, GS; Mitchell, CS; Agnew, J (2000). "Interventions for the primary prevention of work-related carpal tunnel syndrome". *American Journal of Preventive Medicine*. **18** (4 Suppl): 37–50. doi:10.1016/S0749-3797(00)00140-9. PMID 10793280.
85. ^ Verhagen, Arianne P; Karels, Celinde C; Bierma-Zeinstra, Sita MA; Burdorf, Lex L; Feleus, Anita; Dahaghin, Saede SD; De Vet, Henrica CW; Koes, Bart W; Verhagen, Arianne P (2006). Verhagen, Arianne P, ed. "Ergonomic and physiotherapeutic interventions for treating work-related complaints of the arm, neck or shoulder in adults". *Cochrane Database of Systematic Reviews*. **3** (3): CD003471. doi:10.1002/14651858.CD003471.pub3. PMID 16856010.
86. ^ Olsen, K. M.; Knudson, D. V. (2001). "Change in Strength and Dexterity after Open Carpal Tunnel Release". *International Journal of Sports Medicine*. **22** (4): 301–3. doi:10.1055/s-2001-13815. PMID 11414675.
87. ^ King, Bradley A.; Stern, Peter J.; Kiefhaber, Thomas R. (2013). "The incidence of trigger finger or de Quervain's tendinitis after carpal tunnel release". *Journal of Hand Surgery (European Volume)*. **38** (1): 82–3. doi:10.1177/1753193412453424. PMID 22791612.
88. ^ Katz, Jeffrey N.; Losina, Elena; Amick, Benjamin C.; Fossel, Anne H.; Bessette, Louis; Keller, Robert B. (2001). "Predictors of outcomes of carpal tunnel release". *Arthritis & Rheumatism*. **44** (5): 1184–93. doi:10.1002/1529-0131(200105)44:5<1184::AID-ANR202>3.0.CO;2-A.
89. ^ Ruch, DS; Seal, CN; Bliss, MS; Smith, BP (2002). "Carpal tunnel release: efficacy and recurrence rate after a limited incision release". *Journal of the Southern Orthopaedic Association*. **11** (3): 144–7. PMID 12539938.[*unreliable medical source?*]
90. ^ Ibrahim I.; Khan W. S.; Goddard N.; Smitham P. (2012). "Suppl 1: Carpal Tunnel Syndrome: A Review of the Recent Literature". *The open orthopaedics journal*. **6**: 69.
91. ^ *a b* Ashworth, Nigel L. (December 4, 2008). "Carpal Tunnel Syndrome". eMedicine.
92. ^ Luckhaupt SE, Dahlhamer JM, Ward BW, Sweeney MH, Sestito JP, Calvert GM (June 2013). "Prevalence and work-relatedness of carpal tunnel syndrome in the working population, United States, 2010 National Health Interview Survey". *American Journal of Industrial Medicine*. **56** (6): 615–24. doi:10.1002/ajim.22048. PMID 22495886.
93. ^ *a b* Fuller, David A. (September 22, 2010). "Carpal Tunnel Syndrome". eMedicine.
94. ^ "Prince Philip undergoes minor surgery on hand". BBC News. June 8, 2010.
95. ^ Rosen, Steven (Autumn 2004). "Green Day". *Total Guitar*: 24–30. Archived from the original on 2010-12-04.

## External links [edit]

- Carpal Tunnel Syndrome Fact Sheet (National Institute of Neurological Disorders and Stroke)
- NHS website carpal-tunnel.net provides a free to use, validated, online self diagnosis questionnaire for CTS

| v · t · e | **Nervous system pathology, PNS, somatic (G50–G64, 350–357)** |
|---|---|
| | **Nerve, nerve root, plexus** |
| **Cranial nerve disease** | *V* Trigeminal neuralgia · Anesthesia dolorosa · *VII* Facial nerve paralysis · Bell's palsy · Melkersson–Rosenthal syndrome · Parry–Romberg syndrome · Central seven · *XI* Accessory nerve disorder · |
| **Radiculopathy, plexopathy** | *brachial plexus* Brachial plexus lesion · Thoracic outlet syndrome · Phantom limb · |

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|---|---|---|---|
| **Mono-neuropathy** | **Upper limb** | *median nerve:* | **Carpal tunnel syndrome** · Ape hand deformity · |
| | | *ulnar nerve:* | Ulnar nerve entrapment · Froment's sign · Guyon's canal syndrome · Ulnar claw · |
| | | *radial nerve:* | Radial neuropathy · Wrist drop · Cheiralgia paresthetica · |
| | | *long thoracic nerve:* | Winged scapula · Backpack palsy · |
| | **Lower limb** | *lateral cutaneous nerve of thigh:* | Meralgia paraesthetica · |
| | | *tibial nerve:* | Tarsal tunnel syndrome · |
| | | *plantar nerve:* | Morton's neuroma · |
| | | *superior gluteal nerve:* | Trendelenburg's sign · |
| | | *sciatic nerve:* | Piriformis syndrome · |
| | **General** | | Causalgia · Mononeuritis multiplex · Neuropathy Neuralgia/Neuritis · Nerve compression syndrome · |
| **Polyneuropathies/Polyradiculoneuropathy** | | | |
| **HMSN** | | | Charcot–Marie–Tooth disease · Dejerine–Sottas disease · Refsum's disease · Hereditary spastic paraplegia · Hereditary neuropathy with liability to pressure palsy · Familial amyloid neuropathy · |
| **Autoimmune/demyelinating** | | | Guillain–Barré syndrome · Chronic inflammatory demyelinating polyneuropathy · |
| **Other** | | | Alcoholic polyneuropathy · |

Categories: Syndromes | Mononeuropathies of upper limb | Physical ergonomics




# Fibromyalgia

From Wikipedia, the free encyclopedia

**Fibromyalgia** (**FM**) is a medical condition characterised by chronic widespread pain and a heightened pain response to pressure.[2] Other symptoms include feeling tired to a degree that normal activities are affected, sleep problems, and troubles with memory.[3] Some people also report restless legs syndrome, bowel or bladder problems, numbness and tingling, and sensitivity to noise, lights or temperature.[4] Fibromyalgia is frequently associated with depression, anxiety, and posttraumatic stress disorder. Other types of chronic pain are also frequently present.[3]

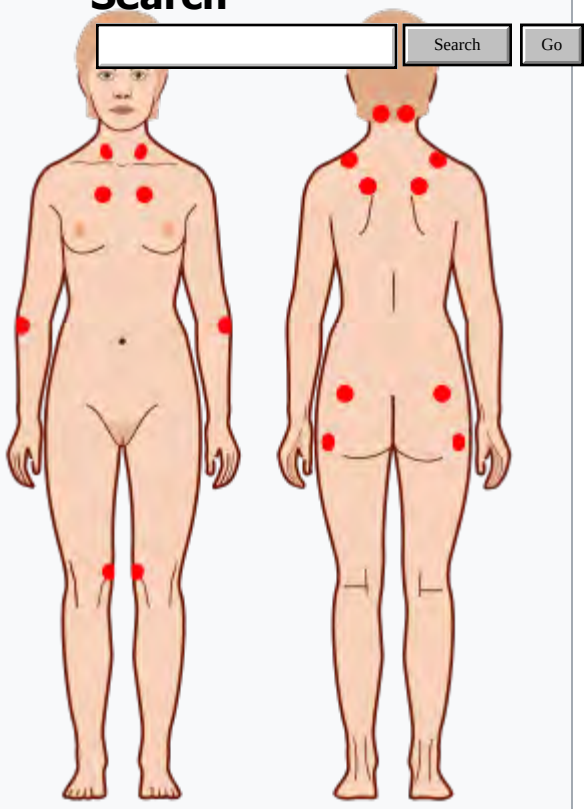
The cause of fibromyalgia is unknown but believed to involve a combination of genetic and environmental factors with half the risk attributed to each.[3][4] The condition runs in families and many genes are believed to be involved.[5] Environmental factors may include psychological stress, trauma, and certain infections.[3] The pain appears to result from processes in the central nervous system and the condition is referred to as a "central sensitization syndrome".[2][3] Fibromyalgia is recognized as a disorder by the US National Institutes of Health and the American College of Rheumatology.[4][6] There is no specific diagnostic test.[4] Diagnosis involves first ruling out other potential causes and verifying that a set number of symptoms are present.[3][4]

The treatment of fibromyalgia can be difficult. Recommendations often include getting enough sleep, exercising regularly, and eating a healthy diet.[4] Cognitive behavioral therapy may also be helpful.[3] The medications duloxetine, milnacipran, or pregabalin may be used.[4] Use of opioid pain medication is controversial with some stating their use is poorly supported by evidence[4][7] and others saying that weak opioids may be reasonable if other medications are not effective.[8] Dietary supplements also lack evidence to support their use. While fibromyalgia can last a long time, it does not result in death or tissue damage.[4]

Fibromyalgia is estimated to affect 2–8% of the population. Females are affected about twice as often as males. Rates appear similar in different areas of the world and among different cultures. Fibromyalgia was first defined in 1990 with updated criteria in 2011.[3] There is controversy about the classification, diagnosis, and treatment of fibromyalgia.[9][10]

## Fibromyalgia

**Synonyms** Fibromyalgia syndrome (FMS)



The location of the nine paired tender points that constitute the 1990 American College of Rheumatology criteria for fibromyalgia.

**Pronunciation** /ˌfaɪbroʊmaɪˈældʒə/[1]

| Classification and external resources | |
|---|---|
| **Specialty** | Rheumatology |
| **ICD-10** | M79.7 – Fibromyalgia |
| **ICD-9-CM** | 729.1 – Myalgia and myositis, unspecified |
| **MedlinePlus** | 000427 |
| **eMedicine** | med/790 med/2934 |

While some feel the diagnosis of fibromyalgia may negatively affect a person, other research finds it to be beneficial.[3] The term "fibromyalgia" is from New Latin, *fibro-*, meaning "fibrous tissues", Greek μυώ *myo-*, "muscle", and Greek ἀλγος *algos*, "pain"; thus the term literally means "muscle and fibrous connective tissue pain".[11]

| | |
|---|---|
| | ped/777 pmr/47 |
| **Patient UK** | Fibromyalgia |
| **MeSH** | D005356 |

[edit on Wikidata]

**Contents**



## Classification [edit]

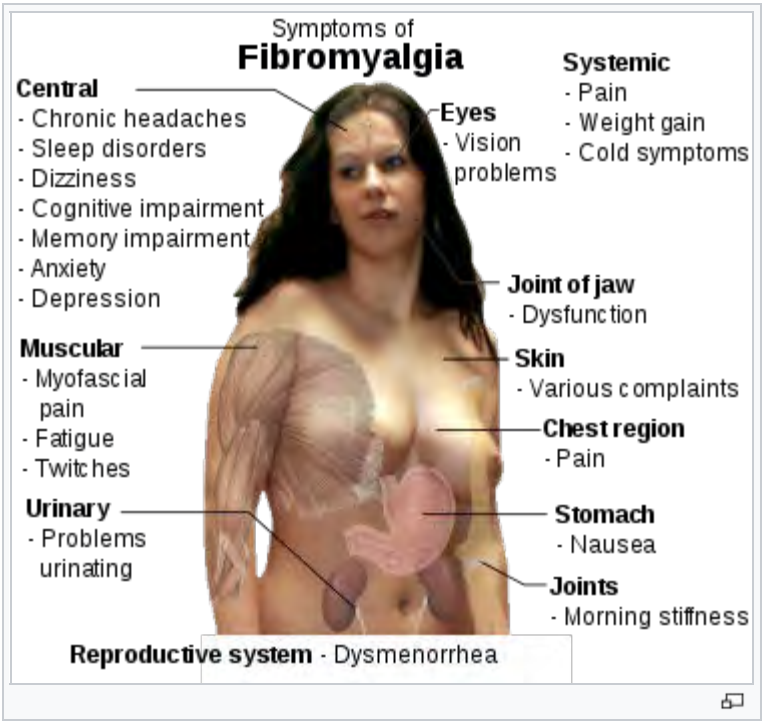
Fibromyalgia is classed as a disorder of pain processing due to abnormalities in how pain signals are processed in the central nervous system.[12] The American College of Rheumatology classify fibromyalgia as being a functional somatic syndrome.[9] The expert committee of the European League Against Rheumatism classify fibromyalgia as a neurobiological disorder and as a result exclusively give pharmacotherapy their highest level of support.[9] The International Classification of Diseases (ICD-10) lists fibromyalgia as a diagnosable disease under "Diseases of the musculoskeletal system and connective tissue," under the code

M79-7, and states that fibromyalgia syndrome should be classified as a functional somatic syndrome rather than a mental disorder. Although mental disorders and some physical disorders commonly are co-morbid with fibromyalgia – especially anxiety, depression, irritable bowel syndrome, and chronic fatigue syndrome – the ICD states that these should be diagnosed separately.[9]

Differences in psychological and autonomic nervous system profiles among affected individuals may indicate the existence of fibromyalgia subtypes. A 2007 review divides individuals with fibromyalgia into four groups as well as "mixed types":[13]

1. "extreme sensitivity to pain but no associated psychiatric conditions" (may respond to medications that block the 5-HT3 receptor)
2. "fibromyalgia and comorbid, pain-related depression" (may respond to antidepressants)
3. "depression with concomitant fibromyalgia syndrome" (may respond to antidepressants)
4. "fibromyalgia due to somatization" (may respond to psychotherapy)

## Signs and symptoms [edit]




The defining symptoms of fibromyalgia are chronic widespread pain, fatigue, sleep disturbance, and heightened pain in response to tactile pressure (allodynia).[14] Other symptoms may include tingling of the skin (paresthesias),[14] prolonged muscle spasms, weakness in the limbs, nerve pain, muscle twitching, palpitations,[15] and functional bowel disturbances.[16][17]

Many people experience cognitive dysfunction[14][18] (known as "fibrofog"), which may be characterized by impaired concentration,[19] problems with short[19][20] and long-term memory, short-term memory consolidation,[20] impaired speed of performance,[19][20] inability to multi-task, cognitive overload,[19][20] and diminished attention span. Fibromyalgia is often associated with anxiety and depressive symptoms.[20]

Other symptoms often attributed to fibromyalgia that may be due to a comorbid disorder include myofascial pain syndrome, also referred to as chronic myofascial pain, diffuse non-dermatomal paresthesias, functional bowel disturbances and irritable bowel syndrome, genitourinary symptoms and interstitial cystitis, dermatological disorders, headaches, myoclonic twitches, and symptomatic hypoglycemia. Although fibromyalgia is classified based on the presence of chronic widespread pain, pain may also be localized in areas such as the shoulders, neck, low back, hips, or other areas. Many sufferers also experience varying degrees of myofascial pain and have high rates of comorbid temporomandibular joint dysfunction. 20–30% of people with rheumatoid arthritis and systemic lupus erythematosus may also have fibromyalgia.[21]

## Cause [edit]

The cause of fibromyalgia is unknown. However, several hypotheses have been developed including "central sensitization".[14] This theory proposes that people with fibromyalgia have a lower threshold for pain because of increased reactivity of pain-sensitive nerve cells in the spinal cord or brain.[2] Neuropathic pain and major depressive disorder often co-occur with fibromyalgia – the reason for this comorbidity appears to be due to shared genetic abnormalities, which leads to impairments in monoaminergic, glutamatergic,

neurotrophic, opioid and proinflammatory cytokine signaling. In these vulnerable individuals, psychological stress or illness can cause abnormalities in inflammatory and stress pathways which regulate mood and pain. Eventually, a sensitization and kindling effect occur in certain neurons leading to the establishment of fibromyalgia and sometimes a mood disorder.[22] The evidence suggests that the pain in fibromyalgia results primarily from pain processing pathways functioning abnormally. In simple terms, it can be described as the volume of the neurons being set too high and this hyper-excitability of pain processing pathways and under-activity of inhibitory pain pathways in the brain results in the affected individual experiencing pain. Some neurochemical abnormalities that occur in fibromyalgia also regulate mood, sleep, and energy, thus explaining why mood, sleep, and fatigue problems are commonly co-morbid with fibromyalgia.[12]

## Genetics [edit]

A mode of inheritance is currently unknown, but it is most probably polygenic.[5] Research has also demonstrated that fibromyalgia is potentially associated with polymorphisms of genes in the serotoninergic,[23] dopaminergic[24] and catecholaminergic systems.[25] However, these polymorphisms are not specific for fibromyalgia and are associated with a variety of allied disorders (e.g. chronic fatigue syndrome,[26] irritable bowel syndrome[27]) and with depression.[28] Individuals with the 5-HT2A receptor 102T/C polymorphism have been found to be at increased risk of developing fibromyalgia.[29]

## Lifestyle [edit]

Stress may be an important precipitating factor in the development of fibromyalgia.[30] Fibromyalgia is frequently comorbid with stress-related disorders such as chronic fatigue syndrome, posttraumatic stress disorder, irritable bowel syndrome and depression.[31] A systematic review found significant association between fibromyalgia and physical and sexual abuse in both childhood and adulthood, although the quality of studies was poor.[32] Poor lifestyles including being a smoker, obesity and lack of physical activity may increase the risk of an individual developing fibromyalgia.[33]

Two studies that employed single-voxel magnetic resonance spectroscopy (1H-MRS) reported metabolic abnormalities within the hippocampal complex in people with fibromyalgia. As the hippocampus plays crucial roles in maintenance of cognitive functions, sleep regulation, and pain perception, it was suggested that metabolic dysfunction of the hippocampus may be implicated in the appearance of these symptoms.[34][35]

Some authors have proposed that, because exposure to stressful conditions can alter the function of the hypothalamic-pituitary-adrenal (HPA) axis, the development of fibromyalgia may stem from stress-induced disruption of the HPA axis.[36]

## Sleep disturbances [edit]

In 1975, Moldofsky and colleagues reported the presence of anomalous alpha wave activity (typically associated with arousal states) measured by electroencephalogram (EEG) during non-rapid eye movement sleep of "fibrositis syndrome".[17] By disrupting stage IV sleep consistently in young, healthy subjects, the researchers reproduced a significant increase in muscle tenderness similar to that experienced in "neurasthenic musculoskeletal pain syndrome" but which resolved when the subjects were able to resume their normal sleep patterns.[37]

## Psychological factors [edit]

There is strong evidence that major depression is associated with fibromyalgia (1999),[38] although the nature of the association is debated.[39] A comprehensive review into the relationship between fibromyalgia and major depressive disorder (MDD) found substantial similarities in neuroendocrine abnormalities, psychological characteristics, physical symptoms and treatments between fibromyalgia and MDD, but currently available findings do not support the assumption that MDD and fibromyalgia refer to the same underlying construct or can be seen as subsidiaries of one disease concept.[40] Indeed, the sensation of

pain has at least two dimensions: a sensory dimension which processes the magnitude and location of the pain, and an affective-motivational dimension which processes the unpleasantness. Accordingly, a study that employed functional magnetic resonance imaging to evaluate brain responses to experimental pain among people with fibromyalgia found that depressive symptoms were associated with the magnitude of clinically induced pain response specifically in areas of the brain that participate in affective pain processing, but not in areas involved in sensory processing which indicates that the amplification of the sensory dimension of pain in fibromyalgia occurs independently of mood or emotional processes.[41] Fibromyalgia has also been linked with bipolar disorder, particularly the hypomania component.[42]

### Non-celiac gluten sensitivity [edit]

Non-celiac gluten sensitivity (NCGS) may be an underlying cause of fibromyalgia symptoms but further research is needed.[43][44]

## Pathophysiology [edit]

The brains of people with fibromyalgia show functional and structural differences from those of people without fibromyalgia, but it is unclear whether the brain anomalies cause fibromyalgia symptoms, or are the product of an unknown underlying common cause. Some research suggests that these brain anomalies may be the result of childhood stress, or prolonged or severe stress.[31]

### Monoamines [edit]

The "dopamine hypothesis of fibromyalgia" proposes that the central abnormality responsible for symptoms associated with fibromyalgia is a disruption of normal dopamine-related neurotransmission.[45] Decreased CSF levels of dopamine were reported in 1992, which may explain the efficacy of some dopaminergic agents in fibromyalgia.[46]

Serotonin is a neurotransmitter involved in pathways that project to the dorsal horns and inhibit pain perception. In 1975, researchers hypothesized that serotonin could be involved in the pathophysiology of fibromyalgia-associated symptoms.[17] In 1992, decreased serotonin metabolites in people's blood samples[47] and cerebrospinal fluid were reported.[46]However, the relevance of dysregulated serotonin metabolism to pathophysiology is a matter of debate.[48] Complicating the analysis, one of the more effective types of medication for the treatment of the disorder (i.e. serotonin 5-HT3 antagonists) actually blocks some effects of serotonin.[49]

Decreased metabolites of norepinephrine, another monoamine involved in the descending pain inhibitory pathways, have been observed.[50]

### Poly-modal sensitivity [edit]

Results from studies examining responses to experimental stimulation suggest that people with fibromyalgia may have heightened sensitivity of the nociceptive system, which senses pressure, heat, cold, electrical and chemical stimulation.[51] Experiments examining pain regulatory systems have shown that people with fibromyalgia display an exaggerated wind-up in response to repetitive stimulation[52] and an absence of exercise-induced analgesic response.[53]

### Neuroendocrine disruption [edit]

Levels of hormones under the direct or indirect control of growth hormone (GH), including insulin-like growth factor 1 (IGF-1), cortisol, leptin and neuropeptide Y may be abnormal in people with fibromyalgia.[54] Support for a causal role for growth hormone deficiency comes from observations that such deficiency in adults has been associated with many of the symptoms described by people with fibromyalgia. Growth hormone is important in maintaining muscle homeostasis, and it has been suggested [55]

that low levels may be responsible for delayed healing of muscle microtrauma in fibromyalgia. Low (IGF-1) levels in some people with fibromyalgia have led to the theory that these people may actually have a different, treatable syndrome, adult growth hormone deficiency.[56] However, there remains some disagreement about the role of HGH in fibromyalgia.[57] It has been hypothesized that the decreased IGF-1 may be a result of slow wave sleep disruption found in fibromyalgia patients.[58]

People with fibromyalgia may have alterations of normal neuroendocrine function, characterized by mild hypocortisolemia,[59] hyperreactivity of pituitary adrenocorticotropin hormone release in response to challenge, and glucocorticoid feedback resistance.[60]

Other abnormalities include reduced responsivity of thyrotropin and thyroid hormones to thyroid-releasing hormone,[61] a mild elevation of prolactin levels with disinhibition of prolactin release in response to challenge[62] and hyposecretion of adrenal androgens.[63]

These changes might result from chronic stress, which, after being perceived and processed by the central nervous system, activates hypothalamic corticotrophin-releasing hormone neurons. Chronic overactivity of these neurons could disrupt normal function of the pituitary-adrenal axis and cause an increased stimulation of hypothalamic somatostatin secretion, which, in turn, could inhibit the secretion of other hormones.[64]

## Sympathetic hyperactivity [edit]

Functional analysis of the autonomic system in people with fibromyalgia has demonstrated disturbed activity characterized by hyperactivity of the sympathetic nervous system at baseline[65] with reduced sympathoadrenal reactivity in response to a variety of stressors including physical exertion and mental stress.[66][67] People with fibromyalgia demonstrate lower heart rate variability, an index of sympathetic/parasympathetic balance, indicating sustained sympathetic hyperactivity, especially at night.[68] In addition, plasma levels of neuropeptide Y, which is co-localized with norepinephrine in the sympathetic nervous system, have been reported as low in people with fibromyalgia,[69] while circulating levels of epinephrine and norepinephrine have been variously reported as low, normal and high.[70][71] Administration of interleukin-6, a cytokine capable of stimulating the release of hypothalamic corticotropin-releasing hormone which in turn stimulates activity within the sympathetic nervous system, results in a dramatic increase in circulating norepinephrine levels and a significantly greater increase in heart rate over baseline in people with fibromyalgia as compared to healthy controls.[72]

## Cerebrospinal fluid [edit]

One of the most reproduced laboratory finding in people with fibromyalgia is an elevation in cerebrospinal fluid levels of substance P, a putative nociceptive neurotransmitter.[73][74] However, despite increased CSF levels of substance P, drugs that manipulate this system have failed to be effective in treating fibromyalgia.[75] Metabolites for the monoamine neurotransmitters serotonin, norepinephrine, and dopamine – all of which play a role in natural analgesia – have been shown to be lower,[76] while concentrations of endogenous opioids (i.e., endorphins and enkephalins) appear to be higher.[77] The mean concentration of nerve growth factor, a substance known to participate in structural and functional plasticity of nociceptive pathways within the dorsal root ganglia and spinal cord, is elevated.[78] There is also evidence for increased excitatory amino acid release within cerebrospinal fluid, with a correlation demonstrated between levels for metabolites of glutamate and nitric oxide and clinical indices of pain.[79] Increased levels of glutamate have also been observed in the insula, a region involved in pain processing.[80]

## Brain imaging studies [edit]

Evidence of abnormal brain involvement in fibromyalgia has been provided via functional neuroimaging. The first findings reported were decreased blood flow within the thalamus and elements of the basal ganglia and mid-brain (i.e., pontine nucleus).[81][82] Differential activation in response to painful stimulation has [83][84]

also been demonstrated. Brain centers showing hyperactivation in response to noxious stimulation include such pain-related brain centers as the primary and secondary somatosensory cortices, anterior cingulate cortex, and insular cortex. People also exhibit neural activation in brain regions associated with pain perception in response to nonpainful stimuli in such areas as the prefrontal, supplemental motor, insular, and cingulate cortices.

Evidence of hippocampal disruption indicated by reduced brain metabolite ratios has been demonstrated by studies using single-voxel magnetic resonance spectroscopy (1H-MRS).[34][35] A significant negative correlation was demonstrated between abnormal metabolite ratios and a validated index of the clinical severity (i.e. the Fibromyalgia Impact Questionnaire).[85] Correlations between clinical pain severity and concentrations of the excitatory amino acid neurotransmitter glutamate within the insular cortex have also been demonstrated using 1H-MRS.[86]

An acceleration of normal age-related brain atrophy has been demonstrated using voxel-based morphometry (VBM) with areas of reduced gray matter located in the cingulate cortex, insula and parahippocampal gyrus. Grey matter loss appears to increase 9.5 times the normal rate with each year.[87] Studies utilizing positron emission tomography have demonstrated reduced dopamine synthesis in the brainstem and elements of the limbic cortex.[88]

A significant negative correlation between pain severity and dopamine synthesis was demonstrated within the insular cortex. A subsequent study demonstrated gross disruption of dopaminergic reactivity in response to a tonic pain stimulus within the basal ganglia with a significant positive correlation between the defining feature of the disorder (i.e. tender point index) and dopamine D2 receptor binding potential specifically in the right putamen.[89]

Finally, reduced availability of mu-opioid receptors in the ventral striatum/nucleus accumbens and cingulate cortex has been demonstrated, with a significant negative correlation between affective pain levels and receptor availability in the nucleus accumbens.[90]

People with FMS consistently demonstrate altered activity in the insula, amygdala, anterior/mid cingulate cortex, superior temporal gyrus, the primary and secondary somatosensory cortex, and lingual gyrus. The changes show similarities to those found in other chronic pain conditions, but it is not known whether these specific features relate to all chronic pain or just to FMS.[91]

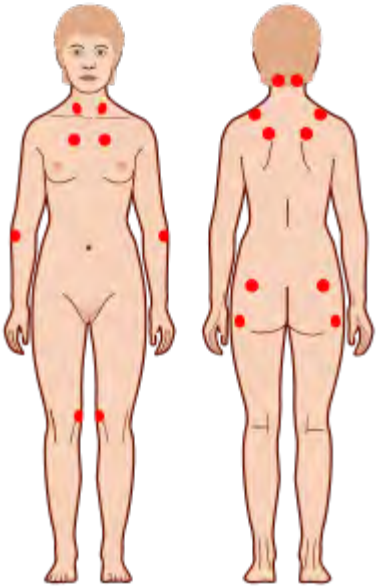
### Inflammation [edit]

Increased circulating levels of IL-1RA, IL-6, IL-8 and chemokines have been observed in patients with fibromyalgia.[92][93]

## Diagnosis [edit]

There is no single test that can fully diagnose fibromyalgia and there is debate over what should be considered essential diagnostic criteria and whether an objective diagnosis is possible. In most cases, people with fibromyalgia symptoms may also have laboratory test results that appear normal and many of their symptoms may mimic those of other rheumatic conditions such as arthritis or osteoporosis. The most widely accepted set of classification criteria for research purposes was elaborated in 1990 by the Multicenter Criteria Committee of the American College of Rheumatology. These criteria, which are known informally as "the ACR 1990", define fibromyalgia according to the presence of the following criteria:

- A history of widespread pain lasting more than three months – affecting all four quadrants of the body, i.e., both sides, and above and below the waist.
- Tender points – there are 18 designated possible tender points



The location of the nine paired tender points that comprise the 1990 American College of Rheumatology criteria for fibromyalgia.

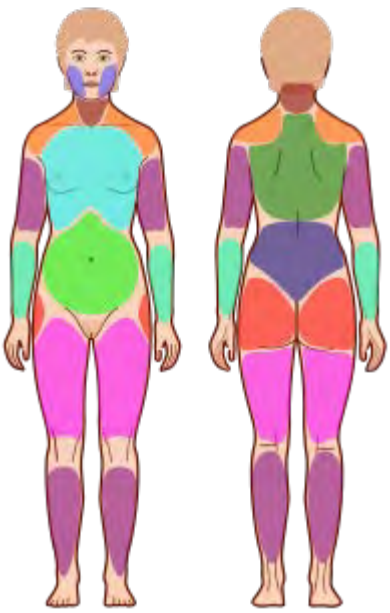
(although a person with the disorder may feel pain in other areas as well). Diagnosis is no longer based on the number of tender points.[94][95]

The ACR criteria for the classification of patients were originally established as inclusion criteria for research purposes and were not intended for clinical diagnosis but have now become the *de facto* diagnostic criteria in the clinical setting. It should be noted that the number of tender points that may be active at any one time may vary with time and circumstance. A controversial study was done by a legal team looking to prove their client's disability based primarily on tender points and their widespread presence in non-litigious communities prompted the lead author of the ACR criteria to question now the useful validity of tender points in diagnosis.[96] Use of control points has been used to cast doubt on whether a person has fibromyalgia, and to claim the person is malingering; however, no research has been done for the use of control points to diagnose fibromyalgia, and such diagnostic tests have been advised against, and people complaining of pain all over should still have fibromyalgia considered as a diagnosis.[9]

## 2010 provisional criteria [edit]

In 2010, the American College of Rheumatology approved provisional revised diagnostic criteria for fibromyalgia that eliminated the 1990 criteria's reliance on tender point testing.[97] The revised criteria use a widespread pain index (WPI) and symptom severity scale (SS) in place of tender point testing under the 1990 criteria. The WPI counts up to 19 general body areas[a] in which the person has experienced pain in the preceding two weeks. The SS rates the severity of the person's fatigue, unrefreshed waking, cognitive symptoms, and general somatic symptoms,[b] each on a scale from 0 to 3, for a composite score ranging from 0 to 12. The revised criteria for diagnosis are:

- WPI ≥ 7 and SS ≥ 5 *OR* WPI 3–6 and SS ≥ 9,
- Symptoms have been present at a similar level for at least three months, *and*
- No other diagnosable disorder otherwise explains the pain.[97]:607



Widespread Pain Index (WPI) Areas

## Differential diagnosis [edit]

Two patients initially diagnosed with fibromyalgia were subsequently shown to have myotonia congenita.[98] Both patients had been seen by rheumatologists and diagnosed with fibromyalgia. The diagnoses were revised when electromyographic studies revealed myotonic discharges in

some of the muscles. Genetic analysis of the skeletal muscle chloride channel which is the underlying cause of myotonia congenita revealed that both patients had mutations in this gene. Over 130 mutations in this gene have been described and the phenotype is very variable which may account for the difficulty in the initial diagnosis.[99][100]

## Management [edit]

As with many other medically unexplained syndromes, there is no universally accepted treatment or cure for fibromyalgia, and treatment typically consists of symptom management. Developments in the understanding of the pathophysiology of the disorder have led to improvements in treatment, which include prescription medication, behavioral intervention, and exercise. Indeed, integrated treatment plans that incorporate medication, patient education, aerobic exercise and cognitive behavioral therapy have been shown to be effective in alleviating pain and other fibromyalgia-related symptoms.[101]

The Association of the Scientific Medical Societies in Germany,[102] the European League Against Rheumatism[103] and the Canadian Pain Society[104] currently publish guidelines for the diagnosis and management of FMS.

### Medications [edit]

Health Canada and the US Food and Drug Administration (FDA) have approved pregabalin[105] and duloxetine, for the management of fibromyalgia. The FDA also approved milnacipran, but the European Medicines Agency refused marketing authority.[106]

### Antidepressants [edit]

Antidepressants are "associated with improvements in pain, depression, fatigue, sleep disturbances, and health-related quality of life in people with FMS."[107] The goal of antidepressants should be symptom reduction and if used long term, their effects should be evaluated against side effects. A small number of people benefit significantly from the SNRIs duloxetine and milnacipran and the tricyclic antidepressants (TCAs), such as amitriptyline. However many people experience more adverse effects than benefits.[108][109] While amitriptyline has been used as a first line treatment, the quality of evidence to support this use is poor.[110]

It can take up to three months to derive benefit from the antidepressant amitriptyline and up to six months to gain the maximal response from duloxetine, milnacipran, and pregabalin. Some medications have the potential to cause withdrawal symptoms when stopping so gradual discontinuation may be warranted particularly for antidepressants and pregabalin.[9]

SSRIs and (TCAs) have more favorable response rates and fewer side effects compared to Pregabalin and the SNRIs Duloxetine and Milnacipram, making them the most effective agents for treating fibromyalgia.[111]

### Anti-seizure medication [edit]

The anti-convulsant drugs gabapentin[112] and pregabalin can be used to reduce pain.[113] Gabapentin is of a significant benefit in about 30% of people who take it. However, it is commonly associated with adverse effects.[112] Pregabalin demonstrates a substantial benefit in about 9% of people.[114] Pregabalin reduced time off work by 0.2 days per week.[115]

### Opioids [edit]

The use of opioids is controversial. As of 2015, no opioid is approved for use in this condition by the FDA.[116] The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) in 2014 stated that there was a lack of evidence for opioids.[4] The Association of the Scientific Medical Societies in

Germany in 2012 made no recommendation either for or against the use of weak opioids because of the limited amount of scientific research addressing their use in the treatment of FM. They strongly advise against using strong opioids.[102] The Canadian Pain Society in 2012 said that opioids, starting with a weak opioid like tramadol, can be tried but only for people with moderate to severe pain that is not well-controlled by non-opioid painkillers. They discourage the use of strong opioids and only recommend using them while they continue to provide improved pain and functioning. Healthcare providers should monitor people on opioids for ongoing effectiveness, side effects and possible unwanted drug behaviors.[104]

The European League Against Rheumatism in 2008 recommends tramadol and other weak opioids may be used for pain but not strong opioids.[103] A 2015 review found fair evidence to support tramadol use if other medications do not work.[116] Goldenberg *et al* suggest that tramadol works via its serotonin and norepinephrine reuptake inhibition, rather than via its action as a weak opioid receptor agonist.[7] The combination of tramadol and paracetemol has demonstrated efficacy, safety and tolerability (for up to two years in the management of other pain conditions) without the development of tolerance. It is as effective as a combination of codeine (another mild opioid) and paracetamol but produces less sleepiness and constipation.[117]

A large study of US people with fibromyalgia found that between 2005 and 2007 37.4% were prescribed short-acting opioids and 8.3% were prescribed long-acting opioids,[118] with around 10% of those prescribed short-acting opioids using tramadol;[119] and a 2011 Canadian study of 457 people with FM found 32% used opioids and two thirds of those used strong opioids.[104]

## Others [edit]

A 2007 review of three randomized placebo controlled studies concluded that a period of nine months of growth hormone was required to reduce fibromyalgia symptoms and normalize IGF-1.[120] A 2014 also found some evidence support its use.[121] Sodium oxybate increases growth hormone production levels through increased slow-wave sleep patterns. However, this medication was not approved by the FDA for the indication for use in people with fibromyalgia due to the concern for abuse.[122]

The muscle relaxants cyclobenzaprine and tizanidine are sometimes used to treat fibromyalgia; however as of 2015 they are not approved for this use in the United States.[123] The use of NSAIDs is not recommended as first line therapy.[124]

Dopamine agonists (e.g. pramipexole and ropinirole) resulted in some improvement in a minority of people,[125] but numerous side effects, including the onset of impulse control disorders like compulsive gambling and shopping, have led to concern about this approach.[126]

There is some evidence that $5HT_3$ antagonists may be beneficial.[127] Preliminary clinical data finds that low-dose naltrexone (LDN) may provide symptomatic improvement.[128]

## Therapy [edit]

Due to the uncertainty about the pathogenesis of FM, current treatment approaches focus on management of symptoms to improve quality of life,[129] using integrated pharmacological and non-pharmacological approaches.[130] There is no single intervention shown to be effective for all patients [131] and no gold treatment standard exists for FM.[132] Multimodal/multidisciplinary therapy is recommended to target multiple underlying factors of FM.[133] A meta-analysis of 1,119 subjects found "strong evidence that multicomponent treatment has beneficial short-term effects on key symptoms of FMS." [134]

## Cognitive behavioural therapy [edit]

Non-pharmacological components include cognitive-behavioural therapy (CBT), exercise and psychoeducation (specifically, sleep hygiene).[135][136][137][138] CBT and related psychological and behavioural therapies have a small to moderate effect in reducing symptoms of fibromyalgia.[139][140] Effect

sizes tend to be small when CBT is used as a stand-alone treatment for FM patients, but these improve significantly when CBT is part of a wider multidisciplinary treatment program.[141] The greatest benefit occurs when CBT is used along with exercise.[101][142]

A 2010 systematic review of 14 studies reported that CBT improves self-efficacy or coping with pain and reduces the number of physician visits at post-treatment, but has no significant effect on pain, fatigue, sleep or health-related quality of life at post-treatment or follow-up. Depressed mood was also improved but this could not be distinguished from some risks of bias.[143]

### Exercise [edit]

Exercise improves fitness and sleep and may reduce pain and fatigue in some people with fibromyalgia.[144][145] In particular, there is strong evidence that cardiovascular exercise is effective for some people.[146] Long-term aquatic-based exercise has been proven beneficial as it combines cardiovascular exercise with resistance training.[147]

In children, fibromyalgia is often treated with an intense physical and occupational therapy program for amplified musculoskeletal pain syndromes. These programs also employ counseling, art therapy, and music therapy. These programs are evidence-based and report long-term total pain resolution rates as high as 88%.[148]

## Prognosis [edit]

Although in itself neither degenerative nor fatal, the chronic pain of fibromyalgia is pervasive and persistent. Most people with fibromyalgia report that their symptoms do not improve over time. An evaluation of 332 consecutive new people with fibromyalgia found that disease-related factors such as pain and psychological factors such as work status, helplessness, education, and coping ability had an independent and significant relationship to FM symptom severity and function.[149]

## Epidemiology [edit]

Fibromyalgia is estimated to affect 2–8% of the population,[3][150] with a female to male incidence ratio that is somewhere between 7:1 and 9:1.[14][151]

Fibromyalgia may not be diagnosed in up to 75% of affected people.[12]

## History [edit]

Chronic widespread pain had already been described in the literature in the 19th century but the term fibromyalgia was not used until 1976 when Dr P.K. Hench used it to describe these symptoms.[9] Many names, including "muscular rheumatism", "fibrositis", "psychogenic rheumatism", and "neurasthenia" were applied historically to symptoms resembling those of fibromyalgia.[152] The term *fibromyalgia* was coined by researcher Mohammed Yunus as a synonym for fibrositis and was first used in a scientific publication in 1981.[153] Fibromyalgia is from the Latin *fibra* (fiber)[154] and the Greek words *myo* (muscle)[155] and *algos* (pain).[156]

Historical perspectives on the development of the fibromyalgia concept note the "central importance" of a 1977 paper by Smythe and Moldofsky on fibrositis.[157][158] The first clinical, controlled study of the characteristics of fibromyalgia syndrome was published in 1981,[159] providing support for symptom associations. In 1984, an interconnection between fibromyalgia syndrome and other similar conditions was proposed,[160] and in 1986, trials of the first proposed medications for fibromyalgia were published.[160]

A 1987 article in the *Journal of the American Medical Association* used the term "fibromyalgia syndrome"[161]

while saying it was a "controversial condition". The American College of Rheumatology (ACR) published its first classification criteria for fibromyalgia in 1990,[162] although these are not strictly diagnostic criteria.[13]

# Society and culture [edit]

*See also: Living With Fibromyalgia*

## Economics [edit]

People with fibromyalgia generally have higher health care costs and utilization rates. A study of almost 20,000 Humana members enrolled in Medicare Advantage and commercial plans compared costs and medical utilizations and found that people with fibromyalgia used twice as much pain-related medication as those without fibromyalgia. Furthermore, the use of medications and medical necessities increased markedly across many measures once diagnosis was made.[163]

## Controversies [edit]

Being a disorder defined relatively recently and still not completely understood, fibromyalgia continues to be a diagnosis that sometimes is disputed. Dr. Frederick Wolfe, lead author of the 1990 paper that first defined the diagnostic guidelines for fibromyalgia, stated in 2008, that he believed it "clearly" not to be a disease but instead a physical response to depression and stress,[164] and in 2013 that its causes "are controversial in a sense" and "there are many factors that produce these symptoms – some are psychological and some are physical and it does exist on a continuum".[165]

Some members of the medical community do not consider fibromyalgia a disease because of a lack of abnormalities on physical examination and the absence of objective diagnostic tests.[157][166] Yunus objects to the psychological characterization of FM. He argues that data indicating it is not psychological has been ignored or manipulated.[167]

Neurologists and pain specialists tend to view fibromyalgia as a pathology due to dysfunction of muscles and connective tissue as well as functional abnormalities in the central nervous system. Rheumatologists define the syndrome in the context of "central sensitization" – heightened brain response to normal stimuli in the absence of disorders of the muscles, joints, or connective tissues. On the other hand, psychiatrists often view fibromyalgia as a type of affective disorder, whereas specialists in psychosomatic medicine tend to view fibromyalgia as being a somatic symptom disorder. However, there is extensive research evidence to support the view that the central symptom of fibromyalgia, namely pain, has a neurogenic origin. These controversies don't engage healthcare specialists alone; some patients object to fibromyalgia being described in purely somatic terms.[9][12]

The validity of fibromyalgia as a unique clinical entity is a matter of contention because "no discrete boundary separates syndromes such as FMS, chronic fatigue syndrome, irritable bowel syndrome, or chronic muscular headaches".[146][168] Because of this symptomatic overlap, some researchers have proposed that fibromyalgia and other analogous syndromes be classified together as functional somatic syndromes for some purposes.[169]

# Research [edit]

Investigational medications include cannabinoids and the 5-HT3 receptor antagonist tropisetron.[170] Low quality evidence found an improvement in symptoms with a gluten free diet among those without celiac disease.[171] A controlled study of guaifenesin failed to demonstrate any benefits from this treatment.[172][173]

# Notes [edit]

a. ^ Shoulder girdle (left & right), upper arm (left & right), lower arm (left & right), hip/buttock/trochanter (left & right), upper leg (left & right), lower leg (left & right), jaw (left & right), chest, abdomen, back (upper & lower), and neck.[97]:607
b. ^ Somatic symptoms include, but are not limited to: muscle pain, irritable bowel syndrome, fatigue or tiredness, problems thinking or remembering, muscle weakness, headache, pain or cramps in the abdomen, numbness or tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives or welts, ringing in the ears, vomiting, heartburn, oral ulcers, loss of or changes in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent or painful urination, and bladder spasms.[97]:607

# References [edit]


1. ^ "fibromyalgia". *Collins Dictionaries*. Retrieved 16 March 2016.
2. ^ a b c Ngian GS, Guymer EK, Littlejohn GO (February 2011). "The use of opioids in fibromyalgia". *Int J Rheum Dis*. **14** (1): 6–11. doi:10.1111/j.1756-185X.2010.01567.x. PMID 21303476.
3. ^ a b c d e f g h i j Clauw, Daniel J. (16 April 2014). "Fibromyalgia". *JAMA*. **311** (15): 1547–55. doi:10.1001/jama.2014.3266. PMID 24737367.
4. ^ a b c d e f g h i j "Questions and Answers about Fibromyalgia". *NIAMS*. July 2014. Retrieved 15 March 2016.
5. ^ a b Buskila D, Sarzi-Puttini P (2006). "Biology and therapy of fibromyalgia. Genetic aspects of fibromyalgia syndrome". *Arthritis Research & Therapy*. **8** (5): 218. doi:10.1186/ar2005. PMC 1779444. PMID 16887010.
6. ^ "Fibromyalgia". *American College of Rheumatology*. May 2015. Retrieved 16 March 2016.
7. ^ a b Goldenberg, DL; Clauw, DJ; Palmer, RE; Clair, AG (May 2016). "Opioid Use in Fibromyalgia: A Cautionary Tale.". *Mayo Clinic Proceedings* (Review). **91** (5): 640–8. doi:10.1016/j.mayocp.2016.02.002. PMID 26975749.
8. ^ Sumpton, JE; Moulin, DE (2014). "Fibromyalgia.". *Handbook of clinical neurology*. **119**: 513–27. doi:10.1016/B978-0-7020-4086-3.00033-3. PMID 24365316.
9. ^ a b c d e f g h Häuser W, Eich W, Herrmann M, Nutzinger DO, Schiltenwolf M, Henningsen P (June 2009). "Fibromyalgia syndrome: classification, diagnosis, and treatment". *Dtsch Arztebl Int*. **106** (23): 383–91. doi:10.3238/arztebl.2009.0383. PMC 2712241. PMID 19623319.
10. ^ Wang, SM; Han, C; Lee, SJ; Patkar, AA; Masand, PS; Pae, CU (June 2015). "Fibromyalgia diagnosis: a review of the past, present and future.". *Expert Review of Neurotherapeutics*. **15** (6): 667–79. doi:10.1586/14737175.2015.1046841. PMID 26035624.
11. ^ Bergmann, Uri (2012). *Neurobiological foundations for EMDR practice*. New York, NY: Springer Pub. Co. p. 165. ISBN 9780826109385.
12. ^ a b c d Clauw DJ, Arnold LM, McCarberg BH (September 2011). "The science of fibromyalgia". *Mayo Clin Proc*. **86** (9): 907–11. doi:10.4065/mcp.2011.0206. PMC 3258006. PMID 21878603.
13. ^ a b Müller W, Schneider EM, Stratz T (September 2007). "The classification of fibromyalgia syndrome". *Rheumatol Int*. **27** (11): 1005–10. doi:10.1007/s00296-007-0403-9. PMID 17653720.
14. ^ a b c d e Hawkins RA (September 2013). "Fibromyalgia: A Clinical Update". *Journal of the American Osteopathic Association*. **113** (9): 680–689. doi:10.7556/jaoa.2013.034. PMID 24005088.
15. ^ "Information on Fibromyalgia". Healthline.com. 21 August 2012. Retrieved 26 August 2012.
16. ^ Wallace DJ, Hallegua DS (October 2002). "Fibromyalgia: the gastrointestinal link". *Curr Pain Headache Rep*. **8** (5): 364–8. doi:10.1007/s11916-996-0009-z. PMID 15361320.
17. ^ a b c Moldofsky H, Scarisbrick P, England R, Smythe H (1975). "Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects". *Psychosom Med*. **37** (4): 341–51. doi:10.1097/00006842-197507000-00008. PMID 169541. Retrieved 21 May 2008.
18. ^ Glass JM (December 2006). "Cognitive dysfunction in fibromyalgia and chronic fatigue syndrome: new trends and future directions". *Curr Rheumatol Rep*. **8** (6): 425–9. doi:10.1007/s11926-006-0036-0. PMID 17092441.
19. ^ a b c d Leavitt F, Katz RS, Mills M, Heard AR (2002). "Cognitive and Dissociative Manifestations in Fibromyalgia". *J Clin Rheumatol*. **8** (2): 77–84. doi:10.1097/00124743-200204000-00003. PMID 17041327.
20. ^ a b c d e Buskila D, Cohen H (October 2007). "Comorbidity of fibromyalgia and psychiatric disorders". *Curr Pain Headache Rep*. **11** (5): 333–8. doi:10.1007/s11916-007-0214-4. PMID 17894922.
21. ^ Yunus MB (June 2007). "Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a

patient with widespread pain". *Best Pract Res Clin Rheumatol*. **21** (3): 481–97. doi:10.1016/j.berh.2007.03.006. PMID 17602995.
22. ^ Maletic V, Raison CL (2009). "Neurobiology of depression, fibromyalgia and neuropathic pain". *Front Biosci*. **14**: 5291–338. doi:10.2741/3598. PMID 19482616.
23. ^ Cohen H, Buskila D, Neumann L, Ebstein RP (March 2002). "Confirmation of an association between fibromyalgia and serotonin transporter promoter region (5- HTTLPR) polymorphism, and relationship to anxiety-related personality traits". *Arthritis Rheum*. **46** (3): 845–7. doi:10.1002/art.10103. PMID 11920428.
24. ^ Buskila D, Dan B, Cohen H, Hagit C, Neumann L, Lily N, Ebstein RP (August 2004). "An association between fibromyalgia and the dopamine D4 receptor exon III repeat polymorphism and relationship to novelty seeking personality traits". *Mol. Psychiatry*. **9** (8): 730–1. doi:10.1038/sj.mp.4001506. PMID 15052273.
25. ^ Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D (February 2003). "COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor". *Science*. **299** (5610): 1240–3. doi:10.1126/science.1078546. PMID 12595695.
26. ^ Narita M, Nishigami N, Narita N, Yamaguti K, Okado N, Watanabe Y, Kuratsune H (November 2003). "Association between serotonin transporter gene polymorphism and chronic fatigue syndrome". *Biochem. Biophys. Res. Commun*. **311** (2): 264–6. doi:10.1016/j.bbrc.2003.09.207. PMID 14592408.
27. ^ Camilleri M, Atanasova E, Carlson PJ, Ahmad U, Kim HJ, Viramontes BE, McKinzie S, Urrutia R (August 2002). "Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome". *Gastroenterology*. **123** (2): 425–32. doi:10.1053/gast.2002.34780. PMID 12145795.
28. ^ Hudson JI, Mangweth B, Pope HG, De Col C, Hausmann A, Gutweniger S, Laird NM, Biebl W, Tsuang MT (February 2003). "Family study of affective spectrum disorder". *Arch. Gen. Psychiatry*. **60** (2): 170–7. doi:10.1001/archpsyc.60.2.170. PMID 12578434.
29. ^ Lee YH, Choi SJ, Ji JD, Song GG (February 2012). "Candidate gene studies of fibromyalgia: a systematic review and meta-analysis". *Rheumatol. Int*. **32** (2): 417–26. doi:10.1007/s00296-010-1678-9. PMID 21120487.
30. ^ Anderberg UM, Marteinsdottir I, Theorell T, von Knorring L (August 2000). "The impact of life events in female patients with fibromyalgia and in female healthy controls". *Eur Psychiatry*. **15** (5): 33–41. doi:10.1016/S0924-9338(00)00397-7. PMID 10954873.
31. ^ *a b* Schweinhardt P, Sauro KM, Bushnell MC (October 2008). "Fibromyalgia: a disorder of the brain?". *Neuroscientist*. **14** (5): 415–21. doi:10.1177/1073858407312521. PMID 18270311.
32. ^ Häuser W, Kosseva M, Üceyler N, Klose P, Sommer C (2011). "Emotional, physical, and sexual abuse in fibromyalgia syndrome: A systematic review with meta-analysis". *Arthritis Care & Research*. **63** (6): 808–820. doi:10.1002/acr.20328. PMID 20722042.
33. ^ Sommer C, Häuser W, Burgmer M, Engelhardt R, Gerhold K, Petzke F, Schmidt-Wilcke T, Späth M, Tölle T, Uçeyler N, Wang H, Winkelmann A, Thieme K (June 2012). "[Etiology and pathophysiology of fibromyalgia syndrome]". *Schmerz*. **26** (3): 259–67. doi:10.1007/s00482-012-1174-0. PMID 22760458.
34. ^ *a b* Emad Y, Ragab Y, Zeinhom F, El-Khouly G, Abou-Zeid A, Rasker JJ (July 2008). "Hippocampus dysfunction may explain symptoms of fibromyalgia syndrome. A study with single-voxel magnetic resonance spectroscopy". *J. Rheumatol.* **35** (7): 1371–7. PMID 18484688.
35. ^ *a b* Wood PB, Ledbetter CR, Glabus MF, Broadwell LK, Patterson JC (2008). "Hippocampal Metabolite Abnormalities in Fibromyalgia: Correlation With Clinical Features". *J Pain*. **10** (1): 47–52. doi:10.1016/j.jpain.2008.07.003. PMID 18771960.
36. ^ McBeth J, Chiu YH, Silman AJ, Ray D, Morriss R, Dickens C, Gupta A, Macfarlane GJ (2005). "Hypothalamic-pituitary-adrenal stress axis function and the relationship with chronic widespread pain and its antecedents". *Arthritis Research & Therapy*. **7** (5): R992–R1000. doi:10.1186/ar1772. PMC 1257426. PMID 16207340.
37. ^ Moldofsky H, Scarisbrick P (January–February 1976). "Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation". *Psychosom Med*. **38** (1): 35–44. doi:10.1097/00006842-197601000-00006. PMID 176677.
38. ^ Goldenberg DL (April 1999). "Fibromyalgia syndrome a decade later: what have we learned?". *Arch. Intern. Med*. **159** (8): 777–85. doi:10.1001/archinte.159.8.777. PMID 10219923.
39. ^ Geoffroy PA, Amad A, Gangloff C, Thomas P (May 2012). "Fibromyalgia and psychiatry: 35 years later… what's new?". *Presse Med*. **41** (5): 555–65. doi:10.1016/j.lpm.2011.08.008. PMID 21993145.
40. ^ Pae CU, Luyten P, Marks DM, Han C, Park SH, Patkar AA, Masand PS, Van Houdenhove B (August 2008). "The relationship between fibromyalgia and major depressive disorder: a comprehensive review". *Curr Med Res Opin*. **24** (8): 2359–71. doi:10.1185/03007990802288338. PMID 18606054.
41. ^ Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ (May 2005). "The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort". *Arthritis Rheum*. **52** (5): 1577–84. doi:10.1002/art.21008. PMID 15880832.
42. ^ Alciati A, Sarzi-Puttini P, Batticiotto A, Torta R, Gesuele F, Atzeni F, Angst J (2012). "Overactive lifestyle in patients

with fibromyalgia as a core feature of bipolar spectrum disorder". *Clinical and Experimental Rheumatology*. **30** (6): 122–128. PMID 23261011.
43. ^ Rossi A, Di Lollo AC, Guzzo MP, Giacomelli C, Atzeni F, Bazzichi L, Di Franco M (2015). "Fibromyalgia and nutrition: what news?". *Clin Exp Rheumatol*. **33** (1 Suppl 88): S117–25. PMID 25786053.
44. ^ San Mauro Martín I, Garicano Vilar E, Collado Yurrutia L, Ciudad Cabañas MJ (Dec 2014). "[Is gluten the great etiopathogenic agent of disease in the XXI century?] [Article in Spanish]" (PDF). *Nutr Hosp*. **30** (6): 1203–10. doi:10.3305/nh.2014.30.6.7866. PMID 25433099.
45. ^ Wood PB (2004). "Stress and dopamine: implications for the pathophysiology of chronic widespread pain". *Medical Hypotheses*. **62** (3): 420–424. doi:10.1016/j.mehy.2003.10.013. PMID 14975515.
46. ^ [a] [b] Bradley, Laurence A. (1 December 2016). "Pathophysiology of Fibromyalgia". *The American Journal of Medicine*. **122** (12 Suppl): S22. doi:10.1016/j.amjmed.2009.09.008. ISSN 0002-9343. PMC 2821819. PMID 19962493.
47. ^ Russell IJ, Michalek JE, Vipraio GA, Fletcher EM, Javors MA, Bowden CA (January 1992). "Platelet 3H-imipramine uptake receptor density and serum serotonin levels in patients with fibromyalgia/fibrositis syndrome". *Journal of Rheumatology*. **19** (1): 104–9. PMID 1313504.
48. ^ Jaschko G, Hepp U, Berkhoff M, Schmet M, Michel BA, Gay S, Sprott H (September 2007). "Serum serotonin levels are not useful in diagnosing fibromyalgia". *Ann. Rheum. Dis.* **66** (9): 1267–8. doi:10.1136/ard.2006.058842. PMC 1955138. PMID 17693607.
49. ^ Späth M (May 2002). "Current experience with 5-HT3 receptor antagonists in fibromyalgia". *Rheum Dis Clin North Am*. **28** (2): 319–28. doi:10.1016/S0889-857X(01)00014-X. PMID 12122920.
50. ^ Di Franco, Manuela; Iannuccelli, Cristina; Valesini, Guido (1 April 2010). "Neuroendocrine immunology of fibromyalgia". *Annals of the New York Academy of Sciences*. **1193**: 84–90. doi:10.1111/j.1749-6632.2009.05344.x. ISSN 1749-6632. PMID 20398012.
51. ^ Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, Dayer P, Vischer TL (May 2003). "Neurophysiologic evidence for a central sensitization in patients with fibromyalgia". *Arthritis Rheum*. **48** (5): 1420–9. doi:10.1002/art.10893. PMID 12746916.
52. ^ Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD (March 2001). "Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome". *Pain*. **91** (1–2): 165–75. doi:10.1016/S0304-3959(00)00432-2. PMID 11240089.
53. ^ Staud R, Robinson ME, Price DD (November 2005). "Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls". *Pain*. **118** (1–2): 176–84. doi:10.1016/j.pain.2005.08.007. PMID 16154700.
54. ^ Bellato, Enrico; Marini, Eleonora; Castoldi, Filippo; Barbasetti, Nicola; Mattei, Lorenzo; Bonasia, Davide Edoardo; Blonna, Davide (1 January 2012). "Fibromyalgia Syndrome: Etiology, Pathogenesis, Diagnosis, and Treatment". *Pain Research and Treatment*. **2012**: 1–17. doi:10.1155/2012/426130. ISSN 2090-1542. PMC 3503476. PMID 23213512.
55. ^ Gupta & Silman. "Psychological stress and fibromyalgia: a review of the evidence suggesting a neuroendocrine link". *Arthritis Research & Therapy*. Retrieved 9 August 2013.
56. ^ Bennett RM (August 2002). "Adult growth hormone deficiency in patients with fibromyalgia". *Curr Rheumatol Rep*. **4** (4): 306–12. doi:10.1007/s11926-002-0039-4. PMID 12126582.
57. ^ Shuer ML (2003). "Fibromyalgia: symptom constellation and potential therapeutic options". *Endocrine*. **22** (1): 67–76. doi:10.1385/ENDO:22:1:67. PMID 14610300.
58. ^ Di Franco, Manuela; Iannuccelli, Cristina; Valesini, Guido (1 April 2010). "Neuroendocrine immunology of fibromyalgia". *Annals of the New York Academy of Sciences*. **1193**: 84–90. doi:10.1111/j.1749-6632.2009.05344.x. ISSN 1749-6632. PMID 20398012.
59. ^ Gur A, Cevik R, Sarac AJ, Colpan L, Em S (November 2004). "Hypothalamic-pituitary-gonadal axis and cortisol in young women with primary fibromyalgia: the potential roles of depression, fatigue, and sleep disturbance in the occurrence of hypocortisolism". *Ann. Rheum. Dis.* **63** (11): 1504–6. doi:10.1136/ard.2003.014969. PMC 1754816. PMID 15479904.
60. ^ Griep EN, Boersma JW, Lentjes EG, Prins AP, van der Korst JK, de Kloet ER (July 1998). "Function of the hypothalamic-pituitary-adrenal axis in patients with fibromyalgia and low back pain". *J. Rheumatol*. **25** (7): 1374–81. PMID 9676772.
61. ^ Neeck G, Riedel W (July 1992). "Thyroid function in patients with fibromyalgia syndrome". *J. Rheumatol*. **19** (7): 1120–2. PMID 1512769.
62. ^ Riedel W, Layka H, Neeck G (1998). "Secretory pattern of GH, TSH, thyroid hormones, ACTH, cortisol, FSH, and LH in patients with fibromyalgia syndrome following systemic injection of the relevant hypothalamic-releasing hormones". *Z Rheumatol*. 57 Suppl 2 (8): 81–7. doi:10.1007/s003930050242. PMID 10025090.[*permanent dead link*]

63. ^ Dessein PH, Shipton EA, Joffe BI, Hadebe DP, Stanwix AE, Van der Merwe BA (November 1999). "Hyposecretion of adrenal androgens and the relation of serum adrenal steroids, serotonin and insulin-like growth factor-1 to clinical features in women with fibromyalgia". *Pain*. **83** (2): 313–9. doi:10.1016/S0304-3959(99)00113-X. PMID 10534604.
64. ^ Neeck G, Crofford LJ (November 2000). "Neuroendocrine perturbations in fibromyalgia and chronic fatigue syndrome". *Rheum. Dis. Clin. North Am*. **26** (4): 989–1002. doi:10.1016/S0889-857X(05)70180-0. PMID 11084955.
65. ^ Martinez-Lavin M (2007). "Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia". *Arthritis Research & Therapy*. **9** (4): 216. doi:10.1186/ar2146. PMC 2206360. PMID 17626613.
66. ^ Giske L, Vøllestad NK, Mengshoel AM, Jensen J, Knardahl S, Røe C (April 2008). "Attenuated adrenergic responses to exercise in women with fibromyalgia – A controlled study". *Eur J Pain*. **12** (3): 351–60. doi:10.1016/j.ejpain.2007.07.007. PMID 17827042.
67. ^ Nilsen KB, Sand T, Westgaard RH, Stovner LJ, White LR, Bang Leistad R, Helde G, Rø M (October 2007). "Autonomic activation and pain in response to low-grade mental stress in fibromyalgia and shoulder/neck pain patients". *Eur J Pain*. **11** (7): 743–55. doi:10.1016/j.ejpain.2006.11.004. PMID 17224287.
68. ^ Martínez-Lavín M, Hermosillo AG, Mendoza C, Ortiz R, Cajigas JC, Pineda C, Nava A, Vallejo M (April 1997). "Orthostatic sympathetic derangement in subjects with fibromyalgia". *J. Rheumatol*. **24** (4): 714–8. PMID 9101507.
69. ^ Anderberg UM, Liu Z, Berglund L, Nyberg F (1999). "Elevated plasma levels of neuropeptide Y in female fibromyalgia patients". *Eur J Pain*. **3** (1): 19–30. doi:10.1016/S1090-3801(99)90185-4. PMID 10700334.
70. ^ van Denderen JC, Boersma JW, Zeinstra P, Hollander AP, van Neerbos BR (1992). "Physiological effects of exhaustive physical exercise in primary fibromyalgia syndrome (PFS): is PFS a disorder of neuroendocrine reactivity? ". *Scand. J. Rheumatol*. **21** (1): 35–7. doi:10.3109/03009749209095060. PMID 1570485.
71. ^ Adler GK, Kinsley BT, Hurwitz S, Mossey CJ, Goldenberg DL (May 1999). "Reduced hypothalamic-pituitary and sympathoadrenal responses to hypoglycemia in women with fibromyalgia syndrome". *Am J Med*. **106** (5): 534–43. doi:10.1016/S0002-9343(99)00074-1. PMID 10335725.
72. ^ Torpy DJ, Papanicolaou DA, Lotsikas AJ, Wilder RL, Chrousos GP, Pillemer SR (April 2000). "Responses of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis to interleukin-6: a pilot study in fibromyalgia". *Arthritis Rheum*. **43** (4): 872–80. doi:10.1002/1529-0131(200004)43:4<872::AID-ANR19>3.0.CO;2-T. PMID 10765933.
73. ^ Russell IJ, Orr MD, Littman B, Vipraio GA, Alboukrek D, Michalek JE, Lopez Y, MacKillip F (November 1994). "Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome". *Arthritis Rheum*. **37** (11): 1593–601. doi:10.1002/art.1780371106. PMID 7526868.
74. ^ Vaerøy H, Helle R, Førre O, Kåss E, Terenius L (January 1988). "Elevated CSF levels of substance P and high incidence of Raynaud phenomenon in patients with fibromyalgia: new features for diagnosis". *Pain*. **32** (1): 21–6. doi:10.1016/0304-3959(88)90019-X. PMID 2448729.
75. ^ Sluka, Kathleen A.; Clauw, Daniel J. (3 December 2016). "Neurobiology of fibromyalgia and chronic widespread pain". *Neuroscience*. **338**: 114–129. doi:10.1016/j.neuroscience.2016.06.006. ISSN 1873-7544. PMC 5083139. PMID 27291641.
76. ^ Russell IJ, Vaeroy H, Javors M, Nyberg F (May 1992). "Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis". *Arthritis Rheum*. **35** (5): 550–6. doi:10.1002/art.1780350509. PMID 1374252.
77. ^ Vaerøy H, Nyberg F, Terenius L (August 1991). "No evidence for endorphin deficiency in fibromyalgia following investigation of cerebrospinal fluid (CSF) dynorphin A and Met-enkephalin-Arg6-Phe7". *Pain*. **46** (2): 139–43. doi:10.1016/0304-3959(91)90068-9. PMID 1684241.
78. ^ Giovengo SL, Russell IJ, Larson AA (July 1999). "Increased concentrations of nerve growth factor in cerebrospinal fluid of patients with fibromyalgia". *J. Rheumatol.* **26** (7): 1564–9. PMID 10405946.
79. ^ Larson AA, Giovengo SL, Russell IJ, Michalek JE (August 2000). "Changes in the concentrations of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: implications for nitric oxide pathways". *Pain*. **87** (2): 201–11. doi:10.1016/S0304-3959(00)00284-0. PMID 10924813.
80. ^ Sluka, Kathleen A.; Clauw, Daniel J. (3 December 2016). "Neurobiology of fibromyalgia and chronic widespread pain". *Neuroscience*. **338**: 114–129. doi:10.1016/j.neuroscience.2016.06.006. ISSN 1873-7544. PMC 5083139. PMID 27291641.
81. ^ Mountz JM, Bradley LA, Modell JG, Alexander RW, Triana-Alexander M, Aaron LA, Stewart KE, Alarcón GS, Mountz JD (July 1995). "Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels". *Arthritis Rheum*. **38** (7): 926–38. doi:10.1002/art.1780380708. PMID 7612042.
82. ^ Kwiatek R, Barnden L, Tedman R, Jarrett R, Chew J, Rowe C, Pile K (December 2000). "Regional cerebral blood

flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami". *Arthritis Rheum*. **43** (12): 2823–33. doi:10.1002/1529-0131(200012)43:12<2823::AID-ANR24>3.0.CO;2-E. PMID 11145042.

83. ^ Gracely RH, Petzke F, Wolf JM, Clauw DJ (May 2002). "Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia". *Arthritis Rheum*. **46** (5): 1333–43. doi:10.1002/art.10225. PMID 12115241.
84. ^ Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH (February 2004). "Functional imaging of pain in patients with primary fibromyalgia". *J. Rheumatol.* **31** (2): 364–78. doi:10.1093/rheumatology/31.6.364. PMID 14760810.
85. ^ Burckhardt CS, Clark SR, Bennett RM (May 1991). "The fibromyalgia impact questionnaire: development and validation". *J. Rheumatol.* **18** (5): 728–33. PMID 1865419.
86. ^ Harris RE, Sundgren PC, Pang Y, Hsu M, Petrou M, Kim SH, McLean SA, Gracely RH, Clauw DJ (March 2008). "Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia". *Arthritis Rheum*. **58** (3): 903–7. doi:10.1002/art.23223. PMID 18311814.
87. ^ Kuchinad A, Schweinhardt P, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC (April 2007). "Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain?". *J Neurosci*. **27** (15): 4004–7. doi:10.1523/JNEUROSCI.0098-07.2007. PMID 17428976.
88. ^ Wood PB, Patterson JC, Sunderland JJ, Tainter KH, Glabus MF, Lilien DL (January 2007). "Reduced presynaptic dopamine activity in fibromyalgia syndrome demonstrated with positron emission tomography: a pilot study". *J Pain*. **8** (1): 51–8. doi:10.1016/j.jpain.2006.05.014. PMID 17023218.
89. ^ Wood PB, Schweinhardt P, Jaeger E, Dagher A, Hakyemez H, Rabiner EA, Bushnell MC, Chizh BA (June 2007). "Fibromyalgia patients show an abnormal dopamine response to pain". *Eur J Neurosci*. **25** (12): 3576–82. doi:10.1111/j.1460-9568.2007.05623.x. PMID 17610577.
90. ^ Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK (September 2007). "Decreased central mu-opioid receptor availability in fibromyalgia". *J Neurosci*. **27** (37): 10000–6. doi:10.1523/JNEUROSCI.2849-07.2007. PMID 17855614.
91. ^ Dehghan, Mahboobeh; Schmidt-Wilcke, Tobias; Pfleiderer, Bettina; Eickhoff, Simon B.; Petzke, Frank; Harris, Richard E.; Montoya, Pedro; Burgmer, Markus (1 May 2016). "Coordinate-based (ALE) meta-analysis of brain activation in patients with fibromyalgia". *Human Brain Mapping*. **37** (5): 1749–1758. doi:10.1002/hbm.23132. ISSN 1097-0193. PMID 26864780.
92. ^ Rodriguez-Pintó, Ignasi; Agmon-Levin, Nancy; Howard, Amital; Shoenfeld, Yehuda (1 October 2014). "Fibromyalgia and cytokines". *Immunology Letters*. **161** (2): 200–203. doi:10.1016/j.imlet.2014.01.009.
93. ^ Uçeyler, Nurcan; Häuser, Winfried; Sommer, Claudia (28 October 2011). "Systematic review with meta-analysis: cytokines in fibromyalgia syndrome". *BMC musculoskeletal disorders*. **12**: 245. doi:10.1186/1471-2474-12-245. ISSN 1471-2474. PMC 3234198. PMID 22034969.
94. ^ http://www.niams.nih.gov/Health_Info/Fibromyalgia/default.asp
95. ^ http://www.rheumatology.org/Practice/Clinical/Patients/Diseases_And_Conditions/Fibromyalgia/
96. ^ Wolfe F (August 2003). "Stop using the American College of Rheumatology criteria in the clinic". *J. Rheumatol.* **30** (8): 1671–2. PMID 12913920.
97. ^ *a b c d* Wolfe, F; et al. (May 2010). "The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity" (PDF). *Arthritis Care Res*. **62** (5): 600–610. doi:10.1002/acr.20140. PMID 20461783.
98. ^ Nam TS, Choi SY, Park DJ, Lee SS, Kim YO, Kim MK (2015). "The Overlap between Fibromyalgia Syndrome and Myotonia Congenita". *J Clin Neurol*. **11** (2): 188–91. doi:10.3988/jcn.2015.11.2.188.
99. ^ Colding-Jørgensen E (2005). "Phenotypic variability in myotonia congenita". *Muscle Nerve*. **32** (1): 19–34. doi:10.1002/mus.20295. PMID 15786415.
100. ^ Lossin C, George AL Jr (2008). "Myotonia congenita". *Adv Genet*. **63**: 25–55. doi:10.1016/S0065-2660(08)01002-X. PMID 19185184.
101. ^ *a b* Goldenberg DL (2008). "Multidisciplinary modalities in the treatment of fibromyalgia". *J Clin Psychiatry*. **69** (2): 30–4. PMID 18537461.
102. ^ *a b* Sommer C, Häuser W, Alten R, Petzke F, Späth M, Tölle T, Uçeyler N, Winkelmann A, Winter E, Bär KJ (June 2012). "Drug therapy of fibromyalgia syndrome. Systematic review, meta-analysis and guideline" (PDF). *Schmerz*. **26** (3): 297–310. doi:10.1007/s00482-012-1172-2. PMID 22760463.
103. ^ *a b* Carville SF, Arendt-Nielsen S, Bliddal H, Blotman F, Branco JC, Buskila D, Da Silva JA, Danneskiold-Samsøe B, Dincer F, Henriksson C, Henriksson KG, Kosek E, Longley K, McCarthy GM, Perrot S, Puszczewicz M, Sarzi-Puttini P, Silman A, Späth M, Choy EH (April 2008). "EULAR evidence-based recommendations for the management of fibromyalgia syndrome" (PDF). *Ann. Rheum. Dis.* **67** (4): 536–41. doi:10.1136/ard.2007.071522. PMID 17644548.

104. ^ [a] [b] [c] 2012 Canadian guidelines for the diagnosis and management of fibromyalgia syndrome
105. ^ "FDA Approves First Drug for Treating Fibromyalgia" (Press release). U.S. Food and Drug Administration. 21 June 2007. Retrieved 14 January 2008.
106. ^ European Medicines Agency. "Questions and answers on the recommendati on for the refusal of the marketing authorisation for Milnacipran Pierre Fabre Médicament/Impulsor" (PDF). European Medicines Agency. Retrieved 30 May 2013.
107. ^ Häuser W, Bernardy K, Uçeyler N, Sommer C (January 2009). "Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis". *JAMA*. **301** (2): 198–209. doi:10.1001/jama.2008.944. PMID 19141768.
108. ^ Häuser W, Wolfe F, Tölle T, Uçeyler N, Sommer C (April 2012). "The role of antidepressants in the management of fibromyalgia syndrome: a systematic review and meta-analysis". *CNS Drugs*. **26** (4): 297–307. doi:10.2165/11598970-000000000-00000. PMID 22452526.
109. ^ Derry S, Gill D, Phillips T, Moore RA (14 March 2012). Derry, Sheena, ed. "Milnacipran for neuropathic pain and fibromyalgia in adults". *Cochrane database of systematic reviews (Online)*. **3**: CD008244. doi:10.1002/14651858.CD008244.pub2. PMID 22419330.
110. ^ Moore, RA; Derry, S; Aldington, D; Cole, P; Wiffen, PJ (31 July 2015). "Amitriptyline for fibromyalgia in adults.". *The Cochrane database of systematic reviews*. **7**: CD011824. doi:10.1002/14651858.CD011824. PMID 26230384.
111. ^ Häuser, Winfried; Walitt, Brian; Fitzcharles, Mary-Ann; Sommer, Claudia (1 January 2014). "Review of pharmacological therapies in fibromyalgia syndrome". *Arthritis Research & Therapy*. **16**: 201. doi:10.1186/ar4441. ISSN 1478-6362.
112. ^ [a] [b] Moore RA, Wiffen PJ, Derry S, McQuay HJ (16 March 2011). Moore, R Andrew, ed. "Gabapentin for chronic neuropathic pain and fibromyalgia in adults". *Cochrane database of systematic reviews (Online)* (3): CD007938. doi:10.1002/14651858.CD007938.pub2. PMID 21412914.
113. ^ Üçeyler N, Sommer C, Walitt B, Häuser W (2013). "Anticonvulsants for fibromyalgia". *Cochrane Database Syst Rev*. **10**: CD010782. doi:10.1002/14651858.CD010782. PMID 24129853.
114. ^ Derry, Sheena; Cording, Malene; Wiffen, Philip J.; Law, Simon; Phillips, Tudor; Moore, R. Andrew (2016-09-29). "Pregabalin for pain in fibromyalgia in adults". *The Cochrane Database of Systematic Reviews*. **9**: CD011790. doi:10.1002/14651858.CD011790.pub2. ISSN 1469-493X. PMID 27684492.
115. ^ Straube S, Moore RA, Paine J, Derry S, Phillips CJ, Hallier E, McQuay HJ (2011). "Interference with work in fibromyalgia – effect of treatment with pregabalin and relation to pain response". *BMC Musculoskelet Disord*. **12**: 125. doi:10.1186/1471-2474-12-125. PMC 3118156. PMID 21639874.
116. ^ [a] [b] MacLean, AJ; Schwartz, TL (May 2015). "Tramadol for the treatment of fibromyalgia.". *Expert Review of Neurotherapeutics*. **15** (5): 469–75. doi:10.1586/14737175.2015.1034693. PMID 25896486.
117. ^ Schug SA. Combination analgesia in 2005 – a rational approach: focus on paracetamol-tramadol. *Clinical rheumatology*. 2006;25(Supplement). doi:10.1007/s10067-006-0202-9. PMID 16741784.
118. ^ Ngian GS, Guymer EK, Littlejohn GO (February 2011). "The use of opioids in fibromyalgia". *Int J Rheum Dis*. **14** (1): 6–11. doi:10.1111/j.1756-185X.2010.01567.x. PMID 21303476.
119. ^ Berger A. Patterns of use of opioids in patients with fibromyalgia In: EULAR; 2009:SAT0461
120. ^ Jones KD, Deodhar P, Lorentzen A, Bennett RM, Deodhar AA (2007). "Growth hormone perturbations in fibromyalgia: a review". *Seminars in Arthritis and Rheumatism*. **36** (6): 357–79. doi:10.1016/j.semarthrit.2006.09.006. PMID 17224178.
121. ^ Cuatrecasas, G.; Alegre, C.; Casanueva, FF. (June 2014). "GH/IGF1 axis disturbances in the fibromyalgia syndrome: is there a rationale for GH treatment?". *Pituitary*. **17** (3): 277–83. doi:10.1007/s11102-013-0486-0. PMID 23568565.
122. ^ Staud R (August 2011). "Sodium oxybate for the treatment of fibromyalgia". *Expert Opin Pharmacother*. **12** (11): 1789–98. doi:10.1517/14656566.2011.589836. PMID 21679091.
123. ^ See S, Ginzburg R. (1 August 2008). "Choosing a Skeletal Muscle Relaxant". *Am Fam Physician*. **78** (3): 365–70.
124. ^ Heymann RE, Paiva Edos S, Helfenstein M, Pollak DF, Martinez JE, Provenza JR, Paula AP, Althoff AC, Souza EJ, Neubarth F, Lage LV, Rezende MC, de Assis MR, Lopes ML, Jennings F, Araújo RL, Cristo VV, Costa ED, Kaziyama HH, Yeng LT, Iamamura M, Saron TR, Nascimento OJ, Kimura LK, Leite VM, Oliveira J, de Araújo GT, Fonseca MC (2010). "Brazilian consensus on the treatment of fibromyalgia". *Rev Bras Reumatol*. **50** (1): 56–66. doi:10.1590/S0482-50042010000100006. PMID 21125141.
125. ^ Holman AJ, Myers RR (August 2005). "A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications". *Arthritis & Rheumatism*. **52** (8): 2495–505. doi:10.1002/art.21191. PMID 16052595.
126. ^ Holman AJ (September 2009). "Impulse control disorder behaviors associated with pramipexole used to treat fibromyalgia". *J Gambl Stud*. **25** (3): 425–31. doi:10.1007/s10899-009-9123-2. PMID 19241148.
127. ^ Späth, M (May 2002). "Current experience with 5-HT3 receptor antagonists in fibromyalgia.". *Rheumatic diseases*

*clinics of North America*. **28** (2): 319–28. doi:10.1016/s0889-857x(01)00014-x. PMID 12122920.
128. ^ Younger J, Parkitny L, McLain D (2014). "The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain". *Clin Rheumatol*. **33** (4): 451–459. doi:10.1007/s10067-014-2517-2. PMC 3962576. PMID 24526250.
129. ^ Arnold, L.M.; Gebke, K.B.; Choy, E.H.S. (2016). "Fibromyalgia: Management strategies for primary care providers". *The International Journal of Clinical Practice*. **70**: 99–112. doi:10.1111/ijcp.12757.
130. ^ Clauw, D. (2014). "Fibromyalgia: A clinical review". *Journal of the American Medical Association*. **311**: 1547–1555. doi:10.1001/jama.2014.3266. PMID 24737367.
131. ^ Okifuji, A.; Hare, B.D. (2013). "Management of fibromyalgia syndrome: Review of evidence". *Pain Therapy*. **2**: 87–104. doi:10.1007/s40122-013-0016-9.
132. ^ Williams, A.C.D.; Eccleston, C.; Morley, S. (2009). "Psychological therapies for the management of chronic pain (excluding headache) in adults.". *Cochraine Database Systematic Review*. **11**: 108–111. doi:10.1002/14651858.CD007407.pub3.
133. ^ Abeles, M.; Solitar, B.M.; Pillinger, M.H.; Abeles, A.M. (2008). "Update of fibromyalgia therapy". *American Journal of Medicine*. **121**: 555–561. doi:10.1016/j.amjmed.2008.02.036.
134. ^ Hauser W, Bernardy K, Arnold B, Offenbacher M, Schiltenwolf M (2009). "Efficacy of multicomponent treatment in fibromyalgia syndrome: A meta-analysis of randomized controlled clinical trials". *Arthritis Care & Research*. **61** (2): 216–224. doi:10.1002/art.24276.
135. ^ Arnold, L.M.; Clauw, D.; Dunegan, J.; Turk, D.C. (2012). "A framework for fibromyalgia management for primary care providers". *Mayo Clinic Proceedings*. **87**: 488–496. doi:10.1016/j.mayocp.2012.02.010.
136. ^ Glombiewski, J.A.; Sawyer, A.T.; Gutermann, A.T.; Koenig, K.; Rief, W.; Hofmann, S.G. (2010). "Psychological treatments for fibromyalgia: A meta-analysis". *Pain*. **151**: 280–295. doi:10.1016/j.pain.2010.06.011. PMID 20727679.
137. ^ Okifuji, A.; Hare, B.C. (2013). "Management of fibromyalgia syndrome: Review of evidence". *Pain Therapy*. **2**: 87–104. doi:10.1007/s40122-013-0016-9.
138. ^ Howard, S.; Smith, M.D.; Barkin, R.L. (2011). "Fibromyalgia syndrome: a discussionof the syndrome and pharmacotherapy". *American Journal of Therapeutics*. **17**: 418–439. doi:10.1097/MJT.0b013e3181df8e1b.
139. ^ Bernardy K, Klose P, Busch AJ, Choy EH, Häuser W (10 September 2013). "Cognitive behavioral therapies for fibromyalgia.". *The Cochrane database of systematic reviews*. **9**: CD009796. doi:10.1002/14651858.CD009796.pub2. PMID 24018611.
140. ^ Glombiewski JA, Sawyer AT, Gutermann J, Koenig K, Rief W, Hofmann SG (November 2010). "Psychological treatments for fibromyalgia: a meta-analysis". *Pain*. **151** (2): 280–95. doi:10.1016/j.pain.2010.06.011. PMID 20727679.
141. ^ Glombiewski, J.A.; Sawyer, A.T.; Gutermann, A.T.; Koenig, K.; Rief, W.; Hofmann, S.G. (2010). "Psychological treatments for fibromyalgia: A meta analysis". *Pain*. **151**: 280–295. doi:10.1016/j.pain.2010.06.011. PMID 20727679.
142. ^ Williams DA (August 2003). "Psychological and behavioral therapies in fibromyalgia and related syndromes". *Best Pract Res Clin Rheumatol*. **17** (4): 649–65. doi:10.1016/S1521-6942(03)00034-2. PMID 12849717.
143. ^ Bernardy K, Füber N, Köllner V, Häuser W (October 2010). "Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome – a systematic review and meta-analysis of randomized controlled trials". *J. Rheumatol.* **37** (10): 1991–2005. doi:10.3899/jrheum.100104. PMID 20682676.
144. ^ Busch A, Schachter CL, Peloso PM, Bombardier C (2002). Busch, Angela, ed. "Exercise for treating fibromyalgia syndrome". *Cochrane database of systematic reviews (Online)* (3): CD003786. doi:10.1002/14651858.CD003786. PMID 12137713.
145. ^ Gowans SE, deHueck A (2004). "Effectiveness of exercise in management of fibromyalgia". *Current Opinion in Rheumatology*. **16** (2): 138–42. doi:10.1097/00002281-200403000-00012. PMID 14770100.
146. ^ *a b* Goldenberg DL, Burckhardt C, Crofford L (Nov 2004). "Management of fibromyalgia syndrome" (Free full text). *Journal of the American Medical Association*. **292** (19): 2388–2395. doi:10.1001/jama.292.19.2388. ISSN 0098-7484. PMID 15547167.
147. ^ Mannerkorpi K, Nyberg B, Ahlmén M, Ekdahl C (2000). "Pool exercise combined with an education program for patients with fibromyalgia syndrome: a prospective, randomized study". *Journal of Rheumatology*. **27** (10): 2473–2481. PMID 11036846.
148. ^ http://www.chop.edu/service/amplified-musculoskeletal-pain-syndrome/about-amps/amps-treatment.html
149. ^ Goldenberg DL, Mossey CJ, Schmid CH (December 1995). "A model to assess severity and impact of fibromyalgia". *J. Rheumatol.* **22** (12): 2313–8. PMID 8835568.
150. ^ Chakrabarty S, Zoorob R (July 2007). "Fibromyalgia". *American Family Physician*. **76** (2): 247–254. PMID 17695569. Retrieved 6 January 2008.
151. ^ Bartels EM, Dreyer L, Jacobsen S, Jespersen A, Bliddal H, Danneskiold-Samsøe B (2009). "Fibromyalgia, diagnosis and prevalence. Are gender differences explainable?". *Ugeskrift for Lægerer*. **171** (49): 3588–92. PMID 19954696.

152. ^ Health Information Team (February 2004). "Fibromyalgia". BUPA insurance.
153. ^ Yunus M, Masi AT, Calabro JJ, Miller KA, Feigenbaum SL (Aug 1981). "Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls". *Seminars in arthritis and rheumatism*. **11** (1): 151–171. doi:10.1016/0049-0172(81)90096-2. ISSN 0049-0172. PMID 6944796.
154. ^ "Fibro-". Dictionary.com. Retrieved 21 May 2008.
155. ^ "Meaning of myo". Web.archive.org. 12 April 2009. Archived from the original on 12 April 2009. Retrieved 26 August 2012.
156. ^ "Meaning of algos". Web.archive.org. 12 April 2009. Archived from the original on 12 April 2009. Retrieved 26 August 2012.
157. ^ *a b* Wolfe F (2009). "Fibromyalgia wars". *J. Rheumatol.* **36** (4): 671–8. doi:10.3899/jrheum.081180. PMID 19342721.
158. ^ Smythe HA, Moldofsky H (1977). "Two contributions to understanding of the "fibrositis" syndrome". *Bull Rheum Dis*. **28** (1): 928–31. PMID 199304.
159. ^ Winfield JB (June 2007). "Fibromyalgia and related central sensitivity syndromes: twenty-five years of progress". *Semin. Arthritis Rheum*. **36** (6): 335–8. doi:10.1016/j.semarthrit.2006.12.001. PMID 17303220. Retrieved 21 May 2008.
160. ^ *a b* Inanici F, Yunus MB (October 2004). "History of fibromyalgia: past to present". *Curr Pain Headache Rep*. **8** (5): 369–78. doi:10.1007/s11916-996-0010-6. PMID 15361321.
161. ^ Goldenberg DL (May 1987). "Fibromyalgia syndrome. An emerging but controversial condition". *JAMA*. **257** (20): 2782–7. doi:10.1001/jama.257.20.2782. PMID 3553636.
162. ^ Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P (February 1990). "The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee". *Arthritis Rheum*. **33** (2): 160–72. doi:10.1002/art.1780330203. PMID 2306288.
163. ^ "High health care utilization and costs in patients with fibromyalgia". *Drug Benefit Trends*. **22** (4): 111. 2010.
164. ^ Berenson. "Drug Approved. Is Disease Real?". The New York Times. Retrieved 26 March 2014.
165. ^ http://www.news-medical.net/news/20130322/Fibromyalgia-an-interview-with-Dr-Frederick-Wolfe-University-of-Kansas-School-of-Medicine.aspx
166. ^ Goldenberg DL (January 1995). "Fibromyalgia: why such controversy?". *Ann. Rheum. Dis*. **54** (1): 3–5. doi:10.1136/ard.54.1.3. PMC 1005499. PMID 7880118.
167. ^ Celeste Cooper; Jeffrey Miller (2010). *Integrative Therapies for Fibromyalgia, Chronic Fatigue Syndrome, and Myofascial Pain: The Mind-Body Connection*. Inner Traditions / Bear & Co. p. 114. ISBN 1594773238. Retrieved 16 July 2012.
168. ^ Kroenke K, Harris L (May 2001). "Symptoms research: a fertile field". *Annals of Internal Medicine*. **134** (9 Pt 2): 801–802. doi:10.7326/0003-4819-134-9_Part_2-200105011-00001. ISSN 0003-4819. PMID 11346313.
169. ^ Kanaan RA, Lepine JP, Wessely SC (December 2007). "The association or otherwise of the functional somatic syndromes". *Psychosom Med*. **69** (9): 855–9. doi:10.1097/PSY.0b013e31815b001a. PMC 2575798. PMID 18040094.
170. ^ Wood PB, Holman AJ, Jones KD (June 2007). "Novel pharmacotherapy for fibromyalgia". *Expert Opin Investig Drugs*. **16** (6): 829–41. doi:10.1517/13543784.16.6.829. PMID 17501695.
171. ^ Aziz, I; Hadjivassiliou, M; Sanders, DS (September 2015). "The spectrum of noncoeliac gluten sensitivity.". *Nature reviews. Gastroenterology & hepatology*. **12** (9): 516–26. doi:10.1038/nrgastro.2015.107. PMID 26122473.
172. ^ Bennett RM, De Garmo P, Clark SR (1996). "A Randomized, Prospective, 12 Month Study To Compare The Efficacy Of Guaifenesin Versus Placebo In The Management Of Fibromyalgia" (reprint). *Arthritis and Rheumatism*. **39** (10): S212. doi:10.1002/art.1780391004.
173. ^ Kristin Thorson (1997). "Is One Placebo Better Than Another? – The Guaifenesin Story *(Lay summary and report)*". *Fibromyalgia Network*. Fibromyalgia Network.


## External links [edit]

- Fibromyalgia at DMOZ
- Arthritis – Types – Fibromyalgia by the CDC
- Questions and Answers About Fibromyalgia by the National Institute of Arthritis and Musculoskeletal and Skin Diseases
- National Institute of Arthritis and Musculoskeletal and Skin Diseases - US National Institute of Arthritis and Musculoskeletal and Skin Diseases

Wikimedia Commons has media related to *Fibromyalgia*.

| v · t · e · | Myopathy (M60–M63, 728.0–3,8) |
|---|---|
| Pain | Myalgia (**Fibromyalgia** · · |
| Inflammation | Myositis (Pyomyositis · · |
| Lytic | Muscle weakness · Rhabdomyolysis · Muscle atrophy/Amyotrophy · |
| Other | Myositis ossificans (Fibrodysplasia ossificans progressiva · · Compartment syndrome (Anterior · · Diastasis of muscle (Diastasis recti · · Muscle spasm · |

| v · t · e · | Neuropathic pain and fibromyalgia pharmacotherapies |
|---|---|
| Monoaminergics | SNRIs (e.g., duloxetine, milnacipran) · TCAs (e.g., amitriptyline, nortriptyline, dosulepin) · Tapentadol · Tramadol · |
| Ion channel blockers | Anticonvulsants (e.g., gabapentin, pregabalin, carbamazepine, oxcarbazepine, lacosamide, lamotrigine) · Local anesthetics (e.g., lidocaine) · Mexiletine · TCAs (e.g., amitriptyline, nortriptyline, desipramine) · Ziconotide · |
| Others | Alpha lipoic acid · Benfotiamine · Botulinum toxin A · Bupropion · Cannabinoids (e.g., cannabis, dronabinol, nabilone) · NMDAR antagonists (e.g., ketamine, dextromethorphan, methadone) · Opioids (e.g., hydrocodone, morphine, oxycodone, methadone, buprenorphine, tramadol, tapentadol) · Sodium oxybate (GHB) · |

| v · t · e · | Arthritis in children | |
|---|---|---|
| Inflammatory | Idiopathic | Juvenile idiopathic arthritis · |
| | Inflammatory disease | Inflammatory bowel disease · Sarcoidosis · Cystic fibrosis · Autoimmune hepatitis · |
| | Hematological malignancy | Acute lymphoblastic leukemia · Lymphoma · |
| | Malignancy | Neuroblastoma · |
| | Reactive | post-streptococcal · Rheumatic fever · postenteric, post-viral · |
| | Infection | Septic arthritis · Osteomyelitis · Tuberculosis · Lyme arthritis · |
| Mechanical | Osgood–Schlatter disease · | |
| Tumours of cartilage bone or muscle | Benign | Osteoid osteoma · Pigmented villonodular synovitis · Hemangioma · |
| | Malignant | Synovial sarcoma · Rhabdomyosarcoma · Ewing's sarcoma · |
| Central Nervous System | Idiopathic pain syndromes · **Local:** Complex regional pain syndrome/Reflex sympathetic dystrophy · **Generalized: Fibromyalgia** · | |

| Authority control | NDL: 01088116 · |
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Categories: Ailments of unknown etiology | Chronic pain syndromes | Disorders of fascia | Rheumatology

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# Gout

From Wikipedia, the free encyclopedia

*"Podagra" redirects here. For the moth genus, see Podagra (moth).*

**Gout** is a form of inflammatory arthritis characterized by recurrent attacks of a red, tender, hot, and swollen joint.[3] Pain typically comes on rapidly in less than twelve hours.[5] The joint at the base of the big toe is affected in about half of cases.[6] It may also result in tophi, kidney stones, or urate nephropathy.[5]

Gout is due to elevated levels of uric acid in the blood. This occurs due to a combination of diet and genetic factors. At high levels, uric acid crystallizes and the crystals deposit in joints, tendons and surrounding tissues, resulting in an attack of gout. Gout occurs more commonly in those who eat a lot of meat, drink a lot of beer, or are overweight. Diagnosis of gout may be confirmed by seeing the crystals in joint fluid or tophus. Blood uric acid levels may be normal during an attack.[5]

Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, or colchicine improves symptoms. Once the acute attack subsides, levels of uric acid can be lowered via lifestyle changes and in those with frequent attacks, allopurinol or probenecid provides long-term prevention.[5] Taking vitamin C and eating a diet high in low fat dairy products may be preventive.[7]

Gout affects about 1 to 2% of the Western population at some point in their lives. It has become more common in recent decades. This is believed to be due to increasing risk factors in the population, such as metabolic syndrome, longer life expectancy and changes in diet. Older males are most commonly affected.[5] Gout was historically known as "the disease of kings" or "rich man's disease".[5][8] It has been recognized at least since the time of the ancient Egyptians.[5]

Contents





**Gout**
podagra

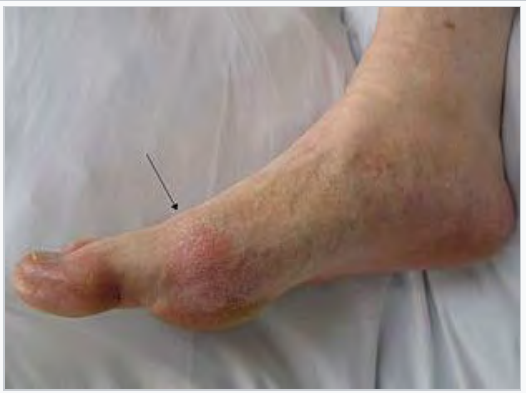

*The Gout* (James Gillray, 1799) depicts the pain of the artist's podagra as a demon or dragon.[1][2]

| | |
|---|---|
| **Specialty** | Rheumatology |
| **Symptoms** | joint pain, swelling, and redness[3] |
| **Differential diagnosis** | joint infection, reactive arthritis, pseudogout, others[4] |
| **Prevention** | weight loss, vitamin C, not drinking alcohol[5] |
| **Medication** | NSAIDs, steroids, colchicine, allopurinol[5] |
| **Frequency** | 1 to 2% (developed world)[5] |

[edit on Wikidata]

## Signs and symptoms

Gout can present in multiple ways, although the most usual is a recurrent attack of acute inflammatory arthritis (a red, tender, hot, swollen joint).[3] The metatarsal-phalangeal joint at the base of the big toe is affected most often, accounting for half of cases.[6] Other joints, such as the heels, knees, wrists and fingers, may also be affected.[6] Joint pain usually begins over 2–4 hours and during the night.[6] This is mainly due to lower body temperature.[9] Other symptoms may rarely occur along with the joint pain, including fatigue and a high fever.[6][9]



Gout presenting in the metatarsal-phalangeal joint of the big toe: Note the slight redness of the skin overlying the joint.

Long-standing elevated uric acid levels (hyperuricemia) may result in other symptoms, including hard, painless deposits of uric acid crystals known as tophi. Extensive tophi may lead to chronic arthritis due to bone erosion.[10] Elevated levels of uric acid may also lead to crystals precipitating in the kidneys, resulting in stone formation and subsequent urate nephropathy.[11]

## Cause

The crystallization of uric acid, often related to relatively high levels in the blood, is the underlying cause of gout. This can occur because of diet, genetic predisposition, or underexcretion of urate, the salts of uric acid.[3] Underexcretion of uric acid by the kidney is the primary cause of hyperuricemia in about 90% of cases, while overproduction is the cause in less than 10%.[5] About 10% of people with hyperuricemia develop gout at some point in their lifetimes.[12] The risk, however, varies depending on the degree of hyperuricemia. When levels are between 415 and 530 μmol/l (7 and 8.9 mg/dl), the risk is 0.5% per year, while in those with a level greater than 535 μmol/l (9 mg/dL), the risk is 4.5% per year.[9]

### Lifestyle

Dietary causes account for about 12% of gout,[3] and include a strong association with the consumption of alcohol, fructose-sweetened drinks, meat, and seafood.[10][13] Other triggers include physical trauma and surgery.[5]

Studies in the early 2000s found that other dietary factors are not relevant.[13][14] Specifically, moderate consumption of purine-rich vegetables (e.g., beans, peas, lentils and spinach) are not associated with gout.[15] Neither is total consumption of protein.[14][15] Alcohol consumption is strongly associated with an increased risk, with wine presenting somewhat less of a risk than beer and spirits.[15][16]

The consumption of coffee, vitamin C and dairy products, as well as physical fitness, appear to decrease the risk.[17][18][19][20] This is believed to be partly due to their effect in reducing insulin resistance.[19]

### Genetics

Gout is partly genetic, contributing to about 60% of variability in uric acid level.[5] The *SLC2A9*, *SLC22A12* and *ABCG2* genes have been found to be commonly associated with gout and variations in them can approximately double the risk.[21][22] Loss-of-function mutations in *SLC2A9* and *SLC22A12* cause hereditary hypouricaemia by reducing urate absorption and unopposed urate secretion.[22] The rare genetic disorders familial juvenile hyperuricemic nephropathy, medullary cystic kidney disease, phosphoribosylpyrophosphate synthetase superactivity and hypoxanthine-guanine phosphoribosyltransferase deficiency as seen in Lesch-Nyhan syndrome, are complicated by gout.[5]

### Medical conditions

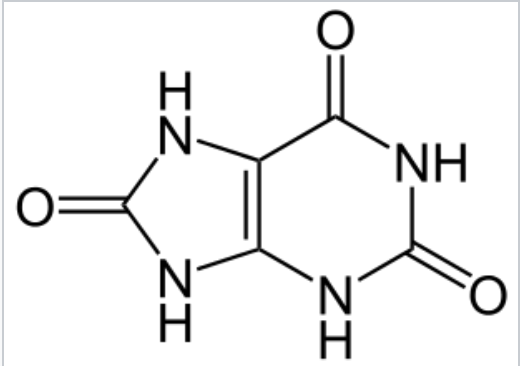
Gout frequently occurs in combination with other medical problems. Metabolic syndrome, a combination of abdominal obesity, hypertension, insulin resistance and abnormal lipid levels, occurs in nearly 75% of cases.[6] Other conditions commonly complicated by gout include polycythemia, lead poisoning, kidney failure, hemolytic anemia, psoriasis and solid organ transplants.[5][23] A body mass index greater than or equal to 35 increases male risk of gout threefold.[13] Chronic lead exposure and lead-contaminated alcohol are risk factors for gout due to the harmful effect of lead on kidney function.[24] Lesch-Nyhan syndrome is often associated with gouty arthritis.

### Medication

Diuretics have been associated with attacks of gout. However, a low dose of hydrochlorothiazide does not seem to increase risk.[25] Other medications that increase the risk include niacin, aspirin (acetylsalicylic acid), ACE inhibitors, angiotensin receptor blockers (except losartan), beta blockers, ritonavir, and pyrazinamide.[10][26] The immunosuppressive drugs ciclosporin and tacrolimus are also associated with gout,[5] the former more so when used in combination with hydrochlorothiazide.[27]

## Pathophysiology

Gout is a disorder of purine metabolism,[5] and occurs when its final metabolite, uric acid, crystallizes in the form of monosodium urate, precipitating and forming deposits (tophi) in joints, on tendons and in the surrounding tissues.[10] Microscopic tophi may be walled off by a ring of proteins, which blocks interaction of the crystals with cells and therefore avoids inflammation.[28] Naked crystals may break out of walled-off tophi due to minor physical damage to the joint, medical or surgical stress, or rapid changes in uric acid levels.[28] When they break through the tophi, they trigger a local immune-mediated inflammatory reaction in macrophages, which is initiated by the NLRP3 inflammasome protein complex.[10][26][28] Activation of the NLRP3 inflammasome recruits the enzyme caspase 1, which converts pro-interleukin 1β into active interleukin 1β, one of the key proteins in the inflammatory cascade.[26] An evolutionary loss of urate oxidase (uricase), which breaks down uric acid, in humans and higher primates has made this condition common.[5]

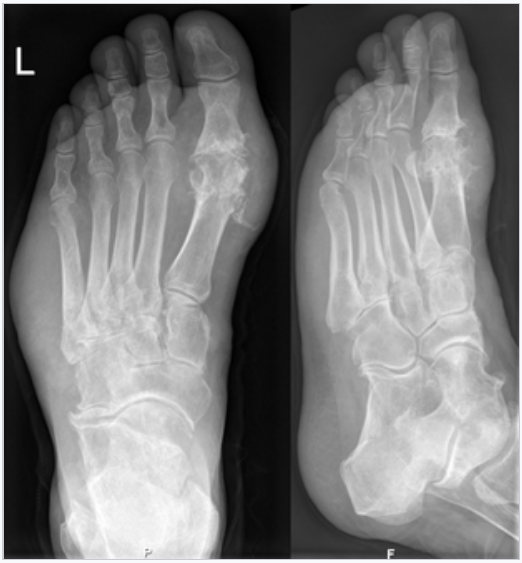


Chemical structure of uric acid

The triggers for precipitation of uric acid are not well understood. While it may crystallize at normal levels, it is more likely to do so as levels increase.[10][29] Other triggers believed to be important in acute episodes of arthritis include cool temperatures, rapid changes in uric acid levels, acidosis,[30][31] articular hydration and extracellular matrix proteins, such as proteoglycans, collagens and chondroitin sulfate.[5] The increased precipitation at low temperatures partly explains why the joints in the feet are most commonly affected.[3] Rapid changes in uric acid may occur due to factors including trauma, surgery, chemotherapy, diuretics and stopping or starting allopurinol.[9] Calcium channel blockers and losartan are associated with a lower risk of gout compared to other medications for hypertension.[32]

## Diagnosis

Gout may be diagnosed and treated without further investigations in someone with hyperuricemia and the classic acute arthritis of the base of the great toe (known as podagra). Synovial fluid analysis should be done, however, if the diagnosis is in doubt.[9] X-rays, while useful for identifying chronic gout, have little utility in acute attacks.[5]



Gout on X-rays of a left foot. The typical location is the big toe joint. Note also the soft tissue swelling at the lateral border of the foot.

### Synovial fluid

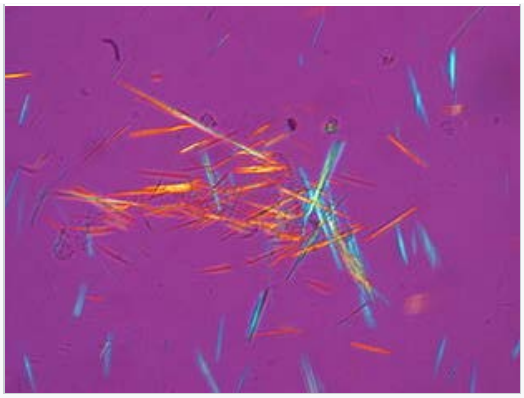
A definitive diagnosis of gout is based upon the identification of monosodium urate crystals in synovial fluid or a tophus.[6] All synovial fluid samples obtained from undiagnosed inflamed joints by arthrocentesis should be examined for these crystals.[5] Under polarized light microscopy, they have a needle-like morphology and strong negative birefringence. This test is difficult to perform and requires a trained observer.[33] The fluid must be examined relatively soon after aspiration, as temperature and pH affect solubility.[5]

### Blood tests

Hyperuricemia is a classic feature of gout, but it occurs nearly half of the time without hyperuricemia and most people with raised uric acid levels never develop gout.[6][34] Thus, the diagnostic utility of measuring uric acid levels is limited.[6] Hyperuricemia is defined as a plasma urate level greater than 420 μmol/l (7.0 mg/dl) in males and 360 μmol/l (6.0 mg/dl) in females.[35] Other blood tests commonly performed are white blood cell count, electrolytes, kidney function and erythrocyte sedimentation rate (ESR). However, both the white blood cells and ESR may be elevated due to gout in the absence of infection.[36][37] A white blood cell count as high as $40.0\times10^9$/l (40,000/mm$^3$) has been documented.[9]

### Differential diagnosis

The most important differential diagnosis in gout is septic arthritis.[5][6] This should be considered in those with signs of infection or those who do not improve with treatment.[6] To help with diagnosis, a synovial fluid Gram stain and culture may be performed.[6] Other conditions that can look similar include pseudogout, rheumatoid arthritis, psoriatic arthritis, and reactive arthritis.[6][26] Gouty tophi, in particular when not located in a joint, can be mistaken for basal cell carcinoma[38]



Spiked rods of uric acid crystals from a synovial fluid sample photographed under a microscope with polarized light. Formation of uric acid crystals in the joints is associated with gout.

or other neoplasms.[39]

## Prevention

Both lifestyle changes and medications can decrease uric acid levels. Dietary and lifestyle choices that are effective include reducing intake of purine-rich foods of animal origin such as meat and seafood, alcohol, and fructose (especially high fructose corn syrup).[40] Eating dairy products, vitamin C, coffee, and cherries may help prevent gout attacks, as does losing weight.[40][41] Gout may be secondary to sleep apnea via the release of purines from oxygen-starved cells. Treatment of apnea can lessen the occurrence of attacks.[42]

## Treatment

The initial aim of treatment is to settle the symptoms of an acute attack.[43] Repeated attacks can be prevented by medications that reduce serum uric acid levels.[43] Tentative evidence supports the application of ice for 20 to 30 minutes several times a day to decrease pain.[44] Options for acute treatment include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine and steroids,[3] while options for prevention include allopurinol, febuxostat, and probenecid. Lowering uric acid levels can cure the disease.[5] Treatment of associated health problems is also important.[5] Lifestyle interventions have been poorly studied.[44] It is unclear whether dietary supplements have an effect in people with gout.[45]

### NSAIDs

NSAIDs are the usual first-line treatment for gout. No specific agent is significantly more or less effective than any other.[3] Improvement may be seen within four hours and treatment is recommended for one to two weeks.[3][5] They are not recommended, however, in those with certain other health problems, such as gastrointestinal bleeding, kidney failure, or heart failure.[46] While indometacin has historically been the most commonly used NSAID, an alternative, such as ibuprofen, may be preferred due to its better side effect profile in the absence of superior effectiveness.[25] For those at risk of gastric side effects from NSAIDs, an additional proton pump inhibitor may be given.[47] There is some evidence that COX-2 inhibitors may work as well as nonselective NSAIDs for acute gout attack with fewer side effects.[48][49]

### Colchicine

Colchicine is an alternative for those unable to tolerate NSAIDs.[3] At high doses, side effects (primarily gastrointestinal upset) limit its usage.[50] At lower doses, which are still effective, it is well tolerated.[25][51] Colchicine may interact with other commonly prescribed drugs, such as atorvastatin and erythromycin, among others.[50]

### Steroids

Glucocorticoids have been found to be as effective as NSAIDs[52][53] and may be used if contraindications exist for NSAIDs. They also lead to improvement when injected into the joint. A joint infection must be excluded, however, as steroids worsen this condition.[3]

### Pegloticase

Pegloticase was approved in the USA to treat gout in 2010.[54] It is an option for the 3% of people who are intolerant to other medications.[54] Pegloticase is administered as an intravenous infusion every two weeks,[54] and reduces uric acid levels.[55] It is likely useful for tophi but has a high rate of side effects.[56]

### Prophylaxis

A number of medications are useful for preventing further episodes of gout, including xanthine oxidase inhibitors (including

allopurinol and febuxostat) and uricosurics (including probenecid and sulfinpyrazone). They are not usually started until one to two weeks after an acute flare has resolved, due to theoretical concerns of worsening the attack.[3] They are often used in combination with either an NSAID or colchicine for the first three to six months.[5] They are not recommended until a person has had two attacks of gout,[3] unless destructive joint changes, tophi, or urate nephropathy exist,[11] because the medications have not been found to be cost-effective.[3] Urate-lowering measures should be increased until serum uric acid levels are below 300–360 µmol/l (5.0–6.0 mg/dl) and continue indefinitely.[3][5][57] If these medications are in chronic use at the time of an attack, discontinuation is recommended.[6] Levels that cannot be brought below 6.0 mg/dl while attacks continue indicates treatment failure or refractory gout.[58] Overall, probenecid appears to be less effective than allopurinol.[3]

Uricosuric medications are typically preferred if undersecretion of uric acid, as indicated by a 24-hour collection of urine results in a uric acid amount of less than 800 mg, is found.[59] They are, however, not recommended if a person has a history of kidney stones.[59] A 24-hour urine excretion of more than 800 mg, which indicates overproduction, is an indication for a xanthine oxidase inhibitor.[59]

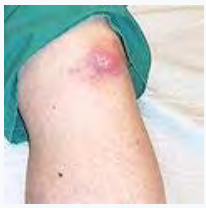
Xanthine oxidase inhibitors block uric acid production. Long-term therapy is safe and well tolerated and can be used in people with decreased kidney function or urate stones, although allopurinol has caused hypersensitivity in a small number of individuals.[3] In such cases febuxostat is recommended.[60]

## Prognosis

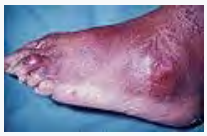
Without treatment, an acute attack of gout usually resolves in five to seven days; however, 60% of people have a second attack within one year.[9] Those with gout are at increased risk of hypertension, diabetes mellitus, metabolic syndrome and kidney and cardiovascular disease and thus are at increased risk of death.[5][61] This may be partly due to its association with insulin resistance and obesity, but some of the increased risk appears to be independent.[61]

Without treatment, episodes of acute gout may develop into chronic gout with destruction of joint surfaces, joint deformity and painless tophi.[5] These tophi occur in 30% of those who are untreated for five years, often in the helix of the ear, over the olecranon processes, or on the Achilles tendons.[5] With aggressive treatment, they may dissolve. Kidney stones also frequently complicate gout, affecting between 10 and 40% of people and occur due to low urine pH promoting the precipitation of uric acid.[5] Other forms of chronic kidney dysfunction may occur.[5]

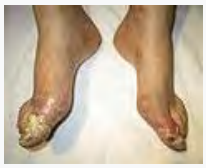
Nodules of the finger and helix of the ear representing gouty tophi



Tophus of the knee



Tophus of the toe, and over the external malleolus



Gout complicated by ruptured tophi (exudate tested positive for uric acid crystals)

Gout of the right MP joint of the big toe

## Epidemiology

Gout affects around 1–2% of the Western population at some point in their lifetimes and is becoming more common.[3][5] Some 5.8 million people were affected in 2013.[62] Rates of gout approximately doubled between 1990 and 2010.[10] This rise is believed to be due to increasing life expectancy, changes in diet and an increase in diseases associated with gout, such as metabolic syndrome and high blood pressure.[13] Factors that influence rates of gout, include age, race and the season of the year. In men over 30 and women over 50, rates are 2%.[46]

In the United States, gout is twice as likely in males of African descent than those of European descent.[63] Rates are high among Pacific Islanders and the Māori, but rare in aboriginal Australians, despite a higher mean uric acid serum concentration in the latter group.[64] It has become common in China, Polynesia and urban sub-Saharan Africa.[5] Some studies found that attacks of gout occur more frequently in the spring. This has been attributed to seasonal changes in diet, alcohol consumption, physical activity and temperature.[65]

## History

The term "gout" was initially used by Randolphus of Bocking, around 1200 AD. It is [66]

derived from the Latin word *gutta*, meaning "a drop" (of liquid). According to the Oxford English Dictionary, this is derived from humorism and "the notion of the 'dropping' of a morbid material from the blood in and around the joints".[67]

Gout has been known since antiquity. Historically, it was referred to as "the king of diseases and the disease of kings"[5][68] or "rich man's disease".[8] The first documentation of the disease is from Egypt in 2,600 BC in a description of arthritis of the big toe. Greek physician Hippocrates around 400 BC commented on it in his *Aphorisms*, noting its absence in eunuchs and premenopausal women.[66][69] Aulus Cornelius Celsus (30 AD) described the linkage with alcohol, later onset in women and associated kidney problems:

> Again thick urine, the sediment from which is white, indicates that pain and disease are to be apprehended in the region of joints or viscera... Joint troubles in the hands and feet are very frequent and persistent, such as occur in cases of podagra and cheiragra. These seldom attack eunuchs or boys before coition with a woman, or women except those in whom the menses have become suppressed... some have obtained lifelong security by refraining from wine, mead and venery.[70]

In 1683, Thomas Sydenham, an English physician, described its occurrence in the early hours of the morning and its predilection for older males:

> Gouty patients are, generally, either old men or men who have so worn themselves out in youth as to have brought on a premature old age—of such dissolute habits none being more common than the premature and excessive indulgence in venery and the like exhausting passions. The victim goes to bed and sleeps in good health. About two o'clock in the morning he is awakened by a severe pain in the great toe; more rarely in the heel, ankle or instep. The pain is like that of a dislocation and yet parts feel as if cold water were poured over them. Then follows chills and shivers and a little fever... The night is passed in torture, sleeplessness, turning the part affected and perpetual change of posture; the tossing about of body being as incessant as the pain of the tortured joint and being worse as the fit comes on.[71]

Antonie van Leeuwenhoek described the microscopic appearance of uric acid crystals in 1679.[66]

Dutch scientist Antonie van Leeuwenhoek first described the microscopic appearance of urate crystals in 1679.[66] In 1848, English physician Alfred Baring Garrod identified excess uric acid in the blood as the cause of gout.[72]

## Other animals

Gout is rare in most other animals due to their ability to produce uricase, which breaks down uric acid.[73] Humans and other great apes do not have this ability, thus gout is common.[9][73] Other animals with uricase include fish, amphibians and most non primate mammals.[74] The *Tyrannosaurus rex* specimen known as "Sue", however, is believed to have suffered from gout.[75]

## Research

A number of new medications are under study for treating gout, including anakinra, canakinumab and rilonacept.[76] Canakinumab may result in better outcomes than a low dose of a steroid but costs five thousand times more.[77] A recombinant uricase enzyme (rasburicase) is available; its use, however, is limited, as it triggers an immune response. Less antigenic versions are in development.[9]

## References


1. ^ Brookhiser, Richard (2008). *Gentleman Revolutionary: Gouverneur Morris, the Rake Who Wrote the Constitution*. Simon and Schuster. p. 212. ISBN 9781439104088.
2. ^ Haslam, Fiona (1996). *From Hogarth to Rowlandson : medicine in art in eighteenth-century Britain* (1. publ. ed.). Liverpool: Liverpool University Press. p. 143. ISBN 9780853236405.
3. ^ *a b c d e f g h i j k l m n o p q r* Chen LX, Schumacher HR (October 2008). "Gout: an evidence-based review". *J Clin* **129** (11): 1153–1158. doi:10.1016/j.amjmed.2016.06.040. PMID 27452679.
41. ^ Bitik, B; Öztürk, MA (June 2014). "An old disease with new insights: Update on diagnosis and treatment of gout." (PDF). *European Journal of Rheumatology*. **1** (2): 72–77. doi:10.5152/eurjrheumatol.2014.021. PMC 5042282. PMID 27708879.
42. ^ Abrams, B (2009). "Sleep Apnea as a Cause of Gout Flares". *The Medscape Journal of Medicine*. **11** (1): 3. PMC 2654686.

*Rheumatol*. **14** (5 Suppl): S55–62. doi:10.1097/RHU.0b013e3181896921. PMID 18830092.
4. ^ Stein, John J. Cush, Arthur Kavanaugh, C. Michael (2005). *Rheumatology : diagnosis and therapeutics* (2nd ed.). Philadelphia: Lippincott, Williams & Wilkins. p. 192. ISBN 9780781757324.
5. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af ag ah ai aj* Richette P, Bardin T (January 2010). "Gout". *Lancet*. **375** (9711): 318–28. doi:10.1016/S0140-6736(09)60883-7. PMID 19692116.
6. ^ *a b c d e f g h i j k l m n* Schlesinger N (March 2010). "Diagnosing and treating gout: a review to aid primary care physicians". *Postgrad Med*. **122** (2): 157–61. doi:10.3810/pgm.2010.03.2133. PMID 20203467.
7. ^ "Questions and Answers about Gout". *National Institute of Arthritis and Musculoskeletal and Skin Diseases*. June 2015. Retrieved 2 February 2016.
8. ^ *a b* "Rich Man's Disease – definition of Rich Man's Disease in the Medical dictionary". *Free Online Medical Dictionary, Thesaurus and Encyclopedia*.
9. ^ *a b c d e f g h i* Eggebeen AT (2007). "Gout: an update". *Am Fam Physician*. **76** (6): 801–8. PMID 17910294.
10. ^ *a b c d e f g* Terkeltaub R (January 2010). "Update on gout: new therapeutic strategies and options". *Nature Reviews Rheumatology*. **6** (1): 30–8. doi:10.1038/nrrheum.2009.236. PMID 20046204.
11. ^ *a b* Tausche AK, Jansen TL, Schröder HE, Bornstein SR, Aringer M, Müller-Ladner U (August 2009). "Gout—current diagnosis and treatment". *Dtsch Arztebl Int*. **106** (34–35): 549–55. doi:10.3238/arztebl.2009.0549. PMC 2754667. PMID 19795010.
12. ^ Vitart V, Rudan I, Hayward C, et al. (April 2008). "SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout". *Nat. Genet*. **40** (4): 437–42. doi:10.1038/ng.106. PMID 18327257.
13. ^ *a b c d* Weaver, AL (July 2008). "Epidemiology of gout". *Cleveland Clinic journal of medicine*. 75 Suppl 5: S9–12. doi:10.3949/ccjm.75.Suppl_5.S9. PMID 18819329.
14. ^ *a b* Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G (March 2004). "Purine-rich foods, dairy and protein intake, and the risk of gout in men". *N. Engl. J. Med.* **350** (11): 1093–103. doi:10.1056/NEJMoa035700. PMID 15014182.
15. ^ *a b c* Singh, JA; Reddy, SG; Kundukulam, J (March 2011). "Risk factors for gout and prevention: a systematic review of the literature.". *Current opinion in rheumatology*. **23** (2): 192–202. doi:10.1097/BOR.0b013e3283438e13. PMID 21285714.
16. ^ Roddy, Edward (Oct 1, 2013). "Gout". *BMJ*. **347**: f5648. doi:10.1136/bmj.f5648.
17. ^ Hak AE, Choi HK (March 2008). "Lifestyle and gout". *Curr Opin Rheumatol*. **20** (2): 179–86. doi:10.1097/BOR.0b013e3282f524a2. PMID 18349748.
18. ^ Williams PT (May 2008). "Effects of diet, physical activity and performance, and body weight on incident gout in ostensibly healthy, vigorously active men". *Am. J. Clin. Nutr.* **87** (5): 1480–7. PMID 18469274.
19. ^ *a b* Choi HK (March 2010). "A prescription for lifestyle change in patients with hyperuricemia and gout". *Curr Opin Rheumatol*. **22** (2): 165–72. doi:10.1097/BOR.0b013e328335ef38. PMID 20035225.
20. ^ Park, Kyu Yong; Kim, Hyun Jung; Ahn, Hyeong Sik; Kim, Sun Hee; Park, Eun Ji; Yim, Shin-Young; Jun, Jae-Bum (April 2016). "Effects of coffee consumption on serum uric acid: systematic review and meta-analysis". *Seminars in Arthritis and Rheumatism*. **45** (5): 580–586. doi:10.1016/j.semarthrit.2016.01.003.
21. ^ Merriman, TR; Dalbeth, N (2011). "The genetic basis of hyperuricaemia and gout.". *Joint, bone, spine : revue du rhumatisme*. **78** (1): 35–40. doi:10.1016/j.jbspin.2010.02.027. PMID 20472486.
22. ^ *a b* Reginato AM, Mount DB, Yang I, Choi HK (2012). "The PMID 19295924.
43. ^ *a b* Zhang W, Doherty M, Bardin T, et al. (October 2006). "EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)". *Ann. Rheum. Dis.* **65** (10): 1312–24. doi:10.1136/ard.2006.055269. PMC 1798308. PMID 16707532.
44. ^ *a b* Moi, JH; Sriranganathan, MK; Edwards, CJ; Buchbinder, R (4 November 2013). "Lifestyle interventions for acute gout". *The Cochrane database of systematic reviews*. **11**: CD010519. doi:10.1002/14651858.CD010519.pub2. PMID 24186771.
45. ^ Andrés, M; Sivera, F; Falzon, L; Buchbinder, R; Carmona, L (Oct 7, 2014). "Dietary supplements for chronic gout.". *The Cochrane database of systematic reviews*. **10**: CD010156. doi:10.1002/14651858.CD010156.pub2. PMID 25287939.
46. ^ *a b* Winzenberg T, Buchbinder R (2009). "Cochrane Musculoskeletal Group review: acute gout. Steroids or NSAIDs? Let this overview from the Cochrane Group help you decide what's best for your patient". *J Fam Pract*. **58** (7): E1–4. PMID 19607767.
47. ^ Cronstein, BN; Terkeltaub, R (2006). "The inflammatory process of gout and its treatment.". *Arthritis research & therapy*. 8 Suppl 1: S3. doi:10.1186/ar1908. PMC 3226108. PMID 16820042.
48. ^ van Durme, CM; Wechalekar, MD; Landewé, RB (9 June 2015). "Nonsteroidal anti-inflammatory drugs for treatment of acute gout.". *JAMA*. **313** (22): 2276–7. doi:10.1001/jama.2015.1881. PMID 26057289.
49. ^ van Durme, CM; Wechalekar, MD; Buchbinder, R; Schlesinger, N; van der Heijde, D; Landewé, RB (16 September 2014). "Non-steroidal anti-inflammatory drugs for acute gout.". *The Cochrane database of systematic reviews*. **9**: CD010120. doi:10.1002/14651858.CD010120.pub2. PMID 25225849.
50. ^ *a b* "Information for Healthcare Professionals: New Safety Information for Colchicine (marketed as Colcrys)". U.S. Food and Drug Administration.
51. ^ van Echteld, I; Wechalekar, MD; Schlesinger, N; Buchbinder, R; Aletaha, D (Aug 15, 2014). "Colchicine for acute gout.". *The Cochrane database of systematic reviews*. **8**: CD006190. doi:10.1002/14651858.CD006190.pub2. PMID 25123076.
52. ^ Man CY, Cheung IT, Cameron PA, Rainer TH (2007). "Comparison of oral prednisolone/paracetamol and oral indomethacin/paracetamol combination therapy in the treatment of acute goutlike arthritis: a double-blind, randomized, controlled trial". *Annals of Emergency Medicine*. **49** (5): 670–7. doi:10.1016/j.annemergmed.2006.11.014. PMID 17276548.
53. ^ van Durme, CM; Wechalekar, MD; Buchbinder, R; Schlesinger, N; van der Heijde, D; Landewé, RB (Sep 16, 2014). "Non-steroidal anti-inflammatory drugs for acute gout.". *The Cochrane database of systematic reviews*. **9**: CD010120. doi:10.1002/14651858.CD010120.pub2. PMID 25225849.
54. ^ *a b c* "FDA approves new drug for gout". *FDA*. September 14, 2010.
55. ^ Sundy JS, Baraf HS, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, Vázquez-Mellado J, White WB, Lipsky PE, Horowitz Z, Huang W, Maroli AN, Waltrip RW, Hamburger SA, Becker MA (Aug 17, 2011). "Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials". *JAMA: The Journal of the American Medical Association*. **306** (7): 711–20. doi:10.1001/jama.2011.1169. PMID 21846852.
56. ^ Sriranganathan, MK; Vinik, O; Bombardier, C; Edwards, CJ (Oct 20, 2014). "Interventions for tophi in gout.". *The Cochrane database of systematic reviews*. **10**: CD010069. doi:10.1002/14651858.CD010069.pub2. PMID 25330136.
57. ^ Ruoff, G; Edwards, NL (September 2016). "Overview of Serum Uric Acid Treatment Targets in Gout: Why Less Than 6 mg/dL?". *Postgraduate Medicine*. **128** (7): 706–15. doi:10.1080/00325481.2016.1221732. PMID 27558643.
58. ^ Ali, S; Lally, EV (November 2009). "Treatment failure gout".

genetics of hyperuricaemia and gout". *Nature Reviews Rheumatology*. **8** (10): 610–21. doi:10.1038/nrrheum.2012.144. PMC 3645862. PMID 22945592.
23. ^ Stamp L, Searle M, O'Donnell J, Chapman P (2005). "Gout in solid organ transplantation: a challenging clinical problem". *Drugs*. **65** (18): 2593–611. doi:10.2165/00003495-200565180-00004. PMID 16392875.
24. ^ Loghman-Adham M (September 1997). "Renal effects of environmental and occupational lead exposure". *Environ. Health Perspect*. Brogan & Partners. **105** (9): 928–38. doi:10.2307/3433873. JSTOR 3433873. PMC 1470371. PMID 9300927.
25. ^ [a] [b] [c] Laubscher T, Dumont Z, Regier L, Jensen B (December 2009). "Taking the stress out of managing gout". *Can Fam Physician*. **55** (12): 1209–12. PMC 2793228. PMID 20008601.
26. ^ [a] [b] [c] [d] Dalbeth, N; Merriman, TR; Stamp, LK (April 2016). "Gout". *Lancet* (Review). **388** (10055): 2039–52. doi:10.1016/S0140-6736(16)00346-9. PMID 27112094.
27. ^ Firestein, MD, Gary S.; Budd, MD, Ralph C.; Harris Jr., MD, Edward D.; McInnes PhD, FRCP, Iain B.; Ruddy, MD, Shaun; Sergent, MD, John S., eds. (2008). "Chapter 87: Gout and Hyperuricemia". *Kelley's Textbook of Rheumatology* (8th ed.). Elsevier. ISBN 978-1-4160-4842-8.
28. ^ [a] [b] [c] Liu-Bryan, Ru; Terkeltaub, Robert (2006). "Evil humors take their Toll as innate immunity makes gouty joints TREM-ble". *Arthritis & Rheumatism*. **54** (2): 383–386. doi:10.1002/art.21634.
29. ^ Virsaladze DK, Tetradze LO, Dzhavashvili LV, Esaliia NG, Tananashvili DE (2007). "[Levels of uric acid in serum in patients with metabolic syndrome]" [Levels of uric acid in serum in patients with metabolic syndrome]. *Georgian Med News* (in Russian) (146): 35–7. PMID 17595458.
30. ^ Moyer RA, John DS (2003). "Acute gout precipitated by total parenteral nutrition". *The Journal of rheumatology*. **30** (4): 849–50. PMID 12672211.
31. ^ Halabe A, Sperling O (1994). "Uric acid nephrolithiasis". *Mineral and electrolyte metabolism*. **20** (6): 424–31. PMID 7783706.
32. ^ Choi HK, Soriano LC, Zhang Y, Rodríguez LA (2012). "Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study". *BMJ*. **344**: d8190. doi:10.1136/bmj.d8190. PMC 3257215. PMID 22240117.
33. ^ Schlesinger N (2007). "Diagnosis of gout". *Minerva Med*. **98** (6): 759–67. PMID 18299687.
34. ^ Sturrock R (2000). "Gout. Easy to misdiagnose". *BMJ*. **320** (7228): 132–33. doi:10.1136/bmj.320.7228.132. PMC 1128728. PMID 10634714.
35. ^ Sachs L, Batra KL, Zimmermann B (2009). "Medical implications of hyperuricemia". *Med Health R I*. **92** (11): 353–55. PMID 19999892.
36. ^ "Gout: Differential Diagnoses & Workup – eMedicine Rheumatology". *Medscape*.
37. ^ "Gout and Pseudogout: Differential Diagnoses & Workup – eMedicine Emergency Medicine". *Medscape*.
38. ^ Jordan DR, Belliveau MJ, Brownstein S, McEachren T, Kyrollos M (2008). "Medial canthal tophus". *Ophthal Plast Reconstr Surg*. **24** (5): 403–4. doi:10.1097/IOP.0b013e3181837a31. PMID 18806664.
39. ^ Sano K, Kohakura Y, Kimura K, Ozeki S (March 2009). "Atypical Triggering at the Wrist due to Intratendinous Infiltration of Tophaceous Gout". *Hand (N Y)*. **4** (1): 78–80. doi:10.1007/s11552-008-9120-4. PMC 2654956. PMID 18780009.
40. ^ [a] [b] Beyl Jr, R. N.; Hughes, L; Morgan, S (2016). "Update on Importance of Diet in Gout". *The American Journal of Medicine*. *Medicine and health, Rhode Island*. **92** (11): 369–71. PMID 19999896.
59. ^ [a] [b] [c] Elizabeth D Agabegi; Agabegi, Steven S. (2008). *Step-Up to Medicine (Step-Up Series)*. Hagerstwon, MD: Lippincott Williams & Wilkins. p. 251. ISBN 0-7817-7153-6.
60. ^ "Febuxostat for the management of hyperuricaemia in people with gout (TA164) Chapter 4. Consideration of the evidence". Guidance.nice.org.uk. Archived from the original on October 6, 2010. Retrieved 2011-08-20.
61. ^ [a] [b] Kim SY, De Vera MA, Choi HK (2008). "Gout and mortality". *Clin. Exp. Rheumatol*. **26** (5 Suppl 51): S115–9. PMID 19026153.
62. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013." *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
63. ^ Rheumatology Therapeutics Medical Center. "What Are the Risk Factors for Gout?". Retrieved 2007-01-26.
64. ^ Roberts-Thomson RA, Roberts-Thomson PJ (May 1999). "Rheumatic disease and the Australian aborigine". *Ann. Rheum. Dis*. **58** (5): 266–70. doi:10.1136/ard.58.5.266. PMC 1752880. PMID 10225809.
65. ^ Fam AG (May 2000). "What is new about crystals other than monosodium urate?". *Curr Opin Rheumatol*. **12** (3): 228–34. doi:10.1097/00002281-200005000-00013. PMID 10803754.
66. ^ [a] [b] [c] [d] Pillinger, MH; Rosenthal P; Abeles AM (2007). "Hyperuricemia and gout: new insights into pathogenesis and treatment". *Bulletin of the NYU Hospital for Joint Diseases*. **65** (3): 215–221. PMID 17922673.
67. ^ "gout, n.1.". *Oxford English Dictionary, Second edition, 1989*. Retrieved 18 September 2011.
68. ^ "The Disease Of Kings - Forbes.com". *Forbes*.
69. ^ "The Internet Classics Archive Aphorisms by Hippocrates". *MIT*. Retrieved July 27, 2010.
70. ^ A. Cornelius Celsus. "On Medicine". *University of Chicago*. Book IV.
71. ^ "Gout – The Affliction of Kings". *h2g2*. BBC. December 23, 2012.
72. ^ Storey GD (October 2001). "Alfred Baring Garrod (1819–1907)". *Rheumatology (Oxford, England)*. **40** (10): 1189–90. doi:10.1093/rheumatology/40.10.1189. PMID 11600751.
73. ^ [a] [b] Agudelo CA, Wise CM (2001). "Gout: diagnosis, pathogenesis, and clinical manifestations". *Curr Opin Rheumatol*. **13** (3): 234–9. doi:10.1097/00002281-200105000-00015. PMID 11333355.
74. ^ Choi, HK; Mount, DB; Reginato, AM; American College of, Physicians; American Physiological, Society (4 October 2005). "Pathogenesis of gout.". *Annals of Internal Medicine*. **143** (7): 499–516. doi:10.7326/0003-4819-143-7-200510040-00009. PMID 16204163.
75. ^ Rothschild, BM; Tanke D; Carpenter K (1997). "Tyrannosaurs suffered from gout". *Nature*. **387** (6631): 357. doi:10.1038/387357a0. PMID 9163417.
76. ^ Abeles, A. M.; Pillinger, M. H. (March 8, 2010). "New therapeutic options for gout here and on the horizon". *Journal of Musculoskeletal Medicine*.
77. ^ Sivera, F; Wechalekar, MD; Andrés, M; Buchbinder, R; Carmona, L (Sep 1, 2014). "Interleukin-1 inhibitors for acute gout.". *The Cochrane database of systematic reviews*. **9**: CD009993. doi:10.1002/14651858.CD009993.pub2. PMID 25177840.

# External links

- Gout at DMOZ

Wikimedia Commons has

Chisholm, Hugh, ed. (1911). "Gout". *Encyclopædia Britannica*. **12** (11th ed.). Cambridge University Press. pp. 289–291.

media related to *Gout*.

| | |
|---|---|
| **Classification** | **ICD-10**: M10 · **ICD-9-CM**: 274.00 274.1 274.8 274.9 · **OMIM**: 138900 300323 · **MeSH**: D006073 · **DiseasesDB**: 29031 · |
| **External resources** | **MedlinePlus**: 000422 · **eMedicine**: emerg/221 med/924 med/1112 oph/506 orthoped/124 radio/313 · **Patient UK**: Gout · |

| v · t · e · **Diseases of joints (M00–M19, 711–719)** | | | |
|---|---|---|---|
| **Arthritis (one joint / multiple)** | **Inflammation** | **Infectious** | Septic arthritis · Tuberculosis arthritis · Reactive arthritis (indirectly) · |
| | | **Noninfectious** | 1. Seronegative spondyloarthropathy: (Reactive arthritis*Psoriatic arthritis*Juvenile idiopathic arthritis*Ankylosing spondylitis · · 2.*Rheumatoid arthritis:* · Adult-onset Still's disease · Felty's syndrome · 3.*Crystal arthropathy:* **Gout** · Chondrocalcinosis · |
| | **Noninflammatory** | | *Osteoarthritis:* Heberden's node · Bouchard's nodes · |
| **Other** | Bleeding · pain · Osteophyte · *villonodular synovitis* (Pigmented villonodular synovitis · · stiffness · | | |
| **Authority control** | NDL: 00573499 · | | |

Categories: Gout | Uric acid | Arthritis | Rheumatology | Skin conditions resulting from errors in metabolism | Inflammatory polyarthropathies | Inborn errors of purine-pyrimidine metabolism | Steroid-responsive inflammatory conditions

# Low back pain





From Wikipedia, the free encyclopedia

**Low back pain** (**LBP**) is a common disorder involving the muscles, nerves, and bones of the back.[1] Pain can vary from a dull constant ache to a sudden sharp feeling.[1] Low back pain may be classified by duration as acute (pain lasting less than 6 weeks), sub-chronic (6 to 12 weeks), or chronic (more than 12 weeks).[2] The condition may be further classified by the underlying cause as either mechanical, non-mechanical, or referred pain.[3] The symptoms of low back pain usually improve within a few weeks from the time they start, with 40-90% of people completely better by six weeks.[4]

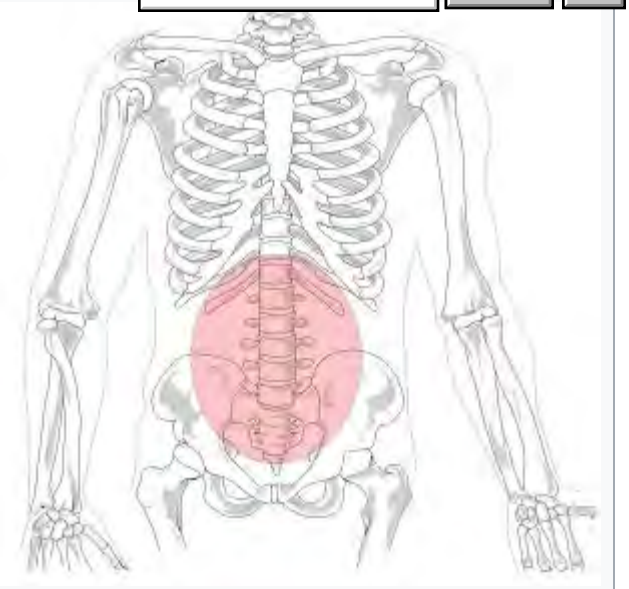
In most episodes of low back pain, a specific underlying cause is not identified or even looked for, with the pain believed to be due to mechanical problems such as muscle or joint strain.[1][5] If the pain does not go away with conservative treatment or if it is accompanied by "red flags" such as unexplained weight loss, fever, or significant problems with feeling or movement, further testing may be needed to look for a serious underlying problem.[3] In most cases, imaging tools such as X-ray computed tomography are not useful and carry their own risks.[6][7] Despite this, the use of imaging in low back pain has increased.[8] Some low back pain is caused by damaged intervertebral discs, and the straight leg raise test is useful to identify this cause.[3] In those with chronic pain, the pain processing system may malfunction, causing large amounts of pain in response to non-serious events.[9]

The treatment of acute nonspecific low back pain of rapid onset is typically with simple pain medications and the continuation of as much normal activity as the pain allows.[4] Medications are recommended for the duration that they are helpful, with paracetamol (also known as acetaminophen) as the preferred first medication.[10] A number of other options are available for those who do not improve with usual treatment. Opioids may be useful if simple pain medications are not enough, but they are not generally recommended due to side effects.[1][10] Surgery may be beneficial for those with disc-related chronic pain and disability or spinal stenosis.[11][12] No clear benefit has been found for other cases of non-specific low back pain.[11] Low back pain often affects mood, which may be improved by counseling or antidepressants.[10][13] Additionally, there are many alternative medicine therapies, including the Alexander technique and herbal remedies, but there is not enough evidence to recommend them confidently.[14] The evidence for chiropractic care[15] and spinal manipulation is mixed.[14][16][17][18]

## Variants

**Low back pain**

**Synonyms** lower back pain, lumbago



Low back pain is a common and costly complaint.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Orthopedics, rheumatology |
| **ICD-10** | M54.5 |
| **ICD-9-CM** | 724.2 |
| **MedlinePlus** | 007422 *007425* |
| **eMedicine** | pmr/73 |
| **MeSH** | D017116 |

[edit on Wikidata]

Approximately 9 to 12% of people (632 million) have LBP at any given point in time, and nearly 25% report having it at some point over any one-month period.[19][20] About 40% of people have LBP at some point in their lives,[19] with estimates as high as 80% among people in the developed world.[21] Difficulty most often begins between 20 and 40 years of age.[5] Men and women are equally affected.[1] Low back pain is more common among people aged 40–80 years, with the overall number of individuals affected expected to increase as the population ages.[19]

**Contents**




Play media

Video explanation

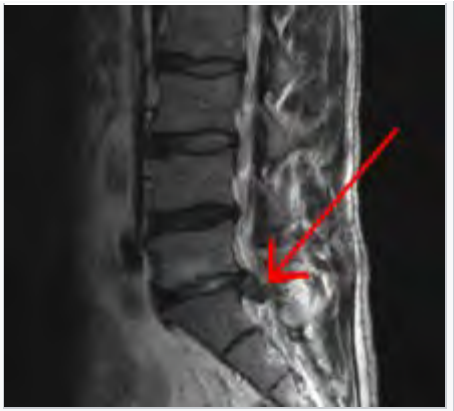
## Signs and symptoms [edit]

In the common presentation of acute low back pain, pain develops after movements that involve lifting, twisting, or forward-bending. The symptoms may start soon after the movements or upon waking up the following morning. The description of the symptoms may range from tenderness at a particular point to diffuse pain. It may or may not worsen with certain movements, such as raising a leg, or positions, such as sitting or standing. Pain radiating down the legs (known as sciatica) may be present. The first experience of acute low back pain is typically between the ages of 20 and 40. This is often a person's first reason to see a medical professional as an adult.[5] Recurrent episodes occur in more than half of people[22] with the repeated episodes being generally more painful than the first.[5]

Other problems may occur along with low back pain. Chronic low back pain is associated with sleep problems, including a greater amount of time needed to fall asleep, disturbances during sleep, a shorter duration of sleep, and less satisfaction with sleep.[23] In addition, a majority of those with chronic low back pain show symptoms of depression[10] or anxiety.[14]

## Causes [edit]

Low back pain is not a specific disease but rather a complaint that may be caused by a large number of underlying problems of varying levels of seriousness.[24] The majority of LBP does not have a clear cause[5] but is believed to be the result of non-serious muscle or skeletal issues such



A herniated disc as seen on MRI, one possible cause of low back pain

as sprains or strains.[25] Obesity, smoking, weight gain during pregnancy, stress, poor physical condition, poor posture and poor sleeping position may also contribute to low back pain.[25] A full list of possible causes includes many less common conditions.[3] Physical causes may include osteoarthritis, degeneration of the discs between the vertebrae or a spinal disc herniation, broken vertebra(e) (such as from osteoporosis) or, rarely, an infection or tumor of the spine.[26]

Women may have acute low back pain from medical conditions affecting the female reproductive system, including endometriosis, ovarian cysts, ovarian cancer, or uterine fibroids.[27] Nearly half of all pregnant women report pain in the lower back or sacral area during pregnancy, due to changes in their posture and center of gravity causing muscle and ligament strain.[28]

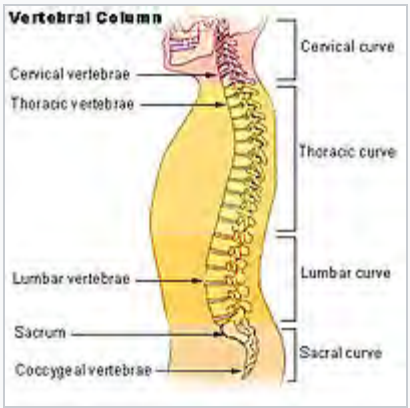
Low back pain can be broadly classified into four main categories:

- Musculoskeletal - mechanical (including muscle strain, muscle spasm, or osteoarthritis); herniated nucleus pulposus, herniated disk; spinal stenosis; or compression fracture
- Inflammatory - HLA-B27 associated arthritis including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease
- Malignancy - bone metastasis from lung, breast, prostate, thyroid, among others
- Infectious - osteomyelitis; abscess

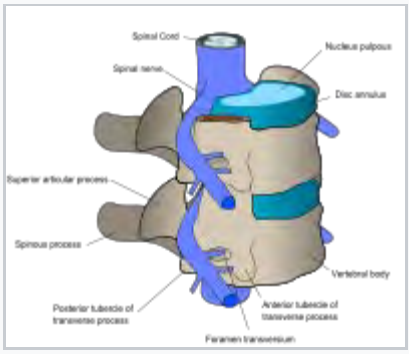
# Pathophysiology [edit]

## Back structures [edit]

The lumbar (or lower back) region is made up of five vertebrae (L1-L5), sometimes including the sacrum. In between these vertebrae are fibrocartilaginous discs, which act as cushions, preventing the vertebrae from rubbing together while at the same time protecting the spinal cord. Nerves come from and go to the spinal cord through specific openings between the vertebrae, providing the skin with sensations and messages to muscles. Stability of the spine is provided by the ligaments and muscles of the back and abdomen. Small joints called facet joints limit and direct the motion of the spine.[29]




The five lumbar vertebrae define the lower back region.



The structures surrounding and supporting the vertebrae can be sources of low back pain.

The multifidus muscles run up and down along the back of the spine, and are important for keeping the spine straight and stable during many common movements such as sitting, walking and lifting.[9] A problem with these muscles is often found in someone with chronic low back pain, because the back pain causes the person to use the back muscles improperly in trying to avoid the pain.[30] The problem with the multifidus muscles continues even after the pain goes away, and is probably an important reason why the pain comes back.[30] Teaching people with chronic low back pain how to use these muscles is recommended as part of a recovery program.[30]

An intervertebral disc has a gelatinous core surrounded by a fibrous ring.[31] When in its normal, uninjured state, most of the disc is not served by either the circulatory or nervous systems – blood and nerves only run to the outside of the disc.[31] Specialized cells that can survive without direct blood supply are in the inside of the disc.[31] Over time, the discs lose flexibility and the ability to absorb physical forces.[24] This decreased ability to handle physical forces increases stresses on other parts of the spine, causing the ligaments of the spine to thicken and bony growths to develop on the vertebrae.[24] As a result, there is less space through which the spinal cord and nerve roots may pass.[24] When a disc degenerates as a result of injury or disease, the makeup of a disc changes: blood vessels and nerves may grow into its interior and/or herniated disc material can push directly on a nerve root.[31] Any of these changes may result in back pain.[31]

### Pain sensation [edit]

Pain is generally an unpleasant feeling in response to an event that either damages or can potentially damage the body's tissues. There are four main steps in the process of feeling pain: transduction, transmission, perception, and modulation.[9] The nerve cells that detect pain have cell bodies located in the dorsal root ganglia and fibers that transmit these signals to the spinal cord.[32] The process of pain sensation starts when the pain-causing event triggers the endings of appropriate sensory nerve cells. This type of cell converts the event into an electrical signal by transduction. Several different types of nerve fibers carry out the transmission of the electrical signal from the transducing cell to the posterior horn of spinal cord, from there to the brain stem, and then from the brain stem to the various parts of the brain such as the thalamus and the limbic system. In the brain, the pain signals are processed and given context in the process of pain perception. Through modulation, the brain can modify the sending of further nerve impulses by decreasing or increasing the release of neurotransmitters.[9]

Parts of the pain sensation and processing system may not function properly; creating the feeling of pain when no outside cause exists, signaling too much pain from a particular cause, or signaling pain from a normally non-painful event. Additionally, the pain modulation mechanisms may not function properly. These phenomena are involved in chronic pain.[9]

## Diagnosis [edit]

As the structure of the back is complex and the reporting of pain is subjective and affected by social factors, the diagnosis of low back pain is not straightforward.[3] While most low back pain is caused by muscle and joint problems, this cause must be separated from neurological problems, spinal tumors, fracture of the spine, and infections, among others.[2][5]

### Classification [edit]

There are a number of ways to classify low back pain with no consensus that any one method is best.[3] There are three general types of low back pain by cause: mechanical back pain (including nonspecific musculoskeletal strains, herniated discs, compressed nerve roots, degenerative discs or joint disease, and broken vertebra), non-mechanical back pain (tumors, inflammatory conditions such as spondyloarthritis, and infections), and referred pain from internal organs (gallbladder disease, kidney stones, kidney infections, and aortic aneurysm, among others).[3] Mechanical or musculoskeletal problems underlie most cases (around 90% or more),[3][33] and of those, most (around 75%) do not have a specific cause identified, but are thought to be due to muscle strain or injury to ligaments.[3][33] Rarely, complaints of low back pain result from systemic or psychological problems, such as fibromyalgia and somatoform disorders.[33]

Low back pain may be classified based on the signs and symptoms. Diffuse pain that does not change in response to particular movements, and is localized to the lower back without radiating beyond the buttocks, is classified as *nonspecific*, the most common classification.[3] Pain that radiates down the leg below the knee, is located on one side (in the case of disc herniation), or is on both sides (in spinal stenosis), and

changes in severity in response to certain positions or maneuvers is *radicular*, making up 7% of cases.[3] Pain that is accompanied by red flags such as trauma, fever, a history of cancer or significant muscle weakness may indicate a more serious underlying problem and is classified as *needing urgent or specialized attention*.[3]

The symptoms can also be classified by duration as acute, sub-chronic (also known as sub-acute), or chronic. The specific duration required to meet each of these is not universally agreed upon, but generally pain lasting less than six weeks is classified as *acute*, pain lasting six to twelve weeks is *sub-chronic*, and more than twelve weeks is *chronic*.[2] Management and prognosis may change based on the duration of symptoms.

## Red flags [edit]

The presence of certain signs, termed *red flags*, indicate the need for further testing to look for more serious underlying problems, which may require immediate or specific treatment.[3][35] The presence of a red flag does not mean that there is a significant problem. It is only suggestive,[36][37] and most people with red flags have no serious underlying problem.[2][5] If no red flags are present, performing diagnostic imaging or laboratory testing in the first four weeks after the start of the symptoms has not been shown to be useful.[3]

The usefulness of many red flags are poorly supported by evidence.[38] The most useful for detecting a fracture are: older age, corticosteroid use, and significant trauma especially if it results in skin markings.[38] The best determinant of the presence of cancer is a history of the same.[38]

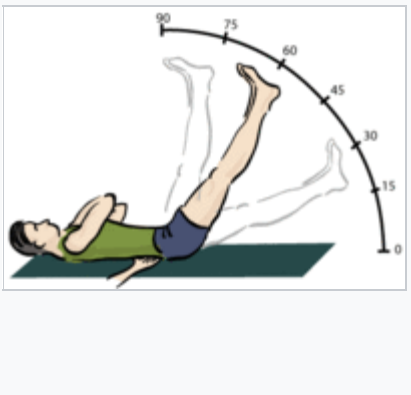
With other causes ruled out, people with non-specific low back pain are typically treated symptomatically, without exact determination of the cause.[2][5] Efforts to uncover factors that might complicate the diagnosis, such as depression, substance abuse, or an agenda concerning insurance payments may be helpful.[3]

| Red flag[34] | Possible cause[5] |
|---|---|
| Previous history of cancer | Cancer |
| Unintentional weight loss | |
| Loss of bladder or bowel control | Cauda equina syndrome |
| Significant motor weakness or sensory problems | |
| Loss of sensation in the buttocks (saddle anesthesia) | |
| Significant trauma related to age | Fracture |
| Chronic corticosteroid use | |
| Osteoporosis | |
| Severe pain after lumbar surgery in past year | Infection |
| Fever | |
| Urinary tract infection | |
| Immunosuppression | |
| Intravenous drug use | |

Red flags are warning signs that may indicate a more serious problem

## Tests [edit]

Imaging is indicated when there are red flags, ongoing neurological symptoms that do not resolve, or ongoing or worsening pain.[3] In particular, early use of imaging (either MRI or CT) is recommended for suspected cancer, infection, or cauda equina syndrome.[3] MRI is slightly better than CT for identifying disc disease; the two technologies are equally useful for diagnosing spinal stenosis.[3] Only a few physical diagnostic tests are helpful.[3] The straight leg raise test is almost always positive in those with disc herniation.[3] Lumbar provocative discography may be useful to identify a specific disc




The straight leg raise test can detect pain originating

from a herniated disc. When warranted, imaging such as MRI can provide clear detail about disc related causes of back pain (L4–L5 disc herniation shown)

causing pain in those with chronic high levels of low back pain.[39] Similarly, therapeutic procedures such as nerve blocks can be used to determine a specific source of pain.[3] Some evidence supports the use of facet joint injections, transforminal epidural injections and sacroilliac injections as diagnostic tests.[3] Most other physical tests, such as evaluating for scoliosis, muscle weakness or wasting, and impaired reflexes, are of little use.[3]

Complaints of low back pain are one of the most common reasons people visit doctors.[6][40] For pain that has lasted only a few weeks, the pain is likely to subside on its own.[41] Thus, if a person's medical history and physical examination do not suggest a specific disease as the cause, medical societies advise against imaging tests such as X-rays, CT scans, and MRIs.[40] Individuals may want such tests but, unless red flags are present,[7][42] they are unnecessary health care.[6][41] Routine imaging increases costs, is associated with higher rates of surgery with no overall benefit,[43][44] and the radiation used may be harmful to one's health.[43] Fewer than 1% of imaging tests identify the cause of the problem.[6] Imaging may also detect harmless abnormalities, encouraging people to request further unnecessary testing or to worry.[6] Even so, MRI scans of the lumbar region increased by more than 300% among United States Medicare beneficiaries from 1994 to 2006.[8]

## Prevention [edit]

Exercise appears to be useful for preventing low back pain.[45] Exercise is also probably effective in preventing recurrences in those with pain that has lasted more than six weeks.[5][46] Medium-firm mattresses are more beneficial for chronic pain than firm mattresses.[47] There is little to no evidence that back belts are any more helpful in preventing low back pain than education about proper lifting techniques.[45][48] Shoe insoles do not help prevent low back pain.[45][49]

## Management [edit]

Management of low back pain depends on which of the three general categories is the cause: mechanical problems, non-mechanical problems, or referred pain.[50] For acute pain that is causing only mild to moderate problems, the goals are to restore normal function, return the individual to work, and minimize pain. The condition is normally not serious, resolves without much being done, and recovery is helped by attempting to return to normal activities as soon as possible within the limits of pain.[2] Providing individuals with coping skills through reassurance of these facts is useful in speeding recovery.[5] For those with sub-chronic or chronic low back pain, multidisciplinary treatment programs may help.[51]

### Physical management [edit]

Increasing general physical activity has been recommended, but no clear relationship to pain or disability has been found when used for the treatment of an acute episode of pain.[46][52] For acute pain, low- to moderate-quality evidence supports walking.[53] Treatment according to McKenzie method is somewhat effective for recurrent acute low back pain, but its benefit in the short term does not appear significant.[5] There is tentative evidence to support the use of heat therapy for acute and sub-chronic low back pain[54] but little evidence for the use of either heat or cold therapy in chronic pain.[55] Weak evidence suggests that back belts might decrease the number of missed workdays, but there is nothing to suggest that they will help with the pain.[48] Ultrasound and shock wave therapies do not appear effective and therefore are not recommended.[56][57]

Exercise therapy is effective in decreasing pain and improving function for those with chronic low back

pain.[48] It also appears to reduce recurrence rates for as long as six months after the completion of program[58] and improves long-term function.[55] There is no evidence that one particular type of exercise therapy is more effective than another.[59] The Alexander technique appears useful for chronic back pain,[60] and there is tentative evidence to support the use of yoga.[61] Transcutaneous electrical nerve stimulation (TENS) has not been found to be effective in chronic low back pain.[62] Evidence for the use of shoe insoles as a treatment is inconclusive.[49] Peripheral nerve stimulation, a minimally-invasive procedure, may be useful in cases of chronic low back pain that do not respond to other measures, although the evidence supporting it is not conclusive, and it is not effective for pain that radiates into the leg.[63]

## Medications [edit]

The management of low back pain often includes medications for the duration that they are beneficial. With the first episode of low back pain the hope is a complete cure; however, if the problem becomes chronic, the goals may change to pain management and the recovery of as much function as possible. As pain medications are only somewhat effective, expectations regarding their benefit may differ from reality, and this can lead to decreased satisfaction.[10]

The medication typically recommended first is acetaminophen (paracetamol) or NSAIDs (though not aspirin), and these are enough for most people. Standard doses of acetaminophen are very safe; however, high doses may cause liver problems, and very high doses can be fatal.[10] High-quality reviews have found acetaminophen (paracetamol) to be no more effective than placebo at improving pain, quality of life, or function.[64][65] NSAIDs are more effective for acute episodes than acetaminophen; however, they carry a greater risk of side effects including: kidney failure, stomach ulcers and possibly heart problems. Thus, NSAIDs are a second choice to acetaminophen, recommended only when the pain is not handled by the latter. NSAIDs are available in several different classes; there is no evidence to support the use of COX-2 inhibitors over any other class of NSAIDs with respect to benefits.[10][66] With respect to safety naproxen may be best.[67] Muscle relaxants may be beneficial.[10]

If the pain is still not managed adequately, short term use of opioids such as morphine may be useful.[68][10] These medications carry a risk of addiction, may have negative interactions with other drugs, and have a greater risk of side effects, including dizziness, nausea, and constipation.[10] The effect of long term use is unknown.[69] Specialist groups advise against general long-term use of opioids for chronic low back pain.[10][70]

For older people with chronic pain, opioids may be used in those for whom NSAIDs present too great a risk, including those with diabetes, stomach or heart problems. They may also be useful for a select group of people with neuropathic pain.[71]

Antidepressants may be effective for treating chronic pain associated with symptoms of depression, but they have a risk of side effects. Although the antiseizure drugs gabapentin and carbamazepine are sometimes used for chronic low back pain and may relieve sciatic pain, there is insufficient evidence to support their use.[10] Systemic oral steroids have not been shown to be useful in low back pain.[5][10] Facet joint injections and steroid injections into the discs have not been found to be effective in those with persistent, non-radiating pain; however, they may be considered for those with persistent sciatic pain.[72] Epidural corticosteroid injections provide a slight and questionable short-term improvement in those with sciatica but are of no long term benefit.[73] There are also concerns of potential side effects.[74]

## Surgery [edit]

Surgery may be useful in those with a herniated disc that is causing significant pain radiating into the leg, significant leg weakness, bladder problems, or loss of bowel control.[11] It may also be useful in those with spinal stenosis.[12] In the absence of these issues, there is no clear evidence of a benefit from surgery.[11]

Discectomy (the partial removal of a disc that is causing leg pain) can provide pain relief sooner than nonsurgical treatments.[11] Discectomy has better outcomes at one year but not at four to ten years.[11]

The less invasive microdiscectomy has not been shown to result in a different outcome than regular discectomy.[11] For most other conditions, there is not enough evidence to provide recommendations for surgical options.[11] The long-term effect surgery has on degenerative disc disease is not clear.[11] Less invasive surgical options have improved recovery times, but evidence regarding effectiveness is insufficient.[11]

For those with pain localized to the lower back due to disc degeneration, fair evidence supports spinal fusion as equal to intensive physical therapy and slightly better than low-intensity nonsurgical measures.[12] Fusion may be considered for those with low back pain from acquired displaced vertebra that does not improve with conservative treatment,[11] although only a few of those who have spinal fusion experience good results.[12] There are a number of different surgical procedures to achieve fusion, with no clear evidence of one being better than the others.[75] Adding spinal implant devices during fusion increases the risks but provides no added improvement in pain or function.[8]

## Alternative medicine [edit]

It is unclear if chiropractic care or spinal manipulation therapy (SMT) improves outcomes in those with low back pain more or less than other treatments.[15] Some reviews find that SMT results in equal or better improvements in pain and function when compared with other commonly used interventions for short, intermediate, and long-term follow-up;[16][17] other reviews find it to be no more effective in reducing pain than either inert interventions, sham manipulation, or other treatments, and conclude that adding SMT to other treatments does improve outcomes.[14][18] National guidelines reach different conclusions, with some not recommending spinal manipulation, some describing manipulation as optional, and others recommending a short course for those who do not improve with other treatments.[2] Manipulation under anaesthesia, or medically assisted manipulation, has not enough evidence to make any confident recommendation.[76]

Acupuncture is no better than placebo, usual care, or sham acupuncture for nonspecific acute pain or sub-chronic pain.[77] For those with chronic pain, it improves pain a little more than no treatment and about the same as medications, but it does not help with disability.[77] This pain benefit is only present right after treatment and not at follow-up.[77] Acupuncture may be a reasonable method to try for those with chronic pain that does not respond to other treatments like conservative care and medications.[5][78]

While massage therapy does not appear to provide much benefit for acute low back pain,[5] it may help those with sub-chronic and chronic pain, particularly when combined with physical exercises and education.[79][*needs update*] Tentative evidence suggests that acupuncture and massage together may be better than massage alone.[79]

Prolotherapy – the practice of injecting solutions into joints (or other areas) to cause inflammation and thereby stimulate the body's healing response – has not been found to be effective by itself, although it may be helpful when added to another therapy.[14]

Herbal medicines, as a whole, are poorly supported by evidence.[80] The herbal treatments Devil's claw and white willow may reduce the number of individuals reporting high levels of pain; however, for those taking pain relievers, this difference is not significant.[14] Capsicum, in the form of either a gel or a plaster cast, has been found to reduce pain and increase function.[14]

Behavioral therapy may be useful for chronic pain.[13] There are several types available, including operant conditioning, which uses reinforcement to reduce undesirable behaviors and increase desirable behaviors; cognitive behavioral therapy, which helps people identify and correct negative thinking and behavior; and respondent conditioning, which can modify an individual's physiological response to pain. Medical providers may develop an integrated program of behavioral therapies.[14] The evidence is inconclusive as to whether mindfulness-based stress reduction reduces chronic back pain intensity or associated disability, although it suggests that it may be useful in improving the acceptance of existing pain.[81]

Tentative evidence supports neuroreflexotherapy (NRT), in which small pieces of metal are placed just

under the skin of the ear and back, for non-specific low back pain.[82][83]

## Prognosis [edit]

Overall, the outcome for acute low back pain is positive. Pain and disability usually improve a great deal in the first six weeks, with complete recovery reported by 40 to 90%.[4] In those who still have symptoms after six weeks, improvement is generally slower with only small gains up to one year. At one year, pain and disability levels are low to minimal in most people. Distress, previous low back pain, and job satisfaction are predictors of long-term outcome after an episode of acute pain.[4] Certain psychological problems such as depression, or unhappiness due to loss of employment may prolong the episode of low back pain.[10] Following a first episode of back pain, recurrences occur in more than half of people.[22]

For persistent low back pain, the short-term outcome is also positive, with improvement in the first six weeks but very little improvement after that. At one year, those with chronic low back pain usually continue to have moderate pain and disability.[4] People at higher risk of long-term disability include those with poor coping skills or with fear of activity (2.5 times more likely to have poor outcomes at one year),[84] those with a poor ability to cope with pain, functional impairments, poor general health, or a significant psychiatric or psychological component to the pain (Waddell's signs).[84]

## Epidemiology [edit]

Low back pain that lasts at least one day and limits activity is a common complaint.[19] Globally, about 40% of people have LBP at some point in their lives,[19] with estimates as high as 80% of people in the developed world.[21] Approximately 9 to 12% of people (632 million) have LBP at any given point in time, and nearly one quarter (23.2%) report having it at some point over any one-month period.[19][20] Difficulty most often begins between 20 and 40 years of age.[5] Low back pain is more common among people aged 40–80 years, with the overall number of individuals affected expected to increase as the population ages.[19]

It is not clear whether men or women have higher rates of low back pain.[19][20] A 2012 review reported a rate of 9.6% among males and 8.7% among females.[20] Another 2012 review found a higher rate in females than males, which the reviewers felt was possibly due to greater rates of pains due to osteoporosis, menstruation, and pregnancy among women, or possibly because women were more willing to report pain than men.[19] An estimated 70% of women experience back pain during pregnancy with the rate being higher the further along in pregnancy.[85] Current smokers – and especially those who are adolescents – are more likely to have low back pain than former smokers, and former smokers are more likely to have low back pain than those who have never smoked.[86]

## History [edit]

Low back pain has been with humans since at least the Bronze Age. The oldest known surgical treatise – the Edwin Smith Papyrus, dating to about 1500 BCE – describes a diagnostic test and treatment for a vertebral sprain. Hippocrates (c. 460 BCE – c. 370 BCE) was the first to use a term for sciatic pain and low back pain; Galen (active mid to late second century CE) described the concept in some detail. Physicians through the end of the first millennium did not attempt back surgery and recommended watchful waiting. Through the Medieval period, folk medicine practitioners provided treatments for back pain based on the belief that it was caused by spirits.[87]

At the start of the 20th century, physicians thought low back pain was


Harvey Williams Cushing, 1920s

caused by inflammation of or damage to the nerves,[87] with neuralgia and neuritis frequently mentioned by them in the medical literature of the time.[88] The popularity of such proposed causes decreased during the 20th century.[88] In the early 20th century, American neurosurgeon Harvey Williams Cushing increased the acceptance of surgical treatments for low back pain.[11] In the 1920s and 1930s, new theories of the cause arose, with physicians proposing a combination of nervous system and psychological disorders such as nerve weakness (neurasthenia) and female hysteria.[87] Muscular rheumatism (now called fibromyalgia) was also cited with increasing frequency.[88]

Emerging technologies such as X-rays gave physicians new diagnostic tools, revealing the intervertebral disc as a source for back pain in some cases. In 1938, orthopedic surgeon Joseph S. Barr reported on cases of disc-related sciatica improved or cured with back surgery.[88] As a result of this work, in the 1940s, the vertebral disc model of low back pain took over,[87] dominating the literature through the 1980s, aiding further by the rise of new imaging technologies such as CT and MRI.[88] The discussion subsided as research showed disc problems to be a relatively uncommon cause of the pain. Since then, physicians have come to realize that it is unlikely that a specific cause for low back pain can be identified in many cases and question the need to find one at all as most of the time symptoms resolve within 6 to 12 weeks regardless of treatment.[87]

## Society and culture [edit]

Low back pain results in large economic costs. In the United States, it is the most common type of pain in adults, responsible for a large number of missed work days, and is the most common musculoskeletal complaint seen in the emergency department.[24] In 1998, it was estimated to be responsible for $90 billion in annual health care costs, with 5% of individuals incurring most (75%) of the costs.[24] Between 1990 and 2001 there was a more than twofold increase in spinal fusion surgeries in the US, despite the fact that there were no changes to the indications for surgery or new evidence of greater usefulness.[8] Further costs occur in the form of lost income and productivity, with low back pain responsible for 40% of all missed work days in the United States.[89] Low back pain causes disability in a larger percentage of the workforce in Canada, Great Britain, the Netherlands and Sweden than in the US or Germany.[89]

Workers who experience acute low back pain as a result of a work injury may be asked by their employers to have x-rays.[90] As in other cases, testing is not indicated unless red flags are present.[90] An employer's concern about legal liability is not a medical indication and should not be used to justify medical testing when it is not indicated.[90] There should be no legal reason for encouraging people to have tests which a health care provider determines are not indicated.[90]

## Research [edit]

Total disc replacement is an experimental option,[31] but no significant evidence supports its use over

lumbar fusion.[11] Researchers are investigating the possibility of growing new intervertebral structures through the use of injected human growth factors, implanted substances, cell therapy, and tissue engineering.[31]

## References [edit]


1. ^ a b c d e "Low Back Pain Fact Sheet". *National Institute of Neurological Disorders and Stroke*. November 3, 2015. Retrieved 5 March 2016.
2. ^ a b c d e f g Koes BW, van Tulder M, Lin CW, Macedo LG, McAuley J, Maher C (December 2010). "An updated overview of clinical guidelines for the management of non-specific low back pain in primary care.". *European Spine Journal*. **19** (12): 2075–94. doi:10.1007/s00586-010-1502-y. PMID 20602122.
3. ^ a b c d e f g h i j k l m n o p q r s t u v w Manusov EG (September 2012). "Evaluation and diagnosis of low back pain". *Prim. Care*. **39** (3): 471–9. doi:10.1016/j.pop.2012.06.003. PMID 22958556.
4. ^ a b c d e Menezes Costa Lda, C; Maher, CG; Hancock, MJ; McAuley, JH; Herbert, RD; Costa, LO (7 August 2012). "The prognosis of acute and persistent low-back pain: a meta-analysis.". *CMAJ : Canadian Medical Association*. **184** (11): E613–24. doi:10.1503/cmaj.111271. PMC 3414626. PMID 22586331.
5. ^ a b c d e f g h i j k l m n o p Casazza, BA (15 February 2012). "Diagnosis and treatment of acute low back pain". *American family physician*. **85** (4): 343–50. PMID 22335313.
6. ^ a b c d e "Use of imaging studies for low back pain: percentage of members with a primary diagnosis of low back pain who did not have an imaging study (plain x-ray, MRI, CT scan) within 28 days of the diagnosis". Agency for Healthcare Research and Quality. 2013. Retrieved 11 June 2013.
7. ^ a b Chou, R; Fu, R; Carrino, JA; Deyo, RA (7 February 2009). "Imaging strategies for low-back pain: systematic review and meta-analysis.". *Lancet*. **373** (9662): 463–72. doi:10.1016/S0140-6736(09)60172-0. PMID 19200918.
8. ^ a b c d Deyo, RA; Mirza, SK; Turner, JA; Martin, BI (2009). "Overtreating Chronic Back Pain: Time to Back Off?". *Journal of the American Board of Family Medicine : JABFM*. **22** (1): 62–8. doi:10.3122/jabfm.2009.01.080102. PMC 2729142. PMID 19124635.
9. ^ a b c d e Salzberg L (September 2012). "The physiology of low back pain". *Prim. Care*. **39** (3): 487–98. doi:10.1016/j.pop.2012.06.014. PMID 22958558.
10. ^ a b c d e f g h i j k l m n Miller SM (September 2012). "Low back pain: pharmacologic management". *Prim. Care*. **39** (3): 499–510. doi:10.1016/j.pop.2012.06.005. PMID 22958559.
48. ^ a b c Guild DG (September 2012). "Mechanical therapy for low back pain". *Prim. Care*. **39** (3): 511–6. doi:10.1016/j.pop.2012.06.006. PMID 22958560.
49. ^ a b Sahar T, Cohen MJ, Uval-Ne'eman V, et al. (April 2009). "Insoles for prevention and treatment of back pain: a systematic review within the framework of the Cochrane Collaboration Back Review Group". *Spine*. **34** (9): 924–33. doi:10.1097/BRS.0b013e31819f29be. PMID 19359999.
50. ^ Sprouse R (September 2012). "Treatment: current treatment recommendations for acute and chronic undifferentiated low back pain". *Prim. Care*. **39** (3): 481–6. doi:10.1016/j.pop.2012.06.004. PMID 22958557.
51. ^ Momsen AM, Rasmussen JO, Nielsen CV, Iversen MD, Lund H (November 2012). "Multidisciplinary team care in rehabilitation: an overview of reviews". *J Rehabil Med*. **44** (11): 901–12. doi:10.2340/16501977-1040. PMID 23026978.
52. ^ Hendrick P, Milosavljevic S, Hale L, et al. (March 2011). "The relationship between physical activity and low back pain outcomes: a systematic review of observational studies". *Eur Spine J*. **20** (3): 464–74. doi:10.1007/s00586-010-1616-2. PMC 3048226. PMID 21053026.
53. ^ Hendrick P, Te Wake AM, Tikkisetty AS, Wulff L, Yap C, Milosavljevic S (October 2010). "The effectiveness of walking as an intervention for low back pain: a systematic review". *Eur Spine J*. **19** (10): 1613–20. doi:10.1007/s00586-010-1412-z. PMC 2989236. PMID 20414688.
54. ^ French, SD.; Cameron, M.; Walker, BF.; Reggars, JW.; Esterman, AJ. (2006). "Superficial heat or cold for low back pain.". *Cochrane Database of Systematic Reviews* (1): CD004750. doi:10.1002/14651858.CD004750.pub2. PMID 16437495.
55. ^ a b van Middelkoop M, Rubinstein SM, Kuijpers T, Verhagen AP, Ostelo R, Koes BW, van Tulder MW (2011). "A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain". *Eur Spine J*. **20** (1): 19–39. doi:10.1007/s00586-010-1518-3. PMC 3036018. PMID 20640863.
56. ^ Seco J, Kovacs FM, Urrutia G (October 2011). "The efficacy, safety, effectiveness, and cost-effectiveness of ultrasound and shock wave therapies for low back pain: a systematic review". *Spine J*. **11** (10): 966–77. doi:10.1016/j.spinee.2011.02.002.

11. ^ a b c d e f g h i j k l m Manusov, EG (September 2012). "Surgical treatment of low back pain.". *Primary care*. **39** (3): 525–31. doi:10.1016/j.pop.2012.06.010. PMID 22958562.
12. ^ a b c d Chou R, Baisden J, Carragee EJ, Resnick DK, Shaffer WO, Loeser JD (May 2009). "Surgery for low back pain: a review of the evidence for an American Pain Society Clinical Practice Guideline". *Spine*. **34** (10): 1094–109. doi:10.1097/BRS.0b013e3181a105fc. PMID 19363455.
13. ^ a b Henschke N, Ostelo RW, van Tulder MW, et al. (2010). "Behavioural treatment for chronic low-back pain". *Cochrane Database of Systematic Reviews* (7): CD002014. doi:10.1002/14651858.CD002014.pub3. PMID 20614428.
14. ^ a b c d e f g h Marlowe D (September 2012). "Complementary and alternative medicine treatments for low back pain". *Prim. Care*. **39** (3): 533–46. doi:10.1016/j.pop.2012.06.008. PMID 22958563.
15. ^ a b Walker, BF; French, SD; Grant, W; Green, S (1 February 2011). "A Cochrane review of combined chiropractic interventions for low-back pain". *Spine*. **36** (3): 230–42. doi:10.1097/BRS.0b013e318202ac73. PMID 21248591.
16. ^ a b Dagenais, S; Gay, RE; Tricco, AC; Freeman, MD; Mayer, JM (2010). "NASS Contemporary Concepts in Spine Care: spinal manipulation therapy for acute low back pain". *The Spine Journal*. **10** (10): 918–40. doi:10.1016/j.spinee.2010.07.389. PMID 20869008.
17. ^ a b Rubinstein SM, van Middelkoop M, Assendelft WJ, de Boer MR, van Tulder MW (2011). Rubinstein SM, ed. "Spinal manipulative therapy for chronic low-back pain". *Cochrane Database of Systematic Reviews* (2): CD008112. doi:10.1002/14651858.CD008112.pub2. PMID 21328304.
18. ^ a b Rubinstein SM, Terwee CB, Assendelft WJ, de Boer MR, van Tulder MW (12 September 2012). "Spinal manipulative therapy for acute low-back pain.". *Cochrane Database of Systematic Reviews*. **9**: CD008880. doi:10.1002/14651858.CD008880.pub2. PMID 22972127.
19. ^ a b c d e f g h i Hoy D, Bain C, Williams G, et al. (June 2012). "A systematic review of the global prevalence of low back pain". *Arthritis Rheum*. **64** (6): 2028–37. doi:10.1002/art.34347. PMID 22231424.
20. ^ a b c d Vos, T (15 December 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010.". *Lancet*. **380** (9859): 2163–96. PMID 21482199.
57. ^ Ebadi, S.; Henschke, N.; Nakhostin Ansari, N.; Fallah, E.; van Tulder, MW. (2014). "Therapeutic ultrasound for chronic low-back pain.". *Cochrane Database Syst Rev*. **3**: CD009169. doi:10.1002/14651858.CD009169.pub2. PMID 24627326.
58. ^ Smith C, Grimmer-Somers K (2010). "The treatment effect of exercise programmes for chronic low back pain". *J Eval Clin Pract*. **16** (3): 484–91. doi:10.1111/j.1365-2753.2009.01174.x. PMID 20438611.
59. ^ van Middelkoop M, Rubinstein SM, Verhagen AP, Ostelo RW, Koes BW, van Tulder MW (2010). "Exercise therapy for chronic nonspecific low-back pain". *Best Pract Res Clin Rheumatol*. **24** (2): 193–204. doi:10.1016/j.berh.2010.01.002. PMID 20227641.
60. ^ Woodman, JP; Moore, NR (January 2012). "Evidence for the effectiveness of Alexander Technique lessons in medical and health-related conditions: a systematic review.". *International journal of clinical practice*. **66** (1): 98–112. doi:10.1111/j.1742-1241.2011.02817.x. PMID 22171910.
61. ^ Posadzki, P; Ernst, E (September 2011). "Yoga for low back pain: a systematic review of randomized clinical trials.". *Clinical rheumatology*. **30** (9): 1257–62. doi:10.1007/s10067-011-1764-8. PMID 21590293.
62. ^ Dubinsky, R. M.; Miyasaki, J. (2009). "Assessment: Efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology". *Neurology*. **74** (2): 173–6. doi:10.1212/WNL.0b013e3181c918fc. PMID 20042705.
63. ^ Nizard J, Raoul S, Nguyen JP, Lefaucheur JP (October 2012). "Invasive stimulation therapies for the treatment of refractory pain". *Discov Med*. **14** (77): 237–46. PMID 23114579.
64. ^ Saragiotto, BT; Machado, GC; et al. (June 2016). "Paracetamol for low back pain". *The Cochrane database of systematic reviews*. doi:10.1002/14651858.CD012230.
65. ^ Machado, GC; Maher, CG; Ferreira, PH; Pinheiro, MB; Lin, CW; Day, RO; McLachlan, AJ; Ferreira, ML (31 March 2015). "Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials.". *BMJ (Clinical research ed.)*. **350**: h1225. doi:10.1136/bmj.h1225. PMID 25828856.
66. ^ Enthoven, WT; Roelofs, PD; Deyo, RA; van Tulder, MW; Koes, BW (10 February 2016). "Non-steroidal anti-inflammatory drugs for chronic low back pain.". *The Cochrane database of systematic reviews*. **2**: CD012087. doi:10.1002/14651858.CD012087. PMID 26863524.
67. ^ Coxib and traditional NSAID Trialists' (CNT)

doi:10.1016/S0140-6736(12)61729-2 . PMID 23245607.

21. ^ a b Vinod Malhotra; Yao, Fun-Sun F.; Fontes, Manuel da Costa (2011). *Yao and Artusio's Anesthesiology: Problem-Oriented Patient Management*. Hagerstwon, MD: Lippincott Williams & Wilkins. pp. Chapter 49. ISBN 1-4511-0265-8.
22. ^ a b Stanton, TR; Latimer, J; Maher, CG; Hancock, MJ (April 2010). "How do we define the condition 'recurrent low back pain'? A systematic review.". *European Spine Journal*. **19** (4): 533–9. doi:10.1007/s00586-009-1214-3. PMID 19921522.
23. ^ Kelly GA, Blake C, Power CK, O'keeffe D, Fullen BM (February 2011). "The association between chronic low back pain and sleep: a systematic review". *Clin J Pain*. **27** (2): 169–81. doi:10.1097/AJP.0b013e3181f3bdd5. PMID 20842008.
24. ^ a b c d e f Borczuk, Pierre (July 2013). "An Evidence-Based Approach to the Evaluation and Treatment of Low Back Pin in the Emergency Department". *Emergency Medicine Practice*. **15** (7).
25. ^ a b "Low Back Pain Fact Sheet". *National Institute of Neurological Disorders and Stroke*. National Institute of Health. Retrieved 12 July 2013.
26. ^ "Fast Facts About Back Pain". *National Institute of Arthritis and Musculoskeletal and Skin Diseases*. National Institute of Health. September 2009. Retrieved 10 June 2013.
27. ^ "Low back pain – acute". U.S. Department of Health and Human Services – National Institutes of Health. Retrieved 1 April 2013.
28. ^ Majchrzycki M, Mrozikiewicz PM, Kocur P, et al. (November 2010). "[Low back pain in pregnant women]". *Ginekol. Pol.* (in Polish). **81** (11): 851–5. PMID 21365902.
29. ^ Floyd, R., & Thompson, Clem. (2008). Manual of structural kinesiology. New York, NY: McGraw-Hill Humanities/Social Sciences/Languages.
30. ^ a b c Freedman MD, Woodham MA, Woodham AW (March 2010). "The role of the lumbar multifidus in chronic low back pain: a review.". *PM&R*. **2** (2): 142–6. doi:10.1016/j.pmrj.2009.11.006. PMID 20193941.
31. ^ a b c d e f g Hughes SP, Freemont AJ, Hukins DW, McGregor AH, Roberts S (October 2012). "The pathogenesis of degeneration of the intervertebral disc and emerging therapies in the management of back pain" (PDF). *J Bone Joint Surg Br*. **94** (10): 1298–304. doi:10.1302/0301-620X.94B10.28986. PMID 23015552.
32. ^ Patel, NB (2010). "Chapter 3: Physiology of Pain". In Kopf A, Patel NB. *Guide to Pain Management in Low-Resource Settings*.
33. ^ a b c Cohen SP, Argoff CE, Carragee EJ (2008). "Management of low back pain". *BMJ*. **337**: a2718. Collaboration, Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, Bombardier C, Cannon C, Farkouh ME, FitzGerald GA, Goss P, Halls H, Hawk E, Hawkey C, Hennekens C, Hochberg M, Holland LE, Kearney PM, Laine L, Lanas A, Lance P, Laupacis A, Oates J, Patrono C, Schnitzer TJ, Solomon S, Tugwell P, Wilson K, Wittes J, Baigent C (Aug 31, 2013). "Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials.". *Lancet*. **382** (9894): 769–79. doi:10.1016/S0140-6736(13)60900-9. PMC 3778977. PMID 23726390.
68. ^ Chaparro, LE; Furlan, AD; Deshpande, A; Mailis-Gagnon, A; Atlas, S; Turk, DC (Apr 1, 2014). "Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review.". *Spine*. **39** (7): 556–63. doi:10.1097/BRS.0000000000000249. PMID 24480962.
69. ^ Abdel Shaheed, C; Maher, CG; Williams, KA; Day, R; McLachlan, AJ (1 July 2016). "Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-analysis.". *JAMA internal medicine*. **176** (7): 958–68. doi:10.1001/jamainternmed.2016.1251. PMID 27213267.
70. ^ Franklin, G. M. (29 September 2014). "Opioids for chronic noncancer pain: A position paper of the American Academy of Neurology". *Neurology*. **83** (14): 1277–1284. doi:10.1212/WNL.0000000000000839. PMID 25267983.
71. ^ de Leon-Casasola OA (March 2013). "Opioids for chronic pain: new evidence, new strategies, safe prescribing". *Am. J. Med*. **126** (3 Suppl 1): S3–11. doi:10.1016/j.amjmed.2012.11.011. PMID 23414718.
72. ^ Chou R, Loeser JD, Owens DK, Rosenquist RW, Atlas SJ, Baisden J, Carragee EJ, Grabois M, Murphy DR, Resnick DK, Stanos SP, Shaffer WO, Wall EM, American Pain Society Low Back Pain Guideline Panel (2009). "Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: An evidence-based clinical practice guideline from the American Pain Society". *Spine*. **34** (10): 1066–77. doi:10.1097/BRS.0b013e3181a1390d. PMID 19363457.
73. ^ Pinto, RZ; Maher, CG; Ferreira, ML; Hancock, M; Oliveira, VC; McLachlan, AJ; Koes, B; Ferreira, PH (18 December 2012). "Epidural corticosteroid injections in the management of sciatica: a systematic review and meta-analysis.". *Annals of Internal Medicine*. **157** (12): 865–77. doi:10.7326/0003-4819-157-12-201212180-00564. PMID 23362516.
74. ^ "Epidural Corticosteroid Injection: Drug Safety Communication - Risk of Rare But Serious Neurologic Problems". *FDA*. 2014-04-23. Retrieved 24 April

doi:10.1136/bmj.a2718. PMID 19103627.
34. ^ Davis PC, Wippold II FJ, Cornelius RS, et al. (2011). "American College of Radiology ACR Appropriateness Criteria – Low Back Pain" (PDF).
35. ^ North American Spine Society (February 2013), "Five Things Physicians and Patients Should Question", *Choosing Wisely: an initiative of the ABIM Foundation*, North American Spine Society, retrieved 25 March 2013, which cites
    - Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, Owens DK, Clinical Efficacy Assessment Subcommittee of the American College of Physicians, American College of Physicians, American Pain Society Low Back Pain Guidelines Panel (Oct 2, 2007). "Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society.". *Annals of Internal Medicine*. **147** (7): 478–91. doi:10.7326/0003-4819-147-7-200710020-00006. PMID 17909209.
    - Forseen, SE; Corey, AS (Oct 2012). "Clinical decision support and acute low back pain: evidence-based order sets.". *Journal of the American College of Radiology : JACR*. **9** (10): 704–712.e4. doi:10.1016/j.jacr.2012.02.014. PMID 23025864.
36. ^ Williams CM, Henschke N, Maher CG, et al. (2013). "Red flags to screen for vertebral fracture in patients presenting with low-back pain". *Cochrane Database of Systematic Reviews*. **1**: CD008643. doi:10.1002/14651858.CD008643.pub2. PMID 23440831.
37. ^ Henschke N, Maher CG, Ostelo RW, de Vet HC, Macaskill P, Irwig L (2013). "Red flags to screen for malignancy in patients with low-back pain". *Cochrane Database of Systematic Reviews*. **2**: CD008686. doi:10.1002/14651858.CD008686.pub2. PMID 23450586.
38. ^ *a b c* Downie A, Williams CM, Henschke N, Hancock MJ, Ostelo RW, de Vet HC, Macaskill P, Irwig L, van Tulder MW, Koes BW, Maher CG (11 December 2013). "Red flags to screen for malignancy and fracture in patients with low back pain: systematic review". *BMJ*. **347** (dec11 1): f7095–f7095. doi:10.1136/bmj.f7095. PMID 24335669.
39. ^ Manchikanti L, Glaser SE, Wolfer L, Derby R, Cohen SP (2009). "Systematic review of lumbar discography as a diagnostic test for chronic low back pain". *Pain Physician*. **12** (3): 541–59. PMID 19461822.
40. ^ *a b* American Academy of Family Physicians, "Ten Things Physicians and Patients Should Question", *Choosing Wisely: an initiative of the ABIM Foundation*, American Academy of Family Physicians, retrieved September 5, 2012
41. ^ *a b* American College of Physicians, "Five Things Physicians and Patients Should Question", 2014.
75. ^ Lee, CS; Hwang, CJ; Lee, DH; Kim, YT; Lee, HS (March 2011). "Fusion rates of instrumented lumbar spinal arthrodesis according to surgical approach: a systematic review of randomized trials.". *Clinics in orthopedic surgery*. **3** (1): 39–47. doi:10.4055/cios.2011.3.1.39. PMC 3042168. PMID 21369477.
76. ^ Dagenais, S; Mayer, J; Wooley, J; Haldeman, S (2008). "Evidence-informed management of chronic low back pain with medicine-assisted manipulation". *The Spine Journal*. **8** (1): 142–9. doi:10.1016/j.spinee.2007.09.010. PMID 18164462.
77. ^ *a b c* Furlan AD, Yazdi F, Tsertsvadze A, Gross A, Van Tulder M, Santaguida L, Gagnier J, Ammendolia C, Dryden T, Doucette S, Skidmore B, Daniel R, Ostermann T, Tsouros S (2012). "A systematic review and meta-analysis of efficacy, cost-effectiveness, and safety of selected complementary and alternative medicine for neck and low-back pain". *Evidence-Based Complementary and Alternative Medicine*. **2012**: 953139. doi:10.1155/2012/953139. PMID 22203884.
78. ^ Lin CW, Haas M, Maher CG, Machado LA, van Tulder MW (July 2011). "Cost-effectiveness of guideline-endorsed treatments for low back pain: a systematic review". *Eur Spine J*. **20** (7): 1024–38. doi:10.1007/s00586-010-1676-3. PMC 3176706. PMID 21229367.
79. ^ *a b* Furlan AD, Imamura M, Dryden T, Irvin E (2008). "Massage for low-back pain". *Cochrane Database of Systematic Reviews* (4): CD001929. doi:10.1002/14651858.CD001929.pub2. PMID 18843627.
80. ^ Gagnier, JJ; Oltean, H; van Tulder, MW; Berman, BM; Bombardier, C; Robbins, CB (January 2016). "Herbal Medicine for Low Back Pain: A Cochrane Review.". *Spine*. **41** (2): 116–33. doi:10.1097/brs.0000000000001310. PMID 26630428.
81. ^ Cramer H, Haller H, Lauche R, Dobos G (2012). "Mindfulness-based stress reduction for low back pain. A systematic review". *BMC Complement Altern Med*. **12**: 162. doi:10.1186/1472-6882-12-162. PMC 3520871. PMID 23009599.
82. ^ Urrútia G, Burton K, Morral A, Bonfill X, Zanoli G (March 2005). "Neuroreflexotherapy for nonspecific low back pain: a systematic review". *Spine*. **30** (6): E148–53. doi:10.1097/01.brs.0000155575.85223.14. PMID 15770167.
83. ^ Marlowe, D (September 2012). "Complementary and alternative medicine treatments for low back pain.". *Primary care*. **39** (3): 533–46. doi:10.1016/j.pop.2012.06.008. PMID 22958563.
84. ^ *a b* Chou, R; Shekelle, P (2010). "Will this patient develop persistent disabling low back pain?". *JAMA: The Journal of the American Medical Association*.

*Choosing Wisely: an initiative of the ABIM Foundation*, American College of Physicians, retrieved 5 September 2013
42. ^ Crownover BK, Bepko JL (April 2013). "Appropriate and safe use of diagnostic imaging". *Am Fam Physician*. **87** (7): 494–501. PMID 23547591.
43. ^ a b Chou R, Qaseem A, Owens DK, Shekelle P, Clinical Guidelines Committee of the American College of Physicians (1 February 2011). "Diagnostic imaging for low back pain: advice for high-value health care from the American College of Physicians". *Annals of Internal Medicine*. **154** (3): 181–9. doi:10.1059/0003-4819-154-3-201102010-00008. PMID 21282698.
44. ^ Flynn TW, Smith B, Chou R (November 2011). "Appropriate use of diagnostic imaging in low back pain: a reminder that unnecessary imaging may do as much harm as good". *J Orthop Sports Phys Ther*. **41** (11): 838–46. doi:10.2519/jospt.2011.3618. PMID 21642763.
45. ^ a b c Steffens, Daniel; Maher, Chris G.; Pereira, Leani S. M.; Stevens, Matthew L; Oliveira, Vinicius C.; Chapple, Meredith; Teixeira-Salmela, Luci F.; Hancock, Mark J. (11 January 2016). "Prevention of Low Back Pain". *JAMA Internal Medicine*. **176**: 199–208. doi:10.1001/jamainternmed.2015.7431. PMID 26752509.
46. ^ a b Choi BK, Verbeek JH, Tam WW, Jiang JY (2010). Choi, Brian KL, ed. "Exercises for prevention of recurrences of low-back pain". *Cochrane Database of Systematic Reviews* (1): CD006555. doi:10.1002/14651858.CD006555.pub2. PMID 20091596.
47. ^ Chou R, Qaseem A, Snow V, et al. (October 2007). "Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society". *Annals of Internal Medicine*. **147** (7): 478–91. doi:10.7326/0003-4819-147-7-200710020-00006. PMID 17909209.
**303** (13): 1295–302. doi:10.1001/jama.2010.344. PMID 20371789.
85. ^ Cunningham, F (2009). *Williams Obstetrics* (23 ed.). McGraw Hill Professional. p. 210. ISBN 9780071702850.
86. ^ Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E (January 2010). "The association between smoking and low back pain: a meta-analysis". *Am. J. Med.* **123** (1): 87.e7–35. doi:10.1016/j.amjmed.2009.05.028. PMID 20102998.
87. ^ a b c d e Maharty DC (September 2012). "The history of lower back pain: a look "back" through the centuries". *Prim. Care*. **39** (3): 463–70. doi:10.1016/j.pop.2012.06.002. PMID 22958555.
88. ^ a b c d e Lutz GK, Butzlaff M, Schultz-Venrath U (August 2003). "Looking back on back pain: trial and error of diagnoses in the 20th century". *Spine*. **28** (16): 1899–905. doi:10.1097/01.BRS.0000083365.41261.CF. PMID 12923482.
89. ^ a b Manchikanti L, Singh V, Datta S, Cohen SP, Hirsch JA, ASIPP (2009). "Comprehensive review of epidemiology, scope, and impact of spinal pain". *Pain Physician*. **12** (4): E35–70. PMID 19668291.
90. ^ a b c d American College of Occupational and Environmental Medicine (February 2014), "Five Things Physicians and Patients Should Question", *Choosing Wisely: an initiative of the ABIM Foundation*, American College of Occupational and Environmental Medicine, retrieved 24 February 2014, which cites
    - Talmage, J; Belcourt, R; Galper, J; et al. (2011). "Low back disorders". In Kurt T. Hegmann. *Occupational medicine practice guidelines : evaluation and management of common health problems and functional recovery in workers* (3rd ed.). Elk Grove Village, IL: American College of Occupational and Environmental Medicine. pp. 336, 373, 376–377. ISBN 978-0615452272.

## External links [edit]

- Back and spine at DMOZ

| v · t · e | Spinal disease (M40–M54, 720–724, 737) | |
|---|---|---|
| **Deforming** | **Spinal curvature** | Kyphosis · Lordosis · Scoliosis · |
| | **Other** | Scheuermann's disease · Torticollis · |
| **Spondylopathy** | **inflammatory** | Spondylitis (Ankylosing spondylitis · · Sacroiliitis · Discitis · Spondylodiscitis · Pott disease · |
| | **non inflammatory** | Spondylosis · Spondylolysis · Spondylolisthesis · Retrolisthesis · Spinal stenosis · Facet syndrome · |
| | Neck pain · Upper back pain · **Low back pain** (Coccydynia · Sciatica · · | |

| | |
|---|---|
| **Back pain** | Radiculopathy · |
| **Intervertebral disc disorder** | Schmorl's nodes · Degenerative disc disease · Spinal disc herniation · Facet joint arthrosis · |

| v · t · e · | **Pain and nociception** | |
|---|---|---|
| **By region/system** | **HEENT** | Headache · Neck · Odynophagia (swallowing) · Toothache · |
| | **Respiratory system** | Sore throat · Pleurodynia · |
| | **Musculoskeletal** | Arthralgia (joint) · Bone pain · Myalgia (muscle) · Muscle soreness: Acute / Delayed onset · |
| | **Neurologic** | Congenital insensitivity to pain · HSAN (Type I · II congenital sensory neuropathy · III familial dysautonomia · IV congenital insensitivity to pain with anhidrosis · V congenital insensitivity to pain with partial anhidrosis · · Neuralgia · Pain asymbolia · Pain disorder · Paroxysmal extreme pain disorder · Allodynia · Chronic pain · Hyperalgesia · Hypoalgesia · Hyperpathia · Phantom pain · Referred pain · |
| | **Other** | Pelvic pain · Proctalgia · Back · |
| **Tests** | | Cold pressor test · Dolorimeter · Grimace scale (animals) · Hot plate test · Tail flick test · |
| **Related concepts** | | Anterolateral system · Pain management (Anesthesia · Cordotomy · · Pain scale · Pain threshold · Pain tolerance · Posteromarginal nucleus · Substance P · Suffering · OPQRST · Philosophy of pain · Cancer pain · Drug-seeking behavior · |

| | |
|---|---|
| **Authority control** | NDL: 00574378 · |

Categories: Disability | Symptoms and signs: musculoskeletal system | Pain | Human back




# Osteoarthritis

From Wikipedia, the free encyclopedia

**Osteoarthritis** (**OA**) is a type of joint disease that results from breakdown of joint cartilage and underlying bone.[1] The most common symptoms are joint pain and stiffness. Initially, symptoms may occur only following exercise, but over time may become constant. Other symptoms may include joint swelling, decreased range of motion, and when the back is affected weakness or numbness of the arms and legs. The most commonly involved joints are those near the ends of the fingers, at the base of the thumb, neck, lower back, knee, and hips. Joints on one side of the body are often more affected than those on the other. Usually the symptoms come on over years. It can affect work and normal daily activities. Unlike other types of arthritis, only the joints are typically affected.[2]

Causes include previous joint injury, abnormal joint or limb development, and inherited factors. Risk is greater in those who are overweight, have one leg of a different length, and have jobs that result in high levels of joint stress.[2][3] Osteoarthritis is believed to be caused by mechanical stress on the joint and low grade inflammatory processes.[4] It develops as cartilage is lost and the underlying bone becomes affected.[2] As pain may make it difficult to exercise, muscle loss may occur.[3][5] Diagnosis is typically based on signs and symptoms, with medical imaging and other tests occasionally used to either support or rule out other problems. In contrast to rheumatoid arthritis, which is primarily an inflammatory condition, in osteoarthritis, the joints do not typically become hot or red.[2]

Treatment includes exercise, efforts to decrease joint stress, support groups, and pain medications.[2][6] Efforts to decrease joint stress include resting and the use of a cane. Weight loss may help in those who are overweight. Pain medications may include paracetamol (acetaminophen) as well as NSAIDs such as naproxen or ibuprofen.[2] Long-term opioid use is generally discouraged due to lack of information on benefits as well as risks of addiction and other side effects.[2][6] If pain interferes with normal life despite other treatments, joint replacement surgery may help.[3] An artificial joint typically lasts 10 to 15 years.[7]

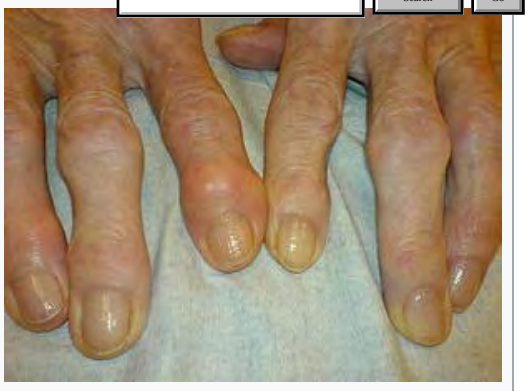
Osteoarthritis is the most common form of arthritis with disease of the knee and hip affecting about 3.8% of people as of 2010.[8][9] Among those over 60 years old, about 10% of males and 18% of females are affected.[3] It is the cause of about 2% of years lived with disability.[9] In Australia, about 1.9 million people are affected,[10] and in the United States, 30 to 52.5 million people are affected.[11][12] It becomes more common in both sexes as people become older.[2]

Contents



## Osteoarthritis

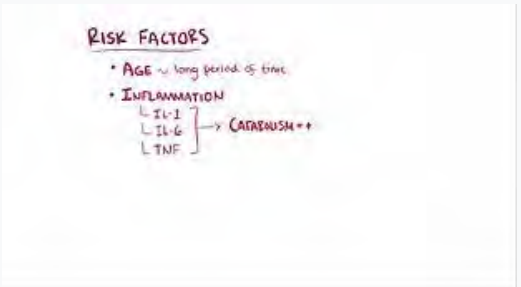
**Synonyms** degenerative arthritis, degenerative joint disease, osteoarthrosis



The formation of hard nobs at the middle finger joints (known as Bouchard's nodes) and at the farther away finger joint (known as Heberden's node) are a common feature of osteoarthritis in the hands.

| Classification and external resources | |
|---|---|
| **Specialty** | Rheumatology, orthopedics |
| **ICD-10** | M15-M19, M47 |
| **ICD-9-CM** | 715 |
| **OMIM** | 165720 |
| **DiseasesDB** | 9313 |
| **MedlinePlus** | 000423 |
| **eMedicine** | med/1682 orthoped/427 pmr/93 radio/492 |
| **Patient UK** | Osteoarthritis |
| **MeSH** | D010003 |

[edit on Wikidata]




Play media

Video explanation

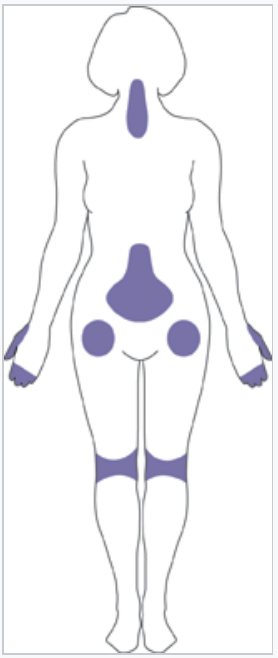
## Signs and symptoms [edit]

The main symptom is pain, causing loss of ability and often stiffness. "Pain" is generally described as a sharp ache or a burning sensation in the associated muscles and tendons, and is typically made worse by prolonged activity and relieved by rest. Stiffness is most common in the morning, and typically lasts less than thirty minutes after beginning daily activities, but may return after periods of inactivity. Osteoarthritis can cause a crackling noise (called "crepitus") when the affected joint is moved or touched and people may experience muscle spasms and contractions in the tendons. Occasionally, the joints may also be filled with fluid.[13] Some people report increased pain associated with cold temperature, high humidity, and/or a drop in barometric pressure, but studies have had mixed results.[14]

Osteoarthritis commonly affects the hands, feet, spine, and the large weight-bearing joints, such as the hips and knees, although in theory, any joint in the body can be affected. As osteoarthritis progresses, the affected joints appear larger, are stiff, painful and may swell, but usually feel better with gentle use but worse with excessive or prolonged use, thus distinguishing it from rheumatoid arthritis. [*citation needed*]

In smaller joints, such as at the fingers, hard bony enlargements, called Heberden's nodes (on the distal interphalangeal joints) and/or Bouchard's nodes (on the proximal interphalangeal joints), may form, and though they are not necessarily painful, they do limit the movement of the fingers significantly. Osteoarthritis at the toes leads to the formation of bunions, rendering them red or swollen. Some people notice these physical changes before they experience any pain, in part because the cartilage damage in osteoarthritis is generally painless because cartilage is aneural.[*citation needed*]

Osteoarthritis is the most common cause of a joint effusion of the knee.[15]



Osteoarthritis most often occurs in the hands (at the ends of the fingers and thumbs), neck, lower back, knees, and hips

## Risk factors [edit]

Damage from mechanical stress with insufficient self repair by joints is believed to be the primary cause of osteoarthritis.[16] Sources of this stress may include misalignments of bones caused by congenital or pathogenic causes; mechanical injury; excess body weight; loss of strength in the muscles supporting a joint; and impairment of peripheral nerves, leading to sudden or uncoordinated movements.[16] However exercise, including running in the absence of injury, has not been found to increase the risk.[17] Nor has cracking one's knuckles been found to play a role.[18]

### Primary [edit]

A number of studies have shown that there is a greater prevalence of the disease among siblings and especially identical twins, indicating a hereditary basis.[19] Although a single factor is not generally sufficient to cause the disease, about half of the variation in susceptibility has been assigned to genetic factors.[20]

As early human ancestors evolved into bipeds, changes occurred in the pelvis, hip joint and spine which increased the risk of osteoarthritis.[21] Additionally genetic variations that increase the risk were likely not selected against because usually problems only occur after reproductive success.[22]

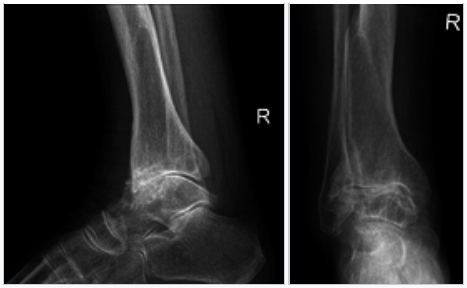
The development of osteoarthritis is correlated with a history of previous joint injury and with obesity, especially with respect to knees.[23] Since the correlation with obesity has been observed not only for knees but also for non-weight bearing joints and the loss of body fat is more closely related to symptom relief than the loss of body weight, it has been suggested that there may be a metabolic link to body fat as opposed to just mechanical loading.[24]

Changes in sex hormone levels may play a role in the development of osteoarthritis as it is more prevalent among post-menopausal women than among men of the same age.[25][26] A study of mice found natural female hormones to be protective while injections of the male hormone dihydrotestosterone reduced protection.[27]

### Secondary [edit]

This type of osteoarthritis is caused by other factors but the resulting pathology is the same as for primary osteoarthritis:

- Alkaptonuria
- Congenital disorders of joints




lateral front

Secondary osteoarthritis (due to an old injury with fracture) of the ankle in a woman of 82 years old

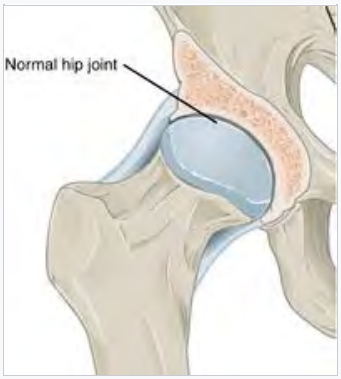
Diabetes doubles the risk of having a joint replacement due to osteoarthritis and people with diabetes have joint replacements at a younger age than those without diabetes.[28]
- Ehlers-Danlos Syndrome
- Hemochromatosis and Wilson's disease
- Inflammatory diseases (such as Perthes' disease), (Lyme disease), and all chronic forms of arthritis (e.g., costochondritis, gout, and rheumatoid arthritis). In gout, uric acid crystals cause the cartilage to degenerate at a faster pace.
- Injury to joints or ligaments (such as the ACL), as a result of an accident or orthopedic operations.
- Ligamentous deterioration or instability may be a factor.
- Marfan syndrome
- Obesity
- Joint infection

## Pathophysiology [edit]

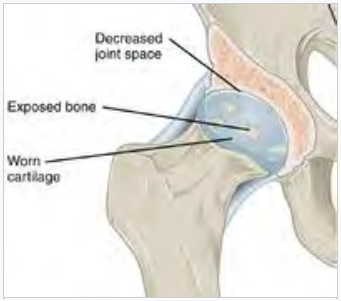
While osteoarthritis is a degenerative joint disease that may cause gross cartilage loss and morphological damage to other joint tissues, more subtle biochemical changes occur in the earliest stages of osteoarthritis progression. The water content of healthy cartilage is finely balanced by compressive force driving water out and hydrostatic and osmotic pressure drawing water in.[30][31] Collagen fibres exert the compressive force, whereas the Gibbs–Donnan effect and cartilage proteoglycans create osmotic pressure which tends to draw water in.[31]

However, during onset of osteoarthritis, the collagen matrix becomes more disorganized and there is a decrease in proteoglycan content within cartilage. The breakdown of collagen fibers results in a net increase in water content.[32][33][34][35][36] This increase occurs because whilst there is an overall loss of proteoglycans (and thus a decreased osmotic pull),[33][37] it is outweighed by a loss of collagen.[31][37] Without the protective effects of the proteoglycans, the collagen fibers of the cartilage can become susceptible to degradation and thus exacerbate the degeneration. Inflammation of the synovium (joint cavity lining) and the surrounding joint capsule can also occur, though often mild (compared to the synovial inflammation that occurs in rheumatoid arthritis). This can happen as breakdown products from the cartilage are released into the synovial space, and the cells lining the joint attempt to remove them.[*citation needed*]

Other structures within the joint can also be affected.[38] The ligaments within the joint become thickened and fibrotic and the menisci can become damaged and wear away.[39] Menisci can be completely absent by the time a person undergoes a joint replacement. New bone outgrowths, called "spurs" or osteophytes, can form on the margins of the joints, possibly in an attempt to improve the congruence of the articular cartilage surfaces in the absence of the menisci. The subchondral bone volume increases and becomes less mineralized (hypomineralization).[40] All these changes can cause problems functioning. The pain in an osteoarthritic joint has been related to thickened synovium[41] and subchondral bone lesions.[42]




*Normal hip joint*



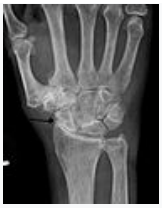

*Hip joint with osteoarthritis*[29]

## Diagnosis [edit]

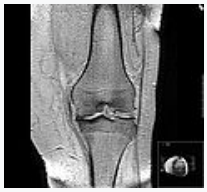
Diagnosis is made with reasonable certainty based on history and clinical examination.[43][44] X-rays may confirm the diagnosis. The typical changes seen on X-ray include: joint space narrowing, subchondral sclerosis (increased bone formation around the joint), subchondral cyst formation, and osteophytes.[45] Plain films may not correlate with the findings on physical examination or with the degree of pain.[46] Usually other imaging techniques are not necessary to clinically diagnose osteoarthritis.

In 1990, the American College of Rheumatology, using data from a multi-center study, developed a set of criteria for the diagnosis of hand osteoarthritis based on hard tissue enlargement and swelling of certain joints.[47] These criteria were found to be 92% sensitive and 98% specific for hand osteoarthritis versus other entities such as rheumatoid arthritis and spondyloarthropathies.[48]

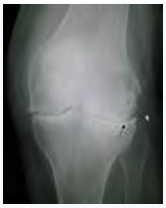
Related pathologies whose names may be confused with osteoarthritis include pseudo-arthrosis. This is derived from the Greek roots *pseudo-*, meaning "false", and *arthr-*, meaning "joint", together with the ending *-osis* used for disorders. Radiographic diagnosis results in diagnosis of a fracture within a joint, which is not to be confused with osteoarthritis which is a degenerative pathology affecting a high incidence of distal phalangeal joints of female patients. A polished ivory-like appearance may also develop on the bones of the affected joints, reflecting a change called eburnation.[49]



Severe osteoarthritis and osteopenia of the carpal joint and 1st carpometacarpel joint.

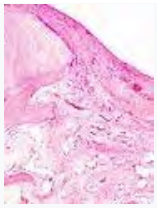


MRI of osteoarthritis in the knee, with characteristic narrowing of the joint space.

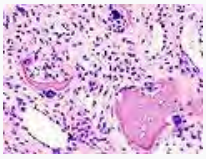


Primary osteoarthritis of the left knee. Note the osteophytes, narrowing of the joint space (arrow), and increased subchondral bone density (arrow).

Damaged cartilage from sows. (a) cartilage erosion (b)cartilage ulceration (c)cartilage repair (d)osteophyte (bone spur) formation.

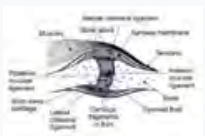


Histopathology of osteoarthrosis of a knee joint in an elderly female.

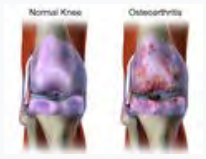


Histopathology of osteoarthrosis of a knee joint in an elderly female.

In a healthy joint, the ends of bones are encased in smooth cartilage. Together, they are protected by a joint capsule lined with a synovial membrane that produces synovial fluid. The capsule and fluid protect the cartilage, muscles, and connective tissues.



With osteoarthritis, the cartilage becomes worn away. Spurs grow out from the edge of the bone, and synovial fluid increases. Altogether, the joint feels stiff and sore.




Osteoarthritis

## Classification [edit]

*Further information: Radiographic classification of osteoarthritis*

A number of classification systems are used for gradation of osteoarthritis:

- WOMAC scale, taking into account pain, stiffness and functional limitation.[50]
- Kellgren-Lawrence grading scale for osteoarthritis of the knee. It uses only projectional radiography features.
- Tönnis classification for osteoarthritis of the hip joint, also using only projectional radiography features.[51]

Osteoarthritis can be classified into either primary or secondary depending on whether or not there is an identifiable underlying cause.

Both primary generalized nodal osteoarthritis and erosive osteoarthritis (EOA, also called inflammatory osteoarthritis) are sub-sets of primary osteoarthritis. EOA is a much less common, and more aggressive inflammatory form of osteoarthritis which often affects the distal interphalangeal joints of the hand and has characteristic articular erosive changes on x-ray.[52]

# Management [edit]

Lifestyle modification (such as weight loss and exercise) and analgesics are the mainstays of treatment. Acetaminophen (also known as paracetamol) is recommended first line with NSAIDs being used as add on therapy only if pain relief is not sufficient.[53] This is due to the relative greater safety of acetaminophen.[53]

## Lifestyle changes [edit]

For overweight people, weight loss may be an important factor.[54] Patient education has been shown to be helpful in the self-management of arthritis.[54] It decreases pain, improves


People with osteoarthritis should do different kinds of exercise for different benefits to the body.

function, reduces stiffness and fatigue, and reduces medical usage.[54] Patient education can provide on average 20% more pain relief when compared to NSAIDs alone in patients with hip osteoarthritis.[54]

## Physical measures [edit]

Moderate exercise is beneficial with respect to pain and function in those with osteoarthritis of the knee and hip.[55][56] These exercises should occur at least three times per week.[57] While some evidence supports certain physical therapies, evidence for a combined program is limited.[58] There is not enough evidence to determine the effectiveness of massage therapy.[59] The evidence for manual therapy is inconclusive.[60] Functional, gait, and balance training have been recommended to address impairments of position sense, balance, and strength in individuals with lower extremity arthritis as these can contribute to a higher rate of falls in older individuals.[61]

Lateral wedge insoles and neutral insoles do not appear to be useful in osteoarthritis of the knee.[62][63][64] Knee braces may help[65] but their usefulness has also been disputed.[64] For pain management heat can be used to relieve stiffness, and cold can relieve muscle spasms and pain.[66] Among people with hip and knee osteoarthritis, exercise in water may reduce pain and disability, and increase quality of life in the short term.[67]

## Medication [edit]

The pain medication acetaminophen is the first line treatment for osteoarthritis.[53][69] However, a 2015 review found acetaminophen to only have a small short term benefit.[70] For mild to moderate symptoms effectiveness is similar to non-steroidal anti-inflammatory drugs (NSAIDs), though for more severe symptoms NSAIDs may be more effective.[53] NSAIDs such as naproxen, while more effective in severe cases, are associated with greater side effects, such as gastrointestinal bleeding.[53] Diclofenac may be the most effective NSAID.[71]

| Treatment recommendations by risk factors | | |
|---|---|---|
| **GI risk** | **CVD risk** | **Option** |
| Low | Low | NSAID, or paracetamol[68] |
| Moderate | Low | Paracetamol, or low dose NSAID with antacid[68] |
| Low | Moderate | Paracetamol, or low dose aspirin with an antacid[68] |
| Moderate | Moderate | Low dose paracetamol, aspirin, and antacid. Monitoring for abdominal pain or black stool.[68] |

Another class of NSAIDs, COX-2 selective inhibitors (such as celecoxib) are equally effective when compared to nonselective NSAIDs, and have lower rates of adverse gastrointestinal effects, but higher rates of cardiovascular disease such as myocardial infarction.[72] They are also more expensive than non-specific NSAIDs.[73] Benefits and risks vary in individuals and need consideration when making treatment decisions.[74] NSAIDS applied topically are effective for a small number of people.[75]

Failure to achieve desired pain relief in osteoarthritis after 2 weeks should trigger reassessment of dosage and pain medication.[76] Opioids by mouth, including both weak opioids such as tramadol and stronger opioids, are also often prescribed. Their appropriateness is uncertain, and opioids are often recommended only when first line therapies have failed or are contraindicated.[77][78] This is due to their small benefit and relatively large risk of side effects.[79] Oral steroids are not recommended in the treatment of osteoarthritis.[69]

There are several NSAIDs available for topical use, including diclofenac. A Cochrane review from 2016 concluded that reasonably reliable evidence is available only for use of topical diclofenac and ketoprofen in people aged over 40 years with painful knee arthritis.[80] Transdermal opioid pain medications are not typically recommended in the treatment of osteoarthritis.[81] The use of topical capsaicin to treat osteoarthritis is controversial, as some reviews found benefit[82][83] while others did not.[84]

Joint injections of glucocorticoids (such as hydrocortisone) leads to short term pain relief that may last between a few weeks and a few months.[85] Injections of hyaluronic acid have not been found to lead to much improvement compared to placebo when the knee joint is affected[86][87] but have been associated with harm.[86] This may stand true for hip osteoarthritis. In ankle osteoarthritis, evidence is unclear.[88] The effectiveness of injections of platelet-rich plasma is unclear; there are suggestions that such injections improve function but not pain, and are associated with increased risk.[*vague*][89][90]

## Surgery [edit]

If the impact of symptoms of osteoarthritis on quality of life is significant and more conservative management is ineffective, joint replacement surgery or resurfacing may be recommended. Evidence supports joint replacement for both knees and hips as it is both clinically effective,[91][92] and cost-effective.[93][94] Surgery to transfer articular cartilage from a non-weight-bearing area to the damaged area is one possible procedure that has some success, but there are problems getting the transferred cartilage to integrate well with the existing cartilage at the transfer site.[95]

Osteotomy may be useful in people with knee osteoarthritis, but has not been well studied.[96] Arthroscopic surgery is largely not recommended, as it does not improve outcomes in knee osteoarthritis,[97][98] and may result in harm.[99]

## Alternative medicine [edit]

### Glucosamine and chondroitin [edit]

The effectiveness of glucosamine is controversial.[100] Reviews have found it to be equal to[101][102] or slightly better than placebo.[103][104] A difference may exist between glucosamine sulfate and glucosamine hydrochloride, with glucosamine sulfate showing a benefit and glucosamine hydrochloride not.[105] The evidence for glucosamine sulfate having an effect on osteoarthritis progression is somewhat unclear and if present likely modest.[106] The Osteoarthritis Research Society International recommends that glucosamine be discontinued if no effect is observed after six months[107] and the National Institute for Health and Care Excellence no longer recommends its use.[5] Despite the difficulty in determining the efficacy of glucosamine, it remains a viable treatment option.[108] Its use as a therapy for osteoarthritis is usually safe.[108][109]

A 2015 Cochrane review of clinical trials of chondroitin found that most were of low quality, but that there was some evidence of short-term improvement in pain and few side effects; it does not appear to improve or maintain the health of affected joints.[64] Glucosamine and chondroitin are generally manufactured from fish or animal products, respectively,[110][111] although there are some glucosamine products derived from fungi or plants.[112]

### Other remedies [edit]

Avocado/soybean unsaponifiables (ASU) is an extract made from avocado oil and soybean oil[113] that is sold under many brand names worldwide as a dietary supplement[114] and as a drug in France.[115] A 2014 Cochrane review found that while ASU might help relieve pain in the short term for some people with osteoarthritis, it does not appear to improve or maintain the health of affected joints; the review noted a high quality two year clinical trial comparing to ASU to chondroitin, which has uncertain efficacy in arthritis—the study found no difference between the two.[113] The review also found that while ASU appears to be safe, it has not been adequately studied to be sure.[113]

SKI 306X (trade name, Joins) is marketed as a botanical drug in Korea for osteoarthritis; it is a combination of standardized extracts of *Clematis mandshurica*, *Trichosanthes kirilowii*, and *Prunella vulgaris*, each of which has a history in traditional Korean medicine as well as in other asian cultures.[116] Joins has been marketed in Korea as a drug since since 2001 and has been marketed as a dietary supplement outside Korea; its approval and use has been controversial in Korea and other countries.[117]

Phytodolor is a brand name herbal remedy composed of extracts from European aspen leaf and bark, common ash bark, and goldenrod; clinical trials have been conducted by its manufacturer and have not provided sufficient evidence to determine if the remedy is safe or effective to treat osteoarthritis.[113]

Devil's claw,[118] Curcumin[119] and SAMe,[82][120] may be effective in improving pain. There is tentative evidence to support ashwagandha,[121] cat's claw,[122] hyaluronan,[123] MSM,[82] and rose hip.[82] A few high-quality studies of *Boswellia serrata* show consistent, but small, improvements in pain and function.[113]

There is little evidence supporting benefits for some supplements, including: the Ayurvedic herbal preparations with brand names Articulin F and Eazmov, collagen, Duhuo Jisheng Wan (a Chinese herbal preparation), fish liver oil, ginger, the herbal preparation gitadyl, omega-3 fatty acids, the brand-name product Reumalax, stinging nettle, vitamins A, C, and E in combination, vitamin E alone, vitamin K and willow bark. There is insufficient evidence to make a recommendation about the safety and efficacy of these treatments.[82][122]

### Acupuncture and other interventions [edit]

While acupuncture leads to improvements in pain relief, this improvement is small and may be of questionable importance. Waiting list-controlled trials for peripheral joint osteoarthritis do show clinically relevant benefits, but these may be due to placebo effects.[124] Acupuncture does not seem to produce long-term benefits.[125] While electrostimulation techniques such as TENS have been used for twenty years to treat osteoarthritis in the knee, there is no conclusive evidence to show that it reduces pain or disability.[126]

A Cochrane review of low level laser therapy found unclear evidence of benefit.[127] Another review found short term pain relief for osteoarthritic knees.[128]

## Epidemiology [edit]

Globally as of 2010, approximately 250 million people had osteoarthritis of the knee (3.6% of the population).[8][130] Hip osteoarthritis affects about 0.85% of the population.[8]

As of 2004, osteoarthritis globally causes moderate to severe disability in 43.4 million people.[131] Together, knee and hip osteoarthritis had a ranking for disability globally of 11th among 291 disease conditions assessed.[8]

Disability-adjusted life year for osteoarthritis per 100,000 inhabitants in 2004.[129]

| | |
|---|---|
| no data | 300–320 |
| ≤ 200 | 320–340 |
| 200–220 | 340–360 |
| 220–240 | 360–380 |
| 240–260 | 380–400 |
| 260–280 | ≥ 400 |
| 280–300 | |

### United States [edit]

As of 2012, osteoarthritis affected 52.5 million people in the United States, approximately 50% of whom were 65 years and older.[11] It is estimated that 80% of the population have radiographic evidence of osteoarthritis by age 65, although only 60% of those will have symptoms.[132] The rate of osteoarthritis in the United States is forecast to be 78 million (26%) adults by 2040.[11]

In the United States, there were approximately 964,000 hospitalizations for osteoarthritis in 2011, a rate of 31 stays per 10,000 population.[133] With an aggregate cost of $14.8 billion ($15,400 per stay), it was the second-most expensive condition seen in U.S. hospital stays in 2011. By payer, it was the second-most costly condition billed to Medicare and private insurance.[134][135]

## History [edit]

Evidence for osteoarthritis found in the fossil record is studied by paleopathologists, specialists in ancient disease and injury. Osteoarthritis has been reported in fossils of the large carnivorous dinosaur *Allosaurus fragilis*.[136]

### Etymology [edit]

Osteoarthritis is derived from the Greek word part *osteo-*, meaning "of the bone", combined with *arthritis*: *arthr-*, meaning "joint", and *-itis*, the meaning of which has come to be associated with inflammation.[137] The *-itis* of osteoarthritis could be considered misleading as inflammation is not a conspicuous feature. Some clinicians refer to this condition as *osteoarthrosis* to signify the lack of inflammatory response.[*citation needed*]

## Research [edit]

There are ongoing efforts to determine if there are agents that modify outcomes in osteoarthritis. Sprifermin is one candidate drug. There is also tentative evidence that strontium ranelate may decrease degeneration in osteoarthritis and improve outcomes.[138][139]

As well as attempting to find disease-modifying agents for osteoarthritis, there is emerging evidence that a system-based approach is necessary to find the causes of osteoarthritis.[140] Changes may occur before clinical disease is evident due to abnormalities in biomechanics, biology and/or structure of joints that predispose them to develop clinical disease. Research is thus focusing on defining these early pre-osteoarthritis changes using biological, mechanical, and imaging markers of osteoarthritis risk, emphasising multi-disciplinary approaches, and looking into personalized interventions that can reverse osteoarthritis risk in healthy joints before the disease becomes evident.

Gene transfer strategies aim to target the disease process rather than the symptoms.[141]

### Biomarkers [edit]

Guidelines outlining requirements for inclusion of soluble biomarkers in osteoarthritis clinical trials were published in 2015,[142] but as yet, there are no validated biomarkers for osteoarthritis. A 2015 systematic review of biomarkers for osteoarthritis looking for molecules that could be used for risk assessments found 37 different biochemical markers of bone and cartilage turnover in 25 publications.[143] The strongest evidence was for urinary C-terminal telopeptide of collagen type II (uCTX-II) as a prognostic marker for knee osteoarthritis progression and serum cartilage oligomeric protein (COMP) levels as a prognostic marker for incidence of both knee and hip osteoarthritis. A review of biomarkers in hip osteoarthritis also found associations with uCTXII.[144]

One problem with using a specific collagen type II biomarker from the breakdown of articular cartilage is that the amount of cartilage is reduced (worn away) over time with progression of the disease so a patient can eventually have very advanced osteoarthritis with none of this biomarker detectable in their urine. Another problem with a systemic biomarker is that a patient can have osteoarthritis in multiple joints at different stages of disease at the same time, so the biomarker source cannot be determined. Some other collagen breakdown products in the synovial fluid correlated with each other after acute injuries (a known cause of secondary osteoarthritis) but did not correlate with the severity of the injury.[145]

# References [edit]


1. ^ *Atlas of Osteoarthritis*. Springer. 2015. p. 21. ISBN 9781910315163.
2. ^ a b c d e f g h "Osteoarthritis". *National Institute of Arthritis and Musculoskeletal and Skin Diseases*. April 2015. Retrieved 13 May 2015.
3. ^ a b c d Glyn-Jones, S; Palmer, AJ; Agricola, R; Price, AJ; Vincent, TL; Weinans, H; Carr, AJ (3 March 2015). "Osteoarthritis.". *Lancet*. **386**: 376–87. doi:10.1016/S0140-6736(14)60802-3. PMID 25748615.
4. ^ Berenbaum F (2013). "Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!)". *Osteoarthritis and Cartilage*. **21** (1): 16–21. doi:10.1016/j.joca.2012.11.012. PMID 23194896.
5. ^ a b Conaghan P (2014). "Osteoarthritis — Care and management in adults" (PDF).
6. ^ a b McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H, Kwoh K, Lohmander S, Rannou F, Roos EM, Underwood M (2014). "OARSI guidelines for the non-surgical management of knee osteoarthritis". *Osteoarthr. Cartil.* **22** (3): 363–88. doi:10.1016/j.joca.2014.01.003. PMID 24462672.
7. ^ Di Puccio, F; Mattei, L (18 January 2015). "Biotribology of artificial hip joints.". *World journal of orthopedics*. **6** (1): 77–94. doi:10.5312/wjo.v6.i1.77. PMC 4303792. PMID 25621213.
8. ^ a b c d Cross, M; Smith, E; Hoy, D; Nolte, S; Ackerman, I; Fransen, M; Bridgett, L; Williams, S; Guillemin, F; Hill, C. L.; Laslett, L. L.; Jones, G; Cicuttini, F; Osborne, R; Vos, T; Buchbinder, R; Woolf, A; March, L (2014). "The global burden of hip and knee osteoarthritis: Estimates from the global burden of disease 2010 study". *Annals of the Rheumatic Diseases*. **73** (7): 1323–30. doi:10.1136/annrheumdis-2013-204763. PMID 24553908.
9. ^ a b March L (2014). "Burden of disability due to musculoskeletal (MSK) disorders". *Best Pract Res Clin Rheumatol*. **28** (3): 353–66. doi:10.1016/j.berh.2014.08.002. PMID 25481420.
10. ^ Elsternwick (2013). "A problem worth solving.". *Arthritis and Osteoporosis Victoria*.
11. ^ a b c "Arthritis-Related Statistics: Prevalence of Arthritis in the United States". Centers for Disease Control and Prevention, US Department of Health and Human Services. 9 November 2016.
12. ^ Cisternas MG, Murphy L, Sacks JJ, Solomon DH, Pasta DJ, Helmick CG (May 2016). "Alternative Methods for Defining Osteoarthritis and the Impact on Estimating Prevalence in a US Population-Based Survey". *Arthritis Care Res (Hoboken)*. **68** (5): 574–80. doi:10.1002/acr.22721.
13. ^ MedlinePlus Encyclopedia *Osteoarthritis*
14. ^ de Figueiredo EC, Figueiredo GC, Dantas RT (December 2011). "Influência de elementos meteorológicos na dor de pacientes com osteoartrite: Revisão da literatura" [Influence of meteorological elements on osteoarthritis pain: a review of the literature]. *Rev Bras Reumatol* (in Portuguese). **51** (6): 622–8. doi:10.1590/S0482-50042011000600008. PMID 22124595.
15. ^ "Water on the knee". MayoClinic.com.
16. ^ a b Brandt KD, Dieppe P, Radin E (January 2009). "Etiopathogenesis of osteoarthritis". *Med. Clin. North Am.* **93** (1): 1–24, xv. doi:10.1016/j.mcna.2008.08.009. PMID 19059018.
17. ^ Bosomworth NJ (September 2009). "Exercise and knee osteoarthritis: benefit or hazard?". *Can Fam Physician*. **55** (9): 871–8. PMC 2743580. PMID 19752252.
18. ^ Deweber K, Olszewski M, Ortolano R (2011). "Knuckle cracking and hand osteoarthritis". *J Am Board Fam Med*. **24** (2): 169–74. doi:10.3122/jabfm.2011.02.100156. PMID 21383216.
19. ^ Valdes AM, Spector TD (August 2008). "The contribution of genes to osteoarthritis". *Rheum. Dis. Clin. North Am.* **34** (3): 581–603. doi:10.1016/j.rdc.2008.04.008. PMID 18687274.
20. ^ Spector TD, MacGregor AJ (2004). "Risk factors for osteoarthritis: genetics". *Osteoarthr. Cartil.* 12 Suppl A: S39–44.
77. ^ McAlindon, TE; Bannuru, RR; Sullivan, MC; Arden, NK; Berenbaum, F; Bierma-Zeinstra, SM; Hawker, GA; Henrotin, Y; Hunter, DJ; Kawaguchi, H; Kwoh, K; Lohmander, S; Rannou, F; Roos, EM; Underwood, M (March 2014). "OARSI guidelines for the non-surgical management of knee osteoarthritis.". *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society*. **22** (3): 363–88. doi:10.1016/j.joca.2014.01.003. PMID 24462672.
78. ^ Hochberg, MC; Altman, RD; April, KT; Benkhalti, M; Guyatt, G; McGowan, J; Towheed, T; Welch, V; Wells, G; Tugwell, P; American College of, Rheumatology (April 2012). "American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee.". *Arthritis Care & Research*. **64** (4): 465–74. doi:10.1002/acr.21596. PMID 22563589.
79. ^ da Costa, BR; Nüesch, E; Kasteler, R; Husni, E; Welch, V; Rutjes, AW; Jüni, P (17 September 2014). "Oral or transdermal opioids for osteoarthritis of the knee or hip.". *The Cochrane database of systematic reviews*. **9**: CD003115. doi:10.1002/14651858.CD003115.pub4. PMID 25229835.
80. ^ Derry, Sheena; Conaghan, Philip; Da Silva, José António P; Wiffen, Philip J; Moore, R Andrew (22 April 2016). "Topical NSAIDs for chronic musculoskeletal pain in adults". *Cochrane Database of Systematic Reviews*. **4**: CD007400. doi:10.1002/14651858.cd007400.pub3. PMID 27103611. Retrieved 26 April 2016.
81. ^ da Costa BR, Nüesch E, Kasteler R, Husni E, Welch V, Rutjes AW, Jüni P (2014). "Oral or transdermal opioids for osteoarthritis of the knee or hip.". *The Cochrane database of systematic reviews*. **9**: CD003115. doi:10.1002/14651858.CD003115.pub4. PMID 25229835.
82. ^ a b c d e De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ (May 2011). "Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: a systematic review". *Rheumatology (Oxford)*. **50** (5): 911–20. doi:10.1093/rheumatology/keq379. PMID 21169345.
83. ^ Cameron M, Gagnier JJ, Little CV, Parsons TJ, Blümle A, Chrubasik S (November 2009). "Evidence of effectiveness of herbal medicinal products in the treatment of arthritis. Part I: Osteoarthritis". *Phytother Res*. **23** (11): 1497–515. doi:10.1002/ptr.3007. PMID 19856319.
84. ^ Altman R, Barkin RL (March 2009). "Topical therapy for osteoarthritis: clinical and pharmacologic perspectives". *Postgrad Med*. **121** (2): 139–47. doi:10.3810/pgm.2009.03.1986. PMID 19332972.
85. ^ Arroll B, Goodyear-Smith F (April 2004). "Corticosteroid injections for osteoarthritis of the knee: meta-analysis". *BMJ*. **328** (7444): 869. doi:10.1136/bmj.38039.573970.7C. PMC 387479. PMID 15039276.
86. ^ a b Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S (August 2012). "Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis". *Annals of Internal Medicine*. **157** (3): 180–91. doi:10.7326/0003-4819-157-3-201208070-00473. PMID 22868835.
87. ^ Jevsevar, D; Donnelly, P; Brown, GA; Cummins, DS (16 December 2015). "Viscosupplementation for Osteoarthritis of the Knee: A Systematic Review of the Evidence.". *The Journal of bone and joint surgery. American volume*. **97** (24): 2047–60. doi:10.2106/jbjs.n.00743. PMID 26677239.
88. ^ Witteveen, AG; Hofstad, CJ; Kerkhoffs, GM (17 October 2015). "Hyaluronic acid and other conservative treatment options for osteoarthritis of the ankle". *The Cochrane database of systematic reviews*. **10** (10): CD010643.

doi:10.1016/j.joca.2003.09.005. PMID 14698640.
21. ^ Hogervorst T, Bouma HW, de Vos J (August 2009). "Evolution of the hip and pelvis.". *Acta Orthopaedica Supplementum*. **80** (336): 1–39. doi:10.1080/17453690610046620. PMID 19919389.
22. ^ van der Kraan PM, van den Berg WB (April 2008). "Osteoarthritis in the context of ageing and evolution. Loss of chondrocyte differentiation block during ageing.". *Ageing Research Reviews*. **7** (2): 106–13. doi:10.1016/j.arr.2007.10.001. PMID 18054526.
23. ^ Coggon D, Reading I, Croft P, McLaren M, Barrett D, Cooper C (May 2001). "Knee osteoarthritis and obesity". *Int. J. Obes. Relat. Metab. Disord*. **25** (5): 622–7. doi:10.1038/sj.ijo.0801585. PMID 11360143.
24. ^ Pottie P, Presle N, Terlain B, Netter P, Mainard D, Berenbaum F (November 2006). "Obesity and osteoarthritis: more complex than predicted!". *Ann. Rheum. Dis*. **65** (11): 1403–5. doi:10.1136/ard.2006.061994. PMC 1798356. PMID 17038451.
25. ^ Linn S, Murtaugh B, Casey E (May 2012). "Role of sex hormones in the development of osteoarthritis". *PM&R*. **4** (5 Suppl): S169–73. doi:10.1016/j.pmrj.2012.01.013. PMID 22632696.
26. ^ Tanamas SK, Wijethilake P, Wluka AE, Davies-Tuck ML, Urquhart DM, Wang Y, Cicuttini FM (June 2011). "Sex hormones and structural changes in osteoarthritis: a systematic review". *Maturitas*. **69** (2): 141–56. doi:10.1016/j.maturitas.2011.03.019. PMID 21481553.
27. ^ Ma HL, Blanchet TJ, Peluso D, Hopkins B, Morris EA, Glasson SS (June 2007). "Osteoarthritis severity is sex dependent in a surgical mouse model". *Osteoarthr. Cartil*. **15** (6): 695–700. doi:10.1016/j.joca.2006.11.005. PMID 17207643.
28. ^ King KB, Rosenthal AK (2015). "The adverse effects of diabetes on osteoarthritis: update on clinical evidence and molecular mechanisms". *Osteoarthritis Cartilage*. **23** (6): 841–50. doi:10.1016/j.joca.2015.03.031. PMID 25837996.
29. ^ "OpenStax CNX". *cnx.org*. Retrieved 2015-10-14.
30. ^ Sanchez-Adams J, Leddy HA, McNulty AL, O'Conor CJ, Guilak F (2014). "The mechanobiology of articular cartilage: bearing the burden of osteoarthritis". *Curr Rheumatol Rep*. **16** (10): 451. doi:10.1007/s11926-014-0451-6. PMC 4682660. PMID 25182679.
31. ^ [a] [b] [c] Maroudas AI (April 1976). "Balance between swelling pressure and collagen tension in normal and degenerate cartilage". *Nature*. **260** (5554): 808–9. doi:10.1038/260808a0. PMID 1264261.
32. ^ Bollet AJ, Nance JL (July 1966). "Biochemical Findings in Normal and Osteoarthritic Articular Cartilage. II. Chondroitin Sulfate Concentration and Chain Length, Water, and Ash Content". *J. Clin. Invest*. **45** (7): 1170–7. doi:10.1172/JCI105423. PMC 292789. PMID 16695915.
33. ^ [a] [b] Brocklehurst R, Bayliss MT, Maroudas A, Coysh HL, Freeman MA, Revell PA, Ali SY (January 1984). "The composition of normal and osteoarthritic articular cartilage from human knee joints. With special reference to unicompartmental replacement and osteotomy of the knee". *J Bone Joint Surg Am*. **66** (1): 95–106. PMID 6690447.
34. ^ Chou MC, Tsai PH, Huang GS, Lee HS, Lee CH, Lin MH, Lin CY, Chung HW (April 2009). "Correlation between the MR T2 value at 4.7 T and relative water content in articular cartilage in experimental osteoarthritis induced by ACL transection". *Osteoarthr. Cartil*. **17** (4): 441–7. doi:10.1016/j.joca.2008.09.009. PMID 18990590.
35. ^ Grushko G, Schneiderman R, Maroudas A (1989). "Some biochemical and biophysical parameters for the study of the pathogenesis of osteoarthritis: a comparison between the processes of ageing and degeneration in human hip cartilage". *Connect. Tissue Res*. **19** (2–4): 149–76. doi:10.3109/03008208909043895. PMID 2805680.
36. ^ Mankin HJ, Thrasher AZ (January 1975). "Water content and binding in normal and osteoarthritic human cartilage". *J Bone Joint*
doi:10.1002/14651858.CD010643.pub2 . PMID 26475434 . "It is unclear if there is a benefit or harm for HA as treatment for ankle OA"
89. ^ Khoshbin A, Leroux T, Wasserstein D, Marks P, Theodoropoulos J, Ogilvie-Harris D, Gandhi R, Takhar K, Lum G, Chahal J (December 2013). "The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis". *Arthroscopy*. **29** (12): 2037–48. doi:10.1016/j.arthro.2013.09.006. PMID 24286802.
90. ^ Rodriguez-Merchan, EC (September 2013). "Intraarticular Injections of Platelet-rich Plasma (PRP) in the Management of Knee Osteoarthritis". *Archives of bone and joint surgery*. **1** (1): 5–8. PMC 4151401. PMID 25207275.
91. ^ Santaguida PL, Hawker GA, Hudak PL, Glazier R, Mahomed NN, Kreder HJ, Coyte PC, Wright JG (December 2008). "Patient characteristics affecting the prognosis of total hip and knee joint arthroplasty: a systematic review". *Can J Surg*. **51** (6): 428–36. PMC 2592576. PMID 19057730.
92. ^ Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, Beard DJ (April 2012). "Knee replacement". *Lancet*. **379** (9823): 1331–40. doi:10.1016/S0140-6736(11)60752-6. PMID 22398175.
93. ^ Jenkins PJ, Clement ND, Hamilton DF, Gaston P, Patton JT, Howie CR (2013). "Predicting the cost-effectiveness of total hip and knee replacement: A health economic analysis". *The bone & joint journal*. **95–B** (1): 115–21. doi:10.1302/0301-620X.95B1.29835. PMID 23307684.
94. ^ Daigle ME, Weinstein AM, Katz JN, Losina E (2012). "The cost-effectiveness of total joint arthroplasty: A systematic review of published literature". *Best practice & research. Clinical rheumatology*. **26** (5): 649–58. doi:10.1016/j.berh.2012.07.013. PMC 3879923. PMID 23218429.
95. ^ Hunziker EB, Lippuner K, Keel MJ, Shintani N (2015). "An educational review of cartilage repair: precepts & practice – myths & misconceptions – progress & prospects". *Osteoarthritis Cartilage*. **23** (3): 334–50. doi:10.1016/j.joca.2014.12.011. PMID 25534362.
96. ^ Brouwer, RW; Huizinga, MR; Duivenvoorden, T; van Raaij, TM; Verhagen, AP; Bierma-Zeinstra, SM; Verhaar, JA (13 December 2014). "Osteotomy for treating knee osteoarthritis". *The Cochrane database of systematic reviews*. **12** (12): CD004019. doi:10.1002/14651858.CD004019.pub4. PMID 25503775.
97. ^ Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM (2014). "A systematic review of recommendations and guidelines for the management of osteoarthritis: The Chronic Osteoarthritis Management Initiative of the U.S. Bone and Joint Initiative". *Seminars in arthritis and rheumatism*. **43** (6): 701–12. doi:10.1016/j.semarthrit.2013.11.012. PMID 24387819.
98. ^ Katz, JN; Brownlee, SA; Jones, MH (February 2014). "The role of arthroscopy in the management of knee osteoarthritis.". *Best practice & research. Clinical rheumatology*. **28** (1): 143–56. doi:10.1016/j.berh.2014.01.008. PMID 24792949.
99. ^ Thorlund, JB.; Juhl, CB.; Roos, EM.; Lohmander, LS. (2015). "Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms". *BMJ*. **350**: h2747. doi:10.1136/bmj.h2747. PMC 4469973. PMID 26080045.
100. ^ Burdett N, McNeil JD (Sep 2012). "Difficulties with assessing the benefit of glucosamine sulphate as a treatment for osteoarthritis.". *International Journal of Evidence-based Healthcare*. **10** (3): 222–6. doi:10.1111/j.1744-1609.2012.00279.x. PMID 22925619.
101. ^ Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S (Sep 16, 2010). "Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis.". *BMJ (Clinical research ed.)*. **341**: c4675. doi:10.1136/bmj.c4675. PMC 2941572. PMID 20847017.
102. ^ Wu D, Huang Y, Gu Y, Fan W (Jun 2013). "Efficacies of different preparations of glucosamine for the treatment of osteoarthritis: a meta-analysis of randomised, double-blind, placebo-controlled trials.". *International Journal of Clinical Practice*. **67** (6): 585–94. doi:10.1111/ijcp.12115. PMID 23679910.

*Surg Am*. **57** (1): 76–80. PMID 1123375.
37. ^ a b Venn M, Maroudas A (April 1977). "Chemical composition and swelling of normal and osteoarthrotic femoral head cartilage. I. Chemical composition". *Ann. Rheum. Dis.* **36** (2): 121–9. doi:10.1136/ard.36.2.121. PMC 1006646. PMID 856064.
38. ^ Madry H, Luyten FP, Facchini A (2012). "Biological aspects of early osteoarthritis". *Knee Surg. Sports Traumatol. Arthrosc.* **20** (3): 407–22. doi:10.1007/s00167-011-1705-8. PMID 22009557.
39. ^ Englund M, Roemer FW, Hayashi D, Crema MD, Guermazi A (2012). "Meniscus pathology, osteoarthritis and the treatment controversy". *Nat. Rev. Rheumatol.* **8** (7): 412–9. doi:10.1038/nrrheum.2012.69. PMID 22614907.
40. ^ Li G, Yin J, Gao J, Cheng TS, Pavlos NJ, Zhang C, Zheng MH (2013). "Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes". *Arthritis Research & Therapy*. **15** (6): 223. doi:10.1186/ar4405. PMID 24321104.
41. ^ Hill CL, Gale DG, Chaisson CE, Skinner K, Kazis L, Gale ME, Felson DT (2001). "Knee effusions, popliteal cysts, and synovial thickening: association with knee pain in osteoarthritis". *J. Rheumatol.* **28** (6): 1330–7. PMID 11409127.
42. ^ Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM, Kazis L, Gale DR (3 Apr 2001). "The association of bone marrow lesions with pain in knee osteoarthritis". *Ann Intern Med.* **134** (7): 541–9. doi:10.7326/0003-4819-134-7-200104030-00007. PMID 11281736.
43. ^ Zhang W, Doherty M, Peat G, Bierma-Zeinstra MA, Arden NK, Bresnihan B, Herrero-Beaumont G, Kirschner S, Leeb BF, Lohmander LS, Mazières B, Pavelka K, Punzi L, So AK, Tuncer T, Watt I, Bijlsma JW (March 2010). "EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis". *Ann. Rheum. Dis.* **69** (3): 483–9. doi:10.1136/ard.2009.113100. PMID 19762361.
44. ^ Bierma-Zeinstra SM, Oster JD, Bernsen RM, Verhaar JA, Ginai AZ, Bohnen AM (August 2002). "Joint space narrowing and relationship with symptoms and signs in adults consulting for hip pain in primary care". *J. Rheumatol.* **29** (8): 1713–8. PMID 12180735.
45. ^ *Osteoarthritis (OA): Joint Disorders* at Merck Manual of Diagnosis and Therapy Professional Edition
46. ^ Phillips CR, Brasington RD (2010). "Osteoarthritis treatment update: Are NSAIDs still in the picture?". *Journal of Musculoskeletal Medicine*. **27** (2).
47. ^ Kalunian KC (2013). "Patient information: Osteoarthritis symptoms and diagnosis (Beyond the Basics)". UpToDate. Retrieved 15 February 2013.
48. ^ Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, Brown C, Cooke TD, Daniel W, Gray R (November 1990). "The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand". *Arthritis Rheum.* **33** (11): 1601–10. doi:10.1002/art.1780331101. PMID 2242058.
49. ^ Vasan N, Tao L, Vikas B (2010). *First Aid for the USMLE Step 1, 2010 (First Aid USMLE)*. McGraw-Hill Medical. p. 378. ISBN 0-07-163340-5.
50. ^ Quintana, José M.; Escobar, Antonio; Arostegui, Inmaculada; Bilbao, Amaia; Azkarate, Jesús; Goenaga, J. Ignacio; Arenaza, Juan C. (23 January 2006). "Health-Related Quality of Life and Appropriateness of Knee or Hip Joint Replacement". *Archives of Internal Medicine*. **166** (2): 220–226. doi:10.1001/archinte.166.2.220.
51. ^ "Tönnis Classification of Osteoarthritis by Radiographic Changes". *Society of Preventive Hip Surgery*. Retrieved 2016-12-13.
52. ^ Punzi L, Ramonda R, Sfriso P (October 2004). "Erosive osteoarthritis". *Best Pract Res Clin Rheumatol.* **18** (5): 739–58. doi:10.1016/j.berh.2004.05.010. PMID 15454130.
53. ^ a b c d e Flood J (March 2010). "The role of acetaminophen in the treatment of osteoarthritis". *Am J Manag Care*. **16** (Suppl Management): S48–54. PMID 20297877.
54. ^ a b c d Cibulka MT, White DM, Woehrle J, Harris-Hayes M,
103. ^ Chou R, McDonagh MS, Nakamoto E, Griffin J (Oct 2011). "Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review". *PubMed Health, US National Library of Medicine*. PMID 22091473.
104. ^ Miller KL, Clegg DO (February 2011). "Glucosamine and chondroitin sulfate". *Rheumatic Diseases Clinics of North America*. **37** (1): 103–18. doi:10.1016/j.rdc.2010.11.007. PMID 21220090. "The best current evidence suggests that the effect of these supplements, alone or in combination, on OA pain, function, and radiographic change is marginal at best."
105. ^ Rovati LC, Girolami F, Persiani S (Jun 2012). "Crystalline glucosamine sulfate in the management of knee osteoarthritis: efficacy, safety, and pharmacokinetic properties.". *Therapeutic Advances in Musculoskeletal Disease*. **4** (3): 167–80. doi:10.1177/1759720X12437753. PMC 3400104. PMID 22850875.
106. ^ Gregory, PJ; Fellner, C (June 2014). "Dietary supplements as disease-modifying treatments in osteoarthritis: a critical appraisal.". *Pharmacy and Therapeutics*. **39** (6): 436–52. PMC 4103717. PMID 25050057.
107. ^ Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P (February 2008). "OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines" (PDF). *Osteoarthr. Cartil.* **16** (2): 137–62. doi:10.1016/j.joca.2007.12.013. PMID 18279766. Archived from the original (PDF) on July 21, 2011.
108. ^ a b Henrotin Y, Mobasheri A, Marty M (Jan 30, 2012). "Is there any scientific evidence for the use of glucosamine in the management of human osteoarthritis?". *Arthritis Research & Therapy*. **14** (1): 201. doi:10.1186/ar3657. PMC 3392795. PMID 22293240.
109. ^ Vangsness CT, Jr; Spiker, W; Erickson, J (January 2009). "A review of evidence-based medicine for glucosamine and chondroitin sulfate use in knee osteoarthritis.". *Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association*. **25** (1): 86–94. PMID 19111223.
110. ^ Barnhill JG, Fye CL, Williams DW, Reda DJ, Harris CL, Clegg DO (2006). "Chondroitin product selection for the glucosamine/chondroitin arthritis intervention trial". *J Am Pharm Assoc (Wash DC)*. **46** (1): 14–24. doi:10.1331/154434506775268616. PMID 16529337.
111. ^ Murray, Michael T. (2012). "Chapter 94: Glucosamine". In Pizzorno, Jr.,, Joseph E.; Murray, Michael T. *Textbook of natural medicine* (4th ed.). Edinburgh: Churchill Livingstone. p. 790. ISBN 9781437723335.
112. ^ "Another vegetarian glucosamine launched in US". January 25, 2008work=NutraIngredients-USA.com. Archived from the original on April 17, 2009. Check date values in: |date= (help)
113. ^ a b c d e Cameron, M; Chrubasik, S (22 May 2014). "Oral herbal therapies for treating osteoarthritis.". *The Cochrane database of systematic reviews* (5): CD002947. PMC 4494689. PMID 24848732.
114. ^ Christiansen, BA; Bhatti, S; Goudarzi, R; Emami, S (January 2015). "Management of Osteoarthritis with Avocado/Soybean Unsaponifiables.". *Cartilage*. **6** (1): 30–44. PMC 4303902. PMID 25621100.
115. ^ "Piascledine" (PDF). Haute Autorité de santé. July 25, 2013. See [Piascledine HAS index page for Piascledine]
116. ^ We, SR; Jeong, EO; Koog, YH; Min, BI (2012). "Effects of nutraceuticals on knee osteoarthritis: Systematic review". *African Journal of Biotechnology*. **11** (12).
117. ^ Ma, E (April 2015). "Join or be excluded from biomedicine? JOINS and Post-colonial Korea.". *Anthropology & medicine*. **22** (1): 64–74. doi:10.1080/13648470.2015.1004774. PMID 25641583.
118. ^ Sanders, M; Grundmann, O (September 2011). "The use of

Enseki K, Fagerson TL, Slover J, Godges JJ (April 2009). "Hip pain and mobility deficits—hip osteoarthritis: clinical practice guidelines linked to the international classification of functioning, disability, and health from the orthopaedic section of the American Physical Therapy Association". *J Orthop Sports Phys Ther*. **39** (4): A1–25. doi:10.2519/jospt.2009.0301. PMID 19352008.

55. ^ Hagen KB, Dagfinrud H, Moe RH, Østerås N, Kjeken I, Grotle M, Smedslund G (2012). "Exercise therapy for bone and muscle health: an overview of systematic reviews". *BMC Med*. **10**: 167. doi:10.1186/1741-7015-10-167. PMC 3568719. PMID 23253613.
56. ^ Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S (2014). "Exercise for osteoarthritis of the hip.". *Cochrane Database Syst Rev*. **4** (4): CD007912. doi:10.1002/14651858.CD007912.pub2. PMID 24756895.
57. ^ Juhl C, Christensen R, Roos EM, Zhang W, Lund H (Mar 2014). "Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials.". *Arthritis & Rheumatology*. **66** (3): 622–36. doi:10.1002/art.38290. PMID 24574223.
58. ^ Wang SY, Olson-Kellogg B, Shamliyan TA, Choi JY, Ramakrishnan R, Kane RL (November 2012). "Physical therapy interventions for knee pain secondary to osteoarthritis: a systematic review". *Annals of Internal Medicine*. **157** (9): 632–44. doi:10.7326/0003-4819-157-9-201211060-00007. PMID 23128863.
59. ^ De Luigi AJ (May 2012). "Complementary and alternative medicine in osteoarthritis". *PM&R*. **4** (5 Suppl): S122–33. doi:10.1016/j.pmrj.2012.01.012. PMID 22632691.
60. ^ French HP, Brennan A, White B, Cusack T (2011). "Manual therapy for osteoarthritis of the hip or knee — a systematic review". *Man Ther*. **16** (2): 109–117. doi:10.1016/j.math.2010.10.011. PMID 21146444.
61. ^ Sturnieks DL, Tiedemann A, Chapman K, Munro B, Murray SM, Lord SR (November 2004). "Physiological risk factors for falls in older people with lower limb arthritis". *J. Rheumatol*. **31** (11): 2272–9. PMID 15517643.
62. ^ Penny P, Geere J, Smith TO (October 2013). "A systematic review investigating the efficacy of laterally wedged insoles for medial knee osteoarthritis". *Rheumatol. Int*. **33** (10): 2529–38. doi:10.1007/s00296-013-2760-x. PMID 23612781.
63. ^ Parkes MJ, Maricar N, Lunt M, LaValley MP, Jones RK, Segal NA, Takahashi-Narita K, Felson DT (August 2013). "Lateral wedge insoles as a conservative treatment for pain in patients with medial knee osteoarthritis: a meta-analysis". *JAMA*. **310** (7): 722–30. doi:10.1001/jama.2013.243229. PMID 23989797.
64. ^ *a b c* Duivenvoorden, T; Brouwer, RW; van Raaij, TM; Verhagen, AP; Verhaar, JA; Bierma-Zeinstra, SM (16 March 2015). "Braces and orthoses for treating osteoarthritis of the knee.". *The Cochrane database of systematic reviews*. **3**: CD004020. doi:10.1002/14651858.CD004020.pub3. PMID 25773267.

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65. ^ Page CJ, Hinman RS, Bennell KL (2011). "Physiotherapy management of knee osteoarthritis". *Int J Rheum Dis*. **14** (2): 145–152. doi:10.1111/j.1756-185X.2011.01612.x. PMID 21518313.
66. ^ "Osteoarthritis Lifestyle and home remedies". *Diseases and Conditions*. Mayo Clinic.
67. ^ Bartels, EM; Juhl, CB; Christensen, R; Hagen, KB; Danneskiold-Samsøe, B; Dagfinrud, H; Lund, H (23 March 2016). "Aquatic exercise for the treatment of knee and hip osteoarthritis.". *The Cochrane database of systematic reviews*. **3**: CD005523. doi:10.1002/14651858.CD005523.pub3. PMID 27007113. Retrieved 5 April 2016.
68. ^ *a b c d* Consumer Reports Health Best Buy Drugs (July 2013), "The Nonsteroidal Anti-Inflammatory Drugs: Treating Osteoarthritis and Pain. Comparing effectiveness, safety, and price." (PDF), *NSAIDs*, Yonkers, New York: Consumer Reports, retrieved 12 February 2014
glucosamine, devil's claw (Harpagophytum procumbens), and acupuncture as complementary and alternative treatments for osteoarthritis.". *Alternative medicine review : a journal of clinical therapeutic*. **16** (3): 228–38. PMID 21951024.
119. ^ Grover, AK; Samson, SE (5 January 2016). "Benefits of antioxidant supplements for knee osteoarthritis: rationale and reality.". *Nutrition journal*. **15**: 1. PMID 26728196.
120. ^ Lopez HL (May 2012). "Nutritional interventions to prevent and treat osteoarthritis. Part II: focus on micronutrients and supportive nutraceuticals". *Physical Medicine and Rehabilitation*. **4** (5 Suppl): S155–68. doi:10.1016/j.pmrj.2012.02.023. PMID 22632695.
121. ^ Mishra, LC; Singh, BB; Dagenais, S (August 2000). "Scientific basis for the therapeutic use of Withania somnifera (ashwagandha): a review." (PDF). *Alternative Medicine Review*. **5** (4): 334–46. PMID 10956379.
122. ^ *a b* Rosenbaum CC, O'Mathúna DP, Chavez M, Shields K (2010). "Antioxidants and antiinflammatory dietary supplements for osteoarthritis and rheumatoid arthritis". *Altern Ther Health Med*. **16** (2): 32–40. PMID 20232616.
123. ^ Oe, M; Tashiro, T; Yoshida, H; Nishiyama, H; Masuda, Y; Maruyama, K; Koikeda, T; Maruya, R; Fukui, N (27 January 2016). "Oral hyaluronan relieves knee pain: a review.". *Nutrition journal*. **15**: 11. PMID 26818459.
124. ^ Manheimer E, Cheng K, Linde K, Lao L, Yoo J, Wieland S, van der Windt DA, Berman BM, Bouter LM (2010). Manheimer, Eric, ed. "Acupuncture for peripheral joint osteoarthritis". *Cochrane Database of Systematic Reviews* (1): CD001977. doi:10.1002/14651858.CD001977.pub2. PMC 3169099. PMID 20091527.
125. ^ Wang SM, Kain ZN, White PF (February 2008). "Acupuncture analgesia: II. Clinical considerations" (PDF). *Anesthesia and Analgesia*. **106** (2): 611–21, table of contents. doi:10.1213/ane.0b013e318160644d. PMID 18227323.
126. ^ Rutjes AW, Nüesch E, Sterchi R, Kalichman L, Hendriks E, Osiri M, Brosseau L, Reichenbach S, Jüni P (2009). Rutjes, Anne WS, ed. "Transcutaneous electrostimulation for osteoarthritis of the knee". *Cochrane Database of Systematic Reviews* (4): CD002823. doi:10.1002/14651858.CD002823.pub2. PMID 19821296.
127. ^ Brosseau, L; Welch, V; Wells, G; DeBie, R; Gam, A; Harman, K; Morin, M; Shea, B; Tugwell, P (2004). "Low level laser therapy (Classes I, II and III) for treating osteoarthritis.". *Cochrane Database of Systematic Reviews* (3): CD002046. doi:10.1002/14651858.CD002046.pub2. PMID 15266461.
128. ^ Bjordal, J; Johnson, M; Lopes-Martins, R; Bogen, B; Chow, R; Ljunggren, A (2007). "Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials.". *BMC Musculoskeletal Disorders*. **8** (1): 51. doi:10.1186/1471-2474-8-51.
129. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved Nov 11, 2009.
130. ^ Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. (December 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2163–96. doi:10.1016/S0140-6736(12)61729-2. PMID 23245607.
131. ^ "Table 9: Estimated prevalence of moderate and severe disability (millions) for leading disabling conditions by age, for high-income and low- and middle-income countries, 2004". *The Global Burden of Disease: 2004 Update*. Geneva: World Health Organization. 2008. p. 35. ISBN 978-92-4-156371-0.
132. ^ Green GA (2001). "Understanding NSAIDs: from aspirin to COX-2". *Clin Cornerstone*. **3** (5): 50–60. doi:10.1016/S1098-3597(01)90069-9. PMID 11464731.
133. ^ Pfuntner A., Wier L.M., Stocks C. Most Frequent Conditions in U.S. Hospitals, 2011. HCUP Statistical Brief #162. September 2013. Agency for Healthcare Research and Quality, Rockville, Maryland.[1]
134. ^ Torio CM, Andrews RM (August 2013). "National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2011.". *HCUP Statistical Brief #160*. Rockville, Maryland: Agency for

69. ^ a b Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P (September 2007). "OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence". *Osteoarthr. Cartil.* **15** (9): 981–1000. doi:10.1016/j.joca.2007.06.014. PMID 17719803.
70. ^ Machado, GC; Maher, CG; Ferreira, PH; Pinheiro, MB; Lin, CW; Day, RO; McLachlan, AJ; Ferreira, ML (31 March 2015). "Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials.". *BMJ (Clinical research ed.)*. **350**: h1225. doi:10.1136/bmj.h1225. PMID 25828856.
71. ^ da Costa, BR; Reichenbach, S; Keller, N; Nartey, L; Wandel, S; Jüni, P; Trelle, S (21 May 2016). "Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis.". *Lancet (London, England)*. **387** (10033): 2093–105. doi:10.1016/s0140-6736(16)30002-2. PMID 26997557.
72. ^ Chen YF, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, Taylor RS (April 2008). "Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation". *Health Technol Assess.* **12** (11): 1–278, iii. doi:10.3310/hta12110. PMID 18405470.
73. ^ Wielage, RC; Myers, JA; Klein, RW; Happich, M (December 2013). "Cost-effectiveness analyses of osteoarthritis oral therapies: a systematic review.". *Applied Health Economics and Health Policy*. **11** (6): 593–618. doi:10.1007/s40258-013-0061-x. PMID 24214160.
74. ^ van Walsem, Anneloes; Pandhi, Shaloo; Nixon, Richard M.; Guyot, Patricia; Karabis, Andreas; Moore, R. Andrew (2015-01-01). "Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis". *Arthritis Research & Therapy*. **17**: 66. doi:10.1186/s13075-015-0554-0. ISSN 1478-6354. PMC 4411793. PMID 25879879.
75. ^ Derry, S; Conaghan, P; Da Silva, JA; Wiffen, PJ; Moore, RA (22 April 2016). "Topical NSAIDs for chronic musculoskeletal pain in adults.". *The Cochrane database of systematic reviews*. **4**: CD007400. doi:10.1002/14651858.CD007400.pub3. PMID 27103611.
76. ^ Karabis, Andreas; Nikolakopoulos, Stavros; Pandhi, Shaloo; Papadimitropoulou, Katerina; Nixon, Richard; Chaves, Ricardo L.; Moore, R. Andrew (2016-01-01). "High correlation of VAS pain scores after 2 and 6 weeks of treatment with VAS pain scores at Healthcare Research and Quality.
135. ^ Pfuntner, A; Wier, L. M.; Steiner, C (December 2013). "Costs for Hospital Stays in the United States, 2011: Statistical Brief #168". PMID 24455786.
136. ^ Molnar, R. E. (2001). "Therapod Paleopathology: A Literature Survey". In Tanke, Darren H.; Carpenter, Kenneth; Skrepnick, Michael William. *Mesozoic Vertebrate Life*. Indiana University Press. pp. 337–63. ISBN 978-0-253-33907-2.
137. ^ Devaraj TL (2011). "Chapter 41: Nature cure yoga for osteoarthritis". *Nature Cure for Common Diseases*. New Delhi: Arya Publication. p. 368. ISBN 978-8189093747.
138. ^ Civjan N (2012). *Chemical Biology: Approaches to Drug Discovery and Development to Targeting Disease*. John Wiley & Sons. p. 313. ISBN 9781118437674.
139. ^ Bruyère O, Burlet N, Delmas PD, Rizzoli R, Cooper C, Reginster JY (2008). "Evaluation of symptomatic slow-acting drugs in osteoarthritis using the GRADE system". *BMC Musculoskelet Disord*. **9**: 165. doi:10.1186/1471-2474-9-165. PMC 2627841. PMID 19087296.
140. ^ Chu, CR; Andriacchi, TP (2015). "Dance between biology, mechanics, and structure: a systems-based approach to developing osteoarthritis prevention strategies". *J Orthop Res*. **33** (7): 939–947. doi:10.1002/jor.22817. PMID 25639920.
141. ^ T. Pap; J. Schedel; G. Pap; U. Moller-Ladner; R.E. Gay; S. Gay C. Guincamp (2000). "Gene therapy in osteoarthritis". *Joint Bone Spine*. **67** (6): 570–571. doi:10.1016/s1297-319x(00)00215-3. PMID 11195326.
142. ^ Kraus, VB; Blanco, FJ; Englund, M; Henrotin, Y; Lohmander, LS; Losina, E; Onnerfjord, P; Persiani, S (2015). "OARSI Clinical Trials Recommendations: Soluble biomarker assessments in clinical trials in osteoarthritis". *Osteoarthritis Cartilage*. **23** (5): 686–697. doi:10.1016/j.joca.2015.03.002. PMC 4430113. PMID 25952342.
143. ^ Saberi Hosnijeh, F; Runhaar, J; van Meurs, JB; Bierma-Zeinstra, SM (2015). "Biomarkers for osteoarthritis: Can they be used for risk assessment? A systematic review". *Maturitas*. **82** (1): 36–49. doi:10.1016/j.maturitas.2015.04.004. PMID 25963100.
144. ^ Nepple, JJ; Thomason, KM; An, TW; Harris-Hayes, M; Clohisy, JC (2015). "What is the utility of biomarkers for assessing the pathophysiology of hip osteoarthritis? A systematic review". *Clin Orthop Relat Res*. **473** (5): 1683–1701. doi:10.1007/s11999-015-4148-6. PMID 25623593.
145. ^ Kumahashi, N; Swärd, P; Larsson, S; Lohmander, LS; Frobell, R; Struglics, A (2015). "Type II collagen C2C epitope in human synovial fluid and serum after knee injury - associations with molecular and structural markers of injury". *Osteoarthritis Cartilage*. **23** (9): 1506–12. doi:10.1016/j.joca.2015.04.022. PMID 25937025.


## External links [edit]

- American College of Rheumatology Factsheet on OA
- Arthritis Foundation
- National Institute of Arthritis and Musculoskeletal and Skin Diseases

Wikimedia Commons has media related to *Osteoarthritis*.

| v · t · e · | **Diseases of joints (M00–M19, 711–719)** | | |
|---|---|---|---|
| **Arthritis (one joint / multiple)** | **Inflammation** | **Infectious** | Septic arthritis · Tuberculosis arthritis · Reactive arthritis (indirectly) · |
| | | **Noninfectious** | 1. Seronegative spondyloarthropathy: (Reactive arthritis*Psoriatic arthritis*Juvenile idiopathic arthritis*Ankylosing spondylitis · · 2. *Rheumatoid arthritis:* · Adult-onset Still's disease · Felty's syndrome · 3. *Crystal arthropathy:* Gout · Chondrocalcinosis · |
| | **Noninflammatory** | | *Osteoarthritis:* Heberden's node · Bouchard's nodes · |
| **Other** | Bleeding · pain · Osteophyte · *villonodular synovitis* (Pigmented villonodular synovitis · · stiffness · | | |

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Categories: Arthritis | Skeletal disorders

# Osteoporosis

From Wikipedia, the free encyclopedia

**Osteoporosis** is a disease where decreased bone strength increases the risk of a broken bone. It is the most common reason for a broken bone among the elderly.[3] Bones that commonly break include the back bones, the bones of the forearm, and the hip.[4] Until a broken bone occurs there are typically no symptoms. Bones may weaken to such a degree that a break may occur with minor stress or spontaneously. Chronic pain and a decreased ability to carry out normal activities may occur following a broken bone.[3]

Osteoporosis may be due to lower than normal peak bone mass and greater than normal bone loss. Bone loss increases after menopause due to lower levels of estrogen. Osteoporosis may also occur due to a number of diseases or treatments including alcoholism, anorexia, hyperthyroidism, surgical removal of the ovaries, and kidney disease. Certain medications increase the rate of bone loss including some antiseizure medications, chemotherapy, proton pump inhibitors, selective serotonin reuptake inhibitors, and steroids. Not enough exercise and smoking are also risk factors.[3] Osteoporosis is defined as a bone density of 2.5 standard deviations below that of a young adult.[5] This is typically measured by dual-energy X-ray absorptiometry at the hip.[5]

Prevention of osteoporosis includes a proper diet during childhood and efforts to avoid medications that cause the condition. Efforts to prevent broken bones in those with osteoporosis include a good diet, exercise, and fall prevention. Lifestyle changes such as stopping smoking and not drinking alcohol may help.[3] Medication of the bisphosphonate type are useful in those with previous broken bones due to osteoporosis.[6][7] In those with osteoporosis but no previous broken bones they are less effective.[6][7][8] A number of other medications may also be useful.[3][9]

Osteoporosis becomes more common with age.[3] About 15% of white people in their 50s and 70% of those over 80 are affected.[10] It is more common in women than men.[3] In the developed world, depending on the method of diagnosis, 2% to 8% of males and 9% to 38% of females are affected.[11] Rates of disease in the developing world are unclear.[12] About 22 million women and 5.5 million men in the European Union had osteoporosis in 2010.[13] In the

**Osteoporosis**

Elderly woman with osteoporosis showing a curved back from compression fractures of her back bones.

**Pronunciation** /ˌɒstioʊpəˈroʊsɪs, -pɔː-/[1][2]

| Classification and external resources | |
|---|---|
| **Specialty** | Rheumatology |
| **ICD-10** | M80-M82 |
| **ICD-9-CM** | 733.0 |
| **OMIM** | 166710 |

United States in 2010 about eight million women and one to two million men had osteoporosis.[11][14] White and Asian people are at greater risk.[3] The word osteoporosis is from the Greek terms for "porous bones".[15]

| | |
|---|---|
| **DiseasesDB** | 9385 |
| **MedlinePlus** | 000360 |
| **eMedicine** | med/1693 ped/1683 pmr/94 pmr/95 |
| **Patient UK** | Osteoporosis |
| **MeSH** | D010024 |

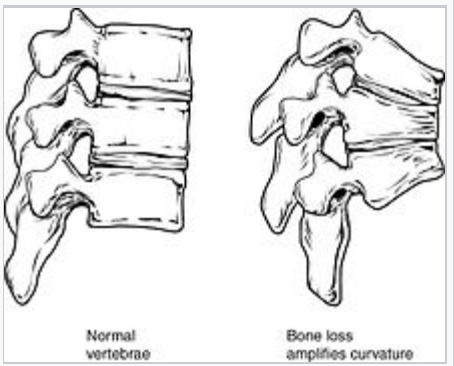
[edit on Wikidata]





# Signs and symptoms [edit]

Osteoporosis itself has no symptoms; its main consequence is the increased risk of bone fractures. Osteoporotic fractures occur in situations where healthy people would not normally break a bone; they are therefore regarded as fragility fractures. Typical fragility fractures occur in the vertebral column, rib, hip and wrist.




Osteoporosis is an age-related disorder that causes the gradual loss of bone density and strength.

## Fractures [edit]

Fractures are the most dangerous aspect of osteoporosis. Debilitating acute and chronic pain in the elderly is often attributed to fractures from osteoporosis and can lead to further disability and early mortality.[16] These fractures may also be asymptomatic. The most common osteoporotic fractures are of the wrist, spine, shoulder and hip. The

symptoms of a vertebral collapse ("compression fracture") are sudden back pain, often with radicular pain (shooting pain due to nerve root compression) and rarely with spinal cord compression or cauda equina syndrome. Multiple vertebral fractures lead to a stooped posture, loss of height, and chronic pain with resultant reduction in mobility.[17]

When the thoracic vertebrae are affected, there can be a gradual collapse of the vertebrae. This results in kyphosis, an excessive curvature of the thoracic region.

Fractures of the long bones acutely impair mobility and may require surgery. Hip fracture, in particular, usually requires prompt surgery, as serious risks are associated with it, such as deep vein thrombosis and pulmonary embolism, and increased mortality.

Fracture risk calculators assess the risk of fracture based upon several criteria, including BMD, age, smoking, alcohol usage, weight, and gender. Recognized calculators include FRAX[18] and Dubbo.

The term "established osteoporosis" is used when a broken bone due to osteoporosis has occurred.[19] Osteoporosis is a part of frailty syndrome.

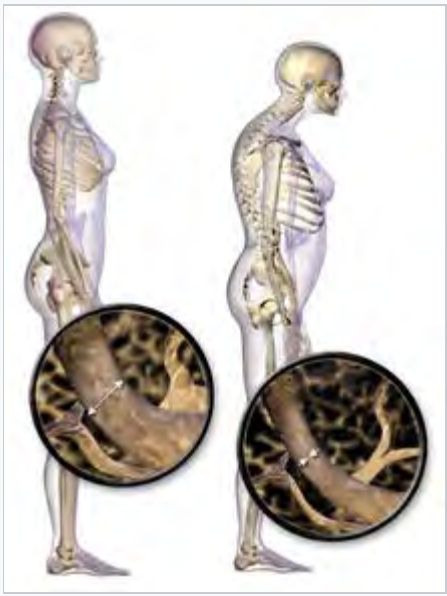


Illustration depicting normal standing posture and osteoporosis

## Falls risk [edit]

The increased risk of falling associated with aging leads to fractures of the wrist, spine, and hip. The risk of falling, in turn, is increased by impaired eyesight due to any cause (e.g. glaucoma, macular degeneration), balance disorder, movement disorders (e.g. Parkinson's disease), dementia, and sarcopenia (age-related loss of skeletal muscle). Collapse (transient loss of postural tone with or without loss of consciousness) leads to a significant risk of falls; causes of syncope are manifold, but may include cardiac arrhythmias (irregular heart beat), vasovagal syncope, orthostatic hypotension (abnormal drop in blood pressure on standing up), and seizures. Removal of obstacles and loose carpets in the living environment may substantially reduce falls. Those with previous falls, as well as those with gait or balance disorders, are most at risk.[20]

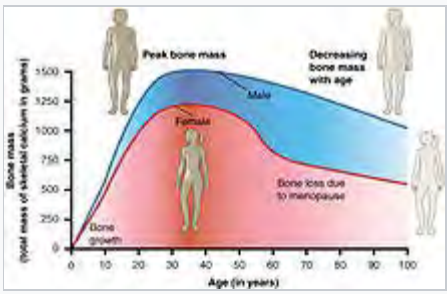
# Risk factors [edit]

Risk factors for osteoporotic fracture can be split between nonmodifiable and (potentially) modifiable. In addition, osteoporosis is a recognized complication of specific diseases and disorders. Medication use is theoretically modifiable, although in many cases, the use of medication that increases osteoporosis risk may be unavoidable. Caffeine is not a risk factor for osteoporosis.[21]

It is more likely in females than males.[3]

## Nonmodifiable [edit]

- The most important risk factors for osteoporosis are advanced age (in both men and women) and female sex; estrogen deficiency following menopause or surgical removal of the ovaries is correlated with a rapid reduction in bone mineral density, while in men, a decrease in testosterone levels has a comparable (but less pronounced) effect.[23][24]
- Race: While osteoporosis occurs in people from all ethnic groups, European or Asian ancestry predisposes for osteoporosis.[25]
- Heredity: Those with a family history of fracture or osteoporosis are at an increased risk; the heritability of the fracture, as well as low bone mineral density, is relatively high, ranging from 25 to 80%. At least 30 genes are associated with the development of [26]




Bone density peaks at about 30 years of age. Women lose bone mass more rapidly than men.[22]

osteoporosis.
- Those who have already had a fracture are at least twice as likely to have another fracture compared to someone of the same age and sex.[27] Early menopause/hysterectomy is another predisposing factor.
- Build: A small stature is also a nonmodifiable risk factor associated with the development of osteoporosis.[28]

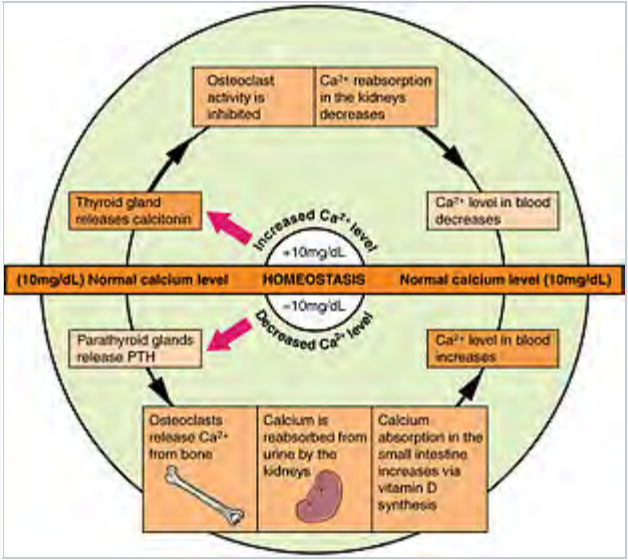
## Potentially modifiable [edit]

- Excess consumption of alcohol: Although small amounts of alcohol are probably beneficial (bone density increases with increasing alcohol intake), chronic heavy drinking (alcohol intake greater than three units/day) probably increases fracture risk despite any beneficial effects on bone density.[29][30]
- Vitamin D deficiency:[31][32] Low circulating Vitamin D is common among the elderly worldwide.[5] Mild vitamin D insufficiency is associated with increased parathyroid hormone (PTH) production.[5] PTH increases bone resorption, leading to bone loss. A positive association exists between serum 1,25-dihydroxycholecalciferol levels and bone mineral density, while PTH is negatively associated with bone mineral density.[5]
- Tobacco smoking: Many studies have associated smoking with decreased bone health, but the mechanisms are unclear. Tobacco smoking has been proposed to inhibit the activity of osteoblasts, and is an independent risk factor for osteoporosis.[29][33] Smoking also results in increased breakdown of exogenous estrogen, lower body weight and earlier menopause, all of which contribute to lower bone mineral density.[5]
- Malnutrition: Nutrition has an important and complex role in maintenance of good bone. Identified risk factors include low dietary calcium and/or phosphorus, magnesium, zinc, boron, iron, fluoride, copper, vitamins A, K, E and C (and D where skin exposure to sunlight provides an inadequate supply). Excess sodium is a risk factor. High blood acidity may be diet-related, and is a known antagonist of bone.[34] Some have identified low protein intake as associated with lower peak bone mass during adolescence and lower bone mineral density in elderly populations.[5] Conversely, some have identified low protein intake as a positive factor, protein is among the causes of dietary acidity. Imbalance of omega-6 to omega-3 polyunsaturated fats is yet another identified risk factor.[35]
- High dietary protein from animal sources: Research has found an association between diets high in animal protein and increased urinary calcium,[36][37][38] and have been linked to an increase in fractures.[39] However, the relevance of this observation to bone density is unclear[*citation needed*], since higher protein diets tend to increase absorption of calcium from the diet and are associated with higher bone density.[40] Indeed, it has recently been argued that low protein diets cause poor bone health.[41] No interventional trials have been performed on dietary protein in the prevention and treatment of osteoporosis.[42]
- Underweight/inactive: Bone remodeling occurs in response to physical stress, so physical inactivity can lead to significant bone loss.[5] Weight bearing exercise can increase peak bone mass achieved in adolescence,[5] and a highly significant correlation between bone strength and muscle strength has been determined.[43] The incidence of osteoporosis is lower in overweight people.[44]
- Endurance training: In female endurance athletes, large volumes of training can lead to decreased bone density and an increased risk of osteoporosis.[45] This effect might be caused by intense training suppressing menstruation, producing amenorrhea, and it is part of the female athlete triad.[46] However, for male athletes, the situation is less clear, and although some studies have reported low bone density in elite male endurance athletes,[47] others have instead seen increased leg bone density.[48][49]
- Heavy metals: A strong association between cadmium and lead with bone disease has been established. Low-level exposure to cadmium is associated with an increased loss of bone mineral density readily in both genders, leading to pain and increased risk of fractures, especially in the elderly and in females. Higher cadmium exposure results in osteomalacia (softening of the bone).[50]
- Soft drinks: Some studies indicate soft drinks (many of which contain phosphoric acid) may increase risk [51]

of osteoporosis, at least in women. Others suggest soft drinks may displace calcium-containing drinks from the diet rather than directly causing osteoporosis.[52]
- Proton pump inhibitors (such as lansoprazole, esomeprazole, or omeprazole) that decrease stomach acid, are a risk for bone fractures if taken for two or more years, due to decreased absorption of calcium in the stomach.[53]

## Medical disorders [edit]

Many diseases and disorders have been associated with osteoporosis.[54] For some, the underlying mechanism influencing the bone metabolism is straightforward, whereas for others the causes are multiple or unknown.



The body regulates calcium homeostasis with two pathways; one is signaled to turn on when blood calcium levels drop below normal and one is the pathway that is signaled to turn on when blood calcium levels are elevated.

- In general, immobilization causes bone loss (following the 'use it or lose it' rule). For example, localized osteoporosis can occur after prolonged immobilization of a fractured limb in a cast. This is also more common in active people with a high bone turn-over (for example, athletes). Other examples include bone loss during space flight or in people who are bedridden or use wheelchairs for various reasons.
- Hypogonadal states can cause secondary osteoporosis. These include Turner syndrome, Klinefelter syndrome, Kallmann syndrome, anorexia nervosa, andropause,[55] hypothalamic amenorrhea or hyperprolactinemia.[55] In females, the effect of hypogonadism is mediated by estrogen deficiency. It can appear as early menopause (<45 years) or from prolonged premenopausal amenorrhea (>1 year). Bilateral oophorectomy (surgical removal of the ovaries) and premature ovarian failure cause deficient estrogen production. In males, testosterone deficiency is the cause (for example, andropause or after surgical removal of the testes).
- Endocrine disorders that can induce bone loss include Cushing's syndrome,[5] hyperparathyroidism,[5] hyperthyroidism,[5] hypothyroidism, diabetes mellitus type 1 and 2,[56] acromegaly, and adrenal insufficiency. In pregnancy and lactation can cause reversible bone loss.[54]
- Malnutrition, parenteral nutrition[5] and malabsorption can lead to osteoporosis. Nutritional and gastrointestinal disorders that can predispose to osteoporosis include undiagnosed and untreated coeliac disease (both symptomatic and asymptomatic people),[5][57] Crohn's disease,[58] ulcerative colitis,[58] cystic fibrosis,[58] surgery[55] (after gastrectomy, intestinal bypass surgery or bowel resection) and severe liver disease (especially primary biliary cirrhosis).[55] People with lactose intolerance or milk allergy may develop osteoporosis due to restrictions of calcium-containing foods.[59] Individuals with bulimia can also develop osteoporosis. Those with an otherwise adequate calcium intake can develop osteoporosis due to the inability to absorb calcium and/or vitamin D. Other micronutrients such as vitamin K or vitamin $B_{12}$ deficiency may also contribute.
- People with rheumatologic disorders such as rheumatoid arthritis,[55] ankylosing spondylitis,[55] systemic lupus erythematosus and polyarticular juvenile idiopathic arthritis are at increased risk of osteoporosis, either as part of their disease or because of other risk factors (notably corticosteroid therapy). Systemic diseases such as amyloidosis and sarcoidosis can also lead to osteoporosis.
- Renal insufficiency can lead to renal osteodystrophy.
- Hematologic disorders linked to osteoporosis are multiple myeloma[55] and other monoclonal gammopathies,[56] lymphoma and leukemia, mastocytosis,[55] hemophilia, sickle-cell disease and thalassemia.
- Several inherited disorders have been linked to osteoporosis. These include osteogenesis imperfecta,[55]

Marfan syndrome,[55] hemochromatosis,[5] hypophosphatasia[60] (for which it is often misdiagnosed),[61] glycogen storage diseases, homocystinuria,[55] Ehlers–Danlos syndrome,[55] porphyria, Menkes' syndrome, epidermolysis bullosa and Gaucher's disease.

- People with scoliosis of unknown cause also have a higher risk of osteoporosis. Bone loss can be a feature of complex regional pain syndrome. It is also more frequent in people with Parkinson's disease and chronic obstructive pulmonary disease.
- People with Parkinson's disease have a higher risk of broken bones. This is related to poor balance and poor bone density.[62] In Parkinson's disease there may be a link between the loss of dopaminergic neurons and altered calcium metabolism[63] (and iron metabolism) causing a stiffening of the skeleton and kyphosis.

### Medication [edit]

Certain medications have been associated with an increase in osteoporosis risk; only steroids and anticonvulsants are classically associated, but evidence is emerging with regard to other drugs.

- Steroid-induced osteoporosis (SIOP) arises due to use of glucocorticoids – analogous to Cushing's syndrome and involving mainly the axial skeleton. The synthetic glucocorticoid prescription drug prednisone is a main candidate after prolonged intake. Some professional guidelines recommend prophylaxis in patients who take the equivalent of more than 30 mg hydrocortisone (7.5 mg of prednisolone), especially when this is in excess of three months.[64] Alternate day use may not prevent this complication.[65]
- Barbiturates, phenytoin and some other enzyme-inducing antiepileptics – these probably accelerate the metabolism of vitamin D.[66]
- L-Thyroxine over-replacement may contribute to osteoporosis, in a similar fashion as thyrotoxicosis does.[54] This can be relevant in subclinical hypothyroidism.
- Several drugs induce hypogonadism, for example aromatase inhibitors used in breast cancer, methotrexate and other antimetabolite drugs, depot progesterone and gonadotropin-releasing hormone agonists.
- Anticoagulants – long-term use of heparin is associated with a decrease in bone density,[67] and warfarin (and related coumarins) have been linked with an increased risk in osteoporotic fracture in long-term use.[68]
- Proton pump inhibitors – these drugs inhibit the production of stomach acid; this is thought to interfere with calcium absorption.[69] Chronic phosphate binding may also occur with aluminium-containing antacids.[54]
- Thiazolidinediones (used for diabetes) – rosiglitazone and possibly pioglitazone, inhibitors of PPARγ, have been linked with an increased risk of osteoporosis and fracture.[70]
- Chronic lithium therapy has been associated with osteoporosis.[54]

### Evolutionary [edit]

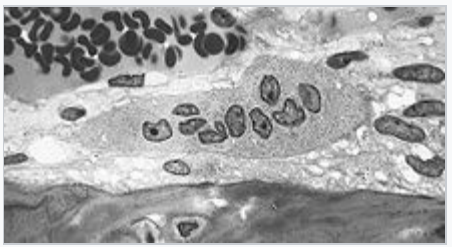
Age-related bone loss is common among humans due to exhibiting less dense bones than other primate species.[71] Because of the more porous bones of humans, frequency of severe osteoporosis and osteoporosis related fractures is higher.[72] The human vulnerability to osteoporosis is an obvious cost but it can be justified by the advantage of bipedalism inferring that this vulnerability is the byproduct of such.[72] It has been suggested that porous bones help to absorb the increased stress that we have on two surfaces compared to our primate counterparts who have four surfaces to disperse the force.[71] In addition, the porosity allows for more flexibility and a lighter skeleton that is easier to support.[72] One other consideration may be that diets today have much lower amounts of calcium than the diets of other primates or the tetrapedal ancestors to humans which may lead to higher likelihood to show signs of osteoporosis.[73]

## Pathogenesis [edit]

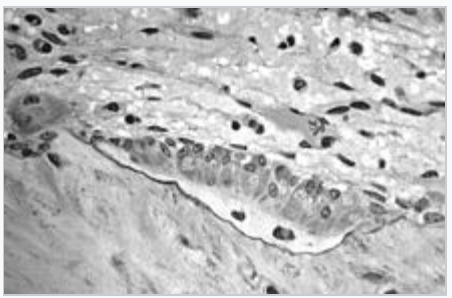
The underlying mechanism in all cases of osteoporosis is an imbalance between bone resorption and bone formation. In normal bone, matrix remodeling of bone is constant; up to 10% of all bone mass may be undergoing remodeling at any point in time. The process takes place in bone multicellular units (BMUs) as first described by Frost & Thomas in 1963.[74] Osteoclasts are assisted by transcription factor PU.1 to degrade the bone matrix, while osteoblasts rebuild the bone matrix. Low bone mass density can then occur when osteoclasts are degrading the bone matrix faster than the osteoblasts are rebuilding the bone.[75]

Osteoporosis locations

The three main mechanisms by which osteoporosis develops are an inadequate peak bone mass (the skeleton develops insufficient mass and strength during growth), excessive bone resorption, and inadequate formation of new bone during remodeling. An interplay of these three mechanisms underlies the development of fragile bone tissue.[26] Hormonal factors strongly determine the rate of bone resorption; lack of estrogen (e.g. as a result of menopause) increases bone resorption, as well as decreasing the deposition of new bone that normally takes place in weight-bearing bones. The amount of estrogen needed to suppress this process is lower than that normally needed to stimulate the uterus and breast gland. The α-form of the estrogen receptor appears to be the most important in regulating bone turnover.[26] In addition to estrogen, calcium metabolism plays a significant role in bone turnover, and deficiency of calcium and vitamin D leads to impaired bone deposition; in addition, the parathyroid glands react to low calcium levels by secreting parathyroid hormone (parathormone, PTH), which increases bone resorption to ensure sufficient calcium in the blood. The role of calcitonin, a hormone generated by the thyroid that increases bone deposition, is less clear and probably not as significant as that of PTH.[26]


Light micrograph of an osteoclast displaying typical distinguishing characteristics: a large cell with multiple nuclei and a "foamy" cytosol.

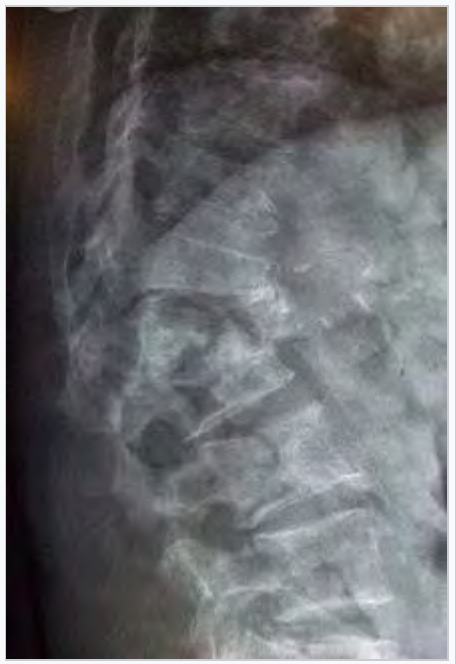
The activation of osteoclasts is regulated by various molecular signals, of which RANKL (receptor activator of nuclear factor kappa-B ligand) (receptor activator of nuclear factor kappa-B ligand) is one of the best studied. This molecule is produced by osteoblasts and other cells (e.g. lymphocytes), and stimulates RANK (receptor activator of nuclear factor κB). Osteoprotegerin (OPG) binds RANKL before it has an opportunity to bind to RANK, and hence suppresses its ability to increase bone resorption. RANKL, RANK and OPG are closely related to tumor necrosis factor and its receptors. The role of the Wnt signaling pathway is recognized, but less well understood. Local production of eicosanoids and interleukins is thought to participate in the regulation of bone turnover, and excess or reduced production of these mediators may underlie the development of osteoporosis.[26]


Light micrograph of osteoblasts, several displaying a prominent Golgi apparatus, actively synthesizing osteoid containing two osteocytes.

Trabecular bone (or cancellous bone) is the sponge-like bone in the ends of long bones and vertebrae. Cortical bone is the hard outer shell of bones and the middle of long bones. Because osteoblasts and osteoclasts inhabit the surface of bones, trabecular bone is more active and is more subject to bone turnover and remodeling. Not only is bone density decreased, but the microarchitecture of bone is also disrupted. The weaker spicules of trabecular bone break ("microcracks"), and are replaced by weaker bone. Common osteoporotic fracture sites, the wrist, the hip and the spine, have a relatively high trabecular bone to cortical bone ratio. These areas rely on the trabecular bone for strength, so the intense remodeling causes these areas to degenerate most when the remodeling is imbalanced.[*citation needed*] Around the ages of 30–35, cancellous or trabecular bone loss begins. Women may lose as much as 50%, while men lose about 30%.[28]

# Diagnosis [edit]

The diagnosis of osteoporosis can be made using conventional radiography and by measuring the bone mineral density (BMD).[76] The most popular method of measuring BMD is dual-energy X-ray absorptiometry. In addition to the detection of abnormal BMD, the diagnosis of osteoporosis requires investigations into potentially modifiable underlying causes; this may be done with blood tests. Depending on the likelihood of an underlying problem, investigations for cancer with metastasis to the bone, multiple myeloma, Cushing's disease and other above-mentioned causes may be performed.



Multiple osteoporotic wedge fractures demonstrated on a lateral thoraco-lumbar spine X-ray

## Conventional radiography [edit]

Conventional radiography is useful, both by itself and in conjunction with CT or MRI, for detecting complications of osteopenia (reduced bone mass; pre-osteoporosis), such as fractures; for differential diagnosis of osteopenia; or for follow-up examinations in specific clinical settings, such as soft tissue calcifications, secondary hyperparathyroidism, or osteomalacia in renal osteodystrophy. However, radiography is relatively insensitive to detection of early disease and requires a substantial amount of bone loss (about 30%) to be apparent on X-ray images.

The main radiographic features of generalized osteoporosis are cortical thinning and increased radiolucency. Frequent complications of osteoporosis are vertebral fractures for which spinal radiography can help considerably in diagnosis and follow-up. Vertebral height measurements can objectively be made using plain-film X-rays by using several methods such as height loss together with area reduction, particularly when looking at vertical deformity in T4-L4, or by determining a spinal fracture index that takes into account the number of vertebrae involved. Involvement of multiple vertebral bodies leads to kyphosis of the thoracic spine, leading to what is known as dowager's hump.

## Dual-energy X-ray [edit]

Dual-energy X-ray absorptiometry (DXA) is considered the gold standard for the diagnosis of osteoporosis. Osteoporosis is diagnosed when the bone mineral density is less than or equal to 2.5 standard deviations below that of a young (30–40-year-old[5]:58), healthy adult women reference population. This is translated as a T-score. But because bone density decreases with age, more people become osteoporotic with increasing age.[5]:58 The World Health Organization has established the following diagnostic guidelines:[5][19]

| Category | T-score range | % young women |
|---|---|---|
| Normal | T-score ≥ −1.0 | 85% |
| Osteopenia | −2.5 < T-score < −1.0 | 14% |
| Osteoporosis | T-score ≤ −2.5 | 0.6% |
| Severe osteoporosis | T-score ≤ −2.5 with fragility fracture[19] | |

The International Society for Clinical Densitometry takes the position that a diagnosis of osteoporosis in men under 50 years of age should not be made on the basis of densitometric criteria alone. It also states, for premenopausal women, Z-scores (comparison with age group rather than peak bone mass) rather than T-scores should be used, and the diagnosis of osteoporosis in such women also should not be made on the basis of densitometric criteria alone.[77]

## Biomarkers [edit]

Chemical biomarkers are a useful tool in detecting bone degradation. The enzyme cathepsin K breaks down type-I collagen protein, an important constituent in bones. Prepared antibodies can recognize the resulting fragment, called a neoepitope, as a way to diagnose osteoporosis.[78] Increased urinary excretion of C-telopeptides, a type-I collagen breakdown product, also serves as a biomarker for osteoporosis.[79]

**Comparison of bone pathology**

| view · talk · edit · Condition | Calcium | Phosphate | Alkaline phosphatase | Parathyroid hormone | Comments |
|---|---|---|---|---|---|
| Osteopenia | unaffected | unaffected | normal | unaffected | decreased bone mass |
| Osteopetrosis | unaffected | unaffected | elevated | unaffected[*citation needed*] | thick dense bones also known as marble bone |
| Osteomalacia and rickets | decreased | decreased | elevated | elevated | soft bones |
| Osteitis fibrosa cystica | elevated | decreased | elevated | elevated | brown tumors |
| Paget's disease of bone | unaffected | unaffected | variable (depending on stage of disease) | unaffected | abnormal bone architecture |

## Other measuring tools [edit]

Quantitative computed tomography differs from DXA in that it gives separate estimates of BMD for trabecular and cortical bone and reports precise volumetric mineral density in $mg/cm^3$ rather than BMD's relative Z score. Among QCT's advantages: it can be performed at axial and peripheral sites, can be calculated from existing CT scans without a separate radiation dose, is sensitive to change over time, can analyze a region of any size or shape, excludes irrelevant tissue such as fat, muscle, and air, and does not require knowledge of the patient's subpopulation in order to create a clinical score (e.g. the Z-score of all females of a certain age). Among QCT's disadvantages: it requires a high radiation dose compared to DXA, CT scanners are large and expensive, and because its practice has been less standardized than BMD, its results are more operator-dependent. Peripheral QCT has been introduced to improve upon the limitations of DXA and QCT.[76]

Quantitative ultrasound has many advantages in assessing osteoporosis. The modality is small, no ionizing radiation is involved, measurements can be made quickly and easily, and the cost of the device is low compared with DXA and QCT devices. The calcaneus is the most common skeletal site for quantitative ultrasound assessment because it has a high percentage of trabecular bone that is replaced more often than cortical bone, providing early evidence of metabolic change. Also, the calcaneus is fairly flat and parallel, reducing repositioning errors. The method can be applied to children, neonates, and preterm infants, just as well as to adults.[76] Some ultrasound devices can be used on the tibia.[80]

## Screening [edit]

The U.S. Preventive Services Task Force (USPSTF) recommend that all women 65 years of age or older be screened by bone densitometry.[81] Additionally they recommend screening women with increased risk factors that puts them at risk equivalent to a 65 year old.[81] There is insufficient evidence to make recommendations about the intervals for repeated screening and the appropriate age to stop screening.[81] In men the harm versus benefit of screening for osteoporosis is unknown.[81] The International Society for Clinical Densitometry, however, suggest BMD testing for men 70 or older, or those who are indicated for

risk equal to that of a 70 year old.[82] A number of tools exist to help determine who is reasonable to test.[83]

# Prevention [edit]

Lifestyle prevention of osteoporosis is in many aspects the inverse of the potentially modifiable risk factors.[84] As tobacco smoking and high alcohol intake have been linked with osteoporosis, smoking cessation and moderation of alcohol intake are commonly recommended as ways to help prevent it.[85]

In people with coeliac disease adherence to a gluten-free diet decreases the risk of developing osteoporosis[86] and increases bone density.[57] The diet must ensure optimal calcium intake (of at least one gram daily) and measuring vitamin D levels is recommended, and to take specific supplements if necessary.[86]

## Nutrition [edit]

Studies of the benefits of supplementation with calcium and vitamin D are conflicting, possibly because most studies did not have people with low dietary intakes.[87] A 2013 review by the USPSTF found insufficient evidence to determine if supplementation with calcium and vitamin D results in greater harm or benefit in men and premenopausal women.[88] The USPSTF did not recommend low dose supplementation (less than 1 g of calcium and 400 IU of vitamin D) in postmenopausal women as there does not appear to be a difference in fracture risk.[88] It is unknown what effect higher doses have.[88] A 2015 review found little data that supplementation of calcium decreases the risk of fractures.[89]

While some meta-analyses have found a benefit of vitamin D supplements combined with calcium for fractures, they did not find a benefit of vitamin D supplements alone.[90][91]

While supplementation does not appear to affect the risk of death,[91] there is an increased risk of myocardial infarctions with calcium supplementation,[92][93] kidney stones,[88] and stomach problems.[91]

Vitamin K deficiency is also a risk factor for osteoporotic fractures. The gene gamma-glutamylcarboxylase (GGCX) is dependent on vitamin K. Functional polymorphisms in the gene could attribute to variation in bone metabolism and BMD. Vitamin K2 is also used as a means of treatment for osteoporosis and the polymorphisms of GGCX could explain the individual variation in the response to treatment of vitamin K.[94] Vitamin K supplementation may reduce the risk of fractures in postmenopausal women;[95] however, there is no evidence for men.[96]

## Physical exercise [edit]

A 2011 review reported a small benefit of physical exercise on bone density of postmenopausal women.[97] The chances of having a fracture were also slightly reduced (absolute difference 4%).[97] People who exercised had on average less bone loss (0.85% at the spine, 1.03% at the hip).[97]

# Management [edit]

## Lifestyle [edit]

Weight-bearing endurance exercise and/or exercises to strengthen muscles improve bone strength in those with osteoporosis.[97][98] Aerobics, weight bearing, and resistance exercises all maintain or increase BMD in postmenopausal women.[97] Fall prevention can help prevent osteoporosis complications. There is some evidence for hip protectors specifically among those who are in care homes.[99]

## Medications [edit]

Bisphosphonates are useful in decreasing the risk of future fractures in those who have already sustained a fracture due to osteoporosis.[6][7][85] This benefit is present when taken for three to four years.[100] Different bisphosphonates have not been directly compared, therefore it is unknown if one is better than another.[85] Fracture risk reduction is between 25 and 70% depending on the bone involved.[85] There are concerns of atypical femoral fractures and osteonecrosis of the jaw with long-term use, but these risks are low.[85][101] With evidence of little benefit when used for more than three to five years and in light of the potential adverse events, it may be appropriate to stop treatment after this time in some.[100] One medical organization recommends that after five years of medications by mouth or three years of intravenous medication among those at low risk, bisphosphonate treatment can be stopped.[102] In those at higher risk they recommend up to ten years of medication by mouth or six years of intravenous treatment.[102]

For those with osteoporosis but who have not had a fracture evidence does not support a reduction in fracture risk with risedronate[7] or etidronate.[8] Alendronate decreases fractures of the spine but does not have any effect on other types of fractures.[6] Half stop their medications within a year.[103]

Fluoride supplementation does not appear to be effective in postmenopausal osteoporosis, as even though it increases bone density, it does not decrease the risk of fractures.[104][105]

Teriparatide ( a recombinant parathyroid hormone ) has been shown to be effective in treatment of women with postmenopausal osteoporosis.[106] Some evidence also indicates strontium ranelate is effective in decreasing the risk of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis.[107] Hormone replacement therapy, while effective for osteoporosis, is only recommended in women who also have menopausal symptoms.[85] Raloxifene, while effective in decreasing vertebral fractures, does not affect the risk of nonvertebral fracture.[85] And while it reduces the risk of breast cancer, it increases the risk of blood clots and strokes.[85] Denosumab is also effective for preventing osteoporotic fractures.[85] In hypogonadal men, testosterone has been shown to improve bone quantity and quality, but, as of 2008, no studies evaluated its effect on fracture risk or in men with a normal testosterone levels.[56] Calcitonin while once recommended is no longer due to the associated risk of cancer with its use and questionable effect on fracture risk.[108]

Certain medications like alendronate, etidronate, risedronate, raloxifene and strontium ranelate can be helpful for the preventing of osteoporotic fragility fractures in postmenopausal women with osteoporosis.[109]

# Prognosis [edit]

Although osteoporosis patients have an increased mortality rate due to the complications of fracture, it is rarely lethal.

**Hip fractures per 1000 person-years**[110]

| WHO category | Age 50–64 | Age > 64 | Overall |
|---|---|---|---|
| Normal | 5.3 | 9.4 | 6.6 |
| Osteopenia | 11.4 | 19.6 | 15.7 |
| Osteoporosis | 22.4 | 46.6 | 40.6 |

Hip fractures can lead to decreased mobility and additional risks of numerous complications (such as deep venous thrombosis and/or pulmonary embolism, and pneumonia). The six-month mortality rate following hip fracture is around 13.5%, and a substantial proportion (almost 13%) of people who have suffered a hip fracture need total assistance to mobilize after a hip fracture.[111]

Vertebral fractures, while having a smaller impact on mortality, can lead to a severe chronic pain of neurogenic origin, which can be hard to control, as well as deformity. Though rare, multiple vertebral fractures can lead to such severe hunch back (kyphosis), the resulting pressure on internal organs can impair one's ability to breathe.

Apart from risk of death and other complications, osteoporotic fractures are associated with a reduced

health-related quality of life.[112]

The condition is responsible for millions of fractures annually, mostly involving the lumbar vertebrae, hip, and wrist. Fragility fractures of ribs are also common in men.

### Hip fractures [edit]

Hip fractures are responsible for the most serious consequences of osteoporosis. In the United States, more than 250,000 hip fractures annually are attributable to osteoporosis.[113] A 50-year-old white woman is estimated to have a 17.5% lifetime risk of fracture of the proximal femur. The incidence of hip fractures increases each decade from the sixth through the ninth for both women and men for all populations. The highest incidence is found among men and women ages 80 or older.[114]

### Vertebral fractures [edit]

Between 35 and 50% of all women over 50 had at least one vertebral fracture. In the United States, 700,000 vertebral fractures occur annually, but only about a third are recognized. In a series of 9704 women aged 68.8 on average studied for 15 years, 324 had already suffered a vertebral fracture at entry into the study and 18.2% developed a vertebral fracture, but that risk rose to 41.4% in women who had a previous vertebral fracture.[115]

### Wrist fractures [edit]

In the United States, 250,000 wrist fractures annually are attributable to osteoporosis.[113] Wrist fractures are the third most common type of osteoporotic fractures. The lifetime risk of sustaining a Colles' fracture is about 16% for white women. By the time women reach age 70, about 20% have had at least one wrist fracture.[114]

### Rib fractures [edit]

Fragility fractures of the ribs are common in men as young as age 35. These are often overlooked as signs of osteoporosis, as these men are often physically active and suffer the fracture in the course of physical activity. An example would be as a result of falling while water skiing or jet skiing. However, a quick test of the individual's testosterone level following the diagnosis of the fracture will readily reveal whether that individual might be at risk.

## Epidemiology [edit]

It is estimated that 200 million people have osteoporosis.[116] Osteoporosis becomes more common with age.[3] About 15% of White people in their 50s and 70% of those over 80 are affected.[10] It is more common in women than men.[3] In the developed world, depending on the method of diagnosis, 2% to 8% of males and 9% to 38% of females are affected.[11] Rates of disease in the developing world are unclear.[12]

There are 8.9 million fractures worldwide per year due to osteoporosis.[117] Globally, 1 in 3 women and 1 in 5 men over the age of 50 will have an osteoporotic fracture.[117] Data from the United States shows a decrease in osteoporosis within the general population and in white women, from 18% in 1994 to 10% in 2006.[118] White and Asian people are at greater risk.[3] People of African descent are at a decreased risk of fractures due to osteoporosis, although they have the highest risk of death following an osteoporotic fracture.[118]

It has been shown that latitude affects risk of osteoporotic fracture.[119] Areas of higher latitude such as Northern Europe receive less Vitamin D through sunlight compared to regions closer to the equator, and consequently have higher fracture rates in comparison to lower latitudes.[119] For example, Swedish men and women have a 13.% and 28.5% risk of hip fracture by age 50, respectively, whereas this risk is only

1.9% and 2.4% in Chinese men and women.[118] Diet may also be a factor that is responsible for this difference, as vitamin D, calcium, magnesium, and folate are all linked to bone mineral density.[120]

About 22 million women and 5.5 million men in the European Union had osteoporosis in 2010.[13] In the United States in 2010 about 8 million women and one to 2 million men had osteoporosis.[11][14] This places a large economic burden on the healthcare system due to costs of treatment, long-term disability, and loss of productivity in the working population. The EU spends 37 billion euros per year in healthcare costs related to osteoporosis, and the USA spends an estimated 19 billion USD annually for related healthcare costs.[117]

## History [edit]

The link between age-related reductions in bone density and fracture risk goes back at least to Astley Cooper, and the term "osteoporosis" and recognition of its pathological appearance is generally attributed to the French pathologist Jean Lobstein.[121] The American endocrinologist Fuller Albright linked osteoporosis with the postmenopausal state.[122] Bisphosphonates were discovered in the 1960s.[123]

Anthropologists have studied skeletal remains that showed loss of bone density and associated structural changes that were linked to a chronic malnutrition in the agricultural area in which these individuals lived. "It follows that the skeletal deformation may be attributed to their heavy labor in agriculture as well as to their chronic malnutrition", causing the osteoporosis seen when radiographs of the remains were made.[124]

Osteoporosis means "porous bones", from Greek: οστούν/*ostoun* meaning "bone" and πόρος/*poros* meaning "pore".

## References [edit]


1. ^ Jones, Daniel (2003) [1917], Peter Roach, James Hartmann and Jane Setter, eds., *English Pronouncing Dictionary*, Cambridge: Cambridge University Press, ISBN 3-12-539683-2
2. ^ "Osteoporosis". *Merriam-Webster Dictionary*.
3. ^ *a b c d e f g h i j k l* "Handout on Health: Osteoporosis". August 2014. Retrieved 16 May 2015.
4. ^ Golob, AL; Laya, MB (May 2015). "Osteoporosis: Screening, Prevention, and Management.". *The Medical clinics of North America*. **99** (3): 587–606. doi:10.1016/j.mcna.2015.01.010. PMID 25841602.
5. ^ *a b c d e f g h i j k l m n o p q r* WHO Scientific Group on the Prevention and Management of Osteoporosis (2000 : Geneva, Switzerland) (2003). "Prevention and management of osteoporosis : report of a WHO scientific group" (PDF). pp. 7, 31. ISBN 9241209216.
6. ^ *a b c d* Wells, GA; Cranney, A; Peterson, J; Boucher, M; Shea, B; Robinson, V; Coyle, D; Tugwell, P (23 January 2008). "Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women.". *The Cochrane database of systematic reviews* (1): CD001155. doi:10.1002/14651858.CD001155.pub2. PMID 18253985.
7. ^ *a b c d* Wells, G; Cranney, A; Peterson, J; Boucher, M; Shea, B; Robinson, V; Coyle, D; Tugwell, P (23 January 2008). "Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women.". *The Cochrane database of systematic reviews* (1): CD004523. doi:10.1002/14651858.CD004523.pub3. PMID 18254053.
8. ^ *a b* Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P (Jan 23, 2008). "Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women". *Cochrane Database of Systematic Reviews* (1): CD003376. doi:10.1002/14651858.CD003376.pub3. PMID 18254018.
9. ^ Nelson HD, Haney EM, Chou R, Dana T, Fu R, Bougatsos C (2010). "Screening for Osteoporosis: Systematic Review to Update the 2002 U.S. Preventive Services Task Force Recommendation [Internet].". *Agency for Healthcare Research and Quality*. PMID 20722176.
10. ^ *a b* "Chronic rheumatic conditions". *World Health Organization*. Retrieved 18 May 2015.
11. ^ *a b c d* Wade, SW; Strader, C; Fitzpatrick, LA; Anthony, MS; O'Malley, CD (2014). "Estimating prevalence of osteoporosis: examples from industrialized countries.". *Archives of osteoporosis*. **9** (1): 182. doi:10.1007/s11657-014-0182-3. PMID 24847682.

12. ^ [a] [b] Handa, R; Ali Kalla, A; Maalouf, G (August 2008). "Osteoporosis in developing countries.". *Best practice & research. Clinical rheumatology*. **22** (4): 693–708. doi:10.1016/j.berh.2008.04.002. PMID 18783745.
13. ^ [a] [b] Svedbom, A; Hernlund, E; Ivergård, M; Compston, J; Cooper, C; Stenmark, J; McCloskey, EV; Jönsson, B; Kanis, JA; EU Review Panel of, IOF (2013). "Osteoporosis in the European Union: a compendium of country-specific reports.". *Archives of osteoporosis*. **8** (1-2): 137. doi:10.1007/s11657-013-0137-0. PMID 24113838.
14. ^ [a] [b] Willson, T; Nelson, SD; Newbold, J; Nelson, RE; LaFleur, J (2015). "The clinical epidemiology of male osteoporosis: a review of the recent literature.". *Clinical epidemiology*. **7**: 65–76. doi:10.2147/CLEP.S40966. PMID 25657593.
15. ^ King, Tekoa L.; Brucker, Mary C. (2011). *Pharmacology for women's health*. Sudbury, Mass.: Jones and Bartlett Publishers. p. 1004. ISBN 9780763753290.
16. ^ Old JL, Calvert M (2004). "Vertebral compression fractures in the elderly". *American Family Physician*. **69** (1): 111–6. PMID 14727827. Retrieved 31 March 2011.
17. ^ Kim DH, Vaccaro AR (2006). "Osteoporotic compression fractures of the spine; current options and considerations for treatment". *The Spine Journal*. **6** (5): 479–87. doi:10.1016/j.spinee.2006.04.013. PMID 16934715.
18. ^ Susan Ott. "Fracture Risk Calculator". Retrieved 2009-11-03.
19. ^ [a] [b] [c] WHO (1994). "Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group". *World Health Organization technical report series*. **843**: 1–129. PMID 7941614.
20. ^ Ganz DA, Bao Y, Shekelle PG, Rubenstein LZ (2007). "Will my patient fall?". *JAMA*. **297** (1): 77–86. doi:10.1001/jama.297.1.77. PMID 17200478.
21. ^ Waugh EJ, Lam MA, Hawker GA, McGowan J, Papaioannou A, Cheung AM, Hodsman AB, Leslie WD, Siminoski K, Jamal SA (January 2009). "Risk factors for low bone mass in healthy 40–60 year old women: a systematic review of the literature". *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. **20** (1): 1–21. doi:10.1007/s00198-008-0643-x. PMID 18523710.
22. ^ "6.6 Exercise, Nutrition, Hormones, and Bone Tissue". *Anatomy & Physiology*. Openstax CNX. ISBN 978-1-938168-13-0.
23. ^ Sinnesael M, Claessens F, Boonen S, Vanderschueren D (2013). "Novel insights in the regulation and mechanism of androgen action on bone". *Current Opinion in Endocrinology & Diabetes and Obesity*. **20** (3): 240–4. doi:10.1097/MED.0b013e32835f7d04. PMID 23449008.
24. ^ Sinnesael M, Boonen S, Claessens F, Gielen E, Vanderschueren D (2011). "Testosterone and the male skeleton: a dual mode of action". *Journal of Osteoporosis*. **2011**: 240328. doi:10.4061/2011/240328. PMC 3173882. PMID 21941679.
25. ^ Melton LJ (2003). "Epidemiology worldwide". *Endocrinol. Metab. Clin. North Am*. **32** (1): 1–13, v. doi:10.1016/S0889-8529(02)00061-0. PMID 12699289.
26. ^ [a] [b] [c] [d] [e] Raisz L (2005). "Pathogenesis of osteoporosis: concepts, conflicts, and prospects". *J Clin Invest*. **115** (12): 3318–25. doi:10.1172/JCI27071. PMC 1297264. PMID 16322775.
27. ^ Ojo F, Al Snih S, Ray LA, Raji MA, Markides KS (2007). "History of fractures as predictor of subsequent hip and nonhip fractures among older Mexican Americans". *Journal of the National Medical Association*. **99** (4): 412–8. PMC 2569658. PMID 17444431.
28. ^ [a] [b] Brian K Alldredge; Koda-Kimble, Mary Anne; Young, Lloyd Y.; Wayne A Kradjan; B. Joseph Guglielmo (2009). *Applied therapeutics: the clinical use of drugs*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. pp. 101–3. ISBN 0-7817-6555-2.
29. ^ [a] [b] Poole KE, Compston JE (December 2006). "Osteoporosis and its management". *BMJ*. **333** (7581): 1251–6. doi:10.1136/bmj.39050.597350.47. PMC 1702459. PMID 17170416.
30. ^ Berg KM, Kunins HV, Jackson JL, Nahvi S, Chaudhry A, Harris KA, Malik R, Arnsten JH (2008). "Association between alcohol consumption and both osteoporotic fracture and bone density". *Am J Med*. **121** (5): 406–18. doi:10.1016/j.amjmed.2007.12.012. PMC 2692368. PMID 18456037.
31. ^ Nieves JW (2005). "Osteoporosis: the role of micronutrients". *Am J Clin Nutr*. **81** (5): 1232S–9S. PMID 15883457.
32. ^ Gielen E, Boonen S, Vanderschueren D, Sinnesael M, Verstuyf A, Claessens F, Milisen K, Verschueren S (2011). "Calcium and vitamin d supplementation in men". *Journal of Osteoporosis*. **2011**: 875249. doi:10.4061/2011/875249. PMC 3163142. PMID 21876835.
33. ^ Wong PK, Christie JJ, Wark JD (2007). "The effects of smoking on bone health". *Clin. Sci*. **113** (5): 233–41. doi:10.1042/CS20060173. PMID 17663660.
34. ^ Ilich JZ, Kerstetter JE (2000). "Nutrition in Bone Health Revisited: A Story Beyond Calcium". *Journal of the American College of Nutrition*. **19** (6): 715–737. doi:10.1080/07315724.2000.10718070. PMID 11194525.
35. ^ Weiss LA, Barrett-Connor E, von Mühlen D (2005). "Ratio of n–6 to n–3 fatty acids and bone mineral density in

older adults: the Rancho Bernardo Study". *Am J Clin Nutr April*. **81** (4): 934–938. PMID 15817874.
36. ^ Abelow BJ, Holford TR, Insogna KL (1992). "Cross-cultural association between dietary animal protein and hip fracture: a hypothesis". *Calcified tissue international*. **50** (1): 14–18. doi:10.1007/BF00297291. PMID 1739864.
37. ^ Hegsted M, Schuette SA, Zemel MB, Linkswiler HM (1981). "Urinary calcium and calcium balance in young men as affected by level of protein and phosphorus intake". *The Journal of Nutrition*. **111** (3): 553–562. PMID 7205408.
38. ^ Kerstetter JE, Allen LH (1990). "Dietary protein increases urinary calcium" (PDF). *Journal of Nutrition*. **120** (1): 134–6. PMID 2406396.
39. ^ Feskanich D, Willett WC, Stampfer MJ, Colditz GA (1996). "Protein consumption and bone fractures in women". *Am. J. Epidemiol*. **143** (5): 472–79. doi:10.1093/oxfordjournals.aje.a008767. PMID 8610662.
40. ^ Kerstetter JE, Kenny AM, Insogna KL (2011). "Dietary protein and skeletal health: A review of recent human research". *Current Opinion in Lipidology*. **22** (1): 16–20. doi:10.1097/MOL.0b013e3283419441. PMID 21102327.
41. ^ Bonjour JP (2005). "Dietary protein: An essential nutrient for bone health". *Journal of the American College of Nutrition*. **24** (6 Suppl): 526S–536S. doi:10.1080/07315724.2005.10719501. PMID 16373952.
42. ^ Kerstetter JE, O'Brien KO, Insogna KL (2003). "Dietary protein, calcium metabolism, and skeletal homeostasis revisited". *Am. J. Clin. Nutr*. **78** (3 Suppl): 584S–592S. PMID 12936953.
43. ^ Schönau E, Werhahn E, Schiedermaier U, Mokow E, Schiessl H, Scheidhauer K, Michalk D (1996). "Influence of muscle strength on bone strength during childhood and adolescence". *Hormone Research*. **45** (Suppl. 1): 63–66. doi:10.1159/000184834. PMID 8805035.
44. ^ Shapses SA, Riedt CS (1 June 2006). "Bone, body weight, and weight reduction: what are the concerns?". *J. Nutr*. **136** (6): 1453–6. PMID 16702302.
45. ^ Pollock N, Grogan C, Perry M, Pedlar C, Cooke K, Morrissey D, Dimitriou L (2010). "Bone-mineral density and other features of the female athlete triad in elite endurance runners: A longitudinal and cross-sectional observational study". *International journal of sport nutrition and exercise metabolism*. **20** (5): 418–426. PMID 20975110.
46. ^ Gibson JH, Mitchell A, Harries MG, Reeve J (2004). "Nutritional and exercise-related determinants of bone density in elite female runners". *Osteoporosis International*. **15** (8): 611–618. doi:10.1007/s00198-004-1589-2. PMID 15048548.
47. ^ Hetland ML, Haarbo J, Christiansen C (1993). "Low bone mass and high bone turnover in male long distance runners". *The Journal of Clinical Endocrinology and Metabolism*. **77** (3): 770–775. doi:10.1210/jcem.77.3.8370698. PMID 8370698.
48. ^ Brahm H, Ström H, Piehl-Aulin K, Mallmin H, Ljunghall S (1997). "Bone metabolism in endurance trained athletes: A comparison to population-based controls based on DXA, SXA, quantitative ultrasound, and biochemical markers". *Calcified tissue international*. **61** (6): 448–454. doi:10.1007/s002239900366. PMID 9383270.
49. ^ MacKelvie KJ, Taunton JE, McKay HA, Khan KM (2000). "Bone mineral density and serum testosterone in chronically trained, high mileage 40–55 year old male runners". *British journal of sports medicine*. **34** (4): 273–278. doi:10.1136/bjsm.34.4.273. PMC 1724199. PMID 10953900.
50. ^ Staessen JA, Roels HA, Emelianov D, Kuznetsova T, Thijs L, Vangronsveld J, Fagard R (1999). "Environmental exposure to cadmium, forearm bone density, and risk of fractures: prospective population study. Public Health and Environmental Exposure to Cadmium (PheeCad) Study Group". *Lancet*. **353** (9159): 1140–4. doi:10.1016/S0140-6736(98)09356-8. PMID 10209978.
51. ^ Tucker KL, Morita K, Qiao N, Hannan MT, Cupples LA, Kiel DP (2006). "Colas, but not other carbonated beverages, are associated with low bone mineral density in older women: The Framingham Osteoporosis Study". *Am. J. Clin. Nutr*. **84** (4): 936–42. PMID 17023723.
52. ^ "Soft drinks in schools". *Pediatrics*. **113** (1 Pt 1): 152–4. 2004. doi:10.1542/peds.113.1.152. PMID 14702469.
53. ^ Zhou, B.; Huang, Y.; Li, H.; Sun, W.; Liu, J. (13 October 2015). "Proton-pump inhibitors and risk of fractures: an update meta-analysis". *Osteoporosis International*. **27** (1): 339–347. doi:10.1007/s00198-015-3365-x.
54. ^ *a b c d e* Simonelli, C; et al. (July 2006). "ICSI Health Care Guideline: Diagnosis and Treatment of Osteoporosis, 5th edition". Institute for Clinical Systems Improvement. Archived from the original (PDF) on July 18, 2007. Retrieved 2008-04-08.
55. ^ *a b c d e f g h i j k l* Kohlmeier, Lynn Kohlmeier (1998). "Osteoporosis – Risk Factors, Screening, and Treatment". Medscape Portals. Retrieved 2008-05-11.
56. ^ *a b c* Ebeling PR (2008). "Clinical practice. Osteoporosis in men". *N Engl J Med*. **358** (14): 1474–82. doi:10.1056/NEJMcp0707217. PMID 18385499.
57. ^ *a b* Mirza F, Canalis E (Sep 2015). "Management of endocrine disease: Secondary osteoporosis: pathophysiology and management" (PDF). *Eur J Endocrinol* (Review). **173** (3): R131–51. doi:10.1530/EJE-15-0118. PMID 25971649.
58. ^ *a b c* Henwood MJ, Binkovitz L (2009). "Update on pediatric bone health". *The Journal of the American Osteopathic Association*. **109** (1): 5–12. PMID 19193819.

59. ^ Beto JA (Jan 2015). "The role of calcium in human aging". *Clin Nutr Res* (Review). **4** (1): 1–8. doi:10.7762/cnr.2015.4.1.1. PMC 4337919. PMID 25713787.
60. ^ Mornet, PhD, Etienne; Nunes, MD, Mark E (2007-11-20). *GeneReviews: Hypophostasia*. NCBI.
61. ^ "Hypophosphatasia Case Studies: Dangers of Misdiagnosis". *Hypophosphatasia.com*. Retrieved 5 August 2014.
62. ^ Invernizzi M, Carda S, Viscontini GS, Cisari C (2009). "Osteoporosis in Parkinson's disease". *Parkinsonism & Related Disorders*. **15** (5): 339–46. doi:10.1016/j.parkreldis.2009.02.009. PMID 19346153.
63. ^ Celsi F, Pizzo P, Brini M, Leo S, Fotino C, Pinton P, Rizzuto R (2009). "Mitochondria, calcium and cell death: A deadly triad in neurodegeneration". *Biochimica et Biophysica Acta (BBA) - Bioenergetics*. **1787** (5): 335–44. doi:10.1016/j.bbabio.2009.02.021. PMC 2696196. PMID 19268425.
64. ^ Bone and Tooth Society of Great Britain, National Osteoporosis Society, Royal College of Physicians (2003). *Glucocorticoid-induced Osteoporosis* (PDF). London, UK: Royal College of Physicians of London. ISBN 1-86016-173-1.
65. ^ Gourlay M, Franceschini N, Sheyn Y (2007). "Prevention and treatment strategies for glucocorticoid-induced osteoporotic fractures". *Clin Rheumatol*. **26** (2): 144–53. doi:10.1007/s10067-006-0315-1. PMID 16670825.
66. ^ Petty SJ, O'Brien TJ, Wark JD (2007). "Anti-epileptic medication and bone health". *Osteoporosis international*. **18** (2): 129–42. doi:10.1007/s00198-006-0185-z. PMID 17091219.
67. ^ Ruiz-Irastorza G, Khamashta MA, Hughes GR (2002). "Heparin and osteoporosis during pregnancy: 2002 update". *Lupus*. **11** (10): 680–2. doi:10.1191/0961203302lu262oa. PMID 12413068.
68. ^ Gage BF, Birman-Deych E, Radford MJ, Nilasena DS, Binder EF (2006). "Risk of osteoporotic fracture in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2". *Arch. Intern. Med*. **166** (2): 241–6. doi:10.1001/archinte.166.2.241. PMID 16432096.
69. ^ Yang YX, Lewis JD, Epstein S, Metz DC (2006). "Long-term proton pump inhibitor therapy and risk of hip fracture". *JAMA*. **296** (24): 2947–53. doi:10.1001/jama.296.24.2947. PMID 17190895.
70. ^ Murphy CE, Rodgers PT (2007). "Effects of thiazolidinediones on bone loss and fracture". *Annals of Pharmacotherapy*. **41** (12): 2014–8. doi:10.1345/aph.1K286. PMID 17940125.
71. ^ *a b* Latimer B (2005). "The perils of being bipedal". *Ann Biomed Eng*. **33** (1): 3–6. doi:10.1007/s10439-005-8957-8. PMID 15709701.
72. ^ *a b c* Cotter M et. al (2011). "Human evolution and osteoporosis-related spinal fractures". *PLoS ONE*. **6** (10): e26658. doi:10.1371/journal.pone.0026658.
73. ^ Eaton SB, Nelson DA (1991). "Calcium in evolutionary perspective". *Am. J. Clin. Nutr*. **54** (1 Suppl): 281S–287S. PMID 2053574.
74. ^ Frost HM, Thomas CC. Bone Remodeling Dynamics. Springfield, IL: 1963.
75. ^ Wu, Shuyan (2013). "Genome-wide approaches for identifying genetic risk factors for osteoporosis". *Genome Med*. **5**: 44. doi:10.1186/gm448.
76. ^ *a b c* Guglielmi G, Scalzo G (May 6, 2010). "Imaging tools transform diagnosis of osteoporosis". *Diagnostic Imaging Europe*. **26**: 7–11.
77. ^ Leib ES, Lewiecki EM, Binkley N, Hamdy RC (2004). "Official positions of the International Society for Clinical Densitometry". *J Clin Densitom*. **7** (1): 1–5. doi:10.1385/JCD:7:1:1. PMID 14742881. quoted in: "Diagnosis of osteoporosis in men, premenopausal women, and children"
78. ^ Yasuda Y, Kaleta J, Brömme D (2005). "The role of cathepsins in osteoporosis and arthritis: rationale for the design of new therapeutics". *Adv. Drug Deliv. Rev*. **57** (7): 973–93. doi:10.1016/j.addr.2004.12.013. PMID 15876399.
79. ^ Meunier, Pierre (1998). *Osteoporosis: Diagnosis and Management*. London: Taylor and Francis. ISBN 1-85317-412-2.
80. ^ Bindex, a Radiation-Free Device for Osteoporosis Screening, FDA Cleared. May 2016
81. ^ *a b c d* U.S. Preventive Services Task, Force (2011-03-01). "Screening for osteoporosis: U.S. preventive services task force recommendation statement". *Annals of Internal Medicine*. **154** (5): 356–64. doi:10.1059/0003-4819-154-5-201103010-00307. PMID 21242341.
82. ^ International Society for Clinical Densitometry (ISCD). 2013 ISCD Official Positions - Adult. (2013). at http://www.iscd.org/official-positions/2013-iscd-official-positions-adult
83. ^ Rud B, Hilden J, Hyldstrup L, Hróbjartsson A (2009). "The Osteoporosis Self-Assessment Tool versus alternative tests for selecting postmenopausal women for bone mineral density assessment: a comparative systematic review of accuracy". *Osteoporos Int*. **20** (4): 599–607. doi:10.1007/s00198-008-0713-0. PMID 18716823.
84. ^ Ebeling, PR.; Daly, RM.; Kerr, DA.; Kimlin, MG. (Oct 2013). "Building healthy bones throughout life: an evidence-informed strategy to prevent osteoporosis in Australia.". *Med J Aust*. **199** (7 Suppl): S1. PMID 25370432.
85. ^ *a b c d e f g h i* Body JJ (2011). "How to manage postmenopausal osteoporosis?". *Acta Clin Belg*. **66** (6): 443–7. doi:10.1179/ACB.66.6.2062612. PMID 22338309.
    *a b*

86. ^ Ludvigsson JF, Bai JC, Biagi F, Card TR, Ciacci C, Ciclitira PJ, Green PH, Hadjivassiliou M, Holdoway A, van Heel DA, Kaukinen K, Leffler DA, Leonard JN, Lundin KE, McGough N, Davidson M, Murray JA, Swift GL, Walker MM, Zingone F, Sanders DS; BSG Coeliac Disease Guidelines Development Group; British Society of Gastroenterology (Aug 2014). "Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology". *Gut* (Review). **63** (8): 1210–28. doi:10.1136/gutjnl-2013-306578. PMC 4112432. PMID 24917550.
87. ^ "Drugs for Postmenopausal Osteoporosis". *The Medical Letter on Drugs and Therapeutics*. **56** (1452): 91–96. September 29, 2014.
88. ^ *a b c d* Moyer, VA; on behalf of the U.S. Preventive Services Task, Force* (Feb 26, 2013). "Vitamin D and Calcium Supplementation to Prevent Fractures in Adults: U.S. Preventive Services Task Force Recommendation Statement". *Annals of Internal Medicine*. **158** (9): 691–6. doi:10.7326/0003-4819-158-9-201305070-00603. PMID 23440163.
89. ^ Bolland, MJ; Leung, W; Tai, V; Bastin, S; Gamble, GD; Grey, A; Reid, IR (29 September 2015). "Calcium intake and risk of fracture: systematic review.". *BMJ (Clinical research ed.)*. **351**: h4580. PMID 26420387.
90. ^ DIPART (vitamin D Individual Patient Analysis of Randomized Trials) (2010). "Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe". *BMJ*. **340**: b5463. doi:10.1136/bmj.b5463. PMC 2806633. PMID 20068257.
91. ^ *a b c* Avenell, A; Mak, JC; O'Connell, D (14 April 2014). "Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men.". *The Cochrane database of systematic reviews*. **4**: CD000227. doi:10.1002/14651858.CD000227.pub4. PMID 24729336.
92. ^ Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR (2010). "Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis". *BMJ (Clinical research ed.)*. **341**: c3691. doi:10.1136/bmj.c3691. PMC 2912459. PMID 20671013.
93. ^ Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR (2011). "Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis". *BMJ*. **342**: d2040. doi:10.1136/bmj.d2040. PMC 3079822. PMID 21505219.
94. ^ Hosoi, T (2010). "Genetic aspects of osteoporosis". *Journal of Bone and Mineral Metabolism*. **28**: 601–607. doi:10.1007/s00774-010-0217-9.
95. ^ Cockayne S, Adamson J, Lanham-New S, Shearer MJ, Gilbody S, Torgerson DJ (2006). "Vitamin K and the Prevention of Fractures: Systematic Review and Meta-analysis of Randomized Controlled Trials". *Archives of Internal Medicine*. **166** (12): 1256–61. doi:10.1001/archinte.166.12.1256. PMID 16801507.
96. ^ Iwamoto J, Sato Y (2013). "Menatetrenone for the treatment of osteoporosis". *Expert Opin Pharmacother*. **14** (4): 449–58. doi:10.1517/14656566.2013.763796. PMID 23346882.
97. ^ *a b c d e* Howe TE, Shea B, Dawson LJ, Downie F, Murray A, Ross C, Harbour RT, Caldwell LM, Creed G (2011). "Exercise for preventing and treating osteoporosis in postmenopausal women.". *Cochrane Database of Systematic Reviews*. Art. No.: CD000333 (7). doi:10.1002/14651858.CD000333.pub2 – via Cochrane Database of Systematic Reviews.
98. ^ Body JJ, Bergmann P, Boonen S, Boutsen Y, Bruyere O, Devogelaer JP, Goemaere S, Hollevoet N, Kaufman JM, Milisen K, Rozenberg S, Reginster JY (2011). "Non-pharmacological management of osteoporosis: a consensus of the Belgian Bone Club". *Osteoporos Int*. **22** (11): 2769–88. doi:10.1007/s00198-011-1545-x. PMC 3186889. PMID 21360219.
99. ^ Kasturi GC, Adler RA (2011). "Osteoporosis: nonpharmacologic management". *PM&R*. **3** (6): 562–72. doi:10.1016/j.pmrj.2010.12.014. PMID 21478069.
100. ^ *a b* Whitaker M, Guo J, Kehoe T, Benson G (2012). "Bisphosphonates for osteoporosis — where do we go from here?". *N. Engl. J. Med*. **366** (22): 2048–51. doi:10.1056/NEJMp1202619. PMID 22571168.
101. ^ Suresh E, Pazianas M, Abrahamsen B (Jan 2014). "Safety issues with bisphosphonate therapy for osteoporosis.". *Rheumatology (Oxford, England)*. **53** (1): 19–31. doi:10.1093/rheumatology/ket236. PMID 23838024.
102. ^ *a b* Adler, Robert A; El-Hajj Fuleihan, Ghada; Bauer, Douglas C; Camacho, Pauline M; Clarke, Bart L; Clines, Gregory A; Compston, Juliet E; Drake, Matthew T; Edwards, Beatrice J; Favus, Murray J; Greenspan, Susan L; McKinney, Ross; Pignolo, Robert J; Sellmeyer, Deborah E (January 2016). "Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research". *Journal of Bone and Mineral Research*. **31** (1): 16–35. doi:10.1002/jbmr.2708.
103. ^ Davis S, Sachdeva A, Goeckeritz B, Oliver A (2010). "Approved treatments for osteoporosis and what's in the pipeline". *Drug Benefit Trends*. **22** (4): 121–124.
104. ^ Haguenauer, D; Welch, V; Shea, B; Tugwell, P; Wells, G (2000). "Fluoride for treating postmenopausal osteoporosis.". *The Cochrane database of systematic reviews* (4): CD002825. doi:10.1002/14651858.CD002825. PMID 11034769.
105. ^ Vestergaard, P; Jorgensen, NR; Schwarz, P; Mosekilde, L (March 2008). "Effects of treatment with fluoride on

bone mineral density and fracture risk--a meta-analysis.". *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. **19** (3): 257–68. doi:10.1007/s00198-007-0437-6. PMID 17701094.

106. ^ Han SL, Wan SL (February 2012). "Effect of teriparatide on bone mineral density and fracture in postmenopausal osteoporosis: meta-analysis of randomised controlled trials". *International journal of clinical practice*. **66** (2): 199–209. doi:10.1111/j.1742-1241.2011.02837.x. PMID 22257045.
107. ^ O'Donnell, S.; Cranney, A.; Wells, G. A.; Adachi, J. D.; Reginster, J. Y. (2006-10-18). "Strontium ranelate for preventing and treating postmenopausal osteoporosis". *The Cochrane Database of Systematic Reviews* (4): CD005326. doi:10.1002/14651858.CD005326.pub3. ISSN 1469-493X. PMID 17054253.
108. ^ "Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee" (PDF). FDA. Mar 2013.
109. ^ "Osteoporosis - primary prevention (TA160) : Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women". UK: National Institute for Health and Care Excellence (NICE). January 2011.
110. ^ Cranney A, Jamal SA, Tsang JF, Josse RG, Leslie WD (2007). "Low bone mineral density and fracture burden in postmenopausal women". *CMAJ*. **177** (6): 575–80. doi:10.1503/cmaj.070234. PMC 1963365. PMID 17846439.
111. ^ Hannan EL, Magaziner J, Wang JJ, Eastwood EA, Silberzweig SB, Gilbert M, Morrison RS, McLaughlin MA, Orosz GM, Siu AL (2001). "Mortality and locomotion 6 months after hospitalization for hip fracture: risk factors and risk-adjusted hospital outcomes". *JAMA*. **285** (21): 2736–42. doi:10.1001/jama.285.21.2736. PMID 11386929.
112. ^ Brenneman SK, Barrett-Connor E, Sajjan S, Markson LE, Siris ES (2006). "Impact of recent fracture on health-related quality of life in postmenopausal women". *J. Bone Miner. Res.* **21** (6): 809–16. doi:10.1359/jbmr.060301. PMID 16753011.
113. ^ *a b* Riggs BL, Melton LJ (1995). "The worldwide problem of osteoporosis: insights afforded by epidemiology". *Bone*. **17** (5 Suppl): 505S–511S. doi:10.1016/8756-3282(95)00258-4. PMID 8573428.
114. ^ *a b* "MerckMedicus Modules: Osteoporosis – Epidemiology". Merck & Co., Inc. Archived from the original on 2007-12-28. Retrieved 2008-06-13.
115. ^ Cauley JA, Hochberg MC, Lui LY, Palermo L, Ensrud KE, Hillier TA, Nevitt MC, Cummings SR (2007). "Long-term risk of incident vertebral fractures". *JAMA*. **298** (23): 2761–7. doi:10.1001/jama.298.23.2761. PMID 18165669.
116. ^ International Osteoporosis Foundation. *Epidemiology*.
117. ^ *a b c* "The Global Burden of Osteoporosis | International Osteoporosis Foundation". *www.iofbonehealth.org*. Retrieved 2016-02-09.
118. ^ *a b c* Cauley, Jane A. (2011-03-23). "Defining Ethnic and Racial Differences in Osteoporosis and Fragility Fractures". *Clinical Orthopaedics and Related Research®*. **469** (7): 1891–1899. doi:10.1007/s11999-011-1863-5. ISSN 0009-921X. PMC 3111798. PMID 21431462.
119. ^ *a b* Kanis, J. A.; Odén, A.; McCloskey, E. V.; Johansson, H.; Wahl, D. A.; Cooper, C.; Life, on behalf of the IOF Working Group on Epidemiology and Quality of (2012-03-15). "A systematic review of hip fracture incidence and probability of fracture worldwide". *Osteoporosis International*. **23** (9): 2239–2256. doi:10.1007/s00198-012-1964-3. ISSN 0937-941X. PMC 3421108. PMID 22419370.
120. ^ Herrmann, Markus; Schmidt, Johannes Peter; Umanskaya, Natalia; Wagner, Alexandra; Taban-Shomal, Omid; Widmann, Thomas; Colaianni, Graziana; Wildemann, Britt; Herrmann, Wolfgang (2007). "The role of hyperhomocysteinemia as well as folate, vitamin B6 and B12 deficiencies in osteoporosis – a systematic review". *Clinical Chemical Laboratory Medicine*. **45** (12). doi:10.1515/cclm.2007.362.
121. ^ Gerald N. Grob (2014). *Aging Bones: A Short History of Osteoporosis*. Johns Hopkins UP. p. 5. ISBN 9781421413181.
122. ^ Albright F, Bloomberg E, Smith PH (1940). "Postmenopausal osteoporosis". *Trans. Assoc. Am. Physicians*. **55**: 298–305.
123. ^ Patlak M (2001). "Bone builders: the discoveries behind preventing and treating osteoporosis". *FASEB J.* **15** (10): 1677E–E. doi:10.1096/fj.15.10.1677e. PMID 11481214.
124. ^ Hirata, K.; Morimoto, I. (1994). "Vertebral Osteoporosis in Late Edo Japanese". *Anthropological Science*. **102** (4): 345–361. doi:10.1537/ase.102.345. Retrieved December 18, 2015.

## External links [edit]

- Osteoporosis at DMOZ
- Handout on Health: Osteoporosis - US National Institute of Arthritis and Musculoskeletal and Skin Diseases

- Osteoporosis - NIH Osteoporosis and Related Bone Diseases ~ National Resource Center
- Office of the Surgeon General (2004). *Bone Health and Osteoporosis: A Report of the Surgeon General*. Rockville, MD: U.S. Department of Health and Human Services. PMID 20945569. Retrieved 18 July 2016.


| v · t · e · | **Bone and joint disease (M80–M94, 730–733)** | | |
|---|---|---|---|
| **Bone** | **Inflammation** | *endocrine:* | Osteitis fibrosa cystica (Brown tumor · · |
| | | *infection:* | Osteomyelitis (Sequestrum · Involucrum · · Sesamoiditis · Brodie abscess · Periostitis · Vertebral osteomyelitis · |
| | **Metabolic** | | Bone density · **Osteoporosis** (Juvenile · · Osteopenia · Osteomalacia · Paget's disease of bone · |
| | **Bone resorption** | | Osteolysis · Hajdu-Cheney syndrome · Ainhum · |
| | **Other** | | Ischaemia (Avascular necrosis · Osteonecrosis of the jaw · · Algoneurodystrophy · Hypertrophic pulmonary osteoarthropathy · Nonossifying fibroma · Pseudarthrosis · Stress fracture · Fibrous dysplasia (Monostotic · Polyostotic · · Skeletal fluorosis · *bone cyst* (Aneurysmal bone cyst · · Hyperostosis (Infantile cortical hyperostosis · · Osteosclerosis (Melorheostosis · · Pycnodysostosis · |
| **Joint** | **Chondritis** | | Relapsing polychondritis · |
| | **Other** | | Tietze's syndrome · |
| **Combined** | **Osteochondritis** | | Osteochondritis dissecans · |
| | **Child** | *leg:* | hip (Legg–Calvé–Perthes syndrome · · tibia (Osgood-Schlatter disease · Blount's disease · · foot (Köhler disease · Sever's disease · · |
| | | *spine* | (Scheuermann's disease · · |
| | | *arm:* | wrist (Kienbock's disease · · elbow (Panner disease · · |
| **Authority control** | NDL: 00575859 · | | |

Categories: Aging-associated diseases | Endocrine diseases | Osteopathies

# Plantar fasciitis

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**Plantar fasciitis** is a [disorder] that results in [pain] in the [heel] and bottom of the foot.[1] The pain is usually most severe with the first steps of the day or following a period of rest.[2] Pain is also frequently brought on by [bending the foot and toes up towards the shin] and may be worsened by a tight [Achilles tendon].[2][3] The condition typically comes on slowly.[3] In about a third of people both legs are affected.[1] Typically there are no [fevers] or night sweats.[3]

The causes of plantar fasciitis are not entirely clear. Risk factors include overuse such as from long periods of standing, an increase in [exercise], and [obesity].[1] It is also associated with [inward rolling of the foot] and a lifestyle that involves little exercise.[1][2] While [heel spurs] are frequently found it is unclear if they have a role in causing the condition. Plantar fasciitis is a [disorder of the insertion site of the ligament on the bone] characterized by micro tears, breakdown of collagen, and scarring.[1] As [inflammation] plays a lesser role, many feel the condition should be renamed plantar fasciosis.[1][4] The diagnosis is typically based on signs and symptoms with [ultrasound] sometimes used to help.[1] Other conditions with similar symptoms include [osteoarthritis], [ankylosing spondylitis], [heel pad syndrome], and [reactive arthritis].[5][6]

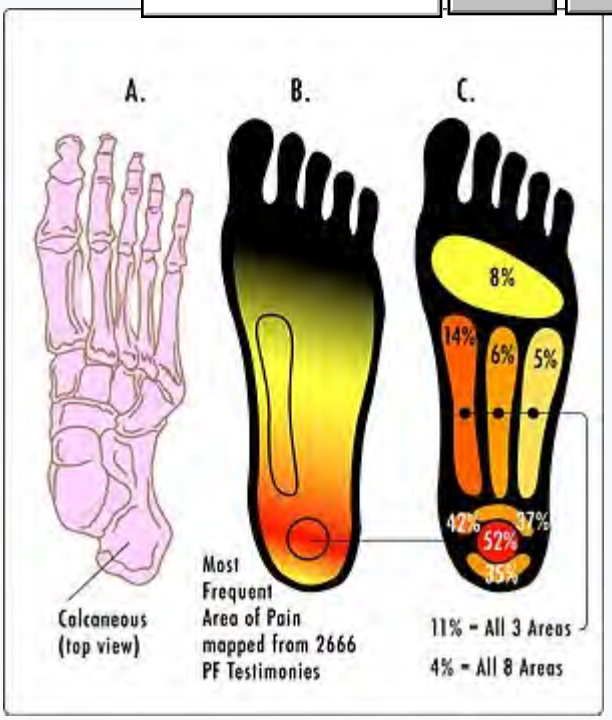
Most cases of plantar fasciitis resolve with time and conservative methods of treatment.[2][7] Usually for the first few weeks people are advised to rest, change their activities, take [pain medications], and stretch. If this is not sufficient [physiotherapy], [orthotics], [splinting], or [steroid injections] may be options. If other measures do not work [extracorporeal shockwave therapy] or surgery may be tried.[2]

Between 4% and 7% of people have heel pain at any given time and about 80% of these cases are due to plantar fasciitis.[1][5] Approximately 10% of people have the disorder at some point during their life.[8] It becomes more common with age. It is unclear if one sex is more affected than the other.[1]

Contents


**Plantar fasciitis**

**Synonyms** plantar fasciosis, plantar fasciopathy, jogger's heel




**Classification and external resources**

| | |
|---|---|
| **Specialty** | Orthopedics, sports medicine, plastic surgery, podiatry |
| **ICD-10** | M72.2 |
| **ICD-9-CM** | 728.71 |
| **DiseasesDB** | 10114 |
| **MedlinePlus** | 007021 |
| **eMedicine** | pmr/107 orthoped/142 |
| **Patient UK** | Plantar fasciitis |
| **MeSH** | D036981 |

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## Signs and symptoms [edit]

When plantar fasciitis occurs, the pain is typically sharp[9] and usually unilateral (70% of cases).[7] Heel pain is worsened by bearing weight on the heel after long periods of rest.[10] Individuals with plantar fasciitis often report their symptoms are most intense during their first steps after getting out of bed or after prolonged periods of sitting.[2] Improvement of symptoms is usually seen with continued walking.[2][6][9] Rare, but reported symptoms include numbness, tingling, swelling, or radiating pain.[11]

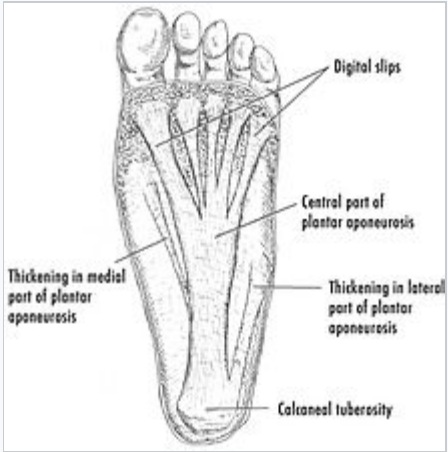
If the plantar fascia continues to be overused in the setting of plantar fasciitis, the plantar fascia can rupture. Typical signs and symptoms of plantar fascia rupture include a clicking or snapping sound, significant local swelling, and acute pain in the sole of the foot.[9]

## Risk factors [edit]

Identified risk factors for plantar fasciitis include excessive running, standing on hard surfaces for prolonged periods of time, high arches of the feet, the presence of a leg length inequality, and flat feet. The tendency of flat feet to excessively roll inward during walking or running makes them more susceptible to plantar fasciitis.[2][10][12] Obesity is seen in 70% of individuals who present with plantar fasciitis and is an independent risk factor.[3] Studies have suggested a strong association exists between an increased body mass index and the development of plantar fasciitis in the non-athletic population; this association between weight and plantar fasciitis has not been observed in the athletic population.[7] Achilles tendon tightness and inappropriate footwear have also been identified as significant risk factors.[13]

## Pathophysiology [edit]

The cause of plantar fasciitis is poorly understood and is thought to likely have several contributing factors.[13] The plantar fascia is a thick fibrous band of connective tissue that originates from the medial tubercle and anterior aspect of the heel bone. From there, the fascia extends along the sole of the foot before inserting at the base of the toes, and supports the arch of the foot.[3][10][12]



Drawing of the plantar fascia of

Originally, plantar fasciitis was believed to be an inflammatory condition of the plantar fascia. However, within the last decade, studies have observed microscopic anatomical changes indicating that plantar fasciitis is actually due to a noninflammatory structural breakdown of the plantar fascia rather than an inflammatory process.[7][13]

Due to this shift in thought about the underlying mechanisms in plantar fasciitis, many in the academic community have stated the condition should be renamed plantar fasciosis.[6] The structural breakdown of the

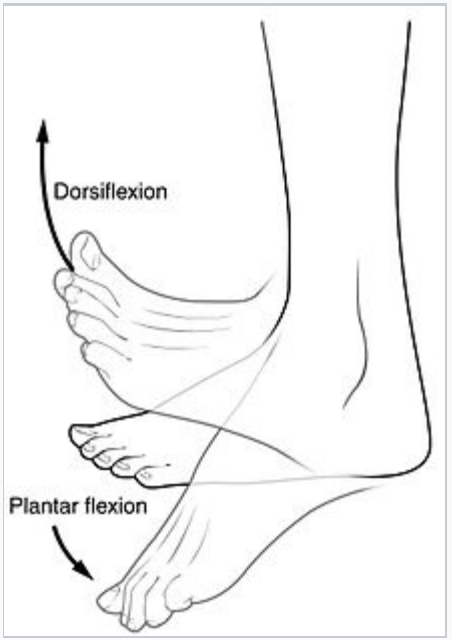
the foot

plantar fascia is believed to be the result of repetitive microtrauma (small tears).[11][12] Microscopic examination of the plantar fascia often shows myxomatous degeneration, connective tissue calcium deposits, and disorganized collagen fibers.[4]

Disruptions in the plantar fascia's normal mechanical movement during standing and walking (known as the Windlass mechanism) are thought to contribute to the development of plantar fasciitis by placing excess strain on the calcaneal tuberosity.[13] Other studies have also suggested that plantar fasciitis is not actually due to inflamed plantar fascia, but may be a tendon injury involving the flexor digitorum brevis muscle located immediately deep to the plantar fascia.[12]

## Diagnosis [edit]

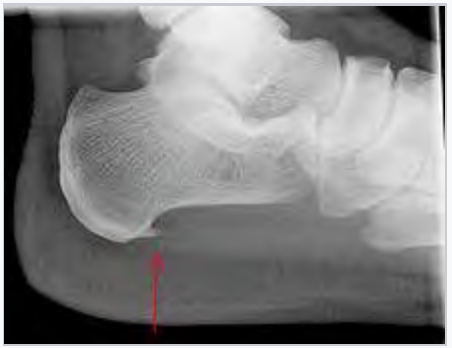
Plantar fasciitis is usually diagnosed by a health care provider after consideration of a person's presenting history, risk factors, and clinical examination.[2][14][15] Tenderness to palpation along the inner aspect of the heel bone on the sole of the foot may be elicited during the physical examination.[2][10] The foot may have limited dorsiflexion due to tightness of the calf muscles or the Achilles tendon.[7] Dorsiflexion of the foot may elicit the pain due to stretching of the plantar fascia with this motion.[2][11] Diagnostic imaging studies are not usually needed to diagnose plantar fasciitis.[7] However, in certain cases a physician may decide imaging studies (such as X-rays, diagnostic ultrasound or MRI) are warranted to rule out serious causes of foot pain.



Achilles tendon tightness is a risk factor for plantar fasciitis. It can lead to decreased dorsiflexion of the foot.

Other diagnoses that are typically considered include fractures, tumors, or systemic disease if plantar fasciitis pain fails to respond appropriately to conservative medical treatments.[2][10] Bilateral heel pain or heel pain in the context of a systemic illness may indicate a need for a more in-depth diagnostic investigation. Diagnostic tests such as a CBC or serological markers of inflammation, infection, or autoimmune disease such as C-reactive protein, erythrocyte sedimentation rate, anti-nuclear antibodies, rheumatoid factor, HLA-B27, uric acid, or Lyme disease antibodies may also be obtained.[5] Neurological deficits may prompt an investigation with electromyography to evaluate for damage to the nerves or muscles.[11]

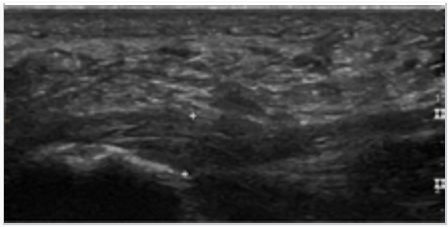
An incidental finding associated with this condition is a heel spur, a small bony calcification on the calcaneus (heel bone), which can be found in up to 50% of those with plantar fasciitis.[6] In such cases, it is the underlying plantar fasciitis that produces the heel pain, and not the spur itself.[12] The condition is responsible for the creation of the spur though the clinical significance of heel spurs in plantar fasciitis remains unclear.[11]


Heel bone with heel spur (red arrow)

### Imaging [edit]

Medical imaging is not routinely needed as it is expensive and does not typically change how plantar fasciitis is managed.[13] When the diagnosis is not clinically apparent, lateral view x-rays of the ankle are the recommended imaging modality to assess for other causes of heel pain such as stress fractures or bone spur development.[7]

Normally the plantar fascia has three fascicles with the central fascicle thickest at 4 mm, the lateral fascicle at 2 mm and the medial at less


Thickened plantar fascia in ultrasound

than a millimeter in thickness.[16] In theory, the likeliness of fasciitis increases with increasing thickness of plantar fascia at the calcaneal insertion, with thickness of more than 4.5 mm being somewhat useful on ultrasound and 4 mm on MRI.[17] Findings on imaging such as plantar aponeurosis thickening, however, may be absent in symptomatic individuals or present in asymptomatic individuals thereby limiting the utility of such observations.[12]

3-phase bone scan is a sensitive modality to detect active plantar fasciitis. Furthermore, 3-phase bone scan can be used to monitor response to therapy, as demonstrated by decreased uptake after corticosteroid injections.[18]

### Differential diagnosis [edit]

The differential diagnosis for heel pain is extensive and includes pathological entities including, but not limited to the following: calcaneal stress fracture, calcaneal bursitis, osteoarthritis, spinal stenosis involving the nerve roots of lumbar spinal nerve 5 (L5) or sacral spinal nerve 1 (S1), calcaneal fat pad syndrome, hypothyroidism, seronegative spondyloparthopathies such as reactive arthritis, ankylosing spondylitis, or rheumatoid arthritis (more likely if pain is present in both heels),[5] plantar fascia rupture, and compression neuropathies such as tarsal tunnel syndrome or impingement of the medial calcaneal nerve.[3][5][7]

A determination about a diagnosis of plantar fasciitis can usually be made based on a person's medical history and physical examination.[19] In cases in which the physician suspects fracture, infection, or some other serious underlying condition, an x-ray may be used to make a differential diagnosis.[19] However, and especially for people who stand or walk a lot at work, x-rays should not be used to screen for plantar fasciitis unless imaging is otherwise indicated as using it outside of medical guidelines is unnecessary health care.[19]

## Treatment [edit]

### Non-surgical [edit]

About 90% of plantar fasciitis cases will improve within six months with conservative treatment,[8] and within a year regardless of treatment.[2][7] Many treatments have been proposed for plantar fasciitis. Most have not been adequately investigated and there is little evidence to support recommendations for such treatments.[2] First-line conservative approaches include rest, heat, ice, and calf-strengthening exercises; techniques to stretch the calf muscles, Achilles tendon, and plantar fascia; weight reduction in the overweight or obese; and nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen.[6][10][20] NSAIDs are commonly used to treat plantar fasciitis, but fail to resolve the pain in 20% of people.[10]

Extracorporeal shockwave therapy (ESWT) is an effective treatment modality for plantar fasciitis pain unresponsive to conservative nonsurgical measures for at least three months. Evidence from meta-analyses suggests significant pain relief lasts up to one year after the procedure.[8][21] However, debate about the therapy's efficacy has persisted.[4] ESWT can be performed with or without anesthesia though studies have suggested that the therapy is less effective when anesthesia is given.[22] Complications from ESWT are rare and typically mild when present.[22] Known complications of ESWT include the development of a mild hematoma or an ecchymosis, redness around the site of the procedure, or migraine.[22]

Corticosteroid injections are sometimes used for cases of plantar fasciitis refractory to more conservative measures. The injections may be an effective modality for short-term pain relief up to one month, but studies failed to show effective pain relief after three months.[4] Notable risks of corticosteroid injections for [3]

plantar fasciitis include plantar fascia rupture, skin infection, nerve or muscle injury, or atrophy of the plantar fat pad.[2][10] Custom orthotic devices have been demonstrated as an effective method to reduce plantar fasciitis pain for up to 12 weeks.[23] The long-term effectiveness of custom orthotics for plantar fasciitis pain reduction requires additional study.[24] Orthotic devices and certain taping techniques are proposed to reduce pronation of the foot and therefore reduce load on the plantar fascia resulting in pain improvement.[12]

Another treatment technique known as plantar iontophoresis involves applying anti-inflammatory substances such as dexamethasone or acetic acid topically to the foot and transmitting these substances through the skin with an electric current.[10] Moderate evidence exists to support the use of night splints for 1–3 months to relieve plantar fasciitis pain that has persisted for six months.[7] The night splints are designed to position and maintain the ankle in a neutral position thereby passively stretching the calf and plantar fascia overnight during sleep.[7] Other treatment approaches may include supportive footwear, arch taping, and physical therapy.[6]

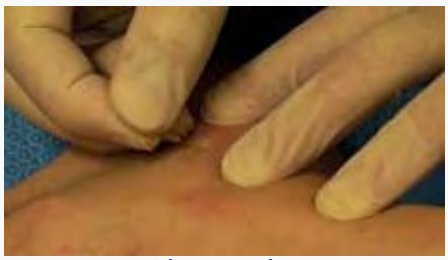
### Surgery [edit]

Plantar fasciotomy is often considered after conservative treatment has failed to resolve the issue after six months and is viewed as a last resort.[2][6] Minimally invasive and endoscopic approaches to plantar fasciotomy exist but require a specialist who is familiar with certain equipment. The availability of these surgical techniques is currently limited.[5] A 2012 study found 76% of patients who underwent endoscopic plantar fasciotomy had complete relief of their symptoms and had few complications (level IV evidence).[4] Heel spur removal during plantar fasciotomy has not been found to improve the surgical outcome.[25] Plantar heel pain may occur for multiple reasons and release of the lateral plantar nerve branch may be performed alongside the plantar fasciotomy in select cases.[5][25] Possible complications of plantar fasciotomy include nerve injury, instability of the medial longitudinal arch of the foot,[26] fracture of the calcaneus, prolonged recovery time, infection, rupture of the plantar fascia, and failure to improve the pain.[2] Coblation surgery has recently been proposed as alternative surgical approaches for the treatment of recalcitrant plantar fasciitis.[25]

### Unproven treatments [edit]

Botulinum Toxin A injections as well as similar techniques such as platelet-rich plasma injections and prolotherapy remain controversial.[4][7][10][27]

Dry needling is also being researched for treatment of plantar fasciitis.[28] A systematic review of available research found limited evidence of effectiveness for this technique.[29] The studies were reported to be inadequate in quality and too diverse in methodology to enable reaching a firm conclusion.[29]



Play media

Dry needling is being researched for treatment of plantar fasciitis

## Epidemiology [edit]

Plantar fasciitis is the most common type of plantar fascia injury[9] and is the most common reason for heel pain, responsible for 80% of cases. The condition tends to occur more often in women, military recruits, older athletes, the obese, and young male athletes.[7][11][12]

Plantar fasciitis is estimated to affect 1 in 10 people at some point during their lifetime and most commonly affects people between 40–60 years of age.[3][4] In the United States alone, more than two million people receive treatment for plantar fasciitis.[3] The cost of treating plantar fasciitis in the United States is estimated to be $284 million each year.[3]

# References [edit]


1. ^ a b c d e f g h i Beeson P (September 2014). "Plantar fasciopathy: revisiting the risk factors". *Foot and Ankle Surgery*. **20** (3): 160–5. doi:10.1016/j.fas.2014.03.003. PMID 25103701.
2. ^ a b c d e f g h i j k l m n o p q Goff JD, Crawford R (September 2011). "Diagnosis and treatment of plantar fasciitis". *Am Fam Physician*. **84** (6): 676–82. PMID 21916393.
3. ^ a b c d e f g h i j Rosenbaum AJ, DiPreta JA, Misener D (March 2014). "Plantar Heel Pain". *Med Clin North Am*. **98** (2): 339–52. doi:10.1016/j.mcna.2013.10.009. PMID 24559879.
4. ^ a b c d e f g Lareau CR, Sawyer GA, Wang JH, DiGiovanni CW (June 2014). "Plantar and Medial Heel Pain: Diagnosis and Management". *The Journal of the American Academy of Orthopaedic Surgeons*. **22** (6): 372–80. doi:10.5435/JAAOS-22-06-372. PMID 24860133.
5. ^ a b c d e f g Cutts S, Obi N, Pasapula C, Chan W (November 2012). "Plantar fasciitis". *Ann R Coll Surg Engl*. **94** (8): 539–42. doi:10.1308/003588412X13171221592456. PMC 3954277. PMID 23131221.
6. ^ a b c d e f g Tu P, Bytomski JR (October 2011). "Diagnosis of heel pain". *Am Fam Physician*. **84** (8): 909–16. PMID 22010770.
7. ^ a b c d e f g h i j k l m Tahririan MA, Motififard M, Tahmasebi MN, Siavashi B (August 2012). "Plantar fasciitis". *J Res Med Sci*. **17** (8): 799–804. PMC 3687890. PMID 23798950.
8. ^ a b c Zhiyun L, Tao J, Zengwu S (July 2013). "Meta-analysis of high-energy extracorporeal shock wave therapy in recalcitrant plantar fasciitis". *Swiss Med Wkly*. **143**: w13825. doi:10.4414/smw.2013.13825. PMID 23832373.
9. ^ a b c d Jeswani T, Morlese J, McNally EG (September 2009). "Getting to the heel of the problem: plantar fascia lesions". *Clin Radiol*. **64** (9): 931–9. doi:10.1016/j.crad.2009.02.020. PMID 19664484.
10. ^ a b c d e f g h i j Molloy LA (November 2012). "Managing chronic plantar fasciitis: when conservative strategies fail". *JAAPA*. **25** (11): 48, 50, 52–53. doi:10.1097/01720610-201211000-00009. PMID 23620924.
11. ^ a b c d e f Monto RR (December 2013). "Platelet-rich plasma and plantar fasciitis". *Sports Med Arthrosc*. **21** (4): 220–4. doi:10.1097/JSA.0b013e318297fa8d. PMID 24212370.
12. ^ a b c d e f g h Orchard J (October 2012). "Plantar fasciitis". *BMJ*. **10** (345): e6603. doi:10.1136/bmj.e6603. PMID 23054045.
17. ^ League, AC (March 2008). "Current concepts review: plantar fasciitis.". *Foot & ankle international*. **29** (3): 358–66. doi:10.3113/fai.2008.0358. PMID 18348838.
18. ^ Pelletier-Galarneau M, Martineau P, Gaudreault M, Pham X (2015). "Review of running injuries of the foot and ankle: clinical presentation and SPECT-CT imaging patterns". *Am J Nucl Med Mol Imaging*. **5** (4): 305–16. PMC 4529586. PMID 26269770.
19. ^ a b c American College of Occupational and Environmental Medicine (February 2014), "Five Things Physicians and Patients Should Question", *Choosing Wisely: an initiative of the ABIM Foundation*, American College of Occupational and Environmental Medicine, retrieved 24 February 2014, which cites
    - Haas, N; Beecher, P; Easly, M; et al. (2011). "Ankle and foot disorders". In Kurt T. Hegmann. *Occupational medicine practice guidelines : evaluation and management of common health problems and functional recovery in workers* (3rd ed.). Elk Grove Village, IL: American College of Occupational and Environmental Medicine. p. 1182. ISBN 978-0615452272.
20. ^ "Plantar Fasciitis and Bone Spurs". American Academy of Orthopaedic Surgeons. 2010. Retrieved 24 June 2014.
21. ^ Aqil A, Siddiqui MR, Solan M, Redfern DJ, Gulati V, Cobb JP (November 2013). "Extracorporeal shock wave therapy is effective in treating chronic plantar fasciitis: a meta-analysis of RCTs". *Clin Orthop Relat Resl*. **471** (11): 3645–52. doi:10.1007/s11999-013-3132-2. PMID 23813184.
22. ^ a b c Wang CJ (March 2012). "Extracorporeal shockwave therapy in musculoskeletal disorders". *J Orthop Surg Res*. **7** (1): 11–8. doi:10.1186/1749-799X-7-11. PMC 3342893. PMID 22433113.
23. ^ Lee SY, McKeon P, Hertel J (February 2009). "Does the use of orthoses improve self-reported pain and function measures in patients with plantar fasciitis? A meta-analysis". *Phys There Sport*. **10** (1): 12–8. doi:10.1016/j.ptsp.2008.09.002. PMID 19218074.
24. ^ Anderson J, Stanek J (May 2013). "Effect of foot orthoses as treatment for plantar fasciitis or heel pain". *J Sport Rehabil*. **22** (2): 130–6. PMID 23037146.
25. ^ a b c Thomas JL, Christensen JC, Kravitz SR, Mendicino RW, Schuberth JM, Vanore JV, Weil LS, Zlotoff HJ, Bouché R, Baker J (May–June 2010). "The diagnosis and treatment of heel pain: a clinical practice guideline-revision 2010". *J Foot Ankle Surg*. **49** (3 Suppl): S1–19. doi:10.1053/j.jfas.2010.01.001. PMID 20439021.
26. ^ Tweed JL, Barnes MR, Allen MJ, Campbell JA (September–October 2009). "Biomechanical

13. ^ *a b c d e* Yin MC, Ye J, Yao M, Cui XJ, Xia Y, Shen QX, Tong ZY, Wu XQ, Ma JM, Mo W (March 2014). "Is Extracorporeal Shock Wave Therapy Clinical Efficacy for Relief of Chronic, Recalcitrant Plantar Fasciitis? A Systematic Review and Meta-Analysis of Randomized Placebo or Active-Treatment Controlled Trials". *Arch Phys Med Rehabil*. **95**: 1585–1593. doi:10.1016/j.apmr.2014.01.033. PMID 24662810.
14. ^ Buchbinder R (May 2004). "Plantar Fasciitis". *New England Journal of Medicine*. **350** (21): 2159–66. doi:10.1056/NEJMcp032745. PMID 15152061.
15. ^ Cole C, Seto C, Gazewood J (December 2005). "Plantar fasciitis: Evidence-based review of diagnosis and therapy". *American Family Physician*. **72** (11): 2237–42. PMID 16342847.
16. ^ Ehrmann, C; Maier, M; Mengiardi, B; Pfirrmann, CW; Sutter, R (September 2014). "Calcaneal attachment of the plantar fascia: MR findings in asymptomatic volunteers.". *Radiology*. **272** (3): 807–14. doi:10.1148/radiol.14131410. PMID 24814176.

consequences of total plantar fasciotomy: a review of the literature". *J Am Podiatr Med Assoc*. **99** (5): 422–30. PMID 19767549.
27. ^ Monto R (April 2014). "Platelet-rich plasma efficacy versus corticosteroid injection treatment for chronic severe plantar fasciitis". *Foot and Ankle International*. **35** (4): 313–318. doi:10.1177/1071100713519778. PMID 24419823.
28. ^ Cotchett MP, Landorf KB, Munteanu SE, Raspovic A (January 2011). "Effectiveness of trigger point dry needling for plantar heel pain: study protocol for a randomised controlled trial". *Journal of Foot and Ankle Research*. **4** (1): 5. doi:10.1186/1757-1146-4-5. PMC 3035595. PMID 21255460.
29. ^ *a b* Cotchett MP, Landorf KB, Munteanu SE (September 2010). "Effectiveness of dry needling and injections of myofascial trigger points associated with plantar heel pain: a systematic review". *Journal of Foot and Ankle Research*. **3** (1): 18. doi:10.1186/1757-1146-3-18. PMC 2942821. PMID 20807448.


## External links [edit]

- "Plantar fasciitis and bone spurs". American Academy of Orthopedic Surgeons.

| v · t · e · **Soft tissue disorders / Rheumatism / Connective tissue arthropathy (M65–M79, 725–728)** | | | |
|---|---|---|---|
| **Capsular joint** | **Synoviopathy** | Synovitis/Tenosynovitis (Calcific tendinitis · Stenosing tenosynovitis · Trigger finger · DeQuervain's syndrome · · Transient synovitis · Ganglion cyst · *osteochondromatosis* (Synovial osteochondromatosis · · Plica syndrome · *villonodular synovitis* (Giant cell tumor of the tendon sheath · · | |
| | **Bursopathy** | Bursitis (Olecranon · Prepatellar · Trochanteric · Subacromial · Achilles · Retrocalcaneal · Ischial · Iliopsoas · · Synovial cyst (Baker's cyst · · Calcific bursitis · | |
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Categories: Inflammations | Disorders of fascia | Overuse injuries | Foot diseases | Soft tissue disorders




# Rheumatoid arthritis

From Wikipedia, the free encyclopedia



**Rheumatoid arthritis** (**RA**) is a long-lasting autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest. Most commonly, the wrist and hands are involved, with the same joints typically involved on both sides of the body. The disease may also affect other parts of the body. This may result in a low red blood cell count, inflammation around the lungs, and inflammation around the heart. Fever and low energy may also be present.[1] Often, symptoms come on gradually over weeks to months.[2]

While the cause of rheumatoid arthritis is not clear, it is believed to involve a combination of genetic and environmental factors. The underlying mechanism involves the body's immune system attacking the joints. This results in inflammation and thickening of the joint capsule. It also affects the underlying bone and cartilage.[1] The diagnosis is made mostly on the basis of a person's signs and symptoms.[2] X-rays and laboratory testing may support a diagnosis or exclude other diseases with similar symptoms.[1] Other diseases that may present similarly include systemic lupus erythematosus, psoriatic arthritis, and fibromyalgia among others.[2]

The goal of treatment is to reduce pain, decrease inflammation, and improve a person's overall functioning. This may be helped by balancing rest and exercise, the use of splints and braces, or the use of assistive devices. Pain medications, steroids, and NSAIDs are frequently used to help with symptoms. A group of medications called disease-modifying antirheumatic drugs (DMARDs) may be used to try to slow the progression of disease. They include the medications hydroxychloroquine and methotrexate.[1] Biological DMARDs may be used when disease does not respond to other treatments.[3] However, they may have a greater rate of adverse effects.[4] Surgery to repair, replace, or fuse joints may help in certain situations.[1] Most alternative medicine treatments are not supported by evidence.[5][6]

RA affects between 0.5 and 1% of adults in the developed world with between 5 and 50 per 100,000 people newly developing the condition each year.[3] Onset is most frequent during middle age and women are affected 2.5 times as frequently as men.[1] In 2013, it resulted in 38,000 deaths up from 28,000 deaths in 1990.[7] The first recognized description of RA was made in 1800 by Dr. Augustin Jacob Landré-Beauvais (1772–1840) of Paris.[8] The term *rheumatoid arthritis* is based on the Greek for watery and inflamed joints.[9]

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Rheumatoid arthritis

A hand affected by rheumatoid arthritis

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| **ICD-10** | M05-M06 |
| **ICD-9-CM** | 714 |
| **OMIM** | 180300 |
| **DiseasesDB** | 11506 |
| **MedlinePlus** | 000431 |
| **eMedicine** | article/331715<br>article/1266195<br>article/305417<br>article/401271<br>article/335186<br>article/808419 |
| **Patient UK** | Rheumatoid arthritis |
| **MeSH** | D001172 |

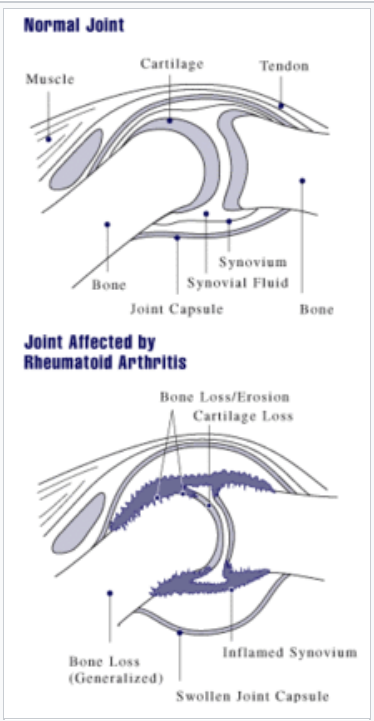
[edit on Wikidata]

## Signs and symptoms [edit]

RA primarily affects joints, but it also affects other organs in more than 15–25% of individuals.[10]

### Joints [edit]

Arthritis of joints involves inflammation of the synovial membrane. Joints become swollen, tender and warm, and stiffness limits their movement. With time, multiple joints are affected (polyarthritis). Most commonly involved are the small joints of the hands, feet and cervical spine, but larger joints like the shoulder and knee can also be involved.[11]:1089 Synovitis can lead to tethering of tissue with loss of movement and erosion of the joint surface causing deformity and loss of function.[2]



A diagram showing how rheumatoid arthritis affects a joint

RA typically manifests with signs of inflammation, with the affected joints being swollen, warm, painful and stiff, particularly early in the morning on waking or following prolonged inactivity. Increased stiffness early in the morning is often a prominent feature of the disease and typically lasts for more than an hour. Gentle movements may relieve symptoms in early stages of the disease. These signs help distinguish rheumatoid from non-inflammatory problems of the joints, often referred to as osteoarthritis. In arthritis of non-inflammatory causes, signs of inflammation and early morning stiffness are less prominent with stiffness typically less than one hour, and movements induce pain caused by mechanical arthritis.[12] The pain associated with RA is induced at the site of inflammation and classified as nociceptive as opposed to neuropathic.[13] The joints are often affected in a fairly symmetrical fashion, although this is not specific, and the initial presentation may be asymmetrical.[11]:1089

As the pathology progresses the inflammatory activity leads to tendon tethering and erosion and destruction of the joint surface, which impairs range of movement and leads to deformity. The fingers may suffer from almost any deformity depending on which joints are most involved. Specific deformities, which also occur in osteoarthritis, include ulnar deviation, boutonniere deformity (also "buttonhole deformity", flexion of proximal interphalangeal joint and extension of distal interphalangeal joint), swan neck deformity (hyperextension at proximal interphalangeal joint and flexion at distal interphalangeal joint) and "Z-thumb." "Z-thumb" or "Z-deformity" consists of hyperextension of the interphalangeal joint, fixed flexion and subluxation of the metacarpophalangeal joint and gives a "Z" appearance to the thumb.[11]:1089 The hammer toe deformity may be seen. In the worst case, joints are known as arthritis mutilans due to the mutilating nature of the deformities.[14] "Spindling of fingers" of hand occurs due to swelling of the PIP but not DIP joints. "Piano key movement" of the ulnar styloid occurs due to inflammation around the ulnar styloid and tenosynovitis of extensor carpi ulnaris.[*citation needed*]

### Skin [edit]

The rheumatoid nodule, which is sometimes in the skin, is the most common non joint feature.[15] They occur in 30% of people.[15] It is a type of inflammatory reaction known to pathologists as a "necrotizing granuloma". The initial pathologic process in nodule formation is unknown but may be essentially the same as the synovitis, since similar structural features occur in both. The nodule has a central area of fibrinoid necrosis that may be fissured and which corresponds to the fibrin-rich necrotic material found in and around an affected synovial space. Surrounding the necrosis is a layer of palisading macrophages and fibroblasts, corresponding to the intimal layer in synovium and a cuff of connective tissue containing clusters of lymphocytes and plasma cells, corresponding to the subintimal zone in synovitis. The typical rheumatoid nodule may be a few millimetres to a few centimetres in diameter and is usually found over bony prominences, such as the elbow, the heel, the knuckles, or other areas that sustain repeated mechanical stress. Nodules are associated with a positive RF (rheumatoid factor) titer and severe erosive arthritis. Rarely, these can occur in internal organs or at diverse sites on the body.[*citation needed*]

Several forms of *vasculitis* occur in RA. A benign form occurs as microinfarcts around the nailfolds. More severe forms include livedo reticularis, which is a network (reticulum) of erythematous to purplish discoloration of the skin caused by the presence of an obliterative cutaneous capillaropathy.[*citation needed*].

Other, rather rare, skin associated symptoms include pyoderma gangrenosum, Sweet's syndrome, drug reactions, erythema nodosum, lobe panniculitis, atrophy of finger skin, palmar erythema, diffuse thinning (rice paper skin), and skin fragility (often worsened by corticosteroid use).[*citation needed*].

## Lungs [edit]

Fibrosis of the lungs is a recognized response to rheumatoid disease. It is also a rare but well-recognized consequence of therapy (for example with methotrexate and leflunomide). Caplan's syndrome describes lung nodules in individuals with RA and additional exposure to coal dust. Pleural effusions are also associated with RA. Another complication of RA is Rheumatoid Lung Disease. It is estimated that about one-quarter of Americans with RA develop Rheumatoid Lung Disease.[16]

## Kidneys [edit]

Renal amyloidosis can occur as a consequence of chronic inflammation.[17] RA may affect the kidney glomerulus directly through a vasculopathy or a mesangial infiltrate but this is less well documented (though this is not surprising, considering immune complex-mediated hypersensitivities are known for pathogenic deposition of immune complexes in organs where blood is filtered at high pressure to form other fluids, such as urine and synovial fluid[18]). Treatment with penicillamine and gold salts are recognized causes of membranous nephropathy.

## Heart and blood vessels [edit]

People with RA are more prone to atherosclerosis, and risk of myocardial infarction (heart attack) and stroke is markedly increased.[19][20] Other possible complications that may arise include: pericarditis, endocarditis, left ventricular failure, valvulitis and fibrosis.[21] Many people with RA do not experience the same chest pain that others feel when they have angina or myocardial infarction. To reduce cardiovascular risk, it is crucial to maintain optimal control of the inflammation caused by RA (which may be involved in causing the cardiovascular risk), and to use exercise and medications appropriately to reduce other cardiovascular risk factors such as blood lipids and blood pressure. Doctors who treat people with RA should be sensitive to cardiovascular risk when prescribing anti-inflammatory medications, and may want to consider prescribing routine use of low doses of aspirin if the gastrointestinal effects are tolerable.[21]

## Other [edit]

**Eyes**

The eye can be directly affected in the form of episcleritis or scleritis. Scleritis when severe can very rarely progress to perforating scleromalacia. Rather more common is the indirect effect of keratoconjunctivitis sicca, which is a dryness of eyes and mouth caused by lymphocyte infiltration of lacrimal and salivary glands. When severe, dryness of the cornea can lead to keratitis and loss of vision. Preventive treatment of severe dryness with measures such as nasolacrimal duct blockage is important.

**Liver**

Liver problems in people with rheumatoid arthritis may be due to the underlying disease process or as a result of the medications used to treat the disease.[22] A coexisting autoimmune liver disease, such as primary biliary cirrhosis or autoimmune hepatitis may also cause problems.[22]

**Blood**

Anemia is by far the most common abnormality of the blood cells which can be caused by a variety of mechanisms. The chronic inflammation caused by RA leads to raised hepcidin levels, leading to anemia of chronic disease where iron is poorly absorbed and also sequestered into macrophages. RA may also cause a warm autoimmune hemolytic anemia.[23] The red cells are of normal size and color (normocytic and normochromic). A low white blood cell count usually only occurs in people with Felty's syndrome with an enlarged liver and spleen. The mechanism of neutropenia is complex. An increased platelet count occurs when inflammation is uncontrolled.

**Neurological**

Peripheral neuropathy and mononeuritis multiplex may occur. The most common problem is carpal tunnel syndrome caused by compression of the median nerve by swelling around the wrist. Atlanto-axial subluxation can occur, owing to erosion of the odontoid process and/or transverse ligaments in the cervical spine's connection to the skull. Such an erosion (>3mm) can give rise to vertebrae slipping over one another and compressing the spinal cord. Clumsiness is initially experienced, but without due care, this can progress to quadriplegia.

**Constitutional symptoms**

Constitutional symptoms including fatigue, low grade fever, malaise, morning stiffness, loss of appetite and loss of weight are common systemic manifestations seen in people with active RA.

**Bones**

Local osteoporosis occurs in RA around inflamed joints. It is postulated to be partially caused by inflammatory cytokines. More general osteoporosis is probably contributed to by immobility, systemic cytokine effects, local cytokine release in bone marrow

and corticosteroid therapy.

**Cancer**

The incidence of lymphoma is increased in RA, although it is uncommon.[24][25]

## Causes [edit]

RA is a chronic autoimmune disorder the causes of which are not completely understood. It is a systemic (whole body) disorder principally affecting synovial tissues. There is no evidence that physical and emotional effects or stress could be a trigger for the disease. The many negative findings suggest that either the trigger varies, or that it might, in fact, be a chance event inherent with the immune response.[26]

Half of the risk for RA is believed to be genetic.[3] It is strongly associated with the inherited tissue type major histocompatibility complex (MHC) antigen HLA-DRB1 (most specifically the shared epitope alleles, including *0401 and born 0404), and the genes PTPN22 and PADI4—hence family history is an important risk factor.[27][28] Inheriting the PTPN22 gene has been shown to double a person's susceptibility to RA. PADI4 has been identified as a major risk factor in people of Asian descent, but not in those of European descent.[29] First-degree relatives prevalence rate is 2–3% and disease genetic concordance in monozygotic twins is approximately 15–20%.[30][31]

Smoking is the most significant non-genetic risk[3] with RA being up to three times more common in smokers than non-smokers, particularly in men, heavy smokers, and those who are rheumatoid factor positive.[32] Modest alcohol consumption may be protective.[33]

Epidemiological studies have confirmed a potential association between RA and two herpesvirus infections: Epstein-Barr virus (EBV) and Human Herpes Virus 6 (HHV-6).[34] Individuals with RA are more likely to exhibit an abnormal immune response to EBV and have high levels of anti-EBV antibodies.[35]

Vitamin D deficiency is more common in people with rheumatoid arthritis than in the general population.[36][37] However, whether vitamin D deficiency is a cause or a consequence of the disease remains unclear.[38] 1α,25-dihydroxyvitamin D3 (1,25D), an active metabolite of vitamin D, affects bone metabolism indirectly through control of calcium and phosphate homeostasis. Interaction between 1,25D and the vitamin D receptor (VDR) affects the production of RANKL and delays osteoclastogenesis.[39] Some trials have found a decreased risk for RA with vitamin D supplementation while others have not.[37]

## Pathophysiology [edit]

Both genetic, as well as environmental factors, are implicated in the pathophysiology of the disease. Smoking is the main environmental risk to RA.[3] 50% of the risk of having RA is attributable to genetic factors.[3] No infectious agent has been consistently linked with RA and there is no evidence of disease clustering to indicate its infectious etiology.[40] HLA-DR4 is the major genetic factor implicated – but its relative importance varies across ethnic groups.[40][41] Related allotypes of MHC Class II and the T cell-associated protein PTPN22 has also been found associated in many studies.[41]

RA primarily starts as a state of persistent cellular activation leading to autoimmunity and immune complexes in both joints and other, organs where it manifests. The initial site of disease is the synovial membrane, where swelling and congestion leads to infiltration by immune cells. The various phases of progression of RA are:[14]

- Initiation phase, due to non-specific inflammation.
- Amplification phase, due to T cell activation
- Chronic inflammatory phase with tissue injury, due to cytokines IL–1, TNF-alpha and IL–6.

The factors that allow an abnormal immune response, once initiated, to become permanent and chronic, are becoming more clearly understood. The genetic association with HLA-DR4, as well as the newly discovered associations with the gene PTPN22 and with two additional genes,[41] all implicate altered thresholds in regulation of the adaptive immune response. It has also become clear from recent studies that these genetic factors may interact with the most clearly defined environmental risk factor for RA, namely cigarette smoking.[32][42] Other environmental factors also appear to modulate the risk of acquiring RA, and hormonal factors in the individual may explain some features of the disease, such as the higher occurrence in women, the not-infrequent onset after childbirth, and the (slight) modulation of disease risk by hormonal medications. Exactly how altered regulatory thresholds allow the triggering of a specific autoimmune response remains uncertain. However, one possibility is that negative feedback mechanisms that normally maintain tolerance of self are overtaken by aberrant positive feedback mechanisms for certain antigens such as IgG Fc (bound by RF) and citrullinated fibrinogen (bound by ACPA) (see the entry on autoimmunity).The debate on the relative roles of immune complexes and T cell products in inflammation in RA has continued for 30 years. There is little doubt that both B and T cells are essential to the disease. However, there is good evidence for neither cell being necessary at the site of inflammation. This tends to favor immune complexes (based on antibody synthesized elsewhere) as the initiators, even if not the sole perpetuators of inflammation.[*citation needed*] The presence of autoantibodies to IgGFc, known as rheumatoid factors (RF), and antibodies to citrullinated peptides (ACPA) is an integral part of RA disease process. As is the case with many other autoimmune diseases, people with RA have abnormally glycosylated antibodies.[43] It is believed that these glycan (oligosaccharide) alterations promote joint inflammation.[43]

Once the abnormal immune response has become established (which may take several years before any symptoms occur), plasma cells derived from B lymphocytes produce rheumatoid factors and ACPA of the IgG and IgM classes in large quantities. These are not deposited in the way that they are in systemic lupus. Rather, they activate macrophages through Fc receptor and complement binding, which seems to play an important role in the intense inflammatory response present in RA.[44] Binding of an autoreactive antibody to the Fc receptors is mediated through the antibody's N-glycans, which are altered to promote inflammation in people with RA.[43] This contributes to inflammation of the synovium, in terms of edema, vasodilation and infiltration by activated T-cells (mainly CD4 in nodular aggregates and CD8 in diffuse infiltrates). Synovial macrophages and dendritic cells further function as antigen presenting cells by expressing MHC class II molecules, leading to an established local immune reaction in the tissue. The disease progresses in concert with the formation of granulation tissue at the edges of the synovial lining (pannus) with extensive angiogenesis and production of enzymes that cause tissue damage. Modern pharmacological treatments of RA target these mediators. Once the inflammatory reaction is established, the synovium thickens, the cartilage and the underlying bone begins to disintegrate and evidence of joint destruction accrues.

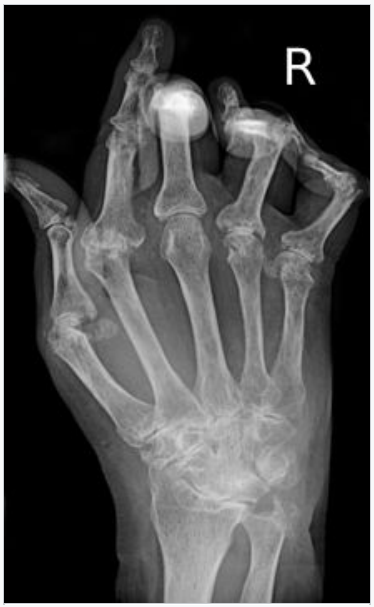
TNF (alpha) plays a major role in the pathogenesis of RA. There are several theories on how TNF release happens in disease process. If TNF release is stimulated by B cell products in the form of RF or ACPA -containing immune complexes, through activation of immunoglobulin Fc receptors, then RA can be seen as a form of Type III hypersensitivity.[45][46] If TNF release is stimulated by T cell products such as interleukin-17 it might be considered closer to type IV hypersensitivity although this terminology may be getting somewhat dated and unhelpful.[47]

Although TNF appears to be the dominant, other cytokines (chemical mediators) are likely to be involved in inflammation in RA. Blockade of TNF does not benefit all persons or all tissues (lung disease and nodules may get worse). Blockade of IL-1, IL-15 and IL-6 also have beneficial effects and IL-17 may be important.[*citation needed*] Constitutional symptoms such as fever, malaise, loss of appetite and weight loss are also caused by cytokines released into the blood stream. As with most autoimmune diseases, it is important to distinguish between the cause(s) that trigger the process and those that may permit it to persist and progress.[*citation needed*]

## Diagnosis [edit]

### Imaging [edit]

X-rays of the hands and feet are generally performed in people with many joints affected. In RA, there may be no changes in the early stages of the disease or the x-ray may demonstrate juxta-articular osteopenia, soft tissue swelling, and loss of joint space. As the disease advances, there may be bony erosions and subluxation. X-rays of other joints may be taken if symptoms of pain or swelling occur in those joints.



X-ray of the hand in rheumatoid arthritis.

Other medical imaging techniques such as magnetic resonance imaging (MRI) and ultrasound are also used in RA.[14]

There have been technical advances in ultrasonography. High-frequency transducers (10 MHz or higher) have improved the spatial resolution of ultrasound images; these images can depict 20% more erosions than conventional radiography. Also, color Doppler and power Doppler ultrasound, which show vascular signals of active synovitis depending on the degree of inflammation, are useful in assessing synovial inflammation. This is important, since in the early stages of RA, the synovium is primarily affected, and synovitis seems to be the best predictive marker of future joint damage.[48]

### Blood tests [edit]

When RA is clinically suspected, testing for the presence of rheumatoid factor (RF, a non-specific antibody) and (ACPAs) may be required.[49] A negative RF does not rule out RA; rather, the arthritis is called *seronegative*. This is the case in about 15% of people with RA.[50][51] During the first year of illness, rheumatoid factor is more likely to be negative with some individuals converting to seropositive status over time. RF is also seen in other illnesses, for example Sjögren's syndrome, hepatitis C, systemic lupus erythematosus, chronic infections and in approximately 10% of the healthy population, therefore the test is not very specific.[14]

Because of this low specificity, new serological tests have been developed, which test for the presence of the anti-citrullinated protein antibodies (ACPAs) or anti-CCP. Like RF, these tests are positive in only a proportion (67%) of all RA cases, but are rarely positive if RA is not present, giving it a specificity of around 95%.[50] As with RF, there is evidence for ACPAs being present in many cases even before onset of clinical disease.[14]

The most common tests for ACPAs are the anti-CCP (cyclic citrullinated peptide) test and the Anti-MCV assay (antibodies against mutated citrullinated Vimentin). Recently a serological point-of-care test (POCT) for the early detection of RA has been developed. This assay combines the detection of rheumatoid factor and anti-MCV for diagnosis of RA and shows a sensitivity of 72% and specificity of 99.7%.[52][53]

Appearance of synovial fluid from a joint with inflammatory arthritis.

Also, several other blood tests are usually done to allow for other causes of arthritis, such as lupus erythematosus. The erythrocyte sedimentation rate (ESR), C-reactive protein, full blood count, kidney function, liver enzymes and other immunological tests (e.g., antinuclear antibody/ANA) are all performed at this stage. Elevated ferritin levels can reveal hemochromatosis, a mimic of RA, or be a sign of Still's disease, a seronegative, usually juvenile, variant of rheumatoid arthritis.[*citation needed*]

## Classification Criteria [edit]

In 2010 the *2010 ACR / EULAR Rheumatoid Arthritis Classification Criteria* were introduced.[54][55] The new criterion is not a diagnostic criterion but a classification criterion to identify disease with a high likelihood of developing a chronic form.[14] However a score of 6 or greater unequivocally classifies a person with a diagnosis of rheumatoid arthritis.

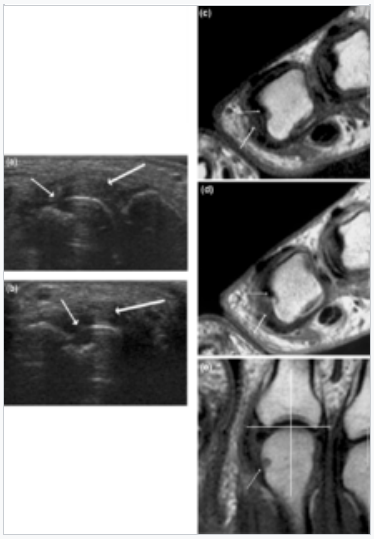
These new classification criteria overruled the "old" ACR criteria of 1987 and are adapted for early RA diagnosis. The "new" classification criteria, jointly published by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) establish a point value between 0 and 10. Four areas are covered in the diagnosis:[54]

- joint involvement, designating the metacarpophalangeal joints, proximal interphalangeal joints, the interphalangeal joint of the thumb, second through fifth metatarsophalangeal joint and wrist as *small joints*, and shoulders, elbows, hip joints, knees, and ankles as *large joints*:
  - Involvement of 1 large joint gives 0 points
  - Involvement of 2–10 large joints gives 1 point
  - Involvement of 1–3 small joints (with or without involvement of large joints) gives 2 points
  - Involvement of 4–10 small joints (with or without involvement of large joints) gives 3 points
  - Involvement of more than 10 joints (with involvement of at least 1 small joint) gives 5 points
- serological parameters – including the rheumatoid factor as well as ACPA – "ACPA" stands for "anti-citrullinated protein antibody":
  - Negative RF *and* negative ACPA gives 0 points
  - Low-positive RF *or* low-positive ACPA gives 2 points
  - High-positive RF *or* high-positive ACPA gives 3 points
- acute phase reactants: 1 point for elevated erythrocyte sedimentation rate, ESR, or elevated CRP value (c-reactive protein)
- duration of arthritis: 1 point for symptoms lasting six weeks or longer

The new criteria accommodate to the growing understanding of RA and the improvements in diagnosing RA and disease treatment. In the "new" criteria serology and autoimmune diagnostics carries major weight, as ACPA detection is appropriate to diagnose the disease in an early state, before joints destructions occur. Destruction of the joints viewed in radiological images was a significant point of the ACR criteria from 1987.[56] This criterion no longer is regarded to be relevant, as this is just the type of damage that treatment is meant to avoid.

In clinical practice, the following criteria apply:[*citation needed*]

- two or more swollen joints
- morning stiffness lasting more than one hour for at least six weeks
- the detection of rheumatoid factors or autoantibodies against ACPA such as autoantibodies to mutated citrullinated vimentin can confirm the suspicion of RA. A negative autoantibody result does not exclude a diagnosis of RA.



Signs of destruction and inflammation on ultrasonography and magnetic resonance imaging in the second metacarpophalangeal joint in established RA. Thin arrows indicate an erosive change; thick arrows indicate synovitis. Ultrasonography (left side of image) in the (a) longitudinal and (b) the transverse planes shows both signs of destruction and inflammation. Axial T1-weighted magnetic resonance images were obtained (c) before and (d) after contrast administration, also demonstrating synovitis. Additionally, a coronal T1-weighted magnetic resonance image (e) before contrast administration visualizes the same bone erosion as shown in panels c and d.

## Differential diagnoses [edit]

Several other medical conditions can resemble RA, and usually need to be distinguished from it [57][58]

at the time of diagnosis:

- Crystal induced arthritis (gout, and pseudogout) – usually involves particular joints (knee, MTP1, heels) and can be distinguished with an aspiration of joint fluid if in doubt. Redness, asymmetric distribution of affected joints, pain occurs at night and the starting pain is less than an hour with gout.
- Osteoarthritis – distinguished with X-rays of the affected joints and blood tests, age (mostly older persons), starting pain less than an hour, asymmetric distribution of affected joints and pain worsens when using joint for longer periods.
- Systemic lupus erythematosus (SLE) – distinguished by specific clinical symptoms and blood tests (antibodies against double-stranded DNA)
- One of the several types of psoriatic arthritis resembles RA – nail changes and skin symptoms distinguish between them
- Lyme disease causes erosive arthritis and may closely resemble RA – it may be distinguished by blood test in endemic areas
- Reactive arthritis (previously Reiter's disease) – asymmetrically involves heel, sacroiliac joints and large joints of the leg. It is usually associated with urethritis, conjunctivitis, iritis, painless buccal ulcers, and keratoderma blennorrhagica.
- Ankylosing spondylitis – this involves the spine, although an RA-like symmetrical small-joint polyarthritis may occur in the context of this condition.
- Hepatitis C – RA-like symmetrical small-joint polyarthritis may occur in the context of this condition. Hepatitis C may also induce Rheumatoid Factor auto-antibodies

Rarer causes that usually behave differently but may cause joint pains:[57]

- Sarcoidosis, amyloidosis, and Whipple's disease can also resemble RA.
- Hemochromatosis may cause hand joint arthritis.
- Acute rheumatic fever can be differentiated from RA by a migratory pattern of joint involvement and evidence of antecedent streptococcal infection. Bacterial arthritis (such as by *Streptococcus*) is usually asymmetric, while RA usually involves both sides of the body symmetrically.
- Gonococcal arthritis (another bacterial arthritis) is also initially migratory and can involve tendons around the wrists and ankles.

### Monitoring progression [edit]

There are many tools available for monitoring remission in rheumatoid arthritis.

**DAS28**

*Disease Activity Score of 28 joints* (DAS28) is widely used as an indicator of RA disease activity and response to treatment, but is not always a reliable indicator of treatment effect.[59] The joints included in DAS28 are (bilaterally): proximal interphalangeal joints (10 joints), metacarpophalangeal joints (10), wrists (2), elbows (2), shoulders (2) and knees (2). When looking at these joints, both the number of joints with tenderness upon touching (TEN28) and swelling (SW28) are counted. In addition, the erythrocyte sedimentation rate (ESR) is measured. Also, the affected person makes a subjective assessment (SA) of disease activity during the preceding 7 days on a scale between 0 and 100, where 0 is "no activity" and 100 is "highest activity possible". With these parameters, DAS28 is calculated as:[60]

From this, the disease activity of the affected person can be classified as follows:[60]

| Current DAS28 | | DAS28 decrease from initial value | | |
|---|---|---|---|---|
| | | > 1.2 | > 0.6 but ≤ 1.2 | ≤ 0.6 |
| ≤ 3.2 | Inactive | Good improvement | Moderate improvement | No improvement |
| > 3.2 but ≤ 5.1 | Moderate | Moderate improvement | Moderate improvement | No improvement |
| > 5.1 | Very active | Moderate improvement | No improvement | No improvement |

One major limitation of use of the DAS28 score in clinical setting is low-grade synovitis may be missed.[*citation needed*]

**Other**

Other tools to monitor remission in rheumatoid arthritis are: ACR-EULAR Provisional Definition of Remission of Rheumatoid arthritis, Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI).[61]

## Prevention [edit]

There is no known prevention for the condition other than the reduction of risk factors.[62]

## Management [edit]

There is no cure for RA, but treatments can improve symptoms and slow the progress of the disease. Disease-modifying treatment has the best results when it is started early and aggressively.[63]

The goals of treatment are to minimize symptoms such as pain and swelling, to prevent bone deformity (for example, bone erosions visible in X-rays), and to maintain day-to-day functioning.[64] This can often be achieved using two main classes of

medications: analgesics such as NSAIDs, and disease-modifying antirheumatic drugs (DMARDs).[65] RA should generally be treated with at least one specific anti-rheumatic medication.[63] The use of benzodiazepines (such as diazepam) to treat the pain is not recommended as it does not appear to help and is associated with risks.[66] Analgesics, other than NSAIDs, offer lesser, but some benefit with respect to pain whilst not causing the same level of gastrointestinal irritation.[3]

## Lifestyle [edit]

Regular exercise is recommended as both safe and useful to maintain muscles strength and overall physical function.[67] It is uncertain if specific dietary measures have an effect.[68] Physical activity is beneficial for persons with Rheumatoid arthritis complaining of fatigue.[69] Occupational therapy has a positive role to play in improving functional ability of persons with rheumatoid arthritis.[70]

## Disease modifying agents [edit]

Disease-modifying antirheumatic drugs (DMARDs) are the primary treatment for RA.[3] They are a diverse collection of drugs, grouped by use and convention. They have been found to improve symptoms, decrease joint damage, and improve overall functional abilities.[3] DMARDs should be started early in the disease as they result in disease remission in approximately half of people and improved outcomes overall.[71] The following drugs are considered as DMARDs: methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, TNF-alpha inhibitors (certolizumab, infliximab and etanercept), abatacept, and anakinra. Rituximab and tocilizumab are monoclonal antibodies and are also DMARDs.

The most commonly used agent is methotrexate with other frequently used agents including sulfasalazine and leflunomide. Sodium aurothiomalate (gold) and cyclosporin are less commonly used due to more common adverse effects. Agents may be used in combinations.[3] Methotrexate is the most important and useful DMARD and is usually the first treatment.[64][65][72] Adverse effects should be monitored regularly with toxicity including gastrointestinal, hematologic, pulmonary, and hepatic.[72] Side effects such as nausea, vomiting or abdominal pain can be reduced by taking folic acid.[73] The most common undesirable effect is that it increases liver enzymes in almost 15% of people.[72] It is thus recommended that those who consistently demonstrate abnormal levels of liver enzymes or have a history of liver disease or alcohol use undergo liver biopsies.[74]

Biological agents should generally only be used if methotrexate and other conventional agents are not effective after a trial of three months.[75] They are associated with a higher rate of serious infections as compared to other DMARDs.[76] These agents used to treat rheumatoid arthritis include: tumor necrosis factor alpha (TNFα) blockers[3] such as infliximab; interleukin 1 blockers such as anakinra, monoclonal antibodies against B cells such as rituximab and tocilizumab,[77] T cell costimulation blocker such as abatacept among others. They are often used in combination with either methotrexate or leflunomide.[3] In those who are well controlled on TNF blockers decreasing the dose does not appear to affect overall function.[78] Persons should be screened for latent tuberculosis before starting any TNF blockers therapy to avoid reactivation.[14]

TNF blockers and methotrexate appear to have similar effectiveness when used alone and better results are obtained when used together. TNF blockers appear to have equivalent effectiveness with etanercept appearing to be the safest.[79] Abatacept appears effective for RA with 20% more people improving with treatment than without but long term safety studies are yet unavailable.[80] However, there is a lack of evidence to distinguish between the biologics available for RA.[81] Issues with the biologics include their high cost and association with infections including tuberculosis.[3]

## Anti-inflammatory agents [edit]

NSAIDs reduce both pain and stiffness in those with RA.[3] Generally they appear to have no effect on people's long term disease course and thus are no longer first line agents.[3][82] NSAIDs should be used with caution in those with gastrointestinal, cardiovascular, or kidney problems.[83][84][85] Use of methotrexate together with NSAIDS is safe, if adequate monitoring is done.[86]

COX-2 inhibitors, such as celecoxib, and NSAIDs are equally effective.[87] They have a similar gastrointestinal risk as an NSAIDs plus a proton pump inhibitor.[88] In the elderly there is less gastrointestinal intolerance to celecoxib than to NSAIDs alone.[89] There however is an increased risk of myocardial infarction with COX-2 inhibitors.[87] Anti-ulcer medications are not recommended routinely but only in those high risk of gastrointestinal problems.[90]

Glucocorticoids can be used in the short term for flare-ups, while waiting for slow-onset drugs to take effect.[3] Injection of glucocorticoids into individual joints is also effective.[3] While long-term use reduces joint damage it also results in osteoporosis and susceptibility to infections, and thus is not recommended.[3]

## Surgery [edit]

In early phases of the disease, an arthroscopic or open synovectomy may be performed. It consists of the removal of the inflamed synovia and prevents a quick destruction of the affected joints. Severely affected joints may require joint replacement surgery, such as knee replacement.[3] Postoperatively, physiotherapy is always necessary.

## Alternative medicine [edit]

In general, there is not enough evidence to support any complementary health approaches for RA, with safety concerns for some of them. Some mind and body practices and dietary supplements may help people with symptoms and therefore may be beneficial additions to conventional treatments, but there is not enough evidence to draw conclusions.[6] A systematic review of CAM modalities (excluding fish oil) found that " The available evidence does not support their current use in the management of RA.".[91] Studies showing beneficial effects in RA on a wide variety of CAM modalities are often affected by publication bias and are generally not high quality evidence such as randomized controlled trials (RCTs).[5]

A 2005 Cochrane review states that low level laser therapy can be tried to improve pain and morning stiffness due to rheumatoid arthritis as there are few side-effects.[92]

There is some evidence that Tai Chi improves the range of motion of a joint in persons with rheumatoid arthritis.[93] The evidence for acupuncture is inconclusive[94] with it appearing to be equivalent to sham acupuncture.[95]

## Dietary supplements [edit]

### Omega-3

Some evidence supports omega-3 fatty acids and gamma-linolenic acid in RA.[96] The benefit from omega-3 appears modest but consistent,[97] though the current evidence is not strong enough to determine that supplementation with omega-3 polyunsaturated fatty acids (found in fish oil) is an effective treatment for RA.[98] Gamma-linolenic acid, which may reduce pain, tender joint count and stiffness, is generally safe.[99]

### Herbal

The American College of Rheumatology states that no herbal medicines have health claims supported by high-quality evidence and thus they do not recommend their use.[100] There is no scientific basis to suggest that herbal supplements advertised as "natural" are safer for use than conventional medications as both are chemicals. Herbal medications, although labelled "natural", may be toxic or fatal if consumed.[100]

Due to the false belief that herbal supplements are always safe, there is sometimes a hesitancy to report their use which may increase the risk of adverse reaction.[5]

The following are under investigation for treatments for RA, based on preliminary promising results (not recommended for clinical use yet): boswellic acid,[101] curcumin,[102] devil's claw,[103][104] Euonymus alatus,[105] and thunder god vine (*Tripterygium wilfordii*).[106] NCCIH has noted that, "In particular, the herb thunder god vine (Tripterygium wilfordii) can have serious side effects."[6]

There is conflicting evidence on the role of erythropoiesis-stimulating agents for treatment of anemia in persons with rheumatoid arthritis.[107]

## Pregnancy [edit]

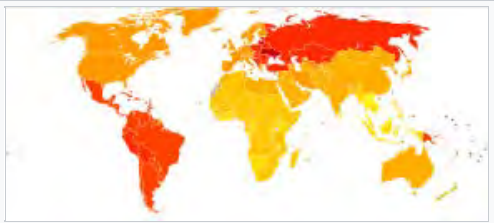
More than 75% of people with rheumatoid arthritis have symptoms improve during pregnancy but might have worsenings after delivery.[14] Methotrexate and leflunomide are teratogenic (harmful to foetus) and not used in pregnancy. It is recommended women of childbearing age should use contraceptives to avoid pregnancy and to discontinue its use if pregnancy is planned.[64][72] Low dose of prednisolone, hydroxychloroquine and sulfasalazine are considered safe in pregnant persons with rheumatoid arthritis.

## Vaccinations [edit]

People with RA have an increased risk of infections and mortality and recommended vaccinations can reduce these risks.[108] The inactivated influenza vaccine should be received annually.[109] The pneumococcal vaccine should be administered twice for people under the age 65 and once for those over 65.[110] Lastly, the live-attenuated zoster vaccine should be administered once after the age 60, but is not recommended in people on a tumor necrosis factor alpha blocker.[111]

# Prognosis [edit]

The course of the disease varies greatly. Some people have mild short-term symptoms, but in most the disease is progressive for life. Around 20%–30% will have subcutaneous nodules (known as rheumatoid nodules); this is associated with a poor prognosis.[*citation needed*]



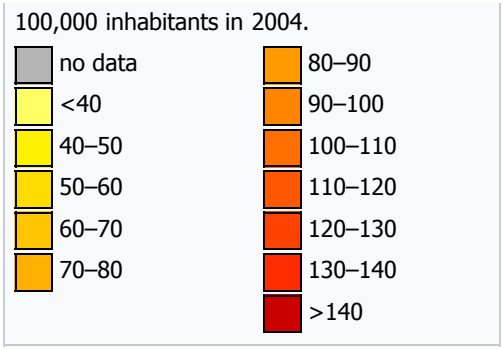
Disability-adjusted life year for RA per [112]

## Prognostic factors [edit]

Poor prognostic factors include,

- Persistent synovitis

Early erosive disease
- Extra-articular findings (including subcutaneous rheumatoid nodules)
- Positive serum RF findings
- Positive serum anti-CCP autoantibodies
- Carriership of HLA-DR4 "Shared Epitope" alleles
- Family history of RA
- Poor functional status
- Socioeconomic factors
- Elevated acute phase response (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP])
- Increased clinical severity.

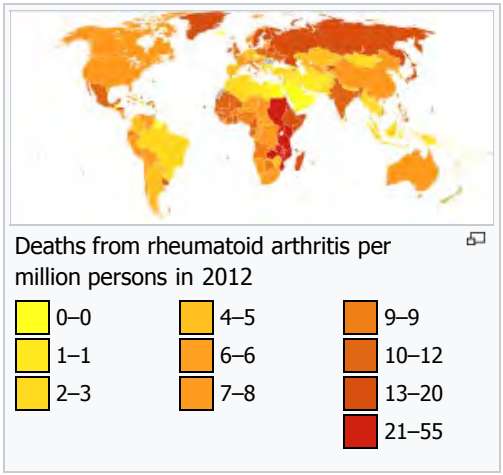



## Mortality [edit]

RA reduces lifespan on average from three to twelve years.[64] According to the UK's National Rheumatoid Arthritis Society, Young age at onset, long disease duration, the concurrent presence of other health problems (called co-morbidity), and characteristics of severe RA—such as poor functional ability or overall health status, a lot of joint damage on x-rays, the need for hospitalisation or involvement of organs other than the joints—have been shown to associate with higher mortality".[113] Positive responses to treatment may indicate a better prognosis. A 2005 study by the Mayo Clinic noted that RA sufferers suffer a doubled risk of heart disease,[114] independent of other risk factors such as diabetes, alcohol abuse, and elevated cholesterol, blood pressure and body mass index. The mechanism by which RA causes this increased risk remains unknown; the presence of chronic inflammation has been proposed as a contributing factor.[115] It is possible that the use of new biologic drug therapies extend the lifespan of people with RA and reduce the risk and progression of atherosclerosis.[116] This is based on cohort and registry studies, and still remains hypothetical. It is still uncertain whether biologics improve vascular function in RA or not. There was an increase in total cholesterol and HDLc levels and no improvement of the atherogenic index.[117]

# Epidemiology [edit]

RA affects between 0.5 and 1% of adults in the developed world with between 5 and 50 per 100,000 people newly developing the condition each year.[3] In 2010 it resulted in about 49,000 deaths globally.[118]




Onset is uncommon under the age of 15 and from then on the incidence rises with age until the age of 80. Women are affected three to five times as often as men.[14]

The age at which the disease most commonly starts is in women between 40 and 50 years of age, and for men somewhat later.[119] RA is a chronic disease, and although rarely, a spontaneous remission may occur, the natural course is almost invariably one of the persistent symptoms, waxing and waning in intensity, and a progressive deterioration of joint structures leading to deformations and disability.

# History [edit]

The first known traces of arthritis date back at least as far as 4500 BC. A text dated 123 AD first describes symptoms very similar to RA.[*citation needed*] It was noted in skeletal remains of Native Americans found in Tennessee.[120] In Europe, the disease is vanishingly rare before the 17th century.[121] The first recognized description of RA in modern medicine was in 1800 by the French physician Dr Augustin Jacob Landré-Beauvais (1772–1840) who was based in the famed Salpêtrière Hospital in Paris.[8] The name "rheumatoid arthritis" itself was coined in 1859 by British rheumatologist Dr Alfred Baring Garrod.[122]

An anomaly has been noticed from the investigation of Pre-Columbian bones. The bones from the Tennessee site show no signs of tuberculosis even though it was prevalent at the time throughout the Americas.[123]

The art of Peter Paul Rubens may possibly depict the effects of RA. In his later paintings, his rendered hands show, in the opinion of some physicians, increasing deformity consistent with the symptoms of the disease.[124][125] RA appears to some to have been depicted in 16th-century paintings.[126] However, it is generally recognized in art historical circles that the painting of hands in the 16th and 17th century followed certain stylized conventions, most clearly seen in the Mannerist movement. It was conventional, for instance, to show the upheld right hand of Christ in what now appears a deformed posture. These conventions are easily misinterpreted as portrayals of disease.

Historic treatments for RA have also included: rest, ice, compression and elevation, apple diet, nutmeg, some light exercise every now and then, nettles, bee venom, copper bracelets, rhubarb diet, extractions of teeth, fasting, honey, vitamins, insulin, magnets, and electroconvulsive therapy (ECT).[127] The Prosorba column blood filtering device (removing IgG) was approved by the FDA in 1999 for treatment of RA[128] However it was discontinued at the end of 2006.[129]

[edit]

## Etymology

Rheumatoid arthritis is derived from the Greek word *ῥεύμα-rheuma (nom.), ῥεύματος-rheumatos (gen.)* ("flow, current"). The suffix *-oid* ("resembling") gives the translation as *joint inflammation that resembles rheumatic fever*. Rhuma which means watery discharge might refer to the fact that the joints are swollen or that the disease may be made worse by wet weather.[9]

# References [edit]


1. ^ a b c d e f "Handout on Health: Rheumatoid Arthritis". *National Institute of Arthritis and Musculoskeletal and Skin Diseases*. August 2014. Retrieved July 2, 2015.
2. ^ a b c d Majithia V, Geraci SA (2007). "Rheumatoid arthritis: diagnosis and management". *Am. J. Med.* **120** (11): 936–9. doi:10.1016/j.amjmed.2007.04.005. PMID 17976416.
3. ^ a b c d e f g h i j k l m n o p q r s t Scott DL, Wolfe F, Huizinga TW (Sep 25, 2010). "Rheumatoid arthritis". *Lancet*. **376** (9746): 1094–108. doi:10.1016/S0140-6736(10)60826-4. PMID 20870100.
4. ^ Singh, JA; Wells, GA; Christensen, R; Tanjong Ghogomu, E; Maxwell, L; Macdonald, JK; Filippini, G; Skoetz, N; Francis, D; Lopes, LC; Guyatt, GH; Schmitt, J; La Mantia, L; Weberschock, T; Roos, JF; Siebert, H; Hershan, S; Lunn, MP; Tugwell, P; Buchbinder, R (16 February 2011). "Adverse effects of biologics: a network meta-analysis and Cochrane overview.". *The Cochrane database of systematic reviews* (2): CD008794. doi:10.1002/14651858.CD008794.pub2. PMID 21328309.
5. ^ a b c Efthimiou P, Kukar M (2010). "Complementary and alternative medicine use in rheumatoid arthritis: proposed mechanism of action and efficacy of commonly used modalities". *Rheumatology international*. **30** (5): 571–86. doi:10.1007/s00296-009-1206-y. PMID 19876631.
6. ^ a b c "Rheumatoid Arthritis and Complementary Health Approaches". National Center for Complementary and Integrative Health. Retrieved July 1, 2015.
7. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385** (9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
8. ^ a b Landré-Beauvais AJ (1800). *La goutte asthénique primitive (doctoral thesis)*. Paris. reproduced in Landré-Beauvais AJ (2001). "The first description of rheumatoid arthritis. Unabridged text of the doctoral dissertation presented in 1800". *Joint Bone Spine*. **68** (2): 130–43. doi:10.1016/S1297-319X(00)00247-5. PMID 11324929.
9. ^ a b Paget, Stephen A.; Lockshin, Michael D.; Loebl, Suzanne (2002). *The Hospital for Special Surgery Rheumatoid Arthritis Handbook Everything You Need to Know.* New York: John Wiley & Sons. p. 32. ISBN 9780471223344.
10. ^ Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL (2003). "Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years". *Ann. Rheum. Dis.* **62** (8): 722–7. doi:10.1136/ard.62.8.722. PMC 1754626. PMID 12860726.
11. ^ a b c Nicki R. Colledge, Brian R. Walker, Stuart H. Ralston, eds. (2010). *Davidson's principles and practice of medicine.* (21st ed.). Edinburgh: Churchill Livingstone/Elsevier. ISBN 978-0-7020-3084-0.
12. ^ "An approach to Early Arthritis". Pn.lifehugger.com. 12 January 2009. Archived from the original on May 27, 2010.
13. ^ Gaffo A, Saag KG, Curtis JR (2006). "Treatment of rheumatoid arthritis". *Am J Health Syst Pharm.* **63** (24): 2451–2465. doi:10.2146/ajhp050514. PMID 17158693.
14. ^ a b c d e f g h i Shah, Ankur. *Harrison's Principle of Internal Medicine* (18th ed.). United States: McGraw Hill. p. 2738. ISBN 978-0-07174889-6.
    a b
PMID 22258993.
67. ^ Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, Schoones J, Van den Ende EC (Oct 7, 2009). Hurkmans, Emalie, ed. "Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis". *Cochrane database of systematic reviews (Online)* (4): CD006853. doi:10.1002/14651858.CD006853.pub2. PMID 19821388.
68. ^ Hagen KB, Byfuglien MG, Falzon L, Olsen SU, Smedslund G (Jan 21, 2009). Hagen, Kåre Birger, ed. "Dietary interventions for rheumatoid arthritis". *Cochrane database of systematic reviews (Online)* (1): CD006400. doi:10.1002/14651858.CD006400.pub2. PMID 19160281.
69. ^ Cramp, Fiona (2013). "Non-pharmacological interventions for fatigue in rheumatoid arthritis.". *Cochrane Database of Systematic Reviews* (8): Art. No.: CD008322. doi:10.1002/14651858.CD008322.pub2.
70. ^ Steultjens, Esther EMJ (2004). "Occupational therapy for rheumatoid arthritis". *Cochrane Database of Systematic Reviews* (1). doi:10.1002/14651858.CD003114.pub2.
71. ^ Gramling A, O'Dell JR (2012). "Initial management of rheumatoid arthritis". *Rheum. Dis. Clin. North Am.* **38** (2): 311–25. doi:10.1016/j.rdc.2012.05.003. PMID 22819086.
72. ^ a b c d DiPiro, Joseph T., Robert L. Talbert, Gary C. Yee, Gary R. Matzke, Barbara G. Wells, and L. Michael Posey (2008) Pharmacotherapy: a pathophysiologic approach. 7th ed. New York: McGraw-Hill, ISBN 978-0-07-147899-1.
73. ^ Shea, B.; Swinden, M.V.; Tanjong Ghogomu, E.; Ortiz, Z.; Katchamart, W.; Rader, T.; Bombardier, C.; Wells, George A; Tugwell, Peter (May 31, 2013). "Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis". *The Cochrane database of systematic reviews.* **5** (5): CD000951. doi:10.1002/14651858.CD000951.pub2. PMID 23728635.
74. ^ American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines (2002). "Guidelines for the management of rheumatoid arthritis: 2002 Update". *Arthritis & Rheumatism.* **46** (2): 328–346. doi:10.1002/art.10148.
75. ^ Singh, JA; Furst, DE; Bharat, A; Curtis, JR; Kavanaugh, AF; Kremer, JM; Moreland, LW; O'Dell, J; Winthrop, KL; Beukelman, T; Bridges SL, Jr; Chatham, WW; Paulus, HE; Suarez-Almazor, M; Bombardier, C; Dougados, M; Khanna, D; King, CM; Leong, AL; Matteson, EL; Schousboe, JT; Moynihan, E; Kolba, KS; Jain, A; Volkmann, ER; Agrawal, H; Bae, S; Mudano, AS; Patkar, NM; Saag, KG (May 2012). "2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis.". *Arthritis Care & Research*. **64** (5): 625–39. doi:10.1002/acr.21641. PMID 22473917.
76. ^ Singh, Jasvinder A; Cameron, Chris; Noorbaloochi, Shahrzad; Cullis, Tyler; Tucker, Matthew; Christensen, Robin; Ghogomu, Elizabeth Tanjong; Coyle, Doug; Clifford, Tammy; Tugwell, Peter; Wells, George A (May 2015). "Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis". *The Lancet*. **386** (9990): 258–265. doi:10.1016/S0140-6736(14)61704-9.
77. ^ Edwards J, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close D, Stevens R, Shaw T; Szczepanski; Szechinski; Filipowicz-Sosnowska; Emery; Close; Stevens; Shaw (2004). "Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis". *N Engl J Med.* **350** (25): 2572–81. doi:10.1056/NEJMoa032534. PMID 15201414.
78. ^ van Herwaarden, N; den Broeder, AA; Jacobs, W; van der

15. ^ Turesson, C (May 2013). "Extra-articular rheumatoid arthritis.". *Current opinion in rheumatology*. **25** (3): 360–6. doi:10.1097/bor.0b013e32835f693f. PMID 23425964.
16. ^ "Rheumatoid Lung Disease – What Is Rheumatoid Lung Disease?". Arthritis.about.com. February 27, 2011. Retrieved March 3, 2011.
17. ^ de Groot K (August 2007). "[Renal manifestations in rheumatic diseases]". *Internist (Berl)*. **48** (8): 779–85. doi:10.1007/s00108-007-1887-9. PMID 17571244.
18. ^ Robbins, Stanley Leonard; Kumar, Vinay; Abbas, Abdul K.; Cotran, Ramzi S.; Fausto, Nelson (2010). Vinay Kumar, Abul K. Abbas, Nelson Fausto, eds. *Robbins and Cotran pathologic basis of disease*. *Robbins Pathology Series*. Elsevier. p. 205. ISBN 978-1-4160-3121-5.
19. ^ Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, Spitz PW, Haga M, Kleinheksel SM, Cathey MA (April 1994). "The mortality of rheumatoid arthritis". *Arthritis Rheum*. **37** (4): 481–94. doi:10.1002/art.1780370408. PMID 8147925.
20. ^ Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D (2008). "Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies". *Arthritis Rheum*. **59** (12): 1690–1697. doi:10.1002/art.24092. PMID 19035419.
21. ^ [a] [b] Gupta A, Fomberstein B (2009). "Evaluating cardiovascular risk in rheumatoid arthritis". *Journal of Musculoskeletal Medicine*. **26** (8): 481–94.
22. ^ [a] [b] Selmi, Carlo; Santis, Maria De; Gershwin, M Eric (2011). "Liver involvement in subjects with rheumatic disease". *Arthritis Research & Therapy*. BioMed Central. **13** (3): 226. doi:10.1186/ar3319. PMID 21722332.
23. ^ Citation: H. Rehman : Hemolytic Anemia following Mycoplasma Infection. The Internet Journal of Hematology. 2008 Volume 4 Number 1 [1]
24. ^ Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, Catrina AI, Rosenquist R, Feltelius N, Sundström C, Klareskog L (2006). "Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis". *Arthritis & Rheumatism*. **54** (3): 692–701. doi:10.1002/art.21675. PMID 16508929.
25. ^ Franklin J, Lunt M, Bunn D, Symmons D, Silman A (2006). "Incidence of lymphoma in a large primary care derived cohort of cases of inflammatory polyarthritis". *Annals of the Rheumatic Diseases*. **65** (5): 617–622. doi:10.1136/ard.2005.044784. PMC 1798140. PMID 16249224.
26. ^ Edwards JC, Cambridge G, Abrahams VM (1999). "Do self-perpetuating B lymphocytes drive human autoimmune disease?". *Immunology*. **97** (2): 188–96. doi:10.1046/j.1365-2567.1999.00772.x. PMC 2326840. PMID 10447731.
27. ^ Plenge RM, Seielstad M, Padyukov L, Lee AT, Remmers EF, Ding B, Liew A, Khalili H, Chandrasekaran A, Davies LR, Li W, Tan AK, Bonnard C, Ong RT, Thalamuthu A, Pettersson S, Liu C, Tian C, Chen WV, Carulli JP, Beckman EM, Altshuler D, Alfredsson L, Criswell LA, Amos CI, Seldin MF, Kastner DL, Klareskog L, Gregersen PK (20 September 2007). "TRAF1–C5 as a Risk Locus for Rheumatoid Arthritis — A Genomewide Study". *The New England Journal of Medicine*. **357** (12): 1199–209. doi:10.1056/NEJMoa073491. PMC 2636867. PMID 17804836.
28. ^ Goeldner I, Skare TL, de Messias Reason IT, Nisihara RM, Silva MB, Utiyama SR (Aug 2010). "Anti-cyclic citrullinated peptide antibodies and rheumatoid factor in rheumatoid arthritis patients and relatives from Brazil". *Rheumatology (Oxford)*. **49** (8): 1590–3. doi:10.1093/rheumatology/keq134. PMID 20457731.
29. ^ "The Genetics Behind Rheumatoid Arthritis". Arthritis Foundation. Retrieved December 17, 2012.
30. ^ Silman AJ, MacGregor AJ, Thomson W, Holligan S, Carthy D, Farhan A, Ollier WE (1993). "Twin concordance rates for rheumatoid arthritis: Results from a nationwide study". *British journal of rheumatology*. **32** (10): 903–907. doi:10.1093/rheumatology/32.10.903. PMID 8402000.
31. ^ Bellamy N, Duffy D, Martin N, Mathews J (1992). "Rheumatoid Maas, A; Bijlsma, JW; van Vollenhoven, RF; van den Bemt, BH (Sep 29, 2014). "Down-titration and discontinuation strategies of tumor necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity". *The Cochrane database of systematic reviews*. **9** (9): CD010455. doi:10.1002/14651858.CD010455.pub2. PMID 25264908.
79. ^ Aaltonen KJ, Virkki LM, Malmivaara A, Konttinen YT, Nordström DC, Blom M; Virkki; Malmivaara; Konttinen; Nordström; Blom (2012). Hernandez, Adrian V, ed. "Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis". *PLoS ONE*. **7** (1): e30275. doi:10.1371/journal.pone.0030275. PMC 3260264. PMID 22272322.
80. ^ Maxwell L, Singh JA; Singh (Oct 7, 2009). Maxwell, Lara, ed. "Abatacept for rheumatoid arthritis". *Cochrane database of systematic reviews (Online)* (4): CD007277. doi:10.1002/14651858.CD007277.pub2. PMID 19821401.
81. ^ Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Tanjong Ghogomu E, Tugwell P; Christensen; Wells; Suarez-Almazor; Buchbinder; Lopez-Olivo; Tanjong Ghogomu; Tugwell (Oct 7, 2009). Singh, Jasvinder A, ed. "Biologics for rheumatoid arthritis: an overview of Cochrane reviews". *Cochrane database of systematic reviews (Online)* (4): CD007848. doi:10.1002/14651858.CD007848.pub2. PMID 19821440.
82. ^ Tarp S, Bartels EM, Bliddal H, Furst DE, Boers M, Danneskiold-Samsøe B, Rasmussen M, Christensen R; Bartels; Bliddal; Furst; Boers; Danneskiold-Samsøe; Rasmussen; Christensen (November 2012). "Effect of nonsteroidal antiinflammatory drugs on the C-reactive protein level in rheumatoid arthritis: a meta-analysis of randomized controlled trials". *Arthritis and rheumatism*. **64** (11): 3511–21. doi:10.1002/art.34644. PMID 22833186.
83. ^ Radner H, Ramiro S, Buchbinder R, Landewé RB, van der Heijde D, Aletaha D; Ramiro; Buchbinder; Landewé; Van Der Heijde; Aletaha (Jan 18, 2012). Radner, Helga, ed. "Pain management for inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and other spondylarthritis) and gastrointestinal or liver comorbidity". *Cochrane database of systematic reviews (Online)*. **1**: CD008951. doi:10.1002/14651858.CD008951.pub2. PMID 22258995.
84. ^ McCormack PL (2011). "Celecoxib: a review of its use for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis". *Drugs*. **71** (18): 2457–89. doi:10.2165/11208240-000000000-00000. PMID 22141388.
85. ^ Marks JL, Colebatch AN, Buchbinder R, Edwards CJ; Colebatch; Buchbinder; Edwards (Oct 5, 2011). Marks, Jonathan L, ed. "Pain management for rheumatoid arthritis and cardiovascular or renal comorbidity". *Cochrane database of systematic reviews (Online)* (10): CD008952. doi:10.1002/14651858.CD008952.pub2. PMID 21975789.
86. ^ Colebatch, AN; Marks, Jonathan L; Edwards, Christopher J (2011). "Safety of non-steroidal anti-inflammatory drugs, including aspirin and paracetamol (acetaminophen) in people receiving methotrexate for inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis)". *Cochrane Database of Systematic Reviews*. doi:10.1002/14651858.CD008872.pub2.
87. ^ [a] [b] Chen YF, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, Taylor RS; Jobanputra; Barton; Bryan; Fry-Smith; Harris; Taylor (April 2008). "Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation". *Health technology assessment (Winchester, England)*. **12** (11): 1–278, iii. doi:10.3310/hta12110. PMID 18405470.
88. ^ Wang X, Tian HJ, Yang HK, Wanyan P, Peng YJ; Tian; Yang; Wanyan; Peng (October 2011). "Meta-analysis: cyclooxygenase-2 inhibitors are no better than nonselective nonsteroidal anti-inflammatory drugs with proton pump inhibitors in regard to gastrointestinal adverse events in osteoarthritis and rheumatoid arthritis". *European journal of gastroenterology & hepatology*. **23** (10): 876–80. doi:10.1097/MEG.0b013e328349de81.

arthritis in twins: A study of aetiopathogenesis based on the Australian Twin Registry". *Annals of the rheumatic diseases*. **51** (5): 588–593. doi:10.1136/ard.51.5.588. PMC 1005687. PMID 1616321.
32. ^ a b Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, Kumagai S (2010). "Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies". *Ann. Rheum. Dis.* **69** (1): 70–81. doi:10.1136/ard.2008.096487. PMID 19174392.
33. ^ Liao KP, Alfredsson L, Karlson EW (May 2009). "Environmental influences on risk for rheumatoid arthritis". *Current Opinion in Rheumatology*. **21** (3): 279–83. doi:10.1097/BOR.0b013e32832a2e16. PMC 2898190. PMID 19318947.
34. ^ Alvarez-Lafuente R, Fernández-Gutiérrez B, de Miguel S, Jover JA, Rollin R, Loza E, Clemente D, Lamas JR (September 2005). "Potential relationship between herpes viruses and rheumatoid arthritis: analysis with quantitative real time polymerase chain reaction". *Ann. Rheum. Dis.* **64** (9): 1357–9. doi:10.1136/ard.2004.033514. PMC 1755640. PMID 16100341.
35. ^ Balandraud N, Roudier J, Roudier C (2004). "Epstein-Barr virus and rheumatoid arthritis". *Autoimmun Rev*. **3** (5): 362–7. doi:10.1016/j.autrev.2004.02.002. PMID 15288002.
36. ^ Gatenby P, Lucas R, Swaminathan A (2013). "Vitamin D deficiency and risk for rheumatic diseases: an update". *Curr Opin Rheumatol*. **25** (2): 184–91. doi:10.1097/BOR.0b013e32835cfc16. PMID 23370372.
37. ^ a b Wen H, Baker JF (March 2011). "Vitamin D, immunoregulation, and rheumatoid arthritis". *Journal of Clinical Rheumatology*. **17** (2): 102–7. doi:10.1097/RHU.0b013e31820edd18. PMID 21364350.
38. ^ Guillot X, Semerano L, Saidenberg-Kermanac'h N, Falgarone G, Boissier MC (2010). "Vitamin D and inflammation". *Joint Bone Spine*. **77** (6): 552–7. doi:10.1016/j.jbspin.2010.09.018. PMID 21067953.
39. ^ St-Arnaud R. "The direct role of vitamin D on bone homeostasis". *Arch Biochem Biophys*. **473**: 225–30. doi:10.1016/j.abb.2008.03.038. PMID 18424254.
40. ^ a b Doherty, M; Lanyon, P; Ralston, SH. *Musculosketal Disorders-Davidson's Principle of Internal Medicine* (20th ed.). Elsevier. pp. 1100–1106.
41. ^ a b c Plenge RM, Seielstad M, Padyukov L, Lee AT, Remmers EF, Ding B, Liew A, Khalili H, Chandrasekaran A, Davies LR, Li W, Tan AK, Bonnard C, Ong RT, Thalamuthu A, Pettersson S, Liu C, Tian C, Chen WV, Carulli JP, Beckman EM, Altshuler D, Alfredsson L, Criswell LA, Amos CI, Seldin MF, Kastner DL, Klareskog L, Gregersen PK (2007). "TRAF1-C5 as a Risk Locus for Rheumatoid Arthritis — A Genomewide Study". *N. Engl. J. Med.* **357** (12): 1199–209. doi:10.1056/NEJMoa073491. PMC 2636867. PMID 17804836.
42. ^ Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L (2004). "A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis". *Arthritis Rheum*. **50** (10): 3085–92. doi:10.1002/art.20553. PMID 15476204.
43. ^ a b c Maverakis E, Kim K, Shimoda M, Gershwin M, Patel F, Wilken R, Raychaudhuri S, Ruhaak LR, Lebrilla CB (2015). "Glycans in the immune system and The Altered Glycan Theory of Autoimmunity". *J Autoimmun*. **57** (6): 1–13. doi:10.1016/j.jaut.2014.12.002. PMC 4340844. PMID 25578468.
44. ^ Boldt AB, Goeldner I, de Messias-Reason IJ. "Relevance of the lectin pathway of complement in rheumatic diseases". *Adv Clin Chem*. **56**: 105–53. doi:10.1016/B978-0-12-394317-0.00012-1. PMID 22397030.
45. ^ "HBP310 Immunology". *SUNY Stony Brook Pathology Department*. Archived from the original on August 7, 2006. Retrieved September 20, 2008.
46. ^ Ghaffar, Abdul. "Hypersensitivity States". *University of South Carolina School of Medicine*. Retrieved May 29, 2016.
PMID 21900785.
89. ^ Mallen SR, Essex MN, Zhang R; Essex; Zhang (July 2011). "Gastrointestinal tolerability of NSAIDs in elderly patients: a pooled analysis of 21 randomized clinical trials with celecoxib and nonselective NSAIDs". *Current medical research and opinion*. **27** (7): 1359–66. doi:10.1185/03007995.2011.581274. PMID 21561397.
90. ^ "Nonsteroidal anti-inflammatory drugs: add an anti-ulcer drug for patients at high risk only. Always limit the dose and duration of treatment with NSAIDs". *Prescrire Int*. **20** (119): 216–9. 2011. PMID 21954519.
91. ^ Macfarlane GJ, El-Metwally A, De Silva V, Ernst E, Dowds GL, Moots RJ; El-Metwally; De Silva; Ernst; Dowds; Moots; Arthritis Research UK Working Group on Complementary Alternative Medicines (2011). "Evidence for the efficacy of complementary and alternative medicines in the management of rheumatoid arthritis: a systematic review". *Rheumatology (Oxford)*. **50** (9): 1672–83. doi:10.1093/rheumatology/ker119. PMID 21652584.
92. ^ Brosseau L, Robinson V, Wells G, Debie R, Gam A, Harman K, Morin M, Shea B, Tugwell P (2005). "Low level laser therapy (Classes I, II and III) for treating rheumatoid arthritis". *Cochrane Database Syst Rev*. **4** (4): CD002049. doi:10.1002/14651858.CD002049.pub2. PMID 16235295.
93. ^ Han, Alcie; Judd, Maria; Welch, Vivian; Wu, Taixiang; Tugwell, Peter; Wells, George A (2004). "Tai chi for treating rheumatoid arthritis". *Cochrane Database of Systematic Reviews* (3). doi:10.1002/14651858.CD004849.
94. ^ Lee MS, Shin B-C, Ernst E; Shin; Ernst (2008). "Acupuncture for rheumatoid arthritis: a systematic review". *Rheumatology*. **47** (12): 1747–53. doi:10.1093/rheumatology/ken330. PMID 18710899.
95. ^ Macfarlane GJ, Paudyal P, Doherty M, Ernst E, Lewith G, MacPherson H, Sim J, Jones GT; Paudyal; Doherty; Ernst; Lewith; MacPherson; Sim; Jones; Arthritis Research UK Working Group on Complementary Alternative Therapies for the Management of the Rheumatic Diseases (2012). "A systematic review of evidence for the effectiveness of practitioner-based complementary and alternative therapies in the management of rheumatic diseases: rheumatoid arthritis". *Rheumatology*. **51** (9): 1707–13. doi:10.1093/rheumatology/kes133. PMID 22661556.
96. ^ Pirotta, M (September 2010). "Arthritis disease – the use of complementary therapies". *Australian family physician*. **39** (9): 638–40. PMID 20877766.
97. ^ Miles EA, Calder PC; Calder (June 2012). "Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis". *The British journal of nutrition*. 107 Suppl 2 (S2): S171–84. doi:10.1017/S0007114512001560. PMID 22591891.
98. ^ Ruggiero C, Lattanzio F, Lauretani F, Gasperini B, Andres-Lacueva C, Cherubini A; Lattanzio; Lauretani; Gasperini; Andres-Lacueva; Cherubini (2009). "Omega-3 polyunsaturated fatty acids and immune-mediated diseases: inflammatory bowel disease and rheumatoid arthritis" (PDF). *Current pharmaceutical design*. **15** (36): 4135–48. doi:10.2174/138161209789909746. PMID 20041815.
99. ^ Soeken, K L; Miller, S A; Ernst, E. "Herbal medicines for the treatment of rheumatoid arthritis: a systematic review". *Centre for Reviews and Dissemination*. National Institute for Health Research. Retrieved March 23, 2013.
100. ^ a b "Herbal Remedies, Supplements and Acupuncture for Arthritis". American College of Rheumatology. Retrieved May 3, 2013.
101. ^ Abdel-Tawab M, Werz O, Schubert-Zsilavecz M; Werz; Schubert-Zsilavecz (June 2011). "Boswellia serrata: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data". *Clinical pharmacokinetics*. **50** (6): 349–69. doi:10.2165/11586800-000000000-00000. PMID 21553931.
102. ^ White B, Judkins DZ; Judkins (March 2011). "Clinical Inquiry. Does turmeric relieve inflammatory conditions?". *The Journal of*

47. ^ Holmes, N. (1999). "Lecture 14: Hypersensitivity". *Immunology Division, Department of Pathology, University of Cambridge*. Archived from the original on February 6, 2006. Retrieved September 20, 2008.
48. ^ Schueller-Weidekamm C. Modern ultrasound methods yield stronger arthritis work-up. Diagnostic Imaging. May 2010:20–22.
49. ^ Westwood OM, Nelson PN, Hay FC (2006). "Rheumatoid factors: what's new?". *Rheumatology (Oxford)*. **45** (4): 379–85. doi:10.1093/rheumatology/kei228. PMID 16418203.
50. ^ [a] [b] Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, Saigo K, Morinobu A, Koshiba M, Kuntz KM, Kamae I, Kumagai S (2007). "Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis". *Ann. Intern. Med.* **146** (11): 797–808. doi:10.7326/0003-4819-146-11-200706050-00008. PMID 17548411.
51. ^ Nishimura K; Sugiyama D; Kogata Y; Tsuji, G; Nakazawa, T; Kawano, S; Saigo, K; Morinobu, A; et al. (2007). "Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis". *Ann. Intern. Med.* **146** (11): 797–808. doi:10.7326/0003-4819-146-11-200706050-00008. PMID 17548411.
52. ^ Renger F, Bang H, Fredenhagen G, Natusch A, Backhaus M, Feist E, Egerer K, Burmester GR. "Anti-MCV Antibody Test for the Diagnosis of Rheumatoid Arthritis Using a POCT-Immunoassay". *American College of Rheumatology, 2008 Annual Scientific Meeting, poster presentation*.
53. ^ Luime JJ, Colin EM, Hazes JM, Lubberts E (2009). "Does anti-MCV has additional value as serological marker in the diagnostic and prognostic work-up of patients with rheumatoid arthritis? A systematic review". *Ann Rheum Dis.* **69** (2): 337–44. doi:10.1136/ard.2008.103283. PMID 19289382.
54. ^ [a] [b] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovsky J, Wolfe F, Hawker G (2010). "2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative" (PDF). *Ann. Rheum. Dis.* **69** (9): 1580–8. doi:10.1136/ard.2010.138461. PMID 20699241. Archived from the original (PDF) on August 21, 2010.
55. ^ Aletaha, Daniel; Neogi, Tuhina; Silman, Alan J.; Funovits, Julia; Felson, David T.; Bingham, Clifton O.; Birnbaum, Neal S.; Burmester, Gerd R.; Bykerk, Vivian P.; Cohen, Marc D.; Combe, Bernard; Costenbader, Karen H.; Dougados, Maxime; Emery, Paul; Ferraccioli, Gianfranco; Hazes, Johanna M. W.; Hobbs, Kathryn; Huizinga, Tom W. J.; Kavanaugh, Arthur; Kay, Jonathan; Kvien, Tore K.; Laing, Timothy; Mease, Philip; Ménard, Henri A.; Moreland, Larry W.; Naden, Raymond L.; Pincus, Theodore; Smolen, Josef S.; Stanislawska-Biernat, Ewa; Symmons, Deborah; Tak, Paul P.; Upchurch, Katherine S.; Vencovský, Jiří; Wolfe, Frederick; Hawker, Gillian. "2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative". *Arthritis & Rheumatism*. **62** (9): 2569–2581. doi:10.1002/art.27584.
56. ^ Arnett F, Edworthy S, Bloch D, McShane D, Fries J, Cooper N, Healey L, Kaplan S, Liang M, Luthra H (1988). "The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis" (PDF). *Arthritis Rheum.* **31** (3): 315–24. doi:10.1002/art.1780310302. PMID 3358796. Archived from the original (PDF) on January 24, 2011. Retrieved February 8, 2011.
57. ^ [a] [b] Berkow R, ed. (1992). *The Merck Manual* (16th ed.). Merck Publishing Group. pp. 1307–08. ISBN 0-911910-16-6.
58. ^ Lovy MR, Starkebaum G, Uberoi S (1996). "Hepatitis C infection presenting with rheumatic manifestations: a mimic of rheumatoid family practice. **60** (3): 155–6. PMID 21369559 .
103. ^ Wegener, T. (1999). "Therapy of degenerative diseases of the musculoskeletal system with South African devil's claw (Harpagophytum procumbens DC)". *Wiener medizinische Wochenschrift (1946)*. **149** (8–10): 254–257. PMID 10483693.
104. ^ Denner SS (2007). "A review of the efficacy and safety of devil's claw for pain associated with degenerative musculoskeletal diseases, rheumatoid, and osteoarthritis". *Holist Nurs Pract*. **21** (4): 203–7. doi:10.1097/01.HNP.0000280932.65581.72. PMID 17627199.
105. ^ Zhang LF, Zhao JX; Zhao (December 2005). "The recent research situation of Euonymus alatus". *Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi = China journal of Chinese materia medica*. **30** (24): 1895–8. PMID 16494017.
106. ^ Bao J, Dai SM; Dai (2011). "A Chinese herb Tripterygium wilfordii Hook F in the treatment of rheumatoid arthritis: mechanism, efficacy, and safety". *Rheumatol. Int.* **31** (9): 1123–9. doi:10.1007/s00296-011-1841-y. PMID 21365177.
107. ^ Martí-Carvajal, Arturo J; Agreda-Pérez, Luis H; Solà, Ivan; Simancas-Racines, Daniel (2013). "Erythropoiesis-stimulating agents for anemia in rheumatoid arthritis". *Cochrane Database of Systematic Reviews*. doi:10.1002/14651858.CD000332.pub3.
108. ^ Perry, Lisa M.; Winthrop, Kevin L.; Curtis, Jeffrey R. (13 June 2014). "Vaccinations for Rheumatoid Arthritis". *Current Rheumatology Reports*. **16** (8). doi:10.1007/s11926-014-0431-x.
109. ^ Grohskopf, LA; Olsen, SJ; Sokolow, LZ; Bresee, JS; Cox, NJ; Broder, KR; Karron, RA; Walter, EB; Centers for Disease Control and, Prevention (15 August 2014). "Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) – United States, 2014–15 influenza season". *MMWR. Morbidity and mortality weekly report*. **63** (32): 691–7. PMID 25121712.
110. ^ Black, CL; Yue, X; Ball, SW; Donahue, SM; Izrael, D; de Perio, MA; Laney, AS; Lindley, MC; Graitcer, SB; Lu, PJ; Williams, WW; Bridges, CB; DiSogra, C; Sokolowski, J; Walker, DK; Greby, SM (19 September 2014). "Influenza vaccination coverage among health care personnel – United States, 2013–14 influenza season.". *MMWR. Morbidity and mortality weekly report*. **63** (37): 805–11. PMID 25233281.
111. ^ Hales, CM; Harpaz, R; Ortega-Sanchez, I; Bialek, SR; Centers for Disease Control and Prevention, (CDC) (22 August 2014). "Update on recommendations for use of herpes zoster vaccine.". *MMWR. Morbidity and mortality weekly report*. **63** (33): 729–31. PMID 25144544.
112. ^ "WHO Disease and injury country estimates". *World Health Organization*. 2009. Retrieved November 11, 2009.
113. ^ Kitas, George (4 April 2006) Why is life span shortened by Rheumatoid Arthritis? National Rheumatoid Arthritis Society
114. ^ Rheumatoid Arthritis Patients Have Double the Risk of Heart Failure. mayoclinic.org (3 February 2005).
115. ^ "Cardiac disease in rheumatoid arthritis". Johns Hopkins University. 2002. Archived from the original on October 9, 2006.
116. ^ Atzeni F, Turiel M, Caporali R, Cavagna L, Tomasoni L, Sitia S, Sarzi-Puttini P; Turiel; Caporali; Cavagna; Tomasoni; Sitia; Sarzi-Puttini (2010). "The effect of pharmacological therapy on the cardiovascular system of patients with systemic rheumatic diseases". *Autoimmun Rev*. **9** (12): 835–9. doi:10.1016/j.autrev.2010.07.018. PMID 20678592.
117. ^ Damjanov, N; Nurmohamed, MT; Szekanecz, Z (Mar 18, 2014). "Biologics, cardiovascular effects and cancer.". *BMC medicine*. **12** (1): 48. doi:10.1186/1741-7015-12-48. PMC 3984692. PMID 24642038.
118. ^ Lozano, 1R; Naghavi, M; Foreman, K; Lim, S; Shibuya, K; Aboyans, V; Abraham, J; Adair, T; et al. (Dec 15, 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. PMID 23245604.
119. ^ Alamanos Y, Voulgari PV, Drosos AA; Voulgari; Drosos (2006). "Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic

arthritis". *J. Rheumatol.* **23** (6): 1238–9. PMID 8782126.
59. ^ Kelly, Janis (22 February 2005) DAS28 not always a reliable indicator of treatment effect in RA, Medscape Medical News.
60. ^ *a b* Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL (1995). "Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis". *Arthritis Rheum.* **38** (1): 44–8. doi:10.1002/art.1780380107. PMID 7818570.
61. ^ Yazici, Yusuf (2013). "Tools for monitoring remission in rheumatoid arthritis: any will do, let's just pick one and start measuring" (PDF). *Arthritis Research & Therapy*. **15**: 104. doi:10.1186/ar4139. Retrieved October 20, 2014.
62. ^ Spriggs, Brenda B. "Rheumatoid Arthritis Prevention". Healthline Networks. Retrieved September 16, 2014.
63. ^ *a b* Saag KG, Teng GG, Patkar NM, et al. (2008). "American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis". *Arthritis Rheum.* **59** (6): 762–84. doi:10.1002/art.23721. PMID 18512708.
64. ^ *a b c d* Amy M. Wasserman (2011). "Diagnosis and Management of Rheumatoid Arthritis". *American Family Physician*. **84** (11): 1245–1252. PMID 22150658.
65. ^ *a b* Chris Deighton; Rachel O'Mahony; Jonathan Tosh; Claire Turner; Michael Rudolf; Guideline Development Group (2009). "Management of rheumatoid arthritis: summary of NICE guidance". *British Medical Journal*. **338**: 710–712. doi:10.1136/bmj.b702.
66. ^ Richards BL, Whittle SL, Buchbinder R (Jan 18, 2012). Richards, Bethan L, ed. "Muscle relaxants for pain management in rheumatoid arthritis". *Cochrane database of systematic reviews (Online)*. **1**: CD008922. doi:10.1002/14651858.CD008922.pub2.
review". *Semin. Arthritis Rheum.* **36** (3): 182–8. doi:10.1016/j.semarthrit.2006.08.006. PMID 17045630.
120. ^ Rothschild, Bruce M. "Tennessee Origins of Rheumatoid Arthritis". Mcclungmuseum.utk.edu. Archived from the original on February 2, 2012. Retrieved March 3, 2011.
121. ^ "Bones of contention". *Arthritis Research UK*. April 1999. Archived from the original on February 19, 2003. Retrieved February 5, 2013.
122. ^ Garrod AB (1859). *The Nature and Treatment of Gout and Rheumatic Gout*. London: Walton and Maberly.
123. ^ Rothschild BM, Rothschild C, Helbling M; Rothschild; Helbling (2003). "Unified theory of the origins of erosive arthritis: conditioning as a protective/directing mechanism?". *J. Rheumatol.* **30** (10): 2095–102. PMID 14528501.
124. ^ Appelboom T, de Boelpaepe C, Ehrlich GE, Famaey JP; De Boelpaepe; Ehrlich; Famaey (1981). "Rubens and the question of antiquity of rheumatoid arthritis". *JAMA*. **245** (5): 483–6. doi:10.1001/jama.245.5.483. PMID 7005475.
125. ^ Kelly, Janis (14 June 2005). "Did RA travel from New World to Old? The Rubens connection". Medscape. Retrieved March 3, 2011.
126. ^ Dequeker J.; Rico H. (1992). "Rheumatoid arthritis-like deformities in an early 16th-century painting of the Flemish-Dutch school". *JAMA*. **268** (2): 249–251. doi:10.1001/jama.268.2.249. PMID 1608144.
127. ^ Hart FD (1976). "History of the treatment of rheumatoid arthritis". *Br Med J.* **1** (6012): 763–5. doi:10.1136/bmj.1.6012.763. PMC 1639217. PMID 177148.
128. ^ Fresenius HemoCare, Inc., "New Hope for Rheumatoid Arthritis Patients," press release, September 17, 1999.
129. ^ "Prosorba Column – Which Rheumatoid Arthritis Patients Are Good Candidates for the Prosorba Column?". Arthritis.about.com. Retrieved March 3, 2011.

## External links [edit]

- Rheumatoid arthritis at DMOZ
- Charles Weber. "History of rheumatoid arthritis".
- Singh, JA; Saag, KG; Bridges SL, Jr; Akl, EA; Bannuru, RR; Sullivan, MC; Vaysbrot, E; McNaughton, C; Osani, M; Shmerling, RH; Curtis, JR; Furst, DE; Parks, D; Kavanaugh, A; O'Dell, J; King, C; Leong, A; Matteson, EL; Schousboe, JT; Drevlow, B; Ginsberg, S; Grober, J; St Clair, EW; Tindall, E; Miller, AS; McAlindon, T (January 2016). "2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis.". *Arthritis & rheumatology (Hoboken, N.J.)*. **68** (1): 1–26. doi:10.1002/art.39480. PMID 26545940.



| v · t · e · | **Diseases of joints (M00–M19, 711–719)** | | |
|---|---|---|---|
| **Arthritis (one joint / multiple)** | **Inflammation** | **Infectious** | Septic arthritis · Tuberculosis arthritis · Reactive arthritis (indirectly) · |
| | | **Noninfectious** | 1. Seronegative spondyloarthropathy: (Reactive arthritis*Psoriatic arthritis*Juvenile idiopathic arthritis*Ankylosing spondylitis · · 2.*Rheumatoid arthritis:* · Adult-onset Still's disease · Felty's syndrome · 3.*Crystal arthropathy:* Gout · Chondrocalcinosis · |
| | **Noninflammatory** | | *Osteoarthritis:* Heberden's node · Bouchard's nodes · |
| **Other** | Bleeding · pain · Osteophyte · *villonodular synovitis* (Pigmented villonodular synovitis · · stiffness · | | |

| v · t · e · | **Hypersensitivity and autoimmune diseases (279.5–6)** | |
|---|---|---|
| **Type I / allergy / atopy (IgE)** | **Foreign** | Atopic eczema · Allergic urticaria · Allergic rhinitis (Hay fever) · Allergic asthma · Anaphylaxis · Food allergy (common allergies include: Milk · Egg · Peanut · Tree nut · Seafood · Soy · Wheat · · Penicillin allergy · |
| | **Autoimmune** | Eosinophilic esophagitis · |
| | **Foreign** | Hemolytic disease of the newborn · |
| | | Autoimmune hemolytic anemia · Immune thrombocytopenic purpura · |

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|---|---|---|---|
| **Type II/ADCC (IgM · IgG · ·** | **Autoimmune** | **Cytotoxic** | Bullous pemphigoid · Pemphigus vulgaris · Rheumatic fever · Goodpasture's syndrome · Guillain–Barré syndrome · |
| | | **"Type V"/receptor** | Graves' disease · Myasthenia gravis · Pernicious anemia · |
| **Type III (Immune complex)** | **Foreign** | | Henoch–Schönlein purpura · Hypersensitivity vasculitis · Reactive arthritis · Farmer's lung · Post-streptococcal glomerulonephritis · Serum sickness · Arthus reaction · |
| | **Autoimmune** | | Systemic lupus erythematosus · Subacute bacterial endocarditis · **Rheumatoid arthritis** · |
| **Type IV/cell-mediated (T cells)** | **Foreign** | | Allergic contact dermatitis · Mantoux test · |
| | **Autoimmune** | | Diabetes mellitus type 1 · Hashimoto's thyroiditis · Multiple sclerosis · Coeliac disease · Giant-cell arteritis · Postorgasmic illness syndrome · Reactive arthritis · |
| | **GVHD** | | Transfusion-associated graft versus host disease · |
| **Unknown/ multiple** | **Foreign** | | Hypersensitivity pneumonitis (Allergic bronchopulmonary aspergillosis · · Transplant rejection · Latex allergy (I+IV) · |
| | **Autoimmune** | | Sjögren's syndrome · Autoimmune hepatitis · Autoimmune polyendocrine syndrome (APS1 · APS2 · · Autoimmune adrenalitis · Systemic autoimmune disease · |

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|---|---|
| **Authority control** | GND: 4076708-5 · NDL: 00564944 · |

Categories: Connective tissue diseases | Arthritis | Autoimmune diseases | Disorders of fascia | Steroid-responsive inflammatory conditions

# Sarcoidosis

From Wikipedia, the free encyclopedia

**Sarcoidosis** is a disease involving abnormal collections of inflammatory cells that form lumps known as granulomas.[1] The disease usually begins in the lungs, skin, or lymph nodes. Less commonly affected are the eyes, liver, heart, and brain. Any organ, however, can be affected. The signs and symptoms depend on the organ involved. Often there are no, or only mild, symptoms.[1] When it affects the lungs there may be wheezing, cough, shortness of breath, or chest pain.[2] Some may have Löfgren's syndrome in which there is fever, large lymph nodes, arthritis, and a rash known as erythema nodosum.[1]

The cause of sarcoidosis is unknown.[1] Some believe it may be due to an immune reaction to a trigger such as an infection or chemicals in those who are genetically predisposed.[3][4] Those with affected family members are at greater risk.[5] Diagnosis is partly based on signs and symptoms, which may be supported by biopsy. Findings that make it likely include large lymph nodes at the root of the lung on both sides, high blood calcium with a normal parathyroid hormone level, or elevated levels of angiotensin converting enzyme (ACE) in the blood. The diagnosis should only be made after excluding other possible causes of similar symptoms such as tuberculosis.[6]

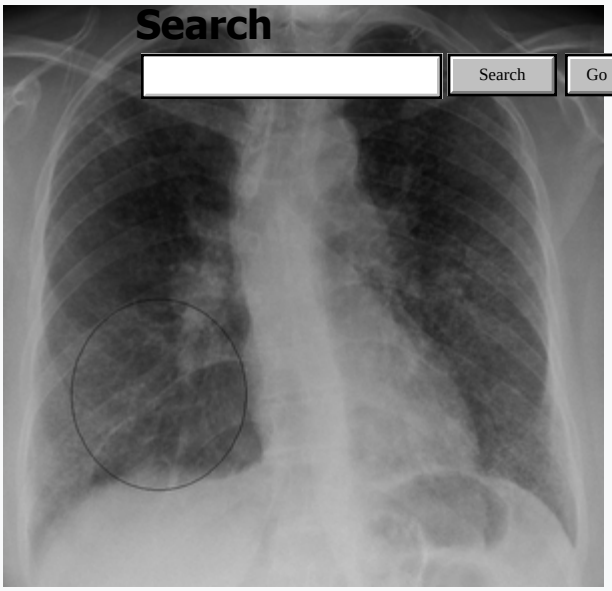
Many people clear up without any treatment within a few years.[1][7] However some may have long term or severe disease.[7] Some symptoms may be improved with the use of anti-inflammatory drugs such as ibuprofen.[8] In cases where the condition causes significant health problems steroids such as prednisone are indicated. Alternatively, medications such as methotrexate, chloroquine, or azathioprine may occasionally be used in an effort to decrease the side effects of steroids.[9] The risk of death is between one and seven percent.[7] There is a less than five percent chance of the disease returning in someone who has had it previously.[1]

In 2013 pulmonary sarcoidosis and interstitial lung disease affected 595,000 people globally.[10] These two diseases resulted in 471,000 deaths.[11] It is most common in Scandinavians but occurs in all parts of the world. In the United States risk is greater among black as opposed to white people.[12] It usually begins between the ages of 20–50.[5] It occurs more often in women than men.[5]

Sarcoidosis was first described in 1877 by the English doctor Jonathan Hutchinson as a non painful skin

**Sarcoidosis**

| | |
|---|---|
| **Synonyms** | sarcoïdosis, sarcoid |



Chest X-ray showing the typical nodularity of sarcoidosis in the base of the lungs.

| | |
|---|---|
| **Pronunciation** | sar-koy-DO-sis |

**Classification and external resources**

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|---|---|
| **Specialty** | Rheumatology |
| **ICD-10** | D86 |
| **ICD-9-CM** | 135 |
| **OMIM** | 181000 |
| **DiseasesDB** | 11797 |
| **MedlinePlus** | 000076 |
| **eMedicine** | med/2063 |
| **Patient UK** | Sarcoidosis |
| **MeSH** | D012507 |

[edit on Wikidata]

disease.[13]



**Contents**

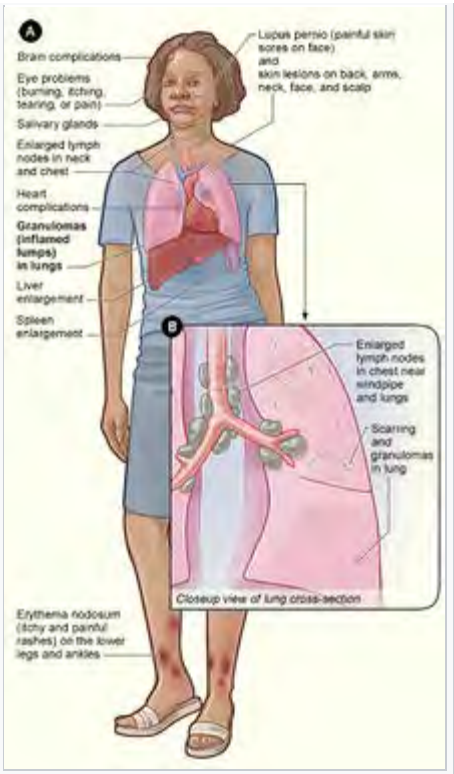




## Signs and symptoms [edit]

Sarcoidosis is a systemic inflammatory disease that can affect any organ, although it can be asymptomatic and is discovered by accident in about 5% of cases.[15] Common symptoms, which tend to be vague, include fatigue (unrelieved by sleep; occurs in 66% of cases), lack of energy, weight loss, joint aches and pains (which occur in about 70% of cases),[16] arthritis (14–38% of persons), dry eyes, swelling of the knees, blurry vision, shortness of breath, a dry, hacking cough, or skin lesions.[17][18][19][20] Less commonly, people may cough up blood.[17] The cutaneous symptoms vary, and range from rashes and noduli (small bumps) to erythema nodosum, granuloma annulare, or lupus pernio. Sarcoidosis and cancer may mimic one another, making the distinction difficult.[21]

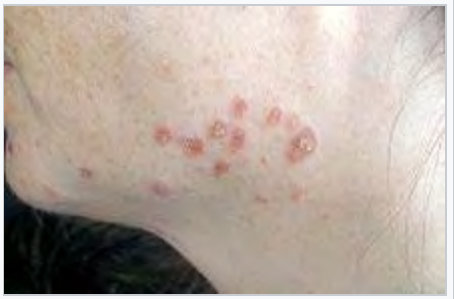
The combination of erythema nodosum, bilateral hilar lymphadenopathy, and joint pain is called Löfgren syndrome, which has a relatively good prognosis.[17] This form of the disease occurs significantly more often in Scandinavian patients than in those of non-Scandinavian origin.[22]




Signs and symptoms of sarcoidosis.[14]

## Respiratory tract [edit]

Localization to the lungs is by far the most common manifestation of sarcoidosis.[23] At least 90% of affected persons experience lung involvement.[24] Overall, about 50% develop permanent pulmonary abnormalities, and 5 to 15% have progressive fibrosis of the lung parenchyma. Sarcoidosis of the lung is primarily an interstitial lung disease in which the inflammatory process involves the alveoli, small bronchi and small blood vessels.[25] In acute and subacute cases, physical examination usually reveals dry crackles.[24] At least 5% of persons will suffer pulmonary arterial hypertension.[24][26] Less commonly, the upper respiratory tract (including the larynx, pharynx, and sinuses) may be affected, which occurs in between 5 and 10% of cases.[27]



Sarcoid affecting the skin

There are four stages of pulmonary involvement based on radiological stage of the disease, which is helpful in prognosis:[28]

- Stage I: bilateral hilar lymphadenopathy (BHL) alone
- Stage II: BHL with pulmonary infiltrates
- Stage III: pulmonary infiltrates without BHL
- Stage IV: fibrosis.

Use of the Scadding scale only provides general information regarding the prognosis of the pulmonary disease over time. Caution is recommended as it only shows a general relation with physiological markers of the disease and the variation is such that it has limited applicability in individual assessments, including treatment decisions.[29]

## Skin [edit]

*Main article: Skin manifestations of sarcoidosis*

Sarcoidosis involves the skin in between 9 and 37% of persons and is more common in African Americans than in European Americans.[24] The skin is the second most commonly affected organ after the lungs.[30] The most common lesions are erythema nodosum, plaques, maculopapular eruptions, subcutaneous nodules, and lupus pernio.[30] Treatment is not required, since the lesions usually resolve spontaneously in two to four weeks. Although it may be disfiguring, cutaneous sarcoidosis rarely causes major problems.[24][31][32] Sarcoidosis of the scalp presents with diffuse or patchy hair loss.[33][34]

## Heart [edit]

The frequency of cardiac involvement varies and is significantly influenced by race; in Japan more than 25% of persons with sarcoidosis have symptomatic cardiac involvement, whereas in the US and Europe only about 5% of cases present with cardiac involvement.[24] Autopsy studies in the US have revealed a frequency of cardiac involvement of about 20–30%, whereas autopsy studies in Japan have shown a frequency of 60%.[19] The presentation of cardiac sarcoidosis can range from asymptomatic conduction abnormalities to fatal ventricular arrhythmia.[35][36] Conduction abnormalities are the most common cardiac manifestations of sarcoidosis in humans and can include complete heart block.[37] Second to conduction abnormalities, in frequency, are ventricular arrhythmias, which occurs in about 23% of persons with cardiac involvement.[37] Sudden cardiac death, either due to ventricular arrhythmias or complete heart block is a rare complication of cardiac sarcoidosis.[38][39] Cardiac sarcoidosis can cause fibrosis, granuloma formation, or the accumulation of fluid in the interstitium of the heart, or a combination of the former two.[40][41]

## Eye [edit]

Eye involvement occurs in about 10–90% of cases.[19] Manifestations in the eye include uveitis, uveoparotitis, and retinal inflammation, which may result in loss of visual acuity or blindness.[42] The most common ophthalmologic manifestation of sarcoidosis is uveitis.[19][43][44] The combination of anterior uveitis, parotitis, VII cranial nerve paralysis and fever is called uveoparotid fever or Heerfordt syndrome (D86.8). Development of scleral nodule associated with sarcoidosis has been observed.[45]

## Nervous system [edit]

*Main article: Neurosarcoidosis*

Any of the components of the nervous system can be involved.[46] Sarcoidosis affecting the nervous system is known as neurosarcoidosis.[46] Cranial nerves are most commonly affected, accounting for about 5–30% of neurosarcoidosis cases, and peripheral facial nerve palsy, often bilateral, is the most common neurological manifestation of sarcoidosis.[46][47][48] It occurs suddenly and is usually transient. The central nervous system involvement is present in 10–25% of sarcoidosis cases.[27] Other common manifestations of neurosarcoidosis include optic nerve dysfunction, papilledema, palate dysfunction, neuroendocrine changes, hearing abnormalities, hypothalamic and pituitary abnormalities, chronic meningitis, and peripheral neuropathy.[24] Myelopathy, that is spinal cord involvement, occurs in about 16–43% of neurosarcoidosis cases and is often associated with the poorest prognosis of the neurosarcoidosis subtypes.[46] Whereas facial nerve palsies and acute meningitis due to sarcoidosis tends to have the most favourable prognosis.[46] Another common finding in sarcoidosis with neurological involvement is autonomic or sensory small fiber neuropathy.[49][50] Neuroendocrine sarcoidosis accounts for about 5–10% of neurosarcoidosis cases and can lead to diabetes insipidus, changes in menstrual cycle and hypothalamic dysfunction.[46][48] The latter can lead to changes in body temperature, mood and prolactin (see the endocrine and exocrine section for details).[46]

## Endocrine and exocrine [edit]

Prolactin is frequently increased in sarcoidosis, between 3% and 32% of cases have hyperprolactinemia[51] this frequently leads to amenorrhea, galactorrhea, or nonpuerperal mastitis in women. It also frequently causes an increase in 1,25-dihydroxy vitamin D, the active metabolite of vitamin D, which is usually hydrolysed within the kidney, but in sarcoidosis patients hydroxylation of vitamin D can occur outside the kidneys, namely inside the immune cells found in the granulomas the condition produces. 1 alpha, 25(OH)2D3 is the main cause for hypercalcemia in sarcoidosis and overproduced by sarcoid granulomata. Gamma-interferon produced by activated lymphocytes and macrophages plays a major role in the synthesis of 1 alpha, 25(OH)2D3.[52] Hypercalciuria (excessive secretion of calcium in one's urine) and hypercalcemia (an excessively high amount of calcium in the blood) are seen in <10% of individuals and likely results from [53]

the increased 1,25-dihydroxy vitamin D production. Thyroid dysfunction is seen in 4.2–4.6% of cases.[54][55]

Parotid enlargement occurs in about 5–10% of persons.[16] Bilateral involvement is the rule. The gland is usually not tender, but firm and smooth. Dry mouth can occur; other exocrine glands are affected only rarely.[24] The eyes, their glands, or the parotid glands are affected in 20–50% of cases.[56]

## Gastrointestinal and genitourinary [edit]

Symptomatic GI involvement occurs in less than 1% of persons (note that this is if one excludes the liver), and most commonly the stomach is affected, although the small or large intestine may also be affected in a small portion of cases.[16][57] Studies at autopsy have revealed GI involvement in less than 10% of people.[48] These cases would likely mimic Crohn's disease, which is a more commonly intestine-affecting granulomatous disease.[16] About 1–3% of people have evidence of pancreatic involvement at autopsy.[48] Symptomatic kidney involvement occurs in just 0.7% of cases, although evidence of kidney involvement at autopsy has been reported in up to 22% of people and occurs exclusively in cases of chronic disease.[16][19][48] Symptomatic kidney involvement is usually nephrocalcinosis, although granulomatous interstitial nephritis that presents with reduced creatinine clearance and little proteinuria is a close second.[16][48] Less commonly, the epididymis, testicles, prostate, ovaries, fallopian tubes, uterus, or the vulva may be affected, the latter may cause vulva itchiness.[19][58][59] Testicular involvement has been reported in about 5% of people at autopsy.[48][59] In males, sarcoidosis may lead to infertility.[60]

Around 70% of people have granulomas in their livers, although only in about 20–30% of cases liver function test anomalies reflecting this fact are seen.[17][24] About 5–15% of persons exhibit hepatomegaly, that is an enlarged liver.[19] Only 5–30% of cases of liver involvement are symptomatic.[61] Usually, these changes reflect a cholestatic pattern and include raised levels of alkaline phosphatase (which is the most common liver function test anomaly seen in persons with sarcoidosis), while bilirubin and aminotransferases are only mildly elevated. Jaundice is rare.[16][24]

## Blood [edit]

Abnormal blood tests are frequent, accounting for over 50% of cases, but is not diagnostic.[24][27] Lymphopenia is the most common blood anomaly in sarcoidosis.[24] Anemia occurs in about 20% of people with sarcoidosis.[24] Leukopenia is less common and occurs in even fewer persons but is rarely severe.[24] Thrombocytopenia and hemolytic anemia are fairly rare.[16] In the absence of splenomegaly, leukopenia may reflect bone marrow involvement, but the most common mechanism is a redistribution of blood T cells to sites of disease.[62] Other nonspecific findings include monocytosis, occurring in the majority of sarcoidosis cases,[63] increased hepatic enzymes or alkaline phosphatase. People with sarcoidosis often have immunologic anomalies like allergies to test antigens such as *Candida* or purified protein derivative (PPD).[56] Polyclonal hypergammaglobulinemia is also a fairly common immunologic anomaly seen in sarcoidosis.[56]

Lymphadenopathy (swollen glands) is common in sarcoidosis and occurs in 15% of cases.[20] Intrathoracic nodes are enlarged in 75 to 90% of all people; usually this involves the hilar nodes, but the paratracheal nodes are commonly involved. Peripheral lymphadenopathy is very common, particularly involving the cervical (the most common head and neck manifestation of the disease), axillary, epitrochlear, and inguinal nodes.[64] Approximately 75% of cases show microscopic involvement of the spleen, although only in about 5–10% of cases does splenomegaly appear.[16][56]

## Bone, joints, and muscles [edit]

Sarcoidosis can be involved with the joints, bones and muscles. This causes a wide variety of musculoskeletal complaints that act through different mechanisms.[65] About 5–15% of cases affect the bones, joints, or muscles.[27]

Arthritic syndromes can be categorized in two ways: as acute or chronic.[65] Sarcoidosis patients suffering acute arthritis often also have bilateral Hilar lymphadenopathy and Erythema nodosum. These three associated syndromes often occur together in Löfgren syndrome.[65] The arthritis symptoms of Löfgren syndrome occur most frequently in the ankles, followed by the knees, wrists, elbows, and metacarpophalangeal joints.[65] Usually true arthritis is not present, but instead, periarthritis appears as a swelling in the soft tissue around the joints that can be seen by ultrasonographic methods.[65] These joint symptoms tend to precede or occur at the same time as erythema nodosum develops.[65] Even when erythema nodosum is absent, it is believed that the combination of hilar lymphadenopathy and ankle periarthritis can be considered as a variant of Löfgren syndrome.[65] Enthesitis also occurs in about one-third of patients with acute sarcoid arthritis, mainly affecting the Achilles tendon and heels.[65] Soft tissue swelling of the ankles can be prominent, and biopsy of this soft tissue reveals no granulomas but does show panniculitis that is similar to erythema nodosum.[65]

Chronic sarcoid arthritis usually occurs in the setting of more diffuse organ involvement.[65] The ankles, knees, wrists, elbows, and hands may all be affected in the chronic form and often this presents itself in a polyarticular pattern.[65] Dactylitis similar to that seen in Psoriatic arthritis, that is associated with pain, swelling, overlying skin erythema, and underlying bony changes may also occur.[65] Development of Jaccoud arthropathy (a nonerosive deformity) is very rarely seen.[65]

Bone involvement in sarcoidosis has been reported in 1–13% of cases.[48] The most frequent sites of involvement are the hands and feet, whereas the spine is less commonly affected.[65] Half of the patients with bony lesions experience pain and stiffness, whereas the other half remain asymptomatic.[65] Periostitis is rarely seen in Sarcoidosis and has been found to present itself at the femoral bone.[66][67]

## Cause [edit]

The exact cause of sarcoidosis is not known.[1] The current working hypothesis is, in genetically susceptible individuals, sarcoidosis is caused through alteration to the immune response after exposure to an environmental, occupational, or infectious agent.[68] Some cases may be caused by treatment with TNF inhibitors like etanercept.[69]

### Genetics [edit]

The heritability of sarcoidosis varies according to race, about 20% of African Americans with sarcoidosis have a family member with the condition, whereas the same figure for whites is about 5%.[22] Investigations of genetic susceptibility yielded many candidate genes, but only few were confirmed by further investigations and no reliable genetic markers are known. Currently, the most interesting candidate gene is *BTNL2*; several *HLA-DR* risk alleles are also being investigated.[70][71] In persistent sarcoidosis, the HLA haplotype *HLA-B7-DR15* are either cooperating in disease or another gene between these two loci is associated. In nonpersistent disease, there is a strong genetic association with HLA DR3-DQ2.[72][73] Cardiac sarcoid has been connected to TNFA variants.[74]

### Infectious agents [edit]

Several infectious agents appear to be significantly associated with sarcoidosis, but none of the known associations is specific enough to suggest a direct causative role.[75] The major implicated infectious agents include: mycobacteria, fungi, borrelia, and rickettsia.[76] A meta-analysis investigating the role of mycobacteria in sarcoidosis found it was present in 26.4% of cases, but they also detected a possible publication bias, so the results need further confirmation.[77][78] *Mycobacterium tuberculosis* catalase-peroxidase has been identified as a possible antigen catalyst of sarcoidosis.[79] The disease has also been reported by transmission via organ transplants.[80]

### Autoimmune [edit]

Association of autoimmune disorders has been frequently observed. The exact mechanism of this relation is not known, but some evidence supports the hypothesis that this is a consequence of Th1 lymphokine prevalence.[54][81] Tests of delayed cutaneous hypersensitivity have been used to measure progression.[82]

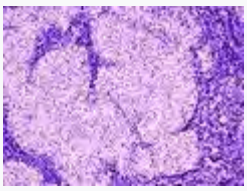
## Pathophysiology [edit]

Granulomatous inflammation is characterized primarily by accumulation of monocytes, macrophages, and activated T-lymphocytes, with increased production of key inflammatory mediators, TNF, IFN-γ, IL-2, IL-8, IL-10, IL-12, IL-18, IL-23 and TGF-β, indicative of a Th1-mediated immune response.[76][83] Sarcoidosis has paradoxical effects on inflammatory processes; it is characterized by increased macrophage and CD4 helper T-cell activation, resulting in accelerated inflammation, but immune response to antigen challenges such as tuberculin is suppressed. This paradoxic state of simultaneous hyper- and hypoactivity is suggestive of a state of anergy. The anergy may also be responsible for the increased risk of infections and cancer.

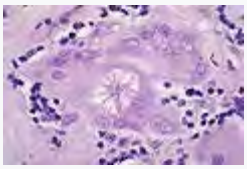
The regulatory T-lymphocytes in the periphery of sarcoid granulomas appear to suppress IL-2 secretion, which is hypothesized to cause the state of anergy by preventing antigen-specific memory responses.[84] Schaumann bodies seen in sarcoidosis are calcium and protein inclusions inside of Langhans giant cells as part of a granuloma.

While TNF is widely believed to play an important role in the formation of granulomas (which is further supported by the finding that in animal models of mycobacterial granuloma formation inhibition of either TNF or IFN-γ production inhibits granuloma formation), sarcoidosis can and does still develop in persons being treated with TNF antagonists like etanercept.[85] B cells also likely play a role in the pathophysiology of sarcoidosis.[22] Serum levels of soluble HLA class I antigens and ACE are higher in persons with sarcoidosis.[22] Likewise the ratio of CD4/CD8 T cells in bronchoalveolar lavage is usually higher in persons with pulmonary sarcoidosis (usually >3.5), although it can be normal or even abnormally low in some cases.[22] Serum ACE levels have been found to usually correlate with total granuloma load.[76]

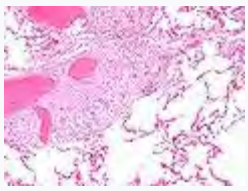
Cases of sarcoidosis have also been reported as part of the immune reconstitution syndrome of HIV, that is, when people receive treatment for HIV their immune system rebounds and the result is that it starts to attack the antigens of opportunistic infections caught prior to said rebound and the resulting immune response starts to damage healthy tissue.[83]



Sarcoidosis in a lymph node



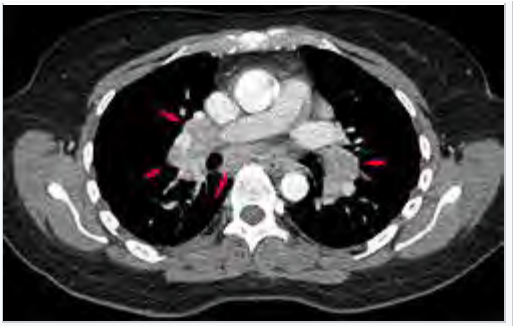
Asteroid body in sarcoidosis



Micrograph showing pulmonary sarcoidosis with granulomas with asteroid bodies, H&E stain

## Diagnosis [edit]

Diagnosis of sarcoidosis is a matter of exclusion, as there is no specific test for the condition. To exclude sarcoidosis in a case presenting with pulmonary symptoms might involve a chest



CT scan of the chest showing lymphadenopathy (arrows) in the mediastinum due to sarcoidosis

radiograph, CT scan of chest, PET scan, CT-guided biopsy, mediastinoscopy, open lung biopsy, bronchoscopy with biopsy, endobronchial ultrasound, and endoscopic ultrasound with fine-needle aspiration of mediastinal lymph nodes (EBUS FNA). Tissue from biopsy of lymph nodes is subjected to both flow cytometry to rule out cancer and special stains (acid fast bacilli stain and Gömöri methenamine silver stain) to rule out microorganisms and fungi.[86][87][88][89]

Serum markers of sarcoidosis, include: serum amyloid A, soluble interleukin 2 receptor, lysozyme, angiotensin converting enzyme, and the glycoprotein KL-6.[90] Angiotensin-converting enzyme blood levels are used in the monitoring of sarcoidosis.[90] A bronchoalveolar lavage can show an elevated (of at least 3.5) CD4/CD8 T cell ratio, which is indicative (but not proof) of pulmonary sarcoidosis.[22] In at least one study the induced sputum ratio of CD4/CD8 and level of TNF was correlated to those in the lavage fluid.[90] A sarcoidosis-like lung disease called Granulomatous–lymphocytic interstitial lung disease can be seen in patients with Common variable immunodeficiency (CVID) and therefore serum antibody levels should be measured to exclude CVID.

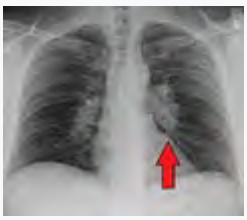
Differential diagnosis includes metastatic disease, lymphoma, septic emboli, rheumatoid nodules, granulomatosis with polyangiitis, varicella infection, tuberculosis, and atypical infections, such as *Mycobacterium avium* complex, cytomegalovirus, and cryptococcus.[91] Sarcoidosis is confused most commonly with neoplastic diseases, such as lymphoma, or with disorders characterized also by a mononuclear cell granulomatous inflammatory process, such as the mycobacterial and fungal disorders.[24]

Chest radiograph changes are divided into four stages:[92]

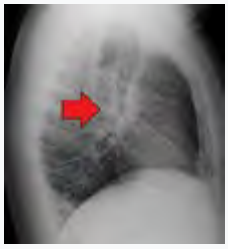
1. bihilar lymphadenopathy
2. bihilar lymphadenopathy and reticulonodular infiltrates
3. bilateral pulmonary infiltrates
4. fibrocystic sarcoidosis typically with upward hilar retraction, cystic and bullous changes

Although people with stage 1 radiographs tend to have the acute or subacute, reversible form of the disease, those with stages 2 and 3 often have the chronic, progressive disease; these patterns do not represent consecutive "stages" of sarcoidosis. Thus, except for epidemiologic purposes, this categorization is mostly of historic interest.[24]

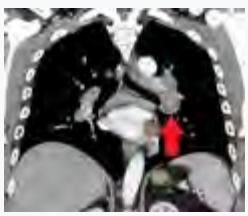
In sarcoidosis presenting in the Caucasian population, hilar adenopathy and erythema nodosum are the most common initial symptoms. In this population, a biopsy of the gastrocnemius muscle is a useful tool in correctly diagnosing the person. The presence of a noncaseating epithelioid granuloma in a gastrocnemius specimen is definitive evidence of sarcoidosis, as other tuberculoid and fungal diseases extremely rarely present histologically in this muscle.[93]



Hilar adenopathy especially on the person's left (AP CXR)



Hilar adenopathy especially on the person's left (lateral CXR)



Hilar adenopathy especially on the person's left (coronal CT)

Hilar adenopathy especially on the person's left (transverse CT)]]

## Classification [edit]

Sarcoidosis may be divided into the following types:[33]

- Annular sarcoidosis
- Erythrodermic sarcoidosis
- Ichthyosiform sarcoidosis
- Hypopigmented sarcoidosis
- Löfgren syndrome
- Lupus pernio
- Morpheaform
- Mucosal sarcoidosis
- Neurosarcoidosis
- Papular sarcoid
- Scar sarcoid
- Subcutaneous sarcoidosis
- Systemic sarcoidosis
- Ulcerative sarcoidosis

# Treatment [edit]

Treatments for sarcoidosis vary greatly depending on the patient.[94] At least half of patients require no systemic therapy.[95] Most persons (>75%) only require symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen or aspirin.[96] For persons presenting with lung symptoms, unless the respiratory impairment is devastating, active pulmonary sarcoidosis is observed usually without therapy for two to three months; if the inflammation does not subside spontaneously, therapy is instituted.[24]

Major categories of drug interventions include glucocorticoids, antimetabolites, biologic agents especially monoclonal anti-tumor necrosis factor antibodies, and more recently, specific antibiotic combinations and mesenchymal stem cells.[95] If drug intervention is indicated, a step-wise approach is often used to explore alternatives in order of increasing side effects and to monitor potentially toxic effects.[95]

Corticosteroids, most commonly prednisone or prednisolone, have been the standard treatment for many years.[16] In some people, this treatment can slow or reverse the course of the disease, but other people do not respond to steroid therapy. The use of corticosteroids in mild disease is controversial because in many cases the disease remits spontaneously.[97][98]

## Antimetabolites [edit]

Antimetabolites, also categorized as steroid-sparing agents, such as azathioprine, methotrexate, mycophenolic acid, and leflunomide[99][100] are often used as alternatives to corticosteroids.[16][101] Of these, methotrexate is most widely used and studied.[101][102] Methotrexate is considered a first-line treatment in neurosarcoidosis, often in conjunction with corticosteroids.[46][101] Long-term treatment with methotrexate is associated with liver damage in about 10% of people and hence may be a significant concern in people with liver involvement and requires regular liver function test monitoring.[16] Methotrexate can also lead to pulmonary toxicity (lung damage), although this is fairly uncommon and more commonly it can confound the leukopenia caused by sarcoidosis.[16] Due to these safety concerns it is often recommended that methotrexate is combined with folic acid in order to prevent toxicity.[16] Azathioprine treatment can also lead to liver damage.[102] Leflunomide is being used as a replacement for methotrexate, possibly due to its purportedly lower rate of pulmonary toxicity.[102] Mycophenolic acid has been used successfully in uveal sarcoidosis,[103] neurosarcoidosis (especially CNS sarcoidosis; minimally effective in sarcoidosis myopathy),[104] and pulmonary sarcoidosis.[105][106]

## Immunosuppressants [edit]

As the granulomas are caused by collections of immune system cells, particularly T cells, there has been some success using immunosuppressants (like cyclophosphamide, cladribine,[107] chlorambucil, and cyclosporine), immunomodulatory (pentoxifylline and thalidomide), and anti-tumor necrosis factor treatment[108][109] (such as infliximab, etanercept, golimumab, and adalimumab).[96][110][111]

In a clinical trial cyclosporine added to prednisone treatment failed to demonstrate any significant benefit

over prednisone alone in people with pulmonary sarcoidosis, although there was evidence of increased toxicity from the addition of cyclosporine to the steroid treatment including infections, malignancies (cancers), hypertension, and kidney dysfunction.[102] Likewise chlorambucil and cyclophosphamide are seldom used in the treatment of sarcoidosis due to their high degree of toxicity, especially their potential for causing malignancies.[112] Infliximab has been used successfully to treat pulmonary sarcoidosis in clinical trials in a number of persons.[102] Etanercept, on the other hand, has failed to demonstrate any significant efficacy in people with uveal sarcoidosis in a couple of clinical trials.[102] Likewise golimumab has failed to show any benefit in persons with pulmonary sarcoidosis.[102] One clinical trial of adalimumab found treatment response in about half of subjects, which is similar to that seen with infliximab, but as adalimumab has better tolerability profile it may be preferred over infliximab.[102]

## Specific organ treatments [edit]

Ursodeoxycholic acid has been used successfully as a treatment for cases with liver involvement.[113] Thalidomide has also been tried successfully as a treatment for treatment-resistant lupus pernio in a clinical trial, which may stem from its anti-TNF activity, although it failed to exhibit any efficacy in a pulmonary sarcoidosis clinical trial.[83][110] Cutaneous disease may be successfully managed with antimalarials (such as chloroquine and hydroxychloroquine) and the tetracycline antibiotic, minocycline.[24][110] Antimalarials have also demonstrated efficacy in treating sarcoidosis-induced hypercalcemia and neurosarcoidosis.[16] Long-term use of antimalarials is limited, however, by their potential to cause irreversible blindness and hence the need for regular ophthalmologic screening.[112] This toxicity is usually less of a problem with hydroxychloroquine than with chloroquine, although hydroxychloroquine can disturb the glucose homeostasis.[112]

Recently selective phosphodiesterase 4 (PDE4) inhibitors like apremilast (a thalidomide derivative), roflumilast, and the less subtype-selective PDE4 inhibitor, pentoxifylline, have been tried as a treatment for sarcoidosis, with successful results being obtained with apremilast in cutaneous sarcoidosis in a small open-label study.[114][115] Pentoxifylline has been used successfully to treat acute disease although its use is greatly limited by its gastrointestinal toxicity (mostly nausea, vomiting, and diarrhea).[100][102][112] Case reports have supported the efficacy of rituximab, an anti-CD20 monoclonal antibody and a clinical trial investigating atorvastatin as a treatment for sarcoidosis is under-way.[116][117] ACE inhibitors have been reported to cause remission in cutaneous sarcoidosis and improvement in pulmonary sarcoidosis, including improvement in pulmonary function, remodeling of lung parenchyma and prevention of pulmonary fibrosis in separate case series'.[118][119][120] Nicotine patches have been found to possess anti-inflammatory effects in sarcoidosis patients, although whether they had disease-modifying effects requires further investigation.[121] Antimycobacterial treatment (drugs that kill off mycobacteria, the causative agents behind tuberculosis and leprosy) has also proven itself effective in treating chronic cutaneous (that is, it affects the skin) sarcoidosis in one clinical trial.[122] Quercetin has also been tried as a treatment for pulmonary sarcoidosis with some early success in one small trial.[123]

Because of its uncommon nature, the treatment of male reproductive tract sarcoidosis is controversial. Since the differential diagnosis includes testicular cancer, some recommend orchiectomy, even if evidence of sarcoidosis in other organs is present. In the newer approach, testicular, epididymal biopsy and resection of the largest lesion has been proposed.[60]

## Symptoms [edit]

People with sarcoidosis may have a range of symptoms that do not correspond with objective physical evidence of disease but that still decrease quality of life.[124]

Physical therapy, rehabilitation, and counseling can help avoid deconditioning,[124]:733 and improve social participation, psychological well-being, and activity levels. Key aspects are avoiding exercise intolerance and muscle weakness.[124]:734

Low or moderate-intensity physical training has been shown to improve fatigue, psychological health, and

physical functioning in people sarcoidosis without adverse effects.[125][126] Inspiratory muscle training has also decreased severe fatigue perception in subjects with early stages of sarcoidosis, as well as improving functional and maximal exercise capacity and respiratory muscle strength.[127] The duration, frequency, and physical intensity of exercise needs to accommodate impairments such as joint pain, muscle pain, and fatigue.[124]:734 [126][128]

Neurostimulants such as methylphenidate and modafinil have shown some effectiveness as an adjunct for treatment of sarcoidosis fatigue.[124]:733[129]

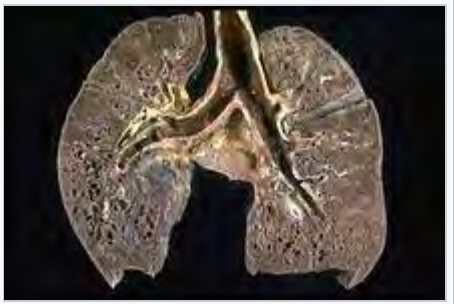
Counseling have also benefitted sarcoidosis patients and helped them manage their own conditions.[125]

Treatments for symptomatic neuropathic pain in sarcoidosis patients is similar to that for other causes, and include antidepressants, anticonvulsants and prolonged-release opioids, however only 30-60% of patients experience limited pain relief.[124]:733

## Prognosis [edit]

The disease can remit spontaneously or become chronic, with exacerbations and remissions. In some persons, it can progress to pulmonary fibrosis and death. About half of cases resolve without treatment or can be cured within 12–36 months, and most within five years. Some cases, however, may persist several decades.[16] Two-thirds of people with the condition achieve a remission within 10 years of the diagnosis.[130] When the heart is involved, the prognosis is generally less favourable, although, corticosteroids appear effective in improving AV conduction.[131][132] The prognosis tends to be less favourable in African Americans, compared to white Americans.[22]

Persons with sarcoidosis appear to be at significantly increased risk for cancer, in particular lung cancer, lymphomas,[133] and cancer in other organs known to be affected in sarcoidosis.[134][135] In sarcoidosis-lymphoma syndrome, sarcoidosis is followed by the development of a lymphoproliferative disorder such as non-Hodgkin lymphoma.[136] This may be attributed to the underlying immunological abnormalities that occur during the sarcoidosis disease process.[137] Sarcoidosis can also follow cancer[138][139] or occur concurrently with cancer.[140][141] There have been reports of hairy cell leukemia,[142] acute myeloid leukemia,[143] and acute myeloblastic leukemia[144] associated with sarcoidosis. Sometimes, sarcoidosis, even untreated, can complicated by opportunistic infections.[145][146]



Gross pathology image showing sarcoidosis with honeycombing: Prominent honeycombing is present in the lower lobes accompanied by fibrosis and some honeycombing in the upper lungs. Honeycombing consists of cystically dilated airways separated by scar tissue resembling the honeycomb of bees. It is a nonspecific end stage of many types of interstitial lung disease.

## Epidemiology [edit]

Sarcoidosis most commonly affects young adults of both sexes, although studies have reported more cases in females. Incidence is highest for individuals younger than 40 and peaks in the age-group from 20 to 29 years; a second peak is observed for women over 50.[16][131]

Sarcoidosis occurs throughout the world in all races with an average incidence of 16.5 per 100,000 in men and 19 per 100,000 in women. The disease is most common in Northern European countries and the highest annual incidence of 60 per 100,000 is found in Sweden and Iceland. In the United Kingdom the prevalence is 16 in 100,000.[147] In the United States, sarcoidosis is more common in people of African descent than Caucasians, with annual incidence reported as 35.5 and 10.9 per 100,000, respectively.[148] Sarcoidosis is less commonly reported in South America, Spain, India, Canada, and the Philippines. There may be a higher susceptibility to sarcoidosis in those with celiac disease. An association between the two

disorders has been suggested.[149]

There also has been a seasonal clustering observed in sarcoidosis-affected individuals.[150] In Greece about 70% of diagnoses occur between March and May every year, in Spain about 50% of diagnoses occur between April and June, and in Japan it is mostly diagnosed during June and July.[150]

The differing incidence across the world may be at least partially attributable to the lack of screening programs in certain regions of the world, and the overshadowing presence of other granulomatous diseases, such as tuberculosis, that may interfere with the diagnosis of sarcoidosis where they are prevalent.[131] There may also be differences in the severity of the disease between people of different ethnicities. Several studies suggest the presentation in people of African origin may be more severe and disseminated than for Caucasians, who are more likely to have asymptomatic disease.[62] Manifestation appears to be slightly different according to race and sex. Erythema nodosum is far more common in men than in women and in Caucasians than in other races. In Japanese persons, ophthalmologic and cardiac involvement are more common than in other races.[16]

It is more common in certain occupations, namely firefighters, educators, military personnel, persons who work in industries where pesticides are used, law enforcement, and healthcare personnel.[151] In the year after the September 11 attacks, the rate of sarcoidosis incidence went up four-fold (to 86 cases per 100,000).[27][151]

## History [edit]

It was first described in 1877 by Dr. Jonathan Hutchinson, a dermatologist as a condition causing red, raised rashes on the face, arms, and hands.[13] In 1888 the term Lupus pernio was coined by Dr. Ernest Besnier, another dermatologist.[152] Later in 1892 lupus pernio's histology was defined.[152] In 1902 bone involvement was first described by a group of three doctors.[152] Between 1909 and 1910 uveitis in sarcoidosis was first described, and later in 1915 it was emphasised, by Dr. Schaumann, that it was a systemic condition.[152] This same year lung involvement was also described.[152] In 1937 uveoparotid fever was first described and likewise in 1941 Löfgren syndrome was first described.[152] In 1958 the first international conference on sarcoidosis was called in London, likewise the first USA sarcoidosis conference occurred in Washington, DC in the year 1961.[152] It has also been called Besnier-Boeck disease or Besnier-Boeck-Schaumann disease.[153]

### Etymology [edit]

The word "sarcoidosis" comes from Greek [σάρκο-] *sarco-* meaning "flesh", the suffix *-(e)ido* (from the Greek εἶδος -eidos [usually omitting the initial e in English as the diphthong epsilon-iota in Classic Greek stands for a long "i" = English ee]) meaning "type", " resembles" or "like", and *-sis*, a common suffix in Greek meaning "condition". Thus the whole word means "a condition that resembles crude flesh". The first cases of sarcoïdosis, which were recognised as a new pathological entity, in Scandinavia, at the end of the 19th century exhibited skin nodules resembling cutaneous sarcomas, hence the name initially given.

## Society and culture [edit]

The World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) is an organisation of physicians involved in the diagnosis and treatment of sarcoidosis and related conditions.[154] WASOG publishes the journal *Sarcoidosis, Vasculitis and Diffuse Lung Diseases*.[155] Additionally, the Foundation for Sarcoidosis Research (FSR) is devoted to supporting research into sarcoidosis and its possible treatments.[156] Online communities provide support for those affected by sarcoidosis.[157]

There have been concerns that World Trade Center rescue workers are at a heightened risk for sarcoidosis.[158][159]

Comedian & actor Bernie Mac suffered from sarcoidosis. In 2005, he mentioned that the disease was in remission.[160] His death on August 9, 2008 was caused by complications from pneumonia, which was precipitated by pulmonary scarring attributed to his sarcoidosis.

In 2014, in a letter to the British medical journal The Lancet, it was suggested that the French Revolution leader Maximilien Robespierre suffered from sarcoidosis, and suggested that the condition caused him a notable impairment during his time as the head of the Reign of Terror.[161]

## Pregnancy [edit]

Sarcoidosis generally does not prevent successful pregnancy and delivery; the increase in estrogen levels during pregnancy may even have a slightly beneficial immunomodulatory effect. In most cases, the course of the disease is unaffected by pregnancy, with improvement in a few cases and worsening of symptoms in very few cases, although it is worth noting that a number of the immunosuppressants (such as methotrexate, cyclophosphamide, and azathioprine) used in corticosteroid-refractory sarcoidosis are known teratogens.[162]

## References [edit]


1. ^ *a b c d e f g* "What Is Sarcoidosis?". *NHLBI*. June 14, 2013. Retrieved 28 March 2016.
2. ^ "What Are the Signs and Symptoms of Sarcoidosis?". *NHLBI*. June 14, 2013. Retrieved 29 March 2016.
3. ^ Baughman RP, Culver DA, Judson MA; Culver; Judson (March 2011). "A concise review of pulmonary sarcoidosis". *American Journal of Respiratory and Critical Care Medicine*. **183** (5): 573–81. doi:10.1164/rccm.201006-0865CI. PMC 3081278. PMID 21037016.
4. ^ "What Causes Sarcoidosis?". *NHLBI*. June 14, 2013. Retrieved 28 March 2016.
5. ^ *a b c* "Who Is at Risk for Sarcoidosis?". *NHLBI*. June 14, 2013. Retrieved 28 March 2016.
6. ^ Govender, P; Berman, JS (December 2015). "The Diagnosis of Sarcoidosis.". *Clinics in chest medicine*. **36** (4): 585–602. doi:10.1016/j.ccm.2015.08.003. PMID 26593135.
7. ^ *a b c* Wijsenbeek, MS; Culver, DA (December 2015). "Treatment of Sarcoidosis.". *Clinics in chest medicine*. **36** (4): 751–67. doi:10.1016/j.ccm.2015.08.015. PMID 26593147.
8. ^ Drent, M; Cremers, JP; Jansen, TL (May 2014). "Pulmonology meets rheumatology in sarcoidosis: a review on the therapeutic approach.". *Current opinion in rheumatology*. **26** (3): 276–84. doi:10.1097/bor.0000000000000052. PMID 24614277.
9. ^ Judson, MA (February 2016). "Corticosteroids in Sarcoidosis.". *Rheumatic diseases clinics of North America*. **42** (1): 119–35, ix. doi:10.1016/j.rdc.2015.08.012. PMID 26611555.
10. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived

doi:10.1007/s00296-011-1969-9. PMID 21644041.

84. ^ Kettritz R, Goebel U, Fiebeler A, Schneider W, Luft F; Goebel; Fiebeler; Schneider; Luft (October 2006). "The protean face of sarcoidosis revisited" (PDF). *Nephrology, Dialysis, Transplantation*. **21** (10): 2690–4. doi:10.1093/ndt/gfl369. PMID 16861724.
85. ^ Verschueren K, Van Essche E, Verschueren P, Taelman V, Westhovens R; Van Essche; Verschueren; Taelman; Westhovens (November 2007). "Development of sarcoidosis in etanercept-treated rheumatoid arthritis patients". *Clin. Rheumatol*. **26** (11): 1969–71. doi:10.1007/s10067-007-0594-1. PMID 17340045.
86. ^ Parrish S, Turner JF; Turner (November 2009). "Diagnosis of sarcoidosis". *Disease-a-month*. **55** (11): 693–703. doi:10.1016/j.disamonth.2009.06.001. PMID 19857643.
87. ^ Hawtin KE, Roddie ME, Mauri FA, Copley SJ; Roddie; Mauri; Copley (August 2010). "Pulmonary sarcoidosis: the 'Great Pretender'". *Clinical Radiology*. **65** (8): 642–50. doi:10.1016/j.crad.2010.03.004. PMID 20599067.
88. ^ Baughman RP, Culver DA, Judson MA; Culver; Judson (1 March 2011). "A concise review of pulmonary sarcoidosis". *American Journal of Respiratory and Critical Care Medicine*. **183** (5): 573–81. doi:10.1164/rccm.201006-0865CI. PMC 3081278. PMID 21037016.
89. ^ Miliauskas S, Zemaitis M, Sakalauskas R; Zemaitis; Sakalauskas (2010). "Sarcoidosis—moving to the new standard of diagnosis?" (PDF). *Medicina*. **46** (7): 443–6. PMID 20966615.
90. ^ *a b c* Kamangar, N; Rohani, P; Shorr, AF (6 February 2014). Peters, SP; Talavera, F; Rice, TD;

with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013." . *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.

11. ^ GBD 2013 Mortality and Causes of Death, Collaborators (10 January 2015). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013." . *Lancet (London, England)*. **385** (9963): 117–71. doi:10.1016/s0140-6736(14)61682-2. PMC 4340604. PMID 25530442.:Table 2
12. ^ Kobak, S (October 2015). "Sarcoidosis: a rheumatologist's perspective." . *Therapeutic advances in musculoskeletal disease*. **7** (5): 196–205. doi:10.1177/1759720x15591310. PMC 4572362. PMID 26425148.
13. ^ *a b* James DG, Sharma OP (September 2002). "From Hutchinson to now: a historical glimpse" (PDF). *Current Opinion in Pulmonary Medicine*. **8** (5): 416–23. doi:10.1097/00063198-200209000-00013. PMID 12172446.
14. ^ "Lung Diseases: Sarcoidosis: Signs & Symptoms". National Heart, Lung, and Blood Institute. Retrieved May 9, 2009.
15. ^ Kamangar, N; Rohani, P; Shorr, AF (6 February 2014). Peters, SP; Talavera, F; Rice, TD; Mosenifar, Z, eds. "Sarcoidosis Clinical Presentation". *Medscape Reference*. WebMD. Retrieved 19 February 2014.
16. ^ *a b c d e f g h i j k l m n o p q r* Nunes H, Bouvry D, Soler P, Valeyre D; Bouvry; Soler; Valeyre (2007). "Sarcoidosis". *Orphanet J Rare Dis*. **2**: 46. doi:10.1186/1750-1172-2-46. PMC 2169207. PMID 18021432.
17. ^ *a b c d* King, TE, Jr. (March 2008). "Sarcoidosis: Interstitial Lung Diseases: Merck Manual Home Edition". *The Merck Manual Home Edition*. Merck Sharp & Dohme Corp. Retrieved 19 February 2014.
18. ^ Sweiss NJ, Patterson K, Sawaqed R, Jabbar U, Korsten P, Hogarth K, Wollman R, Garcia JG, Niewold TB, Baughman RP; Patterson; Sawaqed; Jabbar; Korsten; Hogarth; Wollman; Garcia; Niewold; Baughman (August 2010). "Rheumatologic manifestations of sarcoidosis". *Seminars in Respiratory and Critical Care Medicine*. **31** (4): 463–73. doi:10.1055/s-0030-1262214. PMC 3314339. PMID 20665396.
19. ^ *a b c d e f g* Holmes J, Lazarus A; Lazarus (November 2009). "Sarcoidosis: extrathoracic manifestations". *Disease-a-month*. **55** (11): 675–92. doi:10.1016/j.disamonth.2009.05.002. PMID 19857642.
20. ^ *a b* Dempsey OJ, Paterson EW, Kerr KM, Denison AR; Paterson; Kerr; Denison (28 August 2009). Mosenifar, Z, eds. "Sarcoidosis Workup". *Medscape Reference*. WebMD. Retrieved 19 February 2014.
91. ^ Allmendinger A, Perone R (2009). "Case of the Month". *Diagnostic Imaging*. **31** (9): 10.
92. ^ Joanne Mambretti (2004). "Chest X-ray Stages of Sarcoidosis" (PDF). *Journal of Insurance Medicine*: 91–92. Retrieved June 3, 2012.
93. ^ Andonopoulos AP, Papadimitriou C, Melachrinou M, et al. (2001). "Asymptomatic gastrocnemius muscle biopsy: an extremely sensitive and specific test in the pathologic confirmation of sarcoidosis presenting with hilar adenopathy" (PDF). *Clin. Exp. Rheumatol*. **19** (5): 569–72. PMID 11579718.
94. ^ Baughman, Robert (August 2015). "Treatment of Sarcoidosis". *Clinical Reviews in Allergy and Immunology*. **49** (1): 79–92. doi:10.1007/s12016-015-8492-9. Retrieved 9 April 2016.
95. ^ *a b c* Baughman, Robert; Grutters, Jan (October 2015). "New treatment strategies for pulmonary sarcoidosis: antimetabolites, biological drugs, and other treatment approaches". *The Lancet Respiratory Medicine*. **3**: 813–822. doi:10.1016/S2213-2600(15)00199-X. Retrieved 9 April 2016.
96. ^ *a b* Kamangar, N; Rohani, P; Shorr, AF (6 February 2014). Peters, SP; Talavera, F; Rice, TD; Mosenifar, Z, eds. "Sarcoidosis Treatment & Management". *Medscape Reference*. WebMD. Retrieved 19 February 2014.
97. ^ White, ES; Lynch Jp, 3rd (June 2007). "Current and emerging strategies for the management of sarcoidosis". *Expert Opinion on Pharmacotherapy*. **8** (9): 1293–1311. doi:10.1517/14656566.8.9.1293. PMID 17563264.
98. ^ Paramothayan NS, Lasserson TJ, Jones PW; Lasserson; Jones (18 April 2005). "Corticosteroids for pulmonary sarcoidosis". *The Cochrane Database of Systematic Reviews* (2): CD001114. doi:10.1002/14651858.CD001114.pub2. PMID 15846612.
99. ^ Sahoo DH, Bandyopadhyay D, Xu M, Pearson K, Parambil JG, Lazar CA, Chapman JT, Culver DA; Bandyopadhyay; Xu; Pearson; Parambil; Lazar; Chapman; Culver (November 2011). "Effectiveness and safety of leflunomide for pulmonary and extrapulmonary sarcoidosis" (PDF). *The European Respiratory Journal*. **38** (5): 1145–50. doi:10.1183/09031936.00195010. PMID 21565914.
100. ^ *a b* Panselinas E, Judson MA; Judson (October 2012). "Acute pulmonary exacerbations of sarcoidosis" (PDF). *Chest*. **142** (4): 827–36. doi:10.1378/chest.12-1060. PMID 23032450.
101. ^ *a b c* King CS, Kelly W; Kelly (November 2009). "Treatment of sarcoidosis". *Disease-a-month*. **55** (11): 704–18. doi:10.1016/j.disamonth.2009.06.002. PMID 19857644.

"Sarcoidosis". *BMJ*. **339**: b3206. doi:10.1136/bmj.b3206. PMID 19717499.
21. ^ Tolaney SM, Colson YL, Gill RR, et al. (October 2007). "Sarcoidosis mimicking metastatic breast cancer". *Clin. Breast Cancer*. **7** (10): 804–10. doi:10.3816/CBC.2007.n.044. PMID 18021484.
22. ^ *a b c d e f g* Kamangar, N; Rohani, P; Shorr, AF (6 February 2014). Peters, SP; Talavera, F; Rice, TD; Mosenifar, Z, eds. "Sarcoidosis". *Medscape Reference*. WebMD. Retrieved 19 February 2014.
23. ^ Baughman RP, Lower EE, Gibson K; Lower; Gibson (June 2012). "Pulmonary manifestations of sarcoidosis". *Presse medicale*. **41** (6 Pt 2): e289–302. doi:10.1016/j.lpm.2012.03.019. PMID 22579234.
24. ^ *a b c d e f g h i j k l m n o p q r* Fauci, A.; Kasper, D.; Hauser, S.; Jameson, J.; Loscalzo, J. (2011). *Harrison's Principles of Internal Medicine* (18 ed.). New York: McGraw-Hill Professional. ISBN 978-0-07174889-6.
25. ^ Fuhrer G, Myers JN; Myers (November 2009). "Intrathoracic sarcoidosis". *Disease-a-month*. **55** (11): 661–74. doi:10.1016/j.disamonth.2009.04.009. PMID 19857641.
26. ^ Nunes H, Uzunhan Y, Freynet O, Humbert M, Brillet PY, Kambouchner M, Valeyre D; Uzunhan; Freynet; Humbert; Brillet; Kambouchner; Valeyre (June 2012). "Pulmonary hypertension complicating sarcoidosis". *Presse medicale*. **41** (6 Pt 2): e303–16. doi:10.1016/j.lpm.2012.04.003. PMID 22608948.
27. ^ *a b c d e* Chen ES, Moller DR; Moller (12 July 2011). "Sarcoidosis—scientific progress and clinical challenges". *Nature reviews. Rheumatology*. **7** (8): 457–67. doi:10.1038/nrrheum.2011.93. PMID 21750528.
28. ^ Kumar and clark clinical medicine 8th edition page 846
29. ^ Baughman, Robert P.; Culver, Daniel A.; Judson, Marc A. (2011-03-01). "A Concise Review of Pulmonary Sarcoidosis". *American Journal of Respiratory and Critical Care Medicine*. **183** (5): 573–581. doi:10.1164/rccm.201006-0865CI. ISSN 1073-449X. PMC 3081278. PMID 21037016.
30. ^ *a b* Mañá J, Marcoval J; Marcoval (June 2012). "Skin manifestations of sarcoidosis". *Presse medicale*. **41** (6 Pt 2): e355–74. doi:10.1016/j.lpm.2012.02.046. PMID 22579238.
31. ^ Heath CR, David J, Taylor SC; David; Taylor (January 2012). "Sarcoidosis: Are there differences in your skin of color patients?". *Journal of the American Academy of Dermatology*. **66** (1): 121.e1–14. doi:10.1016/j.jaad.2010.06.068. PMID 22000704.
32. ^ Lodha S, Sanchez M, Prystowsky S; Sanchez; Prystowsky (August 2009). "Sarcoidosis of the skin: a review for the pulmonologist" (PDF). *Chest*. **136** (2): 583–96. doi:10.1378/chest.08-1527.
102. ^ *a b c d e f g h i* Baughman RP, Nunes H, Sweiss NJ, Lower EE; Nunes; Sweiss; Lower (June 2013). "Established and experimental medical therapy of pulmonary sarcoidosis". *The European Respiratory Journal*. **41** (6): 1424–38. doi:10.1183/09031936.00060612. PMID 23397302.
103. ^ Bhat P, Cervantes-Castañeda RA, Doctor PP, Anzaar F, Foster CS; Cervantes-Castañeda; Doctor; Anzaar; Foster (May–June 2009). "Mycophenolate mofetil therapy for sarcoidosis-associated uveitis". *Ocular Immunology and Inflammation*. **17** (3): 185–90. doi:10.1080/09273940902862992. PMID 19585361.
104. ^ Androdias G, Maillet D, Marignier R, Pinède L, Confavreux C, Broussolle C, Vukusic S, Sève P; Maillet; Marignier; Pinède; Confavreux; Broussolle; Vukusic; Sève (29 May 2011). "Mycophenolate mofetil may be effective in CNS sarcoidosis but not in sarcoid myopathy". *Neurology*. **76** (13): 1168–72. doi:10.1212/WNL.0b013e318212aafb. PMID 21444902.
105. ^ Judson, MA (October 2012). "The treatment of pulmonary sarcoidosis". *Respiratory Medicine*. **106** (10): 1351–1361. doi:10.1016/j.rmed.2012.01.013. PMID 22495110.
106. ^ Brill AK, Ott SR, Geiser T; Ott; Geiser (2013). "Effect and safety of mycophenolate mofetil in chronic pulmonary sarcoidosis: a retrospective study". *Respiration*. **86** (5): 376–83. doi:10.1159/000345596. PMID 23295253.
107. ^ Tikoo RK, Kupersmith MJ, Finlay JL; Kupersmith; Finlay (22 April 2004). "Treatment of Refractory Neurosarcoidosis with Cladribine" (PDF). *New England Journal of Medicine*. **350** (17): 1798–1799. doi:10.1056/NEJMc032345. PMID 15103013.
108. ^ Maneiro JR, Salgado E, Gomez-Reino JJ, Carmona L; Salgado; Gomez-Reino; Carmona; Biobadaser Study (August 2012). "Efficacy and safety of TNF antagonists in sarcoidosis: data from the Spanish registry of biologics BIOBADASER and a systematic review". *Seminars in Arthritis and Rheumatism*. **42** (1): 89–103. doi:10.1016/j.semarthrit.2011.12.006. PMID 22387045.
109. ^ Antoniu, SA (January 2010). "Targeting the TNF-alpha pathway in sarcoidosis.". *Expert Opinion on Therapeutic Targets*. **14** (1): 21–9. doi:10.1517/14728220903449244. PMID 20001207.
110. ^ *a b c* Beegle SH, Barba K, Gobunsuy R, Judson MA; Barba; Gobunsuy; Judson (2013). "Current and emerging pharmacological treatments for sarcoidosis: a review". *Drug Design, Development and Therapy*. **7**: 325–38. doi:10.2147/DDDT.S31064. PMC 3627473. PMID 23596348.
111. ^ Callejas-Rubio JL, López-Pérez L, Ortego-Centeno N; López-Pérez; Ortego-Centeno (December 2008). "Tumor necrosis factor-alpha inhibitor treatment for

PMID 19666758.
33. ^ a b James, WD; Berger, T; Dirk, M (2006). *Andrew's diseases of the skin: clinical dermatology* (10th ed.). Philadelphia: Saunders Elsevier. pp. 708–711. ISBN 978-0808923510.
34. ^ House NS, Welsh JP, English JC; Welsh; English Jc (15 August 2012). "Sarcoidosis-induced alopecia". *Dermatology Online Journal*. **18** (8): 4. PMID 22948054.
35. ^ Birnie, David (July 2014). "HRS Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated With Cardiac Sarcoidosis". *Heart Rhythm*. **11** (7): 1304–1323. doi:10.1016/j.hrthm.2014.03.043.
36. ^ Doughan DA, Williams BR; Williams (2006). "Cardiac sarcoidosis". *Heart*. **92** (2): 282–8. doi:10.1136/hrt.2005.080481. PMC 1860791. PMID 16415205.
37. ^ a b Youssef G, Beanlands RS, Birnie DH, Nery PB; Beanlands; Birnie; Nery (December 2011). "Cardiac sarcoidosis: applications of imaging in diagnosis and directing treatment". *Heart*. **97** (24): 2078–87. doi:10.1136/hrt.2011.226076. PMID 22116891.
38. ^ Reuhl J, Schneider M, Sievert H, Lutz FU, Zieger G; Schneider; Sievert; Lutz; Zieger (October 1997). "Myocardial sarcoidosis as a rare cause of sudden cardiac death". *Forensic Sci. Int.* **89** (3): 145–53. doi:10.1016/S0379-0738(97)00106-0. PMID 9363623.
39. ^ Rajasenan V, Cooper ES; Cooper (1969). "Myocardial sarcoidosis, bouts of ventricular tachycardia, psychiatric manifestations and sudden death. A case report". *J Natl Med Assoc*. **61** (4): 306–9. PMC 2611747. PMID 5796402.
40. ^ Chapelon-Abric C (2012). "Cardiac sarcoidosis". *Presse Med*. **41** (6 Pt 2): e317–30. doi:10.1016/j.lpm.2012.04.002. PMID 22608949.
41. ^ Hulten, E; Aslam, S; Osborne, M; Abbasi, S; Bittencourt, MS; Blankstein, R (February 2016). "Cardiac sarcoidosis-state of the art review.". *Cardiovascular diagnosis and therapy*. **6** (1): 50–63. doi:10.3978/j.issn.2223-3652.2015.12.13. PMC 4731586. PMID 26885492.
42. ^ Bodaghi B, Touitou V, Fardeau C, Chapelon C, LeHoang P; Touitou; Fardeau; Chapelon; Lehoang (June 2012). "Ocular sarcoidosis". *Presse medicale*. **41** (6 Pt 2): e349–54. doi:10.1016/j.lpm.2012.04.004. PMID 22595776.
43. ^ Jamilloux, Y; Kodjikian, L; Broussolle, C; Sève, P (August 2014). "Sarcoidosis and uveitis.". *Autoimmunity reviews*. **13** (8): 840–9. PMID 24704868.
44. ^ Papadia M, Herbort CP, Mochizuki M; Herbort; Mochizuki (December 2010). "Diagnosis of ocular sarcoidosis". *Ocular Immunology and Inflammation*. **18** (6): 432–41. doi:10.3109/09273948.2010.524344. PMID 21091056.
sarcoidosis". *Therapeutics and Clinical Risk Management*. **4** (6): 1305–13. doi:10.2147/TCRM.S967 (inactive 2015-02-01). PMC 2643111. PMID 19337437.
112. ^ a b c d Dastoori M, Fedele S, Leao JC, Porter SR; Fedele; Leao; Porter (April 2013). "Sarcoidosis — a clinically orientated review". *Journal of Oral Pathology & Medicine*. **42** (4): 281–9. doi:10.1111/j.1600-0714.2012.01198.x. PMID 22845844.
113. ^ Bakker GJ, Haan YC, Maillette de Buy Wenniger LJ, Beuers U; Haan; Maillette de Buy Wenniger LJ; Beuers (October 2012). "Sarcoidosis of the liver: to treat or not to treat?" (PDF). *The Netherlands Journal of Medicine*. **70** (8): 349–56. PMID 23065982.
114. ^ Baughman RP, Judson MA, Ingledue R, Craft NL, Lower EE; Judson; Ingledue; Craft; Lower (February 2012). "Efficacy and safety of apremilast in chronic cutaneous sarcoidosis" (PDF). *Archives of Dermatology*. **148** (2): 262–4. doi:10.1001/archdermatol.2011.301. PMID 22004880.
115. ^ Clinical trial number *NCT01830959* for "Use of Roflumilast to Prevent Exacerbations in Fibrotic Sarcoidosis Patients (REFS)" at ClinicalTrials.gov
116. ^ Belkhou A, Younsi R, El Bouchti I, El Hassani S; Younsi; El Bouchti; El Hassani (July 2008). "Rituximab as a treatment alternative in sarcoidosis". *Joint, Bone, Spine*. **75** (4): 511–2. doi:10.1016/j.jbspin.2008.01.025. PMID 18562234.
117. ^ Clinical trial number *NCT00279708* for "Atorvastatin to Treat Pulmonary Sarcoidosis" at ClinicalTrials.gov
118. ^ Kaura V., Kaura NV., Kaura BN., Kaura. "Angiotensin-converting enzyme inhibitors in the treatment of sarcoidosis and association with ACE gene polymorphism: case series.".". *Indian J Chest Dis Allied Sci*. **55** (2): 105–7. PMID 24047001.
119. ^ Kaura Vinod; Kaura Samantha H.; Kaura Claire S. (2007). "ACE Inhibitor in the Treatment of Cutaneous and Lymphatic Sarcoidosis". *American Journal of Clinical Dermatology*. **8** (3): 183–186. doi:10.2165/00128071-200708030-00006.
120. ^ Rosenbloom J, Castro SV, Jimenez S (2010). "Fibrotic diseases: cellular and molecular mechanisms and novel therapies". *Ann Intern Med*. **152**: 159–66. doi:10.7326/0003-4819-152-3-201002020-00007.
121. ^ Julian MW, Shao G, Schlesinger LS, Huang Q, Cosmar DG, Bhatt NY, Culver DA, Baughman RP, Wood KL, Crouser ED; Shao; Schlesinger; Huang; Cosmar; Bhatt; Culver; Baughman; Wood; Crouser (1 February 2013). "Nicotine treatment improves Toll-like receptor 2 and Toll-like receptor 9 responsiveness in active pulmonary sarcoidosis" (PDF). *Chest*. **143** (2): 461–70. doi:10.1378/chest.12-0383. PMID 22878868.
122. ^ Drake WP, Oswald-Richter K, Richmond BW, Isom

45. ^ Qazi FA, Thorne JE, Jabs DA; Thorne; Jabs (October 2003). "Scleral nodule associated with sarcoidosis". *American Journal of Ophthalmology*. **136** (4): 752–4. doi:10.1016/S0002-9394(03)00454-9. PMID 14516826.
46. ^ a b c d e f g h Nozaki K, Judson MA; Judson (June 2012). "Neurosarcoidosis: Clinical manifestations, diagnosis and treatment". *Presse medicale*. **41** (6 Pt 2): e331–48. doi:10.1016/j.lpm.2011.12.017. PMID 22595777.
47. ^ Said G, Lacroix C, Plante-Bordeneuve V; Lacroix; Planté-Bordeneuve; Le Page; Pico; Presles; Senant; Remy; Rondepierre; Mallecourt (2002). "Nerve granulomas and vasculitis in sarcoid peripheral neuropathy". *Brain*. **125** (Pt 2): 264–75. doi:10.1093/brain/awf027. PMID 11844727.
48. ^ a b c d e f g h Vardhanabhuti V, Venkatanarasimha N, Bhatnagar G, Maviki M, Iyengar S, Adams WM, Suresh P; Venkatanarasimha; Bhatnagar; Maviki; Iyengar; Adams; Suresh (March 2012). "Extra-pulmonary manifestations of sarcoidosis" (PDF). *Clinical Radiology*. **67** (3): 263–76. doi:10.1016/j.crad.2011.04.018. PMID 22094184.
49. ^ Tavee J, Culver D; Culver (2011). "Sarcoidosis and small-fiber neuropathy". *Curr Pain Headache Rep*. **15** (3): 201–6. doi:10.1007/s11916-011-0180-8. PMID 21298560.
50. ^ Heij L, Dahan A, Hoitsma E; Dahan; Hoitsma (2012). "Sarcoidosis and Pain Caused by Small-Fiber Neuropathy". *Pain Research and Treatment*. **2012**: 256024. doi:10.1155/2012/256024. PMC 3523152. PMID 23304492.
51. ^ Porter N, Beynon HL, Randeva HS; Beynon; Randeva (2003). "Endocrine and reproductive manifestations of sarcoidosis". *QJM*. **96** (8): 553–61. doi:10.1093/qjmed/hcg103. PMID 12897340.
52. ^ Barbour GL, Coburn JW, Slatopolsky E, Norman AW, Horst RL; Coburn; Slatopolsky; Norman; Horst (August 1981). "Hypercalcemia in an anephric patient with sarcoidosis: evidence for extrarenal generation of 1,25-dihydroxyvitamin D". *N. Engl. J. Med*. **305** (8): 440–3. doi:10.1056/NEJM198108203050807. PMID 6894783.
53. ^ *Rheumatology Diagnosis & Therapies* (2nd ed.). Philadelphia: Lippincott Williams & Wilkins. 2005. p. 342.
54. ^ a b Antonelli A, Fazzi P, Fallahi P, Ferrari SM, Ferrannini E; Fazzi; Fallahi; Ferrari; Ferrannini (August 2006). "Prevalence of hypothyroidism and Graves disease in sarcoidosis". *Chest*. **130** (2): 526–32. doi:10.1378/chest.130.2.526. PMID 16899854.
55. ^ Manchanda A, Patel S, Jiang JJ, Babu AR; Patel; Jiang; Babu (March–April 2013). "Thyroid: an unusual hideout for sarcoidosis" (PDF). *Endocrine Practice*. **19** (2): e40–3. doi:10.4158/EP12131.CR. PMID 23337134.
123. ^ Boots AW, Drent M, de Boer VC, Bast A, Haenen GR; Drent; De Boer; Bast; Haenen (August 2011). "Quercetin reduces markers of oxidative stress and inflammation in sarcoidosis". *Clinical Nutrition*. **30** (4): 506–12. doi:10.1016/j.clnu.2011.01.010. PMID 21324570.
124. ^ a b c d e f Drent, Marjolein (2015). "Consequences of Sarcoidosis". *Clinical Chest Medicine*. **36**: 727–737. doi:10.1016/j.ccm.2015.08.013. Retrieved 9 April 2016.
125. ^ a b Marcellis, Rik G. J.; van der Veeke, M. A. F.; Mesters, I.; Drent, M; de Bie, R. A.; de Vries, G. J.; Lenssen, A.F. (2015). "Does physical training reduce fatigue in sarcoidosis?" (PDF). *Sarcoidosis, Vasculitis and Diffuse Lung Diseases*. **32** (1): 53–62. Retrieved 9 April 2016.
126. ^ a b Strookappe, Bert; et al. (2015). "Benefits of Physical Training in Sarcoidosis". *Lung*. **193**: 701–708. doi:10.1007/s00408-015-9784-9. Retrieved 9 April 2016.
127. ^ Karadalli, Muserrefe Nur; Bosnak-Gulcli, Meral; Camicioglu, Burcu; Kokturk, Nurdan; TUrktas, Haluk (April 2016). "Effects of Inspiratory Muscle Training in Subjects With Sarcoidosis: A Randomized Controlled Clinical Trial". *Respiratory Care*. **61** (4): 483–494. doi:10.4187/respcare.04312.
128. ^ Spruit, MA; Wouters, EFM; Gosselink, R (2005). "Rehabilitation programmes in sarcoidosis: a multidisciplinary approach". *European Respiratory Journal*. **32** (3): 316–326.
129. ^ Baughman, Robert; Nunes, Hilario (2013). "Sarcoidosis-associated fatigue: an often forgotten symptom – author reply". *Expert Reviews in Clinical Immunology*. **9** (2): 111. doi:10.1586/ECI.12.93. Retrieved 10 April 2016.
130. ^ "What Is Sarcoidosis?". *National Heart, Lung and Blood Institute*. National Institutes of Health. 14 June 2013. Retrieved 21 February 2014.
131. ^ a b c Syed J, Myers R; Myers (January 2004). "Sarcoid heart disease". *Can J Cardiol*. **20** (1): 89–93. PMID 14968147.
132. ^ Sadek MM, Yung D, Birnie DH, Beanlands RS, Nery PB; Yung; Birnie; Beanlands; Nery (September 2013). "Corticosteroid therapy for cardiac sarcoidosis: a systematic review". *Can J Cardiol*. **29** (9): 1034–41. doi:10.1016/j.cjca.2013.02.004. PMID 23623644.
133. ^ Karakantza M, Matutes E, MacLennan K, O'Connor NT, Srivastava PC, Catovsky D; Matutes; MacLennan; J, Burke VE, Algood H, Braun N, Taylor T, Pandit KV, Aboud C, Yu C, Kaminski N, Boyd AS, King LE; Oswald-Richter; Richmond; Isom; Burke; Algood; Braun; Taylor; Pandit; Aboud; Yu; Kaminski; Boyd; King (September 2013). "Oral antimycobacterial therapy in chronic cutaneous sarcoidosis: a randomized, single-masked, placebo-controlled study". *JAMA Dermatology*. **149** (9): 1040–9. doi:10.1001/jamadermatol.2013.4646. PMC 3927541. PMID 23863960.

56. ^ [a b c d] Fausto N, Abbas A (2004). *Robbins and Cotran Pathologic Basis of disease.* (7th ed.). Philadelphia, PA: Elsevier/Saunders. pp. 737–9. ISBN 978-0721601878.
57. ^ Tokala, Hemasri; Polsani, Karthik; Kalavakunta, Jagadeesh K. (2013-01-01). "Gastric sarcoidosis: a rare clinical presentation". *Case Reports in Gastrointestinal Medicine*. **2013**: 260704. doi:10.1155/2013/260704. ISSN 2090-6528. PMC 3867894. PMID 24368949.
58. ^ Vera C, Funaro D, Bouffard D; Funaro; Bouffard (July–August 2013). "Vulvar sarcoidosis: case report and review of the literature". *Journal of Cutaneous Medicine and Surgery*. **17** (4): 287–90. PMID 23815963.
59. ^ [a b] Paknejad O, Gilani MA, Khoshchehreh M; Gilani; Khoshchehreh (April–June 2011). "Testicular masses in a man with a plausible sarcoidosis". *Indian J Urol*. **27** (2): 269–27. doi:10.4103/0970-1591.82848. PMC 3142840. PMID 21814320.
60. ^ [a b] Paknejad O, Gilani MA, Khoshchehreh M; Gilani; Khoshchehreh (April–June 2011). "Testicular masses in a man with a plausible sarcoidosis". *Indian Journal of Urology*. **27** (2): 269–27. doi:10.4103/0970-1591.82848. PMC 3142840. PMID 21814320.
61. ^ Cremers JP, Drent M, Baughman RP, Wijnen PA, Koek GH; Drent; Baughman; Wijnen; Koek (September 2012). "Therapeutic approach of hepatic sarcoidosis". *Curr Opin Pulm Med*. **18** (5): 472–82. doi:10.1097/MCP.0b013e3283541626. PMID 22617809.
62. ^ [a b] "Statement on Sarcoidosis" (PDF). *American Journal of Respiratory and Critical Care Medicine*. **160** (2): 736–755. August 1999. doi:10.1164/ajrccm.160.2.ats4-99. PMID 10430755.
63. ^ Wurm K, Löhr G; Löhr (1986). "Immuno-cytological blood tests in cases of sarcoidosis". *Sarcoidosis*. **3** (1): 52–9. PMID 3033787.
64. ^ Chen HC, Kang BH, Lai CT, Lin YS; Kang; Lai; Lin (July 2005). "Sarcoidal granuloma in cervical lymph nodes". *Journal of the Chinese Medical Association*. **68** (7): 339–42. doi:10.1016/S1726-4901(09)70172-8. PMID 16038376.
65. ^ [a b c d e f g h i j k l m n o] Rao, DA; Dellaripa, PF (May 2013). "Extrapulmonary manifestations of sarcoidosis.". *Rheumatic diseases clinics of North America*. **39** (2): 277–97. doi:10.1016/j.rdc.2013.02.007. PMID 23597964.
66. ^ Shimamura, Y; Taniguchi, Y; Yoshimatsu, R; Kawase, S; Yamagami, T; Terada, Y (28 August 2015). "Granulomatous periostitis and tracheal involvement in sarcoidosis.". *Rheumatology (Oxford, England)*. **55**: 102. doi:10.1093/rheumatology/kev319. PMID 26320137.
67. ^ Korkmaz, C; Efe, B; Tel, N; Kabukçuoglu, S; O'Connor; Srivastava; Catovsky (1996). "Association between sarcoidosis and lymphoma revisited". *J. Clin. Pathol*. **49** (3): 208–12. doi:10.1136/jcp.49.3.208. PMC 500399. PMID 8675730.
134. ^ Askling J, Grunewald J, Eklund A, Hillerdal G, Ekbom A; Grunewald; Eklund; Hillerdal; Ekbom (November 1999). "Increased risk for cancer following sarcoidosis". *Am. J. Respir. Crit. Care Med*. **160** (5 Pt 1): 1668–72. doi:10.1164/ajrccm.160.5.9904045. PMID 10556138.
135. ^ Tana C, Giamberardino MA, Di Gioacchino M, Mezzetti A, Schiavone C; Giamberardino; Di Gioacchino; Mezzetti; Schiavone (April–June 2013). "Immunopathogenesis of sarcoidosis and risk of malignancy: a lost truth?". *International Journal of Immunopathology and Pharmacology*. **26** (2): 305–13. PMID 23755746.
136. ^ Kornacker M, Kraemer A, Leo E, Ho AD; Kraemer; Leo; Ho (2002). "Occurrence of sarcoidosis subsequent to chemotherapy for non-Hodgkin's lymphoma: report of two cases". *Ann. Hematol*. **81** (2): 103–5. doi:10.1007/s00277-001-0415-6. PMID 11907791.
137. ^ Suvajdzic N, Milenkovic B, Perunicic M, Stojsic J, Jankovic S; Milenkovic; Perunicic; Stojsic; Jankovic (2007). "Two cases of sarcoidosis-lymphoma syndrome". *Med. Oncol*. **24** (4): 469–71. doi:10.1007/s12032-007-0026-8. PMID 17917102.
138. ^ London, Jonathan (2014). "Sarcoidosis Occurring After Lymphoma". *Medicine (Baltimore)*. **93**: e121. doi:10.1097/MD.0000000000000121. PMC 4616278. PMID 25380084.
139. ^ Yao M, Funk GF, Goldstein DP, DeYoung BR, Graham MM; Funk; Goldstein; Deyoung; Graham (2005). "Benign lesions in cancer patients: Case 1. Sarcoidosis after chemoradiation for head and neck cancer". *J. Clin. Oncol*. **23** (3): 640–1. doi:10.1200/JCO.2005.02.089. PMID 15659510.
140. ^ Yamasawa H, Ishii Y, Kitamura S; Ishii; Kitamura (2000). "Concurrence of sarcoidosis and lung cancer. A report of four cases". *Respiration*. **67** (1): 90–3. doi:10.1159/000029470. PMID 10705270.
141. ^ Zambrana F, Antúnez A, García-Mata J, Mellado JM, Villar JL; Antúnez; García-Mata; Mellado; Villar (2009). "Sarcoidosis as a diagnostic pitfall of pancreatic cancer". *Clin Transl Oncol*. **11** (6): 396–8. doi:10.1007/s12094-009-0375-1. PMID 19531456.
142. ^ Schiller G, Said J, Pal S; Said; Pal (2003). "Hairy cell leukemia and sarcoidosis: a case report and review of the literature". *Leukemia*. **17** (10): 2057–9. doi:10.1038/sj.leu.2403074. PMID 14513061.
143. ^ Maloisel F, Oberling F; Oberling (1992). "Acute myeloid leukemia complicating sarcoidosis". *J R Soc Med*. **85** (1): 58–9. PMC 1293471. PMID 1548666.

Erenoglu, E (March 1999). "Sarcoidosis with palpable nodular myositis, periostitis and large-vessel vasculitis stimulating Takayasu's arteritis.". *Rheumatology (Oxford, England)*. **38** (3): 287–8. doi:10.1093/rheumatology/38.3.287. PMID 10325674.

68. ^ Rossman MD, Kreider ME; Kreider (August 2007). "Lesson learned from ACCESS (A Case Controlled Etiologic Study of Sarcoidosis)". *Proc Am Thorac Soc*. **4** (5): 453–6. doi:10.1513/pats.200607-138MS. PMID 17684288.
69. ^ Cathcart S, Sami N, Elewski B; Sami; Elewski (May 2012). "Sarcoidosis as an adverse effect of tumor necrosis factor inhibitors". *Journal of Drugs in Dermatology*. **11** (5): 609–12. PMID 22527429.
70. ^ Iannuzzi MC (August 2007). "Advances in the genetics of sarcoidosis". *Proc Am Thorac Soc*. **4** (5): 457–60. doi:10.1513/pats.200606-136MS. PMID 17684289.
71. ^ Spagnolo P, Grunewald J; Grunewald (May 2013). "Recent advances in the genetics of sarcoidosis". *Journal of Medical Genetics*. **50** (5): 290–7. doi:10.1136/jmedgenet-2013-101532. PMID 23526832.
72. ^ Grunewald J, Eklund A, Olerup O; Eklund; Olerup (March 2004). "Human leukocyte antigen class I alleles and the disease course in sarcoidosis patients". *Am. J. Respir. Crit. Care Med*. **169** (6): 696–702. doi:10.1164/rccm.200303-459OC. PMID 14656748.
73. ^ Grunewald, J (August 2010). "Review: role of genetics in susceptibility and outcome of sarcoidosis.". *Seminars in Respiratory and Critical Care Medicine*. **31** (4): 380–9. doi:10.1055/s-0030-1262206. PMID 20665388.
74. ^ Gialafos, Elias; Triposkiadis, Filippos; Kouranos, Vassilios; Rapti, Aggeliki; Kosmas, Ilias; Manali, Efrosini; Giamouzis, Grigorios; Elezoglou, Antonia; Peros, Ilias (2014-12-01). "Relationship between tumor necrosis factor-α (TNFA) gene polymorphisms and cardiac sarcoidosis". *In Vivo (Athens, Greece)*. **28** (6): 1125–1129. ISSN 1791-7549. PMID 25398810.
75. ^ Saidha S, Sotirchos ES, Eckstein C; Sotirchos; Eckstein (March 2012). "Etiology of sarcoidosis: does infection play a role?". *The Yale Journal of Biology and Medicine*. **85** (1): 133–41. PMC 3313528. PMID 22461752.
76. ^ *a b c* Müller-Quernheim J, Prasse A, Zissel G; Prasse; Zissel (June 2012). "Pathogenesis of sarcoidosis". *Presse medicale*. **41** (6 Pt 2): e275–87. doi:10.1016/j.lpm.2012.03.018. PMID 22595775.
77. ^ Gupta D, Agarwal R, Aggarwal AN, Jindal SK; Agarwal; Aggarwal; Jindal (September 2007). "Molecular evidence for the role of mycobacteria in sarcoidosis: a meta-analysis". *Eur. Respir. J*. **30** (3): 508–16. doi:10.1183/09031936.00002607. PMID 17537780.
78. ^ Almenoff PL, Johnson A, Lesser M, Mattman LH; Reich JM (1985). "Acute myeloblastic leukemia and sarcoidosis. Implications for pathogenesis". *Cancer*. **55** (2): 366–9. doi:10.1002/1097-0142(19850115)55:2<366::AID-CNCR2820550212>3.0.CO;2-1. PMID 3855267.
145. ^ Jamilloux, Y; Valeyre, D; Lortholary, O; Bernard, C; Kerever, S; Lelievre, L; Neel, A; Broussolle, C; Seve, P (January 2015). "The spectrum of opportunistic diseases complicating sarcoidosis.". *Autoimmunity reviews*. **14** (1): 64–74. PMID 25305373.
146. ^ Jamilloux, Y; Néel, A; Lecouffe-Desprets, M; Fèvre, A; Kerever, S; Guillon, B; Bouvry, D; Varron, L; Redares, C; Dominique, S; Roux, M; Chapelon-Abric, C; Valeyre, D; Ducray, F; Bernard, C; Broussolle, C; Hamidou, M; Sève, P (15 April 2014). "Progressive multifocal leukoencephalopathy in patients with sarcoidosis.". *Neurology*. **82** (15): 1307–13. PMID 24610328.
147. ^ Sam, Amir H.; James T.H. Teo (2010). *Rapid Medicine*. Wiley-Blackwell. ISBN 1405183233.
148. ^ Henke CE, Henke G, Elveback LR, Beard CM, Ballard DJ, Kurland LT; Henke; Elveback; Beard; Ballard; Kurland (1986). "The epidemiology of sarcoidosis in Rochester, Minnesota: a population-based study of incidence and survival" (PDF). *Am. J. Epidemiol*. **123** (5): 840–5. PMID 3962966.
149. ^ Rutherford RM, Brutsche MH, Kearns M, Bourke M, Stevens F, Gilmartin JJ; Brutsche; Kearns; Bourke; Stevens; Gilmartin (September 2004). "Prevalence of coeliac disease in patients with sarcoidosis". *Eur J Gastroenterol Hepatol*. **16** (9): 911–5. doi:10.1097/00042737-200409000-00016. PMID 15316417.
150. ^ *a b* Baughman RP, Lower EE, du Bois RM; Lower; Du Bois (29 March 2003). "Sarcoidosis". *Lancet*. **361** (9363): 1111–8. doi:10.1016/S0140-6736(03)12888-7. PMID 12672326.
151. ^ *a b* Lazarus, A (November 2009). "Sarcoidosis: epidemiology, etiology, pathogenesis, and genetics.". *Disease-a-month*. **55** (11): 649–60. doi:10.1016/j.disamonth.2009.04.008. PMID 19857640.
152. ^ *a b c d e f g* Sharma, OP (2005). "Chapter 1: Definition and history of sarcoidosis". *Sarcoidosis*. Sheffield: European Respiratory Society Journals. ISBN 9781904097884.
153. ^ Babalian, L (26 January 1939). "Disease of Besnier-Boeck-Schaumann". *New England Journal of Medicine*. **220** (4): 143–145. doi:10.1056/NEJM193901262200404.
154. ^ "Join WASOG". *wasog.org*. World Association of Sarcoidosis and Other Granulomatous Disorders. Retrieved 21 February 2014.
155. ^ "Index". *Sarcoidosis, Vasculitis and Diffuse Lung Diseases*. 2016. Retrieved 9 April 2016.
156. ^ "Mission & Goals". *Foundation for Sarcoidosis Research*. Retrieved 21 February 2014.
157. ^ "Stop Sarcoidosis Support Group & Community -

Johnson; Lesser; Mattman (May 1996). "Growth of acid fast L forms from the blood of patients with sarcoidosis". *Thorax*. **51** (5): 530–3. doi:10.1136/thx.51.5.530. PMC 473601. PMID 8711683.
79. ^ Morgenthau AS, Iannuzzi MC; Iannuzzi (January 2011). "Recent advances in sarcoidosis" (PDF). *Chest*. **139** (1): 174–82. doi:10.1378/chest.10-0188. PMID 21208877.
80. ^ Padilla ML, Schilero GJ, Teirstein AS; Schilero; Teirstein (March 2002). "Donor-acquired sarcoidosis". *Sarcoidosis, Vasculitis and Diffuse Lung Diseases*. **19** (1): 18–24. PMID 12002380.
81. ^ Romagnani S (June 1997). "The Th1/Th2 paradigm". *Immunol. Today*. **18** (6): 263–6. doi:10.1016/S0167-5699(97)80019-9. PMID 9190109.
82. ^ Morell F, Levy G, Orriols R, Ferrer J, De Gracia J, Sampol G; Levy; Orriols; Ferrer; De Gracia; Sampol (April 2002). "Delayed cutaneous hypersensitivity tests and lymphopenia as activity markers in sarcoidosis". *Chest*. **121** (4): 1239–44. doi:10.1378/chest.121.4.1239. PMID 11948059.
83. ^ *a b c* Bargagli E, Olivieri C, Rottoli P; Olivieri; Rottoli (December 2011). "Cytokine modulators in the treatment of sarcoidosis". *Rheumatology International*. **31** (12): 1539–44.
Inspire". *Stop Sarcoidosis*. Inspire.com. Retrieved 9 April 2016.
158. ^ Izbicki G, Chavko R, Banauch GI, Weiden MD, Berger KI, Aldrich TK, Hall C, Kelly KJ, Prezant DJ; Chavko; Banauch; Weiden; Berger; Aldrich; Hall; Kelly; Prezant (May 2007). "World Trade Center "sarcoid-like" granulomatous pulmonary disease in New York City Fire Department rescue workers" (PDF). *Chest*. **131** (5): 1414–23. doi:10.1378/chest.06-2114. PMID 17400664.
159. ^ "9/11 Health - What We Know About the Health Effects of 9/11". *NYC*. US Government. Retrieved 22 February 2014.
160. ^ Grimes, William (10 Aug 2008). "Bernie Mac, Acerbic Stand-Up Comedian and Irascible TV Dad, Dies at 50". *The New York Times*. Retrieved 30 April 2014.
161. ^ Charlier P, Froesch P; Froesch (2013). "Robespierre: the oldest case of sarcoidosis?". *Lancet*. **382** (9910): 2068. doi:10.1016/S0140-6736(13)62694-X. PMID 24360387.
162. ^ Subramanian P, Chinthalapalli H, Krishnan M; Chinthalapalli; Krishnan; Tarlo; Lobbedez; Pineda; Oreopoulos (September 2004). "Pregnancy and sarcoidosis: an insight into the pathogenesis of hypercalciuria". *Chest*. **126** (3): 995–8. doi:10.1378/chest.126.3.995. PMID 15364785.

## External links [edit]

King, Jr., TE (March 2008). "Sarcoidosis: Interstitial Lung Diseases: Merck Manual Home Edition". *The Merck Manual Home Edition*. Merck Sharp & Dohme Corp. Retrieved 19 February 2014.

| v · t · e · **Sarcoidosis (D86, 135)** | | |
|---|---|---|
| Skin · Lupus pernio · Neurosarcoidosis · Löfgren syndrome · Heerfordt's syndrome · | | |

| v · t · e · **Arthritis in children** | | |
|---|---|---|
| **Inflammatory** | **Idiopathic** | Juvenile idiopathic arthritis · |
| | **Inflammatory disease** | Inflammatory bowel disease · **Sarcoidosis** · Cystic fibrosis · Autoimmune hepatitis · |
| | **Hematological malignancy** | Acute lymphoblastic leukemia · Lymphoma · |
| | **Malignancy** | Neuroblastoma · |
| | **Reactive** | post-streptococcal · Rheumatic fever · postenteric, post-viral · |
| | **Infection** | Septic arthritis · Osteomyelitis · Tuberculosis · Lyme arthritis · |
| **Mechanical** | Osgood–Schlatter disease · | |
| | Osteoid osteoma · Pigmented villonodular synovitis · | |

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|---|---|---|
| **Tumours of cartilage bone or muscle** | **Benign** | Hemangioma · |
| | **Malignant** | Synovial sarcoma · Rhabdomyosarcoma · Ewing's sarcoma · |
| **Central Nervous System** | Idiopathic pain syndromes · **Local:** Complex regional pain syndrome/Reflex sympathetic dystrophy · **Generalized:** Fibromyalgia · | |
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Categories: Ailments of unknown etiology | Lung disorders | Abdominal pain | Rare diseases | Monocyte- and macrophage-related cutaneous conditions | Autoimmune diseases | Steroid-responsive inflammatory conditions




# Sciatica

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**Sciatica** is a medical condition characterized by pain going down the leg from the lower back.[1] This pain may go down the back, outside, or front of the leg. Typically, symptoms are only on one side of the body. Certain causes, however, may result in pain on both sides. Lower back pain is sometimes but not always present. Weakness or numbness may occur in various parts of the affected leg and foot.[2]

About 90% of the time sciatica is due to a spinal disc herniation pressing on one of the lumbar or sacral nerve roots.[3] Other problems that may result in sciatica include spondylolisthesis, spinal stenosis, piriformis syndrome, pelvic tumors, and compression by a baby's head during pregnancy. The straight leg-raising test is often helpful in diagnosis. The test is positive if, when the leg is raised while a person is lying on their back, pain shoots below the knee.[2] In most cases medical imaging is not needed. Exceptions to this are when bowel or bladder function is affected, there is significant loss of feeling or weakness, symptoms are long standing, or there is a concern of a tumor or infection.[4] Conditions that may present similarly are diseases of the hip and early herpes zoster before the rash appears.[2]

Treatment initially is typically with pain medications.[4] It is generally recommended that people continue with activities to the best of their abilities.[2] Often all that is required is time: in about 90% of people the problem goes away in less than six weeks. If the pain is severe and lasts for more than six weeks then surgery may be an option.[4] While surgery often speeds pain improvement, long term benefits are unclear.[2] Surgery may be required if complications occur such as bowel or bladder problems.[4] Many treatments, including steroids, gabapentin, acupuncture, heat or ice, and spinal manipulation, have poor evidence for their use.[2][5]

Depending on how it is defined, 2% to 40% of people have sciatica at some point in time.[3] It is most common during people's 40s and 50s, and men are more frequently affected than women.[2][4] The condition has been known since ancient times.[2] The first known use of the word *sciatica* dates from 1451.[6]

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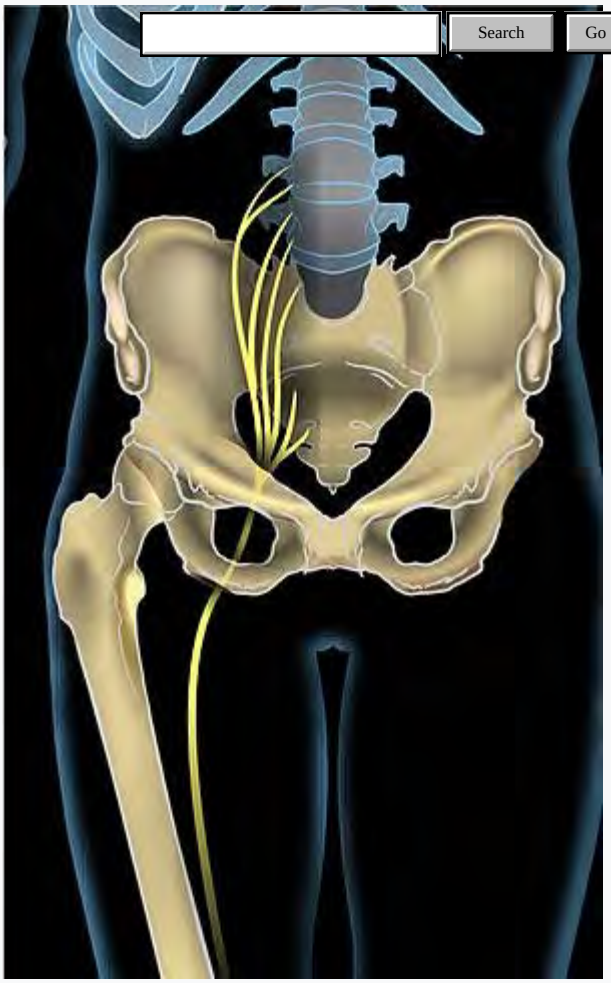
**Sciatica**

**Synonyms** Sciatic neuritis, sciatic neuralgia, lumbar radiculopathy



Anterior view showing the sciatic nerve going down the right leg

**Pronunciation** /saɪˈætɪkə/ *sy-AT-ik-uh*

| Classification and external resources | |
|---|---|
| **Specialty** | Orthopedics, neurology |
| **ICD-10** | M54.3-M54.4 |
| **ICD-9-CM** | 724.3 |

| | |
|---|---|
| **MedlinePlus** | 000686 |
| **eMedicine** | emerg/303 |
| **MeSH** | D012585 |

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## Definition [edit]

The term "sciatica" describes a symptom— pain along the sciatic nerve pathway— rather than a specific condition, illness, or disease. Some use it to mean any pain starting in the lower back and going down the leg. Others use the term more specifically to mean a nerve dysfunction caused by compression of one or more lumbar or sacral nerve roots from a spinal disc herniation. though in this second use it is a diagnosis (i.e., it indicates a cause and effect). Pain typically occurs in the distribution of a dermatome and goes below the knee to the foot. It may be associated with neurological dysfunction, such as weakness.[3] The pain is characteristically of a shooting type, quickly traveling along the course of the nerve.[7]

## Causes [edit]

### Spinal disc herniation [edit]

*Main article: Spinal disc herniation*

Spinal disc herniation pressing on one of the lumbar or sacral nerve roots is the most frequent cause of sciatica, being present in about 90% of cases.[3]

Sciatica caused by pressure from a disc herniation and swelling of surrounding tissue can spontaneously subside if the tear in the disc heals and the pulposus extrusion and inflammation cease.

### Spinal stenosis [edit]

*Main article: Lumbar spinal stenosis*

Other compressive spinal causes include lumbar spinal stenosis, a condition in which the spinal canal (the spaces the spinal cord runs through) narrows and compresses the spinal cord, cauda equina, or sciatic nerve roots. This narrowing can be caused by bone spurs, spondylolisthesis, inflammation, or a herniated disc, which decreases available space for the spinal cord, thus pinching and irritating nerves from the spinal cord that travel to the sciatic nerves.

### Piriformis syndrome [edit]

*Main article: Piriformis syndrome*

Piriformis syndrome is a controversial condition that, depending on the analysis, varies from a "very rare" cause to contributing to up to 8% of low back or buttock pain.[8] In 17% of the population, the sciatic nerve runs through the piriformis muscle rather than beneath it. When the muscle shortens or spasms due to trauma or overuse, it is posited that this causes compression of the sciatic nerve.[8] It has colloquially

been referred to as "wallet sciatica" since a wallet carried in a rear hip pocket compresses the buttock muscles and sciatic nerve when the bearer sits down. Piriformis syndrome causes sciatica when the nerve root itself remains normal and no herniation of a spinal disc is apparent.[9][10]

### Pregnancy [edit]

Sciatica may also occur during pregnancy as a result of the weight of the fetus pressing on the sciatic nerve during sitting or during leg spasms. While most cases do not directly harm the fetus or the mother, indirect harm may come from the numbing effect on the legs, which can cause loss of balance and falls. There is no standard treatment for pregnancy-induced sciatica.[11]

### Other [edit]

Sciatica can also be caused by tumors impinging on the spinal cord or the nerve roots.[3] Severe back pain extending to the hips and feet, loss of bladder or bowel control, or muscle weakness may result from spinal tumors or cauda equina syndrome. Trauma to the spine, such as from a car accident, may also lead to sciatica.

## Pathophysiology [edit]

Sciatica is generally caused by the compression of lumbar nerves L4, or L5 or sacral nerves S1, S2, or S3, or by compression of the sciatic nerve itself. When sciatica is caused by compression of a dorsal nerve root (radix), it is considered a lumbar radiculopathy (or radiculitis when accompanied with an inflammatory response). This can occur as a result of a spinal disk bulge or spinal disc herniation (a herniated intervertebral disc), or from roughening, enlarging, or misalignment (*spondylolisthesis*) of the vertebrae, or as a result of degenerated discs that can reduce the diameter of the lateral foramen (natural hole) through which nerve roots exit the spine. The intervertebral discs consist of an annulus fibrosus, which forms a ring surrounding the inner nucleus pulposus. When there is a tear in the anulus fibrosus, the nucleus pulposus (pulp) may extrude through the tear and press against spinal nerves within the spinal cord, cauda equina, or exiting nerve roots, causing inflammation, numbness, or excruciating pain. Inflammation of the spinal canal can also spread to adjacent facet joints and cause lower back pain and/or referred pain in the posterior thigh(s). Pseudosciatic pain can also be caused by compression of peripheral sections of the nerve, usually from soft tissue tension in the piriformis or related muscles.

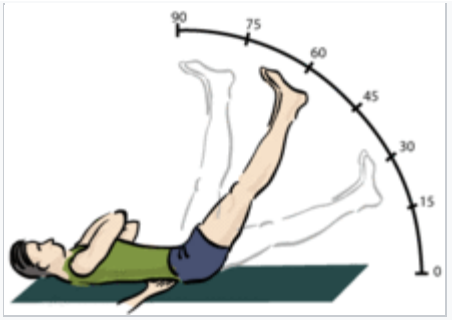
The spinal discs are composed of a tough spongiform ring of cartilage ("anulus fibrosus") with a more malleable center ("nucleus pulposus"). The discs separate the vertebrae, thereby allowing room for the nerve roots to properly exit through the spaces between the vertebrae. The discs cushion the spine from compressive forces, but are weak to pressure applied during rotational movements. That is why a person who bends to one side, at a bad angle to pick something up, may more likely herniate a spinal disc than a person jumping from a ladder and landing on their feet.

Herniation of a disc occurs when the liquid center of the disc bulges outwards, tearing the external ring of fibers, extrudes into the spinal canal, and compresses a nerve root against the lamina or pedicle of a vertebra, thus causing sciatica. This extruded liquid from the "nucleus pulposus" may cause inflammation and swelling of surrounding tissue, which may cause further compression of the nerve root in the confined space in the spinal canal. Many herniated discs themselves, however, cause no pain or discomfort: only occasionally does a disc herniation cause sciatica.

## Diagnosis [edit]

Sciatica is typically diagnosed by physical examination, and the history of the symptoms.[3] Generally if a person reports the typical radiating pain in one leg as well as one or more neurological indications of nerve root tension or neurological deficit, sciatica can be diagnosed.[12]

The most applied diagnostic test is the straight leg raise to produce



Straight Leg test sometimes used to help diagnose a lumbar herniated disc

Lasègue's sign, which is considered positive if pain in the distribution of the sciatic nerve is reproduced with passive flexion of the straight leg between 30 and 70 degrees.[13] While this test is positive in about 90% of people with sciatica, approximately 75% of people with a positive test do not have sciatica.[3]

Imaging tests such as computerised tomography or magnetic resonance imaging can help with the diagnosis of lumbar disc herniation.[14] The utility of MR neurography in the diagnoses of piriformis syndrome is controversial.[8]

## Management [edit]

When the cause of sciatica is lumbar disc herniation, most cases resolve spontaneously over weeks to months.[15] Initially treatment in the first 6–8 weeks should be conservative.[3] There does not appear to be a significant difference in outcomes between advice to stay active and recommendations of bed rest.[16] Similarly, physical therapy (directed exercise) has not been found better than bed rest.[17]

### Medication [edit]

Medicines are commonly prescribed for the treatment of sciatica, but evidence for pain medication is poor.[18] Specifically, low-quality evidence indicates that NSAIDs do not appear to improve immediate pain and all NSAIDs appear about equivalent.[18][19] Evidence is also lacking in use of opioids and muscle relaxants by usual means.[18] In those with sciatica due to piriformis syndrome, botulinum toxin injections may improve pain and or function.[20] There is little evidence for steroids, either epidural or by pill.[21][22] Low-quality evidence supports the use of gabapentin for acute pain relief in those with chronic sciatica.[18]

### Surgery [edit]

Surgery for unilateral sciatica involves the removal of part of the disc, which is known as a discectomy. While it results in short-term benefits, the long-term benefits appear to be equivalent to conservative care.[3][23] Treatment of the underlying cause of the compression is needed in cases of epidural abscess, epidural tumors, and cauda equina syndrome.

### Alternative medicine [edit]

Low to moderate-quality evidence suggests that spinal manipulation is an effective treatment for acute sciatica.[2][24] For chronic sciatica, the evidence is poor.[24] Spinal manipulation has been found generally safe for the treatment of disc-related pain; however, case reports have found an association with cauda equina syndrome[25] and it is contraindicated when there are progressive neurological deficits.[26]

## Epidemiology [edit]

Depending on how it is defined, 2% to 40% of people have sciatica at some point in time.[3] It is most common during people's 40s and 50s and men are more frequently affected than women.[2][4]

## References [edit]

1. ^ "Sciatica". Retrieved 2 July 2015.
2. ^ a b c d e f g h i j Ropper, AH; Zafonte, RD (26 March 2015). "Sciatica.". *The New England Journal of Medicine*. **372** (13): 1240–8. doi:10.1056/NEJMra1410151. PMID 25806916.
3. ^ a b c d e f g h i j Valat, JP; Genevay, S; Marty, M; Rozenberg, S; Koes, B (April 2010). "Sciatica.". *Best practice & research. Clinical rheumatology*. **24** (2): 241–52. doi:10.1016/j.berh.2009.11.005. PMID 20227645.
4. ^ a b c d e f Institute for Quality and Efficiency in Health Care (October 9, 2014). "Slipped disk: Overview". Retrieved 2 July 2015.
5. ^ Markova, Tsvetio (2007). "Treatment of Acute Sciatica". *Am Fam Physician*. **75** (1): 99–100.
6. ^ Simpson, John (2009). *Oxford English dictionary* (2nd ed.). Oxford: Oxford University Press. ISBN 0199563837.
7. ^ Bhat, Sriram (2013). *SRB's Manual of Surgery*. p. 364. ISBN 9789350259443.
8. ^ a b c Miller TA, White KP, Ross DC (September 2012). "The diagnosis and management of Piriformis Syndrome: myths and facts". *Can J Neurol Sci*. **39** (5): 577–83. doi:10.1017/s0317167100015298. PMID 22931697.
9. ^ Kirschner, Jonathan S.; Foye, Patrick M.; Cole, Jeffrey L. (2009). "Piriformis syndrome, diagnosis and treatment". *Muscle & Nerve*. **40** (1): 10–18. doi:10.1002/mus.21318. PMID 19466717.
10. ^ Lewis, A. M.; Layzer, R.; Engstrom, J. W.; Barbaro, N. M.; Chin, C. T. (2006). "Magnetic Resonance Neurography in Extraspinal Sciatica". *Archives of Neurology*. **63** (10): 1469–1472. doi:10.1001/archneur.63.10.1469. PMID 17030664.
11. ^ Sciatic nerve compression during pregnancy
12. ^ Koes, B W; Van Tulder, M W; Peul, W C (2007). "Diagnosis and treatment of sciatica". *BMJ*. **334** (7607): 1313–1317. doi:10.1136/bmj.39223.428495.BE. PMC 1895638. PMID 17585160.
13. ^ Speed, C (May 8, 2004). "Low back pain.". *BMJ (Clinical research ed.)*. **328** (7448): 1119–21. doi:10.1136/bmj.328.7448.1119. PMC 406328. PMID 15130982.
14. ^ Gregory, DS; Seto, CK; Wortley, GC; Shugart, CM (2008). "Acute lumbar disk pain: navigating evaluation and treatment choices". *American family physician*. **78** (7): 835–42. PMID 18841731.
15. ^ Casey, E (February 2011). "Natural history of radiculopathy.". *Physical Medicine and Rehabilitation Clinics of North America*. **22** (1): 1–5. doi:10.1016/j.pmr.2010.10.001. PMID 21292142.
16. ^ Hagen, KB; Hilde, G; Jamtvedt, G; Winnem, M (Oct 18, 2004). "Bed rest for acute low-back pain and sciatica.". *Cochrane database of systematic reviews (Online)* (4): CD001254. doi:10.1002/14651858.CD001254.pub2. PMID 15495012.
17. ^ Luijsterburg, Pim A. J.; Verhagen, Arianne P.; Ostelo, Raymond W. J. G.; Os, Ton A. G.; Peul, Wilco C.; Koes, Bart W. (2007). "Effectiveness of conservative treatments for the lumbosacral radicular syndrome: a systematic review". *European Spine Journal*. **16** (7): 881–899. doi:10.1007/s00586-007-0367-1. PMC 2219647. PMID 17415595.
18. ^ a b c d Pinto, RZ; Maher, CG; Ferreira, ML; Ferreira, PH; Hancock, M; Oliveira, VC; McLachlan, AJ; Koes, B (Feb 13, 2012). "Drugs for relief of pain in patients with sciatica: systematic review and meta-analysis.". *BMJ (Clinical research ed.)*. **344**: e497. doi:10.1136/bmj.e497. PMC 3278391. PMID 22331277.
19. ^ Rasmussen-Barr, Eva; Held, Ulrike; Grooten, Wilhelmus Ja; Roelofs, Pepijn Ddm; Koes, Bart W.; van Tulder, Maurits W.; Wertli, Maria M. (15 October 2016). "Non-steroidal anti-inflammatory drugs for sciatica". *The Cochrane Database of Systematic Reviews*. **10**: CD012382. doi:10.1002/14651858.CD012382. ISSN 1469-493X. PMID 27743405.
20. ^ Waseem, Z; Boulias, C; Gordon, A; Ismail, F; Sheean, G; Furlan, AD (Jan 19, 2011). "Botulinum toxin injections for low-back pain and sciatica.". *Cochrane database of systematic reviews (Online)* (1): CD008257. doi:10.1002/14651858.CD008257.pub2. PMID 21249702.
21. ^ Balagué, F.; Piguet, V.; Dudler, J. (2012). "Steroids for LBP - from rationale to inconvenient truth.". *Swiss Med Wkly*. **142**: w13566. doi:10.4414/smw.2012.13566. PMID 22495738.
22. ^ Chou, R; Hashimoto, R; Friedly, J; Fu, R; Bougatsos, C; Dana, T; Sullivan, SD; Jarvik, J (25 August 2015). "Epidural Corticosteroid Injections for Radiculopathy and Spinal Stenosis: A Systematic Review and Meta-analysis.". *Annals of Internal Medicine*. **163**: 373–81. doi:10.7326/M15-0934. PMID 26302454.
23. ^ Bruggeman, AJ; Decker, RC (February 2011). "Surgical treatment and outcomes of lumbar radiculopathy.". *Physical Medicine and Rehabilitation Clinics of North America*. **22** (1): 161–77. doi:10.1016/j.pmr.2010.10.002. PMID 21292152.
24. ^ a b Leininger, Brent; Bronfort, Gert; Evans, Roni; Reiter, Todd (2011). "Spinal Manipulation or Mobilization for Radiculopathy: A Systematic Review". *Physical Medicine and Rehabilitation Clinics of North America*. **22** (1): 105–125. doi:10.1016/j.pmr.2010.11.002. PMID 21292148.
25. ^ Tamburrelli, FC; Genitiempo, M; Logroscino, CA (May 2011). "Cauda equina syndrome and spine manipulation: case report and review of the literature.". *European Spine Journal*. 20 Suppl 1: S128–31. doi:10.1007/s00586-011-1745-2. PMC 3087049 . PMID 21404036.

26. ^ WHO guidelines on basic training and safety in chiropractic. "2.1 Absolute contraindications to spinal manipulative therapy", p. 21. WHO

| v · t · e · | Spinal disease (M40–M54, 720–724, 737) | |
|---|---|---|
| Deforming | Spinal curvature | Kyphosis · Lordosis · Scoliosis · |
| | Other | Scheuermann's disease · Torticollis · |
| Spondylopathy | inflammatory | Spondylitis (Ankylosing spondylitis · · Sacroiliitis · Discitis · Spondylodiscitis · Pott disease · |
| | non inflammatory | Spondylosis · Spondylolysis · Spondylolisthesis · Retrolisthesis · Spinal stenosis · Facet syndrome · |
| Back pain | | Neck pain · Upper back pain · Low back pain (Coccydynia · **Sciatica** · · Radiculopathy · |
| Intervertebral disc disorder | | Schmorl's nodes · Degenerative disc disease · Spinal disc herniation · Facet joint arthrosis · |

| v · t · e · | Nervous system pathology, PNS, somatic (G50–G64, 350–357) | | |
|---|---|---|---|
| **Nerve, nerve root, plexus** | | | |
| Cranial nerve disease | | | *V* Trigeminal neuralgia · Anesthesia dolorosa · *VII* Facial nerve paralysis · Bell's palsy · Melkersson–Rosenthal syndrome · Parry–Romberg syndrome · Central seven · *XI* Accessory nerve disorder · |
| Radiculopathy, plexopathy | | | *brachial plexus* Brachial plexus lesion · Thoracic outlet syndrome · Phantom limb · |
| Mono-neuropathy | Upper limb | *median nerve:* | Carpal tunnel syndrome · Ape hand deformity · |
| | | *ulnar nerve:* | Ulnar nerve entrapment · Froment's sign · Guyon's canal syndrome · Ulnar claw · |
| | | *radial nerve:* | Radial neuropathy · Wrist drop · Cheiralgia paresthetica · |
| | | *long thoracic nerve:* | Winged scapula · Backpack palsy · |
| | Lower limb | *lateral cutaneous nerve of thigh:* | Meralgia paraesthetica · |
| | | *tibial nerve:* | Tarsal tunnel syndrome · |
| | | *plantar nerve:* | Morton's neuroma · |
| | | *superior gluteal nerve:* | Trendelenburg's sign · |
| | | *sciatic nerve:* | Piriformis syndrome · |
| | General | | Causalgia · Mononeuritis multiplex · Neuropathy Neuralgia/Neuritis · Nerve compression syndrome · |
| **Polyneuropathies/Polyradiculoneuropathy** | | | |
| HMSN | | | Charcot–Marie–Tooth disease · Dejerine–Sottas disease · Refsum's disease · Hereditary spastic paraplegia · Hereditary neuropathy with liability to pressure palsy · Familial amyloid neuropathy · |
| Autoimmune/demyelinating | | | Guillain–Barré syndrome · Chronic inflammatory demyelinating polyneuropathy · |

| | |
|---|---|
| **Other** | Alcoholic polyneuropathy · |

Categories: Peripheral nervous system disorders




# Book:Women's health

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## Obs

- Pregnancy
- Teenage pregnancy
- Ectopic pregnancy
- Abortion
- Pre eclampsia
- Eclampsia
- Nausea and vomiting of pregnancy
- Hyperemesis gravidarum
- C-section
- Childbirth
- Obstructed labor
- Mastitis
- Breastfeeding
- Preterm birth

## Gyn

- Bartholin cyst
- Uterine prolapse
- Human papillomavirus
- Menstrual cycle
- Domestic violence
- Rape
- Polycystic ovary syndrome
- Sexually transmitted disease
- Anorexia nervosa
- Scoliosis

- Puberty
- Gonorrhea
- Candidiasis
- In vitro fertilisation
- Bulimia nervosa
- Chlamydia infection
- Menopause
- Menstruation
- Kegel exercise
- Placenta
- Pap test
- Uterine fibroid
- Vaginismus
- Dysmenorrhea
- Eating disorder
- Hysterectomy
- Premenstrual syndrome
- Douche
- Endometriosis

**Cancer**

- Cervical cancer
- Breast cancer
- Endometrial cancer
- Ovarian cancer

Categories: Wikipedia books (community books)






# Abortion



From Wikipedia, the free encyclopedia

*For other uses, see Abortion (disambiguation).*



**Abortion** is the ending of pregnancy by removing a fetus or embryo before it can survive outside the uterus.[note 1] An abortion which occurs spontaneously is also known as a miscarriage. An abortion may be caused purposely and is then called an induced abortion, or less frequently, "induced miscarriage". The word *abortion* is often used to mean only induced abortions. A similar procedure after the fetus could potentially survive outside the womb is known as a "late termination of pregnancy".[1]

When allowed by local law, abortion in the developed world is one of the safest procedures in medicine.[2][3] Modern methods use medication or surgery for abortions.[4] The drug mifepristone in combination with prostaglandin appears to be as safe and effective as surgery during the first and second trimester of pregnancy.[4][5] Birth control, such as the pill or intrauterine devices, can be used immediately following abortion.[5] When performed legally and safely, induced abortions do not increase the risk of long-term mental or physical problems.[6] In contrast, unsafe abortions cause 47,000 deaths and 5 million hospital admissions each year.[6][7] The World Health Organization recommends safe and legal abortions be available to all women.[8]

Around 56 million abortions occur each year in the world,[9] with a little under half done unsafely.[10] Abortion rates changed little between 2003 and 2008,[10] before which they decreased for at least two decades as access to family planning and birth control increased.[11] As of 2008, 40% of the world's women had access to legal abortions without limits as to reason.[12] Countries that permit abortions have different limits on how late in pregnancy abortion is allowed.[12]

Since ancient times, abortions have been done using herbal medicines, sharp tools, with force, or through other traditional methods.[13] Abortion laws and cultural or religious views of abortions are different around the world. In some areas abortion is legal only in specific cases such as rape, problems with the fetus, poverty, risk to a woman's health, or incest.[14] In many places there is much debate over the moral, ethical, and legal issues of abortion.[15][16] Those who oppose abortion often maintain that an embryo or fetus is a human with a right to life and may compare abortion to murder.[17][18] Those who favor the legality of abortion often hold that a woman has a right to make decisions about her own body.[19]



## Variants



**Induced abortion**

| Classif... | ...s |
|---|---|
| **Specialty** | Obstetrics and gynecology |
| **ICD-10** | O04 |
| **ICD-9-CM** | 779.6 |
| **DiseasesDB** | 4153 |
| **MedlinePlus** | 002912 |
| **eMedicine** | article/252560 |
| **Patient UK** | Abortion |
| **MeSH** | D000028 |

[edit on Wikidata]

# Types

## Induced

Approximately 205 million pregnancies occur each year worldwide. Over a third are unintended and about a fifth end in induced abortion.[10][20] Most abortions result from unintended pregnancies.[21][22] In the United Kingdom, 1 to 2% of abortions are done due to genetic problems in the fetus.[6] A pregnancy can be intentionally aborted in several ways. The manner selected often depends upon the gestational age of the embryo or fetus, which increases in size as the pregnancy progresses.[23][24] Specific procedures may also be selected due to legality, regional availability, and doctor or a women's personal preference.

Reasons for procuring induced abortions are typically characterized as either therapeutic or elective. An abortion is medically referred to as a therapeutic abortion when it is performed to save the life of the pregnant woman; prevent harm to the woman's physical or mental health; terminate a pregnancy where indications are that the child will have a significantly increased chance of premature morbidity or mortality or be otherwise disabled; or to selectively reduce the number of fetuses to lessen health risks associated with multiple pregnancy.[25][26] An abortion is referred to as an elective or voluntary abortion when it is performed at the request of the woman for non-medical reasons.[26] Confusion sometimes arises over the term "elective" because "elective surgery" generally refers to all scheduled surgery, whether medically necessary or not.[27]

## Spontaneous

*Main article: Miscarriage*

Spontaneous abortion, also known as miscarriage, is the unintentional expulsion of an embryo or fetus before the 24th week of gestation.[28] A pregnancy that ends before 37 weeks of gestation resulting in a live-born infant is known as a "premature birth" or a "preterm birth".[29] When a fetus dies in utero after viability, or during delivery, it is usually termed "stillborn".[30] Premature births and stillbirths are generally

not considered to be miscarriages although usage of these terms can sometimes overlap.[31]

Only 30% to 50% of conceptions progress past the first trimester.[32] The vast majority of those that do not progress are lost before the woman is aware of the conception,[26] and many pregnancies are lost before medical practitioners can detect an embryo.[33] Between 15% and 30% of known pregnancies end in clinically apparent miscarriage, depending upon the age and health of the pregnant woman.[34] 80% of these spontaneous abortions happen in the first trimester.[35]

The most common cause of spontaneous abortion during the first trimester is chromosomal abnormalities of the embryo or fetus,[26][36] accounting for at least 50% of sampled early pregnancy losses.[37] Other causes include vascular disease (such as lupus), diabetes, other hormonal problems, infection, and abnormalities of the uterus.[36] Advancing maternal age and a women's history of previous spontaneous abortions are the two leading factors associated with a greater risk of spontaneous abortion.[37] A spontaneous abortion can also be caused by accidental trauma; intentional trauma or stress to cause miscarriage is considered induced abortion or feticide.[38]

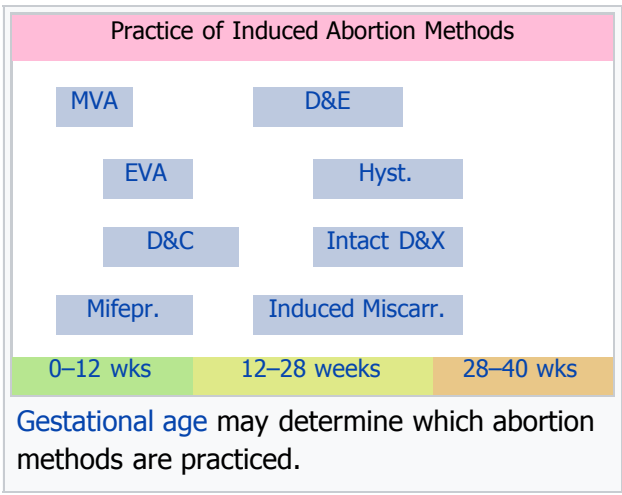


# Methods

## Medical

*Main article: Medical abortion*

Medical abortions are those induced by abortifacient pharmaceuticals. Medical abortion became an alternative method of abortion with the availability of prostaglandin analogs in the 1970s and the antiprogestogen mifepristone (also known as RU-486) in the 1980s.[4][5][39][40][41]



Gestational age may determine which abortion methods are practiced.

The most common early first-trimester medical abortion regimens use mifepristone in combination with a prostaglandin analog (misoprostol or gemeprost) up to 9 weeks gestational age, methotrexate in combination with a prostaglandin analog up to 7 weeks gestation, or a prostaglandin analog alone.[39] Mifepristone–misoprostol combination regimens work faster and are more effective at later gestational ages than methotrexate–misoprostol combination regimens, and combination regimens are more effective than misoprostol alone.[40] This regime is effective in the second trimester.[42]

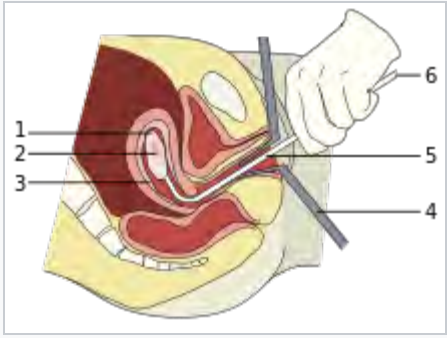
In very early abortions, up to 7 weeks gestation, medical abortion using a mifepristone–misoprostol combination regimen is considered to be more effective than surgical abortion (vacuum aspiration), especially when clinical practice does not include detailed inspection of aspirated tissue.[43] Early medical abortion regimens using mifepristone, followed 24–48 hours later by buccal or vaginal misoprostol are 98% effective up to 9 weeks gestational age.[44] If medical abortion fails, surgical abortion must be used to complete the procedure.[45]

Early medical abortions account for the majority of abortions before 9 weeks gestation in Britain,[46][47] France,[48] Switzerland,[49] and the Nordic countries.[50] In the United States, the percentage of early medical abortions is far lower.[51][52]

Medical abortion regimens using mifepristone in combination with a prostaglandin analog are the most common methods used for second-trimester abortions in Canada, most of Europe, China and India,[41] in contrast to the United States where 96% of second-trimester abortions are performed surgically by dilation and evacuation.[53]

## Surgical

Up to 15 weeks' gestation, suction-aspiration or vacuum aspiration are the most common surgical methods of induced abortion.[54] *Manual vacuum aspiration* (MVA) consists of removing the fetus or embryo, placenta, and membranes by suction using a manual syringe, while *electric vacuum aspiration* (EVA) uses an electric pump. These techniques differ in the mechanism used to apply suction, in how early in pregnancy they can be used, and in whether cervical dilation is necessary.




A vacuum aspiration abortion at eight weeks gestational age (six weeks after fertilization).
**1:** Amniotic sac
**2:** Embryo
**3:** Uterine lining
**4:** Speculum
**5:** Vacurette
**6:** Attached to a suction pump

MVA, also known as "mini-suction" and "menstrual extraction", can be used in very early pregnancy, and does not require cervical dilation. Dilation and curettage (D&C), the second most common method of surgical abortion, is a standard gynecological procedure performed for a variety of reasons, including examination of the uterine lining for possible malignancy, investigation of abnormal bleeding, and abortion. Curettage refers to cleaning the walls of the uterus with a curette. The World Health Organization recommends this procedure, also called *sharp curettage,* only when MVA is unavailable.[55]

From the 15th week of gestation until approximately the 26th, other techniques must be used. Dilation and evacuation (D&E) consists of opening the cervix of the uterus and emptying it using surgical instruments and suction. After the 16th week of gestation, abortions can also be induced by intact dilation and extraction (IDX) (also called intrauterine cranial decompression), which requires surgical decompression of the fetus's head before evacuation. IDX is sometimes called "partial-birth abortion", which has been federally banned in the United States.

In the third trimester of pregnancy, induced abortion may be performed surgically by intact dilation and extraction or by hysterotomy. Hysterotomy abortion is a procedure similar to a caesarean section and is performed under general anesthesia. It requires a smaller incision than a caesarean section and is used during later stages of pregnancy.[56]

First-trimester procedures can generally be performed using local anesthesia, while second-trimester methods may require deep sedation or general anesthesia.[52]

## Labor induction abortion

In places lacking the necessary medical skill for dilation and extraction, or where preferred by practitioners, an abortion can be induced by first inducing labor and then inducing fetal demise if necessary.[57] This is sometimes called "induced miscarriage". This procedure may be performed from 13 weeks gestation to the third trimester. Although it is very uncommon in the United States, more than 80% of induced abortions throughout the second trimester are labor induced abortions in Sweden and other nearby countries.[58]

Only limited data are available comparing this method with dilation and extraction.[58] Unlike D&E, labor induced abortions after 18 weeks may be complicated by the occurrence of brief fetal survival, which may be legally characterized as live birth. For this reason, labor induced abortion is legally risky in the U.S.[58][59]

## Other methods

Historically, a number of herbs reputed to possess abortifacient properties have been used in folk medicine: tansy, pennyroyal, black cohosh, and the now-extinct silphium.[60] The use of herbs in such a manner can cause serious—even lethal—side effects, such as multiple organ failure, and is not recommended by physicians.[61]

Abortion is sometimes attempted by causing trauma to the abdomen. The degree of force, if severe, can cause serious internal injuries without necessarily succeeding in inducing miscarriage.[62] In Southeast Asia,

there is an ancient tradition of attempting abortion through forceful abdominal massage.[63] One of the bas reliefs decorating the temple of Angkor Wat in Cambodia depicts a demon performing such an abortion upon a woman who has been sent to the underworld.[63]

Reported methods of unsafe, self-induced abortion include misuse of misoprostol, and insertion of non-surgical implements such as knitting needles and clothes hangers into the uterus. These methods are rarely seen in developed countries where surgical abortion is legal and available.[64] All of these, and any other method to terminate pregnancy may be called "induced miscarriage".

# Safety

An abortion flyer in South Africa

The health risks of abortion depend principally upon whether the procedure is performed safely or unsafely. The World Health Organization defines unsafe abortions as those performed by unskilled individuals, with hazardous equipment, or in unsanitary facilities.[65] Legal abortions performed in the developed world are among the safest procedures in medicine.[2][66] In the US, the risk of maternal death from abortion is 0.7 per 100,000 procedures,[3] making abortion about 13 times safer for women than childbirth (8.8 maternal deaths per 100,000 live births).[67][68] The risk of abortion-related mortality increases with gestational age, but remains lower than that of childbirth through at least 21 weeks' gestation.[69][70][71] Outpatient abortion is as safe and effective from 64 to 70 days' gestation as it is from 57 to 63 days.[72] In the United States from 2000 to 2009, abortion had a lower mortality rate than plastic surgery.[73]

Vacuum aspiration in the first trimester is the safest method of surgical abortion, and can be performed in a primary care office, abortion clinic, or hospital. Complications are rare and can include uterine perforation, pelvic infection, and retained products of conception requiring a second procedure to evacuate.[74] Infections account for one-third of abortion-related deaths in the United States.[75] The rate of complications of vacuum aspiration abortion in the first trimester is similar regardless of whether the procedure is performed in a hospital, surgical center, or office.[76] Preventive antibiotics (such as doxycycline or metronidazole) are typically given before elective abortion,[77] as they are believed to substantially reduce the risk of postoperative uterine infection.[52][78] Complications after second-trimester abortion are similar to those after first-trimester abortion, and depend somewhat on the method chosen.

There is little difference in terms of safety and efficacy between medical abortion using a combined regimen of mifepristone and misoprostol and surgical abortion (vacuum aspiration) in early first trimester abortions up to 9 weeks gestation.[43] Medical abortion using the prostaglandin analog misoprostol alone is less effective and more painful than medical abortion using a combined regimen of mifepristone and misoprostol or surgical abortion.[79][80]

Some purported risks of abortion are promoted primarily by anti-abortion groups, but lack scientific support.[81] For example, the question of a link between induced abortion and breast cancer has been investigated extensively. Major medical and scientific bodies (including the World Health Organization, the US National Cancer Institute, the American Cancer Society, the Royal College of Obstetricians and Gynaecologists and the American Congress of Obstetricians and Gynecologists) have concluded that abortion does not cause breast cancer,[82] although such a link continues to be studied[83][84] and promoted by anti-abortion groups.[81][85]

## Mental health

*Main article: Abortion and mental health*

There is no relationship between most induced abortions and mental-health problems[6][86] other than

those expected for any unwanted pregnancy.[87] The American Psychological Association has concluded that a woman's first abortion is not a threat to mental health when carried out in the first trimester, with such women no more likely to have mental-health problems than those carrying an unwanted pregnancy to term; the mental-health outcome of a woman's second or greater abortion is less certain.[87][88] Although some studies show negative mental-health outcomes in women who choose abortions after the first trimester because of fetal abnormalities,[89] more rigorous research would be needed to show this conclusively.[90] Some proposed negative psychological effects of abortion have been referred to by anti-abortion advocates as a separate condition called "post-abortion syndrome", which is not recognized by medical or psychological professionals in the United States.[91]

## Unsafe abortion

*Main article: Unsafe abortion*

Women seeking to terminate their pregnancies sometimes resort to unsafe methods, particularly when access to legal abortion is restricted. They may attempt to self-abort or rely on another person who does not have proper medical training or access to proper facilities. This has a tendency to lead to severe complications, such as incomplete abortion, sepsis, hemorrhage, and damage to internal organs.[92]

Soviet poster circa 1925, warning against midwives performing abortions. Title translation: "Abortions performed by either trained or self-taught midwives not only maim the woman, they also often lead to death."

Unsafe abortions are a major cause of injury and death among women worldwide. Although data are imprecise, it is estimated that approximately 20 million unsafe abortions are performed annually, with 97% taking place in developing countries.[2] Unsafe abortions are believed to result in millions of injuries.[2][93] Estimates of deaths vary according to methodology, and have ranged from 37,000 to 70,000 in the past decade;[2][7][94] deaths from unsafe abortion account for around 13% of all maternal deaths.[95] The World Health Organization believes that mortality has fallen since the 1990s.[96] To reduce the number of unsafe abortions, public health organizations have generally advocated emphasizing the legalization of abortion, training of medical personnel, and ensuring access to reproductive-health services.[97] However, the Dublin Declaration on Maternal Health, signed in 2012, notes that "the prohibition of abortion does not affect, in any way, the availability of optimal care to pregnant women".[98]

A major factor in whether abortions are performed safely or not is the legal standing of abortion. Countries with restrictive abortion laws have higher rates of unsafe abortion and similar overall abortion rates compared to those where abortion is legal and available.[7][10][97][99][100][101][102] For example, the 1996 legalization of abortion in South Africa had an immediate positive impact on the frequency of abortion-related complications,[103] with abortion-related deaths dropping by more than 90%.[104] A 2011 study concluded that in the United States, some state-level anti-abortion laws are correlated with lower rates of abortion in that state.[105] The analysis, however, did not take into account travel to other states without such laws to obtain an abortion.[106] In addition, a lack of access to effective contraception contributes to unsafe abortion. It has been estimated that the incidence of unsafe abortion could be reduced by up to 75% (from 20 million to 5 million annually) if modern family planning and maternal health services were readily available globally.[107] Rates of such abortions may be difficult to measure because they can be reported variously as miscarriage, "induced miscarriage", "menstrual regulation", "mini-abortion", and "regulation of a delayed/suspended menstruation".[108][109]

Forty percent of the world's women are able to access therapeutic and elective abortions within gestational limits,[12] while an additional 35 percent have access to legal abortion if they meet certain physical, mental, or socioeconomic criteria.[14] While maternal mortality seldom results from safe abortions, unsafe abortions result in 70,000 deaths and 5 million disabilities per year.[7] Complications of unsafe abortion account for

approximately an eighth of maternal mortalities worldwide,[110] though this varies by region.[111] Secondary infertility caused by an unsafe abortion affects an estimated 24 million women.[100] The rate of unsafe abortions has increased from 44% to 49% between 1995 and 2008.[10] Health education, access to family planning, and improvements in health care during and after abortion have been proposed to address this phenomenon.[112]

### Live birth

Although it is very uncommon, women undergoing surgical abortion after 18 weeks gestation sometimes give birth to a fetus that may survive briefly.[113][114][115] Longer term survival is possible after 22 weeks.[116]

If medical staff observe signs of life, they may be required to provide care: emergency medical care if the child has a good chance of survival and palliative care if not.[117][118][119] Induced fetal demise before termination of pregnancy after 20–21 weeks gestation is recommended to avoid this.[120][121][122][123][124]

Death following live birth which is caused by abortion is given the ICD-10 underlying cause description code of P96.4; data are identified as either fetus or newborn. Between 1999 and 2013, in the U.S., the CDC recorded 531 such deaths for newborns,[125] approximately 4 per 100,000 abortions.[126]

## Incidence

There are two commonly used methods of measuring the incidence of abortion:

- Abortion rate – number of abortions per 1000 women between 15 and 44 years of age
- Abortion percentage – number of abortions out of 100 known pregnancies (pregnancies include live births, abortions and miscarriages)

In many places, where abortion is illegal or carries a heavy social stigma, medical reporting of abortion is not reliable.[99] For this reason, estimates of the incidence of abortion must be made without determining certainty related to standard error.[10]

The number of abortions performed worldwide seems to have remained stable in recent years, with 41.6 million having been performed in 2003 and 43.8 million having been performed in 2008.[10] The abortion rate worldwide was 28 per 1000 women, though it was 24 per 1000 women for developed countries and 29 per 1000 women for developing countries.[10] The same 2012 study indicated that in 2008, the estimated abortion percentage of known pregnancies was at 21% worldwide, with 26% in developed countries and 20% in developing countries.[10]

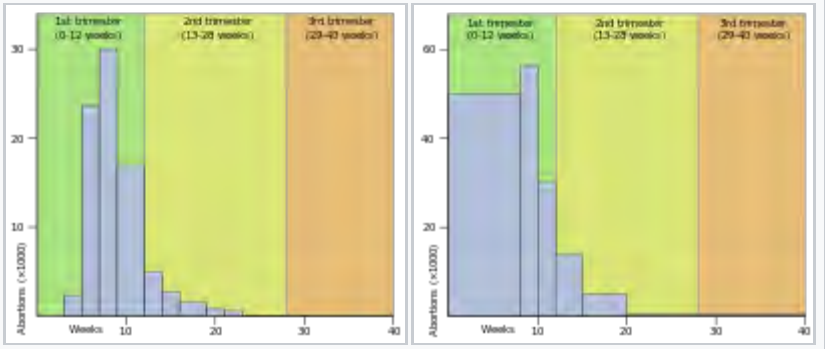
On average, the incidence of abortion is similar in countries with restrictive abortion laws and those with more liberal access to abortion. However, restrictive abortion laws are associated with increases in the percentage of abortions which are performed unsafely.[12][127][128] The unsafe abortion rate in developing countries is partly attributable to lack of access to modern contraceptives; according to the Guttmacher Institute, providing access to contraceptives would result in about 14.5 million fewer unsafe abortions and 38,000 fewer deaths from unsafe abortion annually worldwide.[129]

The rate of legal, induced abortion varies extensively worldwide. According to the report of employees of Guttmacher Institute it ranged from 7 per 1000 women (Germany and Switzerland) to 30 per 1000 women (Estonia) in countries with complete statistics in 2008. The proportion of pregnancies that ended in induced abortion ranged from about 10% (Israel, the Netherlands and Switzerland) to 30% (Estonia) in the same group, though it might be as high as 36% in Hungary and Romania, whose statistics were deemed incomplete.[130][131]

The abortion rate may also be expressed as the average number of abortions a woman has during her reproductive years; this is referred to as *total abortion rate* (TAR).

### Gestational age and method

Abortion rates also vary depending on the stage of pregnancy and the method practiced. In 2003, the Centers for Disease Control and Prevention (CDC) reported that 26% of abortions in the United States were known to have been obtained at less than 6 weeks' gestation, 18% at 7 weeks, 15% at 8 weeks, 18% at 9 through 10 weeks, 9.7% at 11 through 12 weeks, 6.2% at 13 through 15 weeks, 4.1% at 16 through 20 weeks and 1.4% at more than 21 weeks. 90.9% of these were classified as having been done by "curettage" (suction-aspiration, dilation and curettage, dilation and evacuation), 7.7% by "medical" means (mifepristone), 0.4% by "intrauterine instillation" (saline or prostaglandin), and 1.0% by "other" (including hysterotomy and hysterectomy).[132]



Histogram of abortions by gestational age in England and Wales during 2004. (left)

Abortion in the United States by gestational age, 2004. (right)

According to the CDC, due to data collection difficulties the data must be viewed as tentative and some fetal deaths reported beyond 20 weeks may be natural deaths erroneously classified as abortions if the removal of the dead fetus is accomplished by the same procedure as an induced abortion.[133]

The Guttmacher Institute estimated there were 2,200 intact dilation and extraction procedures in the US during 2000; this accounts for 0.17% of the total number of abortions performed that year.[134] Similarly, in England and Wales in 2006, 89% of terminations occurred at or under 12 weeks, 9% between 13 and 19 weeks, and 1.5% at or over 20 weeks. 64% of those reported were by vacuum aspiration, 6% by D&E, and 30% were medical.[135] There are more second trimester abortions in developing countries such as China, India and Vietnam than in developed countries.[136]

# Motivation

## Personal

The reasons why women have abortions are diverse and vary across the world.[133][137]

Some of the most common reasons are to postpone childbearing to a more suitable time or to focus energies and resources on existing children. Others include being unable to afford a child either in terms of the direct costs of raising a child or the loss of income while caring for the child, lack of support from the father, inability to afford additional children, desire to provide schooling for existing children, disruption of one's own education, relationship problems with their partner, a perception of being too young to have a child, unemployment, and not being willing to raise a child conceived as a result of rape or incest, among others.[137][138]

A bar chart depicting selected data from a 1998 AGI meta-study on the reasons women stated for having an abortion.

## Societal

Some abortions are undergone as the result of societal pressures. These might include the preference for children of a specific sex or race,[139] disapproval of single or early motherhood, stigmatization of people with disabilities, insufficient economic support for families, lack of access to or rejection of contraceptive methods, or efforts toward population control (such as China's one-child policy). These factors can sometimes result in compulsory abortion or sex-selective abortion.[140]

An American study in 2002 concluded that about half of women having abortions were using a form of

contraception at the time of becoming pregnant. Inconsistent use was reported by half of those using condoms and three-quarters of those using the birth-control pill; 42% of those using condoms reported failure through slipping or breakage.[141] The Guttmacher Institute estimated that "most abortions in the United States are obtained by minority women" because minority women "have much higher rates of unintended pregnancy."[142]

## Maternal and fetal health

An additional factor is risk to maternal or fetal health, which was cited as the primary reason for abortion in over a third of cases in some countries and as a significant factor in only a single-digit percentage of abortions in other countries.[133][137]

In the U.S., the Supreme Court decisions in *Roe vs Wade* and *Doe vs Bolton*: "ruled that the state's interest in the life of the fetus became compelling only at the point of viability, defined as the point at which the fetus can survive independently of its mother. Even after the point of viability, the state cannot favor the life of the fetus over the life or health of the pregnant woman. Under the right of privacy, physicians must be free to use their "medical judgment for the preservation of the life or health of the mother." On the same day that the Court decided Roe, it also decided Doe v. Bolton, in which the Court defined health very broadly: "The medical judgment may be exercised in the light of all factors—physical, emotional, psychological, familial, and the woman's age—relevant to the well-being of the patient. All these factors may relate to health. This allows the attending physician the room he needs to make his best medical judgment."[143]:1200–1201

Public opinion shifted in America following television personality Sherri Finkbine's discovery during her fifth month of pregnancy that she had been exposed to thalidomide, unable to abort in the United States she traveled to Sweden. From 1962-65 there was an outbreak of German measles that left 15,000 babies with severe birth defects. In 1967, the American Medical Association publicly supported liberalization of abortion laws. A National Opinion Research Center poll in 1965 showed 73% supported abortion when the mothers life was at risk, 57% when birth defects were present and 59% for pregnancies resulting from rape or incest. [144]

## Cancer

The rate of cancer during pregnancy is 0.02–1%, and in many cases, cancer of the mother leads to consideration of abortion to protect the life of the mother, or in response to the potential damage that may occur to the fetus during treatment. This is particularly true for cervical cancer, the most common type which occurs in 1 of every 2000-13000 pregnancies, for which initiation of treatment "cannot co-exist with preservation of fetal life (unless neoadjuvant chemotherapy is chosen)." Very early stage cervical cancers (I and IIa) may be treated by radical hysterectomy and pelvic lymph node dissection, radiation therapy, or both, while later stages are treated by radiotherapy. Chemotherapy may be used simultaneously. Treatment of breast cancer during pregnancy also involves fetal considerations, because lumpectomy is discouraged in favor of modified radical mastectomy unless late-term pregnancy allows follow-up radiation therapy to be administered after the birth.[145]

Exposure to a single chemotherapy drug is estimated to cause a 7.5–17% risk of teratogenic effects on the fetus, with higher risks for multiple drug treatments. Treatment with more than 40 Gy of radiation usually causes spontaneous abortion. Exposure to much lower doses during the first trimester, especially 8 to 15 weeks of development, can cause intellectual disability or microcephaly, and exposure at this or subsequent stages can cause reduced intrauterine growth and birth weight. Exposures above 0.005–0.025 Gy cause a dose-dependent reduction in IQ.[145] It is possible to greatly reduce exposure to radiation with abdominal shielding, depending on how far the area to be irradiated is from the fetus.[146][147]

The process of birth itself may also put the mother at risk. "Vaginal delivery may result in dissemination of neoplastic cells into lymphovascular channels, haemorrhage, cervical laceration and implantation of malignant cells in the episiotomy site, while abdominal delivery may delay the initiation of non-surgical treatment."[148]

# History and religion

*Main article: History of abortion*

Since ancient times abortions have been done using herbal medicines, sharp tools, with force, or through other traditional methods.[13] Induced abortion has long history, and can be traced back to civilizations as varied as China under Shennong (c. 2700 BCE), Ancient Egypt with its Ebers Papyrus (c. 1550 BCE), and the Roman Empire in the time of Juvenal (c. 200 CE).[13] There is evidence to suggest that pregnancies were terminated through a number of methods, including the administration of abortifacient herbs, the use of sharpened implements, the application of abdominal pressure, and other techniques. One of the earliest known artistic representations of abortion is in a bas relief at Angkor Wat (c. 1150). Found in a series of friezes that represent judgment after death in Hindu and Buddhist culture, it depicts the technique of abdominal abortion.[63]

Bas-relief at Angkor Wat, Cambodia, c. 1150, depicting a demon inducing an abortion by pounding the abdomen of a pregnant woman with a pestle.[63][149]

Some medical scholars and abortion opponents have suggested that the Hippocratic Oath forbade Ancient Greek physicians from performing abortions;[13] other scholars disagree with this interpretation,[13] and state the medical texts of Hippocratic Corpus contain descriptions of abortive techniques right alongside the Oath.[150] The physician Scribonius Largus wrote in 43 CE that the Hippocratic Oath prohibits abortion, as did Soranus, although apparently not all doctors adhered to it strictly at the time. According to Soranus' 1st or 2nd century CE work *Gynaecology*, one party of medical practitioners banished all abortives as required by the Hippocratic Oath; the other party —to which he belonged— was willing to prescribe abortions, but only for the sake of the mother's health.[151][152]

FRENCH PERIODICAL PILLS.

Warranted to have the desired effect in all cases.

THESE Pills contain a portion of the only article in the whole materia medica, which can regulate the system and produce the monthly turns of females that can be taken, without hazarding life, and this article is not to be found in any of the pills or nostrums which are pictured forth so largely in the papers of the day. It has frequently occurred that the unhappy patient has by the use of these pills and nostrums given nature such a shock that they have never since enjoyed health, and they never can. It seems that they are got up and advertised merely for the object of making money, regardless of the consequences, and the venders are usually considered beneath responsibility, by all who know them.

The French Periodical Pills are the result of the combined knowledge and experience of some of the oldest and most distinguished physicians of Europe, and have been used by females embracing the gentility and most of the nobility of France, for the last twenty-three years. To eulogize their virtues would not add to their merits. We will only say TRY THEM, and if they do not prove to be what they are here represented to be, your money shall be refunded.

They contain no medicine detrimental to the constitution, but restore all debilitated constitutions to their wonted energy and healthfulness by removing from the system every impurity.

The only precaution necessary to be observed is ladies married should not take them if they have reason to believe they are en ciente, as they are sure to produce a miscarriage, almost without the knowledge of the patient, so gentle yet active are they.

All letters to be directed to DR. L. MONROE, U. S. Agent and Importer, No 58 Union street, Boston.

N. B. The above Pills can only be obtained at 58 Union street, all sold elsewhere in Boston, are counterfeit, and only calculated to deceive.

N. B Full directions accompanying the Pills.

"French Periodical Pills." An example of a clandestine advertisement published in an 1845 edition of the *Boston Daily Times*.

Aristotle, in his treatise on government *Politics* (350 BCE), condemns infanticide as a means of population control. He preferred abortion in such cases, with the restriction[153] "[that it] must be practised on it before it has developed sensation and life; for the line between lawful and unlawful abortion will be marked by the fact of having sensation and being alive."[154] In Christianity, Pope Sixtus V (1585–90) was the first Pope to declare that abortion is homicide regardless of the stage of pregnancy;[155] the Catholic Church had previously been divided on whether it believed that abortion was murder, and did not begin vigorously opposing abortion until the 19th century.[13] Islamic tradition has traditionally permitted abortion until a point in time when Muslims believe the soul enters the fetus,[13] considered by various theologians to be at conception, 40 days after conception, 120 days after conception, or quickening.[156] However, abortion is largely heavily restricted or forbidden in areas of high Islamic faith such as the Middle East and North Africa.[157]

In Europe and North America, abortion techniques advanced starting in the 17th century. However, conservatism by most physicians with regards to sexual matters prevented the wide expansion of safe abortion techniques.[13] Other medical practitioners in addition to some physicians advertised their services, and they were not widely regulated until the 19th century, when the practice (sometimes called *restellism*)[158] was banned in both the United States and the United Kingdom.[13] Church groups as well as physicians were highly influential in anti-abortion movements.[13] In the US, abortion was more dangerous than childbirth until about 1930 when incremental improvements in abortion procedures relative to

childbirth made abortion safer.[note 2] Soviet Russia (1919), Iceland (1935) and Sweden (1938) were among the first countries to legalize certain or all forms of abortion.[159] In 1935 Nazi Germany, a law was passed permitting abortions for those deemed "hereditarily ill", while women considered of German stock were specifically prohibited from having abortions.[160] Beginning in the second half of the twentieth century, abortion was legalized in a greater number of countries.[13] A bill passed by the state legislature of New York legalizing abortion was signed by Governor Nelson Rockefeller in April 1970.[161]

# Society and culture

## Abortion debate

*Main article: Abortion debate*

Induced abortion has long been the source of considerable debate. Ethical, moral, philosophical, biological, religious and legal issues surrounding abortion are related to value systems. Opinions of abortion may be about fetal rights, governmental authority, and women's rights.

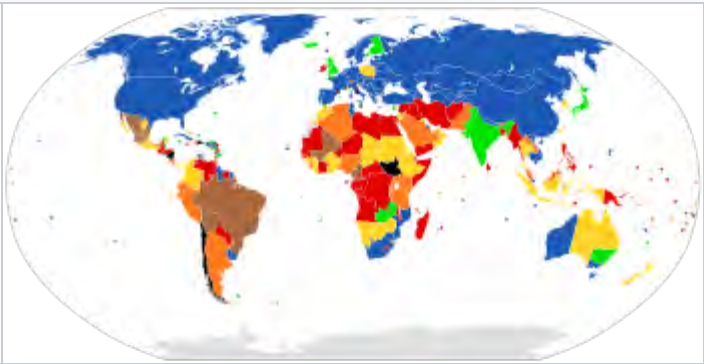
In both public and private debate, arguments presented in favor of or against abortion access focus on either the moral permissibility of an induced abortion, or justification of laws permitting or restricting abortion.[162] The World Medical Association Declaration on Therapeutic Abortion notes that "circumstances bringing the interests of a mother into conflict with the interests of her unborn child create a dilemma and raise the question as to whether or not the pregnancy should be deliberately terminated".[163] Abortion debates, especially pertaining to abortion laws, are often spearheaded by groups advocating one of these two positions. Anti-abortion groups who favor greater legal restrictions on abortion, including complete prohibition, most often describe themselves as "pro-life" while abortion rights groups who are against such legal restrictions describe themselves as "pro-choice".[164] Generally, the former position argues that a human fetus is a human person with a right to live, making abortion morally the same as murder. The latter position argues that a woman has certain reproductive rights, especially the choice whether or not to carry a pregnancy to term.

## Modern abortion law

*Main article: Abortion law*
*See also: History of abortion law debate*

Current laws pertaining to abortion are diverse. Religious, moral, and cultural sensibilities continue to influence abortion laws throughout the world. The right to life, the right to liberty, the right to security of person, and the right to reproductive health are major issues of human rights that are sometimes used as justification for the existence or absence of laws controlling abortion.

In jurisdictions where abortion is legal, certain requirements must often be met before a woman may obtain a safe, legal abortion (an abortion performed without the woman's consent is considered feticide). These requirements usually depend on the age of the fetus, often using a trimester-based system to regulate the window of legality, or as in the U.S., on a doctor's evaluation of the fetus' viability. Some jurisdictions require a waiting period before the procedure, prescribe the distribution of information on fetal development, or require that parents be contacted if their minor daughter requests an



International status of abortion law

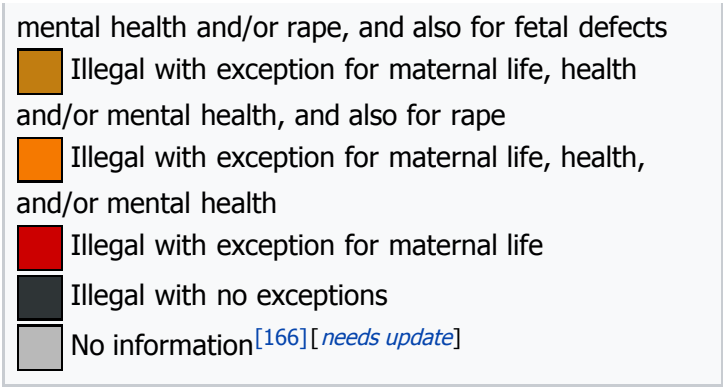
UN 2013 report on abortion law.[165]

Legal on request

Legal for maternal life, health, mental health, rape and/or fetal defects, and also for socioeconomic factors

Illegal with exception for maternal life, health,

abortion.[167] Other jurisdictions may require that a woman obtain the consent of the fetus' father before aborting the fetus, that abortion providers inform women of health risks of the procedure—sometimes including "risks" not supported by the medical literature—and that multiple medical authorities certify that the abortion is either medically or socially necessary. Many restrictions are waived in emergency situations. China, which has ended their[168] one-child policy, and now has a two child policy.[169] [170] has at times incorporated mandatory abortions as part of their population control strategy.[171]




Other jurisdictions ban abortion almost entirely. Many, but not all, of these allow legal abortions in a variety of circumstances. These circumstances vary based on jurisdiction, but may include whether the pregnancy is a result of rape or incest, the fetus' development is impaired, the woman's physical or mental well-being is endangered, or socioeconomic considerations make childbirth a hardship.[14] In countries where abortion is banned entirely, such as Nicaragua, medical authorities have recorded rises in maternal death directly and indirectly due to pregnancy as well as deaths due to doctors' fears of prosecution if they treat other gynecological emergencies.[172][173] Some countries, such as Bangladesh, that nominally ban abortion, may also support clinics that perform abortions under the guise of menstrual hygiene.[174] This is also a terminology in traditional medicine.[175] In places where abortion is illegal or carries heavy social stigma, pregnant women may engage in medical tourism and travel to countries where they can terminate their pregnancies.[176] Women without the means to travel can resort to providers of illegal abortions or attempt to perform an abortion by themselves.[177]

## Sex-selective abortion

*Main article: Sex-selective abortion*

Sonography and amniocentesis allow parents to determine sex before childbirth. The development of this technology has led to sex-selective abortion, or the termination of a fetus based on sex. The selective termination of a female fetus is most common.

Sex-selective abortion is partially responsible for the noticeable disparities between the birth rates of male and female children in some countries. The preference for male children is reported in many areas of Asia, and abortion used to limit female births has been reported in Taiwan, South Korea, India, and China.[178] This deviation from the standard birth rates of males and females occurs despite the fact that the country in question may have officially banned sex-selective abortion or even sex-screening.[179][180][181][182] In China, a historical preference for a male child has been exacerbated by the one-child policy, which was enacted in 1979.[183]

Many countries have taken legislative steps to reduce the incidence of sex-selective abortion. At the International Conference on Population and Development in 1994 over 180 states agreed to eliminate "all forms of discrimination against the girl child and the root causes of son preference",[184] conditions which were also condemned by a PACE resolution in 2011.[185] The World Health Organization and UNICEF, along with other United Nations agencies, have found that measures to reduce access to abortion are much less effective at reducing sex-selective abortions than measures to reduce gender inequality.[184]

## Anti-abortion violence

*Main article: Anti-abortion violence*

In a number of cases, abortion providers and these facilities have been subjected to various forms of violence, including murder, attempted murder, kidnapping, stalking, assault, arson, and bombing. Anti-abortion violence is classified by both governmental and scholarly sources as terrorism.[186][187] Only a

small fraction of those opposed to abortion commit violence.

In the United States, four physicians who performed abortions have been murdered: David Gunn (1993), John Britton (1994), Barnett Slepian (1998), and George Tiller (2009). Also murdered, in the U.S. and Australia, have been other personnel at abortion clinics, including receptionists and security guards such as James Barrett, Shannon Lowney, Lee Ann Nichols, and Robert Sanderson. Woundings (e.g., Garson Romalis) and attempted murders have also taken place in the United States and Canada. Hundreds of bombings, arsons, acid attacks, invasions, and incidents of vandalism against abortion providers have occurred.[188][189] Notable perpetrators of anti-abortion violence include Eric Robert Rudolph, Scott Roeder, Shelley Shannon, and Paul Jennings Hill, the first person to be executed in the United States for murdering an abortion provider.[190]

Legal protection of access to abortion has been brought into some countries where abortion is legal. These laws typically seek to protect abortion clinics from obstruction, vandalism, picketing, and other actions, or to protect women and employees of such facilities from threats and harassment.

Far more common than physical violence is psychological pressure. In 2003, Chris Danze organized pro-life organizations throughout Texas to prevent the construction of a Planned Parenthood facility in Austin. The organizations released the personal information online, of those involved with construction, sending them up to 1200 phone calls a day and contacting their churches.[191] Some protestors record women entering clinics on camera.[191]

## Other animals

*Further information: Miscarriage*

Spontaneous abortion occurs in various animals. For example, in sheep, it may be caused by crowding through doors, or being chased by dogs.[192] In cows, abortion may be caused by contagious disease, such as brucellosis or *Campylobacter*, but can often be controlled by vaccination.[193] Eating pine needles can also induce abortions in cows.[194][195] In horses, a fetus may be aborted or resorbed if it has lethal white syndrome (congenital intestinal aganglionosis). Foal embryos that are homozygous for the dominant white gene (WW) are theorized to also be aborted or resorbed before birth.[196]

Viral infection can cause abortion in dogs.[197] Cats can experience spontaneous abortion for many reasons, including hormonal imbalance. A combined abortion and spaying is performed on pregnant cats, especially in Trap-Neuter-Return programs, to prevent unwanted kittens from being born.[198][199][200] Female rodents may terminate a pregnancy when exposed to the smell of a male not responsible for the pregnancy, known as the Bruce effect.[201]

Abortion may also be induced in animals, in the context of animal husbandry. For example, abortion may be induced in mares that have been mated improperly, or that have been purchased by owners who did not realize the mares were pregnant, or that are pregnant with twin foals.[202] Feticide can occur in horses and zebras due to male harassment of pregnant mares or forced copulation,[203][204][205] although the frequency in the wild has been questioned.[206] Male gray langur monkeys may attack females following male takeover, causing miscarriage.[207]

## References

### Citations


1. ^ Grimes, DA; Stuart, G (2010). "Abortion jabberwocky: the need for better terminology". *Contraception*. **81** (2): 93–6. doi:10.1016/j.contraception.2009.09.005. PMID 20103443.
2. ^ *a b c d e* Grimes, DA; Benson, J; Singh, S; Romero, M; Ganatra, B; Okonofua, FE; Shah, IH (2006). "Unsafe abortion: The preventable pandemic" (PDF). *The Lancet*. **368** (9550): 1908–1919. doi:10.1016/S0140-6736(06)69481-6. PMID 17126724.

3. ^ [a] [b] Raymond, EG; Grossman, D; Weaver, MA; Toti, S; Winikoff, B (November 2014). "Mortality of induced abortion, other outpatient surgical procedures and common activities in the United States". *Contraception*. **90** (5): 476–479. doi:10.1016/j.contraception.2014.07.012. PMID 25152259.
4. ^ [a] [b] [c] Kulier, R; Kapp, N; Gülmezoglu, AM; Hofmeyr, GJ; Cheng, L; Campana, A (9 November 2011). "Medical methods for first trimester abortion.". *Cochrane Database of Systematic Reviews* (11): CD002855. doi:10.1002/14651858.CD002855.pub4. PMID 22071804.
5. ^ [a] [b] [c] Kapp, N; Whyte, P; Tang, J; Jackson, E; Brahmi, D (September 2013). "A review of evidence for safe abortion care". *Contraception*. **88** (3): 350–63. doi:10.1016/j.contraception.2012.10.027. PMID 23261233.
6. ^ [a] [b] [c] [d] Lohr, PA; Fjerstad, M; Desilva, U; Lyus, R (2014). "Abortion". *BMJ*. **348**: f7553. doi:10.1136/bmj.f7553.
7. ^ [a] [b] [c] [d] Shah, I; Ahman, E (December 2009). "Unsafe abortion: global and regional incidence, trends, consequences, and challenges" (PDF). *Journal of Obstetrics and Gynaecology Canada*. **31** (12): 1149–58. PMID 20085681. Archived from the original (PDF) on 16 July 2011.
8. ^ World Health Organization (2012). *Safe abortion: technical and policy guidance for health systems* (PDF) (2nd ed.). Geneva: World Health Organization. p. 8. ISBN 9789241548434.
9. ^ Sedgh, Gilda; Bearak, Jonathan; Singh, Susheela; Bankole, Akinrinola; Popinchalk, Anna; Ganatra, Bela; Rossier, Clémentine; Gerdts, Caitlin; Tunçalp, Özge; Johnson, Brooke Ronald; Johnston, Heidi Bart; Alkema, Leontine (May 2016). "Abortion incidence between 1990 and 2014: global, regional, and subregional levels and trends". *The Lancet*. doi:10.1016/S0140-6736(16)30380-4.
10. ^ [a] [b] [c] [d] [e] [f] [g] [h] [i] Sedgh, G.; Singh, S.; Shah, I. H.; Åhman, E.; Henshaw, S. K.; Bankole, A. (2012). "Induced abortion: Incidence and trends worldwide from 1995 to 2008" (PDF). *The Lancet*. **379** (9816): 625–632. doi:10.1016/S0140-6736(11)61786-8. PMID 22264435. "Because few of the abortion estimates were based on studies of random samples of women, and because we did not use a model-based approach to estimate abortion incidence, it was not possible to compute confidence intervals based on standard errors around the estimates. Drawing on the information available on the accuracy and precision of abortion estimates that were used to develop the subregional, regional, and worldwide rates, we computed intervals of certainty around these rates (webappendix). We computed wider intervals for unsafe abortion rates than for safe abortion rates. The basis for these intervals included published and unpublished assessments of abortion reporting in countries with liberal laws, recently published studies of national unsafe abortion, and high and low estimates of the numbers of unsafe abortion developed by WHO."
11. ^ Sedgh G, Henshaw SK, Singh S, Bankole A, Drescher J (September 2007). "Legal abortion worldwide: incidence and recent trends". *Int Fam Plan Perspect*. **33** (3): 106–116. doi:10.1363/ifpp.33.106.07. PMID 17938093.
12. ^ [a] [b] [c] [d] Culwell KR, Vekemans M, de Silva U, Hurwitz M (July 2010). "Critical gaps in universal access to reproductive health: Contraception and prevention of unsafe abortion". *International Journal of Gynecology & Obstetrics*. **110**: S13–16. doi:10.1016/j.ijgo.2010.04.003. PMID 20451196.
13. ^ [a] [b] [c] [d] [e] [f] [g] [h] [i] [j] [k] Joffe, Carole (2009). "1. Abortion and medicine: A sociopolitical history". In M Paul, ES Lichtenberg, L Borgatta, DA Grimes, PG Stubblefield, MD Creinin. *Management of Unintended and Abnormal Pregnancy* (PDF) (1st ed.). Oxford, United Kingdom: John Wiley & Sons, Ltd. ISBN 978-1-4443-1293-5. Archived from the original on 21 October 2011.
14. ^ [a] [b] [c] Boland, R.; Katzive, L. (2008). "Developments in Laws on Induced Abortion: 1998–2007". *International Family Planning Perspectives*. **34** (3): 110–120. doi:10.1363/ifpp.34.110.08. PMID 18957353.
15. ^ Nixon, edited by Frederick Adolf Paola, Robert Walker, Lois LaCivita (2010). *Medical ethics and humanities*. Sudbury, Mass.: Jones and Bartlett Publishers. p. 249. ISBN 9780763760632.
16. ^ Johnstone, Megan-Jane (2009). *Bioethics a nursing perspective* (5th ed.). Sydney, N.S.W.: Churchill Livingstone/Elsevier. p. 228. ISBN 9780729578738. "Although abortion has been legal in many countries for several decades now, its moral permissibilities continues to be the subject of heated public debate."
17. ^ Pastor Mark Driscoll (18 October 2013). "What do 55 million people have in common?". Fox News. Retrieved 2 July 2014.
18. ^ Hansen, Dale (18 March 2014). "Abortion: Murder, or Medical Procedure?". Huffington Post. Retrieved 2 July 2014.
19. ^ Sifris, Ronli Noa (2013). *Reproductive Freedom, Torture and International Human Rights Challenging the Masculinisation of Torture.* Hoboken: Taylor and Francis. p. 3. ISBN 9781135115227.
20. ^ Cheng L. (1 November 2008). "Surgical versus medical methods for second-trimester induced abortion". *The WHO Reproductive Health Library*. World Health Organization. Archived from the original on 17 June 2011. Retrieved 17 June 2011.
21. ^ Bankole; et al. (1998). "Reasons Why Women Have Induced Abortions: Evidence from 27 Countries". *International Family Planning Perspectives*. **24** (3): 117–127 & 152. doi:10.2307/3038208.
22. ^ Finer, Lawrence B.; Frohwirth, Lori F.; Dauphinee, Lindsay A.; Singh, Susheela; Moore, Ann M. (2005). "Reasons

U.S. Women Have Abortions: Quantitative and Qualitative Perspectives" (PDF). *Perspectives on Sexual and Reproductive Health*. **37** (3): 110–118. doi:10.1111/j.1931-2393.2005.tb00045.x. PMID 16150658.
23. ^ Stubblefield, Phillip G. (2002). "10. Family Planning". In Berek, Jonathan S. *Novak's Gynecology* (13 ed.). Lippincott Williams & Wilkins. ISBN 978-0-7817-3262-8.
24. ^ Bartlett, LA; Berg, CJ; Shulman, HB; Zane, SB; Green, CA; Whitehead, S; Atrash, HK (2004), "Risk factors for legal induced abortion-related mortality in the United States", *Obstetrics & Gynecology*, **103** (4): 729–37, doi:10.1097/01.AOG.0000116260.81570.60, PMID 15051566
25. ^ Roche, Natalie E. (28 September 2004). "Therapeutic Abortion". eMedicine. Archived from the original on 14 December 2004. Retrieved 19 June 2011.
26. ^ *a b c d* Schorge, John O.; Schaffer, Joseph I.; Halvorson, Lisa M.; Hoffman, Barbara L.; Bradshaw, Karen D.; Cunningham, F. Gary, eds. (2008). "6. First-Trimester Abortion". *Williams Gynecology* (1 ed.). McGraw-Hill Medical. ISBN 978-0-07-147257-9.
27. ^ "Elective surgery". Encyclopedia of Surgery. Retrieved 17 December 2012. "An elective surgery is a planned, non-emergency surgical procedure. It may be either medically required (e.g., cataract surgery), or optional (e.g., breast augmentation or implant) surgery.
28. ^ *Churchill Livingstone medical dictionary*. Edinburgh New York: Churchill Livingstone Elsevier. 2008. ISBN 978-0-443-10412-1. "The preferred term for unintentional loss of the product of conception prior to 24 weeks' gestation is miscarriage."
29. ^ Annas, George J.; Elias, Sherman (2007). "51. Legal and Ethical Issues in Obstetric Practice". In Gabbe, Steven G.; Niebyl, Jennifer R.; Simpson, Joe Leigh. *Obstetrics: Normal and Problem Pregnancies* (5 ed.). Churchill Livingstone. p. 669. ISBN 978-0-443-06930-7. "A preterm birth is defined as one that occurs before the completion of 37 menstrual weeks of gestation, regardless of birth weight."
30. ^ "Stillbirth". *Concise Medical Dictionary*. Oxford University Press. 2010. "birth of a fetus that shows no evidence of life (heartbeat, respiration, or independent movement) at any time later than 24 weeks after conception"
31. ^ "7 FAM 1470 Documenting Stillbirth (Fetal Death)". United States Department of State. 18 February 2011. Retrieved 12 Jan 2016.
32. ^ Annas, George J.; Elias, Sherman (2007). "24. Pregnancy loss". In Gabbe, Steven G.; Niebyl, Jennifer R.; Simpson, Joe Leigh. *Obstetrics: Normal and Problem Pregnancies* (5 ed.). Churchill Livingstone. ISBN 978-0-443-06930-7.
33. ^ Katz, Vern L. (2007). "16. Spontaneous and Recurrent Abortion – Etiology, Diagnosis, Treatment". In Katz, Vern L.; Lentz, Gretchen M.; Lobo, Rogerio A.; Gershenson, David M. *Katz: Comprehensive Gynecology* (5 ed.). Mosby. ISBN 978-0-323-02951-3.
34. ^ Stovall, Thomas G. (2002). "17. Early Pregnancy Loss and Ectopic Pregnancy". In Berek, Jonathan S. *Novak's Gynecology* (13 ed.). Lippincott Williams & Wilkins. ISBN 978-0-7817-3262-8.
35. ^ Cunningham, F. Gary; Leveno, Kenneth J.; Bloom, Steven L.; Spong, Catherine Y.; Dashe, Jodi S.; Hoffman, Barbara L.; Casey, Brian M.; Sheffield, Jeanne S., eds. (2014). *Williams Obstetrics* (24th ed.). McGraw Hill Education. ISBN 978-0-07-179893-8.
36. ^ *a b* Stöppler, Melissa Conrad. Shiel, William C., Jr., ed. "Miscarriage (Spontaneous Abortion)". *MedicineNet.com*. WebMD. Archived from the original on 29 August 2004. Retrieved 7 April 2009.
37. ^ *a b* Jauniaux E, Kaminopetros P, El-Rafaey H (1999). "Early pregnancy loss". In Whittle MJ, Rodeck CH. *Fetal medicine: basic science and clinical practice*. Edinburgh: Churchill Livingstone. p. 837. ISBN 978-0-443-05357-3. OCLC 42792567.
38. ^ "Fetal Homicide Laws". National Conference of State Legislatures. Retrieved 7 April 2009.[*dead link*]
39. ^ *a b* Kulier R, Kapp N, Gülmezoglu AM, Hofmeyr GJ, Cheng L, Campana A (2011). "Medical methods for first trimester abortion". *Cochrane Database Syst Rev*. **11** (11): CD002855. doi:10.1002/14651858.CD002855.pub4. PMID 22071804.
40. ^ *a b* Creinin MD, Gemzell-Danielsson K (2009). "Medical abortion in early pregnancy". In Paul M, Lichtenberg ES, Borgatta L, Grimes DA, Stubblefield PG, Creinin MD. *Management of unintended and abnormal pregnancy: comprehensive abortion care*. Oxford: Wiley-Blackwell. pp. 111–134. ISBN 1-4051-7696-2.
41. ^ *a b* Kapp N, von Hertzen H (2009). "Medical methods to induce abortion in the second trimester". In Paul M, Lichtenberg ES, Borgatta L, Grimes DA, Stubblefield PG, Creinin MD. *Management of unintended and abnormal pregnancy: comprehensive abortion care*. Oxford: Wiley-Blackwell. pp. 178–192. ISBN 1-4051-7696-2.
42. ^ Wildschut, H; Both, MI; Medema, S; Thomee, E; Wildhagen, MF; Kapp, N (19 January 2011). "Medical methods for mid-trimester termination of pregnancy.". *Cochrane database of systematic reviews (Online)* (1): CD005216. doi:10.1002/14651858.CD005216.pub2. PMID 21249669.
43. ^ *a b* WHO Department of Reproductive Health and Research (23 November 2006). *Frequently asked clinical questions about medical abortion* (PDF). Geneva: World Health Organization. ISBN 92-4-159484-5. Retrieved

22 November 2011.(subscription required)
44. ^ Fjerstad M, Sivin I, Lichtenberg ES, Trussell J, Cleland K, Cullins V (September 2009). "Effectiveness of medical abortion with mifepristone and buccal misoprostol through 59 gestational days". *Contraception*. **80** (3): 282–286. doi:10.1016/j.contraception.2009.03.010. PMC 3766037. PMID 19698822. The regimen (200 mg of mifepristone, followed 24–48 hours later by 800 mcg of *vaginal* misoprostol) *previously* used by Planned Parenthood clinics in the United States from 2001 to March 2006 was 98.5% effective through 63 days gestation—with an ongoing pregnancy rate of about 0.5%, and an additional 1% of women having uterine evacuation for various reasons, including problematic bleeding, persistent gestational sac, clinician judgment or a women's request. The regimen (200 mg of mifepristone, followed 24–48 hours later by 800 mcg of *buccal* misoprostol) *currently* used by Planned Parenthood clinics in the United States since April 2006 is 98.3% effective through 59 days gestation.
45. ^ Holmquist S, Gilliam M (2008). "Induced abortion". In Gibbs RS, Karlan BY, Haney AF, Nygaard I. *Danforth's obstetrics and gynecology* (10th ed.). Philadelphia: Lippincott Williams & Wilkins. pp. 586–603. ISBN 978-0-7817-6937-2.
46. ^ "Abortion statistics, England and Wales: 2010". London: Department of Health, United Kingdom. 24 May 2011. Retrieved 22 November 2011.[*dead link*]
47. ^ "Abortion statistics, year ending 31 December 2010" (PDF). Edinburgh: ISD, NHS Scotland. 31 May 2011. Retrieved 22 November 2011.
48. ^ Vilain A, Mouquet MC (22 June 2011). "Voluntary terminations of pregnancies in 2008 and 2009" (PDF). Paris: DREES, Ministry of Health, France. Archived from the original (PDF) on 26 September 2011. Retrieved 22 November 2011.
49. ^ . (5 July 2011). "Abortions in Switzerland 2010". Neuchâtel: Office of Federal Statistics, Switzerland. Retrieved 22 November 2011.
50. ^ Gissler M, Heino A (21 February 2011). "Induced abortions in the Nordic countries 2009" (PDF). Helsinki: National Institute for Health and Welfare, Finland. Retrieved 22 November 2011.
51. ^ Jones RK, Kooistra K (March 2011). "Abortion incidence and access to services in the United States, 2008" (PDF). *Perspect Sex Reprod Health*. **43** (1): 41–50. doi:10.1363/4304111. PMID 21388504. Retrieved 22 November 2011.
52. ^ *a b c* Templeton, A.; Grimes, D. A. (2011). "A Request for Abortion". *New England Journal of Medicine*. **365** (23): 2198–2204. doi:10.1056/NEJMcp1103639.
53. ^ Hammond C, Chasen ST (2009). "Dilation and evacuation". In Paul M, Lichtenberg ES, Borgatta L, Grimes DA, Stubblefield PG, Creinin MD. *Management of unintended and abnormal pregnancy: comprehensive abortion care*. Oxford: Wiley-Blackwell. pp. 178–192. ISBN 1-4051-7696-2.
54. ^ Healthwise (2004). "Manual and vacuum aspiration for abortion". WebMD. Archived from the original on 11 February 2007. Retrieved 5 December 2008.
55. ^ World Health Organization (2003). "Dilatation and curettage". *Managing Complications in Pregnancy and Childbirth: A Guide for Midwives and Doctors*. Geneva: World Health Organization. ISBN 978-92-4-154587-7. OCLC 181845530. Retrieved 5 December 2008.
56. ^ McGee, Glenn; Jon F. Merz. "Abortion". *Encarta*. Microsoft. Archived from the original on 31 October 2009. Retrieved 5 December 2008.
57. ^ Borgatta, L (December 2014). "Labor Induction Termination of Pregnancy". *Global Library of Women's Medicine*. GLOWM.10444. doi:10.3843/GLOWM.10444. Retrieved 25 September 2015.
58. ^ *a b c* Society of Family Planning (February 2011). "Clinical Guidelines, Labor induction abortion in the second trimester". *Contraception*. **84** (1): 4–18. doi:10.1016/j.contraception.2011.02.005. Retrieved 25 September 2015. "10. What is the effect of feticide on labor induction abortion outcome? Deliberately causing demise of the fetus before labor induction abortion is performed primarily to avoid transient fetal survival after expulsion; this approach may be for the comfort of both the woman and the staff, to avoid futile resuscitation efforts. Some providers allege that feticide also facilitates delivery, although little data support this claim. Transient fetal survival is very unlikely after intraamniotic installation of saline or urea, which are directly feticidal. Transient survival with misoprostol for labor induction abortion at greater than 18 weeks ranges from 0% to 50% and has been observed in up to 13% of abortions performed with high-dose oxytocin. Factors associated with a higher likelihood of transient fetal survival with labor induction abortion include increasing gestational age, decreasing abortion interval and the use of nonfeticidal inductive agents such as the PGE1 analogues."
59. ^ "2015 Clinical Policy Guidelines" (PDF). *National Abortion Federation*. 2015. Retrieved 30 October 2015. "Policy Statement: Medical induction abortion is a safe and effective method for termination of pregnancies beyond the first trimester when performed by trained clinicians in medical offices, freestanding clinics, ambulatory surgery centers, and hospitals. Feticidal agents may be particularly important when issues of viability arise."
60. ^ Riddle, John M. (1997). *Eve's herbs: a history of contraception and abortion in the West*. Cambridge, Massachusetts: Harvard University Press. ISBN 978-0-674-27024-4. OCLC 36126503.[*page needed*]

61. ^ Ciganda C, Laborde A (2003). "Herbal infusions used for induced abortion". *J. Toxicol. Clin. Toxicol*. **41** (3): 235–239. doi:10.1081/CLT-120021104. PMID 12807304.
62. ^ Smith JP (1998). "Risky choices: The dangers of teens using self-induced abortion attempts". *Journal of Pediatric Health Care*. **12** (3): 147–151. doi:10.1016/S0891-5245(98)90245-0. PMID 9652283.
63. ^ *a b c d* Potts, M.; Graff, M.; Taing, J. (2007). "Thousand-year-old depictions of massage abortion". *Journal of Family Planning and Reproductive Health Care*. **33** (4): 233–234. doi:10.1783/147118907782101904. PMID 17925100.
64. ^ Thapa, S. R.; Rimal, D.; Preston, J. (2006). "Self induction of abortion with instrumentation". *Australian Family Physician*. **35** (9): 697–698. PMID 16969439.
65. ^ "The Prevention and Management of Unsafe Abortion" (PDF). World Health Organization. April 1995. Archived (PDF) from the original on 30 May 2010. Retrieved 1 June 2010.
66. ^ Grimes, DA; Creinin, MD (2004). "Induced abortion: an overview for internists". *Ann. Intern. Med*. **140** (8): 620–6. doi:10.7326/0003-4819-140-8-200404200-00009. PMID 15096333.
67. ^ Raymond, E. G.; Grimes, D. A. (2012). "The Comparative Safety of Legal Induced Abortion and Childbirth in the United States". *Obstetrics & Gynecology*. **119** (2, Part 1): 215–219. doi:10.1097/AOG.0b013e31823fe923. PMID 22270271.
68. ^ Grimes DA (January 2006). "Estimation of pregnancy-related mortality risk by pregnancy outcome, United States, 1991 to 1999". *Am. J. Obstet. Gynecol*. **194** (1): 92–4. doi:10.1016/j.ajog.2005.06.070. PMID 16389015.
69. ^ Bartlett LA; Berg CJ; Shulman HB; et al. (April 2004). "Risk factors for legal induced abortion-related mortality in the United States". *Obstet Gynecol*. **103** (4): 729–37. doi:10.1097/01.AOG.0000116260.81570.60. PMID 15051566.
70. ^ Trupin, Suzanne (27 May 2010). "Elective Abortion". eMedicine. Retrieved 1 June 2010. "At every gestational age, elective abortion is safer for the mother than carrying a pregnancy to term."
71. ^ Pittman, Genevra (23 January 2012). "Abortion safer than giving birth: study". Reuters. Retrieved 4 February 2012.
72. ^ Abbas, D; Chong, E; Raymond, EG (September 2015). "Outpatient medical abortion is safe and effective through 70 days gestation.". *Contraception*. **92** (3): 197–9. doi:10.1016/j.contraception.2015.06.018. PMID 26118638.
73. ^ Raymond, EG; Grossman, D; Weaver, MA; Toti, S; Winikoff, B (November 2014). "Mortality of induced abortion, other outpatient surgical procedures and common activities in the United States.". *Contraception*. **90** (5): 476–9. doi:10.1016/j.contraception.2014.07.012. PMID 25152259.
74. ^ Westfall JM, Sophocles A, Burggraf H, Ellis S (1998). "Manual vacuum aspiration for first-trimester abortion". *Arch Fam Med*. **7** (6): 559–62. doi:10.1001/archfami.7.6.559. PMID 9821831. Archived from the original on 5 April 2005.
75. ^ Dempsey, A (December 2012). "Serious infection associated with induced abortion in the United States.". *Clinical Obstetrics and Gynecology*. **55** (4): 888–92. doi:10.1097/GRF.0b013e31826fd8f8. PMID 23090457.
76. ^ White, Kari; Carroll, Erin; Grossman, Daniel (November 2015). "Complications from first-trimester aspiration abortion: a systematic review of the literature". *Contraception*. **92** (5): 422–438. doi:10.1016/j.contraception.2015.07.013.
77. ^ ACOG Committee on Practice Bulletins—Gynecology (May 2009). "ACOG practice bulletin No. 104: antibiotic prophylaxis for gynecologic procedures". *Obstet Gynecol*. **113** (5): 1180–9. doi:10.1097/AOG.0b013e3181a6d011. PMID 19384149.
78. ^ Sawaya GF, Grady D, Kerlikowske K, Grimes DA (May 1996). "Antibiotics at the time of induced abortion: the case for universal prophylaxis based on a meta-analysis". *Obstet Gynecol*. **87** (5 Pt 2): 884–90. PMID 8677129.
79. ^ Grossman D (3 September 2004). "Medical methods for first trimester abortion: RHL commentary". *Reproductive Health Library*. Geneva: World Health Organization. Retrieved 22 November 2011.
80. ^ Chien P, Thomson M (15 December 2006). "Medical versus surgical methods for first trimester termination of pregnancy: RHL commentary". *Reproductive Health Library*. Geneva: World Health Organization. Archived from the original on 17 May 2010. Retrieved 1 June 2010.
81. ^ *a b* Jasen P (October 2005). "Breast cancer and the politics of abortion in the United States". *Med Hist*. **49** (4): 423–44. doi:10.1017/S0025727300009145. PMC 1251638. PMID 16562329.
82. ^ Position statements of major medical bodies on abortion and breast cancer include:
    - World Health Organization: "Induced abortion does not increase breast cancer risk (Fact sheet N°240)". World Health Organization. Archived from the original on 13 February 2011. Retrieved 6 January 2011.
    - National Cancer Institute: "Abortion, Miscarriage, and Breast Cancer Risk". National Cancer Institute. Archived from the original on 21 December 2010. Retrieved 11 January 2011.
    - American Cancer Society: "Is Abortion Linked to Breast Cancer?". American Cancer Society. 23 September 2010. Archived from the original on 5 June 2011. Retrieved 20 June 2011. "At this time, the scientific evidence does not support the notion that abortion of any kind raises the risk of breast cancer."

- Royal College of Obstetricians and Gynaecologists: "The Care of Women Requesting Induced Abortion" (PDF). Royal College of Obstetricians and Gynaecologists. p. 9. Archived from the original (PDF) on 27 July 2013. Retrieved 29 June 2008. "Induced abortion is not associated with an increase in breast cancer risk."
- American Congress of Obstetricians and Gynecologists: "ACOG Finds No Link Between Abortion and Breast Cancer Risk". American Congress of Obstetricians and Gynecologists. 31 July 2003. Archived from the original on 2 January 2011. Retrieved 11 January 2011.

83. ^ Lanfranchi, Angela; Fagan, Patrick (2014). "Breast Cancer and Induced Abortion: A Comprehensive Review of Breast Development and Pathophysiology, the Epidemiologic Literature, and Proposal for Creation of Databanks to Elucidate All Breast Cancer Risk Factors" (PDF). *Issues in Law & Medicine*. **29** (1): 1–133. Retrieved 11 November 2015. "Given what is known of breast physiology, we can conclude that the following factors are protective, or decrease the likelihood that a woman will develop breast cancer: • Full-term pregnancy or pregnancy lasting longer than 32 weeks • Multiparity (more than one full-term pregnancy) • Short period ("susceptibility window") between menarche and first full-term pregnancy • Full-term pregnancy soon after abortion or second-trimester miscarriage • Breastfeeding"
84. ^ Huang Yubei; Zhang Xiaoliang; et al. (February 2014). "A meta-analysis of the association between induced abortion and breast cancer risk among Chinese females". *Cancer Causes Control*. Springer International Publishing. **25** (2): 227–236. doi:10.1007/s10552-013-0325-7. ISSN 1573-7225. PMID 24272196. Retrieved 11 November 2015. "Compared to people without any history of [induced abortion], an increased risk of breast cancer was observed among females who had at least one [induced abortion]."
85. ^ Schneider, A. Patrick II; Zainer, Christine; et al. (August 2014). "The breast cancer epidemic: 10 facts". *The Linacre Quarterly*. Catholic Medical Association. **81** (3): 244–277. doi:10.1179/2050854914Y.0000000027. Retrieved 11 November 2015. "...an association between [induced abortion] and breast cancer has been found by numerous Western and non-Western researchers from around the world. This is especially true in more recent reports that allow for a sufficient breast cancer latency period since an adoption of a Western life style in sexual and reproductive behavior."
86. ^ Cockburn, Jayne; Pawson, Michael E. (2007). *Psychological Challenges to Obstetrics and Gynecology: The Clinical Management*. Springer. p. 243. ISBN 978-1-84628-807-4.
87. ^ *a b* "APA Task Force Finds Single Abortion Not a Threat to Women's Mental Health" (Press release). American Psychological Association. 12 August 2008. Retrieved 7 September 2011.
88. ^ "Report of the APA Task Force on Mental Health and Abortion" (PDF). Washington, DC: American Psychological Association. 13 August 2008.
89. ^ "Mental Health and Abortion". American Psychological Association. 2008. Retrieved 18 April 2012.
90. ^ Steinberg, J. R. (2011). "Later Abortions and Mental Health: Psychological Experiences of Women Having Later Abortions—A Critical Review of Research". *Women's Health Issues*. **21** (3): S44–S48. doi:10.1016/j.whi.2011.02.002. PMID 21530839.
91. ^ Kelly, Kimberly (February 2014). "The spread of 'Post Abortion Syndrome' as social diagnosis". *Social Science & Medicine*. **102**: 18–25. doi:10.1016/j.socscimed.2013.11.030.
92. ^ Okonofua, F. (2006). "Abortion and maternal mortality in the developing world" (PDF). *Journal of Obstetrics and Gynaecology Canada*. **28** (11): 974–979. PMID 17169222. Archived from the original (PDF) on 11 January 2012.
93. ^ Haddad, LB.; Nour, NM. (2009). "Unsafe abortion: unnecessary maternal mortality". *Rev Obstet Gynecol*. **2** (2): 122–6. PMC 2709326. PMID 19609407.
94. ^ Lozano, R (15 December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.". *Lancet*. **380** (9859): 2095–128. doi:10.1016/S0140-6736(12)61728-0. hdl:10536/DRO/DU:30050819. PMID 23245604.
95. ^ Darney, Leon Speroff, Philip D. (2010). *A clinical guide for contraception* (5th ed.). Philadelphia, Pa.: Lippincott Williams & Wilkins. p. 406. ISBN 1-60831-610-6.
96. ^ World Health Organisation (2011). *Unsafe abortion: global and regional estimates of the incidence of unsafe abortion and associated mortality in 2008* (PDF) (6th ed.). World Health Organisation. p. 27. ISBN 978-92-4-150111-8.
97. ^ *a b* Berer M (2000). "Making abortions safe: a matter of good public health policy and practice". *Bull. World Health Organ*. **78** (5): 580–92. PMC 2560758. PMID 10859852.
98. ^ "Translations". Dublin Declaration. Retrieved 28 October 2015.
99. ^ *a b* Sedgh G, Henshaw S, Singh S, Ahman E, Shah IH (2007). "Induced abortion: estimated rates and trends worldwide". *Lancet*. **370** (9595): 1338–45. CiteSeerX 10.1.1.454.4197. doi:10.1016/S0140-6736(07)61575-X. PMID 17933648.
100. ^ *a b* "Unsafe abortion: Global and regional estimates of the incidence of unsafe abortion and associated mortality in 2003" (PDF). World Health Organization. 2007. Archived (PDF) from the original on 16 February 2011. Retrieved 7 March 2011.

101. ^ Berer M (November 2004). "National laws and unsafe abortion: the parameters of change". *Reprod Health Matters*. **12** (24 Suppl): 1–8. doi:10.1016/S0968-8080(04)24024-1. PMID 15938152.
102. ^ Culwell, Kelly R.; Hurwitz, Manuelle (May 2013). "Addressing barriers to safe abortion". *International Journal of Gynecology & Obstetrics*. **121**: S16–S19. doi:10.1016/j.ijgo.2013.02.003.
103. ^ Jewkes R, Rees H, Dickson K, Brown H, Levin J (March 2005). "The impact of age on the epidemiology of incomplete abortions in South Africa after legislative change". *BJOG*. **112** (3): 355–9. doi:10.1111/j.1471-0528.2004.00422.x. PMID 15713153.
104. ^ Bateman C (December 2007). "Maternal mortalities 90% down as legal TOPs more than triple". *S. Afr. Med. J.* **97** (12): 1238–42. PMID 18264602.
105. ^ New, M. J. (15 February 2011). "Analyzing the Effect of Anti-Abortion U.S. State Legislation in the Post-Casey Era". *State Politics & Policy Quarterly*. **11** (1): 28–47. doi:10.1177/1532440010387397.
106. ^ Medoff, M. H.; Dennis, C. (21 July 2014). "Another Critical Review of New's Reanalysis of the Impact of Antiabortion Legislation". *State Politics & Policy Quarterly*. **14** (3): 269–276. doi:10.1177/1532440014535476.
107. ^ "Facts on Investing in Family Planning and Maternal and Newborn Health" (PDF). Guttmacher Institute. 2010. Archived from the original (PDF) on 24 March 2012. Retrieved 24 May 2012.
108. ^ Grimes, David A. "Unsafe Abortion - The Preventable Pandemic*". Retrieved 2010-01-16.
109. ^ Nations, MK (1997). "Women's hidden transcripts about abortion in Brazil". *Soc Sci Med*. **44**: 1833–45. doi:10.1016/s0277-9536(96)00293-6. PMID 9194245.
110. ^ Maclean, Gaynor (2005). "XI. Dimension, Dynamics and Diversity: A 3D Approach to Appraising Global Maternal and Neonatal Health Initiatives". In Balin, Randell E. *Trends in Midwifery Research*. Nova Publishers. pp. 299–300. ISBN 978-1-59454-477-4.
111. ^ Salter, C.; Johnson, H.B.; Hengen, N. (1997). "Care for Postabortion Complications: Saving Women's Lives". *Population Reports*. Johns Hopkins School of Public Health. **25** (1). Archived from the original on 1 September 2011.
112. ^ UNICEF, United Nations Population Fund, WHO, World Bank (2010). "Packages of interventions: Family planning, safe abortion care, maternal, newborn and child health". Retrieved 31 December 2010.
113. ^ "The Care of Women Requesting Induced Abortion. Evidence-Based Clinical Guideline no. 7" (PDF). *Royal College of Obstetricians and Gynaecologists*. November 2011. Retrieved 31 October 2015. "RECOMMENDATION 6.21 Feticide should be performed before medical abortion after 21 weeks and 6 days of gestation to ensure that there is no risk of a live birth."
114. ^ Society of Family Planning (February 2011). "Clinical Guidelines, Labor induction abortion in the second trimester". *Contraception*. **84** (1): 4–18. doi:10.1016/j.contraception.2011.02.005. "Transient survival with misoprostol for labor induction abortion at greater than 18 weeks ranges from 0% to 50% and has been observed in up to 13% of abortions performed with high-dose oxytocin."
115. ^ Fletcher; Isada; Johnson; Evans (Aug 1992). "Fetal intracardiac potassium chloride injection to avoid the hopeless resuscitation of an abnormal abortus: II. Ethical issues.". *Obstetrics and Gynecology*. **80** (2): 310–313. PMID 1635751. "... following later abortions at greater than 20 weeks, the rare but catastrophic occurrence of live births can lead to fractious controversy over neonatal management."
116. ^ "Termination of Pregnancy for Fetal Abnormality" (PDF). *Royal College of Obstetricians and Gynaecologists*: 29–31. May 2010. Retrieved 26 October 2015.
117. ^ Nuffield Council on Bioethics (2007). "Critical care decisions in fetal and neonatal medicine: a guide to the report" (PDF). Retrieved 29 October 2015. "Under English law, fetuses have no independent legal status. Once born, babies have the same rights to life as other people."
118. ^ Gerri R. Baer; Robert M. Nelson (2007). "Preterm Birth: Causes, Consequences, and Prevention. C: A Review of Ethical Issues Involved in Premature Birth". *Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes;*. "In 2002, the 107th U.S. Congress passed the Born-Alive Infants Protection Act of 2001. This law established personhood for all infants who are born "at any stage of development" who breathe, have a heartbeat, or "definite movement of voluntary muscles," regardless of whether the birth was due to labor or induced abortion."
119. ^ Chabot, Steve (5 August 2002). "H.R. 2175 (107th): Born-Alive Infants Protection Act of 2002". *govtrack.us*. Retrieved 30 October 2015. "The term ``born alive is defined as the complete expulsion or extraction from its mother of that member, at any stage of development, who after such expulsion or extraction breathes or has a beating heart, pulsation of the umbilical cord, or definite movement of the voluntary muscles, regardless of whether the umbilical cord has been cut, and regardless of whether the expulsion or extraction occurs as a result of natural or induced labor, cesarean section, or induced abortion."
120. ^ "Practice Bulletin: Second-Trimester Abortion" (PDF). *Obstetrics & Gynecology*. **121** (6): 1394–1406. June 2013. doi:10.1097/01.AOG.0000431056.79334.cc. PMID 23812485. Retrieved 30 October 2015. "With medical abortion after 20 weeks of gestation, induced fetal demise may be preferable to the woman or provider in order to avoid transient fetal survival after expulsion."

121. ^ "Clinical Guidelines: Induction of fetal demise before abortion" (PDF). *Contraception: a publication of Society of Family Planning*. **81**: 8. January 2010. doi:10.1016/j.contraception.2010.01.018. Retrieved 26 October 2015. "Inducing fetal demise before induction termination avoids signs of live birth that may have beneficial emotional, ethical and legal consequences."
122. ^ Committee on Health Care for Underserved Women (November 2014). "Committee Opinion 613: Increasing Access to Abortion". *Obstetrics & Gynecology*. **124**: 1060–1065. doi:10.1097/01.aog.0000456326.88857.31. Retrieved 28 October 2015. ""“Partial-birth” abortion bans—The federal Partial-Birth Abortion Ban Act of 2003 (upheld by the Supreme Court in 2007) makes it a federal crime to perform procedures that fall within the definition of so-called “partial-birth abortion” contained in the statute, with no exception for procedures necessary to preserve the health of the woman...physicians and lawyers have interpreted the banned procedures as including intact dilation and evacuation unless fetal demise occurs before surgery."
123. ^ "2015 Clinical Policy Guidelines" (PDF). *National Abortion Federation*. 2015. Retrieved 30 October 2015. "Policy Statement: Medical induction abortion is a safe and effective method for termination of pregnancies beyond the first trimester when performed by trained clinicians in medical offices, freestanding clinics, ambulatory surgery centers, and hospitals. Feticidal agents may be particularly important when issues of viability arise."
124. ^ "FIGO (International Federation of Gynecology and Obstetrics) Committee Report: Ethical aspects concerning termination of pregnancy following prenatal diagnosis.". *International Journal of Gynecology and Obstetrics*. **102** (1): 97–98. 2008. doi:10.1016/j.ijgo.2008.03.002. PMID 18423641. "Termination of pregnancy following prenatal diagnosis after 22 weeks must be preceded by a feticide"
125. ^ "Underlying Cause of Death 1999-2013 on CDC WONDER Online Database, released 2015". *Centers for Disease Control and Prevention, National Center for Health Statistics*. Data are from the Multiple Cause of Death Files, 1999-2013, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Retrieved 12 November 2015.
126. ^ Pazol, Karen; et al. (27 November 2009). "Abortion Surveillance - United States, 2006". *Morbidity and Mortality Weekly Report Surveillance Summaries*. **58** (SS08): 1–35. Retrieved 12 November 2015.
127. ^ Shah I, Ahman E (December 2009). "Unsafe abortion: global and regional incidence, trends, consequences, and challenges". *J Obstet Gynaecol Can*. **31** (12): 1149–58. PMID 20085681. "However, a woman's chance of having an abortion is similar whether she lives in a developed or a developing region: in 2003 the rates were 26 abortions per 1000 women aged 15 to 44 in developed areas and 29 per 1000 in developing areas. The main difference is in safety, with abortion being safe and easily accessible in developed countries and generally restricted and unsafe in most developing countries"
128. ^ Rosenthal, Elizabeth (12 October 2007). "Legal or Not, Abortion Rates Compare". *The New York Times*. Retrieved 18 July 2011.
129. ^ "Facts on Investing in Family Planning and Maternal and Newborn Health" (PDF). Guttmacher Institute. November 2010. Archived from the original (PDF) on 20 October 2011. Retrieved 24 October 2011.
130. ^ Sedgh, G.; Singh, S.; Henshaw, S. K.; Bankole, A. (2011). "Legal Abortion Worldwide in 2008: Levels and Recent Trends". *Perspectives on Sexual and Reproductive Health*. **43** (3): 188–198. doi:10.1363/4318811. PMID 21884387.
131. ^ National Institute of Statistics, Romanian Statistical Yearbook, chapter 2, page 62 [*permanent dead link*], 2011
132. ^ Strauss, L. T.; Gamble, S. B.; Parker, W. Y.; Cook, D. A.; Zane, S. B.; Hamdan, S.; Centers for Disease Control Prevention (2006). "Abortion surveillance—United States, 2003". *Morbidity and Mortality Weekly Report Surveillance Summaries*. **55** (SS11): 1–32. PMID 17119534.
133. ^ *a b c* "The Limitations of U.S. Statistics on Abortion". *Issues in Brief*. New York: The Guttmacher Institute. 1997. Archived from the original on 4 April 2012.
134. ^ Finer, L. B.; Henshaw, S. K. (2003). "Abortion Incidence and Services in the United States in 2000". *Perspectives on Sexual and Reproductive Health*. **35** (1): 6–15. doi:10.1363/3500603. PMID 12602752.
135. ^ Department of Health (2007). "Abortion statistics, England and Wales: 2006". Archived from the original on 6 December 2010. Retrieved 12 October 2007.
136. ^ Cheng, Linan (1 November 2008). "Surgical versus medical methods for second-trimester induced abortion: RHL commentary". *The WHO Reproductive Health Library*. Geneva: World Health Organization. Retrieved 10 February 2009. commentary on:
Lohr, Patricia A.; Hayes, Jennifer L.; Gemzell-Danielsson, Kristina (23 January 2008). "Surgical versus medical methods for second trimester abortion". *Cochrane Database of Systematic Reviews* (1): CD006714. doi:10.1002/14651858.CD006714.pub2. PMID 18254113.
137. ^ *a b c* Bankole, Akinrinola; Singh, Susheela; Haas, Taylor (1998). "Reasons Why Women Have Induced Abortions: Evidence from 27 Countries". *International Family Planning Perspectives*. **24** (3): 117–127; 152. doi:10.2307/3038208.
138. ^ Finer, L. B.; Frohwirth, L. F.; Dauphinee, L. A.; Singh, S.; Moore, A. M. (2005). "Reasons U.S. Women Have Abortions: Quantitative and Qualitative Perspectives". *Perspectives on Sexual and Reproductive Health*. **37** (3):

110–118. doi:10.1111/j.1931-2393.2005.tb00045.x. PMID 16150658.
139. ^ "Nuremberg and the Crime of Abortion". *U. Toledo. L. Rev*. **42**: 283. Retrieved 12 July 2014.
140. ^ Oster, Emily (September 2005). "Explaining Asia's "Missing Women": A New Look at the Data – Comment" (PDF). *Population and Development Review*. **31** (3): 529, 535. doi:10.1111/j.1728-4457.2005.00082.x. Retrieved 19 May 2009.
141. ^ Jones, R. K.; Darroch, J. E.; Henshaw, S. K. (2002). "Contraceptive Use Among U.S. Women Having Abortions in 2000–2001" (PDF). *Perspectives on Sexual and Reproductive Health*. **34** (6): 294–303. doi:10.2307/3097748. PMID 12558092.
142. ^ Cohen, SA (2008). "Abortion and Women of Color: The Bigger Picture". *Guttmacher Policy Review*. **11** (3).
143. ^ George J. Annas and Sherman Elias. Legal and Ethical Issues in Obstetrical Practice. Chapter 54 in Obstetrics: Normal and Problem Pregnancies, 6th edition. Eds. Steven G. Gabbe, et al. 2012 Saunders, an imprint of Elsevier. ISBN 978-1-4377-1935-2
144. ^ Doan 2007, p. 57.
145. ^ *a b* Weisz, B; Schiff, E; Lishner, M (2001). "Cancer in pregnancy: maternal and fetal implications" (PDF). *Hum Reprod Update*. **7** (4): 384–393. doi:10.1093/humupd/7.4.384. PMID 11476351.
146. ^ Mayr, NA; Wen, BC; Saw, CB (1998). "Radiation therapy during pregnancy". *Obstet Gynecol Clin North Am*. **25** (2): 301–21. PMID 9629572.
147. ^ Fenig E, Mishaeli M, Kalish Y, Lishner M (2001). "Pregnancy and radiation.". *Cancer Treat Rev*. **27** (1): 1–7. doi:10.1053/ctrv.2000.0193. PMID 11237773.
148. ^ Li WW, Yau TN, Leung CW, Pong WM, Chan MY (2009). "Large-cell neuroendocrine carcinoma of the uterine cervix complicating pregnancy". *Hong Kong Med J*. **15** (1): 69–72. PMID 19197101.
149. ^ Mould R (1996). *Mould's Medical Anecdotes*. CRC Press. p. 406. ISBN 978-0-85274-119-1.
150. ^ Miles, Steven (2005). *The Hippocratic Oath and the Ethics of Medicine*. Oxford University Press. ISBN 978-0-19-518820-2.
151. ^ "Scribonius Largus"
152. ^ Soranus, Owsei Temkin (1956). *Soranus' Gynecology*. I.19.60: JHU Press. Retrieved 6 October 2015.
153. ^ Carrick, Paul (2001). *Medical Ethics in the Ancient World*. Georgetown University Press. ISBN 978-0-87840-849-8.
154. ^ Rackham, H. (1944). "Aristotle, Politics". Harvard University Press. Retrieved 21 June 2011.
155. ^ Brind'Amour, Katherine (2007). "Effraenatam". *Embryo Project Encyclopedia*. Arizona State University. Archived from the original on 1 February 2012.
156. ^ "Religions – Islam: Abortion". BBC. Retrieved 10 December 2011.
157. ^ Dabash, Rasha; Roudi-Fahimi, Farzaneh (2008). "Abortion in the Middle East and North Africa" (PDF). Population Research Bureau. Archived (PDF) from the original on 8 July 2011.
158. ^ Dannenfelser, Marjorie (4 November 2015). "The Suffragettes Would Not Agree With Feminists Today on Abortion". *TIME*. Retrieved 4 November 2015.
159. ^ "Abortion Law, History & Religion". Childbirth By Choice Trust. Retrieved 23 March 2008.[*dead link*]
160. ^ For sources describing abortion policy in Nazi Germany, see:
    - Friedlander, Henry (1995). *The origins of Nazi genocide: from euthanasia to the final solution*. Chapel Hill: University of North Carolina Press. p. 30. ISBN 978-0-8078-4675-9. OCLC 60191622.
    - Proctor, Robert (1988). *Racial Hygiene: Medicine Under the Nazis*. Cambridge, Massachusetts: Harvard University Press. pp. 122, 123 and 366. ISBN 978-0-674-74578-0. OCLC 20760638.
    - Arnot, Margaret L.; Cornelie Usborne (1999). *Gender and Crime in Modern Europe*. New York: Routledge. p. 231. ISBN 978-1-85728-745-5. OCLC 186748539.
    - DiMeglio, Peter M. (1999). "Germany 1933–1945 (National Socialism)". In Helen Tierney. *Women's studies encyclopedia*. Westport, Connecticut: Greenwood Press. p. 589. ISBN 978-0-313-31072-0. OCLC 38504469.
161. ^ Smith, Richard Norton On His Own Terms: A Life of Nelson Rockefeller pages 560-561
162. ^ Farrell, Courtney (2010). *Abortion Debate*. ABDO Publishing Company. pp. 6–7. ISBN 1617852643.
163. ^ "WMA Declaration on Therapeutic Abortion". WMA. Retrieved 28 October 2015.
164. ^ Farrell, p. 8
165. ^ "World Abortion Policies 2013" (PDF). United Nations Department of Economic and Social Affairs, Population Division. Retrieved 31 July 2013.
166. ^ World Abortion Policies 2007, United Nations, Department of Economic and Social Affairs, Population Division.
167. ^ Theodore J. Joyce; Stanley K. Henshaw; Amanda Dennis; Lawrence B. Finer; Kelly Blanchard (April 2009). "The Impact of State Mandatory Counseling and Waiting Period Laws on Abortion: A Literature Review" (PDF). Guttmacher Institute. Archived from the original (PDF) on 14 January 2011. Retrieved 31 December 2010.
168. ^ Phillips, Tom (2015-10-29). "China ends one-child policy after 35 years". *The Guardian*. ISSN 0261-3077. Retrieved 2016-11-30.
169. ^ Buckley, Chris (2015-10-29). "China Ends One-Child Policy, Allowing Families Two Children". *The New York*

*Times*. ISSN 0362-4331. Retrieved 2016-11-30.
170. ^ "China to end one-child policy and allow two". *BBC News*. 2015-10-29. Retrieved 2016-11-30.
171. ^ Restivo, Sal P., ed. (2005). *Science, Technology, and Society: An Encyclopedia*. Oxford University Press. p. 2. ISBN 9780195141931.
172. ^ "European delegation visits Nicaragua to examine effects of abortion ban". Ipas. 26 November 2007. Archived from the original on 17 April 2008. Retrieved 15 June 2009. "More than 82 maternal deaths had been registered in Nicaragua since the change. During this same period, indirect obstetric deaths, or deaths caused by illnesses aggravated by the normal effects of pregnancy and not due to direct obstetric causes, have doubled."
173. ^ "Nicaragua: "The Women's Movement Is in Opposition" ". Montevideo: Inside Costa Rica. IPS. 28 June 2008.
174. ^ "Surgical Abortion: History and Overview". National Abortion Federation. Archived from the original on 22 September 2006. Retrieved 4 September 2006.
175. ^ Nations MK, Misago C, Fonseca W, Correia LL, Campbell OM (June 1997). "Women's hidden transcripts about abortion in Brazil". *Soc Sci Med*. **44** (12): 1833–45. doi:10.1016/s0277-9536(96)00293-6. PMID 9194245. "Two folk medical conditions, "delayed" (atrasada) and "suspended" (suspendida) menstruation, are described as perceived by poor Brazilian women in Northeast Brazil. Culturally prescribed methods to "regulate" these conditions and provoke menstrual bleeding are also described ..."
176. ^ Henshaw, S. K. (1991). "The Accessibility of Abortion Services in the United States". *Family Planning Perspectives*. **23** (6): 246–263. doi:10.2307/2135775.
177. ^ Bloom, Marcy (25 February 2008). "Need Abortion, Will Travel". RH Reality Check. Retrieved 15 June 2009.
178. ^ Banister, Judith. (16 March 1999). Son Preference in Asia – Report of a Symposium. Retrieved 12 January 2006.
179. ^ Reaney, Patricia. "Selective abortion blamed for India's missing girls". Reuters. Archived from the original on 20 February 2006. Retrieved 3 December 2008.
180. ^ Sudha, S.; Rajan, S. Irudaya (July 1999). "Female Demographic Disadvantage in India 1981–1991: Sex Selective Abortions and Female Infanticide". *Development and Change*. **30** (3): 585–618. doi:10.1111/1467-7660.00130. PMID 20162850. Archived from the original on 1 January 2003. Retrieved 3 December 2008.
181. ^ "Sex Selection & Abortion: India". Library of Congress. 4 April 2011. Retrieved 18 July 2011.
182. ^ "China Bans Sex-selection Abortion." (22 March 2002). *Xinhua News Agency.'.' Retrieved 12 January 2006.*
183. ^ Graham, Maureen J.; Larsen; Xu (June 1998). "Son Preference in Anhui Province, China". *International Family Planning Perspectives*. **24** (2): 72–77. doi:10.2307/2991929. Archived from the original on 21 October 2011.
184. ^ *a b* "Preventing gender-biased sex selection" (PDF). UNFPA. Retrieved 1 November 2011.
185. ^ "Prenatal sex selection" (PDF). PACE. Archived from the original (PDF) on 3 October 2011. Retrieved 17 November 2015.
186. ^ Smith, G. Davidson (1998). "Single Issue Terrorism Commentary". Canadian Security Intelligence Service. Archived from the original on 15 October 2007. Retrieved 1 September 2011.
187. ^ Wilson, M.; Lynxwiler, J. (1988). "Abortion clinic violence as terrorism". *Studies in Conflict & Terrorism*. **11** (4): 263–273. doi:10.1080/10576108808435717.
188. ^ "The Death of Dr. Gunn". *New York Times*. 12 March 1993.
189. ^ "Incidence of Violence & Disruption Against Abortion Providers in the U.S. & Canada" (PDF). National Abortion Federation. 2009. Retrieved 9 February 2010.
190. ^ Borger, Julian (3 February 1999). "The bomber under siege". *The Guardian*. London.
191. ^ *a b* Alesha E. Doan (2007). *Opposition and Intimidation:The abortion wars and strategies of political harassment*. University of Michigan. p. 2.
192. ^ Spencer, James B. (1908). *Sheep Husbandry in Canada*. p. 114. OCLC 798508694.
193. ^ "Beef cattle and Beef production: Management and Husbandry of Beef Cattle". *Encyclopaedia of New Zealand*. 1966.
194. ^ Myers, Brandon; Beckett, Jonathon (2001). "Pine needle abortion". *Animal Health Care and Maintenance* (PDF). Tucson, AZ: Arizona Cooperative Extension, University of Arizona. pp. 47–50. Retrieved 10 April 2013.
195. ^ Kim, Ill-Hwa; Choi, Kyung-Chul; An, Beum-Soo; Choi, In-Gyu; Kim, Byung-Ki; Oh, Young-Kyoon; Jeung, Eui-Bae (2003). "Effect on abortion of feeding Korean pine needles to pregnant Korean native cows". *Canadian Journal of Veterinary Research*. Canadian Veterinary Medical Association. **67** (3): 194–197. PMC 227052. PMID 12889725.
196. ^ Overton, Rebecca (March 2003). "By a Hair" (PDF). Paint Horse Journal. Archived from the original (PDF) on 18 February 2013. Retrieved 19 December 2012.
197. ^ "Herpesvirus in dog pups". petMD. Retrieved 18 December 2012.
198. ^ "Spaying Pregnant Females". Carol's Ferals. Retrieved 17 December 2012.
199. ^ Coates, Jennifer (7 May 2007). "Feline abortion: often an unnerving necessity". petMD. Retrieved 18 December 2012.
200. ^ Khuly, Patty (1 April 2011). "Feline abortion: often an unnerving necessity (Part 2)". petMD. Retrieved

18 December 2012.
201. ^ Schwagmeyer, P. L. (1979). "The Bruce Effect: An Evaluation of Male/Female Advantages". *The American Naturalist*. **114** (6): 932–938. doi:10.1086/283541. JSTOR 2460564.
202. ^ McKinnon, Angus O.; Voss, James L. (1993). *Equine Reproduction*. Wiley-Blackwell. p. 563. ISBN 0-8121-1427-2.
203. ^ Berger, Joel W; Vuletić, L; Boberić, J; Milosavljević, A; Dilparić, S; Tomin, R; Naumović, P (5 May 1983). "Induced abortion and social factors in wild horses". *Nature*. **303** (5912): 59–61. doi:10.1038/303059a0. PMID 6682487.
204. ^ Pluháček, Jan; Bartos, L (2000). "Male infanticide in captive plains zebra, Equus burchelli" (PDF). *Animal Behaviour*. **59** (4): 689–694. doi:10.1006/anbe.1999.1371. PMID 10792924. Archived from the original (PDF) on 18 July 2011.
205. ^ Pluháček, Jan (2005). "Further evidence for male infanticide and feticide in captive plains zebra, Equus burchelli" (PDF). *Folia Zool*. **54** (3): 258–262.
206. ^ Kirkpatrick, J. F.; Turner, J. W. (1991). "Changes in Herd Stallions among Feral Horse Bands and the Absence of Forced Copulation and Induced Abortion". *Behavioral Ecology and Sociobiology*. **29** (3): 217–219. doi:10.1007/BF00166404. JSTOR 4600608.
207. ^ Agoramoorthy, G.; Mohnot, S. M.; Sommer, V.; Srivastava, A. (1988). "Abortions in free ranging Hanuman langurs (Presbytis entellus) – a male induced strategy?". *Human Evolution*. **3** (4): 297–308. doi:10.1007/BF02435859.

## Notes

1. ^ Definitions of abortion, as with many words, vary from source to source. Language used to define abortion often reflects societal and political opinions (not only scientific knowledge). The following is a partial list of definitions as stated by obstetrics and gynecology (OB/GYN) textbooks, dictionaries, and other sources:

   **Major OB/GYN textbooks**

   - The National Center for Health Statistics defines an "abortus" as "[a] fetus or embryo removed or expelled from the uterus during the first half of gestation—20 weeks or less, or in the absence of accurate dating criteria, born weighing < 500 g." They also define "birth" as "[t]he complete expulsion or extraction from the mother of a fetus after 20 weeks' gestation. ... in the absence of accurate dating criteria, fetuses weighing <500 g are usually not considered as births, but rather are termed abortuses for purposes of vital statistics." Cunningham, FG; Leveno, KJ; Bloom, SL; et al., eds. (2010). "1. Overview of Obstetrics". *Williams Obstetrics* (23 ed.). McGraw-Hill Medical. ISBN 978-0-07-149701-5.
   - "[T]he standard medical definition of abortion [is] termination of a pregnancy when the fetus is not viable". Annas, George J.; Elias, Sherman (2007). "51. Legal and Ethical Issues in Obstetric Practice". In Gabbe, Steven G.; Niebyl, Jennifer R.; Simpson, Joe Leigh. *Obstetrics: Normal and Problem Pregnancies* (5 ed.). Churchill Livingstone. ISBN 978-0-443-06930-7.
   - "Termination of a pregnancy, whether spontaneous or induced." Kottke, Melissa J.; Zieman, Mimi (2008). "33. Management of Abortion". In Rock, John A.; Jones III, Howard W. *TeLinde's Operative Gynecology* (10 ed.). Lippincott Williams & Wilkins. ISBN 978-0-7817-7234-1.

   **Other OB/GYN textbooks**

   - "Termination of pregnancy before 20 weeks' gestation calculated from date of onset of last menses. An alternative definition is delivery of a fetus with a weight of less than 500 g. If abortion occurs before 12 weeks' gestation, it is called early; from 12 to 20 weeks it is called late." Katz, Vern L. (2007). "16. Spontaneous and Recurrent Abortion – Etiology, Diagnosis, Treatment". In Katz, Vern L.; Lentz, Gretchen M.; Lobo, Rogerio A.; et al. *Katz: Comprehensive Gynecology* (5 ed.). Mosby. ISBN 978-0-323-02951-3.
   - "Abortion is the spontaneous or induced termination of pregnancy before fetal viability. Because popular use of the word abortion implies a deliberate pregnancy termination, some prefer the word miscarriage to refer to spontaneous fetal loss before viability ... The National Center for Health Statistics, the Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO) define abortion as pregnancy termination prior to 20 weeks' gestation or a fetus born weighing less than 500 g. Despite this, definitions vary widely according to state laws." Schorge, John O.; Schaffer, Joseph I.; Halvorson, Lisa M.; Hoffman, Barbara L.; Bradshaw, Karen D.; Cunningham, F. Gary, eds. (2008). "6. First-Trimester Abortion". *Williams Gynecology* (1 ed.). McGraw-Hill Medical. ISBN 978-0-07-147257-9.

   **Major medical dictionaries**

   - "The spontaneous or induced termination of pregnancy before the fetus reaches a viable age." "Taber's Medical Dictionary: abortion". *Taber's Cyclopedic Medical Dictionary*. F.A. Davis. Archived from the original on 14 June 2011. Retrieved 14 June 2011.
   - "Expulsion from the uterus an embryo or fetus prior to the stage of viability (20 weeks' gestation or fetal weight <500g). A distinction made between [abortion] and premature birth: premature infants are those born after the

stage of viability but prior to 37 weeks." *Stedman's Medical Dictionary* (27 ed.). Lippincott Williams & Wilkins. ISBN 0-683-40008-8.
- "[P]remature expulsion from the uterus of the products of conception, either the embryo or a nonviable fetus." *Dorland's Illustrated Medical Dictionary* (31 ed.). Saunders. 2007. ISBN 978-1-4160-2364-7.

**Other medical dictionaries**

- "[T]he termination of a pregnancy after, accompanied by, resulting in, or closely followed by the death of the embryo or fetus". "Medical Dictionary". *Merriam-Webster's Medical Dictionary*. Springfield, Mass.: Merriam-Webster. Archived from the original on 15 June 2011. Retrieved 15 June 2011.
- "Induced termination of pregnancy, involving destruction of the embryo or fetus." "abortion." *The American Heritage Science Dictionary*. Boston: Houghton Mifflin. 2005. ISBN 978-0-618-45504-1.
- "Interruption of pregnancy before the fetus has attained a stage of viability, usually before the 24th gestational week." "abortion." *Cambridge Dictionary of Human Biology and Evolution*. Cambridge; New York: Cambridge University Press. 2005. OCLC 54374716.
- "[A] spontaneous or deliberate ending of pregnancy before the fetus can be expected to survive." "abortion." Miller-Keane (2005). Marie T. O'Toole, ed. *Miller-Keane Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health* (Seventh ed.). United States of America: W. B. Saunders. p. 2304. *Mosby's Emergency Dictionary*. Philadelphia: Elsevier Health Sciences. 1998. OCLC 37553784.[*verification needed*]
- "[A] situation where a fetus leaves the uterus before it is fully developed, especially during the first 28 weeks of pregnancy, or a procedure which causes this to happen ... [T]o have an abortion to have an operation to make a fetus leave the uterus during the first period of pregnancy." ""abortion"". *Dictionary of Medical Terms*. London: A & C Black. 2005. OCLC 55634250.
- "1. Induced termination of a pregnancy with destruction of the fetus or embryo; therapeutic abortion. 2. Spontaneous abortion." *The American Heritage Medical Dictionary* (reprint ed.). Houghton Mifflin. 2008. p. 2. ISBN 0-618-94725-6. OCLC 608212441.
- "Although the term abortion is generic and implies a premature termination of pregnancy for any reason, the lay public better understands the word 'miscarriage' for involuntary fetal loss or fetal wastage." *The Dictionary of Modern Medicine*. Parthenon Publishing. 1992. p. 3. ISBN 1-85070-321-3.
- "The termination of pregnancy or premature expulsion of the products of conception by any means, usually before fetal viability." *Churchill's Medical Dictionary*. Churchill Livingstone. 1989. p. 3. ISBN 0-443-08691-5.

**Bibliographies**

- "An abortion refers to the termination of a pregnancy. It can be *induced* (see Definitions, Terminology, and Reference Resources) through a pharmacological or a surgical procedure, or it may be spontaneous (also called miscarriage)." "Definitions of abortion vary across and within countries as well as among different institutions. Language used to refer to abortion often also reflects societal and political opinions and not only scientific knowledge (Grimes and Gretchen 2010). Popular use of the word abortion implies a deliberate pregnancy termination, whereas a miscarriage is used to refer to spontaneous fetal loss when the fetus is not viable (i.e., not yet unable to survive independently outside the womb)." Kulczycki, Andrzej. "Abortion". Oxford Bibliographies. Retrieved 9 April 2014.

**Major English dictionaries (general-purpose)**

- "1. a. The expulsion or removal from the womb of a developing embryo or fetus, spec. (Med.) in the period before it is capable of independent survival, occurring as a result either of natural causes (more fully spontaneous abortion) or of a deliberate act (more fully induced abortion); the early or premature termination of pregnancy with loss of the fetus; an instance of this." "abortion, n.". *Oxford English Dictionary* (Third ed.). Oxford University Press. September 2009 [online version September 2011].
- "[A]n operation or other procedure to terminate pregnancy before the fetus is viable" or "[T]he premature termination of pregnancy by spontaneous or induced expulsion of a nonviable fetus from the uterus". "abortion". *Collins English Dictionary – Complete & Unabridged 11th Edition*. HarperCollins Publishers. Retrieved 7 October 2012.
- "[T]he removal of an embryo or fetus from the uterus in order to end a pregnancy" or "[A]ny of various surgical methods for terminating a pregnancy, especially during the first six months." "abortion". *Dictionary.com Unabridged*. Random House, Inc. 27 June 2011.
- "1. *medicine* the removal of an embryo or fetus from the uterus before it is sufficiently developed to survive independently, deliberately induced by the use of drugs or by surgical procedures. Also called termination or induced abortion. 2. *medicine* the spontaneous expulsion of an embryo or fetus from the uterus before it is sufficiently developed to survive independently. Also called miscarriage, spontaneous abortion." *Chambers 21st Century Dictionary*. London: Chambers Harrap, 2001.
- "a medical operation to end a pregnancy so that the baby is not born alive". *Longman Dictionary of Contemporary English*, online edition.

**Other dictionaries**

- "The deliberate termination of a pregnancy, usually before the embryo or fetus is capable of independent life." *The American Heritage New Dictionary of Cultural Literacy* (3rd ed.). Houghton Mifflin Company. 2005.
- "A term that, in philosophy, theology, and social debates, often means the deliberate termination of pregnancy before the fetus is able to survive outside the uterus. However, participants in these debates sometimes use the term abortion simply to mean the termination of pregnancy before birth, regardless of whether the fetus is viable or not." "abortion." *Dictionary of World Philosophy*. London: Routledge, 2001.
- "1. An artificially induced termination of a pregnancy for the purpose of destroying an embryo or fetus. 2. The spontaneous expulsion of an embryo or fetus before viability;" Garner, Bryan A. (June 2009). *Black's Law Dictionary* (9th ed.). Thomson West. ISBN 978-0-314-19949-2.

**Encyclopedias**

- "[T]he expulsion of a fetus from the uterus before it has reached the stage of viability (in human beings, usually about the 20th week of gestation)." "Abortion (pregnancy)". *Encyclopædia Britannica Online*. Encyclopædia Britannica. 2011. Archived from the original on 26 June 2011. Retrieved 26 June 2011.
- "Expulsion of the products of conception before the embryo or fetus is viable. Any interruption of human pregnancy prior to the 28th week is known as abortion." "Abortion". *The Columbia Encyclopedia*. New York: Columbia University Press. 2008.
- "The expulsion or removal of a fetus from the womb before it is capable of independent survival." "Abortion". *World Encyclopedia*. Oxford University Press. 2008.
- "[Abortion] is commonly misunderstood outside medical circles. In general terms, the word 'abortion' simply means the failure of something to reach fulfilment or maturity. Medically, abortion means loss of the fetus, for any reason, before it is able to survive outside the womb. The term covers accidental or spontaneous ending, or miscarriage, of pregnancy as well as deliberate termination. The terms 'spontaneous abortion' and 'miscarriage' are synonymous and are defined as loss of the fetus before the twenty-eighth week of pregnancy. This definition implies a legal perception of the age at which a fetus can survive out of the womb. With great advances in recent years in the ability to keep very premature babies alive, this definition is in need of revision." "Abortion and miscarriage". *The Royal Society of Medicine Health Encyclopedia*. London: Bloomsbury Publishing. 2000.
- "Abortion is the intentional removal of a fetus or an embryo from a mother's womb for purposes other than that of either producing a live birth or disposing of a dead embryo." "Abortion". *Encyclopedia of Human Rights Issues since 1945* (1 ed.). Santa Barbara, California: Routledge. 1999. ISBN 978-1-57958-166-4.

**Journal articles about terminology**

- "Abortion can be performed up to viability; thereafter, according to standard dictionaries, other terms should be used for uterine evacuation. "Late" is an acceptable descriptor for abortion; "late-term" is not. Gestational age should be expressed in completed cardinal days, weeks or months; ordinal numbers (and trimesters) should be avoided. "Intact D&E" should be used instead of the oxymoronic "partial-birth abortion" or the mysterious "D&X." " (internal citations removed) Grimes, DA; Stuart, G (2010). "Abortion jabberwocky: the need for better terminology". *Contraception*. **81** (2): 93–96. doi:10.1016/j.contraception.2009.09.005. PMID 20103443.

2. ^ By 1930, medical procedures in the US had improved for both childbirth and abortion but not equally, and induced abortion in the first trimester had become safer than childbirth. In 1973, *Roe vs. Wade* acknowledged that abortion in the first trimester was safer than childbirth:
   - "The 1970s". *Time communication 1940–1989: retrospective*. Time Inc. 1989. "Blackmun was also swayed by the fact that most abortion prohibitions were enacted in the 19th century when the procedure was more dangerous than now."
   - Will, George (1990). *Suddenly: the American idea abroad and at home, 1986–1990*. Free Press. p. 312. ISBN 0-02-934435-2.
   - Lewis, J.; Shimabukuro, Jon O. (28 January 2001). "Abortion Law Development: A Brief Overview". Congressional Research Service. Archived from the original on 14 May 2011. Retrieved 1 May 2011. *Schultz, David Andrew (2002). *Encyclopedia of American law*. Infobase Publishing. p. 1. ISBN 0-8160-4329-9.
   - Lahey, Joanna N. (24 September 2009). "Birthing a Nation: Fertility Control Access and the 19th Century Demographic Transition" (PDF; preliminary version). *Colloquium*. Pomona College.

# External links

- Organization, World Health (2012). *Safe abortion: technical and policy guidance for health systems* (PDF) (2nd ed.). Geneva: World Health Organization. ISBN 9789241548434.
- Abortion Policies: A Global Review, published by the United

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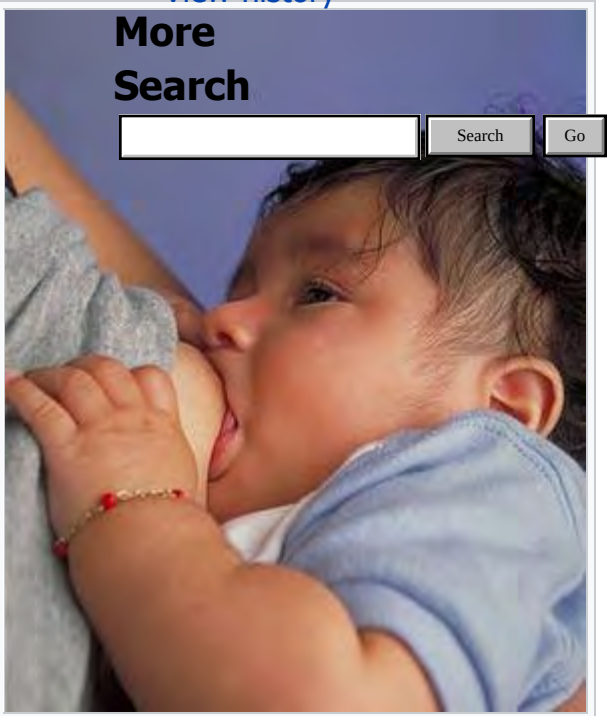
# Breastfeeding

From Wikipedia, the free encyclopedia

*"Suckling" redirects here. For other uses, see Suckling (disambiguation).*

**Breastfeeding**, also known as **nursing**, is the feeding of babies and young children with milk from a woman's breast.[1] Health professionals recommend that breastfeeding begin within the first hour of a baby's life and continue as often and as much as the baby wants.[2][3] During the first few weeks of life babies may nurse roughly every two to three hours. The duration of a feeding is usually ten to fifteen minutes on each breast.[4] Older children feed less often.[5] Mothers may pump milk so that it can be used later when breastfeeding is not possible.[1] Breastfeeding has a number of benefits to both mother and baby, which infant formula lacks.[3][6]


A baby breastfeeding

Deaths of an estimated 820,000 children under the age of five could be prevented globally every year with increased breastfeeding.[7] Breastfeeding decreases the risk of respiratory tract infections and diarrhea, both in developing and developed countries.[2][3] Other benefits include lower risks of asthma, food allergies, celiac disease, type 1 diabetes, and leukemia.[3] Breastfeeding may also improve cognitive development and decrease the risk of obesity in adulthood.[2] Mothers may feel pressure to breastfeed; however in the developed world children generally grow up normally when bottle feed.[8]

Benefits for the mother include less blood loss following delivery, better uterus shrinkage, weight loss, and less postpartum depression. Breastfeeding delays the return of menstruation and fertility, a phenomenon known as lactational amenorrhea. Long term benefits for the mother include decreased risk of breast cancer, cardiovascular disease, and rheumatoid arthritis.[3][7] Breastfeeding is often less expensive than infant formula.[9][10]

Health organizations, including the World Health Organization (WHO), recommend breastfeeding exclusively for six months.[2][11] This means that no other foods or drinks other than possibly vitamin D are typically given.[12] After the introduction of foods at six months of age, recommendations include continued breastfeeding until at least one to two years of age.[2][3] Globally about 38% of infants are only breastfed during their first six months of life.[2] In the United States, about 75% of women begin breastfeeding and about 13% only breastfeed until the age of six months.[3] Medical conditions that do not allow breastfeeding are rare.[3] Mothers who take certain recreational drugs and medications should not breastfeed.[13] Smoking, limited intake of alcohol, and coffee are not reasons to avoid breastfeeding.[14][15][16]

Contents

# Lactation [edit]

*Main article: Lactation*

The endocrine system drives milk production during pregnancy and the first few days after the birth. From the twenty-fourth week of pregnancy (the second and third trimesters), a woman's body produces hormones that stimulate the growth of the breast's milk duct system. Progesterone influences the growth in size of alveoli and lobes; high levels of progesterone, estrogen, prolactin and other hormones inhibit lactation before birth; hormone levels drop after birth, triggering milk production.[17] After birth, the hormone oxytocin contracts the smooth muscle layer of cells surrounding the alveoli to squeeze milk into the duct system. Oxytocin is also necessary for the milk ejection reflex, or *let-down* to occur. Let-down occurs in response to the baby's suckling, though it also may be a conditioned response, e.g. to the cry of the baby. Lactation can also be induced by a combination of physical and psychological stimulation, by drugs or by a combination of these methods.[18][19]

[edit]

# Breast milk

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*Main article: Breast milk*

Edit links

Two 25ml samples of human breast milk. The sample on the left is foremilk, the watery milk coming from a full breast. To the right is hindmilk, the creamy milk coming from a nearly empty breast.[20]

Not all of breast milk's properties are understood, but its nutrient content is relatively consistent. Breast milk is made from nutrients in the mother's bloodstream and bodily stores. Breast milk has an optimal balance of fat, sugar, water, and protein that is needed for a baby's growth and development.[21] Breastfeeding triggers biochemical reactions which allows for the enzymes, hormones, growth factors and immunologic substances to effectively defend against infectious diseases for the infant. The breastmilk also has long-chain polyunsaturated fatty acids which help with normal retinal and neural development.[22] Because breastfeeding requires an average of 500 calories a day, it helps the mother lose weight after giving birth.[23]

The composition of breast milk changes depending on how long the baby nurses at each session, as well as on the child's age.[24] The first type, produced during the first days after childbirth, is called *colostrum*. Colostrum is easy to digest although it is more concentrated than mature milk. It has a laxative effect that helps the infant to pass early stools, aiding in the excretion of excess bilirubin, which helps to prevent jaundice. It also helps to seal the infants gastrointestional tract from foreign substances, which may sensitize the baby to foods that the mother has eaten. Although the baby has received some antibodies through the placenta, colostrum contains a substance which is new to the newborn, secretory immunoglobulin A (IgA). IgA works to attack germs in the mucous membranes of the throat, lungs, and intestines, which are most likely to come under attack from germs.[25]

Himba woman and child

Breasts begin producing mature milk around the third or fourth day after birth. Early in a nursing session, the breasts produce *foremilk*, a thinner milk containing many proteins and vitamins. If the baby keeps nursing, then *hindmilk* is produced. Hindmilk has a creamier color and texture because it contains more fat.[26] The American Academy of Pediatrics (AAP) states that "tobacco smoking by mothers is not a contraindication to breastfeeding."[27] In addition, AAP states that while breastfeeding mothers "should avoid the use of alcoholic beverages", an "occasional celebratory single, small alcoholic drink is acceptable, but breastfeeding should be avoided for 2 hours after the drink."[27] A 2014 review found that "even in a theoretical case of binge drinking, the children would not be subjected to clinically relevant amounts of alcohol [through breastmilk]", and would have no adverse effects on children as long as drinking is "occasional".[28]

## Process [edit]

### Commencement [edit]

Breastfeeding can begin immediately after birth. The baby is placed on the mother and feeding starts as soon as the baby shows interest.

According to some authorities, increasing evidence suggests that early

Newborn rests as caregiver checks breath sounds

skin-to-skin contact (also called kangaroo care) between mother and baby stimulates breastfeeding behavior in the baby.[29] Newborns who are immediately placed on their mother's skin have a natural instinct to latch on to the breast and start nursing, typically within one hour of birth. Immediate skin-to-skin contact may provide a form of imprinting that makes subsequent feeding significantly easier. In addition to more successful breastfeeding and bonding, immediate skin-to-skin contact reduces crying and warms the baby.

According to studies cited by UNICEF, babies naturally follow a process which leads to a first breastfeed. Initially after birth the baby cries with its first breaths. Shortly after, it relaxes and makes small movements of the arms, shoulders and head. The baby crawls towards the breast and begins to feed. After feeding, it is normal for a baby to remain latched to the breast while resting. This is sometimes mistaken for lack of appetite. Absent interruptions, all babies follow this process. Rushing or interrupting the process, such as removing the baby to weigh him/her, may complicate subsequent feeding.[30] Activities such as weighing, measuring, bathing, needle-sticks, and eye prophylaxis wait until after the first feeding."[27]

Children who are born preterm have difficulty in initiating breast feeds immediately after birth. By convention, such children are often fed on expressed breast milk or other supplementary feeds through tubes or bottles until they develop satisfactory ability to suck breast milk. Tube feeding, though commonly used, is not supported by scientific evidence as of October 2016.[31] It has also been reported in the same systematic review that by avoiding bottles and using cups instead to provide supplementary feeds to preterm children, a greater extent of breast feeding for a longer duration can subsequently be achieved.[31]

## Timing [edit]

Newborn babies typically express demand for feeding every 1 to 3 hours (8-12 times in 24 hours) for the first two to four weeks.[32] A newborn has a very small stomach capacity. At one-day old it is 5 to 7 ml, about the size of a marble; at day three it is 0.75-1 oz, about the size of a "shooter" marble; and at day seven it is 1.5-2 oz, or about the size of a ping-pong ball. The amount of breast milk that is produced is timed to meet the infant's needs in that the first milk, colostrum, is concentrated but produced in only very small amounts, gradually increasing in volume to meet the expanding size of the infant's stomach capacity.[25]

According to La Leche League International, "Experienced breastfeeding mothers learn that the sucking patterns and needs of babies vary. While some infants' sucking needs are met primarily during feedings, other babies may need additional sucking at the breast soon after a feeding even though they are not really hungry. Babies may also nurse when they are lonely, frightened or in pain....Comforting and meeting sucking needs at the breast is nature's original design. Pacifiers (dummies, soothers) are a substitute for the mother when she cannot be available. Other reasons to pacify a baby primarily at the breast include superior oral-facial development, prolonged lactational amenorrhea, avoidance of nipple confusion, and stimulation of an adequate milk supply to ensure higher rates of breastfeeding success."[33]

During the newborn period, most breastfeeding sessions take from 20 to 45 minutes.[32] After one breast is empty, the mother may offer the other breast.

## Location [edit]

Most US states now have laws that allow a mother to breastfeed her baby anywhere. In hospitals, rooming-in care permits the baby to stay with the mother and simplifies the process. Some commercial establishments provide breastfeeding rooms, although laws generally specify that mothers may breastfeed anywhere, without requiring a

Rooming-in bassinet

special area. Breastfeeding in public remains controversial in many developed countries.

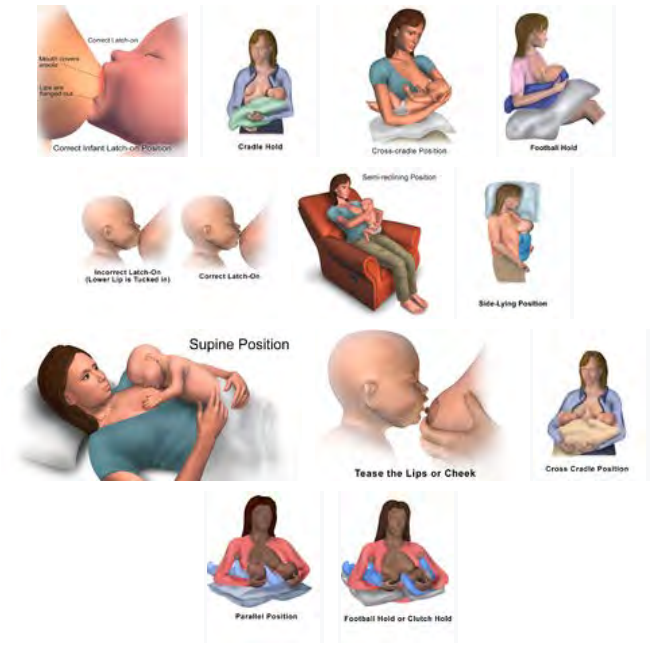
In 2014, newly elected Pope Francis drew world-wide commentary when he encouraged mothers to breastfeed babies in church. During a papal baptism, he said that mothers "should not stand on ceremony" if their children were hungry. "If they are hungry, mothers, feed them, without thinking twice," he said, smiling. "Because they are the most important people here."[34]

## Position [edit]

Correct positioning and technique for latching on are necessary to prevent nipple soreness and allow the baby to obtain enough milk.[35]

Babies can successfully latch on to the breast from multiple positions. Each baby may prefer a particular position. The "football" hold places the baby's legs next to the mother's side with the baby facing the mother. Using the "cradle" or "cross-body" hold, the mother supports the baby's head in the crook of her arm. The "cross-over" hold is similar to the cradle hold, except that the mother supports the baby's head with the opposite hand. The mother may choose a reclining position on her back or side with the baby laying next to her.[36]

## Latching on [edit]




The "rooting reflex" is the baby's natural tendency to turn towards the breast with the mouth open wide; mothers sometimes make use of this by gently stroking the baby's cheek or lips with their nipple to induce the baby to move into position for a breastfeeding session, then quickly moving the baby onto the breast while its mouth is wide open.[37] To prevent nipple soreness and allow the baby to get enough milk, a large part of the breast and areola need to enter the baby's mouth.[38][39] Failure to latch on is one of the main reasons for ineffective feeding and can lead to infant health concerns.

## Weaning [edit]

*Main article: Weaning*

Weaning is the process of replacing breast milk with other foods; the infant is fully weaned after the replacement is complete. Psychological factors affect the weaning process for both mother and infant, as issues of closeness and separation are very prominent.[40] If the baby is less than a year old substitute bottles are necessary; an older baby may accept milk from a cup. Unless a medical emergency necessitates abruptly stopping breastfeeding, it is best to gradually cut back on feedings to allow the breasts to adjust to the decreased demands without becoming engorged. La Leche League advises: "The nighttime feeding is usually the last to go. Make a bedtime routine not centered around breastfeeding. A good book or two will eventually become more important than a long session at the breast."[41]

If breastfeeding is suddenly stopped a woman's breasts are likely to become engorged with milk. Pumping small amounts to relieve discomfort helps to gradually train the breasts to produce less milk. There is

presently no safe medication to prevent engorgement, but cold compresses and ibuprofen may help to relieve pain and swelling. Pain should go away in one to five days. If symptoms continue and comfort measures are not helpful a woman should consider the possibility that a blocked milk duct or infection may be present and seek medical intervention.[42]

When weaning is complete the mother's breasts return to their previous size after several menstrual cycles. If the mother was experiencing lactational amenorrhea her periods will return along with the return of her fertility. When no longer breastfeeding she will need to adjust her diet to avoid weight gain.[43]

## Methods [edit]

### Exclusive [edit]

Exclusive breastfeeding is defined as "an infant's consumption of human milk with no supplementation of any type (no water, no juice, no nonhuman milk and no foods) except for vitamins, minerals and medications."[27] Exclusive breastfeeding till six months of age helps to protect an infant from gastrointestinal infections in both developing and industrialized countries. The risk of death due to diarrhea and other infections increases when babies are either partially breastfed or not breastfed at all.[2]

Measuring how many calories a breastfed baby consumes is complex, although babies normally attempt to meet their own requirements.[44] Babies that fail to eat enough may exhibit symptoms of failure to thrive.[45]

La Leche League says that mothers' most often asked question is, "How can I tell if my baby is getting enough milk?" They advise that for the first few days, while the baby is receiving mostly colostrum, one or two wet diapers per day is normal. Once the mother starts producing milk, usually on the third or fourth day, the baby should have 6-8 wet cloth diapers (5-6 wet disposable diapers) per day. In addition, most young babies have at least two to five bowel movements every 24 hours for the first several months.[46]

La Leache League offers the following additional signs that indicate a baby is receiving enough milk:

- Averages at least 8-12 feedings per 24-hour period.
- Determines the duration of feeding, which may be 10 to 20 minutes per breast or longer.
- Swallowing sounds are audible.
- Gains at least 4-7 ounces per week after the fourth day.
- Is alert and active, appears healthy, has good color, firm skin and is growing in length and head circumference.[46]

### Mixed feeding [edit]

Predominant or mixed breastfeeding means feeding breast milk along with infant formula, baby food and even water, depending on the child's age.[47]

Formula and pumped breastmilk, side-by-side. Note that the formula is of uniform consistency and color, while the

### Expressed milk [edit]

A mother can "express" (produce) her milk for storage and later use. Expression occurs with massage or a breast pump. It can be stored in freezer storage bags, containers made specifically for breastmilk, a supplemental nursing system, or a bottle ready for use. Using someone other than the mother/wet nurse to deliver the bottle maintains the baby's association of nursing with the mother/wet nurse and bottle feeding with other people.

Breast milk may be kept at room temperature for up to six hours, refrigerated for up to eight days or frozen for six to twelve months.[48]

milk exhibits properties of an organic solution, separating into the creamline layer of fat at the top, milk and a watery blue layer at the bottom.

Research suggests that the antioxidant activity in expressed breast milk decreases over time, but remains at higher levels than in infant formula.[49]

Mothers express milk for multiple reasons. Expressing breast milk can maintain a mother's milk supply when she and her child are apart. A sick baby who is unable to nurse can take expressed milk through a nasogastric tube. Some babies are unable or unwilling to nurse. Expressed milk is the feeding method of choice for premature babies.[50] Viral disease transmission can be prevented by expressing breast milk and subjecting it to Holder pasteurisation.[51] Some women donate expressed breast milk (EBM) to others, either directly or through a milk bank. This allows mothers who cannot breastfeed to give their baby the benefits of breast milk.

Manual breast pump

Babies feed differently with artificial nipples than from a breast. With the breast, the infant's tongue massages the milk out rather than sucking, and the nipple does not go as far into the mouth. Drinking from a bottle takes less effort and the milk may come more rapidly, potentially causing the baby to lose desire for the breast. This is called *nursing strike, nipple strike* or *nipple confusion*. To avoid this, expressed milk can be given by means such as spoons or cups.[47]

"Exclusively expressing", "exclusively pumping", and "EPing" are terms for a mother who exclusively feeds her baby expressed milk. With good pumping habits, particularly in the first 12 weeks while establishing the milk supply, it is possible to express enough milk to feed the baby indefinitely. With the improvements in breast pumps, many women exclusively feed expressed milk, expressing milk at work. Women can leave their infants in the care of others while traveling, while maintaining a supply of breast milk.[52]

## Shared nursing [edit]

*Main article: Wet nurse*

Expressed breast milk or infant formula can be fed by bottle

Wet nursing was common throughout history. It remains popular in some developing nations, including those in Africa, for more than one woman to breastfeed a child. Shared breastfeeding is a risk factor for HIV infection in infants.[53] A woman who is engaged to breastfeed another's baby is known as a wet nurse. Shared nursing can sometimes provoke negative reactions in the Anglosphere.[54][55]

## Tandem nursing [edit]

Feeding two children at the same time who are not twins or multiples is called *tandem nursing*. Appetite and feeding habits of each baby may differ, so they may feed at the same or different times, which may involve feeding them simultaneously, one on each breast.

Breastfeeding triplets or larger broods is a challenge given babies' varying appetites. Breasts can respond to the demand and produce larger milk quantities; mothers have breastfed triplets successfully.[56][57][58]

Tandem nursing occurs when a woman gives birth while breastfeeding an older child. During the late stages of pregnancy, the milk changes to colostrum. While some children continue to breastfeed even with this change, others may wean. Breastfeeding a child while pregnant with another may be considered a form of tandem feeding for the nursing mother, as she provides nutrition for two.[59]

## Induced lactation [edit]

Induced lactation, also called *adoptive lactation*, is the process of starting breastfeeding in a woman who did not give birth.[60] This usually requires the adoptive mother to take hormones and other drugs to stimulate breast development and promote milk production. In some cultures, breastfeeding an adoptive child creates milk kinship that built community bonds across class and other hierarchal bonds.[60]

### Re-lactation [edit]

Re-lactation is the process of restarting breastfeeding.[60] In developing countries, mothers may restart breastfeeding after a weaning as part of an oral rehydration treatment for diarrhea. In developed countries, re-lactation is common after early medical problems are resolved, or because a mother changes her mind about breastfeeding.

Re-lactation is most easily accomplished with a newborn or with a baby that was previously breastfeeding; if the baby was initially bottle-fed, the baby may refuse to suckle. If the mother has recently stopped breastfeeding, she is more likely to be able to re-establish her milk supply, and more likely to have an adequate supply. Although some women successfully re-lactate after months-long interruptions, success is higher for shorter interruptions.[60]

Techniques to promote lactation use frequent attempts to breastfeed, extensive skin-to-skin contact with the baby, and frequent, long pumping sessions.[60] Suckling may be encouraged with a tube filled with infant formula, so that the baby associates suckling at the breast with food. A dropper or syringe without the needle may be used to place milk onto the breast while the baby suckles. The mother should allow the infant to suckle at least ten times during 24 hours, and more times if he or she is interested. These times can include every two hours, whenever the baby seems interested, longer at each breast, and when the baby is sleepy when he or she might suckle more readily. In keeping with increasing contact between mother and child, including increasing skin-to-skin contact, grandmothers should pull back and help in other ways. Later on, grandmothers can again provide more direct care for the infant.[61]

These techniques require the mother's commitment over a period of weeks or months. However, even when lactation is established, the supply may not be large enough to breastfeed exclusively. A supportive social environment improves the likelihood of success.[60] As the mother's milk production increases, other feeding can decrease. Parents and other family members should watch the baby's weight gain and urine output to assess nutritional adequacy.[61]

A WHO manual for physicians and senior health workers citing a 1992 source states: "If a baby has been breastfeeding sometimes, the breastmilk supply increases in a few days. If a baby has stopped breastfeeding, it may take 1-2 weeks or more before much breastmilk comes."[61]

### Extended [edit]

*Main article: Extended breastfeeding*

Extended breastfeeding means breastfeeding after the age of 12 or 24 months, depending on the source. Worldwide, infants are weaned on average between ages two and four. Breast-feeding continues until children are six or seven years old in some cultures but in other countries extended breast-feeding is less common. In Western countries such as the United States, Canada, and Great Britain, extended breastfeeding is relatively uncommon and can provoke criticism.[62][63]

In the United States, 22.4% of babies are breastfed for 12 months, the minimum amount of time advised by the American Academy of Pediatrics. In India, mothers commonly breastfeed for 2 to 3 years.[64]

## Health effects [edit]

Breastfeeding decreases the risk of a number of diseases in both mothers and babies.[65] The US Preventive Services Task Force recommends efforts to promote breastfeeding.[66]

## Baby [edit]

Early breastfeeding is associated with fewer nighttime feeding problems.[67] Early skin-to-skin contact between mother and baby improves breastfeeding outcomes, increases cardio-respiratory stability and decreases infant crying.[68] Reviews from 2007 found numerous benefits. Breastfeeding aids general health, growth and development in the infant. Infants who are not breastfed are at mildly increased risk of developing acute and chronic diseases, including lower respiratory infection, ear infections, bacteremia, bacterial meningitis, botulism, urinary tract infection and necrotizing enterocolitis.[69][70] Breastfeeding may protect against sudden infant death syndrome,[71] insulin-dependent diabetes mellitus, Crohn's disease, ulcerative colitis, lymphoma, allergic diseases, digestive diseases and may enhance cognitive development.[27]

## Growth [edit]

The average breastfed baby doubles its birth weight in 5 to 6 months. By one year, a typical breastfed baby weighs about 2½ times its birth weight. At one year, breastfed babies tend to be leaner than formula-fed babies, which improves long-run health.[72]

The Davis Area Research on Lactation, Infant Nutrition and Growth (DARLING) study reported that breastfed and formula-fed groups had similar weight gain during the first 3 months, but the breastfed babies began to drop below the median beginning at 6 to 8 months and were significantly lower weight than the formula-fed group between 6 and 18 months. Length gain and head circumference values were similar between groups, suggesting that the breastfed babies were leaner.[73]

### Infections [edit]

Breast milk contains several anti-infective factors such as bile salt stimulated lipase (protecting against amoebic infections) and lactoferrin (which binds to iron and inhibits the growth of intestinal bacteria).[74][75]

Infants who are exclusively breastfed for the first six months are less likely to die of gastrointestinal infections than infants who switched from exclusive to partial breastfeeding at three to four months.[76]

During breastfeeding, approximately 0.25–0.5 grams per day of secretory IgA antibodies pass to the baby via milk.[77][78] This is one of the important features of colostrum.[79] The main target for these antibodies are probably microorganisms in the baby's intestine. The rest of the body displays some uptake of IgA,[80] but this amount is relatively small.[81]

Maternal vaccinations while breastfeeding is safe for almost all vaccines. Additionally, the mother's immunity obtained by vaccination against tetanus, diphtheria, whooping cough and influenza can protect the baby from these diseases, and breastfeeding can reduce fever rate after infant immunization. However, smallpox and yellow fever vaccines increase the risk of infants developing vaccinia and encephalitis.[82][83]

## Mortality [edit]

Babies who are not breastfed are almost six times more likely to die by the age of one month than those who receive at least some breastmilk.[84]

### Diabetes [edit]

Infants exclusively breastfed have less chance of developing diabetes mellitus type 1 than those with a shorter duration of breastfeeding.[70] Breastfed infants appear to have a lower likelihood of developing diabetes mellitus type 2 later in life.[69][70][85] Breastfeeding is also associated with a lower risk of type 2 diabetes among mothers who practice it.[86]

### Childhood obesity [edit]

The protective effect of breastfeeding against obesity is consistent, though small, across many studies.[69][70][87] A 2013 longitudinal study reported less obesity at ages two and four years among infants who were breastfed for at least four months.[88]

### Allergic diseases [edit]

In children who are at risk for developing allergic diseases (defined as at least one parent or sibling having atopy), atopic syndrome can be prevented or delayed through 4-month exclusive breastfeeding, though these benefits may not persist.[89]

### Other health effects [edit]

Breastfeeding may reduce the risk of necrotizing enterocolitis (NEC).[70]

Breastfeeding or introduction of gluten while breastfeeding don't protect against celiac disease among at-risk children. Breast milk of healthy human mothers who eat gluten-containing foods presents high levels of non-degraded gliadin (the main gluten protein). Early introduction of traces of gluten in babies to potentially induce tolerance doesn't reduce the risk of developing celiac disease. Delaying the introduction of gluten does not prevent, but is associated with a delayed onset of the disease.[90][91]

About 19% of leukemia cases may be prevented by breastfeeding for six months or longer.[92]

Breastfeeding may decrease the risk of cardiovascular disease in later life, as indicated by lower cholesterol and C-reactive protein levels in breastfed adult women.[69] Breastfed infants have somewhat lower blood pressure later in life, but it is unclear how much practical benefit this provides.[69][70]

A 1998 study suggested that breastfed babies have a better chance of good dental health than formula-fed infants because of the developmental effects of breastfeeding on the oral cavity and airway. It was thought that with fewer malocclusions, breastfed children may have a reduced need for orthodontic intervention. The report suggested that children with a well rounded, "U-shaped" dental arch, which is found more commonly in breastfed children, may have fewer problems with snoring and sleep apnea in later life.[93] A 2016 review found that breastfeeding protected against malocclusions.[94]

### Intelligence [edit]

It is unclear whether breastfeeding improves intelligence later in life. Several studies found no relationship after controlling for confounding factors like maternal intelligence (smarter mothers were more likely to breastfeed their babies).[70][95] However, other studies concluded that breastfeeding was associated with increased cognitive development in childhood, although the cause may be increased mother–child interaction rather than nutrition.[69]

## Mother [edit]

Breastfeeding aids maternal physical and emotional health. Breastfeeding and depression in the mother are associated.[96] Mothers who successfully breastfeed are less likely to develop postpartum depression.[97]

## Maternal bond [edit]

Hormones released during breastfeeding help to strengthen the maternal bond.[21] Teaching partners how to manage common difficulties is associated with higher breastfeeding rates.[98] Support for a breastfeeding mother can strengthen familial bonds and help build a paternal bond.[21][99]

## Fertility [edit]

*Main article: Postpartum infertility*

Exclusive breastfeeding usually delays the return of fertility through lactational amenorrhea, although it does not provide reliable birth control. Breastfeeding may delay the return to fertility for some women by

suppressing ovulation. Mothers may not ovulate, or have regular periods, during the entire lactation period. The non-ovulating period varies by individual. This has been used as natural contraception, with greater than 98% effectiveness during the first six months after birth if specific nursing behaviors are followed.[100]

### Hormonal [edit]

Breastfeeding releases beneficial hormones into the mother's body.[78] Oxytocin and prolactin hormones relax the mother and increase her nurturing response.[101] This hormone release can help to enable sleep. Breastfeeding soon after birth increases the mother's oxytocin levels, making her uterus contract more quickly and reducing bleeding. Pitocin, a synthetic hormone used to make the uterus contract during and after labour, is structurally modelled on oxytocin. Syntocinon, another synthetic oxytocic, is commonly used in Australia and the UK rather than Pitocin.[102]

### Weight loss [edit]

It is unclear whether breastfeeding causes mothers to lose weight after giving birth.[70]

### Reduced cancer risk [edit]

For breastfeeding women, long-term health benefits include reduced risk of breast cancer, ovarian cancer, and endometrial cancer.[27][70][103]

## Decision factors [edit]

*Main article: Breastfeeding difficulties*

The majority of mothers intend to breastfeed at birth. Many factors can disrupt this intent. Research done in the U.S. shows that information about breastfeeding is rarely provided by a women's obstetricians during their prenatal visits and some health professionals incorrectly believe that due to recent improvements commercially prepared formula is equal to breast milk in terms of its health benefits.[104] Many hospitals have instituted practices that encourage breastfeeding, however a 2012 survey in the U.S. found that 24% of maternity services were still providing supplements of commercial infant formula as a general practice in the first 48 hours after birth.[3] *The Surgeon General's Call to Action to Support Breastfeeding* attempts to educate practitioners.[105]

### Social support [edit]

Work is the most commonly cited reason for not breastfeeding.[106] In 2012 Save the Children examined maternity leave laws, ranking 36 industrialized countries according to their support for breastfeeding. Norway ranked first, while the United States came in last.[107] Maternity leave in the US varies widely, including by state, despite the Family Medical Leave Act (FMLA), which guarantees most mothers up to 12 weeks unpaid leave. The majority of US mothers resume work earlier.

- Mother – Adolescence is a risk factor for low breastfeeding rates, although classes, books and personal counseling (professional or lay) can help compensate.[108] Some women fear that breastfeeding will negatively impact the look of their breasts. However, a 2008 study found that breastfeeding had no effect on a woman's breasts, other factors did contribute to "drooping" of the breasts, such as advanced age, number of pregnancies and smoking behavior.[109]
- Partner – Partners may lack knowledge of breastfeeding and their role in the practice.

### Healthcare [edit]

Infants that are otherwise healthy uniformly benefit from breastfeeding. "No known disadvantages" stem from breastfeeding.[110] However, extra precautions should be taken or breastfeeding be avoided in circumstances including

*Famille d'un Chef Camacan se préparant pour une Fête* ("Family of a Camacan chief preparing for a celebration") by Jean-Baptiste Debret shows a woman breastfeeding a child in the background.

certain infectious diseases, or use of certain medications.[111] In some cases it may not be feasible for the mother to continue breastfeeding.[112]

A number of hospital-employed procedures have been found to interfere with breastfeeding, including routine mother/baby separation, delayed initiation, vigorous routine suctioning, medications and mode of delivery.[113]

Pain caused from mis-positioning the baby on the breast or a tongue-tie in the infant can cause pain in the mother and discourage her. These problems are generally easy to correct (by re-positioning or clipping the tongue-tie).[114]

Breast surgery, including breast implants or breast reduction surgery, reduces the chances that a woman will have sufficient milk to breastfeed.[115] Women whose pregnancies are unintended are less likely to breast feed their babies.[116]

## Maternal infections [edit]

*Main article: Breastfeeding by HIV infected mothers*

The central concern about breastfeeding in the presence of maternal HIV is risks of the child becoming infected. Factors such as the viral load in the mother's milk complicate breastfeeding recommendations for HIV-positive mothers.[117]

In mothers who are treated with antiretroviral drugs the risk of HIV transmission with breastfeeding is 1 to 2%.[2] Therefore, of breastfeeding is still recommended in areas of the world with death from infectious diseases is common.[2] Infant formula should only be given if this can be safely done.[2]

WHO recommends that national authorities in each country decide which infant feeding practice should be promoted by their maternal and child health services to best avoid HIV transmission from mother to child.[118] Other maternal infection of concern include active untreated tuberculosis or human T-lymphotropic virus.

## Medications [edit]

Breastfeeding mothers should inform their healthcare provider about all of the medications they are taking, including herbal products. Nursing mothers can safely take many over-the-counter drugs and prescription drugs and receive immunizations, but certain drugs, including painkillers and psychiatric drugs, may pose a risk.

The U.S. National Library of Medicine publishes "LactMed", an up-to-date online database of information on drugs and lactation. Geared to both healthcare practitioners and nursing mothers, LactMed contains over 450 drug records with information such as potential drug effects and alternate drugs to consider.[83][119]

Some pollutants in the mother's food and drink are passed to the baby through breast milk, including mercury (found in some carnivorous fish),[120] caffeine,[121] and bisphenol A.[122][123]

## Socioeconomic status [edit]

Race, ethnicity and socioeconomic status affect choice and duration in the United States. A 2011 study found that on average, US women who breastfed had higher levels of education, were older and were more likely to be white.[124]

The reasons for the persistently lower rates of breastfeeding among African American mothers are not well understood, but employment may play a role. They tend to return to work sooner than white mothers, and are more likely to work in unsupportive environments.

Although return to work is associated with early discontinuation, a supportive work environment may encourage mothers to continue.

Low-income mothers are more likely to have unintended pregnancies.[124] Mothers whose pregnancies are unintended are less likely to breastfeed.[116]

## Social acceptance [edit]

*Main article: Breastfeeding in public*

Negative perception of breastfeeding in social settings has led some women to feel discomfort when breastfeeding in public.[125] Public breastfeeding is forbidden in some places, not addressed by law in others, and a granted legal right in others. Even given a legal right, some mothers are reluctant to breastfeed,[126][127] while others may object to the practice.[128] Some public places and workplaces, rooms for mothers to nurse in private have been designated.

Sign for a private nursing area at a museum using the international breastfeeding symbol

The invention of formula was hypothesized as a way for western culture to adapt to negative perceptions of breastfeeding.[129] The breast pump offered a way for mothers to supply breast milk with most of formula feeding's convenience and without enduring possible disapproval of nursing.[130]

Western society tends to perceive breasts in sexual terms instead of for their biological purpose.[131] This view led many to object to breastfeeding because of the implicit association between infant feeding and sex.[132] Many women feel embarrassed to breast-feed in public.[126] These negative cultural connotations may reduce breastfeeding duration.[126][133][134] Maternal guilt and shame is often affected by how a mother feeds her infant. These feelings result from her inability to behave according to her definition of a "good mother". These feelings occur in both bottle- and breast- feeding mothers, although for different reasons. Bottle feeding mothers may feel that they should be breastfeeding.[135] Conversely, breastfeeding mothers may feel forced to feed in uncomfortable circumstances. Some may see breastfeeding as, "indecent, disgusting, animalistic, sexual, and even possibly a perverse act."[131] Advocates use "nurse-ins" to show support for breastfeeding in public.[125] Some advocates emphasize providing women with education on breastfeeding's benefits as well as problem-solving skills.[135]

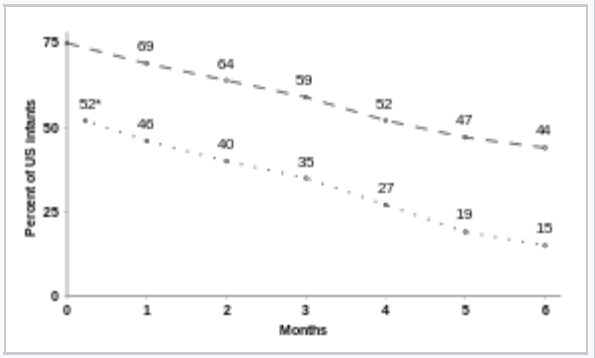
If someone criticizes breastfeeding in public, the La Leche League offers a few ways to respond:

- Ignore the comment or change the subject.
- Share information on breastfeeding with the other person.
- Make a joke about the situation or yourself to lighten the mood.
- Show that you are recognizing the person's viewpoint by asking further questions without agreeing or responding to the criticism.
- Be empathetic — show that you understand the other person's feeling and meaning.[136]

# Prevalence [edit]

Globally about 38% of babies are just breastfeed during their first six months of life.[2] In the United States as of 2012, 75% of women started breastfeeding, 43% breastfeed for six months though only 13% exclusively breastfed, and 23%

Percentage of babies exclusively breastfed for the first six months of life. Data from 2004 to 2011.[137]




Percentage of U.S. infants breastfeeding by month since birth in 2008.
Dotted line: Exclusive breastfeeding
Dashed line Any breastfeeding
* Estimated at 7 days after birth

breastfeed for twelve months.[3][138]

Breastfeeding rates in different parts of China vary considerably.[139]

Breastfeeding rates in the United Kingdom were the lowest in the world in 2015 with only 0.5% of mothers still breastfeeding at a year, while in Germany 23% are doing so, 56% in Brazil and 99% in Senegal.[140]

In Australia for children born in 2004, more than 90% were initially breastfed.[141] In Canada for children born in 2005-06, more than 50% were only breastfed and more than 15% received both breastmilk and other liquids, by the age of 3 months.[142]

## History [edit]

*Main article: History and culture of breastfeeding*

In the Egyptian, Greek and Roman empires, women usually fed only their own children. However, breastfeeding began to be seen as something too common to be done by royalty, and wet nurses were employed to breastfeed the children of the royal families. This extended over time, particularly in western Europe, where noble women often made use of wet nurses. Lower-class women breastfed their infants and used a wet nurse only if they were unable to feed their own infant. Attempts were made in 15th-century Europe to use cow or goat milk, but these attempts were not successful. In the 18th century, flour or cereal mixed with broth were introduced as substitutes for breastfeeding, but this was also unsuccessful.

During the early 1900s, breastfeeding started to be viewed negatively by Western societies, especially Canada and the US. These societies considered it a low class and uncultured practice.[143] This coincided with the appearance of improved infant formulas in the mid 19th century and its increased use, which accelerated after World War II. From the 1960s onwards, breastfeeding experienced a revival which continued into the 2000s, though negative attitudes towards the practice were still entrenched up to 1990s.[143]

Ilkhanate prince Ghazan being breastfed.

## Society and culture [edit]

### Financial considerations [edit]

Breastfeeding is cheaper than alternatives, but is not free of cost. The mother generally must eat more food than otherwise. In the US, the extra money spent on food (about US$13 each week) is usually about half as much money as the cost of infant formula.[144]

Breastfeeding represents an opportunity cost, as the mother must spend hours each day breastfeeding instead of other activities, such as paid

work or home production (such as growing food). In general, the higher the mother's earning power, the less likely she is to save money by breastfeeding.[145]

Breastfeeding reduces health care costs and the cost of caring for sick babies. Parents of breastfed babies are less likely to miss work and lose income because their babies are sick.[144] Looking at three of the most common infant illnesses, lower respiratory tract illnesses, otitis media, and gastrointestinal illness, one study compared infants that had been exclusively breastfed for at least three months to those who had not. It found that in the first year of life there were 2033 excess office visits, 212 excess days of hospitalization, and 609 excess prescriptions for these three illnesses per 1000 never-breastfed infants compared with 1000 infants exclusively breastfed for at least 3 months.[146]

*Macierzyństwo* ("Maternity"), a 1902 painting by Stanisław Wyspiański

## Recommendations [edit]

Support for breastfeeding is universal among major health and children's organizations. WHO states, "Breast milk is the ideal food for the healthy growth and development of infants; breastfeeding is also an integral part of the reproductive process with important implications for the health of mothers.".[147] WHO's guidelines recommend "continue[d] frequent, on-demand breastfeeding until two years of age or beyond."[148][149]

The European Commission,[150][151] the US Centers for Disease Control and Prevention[152] (CDC), UNICEF, AAP,[3] Save The Children and the UK National Health Service[153] (NHS), Australian Department of Health,[154] Health Canada, Canadian Paediatric Society, Dietitians of Canada, and Breastfeeding Committee for Canada,[155] recommend exclusive breastfeeding for six months following birth and continued nursing for an additional eighteen months or more.[2][156] Save the Children states, "Six months of exclusive breastfeeding increases a child's chance of survival at least six-fold."[157]

Authorities generally advise avoiding bottle feeding until the baby is 4–6 weeks old and is nursing successfully.[158]

## Advocacy [edit]

International board certified lactation consultants (IBCLCs) are health care professionals certified in lactation management. They work with mothers to solve breastfeeding problems and educate families and health professionals. Exclusive and partial breastfeeding are more common among mothers who gave birth in IBCLC-equipped hospitals.[160]

There are also controversies and ethical considerations surrounding the means used by public campaigns which attempt to increase breastfeeding rates, relating to pressure put on women, and potential feeling of guilt and shame of women who fail to breastfeed; and social condemnation of women who use formula.[161][162] [163][164] In addition to this, there is also the moral question as to what degree the state or medical community can interfere with the self-determination of a woman: for example in the United Arab Emirates the law requires a woman to breastfeed her baby for at least 2 years and allows her husband to sue her if she does not do so.[165][166]

"See It", a project dedicated to promoting the awareness of breastfeeding in the capital city of Iceland in 2011, by Fiann Paul.[159]

## Infant formula [edit]

Advocates oppose marketing of infant formula, especially in developing countries. They are concerned that mothers who use formula will stop breastfeeding and become dependent upon substitutes that are unaffordable or less safe.[167][168] Through efforts including the Nestlé boycott, they have advocated for bans on free samples of infant formula and for the adoption of pro-breastfeeding codes such as the International Code of Marketing of Breast-milk Substitutes by the World Health Assembly in 1981 and the Innocenti Declaration by WHO and UNICEF policy-makers in August 1990.[167]

## LGBTQ [edit]

Parents who identify as LGBTQ may encounter unique challenges and opportunities with breastfeeding or chestfeeding.

### Chestfeeding [edit]

Many transmasculine, gender non-binary, and gender nonconforming individuals prefer the gender-neutral term "chestfeeding."[169][170] Even if they have had chest masculinization surgery as part of their transition, some trans men choose to chestfeed their infants,[171] which may require use of a supplemental nursing system (SNS) if they do not have a full milk supply.[172] Individuals who have taken or are currently on hormone replacement therapy to develop male secondary sex characteristics may still chestfeed safely and successfully.[171]

### Induced lactation [edit]

Trans women who choose to breastfeed their children have successfully induced lactation.[173] Similarly, lesbian mothers have co-nursed their infants, either by inducing lactation or by using a supplemental nursing system.[174]

## Research [edit]

Breastfeeding research currently focuses on diverse aspects such as prevalence, HIV transmission, pharmacology, costs, benefits, immunology, contraindications, and comparisons to synthetic breast milk substitutes.[175][176] Factors related to the mental health of the nursing mother in the perinatal period have been studied. While cognitive behavior therapy may be the treatment of choice, medications are sometimes used. The use of therapy rather than medication reduces the infant's exposure to medication that may be transmitted through the milk.[177]

## See also [edit]

- Baby Friendly Hospital Initiative
- Baby-led weaning
- Breastfeeding in public
- Breastfeeding promotion
- Breast shell
- Child development
- Dairy allergy
- Public health
- World Alliance for Breastfeeding Action
- Lactation failure
- Human–animal breastfeeding
- Infant formula
- Kangaroo care
- Lactation room
- Milk line
- Nursing chair
- Lactational amenorrhea
- International Code of Marketing of Breast-milk Substitutes

## References [edit]

1. ^ [a](#) [b](#) "Breastfeeding and Breast Milk: Condition Information". 2013-12-19. Retrieved 27 July 2015.
2. ^ [a](#) [b](#) [c](#) [d](#) [e](#) [f](#) [g](#) [h](#) [i](#) [j](#) [k](#) [l](#) "Infant and young child feeding Fact sheet N°342". WHO. February 2014. Retrieved February 8, 2015.
3. ^ [a](#) [b](#) [c](#) [d](#) [e](#) [f](#) [g](#) [h](#) [i](#) [j](#) [k](#) American Academy of Pediatrics Section on Breastfeeding. (March 2012). "Breastfeeding and the use of human milk". *Pediatrics*. **129** (3): 827–841. doi:10.1542/peds.2011-3552. PMID 22371471.
4. ^ "How do I breastfeed? Skip sharing on social media links". 2014-04-14. Retrieved 27 July 2015.
5. ^ "What is weaning and how do I do it?". 2013-12-19. Retrieved 27 July 2015.
6. ^ Ip, S; Chung, M; Raman, G; Trikalinos, TA; Lau, J (October 2009). "A summary of the Agency for Healthcare Research and Quality's evidence report on breastfeeding in developed countries.". *Breastfeeding Medicine*. 4 Suppl 1: S17–30. doi:10.1089/bfm.2009.0050. PMID 19827919.
7. ^ [a](#) [b](#) Victora, CG; Bahl, R; Barros, AJ; França, GV; Horton, S; Krasevec, J; Murch, S; Sankar, MJ; Walker, N; Rollins, NC; Lancet Breastfeeding Series, Group (30 January 2016). "Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect.". *Lancet (London, England)*. **387** (10017): 475–90. doi:10.1016/s0140-6736(15)01024-7. PMID 26869575.
8. ^ Lawrence, Ruth A.; Lawrence, Robert Michael (2011-01-01). *Breastfeeding: A Guide for the Medical Profession*. Elsevier Health Sciences. pp. 227–228. ISBN 1437707882.
9. ^ "Breastfeeding and the use of human milk. American Academy of Pediatrics. Work Group on Breastfeeding (PDF). *Pediatrics*. **100** (6): 1035–9. Dec 1997. doi:10.1542/peds.100.6.1035. PMID 9411381.
10. ^ "What are the benefits of breastfeeding?". 2014-04-14. Retrieved 27 July 2015.
11. ^ Kramer, MS; Kakuma, R (15 August 2012). "Optimal duration of exclusive breastfeeding.". *The Cochrane database of systematic reviews*. **8**: CD003517. doi:10.1002/14651858.CD003517.pub2. PMID 22895934.
12. ^ "What are the recommendations for breastfeeding?". 2014-04-14. Retrieved 27 July 2015.
13. ^ "Are there any special conditions or situations in which I should not breastfeed?". 2013-12-19. Retrieved 27 July 2015.
14. ^ "Breastfeeding and alcohol". *NHS Choices*. NHS.
15. ^ "Breastfeeding and diet". *NHS Choices*. NHS.
16. ^ "Tobacco Use | Breastfeeding | CDC". *www.cdc.gov*. Retrieved 2016-08-04.
17. ^ Mohrbacher, Nancy; Stock, Julie (2003). *The Breastfeeding Answer Book* (3rd ed. (revised) ed.). La Leche League International. ISBN 0-912500-92-1.
18. ^ Sobrinho LG (2003). "Prolactin, psychological stress and environment in humans: adaptation and maladaptation". *Pituitary*. **6** (1): 35–39. doi:10.1023/A:1026229810876. PMID 14674722.
19. ^ Bose CL, D'Ercole AJ, Lester AG, Hunter RS, Barrett JR (1981). "Relactation by mothers of sick and premature infants". *Pediatrics*. **67** (4): 565–569. PMID 6789296.
20. ^ Paul. "Colostrum, Foremilk and Hindmilk".
21. ^ [a](#) [b](#) [c](#) "Mothers and Children Benefit from Breastfeeding". Womenshealth.gov. 27 February 2009. Archived from the original on March 16, 2009.
22. ^ Colen, Cynthia G., and Ramey, David M. "Is breast truly best? Estimating the effects of breastfeeding on long-term child health and wellbeing in the United States using sibling comparisons." Social Science and Medicine. 109. (2014): 55-65. Print.
23. ^ Dewey KG, Heinig MJ, Nommsen LA (August 1993). "Maternal weight-loss patterns during prolonged lactation". *Am. J. Clin. Nutr.* **58** (2): 162–6. PMID 8338042.
24. ^ Hendrickson RG, McKeown NJ (January 2012). "Is maternal opioid use hazardous to breast-fed infants?". *Clinical toxicology (Philadelphia, PA)*. **50** (1): 1–14. doi:10.3109/15563650.2011.635147. PMID 22148986.
25. ^ [a](#) [b](#) "What is colostrum? How does it benefit my baby?". La Leche League. Retrieved 28 November 2015.
26. ^ Northeastern University (2011). "Benefits of Breastfeeding: For Society". Boston, MA: The Educational Technology Center.
27. ^ [a](#) [b](#) [c](#) [d](#) [e](#) [f](#) Gartner LM, Morton J, Lawrence RA, et al. (February 2005). "Breastfeeding and the use of human milk". *Pediatrics*. **115** (2): 496–506. doi:10.1542/peds.2004-2491. PMID 15687461.
28. ^ "Alcohol and breastfeeding.". *Basic Clin Pharmacol Toxicol*. **114** (2): 168–73. Feb 2014. doi:10.1111/bcpt.12149. PMID 24118767.
29. ^ Cornall, D (June 2011). "A review of the breastfeeding literature relevant to osteopathic practice". *International Journal of Osteopathic Medicine*. **14** (2): 61–66. doi:10.1016/j.ijosm.2010.12.003.
30. ^ The Baby Friendly Initiative | Resources | Skin-to-skin contact
31. ^ [a](#) [b](#) Collins, CT; Gillis, J; McPhee, AJ; Suganuma, H; Makrides, M (19 October 2016). "Avoidance of bottles during the establishment of breast feeds in preterm infants.". *The Cochrane database of systematic reviews*. **10**: CD005252. doi:10.1002/14651858.CD005252.pub4. PMID 27756113.
32. ^ [a](#) [b](#) Breastfeeding Frequency from California Pacific Medical Center. Retrieved June 2012.

33. ^ Marasco L (Apr–May 1998). "Common breastfeeding myths". *Leaven*. **34** (2): 21–24. Retrieved 2009-09-21.
34. ^ Davies, Lizzy (12 January 2014). "Pope Francis encourages mothers to breastfeed - even in the Sistine Chapel – via The Guardian.
35. ^ Staff, Healthwise. "Breast-feeding: Learning how to nurse". Retrieved 2009-06-17.
36. ^ "Positions and Tips for Making Breastfeeding Work". *BabyCenter.com*. Retrieved 27 October 2014.
37. ^ "Great Pregnancy. Natural Birth. Healthy Baby.".
38. ^ "Proper positioning and latch-on skills". AskDrSears.com. 2006. Retrieved 2008-09-24.
39. ^ "Breastfeeding Guidelines". Rady Children's Hospital San Diego. Retrieved 2007-03-04.
40. ^ Daws, Dilys (August 1997). "The perils of intimacy: Closeness and distance in feeding and weaning". *Journal of Child Psychotherapy*. **23** (2): 179–199. doi:10.1080/00754179708254541.
41. ^ "How Do I Wean My Baby?". La Leche League International. Retrieved 6 May 2016.
42. ^ "Stopping Breastfeeding Suddenly - Topic Overview". WebMed, LLC. Retrieved 6 May 2016.
43. ^ "Weaning As A Natural Process". La Leche League International. Retrieved 6 May 2016.
44. ^ Iwinski S (2006). "Is Weighing Baby to Measure Milk Intake a Good Idea?". *LEAVEN*. **42** (3): 51–3. Retrieved 2007-04-08.
45. ^ B. F. Habbick; J. W. Gerrard (1984). "Failure to thrive in the contented breast-fed baby". *Can Med Assoc J*. **131** (7): 765–768. PMC 1483563. PMID 6541091.
46. ^ *a b* "LLLI - How can I tell if my baby is getting enough milk?".
47. ^ *a b* "Breast Milk, Breastmilk, Breastfeeding, Breast Feeding - Rehydration Project".
48. ^ "What are the LLLI guidelines for storing my pumped milk?".
49. ^ Hanna N, Ahmed K, Anwar M, Petrova A, Hiatt M, Hegyi T (November 2004). "Effect of storage on breast milk antioxidant activity". *Arch Dis Child Fetal Neonatal Ed*. BMJ Publishing Group Ltd. **89** (6): F518–20. doi:10.1136/adc.2004.049247. PMC 1721790. PMID 15499145.
50. ^ Spatz DL (2006). "State of the science: use of human milk and breast-feeding for vulnerable infants". *J Perinat Neonatal Nurs*. **20** (1): 51–5. doi:10.1097/00005237-200601000-00017. PMID 16508463.
51. ^ Tully DB, Jones F, Tully MR (2001). "Donor milk: what's in it and what's not". *J Hum Lact*. **17** (2): 152–5. doi:10.1177/089033440101700212. PMID 11847831.
52. ^ Sears, W. "Ask Dr. Sears: Leaving Baby for Vacation".
53. ^ Alcorn K (2004-08-24). "Shared breastfeeding identified as new risk factor for HIV". aidsmap. Retrieved 2007-04-10.
54. ^ Groskop, Viv (5 January 2007). "Not your mother's milk" – via The Guardian.
55. ^ Jennifer Baumgardner, *Breast Friends*, Babble, 2007
56. ^ Grunberg R (1992). "Breastfeeding multiples: Breastfeeding triplets". *New Beginnings*. **9** (5): 135–6.
57. ^ Australian Breastfeeding Association: Breastfeeding triplets, quads and higher
58. ^ Association of Radical Midwives: Breastfeeding triplets
59. ^ Flower H (2003). *Adventures in Tandem Nursing: Breastfeeding During Pregnancy and Beyond*. La Leche League International. ISBN 978-0-912500-97-3.
60. ^ *a b c d e f* Morrison, Barbara; Karen Wambach (2014). "Women's Health and Breastfeeding". In Wambach, Karen and Jan Riordan. *Breastfeeding and Human Lactation* (5th ed.). Jones & Bartlett Publishers. pp. 581–588. ISBN 9781449697297.
61. ^ *a b c* THE TREATMENT OF DIARRHOEA, A manual for physicians and other senior health workers, World Health Organization, 2005, page 41 (45 in PDF). Reference: *Helping mothers to breastfeed* by F. Savage King. Revised edition 1992. African Medical and Research Foundation (AMREF), Box 30125, Nairobi, Kenya. Indian adaptation by R.K. Anand, ACASH, P.O. Box 2498, Bombay 400002)
62. ^ "Breastfeeding: Data: Report Card" (PDF). Center for Disease Control and Prevention. Retrieved 2015-11-05.
63. ^ "Infant and toddler health". Mayo Clinic. Retrieved 12 May 2016.
64. ^ Stein MT, Boies EG, Snyder D (2004). "Parental concerns about extended breastfeeding in a toddler". *J Dev Behav Pediatr*. **25** (5 Suppl): S107–11. doi:10.1097/00004703-200410001-00022. PMID 15502526.
65. ^ Ip, S; Chung, M; Raman, G; Chew, P; Magula, N; DeVine, D; Trikalinos, T; Lau, J (April 2007). "Breastfeeding and maternal and infant health outcomes in developed countries.". *Evidence report/technology assessment* (153): 1–186. PMID 17764214.
66. ^ US Preventive Services Task, Force.; Bibbins-Domingo, K; Grossman, DC; Curry, SJ; Davidson, KW; Epling JW, Jr; García, FA; Kemper, AR; Krist, AH; Kurth, AE; Landefeld, CS; Mangione, CM; Phillips, WR; Phipps, MG; Pignone, MP (25 October 2016). "Primary Care Interventions to Support Breastfeeding: US Preventive Services Task Force Recommendation Statement.". *JAMA*. **316** (16): 1688–1693. PMID 27784102.
67. ^ Renfrew MJ, Lang S, Woolridge MW (2000). "Early versus delayed initiation of breastfeeding". *Cochrane Database Syst Rev* (2): CD000043. doi:10.1002/14651858.CD000043. PMID 10796101.

68. ^ Moore, ER; Anderson, GC; Bergman, N; Dowswell, T (May 16, 2012). "Early skin-to-skin contact for mothers and their healthy newborn infants.". *The Cochrane database of systematic reviews*. **5**: CD003519. doi:10.1002/14651858.CD003519.pub3. PMC 3979156. PMID 22592691.
69. ^ *a b c d e f* Horta BL, Bahl R, Martines JC, Victora CG (2007). *Evidence on the long-term effects of breastfeeding: systematic reviews and meta-analyses* (PDF). Geneva, Switzerland: World Health Organization. ISBN 978-92-4-159523-0. Retrieved 2010-04-05.
70. ^ *a b c d e f g h i* Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, Trikalinos T, Lau J (April 2007). "Breastfeeding and maternal and infant health outcomes in developed countries". *Evid Rep Technol Assess (Full Rep)* (153): 1–186. ISBN 978-1-58763-242-6. PMID 17764214.
71. ^ Hauck, F. R.; Thompson, J. M. D.; Tanabe, K. O.; Moon, R. Y.; Vennemann, M. M. (13 June 2011). "Breastfeeding and Reduced Risk of Sudden Infant Death Syndrome: A Meta-analysis". *Pediatrics*. **128** (1): 103–110. doi:10.1542/peds.2010-3000. PMID 21669892.
72. ^ Ministry of Health Health Promotion Council. "Guideline for Management of Child Screening in Primary Care Settings and Outpatient Clinics in the Kingdom of Bahrain" (PDF). Kingdom of Bahrain Ministry of Health Health Promotion Council. Retrieved 23 February 2015.
73. ^ Dewey, Kathryn G; Heinig, Jane M; Nommsen, Laurie A.; Peerson, Janet M.; Lönnerdal, Bo (1991). "Growth of Breast-Fed and Formula-Fed Infants From 0 to 18 Months: The DARLING Study". *article*. Retrieved 23 February 2015.
74. ^ Kunz C, Rodriguez-Palmero M, Koletzko B, Jensen R (June 1999). "Nutritional and biochemical properties of human milk, Part I: General aspects, proteins, and carbohydrates". *Clin Perinatol*. **26** (2): 307–33. PMID 10394490.
75. ^ Rodriguez-Palmero M, Koletzko B, Kunz C, Jensen R (June 1999). "Nutritional and biochemical properties of human milk: II. Lipids, micronutrients, and bioactive factors". *Clin Perinatol*. **26** (2): 335–59. PMID 10394491.
76. ^ Kramer, MS; Kakuma, R (15 August 2012). "Optimal duration of exclusive breastfeeding.". *The Cochrane database of systematic reviews*. **8**: CD003517. doi:10.1002/14651858.CD003517.pub2. PMID 22895934.
77. ^ Hanson LA, Söderström T (1981). "Human milk: Defense against infection". *Prog. Clin. Biol. Res*. **61**: 147–59. PMID 6798576.
78. ^ *a b* Van de Perre P (July 2003). "Transfer of antibody via mother's milk". *Vaccine*. **21** (24): 3374–6. doi:10.1016/S0264-410X(03)00336-0. PMID 12850343.
79. ^ Jackson KM, Nazar AM (April 2006). "Breastfeeding, the immune response, and long-term health". *J Am Osteopath Assoc*. **106** (4): 203–7. PMID 16627775.
80. ^ Vukavic T (1983). "Intestinal absorption of IgA in the newborn". *Journal of pediatric gastroenterology and nutrition*. **2** (2): 248–251. doi:10.1097/00005176-198305000-00006. PMID 6875749.
81. ^ Weaver LT, Wadd N, Taylor CE, Greenwell J, Toms GL (1991). "The ontogeny of serum IgA in the newborn". *Pediatric Allergy and Immunology*. **2** (2): 72–75. doi:10.1111/j.1399-3038.1991.tb00185.x.
82. ^ Winslow, Ron (26 August 2013). "Many Drugs Found Safe for Breast-Feeding Mothers". *Wall Street Journal*. Retrieved 2 September 2013.
83. ^ *a b* Sachs HC (2013). "The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on Selected Topics". *Pediatrics*. The American Academy of Pediatrics. **132** (3): e796–e809. doi:10.1542/peds.2013-1985. PMID 23979084.
84. ^ WHO "strategic directions for improving the health and development of children and adolescents", WHO/FCH/CAH/02.21, Geneva: Department of Child and Adolescent Health and Development, World Health Organization.
85. ^ Owen CG, Martin RM, Whincup PH, Smith GD, Cook DG (November 2006). "Does breastfeeding influence risk of type 2 diabetes in later life? A quantitative analysis of published evidence". *Am. J. Clin. Nutr*. **84** (5): 1043–54. PMID 17093156.
86. ^ Aune, D.; Norat, T.; Romundstad, P.; Vatten, L.J. (February 2014). "Breastfeeding and the maternal risk of type 2 diabetes: A systematic review and dose–response meta-analysis of cohort studies". *Nutrition, Metabolism and Cardiovascular Diseases*. **24** (2): 107–115. doi:10.1016/j.numecd.2013.10.028.
87. ^ Arenz S, Rückerl R, Koletzko B, von Kries R (2004). "Breast-feeding and childhood obesity--a systematic review". *Int. J. Obes. Relat. Metab. Disord*. **28** (10): 1247–56. doi:10.1038/sj.ijo.0802758. PMID 15314625.
88. ^ Moss, B.G.; Yeaton, W.H. (2014). "Early childhood healthy and obese weight status: Potentially protective benefits of breastfeeding and delaying solid foods.". *Maternal and Child Health Journal*. **18** (5): 1224–1232. doi:10.1007/s10995-013-1357-z.
89. ^ Greer FR, Sicherer SH, Burks AW (January 2008). "Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas". *Pediatrics*. **121** (1): 183–91. doi:10.1542/peds.2007-3022. PMID 18166574.

90. ^ Szajewska H, Shamir R, Chmielewska A, Pieścik-Lech M, Auricchio R, Ivarsson A, Kolacek S, Koletzko S, Korponay-Szabo I, Mearin ML, Ribes-Koninckx C, Troncone R; PREVENTCD Study Group (Jun 2015). "Systematic review with meta-analysis: early infant feeding and coeliac disease--update 2015". *Aliment Pharmacol Ther*. **41** (11): 1038–54. doi:10.1111/apt.13163. PMID 25819114.
91. ^ Bethune MT, Khosla C (Feb 2008). "Parallels between pathogens and gluten peptides in celiac sprue". *PLoS Pathog*. **4** (2): e34. doi:10.1371/journal.ppat.0040034. PMC 2323203. PMID 18425213.
92. ^ Amitay, EL; Keinan-Boker, L (1 June 2015). "Breastfeeding and Childhood Leukemia Incidence: A Meta-analysis and Systematic Review.". *JAMA pediatrics*. **169** (6): e151025. doi:10.1001/jamapediatrics.2015.1025. PMID 26030516.
93. ^ Palmer, B (June 1998). "The influence of breastfeeding on the development of the oral cavity: a commentary.". *Journal of Human Lactation*. **14** (2): 93–8. doi:10.1177/089033449801400203. PMID 9775838.
94. ^ Victora, Cesar G; Bahl, Rajiv; Barros, Aluísio J D; França, Giovanny V A; Horton, Susan; Krasevec, Julia; Murch, Simon; Sankar, Mari Jeeva; Walker, Neff; Rollins, Nigel C (January 2016). "Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect". *The Lancet*. **387** (10017): 475–490. doi:10.1016/S0140-6736(15)01024-7. PMID 26869575.
95. ^ Der G, Batty GD, Deary IJ (2006). "Effect of breast feeding on intelligence in children: prospective study, sibling pairs analysis, and meta-analysis". *BMJ*. **333** (7575): 945. doi:10.1136/bmj.38978.699583.55. PMC 1633819. PMID 17020911.
96. ^ Dias, CC; Figueiredo, B (15 January 2015). "Breastfeeding and depression: a systematic review of the literature.". *Journal of Affective Disorders*. **171**: 142–54. doi:10.1016/j.jad.2014.09.022. PMID 25305429.
97. ^ Figueiredo B, Dias CC, Brandão S, Canário C, Nunes-Costa R (2013). "Breastfeeding and postpartum depression: state of the art review". *J Pediatr (Rio J)*. **89** (4): 332–8. doi:10.1016/j.jped.2012.12.002. PMID 23791236.
98. ^ Pisacane A, Continisio GI, Aldinucci M, D'Amora S, Continisio P (October 2005). "A controlled trial of the father's role in breastfeeding promotion". *Pediatrics*. **116** (4): e494–8. doi:10.1542/peds.2005-0479. PMID 16199676.
99. ^ van Willigen J (2002). *Applied anthropology: an introduction*. Westport, CT: Bergin & Garvey. ISBN 0-89789-833-8. [*page needed*]
100. ^ Price C; Robinson S (2004). *Birth: Conceiving, Nurturing and Giving Birth to Your Baby*. McMillan. p. 489. ISBN 1-4050-3612-5.
101. ^ Stuart-Macadam P, Dettwyler K (1995). *Breastfeeding: biocultural perspectives*. Aldine de Gruyter. p. 131. ISBN 978-0-202-01192-9.
102. ^ Chua S, Arulkumaran S, Lim I, Selamat N, Ratnam SS (1994). "Influence of breastfeeding and nipple stimulation on postpartum uterine activity". *Br J Obstet Gynaecol*. **101** (9): 804–5. doi:10.1111/j.1471-0528.1994.tb11950.x. PMID 7947531.
103. ^ Krishnamurthy Arvind; Soundara Viveka; Ramshankar Vijayalakshmi (2016). "Preventive and Risk Reduction Strategies for Women at High Risk of Developing Breast Cancer: a Review.". *Asian Pacific journal of cancer prevention*. **17** (3): 895–904. doi:10.7314/apjcp.2016.17.3.895. PMID 27039715. Retrieved 4 August 2016. "A review of 47 epidemiologic studies comprising of 50,302 women with invasive breast cancer and 96,973 controls estimated that for every year of breastfeeding, the relative risk of breast cancer decreases by 4.3%."
104. ^ "The Surgeon General's Call to Action to Support Breastfeeding" (PDF). U.S. Department of Health and Human Services. Retrieved 12 December 2015.
105. ^ Benjamin RM (2011). "Public health in action: give mothers support for breastfeeding". *Public Health Rep*. **126** (5): 622–3. PMC 3151176. PMID 21886320.
106. ^ Galson SK (July 2008). "Mothers and children benefit from breastfeeding" (PDF). *Journal of the American Dietetic Association*. **108** (7): 1106. doi:10.1016/j.jada.2008.04.028. PMID 18589012. Retrieved 25 August 2012.
107. ^ State of the World's Mothers 2012-Final [*full citation needed*] Archived May 23, 2012, at the Wayback Machine.
108. ^ Woods NK, Chesser AK, Wipperman J (2013). "Describing adolescent breastfeeding environments through focus groups in an urban community". *J Prim Care Community Health*. **4** (4): 307–10. doi:10.1177/2150131913487380. PMID 23799673.
109. ^ Ireland, Jae (20 July 2011). "Will My Breasts Be Ruined After Breastfeeding?". LiveStrong.com. Retrieved 27 Jan 2013.
110. ^ Lawrence, Ruth A. Lawrence, Robert M. (2010). *Breastfeeding : a guide for the medical professional.* (7th ed.). Philadelphia, Pa.: Saunders. p. 266. ISBN 9781437707885.
111. ^ Lawrence, Ruth A. Lawrence, Robert M. (2010). *Breastfeeding : a guide for the medical professional.* (7th ed.). Philadelphia, Pa.: Saunders. pp. 223, 227. ISBN 9781437707885.
112. ^ Lawrence, Ruth A. Lawrence, Robert M. (2010). *Breastfeeding : a guide for the medical professional.* (7th ed.). Philadelphia, Pa.: Saunders. p. 227. ISBN 9781437707885.
113. ^ "Breastfeeding-related maternity practices at hospitals and birth centers—United States, 2007". *MMWR Morb.*

*Mortal. Wkly. Rep.* **57** (23): 621–5. June 2008. PMID 18551096.
114. ^ Ballard J, Chantry C, Howard CR. "Guidelines for the evaluation and management of neonatal ankyloglossia and its complications in the breastfeeding dyad". *ABM Clinical Protocol #11*.
115. ^ "Breast Surgery Likely to Cause Breastfeeding Problems". The Implant Information Project of the Nat. Research Center for Women & Families. February 2008.
116. ^ [a] [b] "Family Planning - Healthy People 2020". Retrieved 2011-08-18.
117. ^ Moland, K, Blystad A (2008). "Counting on Mother's Love: The Global Politics of Prevention of Mother-to-Child Transmission of HIV in Eastern Africa". In Hahn R, Inhorn M. *Anthropology and Public Health: Bridging Differences in Culture and Society*. Oxford University Press. p. 449.
118. ^ Mead MN (2008). "Contaminants in human milk: weighing the risks against the benefits of breastfeeding". *Environ Health Perspect*. **116** (10): A426–34. doi:10.1289/ehp.116-a426. PMC 2569122. PMID 18941560.
119. ^ "AAP Advises Most Medications Are Safe for Breastfeeding Mothers". American Academy of Pediatrics. 26 August 2013. Retrieved 11 July 2015.
120. ^ Myers GJ, Thurston SW, Pearson AT, Davidson PW, Cox C, Shamlaye CF, Cernichiari E, Clarkson TW (2009). "Postnatal exposure to methyl mercury from fish consumption: a review and new data from the Seychelles Child Development Study". *Neurotoxicology*. **30** (3): 338–49. doi:10.1016/j.neuro.2009.01.005. PMC 2743883. PMID 19442817.
121. ^ Howard CR, Lawrence RA (1998). "Breast-feeding and drug exposure". *Obstet Gynecol Clin North Am*. **25** (1): 195–217. doi:10.1016/S0889-8545(05)70365-X. PMID 9547767.
122. ^ Sun Y, Irie M, Kishikawa N, Wada M, Kuroda N, Nakashima K (2004). "Determination of bisphenol a in human breast milk by HPLC with column-switching andfluorescence detection". *Biomedical Chromatography*. **18** (8): 501–507. doi:10.1002/bmc.345. PMID 15386523.
123. ^ Ye X, Kuklenyik Z, Needham LL, Calafat AM (2006). "Measuring environmental phenols and chlorinated organic chemicals in breast milk using automated on-line column-switching–high performance liquid chromatography–isotope dilution tandem mass spectrometry". *Journal of Chromatography B*. **831** (1–2): 110–115. doi:10.1016/j.jchromb.2005.11.050. PMID 16377264.
124. ^ [a] [b] Office of the Surgeon General (US); Centers for Disease Control and Prevention (US); Office on Women's Health (US) (2011). "Call to Action to Support Breastfeeding" (PDF). *Surgeon General's Call to Action*. PMID 21452448.
125. ^ [a] [b] Boyer, K., & Geographies of Care. (March 01, 2011). *The way to break the taboo is to do the taboo thing* breastfeeding in public and citizen-activism in the UK. Health and Place, 17, 2, 430-437.
126. ^ [a] [b] [c] Wolf JH (2008). "Got milk? Not in public!". *International breastfeeding journal*. **3** (1): 11. doi:10.1186/1746-4358-3-11. PMC 2518137. PMID 18680578.
127. ^ "Breastfeeding Legislation in the United States: A General Overview and Implications for Helping Mothers". *LEAVEN*. **41** (3): 51–4. 2005.
128. ^ Jordan, Tim; Pile, Steve, eds. (2002). *Social Change*. Blackwell. p. 233. ISBN 0-631-23311-3.
129. ^ Hausman, B. L. (January 01, 2007). Things (Not) to Do with Breasts in Public: Maternal Embodiment and the Biocultural Politics of Infant Feeding. New Literary History, 38, 3, 479-504.
130. ^ Boyer, K. (January 01, 2010). Of care and commodities: breast milk and the new politics of mobile biosubstances. Progress in Human Geography, 34, 1, 5-20.
131. ^ [a] [b] Forbes GB, Adams-Curtis LE, Hamm NR, White KB (2003). "Perceptions of the Woman Who Breastfeeds: The Role of Erotophobia, Sexism, and Attitudinal Variables". *Sex Roles*. **49** (7/8): 379–388. doi:10.1023/A:1025116305434.
132. ^ A.R. Al-Awadi (14 May 1981). "Draft International Code of Marketing of Breastmilk substitutes" (PDF). *Thirty-fourth World Health Assembly, Agenda item 23.2*. World Health Organization. World Health Organization(Organisation Mondiale de la Sante).
133. ^ Harmon, A. (2005, June 7). 'Lactivists' Taking Their Cause, and Their Babies, to the Streets. The New York Times. Retrieved November 1, 2013
134. ^ Battersby, S. (2010). "Understanding the Social and Cultural Influences on Breast-Feeding Today". *Journal of Family Health Care*. **20** (4): 128–131. PMID 21053661.
135. ^ [a] [b] Taylor EN, Wallace LE (2012). "For Shame: Feminism, Breastfeeding Advocacy, and Maternal Guilt". *Hypatia*. **27** (1): 76–98. doi:10.1111/j.1527-2001.2011.01238.x.
136. ^ "Breastfeeding In Public". *womenshealth.gov*.
137. ^ "Infants exclusively breastfed for the first six months of life (%)". World Health Organization. Retrieved 27 July 2015.
138. ^ Centers for Disease Control and Prevention, (CDC) (8 February 2013). "Progress in increasing breastfeeding and reducing racial/ethnic differences - United States, 2000-2008 births.". *MMWR. Morbidity and mortality weekly report*.

**62** (5): 77–80. PMID 23388550 .
139. ^ Xu, Fenglian; Qiu, Liqian; Binns, Colin W; Liu, Xiaoxian (2009). "Breastfeeding in China: a review". *International Breastfeeding Journal*. **4** (1): 6. doi:10.1186/1746-4358-4-6. ISSN 1746-4358.
140. ^ "UK 'world's worst' at breastfeeding". BBC. 29 January 2016. Retrieved 30 January 2016.
141. ^ "Australia - Breastfeeding rates for children born in 2004".
142. ^ "A Comparison of Breastfeeding Rates by Country • KellyMom.com". *KellyMom.com*. 2012-05-14. Retrieved 2016-05-04.
143. ^ *a b* Nathoo, Tasnim; Ostry, Aleck (2009). *The One Best Way?: Breastfeeding History, Politics, and Policy in Canada*. Wilfrid Laurier Univ. Press. ISBN 978-1-55458-171-9.[*page needed*]
144. ^ *a b* "Breastfeeding and the use of human milk. American Academy of Pediatrics. Work Group on Breastfeeding (PDF). *Pediatrics*. **100**: 1035–9. Dec 1997. doi:10.1542/peds.100.6.1035. PMID 9411381.
145. ^ Cohen, Lloyd R.; Wright, Joshua D. (2011). *Research Handbook on the Economics of Family Law*. Edward Elgar Publishing. p. 185. ISBN 9780857930644.
146. ^ Ball, T.M.; Wright, A.L. (April 1999). "Health care costs of formula-feeding in the first year of life". *Pediatrics*. **103**: 870–6. PMID 10103324.
147. ^ "Up to what age can a baby stay well nourished by just being breastfed?". WHO. July 2013. Retrieved 7 February 2015.
148. ^ World Health Organization. (2003). *Global strategy for infant and young child feeding* (PDF). Geneva, Switzerland: World Health Organization and UNICEF. ISBN 92-4-156221-8. Retrieved 2009-09-20.
149. ^ "Breastfeeding".
150. ^ "Protection, promotion and support of breastfeeding in Europe: a blueprint for action" (PDF). Unit for Health Services Research and International Health. 2008. Retrieved 15 February 2015.
151. ^ Cattaneo A; et al. (Jun 2010). "Protection, promotion and support of breast-feeding in Europe: progress from 2002 to 2007". *Public Health Nutr*. **13** (6): 751–9. doi:10.1017/S1368980009991844. PMID 19860992.
152. ^ "Breastfeeding: Promotion & Support". CDC. August 2, 2011.
153. ^ "Why breastfeed? | National Health Service".
154. ^ "Breastfeeding". Australian Government. 27 May 2014. Retrieved 8 February 2015.
155. ^ "Nutrition for Healthy Term Infants: Recommendations from Birth to Six Months". *A joint statement of Health Canada, Canadian Paediatric Society, Dietitians of Canada, and Breastfeeding Committee for Canada*. Health Canada. reviewed 27 May 2014. Retrieved 7 February 2015. Check date values in: `|date=` (help)
156. ^ "Breastfeeding: Data: Report Card 2012: Outcome Indicators - DNPAO - CDC".
157. ^ "Nutrition in the First 1,000 Days" (PDF). *State of the World's Mothers 2012*. Save the Children. 2012. Retrieved 8 February 2015.
158. ^ Arlene Eisenberg (1989). *What to Expect the First Year*. Workman Publishing Company. ISBN 0-89480-577-0.
159. ^ Baldursdóttir, Ingibjörg. "Pressan.is". *www.pressan.is*. Retrieved 2016-08-26.
160. ^ US Surgeon General Breastfeeding Executive Summary
161. ^ Dailey, Kate (7 August 2012). "Formula v breastfeeding: Should the state step in?" – via www.bbc.com.
162. ^ Mason, Rowena; correspondent, political (3 January 2014). "Parents 'face too much guilt over breastfeeding and work'" – via The Guardian.
163. ^ "Breastfeeding may be best, but bottles of formula milk aren't the end of the world".
164. ^ noodles, Mirah Curzer Lawyer Feminist Photographer Slurper of; Scotch, Drinker of (4 August 2016). "You Can't Call Yourself A Feminist If You Shame Women Who Don't Breastfeed".
165. ^ Graham-Harrison, Emma (7 February 2014). "UAE law requires mothers to breastfeed for first two years" – via The Guardian.
166. ^ "Forcing Mothers to Breastfeed Is No Way to Help Children - Huffington Post".
167. ^ *a b* Milking it Joanna Moorhead, The Guardian, May 15, 2007
168. ^ Baby health crisis in Indonesia as formula companies push products, *The Guardian*, Zoe Williams in Jakarta, 15 Feb. 2013.
169. ^ de la Cretaz, Britni. "What It's Like to Chestfeed". *theatlantic.com*. Retrieved 3 September 2016.
170. ^ Hempel, Jessi (1 September 2016). "My Brother's Pregnancy and the Making of a New American Family". *Time*. Retrieved 3 September 2016.
171. ^ *a b* MacDonald, Trevor. "Transmasculine individuals' experiences with lactation, chestfeeding, and gender identity: a qualitative study". *BioMed Central Pregnancy and Childbirth*. Retrieved 3 September 2016.
172. ^ MacDonald, Trevor (June 29, 2012). "How I Learned to be a Breastfeeding Dad". *Huffington Post*. Retrieved 3 September 2016.
173. ^ MacDonald, Trevor. "Trans Women and Breastfeeding: A Personal Interview". *milkjunkies.net*. Retrieved 3 September 2016.

174. ^ Higham, Barbara. "When Two Women Share Parenting - Breastfeeding Today". *breastfeedingtoday-llli.org*. Retrieved 2016-09-03.
175. ^ Kramer, Michael S; Kakuma, Ritsuko; Kramer, Michael S (2012). "Optimal duration of exclusive breastfeeding". *Cochrane Database Syst Rev*. **8**: CD003517. doi:10.1002/14651858.CD003517.pub2. PMID 22895934.
176. ^ Saha, Moni R.; Ryan, Kath; Amir, Lisa H. (2015). "Postpartum women's use of medicines and breastfeeding practices: a systematic review". *International Breastfeeding Journal*. **10** (1). doi:10.1186/s13006-015-0053-6. ISSN 1746-4358.
177. ^ Marchesi, C.; Ossola, P.; Amerio, A.; Daniel, B.D.; Tonna, M.; De Panfilis, C. (2016). "Clinical management of perinatal anxiety disorders: A systematic review". *Journal of Affective Disorders*. **190**: 543–550. doi:10.1016/j.jad.2015.11.004; Access provided by the University of Pittsburgh Library System


## Further reading [edit]


- Baumslag, Naomi; Michels, Dia L. (1995). *Milk, money, and madness: the culture and politics of breastfeeding*. Westport, Connecticut: Bergin & Garvey. ISBN 9780313360602.
- Cassidy, Tanya and Abdullahi El Tom, eds. *Ethnographies of Breastfeeding: Cultural Contexts and Confrontations* (Bloomsbury Academic; 2015) 255 pages; Scholarly essays on a variety of topics such as networks of milk sharing through Facebook, public-health guidelines on infant feeding and HIV in Malawi, and dilemmas involving breastfeeding and bonding for babies born from surrogate mothers.
- Halili, Hassan Kamal; Che, Musa Norsuhaida (June 2014). "Women's right to breastfeed in the workplace: legal lacunae in Malaysia". *Asian Women*. Research Institute of Asian Women (RIAW). **30** (2): 85–108. doi:10.14431/aw.2014.03.30.2.85.
- Hausman, Bernice L. (2003). *Mother's milk: breastfeeding controversies in American culture*. New York, New York: Routledge. ISBN 9780415966573.


## External links [edit]

- Breastfeeding at DMOZ
- Breastfeeding Resources La Leche League International
- Breast-Feeding Content Resources WHO reports on Breast Feeding
- Human Milk Secretion: An Overview US National Institute of Health
- The World Alliance for Breastfeeding Action (WABA) is a global network of individuals & organisations concerned with the protection, promotion & support of breastfeeding worldwide.
- Center for Disease Control and Prevention Breastfeeding CDC
- LactMed, a database of the safety of drugs to which breastfeeding mothers may be exposed, by the U.S. National Library of Medicine

Wikimedia Commons has media related to *Breastfeeding*.

Look up *breastfeeding* in Wiktionary, the free dictionary.

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|---|---|
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| **From plants** | Plant milk · Almond · Coconut · Hemp · Rice · Peanut · Soy · |
| **Types** | A2 · Baked · Condensed · Evaporated · Filled · Flavored (Anise · Chocolate · Coffee · Vanilla · · Ice · Malted · Organic · Pasteurized · Powdered · Raw · Scalded · Skimmed · Soured · Toned · UHT · Ultrafiltered · |
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| **Egg** | Ovum · Oviposition · Oviparity · Ovoviviparity · Vivipary · |
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# Childbirth

From Wikipedia, the free encyclopedia

*This article is about birth in humans. For birth in other mammals, see birth.*

**Childbirth**, also known as **labour and delivery**, is the ending of a pregnancy by one or more babies leaving a woman's uterus.[1] In 2015 there were about 135 million births globally.[2] About 15 million were born before 37 weeks of gestation,[3] while between 3 and 12% were born after 42 weeks.[4] In the developed world most deliveries occur in hospital,[5][6] while in the developing world most births take place at home with the support of a traditional birth attendant.[7]

The most common way of childbirth is a vaginal delivery.[8] It involves three stages of labour: the shortening and opening of the cervix, descent and birth of the baby, and the pushing out of the placenta.[9] The first stage typically lasts twelve to nineteen hours, the second stage twenty minutes to two hours, and the third stage five to thirty minutes.[10] The first stage begins with crampy abdominal or back pains that last around half a minute and occur every ten to thirty minutes.[9] The crampy pains become stronger and closer together over time.[10] During the second stage pushing with contractions may occur.[10] In the third stage delayed clamping of the umbilical cord is generally recommended.[11] A number of methods can help with pain such as relaxation techniques, opioids, and spinal blocks.[10]

Most babies are born head first; however about 4% are born feet or buttock first, known as breech.[10][12] During labour a women can generally eat and move around as she likes, pushing is not recommended during the first stage or during delivery of the head, and enemas are not recommended.[13] While making a cut to the opening of the vagina is common, known as an episiotomy, it is generally not needed.[10] In 2012, about 23 million deliveries occurred by a surgical procedure known as Caesarean section.[14] Caesarean sections may be recommended for twins, signs of distress in the baby, or breech position.[10] This method of delivery can take longer to heal from.[10]

Each year complications from pregnancy and childbirth result in about 500,000 maternal deaths, 7 million women have serious long term problems, and 50 million women have health negative outcomes following delivery.[15] Most of these occur in the developing world.[15] Specific complications include obstructed labour, postpartum bleeding, eclampsia, and postpartum infection.[15] Complications in the baby include birth asphyxia.[16]

**Variants**

**Childbirth**

**Synonyms** labour, parturition, birth

Newborn infant and mother

**Classification and external resources**

**Specialty** Obstetrics, midwifery

[edit on Wikidata]

**Contents**

## Signs and symptoms [edit]

The most prominent sign of labour is strong repetitive uterine contractions. The distress levels reported by labouring women vary widely. They appear to be influenced by fear and anxiety levels, experience with prior childbirth, cultural ideas of childbirth and pain,[17][18] mobility during labour, and the support received during labour. Personal expectations, the amount of support from caregivers, quality of the caregiver-patient relationship, and involvement in decision-making are more important in women's overall satisfaction with the experience of childbirth than are other factors such as age, socioeconomic status, ethnicity, preparation, physical environment, pain, immobility, or medical interventions.[19]

Luristan bronze, fibula showing a woman giving birth between 2 antelopes, ornamented with flowers, Iranian, 1000 to 650 BCE) at the Louvre museum

### Descriptions [edit]

Pain in contractions has been described as feeling similar to very strong menstrual cramps. Women are often encouraged to refrain from screaming, but moaning and grunting may be encouraged to help lessen pain. Crowning may be experienced as an intense stretching and burning. Even women who show little reaction to labour pains, in comparison to other women, show a substantially severe reaction to crowning.

Back labour is a term for specific pain occurring in the lower back, just above the tailbone, during childbirth.[20]

### Psychological [edit]

Childbirth can be an intense event and strong emotions, both positive and negative, can be brought to the surface. Abnormal and persistent fear of childbirth is known as tokophobia.

During the later stages of gestation there is an increase in abundance of oxytocin, a hormone that is known to evoke feelings of contentment, reductions in anxiety, and feelings of calmness and security around the mate.[21] Oxytocin is further released during labour when the fetus stimulates the cervix and vagina, and it is believed that it plays a major role in the bonding of a mother to her infant and in the establishment of maternal behavior. The act of nursing a child also causes a release of oxytocin.[22]

Between 70% and 80% of mothers in the United States report some feelings of sadness or "baby blues" after giving birth. The symptoms normally occur for a few minutes up to few hours each day and they should lessen and disappear within two weeks after delivery. Postpartum depression may develop in some women; about 10% of mothers in the United States are diagnosed with this condition. Preventive group therapy has proven effective as a prophylactic treatment for postpartum depression.[23][24]

## Normal birth [edit]

*Further information: Vaginal delivery*

Humans are bipedal with an erect stance. The erect posture causes the weight of the abdominal contents to thrust on the

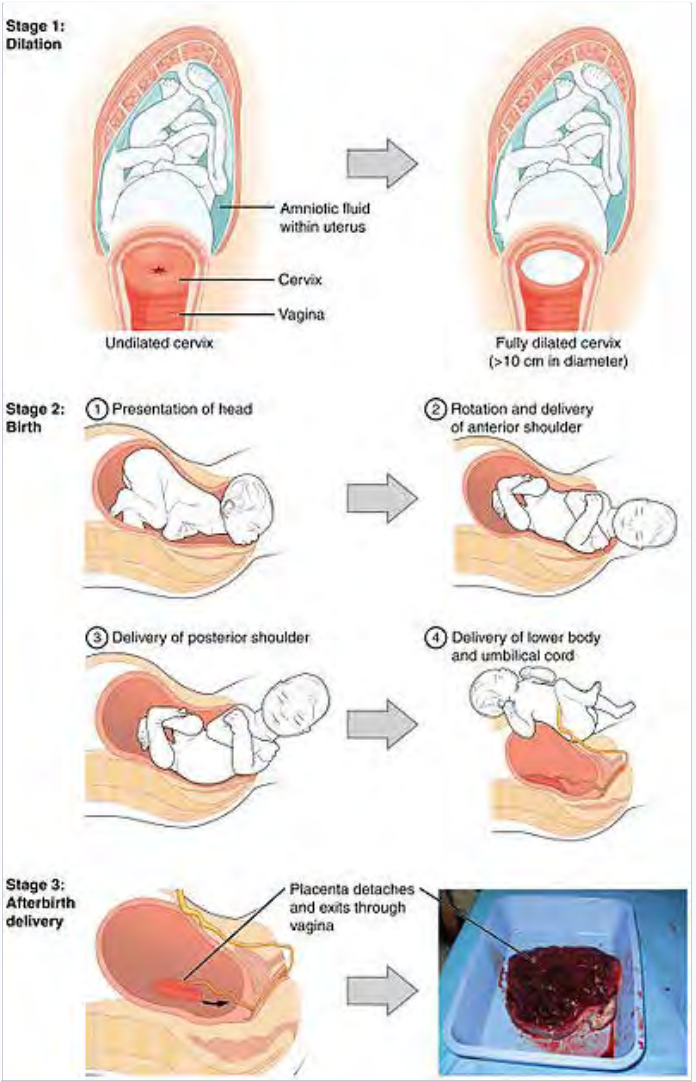
pelvic floor, a complex structure which must not only support this weight but allow, in women, three channels to pass through it: the urethra, the vagina and the rectum. The infant's head and shoulders must go through a specific sequence of maneuvers in order to pass through the ring of the mother's pelvis.

Six phases of a typical vertex (head-first presentation) delivery:

1. **Engagement** of the fetal head in the transverse position. The baby's head is facing across the pelvis at one or other of the mother's hips.
2. **Descent and flexion** of the fetal head.
3. **Internal rotation**. The fetal head rotates 90 degrees to the occipito-anterior position so that the baby's face is towards the mother's rectum.
4. **Delivery by extension**. The fetal head passes out of the birth canal. Its head is tilted forwards so that the crown of its head leads the way through the vagina.
5. **Restitution**. The fetal head turns through 45 degrees to restore its normal relationship with the shoulders, which are still at an angle.
6. **External rotation**. The shoulders repeat the corkscrew movements of the head, which can be seen in the final movements of the fetal head.

**Station** refers to the relationship of the fetal presenting part to the level of the ischial spines. When the presenting part is at the ischial spines the station is 0 (synonymous with engagement). If the presenting fetal part is above the spines, the distance is measured and described as minus stations, which range from −1 to −4 cm. If the presenting part is below the ischial spines, the distance is stated as plus stations ( +1 to +4 cm). At +3 and +4 the presenting part is at the perineum and can be seen.[25]

The fetal head may temporarily change shape substantially (becoming more elongated) as it moves through the birth canal. This change in the shape of the fetal head is called *molding* and is much more prominent in women having their first vaginal delivery.[26]




Sequence of images showing the stages of ordinary childbirth.

## Onset of labour [edit]

There are various definitions of the onset of labour, including:

- Regular uterine contractions at least every six minutes with evidence of change in cervical dilation or cervical effacement between consecutive digital examinations.[27]
- Regular contractions occurring less than 10 min apart and progressive cervical dilation or cervical effacement.[28]
- At least 3 painful regular uterine contractions during a 10-minute period, each lasting more than 45 seconds.[29]

In order to avail for more uniform terminology, the first stage of labour is divided into "latent" and "active" phases, where the latent phase is sometimes included in the definition of labour,[30] and sometimes not.[31]

Some reports note that the onset of term labour more commonly takes place in the late night and early morning hours. This may be a result of a synergism between the nocturnal increase in melatonin and oxytocin.[32]

## First stage: latent phase [edit]

The latent phase of labour is also called the quiescent phase, prodromal labour, or pre-labour. It is a subclassification of the first stage.[33]

The latent phase is generally defined as beginning at the point at which the woman perceives regular uterine contractions.[34] In contrast, Braxton Hicks contractions, which are contractions that may start around 26 weeks gestation and are sometimes called "false labour", should be infrequent, irregular, and involve only mild cramping.[35] The signaling mechanisms responsible for uterine coordination are complex. Electrical propagation is the primary mechanism used for signaling up to several centimeters. Over longer distances, however, signaling may involve a mechanical mechanism.[36]

Cervical effacement, which is the thinning and stretching of the cervix, and cervical dilation occur during the closing weeks of pregnancy and is usually complete or near complete, by the end of the latent phase.[*citation needed*] The degree of cervical effacement may be felt during a vaginal examination. A 'long' cervix implies that effacement has not yet occurred. Latent phase ends with the onset of active first stage, and this transition is defined retrospectively.

## First stage: active phase [edit]

The active stage of labour (or "active phase of first stage" if the previous phase is termed "latent phase of first stage") has geographically differing definitions. In the US, the definition of active labour was changed from 3 to 4 cm, to 5 cm of cervical dilation for multiparous women, mothers who had given birth previously, and at 6 cm for nulliparous women, those who had not given birth before.[37] This has been done in an effort to increase the rates of vaginal delivery.[38]

A definition of active labour in a British journal was having contractions more frequent than every 5 minutes, in addition to either a cervical dilation of 3 cm or more or a cervical effacement of 80% or more.[39]

In Sweden, the onset of the active phase of labour is defined as when two of the following criteria are met:[40]

- three to four contractions every ten minutes
- rupture of membranes
- cervical dilation of 3 to 4 cm

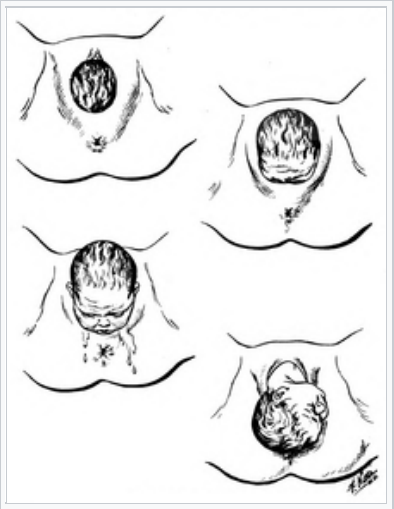
Health care providers may assess a labouring mother's progress in labour by performing a cervical exam to evaluate the cervical dilation, effacement, and station. These factors form the Bishop score. The Bishop score can also be used as a means to predict the success of an induction of labour.

During effacement, the cervix becomes incorporated into the lower segment of the uterus. During a contraction, uterine muscles contract causing shortening of the upper segment and drawing upwards of the lower segment, in a gradual expulsive motion.[*citation needed*] The presenting fetal part then is permitted to descend. Full dilation is reached when the cervix has widened enough to allow passage of the baby's head, around 10 cm dilation for a term baby.

The duration of labour varies widely, but the active phase averages some 8 hours[41] for women giving birth to their first child ("primiparae") and shorter for women who have already given birth ("multiparae"). Active phase prolongation is defined as in a primigravid woman as the failure of the cervix to dilate at a rate of 1.2 cm/h over a period of at least two hours. This definition is based on Friedman's Curve, which plots the typical rate of cervical dilation and fetal descent during active labour.[42] Some practitioners may diagnose "Failure to Progress", and consequently, propose interventions to optimize chances for healthy outcome.[43]

## Second stage: fetal expulsion [edit]

The expulsion stage (stimulated by prostaglandins and oxytocin) begins when the cervix is fully dilated, and ends when the baby is born. As pressure on the cervix increases, women may have the sensation of pelvic pressure and an urge to begin pushing. At the beginning of the normal second stage, the head is fully engaged in the pelvis; the widest diameter of the head has passed below the level of the pelvic inlet. The fetal head then continues descent into the pelvis, below the pubic arch and out through the vaginal introitus (opening). This is assisted by the additional maternal efforts of "bearing down" or pushing. The appearance of the fetal head at the vaginal orifice is termed the "crowning". At this point, the woman will feel an intense burning or stinging sensation.



Stages in the birth of the baby's head.

When the amniotic sac has not ruptured during labour or pushing, the infant can be born with the membranes intact. This is referred to as "delivery en caul".

Complete expulsion of the baby signals the successful completion of the second stage of labour.

The second stage of birth will vary by factors including parity (the number of children a woman has had), fetal size, anesthesia, and the presence of infection. Longer labours are associated with declining rates of spontaneous vaginal delivery and increasing rates of infection, perineal laceration, and obstetric hemorrhage, as well as the need for intensive care of the neonate.[44]

## Third stage: placenta delivery [edit]

*Further information: Umbilical cord and Placental expulsion*

The period from just after the fetus is expelled until just after the placenta is expelled is called the *third stage of labour* or the *involution stage*. Placental expulsion begins as a physiological separation from the wall of the uterus. The average time from delivery of the baby until complete expulsion of the placenta is estimated to be 10–12 minutes dependent on whether active or expectant management is employed[45] In as many as 3% of all

A newborn baby with umbilical cord ready to be clamped

vaginal deliveries, the duration of the third stage is longer than 30 minutes and raises concern for retained placenta.[46]

Placental expulsion can be managed actively or it can be managed expectantly, allowing the placenta to be expelled without medical assistance. Active management is described as the administration of a uterotonic drug within one minute of fetal delivery, controlled traction of the umbilical cord and fundal massage after delivery of the placenta, followed by performance of uterine massage every 15 minutes for two hours.[47] In a joint statement, World Health Organization, the International Federation of Gynaecology and Obstetrics and the International Confederation of Midwives recommend active management of the third stage of labour in all vaginal deliveries to help to prevent postpartum hemorrhage.[48][49][50]

Delaying the clamping of the umbilical cord until at least one minute after birth improves outcomes as long as there is the ability to treat jaundice if it occurs.[51] In some birthing centers, this may be delayed by 5 minutes or more, or omitted entirely. Delayed clamping of the cord decreases the risk of anemia but may increase risk of jaundice. Clamping is followed by cutting of the cord, which is painless due to the absence of nerves.

## Fourth stage [edit]

*Further information: Postnatal*

Newborn rests as caregiver checks breath sounds

The "fourth stage of labour" is the period beginning immediately after the birth of a child and extending for about six weeks. The terms postpartum and postnatal are often used to describe this period.[52] It is the time in which the mother's body, including hormone levels and uterus size, return to a non-pregnant state and the newborn adjusts to life outside the mother's body. The World Health Organization (WHO) describes the postnatal period as the most critical and yet the most neglected phase in the lives of mothers and babies; most deaths occur during the postnatal period.[53]

Following the birth, if the mother had an episiotomy or a tearing of the perineum, it is stitched. The mother should have regular assessments for uterine contraction and fundal height,[54] vaginal bleeding, heart rate and blood pressure, and temperature, for the first 24 hours after birth. The first passing of urine should be documented within 6 hours.[53] Afterpains (pains similar to menstrual cramps), contractions of the uterus to prevent excessive blood flow, continue for several days. Vaginal discharge, termed "lochia", can be expected to continue for several weeks; initially bright red, it gradually becomes pink, changing to brown, and finally to yellow or white.[55]

A 30 minute old infant receiving routine care.

Most authorities suggest the infant be placed in skin-to-skin contact with the mother for 1 –2 hours immediately after birth, putting routine cares off till later.

Until recently babies born in hospitals were removed from their mothers shortly after birth and brought to the mother only at feeding times. Mothers were told that their newborn would be safer in the nursery and that the separation would offer the mother more time to rest. As attitudes began to change, some hospitals offered a "rooming in" option wherein after a period of routine hospital procedures and observation, the infant could be allowed to share the mother's room. However, more recent information has begun to question the standard practice of removing the newborn immediately postpartum for routine postnatal procedures before being returned to the mother. Beginning around 2000, some authorities began to suggest that early skin-to-skin contact (placing the naked baby on the mother's chest) may benefit both mother and infant. Using animal studies that have shown that the intimate contact inherent in skin-to-skin contact promotes neurobehaviors that result in the fulfillment of basic biological needs as a model, recent studies have been done to assess what, if any, advantages may be associated with early skin-to-skin contact for human mothers and their babies. A 2011 medical review looked at existing studies and found that early skin-to-skin contact, sometimes called kangaroo care, resulted in improved breastfeeding outcomes, cardio-respiratory stability, and a decrease in infant crying. [56][57][58] A 2007 Cochrane review of studies found that skin-to-skin contact at birth reduced crying, kept the baby warmer, improved mother-baby interaction, and improved the chances for successful breastfeeding.[59]

As of 2014, early postpartum skin-to-skin contact is endorsed by all major organizations that are responsible for the well-[60]

being of infants, including the American Academy of Pediatrics. The World Health Organization (WHO) states that "the process of childbirth is not finished until the baby has safely transferred from placental to mammary nutrition." They advise that the newborn be placed skin-to-skin with the mother, postponing any routine procedures for at least one to two hours. The WHO suggests that any initial observations of the infant can be done while the infant remains close to the mother, saying that even a brief separation before the baby has had its first feed can disturb the bonding process. They further advise frequent skin-to-skin contact as much as possible during the first days after delivery, especially if it was interrupted for some reason after the delivery.[61] The National Institute for Health and Care Excellence also advises postponing procedures such as weighing, measuring, and bathing for at least 1 hour to insure an initial period of skin-to-skin contact between mother and infant. [62]

## Management [edit]

Deliveries are assisted by a number of professions include: obstetricians, family physicians and midwives. For low risk pregnancies all three result in similar outcomes.[63]

### Preparation [edit]

Eating or drinking during labour is an area of ongoing debate. While some have argued that eating in labour has no harmful effects on outcomes,[64] others continue to have concern regarding the increased possibility of an aspiration event (choking on recently eaten foods) in the event of an emergency delivery due to the increased relaxation of the esophagus in pregnancy, upward pressure of the uterus on the stomach, and the possibility of general anesthetic in the event of an emergency cesarean.[65] A 2013 Cochrane review found that with good obstetrical anaesthesia there is no change in harms from allowing eating and drinking during labour in those who are unlikely to need surgery. They additionally acknowledge that not eating does not mean there is an empty stomach or that its contents are not as acidic. They therefore conclude that "women should be free to eat and drink in labour, or not, as they wish."[66]

At one time shaving of the area around the vagina, was common practice due to the belief that hair removal reduced the risk of infection, made an episiotomy (a surgical cut to enlarge the vaginal entrance) easier, and helped with instrumental deliveries. It is currently less common, though it is still a routine procedure in some countries. A 2009 Cochrane review found no evidence of any benefit with perineal shaving. The review did find side effects including irritation, redness, and multiple superficial scratches from the razor.[67][*needs update*] Another effort to prevent infection has been the use of the antiseptic chlorhexidine or providone-iodine solution in the vagina. Evidence of benefit with chlorhexidine is lacking.[68] A decreased risk is found with providone-iodine when a cesarean section is to be performed.[69]

### Active management [edit]

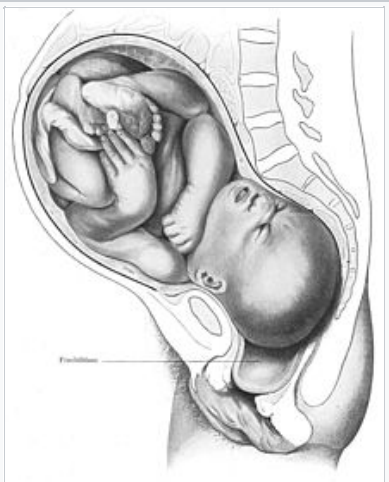
Active management of labour consists of a number of care principles, including frequent assessment of cervical dilatation. If the cervix is not dilating, oxytocin is offered. This management results in a slightly reduced number of caesarean births, but does not change how many women have assisted vaginal births. 75% of women report that they are very satisfied with either active management or normal care.[70]

### Labour induction and elective cesarean [edit]

In many cases and with increasing frequency, childbirth is achieved through induction of labour or caesarean section. Caesarean section is the removal of the neonate through a surgical incision in the abdomen, rather than through vaginal birth.[71] Childbirth by C-Sections increased 50% in the U.S. from 1996 to 2006, and comprise nearly 32% of births in the U.S. and Canada.[71][72] Induced births and elective cesarean before 39 weeks can be harmful to the neonate as well as harmful or without benefit to the mother. Therefore, many guidelines recommend against non-medically required induced births and elective cesarean before 39 weeks.[73] The rate of labour induction in the United States is 22%, and has more than doubled from 1990 to 2006.[74][75]

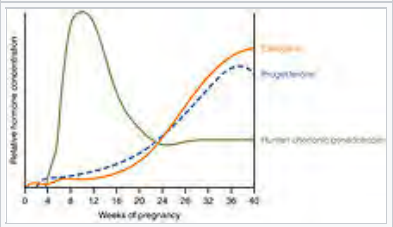
Health conditions that may warrant induced labour or cesarean delivery include gestational or chronic hypertension, preeclampsia, eclampsia, diabetes, premature rupture of membranes, severe fetal growth restriction, and post-term pregnancy. Cesarean section too may be of benefit to both the mother and baby for certain indications including maternal HIV/AIDS, fetal abnormality, breech position, fetal distress, multiple gestations, and maternal medical conditions which would be worsened by labour or vaginal birth.

Pitocin is the most commonly used agent for induction in the United States, and is used to induce uterine contractions. Other methods of inducing labour include stripping of the amniotic membrane, artificial rupturing of the amniotic sac (called amniotomy), or nipple stimulation. Ripening of the cervix can be accomplished with the placement of a Foley [74]



The child as it is passing out through the vagina must pass through the lesser pelvis.

catheter or the use of synthetic prostaglandins such as misoprostol. A large review of methods of induction was published in 2011.[76]


The hormones initiating labour.

The American Congress of Obstetricians and Gynecologists (ACOG) guidelines recommend a full evaluation of the maternal-fetal status, the status of the cervix, and at least a 39 completed weeks (full term) of gestation for optimal health of the newborn when considering elective induction of labour. Per these guidelines, the following conditions may be an indication for induction, including:

- Abruptio placentae
- Chorioamnionitis
- Fetal compromise such as isoimmunization leading to hemolytic disease of the newborn or oligohydramnios
- Fetal demise
- Gestational hypertension
- Maternal conditions such as gestational diabetes or chronic kidney disease
- Preeclampsia or eclampsia
- Premature rupture of membranes
- Postterm pregnancy

Induction is also considered for logistical reasons, such as the distance from hospital or psychosocial conditions, but in these instances gestational age confirmation must be done, and the maturity of the fetal lung must be confirmed by testing.

The ACOG also note that contraindications for induced labour are the same as for spontaneous vaginal delivery, including vasa previa, complete placenta praevia, umbilical cord prolapse or active genital herpes simplex infection.[77]

## Pain control [edit]

### Non pharmaceutical [edit]

Some women prefer to avoid analgesic medication during childbirth. Psychological preparation may be beneficial.[78] A recent Cochrane overview of systematic reviews on non-drug interventions found that relaxation techniques, immersion in water, massage, and acupuncture may provide pain relief. Acupuncture and relaxation were found to decrease the number of caesarean sections required.[79] Immersion in water has been found to relieve pain during the first stage of labor and to reduce the need for anesthesia and shorten the duration of labor, however the safety and efficacy of immersion during birth, water birth, has not been established or associated with maternal or fetal benefit.[80]

Some women like to have someone to support them during labour and birth; such as a midwife, nurse, or doula; or a lay person such as the father of the baby, a family member, or a close friend. Studies have found that continuous support during labor and delivery reduce the need for medication and a caesarean or operative vaginal delivery, and result in an improved Apgar score for the infant.[81] [82]

The injection of small amounts of sterile water into or just below the skin at several points on the back has been a method tried to reduce labour pain, but no good evidence shows that it actually helps.[83]

### Pharmaceutical [edit]

Different measures for pain control have varying degrees of success and side effects to the woman and her baby. In some countries of Europe, doctors commonly prescribe inhaled nitrous oxide gas for pain control, especially as 53% nitrous oxide, 47% oxygen, known as Entonox; in the UK, midwives may use this gas without a doctor's prescription. Opioids such as fentanyl may be used, but if given too close to birth there is a risk of respiratory depression in the infant.

Popular medical pain control in hospitals include the regional anesthetics epidurals (EDA), and spinal anaesthesia. Epidural analgesia is a generally safe and effective method of relieving pain in labour, but is associated with longer labour, more operative intervention (particularly instrument delivery), and increases in cost.[84] Generally, pain and stress hormones rise throughout labour for women without epidurals, while pain, fear, and stress hormones decrease upon administration of epidural analgesia, but rise again later.[85] Medicine administered via epidural can cross the placenta and enter the bloodstream of the fetus.[86] Epidural analgesia has no statistically significant impact on the risk of caesarean section, and does not appear to have an immediate effect on neonatal status as determined by Apgar scores.[87]

## Augmentation [edit]

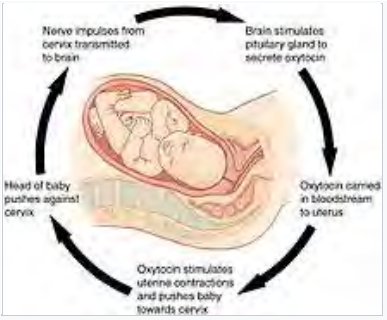
Augmentation is the process of facilitating further labour. Oxytocin has been used to increase the rate of vaginal delivery in those with a slow progress of labour.[88]

Administration of antispasmodics (e.g. hyoscine butylbromide) is not formally regarded as augmentation of labour; however, there is weak evidence that they may shorten labour.[89] There is not enough evidence to make conclusions about unwanted effects in

mothers or babies.[89]

## Episiotomy [edit]

*Further information: Episiotomy*



Oxytocin facilitates labour and will follow a positive feedback loop.

Vaginal tears can occur during childbirth, most often at the vaginal opening as the baby's head passes through, especially if the baby descends quickly. Tears can involve the perineal skin or extend to the muscles and the anal sphincter and anus. The midwife or obstetrician may decide to make a surgical cut to the perineum (episiotomy) to make the baby's birth easier and prevent severe tears that can be difficult to repair. A 2012 Cochrane review compared episiotomy as needed (restrictive) with routine episiotomy to determine the possible benefits and harms for mother and baby. The review found that restrictive episiotomy policies appeared to give a number of benefits compared with using routine episiotomy. Women experienced less severe perineal trauma, less posterior perineal trauma, less suturing and fewer healing complications at seven days with no difference in occurrence of pain, urinary incontinence, painful sex or severe vaginal/perineal trauma after birth, however they found that women experienced more anterior perineal damage with restrictive episiotomy.[90]

## Instrumental delivery [edit]

Obstetric forceps or ventouse may be used to facilitate childbirth.

## Multiple births [edit]

*Main article: Multiple birth*

In cases of a cephalic presenting twin (first baby head down), twins can often be delivered vaginally. In some cases twin delivery is done in a larger delivery room or in an operating theatre, in the event of complication e.g.

- Both twins born vaginally—this can occur both presented head first or where one comes head first and the other is breech and/or helped by a forceps/ventouse delivery
- One twin born vaginally and the other by caesarean section.
- If the twins are joined at any part of the body—called conjoined twins, delivery is mostly by caesarean section.

## Support [edit]

*See also: Men's role in childbirth*


Baby on warming tray attended to by her father.

Historically women have been attended and supported by other women during labour and birth. However currently, as more women are giving birth in a hospital rather than at home, continuous support has become the exception rather than the norm. When women became pregnant any time before the 1950s the husband would not be in the birthing room. It did not matter if it was a home birth; the husband was waiting downstairs or in another room in the home. If it was in a hospital then the husband was in the waiting room. "Her husband was attentive and kind, but, Kirby concluded, Every good woman needs a companion of her own sex."[91] Obstetric care frequently subjects women to institutional routines, which may have adverse effects on the progress of labour. Supportive care during labour may involve emotional support, comfort measures, and information and advocacy which may promote the physical process of labour as well as women's feelings of control and competence, thus reducing the need for obstetric intervention. The continuous support may be provided either by hospital staff such as nurses or midwives, doulas, or by companions of the woman's choice from her social network. There is increasing evidence to show that the participation of the child's father in the birth leads to better birth and also post-birth outcomes, providing the father does not exhibit excessive anxiety.[92]

A recent Cochrane review involving more than 15,000 women in a wide range of settings and circumstances found that "Women who received continuous labour support were more likely to give birth 'spontaneously', i.e. give birth with neither caesarean nor vacuum nor forceps. In addition, women were less likely to use pain medications, were more likely to be satisfied, and had slightly shorter labours. Their babies were less likely to have low five-minute Apgar scores."[81]

## Fetal monitoring [edit]

## External monitoring [edit]

For monitoring of the fetus during childbirth, a simple pinard stethoscope or doppler fetal monitor ("*doptone*") can be used. A

method of external (noninvasive) fetal monitoring (EFM) during childbirth is cardiotocography, using a *cardiotocograph* that consists of two sensors: The *heart* (cardio) sensor is an ultrasonic sensor, similar to a Doppler fetal monitor, that continuously emits ultrasound and detects motion of the fetal heart by the characteristic of the reflected sound. The pressure-sensitive *contraction* transducer, called a *tocodynamometer* (toco) has a flat area that is fixated to the skin by a band around the belly. The pressure required to flatten a section of the wall correlates with the internal pressure, thereby providing an estimate of contraction[93] Monitoring with a cardiotocograph can either be intermittent or continuous.

### Internal monitoring [edit]

A mother's water has to break before internal (invasive) monitoring can be used. More invasive monitoring can involve a fetal scalp electrode to give an additional measure of fetal heart activity, and/or intrauterine pressure catheter (IUPC). It can also involve fetal scalp pH testing.

## Collecting stem cells [edit]

It is currently possible to collect two types of stem cells during childbirth: amniotic stem cells and umbilical cord blood stem cells.[94] They are being studied as possible treatments of a number of conditions.[94]

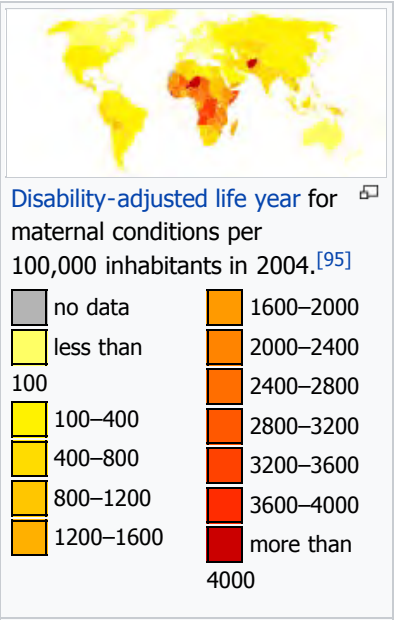
## Complications [edit]

*See also: Birth trauma (physical) and Childbirth-related posttraumatic stress disorder*

The "natural" maternal mortality rate of childbirth—where nothing is done to avert maternal death—has been estimated at 1500 deaths per 100,000 births.[96] (See main articles: neonatal death, maternal death). Each year about 500,000 women die due to pregnancy, 7 million have serious long term complications, and 50 million have negative outcomes following delivery.[15]

Modern medicine has decreased the risk of childbirth complications. In Western countries, such as the United States and Sweden, the current maternal mortality rate is around 10 deaths per 100,000 births.[96]:p.10 As of June 2011, about one third of American births have some complications, "many of which are directly related to the mother's health."[97]

Birthing complications may be maternal or fetal, and long term or short term.



Disability-adjusted life year for maternal conditions per 100,000 inhabitants in 2004.[95]

### Pre-term [edit]

Newborn mortality at 37 weeks may be 2.5 times the number at 40 weeks, and was elevated compared to 38 weeks of gestation. These "early term" births were also associated with increased death during infancy, compared to those occurring at 39 to 41 weeks ("full term").[73] Researchers found benefits to going full term and "no adverse effects" in the health of the mothers or babies.[73]

Medical researchers find that neonates born before 39 weeks experienced significantly more complications (2.5 times more in one study) compared with those delivered at 39 to 40 weeks. Health problems among babies delivered "pre-term" included respiratory distress, jaundice and low blood sugar.[73][98] The American Congress of Obstetricians and Gynecologists and medical policy makers review research studies and find increased incidence of suspected or proven sepsis, RDS, Hypoglycemia, need for respiratory support, need for NICU admission, and need for hospitalization > 4 – 5 days. In the case of cesarean sections, rates of respiratory death were 14 times higher in pre-labour at 37 compared with 40 weeks gestation, and 8.2 times higher for pre-labour cesarean at 38 weeks. In this review, no studies found decreased neonatal morbidity due to non-medically indicated (elective) delivery before 39 weeks.[73]

Disability-adjusted life year for perinatal conditions per 100,000 inhabitants in 2004.[95]

### Labour complications [edit]

The second stage of labour may be delayed or lengthy due to:

- malpresentation (breech birth (i.e. buttocks or feet first), face, brow, or other)
- failure of descent of the fetal head through the pelvic brim or the interspinous diameter
- poor uterine contraction strength
- active phase arrest
- cephalo-pelvic disproportion (CPD)
- shoulder dystocia

4000

Secondary changes may be observed: swelling of the tissues, maternal exhaustion, fetal heart rate abnormalities. Left untreated, severe complications include death of mother and/or baby, and genitovaginal fistula.

## Obstructed labour [edit]

*Main article: Obstructed labour*

Obstructed labour, also known as labor dystocia, is when, even though the uterus is contracting normally, the baby does not exit the pelvis during childbirth due to being physically blocked.[99] Prolonged obstructed labor can result in obstetric fistula, a complication of childbirth where tissue death preforates the rectum or bladder.

## Maternal complications [edit]

**Vaginal birth injury** with visible tears or episiotomies are common. Internal tissue tearing as well as nerve damage to the pelvic structures lead in a proportion of women to problems with prolapse, incontinence of stool or urine and sexual dysfunction. Fifteen percent of women become incontinent, to some degree, of stool or urine after normal delivery, this number rising considerably after these women reach menopause. Vaginal birth injury is a necessary, but not sufficient, cause of all non hysterectomy related prolapse in later life. Risk factors for significant vaginal birth injury include:

- A baby weighing more than 9 pounds.
- The use of forceps or vacuum for delivery. These markers are more likely to be signals for other abnormalities as forceps or vacuum are not used in normal deliveries.
- The need to repair large tears after delivery.

There is tentative evidence that antibiotics may help prevent wound infections in women with third or fourth degree tears.[100]

**Pelvic girdle pain**. Hormones and enzymes work together to produce ligamentous relaxation and widening of the symphysis pubis during the last trimester of pregnancy. Most girdle pain occurs before birthing, and is known as diastasis of the pubic symphysis. Predisposing factors for girdle pain include maternal obesity.

**Infection** remains a major cause of maternal mortality and morbidity in the developing world. The work of Ignaz Semmelweis was seminal in the pathophysiology and treatment of puerperal fever and saved many lives.

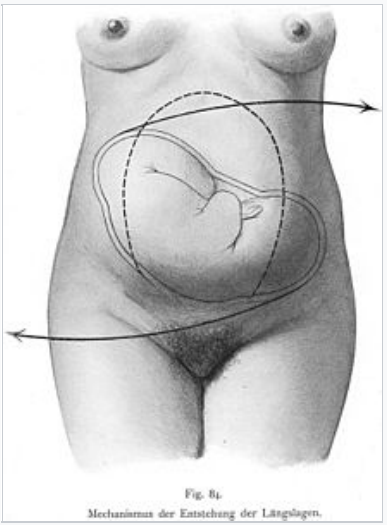
**Hemorrhage,** or heavy blood loss, is still the leading cause of death of birthing mothers in the world today, especially in the developing world. Heavy blood loss leads to hypovolemic shock, insufficient perfusion of vital organs and death if not rapidly treated. Blood transfusion may be life saving. Rare sequelae include Hypopituitarism Sheehan's syndrome.

The maternal mortality rate (MMR) varies from 9 per 100,000 live births in the US and Europe to 900 per 100,000 live births in Sub-Saharan Africa.[101] Every year, more than half a million women die in pregnancy or childbirth.[102]

## Fetal complications [edit]

### Mechanical fetal injury [edit]

Risk factors for fetal birth injury include fetal macrosomia (big baby), maternal obesity, the need for instrumental delivery, and an inexperienced attendant. Specific situations that can contribute to birth injury include breech presentation and shoulder dystocia. Most fetal birth injuries resolve without long term harm, but brachial plexus injury may lead to Erb's palsy or Klumpke's paralysis.[103]



Mechanical fetal injury may be caused by improper rotation of the fetus.

### Neonatal infection [edit]

*Main article: Neonatal infection*

Neonates are prone to infection in the first month of life. Some organisms such as S. agalactiae (Group B Streptococcus) or (GBS) are more prone to cause these occasionally fatal infections. Risk factors for GBS infection include:

- prematurity (birth before 37 weeks gestation)
- a sibling who has had a GBS infection
- prolonged labour or rupture of membranes

Untreated sexually transmitted infections are associated with congenital and perinatal infections in neonates, particularly in the areas where rates of infection remain high. The overall perinatal mortality rate associated with untreated syphilis, for example, is 30%.[105]

### Neonatal death [edit]

Infant deaths (*neonatal deaths* from birth to 28 days, or *perinatal deaths* if including fetal deaths at 28 weeks gestation and later) are around 1% in modernized countries.

The most important factors affecting mortality in childbirth are adequate nutrition and access to quality medical care ("access" is affected both by the cost of available care, and distance from health services).[*citation needed*]

A 1983–1989 study by the Texas Department of State Health Services highlighted the differences in neonatal mortality (NMR) between high risk and low risk pregnancies. NMR was 0.57% for doctor-attended high risk births, and 0.19% for low risk births attended by non-nurse midwives. Around 80% of pregnancies are low-risk. Factors that may make a birth high risk include prematurity, high blood pressure, gestational diabetes and a previous cesarean section.

Disability-adjusted life year for neonatal infections and other (perinatal) conditions per 100,000 inhabitants in 2004. Excludes prematurity and low birth weight, birth asphyxia and birth trauma which have their own maps/data.[104]

no data
less than 150
150–300
300–450
450–600
600–750
750–900
900–1050
1050–1200
1200–1350
1350–1500
1500–1850
more than 1850

### Intrapartum asphyxia [edit]

Intrapartum asphyxia is the impairment of the delivery of oxygen to the brain and vital tissues during the progress of labour. This may exist in a pregnancy already impaired by maternal or fetal disease, or may rarely arise *de novo* in labour. This can be termed *fetal distress*, but this term may be emotive and misleading. True intrapartum asphyxia is not as common as previously believed, and is usually accompanied by multiple other symptoms during the immediate period after delivery. Monitoring might show up problems during birthing, but the interpretation and use of monitoring devices is complex and prone to misinterpretation. Intrapartum asphyxia can cause long-term impairment, particularly when this results in tissue damage through encephalopathy.[106]

## Society and culture [edit]

*Further information: Ageing*

Childbirth routinely occurs in hospitals in much of Western society. Before the 20th century and in some countries to the present day it has more typically occurred at home.[107]

Medieval woman giving birth. France, 12th century

In Western and other cultures, age is reckoned from the date of birth, and sometimes the birthday is celebrated annually. East Asian age reckoning starts newborns at "1", incrementing each Lunar New Year.

Some families view the placenta as a special part of birth, since it has been the child's life support for so many months. The placenta may be eaten by the newborn's family, ceremonially or otherwise (for nutrition; the great majority of animals in fact do this naturally).[108] Most recently there is a category of birth professionals available who will encapsulate placenta for use as placenta medicine by postpartum mothers.

The exact location in which childbirth takes place is an important factor in determining nationality, in particular for birth aboard aircraft and ships.

### Facilities [edit]

Following are facilities that are particularly intended to house women during childbirth:

- A *labour ward*, also called a *delivery ward* or *labour and delivery*, is generally a department of a hospital that focuses on providing health care to women and their children during childbirth. It is generally closely linked to the hospital's neonatal intensive care unit and/or obstetric surgery unit if present. A *maternity ward* or *maternity unit* may include facilities both for childbirth and for postpartum rest and observation of mothers in normal as well as complicated cases.
- A birthing center generally presents a simulated home-like environment. Birthing centers may be located on hospital grounds or "free standing" (i.e., not hospital-affiliated).

In addition, it is possible to have a home birth.

### Associated professions [edit]

Different categories of birth attendants may provide support and care during pregnancy and childbirth, although there are important differences across categories based on professional training and skills, practice regulations, as well as nature of care delivered.

"Childbirth educators" are instructors who aim to educate pregnant women and their partners about the nature of pregnancy, labour signs and stages, techniques for giving birth, breastfeeding and newborn baby care. In the United States and elsewhere, classes for training as a childbirth educator can be found in hospital settings or through many

Model of pelvis used in the beginning of the 19th century to teach technical procedures for a successful childbirth. Museum of the History of Medicine, Porto Alegre, Brazil

independent certifying organizations such as Birthing From Within, BirthWorks, The Bradley Method, Birth Arts International, CAPPA, HypBirth, HypnoBabies, HypnoBirthing,[78] ICTC, ICEA, Lamaze, etc. Each organization teaches its own curriculum and each emphasizes different techniques. Information about each can be obtained through their individual websites.

Doulas are assistants who support mothers during pregnancy, labour, birth, and postpartum. They are not medical attendants; rather, they provide emotional support and non-medical pain relief for women during labour. Like childbirth educators and other assistive personnel, certification to become a doula is not compulsory, thus, anyone can call themself a doula or a childbirth educator.

Confinement nannies are individuals who are employed to provide assistance and stay with the mothers at their home after childbirth. They are usually experienced mothers who took courses on how to take care of mothers and newborn babies.[109]

Midwives are autonomous practitioners who provide basic and emergency health care before, during and after pregnancy and childbirth, generally to women with low-risk pregnancies. Midwives are trained to assist during labour and birth, either through direct-entry or nurse-midwifery education programs. Jurisdictions where midwifery is a regulated profession will typically have a registering and disciplinary body for quality control, such as the American Midwifery Certification Board in the United States,[110] the College of Midwives of British Columbia (CMBC) in Canada[111][112] or the Nursing and Midwifery Council (NMC) in the United Kingdom.[113][114]

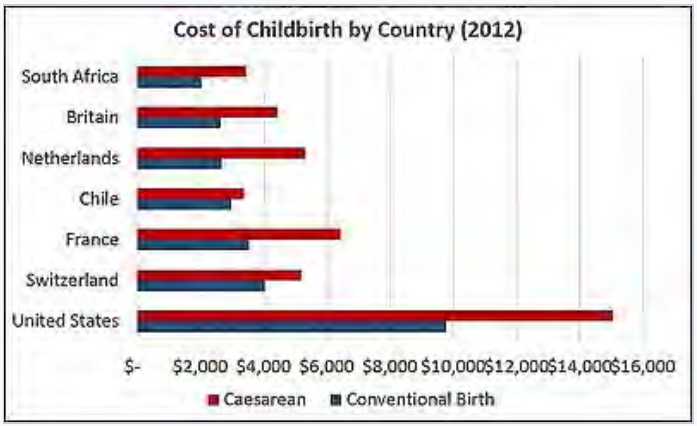
In jurisdictions where midwifery is not a regulated profession, traditional or lay midwives may assist women during childbirth, although they do not typically receive formal health care education and training.

Medical doctors who practice obstetrics include categorically specialized obstetricians, family practitioners and general practitioners whose training, skills and practices include obstetrics, and in some contexts general surgeons. These physicians and surgeons variously provide care across the whole spectrum of normal and abnormal births and pathological labour conditions. Categorically specialized obstetricians are qualified surgeons, so they can undertake surgical procedures relating to childbirth. Some family practitioners or general practitioners also perform obstetrical surgery. Obstetrical procedures include cesarean sections, episiotomies, and assisted delivery. Categorical specialists in obstetrics are commonly dually trained in obstetrics and gynecology (OB/GYN), and may provide other medical and surgical gynecological care, and may incorporate more general, well-woman, primary care elements in their practices. Maternal-fetal medicine specialists are obstetrician/gynecologists subspecialized in managing and treating high-risk pregnancy and delivery.

Anaesthetists or anesthesiologists are medical doctors who specialise in pain relief and the use of drugs to facilitate surgery and other painful procedures. They may contribute to the care of a woman in labour by performing epidurals or by providing anaesthesia (often spinal anaesthesia) for Cesarean section or forceps delivery.

Obstetric nurses assist midwives, doctors, women, and babies before, during, and after the birth process, in the hospital system. Obstetric nurses hold various certifications and typically undergo additional obstetric training in addition to standard nursing training.

## Costs [edit]




Cost of Childbirth in Several Countries in 2012.[115]

According to a 2013 analysis performed commissioned by the New York Times and performed by Truven Healthcare Analytics, the cost of childbirth varies dramatically by country. In the United States the average amount actually paid by insurance companies or other payers in 2012 averaged $9,775 for an uncomplicated conventional delivery and $15,041 for a caesarean birth.[115] The aggregate charges of healthcare facilities for 4 million annual births in the United States was estimated at over $50 billion. The summed cost of prenatal care, childbirth, and newborn care came to $30,000 for a vaginal delivery and $50,000 for a caesarian section.

In the United States, childbirth hospital stays have some of the lowest ICU utilizations. Vaginal delivery with and without complicating diagnoses and caesarean section with and without comorbidities or major comorbidities account for four of the fifteen types of hospital stays with low rates of ICU utilization (where less than 20% of visits were admitted to the ICU). During

stays with ICU services, approximately 20% of costs were attributable to the ICU.[116]

A 2013 study published in BMJ Open found widely varying costs by facility for childbirth expenses in California, varying from $3,296 to $37,227 for vaginal birth and from $8,312 to $70,908 for a caesarean birth.[117]

Beginning in 2014, the United Kingdom National Institute for Health and Care Excellence began recommending that many women give birth at home under the care of a midwife rather than an obstetrician, citing lower expenses and better healthcare outcomes.[118] The median cost associated with home birth was estimated to be about $1,500 vs. about $2,500 in hospital.[119]

## See also [edit]

- Advanced maternal age, when a woman is of an older age at reproduction
- Antinatalism
- Asynclitic birth, an abnormal birth position
- Bradley method of natural childbirth
- Coffin birth
- Kangaroo care
- Lamaze
- Naegele's Rule to calculate the due date for a pregnancy
- Natalism
- Natural childbirth
- Obstetrical Dilemma
- Pre- and perinatal psychology
- Reproductive Health Supplies Coalition
- Traditional birth attendant
- Unassisted childbirth
- Vernix caseosa
- Water birth

## References [edit]


1. ^ Martin, Elizabeth. *Concise Colour Medical Dictionary*. Oxford University Press. p. 375. ISBN 978-0-19-968799-2.
2. ^ "The World Factbook". *www.cia.gov*. July 11, 2016. Retrieved 30 July 2016.
3. ^ "Preterm birth Fact sheet N°363". *WHO*. November 2015. Retrieved 30 July 2016.
4. ^ Buck, Germaine M.; Platt, Robert W. (2011). *Reproductive and perinatal epidemiology*. Oxford: Oxford University Press. p. 163. ISBN 978-0-19-985774-6.
5. ^ Co-Operation, Organisation for Economic; Development (2009). *Doing better for children*. Paris: OECD. p. 105. ISBN 978-92-64-05934-4.
6. ^ Olsen, O; Clausen, JA (12 September 2012). "Planned hospital birth versus planned home birth." *The Cochrane database of systematic reviews* (9): CD000352. doi:10.1002/14651858.CD000352.pub2. PMC 4238062. PMID 22972043.
7. ^ Fossard, Esta de; Bailey, Michael (2016). *Communication for Behavior Change: Volume III: Using Entertainment–Education for Distance Education*. SAGE Publications India. ISBN 978-93-5150-758-1. Retrieved 31 July 2016.
8. ^ Memon, HU; Handa, VL (May 2013). "Vaginal childbirth and pelvic floor disorders." *Women's health (London, England)*. **9** (3): 265–77; quiz 276–7. doi:10.2217/whe.13.17. PMC 3877300. PMID 23638782.
9. ^ [a] [b] "Birth". *The Columbia Electronic Encyclopedia* (6 ed.). Columbia University Press. 2016. Retrieved 2016-07-30 from Encyclopedia.com. Check date values in: `|access-date=` (help)
10. ^ [a] [b] [c] [d] [e] [f] [g] [h] "Pregnancy Labor and Birth". *Women's Health*. September 27, 2010. Retrieved 31 July 2016.
11. ^ McDonald, SJ; Middleton, P; Dowswell, T; Morris, PS (11 July 2013). "Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes.". *The Cochrane database of systematic reviews*. **7**: CD004074. doi:10.1002/14651858.CD004074.pub3. PMID 23843134.
12. ^ Hofmeyr, GJ; Hannah, M; Lawrie, TA (21 July 2015). "Planned caesarean section for term breech delivery.". *The Cochrane database of systematic reviews* (7): CD000166. doi:10.1002/14651858.CD000166.pub2. PMID 26196961.
13. ^ *Childbirth: Labour, Delivery and Immediate Postpartum Care*. World Health Organization. 2015. p. Chapter D.
63. ^ National Institute for Health and Care Excellence (December 2014). "Intrapartum care: care of healthy women and their babies during childbirth". *http://www.nice.org.uk/*. Retrieved 11 February 2015. External link in `|website=` (help)
64. ^ Tranmer, J.E.; Hodnett, E.D.; Hannah, M.E.; Stevens, B.J. (2005). "The effect of unrestricted oral carbohydrate intake on labor progress". *Journal of Obstetric, Gynecologic, & Neonatal Nursing*. **34** (3): 319–26. doi:10.1177/0884217505276155. PMID 15890830.
65. ^ O'Sullivan, G.; Scrutton, M. (2003). "NPO during labor. Is there any scientific validation?". *Anesthesiology Clinics of North America*. **21** (1): 87–98. doi:10.1016/S0889-8537(02)00029-9. PMID 12698834.
66. ^ Singata, M.; Tranmer, J.; Gyte, G.M.L. (2013). Singata, Mandisa, ed. Pregnancy and Childbirth Group. "Restricting oral fluid and food intake during labour". *Cochrane Database of Systematic Reviews*. Cochrane Collaboration. CD003930 (8): CD003930. doi:10.1002/14651858.CD003930.pub3. PMID 23966209. Lay summary – *Cochrane Summaries* (2013-08-22).
67. ^ Basevi, V.; Lavender, T. (2001). Basevi, Vittorio, ed. Pregnancy and Childbirth Group. "Routine perineal shaving on admission in labour". *Cochrane Database of Systematic Reviews*. CD001236 (1): CD001236. doi:10.1002/14651858.CD001236. PMID 11279711. Lay summary – *Cochrane Summaries* (2009-04-15).
68. ^ Lumbiganon, P; Thinkhamrop, J; Thinkhamrop, B; Tolosa, JE (Sep 14, 2014). "Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV).". *The Cochrane database of systematic reviews*. **9**: CD004070. doi:10.1002/14651858.CD004070.pub3. PMID 25218725.
69. ^ Haas, DM; Morgan, S; Contreras, K (21 December 2014). "Vaginal preparation with antiseptic solution before cesarean section for preventing postoperative infections.". *The Cochrane database of systematic reviews*. **12**: CD007892. doi:10.1002/14651858.CD007892.pub5. PMID 25528419.
70. ^ Brown, Heather; Paranjothy S; Dowswell T; Thomas J (September 2013). Brown, Heather C, ed. "Package of care for active management in labour for reducing caesarean section rates in low-risk women". *Cochrane Database of Systematic*

ISBN 978-92-4-154935-6. Retrieved 31 July 2016.
14. ^ Molina, G; Weiser, TG; Lipsitz, SR; Esquivel, MM; Uribe-Leitz, T; Azad, T; Shah, N; Semrau, K; Berry, WR; Gawande, AA; Haynes, AB (1 December 2015). "Relationship Between Cesarean Delivery Rate and Maternal and Neonatal Mortality". *JAMA*. **314** (21): 2263–70. doi:10.1001/jama.2015.15553. PMID 26624825.
15. ^ *a b c d Education material for teachers of midwifery : midwifery education modules* (PDF) (2nd ed.). Geneva [Switzerland]: World Health Organisation. 2008. p. 3. ISBN 978-92-4-154666-9.
16. ^ Martin, Richard J.; Fanaroff, Avroy A.; Walsh, Michele C. *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. Elsevier Health Sciences. p. 116. ISBN 978-0-323-29537-6.
17. ^ Weber, S.E. (1996). "Cultural aspects of pain in childbearing women". *Journal of Obstetric, Gynecologic, & Neonatal Nursing*. **25** (1): 67–72. doi:10.1111/j.1552-6909.1996.tb02515.x. PMID 8627405.
18. ^ Callister, L.C.; Khalaf, I.; Semenic, S.; Kartchner, R.; et al. (2003). "The pain of childbirth: perceptions of culturally diverse women". *Pain Management Nursing*. **4** (4): 145–54. doi:10.1016/S1524-9042(03)00028-6. PMID 14663792.
19. ^ Hodnett, E.D. (2002). "Pain and women's satisfaction with the experience of childbirth: A systematic review". *American Journal of Obstetrics and Gynecology*. **186** (5 (Supplement)): S160–72. doi:10.1016/S0002-9378(02)70189-0. PMID 12011880.
20. ^ Harms, Rogert W. Does back labor really happen?, mayoclinic.com, Retrieved 8 September 2014
21. ^ Meyer, D. (2007). "Selective serotonin reuptake inhibitors and their effects on relationship satisfaction". *The Family Journal*. **15** (4): 392–397. doi:10.1177/1066480707305470.
22. ^ Bowen, R. (July 12, 2010). "Oxytocin". *Hypertexts for Biomedical Sciences*. Retrieved 2013-08-18.
23. ^ Zlotnick, C.; Johnson, S.L.; Miller, I.W.; Pearlstein, T.; et al. (2001). "Postpartum depression in women receiving public assistance: Pilot study of an interpersonal-therapy-oriented group intervention". *American Journal of Psychiatry*. **158** (4): 638–40. doi:10.1176/appi.ajp.158.4.638. PMID 11282702.
24. ^ Chabrol, H.; Teissedre, F.; Saint-Jean, M.; Teisseyre, N.; Sistac, C.; Michaud, C.; Roge, B. (2002). "Detection, prevention and treatment of postpartum depression: A controlled study of 859 patients". *L'Encephale*. **28** (1): 65–70. PMID 11963345.
25. ^ Pillitteri, A. (2010). "Chapter 15: Nursing Care of a Family During Labor and Birth". *Maternal & Child Health Nursing: Care of the Childbearing & Childrearing Family*. Hagerstown, Maryland: Lippincott Williams & Wilkins. p. 350. ISBN 978-1-58255-999-5. Retrieved 2013-08-18.
26. ^ Healthline Staff; Levine, D. (Medical Reviewer) (March 15, 2012). "Types of Forceps Used in Delivery". *Healthline*. Healthline Networks. Retrieved 2013-08-10.
27. ^ Kupferminc, M.; Lessing, J. B.; Yaron, Y.; Peyser, M. R. (1993). "Nifedipine versus ritodrine for suppression of preterm labour". *BJOG: an International Journal of Obstetrics and Gynaecology*. **100** (12): 1090–1094. doi:10.1111/j.1471-0528.1993.tb15171.x.
28. ^ Jokic, M.; Guillois, B.; Cauquelin, B.; Giroux, J. D.; Bessis, J. L.; Morello, R.; Levy, G.; Ballet, J. J. (2000). "Fetal distress increases interleukin-6 and interleukin-8 and decreases tumour necrosis factor-alpha cord blood levels in noninfected full-term neonates". *BJOG: an International Journal of Obstetrics and Gynaecology*. **107** (3): 420–425. doi:10.1111/j.1471-0528.2000.tb13241.x.
29. ^ Lyrenas, S.; Clason, I.; Ulmsten, U. (2001). "In vivo controlled release of PGE2 from a vaginal insert (0.8 mm, 10 mg) during induction of labour". *BJOG: an International Journal of Obstetrics and Gynaecology*. **108** (2): 169–178. doi:10.1111/j.1471-0528.2001.00039.x.

*Reviews* (9). doi:10.1002/14651858.CD004907.pub3.
71. ^ *a b* "Rates for total cesarean section, primary cesarean section, and vaginal birth after cesarean (VBAC), United States, 1989–2010" (PDF). *Childbirth Connection website*. Relentless Rise in Cesarian Rate. August 2012. Retrieved 2013-08-29.
72. ^ "Your Options for Maternity Services".
73. ^ *a b c d e* Main, E.; Oshiro, B.; Chagolla, B.; Bingham, D.; et al. (July 2010). "Elimination of Non-medically Indicated (Elective) Deliveries Before 39 Weeks Gestational Age (California Maternal Quality Care Collaborative Toolkit to Transform Maternity Care)" (PDF). Developed under contract #08-85012 with the California Department of Public Health; Maternal, Child and Adolescent Health Division. (1st ed.). March of Dimes. Archived from the original (PDF) on 2012-11-20. Retrieved 2013-08-29.
74. ^ *a b* "Induction of Labor" (PDF). Retrieved 2012-07-12.[*dead link*]
75. ^ Hamilton, B.E.; Martin, J.A.; Ventura, S.J. (March 18, 2009). "Births: Preliminary data for 2007" (PDF). *National Vital Statistics Reports*. National Vital Statistics System, National Center for Health Statistics, Centers for Disease Control and Prevention, US Department of Health and Human Services. **57** (12): 1–22. Retrieved 2013-08-29.
76. ^ Mozurkewich, E.L.; Chilimigras, J.L.; Berman, D.R.; Perni, U.C.; et al. (October 27, 2011). "Methods of induction of labor: A systematic review". *BMC Pregnancy & Childbirth*. **11**: 84. doi:10.1186/1471-2393-11-84. PMC 3224350. PMID 22032440.
77. ^ ACOG District II Patient Safety and Quality Improvement Committee (December 2011). "Oxytocin for Induction" (PDF). *Optimizing Protocols in Obstetrics*. Series 1. American Congress of Obstetricians and Gynecologists (ACOG). Retrieved 2013-08-29.
78. ^ *a b* Graves, Katharine (2012). *The HypnoBirthing Book - An inspirational guide for a calm, confident, natural birth. ISBN 978-0-9571445-0-7*.
79. ^ Jones L, Othman M, Dowswell T, Alfirevic Z, Gates S, Newburn M, Jordan S, Lavender T, Neilson JP (2012). "Pain management for women in labour: an overview of systematic reviews". *Reviews*. Wiley Online Library. **3**: CD009234. doi:10.1002/14651858.CD009234.pub2. PMID 22419342. Retrieved 27 December 2014.
80. ^ "Immersion in Water During Labor and Delivery". *Pediatrics*. **133** (4): 758–761. 20 March 2014. doi:10.1542/peds.2013-3794.
81. ^ *a b* Hodnett, E.D.; Gates, S.; Hofmeyr, G.J.; Sakala, C. (2013). Hodnett, Ellen D, ed. Pregnancy and Childbirth Group. "Continuous support for women during childbirth". *Cochrane Database of Systematic Reviews*. CD003766 (7): CD003766. doi:10.1002/14651858.CD003766.pub5. PMID 23857334. Lay summary – *Cochrane Summaries* (2013-07-15).
82. ^ "Safe Prevention of the Primary Cesarean Delivery". *American College of Obstetricians and Gynecologists (the College) and the Society for Maternal-Fetal Medicine*. March 2014. Retrieved 20 February 2014.
83. ^ Derry, S.; Straube, S.; Moore, RA.; Hancock, H.; Collins, SL. (2012). Derry, Sheena, ed. "Intracutaneous or subcutaneous sterile water injection compared with blinded controls for pain management in labour". *Cochrane Database Syst Rev*. **1**: CD009107. doi:10.1002/14651858.CD009107.pub2. PMID 22258999.
84. ^ Thorp, J.A.; Breedlove, G. (1996). "Epidural analgesia in labor: An evaluation of risks and benefits". *Birth*. **23** (2): 63–83. doi:10.1111/j.1523-536X.1996.tb00833.x. PMID 8826170.
85. ^ Alehagen, S.; Wijma, B.; Lundberg, U.; Wijma, K. (September 2005). "Fear, pain and stress hormones during childbirth". *Journal of Psychosomatic Obstetrics & Gynecology*.

30. ^ Giacalone, P. L.; Vignal, J.; Daures, J. P.; Boulot, P.; Hedon, B.; Laffargue, F. (2000). "A randomised evaluation of two techniques of management of the third stage of labour in women at low risk of postpartum haemorrhage". *BJOG: an International Journal of Obstetrics and Gynaecology*. **107** (3): 396–400. doi:10.1111/j.1471-0528.2000.tb13236.x.
31. ^ Hantoushzadeh, S.; Alhusseini, N.; Lebaschi, A. H. (2007). "The effects of acupuncture during labour on nulliparous women: A randomised controlled trial". *The Australian and New Zealand Journal of Obstetrics and Gynaecology*. **47** (1): 26–30. doi:10.1111/j.1479-828X.2006.00674.x. PMID 17261096.
32. ^ Reiter, R. J.; Tan, D. X.; Korkmaz, A.; Rosales-Corral, S. A. (2013). "Melatonin and stable circadian rhythms optimize maternal, placental and fetal physiology". *Human Reproduction Update*. **20** (2): 293–307. doi:10.1093/humupd/dmt054. ISSN 1355-4786. PMID 24132226.
33. ^ Usatine, R.P. (developer). "Labor & Delivery". *Maternity Guide (for medical residents)*. Family & Community Medicine Dept, University of Texas Health Science Center at San Antonio. Retrieved 2013-08-18.
34. ^ Satin, A.J. (July 1, 2013). "Latent phase of labor". *UpToDate*. Wolters Kluwer.(subscription required)
35. ^ Murray, L.J.; Hennen, L.; Scott, J. (2005). *The BabyCenter Essential Guide to Pregnancy and Birth: Expert Advice and Real-World Wisdom from the Top Pregnancy and Parenting Resource*. Emmaus, Pennsylvania: Rodale Books. pp. 294–295. ISBN 1-59486-211-7. Retrieved 2013-08-18.
36. ^ Young, Roger (2016). "Mechanotransduction mechanisms for coordinating uterine contractions in human labor.". *Reproduction*. **152**: R51–R61. doi:10.1530/REP-16-0156.
37. ^ Obstetric Data Definitions Issues and Rationale for Change, 2012 by ACOG.
38. ^ Boyle A, Reddy UM, Landy HJ, Huang CC, Driggers RW, Laughon SK (Jul 2013). "Primary cesarean delivery in the United States.". *Obstetrics and gynecology*. **122** (1): 33–40. doi:10.1097/AOG.0b013e3182952242. PMC 3713634. PMID 23743454.
39. ^ Su, M.; Hannah, W. J.; Willan, A.; Ross, S.; Hannah, M. E. (2004). "Planned caesarean section decreases the risk of adverse perinatal outcome due to both labour and delivery complications in the Term Breech Trial". *BJOG: an International Journal of Obstetrics and Gynaecology*. **111** (10): 1065–74. doi:10.1111/j.1471-0528.2004.00266.x. PMID 15383108.
40. ^ Sjukvårdsrådgivningen (In Swedish) - Official information of the County Councils of Sweden. Last updated: 2013-01-16. Reviewer: Roland Boij, gynecologist and obstetrician
41. ^ BabyCentre Medical Advisory Board (September 2012). "Speeding up labour". *BabyCentre*. Johnson & Johnson. Retrieved 2013-08-18.
42. ^ Zhang, J.; Troendle, J.F.; Yancey, M.K. (2002). "Reassessing the labor curve in nulliparous women". *American Journal of Obstetrics and Gynecology*. **187** (4): 824–8. doi:10.1067/mob.2002.127142. PMID 12388957.
43. ^ Peisner, D.B.; Rosen, M.G. (1986). "Transition from latent to active labor". *Obstetrics & Gynecology*. **68** (4): 448–51. PMID 3748488.
44. ^ Rouse, D.J.; Weiner, S.J.; Bloom, S.L.; Varner, M.W.; et al. (2009). "Second-stage labour duration in nulliparous women: Relationship to maternal and perinatal outcomes". *American Journal of Obstetrics and Gynecology*. **201** (4): 357.e1–7. doi:10.1016/j.ajog.2009.08.003. PMC 2768280. PMID 19788967.
45. ^ Jangsten, E.; Mattsson, L.; Lyckestam, I.; Hellström, A.; et al. (2011). "A comparison of active management and expectant management of the third stage of labour: A Swedish randomised controlled trial". *BJOG: an International Journal of Obstetrics & Gynaecology*. **118** (3): 362–9. doi:10.1111/j.1471-0528.2010.02800.x. PMID 21134105.
46. ^ Weeks, A.D. (2008). "The retained placenta". *Best Practice & Research Clinical Obstetrics & Gynaecology*. **22** (3): 153–65. doi:10.1080/01443610400023072. PMID 16295513.
86. ^ Loftus, J.R.; Hill, H.; Cohen, S.E. (August 1995). "Placental transfer and neonatal effects of epidural sufentanil and fentanyl administered with bupivacaine during labor". *Anesthesiology*. **83** (2): 300–8. doi:10.1097/00000542-199508000-00010. PMID 7631952.
87. ^ Anim-Somuah, M.; Smyth, R.M.; Jones, L. (2011). Anim-Somuah, Millicent, ed. Pregnancy and Childbirth Group. "Epidural versus non-epidural or no analgesia in labour". *Cochrane Database of Systematic Reviews*. CD000331 (12): CD000331. doi:10.1002/14651858.CD000331.pub3. PMID 22161362. Lay summary – *Cochrane Summaries* (2011-12-07).
88. ^ Wei, S.Q.; Luo, Z.C.; Xu, H.; Fraser, W.D. (September 2009). "The effect of early oxytocin augmentation in labour: A meta-analysis". *Obstetrics & Gynecology*. **114** (3): 641–9. doi:10.1097/AOG.0b013e3181b11cb8. PMID 19701046.
89. ^ *a b* Rohwer, Anke; Kondowe O; Young T (2013). "Antispasmodics for labour". *Cochrane Database of Systematic Reviews*. **6** (6): CD009243. doi:10.1002/14651858.CD009243.pub3. PMID 23737030.
90. ^ Carroli, G.; Mignini, L. (2009). Carroli, Guillermo, ed. Pregnancy and Childbirth Group. "Episiotomy for vaginal birth". *Cochrane Database of Systematic Reviews*. CD000081 (1): CD000081. doi:10.1002/14651858.CD000081.pub2. PMID 19160176. Lay summary – *Cochrane Summaries* (2012-11-14).
91. ^ Leavitt, Judith W. (1988). *Brought to Bed: Childbearing in America, 1750–1950*. University of Oxford. pp. 90–91. ISBN 978-0-19-505690-7.
92. ^ Vernon, D. "Men At Birth – Should Your Bloke Be There?". *BellyBelly.com.au*. Retrieved 2013-08-23.
93. ^ Hammond, P.; Johnson, A. (1986). "Tocodynamometer". In Brown, M. *The Medical Equipment Dictionary*. London: Chapman & Hall. ISBN 0-412-28290-9. Retrieved 2013-08-23. Online version accessed.
94. ^ *a b* Dziadosz, M; Basch, RS; Young, BK (March 2016). "Human amniotic fluid: a source of stem cells for possible therapeutic use.". *American journal of obstetrics and gynecology*. **214** (3): 321–7. doi:10.1016/j.ajog.2015.12.061. PMID 26767797.
95. ^ *a b* "Mortality and Burden of Disease Estimates for WHO Member States in 2004" (xls). Department of Measurement and Health Information, World Health Organization.
96. ^ *a b* Van Lerberghe, W.; De Brouwere, V. (2001). "Of Blind Alleys and Things That Have Worked: History's Lessons on Reducing Maternal Mortality" (PDF). In De Brouwere, V.; Van Lerberghe, W. *Safe Motherhood Strategies: A Review of the Evidence*. Studies in Health Services Organisation and Policy. **17**. Antwerp: ITG Press. pp. 7–33. ISBN 90-76070-19-9. "Where nothing effective is done to avert maternal death, "natural" mortality is probably of the order of magnitude of 1,500/100,000."
97. ^ Levi, J.; Kohn, D.; Johnson, K. (June 2011). "Healthy Women, Healthy Babies: How health reform can improve the health of women and babies in America" (PDF). Washington, D.C.: Trust for America's Health. Retrieved 2013-08-29.
98. ^ Bates, E.; Rouse, D.J.; Mann, M.L.; Chapman, V.; et al. (December 2010). "Neonatal outcomes after demonstrated fetal lung maturity before 39 weeks of gestation". *Obstetrics & Gynecology*. **116** (6): 1288–95. doi:10.1097/AOG.0b013e3181fb7ece. PMC 4074509. PMID 21099593.
99. ^ *Education material for teachers of midwifery : midwifery education modules* (PDF) (2nd ed.). Geneva [Switzerland]: World Health Organisation. 2008. pp. 17–36. ISBN 978-92-4-154666-9.

*Research Clinical Obstetrics & Gynaecology*. **22** (6): 1103–17. doi:10.1016/j.bpobgyn.2008.07.005. PMID 18793876.
47. ^ Ball, H. (June 2009). "Active management of the third state of labor is rare in some developing countries". *International Perspectives on Sexual and Reproductive Health*. **35** (2).
48. ^ Stanton, C.; Armbruster, D; Knight, R.; Ariawan, I.; et al. (February 13, 2009). "Use of active management of the third stage of labour in seven developing countries". *Bulletin of the World Health Organization*. **87** (3): 207–13. doi:10.2471/BLT.08.052597. PMC 2654655. PMID 19377717.
49. ^ International Confederation of Midwives; International Federation of Gynaecologists Obstetricians (2004). "Joint statement: Management of the third stage of labour to prevent post-partum haemorrhage". *Journal of Midwifery & Women's Health*. **49** (1): 76–7. doi:10.1016/j.jmwh.2003.11.005. PMID 14710151.
50. ^ Mathai, M.; Gülmezoglu, A.M.; Hill, S. (2007). "WHO recommendations for the prevention of postpartum haemorrhage" (PDF). Geneva: World Health Organization, Department of Making Pregnancy Safer. Archived from the original (PDF) on 2009-07-05.
51. ^ McDonald, SJ; Middleton, P; Dowswell, T; Morris, PS (Jul 11, 2013). McDonald, Susan J, ed. "Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes". *The Cochrane database of systematic reviews*. **7**: CD004074. doi:10.1002/14651858.CD004074.pub3. PMID 23843134.
52. ^ Gjerdingen, D.K.; Froberg, D.G. (1991). "The fourth stage of labor: The health of birth mothers and adoptive mothers at six-weeks postpartum". *Family medicine*. **23** (1): 29–35. PMID 2001778.
53. ^ *a b* WHO (2013). "WHO recommendations on postnatal care of the mother and newborn". World Health Organization. Retrieved 22 December 2014.
54. ^ "Postpartum Assessment". ATI Nursing Education. Retrieved 24 December 2014.
55. ^ Mayo clinic staff. "Postpartum care: What to expect after a vaginal delivery". Mayo Clinic. Retrieved 23 December 2014.
56. ^ Saloojee, H. (4 January 2008). "Early skin-to-skin contact for mothers and their healthy newborn infants". *The WHO Reproductive Health Library*. WHO. Retrieved 23 December 2014.
57. ^ Crenshaw, Jennette (2007). "Care Practice #6: No Separation of Mother and Baby, With Unlimited Opportunities for Breastfeeding". *J Perinat Educ*. **16**: 39–43. doi:10.1624/105812407X217147. PMC 1948089. PMID 18566647.
58. ^ Moore, Elizabeth; Anderson, Gene; Bergnam, Nils; Dowswell, Therese (16 May 2012). "Early skin-to-skin contact for mothers and their healthy newborn infants". *Cochrane Database Syst Rev*. **5**: CD003519. doi:10.1002/14651858.CD003519.pub3. PMC 3979156. PMID 22592691.
59. ^ Moore ER, Anderson GC, Bergman N (2007). "Early skin-to-skin contact for mothers and their healthy newborn infants (Review)" (PDF). The Cochrane Collaboration. Retrieved 22 December 2014.
60. ^ Phillips, Raylene. "Uninterrupted Skin-to-Skin Contact Immediately After Birth". Medscape. Retrieved 21 December 2014.
61. ^ "Essential Antenatal, Perinatal and Postpartum Care" (PDF). *Promoting Effective Perinatal Care*. WHO. Retrieved 21 December 2014.
62. ^ "Care of healthy women and their babies during childbirth". *National Collaborating Centre for Women's and Children's Health*. National Institute for Health and Care Excellence. December 2014. Archived from the original on 12
100. ^ Buppasiri, P; Lumbiganon, P; Thinkhamrop, J; Thinkhamrop, B (Oct 7, 2014). "Antibiotic prophylaxis for third- and fourth-degree perineal tear during vaginal birth.". *The Cochrane database of systematic reviews*. **10**: CD005125. doi:10.1002/14651858.CD005125.pub4. PMID 25289960.
101. ^ Say, L.; Inoue, M.; Mills, S.; Suzuki, E. (2008). *Maternal Mortality in 2005 : Estimates Developed by WHO, UNICEF, UNFPA and The World Bank* (PDF). Geneva: Reproductive Health and Research, World Health Organization. ISBN 978-92-4-159621-3.
102. ^ "Maternal mortality ratio falling too slowly to meet goal" (Joint press release). World Health Organization; UNICEF; United Nations Population Fund; World Bank. October 12, 2007. Retrieved 2013-08-30.
103. ^ Warwick, R.; Williams, P.L., eds. (1973). *Gray's Anatomy* (35th British ed.). London: Longman. p. 1046. ISBN 978-0-443-01011-8.
104. ^ "Mortality and Burden of Disease Estimates for WHO Member States in 2004" (xls). Department of Measurement and Health Information, World Health Organization. February 2009.
105. ^ "Sexually transmitted infections (STIs)". World Health Organization. May 2013. Retrieved 2013-08-30.
106. ^ Handel, M.; Swaab, H.; De Vries, L.S.; Jongmans, M.J. (2007). "Long-term cognitive and behavioral consequences of neonatal encephalopathy following perinatal asphyxia: A review". *European Journal of Pediatrics*. **166** (7): 645–54. doi:10.1007/s00431-007-0437-8. PMC 1914268. PMID 17426984.
107. ^ Stearns, P.N., ed. (1993-12-21). *Encyclopedia of Social History*. Garland Reference Library of Social Sciences. V. 780. London: Taylor & Francis. p. 144. ISBN 978-0-8153-0342-8.
108. ^ Vernon, D.M.J., ed. (2005). *Having a Great Birth in Australia: Twenty Stories of Triumph, Power, Love and Delight from the Women and Men who Brought New Life Into the World*. Canberra, Australia: Australian College of Midwives. p. 56. ISBN 978-0-9751674-3-4.
109. ^ "What Is A Confinement Nanny". *NannySOS*. Retrieved 22 December 2016.
110. ^ http://www.amcbmidwife.org/about-amcb
111. ^ "Welcome to the College of Midwives of British Columbia". *College of Midwives of British Columbia website*. Retrieved 2013-08-30.
112. ^ Province of British Columbia (August 21, 2013) [Revised Statues of British Columbia 1996]. "Health Professions Act". *Statues and Regulations of British Columbia internet version*. Vancouver, British Columbia, Canada: Queens Printer. Retrieved 2013-08-30.
113. ^ "Our role". *Nursing & Midwifery Council website*. London, England. 2011-08-31 [Created 2010-02-24]. Retrieved 2013-08-30.
114. ^ "The Nursing and Midwifery Order 2001". London, England: Her Majesty's Stationery Office, The National Archives, Ministry of Justice, Her Majesty's Government. 2002.
115. ^ *a b* "American Way of Birth, Costliest in the World - NYTimes.com".
116. ^ Barrett ML, Smith MW, Elizhauser A, Honigman LS, Pines JM (December 2014). "Utilization of Intensive Care Services, 2011". *HCUP Statistical Brief #185*. Rockville, MD: Agency for Healthcare Research and Quality.
117. ^ Hsia, RY; Akosa Antwi, Y; Weber, E (2014). "Analysis of variation in charges and prices paid for vaginal and caesarean section births: a cross-sectional study". *BMJ Open*. **4** (1): e004017. doi:10.1136/bmjopen-2013-004017. PMC 3902513. PMID 24435892.
118. ^ "www.nice.org.uk". Archived from the original on 2015-02-12.
119. ^ "British Regulator Urges Home Births Over Hospitals for Uncomplicated Pregnancies - NYTimes.com".

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| **Planning** | Assisted reproductive technology • Birth control • Childfree/Childlessness • Parenting (Adoption • **Childbirth** • Foster care • • Reproductive life plan • Safe sex • |
| **Health** | Men's • Women's (Vulvovaginal • • Research (Self-report sexual risk behaviors • • |
| **Pregnancy** | Abortion • Maternal health • Obstetrics • Options counseling • Pregnancy from rape • Pregnant patients' rights • Prenatal care • Teenage pregnancy • Preteen pregnancy • Unintended pregnancy • |
| **Medicine** | Andrology • Genitourinary medicine • Gynaecology • Obstetrics and gynaecology • Reproductive endocrinology and infertility • Sexual medicine • |
| **Disorder** | Disorders of sex development • Infertility • Reproductive system disease • Sexual dysfunction • Sexually transmitted infection (Clinic • • |
| **By country** | China • India • Iran • Ireland • Pakistan • Philippines • Singapore • United Kingdom (Teen • • United States (Teen pregnancy • Birth control • • |
| **History** | Birth control movement in the United States • History of condoms • Social hygiene movement • Timeline of reproductive rights legislation • |
| **Policy** | One-child policy • Two-child policy • Financial (Baby bonus • Bachelor tax • Birth credit • Child benefit • Tax on childlessness • • |

| v • t • e • | **Pregnancy and childbirth** | |
|---|---|---|
| **Planning** | | Birth control • Natural family planning • Pre-conception counseling • |
| **Conception** | | Assisted reproductive technology (Artificial insemination • Fertility medication • In vitro fertilisation • • Fertility awareness • Unintended pregnancy • |
| **Testing** | | 3D ultrasound • Obstetric ultrasonography • Pregnancy test (Home testing • • Prenatal diagnosis • |
| **Prenatal** | **Anatomy** | Amniotic fluid • Amniotic sac • Endometrium • Placenta • |
| | **Development** | Fundal height • Gestational age • Human embryogenesis • Maternal physiological changes • |
| | **Care** | Nutrition (Environmental toxicants • In pregnancy • Prenatal • • Concomitant conditions (Diabetes mellitus • SLE • • Sexual activity during pregnancy • |
| | **Procedures** | Amniocentesis • Cardiotocography • Chorionic villus sampling • Nonstress test • Abortion • |
| **Childbirth** | **Preparation** | Adaptation to extrauterine life • Bradley method • Hypnobirthing • Lamaze • Nesting instinct • |
| | **Roles** | Doula • Men's roles • Midwife • Obstetrician • Perinatal nurse • |
| | **Delivery** | Bloody show • Childbirth positions • Home birth • Multiple birth • Natural childbirth • Pelvimetry / Bishop score (Cervical dilation • Cervical effacement • Position • • Presentation (Breech • Cephalic • Shoulder • • Rupture of membranes • Unassisted childbirth • Uterine contraction • Water birth • |
| **Postpartum** | | Child care • Congenital disorders • Sex after pregnancy • |
| **Obstetric history** | | Gravidity • Parity • TPAL • |

| v • t • e • | **Pathology of pregnancy, childbirth and the puerperium (O, 630–679)** |
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| | | | |
|---|---|---|---|
| **Pregnancy** | **Pregnancy with abortive outcome** | | Ectopic pregnancy (Abdominal pregnancy · Cervical pregnancy · Interstitial pregnancy · Ovarian pregnancy · · Molar pregnancy · Miscarriage · Stillbirth · |
| | **Oedema, proteinuria and hypertensive disorders** | | Gestational hypertension · Pre-eclampsia (HELLP syndrome · · Eclampsia · |
| | **Other, predominantly related to pregnancy** | **Digestive system** | Acute fatty liver of pregnancy · Gestational diabetes · Hepatitis E · Hyperemesis gravidarum · Intrahepatic cholestasis of pregnancy · |
| | | **Integumentary system / dermatoses of pregnancy** | Gestational pemphigoid · Impetigo herpetiformis · Intrahepatic cholestasis of pregnancy · Linea nigra · Prurigo gestationis · Pruritic folliculitis of pregnancy · Pruritic urticarial papules and plaques of pregnancy (PUPPP) · Striae gravidarum · |
| | | **Nervous system** | Chorea gravidarum · |
| | | **Blood** | Gestational thrombocytopenia · Pregnancy-induced hypercoagulability · |
| | **Maternal care related to the fetus and amniotic cavity** | | *amniotic fluid* (Oligohydramnios · Polyhydramnios · · Braxton Hicks contractions · *chorion* / *amnion* (Amniotic band syndrome · Chorioamnionitis · Chorionic hematoma · Monoamniotic twins · Premature rupture of membranes · · Obstetrical hemorrhage (Antepartum · · *placenta* (Circumvallate placenta · Monochorionic twins · Placenta praevia · Placental abruption · Twin-to-twin transfusion syndrome · · |
| **Labor** | | | Amniotic fluid embolism · Cephalopelvic disproportion · Dystocia (Shoulder dystocia · · Fetal distress · Locked twins · Obstetrical hemorrhage (Postpartum · · *placenta* (Placenta accreta · · Preterm birth · Postmature birth · Umbilical cord prolapse · Uterine rupture · Vasa praevia · |
| **Puerperal** | | | Breastfeeding difficulties (Lactation failure · Galactorrhea · Fissure of the nipple · · Breast engorgement · Diastasis symphysis pubis · Peripartum cardiomyopathy · Postpartum depression · Postpartum thyroiditis · Puerperal fever · Puerperal mastitis · |
| **Other** | | | Concomitant conditions (Diabetes mellitus · Systemic lupus erythematosus · Thyroid disorders · · Maternal death · Sexual activity during pregnancy · |
| **Authority control** | | | GND: 4019589-2 · BNF: cb11931223x (data) · NDL: 00572454 · |

Categories: Childbirth | Human development | Human pregnancy | Midwifery | Acute pain

# Dysmenorrhea

From Wikipedia, the free encyclopedia



**Dysmenorrhea**, also known as **dysmenorrhoea**, **painful periods**, or **menstrual cramps**, is pain during menstruation.[1][2] It usually begins around the time that menstruation begins. Symptoms typically last less than three days. The pain is usually in the pelvis or lower abdomen. Other symptoms may include back pain, diarrhea, or nausea.[1]

In young women painful periods often occur without an underlying problem. In older women it is more often due to an underlying issues such as uterine fibroids, adenomyosis, or endometriosis.[3] It is more common among those with heavy periods, irregular periods, whose periods started before twelve years of age, or who have a low body weight.[1] A pelvic exam in those who are sexually active and ultrasound may be useful to help in diagnosis.[1] Conditions that should be ruled out include ectopic pregnancy, pelvic inflammatory disease, interstitial cystitis, and chronic pelvic pain.[1]

Dysmenorrhea occurs less often in those who exercise regularly and those who have children early in life.[1] Treatment may include the use of a heating pad.[3] Medications that may help include NSAIDs such as ibuprofen, hormonal birth control, and the IUD with progestogen.[1][3] Taking vitamin B or magnesium may help.[2] Evidence for yoga, acupuncture, and massage is insufficient.[1] Surgery may be useful if certain underlying problems are present.[2]

Dysmenorrhea is estimated to occur in 20% to 90% of women of reproductive age.[1] It is the most common menstrual disorder.[2] Typically it starts within a year of the first menstrual period.[1] When there is no underlying cause often the pain improves with age or following having a child.[2]

## Dysmenorrhea

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Gynecology |
| **ICD-10** | |
| **ICD-9-CM** | 625.3 |
| **DiseasesDB** | 10634 |
| **MedlinePlus** | 003150 |
| **eMedicine** | article/253812 |
| **Patient UK** | Dysmenorrhea |
| **MeSH** | D004412 |

[edit on Wikidata]

## Contents



## Variants

## Signs and symptoms [edit]



The main symptom of dysmenorrhea is pain concentrated in the lower abdomen or pelvis.[1] It is also commonly felt in the right or left side of the abdomen. It may radiate to the thighs and lower back.[1]

Symptoms often co-occurring with menstrual pain include nausea and vomiting, diarrhea or constipation, headache, dizziness, disorientation, hypersensitivity to sound, light, smell and touch, fainting, and fatigue. Symptoms of dysmenorrhea often begin immediately after ovulation and can last until the end of menstruation. This is because dysmenorrhea is often associated with changes in hormonal levels in the body that occur with ovulation. The use of certain types of birth control pills can prevent the symptoms of dysmenorrhea because they stop ovulation from occurring.

## Causes [edit]

Dysmenorrhea can be classified as either primary or secondary based on the absence or presence of an underlying cause. Secondary dysmenorrhea is dysmenorrhea which is associated with an existing condition.

The most common cause of secondary dysmenorrhea is endometriosis, which can be visually confirmed by laparoscopy in approximately 70% of adolescents with dysmenorrhea.[4]

Other causes of secondary dysmenorrhea include leiomyoma,[5] adenomyosis,[6] ovarian cysts, and pelvic congestion.[7]

Unequal leg length might hypothetically be one of the contributors, as it may contribute to a tilted pelvis, which may cause lower back pain,[8] which in turn may be mistaken for menstrual pain, as women with lower back pain experience increased pain during their periods.

Other skeletal abnormalities, such as scoliosis (sometimes caused by spina bifida) might be possible contributors as well.

## Mechanism [edit]

During a woman's menstrual cycle, the endometrium thickens in preparation for potential pregnancy. After ovulation, if the ovum is not fertilized and there is no pregnancy, the built-up uterine tissue is not needed and thus shed.

Molecular compounds called prostaglandins are released during menstruation, due to the destruction of the endometrial cells, and the resultant release of their contents.[9][*needs update*] Release of prostaglandins and other inflammatory mediators in the uterus cause the uterus to contract. These substances are thought to be a major factor in primary dysmenorrhea.[10] When the uterine muscles contract, they constrict the blood supply to the tissue of the endometrium, which, in turn, breaks down and dies. These uterine contractions continue as they squeeze the old, dead endometrial tissue through the cervix and out of the body through the vagina. These contractions, and the resulting temporary oxygen deprivation to nearby tissues, are responsible for the pain or "cramps" experienced during menstruation.

Compared with other women, women with primary dysmenorrhea have increased activity of the uterine muscle with increased contractility and increased frequency of contractions.[11]

In one research study using MRI, visible features of the uterus were compared in dysmenorrheic and eumenorrheic (normal) participants. The study concluded that in dysmenorrheic patients, visible features on cycle days 1-3 correlated with the degree of pain, and differed significantly from the control group.[12]

## Diagnosis [edit]

The diagnosis of dysmenorrhea is usually made simply on a medical history of menstrual pain that interferes with daily activities. However, there is no universally accepted gold standard technique for quantifying the

severity of menstrual pains.[13] Yet, there are quantification models, called *menstrual symptometrics*, that can be used to estimate the severity of menstrual pains as well as correlate them with pain in other parts of the body, menstrual bleeding and degree of interference with daily activities.[13]

### Further work-up [edit]

Once a diagnosis of dysmenorrhea is made, further workup is required to search for any secondary underlying cause of it, in order to be able to treat it specifically and to avoid the aggravation of a perhaps serious underlying cause.

Further work-up includes a specific medical history of symptoms and menstrual cycles and a pelvic exam.[2] Based on results from these, additional exams and tests may be motivated, such as:

- Laboratory tests[2]
- Gynecologic ultrasonography[2]
- Laparoscopy may be required.[2]

## Management [edit]

### NSAIDs [edit]

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in relieving the pain of primary dysmenorrhea.[14][*needs update*] They can have side effects of nausea, dyspepsia, peptic ulcer, and diarrhea.[15] People who are unable to take the more common NSAIDs may be prescribed a COX-2 inhibitor.[16]

### Hormonal birth control [edit]

Although use of hormonal birth control can improve or relieve symptoms of primary dysmenorrhea,[17][18] a 2001 systematic review found that no conclusions can be made about the efficacy of commonly used modern lower dose combined oral contraceptive pills for primary dysmenorrhea.[19][*needs update*] Norplant[20] and Depo-provera[21][22] are also effective, since these methods often induce amenorrhea. The intrauterine system (Mirena IUD) may be useful in reducing symptoms.[23]

### Other [edit]

A review indicated the effectiveness of transdermal nitroglycerin.[24]

### Alternative medicine [edit]

There is poor evidence for treatments other than medications.[1]

One review found thiamine and vitamin E to be likely effective.[25] It found the effects of fish oil and vitamin B12 to be unknown.[25]

Another review found that Vitamin B1 to be effective. Magnesium supplementation are a promising possible treatment. And insufficient evidence to recommend any other herbal or dietary supplement, including omega-3 fatty acids, vitamin E, vitamin B6 among others which have been studied.[26][*needs update*]

A 2008 review found promising evidence for Chinese herbal medicine for primary dysmenorrhea, but that the evidence was limited by its poor methodological quality.[27] Reviews found tentative evidence that ginger powder may be effective for primary dysmenorrhea.[28][29]

### Procedures [edit]

One review found acupressure, topical heat, transcutaneous electrical nerve stimulation, and behavioral interventions likely effective.[25] It found acupuncture and magnets to be unknown.[25] Another review found tentative evidence for acupuncture.[30][*needs update*]

A 2007 systematic review found some scientific evidence that behavioral interventions may be effective, but that the results should be viewed with caution due to poor quality of the data.[31]

Spinal manipulation does not appear to be helpful.[25] Although claims have been made for chiropractic care, under the theory that treating subluxations in the spine may decrease symptoms,[32] a 2006 systematic review found that overall no evidence suggests that spinal manipulation is effective for treatment of primary and secondary dysmenorrhea.[33]

## Epidemiology [edit]

Dysmenorrhea is estimated to affect approximately 25% of women.[34] Reports of dysmenorrhea are greatest among individuals in their late teens and 20s, with reports usually declining with age. The prevalence in adolescent females has been reported to be 67.2% by one study[35] and 90% by another.[34] It has been stated that there is no significant difference in prevalence or incidence between races.[34] Yet, a study of Hispanic adolescent females indicated a high prevalence and impact in this group.[36] Another study indicated that dysmenorrhea was present in 36.4% of participants, and was significantly associated with lower age and lower parity.[37] Childbearing is said to relieve dysmenorrhea, but this does not always occur. One study indicated that in nulliparous women with primary dysmenorrhea, the severity of menstrual pain decreased significantly after age 40.[38] A questionnaire concluded that menstrual problems, including dysmenorrhea, were more common in females who had been sexually abused.[39]

A survey in Norway showed that 14 percent of females between the ages of 20 to 35 experience symptoms so severe that they stay home from school or work.[40] Among adolescent girls, dysmenorrhea is the leading cause of recurrent short-term school absence.[41]

## References [edit]


1. ^ *a b c d e f g h i j k l m* Osayande, AS; Mehulic, S (1 March 2014). "Diagnosis and initial management of dysmenorrhea.". *American family physician*. **89** (5): 341–6. PMID 24695505.
2. ^ *a b c d e f g h i* American College of Obstetricians and Gynecologists (Jan 2015). "FAQ046 Dysmenorrhea: Painful Periods" (PDF). Retrieved 26 June 2015.
3. ^ *a b c* "Menstruation and the menstrual cycle fact sheet". *Office of Women's Health*. December 23, 2014. Retrieved 25 June 2015.
4. ^ Janssen EB, Rijkers AC, Hoppenbrouwers K, Meuleman C, D'Hooghe TM (2013). "Prevalence of endometriosis diagnosed by laparoscopy in adolescents with dysmenorrhea or chronic pelvic pain: A systematic review". *Human Reproduction Update*. **19** (5): 570–582. doi:10.1093/humupd/dmt016. PMID 23727940.
5. ^ Hilário SG, Bozzini N, Borsari R, Baracat EC (2008). "Action of aromatase inhibitor for treatment of uterine leiomyoma in perimenopausal patients". *Fertil. Steril*. **91** (1): 240–3. doi:10.1016/j.fertnstert.2007.11.006. PMID 18249392.
6. ^ Nabeshima H, Murakami T, Nishimoto M, Sugawara N, Sato N (2008). "Successful total laparoscopic cystic adenomyomectomy after unsuccessful open surgery using transtrocar ultrasonographic guiding". *J Minim Invasive Gynecol*. **15** (2): 227–30. doi:10.1016/j.jmig.2007.10.007. PMID 18312998.
7. ^ Hacker, Neville F., J. George Moore, and Joseph C. Gambone. *Essentials of Obstetrics and Gynecology, 4th ed.* Elsevier Saunders, 2004. ISBN 0-7216-0179-0[*page needed*]
8. ^ Cooperstein R, Lew M (2009). "The relationship between pelvic torsion and anatomical leg length inequality: a review of the literature". *J Chiropr Med*. **8**: 107–18. doi:10.1016/j.jcm.2009.06.001. PMC 2732247. PMID 19703666.
9. ^ Lethaby A, Augood C, Duckitt K, Farquhar C (2007). Lethaby, Anne, ed. "Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding". *Cochrane Database Syst Rev* (4): CD000400. doi:10.1002/14651858.CD000400.pub2. PMID 17943741.

10. ^ Wright, Jason and Solange Wyatt. *The Washington Manual Obstetrics and Gynecology Survival Guide*. Lippincott Williams and Wilkins, 2003. ISBN 0-7817-4363-X[*page needed*]
11. ^ Rosenwaks Z, Seegar-Jones G (October 1980). "Menstrual pain: its origin and pathogenesis". *J Reprod Med*. **25** (4 Suppl): 207–12. PMID 7001019.
12. ^ Kataoka M, Togashi K, Kido A, Nakai A, Fujiwara T, Koyama T, Fujii S (2005). "Dysmenorrhea: evaluation with cine-mode-display MR imaging--initial experience". *Radiology*. **235** (1): 124–31. doi:10.1148/radiol.2351031283. PMID 15731368.
13. ^ *a b* Wyatt KM, Dimmock PW, Hayes-Gill B, Crowe J, O'Brien PM (2002). "Menstrual symptometrics: A simple computer-aided method to quantify menstrual cycle disorders". *Fertility and Sterility*. **78** (1): 96–101. doi:10.1016/s0015-0282(02)03161-8. PMID 12095497.
14. ^ Marjoribanks J, Proctor M, Farquhar C, Derks RS (2010). Marjoribanks, Jane, ed. "Nonsteroidal anti-inflammatory drugs for dysmenorrhoea". *Cochrane database of systematic reviews (Online)* (1): CD001751. doi:10.1002/14651858.CD001751.pub2. PMID 20091521.
15. ^ Rossi S, editor. Australian Medicines Handbook 2006. Adelaide: Australian Medicines Handbook; 2006. ISBN 0-9757919-2-3
16. ^ Chantler I, Mitchell D, Fuller A (2008). "The effect of three cyclo-oxygenase inhibitors on intensity of primary dysmenorrheic pain". *Clin J Pain*. **24** (1): 39–44. doi:10.1097/AJP.0b013e318156dafc. PMID 18180635.
17. ^ Archer DF (November 2006). "Menstrual-cycle-related symptoms: a review of the rationale for continuous use of oral contraceptives". *Contraception*. **74** (5): 359–66. doi:10.1016/j.contraception.2006.06.003. PMID 17046376.
18. ^ Harel Z (December 2006). "Dysmenorrhea in adolescents and young adults: etiology and management". *J Pediatr Adolesc Gynecol*. **19** (6): 363–71. doi:10.1016/j.jpag.2006.09.001. PMID 17174824.
19. ^ Proctor ML, Roberts H, Farquhar CM (2001). Wong, Chooi L, ed. "Combined oral contraceptive pill (OCP) as treatment for primary dysmenorrhoea". *Cochrane Database Syst Rev* (4): CD002120. doi:10.1002/14651858.CD002120. PMID 11687142.
20. ^ Power J, French R, Cowan F (2007). Power, Jo, ed. "Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods of preventing pregnancy". *Cochrane Database Syst Rev* (3): CD001326. doi:10.1002/14651858.CD001326.pub2. PMID 17636668.
21. ^ Glasier, Anna (2006). "Contraception". In DeGroot, Leslie J.; Jameson, J. Larry (eds.). *Endocrinology* (5th ed.). Philadelphia: Elsevier Saunders. pp. 2993–3003. ISBN 0-7216-0376-9.
22. ^ Loose, Davis S.; Stancel, George M. (2006). "Estrogens and Progestins". In Brunton, Laurence L.; Lazo, John S.; Parker, Keith L. *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (11th ed.). New York: McGraw-Hill. pp. 1541–1571. ISBN 0-07-142280-3.
23. ^ Gupta HP, Singh U, Sinha S (2007). "Laevonorgestrel intra-uterine system--a revolutionary intra-uterine device". *J Indian Med Assoc*. **105** (7): 380, 382–5. PMID 18178990.
24. ^ Morgan PJ, Kung R, Tarshis J (2002). "Nitroglycerin as a uterine relaxant: a systematic review". *J Obstet Gynaecol Can*. **24** (5): 403–9. PMID 12196860.
25. ^ *a b c d e* Latthe PM, Champaneria R, Khan KS (Feb 21, 2011). "Dysmenorrhoea". *Clinical evidence*. **2011**. PMC 3275141. PMID 21718556.
26. ^ Proctor ML, Murphy PA (2001). "Herbal and dietary therapies for primary and secondary dysmenorrhoea". *Cochrane Database Syst Rev* (3): CD002124. doi:10.1002/14651858.CD002124. PMID 11687013.
27. ^ Zhu X, Proctor M, Bensoussan A, Wu E, Smith CA (2008). Zhu, Xiaoshu, ed. "Chinese herbal medicine for primary dysmenorrhoea". *Cochrane Database Syst Rev* (2): CD005288. doi:10.1002/14651858.CD005288.pub3. PMID 18425916.
28. ^ Daily, James W.; Zhang, Xin; Kim, Da Sol; Park, Sunmin (2015-12-01). "Efficacy of Ginger for Alleviating the Symptoms of Primary Dysmenorrhea: A Systematic Review and Meta-analysis of Randomized Clinical Trials". *Pain Medicine (Malden, Mass.)*. **16** (12): 2243–2255. doi:10.1111/pme.12853. ISSN 1526-4637. PMID 26177393.
29. ^ Chen, Chen X.; Barrett, Bruce; Kwekkeboom, Kristine L. (2016-05-05). "Efficacy of Oral Ginger (Zingiber officinale) for Dysmenorrhea: A Systematic Review and Meta-Analysis". *Evidence-Based Complementary and Alternative Medicine*. **2016**: 1–10. doi:10.1155/2016/6295737. ISSN 1741-427X. PMC 4871956. PMID 27274753.
30. ^ Smith CA, Zhu X, He L, Song J (2011). "Acupuncture for primary dysmenorrhoea". *Cochrane Database Syst Rev* (1): CD007854. doi:10.1002/14651858.CD007854.pub2. PMID 21249697.
31. ^ Proctor ML, Murphy PA, Pattison HM, Suckling J, Farquhar CM (2007). Proctor, Michelle, ed. "Behavioural interventions for primary and secondary dysmenorrhoea". *Cochrane Database Syst Rev* (3): CD002248. doi:10.1002/14651858.CD002248.pub3. PMID 17636702.
32. ^ Chapman-Smith D (2000). "Scope of practice". *The Chiropractic Profession: Its Education, Practice, Research and Future Directions*. West Des Moines, IA: NCMIC. ISBN 1-892734-02-8.[*page needed*]
33. ^ Proctor ML, Hing W, Johnson TC, Murphy PA (2006). Proctor, Michelle, ed. "Spinal manipulation for primary and

secondary dysmenorrhoea". *Cochrane Database Syst Rev*. **3** (3): CD002119. doi:10.1002/14651858.CD002119.pub3. PMID 16855988.
34. ^ *a b c* eMedicine > Dysmenorrhea By Andre Holder, Laurel D Edmundson and Mert Erogul. Updated: Dec 31, 2009
35. ^ Sharma P, Malhotra C, Taneja DK, Saha R (2008). "Problems related to menstruation amongst adolescent girls". *Indian J Pediatr*. **75** (2): 125–9. doi:10.1007/s12098-008-0018-5. PMID 18334791.
36. ^ Banikarim C, Chacko MR, Kelder SH (2000). "Prevalence and impact of dysmenorrhea on Hispanic female adolescents". *Arch Pediatr Adolesc Med*. **154** (12): 1226–9. doi:10.1001/archpedi.154.12.1226. PMID 11115307.
37. ^ Sule ST, Umar HS, Madugu NH (2007). "Premenstrual symptoms and dysmenorrhoea among Muslim women in Zaria, Nigeria". *Ann Afr Med*. **6** (2): 68–72. doi:10.4103/1596-3519.55713. PMID 18240706.
38. ^ Juang CM, Yen MS, Horng HC, Cheng CY, Yuan CC, Chang CM (2006). "Natural progression of menstrual pain in nulliparous women at reproductive age: an observational study". *J Chin Med Assoc*. **69** (10): 484–8. doi:10.1016/S1726-4901(09)70313-2. PMID 17098673.
39. ^ Vink CW, Labots-Vogelesang SM, Lagro-Janssen AL (2006). "[Menstruation disorders more frequent in women with a history of sexual abuse]". *Ned Tijdschr Geneeskd* (in Dutch and Flemish). **150** (34): 1886–90. PMID 16970013.
40. ^ "Mozon: Sykemelder seg på grunn av menssmerter". Mozon. 2004-10-25. Retrieved 2007-02-02.
41. ^ French L (2008). "Dysmenorrhea in adolescents: diagnosis and treatment". *Paediatr Drugs*. **10** (1): 1–7. doi:10.2165/00148581-200810010-00001. PMID 18162003.

## External links [edit]

- Dysmenorrhea at DMOZ

Wikimedia Commons has media related to *Dysmenorrhea*.

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| | | **Fallopian tube** | Female infertility (Fallopian tube obstruction · · Hematosalpinx · Hydrosalpinx · Salpingitis · |
| | **Uterus** | **Endometrium** | Asherman's syndrome · Dysfunctional uterine bleeding · Endometrial hyperplasia · Endometrial polyp · Endometriosis · Endometritis · |
| | | | *menstruation*: flow (Amenorrhoea · Hypomenorrhea · Oligomenorrhea · · pain (**Dysmenorrhea** · PMS · · timing (Menometrorrhagia · Menorrhagia · Metrorrhagia · · |
| | | | Female infertility (Recurrent miscarriage · · |
| | | **Myometrium** | Adenomyosis · |
| | | **Parametrium** | Parametritis · |
| | | **Cervix** | Cervical dysplasia · Cervical incompetence · Cervical polyp · Cervicitis · Female infertility (Cervical stenosis · · Nabothian cyst · |
| | | **General** | Hematometra / Pyometra · Retroverted uterus · |

| | | |
|---|---|---|
| | **Vagina** | Hematocolpos / Hydrocolpos · Leukorrhea / Vaginal discharge · Vaginitis (Atrophic vaginitis · Bacterial vaginosis · Candidal vulvovaginitis · · |
| | | *Sexual dysfunction*: Dyspareunia · Hypoactive sexual desire disorder · Sexual arousal disorder · Vaginismus · |
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| | | Vaginal bleeding · |
| | **Other / general** | Pelvic congestion syndrome · Pelvic inflammatory disease · |
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| v · t · e · **Menstrual cycle** | | |
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| | **Systems** | Fertility awareness · Calendar-based methods · Billings Ovulation Method · Creighton Model · |
| **Suppression** | | Extended cycle combined hormonal contraceptive · Lactational amenorrhea · |
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| **Related events** | | Folliculogenesis · Menstrual synchrony · Premenstrual syndrome / Premenstrual dysphoric disorder · Sexual activity · |
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Categories: Menstrual disorders

# Eclampsia

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**Eclampsia** is the onset of [seizures](#) (convulsions) in a woman with [pre-eclampsia](#).[1] Pre-eclampsia is a disorder of [pregnancy](#) in which there is [high blood pressure](#) and either large amounts of [protein in the urine](#) or other organ dysfunction.[2][3] Onset may be before, during, or after [delivery](#). Most often it is during the second half of pregnancy. The seizures are of the [tonic–clonic](#) type and typically last about a minute. Following the seizure there is typically either a [period of confusion](#) or [coma](#). Complications include [aspiration pneumonia](#), [cerebral hemorrhage](#), [kidney failure](#), and [cardiac arrest](#). Preeclampsia and eclampsia are part of a larger group of conditions known as [hypertensive disorders of pregnancy](#).[1]

Recommendations for prevention include [aspirin](#) in those at high risk, [calcium supplementation](#) in areas with low intake, and treatment of prior hypertension with medications.[4][5] Exercise during pregnancy may also be useful.[1] The use of intravenous or intramuscular [magnesium sulfate](#) improves outcomes in those with eclampsia and is generally safe.[6][7] This is true in both the [developed](#) and [developing world](#).[6] Breathing may need to be supported. Other treatments may include blood pressure medications such as [hydralazine](#) and emergency delivery of the baby either vaginally or by [cesarean section](#).[1]

| Eclampsia | |
|---|---|
| **Classification and external resources** | |
| **Specialty** | Obstetrics |
| **ICD-10** | |
| **ICD-9-CM** | 642.6 |
| **DiseasesDB** | 4068 |
| **MedlinePlus** | 000899 |
| **eMedicine** | med/1905 emerg/796 |
| **Patient UK** | Eclampsia |
| **MeSH** | D004461 |

[edit on Wikidata]

Pre-eclampsia is estimated to affect about 5% of deliveries while eclampsia affects about 1.4% of deliveries.[8] In the developed world rates are about 1 in 2,000 deliveries due to improved medical care.[1] Hypertensive disorders of pregnancy are one of the most common causes of death in pregnancy.[9] They resulted in 29,000 deaths in 2013 – down from 37,000 deaths in 1990.[10] Around one percent of women with eclampsia die.[1] The word eclampsia is from the Greek term for lightning. The first known description of the condition was by [Hippocrates](#) in the 5th century BCE.[11]

Contents



## Signs and symptoms [edit]

Typically the pregnant woman develops [hypertension](#) and [proteinuria](#) before the onset of a convulsion, the hallmark of eclampsia.[12] Eclampsia is preeclampsia and seizures. Other cerebral signs may immediately precede the convulsion, such as nausea, vomiting, headaches, and [cortical blindness](#). If the complication of multi-organ failure ensues, signs and symptoms of those failing organs will appear, such as abdominal pain, jaundice, shortness of breath, and diminished urine output.

The fetus may develop [intrauterine growth retardation](#), and with maternal convulsions, [bradycardia](#),[13] and [fetal distress](#). Placental bleeding, and [placental abruption](#) may also occur.

Sometimes the pregnant woman becomes comatose without preceding convulsions. Upon awakening from the coma, some experience amaurosis fugax: a "dark" and "fleeting" unilateral temporary blindness.[14]



## Risk factors [edit]

Eclampsia, like pre-eclampsia, tends to occur more commonly in first pregnancies and young mothers where it is thought that novel exposure to paternal antigens is involved. Furthermore, women with pre-existing vascular diseases (hypertension, diabetes, and nephropathy) or thrombophilic diseases such as the antiphospholipid syndrome are at higher risk to develop pre-eclampsia and eclampsia. Having a large placenta (multiple gestation, hydatidiform mole) also predisposes women to eclampsia. In addition, there is a genetic component: a woman whose mother or sister had the condition is at higher risk than otherwise.[15] Women who have experienced eclampsia are at increased risk for pre-eclampsia/eclampsia in a later pregnancy. Pulmonary edema is a rather common complication of severe eclampsia affecting approximately 3% of the people with eclampsia: most is caused by too much intravenous fluid.

## Mechanism [edit]

The presence of a placenta is required, and eclampsia resolves if it is removed.[16] Reduced blood flow to the placenta (placental hypoperfusion) is a key feature of the process. It is accompanied by increased sensitivity of the maternal vasculature to agents which cause constriction of the small arteries, leading to reduced blood flow to multiple organs. Also, an activation of the coagulation cascade may lead to microthrombi formation, which can further impair blood flow. Thirdly, increased vascular permeability results in the shift of extracellular fluid from the blood to the interstitial space, with further reduction in blood flow, and edema. These events lead to hypertension; renal, pulmonary, and hepatic dysfunction; and cerebral edema with cerebral dysfunction and convulsions.[16] Before symptoms appear, increased platelet and endothelial activation[16] may be detected.

Placental hypoperfusion is linked to abnormal modelling of the fetal–maternal placental interface that may be immunologically mediated.[16] The invasion of the trophoblast appears to be incomplete.[17] The placenta produces the potent vasodilator adrenomedullin: it is reduced in pre-eclampsia and eclampsia.[18] Other vasodilators are also reduced, including prostacyclin, thromboxane A2, nitric oxide, and endothelins, also leading to vasoconstriction.[13] Many studies have suggested the importance of a woman's reduced immunological tolerance to her baby's father, whose genes are present in the young fetus and the placenta.[19]

Eclampsia is a form of hypertensive encephalopathy: cerebral vascular resistance is reduced, leading to increased blood flow to the brain, cerebral edema and resultant convulsions.[20] An eclamptic convulsion usually does not cause chronic brain damage unless intracranial haemorrhage occurs.[21]

## Differential diagnosis [edit]

Convulsions during pregnancy that are unrelated to pre-eclampsia need to be distinguished from eclampsia. Such disorders include seizure disorders as well as brain tumor, aneurysm of the brain, and medication- or drug-related seizures. Usually the presence of the signs of severe pre-eclampsia precede and accompany eclampsia, facilitating the diagnosis.

Investigations include: CBC, renal function test (RFT), liver function tests (LFT), coagulation screen, 24-hour urine creatinine and protein, and fetal/placental ultrasound.

## Prevention [edit]

Detection and management of pre-eclampsia is critical to reduce the risk of eclampsia. Appropriate management of women with pre-eclampsia generally involves the use of magnesium sulphate to prevent convulsions.

## Treatment [edit]

The four goals of the treatment of eclampsia are to stop and prevent further convulsions, to control the elevated blood pressure, to deliver the baby as promptly as possible, and to monitor closely for the onset of multi-organ failure.

### Convulsions [edit]

Convulsions are prevented and treated using magnesium sulfate.[22] The study demonstrating the effectiveness of magnesium sulfate for the management of eclampsia was first published in 1955.[23] Serum magnesium concentrations associated with maternal toxicity as well as neonatal depression, hypotonia, and low Apgar scores[24] are:

7.0–10.0 mEq/L: loss of patellar reflex
- 10.0–13.0 mEq/L: respiratory depression
- 15.0–25.0 mEq/L: altered atrioventricular conduction and (further) complete heart block
- >25.0 mEq/L: cardiac arrest

With intravenous administration the onset of anticonvulsant action is fast and lasts about 30 minutes. Following intramuscular administration the onset of action is about one hour and lasts for three to four hours. Effective anticonvulsant serum levels range from 2.5 to 7.5 mEq/liter. Magnesium is excreted solely by the kidneys at a rate proportional to the plasma concentration and glomerular filtration.[25]

Even with therapeutic serum magnesium concentrations, recurrent convulsions may occur, and additional magnesium may be needed, but with close monitoring for respiratory, cardiac, and neurological depression. If magnesium administration with resultant high serum concentrations fail to control convulsions, the addition of other intravenous anticonvulsants may be used, facilitate intubation and mechanical ventilation, and to avoid magnesium toxicity including maternal thoracic muscle paralysis.

Magnesium sulfate results in better outcomes than diazepam, phenytoin or a combination of chlorpromazine, promethazine and pethidine.[26][27][28]

### Blood pressure management [edit]

The agents of choice for blood pressure control during eclampsia are hydralazine and/or labetalol.[13] This is because of their effectiveness, lack of negative effects on the fetus, and mechanism of action.

### Delivery [edit]

If the baby has not yet been delivered, steps need to be taken to stabilize the woman and deliver her speedily. This needs to be done even if the baby is immature, as the eclamptic condition is unsafe for both baby and mother. As eclampsia is a manifestation of a multiorgan failure, other organs (liver, kidney, lungs, cardiovascular system, and coagulation system) need to be assessed in preparation for a delivery (often a caesarean section), unless the woman is already in advanced labor. Regional anesthesia for caesarean section is contraindicated when a coagulopathy has developed.

### Monitoring [edit]

Invasive haemodynamic monitoring may be elected in an eclamptic woman at risk for or with cardiac disease, renal disease, refractory hypertension, pulmonary edema, or poor urine output.[13]

## Etymology [edit]

The Greek noun "ἔκλαμψία", *eklampsía*, denotes a "light burst"; metaphorically, in this context, "sudden occurrence." The New Latin term first appeared in Johannes Varandaeus' 1620 treatise on gynaecology *Tractatus de affectibus Renum et Vesicae*.[29] The term toxemia of pregnancy is no longer recommended: placental toxins are not the cause of eclampsia occurrences, as previously believed.[30]

## Popular culture [edit]

In *Downton Abbey*, an historical drama television series, the character (in season 3, episode 5) Lady Sybil dies of eclampsia shortly after child birth.[31]

In *Call the Midwife*, a medical drama television series set in London in the 1950s and 1960s, the character (in season 1, episode 4) named Margaret Jones is struck with pre-eclampsia, ultimately proceeding from a comatose condition to death. The term "toxemia" was also used for the condition, in the dialogue.[32]

## References [edit]


1. ^ *a b c d e f* "40". *Williams obstetrics* (24th ed.). McGraw-Hill Professional. 2014. ISBN 9780071798938.
2. ^ Lambert, G; Brichant, JF; Hartstein, G; Bonhomme, V; Dewandre, PY (2014). "Preeclampsia: an update.". *Acta Anaesthesiologica Belgica*. **65** (4): 137–49. PMID 25622379.
3. ^ "Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy." (PDF). *Obstet Gynecol*. **122** (5): 1122–31. November 2013. doi:10.1097/01.AOG.0000437382.03963.88. PMID 24150027.
4. ^ *WHO recommendations for prevention and treatment of pre-*

PMID 7726272.
15. ^ Chesley LC, Annitto JE, Cosgrove RA (September 1968). "The familial factor in toxemia of pregnancy". *Obstet Gynecol*. **32** (3): 303–11. PMID 5742111.
16. ^ *a b c d* Roberts JM, Cooper DW (January 2001). "Pathogenesis and genetics of pre-eclampsia". *Lancet*. **357** (9249): 53–6. doi:10.1016/S0140-6736(00)03577-7. PMID 11197372.
17. ^ Zhou Y, Fisher SJ, Janatpour M, et al. (May 1997). "Human cytotrophoblasts adopt a vascular phenotype as they differentiate. A strategy for successful endovascular invasion?

*eclampsia and eclampsia.* (PDF). 2011. ISBN 978-92-4-154833-5.
5. ^ Henderson, JT; Whitlock, EP; O'Connor, E; Senger, CA; Thompson, JH; Rowland, MG (20 May 2014). "Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force.". *Annals of Internal Medicine*. **160** (10): 695–703. doi:10.7326/M13-2844. PMID 24711050.
6. ^ *a b* Smith, JM; Lowe, RF; Fullerton, J; Currie, SM; Harris, L; Felker-Kantor, E (5 February 2013). "An integrative review of the side effects related to the use of magnesium sulfate for pre-eclampsia and eclampsia management.". *BMC pregnancy and childbirth*. **13**: 34. doi:10.1186/1471-2393-13-34. PMC 3570392. PMID 23383864.
7. ^ McDonald, SD; Lutsiv, O; Dzaja, N; Duley, L (August 2012). "A systematic review of maternal and infant outcomes following magnesium sulfate for pre-eclampsia/eclampsia in real-world use.". *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. **118** (2): 90–6. doi:10.1016/j.ijgo.2012.01.028. PMID 22703834.
8. ^ Abalos, E; Cuesta, C; Grosso, AL; Chou, D; Say, L (September 2013). "Global and regional estimates of preeclampsia and eclampsia: a systematic review.". *European journal of obstetrics, gynecology, and reproductive biology*. **170** (1): 1–7. doi:10.1016/j.ejogrb.2013.05.005. PMID 23746796.
9. ^ Arulkumaran, N.; Lightstone, L. (December 2013). "Severe pre-eclampsia and hypertensive crises". *Best Practice & Research Clinical Obstetrics & Gynaecology*. **27** (6): 877–884. doi:10.1016/j.bpobgyn.2013.07.003. PMID 23962474.
10. ^ GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385**: 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
11. ^ Emile R. Mohler (2006). *Advanced Therapy in Hypertension and Vascular Disease*. PMPH-USA. pp. 407–408. ISBN 9781550093186.
12. ^ Kane SC, Dennis A, da Silva Costa F, Kornman L, Brennecke S (2013). "Contemporary Clinical Management of the Cerebral Complications of Preeclampsia". *Obstetrics and Gynecology International*. **2013**: 985606. doi:10.1155/2013/985606. PMC 3893864. PMID 24489551.
13. ^ *a b c d* "ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002". *Obstet Gynecol*. **99** (1): 159–67. January 2002. doi:10.1016/s0029-7844(01)01747-1. PMID 16175681.
14. ^ Cunningham FG, Fernandez CO, Hernandez C (April 1995). "Blindness associated with preeclampsia and eclampsia". *American journal of obstetrics and gynecology*. **172** (4 Pt 1): 1291–8. doi:10.1016/0002-9378(95)91495-1.
"*J. Clin. Invest*. **99** (9): 2139–51. doi:10.1172/JCI119387. PMC 508044. PMID 9151786.
18. ^ Li H, Dakour J, Kaufman S, Guilbert LJ, Winkler-Lowen B, Morrish DW (November 2003). "Adrenomedullin is decreased in preeclampsia because of failed response to epidermal growth factor and impaired syncytialization". *Hypertension*. **42** (5): 895–900. doi:10.1161/01.HYP.0000095613.41961.6E. PMID 14517225.
19. ^ "Sex Primes Women for Sperm". BBC News. 6 February 2002. Retrieved 2007-11-19.
20. ^ Cipolla MJ (July 2007). "Cerebrovascular function in pregnancy and eclampsia". *Hypertension*. **50** (1): 14–24. doi:10.1161/HYPERTENSIONAHA.106.079442. PMID 17548723.
21. ^ Richards A, Graham D, Bullock R (March 1988). "Clinicopathological study of neurological complications due to hypertensive disorders of pregnancy". *J. Neurol. Neurosurg. Psychiatr*. **51** (3): 416–21. doi:10.1136/jnnp.51.3.416. PMC 1032870. PMID 3361333.
22. ^ Rozenberg, P. (Jan 2006). "Magnesium sulphate for the management of preeclampsia". *Gynecol Obstet Fertil* (in French). **34** (1): 54–9. doi:10.1016/j.gyobfe.2005.06.025. PMID 16406662.
23. ^ Pritchard JA (February 1955). "The use of the magnesium ion in the management of eclamptogenic toxemias". *Surg Gynecol Obstet*. **100** (2): 131–40. PMID 13238166.
24. ^ Lu JF, Nightingale CH (April 2000). "Magnesium sulfate in eclampsia and pre-eclampsia: pharmacokinetic principles". *Clin Pharmacokinet*. **38** (4): 305–14. doi:10.2165/00003088-200038040-00002. PMID 10803454.
25. ^ "Magnesium Sulfate - FDA prescribing information, side effects and uses". *drugs.com*. Retrieved 4 September 2016.
26. ^ Duley, L; Henderson-Smart, DJ; Walker, GJ; Chou, D (Dec 8, 2010). "Magnesium sulphate versus diazepam for eclampsia.". *The Cochrane database of systematic reviews* (12): CD000127. doi:10.1002/14651858.CD000127.pub2. PMID 21154341.
27. ^ Duley, L; Henderson-Smart, DJ; Chou, D (Oct 6, 2010). "Magnesium sulphate versus phenytoin for eclampsia.". *The Cochrane database of systematic reviews* (10): CD000128. doi:10.1002/14651858.CD000128.pub2. PMID 20927719.
28. ^ Duley, L; Gülmezoglu, AM; Chou, D (Sep 8, 2010). "Magnesium sulphate versus lytic cocktail for eclampsia.". *The Cochrane database of systematic reviews* (9): CD002960. doi:10.1002/14651858.CD002960.pub2. PMID 20824833.
29. ^ Ong, S. (2003). "Pre-eclampsia: A historical perspective". In Baker, P.N.; Kingdom, J.C.P. *Pr-eclampsia: Current perspectives on management*. Taylor & Francis. pp. 15–24. ISBN 1842141805.
30. ^ FAQ: Toxemia at the Pre-Eclampsia Foundation website
31. ^ Stone, Rachel Marie (January 30, 2013). "Stop With All the Dangerous Childbirth Stories Already". *Christianity Today*. Retrieved March 11, 2016.
32. ^ "Episode #1.4". 5 February 2012. Retrieved 4 September 2016 – via IMDb.

## External links [edit]

- Eclampsia at DMOZ

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| | **Oedema, proteinuria and hypertensive disorders** | Gestational hypertension · Pre-eclampsia (HELLP syndrome · · **Eclampsia** · |
| | | Acute fatty liver of pregnancy · Gestational diabetes · |

| | | | |
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| | | **Integumentary system / dermatoses of pregnancy** | Gestational pemphigoid · Impetigo herpetiformis · Intrahepatic cholestasis of pregnancy · Linea nigra · Prurigo gestationis · Pruritic folliculitis of pregnancy · Pruritic urticarial papules and plaques of pregnancy (PUPPP) · Striae gravidarum · |
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Categories: Medical emergencies | Health issues in pregnancy | Disorders causing seizures

# Ectopic pregnancy

From Wikipedia, the free encyclopedia

**Ectopic pregnancy**, also known as **eccyesis** or **tubal pregnancy**, is a complication of pregnancy in which the embryo attaches outside the uterus.[1] Signs and symptoms classically include abdominal pain and vaginal bleeding. Less than 50 percent of women have both of these symptoms. The pain may be described as sharp, dull, or crampy. Pain may also spread to the shoulder if bleeding into the abdomen has occurred.[2] Severe bleeding may result in a fast heart rate, fainting, or shock.[1][2] With very rare exceptions the fetus is unable to survive.[3]

Risk factors for ectopic pregnancy include: pelvic inflammatory disease, often due to Chlamydia infection, tobacco smoking, prior tubal surgery, a history of infertility, and the use of assisted reproductive technology. Those who have previously had an ectopic pregnancy are at much higher risk of having another one. Most ectopic pregnancies (90%) occur in the Fallopian tube which are known as tubal pregnancies.[4] Implantation can also occur on the cervix, ovaries, or within the abdomen.[2] Detection of ectopic pregnancy is typically by blood tests for human chorionic gonadotropin (hCG) and ultrasound. This may require testing on more than one occasion. Ultrasound works best when performed from within the vagina. Other causes of similar symptoms include: miscarriage, ovarian torsion, and acute appendicitis.[2]

Prevention is by decreasing risk factors such as chlamydia infections through screening and treatment.[5] While some ectopic pregnancies will resolve without treatment, this approach has not been well studied as of 2014. The use of the medication methotrexate works as well as surgery in some cases. Specifically it works well when the beta-HCG is low and the size of the ectopic is small. Surgery is still typically recommended if the tube has ruptured, there is a fetal heartbeat, or the person's vital signs are unstable.[4] The surgery may be laparoscopic or through a larger incision, known as a laparotomy.[1] Outcomes are generally good with treatment.[4]

The rate of ectopic pregnancy is about 1 and 2% that of live births in developed countries, though it may be as high as 4% among those using assisted reproductive technology.[1] It is the most common cause of death during the first trimester at approximately 10% of the total.[4] In the developed world outcomes have improved while in the developing world they often remain poor.[5] The risk of death among those in the developed world is between 0.1 and 0.3 percent while in the developing world it is between one and three percent.[6] The first known description of an ectopic pregnancy is by Albucasis in the 11th century.[5] The word "ectopic" means "out of place".[7]

Contents


**Ectopic pregnancy**

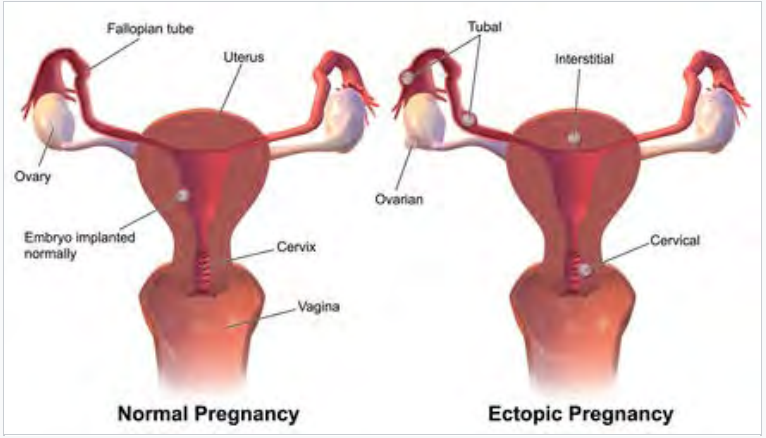
Laparoscopic view, looking down at the uterus (marked by blue arrows). In the left Fallopian tube there is an ectopic pregnancy and bleeding (marked by red arrows). The right tube is normal.

| Classification and external resources | |
|---|---|
| **Specialty** | Obstetrics and gynecology |
| **ICD-10** | O00 |
| **ICD-9-CM** | 633 |
| **DiseasesDB** | 4089 |
| **MedlinePlus** | 000895 |
| **eMedicine** | med/3212 emerg/478 radio/231 |
| **Patient UK** | Ectopic pregnancy |
| **MeSH** | D011271 |

[edit on Wikidata]

## Signs and symptoms [edit]

Up to 10% of women with ectopic pregnancy have no symptoms, and one-third have no medical signs.[1] In many cases the symptoms have low specificity, and can be similar to those of other genitourinary and gastrointestinal disorders, such as appendicitis, salpingitis, rupture of a corpus luteum cyst, miscarriage, ovarian torsion or urinary tract infection.[1] Clinical presentation of ectopic pregnancy occurs at a mean of 7.2 weeks after the last normal menstrual period, with a range of 4 to 8 weeks. Later presentations are more common in communities deprived of modern diagnostic ability.



Ectopic pregnancy.

Signs and symptoms of ectopic pregnancy include increased hCG, vaginal bleeding (in varying amounts), sudden lower abdominal pain,[1] pelvic pain, a tender cervix, an adnexal mass, or adnexal tenderness.[2] In the absence of ultrasound or hCG assessment, heavy vaginal bleeding may lead to a misdiagnosis of miscarriage.[1] Nausea, vomiting and diarrhea are more rare symptoms of ectopic pregnancy.[1]

Rupture of an ectopic pregnancy can lead to symptoms such as abdominal distension, tenderness, peritonism and hypovolemic shock.[1] A woman with ectopic pregnancy may be excessively mobile with upright posturing, in order to decrease intrapelvic blood flow, which can lead to swelling of the abdominal cavity and cause additional pain.[8]

## Causes [edit]

There are a number of risk factors for ectopic pregnancies. However, in as many as one third[9] to one half[10] no risk factors can be identified. Risk factors include: pelvic inflammatory disease, infertility, use of an intrauterine device (IUD), previous exposure to DES, tubal surgery, intrauterine surgery (e.g. D&C), smoking, previous ectopic pregnancy, endometriosis, and tubal ligation.[11][12] A previous induced abortion does not appear to increase the risk.[13]

### Tube damage [edit]

Tubal pregnancy is when the egg is implanted in the Fallopian tubes. Hair-like cilia located on the internal surface of the Fallopian tubes carry the fertilized egg to the uterus. Fallopian cilia are sometimes seen in reduced numbers subsequent to an ectopic pregnancy, leading to a hypothesis that cilia damage in the Fallopian tubes is likely to lead to an ectopic pregnancy.[14] Women who smoke have a higher chance of an ectopic pregnancy in the fallopian tubes. Smoking leads to risk factors of damaging and or killing cilia.[14] As cilia degenerate the amount of time it takes for the fertilized egg to reach the uterus will increase. The fertilized egg, if it doesn't reach the uterus in time, will hatch from the non-adhesive zona pellucida and implant itself inside the fallopian tube, thus causing the pregnancy.

Women with pelvic inflammatory disease (PID) have a high occurrence of ectopic pregnancy.[15] This results from the build-up of scar tissue in the Fallopian tubes, causing damage to cilia.[16] If however both tubes were completely blocked, so that sperm and egg were physically unable to meet, then fertilization of the egg would naturally be impossible, and neither normal pregnancy nor ectopic pregnancy could occur. Intrauterine adhesions (IUA) present in Asherman's syndrome can cause ectopic cervical pregnancy or, if adhesions partially block access to the tubes via the ostia, ectopic tubal pregnancy.[17][18][19] Asherman's syndrome usually occurs from intrauterine surgery, most commonly after D&C.[17] Endometrial/pelvic/genital

tuberculosis, another cause of Asherman's syndrome, can also lead to ectopic pregnancy as infection may lead to tubal adhesions in addition to intrauterine adhesions.[20]

Tubal ligation can predispose to ectopic pregnancy. Reversal of tubal sterilization (Tubal reversal) carries a risk for ectopic pregnancy. This is higher if more destructive methods of tubal ligation (tubal cautery, partial removal of the tubes) have been used than less destructive methods (tubal clipping). A history of a tubal pregnancy increases the risk of future occurrences to about 10%.[16] This risk is not reduced by removing the affected tube, even if the other tube appears normal. The best method for diagnosing this is to do an early ultrasound.

### Other [edit]

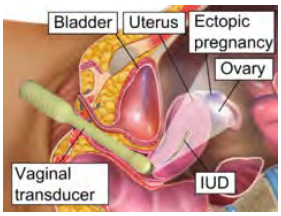
Although some investigations have shown that patients may be at higher risk for ectopic pregnancy with advancing age, it is believed that age is a variable which could act as a surrogate for other risk factors. Vaginal douching is thought by some to increase ectopic pregnancies.[16] Women exposed to diethylstilbestrol (DES) in utero (also known as "DES daughters") also have an elevated risk of ectopic pregnancy.[21] It has also been suggested that pathologic generation of nitric oxide through increased iNOS production may decrease tubal ciliary beats and smooth muscle contractions and thus affect embryo transport, which may consequently result in ectopic pregnancy.[22] The low socioeconomic status may be risk factors for ectopic pregnancy.[23]

## Diagnosis [edit]

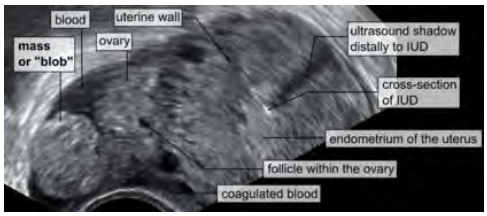
An ectopic pregnancy should be considered as the cause of abdominal pain or vaginal bleeding in every woman who has a positive pregnancy test.[2] The primary goal of diagnostic procedures in possible ectopic pregnancy is to triage according to risk rather than establishing pregnancy location.[1]

### Transvaginal ultrasonography [edit]

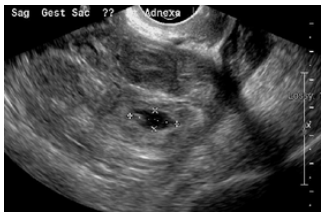
An ultrasound showing a gestational sac with fetal heart in the fallopian tube has a very high specificity of ectopic pregnancy. Transvaginal ultrasonography has a sensitivity of at least 90% for ectopic pregnancy.[1] The diagnostic ultrasonographic finding in ectopic pregnancy is an adnexal mass that moves separately from the ovary. In around 60% of cases, it is an inhomogeneous or a noncystic adnexal mass sometimes known as the "blob sign". It is generally spherical, but a more tubular appearance may be seen in case of hematosalpinx. This sign has been estimated to have a sensitivity of 84% and specificity of 99% in diagnosing ectopic pregnancy.[1] In the study estimating these values, the blob sign had a positive predictive value of 96% and a negative predictive value of 95%.[1] The visualization of an empty extrauterine gestational sac is sometimes known as the "bagel sign", and is present in around 20% of cases.[1] In another 20% of cases, there is visualization of a gestational sac containing a yolk sac and/or an embryo.[1] Ectopic pregnancies where there is visualization of cardiac activity are sometimes termed "viable ectopic".[1]




Transvaginal ultrasonography of an ectopic pregnancy, showing the field of view in the following image.




A "blob sign", which consists of the ectopic pregnancy. The ovary is distinguished from it by having follicles, whereof one is visible in the field. This patient had an intrauterine device (IUD) with progestogen, whose cross-section is visible in the field, leaving an ultrasound shadow distally to it.




Ultrasound image showing an ectopic pregnancy where a gestational sac and fetus has been formed.

The combination of a positive pregnancy test and the presence of what appears to be a normal intrauterine pregnancy does not exclude an ectopic pregnancy, since there may be either a heterotopic pregnancy or a "pseudosac", which is a collection of within the endometrial cavity that may be seen in up to 20% of women.[1]

A small amount of anechogenic free fluid in the rectouterine pouch is commonly found in both intrauterine and ectopic pregnancies.[1] The presence of echogenic fluid is estimated at between 28 and 56% of women with an ectopic pregnancy, and strongly indicates the presence of hemoperitoneum.[1] However, it does not necessarily result from tubal rupture, but is commonly a result from leakage from the distal tubal opening.[1] As a rule of thumb, the finding of free fluid is significant if it reaches the fundus or is present in the vesico-uterine pouch.[1] A further marker of serious intra-abdominal bleeding is the

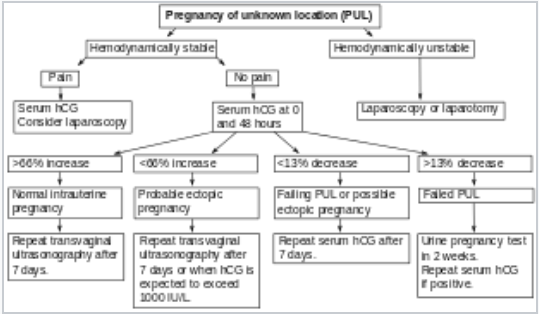
presence of fluid in the hepatorenal recess of the subhepatic space.[1]

Currently, Doppler ultrasonography is not considered to significantly contribute to the diagnosis of ectopic pregnancy.[1]

A common misdiagnosis is of a normal intrauterine pregnancy is where the pregnancy is implanted laterally in an arcuate uterus, potentially being misdiagnosed as an interstitial pregnancy.[1]

## Ultrasonography and β-hCG [edit]

Where no intrauterine pregnancy is seen on ultrasound, measuring β-human chorionic gonadotropin (β-hCG) levels may aid in the diagnosis. The rationale is that a low β-hCG level may indicate that the pregnancy is intrauterine but yet too small to be visible on ultrasonography. While some physicians consider that the threshold where an intrauterine pregnancy should be visible on transvaginal ultrasound is around 1500 IU/ml of β-hCG, a review in the JAMA Rational Clinical Examination Series showed that there is no single threshold for the β-human chorionic gonadotropin that confirms an ectopic pregnancy. Instead, the best test in a pregnant woman is a high resolution transvaginal ultrasound.[2] The presence of an adnexal mass in the absence of an intrauterine pregnancy on transvaginal sonography increases the likelihood of an ectopic pregnancy 100-fold (LR+ 111). When there are no adnexal abnormalities on transvaginal sonography, the likelihood of an ectopic pregnancy decreases (LR- 0.12). An empty uterus with levels higher than 1500 IU/ml may be evidence of an ectopic pregnancy, but may also be consistent with an intrauterine pregnancy which is simply too small to be seen on ultrasound. If the diagnosis is uncertain, it may be necessary to wait a few days and repeat the blood work. This can be done by measuring the β-hCG level approximately 48 hours later and repeating the ultrasound. The serum hCG ratios and logistic regression models appear to be better than absolute single serum hCG level.[24] If the β-hCG falls on repeat examination, this strongly suggests a spontaneous abortion or rupture. The fall in serum hCG over 48 hours may be measured as the hCG ratio, which is calculated as:[1]




Algorithm of the management of a pregnancy of unknown location, that is, a positive pregnancy test but no pregnancy is found on transvaginal ultrasonography.[1] If serum hCG at 0 hours is more than 1000 IU/L and there is no history suggestive of complete miscarriage, the ultrasonography should be repeated as soon as possible.[1]

An hCG ratio of 0.87, that is, a decrease in hCG of 13% over 48 hours, has a sensitivity of 93% and specificity of 97% for predicting a failing PUL.[1] The majority of cases of ectopic pregnancy will have serial serum hCG levels that increase more slowly than would be expected with an IUP (that is, a *suboptimal rise*), or decrease more slowly than would be expected with a failing PUL. However, up to 20% of cases of ectopic pregnancy have serum hCG doubling times similar to that of an IUP, and around 10% of EP cases have hCG patterns similar to a failing PUL.[1]

## Other diagnostic methods [edit]

A laparoscopy or laparotomy can also be performed to visually confirm an ectopic pregnancy. This is generally reserved for women presenting with signs of an acute abdomen and/or hypovolemic shock.[1] Often if a tubal abortion or tubal rupture has occurred, it is difficult to find the pregnancy tissue. A laparoscopy in very early ectopic pregnancy rarely shows a normal looking fallopian tube.

Culdocentesis, in which fluid is retrieved from the space separating the vagina and rectum, is a less commonly performed test that may be used to look for internal bleeding. In this test, a needle is inserted into the space at the very top of the vagina, behind the uterus and in front of the rectum. Any blood or fluid found may have been derived from a ruptured ectopic pregnancy.

Progesterone levels of less than 20 nmol/l have a high predictive value for failing pregnancies, whilst levels over 25 nmol/l are likely to predict viable pregnancies, and levels over 60 nmol/l are strongly so. This may help in identifying failing PULs that are at low risk and thereby needing less follow-up.[1] Inhibin A may also be useful for predicting spontaneous resolution of PUL, but is not as good as progesterone for this purpose.[1]

In addition, there are various mathematical models, such as logistic regression models and Bayesian networks, for the prediction of PUL outcome based on multiple parameters.[1] Mathematical models also aim to identify PULs that are *low risk*, that is, failing PULs and IUPs.[1]

Dilation and curettage is sometimes used to diagnose pregnancy location with the aim of differentiating between an EP and a non-viable IUP in situations where a viable IUP can be ruled out. Specific indications for this procedure include either of the following:[1]

- no visible IUP on transvaginal ultrasonography with a serum hCG of more than 2000 IU/ml
- an abnormal rise in hCG level. A rise of 35% over 48 hours is proposed as the minimal rise consistent with a viable intrauterine pregnancy.

- an abnormal fall in hCG level, such as defined as one of less than 20% in 2 days

## Classification [edit]

### Tubal pregnancy [edit]

The vast majority of ectopic pregnancies implant in the Fallopian tube. Pregnancies can grow in the fimabrial end (5% of all ectopic pregnancies), the ampullary section (80%), the isthmus (12%), and the cornual and interstitial part of the tube (2%).[16] Mortality of a tubal pregnancy at the isthmus or within the uterus (interstitial pregnancy) is higher as there is increased vascularity that may result more likely in sudden major internal bleeding. A review published in 2010 supports the hypothesis that tubal ectopic pregnancy is caused by a combination of retention of the embryo within the fallopian tube due to impaired embryo-tubal transport and alterations in the tubal environment allowing early implantation to occur.[25]

### Nontubal ectopic pregnancy [edit]

Two percent of ectopic pregnancies occur in the ovary, cervix, or are intraabdominal. Transvaginal ultrasound examination is usually able to detect a cervical pregnancy. An ovarian pregnancy is differentiated from a tubal pregnancy by the Spiegelberg criteria.[26]

While a fetus of ectopic pregnancy is typically not viable, very rarely, a live baby has been delivered from an abdominal pregnancy. In such a situation the placenta sits on the intraabdominal organs or the peritoneum and has found sufficient blood supply. This is generally bowel or mesentery, but other sites, such as the renal (kidney), liver or hepatic (liver) artery or even aorta have been described. Support to near viability has occasionally been described, but even in third world countries, the diagnosis is most commonly made at 16 to 20 weeks gestation. Such a fetus would have to be delivered by laparotomy. Maternal morbidity and mortality from extrauterine pregnancy are high as attempts to remove the placenta from the organs to which it is attached usually lead to uncontrollable bleeding from the attachment site. If the organ to which the placenta is attached is removable, such as a section of bowel, then the placenta should be removed together with that organ. This is such a rare occurrence that true data are unavailable and reliance must be made on anecdotal reports.[27][28][29] However, the vast majority of abdominal pregnancies require intervention well before fetal viability because of the risk of bleeding.

### Heterotopic pregnancy [edit]

In rare cases of ectopic pregnancy, there may be two fertilized eggs, one outside the uterus and the other inside. This is called a heterotopic pregnancy.[2] Often the intrauterine pregnancy is discovered later than the ectopic, mainly because of the painful emergency nature of ectopic pregnancies. Since ectopic pregnancies are normally discovered and removed very early in the pregnancy, an ultrasound may not find the additional pregnancy inside the uterus. When hCG levels continue to rise after the removal of the ectopic pregnancy, there is the chance that a pregnancy inside the uterus is still viable. This is normally discovered through an ultrasound.

Although rare, heterotopic pregnancies are becoming more common, likely due to increased use of IVF. The survival rate of the uterine fetus of an ectopic pregnancy is around 70%.[30]

### Persistent ectopic pregnancy [edit]

A persistent ectopic pregnancy refers to the continuation of trophoblastic growth after a surgical intervention to remove an ectopic pregnancy. After a conservative procedure that attempts to preserve the affected fallopian tube such as a salpingotomy, in about 15-20% the major portion of the ectopic growth may have been removed, but some trophoblastic tissue, perhaps deeply embedded, has escaped removal and continues to grow, generating a new rise in hCG levels.[31] After weeks this may lead to new clinical symptoms including bleeding. For this reason hCG levels may have to be monitored after removal of an ectopic pregnancy to assure their decline, also methotrexate can be given at the time of surgery prophylactically.

### Pregnancy of unknown location [edit]

Pregnancy of unknown location (PUL) is the term used for a pregnancy where there is a positive pregnancy test but no pregnancy has been visualized using transvaginal ultrasonography.[1] Specialized early pregnancy departments have estimated that between 8 and 10% of women attending for an ultrasound assessment in early pregnancy will be classified as having a PUL.[1] The true nature of the pregnancy can be an ongoing viable intrauterine pregnancy, a failed pregnancy, an ectopic pregnancy or rarely a persisting PUL.[1]

Because of frequent ambiguity on ultrasonography examinations, the following classification is proposed:[1]

| Condition | Criteria |
|---|---|
| Definite ectopic pregnancy | Extrauterine gestational sac with yolk sac and/or embryo (with or without cardiac activity). |

| | |
|---|---|
| Pregnancy of unknown location - probable ectopic pregnancy | Inhomogeneous adnexal mass or extrauterine sac-like structure. |
| "True" pregnancy of unknown location | No signs of intrauterine nor extrauterine pregnancy on transvaginal ultrasonography. |
| Pregnancy of unknown location - probable intrauterine pregnancy | Intrauterine gestational sac-like structure. |
| Definite intrauterine pregnancy | Intrauterine gestational sac with yolk sac and/or embryo (with or without cardiac activity). |

In women with a pregnancy of unknown location, between 6% and 20% have an ectopic pregnancy.[1] In cases of pregnancy of unknown location and a history of heavy bleeding, is has been estimated that approximately 6% have an underlying ectopic pregnancy.[1] Between 30 and 47% of women with pregnancy of unknown location are ultimately diagnosed with an ongoing intrauterine pregnancy, whereof the majority (50 –70%) will be found to have failing pregnancies where the location is never confirmed.[1]

Persisting PUL is where the hCG level does not spontaneously decline and no intrauterine or ectopic pregnancy is identified on follow-up transvaginal ultrasonography.[1] A persisting PUL is likely either a small ectopic pregnancy that has not been visualized, or a retained trophoblast in the endometrial cavity.[1] Treatment should only be considered when a potentially viable intrauterine pregnancy has been definitively excluded.[1] A *treated persistent PUL* is defined as one managed medically (generally with methotrexate) without confirmation of the location of the pregnancy such as by ultrasound, laparoscopy or uterine evacuation.[1] A *resolved persistent PUL* is defined as serum hCG reaching a non-pregnant value (generally less than 5 IU/l) after expectant management, or after uterine evacuation without evidence of chorionic villi on histopathological examination.[1] In contrast, a relatively low and unresolving level of serum hCG indicates the possibility of an hCG-secreting tumour.[1]

### Differential diagnosis [edit]

Other conditions that cause similar symptoms include: miscarriage, ovarian torsion, and acute appendicitis, ruptured ovarian cyst, kidney stone, and pelvic inflammatory disease, among others.[2]

## Treatment [edit]

### Expectant management [edit]

Most women with a PUL are followed up with serum hCG measurements and repeat TVS examinations until a final diagnosis is confirmed.[1] Low-risk cases of PUL that appear to be failing pregnancies may be followed up with a urinary pregnancy test after 2 weeks and get subsequent telephone advice.[1] Low-risk cases of PUL that are likely intrauterine pregnancies may have another TVS in 2 weeks to access viability.[1] High-risk cases of PUL require further assessment, either with a TVS within 48 h or additional hCG measurement.[1]

### Medical [edit]

Early treatment of an ectopic pregnancy with methotrexate is a viable alternative to surgical treatment[32] which was developed in the 1980s.[33] If administered early in the pregnancy, methotrexate terminates the growth of the developing embryo; this may cause an abortion, or the developing embryo may then be either resorbed by the woman's body or pass with a menstrual period. Contraindications include liver, kidney, or blood disease, as well as an ectopic embryonic mass > 3.5 cm.

Also, it may lead to the inadvertent termination of an undetected intrauterine pregnancy, or severe abnormality in any surviving pregnancy.[1] Therefore, it is recommended that methotrexate should only be administered when hCG has been serially monitored with a rise less than 35% over 48 hours, which practically excludes a viable intrauterine pregnancy.[1]

### Surgical [edit]

If bleeding has already occurred, surgical intervention may be necessary. However, whether to pursue surgical intervention is an often difficult decision in a stable patient with minimal evidence of blood clot on ultrasound.[*citation needed*]

Surgeons use laparoscopy or laparotomy to gain access to the pelvis and can either incise the affected Fallopian and remove only the pregnancy (salpingostomy) or remove the affected tube with the pregnancy (salpingectomy). The first successful surgery for an ectopic pregnancy was performed by Robert Lawson Tait in 1883.[34] It is estimated that

an acceptable rate of PULs that eventually undergo surgery is between 0.5 and 11%.[1]

Autotransfusion of a woman's own blood as drained during surgery may be useful in those who have a lot of bleeding into their abdomen.[35]

Published reports that a re-implanted embryo survived to birth were debunked as false.[36]

## Complications [edit]

The most common complication is rupture with internal bleeding which may lead to hypovolemic shock. Death from rupture is still the leading cause of death in the first trimester of the pregnancy.[*citation needed*]

## Prognosis [edit]

When ectopic pregnancies are treated, the prognosis for the mother is very good in Western countries; maternal death is rare, but most fetuses die or are aborted. For instance, in the UK, between 2003 and 2005 there were 32,100 ectopic pregnancies resulting in 10 maternal deaths (meaning that 1 in 3,210 women with an ectopic pregnancy died).[37]

In the developing world, however, especially in Africa, the death rate is very high, and ectopic pregnancies are a major cause of death among women of childbearing age.

### Future fertility [edit]

Fertility following ectopic pregnancy depends upon several factors, the most important of which is a prior history of infertility.[38] The treatment choice does not play a major role; A randomized study in 2013 concluded that the rates of intrauterine pregnancy 2 years after treatment of ectopic pregnancy are approximately 64% with radical surgery, 67% with medication, and 70% with conservative surgery.[39] In comparison, the cumulative pregnancy rate of women under 40 years of age in the general population over 2 years is over 90%.[40]

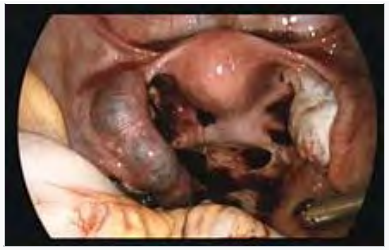
## Epidemiology [edit]

The rate of ectopic pregnancy is about 1 and 2% of that of live births in developed countries, though it is as high as 4% in pregnancies involving assisted reproductive technology.[1] Between 93 and 97% of ectopic pregnancies are located in a Fallopian tube.[2] Of these, in turn, 13% are located in the isthmus, 75% are located in the ampulla, and 12% in the fimbriae.[1] Ectopic pregnancy is responsible for 6% of maternal deaths during the first trimester of pregnancy making it the leading cause of maternal death during this stage of pregnancy.[2]

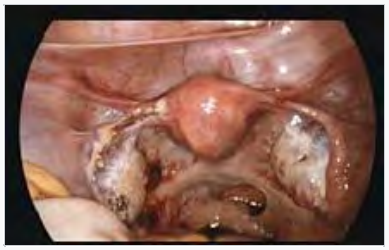
Between 5% and 42% of women seen for ultrasound assessment with a positive pregnancy test have a *pregnancy of unknown location* (PUL), that is a positive pregnancy test but no pregnancy visualized at transvaginal ultrasonography.[1] Between 6 and 20% of PUL are subsequently diagnosed with actual ectopic pregnancy.[1]

## Society and culture [edit]

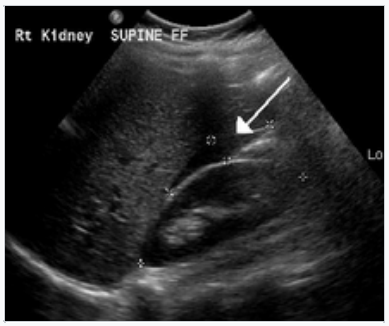
Salpingectomy as a treatment for ectopic pregnancy is one of the common cases when the principle of double effect can be used to justify accelerating the death of the embryo by doctors and patients opposed to outright abortions.[42]



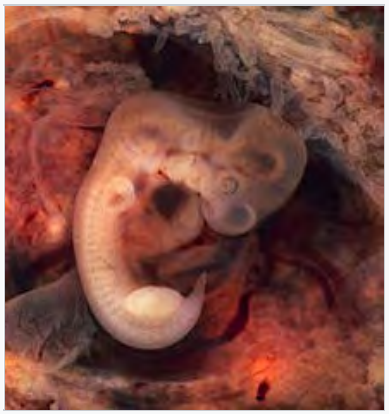
Surgical treatment: Laparoscopic view of an ectopics pregnancy located in the left Fallopian tube, hematosalpinx is present on the left, the right tube is of normal appearance



The left Fallopian tube containing the ectopic pregnancy has been removed (salpingectomy).




Blood in Morrison's pouch between the liver and kidney due to a ruptured ectopic pregnancy



An opened oviduct with an ectopic pregnancy at about 7 [41]

weeks gestational age.

In the Catholic church, there are moral debates on certain treatments. A significant number of Catholic moralists consider use of methotrexate and the salpingostomy procedure to be not "morally permissible" because they destroy the embryo; however situations are considered differently in which the mother's health in endangered, and the whole fallopian tube with the developing embryo inside is removed.[43][44]

## Live birth [edit]

There have been cases where ectopic pregnancy lasted many months and ended in a live baby delivered by laparotomy.

In July 1999, Lori Dalton gave birth by Cesarean section in Ogden, Utah, United States, to a healthy baby girl who had developed outside of the uterus. Previous ultrasounds had not discovered the problem. "[Sage Dalton]'s delivery was slated as a routine Cesarean birth at Ogden Regional Medical Center in Utah. When Dr. Naisbitt performed Lori's Cesarean, he was astonished to find Sage within the amniotic membrane outside the womb [...]."[45] "But what makes this case so rare is that not only did mother and baby survive — they're both in perfect health. John Dalton [(the father)] took home video inside the delivery room. Sage came out doing extremely well because even though she had been implanted outside the womb, a rich blood supply from a uterine fibroid along the outer uterus wall had nourished her with a rich source of blood."[46]

On 19 April 2008 an English woman, Jayne Jones (age 37) who had an ectopic pregnancy attached to the omentum, the fatty covering of her large bowel, gave birth to her son Billy by a laparotomy at 28 weeks gestation. The surgery, the first of its kind to be performed in the UK, was successful, and both mother and baby survived.[47]

On May 29, 2008 an Australian woman, Meera Thangarajah (age 34), who had an ectopic pregnancy in the ovary, gave birth to a healthy full term 6 pound 3 ounce (2.8 kg) baby girl, Durga, via Cesarean section. She had no problems or complications during the 38 week pregnancy.[48][49]

In September 1999 an English woman, Jane Ingram (age 32) gave birth to triplets: Olivia, Mary and Ronan, with an extrauterine fetus (Ronan) below the womb and twins in the womb. All three survived. The twins in the womb were taken out first.[50]

## Other animals [edit]

Ectopic gestation exists in mammals other than humans. In sheep, it can go to term, with mammary preparation to parturition, and expulsion efforts. The fetus can be removed by cesarian section. Pictures of cesarian section of a euthanized ewe, 5 days after parturition signs.

Leg of fetal lamb appearing out of the uterus during cesarian section.

External view of fetal sac, necrotic distal part.

Internal view of fetal sac, before resection of distal necrotic part.

Internal view of fetal sac, the necrotic distal part is to the left.

External side of fetal sac, proximal end, with ovary and uterine horn.

Resected distal part of fetal sac, with attached placenta.

## References [edit]

1. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z aa ab ac ad ae af ag ah ai aj ak al am an ao ap aq ar as at au av aw ax ay az ba bb bc bd be bf bg bh* Kirk E, Bottomley C, Bourne T (2014). "Diagnosing ectopic pregnancy and current concepts in the management of pregnancy of unknown location". *Hum. Reprod. Update*. **20** (2): 250–61. doi:10.1093/humupd/dmt047. PMID 24101604.
2. ^ *a b c d e f g h i j k* Crochet JR, Bastian LA, Chireau MV (2013). "Does this woman have an ectopic pregnancy?: the rational clinical examination systematic review". *JAMA*. **309** (16): 1722–9. doi:10.1001/jama.2013.3914. PMID 23613077.
3. ^ Zhang, J; Li, F; Sheng, Q (2008). "Full-term abdominal pregnancy: a case report and review of the literature.". *Gynecologic and obstetric investigation*. **65** (2): 139–41. doi:10.1159/000110015. PMID 17957101.
4. ^ *a b c d* Cecchino, GN; Araujo Júnior, E; Elito Júnior, J (September 2014). "Methotrexate for ectopic pregnancy: when and how.". *Archives of gynecology and obstetrics*. **290** (3): 417–23. doi:10.1007/s00404-014-3266-9. PMID 24791968.
5. ^ *a b c* Nama, V; Manyonda, I (April 2009). "Tubal ectopic pregnancy: diagnosis and management.". *Archives of gynecology and obstetrics*. **279** (4): 443–53. doi:10.1007/s00404-008-0731-3. PMID 18665380.
6. ^ Mignini L (26 September 2007). "Interventions for tubal ectopic pregnancy". *who.int*. The WHO Reproductive Health Library. Retrieved 12 March 2015.
7. ^ Cornog, Mary Wood (1998). *Merriam-Webster's vocabulary uilder*. Springfield, Mass.: Merriam-Webster. p. 313. ISBN 9780877799108.
8. ^ Skipworth, Richard (17 December 2011). "A new clinical sign in ruptured ectopic pregnancy". *Lancet*. **378** (9809): e27. doi:10.1016/s0140-6736(11)61901-6.
9. ^ Farquhar CM (2005). "Ectopic pregnancy". *Lancet*. **366** (9485): 583–91. doi:10.1016/S0140-6736(05)67103-6. PMID 16099295.
10. ^ Majhi AK, Roy N, Karmakar KS, Banerjee PK (2007). "Ectopic pregnancy--an analysis of 180 cases". *J Indian Med Assoc*. **105** (6): 308, 310, 312 passim. PMID 18232175.
11. ^ "BestBets: Risk Factors for Ectopic Pregnancy".
12. ^ Rana, P; Kazmi, I; Singh, R; Afzal, M; Al-Abbasi, FA; Aseeri, A; Singh, R; Khan, R; Anwar, F (October 2013). "Ectopic pregnancy: a review.". *Archives of gynecology and obstetrics*. **288** (4): 747–57. doi:10.1007/s00404-013-2929-2. PMID 23793551.
13. ^ "16 Answering questions about long term outcomes". *Management of Unintended and Abnormal Pregnancy: Comprehensive Abortion Care*. John Wiley & Sons. 2011. ISBN 9781444358476.
14. ^ *a b* Lyons RA, Saridogan E, Djahanbakhch O (2006). "The reproductive significance of human Fallopian tube cilia". *Hum Reprod Update*. **12** (4): 363–72. doi:10.1093/humupd/dml012. PMID 16565155.
15. ^ Tay JI, Moore J, Walker JJ (2000). "Ectopic pregnancy". *West J. Med*. **173** (2): 131–4. doi:10.1136/ewjm.173.2.131. PMC 1071024. PMID 10924442.
16. ^ *a b c d* Speroff L, Glass RH, Kase NG. *Clinical Gynecological Endocrinology and Infertility, 6th Ed*. Lippincott Williams & Wilkins (1999). p. 1149ff. ISBN 0-683-30379-1.
17. ^ *a b* Schenker JG, Margalioth EJ (1982). "Intra-uterine adhesions: an updated appraisal". *Fertility and Sterility*. **37** (5): 593–610. PMID 6281085.
18. ^ Kłyszejko C, Bogucki J, Kłyszejko D, Ilnicki W, Donotek S, Koźma J (1987). "Cervical pregnancy in Asherman's syndrome [article in Polish].". *Ginekol Pol*. **58** (1): 46–8. PMID 3583040.
19. ^ Dicker D, Feldberg D, Samuel N, Goldman JA (1985). "Etiology of cervical pregnancy. Association with abortion, pelvic pathology, IUDs and Asherman's syndrome.". *J Reprod Med*. **30** (1): 25–7. PMID 4038744.
20. ^ Bukulmez O, Yarali H, Gurgan T (1999). "Total corporal synechiae due to tuberculosis carry a very poor prognosis following hysteroscopic synechialysis". *Human Reproduction*. **14** (8): 1960–1. doi:10.1093/humrep/14.8.1960. PMID 10438408.
21. ^ Schrager S, Potter BE (May 2004). "Diethylstilbestrol exposure". *Am Fam Physician*. **69** (10): 2395–400. PMID 15168959.
22. ^ Al-Azemi M, Refaat B, Amer S, Ola B, Chapman N, Ledger W (May 2009). "The expression of inducible nitric oxide synthase in the human fallopian tube during the menstrual cycle and in ectopic pregnancy". *Fertil. Steril*. **94** (3): 833–840. doi:10.1016/j.fertnstert.2009.04.020. PMID 19482272.
23. ^ Yuk JS, Kim YJ, Hur JY, Shin JH (2013). "Association between socioeconomic status and ectopic pregnancy rate in the Republic of Korea". *Int J Gynaecol Obstet*. **122** (2): 104–7. doi:10.1016/j.ijgo.2013.03.015. PMID 23726169.
24. ^ van Mello NM, Mol F, Opmeer BC, Ankum WM, Barnhart K, Coomarasamy A, Mol BW, van der Veen F, Hajenius PJ (2012). "Diagnostic value of serum hCG on the outcome of pregnancy of unknown location: A systematic review and meta-analysis". *Human Reproduction Update*. **18** (6): 603–617. doi:10.1093/humupd/dms035. PMID 22956411.
25. ^ Shaw JL, Dey SK, Critchley HO, Horne AW (January 2010). "Current knowledge of the aetiology of human tubal ectopic pregnancy". *Hum Reprod Update*. **16** (4): 432–44. doi:10.1093/humupd/dmp057. PMC 2880914. PMID 20071358.
26. ^ *Spiegelberg's criteria* at Who Named It?
27. ^ "'Special' baby grew outside womb". BBC News. 2005-08-30. Retrieved 2006-07-14.
28. ^ "Bowel baby born safely". BBC News. 2005-03-09. Retrieved 2006-11-10.
29. ^ Zhang J, Li F, Sheng Q (2008). "Full-term abdominal pregnancy: a case report and review of the literature". *Gynecol. Obstet. Invest*. **65** (2): 139–41. doi:10.1159/000110015. PMID 17957101.
30. ^ Lau S, Tulandi T (1999). "Conservative medical and surgical management of interstitial ectopic pregnancy". *Fertility and Sterility*. **72** (2): 207–15. doi:10.1016/s0015-0282(99)00242-3. PMID 10438980.
31. ^ Kemmann E, Trout S, Garcia A (February 1994). "Can we predict patients at risk for persistent ectopic pregnancy after laparoscopic salpingotomy?". *The Journal of the American Association of Gynecologic Laparoscopists*. **1** (2): 122–126. doi:10.1016/S1074-3804(05)80774-1. PMID 9050473. Retrieved January 22, 2010.
32. ^ Mahboob U, Mazhar SB (2006). "Management of ectopic pregnancy: a two-year study". *Journal of Ayub Medical College, Abbottabad: JAMC*. **18** (4): 34–7. PMID 17591007.
33. ^ "History, Diagnosis and Management of Ectopic Pregnancy"
34. ^ "eMedicine - Surgical Management of Ectopic Pregnancy: Article Excerpt by R Daniel Braun". Retrieved 2007-09-17.
35. ^ Selo-Ojeme, DO; Onwude, JL; Onwudiegwu, U (February 2003). "Autotransfusion for ruptured ectopic pregnancy.". *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. **80** (2): 103–10. doi:10.1016/s0020-7292(02)00379-x. PMID 12566181.

36. ^ Smith, R (May 2006). "Research misconduct: the poisoning of the well.". *Journal of the Royal Society of Medicine*. **99** (5): 232–7. doi:10.1258/jrsm.99.5.232. PMID 16672756.
37. ^ http://patient.info/doctor/ectopic-pregnancy-pro
38. ^ Togas Tulandi; Tan, S. L; Tan, Seang Lin; Tulandi, T. (2002). *Advances in Reproductive Endocrinology and Infertility: Current Trends and Developments*. Informa Healthcare. p. 240. ISBN 0-8247-0844-X.
39. ^ Fernandez H, Capmas P, Lucot JP, Resch B, Panel P, Bouyer J (2013). "Fertility after ectopic pregnancy: The DEMETER randomized trial". *Human Reproduction*. **28** (5): 1247–1253. doi:10.1093/humrep/det037. PMID 23482340.
40. ^ Fertility: assessment and treatment for people with fertility problems. NICE clinical guideline CG156 - Issued: February 2013
41. ^ Uthman, Ed (2014). "Tubal pregnancy with embryo". *WikiJournal of Medicine*. **1** (2). doi:10.15347/wjm/2014.007.
42. ^ Delgado, George. "Pro-Life Open Forum, Apr 10, 2013 (49min40s)". *Catholic answers*. Retrieved 2 September 2014.
43. ^ Pacholczyk, Rev. Tad, Ph.D. "When Pregnancy Goes Awry". *Making Sense Out of Bioethics (blog)*. National Catholic Bioethics Center. Archived from the original on 2011-11-23.
44. ^ Anderson, MA et al. Ectopic Pregnancy and Catholic Morality. National Catholic Bioethics Quarterly, Spring 2011
45. ^ "Registry Reports" (PDF). *Volume XVI, Number 5*. Ogden, Utah: ARDMS The Ultrasound Choice. October 1999. Retrieved 2011-06-22.
46. ^ "Miracle baby". Ogden, Utah: Utah News from KSL-TV. 1999-08-05. Retrieved 2011-06-22.
47. ^ Collins, Laura (2008-08-31). "Miracle baby Billy grew outside his mother's womb". London: Daily Mail. Retrieved 2008-09-03.
48. ^ "Baby Born After Rare Ovarian Pregnancy". Associated Press. 2008-05-30. Archived from the original on June 3, 2008. Retrieved 2008-05-30.
49. ^ Cavanagh, Rebekah (2008-05-30). "Miracle baby may be a world first". Retrieved 2008-05-30.
50. ^ "Doctors hail 'miracle' baby". *BBC News*. 2009-09-10.


## External links [edit]

- CT of the abdomen showing abdominal ectopic pregnancy
- Brown discharge first trimester - Information and support for pregnant women

Wikimedia Commons has media related to *Ectopic pregnancy*.

| v · t · e | Pathology of pregnancy, childbirth and the puerperium (O, 630–679) | | |
|---|---|---|---|
| **Pregnancy** | **Pregnancy with abortive outcome** | **Ectopic pregnancy** (Abdominal pregnancy · Cervical pregnancy · Interstitial pregnancy · Ovarian pregnancy · · Molar pregnancy · Miscarriage · Stillbirth · | |
| | **Oedema, proteinuria and hypertensive disorders** | Gestational hypertension · Pre-eclampsia (HELLP syndrome · · Eclampsia · | |
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| **Puerperal** | Breastfeeding difficulties (Lactation failure · Galactorrhea · Fissure of the nipple · · Breast engorgement · Diastasis symphysis pubis · Peripartum cardiomyopathy · Postpartum depression · Postpartum thyroiditis · Puerperal fever · Puerperal mastitis · | | |
| | Concomitant conditions (Diabetes mellitus · Systemic lupus erythematosus · Thyroid disorders · · Maternal death · | | |

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|---|---|
| **Other** | Sexual activity during pregnancy · |
| **Authority control** | NDL: 00570984 · |

Categories: Wikipedia articles with sections published in WikiJournal of Medicine | Medical emergencies | Pregnancy with abortive outcome | Health issues in pregnancy | Acute pain




# Endometriosis

From Wikipedia, the free encyclopedia

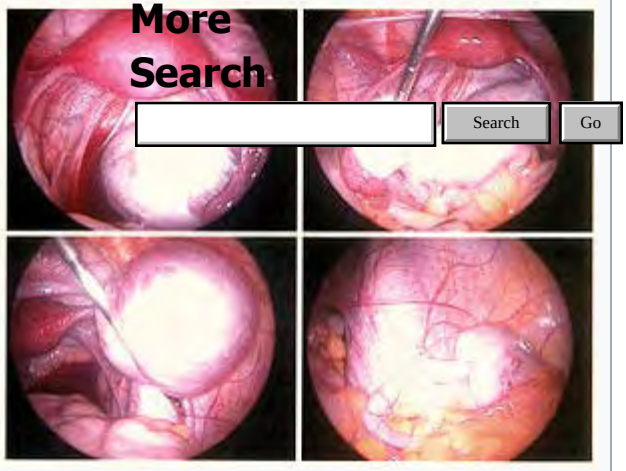
**Endometriosis** is a disease in which tissue that normally grows inside the uterus (endometrium) grows outside it.[1][2] Most often this is on the ovaries, fallopian tubes, and tissue around the uterus and ovaries; however, in rare cases it may also occur in other parts of the body.[3] The main symptoms are pelvic pain and infertility. Nearly half of those affected have chronic pelvic pain, while in 70% pain occurs during menstruation. Pain during sex is also common. Infertility occurs in up to half of women affected.[4] Less common symptoms include urinary or bowel symptoms. About 25% of women have no symptoms.[4] Endometriosis can have both social and psychological effects.[5]

The cause is not entirely clear.[4] Risk factors include having a family history of the condition. The areas of endometriosis bleed each month, resulting in inflammation and scarring.[3][4] The growths due to endometriosis are not cancer.[3] Diagnosis is usually based on symptoms in combination with medical imaging. Biopsy is the most sure method of diagnosis.[3] Other causes of similar symptoms include pelvic inflammatory disease, irritable bowel syndrome, interstitial cystitis, and fibromyalgia.[4]

Tentative evidence suggests that the use of combined oral contraceptives reduces the risk of endometriosis.[6] Exercise and avoiding large amounts of alcohol may also be preventative.[3] There is no cure for endometriosis, but a number of treatments may improve symptoms.[4] This may include pain medication, hormonal treatments, or surgery. The recommended pain medication is usually an NSAID such as naproxen. Taking the active component of the birth control pill continuously or using an intrauterine device with progestogen may also be useful. Gonadotropin-releasing hormone agonist may improve the ability of those who are infertile to get pregnant. Surgical removal of endometriosis may be used to treat those whose symptoms are not manageable with other treatments.[3]

Endometriosis is estimated to occur in roughly 6–10% of women.[4] It is most common in those in their thirties and forties; however, can begin in girls as early as 8 years old.[3][7] It results in few deaths with this being estimated at 200 globally in 2013.[8] Endometriosis was first determined to be a separate condition in the 1920s. Before that time endometriosis and adenomyosis were considered together. It is unclear who first described the disease.[9]

**Endometriosis**



Endometriosis as seen during laparoscopic surgery

| Classification and external resources | |
|---|---|
| **Specialty** | Gynecology |
| **ICD-10** | N80 |
| **ICD-9-CM** | 617.0 |
| **OMIM** | 131200 |
| **DiseasesDB** | 4269 |
| **MedlinePlus** | 000915 |
| **eMedicine** | med/3419 ped/677 emerg/165 |
| **Patient UK** | Endometriosis |
| **MeSH** | D004715 |

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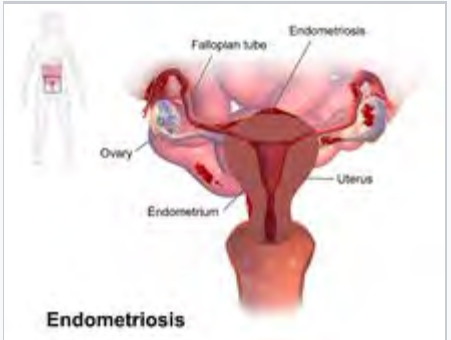
# Signs and symptoms [edit]

Although 20–25% of women with endometriosis have no symptoms, pain and infertility are common signs.[4]




Drawing showing endometriosis.

## Pelvic pain [edit]

A major symptom of endometriosis is recurring pelvic pain. The pain can range from mild to severe cramping or stabbing pain that occurs on both sides of the pelvis, in the lower back and rectal area, and even down the legs. The amount of pain a woman feels correlates poorly with the extent or stage (1 through 4) of endometriosis, with some women having little or no pain despite having extensive endometriosis or endometriosis with scarring, while other women may have severe pain even though they have only a few small areas of endometriosis.[10] Symptoms of endometriosis-related pain may include:[11]

- dysmenorrhea – painful, sometimes disabling cramps during the menstrual period; pain may get worse over time (progressive pain), also lower back pains linked to the pelvis
- chronic pelvic pain – typically accompanied by lower back pain or abdominal pain
- dyspareunia – painful sex
- dysuria – urinary urgency, frequency, and sometimes painful voiding

Throbbing, gnawing, and dragging pain to the legs are reported more commonly by women with

endometriosis.[*unreliable medical source?*][12] Compared with women with superficial endometriosis, those with deep disease appear to be more likely to report shooting rectal pain and a sense of their insides being pulled down.[12] Individual pain areas and pain intensity appears to be unrelated to the surgical diagnosis, and the area of pain unrelated to area of endometriosis.[12]

Endometriosis lesions react to hormonal stimulation and may "bleed" at the time of menstruation. The blood accumulates locally, causes swelling, and triggers inflammatory responses with the activation of cytokines. This process may cause pain. Pain can also occur from adhesions (internal scar tissue) binding internal organs to each other, causing organ dislocation. Fallopian tubes, ovaries, the uterus, the bowels, and the bladder can be bound together in ways that are painful on a daily basis, not just during menstrual periods.[13]

Also, endometriotic lesions can develop their own nerve supply, thereby creating a direct and two-way interaction between lesions and the central nervous system, potentially producing a variety of individual differences in pain that can, in some women, become independent of the disease itself.[10] Nerve fibres and blood vessels are thought to grow into endometriosis lesions by a process known as Neuroangiogenesis.[14]

### Infertility [edit]

*Main article: Endometriosis and infertility*

Many women with infertility may have endometriosis. Among women with endometriosis, up to half may experience infertility.[4]

### Other [edit]

Other symptoms include diarrhea or constipation,[*unreliable medical source?*][12] chronic fatigue,[*medical citation needed*] nausea and vomiting, headaches, low-grade fevers, heavy and/or irregular periods, and hypoglycemia.[*unreliable medical source?*][15]

In addition to pain during menstruation, the pain of endometriosis can occur at other times of the month. There can be a pain with ovulation, pain associated with adhesions, pain caused by inflammation in the pelvic cavity, pain during bowel movements and urination, during general bodily movement like exercise, pain from standing or walking, and pain with intercourse. The most severe pain is typically associated with menstruation. Pain can also start a week before a menstrual period, during and even a week after a menstrual period, or it can be constant. The pain can be debilitating and the emotional stress can take a toll.[16]

There is an association between endometriosis and certain types of cancers, notably some types of ovarian cancer,[17][18] non-Hodgkin's lymphoma and brain cancer.[19] Endometriosis is unrelated to endometrial cancer.[20]

## Risk factors [edit]

### Genetics [edit]

Genetic predisposition plays a role in endometriosis.[21] Daughters or sisters of women with endometriosis are at higher risk of developing endometriosis themselves; low progesterone levels may be genetic, and may contribute to a hormone imbalance.[22] There is an about six-fold increased incidence in women with an affected first-degree relative.[23]

It has been proposed that endometriosis results from a series of multiple hits within target genes, in a mechanism similar to the development of cancer.[21] In this case, the initial mutation may be either somatic or heritable.[21]

Individual genomic changes (found by genotyping including genome-wide association studies) that have been associated with endometriosis include:

- Changes on chromosome 1 near WNT4.[24]
- Changes on chromosome 2 near GREB1.[24]
- Changes on chromosome 6 near ID4.[24]
- Changes on chromosome 7 in the 7p15.2 region.[24][25]
- Changes on chromosome 9 near CDKN2BAS.[24]
- Changes on chromosome 10 at region 10q26.[26]
- Changes on chromosome 12 near VEZT.[24]

In addition, there is a weaker association with changes in the fibronectin gene as well as in the 2p14 region of chromosome 2.[24]

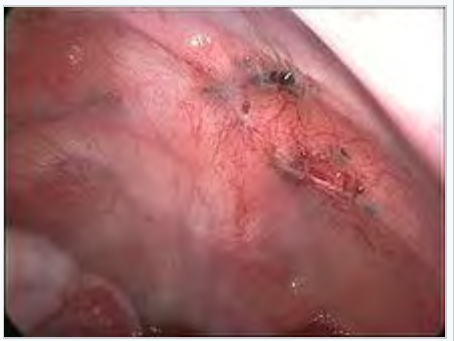
In addition, there are many findings of altered gene expression and epigenetics, but both of these can also be a secondary result of, for example, environmental factors and altered metabolism. Examples of altered gene expression include that of miRNAs.[21]

### Environmental toxins [edit]

Several studies have investigated the potential link between exposure to dioxins and endometriosis, but the evidence is equivocal and potential mechanisms are poorly understood.[27] A 2004 review of studies of dioxin and endometriosis concluded that "the human data supporting the dioxin-endometriosis association are scanty and conflicting",[28] and a 2009 follow-up review also found that there was "insufficient evidence" in support of a link between dioxin exposure and women developing endometriosis.[29] A 2008 review concluded that more work was needed, stating that "although preliminary work suggests a potential involvement of exposure to dioxins in the pathogenesis of endometriosis, much work remains to clearly define cause and effect and to understand the potential mechanism of toxicity".[30]

## Pathophysiology [edit]

While the exact cause of endometriosis remains unknown, many theories have been presented to better understand and explain its development. These concepts do not necessarily exclude each other. The pathophysiology of endometriosis is likely to be multifactorial and to involve an interplay between several factors.[21]



Laparoscopic image of endometriotic lesions at the peritoneum of the pelvic wall.

### Formation [edit]

The main theories for the formation of the ectopic endometrium are retrograde menstruation, müllerianosis, coelomic metaplasia and transplantation, each further described below.

### Retrograde menstruation theory [edit]

The theory of retrograde menstruation (also called the *implantation theory* or *transplantation theory*)[31] is the most widely accepted theory for the formation of ectopic endometrium in endometriosis.[21] It suggests that during a woman's menstrual flow, some of the endometrial debris exits the uterus through the fallopian tubes and attaches itself to the peritoneal surface (the lining of the abdominal cavity) where it can proceed to invade the tissue as endometriosis.[21]

Retrograde menstruation alone is not able to explain all instances of endometriosis, and additional factors such as genetic or immune differences need to be invoked to account for the fact that many women with retrograde menstruation do not have endometriosis. Researchers are investigating the possibility that the

immune system may not be able to cope with the cyclic onslaught of retrograde menstrual fluid. In this context there is interest in studying the relationship of endometriosis to autoimmune disease, allergic reactions, and the impact of toxic materials.[32][33] It is still unclear what, if any, causal relationship exists between toxic materials, autoimmune disease, and endometriosis. There are immune system changes in women with endometriosis, such as an increase macrophage-derived secretion products, but it is unknown if these are contributing to the disorder or are reactions from it.[34]

In addition, at least one study found that endometriotic lesions differ in their biochemistry from artificially transplanted ectopic tissue.[35] This is likely because the cells that give rise to endometriosis are a side population of cells.[21] Similarly, there are changes in for example the mesothelium of the peritoneum in women with endometriosis, such as loss of tight junctions, but it is unknown if these are causes or effects of the disorder.[34]

In rare cases where imperforate hymen does not resolve itself prior to the first menstrual cycle and goes undetected, blood and endometrium are trapped within the uterus of the woman until such time as the problem is resolved by surgical incision. Many health care practitioners never encounter this defect, and due to the flu-like symptoms it is often misdiagnosed or overlooked until multiple menstrual cycles have passed. By the time a correct diagnosis has been made, endometrium and other fluids have filled the uterus and fallopian tubes with results similar to retrograde menstruation resulting in endometriosis. The initial stage of endometriosis may vary based on the time elapsed between onset and surgical procedure.[*citation needed*]

The theory of retrograde menstruation as a cause of endometriosis was first proposed by John A. Sampson.

## Other theories [edit]

- Stem cells: Endometriosis may arise from stem cells from bone marrow and potentially other sources. In particular this theory explains endometriosis found in areas remote from the pelvis such as the brain or lungs.[36]
- Environment; Environmental toxins (e.g.; dioxin, nickel) may cause endometriosis.[37]
- Müllerianosis: A theory supported by foetal autopsy is that cells with the potential to become endometrial, which are laid down in tracts during embryonic development called the female reproductive (Mullerian) tract as it migrates downward at 8–10 weeks of embryonic life, could become dislocated from the migrating uterus and act like seeds or stem cells.[38]
- Coelomic metaplasia: Coelomic cells which are the common ancestor of endometrial and peritoneal cells may undergo metaplasia (transformation) from one type of cell to the other, perhaps triggered by inflammation.[39]
- Vasculogenesis: Up to 37% of the microvascular endothelium of ectopic endometrial tissue originates from endothelial progenitor cells, which result in *de novo* formation of microvessels by the process of vasculogenesis rather than the conventional process of angiogenesis.[40][*clarification needed*]
- Neural growth: An increased expression of new nerve fibres is found in endometriosis, but does not fully explain the formation of ectopic endometrial tissue, and is not definitely correlated with the amount of perceived pain.[41][*clarification needed*]
- Autoimmune: Graves disease is an autoimmune disease characterized by hyperthyroidism, goiter, ophthalmopathy, and dermopathy. Women with endometriosis had higher rates of Graves disease. One of these potential links between Graves disease and endometriosis is autoimmunity.[42][43]

## Localization [edit]

Most endometriosis is found on these structures in the pelvic cavity:[44]

- Ovaries (the most common site)
- Fallopian tubes
- The back of the uterus and the posterior cul-de-sac
- The front of the uterus and the anterior cul-de-sac
- Uterine ligaments such as the broad or round ligament of the uterus
- Pelvic and back wall

possible locations of endometriosis

Intestines, most commonly the rectosigmoid
- Urinary bladder and ureters

Rectovaginal or bowel endometriosis affects approximately 5-12% of women with endometriosis, and can cause severe pain with bowel movements.[45]

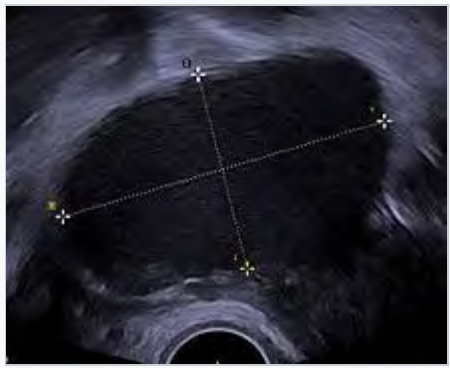
Endometriosis may spread to the cervix and vagina or to sites of a surgical abdominal incision, known as "scar endometriosis."[46] Risk factors for scar endometriosis include previous abdominal surgeries, such as a hysterotomy or cesarean section, or ectopic pregnancies, salpingostomy puerperal sterilization, laparoscopy, amniocentesis, appendectomy, episiotomy, vaginal hysterectomies, and hernia repair.[47][48][49]

Endometriosis may also present with skin lesions in cutaneous endometriosis.

Less commonly lesions can be found on the diaphragm. Diaphragmatic endometriosis is rare, almost always on the right hemidiaphragm, and may inflict the cyclic pain of the right shoulder just before and during a menstrual period. Rarely, endometriosis can be extraperitoneal and is found in the lungs and CNS.[50]

## Diagnosis [edit]

A health history and a physical examination can lead the health care practitioner to suspect endometriosis. Although doctors can often feel the endometrial growths during a pelvic exam, and these symptoms may be signs of endometriosis, diagnosis cannot be confirmed by exam only. Use of pelvic ultrasound may identify large endometriotic cysts (called endometriomas). However, smaller endometriosis implants cannot be visualized with ultrasound technique.[*citation needed*]

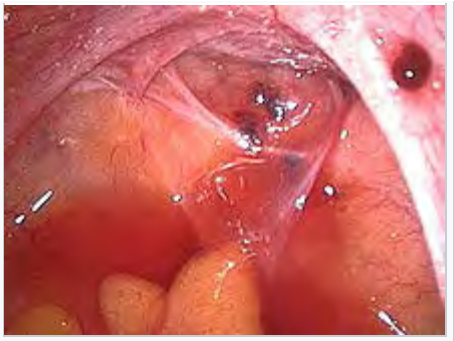


Transvaginal ultrasonography showing a 67 x 40 mm endometrioma as distinguished from other types of ovarian cysts by a somewhat grainy and not completely anechoic content.

### Laparoscopy [edit]

Laparoscopy, a surgical procedure where a camera is used to look inside the abdominal cavity, is the only way to officially diagnose endometriosis as it permits lesion visualization unless the lesion is visible externally, e.g. an endometriotic nodule in the vagina. If the growths are not visible, a biopsy may be taken to determine the diagnosis.[51] Surgery for diagnoses also allows for surgical treatment of endometriosis at the same time.

To the eye, lesions can appear dark blue, powder-burn black, red, white, yellow, brown or non-pigmented. Lesions vary in size. Some within the pelvis walls may not be visible, as normal-appearing peritoneum of infertile women reveals endometriosis on biopsy in 6–13% of cases.[52] Early endometriosis typically occurs on the surfaces of organs in the pelvic and intra-abdominal areas. Health care providers may call areas of endometriosis by different names, such as implants, lesions, or nodules. Larger lesions may be seen within the ovaries as endometriomas or "chocolate cysts", "chocolate" because they contain a thick brownish fluid, mostly old blood.[*citation needed*]



Laparoscopic image of endometriotic lesions in the Pouch of Douglas and on the right sacrouterine ligament.

Frequently during diagnostic laparoscopy, no lesions are found in women with chronic pelvic pain, a symptom common to other disorders including adenomyosis, pelvic adhesions, pelvic inflammatory disease, congenital anomalies of the reproductive tract, and ovarian or tubal masses.[53]

## Staging [edit]

Surgically, endometriosis can be staged I–IV by the revised classification of the American Society of Reproductive Medicine from 1997.[54] The process is a complex point system that assesses lesions and adhesions in the pelvic organs, but it is important to note staging assesses physical disease only, not the level of pain or infertility. A person with Stage I endometriosis may have a little disease and severe pain, while a person with Stage IV endometriosis may have severe disease and no pain or vice versa. In principle the various stages show these findings:[*citation needed*]

**Stage I (Minimal)**
Findings restricted to only superficial lesions and possibly a few filmy adhesions
**Stage II (Mild)**
In addition, some deep lesions are present in the cul-de-sac
**Stage III (Moderate)**
As above, plus the presence of endometriomas on the ovary and more adhesions.
**Stage IV (Severe)**
As above, plus large endometriomas, extensive adhesions.

## Markers [edit]

An area of research is the search for endometriosis markers.[55]

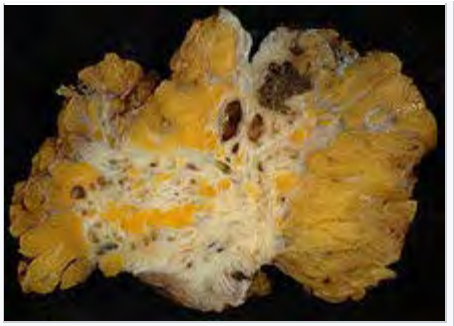
In 2010 essentially all proposed biomarkers for endometriosis were of unclear medical use, although some appear to be promising.[55] The one biomarker that has been in use over the last 20 years is CA-125.[55] A 2016 review found that in those with symptoms of endometriosis and once ovarian cancer has been ruled out, a positive CA-125 may confirm the diagnosis.[56] Its performance in ruling out endometriosis; however, is low.[56] CA-125 levels appear to fall during endometriosis treatment, but has not shown a correlation with disease response.[55]

Another review in 2011 identified several putative biomarkers upon biopsy, including findings of small sensory nerve fibers or defectively expressed β3 integrin subunit.[57] It has been postulated a future diagnostic tool for endometriosis will consist of a panel of several specific and sensitive biomarkers, including both substance concentrations and genetic predisposition.[55]

## Histopathology [edit]

Typical endometriotic lesions show histopathologic features similar to endometrium, namely endometrial stroma, endometrial epithelium, and glands that respond to hormonal stimuli. Older lesions may display no glands but hemosiderin deposits (see photomicrograph on right) as residual.[*citation needed*]

Immunohistochemistry has been found to be useful in diagnosing

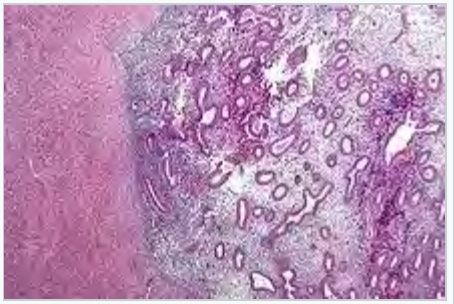


Endometriosis, abdominal wall

endometriosis as stromal cells have a peculiar surface antigen, CD10, thus allowing the pathologist go straight to a staining area and hence confirm the presence of stromal cells and sometimes glandular tissue is thus identified that was missed on routine H&E staining.[58][*better source needed*]

### Pain quantification [edit]

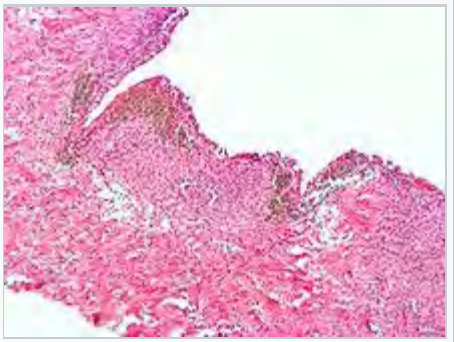
The most common pain scale for quantification of endometriosis-related pain is the visual analogue scale (VAS); VAS and numerical rating scale (NRS) were the best adapted pain scales for pain measurement in endometriosis. For research purposes, and for more detailed pain measurement in clinical practice, VAS or NRS for each type of typical pain related to endometriosis (dysmenorrhea, deep dyspareunia and non-menstrual chronic pelvic pain), combined with the clinical global impression (CGI) and a quality of life scale, are used.[59]



Micrograph showing endometriosis (right) and ovarian stroma (left). H&E stain.

## Prevention [edit]

Limited evidence indicates that the use of combined oral contraceptives is associated with a reduced risk of endometriosis.[6]



Micrograph of the wall of an endometrioma. All features of endometriosis are present (endometrial glands, endometrial stroma and hemosiderin-laden macrophages). H&E stain.

## Management [edit]

While there is no cure for endometriosis, there are two types of interventions; treatment of pain and treatment of endometriosis-associated infertility.[60] In many women menopause (natural or surgical) will abate the process.[61] In women in the reproductive years, endometriosis is merely managed: the goal is to provide pain relief, to restrict progression of the process, and to restore or preserve fertility where needed. In younger women, surgical treatment attempts to remove endometrial tissue and preserve the ovaries without damaging normal tissue.[62]

In general, the diagnosis of endometriosis is confirmed during surgery, at which time ablative steps can be taken. Further steps depend on circumstances: a woman without infertility can be managed with hormonal medication that suppresses the natural cycle and pain medication, while an infertile woman may be treated expectantly after surgery, with fertility medication, or with IVF. As to the surgical procedure, ablation (or fulguration) of endometriosis (burning and vaporizing the lesions with an electric device) has shown a high rate of short-term recurrence after the procedure. The best surgical procedure with much less rate of short-term recurrence is to excise (cut and remove) the lesions completely.[*medical citation needed*]

### Surgery [edit]

Conservative treatment consists of the excision of the endometrium, adhesions, resection of endometriomas, and restoration of normal pelvic anatomy as much as is possible.[63] Endometrioma on the

ovary of any significant size (Approx. 2 cm +) -sometimes misdiagnosed as ovarian cysts- must be removed surgically because hormonal treatment alone will not remove the full endometrioma cyst, which can progress to acute pain from the rupturing of the cyst and internal bleeding.[*medical citation needed*] Laparoscopy, besides being used for diagnosis, can also be used to perform surgery. It's considered a "minimally invasive" surgery because the surgeon makes very small openings (incisions) at (or around) the belly button and lower portion of the belly. A thin telescope-like instrument (the laparoscope) is placed through one incision, which allows the doctor to look for endometriosis using a small camera attached to the laparoscope. Small instruments are inserted through the incisions to remove the endometriosis tissue and adhesions. Because the incisions are very small, there will only be small scars on the skin after the procedure, and all endometriosis can be removed, and women recover from surgery quicker and have a lower risk of adhesions.[64]

55% to 100% of women develop adhesions following pelvic surgery,[65] which can result in infertility, chronic abdominal and pelvic pain, and difficult reoperative surgery. Trehan's temporary ovarian suspension, a technique in which the ovaries are suspended for a week after surgery may be used to reduce the incidence of adhesions after endometriosis surgery.[66][67]

Conservative treatment involves excision of endometriosis while preserving the ovaries and uterus, very important for women wishing to conceive, but may increase the risk of recurrence.[68]

Endometriosis recurrence following conservative surgery is estimated as 21.5% at 2 years and 40-50% at 5 years.[69]

A hysterectomy (removal of the uterus) can be used to treat endometriosis in women who do not wish to conceive. However, this should only be done when combined with removal of the endometriosis by excision, as if endometriosis is not also removed at the time of hysterectomy, pain may persist.[70]

For women with extreme pain, a presacral neurectomy may be very rarely performed where the nerves to the uterus are cut. However, this technique is almost never used due to the high incidence of associated complications including presacral hematoma and irreversible problems with urination and constipation.[70]

## Hormones [edit]

- Progesterone or Progestins: Progesterone counteracts estrogen and inhibits the growth of the endometrium.[71] Such therapy can reduce or eliminate menstruation in a controlled and reversible fashion. Progestins are chemical variants of natural progesterone. An example of a Progestin is Dienogest (Visanne).
- Avoiding products with xenoestrogens, which have a similar effect to naturally produced estrogen and can increase growth of the endometrium.[*medical citation needed*]
- Hormone contraception therapy: Oral contraceptives reduce the menstrual pain associated with endometriosis.[*unreliable medical source?*][72] They may function by reducing or eliminating menstrual flow and providing estrogen support. Typically, it is a long-term approach.
- Danazol (Danocrine) and gestrinone are suppressive steroids with some androgenic activity.[62] Both agents inhibit the growth of endometriosis but their use remains limited as they may cause hirsutism and voice changes.[*medical citation needed*]
- Gonadotropin-releasing hormone (GnRH) agonists: These drugs are thought to work by decreasing hormone levels.[73] A 2010 Cochrane review found that GnRH agonists were more effective for pain relief in endometriosis than no treatment or placebo, but were no more effective than danazol or intrauterine progestagen, and had more side effects than danazol.[73]
- Aromatase inhibitors are medications that block the formation of estrogen and have become of interest for researchers who are treating endometriosis.[74]

## Other medication [edit]

- NSAIDs: Anti-inflammatory. They are commonly used in conjunction with other therapy. For more severe cases narcotic prescription drugs may be used. NSAID injections can be helpful for severe pain or if stomach pain prevents oral NSAID use.

- Opioids: Morphine sulphate tablets and other opioid painkillers work by mimicking the action of naturally occurring pain-reducing chemicals called "endorphins". There are different long acting and short acting medications that can be used alone or in combination to provide appropriate pain control.
- Following laparoscopic surgery women who were given Chinese herbs were reported to have comparable benefits to women with conventional drug treatments, though the journal article that reviewed this study also noted that "the two trials included in this review are of poor methodological quality so these findings must be interpreted cautiously. Better quality randomised controlled trials are needed to investigate a possible role for CHM [Chinese Herbal Medicine] in the treatment of endometriosis."[75]
- Pentoxifylline, an immunomodulating agent, has been theorized to improve pain as well as improve pregnancy rates in women with endometriosis. A 2012 Cochrane review, however, found that there was not enough evidence to support the effectiveness or safety of either of these uses.[76] Current American Congress of Obstetricians and Gynecologists (ACOG) guidelines do not include immune-modulators, such as pentoxifylline, in standard treatment protocols.[77]
- Angiogenesis inhibitors lack clinical evidence of efficacy in endometriosis therapy.[78] Under experimental *in vitro* and *in vivo* conditions, compounds that have been shown to exert inhibitory effects on endometriotic lesions include growth factor inhibitors, endogenous angiogenesis inhibitors, fumagillin analogues, statins, cyclo-oxygenase-2 inhibitors, phytochemical compounds, immunomodulators, dopamine agonists, peroxisome proliferator-activated receptor agonists, progestins, danazol and gonadotropin-releasing hormone agonists.[78] However, many of these agents are associated with undesirable side effects and more research is necessary. An ideal therapy would diminish inflammation and underlying symptoms without being contraceptive.[79][80]

The overall effectiveness of manual physical therapy to treat endometriosis has not yet been identified.[81] There is no evidence to support nutritional therapy as effective.

## Comparison of interventions [edit]

Medicinal and surgical interventions produce roughly equivalent pain-relief benefits. Recurrence of pain was found to be 44 and 53 percent with medicinal and surgical interventions, respectively.[22] Each approach has advantages and disadvantages.[39] Manual therapy showed a decrease in pain for 84 percent of study participants, and a 93 percent improvement in sexual function.[*unreliable medical source?*][82]

Evidence on how effective medication is for relieving pain associated with endometriosis is limited.[60]

The advantages of surgery are demonstrated efficacy for pain control,[83] it is more effective for infertility than medicinal intervention,[62] it provides a definitive diagnosis,[62] and surgery can often be performed as a minimally invasive (laparoscopic) procedure to reduce morbidity and minimize the risk of post-operative adhesions.[84] Efforts to develop effective strategies to reduce or prevent adhesions have been undertaken, but their formation remain a frequent side effect of abdominal surgery.[65]

The advantages of physical therapy techniques are decreased cost, absence of major side-effects, it does not interfere with fertility, and near-universal increase of sexual function.[82] Disadvantages are that there are no large or long-term studies of its use for treating pain or infertility related to endometriosis.[82]

## Treatment of infertility [edit]

*Main article: Endometriosis and infertility*

Surgery is more effective than medicinal intervention for addressing infertility associated with endometriosis.[62] Surgery attempts to remove endometrial tissue and preserve the ovaries without damaging normal tissue.[62] In-vitro fertilization (IVF) procedures are effective in improving fertility in many women with endometriosis.[*medical citation needed*]

# Prognosis [edit]

Proper counseling of women with endometriosis requires attention to several aspects of the disorder. Of primary importance is the initial operative staging of the disease to obtain adequate information on which to base future decisions about therapy. The woman's symptoms and desire for childbearing dictate appropriate therapy. Not all therapy works for all women. Some women have recurrences after surgery or pseudo-menopause. In most cases, treatment will give women significant relief from pelvic pain and assist them in achieving pregnancy.[85]

The underlying process that causes endometriosis may not cease after a surgical or medical intervention. Studies have shown that endometriosis recurs at a rate of 20 to 40 percent within five years following conservative surgery,[*unreliable medical source?*][86] unless hysterectomy is performed or menopause reached. Monitoring of women consists of periodic clinical examinations and sonography.

Vaginal childbirth decreases recurrence of endometriosis. In contrast, endometriosis recurrence rates have been shown to be higher in women who have not given birth vaginally, such as in cesarean section.[*unreliable medical source?*][87]

### Complications [edit]

Complications of endometriosis include internal scarring, adhesions, pelvic cysts, chocolate cyst of ovaries, ruptured cysts, and bowel and ureteral obstruction resulting from pelvic adhesions.[88] Endometriosis-associated infertility can be related to scar formation and anatomical distortions due to the endometriosis.[*medical citation needed*]

Ovarian endometriosis may complicate pregnancy by decidualization,[*clarification needed*] abscess and/or rupture.[89]

Thoracic endometriosis is associated with recurrent pneumothoraces at times of a menstrual period, termed catamenial pneumothorax.[90]

## Epidemiology [edit]

Endometriosis can affect any female, from premenarche to postmenopause, regardless of race or ethnicity or whether or not they have had children. It is primarily a disease of the reproductive years.[91] The number of women affected is between 6–10%.[4] It is more common in women with infertility and chronic pelvic pain (35–50%).[4]

Incidences of endometriosis have occurred in postmenopausal women,[92] and in less common cases, girls may have endometriosis symptoms before they even reach menarche.[93][94]

## History [edit]

Endometriosis was first discovered microscopically by Karl von Rokitansky in 1860,[95] although it was documented in medical texts more than 4,000 years ago.[96] The Hippocratic Corpus outlines symptoms similar to endometriosis, including uterine ulcers, adhesions, and infertility.[96] Historically, women with these symptoms were treated with leeches, straitjackets, bloodletting, chemical douches, genital mutilation, pregnancy (as a form of treatment), hanging upside down, surgical intervention, and even killing due to suspicion of demonic possession.[96] Hippocratic doctors recognized and treated chronic pelvic pain as a true organic disorder 2,500 years ago, but during the Middle Ages, there was a shift into believing that women with pelvic pain were mad, immoral, imagining the pain, or simply misbehaving.[96] The symptoms of inexplicable chronic pelvic pain were often attributed to imagined madness, female weakness, promiscuity, or hysteria.[96] The historical diagnosis of hysteria, which was thought to be a psychological disease, may have indeed been endometriosis.[96] The idea that chronic pelvic pain was related to mental illness influenced modern attitudes regarding women with endometriosis, leading to delays in correct [96]

diagnosis and indifference to the patients' true pain during the 20th century.

Hippocratic doctors believed that delaying childbearing could trigger diseases of the uterus, which caused endometriosis-like symptoms. Women with dysmenorrhea were encouraged to marry and have children at a young age.[96] The fact that Hippocratics were recommending changes in marriage practices due to an endometriosis-like illness implies that this disease was likely common, with rates higher than the 5-15% prevalence that is often cited today.[96] If indeed this disorder was so common historically, this may point away from modern theories that suggest links between endometriosis and dioxins, PCBs, and chemicals.[96]

## Society and culture [edit]

As recently as 1995, reports found that over 50% of women with chronic pelvic pain had no organic cause, with women still often being considered mentally unstable.[97] Self-help groups say practitioners delay making the diagnosis, often because they don't consider it a possibility. In the US, as of 2007, about 27% of women with endometriosis had had the symptoms for at least six years before it is diagnosed.[*needs update*][98]

The economic effects associated with endometriosis are substantial and are similar to that of other chronic diseases such as Crohn's disease, diabetes, or rheumatoid arthritis.[99] This economic burden is attributed mostly to the inability to consistently work and predicted by decreased quality of life.[99]

## References [edit]


1. ^ "Endometriosis: Overview". *http://www.nichd.nih.gov*. 2013-06-24. Retrieved 4 March 2015. External link in |website= (help)
2. ^ "Endometriosis: Condition Information". *NICHD*. Retrieved 14 December 2016.
3. ^ *a b c d e f* "Endometriosis". *http://www.womenshealth.gov/*. December 5, 2014. Retrieved 4 March 2015. External link in |website= (help)
4. ^ *a b c d e f g h i j k* Bulletti C, Coccia ME, Battistoni S, Borini A (August 2010). "Endometriosis and infertility". *J. Assist. Reprod. Genet.* **27** (8): 441–7. doi:10.1007/s10815-010-9436-1. PMC 2941592. PMID 20574791.
5. ^ Culley L, Law C, Hudson N, Denny E, Mitchell H, Baumgarten M, Raine-Fenning N (2013). "The social and psychological impact of endometriosis on women's lives: A critical narrative review". *Human Reproduction Update*. **19** (6): 625–639. doi:10.1093/humupd/dmt027. PMID 23884896.
6. ^ *a b* Vercellini P, Eskenazi B, Consonni D, Somigliana E, Parazzini F, Abbiati A, Fedele L (2011). "Oral contraceptives and risk of endometriosis: a systematic review and meta-analysis". *Hum. Reprod. Update*. **17** (2): 159–70. doi:10.1093/humupd/dmq042. PMID 20833638.
7. ^ McGrath, Patrick J.; Stevens, Bonnie J.; Walker, Suellen M.; Zempsky, William T. (2013). *Oxford Textbook of Paediatric Pain*. OUP Oxford. p. 300. ISBN 9780199642656.
8. ^ GBD 2013 Mortality and Causes of Death Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385**: 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
9. ^ Brosens I (2012). *Endometriosis: Science and Practice*. John Wiley & Sons. p. 3. ISBN 9781444398496.
10. ^ *a b* Stratton P, Berkley KJ (2011). "Chronic pelvic pain and endometriosis: translational evidence of the relationship and implications". *Hum. Reprod. Update*. **17** (3): 327–46. doi:10.1093/humupd/dmq050. PMC 3072022. PMID 21106492.
11. ^ Endometriosis;NIH Pub. No. 02-2413; September 2002
12. ^ *a b c d* [*non-primary source needed*] Ballard K, Lane H, Hudelist G, Banerjee S, Wright J (June 2010). "Can specific pain symptoms help in the diagnosis of endometriosis? A cohort study of women with chronic pelvic pain". *Fertil. Steril*. **94** (1): 20–7. doi:10.1016/j.fertnstert.2009.01.164. PMID 19342028.
13. ^ [*page needed*]Murray MT, Pizzorno J (2012). *The Encyclopedia of Natural Medicine* (3rd ed.). New York, NY: Simon and Schuster.
14. ^ Asante (2011). "Endometriosis: the role of neuroangiogenesis.". *Annu Rev Physiol*. **73**: 163–182. doi:10.1146/annurev-physiol-012110-142158. PMID 21054165.
15. ^ Arbique D, Carter S, van Sell S (2008). "Endometriosis can evade diagnosis: being alert to signs of endometriosis

can arrest the disease before it takes over a patient's life". *RN*. **71** (9): 28–32. PMID 18833741.
16. ^ Colette S, Donnez J (July 2011). "Are aromatase inhibitors effective in endometriosis treatment?". *Expert Opin Investig Drugs*. **20** (7): 917–31. doi:10.1517/13543784.2011.581226. PMID 21529311.
17. ^ Pearce CL, Templeman C, Rossing MA, et al. (2012). "Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies". *Lancet Oncol*. **13** (4): 385–94. doi:10.1016/S1470-2045(11)70404-1. PMC 3664011. PMID 22361336.
18. ^ Nezhat F. Article by Prof. Farr Nezhat, MD, FACOG, FACS, University of Columbia, May 1, 2012
19. ^ Audebert A (April 2005). "La femme endométriosique est-elle différente ?" [Women with endometriosis: are they different from others?]. *Gynécologie, Obstétrique & Fertilité* (in French). **33** (4): 239–46. doi:10.1016/j.gyobfe.2005.03.010. PMID 15894210.
20. ^ Rowlands IJ, Nagle CM, Spurdle AB, Webb PM; Australian National Endometrial Cancer Study Group and Australian Ovarian Cancer Study Group (Dec 2011). "Gynecological conditions and the risk of endometrial cancer". *Gynecol Oncol*. **3**: 537–41.
21. ^ *a b c d e f g h* Fauser BC, Diedrich K, Bouchard P, Domínguez F, Matzuk M, Franks S, Hamamah S, Simón C, Devroey P, Ezcurra D, Howles CM (2011). "Contemporary genetic technologies and female reproduction". *Hum. Reprod. Update*. **17** (6): 829–47. doi:10.1093/humupd/dmr033. PMC 3191938. PMID 21896560.
22. ^ *a b* Kapoor D, Davila W (2005). Endometriosis, *eMedicine*.
23. ^ Giudice LC, Kao LC (2004). "Endometriosis". *Lancet*. **364** (9447): 1789–99. doi:10.1016/S0140-6736(04)17403-5. PMID 15541453.
24. ^ *a b c d e f g* Rahmioglu N, Nyholt DR, Morris AP, et al. (2014). "Genetic variants underlying risk of endometriosis: insights from meta-analysis of eight genome-wide association and replication datasets". *Human Reproduction Update*. **20** (5): 702–716. doi:10.1093/humupd/dmu015. ISSN 1355-4786.
25. ^ Painter JN, Anderson CA, Nyholt DR, et al. (January 2011). "Genome-wide association study identifies a locus at 7p15.2 associated with endometriosis". *Nature Genetics*. **43** (1): 51–4. doi:10.1038/ng.731. PMC 3019124. PMID 21151130.
26. ^ Treloar SA, Wicks J, Nyholt DR, et al. (September 2005). "Genomewide linkage study in 1,176 affected sister pair families identifies a significant susceptibility locus for endometriosis on chromosome 10q26". *American Journal of Human Genetics*. **77** (3): 365–76. doi:10.1086/432960. PMC 1226203. PMID 16080113.
27. ^ Anger DL, Foster WG (2008). "The link between environmental toxicant exposure and endometriosis". *Frontiers in Bioscience*. **13**: 1578–93. doi:10.2741/2782. PMID 17981650.
28. ^ Guo SW (2004). "The link between exposure to dioxin and endometriosis: a critical reappraisal of primate data". *Gynecologic and Obstetric Investigation*. **57** (3): 157–73. doi:10.1159/000076374. PMID 14739528.
29. ^ Guo SW, Simsa P, Kyama CM, et al. (October 2009). "Reassessing the evidence for the link between dioxin and endometriosis: from molecular biology to clinical epidemiology". *Molecular Human Reproduction*. **15** (10): 609–24. doi:10.1093/molehr/gap075. PMID 19744969.
30. ^ Rier S, Foster WG (December 2002). "Environmental dioxins and endometriosis". *Toxicological Sciences*. **70** (2): 161–70. doi:10.1093/toxsci/70.2.161. PMID 12441361.
31. ^ van der Linden PJ (1996). "Theories on the pathogenesis of endometriosis". *Human reproduction (Oxford, England)*. 11 Suppl 3: 53–65. doi:10.1093/humrep/11.suppl_3.53. PMID 9147102.
32. ^ Gleicher N, el-Roeiy A, Confino E, Friberg J (July 1987). "Is endometriosis an autoimmune disease?". *Obstet Gynecol*. **70** (1): 115–22. PMID 3110710.
33. ^ Capellino S, Montagna P, Villaggio B, Sulli A, Soldano S, et al. (June 2006). "Role of estrogens in inflammatory response: expression of estrogen receptors in peritoneal fluid macrophages from endometriosis". *Annals of the New York Academy of Sciences*. **1069**: 263–7. doi:10.1196/annals.1351.024. PMID 16855153.
34. ^ *a b* Young VJ, Brown JK, Saunders PT, Horne AW (2013). "The role of the peritoneum in the pathogenesis of endometriosis". *Human Reproduction Update*. **19** (5): 558–569. doi:10.1093/humupd/dmt024. PMID 23720497.
35. ^ Redwine DB (October 2002). "Was Sampson wrong?". *Fertility and Sterility*. **78** (4): 686–93. doi:10.1016/S0015-0282(02)03329-0. PMID 12372441.
36. ^ Hufnagel, D; Li, F; Cosar, E; Krikun, G; Taylor, HS (September 2015). "The Role of Stem Cells in the Etiology and Pathophysiology of Endometriosis.". *Seminars in reproductive medicine*. **33** (5): 333–40. doi:10.1055/s-0035-1564609. PMID 26375413.
37. ^ Bruner-Tran, K.L.; Yeaman, G.R.; Crispens, M.A.; Igarashi, T.M.; Osteen, K.G. (2008). "Dioxin may promote inflammation-related development of endometriosis.". *Fertility and Sterility*. **89**: 1287–98. doi:10.1016/j.fertnstert.2008.02.102. PMID 18394613.
38. ^ Signorile PG, Baldi F, Bussani R, D'Armiento M, De Falco M, Baldi A (April 2009). "Ectopic endometrium in human foetuses is a common event and sustains the theory of müllerianosis in the pathogenesis of endometriosis, a disease that predisposes to cancer". *Journal of Experimental & Clinical Cancer Research*. **28**: 49. doi:10.1186/1756-9966-28-49. PMC 2671494. PMID 19358700.

39. ^ [a b] "Diagnosis and Treatment of Endometriosis". American Academy of Family Physicians. 1999-10-15. Retrieved 2011-07-26.
40. ^ Laschke MW, Giebels C, Menger MD (2011). "Vasculogenesis: a new piece of the endometriosis puzzle". *Hum. Reprod. Update*. **17** (5): 628–36. doi:10.1093/humupd/dmr023. PMID 21586449.
41. ^ Morotti M, Vincent K, Brawn J, Zondervan KT, Becker CM (2014). "Peripheral changes in endometriosis-associated pain". *Human Reproduction Update*. **20** (5): 717–736. doi:10.1093/humupd/dmu021. ISSN 1355-4786. PMC 4337970. PMID 24859987.
42. ^ Yuk, Jin-Sung; Park, Eun-Ju; Seo, Yong-Soo; Kim, Hee Jin; Kwon, Seon-Young; Park, Won I. (2016). "Graves Disease Is Associated With Endometriosis: A 3-Year Population-Based Cross-Sectional Study". *Medicine*. **95** (10): –2975. doi:10.1097/MD.0000000000002975. ISSN 1536-5964. PMID 26962803.
43. ^ Giudice, Linda C; Kao, Lee C (2004). "Endometriosis". *Lancet*. **364** (9447): 1789–1799. doi:10.1016/S0140-6736(04)17403-5. ISSN 1474-547X. PMID 15541453.
44. ^ Jenkins S, Olive DL, Haney AF (March 1986). "Endometriosis: pathogenetic implications of the anatomic distribution". *Obstetrics and gynecology*. **67** (3): 335–8. PMID 3945444.
45. ^ Weed JC, Ray JE (May 1987). "Endometriosis of the bowel". *Obstetrics and gynecology*. **69** (5): 727–30. PMID 3574800.
46. ^ Uzunçakmak C, Güldaş A, Ozçam H, Dinç K (2013). "Scar endometriosis: a case report of this uncommon entity and review of the literature". *Case reports in obstetrics and gynecology*. **2013**: 386783. doi:10.1155/2013/386783. PMID 23762683.
47. ^ Dwivedi AJ, Agrawal SN, Silva YJ (February 2002). "Abdominal wall endometriomas". *Digestive diseases and sciences*. **47** (2): 456–61. PMID 11855568.
48. ^ Kaunitz A, Di Sant'Agnese PA (December 1979). "Needle tract endometriosis: an unusual complication of amniocentesis". *Obstetrics and gynecology*. **54** (6): 753–5. PMID 160025.
49. ^ Koger KE, Shatney CH, Hodge K, McClenathan JH (September 1993). "Surgical scar endometrioma.". *Surgery, gynecology & obstetrics*. **177** (3): 243–6. PMID 8356497.
50. ^ Daly S (October 18, 2004). "Endometrioma/Endometriosis". WebMD. Retrieved 2006-12-19.
51. ^ Office on Women's Health, U.S. Department of Health and Human Services. (16 July 2012). Endometriosis Fact Sheet. Retrieved from Womenshealth.gov http://www.womenshealth.gov/publications/our-publications/fact-sheet/endometriosis.html
52. ^ Nisolle M, Paindaveine B, Bourdon A, Berlière M, Casanas-Roux F, Donnez J (June 1990). "Histologic study of peritoneal endometriosis in infertile women". *Fertility and Sterility*. **53** (6): 984–8. PMID 2351237.
53. ^ Practice Committee of the American Society for Reproductive, Medicine (April 2014). "Treatment of pelvic pain associated with endometriosis: a committee opinion.". *Fertility and Sterility*. **101** (4): 927–35. doi:10.1016/j.fertnstert.2014.02.012. PMID 24630080.
54. ^ American Society For Reproductive M, (May 1997). "Revised American Society for Reproductive Medicine classification of endometriosis: 1996". *Fertility and Sterility*. **67** (5): 817–21. doi:10.1016/S0015-0282(97)81391-X. PMID 9130884.
55. ^ [a b c d e] May KE, Conduit-Hulbert SA, Villar J, Kirtley S, Kennedy SH, Becker CM (2010). "Peripheral biomarkers of endometriosis: a systematic review". *Hum. Reprod. Update*. **16** (6): 651–74. doi:10.1093/humupd/dmq009. PMC 2953938. PMID 20462942.
56. ^ [a b] Hirsch, M; Duffy, J; Davis, CJ; Nieves Plana, M; Khan, KS; International Collaboration to Harmonise Outcomes and Measures for, Endometriosis. (October 2016). "Diagnostic accuracy of cancer antigen 125 for endometriosis: a systematic review and meta-analysis.". *BJOG : an international journal of obstetrics and gynaecology*. **123** (11): 1761–8. doi:10.1111/1471-0528.14055. PMID 27173590.
57. ^ May KE, Villar J, Kirtley S, Kennedy SH, Becker CM (2011). "Endometrial alterations in endometriosis: a systematic review of putative biomarkers". *Hum. Reprod. Update*. **17** (5): 637–53. doi:10.1093/humupd/dmr013. PMID 21672902.
58. ^ http://www.rfay.com.au/docs/cd10poster.pdf
59. ^ Bourdel N, Alves J, Pickering G, et al. (2014). "Systematic review of endometriosis pain assessment: how to choose a scale?". *Human Reproduction Update*. **21** (1): 136–152. doi:10.1093/humupd/dmu046. ISSN 1355-4786.
60. ^ [a b] "What are the treatments for endometriosis". Eunice Kennedy Shriver National Institute of Child Health and Human Development. Retrieved 20 August 2013.
61. ^ Moen MH, Rees M, Brincat M, et al. (2010). "EMAS position statement: Managing the menopause in women with a past history of endometriosis". *Maturitas*. **67** (1): 94–7. doi:10.1016/j.maturitas.2010.04.018. PMID 20627430.
62. ^ [a b c d e f] Wellbery C (1999). "Diagnosis and treatment of endometriosis". *Am Fam Physician*. **60** (6): 1753–62, 1767–8. PMID 10537390.
63. ^ Speroff L, Glass RH, Kase NG (1999). *Clinical Gynecologic Endocrinology and Infertility* (6th ed.). Lippincott

Willimas Wilkins. p. 1057. ISBN 0-683-30379-1.
64. ^ "Endometriosis and Infertility: Can Surgery Help?" (PDF). American Society for Reproductive Medicine. 2008. Retrieved 31 Oct 2010.
65. ^ *a b* Liakakos T, Thomakos N, Fine PM, Dervenis C, Young RL (2001). "Peritoneal Adhesions: Etiology, Pathophysiology, and Clinical Significance". *Dig Surgery*. **18** (4): 260–273. doi:10.1159/000050149. PMID 11528133.
66. ^ Trehan AK (2002). "Temporary ovarian suspension". *Gynaecological Endoscopy*. **11** (1): 309–314. doi:10.1046/j.1365-2508.2002.00520.x.
67. ^ Abuzeid MI, Ashraf M, Shamma FN (2002). "Temporary ovarian suspension at laparoscopy for prevention of adhesions". *J Am Assoc Gynecol Laparosc*. **9** (1): 98–102. PMID 11821616.
68. ^ Namnoum AB, Hickman TN, Goodman SB, Gehlbach DL, Rock JA (November 1995). "Incidence of symptom recurrence after hysterectomy for endometriosis". *Fertility and Sterility*. **64** (5): 898–902. PMID 7589631.
69. ^ Guo SW (2009). "Recurrence of endometriosis and its control". *Hum. Reprod. Update*. **15** (4): 441–61. doi:10.1093/humupd/dmp007. PMID 19279046.
70. ^ *a b* Johnson NP, Hummelshoj L (June 2013). "Consensus on current management of endometriosis.". *Human Reproduction*. **28** (6): 1552–68. doi:10.1093/humrep/det050. PMID 23528916.
71. ^ Patel B, Elguero S, Thakore S, et al. (2014). "Role of nuclear progesterone receptor isoforms in uterine pathophysiology". *Human Reproduction Update*. **21** (2): 155–173. doi:10.1093/humupd/dmu056. ISSN 1355-4786. PMC 4366574. PMID 25406186.
72. ^ [*non-primary source needed*] Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N (November 2008). "Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial". *Fertility and Sterility*. **90** (5): 1583–8. doi:10.1016/j.fertnstert.2007.08.051. PMID 18164001.
73. ^ *a b* Brown J, Pan A, Hart RJ (2010). "Gonadotrophin-releasing hormone analogues for pain associated with endometriosis". *Cochrane Database Syst Rev* (12): CD008475. doi:10.1002/14651858.CD008475.pub2. PMID 21154398.
74. ^ Attar E, Bulun SE (May 2006). "Aromatase inhibitors: the next generation of therapeutics for endometriosis?". *Fertility and Sterility*. **85** (5): 1307–18. doi:10.1016/j.fertnstert.2005.09.064. PMID 16647373.
75. ^ Flower, Andrew; Liu, Jian Ping; Lewith, George; Little, Paul; Li, Qing (2012-05-16). "Chinese herbal medicine for endometriosis". *The Cochrane Database of Systematic Reviews* (5): CD006568. doi:10.1002/14651858.CD006568.pub3. ISSN 1469-493X. PMID 22592712.
76. ^ Lu D, Song H, Li Y, Clarke J, Shi G (Jan 18, 2012). "Pentoxifylline for endometriosis.". *Cochrane database of systematic reviews (Online)*. **1**: CD007677. doi:10.1002/14651858.CD007677.pub3. PMID 22258970.
77. ^ "Practice bulletin no. 114 management of endometriosis". *Obstet Gynecol*. **116** (1): 223–36. July 2010. doi:10.1097/AOG.0b013e3181e8b073. PMID 20567196.
78. ^ *a b* Laschke MW, Menger MD (2012). "Anti-angiogenic treatment strategies for the therapy of endometriosis". *Human Reproduction Update*. **18** (6): 682–702. doi:10.1093/humupd/dms026. PMID 22718320.
79. ^ Canny GO, Lessey BA (2013). "The role of lipoxin A4 in endometrial biology and endometriosis". *Mucosal Immunol*. **6** (3): 439–50. doi:10.1038/mi.2013.9. PMC 4062302. PMID 23485944.
80. ^ Streuli I, de Ziegler D, Santulli P, et al. (2013). "An update on the pharmacological management of endometriosis". *Expert Opin Pharmacother*. **14** (3): 291–305. doi:10.1517/14656566.2013.767334. PMID 23356536.
81. ^ Valiani M, Ghasemi N, Bahadoran P, Heshmat R (2010). "The effects of massage therapy on dysmenorrhea caused by endometriosis". *Iran J Nurs Midwifery Res*. **15** (4): 167–71. PMC 3093183. PMID 21589790.
82. ^ *a b c* [*non-primary source needed*] Wurn BF, Wurn LJ, Patterson K, King CR, Scharf ES (2011). "Decreasing dyspareunia and dysmenorrhea in women with endometriosis via a manual physical therapy: Results from two independent studies". *Journal of Endometriosis and Pelvic Pain Disorders*. **3**: 188–196. doi:10.5301/JE.2012.9088.
83. ^ Kaiser A, Kopf A, Gericke C, Bartley J, Mechsner S (16 January 2009). "The influence of peritoneal endometriotic lesions on the generation of endometriosis-related pain and pain reduction after surgical excision". *Arch Gynecol Obstet*. **280** (3): 369–73. doi:10.1007/s00404-008-0921-z. PMID 19148660.
84. ^ Radosa MP, Bernardi TS, Georgiev I, Diebolder H, Camara O, Runnebaum IB (June 2010). "Coagulation versus excision of primary superficial endometriosis: a 2-year follow-up". *Eur. J. Obstet. Gynecol. Reprod. Biol*. **150** (2): 195–8. doi:10.1016/j.ejogrb.2010.02.022. PMID 20303642.
85. ^ Memarzadeh S, Muse KN, Fox, MD (September 21, 2006). "Endometriosis". *Differential Diagnosis and Treatment of endometriosis*. Armenian Health Network, Health.am. Retrieved 2006-12-19.
86. ^ [*unreliable medical source?*] "Recurrent Endometriosis: Surgical Management". *Endometriosis*. The Cleveland Clinic. 7 Jan 2010. Retrieved 31 Oct 2010.

87. ^ [*non-primary source needed*] Bulletti C, Montini A, Setti PL, et al. (June 2009). "Vaginal parturition decreases recurrence of endometriosis". *Fertil. Steril*. **94** (3): 850–5. doi:10.1016/j.fertnstert.2009.04.012. PMID 19524893.
88. ^ Acosta S, Leandersson U, Svensson SE, Johnsen J (May 2001). "Fallbeskrivning. Endometrios orsakade kolonileus, uretärobstruktion och hypertoni" [A case report. Endometriosis caused colonic ileus, ureteral obstruction and hypertension]. *Läkartidningen* (in Swedish). **98** (18): 2208–12. PMID 11402601.
89. ^ Ueda Y, Enomoto T, Miyatake T, et al. (June 2010). "A retrospective analysis of ovarian endometriosis during pregnancy". *Fertility and Sterility*. **94** (1): 78–84. doi:10.1016/j.fertnstert.2009.02.092. PMID 19356751.
90. ^ Visouli AN, Zarogoulidis K, Kougioumtzi I, et al. (October 2014). "Catamenial pneumothorax.". *Journal of thoracic disease*. **6** (Suppl 4): S448–60. doi:10.3978/j.issn.2072-1439.2014.08.49. PMID 25337402.
91. ^ Nothnick WB (2011). "The emerging use of aromatase inhibitors for endometriosis treatment". *Reprod. Biol. Endocrinol*. **9**: 87. doi:10.1186/1477-7827-9-87. PMC 3135533. PMID 21693036.
92. ^ Bulun SE, Zeitoun K, Sasano H, Simpson ER (1999). "Aromatase in aging women". *Seminars in Reproductive Endocrinology*. **17** (4): 349–58. doi:10.1055/s-2007-1016244. PMID 10851574.
93. ^ Batt RE, Mitwally MF (December 2003). "Endometriosis from thelarche to midteens: pathogenesis and prognosis, prevention and pedagogy". *Journal of Pediatric and Adolescent Gynecology*. **16** (6): 337–47. doi:10.1016/j.jpag.2003.09.008. PMID 14642954.
94. ^ Marsh EE, Laufer MR (March 2005). "Endometriosis in premenarcheal girls who do not have an associated obstructive anomaly". *Fertility and Sterility*. **83** (3): 758–60. doi:10.1016/j.fertnstert.2004.08.025. PMID 15749511.
95. ^ Batt, Ronald E. (2011). *A history of endometriosis*. London: Springer. pp. 13–38. ISBN 978-0-85729-585-9.
96. ^ *a b c d e f g h i j* Nezhat C, Nezhat F, Nezhat C (December 2012). "Endometriosis: ancient disease, ancient treatments.". *Fertility and Sterility*. **98** (6 Suppl): S1–62. doi:10.1016/j.fertnstert.2012.08.001. PMID 23084567.
97. ^ [*page needed*] Gomel V, Taylor PJ (1995). *Diagnostic and operative gynecologic laparoscopy*. St. Louis, MO: Mosby.
98. ^ Overton C, Davis C, McMillan L, Shaw RW (2007). *An atlas of endometriosis* (3rd ed.). London: Informa Healthcare. pp. 9–10.
99. ^ *a b* Simoens S, Dunselman G, Dirksen C, et al. (14 March 2012). "The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres". *Human Reproduction*. **27** (5): 1292–1299. doi:10.1093/humrep/des073.


## External links [edit]

- Endometriosis at DMOZ
- Endometriosis fact sheet from womenshealth.gov

Wikimedia Commons has media related to *Endometriosis*.

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Categories: Noninflammatory disorders of female genital tract | Menstrual cycle

# Hyperemesis gravidarum

From Wikipedia, the free encyclopedia

**Hyperemesis gravidarum** (**HG**) is a complication of pregnancy that is characterized by severe nausea and vomiting such that weight loss and dehydration occur.[1] Signs and symptoms may include vomiting several times a day and feeling faint. It is more severe than morning sickness. Often symptoms get better after the 20th week of pregnancy but may last the entire pregnancy.[2]

The exact cause of hyperemesis gravidarum is not known.[3] Risk factors include the first pregnancy, multiple pregnancy, obesity, prior or family history of hyperemesis gravidarum, trophoblastic disorder, and a history of an eating disorder.[3][4] The diagnosis is usually made based on the signs and symptoms. It has been technically defined as more than three episodes of vomiting per day such that weight loss of 5% or three kilograms has occurred and ketones are present in the urine.[3] Other potential causes of the symptoms should be excluded including urinary tract infection and high thyroid levels.[5]

Treatment includes drinking fluids and a bland diet.[2] Recommendations may include electrolyte-replacement drinks, thiamine, and a higher protein diet.[3][6] Some women require intravenous fluids.[2] With respect to medications pyridoxine or metoclopramide are preferred.[5] Prochlorperazine, dimenhydrinate, or ondansetron may be used if these are not effective.[3][5] Hospitalization may be required. Psychotherapy may improve outcomes. Evidence for acupressure is poor.[3]

While vomiting in pregnancy has been described as early as 2,000 BC, the first clear medical description of hyperemesis gravidarum was in 1852 by Antoine Dubois.[7] Hyperemesis gravidarum is estimated to affect 0.3–2.0% of pregnant women.[8] While previously a common cause of death in pregnancy, with proper treatment this is now very rare.[9][10] Those affected have a low risk of miscarriage but a higher risk of premature birth.[4] Some women opt to have an abortion because of the symptoms.[6]

| Hyperemesis gravidarum | |
|---|---|
| Classification and external resources | |
| Specialty | Gynecology |
| ICD-10 | |
| ICD-9-CM | 643.1 |
| MedlinePlus | 001499 |

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## Signs and symptoms [edit]

When vomiting is severe it may result in the following:[11]

- Loss of 5% or more of pre-pregnancy body weight [12]

Dehydration, causing ketosis, and constipation
- Nutritional disorders such as vitamin B1 (thiamine) deficiency, vitamin B6 deficiency or vitamin B12 deficiency
- Metabolic imbalances such as metabolic ketoacidosis[11] or thyrotoxicosis[13]
- Physical and emotional stress of pregnancy on the body
- Difficulty with activities of daily living

Symptoms can be aggravated by hunger, fatigue, prenatal vitamins (especially those containing iron), and diet.[14] Many people with HG are extremely sensitive to odors in their environment; certain smells may exacerbate symptoms. This is known as hyperolfaction. Ptyalism, or hypersalivation, is another symptom experienced by some women suffering from HG.

Hyperemesis gravidarum tends to occur in the first trimester of pregnancy[12] and lasts significantly longer than morning sickness. While most women will experience near-complete relief of morning sickness symptoms near the beginning of their second trimester, some sufferers of HG will experience severe symptoms until they give birth to their baby, and sometimes even after giving birth.[15]

A small percentage rarely vomit, but the nausea still causes most (if not all) of the same issues that hyperemesis with vomiting does.[*citation needed*]

## Causes [edit]

There are numerous theories regarding the cause of HG, but the cause remains controversial. It is thought that HG is due to a combination of factors which may vary between women and include genetics.[11] Women with family members who had Hyperemesis are more likely to develop the disease.[16]

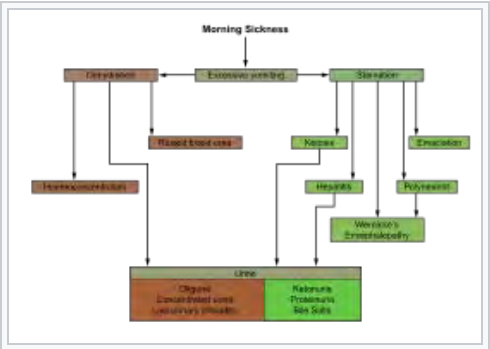
One factor is an adverse reaction to the hormonal changes of pregnancy, in particular, elevated levels of beta human chorionic gonadotropin (hCG).[17][18] This theory would also explain why hyperemesis gravidarum is most frequently encountered in the first trimester (often around 8–12 weeks of gestation), as hCG levels are highest at that time and decline afterward. Another postulated cause of HG is an increase in maternal levels of estrogens (decreasing intestinal motility and gastric emptying leading to nausea/vomiting).[11]

## Pathophysiology [edit]

Although the pathophysiology of HG is poorly understood, the most commonly accepted theory suggests that levels of hCG are associated with it.[5] Leptin may also play a role.[19]

Possible pathophysiological processes involved are summarized in the following table:[20]

| Source | Etiology | Pathophysiology |
|---|---|---|
| ▪ Placenta<br>▪ Corpus luteum | hCG | ▪ Distention of gastrointestinal tract<br>▪ Crossover with TSH, causing gestational thyrotoxicosis[5] |
| Placenta | ▪ Estrogen<br>▪ Progesterone | ▪ Decreased gut mobility<br>▪ Elevated liver enzymes<br>▪ Decreased lower esophageal sphincter pressure<br>▪ Increased levels of sex steroids in hepatic portal system[21] |
| Gastrointestinal tract | *Helicobacter pylori* | Increased steroid levels in circulation[22] |



Morning sickness

## Diagnosis [edit]

Hyperemesis gravidarum is considered a diagnosis of exclusion.[11] HG can be associated with serious problems in the mother or baby, such as Wernicke's encephalopathy, coagulopathy, peripheral neuropathy.[5]

Women experiencing hyperemesis gravidarum often are dehydrated and lose weight despite efforts to eat.[23][24] The onset of the nausea and vomiting in hyperemesis gravidarum is typically before the twenty-second week of pregnancy.[11]

## Differential diagnosis [edit]

Diagnoses to be ruled out include the following:[20]

| Type | Differential diagnoses |
|---|---|
| Infections<br>(usually accompanied by fever or associated neurological symptoms) | ▪ Urinary tract infection<br>▪ Hepatitis<br>▪ Meningitis<br>▪ Gastroenteritis |
| Gastrointestinal disorders<br>(usually accompanied by abdominal pain) | ▪ Appendicitis<br>▪ Cholecystitis<br>▪ Pancreatitis<br>▪ Fatty liver<br>▪ Peptic ulcer<br>▪ Small bowel obstruction |
| Metabolic | ▪ Thyrotoxicosis (common in Asian subcontinent)[5]<br>▪ Addison's disease<br>▪ Diabetic ketoacidosis<br>▪ Hyperparathyroidism |
| Drugs | ▪ Antibiotics<br>▪ Iron supplements |
| Gestational trophoblastic diseases (rule out with urine β-hCG) | ▪ Molar pregnancy<br>▪ choriocarcinoma |

## Investigations [edit]

Common investigations include blood urea nitrogen (BUN) and electrolytes, liver function tests, urinalysis,[24] and thyroid function tests. Hematological investigations include hematocrit levels, which are usually raised in HG.[24] An ultrasound scan may be needed to know gestational status and to exclude molar or partial molar pregnancy.[25]

# Management [edit]

Dry bland food and oral rehydration are first-line treatments.[26] Due to the potential for severe dehydration and other complications, HG is treated as an emergency. If conservative dietary measures fail, more extensive treatment such as the use of antiemetic medications and intravenous rehydration may be required. If oral nutrition is insufficient, intravenous nutritional support may be needed.[12] For women who require hospital admission, thromboembolic stockings or low-molecular-weight heparin may be used as measures to prevent the formation of a blood clot.[20]

## Intravenous fluids [edit]

Intravenous (IV) hydration often includes supplementation of electrolytes as persistent vomiting frequently leads to a deficiency. Likewise, supplementation for lost thiamine (Vitamin $B_1$) must be considered to reduce the risk of Wernicke's encephalopathy.[27] A and B vitamins are depleted within two weeks, so extended malnutrition indicates a need for evaluation and supplementation. In addition, electrolyte levels should be monitored and supplemented; of particular concern are sodium and potassium.

After IV rehydration is completed, patients in general progress to frequent small liquid or bland meals. After rehydration, treatment focuses on managing symptoms to allow normal intake of food. However, cycles of hydration and dehydration can occur, making continuing care necessary. Home care is available in the form of a PICC line for hydration and nutrition (called total parenteral nutrition).[28] Home treatment is often less expensive than long-term or repeated hospitalizations.

## Medications [edit]

A number of antiemetics are effective and safe in pregnancy including: pyridoxine/doxylamine, antihistamines (such as diphenhydramine), and phenothiazines (such as promethazine).[29] With respect to effectiveness, it is unknown if one is superior to another,[29] and there is even limited evidence of significant effect at all of pharmacological therapy in hyperemesis gravidarum.[30]

While pyridoxine/doxylamine, a combination of vitamin $B_6$ and doxylamine, is effective in nausea and vomiting of pregnancy,[31] some have questioned its effectiveness in HG.[32] Ondansetron may be beneficial, however, there are some concerns regarding an association with cleft palate,[33] and there is little high-quality data.[29] Metoclopramide is also used and relatively well tolerated.[34] Evidence for the use of corticosteroids is weak; there is some evidence that corticosteroid use in pregnant women may slightly increase the risk of oral facial clefts in the infant and may suppress fetal adrenal activity.[11][35] However, hydrocortisone and prednisolone are inactivated in the placenta and may be used in the treatment of hyperemesis gravidarum after 12 weeks.[11]

### Nutritional support [edit]

Women not responding to IV rehydration and medication may require nutritional support. Patients might receive parenteral nutrition (intravenous feeding via a PICC line) or enteral nutrition (via a nasogastric tube or a nasojejunal tube). There is only limited evidence from trials to support the use of vitamin B6 to improve outcome.[30] Hyperalimentation may be necessary in certain cases to help maintain volume requirements and allow weight gain.[25] A physician might also prescribe Vitamin B1 (to prevent Wernicke's encephalopathy) and folic acid supplementation.[20]

### Alternative medicine [edit]

Acupuncture (both with P6 and traditional method) has been found to be ineffective.[30][*needs update*][36][*needs update*] The use of ginger products may be helpful, but evidence of effectiveness is limited and inconsistent, though two recent studies support ginger over placebo.[30]

## Complications [edit]

### Pregnant woman [edit]

If HG is inadequately treated, anemia,[11] hyponatremia,[11] Wernicke's encephalopathy,[11] kidney failure, central pontine myelinolysis, coagulopathy, atrophy, Mallory-Weiss tears,[11] hypoglycemia, jaundice, malnutrition, pneumomediastinum, rhabdomyolysis, deconditioning, deep vein thrombosis, pulmonary embolism, splenic avulsion, or vasospasms of cerebral arteries are possible consequences. Depression and PTSD [37] are common secondary complications of HG and emotional support can be beneficial.[11]

### Infant [edit]

The effects of HG on the fetus are mainly due to electrolyte imbalances caused by HG in the mother.[20] Infants of women with severe hyperemesis who gain less than 7 kg (15.4 lb) during pregnancy tend to be of lower birth weight, small for gestational age, and born before 37 weeks gestation.[12] In contrast, infants of women with hyperemesis who have a pregnancy weight gain of more than 7 kg appear similar to infants from uncomplicated pregnancies.[38] There is no significant difference in the neonatal death rate in infants born to mothers with HG compared to infants born to mothers who do not have HG.[11] Children born to mothers with undertreated Hyperemesis have a fourfold increase in neurobehavioral diagnoses.[39]

## Epidemiology [edit]

Vomiting is a common condition affecting about 50% of pregnant women, with another 25% having nausea.[40] However, the incidence of HG is only 0.3–1.5%.[5] After preterm labor, hyperemesis gravidarum is the second most common reason for hospital admission during the first half of pregnancy.[11] Factors such as infection with *Helicobacter pylori*, a rise in thyroid hormone production, low age, low body mass index prior to pregnancy, multiple pregnancies, molar pregnancies, and a past history of hyperemesis gravidarum have been associated with the development of HG.[11]

## History [edit]

Thalidomide was prescribed for treatment of HG in Europe until it was recognized that thalidomide is teratogenic and is a cause of phocomelia in neonates.[41]

### Etymology [edit]

Hyperemesis gravidarum is from the Greek *hyper-*, meaning excessive, and *emesis*, meaning vomiting, and the Latin *gravidarum*, the feminine genitive plural form of an adjective, here used as a noun, meaning "pregnant [woman]". Therefore,

hyperemesis gravidarum means "excessive vomiting of pregnant women".

## Notable cases [edit]

Author Charlotte Brontë is often thought to have suffered from hyperemesis gravidarum. She died in 1855 while four months pregnant, having been afflicted by intractable nausea and vomiting throughout her pregnancy, and was unable to tolerate food or even water.[42]

Catherine, Duchess of Cambridge was hospitalised due to hyperemesis gravidarum during her first pregnancy, and was treated for a similar condition during her second pregnancy.[43]

The Saturdays singer Frankie Bridge had hyperemesis gravidarum during her second pregnancy.[44]

## References [edit]


1. ^ "Management of hyperemesis gravidarum.". *Drug Ther Bull*. **51** (11): 129–9. November 2013. doi:10.1136/dtb.2013.11.0215. PMID 24227770.
2. ^ a b c "Pregnancy". *Office on Women's Health*. September 27, 2010. Retrieved 5 December 2015.
3. ^ a b c d e f Jueckstock, JK; Kaestner, R; Mylonas, I (15 July 2010). "Managing hyperemesis gravidarum: a multimodal challenge.". *BMC medicine*. **8**: 46. doi:10.1186/1741-7015-8-46. PMC 2913953. PMID 20633258.
4. ^ a b Ferri, Fred F. (2012). *Ferri's clinical advisor 2013 5 books in 1* (1st ed.). Elsevier Mosby. p. 538. ISBN 9780323083737.
5. ^ a b c d e f g h Sheehan, P (September 2007). "Hyperemesis gravidarum—assessment and management" (PDF). *Australian Family Physician*. **36** (9): 698–701. PMID 17885701.
6. ^ a b Gabbe, Steven G. (2012). *Obstetrics : normal and problem pregnancies* (6th ed.). Elsevier/Saunders. p. 117. ISBN 9781437719352.
7. ^ Davis, Christopher J. (1986). *Nausea and Vomiting : Mechanisms and Treatment*. Springer. p. 152. ISBN 9783642704796.
8. ^ Goodwin, TM (September 2008). "Hyperemesis gravidarum". *Obstetrics and gynecology clinics of North America*. **35** (3): 401–17, viii. doi:10.1016/j.ogc.2008.04.002. PMID 18760227.
9. ^ Kumar, Geeta (2011). *Early Pregnancy Issues for the MRCOG and Beyond*. Cambridge University Press. p. Chapter 6. ISBN 9781107717992.
10. ^ DeLegge, Mark H. (2007). *Handbook of home nutrition support*. Sudbury, Mass.: Jones and Bartlett. p. 320. ISBN 9780763747695.
11. ^ a b c d e f g h i j k l m n o p Summers A (2012). "Emergency management of hyperemesis gravidarum". *Emergency Nurse*. **20** (4): 24–8. doi:10.7748/en2012.07.20.4.24.c9206. PMID 22876404.
12. ^ a b c d Ahmed KT, Almashhrawi AA, Rahman RN, Hammoud GM, Ibdah JA; Almashhrawi; Rahman; Hammoud; Ibdah (November 2013). "Liver diseases in pregnancy: diseases unique to pregnancy". *World J Gastroenterol*. **19** (43): 7639–46. doi:10.3748/wjg.v19.i43.7639. PMC 3837262. PMID 24282353.
13. ^ Matthews DC, Syed AA (2011). "The role of TSH receptor antibodies in the management of Graves' disease". *European Journal of Internal Medicine*. **22** (3): 213–6. doi:10.1016/j.ejim.2011.02.006. PMID 21570635.
14. ^ Carlson, Karen J., MD; Eisenstat, Stephanie J., MD; Ziporyn, Terra (2004). *The New Harvard Guide to Women's Health*. Harvard University Press. pp. 392–3. ISBN 0-674-01343-3.
15. ^ "Do I Have Morning Sickness or HG?". H.E.R. Foundation. Retrieved 6 December 2012.
16. ^ Zhang Y, Cantor RM, MacGibbon K, Romero R, Goodwin TM, Mullin PM, Fejzo MS (2011). "Familial aggregation of
23. ^ "Hyperemesis Gravidarum (Severe Nausea and Vomiting During Pregnancy)". Cleveland Clinic. 2012. Retrieved 23 January 2013.
24. ^ a b c Medline Plus (2012). "Hyperemesis gravidarum". National Institutes of Health. Retrieved 30 January 2013.
25. ^ a b Evans, Arthur T., ed. (2007). *Manual of obstetrics* (7th ed.). Wolters Kluwer / Lippincott Williams & Wilkins. pp. 265–8. ISBN 9780781796965.
26. ^ Office on Women's Health (2010). "Pregnancy Complications". U.S. Department of Health and Human Services. Retrieved 27 October 2013.
27. ^ British National Formulary (March 2003). "4.6 Drugs used in nausea and vertigo – Vomiting of pregnancy". *BNF* (45 ed.).
28. ^ Tuot, D; Gibson, S; Caughey, AB; Frassetto, LA (March 2010). "Intradialytic hyperalimentation as adjuvant support in pregnant hemodialysis patients: case report and review of the literature". *International urology and nephrology*. **42** (1): 233–7. doi:10.1007/s11255-009-9671-5. PMC 2844957. PMID 19911296.
29. ^ a b c Jarvis, S; Nelson-Piercy, C (June 2011). "Management of nausea and vomiting in pregnancy.". *BMJ (Clinical research ed.)*. **342**: d3606. doi:10.1136/bmj.d3606. PMID 21685438.
30. ^ a b c d Matthews, Anne; Haas, David M; O'Mathúna, Dónal P; Dowswell, Therese; Doyle, Mary; Matthews, Anne (2014). "Interventions for nausea and vomiting in early pregnancy". *Cochrane Database of Systematic Reviews*. **3**: CD007575. doi:10.1002/14651858.CD007575.pub3. PMID 24659261.
31. ^ Tan, PC; Omar, SZ (April 2011). "Contemporary approaches to hyperemesis during pregnancy". *Current Opinion in Obstetrics and Gynecology*. **23** (2): 87–93. doi:10.1097/GCO.0b013e328342d208. PMID 21297474.
32. ^ Tamay, AG; Kuşçu, NK (November 2011). "Hyperemesis gravidarum: current aspect". *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology*. **31** (8): 708–12. doi:10.3109/01443615.2011.611918. PMID 22085059.
33. ^ Koren, G (October 2012). "Motherisk update. Is ondansetron safe for use during pregnancy?". *Canadian Family Physician*. **58** (10): 1092–3. PMC 3470505. PMID 23064917.
34. ^ Tan, PC; Omar, SZ (April 2011). "Contemporary approaches to hyperemesis during pregnancy". *Current Opinion in Obstetrics and Gynecology*. **23** (2): 87–93. doi:10.1097/GCO.0b013e328342d208. PMID 21297474.
35. ^ Poon, SL (October 2011). "Towards evidence-based emergency medicine: Best BETs from the Manchester Royal Infirmary. BET 2: Steroid therapy in the treatment of intractable hyperemesis gravidarum". *Emergency medicine journal : EMJ*. **28** (10): 898–900. doi:10.1136/emermed-2011-200636. PMID 21918097.
36. ^ Matthews, A; Dowswell, T; Haas, DM; Doyle, M; O'Mathúna,

hyperemesis gravidarum". *American Journal of Obstetrics and Gynecology*. **204** (3): 230.e1–7. doi:10.1016/j.ajog.2010.09.018. PMC 3030697. PMID 20974461.
17. ^ Cole, LA (August 2010). "Biological functions of hCG and hCG-related molecules". *Reproductive biology and endocrinology*. **8** (102): 102. doi:10.1186/1477-7827-8-102. PMC 2936313. PMID 20735820.
18. ^ Hershman JM (June 2004). "Physiological and pathological aspects of the effect of human chorionic gonadotropin on the thyroid". *Best Pract. Res. Clin. Endocrinol. Metab.* **18** (2): 249–65. doi:10.1016/j.beem.2004.03.010. PMID 15157839.
19. ^ Aka N, Atalay S, Sayharman S, Kiliç D, Köse G, Küçüközkan T; Atalay; Sayharman; Kiliç; Köse; Küçüközkan (2006). "Leptin and leptin receptor levels in pregnant women with hyperemesis gravidarum". *The Australian & New Zealand journal of obstetrics & gynaecology*. **46** (4): 274–7. doi:10.1111/j.1479-828X.2006.00590.x. PMID 16866785.
20. ^ *a b c d e* Bourne,, Thomas H.; Condous, George, eds. (2006). *Handbook of early pregnancy care*. Informa Healthcare. pp. 149–154. ISBN 9781842143230.
21. ^ Verberg, MF; Gillott, DJ; Al-Fardan, N; Grudzinskas, JG (September–October 2005). "Hyperemesis gravidarum, a literature review". *Human Reproduction Update*. **11** (5): 527–539. doi:10.1093/humupd/dmi021. PMID 16006438.
22. ^ Bagis, T; Gumurdulu, Y; Kayaselcuk, F; Yilmaz, ES; Killicadag, E; Tarim, E (November 2002). "Endoscopy in hyperemesis gravidarum and *Helicobacter pylori* infection". *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. **79** (2): 105–9. doi:10.1016/s0020-7292(02)00230-8. PMID 12427393.

DP (September 2010). "Interventions for nausea and vomiting in early pregnancy". *Cochrane database of systematic reviews (Online)* (9): CD007575. doi:10.1002/14651858.CD007575.pub2. PMC 4004939. PMID 20824863.
37. ^ Christodoulou-Smith J, Gold JI, Romero R, Goodwin TM, Macgibbon KW, Mullin PM, Fejzo MS (2011). "Posttraumatic stress symptoms following pregnancy complicated by hyperemesis gravidarum". *The Journal of Maternal-fetal & Neonatal Medicine*. **24** (11): 1307–11. doi:10.3109/14767058.2011.582904. PMC 3514078. PMID 21635201.
38. ^ Dodds L, Fell DB, Joseph KS, Allen VM, Butler B.; Fell; Joseph; Allen; Butler (2006). "Outcomes of pregnancies complicated by hyperemesis gravidarum". *Obstet Gynecol*. **107** (2 Pt 1): 285–92. doi:10.1097/01.AOG.0000195060.22832.cd. PMID 16449113.
39. ^ Fejzo MS, Magtira A, Schoenberg FP, Macgibbon K, Mullin PM (June 2015). "Neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum" (PDF). *Eur J Obstet Gynecol Reprod Biol*. **189**: 79–84. doi:10.1016/j.ejogrb.2015.03.028. PMID 25898368.
40. ^ Niebyl, Jennifer R. (2010). "Nausea and Vomiting in Pregnancy". *New England Journal of Medicine*. **363** (16): 1544–50. doi:10.1056/NEJMcp1003896. PMID 20942670.
41. ^ Cohen, Wayne R., ed. (2000). *Cherry and Merkatz's complications of pregnancy.* (5th ed.). Lippincott Williams & Wilkins. p. 124. ISBN 9780683016734.
42. ^ McSweeny, Linda (2010-06-03). "What is acute morning sickness?". *The Age*. Retrieved 2012-12-04.
43. ^ "Prince William, Kate expecting 2nd child". 8 September 2014. Retrieved 8 September 2014.
44. ^ "Frankie Bridge gives birth to baby boy". 15 August 2015.

v · t · e · **Pathology of pregnancy, childbirth and the puerperium (O, 630–679)**

| | | | |
|---|---|---|---|
| **Pregnancy** | **Pregnancy with abortive outcome** | | Ectopic pregnancy (Abdominal pregnancy · Cervical pregnancy · Interstitial pregnancy · Ovarian pregnancy · · Molar pregnancy · Miscarriage · Stillbirth · |
| | **Oedema, proteinuria and hypertensive disorders** | | Gestational hypertension · Pre-eclampsia (HELLP syndrome · · Eclampsia · |
| | **Other, predominantly related to pregnancy** | **Digestive system** | Acute fatty liver of pregnancy · Gestational diabetes · Hepatitis E · **Hyperemesis gravidarum** · Intrahepatic cholestasis of pregnancy · |
| | | **Integumentary system / dermatoses of pregnancy** | Gestational pemphigoid · Impetigo herpetiformis · Intrahepatic cholestasis of pregnancy · Linea nigra · Prurigo gestationis · Pruritic folliculitis of pregnancy · Pruritic urticarial papules and plaques of pregnancy (PUPPP) · Striae gravidarum · |
| | | **Nervous system** | Chorea gravidarum · |
| | | **Blood** | Gestational thrombocytopenia · Pregnancy-induced hypercoagulability · |
| | **Maternal care related to the fetus and amniotic cavity** | | *amniotic fluid* (Oligohydramnios · Polyhydramnios · · Braxton Hicks contractions · *chorion* / *amnion* (Amniotic band syndrome · Chorioamnionitis · Chorionic hematoma · Monoamniotic twins · Premature rupture of membranes · · Obstetrical hemorrhage (Antepartum · · *placenta* (Circumvallate placenta · Monochorionic twins · Placenta praevia · Placental abruption · Twin-to-twin transfusion syndrome · · |
| **Labor** | | | Amniotic fluid embolism · Cephalopelvic disproportion · Dystocia (Shoulder dystocia · · Fetal distress · Locked twins · Obstetrical hemorrhage (Postpartum · · *placenta* (Placenta accreta · · Preterm birth · Postmature birth · Umbilical cord prolapse · Uterine rupture · Vasa praevia · |

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| **Puerperal** | Breastfeeding difficulties (Lactation failure · Galactorrhea · Fissure of the nipple · · Breast engorgement · Diastasis symphysis pubis · Peripartum cardiomyopathy · Postpartum depression · Postpartum thyroiditis · Puerperal fever · Puerperal mastitis · |
| **Other** | Concomitant conditions (Diabetes mellitus · Systemic lupus erythematosus · Thyroid disorders · · Maternal death · Sexual activity during pregnancy · |

Categories: Health issues in pregnancy | Vomiting | Women's health




# Menopause

From Wikipedia, the free encyclopedia

*This article is about women. For the condition called male menopause, see Andropause. For the medical journal, see Menopause (journal).*

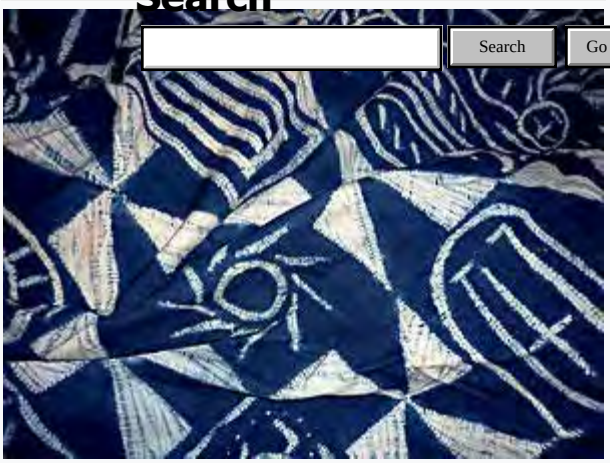
**Menopause**, also known as the **climacteric**, is the time in most women's lives when menstrual periods stop permanently, and they are no longer able to bear children.[2][3] Menopause typically occurs between 49 and 52 years of age.[4] Medical professionals often define menopause as having occurred when a woman has not had any vaginal bleeding for a year.[5] It may also be defined by a decrease in hormone production by the ovaries.[6] In those who have had surgery to remove their uterus but they still have ovaries, menopause may be viewed to have occurred at the time of the surgery or when their hormone levels fell.[6] Following the removal of the uterus, symptoms typically occur earlier, at an average of 45 years of age.[7]

Before menopause, a woman's periods typically become irregular, which means that periods may be longer or shorter in duration or be lighter or heavier in the amount of flow. During this time, women often experience hot flashes; these typically last from 30 seconds to ten minutes and may be associated with shivering, sweating, and reddening of the skin.[8] Hot flashes often stop occurring after a year or two.[3] Other symptoms may include vaginal dryness, trouble sleeping, and mood changes.[8] The severity of symptoms varies between women.[3] While menopause is often thought to be linked to an increase in heart disease, this primarily occurs due to increasing age and does not have a direct relationship with menopause. In some women, problems that were present like endometriosis or painful periods will improve after menopause.[3]

Menopause is usually a natural change.[9] It can occur earlier in those who smoke tobacco.[5][10] Other causes include surgery that removes both ovaries or some types of chemotherapy.[5] At the physiological level, menopause happens because of a decrease in the ovaries' production of the hormones estrogen and progesterone.[2] While typically not needed, a diagnosis of menopause can be confirmed by measuring hormone levels in the blood or urine.[11] Menopause is the opposite of menarche, the time when a girl's periods start.[12]

Specific treatment is not usually needed. Some symptoms, however, may be improved with treatment. With respect to hot flashes, avoiding smoking, caffeine, and alcohol is often recommended. Sleeping in a cool room and using a fan may help.[13] The following medications may help: menopausal hormone therapy

**Menopause**



An *Ukara Ekpe* textile from the Igbo culture which is secretly dyed by post-menopausal women.[1]

| Classification and external resources | |
|---|---|
| **Specialty** | Gynecology |
| **ICD-10** | N95.0 |
| **ICD-9-CM** | 627.2 |
| **DiseasesDB** | 8034 |
| **MedlinePlus** | 000894 |
| **eMedicine** | article/264088 |
| **MeSH** | D008593 |

[edit on Wikidata]

(MHT), clonidine, gabapentin, or selective serotonin reuptake inhibitors.[13][14] Exercise may help with sleeping problems. While MHT was once routinely prescribed, it is now only recommended in those with significant symptoms, as there are concerns about side effects.[13] High-quality evidence for the effectiveness of alternative medicine has not been found.[3] There is tentative evidence for soy isoflavones.[15]





## Signs and symptoms [edit]

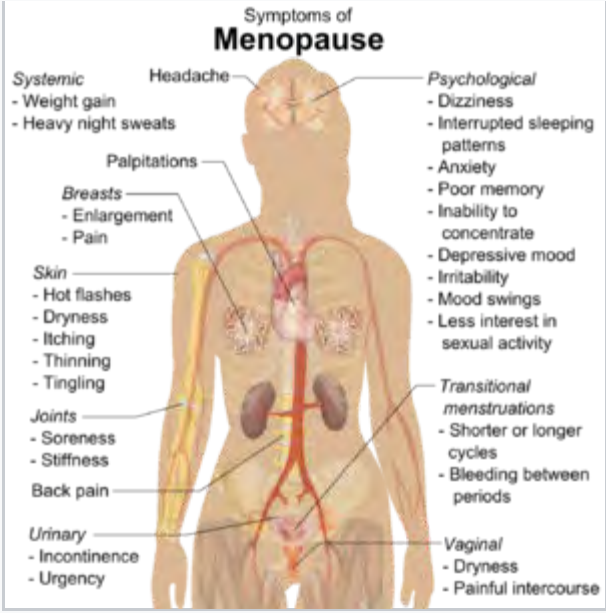
During early menopause transition, the menstrual cycles remain regular but the interval between cycles begins to lengthen. Hormone levels begin to fluctuate. Ovulation may not occur with each cycle.[16]

The date of the final menstrual period is usually taken as the point when menopause has occurred.[16] During the menopausal transition and after menopause, women can experience a wide range of symptoms.

Edit links

### Vagina and uterus [edit]

During the transition to menopause, menstrual patterns can show shorter cycling (by 2–7 days);[16] longer cycles remain



Symptoms of menopause

possible.[16] There may be irregular bleeding (lighter, heavier, spotting).[16] Dysfunctional uterine bleeding is often experienced by women approaching menopause due to the hormonal changes that accompany the menopause transition. Spotting or bleeding may simply be related to vaginal atrophy, a benign sore (polyp or lesion), or may be a functional endometrial response. The European Menopause and Andropause Society has released guidelines for assessment of the endometrium, which is usually the main source of spotting or bleeding.[17]

In post-menopausal women, however, any genital bleeding is an alarming symptom that requires an appropriate study to rule out the possibility of malignant diseases.

Symptoms that may appear during menopause and continue through postmenopause include:

- painful intercourse[16]
- vaginal dryness[16]
- atrophic vaginitis — thinning of the membranes of the vulva, the vagina, the cervix, and the outer urinary tract, along with considerable shrinking and loss in elasticity of all of the outer and inner genital areas.


Vaginal canal, normal vs. menopause

## Other physical [edit]

Other physical symptoms of menopause include lack of energy, joint soreness, stiffness,[16] back pain,[16] breast enlargement,[16] breast pain,[16] heart palpitations,[16] headache,[16] dizziness,[16] dry, itchy skin,[16] thinning, tingling skin, weight gain,[16] urinary incontinence,[16][18] urinary urgency,[16] interrupted sleeping patterns,[16][19][20][21] heavy night sweats,[16] hot flashes.[16]

## Psychological [edit]

Psychological symptoms include anxiety,[22] poor memory,[16] inability to concentrate,[16] depressive mood,[16][22] irritability,[16] mood swings,[16] less interest in sexual activity.[16]

## Long term effects [edit]

Menopause confers:

- A possible but contentious increased risk of atherosclerosis.[23] The risk of acute myocardial infarction and other cardiovascular diseases rises sharply after menopause, but the risk can be reduced by managing risk factors, such as tobacco smoking, hypertension, increased blood lipids and body

weight.[24][25]
- Increased risk of osteopenia and osteoporosis[*citation needed*]

Women who experience menopause before 45 years of age have an increased risk of heart disease and death.[26]

## Causes [edit]

### Age [edit]

In the Western world, the typical age of menopause (last period from natural causes) is between 40 and 61[27] and the average age for last period is 51 years.[28] The average age of natural menopause in Australia is 51.7 years.[29] In India and the Philippines, the median age of natural menopause is considerably earlier, at 44 years.[30]

In rare cases, a woman's ovaries stop working at a very early age, ranging anywhere from the age of puberty to age 40. This is known as premature ovarian failure and affects 1 to 2% of women by age 40.[31]

Undiagnosed and untreated coeliac disease is a risk factor for early menopause. Coeliac disease can present with several non-gastrointestinal symptoms, in the absence of gastrointestinal symptoms, and most cases escape timely recognition and go undiagnosed, leading to a risk of long-term complications. A strict gluten-free diet reduces the risk. Women with early diagnosis and treatment of coeliac disease present a normal duration of fertile life span.[32][33]

Women who have undergone hysterectomy with ovary conservation go through menopause on average 3.7 years earlier than the expected age. Other factors that can promote an earlier onset of menopause (usually 1 to 3 years early) are smoking cigarettes or being extremely thin.[34]

### Premature ovarian failure [edit]

Premature ovarian failure (POF) is diagnosed or confirmed by high blood levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) on at least three occasions at least four weeks apart.[35]

Known causes of premature ovarian failure include autoimmune disorders, thyroid disease, diabetes mellitus, chemotherapy, being a carrier of the fragile X syndrome gene, and radiotherapy. However, in the majority of spontaneous cases of premature ovarian failure, the cause is unknown, i.e., it is generally idiopathic.[35]

Women who have a functional disorder affecting the reproductive system (e.g., endometriosis, polycystic ovary syndrome, cancer of the reproductive organs) can go into menopause at a younger age than the normal timeframe. The functional disorders often significantly speed up the menopausal process.

An early menopause can be related to cigarette smoking, higher body mass index, racial and ethnic factors, illnesses, and the surgical removal of the ovaries, with or without the removal of the uterus.[36]

Rates of premature menopause have been found to be significantly higher in fraternal and identical twins; approximately 5% of twins reach menopause before the age of 40. The reasons for this are not completely understood. Transplants of ovarian tissue between identical twins have been successful in restoring fertility.

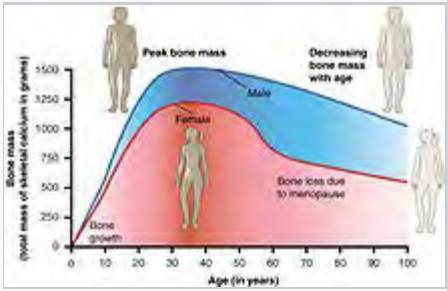
### Surgical menopause [edit]

Menopause can be surgically induced by bilateral oophorectomy (removal of ovaries), which is often, but not always, done in conjunction with removal of the Fallopian tubes (salpingo-oophorectomy) and uterus (hysterectomy).[37] Cessation of menses as a result of removal of the ovaries is called "surgical menopause". The sudden and complete drop in hormone levels usually produces extreme withdrawal symptoms such as hot flashes, etc.

Removal of the uterus *without* removal of the ovaries does *not* directly cause menopause, although pelvic

surgery of this type can often precipitate a somewhat earlier menopause, perhaps because of a compromised blood supply to the ovaries.[*citation needed*]

## Mechanism [edit]



Bone loss due to menopause occurs due to changes in a woman's hormone levels.

The menopausal transition, and postmenopause itself, is a natural change, not usually a disease state or a disorder. The main cause of this transition is the natural depletion and aging of the finite amount of oocytes (ovarian reserve). This process is sometimes accelerated by other conditions and is known to occur earlier after a wide range of gynecologic procedures such as hysterectomy (with and without ovariectomy), endometrial ablation and uterine artery embolisation. The depletion of the ovarian reserve causes an increase in circulating follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels because there are a decreased number of oocytes and follicles responding to these hormones and producing estrogen.

The transition has a variable degree of effects.[38]

The stages of the menopause transition have been classified according to a woman's reported bleeding pattern, supported by changes in the pituitary follicle-stimulating hormone (FSH) levels.[39]

In younger women, during a normal menstrual cycle the ovaries produce estradiol, testosterone and progesterone in a cyclical pattern under the control of FSH and luteinising hormone (LH) which are both produced by the pituitary gland. During perimenopause (approaching menopause), estradiol levels and patterns of production remain relatively unchanged or may increase compared to young women, but the cycles become frequently shorter or irregular.[40] The often observed increase in estrogen is presumed to be in response to elevated FSH levels that, in turn, is hypothesized to be caused by decreased feedback by inhibin.[41] Similarly, decreased inhibin feedback after hysterectomy is hypothesized to contribute to increased ovarian stimulation and earlier menopause.[42][43]

The menopausal transition is characterized by marked, and often dramatic, variations in FSH and estradiol levels. Because of this, measurements of these hormones are *not* considered to be reliable guides to a woman's exact menopausal status.[44]

Menopause occurs because of the sharp decrease of estradiol and progesterone production by the ovaries. After menopause, estrogen continues to be produced mostly by aromatase in fat tissues and is produced in small amounts in many other tissues such as ovaries, bone, blood vessels, and the brain where it acts locally.[45] The substantial fall in circulating estradiol levels at menopause impacts many tissues, from brain to skin.

In contrast to the sudden fall in estradiol during menopause, the levels of total and free testosterone, as well as dehydroepiandrosterone sulfate (DHEAS) and androstenedione appear to decline more or less steadily with age. An effect of natural menopause on circulating androgen levels has not been observed.[46] Thus specific tissue effects of natural menopause cannot be attributed to loss of androgenic hormone production.[47]

Hot flushes and other vasomotor symptoms accompany the menopausal transition. While many sources continue to claim that hot flashes during the menopausal transition are caused by low estrogen levels, this assertion was shown incorrect in 1935 and, in most cases, hot flushes are observed despite elevated estrogen levels. The exact cause of these symptoms is not yet understood, possible factors considered are higher and erratic variation of estradiol level during the cycle, elevated FSH levels which may indicate hypothalamic dysregulation perhaps caused by missing feedback by inhibin. It has been also observed that the vasomotor symptoms differ during early perimenopause and late menopausal transition and it is possible that they are caused by a different mechanism.[40]

Long-term effects of menopause may include osteoporosis, vaginal atrophy as well as changed metabolic

profile resulting in cardiac risks.

### Ovarian aging [edit]

Decreased inhibin feedback after hysterectomy is hypothesized to contribute to increased ovarian stimulation and earlier menopause. Hastened ovarian aging has been observed after endometrial ablation. While it is difficult to prove that these surgeries are causative, it has been hypothesized that the endometrium may be producing endocrine factors contributing to the endocrine feedback and regulation of the ovarian stimulation. Elimination of this factors contributes to faster depletion of the ovarian reserve. Reduced blood supply to the ovaries that may occur as a consequence of hysterectomy and uterine artery embolisation has been hypothesized to contribute to this effect.[42][43]

Impaired DNA repair mechanisms may contribute to earlier depletion of the ovarian reserve during aging.[48] As women age, double-strand breaks accumulate in the DNA of their primordial follicles. Primordial follicles are immature primary oocytes surrounded by a single layer of granulosa cells. An enzyme system is present in oocytes that ordinarily accurately repairs DNA double-strand breaks. This repair system is called "homologous recombinational repair", and it is especially effective during meiosis. Meiosis is the general process by which germ cells are formed in all sexual eukaryotes; it appears to be an adaptation for efficiently removing damages in germ line DNA.[49] (See Meiosis.)

Human primary oocytes are present at an intermediate stage of meiosis, termed prophase I (see Oogenesis). Expression of four key DNA repair genes that are necessary for homologous recombinational repair during meiosis (BRCA1, MRE11, Rad51, and ATM) decline with age in oocytes.[48] This age-related decline in ability to repair DNA double-strand damages can account for the accumulation of these damages, that then likely contributes to the depletion of the ovarian reserve.

## Diagnosis [edit]

One way of assessing the impact on women of some of these menopause effects are the Greene Climacteric Scale questionnaire,[50] the Cervantes Scale[51] and the Menopause Rating Scale.[19]

### Premenopause [edit]

Premenopause is a term used to mean the years leading up to the last period, when the levels of reproductive hormones are becoming more variable and lower, and the effects of hormone withdrawal are present.[37] Premenopause starts some time before the monthly cycles become noticeably irregular in timing.[52]

### Perimenopause [edit]

The term "perimenopause", which literally means "around the menopause", refers to the menopause transition years, a time before *and* after the date of the final episode of flow. According to the North American Menopause Society, this transition can last for four to eight years.[53] The Centre for Menstrual Cycle and Ovulation Research describes it as a six- to ten-year phase ending 12 months after the last menstrual period.[54]

During perimenopause, estrogen levels average about 20–30% higher than during premenopause, often with wide fluctuations.[54] These fluctuations cause many of the physical changes during perimenopause as well as menopause.[55] Some of these changes are hot flashes, night sweats, difficulty sleeping, vaginal dryness or atrophy, incontinence, osteoporosis, and heart disease.[54] During this period, fertility diminishes but is not considered to reach zero until the official date of menopause. The official date is determined retroactively, once 12 months have passed after the last appearance of menstrual blood.

The menopause transition typically begins between 40 and 50 years of age (average 47.5).[56][57] The duration of perimenopause may be for up to eight years.[57] Women will often, but not always, start these [58]

transitions (perimenopause and menopause) about the same time as their mother did.

In some women, menopause may bring about a sense of loss related to the end of fertility. In addition, this change often occurs when other stressors may be present in a woman's life:

- Caring for, and/or the death of, elderly parents
- Empty nest syndrome when children leave home
- The birth of grandchildren, which places people of "middle age" into a new category of "older people" (especially in cultures where being older is a state that is looked down on)

Some research appears to show that melatonin supplementation in perimenopausal women can improve thyroid function and gonadotropin levels, as well as restoring fertility and menstruation and preventing depression associated with menopause.[59]

### Postmenopause [edit]

The term "postmenopausal" describes women who have not experienced any menstrual flow for a minimum of 12 months, assuming that they have a uterus and are not pregnant or lactating.[37] In women without a uterus, menopause or postmenopause can be identified by a blood test showing a very high FSH level. Thus postmenopause the time in a woman's life that take place after her last period or, more accurately, after the point when her ovaries become inactive.

The reason for this delay in declaring postmenopause is because periods are usually erratic at this time of life. Therefore, a reasonably long stretch of time is necessary to be sure that the cycling has ceased. At this point a woman is considered infertile; however, the possibility of becoming pregnant has usually been very low (but not quite zero) for a number of years before this point is reached.

A woman's reproductive hormone levels continue to drop and fluctuate for some time into post-menopause, so hormone withdrawal effects such as hot flashes may take several years to disappear.

Any period-like flow during postmenopause, even spotting, must be reported to a doctor. The cause may be minor, but the possibility of endometrial cancer must be checked for.

## Management [edit]

Perimenopause is a natural stage of life. It is not a disease or a disorder. Therefore, it does not automatically require any kind of medical treatment. However, in those cases where the physical, mental, and emotional effects of perimenopause are strong enough that they significantly disrupt the life of the woman experiencing them, palliative medical therapy may sometimes be appropriate.

### Hormone replacement therapy [edit]

*Main article: Hormone replacement therapy (menopause)*

In the context of the menopause, hormone replacement therapy (HRT) is the use of estrogen in women without a uterus and estrogen plus progestin in women who have an intact uterus.[60]

HRT may be reasonable for the treatment of menopausal symptoms, such as hot flashes and osteoporosis.[61] Its use appears to increase the risk of strokes and blood clots.[62] When used for menopausal symptoms it should be used for the shortest time possible and at the lowest dose possible.[62] The response to HRT in each postmenopausal woman may not be the same. Genetic polymorphism in estrogen receptors appears to be associated with inter-individual variability in metabolic response to HRT in postmenopausal women.[63]

It also appears effective for preventing bone loss and osteoporotic fracture.[64] It is often seen as a second line agent for this purpose.[65] There is some concern that this treatment increases the risk of breast cancer.[66]

Adding testosterone to hormone therapy has a positive effect on sexual function in postmenopausal women, although it may be accompanied by hair growth, acne and a reduction in high-density lipoprotein (HDL)

cholesterol.[67] These side effects diverge depending on the doses and methods of using testosterone.[67]

### Selective estrogen receptor modulators [edit]

SERMs are a category of drugs, either synthetically produced or derived from a botanical source, that act selectively as agonists or antagonists on the estrogen receptors throughout the body. The most commonly prescribed SERMs are raloxifene and tamoxifen. Raloxifene exhibits oestrogen agonist activity on bone and lipids, and antagonist activity on breast and the endometrium.[68] Tamoxifen is in widespread use for treatment of hormone sensitive breast cancer. Raloxifene prevents vertebral fractures in postmenopausal, osteoporotic women and reduces the risk of invasive breast cancer.[69]

### Other medication [edit]

Some of the SSRIs and SNRIs appear to provide some relief.[14] Low dose paroxetine has been FDA-approved for hot moderate-to-severe vasomotor symptoms associated with menopause.[70] They may, however, be associated with sleeping problems.[14]

Gabapentin or clonidine may help but does not work as well as hormone therapy.[14] Clonidine may be associated with constipation and sleeping problems.[14]

### Alternative medicine [edit]

There is no evidence of consistent benefit of alternative therapies for menopausal symptoms despite their popularity.[71] The effect of soy isoflavones on menopausal symptoms is promising for reduction of hot flashes and vaginal dryness.[15][72] Evidence does not support a benefit from phytoestrogens such as coumestrol,[73] femarelle,[74] or black cohosh.[15][75] There is no evidence to support the efficacy of acupuncture as a management for menopausal symptoms.[76] As of 2011 there is no support for herbal or dietary supplements in the prevention or treatment of the mental changes that occur around menopause.[77] A 2016 Cochrane review found not enough evidence to show a difference between Chinese herbal medicine and placebo for the vasomotor symptoms.[78]

### Other therapies [edit]

- Lack of lubrication is a common problem during and after perimenopause. Vaginal moisturizers can help women with overall dryness, and lubricants can help with lubrication difficulties that may be present during intercourse. It is worth pointing out that moisturizers and lubricants are different products for different issues: some women complain that their genitalia are uncomfortably dry all the time, and they may do better with moisturizers. Those who need only lubricants do well using them only during intercourse.
- Low-dose prescription vaginal estrogen products such as estrogen creams are generally a safe way to use estrogen topically, to help vaginal thinning and dryness problems (see vaginal atrophy) while only minimally increasing the levels of estrogen in the bloodstream.
- In terms of managing hot flashes, lifestyle measures such as drinking cold liquids, staying in cool rooms, using fans, removing excess clothing, and avoiding hot flash triggers such as hot drinks, spicy foods, etc., may partially supplement (or even obviate) the use of medications for some women.
- Individual counseling or support groups can sometimes be helpful to handle sad, depressed, anxious or confused feelings women may be having as they pass through what can be for some a very challenging transition time.
- Osteoporosis can be minimized by smoking cessation, adequate vitamin D intake and regular weight-bearing exercise. The bisphosphate drug alendronate may decrease the risk of a fracture, in women that have both bone loss and a previous fracture and less so for those with just osteoporosis.[79]

## Society and culture [edit]

The cultural context within which a woman lives can have a significant impact on the way she experiences the menopausal transition. Menopause has been described as a subjective experience, with social and cultural factors playing a prominent role in the way menopause is experienced and perceived.

Within the United States, social location affects the way women perceive menopause and its related biological effects. Research indicates that whether a woman views menopause as a medical issue or an expected life change is correlated with her socio-economic status.[80] The paradigm within which a woman considers menopause influences the way she views it: Women who understand menopause as a medical condition rate it significantly more negatively than those who view it as a life transition or a symbol of aging.[81]

Ethnicity and geography play roles in the experience of menopause. American women of different ethnicities report significantly different types of menopausal effects. One major study found Caucasian women most likely to report what are sometimes described as psychosomatic symptoms, while African-American women were more likely to report vasomotor symptoms.[82]

It seems that Japanese women experience menopause effects, or *konenki*, in a different way from American women.[83] Japanese women report lower rates of hot flashes and night sweats; this can be attributed to a variety of factors, both biological and social. Historically, konenki was associated with wealthy middle-class housewives in Japan, i.e., it was a "luxury disease" that women from traditional, inter-generational rural households did not report. Menopause in Japan was viewed as a symptom of the inevitable process of aging, rather than a "revolutionary transition", or a "deficiency disease" in need of management.[83]

In Japanese culture, reporting of vasomotor symptoms has been on the increase, with research conducted by Melissa Melby in 2005 finding that of 140 Japanese participants, hot flashes were prevalent in 22.1%.[84] This was almost double that of 20 years prior.[85] Whilst the exact cause for this is unknown, possible contributing factors include significant dietary changes, increased medicalisation of middle-aged women and increased media attention on the subject.[85] However, reporting of vasomotor symptoms is still significantly lower than North America.[86]

Additionally, while most women in the United States apparently have a negative view of menopause as a time of deterioration or decline, some studies seem to indicate that women from some Asian cultures have an understanding of menopause that focuses on a sense of liberation and celebrates the freedom from the risk of pregnancy.[87] Postmenopausal Indian women can enter Hindu temples and participate in rituals, marking it as a celebration for reaching an age of wisdom and experience.

Diverging from these conclusions, one study appeared to show that many American women "experience this time as one of liberation and self-actualization".[88]

Generally speaking, women raised in the Western world or developed countries in Asia live long enough so that a third of their life is spent in post-menopause. For some women, the menopausal transition represents a major life change, similar to menarche in the magnitude of its social and psychological significance. Although the significance of the changes that surround menarche is fairly well recognized, in countries such as the United States, the social and psychological ramifications of the menopause transition are frequently ignored or underestimated.[*citation needed*]

## Medicalization [edit]

The medicalization of menopause within biomedical practice began in the early 19th century and has affected the way menopause is viewed within society. By the 1930s in North America and Europe, biomedicine practitioners began to think of menopause as a disease-like state. This idea coincided with the concept of the "standardization of the body". The bodies of young premenopausal women began to be considered the "normal", against which all female bodies were compared.[89]

## Etymology [edit]

Menopause literally means the "end of monthly cycles" (the end of monthly periods or menstruation), from

the Greek word *pausis* ("pause") and *mēn* ("month"). This is a medical calque; the Greek word for menses is actually different. In Ancient Greek, the menses were described in the plural, *ta emmēnia*, ("the monthlies"), and its modern descendant has been clipped to *ta emmēna*. The Modern Greek medical term is *emmenopausis* in Katharevousa or *emmenopausi* in Demotic Greek.

The word "menopause" was coined specifically for human females, where the end of fertility is traditionally indicated by the permanent stopping of monthly menstruations. However, menopause exists in some other animals, many of which do not have monthly menstruation;[90] in this case, the term means a natural end to fertility that occurs before the end of the natural lifespan.

## Evolutionary rationale [edit]

Various theories have been suggested that attempt to suggest evolutionary benefits to the human species stemming from the cessation of women's reproductive capability before the end of their natural lifespan. Explanations can be categorized as adaptive and non-adaptive:

### Non-adaptive hypotheses [edit]

The high cost of female investment in offspring may lead to physiological deteriorations that amplify susceptibility to becoming infertile. This hypothesis suggests the reproductive lifespan in humans has been optimized, but it has proven more difficult in females and thus their reproductive span is shorter. If this hypothesis were true, however, age at menopause should be negatively correlated with reproductive effort[91] and the available data does not support this.[92]

A recent increase in female longevity due to improvements in the standard of living and social care has also been suggested.[93] It is difficult for selection, however, to favour aid to offspring from parents and grandparents.[94] Irrespective of living standards, adaptive responses are limited by physiological mechanisms. In other words, senescence is programmed and regulated by specific genes.[95]

### Adaptive hypotheses [edit]

#### "Survival of the fittest" hypothesis [edit]

This hypothesis suggests that younger mothers and offspring under their care will fare better in a difficult and predatory environment because a younger mother will be stronger and more agile in providing protection and sustenance for herself and a nursing baby. The various biological factors associated with menopause had the effect of male members of the species investing their effort with the most viable of potential female mates.[96][*page needed*] One problem with this hypothesis is that we would expect to see menopause exhibited in the animal kingdom.[90]

#### Mother hypothesis [edit]

The mother hypothesis suggests that menopause was selected for humans because of the extended development period of human offspring and high costs of reproduction so that mothers gain an advantage in reproductive fitness by redirecting their effort from new offspring with a low survival chance to existing children with a higher survival chance.[97]

#### Grandmother hypothesis [edit]

The Grandmother hypothesis suggests that menopause was selected for humans because it promotes the survival of grandchildren. According to this hypothesis, post-reproductive women feed and care for children, adult nursing daughters, and grandchildren whose mothers have weaned them. Human babies require large and steady supplies of glucose to feed the growing brain. In infants in the first year of life, the brain consumes 60% of all calories, so both babies and their mothers require a dependable food supply. Some evidence suggests that hunters contribute less than half the total food budget of most hunter-gatherer

societies, and often much less than half, so that foraging grandmothers can contribute substantially to the survival of grandchildren at times when mothers and fathers are unable to gather enough food for all of their children. In general, selection operates most powerfully during times of famine or other privation. So although grandmothers might not be necessary during good times, many grandchildren cannot survive without them during times of famine. Arguably, however, there is no firm consensus on the supposed evolutionary advantages (or simply neutrality) of menopause to the survival of the species in the evolutionary past.

Indeed, analysis of historical data found that the length of a female's post-reproductive lifespan was reflected in the reproductive success of her offspring and the survival of her grandchildren.[98] Interestingly, another study found comparative effects but only in the maternal grandmother—paternal grandmothers had a detrimental effect on infant mortality (probably due to paternity uncertainty).[99] Differing assistance strategies for maternal and paternal grandmothers have also been demonstrated. Maternal grandmothers concentrate on offspring survival, whereas paternal grandmothers increase birth rates.[100]

Some believe a problem concerning the grandmother hypothesis is that it requires a history of female philopatry while in the present day the majority of hunter-gatherer societies are patriarchal.[101] However, there is disagreement split along ideological lines about whether patrilineality would have existed before modern times.[102] Some believe variations on the mother, or grandmother effect fail to explain longevity with continued spermatogenesis in males (oldest verified paternity is 94 years, 35 years beyond the oldest documented birth attributed to females).[103] Notably, the survival time past menopause is roughly the same as the maturation time for a human child. That a mother's presence could aid in the survival of a developing child, while an unidentified father's absence might not have affected survival, could explain the paternal fertility near the end of the father's lifespan.[104] A man with no certainty of which children are his may merely attempt to father additional children, with support of existing children present but small. Note the existence of partible paternity supporting this.[105] Some argue that the mother and grandmother hypotheses fail to explain the detrimental effects of losing ovarian follicular activity, such as osteoporosis, osteoarthritis, Alzheimer's disease and coronary artery disease.[106]

The theories discussed above assume that evolution directly selected for menopause. Another theory states that menopause is the byproduct of the evolutionary selection for follicular atresia, a factor that causes menopause. Menopause results from having too few ovarian follicles to produce enough estrogen to maintain the ovarian-pituitary-hypothalamic loop, which results in the cessation of menses and the beginning of menopause. Human females are born with approximately a million oocytes, and approximately 400 oocytes are lost to ovulation throughout life.[107][108]

## Other animals [edit]

Menopause in the animal kingdom appears to be uncommon, but the presence of this phenomenon in different species has not been thoroughly researched. Life histories show a varying degree of senescence; rapid senescing organisms (e.g., Pacific salmon and annual plants) do not have a post-reproductive life-stage. Gradual senescence is exhibited by all placental mammalian life histories.

Menopause has been observed in several species of nonhuman primates,[90] including rhesus monkeys,[109] and chimpanzees.[110] Menopause also has been reported in a variety of other vertebrate species including elephants,[111] short-finned pilot whales,[112] killer whales,[113] and other cetaceans,[114][115] the guppy,[116] the platyfish, the budgerigar, the laboratory rat and mouse, and the opossum. However, with the exception of the short-finned pilot whale, such examples tend to be from captive individuals, and thus they are not necessarily representative of what happens in natural populations in the wild.

Dogs do not experience menopause; the canine estrus cycle simply becomes irregular and infrequent. Although older female dogs are not considered good candidates for breeding, offspring have been produced by older animals.[117] Similar observations have been made in cats.[118]

## See also [edit]

- Folliculogenesis
- Ovarian reserve
- European Menopause and Andropause Society
- Pregnancy over age 50

## References [edit]


1. ^ Chuku, Gloria (2005). *Igbo women and economic transformation in southeastern Nigeria, 1900–1960*. Paragraph 3: Routledge. p. 73. ISBN 0415972108.
2. ^ *a b* "Menopause: Overview". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 2013-06-28. Retrieved 8 March 2015.
3. ^ *a b c d e* "Menopause: Overview". PubMedHealth. 29 August 2013. Retrieved 8 March 2015.
4. ^ Takahashi, TA; Johnson, KM (May 2015). "Menopause.". *The Medical clinics of North America*. **99** (3): 521–34. doi:10.1016/j.mcna.2015.01.006. PMID 25841598.
5. ^ *a b c* "What is menopause?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 2013-06-28. Retrieved 8 March 2015.
6. ^ *a b* Sievert, Lynnette Leidy (2006). *Menopause : a biocultural perspective* ([Online-Ausg.] ed.). New Brunswick, N.J.: Rutgers University Press. p. 81. ISBN 9780813538563.
7. ^ *International position paper on women's health and menopause : a comprehensive approach*. DIANE Publishing. 2002. p. 36. ISBN 9781428905214.
8. ^ *a b* "What are the symptoms of menopause?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 6 May 2013. Retrieved 8 March 2015.
9. ^ "What causes menopause?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 6 May 2013. Retrieved 8 March 2015.
10. ^ Warren, volume editors, Claudio N. Soares, Michelle (2009). *The menopausal transition : interface between gynecology and psychiatry* ([Online-Ausg.] ed.). Basel: Karger. p. 73. ISBN 978-3805591010.
11. ^ "How do health care providers diagnose menopause?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 6 May 2013. Retrieved 8 March 2015.
12. ^ Wood, James. "9". *Dynamics of Human Reproduction: Biology, Biometry, Demography*. Transaction Publishers. p. 401. ISBN 9780202365701.
13. ^ *a b c* "What are the treatments for other symptoms of menopause?". Eunice Kennedy Shriver National Institute of Child Health and Human Development. 2013-06-28. Retrieved 8 March 2015.
14. ^ *a b c d e* Krause, MS; Nakajima, ST (March 2015). "Hormonal and Nonhormonal Treatment of Vasomotor Symptoms.". *Obstetrics and Gynecology Clinics of North America*. **42** (1): 163–179. doi:10.1016/j.ogc.2014.09.008. PMID 25681847.
15. ^ *a b c* Franco, Oscar H.; Chowdhury, Rajiv; Troup, Jenna; Voortman, Trudy; Kunutsor, Setor; Kavousi, Maryam; Oliver-Williams, Clare; Muka, Taulant (21 June 2016). "Use of Plant-Based Therapies and Menopausal Symptoms". *JAMA*. **315** (23): 2554–63. doi:10.1001/jama.2016.8012. PMID 27327802.
16. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y z aa* Hoffman, Barbara (2012). *Williams gynecology*. New York: McGraw-Hill Medical. pp. 555–556. ISBN 9780071716727.
17. ^ Dreisler, E; Poulsen, LG; Antonsen, SL; Ceausu, I; Depypere, H; Erel, CT; Lambrinoudaki, I; Pérez-López, FR; Simoncini, T; Tremollieres, F; Rees, M; Ulrich, LG (2013). "EMAS clinical guide: Assessment of the endometrium in peri and postmenopausal women". *Maturitas*. **75** (2): 181–90. doi:10.1016/j.maturitas.2013.03.011. PMID 23619009.
18. ^ Pérez-López, FR; Cuadros, JL; Fernández-Alonso, AM; Chedraui, P; Sánchez-Borrego, R; Monterrosa-Castro, A (2012). "Quality of life in a large cohort of mid-aged Colombian women assessed using the Cervantes Scale". *Maturitas*. **73** (4): 369–72. doi:10.1016/j.maturitas.2012.09.004. PMID 23041251.
19. ^ *a b* Chedraui, P; Pérez-López, FR; Mendoza, M; Leimberg, ML; Martínez, MA; Vallarino, V; Hidalgo, L (2010). "Factors related to increased daytime sleepiness during the menopausal transition as evaluated by the Epworth sleepiness scale". *Maturitas*. **65** (1): 75–80. doi:10.1016/j.maturitas.2009.11.003. PMID 19945237.
20. ^ Arakane, M; Castillo, C; Rosero, MF; Peñafiel, R; Pérez-López, FR; Chedraui, P (2011). "Factors relating to insomnia during the menopausal transition as evaluated by the Insomnia Severity Index.". *Maturitas*. **69** (2): 157–161. doi:10.1016/j.maturitas.2011.02.015. PMID 21444163.

21. ^ Monterrosa-Castro, A; Marrugo-Flórez, M; Romero-Pérez, I; Chedraui, P; Fernández-Alonso, AM; Pérez-López, FR (2013). "Prevalence of insomnia and related factors in a large mid-aged female Colombian sample". *Maturitas*. **74** (4): 346–51. doi:10.1016/j.maturitas.2013.01.009. PMID 23391501.
22. ^ [a] [b] Llaneza, P; García-Portilla, MP; Llaneza-Suárez, D; Armott, B; Pérez-López, FR (2012). "Depressive disorders and the menopause transition". *Maturitas*. **71** (2): 120–30. doi:10.1016/j.maturitas.2011.11.017. PMID 22196311.
23. ^ Mitchell, Richard Sheppard; Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson (2007). *Robbins Basic Pathology: With Student Consult Online Access*. Philadelphia: Saunders. p. 344. ISBN 1-4160-2973-7. 8th edition
24. ^ Souza, Hugo (2013). "Autonomic Cardiovascular Damage during Post-menopause: the Role of Physical Training". *Aging and Disease*. **4** (6): 320–328. doi:10.14336/AD.2013.0400320. ISSN 2152-5250.
25. ^ "Perimenopausal risk factors and future health". *Human Reproduction Update*. **17** (5): 706–717. 2011. doi:10.1093/humupd/dmr020. PMID 21565809.
26. ^ Muka, Taulant; Oliver-Williams, Clare; Kunutsor, Setor; Laven, Joop S. E.; Fauser, Bart C. J. M.; Chowdhury, Rajiv; Kavousi, Maryam; Franco, Oscar H. (14 September 2016). "Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality". *JAMA Cardiology*. **1**: 767. doi:10.1001/jamacardio.2016.2415.
27. ^ Minkin, Mary Jane; et al. (1997). *What Every Woman Needs to Know about Menopause*. Yale University Press. ISBN 0-300-07261-9.
28. ^ Kato, I; Toniolo, P; Akhmedkhanov, A; Koenig, KL; Shore, R; Zeleniuch-Jacquotte, A (1998). "Prospective study of factors influencing the onset of natural menopause". *J Clin Epidemiol*. **51** (12): 1271–1276. doi:10.1016/S0895-4356(98)00119-X. PMID 10086819.
29. ^ Do, KA; Treloar, SA; Pandeya, N; Purdie, D; Green, AC; Heath, AC; Martin, NG (1998). "Predictive factors of age at menopause in a large Australian twin study". *Hum Biol*. **70** (6): 1073–91. PMID 9825597.
30. ^ Ringa, V. (2000). "Menopause and treatments". *Quality of Life Research*. **9** (6): 695–707. doi:10.1023/A:1008913605129. JSTOR 4036942.
31. ^ Podfigurna-Stopa, A; et al. (September 2016). "Premature ovarian insufficiency: the context of long-term effects.". *Journal of endocrinological investigation*. **39** (9): 983–90. doi:10.1007/s40618-016-0467-z. PMC 4987394. PMID 27091671.
32. ^ Tersigni C, Castellani R, de Waure C, Fattorossi A, De Spirito M, Gasbarrini A, Scambia G, Di Simone N (2014). "Celiac disease and reproductive disorders: meta-analysis of epidemiologic associations and potential pathogenic mechanisms". *Hum Reprod Update*. **20** (4): 582–93. doi:10.1093/humupd/dmu007. PMID 24619876.
33. ^ Lasa, JS; Zubiaurre, I; Soifer, LO (2014). "Risk of infertility in patients with celiac disease: a meta-analysis of observational studies". *Arq Gastroenterol*. **51** (2): 144–50. doi:10.1590/S0004-28032014000200014. PMID 25003268.
34. ^ Healthline. "What causes early menopause". Healthline.
35. ^ [a] [b] Kalantaridou SN, Davis SR, Nelson LM. *Endocrinology Metabolism Clinics of North America*, December 1998; 27(4) 989–1006.
36. ^ Bucher, et al. 1930
37. ^ [a] [b] [c] Harlow, SD; Gass, M; Hall, JE; Lobo, R; Maki, P; Rebar, RW; Sherman, S; Sluss, PM; de Villiers, TJ (2012). "Executive summary of the Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging". *Fertility and Sterility*. **97** (4): 398–406. doi:10.1016/j.fertnstert.2012.01.128. PMID 22341880.
38. ^ Lee S. Cohen; Claudio N. Soares; Allison F. Vitonis; Michael W. Otto; Bernard L. Harlow; et al. (April 2006). "Risk for New Onset of Depression During the Menopausal Transition". *Archives of General Psychiatry*. The Harvard Study of Moods and Cycles. **63** (4): 385–390. doi:10.1001/archpsyc.63.4.385. Retrieved 28 September 2013.
39. ^ Soules, MR; Sherman, S; Parrott, E; Rebar, R; Santoro, N; Utian, W; Woods, N (2001). "Executive summary: Stages of Reproductive Aging Workshop (STRAW)". *Climacteric*. **4** (4): 267–72. doi:10.1080/cmt.4.4.267.272. PMID 11770182.
40. ^ [a] [b] Prior, JC. "Perimenopause: The Complex Endocrinology of the Menopausal Transition". *Endocrine Reviews*. **19**: 397–428. doi:10.1210/edrv.19.4.0341.
41. ^ Burger, HG (1994). "Diagnostic role of follicle stimulating hormone (FSH) measurements during menopausal transition – an analysis of FSH, oestradiol and inhibin". *European Journal of Endocrinology*. **130** (1): 38–42. doi:10.1530/eje.0.1300038. PMID 8124478.
42. ^ [a] [b] Nahás E, Pontes A, Traiman P, NahásNeto J, Dalben I, De Luca L (2003). "Inhibin B and ovarian function after total abdominal hysterectomy in women of reproductive age". *Gynecol. Endocrinol*. **17**: 125–31. doi:10.1080/713603218. PMID 12737673.
43. ^ [a] [b] Petri Nahás EA, Pontes A, Nahas-Neto J, Borges VT, Dias R, Traiman P (February 2005). "Effect of total abdominal hysterectomy on ovarian blood supply in women of reproductive age". *J Ultrasound Med*. **24**: 169–74.

PMID 15661947.
44. ^ Burger, HG (1994). "Diagnostic role of follicle stimulating hormone (FSH) measurements during menopausal transition – an analysis of FSH, oestraiol and inhibin". *European Journal of Endocrinology*. **130** (1): 38–42. doi:10.1530/eje.0.1300038. PMID 8124478.
45. ^ Simpson, ER; Davis, SR (2001). "Minireview: aromatase and the regulation of estrogen biosynthesis – some new perspectives". *Endocrinology*. **142** (11): 4589–94. doi:10.1210/en.142.11.4589. PMID 11606422.
46. ^ Davison, SL; Bell, R; Donath, S; Montalto, JG; Davis, SR (2005). "Androgen levels in adult females: changes with age, menopause, and oophorectomy". *J Clin Endocrinol Metab*. **90** (7): 3847–53. doi:10.1210/jc.2005-0212. PMID 15827095.
47. ^ Robin H. Fogle; Frank Z. Stanczyk; Xiaohua Zhang; Richard J. Paulson. "Ovarian Androgen Production in Postmenopausal Women". *The Journal of Clinical Endocrinology & Metabolism*. **92** (8): 3040–3043. doi:10.1210/jc.2007-0581. Retrieved 27 September 2013.
48. ^ *a b* Titus, S; Li, F; Stobezki, R; Akula, K; Unsal, E; Jeong, K; Dickler, M; Robson, M; Moy, F; Goswami, S; Oktay, K (2013). "Impairment of BRCA1-related DNA double-strand break repair leads to ovarian aging in mice and humans". *Science Translational Medicine*. **5** (172): 172ra21. doi:10.1126/scitranslmed.3004925. PMID 23408054.
49. ^ Harris Bernstein, Carol Bernstein and Richard E. Michod (2011). Meiosis as an Evolutionary Adaptation for DNA Repair. Chapter 19 in *DNA Repair*. Inna Kruman editor. InTech Open Publisher. DOI: 10.5772/25117 http://www.intechopen.com/books/dna-repair/meiosis-as-an-evolutionary-adaptation-for-dna-repair
50. ^ Greene, JG (1998). "Constructing a standard climacteric scale". *Maturitas*. **29** (1): 25–31. doi:10.1016/s0378-5122(98)00025-5. PMID 9643514.
51. ^ Monterrosa-Castro, A; Romero-Pérez, I; Marrugo-Flórez, M; Fernández-Alonso, AM; Chedraui, P; Pérez-López, FR (2012). "Quality of life in a large cohort of mid-aged Colombian women assessed using the Cervantes Scale". *Menopause*. **19** (8): 924–30. doi:10.1097/gme.0b013e318247908d. PMID 22549166.
52. ^ Schneider, Hermann P.G.; Naftolin, Frederick (2005). *Climacteric medicine where do we go?*. London: Taylor & Francis. p. 28. ISBN 9780203024966.
53. ^ "Menopause 101". *A primer for the perimenopausal*. The North American Menopause Society. Retrieved 11 April 2013.
54. ^ *a b c* Prior, Jerilynn. "Perimenopause". Centre for Menstrual Cycle and Ovulation Research (CeMCOR). Retrieved 10 May 2013.
55. ^ Chichester, Melanie; Ciranni, Patricia (August–September 2011). "Approaching Menopause (But Not There Yet!)". *Nursing for Women's Health*. **15** (4): 320. doi:10.1111/j.175-486X.2011.01652.x. Retrieved 11 April 2013.
56. ^ Hurst, Bradley S. (2011). *Disorders of menstruation*. Chichester, West Sussex: Wiley-Blackwell. ISBN 9781444391817.
57. ^ *a b* McNamara, M; Batur, P; DeSapri, KT (3 February 2015). "In the clinic. Perimenopause.". *Annals of Internal Medicine*. **162** (3): ITC1–15. doi:10.7326/AITC201502030. PMID 25643316.
58. ^ Kessenich, Cathy. "Inevitable Menopause". Retrieved 11 April 2013.
59. ^ Bellipanni, G; Di Marzo, F; Blasi, F; Di Marzo, A (December 2005). "Effects of melatonin in perimenopausal and menopausal women: our personal experience. 2005". *Annals of the New York Academy of Sciences*. **1057** (1): 393–402. doi:10.1196/annals.1356.030. PMID 16399909.
60. ^ The Woman's Health Program Monash University, Oestrogen and Progestin as Hormone Therapy
61. ^ "Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society". *Menopause (New York, N.Y.)*. **17** (2): 242–55. Mar 2010. doi:10.1097/gme.0b013e3181d0f6b9. PMID 20154637.
62. ^ *a b* Boardman, Henry M. P.; Hartley, Louise; Eisinga, Anne; Main, Caroline; Roqué i Figuls, Marta; Bonfill Cosp, Xavier; Gabriel Sanchez, Rafael; Knight, Beatrice (2015-03-10). "Hormone therapy for preventing cardiovascular disease in post-menopausal women". *The Cochrane Database of Systematic Reviews* (3): CD002229. doi:10.1002/14651858.CD002229.pub4. ISSN 1469-493X. PMID 25754617.
63. ^ Maryam Darabi; Mohsen Ani; Mojtaba Panjehpour; Mohammed Rabbani; Ahmad Movahedian; Elahe Zarean (January–February 2011). "Effect of estrogen receptor beta A1730G polymorphism on ABCA1 gene expression response to postmenopausal hormone replacement therapy". *Genetic Testing and Molecular Biomarkers*. **15** (1–2): 11–15. doi:10.1089/gtmb.2010.0106. PMID 21117950.
64. ^ de Villiers, TJ; Stevenson, JC (June 2012). "The WHI: the effect of hormone replacement therapy on fracture prevention". *Climacteric*. **15** (3): 263–6. doi:10.3109/13697137.2012.659975. PMID 22612613.
65. ^ Marjoribanks, J; Farquhar, C; Roberts, H; Lethaby, A (11 July 2012). "Long term hormone therapy for perimenopausal and postmenopausal women". *Cochrane Database of Systematic Reviews*. **7**: CD004143. doi:10.1002/14651858.CD004143.pub4. PMID 22786488.
66. ^ Chlebowski, R. T.; Anderson, G. L. (2015). "Menopausal hormone therapy and breast cancer mortality: clinical

implications". *Therapeutic Advances in Drug Safety*. **6** (2): 45–56. doi:10.1177/2042098614568300. ISSN 2042-0986.

67. ^ [a] [b] Somboonporn, W.; Davis, S.; Seif, M. W.; Bell, R. (2005-10-19). "Testosterone for peri- and postmenopausal women". *The Cochrane Database of Systematic Reviews* (4): CD004509. doi:10.1002/14651858.CD004509.pub2. ISSN 1469-493X. PMID 16235365.
68. ^ Davis, SR; Dinatale, I; Rivera-Woll, L; Davison, S (2005). "Postmenopausal hormone therapy: from monkey glands to transdermal patches". *J Endocrinol*. **185** (2): 207–22. doi:10.1677/joe.1.05847. PMID 15845914.
69. ^ Bevers, TB (2007). "The STAR Trial: Evidence for Raloxifene as a Breast Cancer Risk Reduction Agent for Postmenopausal Women". *J Natl Compr Canc Netw*. **5** (8): 817–22.
70. ^ Orleans, RJ; Li, L; Kim, MJ; Guo, J; Sobhan, M; Soule, L; Joffe, HV (2014). "FDA approval of paroxetine for menopausal hot flushes". *The New England Journal of Medicine*. **370** (19): 1777–9. doi:10.1056/NEJMp1402080. PMID 24806158.
71. ^ Nedrow, A; Miller, J; Walker, M; Nygren, P; Huffman, LH; Nelson, HD (2006). "Complementary and alternative therapies for the management of menopause-related symptoms: a systematic evidence review". *Arch Intern Med*. **166** (14): 1453–65. doi:10.1001/archinte.166.14.1453.
72. ^ Bolaños, R; Del Castillo, A; Francia, J (2010). "Soy isoflavones versus placebo in the treatment of climacteric vasomotor symptoms: systematic review and meta-analysis.". *Menopause*. **17** (3): 660–6. doi:10.1097/gme.0b013e3181cb4fb5. PMID 20464785.
73. ^ Lethaby, A; Marjoribanks, J; Kronenberg, F; Roberts, H; Eden, J; Brown, J (10 December 2013). "Phytoestrogens for menopausal vasomotor symptoms.". *Cochrane Database of Systematic Reviews*. **12**: CD001395. doi:10.1002/14651858.CD001395.pub4. PMID 24323914.
74. ^ EFSA Femarelle® and bone mineral density Scientific substantiation of a health claim related to "Femarelle®" and "induces bone formation and increases bone mineral density reducing the risk for osteoporosis and other bone disorders" pursuant to Article 14 of the Regulation (EC) No 1924/20061 Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies. The EFSA Journal (2008) 785, pp. 1–10]
75. ^ Leach, MJ; Moore, V (12 September 2012). "Black cohosh (Cimicifuga spp.) for menopausal symptoms.". *Cochrane Database of Systematic Reviews*. **9**: CD007244. doi:10.1002/14651858.CD007244.pub2. PMID 22972105.
76. ^ Dodin, S; Blanchet, C; Marc, I; Ernst, E; Wu, T; Vaillancourt, C; Paquette, J; Maunsell, E (30 July 2013). "Acupuncture for menopausal hot flushes.". *Cochrane Database of Systematic Reviews*. **7**: CD007410. doi:10.1002/14651858.CD007410.pub2. PMID 23897589.
77. ^ Clement, YN; Onakpoya, I; Hung, SK; Ernst, E (March 2011). "Effects of herbal and dietary supplements on cognition in menopause: a systematic review.". *Maturitas*. **68** (3): 256–63. doi:10.1016/j.maturitas.2010.12.005. PMID 21237589.
78. ^ Zhu, X; Liew, Y; Liu, ZL (15 March 2016). "Chinese herbal medicine for menopausal symptoms.". *The Cochrane database of systematic reviews*. **3**: CD009023. doi:10.1002/14651858.CD009023.pub2. PMID 26976671. Retrieved 18 March 2016.
79. ^ Wells, GA; Cranney, A; Peterson, J; Boucher, M; Shea, B; Robinson, V; Coyle, D; Tugwell, P (Jan 23, 2008). "Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women". *Cochrane Database of Systematic Reviews* (1): CD001155. doi:10.1002/14651858.CD001155.pub2. PMID 18253985.
80. ^ Winterich, J. (August 2008). "Gender, medicine, and the menopausal body: How biology and culture influence women's experiences with menopause". Paper presented at the annual meeting of the American Sociological Association, New York. Retrieved 11 November 2008 from Allacademic.com
81. ^ Gannon, L; Ekstrom, B (1993). "Attitudes toward menopause: The influence of sociocultural paradigms". *Psychology of Women Quarterly*. **17**: 275–288. doi:10.1111/j.1471-6402.1993.tb00487.x.
82. ^ Avis, N.; Stellato, R. Crawford; Bromberger, J.; Gan, P.; Cain, V.; Kagawa-Singer, M (2001). "Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic group". *Social Science & Medicine*. **52** (3): 345–356. doi:10.1016/S0277-9536(00)00147-7.
83. ^ [a] [b] Lock, M (1998). "Menopause: lessons from anthropology". *Psychosomatic Medicine*. **60** (4): 410–9. doi:10.1097/00006842-199807000-00005. PMID 9710286.
84. ^ Melby, MK (2005). "Factor analysis of climacteric symptoms in Japan". *Maturitas*. **52** (3–4): 205–22. doi:10.1016/j.maturitas.2005.02.002. PMID 16154301.
85. ^ [a] [b] Lock, M. & Nguyen, V. (2010) *An Anthropology of Biomedicine*, Chapter 4 "Local Biologies and Human Difference" (pp. 84–89), West Sussex, Wiley-Blackwell
86. ^ Gold, EB; Block, G; Crawford, S; Lachance, L; FitzGerald, G; Miracle, H; Sherman, S (2004). "Lifestyle and demographic factors in relation to vasomotor symptoms: baseline results from the Study of Women's Health Across the Nation". *American Journal of Epidemiology*. **159** (12): 1189–99. doi:10.1093/aje/kwh168. PMID 15191936.

87. ^ Maoz, B.; Dowty, N.; Antonovsky, A.; Wisjenbeck, H. (1970). "Female attitudes to menopause". *Social Psychiatry*. **5**: 35–40. doi:10.1007/BF01539794.
88. ^ Stotland, N. L. (2002). "Menopause: Social expectations, women's realities". *Archives of Women's Mental Health*. **5**: 5–8. doi:10.1007/s007370200016.
89. ^ Lock, Margaret M., and Vinh-Kim Nguyen. "Chapter 2". *An Anthropology of Biomedicine*. Chichester, West Sussex: Wiley-Blackwell, 2010. pp. 32–56. Print.
90. ^ *a b c* Walker, ML; Herndon, JG (2008). "Menopause in nonhuman primates?". *Biology of Reproduction*. **79** (3): 398–406. doi:10.1095/biolreprod.108.068536. PMC 2553520. PMID 18495681.
91. ^ Gaulin, SJ (1980). "Sexual Dimorphism in the Human Post-reproductive Life-span: Possible Causes". *Journal of Human Evolution*. **9** (3): 227–232. doi:10.1016/0047-2484(80)90024-X.
92. ^ Holmberg, I. (1970), "Fecundity, Fertility and Family Planning". Demography Institute University of Gothenburg Reports. 10: pp. 1–109
93. ^ Washburn, S.L. (1981). "Longevity in Primates". In: Aging: Biology and Behavior by McGaugh, J.L. and S. B. Kiesler, S.B. (eds). pp. 11–29. Academic Press.
94. ^ Hawkes, K (2004). "Human longevity: The grandmother effect". *Nature*. **428** (6979): 128–129. doi:10.1038/428128a. PMID 15014476.
95. ^ Ricklefs, RE; Wikelski, M (2002). "The Physiology/Life-history Nexus". *Trends in Ecology & Evolution*. **17** (10): 462–468. doi:10.1016/S0169-5347(02)02578-8.
96. ^ Darwin, Charles. *Origin of Species*. Retrieved 24 September 2013.
97. ^ Peccei, JS (2001). "Menopause: Adaptation or Epiphenomenon?". *Evolutionary Anthropology*. **10** (2): 43–57. doi:10.1002/evan.1013.
98. ^ Lahdenperä, M; Lummaa, V; Helle, S; Tremblay, M; Russell, AF (2004). "Fitness benefits of prolonged post-reproductive lifespan in women". *Nature*. **428** (6979): 178–181. doi:10.1038/nature02367. PMID 15014499.
99. ^ Voland, E. and Beise, J. (2002). "Opposite Effects of Maternal and Paternal Grandmothers on Infant Survival in Historical Krummörn". MPIDR WP 2001–026.
100. ^ Mace, R and Sear, R. (2004). "Are Humans Communal Breeders?" In: Voland, E., Chasiotis, A. and Schiefenhoevel, W. (eds). *Grandmotherhood—the Evolutionary Significance of the Second Half of Female Life*. Rutgers University Press.
101. ^ Peccei, JS (2001). "A critique of the grandmother hypotheses: Old and new". *American Journal of Human Biology*. **13** (4): 434–452. doi:10.1002/ajhb.1076. PMID 11400215.
102. ^ "Engels was Right: Early Human Kinship was Matrilineal".
103. ^ 10. Finch, C.E. 1990. Longevity senescence and the genome. University of Chicago Press. London.
104. ^ Pavard, S; Sibert, A; Heyer, E (2007). "The effect of maternal care on child survival: a demographic, genetic, and evolutionary perspective". *Evolution*. **61** (5): 1153–61. doi:10.1111/j.1558-5646.2007.00086.x. PMID 17492968.
105. ^ Walker R, S; Flinn, MV; Hill, KR (2010). "Evolutionary history of partible paternity in lowland South America". *Proceedings of the National Academy of Sciences of the United States of America*. **107** (45): 19195–200. doi:10.1073/pnas.1002598107. PMC 2984172. PMID 20974947.
106. ^ Massart, F; Reginster, JY; Brandi, ML (2001). "Genetics of Menopause-Associatred Diseases". *Maturitas*. **40** (2): 103–116. doi:10.1016/S0378-5122(01)00283-3. PMID 11716989.
107. ^ Leidy, L. "Menopause in evolutionary perspective". in: Trevathan WR, McKenna JJ, Smith EO (Eds.) *Evolutionary Medicine*. Oxford University Press, pp. 407–427
108. ^ *Clinical Obstetrics and Gynaecology* (3 ed.). Elsevier Health Sciences. 2014. p. 69. ISBN 9780702054105.
109. ^ Walker, ML (1995). "Menopause in female rhesus monkeys". *Am J Primatol*. **35**: 59–71. doi:10.1002/ajp.1350350106.
110. ^ Bowden, D. M. and Williams, D. D. (1985). Aging. Adv.Vet.Sci.Comp.Med. 28: 306–341
111. ^ *The Asian Elephant*.
112. ^ Marsh, H and Kasuya, T. (1986). Evidence for Reproductive Senescence in Female Cetaceans. Report of the International Whaling Commission. 8: pp. 57–74.
113. ^ Brent L.J.N., Franks D.W.; et al. (2015). "Ecological Knowledge, Leadership, and the Evolution of Menopause in Killer Whales". *Current Biology*. **25** (6): 746–750. doi:10.1016/j.cub.2015.01.037.
114. ^ McAuliffe, K; Whitehead, H (2005). "Eusociality, menopause and information in matrilineal whales". *Trends Ecol Evolution*. **20** (12): 650. doi:10.1016/j.tree.2005.09.003. PMID 16701451.
115. ^ DAL.ca
116. ^ Reznick, D; Bryant, M; Holmes, D (January 2006). "The evolution of senescence and post-reproductive lifespan in guppies (Poecilia reticulata)". *PLoS Biology*. **4** (1): e7. doi:10.1371/journal.pbio.0040007. PMC 1318473. PMID 16363919.
117. ^ Canine reproduction

118. ^ dead link Archived 10 June 2015 at the Wayback Machine.

## External links [edit]

- European Menopause and Andropause Society
- Menopause: MedlinePlus
- Menopause and Menopause Treatments
- Menopause.org, The Official Website of The North American Menopause Society

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# Menstruation



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From Wikipedia, the free encyclopedia

*This article is about humans. For other mammals, see Menstruation (mammals).*

**Menstruation**, also known as a **period** or **monthly**,[1] is the regular discharge of blood and mucosal tissue from the inner lining of the uterus through the vagina.[2] The first period usually begins between twelve and fifteen years of age, a point in time known as menarche.[1] However, periods may occasionally start as young as eight years old and still be considered normal.[2] The average age of the first period is generally later in the developing world, and earlier in the developed world. The typical length of time between the first day of one period and the first day of the next is 21 to 45 days in young women, and 21 to 31 days in adults (an average of 28 days).[2][3] Bleeding usually lasts around 2 to 7 days.[2] Menstruation stops occurring after menopause, which usually occurs between 45 and 55 years of age.[4] Periods also stop during pregnancy and typically do not resume during the initial months of breastfeeding.[2]

Up to 80% of women report having some symptoms prior to menstruation.[5] Common signs and symptoms include acne, tender breasts, bloating, feeling tired, irritability, and mood changes.[6] These may interfere with normal life, therefore qualifying as premenstrual syndrome, in 20 to 30% of women. In 3 to 8%, symptoms are severe.[5]

A lack of periods, known as amenorrhea, is when periods do not occur by age 15 or have not occurred in 90 days. Other problems with the menstrual cycle include painful periods and abnormal bleeding such as bleeding between periods or heavy bleeding.[2] Menstruation in other animals occurs in primates, such as apes and monkeys, as well as bats and the elephant shrew.[7][8]

The menstrual cycle occurs due to the rise and fall of hormones. This cycle results in the thickening of the lining of the uterus, and the growth of an egg, (which is required for pregnancy). The egg is released from an ovary around day fourteen in the cycle; the thickened lining of the uterus provides nutrients to an embryo after implantation. If pregnancy does not occur, the lining is released in what is known as menstruation.[2]

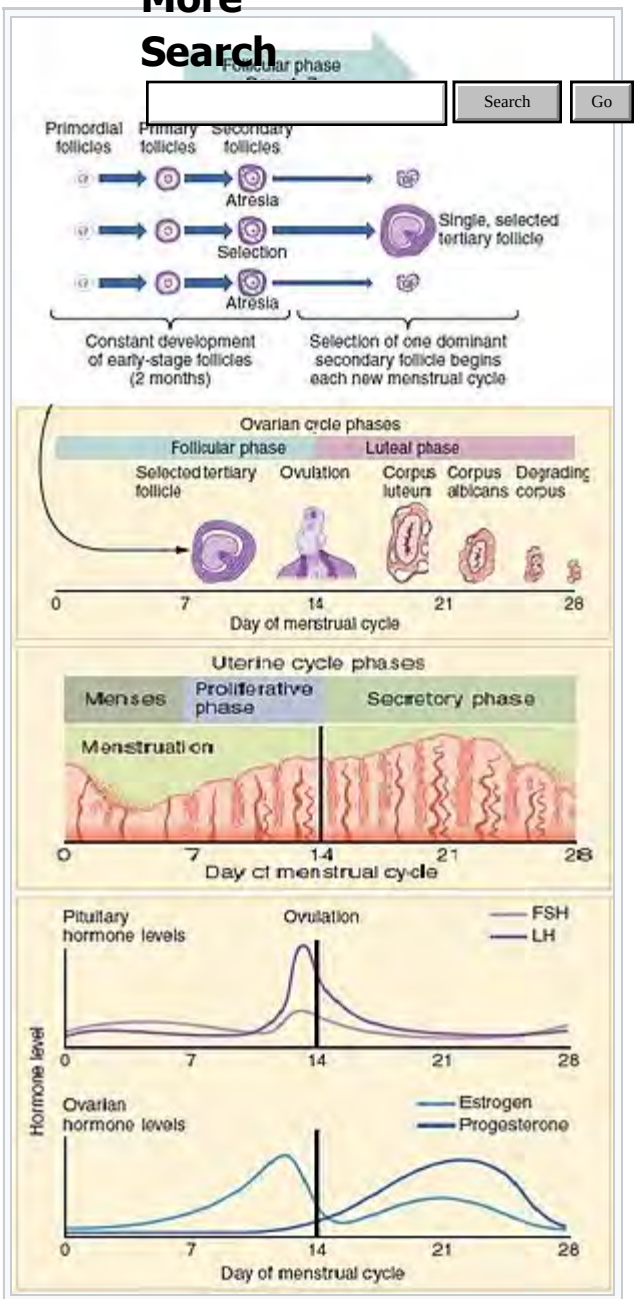



Figure showing the progression of the menstrual cycle and the different hormones contributing to it.

## Contents

## Variants

## Onset and frequency

The first menstrual period occurs after the onset of pubertal growth, and is called menarche. The average age of menarche is 12 to 15.[1][9] However, it may start as early as eight.[2] The average age of the first period is generally later in the developing world, and earlier in the developed world.[3] The average age of menarche has changed little in the United States since the 1950s.[3]

Diagram illustrating how the uterus lining builds up and breaks down during the menstrual cycle.

Menstruation is the most visible phase of the menstrual cycle and its beginning is used as the marker between cycles. The first day of menstrual bleeding is the date used for the last menstrual period (LMP). The typical length of time between the first day of one period and the first day of the next is 21 to 45 days in young women, and 21 to 31 days in adults (an average of 28 days).[2][3]

Perimenopause is when fertility in a female declines, and menstruation occurs less regularly in the years leading up to the final menstrual period, when a female stops menstruating completely and is no longer fertile. The medical definition of menopause is one year without a period and typically occurs between 45 and 55 in Western countries.[4][10]:p. 381

During pregnancy and for some time after childbirth, menstruation does not occur; this state is known as amenorrhoea. If menstruation has not resumed, fertility is low during lactation. The average length of postpartum amenorrhoea is longer when certain breastfeeding practices are followed; this may be done intentionally as birth control.

## Health effects

*Further information: Premenstrual syndrome*

In most women, various physical changes are brought about by fluctuations in hormone levels during the

menstrual cycle. This includes muscle contractions of the uterus (menstrual cramping) that can precede or accompany menstruation. Some may notice water retention, changes in sex drive, fatigue, breast tenderness, or nausea. Breast swelling and discomfort may be caused by water retention during menstruation.[11] Usually, such sensations are mild, and some females notice very few physical changes associated with menstruation. A healthy diet, reduced consumption of salt, caffeine and alcohol, and regular exercise may be effective for women in controlling some symptoms.[12] Severe symptoms that disrupt daily activities and functioning may be diagnosed as premenstrual dysphoric disorder. Symptoms before menstruation are known as premenstrual molimina.



## Cramps

*Further information: Dysmenorrhea*

Many women experience painful cramps, also known as dysmenorrhea, during menstruation.[*citation needed*] Pain results from ischemia and muscle contractions. Spiral arteries in the secretory endometrium constrict, resulting in ischemia to the secretory endometrium. This allows the uterine lining to slough off. The myometrium contracts spasmodically in order to push the menstrual fluid through the cervix and out of the vagina. The contractions are mediated by a release of prostaglandins.

Painful menstrual cramps that result from an excess of prostaglandin release are referred to as primary dysmenorrhea. Primary dysmenorrhea usually begins within a year or two of menarche, typically with the onset of ovulatory cycles.[13] Treatments that target the mechanism of pain include non-steroidal anti-inflammatory drugs (NSAIDs) and hormonal contraceptives. NSAIDs inhibit prostaglandin production. With long-term treatment, hormonal birth control reduces the amount of uterine fluid/tissue expelled from the uterus. Thus resulting in shorter, less painful menstruation.[14] These drugs are typically more effective than treatments that do not target the source of the pain (e.g. acetaminophen).[15][*needs update*] Risk factors for primary dysmenorrhea include: early age at menarche, long or heavy menstrual periods, smoking, and a family history of dysmenorrhea.[13] Regular physical activity may limit the severity of uterine cramps.[13]

For many women, primary dysmenorrhea gradually subsides in late second generation. Pregnancy has also been demonstrated to lessen the severity of dysmenorrhea, when menstruation resumes. However, dysmenorrhea can continue until menopause. 5–15% of women with dysmenorrhea experience symptoms severe enough to interfere with daily activities.[13]

Secondary dysmenorrhea is the diagnosis given when menstruation pain is a secondary cause to another disorder. Conditions causing secondary dysmenorrhea include endometriosis, uterine fibroids, and uterine adenomyosis. Rarely, congenital malformations, intrauterine devices, certain cancers, and pelvic infections cause secondary dysmenorrhea.[13] Symptoms include pain spreading to hips, lower back and thighs, nausea, and frequent diarrhea or constipation.[16] If the pain occurs between menstrual periods, lasts longer than the first few days of the period, or is not adequately relieved by the use of non-steroidal anti-inflammatory drugs (NSAIDs) or hormonal contraceptives, women should be evaluated for secondary causes of dysmenorrhea.[10]:p. 379

When severe pelvic pain and bleeding suddenly occur or worsen during a cycle, the woman or girl should be evaluated for ectopic pregnancy and spontaneous abortion. This evaluation begins with a pregnancy test and should be done as soon as unusual pain begins, because ectopic pregnancies can be life threatening.[17]

In some cases, stronger physical and emotional or psychological sensations may interfere with normal activities, and include menstrual pain (dysmenorrhea), migraine headaches, and depression. Dysmenorrhea, or severe uterine pain, is particularly common for young females (one study found that 67.2% of girls aged 13–19 have it).[18]

The medications in the non-steroidal anti-inflammatory drugs (NSAIDs) class are commonly used to relieve menstrual cramps. Some herbs are also claimed to help.

## Mood and behavior

Some women experience emotional disturbances starting one or two weeks before their period, and stopping soon after the period has started.[6] Symptoms may include mental tension, irritability, mood swings, and crying spells. Problems with concentration and memory may occur.[6] There may also be depression or anxiety.[6]

This is part of premenstrual syndrome (PMS) and is estimated to occur in 20 to 30% of women. In 3 to 8% it is severe.[5]

More severe symptoms of anxiety or depression may be signs of premenstrual dysphoric disorder (PMDD). Rarely, in individuals who are susceptible, menstruation may be a trigger for menstrual psychosis.

## Bleeding

The average volume of menstrual fluid during a monthly menstrual period is 35 milliliters (2.4 tablespoons of menstrual fluid) with 10–80 milliliters (1–6 tablespoons of menstrual fluid) considered typical. Menstrual fluid is the correct name for the flow, although many people prefer to refer to it as menstrual blood. Menstrual fluid contains some blood, as well as cervical mucus, vaginal secretions, and endometrial tissue. Menstrual fluid is reddish-brown, a slightly darker color than venous blood.[10]:p. 381

Unless a woman has a bloodborne illness, menstrual fluid is harmless. No toxins are released in menstrual flow, as this is a lining that must be pure and clean enough to have nurtured a baby. Menstrual fluid is no more dangerous than regular blood.

About half of menstrual fluid is blood. This blood contains sodium, calcium, phosphate, iron, and chloride, the extent of which depends on the woman. As well as blood, the fluid consists of cervical mucus, vaginal secretions, and endometrial tissue. Vaginal fluids in menses mainly contribute water, common electrolytes, organ moieties, and at least 14 proteins, including glycoproteins.[19]

Many mature females notice blood clots during menstruation. These appear as clumps of blood that may look like tissue. If there are questions (for example, was there a miscarriage?), examination under a microscope can confirm if it was endometrial tissue or pregnancy tissue (products of conception) that was shed.[20] Sometimes menstrual clots or shed endometrial tissue is incorrectly thought to indicate an early-term miscarriage of an embryo. An enzyme called plasmin – contained in the endometrium – tends to inhibit the blood from clotting.

The amount of iron lost in menstrual fluid is relatively small for most women.[21] In one study, premenopausal women who exhibited symptoms of iron deficiency were given endoscopies. 86% of them actually had gastrointestinal disease and were at risk of being misdiagnosed simply because they were menstruating.[22] Heavy menstrual bleeding, occurring monthly, can result in anemia.

## Menstrual disorders

There is a wide spectrum of differences in how women experience menstruation. There are several ways that someone's menstrual cycle can differ from the norm, any of which should be discussed with a doctor to identify the underlying cause:

| Symptom | See article |
|---|---|
| Infrequent periods | Oligomenorrhea |
| Short or extremely light periods | Hypomenorrhea |
| Too-frequent periods (defined as more frequently than every 21 days) | Polymenorrhea |
| Extremely heavy or long periods (one guideline is soaking a sanitary napkin or tampon every hour or so, or menstruating for longer than 7 days) | Hypermenorrhea |
| Extremely painful periods | Dysmenorrhea |
| Breakthrough bleeding (also called spotting) between periods; normal in many females | Metrorrhagia |
| Absent periods | Amenorrhea |

There is a movement among gynecologists to discard the terms noted above, which although they are widely used, do not have precise definitions. Many now argue to describe menstruation in simple terminology, including:

- Cycle regularity (irregular, regular, or absent)
- Frequency of menstruation (frequent, normal, or infrequent)
- Duration of menstrual flow (prolonged, normal, or shortened)
- Volume of menstrual flow (heavy, normal, or light)[23]

Dysfunctional uterine bleeding is a hormonally caused bleeding abnormality. Dysfunctional uterine bleeding typically occurs in premenopausal women who do not ovulate normally (i.e. are anovulatory). All these bleeding abnormalities need medical attention; they may indicate hormone imbalances, uterine fibroids, or other problems. As pregnant women may bleed, a pregnancy test forms part of the evaluation of abnormal bleeding.

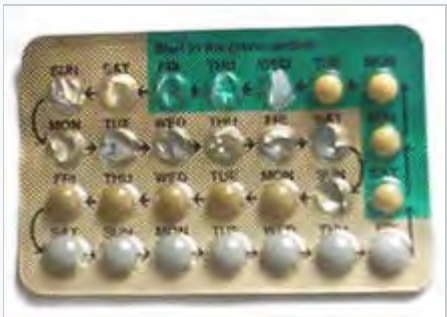
Women who had undergone female genital mutilation (particularly type III- infibulation) a practice common in parts of Africa, may experience menstrual problems, such as slow and painful menstruation, that is caused by the near-complete sealing off of the vagina.[24]

Premature or delayed menarche should be investigated if menarche begins before 9 years, if menarche has not begun by age 15, if there is no breast development by age 13, or if there is no period by 3 years after the onset of breast development.[3]

# Ovulation suppression

## Birth control

*Main article: Hormonal contraception*



Half-used blister pack of a combined oral contraceptive. The white pills are placebos, mainly for the purpose of reminding the woman to continue taking the pills.

Since the late 1960s, many women have chosen to control the frequency of menstruation with hormonal birth control pills. They are most often combined hormone pills containing estrogen and are taken in 28-day cycles, 21 hormonal pills with either a 7-day break from pills, or 7 placebo pills during which the woman menstruates. Hormonal birth control acts by using low doses of hormones to prevent ovulation, and thus prevent pregnancy in sexually active women. But by using placebo pills for a 7-day span during the month, a regular bleeding period is still experienced.

Injections such as depo-provera became available in the 1960s. Progestogen implants such as Norplant in the 1980s and extended cycle combined oral contraceptive pills in the early 2000s.

Using synthetic hormones, it is possible for a woman to completely eliminate menstrual periods.[25] When using progestogen implants, menstruation may be reduced to 3 or 4 menstrual periods per year. By taking progestogen-only contraceptive pills (sometimes called the 'mini-pill') continuously without a 7-day span of using placebo pills, menstrual periods do not occur. Some women do this simply for convenience in the short-term,[26] while others prefer to eliminate periods altogether when possible.

Some women use hormonal contraception in this way to eliminate their periods for months or years at a time, a practice called menstrual suppression. When the first birth control pill was being developed, the researchers were aware that they could use the contraceptive to space menstrual periods up to 90 days apart, but they settled on a 28-day cycle that would mimic a natural menstrual cycle and produce monthly periods. The intention behind this decision was the hope of the inventor, John Rock, to win approval for his invention from the Roman Catholic Church. That attempt failed, but the 28-day cycle remained the standard when the pill became available to the public.[27] There is debate among medical researchers about the

potential long-term impacts of these practices upon female health. Some researchers point to the fact that historically, females have had far fewer menstrual periods throughout their lifetimes, a result of shorter life expectancies, as well as a greater length of time spent pregnant or breast-feeding, which reduced the number of periods experienced by females.[28] These researchers believe that the higher number of menstrual periods by females in modern societies may have a negative impact upon their health. On the other hand, some researchers believe there is a greater potential for negative impacts from exposing females perhaps unnecessarily to regular low doses of synthetic hormones over their reproductive years.[29]

### Breastfeeding

*Main article: Lactational amenorrhea method*

Breastfeeding causes negative feedback to occur on pulse secretion of gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH). Depending on the strength of the negative feedback, breastfeeding women may experience complete suppression of follicular development, follicular development but no ovulation, or normal menstrual cycles may resume.[30] Suppression of ovulation is more likely when suckling occurs more frequently.[31] The production of prolactin in response to suckling is important to maintaining lactational amenorrhea.[32] On average, women who are fully breastfeeding whose infants suckle frequently experience a return of menstruation at fourteen and a half months postpartum. There is a wide range of response among individual breastfeeding women, however, with some experiencing return of menstruation at two months and others remaining amenorrheic for up to 42 months postpartum.[33]

## Menstrual management

*Further information: Menstrual hygiene day*

Menstruation is managed by menstruating women to avoid damage to clothing or to accord with norms of public life. Menstrual management practices range from medical suppression of menstruation, through wearing special garments or other items, washing or avoidance of washing, disposal and laundry of stained materials, to separation of menstruators to particular places or activities.

Menstrual products (also called "feminine hygiene" products) are made to absorb or catch menstrual blood. A number of different products are available - some are disposable, some are reusable. Where women can afford it, items used to absorb or catch menses are usually commercially manufactured products. In developing countries, many women may not afford these products and use materials found in the environment or other improvised materials.

### Disposable items

- Sanitary napkins (Sanitary towels) or pads – Somewhat rectangular pieces of material worn in the underwear to absorb menstrual flow, often with "wings", pieces that fold around the undergarment and/or an adhesive backing to hold the pad in place. Disposable pads may contain wood pulp or gel products, usually with a plastic lining and bleached. Some sanitary napkins, particularly older styles, are held in place by a belt-like apparatus, instead of adhesive or wings.
- Tampons – Disposable cylinders of treated rayon/cotton blends or all-cotton fleece, usually bleached, that are inserted into the vagina to absorb menstrual flow.
- Padettes – Disposable wads of treated rayon/cotton blend fleece that are placed within the inner labia to absorb menstrual flow.
- Disposable menstrual cups – A firm, flexible cup-shaped device worn

Disposable softcup

Disposable sanitary napkin

Tampon in plastic applicator

inside the vagina to catch menstrual flow. Disposable cups are made of soft plastic.

## Reusable items

- Reusable cloth pads – Pads that are made of cotton (often organic), terrycloth, or flannel, and may be handsewn (from material or reused old clothes and towels) or storebought.
- Menstrual cups – A firm, flexible bell-shaped device worn inside the vagina for about half a day or overnight to catch menstrual flow. They are emptied into the toilet or sink when full, washed and re-inserted (washing hands with soap before doing so is crucial). Menstrual cups are usually made of silicone and can last 5 years or longer. At the end of the period, they are sterilised, usually by boiling in water.
- Sea sponges – Natural sponges, worn internally like a tampon to absorb menstrual flow.
- Padded panties – Reusable cloth (usually cotton) underwear with extra absorbent layers sewn in to absorb flow.
- Blanket, towel – (also known as a draw sheet) – large reusable piece of cloth, most often used at night, placed between legs to absorb menstrual flow.

Menstrual cup

Cloth menstrual pad

## Non-commercial materials

Absorption materials that may be used by women who cannot afford anything else include: sand, ash, small hole in earth,[34] cloth - new or re-used, whole leaf, leaf fibre (such as water hyacinth, banana, papyrus, cotton fibre), paper (toilet paper, re-used newspaper, pulped and dried paper),[35] animal pelt e.g. goat skin,[34] double layer of underwear, skirt or sari.[36]

# Society and culture

## Traditions and taboos

*Main article: Culture and menstruation*
*Further information: Menstrual taboo*


Amra Padatik India, celebration of Menstrual Hygiene Day in India

Many religions have menstruation-related traditions, for example the laws of Niddah in Judaism. These may ban certain actions during menstruation (such as sexual intercourse in some movements of Judaism and Islam), or rituals performed at the end of each menses (such as the *mikvah* in Judaism and the *ghusl* in Islam). Some traditional societies sequester women in residences called "menstrual huts" that are reserved for that exclusive purpose.

In Hinduism, it is also frowned upon to go to a temple and do *pooja* (i.e., pray) or do *pooja* at religious events if you are menstruating. Saraswati, the Hindu goddess of knowledge, is associated with menstruation; the literal translation of her name is "flow – woman". Metaformic Theory, as proposed by cultural theorist Judy Grahn and others, places menstruation as a central organizing idea in the creation of

culture[*citation needed*] and the formation of humans' earliest rituals.

Although most Christian denominations do not follow any specific or prescribed rites for menstruation, the Western civilization, which has been predominantly Christian, has a history of menstrual taboos, with menstruating women having been believed to be dangerous.[37][38]

Anthropologists, Lock and Nguyen (2010), have noted that the heavy medicalization of the reproductive life-stages of women in the West, mimic power structures that are deemed, in other cultural practices, to function as a form of "social control".[39] Medicalization of the stages of women's lives, such as birth and menstruation, has enlivened a feminist perspective that investigates the social implications of biomedicine's practice. "[C]ultural analysis of reproduction…attempts to show how women…exhibit resistance and create dominant alternative meanings about the body and reproduction to those dominant among the medical profession."[39]

In some parts of South Asia, women are isolated during menstruation. In 2005, in Nepal, the Supreme Court abolished the practice of chhaupadi, keeping women in cow-sheds during menstruation.[40]

### Sexual activity

Sexual intercourse during menstruation does not cause damage in and of itself, but the woman's body is more vulnerable during this time. Vaginal pH is higher and less acidic than normal,[41] the cervix is lower in its position, the cervical opening is more dilated, and the uterine endometrial lining is absent, thus allowing organisms direct access to the blood stream through the numerous blood vessels that nourish the uterus. All these conditions increase the chance of infection during menstruation.[*citation needed*]

### Other aspects

Male menstruation is a term used colloquially for a type of bleeding in the urine or faeces of males, reported in some tropical countries. It is actually caused by parasite infestation of the urinary tract or intestines by Schistosoma haematobium, and cases of it are actually schistosomiasis, formerly known as bilharziasis.

## Evolution

All female placental mammals have a uterine lining that builds up when the animal is fertile, but it is dismantled when the animal is infertile. Most female mammals have an estrous cycle, yet only primates (including humans), several species of bats, and elephant shrews have a menstrual cycle.[42] Some anthropologists have questioned the energy cost of rebuilding the endometrium every fertility cycle. However, anthropologist Beverly Strassmann has proposed that the energy savings of not having to *continuously* maintain the uterine lining more than offsets energy cost of having to rebuild the lining in the next fertility cycle, even in species such as humans where much of the lining is lost through bleeding (overt menstruation) rather than reabsorbed (covert menstruation).[43][44]

Many have questioned the evolution of overt menstruation in humans and related species, speculating on what advantage there could be to losing blood associated with dismantling the endometrium, rather than absorbing it, as most mammals do. Humans do, in fact, reabsorb about two-thirds of the endometrium each cycle. Strassmann asserts that overt menstruation occurs not because it is beneficial in itself. Rather, the fetal development of these species requires a more developed endometrium, one which is too thick to reabsorb completely. Strassman correlates species that have overt menstruation to those that have a large uterus relative to the adult female body size.[43]

Beginning in 1971, some research suggested that menstrual cycles of cohabiting human females became synchronized. A few anthropologists hypothesized that in hunter-gatherer societies, males would go on hunting journeys whilst the females of the tribe were menstruating, speculating that the females would not have been as receptive to sexual relations while menstruating.[45][46] However, there is currently significant dispute as to whether menstrual synchrony exists.[47]

## See also

- Menstrual cycle
- Menstrual Hygiene Day

## References


1. ^ a b c *Women's Gynecologic Health*. Jones & Bartlett Publishers. 2011. p. 94. ISBN 9780763756376.
2. ^ a b c d e f g h i "Menstruation and the menstrual cycle fact sheet". *Office of Women's Health*. December 23, 2014. Retrieved 25 June 2015.
3. ^ a b c d e American Academy of Pediatrics Committee on, Adolescence; American College of Obstetricians and Gynecologists Committee on Adolescent Health, Care; Diaz, A; Laufer, MR; Breech, LL (November 2006). "Menstruation in girls and adolescents: using the menstrual cycle as a vital sign.". *Pediatrics*. **118** (5): 2245–50. doi:10.1542/peds.2006-2481. PMID 17079600.
4. ^ a b "Menopause: Overview". *http://www.nichd.nih.gov*. 2013-06-28. Retrieved 8 March 2015. External link in |website= (help)
5. ^ a b c Biggs, WS; Demuth, RH (15 October 2011). "Premenstrual syndrome and premenstrual dysphoric disorder.". *American family physician*. **84** (8): 918–24. PMID 22010771.
6. ^ a b c d "Premenstrual syndrome (PMS) fact sheet". *Office on Women's Health*. December 23, 2014. Retrieved 23 June 2015.
7. ^ Kristin H. Lopez (2013). *Human Reproductive Biology*. Academic Press. p. 53. ISBN 9780123821850.
8. ^ Martin RD (2007). "The evolution of human reproduction: a primatological perspective". *Am. J. Phys. Anthropol.* Suppl 45: 59–84. doi:10.1002/ajpa.20734. PMID 18046752.
9. ^ Karapanou, O.; Papadimitriou, A. (2010). "Determinants of menarche.". *Reprod Biol Endocrinol*. **8**: 115. doi:10.1186/1477-7827-8-115. PMID 20920296.
10. ^ a b c Ziporyn, Karen J. Carlson, Stephanie A. Eisenstat, Terra (2004). *The new Harvard guide to women's health*. Cambridge, Mass.: Harvard University Press. ISBN 0-674-01343-3.
11. ^ Price WA, Giannini AJ (1983). "Binge eating during menstruation". *The Journal of Clinical Psychiatry*. **44** (11): 431. PMID 6580290.
12. ^ "Water retention: Relieve this premenstrual symptom". Mayo Clinic. Retrieved 20 September 2011.
13. ^ a b c d e Dysmenorrhea: Menstrual Abnormalities: Merck Manual Professional
14. ^ Menstrual Reduction With Extended Use of Combination Oral Co... : Obstetrics & Gynecology
ealth_consequences_fgm/en/
25. ^ "Delaying your period with birth control pills". Mayo Clinic. Retrieved 20 September 2011.
26. ^ "How can I delay my period while on holiday?". National Health Service, United Kingdom. Retrieved 20 September 2011.
27. ^ "Do you really need to have a period every month?". Discovery Health. Retrieved 20 September 2011.
28. ^ Amy Lind; Stephanie Brzuzy (2007). *Battleground: Women, Gender, and Sexuality: Volume 2: M–Z*. Greenwood. p. 348. ISBN 978-0-313-34039-0.
29. ^ Kam, Katherine. "Eliminate periods with birth control?". WebMD. Retrieved 20 September 2011.
30. ^ McNeilly AS (2001). "Lactational control of reproduction". *Reprod. Fertil. Dev.* **13** (7–8): 583–90. doi:10.1071/RD01056. PMID 11999309.
31. ^ Kippley, John; Sheila Kippley (1996). *The Art of Natural Family Planning* (4th ed.). Cincinnati, OH: The Couple to Couple League. p. 347. ISBN 0-926412-13-2.
32. ^ Stallings JF, Worthman CM, Panter-Brick C, Coates RJ (February 1996). "Prolactin response to suckling and maintenance of postpartum amenorrhea among intensively breastfeeding Nepali women". *Endocr. Res.* **22** (1): 1–28. doi:10.3109/07435809609030495. PMID 8690004.
33. ^ "Breastfeeding: Does It Really Space Babies?". *The Couple to Couple League International*. Internet Archive. 17 January 2008. Archived from the original on 17 January 2008. Retrieved 21 September 2008., which cites:
    Kippley SK, Kippley JF (November–December 1972). "The relation between breastfeeding and amenorrhea". *Journal of obstetric, gynecologic, and neonatal nursing*. **1** (4): 15–21. doi:10.1111/j.1552-6909.1972.tb00558.x. PMID 4485271.
    Sheila Kippley (November–December 1986 and January–February 1987). "Breastfeeding survey results similar to 1971 study". *The CCL News*. **13** (3): 10. Check date values in: |date= (help) and **13**(4): 5.
34. ^ a b Tamiru, S., Mamo, K., Acidria, P., Mushi, R., Satya Ali, C., Ndebele, L. (2015) Towards a sustainable solution for school menstrual hygiene management: cases of Ethiopia, Uganda, South-Sudan, Tanzania, and Zimbabwe. Waterlines, Vol. 34, No.1

15. ^ Marjoribanks, J; Proctor, M; Farquhar, C; Derks, RS (20 January 2010). "Nonsteroidal anti-inflammatory drugs for dysmenorrhoea.". *The Cochrane database of systematic reviews* (1): CD001751. doi:10.1002/14651858.CD001751.pub2. PMID 20091521.
16. ^ "Period makeovers: Fixes for heavy bleeding, cramps, PMS - CNN.com". *CNN*. 25 September 2007.
17. ^ Medscape: Medscape Access
18. ^ Sharma P, Malhotra C, Taneja DK, Saha R (2008). "Problems related to menstruation amongst adolescent girls". *Indian J Pediatr*. **75** (2): 125–9. doi:10.1007/s12098-008-0018-5. PMID 18334791.
19. ^ Farage, Miranda (Mar 22, 2013). *The Vulva: Anatomy, Physiology, and Pathology*. CRC Press. pp. 155–158.
20. ^ "Menstrual blood problems: Clots, color and thickness". WebMD. Retrieved 20 September 2011.
21. ^ Clancy, Kate (27 July 2011). "Iron-deficiency is not something you get just for being a lady". SciAm.
22. ^ Kepczyk T, Cremins JE, Long BD, Bachinski MB, Smith LR, McNally PR (January 1999). "A prospective, multidisciplinary evaluation of premenopausal women with iron-deficiency anemia". *Am. J. Gastroenterol*. **94** (1): 109–15. doi:10.1111/j.1572-0241.1999.00780.x. PMID 9934740.
23. ^ Fraser IS, Critchley HO, Munro MG, Broder M (2007). "Can we achieve international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding?". *Hum Reprod*. **22** (3): 635–43. doi:10.1093/humrep/del478. PMID 17204526.
24. ^ http://www.who.int/reproductivehealth/topics/fgm/h
35. ^ House, S., Mahon, T., Cavill, S. (2012). Menstrual hygiene matters - A resource for improving menstrual hygiene around the world. WaterAid, UK
36. ^ Chin, L. (2014) Period of shame - The Effects of Menstrual Hygiene Management on Rural Women and Girls' Quality of Life in Savannakhet, Laos [Master's thesis] LUMID International Master programme in applied International Development and Management http://lup.lub.lu.se/student-papers/record/4442938 [accessed 10 August 2015]
37. ^ http://ispub.com/IJWH/5/2/8213
38. ^ http://ebooks.adelaide.edu.au/f/frazer/james/golden/chapter60.html
39. ^ *a b* Lock, M. & Nguyen, V.-K., 2010. *An Anthropology of Biomedicine*. Oxford: Wiley-Blackwell.
40. ^ Sushil Sharma, "Women hail menstruation ruling", *BBC News*, 15 September 2005.
41. ^ *Ann Intern Med.* 1982 Jun; 96(6 Pt 2):921–3. "Vaginal physiology during menstruation."
42. ^ "Why do women menstruate?". *ScienceBlogs*. 2011. Retrieved 15 January 2013.
43. ^ *a b* Strassmann BI (1996). "The evolution of endometrial cycles and menstruation". *The Quarterly Review of Biology*. **71** (2): 181–220. doi:10.1086/419369. PMID 8693059.
44. ^ Kathleen O'Grady (2000). "Is Menstruation Obsolete?". The Canadian Women's Health Network. Retrieved 21 January 2007.
45. ^ Desmond Morris (1997). "The Human Sexes". Cambridge University Press.
46. ^ Chris Knight (1991). *Blood relations: menstruation and the origins of culture*. New Haven, Conn: Yale University Press. ISBN 0-300-06308-3.
47. ^ Adams, Cecil (20 December 2002). "Does menstrual synchrony really exist?". *The Straight Dope*. The Chicago Reader. Retrieved 10 January 2007.


## Further reading


- Howie, Gillian; Shail, Andrew (2005). *Menstruation: A Cultural History*. Palgrave Macmillan. ISBN 1-4039-3935-7. Retrieved 2013-11-09.
- Knight, Chris (1995). *Blood Relations: Menstruation and the Origins of Culture*. New Haven and London: Yale University. ISBN 0-300-04911-0. Retrieved 2013-11-09.


## External links

- Museum of Menstruation

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Categories: Menstrual cycle | Midwifery

# Morning sickness

From Wikipedia, the free encyclopedia

**Morning sickness**, also called **nausea and vomiting of pregnancy** (**NVP**), is a symptom of pregnancy that involves nausea or vomiting.[1] Despite the name, nausea or vomiting can occur at any time during the day. Typically these symptoms occur between the 4th and 16th week of pregnancy. About 10% of women still have symptoms after the 20th week of pregnancy.[2] A severe form of the condition is known as hyperemesis gravidarum and results in weight loss.[1][3]

The cause of morning sickness is unknown but may be related to changing levels of the hormone human chorionic gonadotrophin.[2] Some have proposed that it may be useful from an evolutionary point of view.[1] Diagnosis should only occur after other possible causes have been ruled out.[4] Abdominal pain, fever, or headaches are typically not present in morning sickness.[1]

Taking prenatal vitamins before pregnancy may decrease the risk.[4] Specific treatment other than a bland diet may not be required for mild cases.[2][3][4] If treatment is used the combination of doxylamine and pyridoxine is recommended initially.[4][5] Tentative evidence supports the use of ginger.[4][6] For severe cases that have not improved with other measures methylprednisolone may be tried. Tube feeding may be required in women who are losing weight.[4]

Morning sickness affects about 70-80% of all pregnant women to some extent.[5][7] About 60% of women have vomiting.[2] Hyperemesis gravidarum occurs in about 1.6% of pregnancies.[1] Morning sickness can negatively affect quality of life, result in decreased ability to work while pregnant, and result in health care expenses.[4] Generally mild to moderate cases have no effect on the baby. Most severe cases also have normal outcomes. Some women choose to have an abortion due to the severity of symptoms. Complications such as Wernicke encephalopathy or esophageal rupture may occur but are very rare.[1]

**Morning sickness**

| | |
|---|---|
| **Synonyms** | nausea and vomiting of pregnancy, nausea gravidarum, [illegible] pregnancy, sickness |
| **Classification and external resources** | |
| **Specialty** | Obstetrics |
| **ICD-10** | O21.0 |
| **ICD-9-CM** | 643.0 |
| **MedlinePlus** | 003119 |

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Contents



## Signs and symptoms [edit]

About 66% of women have both nausea and vomiting while 33% have just nausea.[1]

## Cause [edit]

The cause of morning sickness is unknown.[1] While some have claimed it to be due to psychological reasons, this is not supported by evidence.[1]

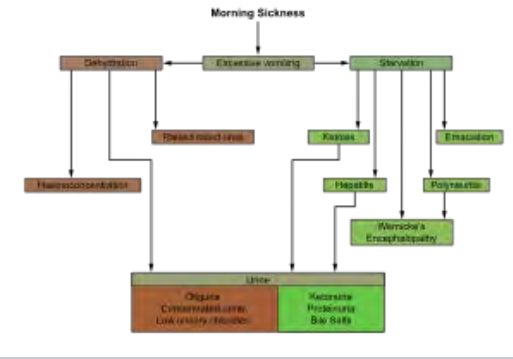
Nausea and vomiting may also occur with molar pregnancy.[8]

Edit links

# Pathophysiology [edit]

## Hormone changes [edit]

- An increase in the circulating level of the hormone estrogen.[9] However, there is no consistent evidence of differences in estrogen levels and levels of bilirubin between women that experience sickness and those that do not.[10] Related to increased estrogen levels, a similar form of nausea is also seen in some women who use hormonal contraception or hormone replacement therapy.
- An increase in progesterone relaxes the muscles in the uterus, which prevents early childbirth, but may also relax the stomach and intestines, leading to excess stomach acids and gastroesophageal reflux disease (GERD).
- An increase in human chorionic gonadotropin. It is probably not the human chorionic gonadotropin itself that causes the nausea. More likely, it is the human chorionic gonadotropin stimulating the maternal ovaries to secrete estrogen, which in turn causes the nausea.[11]



Pathophysiology of vomiting in pregnancy

## Defense mechanism [edit]

Morning sickness may be an evolved trait that protects the baby against toxins ingested by the mother. Evidence in support of this theory, including:[12][13]

- Morning sickness is very common among pregnant women, which argues in favor of its being a functional adaptation and against the idea that it is a pathology.
- Fetal vulnerability to toxins peaks at around 3 months, which is also the time of peak susceptibility to morning sickness.
- There is a good correlation between toxin concentrations in foods, and the tastes and odors that cause revulsion.

Women who have *no* morning sickness are more likely to miscarry.[14] This may be because such women are more likely to ingest substances that are harmful to the fetus.[15]

In addition to protecting the fetus, morning sickness may also protect the mother. A pregnant woman's immune system is suppressed during pregnancy, presumably to reduce the chances of rejecting tissues of her own offspring.[16] Because of this, animal products containing parasites and harmful bacteria can be especially dangerous to pregnant women. There is evidence that morning sickness is often triggered by animal products including meat and fish.[17]

If morning sickness is a defense mechanism against the ingestion of toxins, the prescribing of anti-nausea medication to pregnant women may have the undesired side effect of causing birth defects or miscarriages by encouraging harmful dietary choices.[12]

# Treatments [edit]

There is unclear evidence about the effectiveness of home treatments for morning sickness.[18][*needs update*]

## Medications [edit]

A number of antiemetics are effective and safe in pregnancy including: pyridoxine/doxylamine, antihistamines (such as diphenhydramine), metoclopramide, and phenothiazines (such as promethazine).[19][20] With respect to effectiveness it is unknown if one is superior to another.[19] In the United States and Canada, the doxylamine-pyridoxine combination (as Diclegis in US and Diclectin in Canada) is the only approved pregnancy category "A" prescription treatment for nausea and vomiting of pregnancy.[20]

Ondansetron may be beneficial, but there are some concerns regarding an association with cleft palate,[21] and there is little high quality data.[19] Metoclopramide is also used and relatively well tolerated.[22] Evidence for the use of corticosteroids is weak.[23]

## Alternative medicine [edit]

There is tentative evidence that ginger may be useful; however, it is not clear.[24][*needs update*][25] Safety concerns have been raised regarding its anticoagulant properties.[26][27]

# History [edit]

## Thalidomide [edit]

Thalidomide was originally developed and prescribed as a cure for morning sickness in West Germany, but its use was discontinued when it was found to cause birth defects. The United States Food and Drug Administration never approved thalidomide for use as a cure for morning sickness.

# References [edit]


1. ^ a b c d e f g h i "Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy.". *Obstetrics and gynecology*. **126** (3): e12–24. September 2015. doi:10.1097/AOG.0000000000001048. PMID 26287788.
2. ^ a b c d Festin, M (3 June 2009). "Nausea and vomiting in early pregnancy.". *BMJ clinical evidence*. **2009**. PMC 2907767. PMID 21726485.
3. ^ a b "Pregnancy". *Office on Women's Health*. September 27, 2010. Retrieved 5 December 2015.
4. ^ a b c d e f g "Practice Bulletin Summary No. 153: Nausea and Vomiting of Pregnancy.". *Obstetrics and gynecology*. **126** (3): 687–8. September 2015. doi:10.1097/01.aog.0000471177.80067.19. PMID 26287781.
5. ^ a b Koren, G (December 2014). "Treating morning sickness in the United States--changes in prescribing are needed.". *American Journal of Obstetrics and Gynecology*. **211** (6): 602–6. doi:10.1016/j.ajog.2014.08.017. PMID 25151184.
6. ^ Matthews, A; Haas, DM; O'Mathúna, DP; Dowswell, T (8 September 2015). "Interventions for nausea and vomiting in early pregnancy.". *The Cochrane database of systematic reviews* (9): CD007575. doi:10.1002/14651858.CD007575.pub4. PMID 26348534.
7. ^ Einarson, Thomas R.; Piwko, Charles; Koren, Gideon (2013-01-01). "Prevalence of nausea and vomiting of pregnancy in the USA: a meta analysis". *Journal of Population Therapeutics and Clinical Pharmacology = Journal De La Therapeutique Des Populations Et De La Pharamcologie Clinique*. **20** (2): e163–170. ISSN 1710-6222. PMID 23863545.
8. ^ Verberg, MF; Gillott, DJ; Al-Fardan, N; Grudzinskas, JG (2005). "Hyperemesis gravidarum, a literature review.". *Human Reproduction Update*. **11** (5): 527–39. doi:10.1093/humupd/dmi021. PMID 16006438.
9. ^ Lagiou, P; Tamimi, R; Mucci, LA; Trichopoulos, D; Adami, HO; Hsieh, CC (April 2003). "Nausea and vomiting in pregnancy in relation to prolactin, estrogens, and progesterone: a prospective study". *Obstetrics and gynecology*. **101** (4): 639–44. doi:10.1016/s0029-7844(02)02730-8. PMID 12681864.
10. ^ Elizabeth Bauchner; Wendy Marquez. "Morning Sickness: Coping With The Worst". NY Metro Parents Magazine. Retrieved 2008-07-06.
11. ^ Niebyl, Jennifer R. (2010). "Nausea and Vomiting in Pregnancy". *New England Journal of Medicine*. **363** (16): 1544–1550. doi:10.1056/NEJMcp1003896. PMID 20942670.
12. ^ a b Nesse, Randolphe M; Williams, George C (1996). *Why We Get Sick* (1st ed.). New York: Vintage Books. p. 290.
13. ^ Pepper GV, Craig Roberts S (October 2006). "Rates of nausea and vomiting in pregnancy and dietary characteristics across populations". *Proceedings of the Royal Society B*. **273** (1601): 2675–2679. doi:10.1098/rspb.2006.3633. PMC 1635459. PMID 17002954.
14. ^ Chan, Ronna L.; Olshan, A. F.; Savitz, D. A.; Herring, A. H.; Daniels, J. L.; Peterson, H. B.; Martin, S. L.; et al. (Sep 22, 2010). "Severity and duration of nausea and vomiting symptoms in pregnancy and spontaneous abortion". *Human Reproduction*. **25** (11): 2907–12. doi:10.1093/humrep/deq260. PMC 3140259. PMID 20861299.
15. ^ Sherman, Paul W.; Flaxman, Samuel M. (2002). "Nausea and vomiting of pregnancy in an evolutionary perspective". *Am J Obstet Gynecol*. **186** (5): S190–S197. doi:10.1067/mob.2002.122593. PMID 12011885.
16. ^ Haig, David (October 1993). "Genetic conflicts in human pregnancy". *Quarterly Review of Biology*. **68** (4): 495–532. doi:10.1086/418300. PMID 8115596.
17. ^ Flaxman, Samuel M.; Sherman, Paul W. (June 2000). "Morning sickness: a mechanism for protecting mother and embryo". *Quarterly Review of Biology*. **75** (2): 113–148. doi:10.1086/393377. PMID 10858967.
18. ^ Matthews, A.; Haas, D. M.; O'Mathúna, D. N. P.; Dowswell, T.; Doyle, M. (2014). "Interventions for nausea and vomiting in early pregnancy". *The Cochrane Library*: CD007575. doi:10.1002/14651858.CD007575.pub3. PMID 24659261.
19. ^ a b c Jarvis, S; Nelson-Piercy, C (Jun 17, 2011). "Management of nausea and vomiting in pregnancy.". *BMJ (Clinical research ed.)*. **342**: d3606. doi:10.1136/bmj.d3606. PMID 21685438.
20. ^ a b Clark SM, Dutta E, Hankins GD (September 2014). "The outpatient management and special considerations of nausea and vomiting in pregnancy". *Semin Perinatol*. **38** (14): 496–502. doi:10.1053/j.semperi.2014.08.014. PMID 25267280.
21. ^ Koren, G (October 2012). "Motherisk update. Is ondansetron safe for use during pregnancy?". *Canadian Family Physician*. **58** (10): 1092–3. PMC 3470505. PMID 23064917.
22. ^ Tan, PC; Omar, SZ (April 2011). "Contemporary approaches to hyperemesis during pregnancy.". *Current opinion in obstetrics & gynecology*. **23** (2): 87–93. doi:10.1097/GCO.0b013e328342d208. PMID 21297474.
23. ^ Poon, SL (October 2011). "Towards evidence-based emergency medicine: Best BETs from the Manchester Royal Infirmary. BET 2: Steroid therapy in the treatment of intractable hyperemesis gravidarum.". *Emergency medicine journal : EMJ*. **28** (10): 898–900. doi:10.1136/emermed-2011-200636. PMID 21918097.
24. ^ Matthews, A; Haas, DM; O'Mathúna, DP; Dowswell, T; Doyle, M (21 March 2014). "Interventions for nausea and vomiting in early pregnancy.". *The Cochrane database of systematic reviews*. **3**: CD007575. doi:10.1002/14651858.CD007575.pub3. PMID 24659261.
25. ^ Thomson, M.; Corbin, R.; Leung, L. (2014). "Effects of Ginger for Nausea and Vomiting in Early Pregnancy: A Meta-Analysis". *The Journal of the American Board of Family Medicine*. **27** (1): 115–122. doi:10.3122/jabfm.2014.01.130167. ISSN 1557-2625.
26. ^ Borrelli F, Capasso R, Aviello G, Pittler MH, Izzo AA (2005). "Effectiveness and safety of ginger in the treatment of pregnancy-induced nausea and vomiting". *Obstetrics and gynecology*. **105** (4): 849–56. doi:10.1097/01.AOG.0000154890.47642.23. PMID 15802416.
27. ^ Tiran, Denise (Feb 2012). "Ginger to reduce nausea and vomiting during pregnancy: Evidence of effectiveness is not the same as proof of safety". *Complementary Therapies in Clinical Practice*. **18** (1): 22–25. doi:10.1016/j.ctcp.2011.08.007. ISSN 1744-3881.

| v · t · e · | Pathology of pregnancy, childbirth and the puerperium (O, 630–679) | | |
|---|---|---|---|
| Pregnancy | Pregnancy with abortive outcome | Ectopic pregnancy (Abdominal pregnancy · Cervical pregnancy · Interstitial pregnancy · Ovarian pregnancy · · Molar pregnancy · Miscarriage · Stillbirth · | |
| | Oedema, proteinuria and hypertensive disorders | Gestational hypertension · Pre-eclampsia (HELLP syndrome · · Eclampsia · | |
| | Other, predominantly related to pregnancy | Digestive system | Acute fatty liver of pregnancy · Gestational diabetes · Hepatitis E · Hyperemesis gravidarum · Intrahepatic cholestasis of pregnancy · |
| | | Integumentary system / dermatoses of pregnancy | Gestational pemphigoid · Impetigo herpetiformis · Intrahepatic cholestasis of pregnancy · Linea nigra · Prurigo gestationis · Pruritic folliculitis of pregnancy · Pruritic urticarial papules and plaques of pregnancy (PUPPP) · Striae gravidarum · |
| | | Nervous system | Chorea gravidarum · |
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| | Maternal care related to the fetus and amniotic cavity | *amniotic fluid* (Oligohydramnios · Polyhydramnios · · Braxton Hicks contractions · *chorion* / *amnion* (Amniotic band syndrome · Chorioamnionitis · Chorionic hematoma · Monoamniotic twins · Premature rupture of membranes · · Obstetrical hemorrhage (Antepartum · · *placenta* (Circumvallate placenta · Monochorionic twins · Placenta praevia · Placental abruption · Twin-to-twin transfusion syndrome · · | |
| Labor | Amniotic fluid embolism · Cephalopelvic disproportion · Dystocia (Shoulder dystocia · · Fetal distress · Locked twins · Obstetrical hemorrhage (Postpartum · · *placenta* (Placenta accreta · · Preterm birth · Postmature birth · Umbilical cord prolapse · Uterine rupture · Vasa praevia · | | |
| Puerperal | Breastfeeding difficulties (Lactation failure · Galactorrhea · Fissure of the nipple · · Breast engorgement · Diastasis symphysis pubis · Peripartum cardiomyopathy · Postpartum depression · Postpartum thyroiditis · Puerperal fever · Puerperal mastitis · | | |
| Other | Concomitant conditions (Diabetes mellitus · Systemic lupus erythematosus · Thyroid disorders · · Maternal death · Sexual activity during pregnancy · | | |
| Authority control | NDL: 00568956 · | | |

Categories: Health issues in pregnancy | Vomiting | Gynaecology | Obstetrics | Midwifery

# Obstructed labour

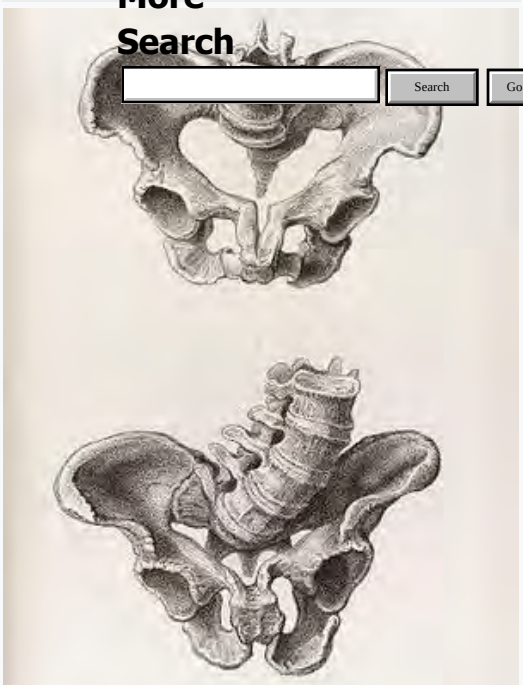
(Redirected from Obstructed labour)

**Obstructed labour**, also known as **labour dystocia**, is when, even though the uterus is contracting normally, the baby does not exit the pelvis during childbirth due to being physically blocked.[1] Complications for the baby include not getting enough oxygen which may result in death. It increases the risk of the mother getting an infection, having uterine rupture, or having post-partum bleeding.[2] Long term complications for the mother include obstetrical fistula. Obstructed labour is said to result in prolonged labour, when the active phase of labour is longer than twelve hours.[1]

The main causes of obstructed labour include: a large or abnormally positioned baby, a small pelvis, and problems with the birth canal. Abnormal positioning includes shoulder dystocia where the anterior shoulder does not pass easily below the pubic bone.[1] Risk factors for a small pelvis include malnutrition and a lack of exposure to sunlight causing vitamin D deficiency.[3] It is also more common in adolescence as the pelvis may not have finished growing.[2] Problems with the birth canal include a narrow vagina and perineum which may be due to female genital mutilation or tumors.[1] A partograph is often used to track labour progression and diagnose problems.[2] This combined with physical examination may identify obstructed labour.[4]

The treatment of obstructed labour may require cesarean section or vacuum extraction with possible surgical opening of the symphysis pubis. Other measures include: keeping the women hydrated and antibiotics if the membranes have been ruptured for more than 18 hours.[5] In Africa and Asia obstructed labor effects between two and five percent of deliveries.[6] In 2013 about 5.1 cases of obstructed labour occurred.[7] This resulted in 19,000 deaths down from 29,000 deaths in 1990 (about 8% of all deaths related to pregnancy).[1][8] Most deaths due to this condition occur in the developing world.[2]

**Obstructed labour**



An image of a deformed pelvis, a risk factor for obstructed labour

| Classification and external resources | |
|---|---|
| **Specialty** | obstetrics |
| **ICD-10** | O64 – O66 |
| **DiseasesDB** | 4025 |
| **eMedicine** | med/3280 |
| **Patient UK** | Obstructed labour |
| **MeSH** | D004420 |

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Contents


## Cause [edit]

The main causes of obstructed labour include: a large or abnormally positioned baby, a small pelvis, and problems with the birth canal.[1] Abnormal positioning includes shoulder dystocia where the anterior shoulder does not pass easily below the pubic bone.[1] Risk factors for a small pelvis include malnutrition and a lack of exposure to sunlight causing vitamin D deficiency.[3] while problems with the birth canal include a narrow vagina and perineum which may be due to female genital mutilation or tumors.[1]

Edit links

## Diagnosis [edit]

Obstructed labour may be diagnosed based on physical examination.[4]

## Treatment [edit]

The treatment of obstructed labour may require cesarean section or vacuum extraction with possible surgical opening of the symphysis pubis.[5] Other measures include: keeping the women hydrated and antibiotics if the membranes have been ruptured for more than 18 hours.[5]

## Epidemiology [edit]

In 2013 it resulted in 19,000 deaths down from 29,000 deaths in 1990.[8]

## Etymology [edit]

The word dystocia means difficult labour.[2] Its antonym is eutocia (Ancient Greek: τόκος *tókos* "childbirth") or easy labour.

Other terms for obstructed labour include: difficult labour, abnormal labour, difficult childbirth, abnormal childbirth, and dysfunctional labour.

## Other animals [edit]

The term can also be used in the context of various animals. Dystocia pertaining to birds and reptiles is also called egg binding.

## References [edit]


1. ^ *a b c d e f g h* *Education material for teachers of midwifery : midwifery education modules* (PDF) (2nd ed.). Geneva [Switzerland]: World Health Organisation. 2008. pp. 17–36. ISBN 9789241546669.
2. ^ *a b c d e* Neilson, JP; Lavender, T; Quenby, S; Wray, S (2003). "Obstructed labour.". *British medical bulletin*. **67**: 191–204. doi:10.1093/bmb/ldg018. PMID 14711764.
3. ^ *a b* *Education material for teachers of midwifery : midwifery education modules* (PDF) (2nd ed.). Geneva [Switzerland]: World Health Organisation. 2008. pp. 38–44. ISBN 9789241546669.
4. ^ *a b* *Education material for teachers of midwifery : midwifery education modules* (PDF) (2nd ed.). Geneva [Switzerland]: World Health Organisation. 2008. pp. 45–52. ISBN 9789241546669.
5. ^ *a b c* *Education material for teachers of midwifery : midwifery education modules* (PDF) (2nd ed.). Geneva [Switzerland]: World Health Organisation. 2008. pp. 89–104. ISBN 9789241546669.
6. ^ Usha, Krishna (2004). *Pregnancy at risk : current concepts*. New Delhi: Jaypee Bros. p. 451. ISBN 9788171798261.
7. ^ Global Burden of Disease Study 2013, Collaborators (22 August 2015). "Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet (London, England)*. **386** (9995): 743–800. doi:10.1016/s0140-6736(15)60692-4. PMC 4561509. PMID 26063472.
8. ^ *a b* GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". *Lancet*. **385**: 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.


## Further reading [edit]


- *Education material for teachers of midwifery : midwifery education modules* (PDF) (2nd ed.). Geneva [Switzerland]: World Health Organisation. 2008. ISBN 9789241546669.


| v · t · e · | Pathology of pregnancy, childbirth and the puerperium (O, 630–679) | |
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| | **Pregnancy with abortive outcome** | Ectopic pregnancy (Abdominal pregnancy · Cervical pregnancy · Interstitial pregnancy · Ovarian pregnancy · · Molar pregnancy · Miscarriage · Stillbirth · |
| | **Oedema, proteinuria and hypertensive disorders** | Gestational hypertension · Pre-eclampsia (HELLP syndrome · · Eclampsia · |
| | | Acute fatty liver of pregnancy · Gestational diabetes · |

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| **Pregnancy** | **Other, predominantly related to pregnancy** | **Digestive system** | Hepatitis E · Hyperemesis gravidarum · Intrahepatic cholestasis of pregnancy · |
| | | **Integumentary system / dermatoses of pregnancy** | Gestational pemphigoid · Impetigo herpetiformis · Intrahepatic cholestasis of pregnancy · Linea nigra · Prurigo gestationis · Pruritic folliculitis of pregnancy · Pruritic urticarial papules and plaques of pregnancy (PUPPP) · Striae gravidarum · |
| | | **Nervous system** | Chorea gravidarum · |
| | | **Blood** | Gestational thrombocytopenia · Pregnancy-induced hypercoagulability · |
| | **Maternal care related to the fetus and amniotic cavity** | | *amniotic fluid* (Oligohydramnios · Polyhydramnios · · Braxton Hicks contractions · *chorion* / *amnion* (Amniotic band syndrome · Chorioamnionitis · Chorionic hematoma · Monoamniotic twins · Premature rupture of membranes · · Obstetrical hemorrhage (Antepartum · · *placenta* (Circumvallate placenta · Monochorionic twins · Placenta praevia · Placental abruption · Twin-to-twin transfusion syndrome · · |
| **Labor** | Amniotic fluid embolism · Cephalopelvic disproportion · Dystocia (Shoulder dystocia · · Fetal distress · Locked twins · Obstetrical hemorrhage (Postpartum · · *placenta* (Placenta accreta · · Preterm birth · Postmature birth · Umbilical cord prolapse · Uterine rupture · Vasa praevia · | | |
| **Puerperal** | Breastfeeding difficulties (Lactation failure · Galactorrhea · Fissure of the nipple · · Breast engorgement · Diastasis symphysis pubis · Peripartum cardiomyopathy · Postpartum depression · Postpartum thyroiditis · Puerperal fever · Puerperal mastitis · | | |
| **Other** | Concomitant conditions (Diabetes mellitus · Systemic lupus erythematosus · Thyroid disorders · · Maternal death · Sexual activity during pregnancy · | | |

Categories: Complications of labour and delivery | Midwifery




# Ovarian cyst

From Wikipedia, the free encyclopedia

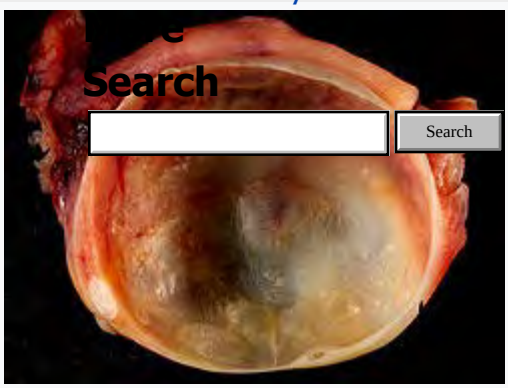
An **ovarian cyst** is a fluid-filled sac within the ovary. Often they cause no symptoms. Occasionally they may produce bloating, lower abdominal pain, or lower back pain. If the cyst either breaks open or causes twisting of the ovary severe pain may occur. This may result in vomiting or feeling faint. The majority of cysts are, however, harmless.[1]

Most ovarian cysts are related to ovulation being either follicular cysts or corpus luteum cysts. Other types include cysts due to endometriosis, dermoid cysts, and cystadenomas. Many small cysts occur in both ovaries in polycystic ovarian syndrome. Pelvic inflammatory disease may also result in cysts. Rarely cysts may be a form of ovarian cancer. Diagnosis is undertaken by pelvic examination with an ultrasound or other testing used to gather further details.[1]

Often cysts are simply observed over time. If they cause pain, medications such as paracetamol (acetaminophen) or ibuprofen may be used. Hormonal birth control may be used to prevent further cysts in those who are frequently affected.[1] However, evidence does not support birth control as a treatment of current cysts.[2] If they do not go away after several months, get larger, look unusual, or cause pain they may be removed by surgery.[1]

Most women of reproductive age develop small cysts each month. Large cysts that cause problems occur in about 8% of women before menopause.[1] Ovarian cysts are present in about 16% of women after menopause and if present are more likely to be cancer.[1][3]

**Ovarian cyst**



A simple ovarian cyst of most likely follicular origin

| Classification and external resources | |
|---|---|
| **Specialty** | Gynecology |
| **ICD-10** | N83.0-N83.2 |
| **ICD-9-CM** | 620.0-620.2 |
| **DiseasesDB** | 9433 |
| **MedlinePlus** | 001504 |
| **eMedicine** | med/1699 emerg/352 |
| **MeSH** | D010048 |

[edit on Wikidata]

Contents

## Signs and symptoms [edit]

Some or all of the following symptoms may be present, though it is possible not to experience any symptoms:[4]

- Abdominal pain. Dull aching pain within the abdomen or pelvis, especially during intercourse.
- Uterine bleeding. Pain during or shortly after beginning or end of menstrual period; irregular periods, or abnormal uterine bleeding or spotting.
- Fullness, heaviness, pressure, swelling, or bloating in the abdomen.
- When a cyst ruptures from the ovary, there may be sudden and sharp pain in the lower abdomen on one side.
- Change in frequency or ease of urination (such as inability to fully empty the bladder), or difficulty with bowel movements due to pressure on adjacent pelvic anatomy.
- Constitutional symptoms such as fatigue, headaches
- Nausea or vomiting
- Weight gain

Other symptoms may depend on the cause of the cysts:[4]

- Symptoms that may occur if the cause of the cysts is polycystic ovarian syndrome (PCOS) may include increased facial hair or body hair, acne, obesity and infertility.
- If the cause is endometriosis, then periods may be heavy, and intercourse painful.

The effect of cysts not related to PCOS on fertility is unclear.[5]

### Cyst rupture [edit]

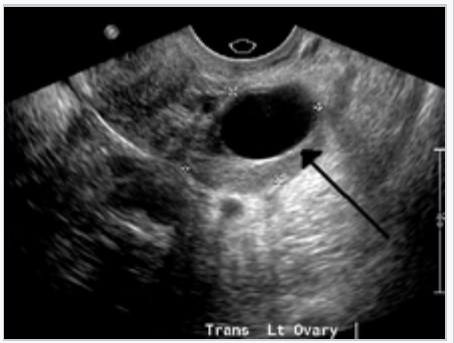
A ruptured ovarian cyst is usually self-limiting, and only requires keeping an eye on the situation and pain medications. The main symptom is abdominal pain, but they can also be asymptomatic. The pain may last from a few days to several weeks.[6] Rupture of large ovarian cysts can cause bleeding inside the abdominal cavity and in some cases shock.

### Ovarian torsion [edit]

Ovarian cysts increase the risk for ovarian torsion, cysts larger than 4 cm are associated with approximately 17% risk. The torsion can cause obstruction of blood flow and lead to infarction.[7]

## Diagnosis [edit]

Ovarian cysts are usually diagnosed by either ultrasound, CT scan or MRI, and correlated with clinical presentation and endocrinologic tests as appropriate.



A 2cm left ovarian cyst as seen on ultrasound

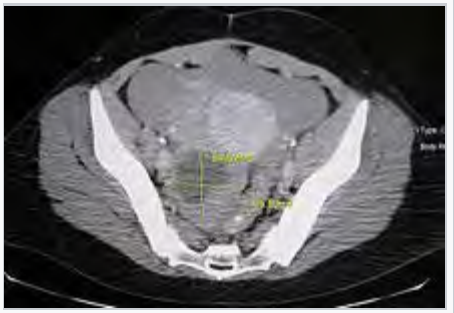
### Ultrasound [edit]

Follow-up imaging in women of reproductive age for incidentally discovered simple cysts on ultrasound is not needed until 5 cm, as these are usually normal ovarian follicles. For simple cysts greater than 5 cm but less than 7 cm in premenopausal females, cysts should be followed yearly. For simple cysts greater than 7 cm, further imaging with MRI or surgical assessment is mandated as, because of their large size, these cysts cannot be reliably assessed by ultrasound alone. The primary

concern for larger cysts is the potential for non-visualization of soft tissue nodularity or thickened septation at their posterior wall due to limited penetrance of the ultrasound beam. For the corpus luteum, a dominant ovulating follicle that typically appears as a cyst with circumferentially thickened walls and crenulated inner margins, follow up is not needed if the cyst is less than 3 cm in diameter. In postmenopausal patients, any simple cyst greater than 1 cm but less than 7 cm needs yearly follow-up, while those greater than 7 cm need MRI or surgical evaluation, similar to reproductive age females.[8]

For incidentally discovered dermoids, diagnosed on ultrasound by their pathognomonic echogenic fat, either surgical removal or yearly follow up is indicated, regardless of patient age. For peritoneal inclusion cysts, which have a crumpled tissue-paper appearance and tend to follow the contour of adjacent organs, follow up is based on clinical history. Hydrosalpinx, or fallopian tube dilation, can be mistaken for an ovarian cyst due to its anechoic appearance. Follow-up for this is also based on clinical presentation.[8]

For multiloculate cysts with thin septation less than 3 mm, surgical evaluation is recommended. The presence of multiloculation suggests a neoplasm, although the thin septation implies that the neoplasm is benign. For any thickened septation, nodularity, or vascular flow on color doppler assessment, surgical removal should be considered due to concern for malignancy.[8]



An Axial CT demonstrating a large hemorrhagic ovarian cyst. The cyst is delineated by the yellow bars with blood seen anteriorly.

## Scoring systems [edit]

There are several systems to assess risk of an ovarian cyst of being an ovarian cancer, including the RMI (risk of malignancy index), LR2 and SR (simple rules). Sensitivities and specificities of these systems are given in tables below:[9]

| Scoring systems | Premenopausal | | Postmenopausal | |
|---|---|---|---|---|
| | Sensitivity | Specificity | Sensitivity | Specificity |
| RMI I | 44% | 95% | 79% | 90% |
| LR2 | 85% | 91% | 94% | 70% |
| SR | 93% | 83% | 93% | 76% |

Ovarian cysts may be classified according to whether they are a variant of the normal menstrual cycle, referred to as a functional or follicular cyst.[4]

Ovarian cysts are considered large when they are over 5 cm and giant when they are over 15 cm. In children ovarian cysts reaching above the level of the umbilicus are considered giant.

## Functional [edit]

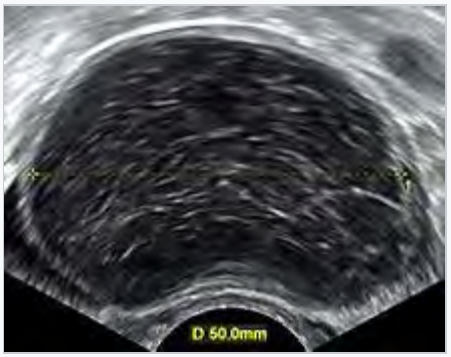
Functional cysts form as a normal part of the menstrual cycle. There are several types of cysts:

- Follicular cyst, the most common type of ovarian cyst. In menstruating women, a follicle containing the ovum (unfertilized egg) will rupture during ovulation. If this does not occur, a follicular cyst of more than 2.5 cm diameter may result.[4]
- Corpus luteum cysts appear after ovulation. The corpus luteum is the remnant of the follicle after the ovum has moved to the fallopian tubes. This normally degrades within 5–9 days. A corpus luteum that is more than 3 cm is defined as cystic.[4]
- Theca lutein cysts occur within the thecal layer of cells surrounding developing oocytes. Under the influence of excessive hCG, thecal cells may proliferate and become cystic. This is usually on both ovaries.[4]

## Non-functional [edit]

Non-functional cysts may include the following:

- An ovary with many cysts, which may be found in normal women, or within the setting of polycystic ovary syndrome.
- Cysts caused by endometriosis, known as chocolate cysts.
- Hemorrhagic ovarian cyst
- Dermoid cyst
- Ovarian serous cystadenoma
- Ovarian mucinous cystadenoma
- Paraovarian cyst
- Cystic adenofibroma
- Borderline tumoral cysts




Transvaginal ultrasonography of a hemorrhagic ovarian cyst, probably originating from a corpus luteum cyst. The coagulating blood gives the content a cobweb-like appearance.

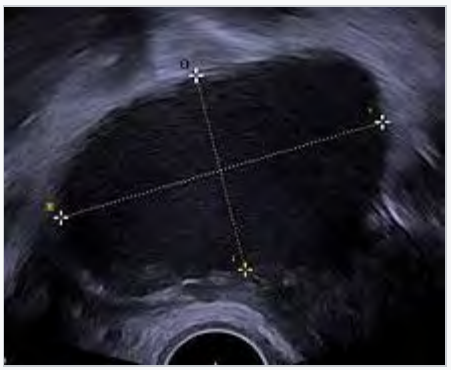
## Associated medical conditions [edit]

In juvenile hypothyroidism multicystic ovaries are present in about 75% of cases, while large ovarian cysts and elevated ovarian tumor marks are one of the symptoms of the Van Wyk and Grumbach syndrome.[10]

The CA-125 marker in children and adolescents can be frequently elevated even in absence of malignancy and conservative management should be considered.

Polycystic ovarian syndrome involves the development of multiple small cysts in both ovaries due to an elevated ratio of leutenizing hormone to follicle stimulating hormone, typically more than 25 cysts in each ovary, or an ovarian volume of greater than 10 mL.[11]

Larger bilateral cysts can develop as a result of fertility treatment due to elevated levels of HCG, as can be seen with the use of clomifene for follicular induction, in extreme cases resulting in a condition known as ovarian hyperstimulation syndrome.[12] Certain malignancies can mimic the effects of clomifene on the ovaries, also due to increased HCG, in particular gestational trophoblastic disease. Ovarian hyperstimulation occurs more often with invasive moles and choriocarcinoma than complete molar pregnancies.[13]



Transvaginal ultrasonography showing a 67 x 40 mm endometrioma, with a somewhat grainy content.

## Risk of cancer [edit]

A widely recognised method of estimating the risk of malignant ovarian cancer based on initial workup is the *risk of malignancy index* (RMI).[14] It is recommended that women with an RMI score over 200 should be referred to a centre with experience in ovarian cancer surgery.[15]

The RMI is calculated as follows:[15]

RMI = ultrasound score x menopausal score x CA-125 level in U/ml.

There are two methods to determine the ultrasound score and menopausal score, with the resultant RMI being called RMI 1 and RMI 2, respectively, depending on what method is used:[15]

| Feature | RMI 1 | RMI 2 |
|---|---|---|
| Ultrasound abnormalities:<br>▪ multilocular cyst<br>▪ solid areas<br>▪ bilateral lesions<br>▪ ascites | 0 = no abnormality<br>1 = one abnormality<br>3 = two or more abnormalities | 0 = none<br>1 = one abnormality<br>4 = two or more abnormalities |

| | | |
|---|---|---|
| ▪ intra-abdominal metastases | | |
| Menopausal score | 1 = premenopausal<br>3 = postmenopausal | 1 = premenopausal<br>4 = postmenopausal |
| CA-125 | Quantity in U/ml | Quantity in U/ml |

An RMI 2 of over 200 has been estimated to have a sensitivity of 74 to 80%, a specificity of 89 to 92% and a positive predictive value of around 80% of ovarian cancer.[15] RMI 2 is regarded as more sensitive than RMI 1.[15]

# Treatment [edit]

Cysts associated with hypothyroidism or other endocrine problems are managed by treating the underlying condition.

About 95% of ovarian cysts are benign, not cancerous.[16]

Functional cysts and hemorrhagic ovarian cysts usually resolve spontaneously.[17] However the bigger an ovarian cyst is, the less likely it is to disappear on its own.[18] Treatment may be required if cysts persist over several months, grow or cause increasing pain.[19]

Cysts that persist beyond two or three menstrual cycles, or occur in post-menopausal women, may indicate more serious disease and should be investigated through ultrasonography and laparoscopy, especially in cases where family members have had ovarian cancer. Such cysts may require surgical biopsy. Additionally, a blood test may be taken before surgery to check for elevated CA-125, a tumour marker, which is often found in increased levels in ovarian cancer, although it can also be elevated by other conditions resulting in a large number of false positives.[20]

## Pain [edit]

Pain associated with ovarian cysts may be treated in several ways:

- Pain relievers such as acetaminophen, nonsteroidal anti-inflammatory drugs,[1] or opioids.
- While hormonal birth control prevents the development of new cysts in those who frequently get them,[1] it is not useful for the treatment of current cysts.[2]

## Surgery [edit]

Although most cases of ovarian cysts involve monitoring, some cases require surgery.[21] This may involve removing the cyst, or one or both ovaries.[22] Technique is typically laparoscopic, unless the cyst is particularly large, or if pre-operative imaging suggests malignancy or complex anatomy.[23] In certain situations, the cyst is entirely removed, while with cysts with low recurrence risk, younger patients, or which are in anatomically eloquent areas of the pelvis, they can be drained.[24][25] Features that may indicate the need for surgery include:[26]

- Persistent complex ovarian cysts
- Persistent cysts that are causing symptoms
- Complex ovarian cysts larger than 5 cm
- Simple ovarian cysts larger 10 centimeters or larger than 5 cm in postmenopausal patients
- Women who are menopausal or perimenopausal

# Frequency [edit]

Most women of reproductive age develop small cysts each month. Large cysts that cause problems occur in about 8% of women before menopause.[1] Ovarian cysts are present in about 16% of women after [1][3]

menopause and if present are more likely to be cancer.

Benign ovarian cysts are common in asymptomatic premenarchal girls and found in approximately 68% of ovaries of girls 2–12 years old and in 84% of ovaries of girls 0–2 years old. Most of them are smaller than 9 mm while about 10-20% are larger macrocysts. While the smaller cysts mostly disappear within 6 months the larger ones appear to be more persistent.[27][28]

## References [edit]


1. ^ *a b c d e f g h i j* "Ovarian cysts". *Office on Women's Health*. November 19, 2014. Retrieved 27 June 2015.
2. ^ *a b* Grimes, DA; Jones, LB; Lopez, LM; Schulz, KF (29 April 2014). "Oral contraceptives for functional ovarian cysts.". *The Cochrane database of systematic reviews*. **4**: CD006134. doi:10.1002/14651858.CD006134.pub5. PMID 24782304.
3. ^ *a b* Mimoun, C; Fritel, X; Fauconnier, A; Deffieux, X; Dumont, A; Huchon, C (December 2013). "[Epidemiology of presumed benign ovarian tumors].". *Journal de gynecologie, obstetrique et biologie de la reproduction*. **42** (8): 722–9. doi:10.1016/j.jgyn.2013.09.027. PMID 24210235.
4. ^ *a b c d e f* Helm, William. "Ovarian Cysts". Retrieved 30 August 2013.
5. ^ Legendre, G; Catala, L; Morinière, C; Lacoeuille, C; Boussion, F; Sentilhes, L; Descamps, P (March 2014). "Relationship between ovarian cysts and infertility: what surgery and when?". *Fertility and Sterility*. **101** (3): 608–14. doi:10.1016/j.fertnstert.2014.01.021. PMID 24559614.
6. ^ Ovarian Cyst Rupture at Medscape. Authors: Nathan Webb and David Chelmow. Updated: Nov 30, 2012
7. ^ "Ovarian Cysts Causes, Symptoms, Diagnosis, and Treatment". *eMedicineHealth.com*.
8. ^ *a b c* Levine, D; Brown, DL; Andreotti, RF; Benacerraf, B; Benson, CB; Brewster, WR; Coleman, B; Depriest, P; Doubilet, PM; Goldstein, SR; Hamper, UM; Hecht, JL; Horrow, M; Hur, HC; Marnach, M; Patel, MD; Platt, LD; Puscheck, E; Smith-Bindman, R (September 2010). "Management of asymptomatic ovarian and other adnexal cysts imaged at US: Society of Radiologists in Ultrasound Consensus Conference Statement.". *Radiology*. **256** (3): 943–54. doi:10.1148/radiol.10100213. PMID 20505067.
9. ^ Kaijser J, Sayasneh A, Van Hoorde K, Ghaem-Maghami S, Bourne T, Timmerman D, Van Calster B (2013). "Presurgical diagnosis of adnexal tumours using mathematical models and scoring systems: a systematic review and meta-analysis". *Human Reproduction Update*. **20** (3): 449–462. doi:10.1093/humupd/dmt059. ISSN 1355-4786. PMID 24327552.
10. ^ Durbin KL, Diaz-Montes T, Loveless MB (2011). "Van wyk and grumbach syndrome: An unusual case and review of the literature". *Journal of pediatric and adolescent gynecology*. **24** (4): e93–6. doi:10.1016/j.jpag.2010.08.003. PMID 21600802.
11. ^ Dewailly, D; Lujan, ME; Carmina, E; Cedars, MI; Laven, J; Norman, RJ; Escobar-Morreale, HF (May 2014). "Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society.". *Human Reproduction Update*. **20** (3): 334–52. doi:10.1093/humupd/dmt061. PMID 24345633.
12. ^ Altinkaya, SO; Talas, BB; Gungor, T; Gulerman, C (October 2009). "Treatment of clomiphene citrate-related ovarian cysts in a prospective randomized study. A single center experience.". *The journal of obstetrics and gynaecology research*. **35** (5): 940–5. doi:10.1111/j.1447-0756.2009.01041.x. PMID 20149045.
13. ^ Suzuki, H; Matsubara, S; Uchida, S; Ohkuchi, A (October 2014). "Ovary hyperstimulation syndrome accompanying molar pregnancy: case report and review of the literature.". *Archives of gynecology and obstetrics*. **290** (4): 803–6. doi:10.1007/s00404-014-3319-0. PMID 24966119.
14. ^ NICE clinical guidelines Issued: April 2011. Guideline CG122. Ovarian cancer: The recognition and initial management of ovarian cancer, Appendix D: Risk of malignancy index (RMI I).
15. ^ *a b c d e* Network, Scottish Intercollegiate Guidelines (2003). "EPITHELIAL OVARIAN CANCER SECTION 3: DIAGNOSIS". *Epithelial ovarian cancer : a national clinical guideline.* Edinburgh: SIGN. ISBN 1899893938.
16. ^ http://www.nhs.uk/Conditions/Ovarian-cyst/Pages/Symptoms.aspx
17. ^ V.T. (14 May 2014). *Understanding Ovarian Cyst*. V.T. pp. 25–. GGKEY:JTX84XQARW9.
18. ^ Edward I. Bluth (2000). *Ultrasound: A Practical Approach to Clinical Problems*. Thieme. p. 190. ISBN 978-0-86577-861-0.
19. ^ Susan A. Orshan (2008). *Maternity, Newborn, and Women's Health Nursing: Comprehensive Care Across the Lifespan*. Lippincott Williams & Wilkins. p. 161. ISBN 978-0-7817-4254-2.
20. ^ MedlinePlus Encyclopedia *CA-125*
21. ^ Tamparo, Carol; Lewis, Marcia (2011). *Diseases of the Human Body*. Philadelphia, PA: Library of Congress. p. 475. ISBN 978-0-8036-2505-1.

22. ^ "HealthHints: Gynecologic Health (January/February, 2003)". *Texas AgriLife Extension Service: HealthHints*.
23. ^ Surgit, O; Inegol Gumus, I (2014). "Single-port Laparoscopic Total Hysterectomy and Bilateral Salpingo-oopherectomy Combined with Burch Colposuspension.". *Acta chirurgica Belgica*. **114** (4): 0. PMID 26021429.
24. ^ Cho, MJ; Kim, DY; Kim, SC (October 2015). "Ovarian Cyst Aspiration in the Neonate: Minimally Invasive Surgery.". *Journal of pediatric and adolescent gynecology*. **28** (5): 348–53. doi:10.1016/j.jpag.2014.10.003. PMID 26148782.
25. ^ Nohuz, E (11 December 2015). "[How I do...the aspiration of an adnexal cyst without iterative needle punctures neither irrigation-aspiration device during a laparoscopy].". *Gynecologie, obstetrique & fertilite*. **44**: 63–6. doi:10.1016/j.gyobfe.2015.11.001. PMID 26701109.
26. ^ Ovarian cysts from MedlinePlus. Update Date: 2/26/2012. Updated by: Linda J. Vorvick and Susan Storck. Also reviewed by David Zieve
27. ^ Cohen HL, Eisenberg P, Mandel F, Haller JO (1992). "Ovarian cysts are common in premenarchal girls: A sonographic study of 101 children 2-12 years old". *AJR. American journal of roentgenology*. **159** (1): 89–91. doi:10.2214/ajr.159.1.1609728. PMID 1609728.
28. ^ Qublan HS, Abdel-hadi J (2000). "Simple ovarian cysts: Frequency and outcome in girls aged 2-9 years". *Clinical and experimental obstetrics & gynecology*. **27** (1): 51–3. PMID 10758801.


# External links [edit]

Categories: Noninflammatory disorders of female genital tract | Cysts




# Polycystic ovary syndrome

From Wikipedia, the free encyclopedia

(Redirected from Polycystic ovarian syndrome)

*"PCOS" redirects here. For the Colombian political party, see Comunitarian Party Option Seven.*

**Polycystic ovary syndrome** (**PCOS**) is a set of symptoms due to elevated androgens (male hormones) in women.[3][4] Signs and symptoms of PCOS include irregular or no menstrual periods, heavy periods, excess body and facial hair, acne, pelvic pain, difficulty getting pregnant, and patches of thick, darker, velvety skin.[5] Associated conditions include type 2 diabetes, obesity, obstructive sleep apnea, heart disease, mood disorders, and endometrial cancer.[3]

PCOS is due to a combination of genetic and environmental factors.[6][7][8] Risk factors include obesity, not enough physical exercise, and a family history of someone with the condition.[9] Diagnosis is based on two of the following three findings: no ovulation, high androgen levels, and ovarian cysts.[5] Cysts may be detectable by ultrasound. Other conditions that produce similar symptoms include adrenal hyperplasia, hypothyroidism, and hyperprolactinemia.[10]

PCOS has no cure.[11] Treatment may involve lifestyle changes such as weight loss and exercise.[12][13] Birth control pills may help with improving the regularity of periods, excess hair growth, and acne. Metformin and anti-androgens may also help. Other typical acne treatments and hair removal techniques may be used.[14] Efforts to improve fertility include weight loss, clomiphene, or metformin. In vitro fertilization is used by some in whom other measures are not effective.[15]

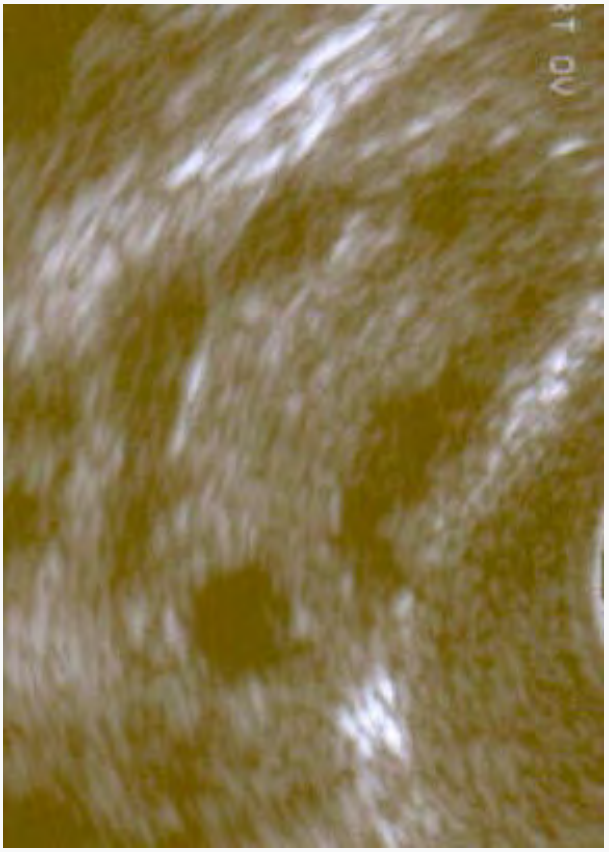
PCOS is the most common endocrine disorder among women between the ages of 18 and 44.[16] It affects approximately 2% to 20% of this age group depending on how it is defined.[9][17] It is one of the leading causes of poor fertility.[3] The earliest known description of what is now recognized as PCOS dates from 1721 in Italy.[18]

**Contents**



**Polycystic ovary syndrome**

**Synonyms** hyperandrogenic anovulation (HA),[1] Stein–Leventhal syndrome[2]



A polycystic ovary shown on an ultrasound image.

**Classification and external resources**

| | |
|---|---|
| **Specialty** | Gynecology |
| **ICD-10** | E28.2 |
| **ICD-9-CM** | 256.4 |
| **OMIM** | 184700 |
| **MedlinePlus** | 000369 |

| | |
|---|---|
| **eMedicine** | med/2173 ped/2155 radio/565 |
| **Patient UK** | Polycystic ovary syndrome |
| **MeSH** | D011085 |

[edit on Wikidata]

## Signs and symptoms [edit]

*Further information: Infertility in polycystic ovary syndrome*

Common signs and symptoms of PCOS include the following:

- Menstrual disorders: PCOS mostly produces oligomenorrhea (fewer than nine menstrual periods in a year) or amenorrhea (no menstrual periods for three or more consecutive months), but other types of menstrual disorders may also occur.[16][19]
- Infertility:[19] This generally results directly from chronic anovulation (lack of ovulation).[16]
- High levels of masculinizing hormones: Known as hyperandrogenism, the most common signs are acne and hirsutism (male pattern of hair growth, such as on the chin or chest), but it may produce hypermenorrhea (heavy and prolonged menstrual periods), androgenic alopecia (increased hair thinning or diffuse hair loss), or other symptoms.[16][20] Approximately three-quarters of women with PCOS (by the diagnostic criteria of NIH/NICHD 1990) have evidence of hyperandrogenemia.[21]
- Metabolic syndrome:[19] This appears as a tendency towards central obesity and other symptoms associated with insulin resistance.[16] Serum insulin, insulin resistance, and homocysteine levels are higher in women with PCOS.[22]

Asians affected by PCOS are less likely to develop hirsutism than those of other ethnic backgrounds.[23]

## Cause [edit]

PCOS is a heterogeneous disorder of uncertain cause.[19][24][25] There is some evidence that it is a genetic disease. Such evidence includes the familial clustering of cases, greater concordance in monozygotic compared with dizygotic twins and heritability of endocrine and metabolic features of PCOS.[8][24][25]

The genetic component appears to be inherited in an autosomal dominant fashion with high genetic penetrance but variable expressivity in females; this means that each child has a 50% chance of inheriting the predisposing genetic variant(s) from a parent, and, if a daughter receives the variant(s), the daughter will have the disease to some extent.[25][26][27][28] The genetic variant(s) can be inherited from either the father or the mother, and can be passed along to both sons (who may be asymptomatic carriers or may have symptoms such as early baldness and/or excessive hair) and daughters, who will show signs of PCOS.[26][28] The phenotype appears to manifest itself at least partially via heightened androgen levels secreted by ovarian follicle theca cells from women with the allele.[27] The exact gene affected has not yet been identified.[8][25][29] In rare instances, single-gene mutations can give rise to the phenotype of the syndrome.[30] Current understanding of the pathogenesis of the syndrome suggests, however, that it is a

complex multigenic disorder.[31]

The severity of PCOS symptoms appears to be largely determined by factors such as obesity.[8][16]

PCOS has some aspects of a metabolic disorder, since its symptoms are partly reversible. Even though considered as a gynecological problem, PCOS consists of 28 clinical symptoms.

Even though the name suggests that the ovaries are central to disease pathology, cysts are a symptom instead of the cause of the disease. Some symptoms of PCOS will persist even if both ovaries are removed; the disease can appear even if cysts are absent. Since its first description by Stein and Leventhal in 1935, the criteria of diagnosis, symptoms, and causative factors are subject to debate. Gynecologists often see it as a gynecological problem, with the ovaries being the primary organ affected. However, recent insights show a multisystem disorder, with the primary problem lying in hormonal regulation in the hypothalamus, with the involvement of many organs. The name PCOD is used when there is ultrasonographic evidence. The term PCOS is used since there is a wide spectrum of symptoms possible, and cysts in the ovaries are seen only in 15% of people.[32]

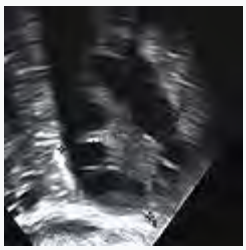
PCOS may be related to or worsened by exposures during the prenatal period, epigenetic factors, environmental impacts (especially industrial endocrine disruptors[33] such as bisphenol A and certain drugs) and the increasing rates of obesity.[33][34][35][36][37][38][39]

## Diagnosis [edit]

Not everyone with PCOS has polycystic ovaries (PCO), nor does everyone with ovarian cysts have PCOS; although a pelvic ultrasound is a major diagnostic tool, it is not the only one.[40] The diagnosis is straightforward using the Rotterdam criteria, even when the syndrome is associated with a wide range of symptoms.

Polycystic Ovary as seen on Sonography

Transvaginal ultrasound scan of polycystic ovary



Polycystic Ovary as seen on Sonography

### Definition [edit]

Two definitions are commonly used:

#### NIH [edit]

In 1990 a consensus workshop sponsored by the NIH/NICHD suggested that a person has PCOS if they have all of the following:[41]

1. oligoovulation
2. signs of androgen excess (clinical or biochemical)
3. exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism

#### Rotterdam [edit]

In 2003 a consensus workshop sponsored by ESHRE/ASRM in Rotterdam indicated PCOS to be present if

any 2 out of 3 criteria are met, in the absence of other entities that might cause these findings[16][42][43]

1. oligoovulation and/or anovulation
2. excess androgen activity
3. polycystic ovaries (by gynecologic ultrasound)

The Rotterdam definition is wider, including many more women, the most notable ones being women without androgen excess. Critics say that findings obtained from the study of women with androgen excess cannot necessarily be extrapolated to women without androgen excess.[44][45]

**Androgen Excess PCOS Society**

In 2006, the Androgen Excess PCOS Society suggested a tightening of the diagnostic criteria to all of the following:[16]

1. excess androgen activity
2. oligoovulation/anovulation and/or polycystic ovaries
3. exclusion of other entities that would cause excess androgen activity

## Standard diagnostic assessments [edit]

- History-taking, specifically for menstrual pattern, obesity, hirsutism and acne. A clinical prediction rule found that these four questions can diagnose PCOS with a sensitivity of 77.1% (95% confidence interval [CI] 62.7%–88.0%) and a specificity of 93.8% (95% CI 82.8%–98.7%).[46]
- Gynecologic ultrasonography, specifically looking for small ovarian follicles. These are believed to be the result of disturbed ovarian function with failed ovulation, reflected by the infrequent or absent menstruation that is typical of the condition. In a normal menstrual cycle, one egg is released from a dominant follicle – in essence, a cyst that bursts to release the egg. After ovulation, the follicle remnant is transformed into a progesterone-producing corpus luteum, which shrinks and disappears after approximately 12–14 days. In PCOS, there is a so-called "follicular arrest"; i.e., several follicles develop to a size of 5–7 mm, but not further. No single follicle reaches the preovulatory size (16 mm or more). According to the Rotterdam criteria, which are widely used for diagnosis,[12] 12 or more small follicles should be seen in an ovary on ultrasound examination.[41] More recent research suggests that there should be at least 25 follicles in an ovary to designate it as having polycystic ovarian morphology (PCOM) in women aged 18–35 years.[47] The follicles may be oriented in the periphery, giving the appearance of a 'string of pearls'.[48] If a high resolution transvaginal ultrasonography machine is not available, an ovarian volume of at least 10 ml is regarded as an acceptable definition of having polycystic ovarian morphology instead of follicle count.[47]
- Laparoscopic examination may reveal a thickened, smooth, pearl-white outer surface of the ovary. (This would usually be an incidental finding if laparoscopy were performed for some other reason, as it would not be routine to examine the ovaries in this way to confirm a diagnosis of PCOS.)[*citation needed*]
- Serum (blood) levels of androgens (hormones associated with male development), including androstenedione and testosterone may be elevated.[16] Dehydroepiandrosterone sulfate levels above 700-800 µg/dL are highly suggestive of adrenal dysfunction because DHEA-S is made exclusively by the adrenal glands.[49][50] The free testosterone level is thought to be the best measure,[50][51] with ~60% of PCOS patients demonstrating supranormal levels.[21] The Free androgen index (FAI) of the ratio of testosterone to sex hormone-binding globulin (SHBG) is high[16][50] and is meant to be a predictor of free testosterone, but is a poor parameter for this and is no better than testosterone alone as a marker for PCOS,[52] possibly because FAI is correlated with the degree of obesity.[53]

Some other blood tests are suggestive but not diagnostic. The ratio of LH (Luteinizing hormone) to FSH (Follicle-stimulating hormone), when measured in international units, is elevated in women with PCOS. Common cut-offs to designate abnormally high LH/FSH ratios are 2:1[54] or 3:1[50] as tested on Day 3 of the menstrual cycle. The pattern is not very sensitive; a ratio of 2:1 or higher was present in less than 50% of women with PCOS in one study.[54] There are often low levels of sex hormone-binding globulin,[50] in particular among obese or overweight women.[*citation needed*]

Anti-Müllerian hormone (AMH) is increased in PCOS, and may become part of its diagnostic criteria.[55][56][57]

### Associated conditions [edit]

- Fasting biochemical screen and lipid profile[50]
- 2-Hour oral glucose tolerance test (GTT) in women with risk factors (obesity, family history, history of gestational diabetes)[16] may indicate impaired glucose tolerance (insulin resistance) in 15–33% of women with PCOS.[50] Frank diabetes can be seen in 65–68% of women with this condition.[*citation needed*] Insulin resistance can be observed in both normal weight and overweight people, although it is more common in the latter (and in those matching the stricter NIH criteria for diagnosis); 50–80% of people with PCOS may have insulin resistance at some level.[16]
- Fasting insulin level or GTT with insulin levels (also called IGTT). Elevated insulin levels have been helpful to predict response to medication and may indicate women needing higher dosages of metformin or the use of a second medication to significantly lower insulin levels. Elevated blood sugar and insulin values do not predict who responds to an insulin-lowering medication, low-glycemic diet, and exercise. Many women with normal levels may benefit from combination therapy. A hypoglycemic response in which the two-hour insulin level is higher and the blood sugar lower than fasting is consistent with insulin resistance. A mathematical derivation known as the HOMAI, calculated from the fasting values in glucose and insulin concentrations, allows a direct and moderately accurate measure of insulin sensitivity (glucose-level x insulin-level/22.5).[*citation needed*]
- Glucose tolerance testing (GTT) instead of fasting glucose can increase diagnosis of impaired glucose tolerance and frank diabetes among people with PCOS according to a prospective controlled trial.[58] While fasting glucose levels may remain within normal limits, oral glucose tests revealed that up to 38% of asymptomatic women with PCOS (versus 8.5% in the general population) actually had impaired glucose tolerance, 7.5% of those with frank diabetes according to ADA guidelines.[58]

### Differential diagnosis [edit]

Other causes of irregular or absent menstruation and hirsutism, such as hypothyroidism, congenital adrenal hyperplasia (21-hydroxylase deficiency), Cushing's syndrome, hyperprolactinemia, androgen secreting neoplasms, and other pituitary or adrenal disorders, should be investigated.[16][43][50]

## Pathogenesis [edit]

Polycystic ovaries develop when the ovaries are stimulated to produce excessive amounts of androgenic hormones, in particular testosterone, by either one or a combination of the following (almost certainly combined with genetic susceptibility[27]):

- the release of excessive luteinizing hormone (LH) by the anterior pituitary gland[*citation needed*]
- through high levels of insulin in the blood (hyperinsulinaemia) in women whose ovaries are sensitive to this stimulus[19]

The syndrome acquired its most widely used name due to the common sign on ultrasound examination of multiple (poly) ovarian cysts. These "cysts" are actually immature follicles not cysts. The follicles have developed from primordial follicles, but the development has stopped ("arrested") at an early antral stage due to the disturbed ovarian function. The follicles may be oriented along the ovarian periphery, appearing as a 'string of pearls' on ultrasound examination.[*citation needed*]

Women with PCOS experience an increased frequency of hypothalamic GnRH pulses, which in turn results in an increase in the LH/FSH ratio.[59]

A majority of women with PCOS have insulin resistance and/or are obese. Their elevated insulin levels contribute to or cause the abnormalities seen in the hypothalamic-pituitary-ovarian axis that lead to PCOS. Hyperinsulinemia increases GnRH pulse frequency, LH over FSH dominance, increased ovarian androgen production,[19] decreased follicular maturation, and decreased SHBG binding. Furthermore, excessive

insulin, acting through its cognate receptor in the presence of component cAMP signalling, upregulates 17α-hydroxylase activity via PI3K, 17α-hydroxylase activity being responsible for synthesising androgen precursors.[60] The combined effects of hyperinsulinemia contribute to an increased risk of PCOS.[61] Insulin resistance is a common finding among women with a normal weight as well as overweight women.[16][22][12]

Adipose tissue possesses aromatase, an enzyme that converts androstenedione to estrone and testosterone to estradiol. The excess of adipose tissue in obese women creates the paradox of having both excess androgens (which are responsible for hirsutism and virilization) and estrogens (which inhibits FSH via negative feedback).[62]

PCOS may be associated with chronic inflammation,[19][63] with several investigators correlating inflammatory mediators with anovulation and other PCOS symptoms.[64][65] Similarly, there seems to be a relation between PCOS and increased level of oxidative stress.[66]

It has previously been suggested that the excessive androgen production in PCOS could be caused by a decreased serum level of IGFBP-1, in turn increasing the level of free IGF-I, which stimulates ovarian androgen production, but recent data concludes this mechanism to be unlikely.[67]

PCOS has also been associated with a specific FMR1 sub-genotype. The research suggests that women with *heterozygous-normal/low* FMR1 have polycystic-like symptoms of excessive follicle-activity and hyperactive ovarian function.[68]

Transgender men may experience a higher than expected rate of PCOS due to increased testosterone, if they choose to take hormone therapy as part of their gender presentation.[69][70]

## Management [edit]

The primary treatments for PCOS include: lifestyle changes, medications and surgery.[71][*needs update*]

Goals of treatment may be considered under four categories:

- Lowering of insulin resistance levels
- Restoration of fertility
- Treatment of hirsutism or acne
- Restoration of regular menstruation, and prevention of endometrial hyperplasia and endometrial cancer

In each of these areas, there is considerable debate as to the optimal treatment. One of the major reasons for this is the lack of large-scale clinical trials comparing different treatments. Smaller trials tend to be less reliable and hence may produce conflicting results.

General interventions that help to reduce weight or insulin resistance can be beneficial for all these aims, because they address what is believed to be the underlying cause.

As PCOS appears to cause significant emotional distress, appropriate support may be useful.[72]

### Diet [edit]

Where PCOS is associated with overweight or obesity, successful weight loss is the most effective method of restoring normal ovulation/menstruation, but many women find it very difficult to achieve and sustain significant weight loss. A scientific review in 2013 found similar decreases in weight and body composition and improvements in pregnancy rate, menstrual regularity, ovulation, hyperandrogenism, insulin resistance, lipids, and quality of life to occur with weight loss independent of diet composition.[73] Still, a low GI diet, in which a significant part of total carbohydrates are obtained from fruit, vegetables, and whole-grain sources, has resulted in greater menstrual regularity than a macronutrient-matched healthy diet.[73]

Vitamin D deficiency may play some role in the development of the metabolic syndrome, so treatment of any such deficiency is indicated.[74][75] However, a systematic review of 2015 found no evidence that vitamin D supplementation reduced or mitigated metabolic and hormonal dysregulations in PCOS.[76] As of

2012, interventions using dietary supplements to correct metabolic deficiencies in people with PCOS had been tested in small, uncontrolled and nonrandomized clinical trials; the resulting data is insufficient to recommend their use.[77]

## Medications [edit]

Medications for PCOS include oral contraceptives and metformin. The oral contraceptives increase sex hormone binding globulin production, which increases binding of free testosterone. This reduces the symptoms of hirsutism caused by high testosterone and regulates return to normal menstrual periods. Metformin is a drug commonly used in type 2 diabetes to reduce insulin resistance, and is used off label (in the UK, US, AU and EU) to treat insulin resistance seen in PCOS. In many cases, metformin also supports ovarian function and return to normal ovulation.[19][74][78] Spironolactone can be used for its antiandrogenic effects, and the topical cream eflornithine can be used to reduce facial hair. A newer insulin resistance drug class, the thiazolidinediones (glitazones), have shown equivalent efficacy to metformin, but metformin has a more favorable side effect profile.[79][80] The United Kingdom's National Institute for Health and Clinical Excellence recommended in 2004 that women with PCOS and a body mass index above 25 be given metformin when other therapy has failed to produce results.[81][82] Metformin may not be effective in every type of PCOS, and therefore there is some disagreement about whether it should be used as a general first line therapy.[83] The use of statins in the management of underlying metabolic syndrome remains unclear.[84]

It can be difficult to become pregnant with PCOS because it causes irregular ovulation. Medications to induce fertility when trying to conceive include the ovulation inducer clomiphene or pulsatile leuprolide. Metformin improves the efficacy of fertility treatment when used in combination with clomiphene.[85] Metformin is thought to be safe to use during pregnancy (pregnancy category B in the US).[86] A review in 2014 concluded that the use of metformin does not increase the risk of major birth defects in women treated with metformin during the first trimester.[87]

## Infertility [edit]

*Main article: Infertility in polycystic ovary syndrome*

Not all women with PCOS have difficulty becoming pregnant. For those that do, anovulation or infrequent ovulation is a common cause. Other factors include changed levels of gonadotropins, hyperandrogenemia and hyperinsulinemia.[88] Like women without PCOS, women with PCOS that are ovulating may be infertile due to other causes, such as tubal blockages due to a history of sexually transmitted diseases.

For overweight, anovulatory women with PCOS, weight loss and diet adjustments, especially to reduce the intake of simple carbohydrates, are associated with resumption of natural ovulation.

For those women that after weight loss still are anovulatory or for anovulatory lean women, then the ovulation-inducing medications clomiphene citrate[74] and FSH are the principal treatments used to promote ovulation.[19] Previously, the anti-diabetes medication metformin was recommended treatment for anovulation,[19] but it appears less effective than clomiphene.[89]

For women not responsive to clomiphene and diet and lifestyle modification, there are options available including assisted reproductive technology procedures such as controlled ovarian hyperstimulation with follicle-stimulating hormone (FSH) injections followed by in vitro fertilisation (IVF).

Though surgery is not commonly performed, the polycystic ovaries can be treated with a laparoscopic procedure called "ovarian drilling" (puncture of 4–10 small follicles with electrocautery, laser, or biopsy needles), which often results in either resumption of spontaneous ovulations[74] or ovulations after adjuvant treatment with clomiphene or FSH.[*citation needed*] (Ovarian wedge resection is no longer used as much due to complications such as adhesions and the presence of frequently effective medications.) There are, however, concerns about the long-term effects of ovarian drilling on ovarian function.[74]

## Hirsutism and acne [edit]

*For more details on this topic, see Hirsutism.*

When appropriate (e.g., in women of child-bearing age who require contraception), a standard contraceptive pill is frequently effective in reducing hirsutism.[19][74] Progestogens such as norgestrel and levonorgestrel should be avoided due to their androgenic effects.[74]

Other drugs with anti-androgen effects include flutamide,[90] and spironolactone,[19][74] which can give some improvement in hirsutism. Metformin can reduce hirsutism, perhaps by reducing insulin resistance, and is often used if there are other features such as insulin resistance, diabetes, or obesity that should also benefit from metformin. Eflornithine (Vaniqa) is a drug that is applied to the skin in cream form, and acts directly on the hair follicles to inhibit hair growth. It is usually applied to the face.[74] 5-alpha reductase inhibitors (such as finasteride and dutasteride) may also be used;[91] they work by blocking the conversion of testosterone to dihydrotestosterone (the latter of which responsible for most hair growth alterations and androgenic acne).

Although these agents have shown significant efficacy in clinical trials (for oral contraceptives, in 60–100% of individuals[74]), the reduction in hair growth may not be enough to eliminate the social embarrassment of hirsutism, or the inconvenience of plucking or shaving. Individuals vary in their response to different therapies. It is usually worth trying other drug treatments if one does not work, but drug treatments do not work well for all individuals.

### Menstrual irregularity [edit]

If fertility is not the primary aim, then menstruation can usually be regulated with a contraceptive pill.[19][74] The purpose of regulating menstruation, in essence, is for the woman's convenience, and perhaps her sense of well-being; there is no medical requirement for regular periods, as long as they occur sufficiently often.

If a regular menstrual cycle is not desired, then therapy for an irregular cycle is not necessarily required. Most experts say that, if a menstrual bleed occurs at least every three months, then the endometrium (womb lining) is being shed sufficiently often to prevent an increased risk of endometrial abnormalities or cancer.[92] If menstruation occurs less often or not at all, some form of progestogen replacement is recommended.[91] An alternative is oral progestogen taken at intervals (e.g., every three months) to induce a predictable menstrual bleeding.[19]

### Alternative medicine [edit]

There is not enough evidence to conclude any beneficial effect from D-chiro-inositol.[93] Based on a systematic review, myo-inositol supplementation, however, appears to be effective in improving several of the hormonal disturbances of PCOS.[94] There is also not evidence to support the use of acupuncture for treatment of ovulation disorders in women with PCOS.[95]

## Prognosis [edit]

A diagnosis of PCOS suggests an increased risk of the following:

- Endometrial hyperplasia and endometrial cancer (cancer of the uterine lining) are possible, due to overaccumulation of uterine lining, and also lack of progesterone resulting in prolonged stimulation of uterine cells by estrogen.[19][41][96] It is not clear whether this risk is directly due to the syndrome or from the associated obesity, hyperinsulinemia, and hyperandrogenism.[97][98][99]
- Insulin resistance/Type II diabetes.[19] A review published in 2010 concluded that women with PCOS have an elevated prevalence of insulin resistance and type II diabetes, even when controlling for body mass index (BMI).[41][100] PCOS also makes a woman, particularly if obese, prone to gestational diabetes.[19]
- High blood pressure, in particular if obese or during pregnancy[19]

- Depression and anxiety[16][101]
- Dyslipidemia[19] – disorders of lipid metabolism — cholesterol and triglycerides. Women with PCOS show a decreased removal of atherosclerosis-inducing remnants, seemingly independent of insulin resistance/Type II diabetes.[102]
- Cardiovascular disease,[19][41] with a meta-analysis estimating a 2-fold risk of arterial disease for women with PCOS relative to women without PCOS, independent of BMI.[103]
- Strokes[41]
- Weight gain[19]
- Miscarriage[104][105]
- Sleep apnea, particularly if obesity is present[19]
- Non-alcoholic fatty liver disease, again particularly if obesity is present[19]
- Acanthosis nigricans (patches of darkened skin under the arms, in the groin area, on the back of the neck)[41]
- Autoimmune thyroiditis[106]

Early diagnosis and treatment may reduce the risk of some of these, such as type 2 diabetes and heart disease.[19]

The risk of ovarian cancer and breast cancer is not significantly increased overall.[96]

## Epidemiology [edit]

The prevalence of PCOS depends on the choice of diagnostic criteria. The World Health Organization estimates that it affects 116 million women worldwide as of 2010 (3.4% of women).[107] One community-based prevalence study using the Rotterdam criteria found that about 18% of women had PCOS, and that 70% of them were previously undiagnosed.[16]

One study in the United Kingdom concluded that the risk of PCOS development was higher in lesbian women than in heterosexuals.[108] However, two subsequent studies of women with PCOS have not replicated this finding.[109][110] Ultrasonographic findings of polycystic ovaries are found in 8-25% of normal women.[111][112][113][114] 14% women on oral contraceptives are found to have polycystic ovaries.[112] Ovarian cysts are also a common side effect of intrauterine devices (IUDs).[115]

## History [edit]

The condition was first described in 1935 by American gynecologists Irving F. Stein, Sr. and Michael L. Leventhal, from whom its original name of *Stein–Leventhal syndrome* is taken.[40][41]

The earliest published description of a person with what is now recognized as PCOS was in 1721 in Italy.[18] Cyst-related changes to the ovaries were described in 1844.[18]

### Names [edit]

Other names for this syndrome include polycystic ovary disease, functional ovarian hyperandrogenism, ovarian hyperthecosis, sclerocystic ovary syndrome, and Stein–Leventhal syndrome. The eponymous last option is the original name; it is now used, if at all, only for the subset of women with all the symptoms of amenorrhea with infertility, hirsutism, and enlarged polycystic ovaries.[40]

Most common names for this disease derive from a typical finding on medical images, called a polycystic ovary.[19] A polycystic ovary has an abnormally large number of developing eggs visible near its surface,[40] looking like many small cysts[116] or a string of pearls.

## See also [edit]

- Androgen-dependent syndromes
- *PCOS Challenge* (reality television series)

## References [edit]


1. ^ Kollmann M, Martins WP, Raine-Fenning N (2014). "Terms and thresholds for the ultrasound evaluation of the ovaries in women with hyperandrogenic anovulation". *Hum. Reprod. Update*. **20** (3): 463–4. doi:10.1093/humupd/dmu005. PMID 24516084.
2. ^ "USMLE-Rx". MedIQ Learning, LLC. 2014. "Stein-Leventhal syndrome, also known as polycystic ovary syndrome (PCOS), is a disorder characterized by hirsutism, obesity, and amenorrhea because of luteinizing hormone-resistant cystic ovaries."
3. ^ *a b c d* "Polycystic Ovary Syndrome (PCOS): Condition Information". *http://www.nichd.nih.gov/*. 2013-05-23. Retrieved 13 March 2015. External link in `|website=` (help)
4. ^ "Polycystic ovary syndrome (PCOS) fact sheet". *Womens Health*. December 23, 2014. Retrieved 11 August 2016.
5. ^ "What are the symptoms of PCOS?" (05/23/2013). *http://www.nichd.nih.gov*. Retrieved 13 March 2015. External link in `|website=` (help)
6. ^ De Leo V, Musacchio MC, Cappelli V, Massaro MG, Morgante G, Petraglia F (2016). "Genetic, hormonal and metabolic aspects of PCOS: an update". *Reproductive Biology and Endocrinology : RB&E* (Review). **14** (1): 38. doi:10.1186/s12958-016-0173-x. PMC 4947298. PMID 27423183.
7. ^ Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS (2015). "Scientific Statement on the Diagnostic Criteria, Epidemiology, Pathophysiology, and Molecular Genetics of Polycystic Ovary Syndrome". *Endocrine Reviews* (Review). **36** (5): 487–525. doi:10.1210/er.2015-1018. PMC 4591526. PMID 26426951.
8. ^ *a b c d* Diamanti-Kandarakis E, Kandarakis H, Legro RS (2006). "The role of genes and environment in the etiology of PCOS". *Endocrine*. **30** (1): 19–26. doi:10.1385/ENDO:30:1:19. PMID 17185788.
9. ^ *a b* "How many people are affected or at risk for PCOS?". *http://www.nichd.nih.gov*. 2013-05-23. Retrieved 13 March 2015. External link in `|website=` (help)
10. ^ "How do health care providers diagnose PCOS?". *http://www.nichd.nih.gov/*. 2013-05-23. Retrieved 13 March 2015. External link in `|website=` (help)
11. ^ "http://www.nichd.nih.gov". *Is there a cure for PCOS?*. 2013-05-23. Retrieved 13 March 2015. External link in `|title=` (help)
12. ^ *a b c* Mortada R, Williams T (2015). "Metabolic Syndrome: Polycystic Ovary Syndrome". *FP Essentials* (Review). **435**: 30–42. PMID 26280343.
13. ^ Giallauria F, Palomba S, Vigorito C, Tafuri MG, Colao A, Lombardi G, Orio F (2009). "Androgens in polycystic ovary syndrome: the role of exercise and diet". *Seminars in Reproductive Medicine* (Review). **27** (4): 306–15. doi:10.1055/s-0029-1225258. PMID 19530064.
14. ^ "Treatments to Relieve Symptoms of PCOS". *http://www.nichd.nih.gov/*. 2014-07-14. Retrieved 13 March 2015. External link in `|website=` (help)
15. ^ "Treatments for Infertility Resulting from PCOS". *http://www.nichd.nih.gov/*. 2014-07-14. Retrieved 13 March 2015. External link in `|website=` (help)
16. ^ *a b c d e f g h i j k l m n o p* Teede H, Deeks A, Moran L (2010). "Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan". *BMC Med.* **8** (1): 41. doi:10.1186/1741-7015-8-41. PMC 2909929. PMID 20591140.
17. ^ editor, Lubna Pal, (2013). "Diagnostic Criteria and Epidemiology of PCOS". *Polycystic Ovary Syndrome Current and Emerging Concepts.* Dordrecht: Springer. p. 7. ISBN 9781461483946.
18. ^ *a b c* Kovacs, Gabor T.; Norman, Robert (2007-02-22). *Polycystic Ovary Syndrome*. Cambridge University Press. p. 4. ISBN 9781139462037. Retrieved 29 March 2013.
19. ^ *a b c d e f g h i j k l m n o p q r s t u v w x y* Mayo Clinic Staff (4 April 2011). "Polycystic Ovary Syndrome – All". *MayoClinic.com*. Mayo Clinic. Retrieved 15 November 2011.
20. ^ Christine Cortet-Rudelli; Didier Dewailly (Sep 21, 2006). "Diagnosis of Hyperandrogenism in Female Adolescents". *Hyperandrogenism in Adolescent Girls*. Armenian Health Network, Health.am. Retrieved 2006-11-21.
21. ^ *a b* Huang A, Brennan K, Azziz R (2010). "Prevalence of hyperandrogenemia in the polycystic ovary syndrome diagnosed by the National Institutes of Health 1990 criteria". *Fertil. Steril.* **93** (6): 1938–41.

doi:10.1016/j.fertnstert.2008.12.138. PMC 2859983. PMID 19249030.

22. ^ a b Nafiye Y, Sevtap K, Muammer D, Emre O, Senol K, Leyla M (2010). "The effect of serum and intrafollicular insulin resistance parameters and homocysteine levels of nonobese, nonhyperandrogenemic polycystic ovary syndrome patients on in vitro fertilization outcome". *Fertil. Steril*. **93** (6): 1864–9. doi:10.1016/j.fertnstert.2008.12.024. PMID 19171332.
23. ^ Carmina E, Koyama T, Chang L, Stanczyk FZ, Lobo RA (1992). "Does ethnicity influence the prevalence of adrenal hyperandrogenism and insulin resistance in polycystic ovary syndrome?". *Am. J. Obstet. Gynecol*. **167** (6): 1807–12. doi:10.1016/0002-9378(92)91779-a. PMID 1471702.
24. ^ a b Page 836 (Section: *Polycystic ovary syndrome*) in: Fauser BC, Diedrich K, Bouchard P, Domínguez F, Matzuk M, Franks S, Hamamah S, Simón C, Devroey P, Ezcurra D, Howles CM (2011). "Contemporary genetic technologies and female reproduction". *Hum. Reprod. Update*. **17** (6): 829–47. doi:10.1093/humupd/dmr033. PMC 3191938. PMID 21896560.
25. ^ a b c d Legro RS, Strauss JF (2002). "Molecular progress in infertility: polycystic ovary syndrome". *Fertil. Steril*. **78** (3): 569–76. doi:10.1016/S0015-0282(02)03275-2. PMID 12215335.
26. ^ a b Crosignani PG, Nicolosi AE (2001). "Polycystic ovarian disease: heritability and heterogeneity". *Hum. Reprod. Update*. **7** (1): 3–7. doi:10.1093/humupd/7.1.3. PMID 11212071.
27. ^ a b c Strauss JF (2003). "Some new thoughts on the pathophysiology and genetics of polycystic ovary syndrome". *Ann. N. Y. Acad. Sci*. **997**: 42–8. Bibcode:2003NYASA.997...42S. doi:10.1196/annals.1290.005. PMID 14644808.
28. ^ a b Ada Hamosh (12 September 2011). "POLYCYSTIC OVARY SYNDROME 1; PCOS1". *OMIM*. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine. Retrieved 15 November 2011.
29. ^ Amato P, Simpson JL (2004). "The genetics of polycystic ovary syndrome". *Best Pract Res Clin Obstet Gynaecol*. **18** (5): 707–18. doi:10.1016/j.bpobgyn.2004.05.002. PMID 15380142.
30. ^ Draper; et al. (2003). "Mutations in the genes encoding 11β-hydroxysteroid dehydrogenase type 1 and hexose-6-phosphate dehydrogenase interact to cause cortisone reductase deficiency". *Nature Genetics*. **34**: 434–439. doi:10.1038/ng1214. PMID 12858176.
31. ^ Ehrmann David A (2005). "Polycystic Ovary Syndrome". *N Engl J Med*. **352**: 1223–1236. doi:10.1056/NEJMra041536.
32. ^ Dunaif A, Fauser BC (2013). "Renaming PCOS--a two-state solution". *J. Clin. Endocrinol. Metab*. **98** (11): 4325–8. doi:10.1210/jc.2013-2040. PMID 24009134.
33. ^ a b Palioura E, Diamanti-Kandarakis E (2013). "Industrial endocrine disruptors and polycystic ovary syndrome". *J. Endocrinol. Invest*. **36** (11): 1105–11. doi:10.1007/bf03346762. PMID 24445124.
34. ^ Hoeger KM (2014). "Developmental origins and future fate in PCOS". *Semin. Reprod. Med*. **32** (3): 157–158. doi:10.1055/s-0034-1371086. PMID 24715509.
35. ^ Harden CL (2005). "Polycystic ovaries and polycystic ovary syndrome in epilepsy: evidence for neurogonadal disease". *Epilepsy Curr*. **5** (4): 142–6. doi:10.1111/j.1535-7511.2005.00039.x. PMC 1198730. PMID 16151523.
36. ^ Rasgon N (2004). "The relationship between polycystic ovary syndrome and antiepileptic drugs: a review of the evidence". *J Clin Psychopharmacol*. **24** (3): 322–34. doi:10.1097/01.jcp.0000125745.60149.c6. PMID 15118487.
37. ^ Hu X, Wang J, Dong W, Fang Q, Hu L, Liu C (2011). "A meta-analysis of polycystic ovary syndrome in women taking valproate for epilepsy". *Epilepsy Res*. **97** (1-2): 73–82. doi:10.1016/j.eplepsyres.2011.07.006. PMID 21820873.
38. ^ Abbott DH, Barnett DK, Bruns CM, Dumesic DA (2005). "Androgen excess fetal programming of female reproduction: a developmental aetiology for polycystic ovary syndrome?". *Hum. Reprod. Update*. **11** (4): 357–74. doi:10.1093/humupd/dmi013. PMID 15941725.
39. ^ Rutkowska A, Rachoń D (2014). "Bisphenol A (BPA) and its potential role in the pathogenesis of the polycystic ovary syndrome (PCOS)". *Gynecol. Endocrinol*. **30** (4): 260–5. doi:10.3109/09513590.2013.871517. PMID 24397396.
40. ^ a b c d Marrinan, Greg (20 April 2011). Lin, Eugene C, ed. "Imaging in Polycystic Ovary Disease". *eMedicine*. eMedicine. Retrieved 19 November 2011.
41. ^ a b c d e f g h Richard Scott Lucidi (25 October 2011). "Polycystic Ovarian Syndrome". eMedicine. Retrieved 19 November 2011.
42. ^ Azziz R (2006). "Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: the Rotterdam criteria are premature". *J. Clin. Endocrinol. Metab*. **91** (3): 781–5. doi:10.1210/jc.2005-2153. PMID 16418211.
43. ^ a b "Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS)". *Hum. Reprod*. **19** (1): 41–7. 2004. doi:10.1093/humrep/deh098. PMID 14688154.
44. ^ Carmina E (2004). "Diagnosis of polycystic ovary syndrome: from NIH criteria to ESHRE-ASRM guidelines".

*Minerva Ginecol*. **56** (1): 1–6. PMID 14973405.
45. ^ Hart R, Hickey M, Franks S (2004). "Definitions, prevalence and symptoms of polycystic ovaries and polycystic ovary syndrome". *Best Pract Res Clin Obstet Gynaecol*. **18** (5): 671–83. doi:10.1016/j.bpobgyn.2004.05.001. PMID 15380140.
46. ^ Pedersen SD, Brar S, Faris P, Corenblum B (2007). "Polycystic ovary syndrome: validated questionnaire for use in diagnosis". *Can Fam Physician*. **53** (6): 1042–7, 1041. PMC 1949220. PMID 17872783.
47. ^ *a b* Dewailly D, Lujan ME, Carmina E, Cedars MI, Laven J, Norman RJ, Escobar-Morreale HF (2013). "Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society". *Hum. Reprod. Update*. **20** (3): 334–52. doi:10.1093/humupd/dmt061. PMID 24345633.
48. ^ O'Brien, William T. (1 January 2011). *Top 3 Differentials in Radiology*. Thieme. p. 369. ISBN 978-1-60406-228-1. Retrieved 30 August 2014. "Ultrasound findings in PCOS include enlarged ovaries with peripheral follicles in a "string of pearls" configuration."
49. ^ Somani N, Harrison S, Bergfeld WF (2008). "The clinical evaluation of hirsutism". *Dermatol Ther*. **21** (5): 376–91. doi:10.1111/j.1529-8019.2008.00219.x. PMID 18844715.
50. ^ *a b c d e f g h* "Polycystic Ovarian Syndrome Workup". eMedicine. 25 October 2011. Retrieved 19 November 2011.
51. ^ Sharquie KE, Al-Bayatti AA, Al-Ajeel AI, Al-Bahar AJ, Al-Nuaimy AA (2007). "Free testosterone, luteinizing hormone/follicle stimulating hormone ratio and pelvic sonography in relation to skin manifestations in patients with polycystic ovary syndrome". *Saudi Med J*. **28** (7): 1039–43. PMID 17603706.
52. ^ Robinson S, Rodin DA, Deacon A, Wheeler MJ, Clayton RN (1992). "Which hormone tests for the diagnosis of polycystic ovary syndrome?". *Br J Obstet Gynaecol*. **99** (3): 232–8. doi:10.1111/j.1471-0528.1992.tb14505.x. PMID 1296589.
53. ^ Li X, Lin JF (2005). "[Clinical features, hormonal profile, and metabolic abnormalities of obese women with obese polycystic ovary syndrome]". *Zhonghua Yi Xue Za Zhi* (in Chinese). **85** (46): 3266–71. PMID 16409817.
54. ^ *a b* Banaszewska B, Spaczyński RZ, Pelesz M, Pawelczyk L (2003). "Incidence of elevated LH/FSH ratio in polycystic ovary syndrome women with normo- and hyperinsulinemia". *Rocz. Akad. Med. Bialymst*. **48**: 131–4. PMID 14737959.
55. ^ Dumont A, Robin G, Catteau-Jonard S, Dewailly D (2015). "Role of Anti-Müllerian Hormone in pathophysiology, diagnosis and treatment of Polycystic Ovary Syndrome: a review". *Reproductive Biology and Endocrinology : RB&E* (Review). **13**: 137. doi:10.1186/s12958-015-0134-9. PMC 4687350. PMID 26691645.
56. ^ Dewailly D, Andersen CY, Balen A, Broekmans F, Dilaver N, Fanchin R, Griesinger G, Kelsey TW, La Marca A, Lambalk C, Mason H, Nelson SM, Visser JA, Wallace WH, Anderson RA (2014). "The physiology and clinical utility of anti-Mullerian hormone in women". *Human Reproduction Update* (Review). **20** (3): 370–85. doi:10.1093/humupd/dmt062. PMID 24430863.
57. ^ Broer SL, Broekmans FJ, Laven JS, Fauser BC (2014). "Anti-Müllerian hormone: ovarian reserve testing and its potential clinical implications". *Hum. Reprod. Update*. **20** (5): 688–701. doi:10.1093/humupd/dmu020. PMID 24821925.
58. ^ *a b* Legro RS, Kunselman AR, Dodson WC, Dunaif A (1999). "Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women". *J. Clin. Endocrinol. Metab*. **84** (1): 165–9. doi:10.1210/jcem.84.1.5393. PMID 9920077.
59. ^ Lewandowski KC, Cajdler-Łuba A, Salata I, Bieńkiewicz M, Lewiński A (2011). "The utility of the gonadotrophin releasing hormone (GnRH) test in the diagnosis of polycystic ovary syndrome (PCOS)". *Endokrynol Pol*. **62** (2): 120–8. PMID 21528473.
60. ^ Munir, Iqbal; Yen, Hui-Wen; Geller, David H.; Torbati, Donna; Bierden, Rebecca M.; Weitsman, Stacy R.; Agarwal, Sanjay K.; Magoffin, Denis A. (January 2004). "Insulin Augmentation of 17α-Hydroxylase Activity Is Mediated by Phosphatidyl Inositol 3-Kinase But Not Extracellular Signal-Regulated Kinase-1/2 in Human Ovarian Theca Cells". *Endocrinology*. **145** (1): 175–183. doi:10.1210/en.2003-0329.
61. ^ Diamanti-Kandarakis, Evanthia; Dunaif, Andrea (December 2012). "Insulin Resistance and the Polycystic Ovary Syndrome Revisited: An Update on Mechanisms and Implications". *Endocrine Reviews*. **33** (6): 981–1030. doi:10.1210/er.2011-1034.
62. ^ Kumar Cotran Robbins: Basic Pathology 6th ed. / Saunders 1996[*page needed*]
63. ^ Sathyapalan T, Atkin SL (2010). "Mediators of inflammation in polycystic ovary syndrome in relation to adiposity". *Mediators Inflamm*. **2010**: 1–5. doi:10.1155/2010/758656. PMC 2852606. PMID 20396393.
64. ^ Fukuoka M, Yasuda K, Fujiwara H, Kanzaki H, Mori T (1992). "Interactions between interferon gamma, tumour necrosis factor alpha, and interleukin-1 in modulating progesterone and oestradiol production by human luteinized granulosa cells in culture". *Hum. Reprod*. **7** (10): 1361–4. PMID 1291559.
65. ^ González F, Rote NS, Minium J, Kirwan JP (2006). "Reactive oxygen species-induced oxidative stress in the

development of insulin resistance and hyperandrogenism in polycystic ovary syndrome". *J. Clin. Endocrinol. Metab.* **91** (1): 336–40. doi:10.1210/jc.2005-1696. PMID 16249279.

66. ^ Murri M, Luque-Ramírez M, Insenser M, Ojeda-Ojeda M, Escobar-Morreale HF (2013). "Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-analysis". *Hum. Reprod. Update*. **19** (3): 268–88. doi:10.1093/humupd/dms059. PMID 23303572.
67. ^ Kelly CJ, Stenton SR, Lashen H (2010). "Insulin-like growth factor binding protein-1 in PCOS: a systematic review and meta-analysis". *Hum. Reprod. Update*. **17** (1): 4–16. doi:10.1093/humupd/dmq027. PMID 20634211.
68. ^ Gleicher N, Weghofer A, Lee IH, Barad DH (2010). "FMR1 genotype with autoimmunity-associated polycystic ovary-like phenotype and decreased pregnancy chance". *PLoS ONE*. **5** (12): e15303. Bibcode:2010PLoSO...515303G. doi:10.1371/journal.pone.0015303. PMC 3002956. PMID 21179569.
69. ^ http://www.obgyn.net/articles/transgenderpcos[*full citation needed*]
70. ^ http://www.cancer-network.org/cancer_information/transgender_gender-nonconforming_people_and_cancer/transgender_men_and_ovarian_cancer.php[*full citation needed*]
71. ^ Lim DC, Chen W, Cheng LN, Xue CC, Wong FW, O'Sullivan AJ, Liu JP (2011). "Acupuncture for polycystic ovarian syndrome". *Cochrane Database Syst Rev* (8): CD007689. doi:10.1002/14651858.CD007689.pub2. PMID 21833961.
72. ^ Veltman-Verhulst SM, Boivin J, Eijkemans MJ, Fauser BJ (2012). "Emotional distress is a common risk in women with polycystic ovary syndrome: a systematic review and meta-analysis of 28 studies". *Hum. Reprod. Update*. **18** (6): 638–51. doi:10.1093/humupd/dms029. PMID 22824735.
73. ^ *a b* Moran LJ, Ko H, Misso M, Marsh K, Noakes M, Talbot M, Frearson M, Thondan M, Stepto N, Teede HJ (2013). "Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines". *Hum. Reprod. Update*. **19** (5): 432. doi:10.1093/humupd/dmt015. PMID 23727939.
74. ^ *a b c d e f g h i j k* "Polycystic Ovarian Syndrome Treatment & Management". eMedicine. 25 October 2011. Retrieved 19 November 2011.
75. ^ Krul-Poel YH, Snackey C, Louwers Y, Lips P, Lambalk CB, Laven JS, Simsek S (2013). "The role of vitamin D in metabolic disturbances in polycystic ovary syndrome: a systematic review". *European Journal of Endocrinology* (Review). **169** (6): 853–65. doi:10.1530/EJE-13-0617. PMID 24044903.
76. ^ He C, Lin Z, Robb SW, Ezeamama AE (2015). "Serum Vitamin D Levels and Polycystic Ovary syndrome: A Systematic Review and Meta-Analysis". *Nutrients* (Meta-analysis). **7** (6): 4555–77. doi:10.3390/nu7064555. PMC 4488802. PMID 26061015.
77. ^ Huang, G; Coviello, A (December 2012). "Clinical update on screening, diagnosis and management of metabolic disorders and cardiovascular risk factors associated with polycystic ovary syndrome.". *Current opinion in endocrinology, diabetes, and obesity*. **19** (6): 512–9. doi:10.1097/med.0b013e32835a000e. PMID 23108199.
78. ^ Lord JM, Flight IH, Norman RJ (2003). "Metformin in polycystic ovary syndrome: systematic review and meta-analysis". *BMJ*. **327** (7421): 951–3. doi:10.1136/bmj.327.7421.951. PMC 259161. PMID 14576245.
79. ^ Li, X.-J.; Yu, Y.-X.; Liu, C.-Q.; Zhang, W.; Zhang, H.-J.; Yan, B.; Wang, L.-Y.; Yang, S.-Y.; Zhang, S.-H. (2011-03). "Metformin vs thiazolidinediones for treatment of clinical, hormonal and metabolic characteristics of polycystic ovary syndrome: a meta-analysis". *Clinical Endocrinology*. **74** (3): 332–339. doi:10.1111/j.1365-2265.2010.03917.x. ISSN 1365-2265. PMID 21050251. Check date values in: `|date=` (help)
80. ^ Grover, Anjali; Yialamas, Maria A. (2011-03). "Metformin or thiazolidinedione therapy in PCOS?". *Nature Reviews Endocrinology*. **7** (3): 128–. doi:10.1038/nrendo.2011.16. ISSN 1759-5029. Retrieved 2015-05-24. Check date values in: `|date=` (help)
81. ^ National Institute for Health and Clinical Excellence. *11 Clinical guideline 11 : Fertility: assessment and treatment for people with fertility problems* . London, 2004.
82. ^ Balen A (December 2008). "Metformin therapy for the management of infertility in women with polycystic ovary syndrome" (PDF). *Scientific Advisory Committee Opinion Paper 13*. Royal College of Obstetricians and Gynaecologists. Retrieved 2009-12-13.
83. ^ Leeman L, Acharya U (2009). "The use of metformin in the management of polycystic ovary syndrome and associated anovulatory infertility: the current evidence". *J Obstet Gynaecol*. **29** (6): 467–72. doi:10.1080/01443610902829414. PMID 19697191.
84. ^ Legro, RS; Arslanian, SA; Ehrmann, DA; Hoeger, KM; Murad, MH; Pasquali, R; Welt, CK; Endocrine, Society (December 2013). "Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline.". *The Journal of Clinical Endocrinology and Metabolism*. **98** (12): 4565–92. doi:10.1210/jc.2013-2350. PMID 24151290.
85. ^ Nestler, John E.; Jakubowicz, Daniela J.; Evans, William S.; Pasquali, Renato (1998-06-25). "Effects of Metformin on Spontaneous and Clomiphene-Induced Ovulation in the Polycystic Ovary Syndrome". *New England Journal of Medicine*. **338** (26): 1876–1880. doi:10.1056/NEJM199806253382603. ISSN 0028-4793. PMID 9637806. Retrieved 2015-05-24.

86. ^ Feig, Denice S.; Moses, Robert G. (2011-10-01). "Metformin Therapy During Pregnancy Good for the goose and good for the gosling too?". *Diabetes Care*. **34** (10): 2329–2330. doi:10.2337/dc11-1153. ISSN 0149-5992. PMID 21949224. Retrieved 2015-05-24.
87. ^ Cassina M, Donà M, Di Gianantonio E, Litta P, Clementi M (2014). "First-trimester exposure to metformin and risk of birth defects: a systematic review and meta-analysis". *Hum. Reprod. Update*. **20** (5): 656–69. doi:10.1093/humupd/dmu022. PMID 24861556.
88. ^ Qiao J, Feng HL (2010). "Extra- and intra-ovarian factors in polycystic ovary syndrome: impact on oocyte maturation and embryo developmental competence". *Hum. Reprod. Update*. **17** (1): 17–33. doi:10.1093/humupd/dmq032. PMC 3001338. PMID 20639519.
89. ^ Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, Steinkampf MP, Coutifaris C, McGovern PG, Cataldo NA, Gosman GG, Nestler JE, Giudice LC, Leppert PC, Myers ER (2007). "Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome". *N. Engl. J. Med.* **356** (6): 551–66. doi:10.1056/NEJMoa063971. PMID 17287476.
90. ^ "Polycystic ovary syndrome – Treatment". United Kingdom: National Health Service. 17 October 2011. Retrieved 19 November 2011.
91. ^ *a b* Richard Scott Lucidi (25 October 2011). "Polycystic Ovarian Syndrome Medication". eMedicine. Retrieved 19 November 2011.
92. ^ "What are the health risks of PCOS?". *Verity – PCOS Charity*. Verity. 2011. Retrieved 21 November 2011.
93. ^ Galazis N, Galazi M, Atiomo W (2011). "D-Chiro-inositol and its significance in polycystic ovary syndrome: a systematic review". *Gynecol. Endocrinol*. **27** (4): 256–62. doi:10.3109/09513590.2010.538099. PMID 21142777.
94. ^ Unfer V, Carlomagno G, Dante G, Facchinetti F (2012). "Effects of myo-inositol in women with PCOS: a systematic review of randomized controlled trials". *Gynecol. Endocrinol*. **28** (7): 509–15. doi:10.3109/09513590.2011.650660. PMID 22296306.
95. ^ Lim, Chi Eung Danforn; Ng, Rachel WC; Xu, Ke; Cheng, Nga Chong Lisa; Xue, Charlie CL; Liu, Jian Ping; Chen, Nini (3 May 2016). "Acupuncture for polycystic ovarian syndrome". *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd: CD007689. doi:10.1002/14651858.cd007689.pub3. PMID 27136291.
96. ^ *a b* Barry JA, Azizia MM, Hardiman PJ (2014). "Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis". *Hum. Reprod. Update*. **20** (5): 748–758. doi:10.1093/humupd/dmu012. PMID 24688118.
97. ^ New MI (1993). "Nonclassical congenital adrenal hyperplasia and the polycystic ovarian syndrome". *Ann. N. Y. Acad. Sci*. **687**: 193–205. Bibcode:1993NYASA.687..193N. doi:10.1111/j.1749-6632.1993.tb43866.x. PMID 8323173.
98. ^ Hardiman P, Pillay OC, Atiomo W (2003). "Polycystic ovary syndrome and endometrial carcinoma". *Lancet*. **361** (9371): 1810–2. doi:10.1016/S0140-6736(03)13409-5. PMID 12781553.
99. ^ Mather KJ, Kwan F, Corenblum B (2000). "Hyperinsulinemia in polycystic ovary syndrome correlates with increased cardiovascular risk independent of obesity". *Fertil. Steril*. **73** (1): 150–6. doi:10.1016/S0015-0282(99)00468-9. PMID 10632431.
100. ^ Moran LJ, Misso ML, Wild RA, Norman RJ (2010). "Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis". *Hum. Reprod. Update*. **16** (4): 347–63. doi:10.1093/humupd/dmq001. PMID 20159883.
101. ^ Barry JA, Kuczmierczyk AR, Hardiman PJ (2011). "Anxiety and depression in polycystic ovary syndrome: a systematic review and meta-analysis". *Hum. Reprod*. **26** (9): 2442–51. doi:10.1093/humrep/der197. PMID 21725075.
102. ^ Rocha MP, Maranhão RC, Seydell TM, Barcellos CR, Baracat EC, Hayashida SA, Bydlowski SP, Marcondes JA (2010). "Metabolism of triglyceride-rich lipoproteins and lipid transfer to high-density lipoprotein in young obese and normal-weight patients with polycystic ovary syndrome". *Fertil. Steril*. **93** (6): 1948–56. doi:10.1016/j.fertnstert.2008.12.044. PMID 19765700.
103. ^ de Groot PC, Dekkers OM, Romijn JA, Dieben SW, Helmerhorst FM (2011). "PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis". *Hum. Reprod. Update*. **17** (4): 495–500. doi:10.1093/humupd/dmr001. PMID 21335359.
104. ^ Goldenberg N, Glueck C (2008). "Medical therapy in women with polycystic ovarian syndrome before and during pregnancy and lactation". *Minerva Ginecol*. **60** (1): 63–75. PMID 18277353.
105. ^ Boomsma CM, Fauser BC, Macklon NS (2008). "Pregnancy complications in women with polycystic ovary syndrome". *Semin. Reprod. Med*. **26** (1): 072–084. doi:10.1055/s-2007-992927. PMID 18181085.
106. ^ Kachuei M, Jafari F, Kachuei A, Keshteli AH (2012). "Prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome". *Archives of Gynecology and Obstetrics*. **285** (3): 853–6. doi:10.1007/s00404-011-2040-5. PMID 21866332.
107. ^ Vos T, Flaxman AD, et al. (2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. **380** (9859): 2163–

96. doi:10.1016/S0140-6736(12)61729-2. PMID 23245607.
108. ^ Agrawal R, Sharma S, Bekir J, Conway G, Bailey J, Balen AH, Prelevic G (2004). "Prevalence of polycystic ovaries and polycystic ovary syndrome in lesbian women compared with heterosexual women". *Fertil. Steril.* **82** (5): 1352–7. doi:10.1016/j.fertnstert.2004.04.041. PMID 15533359.
109. ^ De Sutter P, Dutré T, Vanden Meerschaut F, Stuyver I, Van Maele G, Dhont M (2008). "PCOS in lesbian and heterosexual women treated with artificial donor insemination". *Reprod. Biomed. Online.* **17** (3): 398–402. doi:10.1016/S1472-6483(10)60224-6. PMID 18765011.
110. ^ Smith HA, Markovic N, Matthews AK, Danielson ME, Kalro BN, Youk AO, Talbott EO (2011). "A comparison of polycystic ovary syndrome and related factors between lesbian and heterosexual women". *Womens Health Issues.* **21** (3): 191–8. doi:10.1016/j.whi.2010.11.001. PMID 21310628.
111. ^ Polson DW, Adams J, Wadsworth J, Franks S (1988). "Polycystic ovaries--a common finding in normal women". *Lancet.* **1** (8590): 870–2. doi:10.1016/s0140-6736(88)91612-1. PMID 2895373.
112. ^ *a b* Clayton RN, Ogden V, Hodgkinson J, Worswick L, Rodin DA, Dyer S, Meade TW (1992). "How common are polycystic ovaries in normal women and what is their significance for the fertility of the population?". *Clin. Endocrinol. (Oxf).* **37** (2): 127–34. doi:10.1111/j.1365-2265.1992.tb02296.x. PMID 1395063.
113. ^ Farquhar CM, Birdsall M, Manning P, Mitchell JM, France JT (1994). "The prevalence of polycystic ovaries on ultrasound scanning in a population of randomly selected women". *Aust N Z J Obstet Gynaecol.* **34** (1): 67–72. doi:10.1111/j.1479-828X.1994.tb01041.x. PMID 8053879.
114. ^ van Santbrink EJ, Hop WC, Fauser BC (1997). "Classification of normogonadotropic infertility: polycystic ovaries diagnosed by ultrasound versus endocrine characteristics of polycystic ovary syndrome". *Fertil. Steril.* **67** (3): 452–8. doi:10.1016/S0015-0282(97)80068-4. PMID 9091329.
115. ^ Hardeman J, Weiss BD (2014). "Intrauterine devices: an update.". *Am Fam Physician.* **89** (6): 445–50. PMID 24695563.
116. ^ "What is Polycystic Ovary Syndrome (PCOS)?". *Verity – PCOS Charity*. Verity. 2011. Retrieved 21 November 2011.

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| v · t · e · | Diseases of the endocrine system (E00–E35, 240–259) | | |
|---|---|---|---|
| **Pancreas/ glucose metabolism** | **Hypofunction** | Diabetes mellitus · *types:* (type 1 · type 2 · MODY 1 2 3 4 5 6 · · *complications* (coma · angiopathy · ketoacidosis · nephropathy · neuropathy · retinopathy · cardiomyopathy · · *insulin receptor* (Rabson–Mendenhall syndrome) · Insulin resistance · | |
| | **Hyperfunction** | Hypoglycemia · *beta cell* (Hyperinsulinism) · *G cell* (Zollinger–Ellison syndrome) · | |
| | **Hypothalamus** | *gonadotropin* (Kallmann syndrome · Adiposogenital dystrophy · · *CRH* (Tertiary adrenal insufficiency) · *vasopressin* (Neurogenic diabetes insipidus) · *general* (Hypothalamic hamartoma) · | |
| | **Pituitary** | **Hyperpituitarism** | *anterior* (Acromegaly · Hyperprolactinaemia · Pituitary ACTH hypersecretion · · *posterior* (SIADH) · *general* (Nelson's syndrome) · |
| | | **Hypopituitarism** | *anterior* (Kallmann syndrome · Growth hormone deficiency · Hypoprolactinemia · ACTH deficiency/Secondary adrenal insufficiency · GnRH insensitivity · FSH insensitivity · LH/hCG insensitivity · · *posterior* (Neurogenic |

| | | | |
|---|---|---|---|
| **Hypothalamic/ pituitary axes** | | | diabetes insipidus) · *general* (Empty sella syndrome · Pituitary apoplexy · Sheehan's syndrome · Lymphocytic hypophysitis · · |
| | **Thyroid** | **Hypothyroidism** | Iodine deficiency · Cretinism (Congenital hypothyroidism · · Myxedema · Euthyroid sick syndrome · |
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| | | **Thyroiditis** | Acute infectious · Subacute (De Quervain's · Subacute lymphocytic · · Autoimmune/chronic (Hashimoto's · Postpartum · Riedel's · · |
| | | **Goitre** | Endemic goitre · Toxic nodular goitre · Toxic multinodular goiter · Thyroid nodule · |
| | **Parathyroid** | **Hypoparathyroidism** | Hypoparathyroidism · Pseudohypoparathyroidism · Pseudopseudohypoparathyroidism · |
| | | **Hyperparathyroidism** | Primary · Secondary · Tertiary · Osteitis fibrosa cystica · |
| | **Adrenal** | **Hyperfunction** | *aldosterone:* Hyperaldosteronism/Primary aldosteronism (Conn syndrome · Bartter syndrome · Glucocorticoid remediable aldosteronism · · AME · Liddle's syndrome · 17α CAH · *cortisol:* Cushing's syndrome (Pseudo-Cushing's syndrome) · *sex hormones:* 21α CAH · 11β CAH · |
| | | **Hypofunction/ Adrenal insufficiency (Addison's, WF)** | *aldosterone:* Hypoaldosteronism (21α CAH · 11β CAH · · *cortisol:* CAH (Lipoid · 3β · 11β · 17α · 21α · · *sex hormones:* 17α CAH · |
| | **Gonads** | | *ovarian:* **Polycystic ovary syndrome** · Premature ovarian failure · *testicular: enzymatic* (5α-reductase deficiency · 17β-hydroxysteroid dehydrogenase deficiency · aromatase excess syndrome) · · *Androgen receptor* (Androgen insensitivity syndrome) · *general:* Hypogonadism (Delayed puberty) · Hypergonadism (Precocious puberty · · Hypoandrogenism · Hypoestrogenism · Hyperandrogenism · Hyperestrogenism · Postorgasmic illness syndrome · |
| **Height** | | | Dwarfism/Short stature (Midget · Laron syndrome · Psychosocial · Ateliosis · · Gigantism · |
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